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A SPECIAL MEETING REVIEW EDITION

Highlights in Graft-vs-Host Disease From the 2021 Transplantation & Cellular Therapy (TCT) Meetings of the ASTCT and the CIBMTR

A Review of Selected Presentations From the 2021 TCT Meetings Digital Experience • February 8-12, 2021

Special Reporting on:

- Ruxolitinib Versus Best Available Therapy in Patients With Glucocorticoid-Refractory Chronic Graft-Vs-Host Disease: Primary Findings From the Phase 3, Randomized REACH3 Study
- Calcineurin Inhibitor–Free Graft-Versus-Host Disease Prophylaxis in Hematopoietic Cell Transplantation With Myeloablative Conditioning Regimens and HLA-Matched Donors: Results of the BMT CTN 1301 PROGRESS II Trial
- Ruxolitinib for the Treatment of Chronic GVHD and Overlap Syndrome in Children and Young Adults
- Phase I Study De-Intensifying Exposure of Post-Transplantation Cyclophosphamide After HLA-Haploidentical Hematopoietic Cell Transplantation for Hematologic Malignancies
- Preliminary Safety and Efficacy of Itolizumab, a Novel Targeted Anti-CD6 Therapy, in Newly Diagnosed Severe Acute Graft-Versus-Host Disease: Interim Results From the EQUATE Study
- Durable Discontinuation of Immunosuppressive Therapy: Clinical Results From the Chronic GvHD Consortium
- Belumosudil for Chronic Graft-Versus-Host Disease After 2 or More Prior Lines of Therapy: The ROCKstar Study (KD025-213)
- Health Care Resource Utilization and Costs of Steroid-Related Complications in Patients With Graft-Versus-Host Disease
- Secondary Graft-Versus-Host Disease Prophylaxis With Oral Proteasome Inhibitor Ixazomib Is Associated With Low Incidence of Recurrent, Late Acute, and Chronic GVHD and Facilitated Calcineurin Inhibitor Taper Within the First Year Post-Allogeneic Stem Cell Transplantation

PLUS Meeting Abstract Summaries

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Jakafi®
ruxolitinib (tablets)

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

Indications and Usage

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

Approval Was Based on REACH1[1]

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

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

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

Inclusion criteria included[2]:

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

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

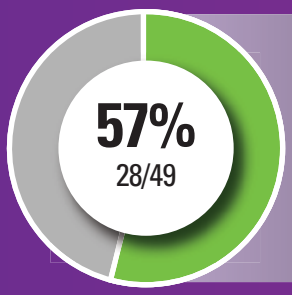
Important Safety Information

- Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated
- Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary
- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi
- Severe neutropenia (ANC $<0.5 \times 10^9$/L) was generally reversible by withholding Jakafi until recovery
- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines
- Tuberculosis (TB) infection has been reported. Observe patients taking Jakafi for signs and symptoms of active TB and manage promptly. Prior to initiating Jakafi, evaluate patients for TB risk factors and test those at higher risk for latent infection. Consult a physician with expertise in the treatment of TB before starting Jakafi in patients with evidence of active or latent TB. Continuation of Jakafi during treatment of active TB should be based on the overall risk-benefit determination
- Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi treatment. If PML is suspected, stop Jakafi and evaluate
- Advise patients about early signs and symptoms of herpes zoster and to seek early treatment
- Increases in hepatitis B viral load with or without associated elevations in alanine aminotransferase and aspartate aminotransferase have been reported in patients with chronic hepatitis B virus (HBV) infections. Monitor and treat patients with chronic HBV infection according to clinical guidelines

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

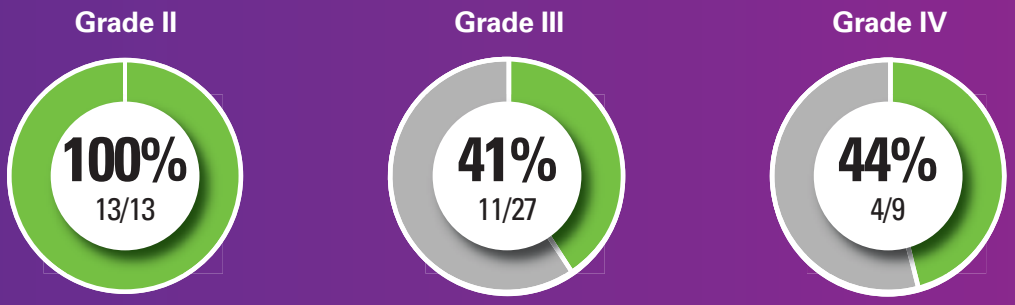
Majority of Patients Achieved a Response at Day 28[1]

Primary Endpoint: ORR at Day 28



Over Half of Responses Were Complete Responses

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



- When discontinuing Jakafi, myeloproliferative neoplasm-related symptoms may return within one week. After discontinuation, some patients with myelofibrosis have experienced fever, respiratory distress, hypotension, DIC, or multi-organ failure. If any of these occur after discontinuation or while tapering Jakafi, evaluate and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi without consulting their physician. When discontinuing or interrupting Jakafi for reasons other than thrombocytopenia or neutropenia, consider gradual tapering rather than abrupt discontinuation
- Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred. Perform periodic skin examinations
- Treatment with Jakafi has been associated with increases in total cholesterol, low-density lipoprotein cholesterol, and triglycerides. Assess lipid parameters 8-12 weeks after initiating Jakafi. Monitor and treat according to clinical guidelines for the management of hyperlipidemia
- In myelofibrosis and polycythemia vera, the most common nonhematologic adverse reactions (incidence ≥15%) were bruising, dizziness, headache, and diarrhea. In acute graft-versus-host disease, the most common nonhematologic adverse reactions (incidence >50%) were infections and edema
- Dose modifications may be required when administering Jakafi with strong CYP3A4 inhibitors or fluconazole or in patients with renal or hepatic impairment. Patients should be closely monitored and the dose titrated based on safety and efficacy
- Use of Jakafi during pregnancy is not recommended and should only be used if the potential benefit justifies the potential risk to the fetus. Women taking Jakafi should not breastfeed during treatment and for 2 weeks after the final dose

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

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

Jakafi®
ruxolitinib (tablets)

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

CONTRAINDICATIONS None.

WARNINGS AND PRECAUTIONS Thrombocytopenia, Anemia and Neutropenia Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia. [*see Dosage and Administration (2.1) in Full Prescribing Information*]. Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary [*see Dosage and Administration (2), and Adverse Reactions (6.1) in Full Prescribing Information*]. Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi. Severe neutropenia (ANC less than 0.5×10^9/L) was generally reversible by withholding Jakafi until recovery [*see Adverse Reactions (6.1) in Full Prescribing Information*]. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated [*see Dosage and Administration (2), and Adverse Reactions (6.1) in Full Prescribing Information*]. **Risk of Infection** Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting therapy with Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines. *Tuberculosis* Tuberculosis infection has been reported in patients receiving Jakafi. Observe patients receiving Jakafi for signs and symptoms of active tuberculosis and manage promptly. Prior to initiating Jakafi, patients should be evaluated for tuberculosis risk factors, and those at higher risk should be tested for latent infection. Risk factors include, but are not limited to, prior residence in or travel to countries with a high prevalence of tuberculosis, close contact with a person with active tuberculosis, and a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed. For patients with evidence of active or latent tuberculosis, consult a physician with expertise in the treatment of tuberculosis before starting Jakafi. The decision to continue Jakafi during treatment of active tuberculosis should be based on the overall risk-benefit determination. *Progressive Multifocal Leukoencephalopathy* Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi treatment. If PML is suspected, stop Jakafi and evaluate. *Herpes Zoster* Advise patients about early signs and symptoms of herpes zoster and to seek treatment as early as possible if suspected [*see Adverse Reactions (6.1) in Full Prescribing Information*]. *Hepatitis B* Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking Jakafi. The effect of Jakafi on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines. **Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi** Following discontinuation of Jakafi, symptoms from myeloproliferative neoplasms may return to pretreatment levels over a period of approximately one week. Some patients with MF have experienced one or more of the following adverse events after discontinuing Jakafi: fever, respiratory distress, hypotension, DIC, or multi-organ failure. If one or more of these occur after discontinuation of, or while tapering the dose of Jakafi, evaluate for and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi therapy without consulting their physician. When discontinuing or interrupting therapy with Jakafi for reasons other than thrombocytopenia or neutropenia [*see Dosage and Administration (2.6) in Full Prescribing Information*], consider tapering the dose of Jakafi gradually rather than discontinuing abruptly. **Non-Melanoma Skin Cancer** Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred in patients treated with Jakafi. Perform periodic skin examinations. **Lipid Elevations** Treatment with Jakafi has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined in patients treated with Jakafi. Assess lipid parameters approximately 8-12 weeks following initiation of Jakafi therapy. Monitor and treat according to clinical guidelines for the management of hyperlipidemia. **ADVERSE REACTIONS** The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling: • Thrombocytopenia, Anemia and Neutropenia [*see Warnings and Precautions (5.1) in Full Prescribing Information*] • Risk of Infection [*see Warnings and Precautions (5.2) in Full Prescribing Information*] • Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi [*see Warnings and Precautions (5.3) in Full Prescribing Information*] • Non-Melanoma Skin Cancer [*see Warnings and Precautions (5.4) in Full Prescribing Information*]. **Clinical Trials Experience in Myelofibrosis** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of Jakafi was assessed in 617 patients in six clinical studies with a median duration of follow-up of 10.9 months, including 301 patients with MF in two Phase 3 studies. In these two Phase 3 studies, patients had a median duration of exposure to Jakafi of 9.5 months (range 0.5 to 17 months), with 89% of patients treated for more than 6 months and 25% treated for more than 12 months. One hundred and eleven (111) patients started treatment at 15 mg twice daily and 190 patients started at 20 mg twice daily. In patients starting treatment with 15 mg twice daily (pretreatment platelet counts of 100 to 200×10^9/L) and 20 mg twice daily (pretreatment platelet counts greater than 200×10^9/L), 65% and 25% of patients, respectively, required a dose reduction below the starting dose within the first 8 weeks of therapy. In a double-blind, randomized, placebo-controlled study of Jakafi, among the 155 patients treated with Jakafi, the most frequent adverse reactions were thrombocytopenia and anemia [*see Table 2*]. Thrombocytopenia, anemia and neutropenia are dose-related effects. The three most frequent nonhematologic adverse reactions were bruising, dizziness and headache [*see Table 1*]. Discontinuation for adverse events, regardless of causality, was observed in 11% of patients treated with Jakafi and 11% of patients treated with placebo. Table 1 presents the most common nonhematologic adverse reactions occurring in patients who received Jakafi in the double-blind, placebo-controlled study during randomized treatment.

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

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

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

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

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

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

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

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

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

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

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

Clinically relevant laboratory abnormalities are shown in Table 4.

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

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

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

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

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

	Jakafi (N=71)	
Adverse Reactions[a]	**All Grades[b] (%)**	**Grade 3-4 (%)**
Infections	55	41
Edema	51	13
Hemorrhage	49	20
Fatigue	37	14
Bacterial infections	32	28
Dyspnea	32	7
Viral infections	31	14
Thrombosis	25	11
Diarrhea	24	7
Rash	23	3
Headache	21	4
Hypertension	20	13
Dizziness	16	0

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

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

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

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

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

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

Revised: January 2020 PLR-JAK-00041

Ruxolitinib Versus Best Available Therapy in Patients With Glucocorticoid-Refractory Chronic Graft-Vs-Host Disease: Primary Findings From the Phase 3, Randomized REACH3 Study

Chronic graft-vs-host disease (GVHD) occurs in approximately 30% to 70% of all patients who undergo allogeneic stem cell transplant (alloSCT), and this condition is a leading cause of nonrelapse mortality and morbidity.[1,2] The standard first-line treatment is systemic corticosteroids. However, approximately 50% of patients become corticosteroid-refractory or corticosteroid-dependent.[3] No standard second-line treatment has been defined. Ruxolitinib is a selective Janus kinase (JAK) 1 and 2 inhibitor. In the open-label, phase 3 REACH2 trial, ruxolitinib improved the median failure-free survival in patients with glucocorticoid-refractory acute GVHD compared with best available therapy.[4]

Dr Stephanie J. Lee presented the primary analysis of REACH3, a randomized, open-label, phase 3 study comparing ruxolitinib vs best available therapy in patients with corticosteroid-refractory or corticosteroid-dependent chronic GVHD.[5] The trial enrolled 329 patients (median age, 49 years; range, 12-76 years) who had undergone alloSCT and had developed moderate or severe corticosteroid-refractory or corticosteroid-dependent chronic GVHD. Approximately 61% of patients were male. Chronic GVHD was moderate in 48% and severe in 52%. Patients were randomly assigned 1:1 to ruxolitinib at 10 mg twice daily or best available therapy. They received six 28-day treatment cycles. Patients could continue previous treatment with glucocorticoids and/or calcineurin inhibitors. The best available therapy was chosen by the investigator and could include extracorporeal photopheresis, low-dose methotrexate, mycophenolate mofetil, everolimus, sirolimus, infliximab, rituximab, pentostatin, imatinib, or ibrutinib. Infection prophylaxis was permitted per institutional practice.

The primary endpoint was overall response rate (ORR) per National Institutes of Health (NIH) consensus criteria at week 24.[5] The key secondary endpoints were failure-free survival

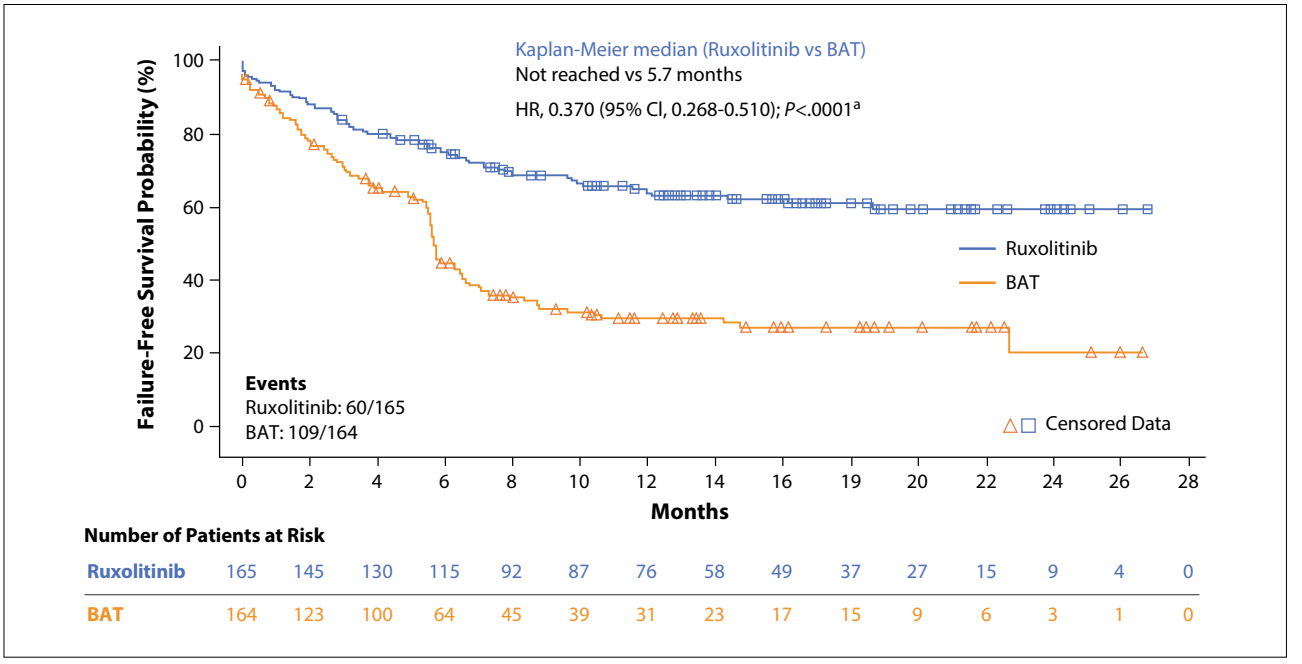


Figure 1. Failure-free survival at week 24 in the phase 3 REACH3 trial, which compared ruxolitinib vs best available therapy in patients with refractory cGVHD. Failure-free survival was defined as the time to recurrence of the underlying disease, the start of new systemic treatment for cGVHD, or death, whichever was earliest. [a]Descriptive *P* value at the primary analysis (non-US testing sequence only) as the efficacy boundary was crossed at the interim analysis (N=196; HR, 0.315; 95% CI, 0.205-0.486; *P*<.0001). For the US testing sequence, the hypothesis was retested at the primary analysis following the overall hierarchical testing procedure. BAT, best available therapy; cGVHD, chronic graft-vs-host disease. Adapted from Zeiser R et al. TCT abstract 82. *Transplant Cell Ther*. 2021;27(3 suppl).[5]

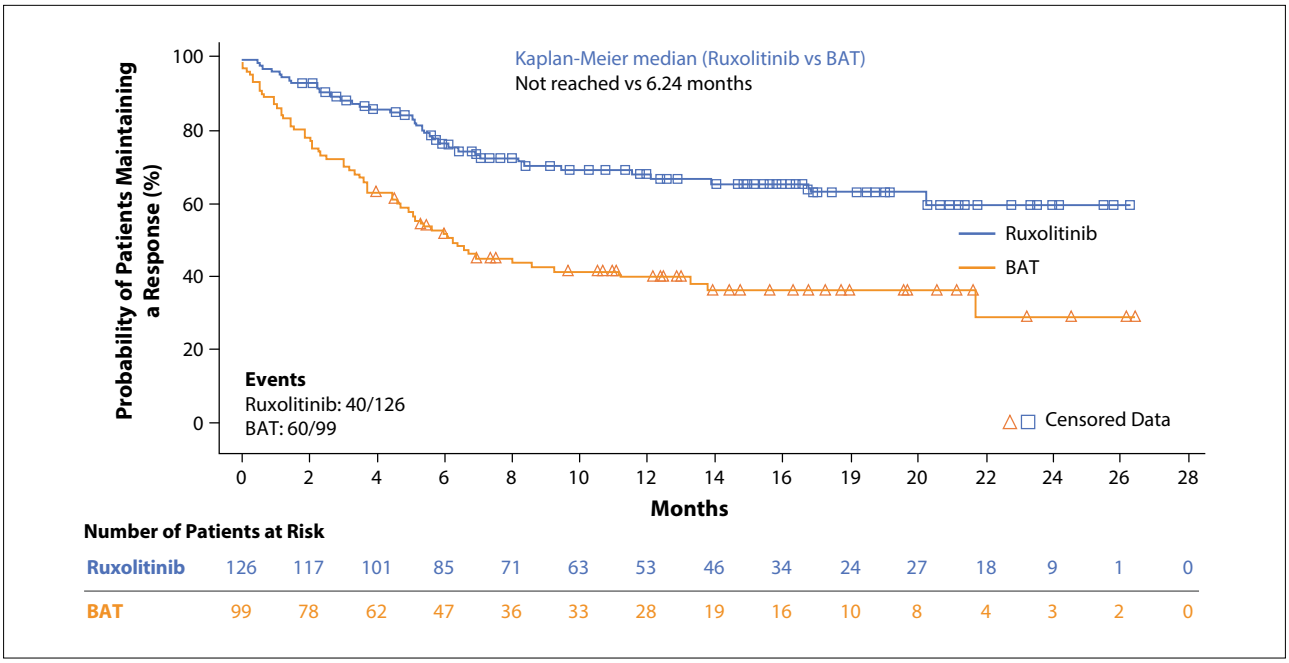


Figure 2. The duration of response in the phase 3 REACH3 trial, which compared ruxolitinib vs best available therapy in patients with refractory chronic graft-vs-host disease. BAT, best available therapy. Adapted from Zeiser R et al. TCT abstract 82. *Transplant Cell Ther.* 2021;27(3 suppl).[5]

and improvement in the modified Lee symptom score (mLSS) of at least 7 points from baseline at week 24. On or after cycle 7, day 1 (week 24), patients in the control group could cross over to ruxolitinib if they did not achieve or maintain a complete response or a partial response, developed toxicity to the best available therapy, or had a chronic GVHD flare.

At the data cutoff of May 8, 2020, 50.3% of the ruxolitinib group and 25.6% of the control group remained on their randomly assigned treatment. In the control group, 37.2% crossed over to ruxolitinib. The most common reasons for discontinuation were lack of efficacy (14.5% with ruxolitinib vs 42.7% control), adverse events (AEs; 17.0% vs 4.9%), and relapse (5.5% vs 4.3%).

The median failure-free survival was significantly longer with ruxolitinib (not reached vs 5.7 months; hazard ratio [HR], 0.370; 95% CI, 0.268-0.510; *P*<.0001; Figure 1).[5] The ORR at week 24 was 49.7% with ruxolitinib and 25.6% with best available therapy (odds ratio [OR], 2.99; 95% CI, 1.86-4.80; *P*<.0001). The best ORR was 76.4% with ruxolitinib and 60.4% with placebo (OR, 2.17; 95% CI, 1.34-3.52). The median duration of the best ORR was not reached in the ruxolitinib arm vs 6.24 months in the control arm (Figure 2). The mLSS responder rate also favored ruxolitinib (24.2% vs 11%; *P*=.0011).

Up to week 24, the AE rate was 97.6% (grade ≥3, 57%) with ruxolitinib and 98.1% (grade ≥3, 57.6%) with the control. The most common grade 3/4 AEs in the ruxolitinib and control arms were anemia (12.7% vs 7.6%), thrombocytopenia (15.2% vs 10.1%), neutropenia (8.5% vs 3.8%), pneumonia (8.5% vs 9.5%), and hypertension (4.8% vs 7.0%). Infections occurred in 63.6% of patients in the ruxolitinib arm and 56.3% of those in the control arm; they included viral (33.9% vs 29.1%), bacterial (27.9% vs 25.9%), and fungal (11.5% vs 5.7%) infections.

The investigators noted that ruxolitinib is the first agent to demonstrate superior efficacy compared with the best available treatment in a phase 3 trial of patients with corticosteroid-refractory or corticosteroid-dependent chronic GVHD, as measured by a higher ORR, higher best ORR, longer failure-free survival, and greater symptom improvement. No unexpected safety signals were reported.

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Calcineurin Inhibitor–Free Graft-Versus-Host Disease Prophylaxis in Hematopoietic Cell Transplantation With Myeloablative Conditioning Regimens and HLA-Matched Donors: Results of the BMT CTN 1301 PROGRESS II Trial

Regimens that include a calcineurin inhibitor are standard for the prevention of GVHD in patients undergoing hematopoietic stem cell transplant (HCT). Treatment with calcineurin inhibitor–free strategies using T-cell depletion, either through CD34-positive–selected T-cell depletion or post-transplant cyclophosphamide, has also been associated with low rates of chronic GVHD.[1,2] Dr Marcelo C. Pasquini presented results from BMT CTN 1301, a phase 3 trial that compared 2 calcineurin inhibitor–free approaches vs a standard regimen among patients with acute leukemia or myelodysplasia and a human leukocyte antigen (HLA)-matched related or unrelated donor.[3]

The patients' median age was 51 years (range, 13-66 years), and 43.1% were female. Patients were randomly assigned to receive a CD34-positive selected peripheral blood stem cell graft without posttransplant immunosuppression (n=114), cyclophosphamide after a bone marrow graft without additional immunosuppression (n=114), or tacrolimus/methotrexate after a bone marrow graft as the control (n=118). The primary endpoint was chronic GVHD (moderate/severe) relapse-free survival (CRFS) at 12 months after enrollment. Secondary endpoints included overall survival and transplant-related mortality.

Among the 346 patients enrolled, 327 received HCT (300 per protocol).[3] The arm receiving CD34-positive selection had the highest rate of noncompliance, with only 86% patients receiving per-protocol therapy. At 1 year, the rate of CRFS was 60.2% for the CD34-positive selection arm (vs control, *P*=.27), 60.3% for the cyclophosphamide arm (vs control; *P*=.41), and 52.6% for the control (Figure 3). There was no significant difference in the CRFS rate between the CD34-positive selection and cyclophosphamide arms (*P*=.72). The 1-year rate of overall survival was 75.7% for the CD34-positive selection arm (HR, 1.74; 95% CI, 1.09-2.80; *P*=.02), 84.6% for the cyclophosphamide arm (HR, 1.02; 95% CI, 0.60-1.72; *P*=.95), and 84.2% for the control. The HR for the comparison between the CD34-positive selection and cyclophosphamide arms for overall survival was 1.78 (95% CI, 1.09-2.89; *P*=.02). Transplant-related mortality rates at 1 year were 16.5% for the CD34-positive arm, 12% for the cyclophosphamide arm, and 7% for the control arm (CD34-positive vs control, *P*=.020;

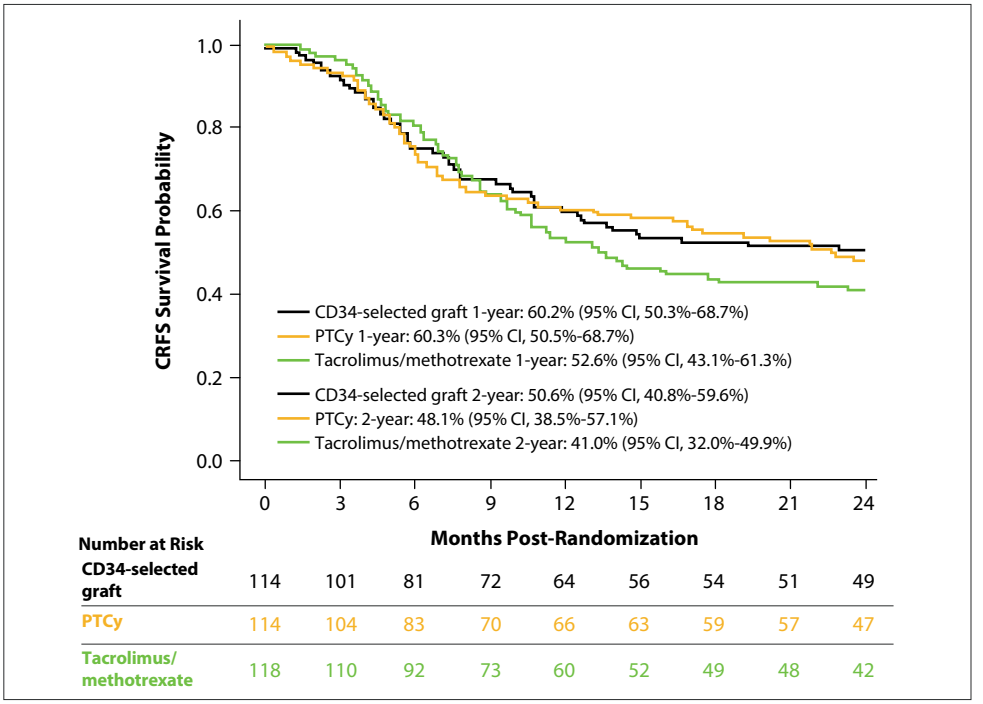

Figure 3. Chronic graft-vs-host disease relapse-free survival in BMT CTN 1301, a phase 3 trial that compared prophylaxis with 2 calcineurin inhibitor–free approaches vs a standard regimen among patients with acute leukemia or myelodysplasia and an HLA-matched related or unrelated donor. CRFS, chronic graft-vs-host disease relapse-free survival; HLA, human leukocyte antigen; PTCy, post-transplant cyclophosphamide. Adapted from Pasquini MC et al. TCT abstract LBA1. *Transplant Cell Ther.* 2021;27(3 suppl).[3]

ABSTRACT SUMMARY Nonrelapse Mortality Among Patients Diagnosed With Chronic Graft-Versus-Host Disease: An Updated Analysis From the Chronic GVHD Consortium

To better understand and identify patients at highest risk for nonrelapse mortality, researchers analyzed the incidence, risk factors, and causes of nonrelapse deaths among patients enrolled in 2 prospective, longitudinal observational trials conducted through the Chronic GVHD Consortium (Abstract 83). Among 937 patients with chronic GVHD requiring new systemic treatment, 54% were incident chronic GVHD cases (occurring <3 months after diagnosis) and 46% were prevalent cases (occurring >3 months after diagnosis). The patients' median age was 52 years (range, 18-78 years), and 50% of patients had previously developed grade 2 to 4 acute GVHD. At a median follow-up of 4 years, there were 333 deaths. Causes of death included chronic GVHD in 37.8%, relapse in 25.0%, infection in 16.9%, and respiratory failure in 9.6%. In a multivariate analysis, nonrelapse mortality was significantly associated with the use of reduced-intensity conditioning, bilirubin levels higher than 2 mg/dL at study enrollment, moderate-to-severe involvement of the skin or lungs at enrollment, worse physical functioning score, and decreased walk test distance.

cyclophosphamide vs control, *P*=.09). The 2-year rates of grade 2/3 infection were 69.2% for the CD34-positive arm, 60.6% for the cyclophosphamide arm, and 43.9% for the control arm (*P*=.0006 for either experimental arm vs the control).

The study investigators concluded that neither of the calcineurin inhibitor–free strategies were superior to tacrolimus/methotrexate in terms of the primary endpoint, CRFS.[3] Rates of infection were significantly higher with either calcineurin inhibitor–free strategy vs tacrolimus/methotrexate. Rates of overall survival were similar for cyclophosphamide without additional immunosuppression and tacrolimus/methotrexate, but those patients treated with CD34-positive–selected peripheral blood stem cell grafts had lower overall survival owing to increased transplant-related mortality.

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Ruxolitinib for the Treatment of Chronic GVHD and Overlap Syndrome in Children and Young Adults

In chronic GVHD, the JAK 1/2 inhibitor ruxolitinib is approved by the US Food and Drug Administration for the treatment of adults.[1] Experience in children younger than 12 years is limited. Dr YunZu Michele Wang described a pediatric dosing strategy for the use of ruxolitinib in children with chronic GVHD.[2] This retrospective chart review examined data from 20 patients (median age, 14.6 years; range, 5-26 years) who received ruxolitinib orally, either at 5 mg twice daily for children who weighed 25 kg or more or 2.5 mg twice daily for those who weighed less than 25 kg. The dose was halved at the study start in patients treated with concurrent triazole antifungal therapy. Doses increased to a maximum of 10 mg twice daily as tolerated. Responses were evaluated using the 2014 NIH consensus panel response criteria. Two hours after administration of ruxolitinib, phosphorylation of STAT5 on lymphocytes was evaluated in a subset of patients using flow cytometry as a surrogate of JAK/STAT5 inhibition. A lower percentage of phosphorylation indicated greater inhibition.

Among the 20 patients enrolled, chronic GVHD was severe in 10, moderate in 9, and mild in 1.[2] The most common organs involved were the skin (n=17), eyes (n=8), mouth (n=6), and gastrointestinal (GI) system (n=6). Four patients had involvement of a single organ. Four patients had overlap syndrome. Sixteen patients were receiving daily prednisone at a median dose of 0.5 mg/kg/day (range, 0.08-1.5 mg/kg/day) at the time of ruxolitinib initiation. The median time from diagnosis of chronic GVHD to initiation of ruxolitinib was 181 days (range, 17-1792 days). The median dose of ruxolitinib at initiation was 5 mg daily (range, 2.5-10 mg daily). Eleven patients were receiving concurrent triazoles at the time of ruxolitinib initiation and began treatment at a 50% dose reduction. Six patients received the maximal daily dose of 20 mg (Figure 4).

Phosphorylation of STAT5 on lymphocytes was absent or decreased 2 hours after ruxolitinib in 5 of 6 evaluated patients, which suggests adequate JAK inhibition in the pediatric population.[2] The ORR was 70%. Two patients with moderate cases of chronic GVHD manifesting in the skin achieved a complete response at 86 and 311 days after starting ruxolitinib, respectively. Twelve patients achieved a partial response, at a median of 48 days (range, 18-120 days) from the first ruxolitinib dose, including 2 of the patients with overlap syndrome at baseline. Among the patients without a response to treatment, 1 had stable disease and 5 had progressive disease. Organs that showed responses to ruxolitinib included the skin, joints, GI tract, liver, and muscle. All 7 patients with sclerotic-type chronic GVHD of the skin had responses to ruxolitinib. Among the 3 patients with lung involvement, pulmonary function tests stabilized in 2. Sixteen of the patients were receiving corticosteroids at the time of enrollment. During the study period, 13 of these patients were able to discontinue corticosteroid treatment or were in the process of doing so. Nine of the 12 patients with a response were continuing treatment with ruxolitinib at the time of the report. The responses were maintained at a median of 411 days (range, 84-1127 days) from the initiation of ruxolitinib.

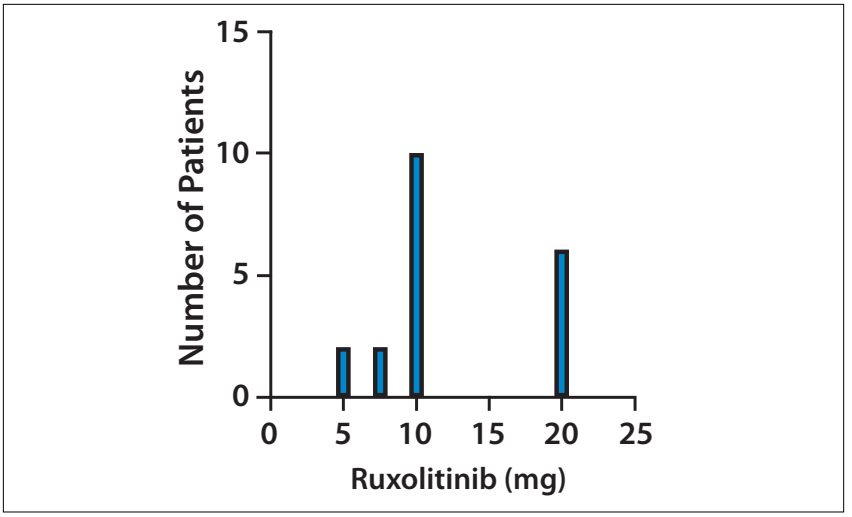

Figure 4. Maximum daily dose of ruxolitinib among children and young adults treated for chronic graft-vs-host disease and overlap syndrome. Adapted from Wang Y et al. TCT abstract 298. *Transplant Cell Ther*. 2021;27(3 suppl).[2]

All patients developed AEs. Ruxolitinib was discontinued in 3 patients, owing to 1 case each of neutropenia, thrombocytopenia, and elevated alanine aminotransferase. No patients developed fungal infections or pneumocystis pneumonia. Two patients died from complications of progressive severe chronic GVHD. The investigators concluded that the pediatric dosing strategy for ruxolitinib in this study was safely tolerated and demonstrated promise for treating chronic GVHD in children.

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Phase I Study De-Intensifying Exposure of Post-Transplantation Cyclophosphamide After HLA-Haploidentical Hematopoietic Cell Transplantation for Hematologic Malignancies

The standard dosage (50 mg/kg/day) and timing (days +3/+4) of cyclophosphamide after HLA-haploidentical HCT were largely extrapolated from murine skin allografting models.[1] In murine HCT, studies have demonstrated that 25 mg/kg/day was superior to 50 mg/kg/day on days +3/+4 at preventing GVHD, and that a single dose of 25 mg/kg given on day +4 was equivalent to 25 mg/kg/day on days +3/+4.[2,3]

Dr Meredith Jo McAdams presented data from a phase 1 dose de-escalation study of cyclophosphamide.[4] The study enrolled 19 patients ages 21 to 47 years; 50% had a disease risk index of high or very high. The patients underwent myeloablative conditioning with daily intravenous busulfan/fludarabine, HLA-haploidentical bone marrow, and GVHD prophylaxis with cyclophosphamide. The first 5 patients received cyclophosphamide at 50 mg/kg/day on days +3/+4 for comparative data (dose level 1), followed by a 3+3 dose de-escalation to 25 mg/kg/day on days +3/+4 (dose level 2; n=7) and then 25 mg/kg on day +4 only (dose level 3; n=7). Then all patients received

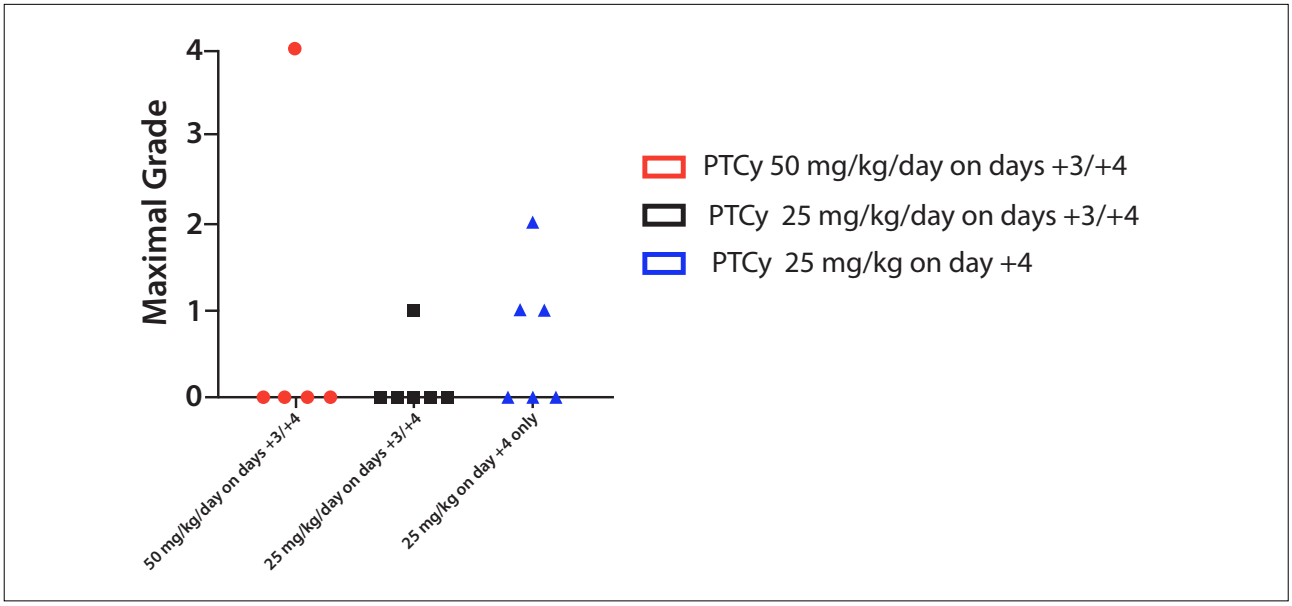

Figure 5. The maximum grade of severe acute graft-vs-host disease among patients in a phase 1 study that evaluated de-intensifying exposure of post-transplant cyclophosphamide after HLA-haploidentical hematopoietic cell transplant. HLA, human leukocyte antigen; PTCy, post-transplant cyclophosphamide. Adapted from McAdams MJ et al. TCT abstract 11. *Transplant Cell Ther*. 2021;27(3 suppl).[4]

mycophenolate mofetil (days +5 to +35) and sirolimus (days +5 to +80). The primary endpoint was to evaluate whether lower doses of post-transplant cyclophosphamide could prevent cases of severe, acute GVHD.

The median duration of follow-up was 294 days (range, 40-473 days).[4] No patients at dose levels 2 or 3 developed grade 3 or 4 acute GVHD (Figure 5), whereas 1 patient at dose level 1 developed grade 4 disease. At dose level 2, 1 patient developed maximal grade 1 acute GVHD. At dose level 3, 2 patients developed maximal grade 1 acute GVHD and 1 developed maximal grade 2 acute GVHD. Neutrophil and platelet engraftment occurred more quickly at dose levels 2 and 3 compared with dose level 1.

Poor graft function was seen in 1 patient at dose level 1. Primary graft failure occurred in 1 patient at dose level 2. Relapse before engraftment occurred in 1 patient at dose level 3. Two patients at dose level 3 developed engraftment syndrome, which resolved rapidly without therapy in both cases. Split chimerism (100% donor myeloid; 0%-6% donor T-cell) was reported in 1 patient treated at dose level 2 and 1 patient treated at dose level 3; the latter patient required a second HCT. Mucositis appeared to be less severe and shorter in duration with lower cyclophosphamide dosing. Fevers within the first month post-HCT were not substantially different at dose level 2 compared with dose level 1, but they were higher and more protracted at dose level 3.

The study investigators concluded that de-escalation of cyclophosphamide dosing after HLA-haploidentical

ABSTRACT SUMMARY Comparable Outcomes for Matched and Mismatched Unrelated Donor Transplantation With the Addition of Abatacept to Standard Graft-Versus-Host Disease Prophylaxis

The multicenter ABA2 trial demonstrated that triple therapy with abatacept plus a calcineurin inhibitor and methotrexate is more effective for acute GVHD prophylaxis than a calcineurin inhibitor plus methotrexate alone, while maintaining an acceptable safety profile. The original trial enrolled 112 patients ages 6 years and older who had hematologic malignancies and received an unrelated donor HCT (Watkins B et al. *J Clin Oncol*. doi:10.1200/JCO.20.01086). Abatacept at 10 mg/kg was administered on days −1, 5, 14, and 28. A secondary analysis of the ABA2 trial compared outcomes from 43 patients who received triple therapy and had a 7/8 HLA donor with those from a control group of 69 patients who received a calcineurin inhibitor plus methotrexate only (plus placebo) and had an 8/8 HLA donor (Abstract 33). The cumulative incidence of grade 3 to 4 acute GVHD at day 180 was significantly lower in the triple therapy (7/8 HLA) group than in the control (8/8 HLA) group (2.3% vs 14.8%, *P*=.03). With a median follow-up of 25 months in survivors, the 2-year event-free survival rate was 74.0% with triple therapy (7/8 HLA) vs 60.3% with control therapy (8/8 HLA) (*P*=.08). A multicenter, randomized controlled trial (ABA3) is opening to determine whether outcomes with 7/8 HLA can be further improved by lengthening abatacept coverage.

HCT appears feasible and effective in maintaining protection against severe acute GVHD, while promoting more rapid engraftment and less early post-transplant toxicity.[4] Further studies across larger cohorts of patients, as well as longer follow-up studies of the impact of de-escalated cyclophosphamide on immune reconstitution, chronic GVHD, relapse, and survival, are needed to confirm whether this strategy is superior to the current dosing schedule.

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Preliminary Safety and Efficacy of Itolizumab, a Novel Targeted Anti-CD6 Therapy, in Newly Diagnosed Severe Acute Graft-Versus-Host Disease: Interim Results From the EQUATE Study

CD6 is a co-stimulatory receptor predominantly expressed on T cells that acts as a crucial regulator of T-cell activation and is implicated in the pathogenesis of multiple autoimmune diseases. Activated leukocyte cell adhesion molecule (ALCAM), a CD6 ligand, is expressed on antigen-presenting cells, as well as epithelial and endothelial cells of acute GVHD target organs, including the skin and the GI tract.[1,2] Previous studies in patients receiving alloHCT showed that ex vivo depletion of donor CD6-positive T cells lowered the incidence of acute GVHD, providing a rationale for therapeutically targeting CD6 in acute GVHD.[3] Itolizumab, a humanized immunoglobulin G1 monoclonal antibody undergoing evaluation as treatment for acute GVHD, binds CD6 and blocks interaction with ALCAM to inhibit T-cell activity and trafficking.[4]

Dr John Koreth presented interim study results from EQUATE, an ongoing phase 1b/2 study of itolizumab in combination with corticosteroids for newly diagnosed severe acute GVHD (grade 3-4) after first alloHCT.[5] The phase 1b portion is an open-label, 3+3 dose-escalation study evaluating doses of 0.4, 0.8, 1.6, and 2.4 mg/kg administered intravenously every 2 weeks through day 57. As of November 13, 2020, 10 patients completed

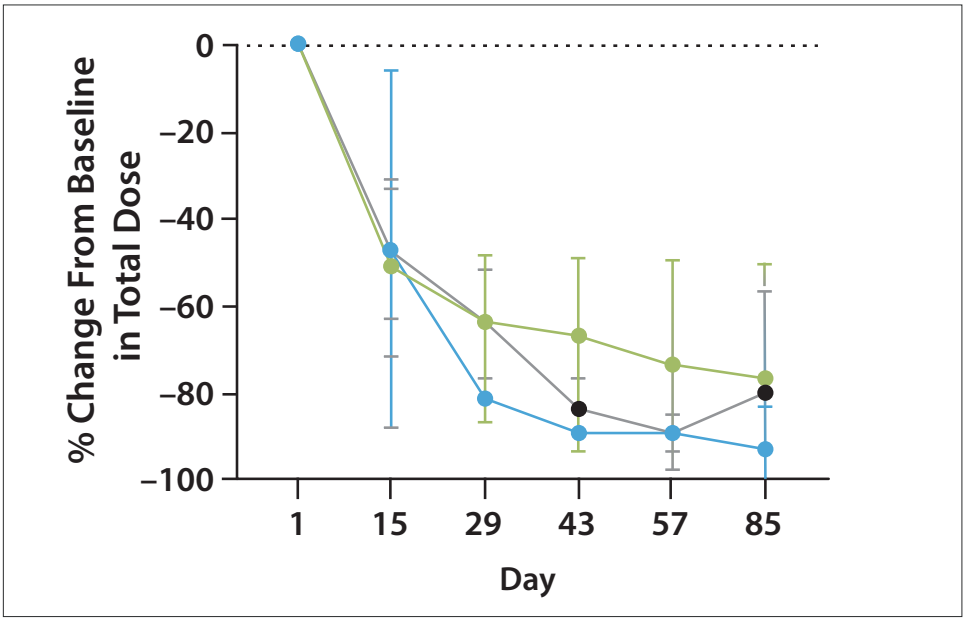

Figure 6. Changes from baseline in the use of systemic corticosteroids among patients with newly diagnosed severe acute graft-vs-host disease who received itolizumab in the phase 1b/2 EQUATE study. Adapted from Koreth J et al. TCT abstract LBA4. *Transplant Cell Ther*. 2021;27(3 suppl).[5]

treatment: 4 with 0.4 mg/kg, 3 with 0.8 mg/kg, and 3 with 1.6 mg/kg. All patients received corticosteroids at an initial dose of 1 to 2 mg/kg/day. Their mean age was 48 years (standard deviation, 15.7 years), 90% were male, and 90% were white. The graft source was peripheral blood for 80% and bone marrow for 20%, and 80% had an HLA-matched donor. The mean time to onset of GVHD was 43 days, and 100% of patients had GI involvement.

At day 57, the ORR was 50% with 0.4 mg/kg, 100% with 0.8 mg/kg, and 100% with 1.6 mg/kg.[5] The median percent corticosteroid dose reduction at day 85 was 93%, 87%, and 91% for the 0.4, 0.8, and 1.6 mg/kg groups, respectively (Figure 6). Itolizumab decreased the CD6 levels on T cells in a dose-dependent manner within 24 hours of the first dose, a reduction that was maintained throughout the treatment period.

Across the dosing cohorts, all patients developed at least 1 AE. Most AEs were mild to moderate in severity.[5] The most common AEs were hypomagnesemia (n=3) and peripheral edema (n=3). One mild infusion reaction was noted. Six patients had serious AEs, including recurrent GVHD (n=1), sepsis (n=2; 1 event was considered a dose-limiting toxicity), fever (n=1), COVID-19 (n=1), and disseminated nocardia (n=1).

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Durable Discontinuation of Immunosuppressive Therapy: Clinical Results From the Chronic GvHD Consortium

Successful treatment of chronic GVHD often requires long-term use of systemic immunosuppressive agents, which can impair immune function, increase the risk of opportunistic infections, and confer a high toxicity burden. Among patients stopping immunosuppressive therapy for the first time, approximately 50% will need to resume therapy, after a median of 3 months.[1] Therefore, durable discontinuation of immunosuppressive therapy may represent a true cure. Prior studies of immunosuppressive therapy discontinuation reported long-term rates between 27% and 68%.[1,2] This variation might be explained by differences in the population, treatment, and graft sources, among other factors.

Dr George L. Chen reported the results of a retrospective analysis of factors associated with durable discontinuation of immunosuppressive therapy.[3] The data were drawn from 2 prospectively followed cohorts from the Chronic GVHD Consortium (n=684). Durable discontinuation of immunosuppressive therapy was defined as cessation of all immunosuppressive therapy for at least 12 months. Data for patients who discontinued immunosuppressive therapy for less than 12 months were censored. Immunosuppressive therapy that was stopped and then restarted before 12 months had elapsed was considered continuous therapy.

The patients' median age was 51.9 years (range, 18.0-78.0 years). The donor type was HLA-matched related for 37.6%, HLA-matched unrelated for 44.7%, and other in 18%. The transplant source was peripheral blood for 89%, bone marrow for 6.6%, and cord blood for 4.4%. The severity of chronic GVHD was mild for 15.2%, moderate for 51.2%, and severe for 32.2%. The median time from allo-HCT to chronic GVHD diagnosis was 7.7 months (range, 1.0-141.3 months), and the median time from chronic GVHD onset to enrollment was 0.9 months (range, 0.0-12.0 months).

During the median follow-up of 95.3 months (range, 11.3-181.5 months), 33% (95% CI, 28%-37%) of patients were able to discontinue immunosuppressive therapy for 12 or more months (Figure 7).[3] In the multivariate analysis controlling for clinical and patient-reported variables, durable immunosuppressive therapy discontinuation was less likely in patients who received myeloablative conditioning, had a platelet count of 100,000/µL or higher, had moderate/severe lower GI involvement, and had a higher (worse) Lee symptom overall score. In contrast, mild lower GI involvement and cord blood (vs peripheral blood) as a graft source were associated with a greater likelihood of immunosuppressive therapy discontinuation. In a second analysis including NIH overall chronic GVHD severity, patients with severe disease were less likely to attain durable discontinuation (HR, 0.53; 95% CI, 0.31-0.90; *P*=.02).

The investigators noted that most patients in this study with chronic

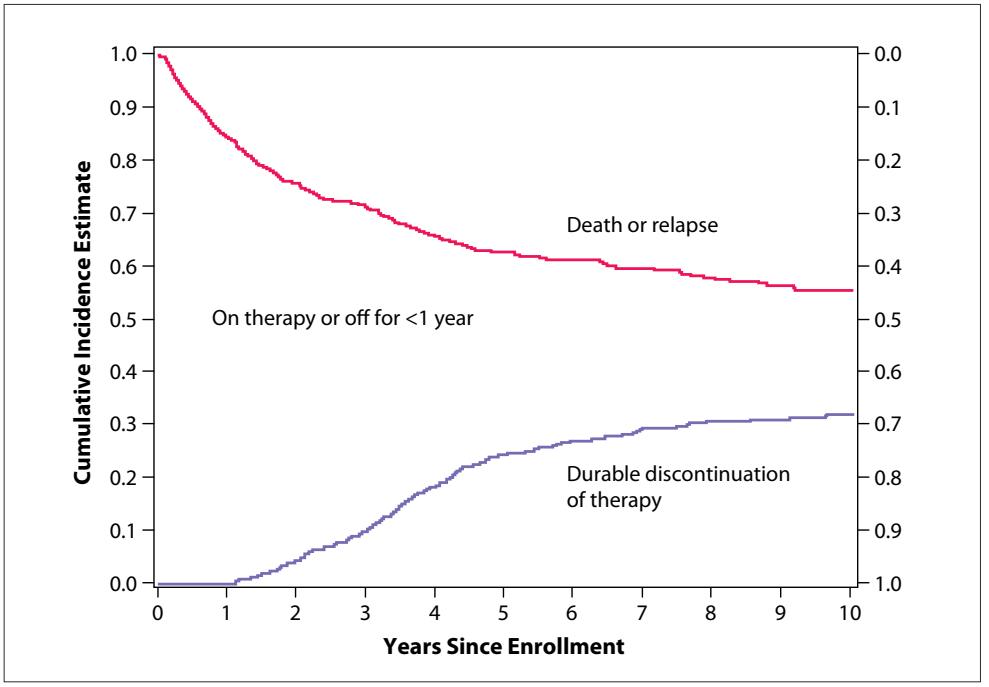

Figure 7. Results in a retrospective analysis evaluating durable discontinuation of immunosuppressive therapy in cohorts from the Chronic GVHD Consortium. Adapted from Chen GL et al. TCT abstract 8. *Transplant Cell Ther.* 2021;27(3 suppl).[3]

GVHD were unable to discontinue immunosuppressive therapy for 12 months or longer.[3] They suggested that chronic GVHD may behave more like an ongoing autoimmune disease without resolution that requires ongoing immunosuppression, rather than a temporary state where eventual tolerance is expected.

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Belumosudil for Chronic Graft-Versus-Host Disease After 2 or More Prior Lines of Therapy: The ROCKstar Study (KD025-213)

Rho-associated coiled-coil kinase 2 (ROCK2) is a critical regulator of both interleukin-21 and interleukin-17. The inhibition of ROCK2 reduces the generation of proinflammatory T helper 17 cells while upregulating the generation of anti-inflammatory regulatory T cells.[1] ROCK2 is also critical in profibrotic processes, including activation of myofibroblasts. ROCK2 inhibitors, which are in development, have prevented collagen deposition, fibrosis, and scarring in multiple tissue and experimental models.[2]

Belumosudil is a novel oral selective ROCK2 inhibitor specifically designed for the treatment of chronic GVHD. In a previous dose-finding phase 2a trial of belumosudil, the ORR was 65% for the dose of 200 mg daily and 69% for the dose of 200 mg twice daily among the 54 enrolled patients.[3] Based on these data, the pivotal phase 2 ROCKstar trial investigated the safety and efficacy of these 2 doses of belumosudil for chronic GVHD in patients already treated with 2 or more lines of therapy. Dr Corey Cutler presented results from a follow-up analysis.[4]

The patients were a median age of 56 years (range, 21-77 years) and had received a mean of 4 (range, 2-5) prior lines of therapy for chronic GVHD.[4] Approximately 66% had severe disease, 34% had received prior ibrutinib, and 52% had involvement of at least 4 organs. Patients were stratified according to chronic GVHD severity and prior ibrutinib use, and then were randomly assigned to receive belumosudil at 200 mg once daily (n=66) or 200 mg twice daily (n=66). Treatment was continued until the patient developed clinically significant progression or unacceptable toxicity. The primary endpoint was ORR per the 2014 NIH

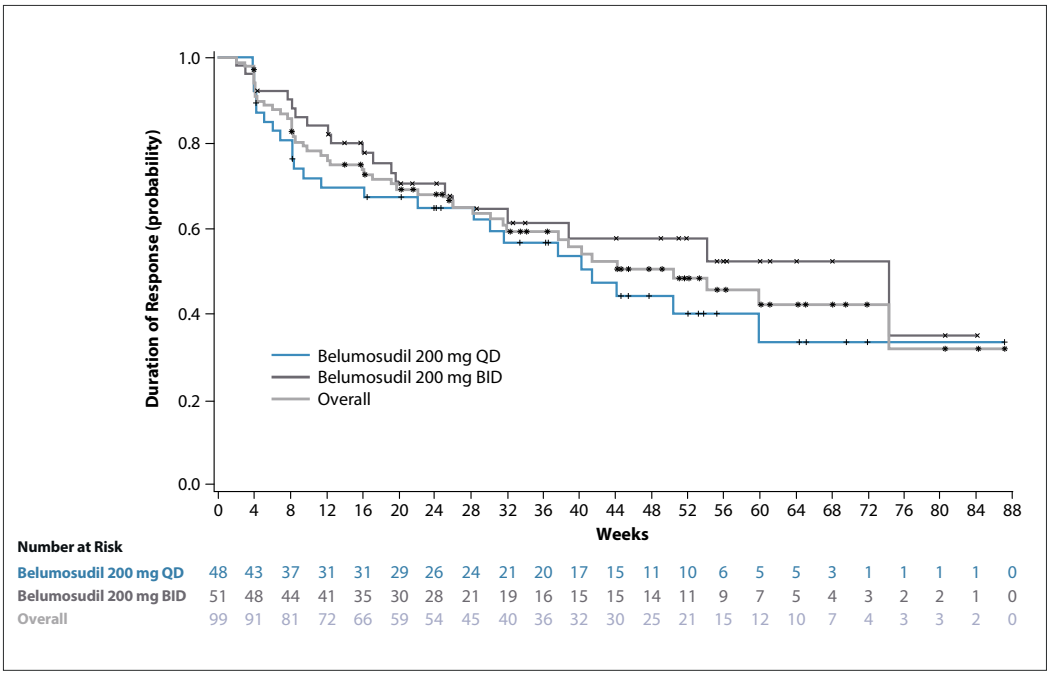

Figure 8. Duration of response in the ROCKstar trial of belumosudil at different doses in patients with previously treated chronic graft-vs-host disease. BID, twice daily; QD, once daily. Adapted from Cutler C et al. TCT abstract 9. *Transplant Cell Ther.* 2021;27(3 suppl).[4]

response criteria, as assessed by the investigators. Additional endpoints included duration of response, failure-free survival, improvement in the mLSS of at least 7 points from baseline, and corticosteroid dose reductions or discontinuations.

The ORR was 73% (95% CI, 60%-83%; *P*<.0001) with daily dosing and 77% (95% CI, 65%-87%; *P*<.0001) with twice-daily dosing. A complete response was reported in 7 patients.[4] The responses were consistent across key subgroups. The median duration of response for both groups pooled was 50 weeks. At 12 months, the median failure-free survival for both groups pooled was 58% (Figure 8). Improvement in the mLSS of at least 7 points from baseline was seen in 60% of patients. Corticosteroid discontinuation and dose reductions were reported in 21% and 64% of patients, respectively.

The most common grade 3/4 AEs were pneumonia (9% in the daily group vs 6% in the twice daily group), hypertension (6% in both groups), and hyperglycemia (5% in both groups).[4] Eight patients died during the study; 5 from AEs (1 possibly related to belumosudil) and 3 during long-term follow-up (>28 days after the last dose). There was 1 case of cytomegalovirus reactivation and 1 case of Epstein-Barr virus reactivation.

ABSTRACT SUMMARY Interferon Lambda Protects Gastrointestinal Stem Cells From Acute GVHD

Direct protection of the intestinal stem cell niche through immunopathologic mechanisms, as opposed to general immunosuppression, may prevent severe GVHD of the GI system while limiting systemic AEs. Preclinical investigations suggested that interferon lambda (IFN-λ) can protect the intestinal stem cell niche after HCT. A preclinical study used murine models to demonstrate an important protective role for IFN-λ in HCT recipient GI tissues (Abstract 81). *Ifnlr1*$^{-/-}$ mice lack the receptor for IFN-λ, and when subjected to HCT, they show a shorter median survival compared with wild-type mice (26 days vs 42 days; *P*<.0001) and worse GVHD pathology in the GI tract (median colon histopathology score of 12 vs 7 for wild-type; *P*=.0004). Administration of pegylated recombinant IL-29, a potent IFN-λ receptor ligand, significantly increased the growth of organoids derived from GI tissue, improved colon histopathology, and prolonged survival in wild-type HCT recipient mice when compared with mice who did not receive pegylated recombinant IL-29. Further preclinical studies are ongoing.

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Health Care Resource Utilization and Costs of Steroid-Related Complications in Patients With Graft-Versus-Host Disease

Corticosteroids are often prescribed to treat GVHD. However, the prevalence, health care resource utilization, and costs of corticosteroid-associated complications are not well quantified. Dr Elizabeth J. Bell described the results of a retrospective cohort study that analyzed the health care resource utilization and costs of complications from corticosteroid use in patients with GVHD.[1] The investigators reviewed the Optum Research Database to identify patients in the United States with a diagnosis of GVHD who received systemic corticosteroids between July 1, 2010 and August 31, 2019 and who were insured with commercial insurance plans or Medicare Advantage plans. Patients with a baseline diagnosis of GVHD were included. Health care resource utilization and costs associated with corticosteroid complications during the 24 months after corticosteroid initiation were calculated, according to International Classification of Diseases codes for any corticosteroid complication in position 1 or 2 on the claims. Corticosteroid complications related to the bone/muscle, GI tract, infections, and metabolic/endocrine system were also described, based on their clinical relevance.

This study included 689 patients.[1] Their median age was 55 years (standard deviation, 18 years), and 60% were male. The median length of corticosteroid use during the 24 months after corticosteroid initiation was 126 days (range, 52 to 273 days). Overall, 97% of patients developed at least 1 type of complication, including infection (80%) and events involving the metabolic/endocrine system (32%), the GI tract (29%), or bone/muscle (20%). Among patients with at least 1 corticosteroid complication, the mean and median costs associated with corticosteroid complications throughout the 24 months from corticosteroid initiation were $164,787 and $50,834, respectively (Figure 9). The mean and median costs in the 408 patients treated with corticosteroids for 3 months or more were $171,434 and $56,542, respectively. In those who had only acute GVHD (n=146), the mean and median costs were $183,944 and $46,093, whereas in those with chronic GVHD (n=142), these costs were $113,199 and $34,285, respectively. Costs were driven primarily by hospitalizations (Figure 10).

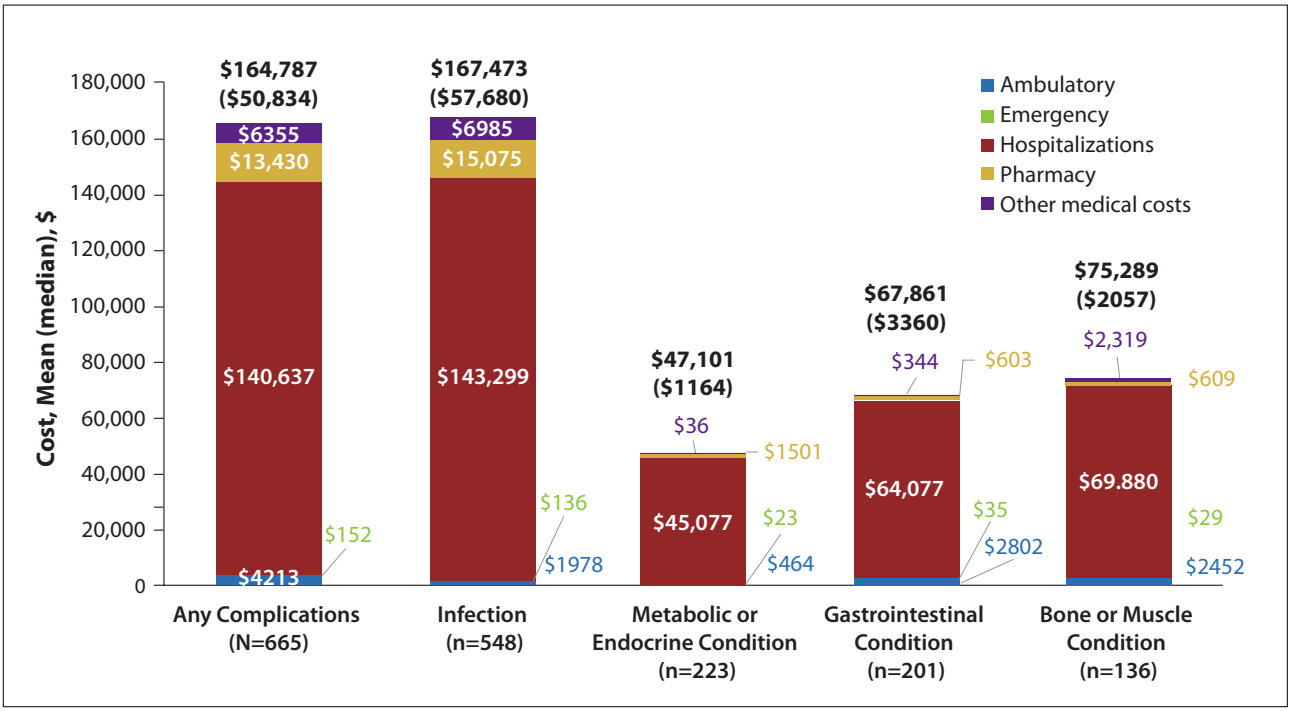

Figure 9. Health care costs related to corticosteroid complications among patients with graft-vs-host disease. Costs are shown during the 2 years after corticosteroid initiation for patients with at least 1 complication. Adapted from Bell EJ et al. TCT abstract 12. *Transplant Cell Ther.* 2021;27(3 suppl).[1]

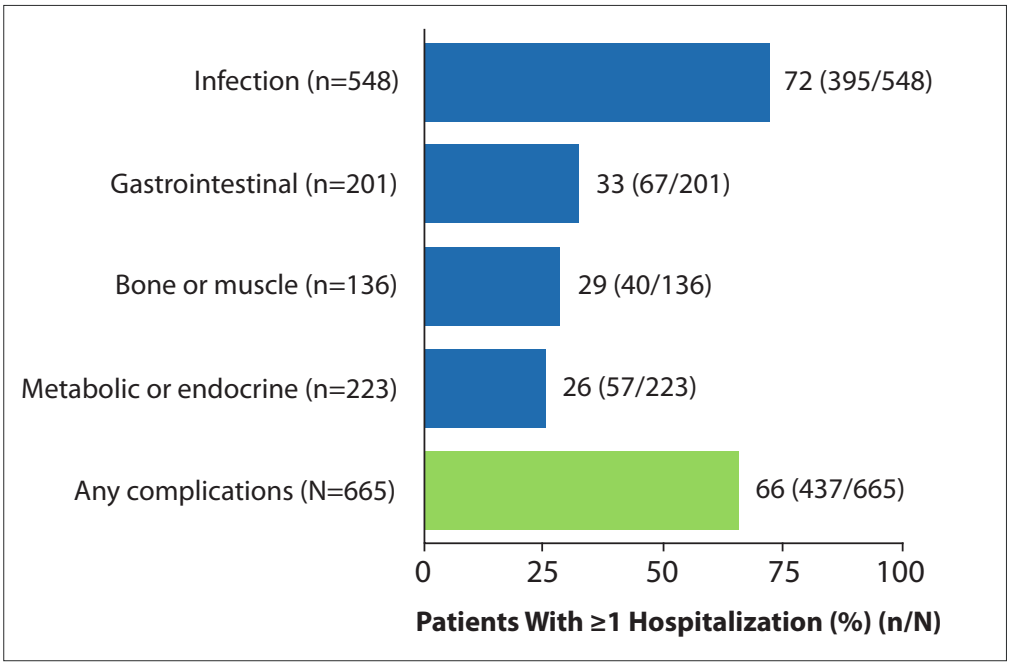

Figure 10. Reasons for hospitalizations related to corticosteroids during the 2 years after treatment initiation among patients with graft-vs-host disease. Adapted from Bell EJ et al. TCT abstract 12. *Transplant Cell Ther.* 2021;27(3 suppl).[1]

The study investigators concluded that there are substantial health care resource utilization and costs associated with corticosteroid-related complications in patients with GVHD.[1] Acute GVHD was associated with higher health care resource utilization and costs than chronic GVHD. A limitation to this study is that some conditions were present at baseline, and worsening of these conditions after corticosteroid initiation could not be accurately identified. Future studies will be needed to elucidate the clinical aspects of the complications, including severity and suspected causality.

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Secondary Graft-Versus-Host Disease Prophylaxis With Oral Proteasome Inhibitor Ixazomib Is Associated With Low Incidence of Recurrent, Late Acute, and Chronic GVHD and Facilitated Calcineurin Inhibitor Taper Within the First Year Post-Allogeneic Stem Cell Transplantation

Recipients of reduced-intensity and nonmyeloablative conditioning with calcineurin inhibitor–based prophylaxis often develop GVHD during tapering of immunosuppression drugs. Ixazomib is an oral proteasome inhibitor with immunomodulatory properties that has a tolerable safety profile.[1] Natasia T. Rodriguez, BSN, RN, presented data from an open-label, prospective, single-center pilot study of ixazomib for secondary GVHD prophylaxis and facilitation of calcineurin inhibitor taper.[2]

Eligible patients had a hematologic malignancy treated with reduced intensity or non-myeloablative allo-HCT and calcineurin inhibitor–based GVHD prophylaxis, had undergone HCT between 100 and 150 days prior to enrollment, and did not have active acute or chronic GVHD.[2] Patients received ixazomib at 4 mg orally once weekly administered in a 3 weeks on, 1 week off schedule. The treatment was continued for 1 year or until the prophylactic calcineurin inhibitor was completely tapered, whichever came first. The primary endpoint was the

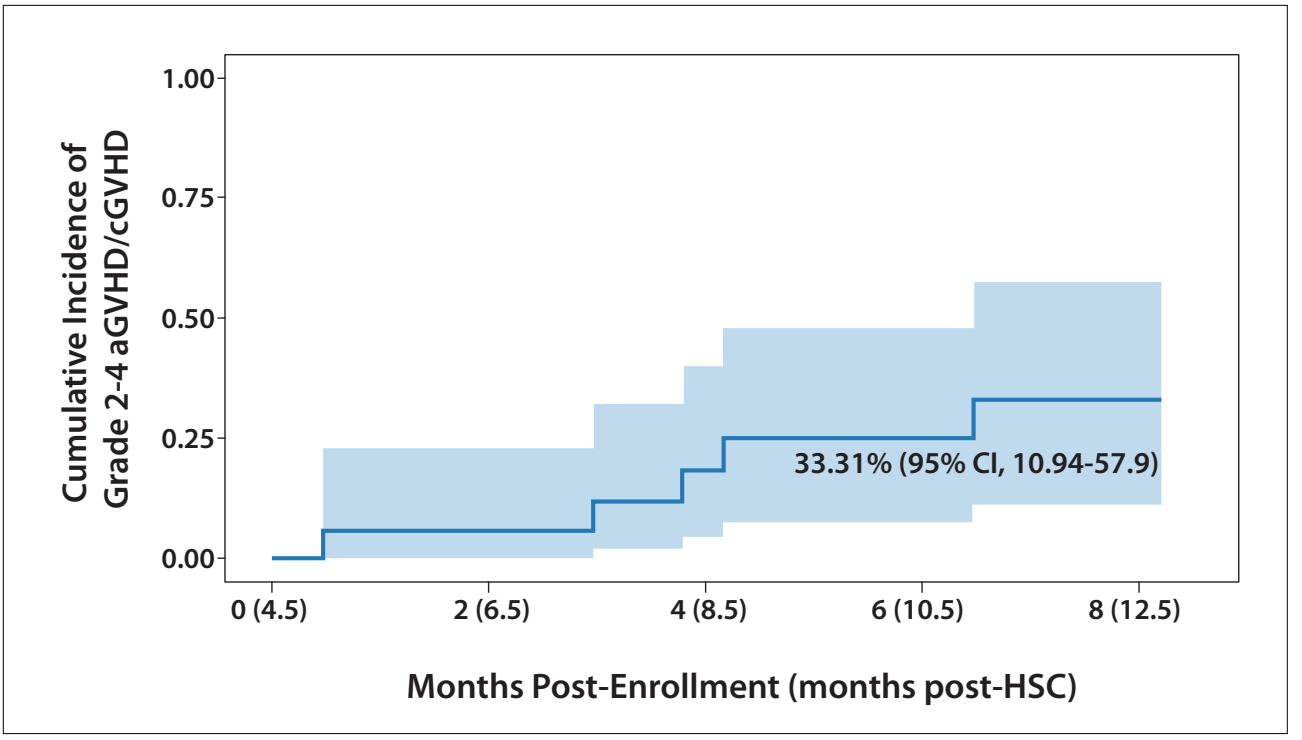

Figure 11. The cumulative incidence of grade 2 to 4 acute and chronic GVHD at 1 year after HCT in patients treated with ixazomib prophylaxis. aGVHD, acute graft-vs-host disease; cGVHD, chronic graft-vs-host disease; HCT, hematopoietic stem cell transplant. Adapted from Rodriguez NT et al. TCT abstract 84. *Transplant Cell Ther*. 2021;27(3 suppl).[2]

efficacy of ixazomib for the prevention of recurrent or late grade 2 to 4 acute GVHD or chronic GVHD at 1 year post-HCT. Additional endpoints included treatment-related mortality, relapse rate, survival analysis, safety, and immune reconstitution.

The trial enrolled 18 patients.[2] Their median age was 58 years (range, 45-69 years). Most patients (89%) were male. All patients had received a peripheral blood stem cell graft, and 16 of the patients (89%) were 10/10 HLA-matched. Four patients developed GVHD, and had either severe overlap syndrome (n=2), mild de novo chronic GVHD (n=1), or recurrent grade 2 acute GVHD (n=1). At 1 year post-HCT, the cumulative incidence of grade 2 to 4 acute and chronic GVHD was 33.3% (95% CI, 10.95%-57.9%; Figure 11). No patients died during the study. The incidence of relapse was low; 1 patient who discontinued ixazomib early relapsed with low-grade follicular lymphoma that did not require therapy.

Progression-free survival at 1 year was 88% (95% CI, 67%-100%), and GVHD-free/relapse-free survival at 1 year was 77% (95% CI, 56%-100%).[2] There was a rapid and sustained recovery in T-cell subpopulations and B-cell reconstitution at 3, 6, and 12 months post-HCT. Grade 3/4 AEs included decreased neutrophil count (n=5), decreased lymphocyte count (n=2), anemia (n=1), and rash (n=1). Seven patients required a dose reduction of ixazomib owing to side effects, and 5 patients left the study owing to toxicity.

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Highlights in Graft-vs-Host Disease From the 2021 Transplantation & Cellular Therapy (TCT) Meetings of the ASTCT and the CIBMTR: Commentary

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Several interesting abstracts on graft-vs-host disease (GVHD) were presented at the 2021 Transplantation & Cellular Therapy (TCT) meetings, which were the combined, all-virtual annual meetings of the American Society for Transplantation and Cellular Therapy and the Center for International Blood & Marrow Transplant Research. There were studies with implications for current clinical practice, as well as future research, in both acute and chronic GVHD.

Prevention of GVHD

Historically, prevention of GVHD has focused on acute GVHD, given the timing of presentation and early effects on long-term outcomes. However, clinical research has recently emphasized the prevention of chronic GVHD as an increasingly important outcome. This shift is emphasized in the composite primary endpoints of several recent major clinical trials.

The phase 3 Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 1301 PROGRESS II trial enrolled patients who had received myeloablative, fully matched transplants from a related or unrelated donor.[1] The motivation behind this trial was to develop a calcineurin inhibitor–free regimen for the prevention of GVHD, possibly as a platform to deliver maintenance therapy or cellular therapy to decrease the risk of disease relapse. The trial randomly assigned patients (≤65 years) undergoing myeloablative transplant to 3 different platforms to prevent graft-vs-host-disease. The control arm consisted of tacrolimus and methotrexate (MTX) with a bone marrow graft source. The second arm evaluated a bone marrow graft source with post-transplant high-dose cyclophosphamide given on days 3 and 4 after transplant. Treatment in the third arm consisted of ex vivo T-cell depletion using CD34-selected peripheral blood stem cells.

The study used an interesting primary endpoint of chronic GVHD-free and relapse-free survival, which was referred to as CRFS.[1] The analysis showed that there was no statistically significant difference in the primary endpoint among the 3 treatment arms. A key secondary endpoint was overall survival, and participants who received T-cell depletion had a lower overall survival of 75.7% at 1 year, compared with approximately 84% in the other 2 arms, which was mostly driven by an increase in transplant-related mortality. It should be noted that chronic GVHD was significantly reduced in the T-cell depleted arm.

Based on these results, it appears that tacrolimus/MTX remains the standard of care in this setting, although post-transplant cyclophosphamide alone appears to be a reasonable alternative. Notably, in routine practice, post-transplant cyclophosphamide is usually given with tacrolimus and mycophenolate, and one wonders if the inclusion of these other agents would have significantly changed the observed results.

Dr Muna Qayed presented data from a subanalysis of the ABA2 trial.[2] The ABA clinical trials are studying the role of abatacept, which is a co-stimulatory inhibitor, for the prevention of GVHD. The ABA2 trial had 2 arms and enrolled patients with fully matched donors (8/8 human leukocyte antigen [HLA]-matched), as well as patients with single-antigen mismatched, unrelated donors (7/8 HLA-matched). The trial compared standard treatment with a calcineurin inhibitor (CNI) plus MTX vs CNI/MTX with the addition of abatacept. Previously published results from the ABA2 trial suggested that the addition of abatacept improved outcomes, especially in patients receiving grafts from 7/8 matched, unrelated donors.[3] This secondary analysis of the ABA2 data compared the outcomes of these 7/8 patients, who received a CNI

with MTX plus abatacept, to the fully matched 8/8 patients treated with CNI/MTX on the ABA2 trial. The primary endpoint was the incidence of severe acute (overall, grades 3-4) GVHD at 6 months. The incidence was strikingly lower in the patients who received abatacept, at 2.3%, vs 14.8% in the 8/8 CNI/MTX arm. There were no significant differences in other outcomes, such as chronic GVHD or overall transplant-related mortality. However, the decrease in severe acute GVHD was quite compelling, with trends toward better progression-free survival and overall survival in the patients who received abatacept.

These results lay the groundwork for the ongoing ABA3 trial, which is focusing on patients receiving 7/8 matched grafts to confirm whether the addition of abatacept can improve outcomes.[4] Currently, there is no standard of care for these patients. Historically, treatment had included the addition of polyclonal antithymocyte globulins. More recently, many clinicians have shifted toward the use of post-transplant cyclophosphamide-based regimens for these patients. It would be an important advance to have data from large clinical trials in this group of patients to determine the standard of care.

Dr Meredith McAdams presented data from a phase 1 study that evaluated de-intensified exposure to post-transplant cyclophosphamide given after HLA haploidentical hematopoietic cell transplant.[5] Post-transplant high-dose cyclophosphamide-based regimens have emerged as the standard of care for patients undergoing haploidentical and mismatched, unrelated donor transplants. As mentioned above, this platform is also being studied in the setting of transplants from fully matched and mismatched unrelated donor transplants. Historically, post-transplant cyclophosphamide is administered at a dose of 50 mg/kg/day given on days 3 and 4 after transplant. Although this schedule appears to successfully prevent GVHD, it is associated with toxicities, such as acute fluid shifts, electrolyte abnormalities, and cardiac events, and it also appears to significantly delay engraftment compared with conventional CNI-based regimens.

The study by Dr McAdams examined whether the dose of cyclophosphamide could be safely reduced.[5] These investigators showed in murine models that 50 mg/kg was not absolutely necessary; instead, 25 mg/kg given only on day 4 seemed to confer equivalent efficacy.[6,7] This phase 1 study followed a dose de-escalation design to test this hypothesis. All of the patients received a myeloablative conditioning regimen, followed by a haploidentical bone marrow graft, and then GVHD prophylaxis consisting of post-transplant cyclophosphamide, sirolimus, and mycophenolate. The dose of cyclophosphamide was then successively lowered in the different cohorts. The first 5 patients received the standard 50 mg/kg/day on both days 3 and 4. The next cohort received 25 mg/kg/day on both days, followed by a third cohort that received 25 mg/kg only on day +4.

Impressively, none of the 11 patients in the dose de-escalated cohorts developed grade 3 to 4 acute GVHD. Although the number of patients in this phase 1 trial was small, the results are compelling. In addition, engraftment of neutrophils and platelets appeared to be faster among patients receiving lower doses of cyclophosphamide. However, some patients in the dose de-escalated cohorts had significant delays in assuming full donor chimerism. Moving forward, as post-transplant cyclophosphamide–based regimens become increasingly popular, these early findings do merit further study, as it should be essential to define the minimum dose of cyclophosphamide needed for utility.

Dr Andrea Henden presented the results of a basic science investigation that evaluated how interferon lambda protects gastrointestinal stem cells from acute GVHD in murine transplant models.[8] Acute GVHD of the lower intestine is responsible for the majority of the morbidity and mortality observed with acute GVHD.

ABSTRACT SUMMARY Orca-T, a Precision T_{reg}-Engineered Donor Product, in Myeloablative HLA-Matched Transplantation Prevents Acute GVHD With Less Immunosuppression in an Early Multicenter Experience

Infusion of donor-derived high-purity regulatory T cells preceding adoptive transfer of conventional T cells may prevent GVHD while maintaining anticancer immunity. Orca-T is an engineered graft product. Purified regulatory T cells are sorted and administered on day 0 of HCT, along with hematopoietic stem cells. Conventional T cells are then administered on day 2. In this phase 1/2 trial, 50 patients with hematologic malignancies undergoing myeloablative conditioning received Orca-T plus GVHD prophylaxis with tacrolimus or sirolimus during HCT with either matched related (n=62) or unrelated (n=38) donors (Abstract 88). The control group (n=144) received standard-of-care treatment with peripheral blood stem cell and prophylaxis with methotrexate plus tacrolimus; 56% of these patients had matched related donors. The incidence of grade 2 to 4 acute GVHD was 10% in the Orca-T group vs 30% in the control group (*P*=.0018). The rates of moderate-to-severe chronic GVHD were 3% vs 46%, respectively (*P*=.016). Preliminary results for 1-year GVHD-free/relapse-free survival rates were 75% with Orca-T vs 31% with control (*P*=.006). No differences in infectious complications were seen.

Recently, studies have shown that the earliest site of infiltration of donor cells in acute GVHD appears to be localized to the crypt base of the intestine, specifically the niche that houses intestinal stem cells.[9] A significant injury to the intestinal stem cell niche impairs the ability of the intestine to heal and re-epithelialize the mucosa, and this is potentially why some patients do not respond clinically to multiple lines of immunosuppressive therapy for acute GVHD.

Recently, novel approaches to the treatment of acute GVHD have not focused on donor T cells, but rather aim to protect the recipient's intestinal stem cells. This study evaluated recombinant interleukin 29, an interferon-lambda receptor ligand. When mice were administered this ligand, their intestinal stem cells appeared to be protected by preservation of gastrointestinal tissue, and clinical outcomes in gastrointestinal GVHD improved. This study provides further preclinical support for the idea that acute GVHD can and should be treated by methods targeting not only adaptive immunity, but organ resiliency as well. The transplant community has acknowledged that the historical limited focus on cumulative immunosuppression for the treatment of acute GVHD has not improved outcomes. Investigation into other avenues, such as targeting specific inflammatory pathways or other mechanisms including intestinal stem cell preservation, are worthy of further study.

Turning to treatment of acute GVHD, Dr John Koreth presented early findings studying the safety and efficacy of itolizumab, a monoclonal antibody targeting CD6, for the treatment of severe acute GVHD.[10] This study is based on older data showing that CD6 is a costimulatory receptor that is expressed on activated T cells. Research in the 1990s provided some evidence that depletion of CD6-positive cells early in transplant could decrease the risk of acute GVHD.[11]

This phase 1b/2 trial evaluated the addition of itolizumab to corticosteroids for the initial treatment of severe, grade 3/4 acute GVHD.[10] The presentation provided early results for the first 10 patients who completed treatment through 8 weeks. Three different doses were tested, and all patients also received corticosteroids at the initial standard dose of 1 to 2 mg/kg/day of the prednisone equivalent. The investigators reported an impressive overall response rate of 80% at day 29, with a complete response in 70% and a very good partial remission in 10%. Importantly, in all of the responding patients, the overall response was sustained through the day 57 follow-up period. Strong correlative data showed that the administration of itolizumab reduced the expression of CD6, or at least decreased the number of cells that expressed CD6. Although the study included a very small number of patients, these early results are compelling, and we look forward to more mature data on a larger number of treated patients.

Chronic GVHD: Insights Into Current Treatment Strategies

Several abstracts at the TCT meeting provided data regarding current thinking and treatments for chronic GVHD. An interesting analysis presented by the Chronic Graft-vs-Host Disease Consortium evaluated rates of successful, durable discontinuation of immunosuppressive therapy in approximately 700 patients.[12] Durable discontinuation, in this study, referred to cessation of immunosuppressive therapy for at least 12 months. Long-term follow-up showed that only one-third of subjects were able to discontinue immunosuppression for longer than one year, whereas all other patients continued to receive therapy or needed to resume treatment after symptoms flared.

The study investigators concluded that, for the majority of patients, chronic GVHD behaves like an ongoing chronic autoimmune disease that requires continued therapy.[12] It is therefore not a temporary state that can be cured with a limited course of therapy, and we should change how we frame expectations for our patients. For most patients, it is likely not possible to achieve a complete remission after chronic GVHD sets in with the currently available therapeutic strategies. These sobering data raise the questions of not only where we should focus future investigation, but also how to design more relevant endpoints for clinical trials focusing on chronic GVHD.

Dr Ben Watkins presented results of a study that questioned whether there is an immunologic signature in patients who develop de novo GVHD.[13] This study examined a subgroup of patients enrolled in the aforementioned ABA2 study who received standard tacrolimus/MTX for the prevention of GVHD. The investigators compared blood samples from 19 patients who developed de novo chronic GVHD (meaning they had no prior acute GVHD) vs 7 patients without GVHD. Around day 100, patients who developed de novo chronic GVHD had a significantly increased proportion of naive CD4-positive T cells relative to controls who never developed chronic GVHD. RNA sequencing of the CD4 T cells revealed a gene signature that differed from that in the patients without chronic GVHD. This study does not yet define a usable platform, but it suggests that there are different immunologic signatures in patients at certain time points after transplant that can help predict events like development of chronic GVHD. In routine clinical practice, if patients can be categorized in real time as higher or lower risk for specific complications such as chronic GVHD, it may be possible to intervene preemptively and perhaps alter outcomes before chronic GVHD is firmly established.

Dr Elizabeth Bell presented results

from a multicenter study that evaluated the Optum research database to identify US commercial and Medicare Advantage patients with acute or chronic GVHD who were treated with corticosteroids.[14] This study evaluated medical records to attempt to quantify the burden and cost of corticosteroid-associated complications. Unfortunately, systemic corticosteroids remain the standard of care for both acute and chronic GVHD. Any successful therapy should not only improve outcomes, but should also allow clinicians to taper corticosteroids quicker, thereby reducing the amount of systemic exposure for patients. Ultimately, one goal is to find a treatment for acute and/or chronic GVHD that can replace corticosteroids for certain subsets of patients. Corticosteroids are well-known to cause a variety of toxicities, including immunosuppression, hypertension, osteoporosis, diabetes, cataracts, mood issues, and body dysmorphia. This study evaluated factors such as bone, muscle, and metabolic endocrine complications, as well as gastrointestinal infections, to quantify the cost of treatment. The investigators found a significant burden of health care resource utilization from corticosteroids, with the majority of the costs quantified within the first year of use and driven by hospitalizations. The study provides an important step in the right direction toward the eventual development of endpoints that could measure the reduction of corticosteroid toxicity in trials to treat GVHD.

Dr Zachariah DeFilipp presented results of an analysis of more than 900 patients who required new systemic therapy from the Chronic Graft-vs-Host Disease Consortium that aimed to identify causes of long-term nonrelapse mortality in patients with chronic GVHD.[15] The patients had undergone transplant between 1987 and 2017, and the median follow-up was 4 years. Approximately one-quarter of the deaths were attributable to disease relapse, meaning relapse of the patient's cancer. Nonrelapse mortality accounted for approximately 40% of deaths, with no plateau observed on the Kaplan-Meier curve. The most common identifiable causes of nonrelapse mortality were chronic GVHD plus infection, followed by infection alone. These events are closely related owing to inherent chronic GVHD-associated immune dysregulation and the nature of treatments used for chronic GVHD.

The results of the study underscore the observation that for patients with chronic GVHD, the risk for morbidity and mortality does not end.[15] As patients continue to experience the clinical burden of disease, their cumulative risk of nonrelapse mortality continues to increase. This analysis clearly illustrates the unmet need for effective treatments not only to improve chronic GVHD but also to spare patients the toxicities associated with current therapies.

Chronic GVHD: Clinical Trial Data

Dr Corey Cutler presented results from the pivotal, randomized phase 2 ROCKstar trial, which evaluated belumosudil, an oral rho-associated coiled-coil kinase 2 (ROCK2) inhibitor, for the treatment of patients with chronic GVHD who had already received 2 previous therapies.[16] Data from the previously presented phase 2a study were compelling.[17] In this phase 2 trial, 132 patients were randomly assigned to 1 of 2 doses of belumosudil: 200 mg daily or 200 mg twice daily. The observed overall response rate was more than 70% in each arm. Responses were seen across all severities of chronic GVHD, all sites of organ involvement, and in patients previously treated with ibrutinib or ruxolitinib. Belumosudil appeared to have an acceptable toxicity profile, without any signals of increased infections. Inhibition of ROCK2 is thought to decrease inflammation and fibrosis, and the development of this agent is in line with the general theme in newer trials in chronic GVHD: less global immunosuppression and more targeting of specific pathways of inflammation or fibrosis. It should be noted that the ROCKstar trial did not include a placebo arm, and assessment of chronic GVHD can be quite subjective. Based on these data, however, there is a strong chance that the US Food and Drug Administration (FDA) will approve belumosudil for this indication.

Dr Stephanie Lee presented results from the international, randomized phase 3 REACH3 study, which compared ruxolitinib vs best available therapy among patients with corticosteroid-refractory chronic GVHD.[18] Ruxolitinib is a Janus kinase inhibitor (JAK) 1/2 inhibitor that is already approved for the treatment of patients with corticosteroid-refractory acute GVHD.[19] JAK inhibitors are currently being studied in all phases of GVHD, from prevention to initial therapy to treatment of refractory disease. The primary endpoint in REACH3 was the overall response rate at 24 weeks. After that time, patients in the control arm were permitted to cross over to the ruxolitinib arm. This trial was a major undertaking, and the investigators should be applauded for conducting the first phase 3 trial in corticosteroid-refractory chronic GVHD that yielded a positive outcome.

At 24 weeks, the patients who received ruxolitinib had a much higher overall response rate than those receiving best available therapy (which was chosen at the discretion of the investigator), at 50% vs only 26%.[18] Ruxolitinib also significantly improved key secondary endpoints, such as the median failure-free survival and the percentage of patients who had a significant symptom response (as measured by the modified Lee symptom scale).

The adverse events were those expected with ruxolitinib in this population. There was a slight signal of

more infections in the ruxolitinib arm, but the difference was not statistically significant. Based on these results, the FDA will likely approve ruxolitinib in this setting, thereby allowing more patients to access this treatment. There remain several questions regarding the use of ruxolitinib for chronic GVHD, such as the duration of therapy and the durability of responses. Another question that requires study is how to safely discontinue therapy, as a tapering schedule might be necessary for this agent.

A report from Dr YunZu Michele Wang described a single-center case series that evaluated ruxolitinib for the treatment of refractory chronic GVHD among the pediatric population.[20] These investigators developed a weight-based algorithm to determine the starting dose of ruxolitinib. Patients weighing less than 25 kg received a dose of 2.5 mg twice daily. Patients who weighed 25 kg or more received an initial starting dose of 5 mg twice daily. In both arms, the dose was gradually escalated to 10 mg twice daily, when tolerated. Among the 20 patients treated, 14 had a meaningful response, with 12 partial remissions and 2 complete remissions. Impressively, 13 of these responses were durable. As expected, in the majority of patients, it was possible to decrease the dose of systemic corticosteroids. These cases illustrated the safety of a dosing strategy for ruxolitinib in children and young adults with GVHD, and hopefully, ruxolitinib will also become an option for the pediatric population.

Disclosure

Dr Chen has performed consulting for Incyte and Magenta. He is a member of the DSMB Committees of AbbVie, Daiichi, Equillium, Celularity, and Actinium.

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