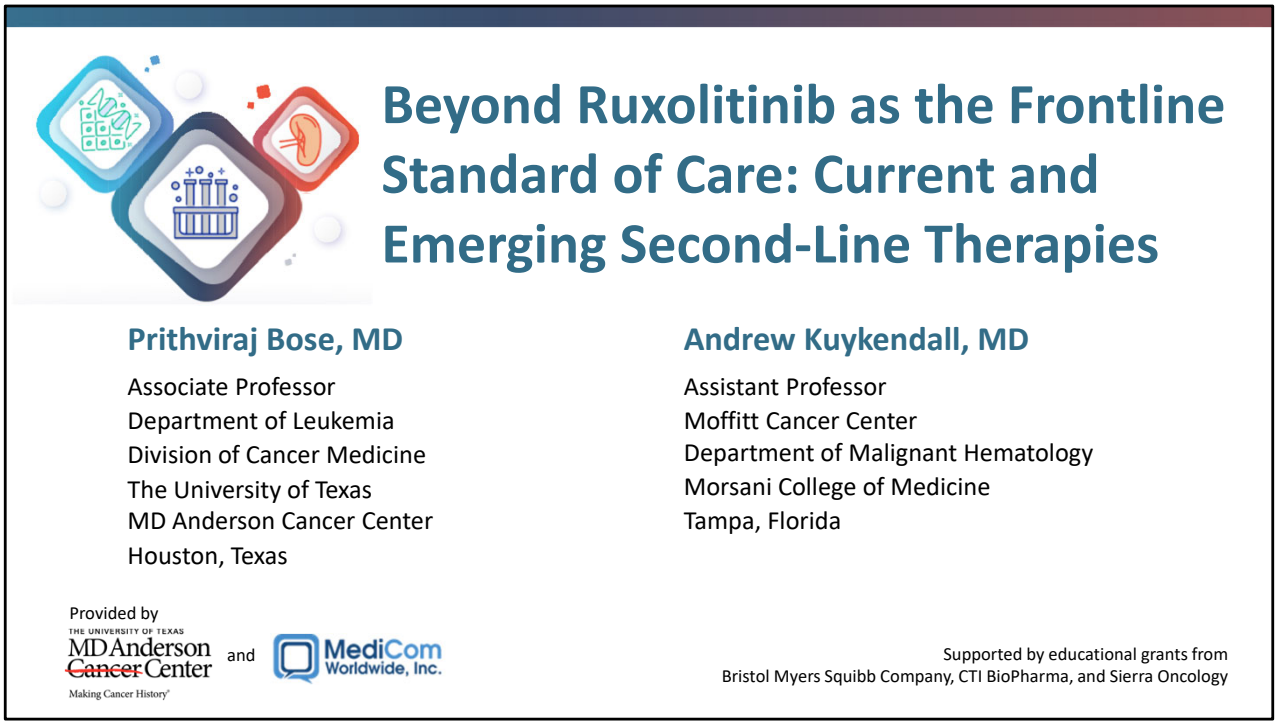
Beyond Ruxolitinib as the Frontline Standard of Care: Current and Emerging Second-Line Therapies



Dr. Prithviraj Bose: Hello, and welcome to today's program. I'm Dr. Prithviraj Bose, an Associate Professor in the Department of Leukemia at the The University of Texas MD Anderson Cancer Center in Houston, Texas. I'm joined today by Dr. Andrew Kuykendall, Assistant Professor in the Department of Malignant Hematology at the Moffitt Cancer Center in Tampa, Florida.

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Faculty Disclosures

Dr. Prithviraj Bose has relevant financial relationships related to advisory activities from AbbVie Inc., Blueprint Medicines, Bristol-Myers Squibb Company, Cogent Biosciences, Inc., Constellation Pharmaceuticals, CTI BioPharma Corp., Karyopharm Therapeutics, MorphoSys AG, Novartis AG, PharmaEssentia Corporation, and Sierra Oncology, Inc. He is on the speakers' bureau for Bristol-Myers Squibb, CTI BioPharma, Incyte Corporation, and Sierra Oncology.

Dr. Andrew Kuykendall has relevant financial relationships related to advisory activities from AbbVie Inc., Blueprint Medicines, Celgene Corporation – A Bristol-Myers Squibb Company, CTI BioPharma Corp., Imago BioSciences, Incyte Corporation, Novartis AG, and Sierra Oncology, Inc. He is on the speakers' bureau for Blueprint Medicines, Celgene Corporation – A Bristol-Myers Squibb Company, and Incyte, and has received research grant(s) from Blueprint Medicines, Celgene Corporation – A Bristol-Myers Squibb Company, and Sierra Oncology.

These are our disclosures.

Beyond Ruxolitinib as the Frontline Standard of Care: Current and Emerging Second-Line Therapies

Learning Objectives

- Describe the clinical practice considerations for the use of new second-line therapies for the treatment of MF
- Discuss the latest data on emerging and investigational second-line therapies for the treatment of MF
- Compare available and emerging strategies for managing patients with identified ruxolitinib resistance, failure, and/or loss of response

Today, we're going to discuss the management of myelofibrosis, essentially in the second and later line setting after failure of ruxolitinib. As you know, there are three JAK inhibitors that are FDA-approved today: ruxolitinib, fedratinib and pacritinib. All have been approved on the basis of pivotal trials that have demonstrated consistent improvements in spleen volume, disease symptoms, and quality of life.

However, at the same time, data shows that there is a high frequency of discontinuation because of either adverse events or more frequently progressive disease that lead to poor outcomes with survival after ruxolitinib discontinuation only in the range of 11 to 14 months across a number of studies.

Today, our learning objectives will focus on describing the clinical practice considerations for the use of new second-line therapies for the treatment of myelofibrosis, the latest data on emerging and investigational second-line therapies for the treatment of myelofibrosis.

In summary, we will review what we believe could be the emerging treatment paradigm and best practices in this era where there are options beyond first-line ruxolitinib, and trying to best manage patients with identified resistance, or intolerance to ruxolitinib.

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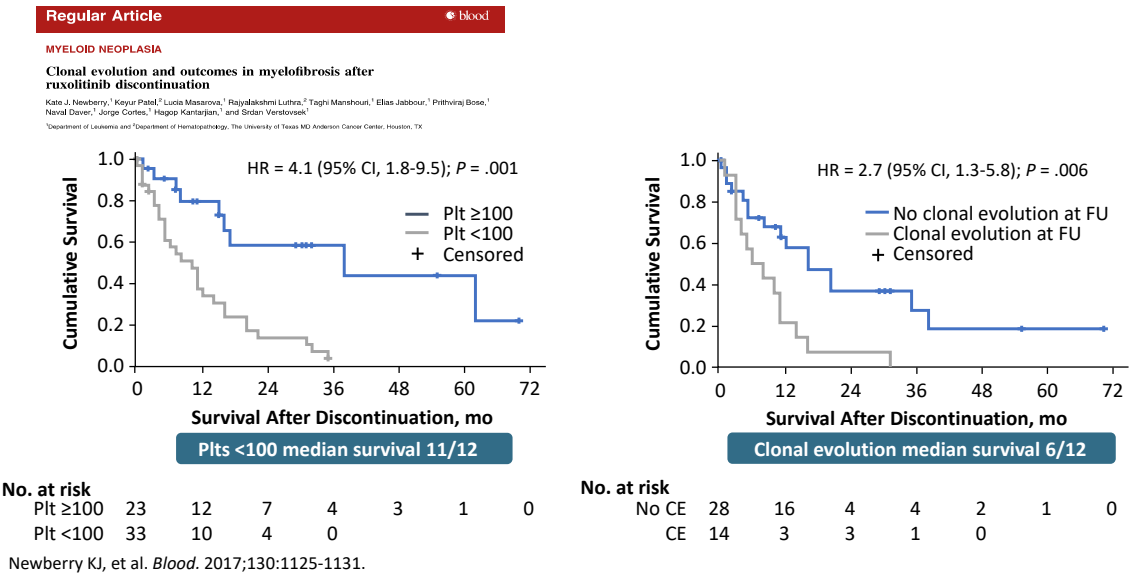
Prognosis After Ruxolitinib Discontinuation



Newberry KJ, et al. *Blood.* 2017;130:1125-1131.

On that note, and I was alluding to this when I said that survival in the post-ruxolitinib discontinuation setting is only in the range of 11 to 14 months. This was work from our group at MD Anderson showing a median survival after ruxolitunib discontinuation of 14 months, and very similar results have been reported by others, including Dr. Kuykendall from Moffitt, and other groups as well.

This just shows you that after you discontinue ruxolitinib, there were two factors, at least in our study, that predicted for even worse outcomes, and one was platelets dropping while on ruxolitinib and the other was clonal evolution on ruxolitinib.

That brings us to this new model published earlier this year in *Blood Advances* that Dr. Kuykendall and colleagues from Italy really developed. I'll let him speak to this, this may be a way of helping clinicians decide which patients may not do so well on ruxolitinib, and perhaps, may need to switch. Andrew.

RR6 Model Predicts Survival After Six Months of Ruxolitinib in Patients with MF

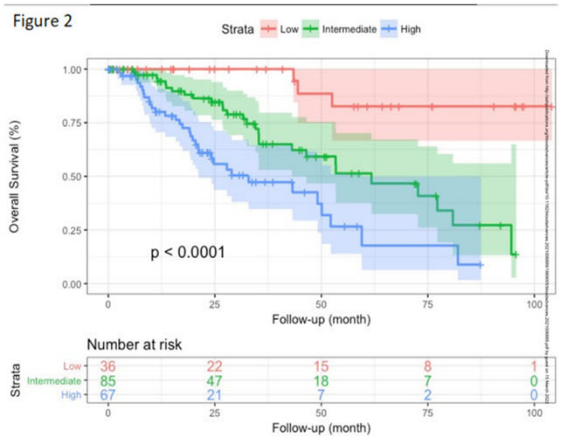


Table 3. Results of univariable and multivariable Cox regressions in the RUXOREL-MF training cohort.

Variable	Univariate, HR (95%CI); p-value	Multivariate, HR (95%CI); p-value
Hb decrease at 6 months *vs.* baseline*	1.02 (0.87-1.21); 0.77	
WBC count increase to >25 x10^9/L at 6 months *vs.* baseline**	1.20 (0.38.3.84); 0.76	
PLT count decrease at 6 months *vs.* baseline		
worsening of one grade[†]	0.81 (0.44-1.47); 0.48	
worsening of two grades[†]	2.57 (1.25-5.25); 0.01	
worsening of at least two grades[†] at 3- and/or 6-months	1.07 (0.67-1.73); 0.77	
Circulating blast cell increase at 6 months *vs.* baseline	1.42 (0.85-2.37); 0.18	
Acquisition of constitutional symptoms at 6 months*	not feasible**	
Splenomegaly reduction ≤30% by palpation at 3 and 6 months	2.54 (1.58-4.08); <0.0001	2.26 (1.40-3.65); 0.0009
RBC transfusion need only at baseline	0.42 (0.10-1.75); 0.23	
RBC transfusion need at 3 and/or 6 months	1.80 (1.05-3.09); 0.03	1.66 (0.95-2.88); 0.07
RBC transfusion need all time points (baseline, 3, and 6 months)	2.88 (1.49-5.54); 0.002	2.32 (1.19-4.54); 0.02
RUX dose below 20 mg BID at all time points (baseline, 3, and 6 months)	2.18 (1.31-3.63); 0.003	1.79 (1.07-3.00); 0.03

* Adjusted for RBC transfusion requirement.
** In patients with WBC ≤25 x10^9/L at baseline.
† PLT count categories: >=200 x10^9/L; 100-199 x10^9/L; 75-99x10^9/L; 50-74 x10^9/L.
* in those without symptoms at baseline.
** Only 3 patients acquire constitutional symptoms at 6 months *vs.* baseline.

HR, hazard ratio; Hb, hemoglobin; RBC, red blood cell; WBC, white blood cells; PLT, platelets; PB, peripheral blood; RUX, ruxolitinib; BID, bis in die, twice a day.

Ruxolitinib Dose < 20 mg BID

RBC Transfusion Need

<30% reduction in palpable splenomegaly

Maffioli M, et al. *Blood Advance.* 2022;6(6):1855-1864.

Dr. Andrew Kuykendall: Thanks, Prithviraj. I think that for a long time, we've known that we've had these agents that do a great job in improving symptoms and spleen, but the question is, when is the right time to switch therapies, or to consider an alternative treatment approach? I think this is something that we've struggled with. I think myelofibrosis is very different than some other diseases that we treat where you get true deep responses, and then maybe you lose a response, and then you know it's time to switch to something else. I think it's a little bit more nuanced with myelofibrosis.

This was a model that I think what was great about this is it largely confirmed things we already knew, but it looked at factors that occur in patients that had been treated with ruxolitinib that predict for worse overall survival. Really, the three things that came out that predicted for this worse survival were being on suboptimal doses of ruxolitinib, being on less than 20 milligrams twice a day, which we know is a very effective dose, and we also know that a lot of the spleen responses at least are dose-dependent.

Being on lower doses predicted for worse overall outcomes, needing red blood cell transfusions throughout therapy, and having a less than 30% reduction in palpable splenomegaly, so really a sub-optimal spleen response. I think this highlights what we've seen before with ruxolitinib therapy, is that patients that can't get on a higher

dose, patients that need a lot of transfusions have a lot of cytopenias, and those that don't get a great spleen response really aren't getting the maximum benefit from ruxolitunib therapy. I think this model helps us to really identify those patients who may benefit from a change in treatment approach.

As we start to look into second-line treatments, I want to quickly set the stage for this discussion, because in recent years, there is this stringent criteria for ruxolitinib failure that has been adopted, because we need to study this across different studies.

We've needed to incorporate this into the more recent clinical trials, but just because these are what we use in trials doesn't mean that it always carries over into what we do in the real-world practice. I'd pose this question back to you, Prithviraj. What do you think about this kind of widely-accepted definition of what we see with ruxolitinib failure on clinical trials, and what do you use in practice?

Dr. Prithviraj Bose: In clinical practice, I don't think it's necessarily practical to apply those in a strict fashion, especially recognizing that progression can occur in so many ways, right? You could have leukocytosis worsening, blasts going up, symptoms worsening. It's not just about the spleen and certainly, cytopenias worsening. I think it comes down to an overall assessment of disease progression by the treating physician, because it comes in so many flavors.

Dr. Andrew Kuykendall: I couldn't agree more. I think that obviously, I always think about, what are our goals of treatment with JAK inhibitors and ruxolitinib specifically. A lot of times, it is improving symptoms and spleen. If those things are getting worse, then I think it is a lot easier to say that maybe there is some failure going on. But, there's a lot of other aspects of the disease that can be worsening in spite of that, so patients can just have profound cytopenias that become very problematic.

Maybe that wouldn't have been considered a failure when we didn't have any other option, but as clinical trials have emerged, and newer agents are being developed that may address those, you start to think, "Okay, well, maybe that is some sort of failure because we have more options." I think it's context-dependent as well.

Towards a Consensus Definition of Ruxolitinib Failure? JAKARTA-2 Re-analysis Using Stringent Criteria

- In the original JAKARTA-2 analysis,[1] fedratinib demonstrated a 55% rate of ≥35% SVR in patients resistant or intolerant to RUX (≥14 days) per investigator assessment
- Reanalysis[2] employed a more stringent definition of RUX failure
- **Relapsed:** Ruxolitinib treatment for ≥3 months with regrowth, defined as <10% SVR or <30% decrease in spleen size from baseline, following an initial response
- **Refractory:** Ruxolitinib treatment for ≥3 months with <10% SVR or <30% decrease in spleen size from baseline
- **Intolerant:** Ruxolitinib treatment for ≥28 days complicated by development of RBC transfusion requirement (≥2 units per month for 2 months); or grade ≥3 thrombocytopenia, anemia, hematoma and/or hemorrhage while receiving ruxolitinib

Main findings
- 79/97 enrolled patients (81%) met the more stringent criteria for RUX R/R (n=65, 82%) or intolerance (n=14, 18%)

Clinically meaningful reductions in splenomegaly and symptom burden in patients with MF who met more stringent criteria
- SVRR = 30%
- Symptoms RR = 27%
- Safety consistent with prior reports

1. Harrison CN, et al. *Lancet Hematol.* 2017;4:e317-324.; 2. Harrison CN, et al. ASCO 2019; abstract 7057.; Harrison CN, et al. *Am J Hematol.* 2020;95:594-603.

We do want to go through looking at some of these second-line or alternative options. I think really the first agent that emerges, the potential second-line option is fedratinib. Obviously, this is approved, agnostic to line of therapy.

This can be used in the frontline or second-line setting, but the data that emerged for second-line use comes from this JAKARTA-2 study, which looked at fedratinib in patients that had previously been exposed to ruxolitinib. Recently, this has actually been re-analyzed using a more stringent criteria for ruxolitinib failure. Whereas in the initial analysis, it wasn't clear if it was really an accepted definition. When it was reanalyzed, the definition of relapse and refractory were very rigidly defined to mean, for relapse disease, they had to receive ruxolitinib for at least three months, and had to have regrowth of the spleen size following an initial response. Then for refractory, there had to have been at least three months with the suboptimal spleen response, somewhere between 10% and 30% decrease, not meeting a true response there. There was clear definitions for refractory and relapsed, and then there was intolerance, which this gets into the cytopenia side of things where you talk about treatment for at least
1 month or 28 days that was complicated by the development of red blood cell transfusions, or grade three or higher thrombocytopenia, anemia, development of bleeding or hematomas while receiving ruxolitinib.

I think this covers multiple different aspects of "treatment failure". You have patients that got a response that then they lost. They didn't have an optimal response, or those that really had treatment that was complicated by the development of low platelets, anemia, transfusions, bleeding, which would mean that an alternative option would be reasonable.

When they read and analyze the study using these stringent criteria of 8 out of 10, 80% or so patients met the stringent criteria for ruxolitunib relapsed refractory, and then within this, you saw that the spleen volume responses in the second-line setting were 30%. Symptom response rate, 27%, suggesting this does have activity as a second line agent.

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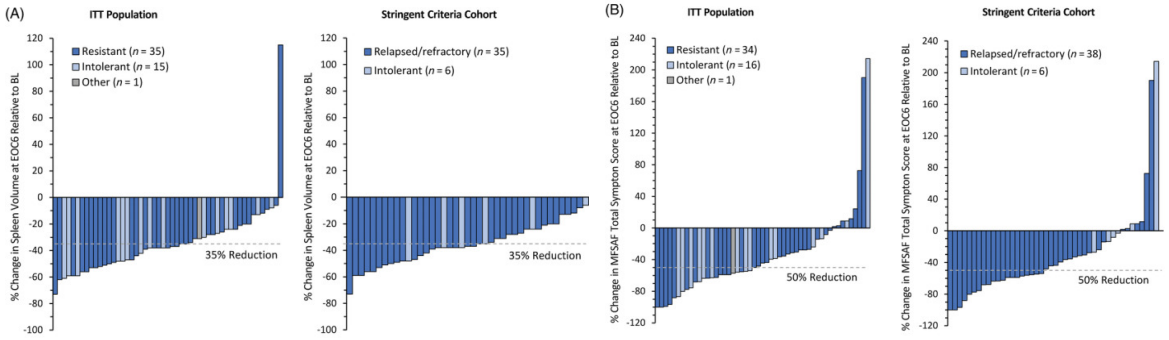
Fedratinib Induces Spleen and Symptom Responses in the Second-line Setting



BL=baseline; EOC6=end of cycle 6; ITT=intention to treat; MFSASF=Myeloma Symptom Assessment Form; TSS=total symptom score
Harrison CN, et al. *Am J Hematol.* 2020;95:594-603.

When you look at fedratinib, and you look at the waterfall plots, this was a single arm study, and these are the waterfall plots looking at improvements in the spleen and symptoms in both the initial intention to tree population, as well as looking at the stringent criteria cohorts.

What we can highlight here is if the bars are going down from zero down, that's an improvement in both spleen, and then symptoms on the right, and you can see that most patients had improvement in their spleen and symptom scores with very few patients having worsening of these disease. So, there does seem to be activity here.

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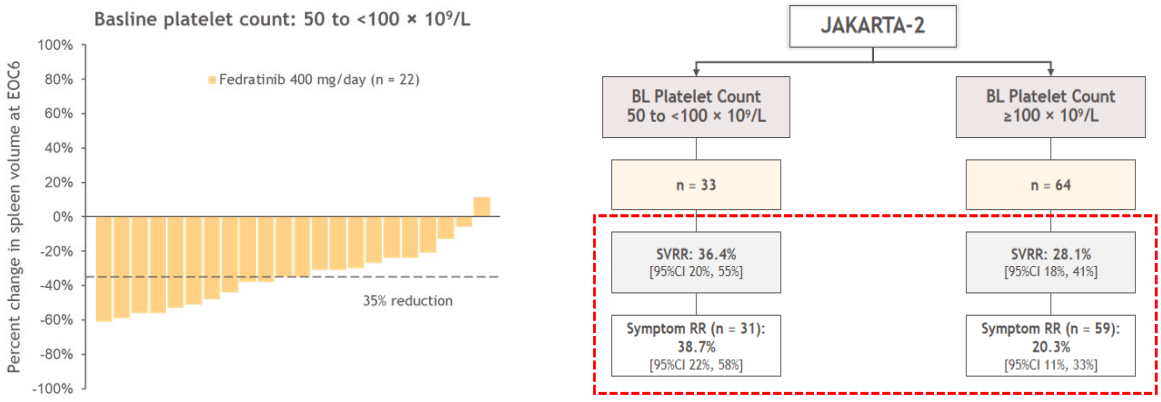
Fedratinib Spleen Volume and Symptom Responses Based on Baseline Platelet Count



Harrison CN, et al. *Blood*. 2019;134:668.

Then when you actually look at this critical cohort of lower platelet patients, this is a patient population that we know is a challenge to treat, especially with ruxolitinib because we have to alter doses for this.

But if you look at those patients that were enrolled on JAKARTA-2 that had platelet count between 50 and a hundred thousand, that was 33 patients, which is not an insignificant number of folks and the spleen volume response within this cohort was 36%, symptom response, 38%, so really did show the ability to achieve these critical responses in a very, I would say suboptimally treated cohort historically.

What's notable about this is, you actually see better spleen responses and symptom responses nominally than you see in patients that have higher platelet counts. I think that can be somewhat confusing, but I would also say that that might be the patient population is more likely to benefit from a switch, because these are the patients that are going to be more suboptimally dosed on ruxolitinib, and then can be fully dosed on fedratinib. So, it may be these patients with marginal platelet counts are more chance to benefit by switching to the full dose of an alternative JAK inhibitor.

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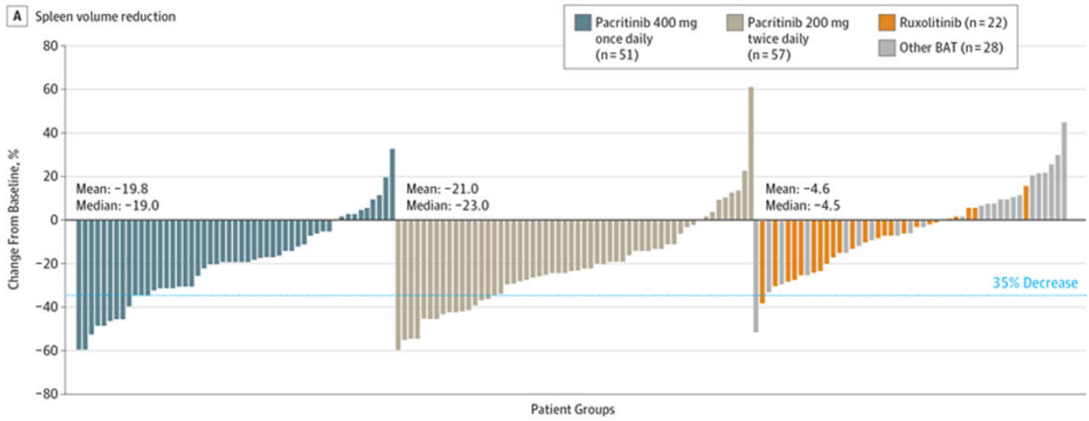
PERSIST-2 Demonstrated Favorable Activity of Pacritinib in MF Patients with Thrombocytopenia



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

Which brings us to talk about pacritinib. Pacritinib recently gained accelerated approval in February of this year really for this markedly thrombocytopenic patient population, less than 50,000 platelets, and the data for that came from several studies, but really, predominantly from this PERSIST-2 study where it enrolled patients with platelets less than 100,000, and treated them with two different doses of pacritinib. We'll really focus on the 200 milligram twice daily dose, because that's the dose that's recommended going forward, and compared them to best available therapy, which included ruxolitinib.

Again, this included ruxolitinib at a suboptimal dosing strategy, so lower doses of ruxolitinib for these patients with less than 100,000 platelets, and then compared their spleen responses and symptom responses in this thrombocytopenic patient cohort. What you can see here when looking at spleen volume reductions is the patients treated with pacritinib 200 milligrams twice a day consistently had reduction in their spleen volume and it seemed superior to that of best available therapy, which is on the far right portion of this, where we did see reduction in spleen volumes, but not as consistently and not as profound. The orange bars and the best available therapy cohort identify those patients that were treated with ruxolitinib, but at a lower dose, so you can see that there's a general trend for those patients to have improvement in spleen volume, but certainly not to the extent that we saw with the pacritinib cohort.

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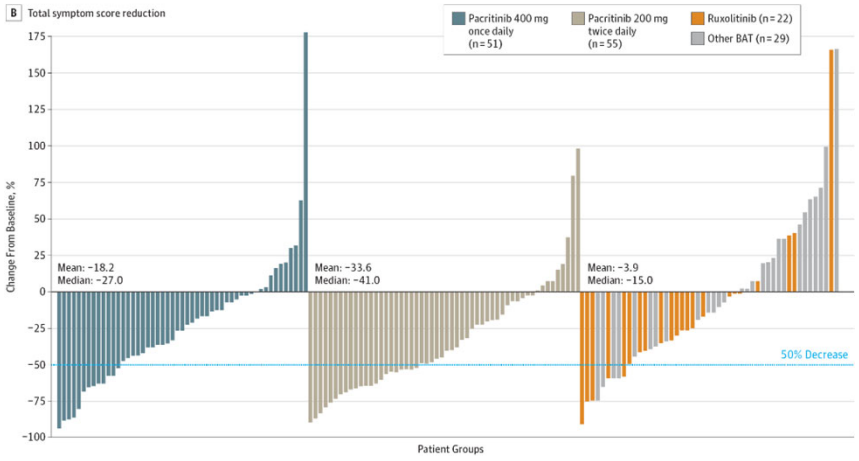
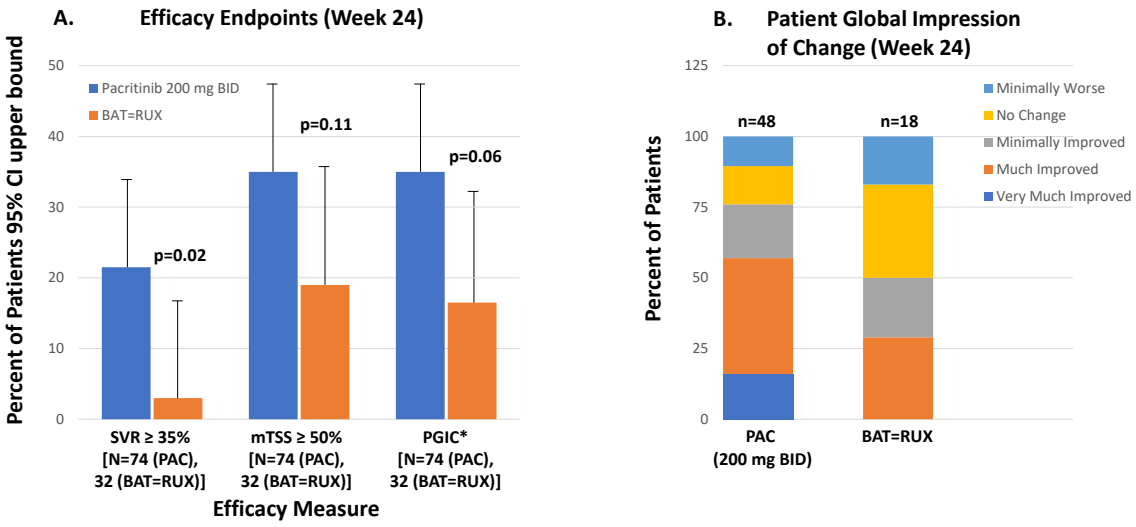
PERSIST-2 Demonstrated Favorable Activity of Pacritinib in MF Patients with Thrombocytopenia



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

Again, when we look at symptoms, in the same way, you start to see a similar picture emerge. Again, ignoring that left graph, which is focusing on pacritinib at 400 milligrams daily, and focusing more on the middle with pacritinib 200 milligrams twice daily, we can see consistent declines in symptom scores, improvements and symptoms greater than what we see with best available therapy.

Retrospective Analysis Supports Superiority of Pacritinib vs Ruxolitinib in Thrombocytopenic Patients



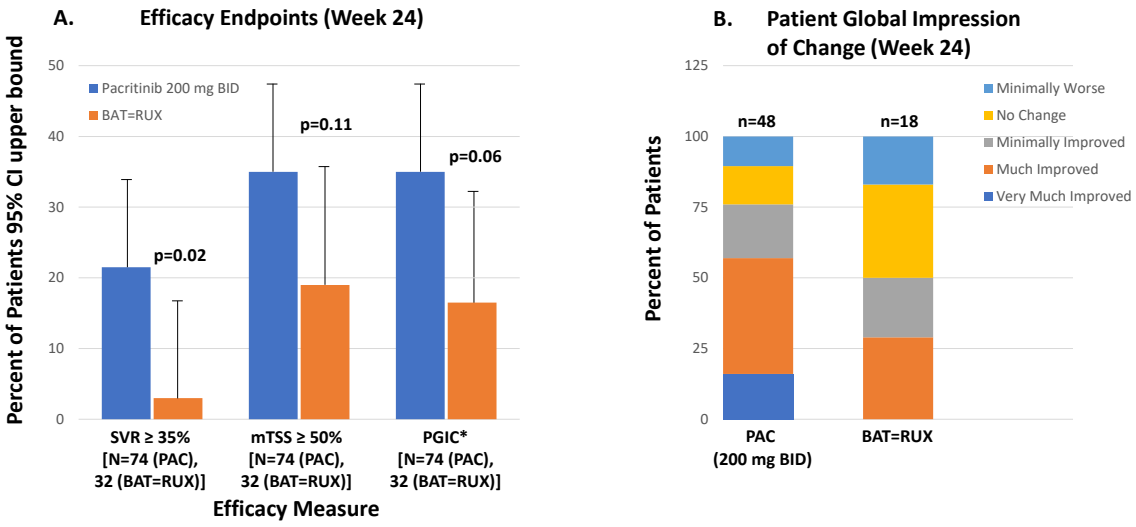
Harrison, et al., Poster Presented at EHA, 2022.

I think this is a chance to bring Prithviraj back in, because I think we think about pacritinib in treating patients that have marked thrombocytopenia. I think this analysis, which was recently presented in poster format at EHA earlier this year really focused on that question and said, "Okay, what about pacritinib versus ruxolitinib in patients with thrombocytopenia? Let's look across the board and see how they do." I think when they look at spleen volume response, symptom score and overall global impression of change, which is this patient reported outcome of how they feel, pacritinib seems superior across the board to ruxolitinib in these patients with lower platelets.

Prithvi, is this where you see pacritinib being used the most? Is this something you would limit to less than 50,000 platelets, or where do you see pacritinib, and what do you think of this analysis?

Dr. Prithviraj Bose: Yes, Andrew, these are compelling data. Like you said, the label for pacritinib is less than 50, but obviously, this study was done in patients with platelets up to a hundred, like you said, and ruxolitinib was allowed as BAT, and clearly, this is what we are showing here, are the pacritinib patients versus the patients who got ruxolitinib as their BAT. Now, being mindful of the fact that some also had prior ruxolitinib. I think, the appeal of this is clearly there, that the spleen response was actually significantly superior for pacritinib, symptoms were certainly numerically superior. I think the only caveat is, Andrew, like you said, that the ruxolitinib dose was generally five milligrams once or twice a day for these patients.

Retrospective Analysis Supports Superiority of Pacritinib vs Ruxolitinib in Thrombocytopenic Patients



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

I think in the 50 to 100, I think one could really go both ways, but clearly, pacritinib has established itself as an attractive option there at the 200 BID, again, full dosing to your point as opposed to suboptimal dosing. I think 10 milligram BID of ruxolitinib is also a reasonable strategy, and one that we have employed when pacritinib was not an option. I think both of those, but certainly I think favoring pacritinib based on this comparison.

Dr. Andrew Kuykendall: Yes, I think you bring up a good point, and we're limited by the label of ruxolitinib, because I think when we've gotten more bold on our dosing of ruxolitinib in these marginal thrombocytopenic patients where we feel like we can maybe try to get to these higher doses, 10 milligrams twice a day, and even push the dose in patients that aren't dropping their platelets as markedly. When you're looking at this on a clinical trial, you certainly have to follow the label, so sometimes this requires us to take a little bit. We have to be very nuanced and thoughtful in how we interpret this data, and really consider that yes patients who cannot tolerate more than five milligrams twice a day, pacritinib clearly appears to be better.

However, it may not be a completely fair comparison as we can't push the dose of ruxolitinib probably a little bit more aggressively in some of these patients.

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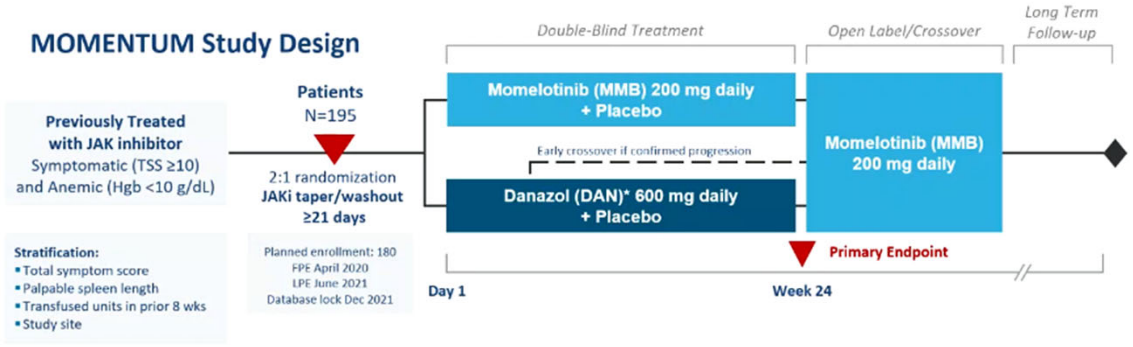
MOMENTUM Assessed Momelotinib in Patients Previously Treated with Ruxolitinib Who Were Symptomatic and Anemic



Primary Endpoint

- Total symptom score (TSS) response rate at Week 24

Key Secondary Endpoints

- Transfusion independence (TI) rate at Week 24
- Splenic response rate (SRR) at Week 24

Verstovsek, S et al. *Future Oncology* 2022;17(12):1449-1458.

Which brings us to the most recently developed JAK inhibitor, which is momelotinib, not currently approved, but have reported positive results from a recently completed phase three clinical trial called MOMENTUM. Momelotinib has a complicated history, but essentially, it was looked at in two studies called the SIMPLIFIED studies that identified that it had significant activity as far as reducing spleen, and symptom improvement, but also had this ability to improve anemia that we hadn't really seen in prior JAK inhibitors.

So, altogether, it was assessed in this MOMENTUM study that looked at patients that had previously been on ruxolitinib for at least 28 days, and then who were anemic and had big spleens, and it randomized them 2:1 to either momelotinib versus danazol, which is certainly another agent that we use in the salvage setting for anemic patients with myelofibrosis. It looked at a primary endpoint of symptom improvement at 24 weeks.

Of course, the primary endpoint may have been symptom improvement, but there's also these key secondary endpoints looking at spleen response rate and transfusion independence as well at week 24, so really trying to get the understanding, is this an agent that's able to help with multiple things? Can it not only help with symptoms, but can it also help with anemia issues, as well as spleen response rates?

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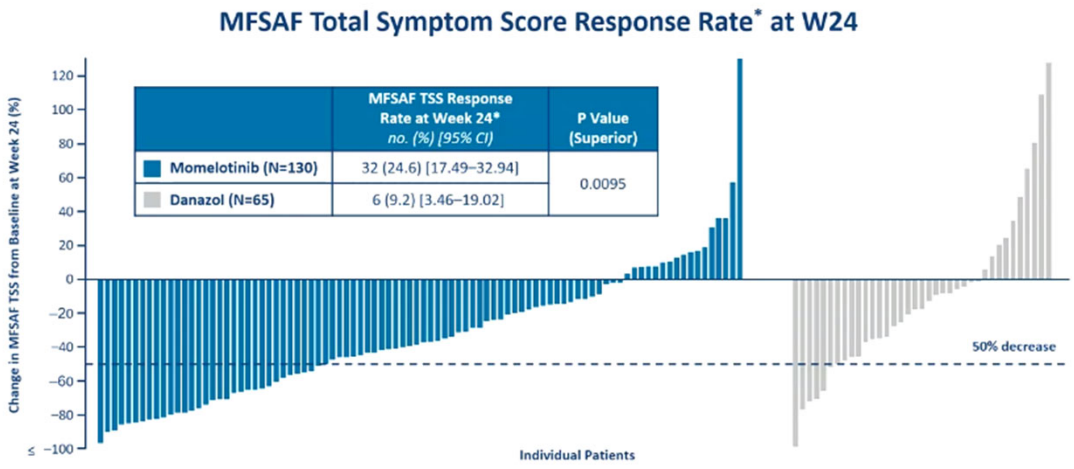
Momelotinib Superior to Danazol in Symptomatic MF Patients with Anemia and Prior Ruxolitinib Treatment



Mesa R, et al. *Clin Lymphoma Myeloma Leuk*. 2022;22(Suppl 2):S339-S340.

What was found was quite exciting in the sense that when we look, and you could see these waterfall plots here are heavily weighted toward the momelotinib because it was a 2:1 randomization, so twice as many patients went on the momelotinib arm as the danazol arm, but when you look at the symptom response rate at week 24, you had 25% of patients able to achieve this 50% reduction in symptom score compared to just 9% on the danazol arm, and that was statistically significant.

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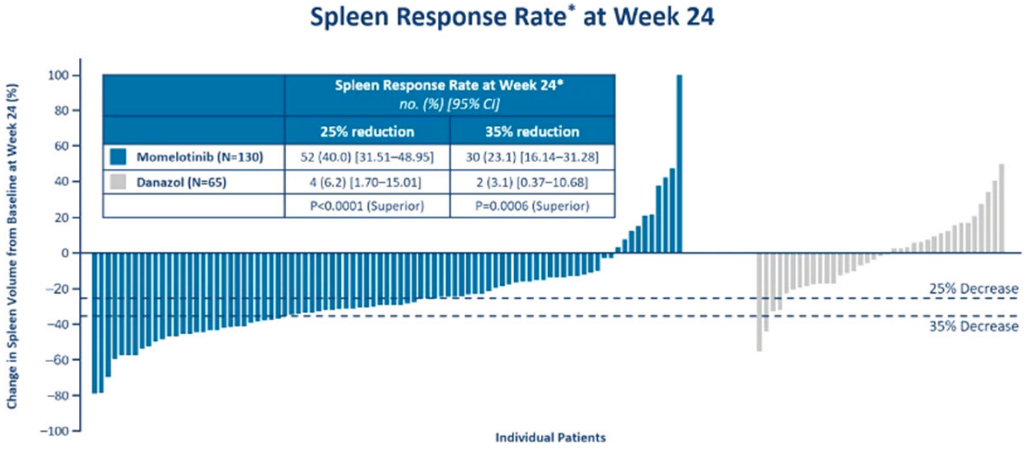
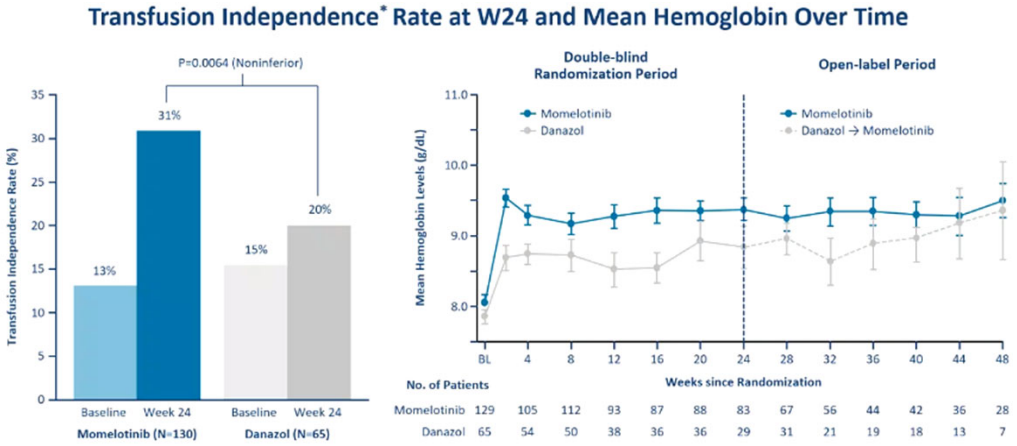
Momelotinib Superior to Danazol in Symptomatic MF Patients with Anemia and Prior Ruxolitinib Treatment



*Defined as the proportion of patients who have a reduction in spleen volume of ≥25% or ≥35% from baseline
Mesa R, et al. *Clin Lymphoma Myeloma Leuk.* 2022;22(Suppl 2):S339-S340.

What we also saw in terms of spleen response rates is that 40% of patients were able to achieve these 25% reduction in spleen volume, 23% able to achieve this classical, 35% reduction in spleen volume. Very few patients on the danazol arm were able to achieve this degree of spleen response, so quite effective in comparison with danazol in terms of spleen and symptoms.

Momelotinib Better than Danazol in Symptomatic MF Patients with Anemia and Prior Ruxolitinib Treatment



*Defined as not requiring red blood cell transfusion in the terminal 12 weeks of the 24-week randomized period, with all the hemoglobin levels during the 12-week interval of ≥8 g/dL

Mesa R, et al. *Clin Lymphoma Myeloma Leuk.* 2022;22(Suppl 2):S339-S340.

Then when we look at the rate of anemia and those anemia parameters, we look at transfusion independence. This is something that's clinically meaningful to patients. At baseline, around 13%, 15% of patients on either arm were transfusion independent. However, at week 24, you had 30% slightly more that were transfusion independent on the momelotinib arm compared to only 20% on the danazol arm, suggesting an improvement in this rate of transfusion independence when treated with momelotinib.

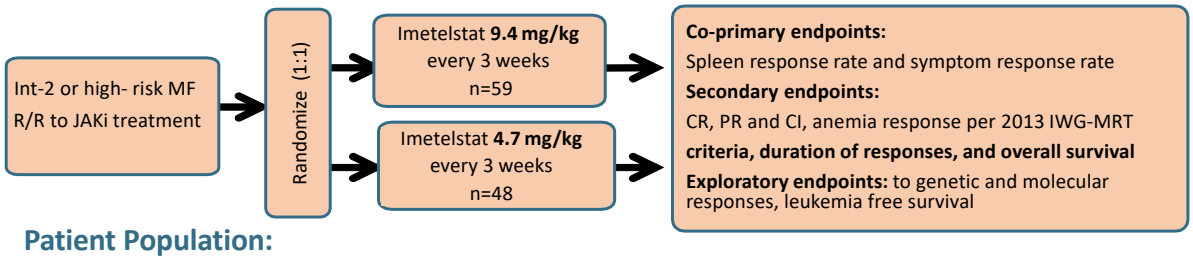
Then when you look at the overall, just mean hemoglobin over time in this line graph here, you can see that those patients treated with momelotinib had this initial peak in their hemoglobin, and then that maintained, and that stayed stable throughout. At week 24, I'd highlight those patients on the gray line who were treated with danazol actually switched over to momelotinib, and you can then see in those next 24 weeks that actually that gray line starts to meet the momelotinib arm, suggesting that those patients who had switched then from danazol to momelotinib then had a subsequent improvement in their hemoglobin or mean hemoglobin over time.

I think that this is certainly very exciting data, and I think this is covering these more novel JAK inhibitors that can be used in the second line setting, and so, I'll get some quick thoughts from Prithviraj, and also turn it over to him to discuss some non JAK inhibitor options.

Dr. Prithviraj Bose: Thanks, Andrew.

Beyond Ruxolitinib as the Frontline Standard of Care: Current and Emerging Second-Line Therapies

IMbark Phase 2 Trial: Study Design



Patient Population:

- Patients with Intermediate-2 or high-risk MF (Int-2/high-risk) patients who have relapsed after or are refractory to prior treatment with a janus kinase (JAK) inhibitor
- Relapsed or refractory to JAKi defined as documented progressive disease during or after JAKi:
  - Patients must have worsening of splenomegaly-related abdominal pain at any time after the start of JAKi therapy and EITHER:
    - No reduction in spleen volume or size after 12 weeks of JAKi therapy, OR
    - Worsening splenomegaly at any time after the start of JAKi therapy documented by:
      - Increase in spleen volume from nadir by 25% measured by MRI or CT, or
      - Increase in spleen size by palpation

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

This is imetelstat, so a little bit of different direction here for the rest of the content today. So these are non-JAK inhibitors, of course, this is the telomerase inhibitor, and this is just to remind you, and Dr. Kuykendall showed you earlier the definition of-- or stringent criteria for ruxolitinib failure in the JAKARTA-2 re-analysis of fedratinib. So note that here is another set of criteria. These were used in the phase II trial of imetelstat that looked at two different doses as you see, this is an IV drug given every three weeks, and note that the criteria, like I was saying earlier, are similar but not the same.
There are sort of variations around the theme of an insufficient spleen response or regrowth after an initial response.

Dose-Related Clinical Benefits with Imetelstat Treatment

Clinical Benefits	4.7 mg/kg (N = 48)	9.4 mg/kg (N = 59)
Median OS, months (95% CI)	19.9 (17.1, 33.9)	28.1 (22.8, 31.6)
Symptom Response at week 24 (TSS reduction ≥50%), n (%)	3 (6.3%)	19 (32.2%)
Spleen response at week 24 (SVR ≥35% by IRC), n (%)	0	6 (10.2%)
Median PFS, months (95% CI)	14.8 (8.3, 17.1)	20.7 (12.0, 23.2)
Clinical improvement, per IWG-MRT, n (%)	8 (16.7%)	15 (25.4%)
Transfusion independence of 12 weeks, n/N (%)	2/14 (14.3%)	3/12 (25.0%)
Reduction in bone marrow fibrosis , n/N (%)	4/20 (20.0%)	16/37(43.2%)
≥25% Reduction in VAF of *JAK2, CALR* or *MPL* , n/N (%)	1/18 (5.6%)	8/19 (42.1%)

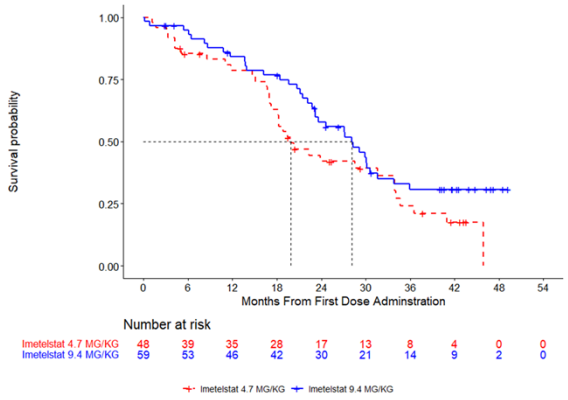
CALR=calreticulin gene; CI=confidence interval; JAK=Janus kinase; IWG-MRT=International Working Group-Myeloproliferative Neoplasms Research and Treatment; MPL=thrombopoietin receptor gene; OS=overall survival; PFS=progression-free survival; SVR=spleen volume reduction; TSS=total symptom score; VAF=variant allele frequency

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

Moving on from there, now this drug has been particularly exciting because of what you see in the top row there. The median overall survival in this post-JAK inhibitor setting was a striking 28.1 months at the higher dose. This is about double of what, for example, our group reported that I showed you earlier, 14 months in the post ruxolitinib failure setting. Symptom and spleen responses were not as impressive, certainly not spleen. However, you note on the table also that if you look at the bottom, the reduction in bone marrow fibrosis and driver mutation allele burden was again quite striking at above a 40% for both of those parameters.

Beyond Ruxolitinib as the Frontline Standard of Care: Current and Emerging Second-Line Therapies

Potential OS Improvement with 9.4 mg/kg Imetelstat Treatment in Patients with MF R/R to JAKi



	4.7 mg/kg (N = 48)	9.4 mg/kg (N = 59)
Number of events, n (%)	35 (72.9%)	36 (61.0%)
Number censored, n (%)	13 (27.1%)	23 (39.0%)
Median Overall Survival (months) (95% CI)	19.9 (17.1, 33.9)	28.1 (22.8, 31.6)
12-months survival rate % (95% CI)	78.6 (63.9, 87.9)	84.0 (71.6, 91.4)
24-months survival rate % (95% CI)	42.0 (27.4, 56.0)	57.9 (43.6, 69.7)

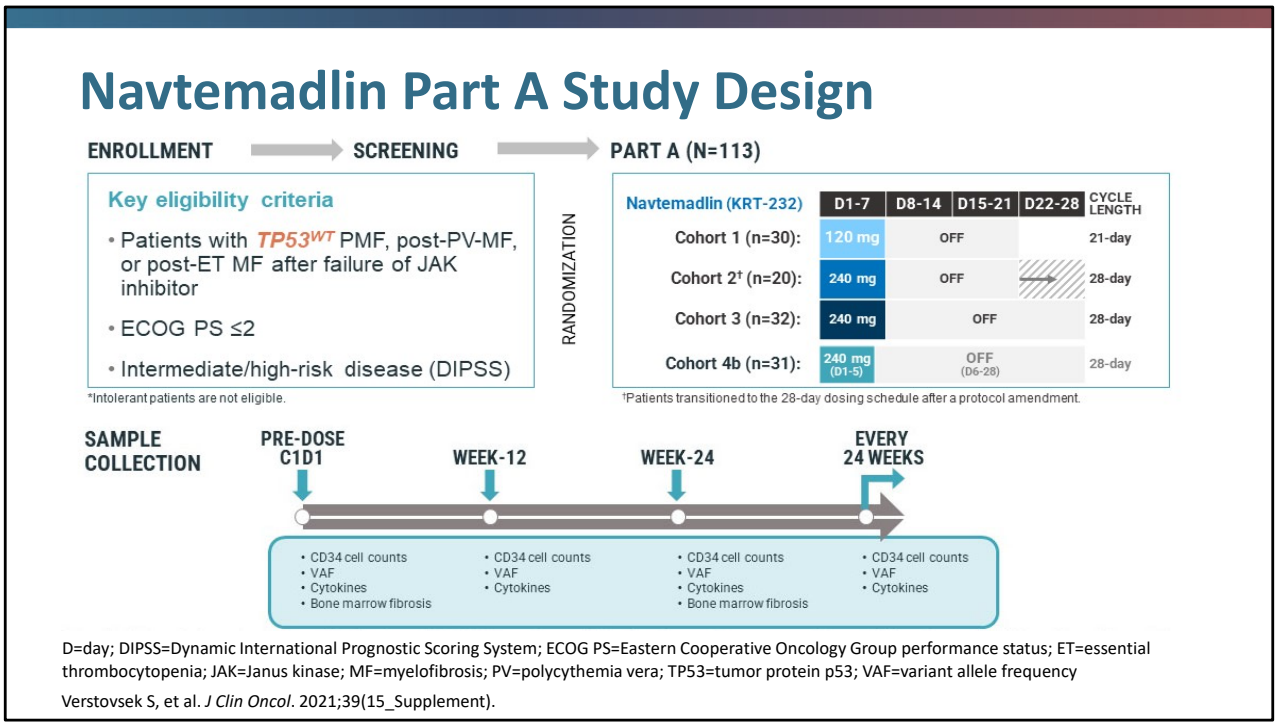
OS analysis was performed based on database lock in April 2020; median follow-up was 41.7 months (range 0.2, 49.2)

Similar results were observed when sensitivity analyses accounted for confounding factors of subsequent therapies, including hematopoietic stem cell transplantation and dose escalation from 4.7 mg/kg to 9.4 mg/kg

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

Again, I already covered this, but the main message that got folks interested in this particular drug, and actually served as the impetus to design the phase III that's currently ongoing with overall survival as the primary endpoint, this is a first in the field. We don't have another phase three that used OS as its primary endpoint. Was this, that in the phase II, they saw this, in excess of 28-month overall survival in the second line setting after ruxolitinib failure.

Beyond Ruxolitinib as the Frontline Standard of Care: Current and Emerging Second-Line Therapies



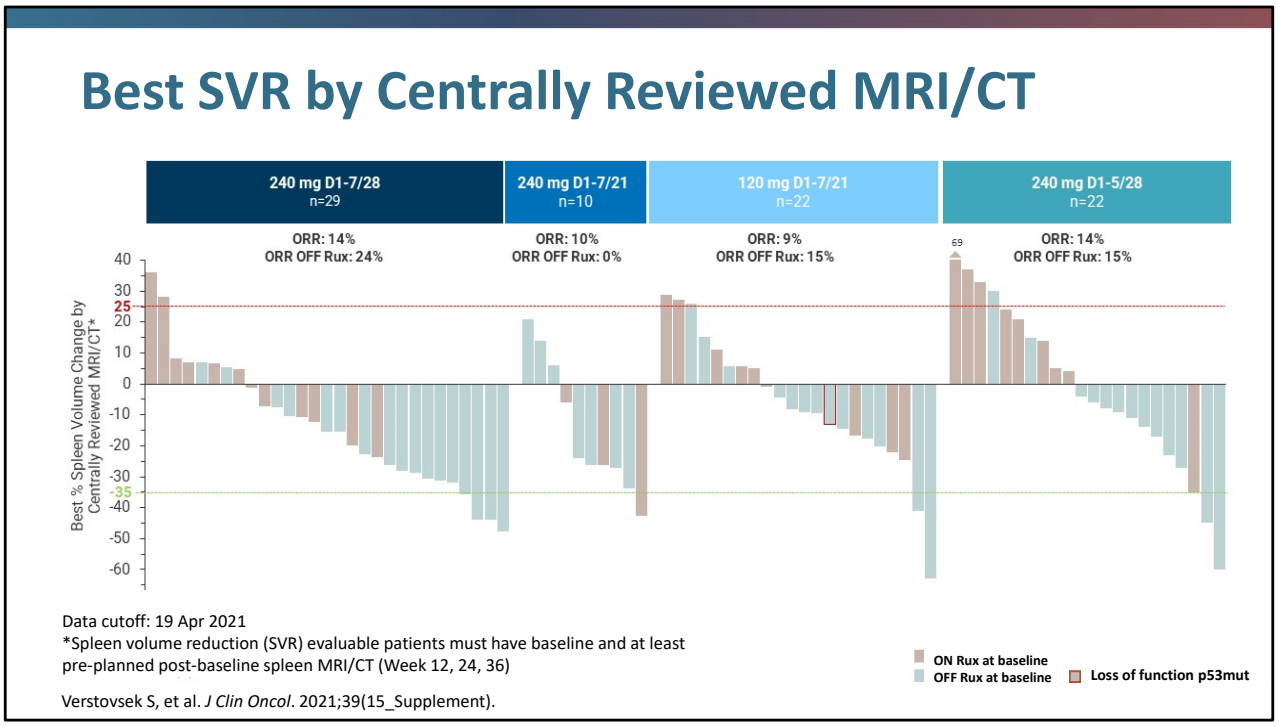
D=day; DIPSS=Dynamic International Prognostic Scoring System; ECOG PS=Eastern Cooperative Oncology Group performance status; ET=essential thrombocytopenia; JAK=Janus kinase; MF=myelofibrosis; PV=polycythemia vera; TP53=tumor protein p53; VAF=variant allele frequency

Verstovsek S, et al. *J Clin Oncol*. 2021;39(15_Supplement).

Now, there is another drug that is being investigated in a similar setting. It's called navtemadlin, it has a name now, was previously called KRT-232. This is a MDM2 inhibitor. So, navtemadlin is also being studied as a single agent against best supportive care or best available therapy, I should say, in the post-JAK inhibitor failure setting. So, similar to imetelstat, however, another thing that they shared in common, the two phase III trials, I mean, is that other JAK inhibitors are actually not allowed in the comparator arm, so it's imetelstat versus best available therapy, and navtemadlin versus best available therapy, excluding JAK inhibitors.

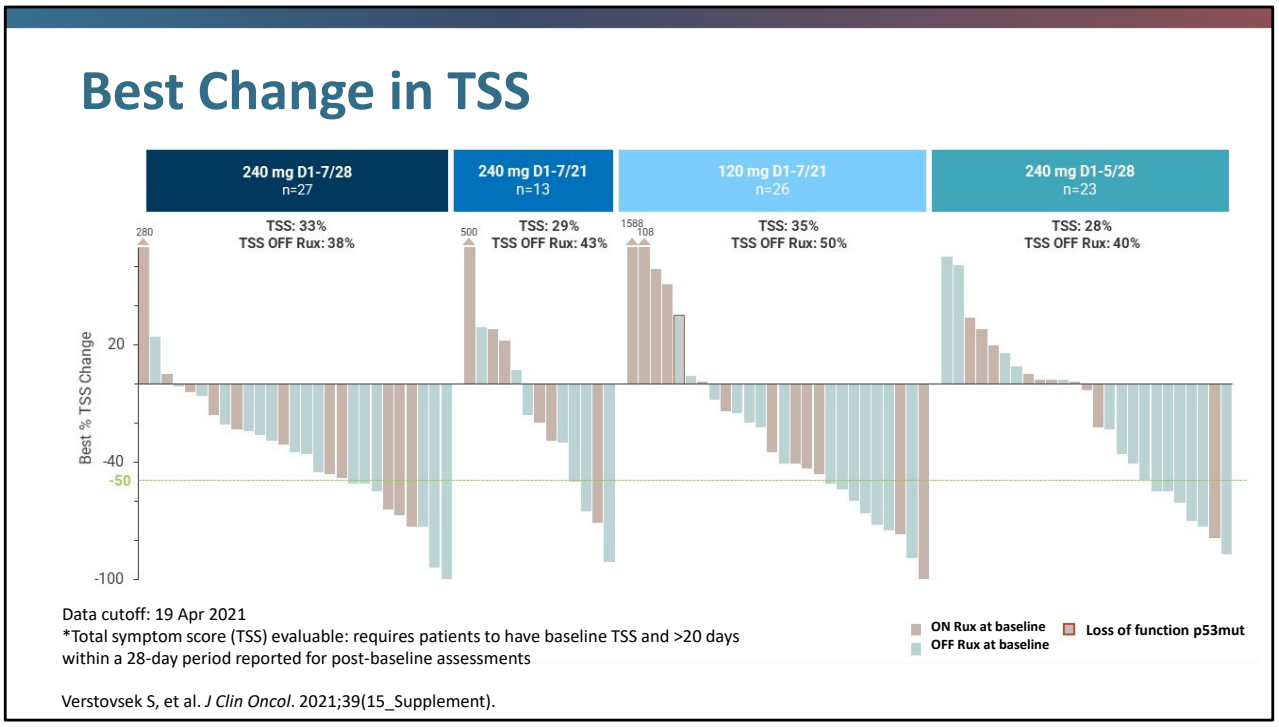
But this particular slide goes back to the phase II trial of this agent, and this was, again, done in a JAK inhibitor resistant refractory population, not an intolerant population. They actually excluded intolerance, so that was a little bit more of a pure homogenous failure population in the sense that these patients were not having enough of a spleen response.

Beyond Ruxolitinib as the Frontline Standard of Care: Current and Emerging Second-Line Therapies



I'm showing you some of the earlier results here presented at EHA 2020, so some time ago now. If you look to the left, because that's the dose that's going forward, the 240 milligrams for a week, and then three weeks off, that is the dosing schedule going forward. So if you look there, the spleen response was a modest 14%. However, there was no washout from ruxolitinib in this study, and when you do that, what can obviously happen is that the spleen could grow after the patient stops the ruxolitinib, and thereby, diminish the apparent benefit from the new drug. They looked at also patients who had been off ruxolitinib already at the time that they began after navtemadlin, and for them, the spleen response was better at 24%, obviously, small numbers here.

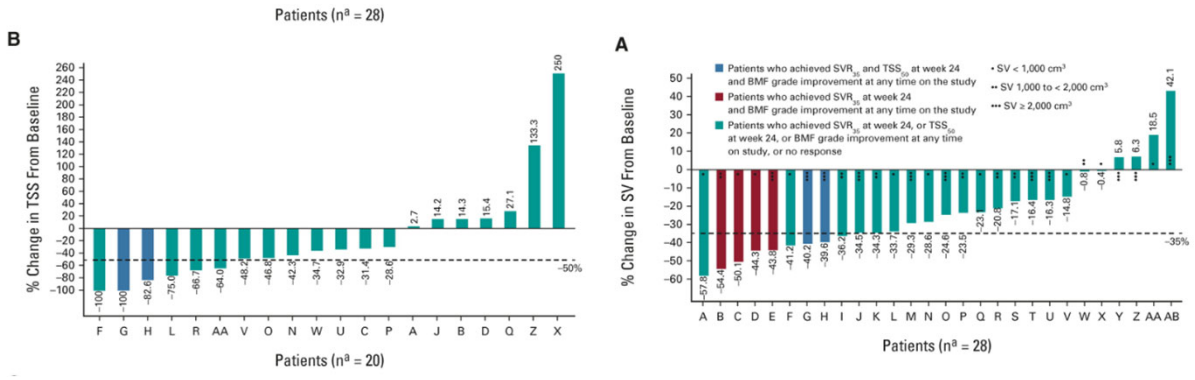
Beyond Ruxolitinib as the Frontline Standard of Care: Current and Emerging Second-Line Therapies



Symptoms, similar story, 33% across the board, and 38% when you looked at just the patients that were off ruxolitinib.

Beyond Ruxolitinib as the Frontline Standard of Care: Current and Emerging Second-Line Therapies

Navitoclax Can Achieve Spleen and Symptom Responses in Patients with Suboptimal Responses to Ruxolitinib



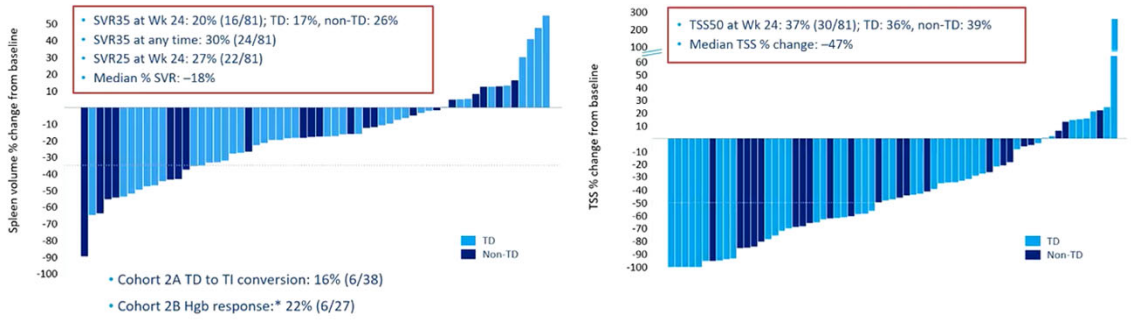
Harrison, et al. *J Clin Oncol.* 2022;40:15:1671-1680.

Now, moving on from there to a slightly different theme here, the concept of add-on therapy. So we now have a profusion actually of agents that are synergistic in the lab with ruxolitinib, which has given rise to this idea of adding them on in patients with so-called "suboptimal responses" to ruxolitinib. So, shown here is the BCL-xL/BCL-2 inhibitor navitoclax, which was studied in this fashion.

These combos have been studied in frontline as well, we won't touch on that in today's presentation, but this is the suboptimal setting, and here patients had to have had at least three months of prior ruxolitinib, and frankly, it was a lot longer. The median prior ruxolitinib duration was like 20 months, so it was people who had been on ruxolitinib for a good amount of time, and had not had a sufficient spleen and symptom response, and there, you saw about a 30% rate of symptom response, and 27% rate of spleen response. By that, I mean the typical TSS 50 and SVR 35 with the addition of navitoclax.

Beyond Ruxolitinib as the Frontline Standard of Care: Current and Emerging Second-Line Therapies

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



Harrison, et al. Preliminary data from the MANIFEST study. Presented at: 2022 EHA Congress; June 9-12, 2022; Vienna, Austria. Abstract S198.

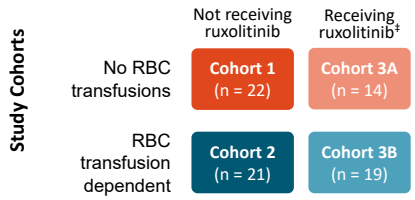
Similar data with pelabresib. Pelabresib is the BET inhibitor, and this again has been studied in frontline, as well as in the add-on setting. Actually, also has monotherapy in the second line setting, but this is, again, the add-on data. Remember, these are all synergistic combinations preclinically, and here we saw about a 20% rate of spleen response, and a 37% rate of symptom response in the add-on setting-folks who had been on ruxolitinib for at least six months, and still had a palpable spleen greater than five centimeter, or a certain volume by MRI, et cetera.

This drug also has an anemia benefit, and if you look towards the bottom in the transfusion independent patients, there was a conversion of 16% to independence, and then the patients who were anemic but not transfusion-dependent by formal criteria, there was a 22% anemia response. So, potentially, a drug that can benefit multiple aspects of the disease.

Beyond Ruxolitinib as the Frontline Standard of Care: Current and Emerging Second-Line Therapies

Luspatercept for Treating Anemia in MF

- Open-label, nonrandomized, multicohort phase II trial of **luspatercept** 1 mg/kg every 21 days for patients with primary or post-ET/post-PV MF and anemia (planned N = 100)



Parameter	RBC Transfusion Dependent	
	No RUX (Cohort 2; n = 21)	RUX (Cohort 3b; n = 19)
RBC transfusion-free ≥ 12 consecutive wks, n (%)*	2 (10)	6 (32)
▪ Median duration of response, wks (range)	32 (16-49)	39 (12-77)
≥ 50% reduction in RBC transfusion burden from BL, n (%)	8 (38)	10 (53)

Hb Increase ≥ 1.5 g/dL From BL for ≥ 12 Consecutive Wks†	No RBC Transfusions	
	No RUX (Cohort 1; n = 22)	RUX (Cohort 3a; n = 14)
Hb increase ≥ 1.5 g/dL at every assessment, n (%)	3 (14)	3 (21)
Mean Hb increase ≥ 1.5 g/dL, n (%)	4 (18)	9 (64)

*Primary endpoint, cohorts 2, 3b. †Primary endpoint, cohorts 1, 3a. ‡Stable dose for ≥16 wks at enrollment

Gerds AT, et al. *Blood*. 2019;134(Supplement_1):557.

Finally, luspatercept, a different combination in the sense that this is viewed as primarily an anemia drug, and not necessarily a synergistic one in pre-clinical studies, but just a logical empiric combination.

Luspatercept obviously is familiar to all of you from its use in MDS and beta thalassemia., and in this trial, somewhat of a complicated design, but really four cohorts, so patients could be on ruxolitinib or not be on ruxolitinib, and they could be formally transfusion-dependent or transfusion independent. Luspatercept was added to the ruxolitinib in those cohorts, as well as used as monotherapy in the folks not on ruxolitinib, and really to summarize the results, the best results were seen in the patients who were on a stable dose of ruxolitinib and transfusion-dependent.
That is where it seemed to provide the greatest benefit, which again served as the stimulus for the phase III study that's currently ongoing, comparing luspatercept to placebo in patients on a stable dose of ruxolitinib and requiring transfusions, so that's ongoing at this time.

We've tried today I think to summarize very quickly what is a plethora of new agents being developed, both JAK inhibitors and non-JAK inhibitors in this space.

Dr. Prithviraj Bose: Andrew, any final thoughts?

Dr. Andrew Kuykendall: No, I think that's a great job Prithviraj. I think certainly this is becoming an emerging area, and I think we're getting more and more options. I think critically we do need to think about, what can we do for the patient? What's the individual goal we have for patients that are sitting in front of us, and really try to target the therapy that we consider with individual patient goals. This should always be an individualized decision with these goals in mind.

Dr. Prithviraj Bose: Thanks, Andrew. Thank you all for listening. This will conclude our presentation for today.