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A SPECIAL MEETING REVIEW EDITION

Highlights in Graft-vs-Host Disease From the 2022 Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR

A Review of Selected Presentations From the 2022 Tandem Meetings • April 23-26, 2022 • Salt Lake City, Utah

Special Reporting on:

- Noninvasive Genomic Characterization of Patients With Nonsclerotic and Superficially Sclerotic Chronic Cutaneous Graft-vs-Host Disease Identified a Novel Gene Signature in Responders to Ruxolitinib Cream
- Interim Results of a Pilot, Prospective, Randomized, Double-Blinded, Vehicle-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
- Use of Belimumab for Prophylaxis of Chronic Graft-vs-Host Disease
- Prolonged Post-Transplant Ruxolitinib Therapy Is Associated With Protection From Severe GVHD After Allogeneic HCT
- Interim Analysis of T-Cell Specific Predictive Biomarkers of Graft-vs-Host Disease and Relapse Following Post-Transplant Cyclophosphamide Prophylaxis
- Validation of Amphiregulin as a Monitoring Biomarker During Treatment of Life-Threatening Acute GVHD: A Secondary Analysis of 2 Prospective Clinical Trials
- Prospective Trial of Ibrutinib for the Treatment of Pediatric Chronic Graft-vs-Host Disease
- Phase II Clinical Trial of Abatacept for Steroid-Refractory Chronic Graft-vs-Host Disease

PLUS Meeting Abstract Summaries

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In adult and pediatric patients 12 years and older

Intervene With Jakafi at the First Sign of Initial Systemic Treatment Failure for cGVHD

Timely Diagnosis and Early Intervention Is Critical to Prevent Potentially Irreversible Organ Damage[1]

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.

REACH3 Primary Endpoint: ORR at Week 24

49.7% (82/165) with Jakafi vs 25.6% (42/164) with BAT (OR: 2.99; 95% CI, 1.86-4.80; *P*<0.0001)[2,3*†]

ORR through Week 24

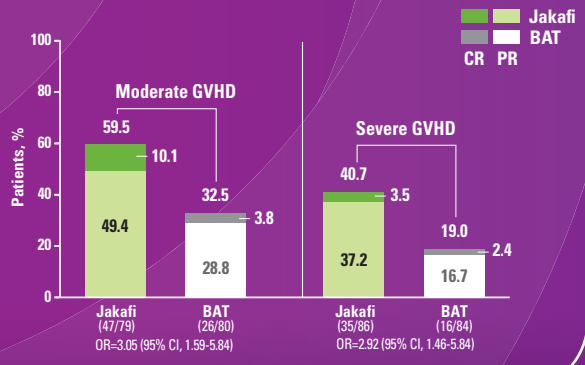
70% (116/165) with Jakafi vs 57% (94/164) with BAT[4‡]

- In the Jakafi Prescribing Information, efficacy was based on ORR through week 24 (Cycle 7 Day 1)[4]

*Overall response rate was defined as the proportion of patients with complete or partial response, according to 2014 NIH consensus criteria, at Week 24.[2]
†One-sided *P* value, odds ratio, and 95% CI were calculated using stratified Cochran-Mantel-Haenszel test, stratifying for moderate and severe cGVHD.[2]
‡Defined as proportion of patients who achieved complete or partial response, according to 2014 NIH response criteria, through Week 24 (Cycle 7 Day 1).[4]

Overall Response Rates Were Higher With Jakafi in Patients With Moderate Disease Severity at Week 24 vs BAT[3]

REACH3 Subgroup Analysis: ORR by Baseline Disease Severity at Week 24[3,5]



BAT=best available therapy; BID=twice daily; CI=confidence interval; CR=complete response; HSCT=hematopoietic stem cell transplant; GI=gastrointestinal; OR=odds ratio; ORR=overall response rate; PR=partial response.

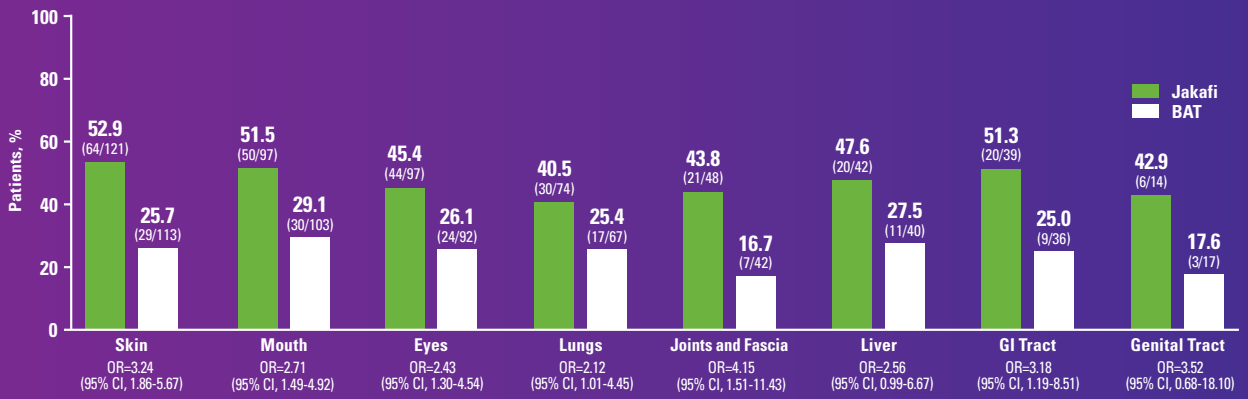
IMPORTANT SAFETY INFORMATION

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

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

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

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



[a]Patients with >1 affected organ were counted in each organ subgroup. Organ involvement was defined as organ score ≥1 based on the cGVHD staging criteria.[3,6]

REACH3 was a randomized, open-label, multicenter, phase 3 study of Jakafi vs BAT in patients with steroid-refractory cGVHD (N=329).[1,2§||¶] 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]

[§]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.[4]

[||]BATs included ibrutinib, extracorporeal photopheresis, low-dose methotrexate, mycophenolate mofetil, rituximab, everolimus, sirolimus, imatinib, infliximab, or pentostatin.[4]

[¶]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.[3,5]

Intervene with Jakafi in your appropriate patients with cGVHD.

Learn more at hcp.Jakafi.com

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.

References: 1. Lee SJ, Flower MED. Recognizing and managing chronic graft-versus-host disease. *Am Soc Hematol.* 2008;(1):134-141. **2.** Zeiser R, Polverelli N, Ram R, et al; for the REACH3 Investigators. Ruxolitinib for glucocorticoid-refractory chronic graft-versus-host disease. *N Engl J Med.* 2021;385(3):228-238. **3.** Zeiser R, Polverelli N, Ram R, et al; for the REACH3 Investigators. Ruxolitinib for glucocorticoid-refractory chronic graft-versus-host disease. *N Engl J Med.* 2021;385(3)(suppl):1-49. **4.** Jakafi [package insert]. Wilmington, DE: Incyte Corporation. **5.** Data on file. Incyte Corporation. Wilmington, DE. **6.** Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. The 2014 Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant.* 2015;21(3):389-401.e1.

Incyte

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 $\times 10^9$/L) and 20 mg twice daily (pretreatment platelet counts greater than 200 $\times 10^9$/L), 65% and 25% of patients, respectively, required a dose reduction below the starting dose within the first 8 weeks of therapy. In a double-blind, randomized, placebo-controlled study of Jakafi, among the 155 patients treated with Jakafi, the most frequent adverse reactions were thrombocytopenia and anemia *[see Table 2]*. Thrombocytopenia, anemia and neutropenia are dose-related effects. The three most frequent nonhematologic adverse reactions were bruising, dizziness and headache *[see Table 1]*. Discontinuation for adverse events, regardless of causality, was observed in 11% of patients treated with Jakafi and 11% of patients treated with placebo. Table 1 presents the most common nonhematologic adverse reactions occurring in patients who received Jakafi in the double-blind, placebo-controlled study during randomized treatment.

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

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

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

Description of Selected Adverse Reactions: Anemia In the two Phase 3 clinical studies, median time to onset of first CTCAE Grade 2 or higher anemia was approximately 6 weeks. One patient (< 1%) discontinued treatment because of anemia. In patients receiving Jakafi, mean decreases in hemoglobin reached a nadir of approximately 1.5 to 2.0 g/dL below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 1.0 g/dL below baseline. This pattern was observed in patients regardless of whether they had received transfusions during therapy. In the randomized, placebo-controlled study, 60% of patients treated with Jakafi and 38% of patients receiving placebo received red blood cell transfusions during randomized treatment. Among transfused patients, the median number of units transfused per month was 1.2 in patients treated with Jakafi and 1.7 in placebo treated patients. **Thrombocytopenia** In the two Phase 3 clinical studies, in patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50×10^9/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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Noninvasive Genomic Characterization of Patients With Nonsclerotic and Superficially Sclerotic Chronic Cutaneous Graft-vs-Host Disease Identified a Novel Gene Signature in Responders to Ruxolitinib Cream

Chronic graft-vs-host disease (GVHD) is a major complication of allogeneic hematopoietic stem cell transplant (HSCT). There are currently no therapies approved by the US Food and Drug Administration (FDA) for the treatment of cutaneous GVHD.[1] Ruxolitinib is an oral inhibitor of Janus kinase 1/2 that is approved for the treatment of acute and chronic GVHD in patients ages 12 years and older who had received unsuccessful treatment with 1 or 2 prior lines of therapy.[2] In 2021, the FDA approved ruxolitinib cream 1.5% for the topical short-term and noncontinuous chronic treatment of mild to moderate atopic dermatitis in patients ages 12 years and older who lack other adequate or suitable therapies.[3]

A double-blind, randomized, controlled phase 3 trial evaluated the safety and efficacy of topical ruxolitinib cream 1.5% vs a vehicle cream, both applied twice daily, for the treatment of cutaneous chronic GVHD. Dr Alina Markova and colleagues presented data from an interim analysis, as well as a genomic analysis.[4,5]

Eligible patients had undergone allogeneic HSCT, were ages 12 years or older, and had 2% of body surface area clinically or histologically confirmed as nonsclerotic or superficially sclerotic, cutaneous chronic GVHD. Among patients who were receiving systemic therapy for GVHD, the regimen had to be stable for at least 4 weeks before study treatment began. Any cutaneous therapies were discontinued before the study treatment was initiated.

The patients received ruxolitinib cream applied to one side of the face and body and the vehicle cream applied to the other side. The primary outcome was the efficacy at day 28 of the ruxolitinib cream vs the vehicle cream, as measured by the involved proportion of body surface area.

The trial randomly assigned 13 patients to treatment. Their mean age was 52.6±20 years, and 53% were female. The most common diagnoses were acute leukemia (62%) and non-Hodgkin lymphoma (23%). The median time from transplant to study enrollment was 665 days (interquartile range [IQR], 433-1355 days), and the median time from chronic GVHD onset to enrollment was 283 days (IQR, 115-867 days). GVHD symptoms were severe in 62% of patients, moderate in 15%, and mild in 23%. The chronic GVHD subtype was classic in 85% and overlap in 15%. Nearly half of patients (46%) had 4 or more organs involved, and 31% had received 3 or more prior lines of systemic therapy. Among the 10 patients with nonsclerotic cutaneous chronic GVHD, subtypes included lichen planus–like (62%), papulosquamous (8%), and maculopapular rash (8%). Prior lines of therapy included topical corticosteroids (77%), topical calcineurin inhibitors (31%), and phototherapy (31%).

On day 14, the primary outcome of involved body surface area was lower on the side treated with ruxolitinib compared with the vehicle cream, but the difference did not reach statistical significance (P=.06). At day 28, the comparison was also not significant (P=.15). In contrast, secondary outcomes did show a significant improvement with ruxolitinib. The Composite Assessment of Index Lesion Severity (CAILS) score was significantly better on the side treated with ruxolitinib vs the vehicle cream at day 14 (P=.02), although not at day 28 (P=.09). The Physician's Global Assessment (PGA)

Table 1. The Most Differentially Expressed Genes in a Study Comparing Ruxolitinib Cream vs Vehicle Cream in Patients With Nonsclerotic and Superficially Sclerotic Chronic Cutaneous GVHD

Gene	Log_2 Fold Change	*P* Value
CAPN12	29.94	1.64E-23
KRT84	–29.87	2.61E-23
FP236383.7	20.69	5.99E-12
CTNNB1	20.37	1.17E-11
TCF7	20.25	1.51E-11
HNRNPU	20.22	1.63E-11
ZNF664	20.13	1.98E-11
GARS1	20.11	2.09E-11
GIGYF2	20.02	2.59E-11
SLC44A1	19.90	3.41E-11

Adapted from Markova A et al. Abstract 33. Presented at: Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; April 23-26, 2022; Salt Lake City, Utah.[4]

of clinical condition was significantly better with ruxolitinib vs the vehicle cream, at both day 14 (*P*=.02) and day 28 (*P*=.026).

Noninvasive skin samples were collected from all study participants using a skin-stripping method. There were 11 samples obtained from the active treatment side and 11 samples obtained from the vehicle treatment side. The study investigators performed RNA sequencing, which was followed by mapping to the human genome and quantification of gene expression levels. Expression analysis showed differential expression of 310 genes by at least 2-fold (*P*<.01) between patients treated with ruxolitinib cream 1.5% vs the vehicle cream (Table 1). Genes showing differential expression were most commonly involved in keratinization, transcriptional regulation by RUNX3, and NOTCH3 activation and signal transduction to the nucleus. The analysis identified 383 genes that were differentially expressed by at least 2-fold (*P*<.01) in patients who responded to treatment with ruxolitinib (n=8) vs those who did not respond (n=3).

References

1. Link-Rachner CS, Sockel K, Schuetz C. Established and emerging treatments of skin GvHD. *Front Immunol*. 2022;13:838494.
2. Jakafi [package insert]. Incyte Corporation; Wilmington, Delaware; 2021.
3. Opzelura [package insert]. Incyte Corporation; Wilmington, Delaware; 2021.
4. Markova A, Whitaker JW, Pan A, et al. Noninvasive genomic characterization of patients with nonsclerotic and superficially sclerotic chronic cutaneous graft-versus-host disease identified a novel gene signature in responders to ruxolitinib cream. Presented at: the Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; April 23-26, 2022; Salt Lake City, Utah. Abstract 33.
5. Markova A, Prockop SE, Dusza S, et al. Interim results of a pilot, prospective, randomized, double-blinded, vehicle-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-versus-host disease. Presented at: the Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; April 23-26, 2022; Salt Lake City, Utah. Abstract 390.

Interim Results of a Pilot, Prospective, Randomized, Double-Blinded, Vehicle-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

Oral ruxolitinib is approved by the FDA for the treatment of acute and chronic GVHD, and it has demonstrated efficacy in clinical studies for the treatment of other pathologies of the skin, including psoriasis, atopic dermatitis, and vitiligo.[1,2] Dr Alina Markova and colleagues presented data from an interim analysis of a double-blind, vehicle-controlled, phase 2 clinical study that evaluated topical ruxolitinib cream 1.5% in patients with chronic GVHD of the skin.[3] A genomic analysis was presented separately.[4]

The trial enrolled patients with GVHD lesions that were histologically or clinically confirmed as cutaneous nonsclerotic (lichen-planus–like or poikilodermatous) or superficially sclerotic (lichen sclerosis or morphea-like), covering at least 2% of the body surface area. Patients receiving systemic therapy were eligible if their regimen had been stable for at least 4 weeks before the study treatment began. The patients were randomly assigned to receive ruxolitinib cream 1.5% applied to either the left or the right side of the face and body and vehicle cream applied to the other side. Each cream was applied twice daily for 28 days. The primary endpoint of this proof-of-concept study was the extent of cutaneous chronic GVHD, as measured by body surface area, on the ruxolitinib side vs the vehicle side on day 28.

Results from 13 evaluable patients were analyzed as part of the interim analysis.[3] The patients were a median age of 52.6±20 years, and 53% were female. The diagnoses included acute leukemia (62%), non-Hodgkin lymphoma (23%), and myeloproliferative neoplasm (8%). Chronic GVHD was severe in 62% of patients, 85% had classic GVHD, and 77% had nonsclerotic cutaneous GVHD.

The extent of cutaneous chronic GVHD, as measured by body surface area, was not significantly different between the 2 treatment sides (Figure 1). However, ruxolitinib was associated with a superior PGA score starting at day 14 (3.3 for the treatment side vs 4.4 for the vehicle side; *P*=.024), with continued improvement at day 28 (2.5 vs 4.0; *P*=.026). Ruxolitinib also improved the CAILS score, starting at day 14 (9.0 vs 13.3; *P*=.02; Figure 2). Skin samples were collected by a noninvasive skin stripping method for gene expression analysis. RNA sequencing identified 310 genes that were differentially expressed by at least 2-fold in lesions that were treated with ruxolitinib cream vs the vehicle cream. The investigators identified 383 differentially expressed genes in patients who responded to ruxolitinib therapy vs those who did not. No serious adverse events (AEs) were reported.

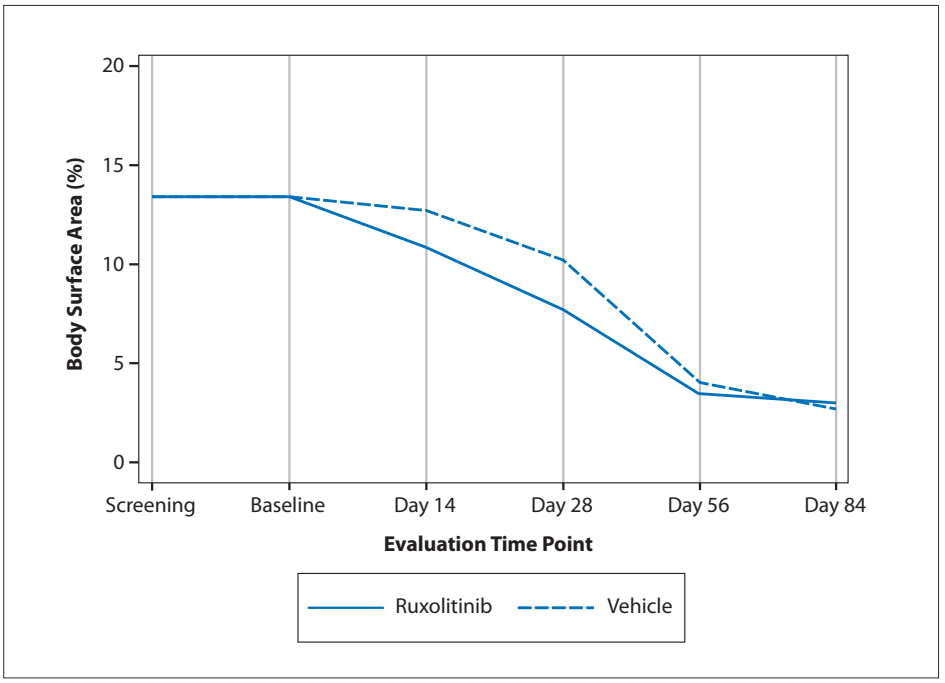

Figure 1. Body surface area affected by nonsclerotic or superficially sclerotic, cutaneous chronic graft-vs-host disease in patients treated with ruxolitinib cream on one side of their body and a vehicle cream on the other side. Adapted from Markova A et al. Abstract 390. Presented at: Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; April 23-26, 2022; Salt Lake City, Utah.[3]

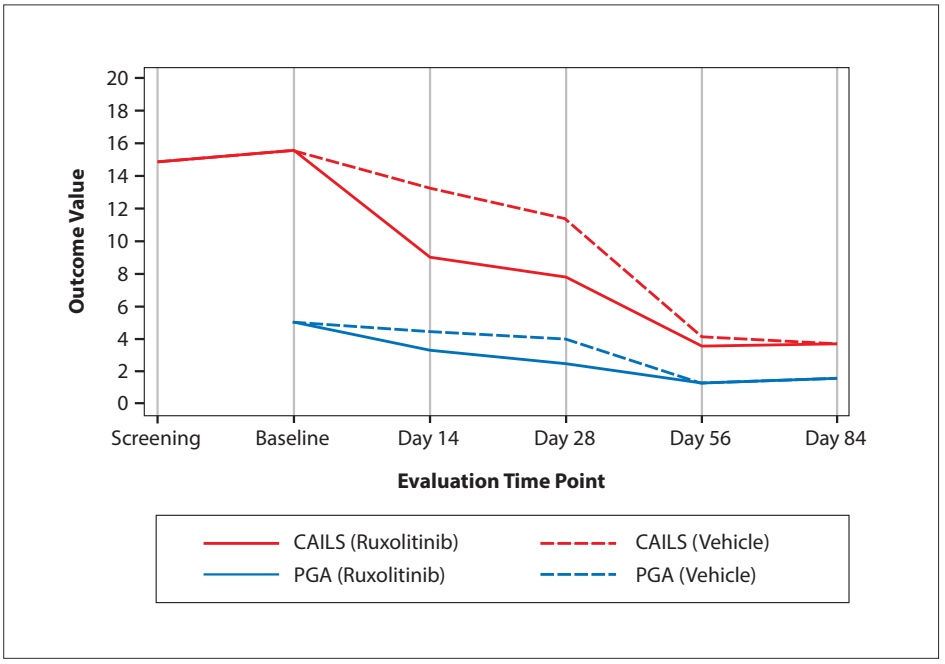

Figure 2. Severity of nonsclerotic or superficially sclerotic, cutaneous chronic graft-vs-host disease as measured by the CAILS and PGA assessment criteria in patients treated with ruxolitinib cream on one side of their body and a vehicle cream on the other side. CAILS, Composite Assessment of Index Lesion Severity; PGA, Physician's Global Assessment. Adapted from Markova A et al. Abstract 390. Presented at: Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; April 23-26, 2022; Salt Lake City, Utah.[3]

References

1. Jakafi [package insert]. Incyte Corporation; Wilmington, Delaware; 2021.
2. Shalabi MMK, Garcia B, Coleman K, Siller A Jr, Miller AC, Tyring SK. Janus kinase and tyrosine kinase inhibitors in dermatology: a review of their utilization, safety profile and future applications. *Skin Therapy Lett.* 2022;27(1):4-9.
3. Markova A, Prockop SE, Dusza S, et al. Interim results of a pilot, prospective, randomized, double-blinded, vehicle-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-versus-host disease. Presented at: the Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; April 23-26, 2022; Salt Lake City, Utah. Abstract 390.
4. Markova A, Whitaker JW, Pan A, et al. Noninvasive genomic characterization of patients with nonsclerotic and superficially sclerotic chronic cutaneous graft-versus-host disease identified a novel gene signature in responders to ruxolitinib cream. Presented at: the Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; April 23-26, 2022; Salt Lake City, Utah. Abstract 33.

Use of Belimumab for Prophylaxis of Chronic Graft-vs-Host Disease

The coordinated involvement of T cells and B cells in GVHD has raised the idea of targeting B cells to manage cutaneous disease.[1] B-cell activating factor (BAFF) is a member of the tumor necrosis factor cytokine family that plays a key role in the survival and differentiation of antigen-activated B cells.[2,3] BAFF regulates B-cell recovery and homeostasis in patients who have undergone allogeneic HSCT. BAFF is present at increased levels in patients with GVHD. Excess BAFF and alloantigen act together to produce alloantibodies and a pool of active B cells.

Belimumab is a human monoclonal antibody that prevents the binding of BAFF to its cognate receptors on B cells, thus reducing the survival of alloreactive B cells.[4] Belimumab is FDA-approved for the treatment of patients with systemic lupus erythematosus and active lupus nephritis. An investigator-initiated, single-center phase 1 study evaluated the efficacy and tolerability of belimumab in the prevention of chronic GVHD.[5] The study enrolled 10 adults in complete remission (CR) after allogeneic HSCT. All patients had received mobilized peripheral blood grafts from human leukocyte antigen (HLA)-matched donors who were related or unrelated. The patients had received a conditioning regimen. All patients were negative for minimal residual disease. They had received tacrolimus and methotrexate for prophylaxis of GVHD, and 1 patient had received cyclophosphamide after transplant. Starting 50 to 80 days after allogeneic HSCT, belimumab was administered intravenously at 10 mg/kg every 2 weeks for 3 doses, followed by 4 subsequent doses given at 1-month intervals.

Among 9 evaluable patients, the median follow-up was 28 months after allogeneic HSCT (range, 12-43 months). The median time since completing belimumab therapy was 23 months (range, 4-29 months). Eight of the 9 patients (89%) had received all 7 doses of belimumab. One patient (11%) had received only 3 doses of belimumab owing to thrombocytopenia and insurance issues.

After more than 20 months of follow-up after belimumab administration, 5 of the 8 patients (63%) who had received all 7 doses of the antibody were alive, not receiving immunosuppressive therapy, and showing no evidence of chronic GVHD. Immune reconstitution is shown in Figure 3. Chronic GVHD occurred in 2 patients (25%). In one of these patients, the severity improved to mild chronic after treatment with tacrolimus, ruxolitinib, and corticosteroids.

One patient died from complications related to pneumonia and liver failure. One patient (13%) relapsed with acute myeloid leukemia (AML) 1 month after receiving the seventh dose of belimumab. This patient developed mild chronic GVHD in the mouth and upper gastrointestinal tract, and was receiving tapering doses of prednisone 16 months after completing belimumab therapy. The 1 patient who received only 3 doses of belimumab experienced a lymphoma relapse 3 months after cessation of study treatment. After treatment with venetoclax and donor leukocyte infusion, this patient's leukemia was in remission,

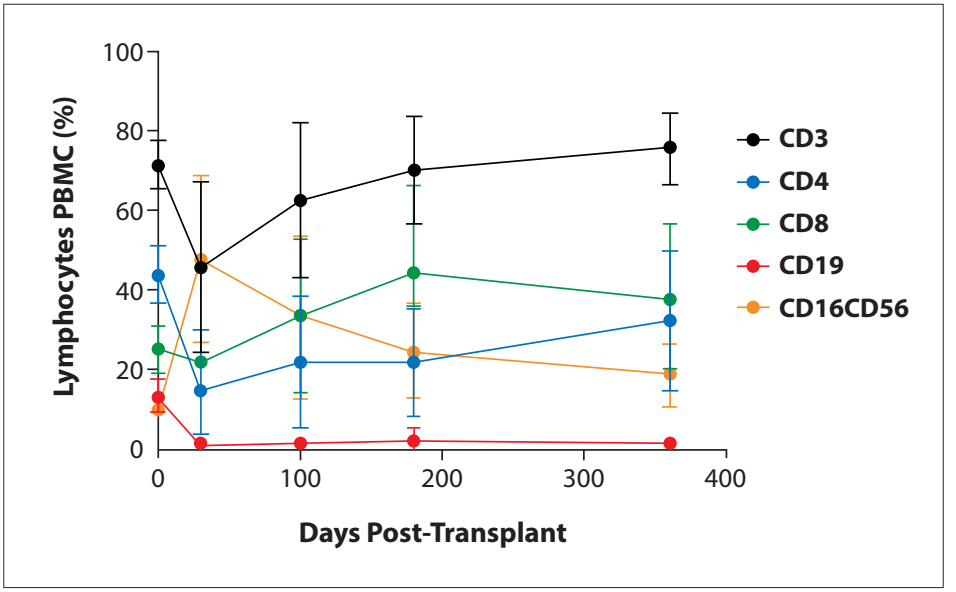

Figure 3. Percentages of immune cells in the peripheral blood after transplant among patients who received belimumab for prophylaxis of chronic graft-vs-host disease. PBMC, peripheral blood mononuclear cell. Adapted from Pusic I et al. Abstract 34. Presented at: Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; April 23-26, 2022; Salt Lake City, Utah.[5]

and he was free of chronic GVHD more than 18 months after salvage therapy.

Belimumab was well tolerated, with no AEs of grade 3 or higher. There were no reports of infusion reactions or hypersensitivity. One patient developed reactivation of cytomegalovirus. However, there were no cases of clinically important infections or myelosuppression. Three patients (33%) developed stage 1 skin acute GVHD. This AE resolved completely with a corticosteroid pulse treatment in 2 of the patients, whereas the other patient developed a case of overlap GVHD.

References

1. McManigle W, Youssef A, Sarantopoulos S. B cells in chronic graft-versus-host disease. *Hum Immunol*. 2019;80(6):393-399.
2. Jia W, Poe JC, Su H, et al. BAFF promotes heightened BCR responsiveness and manifestations of chronic GVHD after allogeneic stem cell transplantation. *Blood*. 2021;137(18):2544-2557.
3. Saliba RM, Sarantopoulos S, Kitko CL, et al. B-cell activating factor (BAFF) plasma level at the time of chronic GvHD diagnosis is a potential predictor of non-relapse mortality. *Bone Marrow Transplant*. 2017;52(7):1010-1015.
4. Benlysta [package insert]. GlaxoSmithKline, LLC; Research Triangle Park, North Carolina; 2021.
5. Pusic I, Johanns T, Sarantopoulos S, et al. Use of belimumab for prophylaxis of chronic graft-versus-host disease. Presented at: the Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; April 23-26, 2022; Salt Lake City, Utah. Abstract 34.

Prolonged Post-Transplant Ruxolitinib Therapy Is Associated With Protection From Severe GVHD After Allogeneic HCT

Two ongoing phase 2 clinical trials are evaluating the safety and efficacy of ruxolitinib administered around the time of allogeneic HSCT, with emphasis on outcomes related to GVHD. Clinical trial NCT03286530 enrolled patients with AML who were in their first CR.[1] These patients received continuous ruxolitinib in 28-day cycles, for up to 24 cycles, starting 30 to 90 days after allogeneic HSCT. Clinical trial NCT03427866 enrolled patients with primary or secondary myelofibrosis.[2] These patients received ruxolitinib before, during, and after allogeneic HSCT, in 28-day cycles starting 14 days prior to HSCT. Patients could receive up to 13 cycles.

Dr Zachariah DeFilipp and colleagues presented the results from an unplanned interim analysis of these 2 trials. The analysis included 54 patients (33 with AML and 21 with myelofibrosis).[3] At the time of their HSCT, the patients were a median age of 67 years (range, 46-79 years). Donor types included matched unrelated donors (n=42; 78%), matched sibling donors (n=11; 20%), and mismatched unrelated donors (n=1; 2%). All HSCTs were conducted with a reduced-intensity conditioning regimen, grafts of peripheral blood stem cells, and standard GVHD prophylaxis with tacrolimus and methotrexate. The median follow-up was 18 months (range, 7-43 months). Among the 33 patients with AML included in the

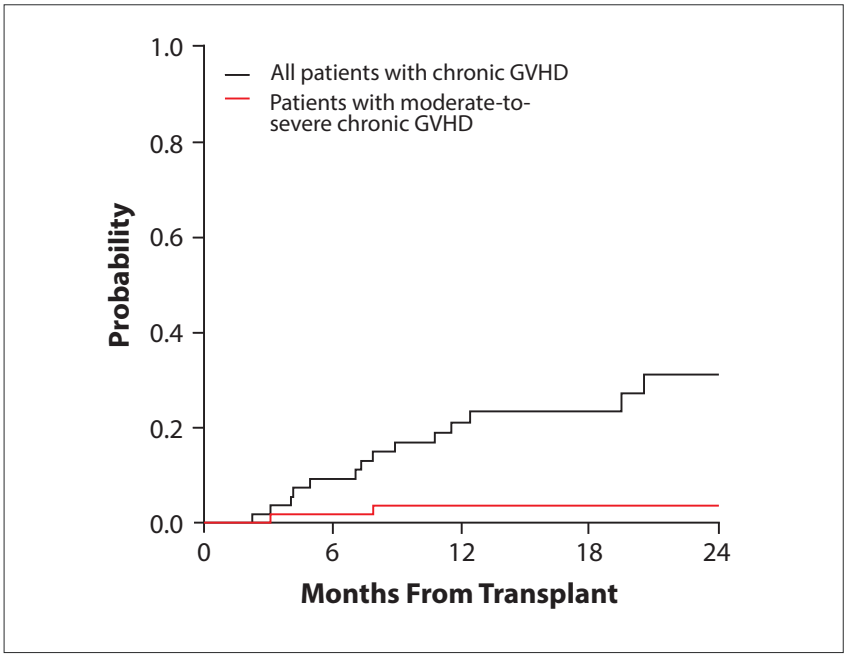

Figure 4. GVHD outcomes among patients treated with prolonged post-transplant ruxolitinib after allogeneic hematopoietic cell transplant. GVHD, graft-vs-host disease. Adapted from DeFilipp Z et al. Abstract 393. Presented at: Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; April 23-26, 2022; Salt Lake City, Utah.[1]

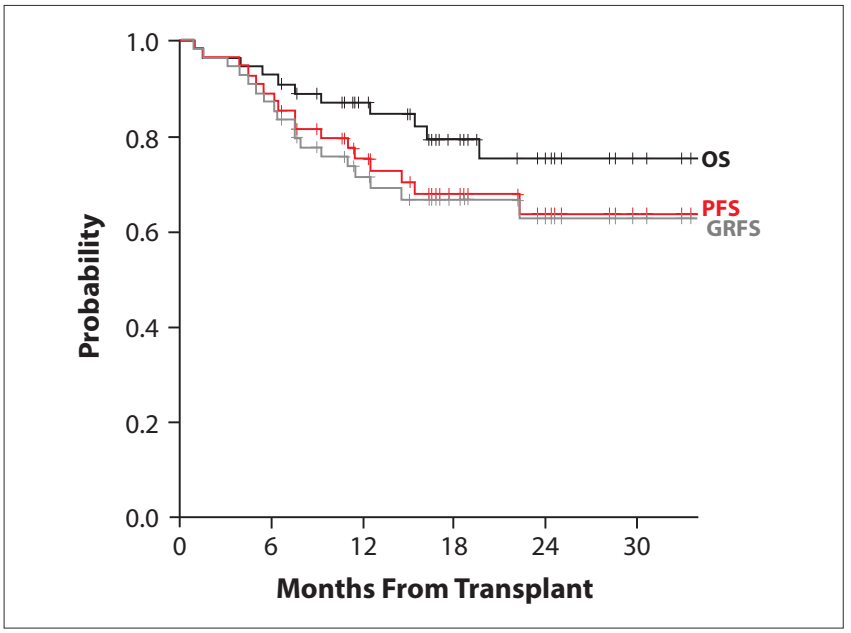

Figure 5. Survival outcomes among patients treated with prolonged post-transplant ruxolitinib after allogeneic hematopoietic cell transplant. GRFS, graft-vs-host disease–relapse-free survival; OS, overall survival; PFS, progression-free survival. Adapted from DeFilipp Z et al. Abstract 393. Presented at: Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; April 23-26, 2022; Salt Lake City, Utah.[1]

analysis, the median number of cycles of ruxolitinib received after HSCT was 19 (range, 1-24). Twenty-six patients (79%) were not receiving treatment. The 21 patients with myelofibrosis received a median of 12 cycles of ruxolitinib (range, 2-13) after allogeneic HSCT. The most common treatment-related AEs of grade 3 or higher were anemia (n=10), neutropenia (n=5), and thrombocytopenia (n=5).

Among all patients, the 6-month cumulative incidence of acute GVHD was 24% (95% CI, 14%-36%), and all cases were grade 2. In the study of patients with AML, 5 of the 6 cases of GVHD occurred before the initiation of ruxolitinib therapy. There were no cases of emergent grade 3 or grade 4 acute GVHD, including no reports of severe lower gastrointestinal tract GVHD. The 12-month incidence of all cases of chronic GVHD was 21% (95% CI, 11%-33%), and the 12-month incidence of moderate-to-severe chronic GVHD requiring systemic therapy was 3.8% (95% CI, 0.7%-12%; Figure 4).

The 18-month cumulative incidence of nonrelapse mortality was 8% (95% CI, 2.5%-18%), and only 1 death was attributed to GVHD. The 18-month cumulative incidence of disease relapse was 24% (95% CI, 13%-37%). The 18-month overall survival rate was 79% (95% CI, 64%-88%). At 18 months, the GVHD relapse–free survival rate was 67% (95% CI, 52%-78%; Figure 5).

ABSTRACT SUMMARY Patient-Reported Treatment Response in Chronic Graft-vs-Host Disease: Unique Dimension of Clinical Benefit Associated With Failure-Free Survival

A retrospective study evaluated patient-reported feedback to assess whether clinical benefits are adequately captured by standard measurements of treatment response in patients with chronic GVHD (Abstract 55). The analysis included 382 patients from 2 prospective, observational, multicenter studies. Patient and clinician responses were categorized as improved or not improved. At baseline, the most commonly involved organs included the skin (73.0%), mouth (60.2%), and eyes (53.8%). Chronic GVHD symptoms were moderate or severe in 89% of patients. At 6 months, patient-reporting tools showed an improvement in chronic GVHD in 71% of patients and no improvement in 29% of patients. There was a limited correlation between the patient-reported response compared with assessments from clinicians (kappa, 0.37) and criteria from the National Institutes of Health (NIH; kappa, 0.18). In a multivariate analysis, NIH responses in the eyes (*P*=.009), mouth (*P*=.01), and lungs (*P*=.03) were significantly associated with patient-reported responses. Patient-reported responses were also significantly associated with failure-free survival (*P*=.005).

References

1. ClinicalTrials.gov. Ruxolitinib + allogeneic stem cell transplantation in AML. https://clinicaltrials.gov/ct2/show/NCT03286530. Identifier: NCT03286530. Accessed May 22, 2022.
2. ClinicalTrials.gov. Ruxolitinib pre-, during- and post-HSCT for patients with primary or secondary myelofibrosis. https://clinicaltrials.gov/ct2/show/NCT03427866. Identifier: NCT03427866. Accessed May 22, 2022.
3. DeFilipp Z, Kim HT, Knight L, et al. Prolonged post-transplant ruxolitinib therapy is associated with protection from severe GVHD after allogeneic HCT. Presented at: the Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; April 23-26, 2022; Salt Lake City, Utah. Abstract 393.

Interim Analysis of T-Cell Specific Predictive Biomarkers of Graft-vs-Host Disease and Relapse Following Post-Transplant Cyclophosphamide Prophylaxis

A key feature of the pathogenesis of GVHD is the reactivity of donor T cells, which attack host tissues such as the gut, liver, and mucous membranes.[1] Biomarkers of T-cell activation are under investigation as potential predictors of acute GVHD. Investigators developed a preclinical model using nonconditioned, immunodeficient NBSGW mice to assess the ability of human T cells to cause GVHD.[2,3] Total mononuclear human bone marrow cells were transplanted into the mice at various doses. GVHD symptoms included lymphocyte infiltration of the liver, kidney, lung, and salivary glands, and the anticipated organ pathology. The mice who developed GVHD also showed decreased body weight. Not all mice who received the xenograft transplant developed GVHD; rather, development of GVHD was associated with the transplant dose, the inflammatory markers of the transplant recipient, and the type of graft. Hallmarks associated with the subsequent development of GVHD included proliferation of the human T cells during the first 1 to 3 weeks after transplant and an increase in the level of human interferon gamma in the plasma. Moreover, these markers of T-cell activation predicted the onset of GVHD up to 6 weeks prior to the development of signs and symptoms. Donor T cells were necessary and sufficient for the development of GVHD in this mouse model.

A clinical study conducted at a single center evaluated the characteristics of human T cells after allogeneic HSCT.[4] This prospective study enrolled patients with any hematologic malignancy, without regard to the conditioning regimen, the GVHD prophylaxis regimen, the graft source, or the type of HLA matching. However, patients were required to have received GVHD prophylaxis with cyclophosphamide after transplant. Starting on day 7 after allogeneic HSCT, blood samples were collected every week for 98 days. T-cell analysis included only cells that were CD45RO$^+$. Eleven metrics pertaining to T cells were evaluated for their ability to predict various patient outcomes, including relapse, acute GVHD of any grade, and acute GVHD of grade 2 or higher.

The investigators collected 417 blood samples from 35 patients during the first 100 days after allogeneic HSCT. Among the 34 patients who were included in the analysis, 5 patients (15%) had relapsed, 10 (29%) had not relapsed and did not have GVHD, 6 (18%) had grade 1 GVHD, and 13 (38%) had grade 2 to 4 GVHD.

Variations in the levels of CD3$^+$/CD45RO$^+$ cells are shown in Figure 6. Three T-cell characteristics were of particular interest. A low number of CD45RO$^+$ T cells was predictive of the likelihood of relapse (P=.026), but not the development of acute GVHD. A reduced proportion of regulatory T cells was predictive of relapse (P<.001), the development of acute GVHD of any grade (P=.048), and the development of GVHD of grade 2 or higher (P<.001). In blood samples taken between day 5 and day 22 after allogeneic HSCT, a higher proportion of CD4$^+$/CD8$^+$ T cells significantly correlated with any-grade acute GVHD (P=.003), as well as acute GVHD of grade 2 or higher (P=.025). Decreased expression of the T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory

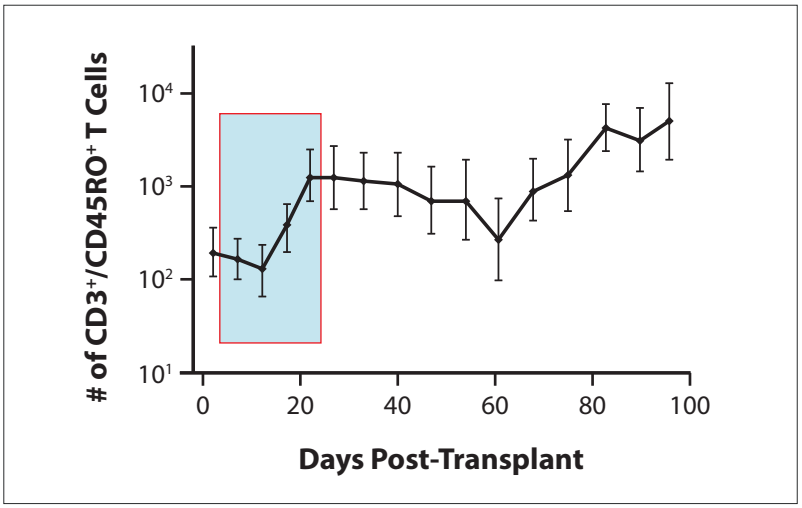

Figure 6. CD3$^+$/CD45RO$^+$ cells among patients who underwent allogeneic hematopoietic stem cell transplant in a study of predictive biomarkers of graft-vs-host disease and relapse after post-transplant cyclophosphamide prophylaxis. Adapted from Hess NJ et al. Abstract 6. Presented at: Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; April 23-26, 2022; Salt Lake City, Utah.[4]

motif domains was associated with the development of acute GVHD.

References

1. Jiang H, Fu D, Bidgoli A, Paczesny S. T cell subsets in graft versus host disease and graft versus tumor. *Front Immunol.* 2021;12:761448.
2. Hess NJ, Brown ME, Capitini CM. GVHD pathogenesis, prevention and treatment: lessons from humanized mouse transplant models. *Front Immunol.* 2021;12:723544.
3. Hess NJ, Hudson AW, Hematti P, Gumperz JE. Early T cell activation metrics predict graft-versus-host disease in a humanized mouse model of hematopoietic stem cell transplantation. *J Immunol.* 2020;205(1):272-281.
4. Hess NJ, Nadiminti K, Hematti P, Capitini CM. Interim analysis of T cell specific predictive biomarkers of graft-vs-host disease and relapse following post transplant cyclophosphamide prophylaxis. Presented at: the Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; April 23-26, 2022; Salt Lake City, Utah. Abstract 6.

Validation of Amphiregulin as a Monitoring Biomarker During Treatment of Life-Threatening Acute GVHD: A Secondary Analysis of 2 Prospective Clinical Trials

Up to half of patients who undergo allogeneic HSCT develop acute GVHD, which can be life-threatening.[1,2] Patient monitoring could be improved with a biomarker that predicts symptom severity. A phase 1 study investigated biomarker levels in the blood of patients with acute GVHD who received urinary-derived human chorionic gonadotropin (uhCG) plus epidermal growth factor (EGF) to enhance epithelial repair.[3] In patients whose GVHD responded to therapy, levels of plasma amphiregulin, a marker of tissue damage, decreased by 4.6-fold from baseline to day 28 of the study (*P*=.006). ST2 and REG3α have also been identified as potential biomarkers related to the severity of acute GVHD.[4]

Blood samples from 2 clinical trials, a trial from the University of Minnesota (UMN) and the REACH1 trial, were evaluated to determine the utility of amphiregulin, ST2, and REG3α as biomarkers of acute GVHD severity in patients who have undergone allogeneic HSCT.[5] Patients in the UMN study received uhCG/EGF, whereas those in the REACH1 study received ruxolitinib. Blood samples from both studies had been taken at baseline and on days 7, 14, 29, and 56. In the UMN study, plasma samples were evaluated with an enzyme-linked immunosorbent assay to measure levels of amphiregulin. Levels of ST2 and REG3α were measured using a bead-based multiplex assay. In the REACH1 study, levels of all 3 biomarkers were evaluated by a microfluidic immunoassay.

In the UMN study, the mean level of amphiregulin decreased by 3-fold from baseline to day 28 in patients who achieved a CR (*P*=.006). This level did not change in patients with a partial response (PR) or no response on day 28. From baseline to day 28, the level of ST2 decreased by 1.4-fold (*P*=.02), whereas the REG3α level did not decrease. Several biomarker cutoff levels were associated with a rapidly fatal course: higher than 212 pg/mL for amphiregulin (median survival, not reached vs 62 days; *P*=.006), higher than 292 ng/mL for ST2 (median survival, not reached vs 239 days; *P*<.001), and higher than 13.5 ng/mL for REG3α (median survival, not reached vs 416 days; *P*=.01). Based on a multivariate analysis, the factors associated with survival were the day 28 response (no response vs CR/PR; relative risk [RR], 4.94; *P*=.02) and the baseline amphiregulin level (>212 pg/mL; RR, 2.50; *P*=.03).

In the REACH1 study, the mean amphiregulin level decreased by 2.8-fold from baseline to day 56 in patients with a CR at day 28 (*P*=.007) and by 2.0-fold in patients with a PR at day 28 (*P*=.017). The level did not decrease in those with disease progression. As measured on day 56 vs baseline, the mean level of ST2 decreased by 2.2-fold (*P*=.021) in patients who achieved a CR by day 28. Levels of REG3α did not change significantly in any disease response cohort. The biomarker cutoff levels associated with a rapidly fatal course were higher than 336 pg/mL

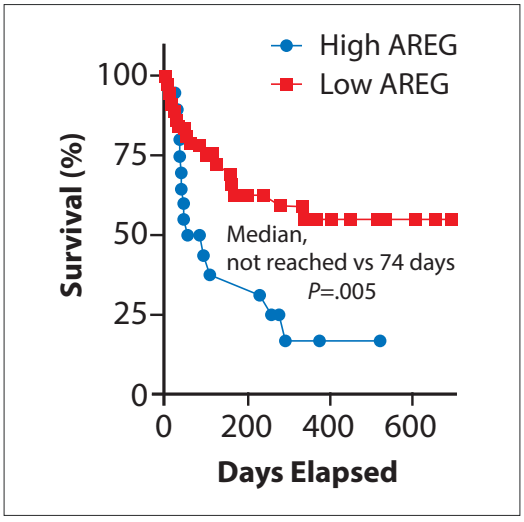

Figure 7. Survival according to high or low levels of AREG among patients treated with ruxolitinib in the REACH1 trial. AREG, amphiregulin. Adapted from Pratta M et al. Abstract 70. Presented at: Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; April 23-26, 2022; Salt Lake City, Utah.[5]

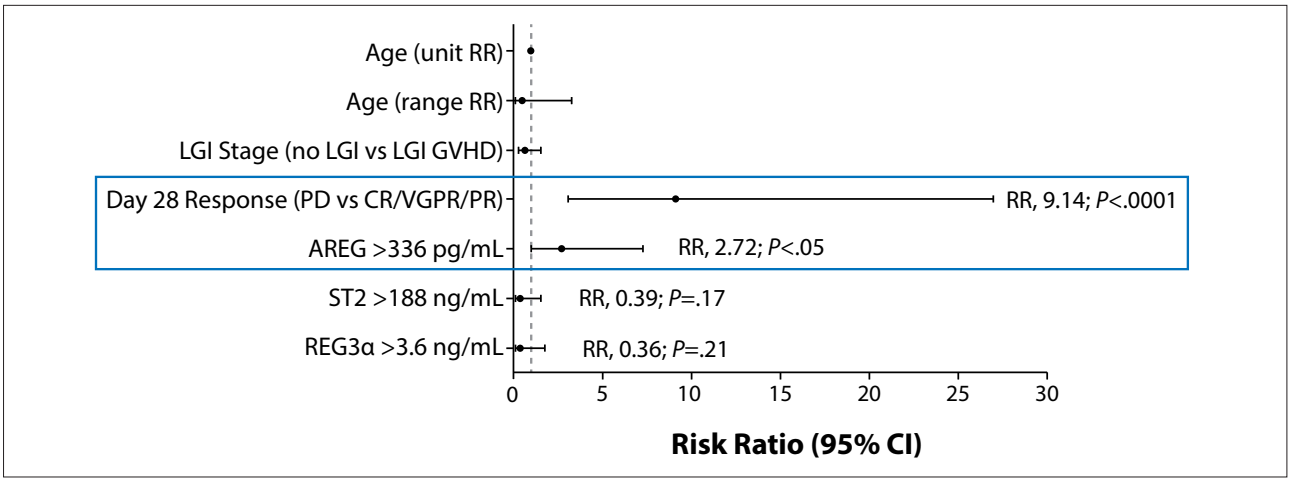

Figure 8. Results from a multivariate analysis for survival among patients treated with ruxolitinib in the REACH1 trial. Response at day 28 and level of AREG were independently associated with survival. A Cox proportional hazards model was used for this multivariate analysis. AREG, amphiregulin; CR, complete response; GVHD, graft-vs-host disease; LGI, lower gastrointestinal tract; PD, progressive disease; PR, partial response; RR, risk ratio; VGPR, very good partial response. Adapted from Pratta M et al. Abstract 70. Presented at: Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; April 23-26, 2022; Salt Lake City, Utah.[5]

for amphiregulin (median survival, not reached vs 74 days; *P*=.005; Figure 7), higher than 188 ng/mL for ST2 (*P*=.09), and higher than 3.6 ng/mL for REG3α (*P*=.3). Based on a multivariate analysis, factors independently associated with survival were the day 28 response (progressive disease vs CR/PR/very good PR; RR, 9.14; *P*<.0001) and the baseline amphiregulin level (>336 pg/mL; RR, 2.72; *P*<.05; Figure 8).

References

1. Nassereddine S, Rafei H, Elbahesh E, Tabbara I. Acute graft versus host disease: a comprehensive review. *Anticancer Res*. 2017;37(4):1547-1555.
2. Zeiser R, Blazar BR. Acute graft-versus-host disease—biologic process, prevention, and therapy. *N Engl J Med*. 2017;377(22):2167-2179.
3. Holtan SG, Hoeschen AL, Cao Q, et al. Facilitating resolution of life-threatening acute GVHD with human chorionic gonadotropin and epidermal growth factor. *Blood Adv*. 2020;4(7):1284-1295.
4. Major-Monfried H, Renteria AS, Pawarode A, et al. MAGIC biomarkers predict long-term outcomes for steroid-resistant acute GVHD. *Blood*. 2018;131(25):2846-2855.
5. Pratta M, Jurdi NE, Rashidi A, et al. Validation of amphiregulin as a monitoring biomarker during treatment of life-threatening acute GVHD: a secondary analysis of 2 prospective clinical trials. Presented at: the Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; April 23-26, 2022; Salt Lake City, Utah. Abstract 70.

Prospective Trial of Ibrutinib for the Treatment of Pediatric Chronic Graft-vs-Host Disease

No medications are approved by the FDA to treat patients with chronic GVHD who are younger than 12 years. The oral immunomodulatory drug ibrutinib inhibits Bruton tyrosine kinase, which mediates key functions of B cells. Preclinical studies have shown that ibrutinib interferes with the activity of interleukin-2–inducible T-cell kinase in T cells, thus attenuating key T-cell activities.[1-3] Ibrutinib is approved for the treatment of adults with chronic GVHD who received unsuccessful treatment with prior systemic therapy.[4,5]

The prospective, open-label, international phase 1/2 IMAGINE study evaluated ibrutinib in children with moderate-to-severe chronic GVHD.[6] Part A of the study enrolled patients ages 1 year to younger than 12 years who had received unsuccessful treatment with at least 1 prior line of systemic therapy. The daily dose of ibrutinib was initiated at 120 mg/m^2 (approximately half of the standard dose for adults) and was escalated to 240 mg/m^2 after 14 days in patients without grade 3 or higher toxicity. Patients in part B were ages 12 years to younger than 22 years and had newly diagnosed GVHD or had previously received unsuccessful treatment with at least 1 prior line of therapy. These patients received once-daily ibrutinib at a dose of 420 mg. Ibrutinib was available in a pill form or as a liquid suspension. Primary endpoints included pharmacokinetics and safety.

The study enrolled 12 patients into part A and 47 into part B. The median follow-up was 20 months. In the overall study population of 59 patients, 12 patients were treatment-naive. At baseline, the most common site of GVHD involvement was the skin (Figure 9). The median time from the initial diagnosis of chronic GVHD to study enrollment was 12 months (range, 0.1-163 months). Previously treated patients had received a median

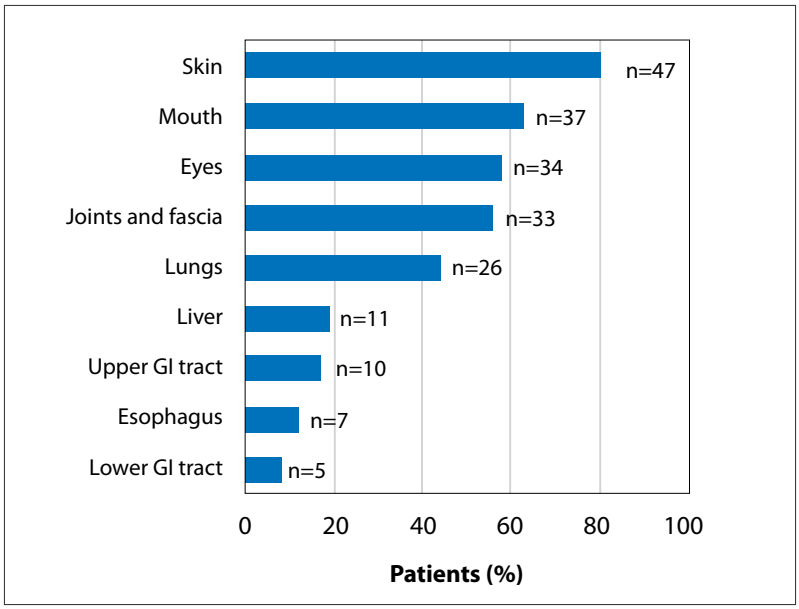

Figure 9. Organ involvement in the phase 1/2 IMAGINE study, which evaluated ibrutinib in children with moderate-to-severe chronic graft-vs-host disease. GI, gastrointestinal. Adapted from Carpenter PA et al. Abstract 126. Presented at: Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; April 23-26, 2022; Salt Lake City, Utah.[6]

of 2 prior therapies for their chronic GVHD (range, 1-12 prior therapies). Plasma-concentration profiles in these young patients were comparable with those of adults with chronic GVHD who received ibrutinib at a dose of 420 mg once daily. This finding resulted in a recommended pediatric equivalent dose of 240 mg/m^2 once daily for patients younger than 12 years and of 420 mg once daily for patients ages 12 years or older.

The objective response rate (ORR) was 78%, with 5 CRs. At 20 weeks, sustained responses were observed in 70% of treatment-naive patients and 58% of previously treated patients who responded to ibrutinib therapy. The response duration was at least 1 year in 60% of treatment-naive patients and in 58% of previously treated patients.

The safety profile was consistent with prior reports of ibrutinib therapy in adult patients with GVHD. A treatment-associated AE of grade 3 or higher was reported in 64% of patients, and 24% experienced an AE that required discontinuation of study treatment. The most common AE of grade 3 or higher was pyrexia (8.5%), followed by neutropenia, stomatitis, hypoxia, and osteonecrosis (each reported in 6.8% of patients). Any-grade stomatitis was observed in 17% of patients. One patient died from causes that were potentially attributable to ibrutinib.

References

1. De Novellis D, Cacace F, Caprioli V, Wierda WG, Mahadeo KM, Tambaro FP. The TKI era in chronic leukemias. *Pharmaceutics*. 2021;13(12):2021.
2. Dubovsky JA, Beckwith KA, Natarajan G, et al. Ibrutinib is an irreversible molecular inhibitor of ITK driving a Th1-selective pressure in T lymphocytes. *Blood*. 2013;122(15):2539-2549.
3. Shirley M. Bruton tyrosine kinase inhibitors in B-cell malignancies: their use and differential features. *Target Oncol*. 2022;17(1):69-84.
4. Miklos D, Cutler CS, Arora M, et al. Ibrutinib for chronic graft-versus-host disease after failure of prior therapy. *Blood*. 2017;130(21):2243-2250.
5. Imbruvica [package insert]. Pharmacyclics, LLC; South San Francisco, California; 2022.
6. Carpenter PA, Kang HJ, Zecca M, et al. Prospective trial of ibrutinib for the treatment of pediatric chronic graft-versus-host disease. Presented at: the Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; April 23-26, 2022; Salt Lake City, Utah. Abstract 126.

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

Abatacept is a recombinant protein that consists of the extracellular domain of the human cytotoxic T lymphocyte–associated antigen fused to a modified Fc domain of human immunoglobulin G1.[1] In the placebo-controlled phase 2 ABA2 trial, abatacept was evaluated in combination with calcineurin inhibition and methotrexate for the prevention of acute GVHD among adults and children who had undergone an allogeneic HSCT with an unrelated donor.[2] The addition of abatacept reduced the incidence of severe, acute GVHD compared with placebo and improved the rate of severe, acute GVHD–free survival.

A phase 1 trial evaluated abatacept for the treatment of patients with corticosteroid-refractory chronic GVHD.[3] The treatment was generally well tolerated, and 44% of patients achieved a PR. These findings led to a phase 2 clinical study that evaluated the efficacy and safety of abatacept in patients with corticosteroid-refractory

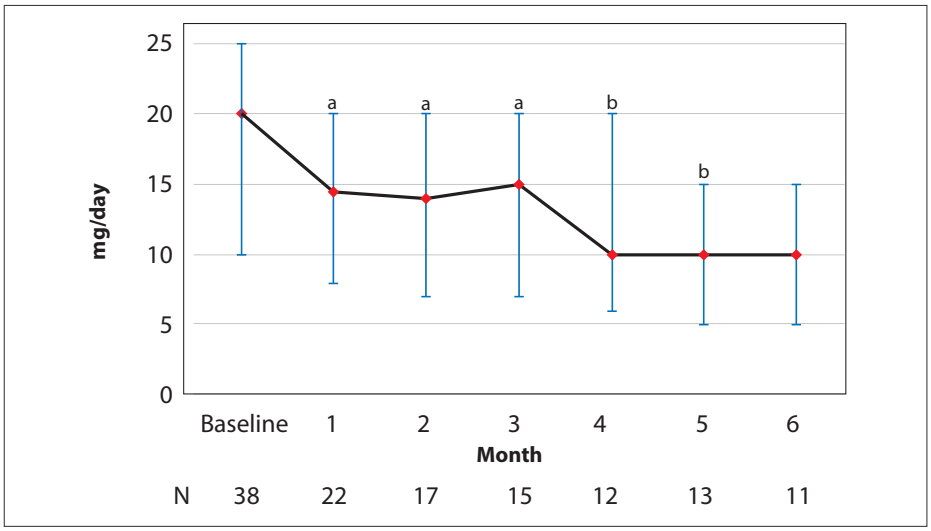

Figure 10. Treatment with abatacept led to a durable reduction in the dose of prednisone in a phase 2 trial of patients with corticosteroid-refractory chronic graft-vs-host disease. [a]*P*<.01; [b]*P*<.05. Adapted from Koshy AG et al. Abstract 32. Presented at: Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; April 23-26, 2022; Salt Lake City, Utah.[4]

chronic GVHD.[4] Eligible patients had undergone an allogeneic bone marrow or stem cell transplant at least 100 days prior to study enrollment. All patients had received a stable immunosuppressive regimen for 2 weeks before study enrollment. Abatacept was administered at a dose of 10 mg/kg every 2 weeks, for a total of 3 doses. After a 1-month interval, the patients received abatacept at 10 mg/kg every 4 weeks for 3 doses. Clinical responses were assessed 1 month after the sixth dose of abatacept. Patients who achieved a CR or PR were eligible to receive up to 12 additional doses of abatacept, administered at 1-month intervals.

Among the 39 enrolled patients, 4 (10.3%) had received a bone marrow transplant and 35 (89.7%) had received a stem cell transplant. The conditioning regimen was myeloablative in 61.5% and nonmyeloablative in 35.9%. The HLA status was matched, unrelated in 56% of patients; matched, related in 38%; mismatched, related in 2.6%; and mismatched, unrelated in 2.6%. The patients had received a median of 5 previous treatments for chronic GVHD (range, 1-11 prior treatments). The symptoms of chronic GVHD were moderate in 18 patients and severe in 21 patients. Symptoms most commonly manifested in the skin (84%), joints (92%), eyes (72%), and lungs (56%).

The ORR was 58%, with no CRs. Responses most often occurred in the lungs (36%), eyes (25%), skin (22%), mouth (22%), and joints (22%). Disease progression occurred in 33% of patients. Treatment with abatacept led to durable reductions in the prednisone dose (*P*<.05; Figure 10).

Abatacept was generally well tolerated. Serious AEs possibly related to treatment with abatacept included grade 3 lung infection (2 events) and grade 4 lung infection (1 event). In addition, a single patient experienced grade 4 hemolysis, respiratory failure, and liver failure. This patient's eventual death was attributed to concurrent infection with herpes simplex virus.

ABSTRACT SUMMARY 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

A phase 1/2 trial evaluated axatilimab for the treatment of active chronic GVHD in patients ages 6 years and older who had received unsuccessful treatment with at least 2 prior systemic therapies (Abstract 35). The trial enrolled 40 patients. At baseline, the patients had received a median of 4 prior lines of therapy (range, 1-11). The median number of involved organs was 4 (range, 1-9). The ORR was 68%, with responses observed in the joints and fascia. Improvements in severe skin sclerosis were observed in 4 patients. Based on the Lee symptom scale, 53% of patients reported an improvement in quality of life after treatment with axatilimab. Reasons for treatment discontinuation included disease progression (18%), physician decision (15%), AEs (10%), and patient decision (5%). Thirteen percent of patients experienced an AE of at least grade 3. No cases of viral reactivation were observed.

References

1. Blazar BR, Taylor PA, Linsley PS, Vallera DA. In vivo blockade of CD28/CTLA4: B7/BB1 interaction with CTLA4-Ig reduces lethal murine graft-versus-host disease across the major histocompatibility complex barrier in mice. *Blood*. 1994;83(12):3815-3825.
2. Watkins B, Qayed M, McCracken C, et al. Phase II trial of costimulation blockade with abatacept for prevention of acute GVHD. *J Clin Oncol*. 2021;39(17):1865-1877.
3. Nahas MR, Soiffer RJ, Kim HT, et al. Phase 1 clinical trial evaluating abatacept in patients with steroid-refractory chronic graft-versus-host disease. *Blood*. 2018;131(25):2836-2845.
4. Koshy AG, Kim HT, Stroopinsky D, et al. Phase II clinical trial of abatacept for steroid-refractory chronic graft versus host disease. Presented at: the Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; April 23-26, 2022; Salt Lake City, Utah. Abstract 32.

Highlights in Graft-vs-Host Disease From the 2022 Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR: Commentary

Yi-Bin Chen, MD

Presentations on graft-vs-host disease (GVHD) at the Tandem Meetings | Transplantation & Cellular Therapy Meetings of the American Society for Transplantation and the Cellular Therapy (ASTCT) and Center for International Blood and Marrow Transplant Research (CIBMTR) provided important new insights regarding prevention and treatment of this disease. Studies presented included evaluations of treatments such as urinary-derived human chorionic gonadotropin (uhCG) plus epidermal growth factor (EGF), belimumab, abatacept, axatilimab, ibrutinib, and ruxolitinib in systemic and topical formulations. Data were also presented for amphiregulin as a monitoring biomarker in patients treated for acute GVHD and for assessment of patient-reported response as an endpoint in chronic GVHD trials.

Acute GVHD

Dr Nicholas Hess presented data from an interim analysis that evaluated T cell–specific biomarkers after post-transplant cyclophosphamide (PTCy)-based transplants, with a focus on disease relapse and acute GVHD.[1] For years, a goal in the transplant community has been to develop noninvasive predictive biomarkers that can help guide management. Many of the complications that occur after transplant are immunologically mediated, and the cascade for these complications starts weeks before the frank clinical manifestations appear. Knowledge of the immunologic processes that precede clinical manifestations might allow clinicians to intervene preemptively and prevent them. Although there are commercially available noninvasive biomarkers in use for risk stratification of acute GVHD, there are no data to suggest that clinical decisions should be based on the measurement of these biomarkers, although ongoing clinical trials are evaluating this issue.

Dr Hess and colleagues had previously performed experiments in a xenogeneic mouse transplant model, which suggested that certain T-cell metrics could predict clinical outcomes.[2] This finding is intuitive because T cells are thought to be the primary driver for acute GVHD, and they also contribute to preventing relapse through a graft-vs-leukemia mechanism. This analysis enrolled 35 patients who received post-transplant cyclophosphamide-based prophylaxis for GVHD at the University of Wisconsin. The patients had weekly samples collected prospectively for the first 98 days. The investigators analyzed specific T-cell subsets through immunophenotyping. It should be noted that the patients were heterogeneous in terms of their underlying disease, conditioning regimens, and donor types, and the analysis was performed on fresh samples.

Dr Hess and colleagues found that increased numbers of $CD3^+$/$CD45RO^+$ cells were associated with the subsequent development of grade 3 to 4 acute GVHD.[1] Lower numbers of these cells were associated with a higher incidence of disease relapse. It should be emphasized that these associations were found early, in the first month after transplant, when the immune system is just beginning to reconstitute. The study also found that higher early numbers of regulatory T cells predicted for a lower risk of GVHD, which confirms previous findings.[3] Dr Hess also discussed a unique population of so-called "double-positive cells," which are T cells that express both CD4 and CD8. Interestingly, this population was observed to increase approximately 2 to 3 weeks before the clinical presentation of acute GVHD. These double-positive cells have not been a focus of interest in the past, and some researchers have even ignored them as an artifact of analysis. Based on these findings, however, it appears that the role of these "double-positive" T cells that express both CD4 and CD8 merits further study. The investigators also analyzed expression of costimulatory molecules on specific T-cell subsets, showing that expression of certain molecules correlated with certain outcomes.

Overall, this interesting analysis evaluated specific T-cell metrics in a transplant platform that is becoming increasingly more common and contributes to our understanding of the mechanisms at play after PTCy. Previous studies have also explored this concept.[4,5] The findings from this analysis merit further study in a larger number of patients to determine if T-cell immunophenotyping can not only add to our understanding of immune reconstitution after PTCy, but also influence management of patients in real time.

Dr Shernan Holtan and colleagues presented results from a phase 2 trial that evaluated uhCG/EGF as an adjunct treatment for high-risk acute GVHD.[6] This product is mainly used to induce ovulation and manage other fertility issues.[7] It was chosen by the investigators for this application because human chorionic gonadotropin helps to promote immune tolerance, as evidenced in the natural relationship of the maternal-fetal chimera. EGF is thought to promote healing or

organ resilience, specifically enhanced epithelialization of the gastrointestinal mucosa. Traditionally, treatment for advanced acute GVHD focused on agents with broad immunosuppression. Newer areas of focus in GVHD treatment now include immunologic tolerance, tissue repair, and organ resiliency. It is important to note that uhCG/EGF has been studied as an adjunct to standard immunosuppression, and is not a treatment unto itself.

This study enrolled 44 patients. Twenty-two patients with Minnesota high-risk disease treated in the first-line setting received uhCG/EGF plus corticosteroids. Another cohort of 22 patients with corticosteroid-refractory disease received uhCG/EGF plus their physician's choice of standard-of-care second-line therapy. The dosing was administered subcutaneously, and the regimen varied according to the indication.

In the first-line setting, the overall response rate by day 28 was 64%. All of the observed responses were complete responses, which is fairly impressive. In the second-line setting, the overall response rate was 73%, with a complete response rate of 50%. Although these results are compelling, it is important to again emphasize that uhCG/EGF was administered as an adjunct to standard-of-care immunosuppressive therapy. A limitation to the interpretation of outcomes in the second-line cohort is that various therapies were chosen for second-line therapy. From a safety perspective, there were some cases of injection-site reactions, headaches, and lower-extremity edema. There was 1 dose-limiting toxicity, which occurred in a patient who developed a cerebral venous sinus thrombosis.

Overall, this study provides compelling evidence for the use of uhCG/EGF as an adjunct in the treatment of acute GVHD. Interest in this agent is driven not only by the novel mechanism of action, but also by the tolerable toxicity profile. Larger, definitive trials will be needed to determine whether uhCG/EGF improves outcomes. A prospective randomized study comparing a standard second-line therapy with placebo vs the same treatment with uhCG/EGF would be very helpful to truly assess benefit.

Dr Holtan also presented data from a secondary analysis of 2 prospective trials that evaluated the use of the molecule amphiregulin as a biomarker for monitoring acute GVHD.[8] Amphiregulin is a ligand of the EGF receptor, which is expressed in many tissues, including the intestine, and is thought to be released at times of injury. A prior study from investigators at the University of Minnesota using uhCG/EGF as an adjunct for GVHD treatment had suggested that amphiregulin has potential use as a monitoring biomarker.[9] The current study was undertaken to validate amphiregulin in a larger cohort of patients treated with uhCG/EGF, as well as in patients in the REACH1 trial who received ruxolitinib for the treatment of corticosteroid-refractory acute GVHD.[10] There were 51 samples from patients treated with uhCG/EGF and 60 samples from patients treated with ruxolitinib in the REACH1 study. This analysis found that both trials showed a significant decrease in amphiregulin from day 0 to day 56 among patients with a complete response at day 28.

The investigators then compared the utility of amphiregulin as a biomarker with plasma levels of ST2 and REG3α, which are well-described, commercially available prognostic biomarkers for acute GVHD.[8] In the study from the University of Minnesota, baseline levels of ST2 and REG3α correlated with clinical response, whereas baseline levels of amphiregulin did not. Among patients with a complete response at day 28, amphiregulin levels at day 56 were much lower relative to baseline and had a stronger correlation to clinical response than levels of ST2 or REG3α. In the REACH1 trial, baseline levels of amphiregulin and ST2 correlated with response to ruxolitinib, whereas baseline levels of REG3α did not. Among patients who had a complete response at day 28 with ruxolitinib, lower levels of amphiregulin at day 56 had a stronger correlation to overall results than levels of ST2 or REG3α.

It is important to note that amphiregulin was not compared with the Mount Sinai Acute GVHD International Consortium (MAGIC) algorithm probability (MAP), which is the best-studied commercially available algorithm that incorporates measurements of both REG3α and ST2, rather than the raw individual levels.[11] It should also be mentioned that the change from baseline to day 56 levels correlated with clinical response at day 28. Therefore, the utility of measuring these biomarkers in real time is unclear. Monitoring might help to refine the assessment of

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 uhCG/EGF in 22 high-risk patients who had not received prior treatment and 22 patients in need of second-line therapy for life-threatening, acute GVHD (Abstract 68). Patients with a CR or PR after initial therapy were eligible for maintenance therapy. At enrollment, 75% of patients had grade 3/4 GVHD, and 52% had grade 3/4 symptoms of the lower gastrointestinal tract. The ORR was 68% among all patients (CRs in 57% and PRs in 11%), 64% among high-risk patients (all CRs), and 73% among previously treated patients (CRs in 50% and PRs in 23%). The 2-year survival rate was 67% in patients who responded to treatment vs 12% in those who did not (P<.01). After a median follow-up of 17 months, 52% of patients had died. These deaths were attributable to GVHD (20.5%), disease relapse (20.5%), infection (6.8%), and organ damage (4.5%).

prognosis moving forward at day 56, or it might be more useful for predicting flares of GVHD from day 28 through day 56. Overall, these interesting findings support the further study of amphiregulin as another potential biomarker for acute GVHD. Moving forward, amphiregulin should be compared with MAP or even incorporated into the algorithm as a third biomarker to see if it is better able to refine the prognostic utility.

Prevention of Chronic GVHD

Traditionally, studies of GVHD prevention focused mostly on acute GVHD, given its historical effect on nonrelapse mortality. More recently, studies have begun to focus specifically on the prevention of chronic GVHD. Some of these trials have explored whether intervention after engraftment could potentially mitigate the risk for chronic GVHD. Throughout the past decade, data have indicated a clear role for B cells in the pathophysiology of chronic GVHD, which has led to the use of therapies that target B cells, such as rituximab and ibrutinib.[12] Ibrutinib was the first of these agents to receive approval from the US Food and Drug Administration (FDA) for the treatment of corticosteroid-refractory chronic GVHD. In addition, studies have shown that levels of B-cell–activating factor (BAFF) are higher in patients with significant chronic GVHD.[13] These high levels of BAFF are thought to promote B-cell survival and to increase production of alloreactive antibodies, contributing to the pathogenesis of chronic GVHD in some patients.

Belimumab is a monoclonal antibody that targets BAFF and inhibits its interaction with cell-surface receptors. Belimumab is approved by the FDA for the treatment of lupus and active lupus nephritis. Dr Iskra Pusic and colleagues presented the results of a phase 1 investigator-initiated trial prompted by the hypothesis that targeting BAFF with belimumab early after transplant might decrease the incidence of chronic GVHD.[14] The presentation included results for the first 9 participants enrolled in the trial. All patients had received peripheral blood stem cell grafts, with a variety of conditioning regimens. Most patients received tacrolimus-based prophylaxis, including 7 who also received antithymocyte globulin (ATG), and 1 patient received post-transplant cyclophosphamide. Treatment with belimumab began 50 to 80 days after transplant and was administered every other week for 3 doses, followed by every 4 weeks for 4 doses, for a total of 7 doses.

From a safety perspective, no grade 3 or higher adverse events attributable to treatment were observed. Among the 9 patients, 8 received all 7 planned doses of belimumab. One patient, who developed thrombocytopenia and relapsed disease, received only 3 doses. Importantly, there were no reports of infusion reactions or cytopenias considered related to belimumab. At the time of the presentation, 5 patients were alive and not receiving any immunosuppressive therapy. Two patients developed chronic GVHD: 1 patient with overlap disease and 1 patient with classic severe multiorgan chronic GVHD. There did not appear to be any excess infections in this small cohort. Correlative analyses showed delayed B-cell reconstitution in all patients, consistent with the known mechanism of action of belimumab.

Overall, belimumab appeared to be safe and well tolerated when administered early after hematopoietic cell transplant (HCT). With the very small number of patients in this study, it is impossible to know if treatment with belimumab had an impact on subsequent development of chronic GVHD, especially because the majority of patients also received ATG as part of GVHD prophylaxis. Larger studies in more homogeneous populations, perhaps without the use of ATG, would be crucial to determine whether this strategy is worth exploring.

Janus kinase (JAK) inhibitors are now approved for the treatment of corticosteroid-refractory acute and chronic GVHD. There is interest in using JAK inhibitors in other phases of GVHD treatment, specifically as first-line therapy or even as prevention. Dr Zachariah DeFilipp and colleagues are conducting two phase 2 investigator-initiated studies that introduce ruxolitinib early after the transplant course for patients with either AML or myelofibrosis (MF).[15,16] Dr DeFilipp presented results from an unplanned interim analysis that included participants from both of these studies to describe the incidence of chronic GVHD when initiating ruxolitinib early after transplant and continuing treatment for months afterwards.[17] The analysis provided data for 54 patients: 33 with AML and 21 with MF. All patients received ruxolitinib early after transplant; patients with MF actually started treatment during conditioning therapy and continued throughout the peri-HCT period. Treatment with ruxolitinib continued for 2 years in the AML study and for 1 year in the MF study. The transplants used conventionally fully matched donors, with related or unrelated peripheral blood stem-cell grafts. The patients received reduced-intensity conditioning regimens, as well as standard tacrolimus and methotrexate GVHD prophylaxis.

The median follow-up for survivors was 18 months. Ruxolitinib was well tolerated and feasible for administration early after HCT. As expected, some patients developed cytopenias, specifically anemia and thrombocytopenia, consistent with the known adverse event profile of ruxolitinib. The 6-month cumulative incidence of grade 2 to 4 acute GVHD was 24%; all cases were grade 2. The 12-month cumulative incidence of all cases of chronic GVHD was 21%. Most notably, the incidence of moderate-to-severe chronic GVHD that required systemic therapy was 3.8%, an impressively low figure. No excess

opportunistic infections or relapses were observed. These compelling data have led to much excitement in the field, where there was already strong enthusiasm for JAK inhibitors and their activity in acute and chronic GVHD. Larger, formal, prospective randomized trials are needed with JAK inhibitors paired with standard GVHD prevention to see if progress can be made.

Treatment of Chronic GVHD

Abatacept, in combination with tacrolimus and methotrexate, was recently approved for the prevention of GVHD in patients undergoing unrelated donor transplants. Abatacept is a recombinant fusion protein that consists of the extracellular domain of CTLA-4 fused to the modified Fc region of human immunoglobulin G1, which binds to CD80 and CD86. Through this mechanism, abatacept inhibits CD28-mediated T-cell activation. In a prior phase 1 trial evaluating abatacept for the treatment of corticosteroid-refractory chronic GVHD, the overall response rate was 44%.[18]

Dr Anita Koshy and colleagues presented the interim results of a phase 2 trial evaluating the efficacy of abatacept for the treatment of corticosteroid-refractory chronic GVHD.[19] Abatacept was administered at a dose of 10 mg/kg every other week for 3 doses followed by 10 mg/kg every 4 weeks for 3 doses, for a total of 6 doses. Responders were able to receive long-term maintenance therapy. The trial enrolled and treated 39 patients with heterogeneous transplant platforms, donor types, conditioning regimens, and underlying diseases, but all patients had corticosteroid-refractory chronic GVHD, with a median number of 4 organs involved and a median of 5 prior lines of therapy.

The overall response rate was 58%, which consisted entirely of partial responses, which is not surprising in a refractory chronic GVHD population. Responses were observed in all of the organs involved. Interestingly, an improvement was seen in 36% of patients with pulmonary involvement, which is notoriously difficult to treat. Worrisomely, there were 9 cases of neutropenia, including two grade 3 events and two grade 4 events. If treating with abatacept, physicians should remain alert for neutropenia, given the fragile immunologic status of these patients. Larger trials are needed, as are correlative immunologic studies to understand the mechanism of action, but abatacept appears to be another promising treatment for corticosteroid-refractory chronic GVHD.

The pathologic hallmark of chronic GVHD is fibrosis or scarring.[20] Scleroderma and bronchiolitis obliterans syndrome are considered to be the most difficult-to-treat clinical manifestations of chronic GVHD, and are especially fibrotic in nature. Axatilimab is a humanized monoclonal antibody that targets the colony-stimulating factor 1 receptor (CSF1R) on activated macrophages, which are thought to play a crucial role in the fibrotic process.[21,22] Dr Carrie Kitko and colleagues presented the preliminary results of a phase 1/2 study evaluating axatilimab for the treatment of corticosteroid-refractory chronic GVHD.[22] Participants enrolled were ages 6 years or older and had received unsuccessful treatment with 2 or more lines of therapy. A phase 1 dose-finding part was followed by a phase 2 expansion phase in which patients received 1 mg/kg every other week. A total of 40 patients were treated: 17 in the phase 1 portion and 23 in the phase 2 portion. Patients had received a median of 4 prior lines of therapy for chronic GVHD; several had already received ruxolitinib, belumosudil, or ibrutinib.

From a safety standpoint, only 13% of patients reported grade 3 or higher adverse events, which appeared to be dose-dependent. The notable events included elevations in liver function tests, creatinine kinase, and lipase, as well as periorbital edema. The elevation in liver function tests is thought to be an on-target effect of the expression of CSF1R on the Kupffer cells in the liver. It is important to mention that there were no cases of end organ damage, and full reversibility of liver enzymes was observed once the agent was stopped.

Treatment with axatilimab led to an overall best response rate of 68%, with a median time of 1 month to response. The majority of the responses were partial remissions, as would be expected in this heavily treated population. There were notable improvements in several patients with cutaneous scleroderma and bronchiolitis obliterans syndrome. A significant improvement in the Lee Symptom Scale, the best patient-reported outcome scale to help validate responses in chronic GVHD, was reported in 53% of patients. Among patients with scleroderma that responded to treatment, correlative studies appeared to show tissue-macrophage depletion, as well as reduction in levels of transforming growth factor β consistent with the hypothetical mechanism of action. These findings are exciting for the field and build momentum for the ongoing AGAVE-201 study, which is a pivotal trial evaluating 3 dosing schedules of axatilimab in the treatment of chronic GVHD.[23]

In 2017, ibrutinib was the first agent approved for the treatment of adults with chronic GVHD who had received at least 1 prior unsuccessful systemic therapy. The real-world experience of ibrutinib in this setting has not been as impressive, with fewer responses and more adverse events compared with the reported clinical trial data.[24] Dr Paul Carpenter presented the results of a multicenter, collaborative phase 1/2 trial of ibrutinib among pediatric patients with moderate-to-severe chronic GVHD.[25] Part A evaluated ibrutinib in 12 patients ages 1 year to younger than 12 years who had received unsuccessful treatment with at least 1 line of systemic therapy. Part B evaluated ibrutinib among 47

patients ages 12 years to younger than 22 years. Part A used weight-based dosing, which began at a lower dose of 120 mg/m^2 and then escalated to 240 mg/m^2, if tolerated, after 2 weeks. The weight-based dosing was thought to approximate the flat-based dose used in adults. Part B used a standard flat dose.

In both parts A and B, the best overall response rate was 78%, specifically 83% as first-line therapy and 77% in the relapsed/refractory population. Importantly, the median duration of remission has not been reached thus far, suggesting a durability to these clinical responses. Adverse events led 24% of patients to discontinue ibrutinib, which is a higher rate than that seen in adults. In younger patients, the plasma concentration of ibrutinib achieved with the lower doses was similar to that seen in adults, suggesting that the chosen doses were appropriate.

Overall, this study showed higher response rates for ibrutinib than those described in adults, in both clinical trials and real-world experience. These results merit further study of ibrutinib in larger pediatric populations for confirmation and to hopefully add another treatment option for these patients.

Dr Alina Markova and colleagues presented findings from 2 partner abstracts revolving around the use of topical ruxolitinib for the treatment of cutaneous chronic GVHD.[26,27] Multiple corticosteroid formulations, topical tacrolimus, and other supportive creams are commonly used for chronic GVHD, yet none are approved in this setting by the FDA. Topical ruxolitinib was approved for the treatment of atopic dermatitis in 2021, and there is much enthusiasm in the field for the use of topical ruxolitinib for cutaneous GVHD, given the success with systemic ruxolitinib. Topical ruxolitinib is attractive because it has less toxicity than topical corticosteroids and is thought to spare cutaneous stem cells.

The first abstract presented clinical findings from a randomized phase 2 trial comparing topical ruxolitinib vs a vehicle cream in patients with chronic cutaneous GVHD who did not have deep sclerotic changes.[26] The study was double-blinded. For each patient, topical ruxolitinib was applied to one side of the body, and a vehicle cream was applied to the contralateral side. The primary endpoint of the study was day 28 involvement as measured by body surface area, comparing one side of the body to the other. The secondary endpoints were findings from 2 instruments measuring skin condition: the Physician's Global Assessment and the Composite Assessment of Indexed Lesion Severity, which is a tool used to measure involvement in cutaneous T-cell lymphoma.

This trial enrolled 13 patients. Most participants had moderate-to-severe disease, and they had received multiple ineffective systemic and topical therapies. The overall results showed a trend toward improvement in involved body surface area at day 28 on the side treated with ruxolitinib, although there were improvements observed in both treatment arms.[26] Treatment with topical ruxolitinib significantly improved scores in the Physician's Global Assessment and the Composite Assessment of Indexed Lesion Severity. One interesting finding mentioned in the presentation was that some patients who were receiving systemic ruxolitinib had improvements in response to topical ruxolitinib as well. These preliminary findings suggest that topical ruxolitinib may have a role in the treatment of chronic cutaneous GVHD and raise the question of how to best design a study to adequately measure the impact of topical ruxolitinib to gain regulatory approval and access for our patients.

A second abstract provided information about the genomic characterization of skin samples from patients treated in this study.[27] The investigators analyzed pairs of samples from the skin at day 28. Through RNA-sequencing technology, they then compared gene expression profiles of different populations. First, the investigators compared samples of skin treated with ruxolitinib vs the vehicle cream taken from the same patient. The comparison identified 310 differentially expressed genes, with the most disparate involved in keratinization and Th1/Th2 differentiation. The investigators then compared genomic expression of 8 patients who responded to topical ruxolitinib vs 3 patients who did not respond. This analysis identified 383 differentially expressed genes, with a heat-map analysis showing a characteristic gene profile that was representative of a signature associated with response to ruxolitinib.

Overall, the findings of this small correlative study were interesting and offer potential insight into the mechanism of response to ruxolitinib and whether there may be biomarkers predictive of response that can help guide therapy. To better understand these results, further larger studies are needed that incorporate more controls for gene expression analysis, such as pretreatment baseline samples and samples that were not treated with a vehicle cream.

Historically, clinical trials in chronic GVHD have been difficult to conduct. Chronic GVHD patients represent a heterogeneous population in terms of number and specific organ involvement, among other factors. Response criteria developed by the National Institutes of Health (NIH) have helped improve communication and conduct of clinical trials. However, the criteria are far from perfect, and the introduction of patient-reported outcomes into clinical trials of chronic GVHD is meant to help validate the meaningfulness of certain responses. Modern trials in chronic GVHD are now all using patient-reported outcomes as a standard measure of effect.

Dr Annie Im and colleagues performed an interesting analysis of a specific patient-reported outcome: patient-reported response for chronic GVHD.[28] The aim of the study was to help validate the meaningfulness of a response in chronic GVHD, particularly in cases when formal criteria might not indicate a clinical response. The investigators attempted to correlate

patient assessment of response to treatment with various standard patient-reported outcomes, as well as chronic GVHD symptom measures and organ response. The analysis included 382 patients enrolled in 2 prospective observational studies from the Chronic Graft Versus Host Disease Consortium.

The findings showed that patient-reported response in chronic GVHD had a limited correlation to response as assessed by the physician or with formal NIH response criteria. It is fascinating to learn that what a patient considers to be a response may significantly differ from the physician's assessment, as well as consensus NIH criteria. A multivariate analysis of specific organs showed that responses in the eyes, the mouth, and the lungs were associated with a patient-reported response. A separate multivariate analysis of standard patient-reported outcome tools showed limited correlation with the 36-Item Short Form Survey and the Lee Symptom Scale measures, although specific components of those scales did have some correlation. Interestingly, there was a significant association between failure-free survival and patient-reported response. Failure-free survival has become a highly regarded composite endpoint in modern trials of chronic GVHD.

Overall, the investigators make a strong case for the further study of patient-reported response in detail and in larger cohorts of chronic GVHD. This study also suggests that patient-reported response should be an important endpoint for consideration in future chronic GVHD clinical trials.

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 or endpoint adjudication committees for clinical trials sponsored by AbbVie, Daiichi, Equillium, Celularity, and Actinium.

References

1. Hess NJ, Nadiminti K, Hematti P, Capitini CM. Interim analysis of T cell specific predictive biomarkers of graft-vs-host disease and relapse following post transplant cyclophosphamide prophylaxis. Presented at: the Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; April 23-26, 2022; Salt Lake City, Utah. Abstract 6.
2. Hess NJ, Hudson AW, Hematti P, Gumperz JE. Early T cell activation metrics predict graft-versus-host disease in a humanized mouse model of hematopoietic stem cell transplantation. *J Immunol*. 2020;205(1):272-281.
3. Beres AJ, Drobyski WR. The role of regulatory T cells in the biology of graft versus host disease. *Front Immunol*. 2013;4:163.
4. Bejanyan N, Brunstein CG, Cao Q, et al. Delayed immune reconstitution after allogeneic transplantation increases the risks of mortality and chronic GVHD. *Blood Adv*. 2018;2(8):909-922.
5. Massoud R, Gagelmann N, Fritzsche-Friedland U, et al. Comparison of immune reconstitution between anti-T-lymphocyte globulin and posttransplant cyclophosphamide as acute graft-versus-host disease prophylaxis in allogeneic myeloablative peripheral blood stem cell transplantation. *Haematologica*. 2022;107(4):857-867.
6. Holtan SG, Ustun C, Hoeschen A, et al. Phase 2 results of urinary-derived human chorionic gonadotropin/epidermal growth factor as treatment for life-threatening acute GVHD. Presented at: the Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; April 23-26, 2022; Salt Lake City, Utah. Abstract 68.
7. Smitz J, Platteau P. Influence of human chorionic gonadotrophin during ovarian stimulation: an overview. *Reprod Biol Endocrinol*. 2020;18(1):80.
8. Pratta M, Jurdi NE, Rashidi A, et al. Validation of amphiregulin as a monitoring biomarker during treatment of life-threatening acute GVHD: a secondary analysis of 2 prospective clinical trials. Presented at: the Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; April 23-26, 2022; Salt Lake City, Utah. Abstract 70.
9. Holtan SG, Hoeschen AL, Cao Q, et al. Facilitating resolution of life-threatening acute GVHD with human chorionic gonadotropin and epidermal growth factor. *Blood Adv*. 2020;4(7):1284-1295.
10. Jagasia M, Perales MA, Schroeder MA, et al. Ruxolitinib for the treatment of steroid-refractory acute GVHD (REACH1): a multicenter, open-label phase 2 trial. *Blood*. 2020;135(20):1739-1749.
11. Srinagesh HK, Özbek U, Kapoor U, et al. The MAGIC algorithm probability is a validated response biomarker of treatment of acute graft-versus-host disease. *Blood Adv*. 2019;3(23):4034-4042.
12. McManigle W, Youssef A, Sarantopoulos S. B cells in chronic graft-versus-host disease. *Hum Immunol*. 2019;80(6):393-399.
13. Sarantopoulos S, Stevenson KE, Kim HT, et al. High levels of B-cell activating factor in patients with active chronic graft-versus-host disease. *Clin Cancer Res*. 2007;13(20):6107-6114.
14. Pusic I, Johanns T, Sarantopoulos S, et al. Use of belimumab for prophylaxis of chronic graft-versus-host disease. Presented at: the Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; April 23-26, 2022; Salt Lake City, Utah. Abstract 34.
15. ClinicalTrials.gov. Ruxolitinib + allogeneic stem cell transplantation in AML. https://clinicaltrials.gov/ct2/show/NCT03286530. Identifier: NCT03286530. Accessed May 16, 2022.
16. ClinicalTrials.gov. Ruxolitinib pre-, during- and post-HSCT for patients with primary or secondary myelofibrosis. https://clinicaltrials.gov/ct2/show/NCT03427866. Identifier: NCT03427866. Accessed May 16, 2022.
17. DeFilipp Z, Kim HT, Knight L, et al. Prolonged post-transplant ruxolitinib therapy is associated with protection from severe GVHD after allogeneic HCT. Presented at: the Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; April 23-26, 2022; Salt Lake City, Utah. Abstract 393.
18. Nahas MR, Soiffer RJ, Kim HT, et al. Phase 1 clinical trial evaluating abatacept in patients with steroid-refractory chronic graft-versus-host disease. *Blood*. 2018;131(25):2836-2845.
19. Koshy AG, Kim HT, Stroopinsky D, et al. Phase II clinical trial of abatacept for steroid-refractory chronic graft versus host disease. Presented at: the Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; April 23-26, 2022; Salt Lake City, Utah. Abstract 32.
20. Kitko CL, White ES, Baird K. Fibrotic and sclerotic manifestations of chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2012;18(1)(suppl):S46-S52.
21. Alexander KA, Flynn R, Lineburg KE, et al. CSF-1-dependant donor-derived macrophages mediate chronic graft-versus-host disease. *J Clin Invest*. 2014;124(10):4266-4280.
22. Kitko CL, Arora M, Zaid MA, et al. Safety, tolerability, and efficacy of axatilimab, a CSF-1R humanized antibody, for chronic graft-versus-host disease after 2 or more lines of systemic treatment. Presented at: the Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; April 23-26, 2022; Salt Lake City, Utah. Abstract 35.
23. ClinicalTrials.gov. A study of axatilimab at 3 different doses in participants with chronic graft versus host disease (cGVHD) (AGAVE-201). https://clinicaltrials.gov/ct2/show/NCT04710576. Identifier: NCT04710576. Accessed May 16, 2022.
24. Chin KK, Kim HT, Inyang EA, et al. Ibrutinib in steroid-refractory chronic graft-versus-host disease, a single-center experience. *Transplant Cell Ther*. 2021;27(12):990.e1-990.e7.
25. Carpenter PA, Kang HJ, Zecca M, et al. Prospective trial of ibrutinib for the treatment of pediatric chronic graft-versus-host disease. Presented at: the Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; April 23-26, 2022; Salt Lake City, Utah. Abstract 126.
26. Markova A, Prockop SE, Dusza S, et al. Interim results of a pilot, prospective, randomized, double-blinded, vehicle-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-versus-host disease. Presented at: the Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; April 23-26, 2022; Salt Lake City, Utah. Abstract 390.
27. Markova A, Whitaker JW, Pan A, et al. Noninvasive genomic characterization of patients with nonsclerotic and superficially sclerotic chronic cutaneous graft-versus-host disease identified a novel gene signature in responders to ruxolitinib cream. Presented at: the Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; April 23-26, 2022; Salt Lake City, Utah. Abstract 33.
28. Im A, Pusic I, Onstad, L, et al. Patient-reported treatment response in chronic graft-vs-host disease: unique dimension of clinical benefit associated with failure-free survival. Presented at: the Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; April 23-26, 2022; Salt Lake City, Utah. Abstract 55.