Clinical Advances in
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A SPECIAL MEETING REVIEW EDITION

Highlights in Graft-vs-Host Disease From the 63rd American Society of Hematology Annual Meeting and Exposition

A Review of Selected Presentations From the 63rd ASH Meeting and Exposition • December 11-14, 2021 • Atlanta, Georgia

Special Reporting on:

- Patient-Reported Outcomes Among Patients With Corticosteroid-Refractory or -Dependent Chronic Graft-vs-Host Disease Randomized to Ruxolitinib vs Best Available Therapy
- Phase II Clinical Trial of Abatacept for Corticosteroid-Refractory Chronic Graft vs Host Disease
- A Phase II Study of Ruxolitinib Pre-, During- and Post-Hematopoietic Cell Transplantation for Patients With Primary or Secondary Myelofibrosis
- Safety, Tolerability, and Efficacy of Axatilimab, a CSF-1R Humanized Antibody, for Chronic Graft-vs-Host Disease After 2 or More Lines of Systemic Treatment
- Update of a Multicenter, Retrospective Evaluation of Overall Response and Failure-Free Survival Following Ruxolitinib Therapy for Heavily Pretreated Chronic GVHD Patients With Corticosteroid-Failure: A Proposal of a Risk Score Model for Failure-Free Survival
- Propensity Score Matching Analysis Comparing Ruxolitinib vs Historical Controls in Second-Line or Beyond Treatment for Chronic GVHD After Therapy Failure
- Belumosudil for Patients With Chronic Graft-vs-Host Disease: Combined Analysis of Failure-Free Survival in the KD025-208 and Pivotal ROCKstar Trials
- Pooled Allogenic Fecal Microbiotherapy MaaT013 for the Treatment of Corticosteroid-Refractory Gastrointestinal Acute Graft-vs-Host Disease: Results From the Phase IIa HERACLES Study and Expanded Access Program

PLUS Meeting Abstract Summaries

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NOW APPROVED for cGVHD

For treatment of chronic graft-versus-host disease (cGVHD) after failure of one or two lines of systemic therapy in adult and pediatric patients 12 years and older

REACH3 Primary Endpoint: ORR at Week 24[1,a]

49.7% with Jakafi (82/165) **vs** **25.6%** with BAT (42/164)

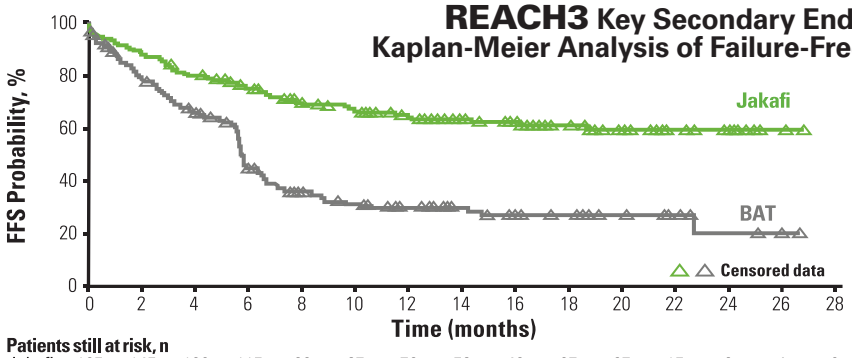
(OR, 2.99; 95% CI: 1.86, 4.80; $P < 0.0001$)[b]

ORR through Week 24[2,c,d]

70% with Jakafi (116/165) **vs** **57%** with BAT (94/164)

Significantly Longer Median Failure-Free Survival With Jakafi vs BAT[1]

REACH3 Key Secondary Endpoint: Kaplan-Meier Analysis of Failure-Free Survival[1,e]



Patients still at risk, n

Jakafi	165	145	130	115	92	87	76	58	49	37	27	15	9	4	0
BAT	164	123	100	64	45	39	31	23	17	15	9	6	3	1	0

Median FFS[f]

>18.6 months with Jakafi **vs** **5.7 months** with BAT

(HR, 0.370; 95% CI: 0.268, 0.510; $P < 0.0001$)[g]

[a] Overall response rate was defined as the proportion of patients with complete response or partial response, according to 2014 NIH consensus criteria, at Week 24.[1]
[b] One-sided *P* value, odds ratio, and 95% CI were calculated using stratified Cochran-Mantel-Haenszel test, stratifying for moderate and severe cGVHD.[1]
[c] Defined as proportion of patients who achieved complete or partial response, according to 2014 NIH Response Criteria, through Week 24 (Cycle 7 Day 1).[2]
[d] In the Jakafi Prescribing Information, efficacy was based on ORR through Week 24 (Cycle 7 Day 1).[2]
[e] Defined as the earliest time from date of randomization to relapse or recurrence of underlying disease or death due to underlying disease, nonrelapse mortality, or addition or initiation of another systemic therapy for cGVHD.[1]
[f] Median FFS with Jakafi was not reached; the lower bound of the 95% CI was estimated at 18.6 months.[1]
[g] Descriptive *P* value (ex-US only). Efficacy boundary crossed at the interim analysis (HR, 0.315; 95% CI: 0.205, 0.486; $P < 0.0001$). For US, the *P* value gives the result of the retested hypothesis at the primary analysis, following the overall hierarchal testing procedure.[3]

Indications and Usage

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

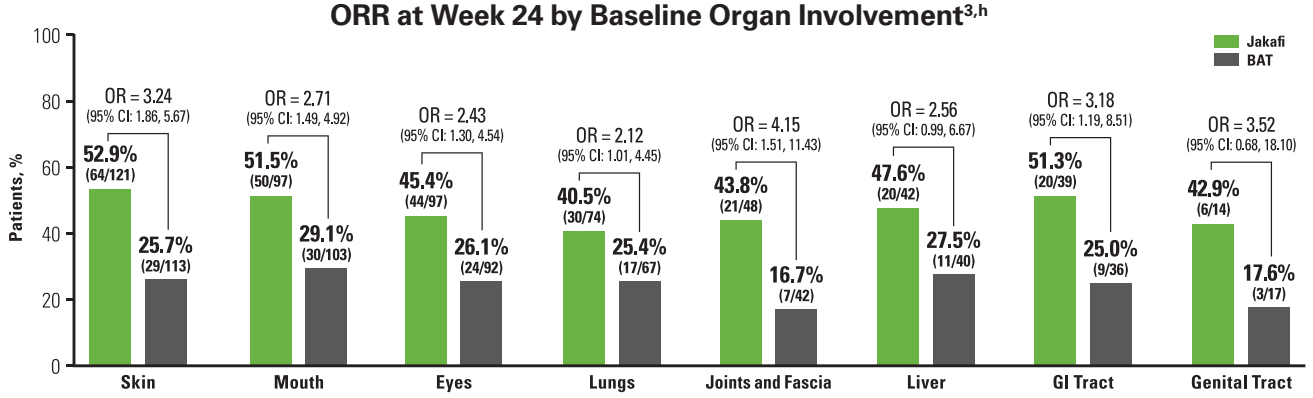
Important Safety Information

- Treatment with Jakafi® (ruxolitinib) can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated
- Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary
- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi
- Severe neutropenia (ANC $<0.5 \times 10^9$/L) was generally reversible by withholding Jakafi until recovery
- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines
- Tuberculosis (TB) infection has been reported. Observe patients taking Jakafi for signs and symptoms of active TB and manage promptly. Prior to initiating Jakafi, evaluate patients for TB risk factors and test those at higher risk for latent infection. Consult a physician with expertise in the treatment of TB before starting Jakafi in patients with evidence of active or latent TB. Continuation of Jakafi during treatment of active TB should be based on the overall risk-benefit determination
- Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi treatment. If PML is suspected, stop Jakafi and evaluate
- 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
- 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

Intervene With Jakafi® (ruxolitinib) at the *First Sign* of Initial Systemic Treatment Failure *Regardless of Organs Involved*

Overall Response Rates Were Higher With Jakafi at Week 24 Regardless of Organs Involved at Baseline vs BAT[3]

REACH3 Subgroup Analysis:
ORR at Week 24 by Baseline Organ Involvement[3,h]



REACH3 a randomized, open-label, multicenter, Phase 3 study of Jakafi vs BAT in patients with steroid-refractory cGVHD (N = 329).[1,2,i-k] The starting dose for Jakafi was 10 mg BID. Crossover from BAT to Jakafi was permitted on or after Week 24 if patients progressed, had a mixed or unchanged response, developed toxicity to BAT, or experienced a cGVHD flare.[1]

[h] Patients with >1 affected organ were were counted in each organ subgroup. Organ involvement was defined as organ score ≥1 based on the cGVHD staging criteria.[3]
[i] Patients included in the study were 12 years and older, had undergone allogeneic HSCT from any donor source/type, and had evident myeloid and platelet engraftment.[3]
[j] BAT was chosen by the investigator prior to randomization, options included: ibrutinib, extracorporeal photopheresis, low-dose methotrexate, mycophenolate mofetil, rituximab, everolimus, sirolimus, imatinib, infliximab, or pentostatin.[1,2]
[k] Steroid-refractory disease was defined as lack of response or disease progression after ≥1 week of prednisone 1 mg/kg/day, disease persistence without improvement after ≥4 weeks of prednisone >0.5 mg/kg/day or 1 mg/kg every other day, or increase in prednisone dose to >0.25 mg/kg/day after 2 unsuccessful attempts to taper the dose.[3]

Visit **hcp.Jakafi.com** to learn more

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

Please see Brief Summary of Full Prescribing Information for Jakafi on the following pages.

BAT, best available therapy; BID, twice daily; cGVHD, chronic graft-versus-host disease; FFS, failure-free survival; GI, gastrointestinal; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplant; HR, hazard ratio; OR, odds ratio; ORR, overall response rate; REACH, Ruxolitinib in PatiEnts with RefrACtory Graft-Versus-Host Disease After Allogeneic Stem Cell Transplantation.

References: 1. Zeiser R, et al. *N Engl J Med*. 2021;385(3):228-238. **2.** Jakafi Prescribing Information. Wilmington, DE: Incyte Corporation. **3.** Zeiser R, et al. [Supplementary appendix]. *N Engl J Med*. 2021;385(3):228-238.

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

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

INDICATIONS AND USAGE Myelofibrosis Jakafi is indicated for treatment of intermediate or high-risk myelofibrosis (MF), including primary MF, post-polycythemia vera MF and post-essential thrombocythemia MF in adults. **Polycythemia Vera** Jakafi is indicated for treatment of polycythemia vera (PV) in adults who have had an inadequate response to or are intolerant of hydroxyurea. **Acute Graft-Versus-Host Disease** Jakafi is indicated for treatment of steroid-refractory acute graft-versus-host disease (aGVHD) in adult and pediatric patients 12 years and older. **Chronic Graft-Versus-Host Disease** Jakafi is indicated for treatment of chronic graft-versus-host disease (cGVHD) after failure of one or two lines of systemic therapy in adult and pediatric patients 12 years and older.

CONTRAINDICATIONS None.

WARNINGS AND PRECAUTIONS Thrombocytopenia, Anemia and Neutropenia Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia. *[see Adverse Reactions (6.1) in Full Prescribing Information].* Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary *[see Dosage and Administration (2) in Full Prescribing Information].* Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi. Severe neutropenia (ANC less than 0.5×10^9/L) was generally reversible by withholding Jakafi until recovery. 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) in Full Prescribing Information].* **Risk of Infection** Serious bacterial, mycobacterial, fungal and viral infections have occurred *[see Adverse Reactions (6.1) in Full Prescribing Information].* 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. *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 (2.7) in Full Prescribing Information]*, consider tapering the dose of Jakafi gradually rather than discontinuing abruptly. **Non-Melanoma Skin Cancer (NMSC)** 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 *[see Adverse Reactions (6.1) in Full Prescribing Information].* 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. **Major Adverse Cardiovascular Events (MACE)** Another JAK-inhibitor has increased the risk of MACE, including cardiovascular death, myocardial infarction, and stroke (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Jakafi particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur. **Thrombosis** Another JAK-inhibitor has increased the risk of thrombosis, including deep venous thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. In patients with MF and PV treated with Jakafi in clinical trials, the rates of thromboembolic events were similar in Jakafi and control treated patients. Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately. **Secondary Malignancies** Another JAK-inhibitor has increased the risk of lymphoma and other malignancies excluding NMSC (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. Patients who are current or past smokers are at additional increased risk. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Jakafi, particularly in patients with a known secondary malignancy (other than a successfully treated NMSC), patients who develop a malignancy, and patients who are current or past smokers. **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]* • Lipid Elevations *[see Warnings and Precautions (5.5) in Full Prescribing Information]* • Major Adverse Cardiovascular Events (MACE) *[see Warnings and Precautions (5.6) in Full Prescribing Information]* • Thrombosis *[see Warnings and Precautions (5.7) in Full Prescribing Information]* • Secondary Malignancies *[see Warnings and Precautions (5.8) in Full Prescribing Information].* **Clinical Trials Experience** 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.

Myelofibrosis 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 200×10^9/L) and 20 mg twice daily (pretreatment platelet counts greater than 200×10^9/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 50×10^9/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 × 10^9/L to 200 × 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 × 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. 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

Acute Graft-Versus-Host Disease In a single-arm, open-label study, 71 adults (ages 18-73 years) were treated with Jakafi for aGVHD 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 (pathogen not specified)	55	41
Edema	51	13
Hemorrhage	49	20
Fatigue	37	14
Bacterial infections	32	28
Dyspnea	32	7
Viral infections	31	14
Thrombosis	25	11
Diarrhea	24	7
Rash	23	3
Headache	21	4
Hypertension	20	13
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

Chronic Graft-Versus-Host Disease In a Phase 3, randomized, open-label, multi-center study, 165 patients were treated with Jakafi and 158 patients were treated with best available therapy for cGVHD failing treatment with steroids with or without other immunosuppressive drugs *[see Clinical Studies (14.4) in full Prescribing Information]*; sixty-five patients crossed over from best available therapy to treatment with Jakafi, for a total of 230 patients treated with Jakafi. The median duration of exposure to Jakafi for the study was 49.7 weeks (range, 0.7 to 144.9 weeks) in the Jakafi arm. One hundred and nine (47%) patients were on Jakafi for at least 1 year. There were five fatal adverse reactions to Jakafi, including 1 from toxic epidermal necrolysis and 4 from neutropenia, anemia and/or thrombocytopenia. An adverse reaction resulting in treatment discontinuation occurred in 18% of patients treated with Jakafi. An adverse reaction resulting in dose modification occurred in 27%, and an adverse reaction resulting in treatment interruption occurred in 23%. The most common hematologic adverse reactions (incidence > 35%) are anemia and thrombocytopenia. The most common nonhematologic adverse reactions (incidence ≥ 20%) are infections (pathogen not specified) and viral infection. Table 7 presents the most frequent nonlaboratory adverse reactions occurring up to Cycle 7 Day 1 of randomized treatment.

Table 7: Chronic Graft-Versus-Host Disease: All-Grade (≥ 10%) and Grades 3-5 (≥ 3%) Nonlaboratory Adverse Reactions Occurring in Patients in the Open-Label, Active-controlled Study up to Cycle 7 Day 1 of Randomized Treatment

	Jakafi (N = 165)		Best Available Therapy (N = 158)	
Adverse Reactions[b]	All Grades[a] (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Infections and infestations				
Infections (pathogen not specified)	45	15	44	16
Viral infections	28	5	23	5
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain	18	1	13	0
General disorders and administration site conditions				
Pyrexia	16	2	9	1
Fatigue	13	1	10	2
Edema	10	1	12	1
Vascular disorders				
Hypertension	16	5	13	7
Hemorrhage	12	2	15	2
Respiratory, thoracic and mediastinal disorders				
Cough	13	0	8	0
Dyspnea	11	1	8	1
Gastrointestinal disorders				
Nausea	12	0	13	2
Diarrhea	10	1	13	1

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03
[b] Grouped terms that are composites of applicable adverse reaction terms.

Clinically relevant laboratory abnormalities are shown in Table 8.

Table 8: Chronic Graft-Versus-Host Disease: Selected Laboratory Abnormalities in the Open-Label, Active-controlled Study up to Cycle 7 Day 1 of Randomized Treatment[a]

	Jakafi (N=165)		Best Available Therapy (N=158)	
Laboratory Test	All Grades[b] (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Hematology				
Anemia	82	13	75	8
Thrombocytopenia	27	12	23	9
Neutropenia	58	20	54	17
Chemistry				
Hypercholesterolemia	88	10	85	8
Elevated AST	65	5	54	6
Elevated ALT	73	11	71	16
Gamma glutamyltransferase increased	81	42	75	38
Creatinine increased	47	1	40	2
Elevated lipase	38	12	30	9
Elevated amylase	35	8	25	4

[a] Presented values are worst Grade values regardless of baseline
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03

DRUG INTERACTIONS Fluconazole Concomitant use of Jakafi with fluconazole increases ruxolitinib exposure *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*, which may increase the risk of exposure-related adverse reactions. Avoid concomitant use of Jakafi with fluconazole doses of greater than 200 mg daily. Reduce the Jakafi dosage when used concomitantly with fluconazole doses of less than or equal to 200 mg *[see Dosage and Administration (2.5) in Full Prescribing Information]*. **Strong CYP3A4 Inhibitors** Concomitant use of Jakafi with strong CYP3A4 inhibitors increases ruxolitinib exposure *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*, which may increase the risk of exposure-related adverse reactions. Reduce the Jakafi dosage when used concomitantly with strong CYP3A4 inhibitors except in patients with aGVHD or cGVHD *[see Dosage and Administration (2.5) in Full Prescribing Information]*. **Strong CYP3A4 Inducers** Concomitant use of Jakafi with strong CYP3A4 inducers may decrease ruxolitinib exposure *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*, which may reduce efficacy of Jakafi. 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 aGVHD has been established for treatment of children 12 years and older. Use of Jakafi in pediatric patients with steroid-refractory aGVHD is supported by evidence from adequate and well-controlled trials of Jakafi in adults *[see Clinical Studies (14.3) in Full Prescribing Information]* and additional pharmacokinetic and safety data in pediatric patients. The safety and effectiveness of Jakafi for treatment of steroid-refractory aGVHD has not been established in pediatric patients younger than 12 years old. The safety and effectiveness of Jakafi for treatment of cGVHD after failure of one or two lines of systemic therapy has been established for treatment of children 12 years and older. Use of Jakafi in pediatric patients with cGVHD after failure of one or two lines of systemic therapy is supported by evidence from adequate and well-controlled trials of Jakafi in adults and adolescents *[see Clinical Studies (14.3, 14.4) in Full Prescribing Information]* and additional pharmacokinetic and safety data in pediatric patients. The safety and effectiveness of Jakafi for treatment of cGVHD has not been established in pediatric patients younger than 12 years old. 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 aGVHD did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects. Of the total number of patients with cGVHD treated with Jakafi in clinical trials, 11% were 65 years and older. No overall differences in safety or effectiveness of Jakafi were observed between these patients and younger patients. **Renal Impairment** Total exposure of ruxolitinib and its active metabolites increased with moderate (CLcr 30 to 59 mL/min) and severe (CLcr 15 to 29 mL/min) renal impairment, and ESRD (CLcr less than 15 mL/min) on dialysis *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. Modify Jakafi dosage as recommended *[see Dosage and Administration (2.6) 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 dosage as recommended in patients with MF or PV with hepatic impairment *[see Dosage and Administration (2.6) in full Prescribing Information]*. Reduce Jakafi dosage as recommended for patients with Stage 4 liver aGVHD. Monitor blood counts more frequently for toxicity and modify the Jakafi dosage for adverse reactions if they occur for patients with Score 3 liver cGVHD *[see Dosage and Administration (2.6) 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.

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Patient-Reported Outcomes Among Patients With Corticosteroid-Refractory or -Dependent Chronic Graft-vs-Host Disease Randomized to Ruxolitinib vs Best Available Therapy

Chronic graft-vs-host disease (GVHD) is a significant complication of hematopoietic cell transplant (HCT), affecting more than 40% of patients.[1] The Janus kinase (JAK) 1/2 inhibitor ruxolitinib was approved by the US Food and Drug Administration (FDA) in 2019 for the treatment of corticosteroid-refractory acute GVHD in adult and pediatric patients ages 12 years and older.[2] The approval was recently expanded to include the treatment of chronic GVHD in patients ages 12 years and older with an inadequate response to 1 or 2 lines of systemic therapy. The approval in chronic GVHD was based on results of the randomized, open-label phase 3 REACH3 trial, which compared ruxolitinib at 10 mg twice daily vs an investigator's choice of best available therapy (BAT) from a list of 10 commonly used options. The trial randomly assigned treatment to 329 patients ages 12 or older with moderate or severe glucocorticoid-refractory or glucocorticoid-dependent chronic GVHD. In REACH3, ruxolitinib was significantly more effective than BAT as assessed by the overall response rate at week 24 (49.7% vs 25.6%; odds ratio [OR], 2.99; P<.001) and median failure-free survival (not reached vs 5.7 months; hazard ratio, 0.37; P<.001).[3]

The investigators also assessed patient-reported outcomes (PROs), given the profound effects of chronic GVHD on quality of life. Symptoms were measured using a modified Lee Symptom Scale (mLSS). As previously reported, ruxolitinib was associated with a significant improvement over BAT in mLSS outcomes.[3]

Stephanie Lee, MD, presented an in-depth analysis of PROs from the REACH3 trial.[4] Overall, patients treated with ruxolitinib were more likely than those receiving BAT to attain a response, defined as a reduction in the mLSS score of 7 points or more from baseline in the summary symptom score, both at week 24 (24.2% vs 11.0%; OR, 1.75; 95% CI, 0.80-3.82; Figure 1) and at any visit (41.8% vs 28.0%; OR, 4.79; 95% CI, 1.70-13.45). Improvements in the summary symptom score were rapid and continued over time (Figure 2). In contrast, improvements in the BAT arm were observed only at week 4. In the ruxolitinib arm, baseline chronic GVHD severity did not affect mLSS responses to ruxolitinib. In contrast, in the BAT arm, mLSS responses were lower in patients with severe chronic GVHD than in those with moderate chronic GVHD. Modified LSS response rates were higher with ruxolitinib vs BAT even among the subset of patients with a complete response (CR) or partial response (PR) to their GVHD therapy (40.2% vs 28.6%; OR, 1.68; 95% CI, 0.76-3.75). The mLSS response rate was higher among patients receiving a corticosteroid dose of less than 7.5 mg/day in both the ruxolitinib arm (39.1% vs 25.9%) and the BAT arm (18.0% vs 13.6%).

An analysis of subscales within the mLSS and individual organ responses

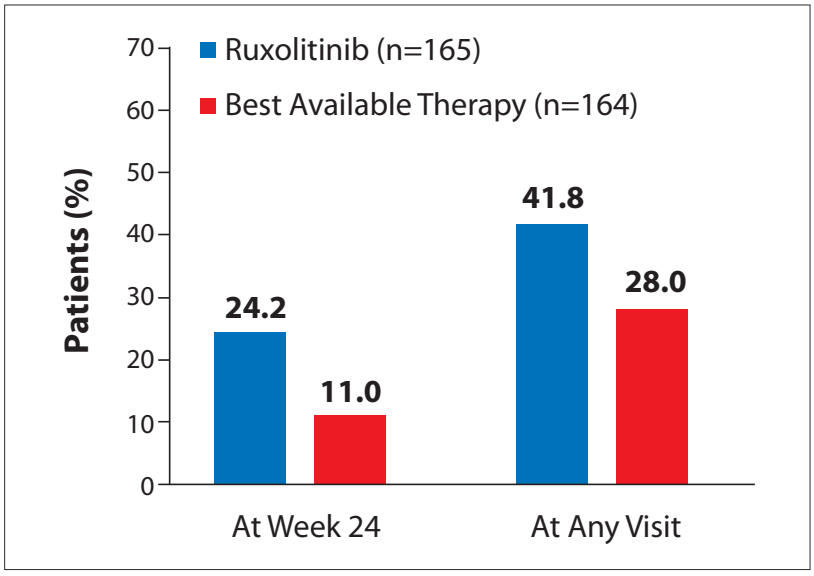

Figure 1. Percentage of patients with an improvement in the mLSS score of 7 or higher in an analysis of PRO data from the phase 3 REACH3 trial, which compared ruxolitinib vs best available therapy in patients with chronic graft-vs-host disease. mLSS, modified Lee Symptom Score; PRO, patient-reported outcome. Adapted from Lee SJ et al. ASH abstract 3909. *Blood*. 2021;138(suppl 1).[4]

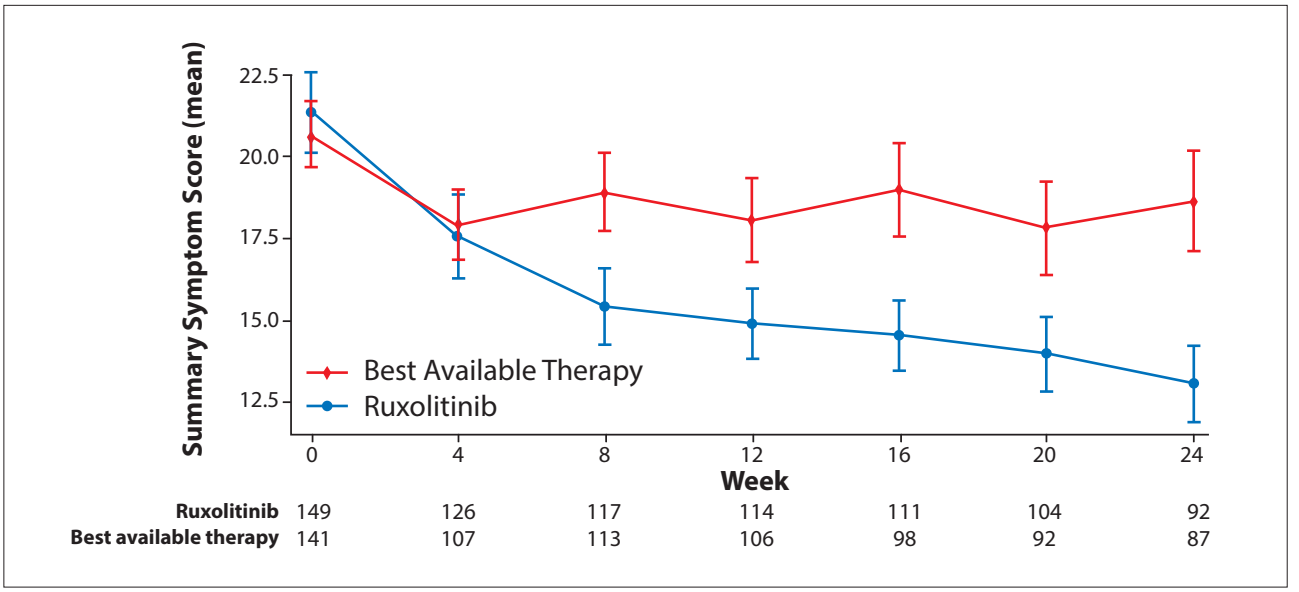

Figure 2. The mean summary symptom score (mLSS) over time in an analysis of PRO data from the phase 3 REACH3 trial, which compared ruxolitinib vs best available therapy in patients with chronic graft-vs-host disease. The scores are shown for patients with data available at each time point. mLSS, modified Lee Symptom Score; PRO, patient-reported outcome. Adapted from Lee SJ et al. ASH abstract 3909. *Blood.* 2021;138(suppl 1).[4]

found greater mean reductions with ruxolitinib vs BAT at week 24 across all measurements. In both arms, greater improvements in organ-specific mLSS subscales were associated with greater objective chronic GVHD responses in the respective organs at week 24. The association between mLSS subscale score and week 24 organ response was maintained after adjusting for treatment and baseline subscale scores.

The investigators also reported data for additional PROs, noting that patients receiving ruxolitinib were more likely than those receiving BAT to report no or mild symptoms according to the Patient Global Impression of Severity and greater symptom improvement according to the Patient Global Impression of Change at week 24. Scores for EQ-5D-5L were numerically higher with ruxolitinib vs BAT. There were no differences between the arms in the Functional Assessment of Cancer Therapy–Bone Marrow Transplantation.

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Phase II Clinical Trial of Abatacept for Corticosteroid-Refractory Chronic Graft vs Host Disease

Systemic corticosteroids are the standard first-line therapy for chronic GVHD.[1] However, the benefit of corticosteroids is limited by inadequate responses and toxicity, and many patients are refractory to treatment. For patients with corticosteroid-refractory chronic GVHD, there are now 3 FDA-approved treatment options: the Janus kinase inhibitor (JAK) 1/2 inhibitor ruxolitinib, the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib, and the Rho-associated coil-coil-containing protein kinase 2 (ROCK2) inhibitor belumosudil. Numerous other agents are used off-label. Anita G. Koshy, MD, and colleagues presented results of a phase 2 trial evaluating the costimulation modulator abatacept for the treatment of corticosteroid-refractory chronic GVHD.[2]

Abatacept is a fusion protein that consists of the extracellular domain of human cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) linked to a modified immunoglobulin G1 Fc region. By binding to the costimulatory ligands CD80/CD86 on antigen-presenting cells, abatacept inhibits T-cell activation and proliferation, and thereby decreases the production of inflammatory mediators.[3] The FDA

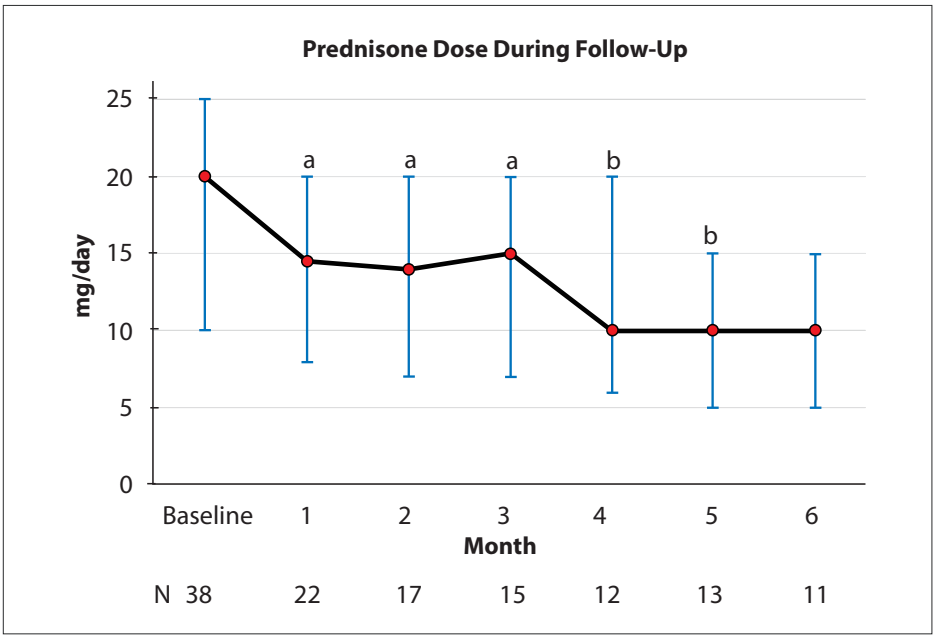

Figure 3. Treatment with abatacept led to significant reductions in doses of prednisone in a phase 2 trial of patients with chronic graft-vs-host disease. [a]*P*<.01 for the comparison of the prednisone dose to the baseline dose. [b]*P*<.05. Adapted from Koshy AG et al. ASH abstract 264. *Blood*. 2021;138(suppl 1).[2]

had previously approved abatacept for the treatment of various inflammatory conditions. In December 2021, the FDA approved abatacept for prophylaxis of acute GVHD in combination with a calcineurin inhibitor and methotrexate in patients ages 2 years or older undergoing HCT from unrelated donors.[4] The approval in acute GVHD was based on results of the phase 2 ABA2 trial, in which the addition of abatacept to a calcineurin inhibitor and methotrexate reduced day +100 grade 3/4 acute GVHD and improved day 180+ severe-acute GVHD-free survival.[5]

After a phase 1 trial suggested that abatacept was active in patients with corticosteroid-refractory chronic GVHD,[6] a phase 2 trial was initiated to further evaluate the agent in this setting. The trial enrolled 39 patients (median age, 62 years; range, 25-77 years) who had undergone bone marrow (10%) or stem cell (90%) transplant with myeloablative (61.5%) or reduced-intensity conditioning (36%). The procedure was performed a median of 43 months prior to study entry (range, 6-173 months). The patients had corticosteroid-refractory chronic GVHD following at least 4 weeks of prednisone (0.5 mg/kg/day). No additions or subtractions of other immunosuppressive medications were allowed for at least 4 weeks before the patient began treatment with abatacept. All patients had received a stable immunosuppressive regimen for 2 weeks before enrollment.[2]

Abatacept at 10 mg/kg was administered every 2 weeks for 3 doses. One month after the third dose, treatment resumed at 10 mg/kg administered every 4 weeks for 3 additional doses. Patients with a clinical response could receive extended duration therapy with monthly abatacept at 10 mg/kg for up to 12 additional doses.

At baseline, 17 patients had moderate chronic GVHD and 22 patients had severe chronic GVHD. The patients had received a median of 5 prior treatments for chronic GVHD (range, 1-11).

ABSTRACT SUMMARY Interim Results of a Pilot, Prospective, Randomized, Double-Blinded, Vehicle- and Comparator-Controlled Trial on Safety and Efficacy of a Topical Inhibitor of Janus Kinase 1/2 (Ruxolitinib INCB018424 Phosphate 1.5% Cream) for Non-Sclerotic and Superficially Sclerotic Chronic Cutaneous Graft-vs-Host Disease

A randomized, double-blind phase 2 trial evaluated topical ruxolitinib in a 1.5% cream formulation in patients ages 12 or older with cutaneous nonsclerotic and superficially sclerotic chronic GVHD (Abstract 3915). Patients had at least 2% of their body surface area affected. Thirteen patients received ruxolitinib 1.5% cream on one side of their face or body and placebo vehicle cream on the contralateral side. Treatment was applied twice daily for 28 days, followed by an optional open-label extension. There was a trend in reduced body surface area of chronic GVHD on the treatment side compared with the vehicle side during the treatment period. Ruxolitinib was associated with improvements in the Composite Assessment of Index Lesion Severity and the Physician's Global Assessment of clinical condition starting at day 14 and continuing through day 28. AEs included a grade 1 headache considered possibly related to therapy, and three grade 1 treatment-emergent AEs deemed definitely or probably unrelated to study therapy.

Abatacept was associated with an overall response rate of 49%. All responses were partial, defined as an improvement in at least 1 organ or site without progression in any other organ or site. Responses were observed in the lung (33%), eyes (23%), joints (21%), skin (15.4%), liver (15.4%), gastrointestinal tract (10%), and genital region (3%). Disease progressed in 10 patients (26%), occurring in the mouth (10%), skin (8%), eyes (5%), joints (5%), and lung (3%). Abatacept was associated with durable reductions in the dose of prednisone starting at month 1 (P<.01; Figure 3).

Adverse events (AEs) considered possibly related to abatacept included grade 2 to 4 neutropenia (n=4), grade 1/2 fatigue (n=5), grade 2 headache (n=4), and grade 2/3 upper respiratory tract infection (n=4). Serious AEs possibly related to abatacept included grade 3/4 lung infection (n=3). One patient who developed grade 4 hemolysis, respiratory failure, and hepatic failure died with concurrent herpes simplex virus hepatitis.

Immune correlative studies in responding patients showed no difference in T-cell expression of interleukin (IL) 10 or interferon gamma before or after treatment. Molecular sequencing is planned to further characterize changes in T-cell activation in response to abatacept.

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A Phase II Study of Ruxolitinib Pre-, During- and Post-Hematopoietic Cell Transplantation for Patients With Primary or Secondary Myelofibrosis

Allogeneic HCT remains an important treatment modality for myelofibrosis and is the only potentially curative therapy. Although there have been improvements in supportive care, outcomes after HCT remain suboptimal owing to significant morbidity and a high rate of transplant-related mortality.[1] Multiple factors can affect outcomes after HCT in patients with myelofibrosis, including the presence of splenomegaly, poor graft function, nonrelapse mortality, and GVHD (both acute and chronic). A Myelofibrosis Transplant Scoring System was recently developed to predict survival after HCT based on the following factors: leukocytes higher than 25 × 10^9/L, platelets less than 150 × 10^9/L, Karnofsky scale below 90%, age older than 57 years, *ASXL1* mutation, *JAK2*-mutated or triple negative, and mismatched unrelated donor. After incorporating these factors into the 4-level Myelofibrosis Transplant Scoring System, 5-year overall survival (OS) rates range from 82% in the low-risk category to 22% in the very high-risk category.

The optimal use of ruxolitinib among patients with myelofibrosis undergoing HCT remains unclear. Ruxolitinib is FDA-approved for the treatment of patients with intermediate- or high-risk myelofibrosis (pretransplant), as well as for the treatment of corticosteroid-refractory acute and chronic GVHD.[2] Discontinuing ruxolitinib in preparation for HCT is challenging because patients can experience a return of symptoms and splenomegaly.[3] There are varying practices regarding the tapering of ruxolitinib pre-HCT, and the role of ruxolitinib during the transplant period has not been prospectively studied. Gabriela Hobbs, MD, and colleagues therefore undertook a multicenter phase 2 study to evaluate the efficacy and safety of ruxolitinib administered before, during, and after HCT in patients with primary or secondary myelofibrosis.[4]

The study enrolled 26 patients. At day –14, patients began or continued ruxolitinib at 5 mg twice daily, and received ruxolitinib throughout the conditioning and transplant period. At day 30, the dose of ruxolitinib was increased to 10 mg twice daily for up to 1 year. The patients received a reduced-intensity conditioning regimen with fludarabine and melphalan, as well as methotrexate and tacrolimus for GVHD prophylaxis. The patients' median age was 66 years (range, 46-75 years). Most patients had intermediate-2 risk (46%) or high-risk (46%) myelofibrosis, and 85% had splenomegaly.

Neutrophil engraftment was attained by day 30 in 23 of 24 patients and by day 60 in 24 of 24 patients. Platelet engraftment was attained by day 30 in 14 of 23 patients, by day 18 in 18 of 23 patients, and by day 150 by all patients. At 1 year, the rate of OS was 77% (Figure 4). The 1-year rate of progression-free survival was 71%. The rate of GVHD-free/relapse-free survival was 65%. The 1-year cumulative incidence of nonrelapse

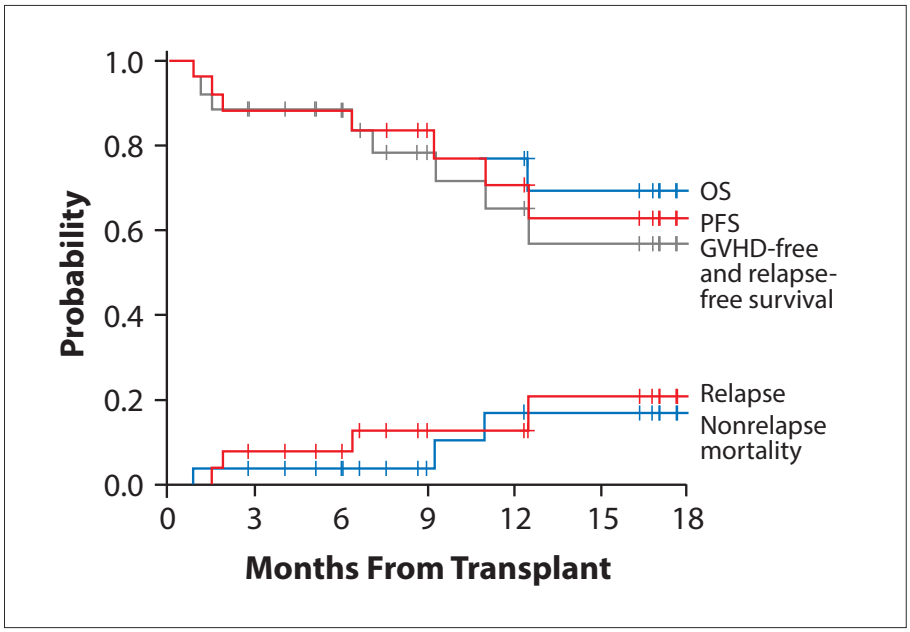

Figure 4. Clinical outcomes in a phase 2 study of ruxolitinib given before, during, and after hematopoietic cell transplant in patients with primary or secondary myelofibrosis. GVHD, graft-vs-host disease; OS, overall survival; PFS, progression-free survival. Adapted from Hobbs G et al. ASH abstract 169. *Blood*. 2021;138(suppl 1).[4]

mortality was 13%. At 6 months, 35% of patients developed grade 2 to 4 acute GVHD, and 4% developed grade 3 to 4 acute GVHD. The 1-year incidence of chronic GVHD was 14%, including moderate or severe cases in 5%. Grade 3/4 AEs included anemia (n=4), platelet count reduction (n=3), and leukopenia (n=2).

The investigators concluded that further studies are needed to establish the role of ruxolitinib after transplant. They plan to perform in-depth molecular testing pre- and post-transplant to better understand clonal dynamics, predict relapse, and intervene early before the onset of overt relapse.

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Safety, Tolerability, and Efficacy of Axatilimab, a CSF-1R Humanized Antibody, for Chronic Graft-vs-Host Disease After 2 or More Lines of Systemic Treatment

Among the novel approaches being evaluated for the treatment of chronic GVHD is axatilimab, a humanized monoclonal antibody directed against the colony-stimulating factor 1 (CSF-1) receptor CSF-1R. CSF-R1–dependent donor macrophages are involved in promoting chronic GVHD, providing a rationale for targeting CSF-1/CSF-1R interactions.[1]

Stephanie Lee, MD, MPH, presented results of a phase 1/2 trial evaluating axatilimab in 40 patients with active chronic GVHD after at least 2 prior treatments.[2] The pages were ages 6 years and older and had a Karnofsky Performance Score of 60 or higher. The phase 1 dose-escalation phase enrolled 17 patients who received axatilimab at doses ranging from 0.15 mg/kg to 3.0 mg/kg every 2 weeks. The phase 2 expansion cohort enrolled 23 patients who received axatilimab at 1.0 mg/kg every 2 weeks.

The patients' median age was 59 years (range, 16-73 years), 63% were male, and 65% had undergone a myeloablative transplant. The patients had received a median of 4 previous treatments (range, 1-11), including ibrutinib (65%), ruxolitinib (53%), and belumosudil (20%). The median interval from the onset of chronic GVHD to initiation of axatilimab was 3.2 years (range, 0.11-15.6 years). At the end of the follow-up period, 12 of 23 patients in the phase 2 portion (52%) were still receiving treatment. Across the phase 1 and 2 studies, 4 of 40 patients (10%) discontinued treatment owing to AEs that included

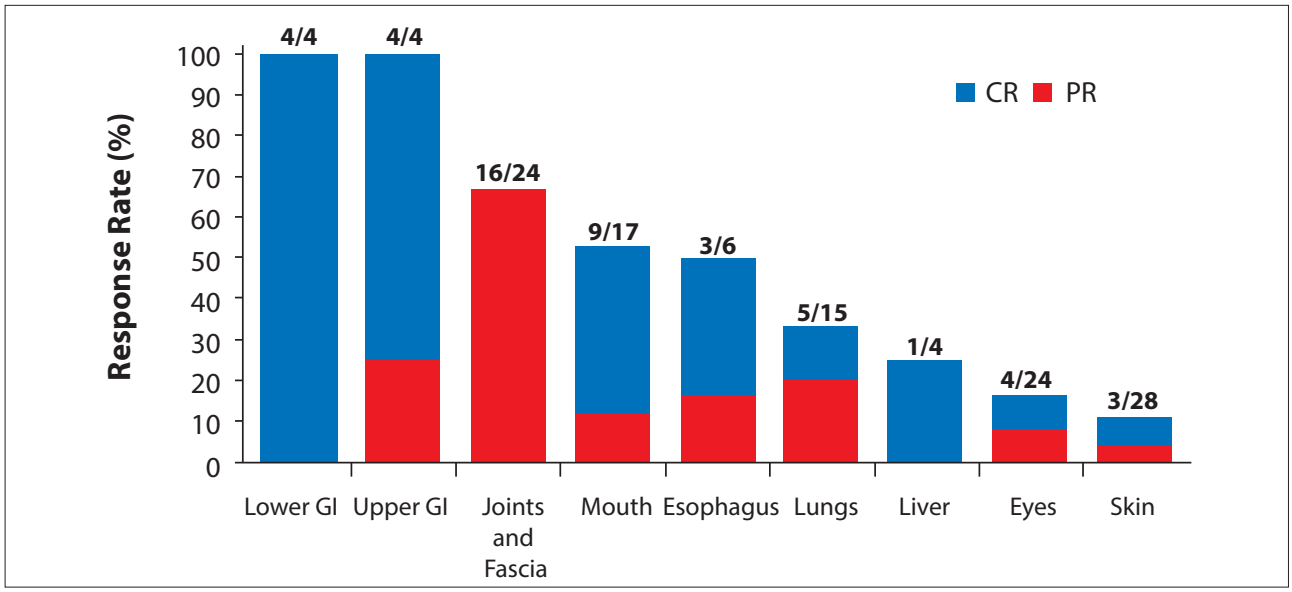

Figure 5. Response rates across organ systems in a phase 1/2 trial evaluating axatilimab in patients with chronic GVHD. Data are shown for patients in phase 1 and phase 2. CR, complete response; GI, gastrointestinal; PR, partial response. Adapted from Lee S et al. ASH abstract 263. *Blood*. 2021;138(suppl 1).[2]

increased levels of creatine phosphokinase, periorbital edema, hypersensitivity, and falls.

The best overall response rate among the 31 patients who received axatilimab at one of the doses that advanced to the pivotal trial was 68%, including 72% (18 of 25) with 1 mg/kg given every 2 weeks and 50% (3 of 6) with 3 mg/kg given every 4 weeks. The median time to response was 0.9 months, and the median time on treatment was 6.7 to 7.7 months. Responses occurred in the lower gastrointestinal tract, upper gastrointestinal tract, joints and fascia, mouth, esophagus, lungs, liver, eyes, and skin (Figure 5). Severe skin sclerosis was present in 25 patients (81%) at baseline. In 4 of these patients (16%), treatment with axatilimab improved sclerosis.

Across all enrolled patients, the most frequent treatment-related AEs (≥25%) were increased aspartate aminotransferase (AST; 35%), increased creatine phosphokinase (33%), fatigue (30%), and increased alanine aminotransferase (ALT; 25%). Grade 3/4 treatment-related AEs occurring in more than 1 patient included increased creatine phosphokinase (n=3; 8%) and increased lipase (n=2; 5%). Dr Lee noted that the serum enzyme elevations observed in axatilimab-treated patients likely reflect on-target effects on Kupffer cells in the liver and were not associated with end organ damage or myositis/pancreatitis. The most common infections were upper respiratory infection (9/40; 18%) and cellulitis (4/20; 10%). No cases of cytomegalovirus or Epstein-Barr virus reactivation were reported. Regarding chronic GVHD symptoms, 53% of evaluable patients (16/30) achieved a 7-point reduction in the LSS from baseline. Improvements in LSS were observed regardless of whether objective responses were attained.

The ongoing randomized, global, open-label phase 2 AGAVE-201 trial is

ABSTRACT SUMMARY Orca-T Results in High GVHD-Free and Relapse-Free Survival Following Myeloablative Conditioning for Hematological Malignancies: Results of a Single Center Phase 2 and a Multicenter Phase 1b Study

Rasmus T. Hoeg, MD, presented results from a phase 1b trial (n=29) and a phase 2 trial (n=80) evaluating the novel high-precision allogeneic cell therapy Orca-T in patients with hematologic malignancies (Abstract 98). Outcomes were compared against a standard-of-care control cohort (n=95). In Orca-T–treated patients, the median time to neutrophil and platelet engraftment was 13 days and 15 days, respectively. Graft failure occurred in 1 of 109 patients. At 200 days, grade 3 or higher acute GVHD rates were 5% in the phase 1b trial, 3% in the phase 2 trial, and 20% in the control group. Rates of moderate to severe chronic GVHD were 5%, 3%, and 43%, respectively. In a combined analysis, the 1-year GVHD-free/relapse-free survival rate was 74% with Orca-T vs 34% with the standard of care. The 1-year nonrelapse mortality rates were 6% and 13%, respectively. During the follow-up period, OS rates were 90% with Orca-T and 78% with the standard of care. Chronic GVHD-free survival rates were 87% vs 45%, respectively.

evaluating 3 different doses of axatilimab (0.3 mg/kg every 2 weeks, 1 mg/kg every 2 weeks, and 3 mg/kg every 4 weeks) in patients with recurrent or refractory active chronic GVHD after treatment with at least 2 lines of systemic therapy.[3]

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Update of a Multicenter, Retrospective Evaluation of Overall Response and Failure-Free Survival Following Ruxolitinib Therapy for Heavily Pretreated Chronic GVHD Patients With Corticosteroid-Failure: A Proposal of a Risk Score Model for Failure-Free Survival

A retrospective analysis provided results for the real-world use of ruxolitinib in patients with corticosteroid-refractory or corticosteroid-dependent chronic GVHD.[1] The analysis included 115 patients who received care at 5 participating Canadian centers from March 2015 to April 2021. The patients' median age was 57.5 years (range, 20-73 years), and 60% were male. The population was heavily pretreated, with the majority receiving ruxolitinib as treatment in the fourth-line or later setting.

The overall response rate was 46.8% at month 3, 61.9% at month 6, and 62.3% at month 12 (Figure 6). The clinical benefit rate, which combined the objective response with reductions in the use of corticosteroids, was 59% at month 3, 74% at month 6, and 80% at month 12, indicating that most patients attained clinical benefit from ruxolitinib. Approximately 64% of patients were receiving prednisone at doses lower than 0.1 mg/kg/day by month 12, and 38% were able to discontinue prednisone. At 12 months, the failure-free survival (FFS) rate was 65% and the OS rate was 83%.

The investigators developed a risk score model for FFS and found that 2 variables were significantly associated with a higher risk of failure: severe grade chronic GVHD when starting ruxolitinib (HR, 2.690; *P*=.02) and a Hematopoietic Cell Transplant Comorbidity Index (HCT-CI) of 3 or higher (HR, 2.642; *P*=.007). After incorporating these variables into a risk score model, the 12-month FFS rates were 85.8% with a score of 0, 58.7% with a score of 1, and 36.8% with a score of 2 (*P*=.008).

The trial investigators concluded that these results were comparable to outcomes reported in the REACH3 trial.[2] Ruxolitinib can provide clinically meaningful benefits in patients with heavily pretreated chronic GVHD.

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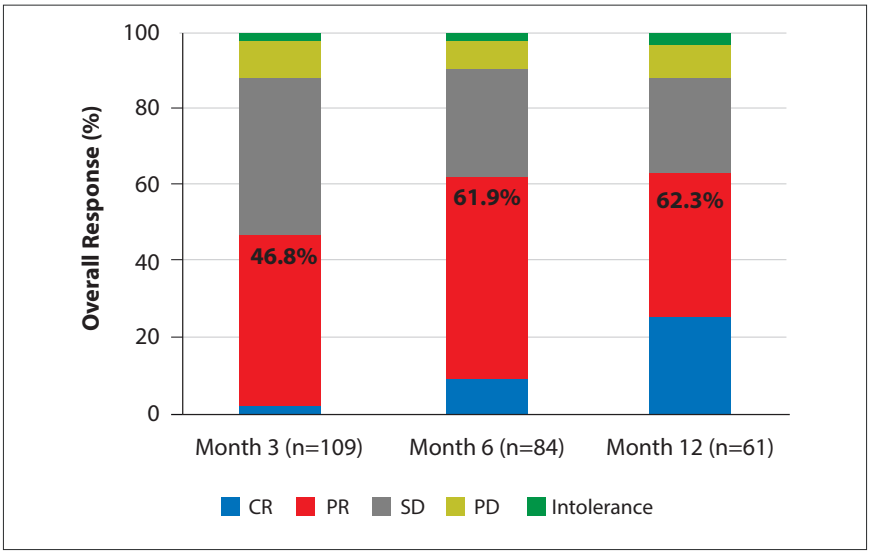

Figure 6. Overall response according to NIH consensus criteria in a multicenter, retrospective evaluation of ruxolitinib for patients with heavily pretreated chronic graft-vs-host disease. CR, complete response; NIH, National Institutes of Health; PD, progressive disease; PR, partial response; SD, stable disease. Adapted from White J et al. ASH abstract 3905. *Blood*. 2021;138(suppl 1).[1]

Propensity Score Matching Analysis Comparing Ruxolitinib vs Historical Controls in Second-Line or Beyond Treatment for Chronic GVHD After Therapy Failure

A real-world analysis of patients with chronic GVHD was conducted in Canada. Results were presented by Igor Novitzky-Basso, MD, PhD, MRCP, FRCPath.[1] In the phase 3 REACH3 trial, ruxolitinib was associated with superior ORR and FFS rates vs BAT in patients with corticosteroid-refractory chronic GVHD.[2] Dr Novitzky-Basso and coworkers retrospectively compared outcomes with ruxolitinib vs BAT. Their data set included 115 patients receiving ruxolitinib and 311 patients receiving BAT.[1] Some GVHD characteristics were not well matched between the groups, including age, donor type, HCT-CI, history of acute GVHD, and chronic GVHD severity. Therefore, propensity score matching was used to adjust and balance these

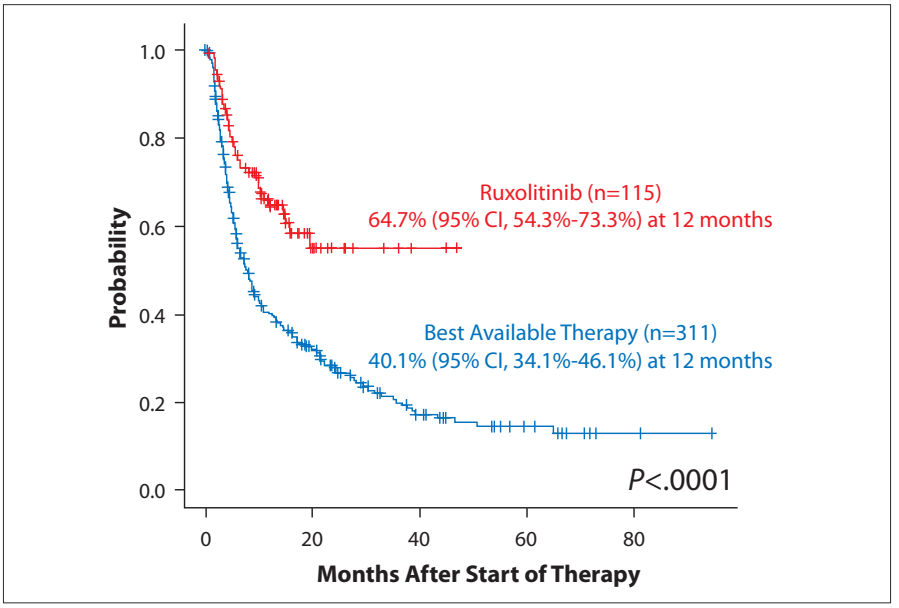

Figure 7. Rates of failure-free survival at 12 months in an analysis comparing ruxolitinib vs historical controls in patients with chronic GVHD. Data are shown for a comparison that lacks a propensity score-matched analysis. Adapted from Novitzky-Basso I et al. ASH abstract 1805. *Blood*. 2021;138(suppl 1).[1]

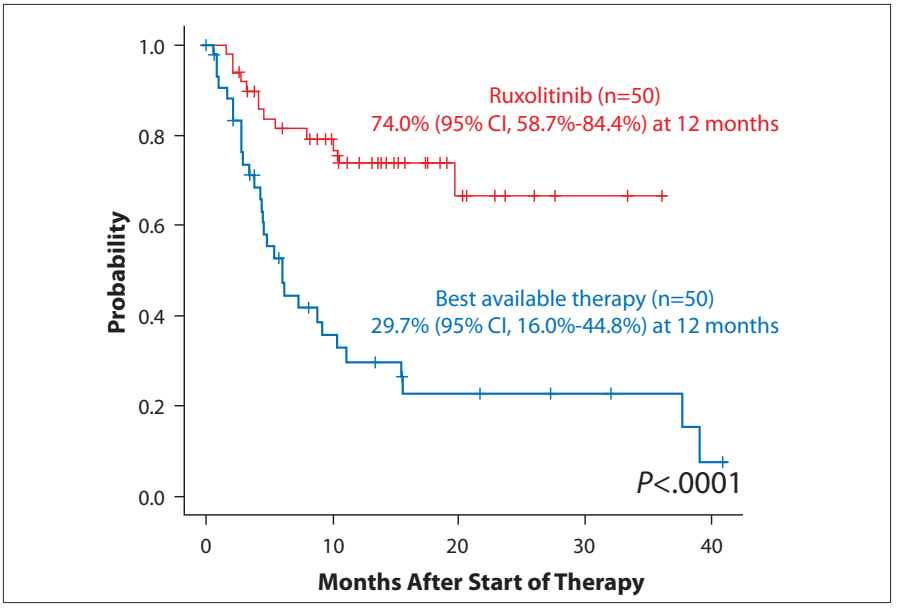

Figure 8. Rates of failure-free survival at 12 months in a propensity score matching analysis comparing ruxolitinib vs historical controls in patients with chronic GVHD. Adapted from Novitzky-Basso I et al. ASH abstract 1805. *Blood*. 2021;138(suppl 1).[1]

risk factors. The analysis was limited to 50 patients receiving ruxolitinib and 50 patients receiving BAT.

In the matched cohorts, the 2 groups were relatively balanced in key patient-related and GVHD characteristics, including organ involvement, line of therapy, and HCT-CI. The cohort was heavily pretreated, with 66% of ruxolitinib-treated patients and 56% of BAT-treated patients in the fourth-line or beyond.

Without the propensity score–matched analysis, ruxolitinib was associated with a significant improvement in FFS vs BAT, with 12-month FFS rates of 64.7% and 40.1%, respectively (P<.0001; Figure 7). The 12-month OS outcomes were similar between the groups, at 83.4% with ruxolitinib and 83.7% with BAT (Figure 7). In the propensity score–matched analysis, the difference in 12-month FFS rates between groups was more substantial, at 74.0% with ruxolitinib and 29.7% with BAT (P<.0001; Figure 8). The 12-month OS rates were 90.5% and 80.2%, respectively (P=.109).

Treatment with ruxolitinib was also associated with larger reductions in the dose of prednisone, as well as discontinuation of the drug. In an unmatched analysis, 47% of patients in the ruxolitinib arm were receiving no more than 0.1 mg/kg/day at 6 months, compared with 21.1% of patients in the BAT arm. Prednisone had been discontinued in 24.1% vs 2% of patients, respectively. In the propensity score–matched analysis, 58.3% of ruxolitinib-treated patients were receiving 0.1 mg/kg/day or less at 6 months, compared with 13.9% of patients receiving BAT. Prednisone had been discontinued in 25% and 2.8% of patients, respectively.

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Belumosudil for Patients With Chronic Graft-vs-Host Disease: Combined Analysis of Failure-Free Survival in the KD025-208 and Pivotal ROCKstar Trials

Belumosudil is a novel oral selective inhibitor of ROCK2 that is FDA-approved for use in patients ages 12 years and older with chronic GVHD after failure of at least 2 prior lines of systemic therapy.[1] ROCK2 is a kinase that drives proinflammatory responses and promotes fibrosis, both characteristics of chronic GVHD.[2] By blocking the signaling of ROCK2, belumosudil inhibits proinflammatory type 17 helper T cells, increases regulatory T-cell production, and decreases mediators of fibrosis. Belumosudil was evaluated in 2 trials in chronic GVHD: the phase 2a dose-finding KD025-213, which enrolled 54 patients who had received 1 to 3 prior lines of systemic therapy, and the pivotal phase 2 open-label, randomized ROCKstar trial, which enrolled 132 patients who had received 2 to 5 prior lines of systemic therapy.[3,4] The FDA-approved dosage is 200 mg once daily.[1]

Aleksandr Lazaryan, MD, MPH, PhD, presented an analysis of FFS outcomes in the KD025-208 and ROCKstar trials.[5] FFS is an endpoint that encompasses absence of subsequent treatment, nonrelapse mortality, and recurrent malignancy. Among the 186 patients enrolled in the 2 trials, 70% had severe chronic GVHD according to the NIH global score, 52% had at least 4 organs involved, and 37% had received more than 3 prior lines of systemic therapy. The median duration of belumosudil treatment was 9.9 months (range, 0.4-44.7 months); 10% of patients discontinued therapy owing to AEs that were possibly drug-related.

Overall, the median FFS across both trials was 14 months. FFS was 75% at 6 months, 54% at 12 months, and 38% at 24 months. Dr Lazaryan noted that these outcomes compare favorably to historic data. In a 2013 observational study of patients with chronic GVHD receiving conventional second-line therapy, FFS rates at 6, 12, and 24 months were 56%, 45%, and 31%, respectively.[6]

In the belumosudil trials, the most common cause of failure was relapse, which occurred in 43% of patients. The nonrelapse mortality rate was 7% (n=12) and the relapse rate was 6% (n=11). Factors associated with an increased risk of treatment failure in multivariate analyses included progressive onset of chronic GVHD (HR, 2.1; P<.01), the absence of glucocorticoids in upfront therapy for chronic GVHD (HR, 2.2; P<.01), and at least 2 prior lines of systemic therapy (P=.03).

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Pooled Allogenic Fecal Microbiotherapy MaaT013 for the Treatment of Corticosteroid-Refractory Gastrointestinal Acute Graft-vs-Host Disease: Results From the Phase IIa HERACLES Study and Expanded Access Program

Multiple studies have demonstrated an association between intestinal microbiota and acute GVHD pathogenesis. Dysbiosis of the microbiota is associated with poor prognosis in patients with acute GVHD.[1] The prospective phase 2a HERACLES study evaluated MaaT013, an allogeneic fecal microbiotherapy, for the treatment of corticosteroid-refractory gastrointestinal acute GVHD. Florent Malard, MD, PhD, and colleagues presented results of the HERACLES study and an expanded access program of MaaT013.[2] The HERACLES study, conducted at 24 European sites, enrolled 24 adults with a first episode of stage 3 or 4 gastrointestinal acute GVHD with gut predominance resistant to first-line corticosteroids. The patients received 3 doses of MaaT013 delivered via an enema. The patient's median age was 61 years (range, 20-69).

At day 28, the gastrointestinal acute GVHD response rate was 38%, including CRs in 21%. The best gastrointestinal acute GVHD response rate until day 28 was 54%, including CRs in 38%. The 6-month and 12-month OS rates were 29% and 25%, respectively. At 12 months, OS was significantly longer for patients with an objective response to MaaT013 than for those with no response (44% vs 13%; *P*=.047; Figure 9). AEs reported within 24 hours of MaaT013 administration included a grade 4 cerebral infarction, a grade 3 thrombotic microangiopathy, a case of fatal general physical health deterioration, and a case of grade 3 *Escherichia* sepsis (from a different *E. coli* strain than that in MaaT013).

Patients who were not eligible for the HERACLES trial could receive treatment with MaaT013 through an expanded access program. The program enrolled patients with any-grade corticosteroid-refractory or corticosteroid-dependent acute GVHD with gut involvement in any line of treatment. Patients could receive MaaT013 as monotherapy and/or as combination therapy. The expanded access program enrolled 52 patients, whose median age was 57 years (range, 18-73). The patients had received a median of 3 prior treatments (range, 1-6), and 17% had overlap syndrome. All but 1 patient received MaaT013 via an enema. (The remaining patient received the treatment via a nasogastric tube.)

In this cohort, the day 28 gastrointestinal acute GVHD response rate was 58%, including CRs in 33%. The best gastrointestinal acute GVHD response rate until day 28 was 67%, including CRs in 40%. The rate of OS was 49% at 6 months and 38% at 12 months. The 12-month OS rate was 59% in patients with an objective response to MaaT013 and 7% in those with no response (*P*<.0001; Figure 10). In regard to safety, 2 patients reported gastrointestinal symptoms, and 6 patients had infectious complications for which an association to MaaT013 could not be formally excluded.

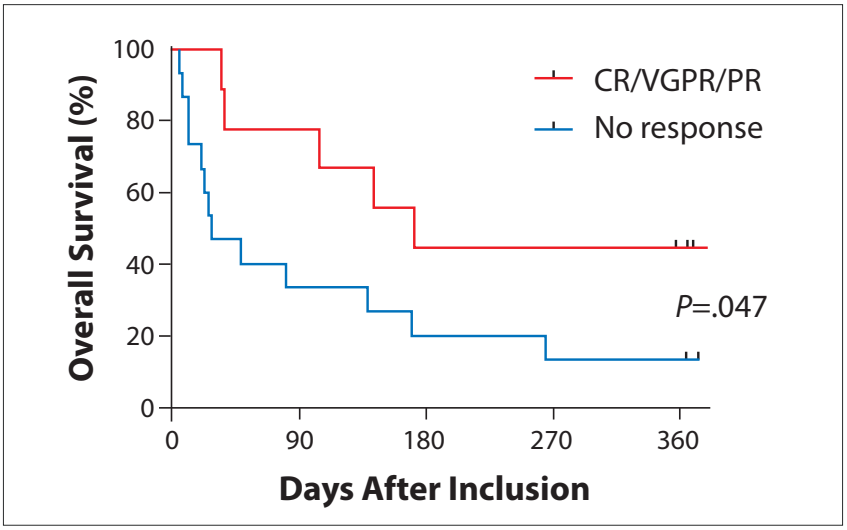

Figure 9. Overall survival according to response to the fecal microbiotherapy MaaT013 among patients with acute graft-vs-host disease in the phase 2a HERACLES study. CR, complete response; PR, partial response; VGPR, very good partial response. Adapted from Malard F et al. ASH abstract 262. *Blood*. 2021;138(suppl 1).[2]

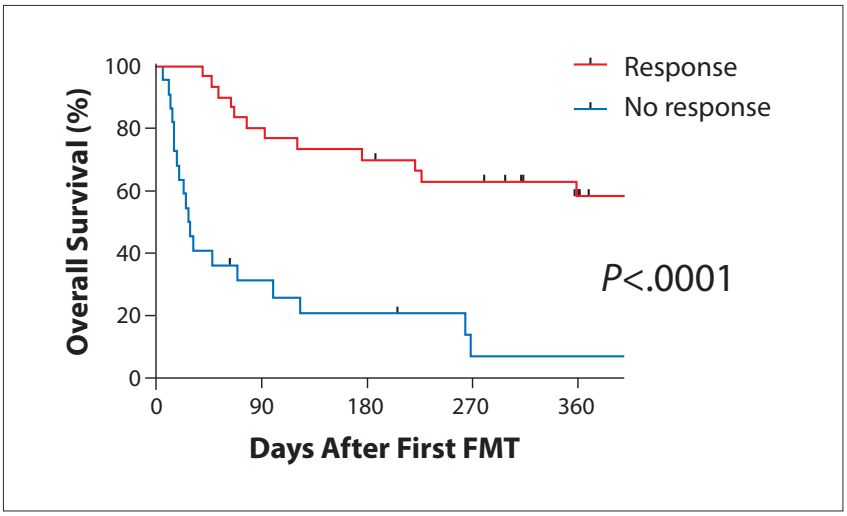

Figure 10. Overall survival according to response to the fecal microbiotherapy MaaT013 among patients with acute graft-vs-host disease in an expanded access program. FMT, fecal microbiota transfer. Adapted from Malard F et al. ASH abstract 262. *Blood*. 2021;138(suppl 1).[2]

The ongoing phase 3 ARES trial is evaluating MaaT013 as third-line treatment in patients with grade 2 to 4 gastrointestinal acute GVHD that is refractory to corticosteroids and ruxolitinib.[3]

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Highlights in Graft-vs-Host Disease From the 63rd American Society of Hematology Annual Meeting and Exposition: Commentary

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Presentations at the 63rd American Society of Hematology (ASH) meeting provided important insights into the prevention of graft-vs-host disease (GVHD), as well as the treatment of acute and chronic GVHD. Data were presented for treatments such as ruxolitinib and belumosudil, and several novel agents.

Prevention of GVHD

Currently, the most popular platform for the prevention of both acute and chronic GVHD is calcineurin inhibitor (CNI)-based, be it cyclosporine or tacrolimus, usually paired with several doses of post-transplant methotrexate.[1] Despite the progress made to develop this strategy, transplant with conventional donors is still associated with a significant incidence of both acute and chronic GVHD.[2] Attempts have been made to improve prophylaxis by adding other agents, such as anti–T-cell globulins or sirolimus, to this backbone.[3] Most recently, the US Food and Drug Administration (FDA) approved abatacept added to CNI-based prophylaxis for the prevention of GVHD in unrelated donor transplantation, which is the first approval in this setting.

Graft manipulation is another modality that has been used for the prevention of GVHD. There is one approved method of performing T-cell

depletion (CD34-positive selection via the CliniMACS system for patients with acute myeloid leukemia in first complete remission), although it has not gained widespread popularity owing to a lack of clear superiority and need for laboratory expertise and resources. At this ASH meeting, Dr Rasmus Hoeg presented early data for a new method of GVHD prevention that involves graft manipulation.[4] This product, known as Orca-T, uses a proprietary graft engineering technology that can purify and sort cellular populations at very efficient rates. The platform sorts a graft into hematopoietic progenitor cells, regulatory T cells, and conventional T cells. To prevent GVHD, the protocol revolves around giving purified progenitor cells with regulatory T cells on day 0, followed by giving back conventional T cells 2 days later.

Dr Hoeg presented results for patients who received Orca-T after myeloablative transplant in a single-arm phase 2 study from Stanford University (n=29) and an ongoing phase 1b multicenter expansion study (n=80).[4] These patients also received single-agent GVHD prophylaxis with tacrolimus or sirolimus. The control group was a contemporaneous cohort of patients treated with conventional CNI-based GVHD prophylaxis at Stanford. The Orca-T product is manufactured centrally and then delivered back to the institution, much like commercial individual cellular therapies, so it requires no capital investment by the center itself. In this study, Orca-T was manufactured reliably and delivered in less than 72 hours for all patients, without any manufacturing failures.

The use of the Orca-T product led to earlier engraftment of neutrophils and platelets, likely owing to the absence of post-transplant methotrexate. The ability of Orca-T to prevent severe GVHD was remarkable, confirming the earlier data presented from the single-center Stanford study.[5] The incidence of grade 3 or higher acute GVHD in all patients treated with Orca-T was 5%, and the incidence of moderate to severe chronic GVHD at 1 year was only 4%. This led to a 72% rate of 1-year GVHD and relapse-free survival (GRFS), which is the composite event-free survival endpoint currently used in trials of GVHD prevention.

Traditionally, any steps taken to decrease GVHD would correspondingly increase the rates of disease relapse or nonrelapse mortality (NRM) from infection. This was not apparent with the Orca-T product; the rates of disease relapse and NRM were quite low. Excitingly, a randomized phase 3 study of Orca-T vs CNI-based GVHD prevention in patients receiving myeloablative HCT is planned to open in 2022.

The use of haploidentical donors has increased throughout the past few years, with the advent of the increasingly popular post-transplant cyclophosphamide platform.[6] In addition, over the last 2 years during the COVID-19 pandemic, uncertainty around the logistics of obtaining unrelated donor products has spurred the increased use of haploidentical transplants. Although the early experience with haploidentical transplants uniformly used bone marrow grafts, clinicians clearly prefer the use of peripheral stem cell grafts for both donor safety and convenience. Therefore, it has become increasingly popular to perform haploidentical transplants with a peripheral blood stem cell graft (PBSC).[7] Haploidentical PBSC grafts are clearly associated with an increased incidence of cytokine release syndrome (CRS) between day 0 and day 4,[8] which is likely caused by immunosuppression-free T-cell alloreactivity between the donor and the host. In many cases, CRS manifests as fevers that are not clinically significant. In certain cases, however, an inflammatory storm leads to third-spacing of fluids, renal failure, and other morbidities. Severe CRS in this setting has been shown to be associated with higher rates of NRM.[9] Dr Ramzi Abboud presented the results of a single-arm, open-label pilot study that added the Janus kinase (JAK) inhibitor 1 itacitinib prior to transplant and through day 100 in an attempt to prevent severe CRS and acute GVHD in 20 patients after haploidentical PBSC transplant.[10] The rationale was based on the important role of interferon gamma and interleukin (IL) 6 signaling in both of those complications. The

ABSTRACT SUMMARY Corticosteroid Treatment Impairs Epithelial Regeneration, Limiting Intestinal Recovery in Experimental Graft vs Host Disease

Preclinical studies have investigated the effects of corticosteroids on the intestinal epithelium and potential implications for the treatment of immune-mediated damage in GVHD (Abstract 88). Intestinal stem cells and mature enterocytes constitutively express glucocorticoid receptors. Administration of corticosteroids suppressed epithelial proliferation in vivo, decreased the size of small intestine organoids in a glucocorticoid-receptor dependent manner in both murine and human cells ex vivo, and reduced stem cell proliferation. Corticosteroid exposure also exacerbated organoid toxicity mediated by T cells or cytokines. In a murine model of corticosteroid-refractory GVHD, corticosteroids impaired epithelial cell regeneration and contributed to intestinal injury. The researchers found that IL-22 treatment counteracted the effects of corticosteroids, both ex vivo and in vivo, suggesting that the intestinal toxicities of corticosteroids could be counterbalanced by therapeutics such as IL-22 that promote epithelial regeneration.

primary outcomes were the incidence of graft failure and the incidence of grade 3 to 4 acute GVHD. There were no cases of engraftment failure during treatment with itacitinib. Impressively, no patients developed grade 3 to 4 acute GVHD and, importantly, there were no cases of severe CRS. In comparison, the historical rate of severe CRS is approximately 15% to 20% in this setting.

Although this study is relatively small, it does provide some insights. It appears that JAK inhibitors, specifically itacitinib, can be safely administered during the early phases of transplant without concern for effects on hematopoietic recovery. Use during this time seems to reduce the incidence of severe CRS and may decrease the rates of significant acute GVHD. Potential effects on the incidence of chronic GVHD will need to be determined with longer follow-up and observation.

Dr Gabriela Hobbs presented results from a phase 2 study that evaluated use of the JAK1/2 inhibitor ruxolitinib during and after transplant in patients with myelofibrosis.[11] Ruxolitinib is now approved by the FDA for the treatment of corticosteroid-refractory GVHD, in both the acute and chronic settings.[12,13] There is thus much interest in using ruxolitinib earlier, either for initial treatment or even prevention of acute GVHD. Ruxolitinib is also approved for the treatment of myelofibrosis, mainly to reduce symptoms and spleen size. In our early experience with myelofibrosis in patients who were receiving ruxolitinib and underwent allogeneic transplant, there were several cases in which we stopped the ruxolitinib fairly quickly, which led to a cytokine surge, or what has been called ruxolitinib withdrawal syndrome. This manifested clinically as fevers and third-spacing, consistent with cytokine release. Therefore, in many centers, it has become standard to continue ruxolitinib through the peritransplant period, with lower doses to minimize toxicities. The aim of this study was to evaluate administration of ruxolitinib during the peritransplant period in patients with myelofibrosis and to describe the safety, adverse events, and subsequent contribution to the prevention of GVHD.

This multicenter, investigator-initiated study enrolled patients with primary or secondary myelofibrosis.[11] The accrual goal is 48 patients, and this abstract described the early results after the first 26 patients were enrolled. Patients began treatment with ruxolitinib prior to transplant or continued treatment if they were already receiving it. The dose of ruxolitinib was decreased during the transplant period and subsequently increased to a goal of 10 mg twice daily after recovery of blood counts and continued for 1 year. All participants received the reduced-intensity regimen of fludarabine and melphalan, as well as standard GVHD prophylaxis with tacrolimus and methotrexate. They received peripheral blood stem cell grafts from either match-related or match-unrelated donors.

The most common adverse events associated with ruxolitinib during transplant were anemia and thrombocytopenia, as expected. There were few nonhematologic adverse effects, and none that required discontinuation of ruxolitinib. The time to neutrophil engraftment was as expected, and engraftment was successful in every patient but one.

After a median follow-up of 12 months, the 1-year GRFS rate was an impressive 65% for this very high-risk population. There were no cases of grade 4 GVHD, and only 1 case of grade 3 acute GVHD. The cumulative incidence of moderate-to-severe chronic GVHD in these patients was only 5%, which is compellingly low compared with historical data.[14] These interim results are exciting, even if drawn from a small number of patients, as conducting hematopoietic cell transplants in patients with myelofibrosis is notoriously difficult. We await completion of accrual of this ongoing trial, and presentation of the final results. This analysis further supports the use of JAK inhibitors during transplant and afterwards, primarily as a tool to better prevent acute and chronic GVHD.

Treatment of Acute GVHD

The overall treatment of acute GVHD remains unsatisfying. High-dose systemic corticosteroids remain the standard initial therapy and appear to be effective in a subset of patients.[15] However, systemic corticosteroids are clearly associated with several toxicities. For the last couple of decades, clinicians have unsuccessfully tried to improve upon systemic corticosteroids for the initial treatment of acute GVHD. A study presented by Dr Viktor Arnhold provided a glimpse into why the ultimate goal may be to replace corticosteroids in this setting.[16] The rationale behind the use of corticosteroids is that they can suppress donor T cells that attack the host. However, there are corticosteroid receptors on cells throughout the body, and expression is seen on cells in the gastrointestinal (GI) epithelium. Among patients with acute GI GVHD, a focus is to heal and re-epithelialize the intestinal mucosa. It is apparent from mouse models and ex vivo experiments that corticosteroids not only affect the immune system, but may also impede the ability of the GI mucosa to heal.[17]

The study by Dr Viktor Arnhold described several experiments.[16] In the first set, a mouse model showed that corticosteroids lower the ability of the epithelium to proliferate and regenerate in the mouse ileum. A series of experiments using ex vivo organoids of specific parts of the intestine showed that corticosteroids decreased the organoid size and impaired growth. By knocking out the glucocorticoid receptor in these organoids, they became resistant to this effect and maintained their ability to grow, suggesting that corticosteroids directly effect the epithelium through the receptor.

The researchers then performed experiments with mouse models of steroid-refractory GVHD. In this setting, corticosteroids decreased regeneration and worsened the pathologic appearance of GVHD. Lastly, the investigators administered IL-22, an epithelial growth factor of the GI epithelium. When IL-22 was given with corticosteroids, it appeared to mitigate the harmful effects that corticosteroids had on the GI epithelium.

This study suggests that although corticosteroids can provide some benefit in controlling immunologic complications such as GVHD, they are not ideal. Duration of treatment likely should be limited because of harmful effects. Although corticosteroids may have some beneficial anti-inflammatory effects, long-term use can delay healing of the GI epithelium, which is essential to recovery. This study gives merit to the entire field of trials that are studying methods of promoting organ resiliency in acute GVHD. Agents such as IL-22 preserve intestinal stem cells and organ healing, providing a novel approach to the treatment of GVHD, which formerly had focused solely on broad immunosuppression.

Dr Shernan Holtan presented the results of a phase 2 study of urinary-derived human chorionic gonadotropin/epidermal growth factor (uhCG/EGF) for the treatment of severe acute GVHD.[18] Results of a phase 1 trial, published in 2020, showed preliminary evidence of activity.[19] The rationale for its use is to take advantage of the immunomodulatory effects of supporting tissue tolerance of human chorionic gonadotropin, as well as the epithelial healing that EGF can promote. This agent exemplifies the focus on organ healing in the development of therapy for acute GVHD.

This phase 2 study enrolled 22 patients with new high-risk GVHD and 22 patients with steroid-refractory disease.[18] The high-risk cohort received standard corticosteroids along with uhCG/EGF. Patients in the steroid-refractory cohort received the physician's choice of standard second-line therapy along with uhCG/EGF. The dosing regimen differed based on the organs involved. The primary endpoint was the overall response rate at day 28. Across both groups, the overall response rate was 68%, with a complete response rate of 57%. There were no significant safety concerns. These results echo the impressive outcomes shown previously in the phase 1 trial.[19] The data warrant further study to determine whether uhCG/EGF would be a valuable adjuvant as supportive therapy. Because uhCG/EGF was given in addition to standard therapy, it is difficult to assess the benefit without a control group.

The microbiome has become a much-studied topic in allogeneic transplant recipients. Large studies have shown that patients with restricted fecal microbiome diversity, also known as dysbiosis, tend to have worse outcomes after transplant, including an increased risk for bacteremia, acute GVHD, NRM, and decreased survival.[20,21] It is unclear whether there is a true cause and effect, or if these relationships are purely associative. Researchers are exploring whether it is possible to modify these outcomes by restoring or preserving the diversity of the microbiome. Fecal microbiota transplant (FMT) is a therapeutic modality that aims to replenish the diversity of the microbiome via a transplant from a healthy donor. Several studies have described the use of this procedure to treat resistant infection with *Clostridioides difficile* and, more recently, to treat corticosteroid-refractory acute GVHD.[22,23]

A study by Dr Florent Malard described the combined experience of 76 patients (24 in a phase 2 study and 52 in an expanded-access protocol) who received MaaT013 to treat corticosteroid-refractory acute GI GVHD.[24] MaaT013 is an off-the-shelf standardized pooled donor FMT product administered by enema. The overall response rate was 38% in the phase 2 trial and 60% in the expanded-access protocol. The survival outcomes were better among the patients who responded, suggesting a durable response. There were no safety issues observed. Infections are a concern when giving this type of therapy, and a few patients developed infections commonly seen with GI GVHD. However, none of these infections were traced back to the FMT product, as has been previously reported.[25]

Although the results of this study do not suggest that this therapy should become a standard treatment, they do show that there is a subset of patients with acute GI GVHD who benefit from microbiome-directed therapy. Further studies are needed to determine if microbiome-modifying therapy can truly impact clinical outcomes after HCT. Such interventions could include administration of prebiotics to preserve diversity, administration of actual probiotics such as FMT, and avoidance of specific broad-spectrum antibiotics for prophylaxis or empiric treatment.

Treatment of Chronic GVHD

Significant recent progress has been made in the treatment of refractory chronic GVHD. There are now 3 approved agents: the Bruton's tyrosine kinase inhibitor ibrutinib, the oral ROCK2 inhibitor belumosudil, and the JAK inhibitor ruxolitinib.

A novel agent under study in a pivotal national trial is axatilimab, a monoclonal antibody directed against the CSF-1R receptor.[26] The CSF-1R receptor is present on activated macrophages that are thought to play a significant role in the cascade of fibrosis, which is the pathologic hallmark of chronic GVHD. By inhibiting these macrophages, the goal is to halt and even possibly reverse fibrotic changes. In a previous report of the phase 1 findings, axatilimab appeared to be safe and showed some signal of efficacy.[26] This abstract presented results for 40

patients: 17 in a phase 1 dose-finding cohort and 23 in a phase 2 dose-expansion cohort. Importantly, several of these patients were already known to be refractory to ibrutinib, ruxolitinib, or belumosudil.[27] This study is therefore relevant to the modern population of patients with refractory chronic GVHD. The rate of overall response to axatilimab was an impressive 66%. In parallel with this finding, 54% of patients had an improvement of at least 7 points on the Lee Symptom Scale, which is the best assessment of patient quality of life in these trials. There were encouraging responses even in patients with lung involvement, as well as facial or joint involvement, which are generally the most difficult-to-treat clinical manifestations in chronic GVHD. Overall, axatilimab was relatively well tolerated in this patient population. The adverse events of note were clinically nonsignificant elevations in liver function tests and creatine kinase, as well as a few cases of periorbital edema. These results set the stage for the ongoing, pivotal phase 2 AGAVE-201 trial, which is randomly assigning patients to 3 different doses of axatilimab to provide data to potentially support regulatory approval of axatilimab for this indication.[28]

Abatacept is a recombinant fusion protein that consists of the extracellular domain of CTLA-4 linked to the Fc portion of the human immunoglobulin G. The drug is meant to impair T-cell co-stimulation, and thus suppress an immune response. Abatacept was recently approved for the prevention of chronic GVHD among patients undergoing unrelated donor transplant. A prior phase 1 trial had shown safety and potential efficacy for the treatment of refractory chronic GVHD.[29] Dr Anita Koshy presented the findings of a phase 2 trial evaluating abatacept for the treatment of steroid-refractory chronic GVHD in 39 patients.[30] Patients were treated every other week for the first 3 doses, and then every 4 weeks for the subsequent 3 doses. They could remain on trial receiving treatment for an extended period, if their physicians deemed they were benefiting. The overall response rate was 49%, with responses across all organs observed, including the lungs. Correspondingly, there was a reduction in the use of systemic corticosteroids by approximately 50% throughout the first 5 months of therapy. An important safety event was neutropenia, which occurred in several patients. Given the observed 49% overall response rate, abatacept merits further study as a treatment for refractory chronic GVHD, although the field has clearly changed with the recent approvals of ibrutinib, belumosudil and ruxolitinib.

In chronic GVHD, topical therapy is used routinely, especially when the eyes, mouth, and skin are involved. Corticosteroids have significant toxicities, and their topical formulations are no different.[31] When topical corticosteroids are applied to the skin, they can result in thinning, bruising, localized infections, and acne. As mentioned, ruxolitinib was recently approved by the FDA for the treatment of corticosteroid-refractory acute and chronic GVHD.

Dr Alina Markova presented results from a prospective randomized phase 2 proof-of-concept trial that evaluated topical ruxolitinib for the treatment of cutaneous chronic GVHD.[32] The trial enrolled 13 patients with cutaneous nonsclerotic or superficially sclerotic disease. The trial followed an interesting design, in which each patient received treatment with topical ruxolitinib on one side of the body and placebo vehicle cream on the other side. The primary endpoint was efficacy as measured by the percent of body surface area involved on the ruxolitinib side vs the placebo side on day 28. The secondary endpoints were the physician's global assessment of clinical condition and a more dermatologic-specific composite assessment of index lesion severity. Most of these patients had previously received unsuccessful treatment with at least 2 topical therapies, so the population was quite resistant to treatment.

Although the primary endpoint was not met, there was a clear trend toward a benefit with ruxolitinib vs placebo. There were also significant differences in the physicians' global assessment and the dermatological composite assessment.

ABSTRACT SUMMARY Phase 2 Results of Urinary-Derived Human Chorionic Gonadotropin/Epidermal Growth Factor as Treatment for Life-Threatening Acute GVHD

A phase 2 study evaluated urinary-derived human chorionic gonadotropin/epidermal growth factor (uhCG/EGF) in patients with life-threatening acute GVHD (Abstract 261). The study enrolled 2 groups of patients: 22 patients with high-risk acute GVHD in the first-line setting, who received uhCG/EGF at 2000 units/m^2 subcutaneously every other day for 7 days plus high-dose corticosteroids and 22 patients in the second-line setting (no response to first-line therapy or GVHD flare), who received uhCG/EGF at 2000 units/m^2 (corticosteroid-dependent) or 5000 units/m^2 (corticosteroid-refractory) subcutaneously every other day for 14 days plus standard-of-care immunosuppression. At day 28, the ORR was 68%, including CRs in 57% (64% in high-risk patients and 50% in second-line patients). The 2-year OS rate was 67% in patients with a response at day 28 vs 12% in those with no response ($P<.01$). There was a single dose-limiting toxicity of an incidental cerebral venous sinus thrombosis that was treated successfully. Exploratory biomarker analyses suggest an association between the metabolomic profile and response to uhCG/EGF.

Clinicians in this field have been eager for the opportunity to treat patients with JAK inhibitors formulated as eyedrops, oral rinses, and topical cutaneous therapies, given the success of systemic ruxolitinib. This study provides the first description of such data. Incorporation of topical JAK inhibitors into clinical practice will require studies with longer follow-up and better ways to assess improvement. The harms of corticosteroids, both systemic and topical, are well recognized, and replacing them in the therapy of GVHD remains a significant unmet need.

As we gain more experience in conducting clinical trials in patients with chronic GVHD, it is becoming apparent that studies should not only consider clinical overall response, which is assessed imperfectly at best, but also patient-reported outcomes (PROs). REACH3 was a randomized phase 3 study that compared ruxolitinib to best available therapy in patients with corticosteroid-refractory chronic GVHD. The study showed a significant advantage for ruxolitinib therapy,[13] which resulted in approval by the FDA in this setting. Dr Stephanie Lee presented an analysis of PROs reported in the REACH3 trial.[33] These outcomes were collected at baseline and then at 4-week intervals through week 24. The main assessment tool was the modified Lee Symptom Score; an improvement of 7 points or more was considered significant. The other assessments included standard assays of quality of life, including the Functional Assessment of Cancer Therapy–Bone Marrow Transplantation and the Patient Global Impression of Severity.

In this analysis, more patients in the ruxolitinib arm had a significant modified Lee Symptom Score response at week 24 or at any time up to week 24, and for more than 2 consecutive visits. Importantly, this analysis also compared all patients who had a response to ruxolitinib or the best available therapy. Among this group, the patients treated with ruxolitinib had an even greater benefit according to the modified Lee Symptom Score vs those treated with the best available therapy. This finding suggests that in patients who had a clinical response, the subjective response in terms of overall symptoms was much better with ruxolitinib compared with the best available therapy.

This analysis illustrates the importance of incorporating standard PROs into clinical trials as tools to assess the benefit of therapies in chronic GVHD. These patients have a low mortality rate in clinical trials, but high morbidity in terms of symptoms. Assessment of clinical response in trials is imperfect, although tools are improving. It is necessary to understand whether these responses are meaningful, and one way to do that is by assessing PROs. Importantly, we must continue to develop more instruments specific to chronic GVHD to truly assess differences in treatment.

Belumosudil is an oral ROCK2 inhibitor recently approved for the treatment of patients with chronic GVHD who have already received at least 2 other therapies. The drug has a novel mechanism of action and targets the ROCK2 kinase, which is thought to be fairly active in the pathway of fibrosis. Belumosudil was evaluated in a dose-finding study, and then results from the pivotal phase 2 ROCKstar trial led to approval.[34,35] The observed overall response rate was 72% across the different dosages studied in the ROCKstar trial.

Dr Aleksandr Lazaryan presented an analysis of the composite endpoint of failure-free survival (FFS) among patients in the phase 2a KD025-208 study and the ROCKstar study.[36] FFS has emerged as an important composite endpoint for patients with chronic GVHD, as it incorporates events such as recurrent malignancy, nonrelapse mortality, and initiation of subsequent therapy. FFS is thought to be a good correlate of overall success for trials in chronic GVHD.

In a large observational study from 2013 of patients with chronic GVHD after second-line systemic therapy, the rates of FFS were 56% at 6 months, 45% at 12 months, and just 31% at 24 months, results that were sobering.[37] Among patients treated with belumosudil in this pooled analysis, the overall

ABSTRACT SUMMARY A Single-Arm, Open-Label, Pilot Study of the JAK1 Selective Inhibitor Itacitinib for the Prophylaxis of Graft-vs-Host Disease and Cytokine Release Syndrome in T-Cell Replete Haploidentical Peripheral Blood Hematopoietic Cell Transplantation

A pilot study evaluated itacitinib for the prevention of GVHD and cytokine release syndrome in patients undergoing T-cell replete haploidentical peripheral blood HCT (Abstract 100). A total of 21 patients enrolled and received itacitinib at 200 mg once daily on days –3 through +100, followed by a taper. There were no primary graft failures. Neutrophils and platelets engrafted after a median of 14.5 days and 19.8 days, respectively. By day 100, grade 1 and 2 acute GVHD were reported in 16% and 11% of patients, respectively. There were no cases of grade 3/4 acute GVHD. Grade 1 cytokine release syndrome occurred in 90% of patients. No patients developed grade 2 or higher cytokine release syndrome. Most patients (86%) experienced no chronic GVHD. The remaining 14% had mild chronic GVHD. At 1 year, the OS rate was 82%, and the rate of GVHD and relapse-free survival was 82%. Two patients died without relapse, and 1 patient with acute myeloid leukemia relapsed. The most frequent treatment-emergent grade 3 or higher AEs were febrile neutropenia (62%), oral mucositis (33%), pneumonia (19%), and ALT/AST increase (19%). An expansion study and correlative studies are underway.

median FFS was 14 months. A time point analysis showed an FFS rate of 75% at 6 months, 54% at 12 months, and 38% at 24 months. In the majority of cases, failure of belumosudil was attributable to initiation of a new therapy for chronic GVHD. This analysis implies that the approval of belumosudil is a step in the right direction, as this agent leads to a significantly higher rate of early FFS. However, the data also illustrate that many patients appear to require additional therapy as more time passes.

Disclosure

Dr Chen has performed consulting for Incyte, Magenta, Jasper, CTI BioPharma, and Gamida Cell. He is a member of the data safety monitoring board committees for clinical trials sponsored by AbbVie, Daiichi, Equillium, Celularity, and Actinium.

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