New and Emerging Directions in Myelofibrosis Treatment:
Seeking to Improve Quality of Life and Prolong Survival

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Dr. Srdan Verstovsek: Hello, and welcome to today's program. I am Srdan Verstovsek. I'm Professor of Medicine at The University of Texas, MD Anderson Cancer Center. Today, I'm joined by Dr. Rami Komrokji, who is Professor of Oncology Sciences at Moffitt Cancer Center, and Dr. Pankit Vachhani, Assistant Professor of Medicine at O'Neill Comprehensive Cancer Center and UAB.

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Faculty Disclosures

- **Dr. Srdan Verstovsek** has relevant financial relationships related to research activities from AstraZeneca, Blueprint Medicines, Celgene Corporation, CTI BioPharma Corp., F. Hoffmann-La Roche Ltd, Genentech, Inc., Gilead, Inc., Incyte Corporation, Italfarmaco, Novartis AG, NS Pharma, Inc., PharmaEssentia Corporation, Promedior, Inc., Protagonist Therapeutics, Inc., and Sierra Oncology, Inc., as well as relevant financial relationships related to consulting from Celgene, Constellation Pharmaceuticals, Incyte, Novartis, Pragmatist, and Sierra.
- **Dr. Rami Komrokji** has relevant financial relationships related to advisory activities from Bristol Myers Squibb Company, CTI BioPharma Corp., Novartis AG, PharmaEssentia Corporation, and Taiho Pharmaceutical Co., Ltd., as well as relevant financial relationships related to consulting from AbbVie Inc., Bristol Myers Squibb, Geron, Gilead, Jazz Pharmaceuticals plc, and Novartis AG. He is on the speakers' bureau for AbbVie, Bristol Myers Squibb, and Jazz.
- **Dr. Pankit Vachhani** has relevant financial relationships related to consulting from Blueprint Medicines, CTI BioPharma Corp., and Incyte Corporation.

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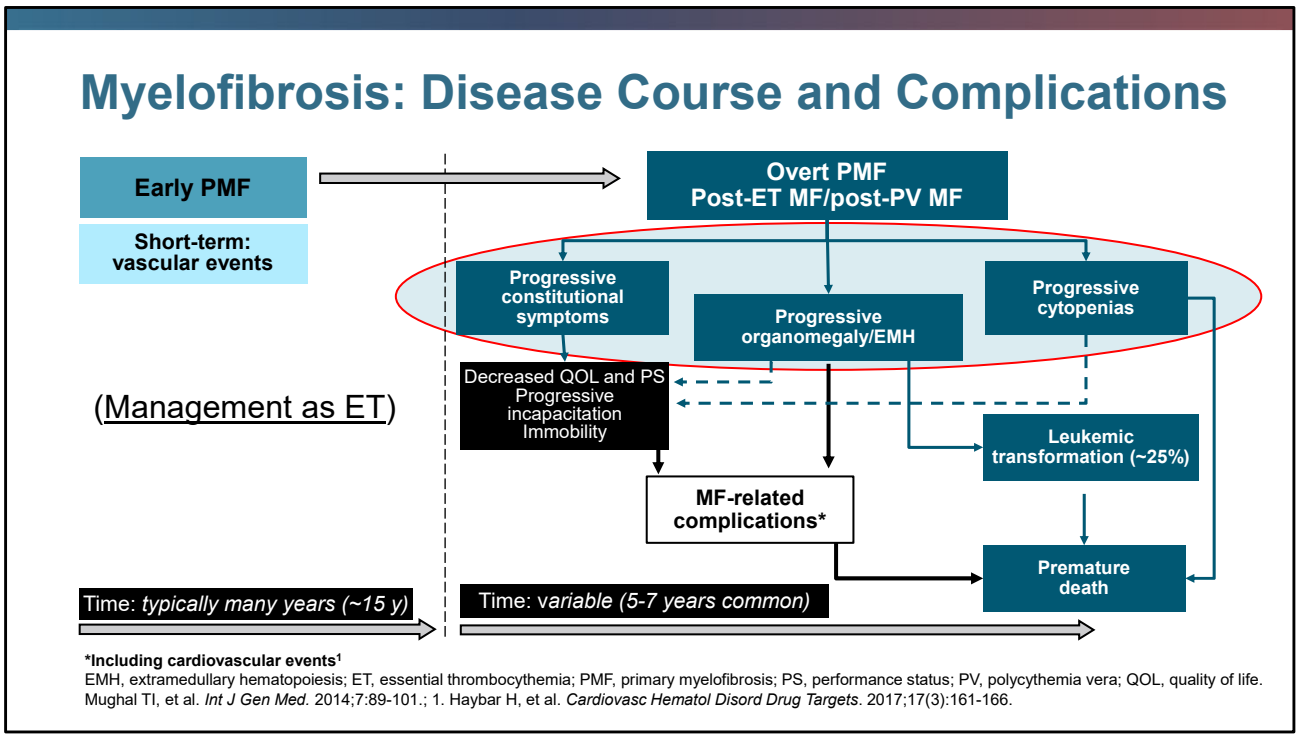
New and Emerging Directions in Myelofibrosis Treatment: Seeking to Improve Quality of Life and Prolong Survival



Let's start our discussion about myelofibrosis. We typically will divide the myelofibrosis in two entities these days; early prefibrotic myelofibrosis, and then overt or fibrotic myelofibrosis, which can be primary, or post-ET, post-PV myelofibrosis.

When we talk about early prefibrotic myelofibrosis, we typically worry about the clotting risk, so-called vascular events. We manage these patients as we typically manage patients with essential thrombocythemia, decreasing the blast cell counts if necessary because life expectancy is about 15 years on average.

The topic today is really to focus on a fibrotic or post-ET post PV myelofibrosis that has a shorter life expectancy, five to seven years, and is driven by progressive constitutional symptoms, progressive organomegaly, particularly splenomegaly and progressive cytopenias as the three markers and clinically relevant problems that we try to manage in everyday practice.

We know that about a quarter of the patients progress to leukemia, but a majority of the patients, unfortunately, have myelofibrosis-related complications and die in between five to seven years from those complications, not with transformation to acute myeloid leukemia. The goal is to control those problems and possibly make people live longer.

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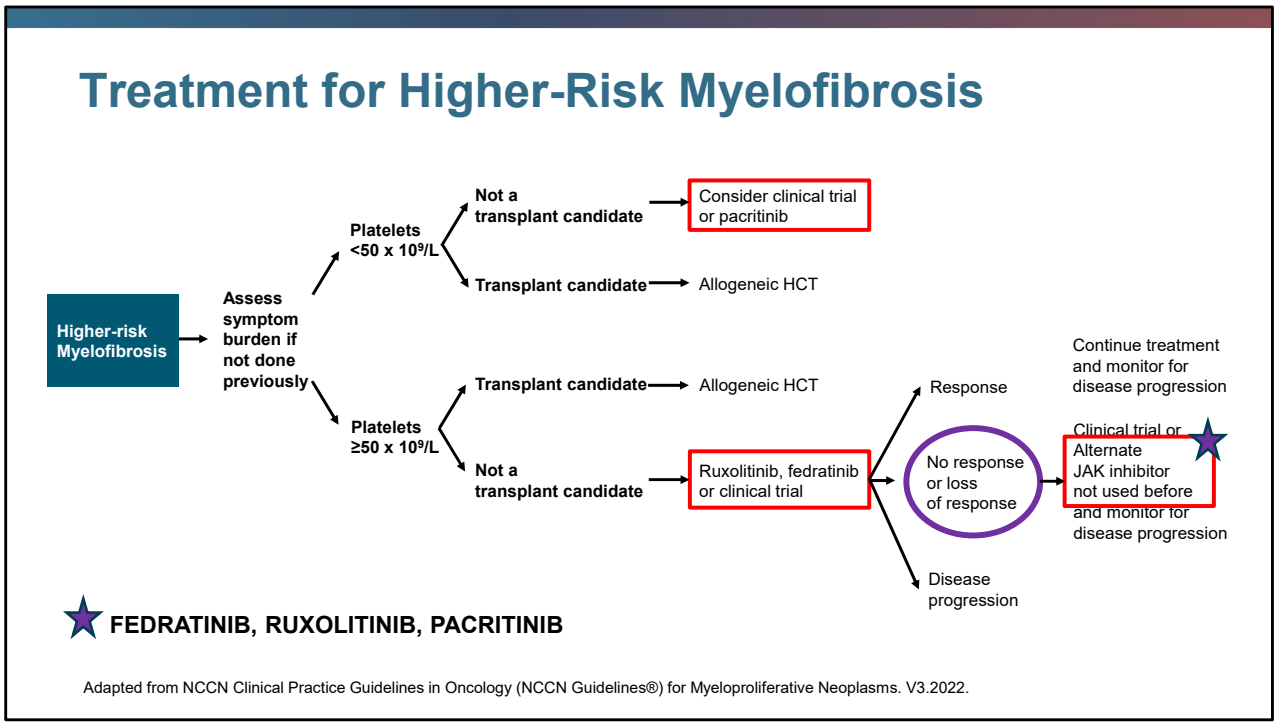

What do the NCCN guidelines suggest? First, of course, we assess the risk of dying if we go from the left to the right, and we will typically, those that have a high risk of dying less than five years, refer to a transplant.

Now, transplant, unfortunately, happens in less than 10% of patients, so the medical care is the number one approach to the therapy of patients with myelofibrosis. When do we start a therapy? Assessing the symptoms with the questionnaire usually is the way to go to objectivize the problem, and then look at the platelet number as you can see, and employ then one of the JAK inhibitors that will control the signs and symptoms in these patients that need therapy. We have ruxolitinib and fedratinib approved therapies for patients with platelets above 50, and pacritinib for those that have platelets below 50.

Of course, in a secondary setting when there is no response or loss of response, an alternative JAK inhibitor that was not used in first-line can be used.

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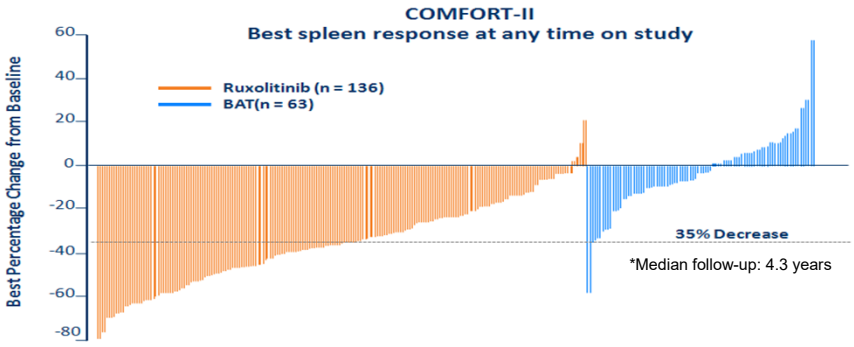
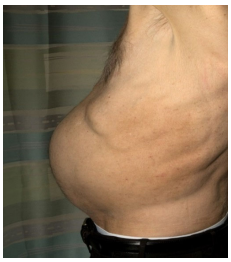
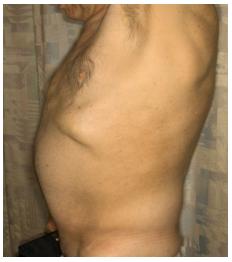
Myelofibrosis: What Are JAK Inhibitors For? Spleen and Symptoms



- Dosed based on platelet number (not recommended for platelets <50K)
- It can cause anemia and thrombocytopenia
- Long-term ruxolitinib therapy prolongs survival (earlier intervention and better the spleen response, longer the survival)



MF Patient Pre-Ruxolitinib Therapy



After 2 Months of Therapy

What do we expect from the JAK inhibitors? I use an example of ruxolitinib that has been around for a long time, approved in 2011. As you know, in this waterfall is clearly seen and by photos even better that majority of the people have a significant decrease in the spleen size, but to different extent. Of course, that's much better than hydroxyurea which was a control in most of the patients as you see in the blue lines.

Now, we know that ruxolitinib needs to be adjusted based on a platelet number.
It can cause anemia and thrombocytopenia that do require those adjustments, but we also know that the long-term ruxolitinib therapy can prolong survival and also evidenced by the label for its use. Over time, we learned that earlier intervention and better spleen response would lead to a longer survival.

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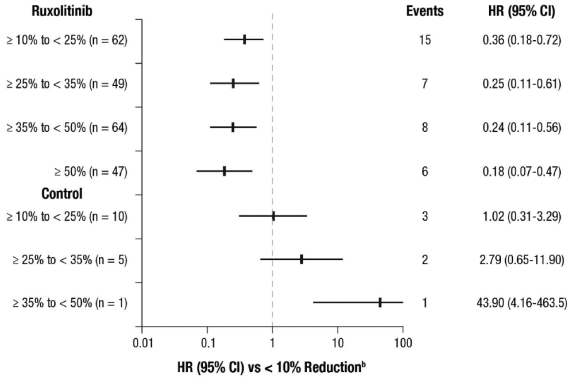
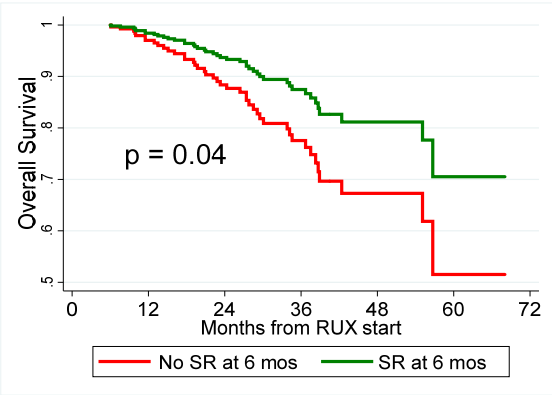
Spleen Response Correlates With Survival



In the pooled COMFORT 1 and 2 analysis, reductions in spleen size with ruxolitinib treatment correlated with longer survival



In a retrospective study on 284 patients treated with ruxolitinib for ≥1 year, spleen response at 6 months correlated with longer survival

HR, hazard ratio; SR, spleen response.
Vannucchi AM, et al. *Haematologica.* 2015;100.; Palandri F, et al. *Leuk Res.* 2018;74:86-88.

One of the major markers as mentioned is the spleen reduction. The smaller the spleen becomes as a marker of a success, the longer durability overall. Control the signs and symptoms of the disease and the longer survival of the patients as you can see in this slide.

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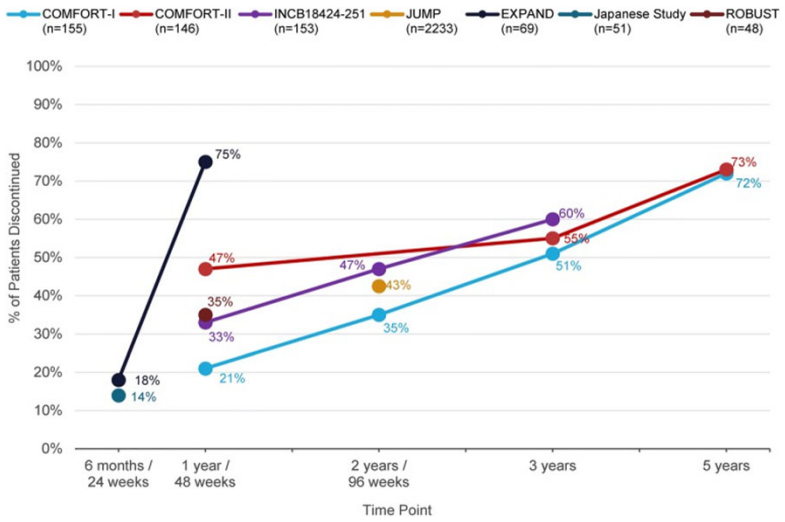
Duration of Ruxolitinib Therapy*



*Rates of ruxolitinib treatment discontinuation at various time points in large clinical trials.

Harrison CN, et al. *Ann Hematol*. 2020;99:1177-1191.

Now, overall, how does the ruxolitinib work? For how long? Unfortunately, patients who then have low platelet numbers which requires low dosing, it doesn't work that long. This is in the black color in this slide. The other studies show that average duration is about three years.

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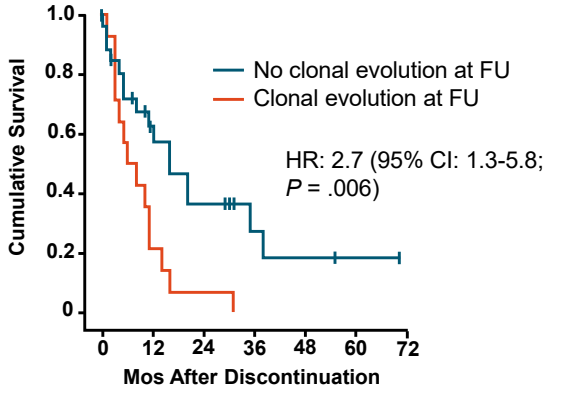
Outcomes After Ruxolitinib Discontinuation

- Retrospective analysis of clonal evolution and outcomes after ruxolitinib discontinuation in an open-label phase I/II study (N = 56)



Newberry K, et al. *Blood*. 2017;130(9):1125-1131.

- Median OS: 14 mos
- Survival improved if baseline platelets ≥260 vs <260 × 10^9/L (HR: 2.7; *P* = .006)
- Survival improved if follow-up platelets ≥100 vs <100 × 10^9/L (HR: 4.1; *P* = .001)
- 35% of patients acquired a new mutation while on ruxolitinib, most commonly *ASXL1*

Certainly there is room for improvement in that setting, particularly because after ruxolitinib, life is relatively short. Depends on symptom characteristics of the patients at that setting, but it is somewhere about a year and a half to two years on average.

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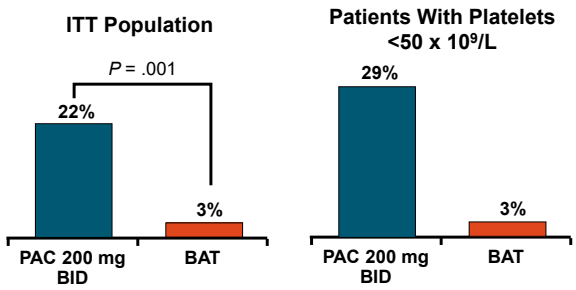
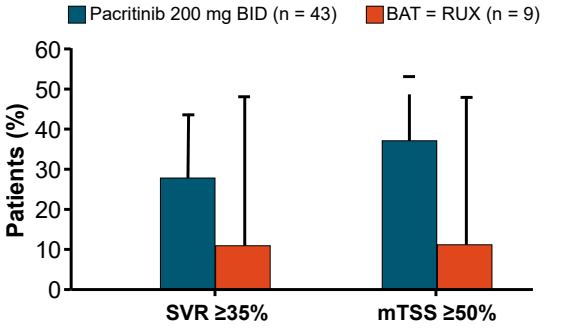
PERSIST-2: Pacritinib vs Best Available Therapy for Patients With MF and Platelets ≤100 x 10^9/L

SVR ≥35%, Week 24



- Proportions of patients with much improved or very much improved scores were 57% with pacritinib 200 mg BID vs 28% with BAT

Efficacy in "First-line" (Ruxolitinib-Naive) Patients



- Patients treated with pacritinib had numerically higher rates of SVR (28% vs 11%) and modified TSS response (37% vs 11%) vs patients treated with ruxolitinib

Mascarenhas J, et al. *JAMA Oncol*. 2018;4:652-659.; Mascarenhas J. ASH. 2021. Abstract 3639.

The pacritinib was approved about a year ago for patients with platelets below 50. Based on a subgroup analysis of this particular study in patients with platelets below 100, where it showed the much better results than best available therapy in controlling the spleen and the symptoms.

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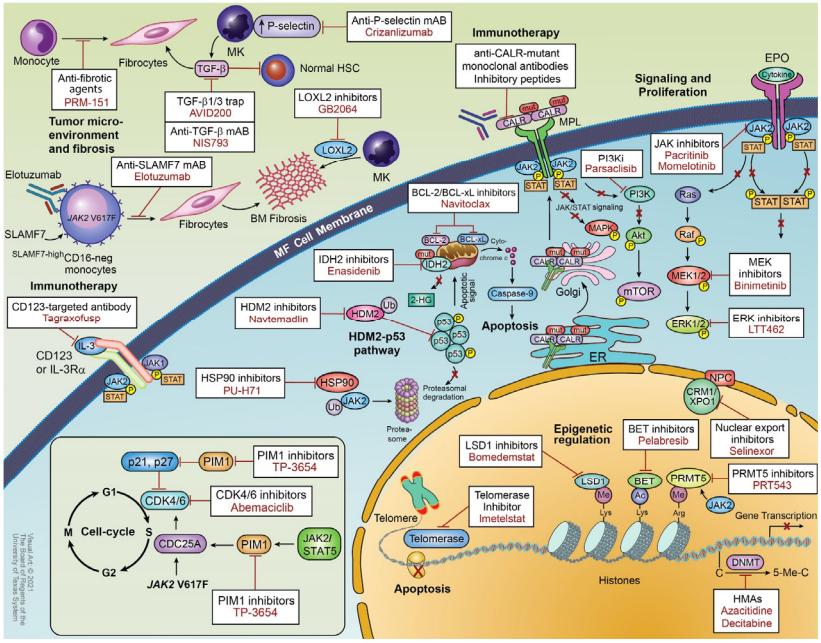
Targets of Novel Therapeutic Agents in Development for MF



Akt, protein kinase B; BET, bromodomain and extra-terminal; BM, bone marrow; CALR, calreticulin, CD, cluster of differentiation; DNMT, deoxyribonucleic acid methyltransferase; EPO, erythropoietin; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; HDM, human double minute; HMA, hypomethylating agent; HSC, hematopoietic stem cell; HSP, heat shock protein; JAK, Janus kinase; LOXL, lysyl oxidase-like; LSD, lysine-specific demethylase; mAB, monoclonal antibody; MEK, mitogen-activated protein kinase; MF, myelofibrosis; MK, mesodermal killer; MPL, thrombopoietin receptor; mTOR, mechanistic target of rapamycin; mut, mutation; PI3K, phosphoinositide 3 kinase; PIM, proviral integration site for Moloney murine leukemia virus kinase; PRMT, protein arginine methyltransferase; Raf, rapidly accelerated fibrosarcoma; Ras, rat sarcoma viral oncogene homolog; SLAM, signaling lymphocytic activation molecule; STAT, signal transducer and activator of transcription; TGF, transforming growth factor; Ub, ubiquitin.

Chifotides HT, et al. *Clin Lymphoma Myeloma Leuk*. 2022;22(4):210-223.

Now, where are we going? Instead of outlining all the therapies, I use this cartoon where in each white box, it's listed the target of therapy and medication that is being developed for myelofibrosis patients beyond the JAK inhibitors. Of course, there are already some of those drugs that are in advanced clinical development.

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Phase 3 Clinical Studies in MF Underway

Investigational agent	Mechanism of action	Ongoing phase 3 clinical trials	Evaluated patients	Comparator agent	Clinical setting
Momelotinib	ACVR1/ALK2 & JAK2 inhibitor	MOMENTUM (NCT04173494)	Symptomatic anemic MF patients who were previously treated with an approved JAK inhibitor	Danazol	Second-line
Pacritinib	JAK2/FLT3 inhibitor	PACIFICA (NCT03165734)	Patients with MF and severe thrombocytopenia (platelets <50 x 10^9/L)	BAT	First-line
Navitoclax (+ ruxolitinib)	BCL-X_L inhibitor	TRANSFORM-1 (NCT04472598)	Patients with MF who were not previously treated with JAK2 inhibitors	Placebo (+ ruxolitinib)	First-line
Navitoclax (+ ruxolitinib)	BCL-X_L inhibitor	TRANSFORM-2 (NCT04468984)	Patients with MF who are refractory/resistant to JAK2 inhibitors	BAT	Second-line
Pelabresib (+ ruxolitinib)	BET inhibitor	MANIFEST-2 (NCT04603495)	Patients with MF who were not previously treated with JAK2 inhibitors	Placebo (+ ruxolitinib)	First-line
Luspatercept	Activin receptor ligand trap	INDEPENDENCE (NCT04717414)	Patients on stable dose of ruxolitinib with MF-associated anemia requiring RBC transfusions	Placebo	Add-on to ruxolitinib
Parsaclisib	PI3Kδ inhibitor	LIMBER-304 (NCT04551053)	Patients with MF who have suboptimal response to ruxolitinib	Placebo	Add-on to ruxolitinib
Parsaclisib (+ ruxolitinib)	PI3Kδ inhibitor	LIMBER-313 (NCT04551066)	Patients with MF who were not previously treated with JAK2 inhibitors	Placebo (+ ruxolitinib)	First-line
KRT-232 (Navtemadlin)	HDM2 inhibitor	BOREAS (NCT03662126)	Patients with MF who are refractory/resistant to JAK2 inhibitors	BAT	Second-line
Imetelstat	Telomerase inhibitor	IMpactMF (NCT04576156)	Patients with Int-2/High-risk MF who are refractory to JAK inhibitors	BAT	Second-line

Chifotides HT, Verstovsek S. *Clin Lymphoma Myeloma Leuk.* 2021;21(S1):S130-S133.

In this slide, in the red boxes, you will see a list of medication data in a Phase 3 randomized study for possible approval in different subpopulation myelofibrosis patients based on a different mode of action.

A very exciting time for us. At this time, I will turn it over to Dr. Komrokji who will discuss the current treatment paradigm in much more detail. Rami?

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Myelofibrosis
The Role of Jak Inhibitors for the Treatment of Myelofibrosis

Rami S. Komrokji, MD
Vice Chair
Malignant Hematology Department
Head of the Leukemia and MDS Section
Moffitt Cancer Center
Tampa, Florida

Dr. Rami Komrokli: Thank you, Serg, for the kind introduction and setting the stage. My role is really to provide an overview of the current available treatments and the paradigm focusing mainly on the available JAK2 inhibitors.

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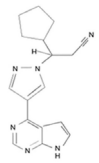
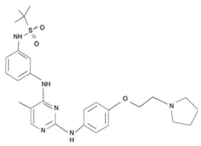
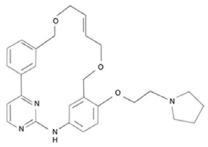
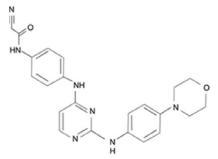
JAK Inhibitors for Treatment of Myelofibrosis

	Ruxolitinib (approved)[2]	Fedratinib (approved)[3]	Pacritinib (approved)[4]	Momelotinib[5]
Structure[1]				
Target	JAK1 and JAK2	JAK2	JAK2, FLT3, IRAK1, and CSF1R	JAK1, JAK2, and ACVR1
Indication	Intermediate or high-risk myelofibrosis	Intermediate-2 or high-risk myelofibrosis	Intermediate or high-risk myelofibrosis with platelet count <50×10^9/L	Not yet approved (Submitted to FDA June 2022)
Notable AEs	Cytopenias (anemia, thrombocytopenia), infection, weight gain	Wernicke encephalopathy, GI toxicity	Hemorrhage, cardiovascular events, GI (diarrhea, nausea)	Cytopenias (anemia, thrombocytopenia), peripheral neuropathy

ACVR1, type 1 kinase activin A receptor; CSF1R, colony stimulating factor 1 receptor; FLT3, FMS-like tyrosine kinase 3; IRAK1, interleukin-1 receptor-associated kinase 1

1. Duenas-Perez AB, et al. *Ther Adv Hematol*. 2015;6(4):186-201. 2. Jakafi (ruxolitinib) [package insert]. Wilmington, DE: Incyte Corporation; September 2021. 3. Inrebic (fedratinib) [package insert]. Summit, NJ: Celgene Corporation; December 2021. 4. Vonjo (pacritinib) [package insert]. Seattle, WA: CTI BioPharma Corporation; February 2022. 5. Mesa RA, et al. ASCO 2022. Oral Presentation 7002.

Currently, we have three JAK2 inhibitors approved by the FDA, and hopefully, by the end of this year we'll have the fourth one: ruxolitinib, fedratinib, pacritinib, and momelotinib. Dr. Verstovsek set the stage talking about some of those medications. I think the message basically, the JAK2 inhibitors are the treatment of choice for patients with constitutional symptoms and splenomegaly.

Those medications work regardless, if the patient has the JAK2 mutation or not, because the JAK/STAT pathway is always overactivated in patients with myelofibrosis. There are slight differences in the targets that explain some of the difference in efficacy and adverse events. For example, ruxolitinib is a JAK1/JAK2 inhibitor, fedratinib is more specific JAK2 inhibitor, pacritinib has other pathways like the IRAK1 that's part of the inflammatory pathway. Finally, momelotinib affects the ACVR1 pathway that's probably thought to be related to the anemia response that we see with momelotinib.

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Ruxolitinib: Overview of Phase 3 Trials COMFORT-I and II[1,2]

- **Patients** with intermediate-2 or high-risk myelofibrosis; platelets ≥100×10^9/L

- **Primary endpoint** was the proportion of patients achieving a reduction in spleen volume of ≥35% (SVR35) from baseline to week 24 (COMFORT-I) or week 48 (COMFORT-II) by MRI or CT
- **Key secondary endpoints** included proportion of patients with ≥50% reduction in total symptom score (TSS50) and OS

Summary

- SVR35 was achieved in 41.9% of patients receiving ruxolitinib and 0.7% receiving placebo (COMFORT-I); 28% of the ruxolitinib arm vs 0% of the best available therapy (BAT) arm (COMFORT-II)
- Main AEs; myelosuppression thrombocytopenia and anemia
- Thrombocytopenia, which occurred frequently, was generally reversible and managed by dose reduction or temporary withholding

1. Verstovsek S, et al. *N Engl J Med.* 2012;366(9):799-807. 2. Harrison CN, et al. *N Engl J Med.* 2012;366(9);787-798.

Obviously, ruxolitinib has been our long-used JAK2 inhibitor, as mentioned, approved back in 2011. This is for patients that have typically a proliferative myelofibrosis, high white count, platelets are above a hundred. It was tested in two trials, the COMFORT-I, COMFORT-II, showed around 30% to 40% of the patients achieved 35% or more spleen volume reduction by MRI, that typically correlates with 50% or more by physical exam. They've been obviously shown to reduce spleen, improve symptoms, and as mentioned, also improve overall survival for those patients.

Now, the main adverse event is really myelosuppression, thrombocytopenia, and anemia that's typically seen around month two and usually is managed by dose reductions or temporary withholding as long as the baseline of the patient platelets and red blood cells were adequate to start with. I think we know that ruxolitinib spleen response is dose-dependent. The symptom response actually does happen at a lower dosing than the ones needed for spleen. Symptom response typically happens quickly within a couple of weeks, while spleen response may take up to three to four months to achieve the optimal spleen response desired.

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Fedratinib: JAKARTA-1 (Phase 3)

- **Patients** with intermediate-2 or high-risk myelofibrosis; platelets ≥50×10^9/L

- **Primary endpoint** was proportion of patients with SVR35 from baseline to week 24 by MRI or CT
- **Key secondary endpoint** was proportion of patients with TSS50 from baseline to week 24

Summary

- SVR35 was 36% and 40% in patients in the fedratinib 400 mg and 500 mg groups, respectively, vs 1% in the placebo group
- TSS50 was 36%, 34%, and 7% in the fedratinib 400 mg, 500 mg, and placebo groups, respectively
- Common adverse events with fedratinib treatment were anemia and gastrointestinal symptoms
- Encephalopathy was reported in 4 women who received fedratinib 500 mg/d

Wernicke's encephalopathy occurred in (1.3%) patients receiving fedratinib in clinical trials
Considerations
• Measure and address thiamine levels prior to treatment initiation
• Do not start fedratinib in patients with thiamine deficiency

Pardanani A, et al. *JAMA Oncol*. 2015;1(5):643-651.

Now, fedratinib is the other drug approved. Again, this is data from the JAKARTA-I study. It allowed patients with intermediate and higher risk myelofibrosis with the platelets above a 50. All those studies were based on either a spleen volume reduction of 35% by MRI and a total symptom score reduction of 50% or more. With the fedratinib, around one-third of the patients achieved the spleen volume reduction and the total symptom control. Again, similar to ruxolitinib, the fedratinib does have some myelosuppressive effect and it also have some GI side effects, namely diarrhea because of the FLT3 inhibition.

There is a rare adverse event that's a black box warning with Wernicke encephalopathy that actually happens very, very rarely, but one should check thiamine levels at baseline and sometimes consider a replacement.

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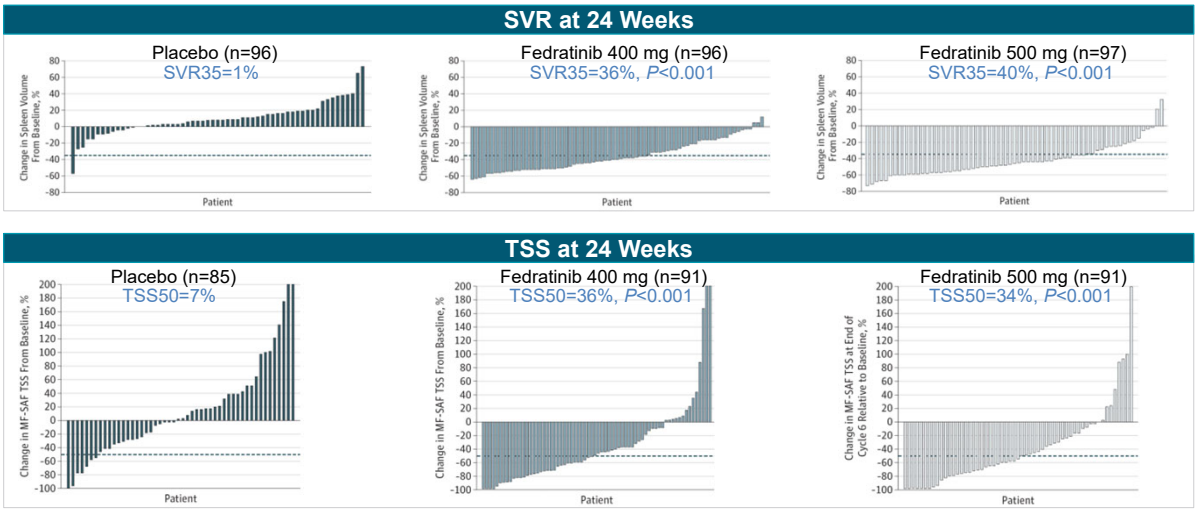
JAKARTA-1: Key Efficacy Endpoints

Approx 1/3 of patients achieved primary endpoint of spleen response and secondary endpoint of symptom response



Pardanani A, et al. *JAMA Oncol*. 2015;1(5):643-651.

Those are the data from the JAKARTA-I again showing the spleen volume reduction as well as the total symptom score. As I mentioned, around one-third of the patients achieved those endpoints.

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JAKARTA-1:
Hematologic Laboratory Test Abnormalities[a]

Hematologic Adverse Reactions	Fedratinib 400/500 mg (n=96/n=97)		Placebo n=95	
	All Grades, %	Grade 3/4, %	All Grades, %	Grade 3/4, %
Thrombocytopenia	63/57	17/27	51	9
Anemia	99/98	43/60	91	25
Neutropenia	28/44	8/18	15	4

- Fedratinib discontinuation due to thrombocytopenia was more frequent among patients with baseline platelet levels <100×10^9/L (31% [400 mg, 5 of 14; 500 mg, 4 of 15] vs <1% [1 of 164] for those with baseline platelet levels ≥100×10^9/μL)

[a] Presented values are worst grade values regardless of baseline (National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0). Pardanani A, et al. *JAMA Oncol*. 2015;1(5):643-651.

Those are the adverse events. It's hard to compare fedratinib with ruxolitinib because the entry cutoff for the counts was different, but I think both fedratinib and ruxolitinib main adverse event is really myelosuppression.

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JAKARTA-1:
Observed Nonhematologic Adverse Reactions[1]

Nonhematologic Adverse Reactions	Fedratinib 400/500 mg (n=96/n=97)		Placebo (n=95)	
	All Grades, %	Grade 3/4, %	All Grades, %	Grade 3/4, %
Diarrhea	66/56	5/5	16	0
Vomiting	42/55	3/9	5	0
Nausea	64/51	0/6	15	0
Constipation	10/18	2/0	7	0
Asthenia	9/16	2/4	6	1
Abdominal pain	15/12	0/1	16	1
Fatigue	16/10	6/5	10	0
Dyspnea	8/10	0/1	6	2
Weight decrease	4/10	0/0	5	0

- FDA placed a clinical hold on fedratinib in November 2013 due to 8 patients across fedratinib studies experiencing neurological symptoms suggestive of Wernicke encephalopathy; after clinical review, this clinical hold was lifted, and fedratinib was ultimately approved by the FDA in August 2019, with a boxed warning on the risk of serious and fatal encephalopathy[2]

1. Pardanani A, et al. *JAMA Oncol*. 2015;1(5):643-651. 2. Mullally A, et al. *Blood Adv*. 2020;4(8):1792-1800.

With fedratinib as I mentioned, we see some GI toxicity related to the FLT3 inhibition.

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JAKARTA-II Reanalysis: Fedratinib for MF After Ruxolitinib

- Aim: confirm efficacy of **fedratinib** in ITT analysis in all enrolled patients, and in subgroups defined using **rigorous definitions of prior ruxolitinib response**

Criteria for Ruxolitinib Failure			
ITT Population		**Ruxolitinib Failure Cohort**	
Resistant	RUX ≥14 days with no response or stable disease, disease progression, or loss of response per investigator	Relapsed	RUX ≥3 months with regrowth (defined as <10% SVR or <30% decrease in spleen size from BL following an initial response)
		Refractory	RUX ≥3 months with <10% SVR or <30% decrease in spleen size from BL
Intolerant	RUX ≥14 days before d/c tx due to unacceptable toxicity	Intolerant	RUX ≥28 days complicated by development of RBC transfusion requirement (≥2 units/months for 2 months); or grade ≥3 thrombocytopenia, anemia, hematoma/hemorrhage while on RUX)

- 79/97 enrolled patients (81%) met the more stringent criteria for RUX R/R (n= 65, 82%) or intolerance (n=14, 18%); median prior RUX duration in RUX failure cohort, 11.5 months (range: 1.0-62.4)
- In RUX failure cohort: median number of FEDR cycles, 7; spleen volume RR 30% (95% CI: 21-42); median spleen response duration, NE (95% CI 7.2-NE); symptom RR 27% (95% CI: 17-39)

Harrison CN, et al. Lancet Haematol. 2017;4(7):317–324; Harrison CN, et al. ASCO 2019. Abstract 2049. Harrison CN, et al. ASCO 2019. Abstract 7057..

Now, fedratinib also had been looked at after ruxolitinib failure. This is from JAKARTA-II that was later on analyzed again with strict criteria to mimic adequate exposure to ruxolitinib, and roughly around one-third of the patients achieved a spleen volume reduction or symptom control. For patients that are still proliferative after ruxolitinib failure, fedratinib as mentioned by Dr. Verstovsek could be a second-line option for those patients.

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Pacritinib: Overview of Phase 3 Trial PERSIST-2

- **Patients** with intermediate or high-risk myelofibrosis; platelets ≤100×10^9/L
- Pacritinib was approved by the FDA for patients with intermediate or high-risk myelofibrosis (MF) with a platelet count below 50x10^9/L*

- **Coprimary endpoints** were SVR35 by MRI/CT and TSS50 from baseline to week 24 in pacritinib vs BAT

Summary

- Pacritinib twice daily led to significant improvements in both endpoints over BAT
- Clinical improvement in hemoglobin and reduction in transfusion burden were greatest with pacritinib twice daily
- Common grade 3/4 adverse events were thrombocytopenia (32%, 18%) and anemia (22%, 14%) in the pacritinib twice daily and BAT arms, respectively

*The PERSIST-2 study allowed patients with platelets <100x10^9/L.

Mascarenhas J, et al. *JAMA Oncol*. 2018;4(5):652-659.

Now, pacritinib is the third drug that was approved, particularly for patients with thrombocytopenia. The PERSIST-2 study allowed patients with platelets less than a hundred.

The package insert was for patients less than 50. Again, it met the endpoints of spleen volume reduction, as well as total symptom score. The major adverse event with the pacritinib is really GI toxicity.

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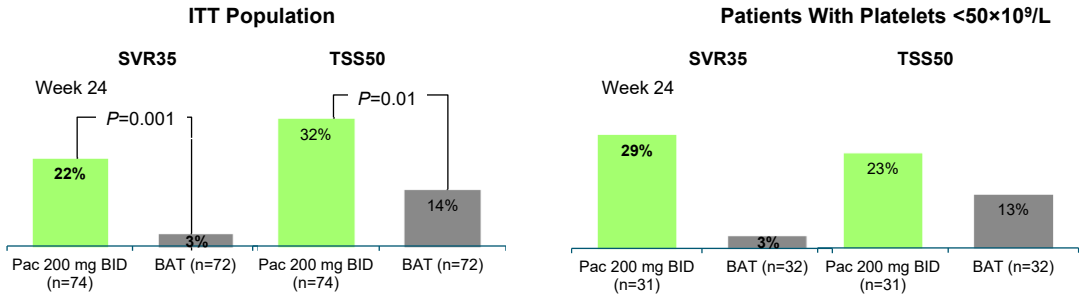
PERSIST-2: Spleen/Symptom Response



Mascarenhas J, et al. *JAMA Oncol*. 2018;4(5):652-659.

Those are data from the PERSIST-2. On the right, are the package insert population or group of patients with platelets less than 50, where we see around 29% of the patients achieve the spleen volume reduction, and 23% of the patients had total symptom score of 50% or more reduction.

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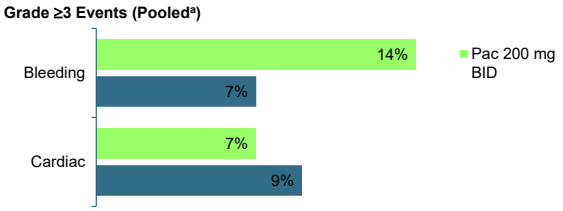
PERSIST-2: Adverse Event Profile[1]

Adverse Reactions	Pac 200 mg BID (n=106)	BAT (n=98)
Any grade AEs in ≥15% of patients in either arm, %		
Diarrhea	48	15
Thrombocytopenia	34	23
Nausea	32	11
Anemia	24	15
Peripheral edema	20	15
Vomiting	19	5
Fatigue	17	16
Grade ≥3 AEs in ≥5% of patients in either arm, %		
Thrombocytopenia	32	18
Anemia	22	14
Neutropenia	7	5
Pneumonia	7	3
Serious AEs in ≥3% of patients in either arm, %		
Anemia	8	3
Thrombocytopenia	6	2
Pneumonia	6	4
Congestive heart failure	4	2

- Diarrhea with pacritinib most often occurred during weeks 1-8, was manageable, and resolved within 1-2 weeks
- Neurological AEs and opportunistic infections rarely reported with pacritinib



- Full clinical hold had been placed on pacritinib by the FDA due to concerns over bleeding and cardiovascular events and deaths on PERSIST-1 and -2; this hold was subsequently lifted and pacritinib is now approved for use in patients with platelets <50×10^9/L[2,3]

[a] Pooled, per standardized MedDRA queries.

1. Mascarenhas J, et al. *JAMA Oncol*. 2018;4(5):652-659. 2. CTI BioPharma Announces Removal Of Full Clinical Hold On Pacritinib. Updated January 5, 2017. Accessed August 1, 2022. https://investors.ctibiopharma.com/news-releases/news-release-details/cti-biopharma-announces-removal-full-clinical-hold-pacritinib/ 3. CTI BioPharma Announces FDA Accelerated Approval of VONJO™ (pacritinib) for the Treatment of Adult Patients with Myelofibrosis and Thrombocytopenia. Updated February 28, 2022. Accessed August 1, 2022. https://investors.ctibiopharma.com/news-releases/news-release-details/cti-biopharma-announces-fda-accelerated-approval-vonjotm/

Again, the toxicity profile is mainly GI toxicity. Some patients will have worsening of the thrombocytopenia, but in majority of the patients, one could maintain the complete dosing in patients with platelets less than 50.

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Momelotinib: Overview of Phase 3 MOMENTUM Trial[1]

- **Patients** with myelofibrosis previously treated with JAK inhibitor; symptomatic and anemic

- **Primary endpoint** was TSS response rate at week 24
- **Key secondary endpoints** included transfusion independence rate at week 24 and SVR at week 24

Summary

- Significant improvements in symptoms, spleen size, and anemia measures in the momelotinib arm (vs danazol)
- Common AEs were hematologic (anemia, thrombocytopenia) and gastrointestinal (diarrhea, nausea)
- Rapid and sustained improvements in hemoglobin levels and transfusion requirements
- Platelet levels remained stable over time in patients with thrombocytopenia[2]
- Findings supported the NDA submitted to the FDA[3]

1. Mesa RA, et al. ASCO 2022. Oral Presentation 7002. 2. Gerds AT, ASCO 2022. Poster Presentation 7061. 3. Sierra Oncology Announces Submission of New Drug Application for Momelotinib to US Food & Drug Administration. Updated June 17, 2022. Accessed June 29, 2022. https://investor.sierraoncology.com/news-releases/

Momelotinib is not yet approved. The results from the MOMENTUM Phase 3 trial were recently published and presented. The momelotinib study had been studied before in different settings. The MOMENTUM study was as a second-line option compared to danazol and it showed significant improvement in spleen symptom, as well as interestingly anemia response and transfusion independence.

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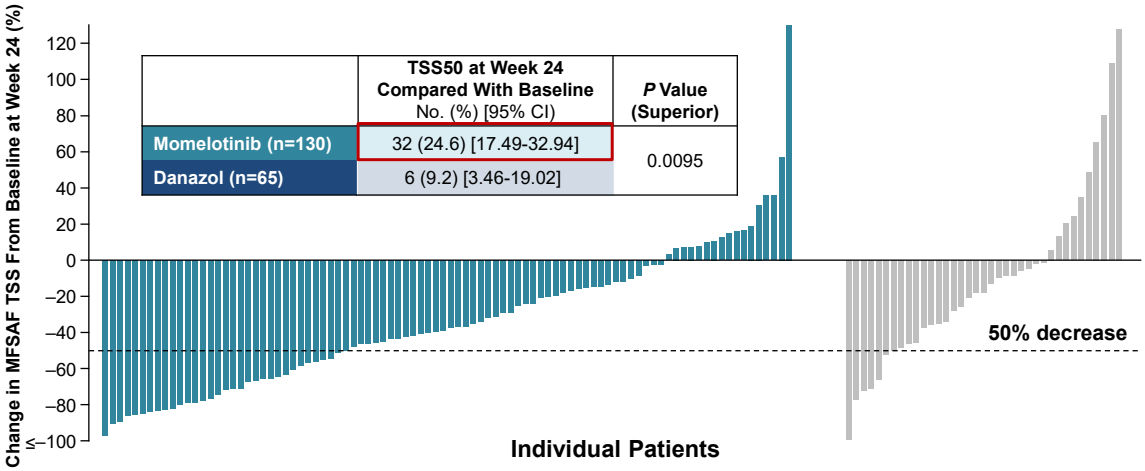
MOMENTUM: Momelotinib Superior to Danazol in Symptomatic MF Patients with Anemia and Prior Ruxolitinib Treatment
TSS50 at Week 24



	TSS50 at Week 24 Compared With Baseline No. (%) [95% CI)	*P* Value (Superior)
Momelotinib (n=130)	32 (24.6) [17.49-32.94]	0.0095
Danazol (n=65)	6 (9.2) [3.46-19.02]	

Mesa RA, et al. ASCO 2022. Oral Presentation 7002.

In terms of the total symptom score, we see here that around 32% of the patients achieved the primary endpoint with momelotinib compared to danazol.

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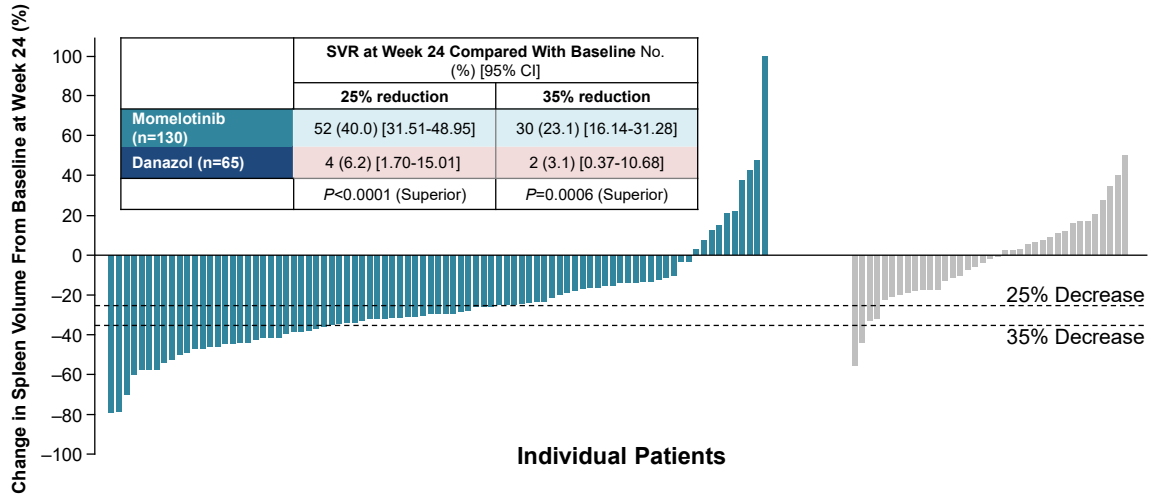
MOMENTUM: Momelotinib Superior to Danazol in Symptomatic MF Patients with Anemia and Prior Ruxolitinib Treatment
SVR (≥25% and ≥35%) at Week 24



	SVR at Week 24 Compared With Baseline No. (%) [95% CI]	
	25% reduction	35% reduction
Momelotinib (n=130)	52 (40.0) [31.51-48.95]	30 (23.1) [16.14-31.28]
Danazol (n=65)	4 (6.2) [1.70-15.01]	2 (3.1) [0.37-10.68]
	P<0.0001 (Superior)	*P*=0.0006 (Superior)

Mesa RA, et al. ASCO 2022. Oral Presentation 7002.

Around 52% of the patients had 25% reduction, and 30% had the 75% reduction compared to almost none of the patients with the danazol.

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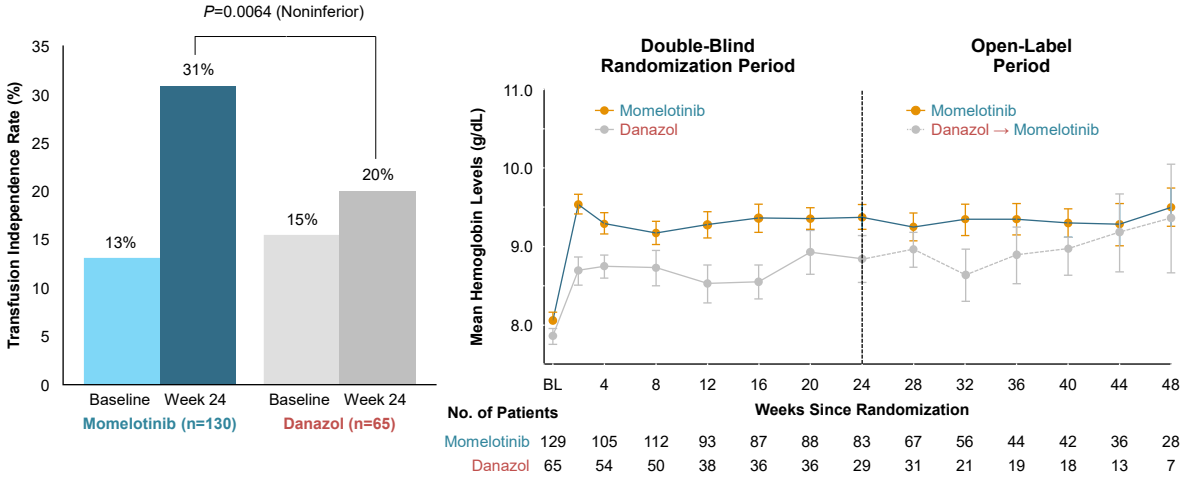
MOMENTUM: Transfusion Independence[a] Rate at Week 24 and Mean Hemoglobin Over Time



[a] Defined as not requiring RBC transfusion in the terminal 12 weeks of the 24-week randomized period, with all hemoglobin levels during the 12-week interval of ≥8 g/dL.
Mesa RA, et al. ASCO 2022. Oral Presentation 7002.

Interestingly, around one-third of the patients became red blood cell transfusion independent.

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MOMENTUM: Adverse Events in ≥10% of Patients in Either Treatment Group During 24-Week Randomized Treatment

	Momelotinib (n=130)		Danazol (n=65)	
	% of patients			
Grade ≥3 adverse events	53.8		64.6	
Serious adverse events	34.6		40.0	
	Any Grade	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Nonhematologic (Preferred term)				
Diarrhea	22.3	0	9.2	1.5
Nausea	16.2	2.3	9.2	3.1
Blood creatinine increased	7.7	0.8	15.4	3.1
Asthenia	13.1	0.8	9.2	1.5
Dyspnea	7.7	2.3	13.8	1.5
Peripheral edema	7.7	1.5	13.8	0
Acute kidney injury	4.6	3.1	12.3	9.2
Fatigue	6.2	0.8	10.8	3.1
Pruritus	10.8	1.5	10.8	0
Weight decreased	10.8	0	6.2	0
Hematologic abnormalities[a]				
Anemia	99.2	60.8	100	75.4
Thrombocytopenia	76.2	27.7	61.5	26.2
Neutropenia	29.2	12.3	26.2	9.2

[a] Hematologic abnormalities are based on laboratory values. Data shown are for events of the worst grade during the randomized treatment phase, regardless of whether this grade was a change from baseline.
AE of prior interest: PN occurred in 4% with momelotinib and 2% with danazol; all cases were low grade and did not prompt study drug discontinuation.
Mesa RA, et al. ASCO 2022. Oral Presentation 7002.

The adverse events also namely GI toxicity, in the original studies, some neuropathy had been reported with momelotinib, had not been seen in the Phase 3 MOMENTUM study.

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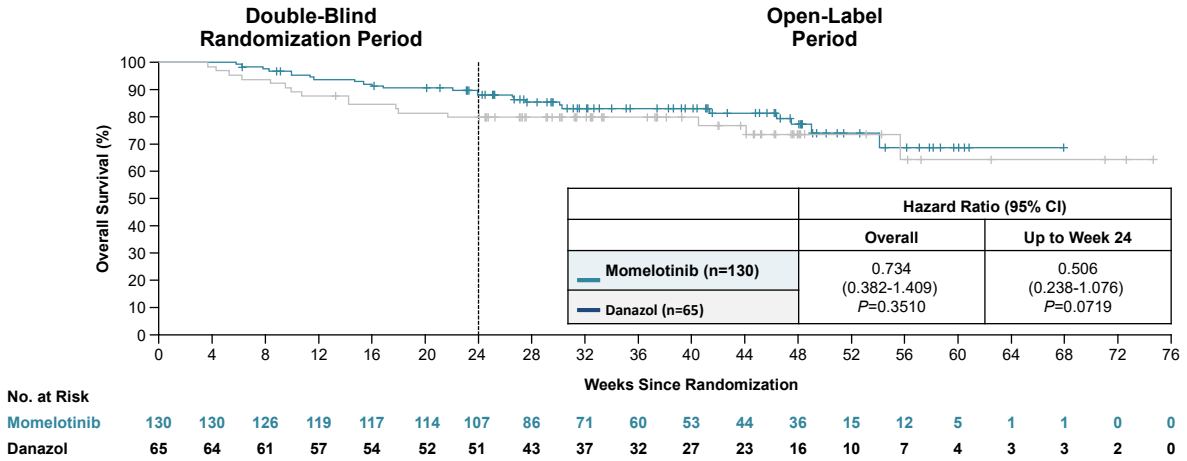
MOMENTUM: Overall Survival



No. at Risk																			
Momelotinib	130	130	126	119	117	114	107	86	71	60	53	44	36	15	12	5	1	1	0	0
Danazol	65	64	61	57	54	52	51	43	37	32	27	23	16	10	7	4	3	3	2	0

Mesa RA, et al. ASCO 2022. Oral Presentation 7002.

Also, there is some suggestion of overall survival improvement with momelotinib and anemia response.

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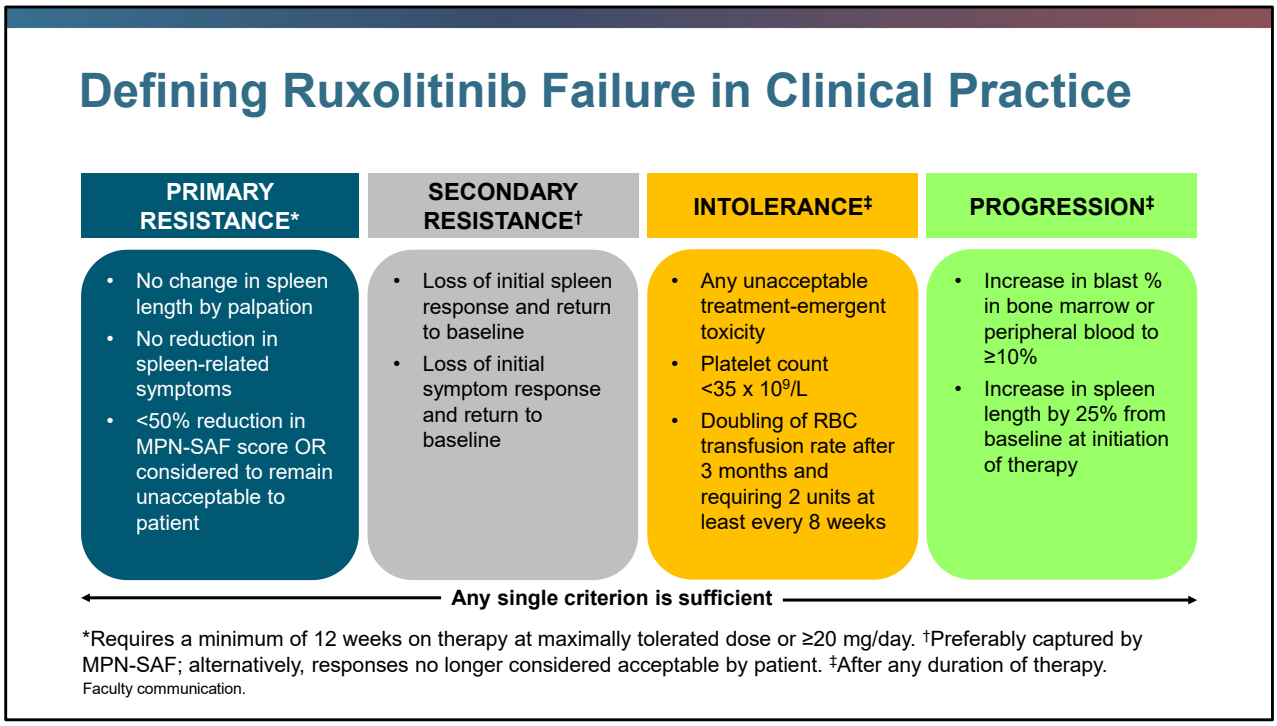

By the end of the year, we'll have four drugs approved. Also, it's probably important to assess the time of failure. Now, we think of failure as a primary failure, patients not achieving a spleen response by three to four months, probably the 25% cutoff of the spleen reduction and no reduction in the spleen-related symptoms, or no improvement in the patient constitutional symptoms. A secondary resistance is loss of initial response, whether it's in the spleen or symptoms.

There are some patients that will be intolerant, namely with cytopenias, and obviously, there is always small subset of patients that will have progression to a higher risk disease with increased blasts or going to accelerated phase.

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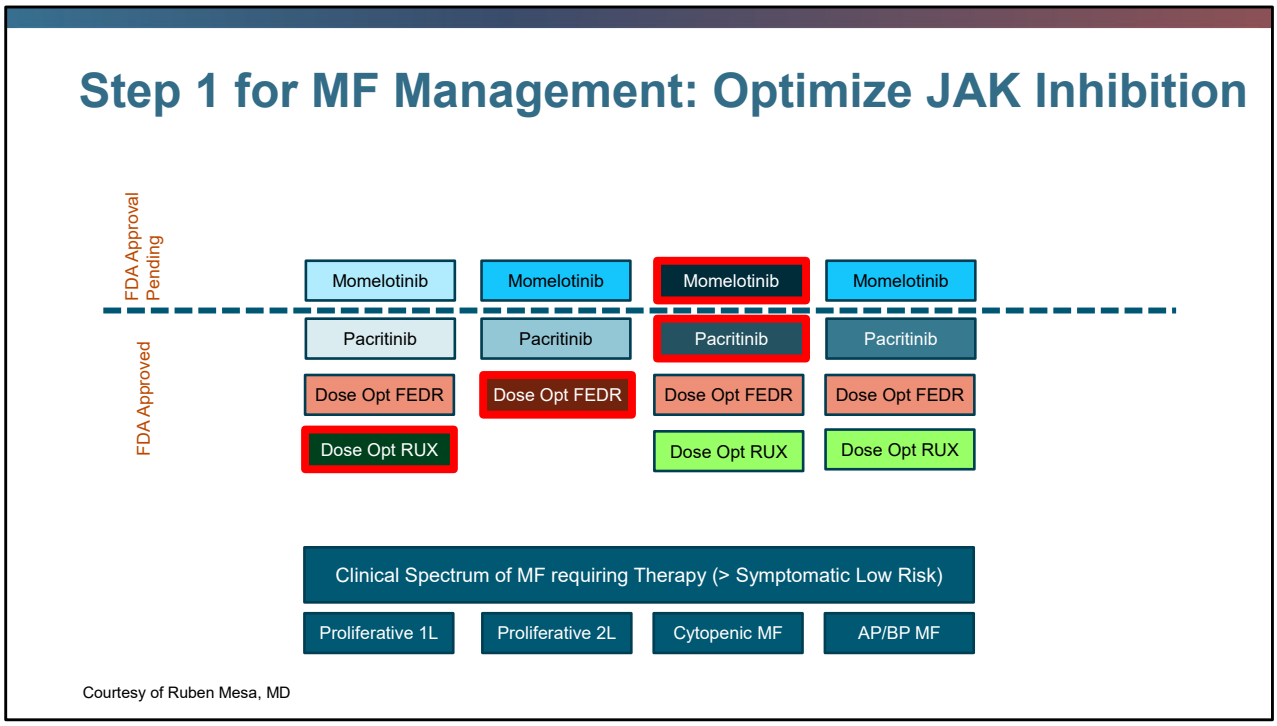

How do we think of all those JAK2 inhibitors? I think for upfront treatment, ruxolitinib is still our preferred choice for patients that have proliferative profile, no cytopenias. Patients with platelets less than 50, pacritinib is currently probably our preferred choice up front. After first JAK2 failure, if patients are still proliferative, fedratinib is probably a reasonable choice for patients with cytopenias or regardless, pacritinib is actually listed as an option for those.

When we get the momelotinib approval, I think that will be a reasonable choice for patients particularly with anemia. Thank you very much, and I will pass it now to Dr. Vachhani to give us an overview of emerging treatment options beyond the traditional JAK2 inhibitors.

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Beyond Traditional JAK inhibitors: Emerging Treatment Options

Pankit Vachhani, MD
Assistant Professor of Medicine
University of Alabama at Birmingham
Associate Scientist of Experimental Therapeutics
Birmingham, Alabama

Dr. Pankit Vachhani: Thank you, Dr. Verstovsek and Dr. Komrokji for setting the stage. It is my delight to talk about some of the new and emerging treatment options for patients with myelofibrosis. As Dr. Verstovsek showed before, there are numerous new drugs which are in investigation. There's no way I can show everything in a short presentation, so I've selected some of those.

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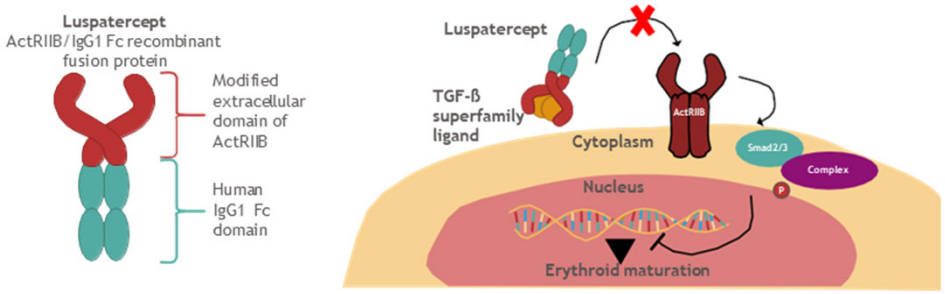
New and Emerging Directions in Myelofibrosis Treatment: Seeking to Improve Quality of Life and Prolong Survival



ActRIIB, human activin receptor type IIB; IgG1 Fc, immunoglobulin G1 fragment crystallizable.

Luspatercept is approved in both the European Union and the USA for treatment of anemia in patients with:

- β-thalassemia who require RBC transfusions, and
- Lower-risk myelodysplastic syndromes with ring sideroblasts who failed ESA treatment and require RBC transfusions

Luspatercept, MF, anemia

- **ACE-536-MF-001:** Open-label, ph2
- **INDEPENDECE:** Placebo-controlled, ph3

Mesa RM, et al. presented at the 63rd American Society of Hematology (ASH) Annual Meeting; December 11–14, 2021; Atlanta, GA, USA.

All right, on that note, let's get started with luspatercept. I think our audience would know luspatercept as the first-in-class erythroid maturation agent. This is a treatment option which is already FDA approved in Europe and in the US for patients with beta thalassemia as well as lower-risk MDS patients who have ring sideroblasts or failed ESA treatments and require transfusions. What luspatercept does is that it binds selectively to TGF beta [00:15:30] superfamily lichens, and in doing so, it diminishes the SMAD2/3 signaling pathway. All that culminates in late stage erythropoiesis. Luspatercept has been studied in myelofibrosis patients with anemia in an open-label phase 2 study, and there's also a placebo-controlled phase 3 study that's ongoing.

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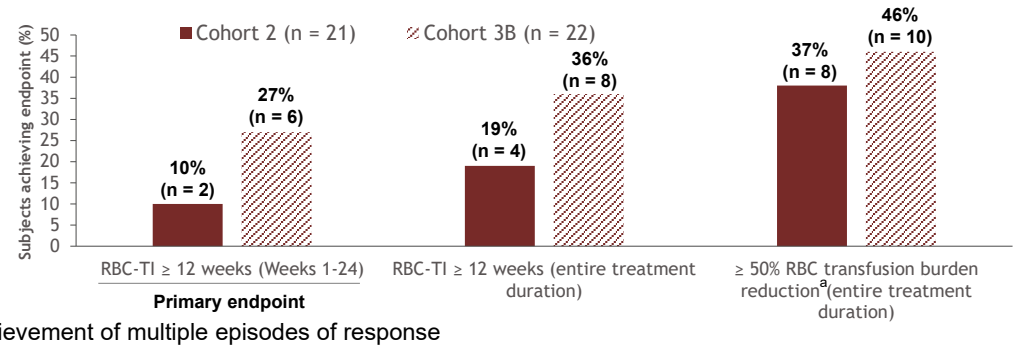
Achievement of RBC-TI ≥12 Weeks, ≥50% Transfusion Burden Reduction, and Multiple Response Episodes

- Rates of RBC-TI and ≥50% transfusion burden reduction ≥12 weeks



Achievement of multiple episodes of response

- Of the RBC-TI ≥12-week responders in both Cohorts 2 and 3B, 25% experienced two separate episodes of RBC-TI ≥12 weeks
- Of the subjects who achieved ≥50% reduction in RBC transfusion burden over any 12 weeks, three subjects in Cohort 2 (38%) and two subjects in Cohort 3B (20%) experienced two separate ≥12-week response episodes
  - One subject (13%) in Cohort 2 experienced three separate episodes of RBC-TI ≥12 weeks

[a]Defined as RBC transfusion burden reduction by ≥50% and by ≥4 RBC U for ≥12 weeks.

What you're seeing here is a previously shown and presented result of the phase 2 study. The dark purple or dark crimson colored bars are those of patients who were transfusion dependent, but not on ruxolitinib. While the dotted bars are from cohort 3B, which is patients who were on ruxolitinib and transfusion dependent. I would suggest looking at the middle section, which is where one sees that patients who were on ruxolitinib and got luspatercept, 36% of them achieve RBC transfusion independence for 12 weeks or more during the entire treatment duration. That number only increases to a more impressive 46% of patients achieving a 50% RBC transfusion burden reduction at any time point.

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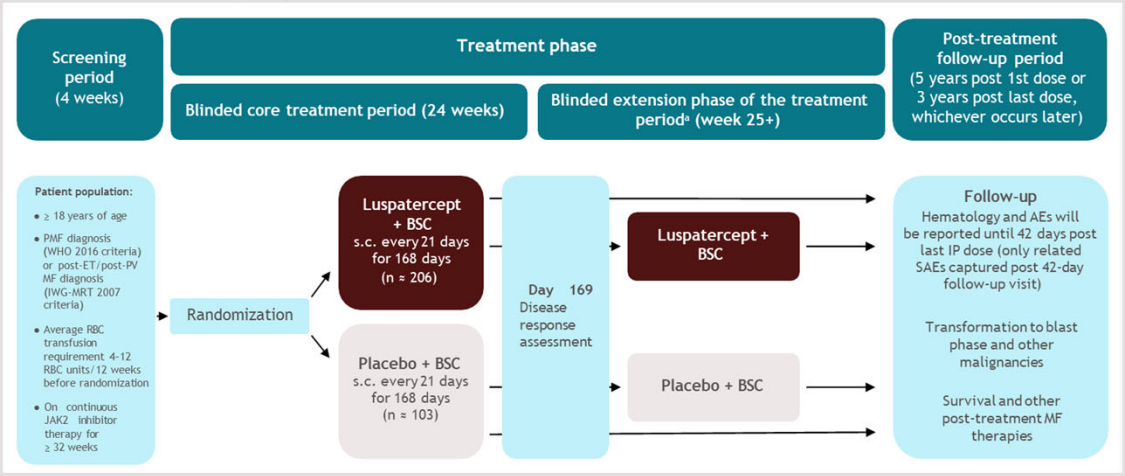
New and Emerging Directions in Myelofibrosis Treatment: Seeking to Improve Quality of Life and Prolong Survival

The INDEPENDENCE trial (NCT04717414) is currently enrolling patients with MF receiving JAK2 inhibitor therapy and RBC transfusions to evaluate the safety and efficacy of luspatercept versus placebo

Figure 2. INDEPENDENCE study design



[a]Patients on study can be unblinded after analysis of the primary endpoint and with data monitoring committee consultation. Patients receiving placebo have the opportunity to receive luspatercept treatment and be treated for ≥ 24 weeks in the open-label extension treatment period as long as they continue to demonstrate benefit from treatment, or they experience transformation to blast phase, unacceptable toxicities, or meet any other criteria for treatment discontinuation.
AE, adverse event; ET, essential thrombocythemia; IP, investigational product; IWG-MRT, International Working Group for Myelofibrosis Research and Treatment; PMF, primary myelofibrosis; PV, polycythemia vera; SAE, serious adverse event; WHO, World Health Organization.

Mesa RM, et al. presented at the 63rd American Society of Hematology (ASH) Annual Meeting; December 11–14, 2021; Atlanta, GA, USA.

What these impressive results have translated into is this, which is the Phase III INDEPENDENCE trial of patients with myelofibrosis on stable dose of JAK inhibitor therapy and requiring 4 to 12 RBC transfusions in the 12 weeks leading to the enrollment on trial. Patients get randomized to luspatercept with best supportive care or placebo with best supportive care. The primary endpoint here is achievement of RBC transfusion independence for 12 weeks or more by day 169 or week 24. Now, while we await the results of this, one should note that the NCCN guidelines do make a note of luspatercept for use in patients with myelofibrosis and anemia even now, should one need.

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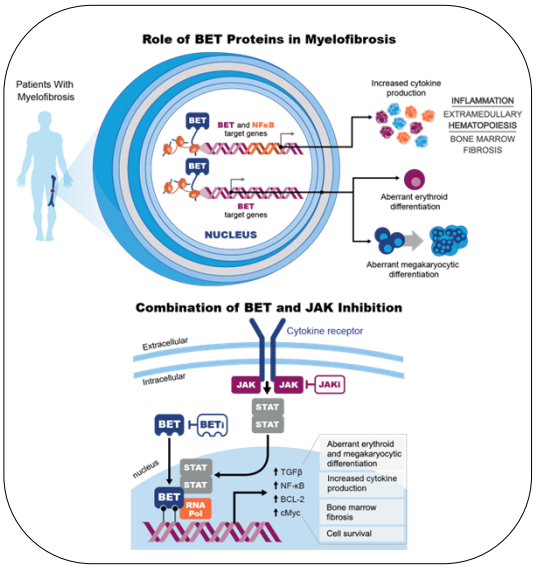
New and Emerging Directions in Myelofibrosis Treatment: Seeking to Improve Quality of Life and Prolong Survival



Simultaneous Inhibition of BET and JAK in MF

A potential therapeutic approach to address heterogenous disease pathology

- JAK inhibition with ruxolitinib is the standard of care in patients with higher-risk MF who are ineligible for HSCT[1]
- Unmet medical need persists due to limited efficacy with currently available JAKi monotherapy, high rates of discontinuation and toxicities[1]
- Preclinical data indicated non-overlapping activity of BET and JAK inhibition in MF[2]
- Pelabresib, a BET inhibitor, downregulates the expression of genes that contribute to the heterogenous pathology of MF[3-7]

BET, bromodomain and extraterminal domain; JAK, Janus kinase; JAKi, Janus kinase inhibitor; NF-κB, nuclear factor kappa B; STAT, signal transducer and activator of transcription; TGFβ, transforming growth factor β.

1. Verstovsek S, et al. *Haematologica.* 2015;100:479-488; 2. Kleppe M, et al. *Cancer Cell.* 2018;33:29-43.e7; 3. Stratton MS, et al. *F1000Res.* 2017; 6:F1000 Faculty Rev–1015; 4. Ding N, et al. *PNAS.* 2015;112:15713-15718; 5. Ceribelli M, et al. *PNAS.* 2014;111:11365-11370; 6. Tefferi A, et al. *J Clin Oncol.* 2011;29: 573-582; 7. Keller P, et al. *Hemasphere.* 2021;5(Suppl 2):515.
Scandura J, et al. ASH 2022. Abstract 630.; Pelabresib (CPI-0610) is an investigational new drug and has not been approved by any regulatory authority

Switching gears, I want to talk about three drugs, which are looking very promising in a combination setting. The first one that is on screen right now here is the pelabresib study in combination with JAK inhibitor. Pelabresib is a BET inhibitor. BET proteins are part of the epigenetic proteins. BET protein, for example, would lead to the transcription of NF Kappa B related target genes, as well as other numerous genes which together lead to increased cytokine production as well as apparent erythroid and megakaryocytic differentiation.

All of that then culminates in more inflammation, extramedullary hematopoiesis, and bone marrow fibrosis, which are some of the cytokine findings of myelofibrosis. A very notable point here is that BET inhibition and JAK inhibition are non-overlapping in terms of their activities. There is more synergy, or if not synergy, then additive effects to be gained by inhibiting both.

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MANIFEST: Clinical Responses and Changes in Biomarkers at Week 24

Parameters assessed at Week 24		Arm 1	Arm 2	Arm 3	Overall
		• Pelabresib monotherapy • Ruxolitinib intolerant, ineligible or refractory patients with MF	• Pelabresib 'add-on' to ruxolitinib • Patients with MF with suboptimal response to ruxolitinib	• Pelabresib + ruxolitinib • JAKi-naïve patients with MF	
Clinical responses	SVR35	10/88 (11%)	15/86 (17%)	57/84 (68%)	82/258 (32%)
	TSS50	22/88 (25%)	32/85 (38%)	46/82 (56%)	100/255 (39%)
	Increase* in Hgb levels	31/96 (32%)	24/87 (28%)	29/84 (35%)	84/267 (32%)
Biomarkers indicative of disease modification	Improvements in BM fibrosis of ≥1 grade	10/60 (17%)	13/51 (26%)	17/63 (27%)	40/174 (23%)
	≥15% increase in distance between nuclei of CD61+ cells in BM [median change]	5/11 (46%) [+5.8%]	9/21 (43%) [+8.4%]	16/27 (59%) [+28.4%]	30/59 (51%)
	≥20% reduction in *JAK2 V617F* VAF (≥20% reduction in allelic fraction)	2/35 (6%)	4/31 (13%)	18/47 (38%)	24/113 (21%)

*Hgb assessment within 2 weeks after RBC transfusion were excluded from the analysis; any level of increase from baseline (ranges of increase: Arm 1, 0.1–4.2 g/dL; Arm 2, 0.1–2.5 g/dL; Arm 3, 0.1–3.8 g/dL).

Data cut-off 29 July 2022. Scandura J, et al. ASH 2022. Abstract 630.
Pelabresib (CPI-0610) is an investigational new drug and has not been approved by any regulatory authority.

The updated results of MANIFEST study, which is a multi-arm study, were presented at ASH 2022. Arm 3 is the arm whereby patients who were JAK inhibitor naive and had myelofibrosis received pelabresib and ruxolitinib.

What one sees there is that the spleen volume reduction of 35% or more was achieved in a very impressive 68% of patients, while the total symptom score reduction of 50% or more was achieved in 56% of patients. Compare this spleen volume reduction rate of 68% to, for example, the one that Dr. Komrokji and Dr. Verstovsek showed of 42% from COMFORT-I or the 28%, 29% from COMFORT-II, but that is not where the story ends. There were a few other disease-modifying endpoint-related improvements that were seen.

For example, increase in hemoglobin level or improvement in bone marrow fibrosis, as well as a few other pharmacodynamic effects which were seen in line with the expectations. Then Arm 2 was the add-on study of pelabresib to ruxolitinib in patients who had suboptimal responses. Once again, there too, very impressive responses were seen.

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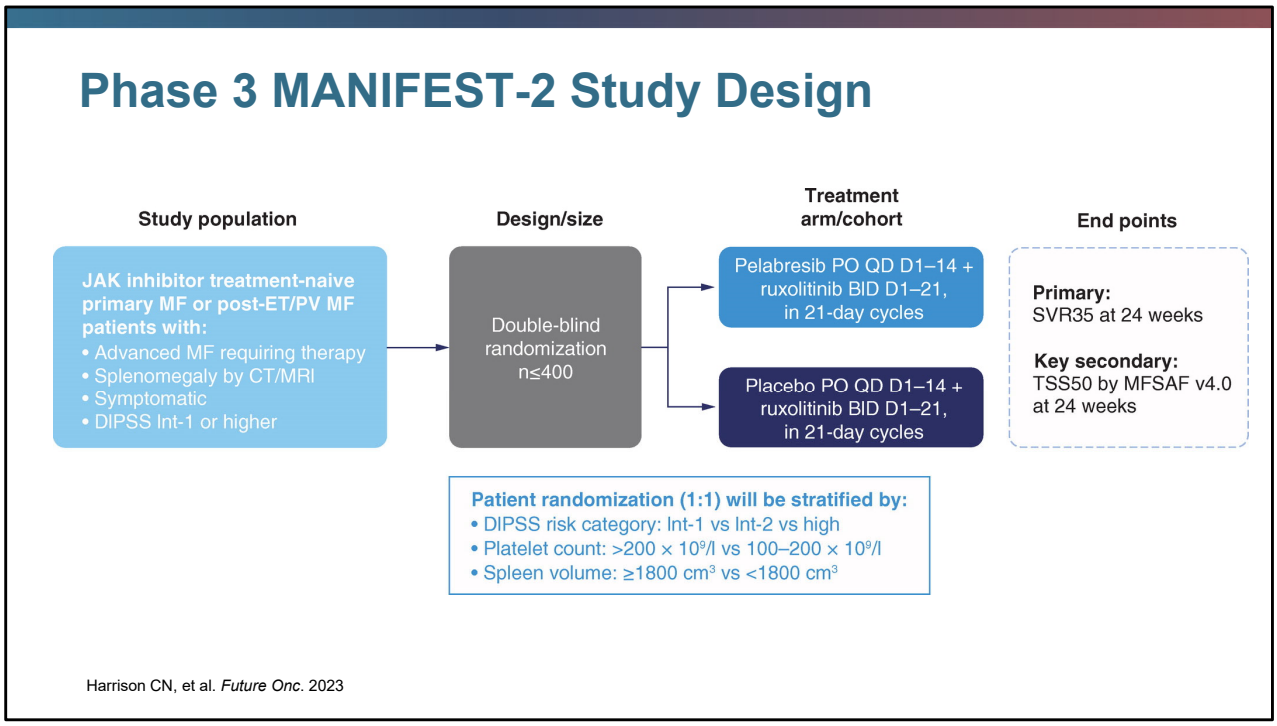

This has resulted in the MANIFEST-2 study, which is a Phase 3 study of patients with intermediate or high treatment-naive myelofibrosis, primary or secondary. Patients there get randomized in a double-blinded fashion to pelabresib given days 1 through 14 of 21-day cycles in addition to ruxolitinib or placebo plus ruxolitinib.

The primary endpoint here is spleen volume reduction of 35% at 24 weeks. This study is close to enrollment and I think we are eagerly awaiting results of that which I hope will be field-changing.

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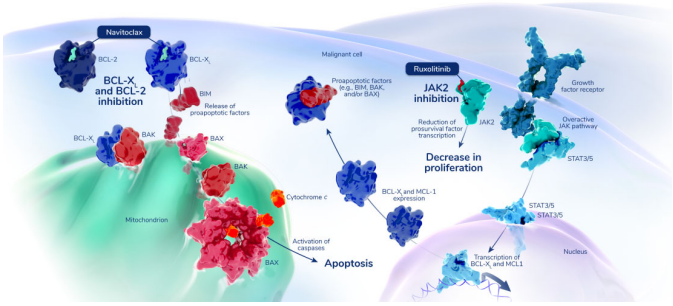
Rationale for Navitoclax for Myelofibrosis

- Navitoclax is a novel, orally available inhibitor of **BCL-X_L and BCL-2**, antiapoptotic members of the BCL-2 family[1]
- Preclinical studies show that a combination of JAK2 and BCL-2/BCL-X_L inhibition can enhance malignant cell death over JAK2 inhibition alone. In addition, JAK2 + BCL-2/BCL-X_L inhibition could overcome acquired resistance to single-agent JAK inhibitor treatment[2]
- A phase 2 study in patients with myelofibrosis (NCT03222609) reported clinical responses after treatment with navitoclax and ruxolitinib in patients who no longer benefited from ruxolitinib[3]



1. Tse C, et al. *Cancer Res*. 2008;68:3421-3428. 2. Waibel M, et al. *Cell Rep*. 2013;5:1047-1059. 3. Harrison CN, et al. *HemaSphere*. 2020;4:EP1081.

Moving on to the second combination drug that is that of navitoclax. Navitoclax, unlike venetoclax, which is a BCL2 inhibitor, navitoclax is an inhibitor of BCL-XL and BCL2. This is a very important point because BCL-XL is a very important protein, especially for MPN cell lines and megakaryopoiesis in particular, for example.

The inhibition of the BCL2, BCL-XL pathway, as well as JAK/STAT pathway could have synergistic effects and could also allow one to overcome the acquired resistance to single-agent JAK inhibitor treatment.

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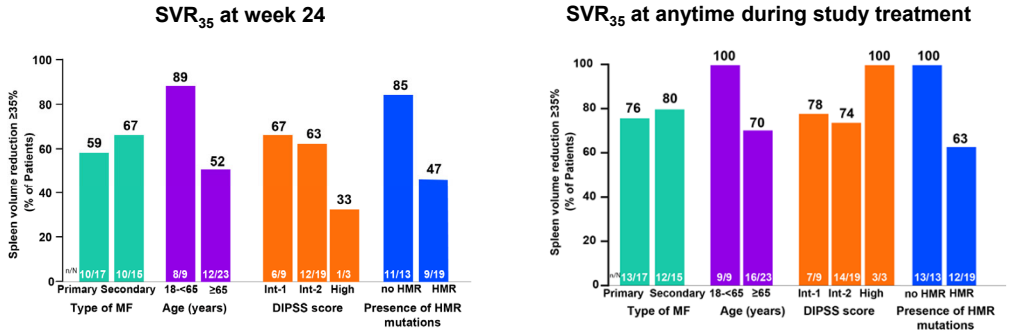
New and Emerging Directions in Myelofibrosis Treatment: Seeking to Improve Quality of Life and Prolong Survival

SVR_{35} was observed in risk groups known to confer poor prognosis

Cohort 3 of Phase 2 REFINE study: treatment-naïve MF



- Median duration of follow-up was 9.75 months (range, 4.4 – 22.4)
- Median duration of exposure for both navitoclax and ruxolitinib was 37.9 weeks (range, 1.0 – 97.0)

DIPSS, Dynamic International Prognostic Scoring System; HMR, High molecular risk; Int, Intermediate; MF, myelofibrosis; SVR, spleen volume reduction.; HMR mutations include *ASXL1, SRSF2, EZH2, U2AF1,* and *IDH2*

REFINE is a Phase 2 study which looked at the combination of ruxolitinib with navitoclax in two arms and navitoclax alone in another arm. Shown here on this slide are the cohort three results from Phase 2 REFINE study. That is the cohort where treatment-naive patients with myelofibrosis received ruxolitinib and navitoclax.

What one sees is that, once again, the spleen volume reduction rate at week 24 was a very impressive 50, 55, 60-plus irrespective of primary or secondary myelofibrosis. There were impressive results in terms of spleen volume reduction seen even for patients with or without the presence of high molecular risk gene mutations. These results were even more impressive if one were to look at the best spleen volume responses. In addition to the spleen volume responses, we have previously also noted symptom score reductions and a lot of other disease modifying endpoints being improved as well.

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Phase 3 TRANSFORM Studies

Study	Phase	Target enrollment	Population	Treatment arms	Primary endpoint
TRANSFORM-1	3	252	1L MF; Int/high by DIPSS+	Arm 1: Navitoclax + ruxolitinib Arm 2: PBO + ruxolitinib	SVR35 at week 24
TRANSFORM-2	3	330	R/R MF; Int/high by DIPSS+	Arm 1: Navitoclax + ruxolitinib Arm 2: Best available therapy	SVR35 at week 24

Together, these have culminated in the Phase 3 TRANSFORM studies. The first one is that of frontline myelofibrosis patients receiving either ruxolitinib or the combination of ruxolitinib with navitoclax. Then there's the TRANSFORM 2 study which is then in relapsed/refractory myelofibrosis patients with intermediate or high-risk myelofibrosis. There the arms are that of the combination or best available therapy.

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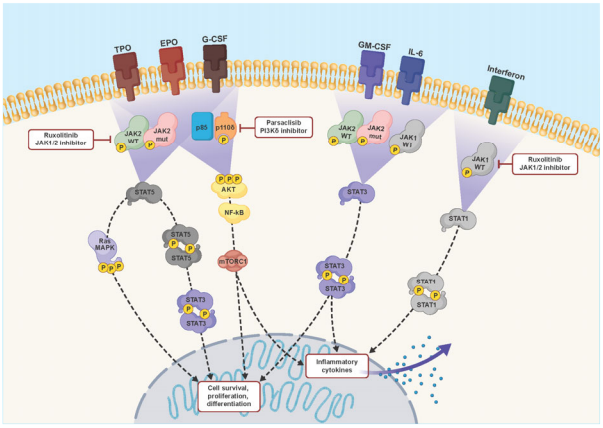
JAK1/2 and PI3K Pathways in Myelofibrosis



- Ruxolitinib, a potent JAK1/2 inhibitor, reduces spleen volume, improves symptoms, and prolongs survival in patients with intermediate- or high-risk MF[1-3]
- Suboptimal responses may occur in a subset of patients, possibly due to continued signaling via the PI3K pathway[4-6] while receiving treatment with JAK inhibitors
- Parsaclisib, a potent and highly selective next-generation PI3Kδ inhibitor, exhibits favorable pharmacokinetics for once-daily dosing[7]
- Combined inhibition of JAK1/2 and PI3K signaling pathways may improve outcomes in MF[6]

JAK, Janus kinase; MF, myelofibrosis; PI3K, phosphatidylinositol 3-kinase.

1. Verstovsek S, et al. *N Engl J Med.* 2012;366:799-807. 2. Harrison C, et al. *N Engl J Med.* 2012;366:787-798. 3. Cervantes F, et al. *Blood.* 2013;122: 4047-4053. 4. Grimwade L, et al. *Br J Haematol.* 2009;147:495-506. 5. Oku S, et al. *Br J Haematol.* 2010;150:334-344. 6. Gerds AT, et al. *Expert Rev Anticancer Ther.* 2022;22:835-843. 7. Shin N, et al. *J Pharmacol Exp Ther.* 2020;374:211-222.

Adapted from "Pathogenesis of Myeloproliferative Neoplasms: Role and Mechanisms of Chronic Inflammation" by Hermouet S, et al. Mediators Inflamm. 2015;2015:145293 is licensed under CC BY 3.0 (https://creativecommons.org/licenses/by/3.0/) and Targeting the PI3K pathway in myeloproliferative neoplasms, Gerds AT et al., Expert Rev Anticancer Ther, 2022, Published by Informa UK Limited, trading as Taylor & Francis Group. Reprinted by permission of the Informa UK Limited trading as Taylor & Francis Ltd, http://www.tandfonline.com

The third combination that I think is very important and exciting is that of parsaclisib with ruxolitinib. Parsaclisib is a novel next-generation PI3-kinase delta inhibitor. The reason why this is important is because JAK pathway or JAK cell pathway inhibition alone through ruxolitinib may not be enough.

PI3-kinase activation may overcome some of the pathway inhibition of JAK/STAT pathway. Therefore, using parsaclisib in addition to ruxolitinib may allow one to harness more benefits.

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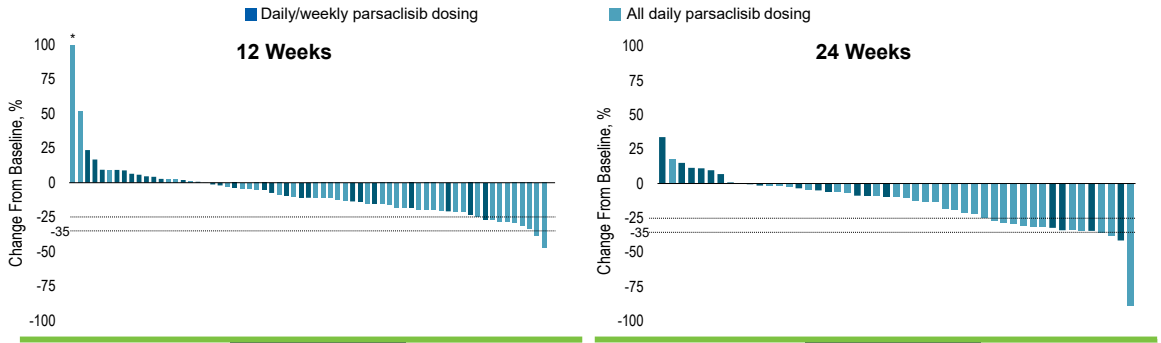
Percentage Change in Spleen Volume and Response Categories at 12 and 24 Weeks



Response Category, n (%)	Daily/Weekly Dosing	All Daily Dosing
Week 12	n=32	n=42
≥10% reduction	9 (28.1)	25 (59.5)
≥25% reduction	1 (3.1)	9 (21.4)
≥35% reduction	0	2 (4.8)

Response Category, n (%)	Daily/Weekly Dosing	All Daily Dosing
Week 24	n=32	n=42
≥10% reduction	4 (12.5)	21 (50.0)
≥25% reduction	4 (12.5)	12 (28.6)
≥35% reduction	1 (3.1)	3 (7.1)

*Patient had best percentage change from baseline to >100%.

We have seen from early phase results the combination results of parsaclisib in addition to ruxolitinib. When this drug parsaclisib was added on to patients who were already on ruxolitinib but had suboptimal response, we had seen some very good and interesting spleen volume reductions.

On the right, for example, one sees that a 35% spleen volume reduction, although it occurred only in 7%, one must remember that these are in addition to the already beneficial effects of ruxolitinib. Then one looks at the 10% or 25% spleen volume reductions, these were, of course, seen in a very notable number of patients. For example, the 10% spleen volume reduction was seen in 50% of the patients.

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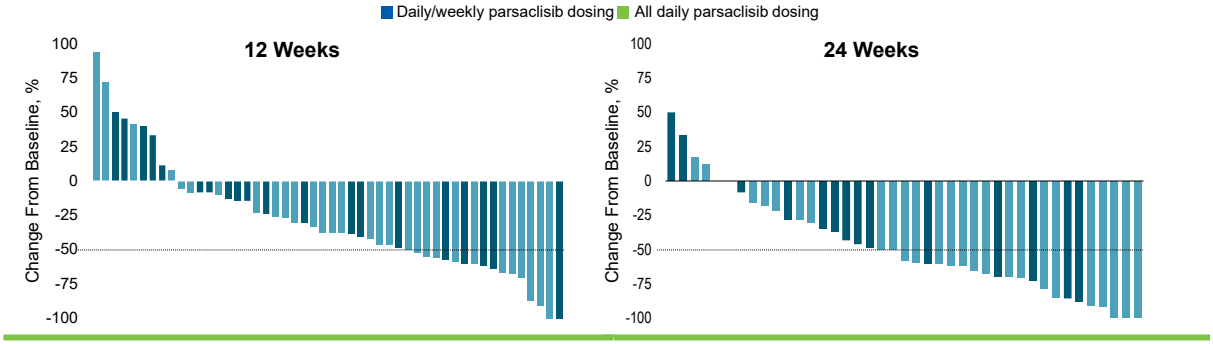
Change in MPN-SAF Symptom Score and Response Categories at 12 and 24 Weeks



Median Change in MPN-TSS at 12 Weeks	n	% Change (Range)	Median Change in MPN-TSS at 24 Weeks	n	% Change (Range)
Daily/weekly dosing	20	-19.2 (-100.0 to 50.0)	Daily/weekly dosing	15	-43.3 (-88.2 to 50.0)
All daily dosing	30	-39.8 (-100.0 to 93.3)	All daily dosing	26	-60.8 (-100.0 to 17.5)
Proportion Reaching 50% Decrease in TSS		**n/N (%)**	**Proportion Reaching 50% Decrease in TSS**		**n/N (%)**
Daily/weekly dosing	27	5/27 (18.5)	Daily/weekly dosing	27	5/27 (18.5)
All daily dosing	37	12/37 (32.4)	All daily dosing	37	18/37 (48.6)

Similarly, for symptom score reduction when given parsaclisib in an all-daily dosing fashion, nearly 50% of the patients had very impressive symptom score reductions once again in addition to the benefits already obtained from ruxolitinib.

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Phase 3 LIMBER Studies

Study	Phase	Target enrollment	Population	Treatment arms	Primary endpoint
LIMBER-304*	3	212	1L+ MF (suboptimal response); Int/high by DIPSS	Arm 1: rux + parsaclisib 5mg qd Arm 2: rux + placebo (crossover at week 24)	SVR at week 24
LIMBER-313	3	440	1L MF; Int/high by DIPSS	Arm 1: rux + parsaclisib 5mg qd Arm 2: rux + placebo (crossover at week 24)	SVR at week 24

*On March 6, 2023 The phase 3 LIMBER-304 trial evaluating parsaclisib plus ruxolitinib in patients with myelofibrosis will be discontinued after results of a preplanned interim analysis indicated that the study is unlikely to meet its primary end point of targeted reduction in spleen volume in the intent-to-treat population. The company noted that the decision to discontinue the trial was not related to safety. Full data from the trial will be submitted for presentation at an upcoming medical meeting.

Incyte provides update on interim analysis of phase 3 LIMBER-304 study of parsaclisib and ruxolitinib in patients with myelofibrosis. News release. Incyte. March 3, 2023. Accessed March 6, 2023. https://investor.incyte.com/news-releases/

Together, these have culminated in or translated into Phase 3 LIMBER studies. The first one is that of patients with myelofibrosis who have a suboptimal response to ruxolitinib alone, while the second one is that of frontline combination therapy in intermediate or high-risk myelofibrosis. Here, the patients get either ruxolitinib plus placebo or they get the ruxolitinib plus parsaclisib five milligrams once a day, and spleen volume responses at week 24 are the primary endpoints. Crossover is allowed in both and I think this is a very exciting combination study, both in suboptimal response patients as well as frontline patients.

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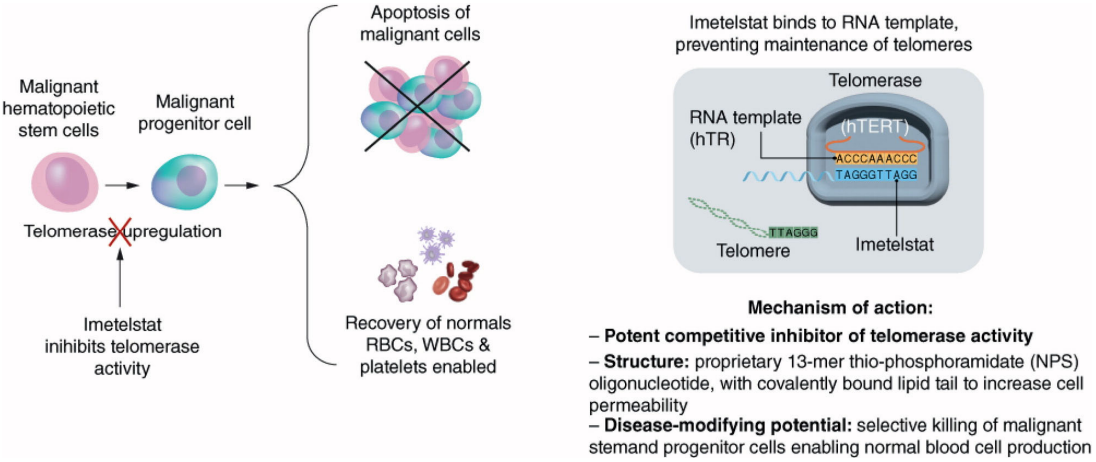
Imetelstat: A First-in-Class Telomerase Inhibitor



Mechanism of action:

– **Potent competitive inhibitor of telomerase activity**

– **Structure:** proprietary 13-mer thio-phosphoramidate (NPS) oligonucleotide, with covalently bound lipid tail to increase cell permeability

– **Disease-modifying potential:** selective killing of malignant stemand progenitor cells enabling normal blood cell production

Phase1 study of **imetelstat** in MF: ORR 21% (n=33), mDOR = 18 mos, reversal of fibrosis in four patients

Switching gears, let me talk about two agents which are being investigated in late-stage trials as monotherapies.

The first one is that of imetelstat. Imetelstat is an oligonucleotide. What it does is that it inhibits the telomerase activity. When it does so, it leads to cell apoptosis as well as cell senescence,and cell arrest. Together, that is a disease-modifying potential effect through killing of malignant stem and progenitor cells. The Phase 1 study of imetelstat had noted a response rate of 21% from 33 patients, and a very impressive actually, four patients achieving a complete response.

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IMbark Randomized, Dose-finding, Study of Imetelstat in R/R MF

Imetelstat was administered as a 2-hour intravenous infusion once every 3 weeks

Table 1. IMbark phase II: key results. (Table view)

Clinical benefit	Imetelstat 4.7 mg/kg (n = 48)	Imetelstat 9.4 mg/kg (n = 59)
Median overall survival, months (95% CI)	19.9 (17.1, 33.9)	28.1 (22.8, 31.6)
Bone marrow fibrosis improvement, n/N (%)	4/20 (20.0%)	15/37 (40.5%)
≥25% reduction in VAF of *JAK2*, *CALR* or *MPL*, n/N (%)	1/18 (5.6%)	8/19 (42.1%)
Symptom response at week 24 (TSS reduction ≥50%), n (%)	3 (6.3%)	19 (32.2%)
Spleen response at week 24 (SVR ≥35% by IRC), n (%)	0	6 (10.2%)
Median progression-free survival, months (95% CI)	16.7 (8.5, 19.5)	23.2 (16.8, 28.3)
Clinical improvement, per IWG-MRT, n (%)	8 (16.7%)	15 (25.4%)
Transfusion independence of 12 weeks, n/N (%)	2/14 (14.3%)	3/12 (25.0%)

IRC: Independent review committee; IWG-MRT: International Working Group-Myeloproliferative Neoplasms Research and Treatment; SVR: Spleen volume reduction; TSS: Total symptom score; VAF: Variant allele frequency.

Mascarenhas J, et al. *Future Onc.* 2022.

This was studied then in a dose-finding IMBARK study in patients with relapsed/ refractory myelofibrosis, whereby imetelstat was administered as a two-hour IV infusion once every three weeks.

If you look at the yellow bars, what they are showing is that the symptom and spleen responses at week 24, although not so impressive, suggested and hinted towards a dose effect. For example, the symptom response at week 24 was 32%, but I think the most important key takeaway point from this study was the median overall survival as indicated through the blue arrow. When you look at the imetelstat 9.4 milligram per kilogram cohort, the median overall survival was 28 months, and as previously shown, many other studies have shown that in this population, the median overall survival ranges somewhere in the 13 to 18-month range. When you compare it to that, the 9.4 milligram per kilogram cohort looks to be showing a very impressive median overall survival of 28 months.

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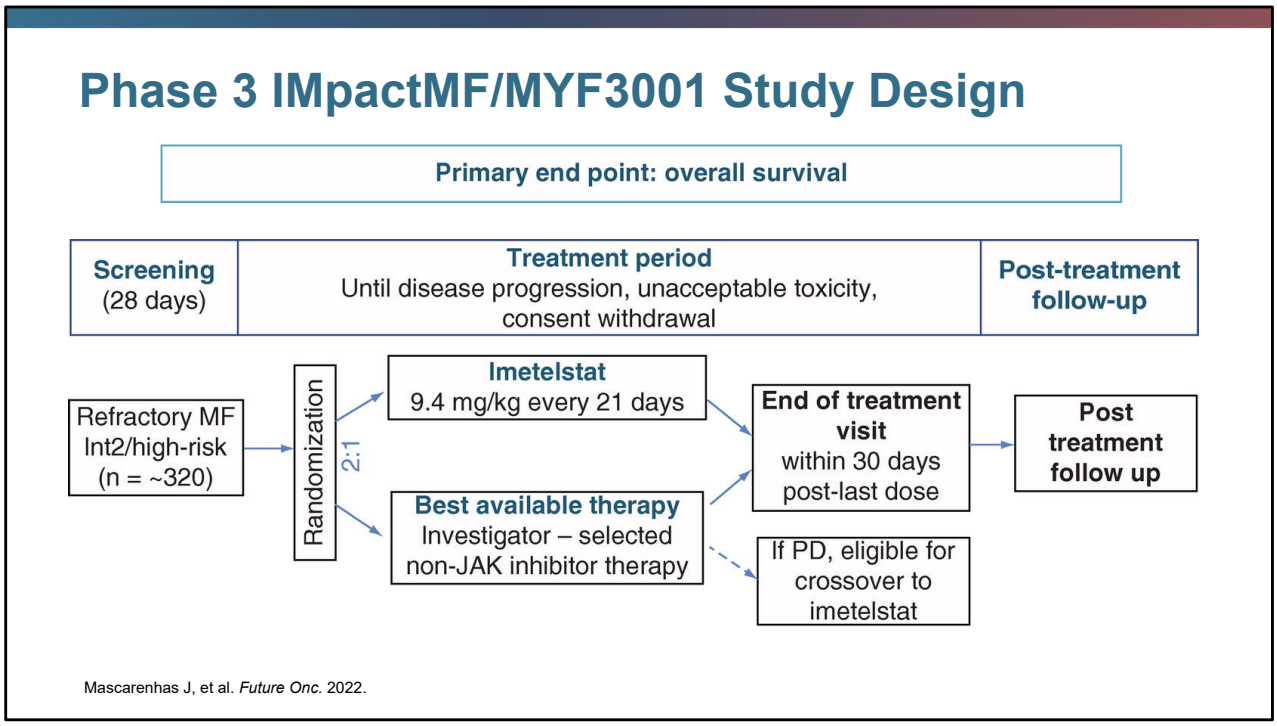

This has led to the IMPACT MF Phase 3 clinical trial, one of the first ones with a primary endpoint of overall survival. Here, patients with relapsed/refractory myelofibrosis get randomized in a two-to-one fashion to imetelstat or best available therapy.

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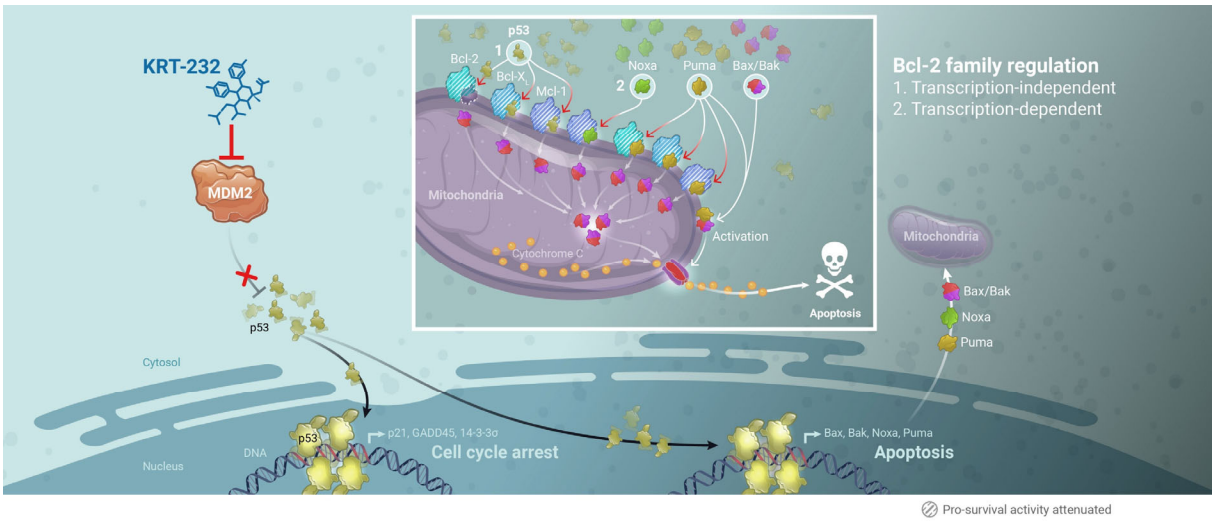
KRT-232 (Navtemadlin): Mechanism of Action



Presented by Verstovsek S. ASCO 2021

Last but not the least, I want to talk about KRT-232. I think we know that p53 is a tumor suppressor protein. It's very important for the body. However, MDM2 negatively regulates p53. A drug like KRT-232 which inhibits MDM2 allows for p53 action or allows it to restore its activity and thereby allow for apoptosis or cell killing of malignant cells.

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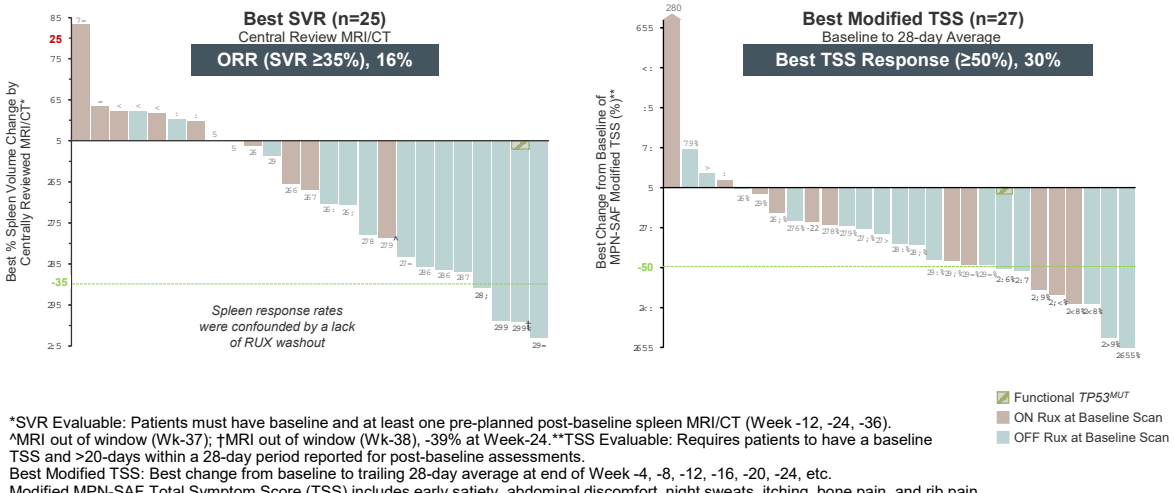
KRT-232, Clinical Proof of Concept in R/R MF

240 mg QD, D1-7/28-day Cycle



*SVR Evaluable: Patients must have baseline and at least one pre-planned post-baseline spleen MRI/CT (Week -12, -24, -36).
^MRI out of window (Wk-37); †MRI out of window (Wk-38), -39% at Week-24.**TSS Evaluable: Requires patients to have a baseline TSS and >20-days within a 28-day period reported for post-baseline assessments.
Best Modified TSS: Best change from baseline to trailing 28-day average at end of Week -4, -8, -12, -16, -20, -24, etc.
Modified MPN-SAF Total Symptom Score (TSS) includes early satiety, abdominal discomfort, night sweats, itching, bone pain, and rib pain.
Presented by Verstovsek S. ASCO 2021.

In the 101A study of KRT-232, the 240 milligram given once daily on days 1 through 7 in a four-week cycle cohort, we had seen results of spleen volume reduction of 16% while the symptom score reduction of 50% or more occurred in 30% in the best available time.

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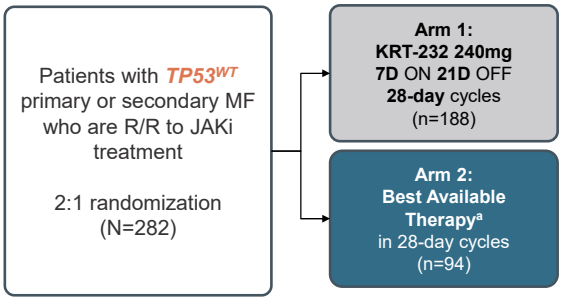
BOREAS Study Design (NCT03662126)



Best available therapy options include hydroxyurea, chemotherapy, or supportive care. JAKi are excluded.

Patient Stratification:
- MF type (primary vs secondary)
- Baseline TSS (≤10 vs >10)

Primary End Point
- **Spleen Response Rate at Week 24:** Rate of SVR ≥35% by MRI/CT at Week 24 (central review)

Key Secondary End Points
- ≥50% reduction in TSS rate at Week 24 (per MFSAF v4.0)
- Overall survival
- Progression-free survival
- Best overall response (SVR ≥35%) at any time by MRI/CT (central review)
- Duration of spleen response
- Rate of conversion from RBC transfusion dependence to transfusion independence

JAKi, Janus kinase inhibitors; MF, myelofibrosis; MFSAF v4.0, Myelofibrosis Symptom Assessment Form version 4.0; MRI/CT, magnetic resonance imaging/computed tomography; RBC, red blood cell; R/R, relapsed/refractory; SVR, spleen volume reduction; *TP53*^{WT}, wild-type tumor protein p53 gene; TSS, total symptom score.
[a]Treatment selection is at the discretion of the investigator. Patients with documented disease progression at any time or those who complete Week-24 assessments may crossover to the KRT-232 arm.

Presented by Verstovsek S. ASCO 2021. Abstract TPS7057. .

This has then translated to the BOREAS Phase 3 clinical trial, which is done in TP53 wild-type patients who are relapsed/refractory to JAK inhibitor therapy. Those patients get randomized to KRT-232 or best available therapy. The primary endpoint here is spleen response at week 24. Thank you.

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Dr. Verstovsek: That is excellent summary. Thank you very much, Rami and Pankit. Before we close, let's discuss the salient points of what you have described.

Rami, you mentioned that ruxolitinib is here to stay as the backbone in a first line, and perhaps for patients with low platelets, pacritinib, and then in a second line setting, perhaps one can also use fedratinib and perhaps also for anemia because that's major problem in a second-line momelotinib. As a single agent, how do we optimize the care of the patients with ruxolitinib alone from the day one?

Dr. Komrokji: Absolutely. I think that's a very important point. I think, first, obviously, selecting the patient profile so those patients that benefit from those treatment are the patient that constitutional symptom splenomegaly. If we have a patient with only cytopenia, those are probably a group of patients who will not benefit much from the treatment. Then the second thing is really the appropriate dosing for the patients if patients' proliferative profile that have platelets above a hundred and they're not anemic, starting with a 20-milligram dosing and making adjustments down the road. In fact, there have been some models trying to look at the responses at three and six months as prediction of how patients will do. It really comes to the dose of the ruxolitinib, the spleen response, and the transfusion requirements as milestones that predict our response. I think appropriate dosing, monitoring the adverse events, adjusting the dosing if needed are very important. Also, important points in terms of safety. If patients are going to discontinue those medications, one should taper them, or if we are still thinking of shifting between one of the current available JAK2 inhibitors, also bridging them. I think, obviously, for cytopenia, sometimes we may have some options to help.

As Pankit mentioned, there are some emerging data on luspatercept. Sometimes in practice, we used ESA to avoid patients getting transfusion dependent. I think a key is really selecting the appropriate patients going to the recommended dose upfront, monitoring the patients and making adjustments early on in the course of the treatment. All three faculty on screen

Dr. Verstovsek: To add to what you just summarized very nicely is for patients that have a platelets low because it's approved for patients with the platelets above 50, we would start with a low dose and build it up. New way of thinking is for patients that have some anemia to do the same. Those that have low platelets or are anemic at the beginning, perhaps starting, it's 5 twice or 10 twice, then going up every month or two to the maximum safe dose to optimize the care.

Along this line, early intervention certainly matters a lot when the people are not so sick and not have anemia and thrombocytopenia because then you can make a case for a high dose right from the beginning and that may last much longer.

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Pankit, you talk about the combinations from the day one. You highlight several and what caught my eye is really good response, both in screen and symptoms with pelabresib. How do you envision that combos will influence what we do right from the day one? Will they, and what do we really need to see to change the standard practice?

Dr. Vachhani: Absolutely. This is, of course, a very relevant question for now since the data is cooking, so to say. I think ultimately, what will be important is the data from all these different phase 3 clinical trials. Pelabresib or the MANIFEST data that you highlighted, of course, is very exciting. I'm eagerly awaiting to see data from both frontline and add-on studies and also try to analyze which subgroups benefit the most and from which particular drug. Also, not just stop over there, but also look at the adverse events profile so we can choose our drugs. For example, I think I want to see what high-risk mutations or what mutations subgroup patients benefit from one drug versus the other.

Ultimately, what we do want to see is survival benefits from this combination therapy as compared to monotherapy, but those data may take a long time to emerge. In the meanwhile, I think what would be wonderful to see from drugs like pelabresib, for example, is improvement in spleen volume responses, symptom score reduction, but also improvement in anemia, improvement in the variant and frequencies going down since we know that these two correlate down the line with some of the more harder endpoints based on some of the data that we have.

Dr. Verstovsek: Ultimately, we would like to prolong survival of the patients. Rami, where is the role for transplant? Is there any role for transplant? Would more patients to transplant? Fewer? How we going to address that issue?

Dr. Komrokji: I think that's a key question, and obviously, for me, the decision of transplant is always based on the benefit and risk. Absolutely, still transplant is a curative option. It's an only curative option we have where we roughly can cure 40% to 50% of the patients, but the offset for that is the almost 20% transplant-related mortality. As you mentioned historically when we have patients who their survival is estimated in the two to three years, I think that's where the maximum gain of survival is with transplant.

If we start now having treatments that could extend patient survival to five or six years, I think we should revisit the question at least of the timing of the transplant. Should we move upfront or maybe start those patients on those combinations and have certain milestones at month 3, 6 and see how those patients are going to do? Because if somebody's survival with those treatments is going to be improving to six or seven years, I think going earlier to transplant may not be associated with the maximum gain of survival. Similar to what we do in MDS actually. The maximum gain of survival in higher risk, to or go early, in lower risk, to wait.

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We've done the same with myelofibrosis, but I think that's always function of how active therapies we have. The more we have active therapies durable responses, we should revisit the question of the timing of transplant among those patients.

Dr. Verstovsek: The last question, Pankit. You already alluded to possibility of individualized patient-centered treatments now that we have, hopefully, we will, a number of different choices. Briefly, what would you be telling your colleagues if you get two or three other new medications approved? How are we going to individualize?

Dr. Vachhani: Absolutely, I think so. We showed a lot of data regarding the safety at least from the early phase studies, but what I didn't show so much is about the adverse events. For example, pelabresib is a drug that we know has some thrombocytopenia, also has some GI toxicities. That's something to keep in mind. Parsaclisib has its own adverse event profile. Navitoclax in particular leads to thrombocytopenia and GI adverse events as well. Similarly with KRT-232, although monotherapy has other clinical trials which are in combination setting.

Focusing on the adverse events and picking the drug for a given patient in terms of their individual cytopenia profile or the hematologic profile will be important. Also, I think what I will look forward to when all the data matures and when we have it is individualizing and looking at your patient, the one that you have in front of you and asking yourself the question, "Hey, what is the most important thing that I want to achieve?" Is it a spleen volume response or is it a person with splenomegaly, but maybe the biggest concern for that patient is anemia? Let's pick the drug which has the best anemia profile benefit in such an individual.

Or is this the case that they happen to have one or more high molecular risk gene mutations? Should one be picking a drug which may have a disease-modifying activity in slowing down the condition of the disease in terms of progressing to accelerated phase or blast phase disease? I think these are the various points amongst many that I would be looking at. Like Dr. Komrokji said, who knows? Maybe with good drugs, we may be able to delay transplant, or we shall see with more data.

Dr. Verstovsek: Wonderful summary. Thank you very much, Pankit and Rami. We have witnessed amazing developments in the field for myelofibrosis.

Remember, the first drug ever approved was ruxolitinib 12 years ago. Now we are expecting the fourth drug momelotinib to be approved. We learned how to optimize the care of the patients with ruxolitinib alone. We discussed some of this today, but for some groups of patients, those with low platelets or in a second-line setting when they are progressing with spleen or with anemia, now we have other options.

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The extra bonus on top of it is that we are learning much more about biology and complexity of it to bring in new drugs that you Pankit reviewed for us very nicely where we can combine to enhance what the JAK inhibitors do, bring additional benefits, perhaps change the natural history of disease and have options, not only in combination but even after JAK inhibitors with some of the new drugs. Very exciting time and I thank you so much for being with me today on this nice review of where the field is going in myelofibrosis therapy. Thank you so much for your expertise and sharing your advice with our colleagues in the field. I hope everybody has a nice day, and until next time, stay well.

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