ORIGINAL ARTICLE

Axatilimab in Recurrent or Refractory Chronic Graft-versus-Host Disease

D. Wolff, C. Cutler, S.J. Lee, I. Pusic, H. Bittencourt, J. White, M. Hamadani, S. Arai, A. Salhotra, J.A. Perez-Simon, A. Alousi, H. Choe, M. Kwon, A. Bermúdez, I. Kim, G. Socié, S. Chhabra, V. Radojcic, T. O'Toole, C. Tian, P. Ordentlich, Z. DeFilipp, and C.L. Kitko, for the AGAVE-201 Investigators*

ABSTRACT

BACKGROUND

Colony-stimulating factor 1 receptor (CSF1R)–dependent monocytes and macrophages are key mediators of chronic graft-versus-host disease (GVHD), a major long-term complication of allogeneic hematopoietic stem-cell transplantation. The CSF1R-blocking antibody axatilimab has shown promising clinical activity in chronic GVHD.

METHODS

In this phase 2, multinational, pivotal, randomized study, we evaluated axatilimab at three different doses in patients with recurrent or refractory chronic GVHD. Patients were randomly assigned to receive axatilimab, administered intravenously, at a dose of 0.3 mg per kilogram of body weight every 2 weeks (0.3-mg dose group), at a dose of 1 mg per kilogram every 2 weeks (1-mg dose group), or at a dose of 3 mg per kilogram every 4 weeks (3-mg dose group). The primary end point was overall response (complete or partial response) in the first six cycles; the key secondary end point was a patient-reported decrease in chronic GVHD symptom burden, as assessed by a reduction of more than 5 points on the modified Lee Symptom Scale (range, 0 to 100, with higher scores indicating worse symptoms). The primary end point would be met if the lower bound of the 95% confidence interval exceeded 30%.

RESULTS

A total of 241 patients were enrolled (80 patients in the 0.3-mg dose group, 81 in the 1-mg dose group, and 80 in the 3-mg dose group). The primary end point was met in all the groups; an overall response was observed in 74% (95% confidence interval [CI], 63 to 83) of the patients in the 0.3-mg dose group, 67% (95% CI, 55 to 77) of the patients in the 1-mg dose group, and 50% (95% CI, 39 to 61) of the patients in the 3-mg dose group. A reduction of more than 5 points on the modified Lee Symptom Scale was reported in 60%, 69%, and 41% of the patients in the three dose groups, respectively. The most common adverse events were dose-dependent transient laboratory abnormalities related to CSF1R blockade. Adverse events leading to discontinuation of axatilimab occurred in 6% of the patients in the 0.3-mg dose group, 22% in the 1-mg dose group, and 18% in the 3-mg dose group.

CONCLUSIONS

Targeting CSF1R-dependent monocytes and macrophages with axatilimab resulted in a high incidence of response among patients with recurrent or refractory chronic GVHD. (Funded by Syndax Pharmaceuticals and Incyte; AGAVE-201 ClinicalTrials.gov number, NCT04710576.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Wolff can be contacted at daniel.wolff@ukr.de or at the Department of Medicine III, University Hospital Regensburg, F.J. Strauss Allee 11, 93051 Regensburg, Germany.

*A list of the AGAVE-201 Investigators is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Wolff, Cutler, Lee, DeFilipp, and Kitko contributed equally to this article.

N Engl J Med 2024;391:1002-14.
DOI: 10.1056/NEJMoa2401537

Allogeneic hematopoietic stem-cell transplantation is a curative therapy for a range of hematologic disorders.[1-3] Chronic graft-versus-host disease (GVHD) affects approximately half of transplant recipients and is a major cause of complications and late nonrelapse-associated death.[4-8] With the increase in allogeneic hematopoietic stem-cell transplantations, the consequent increase in the prevalence of chronic GVHD represents a growing burden among survivors.[2,9-12]

Chronic GVHD is characterized by inflammatory and fibrotic manifestations in multiple organs; it shares clinical features with autoimmune disorders such as systemic sclerosis, systemic lupus erythematosus, and interstitial lung disease.[7,13,14] Frontline chronic GVHD therapies fail to induce durable responses in more than half of patients who, despite increased use of new therapies, have disease that subsequently progresses to end-organ impairment.[4,15-17] Treatments that reduce fibrosis and inflammation in patients with recurrent or refractory chronic GVHD are needed.[18-21]

Colony-stimulating factor 1 (CSF1) and interleukin-34–mediated signaling through the CSF1 receptor (CSF1R) play key roles in regulating the development and function of tissue macrophages in healthy persons and in persons with disease. In addition to their role in promoting tumor-driven immune evasion, CSF1R signaling–dependent monocytes and macrophages are essential mediators of inflammation and fibrosis in chronic GVHD and a range of autoimmune diseases.[22-24] Consequently, blocking CSF1R offers a targeted approach to attenuating monocyte-driven and macrophage-driven disorders and may reduce the manifestations of chronic GVHD.[24-28]

Axatilimab, a high-affinity, humanized IgG4 monoclonal antibody, inhibits ligand-mediated CSF1R signaling and thereby affects the differentiation and function of CSF1R-expressing monocytes and macrophages. A study in mice showed that early post-transplantation administration of a CSF1R blocking antibody targeted donor-derived macrophages and ameliorated chronic GVHD; these findings may translate into new ways to treat patients with established chronic GVHD.[24] In an early-phase clinical study involving patients with recurrent or refractory chronic GVHD, axatilimab showed promising preliminary efficacy and safety results accompanied by the preferential elimination of CSF1R-dependent nonclassical monocytes and tissue macrophages.[26,29] Here we present the results of the primary analysis of AGAVE-201, a phase 2, multinational, pivotal, randomized study that evaluated the efficacy and safety of axatilimab at three different doses.

METHODS

STUDY OVERSIGHT

A Quick Take is available at NEJM.org

The AGAVE-201 study was funded by Syndax Pharmaceuticals and Incyte. Employees of these sponsors designed the study and analyzed the data. Data were entered by investigators into case-report forms. The study was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. The study protocol, available with the full text of this article at NEJM.org, was approved by the institutional review board and independent ethics committee at each site, and written informed consent was provided by all the patients or their legally authorized representatives. The first author developed a draft of the manuscript with review from all the authors and with writing assistance provided by MedThink SciCom, funded by Syndax Pharmaceuticals and Incyte. 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 study to the protocol.

PATIENT ELIGIBILITY

Patients with refractory or recurrent chronic GVHD were eligible for enrollment in the study if they were 2 years of age or older, had active signs and symptoms of chronic GVHD according to the 2014 National Institutes of Health (NIH) Consensus criteria,[30] and had previously received at least two lines of systemic therapy. There were no restrictions regarding the maximum number of previous therapies or the severity of individual organ manifestations. Adequate performance status (a Karnofsky or Lansky score of ≥60 on a scale of 0 to 100, with lower numbers indicating worse disability) and adequate organ function were required for eligibility. Continued use of systemic glucocorticoids, a calcineurin inhibitor (tacrolimus or cyclosporine), or

a mammalian target of rapamycin (mTOR) inhibitor (sirolimus or everolimus) that the patient was taking at the time of randomization was allowed but not required (see the Methods section in the Supplementary Appendix, available at NEJM.org). Other concurrent systemic therapies for chronic GVHD had to be discontinued before randomization. Patients were excluded if they had evidence of relapse of the underlying cancer or post-transplantation lymphoproliferative disease at the time of screening, a history of acute or chronic pancreatitis, a history of myositis, or a history or other evidence of severe illness or uncontrolled infection.

STUDY DESIGN

Patients were randomly assigned, in a 1:1:1 ratio, to receive axatilimab, administered intravenously, at a dose of 0.3 mg per kilogram of body weight every 2 weeks (0.3-mg dose group), 1 mg per kilogram every 2 weeks (1-mg dose group), or 3 mg per kilogram every 4 weeks (3-mg dose group). These doses were based on the safety and efficacy results observed in the earlier phase 1–2 study.[26] Randomization was stratified according to the severity of chronic GVHD (mild or moderate vs. severe)[30] and previous use (yes or no) of at least one of the therapies for chronic GVHD that have been approved by the Food and Drug Administration (ibrutinib, ruxolitinib, or belumosudil). Dose changes that were recommended by the independent data monitoring committee and changes to dosing schedules allowed by the protocol are described in the Supplementary Appendix. Patients received axatilimab until the occurrence of unequivocal progression of chronic GVHD, unacceptable toxic effects, or withdrawal of consent; in addition, axatilimab was discontinued if the patient did not have a partial response by 9 months.

END POINTS

The primary end point was overall response, defined as a complete or partial response according to the NIH Consensus criteria,[27] within the first six cycles after randomization (i.e., from randomization to day 169 or the beginning of cycle 7, whichever was later). The primary end point would be met if the lower bound of the 95% confidence interval exceeded 30%. Organ-specific responses were evaluated with the severity of chronic GVHD at baseline as a reference.[27] Patients with missing response assessments were classified as not having a response. All responses were assessed by investigators at each study site.

The key secondary end point was a clinically significant reduction in symptoms, as measured by the modified 28-item Lee Symptom Scale (i.e., a reduction of >5 points on the scale, which uses a linearly transformed range from 0 to 100, with higher scores indicating worse symptoms).[31] For the analysis of the modified Lee Symptom Scale scores, missing data were handled as described previously.[31,32] Complete information on efficacy and safety assessments, including sensitivity analyses, and details of pharmacokinetic and pharmacodynamic analyses and population pharmacokinetic and pharmacodynamic modeling are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

The intention-to-treat population included all the patients who underwent randomization. The safety analysis included all enrolled patients who received at least one dose of axatilimab, with the grouping based on the actual treatment received on day 1 of cycle 1.

Using Simon's optimal two-stage design to calculate the sample size, we estimated that with 70 patients in each dose group, the study would have 90% power to detect a true overall response of 50% in the first six cycles, at a one-sided significance level of 0.025. The final boundary for efficacy was recalculated to account for enrollment that exceeded the planned number of patients per group. With approximately 80 patients randomly assigned to each dose group, the dose would be considered successful in the final analysis if at least 32 patients had an overall response in the first six cycles. Time-to-event data were analyzed with the use of the Kaplan–Meier method. No multiplicity adjustments were made (see the Methods section in the Supplementary Appendix).

RESULTS

PATIENT DISPOSITION AND CHARACTERISTICS

From March 2021 through August 2022, a total of 241 patients were enrolled across 121 study sites in 16 countries; 239 patients (99%) received axatilimab and 98 (41%) were still receiving

treatment as of the data-cutoff date, April 7, 2023 (Fig. 1). Baseline demographic and clinical characteristics were similar across the three dose groups (Table 1). Most of the patients had severe chronic GVHD and advanced sclerotic manifestations at baseline. The patients had been previously treated with a median of 4 (range, 2 to 15) systemic chronic GVHD therapies, with more than 80% having received ibrutinib, ruxolitinib, belumosudil, or any combination of these therapies. For most of the patients (55%), the disease had progressed with or had not responded to the most recent chronic GVHD therapy.

EFFICACY

The primary end point was met in all the groups, as indicated by the lower bound of the 95% confidence interval exceeding 30%. An overall response in the first six cycles occurred in 74% (95% confidence interval [CI], 63 to 83) of the patients in the 0.3-mg dose group, 67% (95% CI, 55 to 77) of the patients in the 1-mg dose group, and 50% (95% CI, 39 to 61) of the patients in the 3-mg dose group (Fig. 2). In all the dose groups, the efficacy of axatilimab in the first six cycles was consistent across all subgroups defined according to underlying demographic and baseline disease characteristics, including in the subgroup of patients who had previously received ibrutinib, ruxolitinib, or belumosudil (Fig. S2 in the Supplementary Appendix).

The patients had a rapid response to axatilimab, with a median time to response across dose groups of less than 2 months (Table S1). Among the patients who had a response, an estimated 60% in the 0.3-mg dose group, 60% in the 1-mg dose group, and 53% in the 3-mg dose group had a durable response at 12 months (Fig. S3). Among patients with baseline glucocorticoid use, most reported a reduction in the dose or discontinuation of the glucocorticoid by day 1 of cycle 7 (Table S1). The median overall survival was not reached in any of the dose groups (Fig. S4), and the 12-month survival according to Kaplan–Meier estimates was 98% (95% CI, 89 to 100) among the patients in the 0.3-mg dose group,

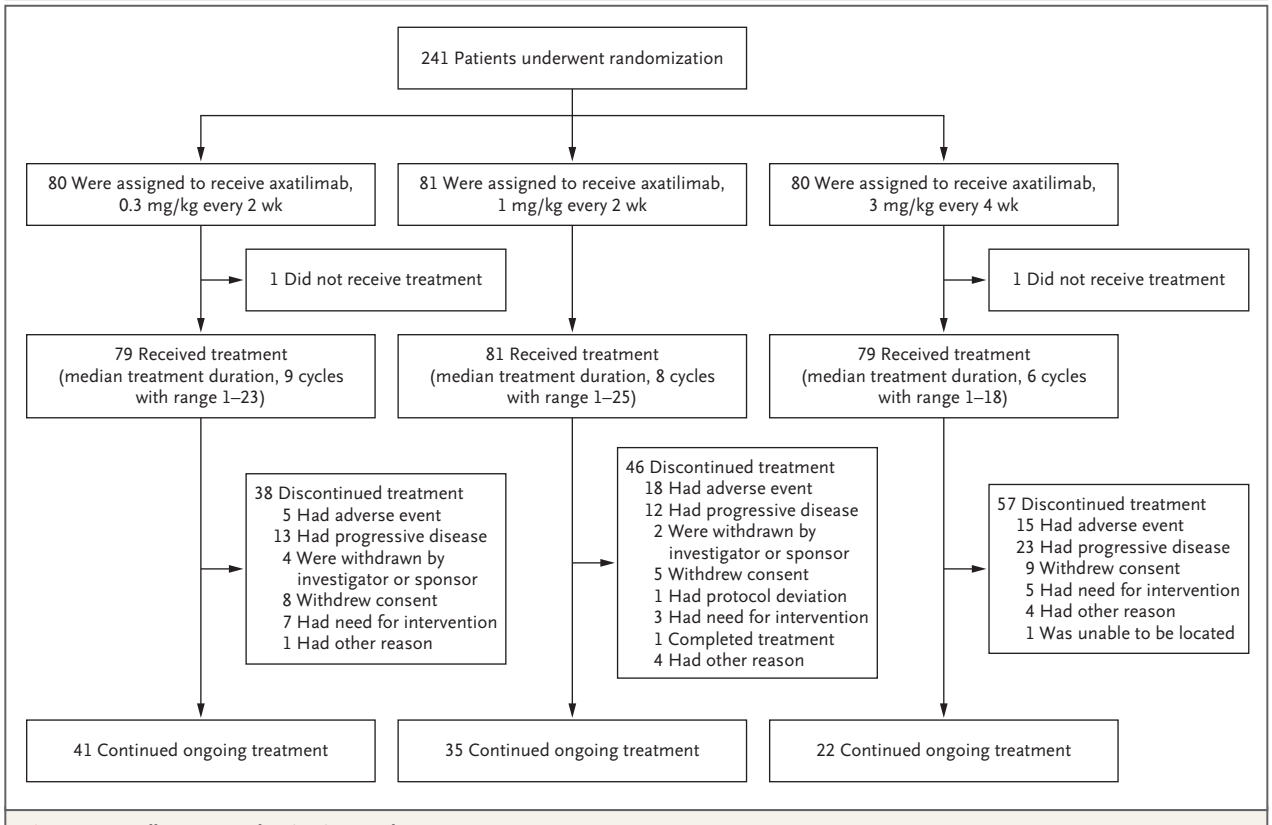

Figure 1. Enrollment, Randomization, and Treatment.

Table 1. Baseline Demographics and Clinical Characteristics.*

Characteristic	0.3-mg Dose Group (N=80)	1-mg Dose Group (N=81)	3-mg Dose Group (N=80)
Median age (range) — yr	50 (7–76)	56 (26–81)	53 (7–79)
Age group — no. (%)			
<17 yr	4 (5)	0	3 (4)
≥17 to <65 yr	55 (69)	62 (77)	61 (76)
≥65 yr	21 (26)	19 (23)	16 (20)
Male sex — no. (%)	47 (59)	51 (63)	53 (66)
Race or ethnic group — no. (%)†			
American Indian or Alaska Native	0	1 (1)	0
Asian	4 (5)	4 (5)	8 (10)
Black or African descent	2 (2)	2 (2)	1 (1)
Native Hawaiian or other Pacific Islander	0	0	1 (1)
White	68 (85)	70 (86)	62 (78)
Not reported	5 (6)	4 (5)	7 (9)
Other	1 (1)	0	1 (1)
Hispanic or Latino ethnic group — no. (%)†			
Yes	5 (6)	9 (11)	5 (6)
No	73 (91)	69 (85)	73 (91)
Not reported or unknown	2 (2)	3 (4)	2 (2)
Median time from chronic GVHD diagnosis to randomization (range) — yr	3.9 (0.4–17.6)	4.1 (0.6–17.1)	3.8 (0.4–15.4)
Global severity rating — no. (%)‡			
Mild or moderate	17 (21)	17 (21)	15 (19)
Severe	63 (79)	64 (79)	65 (81)
Median no. of organs involved (maximum no.)§	4 (8)	4 (7)	3 (7)
Organs involved — no. (%)			
Skin	64 (80)	63 (78)	66 (82)
Eyes	59 (74)	70 (86)	54 (68)
Mouth	40 (50)	40 (49)	32 (40)
Esophagus	23 (29)	18 (22)	20 (25)
Upper GI	11 (14)	8 (10)	9 (11)
Lower GI	9 (11)	5 (6)	4 (5)
Liver	10 (12)	13 (16)	17 (21)
Lungs	32 (40)	41 (51)	35 (44)
Joints and fascia	55 (69)	56 (69)	51 (64)
Median no. of previous systemic chronic GVHD therapy (range)	4 (2–12)	4 (2–14)	4 (2–15)
Previous use of ≥1 FDA-approved systemic chronic GVHD therapy — no. (%)	67 (84)	69 (85)	68 (85)
Ibrutinib	27 (34)	19 (23)	29 (36)
Ruxolitinib	57 (71)	64 (79)	58 (72)
Belumosudil	16 (20)	19 (23)	21 (26)

Table 1. (Continued.)

Characteristic	0.3-mg Dose Group (N=80)	1-mg Dose Group (N=81)	3-mg Dose Group (N=80)
Best response to the most recent previous chronic GVHD treatment — no. (%)			
Complete response	4 (5)	2 (2)	2 (2)
Partial response	26 (32)	27 (33)	21 (26)
No change	32 (40)	39 (48)	45 (56)
Progression	6 (8)	7 (9)	3 (4)
Unknown	12 (15)	6 (7)	9 (11)
Concomitant systemic therapy for chronic GVHD — no./total no. (%)¶			
Glucocorticoids	56/79 (71)	45/81 (56)	55/79 (70)
Calcineurin inhibitor	18/79 (23)	26/81 (32)	22/79 (28)

* Percentages may not total 100% because of rounding. The 0.3-mg dose group received axatilimab, administered intravenously, at a dose of 0.3 mg per kilogram of body weight every 2 weeks, the 1-mg dose group received axatilimab at a dose of 1 mg per kilogram every 2 weeks, and the 3-mg dose group received axatilimab at a dose of 3 mg per kilogram every 4 weeks. GVHD denotes graft-versus-host-disease, and GI gastrointestinal.

† Race and ethnic group were determined by the investigator. Data were then recorded in the electronic case report forms in accordance with the Food and Drug Administration Guidance on Collection of Race and Ethnicity Data in Clinical Trials, issued October 26, 2016.

‡ The global severity rating was based on the National Institutes of Health global severity score.[30]

§ Data on organ involvement were not available for one patient assigned to the 0.3-mg dose group because a serious adverse event occurred in that patient and the patient withdrew consent before day 1 of cycle 1 (the time at which baseline information was to be reported). One patient in the 3-mg dose group had a baseline assessment on day 7 of cycle 1. No patients in the study had zero organs involved.

¶ Use of other concurrent immunosuppressive medications or procedures for chronic GVHD was prohibited. The analysis of concomitant systemic therapy was performed in the safety analysis population, which included all enrolled patients who received at least one dose of axatilimab.

91% (95% CI, 82 to 96) among the patients in the 1-mg dose group, and 83% (95% CI, 72 to 91) among the patients in the 3-mg dose group. The overall survival among the patients in this study aligns with the 2-year overall survival rates shown in other studies.[19,20,33-35]

The median failure-free survival was 11.1 months when dose escalation was considered to be a failure event (Fig. 2B), and the 12-month failure-free survival according to Kaplan–Meier estimates was 49% (95% CI, 35 to 61) in the 0.3-mg dose group, 59% (95% CI, 46 to 70) in the 1-mg dose group, and 44% (95% CI, 31 to 55) in the 3-mg dose group. Since the data did not support greater efficacy of the dose of 1 mg per kilogram than the dose of 0.3 mg per kilogram, a sensitivity analysis of failure-free survival was conducted in the 0.3-mg dose group that excluded the protocol-allowed dose escalation from 0.3 mg per kilogram to 1 mg per kilogram as a failure event. The median failure-free survival from the sensitivity analysis was 17.3 months (95% CI, 14.2 to could not be estimated) (Fig. S1), with 12-month failure-free survival in 64% (95% CI, 50 to 75) of the patients.

A clinically meaningful reduction in chronic GVHD symptoms (>5-point reduction in the modified Lee Symptom Scale score) was reported in 60% of the patients in the 0.3-mg dose group, 69% of the patients in the 1-mg dose group, and 41% of the patients in the 3-mg dose group in the first six cycles (Fig. 3). The median time to a clinically meaningful reduction in symptoms was 1.7 months (range, 0.3 to 8.6) in the 0.3-mg dose group, 1.1 months (range, 1.0 to 9.3) in the 1-mg dose group, and 1.1 months (range, 0.9 to 8.0) in the 3-mg dose group, findings that were similar to the median time to overall response in the three groups.

Organ-specific responses were observed across all organs in all dose groups, including in the organs that had the most fibrotic changes (Fig. 2C

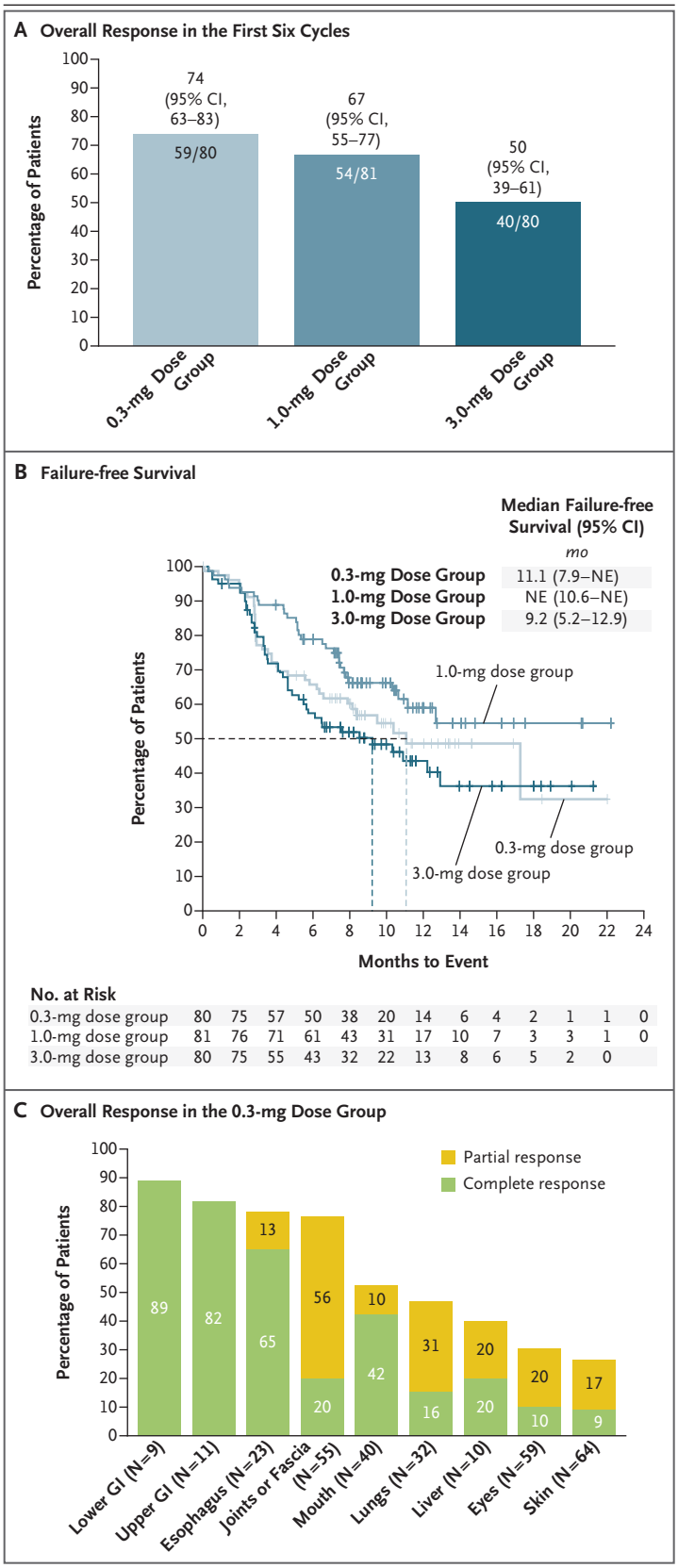

Figure 2. Overall Response and Failure-free Survival (Intention-to-Treat Population).

Panel A shows the percentage of patients with an overall response (complete or partial response) in the first six cycles in the group that received a dose of 0.3 mg per kilogram of body weight every 2 weeks (0.3-mg dose group), 1 mg per kilogram every 2 weeks (1-mg dose group), or 3 mg per kilogram every 4 weeks (3-mg dose group). Panel B shows the Kaplan–Meier curve of estimated failure-free survival in the three groups. The median duration of follow-up was 7.7 months in the 0.3-mg dose group, 8.2 months in the 1-mg dose group, and 6.6 months in the 3-mg dose group. Failure-free survival was defined as the absence of a change in treatment for chronic graft-versus-host disease (GVHD), nonrelapse-related death, and recurrent cancer. In this analysis, dose escalation was considered to be a failure event. For the analysis in which dose escalation was excluded as an event, see Figure S1. Panel C shows the percentage of patients in the 0.3-mg dose group with an overall response according to organ system. GI denotes gastrointestinal, and NE could not be estimated.

and Fig. S5). In patients with sclerotic skin manifestations of chronic GVHD (>90% of patients with chronic GVHD of the skin in each group), a reduction in sclerotic skin surface area was seen in 44% of the patients in the 0.3-mg dose group, 34% of the patients in the 1-mg dose group, and 60% of the patients in the 3-mg dose group, and a reduction in skin tightening was seen in 66%, 56%, and 60% of the patients in the three dose groups, respectively. In findings consistent with these results, a reduction of symptoms related to skin thickening was reported by 73%, 77%, and 68%, respectively (Table S2).

SAFETY

The most common adverse events among the 239 patients who received at least one dose of axatilimab were transient laboratory abnormalities associated with Kupffer cell depletion induced by CSF1R blockade, with increasing incidence and grading associated with escalating dose (Table 2). Axatilimab-driven laboratory abnormalities were not accompanied by end-organ damage, a finding consistent with previous reports. In the entire study, only 1 patient, randomly assigned to the 3-mg dose group, had a grade 3 elevation in the creatine kinase level that was associated with grade 2 myositis, as well as a grade 3 myocardial infarction (attributed to vasospasm), from which the patient recovered fully without cardiac function being affected.

Periorbital edema (any grade), another on-target effect of CSF1R blockade, was dose dependent (occurring in 3% of the patients in the 0.3-mg dose group, 23% in the 1-mg dose group, and 29% in the 3-mg dose group), with no events higher than grade 1 seen in the 0.3-mg dose group.

Infusion-related reactions occurred in 8% of the patients in the 0.3-mg dose group, 5% of the patients in the 1-mg dose group, and 1% of the patients in the 3-mg dose group, with only two patients discontinuing the study drug because of infusion-related reactions (both in the 1-mg dose group). Infections were common in all three groups and occurred in 73% of the patients in the 0.3-mg dose group, 73% of the patients in the 1-mg dose group, and 70% of the patients in the 3-mg dose group; these infections included coronavirus disease 2019, which occurred in approximately 20% of the patients. Cytomegalovirus infection, Epstein–Barr virus infection or reactivation, or invasive fungal infections occurred in 0, 4, and 6 patients in the three dose groups, respectively (Table 2). Serial neurologic assessments showed no cognitive–behavioral abnormalities of clinical significance and no persistent or progressive abnormal changes in any dose group.

Grade 3 or higher adverse events were reported in 49% of the patients in the 0.3-mg dose group, 60% of the patients in the 1-mg dose group, and 71% of the patients in the 3-mg dose group (Table 2). Adverse events leading to discontinuation of axatilimab occurred in 5 patients (6%), 18 patients (22%), and 14 patients (18%) in the three dose groups, respectively, and fatal adverse events occurred in 1 patient (1%), 7 patients (9%), and 6 patients (8%) (Table 2 and Table S3).

PHARMACOKINETICS AND PHARMACODYNAMICS

The peak concentrations of CSF1 and interleukin-34 increased in a dose-dependent manner with doses higher than 0.3 mg per kilogram and were most prominent in the 3-mg dose group (Figs. S6A and S6B). No substantial changes were seen in the 0.3-mg dose group. Simulated pharmacokinetic and pharmacodynamic analyses showed that axatilimab, CSF1, aspartate aminotransferase, and creatine kinase did not accumulate after multiple doses of axatilimab at a dose level below 1 mg per kilogram every 2 weeks but started to accumulate at higher doses, an effect particularly pronounced in the 3-mg dose group (Fig. S6C). Simulated analyses likewise showed transient reduction of nonclassical monocytes lasting less than the duration of the dosing interval in the 0.3-mg and 1-mg dose groups.

DISCUSSION

The AGAVE-201 pivotal phase 2 study evaluated the efficacy and safety of axatilimab monotherapy in a heterogeneous multinational population of patients with recurrent or refractory chronic GVHD who had previously received two or more lines of therapy. The study met its primary end point and showed the efficacy of axatilimab in patients across all three dose groups, with an overall response occurring in 50 to 74% of the patients.

A high incidence of clinical response, including complete response, was seen in all involved organs. The response was durable and was not influenced by key baseline disease characteristics, including the severity of chronic GVHD, the number of organs involved, the duration of chronic GVHD, the number of previous treatments, or the failure of ibrutinib, ruxolitinib, or belumosudil therapy. Responses were seen in patients with inflammatory and fibrotic chronic GVHD manifestations, including prototypic fibrotic manifestations in the lung, esophagus, joints and fascia, and skin. Most patients with skin sclerosis, which affected more than 90% of the patients with chronic GVHD of the skin, had not just disease control but amelioration of skin sclerosis after treatment with axatilimab as measured by the 2014 NIH Consensus secondary disease metrics, the patient-reported symptom scale, or both.[27,36,37] About half the patients reported a rapid, clinically meaningful reduction in symptoms, which further supported the overall assessment of clinical efficacy and the potential for quality-of-life improvements in a patient population with severe complications related to both the disease and the treatment.

Adverse events related to treatment with axatilimab were closely associated with inhibition of CSF1R signaling and included transient elevations of serum enzyme levels and periorbital edema. CSF1R inhibition depletes the resident macrophages in liver (Kupffer cells) and skin, which leads to decreased serum enzyme clearance and proteoglycan accumulation, respectively.[38,39]

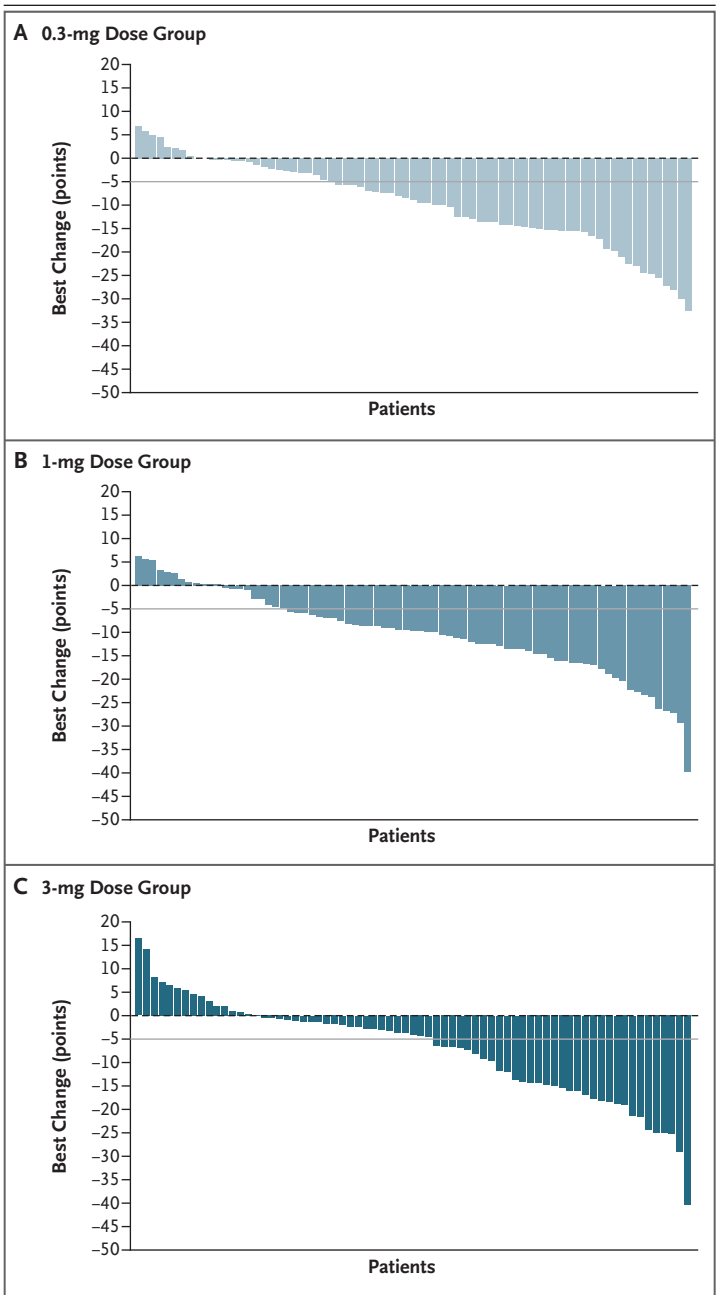

Figure 3. Symptom Burden, According to the Score on the Modified Lee Symptom Scale.

The waterfall plots indicate the best change in chronic GVHD symptoms in the three dose groups, as measured according to the summary score of the modified Lee Symptom Scale (range, 0 to 100, with higher scores indicating worse symptoms). Bars indicate individual patients, and the solid line represents the threshold for clinically meaningful reduction of symptoms (a reduction of >5 points on the modified Lee Symptom Scale).

Whereas in preclinical studies early peritransplantation CSF1R blockade was associated with GVHD exacerbation because of host macrophage depletion, treatment of patients with established chronic GVHD avoids these risks because their macrophages have been replaced with pathogenic donor-derived macrophages.[40,41] The adverse events related to CSF1R inhibition showed a dose dependency in frequency and intensity and were generally transient and asymptomatic. The incidence of infection was not dose dependent, did not differ from that reported with available chronic GVHD therapies, and was reflective of patients with previous prolonged exposure to immunosuppressive therapy.[18-20,27] Invasive mycoses, Epstein–Barr virus infections, and cytomegalovirus reactivations or infections did not develop in the 0.3-mg dose group, although they were seen in the groups receiving higher doses. The primary causes of death in this study did not appear to be related to the known axatilimab mechanism of action, but toxic effects with doses higher than 0.3 mg per kilogram administered every 2 weeks cannot be ruled out as contributing to an increase in the incidence of death (Table S3).

The higher percentage of patients with a response in the lower-dose groups (the 0.3-mg and 1-mg dose groups) than in the highest-dose group was an unexpected finding and is not explained by the increased frequency of adverse events in the highest dose group. The persistent depletion of nonclassical monocytes and the elevation of the serum CSF1 level observed in patients receiving a dose of 3 mg per kilogram highlight a possible biologic rationale. Sustained, nonclassical monocyte ablation may adversely affect the homeostasis of immunomodulatory macrophages necessary for the resolution of inflammation, whereas concurrent CSF1 elevation may contribute to worsening of the ongoing inflammation, as observed in a range of inflammatory and autoimmune conditions.[42-45] At the specific time points evaluated in AGAVE-201, no substantial changes in the serum concentrations of CSF1 and interleukin-34 were seen in the 0.3-mg dose group. However, in healthy volunteers, doses less than 1 mg per kilogram were shown to transiently reduce the serum concentration of nonclassical monocytes with corresponding

Table 2. Safety Overview.*

Adverse Event	0.3-mg Dose Group (N=79)	1-mg Dose Group (N=81)	3-mg Dose Group (N=79)
	number of patients (percent)		
Any adverse event	76 (96)	80 (99)	78 (99)
Grade ≥3	39 (49)	49 (60)	56 (71)
Serious	30 (38)	33 (41)	38 (48)
Fatal	1 (1)	7 (9)	6 (8)
Any grade event in ≥20% of any dose group			
Aspartate aminotransferase level increased	11 (14)	31 (38)	43 (54)
Blood creatine kinase level increased	9 (11)	26 (32)	49 (62)
Lipase level increased	9 (11)	21 (26)	39 (49)
Amylase level increased	3 (4)	10 (12)	34 (43)
Blood lactate dehydrogenase level increased	11 (14)	22 (27)	32 (41)
Alanine aminotransferase level increased	10 (13)	18 (22)	31 (39)
Periorbital edema	2 (3)	19 (23)	23 (29)
Fatigue	18 (23)	16 (20)	21 (27)
γ-Glutamyltransferase level increased	8 (10)	16 (20)	21 (27)
Covid-19	13 (16)	18 (22)	11 (14)
Diarrhea	13 (16)	18 (22)	7 (9)
Blood alkaline phosphatase level increased	5 (6)	4 (5)	17 (22)
Headache	15 (19)	14 (17)	16 (20)
Any grade infection	58 (73)	59 (73)	55 (70)
Any grade key infection or reactivation			
Covid-19	15 (19)	19 (23)	14 (18)
Pneumonia	9 (11)	12 (15)	8 (10)
Aspergillus	0	3 (4)	0
Cytomegalovirus	0	1 (1)	2 (3)
Epstein–Barr virus	0	0	4 (5)
Any grade infusion-related reaction	6 (8)	4 (5)	1 (1)
Any grade ≥3 event in ≥5% of any dose group			
Pneumonia	8 (10)	7 (9)	5 (6)
Blood creatine kinase level increased	1 (1)	6 (7)	12 (15)
Covid-19	3 (4)	5 (6)	5 (6)
Hypertension	3 (4)	5 (6)	4 (5)
γ-Glutamyltransferase level increased	1 (1)	2 (2)	4 (5)
Lipase level increased	1 (1)	1 (1)	4 (5)
Periorbital edema	0	1 (1)	5 (6)
Any serious event in ≥5% of any dose group			
Covid-19	2 (3)	4 (5)	5 (6)
Pneumonia	7 (9)	8 (10)	4 (5)
Any adverse event leading to dose interruption	30 (38)	34 (42)	25 (32)
Any adverse event leading to dose reduction	5 (6)	6 (7)	13 (16)
Any adverse event leading to discontinuation of axatilimab	5 (6)	18 (22)	14 (18)†

* The safety analysis population consisted of all enrolled patients who received at least one dose of axatilimab. Covid-19 denotes coronavirus disease 2019.

† One patient reported the reason for discontinuation as an adverse event. If this patient were included, the number would be 15; however, the data were not included in the safety analysis.

increases in CSF1 and interleukin-34 concentrations.[46,47] Given that these concentrations returned to baseline on or before day 7 in patients receiving doses of less than 1 mg per kilogram, samples collected in the 0.3-mg dose group in this study largely missed capturing the expected pharmacodynamic effects, whereas the observation of on-target adverse events supported the macrophage-targeting activity of the patients in the 0.3-mg dose group. Thus, although the results of this trial confirm that a dosing strategy that uses a transient blockade of CSF1R signaling may represent one of the best possible treatment strategies for patients with chronic GVHD, the precise explanation for this observation, as well as its applicability to other conditions in which pathologic CSF1R signaling plays a role, remains to be elucidated.

A key limitation of the current study is that all the patients received axatilimab and no comparator group was provided, thus introducing a possibility of outcome-reporting bias. A standard comparator group would have been difficult to implement given that multiple standard-care interventions had already failed. Although the study was sufficiently powered to define the best of the three doses of axatilimab for treatment of chronic GVHD, a broader interpretation of the subgroup analyses is limited by the small number of patients in each subgroup. The required discontinuation of systemic chronic GVHD therapy other than glucocorticoids and a calcineurin or mTOR inhibitor limits comparison with common management practice in recurrent or refractory chronic GVHD, in which advancing lines of therapy are often combined. Finally, sample collection was not able to capture the transient pharmacodynamic effects in the 0.3-mg dose group, which limited a comparison of the changes at that dose level with changes at the higher doses tested. Further studies of axatilimab at a dose of 0.3 mg per kilogram every 2 weeks in patients with chronic GVHD are planned (ClinicalTrials.gov number, NCT06388564).

Refractory chronic GVHD with extensive fibrotic manifestations, a condition highly represented in the AGAVE-201 study, continues to present a major therapeutic challenge.[18-20] The AGAVE-201 study showed that single-agent therapy with axatilimab is effective for many patients with recurrent or refractory chronic GVHD, including those in whom standard-of-care therapies failed. Additional studies — such as the Study to Evaluate Axatilimab in Participants with Idiopathic Pulmonary Fibrosis (NCT06132256) — are warranted to evaluate axatilimab in earlier treatment of chronic GVHD and autoimmune diseases in which CSF1R-driven macrophages contribute to inflammation and fibrosis.

Supported by Syndax Pharmaceuticals 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 the patients, caregivers, and health care professionals involved in the AGAVE-201 study; Katie Veleta, Ph.D., and Stephanie Roulias, E.L.S., at MedThink SciCom, for their medical writing and editorial assistance with an earlier version of the manuscript; and Shuyuan Lou, an employee of Incyte, for providing statistical analysis support.

APPENDIX

The authors' full names and academic degrees are as follows: Daniel Wolff, M.D., Corey Cutler, M.D., M.P.H., Stephanie J. Lee, M.D., M.P.H., Iskra Pusic, M.D., M.S.C.I., Henrique Bittencourt, M.D., Ph.D., Jennifer White, M.D., F.R.C.P.C., Mehdi Hamadani, M.D., Sally Arai, M.D., Amandeep Salhotra, M.D., Jose A. Perez-Simon, M.D., Amin Alousi, M.D., Hannah Choe, M.D., Mi Kwon, M.D., Ph.D., Arancha Bermúdez, M.D., Inho Kim, M.D., Ph.D., Gerard Socié, M.D., Ph.D., Saurabh Chhabra, M.D., Vedran Radojcic, M.D., Timothy O'Toole, M.S., Chuan Tian, Ph.D., Peter Ordentlich, Ph.D., Zachariah DeFilipp, M.D., and Carrie L. Kitko, M.D.

The authors' affiliations are as follows: University Hospital Regensburg, Regensburg, Germany (D.W.); Dana–Farber Cancer Institute and Harvard Medical School (C.C.) and Massachusetts General Hospital (Z.D.), Boston, and Syndax Pharmaceuticals, Waltham (V.R., T.O., P.O.) — all in Massachusetts; Fred Hutchinson Cancer Center, Seattle (S.J.L.); Washington University School of Medicine, St. Louis (I.P.); Centre Hospitalier Universitaire Sainte-Justine, Montreal (H.B.), and the University of British Columbia, Vancouver General Hospital, Vancouver (J.W.) — both in Canada; the Medical College of Wisconsin, Milwaukee (M.H., S.C.); Stanford Health Care, Stanford (S.A.), and City of Hope Medical Center, Duarte (A.S.) — both in California; Hospital Universitario Virgen del Rocío Instituto de Biomedicina de Sevilla (IBiS), CSIC, Universidad de Sevilla, Seville (J.A.P.-S.), Hospital General Universitario Gregorio Marañón, Instituto de Investigación Biomédica Gregorio Marañón, and Universidad Complutense de Madrid, Madrid (M.K.), and Hospital Universitario Marqués de Valdecilla (IDIVAL), University of Cantabria, Santander (A.B.) — all in Spain; the M.D. Anderson Cancer Center, Houston (A.A.); the James Cancer Hospital and Solove Research Institute and Ohio State University Wexner Medical Center, Columbus (H.C.); Seoul National University College of Internal Medicine, Seoul, South Korea (I.K.); Hôpital Saint-Louis and University Paris Cité, Paris (G.S.); Incyte Corporation, Wilmington, DE (C.T.); and Vanderbilt University Medical Center, Nashville (C.L.K.).

REFERENCES

1. Niederwieser D, Baldomero H, Bazuaye N, et al. One and a half million hematopoietic stem cell transplants: continuous and differential improvement in worldwide access with the use of non-identical family donors. Haematologica 2022;107:1045-53.
2. Majhail NS, Tao L, Bredeson C, et al. Prevalence of hematopoietic cell transplant survivors in the United States. Biol Blood Marrow Transplant 2013;19:1498-501.
3. Tokaz MC, Baldomero H, Cowan AJ, et al. An analysis of the worldwide utilization of hematopoietic stem cell transplantation for acute myeloid leukemia. Transplant Cell Ther 2023;29(4):279.e1-279.e10.
4. DeFilipp Z, Alousi AM, Pidala JA, et al. Nonrelapse mortality among patients diagnosed with chronic GVHD: an updated analysis from the Chronic GVHD Consortium. Blood Adv 2021;5:4278-84.
5. Styczyński J, Tridello G, Koster L, et al. Death after hematopoietic stem cell transplantation: changes over calendar year time, infections and associated factors. Bone Marrow Transplant 2020;55:126-36.
6. Arai S, Arora M, Wang T, et al. Increasing incidence of chronic graft-versus-host disease in allogeneic transplantation: a report from the Center for International Blood and Marrow Transplant Research. Biol Blood Marrow Transplant 2015;21:266-74.
7. 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.
8. Velickovic VM, McIlwaine E, Zhang R, Spelman T. Adverse events in second- and third-line treatments for acute and chronic graft-*versus*-host disease: systematic review. Ther Adv Hematol 2020;11:2040620720977039.
9. Jones CA, Fernandez LP, Weimersheimer P, et al. Estimating the burden of cost in chronic graft-versus-host disease: a human capital approach. J Health Econ Outcomes Res 2016;4:113-8.
10. Novitzky-Basso I, Schain F, Batyrbekova N, et al. Population-based real-world registry study to evaluate clinical outcomes of chronic graft-versus-host disease. PLoS One 2023;18(3):e0282753.
11. Agh T, Csanadi M, Voko Z, et al. Humanistic burden of patients with chronic graft-versus-host disease — systematic literature review of health-related quality of life and functional status. Expert Rev Hematol 2019;12:295-309.
12. Csanadi M, Agh T, Tordai A, et al. A systematic literature review of incidence, mortality, and relapse of patients diagnosed with chronic graft versus host disease. Expert Rev Hematol 2019;12:311-23.
13. Wood WA, Chai X, Weisdorf D, et al. Comorbidity burden in patients with chronic GVHD. Bone Marrow Transplant 2013;48:1429-36.
14. Archer G, Berger I, Bondeelle L, et al. Interstitial lung diseases after hematopoietic stem cell transplantation: new pattern of lung chronic graft-versus-host disease? Bone Marrow Transplant 2023;58:87-93.
15. Flowers MED, Storer B, Carpenter P, et al. Treatment change as a predictor of outcome among patients with classic chronic graft-versus-host disease. Biol Blood Marrow Transplant 2008;14:1380-4.
16. Inamoto Y, Storer BE, Petersdorf EW, et al. Incidence, risk factors, and outcomes of sclerosis in patients with chronic graft-versus-host disease. Blood 2013;121:5098-103.
17. Lee SJ, Nguyen TD, Onstad L, et al. Success of immunosuppressive treatments in patients with chronic graft-versus-host disease. Biol Blood Marrow Transplant 2018;24:555-62.
18. 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.
19. Cutler C, Lee SJ, Arai S, et al. Belumosudil for chronic graft-versus-host disease after 2 or more prior lines of therapy: the ROCKstar Study. Blood 2021;138:2278-89.
20. Zeiser R, Polverelli N, Ram R, et al. Ruxolitinib for glucocorticoid-refractory chronic graft-versus-host disease. N Engl J Med 2021;385:228-38.
21. Hamilton BK. Updates in chronic graft-versus-host disease. Hematology Am Soc Hematol Educ Program 2021;2021:648-54.
22. Ono R, Watanabe T, Kawakami E, et al. Co-activation of macrophages and T cells contribute to chronic GVHD in human IL-6 transgenic humanised mouse model. EBioMedicine 2019;41:584-96.
23. Jardine L, Cytlak U, Gunawan M, et al. Donor monocyte-derived macrophages promote human acute graft-versus-host disease. J Clin Invest 2020;130:4574-86.
24. Alexander KA, Flynn R, Lineburg KE, et al. CSF-1-dependant donor-derived macrophages mediate chronic graft-versus-host disease. J Clin Invest 2014;124:4266-80.
25. MacDonald KP, Hill GR, Blazar BR. Chronic graft-versus-host disease: biological insights from preclinical and clinical studies. Blood 2017;129:13-21.
26. Kitko CL, Arora M, DeFilipp Z, et al. Axatilimab for chronic graft-versus-host disease after failure of at least two prior systemic therapies: results of a phase I/II study. J Clin Oncol 2023;41:1864-75.
27. 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.
28. Inamoto Y, Lee SJ, Onstad LE, et al. Refined National Institutes of Health response algorithm for chronic graft-versus-host disease in joints and fascia. Blood Adv 2020;4:40-6.
29. Ordentlich P, Wolfreys A, Da Costa A, et al. Targeting colony stimulating factor-1 receptor (CSF-1R) with SNDX-6352, a novel anti-CSF-1R targeted antibody. J Immunother Cancer 2016;4:Suppl 1:402. abstract.
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):389-401.e1.
31. 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.
32. 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.
33. Wu H, Shi J, Luo Y, et al. Evaluation of ruxolitinib for steroid-refractory chronic graft-vs-host disease after allogeneic hematopoietic stem cell transplantation. JAMA Netw Open 2021;4(1):e2034750.
34. Ferreira AM, Szor RS, Molla VC, et al. Long-term follow-up of ruxolitinib in the treatment of steroid-refractory chronic graft-versus-host disease. Transplant Cell Ther 2021;27:777.e1-777.e6.
35. Penack O, Peczynski C, Boreland W, et al. ECP versus ruxolitinib in steroid-refractory chronic GVHD — a retrospective study by the EBMT transplant complications working party. Bone Marrow Transplant 2024;59:380-6.
36. Wolff D, Radojcic V, Lafyatis R, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease. IV. The 2020 highly morbid forms report. Transplant Cell Ther 2021;27:817-35.
37. DeFilipp Z, Couriel DR, Lazaryan A, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: III. The 2020 Treatment of Chronic GVHD Report. Transplant Cell Ther 2021;27:729-37.

38. Cannarile MA, Weisser M, Jacob W, Jegg AM, Ries CH, Rüttinger D. Colony-stimulating factor 1 receptor (CSF1R) inhibitors in cancer therapy. J Immunother Cancer 2017;5:53.
39. Ries CH, Cannarile MA, Hoves S, et al. Targeting tumor-associated macrophages with anti-CSF-1R antibody reveals a strategy for cancer therapy. Cancer Cell 2014;25:846-59.
40. Adams RC, Carter-Cusack D, Llanes GT, et al. CSF1R inhibition promotes neuroinflammation and behavioral deficits during graft-versus-host disease in mice. Blood 2024;143:912-29.
41. Hashimoto D, Chow A, Greter M, et al. Pretransplant CSF-1 therapy expands recipient macrophages and ameliorates GVHD after allogeneic hematopoietic cell transplantation. J Exp Med 2011;208:1069-82.
42. Chitu V, Gokhan Ş, Nandi S, Mehler MF, Stanley ER. Emerging roles for CSF-1 receptor and its ligands in the nervous system. Trends Neurosci 2016;39:378-93.
43. Hume DA, MacDonald KPA. Therapeutic applications of macrophage colony-stimulating factor-1 (CSF-1) and antagonists of CSF-1 receptor (CSF-1R) signaling. Blood 2012;119:1810-20.
44. Hwang D, Seyedsadr MS, Ishikawa LLW, et al. CSF-1 maintains pathogenic but not homeostatic myeloid cells in the central nervous system during autoimmune neuroinflammation. Proc Natl Acad Sci U S A 2022;119(14):e2111804119.
45. Xiang T, Cheng N, Huang B, Zhang X, Zeng P. Important oncogenic and immunogenic roles of SPP1 and CSF1 in hepatocellular carcinoma. Med Oncol 2023;40:158.
46. Suzukawa K, Kinami K, Yang Y, et al. Safety and pharmacokinetics of axatilimab: results from a phase 1, double-blind, dose-escalation study. Presented at the 46th Annual Meeting of the Japanese Society for Transplantation and Cellular Therapy, Tokyo, March 21–23, 2024 (https://cdn.incyte.com/Portals/0/Assets/Poster/2024-JSTCT-Suzukawa.pdf).
47. Tiessen RG, Visser A, Tadema H, et al. First in human, single ascending dose study in healthy volunteers of SNDX-6352, a humanized IgG4 monoclonal antibody targeting colony stimulating factor-1 receptor (CSF-1R). Presented at the Society for the Immunotherapy of Cancer (SITC) Annual Meeting, National Harbor, MD, November 8–12, 2017 (https://cms.syndax.com/wp-content/uploads/2017/11/Tiessen-6352-SAD-poster-FINAL-SITC-2017.pdf).