Jakafi®
ruxolitinib (tablets)
5mg • 10mg • 15mg • 20mg • 25mg

A JAK inhibitor in MF with 5-year OS data[1-4]

For adults with intermediate- or high-risk MF[1]

INTERVENE AT DIAGNOSIS

TO HELP ACHIEVE TREATMENT GOALS

NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY (NCCN GUIDELINES®) RECOMMENDED

Ruxolitinib (Jakafi) is a Category 1* initial treatment option for patients with higher-risk MF† and platelets ≥50 × 10^9/L and a Category 2A‡ treatment option for patients with symptomatic lower-risk MF.[5§]

*Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.[5]
†In patients who are not transplant candidates.[5]
‡Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.[5]
§Lower-risk MF is defined as low or intermediate-1 risk based on DIPSS, DIPSS-Plus, and MYSEC-PM; low or intermediate risk based on MIPSS-70 (threshold of ≤3 prognostic variable points); and very low, low, or intermediate risk based on MIPSS-70+ Version 2.0 (threshold of ≤3 prognostic variable points).[5]

DIPSS=Dynamic International Prognostic Scoring System; JAK=Janus kinase; MF=myelofibrosis; MIPSS=Mutation-enhanced International Prognostic Score System; MYSEC-PM=myelofibrosis secondary to PV and ET-prognostic model; NCCN=National Comprehensive Cancer Network; OS=overall survival.

INDICATIONS AND USAGE

Jakafi® (ruxolitinib) is indicated for treatment of intermediate or high-risk myelofibrosis (MF), including primary MF, post–polycythemia vera MF and post–essential thrombocythemia MF in adults.

IMPORTANT SAFETY INFORMATION

- Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated
- Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary
- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi
- Severe neutropenia (ANC <0.5 × 10^9/L) was generally reversible by withholding Jakafi until recovery

Please see related and other Important Safety Information on pages 14-15.
Please click here for Full Prescribing Information.

MF management should focus on achieving 3 key treatment goals, including overall survival[5,6]

SPLEEN SIZE

MF-RELATED SYMPTOMS

OVERALL SURVIVAL

When managing patients with MF, my goals include control of the **SPLEEN** and **SYMPTOMS**, with an ultimate goal of **OVERALL SURVIVAL**.

—***Ruben Mesa, MD, FACP***
MPN Expert

IMPORTANT SAFETY INFORMATION (continued)

Risk of infection

- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines
- Tuberculosis (TB) infection has been reported. Observe patients taking Jakafi for signs and symptoms of active TB and manage promptly. Prior to initiating Jakafi, evaluate patients for TB risk factors and test those at higher risk for latent infection. Consult a physician with expertise in the treatment of TB before starting Jakafi in patients with evidence of active or latent TB. Continuation of Jakafi during treatment of active TB should be based on the overall risk-benefit determination
- Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi treatment. If PML is suspected, stop Jakafi and evaluate
- Herpes zoster infection has been reported in patients receiving Jakafi. Advise patients about early signs and symptoms of herpes zoster and to seek early treatment. Herpes simplex virus reactivation and/or dissemination has been reported in patients receiving Jakafi. Monitor patients for the development of herpes simplex infections. If a patient develops evidence of dissemination of herpes simplex, consider interrupting treatment with Jakafi; patients should be promptly treated and monitored according to clinical guidelines

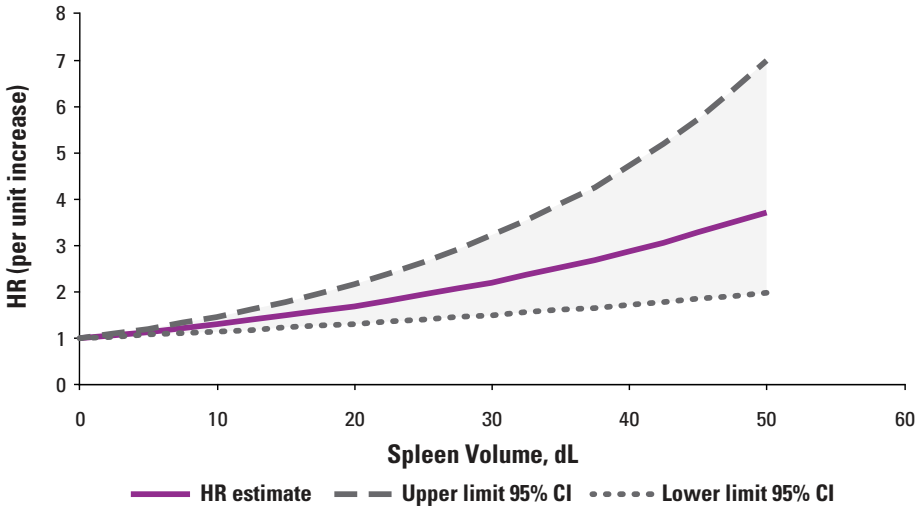
Palpable spleen is a marker of disease progression and is associated with poor overall survival[7,8]

~90% In a study of 1054 patients with primary MF,* approximately 90% of patients had a palpable spleen at diagnosis[9]

- A palpable spleen of ≥5 cm below the left costal margin constitutes progressive disease,† according to the IWG-MRT and ELN response criteria[7]

Larger baseline spleen volume was associated with incremental increases in the risk of death[8]

Relationship Between Spleen Volume and Risk of Death in the COMFORT Studies[8]



- In a post hoc pooled analysis of overall survival in the COMFORT studies (N=528), there was a 14% increase in the risk of death for each additional 5 dL in spleen volume at baseline over 3 years (HR, 1.14; 95% CI, 1.07-1.21)[8‡]
- These increases were seen irrespective of treatment[8]

"When my adult patients with intermediate- to high-risk myelofibrosis are experiencing any degree of splenomegaly at diagnosis, that is a sign that I need to intervene with Jakafi.

—***Salman Fazal, MD,*** *<Allegheny Health Network>*

*Data were available for 768 patients, 681 of whom had palpable splenomegaly.[9]

†Progressive disease assignment for splenomegaly requires confirmation by CT or MRI showing a ≥25% increase in spleen volume from baseline. Baseline values for both physical examination and imaging studies refer to pretreatment baseline and not to posttreatment measurements.[7]

‡A post hoc pooled analysis of overall survival with ruxolitinib was performed using data from the two phase 3 studies: COMFORT-I, a randomized, double-blind, placebo-controlled study with 309 patients with intermediate-2–risk or high-risk MF, and COMFORT-II, a randomized, open-label study with 219 patients with intermediate-2–risk or high-risk MF. The primary endpoint in both studies was the proportion of patients achieving a ≥35% reduction in spleen volume (measured by CT or MRI)—at week 24 in COMFORT-I and at week 48 in COMFORT-II.[4,8,10]

CI=confidence interval; COMFORT=COntrolled MyeloFibrosis study with ORal JAK inhibitor Treatment; CT=computed tomography; ELN=European LeukemiaNet; HR=hazard ratio; IWG-MRT=International Working Group-Myeloproliferative Neoplasms Research and Treatment; MRI=magnetic resonance imaging.

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For adults with intermediate- or high-risk MF[1]

At diagnosis, intervene with Jakafi® (ruxolitinib)...

COMFORT-I primary endpoint*

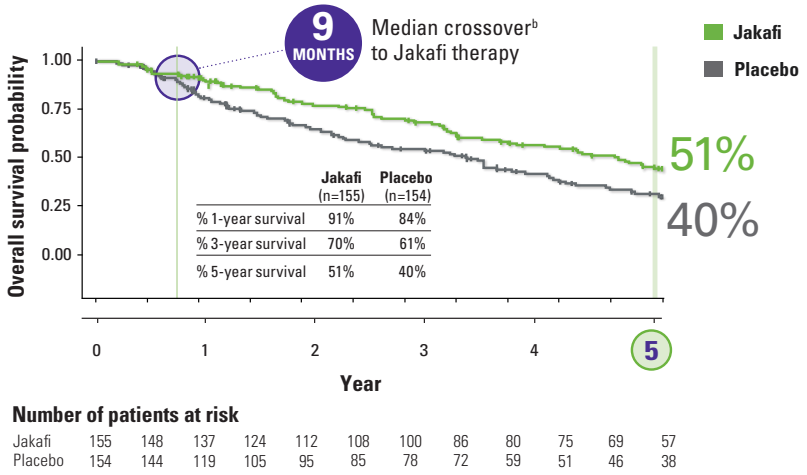
42% of patients receiving Jakafi achieved a ≥35% reduction in spleen volume at week 24 vs 0.7% of patients receiving placebo (P<0.0001)[1,10]

- **4.4 years** median duration of spleen response among primary responders (n=65)[2†]
- **99% of patients** experienced some reduction in spleen volume on Jakafi[10,11]

COMFORT-I 5-year overall survival analysis‡: Jakafi and placebo

- At 3 years, survival probability was 70% for patients originally randomized to Jakafi and 61% for those originally randomized to placebo[1]
- Overall survival was a prespecified secondary endpoint in COMFORT-I[1]

Overall Survival Kaplan-Meier Curves by Treatment Group in COMFORT-I[1-3,a]



All patients in the placebo group either crossed over to Jakafi at a median of 9 months or discontinued.[1]

[a]COMFORT-I was not designed to compare survival probabilities between Jakafi and placebo at 3 or 5 years.[2]

[b]Patients randomized to placebo were eligible to cross over to receive Jakafi because of progression-driven events or at the physician's discretion; however, these patients continued to be grouped within their original randomized assignment for analysis purposes.[2]

"As a clinician, I want a therapy that can help meet my treatment goals. And seeing the impact of Jakafi on spleen volume reduction and overall survival gives me the confidence to intervene with Jakafi at diagnosis, instead of watching and waiting."

—***Ruben Mesa, MD, FACP***
MPN Expert

*COMFORT-I was a randomized, double-blind, placebo-controlled phase 3 study with 309 patients with intermediate-2–risk or high-risk MF. The primary endpoint was the proportion of patients achieving a ≥35% reduction in spleen volume from baseline to week 24 as measured by CT or MRI.[1,10]

†Duration of spleen response was defined as the interval between the first spleen response measurement that was a ≥35% reduction from baseline and the date of the first measurement that was no longer a ≥35% reduction from baseline that was also a >25% increase from nadir.[2]

‡The 5-year overall survival analysis is not included in the Full Prescribing Information for Jakafi. Although the 3-year overall survival analysis is presented in the Full Prescribing Information, P values and hazard ratios are omitted from the overall survival Kaplan-Meier curves.[2]

BAT=best available therapy.

IMPORTANT SAFETY INFORMATION (continued)

Risk of infection (continued)

- Increases in hepatitis B viral load with or without associated elevations in alanine aminotransferase and aspartate aminotransferase have been reported in patients with chronic hepatitis B virus (HBV) infections. Monitor and treat patients with chronic HBV infection according to clinical guidelines

...a treatment with 5-year overall survival data[1-4]

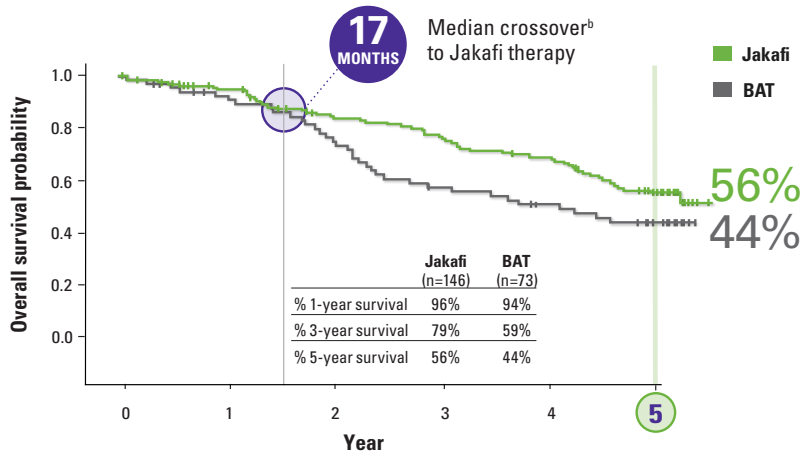
COMFORT-II primary endpoint[§]

29% of patients receiving Jakafi achieved a ≥35% reduction in spleen volume at week 48 vs 0% of patients receiving best available therapy[‖] (*P*<0.0001)[1,12]

COMFORT-II 5-year overall survival analysis[‡]: Jakafi and best available therapy

- At 3 years, survival probability was 79% for patients originally randomized to Jakafi and 59% for those originally randomized to best available therapy[1]
- Overall survival was a prespecified secondary endpoint in COMFORT-II[1]

Overall Survival Kaplan-Meier Curves by Treatment Group in COMFORT-II[1,4,a]



All patients in the best available therapy group either crossed over to Jakafi at a median of 17 months or discontinued.[1]

[a]COMFORT-II was not designed to compare survival probabilities between Jakafi and BAT at 3 or 5 years.[2]

[b]Patients randomized to BAT were eligible to cross over to receive Jakafi because of progression-driven events or at the physician's discretion; however, these patients continued to be grouped within their original randomized assignment for analysis purposes.[2]

I do not use hydroxyurea for my myelofibrosis patients. The overall survival data available from COMFORT studies give me the confidence of prescribing Jakafi for my appropriate patients at diagnosis and not to delay the treatment.

—***Salman Fazal, MD***
<Allegheny Health Network>

[§]COMFORT-II was a randomized, open-label phase 3 study with 219 patients with intermediate-2–risk or high-risk MF. The primary endpoint was the proportion of patients achieving a ≥35% reduction in spleen volume from baseline at week 48 as measured by CT or MRI.[1,4]

[‖]BAT in COMFORT-II included hydroxyurea (46.6%) and glucocorticoids (16.4%), as well as no medication, anagrelide, epoetin alfa, thalidomide, lenalidomide, mercaptopurine, thioguanine, danazol, peginterferon alfa-2a, interferon-α, melphalan, acetylsalicylic acid, cytarabine, and colchicine.[2]

BAT=best available therapy.

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Post hoc pooled analysis of COMFORT trials*

Earlier vs later initiation of Jakafi® (ruxolitinib) and spleen volume reduction

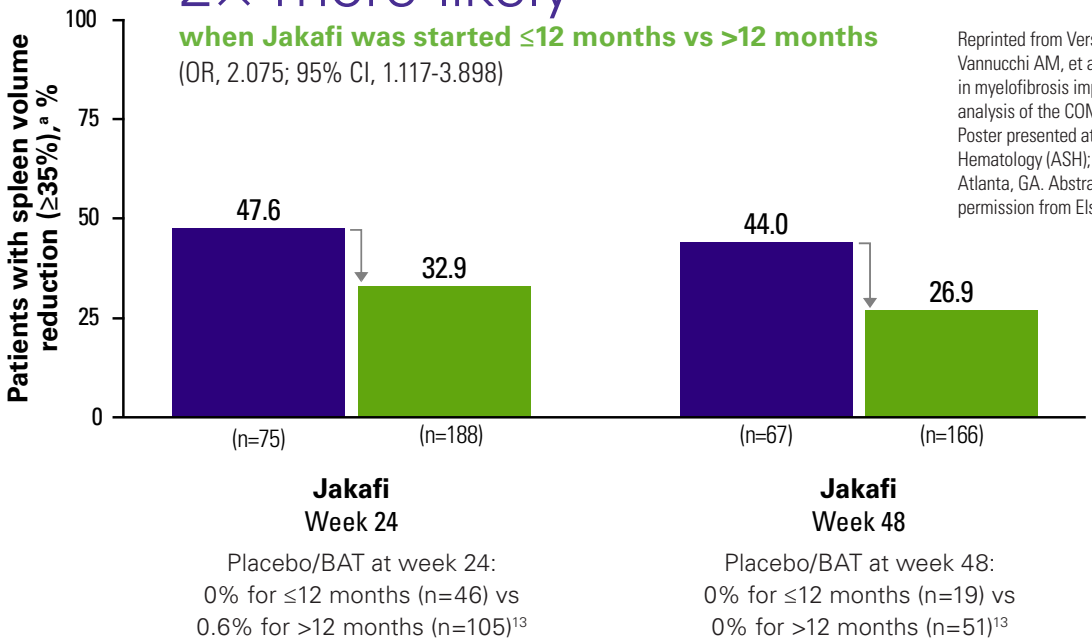
Proportion of Patients Achieving a Reduction in Spleen Volume at Weeks 24 and 48 by MF Disease Duration (≤12 vs >12 Months)[13]

Spleen volume response was

2× more likely

when Jakafi was started ≤12 months vs >12 months

(OR, 2.075; 95% CI, 1.117-3.898)



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[a]Spleen volume reduction data were missing from 111 patients at week 24 (Jakafi ≤12 months, n=9; Jakafi >12 months, n=28) and 222 patients at week 48 (Jakafi ≤12 months, n=17; Jakafi >12 months, n=50).[13]

*A post hoc pooled analysis of COMFORT-I and COMFORT-II assessed the association of MF disease duration before Jakafi treatment (≤12 or >12 months from diagnosis) with disease outcomes. Data from Jakafi-treated patients in both studies were combined and data from the placebo/BAT arms were pooled. COMFORT-I was a randomized, double-blind, placebo-controlled study with 309 patients with intermediate-2–risk or high-risk MF, and COMFORT-II was a randomized, open-label study with 219 patients with intermediate-2–risk or high-risk MF. The primary endpoint in both studies was the proportion of patients achieving a ≥35% reduction in spleen volume (measured by CT or MRI)—at week 24 in COMFORT-I and at week 48 in COMFORT-II.[1,4,10,13]

BAT=best available therapy.

IMPORTANT SAFETY INFORMATION (continued)

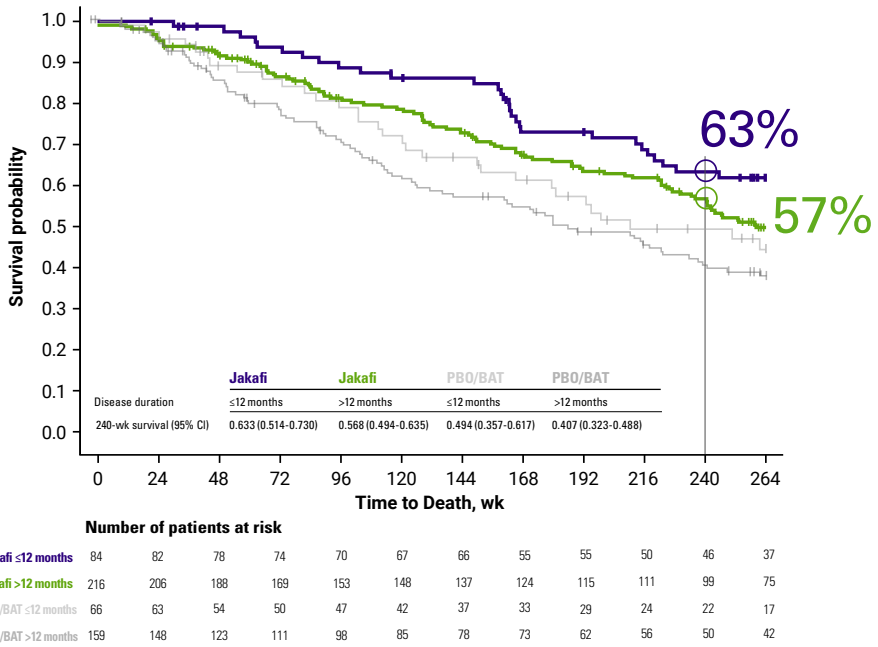
Risk for symptom exacerbation following interruption or discontinuation of Jakafi

- When discontinuing Jakafi, myeloproliferative neoplasm-related symptoms may return within one week. After discontinuation, some patients with myelofibrosis have experienced fever, respiratory distress, hypotension, DIC, or multi-organ failure. If any of these occur after discontinuation or while tapering Jakafi, evaluate and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi without consulting their physician. When discontinuing or interrupting Jakafi for reasons other than thrombocytopenia or neutropenia, consider gradual tapering rather than abrupt discontinuation

Post hoc pooled analysis of COMFORT trials*

Earlier vs later initiation of Jakafi and overall survival outcomes

Pooled OS of Patients With MF From COMFORT by MF Disease Duration From Diagnosis (≤12 vs >12 Months)[13,a]



Treated with Jakafi
- **MF duration ≤12 months** (n=84)
- **MF duration >12 months** (n=216)

Treated with PBO/BAT
- **MF duration ≤12 months** (n=66)
- **MF duration >12 months** (n=159)

Reprinted from Verstovsek S, Kiladjian J-J, Vannucchi AM, et al. Does early intervention in myelofibrosis impact outcomes? A pooled analysis of the COMFORT I and II studies. Poster presented at: American Society of Hematology (ASH); December 11-14, 2021; Atlanta, GA. Abstract 1505. Used with permission from Elsevier.

In a separate post hoc pooled analysis of overall survival in the COMFORT studies, each 10% reduction from baseline in spleen length at week 24 was associated with a 9% reduction in the risk of death for Jakafi-treated patients (HR, 0.91; 95% CI, 0.84-0.99; *P*=0.02).[8]

"

[In the] post hoc pooled analysis of these COMFORT trials, we can see the survival outcomes based on the time of Jakafi initiation. What we found was that there was a separation of the survival curves. These data inform my decision to intervene at diagnosis in my patients with MF, rather than watching and waiting.

—***Ruben Mesa, MD, FACP***
MPN Expert

"

BAT=best available therapy; OR=odds ratio; OS=overall survival; PBO=placebo.

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Jakafi® (ruxolitinib) adverse reactions

COMFORT-I hematologic adverse reactions[1,10]

Hematologic Adverse Reactions	Jakafi (n=155)		Placebo (n=151)	
	All Grades, %	Grades 3 and 4, %	All Grades, %	Grades 3 and 4, %
Anemia	96	45	87	19
Thrombocytopenia	70	13	31	1
Neutropenia	19	7	4	2

- The most frequently observed reactions were thrombocytopenia and anemia[1]
- Perform a pretreatment CBC, and monitor CBCs every 2 to 4 weeks until doses are stabilized and then as clinically indicated[1]

COMFORT-I and COMFORT-II discontinuation rates[1,2]

Hematologic Abnormality	Discontinuation Rate,[2] %	Management[1]
Thrombocytopenia	0.7	Manage by reducing the dose or temporarily interrupting Jakafi; if clinically indicated, platelet transfusions may be administered
Anemia	0.3	Some patients may require blood transfusions and/or dose modifications of Jakafi
Neutropenia	0.3	Generally reversible; temporarily withhold Jakafi until recovery

- At week 24, the discontinuation rates for adverse reactions, regardless of causality, were 11% in patients receiving Jakafi and 11% in patients receiving placebo[1,10]
- In COMFORT-I, 70% of patients required a dose adjustment in the first 12 weeks of therapy and 2% of patients discontinued therapy because of hematologic adverse reactions at week 24[2,14]
- <1% of patients receiving Jakafi in the COMFORT studies discontinued due to anemia or thrombocytopenia[1]

In COMFORT-I:

- 60% of patients treated with Jakafi and 38% of patients receiving placebo had red blood cell transfusions during randomized treatment[1]
- 123 of 155 patients in the group receiving Jakafi were transfusion independent at baseline compared with 119 of 151 patients in the group receiving placebo. Of the 123 transfusion-independent patients in the group receiving Jakafi, 27% became transfusion dependent* during the 8 weeks before data cutoff compared with 14.4% of patients in the group receiving placebo[2]

*New-onset transfusion dependency: the use of 2 or more units of red blood cell products during the final 8 weeks before database lock in a patient who was not transfusion dependent at baseline.[10]

COMFORT-I nonhematologic adverse reactions[1,2]

Nonhematologic Adverse Reactions	Jakafi (n=155)		Placebo (n=151)	
	All Grades, %	Grades 3 and 4, %	All Grades, %	Grades 3 and 4, %
Bruising	23	<1	15	0
Dizziness	18	<1	7	0
Headache	15	0	5	0
Urinary tract infection	9	0	5	1
Weight gain	7	<1	1	<1
Flatulence	5	0	<1	0
Herpes zoster	2	0	<1	0
Additional Nonhematologic Abnormalities	**Jakafi**		**Placebo**	
	All Grades,[a] %	Grades 3 and 4, %	All Grades,[a] %	Grades 3 and 4, %
ALT	27	1	8	0
AST	18	0	7	0
Cholesterol elevation	17	0	<1	0

[a]These lab values represent "new or worsening."

ALT=alanine transaminase; AST=aspartate transaminase; CBC=complete blood count.

IMPORTANT SAFETY INFORMATION (continued)

Other important safety considerations

- Non-melanoma skin cancers (NMSC) including basal cell, squamous cell, and Merkel cell carcinoma have occurred. Perform periodic skin examinations
- Treatment with Jakafi has been associated with increases in total cholesterol, low-density lipoprotein cholesterol, and triglycerides. Assess lipid parameters 8-12 weeks after initiating Jakafi. Monitor and treat according to clinical guidelines for the management of hyperlipidemia
- Another JAK-inhibitor has increased the risk of major adverse cardiovascular events (MACE), including cardiovascular death, myocardial infarction, and stroke (compared to those treated with tumor TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Jakafi particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur

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Jakafi® (ruxolitinib) safety and tolerability data: JUMP expanded-access study

JUMP study design[15]

- JUMP (JAK Inhibitor RUxolitinib in Myelofibrosis Patients) was a single-arm, open-label, phase 3b, expanded-access study that enrolled adult patients with primary or secondary MF classified as intermediate-1–, intermediate-2–, or high-risk MF. Patients with intermediate-1–risk MF were required to have a palpable spleen (≥5 cm from the costal margin)
  - The study enrolled 2233 patients. At study entry, 835 patients had intermediate-1–risk MF, 755 patients had intermediate-2–risk MF, and 194 patients had high-risk MF*†
- The primary endpoint was assessment of Jakafi safety and tolerability by the frequency, duration, and severity of adverse events. Additional endpoints included the proportion of patients with ≥50% reduction in palpable spleen length

JUMP hematologic adverse events[2,15]

Hematologic Adverse Events (≥5% of Patients)	**Full Cohort** (N=2233)*		**Intermediate-1–Risk MF** (n=835)		**Intermediate-2– and High-Risk MF** (n=949)	
	All Grades, %	Grades 3 and 4, %	All Grades, %	Grades 3 and 4, %	All Grades, %	Grades 3 and 4, %
Anemia	60	35	57	23	63	47
Thrombocytopenia	54	19	43	12	47	20
Neutropenia	7	5	6	4	8	6

JUMP nonhematologic adverse events[2,15]

Nonhematologic Adverse Events (≥5% of Patients)	**Full Cohort** (N=2233)*		**Intermediate-1–Risk MF** (n=835)		**Intermediate-2– and High-Risk MF** (n=949)	
	All Grades, %	Grades 3 and 4, %	All Grades, %	Grades 3 and 4, %	All Grades, %	Grades 3 and 4, %
Diarrhea	13	1	11	1	14	1
Pyrexia	16	2	14	1	18	4
Fatigue	10	1	10	1	11	1
Asthenia	15	2	16	2	14	2
Peripheral edema	9	1	8	1	9	1
Headache	9	0	12	0	6	0
Dyspnea	8	2	8	2	10	3
Abdominal pain	8	1	7	1	9	2
Nausea	6	0	6	0	6	0
Cough	9	0	9	0	8	0
Arthralgia	8	1	10	1	7	1
Pain in extremity	7	1	7	1	7	0
Nasopharyngitis	5	0	6	0	5	0
Urinary tract infection	6	1	7	1	6	2
Pruritus	6	0	7	0	5	0
Constipation	6	0	6	0	5	0
Pneumonia	7	5	6	4	10	6
Dizziness	5	0	5	0	6	0
Epistaxis	5	0	5	0	6	1

In the overall JUMP population, the safety profile was generally consistent with previous reports for Jakafi

- 58% of all enrolled patients (n=1283) completed treatment per protocol[15]
  - Completing treatment was defined as undergoing treatment for up to 24 months after the last patient's first visit or transitioning to a commercial drug
- The most common adverse events leading to discontinuation were thrombocytopenia (3%, 58/1784) and anemia (2%, 35/1784)[2]

*DIPSS scores were determined using patient characteristics at baseline. Results are based on a 07/05/17 cutoff date.

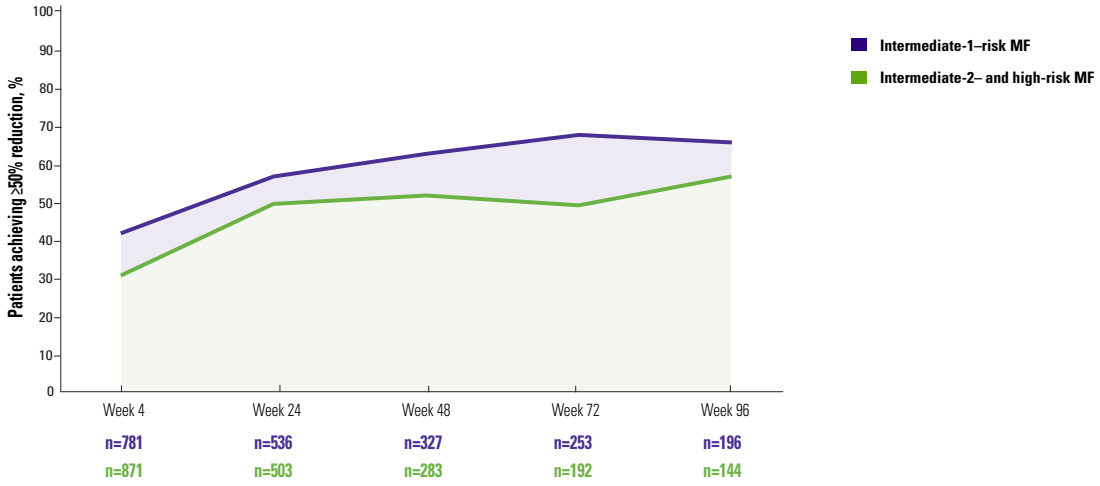
Reduction in spleen length by disease severity

JUMP efficacy data

- At week 96, 67% (423/636) of efficacy-evaluable patients achieved a ≥50% reduction from baseline in palpable spleen length[15]

Intermediate-1–risk MF and intermediate-2–risk MF to high-risk MF[2,15]

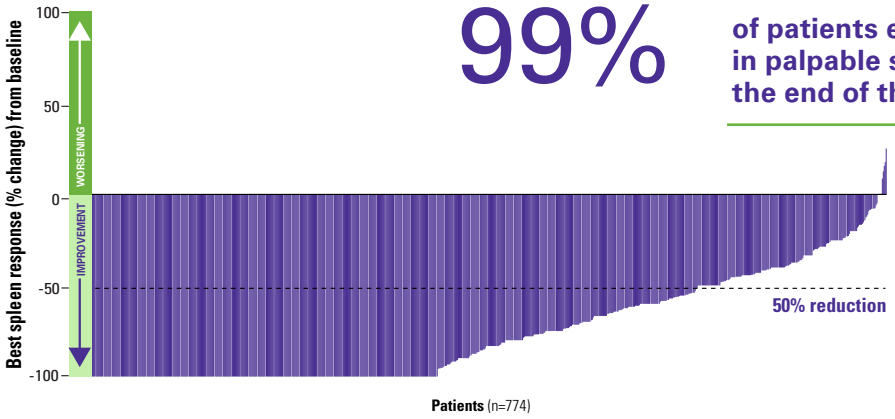
Reduction in Palpable Spleen Length Over Time†



†Patients who were not classified into a risk group (n=389) and patients with low-risk MF (n=60) are not included in the data shown.[15]

Intermediate-1–risk MF[2]

Best Percentage Change From Baseline in Palpable Spleen Length Through End of Study



99%

of patients experienced a reduction in palpable spleen length through the end of the study[2]

"One question I am often asked is...would I initiate Jakafi for my intermediate-1–risk patients or those appropriate patients that are earlier in the course of the disease? And my answer is yes."

—***Salman Fazal, MD,*** *<Allegheny Health Network>*

Please see related and other Important Safety Information on pages 14-15. Please click here for Full Prescribing Information.

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Dose optimization is key to maintaining balance of safety and efficacy

1 START: For adults with intermediate- or high-risk MF, the recommended starting doses are based on platelet counts[1]

- A CBC and platelet count must be performed before initiating Jakafi® (ruxolitinib)[1]

Platelet count
50 to <100 × 10^9/L
5 mg twice daily

Platelet count
100 to 200 × 10^9/L
15 mg twice daily

Platelet count
>200 × 10^9/L
20 mg twice daily

Special populations: Please refer to the Full Prescribing Information for starting dose and other dose modifications, and for when to avoid treatment in patients with renal or hepatic impairment and in those receiving concomitant strong CYP3A4 inhibitors or fluconazole.

2 MONITOR: Monitoring patients after initiation of Jakafi is essential, especially during the first 12 weeks of therapy

- A CBC and platelet count must be performed every 2 to 4 weeks until doses are stabilized, and then as clinically indicated. Doses may be titrated based on safety and efficacy[1]
- 70% of patients receiving Jakafi in COMFORT-I required a dose adjustment in the first 12 weeks of therapy[14]

Monitoring blood counts and using appropriate dose management are essential to achieving desired efficacy and managing cytopenias[1]

IMPORTANT SAFETY INFORMATION (continued)

Other important safety considerations (continued)

- Another JAK-inhibitor has increased the risk of thrombosis, including deep venous thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. In patients with myelofibrosis (MF) and polycythemia vera (PV) treated with Jakafi in clinical trials, the rates of thromboembolic events were similar in Jakafi and control treated patients. Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately

Ensure that your patients are receiving the appropriate dose of Jakafi® (ruxolitinib)

3 OPTIMIZE: Individualize dosing of Jakafi to optimize balance between safety and efficacy[1]

Managing anemia and thrombocytopenia

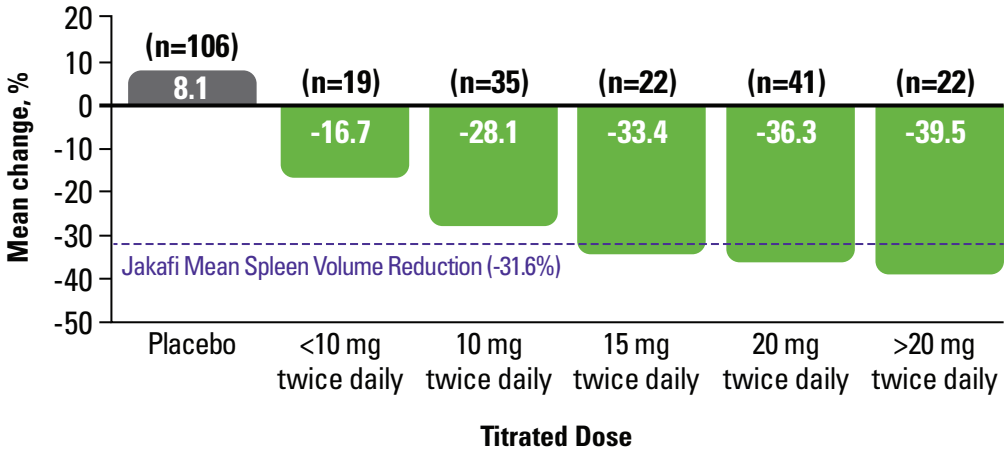
- In COMFORT-I, grades 3 and 4 thrombocytopenia or anemia occurred in 13% and 45% of patients receiving Jakafi, respectively. All grades of thrombocytopenia or anemia occurred in 70% and 96% of patients receiving Jakafi, respectively[1,10]
- Dose modifications, temporarily withholding Jakafi, and/or transfusions may be required for patients developing anemia or thrombocytopenia[1]
- Interrupt treatment for bleeding, neutropenia (ANC <0.5 × 10^9/L), or thrombocytopenia (based on starting platelet count)[1]

<1% of patients receiving Jakafi in the COMFORT studies discontinued due to anemia or thrombocytopenia[1]

Dose may be increased in the case of an insufficient response[1]

Efficacy based on titrated dose

COMFORT-I: Mean Change in Spleen Volume by Dose at Week 24[14]



- Doses may be increased if the response is insufficient and platelet, hemoglobin, and neutrophil counts are adequate and treatment has not been reduced or interrupted in the prior 4 weeks[1]
- Doses should not be increased during the first 4 weeks of therapy and not more frequently than every 2 weeks[1]
- Discontinue Jakafi if there is no spleen size reduction or symptom improvement after 6 months of therapy[1]
- In patients with starting platelet counts ≥100 × 10^9/L, based on limited clinical data, long-term maintenance at a 5-mg twice daily dose has not shown responses. Continued use at this dose should be limited to patients in whom the benefits outweigh the potential risks[1]

ANC=absolute neutrophil count.

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Jakafi® ruxolitinib (tablets)
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IMPORTANT SAFETY INFORMATION

- Treatment with Jakafi® (ruxolitinib) can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated
- Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary
- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi
- Severe neutropenia (ANC $<0.5 \times 10^9$/L) was generally reversible by withholding Jakafi until recovery
- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines
- Tuberculosis (TB) infection has been reported. Observe patients taking Jakafi for signs and symptoms of active TB and manage promptly. Prior to initiating Jakafi, evaluate patients for TB risk factors and test those at higher risk for latent infection. Consult a physician with expertise in the treatment of TB before starting Jakafi in patients with evidence of active or latent TB. Continuation of Jakafi during treatment of active TB should be based on the overall risk-benefit determination
- Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi treatment. If PML is suspected, stop Jakafi and evaluate
- Herpes zoster infection has been reported in patients receiving Jakafi. Advise patients about early signs and symptoms of herpes zoster and to seek early treatment. Herpes simplex virus reactivation and/or dissemination has been reported in patients receiving Jakafi. Monitor patients for the development of herpes simplex infections. If a patient develops evidence of dissemination of herpes simplex, consider interrupting treatment with Jakafi; patients should be promptly treated and monitored according to clinical guidelines
- Increases in hepatitis B viral load with or without associated elevations in alanine aminotransferase and aspartate aminotransferase have been reported in patients with chronic hepatitis B virus (HBV) infections. Monitor and treat patients with chronic HBV infection according to clinical guidelines
- When discontinuing Jakafi, myeloproliferative neoplasm-related symptoms may return within one week. After discontinuation, some patients with myelofibrosis have experienced fever, respiratory distress, hypotension, DIC, or multi-organ failure. If any of these occur after discontinuation or while tapering Jakafi, evaluate and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi without consulting their physician. When discontinuing or interrupting Jakafi for reasons other than thrombocytopenia or neutropenia, consider gradual tapering rather than abrupt discontinuation
- Non-melanoma skin cancers (NMSC) including basal cell, squamous cell, and Merkel cell carcinoma have occurred. Perform periodic skin examinations

IMPORTANT SAFETY INFORMATION (continued)

- Treatment with Jakafi has been associated with increases in total cholesterol, low-density lipoprotein cholesterol, and triglycerides. Assess lipid parameters 8-12 weeks after initiating Jakafi. Monitor and treat according to clinical guidelines for the management of hyperlipidemia
- Another JAK-inhibitor has increased the risk of major adverse cardiovascular events (MACE), including cardiovascular death, myocardial infarction, and stroke (compared to those treated with tumor TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Jakafi particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur
- Another JAK-inhibitor has increased the risk of thrombosis, including deep venous thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. In patients with myelofibrosis (MF) and polycythemia vera (PV) treated with Jakafi in clinical trials, the rates of thromboembolic events were similar in Jakafi and control treated patients. Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately
- Another JAK-inhibitor has increased the risk of lymphoma and other malignancies excluding NMSC (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. Patients who are current or past smokers are at additional increased risk. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Jakafi, particularly in patients with a known secondary malignancy (other than a successfully treated NMSC), patients who develop a malignancy, and patients who are current or past smokers
- In myelofibrosis and polycythemia vera, the most common nonhematologic adverse reactions (incidence ≥15%) were bruising, dizziness, headache, and diarrhea. In acute graft-versus-host disease, the most common nonhematologic adverse reactions (incidence >50%) were infections (pathogen not specified) and edema. In chronic graft-versus-host disease, the most common nonhematologic adverse reactions (incidence >20%) were infections (pathogen not specified) and viral infections
- Avoid concomitant use with fluconazole doses greater than 200 mg. Dose modifications may be required when administering Jakafi with fluconazole doses of 200 mg or less, or with strong CYP3A4 inhibitors, or in patients with renal or hepatic impairment. Patients should be closely monitored and the dose titrated based on safety and efficacy
- Use of Jakafi during pregnancy is not recommended and should only be used if the potential benefit justifies the potential risk to the fetus. Women taking Jakafi should not breastfeed during treatment and for 2 weeks after the final dose

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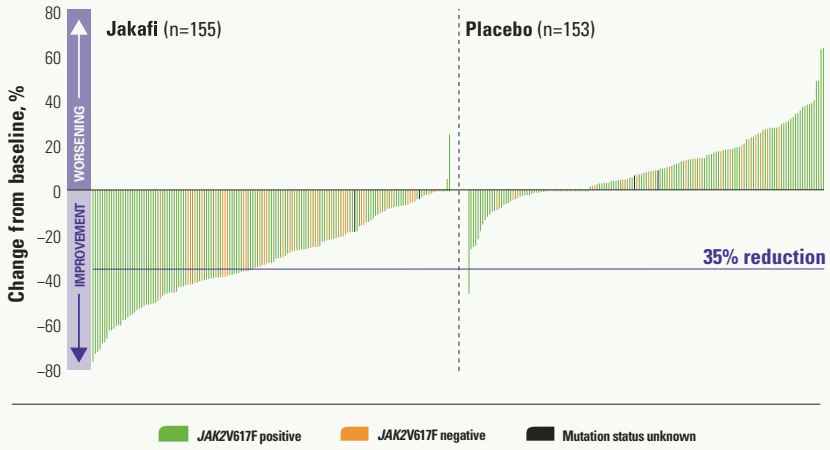
Jakafi® (ruxolitinib) additional information

Nearly all patients receiving Jakafi experienced a decrease in spleen volume[10,11]

COMFORT-I: Percent Change in Spleen Volume in Individual Patients From Baseline to Week 24 or Last Observation[1,2,10]



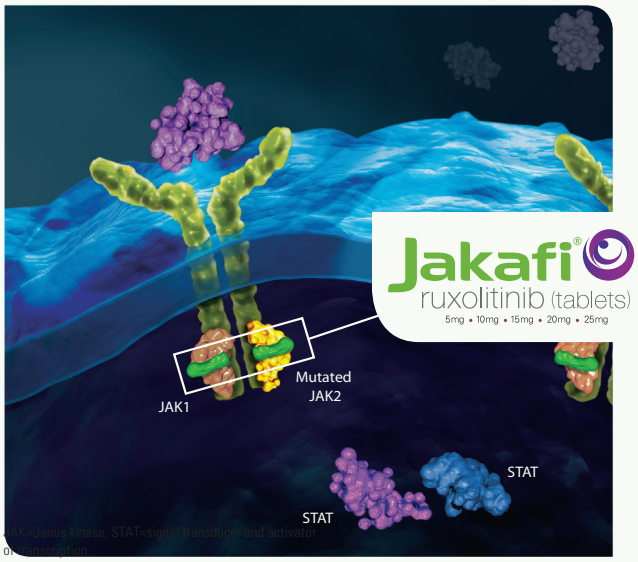
99%

of patients experienced some reduction in spleen volume on Jakafi[10,11]

Most patients receiving placebo experienced an increase in spleen volume.[1,10]

Each bar represents an individual patient's response.
From *The New England Journal of Medicine*, Verstovsek S, Mesa RA, Gotlib J, et al, A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis, 366(9), 799-807. Copyright © 2012 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Jakafi is a potent and highly selective JAK1 and JAK2 inhibitor[16]



JAK=Janus kinase; STAT=signal transducer and activator of transcription.

Jakafi targets a primary driver of MF[1]

JAK1

Plays a major role in signaling of key proinflammatory cytokines[16]

JAK2

Mediates signals for hematopoietic growth factors[16]

Jakafi can be used for appropriate patients regardless of JAK2 mutation status[16,17]

STAT=signal transducer and activator of transcription.

IMPORTANT SAFETY INFORMATION (continued)

Other important safety considerations (continued)

- Another JAK-inhibitor has increased the risk of lymphoma and other malignancies excluding NMSC (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. Patients who are current or past smokers are at additional increased risk. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Jakafi, particularly in patients with a known secondary malignancy (other than a successfully treated NMSC), patients who develop a malignancy, and patients who are current or past smokers
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For adults with intermediate- or high-risk MF[1]

INTERVENE AT DIAGNOSIS

TO HELP ACHIEVE TREATMENT GOALS[1-4]

"Given these data, I actively manage my appropriate patients with MF that have any degree of palpable splenomegaly at diagnosis. The support for intervening with Jakafi at diagnosis comes from the COMFORT trials, which showed the impact of Jakafi on spleen volume reduction and overall survival, a secondary endpoint."

—***Ruben Mesa, MD, FACP***
MPN Expert

COMFORT-I Results

Patients Achieving ≥35% Spleen Volume Reduction

42%

at 24 weeks vs 0.7% for placebo (*P*<0.0001)[1,10]

Overall Survival Probability

3 years:	5 years:
70%	**51%**
and 61% for placebo[1]	**and 40% for placebo[2]**

COMFORT-II Results

Patients Achieving ≥35% Spleen Volume Reduction

29%

at 48 weeks vs 0% for BAT (*P*<0.0001)[1]

Overall Survival Probability

3 years:	5 years:
79%	**56%**
and 59% for BAT[1]	**and 44% for BAT[4]**

BAT=best available therapy.

Actively manage your patient's disease at diagnosis

INDICATIONS AND USAGE

Jakafi® (ruxolitinib) is indicated for treatment of intermediate or high-risk myelofibrosis (MF), including primary MF, post–polycythemia vera MF and post–essential thrombocythemia MF in adults.

Important safety considerations

- Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated. In patients with cytopenias, consider dose reductions, temporarily interrupting Jakafi or transfusions, as clinically indicated
- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines

Please see related and other Important Safety Information on pages 14-15.
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Scan code to hear about when Dr Ruben Mesa intervenes with Jakafi

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