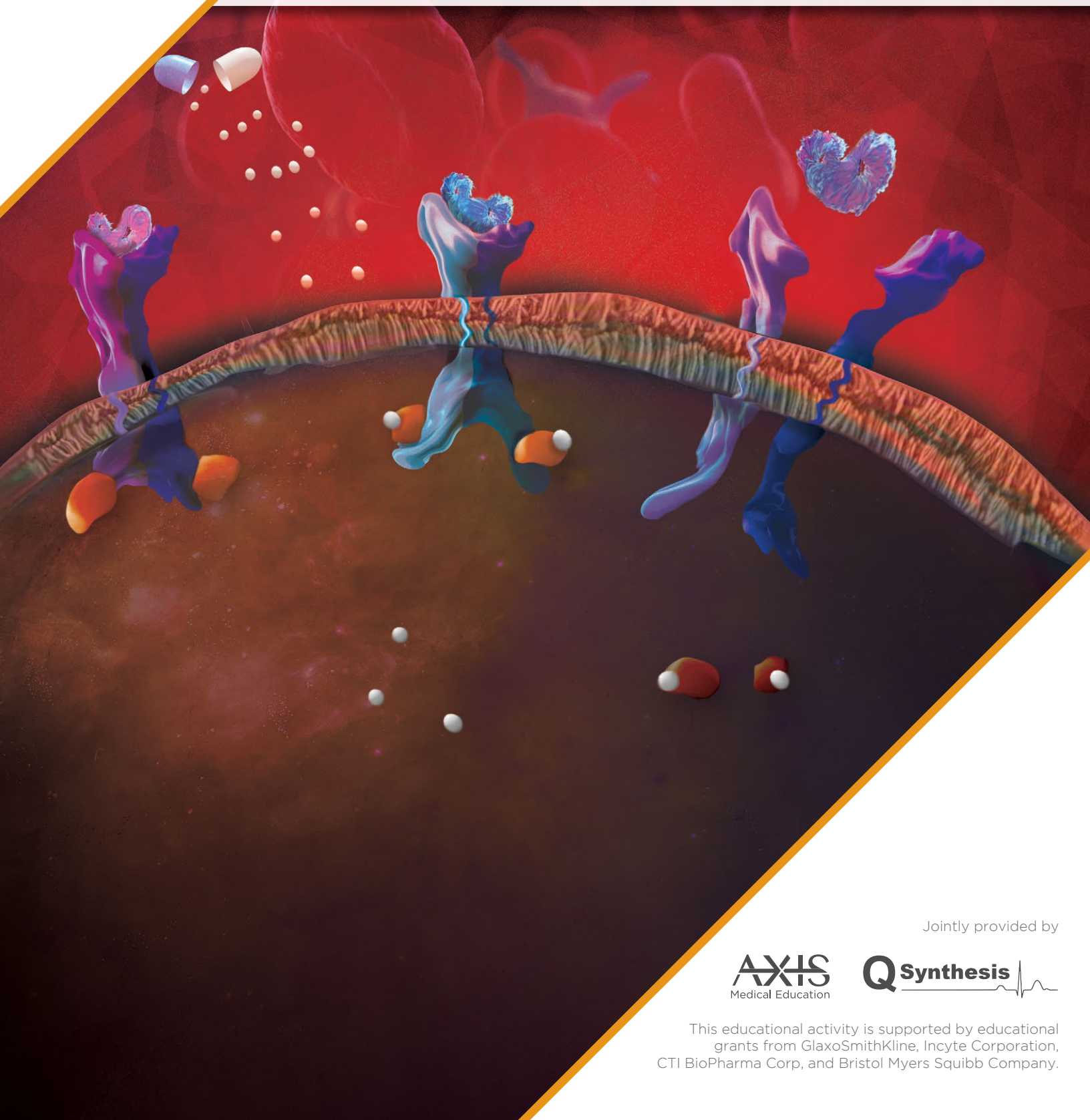
AXIS Medical Education

Incorperating Scientific Advances into Myelofibrosis Treatment Plans:

A Quality Improvement Initiative

This transcript has been edited for style and clarity and includes all slides from the presentation.



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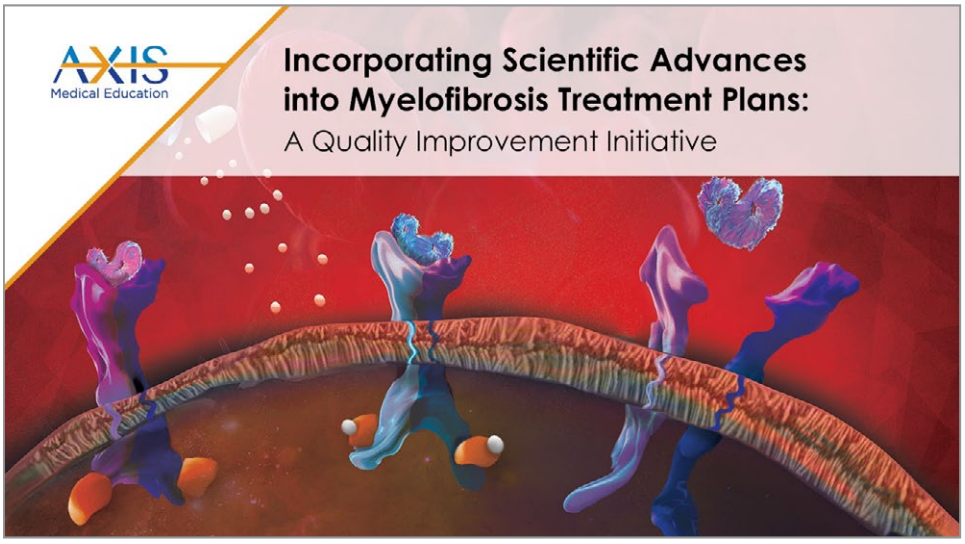
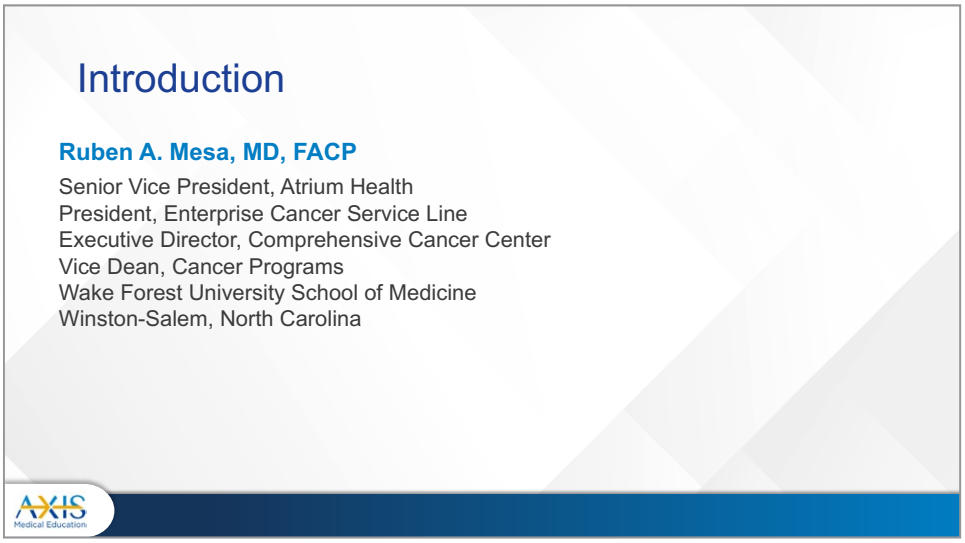
Incorperating Scientific Advances into Myelofibrosis Treatment Plans: A Quality Improvement Initiative

Ruben A Mesa, MD, FACP



Ruben A Mesa, MD, FACP:

Hello, my name is Ruben Mesa, and I'm the Executive Director of the Atrium Health Wake Forest Baptist Comprehensive Cancer Center, as well as President of Atrium Health Levine Cancer. I'm excited today to share with you this presentation regarding incorporating scientific advances into myelofibrosis treatment plans.



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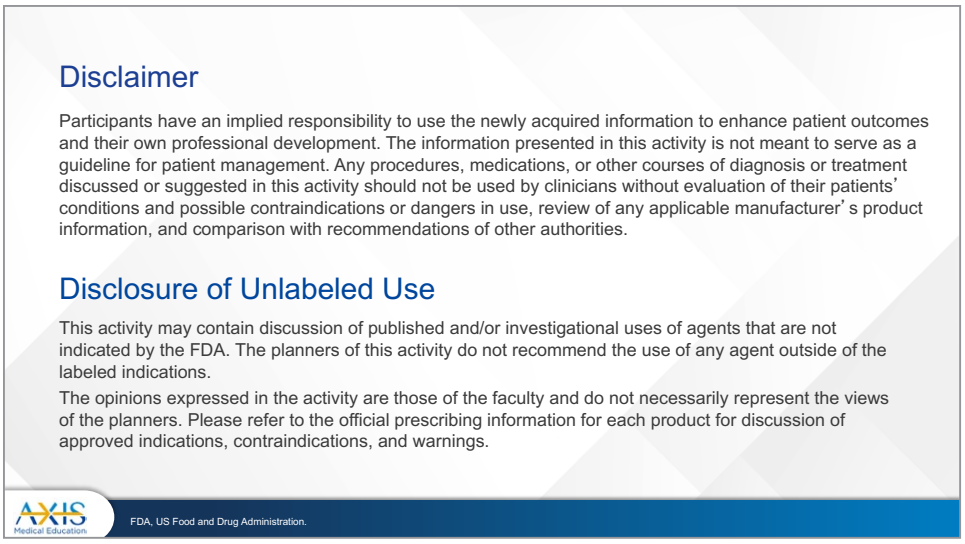
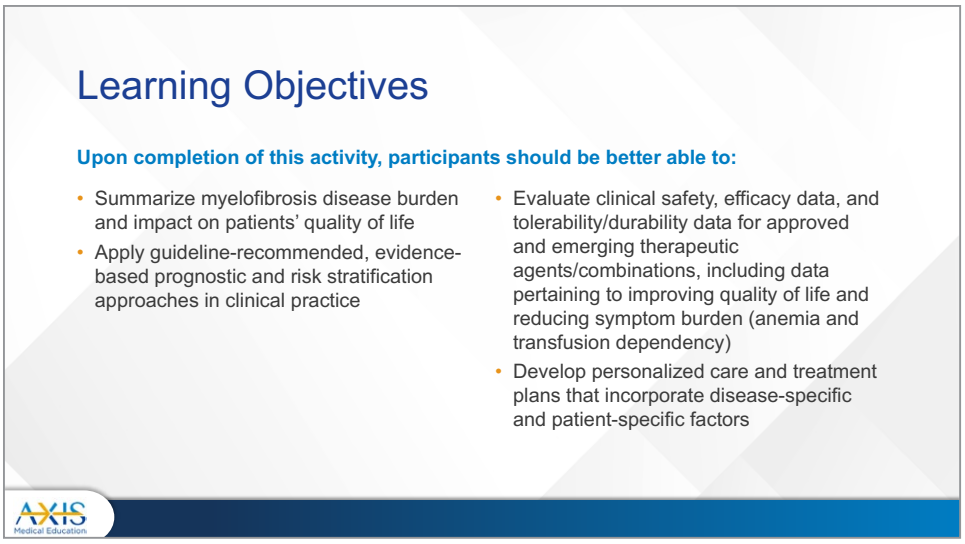
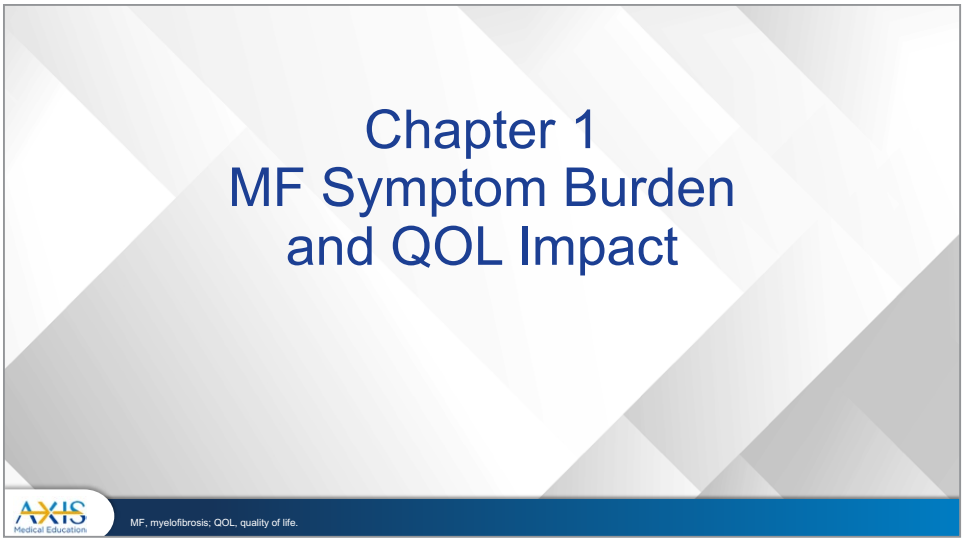


- Disclaimers and any disclosure of unlabeled use.

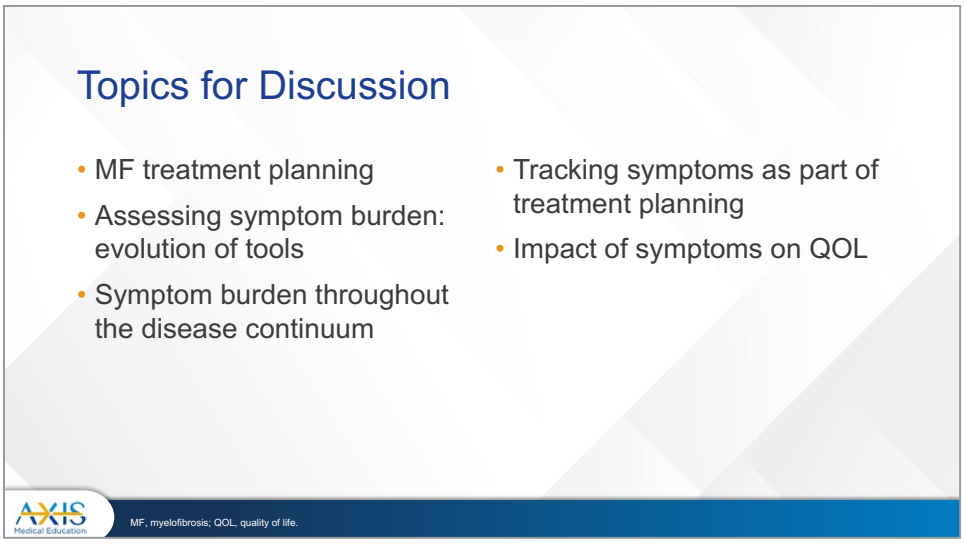
- Here are my conflicts of interest as it relates to the trials I've been involved with and the consulting that I have participated in.



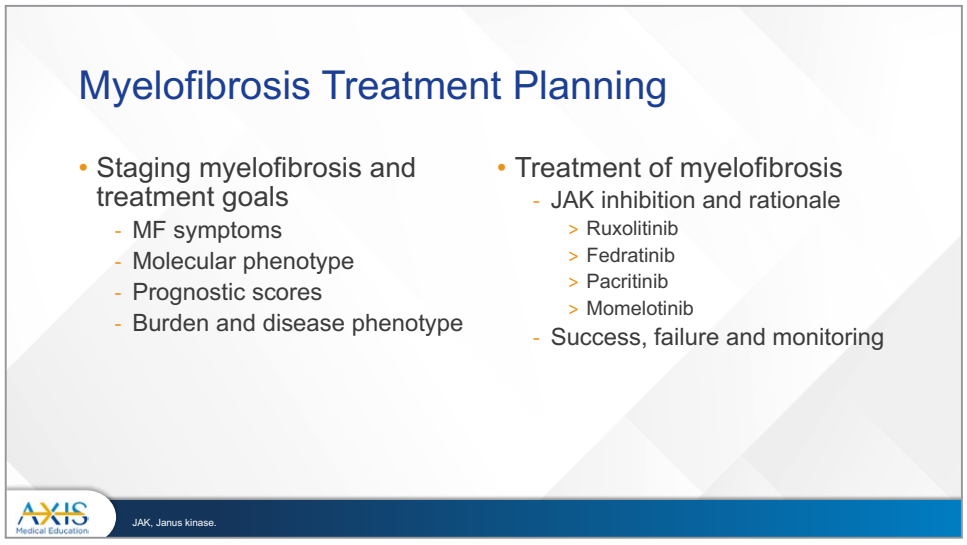
- As learning objectives upon completing this activity, our hope is that you'll have a better sense of myelofibrosis, what is the disease burden, and the impact on patients' quality of life, that you'll be able to apply guideline-recommended and evidence-based prognostic and risk stratification approaches in your practice, that you'll be able to evaluate clinical safety, efficacy, tolerability, and durability data for approved and emerging therapeutic agents and combinations, including data pertaining to improving quality of life and reducing symptom burden, develop personalized care and treatment plans that incorporate disease-specific as well as patient-specific factors.



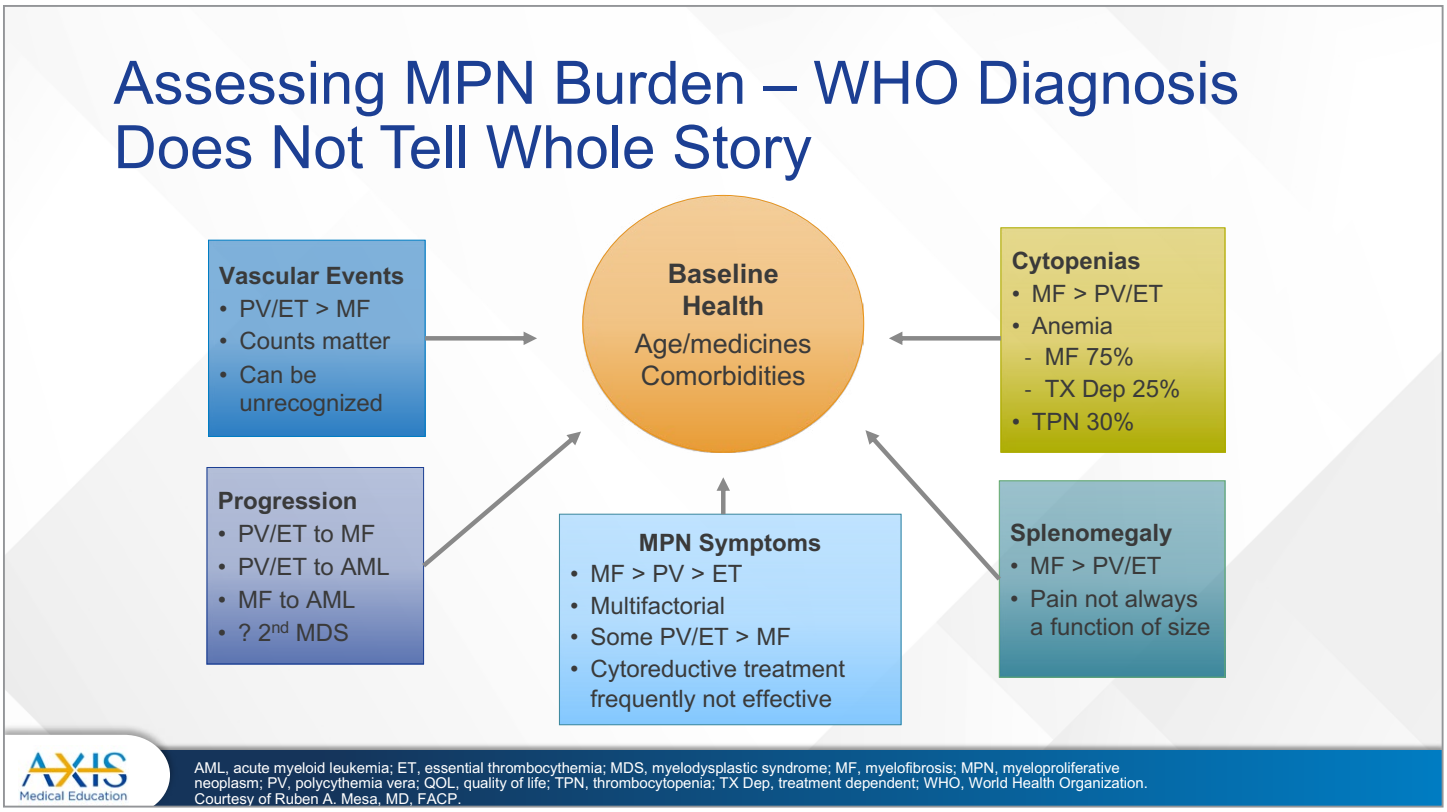
- So let's begin delving into the difficulties these patients can face, both in terms of individual symptoms and quality of life.



So we're going to focus on treatment planning, symptom burden. What are the tools to be able to measure symptoms? What is that spectrum throughout the disease continuum? How do you track symptoms as part of treatment planning? What are the impacts of symptoms on quality of life?



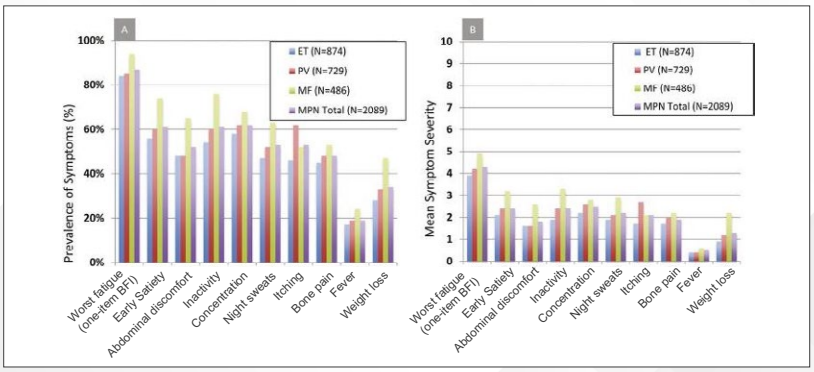
As we think about treating these patients, one, why all this rigamarole regarding symptoms, quality of life, disease burden? Myelofibrosis is a chronic myeloid neoplasm, but it has a latent course. And because of that latent course, we need to be mindful that there's a whole range of factors we have to take in how to treat patients. Indeed, as we try to think about our treatment goals, at the current time, we do not have curative therapies short of stem cell transplantation. And because of that, as we think about medical therapies, we have to think about their benefits and their risks. What are the symptoms a patient faces? What is their molecular phenotype that may impact their prognosis? What is their disease burden and disease phenotype? And then we think about our options, which can include JAK [Janus kinase] inhibitors, three of which are approved and one that is on the cusp of approval, as well as what does success, failure, and monitoring look like?



▶ Now, as we evaluate patients with myelofibrosis, I like to think about it as a portfolio of difficulties that they may face. And not all patients will face each of these. There clearly can be risk of vascular events. Now these are more common in P-vera [polycythemia vera] and ET [essential thrombocythemia]. But it's important to note that they certainly occur at a higher frequency in patients with MF [myelofibrosis], certainly, than age-matched controls. Elevated blood counts can matter, those with significant leukocytosis or thrombocytosis. And sometimes vascular events have occurred and can be unrecognized. Patients may also carry forward the risk of vascular events from their earlier disease, if they had Budd-Chiari syndrome, pulmonary emboli, etc.

They clearly could have cytopenias. These can be more present as the disease progresses. Cytopenias are a much more characteristic feature of myelofibrosis over PV [polycythemia vera] and ET. They clearly can have anemia as predominant over thrombocytopenia, which can be present in about a third of patients. About a quarter can be transfusion dependent. They can have splenomegaly. We think the spleen enlarges for a range of reason, including the sequestration of circulating myeloid progenitor cells. We do not think that the spleen has effective extramedullary hematopoiesis. So, there are cells being made there, but they're really not leaving the spleen. The big spleen can cause symptoms, it can cause pain, it can cause early satiety, it clearly can also cause a hypersplenism and consumption of cells. They clearly can have symptoms, and they are their worst in myelofibrosis. And their origin can be multifactorial, and they are part of our goal of therapy. They clearly can progress to acute leukemia or have other progression. Indeed, for many patients with MPS, it is progression that can make their disease life threatening. Is that PV or ET to myelofibrosis? Is that PV or ET to AML [acute myeloid leukemia]? More often it's MF to AML It is rare these days that PV or ET goes straight to AML. And all of this, of course, is occurring in the setting of an individual that has a baseline level of health, with age, medicines, comorbidities that define that individual.

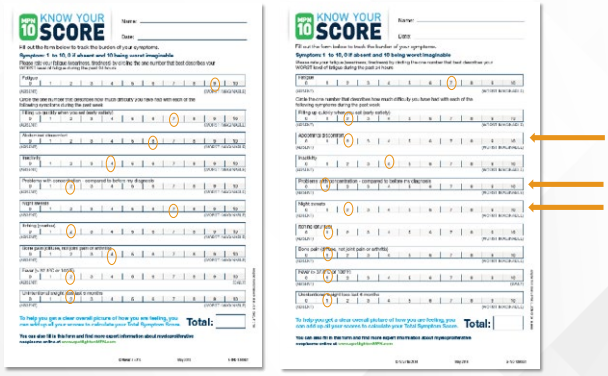
Classic Signs and Symptoms of MPNs



BFI, Brief Fatigue Inventory; ET, essential thrombocytopenia; MF, myelofibrosis; MPNs, myeloproliferative neoplasms; PV, polycythemia vera.
Geyer HL, Mesa RA. *Blood.* 2014;124(24):3529-3537.

- Now, these individuals I mentioned can have frequent symptoms. You'll see here on the left, the prevalence of symptoms, with MF in the green, this is in 2,000 patients, you see those patients having the most significant, and then you see the severity of symptoms on the right. What you'll see in this graph is that fever is the least common. I'll note that there are several symptoms that really are more associated with disease progression: fever, weight loss, bone pain, in particular. Where there's others that are almost universal, such as fatigue. Those are not uncommon for the patient that I see this progress from PV or ET into MF where it's clear that they have more fever or bone pain, or particular weight loss. Weight loss is something in our society that just does not occur without people trying. Sometimes even if they try, they aren't able to lose weight, I know I certainly fall in that category. So if they lose weight without trying, it could be a sign of depression or illness in an MF, most certainly illness.

MPN-10: Allows Visual Assessment



Emanuel RM, et al. *J Clin Oncol.* 2012;30(33):4098-4103.

- Now the [MPN] 10-Items score has now been validated in multiple languages, it's easy to assess serial values, easy for patients to fill out. It's been validated in multiple different ways and through the conduct in many different trials.

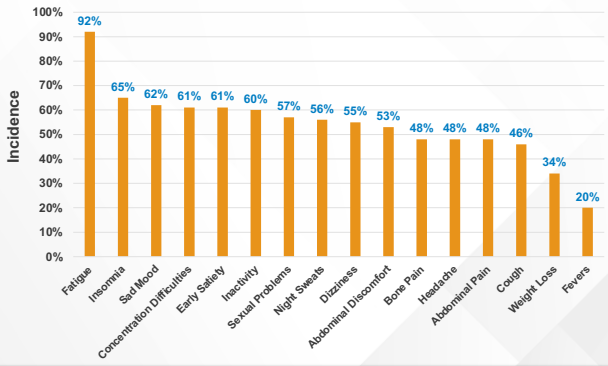
Symptoms/Signs Assessed by Each Measure

Item	MPN-10[2]	MFSAF v2.0[3,4]	MFSAF-revised	MFSAF v4.0[5]
Fatigue	X		X	X
Night sweats	X	X	X	X
Itching	X	X	X	X
Abdominal discomfort	X	X	X	X
Pain under ribs on left side		X	X	X
Early satiety	X	X	X	X
Bone pain	X	X*	X	X
Inactivity	X	X**	X**	
Concentration problems	X			
Fever	X			
Weight loss	X			
Scale score range	0-100	0-60	0-70	0-70

*This item was "bone or muscle pain" for the MFSAF v2.0. **This item was not used to compute the scale score.
MPN, myeloproliferative neoplasm; MFSAF, myelofibrosis symptom assessment form. Adapted from Dueck et al, 2017.
1. Dueck AC, et al. *Blood*. 2017;130(Supplement 1):2168. 2. Emanuel RM, et al. *J Clin Oncol*. 2012;30(33):4098-4103. 3. Mesa RA, et al. *Leuk Res*. 2009;33(9):1199-1203. 4. Mesa RA, et al. EHA 2011.

- There are – perhaps this is too many details for some of you, but I'll share that although we have revised our scores over time, they are interchangeable, and again have these core items.

MPN Symptom Burden: A Diverse, Disabling Constellation of Symptoms



MPN, myeloproliferative neoplasm.
Courtesy of Ruben A. Mesa, MD, FACP.
Data adapted from Scherber R, et al. *Blood*. 2011;118(2):401-408.

- Looking at MF specifically, here you see the decrease in prevalence of these individual symptoms, with fatigue being almost universal.

MPN Recent Phase 3 Trials

MPN Symptom Assessment

Disease	Drug (Trial)	MPN Symptom Tool
MF	Ruxolitinib (COMFORT 1)	MF-SAF 2.0
	Ruxolitinib (COMFORT 2)	FACT-Lym
	Fedratinib (JAKARTA)	MF-SAF
	Pacritinib (PERSIST 1&2)	MPN-SAF
	Momelotinib (SIMPLIFY 1&2)	MPN-SAF
	Pomalidomide (RESUME)	FACT-An
	Ruxolitinib (RETHINK)	MPN-10
PV	Ruxolitinib (RESPONSE)	MPN-SAF
	Ruxolitinib (RELIEF)	MPN-SAF
	PEG INFa2a (MPD-RC 112)	MPN-SAF
ET	Ruxolitinib (MAGIC)	MPN-SAF
	PEG INFa2a (MPD-RC 112)	MPN-SAF

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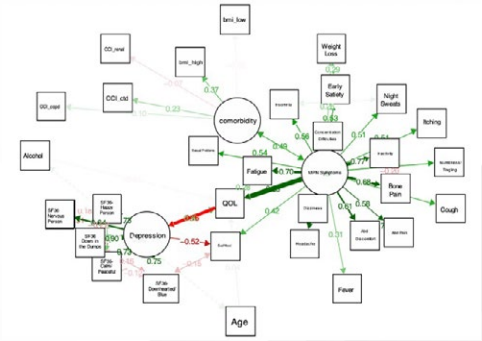
ET, essential thrombocythemia; FACT-An, Functional Assessment of Cancer Therapy–Anemia; FACT-Lym, Functional Assessment of Cancer Therapy–Lymphoma; MF, myelofibrosis; MPN, myeloproliferative neoplasm; PEG INFa2a, pegylated interferon alfa-2a; PV, polycythemia vera; SAF, symptom assessment tool

A Structural Equation Model of QOL in Myeloproliferative Neoplasms

SEM was developed using covariance structural analysis modeling with QOL as a dependent variable



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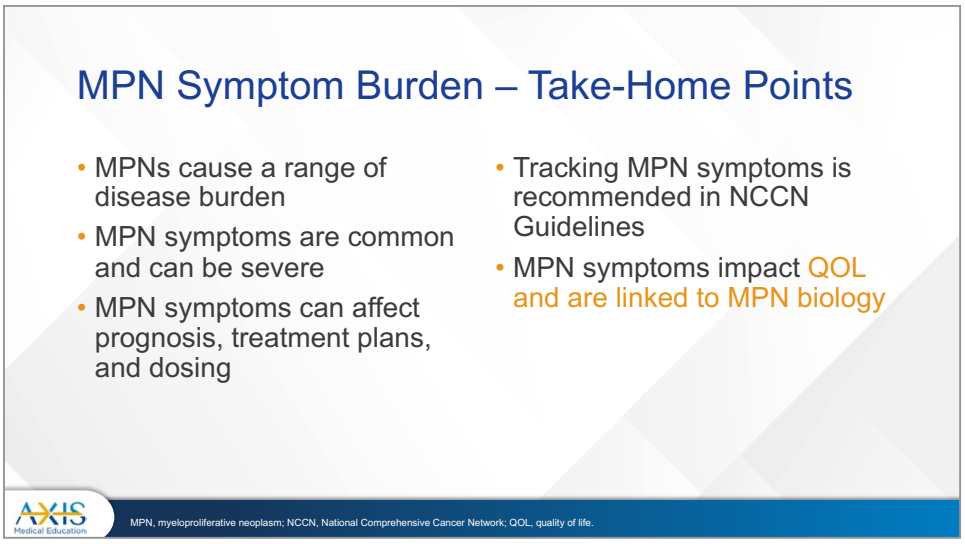
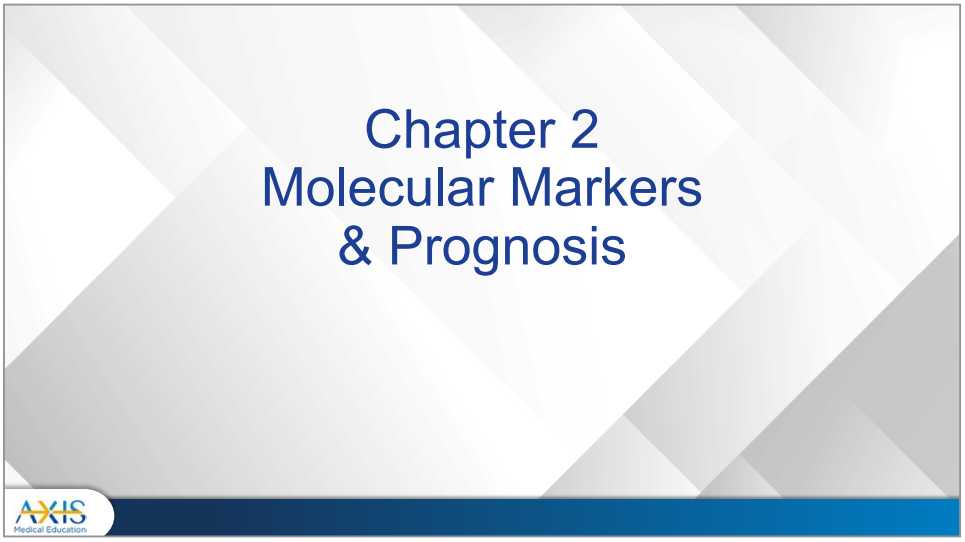
BMI, body mass index. CCI_copd, Charlson Comorbidity Index_chronic obstructive pulmonary disorder; CCI_ctd, Charlson Comorbidity Index_connective tissue disorder; QOL, quality of life; SEM, structural equation model; SF-36, Short Form 36 questionnaire.
Scherber RM, et al. *Blood*. 2019;134(suppl 1):2181.

- This approach has been used in the majority of our clinical trials for JAK inhibitors and other agents in MPNs [myeloproliferative neoplasms].

- Now symptoms can impact your quality of life. Quality of life and symptoms are not the same construct. So quality of life is a broader issue. It is really the perception of where you stand compared to where you think you should be standing. And things can impact your quality of life. Let's use the classic example. Someone you love dearly has died. Your quality of life has decreased dramatically. That has not impacted your health, but it impacts your quality of life. When we speak of things like symptoms, we're really thinking of health-related quality of life. And health-related quality of life can have other contributors, financial toxicity from buying medicines, the hassle of medical care, "I need to go into get blood counts once a week," that's a hassle. "I need to get transfusions once a week," that's a much more significant hassle. In this analysis done with colleagues using statistical correlative approaches, they're able to show that the two biggest things that impact quality of life in MPN patients are either their symptoms or depression. Indeed, as we've looked at multiple different types of analysis, it's important to note that depression is frequently underdiagnosed, clearly can be impactful for these patients, and needs to be on our radar.



- Take-home points, MPN symptom burden. First, MPNs can cause a range of disease burden. Their symptoms are common, and they can be severe. The symptoms, as we'll get to the prognostic scores, can affect prognosis. They clearly can affect treatment plans, the dose of a drug, whether to start a drug, whether to stop a drug. Tracking MPN symptoms is recommended in our current NCCN guidelines, and MPN symptoms can be linked directly to MPN biology. So these symptoms are not just out of the blue; they can be related to elevation and cytokines, elevation in blood counts, decreases in circulation, or avascular biology. So multiple different contributors. And indeed, I like to say are a type of biomarker of the disease that need to be tracked and assessed.



- Next, molecular markers and prognosis.

Topic for Discussion

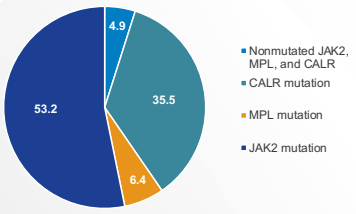
- The role of the JAK-STAT pathway in MF
- Evolution of prognostic models in MF
- Clinical prognostic models
- Mutation-enhanced prognostic scoring systems
- Guideline recommendations for risk stratification of MF
- Scoring systems for sMF and HSCT

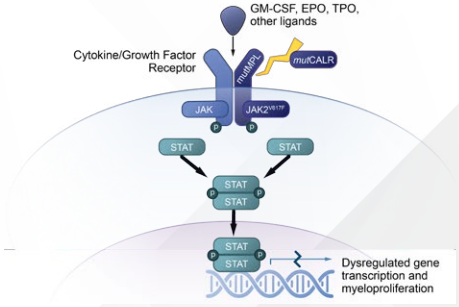
HSCT, hematopoietic stem-cell transplantation; JAK-STAT, Janus kinase-signal transducer and activator of transcription; MF, myelofibrosis; sMF, secondary myelofibrosis.

Here we're going to talk about the role of the JAK-STAT pathway in myelofibrosis, the evolution of prognostic models in myelofibrosis, clinical prognostic models, and how we utilize it, whether they're mutation-enhanced prognostic scoring systems, how we risk stratify, and also scoring systems for secondary myelofibrosis and stem cell transplant.

The Relevance of the JAK-STAT Pathway in MF

- JAK/STAT pathway plays a central role in cell proliferation, differentiation, and survival[1-3]
- JAK2 V617F mutation is present in about half of patients with primary MF.[4]

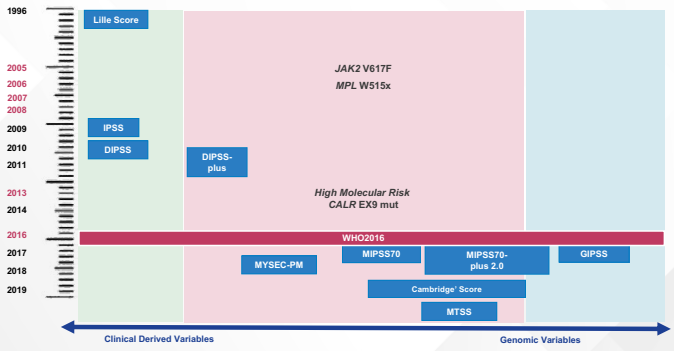




CALR, calreticulin; EPO, erythropoietin; GM-CSF, granulocyte-macrophage colony-stimulating factor; JAK-STAT, Janus kinase-signal transducer and activator of transcription; TPO, thrombopoietin.
1. Schwartz DM, et al. *Nat Rev Drug Discov*. 2017;16:843-862; 2. O'Sullivan JM, Harrison CN. *Mol Cell Endocrinol*. 2017;451:71-79;

Now, I've spent almost 30 years of my career caring for patients with MPNs; 15 years before the JAK inhibitors, 15 plus years after. And with that, we have identified that there are 3 core driver mutations, the JAK2 V617F, calreticulin, and MPL. And with these driver mutations, it's important to note, as you see on the right side of this slide, that all 3 of these mutations are impacting the JAK-STAT pathway, all 3 of them lead to overactivation of the pathway, leading to a dysregulation of gene transcription and proliferation. Therefore, when we speak of JAK inhibitors in later part of the presentation, note that that is inhibiting the JAK-STAT pathway overall. And because of that, inhibiting JAK2, it inhibits the impact of all three of these mutations. Additionally, there are those individuals that are, quote, triple negative, they lack any one of these three mutations. For these individuals, we feel that they likely have other mutations that are still leading to overactivation of this JAK-STAT pathway.

The Evolution of Prognostic Models in MF



DIPSS, Dynamic IPSS; GIPSS, genetically inspired prognostic scoring system; IPSS, International Prognostic Scoring System; MIPSS, Mutation-Enhanced International Prognostic Score System; MTSS, Myelofibrosis Transplant Scoring System; MYSEC-PM, MYelofibrosis SECondary to PV and ET prognostic model; WHO, World Health Organization.

Now, there are many prognostic models that have been developed for myelofibrosis. Part of the origin of this has been given that there's a very heterogeneous prognosis for these patients, there's a great desire to try to better understand the prognosis, so that these individuals may be better served, but also that we may be better able to identify those individuals that might benefit from a stem cell transplant.

"Clinical" Prognostic Models of Myelofibrosis[1]

Parameter	IPSS[2]	DIPSS[3]	DIPSS-Plus[4]
Age > 65 y	Yes (1 point)	Yes (1 point)	Yes[a]
Hgb < 10g/dL	Yes (1 point)	Yes (2 points)	Yes[a]
WBC > $25x10^9$/L	Yes (1 point)	Yes (1 point)	Yes[a]
PB blood blasts ≥ 1%	Yes (1 point)	Yes (1 point)	Yes[a]
Constitutional symptoms	Yes (1 point)	Yes (1 point)	Yes[a]
Unfavorable karyotype[b]	No	No	Yes (1 point)
RBC transfusion dependence[c]	No	No	Yes (1 point)
Platelet count < 100 x 10^9/L	No	No	Yes (1 point)
Can be used at any time point	No (only at diagnosis)	Yes	Yes

	Median Survival, Years		
Risk Group	IPSS [2]	DIPSS [3]	DIPSS-Plus [4]
Low	11.3	Not reached	15.4
Intermediate-1	7.9	14.2	6.5
Intermediate-2	4.0	4.0	2.9
High	2.3	1.5	1.3

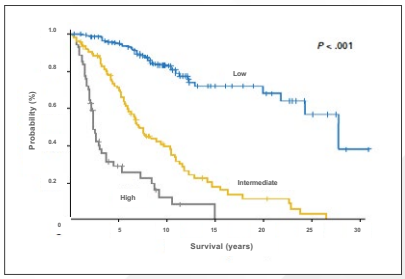
DIPSS, Dynamic IPSS; Hgb, hemoglobin; IPSS, International Prognostic Scoring System; PB, peripheral blasts; RBC, red blood cell; WBC, white blood cell
1. Bose P, Verstovsek S. *Cancer*. 2016;122(5):681-692. 2. Cervantes F, et al. *Blood*. 2009;113(13):2895-2901.
3. Passamonti F, et al. *Blood*. 2010;116(15):2857-2858.

The most utilized internationally are the IPSS and DIPSS. These utilize a variety of clinical parameters and large datasets, so that we're able to stratify patients by prognosis. The DIPSS added in additional factors, and the DIPSS Plus added in karyotype, transfusion dependence, thrombocytopenia. Now for the trainees in my center, I tell them, you know, "Boy, it's not critical that you memorize these scores. It's helpful to know, one, they exist, two, to have some sense of when to apply them, and three, there are clues in terms of the biology of the disease." When you look at the negative prognostic factors, they tell you, "Well, why is the prognosis worse?" For these individuals, one, are they moving more toward acute leukemia? So what happens in acute leukemia? You have more cytopenias, you have more blasts, you have more unfavorable karyotype. So all of that's fairly logical. Two, constitutional symptoms. That's important. Again, the biological surrogate of the disease, and the cytopenias, the worse they are, the worse the outcome. Again, all of that is fairly logical.

MIPSS70-plus: Integrated Genetic and Clinical Score

Variables	Rank
Hb <100g/L	1
WBC >25x10^9/L	2
PLT <100x10^9/L	2
PB blasts ≥2%	1
Constitutional Symptoms	1
Grade ≥2 BM fibrosis	1
Absence CALR Type1	1
HMR category*	1
≥2 HMR mutations	2

Risk category	Score	OS (y)	HR
Low	0-1	27.7	1
Intermediate	2-4	7.1	5.5 (3.8-8.0)
High	≥5	2.3	16.0 (10.2-25.1)



http://www.mipss70score.it/index.html

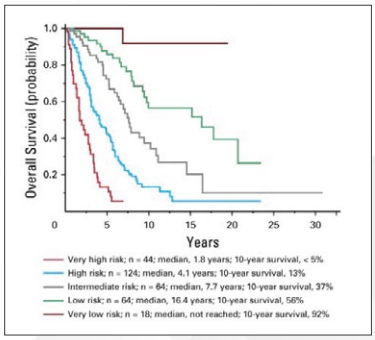
* HMR category = any mutation in: *ASXL1, EZH2, SRSF2, IDH1/2*
BM, bone marrow; CALR, calreticulin; Hb, hemoglobin; HMR, high molecular risk; MIPSS, Mutation-Enhanced International Prognostic Score System; OS, overall survival; PB, peripheral blasts; PLT, platelets; RBC, red blood cell; WBC, white blood cell.

- Now, the second generation of prognostic scorers I think were enhanced when we added in additional molecular phenotype data. The absence of CALR type 1, okay, so that's a bit of an awkward way of saying anything other than CALR type 1, which has a good prognosis, or a high molecular risk mutation. What's included in there? ASXL1, EZH2, SRSF2, IDH1 and 2. If you've got more than one of those, that again is more prognostically diverse. And with this, you can really stratify patients quite a bit. It particularly is helpful, I think, in helping to identify low-risk patients. There's less of a spread between intermediate and high risk. But helping to separate the low-risk patients is probably most helpful really in this whole discussion regarding stem cell transplant.

MIPSS70-plus v2.0: Mutation Enhanced Prognostic Score System

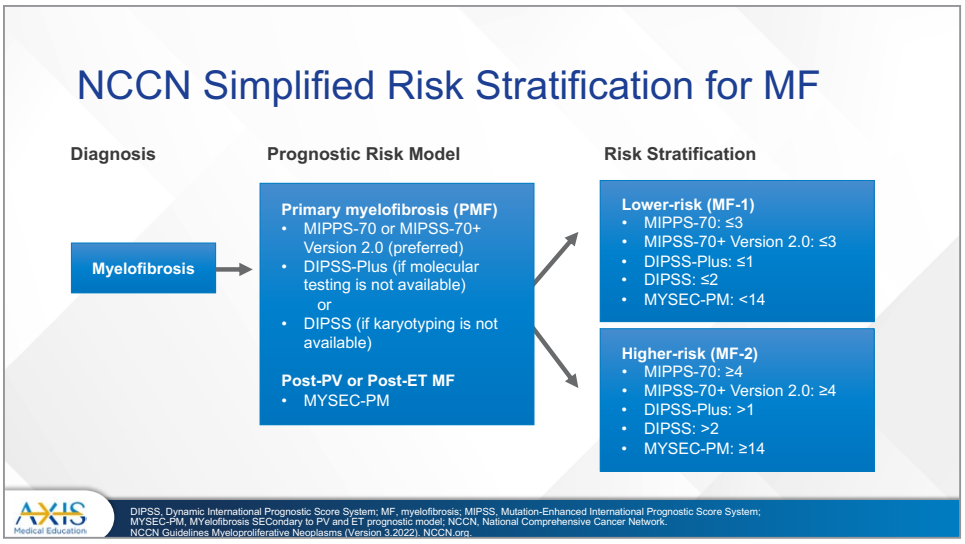
Variables	Weighted Value
Severe anemia: Hb <80 g/L (female); <90 g/L (male)	2
Moderate anemia: Hb 80 to 99 g/L (female); 90 to 100 g/L (male)	1
PB blasts ≥2%	1
Constitutional Symptoms	2
Absence CALR Type1	2
HMR*	2
≥2 HMR mutations	3
Unfavorable Karyotype*	3
Very High Risk Karyotype*	4

Risk category	Score	10-years OS (y)
Very Low	0	92%
Low	1-2	56%
Intermediate	3-4	37%
High	5-8	13%
Very High	≥9	<5%

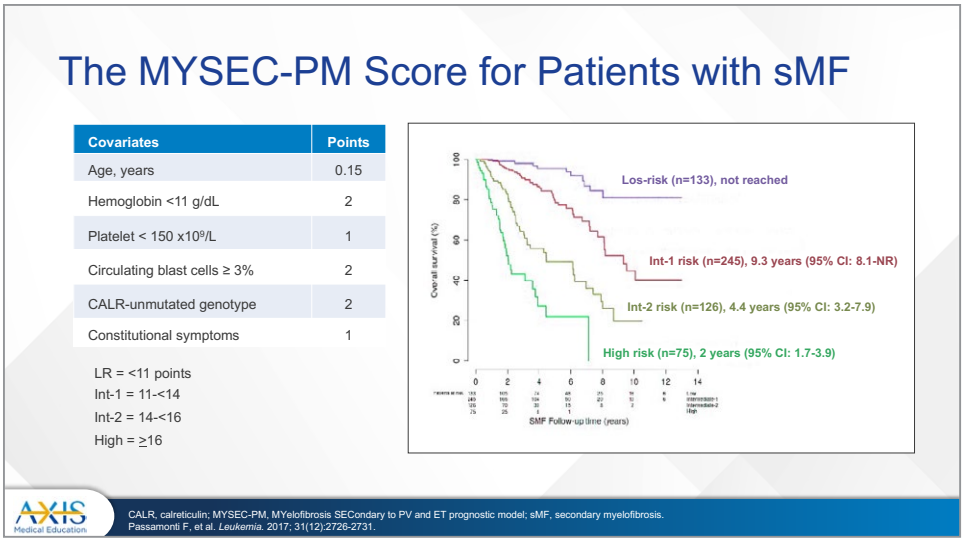


*More information available at: http://www.mipss70score.it/index.html
CALR, calreticulin; Hb, hemoglobin; HMR, high molecular risk; MIPSS, Mutation-Enhanced International Prognostic Score System; OS, overall survival; PB, peripheral blasts.

- Again, more scores than you can imagine. But each of them a bit more refined. Here in the Version 2, they added in karyotype, that, again, still has some additional prognostic relevance, they're helping to further stratify the risk. I think, if we're considering stem cell transplant, the more information the better. And that's where I think these things really excel. These scores have not been particularly helpful in really helping us guide medical therapy, but are helpful regarding transplant.



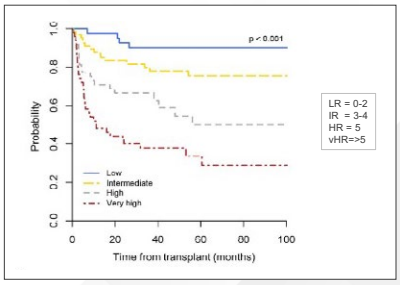
- Now, our colleagues at NCCN, and I was the inaugural panel chair for this group, said, okay, we've got lots of prognostic scores. But in terms of clinical relevance, it's probably sufficient to look at lower risk versus higher risk, regardless of your score, put them in each bucket, with lower risk patients, again, being managed in one way, maybe observation, maybe single-agent JAK inhibitor; higher risk, greater likelihood of transplantation.



- Now the MYSEC-PM, this is for individuals with myelofibrosis ahead of all from ET or PV. Why the need for this score is that in patients with PV and ET, many of them will have higher platelets or hemoglobin than primary MF patients. You can think that they retain some of the over-proliferation from earlier disease. Here again, you can prognosticate them accordingly.

Comprehensive Clinical-Molecular Transplant Scoring System for MF Patients Undergoing HSCT (MTSS)

	Hazard ratio (95% CI)	*P*	Weighted score
Age ≥ 57 years	1.65 (1.15-2.36)	0.006	1
Karnofsky performance status <90%	1.50 (1.06-2.13)	0.021	1
non-CALR/MPL driver mutation genotype	2.40 (1.30-4.71)	0.012	2
ASXL1 mutation	1.42 (1.01-2.01)	0.041	1
HLA-mismatch unrelated donor	2.08 (1.45-2.97)	<0.001	2
WBC count >25x10^9/L	1.57 (1.16-2.41	0.007	1
Platelet count <150x10^9/L	1.67 (1.16-2.40)	0.006	1



The 5-year survival was 90% (low), 77% (intermediate), 50% (high), and 34% (very high) in the training cohort (n = 205) (*P* <0.001, respectively)

CALR, calreticulin; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation. MTSS, Molecular Transplant Scoring System; vHR, very high risk;WBC, white blood cell

Gagelmann N, et al. *Blood*. 2019;133(20):2233-2242.

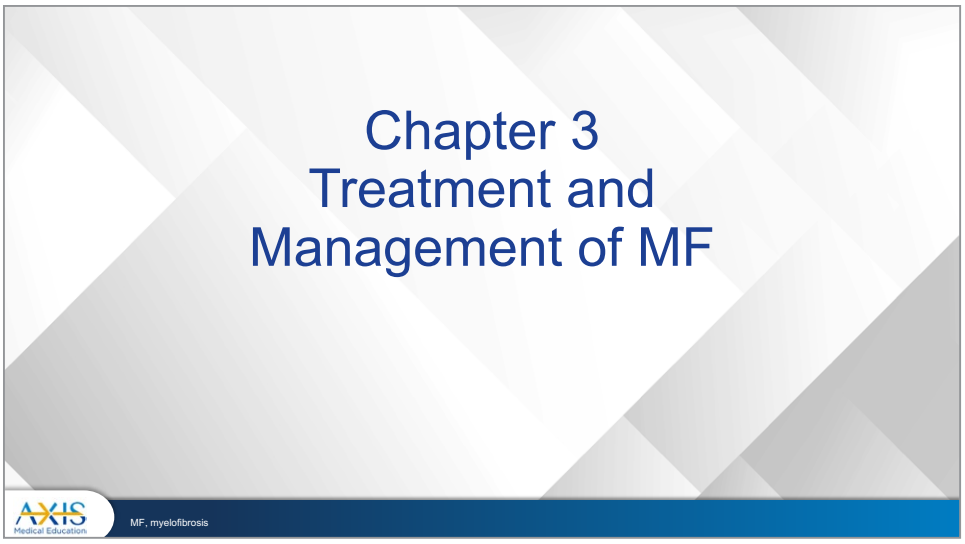
- Now, the MTSS was a prognostic score specifically for those individuals undergoing transplant. I've told you now more than once, that the main value in these scores is for those that are considering transplant. So what you really care about is how well are they going to do with a transplant. This includes some of those other features, the other ones that were relevant, but what they found in patients who actually underwent transplant is that the HLA mismatch donor, that's a factor, the ASXL1 mutation in particular, is prognostically averse. A Karnofsky performance status, anything other than a great Karnofsky. So all of these things can really be helpful. And I think in many ways, this is critical to be calculated in addition to the other factors when they tally looking at considering stem cell transplant is considering that option for patients.

MF Molecular Markers & Prognosis Take Home Points

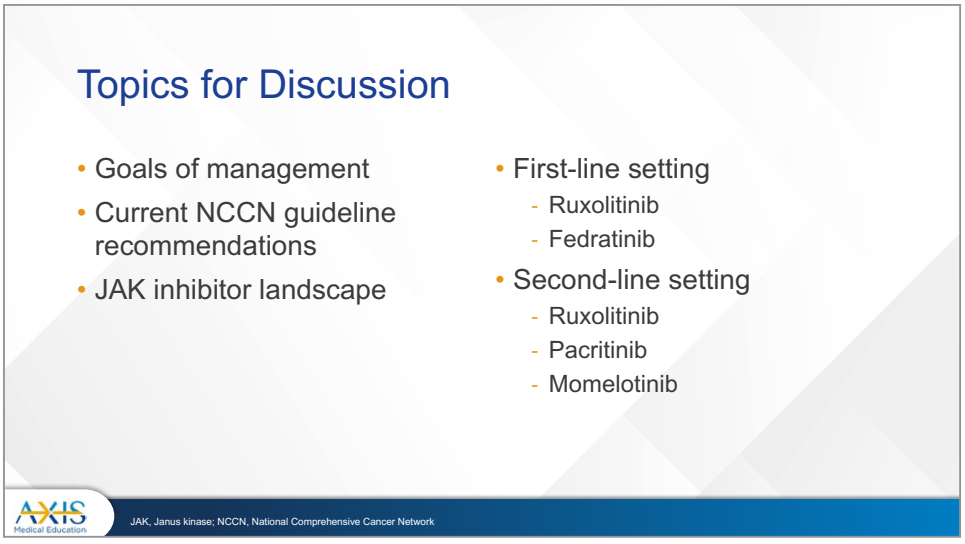
- Driver mutations (JAK2-V617F, CALR, MPL) in vast majority of patients with MF
- Some additional somatic mutations associated with adverse prognosis in MF
- Many prognostic models for MF that incorporate clinical features and molecular findings

CALR, calreticulin; MF, myelofibrosis; JAK, Janus kinase; MPL, thrombopoietin receptor gene.

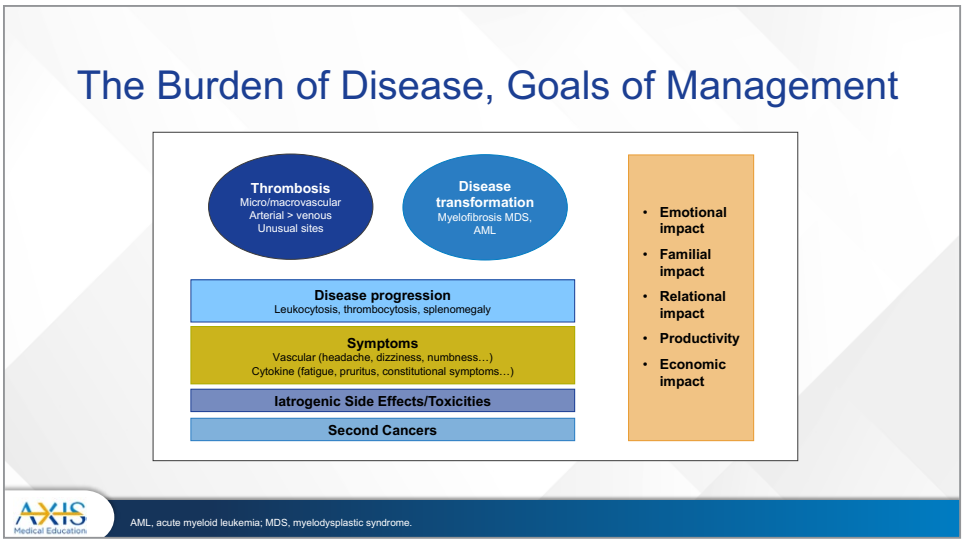
- So take-home points from MF molecular markers and prognosis. One, driver mutations in the vast majority of patients with MF, but they're all acting on the JAK-STAT pathway. Two, additional somatic mutations really can be prognostically very helpful. I am recommending for individuals, but in the majority of cases, they have NGS testing for their myelofibrosis, in particular, at diagnosis, and potentially repeated at some frequency if they are a stem cell transplant. Many prognostic models incorporate these clinical and molecular features. And I would say the IPSS or DIPSS, at the current time, really is inadequate for prognosticating many of these individuals.



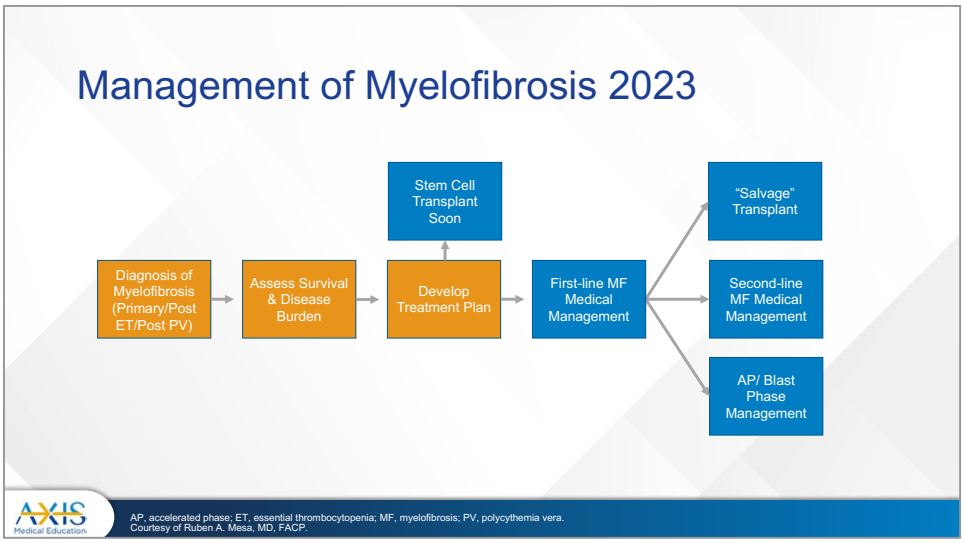
- So let's pivot now to treatment. You saw from these prior scores, these patients sometimes are going to have a very latent disease in terms of prognosis, but can have significant symptoms. So how do we manage them?



- Well, as we're trying to treat a patient, and again saw a patient just this morning newly diagnosed myelofibrosis, what are our goals? What are our treatment guidelines? If we're going to use a JAK inhibitor, what are our expectations? Are JAK inhibitors approved in the frontline setting? Potential use of JAK inhibitors in the second-line setting?



- Indeed, as we're thinking of the goals of management, what are our goals? Well, we're trying to decrease disease progression. We're trying to improve symptoms. We're trying to decrease any downsides of being in a medicine, iatrogenic side effects, secondary cancers. We clearly don't want thrombosis. We clearly want to avoid disease progression. And we need to be mindful of many things that are really relevant to the patient: emotional, financial, family impact, productivity, meaning again, if you're on a medicine, you're feeling better, you're able to do work, there's an economic impact to that in a favorable way. Just the same, there's a very adverse prognostic or economic impact if you're unable to work.



- Now, as we manage patients with myelofibrosis in 2023, we start with an accurate diagnosis. We assess survival and disease burden. Survival is not the only thing that we treat. Again, there's both length of life and quality of life. Both are relevant. If you have a long life, but you feel terrible, you probably still merit treatment. Develop a treatment plan, communicate that plan to the patient. Do they know why they're under therapy? What is [the goal] of therapy? What does success look like? We decide should we be going to a stem cell transplant in the near future, in the long-term future? We discuss frontline medical therapy. Again, what is appropriate in that setting? If they do not benefit, do we move to a salvage transplant, second-line therapy, or do we move to accelerated or blast phase management?

- Now guidelines, I like to say, are the guardrails of medicine. How you apply those guidelines, that is the art of medicine. So I'll use an example. If the guideline says that a frontline therapy for myelofibrosis could include ruxolitinib or fedratinib, or stem cell transplant, or a clinical trial, those are the options. Meaning, if I wanted to give a patient, you know, Adriamycin, it's not in the guidelines, there's no evidence to say that it would be helpful. Again, you'd really be out on your own and without evidence. That clearly is outside of the guardrails of medicine. But which you use, now that is the art, based on the evidence, based on the patient's exact situation, based on your experience and clinical acumen.

NCCN Guidelines® Summary: Treatment For Myelofibrosis

Risk	Risk Stratification	Treatment Options	

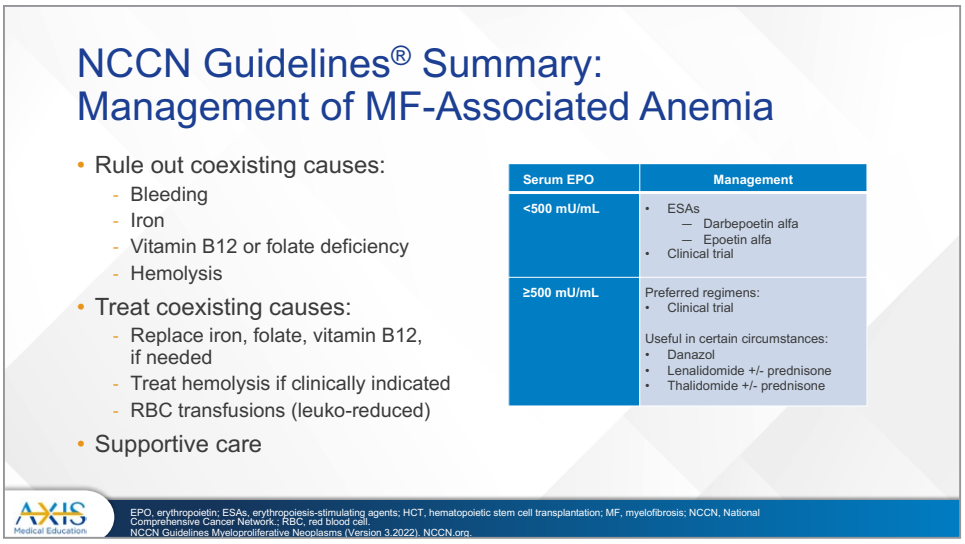
Lower-Risk	• MIPSS-70 ≤3
	• MIPSS-70+ Version 2.0: ≤3
	• DIPSS-Plus: ≤1
	• DIPSS: ≤2
	• MYSEC-PM: <14
		• Clinical trial
		• Observation
		• Useful in certain circumstances:
		  • Ruxolitinib
		  • Peginterferon alfa-2a
		  • Hydroxyurea, if cytoreduction would be symptomatically beneficial	

Higher-Risk	• MIPSS-70 ≥4 • MIPSS-70+ Version 2.0: ≥4 • DIPSS-Plus: >1 • DIPSS: >2 • MYSEC-PM: ≥14	**Transplant candidate**	• Allogeneic HCT
		Platelets <50 x 10^9/L	• Pacritinib or Trial
		Platelets ≥50 x 10^9/L	• Ruxolitinib • Fedratinib • Clinical trial No response or loss of response: • Fedratinib (for patients previously treated with ruxolitinib), Pacritinib PLT <50 x 10^9/L

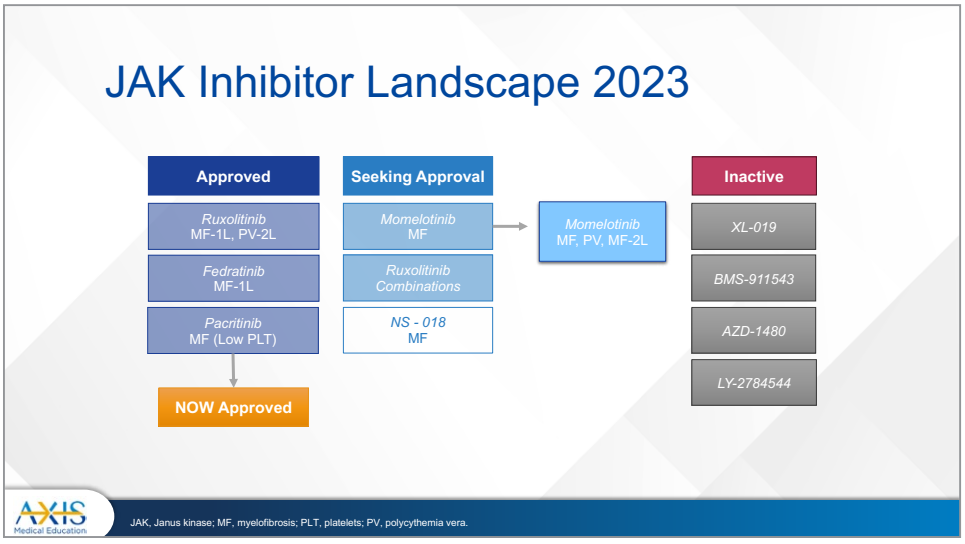
AXIS Medical Education

DIPSS, Dynamic International Prognostic Score System; HCT, hematopoietic stem cell transplantation; MIPSS, Mutation-Enhanced International Prognostic Score System; MYSEC-PM, MYelofibrosis SECondary to PV and ET prognostic model; NCCN, National Comprehensive Cancer; PLT, platelet.
NCCN Guidelines Myeloproliferative Neoplasms (Version 3.2022). NCCN.org.

Now, the NCCN guidelines for low risk, consider clinical trial, observation, or in certain circumstances ruxolitinib, pegylated interferon alfa-2a, or hydroxyurea. Really, this main group tends to be either observation or ruxolitinib, particularly if symptomatic. Pegylated interferon probably helpful with early disease, moving more toward MF trying to avoid progression. Hydroxyurea really is not a mainstay MF therapy. Why this is in here, there are some individuals, again, they have residual thrombocytosis, leukocytosis from earlier disease, they may benefit. The vast majority of patients fall into this other bucket, higher risk. Now, they're a transplant candidate, take them to transplant, although they likely would benefit from a JAK inhibitor on the way to a transplant. And if someone's going to a transplant, they really go immediately. If they're thrombocytopenic, that clearly fits with the FDA approval for pacritinib. If their platelets are greater than 50, again, consider ruxolitinib as a frontline option, fedratinib is approved in this setting. Clinical trial can be always a consideration. Or if they have no response or loss of response, clearly try fedratinib, that's second line, or pacritinib for individuals with marked thrombocytopenia.



- Now for MF-associated anemia, there's their own additional set of guidelines. Rule out other causes of anemia, treat coexisting causes, supportive care. If their EPO level is under 500, give them some EPO, or consider a clinical trial. If they're over 500, consider danazol, consider an IMiD. Again, I would put danazol as a consideration that under 500, if you're not going to give them EPO.



- Now the JAK inhibitor landscape in 2023, we have many drugs on the right that have been tested, but that for a range of reasons, whether toxicity or the competitiveness of the market, are no longer in development. We have 3 approved drugs: ruxolitinib, fedratinib, and pacritinib. Ruxolitinib approved in frontline MF and second line in PV. Fedratinib in the frontline in MF. Pacritinib for individuals with the low platelets. Momelotinib is seeking approval, and again may well be approved in the very near future. Ruxolitinib combinations, a variety of them are in phase 3 clinical trials.

COMFORT-I Study Design

Randomized, double-blind, placebo-controlled, multicenter, phase 3 trial

- Patients (≥ 18 y) with int-2 or high-risk MF
- PMF, PPV-MF, or PET-MF
- PLT count ≥ 100,000
- Palpable spleen ≥ 5 cm
- PB < 10%
- ECOG PS ≤ 3
- Refractory or intolerant to or not candidates for available therapy

N = 309

R 1:1

RUX twice daily
- 15 mg twice daily for a PLT count of 100 × 10^9 to 200 × 10^9/L
- 20 mg twice daily for a count > 200 × 10^9 L

N = 155

Placebo → Crossover for splenomegaly

N = 154 N = 36

- Primary endpoint: Number of patients in whom ≥ 35% SVR was achieved from BL to week 24 as measured by MRI (or CT scan in applicable patients)
- Secondary endpoints: Proportion of patients with ≥ 50% reduction in TSS from BL to week 24 as measured by the MF-SAF 2.0, OS, duration of SVR

BL, baseline; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; MF, myelofibrosis; MF-SAF, Myelofibrosis Symptom Assessment Form; MRI, magnetic resonance imaging; OS, overall survival; PB, peripheral blast; PLT, platelet; PMF, post myelofibrosis; PPV-MF, post-polycythemia vera myelofibrosis; PET-MF, post-essential thrombocythemia myelofibrosis; R, randomized; RUX, ruxolitinib; SVR, spleen volume reduction; TSS, total symptom score.

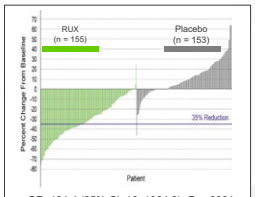
Vannucchi S et al. *N Engl J Med*. 2012;366(9):799-807.

▶ Ruxolitinib enjoys this frontline position due to the highly impactful COMFORT-I study. COMFORT-I and COMFORT-II study now published 11 years ago, ruxolitinib versus placebo with crossover for splenomegaly with primary endpoints of improvement of spleen and symptoms.

COMFORT-I Results

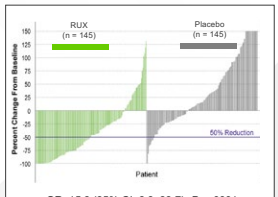
- Primary endpoint: the proportion of patients in whom ≥ 35% SVR was achieved from BL to week 24 (as measured by MRI or CT scan)
  - 41.9% in RUX group reached the primary endpoint vs 0.7% in the placebo group (P < .0001)
  - A similar proportion of patients in the RUX group had a ≥ 50% reduction in palpable spleen length
- SVR responses were seen with RUX in JAK2 V617F-positive patients and JAK2 V617F-negative patients, relative to placebo

SVR at 24 Weeks



OR, 134.4 (95% CI: 18, 1004.9); *P* < .0001

TSS at 24 Weeks

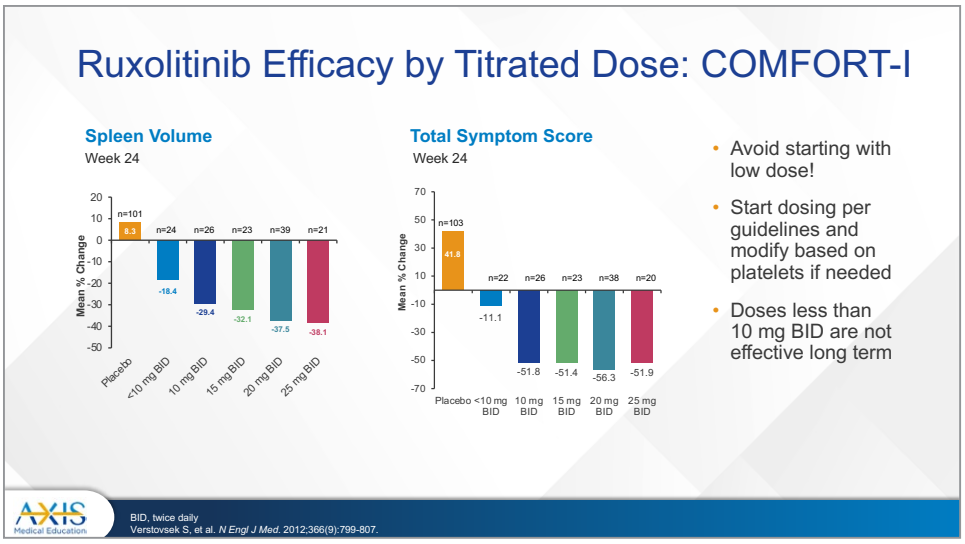


OR, 15.3 (95% CI: 6.9, 33.7); *P* < .0001

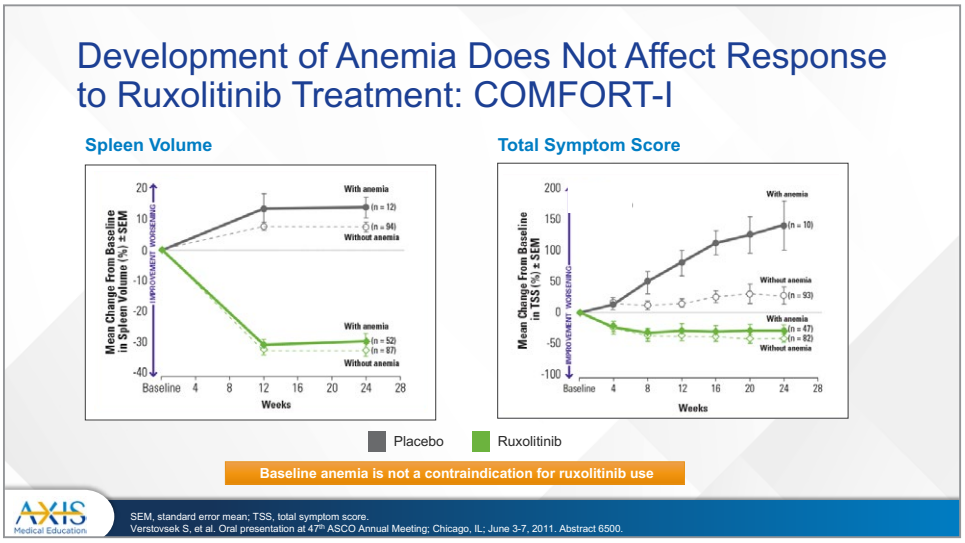
BL, baseline; CT, computed tomography; MRI, magnetic resonance imaging; OR, odds ratio; RUX, ruxolitinib; SVR, spleen volume reduction; TSS, total symptom score.

Vannucchi S et al. *N Engl J Med*. 2012;366(9):799-807.

▶ Here are individuals that had significant benefit, and here showing their waterfall plots, showed superiority in terms of spleen and symptoms compared to placebo.



Over time, we've learned several things, one, dose matters. And if there is an opportunity in patients treated in the U.S., there are too many patients who are treated really with a suboptimal dose. So use an adequate dose, which would be 10 mg twice a day or more, ideally 15 twice a day or more.



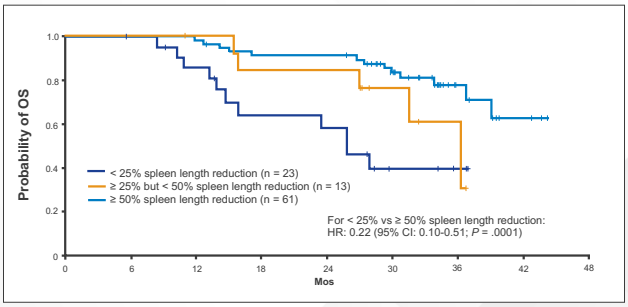
We've learned over time that the development of anemia can be a side effect but is not prognostically detrimental. Baseline anemia is not a contraindication to using ruxolitinib. And you'll see here that reductions in spleen volume, with or without anemia, can benefit. Likewise, a total symptom score can benefit with or without anemia.

We have seen over time that patients can live longer. And this has been validated in multiple different ways. The trial admittedly was not designed with survival as an endpoint. However, real-world evidence and follow-up with these patients show that there is a survival benefit. And someone again, who treated patients for 15 years before JAK inhibitors, there is no question these patients live longer. Now there is not a plateau. These agents are not a cure. But they live longer. I saw a patient in 2022 that had been on ruxolitinib since 2010, who was still on the medicine.

When I went back and calculated that individual's risk, their expected survival was at 3 years when they went on the agent, and they were alive at 12 years. And only then were having signs of progression and we put them on a different clinical trial.

Overall Survival Improves with Spleen Length Reduction in Patients Receiving Ruxolitinib

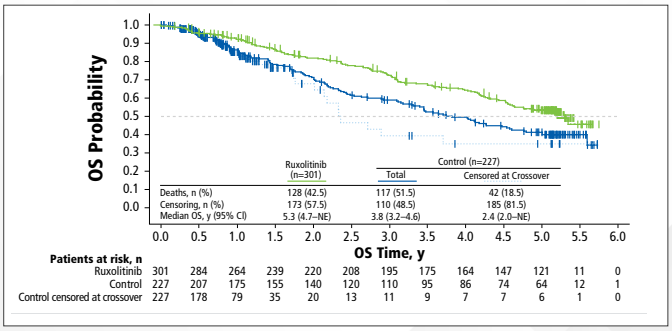
Open-label, single-arm phase 1/2 study (N = 107)



HR, hazard ratio; OS, overall survival.
Verstovsek S, et al. *Blood*. 2012;120(6):1202-1209.

- Here, this graph showing from the phase 1 study that the degree of splenic reduction correlated with the survival benefit. So that achieving response matters. And that gets back to our further validation that having adequate dose intensity probably is very important in terms of having a survival benefit.

Overall Survival Improves with Ruxolitinib: Pooled Analysis 5-Year Data COMFORT-I and COMFORT-II

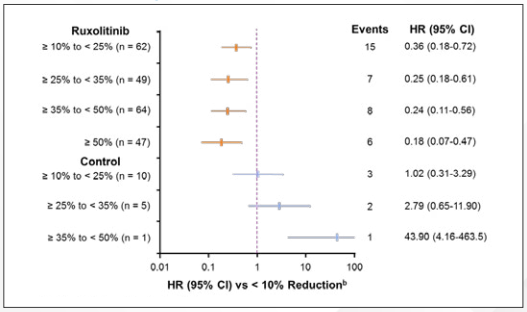


NE, not estimable; OS, overall survival.
Verstovsek S, et al. *J Hematol Oncol*. 2017;10(1):156.

- Here's showing what those survival curves look like in a pooled analysis between COMFORT-I and COMFORT-II.

Correlation of Spleen Volume Reduction at week 24 and OS

Pooled Analysis COMFORT-I and COMFORT-II

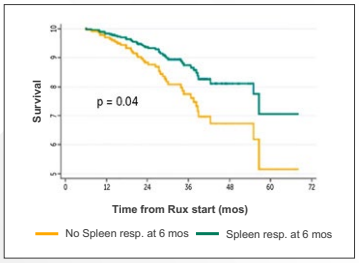


[a] Includes patients known to be alive at week 24. [b] Category includes patients with a < 10% reduction from baseline in spleen volume at week 24 or no assessment (ruxolitinib, n = 64; control, n = 189); among these patients, there were 26 deaths (events) in the pooled ruxolitinib group and 63 deaths in the control group.
HR, hazard ratio; OS, overall survival.

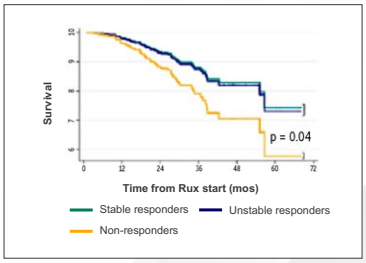
- Here's an analysis showing the correlation of spleen volume reduction at week 24 and with overall survival. Again, the greater the degree of splenic reduction, the greater the benefit.

Spleen Response Affects Outcomes of Ruxolitinib-Treated Patients With MF

OS by spleen response at 6 months[1]



OS by durability of spleen response[1]



Baseline factors associated with lower spleen response to RUX include High/Int-2 disease severity, spleen size >20 cm; high WBC; delay in RUX start after diagnosis, and titrated doses <10 mg BID.[2,3]

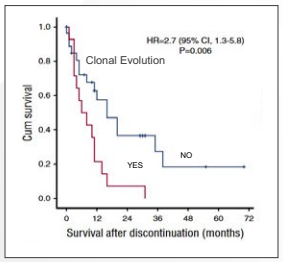
BID, twice daily; MF, myelofibrosis; OS, overall survival; Resp, responders; Rux, ruxolitinib; WBC, white blood cells.
1. Palandri F, et al. *Leuk Res*. 2018;74:86-88; 2. Palandri F, et al. *Oncotarget*. 2017;8(45):79073-79086; 3. Menghrajani K, et al. *Leuk Lymphoma*. 2019;60(4):1036-1042.

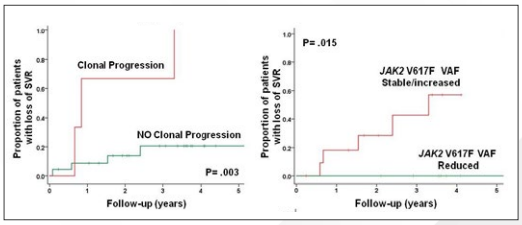
- Here, another analysis but going back to the same issue, patients live longer, that correlates with a degree of reduction in the spleen, correlates with the quality of the response. So patients are on suboptimal doses of ruxolitinib, and you're probably not seeing these kinds of benefits.

  Now what does failure look like? There are many individuals that have asked me over this 10- to 15-year period of time, "Okay ruxolitinib is helpful, but what does failure look like?" I often share the opinion that failure depends on what other options an individual has. So before we had other approved therapies, and fedratinib was the second approved therapy in the fall of 2019, we didn't have much else. So patients stayed on. And we knew that if they came off ruxolitinib, their survival was poor.

Clonal Evolution Contributes to/Indicates Ruxolitinib Failure

- About 50% of responder patients on Rux had lost response by 3 years in COMFORT-I and COMFORT-II study[1,2]



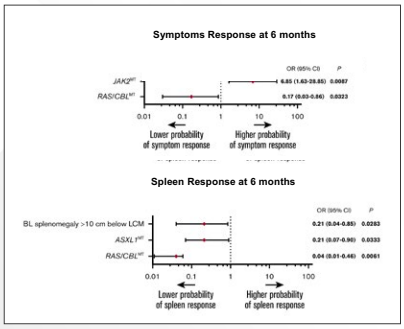


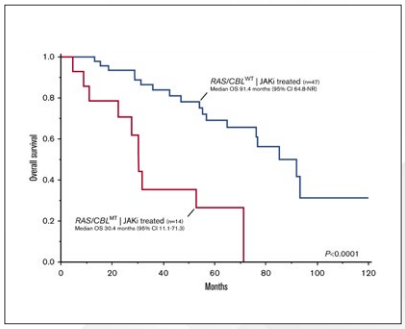
- Median duration of SVR of 10 mo vs not-reached in pts with or w/o clonal progression.[3]
- None of the 7 patients who showed decrease of ≥20% from baseline JAK2V617F VAF lost SVR compared to 6 out of 13 (46.1%) who showed stable or increased JAK2V617F VAF (HR=61.8,95% CI 1.01–870.2)[4]

Cum, cumulative; HR, hazard ratio; Rux, ruxolitinib; SVR, spleen volume reduction; VAF, variant allele frequency.
1. Verstovsek S et al. *J Hematol Oncol*. 2017;10(1):156. 2. Harrison CN et al. *Leukemia*. 2016;30(8):1701-1707. 3. Newberry KJ et al. *Blood*. 2017;130(9):1125-1131. 4. Pacilli A, et al. *Blood Cancer J*. 2018;8(12):122.

- And if they had clonal progression, it was even that much worse. So clonal progression and failing JAK inhibition, associated with worse survival.

RAS/CBL Mutations Predict Resistance to JAKi in MF





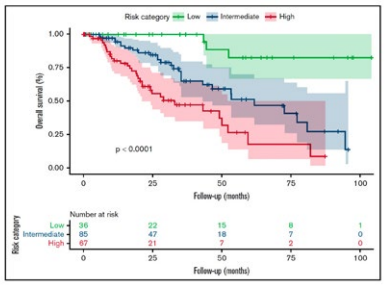
BL, baseline; JAKi, Janus kinase inhibitor; LCM, left costal margin; MF, myelofibrosis; OR, odds ratio; MF, myelofibrosis; MF-RUXO time interval, time interval between myelofibrosis diagnosis and initiation of JAKis.
Coltro G, et al. *Blood Adv*. 2020;4(15):3677-3687.

- There are certain mutations that have been somewhat predictive to resistance. Primary resistance is not common, it's more common secondary, but in particular, the RAS or CBL mutations predicting resistance to ruxolitinib.

RR6, a Model to Predict Survival After 6 Months of Ruxolitinib in MF

Parameters	Points
RUX dose <20 mg BID at BL, 3 mos, 6 mos	1
≤30% spleen length reduction at 3 mos and 6 mos	1.5
RBC transfusions at 3 mos and/or 6 mos	1
RBC transfusions at BL, 3 mos, 6 mos	1.5

Risk category	% of pts	OS (months)	HR	Score
Low	19	NR		0
Intermediate	45	61	43-80	1-2
High	36	33	21-50	≥2.5



RR6 prognostic model[1]

BID, twice daily; BL, baseline; HR, hazard ratio; MF, myelofibrosis; OS, overall survival; RBC, red blood cell; RR6, Response to Ruxolitinib After 6 Months; RUX, ruxolitinib.
1. Maffioli M et al. *Blood Adv*. 2022;6(6):1855-1864.

- There is a new model, prognostic score, giving a sense of survival for individuals after 6 months of therapy with ruxolitinib. And those that are prognostically averse using a lower dose under 20 twice a day, less than a 30% spleen reduction at 3 or 6 months, red cell transfusions at 3 or 6 months, and red cell transfusions at baseline and at 3 and 6 months. With those, you can help differentiate really those with a much poorer survival versus less. And again, a model that can be helpful as we're contemplating an alternative: moving to a trial, stem cell transplant.

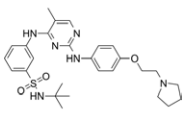
Fedratinib FDA Approved for MF* August 16, 2019

*With intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF).
FDA, US Food and Drug Administration; MF, myelofibrosis.
FDA.gov. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-fedratinib-myelofibrosis.

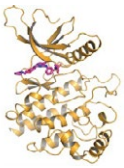
- Now, what about fedratinib. I mentioned that this was the second agent approved August of 2019.

Fedratinib

- Oral, JAK2-selective inhibitor with once-daily dosing approved in the US for treatment of intermediate-2 or high-risk primary or secondary (post-PV or post-ET) MF with platelet counts ≥50 × 10^9/L[1]
- Fedratinib has higher inhibitory activity for JAK2 over JAK1, JAK3, and TYK2[2]
- Fedratinib was investigated for treatment of MF in JAK-inhibitor-naïve patients in the phase 3 JAKARTA trial, and in patients previously treated with RUX in the phase 2 JAKARTA2 trial[3,4]
- JAKARTA and JAKARTA2 allowed enrollment of patients with platelet counts of ≥50 × 10^9/L at study entry[3,4]



FEDRATINIB



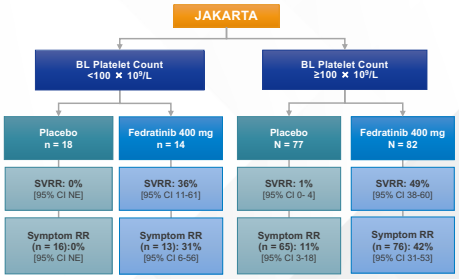
JAK2 KINASE DOMAIN – Fedratinib Complex[5]

1. INREBIC® (fedratinib) prescribing information. BMS; 10/2022. 2. Wernig G, et al. *Cancer Cell*. 2008;13:311-320. 3. Pardanani A, et al. *JAMA Oncol*. 2015;1(5):643-651. 4. Harrison CN, et al. *Lancet Haematol*. 2017;4:e317–324. 5. Hantschel O. *ACS Chem Biol*. 2015;10(1):234-245.

- This, a JAK inhibitor. Inhibitory of [...] JAK2 over JAK1, JAK3 and [TYK2], and also a FLT3 inhibitor. Approved for individuals with a platelet count greater than 50,000, and approved based on trials both in the front-line and second-line setting.

JAKARTA: Spleen Volume and Symptom Responses

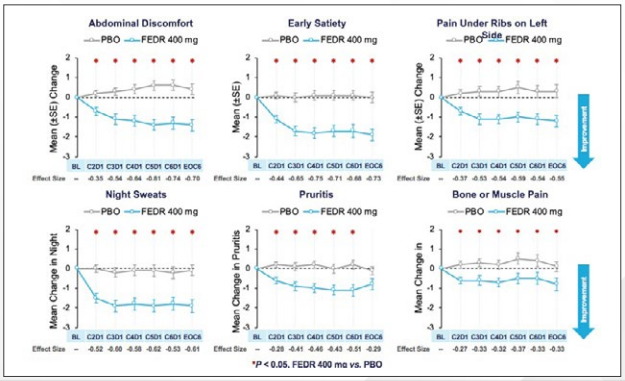
- Among all patients, SVRR (≥35% spleen volume reduction) was significantly higher with fedratinib 400 mg/day versus placebo (47% vs 1%, respectively; *P* < .0001)
- Symptom RR was also significantly improved with fedratinib overall
- Within the fedratinib 400 mg treatment arm there was no statistically significant difference in SVRR or symptom RR between BL platelet count subgroups



Statistical comparisons between BL platelet count subgroups should be interpreted with caution due to small sample sizes.
BL, baseline; NE, not estimable; RR, response rate; SVRR, spleen volume response rate.
Harrison CN, et al. *Blood* 2019;134(suppl 1):668.

- In the front-line setting, in the JAKARTA study for individuals, it was seen superior based on comparison to placebo for control of spleen and symptoms. Additionally, individuals could be treated with a platelet count between 50,000 to 100,000 with good evidence of response in spleen and symptoms, suggesting that it could be dosed fully in that group of individuals.

JAKARTA: Fedratinib Superior to Placebo for Individual Symptom Control

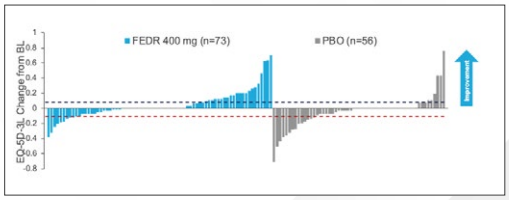


BL, baseline; CxDx, cycle *x* day *x*; EOC6, end of cycle 6; FEDR, fedratinib; PBO, placebo, SE, standard error.
Mesa RA, et al. *Blood* 2019;134(suppl 1):704.

- I led the analysis for the symptoms, and we saw superiority in terms of symptom control, both in aggregate but also by individual symptoms. So if you look at abdominal discomfort, early satiety, pain under the ribs, night sweats, itching, muscle or bone pain, all superior.

JAKARTA: Fedratinib Improved Patient-reported Overall Health Status at EOC6 per EQ-5d-3L

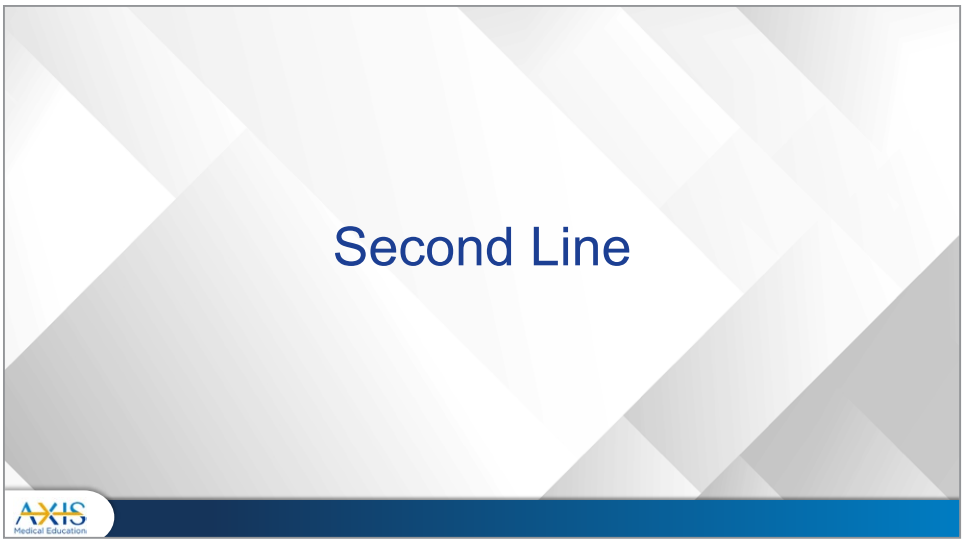
Mean EQ-5D-3L health utility score was clinically meaningfully improved at EOC6 with FEDR 400 mg



	FEDR 400 mg	PBO
LS mean change	0.039	–0.040
P	.008	

Mean EQ-5D-3L health utility score at baseline was 0.70 in the FEDR 400 mg arm and 0.72 in the PBO arm
EOC6, end of cycle 6; EQ-5d-3L, EuroQol with 5 dimensions and 3 levels of severity; FEDR, fedratinib; HRQoL, health-related quality of life; LS, least squares; PBO, placebo.

- There was an improvement in quality of life. Again quality of life assessed by the EQ-5D. And you see here that superiority.



- Now it is also approved in the second-line setting.

JAKARTA2: Patient Cohorts

- Fedratinib 400 mg QD for consecutive 28-day cycles
- ITT population: all 97 patients enrolled in JAKARTA2
- Ruxolitinib failure cohort: 79 patients who met new, stringent definitions of ruxolitinib relapsed/refractory or intolerant
- Sensitivity cohort: the subset of 66 patients within the ruxolitinib failure cohort who received 6 cycles of fedratinib, or who discontinued fedratinib before cycle 6 for reasons other than "study terminated by sponsor"

ITT Population	Ruxolitinib Failure Cohort
• Ruxolitinib treatment for ≥14 days, and resistant or intolerant to ruxolitinib per investigator discretion: – Resistant: No response or stable disease, evidence of disease progression, or loss of response – Intolerant: Discontinuation due to unacceptable toxicity	Relapsed: Ruxolitinib treatment for ≥3 mo with regrowth, defined as <10% SVR or <30% decrease in spleen size from baseline, following an initial response Refractory: Ruxolitinib treatment for ≥3 mo with <10% SVR or <30% decrease in spleen size from baseline Intolerant: Ruxolitinib treatment for ≥28 days complicated by development of RBC transfusion requirement (≥2 U/mo for 2 mo); or grade ≥3 thrombocytopenia, anemia, hematoma, and/or hemorrhage while receiving ruxolitinib

AXIS Medical Education

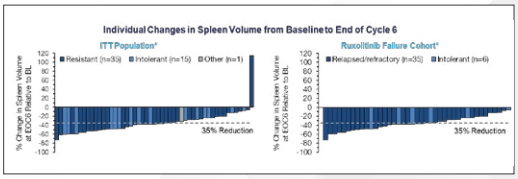
QD, once a day; ITT, intention-to-treat; RBC, red blood cell; SVR, spleen volume reduction.
Harrison CN, et al. European Hematology Association 2019 annual meeting. Abstract PS1459.

- The JAKARTA-2 study was for individuals that had failed ruxolitinib. This was a trial that both myself and my colleague Dr. Claire Harrison, and then we did a subsequent analysis with a stricter definition of ruxolitinib failure and intolerance.

JAKARTA2: Spleen and Symptom Response Rates

- Clinically relevant prognostic baseline disease characteristics indicate a population of difficult-to-treat patients with advanced MF disease and high disease burden
- Spleen volume and symptom response rates were consistent among the 3 patient cohorts
- Median duration of spleen response (months) was not reached (95% CI 7.2-NR) in the ITT population, ruxolitinib failure cohort, or sensitivity cohort

Variable	ITT Population (N = 97)		Ruxolitinib Failure Cohort (N = 79)		Sensitivity Cohort (N = 66)	
	n	% of Patients (95% CI)	n	% of Patients (95% CI)	n	% of Patients (95% CI)
Spleen volume response rate	97	31% (22-41)	79	30% (21-42)	66	36% (25-49)
Symptom response rate*	90	27% (18-37)	74	27% (17-39)	62	32% (21-45)



*Includes patients with an evaluable baseline and ≥1 post-baseline MFSAF assessment.
BL, baseline, EOC6, end of cycle 6; ITT, intention-to-treat; MF, myelofibrosis; NR, not reached.
Harrison CN, et al. European Hematology Association 2019 annual meeting. Abstract PS1459.

With this, we found by more modern standards what is resistant, relapsed, refractory, or intolerant. We saw that about a third of individuals were able to achieve an adequate response in the second-line setting. This is important. This is a drug that I strongly feel is being underutilized for patients with myelofibrosis. Patients have an adequate set of blood counts, they have an inadequate response to ruxolitinib, please consider fedratinib.

FREEDOM: Fedratinib Safety Data – ASH 2022

Any grade AEs	Patients, %
At least one TEAE	89.5%
Serious AEs	7.9%
Anemia	60.5%
Thrombocytopenia	34.2%
GI-related	
Nausea	39.5%
Vomiting	18.4%
Diarrhea	39.5%

- Most GI AEs were grade 1/2 and decreased in subsequent cycles.
- No patients required treatment discontinuation due to low thiamine levels.
- There were no cases of WE reported.
- Few deaths occurred during treatment and follow-up; none were related to study medication.

In this first fedratinib study proactively assessing a GI mitigation strategy and thiamine monitoring, results showed GI AEs were easily mitigated and no WE was reported.

AEs, adverse events; ASH 2022, American Society of Hematology 2022 Annual Meeting; GI, gastrointestinal; TEAE, treatment-emergent adverse event; WE, Wernicke's encephalopathy.
Gupta V, et al. ASH 2022. Abstract 1711.

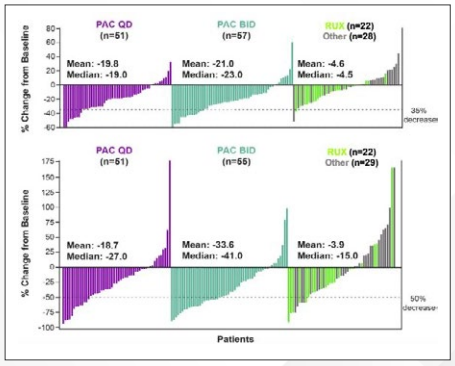
Now, fedratinib has a couple of toxicities one needs to be mindful of. It's not a limiter. But, one, there can be GI side effects, so typically do give them some anti-nausea pills and anti-diarrheal pills. Usually for most, that settles down and is not a major limiter. Two, it does have a black box warning but it's very manageable. We identified in the earlier studies that patients can have a low rate of the development of Wernicke's encephalopathy because of some impact of the agent in a handful of individuals on thiamine metabolites. If they have a low thiamine level, replace it, and monitor thiamine. In my practice, I will share that I just tend to put everybody on thiamine. It's cheap, it's not harmful, it takes care of the issue.

Pacritinib FDA Approved for MF*
February 28, 2022

*Intermediate or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis with a platelet count below 50 × 10^9/L
FDA, US Food and Drug Administration; MF, myelofibrosis.
FDA.gov. https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-drug-adults-rare-form-bone-marrow-disorder

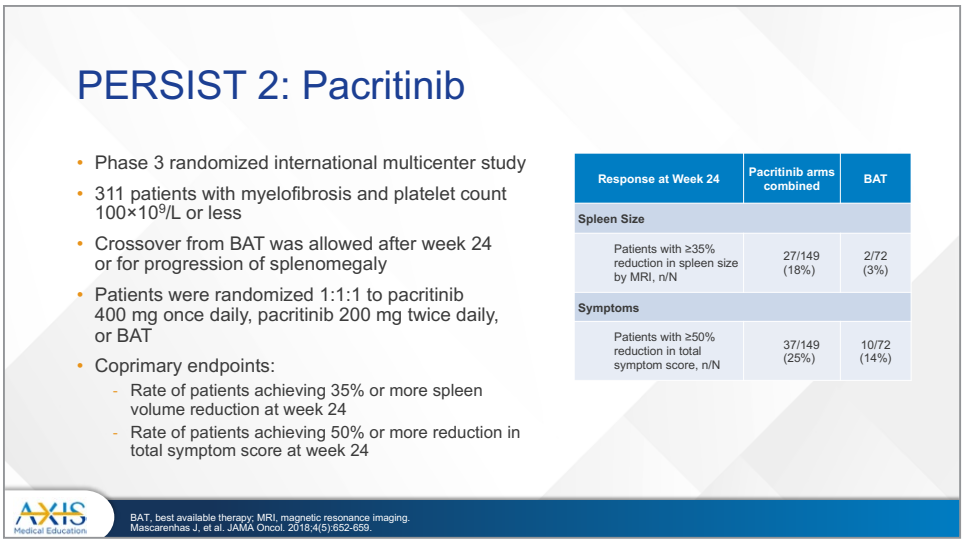
- Pacritinib, the most recently approved of the myelofibrosis drugs approved in February of 2022.

PERSIST 1: Pacritinib Efficacy Analysis by Arm

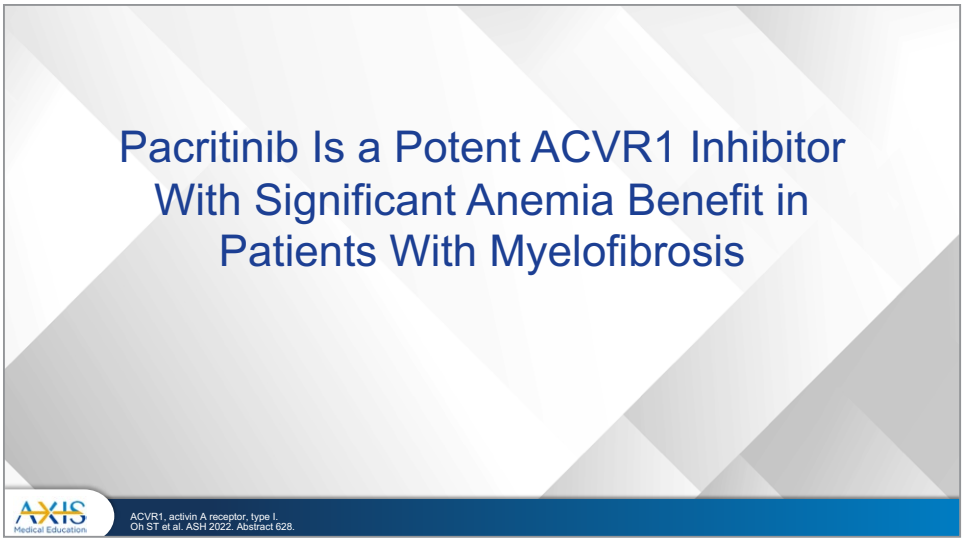


BID, twice daily; PAC, pacritinib; QD, dialy; RUX, ruxolitinib; SVR, spleen volume reduction; TSS, total symptom score.
Adapted from Mesa RA, et al. *Lancet Hematol.* 2017;4(5):E225-E236.

- Pacritinib is a JAK2 inhibitor, a FLT3 inhibitor, inhibits IRAK1, inhibits ACVR1, as well. And what's been identified from early days is that it can help to improve the spleen and symptoms and can be given even in individuals with a marked thrombocytopenia. But it can be given at full dose, even in an individual that is platelet transfusion dependent. That is helpful. This is a clear subset and unmet need for individuals with myelofibrosis. In some of these individuals, the platelets will improve. It does not necessarily improve platelets, but it can. Its main benefit is that it can be given a full dose and be more effective in this group of individuals. We are also seeing some evidence that it might be helpful in terms of improving anemia.



- PERSIST-2 was a trial done with patients with a platelet count of less than 100,000. And here, it was vastly superior to helping control spleen and symptoms compared to those control arms.



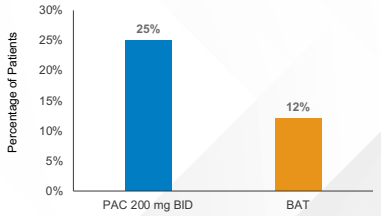
- Now it was shared at the most recent ASH [American Society of Hematology] that it's a potent inhibitor ACVR1. This is a marker of inflammation that we think may help to contribute to anemia. Inhibiting this may help to improve anemia.

Pacritinib in Cytopenic Myelofibrosis

- Approved in patients with MF who have a platelet count <50x10^9/L
- Able to be administered at the full approved dose (200 mg BID) regardless of cytopenias[1-3]
- Demonstrated hemoglobin improvement in randomized PERSIST-2 study[2]
- The underlying mechanism and extent of anemia benefit has not been fully described
- Diarrhea is a common side effect

Clinical Improvement in Hemoglobin[2]

PERSIST-2, Week 24



IWG criteria: among patients with baseline hemoglobin <10 g/dL, increase of ≥2.0 g/dL or RBC transfusion independence for ≥8 weeks

BAT, best available therapy; BID, twice daily; IWG, International Working Group; MF, myelofibrosis; RBC, red blood cell.
1. Mesa R, et al. *Lancet Oncology*. 2017. 2. Mascarenhas J, et al. *JAMA Oncol*. 2018;4(5):652-659. 3. Gerds A, et al. *Blood Advances*. 2020;4(22):5825-5835.

- It was shown in the PERSIST-2 study that there could be real clinical improvement in anemia. I presented the PERSIST-1 study at ASCO [American Society of Clinical Oncology] that showed similar benefits in spleen symptoms and anemia. This too can have GI side effects and overlaps with fedratinib in that regard. There is no blackbox warning as it relates to pacritinib.

Pacritinib Is a Potent ACVR1 Inhibitor

Pacritinib is ~4x more potent than momelotinib against ACVR1

	+ Control LDN 193189[a]	PAC C_{max} 213 nM	MMB C_{max} 168 nM	FED C_{max} 275 nM	RUX C_{max} 47 nM
Replicate 1 ACVR1 IC_{50} (nM)	20.4	22.6	70.2	312.0	>1000
Replicate 2 ACVR1 IC_{50} (nM)	32.4	10.8	34.9	235.0	>1000
Mean ACVR1 IC_{50} (nM)	26.4	16.7	52.6	273.5	>1000
Potency[b] (C_{max}:IC_{50})	N/A	12.7	3.2	1.0	<0.01

Legend

Higher potency

Lower potency

[a]LDN 193189 is an ACVR1 inhibitor.
[b]Cmax is the maximum unbound plasma concentration at the clinical recommended dose in humans.
ACVR1, Activin A receptor type 1; Cmax, peak drug concentration; FED, fedratinib; IC50, inhibitory concentration 50%; MMB, momelotinib; PAC, pacritinib; RUX, ruxolitinib.

- Here showing this inhibitory property against ACVR1, which is shared with momelotinib, and not shared with fedratinib or ruxolitinib. This is one of the key reasons we feel that there is a greater likelihood of benefit for anemia. For pacritinib and momelotinib versus the controls.

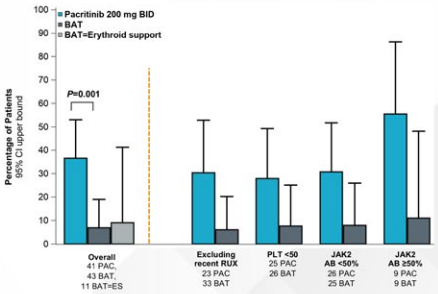
More Pacritinib Patients Achieved TI: PERSIST-2 Post-Hoc Analysis

TI Conversion Rate

Pacritinib N=41	BAT N=43	P-value
37%	7%	0.001

- TI conversion better on pacritinib than BAT, including patients receiving erythroid support agents as BAT
  - Erythroid support agents were prohibited on the pacritinib arm

Rate of TI (Gale criteria) through Week 24



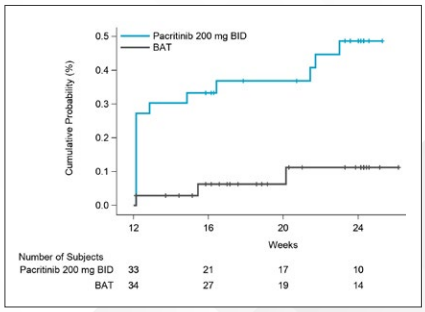
AB, allele burden; BAT, best available therapy; BID, twice daily; ES, erythroid support; JAK, Janus-associated kinase; PAC, pacritinib; PLT, platelets; recent RUX, no ruxolitinib in prior 30 days; TI, transfusion independence
Oh ST, et al. ASH 2022. Abstract 628.

- Here, looking at the achievement of transfusion independence on those on the PERSIST-2 study, you see the different subsets, and then it was better for achieving transfusion independence. Overall, with those who have thrombocytopenia, those with JAK2, different allele burdens, and those excluding recent ruxolitinib. So really, no matter how you're dividing these patients up, it could be potentially beneficial.

TI Conversion Can Occur Late in Treatment

- Many responses occurred early during treatment
- Some responses occurred after several months on treatment

Cumulative Incidence of TI (Gale criteria)

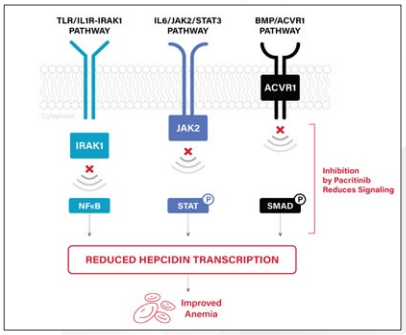


BAT, best available therapy; BID, twice daily; TI, transfusion independence.
Oh ST, et al. ASH 2022. Abstract 628.

- The transfusion independence can sometimes occur late in the course of treatment, here showing a differentiation against the best alternative therapy. Some did take a while. This an agent, give it some time, have some patience, you might see some nice benefits.

Hypothesized Mechanism of Anemia Benefit

- Potent, 24-hour inhibition of ACVR1 may function in conjunction with IRAK1 and JAK2 inhibition to reduce levels of hepcidin
- Hepcidin reduction ameliorates anemia of inflammation that occurs in myelofibrosis



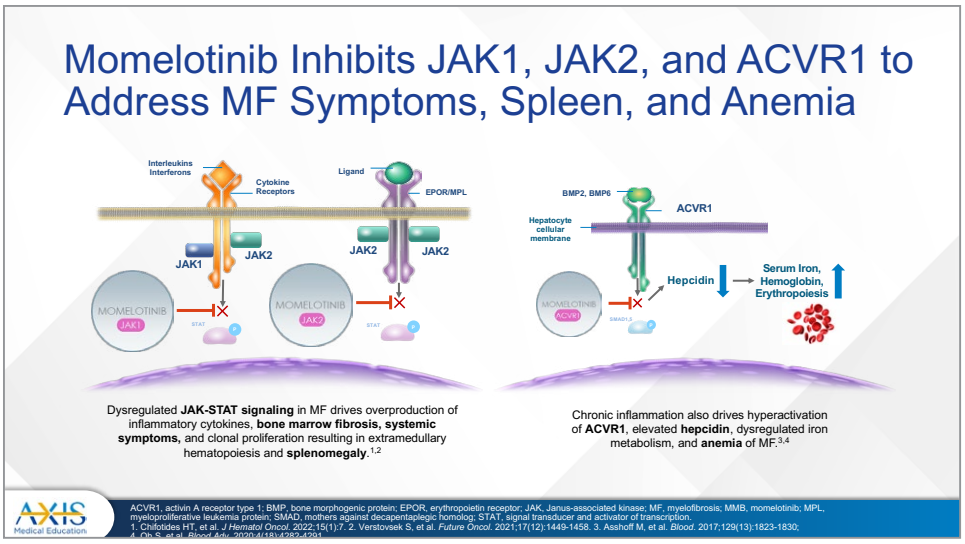
ACVR1, Activin A receptor type 1; BMP, bone morphogenetic protein; JAK2, Janus-associated kinase 2; IL6, interleukin-6; IRAK, interleukin receptor-associated kinase; STAT, signal transducers and activators of transcription; SMAD, suppressor of mother against decapentaplegic; TLR/IL-1R, toll-like receptor/interleukin (IL)-1 receptor. Oh ST, et al. ASH 2022. Abstract 628.

- Why did these things improve? Well, we've done a lot more with biology on this drug after its development. Again, inhibition of these additional pathways that are associated with the inflammasome, with elevations in hepcidin. Hepcidin is felt, again, to be a potential contributor to anemia of chronic disease. So you decrease that inflammation, you're allowing erythropoiesis to proceed more unrestricted, better improvements in anemia.

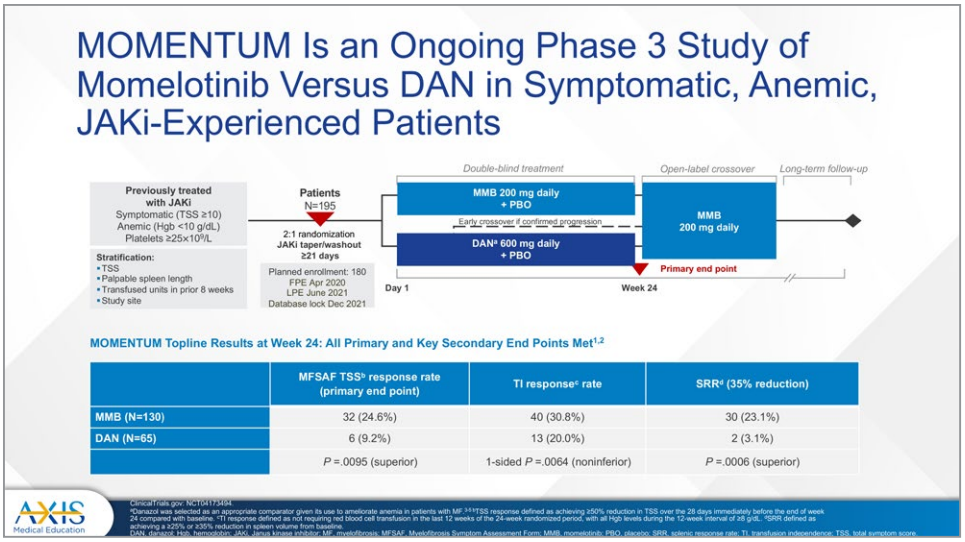
Momelotinib – FDA accepted NDA application for MF August 17, 2022

FDA, US Food and Drug Administration; NDA, new drug application; MF, myelofibrosis.
GSK.com. https://www.gsk.com/en-gb/media/press-releases/us-fda-accepts-new-drug-application-for-gsk-s-momelotinib-for-the-treatment-of-myelofibrosis/.

- Momelotinib is under review for an NDA application and may well be approved soon.

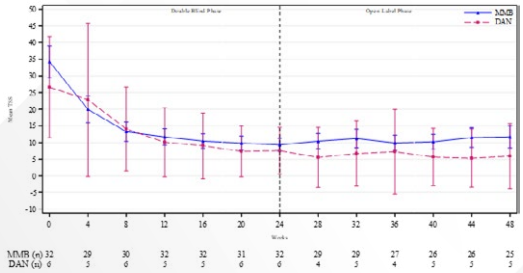


- It impacts, again, this ACVR1 that I was mentioning, with impacts on spleen and symptoms as well. Functionally, we learned of this because we had seen benefits of momelotinib for improving anemia. And then really did subsequent studies to try to figure out the mechanism. And it was really only in those mechanistic studies led by Stephen Oh and others, that identified this hepcidin story.



- Dr. Verstovsek and I, we co-lead the phase 3 study of momelotinib versus danazol in patients who were symptomatic, anemic, and had failed a JAK inhibitor. They were randomized against danazol with an open-label crossover of momelotinib itself. And with this, we were looking at improvements in spleen, symptoms, transfusions. And we saw that the trial met all of its key primary endpoints, superiority for symptoms, superiority for splenomegaly, and non-inferior for anemia.

Sustained Responses Were Observed in Week 24 Symptom Responders[a]



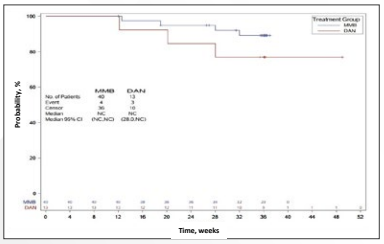
Of TSS responders at week 24, 1 of 32 (3%) MMB→MMB patients and 0 of 6 (0%) DAN→MMB patients had TSS ≥baseline in OL

[a]Defined as the proportion of patients who achieve ≥50% reduction in TSS over the 28 days immediately before the end of week 24 compared with baseline.
DAN, danazol; MMB, momelotinib; OL, open-label; TSS, total symptom score.
Gerds AT, et al. ASH 2022. Abstract 627.

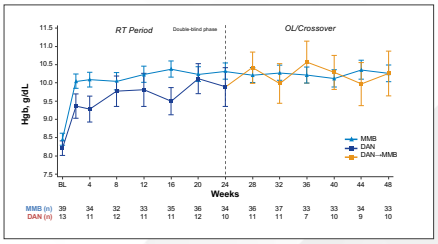
- At ASH of 2022, we showed that these benefits were durable.

Sustained Responses Were Observed in Week 24 TI Response[a]

TI Duration of Response in ITT Population



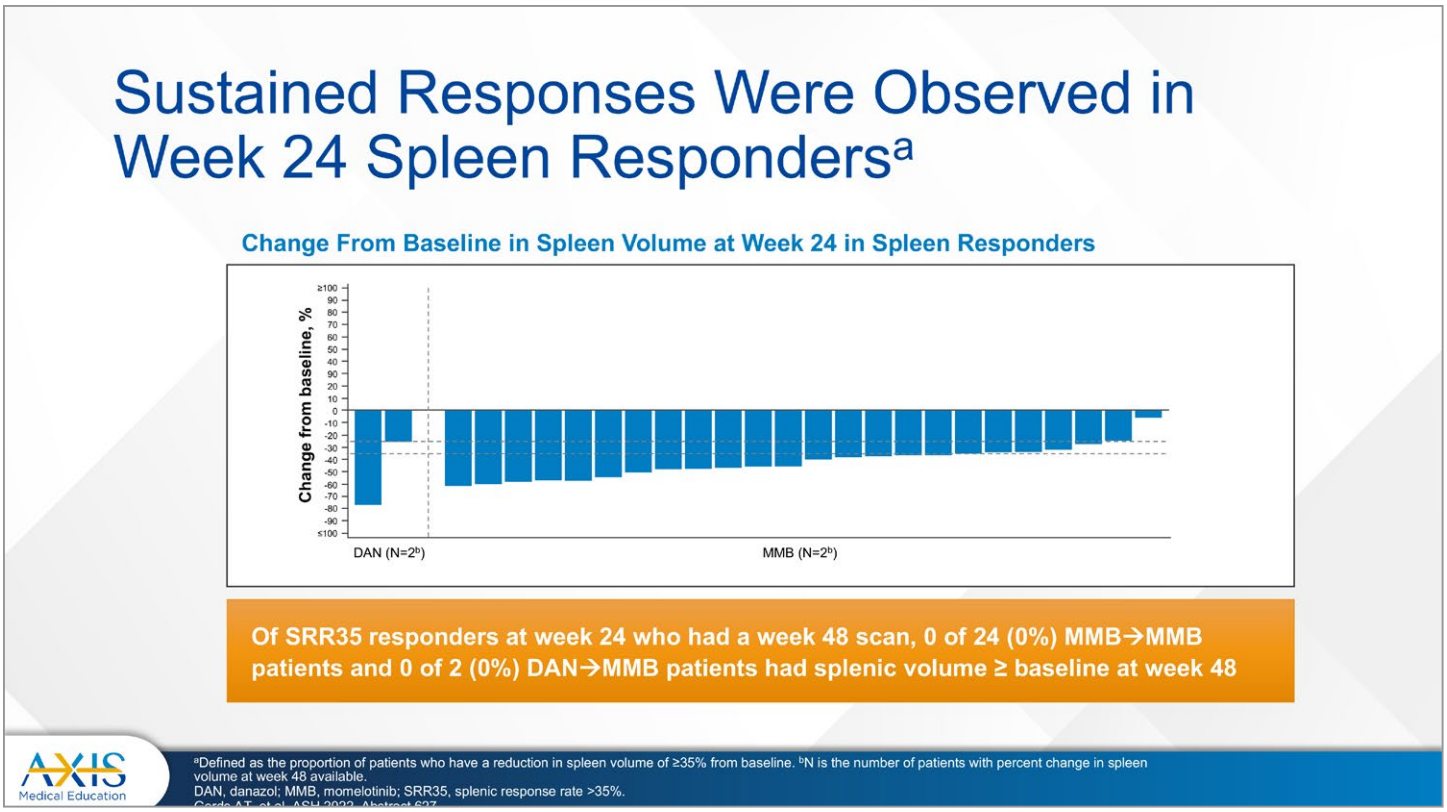
Mean Hgb Over Time in TI Responders



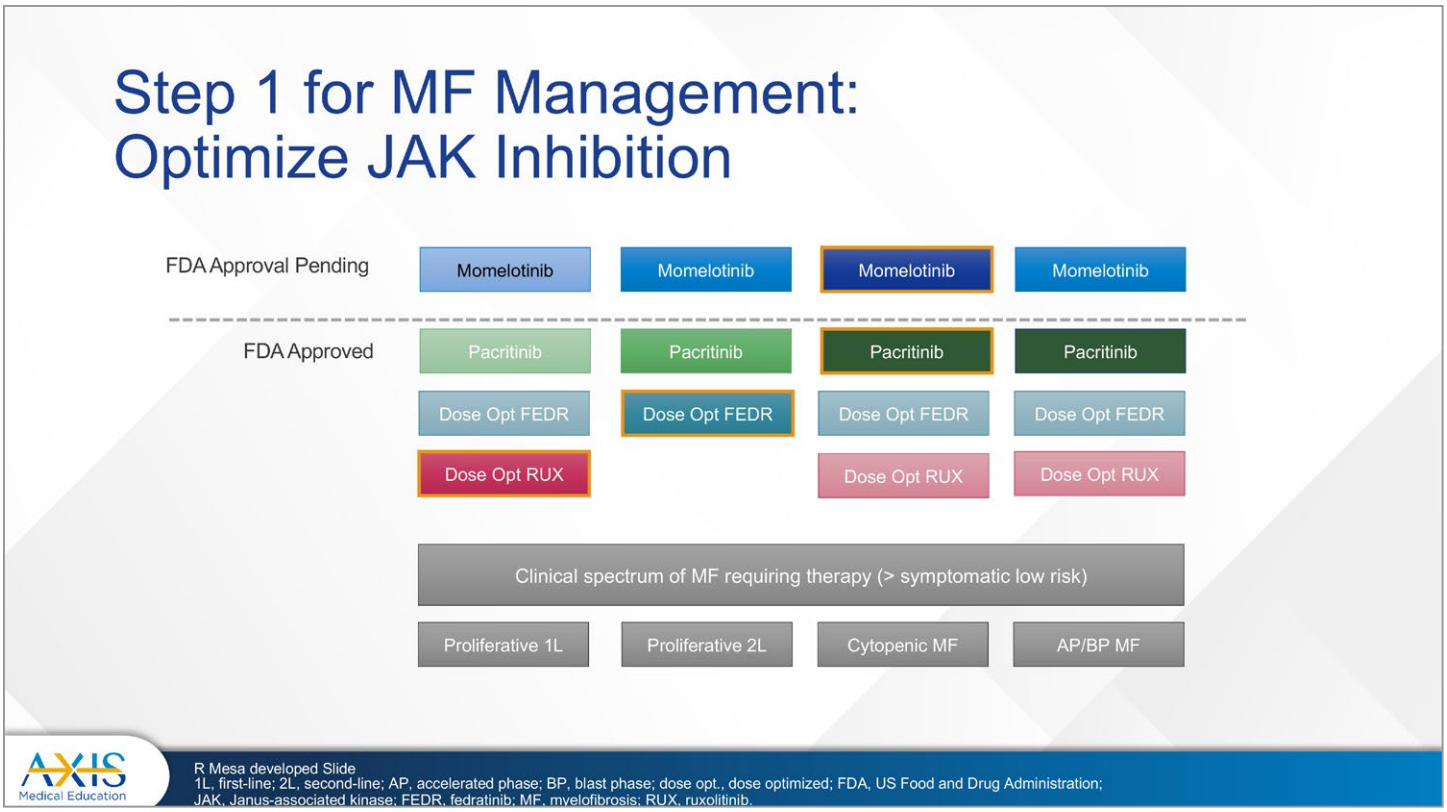
Of TI responders at week 24, 4 of 40 (10%) MMB→MMB patients and 3 of 13 (23%) DAN→MMB patients had an RBC transfusion or Hgb <8 g/dL in OL

[a]Defined as not requiring RBC transfusion in the prior 12 weeks and Hgb levels ≥8 g/dL.
BL, baseline; DAN, danazol; Hgb, hemoglobin; ITT, intention-to-treat; MMB, momelotinib; OL, open-label; RBC, red blood cell; RT, randomized treatment; TI, transfusion independence.

- So sustained responses in week 24 in these individuals. We saw in the transfusion-independent responses that they were stable and we looked on the panel on the right, the mean hemoglobin over time in transfusion-independent responders showed continued improvement, as well as individuals that were crossed over from danazol on to momelotinib had further improvements in their anemia.



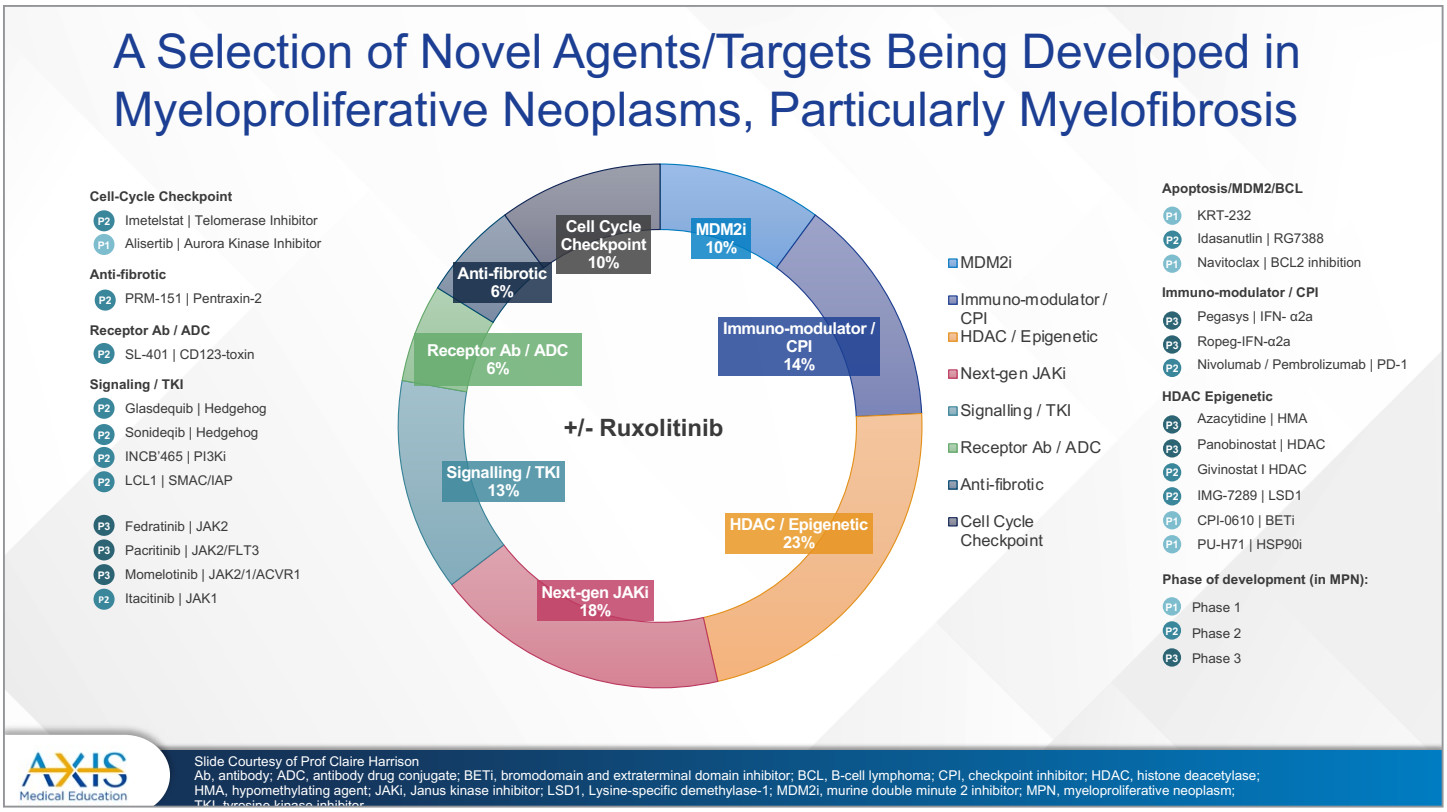
- Here are showing benefits in terms of improvements in splenomegaly. And you see here, as we see with many of these waterfall plots, all the patients had some reduction in splenomegaly, the reduction in 35%, is somewhat arbitrary. If one looks at the second-line improvement in like 25%, that is almost all of the individuals. We have long argued that a 35% volume reduction is probably too high a bar in the second-line setting, because really it's an individual that's already been on a JAK inhibitor, they've already probably had some reduction in splenomegaly. So here you're taking them to the next level.



- So how do you weave these drugs together? Well, if you look at this graph that I've developed for you, we have the approved drugs, and then the drugs where approval is pending. So first, proliferative frontline. Ruxolitinib clearly remains our initial standard, solid counts, normal counts, ruxolitinib. Fedratinib can be used and certainly, if an individual has contraindications to rux, it's a logical choice. They've had skin cancers they are susceptible to immunocompromised infections, they have issues with herpes zoster. Again it's a good drug, it certainly can be used in this setting. Pacritinib can but less likely to be given in this setting. Really rux or fedratinib would be in the NCCN guidelines.

  In the proliferative second-line setting, fedratinib clearly is the choice. You obviously can always consider a clinical trial, but in approved therapies, clearly fedratinib. In cytopenic myelofibrosis, pacritinib is our best choice. Anemia and/or thrombocytopenia, and/or anemia. Pacritinib can be given to individuals with a normal platelet count, and it can be active, although probably less preferred than the other agents, but for cytopenias, go with pacritinib. Ruxolitinib or fedratinib, probably would try pacritinib first but again you can always circle back to these. Momelotinib, if and when hopefully likely to be approved, clearly would overlap in this setting to some degree. Let's say anemia, plus or minus thrombocytopenia. Momelotinib again, has been tested for individuals with anyone with a platelet count of greater than 25,000.

  In accelerated or blast phase, none are great, all have some benefit. Approaches in this group probably have JAK inhibitors in combination, but meaningful impact on the disease likely requires moving toward a stem cell transplant.

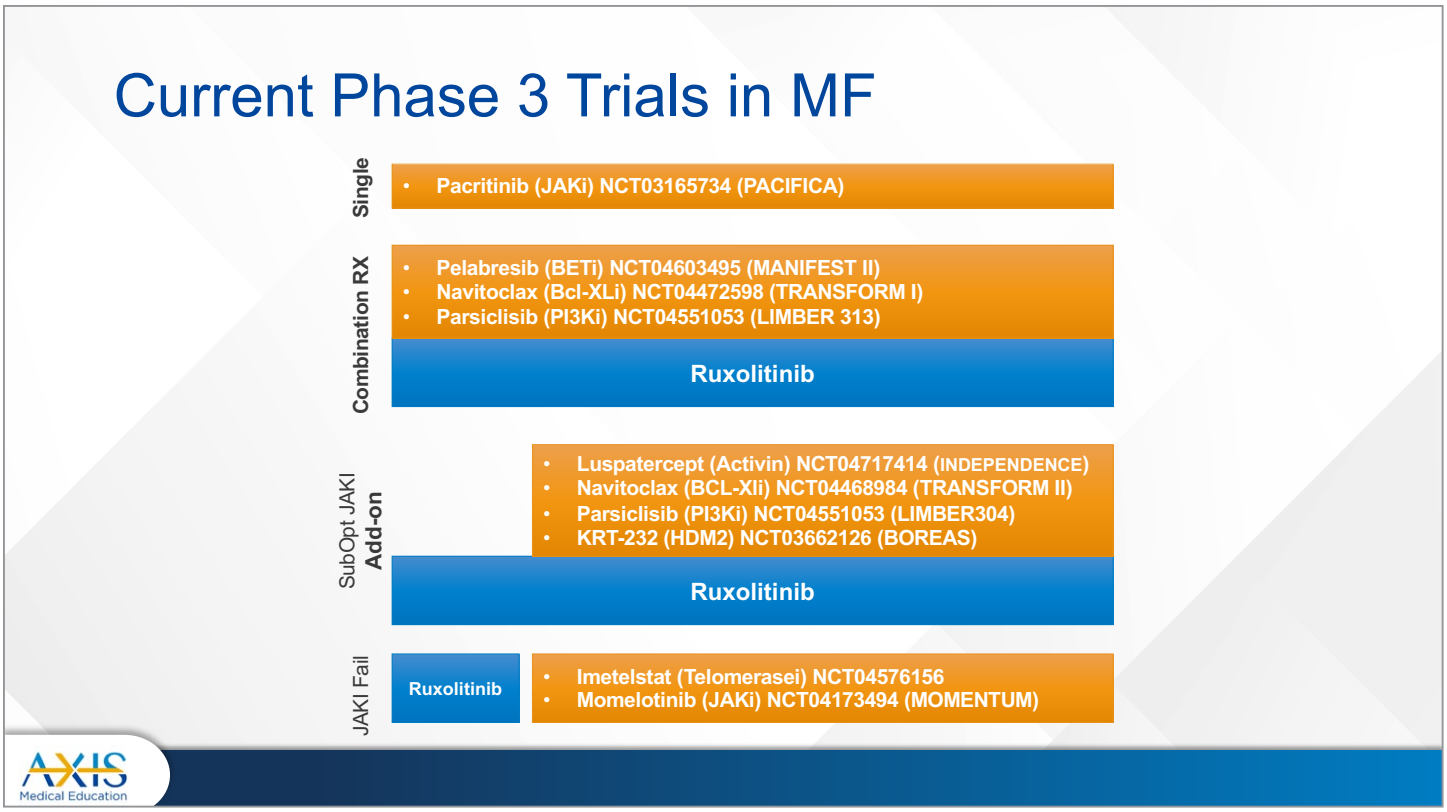


Now what about agents in development? There are many, and this is just a graphic just to show you the spectrum of additional mechanisms of action that are being targeted in addition to using ruxolitinib as a base. Now people ask the logical question, "Well, Ruben, what about if instead we use pacritinib or momelotinib or fedratinib?" All of that is a valid piece, that indeed, that any number of these other drugs may potentially be useful in combination. But however, it is best that they at least have some data to be sure that there is no drug–drug interactions or to get some sense of whether those results are really applicable.

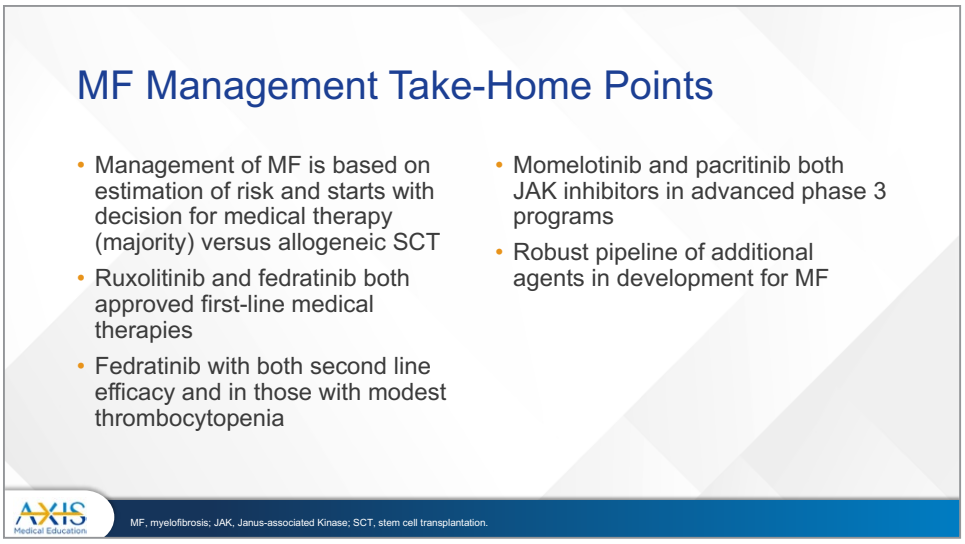
Now in terms of the class, we have really the cell-cycle checkpoint agents, imetelstat being furthest along, and that is in its own phase 3 trial, although as a single agent. We have the anti-fibrosing agent from Roche, PRM-151. We have the SL-401, the CD123 toxin that's undergoing testing. Signaling tyrosine kinase inhibitors, several of these are under testing. The JAK inhibitors, we've already discussed. We have furthest along the agents impacting MDM2. So you have the drug from Kartos, navtemadlin, that there was a couple of favorable abstracts at EHA 2023, may impact survival and other areas. There's idasanutlin, and there's a navitoclax impacting BCL-XL. Again, all interesting.

There are the immunomodulatory drugs, interferons. Interferons have long been used in low-risk MF or early MF. There are studies from ASH 2022, looking at pegylated interferon, along with ruxolitinib to try to improve spleen and symptoms. You have ropeg that there was a study at EHA 2023 looking at early MF. There are the checkpoint inhibitors, although they have been relatively disappointing in myeloid neoplasia, including MF, compared to their data in solid tumors. There are the HDAC inhibitors of which you have several there of interest, panobinostat, givinostat. You've got the BET inhibitor, pelabresib CPI-0610 that probably is the furthest along in phase 3 testing with combination impact.

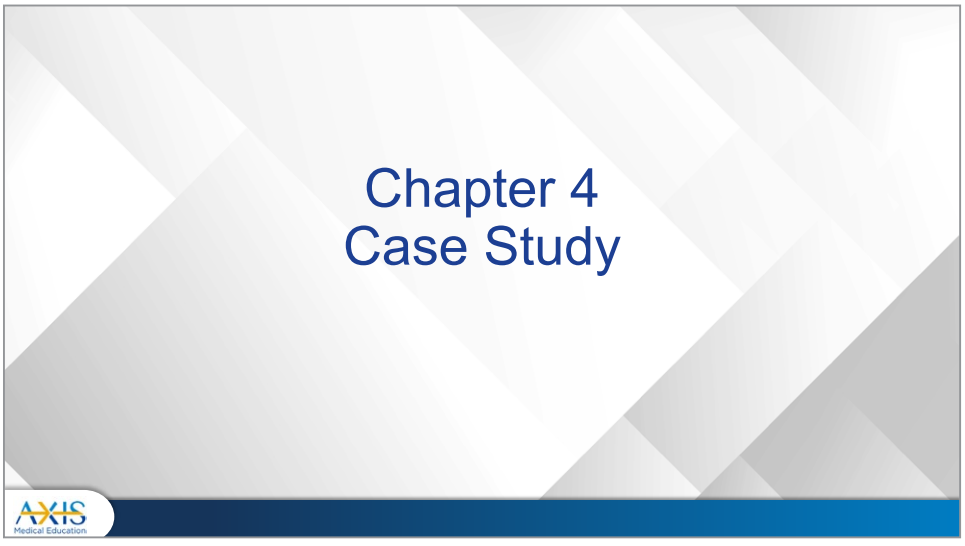
So again, a very robust pipeline of combination approaches, looking at a future with many more doublets for myelofibrosis.



- Indeed, there are currently more phase 3 trials and have ever been in testing at any given point in time for myelofibrosis. You have truly those agents looking at where ruxolitinib has failed. Let's use another drug on its own, momelotinib which was the MOMENTUM study I presented, as well as the telomerase inhibitor, imetelstat. That drug, interestingly, has seen a survival benefit, but with less correlation to improvements in spleen and symptoms, but can be used in and of itself, perhaps a different mechanism of action. You have the suboptimal responses to JAK inhibitors. Well, they again, we add on another agent, luspatercept, navitoclax, parsiclisib, and navtemadlin. I think in many ways, this approach is going to be the most patient friendly: give them a JAK inhibitor, if they don't have a great response, add in another drug. There are the combinations in JAK inhibitor-naïve patients; these are showing deeper levels of response. But will they be better? I think the trials will be really important to see that. Pelabresib plus rux, navitoclax plus rux.



- So, MF management key take-home points. First, the management of MF is based on the estimation of risk, and starts with your decision for medical therapy versus allotransplant. Rux and fedratinib are both approved first-line medical therapies. Now, if you're using, and you're not able to use full dose, and you have an inadequate response, we have other options now. I'd say that it is not infrequent that we're seeing patients being left on these agents too long without considering alternative therapy. Next, fedratinib, another shout-out, please consider it for second-line efficacy and also in those with modest thrombocytopenia. Momelotinib and pacritinib are both JAK inhibitors, and now pacritinib is an approved agent with momelotinib in an advanced phase 3 program. And there's a robust pipeline of additional agents in development for myelofibrosis. Indeed, I'm very hopeful by the potential impact of these agents in development.



- But let me share with you a case study.

Case: Introduction

- 2020: 72-year-old patient with MF
  - Primary MF
  - JAK2 mutated
  - MPN-10: 45 (out of 100)
  - 6 kg (13 lb) weight loss
  - Night sweats
  - Fatigue
- Spleen: 14 cm BLCM
- Hemoglobin: 9.5 g/dL
- White blood cell count: 14 x 10^9/L
- Platelets: 140 x 10^9/L

BLCM, below left costal margin; MF, myelofibrosis; JAK, Janus-associated Kinase; MPN, myeloproliferative neoplasm

- Here's an individual, 72 with MF, primary MF symptoms, weight loss, etc., big spleen, hemoglobin is 9.5, white count 14, platelets at 140.

Case (cont.)

MF Risks - DIPSS	Present
Age ≥65 years	X
Leukocytosis >25x10^9/L	
Hb <10 g/dL	X
Symptoms	X
Blasts >1% PB	

Intermediate 2 Risk MF

MF Patient Burden	Present
Symptoms (MPN-10: 30)	X
Splenomegaly	X
Anemia	X
Signs of progression	
Movement toward AML	

Symptomatic Intermediate 2 MF With Splenomegaly

Initiated Ruxolitinib

AML, acute myeloid leukemia; DIPSS, dynamic international prognostic scoring system; Hb, hemoglobin; MF, myelofibrosis; PB, peripheral blasts.

- This individual has intermediate-2 risk MF by the DIPSS. But by burden, has spleen, symptoms, anemia. This individual in 2023 begins ruxolitinib .

Case: 2023

- Initially had a IWG clinical improvement in
  - Splenomegaly (14 to 2 cm BLCM)
  - Symptoms (MPN-10: from 45 to 10)
  - Developed transfusion dependence
  - Moved away to live near grandkids
- Returns to see you
  - Taking ruxolitinib 5 mg BID
  - Spleen 14 cm BLCM
  - Symptoms MPN-10: 35
  - Hb 7.6 g/dL (last transfusion 3 weeks ago)
  - Platelets 40 x 10^9/L
    - Marrow
    - 3+ reticulin fibrosis
    - Karyotype 13q-
    - Blasts 6%
    - NGS: *JAK2, ASXL1, IDH1* mutation

BID, twice daily; BLCM, below left costal margin; IWG, International Working Group; Hb, hemoglobin; NGS, next-generation sequencing.

Now, let's say this individual initially has a response, the spleen shrinks, the symptoms decrease, but they develop transfusion dependence, and they get lost to follow-up. They're off in another state. They live near their grandkids. But they come back to see you. Now their ruxolitinib dose has dwindled down with their local physician, they advised them, 'Oh, we better cut that dose because of that anemia.' The spleen, back up to baseline. Symptoms, plenty of symptoms. They're needing transfusions, and their platelets are only 40, marrow shows fibrosis, they got 6% blasts. They have multiple mutations.

Case: 2023 (cont.)

MIPSS 70	Present
Hb <10 g/dL	X
WBC >25 x 10^9/L	
PLT <100 x 10^9/L	X
Blasts ≥2%	
Fibrosis >grade 1	X
Constitutional symptoms	X
Absence of CALR mutation	
HMR	
ASXL1	X
EZH2	
SRSF2	
IDH1/2	X
≥2 HMR	X

High-risk MF
5-yr overall survival: 34%

MF Patient Burden	Present
Symptoms (MPN-10: Score 30)	X
Splenomegaly	X
Anemia	X
Signs of progression	X
Movement toward AML	

What now?

AML, acute myeloid leukemia; CALR, calreticulin; Hb, hemoglobin; HMR, high mutation rate; MF, myelofibrosis; MIPSS, Mutation-enhanced International Prognostic Scoring System; Hb, hemoglobin; MF, myelofibrosis; PLT, platelets; WBC, white blood cell.

What should we do? This individual now by the MIPSS70 has a high-risk disease. They have clear disease burden. Do we go to transplant? Do we go to medical therapy?

Case Study Question

Which of the following would be appropriate second-line therapy based on NCCN guidelines?

a) Prescribe fedratinib instead of ruxolitinib
b) Increase dose of ruxolitinib to 10mg BID
c) Add venetoclax and azacitidine
d) Prescribe pacritinib instead of ruxolitinib
e) Unsure

BID, twice daily; NCCN, National Comprehensive Cancer Network.

- In this individual what would you do? Well, here would be some of the options. Should we prescribe fedratinib instead of ruxolitinib? Should we increase the dose of ruxolitinib to 10 twice a day? Should we add venetoclax and azacitidine? Should we prescribe pacritinib instead of ruxolitinib? Or unsure?

  I'll give you the answer. I think pacritinib would be the most preferred of these options. Platelets are under 50,000. They have spleen and symptoms. Venetoclax and azacytidine, pretty strong stuff, probably would not use that in this setting, maybe in acute leukemia but there the data on venetoclax are still mixed as it relates to MF. Increasing the dose further of ruxolitinib, unlikely to be tolerated, unlikely to get incremental benefit. And fedratinib in this setting, would be contraindicated due to the platelets of under 50,000.

Case: 2023 Alternative Labs

- Initially had a IWG clinical improvement in
  - Splenomegaly (14 to 2 cm BLCM)
  - Symptoms (MPN-10: from 45 to 10)
  - Developed transfusion dependence
  - Moved away to live near grandkids
- Returns to see you
  - Taking ruxolitinib 5 mg BID
  - Spleen 14 cm BLCM
  - Symptoms MPN-10: 35
  - Hb 7.6 g/dL (last transfusion 3 weeks ago)
  - Platelets 95 x 10^9/L
    - Marrow
    - 3+ reticulin fibrosis
    - Karyotype 13q-
    - Blasts 6%
    - NGS: *JAK2, ASXL1, IDH1* mutation

BID, twice daily; BLCM, below left costal margin; Hb, hemoglobin; IWG, International Working Group; Hb, hemoglobin; NGS, next-generation sequencing.

- Now what, using the same example, let's say we kept everything the same, but the platelets were higher at 95,000. How does that impact our choices?

Case: 2023 (cont.)

MIPSS 70	Present
Hb <10 g/dL	X
WBC >25 x 10^9/L	
PLT <100 x 10^9/L	X
Blasts ≥2%	
Fibrosis >grade 1	X
Constitutional symptoms	X
Absence of CALR mutation	
HMR	
ASXL1	X
EZH2	
SRSF2	
IDH1/2	X
≥2 HMR	X

High-Risk MF
5-yr overall survival: 34%

MF Patient Burden	Present
Symptoms (MPN-10: Score 30)	X
Splenomegaly	X
Anemia	X
Signs of progression	X
Movement toward AML	

What now?

AML, acute myeloid leukemia; CALR, calreticulin; Hb, hemoglobin; HMR, high mutation rate; MF, myelofibrosis; MIPSS, Mutation-enhanced International Prognostic Scoring System; Hb, hemoglobin; MF, myelofibrosis; PLT, platelets; WBC white blood cell.

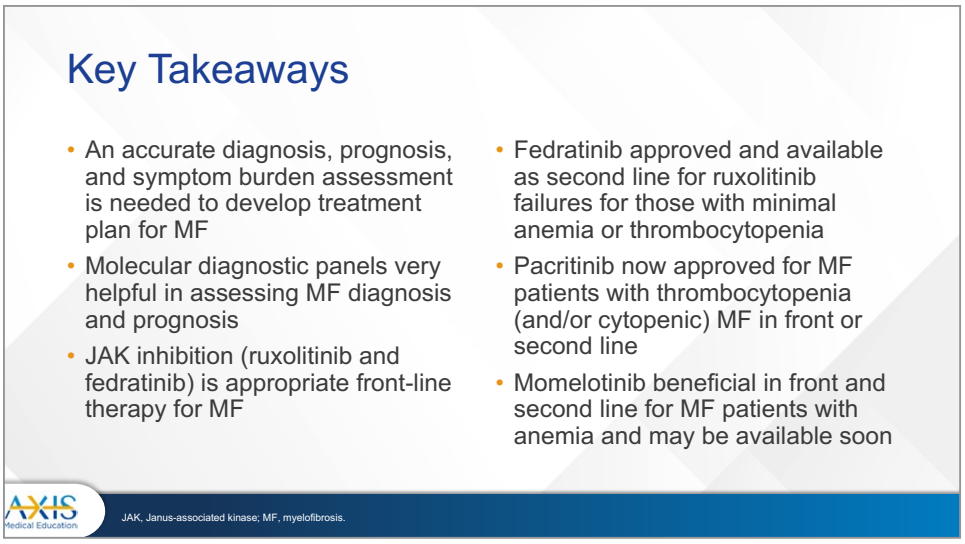
- Again, there's still high risk. What do we do?

Case Study Question

Which of the following would be appropriate second-line therapy for the management of this patient?

a) Prescribe fedratinib in combination with ruxolitinib
b) Add venetoclax and azacitidine
c) Prescribe axitinib instead of ruxolitinib
d) Switch to momelotinib (pending approval)

- So here are our options. Prescribe fedratinib in combination with ruxolitinib? Add venetoclax and azacitidine? Prescribe axitinib? Or switch to momelotinib? So here, the preferred option clearly is momelotinib. It helped to improve anemia, we don't have a label yet, but would fit with this individual. Platelet count well above the 25,000 tested, improved anemia, improved spleen, improved symptoms.



- Key takeaways. First, an accurate diagnosis, prognosis, and symptom burden assessment is needed to develop treatment plans for myelofibrosis. Second, molecular diagnostic panels are very helpful in assessing MF diagnosis and prognosis. JAK inhibition, either rux or fedratinib, are appropriate frontline therapies for MF. Fedratinib is approved and available as second line for ruxolitinib failures for those with minimal anemia and/or thrombocytopenia. Pacritinib now approved for MF patients with thrombocytopenia, for MF in either the front line or second line. And momelotinib is beneficial in the front and second line for MF patients with anemia, and hopefully will be available soon.

  Thank you very much.

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AXIS Medical Education, Inc. is a full-service continuing education company that designs and implements live, web-based, and print-based educational activities for healthcare professionals. AXIS provides convenient opportunities to engage learners based on their individual learning preferences through a full spectrum of educational offerings.

The executive leadership of AXIS combines 75 years of experience in adult learning theory, curriculum design/implementation/assessment, continuing education accreditation standards, and medical meeting planning and logistics. Our team has a deep understanding of the governing guidelines overseeing the medical education industry to ensure compliant delivery of all activities. AXIS employs an experienced team of medical and scientific experts, medical writers, project managers, meeting planners, and logistics professionals. This team is dedicated to meeting the unmet educational needs of healthcare professionals, with the goal of improving patient outcomes.

AXIS believes that partnerships are crucial in our mission to deliver timely, relevant, and high-quality medical education to healthcare professionals. To that end, AXIS partners with other organizations and accredited providers to offer added expertise and assist in expanding access to our educational interventions. AXIS also partners with numerous patient advocacy organizations to provide recommended patient education and caregiver resources in specific disease areas. AXIS finds value in these partnerships because they complement our core clinical curriculum with validated and relevant supplemental resources for busy clinicians and their patients.

The mission of AXIS is to enhance the knowledge, skills, competence, and performance of the interprofessional healthcare team to ensure patients receive quality care, resulting in improved patient outcomes. We engage healthcare professionals in fair-balanced, scientifically rigorous, expert-led certified educational activities designed to foster lifelong learning that is applicable to clinical practice and patient-centered care.

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