Meeting Highlights in Myelofibrosis from the ASH Annual Meeting

Hello. Happy that everyone was able to join us today, along with my colleagues, Dr. Oh and Dr. Ali. I'm Andrew Kuykendall from Moffitt Cancer Center, and we'll be talking about Meeting Highlights in Myelofibrosis from the ASH Annual Meeting today. For myself, I'm an Assistant Professor at Moffitt Cancer Center in Tampa, Florida.

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Faculty Disclosures

- **Dr. Andrew Kuykendall** has relevant financial relationships related to advisory activities from AbbVie Inc., Blueprint Medicines (relationship has ended), Celgene Corporation – A Bristol Myers Squibb Company, CTI BioPharma Corp. (relationship has ended), Imago BioSciences (relationship has ended), Incyte Corporation (relationship has ended), Novartis AG (relationship has ended), and Sierra Oncology, Inc. He is on the speakers' bureau for Blueprint Medicines (relationship has ended), Celgene Corporation – A Bristol Myers Squibb Company, and Incyte, and has received research grant(s) from Blueprint Medicines (relationship has ended), Celgene Corporation – A Bristol Myers Squibb Company, and Sierra Oncology.
- **Dr. Stephen Oh** has relevant financial relationships related to consulting from AbbVie Inc., Bristol Myers Squibb Company, Cogent Biosciences, Inc., Constellation Pharmaceuticals, CTI BioPharma Corp., Geron, Incyte Corporation, Protagonist, and Sierra Oncology, Inc. (now GSK plc) (all relationships listed have ended).
- **Dr. Haris Ali** has relevant financial relationships related to consulting from Incyte Corporation, Bristol Myers Squibb Company, AbbVie Inc., CTI BioPharma Corp., Karyopharm, and PharmaEssentia Corporation. He is on the speakers' bureau for Incyte, Bristol Myers Squibb, and PharmaEssentia, and has received research grant(s) from Incyte.

Here are our disclosures.

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Briefly just want to go over a program overview. We'll get a chance to discuss some of the recent developments that came out of the ASH meeting. Hopefully provide some context to those kind of emerging thoughts.

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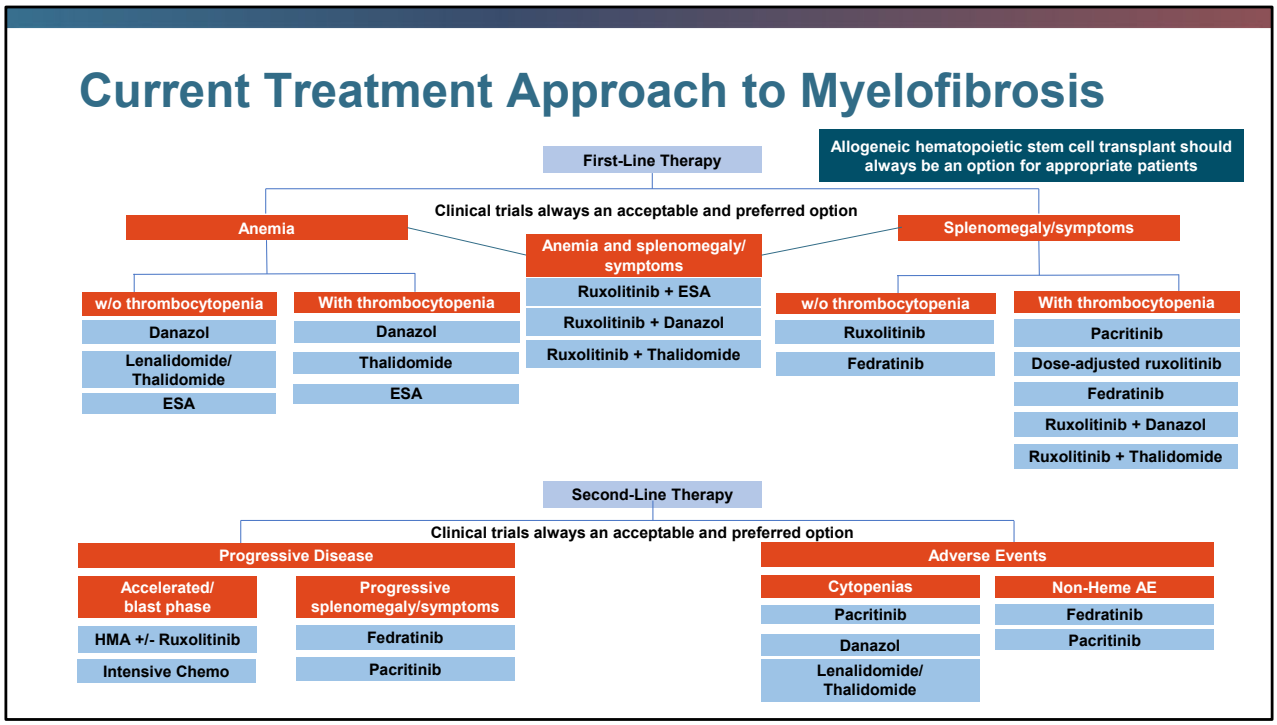

We separate things into maybe first-line or second-line therapy. Obviously, first-line treatment when someone's just presenting, what are you considering when coming up with what your treatment options are?

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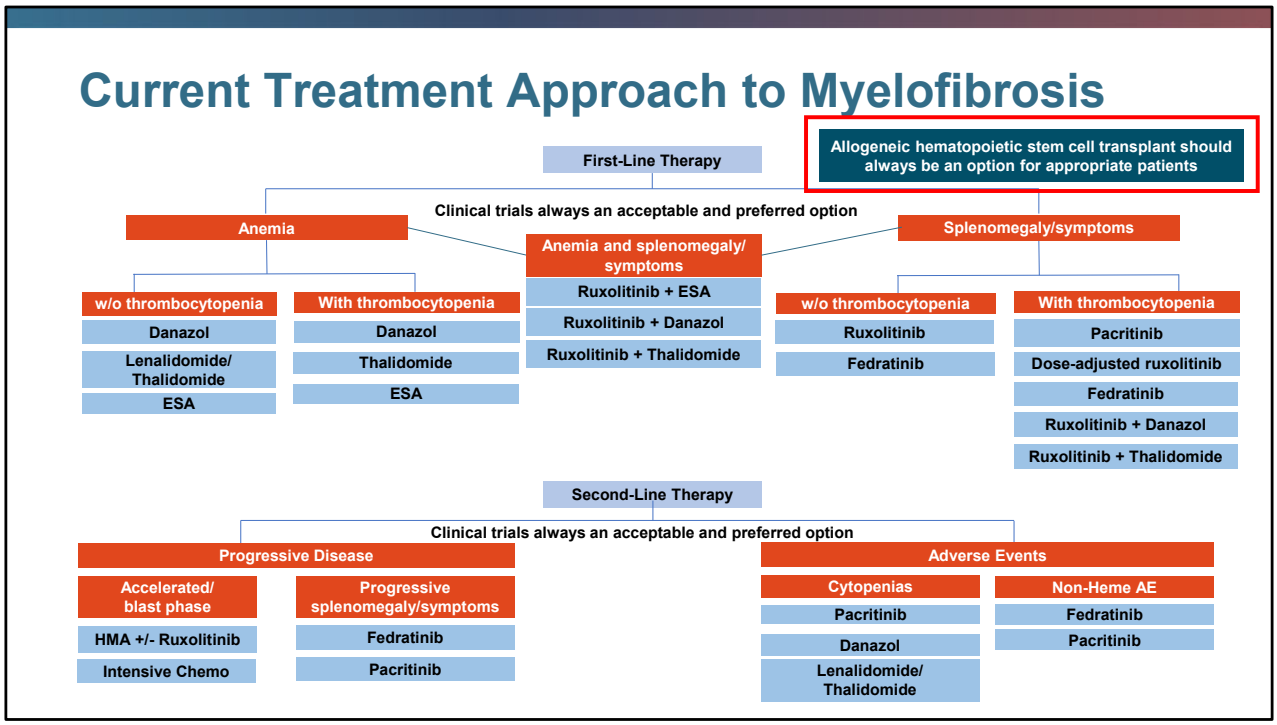

The first thing we've mentioned is that really there's nothing that replaces allogeneic hematopoietic stem cell transplant as this represents the only curative approach we currently have for myelofibrosis. Really this should be evaluated immediately in all patients to see whether or not they're a candidate. Again, this has to do with disease risk as well as patient-specific risk factors, but it should be offered to any patient who is appropriate.

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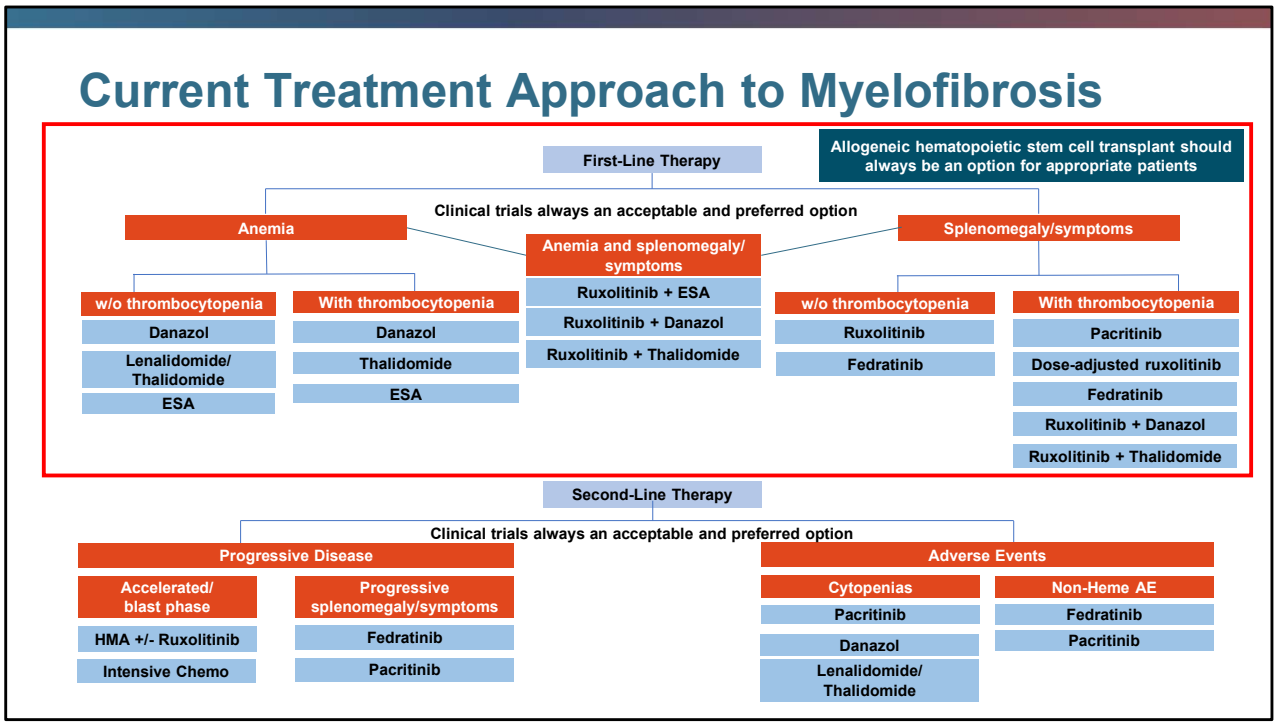

Beyond that, when we think about first-line therapies, I think the simplest thing we think about is splitting people into what are you trying to accomplish. These are not therapies that offer true complete remissions or partial remissions. They don't have great evidence for disease modifications. When we think about that, what we're really trying to do is improve patient-specific factors or disease-specific factors on a patient-by-patient basis. Very roughly, patients can be divided into whether we're targeting splenomegaly or symptoms or if we're targeting anemia.

If we're targeting splenomegaly or constitutional symptoms, things like fevers, chills, night sweats, bone pain, weight loss, oftentimes we're thinking about some JAK inhibitor-based therapy. This is stratified by whether or not patients have intact platelet counts as many of our JAK inhibitors cause worsening of platelet counts. In patients that do not have significant thrombocytopenia, we're often reaching for ruxolitinib, although we could also use fedratinib, which is approved as well with the line agnostic fashion.

In patients that have more thrombocytopenia, specifically platelets less than 50,000, we have the accelerated approval of pacritinib for this patient population that we can use there, but also things such as dose-adjusted ruxolitinib, lower doses. Fedratinib certainly could be an option, especially in this borderline platelet count of 50,000 to 100,000. Then maybe some combinations of ruxolitinib with danazol, ruxolitinib with thalidomide. These are things that have been tested in clinical trials and show some potential there.

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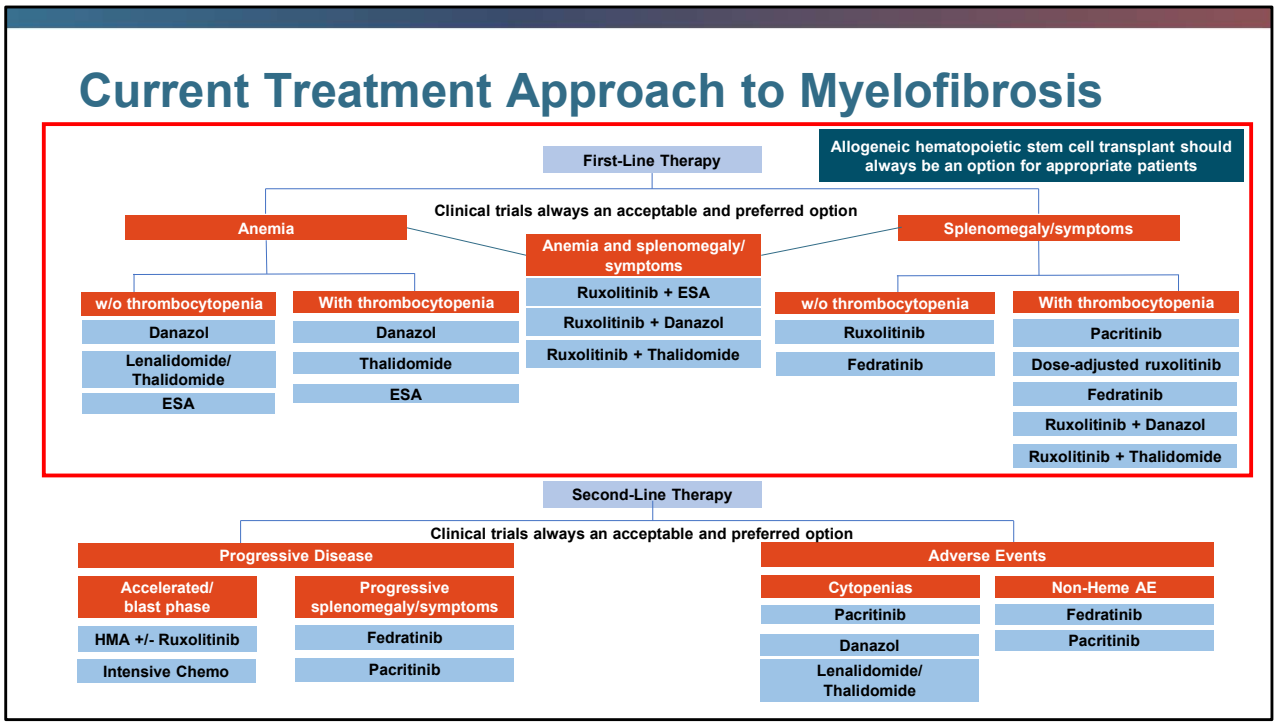
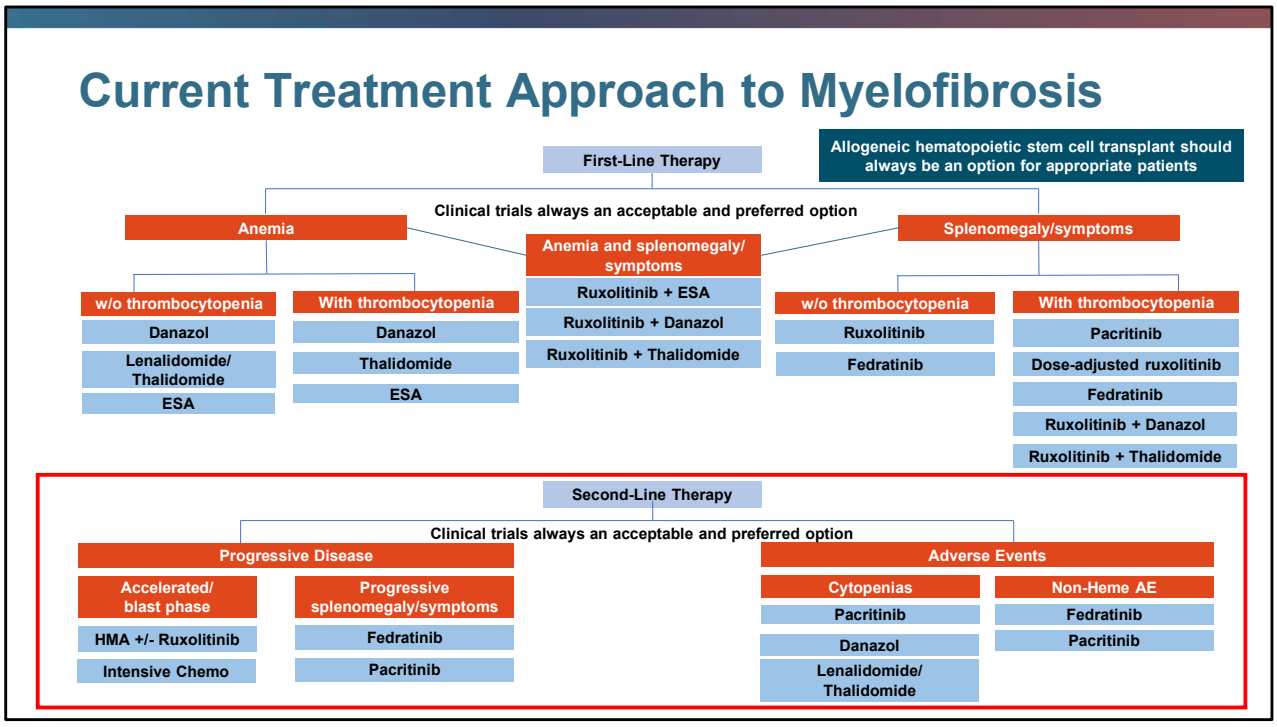


On the other hand, you have some patients, certainly a minority of patients, that may not have substantial splenomegaly or constitutional symptoms, and you may be targeting more anemia in this patient population. Again, we think about low platelets. This can stratify the treatment options we have in patients that have no issues with their platelets but certainly have anemia that needs treated. We can use things like danazol, lenalidomide, thalidomide, erythropoiesis-stimulating agents.

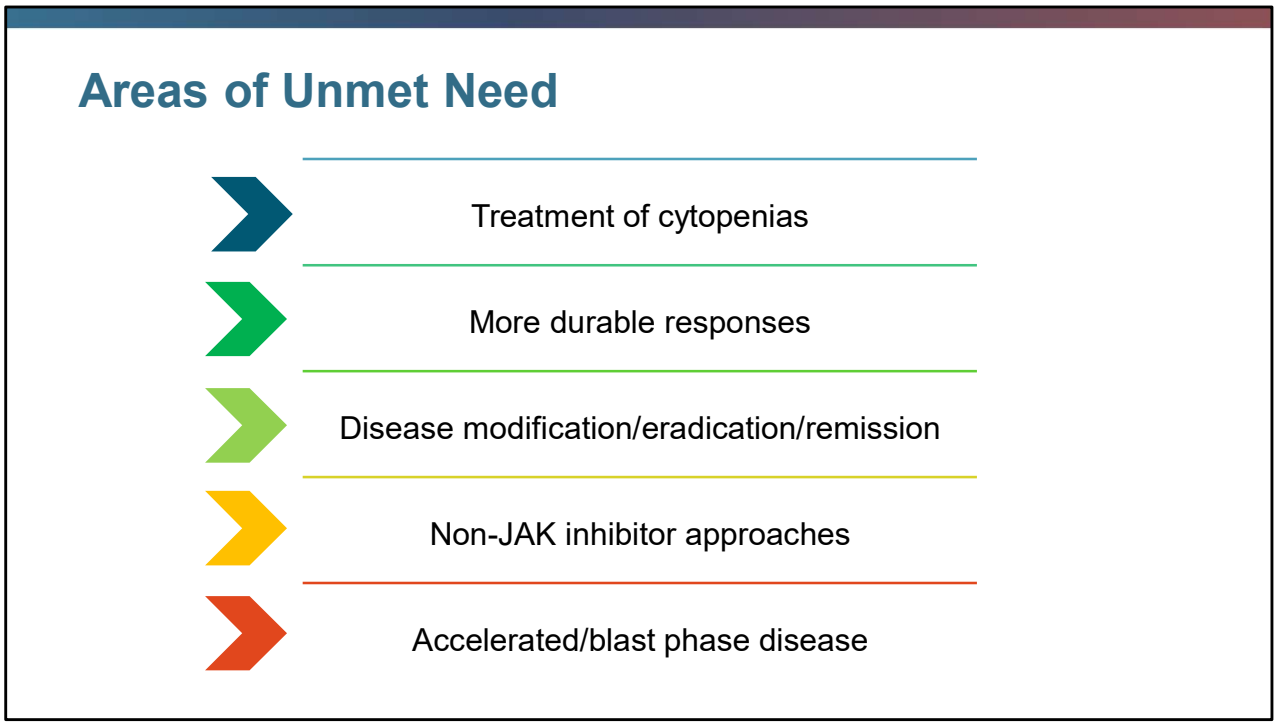
Patients with thrombocytopenia, we often are reaching for some of these same options, but with the exclusion of maybe lenalidomide, which can worsen platelet counts, so we'll use things like danazol, thalidomide, or ESAs. Oftentimes we have an overlap with patients that have both anemia and splenomegaly or symptoms. There we're grasping for combination therapies, often using ruxolitinib, but maybe using an agent that may support the red blood cell count or the platelet count at the same time.



Then when we move to second-line therapy, really we're thinking about the same agents, but we're really thinking about why we're moving to second-line therapy.

In patients that have progressive spleen or symptoms, we're trying an alternative JAK inhibitor, maybe one that can be dosed a little bit more aggressively in lower counts. In patients that have adverse events such as cytopenias, then we need to think about supporting those cytopenias, maybe using pacritinib that can be used to lower platelet counts, or some of these anemia-based agents. Then certainly if we're having nonhematologic AEs, we might choose an alternative JAK inhibitor that may not have the same AE profile.

I'll mention that for accelerated blast phase disease, we have very poor treatment options for this group of patients. We're often using hypomethylating agents plus or minus JAK inhibitors if patients have some degree of splenomegaly, then rarely, but occasionally, we're using intensive chemotherapy, hopefully, as a bridge to allogeneic stem cell transplant.



When we think about areas of unmet need, I think there's certainly a few here. It's the treatment of cytopenias. We need more durable responses.

We need to see true disease modification, or eradication, remission, whatever you want to call it. We need to see the disease going away. We'd like to develop some non-JAK inhibitor approaches. Certainly, we have several JAK inhibitors that are approved, but we know there's more to the disease than that. Then, as I mentioned, accelerated blast phase disease remains an area of critically unmet need.

Emerging Agents of Interest

Agent	Target(s)	Potential Clinical Impact
Pacritinib	→ JAK2, IRAK1, FLT3, ACVR1	→ Spleen, symptoms, anemia
Momelotinib	→ JAK1/JAK2/ACVR1	→ Spleen, symptoms, anemia
Pelabresib	→ BET	→ Synergism with JAKi
Navitoclax	→ BCL2/BCL-xL	→ Synergism with JAKi
Parsaclisib	→ PI3K-δ	→ Synergism with JAKi
Luspatercept	→ Activin receptor ligand trap	→ Anemia
Navtemadlin	→ MDM2	→ Spleen, symptoms, disease modification
Imetelstat	→ Telomerase	→ Disease modification, survival

When you think about emerging agents of interest, these are some agents that are currently in late-phase clinical development.

We have pacritinib, which actually has this accelerated approval for very low platelet counts, but also has an ongoing confirmatory phase III study that's in the works. Momelotinib has a positive result from the phase III study, from the MOMENTUM study, which we'll talk about and certainly, we're hoping for potential approval here in the next few months. Then we have pelabresib, which is a BET inhibitor, shown ability to synergize with JAK inhibitors, as is navitoclax, a Bcl-2, Bcl-xL inhibitor.

Parsaclisib is a PI3 kinase delta inhibitor, which is in development in the frontline setting in combination with JAK inhibitor, although the recent add-on study was just shut down for futility. Luspatercept is an anemia-based agent approved for MDS and thalassemia and is currently in late-stage development, looking at the ability to help anemia with patients with myelofibrosis. Navtemadlin, an MDM2 inhibitor, has some potential for maybe disease modification. It's certainly acting on a biologically relevant pathway, so we'll have to see how it shakes out in the clinic.

Then imetelstat , which is a telomerase inhibitor also in late-stage phase III clinical trial being tested in the relapsed refractory setting.

So now I will pass it over to Dr. Oh.

Thank you, Dr. Kuykendall. It's my pleasure to share with you all, some of the latest updates on JAK inhibitors.

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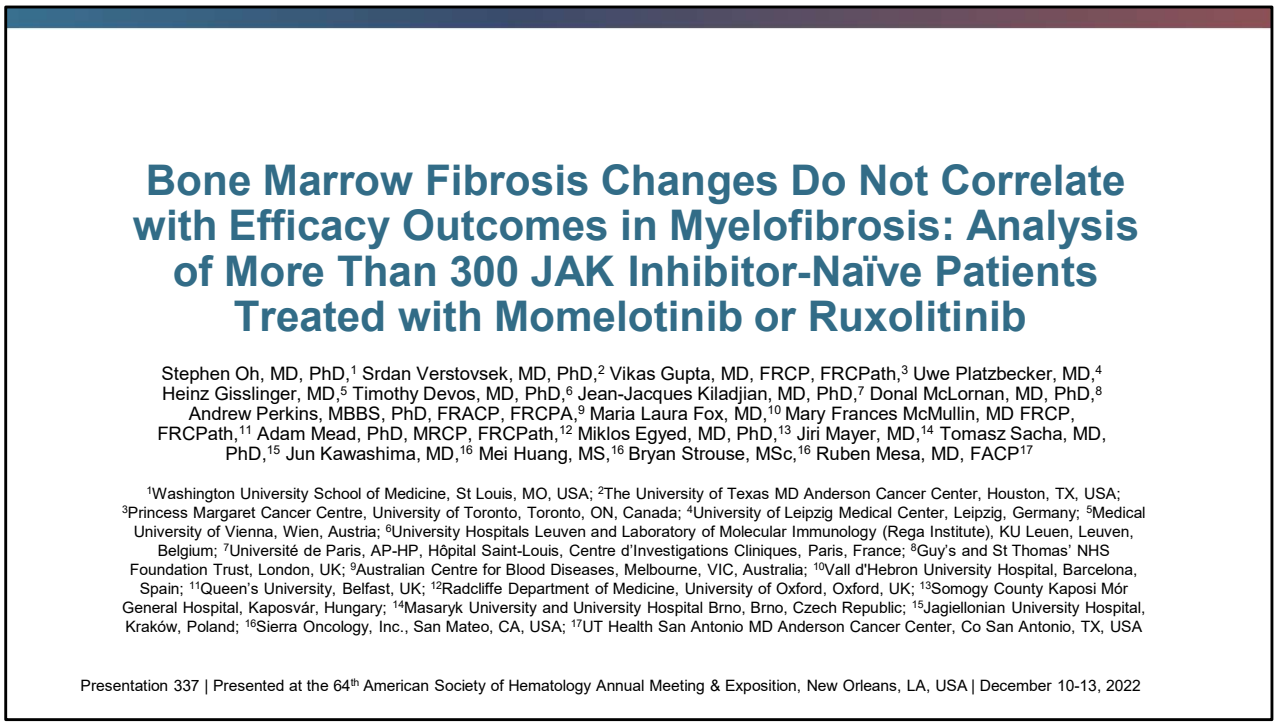

Bone Marrow Fibrosis Changes Do Not Correlate with Efficacy Outcomes in Myelofibrosis: Analysis of More Than 300 JAK Inhibitor-Naïve Patients Treated with Momelotinib or Ruxolitinib

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We're going to start with one of the presentations from the ASH meeting last December in which bone marrow biopsy, analysis of fibrosis changes from the SIMPLIFY-1 study in which patients with myelofibrosis were randomized to treatment with either momelotinib or ruxolitinib were analyzed.

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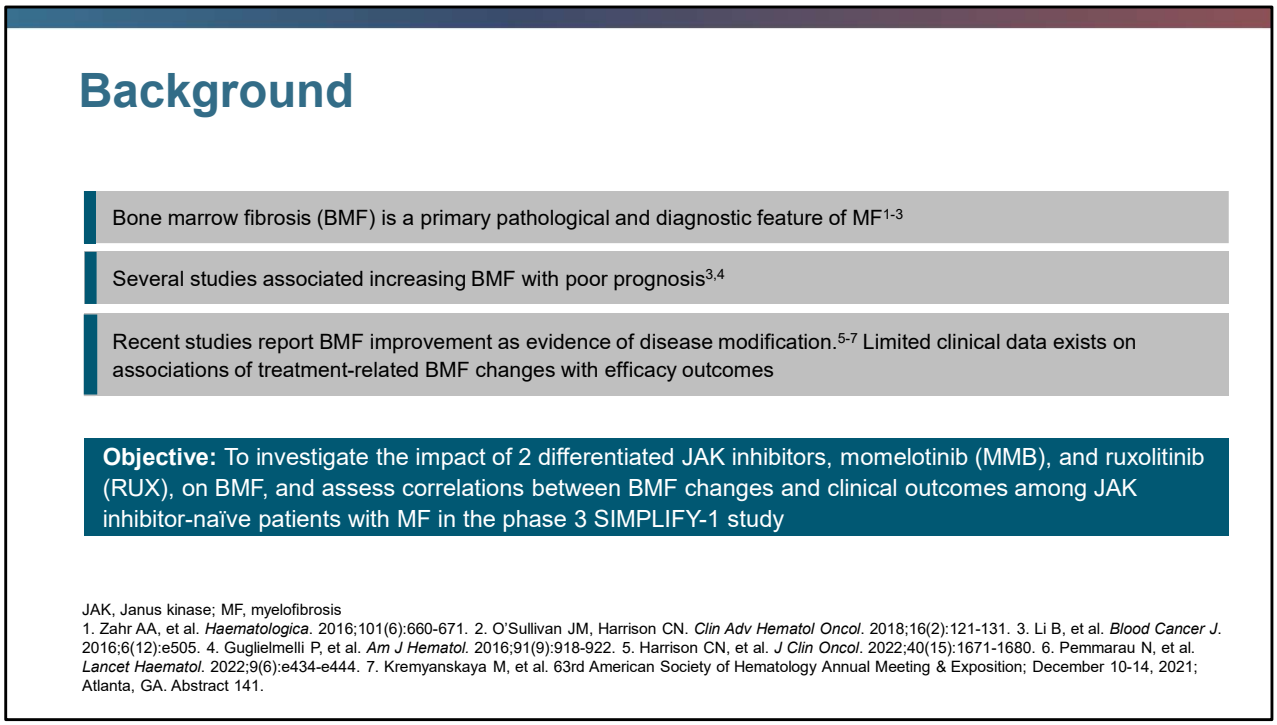

The background here is, of course, we know that bone marrow fibrosis in myelofibrosis is a key hallmark of the disease. There have been several studies that have associated increasing bone marrow fibrosis with poor prognosis.

Additionally, there has been some suggestion with some agents in development as to potential indication of disease modification as it relates to changes or improvement in bone marrow fibrosis. However, there's really limited data out there at the moment in terms of these particular associations. The objective of this study was to look at the impact of two differentiated JAK2 inhibitors, momelotinib and ruxolitinib in terms of bone marrow fibrosis changes, using the existing data from the completed SIMPLIFY-1 study to understand whether any changes in bone marrow fibrosis were correlated with clinical outcomes.

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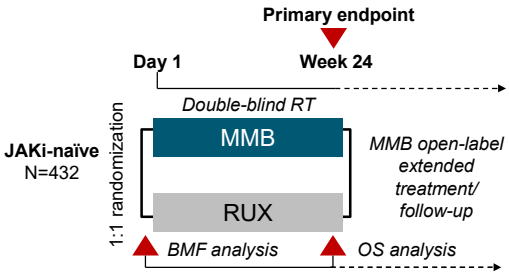
SIMPLIFY-1: Randomized, Head-to-Head, Double-Blind, Phase 3 Study of MMB vs RUX in >400 JAKi-naïve MF Patients

Methods

- BMF biopsies were collected pretreatment and after 24 weeks of momelotinib or RUX RT from >300 patients
- Grading was performed locally using an updated WHO scale from Grade 0 (normal BM) to Grade 3 (diffuse and dense increase in reticulin, etc.)
- The JAKi-naïve setting minimized prior treatment confounders
- The impact of RUX and momelotinib on BMF and MF-associated clinical outcomes were analyzed
- Other efficacy assessments made throughout the study included:
  - MFSAF symptom scoring (during RT period only)
  - Spleen volume imaging
  - TI status and Hgb levels



BMF analysis population (patients with paired baseline and week 24 biopsies read locally)
MMB: n=144; RUX: n=160

BM, bone marrow; BMF, bone marrow fibrosis; Hgb, hemoglobin; JAKi, Janus kinase inhibitor; MFSAF, Myelofibrosis Symptom Assessment Form; MMB, momelotinib; OS, overall survival; RT, randomized treatment; RUX, ruxolitinib; TI, transusion independence; WHO, World Health Organization.
Mesa RA, et al. *J Clin Oncol.* 2017;35:844-3850.

As many of you are probably aware, the SIMPLIFY-1 study again was patients with myelofibrosis randomized to either treatment with momelotinib or ruxolitinib. This was a total of over 400 patients with myelofibrosis who were JAK inhibitor naive. There were over 300 patients for whom there were bone marrow biopsies collected pre-treatment and then after 24 weeks on treatment with either momelotinib or ruxolitinib. This analysis was based on local grading of bone marrow fibrosis using the standard WHO scale of grade zero to grade three.

Again, this is patients who are JAK inhibitor-naive and then looking at associations with clinical outcomes.

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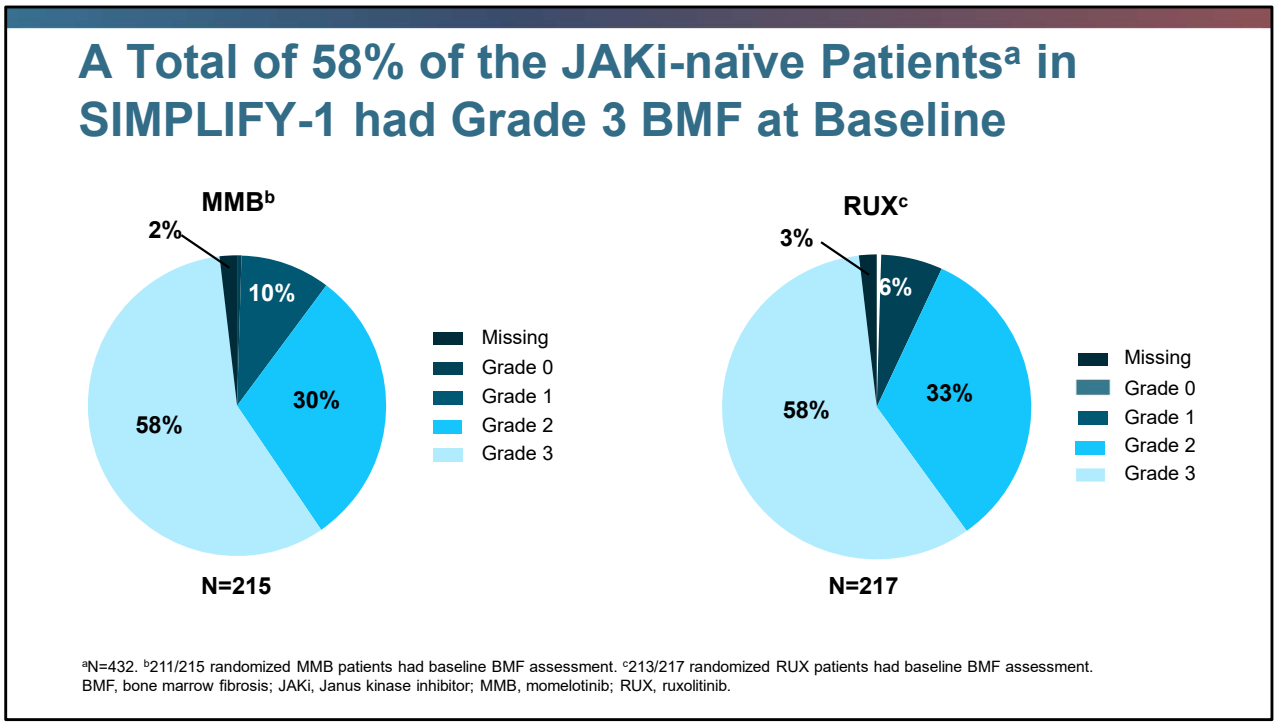

First, just some baseline data. In this study, over 50% of the patients in this study had grade 3 bone marrow fibrosis at baseline.

You can see the pie chart here, showing relatively similar distributions amongst the two groups.

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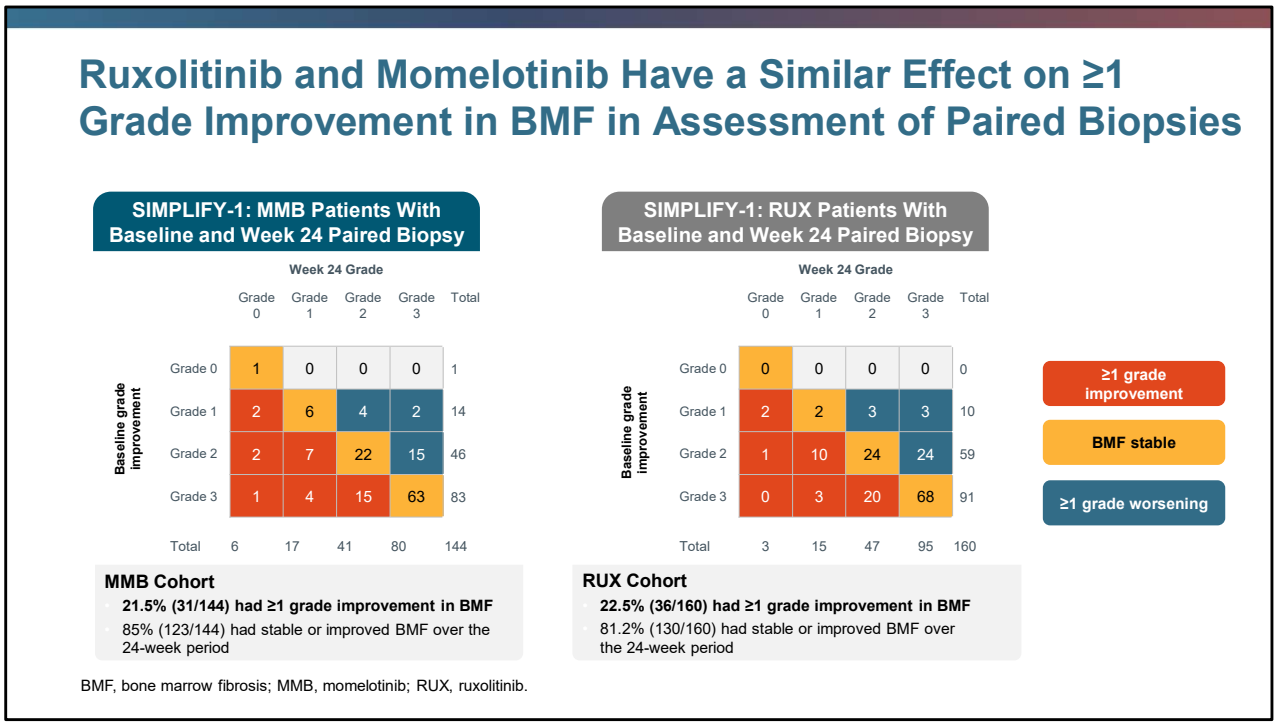

Then looking at the change in bone marrow fibrosis over time, this table color codes in terms of those that had at least a one-grade improvement, or stable bone marrow fibrosis, or in fact worsening. The take-home point here is that they were very similar across the two groups. In both cases, approximately 21%, 22% of patients had at least a grade-one improvement in bone marrow fibrosis.

Again, in terms of patients treated with either momelotinib or ruxolitinib. In this study, similar changes in bone marrow fibrosis were observed.

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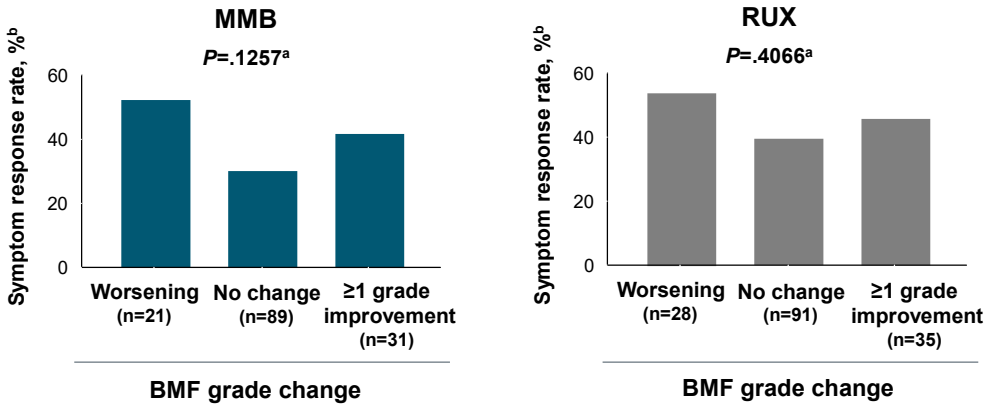
No Associations Between BMF Changes and Week 24 Symptom Response for Either Momelotinib or Ruxolitinib



[a]*P* value was calculated using a chi-square test. [b]Symptom response is defined as achieving ≥50% reduction in MFSAF TSS over the 28 days immediately before the end of week 24 compared with baseline. Percentage is calculated using the BMF change category as denominator (ie, ≥1 grade improvement, no change, or worsening).
BMF, bone marrow fibrosis; MMB, momelotinib; RUX, ruxolitinib

Now, let's look at associations between these bone marrow fibrosis changes and clinical outcomes. Here, looking at symptom response, essentially between the two groups, momelotinib, and ruxolitinib, there were really no associations between bone marrow fibrosis changes, either worsening, stability, or improvement and symptom response. Really no connection in terms of symptom response.

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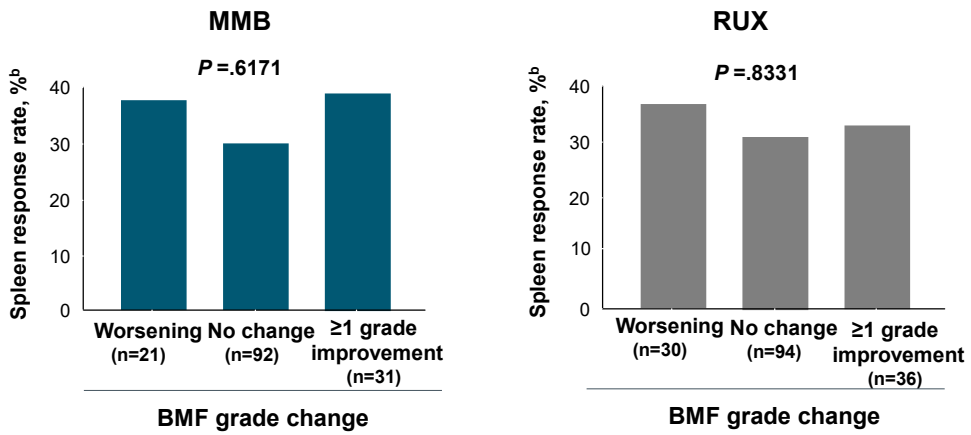
No Associations Between BMF Changes and Week 24 Spleen Response for Either Momelotinib or Ruxolitinib



[a]*P* value was calculated using a chi-square test. [b]Spleen response is defined as achieving a ≥25% or ≥35% reduction in spleen volume from baseline. Percentage is calculated using the BMF change category as denominator (ie, ≥1 grade improvement, no change, or worsening).
BMF, bone marrow fibrosis; MMB, momelotinib; RUX, ruxolitinib.

The same is true when looking at spleen response. No association between specific changes in bone marrow fibrosis in either treatment group with regard to spleen response.

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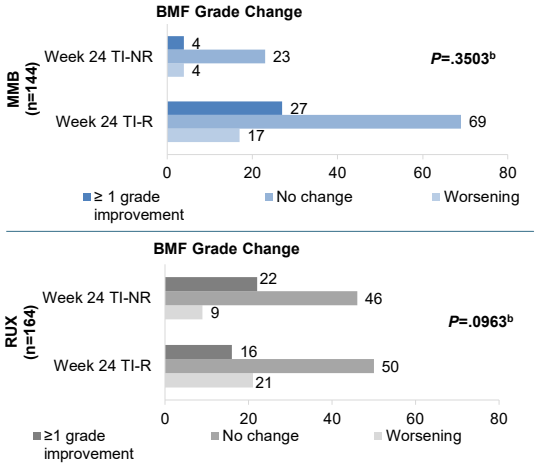
No Associations Between BMF Changes and Week 24 TI-R[a] for Either Momelotinib or Ruxolitinib



- Overall, 78% of patients achieved week 24 TI-R on momelotinib versus 53% on ruxolitinib
- Twice as many patients on momelotinib with ≥1 grade BMF improvement achieved week 24 TI-R compared with ruxolitinib
- Similar TI-R was seen with both momelotinib and ruxolitinib with worsening BMF
- There is no consistent trend in TI responses across BMF groups within each treatment group
- In momelotinib-treated patients, TI responses were achieved regardless of BMF changes, suggesting the anemia benefit of momelotinib is a feature of its JAK1-, JAK2-, and ACVR1-mediated mechanism of action, which is not reciprocated by ruxolitinib

[a]TI-R was defined as absence of RBC transfusions and no Hgb levels <8 g/dL in the 12 weeks before week 24. [b]*P* value was calculated using a chi-square test. ACVR1, activin A receptor type 1; BMF, bone marrow fibrosis; Hgb, hemoglobin; MMB, momelotinib; RBC, red blood cell; RUX, ruxolitinib; TI, transfusion independence; TI-NR, transfusion independence nonresponse; TI-R, transfusion independence response.

Again, in terms of transfusion independence response, no association with changes in bone marrow fibrosis. Now, certainly from this analysis, as has been reported previously from this and other studies with momelotinib, there were a significant number of patients in the momelotinib-treated arm that did achieve or maintain transfusion independence response or TI response. 78% of patients overall in the momelotinib group versus 53% of patients in ruxolitinib.

However, despite this distinction in TI response with momelotinib versus ruxolitinib, there was really no, again, connection to changes in bone marrow fibrosis. That does suggest that potentially, the achievement of TI response or anemia response with momelotinib may be uncoupled or distinct or separate from changes in bone marrow fibrosis and perhaps suggesting or hinting at the mechanisms by which anemia benefit is achieved. Again, not being directly related to changes in bone marrow fibrosis.

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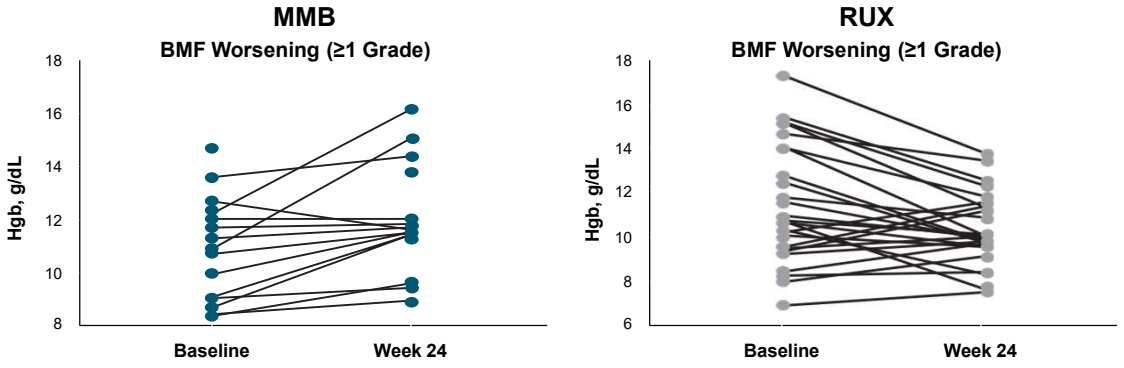
Despite BMF Worsening at Week 24, Hgb Generally Increased on Momelotinib but Decreased on RUX



Mean baseline Hgb[a]	Mean week 24 Hgb
10.7	11.7

Mean baseline Hgb[b]	Mean week 24 Hgb
11.3	10.3

[a]A total of 3/21 patients missing week 24 Hgb measurement. [b]A total of 2/30 patients missing week 24 Hgb measurement.
BMF, bone marrow fibrosis; Hgb, hemoglobin; MMB, momelotinib; RUX, ruxolitinib.-

We're looking at changes in bone marrow fibrosis in relation to changes in hemoglobin. This is specifically looking at those that had worsening of bone marrow fibrosis. What you can see in terms of the changes in hemoglobin is that there was improvement in the hemoglobin, generally speaking, with momelotinib treatment, despite a worsening of bone marrow fibrosis. Again, suggesting that this is not really directly related.

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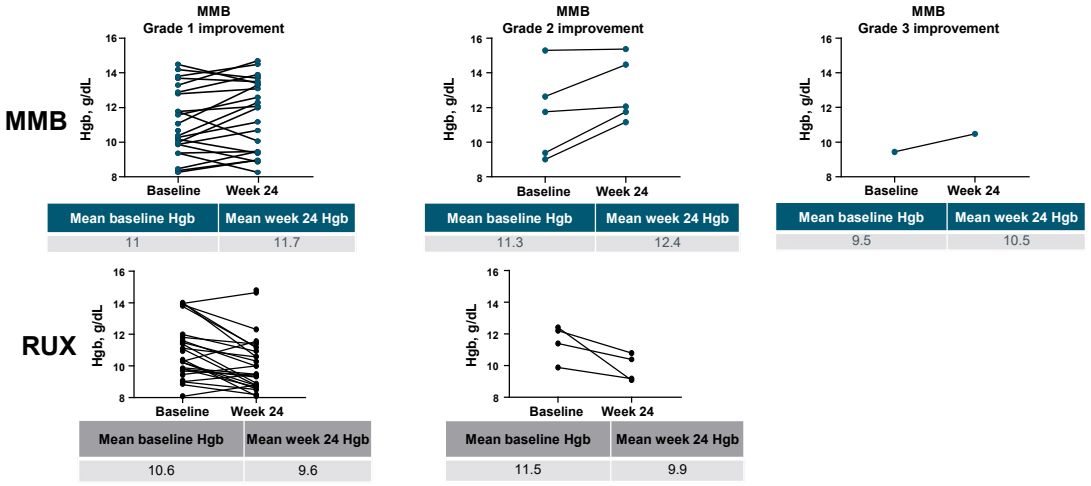
Hgb Levels Increased on MMB but Decreased on RUX Regardless of BMF Improvement or Worsening at Week 24



	Mean baseline Hgb	Mean week 24 Hgb
MMB Grade 1 improvement	11	11.7
MMB Grade 2 improvement	11.3	12.4
MMB Grade 3 improvement	9.5	10.5
RUX Grade 1 improvement	10.6	9.6
RUX Grade 2 improvement	11.5	9.9

BMF, bone marrow fibrosis; Hgb, hemoglobin; MMB, momelotinib; RUX, ruxolitinib.

Then also looking at those that had either improvement or stability of bone marrow fibrosis changes. Here looking specifically at improvement, you could see that whether it's grade 1, 2, or 3 improvement, again, the trend was that there was an increase in hemoglobin with momelotinib treatment, whereas there was a worsening of hemoglobin, generally speaking, with ruxolitinib. Again, not directly related to any changes in bone marrow fibrosis.

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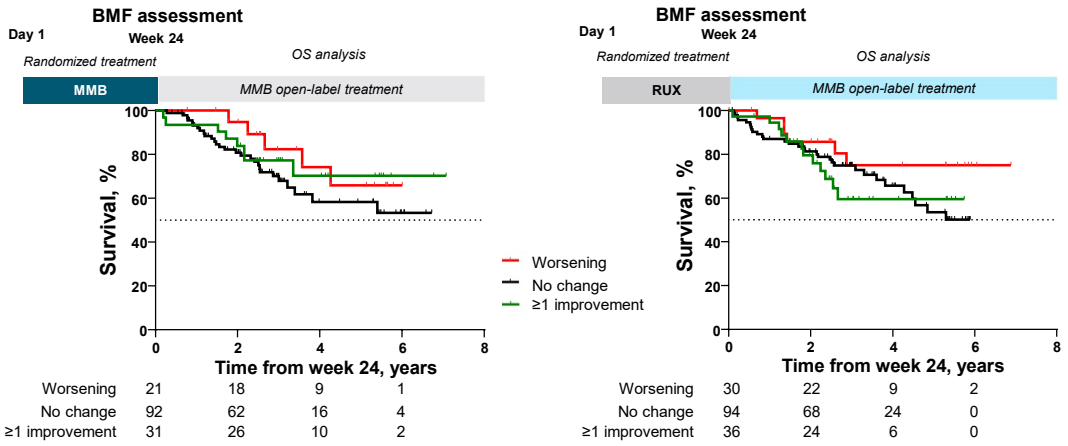
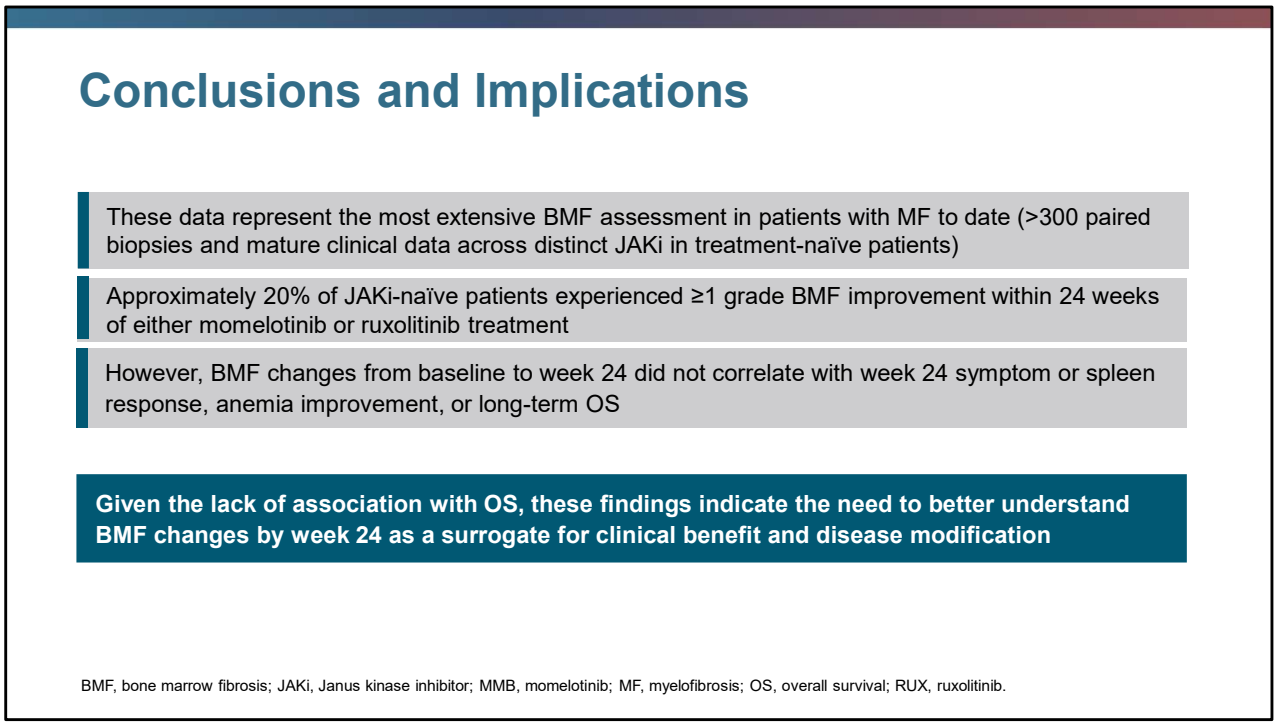
BMF Changes Were Not Associated With OS



BMF, bone marrow fibrosis; MMB, momelotinib; OS, overall survival; RUX, ruxolitinib.

Then lastly, there were no clear associations with overall survival in terms of bone marrow fibrosis changes in either group.



The conclusion of the study is that this first, this study represents really the most extensive assessment of bone marrow fibrosis changes in patients with myelofibrosis to date. More than 300 paired samples or biopsies from the patients in this study, and all of whom were JAK inhibitor naive at baseline.

In both groups, 20% of patients had at least a grade-one improvement in bone marrow fibrosis with 24 weeks of momelotinib and ruxolitinib. This, of course, does not exclude the possibility that longer-term follow-up and analysis of bone marrow fibrosis changes could be relevant to efficacy outcomes, but at least of this 24-week analysis, no association. Again, no specific association with symptom or spleen response, anemia improvement, or long-term overall survival. This really suggests that this is not the relevant marker to look at, at least at 24 weeks. Maybe there are other analyses that would perhaps be more relevant.

Pacritinib Is a Potent ACVR1 Inhibitor with Significant Anemia Benefit in Patients with Myelofibrosis

Session 634. Myeloproliferative Syndromes: Clinical and Epidemiological: Towards Personalized Medicine in Myeloproliferative Neoplasms and Mastocytosis: New and Repurposed Drugs for Unmet Clinical Needs

Dec 11, 2022, #628

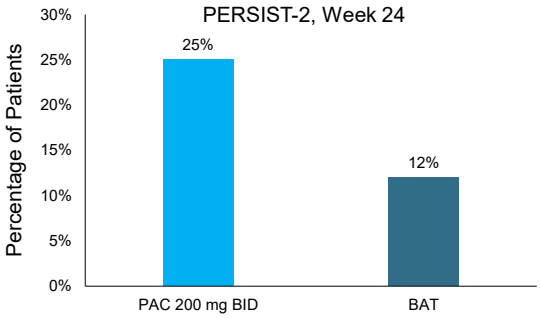
Now, moving on to another abstract presented at ASH. This is focusing on pacritinib. The highlight of this particular study is that pacritinib was demonstrated to have activity against ACVR1, which regulates production of Hepcidin and therefore has relevance to potential anemia benefit with pacritinib in patients with myelofibrosis.

Meeting Highlights in Myelofibrosis from the ASH Annual Meeting

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 mechanism behind/extent of anemia benefit has not been fully described

Clinical Improvement in Hemoglobin[2]



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 Haematol.* 2017;4(5):e225-e236. 2. Mascarenhas J, et al. *JAMA Oncol.* 2018;4(5):652-659. 3. Gerds A, et al. *Blood Advances.* 2020;4(22):5825-5835.

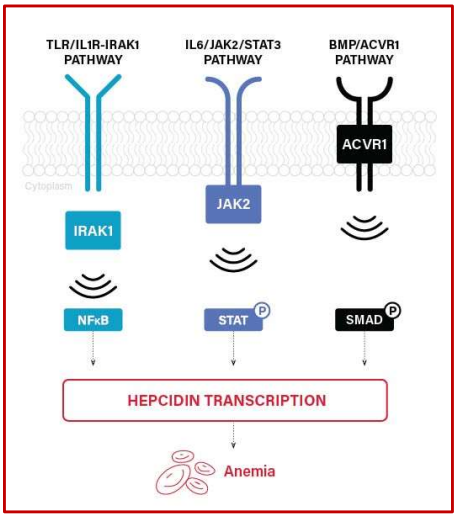
Pacritinib in cytopenic myelofibrosis. The approval indication is specifically for patients with myelofibrosis with a platelet count less than 50,000. That is those specific patients with very severe thrombocytopenia for whom pacritinib is indicated. It is able to be administered to that patient population at the full approved dose of 200 milligrams twice daily.

Previous analysis had shown, as shown on the right , that there was some degree of improvement in hemoglobin from the PERSIST-2 study, but really it hadn't been fully explored, and nor had the mechanism that might explain potential anemia benefit had been described. That was the purpose of this study, was to

Meeting Highlights in Myelofibrosis from the ASH Annual Meeting

Aims

- **Aim 1**: assess pacritinib's *in vitro* potency against ACVR1 and its ability to reduce hepcidin
  - ACVR1 has been implicated in anemia of inflammation in patients with myelofibrosis[1,2]
- **Aim 2**: describe the impact of pacritinib 200 mg BID on RBC transfusion independence in the Phase 3 PERSIST-2 study



ACVR1, Activin A receptor type 1; BID, twice daily; JAK2, Janus associated kinase 2; IL6, interleukin-6; IRAK, interleukin receptor-associated kinase; RBC, red blood cell.
1. Oh ST, et al. *Blood Adv.* 2020;4(18):4282-4291. 2. Asshoff M, et al. *Blood.* 2017;129(13):1823-1830.

investigate the mechanism by which pacritinib could lead to anemia improvement and focusing on ACVR1 as a regulator of hepcidin production, which has been tied to anemia of inflammation in patients with myelofibrosis.

The second aim of this study was to then look more closely at the impact of pacritinib on RBC transfusion independence from the phase-3 PERSIST-2 study data.

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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]C_{max} is the maximum unbound plasma concentration at the clinical recommended dose in humans.

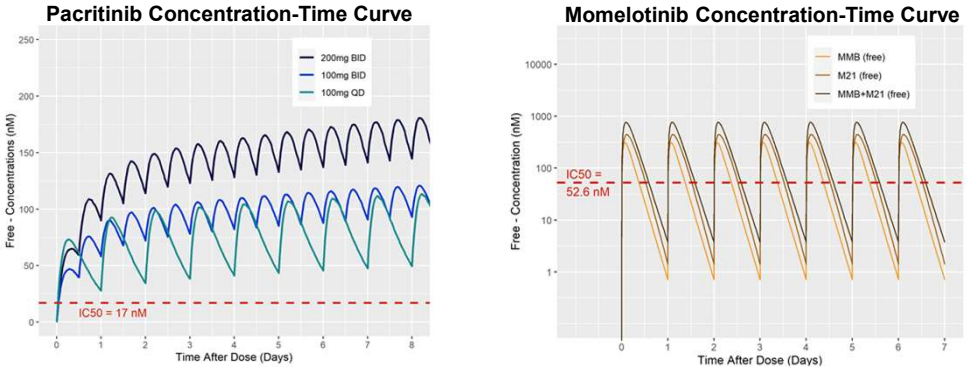
ACVR1, Activin A receptor type 1; FED, fedratinib; IC_{50}, half maximal inhibitory concentration; MOM, momelotinib; PAC, pacritinib; RUX, ruxolitinib.

First, looking at activity against ACVR1 using in vitro kinase assays, this slide shows that when pacritinib was assayed for activity against ACVR1 actually it was found to be a quite potent inhibitor of ACVR1.

In fact, it was four times more potent than momelotinib which had previously been shown to have activity against ACVR1. This is distinct compared with fedratinib which had very weak activity and ruxolitinib which essentially had no activity against ACVR1.

Pacritinib Is a Potent ACVR1 Inhibitor

- Pacritinib concentration exceeds ACVR1 IC_{50} **100% of the time at all dose levels**
- Momelotinib concentration exceeds ACVR1 IC_{50} **55% of the time only** (accounting for both momelotinib and its metabolite [M21])

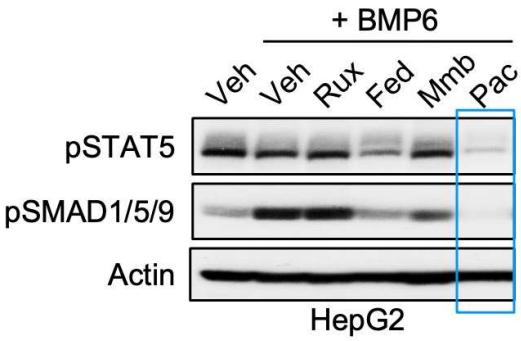


ACVR1, Activin A receptor type 1; BID, twice daily; IC_{50}, half maximal inhibitory concentration; MMB, momelotinib; QD, once daily.

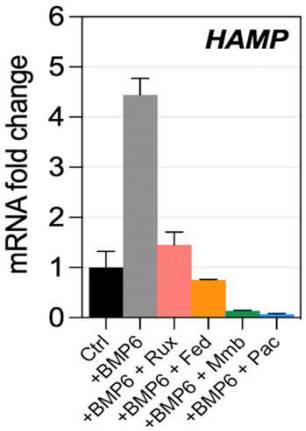
Further, using exposure modeling and looking at the concentration of pacritinib that could be achieved in patients treated with this drug, it suggests that the concentration of pacritinib that could be administered or achieved in patients would exceed the IC50, and especially the level needed to inhibit ACVR1 fully actually at all times in patients treated with this drug. Whereas similar analysis with momelotinib suggests that this effective concentration would only be achieved about 55% of the time.

Pacritinib Decreases Hepcidin Expression *In Vitro*

- **Pacritinib decreases SMAD phosphorylation** (downstream of ACVR1)



- **Pacritinib decreases *HAMP* (hepcidin) mRNA levels**



Concentrations
BMP6: 10 ng/mL
JAK inhibitor: 1uM

BMP6, bone morphogenic protein 6; Ctrl, control; Fed, fedratinib; Mmb, momelotinib; Pac, pacritinib; Rux, ruxolitinib; Veh, vehicle.

Now, ACVR1 is a regulator of hepcidin. Looking downstream with this to confirm its effects, it was demonstrated that pacritinib could inhibit downstream SMAD signaling as shown on the left. Then on the right, looking specifically at production of hepcidin confirming that pacritinib in fact does potently inhibit production of hepcidin in liver cells.

Methods: Analysis of Transfusion Independence

- Evaluated pacritinib 200 mg BID (approved dose) and best available therapy on PERSIST-2 study[1]

PERSIST-2 Population
- Myelofibrosis
- Platelets ≤100 x 10^9/L
- Prior JAK inhibitor therapy allowed

Randomization
- 1:1:1
- N=311

Pacritinib 200 mg BID

Pacritinib 400 mg QD

Best Available Therapy

Co-Primary Endpoints
- Spleen volume response
- Total symptom score response

- Among patients who were not TI at baseline and who were randomized ≥12 weeks prior to study termination, **what percentage became TI on study through week 24**?
  - TI (Gale criteria): no RBC transfusion over 12 weeks
  - TI (SIMPLIFY criteria): no RBC transfusion & no hemoglobin <8 g/dL over 12 weeks

BID, twice daily; QD, once daily; RBC, red blood cell; TI, transfusion independence.
1. Mascarenhas J, et al. *JAMA Oncol.* 2018;4(5):652-659.

Now turning to the clinical data to substantiate that this translates to an anemia benefit with pacritinib, this is from the PERSIST-2 study, and focusing on patients who were not transfusion independent at baseline and who were randomized at least 12 weeks prior to study termination and asking which percentage of these patients became TI or transfusion independent on study through week 24.

Baseline Patient Characteristics

PERSIST-2, Non-TI patients (Gale criteria)

Characteristic	Pacritinib 200 mg BID N=41	BAT N=43
Age in years, median	67	70
Primary myelofibrosis	83%	63%
Time since diagnosis in years, median	2.5	2.9
Prior JAK2 inhibitor	56%	58%
Platelet count x10^9/L, median	41	43
Hemoglobin in g/dL, median	8.7	8.6
RBC transfusions / month (prior 90 days), median	1.5	1.9
JAK2^{V617F} mutation, n Allele burden <50%	35 74%	34 74%

BAT composition

- **42% ruxolitinib**
  - Median 5 mg QD
- **26% erythroid support**
  - Danazol, ESAs, IMiDs, steroids
- **19% watch and wait only**

BAT, best available therapy; ESA, erythropoiesis-stimulating agents; IMiDs, immunomodulatory drugs; JAK, Janus associated kinase; QD, once daily; RBC, red blood cell; TI, transfusion independence.

In terms of the baseline characteristics. Note that in the BAT arm a good chunk of the patients, at 42% of patients, were treated with ruxolitinib.

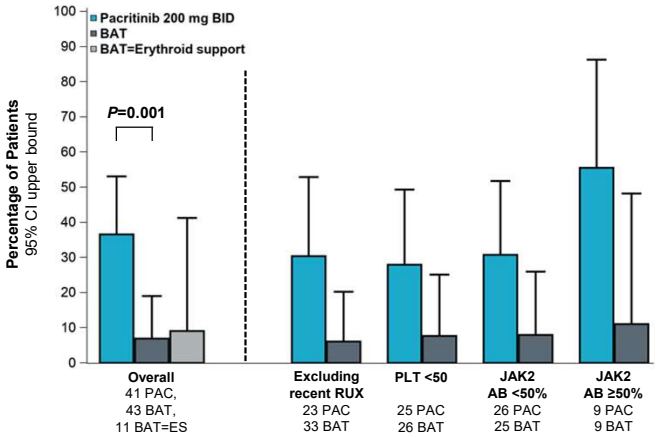
More Pacritinib Patients Achieved TI (Gale)

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; ES, erythroid support; JAK Janus associated kinase; PAC, pacritinib; PLT, platelets; recent RUX, no ruxolitinib in prior 30 days; TI, transfusion independence.

Comparing the two groups, those treated with 200 milligrams BID, the approved dose of pacritinib versus those in the BAT arm, you can see here the TI conversion rate 37% versus 7%. Certainly, better in the arm of patients treated with pacritinib. Also, noting that patients in the BAT arm were allowed to receive erythroid support agents and despite this, there still was a clearly superior benefit in terms of TI response with the pacritinib treatment.

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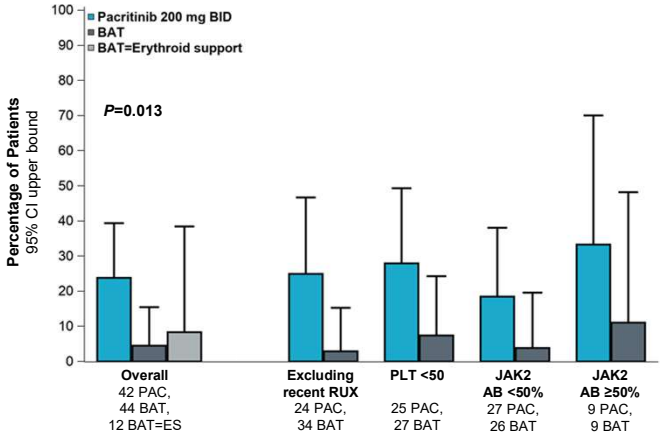
More Pacritinib Patients Achieved TI (SIMPLIFY)

TI Conversion Rate

Pacritinib N=42	BAT N=44	*P*-value
24%	5%	0.013

- Similar results based on SIMPLIFY criteria for TI

Rate of TI (SIMPLIFY 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.

Using more stringent criteria as well, similar analysis or similar difference was observed in terms of pacritinib versus BAT, and in both cases, this was true regardless of JAK to allele burden.

More PAC Patients Had ≥50% Transfusion Reduction

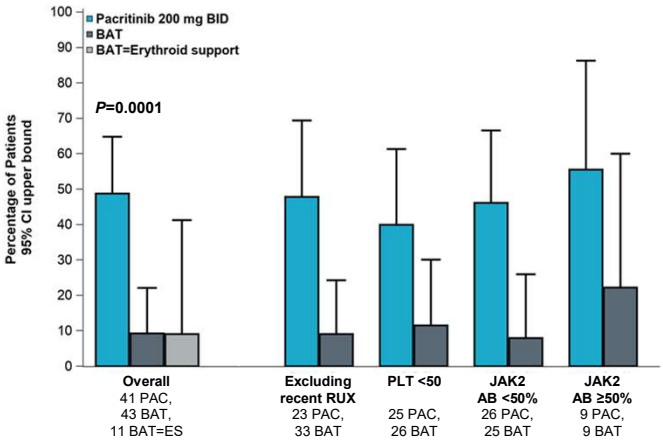
Transfusion Reduction

Pacritinib N=41	BAT N=43	*P*-value
49%	9%	0.0001

- Clinically significant reduction in transfusion burden more common on pacritinib

Rate of ≥50% Transfusion Reduction

Over 12-week interval 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.

Then looking at reduction in transfusion burden, at least a 50% reduction in transfusion burden also, clearly superior with pacritinib versus BAT.

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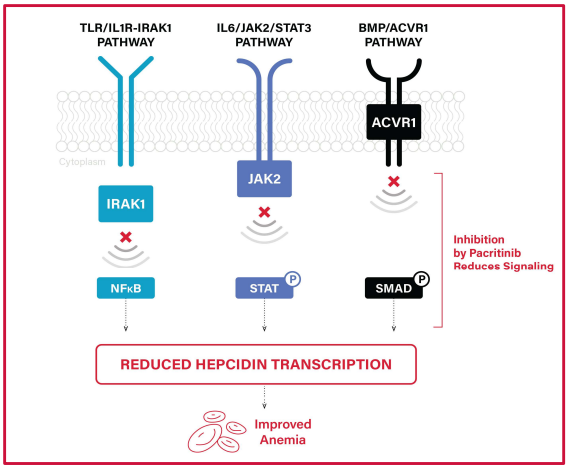
Hypothesized Mechanism of Anemia Benefit

- **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; JAK2, Janus associated kinase 2; IL6, interleukin-6; IRAK, interleukin receptor-associated kinase.

Taking it all together, suggests that pacritinib may achieve anemia benefit in patients with myelofibrosis through its sustained inhibition of ACVR1 activity, and knowing that its other targets include JAK2 and IRAK1, that these targets together may relate to inhibition of inflammatory cytokine production and then translated in terms of reduction in hepcidin production and therefore leading to amelioration of anemia in patients with myelofibrosis.

Conclusions

- Pacritinib is a potent ACVR1 inhibitor (~4x greater potency than MMB)
- Pacritinib is the only known JAK2 inhibitor that provides full-day inhibition of ACVR1 at all doses
- Pacritinib reduces hepcidin levels in vitro
- Pacritinib therapy results in transfusion independence in patients with myelofibrosis who require red blood cell transfusions
- Due to its unique mechanism of action as a JAK2/IRAK1/ACVR1 inhibitor, pacritinib may provide a therapeutic option that affords spleen, symptom, and anemia benefit for patients with myelofibrosis

I think I covered the conclusions, but just to highlight some of the key points here. This study demonstrates that pacritinib is in fact a potent ACVR1 inhibitor and that it can reduce hepcidin levels in vitro and that this therefore potentially translates to achievement of transfusion independence in patients with myelofibrosis treated with pacritinib.

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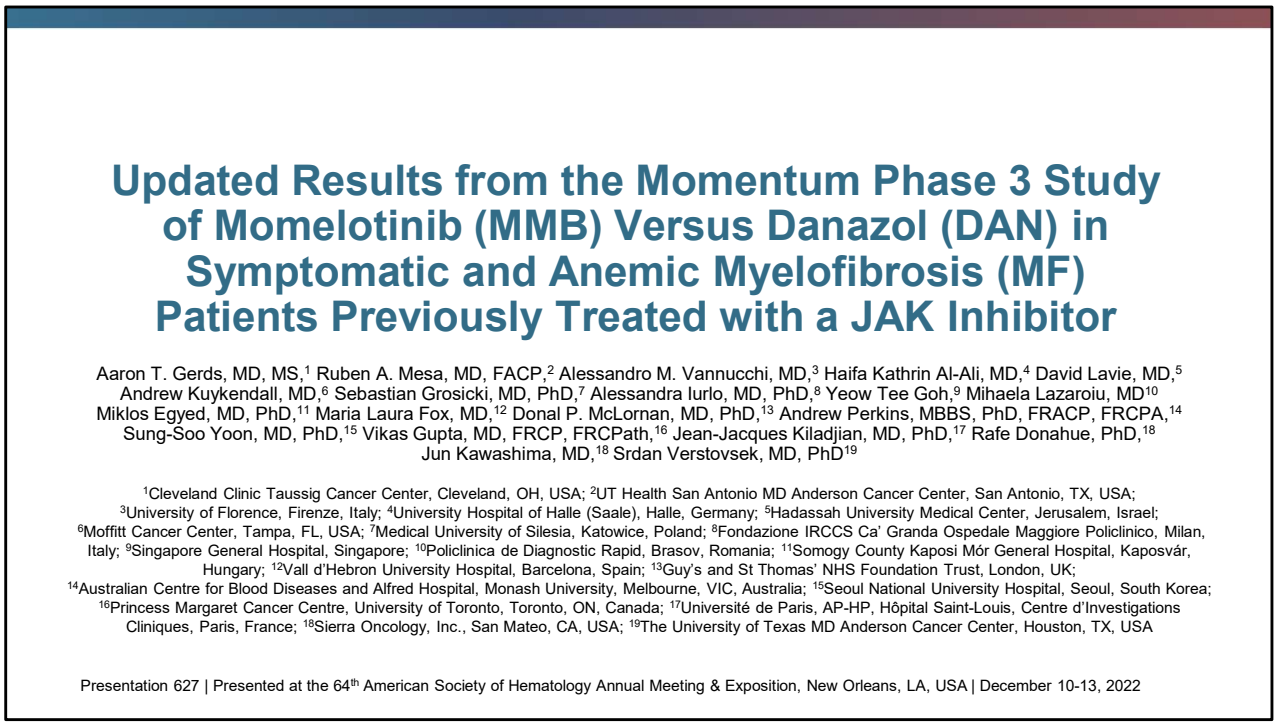

Updated Results from the Momentum Phase 3 Study of Momelotinib (MMB) Versus Danazol (DAN) in Symptomatic and Anemic Myelofibrosis (MF) Patients Previously Treated with a JAK Inhibitor

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]

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Finally, to wrap up my section, just briefly touch on updates from the MOMENTUM phase 3 study of momelotinib versus danazol in patients with myelofibrosis previously treated with a JAK inhibitor.

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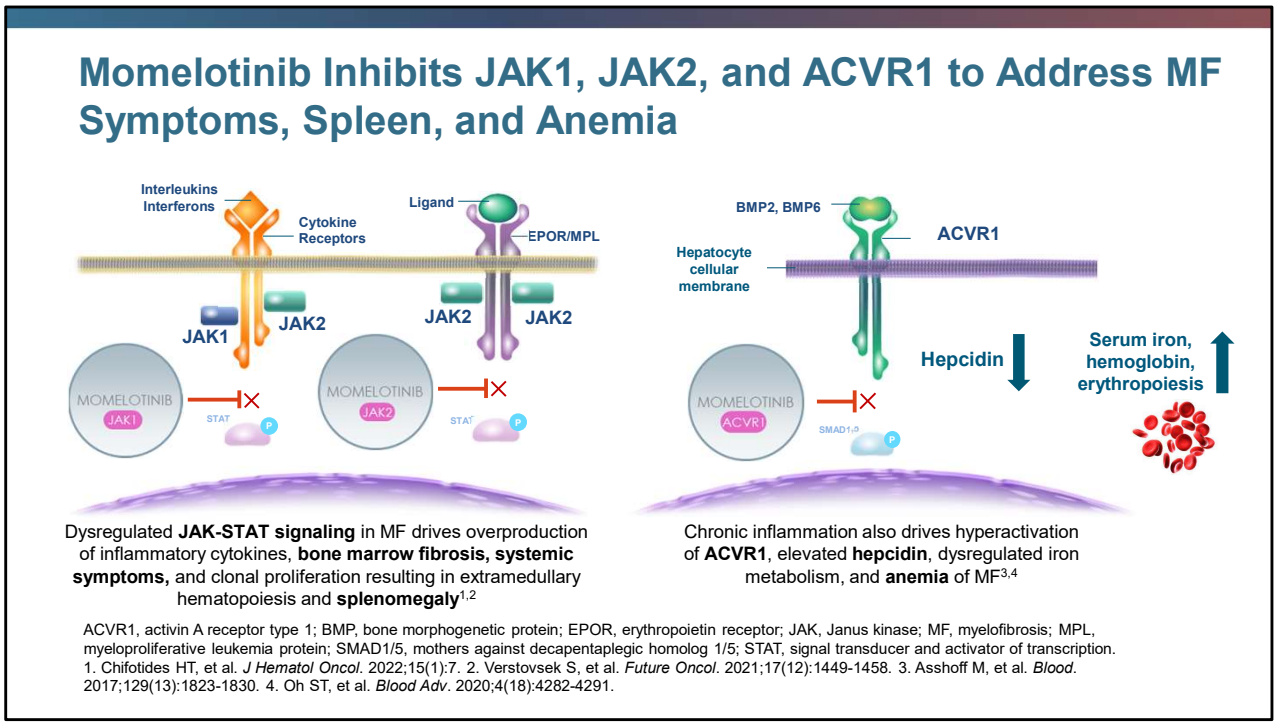

This is just a schematic showing that momelotinib targets both JAK1, JAK2 as well as ACVR1, and these three targets together are thought to lead to momelotinib's capacity to address three of the cardinal hallmarks of MF including symptoms, spleen, and anemia.

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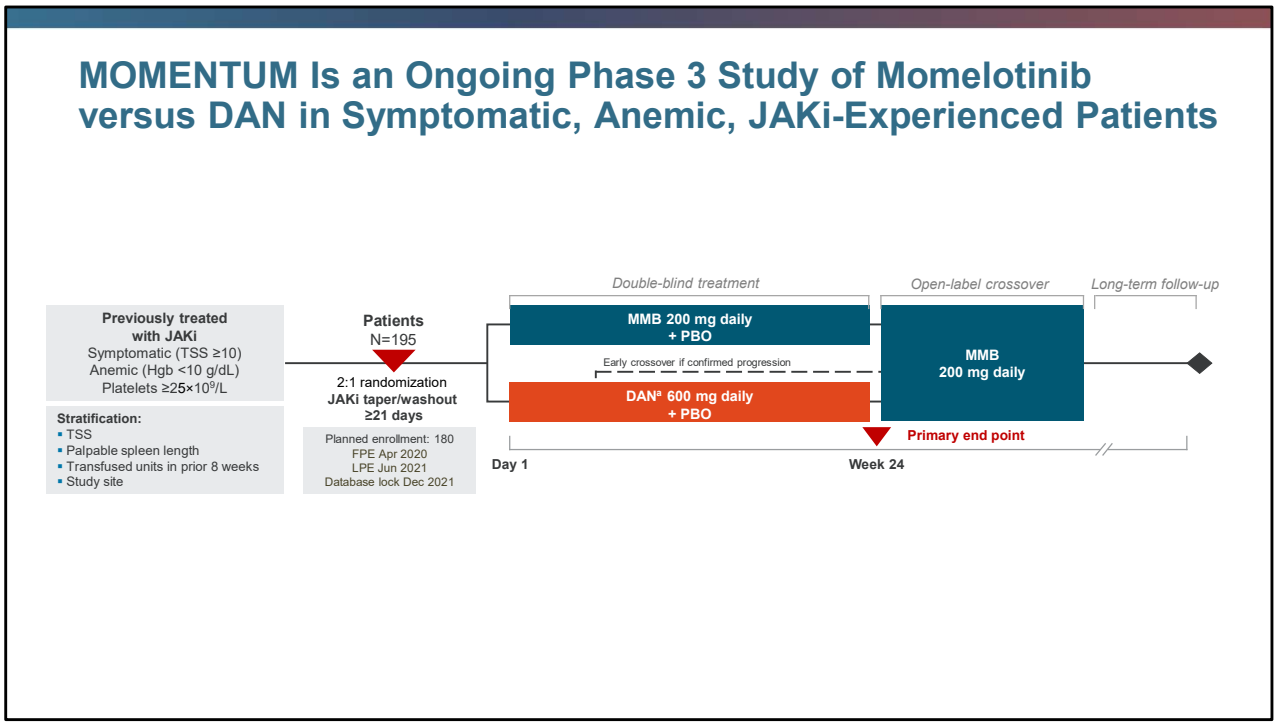

The MOMENTUM study is an ongoing phase 3 study of momelotinib versus danazol in symptomatic anemia or anemic JAK-inhibitor experienced patients. You can see the study schema aligned above.

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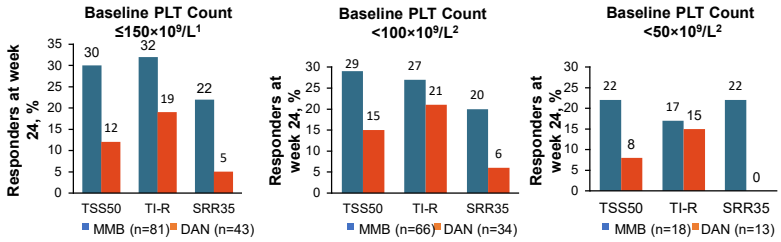
MOMENTUM Results

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



As presented at ASH, these are updated results from the MOMENTUM study. Here we're focusing on the top-line results at week 24. In fact, all of the primary and key secondary endpoints were met including symptom response as shown here on the left of the top part of the slide, superior for momelotinib versus danazol. TI response was assessed in terms of non-inferiority and momelotinib did meet this in terms of 30.8% TI response versus 20% with danazol. Spleen volume response, momelotinib clearly superior to danazol.

Again, momelotinib did meet all of the pre-specified primary and secondary endpoints. The efficacy was maintained in patients with thrombocytopenia, as shown at the bottom, consistent with the overall intention to treat patient population.

MOMENTUM Phase 3 Reported Conclusions

1. Momelotinib inhibits JAK1, JAK2, and ACVR1 to address MF symptoms, spleen, and anemia
2. All prespecified primary and key secondary endpoints were met
3. Significant improvements in symptoms, spleen size and anemia measures with momelotinib vs danazol were reported
4. Favorable safety and trend towards improved overall survival
5. Findings support the future use of momelotinib as an effective treatment in MF patients, especially in those with anemia
6. Momelotinib is the first and only JAK1 and JAK2 inhibitor that also decreases hepcidin through inhibition ACVR-1
    - Rapid and sustained improvements in hemoglobin levels and transfusion requirements

So just the reported conclusions from this analysis. Again, momelotinib inhibits JAK1, JAK2 and ACVR1. These three targets together are thought to provide a benefit in terms of symptom, spleen, and anemia. Again, all the pre-specified primary and key secondary endpoints were met, and this includes significant improvements in symptoms, spleen, and anemia measures with momelotinib versus danazol.

Overall favorable safety and trend towards improved overall survival were reported. Together these findings support potential future use of momelotinib as an effective agent for MF patients, in particular those with anemia. As I covered in the prior presentation with pacritinib, now known activity against ACVR1. Both of these drugs share some capacity to do so. Momelotinib is a little bit distinct from pacritinib in terms of both JAK1 and JAK2. Here with momelotinib, JAK1, JAK2, plus ACVR1.

I'm now going to hand it over to Dr. Ali to take the next section.

Thank you Dr. Oh. It would be a good time to go on the updates on the combination with the JAK inhibitor and other agents after Dr. Oh has talked about updates on the JAK inhibitor updates for MPN.

Current Treatment and Limitation

- JAK inhibitors remain the mainstay of treatment
- They are initially effective but durable responses are only in fewer patients

The current treatment, as we have JAK inhibitors that remains the mainstay of treatment since their approval in 2011, so for last 10-plus years. They are effective initially, but the durability of responses are only seen in few patients and eventually most of the patients they actually progress at some point on the treatment. Therefore, we need the treatment that will be able to have better responses and longer-term responses.

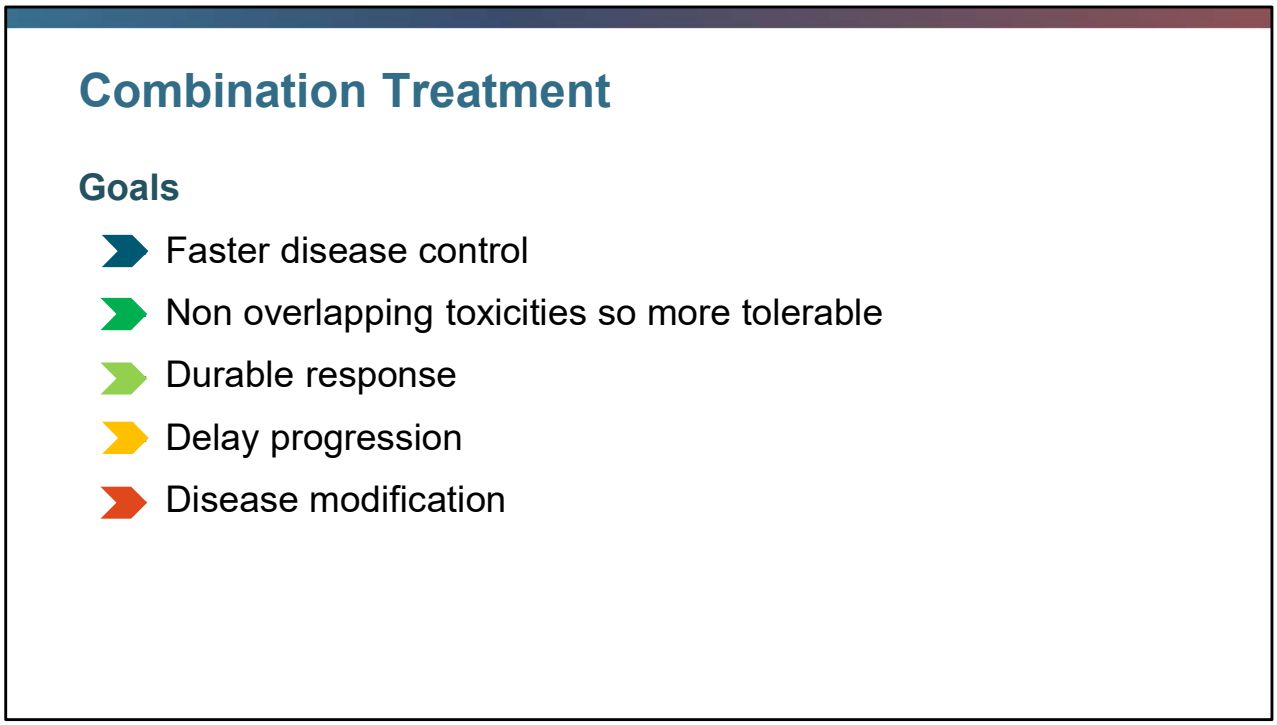
Current JAKi

	Ruxolitinib	Fedratinib	Pacritinib	Momelotinib
Date of FDA approval	November 16, 2011	August 16, 2019	February 28, 2022	Fast track designation*
Spleen volume reduction	42% (COMFORT-1) 29% (COMFORT-2) 29% (SIMPLIFY-1)	36% (JAKARTA-1)	19% (PERSIST-1)	27% (SIMPLIFY-1)
MF Targets	JAK1/2	JAK2	JAK2 ACVR1	JAK1/2 ACVR1
FDA-approved indication	IPSS* High/ intermediate risk	IPSS* High/ Intermediate-2 risk First-line and Second-line	DIPSS** High/ Intermediate risk First-line and Second-line for platelet count <50 10^9/L	Pending approval

Granted FDA Fast Track Designation Feb 2023

These are the current JAK inhibitors that we have, ruxolitinib, fedratinib, pacritinib, and momelotinib as Dr. Oh talked about these updated results and hopefully, will get approved later this year. As you can see that the primary endpoint for most of the study was pre-volume reduction and about 30% to 40% of the patients actually do respond, they get spleen reduction. The targets for ruxolitinib is to inhibit JAK1, JAK2, fedratinib, JAK2, pacritinib JAK2 and ACVR1.

Ruxolitinib is currently approved for intermediate high-risk myelofibrosis. Fedratinib for similarly intermediate high-risk in firstline and second-line setting. Pacritinib is approved mainly for a firstline for patients with platelet count less than 50,000 and as a second line for patients with high-risk intermediate who are either progressing on the other JAK inhibitor.



The goal of the combination with the JAK inhibitor for some of the other agents to get faster disease control and to use these medications which have non-overlapping toxicity, so they're more tolerable. Mainly, have a durable response. Patients are able to benefit from it for a longer period of time and it can delay the progression and hopefully delay the progression to end-stage myelofibrosis and AML. Eventually, through disease modification where there's some changes in the bone marrow fibrosis or allele frequency reduction.

ASH 2022 Abstracts

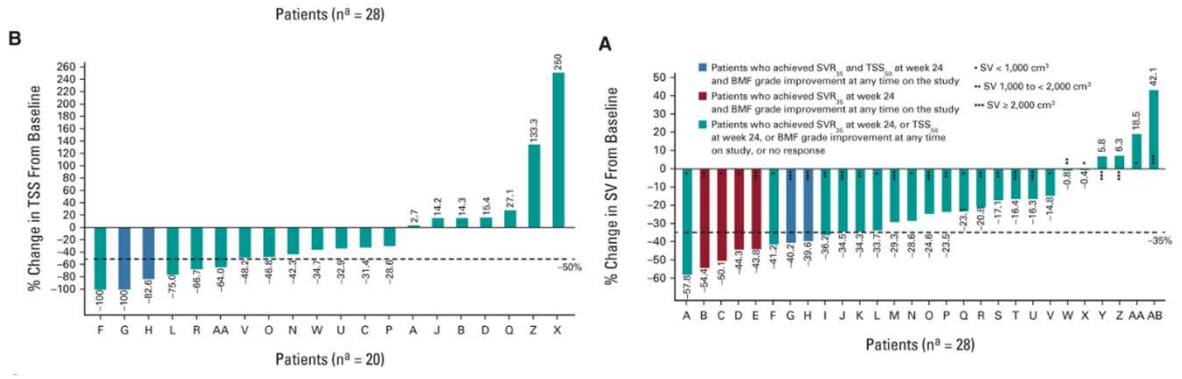
- Add-on parsaclisib to ruxolitinib therapy in MF patients with suboptimal response to ruxolitinib: final results from a phase 2 study
- Navitoclax and ruxolitinib in JAK inhibitor-naive patients with MF
- Pelabresib combined with ruxolitinib for JAK inhibitor treatment naive patients with myelofibrosis

We're going to go over three combinations and three abstracts that were presented at ASH 2022 with the first one, add-on parsaclisib to ruxolitinib therapy in myelofibrosis with suboptimal response to ruxolitinib. The final result from the phase 2 study. Second, navitoclax and ruxolitinib in JAK inhibitor-naive patients with myelofibrosis. The third, pelabresib combined with ruxolitinib for JAK inhibitor treatment naive patients with myelofibrosis.

I'll just add on, like Dr. Kuykendall mentioned, that the study of add-on parsaclisib for patients with suboptimal response to ruxolitinib was terminated due to futility. This is actually included in this presentation.

Meeting Highlights in Myelofibrosis from the ASH Annual Meeting

Navitoclax Can Achieve Spleen and Symptom Responses in Patients with Suboptimal Responses to Ruxolitinib: Phase 11 Safety and Efficacy

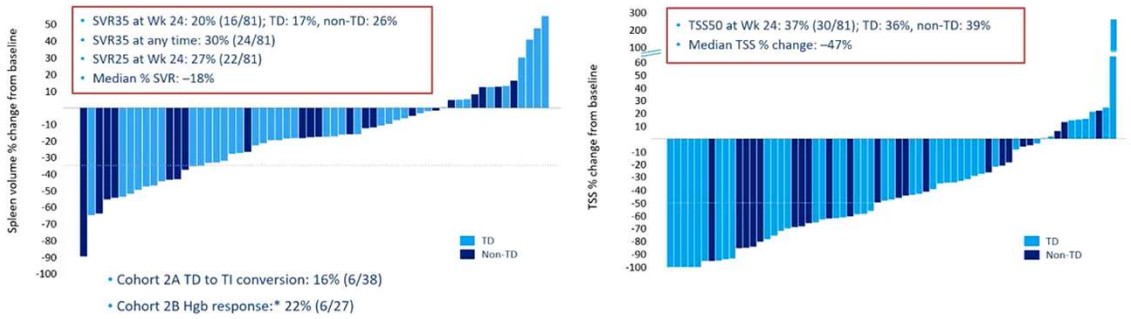


Harrison C, et al. *J Clin Oncol.* 2022;40(15):1671-1680.

There's two different approaches for combination. There's an approach to add-on when someone is having a suboptimal response, and an agent is added to improve the responses combining with the JAK inhibitor, which in this case was ruxolitinib. There was a study done that was presented last year, which was adding on navitoclax to patients who have suboptimal response to ruxolitinib or have progressive disease.

This study included about 34 patients and the doses were 50 milligram to 300 milligram. What they saw the primary endpoint, which was a spleen volume reduction 35% or more was about 26% at 24 weeks. At any time, volume was 41%. Secondary endpoint, which was the 50% total symptom score improvement was about 30%. They also noticed that there was a 64% improvement in the hemoglobin. They noticed that one third of the patient benefited by improvement in the fibrosis on the follow-up bone marrow biopsy. Generally, it was safe and there was some thrombocytopenia, but otherwise it was safe in the setting.

Pelabresib Achieved Spleen and Symptom Responses in the Add-on Setting

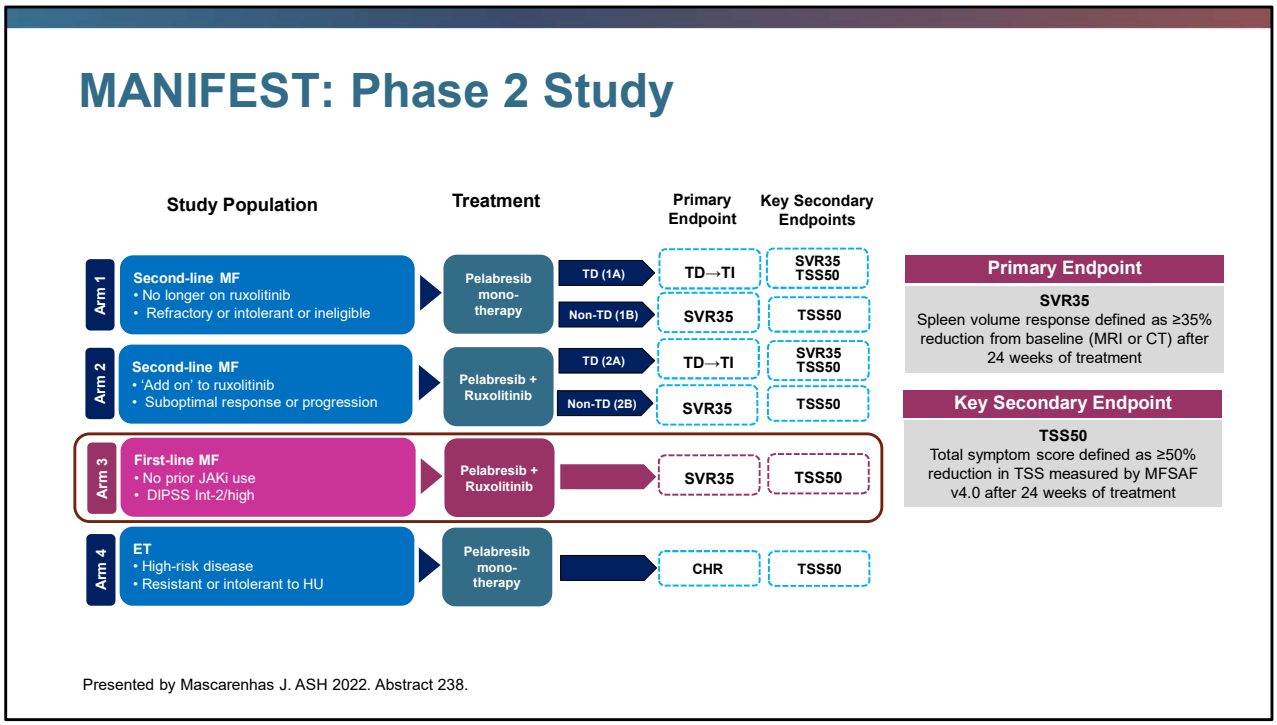


Harrison C, et al. Presented at EHA, 2022.

Similarly as an add-on setting, pelabresib, which is BET inhibitor, was tried. Similarly in the add-on setting, when you look at the primary endpoint which is a spleen volume reduction at 35% at week 34 was about 20%, and it was 17% transfusion dependent, and about 26% in the non-transfusion dependent population.

Whereas, SVR 35 at any time was 30%. If you look at the total symptoms, improvement 50% or more at 24 weeks was about 37%, and which was seen in both transfusion-dependent and non-transfusion-dependent setting.

Meeting Highlights in Myelofibrosis from the ASH Annual Meeting

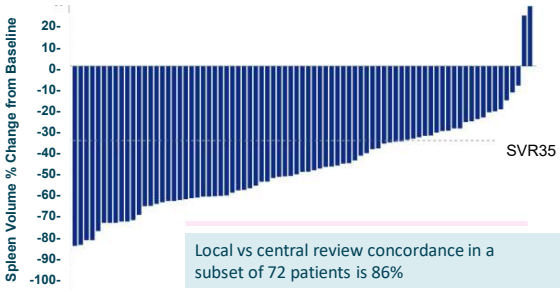


Now we'll go over the results for the combining JAK inhibitor and pelabresib in JAK-naive patients. This was the arm three in the study, and the primary endpoint was spleen volume reduction 35% or more, or a key secondary endpoint was the total symptoms for improvement of 50% at 24 weeks.

Meeting Highlights in Myelofibrosis from the ASH Annual Meeting

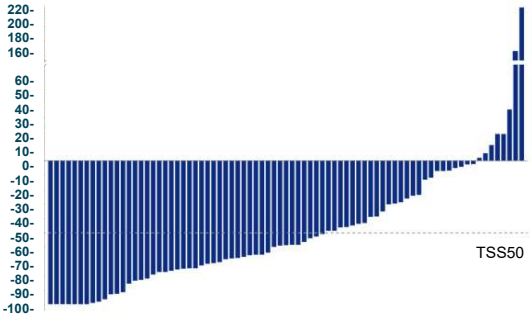
Ruxolitinib + Pelabresib Effectively Reduces Splenomegaly and Improves Symptoms

Spleen Volume at Week 24, by Local Review



Local vs central review concordance in a subset of 72 patients is 86%

Change in Total Symptom Score at Week 24



Arm 3 (N=84)	
SVR35 at Wk 24	68% (57/84), 95% CI 57–78
Median % SVR	–50%
Mean % SVR	–48%

N=84	
TSS50 at Week 24	56% (46/82*), 95% CI 45–67
Median TSS % change	–59%
Mean TSS % change	–47%
TSS50 at any time	83% (68/82*), 95% CI 73–90

Presented by Mascarenhas J. ASH 2022. Abstract 238.

These were the results. As you can see, the spleen volume reduction at week 24, 35% or more volume reduction was 68% in the JAK-naive setting when the two agents were combined and total symptom score improvement was about 56%. If you remember that in the add-on setting, it was about 20% and 30%. Definitely, as an upfront addition, you see much, much better responses as in the combination setting.

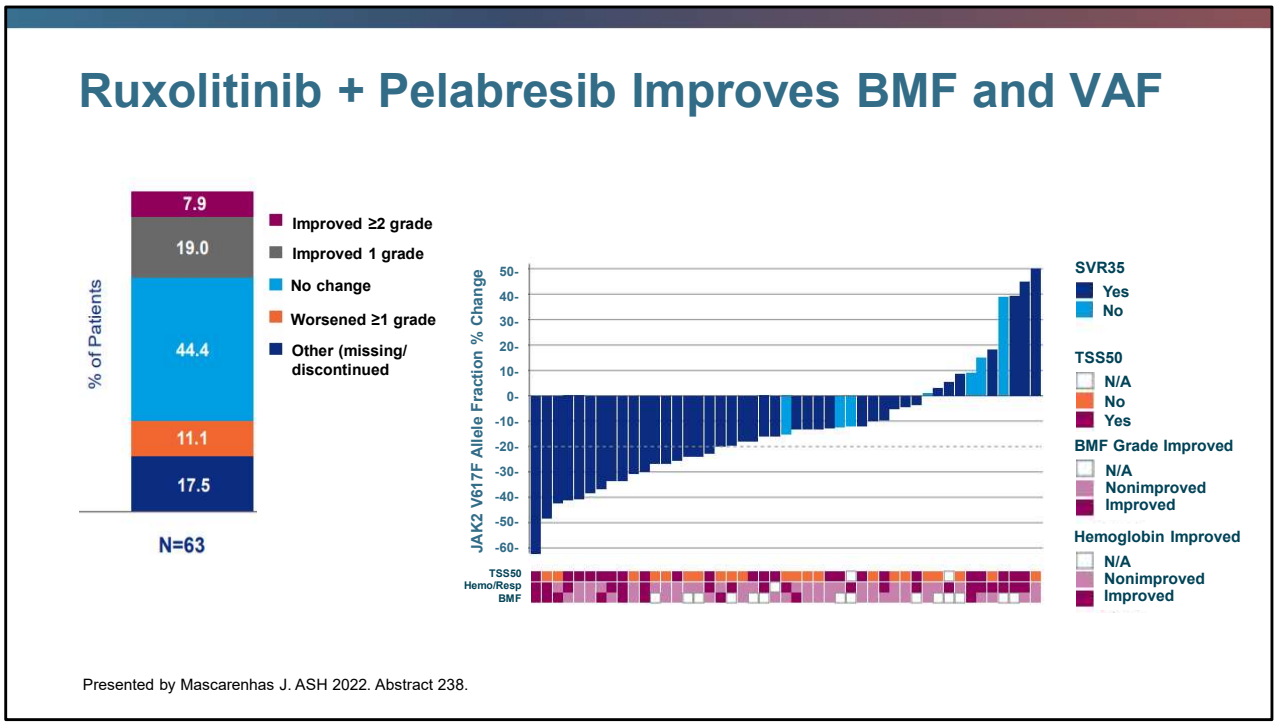
Manifest: Multivariable Biomarker Analysis

- A comprehensive exploratory analysis of pelabresib +/- ruxolitinib treatment effects
  - Association of clinical outcomes/endpoints:
    - Spleen volume changes (SVR35)
    - Symptom improvement (TSS50)
    - Anemia improvement/hemoglobin increase
  - With changes in biomarkers:
    - JAK2 V617F VAF
    - BM morphology (fibrosis, megakaryocyte morphology)
    - Plasma cytokines

Presented by Scandura J. ASH 2022. Abstract 630.

As a supplement to this data, they all looked at some biomarker analysis to try to really understand what's really happening in these patients just beyond the spleen volume reduction and symptom improvement. We've been using these endpoints since the COMFORT studies, but to get more understanding about the biological changes that are developing in patients who are getting these treatments. They look at the JAK2 variant allele frequency reduction. They also look at the bone marrow morphology, looking at the changes in the fibrosis and the megakaryocytic morphology, and also looked at the plasma cytokines.

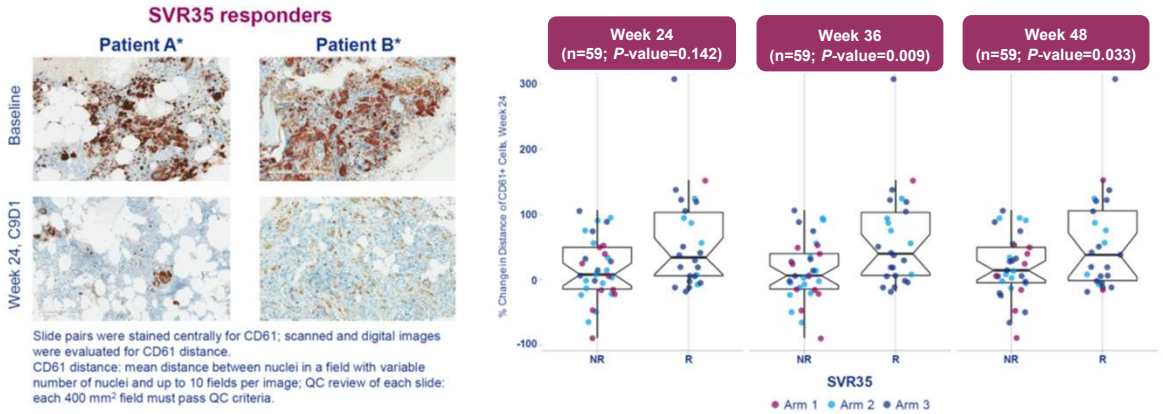
Meeting Highlights in Myelofibrosis from the ASH Annual Meeting



What they notice on this study was that about 27% of the patients had actually bone marrow fibrosis improvement. If you see on the right side, you also see improvement in the variant allele frequency in majority of the patients, 20% or more. Similarly, this correlates well with the hemoglobin improvement as well as the bone marrow fibrosis grade improvement.

Meeting Highlights in Myelofibrosis from the ASH Annual Meeting

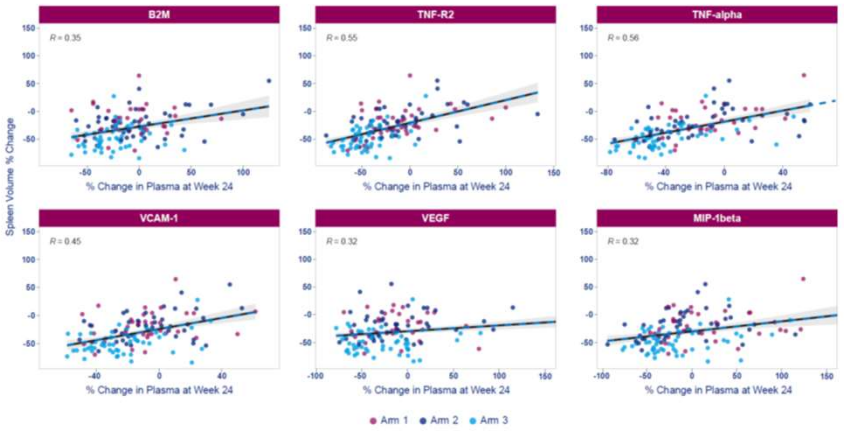
Correlation Between Megakaryocyte 'Declustering' in Bone Marrow and SVR35 Response



Presented by Mascarenhas J. ASH 2022. Abstract 238.

Looking at the morphology of the bone marrow, what they noticed was that there was a declustering of megakaryocyte. A characteristic feature is atypical megakaryocyte in the cluster formation in the MPN, especially in myelofibrosis. What they noticed that the distance between the megakaryocyte was actually increased in patients who were on treatment, and this is shown also on the panel on the right side that the distance actually is increasing on the patient who are on the treatment at 24, 36, and 48 weeks.

Correlation of Plasma Cytokine Changes with Spleen Volume Changes at Week 24



Overview of Cytokines

Cytokine	NF-kB signaling	MF elevated
B2M	√	
TNF-R2	√	√
TNF-alpha	√	√
VCAM-1	√	√
VEGFa	√	√
MIP-1beta	√	√

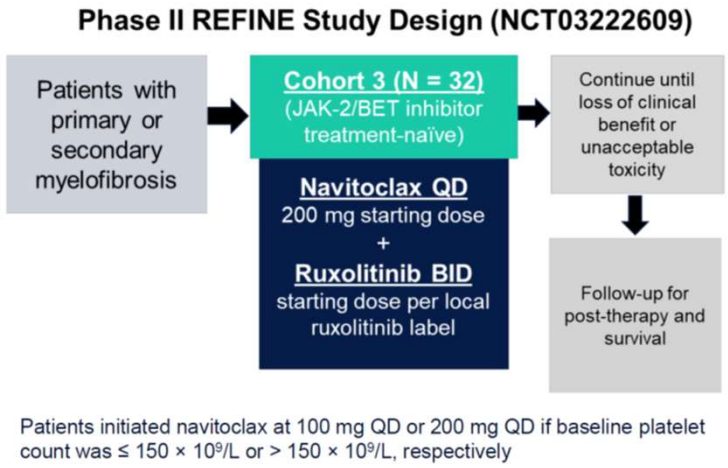
- Reduction in plasma levels of cytokines was associated with spleen volume reduction at Week 24

Presented by Scandura J. ASH 2022. Abstract 630.

Third, they look at the changes in the cytokines. They noticed a patient who were having responsive spleen volume reduction. There was a significant improvement in the cytokine reduction. They look at multiple different cytokine. They are listed on the right panel beta-2 microglobulin, TNF receptor 2, TNF-alpha, VKM1, VGEF-alpha, MIP-1 beta. You can see in the graphs here in the patients who are having spleen volume reduction in the arm three, these are the blue dots, there's a reduction in the inflammatory cytokines.

Meeting Highlights in Myelofibrosis from the ASH Annual Meeting

REFINE: Ruxolitinib + Navitoclax



Primary endpoint

- SVR_{35} from baseline at week 24 assessed by MRI or CT reviewed centrally

Key secondary/ exploration endpoints

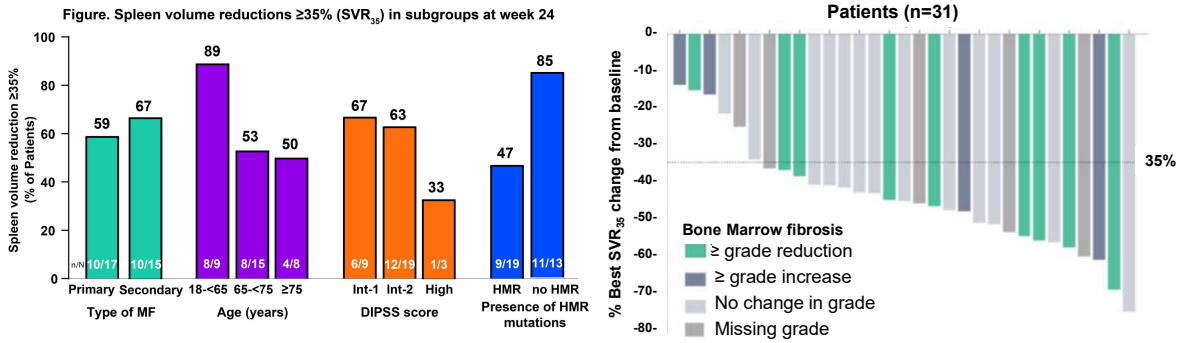
- Change in BMF grade from baseline reviewed locally
- Reduction n VAF for driver mutation determine centrally

Presented by Passamonti F, et al. December 10th, 2022. ASH Annual Meeting.

Next, we'll talk about the REFINE study which is a phase 3 study combining navitoclax with ruxolitinib in JAK-inhibitor-naive patient. Here, patients were given 200 milligram daily starting dose along with the ruxolitinib and the primary endpoint was a spleen volume reduction, 25% from baseline at week 24, as assessed by MRI or CT scan. Key secondary endpoints was the changes in the bone marrow fibrosis and reduction in the variant allele frequency.

Meeting Highlights in Myelofibrosis from the ASH Annual Meeting

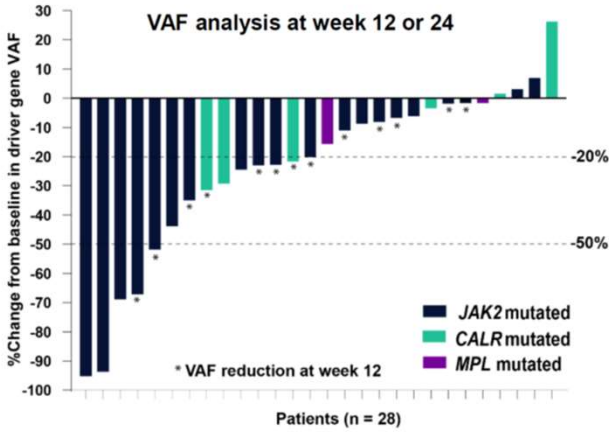
Ruxolitinib + Navitoclax Improves Splenomegaly and Symptoms in Treatment-naïve Patients



Presented by Passamonti F, et al. December 10th, 2022. ASH Annual Meeting.

The results showed that there was a very good reduction in the spleen volume,35% or more. Here you can see in the primary and secondary about 59%, 67% of patients had a spleen volume reduction. Here it is divided by age, DIPSS, and HMR and all of them actually had good improvement in the spleen volume at week 24. On the right panel, you see reduction changes in the bone marrow fibrosis, and the green color is actually for patients who had bone marrow fibrosis reduction. About one third of the patients had a bone marrow fibrosis reduction on treatment. Two of these patients actually had a CR where the fibrosis actually completely resolved on treatment in these patients.

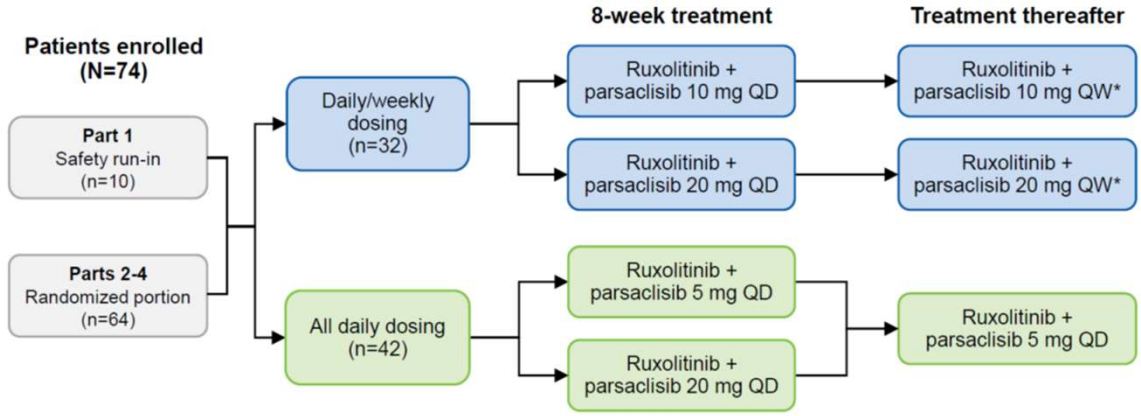
Ruxolitinib + Navitoclax Improves VAF Percent Reduction



Presented by Passamonti F, et al. December 10th, 2022. ASH Annual Meeting.

They also look at the reduction in the JAK variant allele frequency, and 20% or more was noticed in JAK2, and CALR arm. A majority of them, as you can see was JAK2, but there was actually a reduction in the variant allele frequency, 20% more at week 12.

Add-on Parsaclisib to Ruxolitinib Therapy in MF Patients with Suboptimal Response to Ruxolitinib

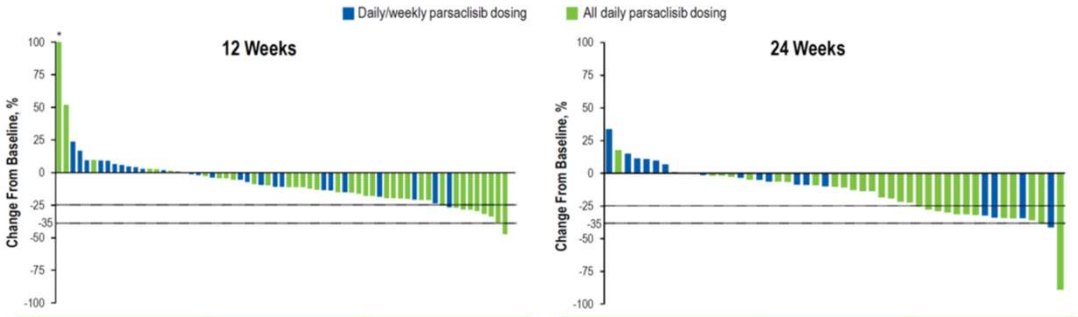


Presented by Yacoub A, et al. December 10th, 2022. ASH Annual Meeting.

Lastly, we'll talk about the add-on parsaclisib, a PI 3-kinase delta inhibitor, and this was a study that was presented. Again, this study has been discontinued due to futility. Here they had two different dosing schema. They had a patient on a daily weekly dosing where a patient received eight week of treatment with 10 milligram or 20 milligram of parsaclisib along with ruxolitinib, but after that, it was transitioned to either 10 milligram or 20 milligram every week dose versus a daily dose of 5 or 20 milligram with a continuation of 5 milligram daily dose after eight weeks.

Meeting Highlights in Myelofibrosis from the ASH Annual Meeting

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



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

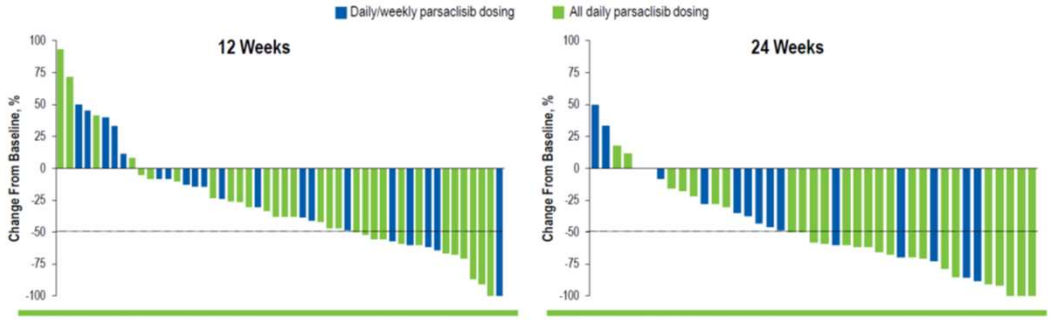
Response Category, n (%)	Daily/Weekly Dosing	All Daily Dosing
Week 24	n=32	n=42
≥10% reduction	4 (12.5)	21 (50.0)
≥25% reduction	4 (12.5)	12 (28.6)
≥35% reduction	1 (3.1)	3 (7.1)

Presented by Yacoub A, et al. December 10th, 2022. ASH Annual Meeting.

Here, the results are on the left side. You see 12 weeks, and on the right side 24 weeks results. Basically, it showed that all daily dosing had much better responses compared to daily weekly dosing. For example, 35% or more volume reduction was not seen at 12 weeks in daily weekly dosing whereas it was seen in about two patients of 4%. By 24 weeks, it was seen only one patient, and daily weekly dosing was three patients. If you look at 25% volume reduction, it was actually much better as well in the all daily dosing arm.

Meeting Highlights in Myelofibrosis from the ASH Annual Meeting

Change in MPNSAF SS and Response Categories at 12 and 24 Weeks



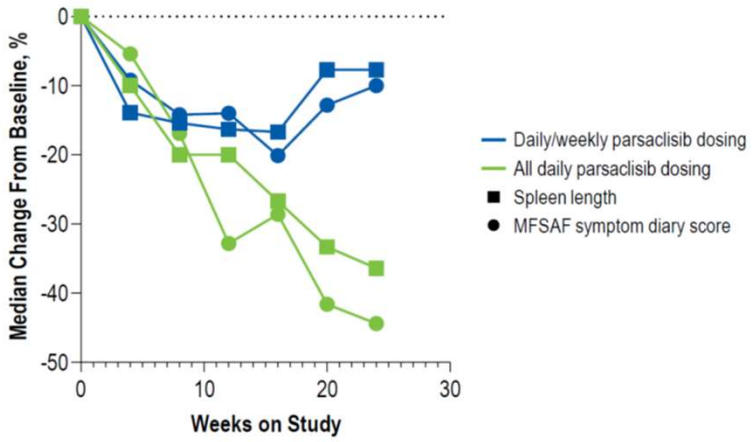
Median Change in MPN-TSS at 12 Weeks	n	% Change (Range)
Daily/weekly dosing	20	-19.2 (-100.0 to 50.0)
All daily dosing	30	-39.8 (-100.0 to 93.3)
Proportion Reaching 50% Decrease in TSS		**n/N (%)**
Daily/weekly dosing	27	5/27 (18.5)
All daily dosing	37	12/37 (32.4)

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

Presented by Yacoub A, et al. December 10th, 2022. ASH Annual Meeting.

Looking at the symptom reduction at 12 versus 24 weeks, similarly, there was improved responses in all the daily dosing arm to 20% versus 30%, and at 12 weeks, it's actually a number of patients. Similarly, if you look at 24 weeks, it was 27 versus 37 patients that had responded.

Change in Spleen Length and Symptom Score by Dosing Group

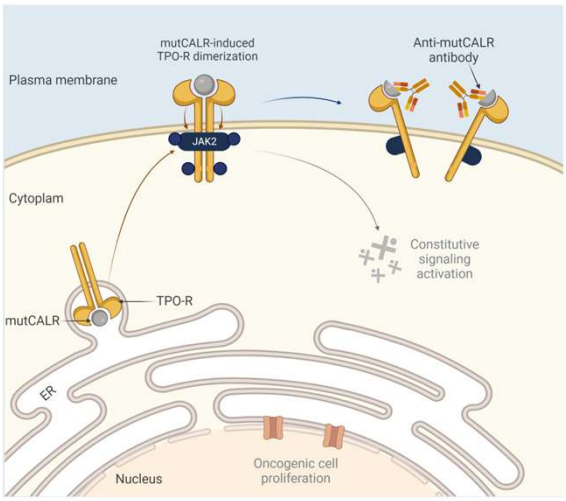


Presented by Yacoub A, et al. December 10th, 2022. ASH Annual Meeting.

They looked at spleen length and symptom score by dosing group. The green is all daily dosing parsaclisib dose, whereas the blue is daily weekly dosing. You can see that there was a progressive response in the spleen length reduction in all daily compared to daily weekly dosing and similarly with the MPN symptoms score improvement.

I'll hand it over to Dr. Kuykendall to go over the updates on future actions in MPN therapy.

INCA033989 – A Monoclonal Antibody Against CALR



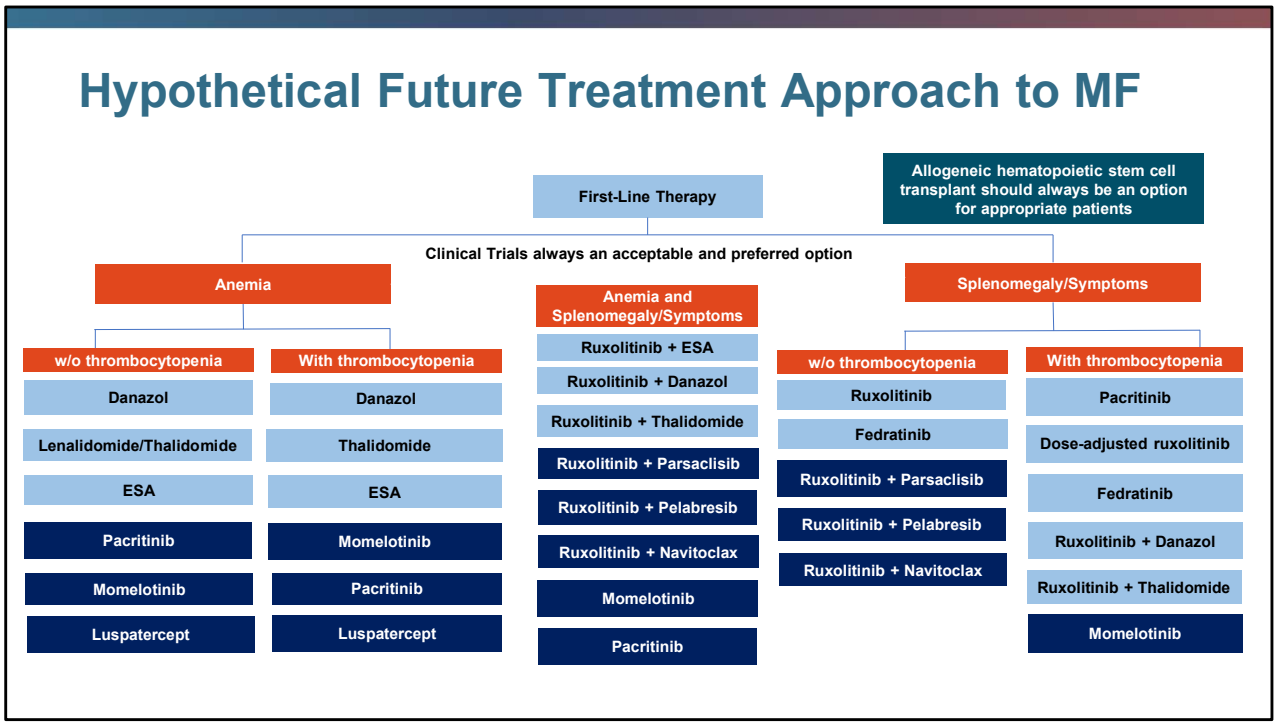
- Fully human IgG1 selective for mutant CALR Inhibits mutant CALR-dependent TPO-R dimerization
- Does not exhibit function effect on Ba/F3 cells no expressing mutant CALR
- Synergism observed between INCA033989 and ruxolitinib
- Showed potential to selectively target mutant CALR HSPCs while preserving proliferation/ differentiation of WT counterparts
- Studied in cell lines, primary CD34+ patient cells and in vivo MPN models

Derived from mpn-hub.com. Adapted from Reis E, et al. Oral abstract #6. 64th ASH Annual Meeting and Exposition. December 11, 2022; New Orleans, LA, USA.

The one last presentation I wanted to take a chance to discuss was actually part of the plenary session at ASH this past year and really focused on INCA033989. You know it's not very far along, but this is actually a monoclonal antibody that has activity against CALR. This is really something we wanted to touch on now, because this is something that's coming into the clinic in the next year or so, but it's something that represents a shift in how we may think about treating these diseases.

This is a fully human IgG1 selective antibody. It's like a mutant form of CALR and inhibits mutant CALR-dependent TPO receptor dimerization. This does not exhibit function against Ba/F3 cells that do not express mutant CALR. This also shows some synergism between this antibody and ruxolitinib. Now importantly, what it did is it showed the ability to selectively target CALR mutated hematopoietic stem cells, while preserving proliferation and differentiation of wild type counterparts. This is something that could potentially be selective to the disease, and promoting the onset of an era where we are really targeting these diseases in a more mutation-specific fashion.

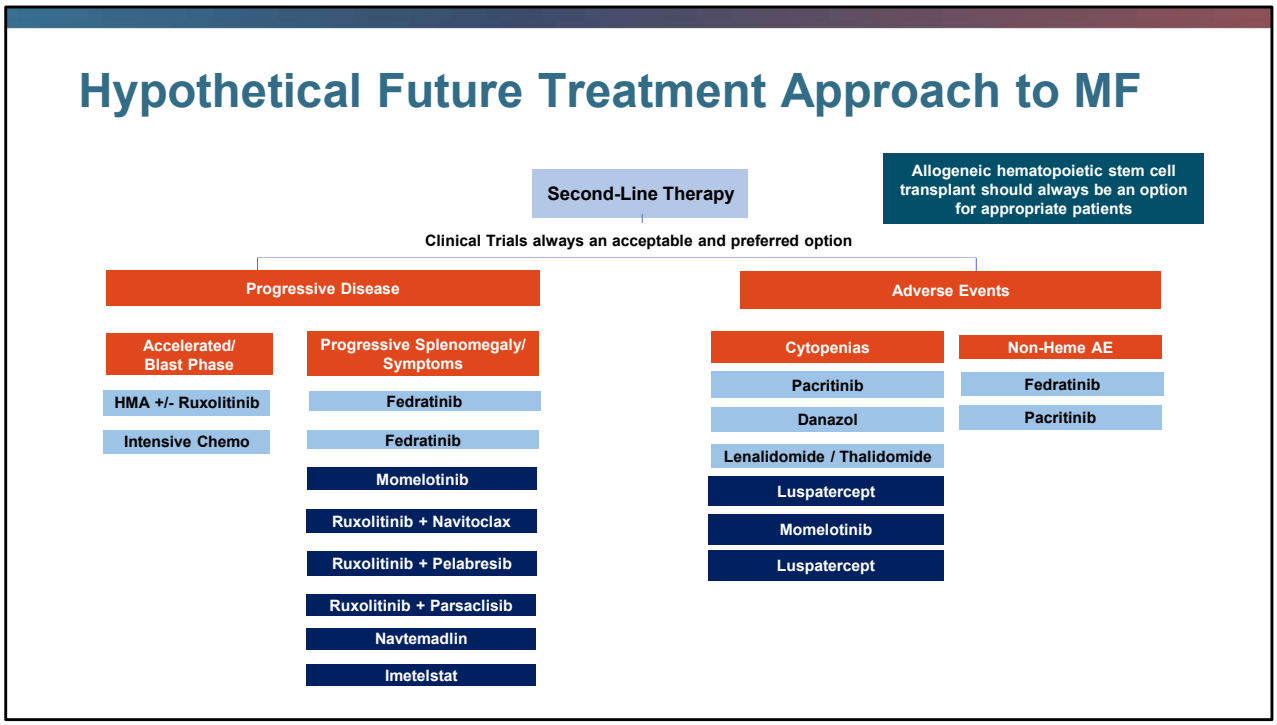
Something we won't mention is there is also the development of a biological model to show that if we were able to do the same thing and target the mutation-specific JAK2 mutation, we would also be able to see eradication of these JAK2 hematopoietic stem cells. While we talked about a lot of different agents that may be able to help with splenomegaly or constitutional symptoms, or even cytopenias and may potentially bring some evidence of disease modification when we use combination therapies, there is this kind of promise in the future that we're going to be able to use agents that really target these driver mutations that ultimately drive the disease.



That brings us to going back to the initial slide we presented to talk about the future of myelofibrosis treatment. What I'd say is that this is kind of what a hypothetical future may look like, and this certainly doesn't call into or integrate the potential of things like a monoclonal antibody against CALR but just talks about the agents we briefly discussed.

In the light blue , you can see what was existing in the first slide we presented of our current treatment algorithm, but in the dark blue , we can see how things may change. I think without going through each of these specifically, what you can see is that we're going to start to have more options for various different phenotypes of myelofibrosis patients. You're going to have more options for those with thrombocytopenia, more options for those with combination of anemia and splenomegaly symptoms, and certainly more options with patients that have anemia.

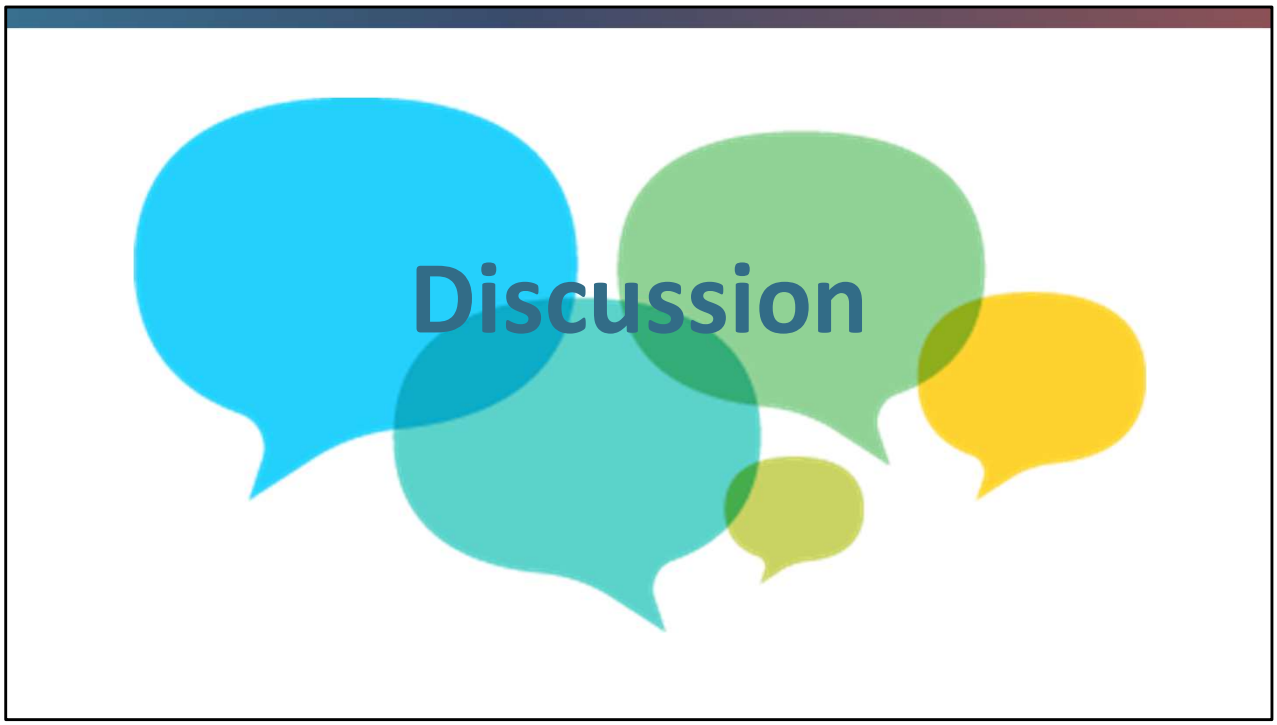
I think we may not be showing true disease modification yet, but what we are doing is being able to bring multiple different options of therapies for patients with myelofibrosis.



Then, we look at second-line therapies. Again, what we see in the navy blue is more options for patients who progress in terms of splenomegaly symptoms and those patients who have cytopenia that is associated with their initial therapy but also, this highlights where we're lacking.

Again, we're not seeing any new promising options for accelerated blast phase disease. This remains an area that we really need to do better. Patients with accelerated blast phase disease have a terrible prognosis and we need to bring more options for them to the table. Similarly, we really need to understand some of these non-hematologic AEs and figure out if all JAK inhibitors have the same risks, or if these are specific to certain JAK inhibitors.

Meeting Highlights in Myelofibrosis from the ASH Annual Meeting



With that, what I do want to do on this discussion slide is certainly, hopefully, bring Dr. Ali and Dr. Oh back and really get maybe a one or two-minute synopsis from each of you guys on where do you see the changes we saw from ASH? I'll start with Dr. Oh.

Dr. Kuykendall: The changes we saw from ASH looking at these novel therapies, you presented on predominantly JAK inhibitor therapies. Where do you see the field going and how do things change based on what you saw and frankly what you presented this year at ASH?

Dr. Oh : Thanks, Dr. Kuykendall. Obviously, I highlighted updates related to,in particular, pacritinib and momelotinib. I do think that in terms of JAK inhibitors at least, that is where there's going to be further evolution and change coming very soon. Of course, we're, in particular, expecting that momelotinib may be approved officially as early as this summer.

So if that becomes an available agent, we will then have four JAK inhibitors approved in different settings for patients with myelofibrosis. I think more broadly, with momelotinib potentially being approved and with the recognition that pacritinib has some capacity to potentially improve anemia in part related to targeting ACVR1, this expands our repertoire with the application of our JAK inhibitors. Not just for spleen and symptoms, but potentially with at least those two JAK inhibitors, the potential or prospect of addressing anemia.

Dr. Kuykendall: Fantastic. Couldn't agree more. I'll pass it off to Dr. Ali. What excites you the most about the different combinations that you presented?

Dr. Ali: I think the two combinations of navitoclax with ruxolitinib, and pelabresib with ruxolitinib, really built on the responses that we saw, for example, in the COMFORT-I and II studies, where the responses were about high 30s and 40% for spleen volume reduction. We are seeing much higher in the approaching close to 70%. Definitely getting a deeper response in terms of spleen volume reduction and symptom improvement. Also, looking more some changes in the biology of a disease, for example, variant allele frequent reduction.

Changes in the bone marrow fibrosis, we don't know exactly how that might really translate into long-term outcomes. Going more into those area of disease modification, I think is interesting with this new combination and the deeper responses.

Dr. Kuykendall: Thank you so much again for joining us. Thank you so much, Dr. Oh, Dr. Ali for participating in this and I hope everyone has a great day.