How I Treat:

When to Intervene With Jakafi® (ruxolitinib) in Patients With Steroid-Refractory Acute GVHD and Cytopenias

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Acute graft-versus-host disease (aGVHD) is a life-threatening complication that may develop after allogeneic hematopoietic stem cell transplantations. aGVHD manifestations arise in the early days after transplant when cytopenias are not uncommon, with only half of patients achieving an adequate response to steroids, which are the standard first-line treatment. When managing steroid-refractory (SR) aGVHD patients, my treatment goals are to achieve a complete response and to taper steroids, regardless of cytopenias. To achieve my treatment goals, and as supported by the REACH trial data and my own clinical experience, I do not wait until aGVHD is severe, and I intervene with Jakafi at the first signs of SR aGVHD in appropriate patients. Cytopenias are not a barrier to my treatment approach as I am comfortable managing through cytopenias by closely monitoring patient blood counts and instituting recommended Jakafi dose modifications when necessary.

Jakafi® (ruxolitinib) is indicated for treatment of steroid-refractory acute graft-versus-host disease (aGVHD) in adult and pediatric patients 12 years and older.

Early Identification of Steroid-Refractory aGVHD

Acute graft-versus-host disease (aGVHD) is a complication that occurs in up to half of patients receiving allogeneic hematopoietic stem cell transplantations (allo HSCT) and is a significant threat to patient outcomes.[1] Donor T-cell–mediated attacks on host tissue lead to clinical manifestations of aGVHD affecting the skin, liver, and upper and lower gastrointestinal tracts.[1] aGVHD is typically diagnosed within the first 100 days post-transplant when the host immune system is still recovering.[2] As such, cytopenias are fairly common in this setting in transplant recipients with aGVHD.

> **My top treatment goals for aGVHD patients are to achieve a complete response and to taper steroids, regardless of cytopenias.**

Because aGVHD symptoms can progress rapidly to threaten the outcome of allo HSCTs, I address my treatment goals in the following ways:

- In appropriate patients showing the first signs of steroid-refractory (SR) aGVHD, I intervene early with Jakafi
- By effectively managing patients using close monitoring of blood counts and dose adjustments, I do not let cytopenias deter my use of Jakafi in appropriate SR aGVHD patients

Do Not Wait Until aGVHD Is Severe Enough to Initiate Second-line Therapy

At the initial diagnosis of aGVHD, systemic steroids are the standard-of-care, but only half of aGVHD patients will achieve an adequate response to steroids.[2-4]

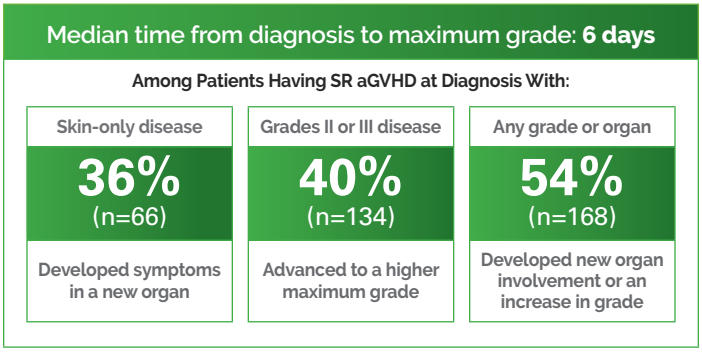
For patients with an initial diagnosis of aGVHD, I tend to start them on a high dose of ≥2 mg/kg/day of prednisone.[5]

> **In my clinical practice, I do not wait when I don't see a response to steroids in 3 days, as the disease can progress to maximum grade in a matter of days.**

It is critical to assess aGVHD symptoms frequently upon steroid dose escalation because the risk of disease progression is high and disease can rapidly worsen to maximum grade in a median time of 6 days (Figure 1).[6]

Figure 1

SR aGVHD Rapid Progression From Diagnosis to Maximum Grade[6,a,b]



aGVHD, acute graft-versus-host disease; SR, steroid refractory; US, United States.
[a] A multicenter, retrospective chart review conducted at 11 large US academic and community transplant centers in patients with steroid-refractory aGVHD who had their first hematopoietic cell transplantation between January 2014 and June 2016. All patients were required to have grade II-IV disease anytime during the course of disease (either at diagnosis or at maximum grade).[6]
[b] Steroid dependence/steroid refractory was defined as the use of additional systemic anti-GVHD therapy, inability to taper high-dose steroids (≥1 mg/kg) by ≥25%, or tapering of systemic corticosteroids dose by ≥25% but not <10 mg/day.[6]

Please see Important Safety Information on pages 4 and 5 and click here for Full Prescribing Information for Jakafi.

My Approach of Intervening With Jakafi at the First Signs of SR aGVHD

My preference is to intervene with Jakafi at the first signs of SR aGVHD in appropriate patients based on support from the clinical data in the REACH1 and REACH2 trials and my own experience.[7,8]

Jakafi was approved based on the positive results of the REACH1 trial. REACH1 was a Phase 2, single-arm, open-label, multicenter study of Jakafi for the treatment of patients with SR aGVHD (N=71). Patients had grades II to IV aGVHD, as defined according to Mount Sinai Acute GVHD International Consortium (MAGIC) criteria, which occurred after allogeneic hematopoietic stem cell transplant.

REACH1 Primary Endpoint

The primary endpoint was overall response rate (ORR) at day 28 (N=49 evaluable patients).* In REACH1, 57.1% (28/49) patients treated with Jakafi achieved an overall response by day 28 [95% CI: 42.2-71.2].[7,9]

Jakafi was also studied in REACH2, a randomized, open-label, multicenter, Phase 3 study comparing the efficacy and safety of Jakafi with control therapy in patients with SR aGVHD (N=309).[8] SR aGVHD definitions were different in REACH2.† The starting dose for Jakafi was 10 mg twice a day plus steroids.‡ REACH2 included endpoints that were not reported in the Jakafi® (ruxolitinib) Prescribing Information. The primary efficacy endpoint of the REACH2 trial supports my choice of Jakafi as the second-line therapy in SR aGVHD.

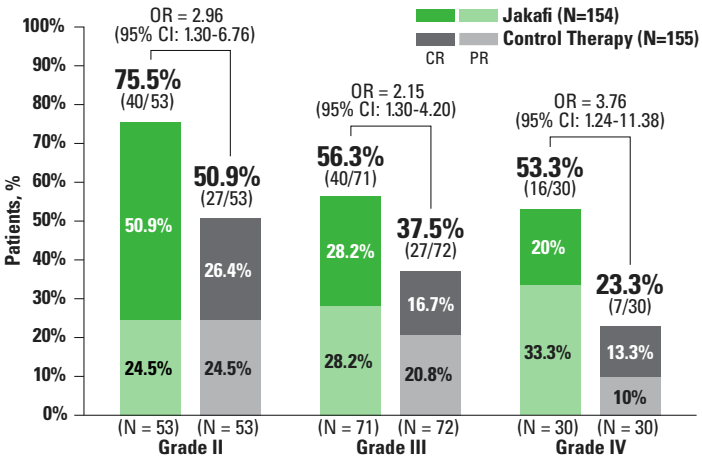
REACH2 Primary Endpoint

Jakafi demonstrated superior overall response at day 28 with a 62.3% (96/154) overall response rate compared to 39.4% (61/155) in the control therapy arm (OR, 2.64 [95% CI: 1.65-4.22]; *P*<0.001). Of the day 28 responders, 55% (53/96) achieved a complete response with Jakafi.[8]

The Jakafi subgroup analysis data and my own clinical experience guide my timing of intervention, and reinforce why I intervene early in the disease with Jakafi to achieve my treatment goals.

Figure 2

REACH2: Subgroup Analysis of ORR by Baseline aGVHD grades II-IV[10,a]



aGVHD, acute graft-versus-host disease; CI, confidence interval; CR, complete response; GI, gastrointestinal; OR, odds ratio; ORR, overall response rate; PR, partial response; REACH2, Ruxolitinib in PatiEnts with RefrACtory Graft-Versus-Host Disease After Allogeneic Stem Cell Transplantation.

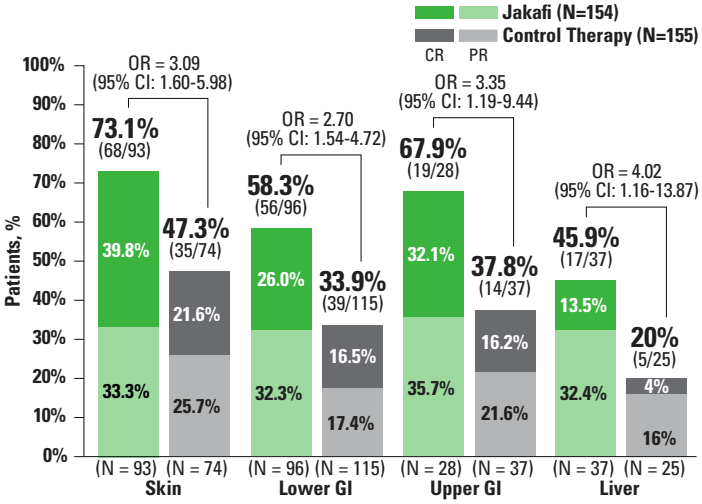
[a] Skin, liver, upper GI, and lower GI.

*The starting dose for Jakafi was 5 mg twice a day plus steroids and the dose could be increased to 10 mg twice a day after 3 days in the absence of toxicity. Twenty-two patients were not included in the efficacy analysis because they received 2 or more prior anti-GVHD therapies (n=12) or did not receive an adequate dose of corticosteroids (n=10). All 71 patients were included in the safety analysis.[7]

Improvement was observed across all grades (II-IV), with highest overall response and complete response seen in grade II patients at 75.5% (40/53) and 50.9% (27/53), respectively (Figure 2).[10] Response to Jakafi was also observed regardless of organs involved (Figure 3).[11]

Figure 3

REACH2: Subgroup Analysis of ORR by Organ Involvement at Baseline[11]



aGVHD, acute graft-versus-host disease; CI, confidence interval; CR, complete response; GI, gastrointestinal; OR, odds ratio; ORR, overall response rate; PR, partial response; REACH, Ruxolitinib in PatiEnts with RefrACtory Graft-Versus-Host Disease After Allogeneic Stem Cell Transplantation.

Additionally, Jakafi therapy also allows me to address my goal of tapering steroids. A total of 21% of patients in the Jakafi arm were able to discontinue steroids by day 56, compared with 14% in the control therapy arm.[8]

Managing Cytopenia Through Jakafi Dose Modifications in SR aGVHD

The way I manage Jakafi therapy with cytopenia in mind is by monitoring complete blood counts (CBCs) closely.

> **I want to highlight that with Jakafi we have the flexibility of reducing the dose to allow patient blood labs to recover, while still potentially maintaining control of GVHD symptoms, instead of prematurely withholding the dose or discontinuing Jakafi altogether.**

If patients exhibit a downward trend in their blood counts or other signs of cytopenias, I first make sure there are no other confounding factors. I then modify the dose of Jakafi (Figure 4).

> **In my practice, I'm comfortable initiating Jakafi in appropriate steroid-refractory aGVHD patients when platelet counts are at or above 20,000, and as long as patients are not transfusion-dependent.**

† Disease progression after ≥3 days of high-dose systemic steroid treatment, lack of improvement after 7 days, or failure to successfully taper steroid. Failure to taper was defined as the need to increase to ≥2 mg/kg/day methylprednisolone or inability to taper below 0.5 mg/kg/day for at least 7 days.[8]

‡ Cross over was permitted after day 28. In the control therapy plus steroids arm, control therapy included antithymocyteglobulin, extracorporeal photopheresis, mesenchymal stromal cells, low-dose methotrexate, mycophenolate mofetil, everolimus, sirolimus, etanercept, or Infliximab. Crossover from control therapy to Jakafi therapy was permitted if patients did not have a response at Day 28 or if they had a loss of response thereafter and received additional systemic therapy and did not have signs of chronic GVHD.[7]

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Figure 4
Jakafi Dose Modification Guidelines for Adverse Reactions[7,a]

Monitor CBCs, including platelet count and ANC, and bilirubin prior to initiating therapy, every 2 to 4 weeks until doses are stabilized, and then as indicated clinically

Parameter	Dosing Recommendations
Clinically significant thrombocytopenia after supportive measures	• Reduce Jakafi by 1 dose level. • When platelets recover to previous values, dosing may return to prior dose level.
ANC less than 1 × 10^9/L considered related to Jakafi	• Hold Jakafi for up to 14 days. • Resume at 1 dose level lower upon recovery.
Total bilirubin elevation, no liver GVHD	• 3-5 × ULN: Continue Jakafi at 1 dose level lower until recovery. • >5-10 × ULN: Hold Jakafi for up to 14 days until bilirubin ≤1.5 × ULN; resume at current dose upon recovery. • Total bilirubin > 10 × ULN: Hold Jakafi for up to 14 days until bilirubin ≤1.5 × ULN; resume at 1 dose level lower upon recovery.
Total bilirubin elevation, liver GVHD	• >3 × ULN: Continue Jakafi at 1 dose level lower until recovery.

- For dose reductions, patients who are currently receiving Jakafi 10 mg twice daily may have their dose reduced to 5 mg twice daily
- Patients receiving 5 mg twice daily may have their dose reduced to 5 mg once daily.
- Patients who are unable to tolerate Jakafi at a dose of 5 mg once daily should have treatment interrupted until their clinical and/or laboratory parameters recover.

ANC, absolute neutrophil count; CBC, complete blood count; GVHD, graft-versus-host disease; ULN, upper limit of normal.
[a]See Full Prescribing Information for further details on dose modifications and use in special populations.

Clinical data support my confidence in managing cytopenias via Jakafi dose adjustment. In the REACH2 trial, the most common hematological adverse events up to day 28 were thrombocytopenia and anemia.[8] Adverse events led to dose modifications in 38% (58/152) of patients on Jakafi compared to 9% (13/150) patients on control therapy.[8]

I counsel my patients with aGVHD about cytopenias, letting them know that blood counts may decrease, but we will monitor that closely.

Clinically meaningful differences in platelet and neutrophil counts were not observed over time between the group taking Jakafi and the control group in REACH2 (Figure 5).[11] These data are consistent with my clinical experience.

Figure 5
REACH2: Platelet and Neutrophil Counts Over Time[11,a,b]

PLATELET COUNTS (10^9/L)

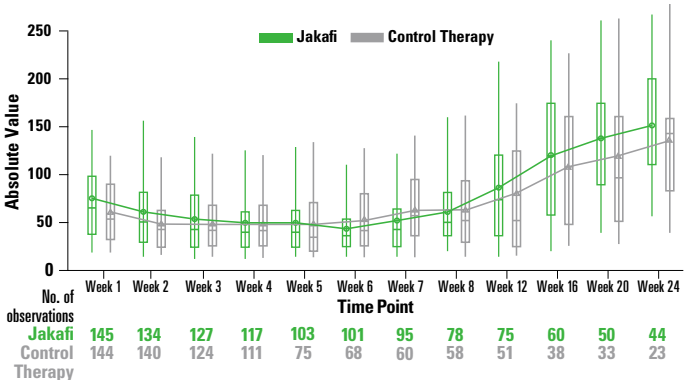
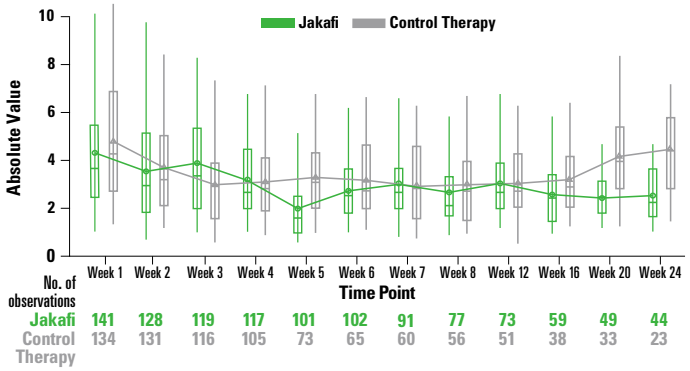


Figure 5 (cont'd)

NEUTROPHIL COUNTS (10^9/L)



REACH, Ruxolitinib in PatiEnts with RefrACtory Graft-Versus-Host Disease After Allogeneic Stem Cell Transplantation.
[a]Plot shows boxes (25th-75th percentiles) with median as horizontal line. The dots in the boxes and joint lines represent mean values. Whiskers (vertical lines) extend to the 10th to 90th percentiles.[11]
[b]Values outside this range are not displayed.[11]

The REACH2 clinical data guide my practice of modifying the dose to manage through cytopenias (Figure 6).[11] Up to day 28, adverse events led to treatment discontinuation in 11% (17/152) with Jakafi compared with 4% (6/150) for control therapy.[11]

Figure 6
REACH2: Incidence of Cytopenia Events Leading to Treatment Discontinuation Up to Day 28[11,a]

Adverse Event n (%)	Jakafi (N = 152)		Control Therapy (N = 150)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Anemia	3 (2)	3 (2)	1 (0.7)	1 (0.7)
Thrombocytopenia	3 (2)	3 (2)	0	0
Pancytopenia	2 (1.3)	2 (1.3)	0	0
Leukopenia	1 (0.7)	1 (0.7)	0	0
Neutrophil count decreased	1 (0.7)	1 (0.7)	0	0

REACH, Ruxolitinib in PatiEnts with RefrACtory Graft-Versus-Host Disease After Allogeneic Stem Cell Transplantation.
[a]Only adverse events related to cytopenias are shown.

I prefer to maintain a therapeutic dose of Jakafi in appropriate patients with cytopenias through dose adjustment rather than discontinuing Jakafi use.

For me, the benefit of treating aGVHD with Jakafi balances the concerns of cytopenias when following recommended patient management approaches.

Most Common Adverse Reactions With Jakafi[7]

The most frequent (occurring in ≥15% patients) adverse reactions with Jakafi (all grades; grade 3-4) are infections with pathogen not specified (55%; 41%), edema (51%; 13%), hemorrhage (49%; 20%), fatigue (37%; 14%), bacterial infections (32%; 28%), dyspnea (32%; 7%), viral infections (31%; 14%), thrombosis (25%; 11%), diarrhea (24%; 7%), rash (23%; 3%), headache (21%; 4%), hypertension (20%; 13%), and dizziness (16%; 0%). Selected hematological laboratory abnormalities (all grades; grade 3-4) include anemia (75%; 45%), thrombocytopenia (75%; 61%), and neutropenia (58%; 40%); selected chemical laboratory abnormalities (all grades; grade 3-4) include elevated alanine aminotransferase (48%; 8%), elevated aspartate aminotransferase (48%; 6%), and hypertriglyceridemia (11%; 1%).[7]

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Summary

- In SR aGVHD, I do not wait until the disease is severe enough to initiate second-line therapy because disease may progress rapidly to maximum grade in a matter of days and threaten the outcome of allo HSCT patients
- I intervene early with Jakafi at the first signs of SR aGVHD because clinical data from the REACH trials and my own experience support this approach
- Cytopenias do not change my treatment goals in SR aGVHD and do not deter my use of Jakafi in appropriate patients because I can track CBCs and adjust Jakafi dosing to manage through it

Scan the QR Code

to watch Pashna Munshi, MD, share her clinical perspective on management of aGVHD.

For additional resources and educational content for advanced practice providers, visit hcp.jakafi.com.

Indications and Usage

Jakafi is indicated for treatment of steroid-refractory acute graft-versus-host disease (aGVHD) in adult and pediatric patients 12 years and older.

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 × 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
- 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

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Important Safety Information (cont'd)

- 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

Please click here to see Full Prescribing Information for Jakafi.

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