ORIGINAL ARTICLE

Ruxolitinib for Glucocorticoid-Refractory Chronic Graft-versus-Host Disease

Robert Zeiser, M.D., Nicola Polverelli, M.D., Ph.D., Ron Ram, M.D., Shahrukh K. Hashmi, M.D., M.P.H., Ronjon Chakraverty, M.D., Ph.D., Jan Moritz Middeke, M.D., Maurizio Musso, M.D., Sebastian Giebel, M.D., Ph.D., Ant Uzay, M.D., Peter Langmuir, M.D., Norbert Hollaender, Ph.D., Maanasa Gowda, Pharm.D., Tommaso Stefanelli, M.D., Stephanie J. Lee, M.D., M.P.H., Takanori Teshima, M.D., Ph.D., and Franco Locatelli, M.D., Ph.D., for the REACH3 Investigators*

ABSTRACT

BACKGROUND

Chronic graft-versus-host disease (GVHD), a major complication of allogeneic stem-cell transplantation, becomes glucocorticoid-refractory or glucocorticoid-dependent in approximately 50% of patients. Robust data from phase 3 randomized studies evaluating second-line therapy for chronic GVHD are lacking. In retrospective surveys, ruxolitinib, a Janus kinase (JAK1–JAK2) inhibitor, showed potential efficacy in patients with glucocorticoid-refractory or -dependent chronic GVHD.

METHODS

This phase 3 open-label, randomized trial evaluated the efficacy and safety of ruxolitinib at a dose of 10 mg twice daily, as compared with the investigator's choice of therapy from a list of 10 commonly used options considered best available care (control), in patients 12 years of age or older with moderate or severe glucocorticoid-refractory or -dependent chronic GVHD. The primary end point was overall response (complete or partial response) at week 24; key secondary end points were failure-free survival and improved score on the modified Lee Symptom Scale at week 24.

RESULTS

A total of 329 patients underwent randomization; 165 patients were assigned to receive ruxolitinib and 164 patients to receive control therapy. Overall response at week 24 was greater in the ruxolitinib group than in the control group (49.7% vs. 25.6%; odds ratio, 2.99; P<0.001). Ruxolitinib led to longer median failure-free survival than control (>18.6 months vs. 5.7 months; hazard ratio, 0.37; P<0.001) and higher symptom response (24.2% vs. 11.0%; odds ratio, 2.62; P=0.001). The most common (occurring in ≥10% patients) adverse events of grade 3 or higher up to week 24 were thrombocytopenia (15.2% in the ruxolitinib group and 10.1% in the control group) and anemia (12.7% and 7.6%, respectively). The incidence of cytomegalovirus infections and reactivations was similar in the two groups.

CONCLUSIONS

Among patients with glucocorticoid-refractory or -dependent chronic GVHD, ruxolitinib led to significantly greater overall response, failure-free survival, and symptom response. The incidence of thrombocytopenia and anemia was greater with ruxolitinib. (Funded by Novartis and Incyte; REACH3 ClinicalTrials.gov number, NCT03112603.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Zeiser at the Department of Medicine I, Faculty of Medicine, Medical Center, University of Freiburg, Freiburg 79085, Germany, or at robert.zeiser@uniklinik-freiburg.de.

*A list of the investigators in the REACH3 Trial Group is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Zeiser and Polverelli and Drs. Teshima and Locatelli contributed equally to this article.

N Engl J Med 2021;385:228-38.
DOI: 10.1056/NEJMoa2033122

Chronic graft-versus-host disease (GVHD) is a serious complication of allogeneic stem-cell transplantation that limits the success of the procedure.[1,2] Chronic GVHD occurs in approximately 30 to 70% of patients who undergo allogeneic stem-cell transplantation[3] and is a leading cause of complications and of nonrelapse-associated death.[2,4-6] Patients with chronic GVHD have impaired physical, social, psychological, and general quality of life, which worsens with disease severity.[7-10]

Standard first-line treatment of chronic GVHD consists of systemic glucocorticoids; however, in approximately 50% of patients the disease becomes glucocorticoid-refractory or glucocorticoid-dependent, greatly increasing the risk of poor outcomes.[11] Second-line treatment of chronic GVHD varies substantially among treatment centers. Although guidelines provide several treatment options, including extracorporeal photopheresis and mycophenolate mofetil, enrolling patients into clinical trials is recommended.[2,12,13] Currently, ibrutinib, a Bruton's tyrosine kinase inhibitor, is the only second-line therapy approved (in the United States and Canada) for treatment of chronic GVHD; it was approved on the basis of a phase 1b–2, open-label, single-group trial (with 42 patients) that showed a best overall response of 67% and alleviation of symptoms.[14] However, since data from large-scale, successful, randomized studies are not available, no standard second-line treatment has been defined.[12]

Preclinical studies showed that Janus kinase 1 and 2 (JAK1–JAK2) signaling is crucial in the steps leading to inflammation and tissue damage in acute GVHD and chronic GVHD[15-19] and that ruxolitinib, a JAK1–JAK2 inhibitor, was an effective treatment in a mouse model of chronic GVHD.[20] In addition, a retrospective survey showed ruxolitinib led to high response and 6-month survival rates in patients with acute or chronic GVHD who were heavily pretreated.[20] After these findings, ruxolitinib was shown to have high response rates in the phase 2 REACH1 trial involving 71 patients, resulting in approval of ruxolitinib in the United States for the treatment of glucocorticoid-refractory acute GVHD in patients 12 years of age or older.[21,22] The phase 3 REACH2 study involving 309 patients with glucocorticoid-refractory acute GVHD showed that ruxolitinib resulted in significant improvements as compared with control therapy.[23] Here we present the primary analysis of REACH3, a phase 3 randomized trial evaluating ruxolitinib as compared with investigator's choice of therapy from a list of 10 commonly used options among patients with glucocorticoid-refractory or -dependent chronic GVHD.

METHODS

PATIENTS

Patients were at least 12 years of age, had undergone allogeneic stem-cell transplantation, and had moderate or severe glucocorticoid-refractory or -dependent chronic GVHD, according to National Institutes of Health (NIH) consensus criteria.[24] (Details on trial design, end points, and statistical analysis are provided in the Supplementary Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org.) Patients who had been treated previously with JAK inhibitors for acute GVHD were included if treatment had resulted in a complete or partial response and if they had discontinued JAK inhibitor treatment at least 8 weeks before receiving the first dose of ruxolitinib or control therapy. Patients treated previously with 2 or more systemic therapies for chronic GVHD in addition to glucocorticoids with or without calcineurin inhibitors were ineligible. Patients were excluded if they had a relapse of the primary cancer or had graft loss within 6 months before treatment initiation or if they had an active, uncontrolled infection.

TRIAL OVERSIGHT

The study sponsors (Novartis and Incyte), in collaboration with the trial steering committee, designed the trial and analyzed the data. Investigators entered data into the electronic case-report forms. After data analysis, the first two and last two authors developed a draft of the manuscript with writing assistance provided by ArticulateScience and funded by Novartis. All the authors reviewed and approved the manuscript for submission and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol (available at NEJM.org). The trial was designed and conducted in accordance with the guidelines for Good Clinical Practice of the International Council for Harmonisation, applicable local regulations, and the principles

of the Declaration of Helsinki. The protocol was approved at each participating center by the relevant institutional review board or ethics committee. An independent data monitoring committee reviewed interim results and safety (a list of the committee members is provided in the Supplementary Appendix). All patients (or their guardians) provided informed consent.

TRIAL DESIGN

REACH3 was a phase 3 randomized, open-label, multicenter trial (Fig. S1 in the Supplementary Appendix). Patients were randomly assigned in a 1:1 ratio to receive ruxolitinib at a dose of 10 mg twice daily or therapy chosen by the investigators from a list of 10 commonly used options described in the protocol (extracorporeal photopheresis, low-dose methotrexate, mycophenolate mofetil, a mammalian target of rapamycin [mTOR] inhibitor [everolimus or sirolimus], infliximab, rituximab, pentostatin, imatinib, or ibrutinib) and were stratified according to the severity of their chronic GVHD. Control therapy included the most widely used second-line treatments,[25] as outlined by the European Society for Blood and Marrow Transplantation.[12] Patients continued to receive glucocorticoids with or without calcineurin inhibitors. Infection prophylaxis was allowed and administered according to local institutional guidelines.

Patients received assigned treatment for at least 6 cycles (28 days per cycle) unless they had unacceptable side effects or progression of chronic GVHD. Glucocorticoids could be tapered after patients had a complete response or partial response; tapering of calcineurin inhibitors or ruxolitinib was allowed on or after cycle 7 day 1 (week 24) and after patients had a complete or partial response. Addition or initiation of a new control therapy was allowed before week 24 because of lack of response, unacceptable side effects, or a flare of chronic GVHD and was considered treatment failure. For patients who did not have or maintain a complete or partial response, had unacceptable side effects from a control therapy, or had a flare of chronic GVHD, crossover from control therapy to ruxolitinib could occur on or after week 24. Patients in the control group who had a complete or partial response at week 24 could not cross over to ruxolitinib unless they had disease progression, mixed response, or unacceptable side effects from the control therapy.

END POINTS

The primary end point was overall response (defined as a complete or partial response according to 2014 NIH consensus criteria)[26] at week 24. The two key secondary end points were failure-free survival (defined as time to recurrence of underlying disease, start of new systemic treatment for chronic GVHD, or death, whichever came first) and response on the modified Lee Symptom Scale[27,28] (defined as a ≥7-point reduction from baseline in total symptom score on the scale, which measures the symptoms of chronic GVHD on a scale of 0 to 100, with higher scores indicating worse symptoms) at week 24. Modifications to the Lee Symptom Scale included changing the measure from "bother" to the severity of each symptom and shortening the recall period from the past month to the past 7 days. Secondary and exploratory end points included subgroup analyses of overall response, individual organ responses, best overall response at any time up to week 24, duration of response, change in glucocorticoid dose over time, overall survival, and changes in quality-of-life measures. Safety analyses included patients who received at least 1 dose of treatment; safety data up to week 24 are presented to ensure similar exposure in the two groups. Given that not all patients who crossed over from the control group to the ruxolitinib group had completed 24 weeks of treatment with ruxolitinib at the time of this analysis, the only result presented for crossover patients is the best overall response up to data cutoff.

STATISTICAL ANALYSIS

Sample size calculations were performed to achieve 90% power for overall response rate and failure-free survival; a sample size of 324 patients was considered adequate. The Cochran–Mantel–Haenszel chi-square test, stratified according to severity of chronic GVHD, was used to compare overall responses and responses on the modified Lee Symptom Scale between the two groups; failure-free survival was compared with the use of a stratified log-rank test. Efficacy analyses were performed on the full analysis set according to the intention-to-treat principle. P values, odds ratios, and hazard ratios including 95% confidence limits were derived from the respective stratified analyses. We calculated adjusted risk ratios by fitting a generalized linear model with the treatment group and chronic GVHD severity as covariates.

An overall hierarchical testing procedure[29] (Fig. S2) was applied to test the primary end point and the two key secondary end points in a two-look, group-sequential design at the interim analysis (196 patients; alpha significance level, 0.01176) and at the primary analysis (329 patients; alpha significance level, 0.01858 if not positive at the interim analysis). The testing sequence for key secondary end points differed between the United States (modified Lee Symptom Scale tested before failure-free survival) and other countries (failure-free survival tested before modified Lee Symptom Scale) because regulatory recommendations for demonstrating additional patient benefits differed between countries. The overall hierarchical testing procedure maintained the overall one-sided type I alpha error of 0.025 for the primary and key secondary end points; one-sided tests were applied to allow sequential testing only in cases in which ruxolitinib was superior to control therapy.

RESULTS

PATIENTS

Between July 11, 2017, and November 18, 2019, a total of 329 patients were randomly assigned to receive ruxolitinib (165 patients) or a control therapy (164 patients) at 149 centers across 28 countries (Fig. 1). Patient characteristics were balanced between treatment groups (Table 1 and Table S1). The median age of the patients was 49 years (range, 12 to 76 years; 12 were between 12 and 17 years of age); 61.1% were male. Overall, 42.9% of the patients had moderate chronic GVHD, and 56.5% of patients had severe chronic GVHD; 71.4% had glucocorticoid-refractory chronic GVHD, and 28.6% had glucocorticoid-dependent disease, as reported by the investigator. Control therapy was primarily extracorporeal photopheresis (34.8%), mycophenolate mofetil (22.2%), and ibrutinib (17.1%). Approximately half the patients received calcineurin inhibitors during the trial (Table S2).

At data cutoff (May 8, 2020; median follow-up, 57.3 weeks), 125 patients (38.0%) continued to receive the randomized treatment; 82 patients (49.7%) discontinued ruxolitinib and 122 patients (74.4%) discontinued control therapy (Fig. 1). Reasons for discontinuation included lack of efficacy (14.5% in the ruxolitinib group vs. 42.7% in the control group), adverse events (17.0% vs. 4.9%), and relapse of underlying disease (5.5% vs. 4.3%); 61 patients (37.2%) in the control group crossed over to ruxolitinib. The median exposure to therapy was 41.3 weeks (range, 0.7 to 127.3) in the ruxolitinib group and 24.1 weeks (range, 0.6 to 108.4) in the control group.

EFFICACY

Overall response at week 24 (the primary end point) was higher with ruxolitinib (82 patients, 49.7%) than with control therapy (42 patients, 25.6%) (odds ratio, 2.99 [95% confidence interval {CI}, 1.86 to 4.80]; risk ratio, 1.93 [95% CI, 1.44 to 2.60]; P<0.001) (Fig. 2A and Table S3). A total of 11 patients (6.7%) in the ruxolitinib group and 5 (3.0%) in the control group had a complete response. The efficacy boundary for overall response was crossed at the interim analysis, with the value being higher with ruxolitinib than with control therapy (50.5% [8 with a complete response, 41 with a partial response] vs. 26.3% [3 with a complete response, 23 with a partial response]; P<0.001). A higher overall response was observed with ruxolitinib than with control therapy regardless of the organs involved (Table S4 and Fig. S3). Although patients were not stratified according to organ involvement, odds ratios favored ruxolitinib in all organ subgroups. Response according to the investigator-selected control drug regimen is shown in Figure S4.

Patients receiving ruxolitinib had longer failure-free survival than patients receiving control therapy (median failure-free survival, >18.6 months vs. 5.7 months; hazard ratio, 0.37; 95% CI, 0.27 to 0.51; P<0.001). The median failure-free survival with ruxolitinib was not reached, but the lower boundary of the 95% confidence interval was estimated as 18.6 months, with the efficacy boundary crossed at the interim analysis (Fig. 2B and Fig. S5). The probability of failure-free survival at 6 months, as estimated with the use of the Kaplan–Meier method, was higher with ruxolitinib (74.9%; 95% CI, 67.5 to 80.9) than with control therapy (44.5%; 95% CI, 36.5 to 52.1). The response on the modified Lee Symptom Scale at 24 weeks was also higher with ruxolitinib than with control therapy (24.2% vs. 11.0%; odds ratio, 2.62 [95% CI, 1.42 to 4.82]; risk ratio, 2.19 [95% CI, 1.31 to 3.65]; P=0.001) (Fig. 2C). The dose of glucocorticoids decreased over time in both groups, with a slightly greater decrease with ruxolitinib (Fig. S6).

A best overall response up to week 24 was

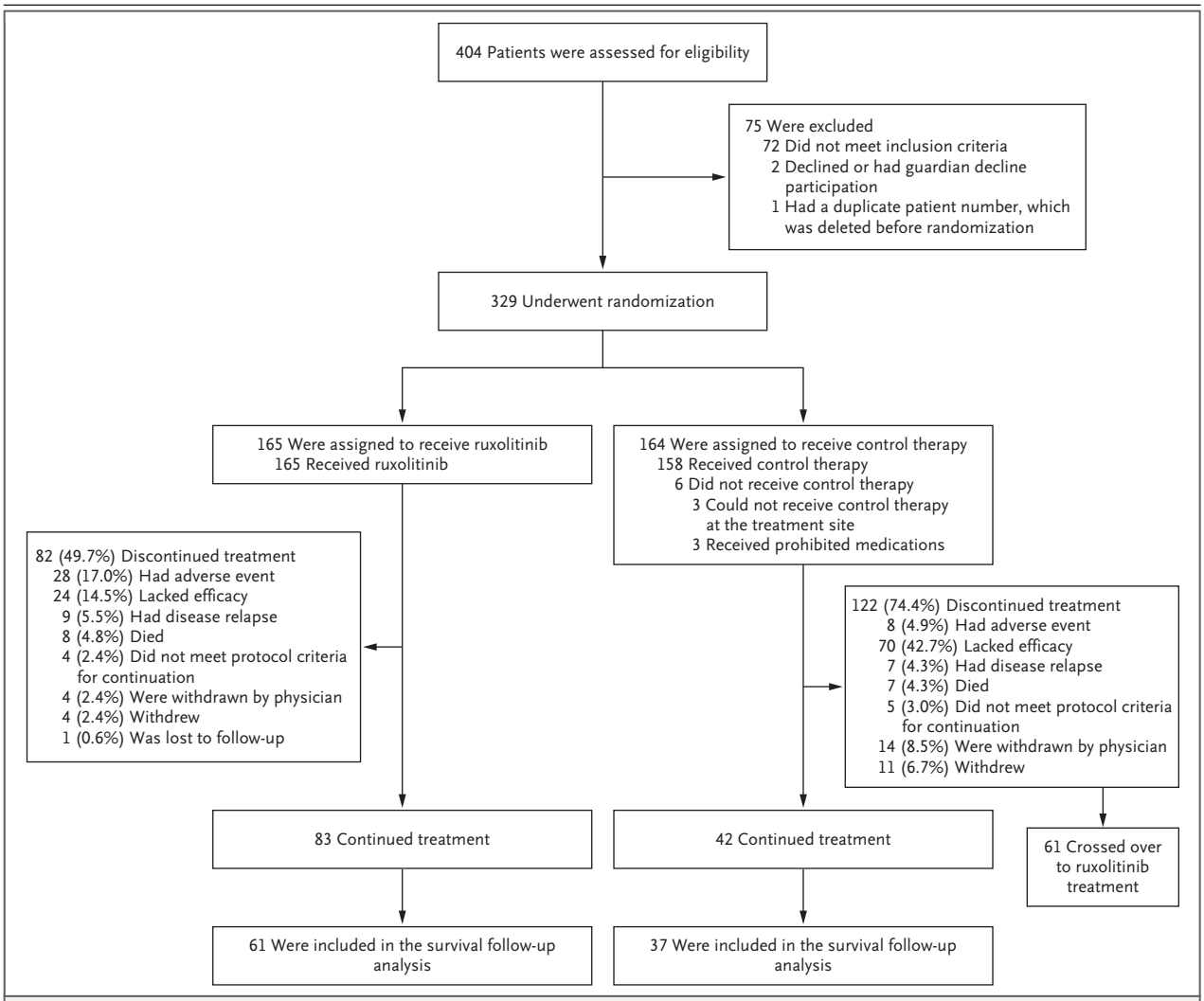

Figure 1. Eligibility, Randomization, and Follow-up.

observed in 76.4% of patients in the ruxolitinib group and in 60.4% in the control group (odds ratio, 2.17 [95% CI, 1.34 to 3.52]; risk ratio, 1.24 [95% CI, 1.07 to 1.43]; P=0.001) (Fig. 3A). Among patients with a response at any time, the estimated probability of maintaining a response at 12 months was 68.5% (95% CI, 58.9 to 76.3) in the ruxolitinib group as compared with 40.3% (95% CI, 30.3 to 50.2) in the control group (Fig. 3B). Patients who crossed over from control therapy to ruxolitinib (61 patients) also had a response, with a best overall response at data cutoff in 78.7% (4 with a complete response and 44 with a partial response), a finding consistent with the best overall response with ruxolitinib in the randomized population. Overall survival data were not mature at data cutoff, and median overall survival was not reached in either group (hazard ratio, 1.09; 95% CI, 0.65 to 1.82) (Fig. S7). At 12 months, the estimated probability of survival was 81.4% with ruxolitinib (95% CI, 74.1 to 86.8) and 83.8% with control therapy (95% CI, 76.5 to 89.0).

SAFETY

Safety analyses included 323 patients (165 in the ruxolitinib group and 158 in the control group) who received at least 1 dose of trial treatment up to week 24. Up to day 179, the median duration of exposure to therapy was 25.6 weeks (range, 0.7 to 25.6) in the ruxolitinib group and 24.0 weeks (range, 0.6 to 25.6) in the control group. Adverse events of any grade up to week 24 occurred in 97.6% of the patients (161) who re-

Table 1. Characteristics of the Patients at Baseline.*

Variable	Ruxolitinib (N=165)	Control (N=164)
Age		
Median (range) — yr	49.0 (13.0–73.0)	50.0 (12.0–76.0)
Distribution — no. (%)		
12 to <18 yr	4 (2.4)	8 (4.9)
18 to 65 yr	143 (86.7)	134 (81.7)
>65 yr	18 (10.9)	22 (13.4)
Sex — no. (%)		
Male	109 (66.1)	92 (56.1)
Female	56 (33.9)	72 (43.9)
Previous acute GVHD — no. (%)	92 (55.8)	88 (53.7)
Chronic GVHD severity — no. (%)†		
Mild	1 (0.6)	1 (0.6)
Moderate	67 (40.6)	74 (45.1)
Severe	97 (58.8)	89 (54.3)
Donor type — no. (%)‡		
Related	91 (54.5)	87 (52.1)
Unrelated	76 (45.5)	80 (47.9)
Previous systemic therapy for chronic GVHD or glucocorticoid-refractory or -dependent chronic GVHD — no. (%)§		
Glucocorticoid only	70 (42.4)	81 (49.4)
Glucocorticoid + calcineurin inhibitors	68 (41.2)	69 (42.1)
Glucocorticoid + calcineurin inhibitors + other systemic therapy	10 (6.1)	4 (2.4)
Glucocorticoid + other systemic therapy	14 (8.5)	9 (5.5)
Missing data	3 (1.8)	1 (0.6)

* GVHD denotes graft-versus-host disease.
† Severity was graded according to National Institutes of Health consensus staging criteria[30] at screening. Enrollment of patients with mild glucocorticoid-refractory or glucocorticoid-dependent chronic GVHD was considered a protocol deviation.
‡ Some patients received more than one transplant.
§ Values for previous treatment of chronic GVHD were obtained from documented patient history of medication; topical or local treatments were not counted.

ceived ruxolitinib as compared with 91.8% of the patients (145) who received control therapy (Table 2 and Table S5). Occurrence of adverse events of grade 3 or higher was similar in the two groups (in 57.0% of the patients who received ruxolitinib and in 57.6% of the patients who received control therapy). The most common adverse events of grade 3 or higher were thrombocytopenia (in 15.2% of patients who received ruxolitinib and 10.1% of patients who received control therapy), anemia (in 12.7% and 7.6%), neutropenia (in 8.5% and 3.8%), and pneumonia (in 8.5% and 9.5%). Serious adverse events up to week 24 occurred in 55 patients (33.3%) who received ruxolitinib and in 58 patients (36.7%) who received control therapy (Table S6).

Adverse events led to treatment discontinuation in 27 patients (16.4%) who received ruxolitinib and in 11 (7.0%) who received control therapy. Clinically documented pneumonia was the only adverse event leading to discontinuation by 2% or more of patients in the ruxolitinib group (4.8%, as compared with 1.3% of patients in the control therapy group) (Table S7). Adverse events leading to dose adjustments or interruptions occurred in 62 patients (37.6%) who received ruxolitinib and in 26 patients (16.5%) who received control therapy.

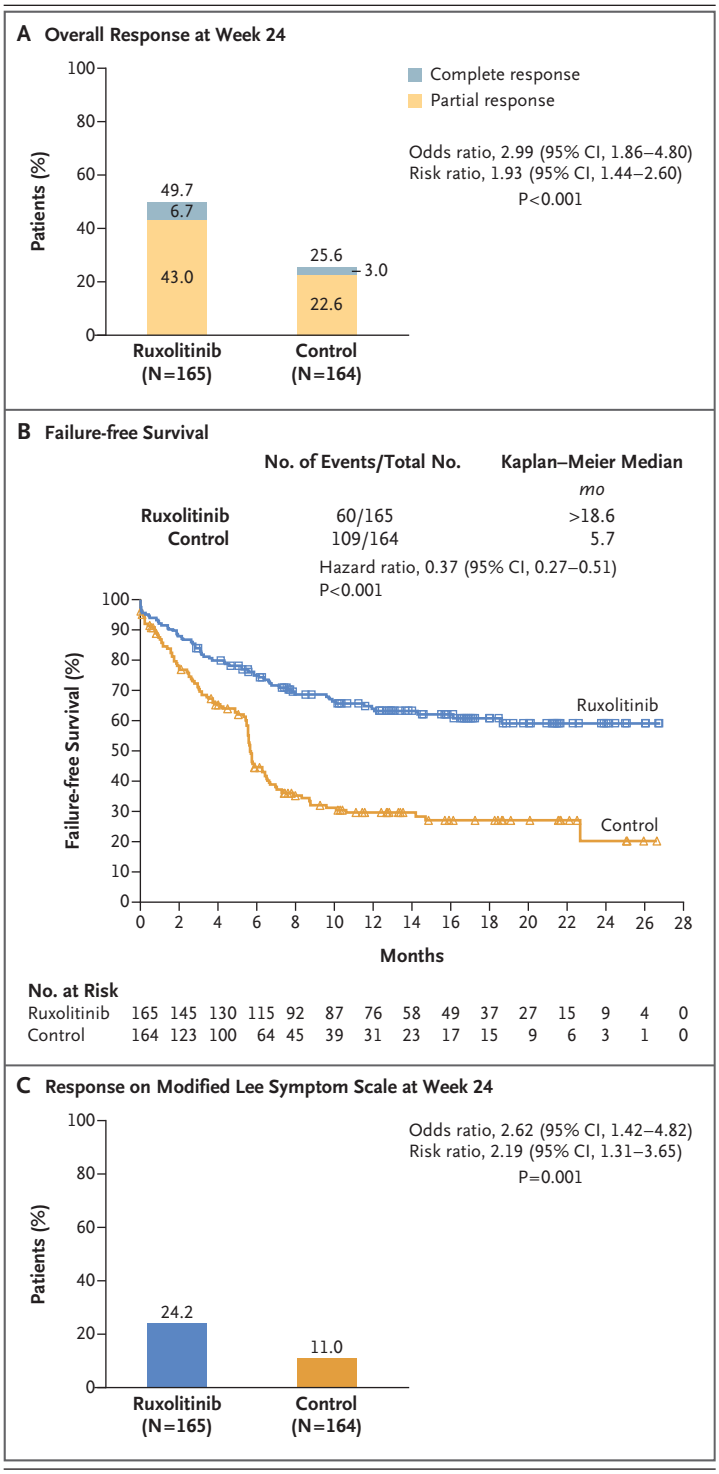

Figure 2. Response at Week 24 and Failure-free Survival.

End points were tested at the interim analysis (196 patients; alpha significance level, 0.01176) and the current primary analysis (329 patients; alpha significance level, 0.01858 if not positive at the interim analysis) according to an overall hierarchical testing procedure to control the one-sided familywise alpha level at 0.025 overall. The test sequence for results among patients outside the United States was overall response, failure-free survival, and score on the modified Lee Symptom Scale; the test sequence for results among patients in the United States was overall response, score on the modified Lee Symptom Scale, and failure-free survival. For the P value for overall response at week 24 (Panel A), the efficacy boundary was crossed at the interim analysis (overall response was 50.5% with ruxolitinib and 26.3% with control therapy; P<0.001). One-sided P value, odds ratio, and 95% confidence interval were calculated with the use of a stratified Cochran–Mantel–Haenszel test, with moderate and severe chronic GVHD as strata. For P values for failure-free survival (Panel B), the efficacy boundary was crossed at the interim analysis for results among patients not in the United States (hazard ratio, 0.32; 95% CI, 0.21 to 0.49; P<0.001). For results among patients in the United States, the hypothesis was retested at the primary analysis according to the overall hierarchical testing procedure (details are provided in the Supplementary Methods section in the Supplementary Appendix). At data cutoff (May 8, 2020), the median failure-free survival was not reached in the ruxolitinib group, but the lower bound of the 95% confidence interval was estimated to be 18.6 months. Patients receiving ruxolitinib had a numerically, but not significantly, higher response (defined as a ≥7-point reduction from baseline in total symptom score) according to the modified Lee Symptom Scale (Panel C) at the interim analysis than those receiving control therapy (19.6% vs. 8.1%; odds ratio, 2.80; P=0.02).

Infections of any type occurred in 63.6% of patients who received ruxolitinib as compared with 56.3% who received control therapy (grade 3 infections, 19.4% vs. 18.4%, according to the grading system described by Cordonnier et al.[31]). Viral infections were the most common (33.9% and 29.1% in the ruxolitinib and control groups, respectively), followed by bacterial (27.9% and 25.9%) and fungal infections (11.5% and 5.7%); infections of unknown type occurred in 21.2% of patients who received ruxolitinib and in 20.3% of patients who received control therapy (Table S8). Cytomegalovirus infection and reactivation were similar in the two groups (5.5% and 8.2%) (Table 2).

As of the data cutoff, 31 patients (18.8%) who received ruxolitinib and 27 patients (16.5%) who received control therapy had died. Deaths were due primarily to complications caused by chronic GVHD disease or treatment (or both) (22 patients [13.3%] who received ruxolitinib vs. 13 patients [7.9%] who received control therapy, including 2 deaths after crossover to ruxolitinib) or infections (2 patients [1.2%] vs. 6 patients

[3.7%]). The incidence of cancer relapse and progression was low in both groups (9 patients [5.8%] and 8 patients [5.0%]). The estimated cumulative incidence of relapse at 6 months was 2.59% (95% CI, 0.85 to 6.08) among patients who received ruxolitinib and 2.65% (95% CI, 0.87 to 6.21) among patients who received control therapy.

DISCUSSION

REACH3 is a phase 3 randomized trial that showed the superiority of ruxolitinib over common second-line therapeutic options, including ibrutinib and extracorporeal photopheresis, for treatment of glucocorticoid-refractory or -dependent chronic GVHD. Ruxolitinib led to a higher overall response than control therapy at week 24 (49.7% vs. 25.6%), regardless of the organs involved, and a higher best overall response (76.4% vs. 60.4%), a longer duration of response, and longer failure-free survival. The results in individual organs showed that ruxolitinib led to higher responses in most organs than control therapy. The response in the lungs and liver was low in both treatment groups, which highlights how difficult treatment can be when these organs are affected. However, subgroup analysis of overall response according to organ involvement showed that chronic GVHD in difficult-to-treat organs did not preclude alleviation of chronic GVHD in other organs in patients receiving ruxolitinib, so the overall response was favorable.

In addition, patients treated with ruxolitinib had greater reduction of symptoms than those treated with control therapy, as measured by the modified Lee Symptom Scale, a scale specific to chronic GVHD.[32] Achievement of complete response or partial response, as measured according to NIH criteria and improvements in the modified Lee Symptom Scale score at 6 months, has been associated with better survival.[33,34] Early data do not suggest a difference in survival between treatment groups. Longer follow-up is needed to evaluate the effect of ruxolitinib on survival.

The absence of a strong end point, such as glucocorticoid-free remission, and the presence of confounders, including concomitant treatments, make determination of the effect on glucocorticoid dose over time with ruxolitinib as compared with commonly used therapies difficult. However, patients treated with ruxolitinib had consistent reductions in glucocorticoid dose over time (Fig. S6), suggesting a glucocorticoid-sparing effect, a finding in line with previous observations.[20]

The safety profile of ruxolitinib was consistent with observations in patients with acute GVHD and expectations in patients with glucocorticoid-refractory or -dependent chronic GVHD. The most common adverse event was anemia, which was expected given the mechanism of action and known safety profile of ruxolitinib.[35,36] Thrombocytopenia, another known side effect of ruxolitinib, was also common, but both ane-

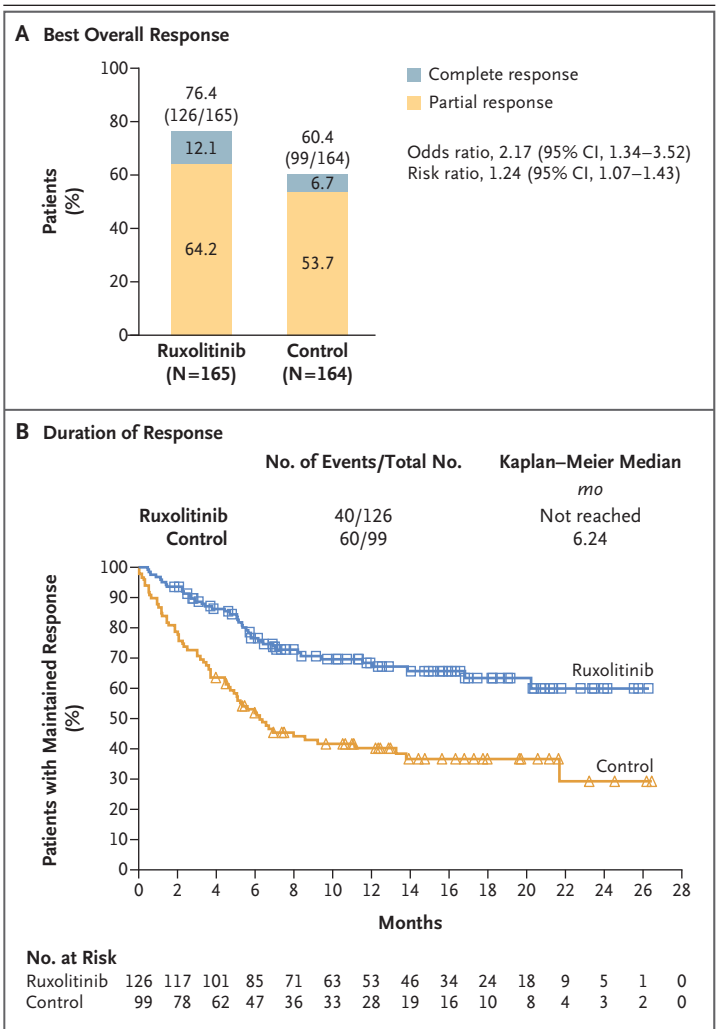

Figure 3. Overall Response and Duration of Response.

The comparisons for overall response (Panel A) and duration of response (Panel B) are based on the subgroup of patients who had a complete or partial response at any time up to week 24. Duration of response to treatment (Panel B) was measured as the time from first documented complete response or partial response.

Table 2. Adverse Events up to Week 24 in 5% or More of Patients Treated with Ruxolitinib.*

Adverse Event	Ruxolitinib (N=165)		Control (N=158)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients with event (percent)			
Any	161 (97.6)	94 (57.0)	145 (91.8)	91 (57.6)
Hematologic event				
Anemia	48 (29.1)	21 (12.7)	20 (12.7)	12 (7.6)
Thrombocytopenia†	35 (21.2)	25 (15.2)	23 (14.6)	16 (10.1)
Neutropenia	18 (10.9)	14 (8.5)	8 (5.1)	6 (3.8)
Gastrointestinal event				
Diarrhea	17 (10.3)	1 (0.6)	21 (13.3)	2 (1.3)
Nausea	15 (9.1)	0	16 (10.1)	2 (1.3)
Vomiting	12 (7.3)	0	10 (6.3)	2 (1.3)
Constipation	12 (7.3)	0	8 (5.1)	0
Infection				
Pneumonia	18 (10.9)	14 (8.5)	20 (12.7)	15 (9.5)
Upper respiratory tract infection	14 (8.5)	0	13 (8.2)	2 (1.3)
Urinary tract infection	11 (6.7)	1 (0.6)	5 (3.2)	2 (1.3)
Nasopharyngitis	10 (6.1)	0	6 (3.8)	0
BK virus infection	9 (5.5)	1 (0.6)	2 (1.3)	0
Cytomegalovirus infection or reactivation	9 (5.5)	2 (1.2)	13 (8.2)	0
Laboratory abnormality				
Alanine aminotransferase increased	25 (15.2)	7 (4.2)	7 (4.4)	0
Creatinine increased	23 (13.9)	0	7 (4.4)	1 (0.6)
Aspartate aminotransferase increased	16 (9.7)	3 (1.8)	4 (2.5)	1 (0.6)
Hypertriglyceridemia	16 (9.7)	8 (4.8)	13 (8.2)	6 (3.8)
γ-glutamyltransferase increased	15 (9.1)	11 (6.7)	5 (3.2)	3 (1.9)
Hyperglycemia	13 (7.9)	8 (4.8)	5 (3.2)	3 (1.9)
Hypokalemia	13 (7.9)	3 (1.8)	16 (10.1)	7 (4.4)
Cholesterol increased	12 (7.3)	4 (2.4)	7 (4.4)	3 (1.9)
Amylase increased	11 (6.7)	5 (3.0)	3 (1.9)	0
Lipase increased	10 (6.1)	4 (2.4)	2 (1.3)	1 (0.6)
Hypercholesterolemia	9 (5.5)	2 (1.2)	2 (1.3)	1 (0.6)
Hyperkalemia	9 (5.5)	3 (1.8)	4 (2.5)	1 (0.6)
Other				
Hypertension	26 (15.8)	8 (4.8)	20 (12.7)	11 (7.0)
Pyrexia	26 (15.8)	3 (1.8)	15 (9.5)	2 (1.3)
Cough	17 (10.3)	0	11 (7.0)	0
Fatigue	17 (10.3)	1 (0.6)	12 (7.6)	3 (1.9)
Dyspnea	16 (9.7)	3 (1.8)	10 (6.3)	2 (1.3)
Headache	14 (8.5)	2 (1.2)	12 (7.6)	1 (0.6)
Peripheral edema	12 (7.3)	1 (0.6)	14 (8.9)	0
Back pain	11 (6.7)	1 (0.6)	11 (7.0)	0
Insomnia	11 (6.7)	0	6 (3.8)	0
Myalgia	11 (6.7)	0	5 (3.2)	0
Arthralgia	10 (6.1)	0	8 (5.1)	0

* The safety data include all patients who received at least one dose of study drug.
† Included are events recorded as thrombocytopenia and decreased platelet count.

mia and thrombocytopenia are reversible and can be managed with dose reductions and supportive care.[35,36] Overall, 37.6% of patients had adverse events leading to dose modifications, and 16.4% had events leading to discontinuation of ruxolitinib. A smaller percentage of patients treated with control therapy than with ruxolitinib had adverse events leading to discontinuation (7.0% vs. 16.4%), but this finding may have been confounded or affected by more than 40% of patients discontinuing control therapy early owing to lack of efficacy or by stricter protocol-defined guidance on ruxolitinib dose modifications if adverse events were suspected to be related to a trial drug. A total of 11 deaths were reported as being related to a trial drug (7 deaths [4.2%] with ruxolitinib and 4 [2.5%] with control therapy).

The incidence of grade 3 infection was similar in the two groups (19.4% vs. 18.4%). The incidence of cytomegalovirus infection or reactivation with ruxolitinib was similar to that with control therapy (Table 2) and was lower than that observed in a retrospective analysis (14.6%).[20] A numerically higher incidence of fungal infections (as classified according to the system described by Cordonnier[31]) was observed with ruxolitinib, which suggests the possible occurrence of opportunistic infections during treatment.[37] Given the risk of infections, patients treated with ruxolitinib should receive prophylaxis against infection, and a low threshold for evaluation of new signs and symptoms should be adopted.

In order to accommodate various control-therapy options, an open-label study design was necessary. To minimize potential bias,[38] we assessed response using the latest NIH consensus response criteria. Better adherence to these objective measures in REACH3 than in previous studies may have resulted in lower overall responses with control therapy and ruxolitinib than have been reported previously. Most studies evaluating the most common therapy options, including ibrutinib[14] and extracorporeal photopheresis,[39] in glucocorticoid-refractory chronic GVHD have been uncontrolled, nonrandomized studies, with the few exceptions showing no superiority over control therapy.[40] In addition, many of the previous studies were conducted before NIH response criteria were established, which probably led to higher treatment effects and overestimated responses, as reported in a meta-analysis assessing the effect of deviations from NIH recommendations.[38] Furthermore, many studies, including the ibrutinib study,[14] included best response (at any time) — referred to as best overall response in our trial — whereas our primary end point was overall response at 24 weeks (a single time point). Indeed, the best overall response in the control group (60.4%, as compared with 76.4% in the ruxolitinib group) was closer to what has been reported for other studies.

Our trial showed that among patients with moderate or severe chronic GVHD in whom glucocorticoids produced an inadequate response, ruxolitinib was superior to control therapies, as evidenced by a greater overall response, longer failure-free survival, and greater reduction in symptoms. Patients receiving ruxolitinib had a higher incidence of grade 3 or worse thrombocytopenia and anemia than those receiving control therapy; no new safety signals were observed.

Supported by Novartis and Incyte.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank Karen Chinchilla, Ph.D., of ArticulateScience, for providing medical writing and editorial support for an earlier version of the manuscript, funded by Novartis in accordance with Good Publication Practice guidelines (http://www.ismpp.org/gpp3).

APPENDIX

The authors' affiliations are as follows: the Department of Medicine I, Faculty of Medicine, Medical Center, University of Freiburg, Freiburg (R.Z.), and Medizinische Klinik und Poliklinik I, Universitätsklinikum Dresden, Dresden (J.M.M.) — both in Germany; the Unit of Blood Diseases and Stem Cell Transplantation, Department of Clinical and Experimental Sciences, ASST Spedali Civili di Brescia, University of Brescia, Brescia (N.P.), UOC di Oncoematologia e TMO, Dipartimento Oncologico "la Maddalena," Palermo (M.M.), and Dipartimento di Oncoematologia Pediatrica, IRCCS, Ospedale Pediatrico Bambino Gesu', Sapienza, Università di Roma, Rome (F.L.) — all in Italy; the BMT Unit, Tel Aviv (Sourasky) Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel (R.R.); the Oncology Center, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia (S.K.H.); the Department of Medicine, Sheikh Shakhbout Medical City, Mayo Clinic, Abu Dhabi, United Arab Emirates (S.K.H.); UCL Cancer Institute, Institute of Immunity and Transplantation, London (R.C.); the Department of Bone Marrow Transplantation and Onco-Hematology, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Gliwice, Poland (S.G.); Acibadem University Hospital, Hematology Department, Istanbul, Turkey (A.U.); Incyte, Wilmington, DE (P.L.); Novartis Pharma, Basel, Switzerland (N.H., T.S.); Novartis Pharmaceuticals, East Hanover, NJ (M.G.); the Fred Hutchinson Cancer Research Center, Seattle (S.J.L.); and the Department of Hematology, Hokkaido University Faculty of Medicine, Sapporo, Japan (T.T.).

REFERENCES

1. Blazar BR, Murphy WJ, Abedi M. Advances in graft-versus-host disease biology and therapy. Nat Rev Immunol 2012;12:443-58.
2. Zeiser R, Blazar BR. Pathophysiology of chronic graft-versus-host disease and therapeutic targets. N Engl J Med 2017;377:2565-79.
3. Arora M, Cutler CS, Jagasia MH, et al. Late acute and chronic graft-versus-host disease after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant 2016;22:449-55.
4. Socié G, Stone JV, Wingard JR, et al. Long-term survival and late deaths after allogeneic bone marrow transplantation. N Engl J Med 1999;341:14-21.
5. Wingard JR, Majhail NS, Brazauskas R, et al. Long-term survival and late deaths after allogeneic hematopoietic cell transplantation. J Clin Oncol 2011;29:2230-9.
6. Lee SJ, Zahrieh D, Alyea EP, et al. Comparison of T-cell-depleted and non-T-cell-depleted unrelated donor transplantation for hematologic diseases: clinical outcomes, quality of life, and costs. Blood 2002;100:2697-702.
7. Pidala J, Kurland B, Chai X, et al. Patient-reported quality of life is associated with severity of chronic graft-versus-host disease as measured by NIH criteria: report on baseline data from the Chronic GVHD Consortium. Blood 2011;117:4651-7.
8. Kurosawa S, Oshima K, Yamaguchi T, et al. Quality of life after allogeneic hematopoietic cell transplantation according to affected organ and severity of chronic graft-versus-host disease. Biol Blood Marrow Transplant 2017;23:1749-58.
9. Jacobs JM, Fishman S, Sommer R, et al. Coping and modifiable psychosocial factors are associated with mood and quality of life in patients with chronic graft-versus-host disease. Biol Blood Marrow Transplant 2019;25:2234-42.
10. Griffith S, Fenech AL, Nelson A, Geer JA, Temel JS, El-Jawahri A. Post-traumatic stress symptoms in hematopoietic stem cell transplant (HCT) recipients. J Clin Oncol 2020;38:Suppl:7505. abstract.
11. Axt L, Naumann A, Toennies J, et al. Retrospective single center analysis of outcome, risk factors and therapy in steroid refractory graft-versus-host disease after allogeneic hematopoietic cell transplantation. Bone Marrow Transplant 2019;54:1805-14.
12. Penack O, Marchetti M, Ruutu T, et al. Prophylaxis and management of graft versus host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European Society for Blood and Marrow Transplantation. Lancet Haematol 2020;7(2):e157-e167.
13. Dignan FL, Amrolia P, Clark A, et al. Diagnosis and management of chronic graft-versus-host disease. Br J Haematol 2012;158:46-61.
14. Miklos D, Cutler CS, Arora M, et al. Ibrutinib for chronic graft-versus-host disease after failure of prior therapy. Blood 2017;130:2243-50.
15. Hechinger A-K, Smith BAH, Flynn R, et al. Therapeutic activity of multiple common γ-chain cytokine inhibition in acute and chronic GVHD. Blood 2015;125:570-80.
16. Choi J, Ziga ED, Ritchey J, et al. IFNγR signaling mediates alloreactive T-cell trafficking and GVHD. Blood 2012;120:4093-103.
17. Nicholson SE, Oates AC, Harpur AG, Ziemiecki A, Wilks AF, Layton JE. Tyrosine kinase JAK1 is associated with the granulocyte-colony-stimulating factor receptor and both become tyrosine-phosphorylated after receptor activation. Proc Natl Acad Sci U S A 1994;91:2985-8.
18. Schwab L, Goroncy L, Palaniyandi S, et al. Neutrophil granulocytes recruited upon translocation of intestinal bacteria enhance graft-versus-host disease via tissue damage. Nat Med 2014;20:648-54.
19. Spoerl S, Mathew NR, Bscheider M, et al. Activity of therapeutic JAK 1/2 blockade in graft-versus-host disease. Blood 2014;123:3832-42.
20. Zeiser R, Burchert A, Lengerke C, et al. Ruxolitinib in corticosteroid-refractory graft-versus-host disease after allogeneic stem cell transplantation: a multicenter survey. Leukemia 2015;29:2062-8.
21. Jagasia M, Perales M-A, Schroeder MA, et al. Ruxolitinib for the treatment of steroid-refractory acute GVHD (REACH1): a multicenter, open-label phase 2 trial. Blood 2020;135:1739-49.
22. Jakafi (ruxolitinib). Wilmington, DE: Incyte, 2020 (prescribing information) (https://www.jakafi.com/pdf/prescribing-information.pdf).
23. Zeiser R, von Bubnoff N, Butler J, et al. Ruxolitinib for glucocorticoid-refractory acute graft-versus-host disease. N Engl J Med 2020;382:1800-10.
24. Martin PJ, Lee SJ, Przepiorka D, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease. VI. The 2014 Clinical Trial Design Working Group report. Biol Blood Marrow Transplant 2015;21:1343-59.
25. Sarantopoulos S, Cardones AR, Sullivan KM. How I treat refractory chronic graft-versus-host disease. Blood 2019;133:1191-200.
26. Lee SJ, Wolff D, Kitko C, et al. Measuring therapeutic response in chronic graft-versus-host disease. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease. IV. The 2014 Response Criteria Working Group report. Biol Blood Marrow Transplant 2015;21:984-99.
27. Lee SK, Cook EF, Soiffer R, Antin JH. Development and validation of a scale to measure symptoms of chronic graft-versus-host disease. Biol Blood Marrow Transplant 2002;8:444-52.
28. Teh C, Onstad L, Lee SJ. Reliability and validity of the modified 7-Day Lee Chronic Graft-versus-Host Disease Symptom Scale. Biol Blood Marrow Transplant 2020;26:562-7.
29. Glimm E, Maurer W, Bretz F. Hierarchical testing of multiple endpoints in group-sequential trials. Stat Med 2010;29:219-28.
30. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease. I. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant 2015;21(3):389.e1-401.e1.
31. Cordonnier C, Maury S, Ribaud P, et al. A grading system based on severity of infection to predict mortality in allogeneic stem cell transplant recipients. Transplantation 2006;82:86-92.
32. Merkel EC, Mitchell SA, Lee SJ. Content validity of the Lee Chronic Graft-versus-Host Disease Symptom Scale as assessed by cognitive interviews. Biol Blood Marrow Transplant 2016;22:752-8.
33. Palmer J, Chai X, Pidala J, et al. Predictors of survival, nonrelapse mortality, and failure-free survival in patients treated for chronic graft-versus-host disease. Blood 2016;127:160-6.
34. Martin PJ, Storer BE, Inamoto Y, et al. An endpoint associated with clinical benefit after initial treatment of chronic graft-versus-host disease. Blood 2017;130:360-7.
35. Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med 2012;366:799-807.
36. Harrison C, Kiladjian J-J, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. N Engl J Med 2012;366:787-98.
37. Polverelli N, Palumbo GA, Binotto G, et al. Epidemiology, outcome, and risk factors for infectious complications in myelofibrosis patients receiving ruxolitinib: a multicenter study on 446 patients. Hematol Oncol 2018 April 6 (Epub ahead of print).
38. Olivieri J, Manfredi L, Postacchini L, et al. Consensus recommendations for improvement of unmet clinical needs — the example of chronic graft-versus-host disease: a systematic review and meta-analysis. Lancet Haematol 2015;2(7):e297-e305.
39. Drexler B, Buser A, Infanti L, Stehle G, Halter J, Holbro A. Extracorporeal photopheresis in graft-versus-host disease. Transfus Med Hemother 2020;47:214-25.
40. Flowers MED, Apperley JF, van Besien K, et al. A multicenter prospective phase 2 randomized study of extracorporeal photopheresis for treatment of chronic graft-versus-host disease. Blood 2008;112:2667-74.