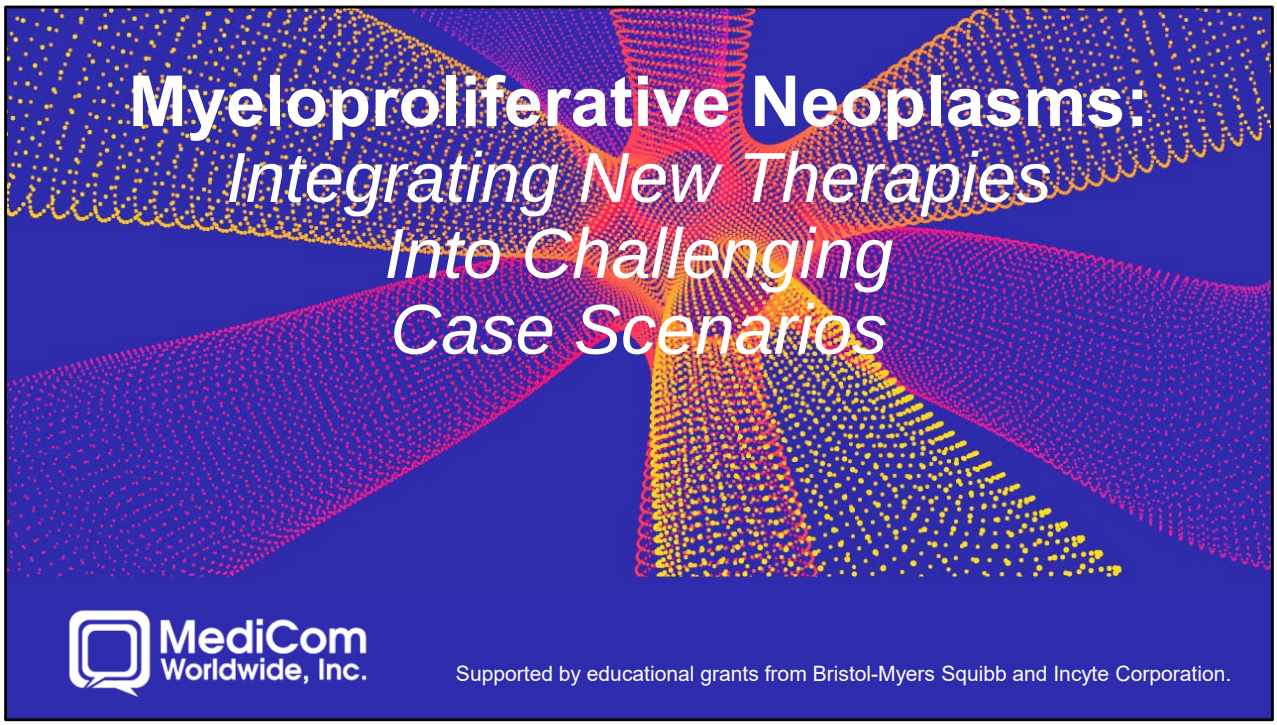
Myeloproliferative Neoplasms:
Integrating New Therapies Into Challenging Case Scenarios



Hello and welcome to this discussion on *Myeloproliferative Neoplasms: Integrating New Therapies into Challenging Case Scenarios*.

Myeloproliferative Neoplasms:
Integrating New Therapies Into Challenging Case Scenarios

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I am Prithvi Bose, an Associate Professor in the Department of Leukemia in the Division of Cancer Medicine at the University of Texas MD Anderson Cancer Center in Houston, Texas, and I am joined tonight by Dr. Ruben Mesa, Director of the Mays Cancer Center at the UT Health San Antonio MD Anderson and the Mays Family Foundation Distinguished University Presidential Chair in San Antonio, Texas, and Dr. Raajit Rampal, Assistant Member and Clinical Director of the Leukemia Service at the Memorial Sloan Kettering Cancer Center in New York.

Disclosures

- **Dr. Prithviraj Bose** has received honoraria related to formal advisory activities from Incyte Corporation, Celgene Corporation - A Bristol-Myers Squibb Company, CTI BioPharma Corp., and Kartos Therapeutics, Inc., as well as consultant fees from Incyte. He has received grant support related to research activities from Astellas Pharma US, Inc., Blueprint Medicines, Celgene, Constellation Pharmaceuticals, CTI BioPharma, Incyte, Kartos Therapeutics, NS Pharma, Inc., Pfizer Inc., and Promedior, Inc.
- **Dr. Ruben Mesa** has received honoraria as a consultant from La Jolla Pharmaceutical Company, Novartis AG, and Sierra Oncology, Inc. He has received grant support related to research activities from AbbVie Inc., Celgene Corporation, CTI BioPharma Corp., Genentech, Inc., Incyte Corporation, Promedior, Inc., and Samus Therapeutics, Inc.
- **Dr. Raajit Rampal** has received honoraria related to formal advisory activities, as well as consultant fees from AbbVie Inc., Blueprint Medicines, Celgene Corporation - A Bristol-Myers Squibb Company, CTI BioPharma, Galecto Biotech, Incyte Corporation, Jazz Pharmaceuticals plc, Kartos Therapeutics, and PharmaEssentia Corporation. He has received grant support related to research activities from Constellation Pharmaceuticals, Incyte, and Stemline Therapeutics, Inc.

These are our disclosures

Planning Committee Disclosures

- The individuals listed below from MediCom Worldwide, Inc. reported the following for this activity: Joan Meyer, RN, MHA, Executive Director, Isabelle Vacher, Vice President of Educational Strategy, Wilma Guerra, Program Director, and Andrea Mathis, Project Manager, have no relevant financial relationships.

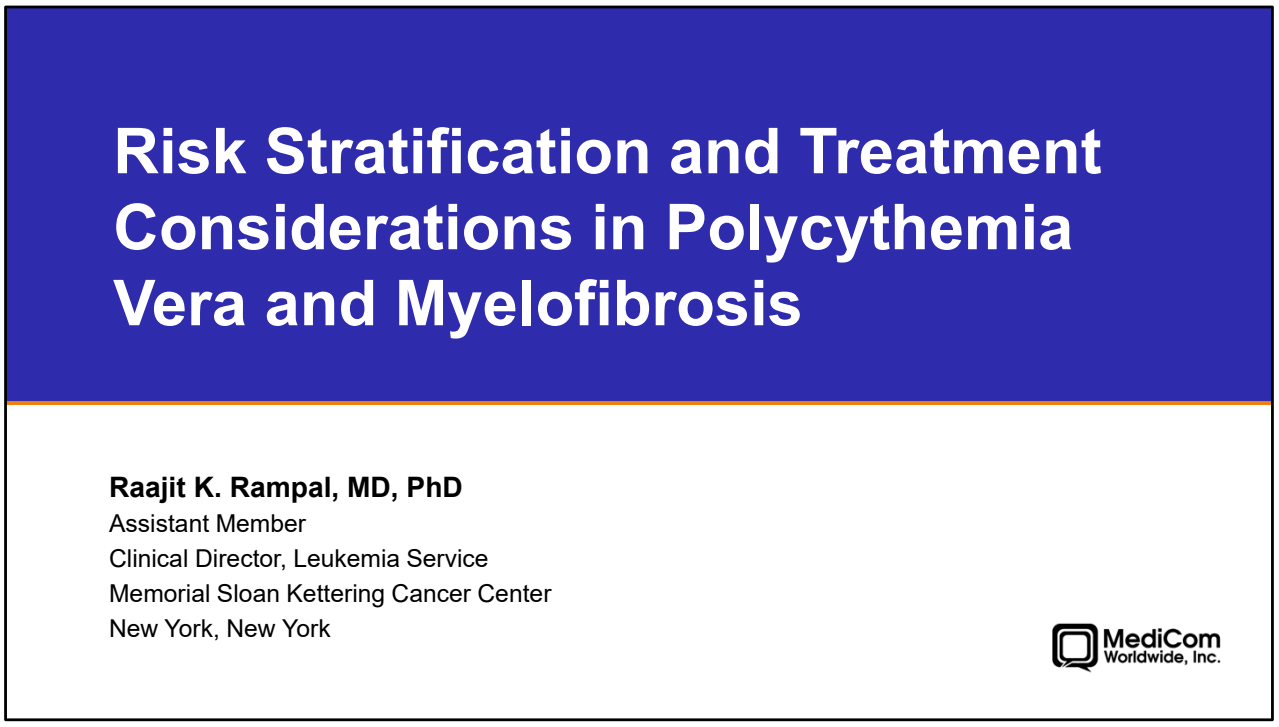
These are the disclosures of the planning committee.

Learning Objectives

- Summarize best practice strategies in molecular and mutational analysis in MPNs, which assist in developing a patient-centered treatment approach
- Articulate knowledge of new and emerging evidence in maintenance therapy as a new standard of care in MPNs
- Outline guidelines and clinical trial evidence to identify appropriate treatment approaches for patients with MPNs
- Describe strategies for identifying and managing treatment including dosing, and management of toxicities associated with novel and emerging therapies in MPNs

We will get started in just a moment here with two overviews, kind of a global bird's eye overview of the field from Dr. Rampal and Dr. Mesa, and then we will get into some cases and share our thoughts on management of those cases.

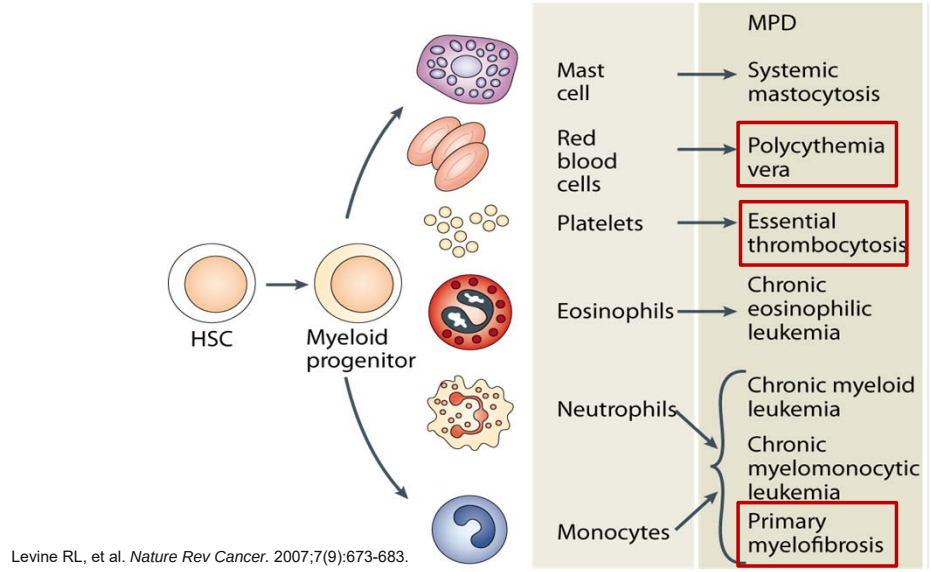
The management of MPNs, as you are aware, is a clinical challenge, particularly for those patients who fail standard first-line therapy and we have some newer therapies now, we have treatment guidelines, but it can be a little overwhelming and a little bit difficult for the community hematologist to integrate all these rapidly changing paradigms into practice recommendations. We will briefly review the current treatment guidelines for polycythemia vera and myelofibrosis, and then get into some cases as I was just alluding to. We will start with the review of the biologic and clinical features of the MPNs and the principles that guide treatment selection.



With that I will turn it over to Dr. Rampal for his talk on risk stratification and treatment considerations in PV and MF.

Raajit Rampal: Thank you so much, Dr. Bose.

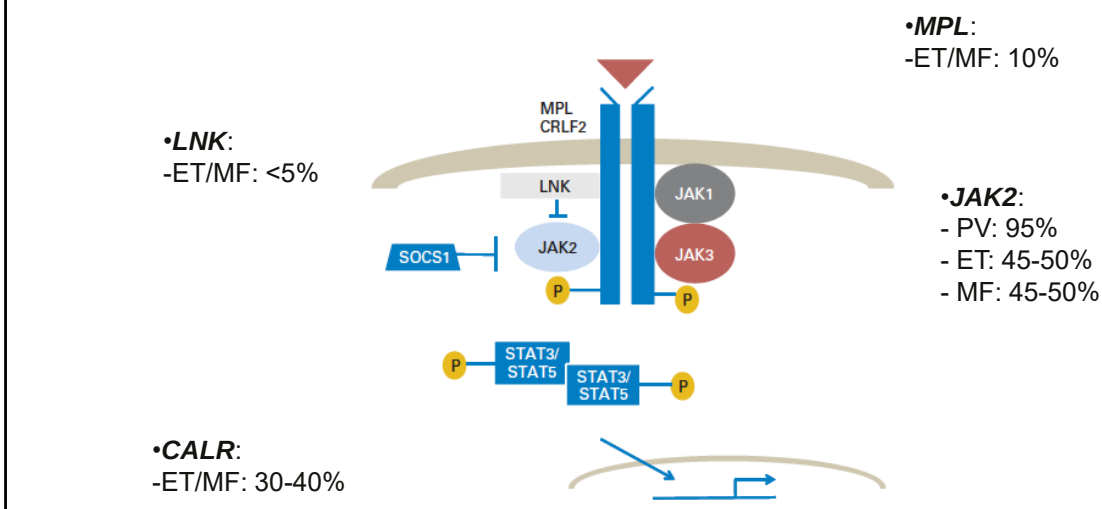
Myeloproliferative Neoplasms



Levine RL, et al. *Nature Rev Cancer.* 2007;7(9):673-683.

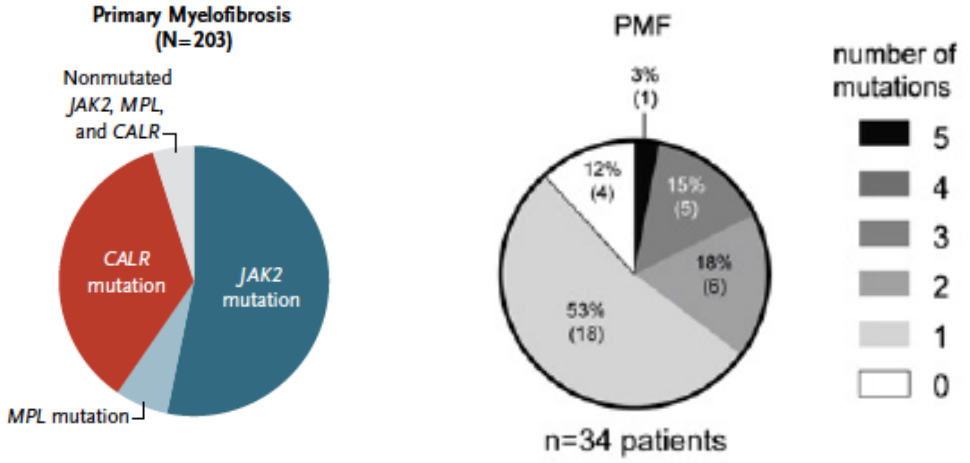
So, the myeloproliferative neoplasms are clonal hematopoietic stem cell disorders that include polycythemia vera, essential thrombocythemia, and myelofibrosis. Importantly, although the phenotypes of the diseases can differ

JAK-STAT Activation Is the Hallmark of MPNs



it is important to recognize that the genomic hallmark of the disease is consistent across the phenotypes, that is activation of the JAK-STAT pathway. What we have known for some time is that activating mutations in a non-receptor tyrosine kinase JAK2 account for the majority of mutations that we see in patients with MPN, but other mutations within this pathway including calreticulin mutations and MEPO mutations certainly account for most of the remaining patients who have an MPN phenotype. It is important to know that there are still about 10% to 15% of patients where we have not identified a drug or mutation. There are very rare mutations as well such as LNK that are also known to cause JAK-STAT activation.

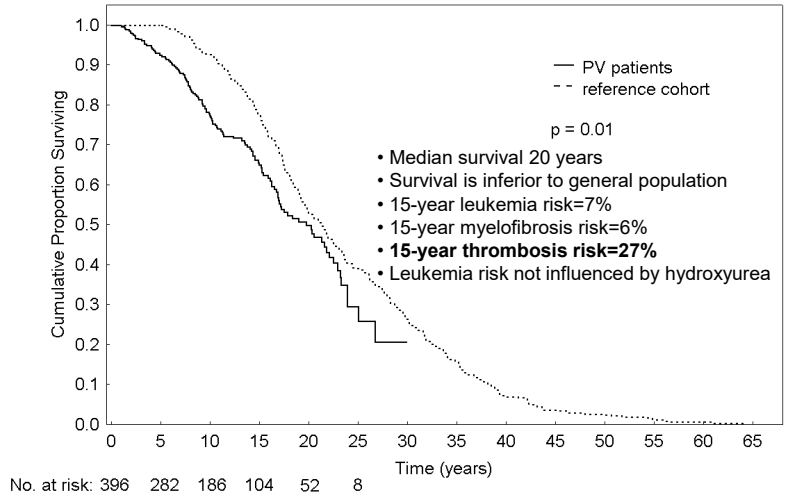
Mutations in Myelofibrosis



Nangalia J, et al. *N Engl J Med.* 2013;369(25):2391-2405.; Klampfl T, et al. *N Engl J Med.* 2013;369(25):2379-2390.; Lundberg P, et al. *Blood.* 2014;123(14):2220-2228.

Now within the MPNs in most patients with ETNPV there is typically only one mutation, a JAK-STAT driver mutation, but certainly other mutations can occur less frequently. The situation in myelofibrosis is somewhat different where a large proportion of patients can have more than one mutation. As we will talk about a little bit later in this talk, that does have prognostic implications.

Natural History of PV



Passamonti F, et al. *Am J Med.* 2004;117(10):755-761.

Let's start by talking about polycythemia vera. So we know that the natural history of polycythemia is such that the median survival is about 20 years from diagnosis, and that does appear to be inferior to that of normal controls. The major thing that we worry about with polycythemia, as you can see from this slide, is thrombosis. The 15-year thrombosis risk is about 27% and by and far that is what our interventions are aimed at trying to prevent. Symptom burden is also an important consideration in these patients as has been well-documented by Dr. Mesa and his group. Those are really the two major things we think about in polycythemia at the time of diagnosis, but it is also important to recognize that transformation to myelofibrosis and acute leukemia are significant risks for our patients, particularly as they have their disease ongoing for a number of years.

Goals of Therapy in PV

- Goals of therapy
  - Reduce symptom burden
  - Decrease risk of thrombotic events
- Therapeutic modalities
  - Therapeutic phlebotomy
  - Cytoreductive therapies: hydroxycarbamide (HU), interferon
  - JAK inhibitors: ruxolitinib
  - Antithrombotic modalities: aspirin, lifestyle modification

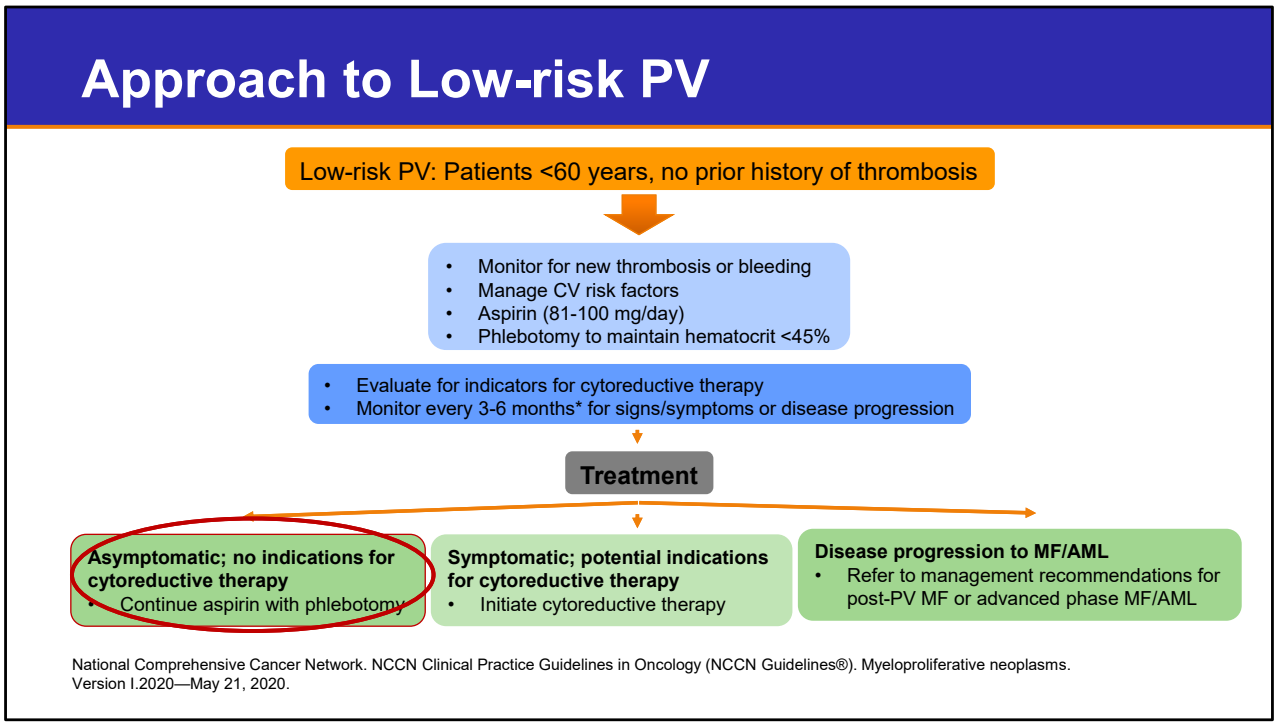
So the goals of therapy really again are to reduce symptom burden and to decrease the risk of thrombotic events. How do we do that? Well, the therapeutic modalities at hand include cytoreductive therapies like hydroxyurea and interferons as well as JAK inhibitors, principally ruxolitinib. It is also important to recognize antithrombotic modalities like aspirin as well as lifestyle modifications. Talk to patients about diet, keeping their cholesterol and keeping their blood sugars in check.

Stratification for Thrombohemorrhagic Complications in PV

Low-risk	**Age<60 years *and* No history of thrombosis *and* Platelet count<1.5 million *and* No cardiovascular risk factors**	**Thrombosis risk is not significantly increased compared to controls**
High-risk	**Age≥60 years *or* Previous thrombosis**	**Thrombosis risk is significantly increased**
Indeterminate risk	**Neither low nor high risk**	**Thrombosis risk is not well studied**

Finazzi G, et al. *Leukemia.* 2008;22(8):1494-1502.; Tefferi A. *Am J Hematol.* 2008;83:491-497.

With the idea that thromboembolic events are our major focus in patients with PV, there is risk-stratification for the management of PV patients, and we deem patients to be low risk if they are under the age of 60 or if they have never had a thrombotic event, as well as if they do not have any overt cardiovascular risk factors, and we deem them to be high-risk if they are over the age of 60 or if they have ever had any thromboembolic event. It is important to also think about this in relative terms. These are relative risks, and we know that patients with MPN do have a higher risk of thrombotic events relative to the general population, so low risk does not mean no risk.



How do we approach patients based on this risk stratification? Well, principally in patients who fall into the low-risk category, the mainstays of therapy are to phlebotomize with the goal of hematocrit less than 45% and to treat with aspirin. If a patient becomes symptomatic, and these symptoms are not controlled by phlebotomy or the use of aspirin, those patients can certainly be considered for cytoreductive therapy, but again these are general principle to low-risk PV patients.

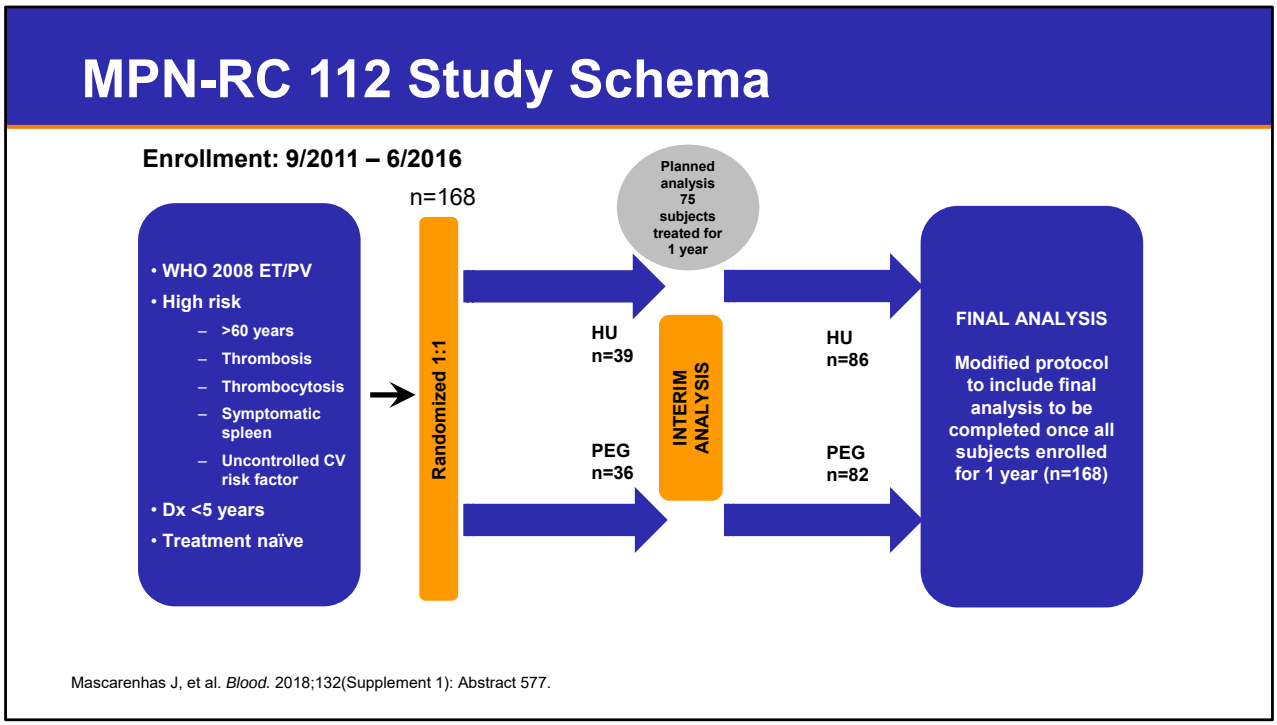
Approach to High-risk PV

High-risk PV: Patients ≥60 years, ± prior history of thrombosis

- Monitor for new thrombosis or bleeding
- Manage CV risk factors
- Aspirin (81-100 mg/day)
- Phlebotomy to maintain hematocrit <45%
- Cytoreductive therapy*
  - Hydroxyurea
  - Peginterferon alfa-2

*Choice of therapy based on age and other individual patient factors
National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Myeloproliferative neoplasms. Version I.2020—May 21, 2020.

What about high risk? Well for patients with high-risk PV, the standard of care is cytoreductive therapy as well as aspirin and phlebotomy as needed intermittently. The agents that are used in practice are hydrea and pegylated interferon. The question that has been discussed for many years in the field now is which one is better, is one better and how do we approach frontline therapy? Several trials have sought to examine this question. I will briefly review two such trials with you.



One was the myeloproliferative research consortium 112 study, and this is a randomized study of patients with PV and ET who required cytoreductive therapy. Patients were randomized to hydroxyurea or to pegylated interferon.

24-Month Response Data

- When considering all 106 patients who were eligible to receive treatment for 24 months (due to study closure)

	HU (n=54)			PEG (n=52)		
	ET	PV	Total	ET	PV	Total
CR	6 (25%)	5 (16.7%)	11 (20.4%)	9 (37.5%)	7 (25%)	15 (28.8%)
PR	2 (8%)	9 (30%)	11 (20.4%)	5 (20.8%)	10 (35.7%)	16 (30.8%)
ORR	**8/24 (33.3%)**	**14/30 (46.7%)**	**22 /54 (40.7%)**	**14/24 (58.3%)**	**17/28 (60.7%)**	**31/52 (59.6%)**

P=.22

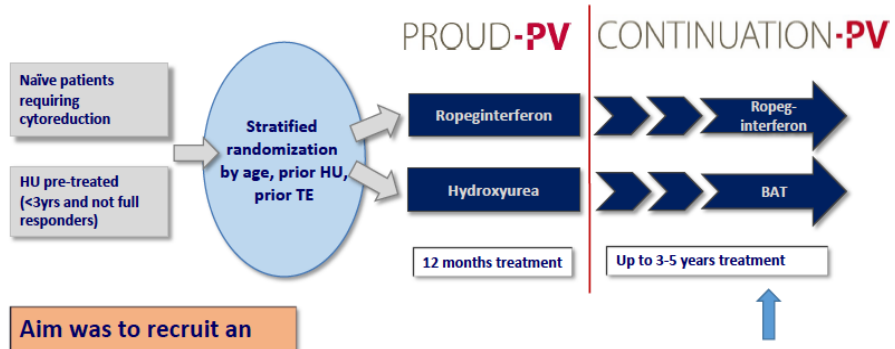
P=.22

22 /48 (45.8%) **31 /52 (59.6%)**

Mascarenhas J, et al. *Blood.* 2018;132(Supplement 1): Abstract 577.

At 24 months after randomization, data demonstrates that the overall response rate, a composite of complete response and partial response, was statistically the same in both treatment groups, indicating that there really was no advantage to either treatment mortality in patients who were being treated upfront.

Ropeginterferon Alfa-2b Phase 3 Development in PV: PROUD-PV and CONTINUATION-PV Studies



Aim was to recruit an "early PV" population.

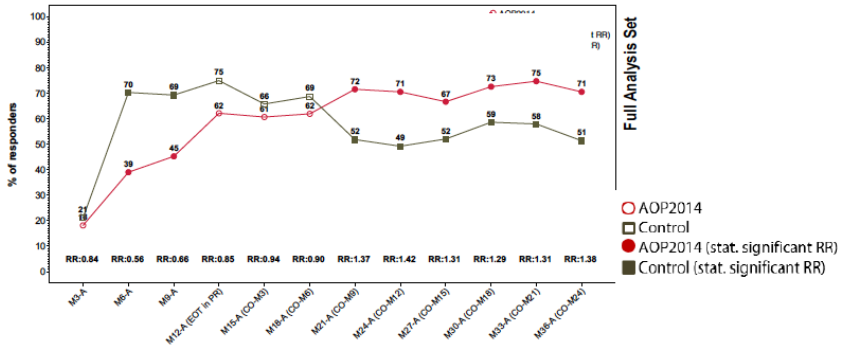
Longitudinal interim analysis after 36 months of treatment (**PROUD-PV and CONTINUATION-PV**) in patients enrolled in CONTINUATION-PV Study:

- **Efficacy data up to 36 months**
- **All available safety data (mean 3.8 years)**

Gisslinger H, et al. *Lancet Haematol.* 2020;7(3):e196-e208.

Now in contrast to that is ropeginterferon, which is a new formulation of interferon that is given every two weeks as opposed to traditional interferon dose which is once a week, and in this trial patients were selected if they had polycythemia vera and were either naïve to treatment or had been treated with hydroxyurea for less than three years. In this study, patients were randomized to ropeginterferon or hydroxyurea.

Complete Hematologic Response

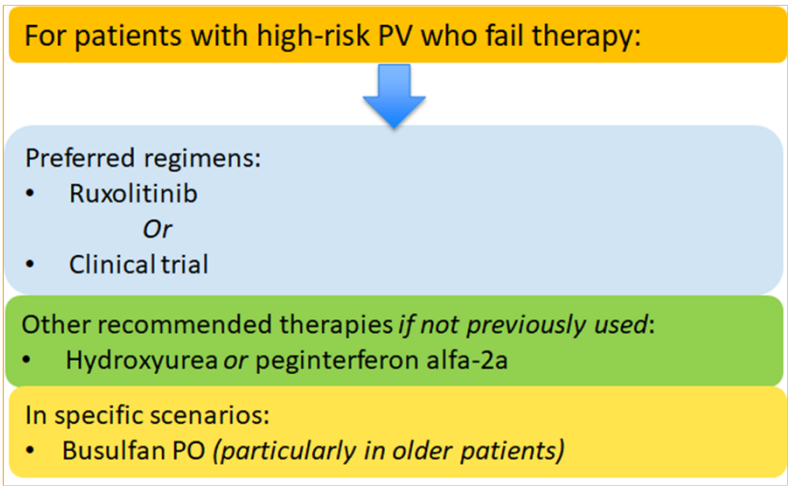


Study Month	Responder/N	Responder %	Responder/N	Responder %	P-value	RR [95% CI] (AOP2014/Control)
	Ropeg (N=95)		Control (N=76)			
MONTH 12 (EOT in PR)	59/95	62.1	57/76	75.0	0.1201	0.85 [0.70-1.04]
MONTH 24	67/95	70.5	33/67	49.3	0.0111	1.42 [1.08-1.87]
MONTH 36	67/95	70.5	38/74	51.4	0.0122	1.38 [1.07-1.79]

Gisslinger H, et al. *Lancet Haematol.* 2020;7(3):e196-e208.

Interestingly, if we look at the data, we have hydroxyurea in green and ropeginterferon in red, if we look at the proportion of patients who had a hematologic response, this is not a bone marrow response but this is a hematologic response, at 12 months there was no difference between either treatment arms, which is very much consistent with the MPN-RC 112 study. However, with further duration of therapy and looking at it at 36 months, we see that the curves actually do flip and there becomes a statistical advantage for ropeginterferon. So based on these data, this drug was actually approved by the European Union last year. It remains to be seen when and if the drug will be approved in the United States and so it is not currently standard treatment that we can offer in the United States.

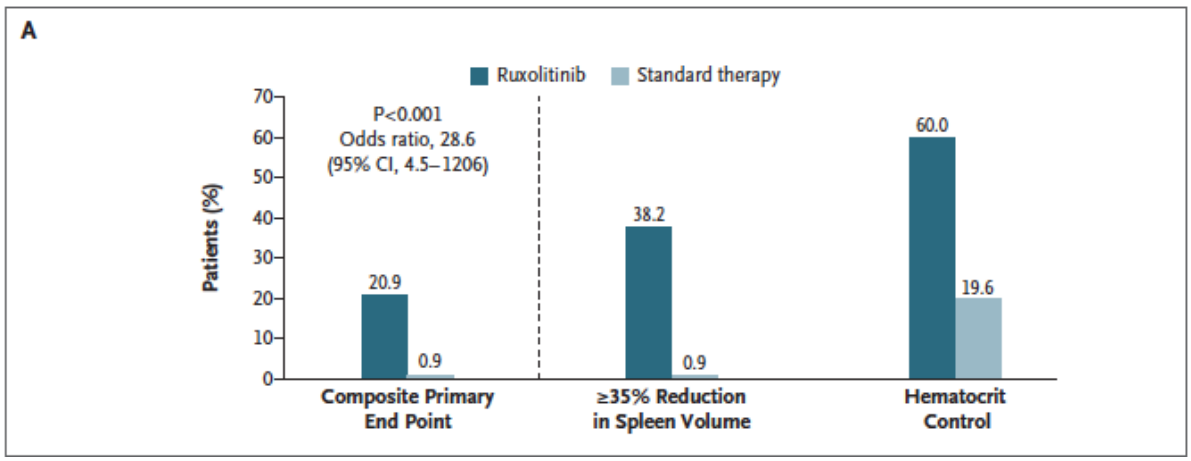
Approach to High-risk PV with Inadequate Response to Therapy or Intolerance to Therapy



National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Myeloproliferative neoplasms. Version I.2020—May 21, 2020.

What about patients who fail therapy, people who are high risk but have been treated and do not respond to therapy or have toxicity that is unacceptable from their therapy? If they start with interferon they can be switched to hydroxyurea, if they started on hydroxyurea they can be switched to interferon, but more recently in the last several years JAK inhibitors, principally ruxolitinib has been studied in this space.

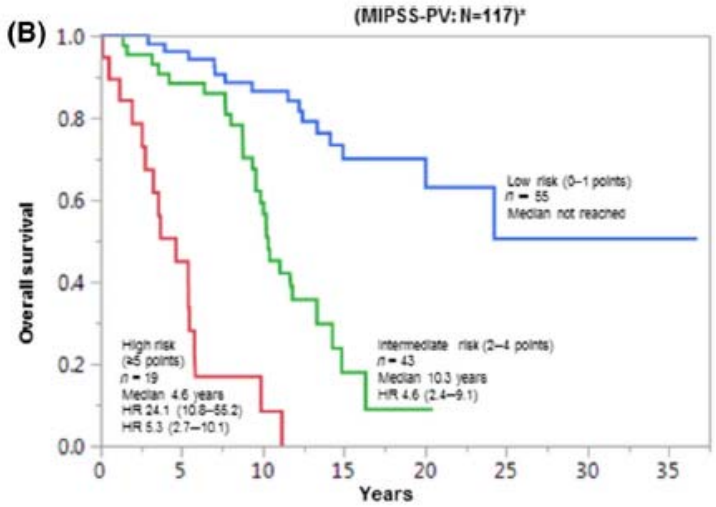
Ruxolitinib vs Best Available Therapy



Vannucchi AM, et al. *N Engl J Med.* 2015;372(5):426-435.

In randomized phase III trial when ruxolitinib was compared to best available therapy in patients who are resistant or intolerant to hydroxyurea, there was superiority in terms of spleen size reduction and hematocrit control observed with ruxolitinib. So based on these findings, ruxolitinib has been approved as a second-line agent to treat polycythemia vera patients who are resistant or intolerant to hydroxyurea.

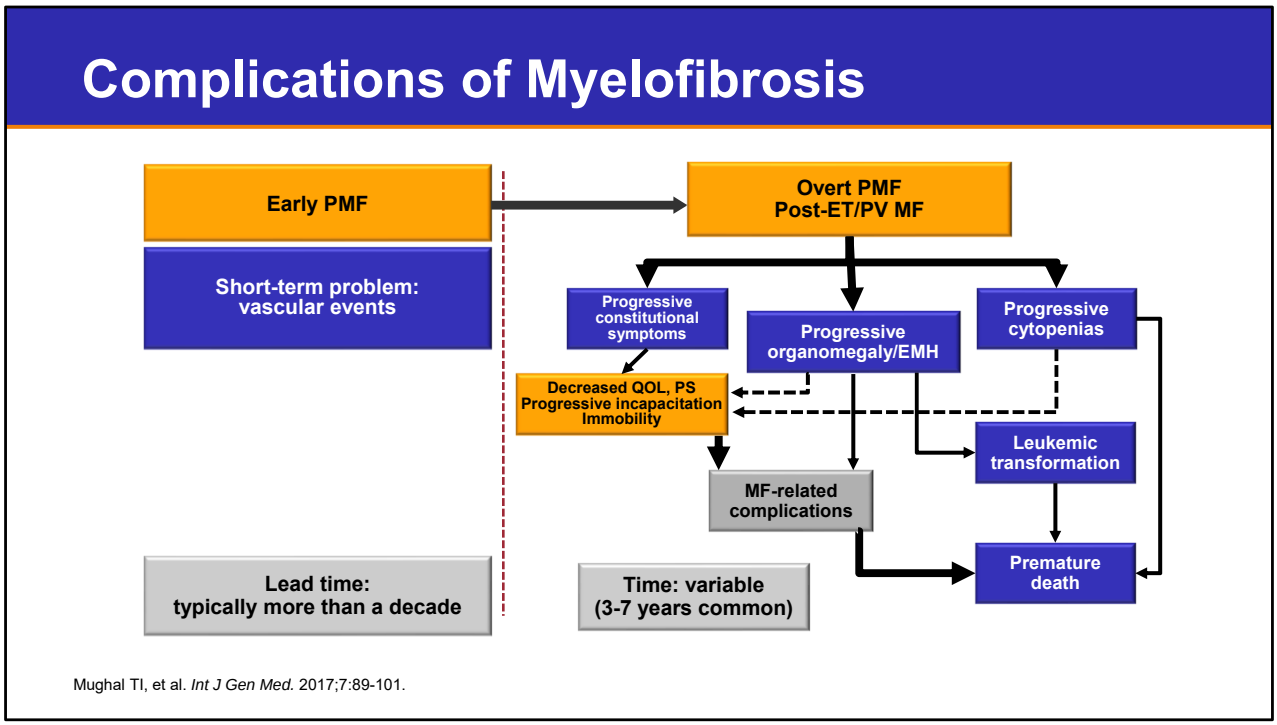
MIPSS-PV



- *SRSF2* mutation
- Abnormal karyotype
- Age >67
- Leukocyte count ≥15 x10^9/L

Tefferi A, et al. *Br J Haematol.* 2020;189(2):291-302.

Finally, with regard to the risk of progression to myelofibrosis or acute leukemia, recent work has started to integrate molecular profiling to try to determine who are the patients who are most at risk of disease progression. A recently published paper from the Mayo Clinic group has identified SRSF2 mutations. SRSF2 is a splicing factor, as a key factor that seems to be associated with an increased risk of disease progression. These findings need to be validated of course in a larger cohort.



Let's switch gears now to myelofibrosis, which I think is a little bit more of a complicated topic because the stratification is not so simple, that is, I think in part because the disease manifestations are multiple. Patients can have progressive symptoms, constitutional symptoms namely, patients can have progressive organomegaly, and they can have progressive cytopenias, and ultimately, they can transform to acute leukemia. So, how we approach the patient is really much individualized based on what their symptom or issue is

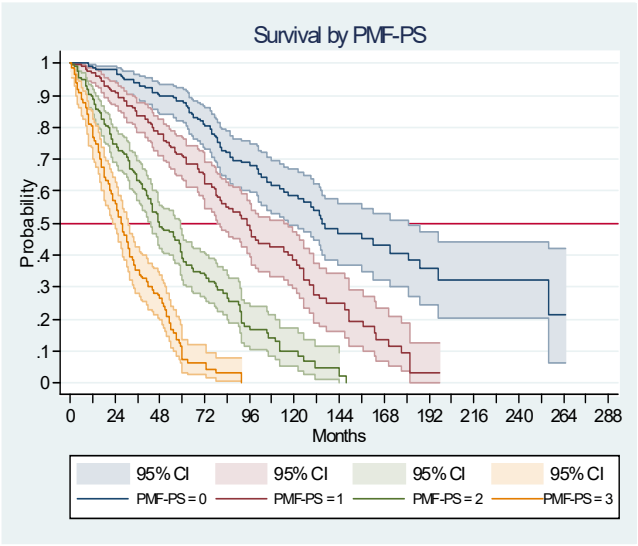
International Prognostic Scoring System (IPSS)

Prognostic

- Age >65 years
- Constitutional symptoms
- Hb <10 g/dL
- Leukocytes >25 x 10^9/L
- Blood blasts ≥1%

Risk groups

• Low	0
• Intermediate-1	1
• Intermediate-2	2
• High	≥3



Cervantes F, et al. *Blood.* 2009;113(13):2895-2901.

At the outset of diagnosis, we can use the International Prognostic Scoring System which incorporates a number of clinical factors including the age, the presence of constitutional symptoms, anemia, leukocytosis, and a peripheral blasts to stratify patients in terms of their expected survival.

Dynamic International Prognostic Scoring System (DIPSS): Survival by Risk Group

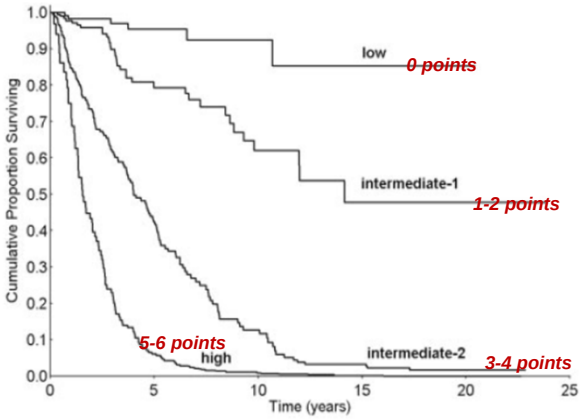


Table 3. DIPSS for survival in primary myelofibrosis

	Value		
Prognostic variable	**0**	**1**	**2**
Age, y	≤ 65	> 65	
White blood cell count, $\times 10^9$/L	≤ 25	> 25	
Hemoglobin, g/dL	≥ 10		< 10
Peripheral blood blast, %	< 1	≥ 1	
Constitutional symptoms, Y/N	N	Y	

The risk category is obtained adding up the values of each prognostic variable. Risk categories are defined as low: 0; intermediate-1: 1 or 2; intermediate-2: 3 or 4; and high: 5 or 6.

DIPSS indicates Dynamic International Prognostic Scoring System.

- Dynamic International Prognostic Scoring System-PLUS (DIPSS-PLUS): takes into account transfusion requirements, platelet count, and karyotype

Passamonti F, et al. *Blood.* 2010;115(9):1703-1708.; Gangat N, et al. *J Clin Oncol.* 2011;29:392-397.

Throughout the duration of their disease we used the Dynamic International Prognostic Scoring System which largely uses the same criteria. There is also the Dynamic International Prognostic Scoring System-Plus which takes into account transfusion requirements and platelet counts as well as karyotype.

Mutations with Prognostic Significance in MPNs

Mutated Gene	Primary Myelofibrosis (PMF)
JAK2V617F	Intermediate prognosis and higher risk of thrombosis compared to patients with *CALR* mutation[1]
MPLW515L/K	Intermediate prognosis and higher risk of thrombosis compared to patients with *CALR* mutation[1]
CALR	Improved survival compared to *JAK2* mutation and "triple-negative" PMF[1-4] Lower risk of thrombosis compared to *JAK2* mutation[1]
CALR Type 1/Type 1-like	Improved overall survival compared to *CALR* type 2/type 2-like and *JAK2* V617F mutation[5-8]
"Triple Negative" (non-mutated *JAK2, MPL, and CALR*)	Inferior leukemia-free survival compared to patients with *JAK2*- and/or *CALR*-mutated PMF[1-3] Inferior overall survival compared to patients with *CALR*-mutated PMF[2]
ASXL1	Independently associated with inferior overall survival* and leukemia-free survival[9]
EZH2	Independently associated with inferior overall survival[9]
IDH1/2	Independently associated with inferior leukemia-free survival[9]
SRSF2	Independently associated with inferior overall survival and leukemia-free survival[9]
Combined *CALR and ASXL1* status	Survival longest for *CALR*(+)*ASXL1*(-) patients (median 10.4 years) and shortest in *CALR*(-)*ASXL1*(+) patients (median 2.3 years)**[10] Intermediate survival (median 5.8 years) for *CALR*(+)*ASXL1*(+) or *CALR*(-)*ASXL1*(-) patients[10]
TP53	Associated with leukemic transformation[11]

Now, as I talked about the beginning of the talk, we know that mutations do play a role in myelofibrosis in terms of the risk of progression, and there are principally four mutations that we know of that are associated with an increased risk of disease progression and transformation to acute leukemia. These are ASXL1, EZH2, IDH1 and 2 and SRSF2. There are other mutations that are emerging like Ras pathway mutations that seem to also have similar implications.

MIPSS70-plus Risk Score

Variables Associated with Reduced OS

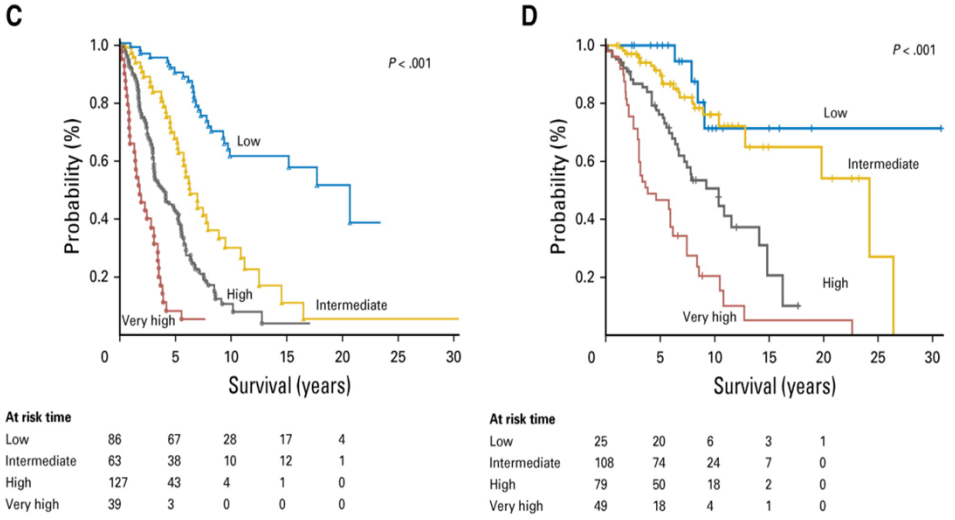
Variables	HR (95% CI)	*P*	Weighted value
Hb <100 g/L	1.5 (1.1-2.0)	.005	**1**
PB blasts ≥2%	1.6 (1.2-2.3)	.002	**1**
Constitutional Symptoms	1.9 (1.4-2.5)	<0.001	**1**
Absence *CALR* Type1	2.4 (1.7-3.5)	<.001	**2**
HMR*	1.8 (1.3-2.5)	<.001	**1**
≥2 HMR mutations	2.4 (1.4-4.0)	<0.001	**2**
Unfavorable Karyotype**	3.1 (2.3-4.3)	<.001	**3**

*Any mutation in: *ASXL1*, *EZH2*, *SRSF2*, *IDH1/2*
**Any abnormal karyotype other than normal karyotype or sole abnormalities of 20q-, 13q-, +9, chr. 1 translocation/duplication, -Y, or sex chromosome abnormality other than -Y.

Guglielmelli P, et al. *J Clin Oncol.* 2018;36(4):310-318.

But these four mutations were used in development of a risk scoring system called the MIPPS70 which incorporates clinical factors, as you can see here, but also the presence of high molecular risk mutations, HMR, as demonstrated here. Also the presence of high molecular risk mutations HMR as demonstrated here and the presence of those mutations or more than one of those mutations have prognostic implications for patients.

MIPSS70-plus Risk Score



At risk time					
Low	86	67	28	17	4
Intermediate	63	38	10	12	1
High	127	43	4	1	0
Very high	39	3	0	0	0

At risk time					
Low	25	20	6	3	1
Intermediate	108	74	24	7	0
High	79	50	18	2	0
Very high	49	18	4	1	0

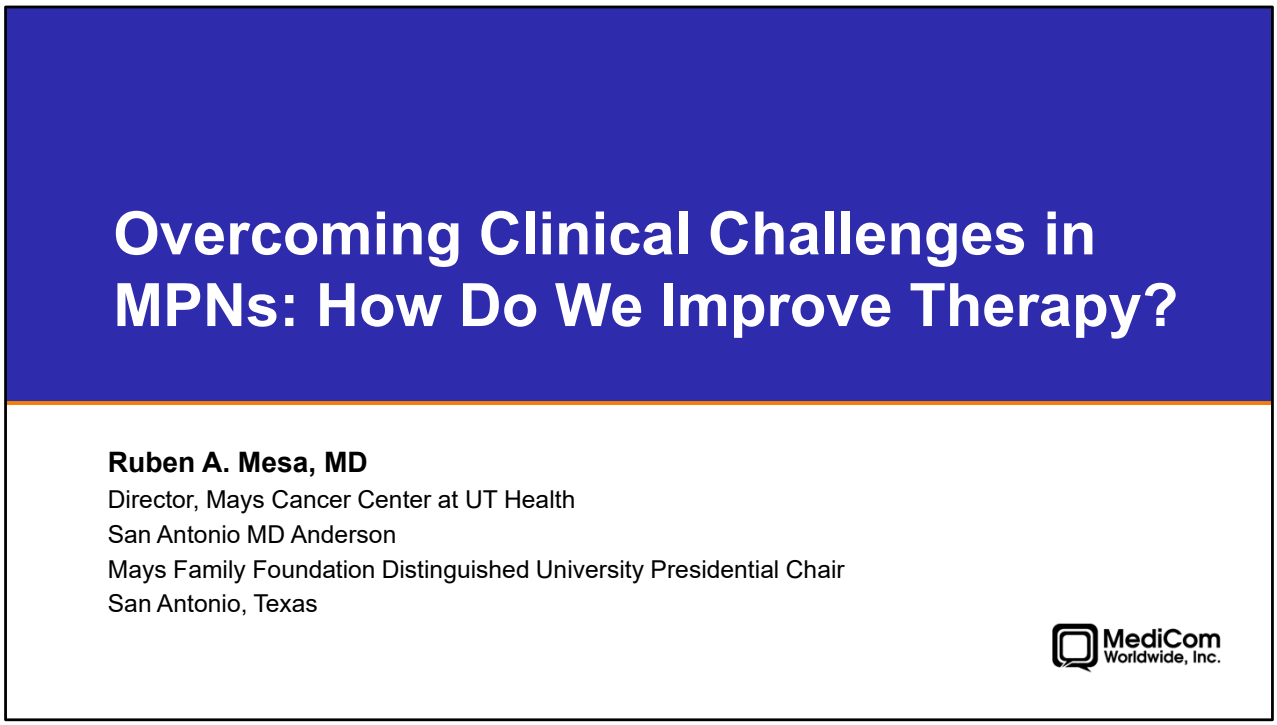
Guglielmelli P, et al. *J Clin Oncol.* 2018;36(4):310-318.

If we look at the incorporation of all of these variables, we see that in this scoring system there is a clear stratification between patients with low-risk disease and those with intermediate- or high-risk or very high-risk disease. Now, it is important to recognize that this does not tell us how to treat the patient, rather it tells us what is the likelihood of the disease progressing, and the major implication may be for timing of allogeneic stem cell transplant. It may be reasonable to defer referral for an allogeneic stem cell transplant for a low-risk patient; however, a patient with high-risk or very high-risk disease likely warrants referral to a transplant specialist.

Clinical Needs-oriented Therapy for MF

Clinical Issue	Treatments	
Anemia	▪ ESAs ▪ Danazol ▪ Corticosteroids	▪ Thalidomide, lenalidomide (IMiDs)
Symptomatic splenomegaly	▪ Ruxolitinib ▪ Fedratinib ▪ Hydroxyurea	▪ Cladribine, IMiDs ▪ Splenectomy
Constitutional symptoms/QoL	▪ Ruxolitinib ▪ Corticosteroids	
Extramedullary hematopoiesis	▪ Radiation therapy	
Hyperproliferative (early) disease	▪ Interferon	
Risk of thrombosis	▪ Low-dose ASA	
Accelerated/blastic phase	▪ Hypomethylating agents	
Improved survival	▪ Allogeneic HCT ▪ Ruxolitinib	

But in terms of how we actually treat MF, as I stated earlier, it really depends on what the major manifestation is. There are a variety of different treatments available for patients with anemia, for patients with enlarged spleens, ruxolitinib and fedratinib are FDA-approved and these are clear indications for their use, as well as for constitutional symptoms. For things like acceleration of disease, hypomethylating agents have been used, but ultimately in order to improve survival stem cell transplant remains our best modality. So, with that I will turn it over to Dr. Mesa.

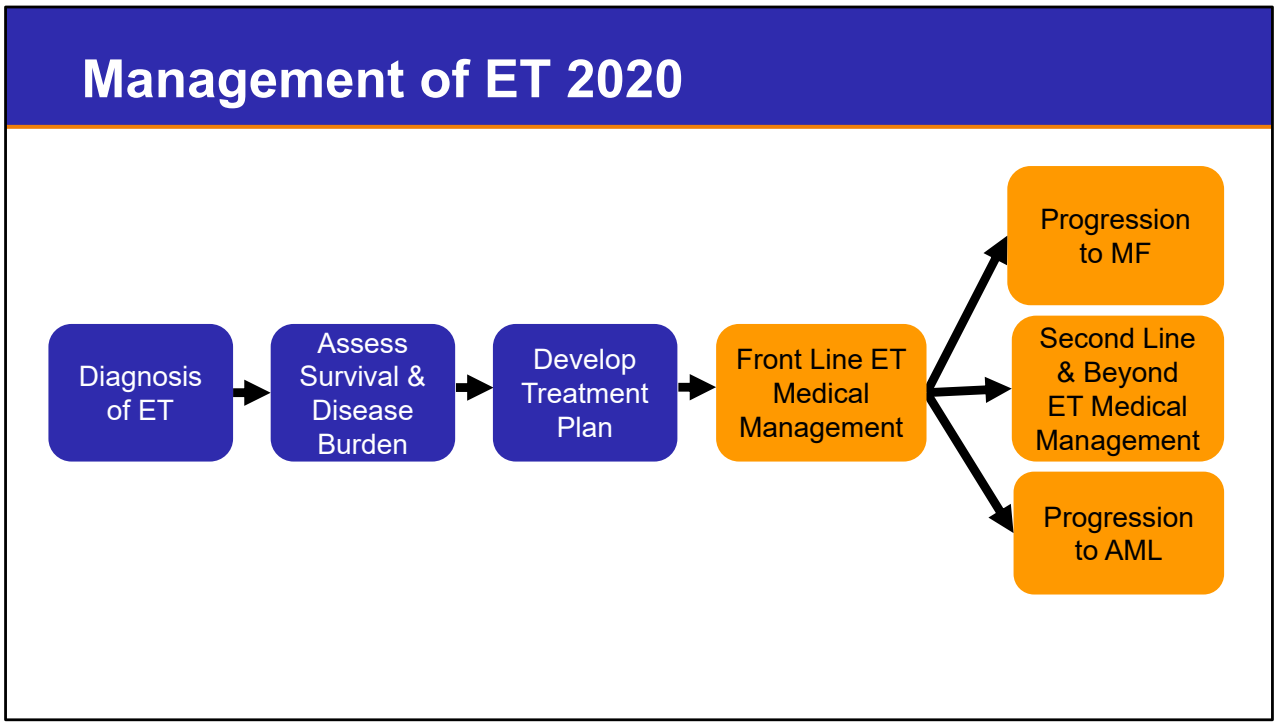


Ruben Mesa: Well, great. What a wonderful discussion, Raajit, and I am going to hopefully add to some of the issues that you've raised to try to frame where are some of our clinical challenges as a transition to we get to some of the cases to really help to discuss some of the challenges and how we overcome them.

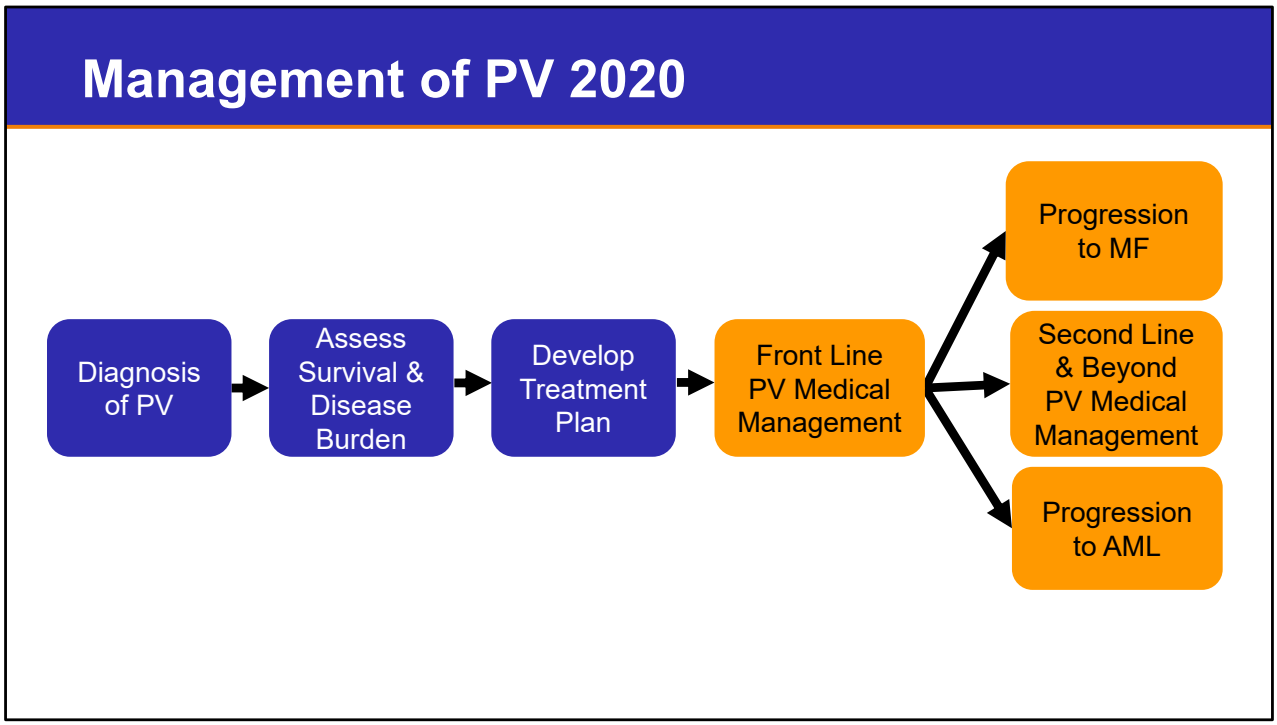
Overcoming Clinical Challenges in MPN: How Do We Improve Therapy?

- Current state
- Key current challenges
- How might new therapies change treatment guidelines?
- Key upcoming trial data

So, first what is our current state?

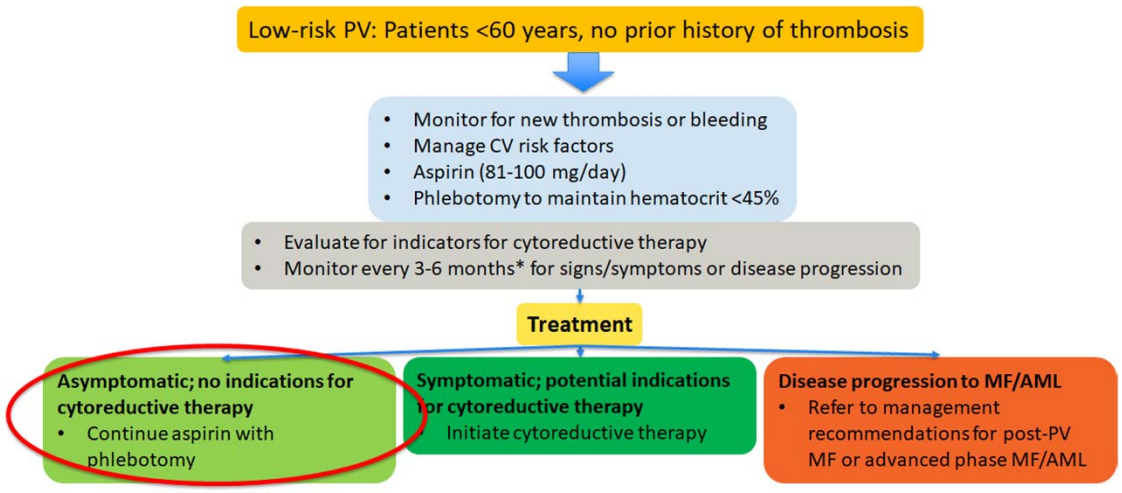


Well, as Raajit was mentioning, I like to think that each of the diseases in a bit of an algorithm. So, I approach the patient with ET in 2020, both my treatment as well as our current guidelines, an accurate diagnosis. I like to think about survival and many of our risk scores can be focused on that, but also the disease burden. Developing a treatment plan, frontline medical management, which with ET is now likely hydroxyurea in terms of cytoreduction, aspirin, perhaps interferon. These individuals may progress to myelofibrosis. We may consider second-line or clinical trials or rarely progression to acute leukemia, although usually they would first go through myelofibrosis.



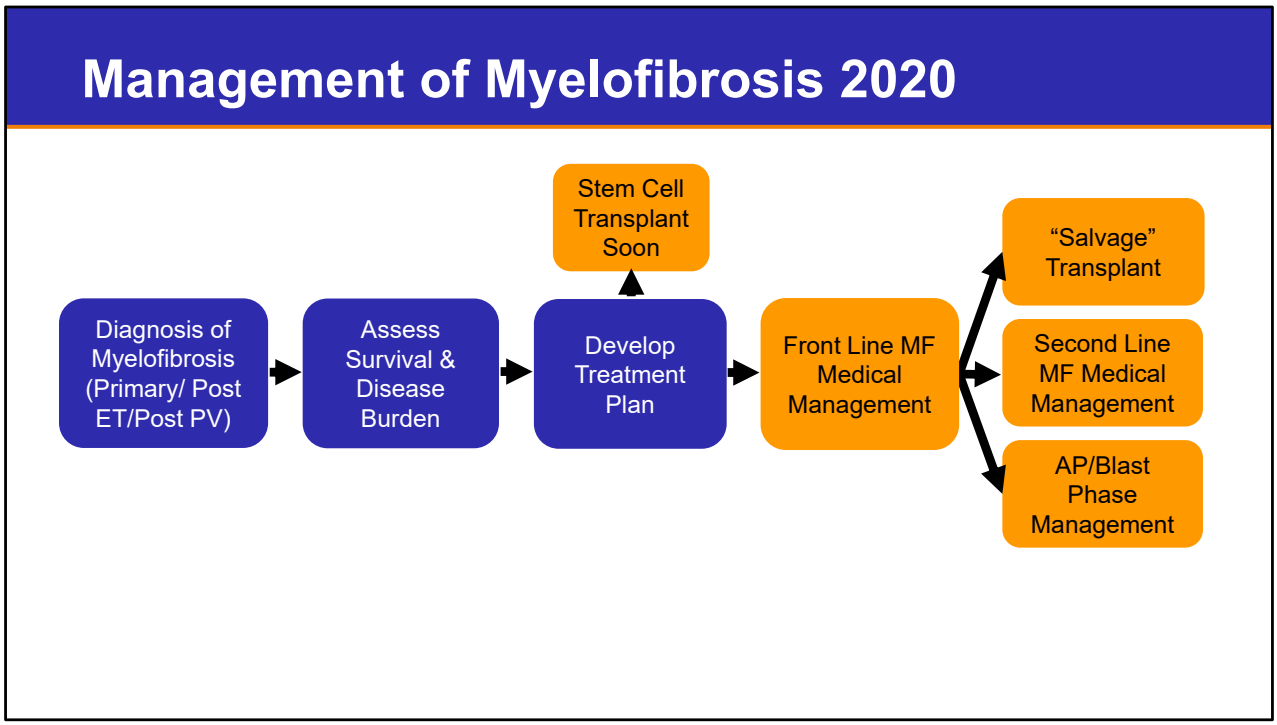
Now, with polycythemia vera, a very similar pathway, although we clearly include in that frontline piece, control of hematocrit whether that be through phlebotomy, and then the use of cytoreductive therapies. Here, I think is more clear that interferon is at least as good as hydroxyurea, if not better. Again, much discussion regarding that piece. These patients can progress, our second-line therapy, including ruxolitinib and JAK inhibition, and again, the comment on acute leukemia.

NCCN Guidelines Version I.2020: Low-Risk PV



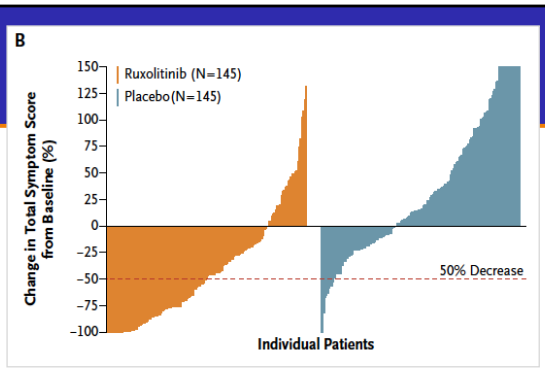
National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Myeloproliferative neoplasms. NCCN Evidence Blocks™. Version I.2020—June 26, 2020.

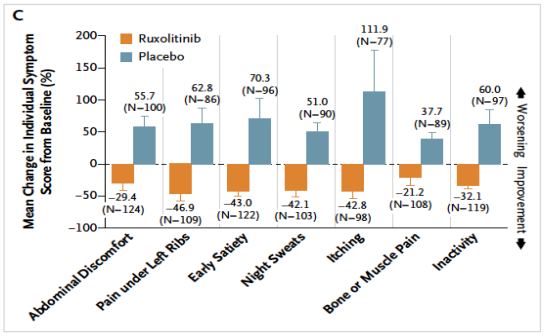
From this, we looked to see what that looks like in terms of our treatment algorithms by our NCCN Guidelines. It really calls into the need for the clinician to first stratify risk, manage cardiovascular risk factors, utilize aspirin, control phlebotomy, a very holistic approach, monitoring for the adequacy of that control, and here is the unmet gap in many individuals, the identification that that is inadequate, whether that be through new events, persistent need for phlebotomies, splenomegaly, symptomatic thrombocytosis, progressive features, and then initiate your cytoreductive therapy or clearly if they have progressed, to follow that algorithm.

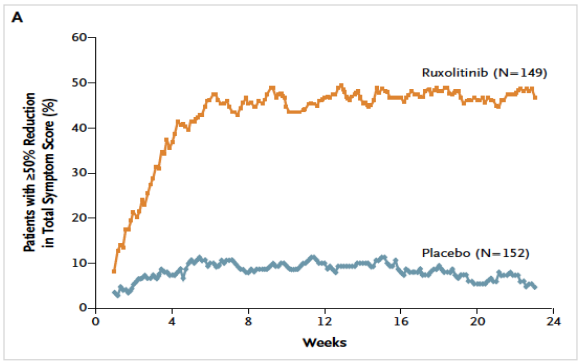


Now, for patients with myelofibrosis, the treatment algorithm is a bit more complex. We need that accurate diagnosis and an unmet gap is frequently not recognition early enough of progression from ET or PV to MF. Survival assessment, those risk scores that Raajit nicely covered, but that; really an assessment of disease burden, developing your treatment plan, and then deciding do they progressed to stem cell transplant? Is that sooner or later? Our frontline medical management, which now includes ruxolitinib and potentially fedratinib, and then if they went to medical therapy, which occurs in the majority, if they progress should we circle back to the transplant, do we move on to alternative second-line therapy, or if they progress do we move along the path of therapy for acute leukemia?

Ruxolitinib Phase 3 MF
(COMFORT I: Symptom Response)







Verstovsek S, et al. *N Engl J Med.* 2012;366(9):799-807.

Now, this algorithm is heavily driven by the important contribution that ruxolitinib played to the therapy of myelofibrosis, with its approval now almost 10 years ago, based on the COMFORT trials which clearly demonstrated improvement in splenomegaly and symptoms compared to placebo and best alternative therapy.

Treatment for Lower-risk Myelofibrosis

- Assess patients with lower-risk MF with the MPN-SAF TSS or MPN-10
- Treatment recommendations:

Asymptomatic Patients

a. Treatment options
   i. Observation
   ii. Clinical trial
b. Monitoring every 3-6 months for signs and symptoms of disease progression
   i. Patients who remain asymptomatic: Observation or clinical trial, and monitoring as above
   ii. Patients who become symptomatic: See recommendations for symptomatic patients

Symptomatic Patients

a. Treatment options
   i. Clinical trial
   ii. Observation
   iii. Ruxolitinib (in specific situations)
   iv. Peginterferon alfa-2a
   v. Hydroxyurea (when cytoreduction would ameliorate symptoms)
b. Monitoring every 3-6 months for response and signs and symptoms of disease progression
   i. Patients responding to treatment: Continue therapy
   ii. Patients with no response or loss of response: Repeat steps a and b
   iii. Patients with disease progression: Follow recommendations for higher-risk MF

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Myeloproliferative neoplasms. NCCN Evidence Blocks™. Version I.2020—June 26, 2020.

Indeed as we look at our NCCN treatment guidelines for myelofibrosis, they similarly build off of this pathway. Now, patients have largely been stratified into lower- or higher-risk based on those survival algorithms, with symptomatic lower-risk patients being considered for medical therapy with ruxolitinib, a clinical trial, or perhaps observation. Now the important piece here is to be monitoring for the quality of that response, and if so, to either continue or seek an alternative approach.

Overcoming Clinical Challenges in MPN: How Do We Improve Therapy?

- Current state
- Key current challenges
- How might new therapies change treatment guidelines?
- Key upcoming trial data

Now, there remain several current key challenges and gaps.

Treatment Gaps: ET

1. What is the optimal front-line therapy for ET?
2. How do we prevent disease progression?
3. What is the role of JAK inhibition?

For ET, I would say that there still is a question, what is that optimal frontline therapy? Is that hydroxyurea? Is that interferon? How do we prevent disease progression? An important goal that we largely do not discuss because we lack good surrogate markers, and what is the role of JAK inhibition in ET? Is it second-line, is it third-line? It is still not fully defined.

Treatment Gaps: PV

1. What is the optimal front-line therapy for PV?
2. How do we prevent disease progression?
3. How early should we consider JAK inhibition?

In PV, this remained a key question, should all patients start on interferon, or hydrea, or should we be considering JAK inhibition earlier in this algorithm? And similarly, how do we prevent disease progression?

ELN Provides Guidelines to Define HU Resistance/Intolerance

Guidelines published by the ELN and IWG-MRT define HU resistance and intolerance[1]

- However, a dosage of ≥2 g/d does not reflect the tolerability of HU use in clinical practice[1-3]
- Therefore, existing guidelines may fail to capture all patients poorly served by HU[1-3]

HU resistance is defined as any one of the following criteria[1]

Need for phlebotomy to keep HCT <45%*

or

Uncontrolled myeloproliferation (ie, platelet count >400 × 10^9/L and WBC count >10 X10^9/L*)

or

Failure to reduce massive splenomegaly by >50% as measured by palpation

or

Failure to completely relieve symptoms related to splenomegaly*

HU intolerance is defined as any one of the following criteria[1]

Absolute neutrophil count <1.0 × 10^9/L *or* platelet count <100 × 10^9/L *or* hemoglobin <10 g/dL at the lowest dose of HU required to achieve complete *or* partial clinico hematologic response

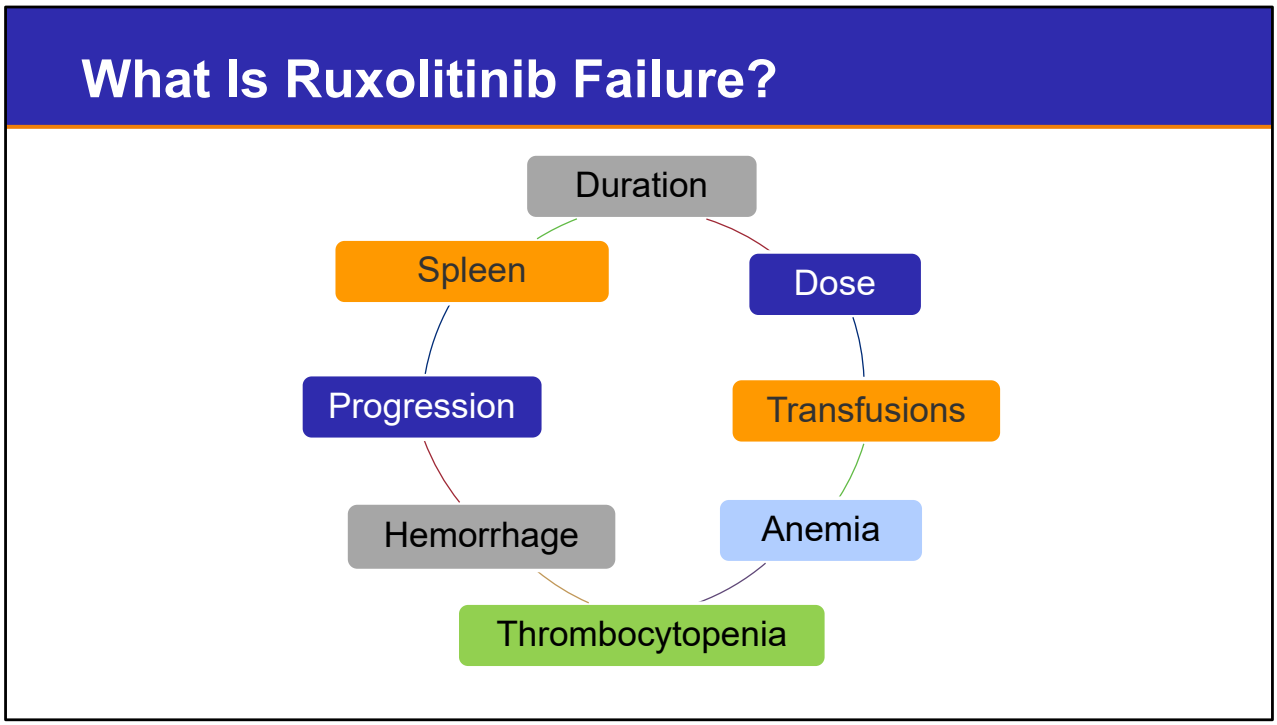
or

Presence of leg ulcers or other unacceptable HU-related non-hematologic toxicities such as mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis, or fever at any dose of HU

*After 3 months of ≥2 g/d of HU.

1. Barbui T, et al. *J Clin Oncol*. 2011;29:761-770. 2. Stein L, et al. *Ann Hematol.* 2014;93:1965-1976. 3. Data on file. Novartis Pharmaceuticals.

We know that with polycythemia vera we, similarly, have the challenge of hydroxyurea failure, and I would say that there are many patients in the United States, in my estimation, who have failed hydrea yet remain on the drug. They are on suboptimal doses, they have inadequate control of the disease, they do not feel well, or they have overt toxicity and there frequently has been a delay in changing them to a second-line therapy with ruxolitinib or even considering moving them to pegylated interferon.



Now, in myelofibrosis, without question, one of the greatest gaps is what to do after ruxolitinib? Now, up to this point in time prior to the approval of fedratinib, we had really no options outside of a clinical trial for initiating second-line therapy. Indeed, one even defined ruxolitinib failure, is difficult to state because it is a continuous variable. Is it based on suboptimal spleen response, if so, what number? What about bleeding or complications or cytopenias? Have they had an adequate dose? Indeed defining failure is a complex topic.

Overcoming Clinical Challenges in MPN: How Do We Improve Therapy?

- Current state
- Key current challenges
- How might new therapies change treatment guidelines?
- Key upcoming trial data

Now, how might our new therapies change our treatment guidelines?

Treatment for Higher-risk Myelofibrosis

	Treatment Recommendation
Transplant candidate	• Allogeneic HCT
Not a transplant candidate with symptomatic anemia only	• Refer to management recommendations for MF-associated anemia **? Luspatercept** **? Momelotinib**
Not a transplant candidate	• Assess symptom burden with the MPN-SAF TSS or MPN10 • If platelets <50 x 10^9/L: o Therapy: Clinical trial **? Pacritinib** • If platelets ≥50 x 10^9/L: o Therapy: Ruxolitinib, fedratinib, or clinical trial **? CPI-0610** o Monitor every 3-6 months for response and signs/symptoms of disease progression ▪ If response: Continue therapy and monitor as above ▪ If no response or loss of response: Fedratinib (if prior ruxolitinib) ▪ If disease progression: Refer to management recommendations for advanced-stage MF/AML

Other JAKi
CPI0610
IMG-7289
Rux combo?

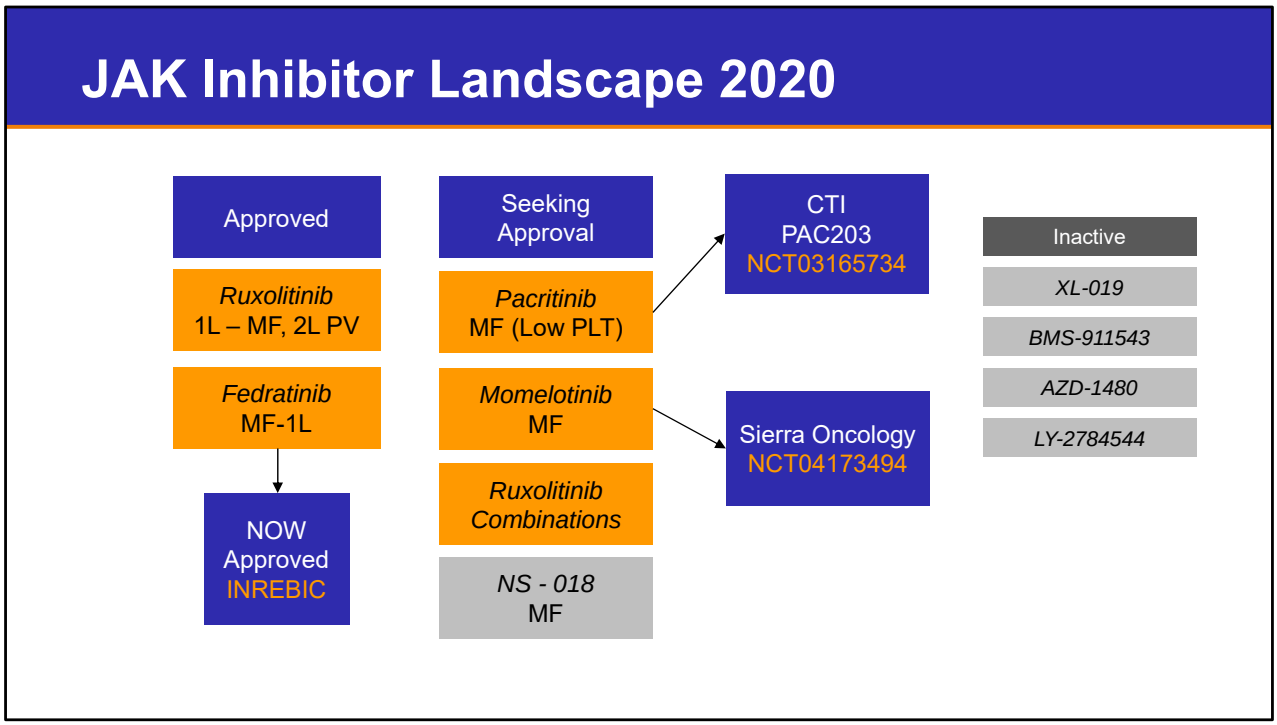
National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Myeloproliferative neoplasms. NCCN Evidence Blocks™. Version I.2020—June 26, 2020.

I have superimposed upon the higher-risk where our new therapies may come into play. You see in green the fedratinib now is an option in our higher-risk patients that have an adequate platelet count, that it has an approval in frontline in parallel with fedratinib. Now if we go across this slide, one, we know of therapies in development such as luspatercept, which is approved now in MDS and hemoglobinopathies, may play a role in aiding MF-associated anemia or the JAK inhibitor momelotinib. We know that the BET inhibitor CPI 610 might play a role in either the frontline in combination or in second line. Other second-line therapies including the LST1 inhibitor-Rux combinations or other JAK inhibitors may play a role. Pacritinib, the JAK inhibitor that is safe in individuals with thrombocytopenia, might have a frontline indication for that group.

Overcoming Clinical Challenges in MPN: How Do We Improve Therapy?

- Current state
- Key current challenges
- How might new therapies change treatment guidelines?
- Key upcoming trial data

And what about new data upcoming?



Indeed there are many important studies ongoing, including registration studies that build on the evidence for pacritinib and momelotinib, and we hope to see those data in the near future that may well lead to approvals.

Myeloproliferative Neoplasms:
Integrating New Therapies Into Challenging Case Scenarios

Selected Novel Agents/Targets Being Developed in MPN Particularly MF

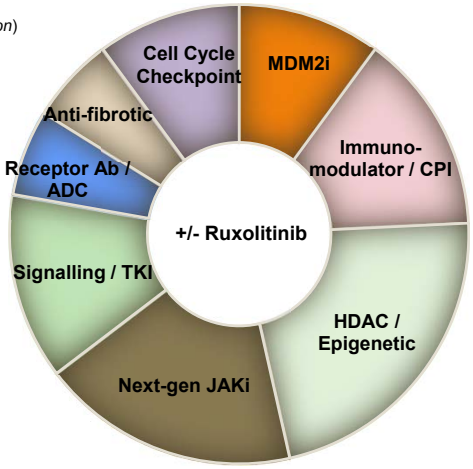
Cell-cycle Checkpoint
- P2 Imetelstat | Telomerase Inhibitor (*Geron*)
- P1 Alisertib | Aurora Kinase Inhibitor (*Takeda*)

Anti-fibrotic
- P2 PRM-151 | Pentraxin-2 (*Promedior*)

Receptor Ab / ADC
- P2 SL-401 | CD123-toxin (*Stemline*)

Signaling / TKI
- P2 Glasdegib | Hedgehog (*Pfizer*)
- P2 Sonidegib | Hedgehog (*Sun*)
- P2 INCB'465 | PI3Ki (*Incyte*)
- P2 LCL1 I SMAC/IAP (Novartis)

Next-gen JAKi
- P3 Fedratinib | JAK2 (*Celgene*)
- P3 Pacritinib | JAK2/FLT3 (*CTI Bio*)
- P3 Momelotinib | JAK2/1/ACVR1 (*Sierra*)
- P2 Itacitinib | JAK1 (*Incyte*)



Apoptosis/MDM2/BCL
- P1 KRT-232 (*Kartos Therapeutics*)
- P2 Idasanutlin / RG7388 (*Roche*)
- P1 Navitoclax | BCL2 inhibition (*Abbvie*)

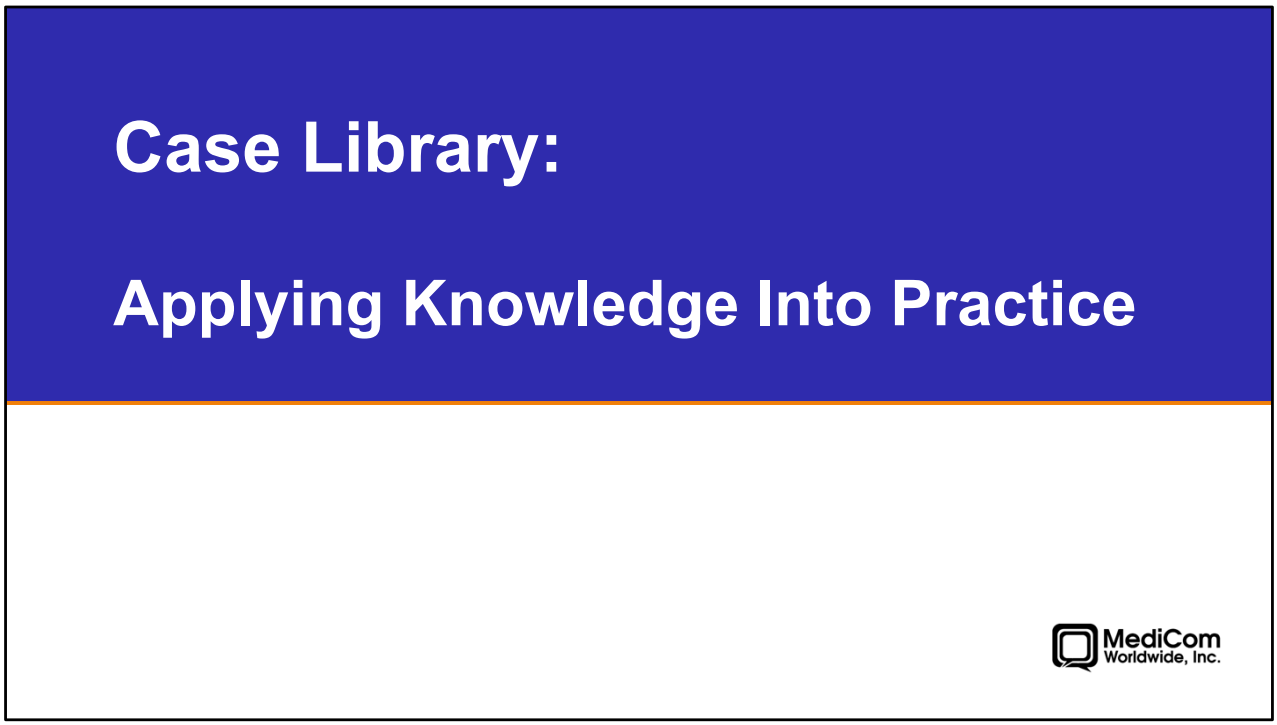
Immuno-modulator / CPI
- P3 Pegasys | IFN-α2a (ESR/Roche)
- P3 Ropeg-IFN-α2b (*PharmaEssentia*)
- P2 Nivolumab / Pembrolizumab | PD-1 (*BMS/ MRK*)

HDAC / Epigenetic
- P3 Azacytidine | HMA (*ESR/Celgene*)
- P3 Panobinostat | HDAC (*Novartis*)
- P2 Givinostat I HDAC (Italfama)
- P2 IMG-7289 | LSD1 (*Imago*)
- P1 CPI-0610 | BETi (*Constellation*)
- P1 PU-H71 | HSP90i (*Samus*)

PHASE OF DEVELOPMENT (IN MPN): P1 P2 P3

Slide Courtesy of Prof Claire Harrison

We also know that there is a very robust pipeline targeting everything from cell-cycle checkpoint, anti-fibrosing agents, signaling tyrosine kinase inhibitors, JAK inhibitors I mentioned, MDM2 inhibitors, immunomodulatory, and several epigenetic modifiers. Indeed it is a robust pipeline of many agents in that have now given us a robust clinical trial portfolio to explore.



So, many unmet gaps, many things in the pipeline, perhaps I'll hand it over back to my colleague Dr. Bose, to walk us through some cases to apply some of these principles that I have raised and that Raajit have raised.

Dr. Prithvi Bose: Thank you Ruben, thank you Raajit. Those are two really phenomenal presentations of a lot of covering, a lot of material and now as Ruben just alluded to, we will try to get him to some of the more nitty-gritties of actually applying some of these concepts in managing patients.

A 55-year-old Patient with PV Resistant to Hydroxyurea

Prithviraj Bose, MD
Associate Professor
Department of Leukemia
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

MediCom Worldwide, Inc.

So, we have three cases for you tonight. I will walk you through the first one, and we will be discussing each of these as we go along. This is a 55-year-old patient with polycythemia vera that is resistant to hydroxyurea and you heard a little bit about the concept of resistance to hydroxyurea and the definitions etc.

Case Presentation

- 55-year-old male smoker evaluated for frequent headaches, dizziness
- Hgb 20.5 g/dL, Hct 63%, WBCs 9.9 x 10^9/L, plts 380 x 10^9/L, MCV 72 fl
- *JAK2*^{V617F} detected, VAF 65%, BM c/w PV → begins phlebotomy and aspirin
- Three phlebotomies in the next 3 months, continuing headaches, dizziness, nausea → HU 1 g/d added
- Five more phlebotomies over the next 3 months → HU increased to 1.5 g/d
- Three months later, still phlebotomy dependent, c/o pruritus → HU increased to 2 g/d
- Two more phlebotomies over the next 3 months, c/o abd fullness, dysgeusia, spleen now palpable 6 cm below LCM

The case is a 55-year-old gentleman who is a smoker, who is evaluated for frequent headaches and dizziness. Hemoglobin is very high as you see here, 20.5, hematocrit 63, white count and platelets are actually normal. They are often elevated in PV but in this case they are normal. The MCV is 72. The JAK2 V617F mutation is detected, again this is found in about 95% of patients with PV. It has a fairly high variant allele fraction. You do normally see a higher VAF in PV than in ET, and the bone marrow is consistent with PV. The patient begins phlebotomy and aspirin. Note, he is younger than 60, so as Raajit described this is a lower-risk patient by age. They are not telling us if they have had a clot. So phlebotomy and aspirin is their standard management, but in the next three months he requires three phlebotomies and has continuing headaches, dizziness and nausea, and hydroxyurea is added. As Ruben showed you, the NCCN guidelines allow for certain situations in which you can add cytoreductive therapy in a low-risk patient, so this will be one example with the continuing symptoms and phlebotomy requirement, but he needs five more phlebotomies over the next three months and at this point the hydroxyurea dose is increased to three pills a day, so 1.5 g a day. The saga continuous and three months later he is still phlebotomy-dependent, and he is complaining of pruritus and at this point the hydroxyurea dose is increased to "maximum of 2 grams per day" and we will come back to that. However, this is not sufficient either and two more phlebotomies are needed over the next few months and now he is complaining of abdominal fullness. You feel his spleen, 6 cm below the left costal margin, and perhaps because of the hydrea, the high dose that he is on, he is complaining of some taste issues.

Panel Discussion

Before we go further into some of the data around this issue, let me ask both Raajit and Ruben how they would approach this patient, what their views are with this information that I have just shown you.

Ruben Mesa: Well, perhaps I can jump in, one I think it is a very typical case, so it is a good one for us to discuss. I do find in particular, although the "risk of vascular events" is still "low" because they are under the age of 60 and they have not had a vascular event. I would say this individual probably has much more risk than that might suggest, he is a smoker, he is almost 60 years of age, probably has other comorbidities that are adding to it. Additionally, he presents with a very high hematocrit and hemoglobin, which suggests to me that he likely will likely be inadequately controlled by phlebotomies alone. I think it is appropriately recognized that there is inadequate symptom control with the phlebotomies alone, which I think is more common than we recognize, and then they have given it a solid try with the hydroxyurea, but it is not uncommon just not tolerating hydroxyurea well and has more aggressive disease features. So, again, this is an individual, particularly in the setting of splenomegaly, it would be very appropriate for consideration of ruxolitinib as second-line therapy. Raajit, what do you think?

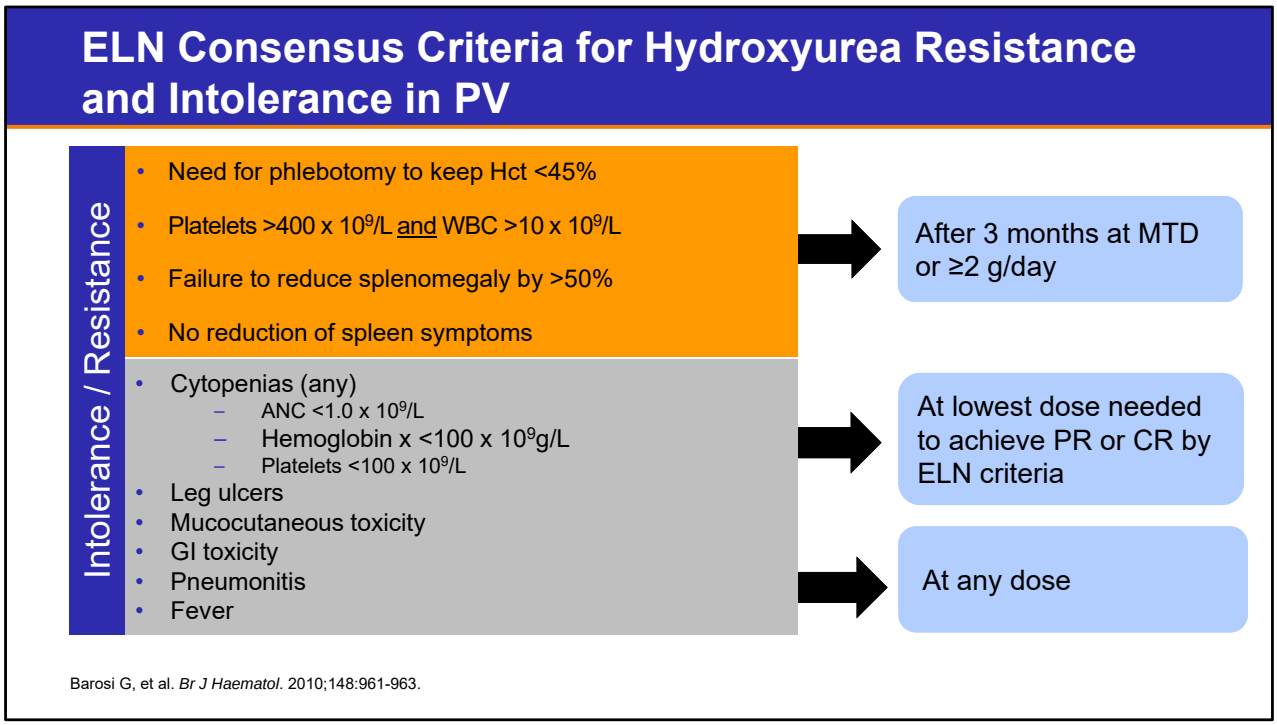
Raajit Rampal: Yeah, Ruben, I think it can make a very important point to our

audience which is that guidelines are guidelines, right? And there is nothing magic about the age of 60 as a demarcating line between the high-risk and the low-risk patient and clearly there are things in this patient's history, the smoking history for example, that are concerning for a thromboembolic event. That makes us concerned. The patient has fairly proliferative disease which is also a concern and that is not something that is taken into account of course and our stratifications, as we were talking about earlier. I think the final thing, of course, is that the disease is not being adequately controlled with the current measures and one is now approaching the point where the drugs being used to control the disease, the hydroxyurea, are becoming intolerable, so I think certainly this is a patient who very much would fit to the criteria for switch to ruxolitinib.

Prithvi Bose: What do both of you make of the phlebotomy requirement here. It seems really very frequent, right? It is more than once a month. You guys think that plays into your decision making as well?

Ruben Mesa: It does, I think frequent phlebotomies, once patients have had the first round of phlebotomies and become iron-deficient, individuals that sort of requiring a lot of phlebotomies, 1) it is a lot of time, hassle, and expense but 2) frequently are inadequately controlled. So, the fact of that still is required suggests to me we need to really move to an alternative approach. I do find that some of these individuals end up needing combination therapy as well if inadequately controlled with one agent.

Prithvi Bose: Thank you, Ruben.

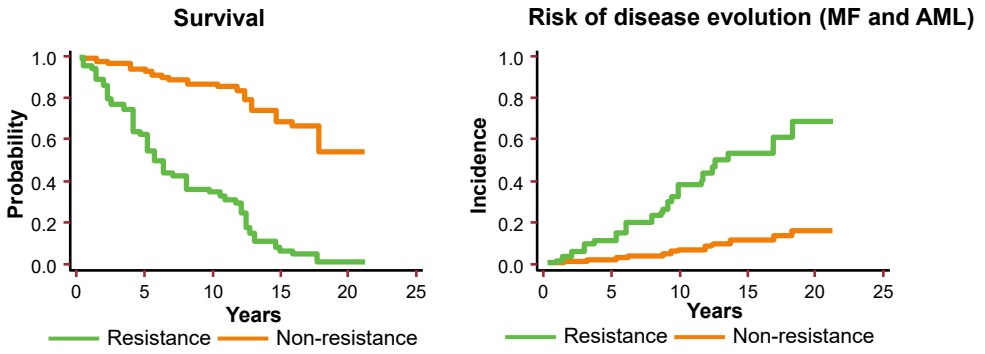


So, moving on here, we have talked about this a little bit earlier. Ruben showed you some of these. These are the formal criteria for hydroxyurea resistance or intolerance and as Raajit nicely pointed out, guidelines are guidelines. You do not always adhere to them, but this is a nice framework, so basically, I won't read through all of this, but the idea is that if you have given them a reasonable dose and duration of hydrea and you are still really not controlling the myeloproliferation, that really is resistance and the specific criteria are listed.

The other aspect of this is intolerance, so if at the lowest dose that you need to maintain remission you are having cytopenias in the white cells in the platelets, or non-heme toxicity as listed on the slide, those would be your criteria for intolerance. This is just a useful framework to remember, and also important to point out that it is not necessarily 2 grams a day for three months because many people cannot tolerate that. Some studies have shown only 6% have gotten up to that dose, but it is really the maximum tolerated dose for the patient and the non-heme toxicity frankly at any dose. The dose is not important there.

Impact of HU-Resistance on Survival and Risk of Transformation to AML/MF

261 PV patients (median follow-up 7.2 years)



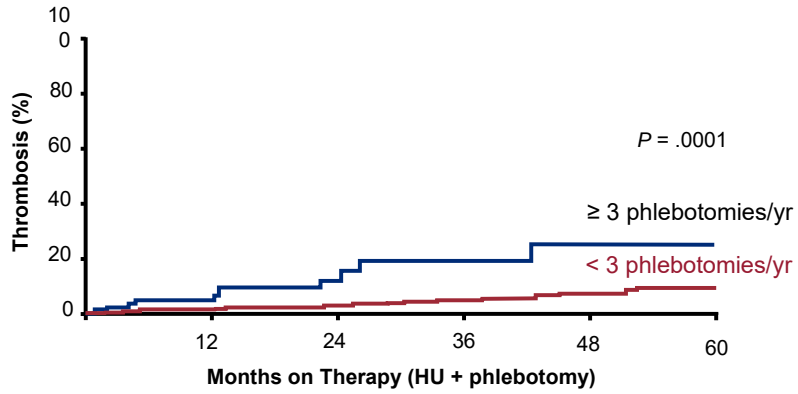
Resistance to HU was associated with a 5.6-fold increase in the risk of death

Alvarez-Larrán A, et al. *Blood*. 2012;119:1363-1369.

This is something I like to point out which is that it is actually maybe more than side effects or not controlling the counts enough or the spleen enough or needing too many phlebotomies, it is probably more serious than that. So, this slide shows you that resistant to hydroxyurea, this is not intolerance, this is resistance, is actually bad from a survival standpoint and a leukemic transformation standpoint. In fact, not shown here, there is some similar data even with intolerance, but only the specific type of intolerance in which the patients get leukopenic. Again, that is not shown here, but this is just reminding you that hydroxyurea resistance is bad from a survival standpoint.

Time to Thrombosis in PV Patients Treated With HU Requiring Ongoing Therapeutic Phlebotomy

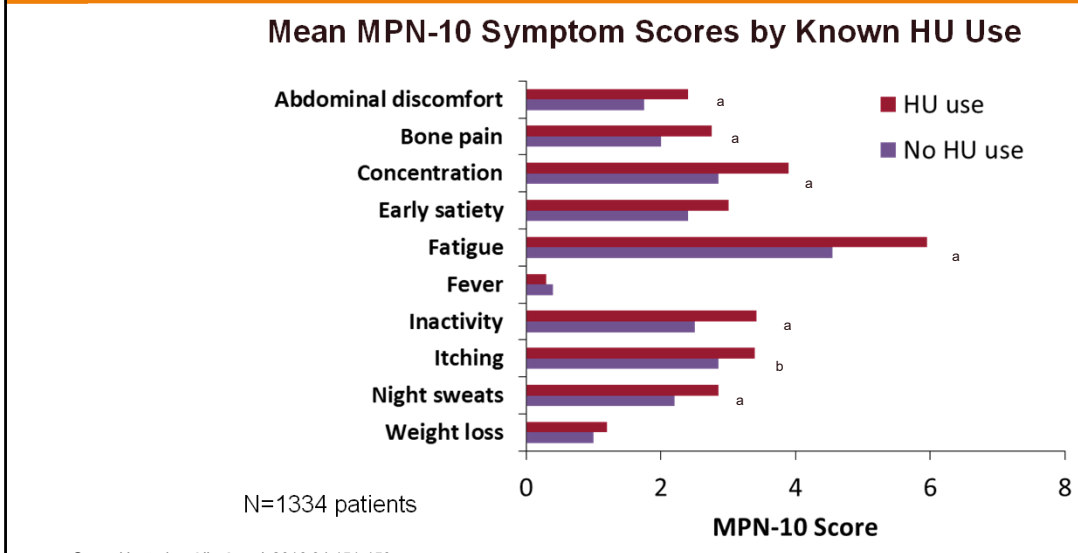
- Retrospective analysis of observational data from first 5 years of hydroxyurea + phlebotomy in patients with PV (N = 533)



Alvarez-Larrán A, et al. *Haematologica.* 2017;102:103-109.

This is what I was alluding to when I asked the question about the phlebotomies. This is something I go by in my own practice. This is data from the Spanish group showing that if you are on hydroxyurea and you are still needing three or more phlebotomies a year, you have a higher rate of thrombosis. So that is something I find practically clinically useful for my decision making when I am trying to think whether I need to switch a patient,

Symptomatic Profiles of PV Patients by HU Use: Implications of Inadequately Controlled Disease



Geyer H, et al. *J Clin Oncol*. 2016;34:151-159.

and then this is work from Ruben's group when he was at the Mayo Clinic a number of years ago showing that the symptom burden of patients on hydroxyurea is quite significant. As you see here, the patients on hydroxyurea were more symptomatic across all these different symptoms than those that were not on hydroxyurea, suggesting that hydroxyurea use is just a marker of more symptomatic disease. Obviously, you are going to use hydroxyurea primarily in high-risk patients, and this is probably a surrogate of the fact that they just have not just more proliferative disease in terms of counts and things like that, but also worse symptoms.

RESPONSE Trials: Ruxolitinib (JAK1/JAK2 Inhibitor) in Patients with PV Resistant or Intolerant to HU

	RESPONSE-2[a] (without splenomegaly) 28 wk endpoint, %		RESPONSE[b] (with splenomegaly) 32 wk endpoint, %	
Endpoint	Ruxolitinib n = 74	BAT n = 75	Ruxolitinib n = 110	BAT n = 112
HCT control	62	19	60	20
CHR	23	5	24	9
≥50% improvement in MPN-SAF TSS	45	23	49	5
Complete resolution of symptoms	50	8	N/A	N/A
≥35% reduction in spleen volume	N/A	N/A	38	1

RESPONSE: At 5 years, the probability of maintaining CHR was 55% (95% CI 51,88).[c]

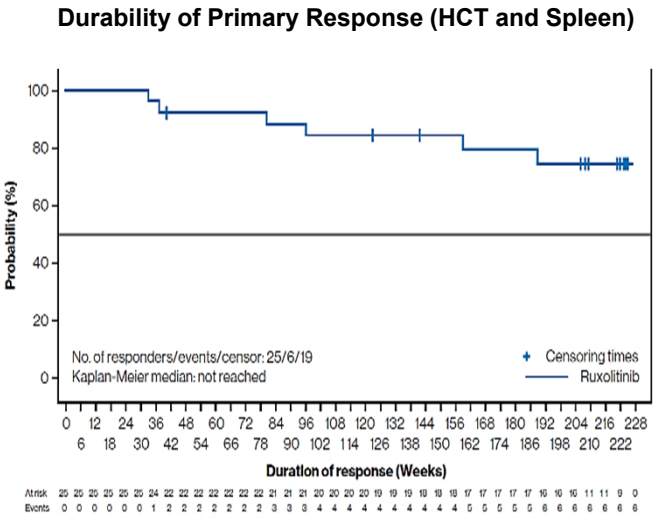
a. Passamonti F, et al. *Lancet Oncol.* 2017;18:88-99; b. Vannucchi A, et al. *N Engl J Med.* 2015;372:426-435; c. Kiladjian JJ, et al. *Lancet Haematol.* 2020;7(3):e226-e237.

Here, shows the RESPONSE trials. So, just to orient you to this slide, the RESPONSE trials again are the trials that got ruxolitinib approved back in 2014 for hydroxyurea resistant or intolerant PV. On the left actually is the RESPONSE-2 data, and on the right are the RESPONSE data. The RESPONSE trial preceded the RESPONSE-2 trial. The latter was mainly conducted in Europe. The RESPONSE trial and the RESPONSE-2 trial were very similarly designed. Hydroxyurea resistant or intolerant patients got either ruxolitinib or best available therapy, and as Ruben alluded to earlier, the best available therapy actually ended up being hydroxyurea in quite a few of these patients because frankly there is not anything very much better for those patients in that group. So, you see the numbers here strikingly similar between the two trials except of course the spleen because that was a fundamental difference in the design or the eligibility, with the response trial being conducted in patients with splenomegaly and the RESPONSE-2 trial being conducted explicitly in patients without splenomegaly. So, with that exception the other data as you see here with the hematocrit control, symptom control, complete hematologic response rates are very, very similar and clearly superior for ruxolitinib compared to the BAT arm.

Long-term Efficacy (5 Years) in RESPONSE, a Phase 3 Study of Ruxolitinib vs BAT in Patients with Hydroxyurea-Resistant/Intolerant PV

K-M estimates of response duration at 224 weeks (starting from week 32):

- Duration of **HCT control: 73%** (95% CI: 60, 83).
- Duration of **maintaining ≥35% reduction in spleen volume: 72%** (95% CI: 34, 91)



Kiladjian JJ, et al. *Lancet Haematol.* 2020;7(3):e226-e237.

And what is longevity, what is the durability of those responses? It is pretty good. So, this is the five-year follow-up of RESPONSE published this year 2020, and it shows you that the duration of hematocrit control or rather as you say the probability of hematocrit control, the probability of maintaining a spleen volume reduction, are greater than 35% were quite high, in the 70% range, and this is five years of follow-up.

Exposure-Adjusted Rates of Thromboembolic Events

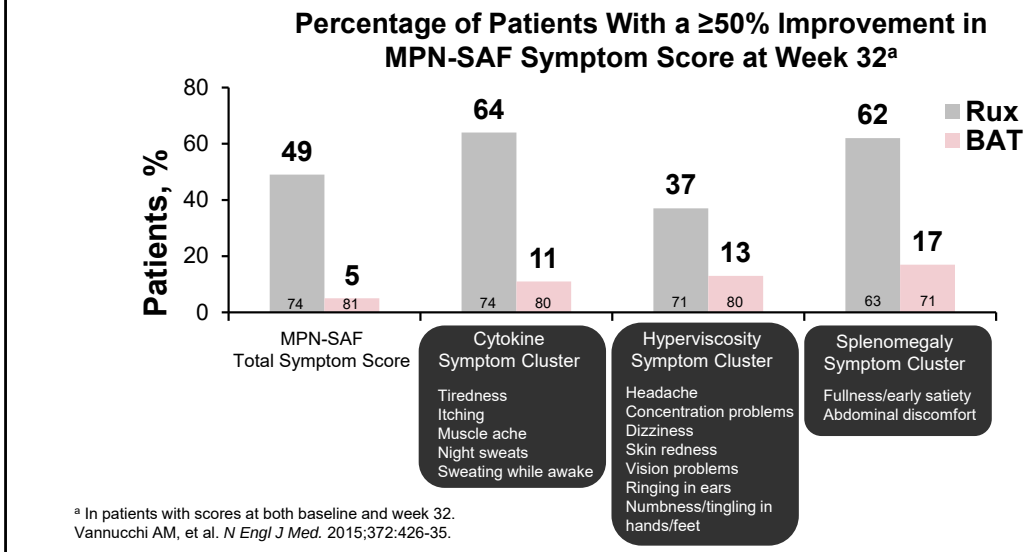
Event[a,b]	Ruxolitinib Rate per 100 Patient-Year of Exposure N = 110 Exposure = 428.4 Patient-Year		BAT Rate per 100 Patient-Year of Exposure N = 111 Exposure = 73.6 Patient-Year		Crossover Rate per 100 Patient-Year of Exposure N = 98 Exposure = 329.9 Patient-Year	
Number of Patients (Rate[b])	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
All thromboembolic events	5 (1.2)	3 (0.7)	6 (8.2)	2 (2.7)	9 (2.7)	5 (1.5)
Cerebral infarction	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ischemic stroke	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)
Transient ischemic attack	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	2 (0.6)
Portal vein thrombosis	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary embolism	1 (0.2)	1 (0.2)	1 (1.4)	1 (1.4)	0 (0.0)	0 (0.0)
Retinal vascular thrombosis	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	1 (0.3)
Acute Myocardial Infarction	0 (0.0)	0 (0.0)	1 (1.4)	1 (1.4)	0 (0.0)	0 (0.0)
Deep vein thrombosis	0 (0.0)	0 (0.0)	2 (2.7)	1 (1.4)	1 (0.3)	0 (0.0)
Thrombophlebitis	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	1 (0.3)	0 (0.0)
Thrombosis	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	1 (0.3)	0 (0.0)
Bone infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Coronary artery occlusion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Disseminated intravascular coagulation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)
Splenic infarction	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)

[a]Events occurring in ≥ 0.2% of patients in any group. MedDRA version 19.1 was used to code the events.
[b]Adjusted rates were calculated as the number of patients with events per 100 patient-year of exposure.

Adapted from Kiladjian JJ, et al. *Lancet Haematol*. 2020;7(3):e226-e237.

Now as we have been saying earlier, thrombosis prevention is the main goal of what we do in PV. This shows you here that the ruxolitinib patients, the patients randomized to ruxolitinib, had a numerically lower rate of thrombotic events; however this was not statistically significant, but clearly numerically lower, and even if you look at the cross-over patients because, as you can imagine, almost everybody crossed over, those patients too, have a much lower incidence of thrombotic events than the BAT patients.

RESPONSE: Improvement in Symptoms with Ruxolitinib



[a] In patients with scores at both baseline and week 32.
Vannucchi AM, et al. *N Engl J Med.* 2015;372:426-35.

Symptoms, so this breaks it down in a little bit more granular detail. We saw earlier that in the ruxolitinib arm about 45% to 49% of patients had that 50% improvement in the total symptom score that we always measure in MPN trials, but here this breaks it down for you a little bit more into these various clusters, again, work pioneered by Ruben and his group. Cytokine symptom-cluster, referring to tiredness, itching, night sweats, daytime sweats, muscle aches, hyperviscosity symptoms as well as the spleen-related symptoms, all of which benefited with ruxolitinib.

A 62-year-old Patient with MF Who Develops Ruxolitinib-refractory Disease

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MediCom Worldwide, Inc.

And with that we will move into MF. Ruxolitinib refractory MF to be specific and Raajit will walk us through this.

Raajit Rampal: Thank you. We are going to talk about a 62-year-old who has MF and develops ruxolitinib refractory disease.

Case Presentation

- Ms. T is a 62-year-old female with primary myelofibrosis
- Due to splenomegaly and constitutional symptoms, started on ruxolitinib 15 mg BID 2 years ago, with improvement in both
- Baseline bone marrow notable for 2/3 reticulin fibrosis
- *JAK2*, *ASXL1*, *TET2* mutations
- Deletion 20q
- Has had progressive splenomegaly over the last 3 months
- WBC: 25 K/mcL, Hgb 9.0 g/dL, Plts 250 K/mcL
- What are her treatment options?

So, Ms T is a 62-year-old female with primary myelofibrosis. Due to splenomegaly and constitutional symptoms the patient was started on ruxolitinib at a dose of 15 mg twice daily two years ago with improvement in both symptoms and spleen size. The baseline bone marrow was notable for 2 out of the 3 reticulum fibrosis. Mutations at the time of diagnosis were JAK2, ASXL1, and TET2. Patient had deletion 20q on cytogenetic studies. Now after being on therapy the patient has begun to experience progressive splenomegaly over the last three months when initially she had an improvement in her symptoms. Currently white count is 25,000, hemoglobin 9, platelets are 250,000. So, what are her treatment options?

Panel Discussion

I guess maybe we can talk about that a little bit more in terms of how you would approach this patient. I guess maybe the first question to throw out to both of you is, given the patient's profile at the beginning, the cytogenetics and the bone marrow fibrosis as well as the genetics, would you have concerns at the very front in terms of when you started treating this patient that there may be risk of failure?

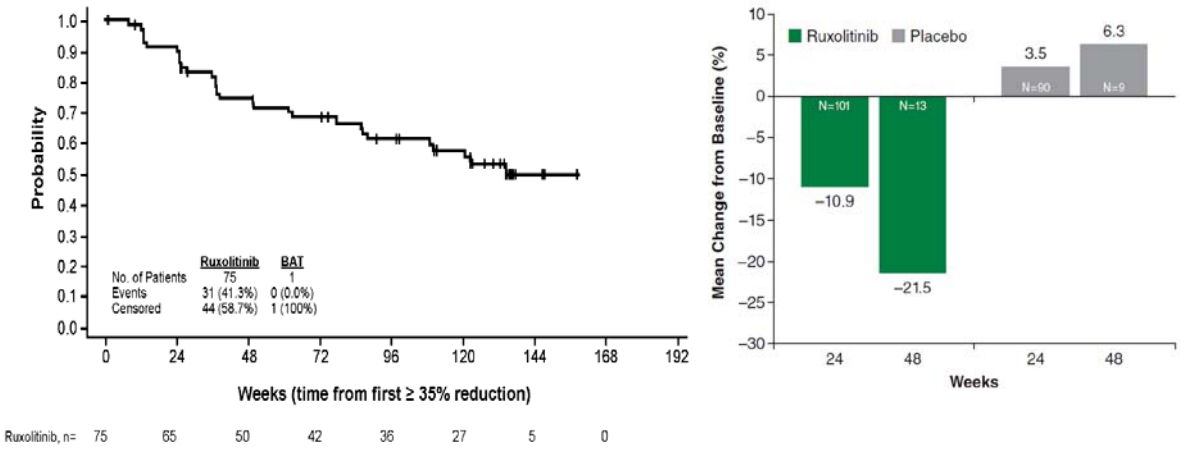
Prithviraj Bose: Well this certainly had the ASXL1 mutation which we know is an adverse one and may predict for a shorter response duration to ruxolitinib, but other than that it is probably somebody that was appropriately started on ruxolitinib and now after a couple of years we are seeing some escape and we are seeing progression here.

Ruben Mesa: Yes I definitely agree with that. I mean, certainly this panel of higher-risk mutations, particularly the ASXL1, would give me concern about long-term prognosis and I do think the stem cell transplanter needs to be a part of the team of this discussion as well as where will transplant potentially fit in along the way, particularly given that age of 62. All of that said, those mutations might suggest for me perhaps in the future we know that the BET inhibitor, which I mentioned from Constellation Pharmaceuticals, is having as some data when in combination with JAK inhibition as frontline and that BET inhibition may play a role in individuals with

ASXL1 mutation. So, this might be an individual that a combination BET inhibitor, JAK inhibitor may play a role. There is other BET inhibitor combination studies, I believe one from Insight is going to be coming up in the future as well, that might be an interesting option for such a patient.

Raajit Rampal: Thank you both for that excellent discussion. I think there were a number of themes, right? And investigational therapy is absolutely something that needs to be considered and fortunately there are some drugs as Dr. Mesa is pointing that looked promising at this point. Clearly, also allogeneic stem cell transplant needs to be a consideration given the patient's age, part of the question of course becomes what is the timing of that and do we start another therapy first and try to get the disease under better control before going to transplant? Do we consider going to transplant in the nearer term? Not questions with easy answers.

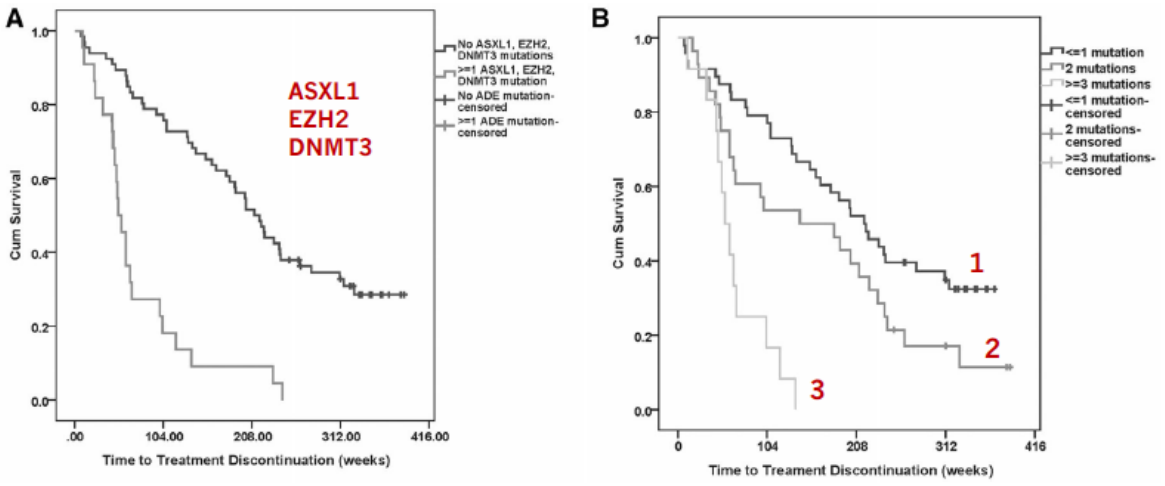
Limits of Duration of Efficacy of Ruxolitinib



Cervantes F, et al. *Blood*. 2013;122(25):4047-4053.; Verstovsek S, et al. *N Engl J Med.* 2012;366(9):799-807.

Let's talk about a little bit of the data that my colleagues have already alluded to. We know that although ruxolitinib has made a major difference in the lives of patients with myelofibrosis, there are limits to the durability of its effect and there are at least reasonably good understandings of some of the biochemical reasons for that, but a large proportion of patients lose their response over time.

Type and Number of Mutations Predict Response Duration

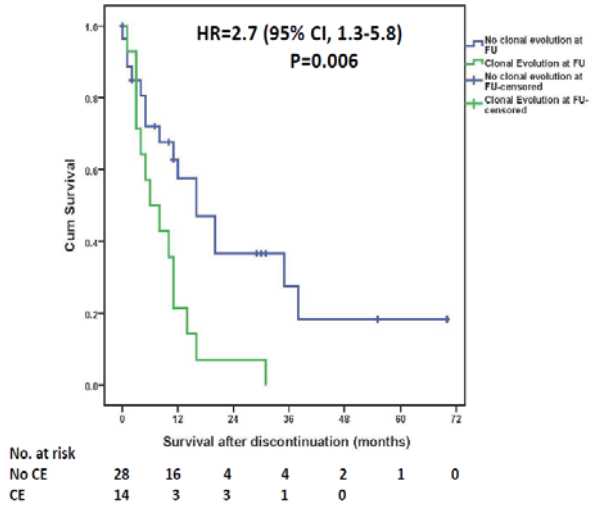


Patel KP, et al. *Blood.* 2015;126(6):790-797.

Now, as we talked about earlier the mutational profile does appear to play a role in predicting who may fail therapy, and there are really two major takeaways. One is that mutations in ASXL1, as is the case here, EZH2 or DNM23A appear to all be associated with a risk of earlier time to treatment failure. As well, the number of mutations appears to play a role. So having three or more mutations is also associated with a much earlier time to treatment failure, as is the case with this patient. The biology behind these observations remains to be determined.

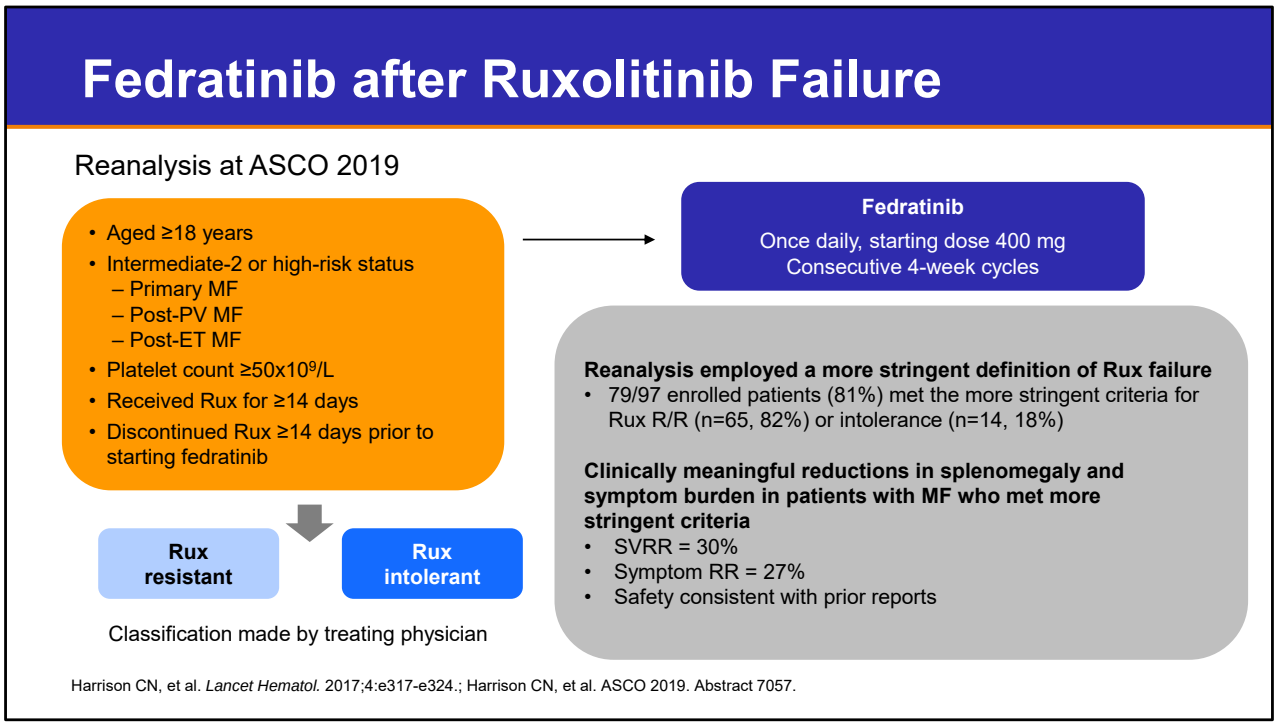
Outcomes of Patients Failing Ruxolitinib

- Survival after ruxolitinib d/c is poor (median 14 months)
- Shorter survival is associated with low platelets at start and end of therapy
- 35% of patients acquired a new mutation while receiving ruxolitinib; 61% *ASXL1*
- Patients showing clonal evolution had significantly shorter survival after d/c (6 vs 16 months, *P*=0.006)



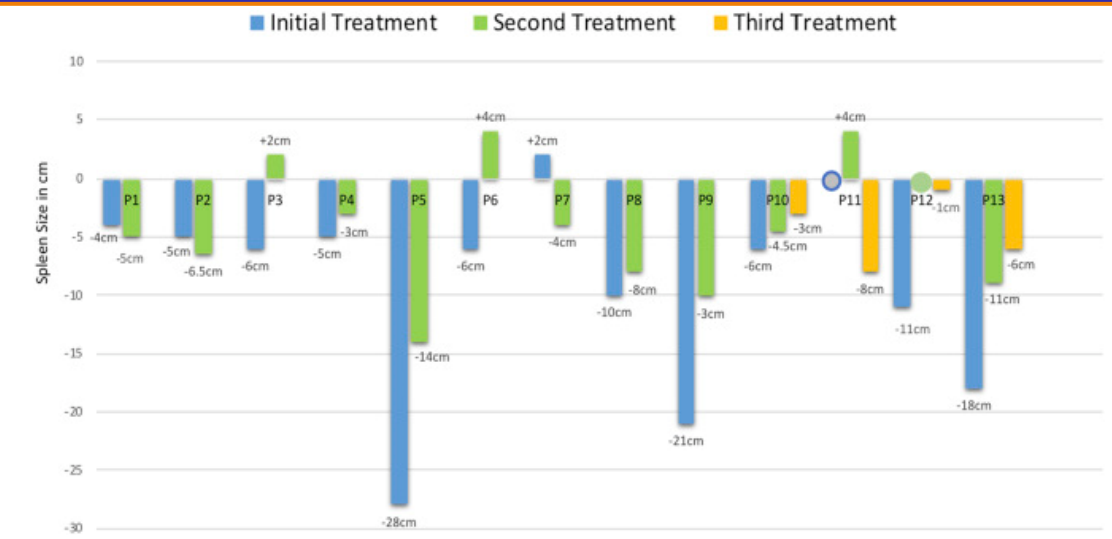
Newberry KJ, et al. *Blood.* 2017;130(9):1125-1131.; Kuykendall AT, et al. *Ann Hematol.* 2018;97(3):435-441.; Gers AT, et al. *Clin Lymphoma Myeloma Leuk.* 2018;18(11):e463-e468.

We also know that when patients do fail ruxolitinib, their outcomes are poor. So in patients who discontinue ruxolitinib, the median survival is about 14 months, and this is made worse if patients have low platelets at the start of their therapy or if they develop a new mutation such as ASXL1 during the course of their therapy or have any other evidence of clonal evolution.



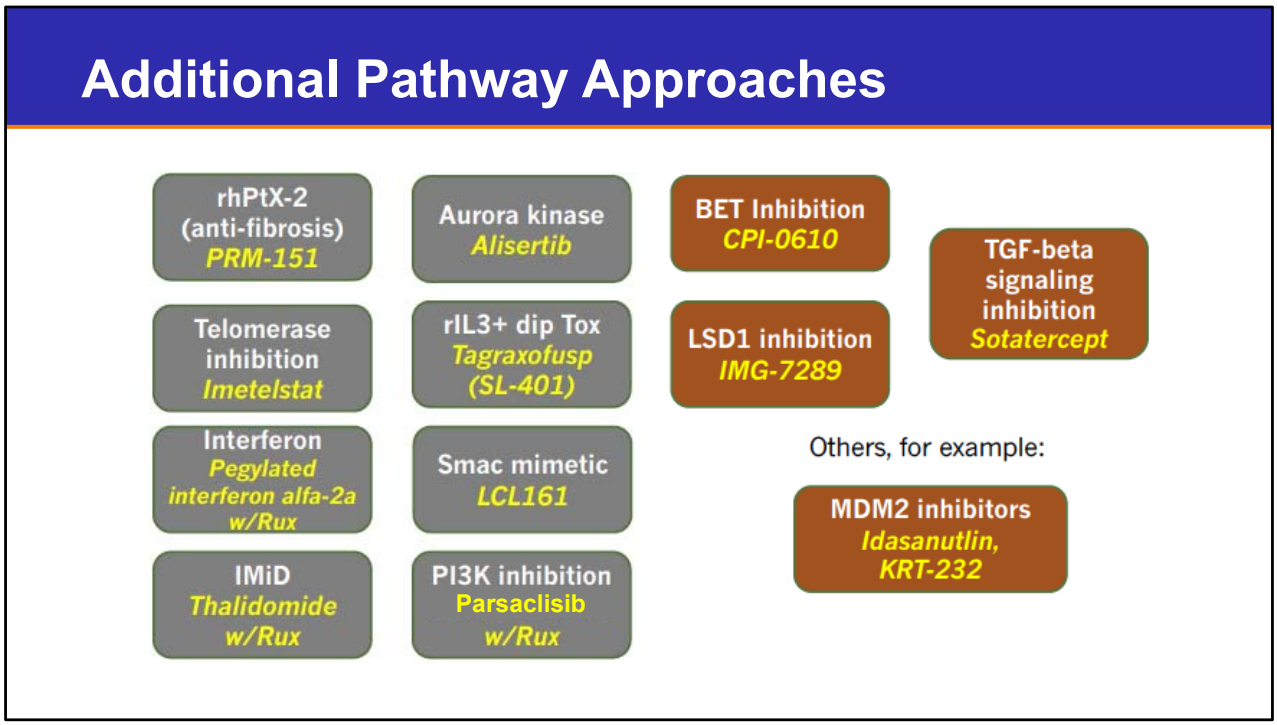
So what are the options? We have talked about some of them from the investigational standpoint, but of course we have the data from the JAKARTA2 trial utilizing fedratinib. Now the initial study allowed the patients on who had ruxolitinib exposure only for a short amount of time, but I think more important than this discussion was the re-analysis that was presented at ASCO 2019 whereby the analysis was focused on patients who had been on ruxolitinib for six months or more. In this population of patients who have had significant ruxolitinib exposure spleen volume response was 30% and symptom response was 27%, and so in at least a portion of patients it seems that one can salvage a response by switching to fedratinib therapy after having had ruxolitinib exposure.

Ruxolitinib Rechallenge



Gerds AT, et al. *Clin Lymphoma Myeloma Leuk.* 2018;18(11):e463-e468.

What about ruxolitinib rechallenge? One idea that has been tried I think more so prior to the approval of fedratinib was to withdraw ruxolitinib and then reintroduce it, and in fact there is a reasonable biochemical explanation for this in that what we know is that with exposure to ruxolitinib JAK stat persistence occurs, meaning that initially the JAK stat pathway is attenuated, but over time heterodimers form, which can actually get around the JAK inhibition and cause reactivation of the JAK stat signaling pathway. So it is a reasonable thing to think about withdrawing the drug and then reintroducing it to try to salvage an effect, but in fact this work from the Cleveland Clinic Group shows that in patients who have an initial treatment response, a second treatment rechallenge in a proportion of these patients can actually result in spleen size reduction. So, that is not an unreasonable option to think about as well.



And, of course as my colleagues talked about, there are a number of investigational options which is a wonderful thing for our patients, and we have talked about the BET inhibitor, the LSC1 inhibitor, there are TGF beta signaling inhibitors. One principle here to note is that these trials encompass not only combination with JAK inhibitors but also single-agent therapy, so much yet to be learned about these agents.

Prithvi Bose: Raajit, let me ask you a question right there, just taking a cue from what you just said, actually a question to both of you. What is your view on keeping the ruxolitinib and adding an agent as in the add-on trials for our patient here versus switching to a different mechanism of action altogether or fedratinib, now that we have so many different choices?

Ruben Mesa: I was going to say, I think it's an excellent question. I think as we have more approved agents the add-on will be more patient friendly, I think in real-world settings we are not going to abruptly stop the ruxolitinib, have a washout and then start another drug. That is a very artificial construct in on the setting of clinical trials. Data, let's say with the navitoclax study where Navitoclax was added to ruxolitinib is a nice model of trying to help patients further, I do think fedratinib is a good second-line option for folks because they can use it at the current time. I think

as we have additional options, again we will weight those pluses and minuses. Whether there is value switching from one JAK inhibitor to another may depend a little bit on the character of what is going on with the patient. A patient that clearly had four years of wonderful response to ruxolitinib and has now clearly progressed may need a different mechanism of action. The individual that has been on the JAK inhibitor and is just suboptimal might benefit from the add-on approach. So, I do think the clinical situation will be important.

Prithvi Bose: Right, thank you, Ruben. Raajit, did you have any thoughts on that?

Raajit Rampal: I would agree with Ruben completely. I think that the add-on strategy is in many cases much more feasible strategy for patients. One of the things we do need to think about which we do not really know that much about is what are the pathways involved in resistance? We know that JAK stat signaling activates a number of different pathways and it is worth asking the question, are they different in different groups of patients and can those pathways be targeted by certain drugs? So we may be in a position, eventually, to select agents that are based on the biology of the patients' relapse, but these are things that are under study at the moment.

Prithvi Bose: Right, personalized therapy for MF. Yes, something we would definitely all like to be there at some point.

A 70-year-old Patient with PMF Who Presents With Splenomegaly and Symptoms

Ruben A. Mesa, MD
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MediCom Worldwide, Inc.

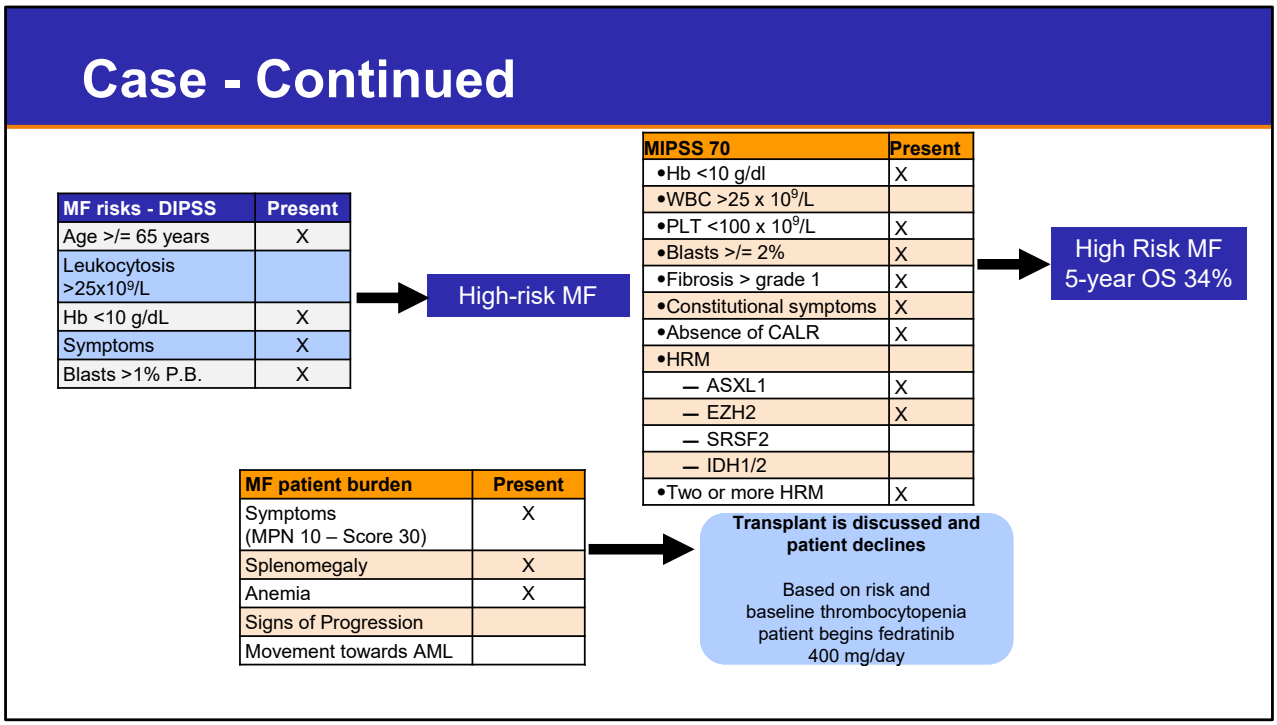
With that we will get into the third case here presented by Dr. Mesa, and this is also a myelofibrosis case.

Ruben Mesa: I wanted to pivot and take a little sort of different situation regarding that choice around frontline therapy.

Case Presentation

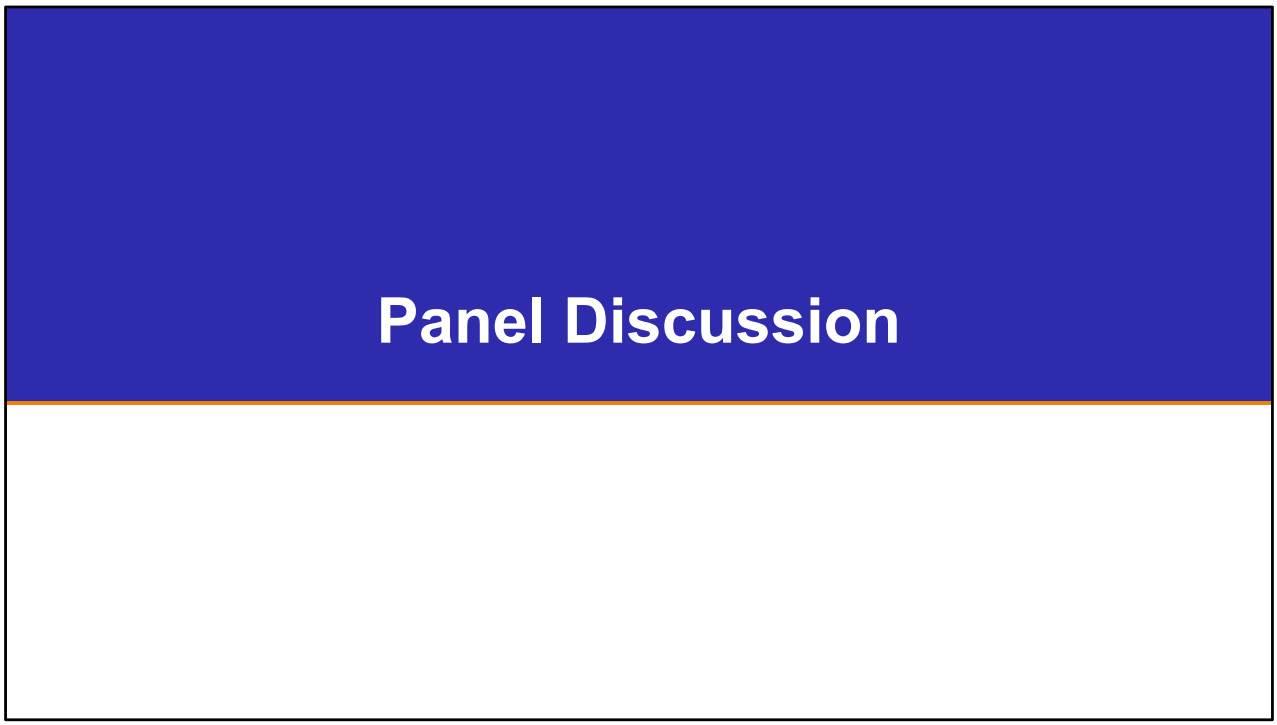
- MPN 10: 44 (out of 100) – 6 kg weight loss, night sweats, fatigue
- Spleen:10 cm BLCM
- Hb: 9.5 g/dL
- WBC: 20 x 10^9/L
- Blasts: 2%
- Platelets: 70 x 10^9/L
- NGS: *ASXL-1, JAK2-V617F, EZH2*

Here is a 70-year-old splenomegaly and symptoms, again difficult disease right out of the shoot. Lost weight, night sweats, fatigue, big spleen, some elevation of the blasts and a high-risk molecular profile of both the ASXL1 and EZH2 mutation. The platelets are 70,000, normal starting for ruxolitinib would suggest a lower dose of ruxolitinib to start with.



How do we think about risk in an individual like this? Well, by our old DIPSS scoring system, this individual would be high-risk, and by the new MIPSS it is also high risk, but I think even with a bit of greater concern is we weave in these high-risk molecular features.

Now, I also like to consider the issue of disease burden in that risk is an assessment of survival and the choice of our medical therapy is guided often by impact on survival but also on burden, so symptoms, splenomegaly, and anemia. The patient, certainly the issue of transplant is a reasonable discussion. At age 70, it is a very, very complex decision and this patient declined, and indeed that is not atypical. I would say that I currently have had patients who on paper are clearly transplant candidates but in practice have decided not to undertake that approach. Based on risk and based on thrombocytopenia, this is someone that I began on fedratinib. Fedratinib, as I will show in a moment, can be dosed at full dose frontline for individuals with a platelet count of 50 to 100,000.



Let me open that up to my colleagues. Fedratinib is now approved in both settings, and this is one of the areas that there may be some clear differentiation in that fedratinib can be dosed at full dose at 400 mg per day and ruxolitinib can be used but frequently would be started at 5 twice a day in such a group. Thoughts?

Prithvi Bose: Yes, Ruben. Actually very intriguing discussion here because I am yet to actually use fedratinib as a frontline treatment but absolutely agree that this is one setting where the data are very interesting as I am sure you are going to show us, fedratinib does not require a dose reduction and has comparable efficacy in this platelet range as in the higher platelets, whereas with Rux you would have to reduce the dose which makes you worry that you'll get less of a spleen response because we know that the spleen response to Rux is dose-dependent. So, definitely an area where fedratinib is a very interesting, very reasonable consideration.

Raajit Rampal: I think absolutely that the platelet counts would mitigate the dose of ruxolitinib, so that makes complete sense and I think this is a good use of fedratinib at this point. We certainly do not know whether the same implications that we know of with ASXL1 that pertain to fedratinib as they do for ruxolitinib. Is it reasonable to suppose that they do? Yes, but we don't have evidence at this point. I think the other thing to point out of course is that given this patient's profile, as Ruben has

pointed out, was very high risk at the beginning and I think this is also a patient that one may consider for an upfront clinical trial if one is available, but absolutely, I think in the real-world setting fedratinib makes a lot of sense for many reasons.

Ruben Mesa: You know, cases like this, as we talk about the new frontline studies like let's say BET inhibition upfront with JAK inhibition. Is it overkill in some cases even it were efficacious? I think higher-risk situation like this might be, again, at places we individualize therapy where more intensive therapy upfront might be worthwhile.

ASH 2019 ABSTRACT 668

Fedratinib Induces Spleen Responses and Reduces Symptom Burden in Patients with Myeloproliferative Neoplasm (MPN)-Associated Myelofibrosis (MF) and Low Platelet Counts, who were Ruxolitinib-Naïve or Previously Treated with Ruxolitinib

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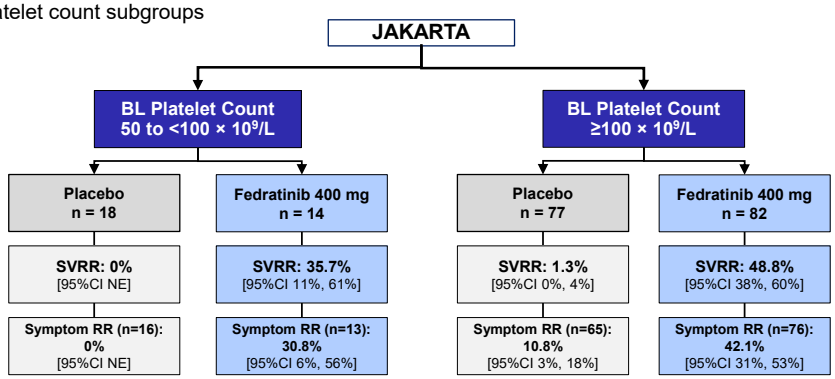
But let me take you through a bit of some of these data and that I think it is important that we continue to learn additional information from analysis of the JAKARTA and JAKARTA2 study. So, this was presented at last year's ASH with myself, Claire Harrison, and many colleagues looking at these data.

JAKARTA: Spleen Volume and Symptom Responses

- Among all patients, SVRR was significantly higher with fedratinib 400 mg/day vs placebo (47% vs 1%, respectively; *P*<.0001)
- Symptom RR was also significantly improved with fedratinib overall
- Within the fedratinib 400 mg treatment arm there was no statistically significant difference in SVRR or symptom RR between BL platelet count subgroups

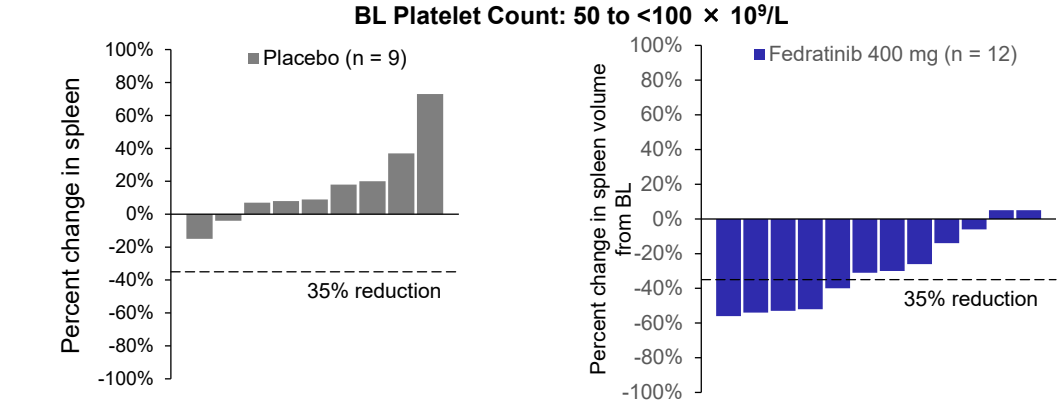


Statistical comparisons between BL platelet count subgroups should be interpreted with caution due to small sample sizes.
Harrison CN, et al. ASH 2019. Abstract 668.

We looked at the individuals under JAKARTA study which had been the frontline study, again fedratinib versus placebo with a baseline platelet count of 50 to 100,000 versus above 100,000, and with that we saw spleen volume response rates and symptom response rates that were vastly superior to placebo. The study was not structured with this as a pre-established stratification factor, so it is not powered to compared between 50 to 100,000 versus above 100,000 but seemed to be very similar in terms of the depth of response.

JAKARTA: Individual Spleen Volume Changes

- Among patients with BL platelet counts of 50 to <100 × 10^9/L with spleen volume data at BL and EOC6, 83% of patients in the fedratinib 400 mg/day arm and 22% of patients in the placebo arm showed spleen volume reductions at EOC6



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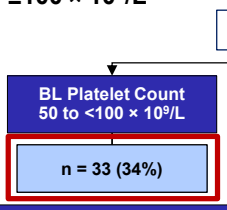
We look here at the individual improvement in the splenomegaly, and again seeing very significant activity and of course not surprising, vastly superior to placebo. It should be noted that, again, the JAKARTA study was very much the parallel study to the COMFORT study, that these drugs were being tested in a similar period of time, fedratinib just slightly after that of ruxolitinib, and compared to placebo because at that point in time this preceded the approval of any other agent.

JAKARTA2: Patients

- JAKARTA2 comprised 97 patients with MF previously treated with RUX
- Median prior RUX duration for all patients was 10.7 months (range 0.1–62.4)
- The proportion of JAKARTA2 patients with BL platelet counts of 50 to <100 × 10^9/L (34%) was more than twice that of JAKARTA (15%)
- **Median exposure to fedratinib on-study was similar for patients with BL platelet counts of 50 to <100 × 10^9/L or ≥100 × 10^9/L**



Fedratinib Exposure	Baseline Platelet Count	
	50 to <100 × 10^9/L n = 33	≥100 × 10^9/L n = 64
Exposure, weeks, median (range)	27 (1–79)	22 (1–71)

Harrison CN, et al. *Lancet Haematol.* 2017;4(7):e317-e324.

Now, JAKARTA-2, this was the second-line study, and again stratification between 50 to 100 versus above 100,000.

JAKARTA2: Baseline Characteristics

- Demographic and disease characteristics were generally similar between BL platelet-count subgroups
  - Median time since diagnosis was ~2x longer in patients with BL platelet counts of 50 to <100 × 10^9/L

	Baseline Platelet Count	
	50 to <100 × 10^9/L n = 33	≥100 × 10^9/L n = 64
Age, years, median (range)	66.0 (51–78)	68.0 (38–83)
Disease setting, n (%)		
Primary MF	19 (58)	34 (53)
Post-PV MF	11 (33)	14 (22)
Post-ET MF	3 (9)	16 (25)
Risk status, n (%)		
Intermediate-1 with symptoms	5 (15)	11 (17)
Intermediate-2	16 (49)	31 (48)
High	12 (36)	22 (34)
Years since MF diagnosis, median (range)	6.5 (0.7–18)	3.0 (0.3–25)
Number of prior MF therapies n (%)		
1	8 (24)	12 (19)
2	17 (52)	30 (47)
≥3	8 (24)	22 (34)
RBC transfusion-dependent, n (%)	3 (9)	11 (17)
Spleen size, cm, median (range)	18.0 (5–28)	18.0 (5–36)
Spleen volume, mL, median (range)	2917 (785–5811)	2870 (737–7815)
MFSAF total symptom score, mean [SD]	n=31 21.0 [12.6]	n=59 20.5 [12.0]

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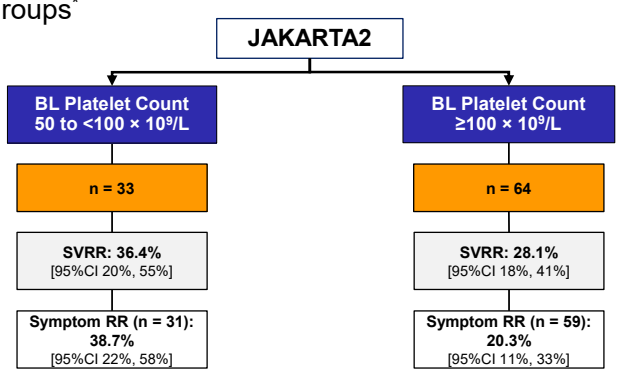
In terms of baseline characteristics, again we see a relatively similar distribution in terms of splenomegaly and burden of disease in individuals regardless of the baseline platelet count

JAKARTA2: Spleen Volume and Symptom Responses

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



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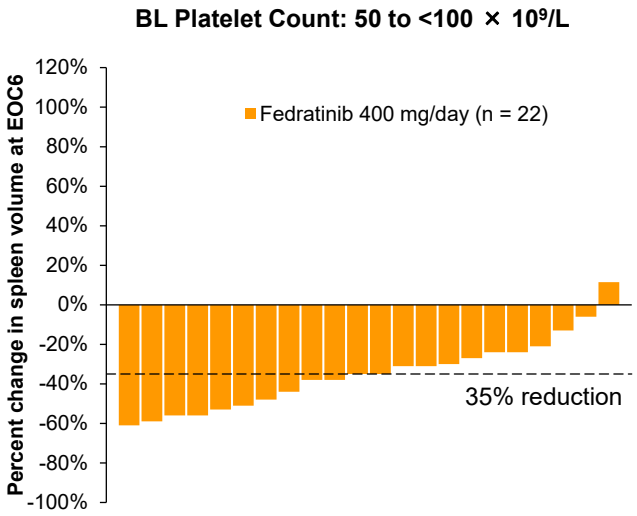
Here again we saw spleen volume response rates and symptom response rates that were very similar in the group with thrombocytopenia as well as the group with a baseline platelet count of above 100,000. In this instance, the numbers are numerically higher, but again I would say that the analysis is not one to directly allow comparison between those two groups.

JAKARTA2: Individual Spleen Volume Changes

- Among JAKARTA2 patients with BL platelet counts of 50 to <100 × 10^9/L and with spleen volume data available at BL and EOC6, all but one had some degree of spleen volume reduction at EOC6



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Here, again, this was a single-arm study so there is no placebo comparison arm, but one sees the significant benefit in terms of improvement in splenomegaly, even in these individuals with thrombocytopenia. Again they were able to get full dose and get the full benefit of the medical therapy.

Treatment for Higher-risk Myelofibrosis

	Treatment Recommendation
Transplant candidate	• Allogeneic HCT
Not a transplant candidate with symptomatic anemia only	• Refer to management recommendations for MF-associated anemia
Not a transplant candidate	• Assess symptom burden with the MPN-SAF TSS or MPN10 • If platelets <50 x 10^9/L: o Therapy: Clinical trial • If platelets ≥50 x 10^9/L: o Therapy: Ruxolitinib, fedratinib, or clinical trial o Monitor every 3-6 months for response and signs/symptoms of disease progression ▪ If response: Continue therapy and monitor as above ▪ If no response or loss of response: Fedratinib (if prior ruxolitinib) ▪ If disease progression: Refer to management recommendations for advanced-stage MF/AML

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Myeloproliferative neoplasms. NCCN Evidence Blocks™. Version I.2020—June 26, 2020.

How does this fit in with our treatment guidelines? Again, emphasizing that according to our NCCN guidelines that fedratinib is a parallel frontline option to ruxolitinib for individuals with a platelet count above 50,000 and I think that group between 50,000 to 100,000 is a group where we know of some differentiation between the two therapies.

Prithvi Bose: So, let me ask you, Ruben, a question, both of you, of course, Ruben and Raajit, what your views are on this? So, sometimes something I struggle with is of course the survival benefit that we know that ruxolitinib has now with five years of follow-up of the COMFORT trials, and also remembering that that survival benefit was in that population, which is the platelets 100 and higher. Do you ever wrestle with that aspect as well as the fedratinib data that Ruben nicely went through just now for us when you pick a frontline option?

Ruben Mesa: I think the point you raised is a good one, it is important to note that with fedratinib its approval process, and we have not gotten that into that in great depth with this evening's discussion, is that it had a period where it was on FDA clinical hold because of concerns regarding Wernicke's encephalopathy, that subsequently was resolved and the drug now approved with a mandate to monitor for thiamine and to watch for a rare possibility of Wernicke's encephalopathy, but because of that the patients did not have long-term data on fedratinib because they were taken off the study. I suspect if they had remained on the study, responding patients would have had a survival benefit. I honestly believe, having been involved with treating so many patients on JAK inhibitors over the years with momelotinib, pacritinib, fedratinib and ruxolitinib, I think patients on JAK inhibition who respond have likely a survival benefit with each of the agents, proving it is a much more complicated matter, but I believe that it likely is a class effect.

Prithvi Bose: Raajit, any concluding thoughts on that?

Raajit Rampal: Yes, I would absolutely agree, I agree the only concern may be is there early toxicity and clearly, we have seen with the JAK inhibitors that there certainly can be differential toxicity profiles. Is that enough to overcome the benefit of JAK inhibitors in the intermediate term in a five-year stand in patients? I do not think that we know but I also do not think that it is very likely.

Ruben Mesa: Yes. I think with fedratinib, what we will find is as treating physicians become more comfortable with it in the second-line setting, I think it will continue to evolve to have at least a solid place as a consideration in frontline as individuals are much more comfortable with its use.

Prithvi Bose: Great points. So, well, thank you both for what I hope was for our viewers an interesting and educational discussion. Thank you for listening. Thank you everybody for joining us this evening. Thank you.