Moderator: Hello, and welcome to our accredited presentation entitled *Strategies for Improving Patient Outcomes in Myelofibrosis*.

Today's program is provided by MediCom Worldwide Incorporated and is supported by educational grants from Constellation Pharmaceuticals Incorporated, a MorphoSys Company; CTI Biopharma Corp.; Incyte Corporation; and Karyopharm Therapeutics Incorporated. It is now my pleasure to turn this webcast over to Dr. Jeanne Palmer, Associate Professor, Section Head of Hematology, Director of Blood and Marrow Transplant Program at the Mayo Clinic in Phoenix, Arizona. Dr. Palmer, the floor is now yours.

Dr. Jeanne Palmer: All right, excellent. Thank you very much for having me. Hopefully today we will learn a little bit more about myelofibrosis.

Learning Objectives

- Outline strategies for effectively and accurately diagnosing MF and for stratifying MF patients according to risk
- Correlate safety and efficacy data for new and emerging therapies in MF with patient types and clinical scenarios most appropriate for each
- Identify treatment emergent adverse events (TEAEs) associated with therapeutic options for MF and outline proactive clinical strategies for minimizing and/or mitigating these TEAEs if and when they develop
- Identify strategies for developing optimized, tailored treatment plans for individual patients with MF

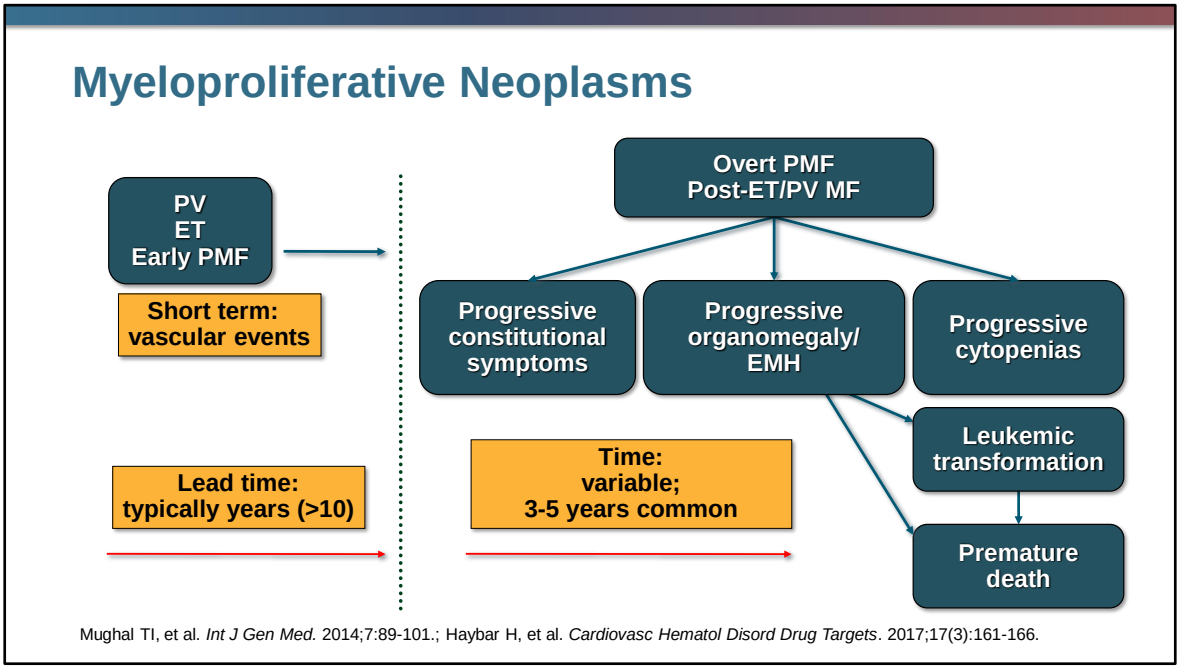
The learning objectives today are first to outline strategies for effectively and accurately diagnosing myelofibrosis and also how to stratify myelofibrosis patients according to risk. We want to correlate safety and efficacy data for the new and emerging therapies of myelofibrosis with patient types and clinical scenarios that are most appropriate. We want to identify treatment emergent adverse events associated with these therapeutic options and outline some proactive clinical strategies for minimizing or mitigating these adverse events when they develop. Finally, how do we identify strategies for developing optimized tailored treatment plans for individuals with myelofibrosis?

Faculty Disclosures

- **Dr. Jeanne Palmer,** faculty for this educational activity, has relevant financial relationships related to research from Celgene Corporation – A Bristol Myers Squibb Company (relationship has ended), MorphoSys AG, PharmaEssentia, Protagonist, and Sierra Oncology, Inc. (now GSK plc).

All of the relevant financial relationships listed for this individual have been mitigated prior to this activity.

These are my disclosures.



Let's start with talking about myeloproliferative neoplasms and how myelofibrosis fits into this category. Myeloproliferative neoplasms include things like polycythemia vera, essential thrombocythemia, early primary myelofibrosis, or prefibrotic myelofibrosis. In these diseases, we typically are worried about vascular events, symptom management and generally speaking, people may have these for a number of years before they develop myelofibrosis. A number of patients will have these diseases and not progress to myelofibrosis. Only about 10 to 15% of patients with PV or ET present to overt myelofibrosis or post-ET or PV myelofibrosis.

Now in the primary myelofibrosis, it got trickier in 2016 because they added this prefibrotic myelofibrosis, which largely behaves a little bit more like essential thrombocythemia. Usually, these patients have high platelets, but there are a couple other abnormalities that would suggest it's more of a prefibrotic myelofibrosis than a straight ET. Nonetheless, if they have a prefibrotic myelofibrosis, they generally are treated more like ET. What we're going to focus on today is overt primary myelofibrosis and post-ET/PV myelofibrosis.

This can be characterized by progressive constitutional symptoms, progressive organomegaly or extramedullary hematopoiesis, and progressive cytopenias. Patients who have this disease have a higher risk of transformation to leukemia and can have premature death. The timeframe in which this happens can vary substantially, three to five years is most common, probably because when people are diagnosed, but there are a number of patients, especially if they have good prognostic features that can go 10, 20 years with this disease.

Case 1: Joan, a 57-year-old Female

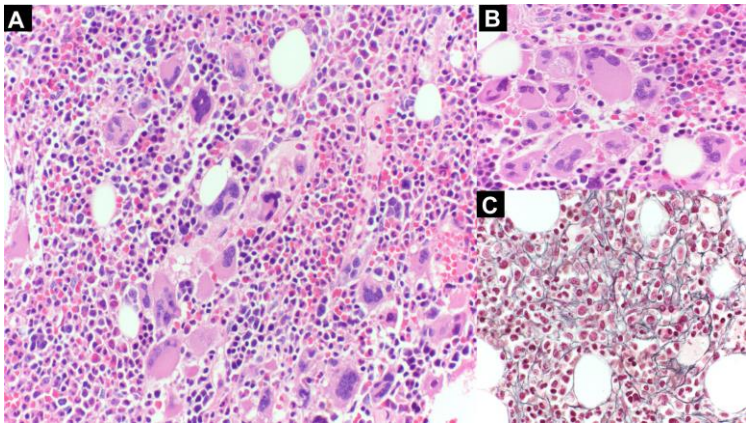
*HIPAA-compliant, stock photo (not actual patient).

Joan*

Patient Notes	• Patient was found to have a mild anemia, and platelets 512. Peripheral blood was found to have a JAK2 mutation • She has no constitutional symptoms and feels well
Work-up	• Iron studies normal, bone marrow biopsy scheduled

Case-based presentations are always a good way to get your mind in the right place so we're going to talk about this patient. Joan, a 57-year-old female. She was found to have mild anemia, platelets of 512, and in her peripheral blood she was found to have a JAK2 mutation. She has no constitutional symptoms and she feels well. She has a workup done to evaluate this and iron studies are normal so she gets bone marrow biopsy.

Bone Marrow Biopsy

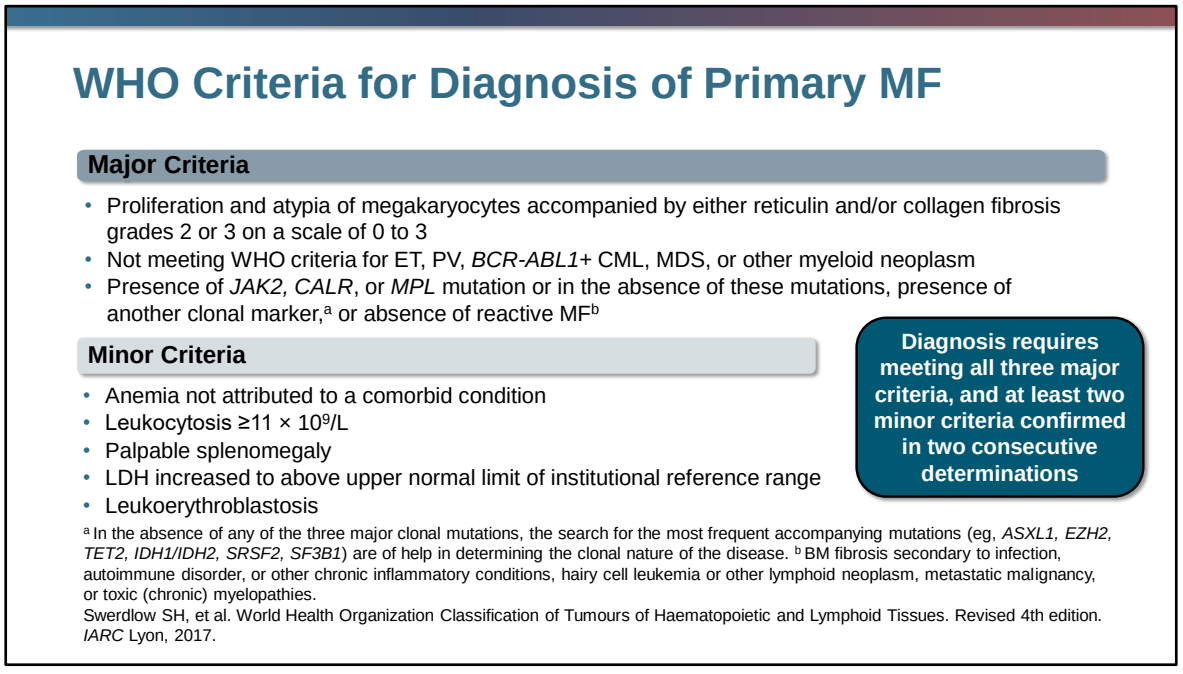


A. Hypercellular marrow, with clustering of atypical megakaryocytes

B. Close up of megakaryocyte clustering

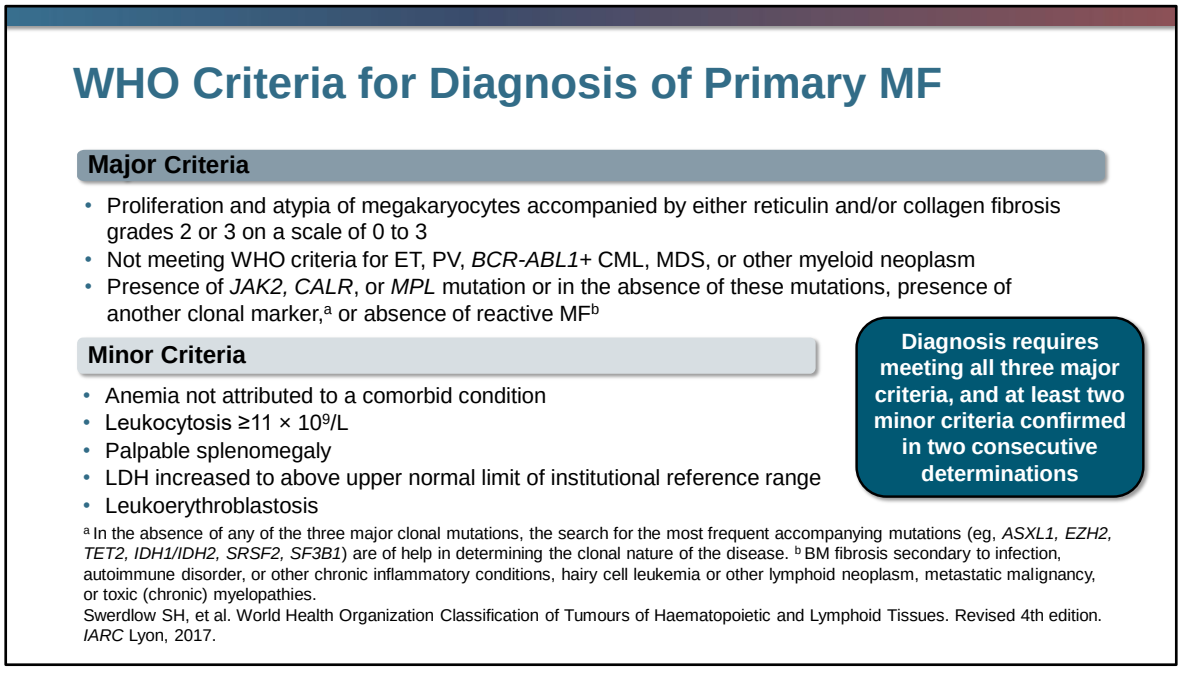
C. Reticulin stain noting dense increase in reticulin with extensive intersections

This is what her bone marrow biopsy looks like. There's a couple features here that are worth noting. First of all, when you look at the megakaryocytes, I'm pointing to those large amorphous pink-looking cells with the purple nuclei in it and those are very atypical. As you can see, they're clustering and you can see that best in the B frame there. In the C frame, you see reticulin staining and this basically looks for evidence of fibrosis. You can see a fair amount of intersecting lines, almost looks like a very disorganized set of country roads, but that is the fibrosis that is present.



When we look at the diagnostic criteria of myelofibrosis, there are three major criteria and five minor criteria. The major criteria, you want to see reticulin or collagen fibrosis of grade 2 to 3. Usually, that's on a scale of 0 to 3. They don't meet criteria for any other disorders, so sometimes patients with myelodysplastic syndrome can have fibrosis, sometimes patients with CML can actually have fibrosis. Just having the fibrosis by itself does not necessarily mean you have a diagnosis of primary myelofibrosis. Even in some cases, you can have reactive fibrosis in the marrow from autoimmune diseases or other malignancies. The other diagnostic criteria is presence of JAK2, calreticulin, or MPL, all three of which are driver mutations. In the absence of mutations, it's always good to see another clonal marker. Sometimes you will not see any of that, and then you want to make sure you're not dealing with a reactive myelofibrosis.

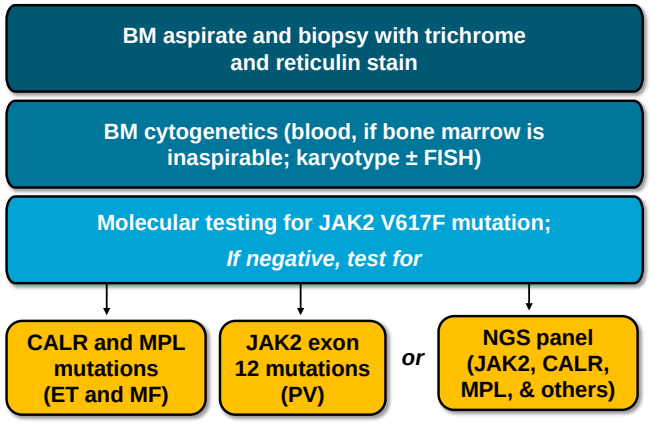
The minor criteria, you want to make sure the anemia is not attributed to a comorbid condition, but anemia is one of the factors that can be a minor criteria. Leukocytosis of greater than 11, palpable splenomegaly, LDH increased to above the upper limit of normal, and leukoerythroblastosis, meaning that you see all sorts of cells that should normally only live in the bone marrow, showing up in the peripheral blood.



The diagnosis requires meeting all three major criteria and at least two minor criteria confirmed in two consecutive determinations. You'll say, well, geez, what about people who don't have driver mutations? If they don't have a driver mutation or another clonal marker, as long as you really feel this is not reactive fibrosis in the marrow, then they would meet that major criteria. That being said, if you don't find any of these mutations, you probably want to really make sure you've done due diligence to rule out other possibilities that could contribute to fibrosis.

Pathology and Molecular Testing

In addition to laboratory workup and symptom assessment, organizations such as the NCCN recommend molecular/ genetic and pathology tests to help confirm a diagnosis, including:



NCCN Clinical Practice Guidelines in Oncology: Myeloproliferative Neoplasms. Version 3.2022. https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf. Accessed 4/12/23

When we think about how we work these patients up, they get a bone marrow biopsy with trichrome and reticulin stain, cytogenetics. Now many of these patients will have dry taps because they have so much scar tissue, you're unable to pull out the marrow. If the bone marrow is inaspirable, you can do fish on peripheral blood and karyotype. After all, many of the cells in the peripheral blood are actually marrow cells because they're growing in the spleen or really pop out into the peripheral blood a lot easier.

Then the molecular testing for JAK2. Now 50% of people who have primary myelofibrosis will have a JAK2 V617F mutation. If that is negative, you can look for CALR and MPL. If somebody you think may have had PV preceding this, there is a JAK2 mutation. It's on exon 12, it's not the same as the V617F mutation. There are next-generation sequencing panels which look for all sorts of other genes like the ASXL1, IDH mutations, etc.

Case 1: Joan, a 57-year-old Female – Additional Findings

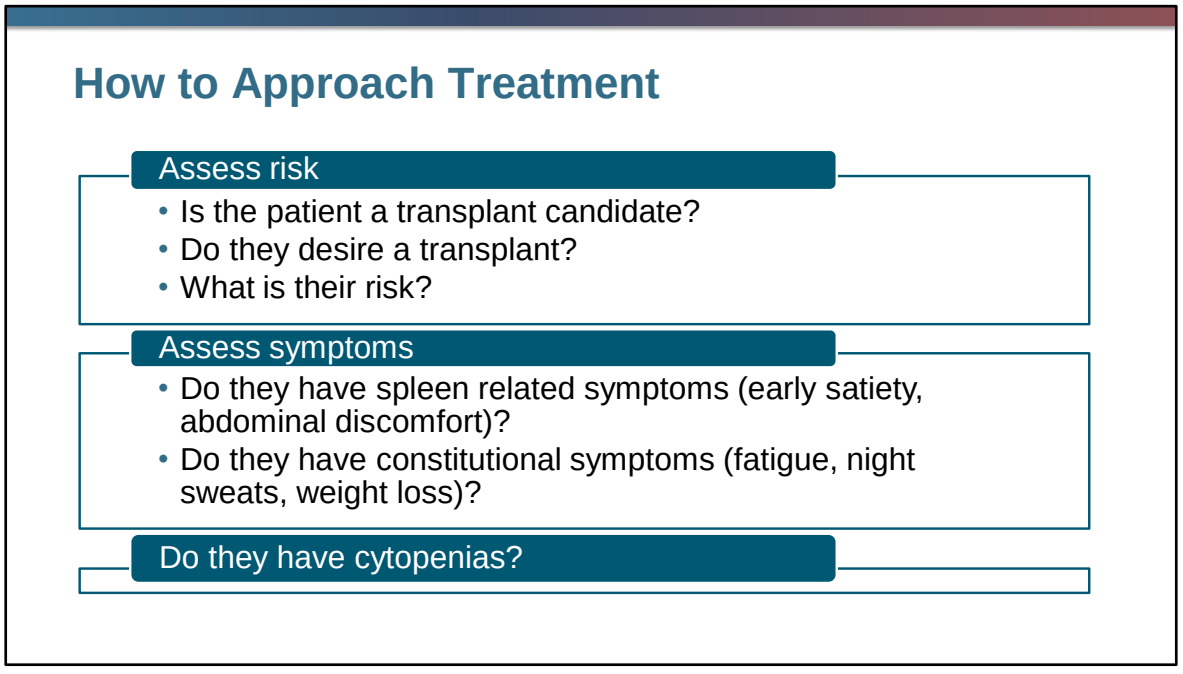
*HIPAA-compliant, stock photo (not actual patient).

Joan*

Additional findings

- Normal cytogenetics
- NGS shows JAK2, DNMT3A mutations
- No increase in blasts
- <1% peripheral blasts

Our patient, she has normal cytogenetics. She has a JAK2 mutation and next-gen sequencing shows a DNMT3A mutation. There's no increase in blasts in her marrow and in her peripheral blood, she has less than 1% peripheral blast.



When this patient is sitting in the office, there's going to be a couple of things that should be going through your mind. First of all, she's 57 and otherwise in good health, so is this patient a transplant candidate? Even if she's not ready for transplant at the given time, it is always important to have this consideration, because it helps get them to see a transplanter and at least start thinking of that, because even if they don't need it at that time, having that knowledge can be very helpful for patients in terms of planning.

Do they desire a transplant? That should be a question answered after they've met a transplanter. What is the risk? Because the risk of their disease largely factors into if they are going to be needing a transplant.

You want to look at their symptoms, and then do they have spleen-related symptoms such as getting full when they eat, having abdominal discomfort or constitutional symptoms such as fatigue, night sweats, and weight loss, and finally, do they have cytopenias?

The Evolution of Risk Stratification Models in MF

Parameter	IPSS	DIPSS	DIPSS Plus
Age >65 y	✓	✓	✓
Constitutional symptoms	✓	✓	✓
WBC >25 x 10^9/L	✓	✓	✓
Hb <10 g/L	✓	✓ **(two points)**	✓
Peripheral blasts ≥1%	✓	✓	✓
Platelet count <100 x 10^9/L			✓
RBC transfusion need			✓
Unfavorable karyotype			✓

Cervantes F, et al. *Blood*. 2009;113:2895-2901.; Passamonti F, et al. *Blood*. 2010;115:1703-1708.; Gangat N, et al. *J Clin Oncol*. 2011;29:392-397.

There's been a lot of risk models that have been developed for myelofibrosis, probably too many. When we look at this, the IPSS is the one that was developed initially and it's gone obsolete. The DIPSS, or the Dynamic International Prognostic Scoring System, is similar to the IPSS but gives more weight to the anemia with a hemoglobin of less than 10. The DIPSS-Plus also takes into account low platelets, the need for red blood cell transfusions, and unfavorable karyotype.

DIPSS and DIPSS-Plus Scoring

DIPSS/DIPSS-plus Scoring

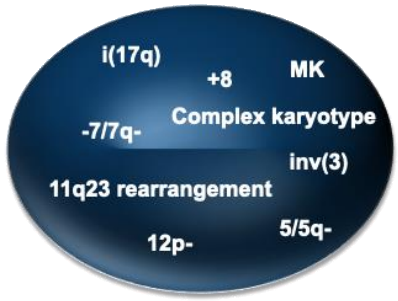
DIPSS Factors	Points
Age >65 ys	1
Symptoms	1
WBC >25,000	1
Hgb <10	2
Blood Myeloblasts >1%	1

DIPSS Risk Category	Points	Value for DIPSS *plus* risk
Low	0	0
Intermediate 1	1	1
Intermediate 2	2-3	2
High	≥4	3

DIPSS plus Factors	Points
Adv. Karyotype	1
Platelets <100k	1
RBC Transf.	1

DIPSS plus Risk	Points	Median survival (ms)
Low	0	185
Intermediate 1	1	78
Intermediate 2	2-3	35
High	4-6	16

Adverse Karyotypes



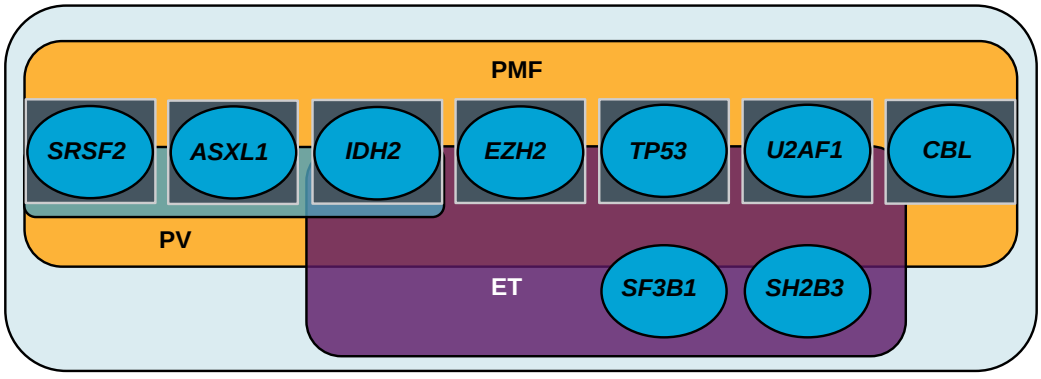
Tefferi A, et al. *Leukemia*. 2012;26:1439-1441.; Gangat N, et al. *J Clin Oncol*. 2011;29:392-397.; Caramazza D, et al. *Leukemia*. 2011;25:82-88.; Passamonti F, et al. *Blood*. 2010;115:1703-1708.

How are these scores generated? The DIPSS is a pretty easy score to generate because you basically add up these points. You can do it in your head in clinic once you've done it enough times. Then when you add on and you take that. Then to get to the DIPSS-Plus, you take the low intermediate, intermediate-2, or high risk, which you can see there really for the DIPSS, and then you add in extra factors. That gives you a number. You add in the extra factors such as adverse karyotype, platelets, or red blood cell transfusions, and ultimately then you get to their DIPSS-Plus risk.

Now there's median survivals given here. I think it's really, really important to remember that these scoring systems were developed prior to the approval of ruxolitinib, which is a very commonly used medication in myelofibrosis and may change survival. When talking to a patient, I'm always reluctant to give them survival times per se, because over the last 10, 15 years, we've really changed our approach to myelofibrosis and improved our treatment, so people are living longer with it. Where these may provide a good set of guardrails to understand a person's risk and are very helpful when thinking about how we define the risk when thinking of transplant, be very cautious in interpreting the survival times.

"Nondriver" Mutations

Prognostically Important Genes Other Than *JAK2/CALR/MPL* in ET, PV, and MF



Tefferi A, et al. *Blood Adv*. 2016;1:21-30.

What are the non-driver mutations? These are things that we look at that are mutations aside from the JAK2, CALR, or MPL. Those are felt to be driver mutations, and they really help develop the disease. Obviously, they're not the sole thing, because somebody can have PV, ET, or myelofibrosis and have a JAK2 mutation, or have the CALR and MPL and have either ET or primary myelofibrosis.

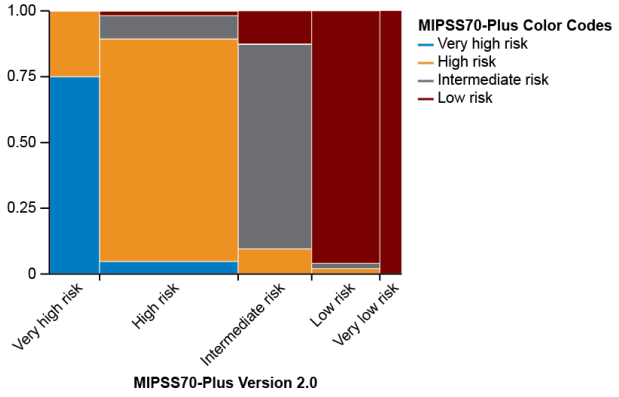
These extra non-driver mutations, there's a whole slew. Every panel has a different number of mutations ranging from 40 to 400. There's a couple of genes that seem to have come to be prognostically important, and that includes some of these genes in this yellow box, that primary myelofibrosis, so the SRSF2, ASXL1, IDH1 and 2, EZH2, TP53 which is fairly uncommon, U2AF1 and CBL.

MIPSS70 and MIPSS70-Plus

Key Elements

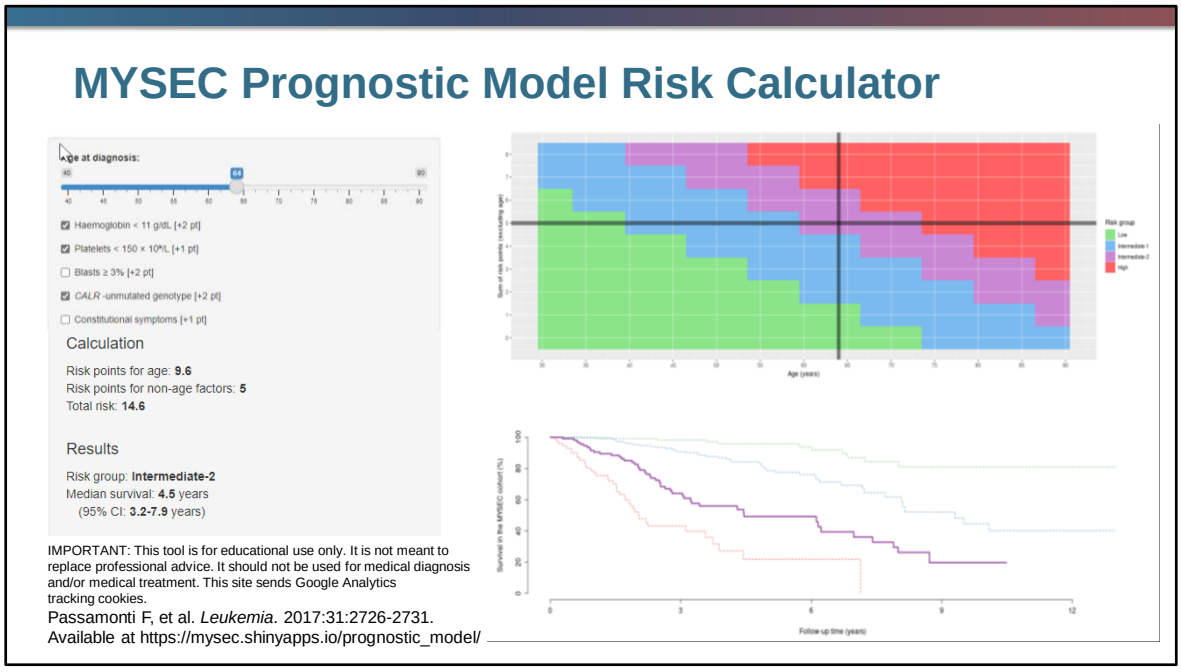
- **Hb <10 g/dL**
- WBC >25 x 10^9/L
- PLT <100 x 10^9/L
- **Blasts ≥2%**
- Fibrosis > grade 1
- **Constitutional symptoms**
- **Absence of type 1–like CALR**
- **HMR**
  - ASXL1
  - EZH2
  - SRSF2
  - IDH1/2
- **Two or more HMR mutation**

Unfavorable karyotype



http://mipss70score.it ; Guglielmelli P, et al. *J Clin Oncol*. 2018;36:310-318.; Vannucchi AM, et al. ASH 2017. Abstract A200.

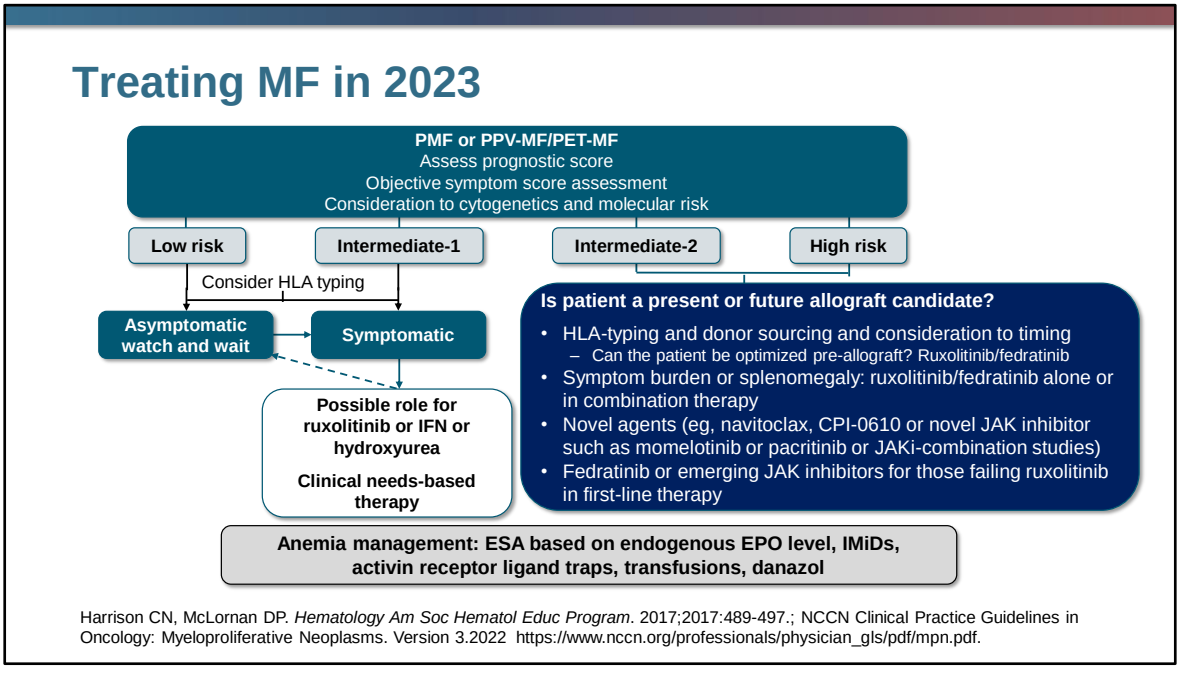
To account for these, they came up with the MIPSS70 and MIPSS70-Plus. Now this is actually a calculator you can go online that is good because then you can type in all their clinical factors and come up with what their risk score is. Then based on factors, now one of the things to keep in mind is that this score is heavily driven by mutations. If somebody has one or two high-risk mutations, it automatically puts them up into a higher-risk category. Nonetheless, this does provide another set of guidelines that may help us determine if we think their disease is going to be more indolent or more aggressive.



Finally, if they have secondary myelofibrosis all these scores I just talked about are actually only validated in primary myelofibrosis. If somebody has secondary myelofibrosis, you can look at the MYSEC score. This is also a calculator online, and that's actually how I do it all the time because it's a normogram. You take into account some clinical and laboratory features, and then you plot this on a normogram based on age, and that gives you what your risk is. For example, in a patient who is 64,who has a hemoglobin of less than 11, platelets of less than 150, and has a CALR unmutated genotype, meaning they have either a JAK2 or MPL, and they're 64, they would be considered intermediate-2 risk. This breaks it down nicely to different survival times.

Now, this was developed in 2017, so this was published after the availability of ruxolitinib. One of the groups that contributed to this, a lot of this came from Europe, and in Europe, they actually had ruxolitinib available to them at a later date. It was approved in the United States first. Many of these patients also were not exposed to ruxolitinib. Taking these actual median survival times, you have to do with caution.

Strategies for Improving Patient Outcomes in Myelofibrosis



Harrison CN, McLornan DP. *Hematology Am Soc Hematol Educ Program*. 2017;2017:489-497.; NCCN Clinical Practice Guidelines in Oncology: Myeloproliferative Neoplasms. Version 3.2022 https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf.

What is our treatment? How do we look at this patient? We have this 57-year-old, she has no symptoms, very mild cytopenia, and actually has thrombocytosis. Do we need to treat her? She would be considered low risk, based on the fact that she doesn't have a very high white blood cell count greater than 25,000. She doesn't have a lot of blasts in her peripheral blood. She doesn't have anemia, so she would actually be considered low-risk.

She's asymptomatic. She doesn't have spleen-related symptoms, doesn't have constitutional symptoms. In this case, a lot of times you can watch and wait. If she had some fatigue or if she had any constitutional symptoms or had high white blood cell count, she might be intermediate-1. Even in that case, if somebody comes in and doesn't have symptoms or spleen enlargement, I'm very, very reluctant to treat them.

Now if they have spleen enlargement, but they're not particularly bothered by it and have no symptoms and it gets into a little bit more gray area of whether they should be treated or not. Now patients who are intermediate to or high risk, even in that setting you have to use ruxolitinib with caution. Even just because they have a JAK2 mutation. If they aren't having spleen-related symptoms and constitutional symptoms, ruxolitinib doesn't really provide a lot of benefit and in fact can actually worsen anemia. When we take these patients, I think the most important thing when saying, what am I going to do for you today, really relies on a good assessment of the spleen and symptoms.

Case 1: Alternative Presentation for Joan, a 57-year-old Female

*HIPAA-compliant, stock photo (not actual patient).

Joan*

Patient Notes	• Patient was found to have a mild anemia (hgb 10.5), and platelets 512. Peripheral blood was found to have a JAK2 mutation • *She reports significant night sweats, fevers, weight loss, fatigue and early satiety*
Work-up	• Iron studies normal, bone marrow biopsy scheduled

Let's change this presentation a little bit. This patient was found to have mild anemia, 10.5. Her platelets are 512. Peripheral blood showed JAK2 mutation, but she reports significant night sweats, low-grade temperatures, weight loss, early satiety, and fatigue.

Case 1: Alternative Presentation for Joan, a 57-year-old Female – Additional Findings

*HIPAA-compliant, stock photo (not actual patient).

Joan*

Additional findings

- Normal cytogenetics
- NGS shows JAK2, DNMT3A mutations
- No increase in blasts
- <1% peripheral blasts

Everything else looks about the same. In this patient, because she has these additional symptoms with this, even though she actually would probably fall into the same risk category because she's so symptomatic, this would be a patient I would consider for ruxolitinib or some type of JAK inhibitor therapy. Let's talk about these JAK inhibitor therapies and how we use them.

Ruxolitinib: Overview of Phase 3 Trials COMFORT-I and II

- **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)
- Thrombocytopenia, which occurred frequently, was generally reversible and managed by dose reduction or temporary withholding

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

Ruxolitinib was the first approved, it was approved in, I think it was 2011 after the COMFORT-I and COMFORT-II studies were published. COMFORT-I took place in the United States and it was ruxolitinib versus placebo. So it was a blinded study. This study looked at a spleen volume reduction of 35% and then reduction in the total symptom score which is a set of questions. You asked that kind of judge symptoms and you want to see that reduced by 50%.

Now these were somewhat arbitrarily chosen. I think at the time it was felt that 35% spleen volume reduction likely represented something that would make somebody feel better and the total symptom score of 50%, again, was a number that was arbitrarily chosen for the purposes of the study. This has lasted for a long time and is an important thing to keep in mind.

What they looked at, they looked at, again, the spleen volume reduction in total symptom score. I will also point out this is really novel. This is probably one of the first studies that actually used patient-reported outcomes as a way of determining therapeutic success. In this summary, when we look at the COMFORT-I study, the spleen volume reduction of 35% was achieved in about 42% of patients receiving ruxolitinib and only 0.7 of those receiving placebo.

Ruxolitinib: Overview of Phase 3 Trials COMFORT-I and II

- **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

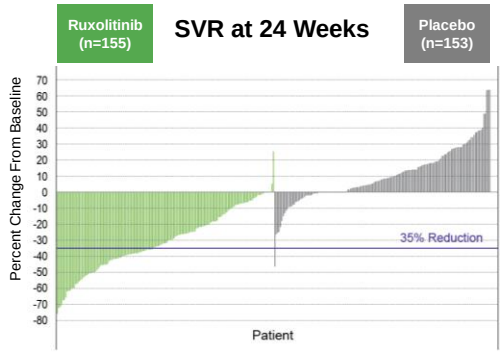
Summary

- 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)
- Thrombocytopenia, which occurred frequently, was generally reversible and managed by dose reduction or temporary withholding

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

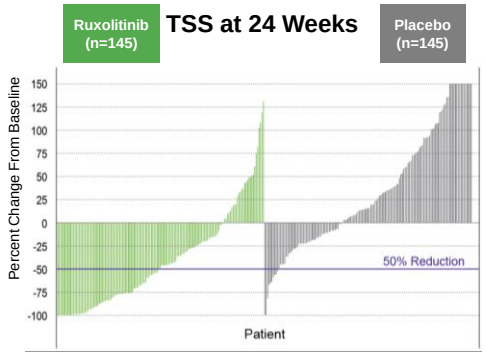
In the COMFORT-II study which was an open-label study using ruxolitinib versus best available therapy, 28% of patients who were in the ruxolitinib arm versus 0% in the best available therapy arm achieved that spleen volume reduction endpoint. Now, the biggest side effects that were seen were things like thrombocytopenia and anemia. This was generally reversible or managed with dose reduction or temporarily withholding the drug.

COMFORT-I: Key Efficacy Endpoints



41.9% ruxolitinib vs 0.7% placebo achieved SVR35[a]; *P*<0.001

OR, 134.4 (95% CI: 18, 1004.9); *P*<0.001



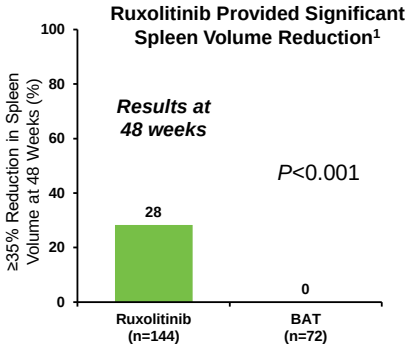
OR, 15.3 (95% CI: 6.9-33.7); *P*<0.001

[a]Changes in palpable spleen length in the ruxolitinib and placebo groups mirrored the changes in spleen volume

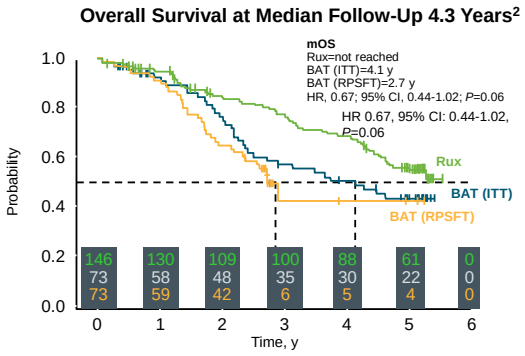
Verstovsek S, et al. *N Engl J Med*. 2012;366(9):799-807.

This is a picture, this is for COMFORT-I, you'll see these are waterfall plots. This is for spleen volume reduction. As you see, the lower it goes, the more the spleen was reduced. You'll see that the 35% reduction, very few people had it in the placebo arm and quite a few more patients had it in the ruxolitinib arm. It's important to note that virtually all these patients, but a few had some reduction in their spleen size. Total symptom score it's not quite as clear cut. I think one of the big questions is total symptom score takes into account a lot of things. Some of these factors that it takes into account like early satiety and fatigue and night sweats may have other causes. I don't think you see as much of a dramatic benefit, but you definitely clearly see a benefit.

COMFORT-II: Efficacy Results



- Median time to response was 12 weeks[1]



- 33% reduced risk of death among patients treated with ruxolitinib vs those treated with BAT[2]
  - Most patients in the BAT arm crossed over to receive ruxolitinib

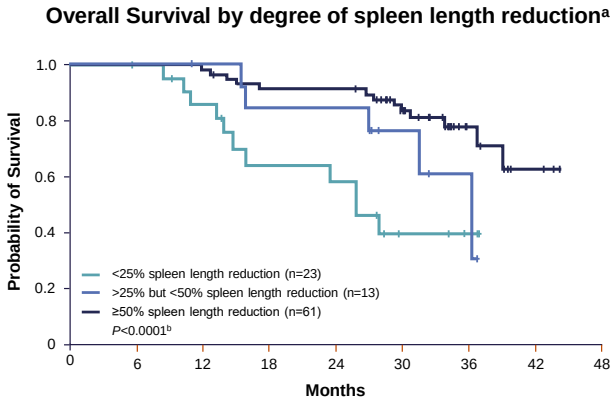
RPSFT, rank-preserving structural failure time
[1]Harrison C, et al. *N Engl J Med*. 2012;366(9):787-798. 2. Harrison CN, et al. *Leukemia.* 2016;30(8);1701-1707.

Now, COMFORT-II, they actually did not look at the total symptom score. They only looked at the spleen. Here you see that 28% had spleen volume reduction. Now one of the things people were asking, well, geez, what does this do for overall survival? Because that really is an important endpoint to patients and because everyone was allowed to crossover. For COMFORT-I, they were allowed to crossover at six months had they not had a response. COMFORT-II, they actually looked at 48 weeks was the primary endpoint and the patient had to progress to switch over. The COMFORT-II data was much more, I think, appropriate for looking at survival advantage.

What they did, because patients still were allowed to crossover when they progressed and obviously without therapy or with just the best available therapy which wasn't that helpful, many of them did progress. What they did was they tried to say, does this improve overall survival? They use this statistical method called Rank-Preserving Structural Failure Time, which ultimately is a method of trying to determine survival when you have crossovers that's allowed, that takes into account different time points and saying, what was the response of this and predicting what would've happened. This is very well validated, it's been used in many settings, this test. I do think that it helps survival and that indeed the data did show that survival was improved in patients who got ruxolitinib.

Achieving a Spleen Response is Associated With Improved Overall Survival

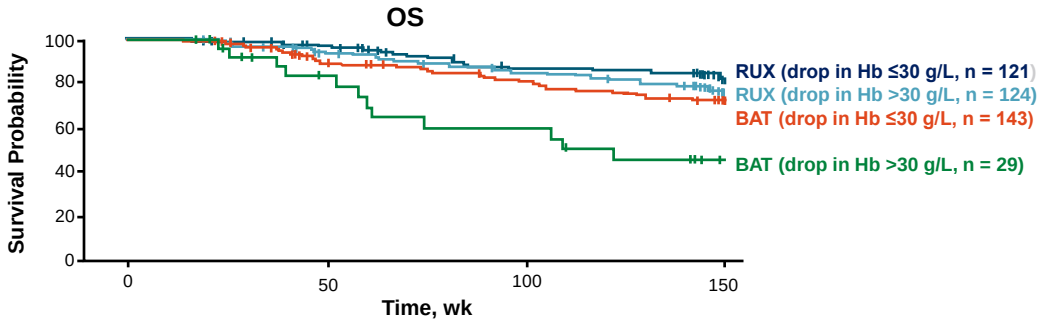
- Achieving ≥50% reduction in palpable spleen length was associated with longer survival compared with <25% reduction



[a] 97 patients with myelofibrosis enrolled at the Mayo Clinic Rochester on a study INCB18424-251 of ruxolitinib.
[b] Comparison of <25% reduction with ≥50% reduction, hazard ratio=0.22, 95% CI, 0.10-0.51.
Verstovsek S, et al. *Blood.* 2012;120:1202-1209.

There's a couple of things that we have learned. Now, this is all post-hoc analysis to try to understand what things predict survival. First of all, if the spleen shrinks in somebody who's on ruxolitinib, they will likely live longer as you see here. If they have a greater than 50% spleen volume reduction that's at top dark blue lines, they actually had a much better survival than if they had less than 25% spleen volume reduction. This is in a pretty small population and had a great P-value. I think that that definitely helps. Now, it's important to note the spleen volume reduction is likely a surrogate. If you take somebody's spleen out, you're not going to see that same survival advantage. The spleen volume reduction, I think, is a surrogate for the JAK2 working well and many things in the body, including all the inflammation and other aspects of the disease.

COMFORT Studies: Ruxolitinib Overcomes Adverse Prognostic Effect of Anemia in MF

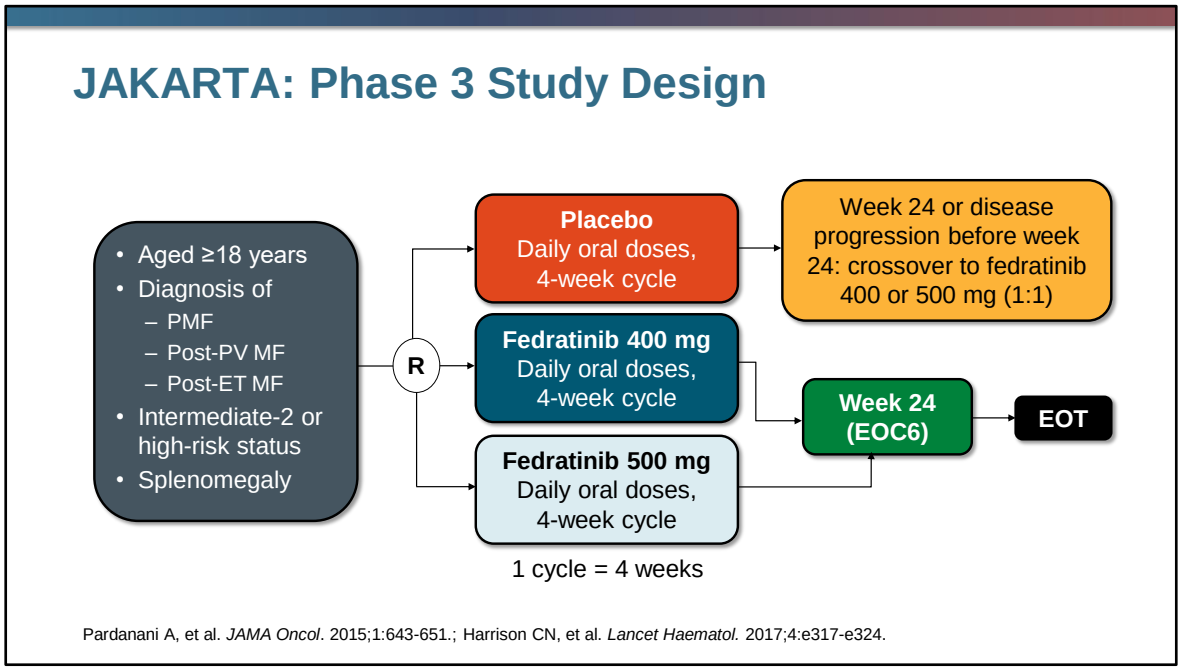


- Anemia is not a contraindication for ruxolitinib use
- Hb changes on ruxolitinib treatment do not bear the same prognostic implications as Hb changes that occur as a consequence of MF pathology

Al-Ali HK, et al. *Leuk Lymph*. 2016;57:2464-2467.; Gupta V, et al. *Haematologica.* 2016;101:e482-e484.

Now one thing that people would ask is, well, geez, you just showed me how important anemia is to figuring out prognosis, but we know that ruxolitinib makes people anemic, so how do we take that into account? They actually went and looked at this and said, well, geez, if we take somebody and we've given them ruxolitinib and their hemoglobin drops, does that have the same implication as somebody who's not on ruxolitinib and hemoglobin drops?

The answer is that a drop from ruxolitinib likely does not have the same prognostic implication as somebody who has anemia without being on ruxolitinib. When somebody's hemoglobin drops, it's not, "Oh-oh, now they're higher risk. This is terrible." It's, "Okay, it's probably because of the drug. It's probably not necessarily a metric of their underlying disease." Now, everyone's hemoglobin drops when you start ruxolitinib, everyone's, it usually comes back up after a few months. It's all about being patient and reassuring the patient that this does not reflect their disease going crazy.



Another JAK2 inhibitor that was studied maybe a few years after ruxolitinib was fedratinib. This was studied in the JAKARTA studies. The initial JAKARTA study actually started before ruxolitinib was approved, so this was placebo. Then two different doses of fedratinib week 24 they looked at the response based on splenomegaly and then the patient was continued on fedratinib or not.

JAKARTA-1: Baseline Characteristics

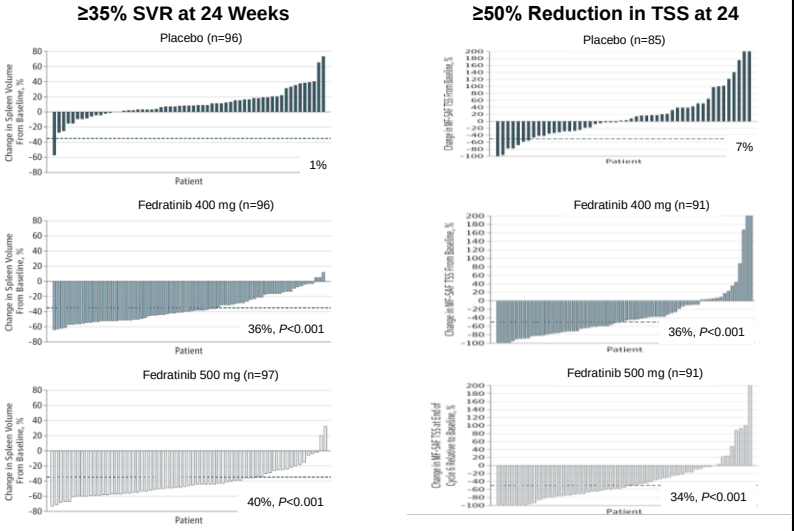
Key Baseline Characteristics	JAKARTA-1	
	Fedratinib 400/500 (n=96/n=97)	Placebo n=154
Median age, years	63/65	66
Male, %	56/63	57
MF diagnosis: PMF, PPV-MF, PET-MF, %	65/65, 25/26, 10/9	60, 28, 11.5
IPSS risk status: Int-2, High, %	59.0/48.5, 41.0/51.5	48, 52
Median palpable length, cm	16/14	17
Median volume, cm	2652/2366	2660
Median platelet count, $x10^9$/L <$100x10^9$/L , % ≥$100x10^9$/L, %	221/241 15/15 85/85	187 20 80
Median hemoglobin, g/dL	10.7/9.8	10.1

Int, intermediate; IPSS, International Prognostic Scoring System; MF, myelofibrosis; NR, not reached; PET-MF, postessential thrombocythemia MF; PMF, primary MF; PPV-MF, postpolycythemia vera MF.

Pardanani A, et al. *JAMA Oncol*. 2015;1:643-651.; Harrison CN, et al. *Lancet Haematol.* 2017;4:e317-e324.

The baseline characteristics of the study showed that they were all very similar in the placebo and the two arms that had different doses of fedratinib.

JAKARTA-1: Key Efficacy Endpoints



SVR, spleen volume reduction;
TSS, total symptom score.

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

When you looked at the spleen volume reduction and total symptom score reduction you saw a fairly consistent in patients who got fedratinib they had 36 to 40%, achieved the 35% spleen volume reduction. In patients who got the fedratinib, you saw a much better reduction or improvement in the symptom score.

JAKARTA-1: Hematologic/Nonhematologic Adverse Reactions

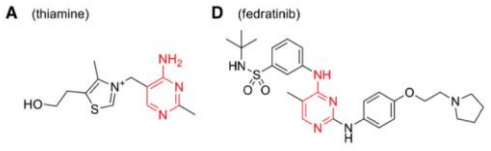
Hematologic Adverse Reactions[a]	Fedratinib 400/500 (n=96/n=97)		Placebo n=95	
	All Grades, %	Grade 3/4, %	All Grades, %	Grade 3/4, %
Thrombocytopenia	63/57	17/27	51	9
Anemia	99/98	43/60	91	25
Neutropenia	28/44	8/18	15	4
Nonhematologic Adverse Reactions	Fedratinib 400/500		Placebo	
	All Grades, %	Grade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

[a] *Presented values are worst grade values regardless of baseline (NCI Common Terminology Criteria for AEs, version 3.0).*
FDA places clinical hold on fedratinib in November 2013 because of WE (n=7 patients)
Pardanani A, et al. *JAMA Oncol*. 2015;1:643-651.; Scott BL, et al. *JAMA Oncol*. 2015;1:651-652.

Now with fedratinib, you see the similar hematologic side effects, thrombocytopenia, anemia, and neutropenia. There's a notable difference in the nonhematologic adverse reactions and that's diarrhea, vomiting, and nausea are much, much more common. It's really, really important to counsel patients on this if they're going to start on fedratinib. Now, as many of these studies have-- unfortunately, you'll see with the JAK inhibitors following ruxolitinib, they all had a bumpy road to getting to be approved.

What happened with fedratinib was that a number of patients were found to have Wernicke's encephalopathy. The FDA put the drug on clinical hold in November of 2013.

Fedratinib Considerations



Black Box Warning!
Wernike's encephalopathy (WE) (ataxia, altered mental status, ophthalmoplegia) occurred in 8 of 608 (1.3%) patients receiving fedratinib in clinical trials

Expert review:
- 3 cases weren't WE
- 1 cases confirmed WE based on MRI in patient with significant GI toxicity
- 2 cases confirmed WE resolved without holding fedratinib
- 2 cases indeterminate

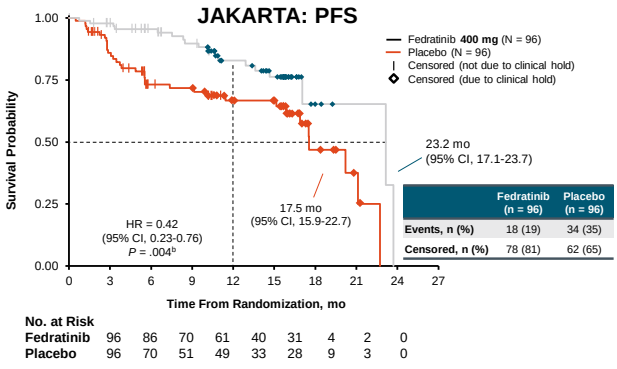
- Check thiamine when starting fedratinib and periodically during treatment
- If patient experiences neurologic symptoms consistent with WE, hold fedratinib and give IV thiamine
- Do not start fedratinib in patients with thiamine deficiency; replete thiamine prior to treatment initiation

Zhang Q, et al. *Drug Metab Dispos.* 2014;42(10):1656-1662.
Harrison C, et al. *Blood.* 2017;130 (Supplement 1):4197.

Even though after very careful review of these patients, only probably one of them actually had Wernicke's encephalopathy. This was thought to be more related to inadequate nutrition rather than a drug effect. They found that many of these cases that were thought to be Wernicke's actually probably weren't. Nonetheless, there is some biological basis for this. There's a very similar structure in thiamine and fedratinib that you can see in red. It's important to check thiamine when starting fedratinib, and if the patient experiences any neurologic symptoms, hold the fedratinib and give IV thiamine. Somebody who is originally thiamine deficient, replace that before starting the fedratinib.

JAKARTA: Progression-Free Survival

- Fedratinib significantly reduced the risk of disease progression vs placebo (*P* = .004)
  - Median PFS was 5.7 mo longer with fedratinib vs placebo (23.2 vs 17.5 mo, respectively)
  - 1-year PFS: fedratinib 83%, placebo 67%
- 80 patients (42%) were still being followed for PFS at the time of clinical hold
  - Median follow-up: fedratinib 10.6 mo; placebo, 9.1 mo
- AML transformation reported in 3 patients (3%) who received fedratinib and 2 patients (2%) in the placebo arm[a]



[a] AML transformation was based on AE reporting, including the preferred terms of "acute myeloid leukemia," "acute leukemia," and "transformation to acute myeloid leukemia." [b] *P* value from log-rank test.
Harrison C, et al. EHA 2021. Abstract S203.

JAKARTA when they did do some of the testing afterwards even taking into account censorship, it did appear to improve progression-free survival in these patients, understanding that these data you have to take with a grain of salt because the drug was held in the middle of clinical studies.

Case 1: Conclusions

*HIPAA-compliant, stock photo (not actual patient).

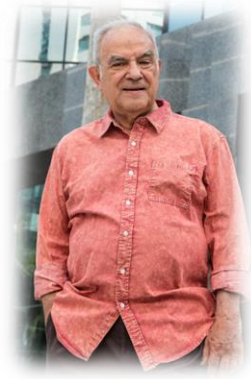
Joan*

- The patient was treated on ruxolitinib and had an excellent response
- Key notes: JAK inhibitors are a great first-line therapy for patients with increased spleen size and symptom burden
  - Must be careful of cytopenias
  - Important to note that anemia related to JAK inhibition is not the same as anemia in the absence of JAK inhibition

The patient was treated with ruxolitinib, had an excellent response. I think there's a key thing to remember. Number one, JAK inhibitors are a great drug. Greatest first-line therapy for patients with increased spleen size and symptom burden. If they do not have that, you don't necessarily need to use it. The other thing that's important to remember about JAK inhibitors, is this is not something that beneficially works on the JAK2 mutation. What the JAK inhibitors do, is they reduce inflammation because the JAK pathway is really involved in inflammation as well. That reduction in inflammation is what gives us the benefit of the drug, not direct inhibition of JAK2.

If somebody has a calreticulin mutation or an MPL mutation, they still may benefit from ruxolitinib (Jakafi). You have to be careful of cytopenias because patients will always develop some mild cytopenias when you start the drug. Reassure them, and they do generally balance out after a few months of treatment.

Case 2: John, a 69-year-old Male

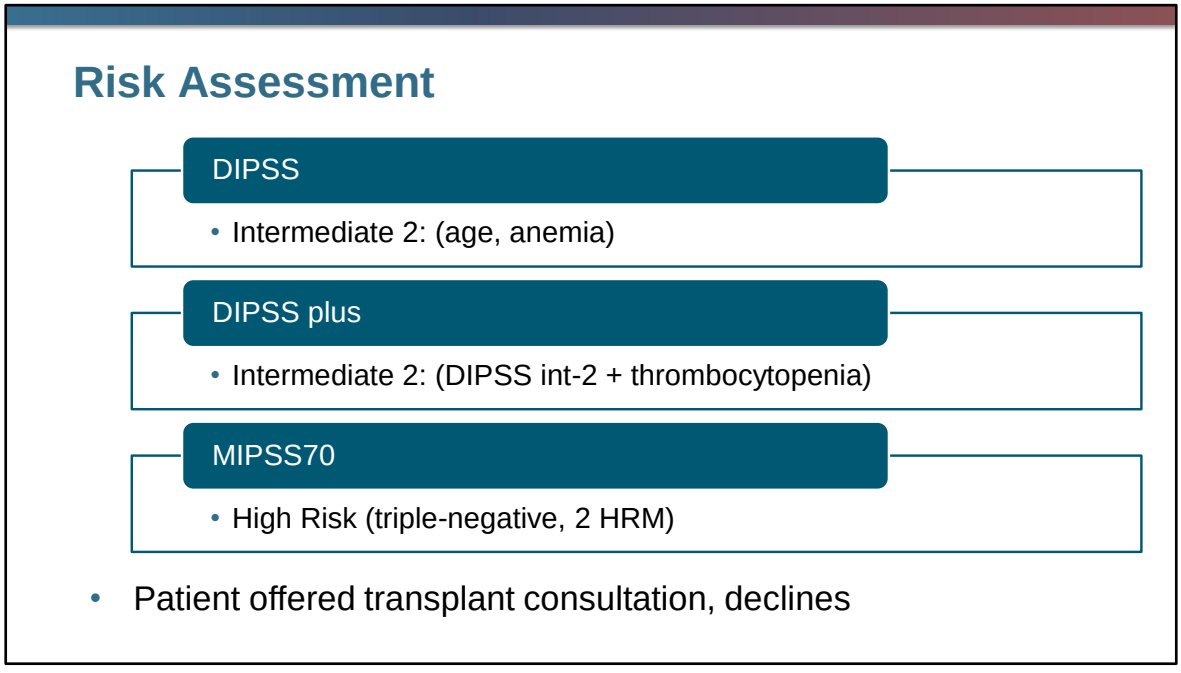


*HIPAA-compliant, stock photo (not actual patient).

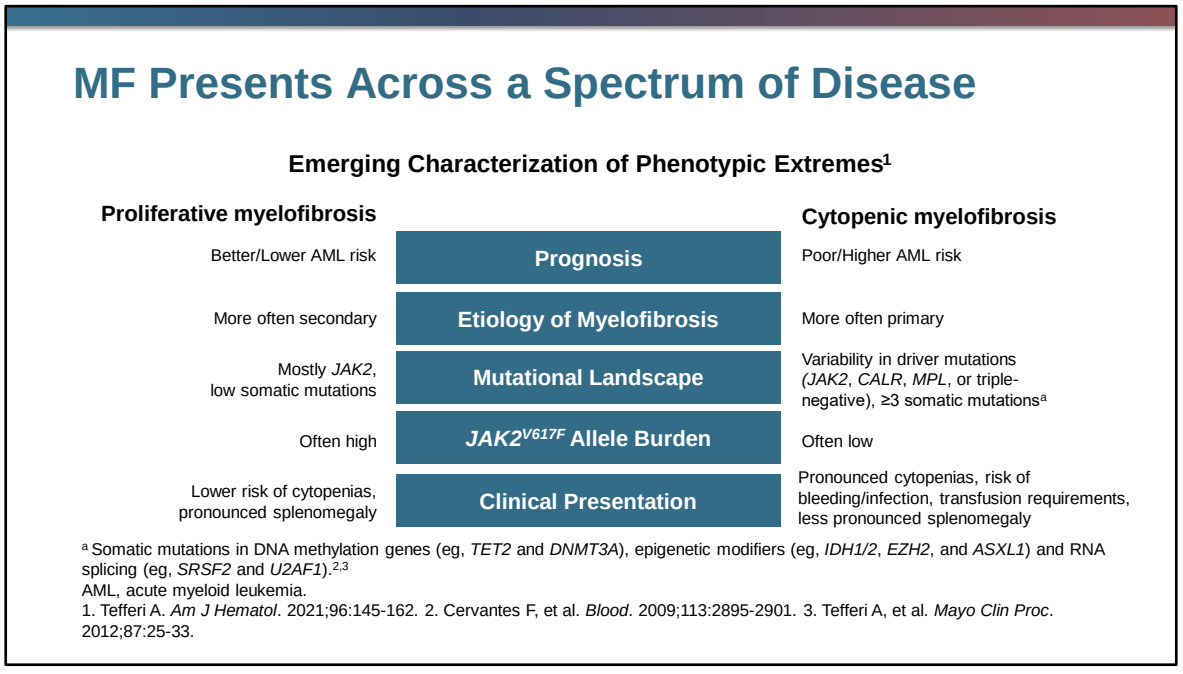
John*

Patient Notes	• Patient with pancytopenia referred for evaluation. Hgb 8.6, plt 70, WBC 2.5 with 1.4 PMN. No peripheral blasts. Patient has noted some LUQ pain and early satiety, as well as night sweats
Work-up	• Bone marrow biopsy shows atypical megakaryocytes, 2-3+/3 fibrosis, no increase in blast • Cytogenetics: NL • NGS: ASXL1, IDH2, *JAK2*, *CAL-R*, *MPL* negative

All right. Going on to our next case. John, he's a 69-year-old gentleman. He presented with pancytopenia and was referred for evaluation. His hemoglobin was 8.6, his platelets were 70, white blood cell count of 2.4, neutrophils of 1.4. He had no peripheral blasts. He has noted some left upper quadrant pain and early satiety as well as night sweats. Bone marrow biopsy shows atypical megakaryocytes, and two to three out of three plus fibrosis, no increase in blasts. He has normal cytogenetics, and he had none of these mutations. Actually, I take that back. He didn't have the JAK2, CALR, MPL. He did have ASXL1 and IDH2 mutation.



When we look at his risk assessment, he really only gets risk for the DIPSS score based on his age and his hemoglobin. He gets his DIPSS-Plus score. He's still intermediate-2, but the thrombocytopenia adds to that. For the MIPSS70, he's high risk because he does not have a driver mutation and he has two high-risk molecular mutations being the ASXL1 and the IDH2, and the lack of the JAK2, CALR, MPL which are driver mutations. Patient is offered a transplant consultation and declines.

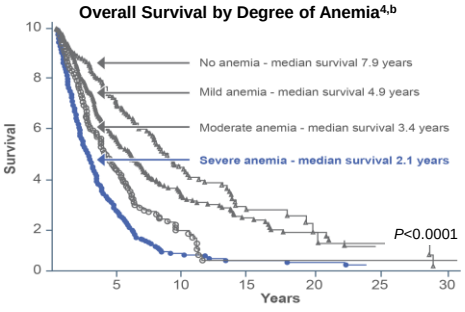


As we learn more about myelofibrosis, we've been able to divide it a little bit, and it's a very sensical division. One of the phenotypic divisions we can make is proliferative myelofibrosis and cytopenic myelofibrosis. Proliferative overall is generally a better one to have, it has a lower risk of progression to AML as compared to cytopenic myelofibrosis. It's more often secondary myelofibrosis, and the mutational landscape, there's a lot of the patients with proliferative myelofibrosis have JAK2 positivity and they have a much lower percentage of somatic mutations. Variability in cytopenic myelofibrosis, they are more likely to be triple-negative and have a higher risk mutations. The JAK2 allele burden may differ between the two although it's unclear that that has a significant prognostic implication. Finally, when patients with proliferative myelofibrosis often present with higher blood counts, pronounced splenomegaly symptoms, whereas patients with cytopenic myelofibrosis more often present with just cytopenias, transfusion requirements, and splenomegaly is less of an issue but still can happen.

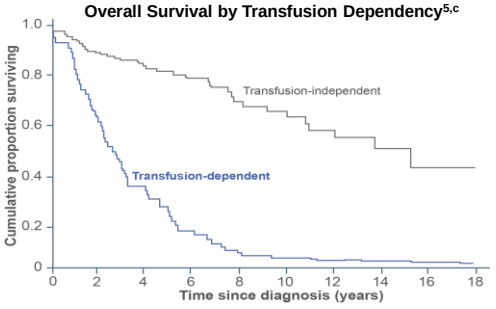
Anemia and RBC Transfusion Are Indicators of Poor Prognosis

- Current prognostic models[a] acknowledge anemia and RBC transfusion needs as risk factors[1-3]

Overall Survival by Degree of Anemia[4,b]



Overall Survival by Transfusion Dependency[5,c]



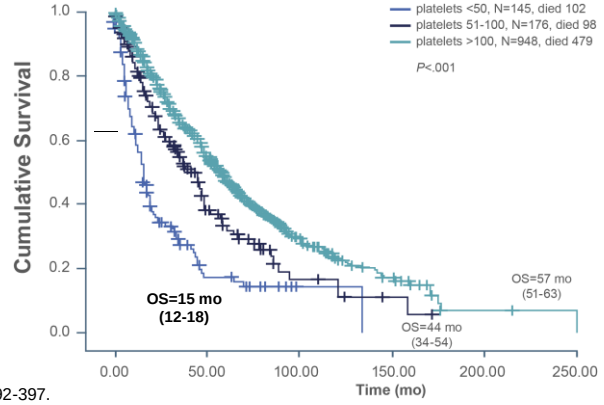
[a] International Prognostic Scoring System (IPSS), Dynamic International Prognostic Scoring System (DIPSS), and DIPSS plus for anemia; DIPSS plus for transfusion needs; anemia defined as hemoglobin <10 g/dL. [b] Survival data in 1109 patients with primary MF diagnosed at a single location. [c] Overall survival in 220 patients with primary MF diagnosed at a single location.
MF, myelofibrosis; RBC, red blood cell.
1. Cervantes F, et al. *Blood*. 2009;113:2895-2901. 2. Passamonti F, et al. *Blood*. 2010;115:1703-1708. 3. Tefferi A, et al. *Mayo Clin Proc*. 2012;87:25-33. 4. Nicolosi M, et al. *Leukemia.* 2018;32:1254-1258. 5. Elena C, et al. *Haematologica.* 2011;96:171-173.

A couple things, so we know that anemia and the need for red blood cell transfusions are indicators of a poor prognosis and decreased survival. As you can see on the left side, you'll see overall survival based on the degree of anemia. No anemia, the median survival is eight years, in severe anemia, it's down to two years. Then if somebody is transfusion-dependent versus transfusion-independent, you do see a marked difference in their survival.

Thrombocytopenia Is an Indicator of Poor Prognosis

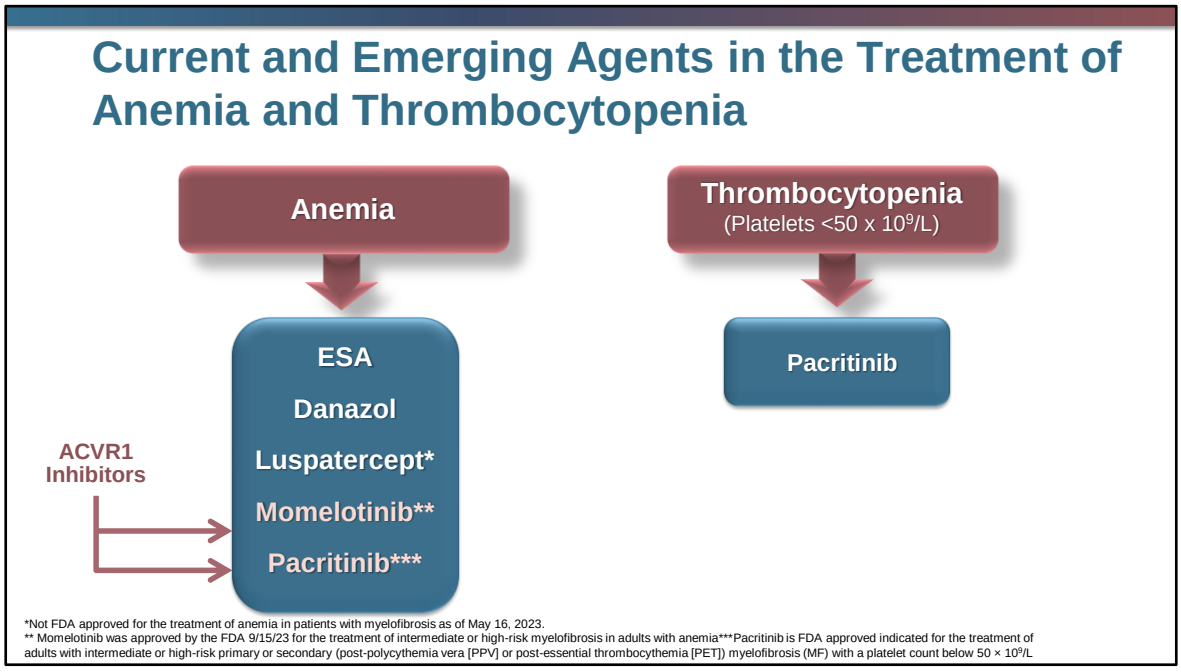
- DIPSS+ acknowledges moderate-to-severe thrombocytopenia[a] as an independent risk factor for prognosis

Overall survival in Patients With Myelofibrosis by Platelet Count[b]



[a]Gangat, et al. J Clin Oncology. 2011. 29 (4):392-397.
[b]Masarova L, et al. *Leuk Res*. 2020. Apr;91:106338.

Thrombocytopenia is also an indicator of poor prognosis. The DIPSS-Plus acknowledges this thrombocytopenia as an independent risk factor for prognosis. As you can see based on this data, you have patients with really low platelet counts as compared to patients with platelets of greater than 100. You do see differences in their survival time.

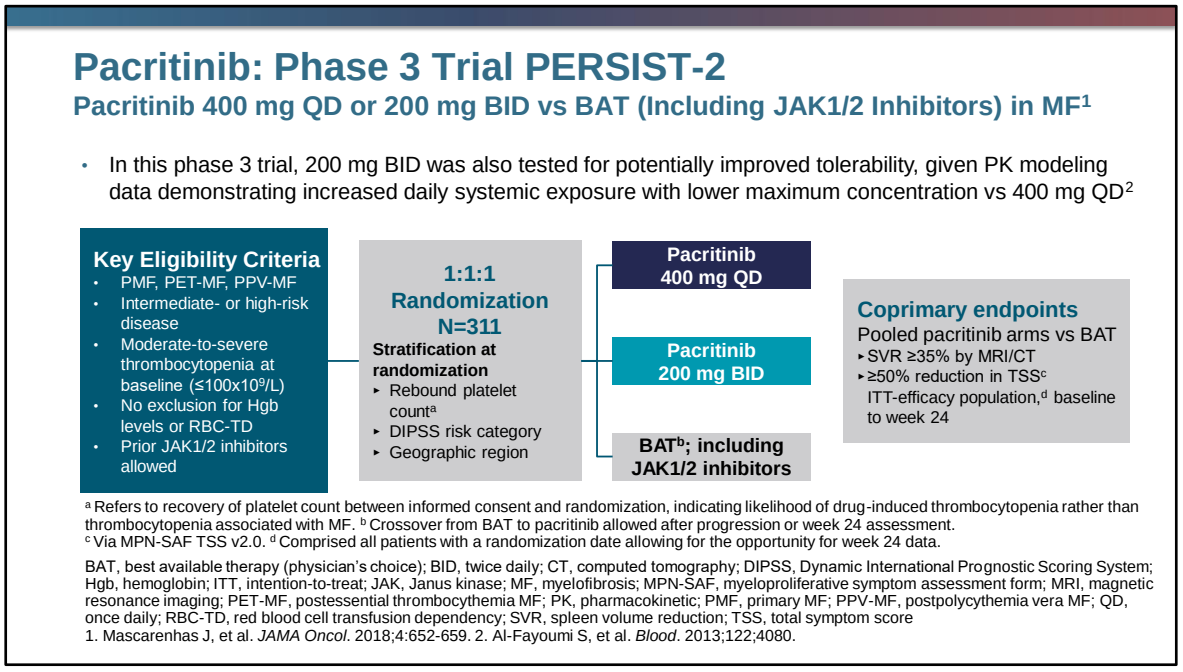


What do we do about these? These patients are tricky to treat because they just told you ruxolitinib and fedratinib, the major side effects you get from these are anemia and thrombocytopenia. What do we do for these patients?

There are current emerging treatments that will help with this. For anemia, there's erythropoietin stimulating agents. Danazol, which is an androgen-like hormone. It's actually been used for a number of years but can be very effective. There's luspatercept. Now, we know luspatercept is approved for myelodysplastic syndrome. It is being studied and not yet FDA-approved for treatment of anemia and myelofibrosis. However, it is often used off-label in that setting and even is mentioned in the NCCN Guidelines as one of the possible treatment options.

Momelotinib and pacritinib are both drugs that have inhibit ACVR1. Inhibition of ACVR1 affects iron metabolism pathway and has actually been shown to improve anemia. What we know in these patients is they often have a high hepcidin level. With ACVR1 inhibition, you can actually lower that hepcidin, and by lowering the hepcidin, the anemia can get better.

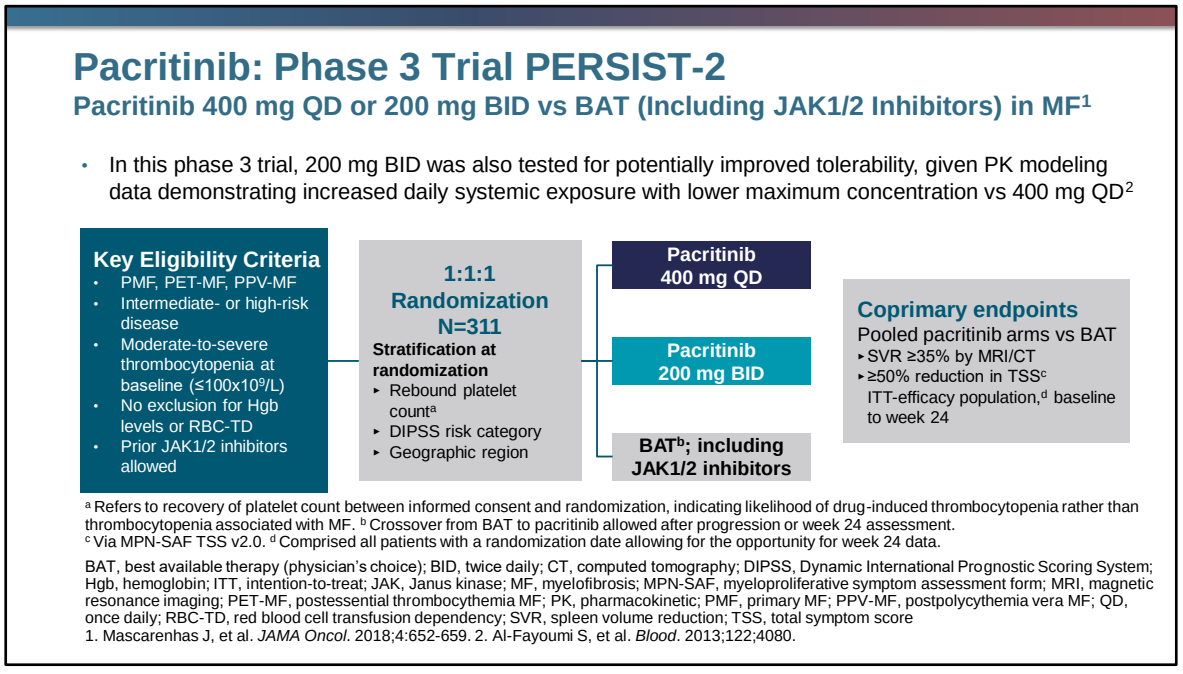
For thrombocytopenia, we're a little bit more limited. We just have pacritinib, and we will talk about these treatments.



Let's first talk about pacritinib. Pacritinib has had a very tumultuous time getting to the point of approval. Pacritinib was first studied with the PERSIST-1 and PERSIST-2 study. I'm going to not talk about the PERSIST-1 study in the interest of time, but the PERSIST-2 study is interesting because we did get a lot of information from this.

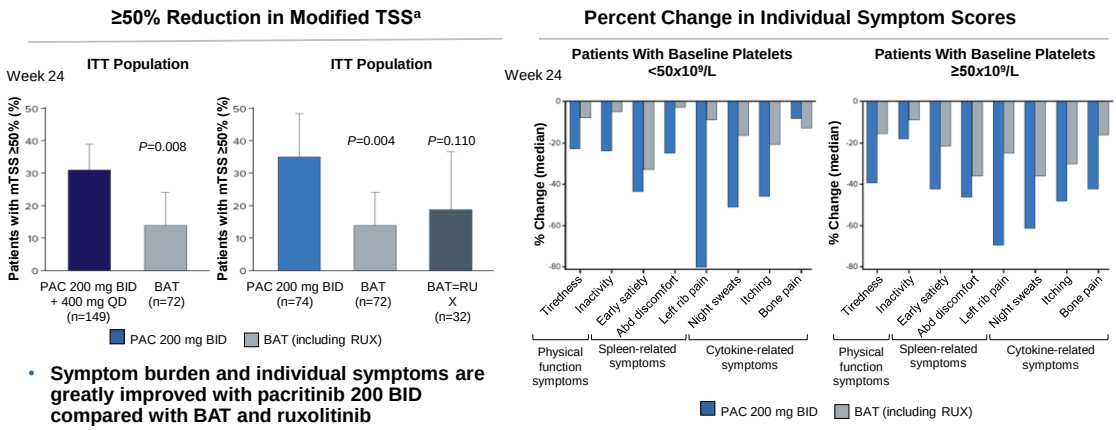
The PERSIST-2 study was a phase 3 trial, and what it compared was different doses of pacritinib along with best available therapy, which could also include JAK inhibitors. Now, there's a couple of things to remember. Number one, a lot of these patients did have prior JAK inhibition therapy. Number two, these patients had moderate to severe thrombocytopenia, so their platelets had to be less than 100 at baseline in order to be enrolled.

When you took these patients, they were being studied, and of course, as would be expected, the endpoints were spleen volume reduction of 35% or greater and greater than 50% reduction total symptom score, meaning that you improved your spleen size and symptom burden. Now, this study was going along and unfortunately, you have a very sick group of patients as you can tell by looking at this inclusion criteria. This study unfortunately was stopped because there was a higher rate of bleeding and major adverse cardiovascular events. It was stopped pretty abruptly and put on a clinical hold.



That clinical hold did not last. I think it lasted for about a year and then CTI fortunately who had the drug at the time and still does, although now they've been bought by somebody else. CTI really pushed ahead, which is a good thing for patients. This data I'm going to show you about the PERSIST-2 study after the fact. Much of it was actually analyses that were done after the fact.

PERSIST-2: Symptom Burden With Pacritinib Versus BAT and Ruxolitinib



- **Symptom burden and individual symptoms are greatly improved with pacritinib 200 BID compared with BAT and ruxolitinib**

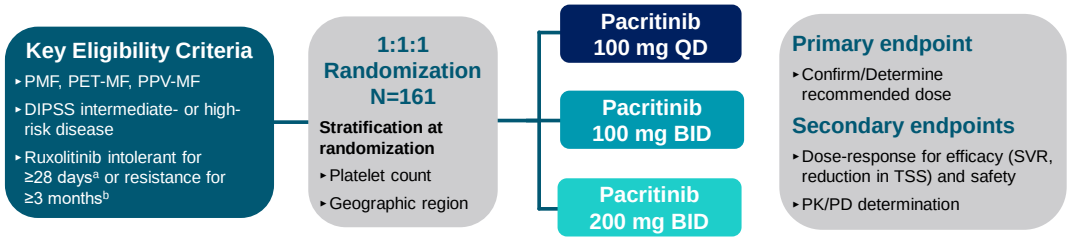
[a] Excludes individual symptom score for tiredness from MPN-SAF TSS v2.0; utilized in pivotal trials for other JAK inhibitors.
Abd, abdominal; BID, twice daily; ITT, intention-to-treat; PAC, pacritinib; QD, once daily; mTSS, modified total symptom score; RUX, ruxolitinib.

Palmer J, et al. ASH. 2021. Abstract 3628.

When you look at symptom burden, we do know that patients who got pacritinib as compared to best available therapy did have improvement in their symptom burden. It's important to note that if the best available therapy was ruxolitinib, this held true, and that's probably because if you get ruxolitinib, you can only usually use like 5 milligrams twice a day when their platelets are low, so you're really not giving an efficacious dose. This, on the right side, you just see the difference in all the symptoms as they decrease.

Pacritinib: Phase 2 Dose-Finding Study PAC203 in Patients With MF Intolerant of or Resistant to Ruxolitinib

PAC203 incorporated risk mitigation factors put in place to address findings from the thorough clinical review of PERSIST data, including enhanced eligibility criteria, patient monitoring, and dose modifications



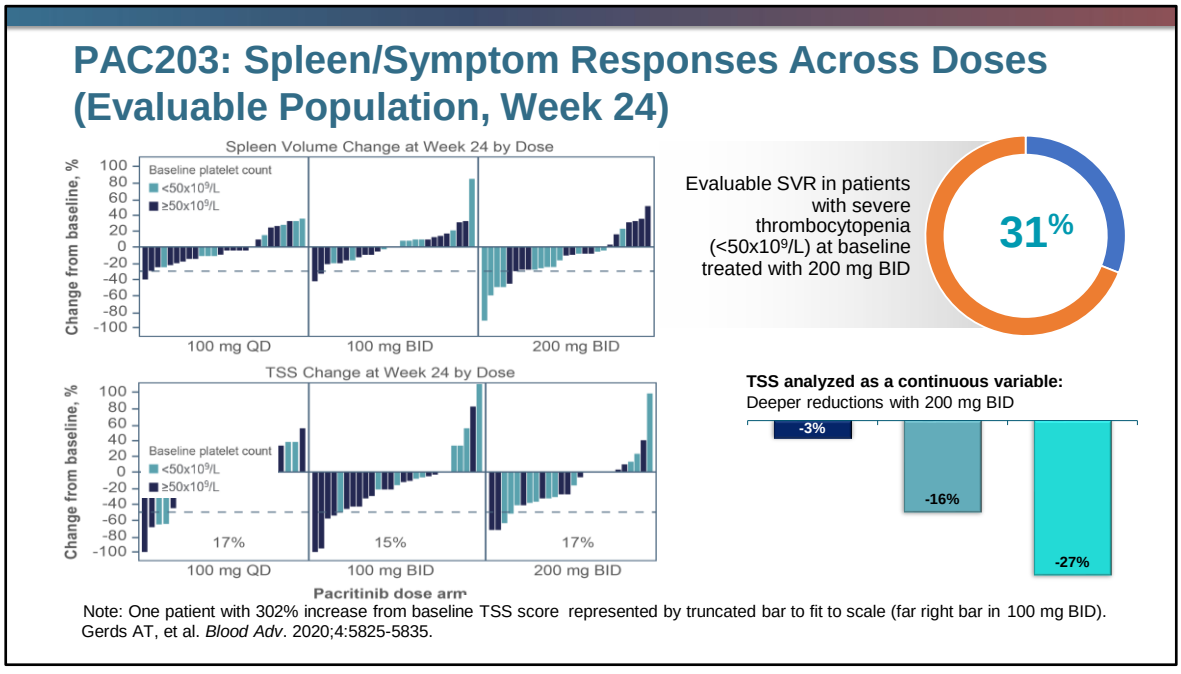
[a] Complicated by red blood cell transfusion, grade ≥3 anemia, thrombocytopenia, hematoma, and/or hemorrhage while treated with a dosage of <20 mg twice daily.
[b] Less than 10% SVR or <30% decrease in spleen length or regrowth of these parameters.

BID, twice daily; DIPSS, Dynamic International Prognostic Scoring System; MF, myelofibrosis; PET-MF, postessential thrombocythemia MF; PK/PD, pharmacokinetic/pharmacodynamic; PMF, primary MF; PPV-MF, postpolycythemia vera MF; QD, once daily; SVR, spleen volume reduction; TSS, total symptom score.

Gerds AT, et al. *Blood Adv*. 2020;4:5825-5835.

Knowing that this drug seemed to work fairly well, they did the PAC203 study. Now, because of all these adverse events that happened with the PERSIST-2 study, the PAC203 study actually had to be started with dose finding. This was a phase 2 dose-finding study that was done, and this would include any patient. Platelets were not part of the inclusion criteria that had myelofibrosis, intermediate or high-risk disease, and they had to either tried ruxolitinib and been intolerant of it for 28 days, or resistant to ruxolitinib after greater than 3 months, or had return of some of their symptoms or disease-related problems.

They were randomized to 100 milligrams daily, twice a day, or 200 milligrams twice a day. Again, the primary endpoint was really to make sure that, A, this was safe to give because of the adverse effects that happened with the PERSIST-2 study and confirm what the appropriate dose was for that.



Note: One patient with 302% increase from baseline TSS score represented by truncated bar to fit to scale (far right bar in 100 mg BID).
Gerds AT, et al. *Blood Adv*. 2020;4:5825-5835.

Now, fortunately, there's two great things that came out of this study. I think number one, we knew that it reduced the spleen size. Now this does seem to be the most efficacious when you look at the 200 milligrams twice daily dosing, as you can see by that waterfall plots on the top there. Then when we look at the total symptom score that one was not as dependent on dose.

This is actually pretty consistent. You see similar findings with ruxolitinib, but 31% of patients with severe thrombocytopenia, I mean their platelets were less than 50, had spleen volume reduction, which is pretty great for a disease that we know that spleen volume reduction can be very helpful. The 200 milligrams twice a day, if we looked at TSS as a continuous variable, not just as plus or minus 50%, did show improvements as you got to higher levels of pacritinib.

Pacritinib Safety Analysis in Patients With MF and Severe Thrombocytopenia

Adverse Reactions	PERSIST-2		PAC203	Total (pooled)
	PAC 200 mg BID (n=47)	BAT[a] (n=42)	PAC 200 mg BID (n=24)	PAC 200 mg BID (n=71)
Treatment-emergent hemorrhage AEs (SMQ)[b], n (%)				
Any-grade bleeding AEs	23 (49)	26 (62)	18 (75)	41 (58)
Serious bleeding AEs	6 (13)	4 (10)	2 (8)	8 (11)
Grade ≥3 bleeding AEs	8 (17)	5 (12)	3 (13)	11 (16)
Treatment-emergent cardiac AEs (SMQ)[b], n (%)				
Any-grade cardiac AEs	16 (34)	19 (45)	13 (54)	29 (41)
Serious cardiac AEs	4 (9)	9 (21)	3 (13)	7 (10)
Grade ≥3 cardiac AEs	4 (9)	8 (19)	2 (8)	6 (9)
Major adverse cardiac event category[c], n (%)				
MACE	0 (0)	2 (5)	0 (0)	0 (0)
MACE death (grade 5)	0 (0)	1 (2)	0 (0)	0 (0)

- The incidences of serious and grade ≥3 bleeding AEs were lower with pacritinib 200 mg BID in PAC203 than those reported with pacritinib 200 mg BID or BAT in PERSIST-2, likely attributable to the additional safety measures in PAC203
- The incidence of cardiac events of any grade and those grade ≥3 were lower in the pooled pacritinib group compared with the BAT group; no patients in the pooled pacritinib group and 2 in the BAT group (1 fatal) had a MACE event

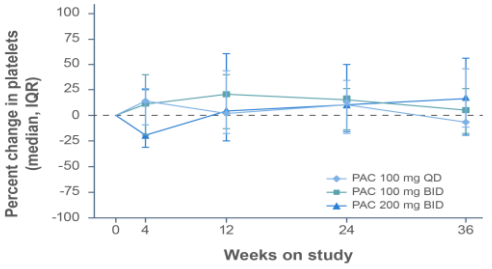
The most common BAT agents were ruxolitinib and watch and wait. [b] Bleeding and cardiac events defined by SMQ include the preferred terms in hemorrhage and cardiac arrhythmias, cardiac failure, ischemic heart disease, and embolic and thrombotic events, respectively.
[c] The MACE category: patients who experienced any of the following treatment-emergent adverse events: (1) fatal (grade 5) cardiac event; (2) ischemic stroke of any grade, based on the Preferred Term "cerebral infarction"; and (3) myocardial infarction of any grade.
AE, adverse event; BAT, best available therapy; BID, twice daily; MACE, major adverse cardiac event; PAC, pacritinib; SMQ, standardized Medical Dictionary for Regulatory Activities query.
Mascarenhas J, et al. ASH. 2021. Abstract 3640.

Now, when we look at the adverse events associated in the PAC203, we did not see the same degree of these major cardiovascular events or bleeding events. These patients were monitored extremely closely with multiple echoes and stuff like that. In terms of the difference, we didn't really see substantial differences between these adverse events' effects in the different dose ranges.

PAC203: Hematologic Stability

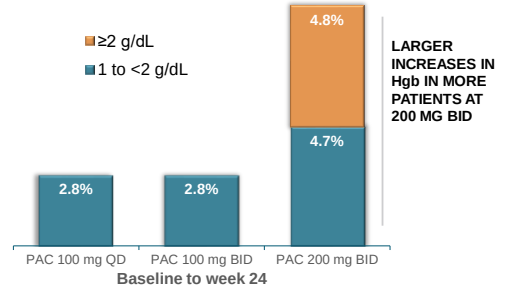
- Platelet counts were stable for most patients on study, including those with severe thrombocytopenia
- Reductions in transfusion burden and achievement of transfusion independence occurred in patients in all arms

Percent Change in Platelet Count From Baseline



Number of Patients					
PAC 100 mg QD	52	44	37	22	11
PAC 100 mg BID	55	49	42	24	16
PAC 200 mg BID	53	49	38	26	14

Hgb Increases in Patients With Baseline Anemia (Hgb ≤10 g/dL)

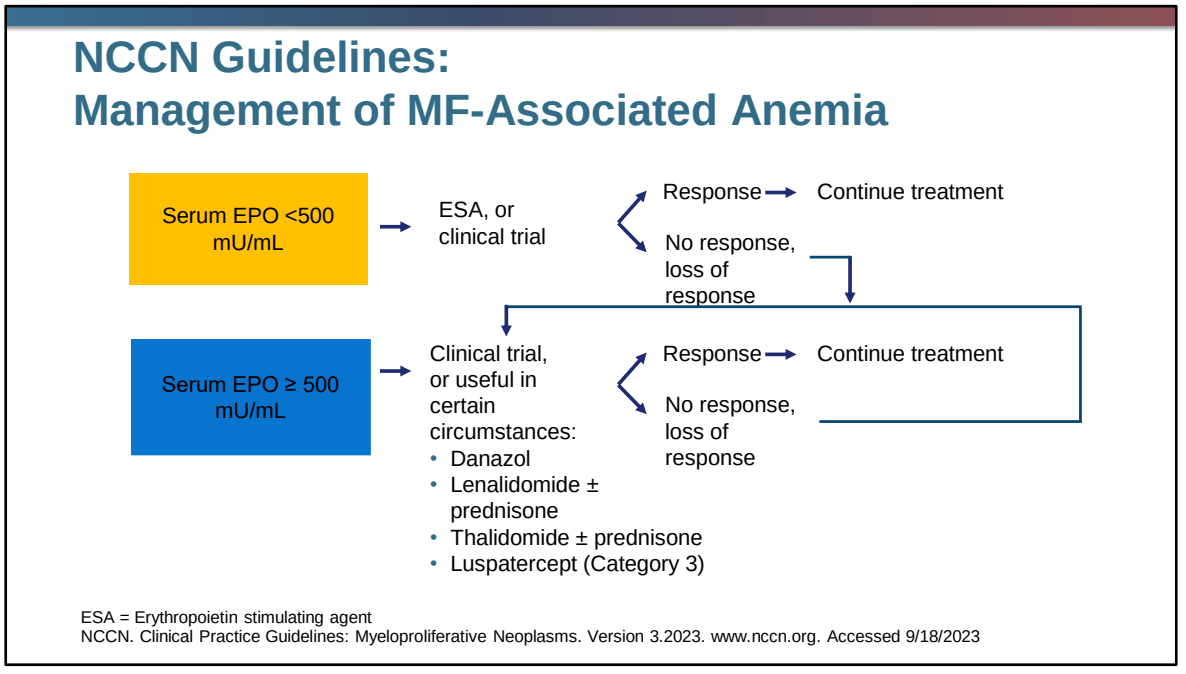


BID, twice daily; Hgb, hemoglobin; IQR, interquartile range; PAC, pacritinib; QD, once daily

Gerds AT, et al. *Blood Adv*. 2020;4:5825-5835.

Now, the other thing that came out of this and that's important to remember is the platelets stayed stable. This will not make your platelets better. You can see a decrease in the platelets, especially initially. You'll see the triangle on the plot on the left-hand side. They can decrease initially, and that is okay. Just, A, they won't go up and B, they may decrease initially, and that's okay are two big things to remember about pacritinib.

The other thing that came out of it was that they actually found that many patients had improvement in their anemia. Then retrospectively they went and looked back and said, "Hey, we have this ACVR1 inhibition, which was one thing that momelotinib touted, but they found that there was a biologic basis for this increase in their anemia.



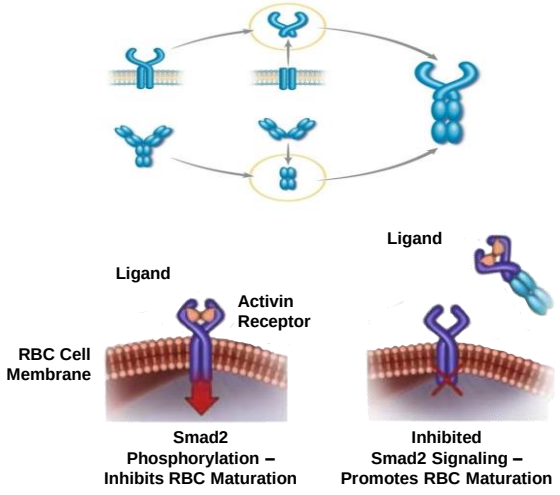
How do we manage myelofibrosis-associated anemia? This is really one of the hardest things to do. Fortunately, we're coming up with more and more treatment options for the patients for this. The biggest division and how we start with the NCCN Guidelines, and I think that persists is that we'd look at their serum erythropoietin level. If it's greater than 500, they're likely not going to respond to erythropoietin-simulating agents. If it's less than 500, you can try them, but really give them 12 weeks. If you don't start to really see a response, I would bag it. The response in myelofibrosis to ESAs isn't fantastic. There are some patients who will benefit, but I wouldn't try it for long periods of time just for the hope that it will work, because if it doesn't work usually within about 12 weeks, it probably won't.

Other options that can be used if the serum erythropoietin level is high or if erythropoietin stimulating agents don't work or things like danazol. Lenalidomide can be used or thalidomide which have both been potentially shown to help anemia. They're usually given with prednisone and then luspatercept. Now, I will say in today's practice, a lot of people are probably using luspatercept, overusing lenalidomide or thalidomide. They've really fallen out of favor, I think, because of some of their side effects. If there's a response, again, you continue treatment. If no response, then you have to go back to the drawing board.

Anemia Therapy in Combination With a JAKi

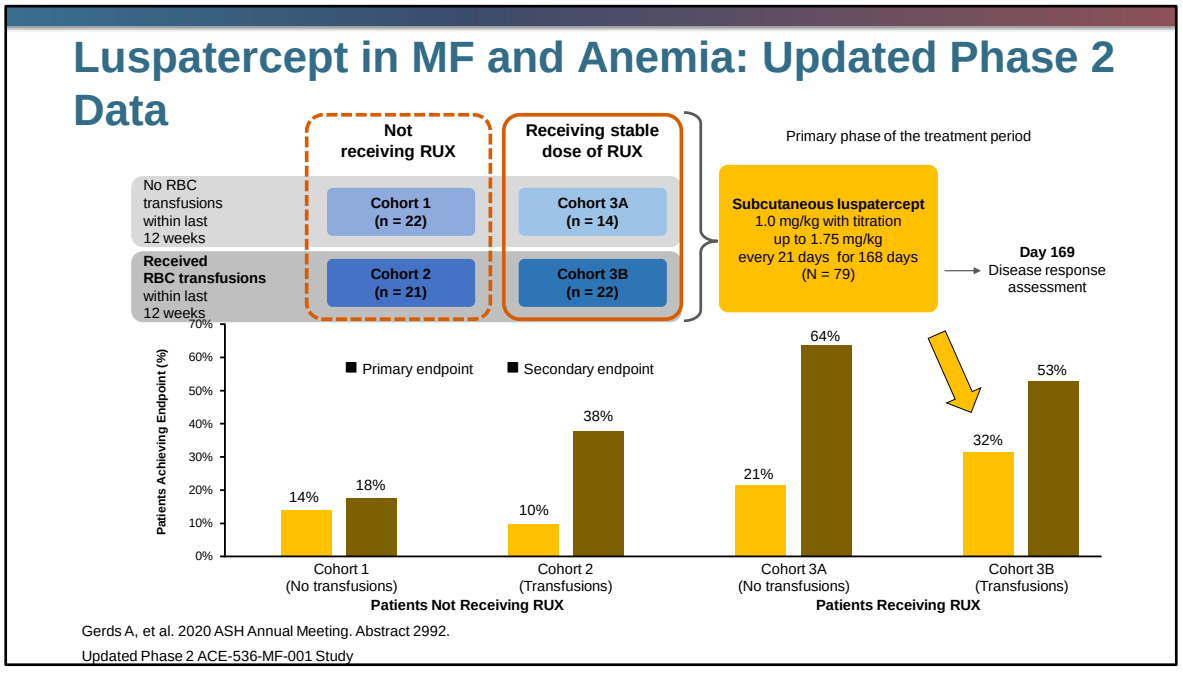
Luspatercept

- Fusion protein that acts as activin receptor ligand trap
- Sequester ligands of TGFß superfamily, (eg, GDF11) secreted by BM stroma, that inhibit terminal erythropoiesis



Iancu-Rubin C et al. *Exp Hematol*. 2013;41(2):155-166; Carrancio S et al. *Br J Haematol*. 2014;165:870-882.

How does luspatercept work? Luspatercept is a drug and it's an activin receptor. Basically what happens is if the activin comes and it binds to the red cell membrane, it actually impairs red cell maturation so that the cell gets stuck and won't proceed forward and become a nice lovely red blood cell that goes in the peripheral blood. If you can bind that activin and hold it out, so it doesn't actually go to the cell and inhibit the red cell maturation, the red cell can improve and become nice, healthy red cell, go out to the peripheral blood.



The data that we have thus far, there was a phase 2 study, it had four different arms, which made it confusing. What you'll see with this is you see the different cohorts. There were two patients either receiving RUX or not receiving RUX and within that group did they need transfusions or did they not need transfusions? Then what you can see is that patients who are achieving the endpoint, which is the reduction in red blood cell transfusions or improvement of the hemoglobin by greater than one and a half. The effect of ruxolitinib in patients who were a little bit more pronounced I think, than the patients who were not receiving ruxolitinib and so they have gone on to further study. It's in a phase 3 study looking at luspatercept in that population. Nonetheless, people have actually started to use it.

Abstract 627

Updated Results from the Momentum Phase 3 Study of Momelotinib (MMB) Versus Danazol (DAN) in Symptomatic and Anemic Myelofibrosis (MF) Patients Previously Treated with a JAK Inhibitor

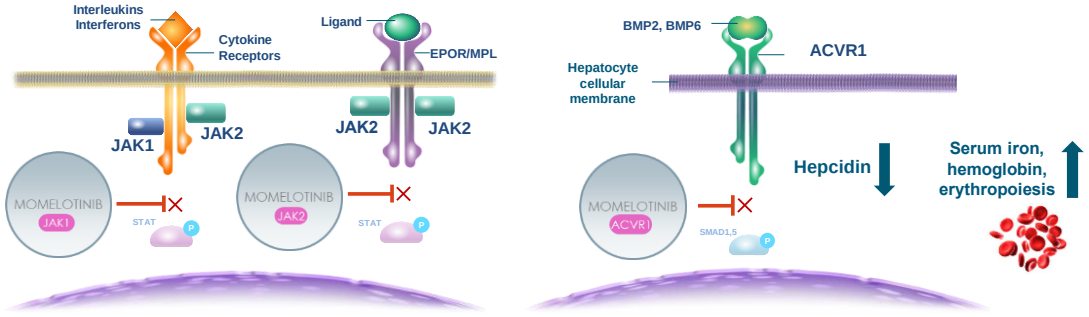
Aaron T. Gerds, MD, MS,[1] Ruben A. Mesa, MD, FACP,[2] Alessandro M. Vannucchi, MD,[3] Haifa Kathrin Al-Ali, MD,[4] David Lavie, MD,[5] Andrew Kuykendall, MD,[6] Sebastian Grosicki, MD, PhD,[7] Alessandra Iurlo, MD, PhD,[8] Yeow Tee Goh,[9] Mihaela Lazaroiu, MD[10] Miklos Egyed, MD, PhD,[11] Maria Laura Fox, MD,[12] Donal P. McLornan, MD, PhD,[13] Andrew Perkins, MBBS, PhD, FRACP, FRCPA,[14] Sung-Soo Yoon, MD, PhD,[15] Vikas Gupta, MD, FRCP, FRCPath,[16] Jean-Jacques Kiladjian, MD, PhD,[17] Rafe Donahue, PhD,[18] Jun Kawashima, MD,[18] Srdan Verstovsek, MD, PhD[19]

[1]Cleveland Clinic Taussig Cancer Center, Cleveland, OH, USA; [2]UT Health San Antonio MD Anderson Cancer Center, San Antonio, TX, USA; [3]University of Florence, Firenze, Italy; [4]University Hospital of Halle (Saale), Halle, Germany; [5]Hadassah University Medical Center, Jerusalem, Israel; [6]Moffitt Cancer Center, Tampa, FL, USA; [7]Medical University of Silesia, Katowice, Poland; [8]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [9]Singapore General Hospital, Singapore; [10]Policlinica de Diagnostic Rapid, Brasov, Romania; [11]Somogy County Kaposi Mór General Hospital, Kaposvár, Hungary; [12]Vall d'Hebron University Hospital, Barcelona, Spain; [13]Guy's and St Thomas' NHS Foundation Trust, London, UK; [14]Australian Centre for Blood Diseases and Alfred Hospital, Monash University, Melbourne, VIC, Australia; [15]Seoul National University Hospital, Seoul, South Korea; [16]Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada; [17]Université de Paris, AP-HP, Hôpital Saint-Louis, Centre d'Investigations Cliniques, Paris, France; [18]Sierra Oncology, Inc., San Mateo, CA, USA; [19]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Presentation 627 | Presented at the 64th American Society of Hematology Annual Meeting & Exposition, New Orleans, LA, USA | December 10-13, 2022

Hopefully, I'm not talking too fast. Finally, there's momelotinib and this one actually just got approved last month, which was a real exciting thing because momelotinib has had some very nice results for patients who have anemia. This also has a fairly prolonged story of how it got approved. I won't go into all the details, but I think the important thing to note about momelotinib is this is a study that got it approved momelotinib versus danazol. When they went to the FDA and said, "How are we going to show you that momelotinib works for approval?" They really went on the approval based on the improvement in anemia? They said, "What's the only treatment we really know that can help anemia and myelofibrosis?" Danazol was chosen as the treatment arm.

Momelotinib Inhibits JAK1, JAK2, and ACVR1 to Address MF Symptoms, Spleen, and Anemia



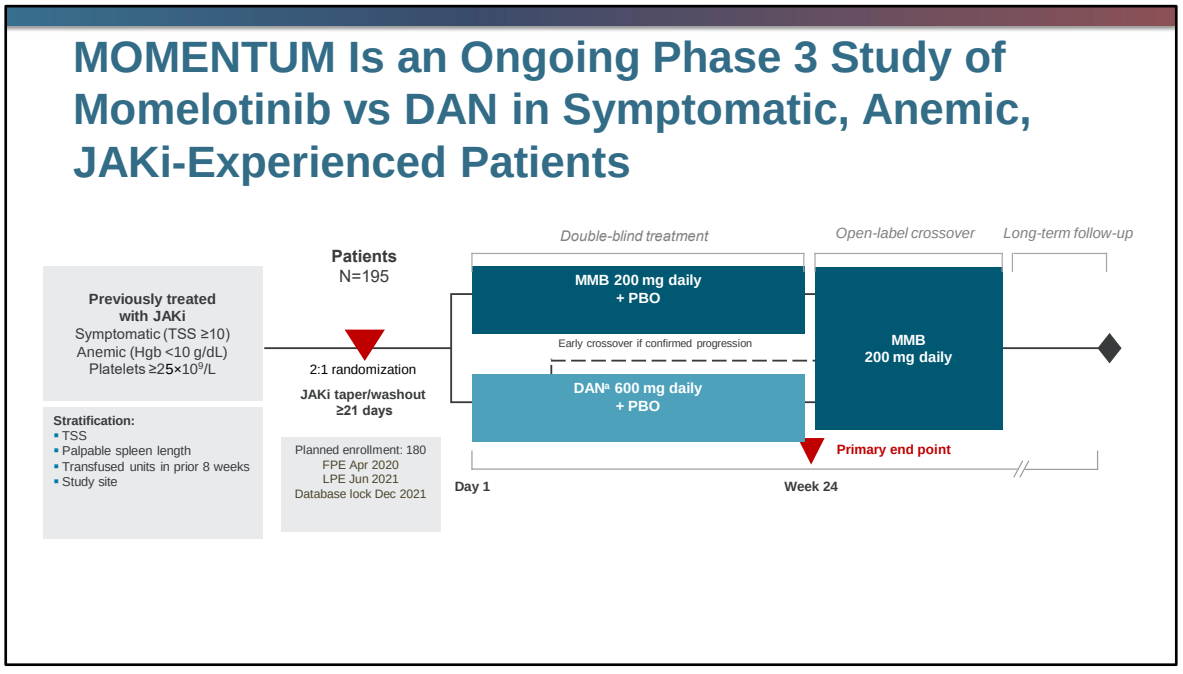
Dysregulated **JAK-STAT signaling** in MF drives overproduction of inflammatory cytokines, **bone marrow fibrosis, systemic symptoms,** and clonal proliferation resulting in extramedullary hematopoiesis and **splenomegaly**[1,2]

Chronic inflammation also drives hyperactivation of **ACVR1**, elevated **hepcidin**, dysregulated iron metabolism, and **anemia** of MF[3,4]

ACVR1, activin A receptor type 1; BMP, bone morphogenetic protein; EPOR, erythropoietin receptor; MPL, myeloproliferative leukemia protein; SMAD1/5, mothers against decapentaplegic homolog 1/5; STAT, signal transducer and activator of transcription.

1. Chifotides HT, et al. *J Hematol Oncol*. 2022;15(1):7. 2. Verstovsek S, et al. *Future Oncol*. 2021;17(12):1449-1458. 3. Asshoff M, et al. *Blood*. 2017;129(13):1823-1830. 4. Oh ST, et al. *Blood Adv*. 2020;4(18):4282-4291.

Momelotinib inhibits JAK1 and JAK2, which is similar to what the other JAK inhibitors do, but the other thing it does is it actually blocks ACVR1 and in doing so, as I said before, decreases hepcidin, which improves anemia.



When it was initially looked at with regards to spleen size and symptom burden, the results were not quite as pronounced as one would hope. Then when you looked at it closer and you said, geez, people who had improvement in their anemia did really well. They really proceeded and pushed forward with this, which was a good thing.

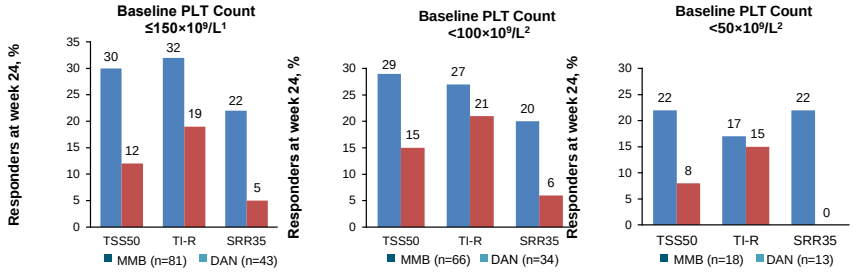
The studied patients who went on MOMENTUM previously treated with a JAK inhibitor symptomatic, they had to have a hemoglobin of less than 10. This study took patients whose platelets could be as low as 25. Now, I'll point out that both ruxolitinib and fedratinib are FDA-approved for patients whose platelets are greater than 50, pacritinib for patients lower than 50, so this is sort of encroaching on that pacritinib space. There's momelotinib versus danazol and they were allowed to crossover at week 24, which is when they did the primary endpoint assessment.

MOMENTUM Results

MOMENTUM Topline Results at Week 24: All Primary and Key Secondary End Points Met[1,2]

	MFSAF TSS[b] response rate (primary end point)	TI response[c] rate	SRR[d] (35% reduction)
MMB (N=130)	32 (24.6%)	40 (30.8%)	30 (23.1%)
DAN (N=65)	6 (9.2%)	13 (20.0%)	2 (3.1%)
	P=.0095 (superior)	1-sided *P*=.0064 (noninferior)	*P*=.0006 (superior)

Efficacy in Patients With Thrombocytopenia Was Consistent With the Overall ITT Patient Population



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

What they found is a couple of things. Number one, more patients who got momelotinib had a symptom response as compared to those who got danazol, which is not unexpected because danazol really only helps anemia. Additionally, you would expect that the spleen volume reduction was much better in momelotinib as danazol because danazol is not designed to shrink the spleen.

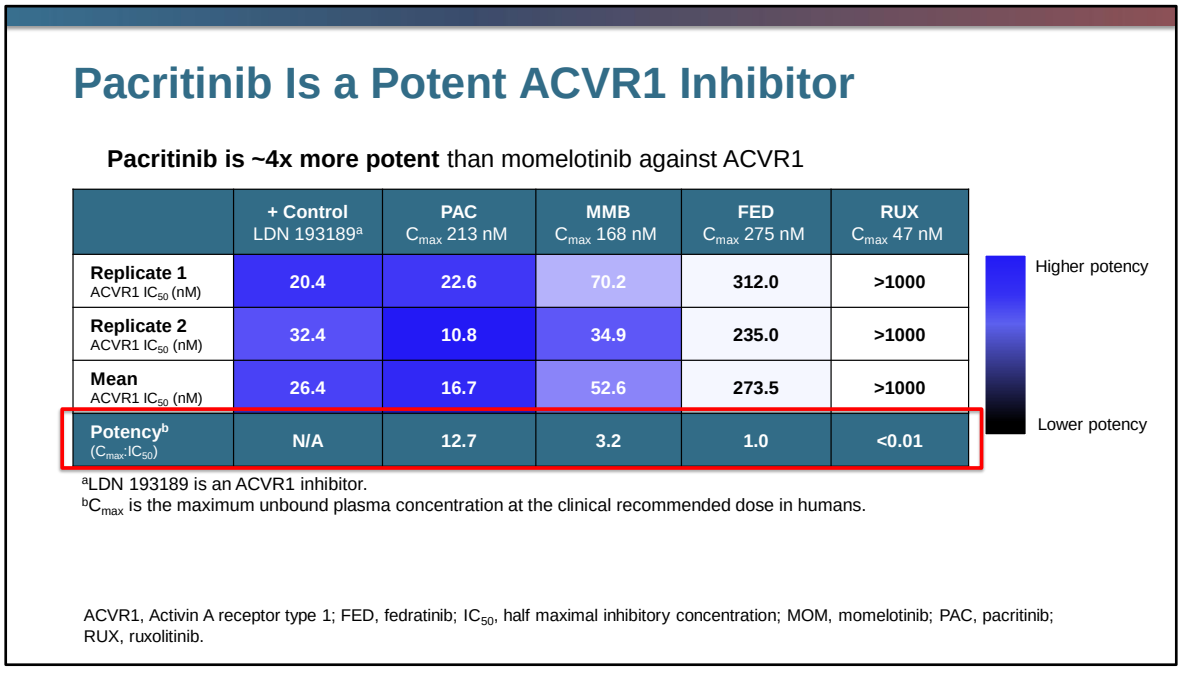
The big thing that people wanted to watch is the transfusion independence rate and then that was found to be non-inferior in momelotinib versus danazol. Going back to that original question of how are these findings, again, it's probably not that important to remember what was the superior versus what was non-inferior. I think the take-home of momelotinib is, not only do we get the benefits of JAK inhibition, which are shrinking the spleen and making you feel better, but you also may get some transfusion independence, which is a big plus to patients for not only reasons of quality of life, but actually, is associated with survival benefit.

TEAEs in ≥10% of Patients During OL MMB Treatment with No New Safety Signals Detected

	MMB→MMB (n=93)		DAN→MMB (n=41)	
	% of patients			
Grade ≥3 adverse events	49.5		46.3	
Serious adverse events	31.2		29.3	
	Any grade	**Grade ≥3**	**Any grade**	**Grade ≥3**
Nonhematologic (preferred term)				
Weight decreased	7.5	0	14.6	0
Diarrhea	14.0	1.1	12.2	0
Pyrexia	14.0	0	7.3	0
Hypertension	3.2	0	12.2	2.4
Asthenia	11.8	3.2	0	0
Hematologic (preferred term)				
Thrombocytopenia	14.0	8.6	17.1	14.6
Anemia	10.8	8.6	7.3	2.4
Neutropenia	5.4	5.4	4.9	0
Other				
COVID-19 (pneumonia)	10.8	5.4	0	0
Peripheral sensory neuropathy	2.2	0	2.4	0

DAN, danazol; MMB, momelotinib; OL, open-label; TEAE, treatment-emergent adverse event
Mesa RA, et al. ASCO 2022. Oral Presentation 7002.

The treatment emergent adverse effects, patients still could get thrombocytopenia, anemia, neutropenia and then this is looking at any grade or grade 3. You also did see some diarrhea in patients. Now, one of the side effects that they were particularly interested in was peripheral neuropathy is in some of the original momelotinib studies that seemed to be a problem. It did not appear to be a problem in this study.



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

Higher potency

Lower potency

[a]LDN 193189 is an ACVR1 inhibitor.
[b]C_{max} is the maximum unbound plasma concentration at the clinical recommended dose in humans.

ACVR1, Activin A receptor type 1; FED, fedratinib; IC_{50}, half maximal inhibitory concentration; MOM, momelotinib; PAC, pacritinib; RUX, ruxolitinib.

Now, when all of this came about and pacritinib started to look at their data and said we improve anemia, they actually also showed that they do inhibit ACVR1 too. When we look at these different drugs, all the different JAK inhibitors, I think the way that I always put them in my head is you have ruxolitinib and fedratinib. Both can cause anemia and thrombocytopenia and are both good for patients who have reasonable counts.

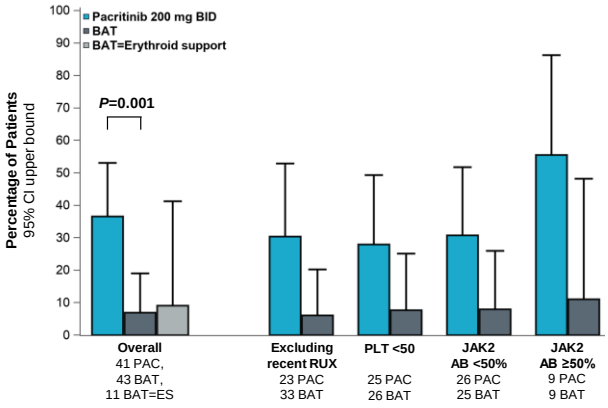
Honestly, I think for patients who have anemia, you have momelotinib and pacritinib. I think pacritinib is probably really good for the patients with super-low platelets. Both of them can be used in anemia. I think a lot of what's going to determine this is people's comfort and how their experience goes with the drug. I think when you look at pacritinib and momelotinib, there are a lot of similarities to the two, and I think they both can provide a really good benefit for patients who otherwise wouldn't have a benefit. There are a lot of data out there trying to compare all these different small molecular aspects of it. Although it's interesting, I don't know that it necessarily is going to change how I practice.

Transfusion Independence

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

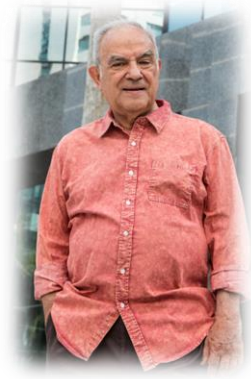
Rate of TI (Gale criteria) through Week 24



AB, allele burden; BAT, best available therapy; ES, erythroid support; JAK, Janus associated kinase; PAC, pacritinib; PLT, platelets; recent RUX, no ruxolitinib in prior 30 days; TI, transfusion independence.

This is looking at transfusion independence in pacritinib.

Case 2: Conclusion



*HIPAA-compliant, stock photo (not actual patient).

Patient continued on ruxolitinib; erythropoietin added
There is initial increase in Hgb and patient is no longer requiring transfusions

- 6 months later: Anemia and thrombocytopenia worsen despite increasing dose of erythropoietin. Dose of RUX is reduced to try to mitigate anemia
- No improvement in anemia is noted and spleen size begins to increase
- Patient is switched to pacritinib 200 mg BID. Spleen size decreases and Hgb is now 9 g/dL

In conclusion, this patient was on ruxolitinib. He had erythropoietin added because his hemoglobin dropped. Six months later, anemia and thrombocytopenia worsened despite increasing doses of erythropoietin. The dose of ruxolitinib is decreased to try to mitigate anemia. Unfortunately, when that happens, the spleen size grows and people feel worse. Then the patient was switched to pacritinib 200 mg twice daily, had an improvement in spleen size, and the hemoglobin now went up. Now, in this patient probably in today's day, and again, we haven't, I don't think, changed these slides since the approval of momelotinib one month ago, you could probably be reasonably using either the pacritinib or the momelotinib especially if their platelets are greater than 25.

Case 3: A Patient with Myelofibrosis on Treatment

Patient Presentation:

76 yo M presents with fatigue, weight loss, and abdominal fullness

- Exam: Splenomegaly (12 cm below costal margin)

Lab Results

- **CBC: WBC 9.5k (3% blasts), Hb 10.5 g/dL, platelets 181k**
- Bone marrow biopsy: 90% cellular marrow with myeloid expansion, dysplastic megakaryocytes in clusters, and MF-3 fibrosis with 5% myeloid blasts
- Cytogenetics: Normal karyotype
- Myeloid NGS panel: *JAK2* V617F+, *ASXL1+*

Treatment

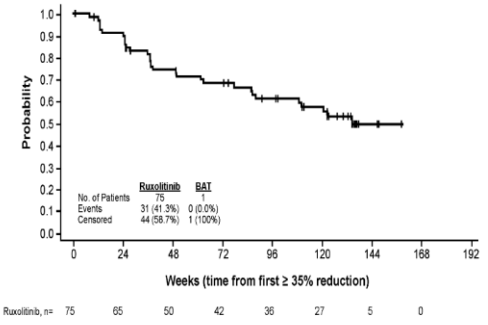
- Started on ruxolitinib 10 mg BID
- Notes improvement in constitutional symptoms and gains weight
- Spleen size reduction on follow-up 6 months after starting ruxolitinib is modest (10 cm)

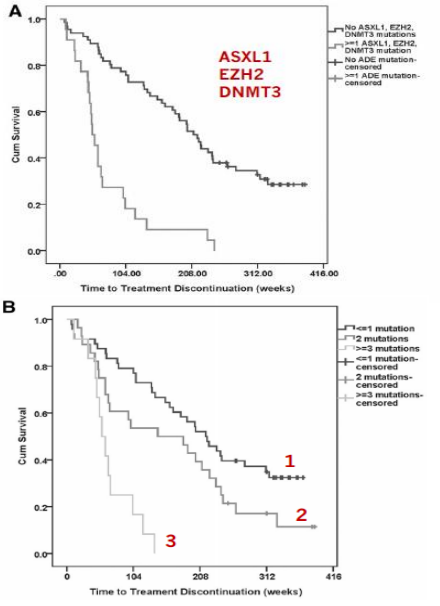
What strategies are emerging to extend the benefits of JAK inhibition?

Then finally, in the last couple minutes before we have questions, this is a patient who is currently on treatment. This is a patient who is 76, has fatigue, weight loss, abdominal fullness, he had splenomegaly, and his blood counts as you see there, white blood cell count of 9.5 with 3% blast, hemoglobin of 10.5, and platelets of 181. Bone marrow biopsy was cellular. He had a little bit of fibrosis and he had 5% blasts in his marrow. Cytogenetics were normal and he had a JAK2 mutation as well as an ASXL1. He was started on ruxolitinib 10 mg twice daily and initially noted some improvement in constitutional symptoms and started to gain weight. His spleen size reduction is not that great. It was only modest so he didn't actually meet those criteria for endpoint.

Now, I think one of the take-home messages here is patients who have these high-risk mutations are less likely to respond to ruxolitinib and their duration of response is shorter. What are we doing for these patients? How can we improve things?

Limits of Duration of Efficacy of Ruxolitinib



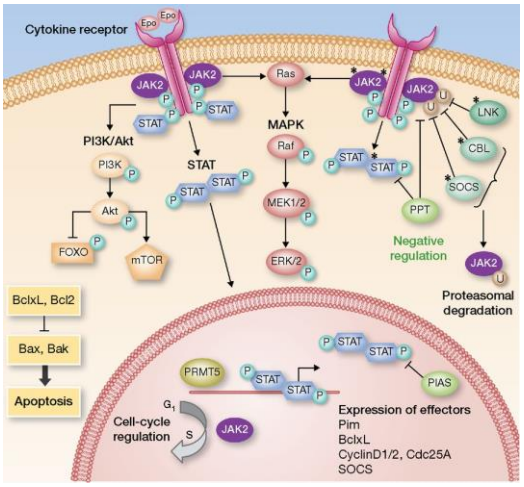


*Pacritinib or fedratinib may be used second line after ruxolitinib

Cervantes F, et al. *Blood.* 2013.122(25):4047-4053.;
Patel K, et al. *Blood.* 2015.;126(6):790-797.

As I pointed out, the ASXL1 some of these mutations, again, decrease the duration of response as well as the likelihood of response in ruxolitinib. If you look at all players who'd get ruxolitinib, especially based on the COMFORT studies, the median time of response is three years. Ultimately, you are looking at a drug that has great efficacy, but it has its limitations.

Activation of Overlapping Cell Signaling Pathways May Provide Novel Therapeutic Targets

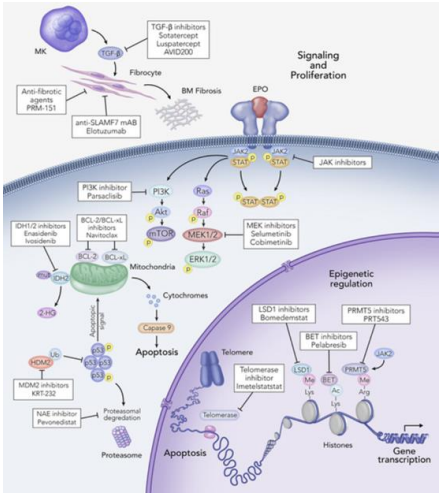


- Co-targeting of aberrantly activated downstream pathways
  - Combination therapy in front-line setting
  - Additive to current JAK inhibitor

Meyer S, Levine R. *Clin Cancer Res*. 2014;20(8):2051–2059.

One of the things that you're going to see coming up is this is a really complex pathway that works into making this disease grow and makes this disease bad. You have a number of different areas like the PI3 kinase pathway, this is the JAK2 and this is the JAK/STAT signaling that is one of the big drivers of it but as you can see, there's a number of other things here. There's PI3 kinase, there's Bcl2, there's a MAPK pathway. There's all these other pathways that we're trying to say, is there a way we can target these pathways to make the response more durable or better? These are drugs that are being currently tested.

Add-on to Ruxolitinib/Post-Ruxolitinib Therapeutic Approaches in Clinical Development



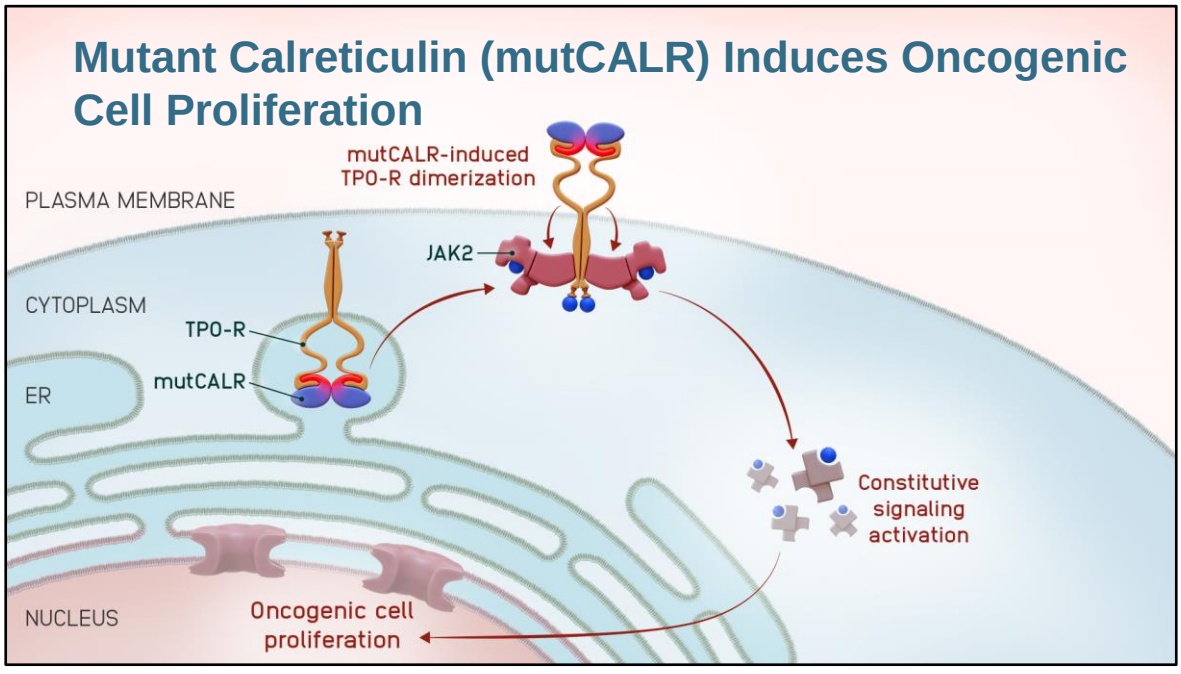
Drug	Mechanism	Phase
CPI-0610	BET inhibitor	III
Navitoclax	BCL-XL-BCL-2 inhibitor	III
Imetelstat	Telomerase inhibitor	III
Bomedemstat	LSD1 inhibitor	II
KRT-232	MDM2 inhibitor	III
Momelotinib	JAK2/ACVR1 inhibitor	III
Selinexor	XPO1 inhibitor	I/II
TP-3654	PIM Kinase Inhibitor	I

- Single agent
- Add-on to ruxolitinib
- Both single agent or add-on to ruxolitinib

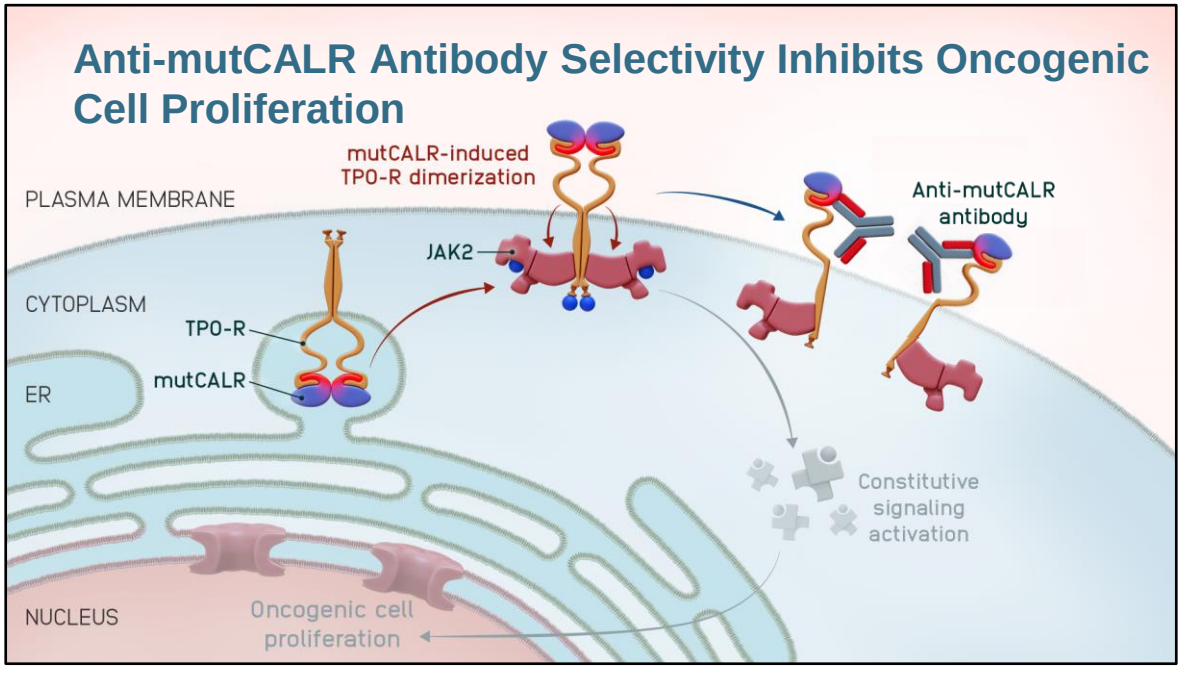
Pettit K, et al. *Am Soc Clin Oncol Educ Book*. 2022;42:1-19.

I think right now, the add-on to RUX or post-ruxolitinib approaches that are in clinical development are CPI-0160. That is a BET inhibitor that's showing some really, really nice responses. Not only as a way to help reduce or improve the response, like if somebody starts losing their response to ruxolitinib but upfront can maybe enhance the response and make it a more durable response. Navitoclax the same thing. These are both in phase 3 studies. Imetelstat, this is a telomerase inhibitor. This is in a phase 3 study. Again, this one actually potentially may have a survival advantage.

There's bomedemstat, which is an LSD1 inhibitor that's really been shown to have great data in essential thrombocythemia but it's also being studied in the setting of myelofibrosis. KRT-232, this is an MDM2 inhibitor that's currently in phase 3 studies. There's momelotinib, which actually we need to take off on clinical development because it's FDA-approved. Selinexor, which also is actually now in phase 3 studies. Then there's a PIM kinase inhibitor as well. There's a number of different things that we're studying to try to really improve our ability to treat these patients above and beyond JAK inhibitors.



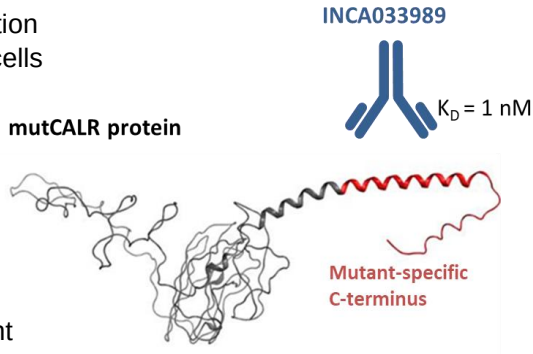
The most exciting thing was actually plenary session abstract to ASH last year. This is targeting the mutant calreticulin. One thing about the calreticulin is that actually, the mutated part of the protein exists outside of the cell not internal to the cell. It's a great target for immunotherapy.



Now they've developed an antibody that actually targets CALR. You see that little blue thing outside of the cell with like the red tail, that's a mutant CALR and then the antibody attaches it and they've shown at least in preliminary lab work that this may be of benefit. Not something that's going to be in primetime in the next few years, but definitely something that's very, very exciting.

INCA033989: A mutCALR-specific Monoclonal Antibody

- Fully human IgG1 selective for mutant CALR Inhibits mutant CALR-dependent TPO-R dimerization
- Does not exhibit function effect on Ba/F3 cells not expressing mutant CALR
- Synergism observed between INCA033989 and ruxolitinib
- Showed potential to selectively target mutant CALR HSPCs while preserving proliferation/ differentiation of WT counterparts
- Studied in cell lines, primary CD34+ patient cells and in vivo MPN models



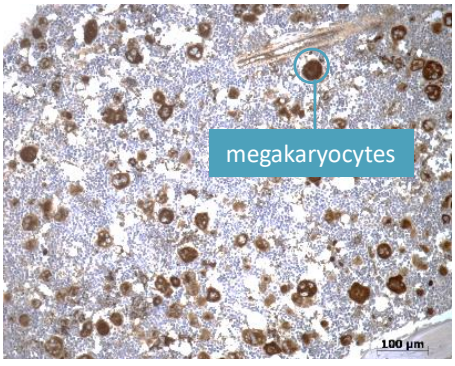
Structure generated with RaptorX (Toyota Technological Institute at Chicago, IL, USA).
IgG, immunoglobulin G; Fc, fragment crystallizable; K_D, equilibrium dissociation constant.

Reis E, et al. Oral abstract #6. 64th ASH Annual Meeting and Exposition. December 11, 2022; New Orleans, LA, USA.

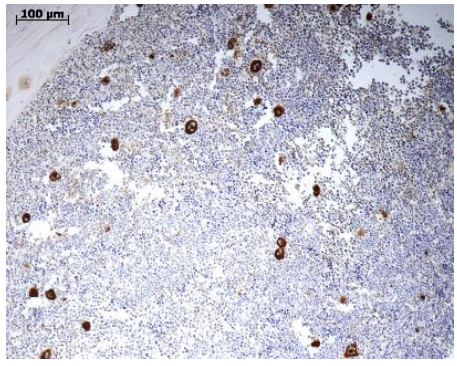
This is the CALR monoclonal antibody

INCA033989 Surrogate Treatment Re-establishes Normal Megakaryopoiesis

Isotype



INCA033989 (mouse surrogate)



Megakaryocytes stained with anti–von Willebrand factor antibody.

Caroline Marty, Elodie Rosa, Maxime Evrard, William Vainchenker, Isabelle Plo. Gustave Roussy Institute, INSERM, Université Paris-Saclay.

And just some of the surrogate endpoints that show that it may work. This is in a mouse, which we know is the best place to start doing research.

Treatment Approaches to Myelofibrosis
Clinical Needs-Oriented Therapy for MF

Clinical Issue	Treatments	
Anemia	• ESAs • Danazol • Corticosteroids	• Thalidomide, lenalidomide (IMiDs)
Symptomatic splenomegaly	• Ruxolitinib • Fedratinib • Pacritinib	• Cladribine, IMiDs • Splenectomy • Hydroxyurea
Constitutional symptoms/QoL	• Ruxolitinib • Fedratinib	• Pacritinib
Extramedullary hematopoiesis	• Radiation therapy	
Hyperproliferative (early) disease	• Interferon	
Risk of thrombosis	• Low-dose ASA	
Accelerated/blastic phase	• Hypomethylating agents	
Improved survival	• Allogeneic HCT	• Ruxolitinib

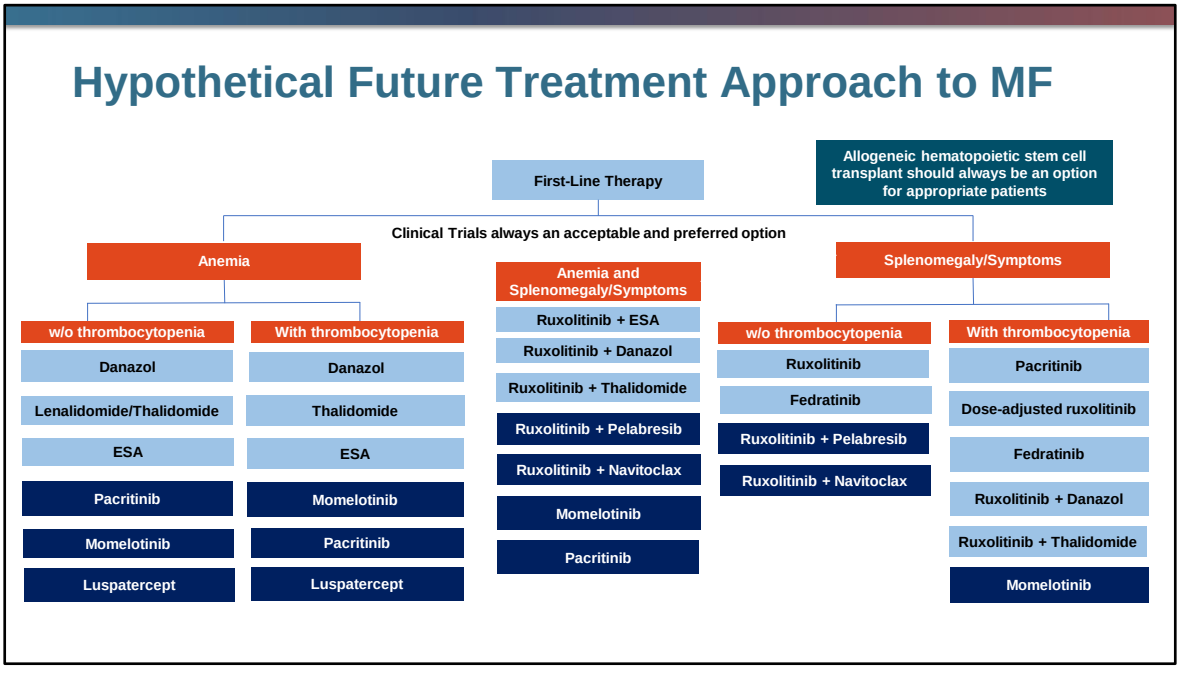
NCCN. Clinical Practice Guidelines: Myeloproliferative Neoplasms. Version 3.2022. www.nccn.org. Accessed 4/10/23

Just to summarize, when we think of treating myelofibrosis, we do want to always think about it from what are the clinical issues that we need to address. With anemia, I think using ESAs, danazol, corticosteroids, luspatercept. When we have symptomatic splenomegaly, things like ruxolitinib, fedratinib, pacritinib, and momelotinib. Constitutional symptoms is still all of the JAK inhibitors because they really do help improve constitutional symptoms and quality of life. If patients have extramedullary hematopoiesis, sometimes we can consider radiation therapy. Then as we go down and these are things we didn't necessarily discuss in the presentation, the risk of thrombosis, accelerated blast phase, and improved survival. I think these are all things that we're working on trying to make better.

Unmet Needs and Future Outlook

- Treatment of Myelofibrosis should be directed toward the major issues affecting the patient; anemia, symptomatic splenomegaly, constitutional symptoms
- JAK inhibitors have demonstrated efficacy in reducing spleen size and alleviating symptom burden
- Anemia and thrombocytopenia remain important challenges in treating Myelofibrosis, but newer and emerging JAK inhibitors such as pacritinib and momelotinib are demonstrating clinical benefit in these situations
- Durability and depth of response to JAK inhibitors remain significant clinical challenges. However, a number of emerging agents are in late-phase clinical development (both in combination with ruxolitinb and as single agents) and have demonstrated promising results in phase II trials

What are the unmet needs and future outlooks? Right now we've really figured out how to harness our treatments against symptoms and spleen, etc., but really patients are saying, "What's going to make me live longer?" That's something that we need to focus on. JAK inhibitors, what do we do when they quit working and how do we make them last longer or be more effective? Anemia and thrombocytopenia, we have therapies now, which is fantastic, but we probably need more. Then again, what can we do to make these JAK inhibitors work better?



This is a hypothetical future approach. You have anemia with and without thrombocytopenia and different approaches you can take. Anemia, splenomegaly, and symptoms. Then when you look at splenomegaly and symptoms with and without thrombocytopenia. There's a number of different things that we can look at in terms of how we approach these patients.

All right. Well, thank you very much for your attention this morning, and hopefully, you'll have at least a little bit more knowledge about myelofibrosis and I didn't make it too overwhelming.

Moderator: Thank you for your great presentation and your teachings and your expertise.