Defining Disease Response and Progression: Treatment Resistance, Failure and/or Loss of Response to JAK Inhibition in Myelofibrosis

Dr. Bose: Hello and welcome to today's webinar on *Defining Disease Response and Progression: Treatment Resistance, Failure and/or Loss of Response to JAK Inhibition in Myelofibrosis*. I'm Prithviraj Bose, I'm an Associate Professor in the Department of Leukemia at The University of Texas MD Anderson Cancer Center in Houston, Texas. I am joined today by Dr. John Mascarenhas, who is the Professor of Medicine at the Icahn School of Medicine at Mount Sinai in New York, Director of their Adult Leukemia Program and also Clinical Lead for their MPN Clinical Research Program.

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. John Mascarenhas** has relevant financial relationships related to consulting from AbbVie Inc., Bristol-Myers Squibb Company, Celgene Corporation – A Bristol-Myers Squibb Company, Constellation Pharmaceuticals, CTI BioPharma Corp., F. Hoffmann-La Roche Ltd, Incyte Corporation, Galecto Biotech, GlaxoSmithKline plc, Geron, Imago BioSciences, Kartos Therapeutics, Inc., Novartis AG, PharmaEssentia Corporation, and Sierra Oncology, Inc. He serves on the Data and Safety Monitoring Board (DSMB) for Karyopharm Therapeutics.

Dr. Bose: Here are our disclosures.

To set the stage for the overarching theme of what we are discussing today, there is an increasing recognition that ruxolitinib failure is not a well defined or well understood entity. It quite heterogeneous as we will discuss through this presentation. Now that we are in an era where we have multiple FDA approved JAK inhibitors, and others on the horizon, and many other non-JAK inhibitors in development as monotherapy or add-on therapies, we are really in a new era where there are so many options for patients and only going to be increasing over time.

Progressive Disease Per IWG MRT 2013 Criteria

- Appearance of a new splenomegaly that is palpable at least 5 cm below the LCM
- A ≥100% increase in palpable distance, below LCM, for baseline splenomegaly of 5-10 cm
- A ≥50% increase in palpable distance, below LCM, for baseline splenomegaly of >10 cm
- Leukemic transformation confirmed by a BM blast count of ≥20%
- A peripheral blood blast content of ≥20% associated with an absolute blast count of ≥1 x 10^9/L lasting for at least 2 weeks

Tefferi A, et al. *Blood.* 2013;122(8):1395-1398.

Dr. Bose: To start with the formal criteria for a disease progression in myelofibrosis, this slide shows you the International Working Group criteria, which as you notice, are really restricted to spleen progression and blast progression when it comes to defining progressive disease. As you see on the slide, it could be new splenomegaly, worsening splenomegaly, which is defined differently based on what the baseline spleen size is and then of course, increasing blasts post NPM AML is of course, 20% and higher. Then as you see in the last bullet, there is some criteria around the absolute blast count.

John, what are your thoughts on these criteria? Obviously fairly restricted or not very comprehensive, I think. Also particularly, how do you think it translates to the real world when seeing a patient?

Dr. Mascarenhas: I think it's an important point because in our practices, we do typically spend a lot of time and try to exact a measure of the spleen with a measuring tape usually at the midclavicular line and below the left costal margin. We try to have reproducibility as we move along with treatments in order to assess change in spleen length. That probably doesn't translate neatly into the community practice where the pace and the tempo and the focus is different. They're likely not measuring spleens in the same way and capturing in the note, the distance from the left costal margins.

Dr. Mascarenhas: I think the other point that is probably worth emphasizing is, we often collectively obtain imaging of the abdomen and will obtain a spleen length either by ultrasound, MRI or CAT scan. It's important to remind the listener that there is a difference between the length that one calculates from the imaging and then by palpation because the imaging will capture the length from cranial caudal direction. Whereas when you palpate, you really only palpating a fraction of that because the rest of the spleen is hidden under the rib cage. Those two numbers are not the same and sometimes are confused when discussing spleen length of response or progressive disease.

Defining Disease Response and Progression: Treatment Resistance, Failure and/or Loss of Response to JAK Inhibition in Myelofibrosis

Identification/Management of Progression/Resistance on Ruxolitinib

Feature	Treatment Options
Spleen	• Threshold: beyond baseline, ↑ by 5 cm, more symptomatic • Optimize dose of ruxolitinib • Switch to alternative JAK inhibitor • Consider splenectomy
Symptoms	• Review cause (eg, mood disturbance, other medications) • Optimize dose of ruxolitinib • Consider alternative treatments (eg, steroid, antihistamine) • Switch to alternative JAK inhibitor
More anemia or thrombocytopenia	• Exclude other causes (eg, drug-drug interaction) • Determine if it needs treating • Add EPO, danazol, thalidomide
Leukocytosis	• Determine the threshold for treatment • Add hydroxycarbamide
Blasts	• Threshold depends on rate of rise </> 10%/15%/20% • Expectant, consider adding HMA or rarely AML induction

Slide courtesy of Prof. Claire N. Harrison

Dr. Bose: That is also a bit of a segue into the fact that progression in real life is not restricted to just the spleen and increasing blasts. It can obviously take the form of worsening cytopenias. It could be worsening symptoms, it could be progressive leukocytosis. Certainly, spleen and blasts are a little bit easier to quantify or formalize in the context of clinical trials, but for patients often, it is worsening cytopenias. I think that's probably the most common presentation of progression that I see and then also symptoms and white count.

Defining Disease Response and Progression: Treatment Resistance, Failure and/or Loss of Response to JAK Inhibition in Myelofibrosis

Prognosis After Ruxolitinib Discontinuation

Regular Article — blood

MYELOID NEOPLASIA

Clonal evolution and outcomes in myelofibrosis after ruxolitinib discontinuation

Kate J. Newberry,[1] Keyur Patel,[2] Lucia Masarova,[1] Rajyalakshmi Luthra,[2] Taghi Manshouri,[1] Elias Jabbour,[1] Prithviraj Bose,[1] Naval Daver,[1] Jorge Cortes,[1] Hagop Kantarjian,[1] and Srdan Verstovsek[1]

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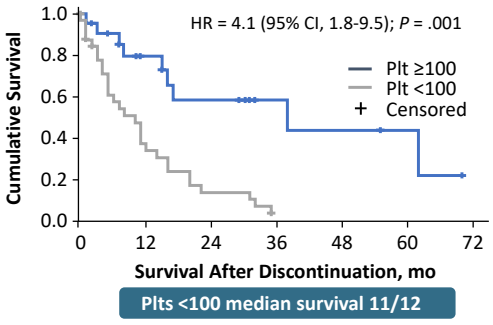
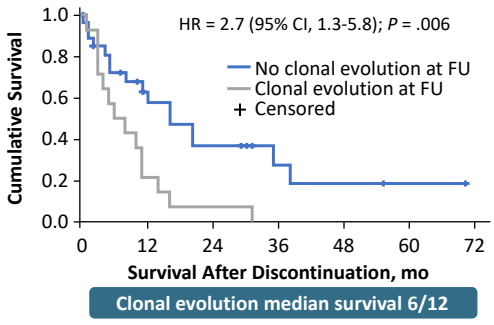


Plts <100 median survival 11/12

No. at risk

Plt ≥100	23	12	7	4	3	1	0
Plt <100	33	10	4	0			



Clonal evolution median survival 6/12

No. at risk

No CE	28	16	4	4	2	1	0
CE	14	3	3	1	0		

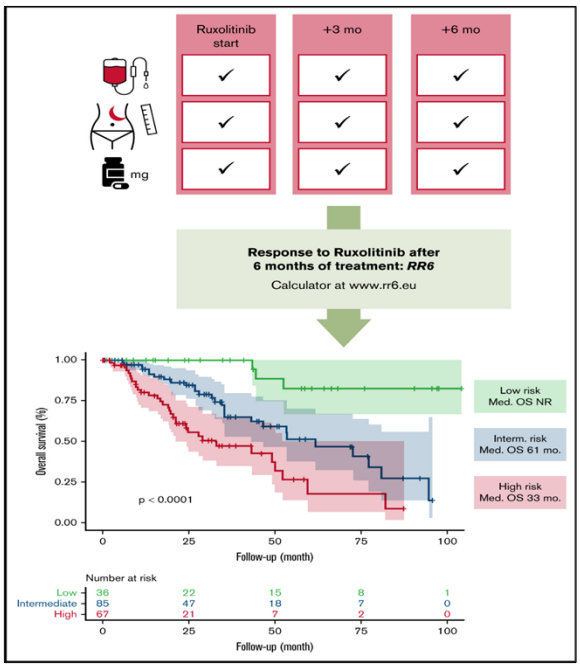
Newberry KJ, et al. *Blood.* 2017;130:1125-1131.

Dr. Bose: Now you and we and others have published on the outcomes after ruxolitinib discontinuation. This is from our group and this shows that the median survival after ruxolitinib discontinuation was 14 months. Very similar results from you John, and Andrew Kuykendall at Moffitt, as well as the Italians. True ruxolitinib failure is bad. You have about 11 to 14 month survival.

Then also shown on this slide is that if you have clonal evolution while you're on ruxolitinib prior to discontinuation, or if your platelets are dropping while on ruxolitinib, those further worsen the outcome after discontinuation.

Defining Disease Response and Progression: Treatment Resistance, Failure and/or Loss of Response to JAK Inhibition in Myelofibrosis

A Prognostic Model to Predict Survival After Six Months of Ruxolitinib in Patients with Myelofibrosis



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

Dr. Bose: Building on this suboptimal scenario that we have for patients who discontinue ruxolitinib, there was a recent attempt by the Italian group led by Dr. Pasamonte and also Andrew Kuykendall at Moffitt, who validated the results to develop a model that could help predict patients who are unlikely to do well on ruxolitinib after six months of treatment. It turned out that there were three variables, no surprise here, fairly intuitive variables, but nice to see it formalized.

There were three variables. One was the ruxolitinib dose, so if it was less than 20 BID at the baseline, three months and six months; need for transfusions at baselines, three months and six months; and also a less than a 30% reduction in spleen size by palpation at three or six months. These were all predictive of an inferior outcome on ruxolitinib for these patients.

Dr. Mascarenhas: Maybe we can spend a minute here just talking about what would be the impact or utility of this RR6 model in the community practice. When I see this model, I find it very intriguing actually in many ways and somewhat intuitive too, but there are a couple things that impressed me with this. One is that, one of the independent prognostic variables is a dose less than 20 milligrams twice daily. You and I know that that would actually encompass the majority of patients who are treated with ruxolitinib probably are on a dose at 0, 3 and 6 months of therapy of less than 20 milligrams twice daily. It already emphasized the idea that that dose matters, and that's an important consideration.

That's something I think that you and Serge Verstovsek have really made a point over the years that one should try to optimize and maximize the dose to get spleen reduction, because here's an example of where it probably does actually correlate with the outcomes that matter a lot at the end of the day, which are survival outcomes. I wonder if you can comment on, what would be the utility in in the community setting after six months of ruxolitinib for a community practitioner to do the RR6? What would they potentially gain from it or advise the patient to do?

Dr. Bose: Certainly. As we've seen with some of the newer prognostic models, there is an online calculator*, which is great. You always need these things to do these things in real time, but John, you make a great point about the dose dependency of ruxolitinib. Ruxolitinib is a highly dose dependent drug. You really see the best outcomes at least 15, if not 20 BID and this model found that less than 20 BID was a factor predicting for worse outcomes. I think that's extremely important, as well as not having enough of a shrinkage in the spleen and the transfusion part there.

I think now with other options available and momelotinib perhaps coming next year, I think it certainly helps. It provides a framework for the practitioner who may not be doing a lot of MF all the time. I think it guides them by somewhat formalizing these variables.

Dr. Mascarenhas: I think the other obvious benefit of this model too, is for those patients who are transplant eligible, who you've put on ruxolitinib and they've met with the transplanters and now they're six months out, it may help provide some sense of balance of where transplant may fit in. Given the clear compromise and survival, if you have a high-risk disease state with this model, that that may push the decision for transplant sooner rather than later and rather than waiting for the patient to ultimately fail ruxolitinib.

Dr. Bose: Absolutely. You always want to send them at the time of optimal response. I think this helps you know that you are not getting there.

*https://qxmd.com/calculate/calculator_315/dipss-plus-score-for-prognosis-in-myelofibrosis

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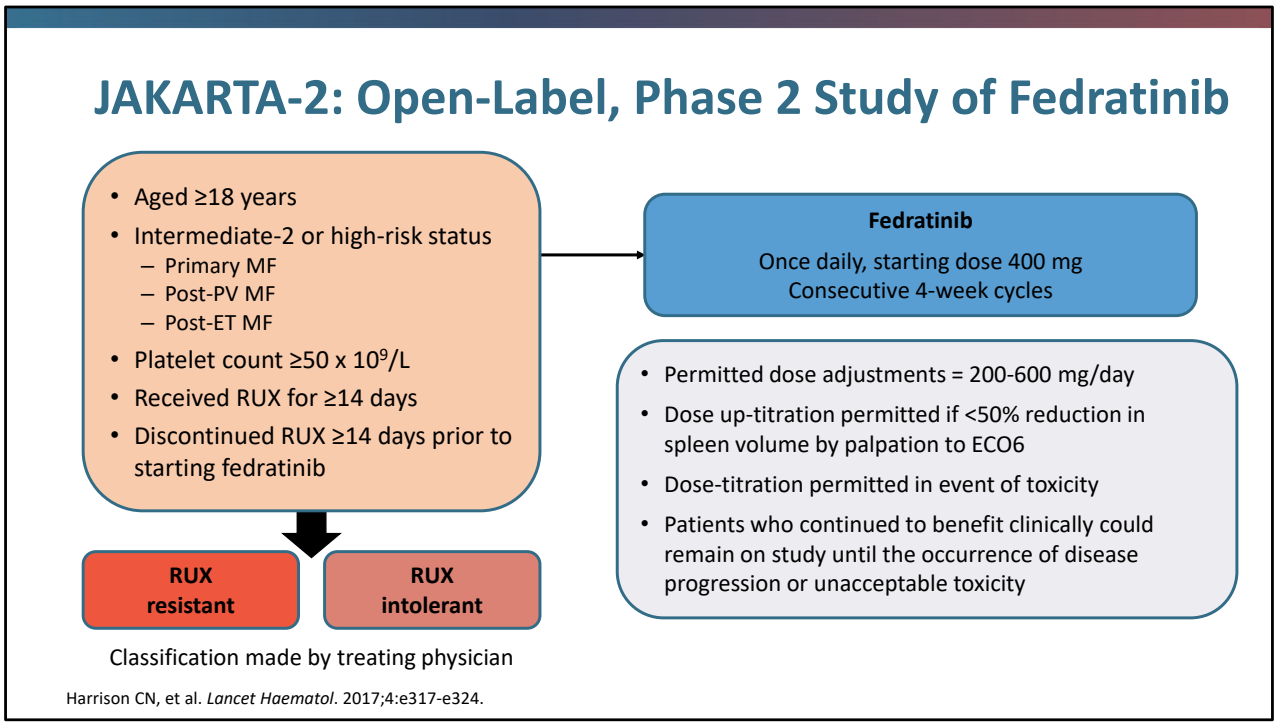

Dr. Bose: Moving on from there, some of the trials that have been done, the options that we have today, and that may be coming. Starting with fedratinib, this was of course approved in August of 2019. This is the second-line study I'm showing you here, the JAKARTA-2 obviously, more relevant to our discussion today.

Now, this one was an open label single arm study and you see some of the inclusion criteria on the left. You notice that there wasn't really a definition of ruxolitinib failure. You just had to have had it for two weeks or more. Now, I should say the median was about 10 months. It certainly was not two weeks. The median prior ruxolitinib was around 10 months, and platelets had to be over 50, and the dose was 400, which of course, is the approved dose of fedratinib.

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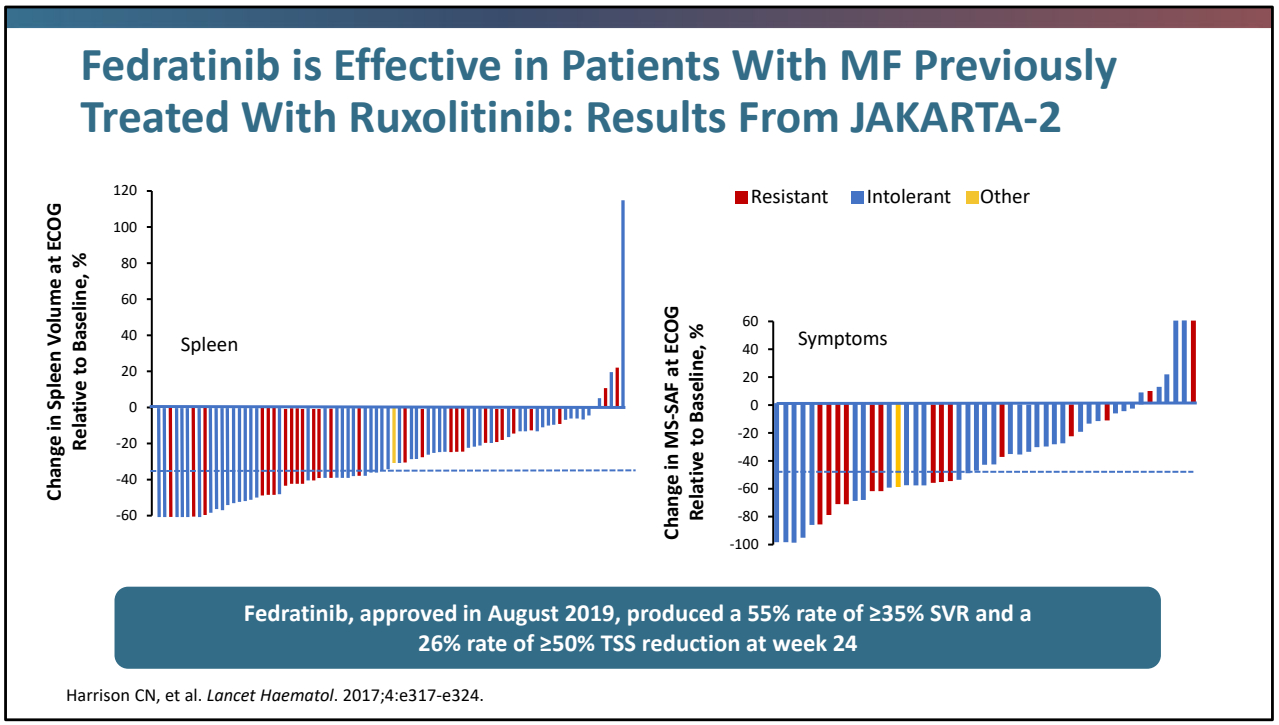

Dr. Bose: Using these criteria the per-protocol analysis was actually yielded remarkably good results for the spleen, 55% rate of spleen response and a 26% rate of symptom response at week 24.

Again, remember this is a per-protocol analysis so because of this, and the fact that there wasn't any requirement to be met, it was really, in the judgment of the treating physician as to who had failed ruxolitinib.

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

- In the original JAKARTA-2 analysis, fedratinib demonstrated a 55% rate of ≥35% SVR in patients resistant or intolerant to RUX (≥14 days) per investigator assessment
- Reanalysis 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

Harrison CN, et al. *Lancet Haematol.* 2017;4:e317-e324.; Harrison CN, et al. ASCO 2019; abstract 7057.; Harrison CN, et al. *Am J Hematol.* 2020;95:594-603.

Dr. Bose: Because of that, perceived shortcoming, there was a re-analysis done using stringent criteria as are shown on the left of this slide. As you see here, it's really to do with an insufficient spleen response or regrowth after a response, and also cytopenia as a transfusion needs, et cetera, which would be more intolerance. Using these stringent criteria, they found that 79 of the 97 patients in this trial met these criteria, so 81%, the majority.

When you looked at just this stringent criteria cohort, the spleen response was 30%, and the symptom response was 27%. Importantly, these numbers are virtually identical to the intention-to-treat results in this trial. The ITT population had 31% spleen and 27% symptoms and as you see, the stringent criteria was 30 and 27, so very, very close. Perhaps the obvious difference from the per-protocol analysis also had something to do with the fact that, as you recall, this drug did have at the time, a clinical hold forcing patients to come off. For that reason, the last observation carried forward method was used and so there was some extrapolation to 24 weeks, based on the 12-week MRI findings.

Dr. Bose: John, thoughts around fedratinib in general?

Dr. Mascarenhas: My experience with fedratinib is it's been a very welcomed addition to the armamentarium and has a clear response rate as shown here. If you have patients who are not attaining the spleen and symptom response with ruxolitinib or have lost the initial response, this is a very reasonable second-line option in which a third of the patients enjoy significant symptom and spleen response. What we're not showing you here in this specific slide is even the patients who didn't have the 35% SVR or 50% TSS, and still gain some degree of improvement, that was better than being on ruxolitinib previously.

I think it's a very reasonable option. What I liked about this re-analysis is it set a tone for, as you pointed out, a more stringent criteria because the way the original study was designed, it was really left up to the investigator to make that call based on their feeling but this creates a little bit more clarity and definition for failure.

Dr. Bose: Absolutely. Could set the tone for future trials.

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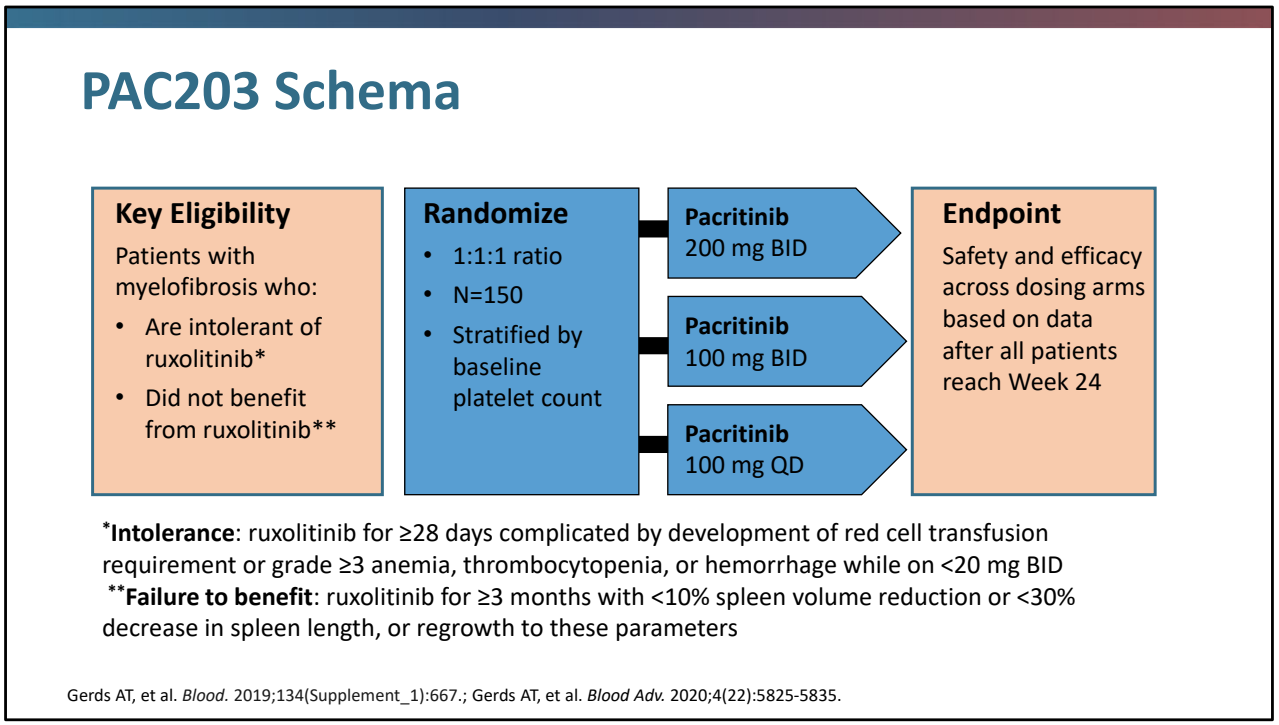

Dr. Bose: Speaking of which the PAC203 study also actually used this definition. Just as a refresher, pacritinib, of course, was approved based on the PERSIST-2 trial that you led, John. This study, the PAC203 was a subsequent safety study that the FDA had asked for since there were some initial concerns from the PERSIST studies and this study looked at patients who had previously had ruxolitinib. It was all second-line or beyond. There were three doses, a 100 once a day, a 100 twice a day, and 200 twice a day, which of course is now the approved dose of pacritinib.

Again, the same definition as used in the re-analysis of JAKARTA-2 was used here in terms of defining who was resistant or intolerant to ruxolitinib. Again, the point of this study was primarily safety.

IMBARK™ Trial: Major Inclusion Criteria

- Int-2/high-risk MF per DIPSS criteria
- 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
- Active symptoms of MF
- Baseline measurable splenomegaly (palpable spleen ≥5 cm below LCM or ≥450 cm3 by MRI)

*Adapted from IWG-MRT response criteria definition of progressive disease.
Mascarenhas J, et al. *Blood.* 2018;132(Supplement 1):685.; Mascarenhas J, et al. *J Clin Oncol.* 2021;39(26):2881-2892.

Dr. Mascarenhas: Prithviraj, thank you, for passing the control over to me. Here, we're showing you the IMBARK trial. This was a trial that was a multicenter, phase two randomized study of two different doses of imetelstat, the telomerase inhibitor in patients who had previously received ruxolitinib and were defined as relapsed or refractory as shown here. These patients were patients that had worsening splenomegaly related abdominal pain at any time after the start of the JAK inhibitor and either they had no reduction in spleen volume or size after 12 weeks of therapy or worsening splenomegaly at any time after the start of a JAK inhibitor therapy.

You could document that either by imaging or by clinical notes demonstrating increase in spleen size by palpation.

They also required the patients to have active symptom burden and imaging at baseline to document a spleen that was at least five centimeters below left costal margin or the equivalent by imaging which is about 450 cubic centimeters.

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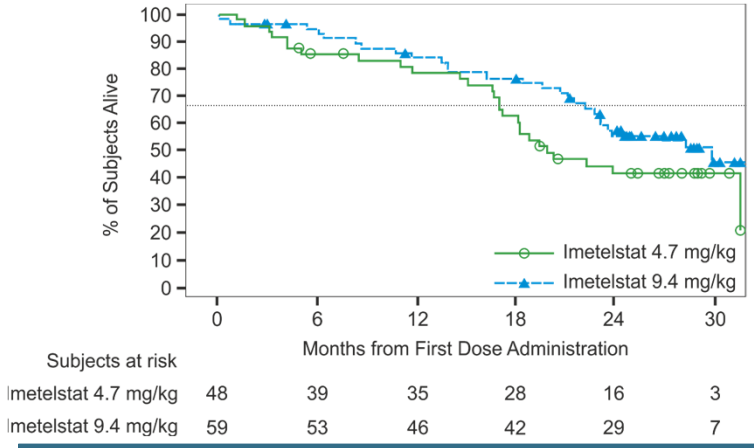
Overall Survival (ITT) for Imetelstat at Different Dose Levels



Subjects at risk						
Imetelstat 4.7 mg/kg	48	39	35	28	16	3
Imetelstat 9.4 mg/kg	59	53	46	42	29	7

- Median follow-up: 27.4 months
- Median survival:
  - 19.9 months (95% CI, 17.1, NE) in 4.7 mg/kg
  - 29.9 months (95% CI, 22.8, NE) in 9.4 mg/kg

Multiple sensitivity analyses were performed (including data censoring at time of dose escalation, censoring at subsequent JAKi or stem cell transplant and excluding patients who were dose escalated or randomized after closure of the 4.7 mg/kg arm), all generating similar results

Mascarenhas J, et al. *Blood.* 2018;132(Supplement 1):685.; Mascarenhas J, et al. *J Clin Oncol.* 2021;39(26):2881-2892.

Dr. Mascarenhas: What this study ultimately showed was if you look at the survival and intention to treat analysis shown here, there appeared to be an improvement in survival in blue in the patients who received the higher dose in this randomized study of imetelstat, which is infused every three weeks at 9.4 milligram per kilogram compared to in green the lower dose of 4.7 milligram per kilogram.

The median survival at the high dose was 29.9 months and at the low dose was 19.9 months. I think it's important to contrast this with the multiple studies that Prithviraj has reviewed today, that would suggest a median survival of approximately 14 to 15 months in this poor-risk population.

This data would suggest a prolongation of survival, particularly with the high dose of drug. This survival was true no matter how you looked at these patients. Sensitivity analysis was performed and it really remained true even accounting for next lines of therapy after discontinuation of imetelstat.

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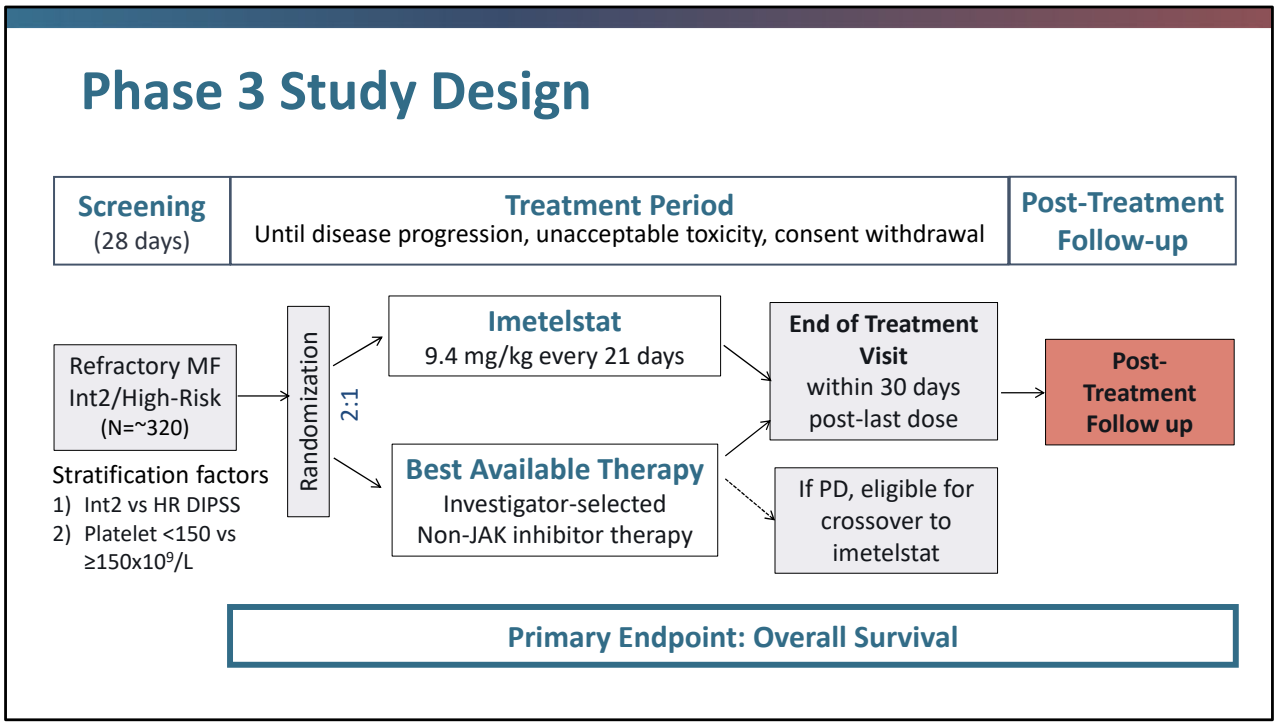

Dr. Mascarenhas: This informed and inspired the ongoing IMpactMF study which we're showing you here. This is a phase three study, a pivotal registration study of patients who have specifically refractory myelofibrosis that are intermediate to or high-risk disease. They're randomized to either imetelstat at that higher dose, 9.4 milligram per kilogram every 21 days or best available therapy which is investigator selected but excludes JAK inhibitor therapy. What's unique about this trial and important is that it has a primary endpoint of overall survival.

Up to this point, really the endpoints that were considered meaningful and registration-worthy in myelofibrosis have been first and foremost reduction in spleen and then more recently symptom improvement. Here for the first time, we're looking at a survival endpoint because we're taking a patient population that is unfortunately predicted to do very poorly and survival is the goal in this study.

Defining Disease Response and Progression: Treatment Resistance, Failure and/or Loss of Response to JAK Inhibition in Myelofibrosis

IMpactMF: Inclusion Criteria

Inclusion Criteria

- Man or woman ≥18 years of age
- Dynamic International Prognostic Scoring System (DIPSS) intermediate-2 or high-risk MF
- Diagnosis of primary MF by WHO or PET-MF or PPV -MF by IWG-MRT
- **Refractory to JAK inhibitor:**
  - **Treated for at least 6 months including two at an optimal dose with no decrease in spleen volume, spleen size, or symptoms OR highly symptomatic per MFSAF at study entry**
  - **Treated for at least 3 months at maximal dose and no decrease in spleen volume, size or symptoms**
- Measurable splenomegaly with palpable spleen ≥5 cm or spleen volume ≥450 cm3
- Active symptoms of MF by MFSAF v4.0
- ANC ≥1.5 x 10^9/L independent of growth factor support
- Platelets ≥75 x 10^9/L independent of platelet support
- Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2

Dr. Mascarenhas: We've highlighted in bold, the definition of refractoriness to JAK inhibitor for the IMpactMF study, which includes treatment for at least six months and an optimal dose with no decrease rather in spleen volume, spleen size or symptoms, or being highly symptomatic on the MFSAF patient reported outcome measure.

They have to be treated for at least three months at the maximal dose and no decrease in spleen volume and/or size. It is really a refractory patient population.

IMpactMF: Exclusion Criteria

Exclusion Criteria

- Peripheral blood blast count ≥10% or bone marrow blast count ≥10%
- Any chemotherapy or MF directed therapy, including investigational drug, immunomodulatory or immunosuppressive therapy, corticosteroids >30 mg/day prednisone or equivalent, and JAK- inhibitor treatment ≤14 days prior to randomization
- Major surgery within 28 days
- Prior treatment with imetelstat

Dr. Mascarenhas: This excludes patients who have intolerance to the drug and it actually excludes patients who had an initial response that may have some degree of loss of response.

It's really picking out in many ways, the patients who are the worst of the worst in terms of their expected outcomes due to JAK inhibitor refractory disease.

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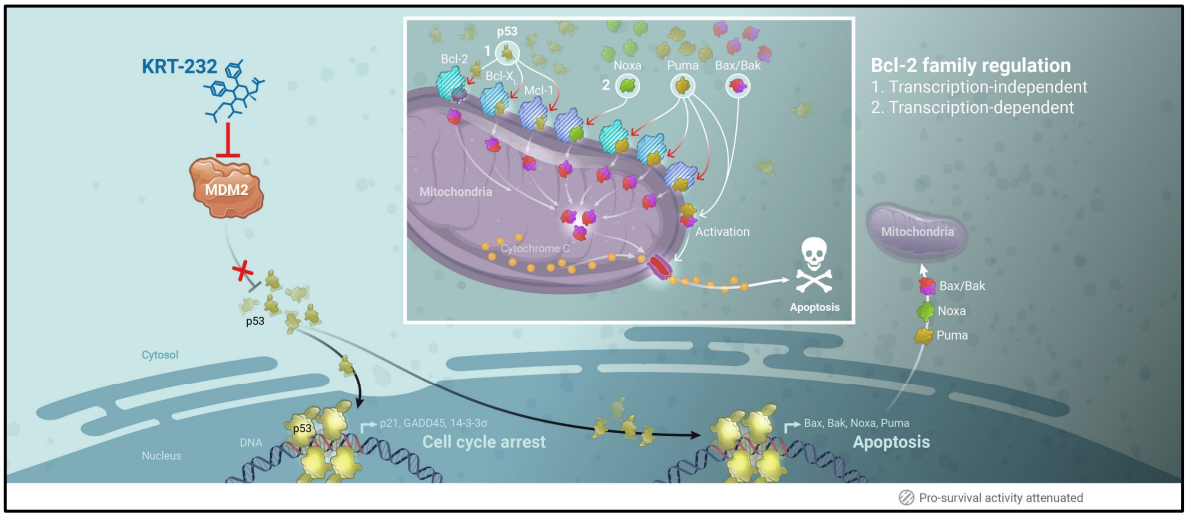
Navtemadlin (KRT-232): A First-in-Class Human Double Minute 2 Inhibitor Studied in the Phase 3 BOREAS Trial



Verstovsek S, et al. *J Clin Oncol*. 2021;39(Suppl. 15):abstract TPS7057.

Dr. Mascarenhas: One of the therapies that's gotten a lot of attention and is worth covering here today is the class of agents called MDM2 inhibitors. These are small molecule inhibitors that interrupt the interaction of MDM2, which is a protein that's upregulated in myelofibrosis patients. It binds p53 and negatively regulates the function of p53 through multiple different mechanisms. MDM2 inhibitors interrupt that and therefore, allow for activation of p53 and the downstream consequences that ultimately lead to apoptosis. This is a pro-apoptotic approach to the disease that's rational and mechanism based. KRT-232 now known as navtemadlin is at the front of the pack of these agents in clinical development in myelofibrosis. This is a very potent MDM2 and selective MDM2 inhibitor.

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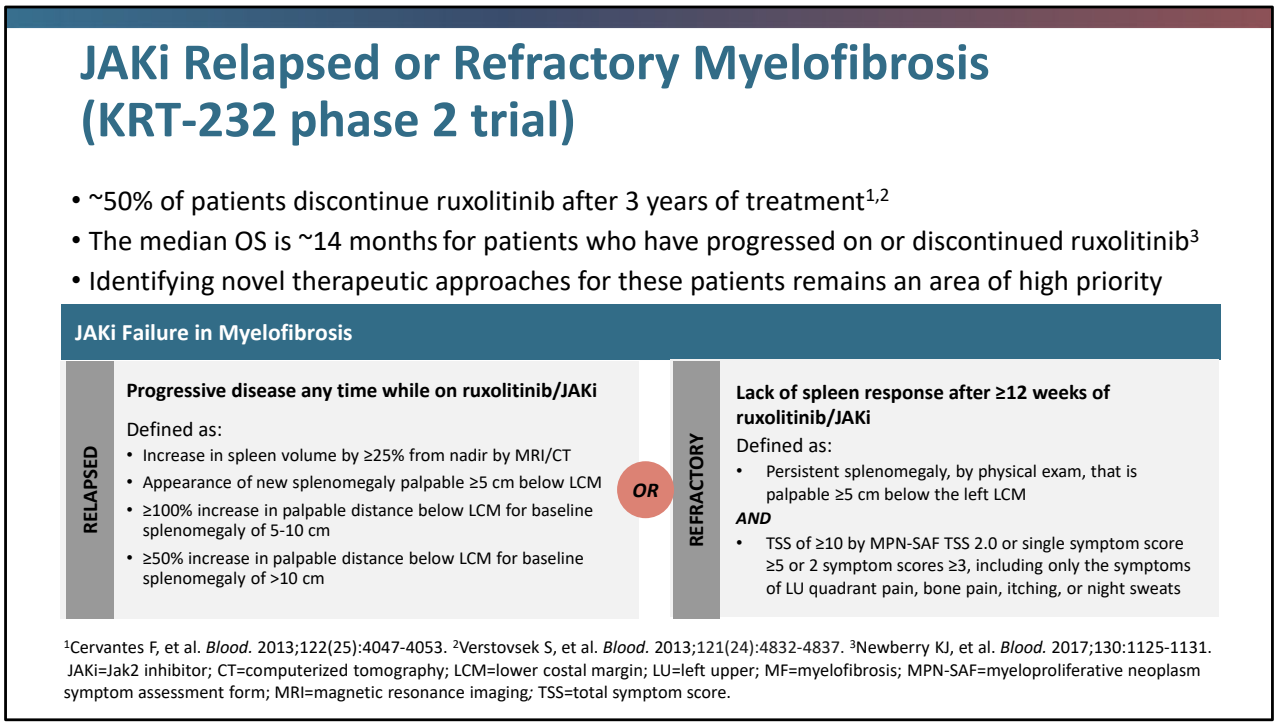


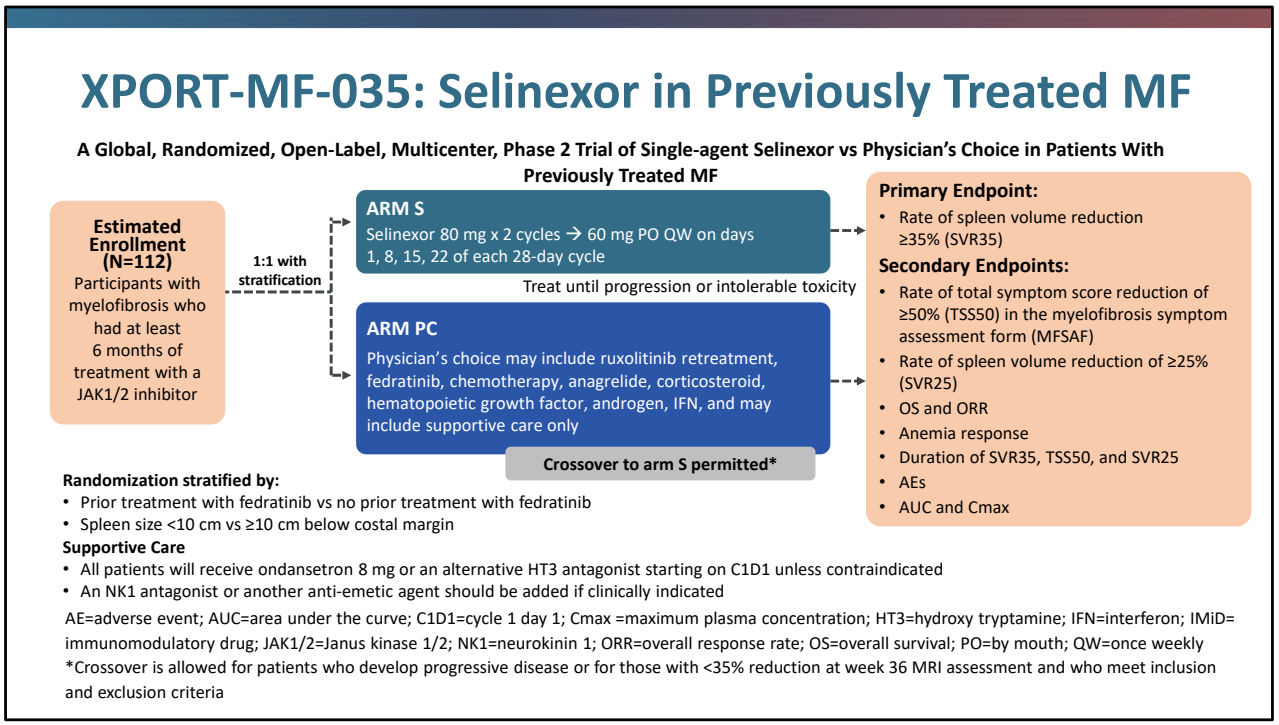
Dr. Mascarenhas: This drug has been studied in a phase two study as a monotherapy, although there's multiple studies that are ongoing right now, including combination studies and studies combining this drug with other rational agents like BTK inhibitors. The study I'm highlighting here is for patients who have previously been treated with ruxolitinib and have progressive disease-- well, they are JAK inhibitor failure patients, I should say. The definition I show you on the left of the slide is for the patients who have the relapsed disease definition with progressive disease at any time while on ruxolitinib therapy.

You can see the various criterion for this type of patient versus the patients who have refractory disease on the right who lack a spleen response after at least 12 weeks of ruxolitinib therapy and have persistent splenomegaly either by exam or by imaging or persistent symptom burden by TSS. It is taking, again, patients who are failing ruxolitinib either by relapsed definition or refractory definition, and the patients would receive the single agent navtemadlin as a salvage therapy. The results that they've been presented so far have been very encouraging in terms of the ability to capture spleen and symptom benefit.

Perhaps more interestingly and more importantly, the ability to significantly reduce in some patients the driver mutation burden, the circulating CD34 cell count and reduction in bone marrow fibrosis, all of which appear to track together and can be correlated with clinical outcomes like spleen response.

What's very interesting, I think and important about these studies, and particularly navtemadlin, is the ability to use biomarkers that are surrogates for disease burden such as driver mutation VAF or circulating CD34 cell or bone marrow fibrosis reduction and associate and correlate that with outcome measures like spleen reduction symptom improvement. It really ties in the mechanism of action as well as the potential for biologic response modification with these drugs. This is a great example of such an effort.

Defining Disease Response and Progression: Treatment Resistance, Failure and/or Loss of Response to JAK Inhibition in Myelofibrosis



Dr. Mascarenhas: Also worth mentioning is selinexor, which is an approved drug for multiple myeloma and non-Hodgkin's lymphoma. This is an exportin inhibitor, and this was taken into the clinic in this randomized phase two setting as a single agent. Again, this is patients who've previously been treated with at least six months of ruxolitinib and are randomized either to selinexor at 80 milligrams once a week. This is about half the weekly dose that is given in multiple myeloma or they get randomized to physician's choice and the options are listed there with the potential to cross over to the experimental arm. Here, the primary endpoint of this phase two study is spleen volume reduction.

Dr. Bose: John, something I really welcomed with this one is that refreshingly, they allow fedratinib in the comparator arm. I thought that was really nice, and something we haven't necessarily seen in some of the other second line phase three studies. Do you have any thoughts about that?

Dr. Mascarenhas: It definitely makes it attractive from a perspective of enrolling a patient. It is a nice option to be able to provide the patient with a trial that gives them access in a randomized fashion, but gives them access to a study drug that has the potential to modify their disease, but is still investigational yet the comparator arm doesn't necessarily limit them to a select group of drugs, but allows them to go on drug that one potentially would use if they were never introduced to this study. That makes it, from a patient perspective, a very attractive study to enroll in.

Key Inclusion/Exclusion in XPORT-MF-035

Key Inclusion

1. Primary MF or post-ET or post-PV MF
2. Previous treatment with JAK inhibitors for at least 6 months
3. Splenomegaly ≥450 cm3
4. Relapsed, refractory or intolerant to JAK inhibitors:
   a. <35% spleen volume reduction by MRI or CT
   b. <50% decrease in spleen size by palpation
   c. Spleen volume increase >25%
   d. Intolerance to JAK inhibitors (definition in protocol)
5. Platelet count ≥75 × 10^9/L
6. ANC ≥1.5 × 10^9/L

Key Exclusion

1. >5% peripheral blasts or >10% marrow blasts (ie, accelerated phase)
2. Previous treatment with selinexor or other XPO1 inhibitors.
3. Use of anti-MF therapy <21 days prior to Cycle 1 Day 1 (hydroxyurea is allowed)

Dr. Mascarenhas: Here, again, I'm showing you the key inclusion and exclusion criteria, and I'll take your attention down to number four, which is the relapse refractory or intolerance to JAK inhibitors which include measurement by imaging, by palpation, spleen volume increase of greater than 25% that's documented, or intolerance to JAK inhibitor therapy.

Intolerance can look like different things. Sometimes, that's non-hematologic, sometimes that's hematologic intolerance. Then the usual platelet and ANC criteria.

Defining Disease Response and Progression: Treatment Resistance, Failure and/or Loss of Response to JAK Inhibition in Myelofibrosis

Phase 2 Study of the JAK 1/2 Inhibitor, Ruxolitinib, and Add-on PI3Kδ Inhibitor, Parsaclisib (NCT02718300)

- Enrolled patients with primary or secondary MF who have suboptimal response with ruxolitinib monotherapy
- Definition of suboptimal response to ruxolitinib:
  - Treated with ruxolitinib for ≥6 months with stable dose for ≥8 weeks immediately prior to enrollment

AND

  - Palpable spleen >10 cm below left subcostal margin on physical examination at screening

OR

  - Palpable spleen 5-10 cm below left subcostal margin on physical examination ***AND*** active symptoms of MF at the screening visit defined as 1 symptom score ≥5 or 2 symptom scores ≥3 each, using the Screening Symptom Form*

*Screening Symptom Form: 10-point scale for each of the 7 symptoms. Symptoms include: night sweats, pruritus, abdominal discomfort, pain under left ribs, early satiety, bone/muscle pain, and inactivity.
MF=myelofibrosis
Yacoub A, et al. EHA 2020.

Dr. Mascarenhas: Here I'm showing you the phase two study of combination of ruxolitinib and an add-on of a PI3-kinase, delta inhibitor parsaclisib. This is a study that is built on rationale that there are other relevant signaling pathways to the pathobiology of myelofibrosis and that there can be complementary, even synergistic effects of shutting down these hyperactive pathways, whether it's JAK stat or the PI3-kinase-mediated pathways. Combining these two drugs, again, has preclinical data to support that.

I think it's important for the listeners today to appreciate that all of the trials that we are reviewing together are all trials that had sufficient preclinical rationale and mechanistic rationale to move into the clinic and to gain the confidence to start treating patients with myelofibrosis and the buy-in of investigators that are looking to evaluate therapies and bring better therapies to patients. I think that's very important. These are not whimsical decisions, but they're really thoughtful decisions that are supported by preclinical data. This study is such a study that's also supported by preclinical data.

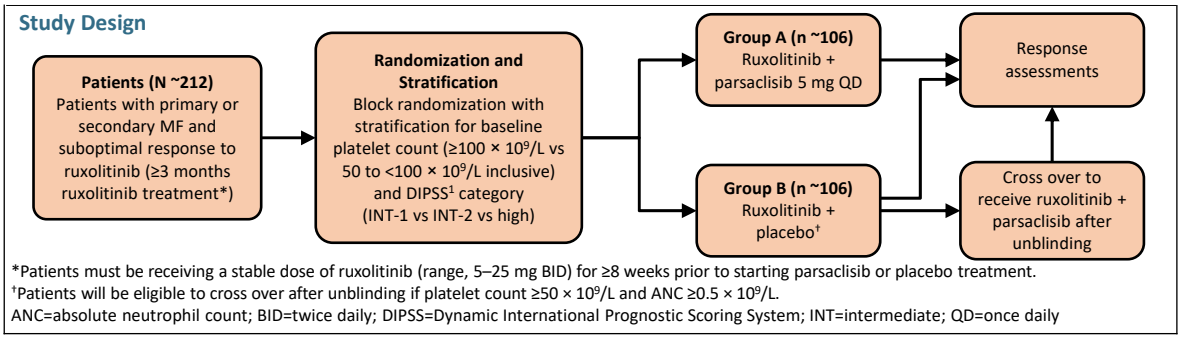
Here, I'm showing you the definition of what a suboptimal response to ruxolitinib is. Here, these patients are on ruxolitinib and if they've been treated for six months or greater with a stable dose for at least the two months prior to enrollment, and still have a spleen that's 10 centimeters or greater below the left costal margin or have a palpable spleen, 5 to 10 centimeters and active symptom burdens as measured by the symptom assessment score, these patients would be considered suboptimal responders to ruxolitinib and eligible for an add-on strategy. Here, one is not getting rid of ruxolitinib and moving on to the next line of therapy, but trying to salvage a response that is suboptimal in nature by adding on this oral PI3-kinase inhibitor.

Defining Disease Response and Progression: Treatment Resistance, Failure and/or Loss of Response to JAK Inhibition in Myelofibrosis

LIMBER-304 Study Design

This phase 3, randomized, double-blind, placebo-controlled study will determine the efficacy and safety of add-on parsaclisib in patients with MF and suboptimal response to stable ruxolitinib treatment (INCB 50465-304; NCT04551053)

- Patients will attend scheduled study visits at screening, baseline, day 1, and at the end of 2, 4, 8, 12, 16, 20, and 24 weeks of treatment
- When a patient has completed 24 weeks of treatment, he/she will be unblinded and if found to be randomized to ruxolitinib plus placebo and with adequate hematology parameters, the patient will be able to cross over to receive ruxolitinib plus add-on parsaclisib
- Early crossover is possible in certain circumstances
- After 24 weeks of treatment, patients may enter the extension period of the study; treatment will continue as long as tolerated and discontinuation criteria are not met



*Patients must be receiving a stable dose of ruxolitinib (range, 5–25 mg BID) for ≥8 weeks prior to starting parsaclisib or placebo treatment.
†Patients will be eligible to cross over after unblinding if platelet count ≥50 × 10^9/L and ANC ≥0.5 × 10^9/L.
ANC=absolute neutrophil count; BID=twice daily; DIPSS=Dynamic International Prognostic Scoring System; INT=intermediate; QD=once daily

Passamonti F, et al. *Blood*. 2010;115:1703-1708.

Dr. Mascarenhas: The data has been presented previously, and what we've seen is in this randomized study that was looking at parsaclisib given at two different doses that the five-milligram daily dose was really the superior way of treating these patients. This inspired the phase three study that is accruing patients currently with this suboptimal response definition.

Patients are randomized either to the addition of parsaclisib as five-milligram QD dosing which was shown to be the superior administration in the phase two study or placebo. Of course, this is a double-blind and controlled in order to assess response by spleen volume reduction at six months. The idea here is can we regain control of the spleen and symptom by adding on a drug to patients who've had inadequate response to single agent ruxolitinib.

Dr. Bose: Just like the ruxolitinib failure situation, here too, with suboptimal response, there's been quite a bit of heterogeneity across, say, trials of pelabresib, navitoclax, and now, parsaclisib. Do you think this is something that also needs a rigorous definition, or do you think this is something better left to the judgment of the treating physician?

Dr. Mascarenhas: It's tricky because I think what makes all of this very challenging, whether it's defining relapsed or refractory to JAK inhibitor therapy, or this definition of suboptimal response to ruxolitinib is it's a moving target and it can look different to different patients and to different physicians. It is challenging. Of course, when constructing a clinical trial, particularly, a phase three registration trial, one does need to have very strict criteria in order to deem patients eligible and have a somewhat uniform patient population in order to adequately determine response.

I think the real question is how would that be utilized if it's approved in the community? Will the exact definitions of suboptimal response to ruxolitinib translate neatly into the community practice? I don't know that I have an answer for that. I think that that will be somewhat challenging. I think the reality is that if a drug like parsaclisib, for example, has positive phase three data and is reviewed positively by the FDA and ultimately approved for commercial use, you will have a different utilization of a drug like this or any drug in this scenario depending on the patients that are being seen at any given practice and the approach of that treating physician.

Some physicians may be more likely to add this drug earlier on, perhaps when the patient hasn't met these strict definitions in the trial, and then other physicians may be late adopters who would be using this drug perhaps when the patient has even more progressive disease by definition than suboptimal response. I think that the use of it will be not uniform and not strict. It will probably be variable and hard to always define. To answer your question, I don't know if there's benefit to necessarily creating a very strict definition because I think at the end of the day, it's really individualized and personalized to the patient you're treating.

Dr. Bose: No, I agree, John. I agree, absolutely. Thank you for all your insights today. We are going to conclude our program here. I hope it was helpful. Thank you all for listening.