ORIGINAL ARTICLE

# Ruxolitinib for Glucocorticoid-Refractory Acute Graft-versus-Host Disease

Robert Zeiser, M.D., Nikolas von Bubnoff, M.D., Jason Butler, F.R.A.C.P., Mohamad Mohty, M.D., Ph.D., Dietger Niederwieser, M.D., Reuven Or, M.D., Jeff Szer, F.R.A.C.P., Eva M. Wagner, M.D., Tsila Zuckerman, M.D., Bruyère Mahuzier, Pharm.D., Judith Xu, M.Sc., Celine Wilke, M.D., Kunal K. Gandhi, M.D., M.P.H., and Gérard Socié, M.D., Ph.D., for the REACH2 Trial Group*

## ABSTRACT

### BACKGROUND

Acute graft-versus-host disease (GVHD) remains a major limitation of allogeneic stem-cell transplantation; not all patients have a response to standard glucocorticoid treatment. In a phase 2 trial, ruxolitinib, a selective Janus kinase (JAK1 and JAK2) inhibitor, showed potential efficacy in patients with glucocorticoid-refractory acute GVHD.

### METHODS

We conducted a multicenter, randomized, open-label, phase 3 trial comparing the efficacy and safety of oral ruxolitinib (10 mg twice daily) with the investigator's choice of therapy from a list of nine commonly used options (control) in patients 12 years of age or older who had glucocorticoid-refractory acute GVHD after allogeneic stem-cell transplantation. The primary end point was overall response (complete response or partial response) at day 28. The key secondary end point was durable overall response at day 56.

### RESULTS

A total of 309 patients underwent randomization; 154 patients were assigned to the ruxolitinib group and 155 to the control group. Overall response at day 28 was higher in the ruxolitinib group than in the control group (62% [96 patients] vs. 39% [61]; odds ratio, 2.64; 95% confidence interval [CI], 1.65 to 4.22; P<0.001). Durable overall response at day 56 was higher in the ruxolitinib group than in the control group (40% [61 patients] vs. 22% [34]; odds ratio, 2.38; 95% CI, 1.43 to 3.94; P<0.001). The estimated cumulative incidence of loss of response at 6 months was 10% in the ruxolitinib group and 39% in the control group. The median failure-free survival was considerably longer with ruxolitinib than with control (5.0 months vs. 1.0 month; hazard ratio for relapse or progression of hematologic disease, non–relapse-related death, or addition of new systemic therapy for acute GVHD, 0.46; 95% CI, 0.35 to 0.60). The median overall survival was 11.1 months in the ruxolitinib group and 6.5 months in the control group (hazard ratio for death, 0.83; 95% CI, 0.60 to 1.15). The most common adverse events up to day 28 were thrombocytopenia (in 50 of 152 patients [33%] in the ruxolitinib group and 27 of 150 [18%] in the control group), anemia (in 46 [30%] and 42 [28%], respectively), and cytomegalovirus infection (in 39 [26%] and 31 [21%]).

### CONCLUSIONS

Ruxolitinib therapy led to significant improvements in efficacy outcomes, with a higher incidence of thrombocytopenia, the most frequent toxic effect, than that observed with control therapy. (Funded by Novartis; REACH2 ClinicalTrials.gov number, NCT02913261.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Zeiser at the Department of Hematology, Oncology, and Stem Cell Transplantation, University Medical Center Freiburg, Hugstetter Str. 55, 79106 Freiburg, Germany, or at robert.zeiser@uniklinik-freiburg.de.

*A list of the investigators in the REACH2 Trial Group is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Zeiser and von Bubnoff contributed equally to this article.

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The incidence of allogeneic stem-cell transplantation is increasing worldwide[1,2] owing to more widespread use of reduced-intensity conditioning regimens and access to alternative stem-cell sources.[2,3] A major limitation of allogeneic stem-cell transplantation is acute graft-versus-host disease (GVHD), a condition in which donor T cells attack host tissue, affecting multiple organs, particularly the skin, liver, and gastrointestinal tract.[4,5] The pathogenesis of GVHD is also influenced by the release of danger-associated molecular patterns[6] and tissue damage caused by neutrophil granulocytes.[7] Despite standard prophylaxis, GVHD develops in approximately 50% of recipients of allogeneic stem-cell transplantation.[5,8,9] GVHD is a substantial cause of death in patients undergoing allogeneic stem-cell transplantation.[10-13] Standard first-line treatment is systemic, high-dose glucocorticoids[4,9]; however, response ranges from approximately 60% in patients with grade II disease to 30 to 40% in patients with grade IV disease.[13,14] Glucocorticoids are also associated with clinically significant side effects, which can lower patients' quality of life and render patients susceptible to infection.[15] For patients with glucocorticoid-refractory acute GVHD, no consensus exists regarding treatment, and outcomes remain poor.[4,5,9,13] Despite numerous phase 2 trials and two previous randomized, phase 3 trials, no treatment has shown superiority over other treatments, and, with the exception of ruxolitinib, no new drugs have been approved either as first-line or second-line treatment for acute GVHD in the past 30 years.[9,12,16,17]

The Janus kinase (JAK) and signal transducers and activators of transcription (STAT) signaling pathways play an important role in immune-cell activation and tissue inflammation during acute GVHD,[18-20] including the activity of dendritic cells[21] and neutrophil granulocytes.[22] Tissue damage that is associated with acute GVHD is driven by inflammatory cytokines, the effects of which are mediated in part by JAKs.[5,23] Ruxolitinib is an oral selective inhibitor of JAK1 and JAK2[8] that reduces the incidence and severity of GVHD in vivo while preserving graft-versus-leukemia effects in preclinical models.[18-20] In a single-group, phase 2 trial of ruxolitinib in patients with glucocorticoid-refractory grade II to IV acute GVHD (REACH1), 54.9% of the patients had a response at day 28.[24] Here we report the results of a randomized, phase 3 trial (REACH2) that was conducted to compare the efficacy and safety of ruxolitinib with the investigator's choice of therapy from a list of nine commonly used options ("best available care") in patients with glucocorticoid-refractory acute GVHD.

## Methods

### Trial Oversight

The trial was designed and data were analyzed by the sponsor (Novartis) in collaboration with the trial steering committee. Writing and editorial assistance was provided by Excerpta Medica, with funding by the sponsor. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol (available with the full text of this article at NEJM.org).

The trial was designed and conducted in accordance with the guidelines for Good Clinical Practice of the International Council for Harmonisation, with applicable local regulations, and with the principles of the Declaration of Helsinki. The protocol was approved at each participating center by the relevant institutional review board, independent ethics committee, or research ethics board.

### Patients

Eligible patients were at least 12 years of age and were recipients of allogeneic stem-cell transplantation (any donor source, any stem-cell source) who had grade II to IV glucocorticoid-refractory acute GVHD that involved the use of systemic immunosuppressive therapy (see the Supplementary Methods section in the Supplementary Appendix, available at NEJM.org).[25] Glucocorticoid-refractory disease was defined as disease progression on the basis of organ assessment after at least 3 days of high-dose systemic glucocorticoid therapy, with or without calcineurin inhibitors; a lack of response (absence of partial response or better) after 7 days; or treatment failure during glucocorticoid taper (i.e., an increase in the methylprednisolone dose to ≥2 mg per kilogram of body weight per day [or equivalent ≥2.5 mg per kilogram per day of prednisone] or an inability to taper the dose to <0.5 mg per kilogram per day of methylprednisolone [or equivalent <0.6 mg per kilogram per day of prednisone] for a minimum of 7 days). Myeloid and platelet engraftment, defined as an absolute neutrophil count of more than 1000 cells per cubic millimeter and a platelet count of at

least 20,000 cells per cubic millimeter, was confirmed within 48 hours before the initiation of treatment. Patients were excluded if their tumor had relapsed after any allogeneic stem-cell transplantation in the previous 6 months; if they had a relapsed primary cancer after undergoing allogeneic stem-cell transplantation; if they had received more than one previous treatment for glucocorticoid-refractory acute GVHD; if they had an active, uncontrolled infection; or if they had received JAK inhibitor therapy for any indication after the initiation of allogeneic stem-cell transplantation conditioning.

### TRIAL DESIGN

REACH2 was a multicenter, randomized, open-label, phase 3 trial. Patients (or their guardians) provided written informed consent, and patients were then assessed for eligibility during a maximum 28-day screening period after the receipt of first-line glucocorticoid treatment. Eligible patients were randomly assigned in a 1:1 ratio to receive either ruxolitinib or the investigator's choice of therapy from a list of nine commonly used options (control; see below) for up to 24 weeks. Randomization was stratified according to the baseline grade of acute GVHD (II vs. III vs. IV).

Ruxolitinib was given orally at a dose of 10 mg twice daily. Guidance was provided for dose modifications for adverse events (see the Supplementary Methods section). Tapering of ruxolitinib was permitted after day 56 in patients who had a response.

The type of control therapy was chosen by the investigator at the time of randomization from the following options: antithymocyte globulin, extracorporeal photopheresis, mesenchymal stromal cells, low-dose methotrexate, mycophenolate mofetil, mammalian target of rapamycin (mTOR) inhibitor (everolimus or sirolimus), etanercept, or infliximab. Crossover from control therapy to ruxolitinib therapy was permitted if patients did not have a response at day 28 or if they had a loss of response thereafter and received additional systemic therapy and did not have signs of chronic GVHD. Standard supportive therapy (including growth factors, anti-infective medication, transfusion support, and other standard supportive care measures) was allowed in both treatment groups in addition to the continued use of calcineurin inhibitors and glucocorticoids. Owing to the increased risk of bleeding after allogeneic stem-cell transplantation, concomitant treatment with aspirin, nonsteroidal antiinflammatory drugs, heparin, warfarin, or related medications was prohibited.

Patient visits occurred weekly from day 1 to day 56 and then every 4 weeks from day 56 through week 24, unless a prolonged tapering period was deemed to be necessary. A safety follow-up visit occurred 30 days after the last dose of trial treatment. Long-term follow-up visits were scheduled at months 6, 9, 12, 18, and 24 after randomization in order to collect data on survival, progression, and safety outcomes.

### END POINTS AND ASSESSMENTS

The primary end point was overall response at day 28, which was defined as the proportion of patients who had a complete response or partial response as compared with baseline organ staging[25] without the use of additional systemic therapy for acute GVHD (see the Supplementary Methods section). We chose day 28 on the basis of previous data on end points in patients with acute GVHD.[26]

The key secondary end point was durable overall response at day 56, which was defined as the proportion of patients in each treatment group who had response at day 28 that was maintained at day 56. Other secondary end points included the duration of response (time from first response to acute GVHD progression or the addition of new systemic therapy for acute GVHD; competing risks were the onset of chronic GVHD or death without progression of acute GVHD), best overall response (proportion of patients with a complete or partial response at any time up to and including day 28 and before the start of additional systemic therapy for acute GVHD), failure-free survival (time from randomization to relapse or progression of hematologic disease, non–relapse-related death, or the addition of new systemic therapy for acute GVHD; the competing risk was the onset of chronic GVHD), overall survival (time from randomization to death due to any cause), and cumulative glucocorticoid use until day 56. The cumulative incidence of the following events was also calculated: non–relapse-related death (time from randomization to death not preceded by hematologic disease relapse or progression; the competing event was relapse or progression of hematologic disease) and relapse or progression of cancer (time from randomization to relapse or progression of hematologic cancer; the competing risk was non–relapse-related death).

Safety was assessed by monitoring the frequency, duration, and severity of adverse events, including the occurrence of any infection or second primary cancer, by means of routine physical examination and laboratory assessments. Adverse events were assessed according to the Common Terminology Criteria for Adverse Events, version 4.03.

### STATISTICAL ANALYSIS

We calculated that a target of 308 patients undergoing randomization would provide the trial with 90% power to test the primary end point (response at day 28) and approximately 90% power to test the secondary end point (response persisting at day 56). The full analysis set included all the patients who underwent randomization. The safety analysis set included all the patients who received at least one dose of trial treatment.

For the primary end point and key secondary end point, outcomes were summarized according to treatment group with the use of descriptive statistics with a two-sided exact binomial 95% confidence interval.[27] The Cochran–Mantel–Haenszel chi-square test, stratified according to the randomization stratification factor (i.e., acute GVHD of grade II vs. III vs. IV), was used to compare end points between the two treatment groups at a two-sided significance level of 5%. (The trial was designed to test the hypothesis that the overall response at day 28 with ruxolitinib therapy would be superior to the overall response at day 28 with control therapy, in alignment with the reported clinical efficacy of ruxolitinib in patients with glucocorticoid-refractory acute GVHD; the protocol prespecified the reporting of one-sided P values, but, in accordance with *Journal* policy, two-sided P values are reported). P values, odds ratios, and 95% Wald confidence limits were calculated.

A hierarchical testing strategy was used to control overall type I error in which the durable response at day 56 was formally tested and interpreted only if the primary analysis of response at day 28 was significant. The familywise alpha level was controlled at 0.025 overall for the two comparisons (primary and key secondary end points). Specifically, the trial would achieve the efficacy objective if the primary end point of response at day 28 showed a significant treatment effect at a one-sided alpha level of 0.025 (reported at a two-sided alpha level of 0.05). Conditional on the significance of the primary end point, the key secondary end point was tested at a one-sided alpha of 0.025 (reported at a two-sided alpha level of 0.05). There was no prespecified plan to control for multiple comparisons of the secondary outcome measures; 95% confidence intervals are reported, without P values. The 95% confidence intervals were not adjusted for multiple comparisons and should not be used to infer definitive treatment effects.

A cumulative-incidence curve for failure-free survival was prepared for each treatment group. Kaplan–Meier curves for failure-free survival and overall survival were plotted, and the hazard ratios were calculated, along with the 95% confidence intervals, with the use of a stratified Cox model. Further details on the statistical analysis plan are provided in the Supplementary Methods section.

## RESULTS

### PATIENTS

Between April 12, 2017, and May 30, 2019, a total of 309 patients from 105 treatment centers in 22 countries were randomly assigned to receive either ruxolitinib (154 patients) or control therapy (155) (Fig. 1). A total of 104 patients (34%) had grade II acute GVHD, 136 (44%) had grade III disease, and 62 (20%) had grade IV disease; the distribution of patients according to acute GVHD grade was similar in the two treatment groups. (Five patients [2%] had grade 0 disease, and 2 [1%] had grade I disease; these patients had undergone randomization in error and were flagged as having a protocol deviation.) The median age of the patients was 54 years (range, 12 to 73), 9 patients were adolescents, and 59% of the patients were male. The baseline demographic characteristics and transplantation-related and disease-related characteristics of the patients were balanced between the two treatment groups (Table 1 and Table S1 in the Supplementary Appendix). The most common initial control therapy was extracorporeal photopheresis, which was received by 41 of 150 patients (27%) (Fig. S1). Of the 155 patients who had been assigned to the control group, 49 (32%) crossed over to receive ruxolitinib on or after day 28. The median follow-up was 5.04 months (range, 0.03 to 24.02) among patients in the ruxolitinib group and 3.58 months (range, 0.03 to 23.62) among those in the control group; the data-cutoff date was July 25, 2019.

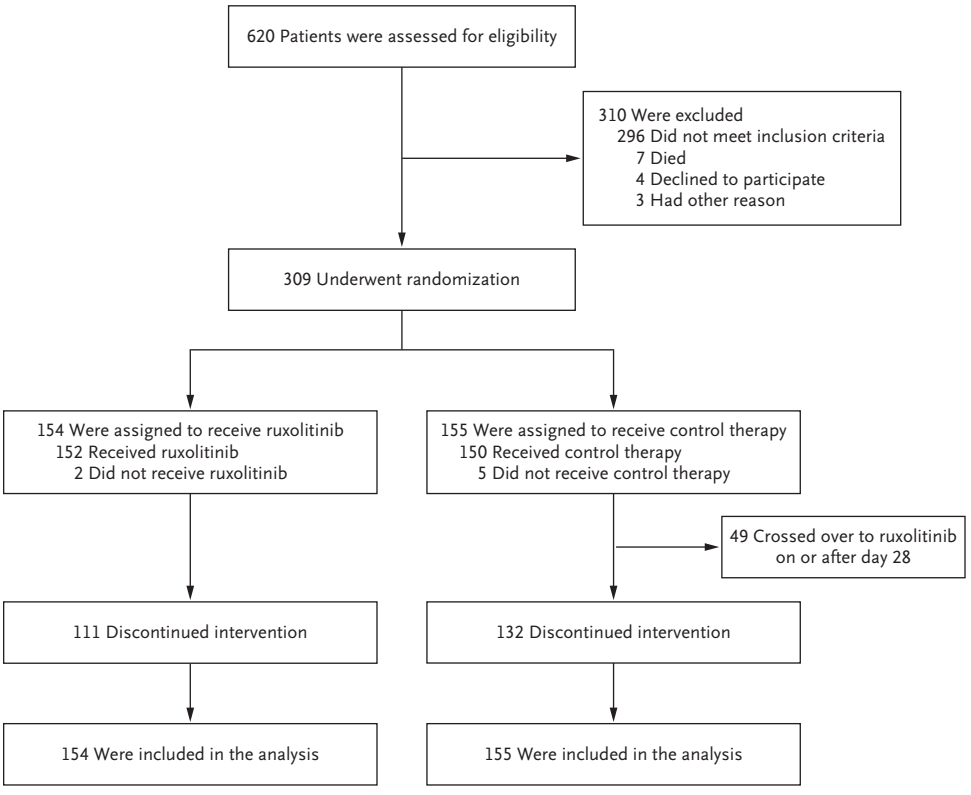


**Figure 1. Eligibility, Randomization, and Follow-up.**

A total of 310 patients with acute graft-versus-host disease (GVHD) underwent randomization, but 1 patient was excluded from all the analyses because written informed consent was not obtained. Patients in the control group were to receive the investigator's choice of therapy from a list of nine commonly used options: antithymocyte globulin, extracorporeal photopheresis, mesenchymal stromal cells, low-dose methotrexate, mycophenolate mofetil, mammalian target of rapamycin (mTOR) inhibitor (everolimus or sirolimus), etanercept, or infliximab. Reasons for discontinuation of the intervention in either group were a lack of efficacy, adverse event, death, the fact that continuation criteria in the protocol were not met, disease relapse, decision by the physician, decision by the patient or guardian, and graft loss.

### EFFICACY

Overall response at day 28 was significantly higher in the ruxolitinib group than in the control group (62% [96 of 154 patients] vs. 39% [61 of 155 patients]; odds ratio, 2.64; 95% confidence interval [CI], 1.65 to 4.22; P<0.001 by the stratified Cochran–Mantel–Haenszel test) (Fig. 2A). The percentage of patients with a complete response was 34% (53 patients) and 19% (30 patients), respectively. The percentage of patients with a response was highest among patients with grade II acute GVHD at baseline (75% [40 of 53 patients] in the ruxolitinib group vs. 51% [27 of 53 patients] in the control group) and among those with grade III acute GVHD (56% [40 of 71 patients] vs. 38% [27 of 72 patients]). However, the odds ratio for response with ruxolitinib as compared with control was highest among patients with grade IV acute GVHD at baseline (53% [16 of 30 patients] vs. 23% [7 of 30 patients]; odds ratio, 3.76; 95% CI, 1.24 to 11.38) (Table S2). Improvement in the acute GVHD grade for skin, liver, upper gastrointestinal, and lower gastrointestinal involvement is shown for each treatment group in Figure S2. Response according to the chosen control therapy is shown in Table S3.

Durable overall response at day 56 was significantly higher in the ruxolitinib group than in the control group (40% [61 patients] vs. 22% [34 patients]; odds ratio, 2.38; 95% CI, 1.43 to 3.94; P<0.001) (Fig. 2B). The best overall response at day 28 (percentage of patients who had a com-

**Table 1. Characteristics of the Patients at Baseline.***

| Characteristic | Ruxolitinib (N=154) | Control (N=155)† | Total (N=309) |
|---|---|---|---|
| Age | | | |
| Median (range) — yr | 52.5 (12–73) | 54.0 (13–71) | 54.0 (12–73) |
| 12 to <18 yr — no. (%) | 5 (3) | 4 (3) | 9 (3) |
| >65 yr — no. (%) | 21 (14) | 25 (16) | 46 (15) |
| Male sex — no. (%) | 92 (60) | 91 (59) | 183 (59) |
| Race — no. (%)‡ | | | |
| White | 111 (72) | 102 (66) | 213 (69) |
| Black | 0 | 1 (1) | 1 (<1) |
| Asian | 19 (12) | 29 (19) | 48 (16) |
| Other | 8 (5) | 4 (3) | 12 (4) |
| Unknown | 16 (10) | 19 (12.3) | 35 (11.3) |
| Median weight (range) — kg§ | 67.7 (28.5–97.0) | 66.2 (32.9–115.5) | 67.0 (28.5–115.5) |
| Median body-mass index (range)¶ | 23.3 (13.5–34.4) | 22.5 (13.9–35.7) | 23.1 (13.5–35.7) |

* The baseline characteristics of the patients were balanced between the two treatment groups. Percentages may not total 100 because of rounding.
† Patients in the control group were to receive the investigator's choice of therapy from a list of nine commonly used options: antithymocyte globulin, extracorporeal photopheresis, mesenchymal stromal cells, low-dose methotrexate, mycophenolate mofetil, mammalian target of rapamycin (mTOR) inhibitor (everolimus or sirolimus), etanercept, or infliximab.
‡ Race was reported by patients or their guardians.
§ Data on weight were missing for 4 patients in the ruxolitinib group and for 3 in the control group (for 7 patients overall).
¶ The body-mass index is the weight in kilograms divided by the square of the height in meters. Data were missing for 8 patients in the ruxolitinib group and for 13 in the control group (for 21 patients overall).

plete or partial response at any time up to and including day 28 and before the start of additional systemic therapy for acute GVHD) was 82% (126 patients) in the ruxolitinib group and 61% (94 patients) in the control group (odds ratio, 3.07; 95% CI, 1.80 to 5.25) (Table S4). The estimated cumulative incidence of loss of response at 6 months was 10% (95% CI, 4 to 17) in the ruxolitinib group and 39% (95% CI, 26 to 52) in the control group (Fig. 3A and Table S5). By day 56, a total of 32 patients (21%) in the ruxolitinib group had discontinued glucocorticoids, as compared with 21 (14%) in the control group.

The median failure-free survival was significantly longer in the ruxolitinib group than in the control group (5.0 months vs. 1.0 month; hazard ratio for relapse or progression of hematologic disease, non–relapse-related death, or addition of new systemic therapy for acute GVHD, 0.46; 95% CI, 0.35 to 0.60) (Fig. 3B), and the cumulative incidence of such events at 1 month was lower in the ruxolitinib group than in the control group (18% vs. 49%) and remained lower at all time points up to 18 months (61% vs. 82%) (Fig. S3 and Table S6). The cumulative incidence of cancer relapse or progression at 18 months was 13% in the ruxolitinib group and 19% in the control group (Fig. S4 and Table S7). The cumulative incidence of non–relapse-related death at 18 months was 49% in the ruxolitinib group and 51% in the control group (Fig. S5 and Table S8). The median overall survival was 11.1 months in the ruxolitinib group and 6.5 months in the control group (hazard ratio for death, 0.83; 95% CI, 0.60 to 1.15) (Fig. S6 and Table S9).

### SAFETY

Treatment discontinuation occurred in 111 of 154 patients (72%) in the ruxolitinib group and in 132 of 155 (85%) in the control group; the most common reason was lack of efficacy (in 32 [21%] and 68 [44%], respectively). The median duration of exposure to therapy was 63 days (range, 6 to 396) in the ruxolitinib group and 29 days (range,

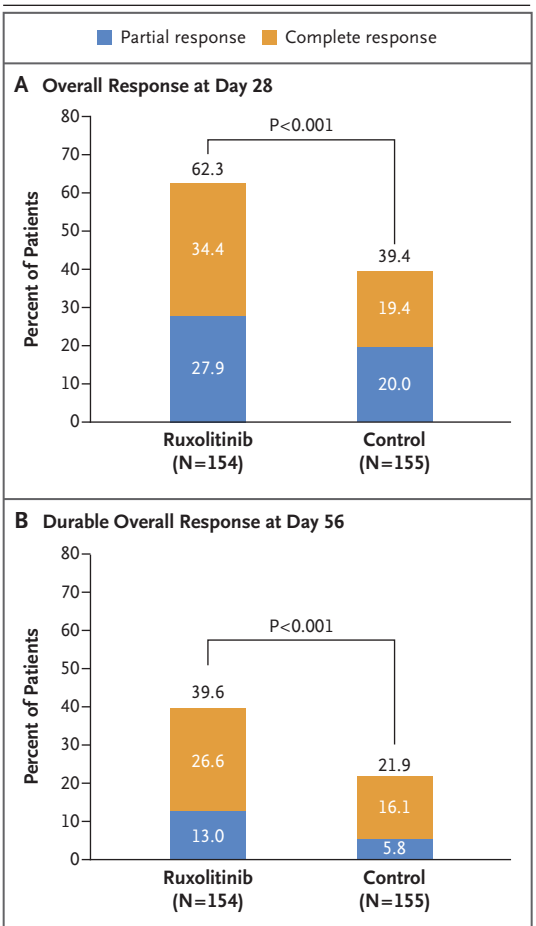


**Figure 2. Overall Response at Day 28 and Durable Overall Response at Day 56.**

The primary end point was overall response (complete response or partial response) at day 28, and the key secondary end point was durable overall response at day 56. Two-sided P values were calculated by a stratified Cochran–Mantel–Haenszel test.

1 to 188) in the control group. The median dose intensity of ruxolitinib was 16.8 mg per day (interquartile range, 11.9 to 19.6).

A total of 152 patients in the ruxolitinib group and 150 in the control group received at least one dose of trial treatment. Adverse events developed in most patients in the two treatment groups (Table 2). The most common events (of any grade and of grade ≥3) up to day 28 were thrombocytopenia, anemia, and cytomegalovirus infection (Table 2). Infection of grade 3 severity up to day 28 occurred in 34 patients (22%) who received ruxolitinib and in 28 patients (19%) who received control therapy; the corresponding values at data cutoff were 56 patients (37%) and 42 patients (28%) (Tables S10 and S11). Among patients with infection, the median time to the first infection of grade 3 severity was 0.8 months with ruxolitinib, as compared with 0.7 months with control therapy; among all the patients (censoring data from patients without events by the Kaplan–Meier method), the median time to the first event was not reached in the ruxolitinib group, as compared with 6.0 months in the control group. At the data-cutoff date, 19 patients (12%) who had received ruxolitinib and 11 (7%) who had received control therapy had grade 3 or higher bleeding (hemorrhage), with serious adverse events being reported in 10 patients (7%) and 8 patients (5%), respectively.

Serious adverse events up to day 28 occurred in 57 patients (38%) who had received ruxolitinib and in 51 patients (34%) who had received control therapy. Up to day 28, adverse events led to dose modifications in 58 patients (38%) who had received ruxolitinib and 13 patients (9%) who had received control therapy and to treatment discontinuation in 17 (11%) and 7 (5%), respectively. A total of 72 patients (47%) in the ruxolitinib group and 77 patients (51%) in the control group had died by the data-cutoff date, including 43 (28%) and 36 (24%), respectively, during the randomized treatment period (median duration of randomized treatment period, 63 days vs. 29 days). Most deaths were attributed to acute GVHD (34 patients [22%] in the ruxolitinib group and 37 [25%] in the control group). The most commonly reported causes of death were underlying disease progression, including neoplasms (in 8 patients in the ruxolitinib group and 8 in the control group), multiple organ dysfunction syndrome (in 3 and 1, respectively), sepsis (in 4 and 3), and septic shock (in 3 and 3).

## DISCUSSION

Poor outcomes have been reported in patients who have glucocorticoid-refractory acute GVHD after allogeneic stem-cell transplantation.[4,5,9,13] Little progress in the development of new treatments has been made in the past three decades.[16,17] This randomized, phase 3 trial showed a significant improvement with a new therapy over standard care in patients with grade II to IV glucocorticoid-refractory acute GVHD. Ruxolitinib therapy was associated with a significantly higher overall response at day 28 than control therapy, and the durable overall response at day 56 was also sig-

nificantly higher in the ruxolitinib group than in the control group. Ruxolitinib therapy was also associated with a longer duration of response than control therapy and a longer failure-free survival. Overall survival data at this point (data cutoff at day 56) are not sufficiently mature to allow conclusions to be drawn regarding survival benefit. However, the percentage of patients who died from acute GVHD did not differ substantially between the groups.

The results of this trial support previously reported findings with ruxolitinib in patients with glucocorticoid-refractory acute GVHD. In a retrospective, multicenter survey involving 54 patients, response (defined as the best response at any time point after starting ruxolitinib and before starting a new drug) was 81.5%, including a complete response in 46.3% of the patients.[23] In a prospective, phase 2 trial of ruxolitinib in patients with primarily grade III or IV acute GVHD (48% and 20% of the patients, respectively), the response was 54.9% at day 28.[24] On the basis of these results, the Food and Drug Administration (FDA) approved ruxolitinib for use in patients 12 years of age or older who had glucocorticoid-refractory acute GVHD.

Few randomized trials have evaluated therapies for glucocorticoid-refractory acute GVHD; no therapy has been approved for this indication other than ruxolitinib, which was recently approved by the FDA. Trials evaluating the anti-CD147 antibody ABX-CBL (also called gavilimomab)[17] or the anti-CD25 antibody inolimomab[16] did not show a significant benefit as compared with standard care. Van Lint et al.[12] found that adding antithymocyte globulin to methylprednisolone did not improve outcomes, and results with other combination regimens have not been promising.[10,28] Given the variations in clinical practice, the current trial allowed, at randomization, the investigator to select one of nine prespecified commonly used second-line therapies in the control group, all of which are recommended by the European Society for Blood and Marrow Transplantation and the European LeukemiaNet.[4] Although individual treatments have shown different efficacy results, the trial was designed to take this mixed pool of control therapies into consideration, on the basis of a meta-analysis by Martin et al.[9]

The safety profile of ruxolitinib in this trial was consistent with the known safety profile of ruxolitinib and was as expected in patients with glucocorticoid-refractory acute GVHD.[23,24] Adverse events up to day 28 were mainly cytopenias, particularly thrombocytopenia and anemia. Although 38% of the patients received modifications to the ruxolitinib dose, the percentage of patients who discontinued ruxolitinib owing to adverse events was 11%. The incidence of infection, which is particularly relevant in acute GVHD,[29,30] was generally similar with ruxolitinib therapy and control

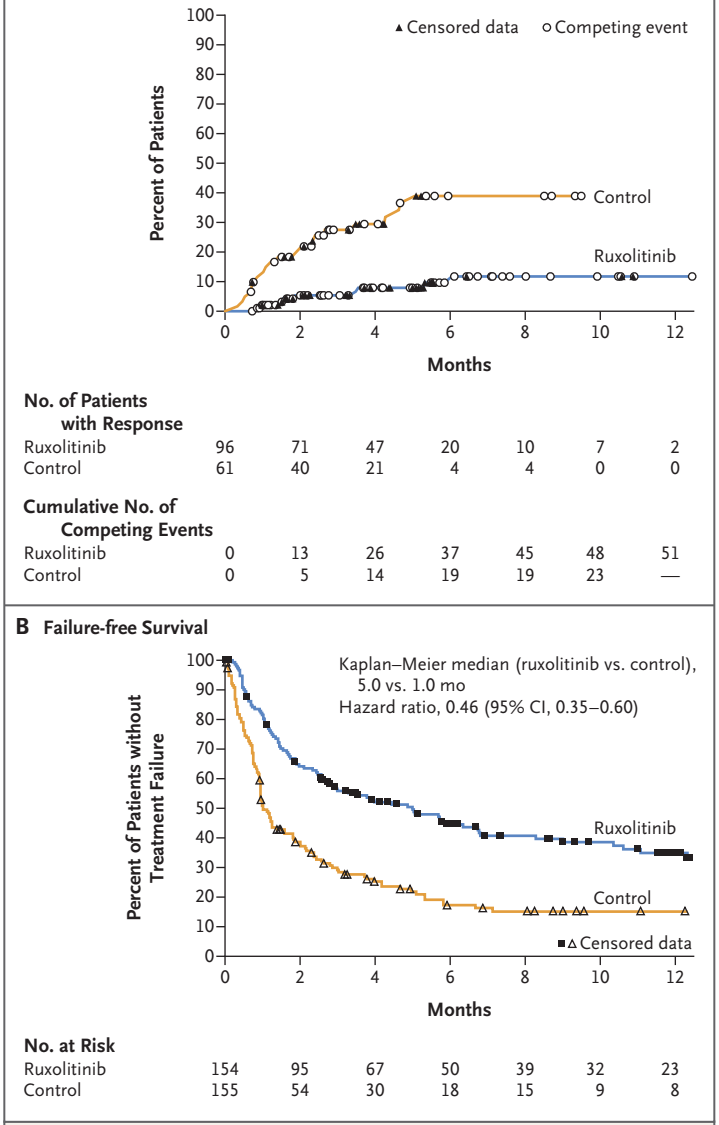


**Figure 3. Duration of Response and Failure-free Survival.**

Competing risks were death without previous observation of progression of acute GVHD and the onset of chronic GVHD. The hazard ratio is for relapse or progression of hematologic disease, non–relapse-related death, or addition of new systemic therapy for acute GVHD

**Table 2. Most Frequent Adverse Events up to Day 28 (Safety Population).***

| Event | Ruxolitinib (N=152) | | Control (N=150) | |
|---|---|---|---|---|
| | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| | *number of patients (percent)* | | | |
| Any adverse event | 145 (95) | 118 (78) | 140 (93) | 117 (78) |
| Thrombocytopenia | 50 (33) | 41 (27) | 27 (18) | 23 (15) |
| Anemia | 46 (30) | 33 (22) | 42 (28) | 28 (19) |
| Cytomegalovirus infection† | 39 (26) | 11 (7) | 31 (21) | 12 (8) |
| Peripheral edema | 28 (18) | 2 (1) | 26 (17) | 1 (1) |
| Platelet count decreased | 26 (17) | 22 (14) | 21 (14) | 20 (13) |
| Neutropenia | 24 (16) | 20 (13) | 19 (13) | 14 (9) |
| Hypokalemia | 20 (13) | 9 (6) | 25 (17) | 9 (6) |
| Hypertension | 16 (11) | 9 (6) | 14 (9) | 6 (4) |
| Hypoalbuminemia | 16 (11) | 6 (4) | 15 (10) | 10 (7) |
| Pyrexia | 16 (11) | 2 (1) | 17 (11) | 2 (1) |
| Hypomagnesemia | 15 (10) | 0 | 20 (13) | 1 (1) |
| Diarrhea | 14 (9) | 7 (5) | 15 (10) | 5 (3) |
| White-cell count decreased | 14 (9) | 11 (7) | 13 (9) | 11 (7) |
| Nausea | 13 (9) | 0 | 9 (6) | 0 |
| Hypocalcemia | 12 (8) | 3 (2) | 10 (7) | 4 (3) |
| Hypophosphatemia | 12 (8) | 5 (3) | 14 (9) | 7 (5) |
| Abdominal pain | 11 (7) | 4 (3) | 7 (5) | 2 (1) |
| Sepsis | 11 (7) | 10 (7) | 6 (4) | 5 (3) |
| Acute kidney injury | 10 (7) | 1 (1) | 3 (2) | 3 (2) |
| Alanine aminotransferase increased | 10 (7) | 3 (2) | 10 (7) | 4 (3) |
| Neutrophil count decreased | 10 (7) | 10 (7) | 14 (9) | 11 (7) |
| Vomiting | 10 (7) | 1 (1) | 6 (4) | 0 |
| Epstein–Barr virus infection | 9 (6) | 0 | 8 (5) | 3 (2) |
| Hyperglycemia | 9 (6) | 5 (3) | 14 (9) | 8 (5) |
| Hypogammaglobulinemia | 9 (6) | 2 (1) | 5 (3) | 0 |
| Fall | 8 (5) | 1 (1) | 1 (1) | 0 |
| Hyperkalemia | 8 (5) | 3 (2) | 6 (4) | 2 (1) |
| Hypotension | 8 (5) | 4 (3) | 9 (6) | 3 (2) |
| Leukopenia | 8 (5) | 7 (5) | 2 (1) | 2 (1) |
| Pancytopenia | 8 (5) | 7 (5) | 6 (4) | 5 (3) |
| Urinary tract infection | 8 (5) | 3 (2) | 6 (4) | 4 (3) |
| Gamma-glutamyltransferase increased | 7 (5) | 3 (2) | 10 (7) | 7 (5) |
| Pneumonia | 6 (4) | 5 (3) | 8 (5) | 7 (5) |
| Blood bilirubin increased | 5 (3) | 3 (2) | 12 (8) | 7 (5) |
| Pain in extremity | 4 (3) | 2 (1) | 8 (5) | 1 (1) |

* Shown are the adverse events that had an incidence of at least 5% in either group. The safety population included all patients who received at least one dose of trial therapy.
† A distinction between cytomegalovirus infection and reactivation was not made in this trial.

therapy, with infection of grade 3 severity occurring in 22% and 19% of the patients, respectively. The incidence of cytomegalovirus infection was 26% in the ruxolitinib group, which is higher than the 19.7% reported in a previous phase 2 trial involving 71 patients.[24] However, it is in line with the incidence of cytomegalovirus reactivation observed during a retrospective trial of ruxolitinib (33.3% and 14.6% among patients with glucocorticoid-refractory acute GVHD and chronic GVHD, respectively[23]); a distinction between cytomegalovirus infection and reactivation was not made in the current trial. Mortality was similar in the two treatment groups, and in both groups the main causes of death were related to progression of either acute GVHD or cancer.

This trial showed that, among patients with grade II to IV glucocorticoid-refractory acute GVHD, ruxolitinib therapy led a significantly higher overall response than control therapy at day 28 and a higher durable overall response at day 56. Patients receiving ruxolitinib had a higher incidence of thrombocytopenia and modestly higher incidence of anemia, infection, and cytomegalovirus infection than those who received control therapy.

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## APPENDIX

The authors' affiliations are as follows: the Department of Medicine I, Faculty of Medicine, Medical Center, University of Freiburg, Freiburg (R.Z.), the Department of Hematology and Oncology, University Hospital Schleswig-Holstein, Campus Lübeck, Lübeck (N.B.), the Department of Hematology and Oncology, University of Leipzig, Leipzig (D.N.), and the Department of Hematology, Oncology, and Pneumology, University Medical Center Mainz, Mainz (E.M.W.) — all in Germany; the Department of Bone Marrow Transplantation, Royal Brisbane and Women's Hospital, Brisbane, QLD (J.B.), and the Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, VIC (J.S.) — all in Australia; Hôpital Saint-Antoine, Assistance Publique–Hôpitaux de Paris (AP-HP), Université Sorbonne and INSERM Unité Mixte de Recherche (UMR) 938 (M.M.), and AP-HP, Hématologie–Transplantation, Hôpital St. Louis, Université de Paris and INSERM UMR 976 (G.S.), Paris, and Novartis Pharma, Rueil-Malmaison (B.M.) — all in France; the Cancer Immunotherapy and Immunobiology Research Center, Hadassah University Hospital, Jerusalem (R.O.), and the Hematology Institute and Bone Marrow Transplantation, Clinical Research Institute at Rambam, Rambam Health Care Campus, Haifa (T.Z.) — both in Israel; Novartis Pharmaceuticals, East Hanover, NJ (J.X., K.K.G.); and Novartis Pharma, Basel, Switzerland (C.W.).

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