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*A SPECIAL MEETING REVIEW EDITION*

# Highlights in Graft-vs-Host Disease From the 62nd American Society of Hematology Annual Meeting and Exposition

## A Review of Selected Presentations From the All-Virtual 62nd ASH Meeting and Exposition • December 5-8, 2020

**Special Reporting on:**

- Ruxolitinib vs Best Available Therapy in Patients With Steroid-Refractory/Steroid-Dependent Chronic Graft-Vs-Host Disease: Primary Findings From the Phase 3, Randomized REACH3 Study
- Follow-Up Analysis of KD025-213 (the ROCKstar study): A Phase 2, Randomized, Multicenter Study to Evaluate the Efficacy and Safety of KD025 in Patients With cGVHD
- Biomarker and Safety Analyses of Patients With Steroid-Refractory Acute Graft-Vs-Host Disease Treated With Ruxolitinib or Best Available Therapy in the Randomized, Phase 3 REACH2 Study
- Efficacy and Safety of Baricitinib in Refractory Chronic Graft-Versus-Host Disease: Preliminary Analysis Results of a Phase 1/2 Study
- Phase 1 Study of Axatilimab (SNDX-6352), a CSF-1R Humanized Antibody, for Chronic Graft-Versus-Host Disease After 2 or More Lines of Systemic Treatment
- A Single-Arm, Open-Label Phase 1 Study of Itacitinib With Calcineurin Inhibitor–Based Interventions for Prophylaxis of Graft-Versus-Host Disease (GRAVITAS-119)
- Comparison of Outcomes After Haploidentical Relative and HLA Matched Unrelated Donor Transplantation With Post-Transplant Cyclophosphamide Containing GVHD Prophylaxis Regimens

**PLUS Meeting Abstract Summaries**

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Jakafi®
ruxolitinib (tablets)

# When steroids are not enough for your patient's acute GVHD

## Indications and Usage

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

## Approval Was Based on REACH1[1]

REACH1 was an open-label, single-arm, multicenter study of Jakafi in combination with steroids in patients who had Grade II-IV steroid-refractory acute GVHD occurring after allogeneic hematopoietic stem cell transplant.[1] A total of 71 patients were enrolled, of whom 49 were refractory to steroids alone and evaluable for efficacy.[1]

The primary endpoint was overall response rate (complete response, very good partial response, or partial response) at Day 28 based on the Center for International Blood and Marrow Transplant Research (CIBMTR) criteria.

## Patients in REACH1 Began Jakafi as Early as 3 Days After Steroid Initiation

Inclusion criteria included[2]:

- **Progression after 3 days** of ≥2 mg/kg/day methylprednisolone or equivalent
- **Failure to improve after 7 days** of ≥2 mg/kg/day methylprednisolone or equivalent
- Treatment with ≥1 mg/kg/day methylprednisolone for **skin GVHD (or skin plus upper GI GVHD) and development of GVHD disease in an additional organ**
- **Inability to achieve a 50% taper of steroid dose** without a return of GVHD

CR, complete response; GI, gastrointestinal; GVHD, graft-versus-host disease; ORR, overall response rate; PR, partial response; REACH, Ruxolitinib in PatiEnts with RefrACtory Graft-Versus-Host Disease After Allogeneic Stem Cell Transplantation; VGPR, very good partial response.

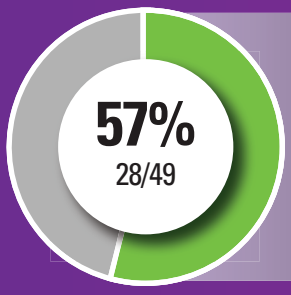
## Important Safety Information

- 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 $<0.5 \times 10^9$/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
- Advise patients about early signs and symptoms of herpes zoster and to seek early treatment
- 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

Visit
**hcp.Jakafi.com/gvhd**
to see
Full Prescribing
Information
and to learn more
about Jakafi

## Majority of Patients Achieved a Response at Day 28[1]

### Primary Endpoint: ORR at Day 28



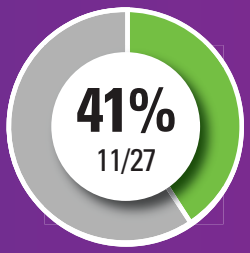

### Over Half of Responses Were Complete Responses



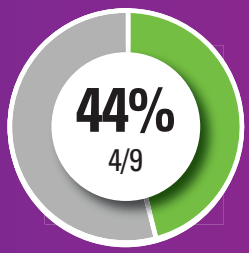

## Subgroup Analysis: ORR at Day 28 by Baseline aGVHD Grade[1]

**Grade II**


**Grade III**




**Grade IV**




- 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 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
- 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 and edema
- Dose modifications may be required when administering Jakafi with strong CYP3A4 inhibitors or fluconazole 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 see Brief Summary of Full Prescribing Information for Jakafi on the following pages.**

**References: 1.** Jakafi Prescribing Information. Wilmington, DE: Incyte Corporation.
**2.** Data on file. Incyte Corporation. Wilmington, DE.

# Jakafi®
ruxolitinib (tablets)

**BRIEF SUMMARY:** For Full Prescribing Information, see package insert.

**CONTRAINDICATIONS** None.

**WARNINGS AND PRECAUTIONS Thrombocytopenia, Anemia and Neutropenia** Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia. [*see Dosage and Administration (2.1) in Full Prescribing Information*]. Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary [*see Dosage and Administration (2), and Adverse Reactions (6.1) in Full Prescribing Information*]. Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi. Severe neutropenia (ANC less than $0.5 \times 10^9$/L) was generally reversible by withholding Jakafi until recovery [*see Adverse Reactions (6.1) in Full Prescribing Information*]. 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 [*see Dosage and Administration (2), and Adverse Reactions (6.1) in Full Prescribing Information*]. **Risk of Infection** Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting therapy with 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* Tuberculosis infection has been reported in patients receiving Jakafi. Observe patients receiving Jakafi for signs and symptoms of active tuberculosis and manage promptly. Prior to initiating Jakafi, patients should be evaluated for tuberculosis risk factors, and those at higher risk should be tested for latent infection. Risk factors include, but are not limited to, prior residence in or travel to countries with a high prevalence of tuberculosis, close contact with a person with active tuberculosis, and a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed. For patients with evidence of active or latent tuberculosis, consult a physician with expertise in the treatment of tuberculosis before starting Jakafi. The decision to continue Jakafi during treatment of active tuberculosis should be based on the overall risk-benefit determination. *Progressive Multifocal Leukoencephalopathy* Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi treatment. If PML is suspected, stop Jakafi and evaluate. *Herpes Zoster* Advise patients about early signs and symptoms of herpes zoster and to seek treatment as early as possible if suspected [*see Adverse Reactions (6.1) in Full Prescribing Information*]. *Hepatitis B* Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking Jakafi. The effect of Jakafi on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines. **Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi** Following discontinuation of Jakafi, symptoms from myeloproliferative neoplasms may return to pretreatment levels over a period of approximately one week. Some patients with MF have experienced one or more of the following adverse events after discontinuing Jakafi: fever, respiratory distress, hypotension, DIC, or multi-organ failure. If one or more of these occur after discontinuation of, or while tapering the dose of Jakafi, evaluate for and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi therapy without consulting their physician. When discontinuing or interrupting therapy with Jakafi for reasons other than thrombocytopenia or neutropenia [*see Dosage and Administration (2.6) in Full Prescribing Information*], consider tapering the dose of Jakafi gradually rather than discontinuing abruptly. **Non-Melanoma Skin Cancer** Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred in patients treated with Jakafi. Perform periodic skin examinations. **Lipid Elevations** Treatment with Jakafi has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined in patients treated with Jakafi. Assess lipid parameters approximately 8-12 weeks following initiation of Jakafi therapy. Monitor and treat according to clinical guidelines for the management of hyperlipidemia. **ADVERSE REACTIONS** The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling: • Thrombocytopenia, Anemia and Neutropenia [*see Warnings and Precautions (5.1) in Full Prescribing Information*] • Risk of Infection [*see Warnings and Precautions (5.2) in Full Prescribing Information*] • Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi [*see Warnings and Precautions (5.3) in Full Prescribing Information*] • Non-Melanoma Skin Cancer [*see Warnings and Precautions (5.4) in Full Prescribing Information*]. **Clinical Trials Experience in Myelofibrosis** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of Jakafi was assessed in 617 patients in six clinical studies with a median duration of follow-up of 10.9 months, including 301 patients with MF in two Phase 3 studies. In these two Phase 3 studies, patients had a median duration of exposure to Jakafi of 9.5 months (range 0.5 to 17 months), with 89% of patients treated for more than 6 months and 25% treated for more than 12 months. One hundred and eleven (111) patients started treatment at 15 mg twice daily and 190 patients started at 20 mg twice daily. In patients starting treatment with 15 mg twice daily (pretreatment platelet counts of 100 to $200 \times 10^9$/L) and 20 mg twice daily (pretreatment platelet counts greater than $200 \times 10^9$/L), 65% and 25% of patients, respectively, required a dose reduction below the starting dose within the first 8 weeks of therapy. In a double-blind, randomized, placebo-controlled study of Jakafi, among the 155 patients treated with Jakafi, the most frequent adverse reactions were thrombocytopenia and anemia [*see Table 2*]. Thrombocytopenia, anemia and neutropenia are dose-related effects. The three most frequent nonhematologic adverse reactions were bruising, dizziness and headache [*see Table 1*]. Discontinuation for adverse events, regardless of causality, was observed in 11% of patients treated with Jakafi and 11% of patients treated with placebo. Table 1 presents the most common nonhematologic adverse reactions occurring in patients who received Jakafi in the double-blind, placebo-controlled study during randomized treatment.

**Table 1: Myelofibrosis: Nonhematologic Adverse Reactions Occurring in Patients on Jakafi in the Double-blind, Placebo-controlled Study During Randomized Treatment**

| | Jakafi (N=155) | | | Placebo (N=151) | | |
|---|---|---|---|---|---|---|
| **Adverse Reactions** | **All Grades[a] (%)** | **Grade 3 (%)** | **Grade 4 (%)** | **All Grades (%)** | **Grade 3 (%)** | **Grade 4 (%)** |
| Bruising[b] | 23 | <1 | 0 | 15 | 0 | 0 |
| Dizziness[c] | 18 | <1 | 0 | 7 | 0 | 0 |
| Headache | 15 | 0 | 0 | 5 | 0 | 0 |
| Urinary Tract Infections[d] | 9 | 0 | 0 | 5 | <1 | <1 |
| Weight Gain[e] | 7 | <1 | 0 | 1 | <1 | 0 |
| Flatulence | 5 | 0 | 0 | <1 | 0 | 0 |
| Herpes Zoster[f] | 2 | 0 | 0 | <1 | 0 | 0 |

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
[b] includes contusion, ecchymosis, hematoma, injection site hematoma, periorbital hematoma, vessel puncture site hematoma, increased tendency to bruise, petechiae, purpura
[c] includes dizziness, postural dizziness, vertigo, balance disorder, Meniere's Disease, labyrinthitis
[d] includes urinary tract infection, cystitis, urosepsis, urinary tract infection bacterial, kidney infection, pyuria, bacteria urine, bacteria urine identified, nitrite urine present
[e] includes weight increased, abnormal weight gain
[f] includes herpes zoster and post-herpetic neuralgia

**Description of Selected Adverse Reactions: Anemia** In the two Phase 3 clinical studies, median time to onset of first CTCAE Grade 2 or higher anemia was approximately 6 weeks. One patient (<1%) discontinued treatment because of anemia. In patients receiving Jakafi, mean decreases in hemoglobin reached a nadir of approximately 1.5 to 2.0 g/dL below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 1.0 g/dL below baseline. This pattern was observed in patients regardless of whether they had received transfusions during therapy. In the randomized, placebo-controlled study, 60% of patients treated with Jakafi and 38% of patients receiving placebo received red blood cell transfusions during randomized treatment. Among transfused patients, the median number of units transfused per month was 1.2 in patients treated with Jakafi and 1.7 in placebo treated patients. **Thrombocytopenia** In the two Phase 3 clinical studies, in patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above $50 \times 10^9$/L was 14 days. Platelet transfusions were administered to 5% of patients receiving Jakafi and to 4% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in <1% of patients receiving Jakafi and <1% of patients receiving control regimens. Patients with a platelet count of $100 \times 10^9$/L to $200 \times 10^9$/L before starting Jakafi had a higher frequency of Grade 3 or 4 thrombocytopenia compared to patients with a platelet count greater than $200 \times 10^9$/L (17% versus 7%). **Neutropenia** In the two Phase 3 clinical studies, 1% of patients reduced or stopped Jakafi because of neutropenia. Table 2 provides the frequency and severity of clinical hematology abnormalities reported for patients receiving treatment with Jakafi or placebo in the placebo-controlled study.

**Table 2: Myelofibrosis: Worst Hematology Laboratory Abnormalities in the Placebo-Controlled Study[a]**

| | Jakafi (N=155) | | | Placebo (N=151) | | |
|---|---|---|---|---|---|---|
| **Laboratory Parameter** | **All Grades[b] (%)** | **Grade 3 (%)** | **Grade 4 (%)** | **All Grades (%)** | **Grade 3 (%)** | **Grade 4 (%)** |
| Thrombocytopenia | 70 | 9 | 4 | 31 | 1 | 0 |
| Anemia | 96 | 34 | 11 | 87 | 16 | 3 |
| Neutropenia | 19 | 5 | 2 | 4 | <1 | 1 |

[a] Presented values are worst Grade values regardless of baseline
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0

**Additional Data from the Placebo-Controlled Study** • 25% of patients treated with Jakafi and 7% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in alanine transaminase (ALT). The incidence of greater than or equal to Grade 2 elevations was 2% for Jakafi with 1% Grade 3 and no Grade 4 ALT elevations. • 17% of patients treated with Jakafi and 6% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in aspartate transaminase (AST). The incidence of Grade 2 AST elevations was <1% for Jakafi with no Grade 3 or 4 AST elevations. • 17% of patients treated with Jakafi and <1% of patients treated with placebo developed newly occurring or worsening Grade 1 elevations in cholesterol. The incidence of Grade 2 cholesterol elevations was <1% for Jakafi with no Grade 3 or 4 cholesterol elevations. **Clinical Trial Experience in Polycythemia Vera** In a randomized, open-label, active-controlled study, 110 patients with PV resistant to or intolerant of hydroxyurea received Jakafi and 111 patients received best available therapy [*see Clinical Studies (14.2) in Full Prescribing Information*]. The most frequent adverse reaction was anemia. Discontinuation for adverse events, regardless of causality, was observed in 4% of patients treated with Jakafi. Table 3 presents the most frequent nonhematologic adverse reactions occurring up to Week 32.

**Table 3: Polycythemia Vera: Nonhematologic Adverse Reactions Occurring in ≥ 5% of Patients on Jakafi in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment**

| | Jakafi (N=110) | | Best Available Therapy (N=111) | |
|---|---|---|---|---|
| **Adverse Reactions** | **All Grades[a] (%)** | **Grade 3-4 (%)** | **All Grades (%)** | **Grade 3-4 (%)** |
| Diarrhea | 15 | 0 | 7 | <1 |
| Dizziness[b] | 15 | 0 | 13 | 0 |
| Dyspnea[c] | 13 | 3 | 4 | 0 |
| Muscle Spasms | 12 | <1 | 5 | 0 |
| Constipation | 8 | 0 | 3 | 0 |
| Herpes Zoster[d] | 6 | <1 | 0 | 0 |
| Nausea | 6 | 0 | 4 | 0 |
| Weight Gain[e] | 6 | 0 | <1 | 0 |
| Urinary Tract Infections[f] | 6 | 0 | 3 | 0 |
| Hypertension | 5 | <1 | 3 | <1 |

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
[b] includes dizziness and vertigo
[c] includes dyspnea and dyspnea exertional
[d] includes herpes zoster and post-herpetic neuralgia
[e] includes weight increased and abnormal weight gain
[f] includes urinary tract infection and cystitis

Clinically relevant laboratory abnormalities are shown in Table 4.

**Table 4: Polycythemia Vera: Selected Laboratory Abnormalities in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment[a]**

| | Jakafi (N=110) | | | Best Available Therapy (N=111) | | |
|---|---|---|---|---|---|---|
| **Laboratory Parameter** | **All Grades[b] (%)** | **Grade 3 (%)** | **Grade 4 (%)** | **All Grades (%)** | **Grade 3 (%)** | **Grade 4 (%)** |
| **Hematology** | | | | | | |
| Anemia | 72 | <1 | <1 | 58 | 0 | 0 |
| Thrombocytopenia | 27 | 5 | <1 | 24 | 3 | <1 |
| Neutropenia | 3 | 0 | <1 | 10 | <1 | 0 |
| **Chemistry** | | | | | | |
| Hypercholesterolemia | 35 | 0 | 0 | 8 | 0 | 0 |
| Elevated ALT | 25 | <1 | 0 | 16 | 0 | 0 |
| Elevated AST | 23 | 0 | 0 | 23 | <1 | 0 |
| Hypertriglyceridemia | 15 | 0 | 0 | 13 | 0 | 0 |

[a] Presented values are worst Grade values regardless of baseline
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0

**Clinical Trial Experience in Acute Graft-Versus-Host Disease** In a single-arm, open-label study, 71 adults (ages 18-73 years) were treated with Jakafi for acute GVHD failing treatment with steroids with or without other immunosuppressive drugs [see *Clinical Studies (14.3) in Full Prescribing Information*]. The median duration of treatment with Jakafi was 46 days (range, 4-382 days). There were no fatal adverse reactions to Jakafi. An adverse reaction resulting in treatment discontinuation occurred in 31% of patients. The most common adverse reaction leading to treatment discontinuation was infection (10%). Table 5 shows the adverse reactions other than laboratory abnormalities.

**Table 5: Acute Graft-Versus-Host Disease: Nonhematologic Adverse Reactions Occurring in ≥ 15% of Patients in the Open-Label, Single-Cohort Study**

| | Jakafi (N=71) | |
|---|---|---|
| **Adverse Reactions[a]** | **All Grades[b] (%)** | **Grade 3-4 (%)** |
| Infections | 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 |
| Dizziness | 16 | 0 |

[a] Selected laboratory abnormalities are listed in Table 6 below
[b] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03

Selected laboratory abnormalities during treatment with Jakafi are shown in Table 6.

**Table 6: Acute Graft-Versus-Host Disease: Selected Laboratory Abnormalities Worsening from Baseline in the Open-Label, Single Cohort Study**

| | Jakafi (N=71) | |
|---|---|---|
| | **Worst grade during treatment** | |
| **Laboratory Parameter** | **All Grades[a] (%)** | **Grade 3-4 (%)** |
| **Hematology** | | |
| Anemia | 75 | 45 |
| Thrombocytopenia | 75 | 61 |
| Neutropenia | 58 | 40 |
| **Chemistry** | | |
| Elevated ALT | 48 | 8 |
| Elevated AST | 48 | 6 |
| Hypertriglyceridemia | 11 | 1 |

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03

**DRUG INTERACTIONS Fluconazole** Concomitant administration of Jakafi with fluconazole doses greater than 200 mg daily may increase ruxolitinib exposure due to inhibition of both the CYP3A4 and CYP2C9 metabolic pathways [*see Clinical Pharmacology (12.3) in Full Prescribing Information*]. Increased exposure may increase the risk of exposure-related adverse reactions. Avoid the concomitant use of Jakafi with fluconazole doses of greater than 200 mg daily except in patients with acute GVHD [*see Dosage and Administration (2.4) in Full Prescribing Information*]. **Strong CYP3A4 inhibitors** Concomitant administration of Jakafi with strong CYP3A4 inhibitors increases ruxolitinib exposure [*see Clinical Pharmacology (12.3) in Full Prescribing Information*]. Increased exposure may increase the risk of exposure-related adverse reactions. Consider dose reduction when administering Jakafi with strong CYP3A4 inhibitors [*see Dosage and Administration (2.4) in Full Prescribing Information*]. In patients with acute GVHD, reduce Jakafi dose as recommended only when coadministered with ketoconazole, and monitor blood counts more frequently for toxicity and adjust the dose if necessary when coadministered with itraconazole. [*see Dosage and Administration (2.4) in Full Prescribing Information*]. **Strong CYP3A4 inducers** Concomitant administration of Jakafi with strong CYP3A4 inducers may decrease ruxolitinib exposure [*see Clinical Pharmacology (12.3) in Full Prescribing Information*]. No dose adjustment is recommended; however, monitor patients frequently and adjust the Jakafi dose based on safety and efficacy [*see Clinical Pharmacology (12.3) in Full Prescribing Information*]. **USE IN SPECIFIC POPULATIONS Pregnancy: Risk Summary** When pregnant rats and rabbits were administered ruxolitinib during the period of organogenesis adverse developmental outcomes occurred at doses associated with maternal toxicity (*see Data*). There are no studies with the use of Jakafi in pregnant women to inform drug-associated risks. The background risk of major birth defects and miscarriage for the indicated populations is unknown. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The background risk in the U.S. general population of major birth defects is 2% to 4% and miscarriage is 15% to 20% of clinically recognized pregnancies. **Data:** *Animal Data* Ruxolitinib was administered orally to pregnant rats or rabbits during the period of organogenesis, at doses of 15, 30 or 60 mg/kg/day in rats and 10, 30 or 60 mg/kg/day in rabbits. There were no treatment-related malformations. Adverse developmental outcomes, such as decreases of approximately 9% in fetal weights were noted in rats at the highest and maternally toxic dose of 60 mg/kg/day. This dose results in an exposure (AUC) that is approximately 2 times the clinical exposure at the maximum recommended dose of 25 mg twice daily. In rabbits, lower fetal weights of approximately 8% and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day. This dose is approximately 7% the clinical exposure at the maximum recommended dose. In a pre- and post-natal development study in rats, pregnant animals were dosed with ruxolitinib from implantation through lactation at doses up to 30 mg/kg/day. There were no drug-related adverse findings in pups for fertility indices or for maternal or embryofetal survival, growth and development parameters at the highest dose evaluated (34% the clinical exposure at the maximum recommended dose of 25 mg twice daily). **Lactation: Risk Summary** No data are available regarding the presence of ruxolitinib in human milk, the effects on the breast fed child, or the effects on milk production. Ruxolitinib and/or its metabolites were present in the milk of lactating rats (*see Data*). Because many drugs are present in human milk and because of the potential for thrombocytopenia and anemia shown for Jakafi in human studies, discontinue breastfeeding during treatment with Jakafi and for two weeks after the final dose. **Data:** *Animal Data* Lactating rats were administered a single dose of [$^{14}$C]-labeled ruxolitinib (30 mg/kg) on postnatal Day 10, after which plasma and milk samples were collected for up to 24 hours. The AUC for total radioactivity in milk was approximately 13-fold the maternal plasma AUC. Additional analysis showed the presence of ruxolitinib and several of its metabolites in milk, all at levels higher than those in maternal plasma. **Pediatric Use** The safety and effectiveness of Jakafi for treatment of myelofibrosis or polycythemia vera in pediatric patients have not been established. The safety and effectiveness of Jakafi for treatment of steroid-refractory acute graft-versus-host disease (GVHD) have been established for treatment of children 12 years and older. Use of Jakafi in pediatric patients with steroid-refractory acute GVHD is supported by evidence from an adequate and well-controlled trial of Jakafi in adults [*see Clinical Studies (14.3) in Full Prescribing Information*] and additional pharmacokinetic and safety data in pediatric patients. Jakafi was evaluated in a single-arm, dose-escalation study (NCT01164163) in 27 pediatric patients with relapsed or refractory solid tumors (Cohort A) and 20 with leukemias or myeloproliferative neoplasms (Cohort B). The patients had a median age of 14 years (range, 2 to 21 years) and included 18 children (age 2 to <12 years), and 14 adolescents (age 12 to <17 years). The dose levels tested were 15, 21, 29, 39, or 50 mg/m$^2$ twice daily in 28-day cycles with up to 6 patients per dose group. Overall, 38 (81%) patients were treated with no more than a single cycle of Jakafi, while 3, 1, 2, and 3 patients received 2, 3, 4, and 5 or more cycles, respectively. A protocol-defined maximal tolerated dose was not observed, but since few patients were treated for multiple cycles, tolerability with continued use was not assessed adequately to establish a recommended Phase 2 dose higher than the recommended dose for adults. The safety profile in children was similar to that seen in adults. *Juvenile Animal Toxicity Data* Administration of ruxolitinib to juvenile rats resulted in effects on growth and bone measures. When administered starting at postnatal day 7 (the equivalent of a human newborn) at doses of 1.5 to 75 mg/kg/day, evidence of fractures occurred at doses ≥ 30 mg/kg/day, and effects on body weight and other bone measures [e.g., bone mineral content, peripheral quantitative computed tomography, and x-ray analysis] occurred at doses ≥ 5 mg/kg/day. When administered starting at postnatal day 21 (the equivalent of a human 2-3 years of age) at doses of 5 to 60 mg/kg/day, effects on body weight and bone occurred at doses ≥ 15 mg/kg/day, which were considered adverse at 60 mg/kg/day. Males were more severely affected than females in all age groups, and effects were generally more severe when administration was initiated earlier in the postnatal period. These findings were observed at exposures that are at least 27% the clinical exposure at the maximum recommended dose of 25 mg twice daily. **Geriatric Use** Of the total number of patients with MF in clinical studies with Jakafi, 52% were 65 years and older, while 15% were 75 years and older. No overall differences in safety or effectiveness of Jakafi were observed between these patients and younger patients. Clinical studies of Jakafi in patients with acute GVHD did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects. **Renal Impairment** Total exposure of ruxolitinib and its active metabolites increased with moderate (CLcr 30 mL/min to 59 mL/min) and severe (CLcr 15 mL/min to 29 mL/min) renal impairment, and ESRD on dialysis [*see Clinical Pharmacology (12.3) in Full Prescribing Information*]. Reduce Jakafi dose as recommended [*see Dosage and Administration (2.5) in Full Prescribing Information*]. **Hepatic Impairment** Exposure of ruxolitinib increased with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment [*see Clinical Pharmacology (12.3) in Full Prescribing Information*]. Reduce Jakafi dose as recommended in patients with MF or PV and any hepatic impairment [*see Dosage and Administration (2.5) in Full Prescribing Information*]. Monitor blood counts more frequently for toxicity and consider 5 mg once daily for patients with Stage 3 or 4 liver GVHD [*see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in Full Prescribing Information*]. **OVERDOSAGE** There is no known antidote for overdoses with Jakafi. Single doses up to 200 mg have been given with acceptable acute tolerability. Higher than recommended repeat doses are associated with increased myelosuppression including leukopenia, anemia and thrombocytopenia. Appropriate supportive treatment should be given. Hemodialysis is not expected to enhance the elimination of Jakafi.

# Ruxolitinib vs Best Available Therapy in Patients With Steroid-Refractory/Steroid-Dependent Chronic Graft-Vs-Host Disease: Primary Findings From the Phase 3, Randomized REACH3 Study

Chronic graft-vs-host disease (GVHD) occurs in approximately 30% to 70% of patients undergoing allogeneic stem cell transplant and is a leading cause of nonrelapse mortality and morbidity.[1-3] The standard first-line therapy consists of systemic corticosteroids; however, 50% of patients become refractory to corticosteroids or dependent on their use.[4,5] Presently, there is no standard second-line treatment and no large, randomized clinical studies have been successfully completed in this setting.

Zeiser and colleagues investigated the efficacy of ruxolitinib vs best available therapy among patients with corticosteroid-refractory chronic GVHD in the randomized, phase 3 REACH3 trial.[6] Eligible patients were ages 12 years and older, had moderate or severe corticosteroid-refractory chronic GVHD, and had evidence of myeloid and platelet engraftment.

Patients were randomly assigned to receive either ruxolitinib 10 mg twice daily (n=165) or investigator's choice of best available therapy (n=164).[6] Patients receiving corticosteroids were permitted to continue this treatment alone or in combination with a calcineurin inhibitor. At week 24, patients in the best available therapy group were permitted to cross over to ruxolitinib if they progressed, had a mixed or unchanged response, developed toxicity to treatment, or experienced a chronic GVHD flare. The primary endpoint was overall response rate (ORR) assessed at week 24 using the National Institutes of Health (NIH) consensus criteria for response.[7] Key secondary endpoints were failure-free survival and modified Lee Symptom Scale response at week 24.

Overall, the patients' baseline characteristics were well matched with respect to age, sex, prior GVHD severity, corticosteroid-refractory criteria, stem cell source, donor type, and cytomegalovirus (CMV) status.[6] As of data cutoff in May 2020, treatment was ongoing for 83 patients (50%) in the ruxolitinib group and 42 patients (26%) in the control group. Adverse events (17% vs 5%) and lack of efficacy (15% vs 43%) were the main reasons for treatment discontinuation. At week 24, 61 patients (37%) crossed over from treatment with best available

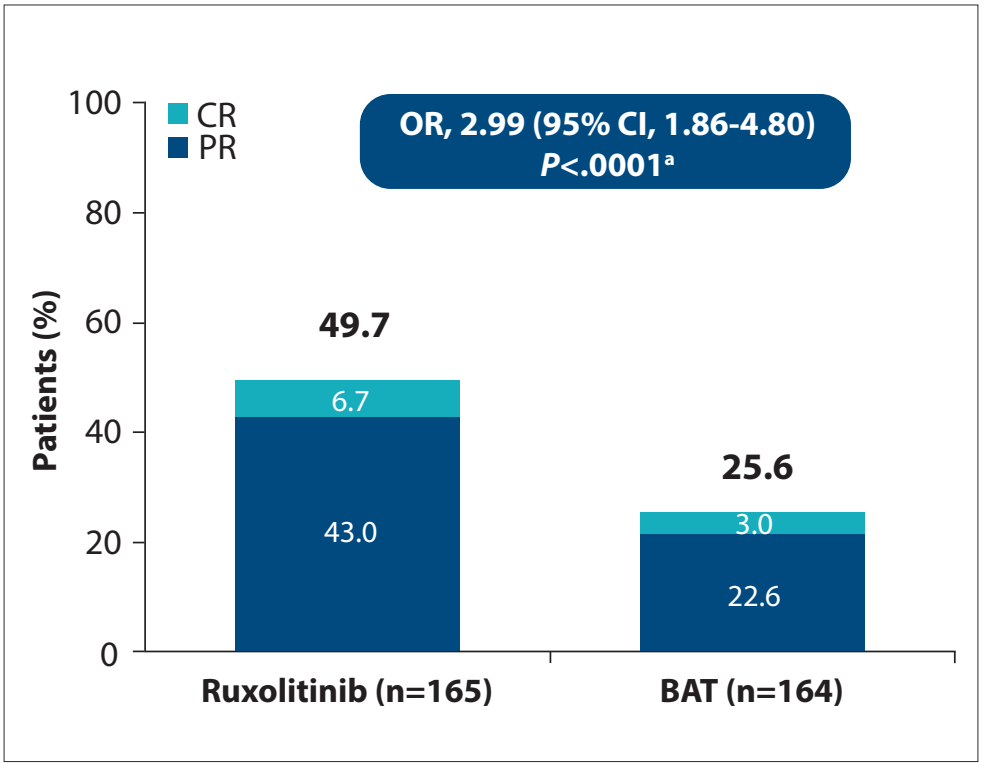



**Figure 1.** Responses in the phase 3 REACH3 trial, which compared ruxolitinib vs best available therapy in patients with corticosteroid-refractory or corticosteroid-dependent chronic graft-vs-host disease. [a]Descriptive *P* value at the primary analysis as the efficacy boundary was crossed at the interim analysis (N=196; ORR was 50.5% with ruxolitinib and 26.3% with BAT; *P*=.0003). One-sided *P* value, OR, and 95% CI were calculated using a stratified Cochran–Mantel–Haenszel test with strata of moderate vs severe chronic graft-vs-host disease. BAT, best available therapy; CR, complete response; OR, odds ratio; ORR, overall response rate; PR, partial response. Adapted from Zeiser R et al. ASH abstract 77. *Blood.* 2020;136(suppl 1).[6]

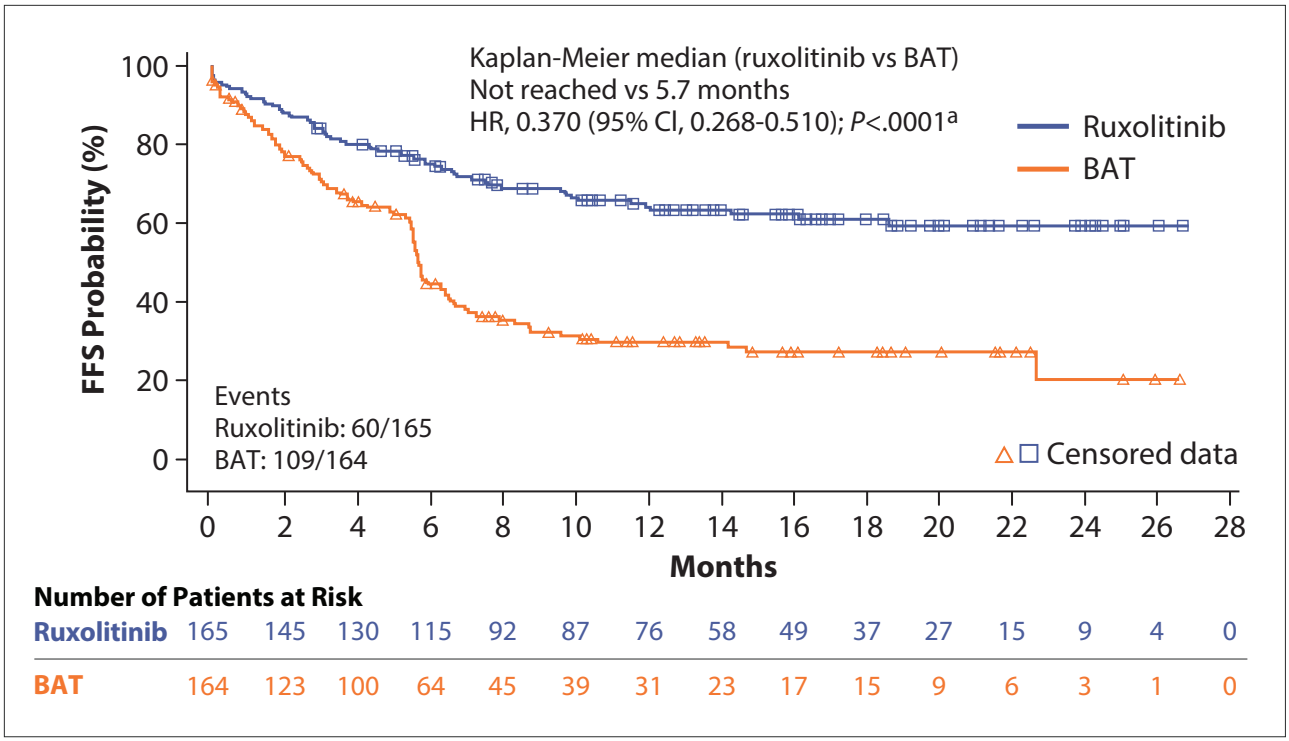



**Figure 2.** Failure-free survival in the phase 3 REACH3 trial, which compared ruxolitinib vs best available therapy in patients with corticosteroid-refractory or corticosteroid-dependent chronic graft-vs-host disease. BAT, best available therapy; FFS, failure-free survival; HR, hazard ratio. Adapted from Zeiser R et al. ASH abstract 77. *Blood.* 2020;136(suppl 1).[6]

therapy to ruxolitinib.

Zeiser and colleagues presented the primary analysis of REACH3. The study met its primary endpoint of ORR at week 24.[6] Among patients treated with ruxolitinib, the ORR was 49.7%, which included a complete response rate of 6.7% (Figure 1). Among patients treated with best available therapy, the ORR was 25.6%, including a complete response rate of 3.0% (*P*<.0001 vs ruxolitinib).

Failure-free survival (defined as time to recurrence of the underlying disease, start of new systemic treatment for chronic GVHD, or death [whichever was earliest]) had not been reached with ruxolitinib compared with 5.7 months with best available therapy (*P*<.0001; Figure 2).[6] Ruxolitinib reduced the risk of progression by 63%, with a clear separation of the failure-free survival curves noticeable within 2 months of initiating treatment. In addition, patients who received ruxolitinib through to week 24 experienced a greater improvement in symptoms, as demonstrated by the proportion of patients with a response at week 24 according to the modified Lee Symptom Scale (24% vs 11%; *P*=.0011).[6]

The best ORR was 76.4% with ruxolitinib compared with 60.4% with best available therapy.[6] The median duration of best overall response, which represents maintenance of response, was not reached in the ruxolitinib arm vs 6.2 months in the best available therapy arm. The median duration of treatment was 41.3 weeks (range, 0.7-127.3) with ruxolitinib and 24.1 weeks (range, 0.6-108.4) with best available therapy.

Among patients treated with ruxolitinib, 57% developed a grade 3 or higher adverse event and 33% had a serious adverse event. These rates were 58% and 37%, respectively, among patients treated with best available therapy.[6] The most common adverse events in the ruxolitinib arm were cytopenias, with grade 3 or higher anemia occurring in 13% vs 8%, thrombocytopenia in 15% vs 10%, and neutropenia in 9% vs 4%. Patients in the ruxolitinib arm had more adverse events leading to dose modifications (38% vs 16%) and treatment discontinuation (16% vs 7%).[6] There was no significant difference in the occurrence of death between the treatment arms (19% vs 17%).

The most common type of infection was viral, which occurred in 34% of the ruxolitinib arm vs 29% of the best available therapy arm.[6] There was no significant difference with respect to CMV infection or reactivation between ruxolitinib and best available therapy (6% vs 8%). Bacterial infections also occurred at a similar frequency (28% vs 26%), although there was a trend toward more fungal infections with ruxolitinib (12% vs 6%).

The investigators concluded that REACH3 is the first successful randomized phase 3 trial in adolescent and adult patients with chronic GVHD with an inadequate response to corticosteroids. Compared with best available therapy at week 24, ruxolitinib demonstrated a significantly higher ORR, significant improvement in failure-free survival, greater symptom score improvement, and a higher best ORR. The safety profile of ruxolitinib was consistent with previous observations, with anemia and thrombocytopenia being the most common adverse events. REACH3 is ongoing and will continue for a total of 3 years.

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# Follow-Up Analysis of KD025-213 (the ROCKstar study): A Phase 2, Randomized, Multicenter Study to Evaluate the Efficacy and Safety of KD025 in Patients With cGVHD

The serine-threonine kinase rho-associated kinase 2 (ROCK2) is 1 of 2 known isoforms of ROCK and plays a key role in immune diseases. ROCK2 inhibition rebalances the immune system by downregulating proinflammatory $T_H17$ and increasing the generation of anti-inflammatory regulatory T cells.[1] In addition, ROCK plays a critical role in the final common final pathway of fibrosis, regulating multiple profibrotic processes, including myofibroblast activation.[2]

Belumosudil (KD025) is a novel orally available small-molecule inhibitor of ROCK2 that targets both the immune and fibrotic pathophysiology of chronic GVHD.[3] In a phase 2a study, treatment with belumosudil resulted in an ORR of 59% in patients with chronic GVHD who had received between 1 and 3 prior lines of systemic therapy.[4] Belumosudil has since been granted breakthrough designation by the US Food and Drug Administration for patients with chronic GVHD who have been treated with at least 2 prior lines of therapy. This drug is undergoing investigation in the ROCKstar study (NCT03640481), a randomized, multicenter, open-label phase 2 trial.[5]

Cutler and colleagues presented a follow-up analysis of ROCKstar that enrolled patients ages 12 years and older who had received 2 to 5 lines of prior systemic therapy for active, chronic GVHD.[5] Patients were randomly assigned to belumosudil at 200 mg administered once daily (n=66) or twice daily (n=66). Treatment continued until the patient developed clinically significant progression or unacceptable toxicity. Corticosteroid doses could be reduced after 2 weeks of belumosudil therapy at the discretion of the treating physician. The primary

**ABSTRACT SUMMARY Vedolizumab for Steroid-Refractory Lower Gastrointestinal Tract Graft Vs Host Disease**

Vedolizumab is a humanized monoclonal antibody that inhibits the interaction of the α4β7 integrin on T cells with their ligand mucosal addressin cell adhesion molecule-1 expressed on endothelial cells in the GI tract. Mehta and colleagues analyzed the outcomes of 20 adult patients with corticosteroid-refractory lower GI acute GVHD treated with vedolizumab 300 mg IV (Abstract 2390). Most patients had GVHD of grade 3/4 (90%) or lower GI GVHD of stage 3/4 (85%) at vedolizumab initiation, and most received vedolizumab as a third or later line of therapy (75%). The median number of vedolizumab doses received was 2.5 (range, 1-5). By day 56, ORR was 25% in both the overall study population and the subgroup with prior ruxolitinib exposure. The actuarial 1-year overall survival was 30% (95% CI, 12-50), and the median overall survival was 2.2 months from the start of vedolizumab therapy. Fifteen patients died (14 from acute GVHD), and therefore nonrelapse mortality and relapse-related mortality were not calculated.

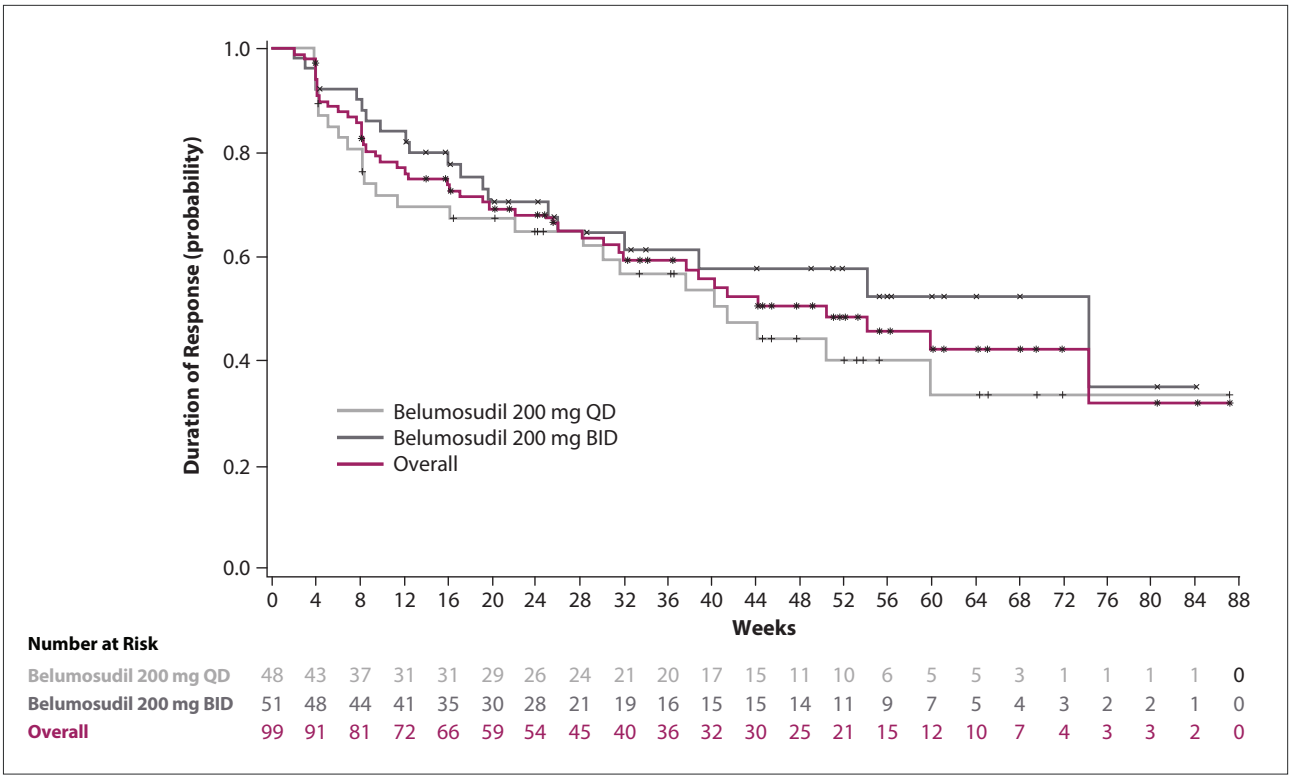


**Figure 3.** Duration of response in the ROCKstar study, which evaluated belumosudil at different dosages in patients with previously treated chronic graft-vs-host disease. BID, twice daily; DOR, duration of response; QD, once daily. Adapted from Cutler C et al. ASH abstract 353. *Blood.* 2020;136(suppl 1).[5]

endpoint was ORR (assessed with the NIH chronic GVHD consensus criteria for response).

The ROCKstar trial fully enrolled patients in less than 10 months across 28 US sites. The baseline patient characteristics were evenly distributed among the 2 randomization cohorts. The median time from chronic GVHD diagnosis to enrollment was 28 months. Two-thirds of patients had severe chronic GVHD. Half of the patients had chronic GVHD that involved at least 4 organs.

Twelve months after the final patient enrolled in the study, treatment was ongoing in 49 patients, with a median treatment duration of 9.4 months in the daily treatment group and 11.8 months in the twice-daily treatment group.[5] The treatment was discontinued by 43 patients in the daily group and 40 patients in the twice-daily group. Chronic GVHD progression and adverse events were the most common reasons for discontinuation of therapy.

The ROCKstar study met its primary endpoint, showing that belumosudil achieved clinically meaningful and statistically significant ORRs in both arms at the follow-up analysis.[5] The ORR was 73% (95% CI, 60%-83%; $P<.0001$) in the once-daily group and 77% (95% CI, 65%-87%; $P<.0001$) in the twice-daily group. (This difference was considered statistically significant because the lower bound of the 95% CI exceeded 30%.) Seven patients achieved a complete response in all affected organs.

The responses occurred rapidly, with a median time to response of 4 weeks (the first assessment time point).[5] The median duration of response was 50 weeks, and 60% of patients maintained responses for at least 20 weeks (Figure 3). Responses were also observed across all key subgroups, including those based on chronic GVHD severity, number of prior lines of systemic therapy, and number of organs involved at baseline. Organ-specific analyses demonstrated that patients receiving twice-daily belumosudil had slightly higher response rates for skin, eye, mouth, liver, and lower gastrointestinal (GI) disease than patients who received once-daily belumosudil. The response rates were also superior in patients with a shorter duration of chronic GVHD prior to study enrollment.

The data for both dosing arms were combined to provide a 1-year failure-free survival of 58% and a 2-year overall survival of 89%.[5] The dose of corticosteroids was reduced for 64% of the patients, while 21% discontinued corticosteroid therapy. Similarly, the dose of calcineurin inhibitors was reduced for 45% of patients, and

22% discontinued therapy. There were clinically meaningful improvements in quality of life (defined as a 7-point reduction in the modified Lee Symptom Scale score), even among those patients considered to be non-responders according to NIH criteria.

Overall, the safety profile of belumosudil was consistent with that expected in patients with chronic GVHD, with no noticeable differences between the 2 dosing regimens.[5] The adverse events observed in the ROCKstar trial were similar to those reported in the initial belumosudil dose-escalation studies. The most common grade 3 or higher adverse events were pneumonia (8%), hypertension (6%), and hyperglycemia (5%). There were 8 deaths during the study (4 in each treatment arm), which were mostly related to infection and respiratory compromise.

The study investigators concluded that once- or twice-daily dosing of belumosudil at 200 mg was well tolerated and led to clinically meaningful outcomes and a high response rate (>70%) in patients with chronic GVHD. Responses were observed across key subgroups and organs with fibrotic disease. Pharmacokinetic and pharmacodynamic data are anticipated in 2021, and a pediatric cohort study is planned.

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# Biomarker and Safety Analyses of Patients With Steroid-Refractory Acute Graft-Vs-Host Disease Treated With Ruxolitinib or Best Available Therapy in the Randomized, Phase 3 REACH2 Study

Acute GVHD is driven by proinflammatory cytokines and chemokines. Inhibition of the Janus kinase (JAK) pathway by ruxolitinib may modulate such cytokines and prognostic markers of GVHD.[1,2] In the phase 3 randomized REACH2 trial, once-daily ruxolitinib at a dose of 10 mg demonstrated superior efficacy over best available therapy in patients with corticosteroid-refractory acute GVHD. The ORR at day 28 was 62% with ruxolitinib vs 39% with best available therapy ($P$<.001), and the durable ORR at day 56 was 40% vs 22%, respectively ($P$<.001).[3]

In this first biomarker study conducted as part of a phase 3 randomized trial in acute GVHD, Socié and colleagues assessed whether baseline levels of proinflammatory cytokines and GVHD markers were prognostic for response and evaluated how these markers change throughout the treatment course.[4] The investigators analyzed several proinflammatory cytokines (interleukin 6 [IL-6], IL-8, tumor necrosis factor alpha [TNF-α]), soluble receptors of cytokines (suppression of tumorigenicity [ST2], IL-2 receptor alpha, and TNF receptor superfamily member 1A [TNFRSF1A]), and tissue-specific markers for GI, liver, and skin GVHD (regenerating family member 3 alpha [REG3A] and hepatocyte growth factor [HGF]). More than 95% of randomized patients (295/309) in the REACH2 study were included in this biomarker analysis.

Higher median baseline levels of the assessed proinflammatory cytokines, soluble cytokines, and tissue-specific GVHD markers were observed among patients exhibiting no response compared with patients who had a complete response (Figure 4).[4] Higher biomarker levels at baseline were associated with a lower probability of response after adjusting for treatment. Patients with skin involvement at baseline had a higher probability of response, regardless of baseline biomarker levels. The presence of liver involvement and elevated IL-6, TNF-α, TNFRSF1A, REG3A, or HGF at baseline were associated with a lower probability of response. In contrast, GI involvement did not have a significant impact on biomarkers, which the investigators suggested is an area of interest for further research.

Von Bubnoff and colleagues reported additional safety data from the REACH2 study up to day 28.[5] A total of 302 patients—152 in the ruxolitinib arm and 150 in the best available therapy arm—received at least 1 dose of study drug and were included in the safety analysis. The rates of adverse events (96% in the ruxolitinib arm vs 95% in the control arm) and serious adverse events (38% vs 34%) were similar between treatment arms. Adverse events leading to treatment

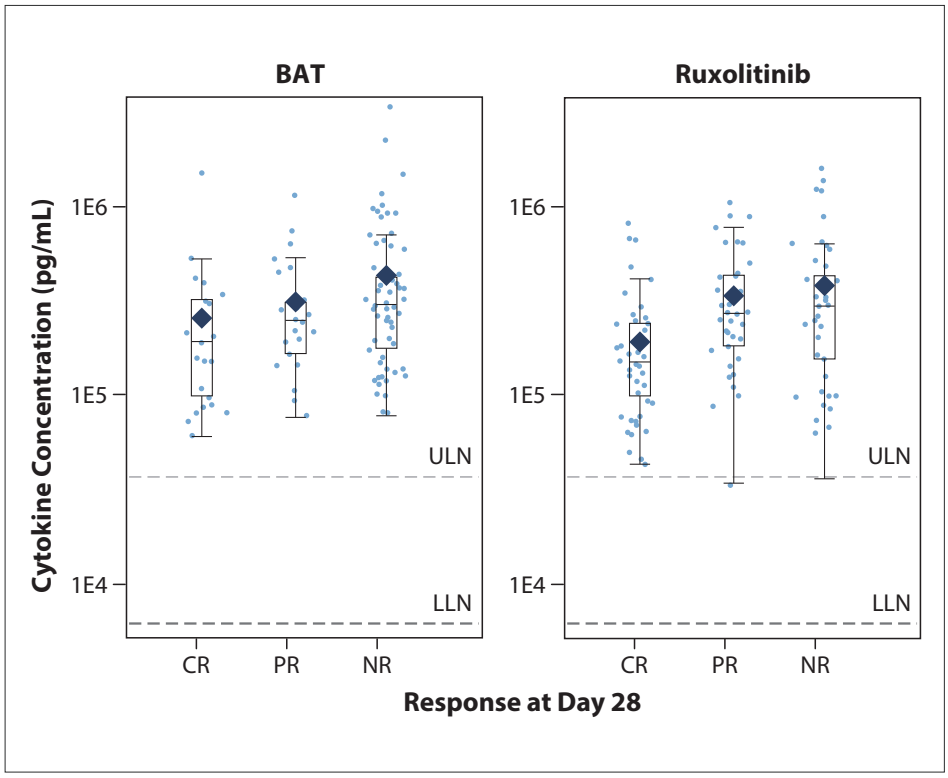


**Figure 4.** Baseline levels of the soluble cytokine receptor ST2 according to response to treatment in the phase 3 REACH2 study, which compared ruxolitinib vs best available therapy in patients with corticosteroid-refractory acute graft-vs-host disease. The median baseline cytokine level is shown as a line inside each box. The mean baseline cytokine levels are represented by black diamonds. BAT, best available therapy; CR, complete response; LLN, lower limit of normal; NR, no response; PR, partial response; ST2, suppression of tumorigenicity 2; ULN, upper limit of normal. Adapted from Socié G et al. ASH abstract 1519. *Blood.* 2020;136(suppl 1).[4]

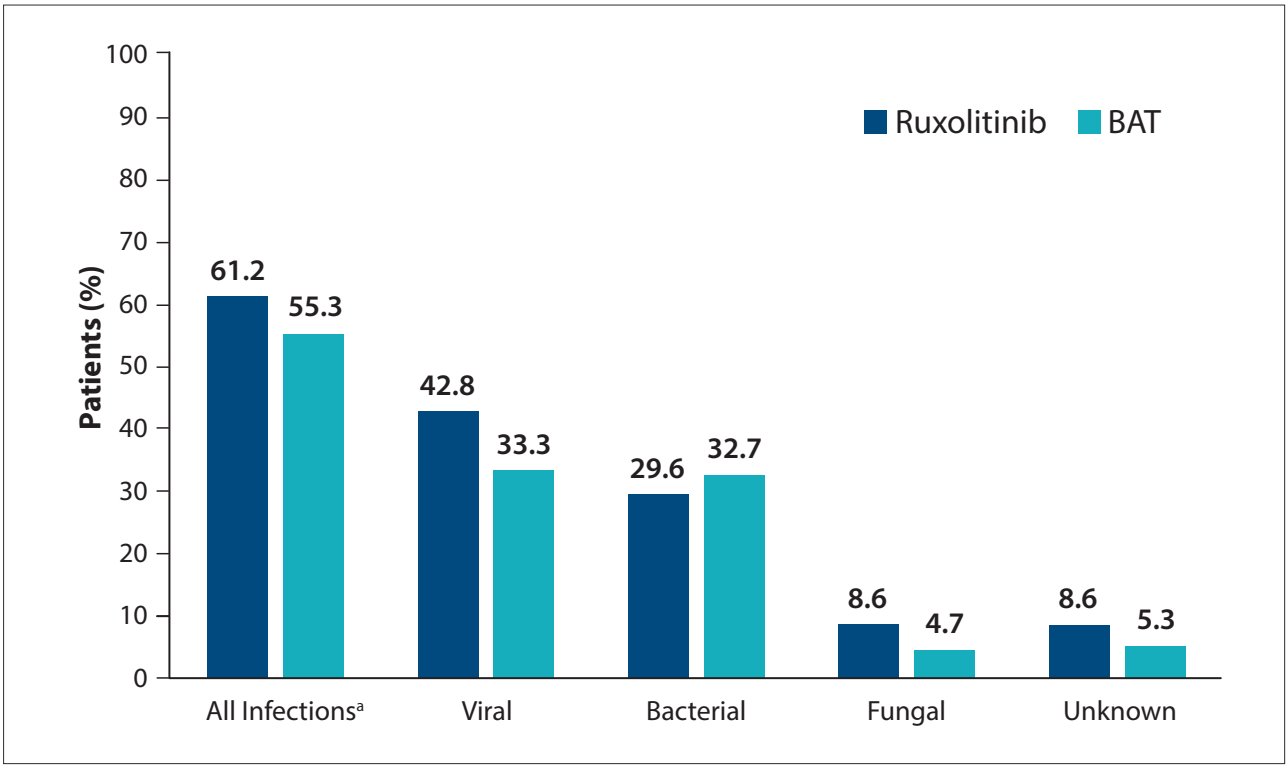


**Figure 5.** Rates of infections in the phase 3 REACH2 study, which compared ruxolitinib vs best available therapy in patients with corticosteroid-refractory acute graft-vs-host disease. [a]Patients with multiple events are counted more than once for each infection type. BAT, best available therapy. Adapted from von Bubnoff N et al. ASH abstract 2440. *Blood.* 2020;136(suppl 1).[5]

discontinuation included anemia (2% in the ruxolitinib arm vs <1% in the control arm), thrombocytopenia (2% vs 0%), and pancytopenia (1% vs 0%). There were 15 deaths in the ruxolitinib arm (10%) and 17 deaths in the control arm (14%). The most common cause of death was acute GVHD. On-treatment deaths from acute GVHD were reported in 6% of the ruxolitinib arm vs 11% of the control arm.

The most frequent adverse events of any grade in the ruxolitinib arm were thrombocytopenia (50% vs 33%), anemia (30% vs 28%), and CMV infection/reactivation (26% vs 21%).[5] Rates of adverse events of grade 3 or higher (78% vs 79%) and serious adverse events (38% vs 34%) were similar between ruxolitinib and the best available therapy. The most commonly reported serious adverse events were sepsis, CMV infection/reactivation, respiratory failure, and septic shock.

Rates of infections are shown in Figure 5. The most common infections were CMV infection/reactivation (23% vs 17%), sepsis/septic shock (5% vs 5%), and oral candidiasis (1% vs 3%).[5] However, the difference in infection rates between the treatment arms was not considered significant. The median time to the first infection was 2.1 weeks with ruxolitinib vs 1.9 weeks with the best available treatment.

Up to day 28, the risk of developing an adverse event of special interest was similar between the treatment arms, with the exception of thrombocytopenia, which was higher with ruxolitinib.[5] The risk of infection (CMV infection and sepsis/septic shock) was similar between the treatment arms. The investigators concluded that no new or unexpected safety issues were observed with ruxolitinib.

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# Efficacy and Safety of Baricitinib in Refractory Chronic Graft-Versus-Host Disease: Preliminary Analysis Results of a Phase 1/2 Study

Baricitinib is an oral inhibitor of JAK1/2 that has shown therapeutic promise in preclinical models of GVHD.[1] A single-arm, intrapatient dose-escalating phase 1/2 trial investigated the use of baricitinib in patients with severe, refractory chronic GVHD. The doses of baricitinib (1 mg, 2 mg, and 4 mg daily) were extrapolated from studies in patients with rheumatoid arthritis.

The trial enrolled 20 patients, who received baricitinib at 2 mg daily for 12 weeks. Patients with a dose-limiting toxicity switched to 1 mg daily for 24 weeks. Among patients with no dose-limiting toxicities, the dose remained at 2 mg daily (complete responders) or was escalated to 4 mg daily (partial responders and patients with stable disease or progressive disease) for a further 12 weeks. Patients receiving 4 mg daily who reported dose-limiting toxicities were required to switch to 2 mg daily until the 6-month primary endpoint. Patients who tolerated baricitinib and did not have disease progression were permitted to remain on therapy for a further 6 months.

The patients' median age was 54 years.[1] The median delay from chronic GVHD diagnosis to study enrollment was 3 years. Chronic GVHD involved a median of 4 organs (range, 2-6). The condition affected at least 3 organs in 75% of patients. Most of the patients (90%) had sclerotic skin involvement. At the time of study enrollment, 17 patients (85%) were receiving concurrent immunosuppressive therapy, with corticosteroids (n=12) and calcineurin inhibitors (n=5) being the most common treatments.

According to the pharmacokinetic analyses, the typical time to peak concentration of baricitinib was 2 hours, and the half-life of the drug was 6 to 7 hours.[1] No significant exposure-response relationship was observed in this small study. No dose-limiting toxicities were reported, and 16 patients reached the 4-mg daily baricitinib dose.

The primary efficacy endpoint, ORR at 6 months as defined by the 2014 NIH chronic GVHD response criteria, was 65% (95% CI, 50%-85%).[1] The best ORR at any time was 90%, and the median time to best response was 1.4 months (range, 1.4-6.3). Nine patients had reached the 12-month assessment, and 8 of these 9 patients had durable responses. Only 3 of the 9 patients progressed, at a median of 7.3 months (range, 6.9-11.9) following study drug discontinuation, with the remainder experiencing stable disease.

The highest rates of organ-specific

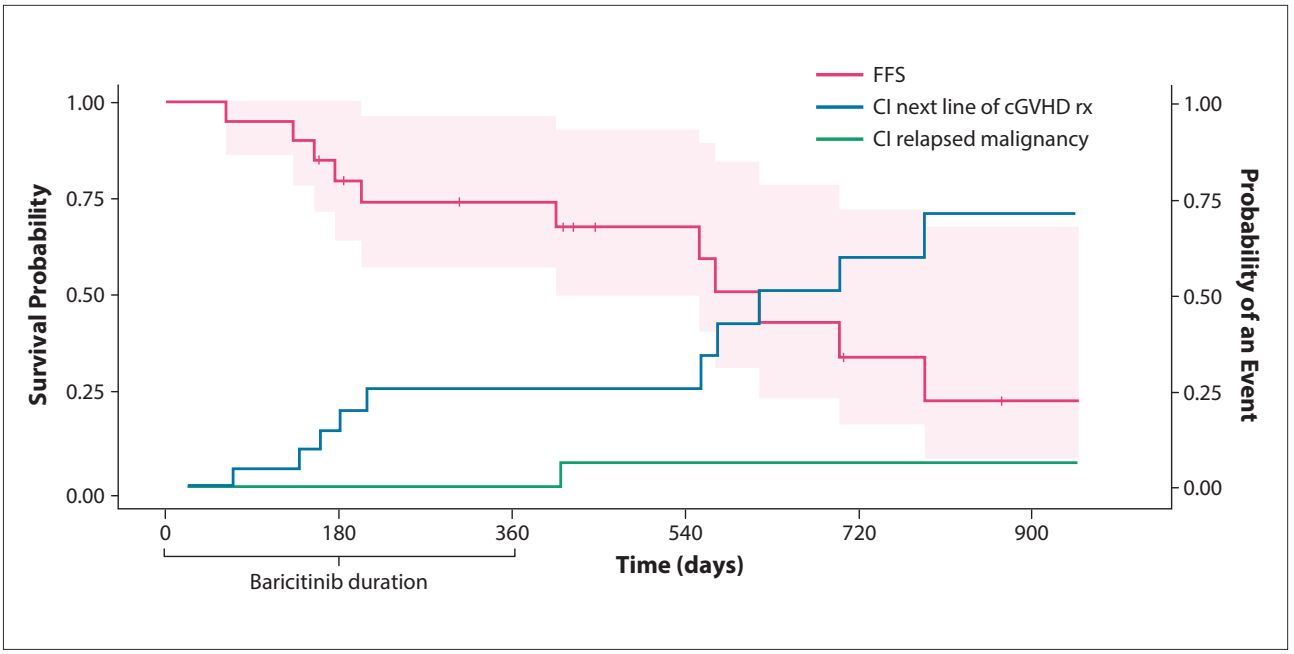


**Figure 6.** Failure-free survival in a phase 1/2 study of baricitinib in patients with refractory cGVHD. cGVHD, chronic graft-vs-host disease; FFS, failure-free survival; Rx, treatment. Adapted from Holtzman NG et al. ASH abstract 357. *Blood.* 2020;136(suppl 1).[1]

response were observed in the lower GI tract (100%), joints/fascia (85%), and mouth (50%), whereas the lowest response rates were observed in the lungs (10%) and skin (0%).[1] The investigators suggested that the lack of response for skin involvement was due to the fact that scleroderma is particularly challenging to resolve.

Treatment with baricitinib permitted 50% of study participants to taper their daily corticosteroid dose, by a median of 4 mg.[1] Furthermore, treatment with baricitinib led to clinically meaningful improvement in patient-reported outcomes as measured by the Lee Symptom Scale in 7 of 14 patients evaluable at 6 months.

Holtzman and colleagues also reported treatment outcomes following long-term follow-up.[1] The median failure-free survival was 20.6 months (range, 19 months to not reached; Figure 6). One-year and 2-year failure-free survival were 74% and 37%, respectively. Two out of 20 patients (10%) experienced relapsed malignancy, at a median of 5.2 months after discontinuing the study drug.

Adverse events possibly related to treatment were reported in 85% of patients. The most common of these events were upper respiratory infection, hypophosphatemia, hypokalemia, neutropenia, and pneumonia. Six patients experienced grade 3 or higher adverse events that were possibly treatment-related. Eleven serious adverse events were reported in 6 patients. Five of these events were possibly drug-related, including hospitalizations for joint infection (n=1), cellulitis (n=2), and viral upper respiratory infection (n=2). Dose interruption was required in 11 patients owing to adverse events, and dose reduction was required in 3 patients owing to neutropenia (n=2) and myalgia (n=1). Nine patients discontinued treatment owing to toxicity (n=3), progressive disease (n=3), and other unrelated causes (n=3). The median time to study discontinuation was 5.6 months (range, 0.8-10.7). There were no relapses of malignancy or deaths during the study.

Given the interest in infectious complications in heavily immunocompromised GVHD populations, the investigators noted that cases of grade 1 viral reactivation of CMV (n=6), Epstein–Barr virus (EBV; n=7), and BK virus (n=5) were detected in the urine of patients.[1] All cases were asymptomatic and self-limiting, and did not require therapy. There were 13 viral upper respiratory infections, mostly observed during the winter months. Several bacterial infections were observed, but there were no mycobacterial or fungal infections. Only 40% of patients received concurrent prophylaxis for fungal infections.

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# Phase 1 Study of Axatilimab (SNDX-6352), a CSF-1R Humanized Antibody, for Chronic Graft-Versus-Host Disease After 2 or More Lines of Systemic Treatment

Ibrutinib is the only approved second-line treatment for patients with chronic GVHD and disease progression or an inadequate response during treatment with corticosteroids.[1] Morbidity and mortality are high among patients who require second or subsequent lines of therapy. Therefore, there is an urgent need to develop novel agents to treat chronic GVHD.

Axatilimab is an immunoglobulin G4 monoclonal antibody directed against the colony-stimulating factor 1 (CSF-1) receptor. Inhibition of the anti–CSF-1 receptor is thought to deplete circulating nonclassical monocytes and tissue macrophage infiltration, and to reduce GVHD-associated tissue pathology.[2] Axatilimab is currently being investigated in a phase 1/2 dose escalation/expansion clinical study in patients ages 6 years and older who have active, chronic GVHD.[1] Additional inclusion criteria include a Karnofsky Performance Scale score of 60 or higher and prior treatment with at least 2 lines of therapy for chronic GVHD.

Fifteen patients were enrolled in the phase 1 dose escalation part. They received sequential treatment with intravenous (IV) axatilimab escalating from 0.15 mg/kg every 2 weeks to 3.0 mg/kg every 2 or 4 weeks.[1] The objective of the phase 1 study was to determine the maximum tolerated dose and to assess the pharmacokinetic and pharmacodynamic properties of axatilimab. The phase 2 dose-expansion part will enroll up to 22 patients and assess the efficacy (ORR) of axatilimab dosed at 1 mg/kg every 2 weeks.

Arora and colleagues presented the findings of the phase 1 dose-escalation study.[1] The median age at transplant was 60 years, with 47% of patients undergoing transplant with myeloablative conditioning and 60% receiving a transplant

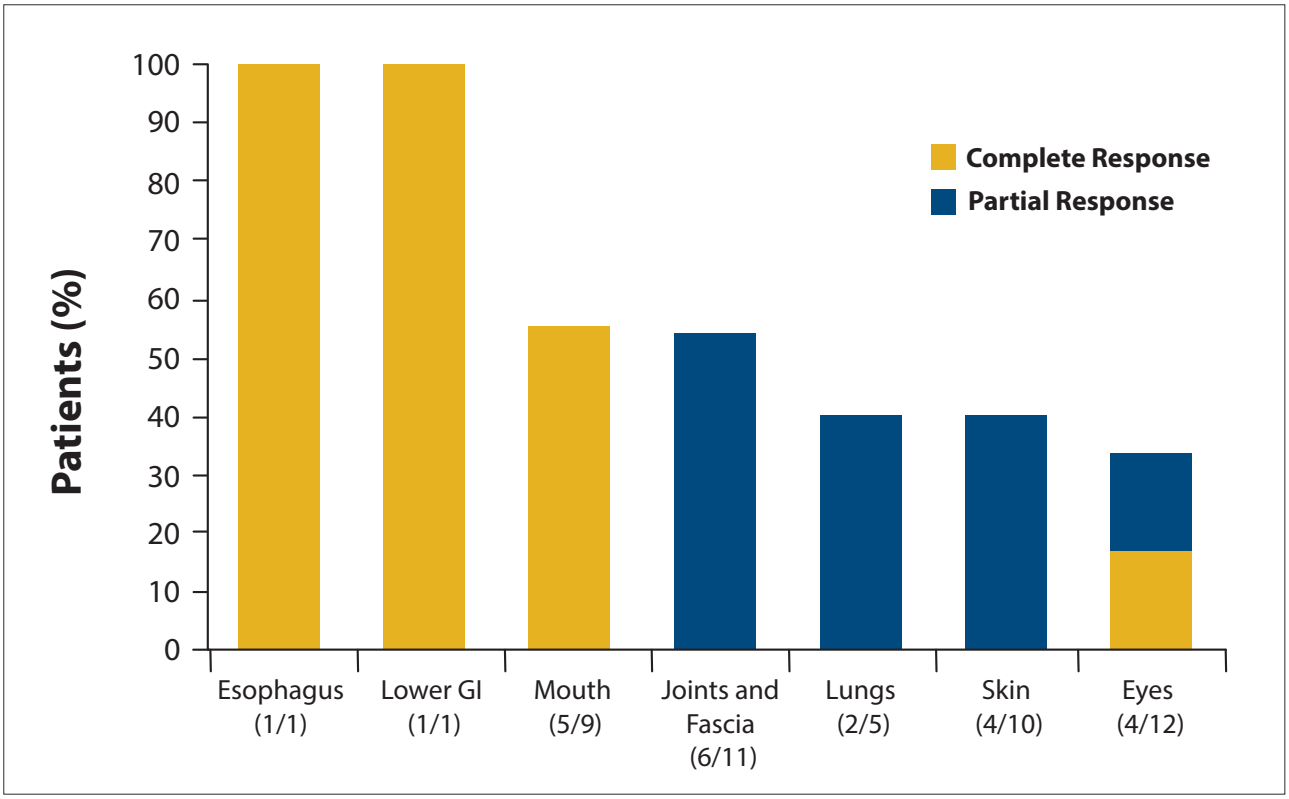


**Figure 7.** Organ-specific response rates in a phase 1 study of axatilimab in patients with previously treated chronic graft-vs-host disease. GI, gastrointestinal. Adapted from Arora M et al. ASH abstract 358. *Blood.* 2020;136(suppl 1).[1]

from a related donor. The median time from transplant to the development of chronic GVHD was 6.8 months, and the median delay to the first cycle of chronic GVHD treatment was 42 months. Half of the enrolled patients had chronic GVHD that affected at least 4 organs. Patients had received a median of 4 prior treatments, including ibrutinib (73%), ruxolitinib (60%), and belumosudil (33%).

Responses to axatilimab were observed across several organ systems (Figure 7), at all dose levels, and after prior treatment with ibrutinib, ruxolitinib, and belumosudil.[1] Complete responses were seen in patients with mouth (5/9), esophageal (1/1), and lower GI involvement (1/1). Four out of 12 patients with eye involvement had a response, of which 50% were complete responses. Partial responses were seen in patients with involvement of the joints and fascia (6/11), lungs (2/5), and skin (4/10). In 1 patient with sclerodermatous chronic GVHD that was unresponsive to prior therapies, axatilimab dosed at 1 mg/kg every 2 weeks led to significant improvements within 2 months of treatment. In another patient, axatilimab dosed at 3 mg/kg every 2 weeks led to significant improvement in lower leg ulceration.

Axatilimab provided early symptom control in heavily pretreated patients with chronic GVHD (Figure 8). An ORR was reported in 57% of patients, and 36% achieved stable disease.[1] The median time to response was 1.9 months (range, 1-11). Axatilimab also provided clinically meaningful improvements in quality of life, as shown by the median 9-point reduction in normalized the Lee Symptom Scale score across all patients. Sixty-seven percent achieved at least a 7-point reduction from baseline. One patient in the 3 mg/kg every 4 week cohort experienced an increase in the Lee Symptom Scale score and discontinued treatment after 3 cycles.

All of the patients experienced a treatment-emergent adverse event related to axatilimab therapy.[1] Nine events of infection with pneumonia, conjunctivitis, gastroenteritis norovirus, influenza, lower respiratory tract infection, pseudomonas infection, and upper respiratory infection were reported in 6 patients, with 2 patients experiencing multiple events. No cases of CMV reactivation were reported.

Grade 3/4 treatment-emergent adverse events occurred in approximately 50% of patients, and primarily consisted of laboratory abnormalities (creatine kinase in 3 patients; increased aspartate aminotransferase

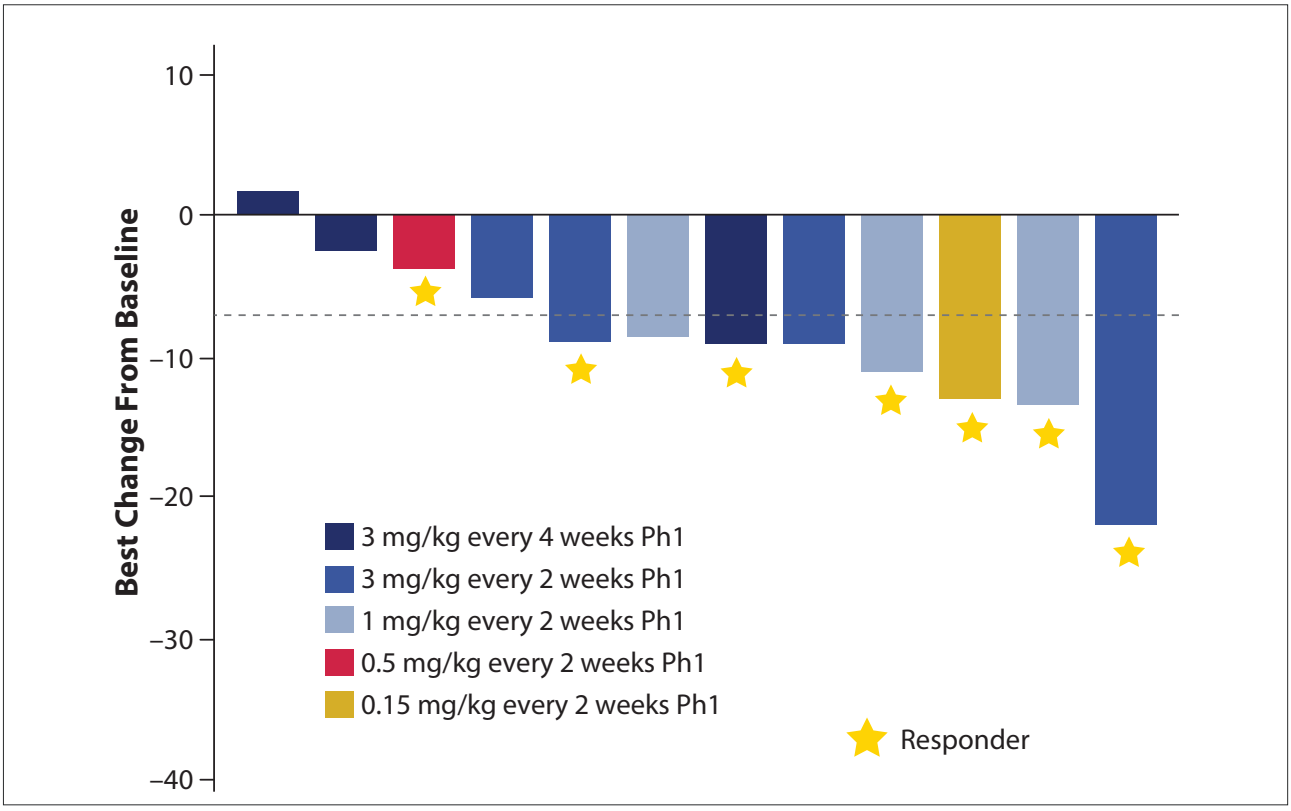


**Figure 8.** Changes in Lee Symptom scores in a phase 1 study of axatilimab in patients with previously treated chronic graft-vs-host disease. Ph1, phase 1. Adapted from Arora M et al. ASH abstract 358. *Blood.* 2020;136(suppl 1).[1]

in 2 patients) and pneumonia (in 2 patients). Among the 8 patients who discontinued treatment, 2 did so owing to disease progression (in the ≤1 mg/kg every 2 weeks dosing groups) and 1 owing to adverse events (in the 3 mg/kg every 2 weeks group).

According to pharmacokinetic and pharmacodynamic analyses, axatilimab follows a dose-dependent nonlinear elimination typical for a monoclonal antibody with target mediated drug disposition.[1] Axatilimab is highly effective at selectively reducing levels of circulating monocytes, with an approximate 95% reduction in profibrotic nonclassical monocytes and a 60% to 75% reduction in proinflammatory intermediate monocytes.

The investigators summarized that axatilimab demonstrated good tolerability and safety with clinical activity, as evidenced by a 57% response rate in a heavily pretreated patient population. Ongoing development of axatilimab will include a multicenter, randomized phase 2 study (AGAVE-201) that will evaluate the efficacy, safety, and tolerability of 3 doses of axatilimab in patients with recurrent or refractory chronic GVHD who have received at least 2 prior systemic therapies.[3]

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# A Single-Arm, Open-Label Phase 1 Study of Itacitinib With Calcineurin Inhibitor–Based Interventions for Prophylaxis of Graft-Versus-Host Disease (GRAVITAS-119)

JAK 1 and 2, which transduce signals from multiple cytokine receptors, have been implicated in the pathogenesis of GVHD.[1] Itacitinib is a potent, selective JAK1 inhibitor that has been administered to patients with acute GVHD in combination with corticosteroids as initial treatment.[2,3]

Choe and colleagues presented the findings of the GRAVITAS-119 single-arm, open-label, nonrandomized phase 1 study.[4] The objective of this proof-of-concept study was to evaluate itacitinib in combination with calcineurin inhibitor–based regimens for prophylactic treatment of GVHD. The trial enrolled adult patients with hematologic malignancies who were candidates for reduced-intensity conditioning and peripheral blood stem cell transplant. Patients received itacitinib at a dose of 200 mg daily 3 days prior to transplant, in combination with tacrolimus/methotrexate (MTX; n=41) or cyclosporine/mycophenolate mofetil (MMF; n=24) with or without antithymocyte globulin (ATG). Itacitinib was reduced to 100 mg daily by day 90 and discontinued by day 180, unless patients required systemic GVHD treatment, experienced a relapse of a malignancy, developed unacceptable toxicity, or withdrew consent.

The median exposure to itacitinib was 140 days (range, 10-187), and 74% of patients received itacitinib for longer than 90 days.[4] More patients in the cyclosporine/MMF arm (50%)

**ABSTRACT SUMMARY Efficacy and Safety of Sabatolimab in Combination With Hypomethylating Agents in Patients With Acute Myeloid Leukemia and High-Risk Myelodysplastic Syndrome: Updated Results From a Phase 1b Study**

Sabatolimab (MBG453) is a humanized monoclonal antibody targeting TIM-3, an inhibitory receptor involved in the regulation of both adaptive and innate immune responses. TIM-3 is expressed on immune cells and leukemic stem cells and blasts, but not normal hematopoietic stem cells. Inhibition of TIM-3 may restore immune function while also directly targeting leukemic stem cells and blasts. The combination of sabatolimab with a hypomethylating agent (either decitabine or azacitidine) was evaluated in a phase 1b, open-label, multicenter, dose-escalation study in patients with AML or high-risk MDS (Abstract 657). At the data cutoff of June 25, 2020, the objective response rate was 41.2% among 34 evaluable patients with newly diagnosed AML, and the estimated 6-month duration of response rate was 85.1% (95% CI, 68-100). Among 35 evaluable patients with high-risk MDS, the objective response rate was 62.9% and the estimated 6-month duration of response rate was 90% (95% CI, 73.2-100). The most common Grade 3 or higher TEAEs were thrombocytopenia (45.8% in newly diagnosed AML and 51.2% in high-risk MDS), neutropenia (50% and 46.1%), febrile neutropenia (29.2% and 41%), anemia (27.1% and 28.2%), and pneumonia (10.4% and 5.1%). Possible immune-mediated adverse events were also reported.

**Table 1.** Hematologic Recovery in a Phase 1 Study of Itacitinib With Calcineurin Inhibitor–Based Interventions for GVHD Prophylaxis

| Characteristic | ITA + Tac/MTX (n=41) | ITA + CsA/MMF (n=24) | Total (N=65) |
|---|---|---|---|
| **ANC Recovery[a]** | | | |
| Evaluable,[b] n | 38 | 23 | 61 |
| Recovery, n (%) | 38 (100) | 23 (100) | 61 (100) |
| Time to recovery, median (range), days | 17.0 (4-31)[d] | 18.0 (11-26) | 17.0 (4-31) |
| **Platelet Recovery[c]** | | | |
| Evaluable,[b] n | 23 | 16 | 39 |
| Recovery, n (%) | 23 (100) | 16 (100) | 39 (100) |
| Time to recovery, median (range), days | 14.0 (11-26) | 14.0 (10-18) | 14.0 (10-26) |

[a]ANC recovery: the first day of 3 consecutive assessments showing ANC ≥500/mm$^3$.
[b]Participants who experienced count nadir (ie, ANC <500/mm$^3$ and/or platelet count <20,000/mm$^3$).
[c]Platelet recovery: the first day of 3 consecutive assessments showing platelet count ≥20,000/mm$^3$ with no transfusion in the preceding 3 days.
[d]ANC recovery was on day 31 for 1 patient with secondary myelofibrosis.
ANC, absolute neutrophil count; CsA, cyclosporine A; GVHD, graft-vs-host disease; ITA, itacitinib; MMF, mycophenolate mofetil; MTX, methotrexate; Tac, tacrolimus.

Adapted from Choe H et al. ASH abstract 356. *Blood.* 2020;136(suppl 1).[4]

than in the tacrolimus/MTX arm (27%) completed the 180-day trial protocol. Adverse events (17% vs 24%) and malignancy relapse (13% vs 20%) were the most common reasons for treatment discontinuation.

The patients' median age was 65 years.[4] Acute myeloid leukemia was the most common underlying hematologic malignancy, and most patients had an intermediate disease risk index at study entry. The investigators compared the baseline characteristics of patients who did not receive ATG (n=41) with those who received ATG (n=24). In the group without ATG, donors were matched related in 61% and matched unrelated in 37%. In the group with ATG, 46% of patients underwent a matched unrelated transplant, while 33% underwent a matched related transplant. The most common conditioning regimen was reduced-intensity busulfan/fludarabine (63% in the group without ATG and 30% in the group with ATG).

All patients achieved hematologic recovery (defined as both neutrophil and platelet recovery).[4] All patients but 1 (99%) achieved the primary endpoint of hematologic recovery at day 28 (Table 1). One patient who had secondary myelofibrosis achieved neutrophil recovery on day 31. Overall, the median times to neutrophil and platelet recovery were 17 and 14 days, respectively, with no significant difference between patients receiving tacrolimus/MTX or cyclosporine/MMF.

Two patients experienced secondary graft failure, 1 during treatment with tacrolimus/MTX/ATG on day 65 and a second during follow-up after treatment with tacrolimus/MTX (approximately 4 months after the last dose of itacitinib). Both patients received transplants from matched unrelated donors and busulfan/fludarabine as a conditioning regimen.

The cumulative incidence of acute GVHD at day 180 was low; grade 3/4 acute GVHD occurred in 5% of patients treated without ATG and in 4% of patients treated with ATG.[4] These rates compare favorably with historical data for calcineurin inhibitor–based regimens.[5,6] One-year overall survival rates higher than 70% were observed in GRAVITAS-119.[4] The cumulative incidence of moderate or severe chronic GVHD was 31% without ATG vs 10% with ATG. Relapse or progression at 1 year was reported in 28% vs 4%, respectively. The investigators noted that these findings should be interpreted with caution based on the small sample size and possible confounding factors, which included concomitant use of rituximab for EBV infection (n=7).

Most patients (88%) experienced at least 1 adverse event of grade 3 or higher.[4] The most common hematologic adverse events were thrombocytopenia (49%), anemia (29%), leukopenia (29%), neutropenia (29%), lymphopenia (26%), and febrile neutropenia (12%). The most common

nonhematologic adverse events were diarrhea (15%), hypertension (14%), hypertriglyceridemia (12%), hyperglycemia (11%), and stomatitis (8%). Fifteen patients (23%) experienced hematologic adverse events that led to dose modification and/or discontinuation, with thrombocytopenia (9%) being the most common.

Up to one-third of patients reported an infection of grade 3 or higher, with viral infections the most common. There were 11 reports of CMV infection (any grade); all occurred in cases when the donor and/or recipient had a positive CMV serostatus. Ten of these cases were reported as CMV viremia, 9 of which required antiviral treatment. One patient who received cyclosporine/MMF/ATG had a resistant CMV infection, and died from acute respiratory distress. There were no cases of post-transplant lymphoproliferative disorder. However, there were 16 deaths during the study, the primary causes being infection during treatment (n=2), and malignancy relapse (n=5) or infection (n=3) during follow-up.

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# Comparison of Outcomes After Haploidentical Relative and HLA Matched Unrelated Donor Transplantation With Post-Transplant Cyclophosphamide Containing GVHD Prophylaxis Regimens

Results from the phase 2 BMT CTN 1203 trial suggested that a GVHD prophylaxis regimen based on post-transplant cyclophosphamide (PT-Cy) improved 1-year GVHD-free, relapse-free survival.[1] It is unclear whether haploidentical donors are superior to matched unrelated donors when PT-Cy-containing GVHD prophylactic regimens are used. Gooptu and colleagues compared outcomes after haploidentical hematopoietic cell transplant and matched unrelated donor hematopoietic cell transplant among patients who received prophylaxis with PT-Cy.[2] The study enrolled patients who underwent haploidentical cell transplant or matched unrelated donor hematopoietic cell transplant for acute myeloid leukemia, acute lymphoblastic leukemia, or myelodysplastic syndrome. The characteristics were well balanced between the patient groups. Age at transplant, sex, performance score, comorbidities, and CMV serostatus were similar. The study separately analyzed 1001 patients who received a myeloablative regimen and 1398 who received a reduced-intensity regimen. All patients who underwent haploidentical hematopoietic cell transplant

**ABSTRACT SUMMARY Ruxolitinib for Steroid-Refractory Chronic GVHD: A Significant Response in Heavily Pretreated Patients After Haploidentical-SCT**

Wu and colleagues described the findings of a retrospective, single-center study that investigated the efficacy of ruxolitinib in patients with corticosteroid-refractory chronic GVHD (Abstract 2398). The median time from chronic GVHD to initial ruxolitinib treatment was 11.0 months (range, 0.6-71.9) in the 41 patients analyzed. After a median duration of 8 months (range, 1.1-24.9) of ruxolitinib treatment, 30 patients (73%) achieved an ORR, which included 15 complete responses. The greatest ORRs were observed in the GI tract (100%), liver (87%), skin (82%), and mouth (81%). In 90% of patients, the therapeutic response to ruxolitinib permitted a decrease in the dose of prednisone. An inadequate response to ruxolitinib was more likely in recipients of a matched related donor and in patients with lung GVHD. Lung infections and CMV/EBV reactivation were the most severe adverse events related to ruxolitinib and highlight the significance of prophylactic strategies against infections.

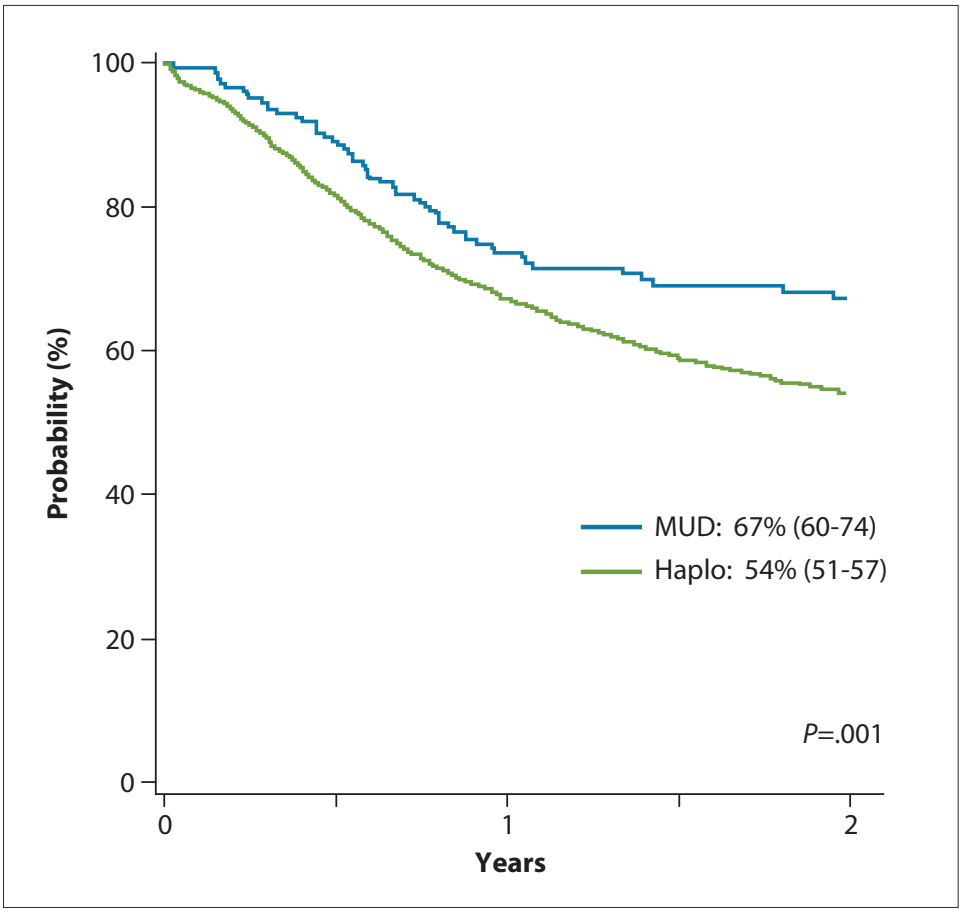


**Figure 9.** Overall survival in a study that compared outcomes between patients who underwent haplo HCT or MUD HCT, with PT-Cy–based prophylaxis. haplo, haploidentical; HCT, hematopoietic cell transplant; MUD, matched unrelated donor; PT-Cy, post-transplant cyclophosphamide. Adapted from Gooptu M et al. ASH abstract 76. *Blood.* 2020;136(suppl 1).[2]

and reduced intensity-conditioning matched unrelated donor hematopoietic cell transplant received PT-Cy, a calcineurin inhibitor, and MMF for GVHD prophylaxis. Among patients who underwent myeloablative conditioning and a matched unrelated donor hematopoietic cell transplant, 55% received PT-Cy, a calcineurin inhibitor, and MMF, while 45% received PT-Cy and a calcineurin inhibitor.

The study found that GVHD outcomes and overall survival were similar between haploidentical and matched unrelated donor transplant when PT-Cy was used in combination with a calcineurin inhibitor and MMF. The risk of grade 2 to 4 acute GVHD was lower among patients treated with the triplet regimen and haploidentical donor transplant compared with GVHD prophylaxis with PT-Cy plus a calcineurin inhibitor following a matched unrelated donor transplant. Among patients treated with less-intense conditioning regimens and GVHD prophylaxis with the triple combination regimen, nonrelapse mortality was 16% with haploidentical transplant vs 8% with matched unrelated donor transplant (*P*=.0008). The rate of disease-free survival was 55% in patients who underwent matched unrelated donor hematopoietic cell transplant vs 41% in those who underwent haploidentical hematopoietic cell transplant (*P*=.002). Overall survival was 67% vs 54%, respectively (*P*=.001; Figure 9).

The investigators concluded that among patients who received myeloablative conditioning and GVHD prophylaxis consisting of received PT-Cy, a calcineurin inhibitor, and MMF, the results were comparable between haploidentical related and matched unrelated transplants. In contrast, for patients who received less-intense conditioning regimens, disease-free survival and overall survival were higher after matched unrelated donor hematopoietic cell transplant compared with haploidentical hematopoietic cell transplant.

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# Highlights in Chronic Graft-vs-Host Disease From the 62nd American Society of Hematology Annual Meeting and Exposition: Commentary

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Presentations in graft-vs-host disease (GVHD) at the 62nd American Society of Hematology (ASH) meeting provided important information regarding treatments such as ruxolitinib, belumosudil, baricitinib, and axatilimab, as well as outcomes after haploidentical transplants vs unrelated donor transplants.

## Ruxolitinib

Dr Robert Zeiser presented primary findings from the phase 3 REACH3 trial, which compared the Janus kinase inhibitor (JAK) ruxolitinib vs best available therapy in patients ages 12 years and older with corticosteroid-refractory or corticosteroid-dependent chronic GVHD.[1] Several studies presented at the ASH meeting evaluated the role of various interventions for chronic GVHD. The REACH3 trial was the first and only randomized prospective study in this setting. It was an open-label trial. The trial randomly assigned patients with moderate or severe chronic GVHD to receive ruxolitinib at 10 mg orally twice a day (n=165) or best available therapy (n=164). Both treatment arms also included corticosteroids with or without a calcineurin inhibitor. The best-available therapy included many different kinds of treatments. The primary endpoint was efficacy (overall response rate [ORR]) at 24 weeks.

The difference was highly statistically significant in favor of ruxolitinib. The ORR at week 24 was 49.7% in the ruxolitinib arm vs 25.6% in the best available therapy arm ($P<.0001$). More important was an improvement in failure-free survival, which was not reached with ruxolitinib vs 5.7 months with best available therapy ($P<.0001$). The best ORR at 24 weeks was 76.4% with ruxolitinib vs 60.4% with best-available therapy.

The only notable complications in the ruxolitinib arm were thrombocytopenia and anemia; these events occurred more frequently with ruxolitinib than with best available therapy. Interestingly, there were no statistically significant differences in bacterial, viral, or fungal infections. This surprising finding suggests that the decrease in blood counts did not impact rates of infections.

The conclusion is that ruxolitinib is an effective therapy for patients with moderate or severe corticosteroid-refractory chronic GVHD. The superiority of ruxolitinib vs best-available therapy was highly statistically significant. The results of the REACH3 study provide hope that patients with progressive and severe corticosteroid-refractory chronic GVHD will benefit from ruxolitinib, which is a balanced JAK1/JAK2 inhibitor. The randomized design of this landmark study is important when interpreting the results and assessing their importance.

## Belumosudil

Dr Cory Cutler presented preliminary results of the multi-institutional phase 2 ROCKstar study, which evaluated the ROCK inhibitor belumosudil.[2] ROCK kinases are serine-threonine kinases that are important in immune inflammation and immune activation. They are activated by several different ligands and in multiple cell types. ROCK inhibitors downregulate specific downstream profibrotic mediators and profibrotic genes. Chronic GVHD is associated with fibrosis and scarring. The ROCKstar study is open-label. A downside is that the trial does not include a control group receiving a single therapy or best available therapy, but only randomly assigned patients to 2 different dosing schedules of the same drug, belumosudil (given once per day or twice per day). The trial enrolled patients with corticosteroid-refractory chronic GVHD who had received 2 to 5 lines of previous therapy for chronic GVHD. These treatments included ruxolitinib and ibrutinib, each reported in approximately one-third of patients. Half of the patients had been treated with more than 4 different therapies. The patient population could be considered a particularly high-risk group. The treatment arms consisted of belumosudil given at 2 different doses: 200 mg once a day or 200 mg twice a day. The trial is still ongoing.

There are several limitations to this study. With 66 patients in each arm, it is relatively small, although reasonably sized for a study of chronic GVHD. The study also lacked a control arm comparing belumosudil with best available therapy.

At 12 months of follow-up, the ORRs were 73% in the once-daily arm and 77% in the twice-daily arm. Response rates were similar for patients who were or were not refractory to their previous lines of systemic therapy (73% vs 74%, respectively). The response was relatively similar among patients with a longer or shorter duration of chronic GVHD before enrollment (68% vs 82%, respectively). The duration of response was approximately 36 weeks, and the median duration of response was 50 weeks. At 24 months, the overall survival was 89%.

Symptoms improved, as measured by Lee Symptoms Scores, in approximately one-third of patients, which is difficult to document in studies of chronic GVHD. It was possible to reduce the calcineurin dose in a quarter of the patients, and two-thirds of patients were able to reduce their dose of corticosteroids. The drug was relatively well tolerated at both doses. The most common side effects were fatigue, diarrhea, and nausea, which are also commonly seen in patients with chronic GVHD who are not receiving treatment.

The rates of response and overall survival are impressive, particularly in this group of heavily pretreated patients. The duration of response was similar to that seen in the REACH3 trial of ruxolitinib,[1] although comparisons cannot be drawn because the patient populations in the studies were different. The REACH3 trial had a better design because it included a control arm.

## Baricitinib

The National Institutes of Health conducted a small phase 1/2 study evaluating baricitinib in patients with refractory chronic GVHD.[3] Baricitinib is structurally similar to ruxolitinib, with balanced JAK1/JAK2 inhibition and an almost identical $IC_{50}$. Baricitinib is approved for the treatment of patients with rheumatoid arthritis. It is now being tested in patients with COVID-associated inflammatory disorders because it has a unique ability to inhibit one of the enzymes (AAK1) that is important for COVID-19 internalization and viral replication. This study treated 20 patients. The dose of the drug was escalated to 4 mg when possible.

The 6-month ORR was 65%.[3] The rate of 1-year freedom from progression was 74%, which is similar to that seen with ruxolitinib in the REACH3 trial and belumosudil in the ROCKstar study.[1,2] Several of the patients who responded had to discontinue treatment. Treatment was relatively safe, with few side effects. There was no evidence of viral reactivation or significant infections. There was some decrease in blood counts.

## Axatilimab

Dr Mukta Arora presented results of a small, multi-institutional phase 1 study evaluating axatilimab, a CSF-1R monoclonal antibody.[4] The CSF-1 receptor is the receptor for macrophage CSF. In mouse models, when the macrophages that express the CSF-1 receptor are genetically or pharmacologically eliminated early after transplant, the mice develop worse GVHD.[5,6] When these macrophages are eliminated late after transplant, then GVHD is diminished. The macrophages that are present early after transplant are of host origin, and they suppress the immune response. Later after transplant, those macrophages are now of donor origin, and they become proinflammatory. The theory is that inhibiting these proinflammatory macrophages reduces GVHD. Because treatment of chronic GVHD occurs late after transplant, the thought is that the macrophages present provide a proinflammatory environment, and that inhibiting them through an antibody that targets the CSF-1 receptor—which is differentially overexpressed on macrophages—will reduce GVHD.

The trial enrolled only 15 patients. In the phase 1 portion, axatilimab is being administered in a dose-escalated manner in individual patient cohorts. A phase 2 expansion phase is evaluating axatilimab given at 1 mg/kg every 2 weeks. Up to 22 patients will be treated in the expansion phase. The primary endpoint is the ORR.

Treatment was well tolerated. There were no major infectious complications. The response rate was 57%. Patients with esophageal disease, lower gastrointestinal disease, and mouth disease had good responses. Responses were lower among patients with lung disease, skin disease, joint disease, and fascial disease. Half of the patients had received ibrutinib and ruxolitinib, and 3 had received the ROCK inhibitor belumosudil. Clinical responses were durable in some of the patients, although the follow-up was not long.

A notable aspect to this study is that treatment appeared to particularly benefit patients who had sclerodermatous disease with ulcers. These patients historically are difficult to treat.

## Outcomes After Haploidentical Transplants vs Unrelated Donor Transplants

A retrospective analysis from the Center for International Blood and Marrow Transplant Research (CIBMTR) compared outcomes after haploidentical transplants vs unrelated donor transplants using post-transplant cyclophosphamide (PT-CY) prophylaxis for GVHD.[7] A conundrum in the transplant setting is how to select a donor for transplant now that haploidentical donors are an option. Most of the studies thus far have shown relatively similar outcomes for unrelated donor transplants and haploidentical stem cell transplants. The haploidentical

transplants have been a mixture of bone marrow and stem cell infusions, which can lead to complicated interpretations. Most of the unrelated donor transplants consisted of peripheral blood stem cells. This study evaluated the impact of PT-CY on the outcomes of patients undergoing transplant from matched unrelated donors (MUDs).

In those patients (both MUD and haploidentical) receiving myeloablative conditioning, the relapse rates for these groups were relatively similar. The nonrelapse mortality between the groups was also relatively similar overall, consistent with smaller studies comparing outcomes of patients undergoing unrelated vs haploidentical transplant. The rates of acute and chronic GVHD were similar between the haploidentical group and the MUD groups. There were no real differences in rates of GVHD relapse, nonrelapse mortality, and overall survival. One difference was that in the myeloablative setting, the use of calcineurin inhibitors as GVHD prophylaxis with PT-CY for MUD transplants was associated with an increased risk for GVHD compared with the use of calcineurin inhibitors plus MMF. Patients undergoing a myeloablative transplant with a MUD should receive the triple combination of calcineurin inhibitors, MMF, and PT-CY. The outcomes associated with this myeloablative regimen are very similar among patients with an HLA-matched unrelated donor vs those undergoing a haploidentical transplant. When possible, myeloablative regimens are increasingly preferred because they are associated with a reduction in relapse compared with reduced-intensity regimens. Reduced-intensity regimens are associated with a higher rate of relapse. Therefore, in patients with high-risk acute leukemias, outcomes were similar in those undergoing a MUD vs a haploidentical transplant when the procedure includes a myeloablative regimen consisting of PT-CY, a calcineurin inhibitor, and MMF. When MMF was omitted, there was a higher rate of acute GVHD in the unrelated donor setting, so this approach is not recommended. This regimen was not tested in the haploidentical setting because all of these patients always receive the 3 drugs together.

For patients undergoing reduced-intensity transplant, a MUD is favored over a haploidentical transplant. Rates of disease-free and overall survival were higher after MUD HCT compared with haploidentical transplant. Compared with haploidentical HCT, acute and chronic GVHD risks did not differ between the treatment groups. However, nonrelapse mortality was lower after MUD-HCT, which led to higher disease-free and overall survival. There was also a slightly increased delay in neutrophil engraftment when haploidentical donors were compared with MUD transplants, which resulted in increased rates of fungal infections compared with matched unrelated donor transplants.

## Conclusions

The studies evaluated drugs with different biologies: inhibition of JAK1/JAK2, inhibition of serine-threonine kinases called ROCK kinases, and inhibition of the CSF-1 receptor pathway. The best-designed study is the REACH3 trial of ruxolitinib because it was controlled, prospective, and randomized.[1] It is difficult to assess chronic GVHD, so randomized studies are particularly important. One drawback to the studies in chronic GVHD of the ROCK inhibitor baricitinib and the CSF-1R inhibitor is that they were open-label and lacked a placebo or best available therapy arm as a comparator group. It is understandable that patients who are doing poorly would not want to receive a placebo. The reality, however, is that it is difficult to identify improvement because of inherent biases among patients, nurses, and physicians. Objective measures of response are not quantitative.

A challenging aspect of chronic GVHD is treatment of bronchiolitis obliterans and progressive pulmonary insufficiency. This debilitating toxicity does not appear to improve with any of these treatments. Even in studies of agents with response rates of 70%, improvement in pulmonary function was negligible. A small Chinese study evaluated ruxolitinib in patients with bronchiolitis obliterans, but the results were unconvincing.[8]

One approach to the treatment of lung toxicity would be to use JAK inhibitors as prophylaxis. Late intervention might prevent further progression or modestly mitigate toxicities. However, the events leading to chronic GVHD occur within the first few days of transplant, although it may take weeks, months, or even years before they are manifest. Therefore, management of chronic GVHD might benefit from earlier administration of all of these agents. Our group and others have published preclinical data supporting this strategy.[9]

Early interventions would also affect acute GVHD. The 2 treatments that are associated with the most significant reproducible reduction in chronic GVHD are thymoglobulin and post-transplant cyclophosphamide.[10,11] These interventions are administered in the immediate post-transplant period, thereby blocking early events that might initially trigger both acute and chronic GVHD.

The studies reviewed here are evaluating interventions that are administered long after the disease has already been established. Thus, it may be difficult to reverse the pathology, and perhaps the best that can be expected is to halt the progression of chronic GVHD. One study presented at the ASH meeting, the phase 1 GRAVITAS-119 study, evaluated a prophylaxis regimen consisting of itacitinib, a JAK1-specific inhibitor, combined with calcineurin.[12] Results were presented for 64 patients who received a prophylaxis regimen consisting of itacitinib with tacrolimus

and methotrexate or with cyclosporine and MMF (per institutional practice). The data from this study are too early to draw firm conclusions. At 180 days, the rate of grade 2 to 4 acute GVHD was surprisingly low (14.3%) and the rate of grade 3 to 4 acute GVHD was also reduced (6.5%).

I anticipate that early intervention with various approaches will have the most significant impact on the outcome of patients undergoing allogeneic stem cell transplant. Prophylaxis can limit early expansion of alloreactive T cells and minimize damage. Less damage will lead to fewer cases of acute and chronic GVHD.

### *Disclosure*

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