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Ibrutinib for Chronic Graft-versus-Host Disease After Failure of Prior Therapy: 1-Year Update of a Phase 1b/2 Study

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A B S T R A C T

Chronic graft-versus-host disease (cGVHD) is a life-threatening complication of allogeneic stem cell transplantation. In a Phase 1b/2, open-label study (PCYC-1129; ClinicalTrials.gov identifier NCT02195869) involving 42 patients with active cGVHD who were steroid-dependent or -refractory, the activity and safety of ibrutinib, a once-daily inhibitor of Bruton's tyrosine kinase, was demonstrated. Here we report extended follow-up for patients in this study. After a median follow-up of 26 months (range, .53 to 36.7 months), best overall response rate in the all treated population was 69% (29 of 42), with 13 patients (31%) achieving a complete response and 16 patients (38%) achieving a partial response. Sustained responses of ≥20, ≥32, and ≥44 weeks were seen in 20 (69%), 18 (62%), and 16 (55%) of the 29 responders, respectively. Of 26 patients with ≥2 involved organs, 19 (73%) showed responses in ≥2 organs. Six of 10 patients (60%) with ≥3 involved organs showed responses in ≥3 organs. Eleven of 18 patients (61%) who had sclerosis at baseline showed a sclerotic response (39% with complete response, 22% with partial response). Twenty-seven of 42 patients (64%) reached a corticosteroid dose of <.15 mg/kg/day during the study; 8 discontinued corticosteroid treatment and remained off corticosteroid at study closure. Safety findings for this updated analysis were consistent with the safety profile seen at the time of the original analysis. Common grade ≥3 adverse events (AEs) were pneumonia (n = 6), fatigue (n = 5), and diarrhea (n = 4). The onset of new grade ≥3 AEs decreased from 71% in the first year of treatment to 25% in the second year (n = 12). AEs leading to discontinuation occurred in 18 patients (43%). At a median follow-up of >2 years, ibrutinib continued to produce durable responses in patients with cGVHD who had failed previous systemic therapy. In this pretreated, high-risk population, clinically meaningful benefit and an acceptable safety profile were observed with additional follow-up for ibrutinib. These results demonstrate a substantial advance in the therapeutic management of patients with cGVHD.

INTRODUCTION

Chronic graft-versus-host disease (cGVHD), a serious and often fatal complication of hematopoietic cell transplantation (HCT), affects as many as 70% of patients post-HCT [1,2]. A substantial proportion of patients with cGVHD fail to receive benefit from frontline therapy and develop steroid-dependent or -refractory disease [3,4]. The efficacy of treatment options for patients

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with steroid-dependent or -refractory cGVHD is mixed, of limited duration, and associated with significant toxicity [3–8]. Thus, steroid-sparing therapies with sustained efficacy and more acceptable adverse event (AE) profiles are needed.

Ibrutinib, a first-in-class, once-daily Bruton's tyrosine kinase (BTK) inhibitor, is the only treatment approved by the US Food and Drug Administration for adults with cGVHD after failure of ≥1 lines of systemic therapy [9]. A Phase 1b/2, open-label, single-arm study (PCYC-1129; ClinicalTrials.gov identifier NCT02195869) that involved 42 patients with active cGVHD who were steroid-dependent or -refractory demonstrated the activity and safety of ibrutinib in these patients [10]. After a median follow-up of 14 months, the best overall cGVHD response rate was 67% (complete response [CR], 21%; partial response [PR], 45%) and AEs were acceptable [9,10]. This report describes an additional 12 months of follow-up for patients in this study.

METHODS

A detailed description of this study has been published previously [10]. In brief, eligible patients had steroid-dependent or -refractory cGVHD after HCT and had received ≤3 previous regimens for cGVHD. Steroid-dependent was defined as the presence of cGVHD manifestations requiring a glucocorticoid dose greater than or equal to prednisone .25 mg/kg/day (.5 mg/kg every other day or equivalent) for ≥12 weeks. Steroid-refractory was defined as the presence of cGVHD manifestations despite treatment with a glucocorticoid dose greater than or equal to prednisone .5 mg/kg/day (1 mg/kg every other day or equivalent) for ≥4 weeks. Patients were also required to have either >25% body surface area in accordance with National Institutes of Health (NIH)-defined criteria for "erythematous rash" or a total mouth score of ≥4 points by NIH-defined criteria [11].

Patients receiving ibrutinib in Phase 1b could continue treatment in Phase 2 if no dose-limiting toxicities were experienced. In these patients, ibrutinib was continued in Phase 2 at the same dose as in Phase 1. The recommended Phase 2 dose identified in Phase 1 of the study was ibrutinib 420 mg/day.

Safety and activity in long-term follow-up were assessed according to previously described criteria [10]. Safety was assessed until 30 days after the last dose of ibrutinib, and response assessments were completed every 12 weeks until progressive disease. Response criteria for patients with sclerosis were based on summing the total percentage of body surface area affected by sclerosis (moveable and nonmoveable) at baseline and determining the proportion of patients with a ≥50% decrease or complete resolution in sclerotic manifestations. Exploratory analysis included failure-free survival (FFS), defined as the interval between the date of first dose and the death date, the date of initiating subsequent cGVHD therapy, or the start date of relapse of underlying malignancy, whichever occurred first. Post hoc analysis of overall survival was calculated as the number of months from first dose date of study treatment to the date of death or last known alive date. Failure-free survival and overall survival were determined using Kaplan-Meier methodology.

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, International Conference on Harmonization Guidelines, and all patients provided written informed consent. Requests for access to individual participant data from clinical studies conducted by Pharmacyclics LLC, an AbbVie Company, can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

RESULTS

As of September 18, 2017, the median follow-up was 26 months (range, .53–36.7 months), and the duration of treatment ranged from .2 to 37 months (median, 4.4 months). A total of 27 patients (64%) were steroid-dependent, 7 (17%) were steroid-refractory, and 8 (19%) had a history of both steroid-dependent and -refractory disease. Most patients (88%) had ≥2 organs involved at baseline (Supplementary Table S1).

With this additional 1 year of follow-up, the best overall cGVHD response rate was 69% (29 of 42) in the all treated population, including 13 patients (31%) who achieved a CR and 16 (38%) who achieved a PR (Figure 1). Individual responses over time for the response-evaluable population are shown in Supplementary Figure S1. Among the 29 responders, sustained responses of ≥20, ≥32, and ≥44 weeks were observed in 20 (69%), 18 (62%), and 16 (55%) patients, respectively. Responses were observed across multiple organs (Supplementary Figure S2).

In an exploratory analysis, the Kaplan-Meier point estimate for failure-free survival in all treated patients at 18 months was 51%. Patients were followed for up to 37 months (median,

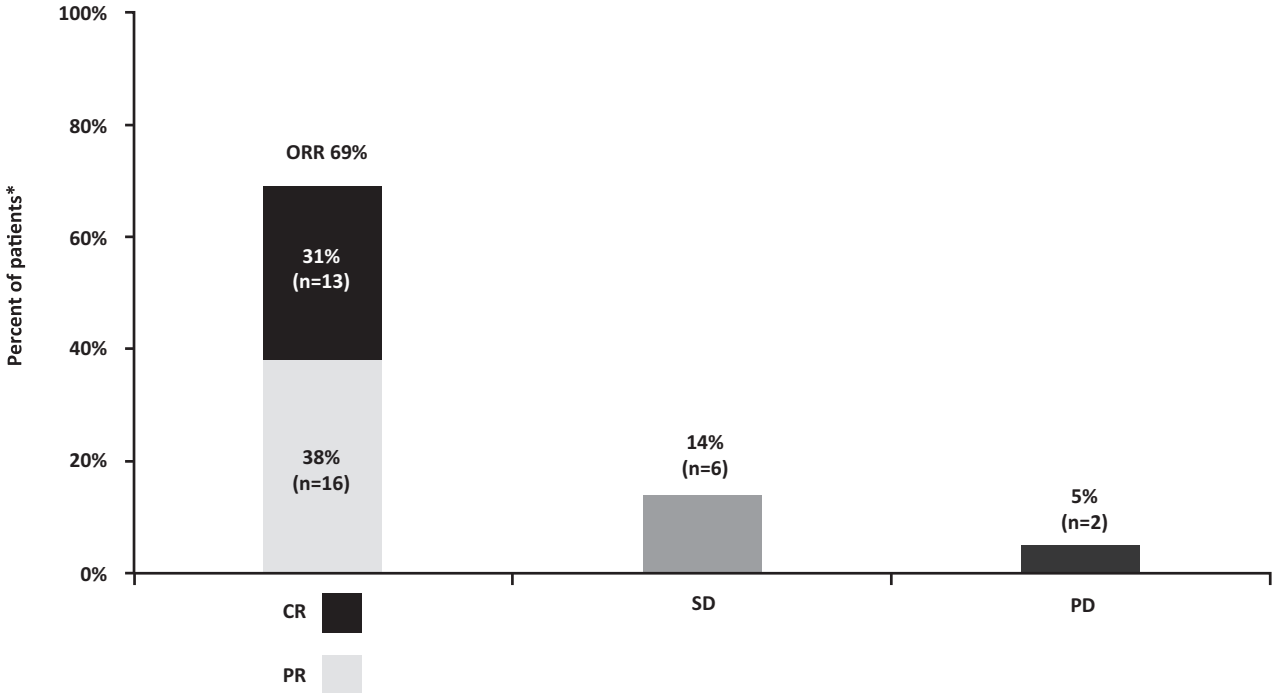

Figure 1. Best overall cGVHD response. cGVHD, chronic graft-versus-host disease; CR, complete response; ORR, overall response rate (ie, best overall cGVHD response rate); PD, progressive disease; PR, partial response; SD, stable disease. *Five patients who had no response assessment during the study were considered nonresponders and are not represented in the figure but are included in the best overall cGVHD response rates reported.

Table 1
Response in Multiple Organs in Patients Who Responded to Ibrutinib

Parameter	Responders, n	Sustained response rate, n (%)	Responders with ≥2 or ≥3 organs involved at baseline, n	Best ORR, n (%)
Sustained response	NA	NA	NA	NA
≥20 wk	29	20 (69)	NA	NA
≥32 wk	29	18 (62)	NA	NA
≥44 wk	29	16 (55)	NA	NA
Organs showing response	NA	NA	NA	NA
≥2 organs	NA	NA	26*	19 (73)
≥3 organs	NA	NA	10†	6 (60)

ORR, overall response rate; N/A, not applicable.
* Number of responders with ≥2 involved organs at baseline.
† Number of responders with ≥3 involved organs at baseline.

26 months), and the estimated survival rate at 24 months was 71% (95% confidence interval, 52% to 83%) based on post hoc overall survival analysis.

Among the 26 responders who had ≥2 organs affected by cGVHD at baseline, 19 (73%) had a response in ≥2 organs (Table 1). Similarly, among the 10 responders who had ≥3 organs affected by cGVHD at baseline, 6 (60%) had a response in ≥3 organs. A total of 18 patients had sclerosis at baseline, with a median body surface area of 45% (range, 9% to 81%) affected by sclerosis. Most patients with sclerosis (61%) had a Karnofsky Performance Status score of 70 to 80. Of the 18 patients with sclerosis at baseline, 11 (61%) showed a decrease in sclerosis (50% decrease or complete resolution).

Among all treated patients (N = 42), 18 (43%) had a clinically meaningful improvement (≥7-point decrease) in the Lee cGVHD Symptom Scale total summary score, with substantially more responders reporting improvement compared with nonresponders (17 of 29 [59%] versus 1 of 13 [8%]). Clinically meaningful improvement in the Lee cGVHD Symptom Scale total summary score on ≥2 consecutive visits was achieved by 12 patients (29%). By week 26, 12 responders (41%) had improvement in the Lee cGVHD Symptom Scale total summary score, compared with 1 nonresponder (8%). By week 52, 16 responders (55%) had improvement in the Lee cGVHD Symptom Scale total summary score, compared with 1 nonresponder (8%).

Among all 42 treated patients, 27 (64%) reached a corticosteroid dose of <.15 mg/kg/day during the study. In the responders, the median corticosteroid dose decreased from .3 mg/kg/day (range, .1 to 1.3 mg/kg/day) at baseline (n = 29) to .1 mg/kg/day (range, 0 to .2 mg/kg/day) at week 52 (n=18) (Figure 2). Eight of 29 responders (28%) discontinued corticosteroid treatment. None of the 8 patients had resumed corticosteroid treatment at the time of study closure, and 7 patients remained in response. The 1 patient who did not maintain response per investigator did not meet the 2005 NIH cGVHD Consensus Panel Response Criteria for progression and was started on subsequent therapy (extracorporeal photopheresis) for cGVHD at 166 days after discontinuation of systemic steroids.

Safety findings for this updated analysis were consistent with those in the original analysis, with treatment-emergent adverse events (TEAEs) being primarily grade 1 and 2 in severity (Table 2). The most common (>20% of patients) all-grade TEAEs were fatigue (57%), diarrhea (40%), muscle spasms (33%), nausea (29%), and bruising (24%), and the most common (≥10% of patients) grade ≥3 TEAEs were pneumonia (14%), fatigue (12%), and diarrhea (10%). Analysis of TEAEs by time period demonstrated that the most frequent (≥10%) TEAEs occurred primarily during the first 6 months (Supplementary Table S2). Serious TEAEs occurred in 22 patients (52%), grade ≥3 serious TEAEs occurred in 19 patients (45%), and there were no new fatal TEAEs (Supplementary Table S3). Similar to all-grade TEAEs, analysis of serious TEAEs by time period demonstrated that most occur primarily during the first 6 months (Supplementary Table S4). There were 6 serious AEs listed as pneumonia. The 1 fatal pneumonia was bacterial (*Enterococcus*). The remaining 5 nonfatal pneumonias included 1 each of bacterial, fungal (*Aspergillus*), and multiagent (bacterial, fungal, and viral) origin and 2 of unknown etiology. At baseline,

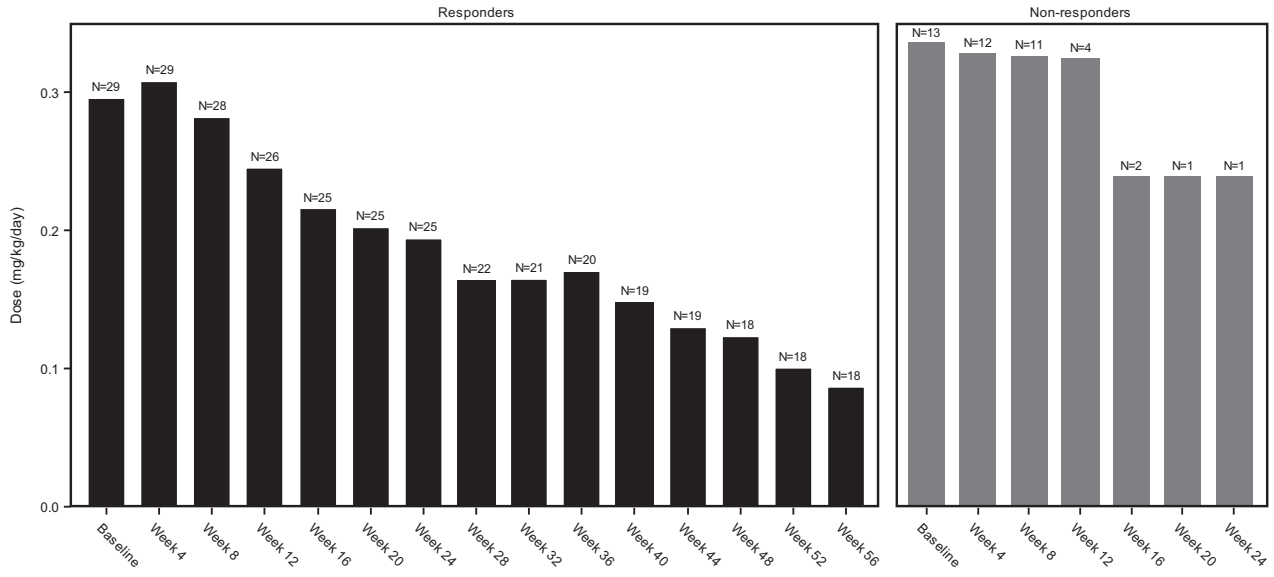

Figure 2. Median corticosteroid doses decreased throughout treatment. N represents the number of patients at each visit. A responder is defined as a patient who achieved a partial response or better. A nonresponder is defined as a patient who did not achieve a partial response or better. For each patient, steroid doses during or after progressive disease (per the 2005 National Institutes of Health's cGVHD Consensus Panel response criteria) are excluded.

Table 2
TEAEs Occurring in ≥10% of Patients Regardless of Cause

TEAE, n (%)	All Grades, n (%)	Grade 1-2, n (%)	Grade 3-4, n (%)	Grade 5, n (%)
Fatigue	24 (57)	19 (45)	5 (12)	0
Diarrhea	17 (40)	13 (31)	4 (10)	0
Muscle spasms	14 (33)	13 (31)	1 (2)	0
Nausea	12 (29)	12 (29)	0	0
Bruising	10 (24)	10 (24)	0	0
Headache	8 (19)	6 (14)	2 (5)	0
Pneumonia	8 (19)	2 (5)	5 (12)	1 (2)
Pyrexia	8 (19)	7 (17)	1 (2)	0
Upper respiratory tract infection	8 (19)	8 (19)	0	0
Dyspnea	7 (17)	5 (12)	2 (5)	0
Fall	7 (17)	7 (17)	0	0
Cough	6 (14)	6 (14)	0	0
Peripheral edema	6 (14)	6 (14)	0	0
Constipation	5 (12)	5 (12)	0	0
Contusion	5 (12)	5 (12)	0	0
Hyperglycemia	5 (12)	2 (5)	3 (7)	0
Hypokalemia	5 (12)	2 (5)	3 (7)	0
Hypophosphatemia	5 (12)	3 (7)	2 (5)	0
Mouth ulceration	5 (12)	5 (12)	0	0
Vomiting	5 (12)	5 (12)	0	0

A second fatal TEAE caused by bronchopulmonary aspergillosis occurred but did not meet the threshold cutoff (10%) for common TEAE.

71% of patients were taking ibrutinib concomitantly with moderate or strong cytochrome P450 3A (CYP3A) inhibitors, and 52% were taking immunosuppressants other than prednisone. Grade ≥3 TEAEs were similar in patients taking ibrutinib concomitantly with CYP3A inhibitors and those without CYP3A inhibitors (73% versus 89%) or immunosuppressants (77% versus 75%). With additional follow-up, there were no new cases of atrial fibrillation (1 case in the initial report [10]) or major hemorrhage.

Grade ≥3 TEAEs decreased over time (Figure 3; Supplementary Table S2). Serious grade ≥3 TEAEs (year 1, 45% [n = 19 of 42]; year 2, 8% [n = 1 of 12]) and any-grade TEAE bleeding events (year 1, 48% [n = 20 of 42]; year 2, 17% [n = 2 of 12]) decreased in the second year of treatment. Furthermore no additional patients required a dose reduction (33%; n = 14). TEAEs leading to discontinuation occurred in 18 patients (43%).

DISCUSSION

This extended follow-up demonstrated durable and clinically meaningful outcomes in patients with cGVHD who failed ≥1 previous therapy. The CR rate increased from 21% to 31%, and the ≥32-week sustained response rate increased from 48% to 62% with continued follow-up [10]. 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 [12]. This is an important clinical benefit with ibrutinib given the numerous serious side effects of corticosteroids, including infection, avascular necrosis, hypertension, poor glycemic control, mood swings, osteoporosis, and weight gain [12,13].

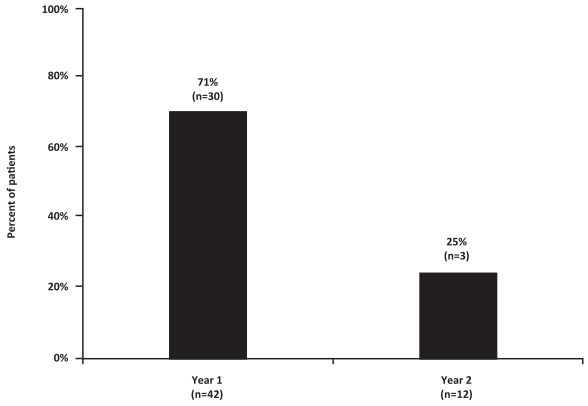

Figure 3. Decreasing frequency of grade ≥3 TEAEs over time.

Sclerotic manifestations represent a challenging aspect of managing cGVHD. Patients with sclerotic manifestations of cGVHD experience functional impairment and report significantly more changes in skin color, skin thickness, and joint stiffness compared with patients without sclerotic cGVHD [14]. Recognizing that improvements in sclerosis may require a longer duration of treatment than was captured in the original analysis, it is notable that more than half of patients with sclerosis in this study had clinically meaningful improvement in sclerosis with ibrutinib treatment with longer follow-up.

Quality of life is substantially impaired in patients with cGVHD [15–17]. The Lee cGVHD Symptom Scale assesses patient-perceived cGVHD symptom burden by evaluating the impact of disease manifestations [18]. Collection of the Lee cGVHD Symptom Scale total summary score continued during the follow-up period, with more than half of responders reporting improvement. Improvement in Lee cGVHD Symptom Scale scores supports the high rate of CR observed and demonstrates the patient-perceived benefit of ibrutinib's effects on reducing symptom burden.

Safety findings for this updated analysis were consistent with the original analysis. No new or unexpected findings were observed. Most AEs were of low-grade severity and consistent with the known tolerability profile of ibrutinib. Common AEs—fatigue, diarrhea, muscle spasms, nausea, and bruising—were consistent with previously reported observations in patients with B-cell malignancies and patients with cGVHD treated with corticosteroid-containing therapies [9,19–22]. Rates of AEs were not higher in patients also receiving CYP3A inhibitors and other

immunosuppressants, suggesting that ibrutinib can be used safely in patients with cGVHD concomitantly taking CYP3A inhibitors or immunosuppressants. Although atrial fibrillation and major hemorrhage have been associated with ibrutinib treatment for B-cell malignancies, no major hemorrhage was observed in this study, and only 1 patient experienced atrial fibrillation, in association with multilobular pneumonia [20,23,24]. With additional follow-up, there were no new fatal TEAEs. In the initial report, [10] 2 fatal TEAEs occurred, 1 due to pneumonia (etiology, *Enterococcus*) and the other due to bronchopulmonary aspergillosis. The patient with bronchopulmonary aspergillosis had a history of fungal pneumonia and was not on anti-fungal prophylaxis. During ibrutinib treatment, patients at risk for opportunistic infection should receive standard-of-care prophylaxis as appropriate and be monitored for infection [9,19]. When medically necessary, anti-infective therapy should be administered accordingly [9,19].

Limitations of this analysis include the open-label design and lack of comparator group. It is also possible that reduced doses of prednisone would have been observed in some patients over time without treatment with ibrutinib. However, patients enrolled in this study were steroid-dependent or -refractory and had been unable to maintain a reduced steroid dose despite previous attempts. Therefore, the reduction in steroid doses observed herein, together with the acceptable tolerability and sustained responses observed with longer-term follow-up, are clinically meaningful and demonstrate a substantial advance in the therapeutic management of patients with cGVHD.

Several questions remain concerning the role of ibrutinib in the treatment landscape for cGVHD. The mechanism of action of ibrutinib in treating steroid-dependent or -refractory cGVHD was initially postulated to involve inhibition of BTK in B cells, leading to reduced production of autoreactive antibodies or inhibition of a homologous enzyme in T cells, interleukin-2-inducible T cell kinase (ITK), leading to selective suppression of Th2 immune responses that may contribute to the pathogenesis of cGVHD [25,26]. Given that the half maximal inhibitory concentration (IC_{50}) of ibrutinib for BTK is 1.5 nM, compared with 4.9 nM for ITK, the clinical efficacy of ibrutinib in treating steroid-refractory cGVHD could be due to BTK inhibition, ITK inhibition, or targeting of enzymatic pathways in both B cells and T cells [27]. The duration of ibrutinib therapy for cGVHD is unknown at this time. It is reassuring that our patients who discontinued ibrutinib did not experience worsening cGVHD or a flare in symptoms (data not shown), and thus there does not seem to be a need to taper ibrutinib. The mechanism of sustained efficacy that developed in patients treated with ibrutinib in whom treatment could be discontinued while maintaining response is of great interest and also remains to be defined. Notably, patients with the most consistent and durable responses to ibrutinib in this study included those with sclerosis, a pathological condition postulated to be mediated in part by Th2-polarized T cells. Ibrutinib is currently being evaluated in the frontline cGVHD setting in the INTEGRATE Phase 3 study (PCYC-1140-IM; ClincalTrials.gov identifier NCT02959944) comparing ibrutinib in combination with corticosteroids versus placebo with corticosteroids in patients with new-onset cGVHD. In this Phase 3 study, patients responding to treatment are able to discontinue ibrutinib after a minimum of 48 weeks of therapy. Finally, in the present study, patients had received ≤3 previous therapeutic regimens for cGVHD, and thus the potential role of ibrutinib in patients with highly resistant disease (ie, failed more than 3 previous regimens) is unknown. As additional evidence for current and emerging therapies expands, the outlook for patients with cGVHD is promising and will continue to evolve as additional evidence is collected.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bbmt.2019.06.023.

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