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Incorporating Scientific Advances into Myelofibrosis Treatment Plans

Dr. Mesa:

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

These are just my background and titles.

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

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

Start of Chapter 1

So let's begin delving into the difficulties these patients can face, both in terms of individual symptoms and quality of life. So we're going to focus on treatment planning, symptom burden; what are the tools to be able to measure symptoms? What is that spectrum throughout the disease continuum?; How do you track symptoms as part of treatment planning?; What are the impact of symptoms on quality of life?

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

Now, as we evaluate patients with myelofibrosis, I like to think about it as a portfolio of difficulties that they may face. And not all patients will face each of these. There clearly can be risk of vascular events. Now these are more common in P-vera and ET. But it's important to note that they certainly occur at a higher frequency in patients with MF, certainly, than age-matched controls elevated blood counts can matter, those with significant leukocytosis or thrombocytosis. In some type of vascular events have occurred and can be unrecognized. Patients may also carry forward the risk of vascular events from their earlier disease, if they had Budd-Chiari syndrome, pulmonary emboli, etcetera. They clearly could have cytopenias. These can be more present as the disease progresses. Cytopenias are a much more characteristic feature of myelofibrosis over PV and ET. They clearly can have anemia as predominant over

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

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

Now the 10-Items score has now been validated in multiple languages, it's easy to assess serial values, easy for patients to fill out. It's been validated in multiple different ways and through the conduct in many different trials. There are – perhaps this is too many details for some of you, but I'll share that although we have revised our scores over time, they are interchangeable, and again have these core items.

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

This approach has been used in the majority of our clinical trials for JAK inhibitors and other agents in MPN.

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

End chapter 1

Start chapter 2

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

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

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

And because of that, inhibiting JAK2, it inhibits the impact of all three of these mutations. Additionally, there are those individuals that, quote, triple negative, they lack any one of these three mutations. For these individuals, we feel that they likely have other mutations that are still leading to overactivation of this JAK-STAT pathway.

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

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

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

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

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

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

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

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

End chapter 2

Start chapter 3

So let's pivot now to treatment. You saw from these prior scores, these patients sometimes are going to have a very latent disease in terms of prognosis, but can have significant symptoms. So how do we manage them? Well, as we're trying to treat a patient, and again saw a patient just this morning newly diagnosed myelofibrosis, what are our goals? What are our treatment guidelines? If we're going to use a JAK inhibitor, what are our expectations? Are JAK inhibitors approved in the frontline setting? Potential use of JAK inhibitors in the second-line setting?

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

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

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

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

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

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

Ruxolitinib enjoys this frontline position due to the highly impactful COMFORT-I study. COMFORT-I and COMFORT-II study now published 11 years ago, ruxolitinib versus placebo with crossover for splenomegaly with primary endpoints of improvement of spleen and symptoms. Here are individuals that had significant benefit, and here showing their waterfall plots, showed superiority in terms of spleen and symptoms compared to placebo.

Over time, we've learned several things, one, dose matters. And if there is an opportunity in patients treated in the U.S., there are too many patients who are treated really with a suboptimal dose. So use an adequate dose, which would be 10 mg twice a day or more, ideally 15 twice a day or more. We've learned over time that the development of anemia can be a side effect but is not prognostically

detrimental. Baseline anemia is not a contraindication to using ruxolitinib. And you'll see here that reductions in spleen volume, with or without anemia, can benefit. Likewise, a total symptom score can benefit with or without anemia.

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

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

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

Here's showing what those survival curves look like in a pooled analysis between COMFORT-I and COMFORT-II. Here's an analysis showing the correlation of spleen volume reduction at a week 24 and with overall survival. Again, the greater the degree of splenic reduction, the greater the benefit. Here, another analysis but going back to the same issue, patients live longer, that correlates with a degree of reduction in the spleen, correlates with the quality of the response. So patients are on suboptimal doses of ruxolitinib, and you're probably not seeing these kinds of benefits.

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

There are certain mutations that have been somewhat predictive to, resistance. Primary resistance is not common, it's more common secondary, but in particular, the RAS or CBL mutations predicting resistance to ruxolitinib. There is a new model, prognostic score, giving a sense of survival for individuals after 6 months of therapy with ruxolitinib. And those that would - are prognostically adverse using a lower dose under 20 twice a day, less than a 30% spleen reduction at 3 or 6 months, red cell transfusions at 3 or 6 months, and red cell transfusions at baseline and at 3 and 6 months. With those, you can help differentiate really those with a much poorer survival versus less. And again, a model that can be helpful as we're contemplating an alternative; moving to a trial, stem cell transplant.

Now, what about fedratinib. I mentioned that this was the second agent approved August of 2019. This a JAK inhibitor. Inhibitory of JAK1,or JAK2 over JAK1, JAK3 and 2, and also a FLT3 inhibitor approved for individuals with a platelet count greater than 50,000. And approved based on trials both in the front-line and second-line setting. In the front-line setting, in the JAKARTA study for individuals, it was seen superior based on comparison to placebo for control of spleen and symptoms. Additionally, individuals could be treated with a platelet count between 50,000 to 100,000 with good evidence of response in spleen and symptoms, suggesting that it could be dosed fully in that group of individuals.

I love the analysis for the symptoms, and we saw superiority in terms of symptom control, both as – both in aggregate but also by individual symptoms. So if you look at abdominal discomfort, early satiety, pain under the ribs, night sweats, itching, muscle or bone pain, all superior. There was an improvement in quality of life. Again quality of life assessed by the EQ-5D. And you see here that superiority.

Now it is also approved in the second-line setting. The JAKARTA-2 study was for individuals that had failed ruxolitinib. This was a trial that both myself and my colleague Dr. Claire Harrison, and then we did a subsequent analysis with a stricter definition of ruxolitinib failure and intolerance. With this, we found by more modern standards what is resistant, relapsed, refractory, or intolerant. We saw that about a third of individuals were able to achieve an adequate response in the second-line setting. This is important. This is a drug that I strongly feel is being underutilized for patients with myelofibrosis. Patients have an adequate set of blood counts, they have an inadequate response to ruxolitinib, please consider fedratinib.

Now, fedratinib has a couple of toxicities one needs to be mindful of. It's not a limiter. But, one, there can be GI side effects, so typically do give them some anti-nausea pills and anti-diarrheal pills. Usually for most, that settles down and is not a major limiter. Two, it does have a blackbox warning but it's very manageable. We identified in the earlier studies that patients can have a low rate of the development of Wernicke’s encephalopathy because of some impact of the agent in a handset – handful of individuals on thiamine tablets 34:58. If they have a low thiamine level, replace it.And monitor thiamine in my practice, I will share that I just tend to put

everybody on thiamine. It's cheap it's not harmful, it takes care of the issue.

Pacritinib, the most recently approved of the myelofibrosis drugs approved in February of 2022. Pacritinib is a JAK2 inhibitor, a FLT3 inhibitor inhibits IRAK1, inhibits ACVR1, as well. And what's been identified from early days is that it can help to – to be – improve the spleen and symptoms and can be given even in individuals with a marked thrombocytopenia. But it can be given at full dose, even in an individual that is platelet transfusion dependent. That is helpful. This is a clear subset and unmet need for individuals with myelofibrosis. In some of these individuals, the platelets will improve. It does not necessarily improve platelets, but it can. Its main benefit is that it can be given a full dose and be more effective in this group of individuals. We are also seeing some evidence that it might be helpful in terms of improving anemia.

PERSIST-2 was a trial done with patients with a platelet count of less than 100,000. And here, it was vastly superior to helping control spleen and symptoms compared to those control arms. Now it was shared at the most recent ASH that it's a potent inhibitor ACVR1. This is a marker of inflammation that we think may help to contribute to anemia. Inhibiting this may help to improve anemia. It was shown in the PERSIST-2 study that there could be real clinical improvement in anemia. I presented the PERSIST-1 study at ASCO that showed similar benefits in spleen symptoms and anemia. This too can have GI side effects and overlaps with fedratinib in that regard. There is no blackbox warning as it relates to pacritinib. Here showing this inhibitory property against ACVR1, which is shared with momelotinib, and not shared with fedratinib or ruxolitinib. This is one of the key reasons we feel that there is a greater likelihood of benefit for anemia. For pacritinib and momelotinib versus the controls. Here, looking at the achievement of transfusion independence on those PER – PERSIST-2 study, you see the different subsets, and then it was better for achieving transfusion independence. Overall, with those who have thrombocytopenia, those with JAK2 different allele burdens, and those excluding recent ruxolitinib. So really, no matter how you're dividing these patients up, it could be potentially beneficial.

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

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

Momelotinib is under review for , an NDA application and it may well be approved soon. It impacts again, this ACVR1 that I was mentioning with impacts on spleen and symptoms as well. Functionally, we learned of this because we had seen benefits of momelotinib for improving anemia. And then really did subsequent studies to try to figure out the mechanism. And it was really only in those mechanistic studies led by Stephen Oh and others, that identified this hepcidin story. Dr. Verstovsek and I, we co-lead the phase 3 study of momelotinib versus danazol in patients who were symptomatic, anemic, and – and had failed a JAK inhibitor. They were randomized against danazol with an open-label crossover of momelotinib itself. And with this, we were looking at improvements in spleen, symptoms, transfusions. And we saw that the trial met all of its key primary endpoints, superiority for symptoms, superiority for splenomegaly, and non-inferior for anemia. At ASH of 2022, we showed that these benefits were durable. So sustained responses in week 24 in these individuals. We saw in the transfusion-independent responses that they were stable and we looked on the panel on the right, the mean hemoglobin over time in transfusion-independent responders showed continued improvement, as well as individuals that were crossed over from danazol on to momelotinib had further improvements in their anemia.

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

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

In the proliferative second-line setting, fedratinib clearly is the choice. You obviously can always consider a clinical trial, but in approved therapies, clearly fedratinib. In cytopenic myelofibrosis, pacritinib is our best choice. Anemia and/or thrombo - thrombocytopenia, and/or

anemia pacritinib can be given to individuals with a normal platelet count, and it can be active, al - although probably not - less preferred than the other agents, but for cytopenias, go with pacritinib. Ruxolitinib or fedratinib, probably would try pacritinib first but again you can always circle back to these. Momelotinib, if and when hopefully likely to be approved, clearly would overlap in this setting to some degree. Let's say anemia, plus or minus thrombocytopenia. Momelotinib again, has been tested for individuals with anyone with a platelet count of greater than 25,000.

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

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

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

There are the immunomodulatory drugs, interferons. Interferons have long been used in low-risk MF or early MF. There are studies from ASH 20-twee – 2022, looking at pegylated interferon, along with ruxolitinib to try to improve spleen and symptoms. You have ropeg that there was a study at ASH – or I'm sorry at EHA 2023 show - looking at an early MF. There are the checkpoint inhibitors, although they have been relatively disappointing in myeloid neoplasia, including MF compared to their data in solid tumors. There are the HDAC inhibitors of which you have several they're of – of interest panobinostat, givinostat you've got the BET inhibitor, pelabresib CPI-0610 that probably is the further along in phase 3 testing with combination impact.

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

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

End Chapter 3

Begin Chapter 4

But let me share with you a case study. Here's an individual 72 with MF, primary MF symptoms, weight loss, etc., big spleen, hemoglobin is 9.5, white count 14, platelets at 140. This individual has intermediate2 risk MF by the DIPSS. And - but by burden, has spleen, symptoms, anemia. This individual in 2023 re - begins ruxolitinib. Now, let's say this individual initially has a response, the spleen shrinks, the symptoms decrease, but they develop transfusion dependence, and they get lost to follow-up. They're off in another state. They live near the grandkids. But they come back to see you. Now their ruxolitinib dose has dwindled down with their local physician, they advised them, 'Oh, we better cut that dose because of that anemia.' The spleen, back up to baseline. Symptoms, plenty of symptoms. They're needing transfusions, and their platelets are only 40, marrow shows fibrosis, they got 6% blasts. They have multiple

mutations. What should we do? This individual now by the MIPSS70 has a high-risk disease. They have clear disease burden. Do we go to transplant? Do we go to medical therapy? In the - this individual what would you do? Well, here would be some of the options. Should we prescribe fedratinib instead of ruxolitinib? Should we increase the dose of ruxolitinib to 10 twice a day? Should we add venetoclax and azacitidine? Should we prescribe pacritinib instead of ruxolitinib? Or unsure?

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

Now what, using the same example, let's say we kept everything the same, but the platelets were higher at 95,000. How does that impact our choices? Again, there's still high risk. What do we do?

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

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

Thank you very much.