How I Treat

Why we Intervene With Jakafi® (ruxolitinib) at First Signs of Initial Systemic Treatment Failure in Chronic Graft-Versus-Host Disease

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This article is sponsored by Incyte and includes commentary provided by Dr Preet Chaudhary during a paid interview.

Timely Intervention in Steroid-Refractory cGVHD

Chronic graft-versus-host disease (cGVHD) is a major threat to patient outcomes after allogeneic hematopoietic stem cell transplantation. Moderate and severe cGVHD lead to increased rates of non-relapse mortality, and severe cGVHD has a 5-year overall survival probability of 22.4%.[1]

> **We consider cGVHD a serious threat to patient survival if left untreated. Therefore, we follow an aggressive approach and do not delay treatment with Jakafi for cGVHD upon initial systemic treatment failure.**

Our top treatment goals are to intervene early to try to avoid letting cGVHD smolder over time, and to help prevent disease progression by having an ongoing response to treatment.

When cGVHD is diagnosed, our approach is typically to start patients on 1 mg/kg/day of prednisone. We look for changes in disease as early as 7 days. If we see no change in symptoms, following the National Institutes of Health criteria,[2] we switch to Jakafi (ruxolitinib) quickly so that we can potentially halt disease progression and have more flexibility on tapering steroids.

Intervening Early With Jakafi Is Supported by the REACH3 Trial Data

Support for intervening early with Jakafi in appropriate patients with cGVHD at the first signs of initial systemic treatment failure comes from our clinical experience and is also based on results from the REACH3 trial.

REACH3 is a randomized, open-label, multicenter, phase 3 study of Jakafi vs best available therapy (BAT)*,† in patients with steroid-refractory cGVHD (N=329).[3,4] The starting dose for Jakafi was 10 mg BID.[4] Crossover from BAT to Jakafi was permitted on or after week 24 if patients experienced disease progression, had a mixed or unchanged response, developed toxicity to BAT, or had a cGVHD flare.[3,4]

The primary efficacy endpoint of the REACH3 trial (Box 1) supports our use of Jakafi as the second-line agent of choice to help achieve the treatment goal of potentially halting disease progression.

Box 1. REACH3 Primary Endpoint

At week 24, significantly more patients achieved a response with Jakafi compared with BAT, with an overall response rate (ORR) of 49.7% (82/165) compared with 25.6% (42/164) (odds ratio, 2.99 [95% confidence interval: 1.86, 4.80]; $P<0.0001$).[4]

BAT, best available therapy; REACH, Ruxolitinib in patiEnts with refrACtory graft-versus-Host disease after allogeneic stem cell transplantation.

The efficacy of Jakafi over BAT, which included various therapies used in current practice,*,† reinforces the choice of Jakafi in our approach to intervene early in appropriate patients with cGVHD.[4,5]

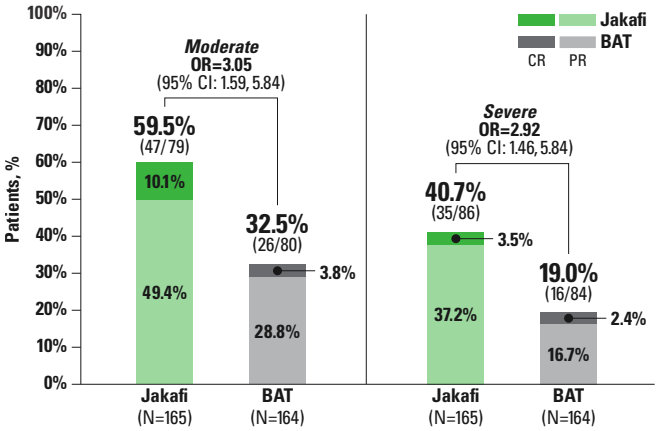
This higher response with Jakafi compared with BAT is also seen through week 24, with an overall response rate of 70% (116/165) vs 57% (94/164).[3,4]

The Jakafi subgroup analysis data based on severity and our own clinical experience guide our timing of intervention (Figure 1).

> **cGVHD can smolder and progress out of control. For us, the subgroup analysis data (baseline disease severity) supports our approach to intervene early with Jakafi, in appropriate patients, so that we have a better chance of halting disease progression.**

Figure 1

REACH3: Subgroup Analysis of Overall Response Rates by Baseline Disease Severity at Week 24[5,6,a,b]



[a]Moderate cGVHD was defined as ≥1 organ (not lung) with a score of 2, ≥3 organs with a score of 1 in each organ, or lung score of 1.[5]
[b]Severe cGVHD was defined as ≥1 organ with a score of 3 or lung score of 2 or 3.[5]
BAT, best available therapy; CR, complete response; cGVHD, chronic graft-versus-host disease; OR, odds ratio; PR, partial response; REACH, Ruxolitinib in patiEnts with refrACtory graft-versus-Host disease after allogeneic stem cell transplantation.

Importantly, initiation of Jakafi in the moderate disease group is associated with a higher overall response rate of 59.5% compared with 40.7% in the severe disease group.[5,6] This guides our approach to intervene as early as appropriate to achieve the treatment goals.

* BAT was chosen by the investigator prior to randomization. Options included ibrutinib, extracorporeal photopheresis, low-dose methotrexate, mycophenolate mofetil, rituximab, everolimus, sirolimus, imatinib, infliximab, or pentostatin.[3]
† 74% of patients on BAT received ibrutinib, extracorporeal photopheresis, or mycophenolate mofetil.[5]

Skin Disease as a Surrogate for Disease Progression in cGVHD

We monitor skin disease as a surrogate marker for disease progression–as cGVHD is a systemic disease, and it may progress[7,8] before it becomes symptomatic in difficult-to-assess organs such as the lungs.

The Jakafi subgroup analysis of response at week 24 based on organ involvement at baseline[4,5] guides our clinical practice and reinforces why we intervene early, when we see changes in skin disease, to help achieve our treatment goals (Figure 2).

In REACH3, patients achieved a higher response with Jakafi regardless of the organs involved. This subgroup analysis guides me and supports my approach to initiate Jakafi at early changes in skin disease for the opportunity to help control cGVHD.

Using Jakafi to Help Achieve an Ongoing Durable Response in Patients With cGVHD

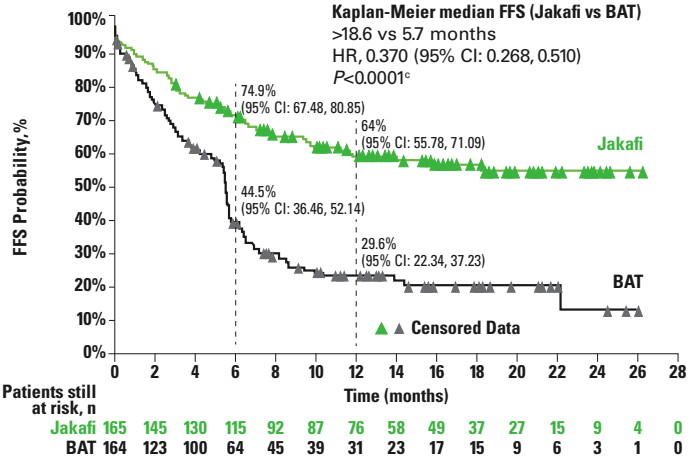
Patients receiving Jakafi had longer failure-free survival (FFS) than patients receiving BAT (median FFS, >18.6 months vs 5.7 months, respectively)[4] (Figure 3).

Failure-free survival is another important measure of the long-term outcomes of treatment we value in our cGVHD patients. In REACH3, patients achieved a significantly longer FFS with Jakafi® (ruxolitinib) vs BAT.[4,6] Median failure-free survival with Jakafi was not reached.[5]

The FFS data provide further evidence to support intervention with Jakafi at the first signs of initial systemic treatment failure and to keep appropriate patients on Jakafi to achieve ongoing response.

Figure 3

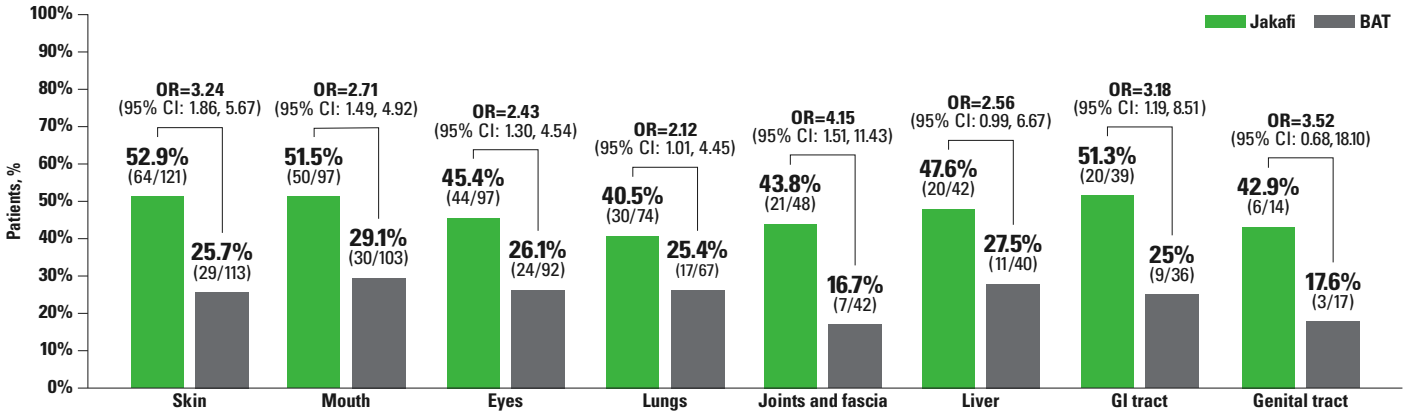
REACH3 Key Secondary Endpoint: KM Analysis of Failure-Free Survival[4,6,a,b]



[a]Defined as the earliest time from date of randomization to relapse or recurrence of underlying disease or death due to underlying disease, non-relapse mortality, or addition or initiation of another systemic therapy for cGVHD.[4,6]
[b]37.2% of patients switched to Jakafi when permitted (after week 24) and were included in the FFS assessment.[4,6]
[c]Descriptive *P* value (ex-US only). Efficacy boundary crossed at the interim analysis. HR, 0.315 (95% CI: 0.205, 0.486); P<0.0001. For US, the *P* value gives the result of the re-tested hypothesis at the primary analysis, following the overall hierarchical testing procedure.[4,6]
BAT, best available therapy; CI, confidence interval; FFS, failure-free survival; HR, hazard ratio; KM, Kaplan-Meier; REACH, Ruxolitinib in patiEnts with refrACtory graft-versus-Host disease after allogeneic stem cell transplantation.

Figure 2

REACH3: Subgroup Analysis of Overall Response Rates at Week 24 by Organ Involvement at Baseline[5,a]



[a]Patients with >1 affected organ were counted in each organ subgroup. Organ involvement was defined as organ score ≥1 based on the cGVHD staging criteria.[5]
BAT, best available therapy; cGVHD, chronic graft-versus-host disease; GI, gastrointestinal; OR, odds ratio; REACH, Ruxolitinib in patiEnts with refrACtory graft-versus-Host disease after allogeneic stem cell transplantation.

Most Common Adverse Reactions With Jakafi vs BAT[3]

The most frequent (occurring in ≥10% patients) adverse reactions (all grades) (Jakafi vs BAT) are infections with pathogen not specified (45% vs 44%), viral infections (28% vs 23%), musculoskeletal pain (18% vs 13%), hypertension (16% vs 13%), pyrexia (16% vs 9%), cough (13% vs 8%), fatigue (13% vs 10%), hemorrhage (12% vs 15%), nausea (12% vs 13%), dyspnea (11% vs 8%), edema (10% vs 12%), and diarrhea (10% vs 13%). Selected hematologic laboratory abnormalities (all grades) (Jakafi vs BAT) include anemia (82% vs 75%), thrombocytopenia (58% vs 54%), and neutropenia (27% vs 23%). Selected chemical laboratory abnormalities (all grades) include hypercholesterolemia (88% vs 85%), increased gamma glutamyl transferase (81% vs 75%), elevated alanine aminotransferase (73% vs 71%), elevated aspartate aminotransferase (65% vs 54%), increased creatinine (47% vs 40%), elevated lipase (38% vs 30%), and elevated amylase (35% vs 25%).[3]

BAT, best available therapy.

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Summary

We implement the following action s in patients with cGVHD to potentially halt disease progression and help patients achieve an ongoing response to treatment

- Assess changes in skin disease as a surrogate marker for disease progression
- Intervene with Jakafi in appropriate patients at the first signs of initial systemic treatment failure in cGVHD
- Maintain appropriate patients on effective therapy with durable response as a goal

References

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Indication and Usage

Jakafi® (ruxolitinib) is indicated for treatment of chronic graft-versus-host disease (cGVHD) after failure of one or two lines of systemic therapy in adult and pediatric patients 12 years and older.

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
- 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
- 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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