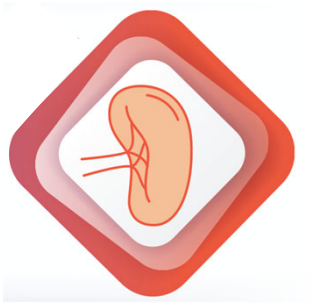


Improving Outcomes for Patients with Myelofibrosis: A Case-based Analysis

John O. Mascarenhas, MD
Professor of Medicine
Tisch Cancer Institute, Division of Hematology/Oncology
Icahn School of Medicine at Mount Sinai
New York, New York

Sandra E. Kurtin, PhD, ANP-C, AOCN, FAPO
Assistant Professor of Clinical Medicine
Adjunct Clinical Professor of Nursing
The University of Arizona
Director, Advanced Practice
The University of Arizona Cancer Center
Tucson, Arizona

Provided by
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®
and
MediCom Worldwide, Inc.

Supported by educational grants from
Bristol Myers Squibb Company, CTI BioPharma, and Sierra Oncology

Dr. John Mascarenhas: Hello and welcome to today's program. I'm Dr. John Mascarenhas, a Professor of Medicine at the Icahn School of Medicine at Mount Sinai. I'm joined by Dr. Sandra Kurtin, an Assistant Professor of Clinical Medicine at the University of Arizona.

Faculty Disclosures

- **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. Sandra Kurtin** has relevant financial relationships related to consulting from AbbVie Inc., Amgen Inc., AstraZeneca, Bristol Myers Squibb Company, Epizyme, Inc., GlaxoSmithKline plc, Incyte Corporation, Pharmacyclics, Inc., and Takeda Oncology.

These are our disclosures.

Learning Objectives

- Align patient presentation and symptomatology with second-line options in MF through a series of case scenarios
- Outline importance and role of shared decision-making and patient/caregiver education in the treatment of MF

Today, our learning objectives will focus on alignment of patient presentation and symptomatology with second-line options and myelofibrosis through a series of case scenarios, and outline importance and role of shared decision-making and patient caregiver education in the treatment of myelofibrosis.

Shared Decision-Making (SDM) in Myelofibrosis

Sandra E. Kurtin, PhD, ANP-C, AOCN, FAPO
Assistant Professor of Clinical Medicine
Adjunct Clinical Assistant Professor of Nursing
The University of Arizona Cancer Center
Tucson, Arizona

Dr. Sandra Kurtin: Thank you for that, Dr. Mascarenhas. I will start by just giving a brief overview of shared decision-making and try to tailor that conversation around those individuals with a diagnosis of myelofibrosis.

Principles of Shared-Decision Making (SDM)

- Patient and caregiver centric communication
  - Must be tailored to the individual patient
  - Requires determination of individual goals of care
  - Consideration of factors contributing to symptom burden and quality of life
  - Limits implicit bias
- Bi-directional and dynamic exchange of information over time
  - Not one visit or one decision
  - Should be intentional
  - Interdisciplinary – requires consistency of message
  - Clarify uncertain elements within the clinical decision-making process
  - Identify patient choices, interests, and expectations
  - Identify or re-examine patient preferences regarding role of medical professionals in decision making
  - Build trust

LeBlanc TW, et al. *Patient Educ Couns.* 2019;102(9):1602-1612.; Legare F, et al. *Patient Educ Couns.* 2014;96(3):281-286.; McCaughan D, et al. *BMJ Open.* 2022;12(3):e050816.; Rood J, et al. *Psychooncology.* 2017;26(12):2040-2047.; Tran Y, et al. *Cancer Med.* 2019;8(1):155-164.

We hear a lot about shared decision-making, and there are basic principles that are important. I think the bottom line is this should include a patient and caregiver-centric communication strategy. In order to do that, it must be tailored to the individual patient. We really need to talk about determination of individual goals of care at the outset of that tailoring process.

Then really, this is going to require for those with myelofibrosis, an assessment of that symptom burden, quality of life, and should be limited in terms of any implicit bias. What we believe a patient should think or might want should be left out of that patient-centric approach. This requires a bidirectional and dynamic exchange of information. It's not one visit, it's not one decision, it's a process that we need to incorporate over time. It should be intentional. You really need to be thinking about this approach when you're meeting with patients and their caregivers.

It requires a team. This is a team sport, taking care of these patients is very complicated, and so we really need to leverage all of the members of our team. Over time, we're going to have to build on those patient experiences and how they basically evolve through their ability to make these kinds of decisions that requires a level of trust.

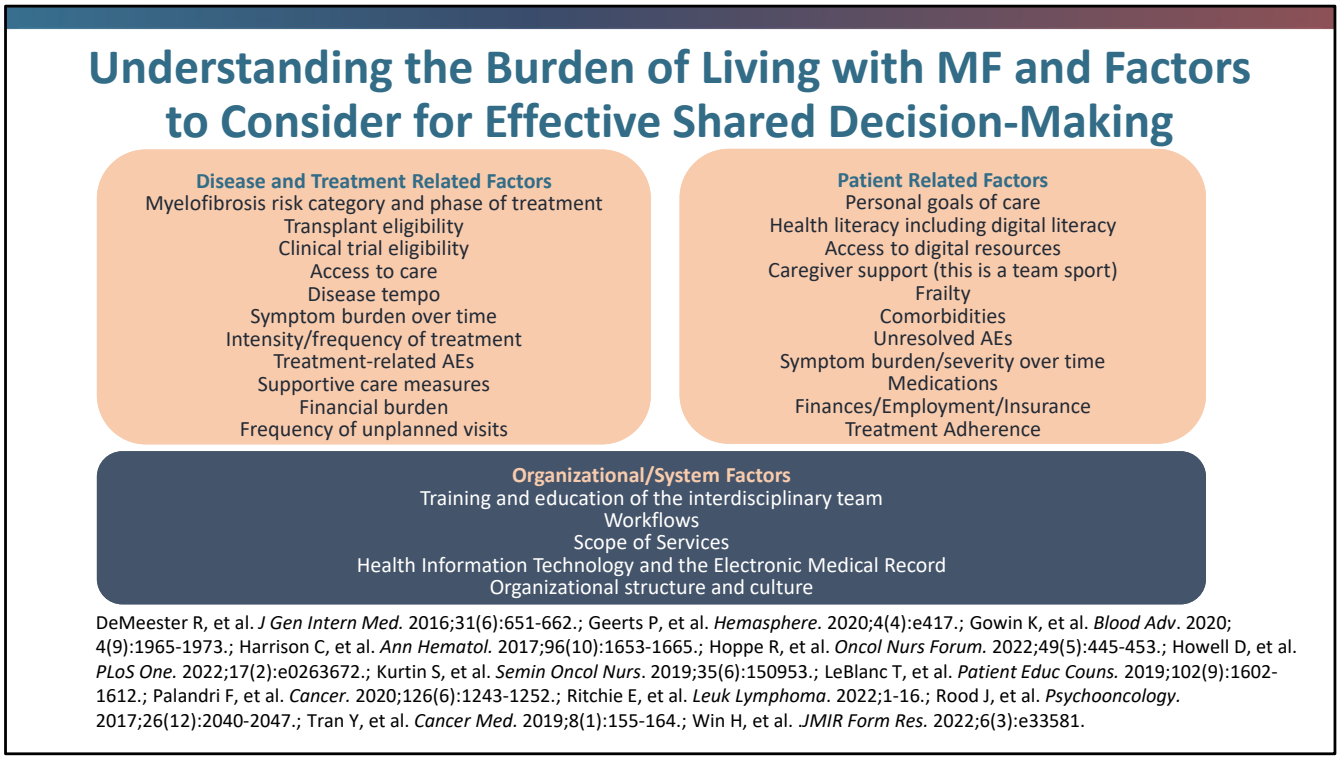
The Challenge of SDM in Myelofibrosis

- Discordant perspectives in the myelofibrosis (MF) patient experience between clinicians and patients
- Rapidly evolving treatment landscape
- Gaps in treatment decision-making tools and resources
- The symptom burden and quality of life impact of MF
- Barriers to care create disparities in access to care
- Limitation in electronic medical record

Emanuel R, et al. *J Clin Oncol.* 2012;30(33):4098-4103.; Gwaltney C, et al. *J Clin Oncol.* 2017;30(33):4098-4103.; Harrison C, et al. *J Clin Oncol.* 2017;30(33):4098-4103.; Howell D, et al. *PLoS One.* 2022;17(2)e0263672.; McCaughan D, et al. *BMJ Open.* 2022;12(3):e050816.; Ritchie E, et al. *Leuk Lymphoma.* 2022;1-16.; Rood J, et al. *Psychooncology.* 2017;26(12):2040-2047.

Still today, we have this discordant perspective, telling us that we need to continue to work at this skill. We also have a very rapidly evolving treatment landscape. That's great news in terms of offering hope to patients, but it also complicates that conversation that we are required to have with them in explaining these options. There are gaps in treatment, decision-making tools and resources. Certainly, for these patients, the symptom burden and their quality of life can impact their ability to really fully engage.

We have other barriers. I'll talk more about that in a moment. Then the forever changing limitations of our electronic medical records, and really being able to find information easily and communicate among the team.



This is a slide that I've created just to really try to talk about the complexity of shared decision-making, and it really requires that we talk or understand and consider disease and treatment-related factors for these patients. That may be the simple process of risk stratification, transplant eligibility, clinical trial eligibility, their disease tempo, and similar other factors.

Patient-related factors, that may be their personal goals of care, their access to health information in the digital era, frailty and comorbidities, and medications, finances. Then there are all these organizational or system-related factors that we may have some or no control over, including workflows and scope of services, and our IT departments. Really understanding this is a very complicated process. It requires consideration of all of these elements.

How Can We Empower Patients and Caregivers?

- Build trust: listen, individualize SDM strategies, provide reassurance, reinforce learning
- Support self-efficacy
  - Encourage patient-caregiver to leverage support networks
    - List current sources of support – consider how each source might assist with specific tasks
    - Knowledge and skills to mitigate stressors and decrease symptom burden
    - Attend/join support group for MF survivors
  - Discuss how to prepare for provider visit, what is expected between visits to improve outcomes
  - Foster communication skills
- Support health literacy using a continuum-based individualized approach
  - Provide education relevant to patient needs at each point in time
  - Referrals and recommendations to vetted information sources and professional resources
  - Begin the discussion of palliative and supportive care early in the diagnosis
- Take action to reduce barriers to care
  - Maximize interdisciplinary resources
  - Build a consistent approach to care and communication with the patient, caregiver, and other clinicians
  - Be prepared to shift based on changing goals of care

What can we do? First and foremost, build trust. That requires that we listen. We all say, talk less, listen more. We need to understand where patients are coming from, what are their challenges and barriers, how can we support self-efficacy, their belief that they can be a partner in their care. Some patients want to do that more than others, and knowing where they're at in that process is important to tailoring your conversations with them. Then fostering those communication skills. This can be tricky as we're all forced to face the computer and type and fill in the blanks.

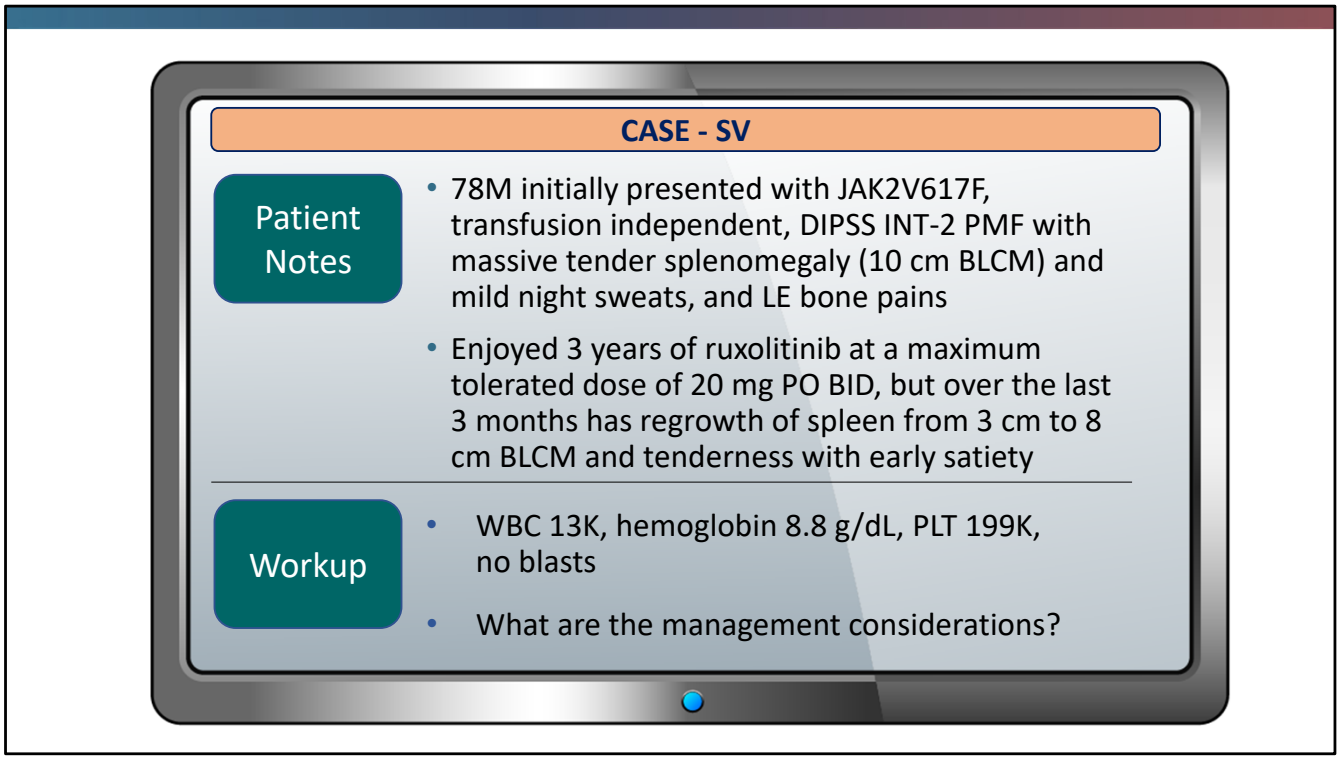
Turning around and looking patients in the eye is something very simple that can really aid in their feeling like they're being heard and understood. Their health literacy and I don't mean, necessarily readability, but their ability to take in new information, synthesize it and then apply that toward their own decision-making. It's something that we need to understand and foster. Having early conversations about supportive care and palliative care to begin to really have them feel like we're looking at the whole scope of what they need and their process of care. Then understanding those barriers that I've just discussed.

I'll turn it back over to you now so we can go through some cases.

Case Presentations: Applying Shared Decision-Making to Practice

John O. Mascarenhas, MD
Professor of Medicine
Tisch Cancer Institute, Division of Hematology/Oncology
Icahn School of Medicine at Mount Sinai
New York, New York

Dr. Mascarenhas: So what I'm hoping to do in the remainder of the program is to use case presentations in order to facilitate the application of shared decision-making into practice. We have several cases that I think will highlight some of these aspects when treating patients with myelofibrosis.



This is the first case of a patient SV, who is a 78-year-old gentleman, initially presented with JAK2 mutant transfusion independent, DIPSS intermediate-2 primary myelofibrosis with a massive tender spleen measuring 10 centimeters below the left costal margin, and mild night sweats, and lower extremity bone pain, usually at night that would disturb quality of sleep.

He initially enjoyed three years of ruxolitinib at a maximum tolerated dose of 20 milligrams twice daily, but over the last three months has regrowth of his spleen from 3 centimeters at its smallest, to now 8 centimeters below the left costal margin. It's more tender, and he's noticing that he's unable to finish his meals as he once did. His white count is 13,000, hemoglobin 8.8, platelets 199,000, and there's no blasts in the peripheral blood smear.

What are your management considerations in a patient who's been on ruxolitinib, who initially enjoyed spleen and symptom benefit for a period of time, and now is losing that aspect mainly from a spleen perspective?

What are the management considerations?

A. Increase dose of ruxolitinib
B. Reduce dose of ruxolitinib
C. Switch to fedratinib
D. Switch to azacytidine
E. Refer to hematopoietic stem cell transplantation

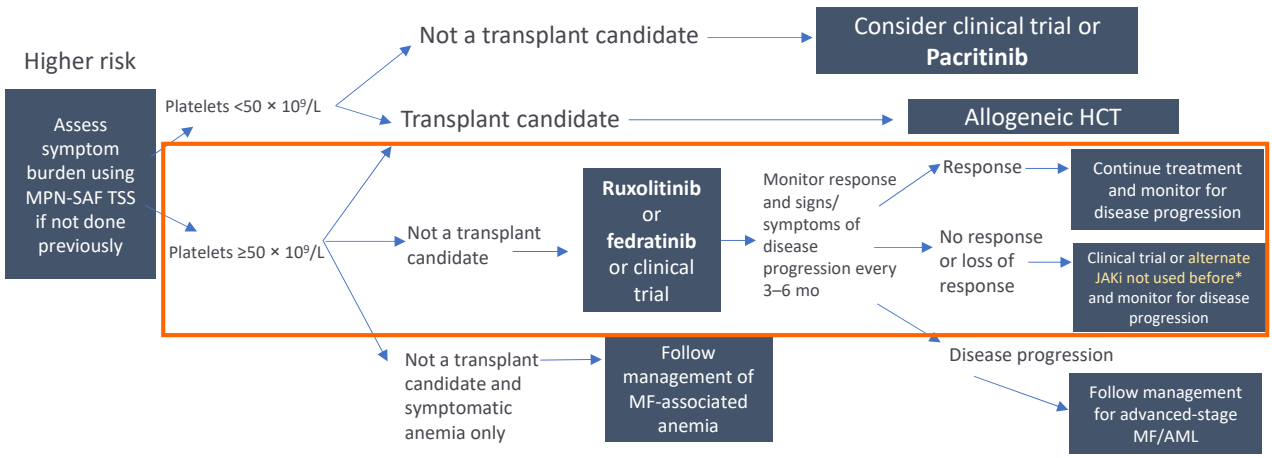
Please select your answer to Poll Question 1 below the video.

In this case, the options would be to increase the dose of ruxolitinib, reduce the dose of ruxolitinib, switch to fedratinib, switch to azacitidine, or refer to hematopoietic stem cell transplantation. Please vote on the most appropriate choice for this patient.

In this case, Option C, which is the switch to fedratinib, is likely the best option, as increasing the dose of ruxolitinib is unlikely to garner better spleen and symptom benefit at this point and was the maximally tolerated dose for the patient. Lowering the dose of ruxolitinib would likely reduce the symptom and spleen benefit that you still have. Switching to azacitidine, which is not an approved drug for myelofibrosis, is usually relegated to patients who have progressive or clonal evolution with increasing blasts or leukemic transformation.

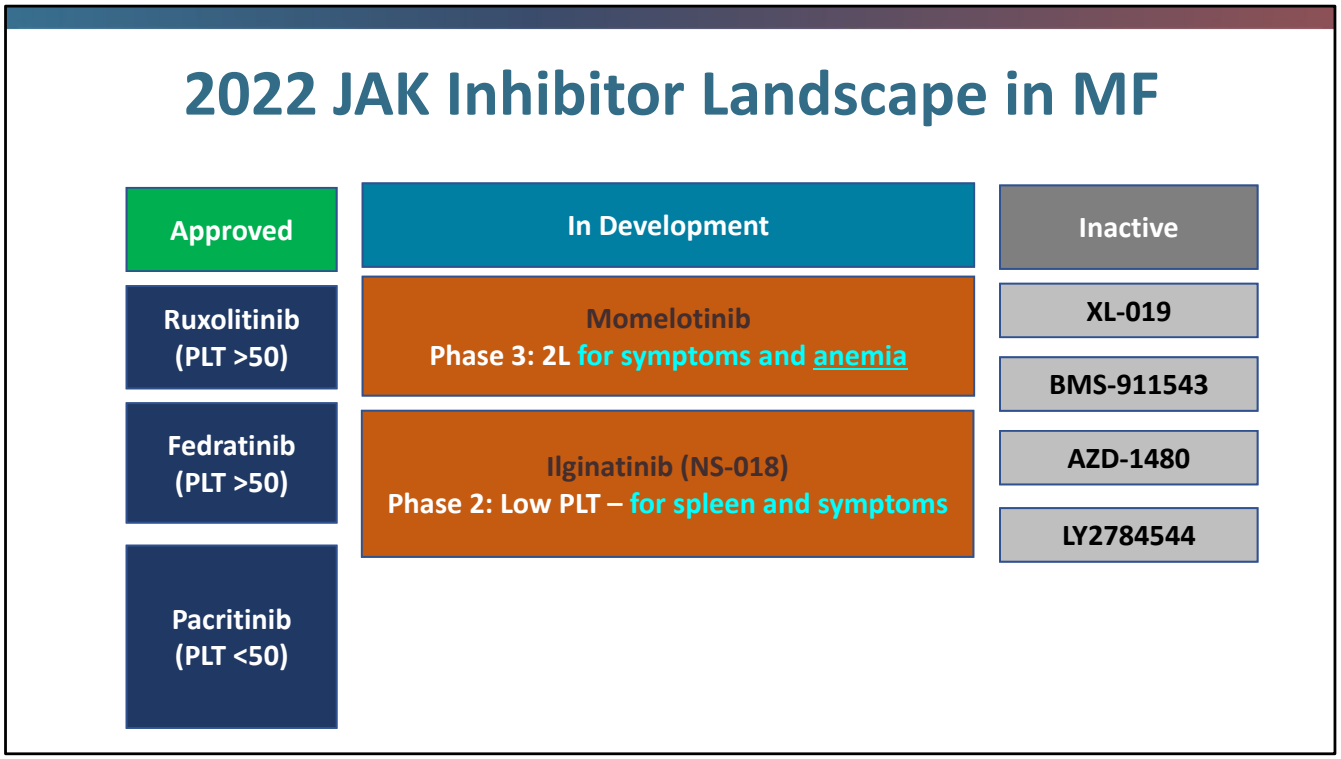
Unfortunately, this patient is too advanced in age to be a viable candidate for hematopoietic stem cell transplantation, which remains the only curative option. Of these options, switching to fedratinib is the most reasonable option in order to use a second-line JAK2 inhibitor to regain spleen control.

NCCN Guidelines: Treatment for Higher-Risk MF



*Consider pacritinib for patients with platelet counts ≥50,000 × 10^9/L with one prior JAK inhibitor.
HCT, hematopoietic stem cell transplant; MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form.
Myeloproliferative neoplasms (Version 3.2022). 2022. Accessed December 1, 2022. https://www.nccn.org/guidelines.

The two options for first-line therapy with a JAK- inhibitor for platelets greater than 50,000 would include ruxolitinib or fedratinib. If patients don't have either a sufficient response at a maximally tolerated dose with either drug in terms of spleen or symptom benefit, or have an initial response and lose response, or don't tolerate the drug due to cytopenias or extramedullary toxicity, then one can switch to the alternative therapy. So, from ruxolitinib to fedratinib, or from fedratinib to ruxolitinib, and also pacritinib is now a third option for the second-line patient population.

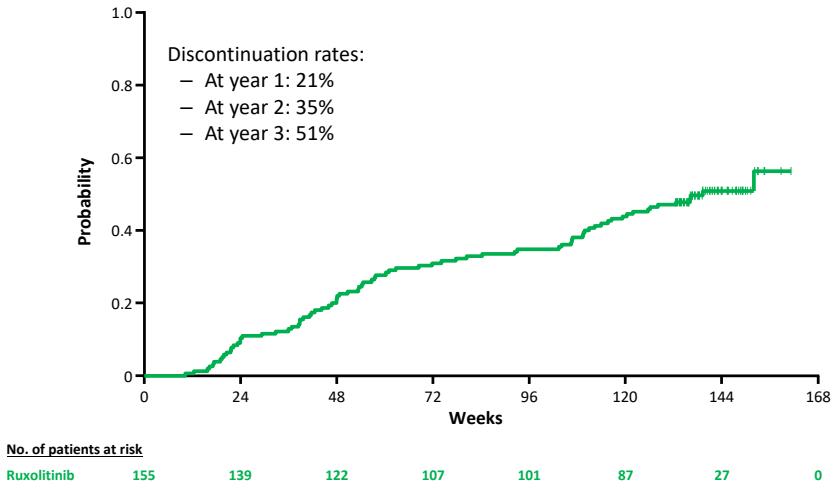


There are three approved JAK inhibitors, as I'm showing you here on the left. Two of those inhibitors, ruxolitinib since 2011 and fedratinib since 2019, were approved for patients with intermediate and high-risk disease that had a platelet count greater than 50,000. Then pacritinib that was approved in February of this year, February 28th, to be specific, for patients with platelet counts, less than 50,000.

You'll see that there are still drugs that are in development that are JAK inhibitors, most notably momelotinib, which has data now from the MOMENTUM study that was presented at ASCO and EHA 2022 demonstrating symptom, spleen, and even anemia responses in patients who've been previously treated with ruxolitinib that continue to have spleen symptom burden and anemia. There are a number of drugs on the right that unfortunately have stalled in clinical development, mostly because of toxicity, sometimes because of lack of sufficient activity.

Ruxolitinib Discontinuation Over Time

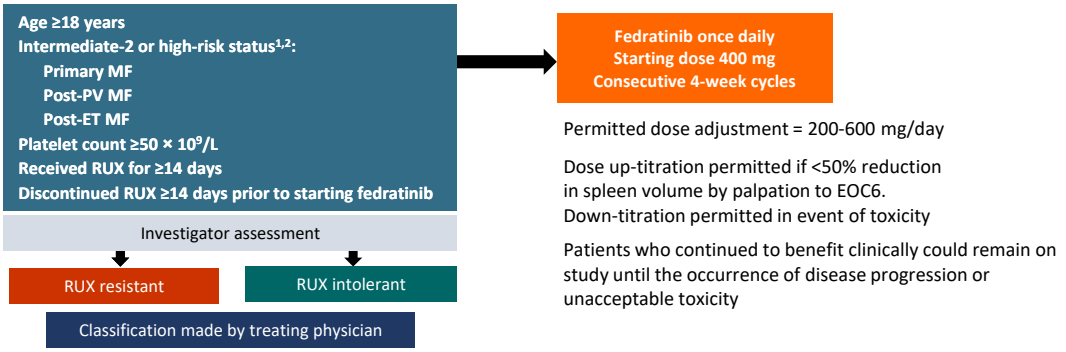
- Approximately 50% of patients originally randomized to ruxolitinib remain on therapy



Ruxolitinib is an excellent drug in the majority of patients that are treated with this oral JAK1/2 inhibitor, they do garner benefits from spleen and symptom burden. However, if you look at the prospective studies in the follow-up at a median of three years, half the patients have discontinued therapy for a variety of different reasons. At five years, 85% of patients have discontinued therapy.

2009 Mar 26;113(14):2895-901.

JAKARTA-2: Single-Arm, Multicenter, Open-Label Study (NCT01523171)



- 70 patients planned to be enrolled
- Primary endpoint for interim analysis: ≥35% reduction in spleen volume from baseline (spleen response) at end of Cycle 3 (Week 12) in the per-protocol population

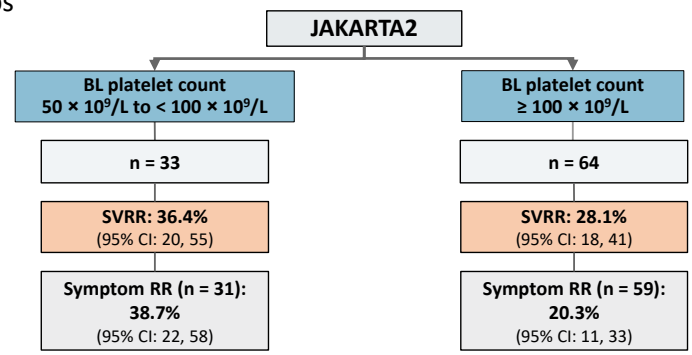
EOC6=end of cycle 6; ET=essential thrombocythemia; MF=myelofibrosis; PV=polycythemia vera; RUX=ruxolitinib
[1]Vardiman JW, et al. *Blood.* 2009;114:937-951. [2]Cervantes F, et al. *Blood.* 2009;113(13):2895-2901.; Harrison C, et al. *Lancet Hematol*. 2017l;4(7):e317-e324.

This leaves an unmet need because once you've discontinued therapy with ruxolitinib, there is unmet spleen and symptom burden, often cytopenias.Unfortunately, multiple studies have shown a poor outcome from a survival perspective.

What I'm showing you here is the data from JAKARTA-2, which was an open-label phase two study of fedratinib, which is a selective JAK2 inhibitor. It spares JAK1, which is different from ruxolitinib, which is an equipotent JAK1/2 inhibitor. In this single-arm study, fedratinib was administered at 400 milligrams daily, which is the approved dose to patients who had at least 14 days of prior ruxolitinib therapy and were either intolerant or refractory to the drug.

Second-line Fedratinib Spleen Volume and Symptom Responses

- Overall SVRR was 31% (95% CI: 22, 41) and symptom RR was 27% (95% CI: 18, 37)
- There was no statistically significant difference in SVRR or symptom RR between BL platelet count subgroups



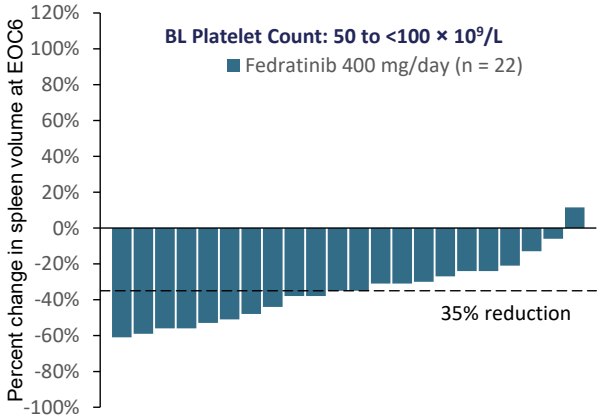
RR, response rate; SVRR, spleen volume response rate.
Statistical comparisons between BL platelet count subgroups should be interpreted with caution due to small sample sizes.
Harrison CN, et al. *Am J Hematol.* 2020;95:594-603.; Harrison CN, et al. *Blood.* 2019;134(suppl 1):4165.

What I'm showing really is the bottom line of this approach of sequentially giving another JAK- inhibitor, in this case, fedratinib in the JAKARTA-2, where despite the previous exposure to ruxolitinib, 30% of patients hit an SVR at 35% and almost 30% of patients hit a TSS 50% or better really indicating that one can still salvage spleen and symptom burden, even with a drug from the same class that differs from the original JAK inhibitor.

Down below, you can see that if you look at platelet counts between 50,000-100,000, which this trial allowed on or greater than 100,000, the response rates were more or less the same. One could still achieve spleen response and even symptom benefit even in these patients with more modest thrombocytopenia between 50,000-100,000. This is data that would support second-line use of fedratinib after ruxolitinib, particularly when trying to capture spleen, but also symptom burden.

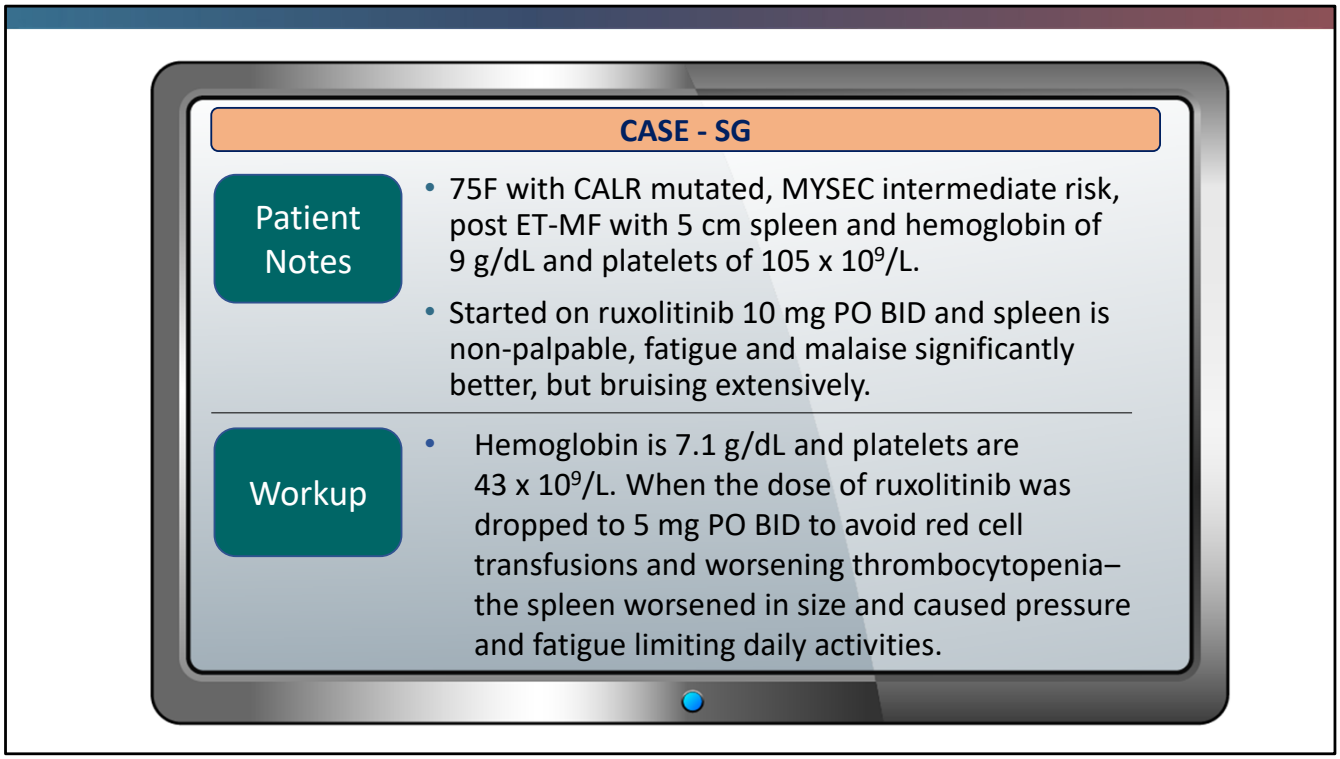
JAKARTA2: Individual Spleen Volume Changes

- Among JAKARTA2 patients with BL platelet counts of 50 to <100 × 109/L and with spleen volume data available at BL and EOC6, all but 1 had some degree of spleen volume reduction at EOC6



BL, baseline; EOC6, end of cycle 6.
Mesa R, et al. ASH 2019.

Here I'm showing the waterfall plot that gives you a sense in the patients with platelets between 50,000-100,000 what the spleen volume response rate looked like, essentially every patient except one enjoyed reduction in their spleen volume. I would make the argument that even patients who have a 20% reduction in spleen volume will likely feel better as a result in terms of the complaint like our gentleman had of early satiety or discomfort or mobility.



The next case is a case of SG. She is a 75-year-old female with CALR-mutated MYSEC intermediate risk, post-essential thrombocythemia related myelofibrosis with a 5-centimeter spleen and a hemoglobin of 9 grams per deciliter and platelets of 105,000. She was started on ruxolitinib 10 milligrams twice daily and the spleen is now non-palpable. Her fatigue and malaise have significantly better, but she does bruise extensively. Her hemoglobin is 7.1 and platelets are now 43,000 from 105,000.

When the dose of ruxolitinib was dropped to 5 milligrams twice daily to avoid red cell transfusion receipt and worsening thrombocytopenia, the problem is the spleen started to worsen in size and cause pressure and early satiety and fatigue started to limit her daily activities.

What are the management considerations in a patient who is enjoying benefit of ruxolitinib that has to be dose reduced for worsening cytopenias and then is losing that benefit from a spleen and symptom perspective at a lower dose of ruxolitinib?

What are the management considerations?

A. Maintain ruxolitinib dose of 5mg BID
B. Maintain ruxolitinib dose of 10 mg BID
C. Switch to fedratinib
D. Switch to pacritinib
E. Refer to hematopoietic stem cell transplant

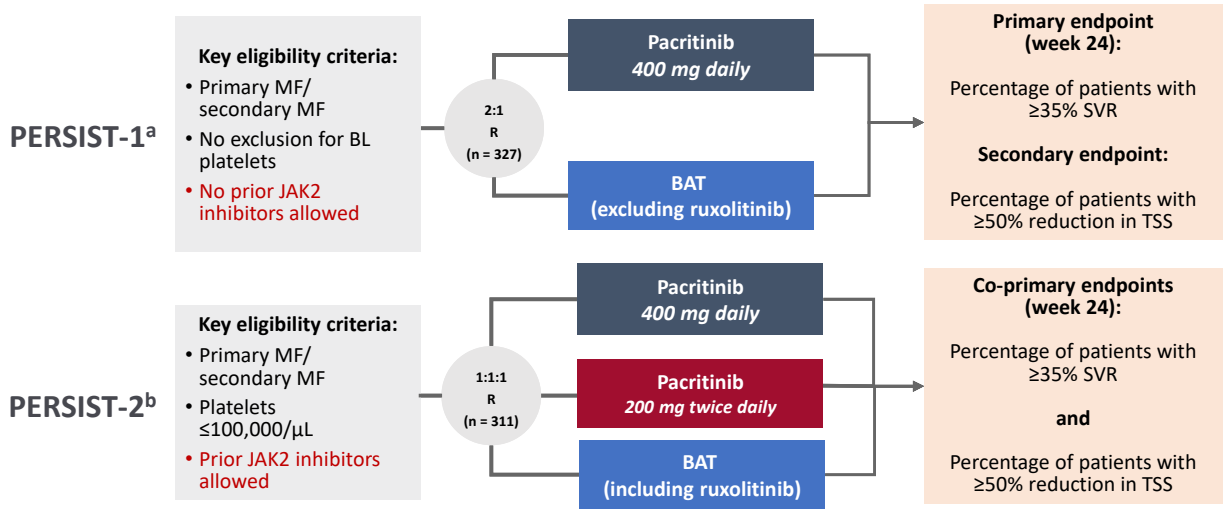
Please select your answer to Poll Question 2 below the video.

In this case, what would you do? Would you maintain the dose for ruxolitinib at 5 milligrams twice daily? Would you try to go back up to 10 milligrams twice daily? Would you switch to fedratinib? Would you switch to pacritinib or refer to hematopoietic stem cell transplantation? Please vote.

The right answer here would be to switch to pacritinib, which is a JAK-2 IRAK1 ACVR1 inhibitor that has been shown in clinical development to be less myelosuppressive and offers a nice alternative to low-dose ruxolitinib in patients who have to dose reduce because of cytopenias where you can deliver the full dose of pacritinib in this patient population. Although fedratinib does have data as I showed you from the JAKARTA-2 study, with platelets between 50,000-100,000, this patient now has platelets less than 50,000.

Fedratinib has not been approved or studied extensively in this patient population.

PERSIST-1 and PERSIST-2: Phase 3 Trials of Pacritinib

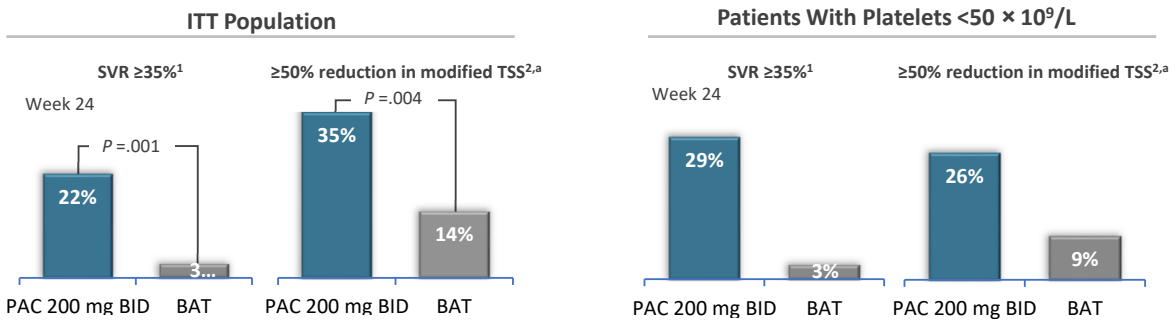


R, randomized; SVR, spleen volume reduction.
[a]Mesa RA, et al. *Lancet Haematol.* 2017;4:e225-e236. [b]Mascarenhas J, et al. *JAMA Oncol*. 2018;4:652-659.

Here are the PERSIST studies, PERSIST-1 up on top and PERSIST-2. These are randomized phase three studies of pacritinib. In PERSIST-1, these are patients who had never seen a JAK-inhibitor previously and were randomized in a two-to-one fashion to pacritinib 400 milligram daily, or best available therapy, which excluded ruxolitinib.

In PERSIST-2, this was an interesting and important study because it took the worst players that we see, the patients with platelet counts less than 100,000. They could have seen a prior JAK inhibitor, and half of them did. They would randomize one-to-one-to-one to pacritinib 400 milligrams daily, 200 milligrams twice daily, or best available therapy, which could include ruxolitinib. Again, almost half the patients received ruxolitinib in the BAT arm. Here it was a very stringent co-primary endpoint at 24 weeks of spleen volume reduction of 35% or greater, and TSS 50% improvement or greater.

PERSIST-2: Spleen/Symptom Response



- The proportions of patients with much improved or very much improved scores were 57% with pacritinib 200 mg BID vs 28% with BAT

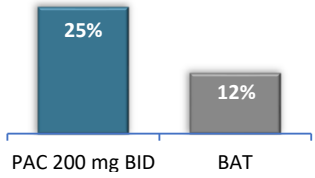
[a]Excludes individual symptom score for tiredness from MPN-SAF TSS v2.0; utilized in pivotal trials for other JAK inhibitors.
BAT, best available therapy; BID, twice daily; ITT, intention-to-treat; MPN-SAF, myeloproliferative symptom assessment form; PAC, pacritinib; SVR, spleen volume reduction; TSS, total symptom score.
[1]Mascarenhas J, et al. *JAMA Oncol*. 2018;4:652-659. [2]Data on File. CTI Biopharma Corp. Pacritinib Clinical Overview.

If we look at the results from the PERSIST-2 the low platelet population, so exclusive to patients with platelet counts less than 100,000, the spleen volume response rate at week 24 was 22% versus 3% in the BAT arm at 200 milligrams twice daily. This was the now-approved dose as of February 28th, 2022. The symptom improvement at 200 milligrams twice daily was 35% versus 14%. If you drill down and look at specifically those patients with less than 50,000, that's what the label doesn't cover for ruxolitinib or fedratinib. The SVR 35% was 29% versus 3% and the TSS 50% was 26% versus 9%. Here there's data for the first time in low platelets where you could give at the full intended dose of the drug, spleen, and symptom benefit.

PERSIST-2: Hematologic Stability

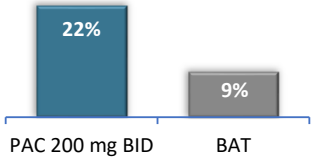
Clinical Improvement in Hemoglobin Levels in Patients With Baseline Anemia[a]

Baseline to week 24



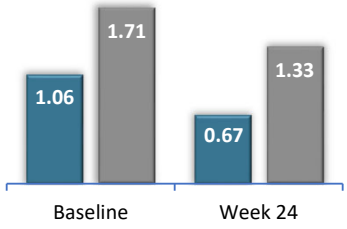
Pacritinib Reduced Transfusion Burden in Patients Not TI at Baseline

Baseline to week 24



Transfusion Burden in Patients Who Received ≥1 RBC Transfusion on Study

Units per month

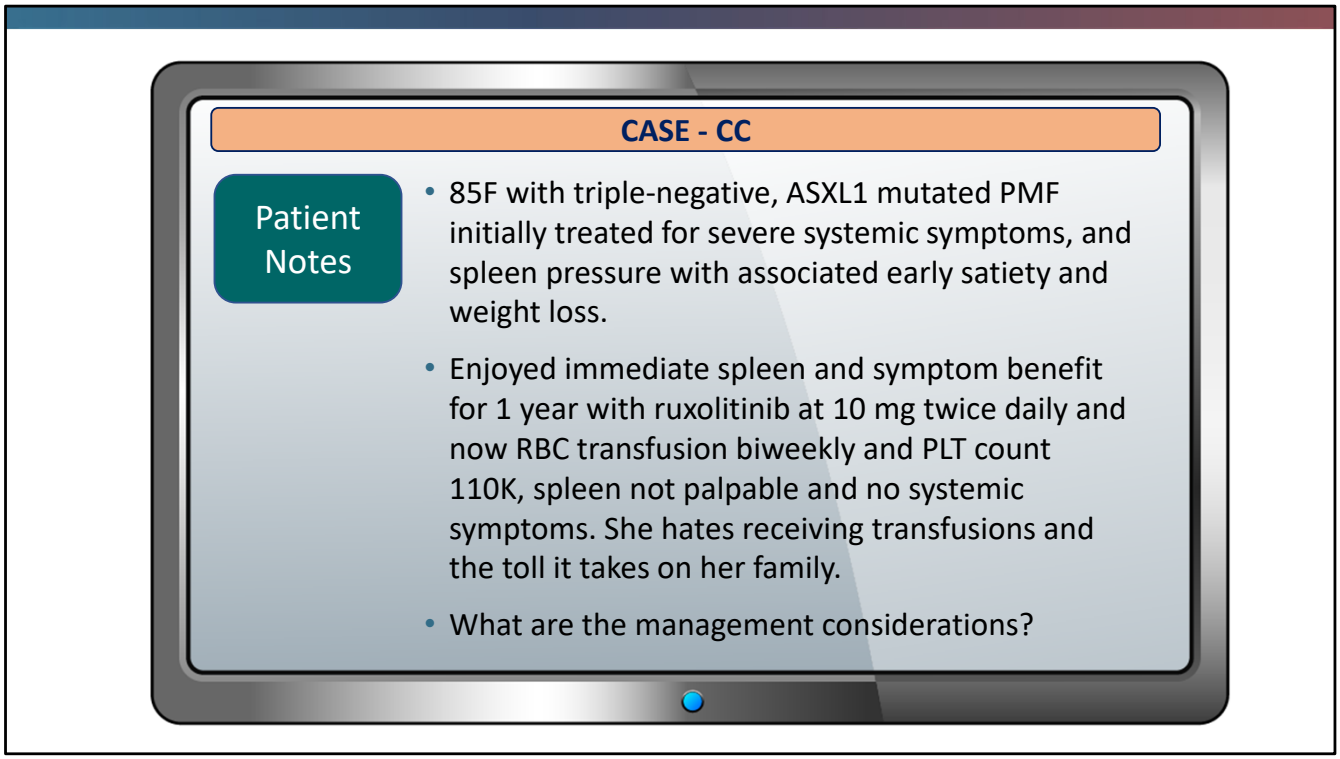


TI defined according to Gale criteria (0 units over the course of 12 weeks).
[a]International Working Group response criteria: increase of ≥2.0 g/dL or RBC transfusion independence for ≥8 weeks prior; anemia defined as hemoglobin <10 g/dL.
BAT, best available therapy; BID, twice daily; ITT, intention-to-treat; PAC, pacritinib; RBC, red blood cell.
Mascarenhas J, et al. *JAMA Oncol*. 2018;4:652-659.

Increasingly importantly, and increasingly recognize that pacritinib is a less myelo-suppression option. It also inhibits ACVR1, and ACVR1 has been linked to hepcidin expression level. This was first noted with momelotinib, the JAK1/2 inhibitor that was presented in the MOMENTUM study results this summer.

This drug also inhibits ACVR1, and between ACVR1 inhibition and IRAK1 inhibition, this might explain why 25% of the patients who received the approved dose, 200 milligrams twice daily of pacritinib, attained a clinical improvement in anemia. These were patients who had at least a 2 gram per deciliter increase in hemoglobin or converted from transfusion dependence to independence. If you look on the right, the mean number of units of red cells that were being received by these patients decreased from 1.06 per month at baseline to 0.67 units per month.

This is important and shouldn't be overlooked, because decreasing the amount of transfusion burden and freeing the patient up from the burden, and the patient's family from the burden of being in the cancer center, or the hospital, or the office getting transfusions which can often consume a whole day and is very tiring and can be discouraging, is a significant benefit. Even in the absence of transfusion independence, I would argue reducing the amount of transfusional needs for patients and freeing them up is a significant benefit to these patients.



The next case is CC. She is an 85-year-old woman with triple negative, meaning lacking JAK2, CALR, MPL. She has ASXL1, primary myelofibrosis, initially treated for severe systemic symptoms and spleen pressure with an associated early satiety and weight loss. She enjoyed immediate spleen and symptom benefit for one year with ruxolitinib at 10 milligrams twice daily, but now she's red blood cell transfusion dependent every two weeks and platelet count is 110,000. Her spleen is not palpable, she has no systemic symptoms, and she really hates receiving transfusions and the toll it takes on her family.

What are the management considerations for a patient who is still enjoying on their JAK inhibitor, ruxolitinib spleen and symptom benefit, but continues to have an unmet need of anemia transfusion dependence?

What are the management considerations?

A. Increase the dose of ruxolitinib
B. Decrease the dose of ruxolitinib
C. Switch to fedratinib
D. Add an erythropoiesis stimulating agent
E. Add an erythropoiesis maturation agent
F. Refer to hematopoietic stem cell transplant

Please select your answer to Poll Question 3 below the video.

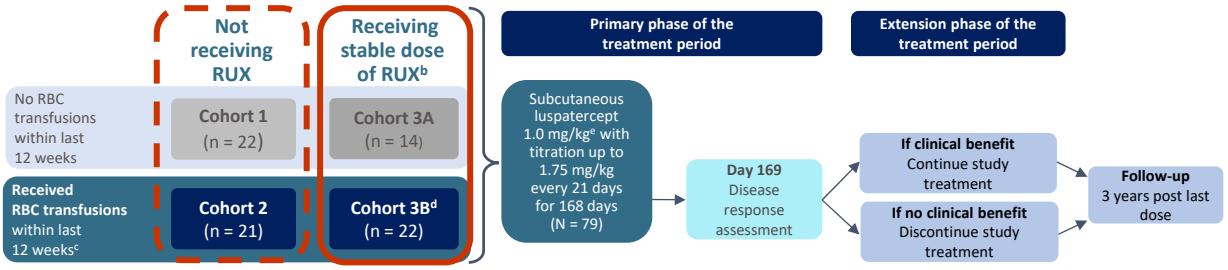
What would you do in this case? Would you increase the dose of ruxolitinib, decrease the dose of ruxolitinib, switch to fedratinib, add an erythropoiesis-stimulating agent, add an erythropoiesis maturation agent, or refer to hematopoietic stem cell transplantation? Please indicate your answer.

The right answer here, I think, is E, to add an erythropoiesis maturation agent. Probably unfairly, I didn't mention that this patient's EPO level was in fact elevated, because if it was low, less than 500, definitely less than 200, maybe a consideration to adding an ESA, like Aranesp (darbepoetin alfa) or Procrit (epoetin alfa) would be reasonable. In this case, this patient had received a lot of transfusions and the EPO level was already high. Unfortunately, adjusting the dose of ruxolitinib will probably not keep the benefit of spleen and symptom and maintain anemia response. You're going to lose something. Switching to fedratinib will probably not benefit the patient, because fedratinib also has a myelosuppressive profile that's similar to ruxolitinib. Unfortunately, at this advanced stage, she's not a real candidate for transplant. Let's explore why an EMA, an erythropoiesis maturation agent, might make sense.

ACE-536-MF-001 Study Design: Luspatercept

- This study reports the results of the ongoing open-label, phase 2 ACE-536-MF-001 trial evaluating luspatercept in subjects with MF and anemia, focusing on response in subjects requiring RBC transfusions (NCT03194542)

Figure 1. ACE-536-MF-001 study design[a]



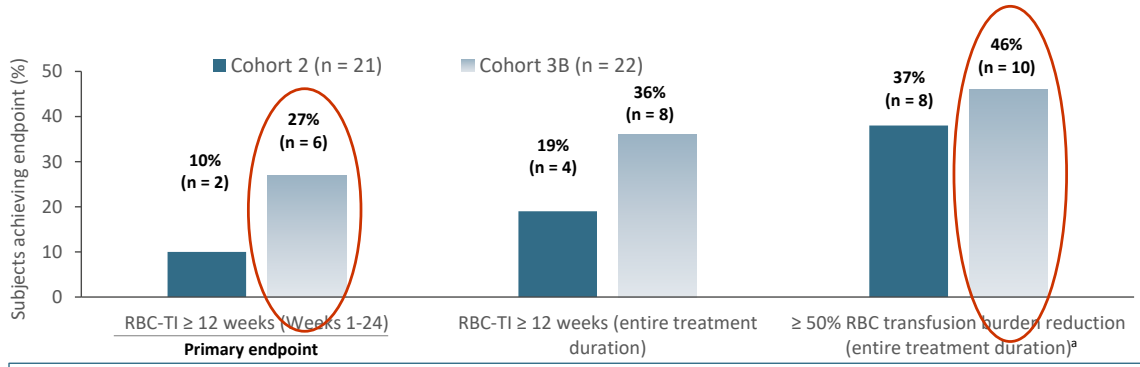
- 79 subjects with MF and anemia had been enrolled by the data cutoff and were included in this updated analysis (March 29, 2020)
- The analyses presented here focus on response in subjects requiring RBC transfusions (Cohorts 2 and 3B); safety is reported for all 79 subjects on study

As of March 29, 2020, 16 (20%) subjects remain on treatment. [a]Enrolled subjects had primary or post-essential thrombocythemia/post-polycythemia vera myelofibrosis; [b]A stable daily dose of RUX for at least 16 weeks at enrollment; for the 3 subjects enrolled in the expansion cohort in Cohort 3B, subjects were receiving a stable RUX dose for 40 weeks; [c]6–12 RBC units/84 days prior to treatment; or 4–12 units/84 days for the 3 subjects enrolled in the expansion cohort in Cohort 3B; [d]Including 3 subjects enrolled in the expansion cohort; [e]The starting dose was 1.33 mg/kg in the expansion cohort subjects. MF, myelofibrosis; RBC, red blood cell; RUX, ruxolitinib.

Gerd A, et al. ASH 2020. Abstract 2992.

This is a phase two study of luspatercept, which is an activin ligand trap, which is part of the TGF-beta superfamily, that when inhibiting this protein, one down-regulates SMAD signaling. What this appears to do is relieve the repression on maturation of red cells. It's a double negative. It allows for red cells to mature. This study was evaluating patients with myelofibrosis who were either receiving ruxolitinib or not receiving ruxolitinib, and then was further stratified by whether they were receiving transfusions or transfusion independent. It was giving this subcutaneous injection of luspatercept every three weeks, much like you give Aranesp (darbepoetin alfa), to these patients to see if there's one goal in mind, can you improve the hemoglobin? This is not a therapy that's directed at spleen and symptom benefit, but one in fact that is to alleviate the anemia.

Achievement of RBC-TI ≥12 Weeks, ≥50% Transfusion Burden Reduction and Multiple Response Episodes



Achievement of multiple episodes of response

- Of the RBC-TI ≥12-week responders in both Cohorts 2 and 3B, 25% experienced 2 separate episodes of RBC-TI ≥12 weeks
- Of the subjects who achieved ≥50% reduction in RBC transfusion burden over any 12 weeks, 3 subjects in Cohort 2 (38%) and 2 subjects in Cohort 3B (20%) experienced 2 separate ≥12-week response episodes
  - One subject (13%) in Cohort 2 experienced 3 separate episodes of RBC-TI ≥12 weeks

[a]Defined as RBC transfusion burden reduction by ≥50% and by ≥4 RBC U for ≥12 weeks.

To jump to the chase where the drug really was probably most beneficial, where in the patients who were receiving ruxolitinib, who were transfusion dependent. About a third of the patients achieved transfusion independence, and almost 50% of the patients had a 50% or greater reduction in their red blood cell transfusion need during the study follow-up.

This was a drug that can be added very easily and comfortably to ruxolitinib to address that one aspect that may not be met in the given individual of anemia. It was very well tolerated with very few significant treatment emergent adverse events. For the most part, if you didn't respond within nine weeks, you were probably unlikely to respond. One could imagine that one wouldn't need to sit on this for six months to necessarily understand whether they would have the benefit of this drug.

One of the points you made early on, which I think is super important that I'd like to convey is, if you don't have the conversation with the patient about what their expectations and goals are, you can really go in opposite directions. I think that's important to set the expectation and understanding upfront so that everyone's on the same page because I see frequently that doesn't happen.

Dr. Kurtin: No, I agree with you. I really try to set expectations at each visit and give people homework, the patient's and their caregivers to say we've talked about a lot of things, I summarize our conversation in like bullet points, I give them things to take away, to talk about amongst themselves, and bring back. It can be challenging when there are different people seeing the patients in visits. I find that just reviewing back what we talked about in a summary at the end of each visit, albeit some of them are short, but then giving them some homework to go home, that really fosters engagement. Then you ask them when they come back, you know we talked about this, I put it in my notes so that if somebody else is seeing the patient, they can follow up on that conversation. But I think that then they feel like I am really a part of this conversation.

Conclusions

- There are three JAK Inhibitors approved for patients with myelofibrosis
  - Ruxolitinib
  - Pacritinib
  - Fedratinib
    - Momelotinib is on the horizon
- The future looks bright
  - Luscpatercept
  - Imetelstat
- Goal of treatment should be to improve quality of life through management of spleen and symptom burden

Dr. Mascarenhas: In summary, in 2022 moving into 2023, there are now three JAK inhibitors that are approved. Likely a fourth on the horizon with momelotinib. What we're seeing and appreciating is that there are niches for these JAK inhibitors and that importantly, one needs to be cognizant and aware of and consider the potential to sequence these JAK inhibitors in order to address spleen and symptom burden and maybe even anemia burden. So ruxolitinib will likely remain the first-line option for most patients with platelet counts of less than 50,000.

Pacritinib is a really good option and the only approved option for these patients. If patients do not do well with ruxolitinib for whatever reason they have to discontinue therapy, fedratinib is an excellent option particularly to address ongoing and unresolved splenomegaly and or symptom burden.

For patients who have good control on their JAK inhibitor with spleen and symptom at bay but anemia still persists, I think those patients may be very well suited in the future for the addition of luspatercept, which is the activin ligand trap. It is approved for transfusion-dependent lower-risk myelodysplastic syndrome and not yet approved for myelofibrosis, but is in phase three testing. Evaluating the ability to address anemia in patients receiving ruxolitinib or fedratinib that continue to have this unmet need.

The future looks very bright for myelofibrosis as we have multiple approved and expanding options for JAK inhibitor treatment for myelofibrosis. Also, what wasn't touched upon today are the many ongoing late-phase clinical trials evaluating combination therapies with JAK inhibitors and other relevant pathway inhibitors, whether it's BET inhibitors, BCL-2 inhibitors, or MDM2 inhibitors.

There are a number of different options I think will continue to improve upon our ability to treat our myelofibrosis patients. Some of these options are even now looking at survival as an endpoint such as imetelstat and the impact MF Study after a ruxolitinib failure. Stay tuned because there's a lot on the horizon but in the time being for those people in practice in the community taking care of myelofibrosis patients, just be aware that there are a number of JAK inhibitors that can serve the purpose of improving quality of life through management of spleen and symptom burden. In some cases, even less myelosuppression and anemia responses.