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Long-term Use of Ibrutinib in Japanese Patients with Steroid Dependent/ Refractory cGVHD: Final Analysis of Multicenter Study

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Abstract

Background: Chronic graft-versus-host disease (cGVHD) is a serious complication after allogeneic stem cell transplantation. Poor prognosis has been shown in patients with cGVHD after the failure of primary steroid-based treatments. A previous report demonstrated the efficacy and safety of ibrutinib in these patients, leading to the approval of ibrutinib for cGVHD in Japan. Here, we report the extended follow-up of patients in this study.
Objectives: To evaluate the safety and efficacy of ibrutinib in Japanese patients with steroid-dependent or refractory cGVHD.
Study Design: An open-label, single-arm, multicenter study of ibrutinib in Japanese patients with steroid-dependent or refractory cGVHD (NCT No.: NCT03474679; Clinical Registry No.: CR108443).
Results: At the time of the final data cutoff, 7/19 (36.8%) patients completed the study treatment, and 12/19 (63.2%) patients discontinued ibrutinib. After a median follow-up of 31.11 months (range:1.9 to 38.6 months), the best overall response rate was 84.2% (16/19 patients; 95% CI:60.4%, 96.6%) in all treated populations, with a median time to response of 2.81 (range:1.0 to 27.6) months. Of 15 responders with ≥2 organs involved at baseline, seven (46.7%) had responses in multiple organs. An improvement in the organ response rate was observed for the skin, eye, mouth, and esophagus compared with that in a previous report. The rate of sustained response for ≥20 weeks, ≥32 weeks, and ≥44 weeks were 68.8%, 62.5%, and 50.0%, respectively for 16 responders. The median daily corticosteroid dose requirement tended to decrease over time for all treated analysis sets. Twelve of 19 patients (63.2%) reached a corticosteroid dose of <0.15 mg/kg/day for at least one week, and four (21.1%) discontinued corticosteroid treatment for at least 28 days during the study. The failure-free and overall survival rates at 30 months were 62.7% and 62.0%, respectively. The safety findings of this updated analysis were consistent with the safety profile observed at the time of the primary analysis and the known ibrutinib safety profile. Common grade ≥3 treatment-emergent adverse events (TEAEs) were pneumonia (6/19 [31.6%] patients), platelet count decreased, and cellulitis (3/19 [15.8%] patients each). After the primary analysis, no new TEAEs leading to death, treatment discontinuation, or dose reduction were reported, and no new patients reported major hemorrhage. Cardiac arrhythmia (Grade 2 atrial flutter) was reported in 1/19 (5.3%) patients. No new safety signs were observed despite prolonged ibrutinib exposure.
Conclusions: The final results support previous conclusions, demonstrating a clinically meaningful response and acceptable safety profile of ibrutinib in Japanese patients with steroid-dependent or refractory cGVHD.

Key words chronic graft-versus-host disease, NIH consensus development project criteria, allogeneic stem cell transplantation, ibrutinib, bruton's tyrosine kinase inhibitor

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Introduction

Chronic graft-versus-host disease (cGVHD) is a major life-threatening complication and a leading cause of late non-relapse mortality after allogeneic hematopoietic stem cell transplantation (allo-HSCT), which leads to poor health-related quality of life (HRQoL)[1-3]. Overall, cGVHD occurs in 30-70% of patients after allo-HSCT, depending on several factors, including donor and graft sources[4-6].

Corticosteroid-based treatment is the standard first-line therapy for cGVHD; however, a significant proportion of patients develop steroid-dependent or steroid-refractory disease and require second-line treatment within 2 years[7-9]. For many years, there have been few effective treatment options for patients with cGVHD, with poor prognosis after failure to corticosteroids[8].

Ibrutinib is a first-in-class, potent inhibitor of Bruton's tyrosine kinase (BTK) and also an inhibitor of interleukin-2-inducible T-cell kinase (ITK), which was approved by the US Food and Drug Administration (FDA) for the treatment of adult patients with cGVHD after the failure of one or more lines of systemic therapy in August 2017, and the indication was expanded for pediatric patients in August 2022 (https://www.rxabbvie.com/pdf/imbruvica_pi.pdf). Since 2017, much progress has been made in the management of cGVHD. After the approval of ibrutinib, two novel therapies, belumosudil and ruxoltinib, were approved by the FDA in 2021, with ruxoltinib showing a superior overall response rate (ORR) to control therapies in a phase 3 study[10].

In Japan, an open-label, single-arm, multicenter study of ibrutinib that involved 19 Japanese patients (≥12 years of age) with active cGVHD who were steroid-dependent or refractory demonstrated clinically meaningful benefits and acceptable safety profiles of ibrutinib, leading to the approval of ibrutinib for cGVHD in Japan. In the primary analysis, the best overall response rate was 73.7% (complete response, 21%; partial response, 63.2%), the rate of sustained response for ≥20 weeks was 71.4% for the responders, and adverse events (AEs) were acceptable[11]. This report describes an additional 22 months of follow-up for the patients in this study.

Materials and Methods

The detailed methodology for this study has been published previously[11]. In brief, eligible patients had steroid-dependent or refractory cGVHD defined according to the modified NIH criteria (2014)[12] with no more than three previous systemic treatments for cGVHD. Patients received oral ibrutinib (420 mg) once daily until they experienced unacceptable toxicity or met other criteria for ibrutinib treatment discontinuation. The dose was reduced to 280 mg/day with the concomitant use of voriconazole.

The study was continued after the primary analysis (at week 37 of the last enrolled patient) until the planned end of the study, resulting in an additional 22 months of follow-up (median follow-up was 31.11 months at final analysis). The efficacy and safety in the additional follow-up period after the primary analysis were assessed according to previously described criteria[11].

The primary efficacy endpoint was the best ORR as defined by the NIH Consensus Development Project Criteria (2014)[13]. Major secondary efficacy endpoints were a sustained response (CR or PR) of ≥20 weeks, duration of response (DOR), cGVHD response rate at each time point, changes in corticosteroid requirement over time, and improvement in the symptom burden as measured by the Lee cGVHD Symptom Scale. The exploratory efficacy endpoints included failure-free survival (FFS) and overall survival (OS). Efficacy analyses were conducted based on all treated analysis sets (n=19) and the response-evaluable analysis set (n=19).

Safety was assessed until 30 days after the final dose of ibrutinib. All enrolled patients who received at least one dose of ibrutinib were included in the safety analysis set. The AEs recorded by the investigators in the case report form (CRF) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1.

Institutional review board/Independent ethics commit-

tee approval was obtained from each participating institution. This study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Guidelines. All patients provided written informed consent.

Results

The study was continued from January 21, 2020 (the primary cut-off date), to November 29, 2021 (the final cut-off date). The median follow-up was extended from 11.9 (range:1.9 to 16.7) months at primary analysis[11] to 31.1 (range:1.9 to 38.6) months at the final analysis, and the median duration of ibrutinib exposure, from 9.6 (range:0.6 to 16.7) months[11] to 16.3 (range:0.6 to 36.2) months. At the time of the final data cutoff, 7/19 (36.8%) patients completed the study treatment, and 12/19 (63.2%) patients discontinued ibrutinib. The reasons for ibrutinib discontinuation were AEs and physician decisions (3/19 [15.8%] patients each), cGVHD progression and withdrawal by the patient (2/19 [10.5%] patients each), relapse of the underlying malignancy, and others (1/19 [5.3%] patients each). A total of 11/19 (57.9%) patients completed study participation and 8/19 (42.1%) patients terminated the study prematurely. The reasons for terminating study participation were death (7/19 [36.8%]) and withdrawal by patient (1/19 [5.3%]) (**Supplementary Table 1**).

At baseline, approximately half of the patients (10/19 [52.6%]) were steroid-dependent and nine (47.4%) were steroid-refractory. The majority of patients (94.7%) had two or more organs involved at baseline, with the most commonly involved being the mouth (15/19 [78.9%]), skin (14/19 [73.7%]), muscles, fascia, and joints (10/19 [52.6%]), and eyes (9/19 [47.4%]). One patient was reconsidered to have mouth involvement at baseline by the investigator after primary analysis. All patients had a history of at least one transplant and an underlying malignancy leading to transplantation (**Table 1**).

Efficacy Findings

Best overall response rate

The prespecified criteria for positive primary efficacy results (lower bound of the 95% CI exceeding 25% for the best ORR) of the study were already met in the primary analysis. With this additional 22 months of follow-up, the best ORR increased from 73.7% (14/19 patients, 95% CI:48.8%, 90.9%) in the primary analysis to 84.2% (16/19 patients; 95% CI:60.4%, 96.6%) in the final analysis in all treated analysis sets, including three patients who achieved CR and 13 patients who achieved PR (**Figure 1**).

Approximately 50% of responders with ≥2 (47.0%) or 3 (56.0%) organ-involvement at baseline responded in multiple organs (**Table 2**). The rate of sustained response for ≥20 weeks, ≥32 weeks, and ≥44 weeks were 68.8% (11/16 responders), 62.5% (10/16 responders), 50.0% (8/16 responders) for responders, and 57.90% (11/19 patients), 52.63% (10/19 patients), and 42.10% (8/19 patients) of all patients, respectively (**Table 3**).

Despite the extended duration of ibrutinib exposure, the median DOR could not be estimated based on Kaplan-Meier estimates (range:1.0, 34.5+). The Kaplan-Meier estimate for the DOR at 30 months was 56.2% (95% CI:26.9%, 77.6%). The median time to response was 2.81 (range:1.0 to 27.6) months for 16 responders, and that to CR was 5.59 (range:1.0 to 19.5) months for three patients with CR, respectively. Responses were observed across the organs involved in cGVHD (**Supplementary Table 2**).

The organ response rates (PR/CR) for the skin, eyes, mouth, and esophagus increased from 35.7%, 11.1%, 35.7%, and 40.0% in the primary analysis to 57.1%, 22.2%, 40.0%, and 60.0%, respectively, in the final analysis. Among patients with sclerotic features (n=6), 3/6 (50.0%) patients reached a skin response with improved skin features score (a score for sclerotic features), and 4/6 (66.7%) patients had ≥2-point improvement on a 0-10 severity scale of the skin or joint tightening (a scale indicating the severity of sclerosis) at the final analysis. cGVHD progression was observed in only three patients during the study (one with progression of liver involvement at day 86, another with new involvement in the lung at day 253, and another was reported 448 days after ibrutinib discontinuation with progression in the eye) (**Sapplementary Figure 1**).

The corticosteroid trend in this updated analysis was consistent with that in the primary analysis. At ibrutinib initiation, the median daily corticosteroid dose requirement decreased over time in all treatment analysis sets. The median daily corticosteroid dose requirement for all treated analysis sets was 0.27 mg/kg/day at baseline, 0.15 mg/kg/day at week 48, 0.14 mg/kg/day at week 96, and 0.14 mg/kg/day at week 144 (**Figure 2**). A total of 4/19 (21.1%) patients stopped steroids for at least 28 days and 12/19 (63.2%) patients used a < 0.15 mg/kg/day average daily dose of steroid for at least one week.

Exploratory Findings

With the extended duration of ibrutinib exposure, the median FFS (range:1.9, 37.3+) and OS (range:1.9, 37.3+) based on Kaplan-Meier estimates could not be estimated. The Kaplan-Meier estimates for FFS and OS at 30 months were 62.7% (95% CI:37.2%, 80.2%) and 62.0% (95% CI:36.3%, 79.8%), respectively (**Supplementary Figure 2**).

Improvement rate in the lee cGVHD symptom scale

After the primary analysis, two additional patients achieved an improvement in the total summary score on

Table 1. Baseline demographic and clinical characteristics

	N=19
Median age (range) (years)	40.0 (13; 64)
Sex, N (%)	
Female	7 (36.8%)
Male	12 (63.2%)
Median weight (range) (kg)	61.50 (25.4; 83.2)
cGVHD disease state	
Steroid dependent	10 (52.6%)
Steroid refractory	9 (47.4%)
Overall severity of cGVHD	
Moderate	10 (52.6%)
Severe	9 (47.4%)
Median (range) months from initial cGVHD diagnosis date	21.36 (5.1; 158.0)
Median (range) months from transplantation to initial cGVHD diagnosis date	8.31 (3.4; 22.8)
Karnofsky/Lansky performance status score at baseline	
90-100	7 (37.0%)
70-80	12 (63.2%)
Number of prior cGVHD treatment regimens, N (%)	
1	8 (42.1%)
2	9 (47.4%)
3	2 (10.5%)
Prior cGVHD therapies, N (%)	
Prednisolone	19 (100.0%)
Tacrolimus	17 (89.5%)
Mycophenolate mofetil	5 (26.3%)
Methotrexate	2 (10.5%)
Ciclosporin	1 (5.3%)
Extracorporeal photopheresis	1 (5.3%)
Rituximab	1 (5.3%)
Teceleukin	1 (5.3%)
Organs involved in cGVHD at baseline, N (%)	
1	1 (5.3%)
2	7 (36.8%)
3	1 (5.3%)
≥ 4	10 (52.6%)
Organs involved in cGVHD at baseline, N (%)	
Mouth	15 (78.9%)
Skin	14 (73.7%)
Muscles, fascia, joints	10 (52.6%)
Eyes	9 (47.4%)
Lung	7 (36.8%)
GI Tract	6 (31.6%)
Nails	2 (10.5%)
Genitalia	2 (10.5%)
Liver	2 (10.5%)
Other	1 (5.3%)
Scalp and body hair	1 (5.3%)
Hematopoietic and Immune	0
Median (range) daily steroid dose per weight at baseline (mg/kg/day)	0.27 (0.1; 1.8)
Patients with 1 or more immunosuppressants at baseline, N (%)	13 (68.4%)
Tacrolimus	12 (63.2%)
Mycophenolate mofetil	4 (21.1%)
Patients with antimycotics for systemic use at baseline, N (%)	13 (68.4%)
Voriconazole	4 (21.1%)
Fluconazole	8 (42.1%)
Micafungin sodium	1 (5.3%)

cGVHD, Chronic Graft Versus Host Disease; GI, Gastrointestinal

the Lee cGVHD Symptom Scale. The improvement rate in the Lee cGVHD Symptom Scale total summary score was 52.6% (10/19 patients; 95% CI:28.9%, 75.6%) for all patients (including both responders and non-responders). At the 6- and 12-month landmarks, the improvement rates in the Lee cGVHD Symptom scores were 26.3% (5/19 patients; 95% CI:9.1%, 51.2%) and 42.1% (8/19 patients; 95% CI:20.3%, 66.5%), respectively.

Safety Findings

The safety findings of this updated analysis were consistent with those of the primary analysis. All 19 treated patients had at least one reported TEAE. The most common TEAEs (≥20% of patients) during the study were pneumonia and stomatitis (9/19 [47.4%] patients each), upper respiratory tract infection, platelet count decreased and cellulitis (6/19 [31.6%] patients each), nausea (5/19 [26.3%] patients), pruritus, edema peripheral, cataract, purpura, headache, and constipation (4/19 [21.1%] patients each) (**Table 4**).

Grade 3 or higher TEAEs were reported in 17/19 (89.5%) patients. The most common (≥15% of patients) Grade 3 or higher TEAEs reported during the study were pneumonia (6/19 [31.6%] patients), platelet count decreased, and cellulitis (3/19 [15.8%] patients each) (**Table 4**).

Treatment-emergent SAEs were reported in 12/19 (63.2%) patients during the study. The most common (≥10% of patients) treatment-emergent SAEs reported during the study were pneumonia (7/19 [36.8%] patients), cellulitis (3/19 [15.8%] patients), and renal impairment (2/19 [10.5%] patients).

The incidence of TEAEs was highest in the first six months and decreased in subsequent periods during ibrutinib treatment. There were no TEAEs with a higher incidence over the course of treatment. Infections (defined as TEAEs in the SOC of infections and infestations) including pneumonia had a decreasing trend over time; 14/19 (73.7%) patients in the first 6 months, 9/16 (56.3%) patients from 6 to ≤12 months, 6/15 (40.0%) patients from 12 to ≤18 months, 1/13 (7.7%) patients from 18 to ≤24 months. The incidence rate was 41.7% after 24 months (**Supplementary Table 3**).

The incidences of Grade 3 or higher infections in patients with and without antimycotic use at baseline were 46.2% (6/13 patients) and 66.7% (4/6 patients), respectively. One patient who received micafungin sodium at baseline developed fungal pneumonia (**Supplementary Table 4**).

Despite the extended duration of ibrutinib exposure, no new TEAEs leading to death, treatment discontinuation, or dose reduction were reported. Three of the 19 (15.8%) patients died because of TEAEs: one had multiple organ dysfunction syndrome (ibrutinib-related), one had fungal pneumonia (ibrutinib-related), and one had subarachnoid hemorrhage (not ibrutinib-related), as previously reported. Among the other four patients who died during the study, one patient had cGVHD progression, one patient had progression of an underlying malignancy, and two patients had other safety events that occurred > 30 days after the last dose of ibrutinib.

TEAEs leading to treatment discontinuation were reported in 3/19 (15.8%) patients (one each with Grade 3 stomatitis, fatal multiple organ dysfunction syndrome, and fatal subarachnoid hemorrhage, respectively). TEAEs leading to dose reduction were reported in 2/19

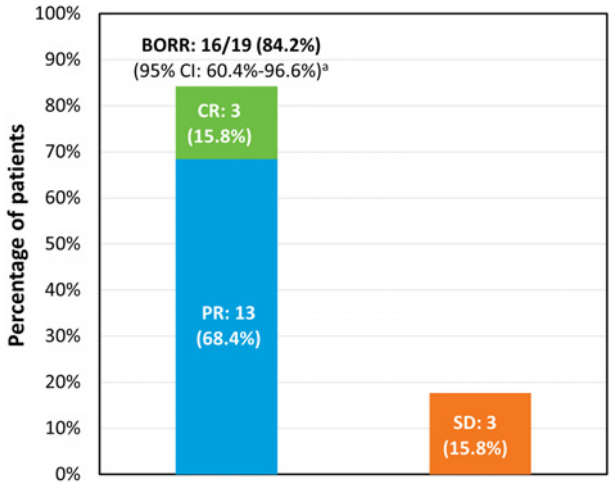

Figure 1. Best overall cGVHD response
[a] 2-sided 95% CI is calculated using the Clopper-Pearson's exact method.
CR, indicates complete response; ORR, overall response rate; PR, partial response; SD, stable disease

Table 2. Maximum number of organs with response

	All Responders N=16	Patients with ≥ 2 Organs Involved at Baseline N=15	Patients with ≥ 3 Organs Involved at Baseline N=9
Number of organs with response			
1	9 (56.3%)	8 (53.3%)	4 (44.4%)
2	1 (6.3%)	1 (6.7%)	0
>=3	6 (37.5%)	6 (40.0%)	5 (55.6%)

Table 3. Patients with sustained response rate

	n=16
Sustained response rate at least 20 weeks	
n (%)	11 (68.8%)
95% CI[a]	(41.3%, 89.0%)
Sustained response rate at least 32 weeks	
n (%)	10 (62.5%)
95% CI[a]	(35.4%, 84.8%)
Sustained response rate at least 44 weeks	
n (%)	8 (50.0%)
95% CI[a]	(24.7%, 75.3%)

[a] 2-sided 95% CI is calculated using the Clopper-Pearson's exact method.
PR, partial response; CI, confidence interval

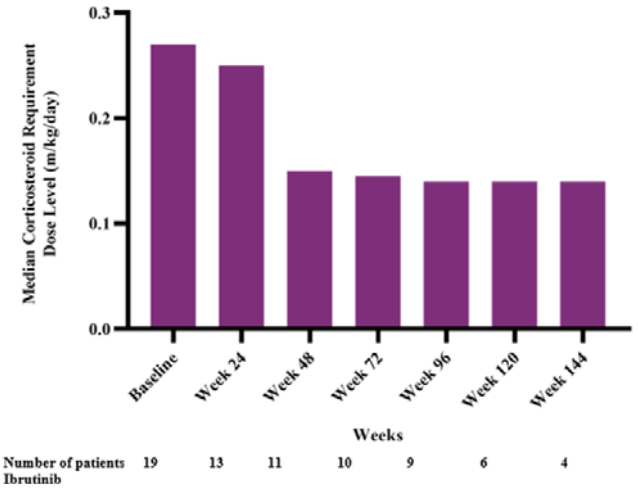

Figure 2. Median of corticosteroid requirement changes over time

(10.5%) patients. During the study, TEAEs leading to dose reduction were gastrointestinal hemorrhage (Grade 3) and stomatitis (Grade 3). All nonfatal TEAEs that led to treatment discontinuation or dose reduction were resolved.

Three of the 19 (15.8%) patients reported major hemorrhagic events in the primary analysis, and no new patients reported major hemorrhage after the primary analysis. One patient had Grade 3 gastrointestinal hemorrhage and Grade 4 immune thrombocytopenia, one patient had Grade 5 subarachnoid hemorrhage, and a third had Grade 3 traumatic hemorrhage.

In other safety observations, 1/19 (5.3%) patients reported cardiac arrhythmia events (serious Grade 2 atrial flutter) after the primary analysis. Infections were reported in 15/19 (78.9%) patients. The most common infection was pneumonia (9/19 [47.4%] patients), cellulitis, and upper respiratory tract infection (6/19 [31.6%] patients each). The most common Grade 3 or higher infections were pneumonia (6/19 [31.6%] patients) and cellulitis (3/19 [15.8%] patients) (**Table 4**). No new safety signs were observed despite the extended duration of ibrutinib exposure.

Pharmacodynamic evaluation

ITK binding occupancy was measured; however, the signal-to-noise ratio was inadequate for quantitative analysis to return precise occupancy.

Discussion

Treatment with ibrutinib at 420 mg/day showed high overall response rates, clinically meaningful sustained responses, and durable clinical activity based on the NIH cGVHD response criteria (2014)[13]. Efficacy results for this updated analysis were generally consistent with those in the primary analysis[11] and comparable with the final results of a phase 1b/2 study of ibrutinib in patients with cGVHD after the failure of prior therapy (the PCYC-1129 study)[14].

With extended treatment, the best ORR increased from 73.7% in the primary analysis[11] to 84.2% in the final analysis (additional one PR and CR each). The rate of sustained response for ≥20 weeks, ≥32 weeks, and ≥ 44 weeks were 68.8%, 62.5%, and 50.0%, respectively, for responders. Similar responses were reported in the updated analysis of the PCYC-1129 study[14]. In which responses were durable, with a sustained response rate and a 30-month DOR of 56.2%. Responses were observed across the organs. Although only one responder was observed in the lungs, the other six patients with lung cGVHD at baseline maintained SD during the study, which was considered an important finding in the management of cGVHD[15]. An improved organ response rate (PR/CR) was reported for the skin, eye, mouth, and esophagus after continued treatment with ibrutinib. Although lower response rates for skin and mouth involvement were observed in this study than in the PCYC-1129 study, they could be attributed to differences in the analyzed population and the inclusion criteria for skin and mouth involvement, as discussed in a previous report[11]. The time to response was varied (range:1.0 to 27.6 months), which may be dependent on the specific manifestation; inflammatory manifestations could improve early (within 4 to 8 weeks) but established sclerosis would require a longer time to improve[12].

Similarly, the median corticosteroid dose continued to decrease over time, to doses associated with minimal toxicity, an important goal in the treatment of patients with cGVHD. This result suggests that ibrutinib has a steroid-sparing effect that could lead to a reduction in the side effects associated with the use of corticosteroids in cGVHD[16]. This is an essential clinical benefit of ibrutinib given the numerous serious side effects of corticosteroids, including infection, avascular necrosis, hy-

Table 4. Treatment-emergent adverse events reported in ≥ 15% of patients (by toxicity grade 3 or higher)

	All Grade	Grade 3 or Higher
Analysis set: Safety	N=19	N=19
Patients with 1 or more TEAE	19 (100.0%)	17 (89.5%)
System organ class/Preferred term		
Gastrointestinal disorders	15 (78.9%)	3 (15.8%)
Stomatitis	9 (47.4%)	2 (10.5%)
Nausea	5 (26.3%)	0
Constipation	4 (21.1%)	0
Abdominal pain upper	3 (15.8%)	0
Diarrhoea	3 (15.8%)	0
Infections and infestations	15 (78.9%)	10 (52.6%)
Pneumonia	9 (47.4%)	6 (31.6%)
Cellulitis	6 (31.6%)	3 (15.8%)
Upper respiratory tract infection	6 (31.6%)	0
Conjunctivitis	3 (15.8%)	0
Nasopharyngitis	3 (15.8%)	0
Paronychia	3 (15.8%)	0
Skin and subcutaneous tissue disorders	13 (68.4%)	0
Pruritus	4 (21.1%)	0
Purpura	4 (21.1%)	0
General disorders and administration site conditions	10 (52.6%)	1 (5.3%)
Oedema peripheral	4 (21.1%)	0
Eye disorders	9 (47.4%)	2 (10.5%)
Cataract	4 (21.1%)	2 (10.5%)
Investigations	9 (47.4%)	5 (26.3%)
Platelet count decreased	6 (31.6%)	3 (15.8%)
Musculoskeletal and connective tissue disorders	8 (42.1%)	2 (10.5%)
Arthralgia	3 (15.8%)	0
Muscle spasms	3 (15.8%)	0
Nervous system disorders	8 (42.1%)	2 (10.5%)
Headache	4 (21.1%)	0
Respiratory, thoracic and mediastinal disorders	8 (42.1%)	1 (5.3%)
Cough	3 (15.8%)	0
Epistaxis	3 (15.8%)	0
Pleural effusion	3 (15.8%)	1 (5.3%)
Blood and lymphatic system disorders	7 (36.8%)	3 (15.8%)
Anaemia	3 (15.8%)	2 (10.5%)
Psychiatric disorders	4 (21.1%)	0
Anxiety	3 (15.8%)	0
Vascular disorders	4 (21.1%)	1 (5.3%)
Hypertension	3 (15.8%)	1 (5.3%)
Immune system disorders	3 (15.8%)	1 (5.3%)

Patients are counted only once for any given event, regardless of the number of times they actually experienced the event. Patients with multiple events with grade 3 or higher for a given preferred term, system organ class are counted once only with maximum severity for each category.
TEAE, treatment-emergent adverse event

pertension, poor glycemic control, mood swings, osteoporosis, and weight gain[17, 18]. Although extended ibrutinib treatment led to increased ORR and discontinuation of steroids in several patients, the median corticosteroid dose levels remained similar after week 48. This may be due to the careful consideration of further steroid tapering in other patients, which did not result in a decrease in the median value.

The clinical efficacy of ibrutinib in cGVHD is further supported by the continued overall improvement in the Lee cGVHD Symptom Scale score in 52.6% of patients, demonstrating the patient-perceived benefit of

ibrutinib on reducing symptom burden[3, 19-21]. The FFS and OS at 30 months were 62.7% and 62.0%, respectively.

Furthermore, the efficacy results in this study were generally similar to those from a phase 3 study of ruxolitinib and a phase 2 study of belumosudil, with best ORR of 76.4% and 76%, respectively[22, 23]. The improvement rate in the Lee cGVHD Symptom Scale score was 24.2% at 24 weeks for ruxolitinib and 61% at any time point for belumosudil. The FFS (18 months-FFS:68.4% in this study, 60.7% in the ruxolitinib study, and 44% in the belumosudil study) may have been affected by a higher number of prior lines of therapy in the belumosudil study than in the other two studies. Given the limited sample size of this study, the ORR of each organ could not be compared with those of other studies.

The safety findings of this updated analysis were consistent with those of the primary analysis. The safety profile of ibrutinib 420 mg/day was generally consistent with the known safety profile of ibrutinib. Given the disease characteristics of moderate and severe cGVHD and the toxicities of corticosteroids, the TEAEs observed in this study can also be considered consistent with the expected safety profile for cGVHD patients with continuous steroid use[17, 24, 25]. No new safety signals were observed since the primary analysis. No increase in the incidence of TEAEs leading to death, treatment discontinuation, or dose reduction was observed after the primary analysis, suggesting that ibrutinib can be used safely in the long term in patients with cGVHD. One patient reported an additional episode of Grade 3 gastrointestinal hemorrhage and one episode of Grade 4 immune thrombocytopenia during long-term follow-up. Additional Grade 3 gastrointestinal hemorrhage resolved after ibrutinib interruption; however, ibrutinib treatment was discontinued after the event was resolved by the investigator, given the risk of recurrent gastrointestinal hemorrhage. Grade 4 immune thrombocytopenia occurred during ibrutinib interruption and was considered unrelated to ibrutinib by the investigator. Infections were reported in 15/19 patients, with 10 patients having Grade 3 or higher infections, including serious Grade 4 pneumonia reported after the primary analysis. However, no increased incidence of infections was observed with long-term treatment. Cardiac arrhythmia (Grade 2 atrial flutter) was reported in one (5.3%) patient, but no ibrutinib discontinuation or reduction was required, and the event did not recur during the study. Overall, the TEAEs reported in this study were generally manageable and consistent with the known safety profile of ibrutinib. No new safety signs were observed in patients with steroid-dependent or refractory cGVHD after extended ibrutinib exposure.

Conclusions

After an additional follow-up of 22 months, the final results of Study 54179060GVH3001 were generally consistent with those of the primary analysis, showing clinically meaningful results for the best ORR and sustained response. The overall safety profile of ibrutinib at 420 mg/day was acceptable for patients aged 12 years and older. No new safety signs were observed in the primary results. The final results support previous conclusions demonstrating a positive benefit-risk profile of ibrutinib in 12 years and older Japanese patients with steroid-dependent or refractory cGVHD.

The major limitations of this analysis were its open-label design, lack of a comparator group, and small sample size. However, it is noteworthy that this study reaffirmed a clinically meaningful response in adolescent and adult patients with cGVHD treated with ibrutinib.

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Author Contributions

M.T., N.D., S.S., T.O., M.O., T.K., M.S., T.I., Y.U., N.Y., and E.F. were involved in the conduct of the research. N.Y. and E.F. were additionally involved in the design, conceptualization, management, and coordination of the research. T.H. performed the statistical analysis. All authors reviewed the manuscript for important intellectual content, approved the final manuscript, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Ethics approval

Institutional review board/Independent ethics committee approval was obtained from each participating institution. This study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Guidelines.

Consent for publication

Informed consent was obtained from each participant or their legally acceptable representative.

Conflicts of Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: M.T. received payment or honoraria from Janssen Pharmaceutical, Sanofi, Takeda Pharmaceutical Co., Nippon Shinyaku Co., Beckman Coulter Inc., Novo Nordisk Pharma., Daiichi Sankyo Co., Chugai Pharmaceutical Co., Asahi Kasei Pharma Corp., and Sumitomo Dainippon Pharma Co. for lectures, presentations, speakers' bureaus, manuscript writing, or educational events. M.S. received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Kyowa Kirin Co. Ltd., Chugai, Pfizer, Astellas, Nippon-Shinyaku, Ono, MSD, Bristol-Myers-Squibb, Asahi Kasei, Novartis, Eisai, Otsuka, Sumitomo-Dainippon, Sanofi, Takeda, Celgene, Mochida, Shire, Mundipharma, abbvie, CSL Behring, Sym-Bio, Janssen, AstraZeneca, DAIICHI SANKYO, and GlaxoSmithKline. N.D. received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Novartis Pharma and Janssen Pharma. Y.U. participated in a Data Safety Monitoring Board or Advisory Board with Sanofi and Otsuka Pharmaceutical. M.O. received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Otsuka Pharmaceutical Co. Ltd. N.Y. is an employee of Janssen Pharmaceutical K.K. and holds stock ownership with Johnson & Johnson. T.H. and E.F. are employees of Janssen Pharmaceutical K.K.

S.S., T.O., T.I., and T.K. declare no conflict of interest. Disclosure forms provided by the authors are available on the website.

Data Sharing Statement

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through the Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

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