# The Expanding Role of JAK Inhibitors in MF


Hello, my name is Ruben Mesa and I am the Executive Director of the Mays Cancer Center at UT Health San Antonio MD Anderson. I'm pleased to be speaking with you today regarding the expanding role of JAK inhibition as a cornerstone of therapy for myelofibrosis.

## Disclosures

- Dr. Ruben Mesa has received honoraria as a consultant from Bristol-Myers Squibb Company, F. Hoffmann-La Roche Ltd, Genentech, Inc., Geron, Novartis AG, Samus Therapeutics, Inc., and Sierra Oncology, Inc. He has received grant support related to research activities from AbbVie Inc., Bristol-Myers Squibb, CTI BioPharma Corp., and Incyte Corporation.

Here are my disclosures.

# The Expanding Role of JAK Inhibitors in MF

## Case Study: Polycythemia Vera

Man diagnosed with polycythemia vera 14 years ago after thrombosis at age 40

- Treated with phlebotomy, aspirin
  - Hydroxyurea
- Now comes to see you now at age 54
  - Worsening fatigue
  - Night sweats
  - Lost 5 kg
  - Exam spleen13 cm BLCM
- Blood counts
  - Hb 9.0 g/dL
  - WBC 14 x $10^9$/L
  - Platelets 105 x $10^9$/L

Let's begin with a case. This is a gentleman diagnosed 14 years ago at the age of 40 with polycythemia vera. It was discovered after having a thrombotic event. It was treated with phlebotomy and aspirin and hydroxyurea. Now comes to see you as a hematologist at age 54, the patient complains of worsening fatigue, night sweats, a loss of 5 kilograms, and with significant splenomegaly 13 centimeters below the costal margin. This individual, the blood counts show some mild anemia, hemoglobin of 9, white count of 14,000, platelets of 105,000.

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## Case Continued

- Peripheral smear
  - Increased myelocytes, metamyelocytes, 1% blasts
- Spleen
  - By exam 7 cm BLCM, by ultrasound 20 cm
- Symptoms
  - MPN10 (35/100 possible score)
- Bone marrow
  - 2-3+ fibrosis, no increase in blasts
  - Del 20q- cytogenetics
  - NGS – JAK2-V617F mutated 30% (TET2 mutation)

On the peripheral smear, the individual has increased myelocytes, metamyelocytes, and 1% blasts. There is splenomegaly, both by exam as well as confirmed by ultrasound. They're significantly symptomatic. With an MPN10 score, the patient reported outcome scores for patients with MPNs of 35 out of a 100. The bone marrow shows two to three plus fibrosis. There's no increase in blasts, a deletion 20q in terms of cytogenetics. By next-generation sequencing, it shows the JAK2 V617F mutation, mutated at 30%. There is also a TET2 mutation that is found as well.

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## Case 1: How Do You Now Plan Therapy in Post PV MF?

- How do you assess risk?
- Who do you consider for allogeneic transplant?
- Who do you consider for medical therapy?

Many questions arise for you. This patient now with the post-PV myelofibrosis. How do we assess risk? When should we consider allotransplant? Should they begin on medical therapy?

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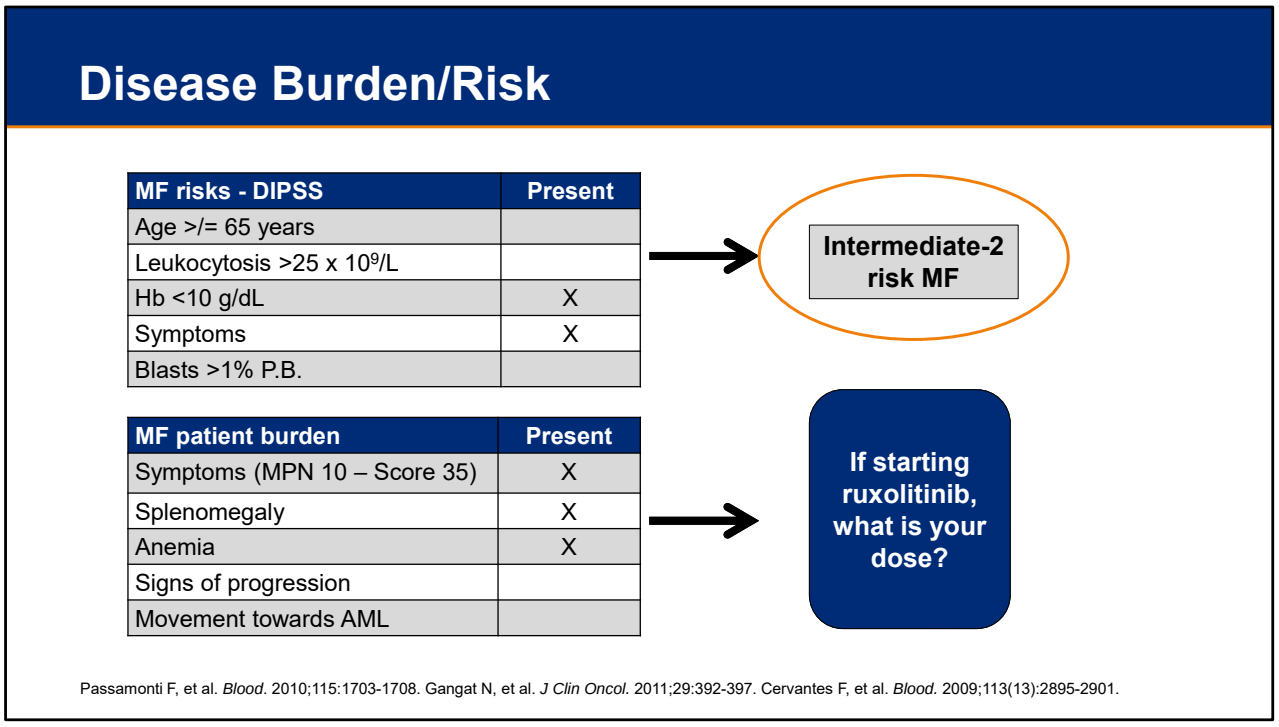


From my end, I like to think of these diseases both as incorporating issues of disease burden as well as risk. In terms of risk, by the Dynamic International Prognostic Scoring System, there's five criteria that are used to judge risk: age over 65, leukocytosis, anemia, significant symptoms, or increase in blasts. This individual has intermediate-2 risk disease. By disease burden, I think both about how long someone's going to live, but what is the burden they're facing? The symptoms, splenomegaly, anemia, risk of progression, movement toward acute leukemia. This individual has three of those five. If we start this individual on medical therapy, and ruxolitinib would be the standard medical therapy we begin, what is the current dose?

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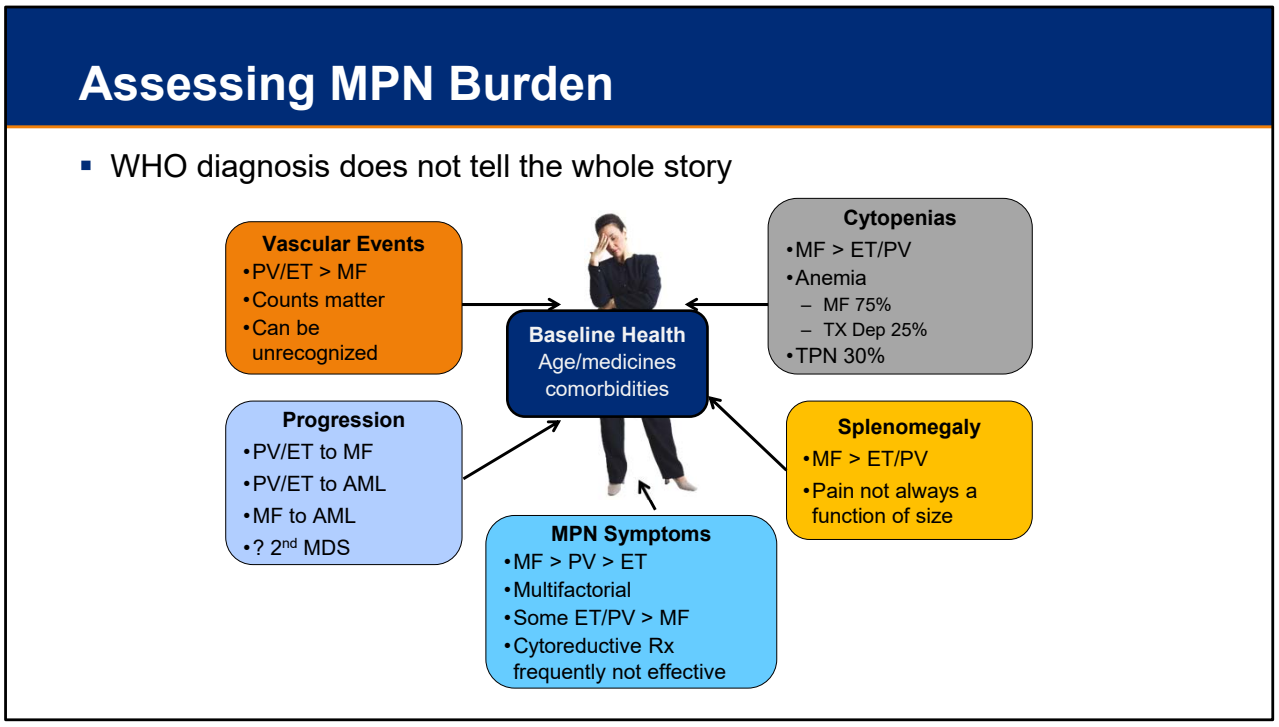


How do we make these decisions? Well, I like to think that these individuals have a heterogeneous disease course and a variable burden. They mentioned for this individual, we consider vascular risk and they've had one in the past. Cytopenias, this individual has mild anemia. Splenomegaly, it can cause symptoms. It can be linked with the biology of the disease and progression. There can be difficult symptoms linked with inflammation and the biology of the disease. It can be a risk of progression to acute leukemia. All of this occurs in the context of the individual's baseline health and comorbidities.

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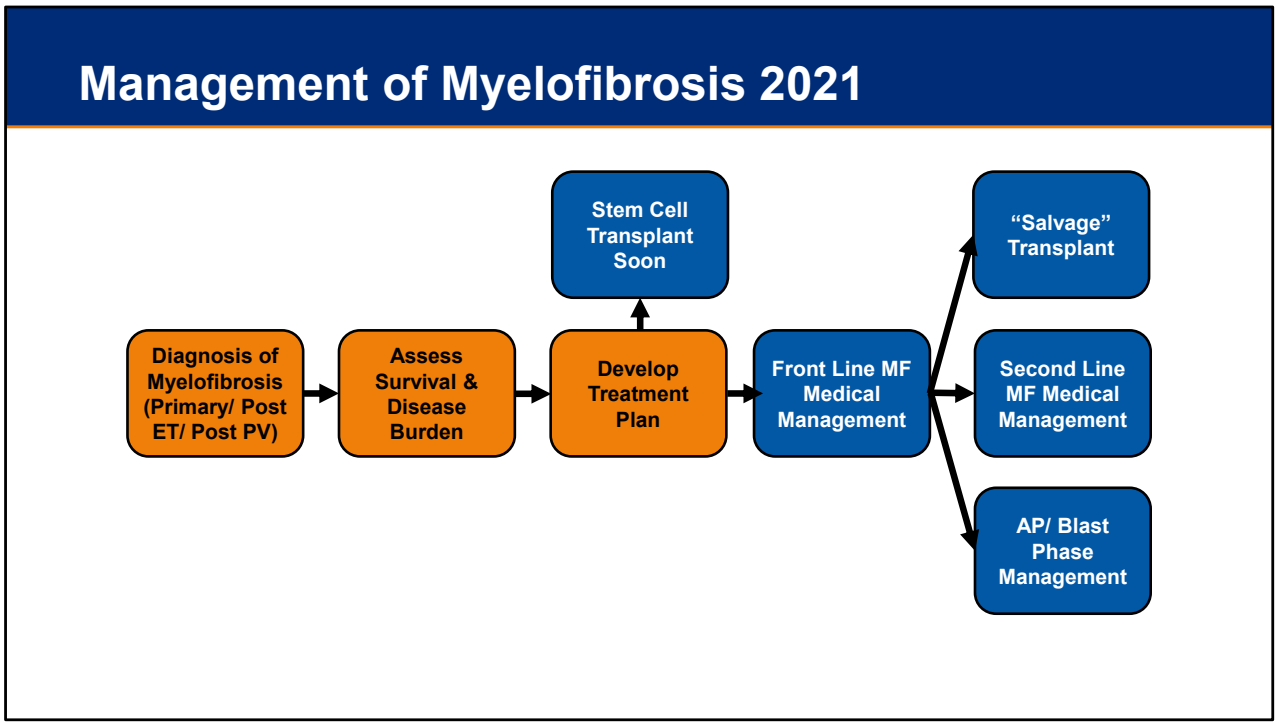


Now, as we manage and develop a treatment plan, we, as I mentioned, have an accurate diagnosis ideally and assess survival and disease burden and develop that treatment plan. Should they move to stem cell transplantation or frontline medical therapy? At age 54, I would typically have such an individual visit with our bone marrow transplanters, have an active discussion, consider whether they would move to transplant in the near future, distant future if the disease progresses, or are they not a candidate due to comorbidities or by patient choice. If they progress from frontline medical therapy, do we move on with salvage transplantation, second-line medical therapy, or accelerated or blast phase management.

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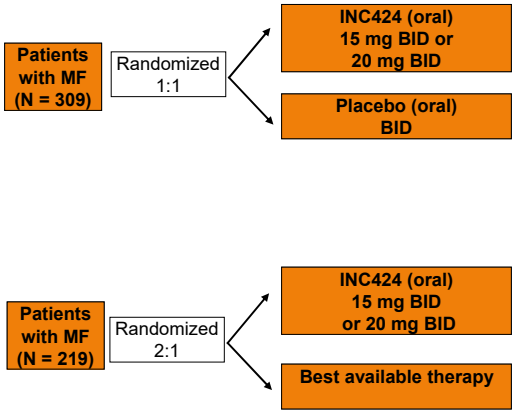
## Ruxolitinib Phase III Trials (COMFORT I & II)






Verstovsek S, et al. *N Engl J Med*. 2012;366(9):799-807.; Harrison C, et al. *N Engl J Med*. 2012;366(9):787-798.

Now, frontline medical therapy has been, for the greater part of the last 10 years, ruxolitinib. That was the first approved therapy for myelofibrosis, a JAK1 and JAK2 inhibitor, and approved on the basis of successful trials of ruxolitinib versus placebo or compared to best alternative therapy.

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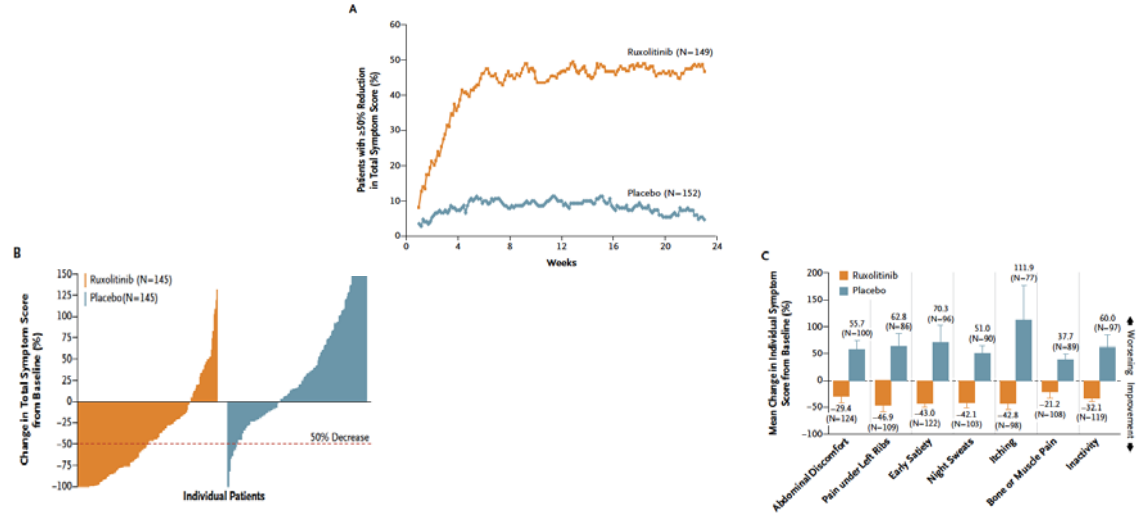
## Ruxolitinib Phase III MF (COMFORT I – Symptom Response)




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

We saw significant improvements in the size of the spleen as well as improvement in disease-associated symptoms, either in aggregate as you see by the waterfall plots on the left or according to individual symptoms as you see on the right.

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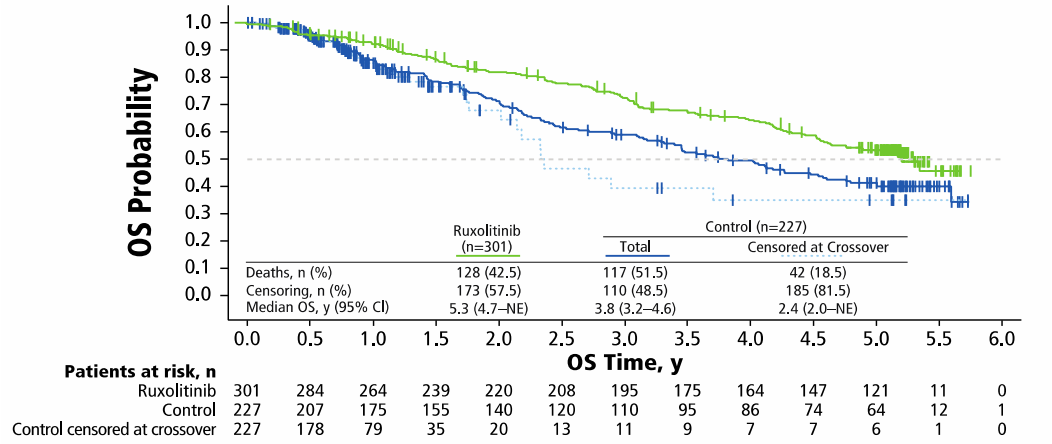
## Pooled OS Analysis of 5-year Data From COMFORT-I/II Trials of Rux for Treatment of MF

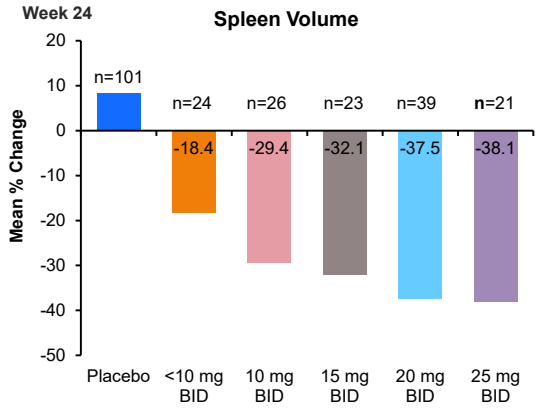


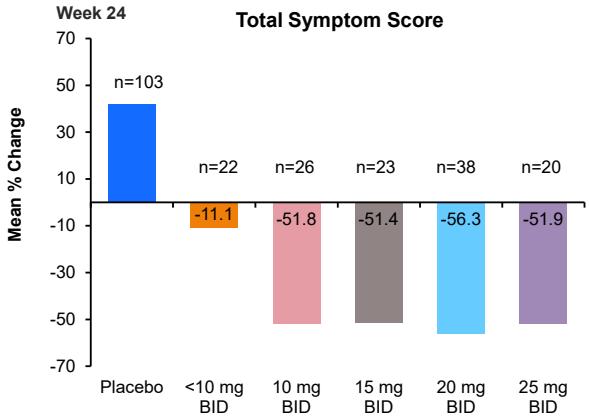

Vannucchi A, et.al. *Haematologica.* 2015;100(9):1139-1145.

We've also seen over time a significant improvement in survival. This is likely multifactorial: decreased clonal evolution, improved performance status, decreased debilitation.

# Ruxolitinib Efficacy by Titrated Dose: COMFORT-I

- Avoid starting with low dose!
- Start dosing per guidelines and modify based on platelets if needed
- Doses less than 10 mg BID are not effective long term



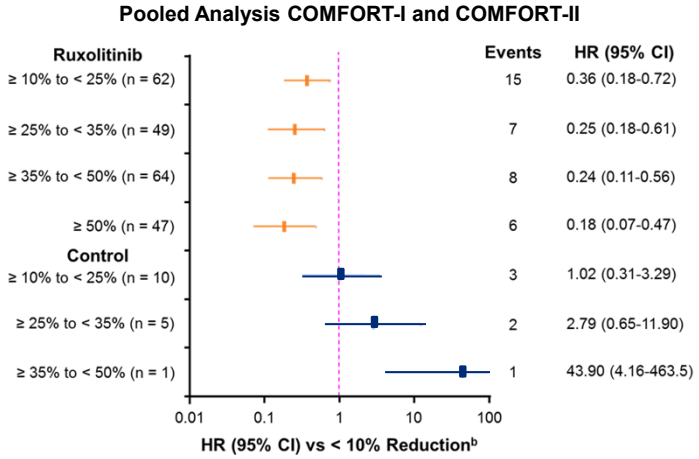




Verstovsek S, et al. *OncoTargets and Therapy.* 2014;7:13-21.

We have learned over time that to achieve survival benefit, there likely needs to be a significant response and that dose matters. Values or levels of the drug less than 10 milligrams twice a day likely have a lower efficacy for improvements of spleen or symptoms. If we've learned anything over time is having an adequate dose of the drug is important as well as important to have a true response.

# The Expanding Role of JAK Inhibitors in MF

## Correlation of Spleen Volume Reduction at Week 24 and OS




[a] includes patients known to be alive at week 24.
[b] Category includes patients with a <10% reduction from baseline in spleen volume at week 24 or no assessment (ruxolitinib, n=64, control, n = 189); among these patients, there were 26 deaths (events) in the pooled ruxolitinib group and 63 deaths in the control group.
Vannucchi AM, et al. *Haematologica.* 2015;100:1139-1145.

We have been able to correlate that the spleen volume reduction is tied to improvements in overall survival.

## Key Points: Ruxolitinib Dosing and Spleen

1. Achieving a spleen response matters for improving overall survival
2. Use product dosing guide for your starting dose the INCREASE if needed to achieve optimal response


Takeaway one I would give you is, first, achieving a spleen response matters for overall survival improvements in myelofibrosis. Second, use the product dosing guide for your starting dose and increase if needed to achieve the optimal dose. There is way too much under-dosing of ruxolitinib, which is currently occurring of 5 milligrams twice a day or 10 milligrams twice a day in suboptimal responders because of concerns about initial anemia. It is best to manage the patient through that initial period of time. Let the hemoglobin come back. Even give a transfusion if it is necessary. That will probably lead to more efficacy, better response, better outcomes for the patient.

## Case Continued

Patient is begun on 5 mg BID and has some improvement in spleen and symptoms, but neither a full response

- When do we increase?
  - 3 months? 6 months?

What if patient had started at 15 mg BID and hemoglobin dropped from 9.0 to 7.5 g/dL?

- Do we stop?
- Dose modify?
- Support with transfusion?

This individual is begun on 5 milligrams twice a day and has improvement, but neither a response. When do we increase the dose? If the patient started at 15 twice a day and they dropped, should we stop? Should we dose modify? Should we support? I would recommend in these situations that we continue the patient on the 15 milligrams twice a day. The drop in the hemoglobin is an on-target effect. Inhibiting JAK2 inhibits erythropoiesis and there is some degree of recovery. I think, over time, we've learned patience in terms of maintaining the dose to achieve an adequate response

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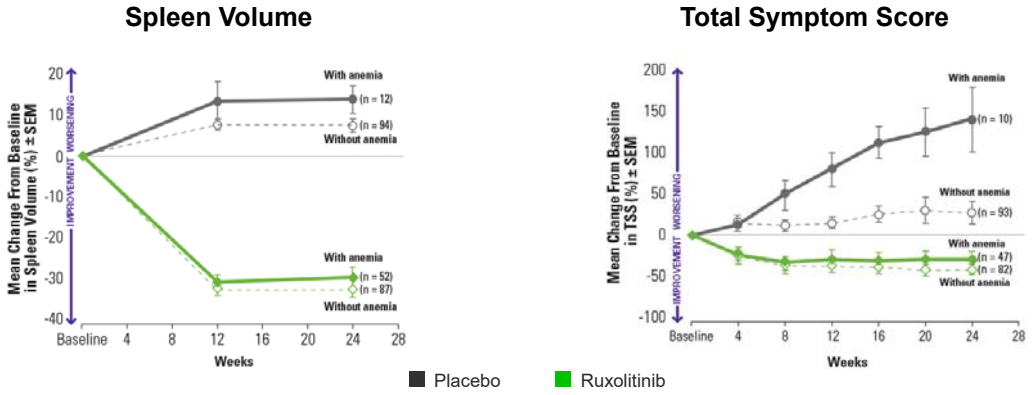
## Development of Anemia Does Not Affect Response to Ruxolitinib Treatment: COMFORT-I




**Baseline anemia is not a contraindication for ruxolitinib use**

Verstovsek S, et al. Oral presentation at ASCO Annual Meeting; June 3-7, 2011. Abstract 6500.

We've learned that the development of anemia does not affect the response to ruxolitinib treatment. Even though they develop anemia, it does not worsen their outcomes. In fact, maintaining through it, the outcomes are the same. This is different than baseline anemia. People ask, "Well, in the DIPSS, anemia is a negative prognostic marker. Isn't that the case if you develop JAK inhibition-induced anemia?" We believe that is likely distinct. The prognostic value of anemia is particularly in the baseline setting.

# The Expanding Role of JAK Inhibitors in MF

## How to Manage Early Onset Cytopenias (First 3 Months)

- Decrease dose or interrupt ruxolitinib depending on severity of thrombocytopenia and neutropenia, until recovery
- Support with RBC/platelet transfusions if necessary
- Check CBCs more frequently
- Add ESA or danazol? Low probability of success, no conclusive safety data (NCT01732445)
- Consider adding steroid +/- thalidomide. Pomalidomide in trials in Germany

Advice in terms of managing those early onset cytopenias. Stick with your dose. Support them as appropriate. Over time if that persists, we might either add an additional agent. Danazol has been added with success in clinical trials, erythropoietin-stimulating agents in individuals that have a suboptimal erythropoietin response. If they have an EPO level, particularly under 100, but by NCCN Guidelines if it is less than 500. Additional options, considering adding either steroids or thalidomide to ruxolitinib for individuals with cytopenias.

# Key Points #2 Cytopenias

1. Optimizing dose important for maximal benefit from ruxolitinib

2. Baseline anemia dose not lessen ruxo benefit, nor subsequent anemia

3. Dose increases with thrombocytopenia have both been tolerated and efficacious when starting at lower doses


Takeaway two. Optimizing the dose is important for maximal benefit from ruxolitinib. The baseline anemia does not lessen the benefit nor will subsequent anemia. Dose increases in patients with thrombocytopenia have been tolerated and efficacious when starting at a lower dose. For example, if there is an individual who begins at 10 milligrams twice a day because of lower platelet counts or even 5 milligrams twice a day, increase that dose as tolerated. There've been individuals with marked thrombocytopenia that have gotten as high as 20 twice a day or 25 twice a day. We don't begin them at those levels, but many people will tolerate that. Thrombocytopenia does not tend to be progressive.

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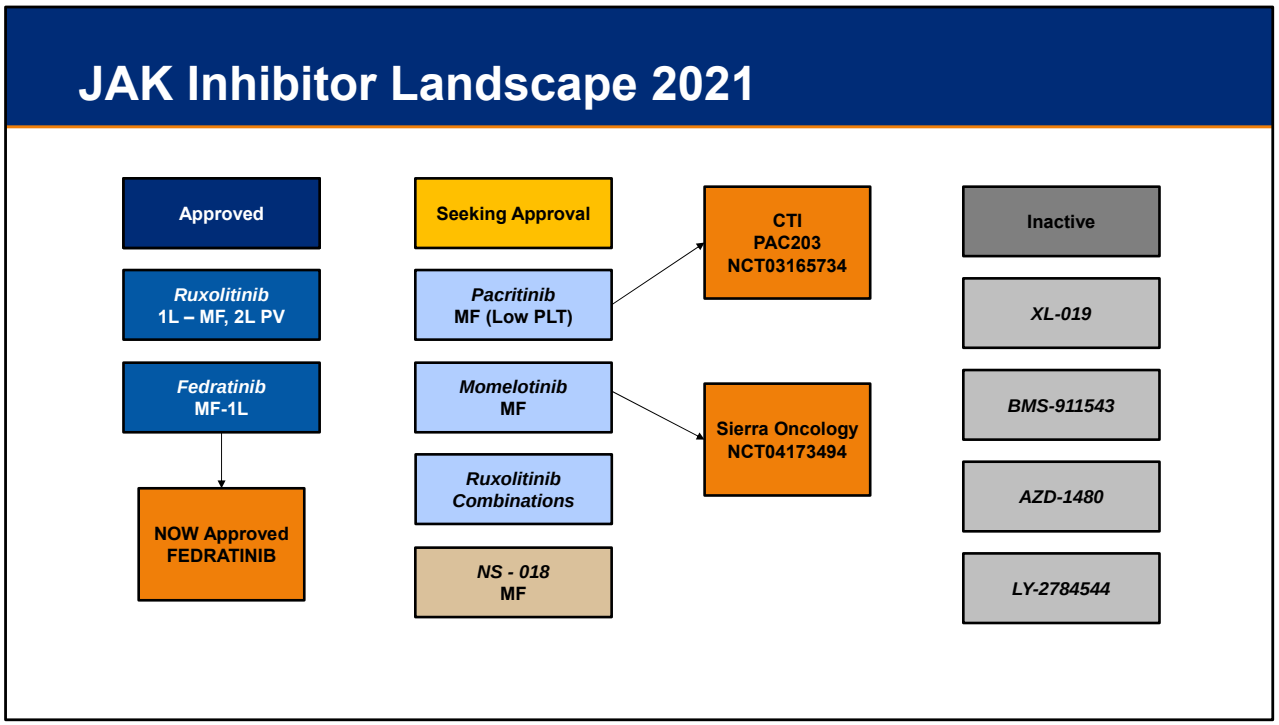


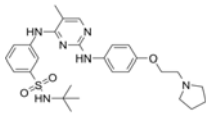

Now, the JAK inhibitor landscape has expanded from ruxolitinib. I'll focus my next comments on fedratinib, which is now approved broadly for both either the frontline or the second-line setting. Subject for a different talk are other JAK inhibitors in the pipeline. We'll mention there's both pacritinib from CTI that is having activity in people with marked thrombocytopenia in the milder depleted phenotype or momelotinib, which also inhibits ACVR1, may inhibit hepcidin, may have to also improve anemia and is in current phase III trials.

# The Expanding Role of JAK Inhibitors in MF

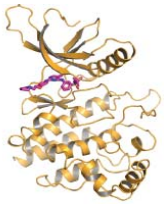
## Fedratinib

INREBIC® (Fedratinib)

- Oral, JAK2-selective inhibitor recently approved in the US for treatment of intermediate-2 or high-risk primary or secondary (post-PV or post-ET) MF with platelet counts ≥50 × $10^9$/L
- Fedratinib has higher inhibitory activity for JAK2 over JAK1, JAK3, and TYK2
- Fedratinib was investigated for treatment of MF in JAK-inhibitor-naïve patients in the phase III JAKARTA trial, and in patients previously treated with RUX in the phase II JAKARTA2 trial
- JAKARTA and JAKARTA2 allowed enrollment of patients with platelet counts of ≥50 × $10^9$/L at study entry



FEDRATINIB



JAK2 KINASE DOMAIN – Fedratinib Complex

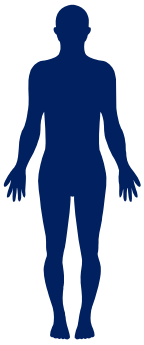
Jakafi (ruxolitinib) prescribing information. Incyte Corporation; 05/2019.; Center for Drug Evaluation and Research. Clinical Pharmacology Genomics Group Review; 2011.; INREBIC® (fedratinib) prescribing information. Celgene Corporation; 08/2019.; Wernig et al. *Cancer Cell*. 2008;13:311-320.; Pardanani et al. *JAMA Oncol*. 2015;1(5):643-651.'Harrison et al. *Lancet Haematol*. 2017;4:e317-324.; Hantschel O. *ACS Chem Biol*. 2015;10(1):234-245.
BL, baseline ET, essential thrombocythemia; JAK, Janus kinase; MF, myelofibrosis; MPN, myeloproliferative neoplasm; PV, polycythemia vera; RUX, ruxolitinib.

Now, fedratinib has been approved since the fall of 2019. It is an oral JAK2 inhibitor and was tested for individuals with platelets greater than 50,000.

# The Expanding Role of JAK Inhibitors in MF

## Fedratinib in Myelofibrosis: JAKARTA Trial

**Phase 3 JAKARTA Trial**
**Fedratinib vs placebo in patients with Int-2/high-risk MF**



| | Fedratinib 400 mg | Fedratinib 500 mg |
|---|---|---|
| Spleen volume reduction ≥35% | 37% | 40% |
| Symptom burden reduction ≥50% | 40% | 34% |
| Discontinuation due to AEs | 14% | 25% |

N = 289

AE = adverse event; Int-2 = Intermediate-2
Pardanani A, et al. *JAMA Oncol*. 2015;1(5):643-651.; Harrison CN, et al. *Lancet Haematol.* 2017;4(7):317-324.; Harrison CN, et al. ASCO 2019. Abstract 7057.

It's approved off the basis of two studies: the JAKARTA and the JAKARTA-2 study. I had the honor of being involved with both of these studies. The JAKARTA study was the frontline JAK inhibitor-naive phase III study of two different doses of fedratinib versus placebo. Both doses were superior to placebo; 400 milligrams a day was the best combination of response in terms of spleen volume reduction, symptom burden reduction, and tolerability.

# The Expanding Role of JAK Inhibitors in MF

## Fedratinib Adverse Events: JAKARTA Trial

| Adverse Event, % | Fedratinib 400 mg (n=96) | | Fedratinib 500 mg (n=97) | | Placebo (n=95) | |
|---|---|---|---|---|---|---|
| | All Grades | Grade 3 or 4 | All Grades | Grade 3 or 4 | All Grades | Grade 3 or 4 |
| **Nonhematologic** | | | | | | |
| Diarrhea | 66 | 5 | 56 | 5 | 16 | 0 |
| Vomiting | 42 | 3 | 55 | 9 | 5 | 0 |
| Nausea | 64 | 0 | 51 | 6 | 15 | 0 |
| Constipation | 10 | 2 | 18 | 0 | 7 | 0 |
| Asthenia | 9 | 2 | 16 | 4 | 6 | 1 |
| Abdominal pain | 15 | 0 | 12 | 1 | 16 | 1 |
| Fatigue | 16 | 6 | 10 | 5 | 1 | 0 |
| **Hematologic** | | | | | | |
| Anemia | 99 | 43 | 98 | 60 | 91 | 25 |
| Thrombocytopenia | 63 | 17 | 57 | 27 | 51 | 9 |
| Lymphopenia | 57 | 21 | 66 | 27 | 54 | 21 |
| Leukopenia | 47 | 6 | 53 | 16 | 19 | 3 |
| Neutropenia | 28 | 8 | 44 | 18 | 15 | 4 |

Pardanani A, et al. *JAMA Oncol*. 2015;1(5):643-651.

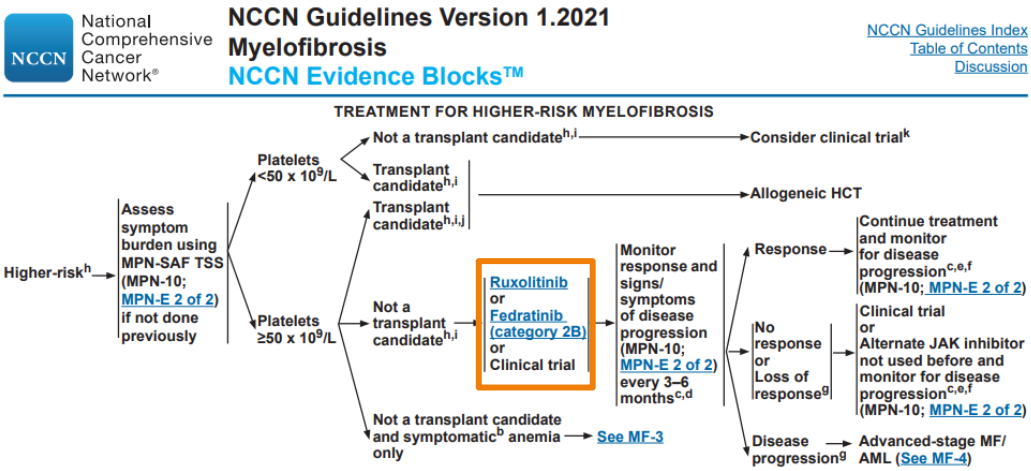
**Black box warning**
- Wernicke's encephalopathy (ataxia, altered mental status, ophthalmoplegia) occurred in 8 of 608 (1.3%) patients receiving fedratinib in clinical trials

**Considerations**
- Measure and address thiamine levels prior to treatment initiation
- Do not start fedratinib in patients with thiamine deficiency

In terms of side effects, it can lead to anemia or thrombocytopenia as there can be with other JAK inhibitors. There can be GI side effects and typically do prophylaxis with Imodium (loperamide) or anti-nausea medicines. There's a rare incidence of Wernicke's encephalopathy, less than 1%. On that basis, there is a black box warning that recommends assessing thiamine levels, replacing thiamine levels of flow, and monitoring for this. With thiamine replacement and monitoring, we feel that this likely will not be a major issue for myelofibrosis patients.

# The Expanding Role of JAK Inhibitors in MF

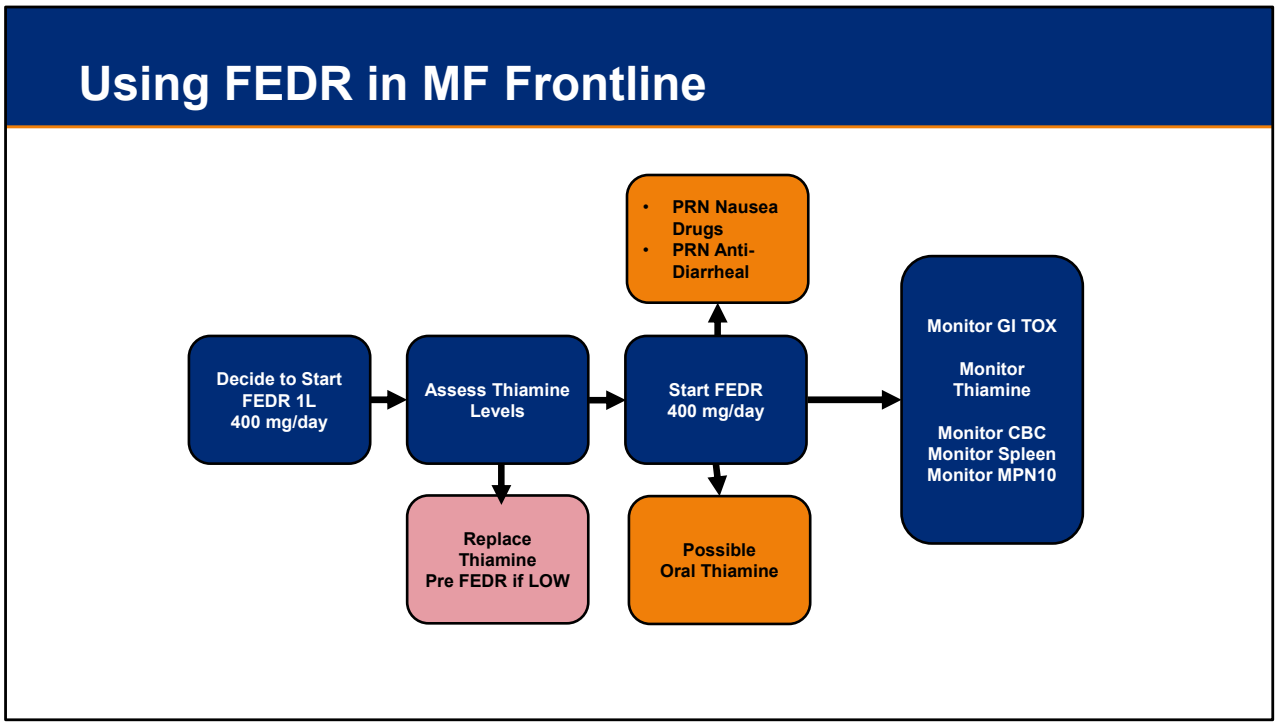
## NCCN Guidelines




https://www.nccn.org/professionals/physician_gls/pdf/mpn_blocks.pdf

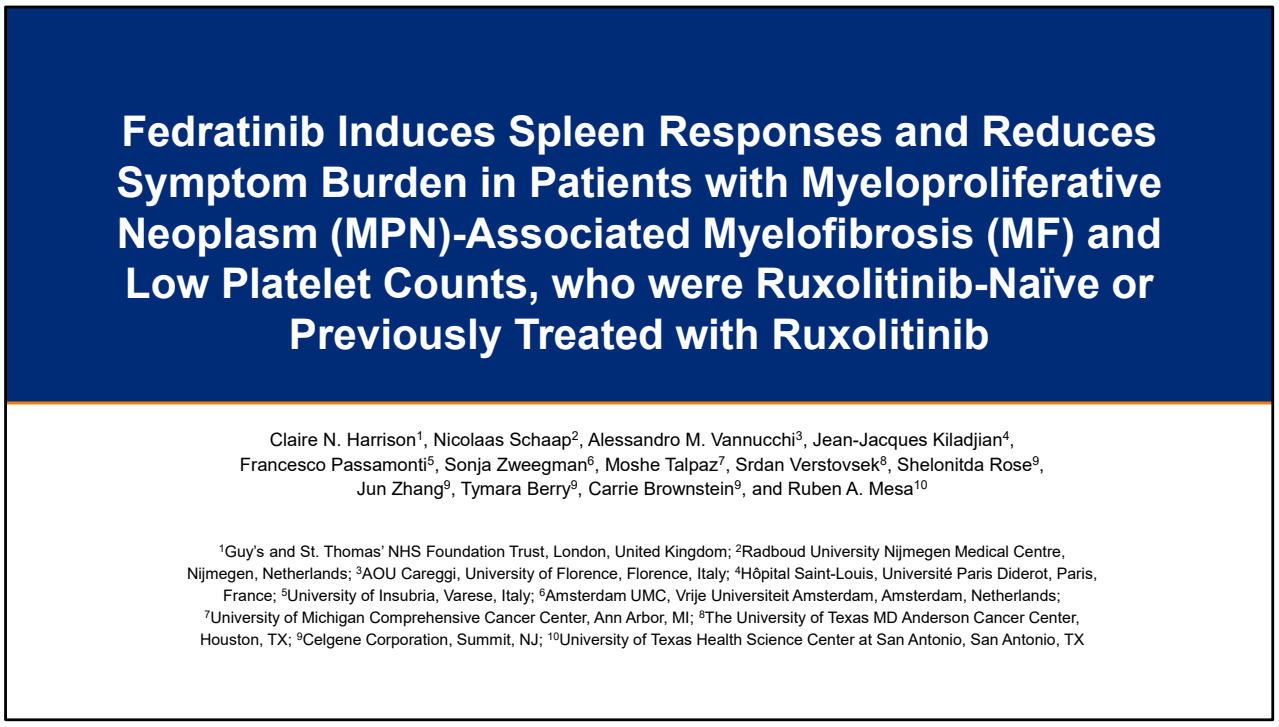
It has been incorporated in the NCCN Guidelines, both as frontline therapy-- and as I'll show you, we're particularly considering individuals with moderate thrombocytopenia of 50,000 to 100,000 platelets because it can be given at full dose. It can be used in the second-line setting and is the sole approved option in the second-line setting for myelofibrosis.

# The Expanding Role of JAK Inhibitors in MF




What is using it in the frontline look like? Well, if I decide to start fedratinib, they get 400 milligrams a day. We assess thiamine levels and replace thiamine if the levels are low. I largely have patients take thiamine anyway. It's very inexpensive. It's easy to take. It's pretty non-toxic and can adjust over time. I will give them PRN nausea and diarrhea drugs. Most patients are able to discontinue those. We start the therapy and monitor for any GI toxicity, monitor for thiamine levels, and, of course, are monitoring for response by blood counts, spleen size, and symptoms using the MPN10.

# The Expanding Role of JAK Inhibitors in MF



**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**

Claire N. Harrison[1], Nicolaas Schaap[2], Alessandro M. Vannucchi[3], Jean-Jacques Kiladjian[4], Francesco Passamonti[5], Sonja Zweegman[6], Moshe Talpaz[7], Srdan Verstovsek[8], Shelonitda Rose[9], Jun Zhang[9], Tymara Berry[9], Carrie Brownstein[9], and Ruben A. Mesa[10]

[1]Guy's and St. Thomas' NHS Foundation Trust, London, United Kingdom; [2]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands; [3]AOU Careggi, University of Florence, Florence, Italy; [4]Hôpital Saint-Louis, Université Paris Diderot, Paris, France; [5]University of Insubria, Varese, Italy; [6]Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, Netherlands; [7]University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; [8]The University of Texas MD Anderson Cancer Center, Houston, TX; [9]Celgene Corporation, Summit, NJ; [10]University of Texas Health Science Center at San Antonio, San Antonio, TX

Now, I mentioned that individuals with a moderate thrombocytopenia were able to dose at full dose. Dr. Harrison and I presented with colleagues,

# The Expanding Role of JAK Inhibitors in MF

## Study Designs

| | JAKARTA | JAKARTA2 |
|---|---|---|
| Study phase | III | II |
| Study design | Randomized, double-blind, placebo-controlled | Single-arm |
| Treatment arms | Placebo<br>FEDR 400<br>FEDR 500 | FEDR 400* |
| Study population | **JAK inhibitor-naïve** | **Prior ruxolitinib treatment** |
| | Int-2, High risk | Int-1 (symptomatic), Int-2, High risk |
| | Primary, post-ET, or post-PV MF | Primary, post-ET, or post-PV MF |
| Primary endpoint | SVRR at EOC6†‡ | SVRR at EOC6† |
| Key secondary endpoint | Symptom RR at EOC6§ | Symptom RR at EOC6§ |

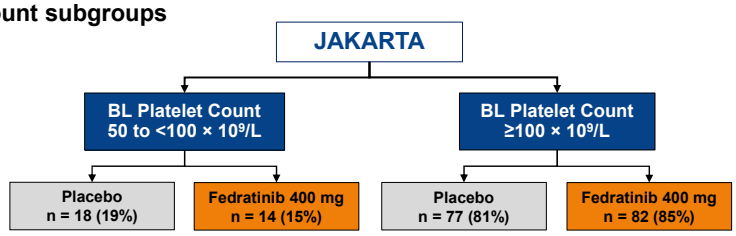
*Starting dose. Dose-escalation was permitted up to 600 mg/day if a patient experienced <50% reduction in spleen size at end of cycle 2 or cycle 4.
†Proportion of patients who achieved a ≥35% reduction in spleen volume from BL to end of cycle 6 (EOC6).
‡For primary analysis, spleen volume responses at EOC6 were confirmed 4 weeks later; this analysis does not require 4-week confirmation.
§Proportion of patients who achieved a ≥50% reduction from BL to EOC6 in total symptom score (TSS) on the modified MFSAF.
EOC6, end of cycle 6; ET, essential thrombocythemia; FEDR, fedratinib; Int, intermediate; JAK, Janus kinase; PV, polycythemia vera; RR, response rate; SVRR, spleen volume RR.
Harrison C, et al. *Blood*. 2019;134(Supplement_1):4165.

a combined abstract for ASH of 2019, looking at individuals who received 400 milligrams of fedratinib with a platelet count of 50,000 to 100,000.

# The Expanding Role of JAK Inhibitors in MF

## Jakarta: Patients

- 96 patients received fedratinib 400 mg/day and 95 received placebo
- **Median duration of exposure for this analysis was 24 weeks in both treatment arms and across BL platelet count subgroups**




**Treatment Exposure**

| | Baseline Platelet Count | | | |
|---|---|---|---|---|
| | 50 to <100 × $10^9$/L | | ≥100 × $10^9$/L | |
| | Placebo | Fedratinib 400 mg | Placebo | Fedratinib 400 mg |
| Exposure, weeks, median (range) | 24 (2–26) | 24 (3–28) | 24 (2–26) | 24 (1–30) |

BL, baseline.

Harrison C, et al. *Blood*. 2019;134(Supplement_1):4165.

We identify here the group of individuals that fell into that category from the JAKARTA study.

# The Expanding Role of JAK Inhibitors in MF

## Jakarta: Baseline Characteristics

- BL characteristics were generally similar between treatment arms and platelet-count subgroups

| | Baseline Platelet Count | | | |
|---|---|---|---|---|
| | 50 to <100 × $10^9$/L | | ≥100 × $10^9$/L | |
| | Placebo (n = 18) | Fedratinib 400 mg (n = 14) | Placebo (n = 77) | Fedratinib 400 mg (n = 82) |
| Age, years, median (range) | 66.5 (38–82) | 68.0 (50–86) | 66.0 (27–85) | 62.5 (39–79) |
| Disease setting, n (%) | | | | |
| Primary MF | 14 (78) | 8 (57) | 43 (56) | 54 (66) |
| Post-PV MF | 1 (6) | 4 (29) | 26 (34) | 20 (24) |
| Post-ET MF | 3 (17) | 2 (14) | 8 (10) | 8 (10) |
| Risk status, n (%) | | | | |
| Intermediate-2 | 7 (39) | 5 (36) | 39 (51) | 52 (63) |
| High | 11 (61) | 9 (64) | 38 (49) | 30 (37) |
| Time since MF diagnosis, months, median (range) | 14 (0.2–126) | 56 (0.8–171) | 34 (0.8–413) | 42 (1.1–311) |
| RBC transfusion-dependent, n (%) | 2 (11) | 2 (14) | 4 (5) | 6 (7) |
| Spleen size >10 cm, n (%) | 12 (67) | 9 (64) | 59 (77) | 59 (72) |
| Spleen volume, mL, median (range) | 2400 (670–6054) | 2867 (1058–5049) | 2773.5 (662–7911) | 2652 (316–6430) |
| MFSAF total symptom score, mean [SD] | n=16<br>15.3 [13.4] | n=13<br>11.8 [10.6] | n=65<br>15.5 [11.5] | n=76<br>13.6 [16.6] |

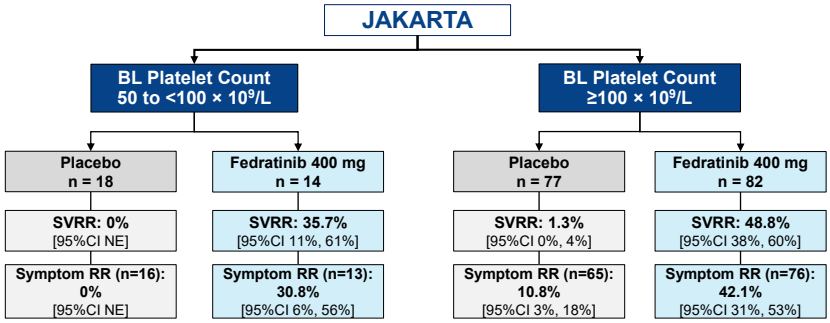
BL, baseline; ET, essential thrombocythemia; MF, myelofibrosis; MFSAF, MF Symptom Assessment Form; PV, polycythemia vera; RBC, red blood cells.
Harrison C, et al. *Blood*. 2019;134(Supplement_1):4165.

Baseline characteristics that were fairly similar with, obviously, very active disease regardless of the platelet count.

# The Expanding Role of JAK Inhibitors in MF

## 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*<0.0001)
- 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.
CI, confidence interval; BL, baseline; NE, not estimable; RR, response rate; SVRR, spleen volume response rate.
Harrison C, et al. *Blood*. 2019;134(Supplement_1):4165.

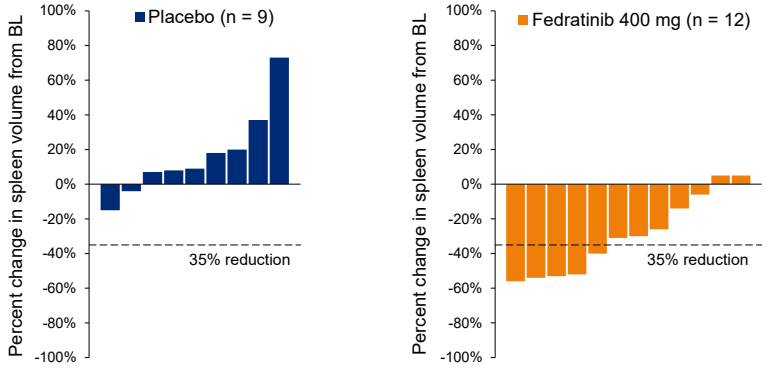
In terms of response, we saw very solid response rates for spleen volume reduction and symptom improvement in individuals with marked thrombocytopenia and that there was no significant increase in toxicity in this group and they were able to be dosed at full dose. Why this matters is that for 50,000 to 100,000 platelets, we typically do dose-reduce ruxolitinib and there may well be an advantage to fully dosing this group of individuals.

# The Expanding Role of JAK Inhibitors in MF

## 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

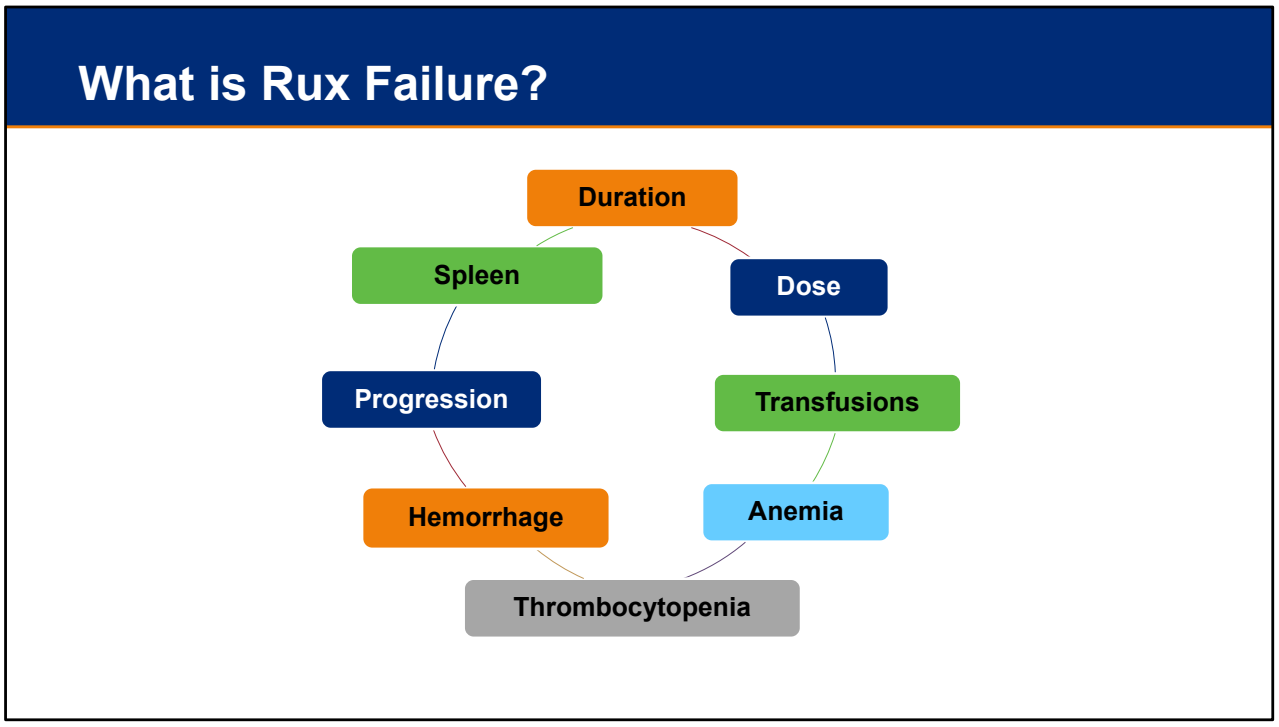
**BL Platelet Count: 50 to <100 × $10^9$/L**




BL, baseline EOC6, end of cycle 6.
Harrison C, et al. *Blood*. 2019;134(Supplement_1):4165.

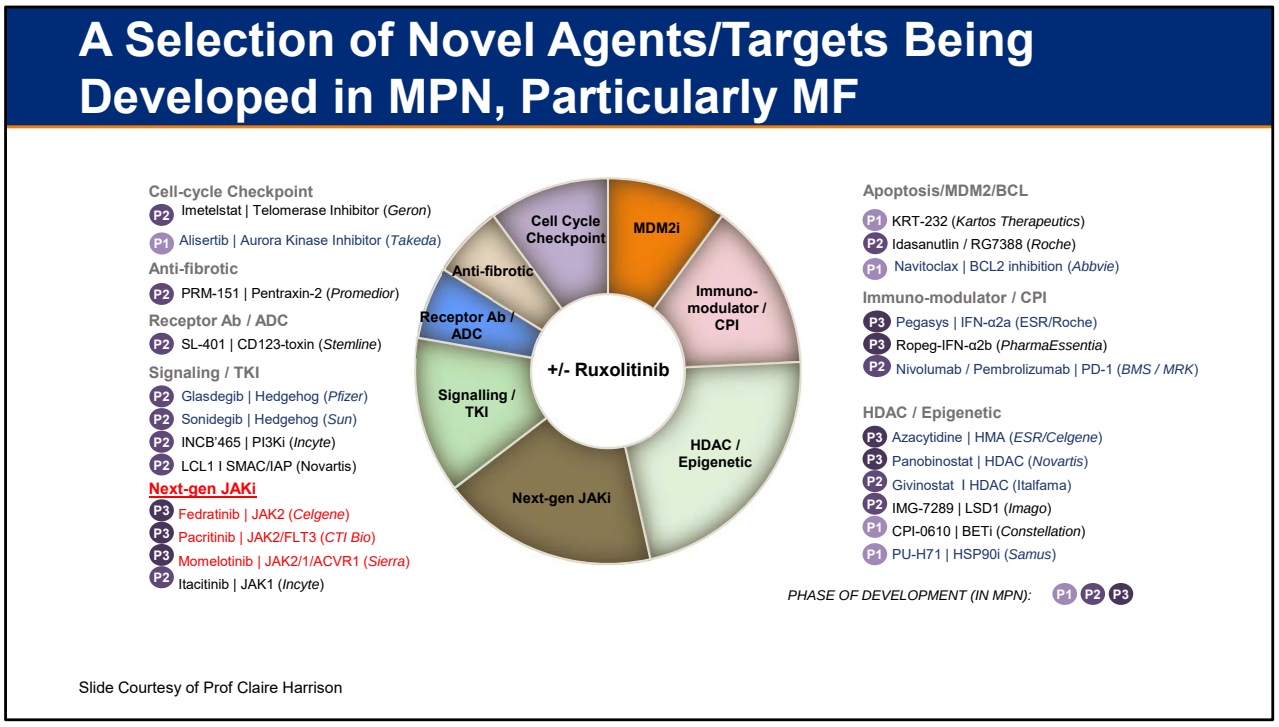
This showing improvement in the spleen volume for this group of individuals with moderate thrombocytopenia.

# The Expanding Role of JAK Inhibitors in MF



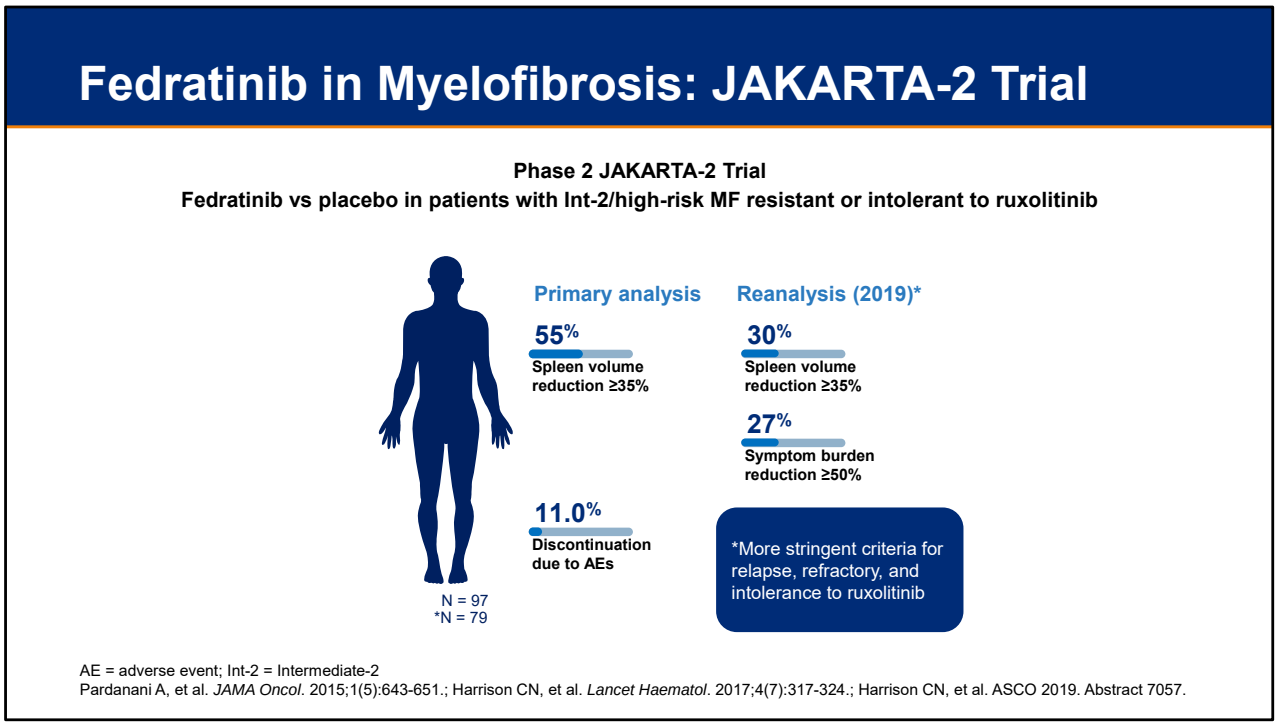

Now, what about second-line? Well, ruxolitinib has been approved and was approved as a sole agent from 2012 through 2019. Certainly, there is great experience in the community using it. What is failure? Well, I like to say that failing a drug is very much dependent upon what the other option is. If you've got many other options, the bar for failing is probably lower. If you don't have any other options, the bar for failing is probably quite high. Things I consider in terms of this discussion is dose, cytopenias, spleen size, et cetera.

# The Expanding Role of JAK Inhibitors in MF




There is a robust pipeline of new therapies being looked at for second-line therapy. I mentioned the other JAK inhibitors in development. There are multiple other approaches. Many of them in combination with a base of JAK inhibition. That might be ruxolitinib, that might be fedratinib, but in cell cycle checkpoint inhibitors, anti-fibrosing agents, other tyrosine kinase inhibitors, agents impacting the apoptotic pathway, immunomodulation, or a lot of activity with epigenetic modifiers, with drugs such as LSD1 inhibitor from Imago, the BET inhibitor from Constellation Pharmaceuticals, all being in advanced clinical trials.

# The Expanding Role of JAK Inhibitors in MF




I mentioned that fedratinib was approved after the basis also of a second-line study. That was the JAKARTA study led by Professor Harrison and I. We had reported an initial response rate but then conducted a reanalysis in 2019 using stricter, more modern criteria of what it meant to respond, what it meant to fail ruxolitinib, and having an adequate trial of the drug to be able to assess.

## The Expanding Role of JAK Inhibitors in MF

# Fedratinib in Patients with Myeloproliferative Neoplasm-Associated Myelofibrosis Previously Treated with Ruxolitinib: A Reanalysis of the Phase 2 JAKARTA2 Study

Claire N. Harrison[1], Nicolaas Schaap[2], Alessandro M Vannucchi[3], Jean-Jacques Kiladjian[4], Eric Jourdan[5], Richard T. Silver[6], Harry C. Schouten[7], Francesco Passamonti[8], Sonja Zweegman[9], Moshe Talpaz[10], Srdan Verstovsek[11], Torsten Gerike[12], Shelonitda Rose[12], Mingyu Li[12], Carrie Brownstein[12], Ruben A Mesa[13]

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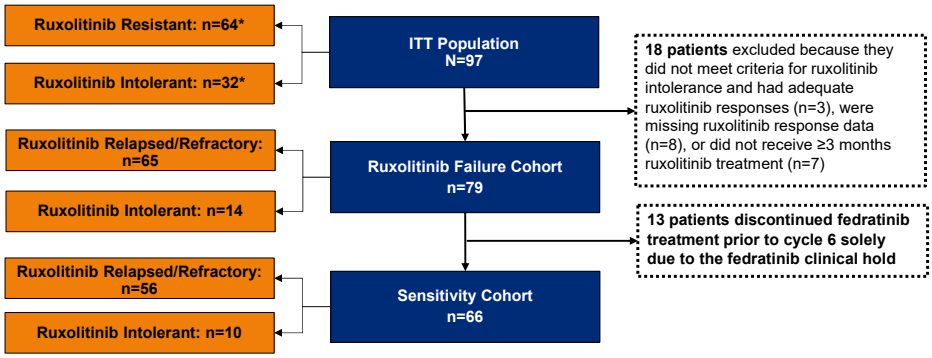
We presented these results at ASH 2019.

# The Expanding Role of JAK Inhibitors in MF

## Patients

- Median prior ruxolitinib treatment durations were 10.7 months (range 1.0 – 62.4) in the ITT population and 11.5 months in both the ruxolitinib failure and sensitivity cohorts




*1 patient categorized as "Other: lack of efficacy"
Harrison CN, et al. *J Hematol.* 2020;95(6):594-603.

And had three cohorts, an overall intention to treat population, those that had failed rux by more modern criteria, and a sensitivity cohort. That group that had both failed by modern criteria and had a sufficient trial of fedratinib to know the benefit.

# The Expanding Role of JAK Inhibitors in MF

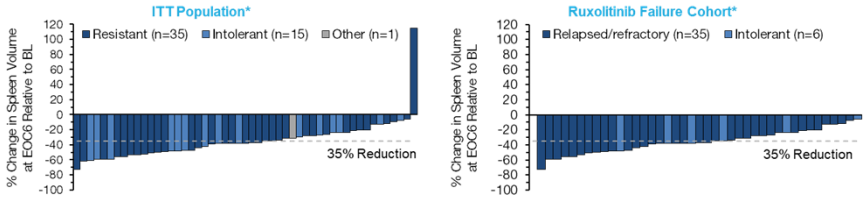
## Spleen and Symptom Response Rates

- Clinically relevant prognostic baseline disease characteristics indicate a population of difficult-to-treat patients with advanced MF disease and high-disease burden
- Spleen volume and symptom response rates were consistent among the three patient cohorts
- Median duration of spleen response was not reached (95% CI 7.2 months, NR) in the ITT population, ruxolitinib failure cohort, or sensitivity cohort

| | ITT Population (N=97) | | Ruxolitinib Failure Cohort (n=79) | | Sensitivity Cohort (n=66) | |
|---|---|---|---|---|---|---|
| | N | % of Patients (95% CI) | N | % of Patients (95% CI) | N | % of Patients (95% CI) |
| Spleen volume response rate | 97 | 31% (22%, 41%) | 79 | 30% (21%, 42%) | 66 | 36% (25%, 49%) |
| Symptom response rate* | 90 | 27% (18%, 37%) | 74 | 27% (17%, 39%) | 62 | 32% (21%, 45%) |

*Includes patients with an evaluable baseline and ≥1 post-baseline MFSAF assessment.

**Individual Changes in Spleen Volume from Baseline to End of Cycle 6**




Harrison CN, et al. *J Hematol.* 2020;95(6):594-603.

Here showing the waterfall plots, you see the improvements in spleen and symptoms. Showing significant activity and response in roughly 27- to 30-something percent of the individuals.

# The Expanding Role of JAK Inhibitors in MF


It is an exciting time for new options for patients with myelofibrosis. We have ruxolitinib that we have learned much about, to use an adequate dose, to adequately achieve a response. We have fedratinib, an option in particular for consideration for individuals with moderate thrombocytopenia and most clearly as an option in the second-line setting. I would encourage you if you have individuals that have failed ruxolitinib, you don't have a good clinical trial, you should definitely be considering fedratinib. We have a robust pipeline of new options being developed. There will be options for patients with myelofibrosis. Looking into the future, I think we really will have a base of, one, the patient optimizes their JAK inhibitor. Is that rux? Is that fedratinib? Is that some other agent? Two, in select individuals based on response, molecular profile, or other parameters. We will then add in another agent. A BET inhibitor, an epigenetic modifier, or some other approach.

With that, I'd like to conclude but certainly thank all of my colleagues. We all participate in trials together. There's much team science in the MPN arena and our work regarding quality of life led by our MPN Quality of Life Study Group. Thank you.