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A SPECIAL MEETING REVIEW EDITION

Highlights in Graft-Versus-Host Disease From the 2023 Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR

A Review of Selected Presentations From the Tandem Meetings • February 15-19, 2023 • Orlando, Florida

Special Reporting on:

- Two Post Hoc Analyses of Data From the Phase 3 REACH-2 Study of Ruxolitinib vs Best Available Therapy in Patients With Acute Steroid-Refractory GVHD
- Three Studies of GVHD Patients Treated With Ruxolitinib
- Inhibition of the Receptor Interactive Protein Kinase 1 (RIP1) Pathway Prevents Acute GVHD
- De Novo Late Acute GVHD: Incidence, Outcomes, and Impact of Biomarkers Compared to Classic Acute GVHD
- Orca-Q Demonstrates Favorable GVHD- and Relapse-Free Survival With Haploidentical Donors Without Posttransplant Cyclophosphamide
- Phase II Study of Myeloablative 8/8- or 7/8-Matched Allotransplantation With Posttransplant Cyclophosphamide, Tacrolimus, and Mycophenolate Mofetil: Marked Reduction in GVHD Risk Without Increased Relapse Risk Compared With Historical Cyclosporine/Methotrexate
- Final Safety and Efficacy Results From EQUATE, an Open-Label Study Evaluating Itolizumab, a Novel Targeted Anti-CD6 Therapy, in Newly Diagnosed Acute Graft-Versus-Host Disease
- Belumosudil Impacts Immunosuppression Pharmacokinetics in Patients With Chronic Graft-Versus-Host Disease
- Vedolizumab for Prophylaxis of Lower Gastrointestinal (GI) Acute Graft-versus-Host Disease (aGVHD) After Allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT) From Unrelated Donors: Results of a Phase 3 Randomized, Double-Blind, Placebo-Controlled Multicenter Study (GRAPHITE)

PLUS Meeting Abstract Summaries

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Two Post Hoc Analyses of Data From the Phase 3 REACH-2 Study of Ruxolitinib vs Best Available Therapy in Patients With Acute Steroid-Refractory GVHD

The open-label phase 3 REACH-2 study evaluated ruxolitinib (10 mg, twice daily) vs best available therapy (BAT) in patients with grade 2 to 4 corticosteroid-refractory acute graft-versus-host-disease (GVHD).[1] Dose modifications were allowed at the physician's discretion according to protocol guidelines. A post hoc study evaluated the treatment response in 309 patients with or without cytopenias from REACH-2.[2] Baseline demographics and disease characteristics were well balanced among patients in the 2 arms. At day 28, ruxolitinib was associated with numerically higher response rates in comparison with BAT in nearly all patient subgroups, including those with low white blood cell, neutrophil, platelet, or hemoglobin levels (Figure 1). Odds ratios reflected the superiority of ruxolitinib vs BAT at day 28 in all cytopenia subgroups as well as in the overall study population. Among patients with a response at day 28, responses were durable according to evaluations at day 56 across all subgroups with or without cytopenias.

Table 1. ORR in Patients Based on Early, Late and Very Late, or Very Late Initiation of Therapy for GVHD

	Early		Late and Very Late		Very Late	
	Ruxolitinib (n=112)	**BAT (n=115)**	**Ruxolitinib (n=42)**	**BAT (n=40)**	**Ruxolitinib (n=24)**	**BAT (n=22)**
ORR, Day 28 (%)	62.5	38.3	61.9	42.5	62.5	40.9
Odds Ratio (95% CI)	2.63 (1.53–5.06)		3.80 (1.06–7.41)		2.94 (0.84–10.35)	

BAT, best available therapy; CI, confidence interval; GVHD, graft-versus-host-disease; ORR, objective response rate. Adapted from a presentation at the Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; February 15-19, 2023; Orlando, Florida.[3]

A second post hoc analysis evaluated the effect of the timing of the initiation of ruxolitinib therapy on outcomes in patients from REACH-2.[3] In the ruxolitinib vs the BAT arm, 112 vs 115 patients were randomized

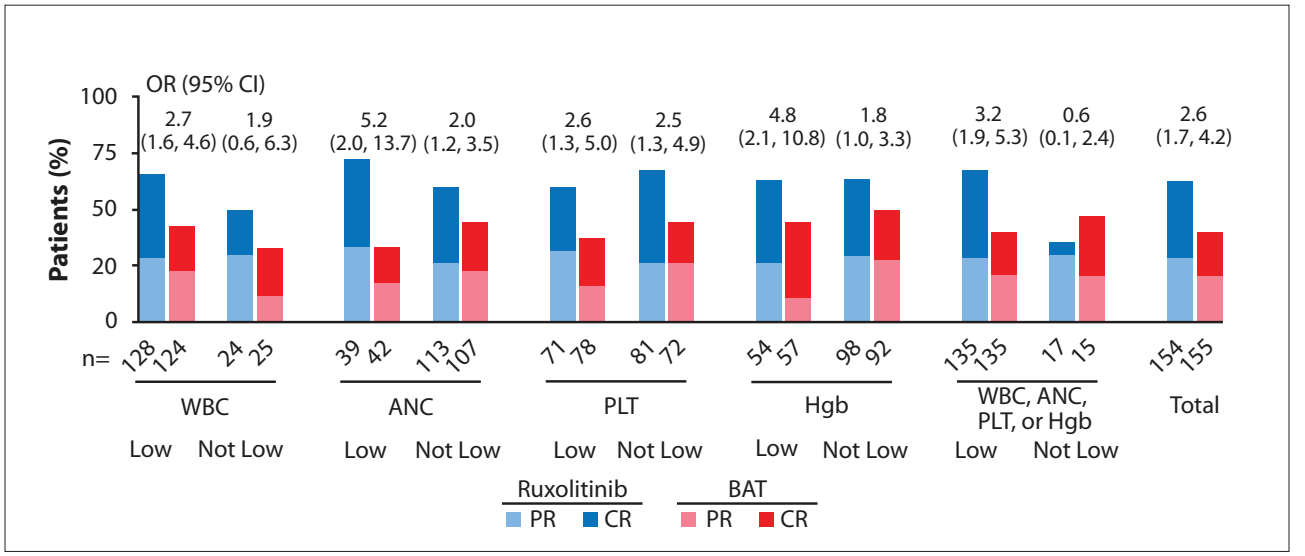

Figure 1. The overall response rate of ruxolitinib vs best available therapy for patients with corticosteroid-refractory acute graft-versus-host disease at day 28 defined by the presence (low) or absence (not low) of white blood cell count, absolute neutrophil count, platelet count, or hemoglobin measure between baseline and week 4. Adapted from a presentation at the Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; February 15-19, 2023; Orlando, Florida.[2]

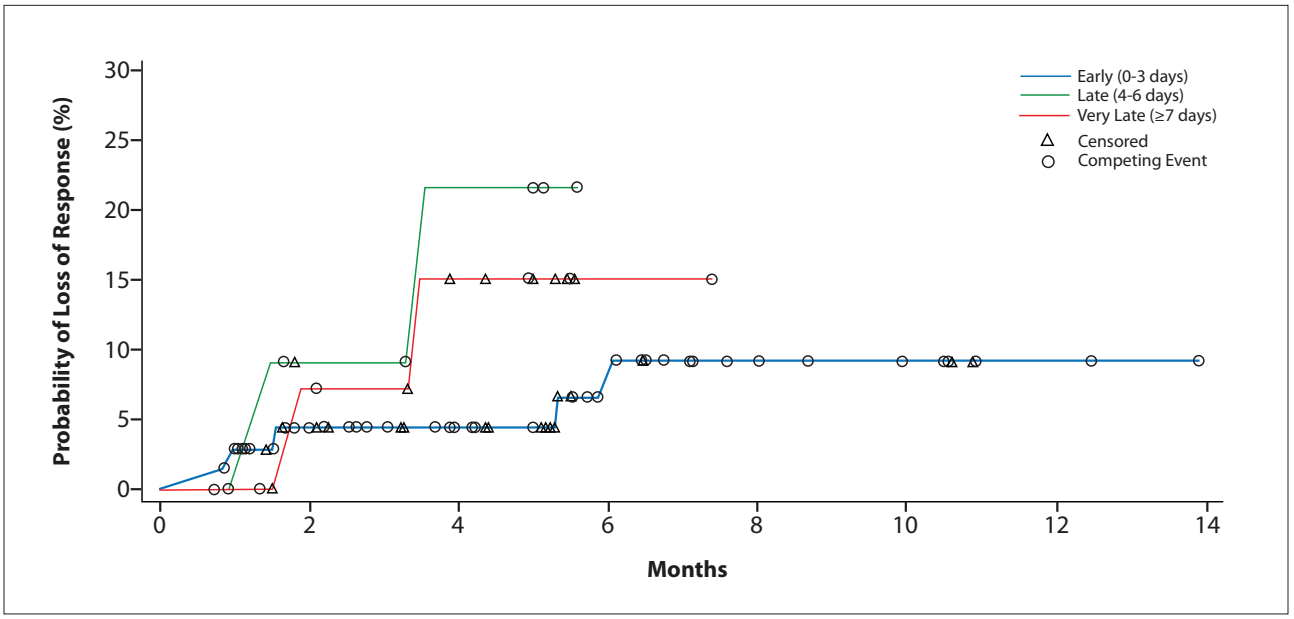

Figure 2. The duration of response (probability of loss of response over time between ruxolitinib-treated groups) by treatment and time to initiation in patients with acute graft-versus-host disease. Adapted from a presentation from the Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; February 15-19, 2023; Orlando, Florida.[3]

to early treatment (0-3 days), 42 vs 40 to late treatment (4 to <7 days), and 24 vs 22 to very late treatment (≥7 days) (Figure 2). The median age among subgroups ranged from 48.5 to 55 years. Most patients had grade 2 or 3 acute GVHD at randomization. At day 28, the objective response rate with ruxolitinib was superior to that with BAT, regardless of the timing of treatment initiation (Table 1). In conclusion, ruxolitinib demonstrated a superior clinical benefit in comparison with BAT, even among patients in whom the initiation of therapy was delayed after the onset of corticosteroid-refractory acute GVHD.

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Three Studies of GVHD Patients Treated With Ruxolitinib

A retrospective study compared outcomes in patients with grade 2 to 4 acute GVHD who underwent allogeneic hematopoietic stem cell transplantation (HSCT) between 2011 and 2015, before the availability of ruxolitinib (n=107), vs outcomes in patients who underwent HSCT between 2016 and 2021 (n=109) at a single treatment center (Figure 3).[1] Patients in the latter cohort were more likely to have obtained a transplant from a haploidentical donor (38.5% vs 4.7%; *P*<.001), and 28 patients in this group received treatment with ruxolitinib. The rate of nonrelapse mortality was 31% in the 2011-to-2015 group vs 13% in the 2016-to-2021 group (*P*=.001), although relapse rates were similar (*P*=.268). Overall survival (OS) rates at 2 years after the onset of acute GVHD were 53% vs 64%, respectively (*P*=.04).

A small study evaluated the pharmacokinetics of ruxolitinib in patients younger than 2 years with acute (n=2) or chronic (n=2) GVHD.[2] Both of the patients with chronic GVHD exhibited a complete response at 6 months, although neither of the patients with steroid-refractory acute GVHD exhibited a response at day 28. Ruxolitinib exposure was lower than expected, on the basis of modeling derived from ruxolitinib data

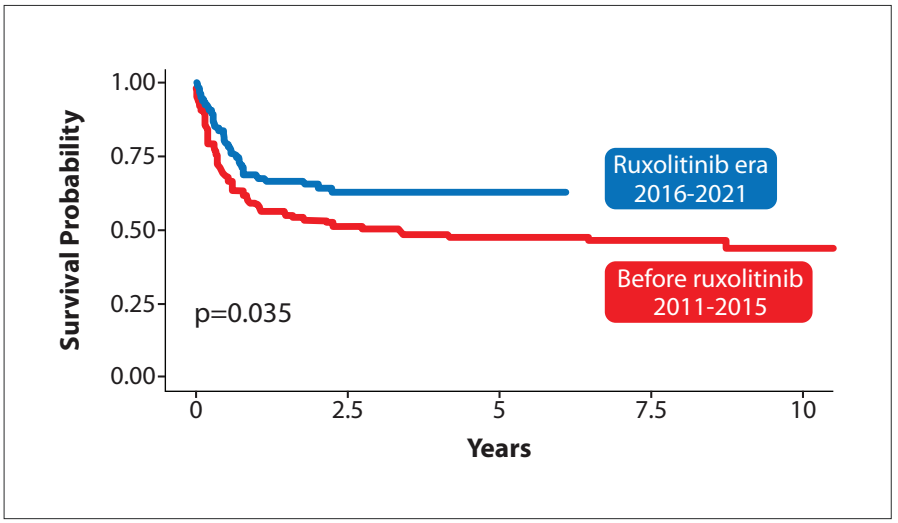

Figure 3. The overall survival probability of patients with acute graft-versus-host disease before and after the introduction of ruxolitinib into clinical practice. Adapted from a presentation from the Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; February 15-19, 2023; Orlando, Florida.[1]

in adults, and may be explained by more rapid drug elimination. The level of expression of pSTAT3 on CD8+ cells stimulated with interferon-γ or interleukin 2 correlated most closely with clinical response. Larger studies are necessary to evaluate the pharmacokinetics and pharmacodynamics of ruxolitinib in young children.

A retrospective study used data from the Center for International Blood and Marrow Transplant Research Registry to evaluate the use of extracorporeal photopheresis (ECP) in patients with chronic GVHD who received treatment with or without ruxolitinib.[3] All of the 200 included patients had received ECP, and 96 patients (48%) had also received ruxolitinib. Other therapies were allowed. Among the patients treated with ECP plus ruxolitinib vs those treated only with ECP, the OS rates at 1 and 2 years after treatment were 77.4% vs 69.6% and 64.7% vs 52.9%, respectively (P>.05). In the ECP-only group, 57% of patients (19/33) stopped corticosteroid therapy less than 6 months after treatment, vs 30% of patients (9/30) in the ECP-plus-ruxolitinib group.

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Inhibition of the Receptor Interactive Protein Kinase 1 (RIP1) Pathway Prevents Acute GVHD

Allogeneic HSCT is performed to restore hematopoiesis in patients with hematologic malignancies and other diseases.[1,2] However, depending on the donor characteristics, graft source, prophylactic therapy, and other factors, GVHD, in which transplanted T cells attack the cells of the transplant recipient, develops in 30% to 60% of patients who undergo allogeneic HSCT. Acute GVHD, which typically involves the skin, liver, and gastrointestinal (GI) tract, is a major cause of nonrelapse mortality. Acute GVHD of the GI tract results in the loss of intestinal stem cells by apoptosis, and although immunosuppressive drugs can often address GVHD symptoms, they increase the risk of infection.[3,4] Thus, non-immunosuppressive strategies that protect the GI epithelium are being explored.

Inhibition of the cell death receptor interactive protein 1 (RIP1) is being investigated as a non-immunosuppressive means to prevent GVHD.[5] Activation of RIP1 kinase by phosphorylation (pRIP1) leads to GI stem cell death and predicted 12-month nonrelapse mortality (NRM), with greater NRM in patients with high RIP1 expression (Figure 4).

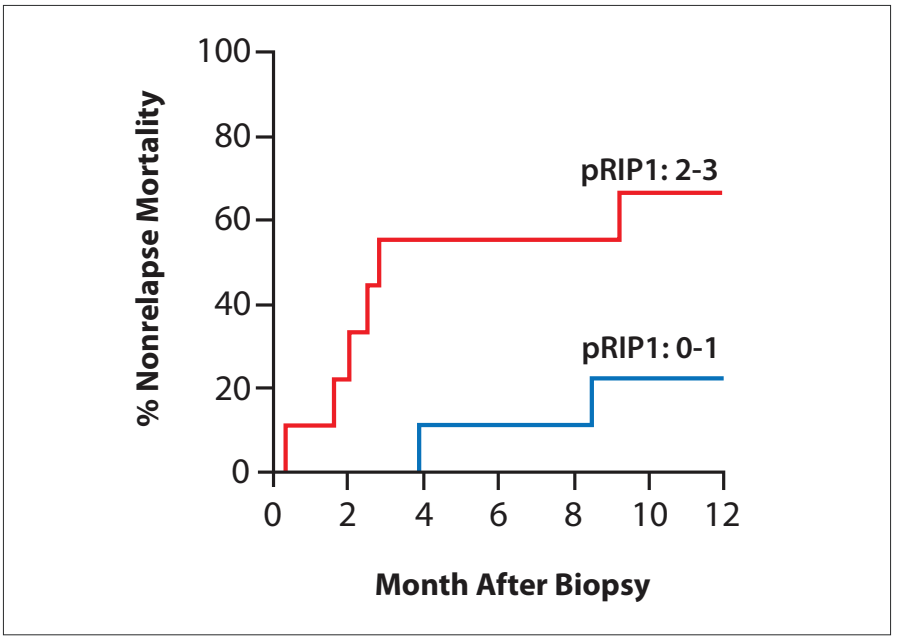

Figure 4. The cumulative incidence of nonrelapse mortality according to posphorylated RIP1 expression in gastrointestinal biopsies obtained from patients with acute graft-versus-host disease. Adapted from a presentation at the Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; February 15-19, 2023; Orlando, Florida.[5]

Therefore, inhibition of RIP1 activity may prevent the symptoms of acute GVHD in the gut. This hypothesis was tested in a mouse model of HSCT. Stem cells for transplant were derived from syngeneic or allogeneic donors. The HSCT recipients were either B6 mice with the wild-type RIP1 gene (RIP1-WT) or B6 mice with a mutation that inactivated RIP1 (B6-RIP1-KD [kinase dead]). As expected, the mice in which GVHD did not develop had a survival rate of 100% at 6 weeks after transplant. Notably, survival rates were significantly higher in the B6-RIP1-KD mice than in the B6-RIP1-WT mice (80% vs 40%; $P<.001$). GNE684, an orally available inhibitor of RIP1, has been shown to reduce arthritis, skin inflammation, and colitis in mice, underscoring the role of RIP1 in inflammation.[6] In both mouse and human organoids derived from intestinal stem cells, inhibition of RIP1 activity by GNE684 prevented apoptosis.[5] In B6-RIP1-WT mice, the daily administration of GNE684 yielded a dose response, such that higher doses of the drug were associated with higher survival rates at 35 days after allogeneic HSCT. Survival of the B6-RIP1-WT mice approximately 5 weeks after transplant was significantly better in the mice who were treated with the RIP1 inhibitor than in the control mice ($P<.05$), although the graft-versus-leukemia effect was preserved. Inhibition of RIP1 was shown to preserve intestinal stem cells by preventing the inflammatory activity mediated by interferon-γ and tumor necrosis factor-α.

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De Novo Late Acute GVHD: Incidence, Outcomes, and Impact of Biomarkers Compared to Classic Acute GVHD

According to criteria published by the National Institutes of Health (NIH) in 2005, GVHD is categorized as acute if symptoms develop by day 100 after HSCT and as late if symptoms develop after day 100.[1,2] According to various other criteria, GVHD may be categorized as classic, persistent, recurrent, de novo late, or chronic. A handful of studies have suggested that late acute GVHD (aGVHD) has a superior rate of survival

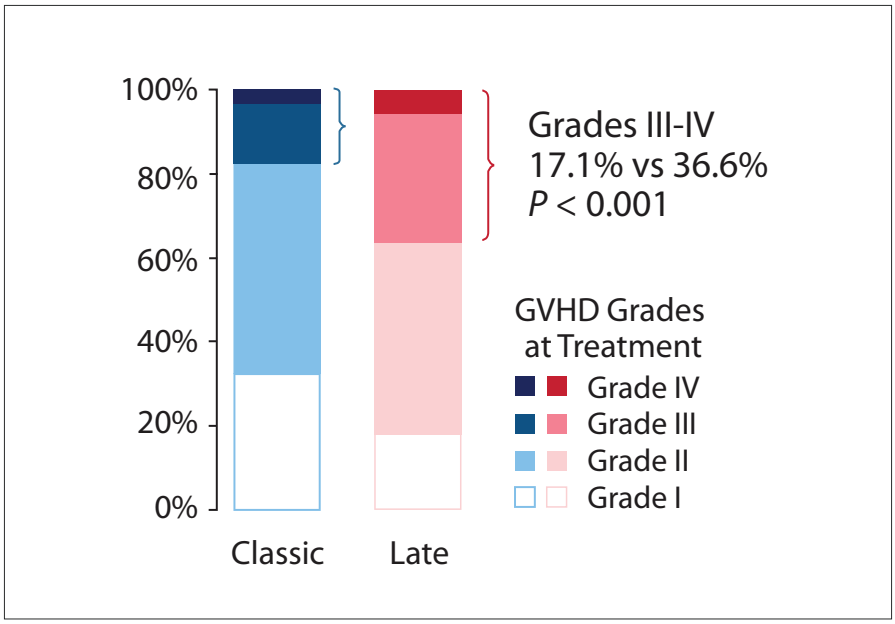

Figure 5. The severity of classic and late acute graft-versus-host disease at treatment. Adapted from a presentation at the Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; February 15-19, 2023; Orlando, Florida.[5]

in comparison with persistent or recurrent GVHD.[3,4] A retrospective study was conducted to compare the incidence, clinical outcomes, and biomarkers in patients with classic aGVHD vs those in patients with late aGVHD.[5] The study included 3542 patients who underwent a first HSCT at one of 24 Mount Sinai Acute GVHD International Consortium (MAGIC) transplant centers in North America, Europe, or Asia between January 2014 and August 2021.

The incidence of late aGVHD was 7.2% (n=256), and the incidence of classic aGVHD was 45.2% (n=1601). Systemic treatment was administered to 5.4% (n=193) of patients with late aGVHD vs 35.1% (n=1245) of patients with classic aGVHD. Late aGVHD was generally more severe than classic aGVHD (Figure 5) according to the proportion of patients with grade 3/4 symptoms (*P*<.001), high Minnesota risk score (*P*<.001), and advanced lower-GI stage (*P*<.001). At day 28 of systemic treatment, the percentage of patients with a partial or complete response was significantly higher among those with classic than among those with late aGVHD (72.0% vs 55.4%; *P*<.001), and fewer patients with classic than with late aGVHD had received second-line therapy by day 28 (14.8% vs 22.8%; *P*=.006). However, 1-year nonrelapse mortality rates did not differ significantly between the patients with classic aGVHD and those with late aGVHD in the overall cohort of patients with GVHD, in patients with grade 1/2 GVHD, and in patients with grade 3/4 GVHD. An algorithm to determine the probability of nonrelapse mortality at 6 months was created with 2 biomarkers. Higher levels of the biomarkers ST2 and Reg3α were associated with a higher cumulative incidence of nonrelapse mortality in patients with late aGVHD. Risk factors associated with late aGVHD included recipient age (≥55, *P*=.007), sex mismatch (*P*=.014), and reduced-intensity conditioning (RIC) (*P*=.008), although prophylaxis with posttransplant cyclophosphamide (PTCy) was protective (*P*<.001). In conclusion, patients

ABSTRACT SUMMARY: Phase 2 Study of Single High-Dose Palifermin for Graft-Versus-Host Disease Prevention After Matched Unrelated Donor Transplantation

A phase 2 study evaluated a single high dose of palifermin (540 or 720 µg/kg) as prophylaxis for GVHD in 28 patients who underwent HSCT with a matched unrelated donor (Abstract 338). In the current trial, 28 patients received palifermin plus tacrolimus, methotrexate, and sirolimus (TMS). Outcomes were compared with results from 31 patients in a previous trial who had received TMS prophylaxis without palifermin. Patients in the TMS-plus-palifermin group were more likely to have acute lymphoblastic leukemia (*P*=.0293), had a higher risk of relapse (*P*=.002), and had received more prior therapies (*P*=.0033). In a prespecified analysis, the cumulative incidence of acute grade 2 to 4 GVHD was lower among patients treated with TMS plus palifermin than in those treated with TMS alone (*P*=.024). However, the cumulative rates of moderate-severe and severe chronic GVHD were similar for patients treated with and those treated without palifermin, regardless of the palifermin dose level (*P*>.05).

with late aGVHD should receive the same treatment as patients with classic aGVHD, with similar clinical trial eligibility.

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Orca-Q Demonstrates Favorable GVHD- and Relapse-Free Survival With Haploidentical Donors Without Posttransplant Cyclophosphamide

The use of PTCy has greatly reduced the incidence of severe acute and chronic GVHD in patients who have undergone allogeneic HSCT and has allowed more patients to receive allogeneic HSCT from alternative haploidentical donors.[1,2] However, the rates of GVHD and relapse are still relatively high in this setting. The use of myeloablative conditioning (MAC) is associated with high rates of GVHD, although RIC is associated with higher rates of relapse. In conventional HSCT, an uncontrolled mix of more than 50 cell types is harvested from the donor, including hematopoietic stem cells, progenitor cells, various types of T cells, and others.

Orca-Q is an investigational, precision-engineered cell therapy comprising defined stem and immune cells that are manipulated ex vivo for use in allogeneic HSCT.[3] The cell mixture contains high-purity populations of hematopoietic stem cells, regulatory T cells, invariant natural killer T cells, and subsets of CD4+/CD8+ T cells. The cellular composition of Orca-Q was chosen specifically to increase the success of allogeneic HSCT by reconstituting the cells of the blood and immune system to control GVHD and enhance the activity of regulatory T cells while maintaining graft-versus-infection and graft-versus-leukemia capabilities. A multicenter phase 1 dose expansion study was conducted to evaluate Orca-Q in patients receiving haploidentical HSCT with MAC and single-agent tacrolimus for prophylaxis of GVHD. Enrolled patients were 18 to 65 of age with high-risk hematologic malignancies, including acute leukemia, myelodysplastic syndrome, and myelofibrosis.

Patients received MAC therapy on days –10 to –2. Single-agent tacrolimus therapy was initiated on day –1 and continued until taper on day 60. On day 0, patients received a fresh

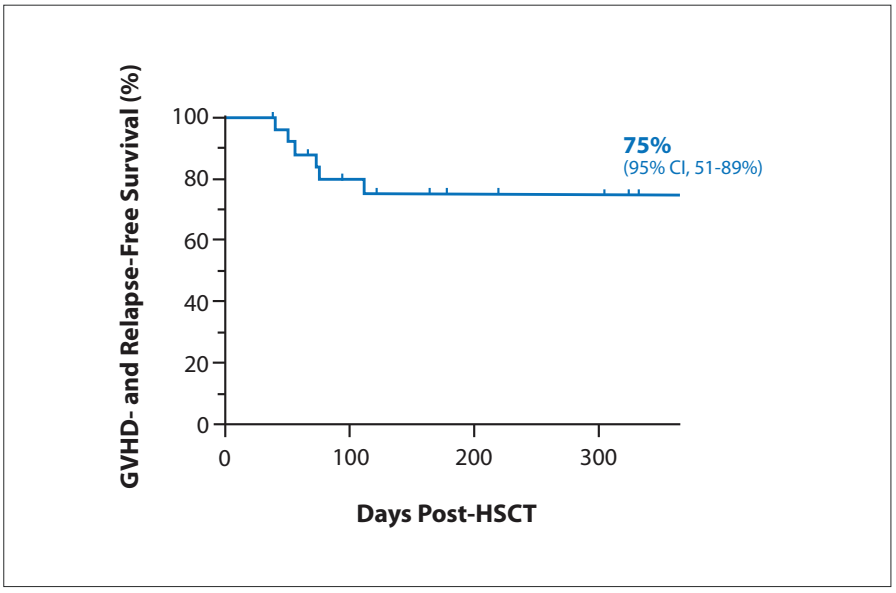

Figure 6. One-year graft-versus-host disease– and relapse-free survival in patients with high-risk hematologic malignancies receiving haploidentical stem cell transplants with Orca-Q. Adapted from a presentation at the Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; February 15-19, 2023; Orlando, Florida.[3]

Orca-Q cell infusion, which was centrally manufactured at a single facility with peripheral blood apheresis. The study enrolled 26 patients with a median age of 43 years (range, 21-63); 69% were male. The disease risk was high or very high in 23% of patients and intermediate in 65%. The median age of donors was 36 years (range, 18-58). None of the patients had primary graft failure. The median times to neutrophil and platelet engraftment were 12 and 16 days, respectively. Grade 1 cytokine release syndrome developed in 2 patients (7.7%), and secondary graft failure developed in 2 patients (7.7%). Severe infections were uncommon; infections of grade 3 or higher occurred in 19% of patients. Infection was the cause of death in 2 patients, one of whom died of pneumonia associated with COVID-19 and the other of pulmonary aspergillosis. Despite the use of single-agent tacrolimus as GVHD prophylaxis, acute GVHD of grade 3 or higher developed in 5% of patients; 8% of patients experienced GVHD of at least grade 2. After a median follow-up of 211 days (range, 32-1125), no moderate-to-severe GVHD was observed. These results compare favorably with the chronic GVHD rates of 24% to 33% observed in historical control cohorts. At 1 year, 75% of the patients (95% CI, 51%-89%) who had received the Orca-Q transplant were GVHD-free and relapse-free, and the OS rate at 1 year was 75% (Figure 6).

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Phase II Study of Myeloablative 8/8- or 7/8-Matched Allotransplantation With Posttransplant Cyclophosphamide, Tacrolimus, and Mycophenolate Mofetil: Marked Reduction in GVHD Risk Without Increased Relapse Risk Compared With Historical Cyclosporine/Methotrexate

The success of allogeneic HSCT is significantly limited by the development of GVHD.[1,2] The ideal prophylactic agents to reduce or prevent GVHD would not interfere with graft-versus-leukemia effects. A prospective, nonrandomized phase 2 study evaluated the hypothesis that the combination of PTCy, tacrolimus, and mycophenolate mofetil (MMF) would reduce the proportion of patients requiring immunosuppressive therapy at 1 year after matched or single antigen–mismatched HSCT, without increasing the risk of relapse.[3] Eligible patients were no more than 60 years of age and had a hematologic malignancy. Matched related or 7/8 or 8/8 unrelated donors were allowed to undergo HSCT with either bone marrow or peripheral blood. MAC was achieved through either total body irradiation or the combination of busulfan plus fludarabine. The GVHD prophylaxis regimen consisted of PTCy (50 mg/kg, days +3 and +4), tacrolimus (beginning day +5), and MMF (beginning day +5). The primary endpoint was the cumulative incidence of chronic GVHD requiring systemic immunosuppression at 1 year after HSCT. Results were compared with prior data from a trial conducted by the same group in which cyclosporine plus methotrexate was used for MAC in patients undergoing matched donor HSCT.

The study enrolled 125 patients, of whom 65 (52%) were male and 22 (17.6%) were pediatric patients. Of the donor sources, 55.2% were 8/8-matched related, 35.2% were 8/8-matched unrelated, and 9.6% were 7/8-matched unrelated. The graft source was peripheral blood in 65.6% and bone marrow in 34.4% of the transplants. For MAC, most of the patients (89.6%) received total body irradiation, and 10.4% received busulfan plus fludarabine. The most common malignancies were acute myeloid leukemia (44.8%) and B-cell acute lymphoblastic leukemia (26.4%). The median time to neutrophil engraftment was 18 days (interquartile range [IQR], 16-20 days), and the median time to platelet engraftment was 25 days (IQR, 20-32 days). Graft failure occurred in 3 patients (2.4%).

The trial showed a low rate of 1-year chronic GVHD of 4%, which compared favorably with prior data in patients treated with cyclosporine plus methotrexate (34%; $P<.01$; Figure 7). Nonrelapse mortality at 1 year was 10% with PTCy/tacrolimus/MMF vs 19% in the comparator population

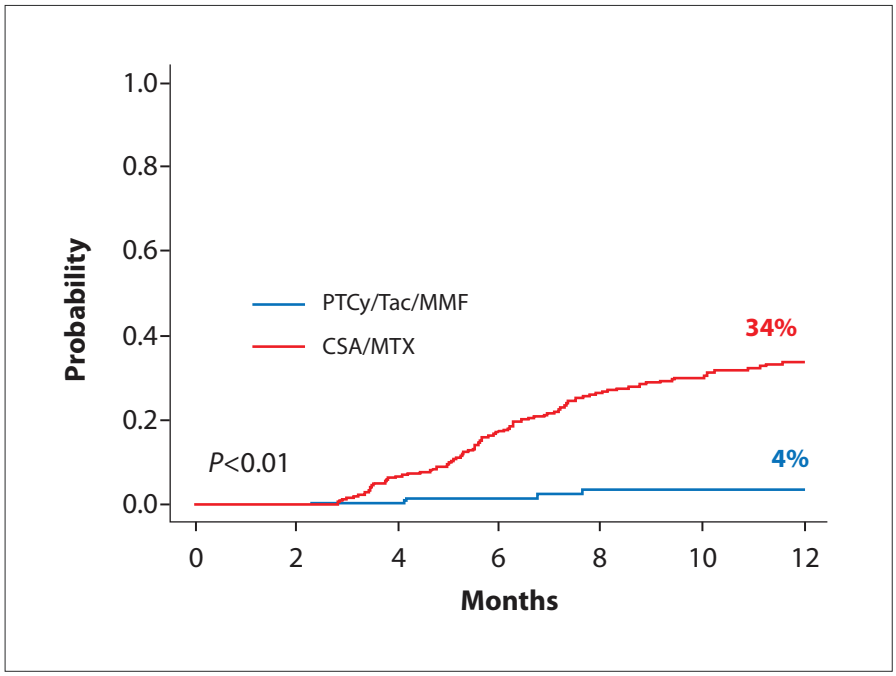

Figure 7. The cumulative incidence of chronic graft-versus-host disease requiring systematic immunosuppression at 1 year post transplant. Adapted from a presentation at the Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; February 15-19, 2023; Orlando, Florida.[3]

(*P*=.03), and rates of acute GVHD were lower with the combination of PTCy/tacrolimus/MMF than in the comparator data, in terms of both grade 2 to 4 GVHD (15% vs 37%; *P*<.01) and grade 3/4 GVHD (4% vs 15%; *P*<.01). The combination of PTCy/tacrolimus/MMF also yielded superior outcomes vs the comparator population in terms of OS (90% vs 64%; *P*=.01) and 2-year GVHD- and relapse-free survival (57% vs 25%; *P*<.01). Multivariate analysis underscored the superior 2-year OS associated with PTCy/tacrolimus/MMF in comparison with cyclosporine plus methotrexate (hazard ratio [HR], 0.49; 95% CI, 0.29-0.81; *P*<.01). The prophylactic 3-drug combination used in the current phase 2 study was associated with a high rate of GI toxicity, with three-fourths of patients requiring total parenteral nutrition. The rates of relapse were 49% in the pediatric population and 13% among patients older than 40 years.

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Final Safety and Efficacy Results From EQUATE, an Open-Label Study Evaluating Itolizumab, a Novel Targeted Anti-CD6 Therapy, in Newly Diagnosed Acute Graft-Versus-Host Disease

CD6 is a costimulatory receptor whose ligand is the activated leukocyte cell adhesion molecule (ALCAM).[1-3] The CD6/ALCAM pathway has been implicated in the pathogenesis of acute GVHD. Itolizumab is a first-in-class monoclonal antibody that binds to CD6 on T cells. Binding induces CD6 receptor shedding, thus reducing T effector cell (T_{eff}) activity and trafficking of these cells to target organs. The open-label phase 1b EQUATE study evaluated itolizumab combined with corticosteroids as a first-line treatment for acute GVHD.[4] The dose escalation study used a standard 3+3 design to evaluate itolizumab in patients with grade 3/4 GVHD. Dose levels ranged from 0.4 to 1.6 mg/kg, and doses were administered biweekly for up to 5 doses. Itolizumab was administered within 72 hours of corticosteroid therapy. The final expansion cohort included 9 patients

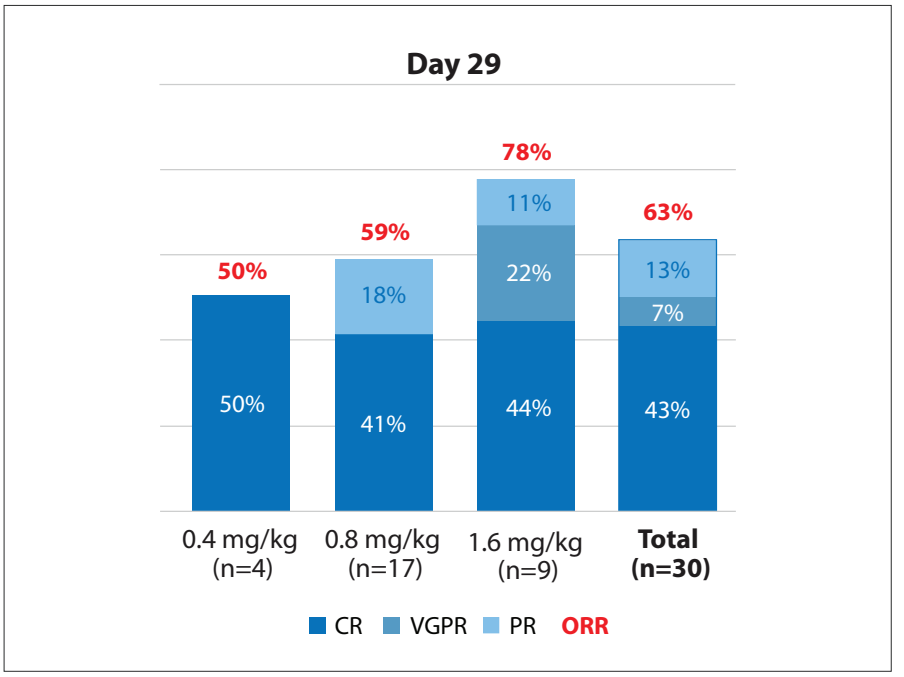

Figure 8. The complete response, very good partial response, partial response, and overall response at day 29 of patients with newly diagnosed severe acute graft-versus-host disease on itolizumab treatment. Adapted from a presentation at the Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; February 15-19, 2023; Orlando, Florida.[4]

who received itolizumab at a dosage of 0.8 mg/kg every 2 weeks. The primary objectives were to evaluate the safety and tolerability of itolizumab and to the determine the optimal dose level of itolizumab.

In the study, 30 patients were enrolled across the 3 initial itolizumab dose levels (0.4 mg/kg, n=4; 0.8 mg/kg, n=17; 1.6 mg/kg, n=9). The median age of the patients was 56±13.2 years, and two-thirds were male. The most common primary disease was acute lymphoblastic leukemia (40%). Nearly all patients (93%) had received a peripheral blood graft, and nearly all patients (97%) had grade 3/4 GVHD. The most common sites of involvement were the lower GI tract (83%), upper GI tract (83%), and liver (43%). One patient experienced a dose-limiting toxicity. None of the 14 deaths were considered related to study therapy. Across the 3 dose levels of itolizumab, the overall response rate at day 29 was 63%, including a complete response rate of 43% (Figure 8). Among 23 patients who had received corticosteroid therapy for 3 days or less, the response rate at day 29 was 65%, with a complete response rate of 48%. Patients who responded to treatment with itolizumab were able to reduce their use of systemic corticosteroids to a meaningful degree, with a mean reduction in corticosteroid use of 70% at day 29 and 99% at day 169. The mean duration of response was 206 days, and the median progression-free survival was 4.6 months for all patients.

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Belumosudil Impacts Immunosuppression Pharmacokinetics in Patients With Chronic Graft-Versus-Host Disease

Belumosudil, which is an inhibitor of Rho-associated coiled-coil–containing protein kinase, is approved for the treatment of chronic GVHD after 2 prior lines of systemic therapy.[1-3] Pharmacokinetic modeling has revealed that belumosudil weakly inhibits cytochrome 450, family 3, subfamily A (CYP3A) and inhibits P-glycoprotein, both of which are involved in the metabolism and excretion of several immunosuppressive agents used for the treatment of chronic GVHD, such as tacrolimus and sirolimus. A retrospective analysis

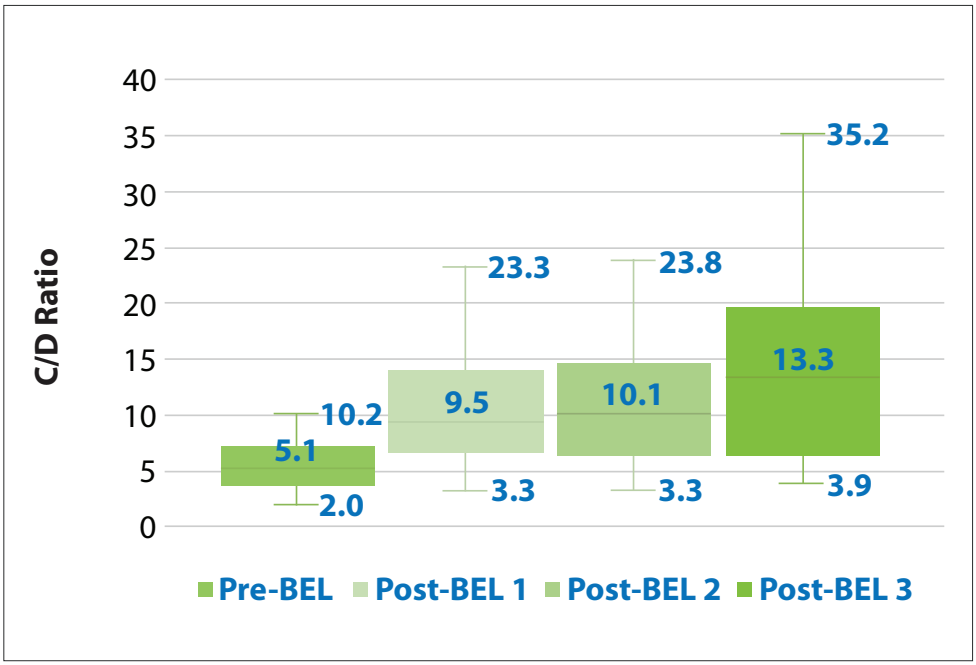

Figure 9. The median concentration/dose ratio change of sirolimus pre- and post-belumosudil for patients with chronic graft-versus-host disease. Adapted a presentation at the Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; February 15-19, 2023; Orlando, Florida.[4]

was conducted at a single treatment center to evaluate the pharmacokinetic interaction between belumosudil and plasma concentrations of tacrolimus and/or sirolimus in adults with chronic GVHD.[4] The plasma immunosuppressant level of enrolled patients was noted before belumosudil administration, and at least one immunosuppressant level was obtained during belumosudil therapy. The median age of 30 included patients was 63 years (range, 27-79), and two-thirds were male. Of the included patients, 26 were taking sirolimus and 12 were taking tacrolimus concurrently with belumosudil. The patients had received a median of 4 prior lines of therapy (range, 1-8), and most of them had moderate (33.3%) or severe (60%) GVHD.

In the patients taking sirolimus or tacrolimus concurrently with belumosudil, a significant increase in the mean concentration-to-dose (C/D) ratio over the baseline values obtained before the initiation of belumosudil was noted after the initiation of belumosudil (P<.001 for sirolimus and P=.014 for tacrolimus; Figure 9). Notably, after the concomitant administration of belumosudil, supratherapeutic levels of immunosuppressant were noted at day 26 in 25% of the patients taking tacrolimus and at day 34.5 in 62% of the patients taking sirolimus. Dose adjustments reduced the plasma drug concentration to therapeutic levels in the patients taking tacrolimus; however, the levels of sirolimus tended to remain supratherapeutic despite dose adjustments.

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Vedolizumab for Prophylaxis of Lower Gastrointestinal (GI) Acute Graft-versus-Host Disease (aGVHD) After Allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT) From Unrelated Donors: Results of a Phase 3 Randomized, Double-Blind, Placebo-Controlled Multicenter Study (GRAPHITE)

Vedolizumab is a humanized monoclonal antibody that binds with high specificity to α4β7-integrin, which is expressed by a class of gastrointestinal-homing T cells.[1,2] The antibody thus confers gut-selective protection from lymphocyte trafficking and resulting inflammation and is approved for the treatment of inflammatory bowel disease. In a phase 1b dose-finding study of 24 patients with severe GI GVHD, vedolizumab was added to standard prophylaxis for GVHD; no dose-limiting toxicities occurred at vedolizumab doses up to 300 mg delivered on days –1, +13, and +42 before and after allo-HSCT.[3]

The phase 3 GRAPHITE study compared vedolizumab vs placebo added to standard GVHD prophylaxis in patients with hematologic malignancy undergoing allogeneic HSCT.[4] Unrelated donors were HLA matched (8/8) or single mismatched (7/8). After patients were stratified by age, HLA match, conditioning regimen, and use of antithymocyte globulin, they were randomized in a 1:1 ratio to receive vedolizumab or placebo. Standard-of-care GVHD prophylaxis included tacrolimus or cyclosporine, paired with either methotrexate or MMF. Patients received the first dose of vedolizumab (300 mg) or placebo on day –1, followed by 6 more doses on days +13, +41, +69, +97, +125, and +153. The primary endpoint was intestinal acute GVHD-free survival at day +180 after allo-HSCT.

Patients were enrolled from February 2019 through May 2022 at 94 centers in North America, South America, Europe, Asia, and Australia. The study had a planned sample size

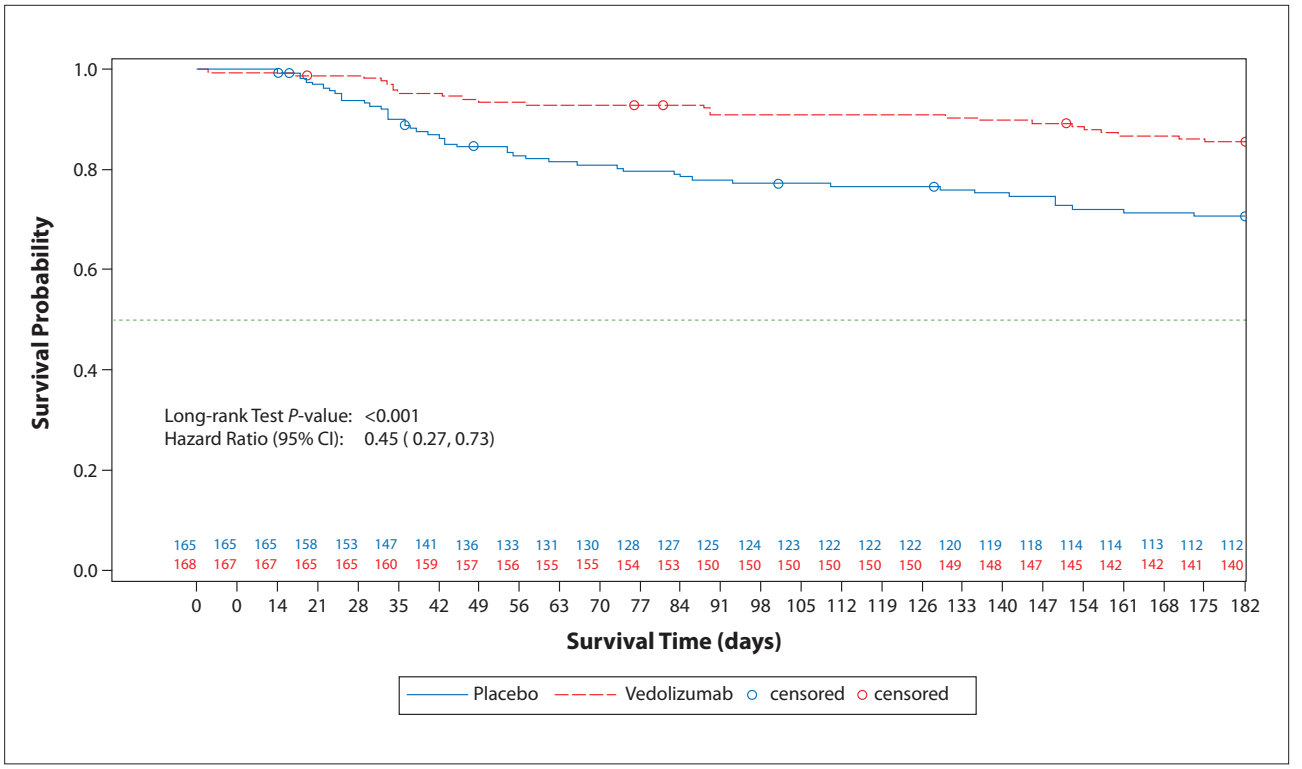

Figure 10. Lower gastrointestinal acute graft-versus-host disease–free survival probability by Day 180 for patients who received vedolizumab treatment compared with placebo. Adapted from a presentation at the Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR; February 15-19, 2023; Orlando, Florida.[4]

of 558 patients; however, enrollment was stopped at 343 patients because of the effect of COVID19 on recruitment. Baseline characteristics were well balanced between the 2 arms. Patients had a median age of 54 years (range, 16-74), and 63% were male. The most common malignancy was acute myeloid leukemia (44%), followed by myelodysplastic syndrome (20%-22%). Most patients (84%-87%) had received a peripheral blood transplant, and 91% received an 8/8-matched transplant. More patients in the placebo arm than in the treatment arm were in their first complete response (84% vs 71%).

The trial met its primary endpoint: at day +180 following allo-HSCT, the rate of intestinal acute GVHD–free survival was higher in patients in the vedolizumab arm than in patients in the placebo arm (85.5% vs 70.9%; HR, 0.45; 95% CI, 0.27-0.73; $P<.001$; Figure 10). Rates of death were similar in the vedolizumab and the placebo arms (9.7% vs 7.1%); however, rates of intestinal acute GVHD were clearly lower in the patients treated with vedolizumab than in those who received placebo (7.1% vs 18.8%, respectively). Rates of stage 2 to 4 intestinal acute GVHD were 8.5% with placebo vs 2.4% with the α4β7-directed antibody. Subgroup analysis revealed the clear superiority of vedolizumab over placebo in patients treated with RIC; with or without antithymocyte globulin prophylaxis; with tacrolimus; and with an 8/8 HLA match. In this phase 3 trial, vedolizumab was associated with a tolerable safety profile, and no new safety signals emerged.

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Highlights in Graft-Versus-Host Disease From the 2023 Tandem Meetings | Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR: Commentary

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Presentations on graft-versus-host disease (GVHD) at the 2023 Tandem Meetings (Transplantation & Cellular Therapy Meetings of the American Society for Transplantation and Cellular Therapy [ASTCT] and the Center for International Blood and Marrow Transplant Research [CIBMTR]) provided new insights into the biology, prevention, and treatment of acute and chronic GVHD. The studies presented evaluated novel agents, including inhibition of receptor interactive protein kinase 1 (RIP1), itolizumab, and vedolizumab, as well as currently approved treatments like ruxolitinib and belumosudil. Other important topics discussed were the effect of biomarkers and the changing landscape of GVHD prevention.

Classification

Traditionally, acute and chronic forms of GVHD have been classified according to the time of presentation after transplant, with day 100 following hematopoietic cell transplant (HCT) serving as an arbitrary cutoff point.[1] However, since the development of heterogeneous transplant platforms that vary in conditioning, regimen intensity, donor cell sources, and GVHD prevention, resulting in different kinetics of immune reconstitution, the modern distinction between acute and chronic GVHD is now based solely on clinical manifestations.[2] Thus, late acute GVHD has been defined as acute GVHD appearing after day 100, with some historical series suggesting it is less severe than classic acute GVHD.[3,4]

The Mount Sinai Acute GVHD International Consortium (MAGIC) analyzed a modern series of patients who underwent transplant between 2014 and 2021 to better describe the incidence and outcomes of late acute GVHD.[5] In more than 3500 patients enrolled in MAGIC, the investigators found a 7% incidence of late acute GVHD vs a 45% incidence of classic acute GVHD in patients treated systemically. They observed that the development of both classic and late acute GVHD was associated with an increased risk of nonrelapse mortality; however, patients who had late acute GVHD appeared to present with more severe disease, as judged by both clinical criteria and MAGIC algorithm probability (MAP) biomarkers. Nevertheless, long-term overall outcomes did not differ between classic and late acute GVHD, and it was possible to use

ABSTRACT SUMMARY: Baricitinib for Refractory Chronic Graft-Versus-Host Disease (cGVHD): Results of a Phase 1/2 Study

A 1-arm phase 1/2 study conducted at a single center investigated baricitinib (1-4 mg daily) in 24 patients with refractory chronic GVHD following HSCT (Abstract 329). Patients had received a median of 4.5 prior therapies (range, 2-11), the median NIH Global Severity score at baseline was 7 (range, 5-10), and the median Lee Chronic Graft-versus-Host Disease Symptom Scale score was 27 (range, 13-66). At 6 months, the objective response rate was 67% (95% CI, 51%-80%). The best response rate achieved at any time was 92% (95% CI, 79%-97%), and the median time to best response was 1.4 months (95% CI, 1.4-6.3). Responses were noted in all involved organs, with 17 organ-specific complete responses observed in 11 patients (46%) during the study. Clinically significant improvement in the Lee Chronic Graft-Versus-Host Disease Symptom Scale score was observed in 9 of 17 patients (53%) evaluable at 6 months. The median failure-free survival was 1.6 years (95% CI, 1.2 years to not reached).

MAP biomarkers to stratify patients effectively. The findings of this study support the notion of continuing to classify patients purely according to clinical manifestations and then combine them in modern risk-stratified clinical trials for the treatment of acute GVHD.

Prevention

Traditionally, 2 main methods are used to prevent GVHD after HCT. The first and more common one involves pharmacologic agents. For decades, the standard pharmacologic regimen consisted of a calcineurin inhibitor (either cyclosporine or tacrolimus) combined with an antimetabolite (either methotrexate or mycophenolate mofetil). High-dose post-transplant cyclophosphamide (PTCy) has emerged as an additional standard pharmacologic regimen, and its use has greatly increased over the last decade. The second modality is ex vivo graft manipulation, which requires far more expertise, resources, and laboratory experience, although newer methods are attempting to make graft manipulation more accessible.

Orca-Q is a cell therapy product manufactured by Orca Biosystems with their proprietary cell-sorting technology. It is being developed to prevent GVHD through graft manipulation in haploidentical transplantation. Orca Biosystems is currently conducting a phase 3 trial of Orca-T for preventing GVHD in patients with well-matched donors; the patients receive sequential infusions of selected progenitor cells in concert with regulatory T cells, followed by a conventional T-cell infusion 2 days later.[6] Orca-Q is Orca Biosystems' selected cell therapy donor product for use in the setting of haploidentical transplantation. Dr Amandeep Salhotra presented interim results of a phase 1 trial in which 21 patients received myeloablative, haploidentical Orca-Q grafts followed by single-agent GVHD prophylaxis with tacrolimus.[7] Thus far, secondary graft failure has occurred in only one patient, and only one case of severe acute GVHD has been observed. These are very encouraging findings for a myeloablative haploidentical transplant population, and final results are awaited once the study is fully accrued.

For decades, the standard pharmacologic GVHD prophylaxis in matched donor transplantation has been the combination of a calcineurin inhibitor plus methotrexate.[8] Recently, this platform has been challenged by regimens based on high doses of PTCy, which is already the standard regimen for mismatched donor transplantation at many sites.[9] At ASH in 2022, the results of BMT CTN 1703 were presented, demonstrating the superiority of a PTCy-based platform over the standard calcineurin-inhibitor–based regimen in the setting of reduced intensity transplantation from well-matched donors.

At Tandem, Dr Shernan Holtan and colleagues from the University of Minnesota presented the results of their phase 2 study, which used PTCy after myeloablative well-matched donor transplantation in 125 pediatric and adult patients who were transplanted between 2018 and 2022.[10] They compared their outcomes with a historical cohort that received a combination of cyclosporine and methotrexate for GVHD prevention. The primary endpoint was the cumulative incidence of patients with chronic GVHD requiring systemic immunosuppression at 1 year post-transplant. Impressively, there was only a 16% incidence of grades 2 through 4 acute GVHD and a 4% incidence of grades 3 through 4 acute GVHD, with no deaths attributed to acute GVHD. At 1 year, only 3 patients had developed chronic GVHD requiring immunosuppression. Nonrelapse mortality and overall survival were significantly improved compared with the historical control. There appeared to be a signal of increased disease relapse in patients who received bone marrow grafts and PTCy, but this needs to be verified in larger studies. Overall, this study adds to the emerging relevance of PTCy-based regimens as a standard in GVHD prevention. Future efforts will likely explore lower doses of cyclophosphamide or additional agents to be added to this backbone.

ABSTRACT SUMMARY: Outcomes of Post-transplant Cyclophosphamide With Mycophenolate and Tacrolimus as Prophylaxis for Graft-Versus-Host Disease in Matched Related and Matched Unrelated Donor Hematopoietic Stem Cell Transplantation: A Single Center Experience

A retrospective study at a single center explored PTCy/MMF/tacrolimus vs methotrexate plus tacrolimus vs PTCy as prophylaxis for GVHD in patients who received matched related (59.5%) or matched unrelated (40.5%) HSCT (Abstract 331). Patients who received PTCy/MMF/tacrolimus (n=40) were more likely to be free of GVHD or relapse throughout the follow-up period than were patients who received methotrexate plus tacrolimus (n=25; HR, 0.39; 95% CI, 16%-94%; *P*=.037). The rate of acute and chronic GVHD was also lower in patients treated with PTCy/MMF/tacrolimus than in those treated with methotrexate plus tacrolimus (32.5% vs 68%, respectively; *P*=.021). The study results support the use of PTCy/MMF/tacrolimus as a safe and effective regimen for GVHD prophylaxis.

Despite advances in preventing and treating acute GVHD, the treatment of acute GVHD in the lower gastrointestinal (GI) tract continues to remain an unmet need for patients, as this form of acute GVHD accounts for most cases of early transplant-related morbidity and mortality.

On behalf of my group, I presented the initial results of the GRAPHITE study, an international, randomized, double-blind, placebo-controlled phase 3 study investigating the efficacy and safety of vedolizumab in preventing lower GI acute GVHD when added to a standard calcineurin inhibitor–based GVHD prevention backbone.[11] Vedolizumab is a monoclonal antibody targeting $\alpha_4\beta_7$-integrin, a cell adhesion molecule essential for the trafficking of lymphocytes to GI tissue. This trial was initially designed to enroll 558 patients, but enrollment was stopped after 333 patients had been accrued as a consequence of COVID-19 pandemic-related dynamics. All patients received unrelated donor grafts, 90% of them from fully matched donors. Approximately half of the patients underwent standard myeloablative conditioning (MAC), and the other half received reduced-intensity conditioning (RIC). In addition, 40% of the patients also received an anti-thymocyte globulin (ATG) product as part of GVHD prophylaxis. Vedolizumab was first given on day –1, and a total of 7 doses was administered through the first 6 months after transplant. The primary endpoint was lower-GI GVHD–free survival at day 180 after transplant. Despite enrolling only approximately 60% of the intended population, the study was able to meet its primary endpoint. The event-free survival rate in patients in the placebo arm was 70.9% vs 85.5% in the patients who received vedolizumab, yielding a statistically significant hazard ratio of 0.45. The secondary endpoints of lower-GI GVHD–free and relapse-free survival, as well as overall severe GVHD-free survival, also showed benefit for vedolizumab. This was the first phase 3 study ever to show a positive result specifically in preventing lower-GI acute GVHD. If vedolizumab gains regulatory approval for GVHD prevention, it remains to be seen how it will be incorporated into standard practice, given the changing landscape of GVHD prevention—specifically, the increased use of PTCy-based prophylaxis.

Treatment of Acute and Chronic GVHD

Despite multiple attempts throughout the last couple of decades to develop novel treatments, systemic high-dose corticosteroids remain the standard treatment for patients with newly diagnosed acute GVHD.

Dr John Koreth presented the final results of the EQUATE study, a phase 1b clinical trial in which itolizumab, a monoclonal antibody directed against CD6, was added to standard systemic corticosteroids for the initial treatment of high-risk acute GVHD.[12,13] CD6, an activated leukocyte cell adhesion molecule located on effector T cells, is thought to play a role in acute GVHD. Historical studies had suggested that the depletion of CD6-positive T cells from donor grafts might contribute to the successful prevention of acute GVHD.[14] EQUATE enrolled 30 patients with grade 3 to 4 acute GVHD or grade 2 acute GVHD with a high Ann Arbor biomarker score of 2 or 3. All patients were treated with systemic corticosteroids in addition to itolizumab at 1 of 3 different doses (0.4, 0.8, or 1.6 mg/kg), which were administered every other week for up to 5 doses. At day 29, the overall response rates in the groups ranged from 50% to 78%, demonstrating an impressive response in a group of high-risk patients. The adverse events reported were not worrisome, given the critically ill nature of the patients, and no safety signals were attributed to itolizumab. On the basis of these data, the investigators have launched a phase 3 placebo-controlled study of itolizumab in addition to corticosteroids for the initial therapy of high-risk acute GVHD.[15]

As mentioned above, the treatment of patients who have acute GVHD with lower-GI symptoms has not been adequately addressed, thus representing an ongoing challenge. These patients historically have high rates of treatment resistance and an overall poor prognosis. Novel therapies targeting different pathways and new methods are needed to prevent and treat this condition. Historically, because acute GVHD was viewed as an immunologic process driven by T cells, the therapies developed were all aimed at immunosuppression of donor T cells, with cumulative immunosuppression being the key. Recent studies have suggested that the intestinal stem cell niche is an early target of acute GVHD, and that the loss of intestinal stem cells impairs the ability of the intestine to heal properly.[16] Therefore, the development of therapies aimed at improving organ resilience or regeneration, with an emphasis on preservation of the intestinal stem cell niche, is an emerging area of investigation for acute GVHD.

Dr James Ferrara and colleagues at the Icahn School of Medicine at Mount Sinai, in conjunction with Genentech, presented an abstract focusing on the RIP1 kinase pathway.[17] The RIP1 pathway appears to have a critical role in inflammation-driven cell death in the GI tract during acute GI GVHD and inhibition of such could lead to enhanced organ healing. Using human organoid models and preclinical mouse models, the investigators showed that inhibiting RIP1 kinase leads to organ growth

and the preservation of intestinal stem cells. In a murine bone marrow transplant model, use of the compound GNE-684 to inhibit RIP1 kinase reversed GVHD-mediated damage, improved survival, and did not affect the desired graft-versus-malignancy effect.[18] On the basis of these interesting findings, a phase 1b clinical trial is investigating GDC-8264, an oral RIP1 kinase inhibitor, as an adjunct in combination with corticosteroids for the initial treatment of high-risk acute GVHD.[19]

Several advances have been made in the treatment of chronic GVHD over the past few years, with 3 novel agents approved: the Bruton tyrosine kinase (BTK) inhibitor ibrutinib, the JAK1/JAK2 inhibitor ruxolitinib, and the ROCK2 inhibitor belumosudil.[20-22] Inhibition of ROCK2 is thought to provide systemic immunomodulation and target the pathway leading to altered fibrosis, thereby mitigating the manifestations of chronic GVHD.

Dr Eric Gaskill of the Moffitt Cancer Center presented a study in which 30 patients with chronic GVHD received belumosudil while still on a baseline backbone immunosuppressant regimen of tacrolimus, sirolimus, or both.[23] The goal of the analysis was to investigate if the addition of belumosudil would affect the plasma concentrations of these common immunosuppressants. Results showed that the addition of belumosudil led to significant increases in the concentrations of both tacrolimus and sirolimus, such that dose adjustments were required in the weeks after dosing. The study is valuable in drawing attention to this effect, and the drug levels of patients who start belumosudil and remain on either tacrolimus or sirolimus should be carefully monitored, with doses adjusted accordingly.

A Focus on Ruxolitinib

The development of ruxolitinib, an oral JAK1/JAK2 inhibitor, has been a huge advance in the treatment of acute and chronic GVHD. For many clinicians, ruxolitinib has become the standard second-line therapy for both types of GVHD in patients with unsatisfactory responses to systemic corticosteroids. Currently, patients with GVHD who are candidates for ruxolitinib treatment include the following: (1) those whose disease progresses on systemic corticosteroids, (2) those whose disease does not respond to corticosteroids, (3) those with a suboptimal partial response to corticosteroids, (4) those in whom corticosteroids are contraindicated, and (5) those in whom a corticosteroid-sparing effect is desired. Several posters and abstracts presented at the Tandem meetings further illustrated the success of ruxolitinib in the real world, as well as specific aspects of certain recent clinical trials.

One analysis of the pivotal REACH-2 study specifically considered the effect of cytopenias in patients treated with ruxolitinib and found that the incidence of cytopenias did not differ between patients who received ruxolitinib and those who received best-available-therapy control agents.[24] The response rates and efficacy were similar in the patients who had cytopenias and received ruxolitinib, and their cytopenias seemed to be fairly well managed while they were on ruxolitinib. Another analysis of REACH-2 studied patients treated earlier vs later with ruxolitinib and found that both subsets benefited from ruxolitinib.[25] However, earlier treatment has become the goal in GVHD, as it is thought that earlier treatment may translate into better outcomes through prevention of end-organ damage. Real-world experiences with ruxolitinib have also been encouraging and have validated its rapid adoption into clinical practice. A single-center study from the Czech Republic showed an improved overall prognosis in patients with acute GVHD over time, with much of the improvement attributed to ruxolitinib, although other advances and changes in practice may also have been contributing factors.[26] Ruxolitinib is being carefully expanded to the pediatric world, with dosing at the extremes of height and weight taken into account and with studies of pharmacokinetic and pharmacodynamics parameters conducted to ensure safety.[27] Finally, as well as investigating additional novel agents in GVHD, it is important to study their use in combination. A recent abstract presented by the CIBMTR in which ruxolitinib was used in combination with photopheresis illustrated the safety of this combination approach; however, more research is needed to determine its efficacy.[28] In looking forward, studies of series of patients receiving ruxolitinib in combination with ibrutinib or belumosudil are sorely needed to better understand how to use these newly approved agents.

Disclosures

Dr Chen has performed consulting for Incyte, Magenta, Daiichi, Equillium, Celularity, Actinium and Vor.

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