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Ibrutinib as Treatment for Patients With Relapsed/Refractory Follicular Lymphoma: Results From the Open-Label, Multicenter, Phase II DAWN Study

Ajay K. Gopal, Stephen J. Schuster, Nathan H. Fowler, Judith Trotman, Georg Hess, Jing-Zhou Hou, Abdulraheem Yacoub, Michael Lill, Peter Martin, Umberto Vitolo, Andrew Spencer, John Radford, Wojciech Jurczak, James Morton, Dolores Caballero, Sanjay Deshpande, Gary J. Gartenberg, Shean-Sheng Wang, Rajendra N. Damle, Michael Schaffer, Sriram Balasubramanian, Jessica Vermeulen, Bruce D. Cheson, and Gilles Salles

Author affiliations and support information (if applicable) appear at the end of this article.

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Corresponding author: Ajay K. Gopal, MD, Seattle Cancer Care Alliance, 825 Eastlake Ave E #G3200, Seattle, WA 98109; e-mail: agopal@u.washington.edu.

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ABSTRACT

Purpose
The Bruton's tyrosine kinase inhibitor ibrutinib has demonstrated clinical activity in B-cell malignancies. The DAWN study assessed the efficacy and safety of single-agent ibrutinib in chemoimmunotherapy relapsed/refractory follicular lymphoma (FL) patients.

Methods
DAWN was an open-label, single-arm, phase II study of ibrutinib in patients with FL with two or more prior lines of therapy. Patients received ibrutinib 560 mg daily until progressive disease/unacceptable toxicity. The primary objective was independent review committee–assessed overall response rate (ORR; complete response plus partial response). Exploratory analyses of T-cell subsets in peripheral blood (baseline/cycle 3) and cytokines/chemokines (baseline/cycle 2) were performed for available samples.

Results
Between March 2013 and May 2016, 110 patients with a median of three prior lines of therapy were enrolled. At median follow-up of 27.7 months, ORR was 20.9% (95% CI, 13.7% to 29.7%, which did not meet the 18% lower-bound threshold for the primary end point). Twelve patients achieved a complete response (11%; 95% CI, 5.8% to 18.3%). Median duration of response was 19.4 months (range, 1 to ≥ 33 months), with a median progression-free survival of 4.6 months and a 30-month overall survival of 61% (95% CI, 0.51% to 0.70%). Lymphoma symptoms resolved in 67%. Seven of 32 patients who experienced initial radiologic progression responded upon continuing therapy (pseudoprogression). The most common adverse events were diarrhea, fatigue, cough, and muscle spasms; 48.2% of patients reported serious adverse events. In patients who experienced a response, regulatory T cells were downregulated at C3D1 ($P = .02$), and Th1-promoting (antitumor) cytokines interferon-γ and interleukin-12 increased ($P \leq .035$).

Conclusion
With an ORR of 20.9%, ibrutinib failed to meet its primary efficacy end point in chemoimmunotherapy in patients with relapsed/refractory FL, although responses were durable and associated with a reduction in regulatory T cells and increases in proinflammatory cytokines.

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ASSOCIATED CONTENT

Data Supplements
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INTRODUCTION

Follicular lymphoma (FL) is the second most common non-Hodgkin lymphoma, comprising 17% to 22% of cases.[1,2] Most patients who are diagnosed with FL initially receive chemoimmunotherapy (CIT) or rituximab[3]; however, despite good initial responses to CIT, FL is incurable in most patients and relapse generally occurs,[4] with poor outcomes after early relapse or CIT-resistant disease.[5]

Therapies that target B-cell receptor (BCR) pathway components, such as spleen tyrosine kinase, phosphatidylinositol 3-kinase, and Bruton's tyrosine kinase (BTK), which are involved in various B-cell malignancies, are being developed.[6] Ibrutinib (Imbruvica; Pharmacyclics, Sunnyvale, CA, and Janssen Biotech, Horsham, PA) covalently binds cysteine 481 on the BTK enzyme and has demonstrated clinical activity in B-cell malignancies, including chronic lymphocytic leukemia (CLL), Waldenström macroglobulinemia, mantle-cell lymphoma, and marginal-zone lymphoma.[7,8] Preliminary data indicate that ibrutinib can yield response rates that range from 25% to 63% in patients with relapsed FL.[9-11]

Data also exist that suggest that the tumor microenvironment may contribute to the development and progression of FL, and the interaction of FL cells with immune cells in the tumor may influence the clinical course and response to therapy.[12,13] Ibrutinib seems to exert immunomodulatory effects on T-cell activity via the inhibition of interleukin-2 (IL-2) –inducible T-cell kinase (ITK), a key regulator of T-cell activity, possibly through the inhibition of T-helper 2 (Th2) –polarized CD4 T cells and activation of Th1 cells.[14] Interferon-γ (IFN-γ)–secreting Th1-type cells are thought to promote antitumor cellular immunity, whereas Th2-type cells may lead to immune suppression and tumor evasion.[15]

On the basis of the safety and efficacy of ibrutinib in other B-cell malignancies, preliminary data in FL, and the potential additional immune mechanism of action of ibrutinib, we conducted this pivotal trial of ibrutinib in patients with CIT-resistant FL.

METHODS

Patients

This study enrolled patients age 18 years or older with a diagnosis of grade 1, 2, or 3a nontransformed FL who had been treated with two or more prior lines of therapy and were refractory or had experienced relapse on the last prior line of therapy with an anti-CD20 monoclonal antibody–containing CIT regimen. Full inclusion and exclusion criteria are presented in the Data Supplement. Patients who did not meet inclusion/exclusion criteria were not enrolled.

The study was conducted in accordance with International Conference on Harmonisation Good Clinical Practice guidelines and was approved by an independent institutional review board. All patients provided written informed consent.

Study Design

This open-label, multicenter, single-arm, phase II study of ibrutinib enrolled patients with CIT-relapsed/refractory FL across 45 centers in 10 countries.

An overview of the study design is presented in the Data Supplement. Eligible patients received ibrutinib 560 mg—four 140-mg capsules—orally once per day until disease progression or unacceptable toxicity. For the first toxicity event (absolute neutrophil count $< 500/mm^3$; platelets $< 25{,}000/mm^3$; platelets $< 50{,}000/mm^3$ with grade $\geq$ 2 bleeding; grade 3 or 4 nausea, vomiting, or diarrhea; grade 4 toxicities; or unmanageable grade 3 drug-related toxicities), ibrutinib treatment was suspended until recovery to grade 1 or less or baseline ($\leq$ 21 consecutive days), then resumed. For the second and third occurrence, ibrutinib was suspended until recovery, then resumed at a lower dose (420 mg and 280 mg per day for the second and third events, respectively). Ibrutinib was discontinued if an event occurred a fourth time.

Concomitant administration of hematopoietic growth factors and supportive care therapies was permitted. To allow for the possibility of including patients who exhibited tumor flare (pseudo–progressive disease [PD]) and delayed responses, the protocol was amended in January 2014 to enable patients with radiologic evidence of PD who were clinically stable or improving or who had signs of tumor flare without confirmation of PD by positron emission tomography (PET) or biopsy to remain on ibrutinib upon investigator request and sponsor approval.[16]

Study Assessments and End Points

Efficacy evaluations included computed tomography scans; magnetic resonance imaging; ^{18}F-labeled fluorodeoxyglucose PET; bone marrow biopsy; physical assessment, including lymphoma-B symptoms; and Eastern Cooperative Oncology Group performance status. Lymphoma-related B symptoms and other lymphoma-related symptoms were assessed at baseline and at each visit. Disease evaluations were performed at screening, every 12 weeks (±7 days) for 96 weeks, then every 24 weeks (± 14 days) until disease progression or 24 months after the last patient was enrolled.

The primary end point of the study was the overall response rate (ORR; complete response [CR] plus partial response [PR]) as assessed by an independent review committee, determined using standard criteria.[17] Patients with confirmed response after pseudo-PD were considered responders and were included in the ORR. Date of progression for patients who continued therapy after PD and did not later have a confirmed response was that of initial PD. Duration of response (DOR), time to response, progression-free survival (PFS), overall survival (OS), time to next therapy (TTNT), and resolution of lymphoma-related symptoms were included as secondary end points. Biomarkers were an exploratory analysis. All biomarker assessments and clinical laboratory tests were analyzed by a central laboratory. Data to describe the safety profile were collected.

Statistical Methods

Sample size was determined to achieve > 85% power to declare the lower bound of the 95% CI of the ORR to exceed 18%, assuming an ORR of 30% for ibrutinib treatment. The all-treated population that was evaluated for primary efficacy and safety included all patients who received at least one dose of the study medication. Patients were described as refractory to the previous line of therapy if they experienced a failure to achieve at least PR to the prior line of therapy or as relapsed if they experienced disease progression $\leq$ 12 months after achieving response with the prior regimen.

OS and PFS were analyzed in the all-treated population, and patients who experienced events after the start of subsequent therapy or those with no event at the clinical cutoff were censored to the last assessment before subsequent therapy. Response distribution was evaluated using the Kaplan-Meier method. Sensitivity analyses were performed using investigator assessment without censoring at subsequent therapy if initiated before disease progression. For time to response and resolution of lymphoma-related B symptoms, descriptive summaries are presented. Statistical analyses were performed using SAS (SAS/STAT User's Guide, Version 9.1; SAS Institute, Cary, NC).

Biomarker Analyses

T-cell subsets in peripheral blood were assessed via flow cytometry at baseline (cycle 1, day 1) and at cycle 3, day 1 (markers included in the Data Supplement). Cytokine/chemokine analysis was performed at cycle 1, day 1 and at cycle 2, day 1 using the SomaLogic SOMAscan Assay (Boulder, CO). Differences in biomarkers between responder subgroups were compared via post hoc analysis using Wilcoxon rank sum test.

RESULTS

Patient Characteristics

Between March 2013 and May 2016, 110 patients who received at least one dose of ibrutinib were included in the analysis (Data Supplement). Patient baseline demographic and disease characteristics are listed in Table 1. Median age was 61.5 years (range, 28 to 87 years), and the majority of patients were male (61%). A total of 64 (58%) of 110 patients had a high (three or

Table 1. Demographics and Baseline Characteristics

Demographic or Characteristic	All Treated (N = 110)
Median age (range), years	61.5 (28.0-87.0)
Male sex	67.0 (60.9)
ECOG performance status	
0	55.0 (50.0)
1	55.0 (50.0)
FL stage	
I	4.0 (3.6)
II	14.0 (12.7)
III	32.0 (29.1)
IV	60.0 (54.5)
FLIPI score	
0-1	21.0 (19.1)
2	25.0 (22.7)
3-5	64.0 (58.2)
Largest tumor ≤ 6 cm	89.0 (80.9)
Median (range) prior lines of therapy	3.0 (2.0-13.0)
LDH > upper limit of normal	49.0 (44.5)
Relapsed within 12 months of prior line of therapy after PR or better	65.0 (59.1)
Prior regimen to which patients were refractory* or relapsed within 6 months	45.0 (40.9)
Rituximab	94.0 (85.5)
Alkylating agent	63.0 (57.3)
Both	63.0 (57.3)

NOTE. Data presented as No. (%) unless otherwise indicated.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; PR, partial response.
*Refractory disease was defined as a failure to achieve at least a partial response to the last regimen before study entry.

more risk factors) FL international prognostic index score.[18] Patients had received a median of three (range, two to 13) prior lines of therapy, and 59% had experienced relapse (relapse/disease progression within 12 months after achieving at least a PR), whereas 41% of patients were refractory to the prior line of therapy, which was defined as having experienced a failure to achieve at least a PR to the last prior treatment. For the last prior line of therapy, median TTNT was 10.0 months (95% CI, 8.6 to 11.6 months), median PFS was 7.4 months (95% CI, 6.3 to 8.6 months), and 85% of patients (94 of 110) experienced relapse or progression within 6 months. Patients were observed for a median of 27.7 months (range, 1.1 to 37.1 months). Patient disposition is presented in Table 2.

Patient Outcomes

Overall, 23 of 110 patients experienced a response to ibrutinib treatment, with an ORR of 20.9% (95% CI, 13.7% to 29.7%), of which 12 patients (11%; 95% CI, 5.8% to 18.3%) had a CR. The study did not meet its primary objective, predefined as an ORR with the lower bound of the 95% CI of > 18%. Median time to initial response was 5.7 months (range, 2.6 to 13.8 months) with a median DOR of 19.4 months (range, 1 to ≥ 33 months), and 33% (36 of 110) of patients experienced stable disease (SD) or better for ≥ 6 months. Figure 1A illustrates the 66% of patients with a reduction in target tumor size. ORR was identical when assessed via PET versus computed tomography scan.

A descriptive subgroup analysis demonstrated that ORR did not differ substantially across age, sex, race, geographic region, prior lines of therapy, baseline Eastern Cooperative Oncology Group performance status, baseline FL histology grade, lymphoma symptoms at baseline, and prior bendamustine treatment, with the exception of patients with bulk > 6-cm or extranodal disease (Data Supplement). A post hoc analysis determined an ORR of 21% (20 of 94) among patients who had not achieved a response or who had experienced progression within 6 months of prior CIT. In addition, ORRs for patients who were refractory to rituximab and/or alkylator therapy were similar to that of the overall study population.

To account for the possibility of tumor flare or delayed response, 32 patients without clinical signs of progression were permitted to continue receiving ibrutinib after initial radiographic evidence of disease progression. Among these patients, seven (23%) had independent review committee–confirmed response—four CR and three PR—after remaining on therapy at a median of 22.0 weeks (range, 11.6 to 59.6 weeks) after starting ibrutinib. Of seven patients with pseudo-PD, three—two CR and one PR—patients maintained their response for > 1 year and two have continued to respond for > 27 months.

Median TTNT was 16.0 months (95% CI, 10.7 to 19.1 months), and 2 years after initiating ibrutinib treatment, 34% (95% CI, 0.25% to 0.44%) of patients did not require subsequent anticancer therapy. Median PFS was 4.6 months (95% CI, 2.8 to 5.5 months; Fig 1B), with a PFS rate at 30 months of 11% (95% CI, 0.05% to 0.18%). Median OS was not reached after 27.7 months of follow-up (Fig 1C). The 12-month OS was 78% (95% CI, 0.69% to 0.85%), whereas the 30-month OS was 61% (95% CI, 0.51% to 0.70%).

Among 39 patients with lymphoma-related symptoms at baseline, resolution of symptoms was observed in two thirds of patients (26 patients [67%]), with a median time to resolution of 0.7 months (95% CI, 0.7 to 1.4 months). Symptom resolution lasted a median of 10.4 months (95% CI, 6.5 months to not estimable). Eight patients achieved a clinical response of PR or better (five CR and three PR, including three with pseudo-PD), 10 had SD, and eight had PD.

Biomarker Analyses

Data on T-cell subsets were obtained from 14 (61%) of 23 patients who achieved a response (CR + PR) and 43 (49%) of

Table 2. Patient Disposition

Patient Status	Ibrutinib (N = 110)
Median treatment duration (range), months	7.0 (1.0-37.0)
Median duration of follow up (range), months	27.7 (1.1-37.1)
Patients with prescribed dose reductions	1.0 (0.9)
Reason for dose reduction	
Neutropenia	1.0 (0.9)
Study treatment phase disposition	
Discontinued study treatment	110.0 (100.0)
Primary reason for discontinuation	
Progressive disease or relapse	72.0 (65.5)
Rolled into long-term extension study (NCT01804686)	13.0 (11.8)
Physician decision	10.0 (9.1)
Death	4.0 (3.6)
Lost to follow-up	1.0 (0.9)
Adverse event	7.0 (6.4)
Withdrawal of consent	3.0 (2.7)

NOTE. Data presented as No. (%) unless otherwise indicated.

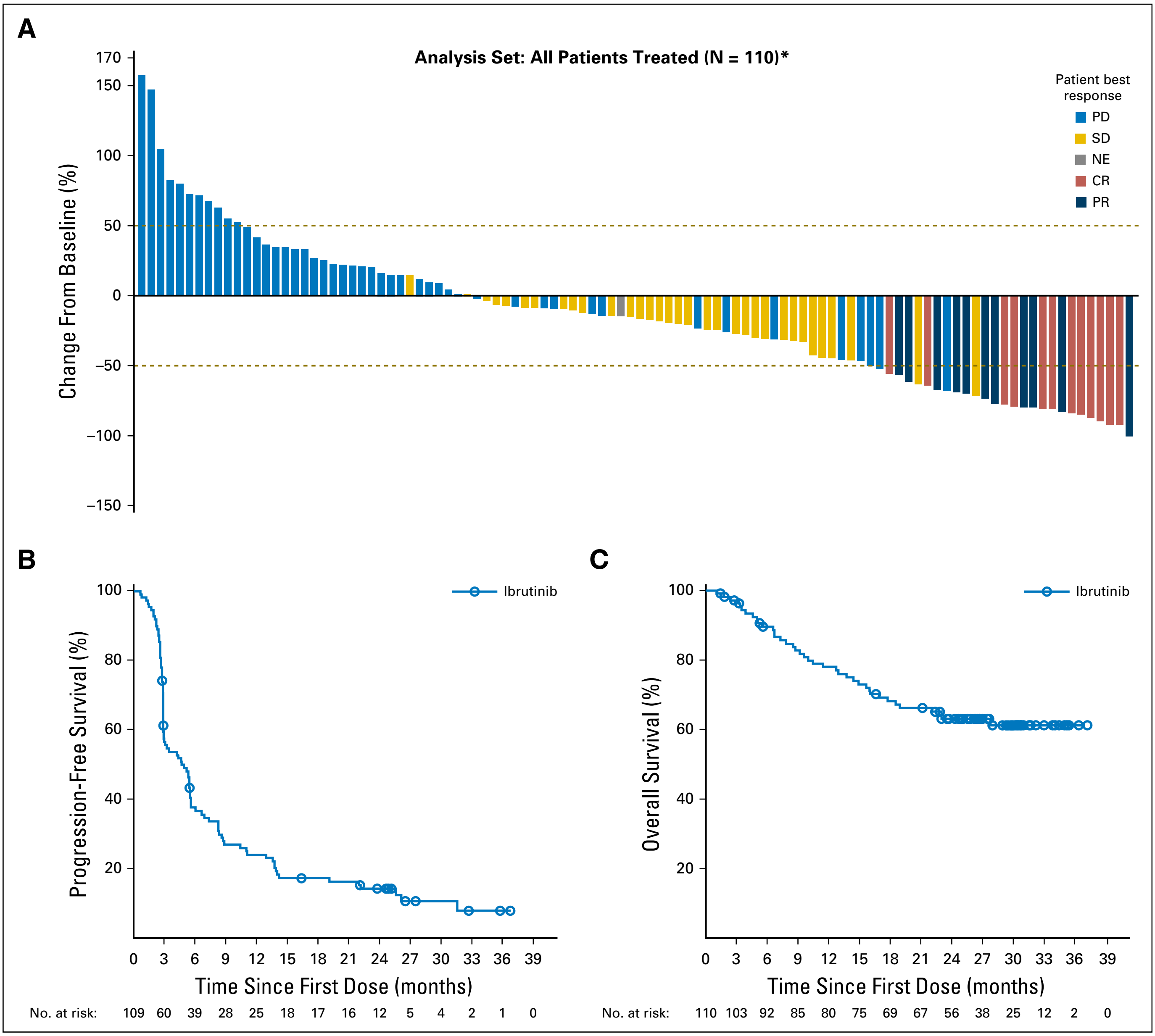

Fig 1. (A) Percent change in tumor size, and Kaplan-Meier curves for (B) progression-free survival and (C) overall survival. CR, complete response; NE, not estimable; PD, progressive disease; PR, partial response; SD, stable disease. (*)Patients in the independent review committee–assessed, all-treated population with both baseline and at least one postbaseline tumor measurement were included.

87 patients who did not achieve a response (SD + PD). T-cell subset analysis revealed significant downregulation of $CD4^{+}CD25^{+}CD127^{-}$ regulatory T-cells (T_{regs}) at cycle 3, day 1 in responders (mean decrease from 17% to 13% of CD4; *P* = .02), but not in nonresponders (12% to 10% of CD4; *P* = .17; Fig 2A). Cytokine analyses performed on samples from 21 (91%) of 23 responders and 29 (33%) of 87 nonresponders found that Th1-promoting cytokines IFN-γ and IL-12 were significantly increased in responders but not in nonresponders (Fig 2B). Specifically, IFN-γ demonstrated a mean increase of 19% in responders versus an 18% decrease in nonresponders at cycle 2, day 1 (*P* = .0025), whereas IL-12 had a mean increase of 7% in responders and a decrease of 6% in nonresponders (*P* = .035). IL-10 demonstrated an increase of 4% in nonresponders versus a decrease of 3% in responders (*P* = .077). IL-4 had a mean increase of 15% in responders versus a decrease of 8% in nonresponders (*P* = .016). Significant changes in inflammatory chemokines included decreases of 13% and 11% in IFN-γ inducible protein 10 kDa (IP-10) and monocyte chemotactic protein 3 (MCP-3), respectively, in responders versus increases of 42% and 11%, respectively, in nonresponders (*P* = .021 and .016, respectively). In samples that were available from six patients with pseudo-PD, IFN-γ and IL-10 changes at cycle 2, day 1 tended to resemble those in nonresponders, whereas changes in IP-10 and MCP-3 were similar to those observed in responders (Table 3).

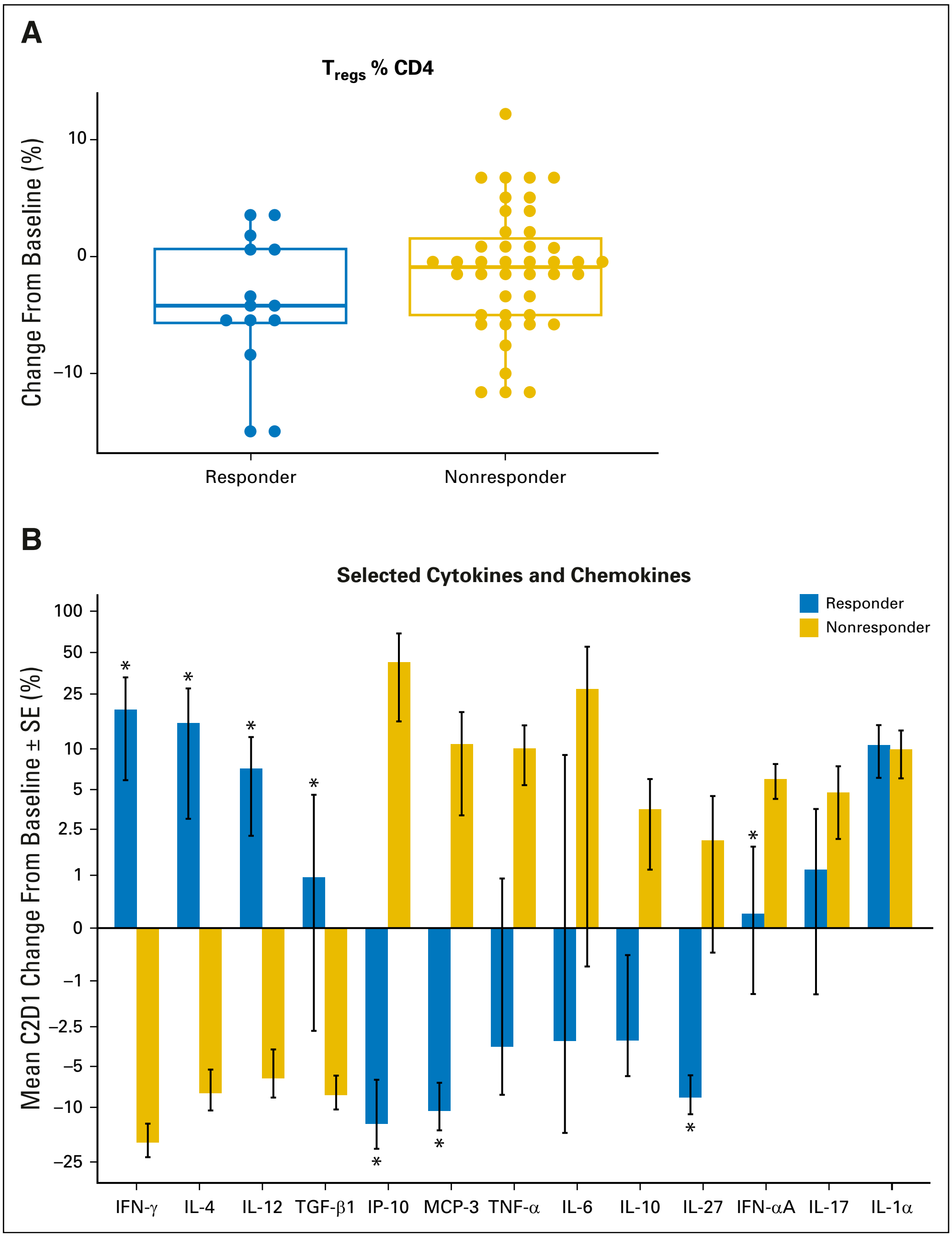

Fig 2. Changes in (A) $CD4^{+}CD25^{+}CD127^{-}$ regulatory T cells (T_{regs}) and (B) cytokines among responders and nonresponders. C2D1, cycle 2, day 1; IFN, interferon; IL, interleukin; IP, interferon-γ–induced protein; MCP, monocyte chemotactic protein; TGF, tumor growth factor.

Treatment Exposure and Safety

Ibrutinib treatment was continued for a median duration of 7.0 months (range, 1 to 37 months) at a mean daily dose of 539 mg (standard deviation, 40.6 mg). Treatment-emergent adverse events were reported in 107 patients (97%), and the most commonly reported adverse events (AEs; ≥ 10% of patients) are summarized in Table 4. Grade 3 or worse AEs occurred in 68 patients (62%; Data Supplement). AEs that occurred in ≥ 5% of patients are presented by toxicity grade in the Data Supplement.

Seven patients (6%) reported AEs as the primary reason of discontinuation, with subdural hematoma that led to discontinuation in two patients (2%). One patient required a dose reduction as a result of neutropenia.

Serious AEs were reported in 53 patients (48%), the most common (≥ 2% of patients) of which were pneumonia and pyrexia (seven patients each [6%]), pleural effusion (four patients [4%]), and sepsis, atrial fibrillation (AF), and diarrhea (three patients each [3%]). Eight patients (7%) died during the study, including three deaths as a result of AEs either during treatment or within 30 days of the last dose of the study drug. The two cases of AEs that led to death that were possibly related to ibrutinib were neutropenic sepsis and pneumonia; death unrelated to ibrutinib was because of embolism. AEs of special interest included major hemorrhage in four patients (4%), and one patient (1%) each reported subdural hematoma and cerebral hemorrhage, subdural hematoma after a head injury, an infected hematoma, and postprocedural hemorrhage. Grade ≥ 3 infections and infestations occurred in

Table 3. Percent Change From Baseline in Selected Cytokines and Chemokines Among Responders, Nonresponders, and Pseudo-PD Patients

Cytokine	Responders (n = 21)	Nonresponders (n = 29)	Pseudo-PD Patients (n = 6)
IFN-γ	19.4 (61.8) *P* = .002	−18.1 (26.6)	−19.7 (17.5)
IL-4	15.2 (55.7) *P* = .016	−7.9 (14.1)	31.3 (103.0)
IL-12	7.2 (22.5) *P* = .035	−6.1 (12.8)	0.7 (30.5)
TGF-β1	1.0 (16.7) *P* = .046	−8.1 (12.0)	−11.7 (11.7)
IP-10	−13.1 (31.4) *P* = .022	42.2 (142)	−17.3 (31.2)
MCP-3	−10.6 (18.5) *P* = .016	10.8 (40.7)	−10.6 (23.5)
TNF-α	−3.6 (20.6) *P* = .099	10.0 (25.1)	11.2 (7.0)
IL-6	−3.2 (55.7) *P* = .640	27.1 (150.0)	20.8 (85.6)
IL-10	−3.2 (12.4) *P* = .077	3.6 (13.1)	4.0 (13.1)
IL-27	−8.5 (12.2) *P* = .007	2.0 (13.2)	−10.1 (18.5)
IFN-αA	0.2 (7.2) *P* = .017	6.0 (9.2)	4.7 (8.1)
IL-17	1.1 (11.3) *P* = .495	4.8 (14.2)	9.5 (4.5)
IL-1α	10.5 (20.0) *P* = .969	9.8 (19.9)	20.1 (26.0)

NOTE. Data are given as mean percent change (standard deviation), unless otherwise noted.
Abbreviations: IFN, interferon; IL, interleukin; IP, interferon-γ–induced protein; MCP, monocyte chemotactic protein; PD, progressive disease; TGF, tumor growth factor.

25 patients (23%). AF occurred in 10 patients (9%), of which four (4%) were grade ≥ 3. Tumor lysis syndrome was reported in one patient (1%).

DISCUSSION

Here, we show that single-agent ibrutinib produced a response in approximately 21% of patients with CIT relapsed/refractory FL. Whereas the study did not achieve its primary objective and the data from this trial are less impressive compared with results observed using ibrutinib for the treatment of CLL, marginal-zone lymphoma, and mantle-cell lymphoma,[19-23] secondary end points, such as a median DOR of 19.4 months, a disease control rate (ORR + SD for ≥ 6 months) of 33%, and a lymphoma symptom resolution rate of 67% suggest benefits of this therapy in some patients. Preclinical data have demonstrated that the phosphorylation of BCR signaling nodes and sensitivity to α-BCR vary dramatically between B-cell lymphoma subtypes, and these findings are associated with sensitivity to BTK-mediated killing.[24] Specifically, a subset of tumor cells within FL has been shown to demonstrate an absence of BCR signaling and resistance to agents that target the BCR signaling pathway.[25] This BCR-resistant clone seems to increase after chemotherapy, potentially explaining the modest efficacy we observed in our trial of patients who were precisely selected on the basis of CIT resistance. These data may also imply that less heavily pretreated FL that contains a greater fraction of tumor cells with active BCR signaling could demonstrate increased sensitivity to ibrutinib.

Ibrutinib treatment tolerability was consistent with previous studies, with 6% of patients discontinuing as a result of toxicity and only one patient requiring dose reduction. Recommendations for patient monitoring and dose adjustments for AEs in the protocol were consistent with US prescribing information, and, given the lack of any new safety signals in this study, no additional considerations emerged for patients with FL treated with ibrutinib.[7] As in previously reported studies of ibrutinib,[22] the majority of AEs was grade 1 and 2, and comparable rates of AF were observed.

We also investigated potential biomarkers at baseline and early in treatment to better understand the potential biologic effect of ibrutinib in FL. No baseline markers that were predictive for response could be identified. Downregulation of T_{regs} after the start of ibrutinib therapy was observed only in patients who achieved a response, which is consistent with previous reports of ibrutinib treatment in patients with CLL that resulted in the downregulation of T_{regs} and a reduction of immune checkpoint protein programmed death-1 expression, which may promote the recovery of normal immune function.[26,27]

Ibrutinib may exert these immunomodulatory effects and prevent tumor-promoting signaling from the microenvironment via inhibition of ITK, a key regulator of T-cell activity. Ibrutinib has

Table 4. Most Common (≥ 10%) Adverse Events

Adverse Event, No. (%)	Safety Analysis Population (N = 110) Grade 1 and 2	Grade 3 and 4	Grade 5
Diarrhea	51.0 (46.4)	5.0 (4.5)	0.0
Fatigue	38.0 (34.5)	6.0 (5.5)	0.0
Cough	39.0 (35.5)	0.0	0.0
Muscle spasms	35.0 (31.8)	0.0	0.0
Nausea	31.0 (28.2)	1.0 (0.9)	0.0
Peripheral edema	30.0 (27.3)	1.0 (0.9)	0.0
Pyrexia	25.0 (22.7)	2.0 (1.8)	0.0
Anemia	15.0 (13.6)	10.0 (9.1)	0.0
Thrombocytopenia	16.0 (14.5)	5.0 (4.5)	0.0
Headache	18.0 (16.4)	1.0 (0.9)	0.0
Upper respiratory tract infection	18.0 (16.4)	1.0 (0.9)	0.0
Rash	18.0 (16.4)	0.0	0.0
Decreased appetite	16.0 (14.5)	0.0	0.0
Neutropenia	1.0 (0.9)	15.0 (13.6)	0.0
Vomiting	15.0 (13.6)	0.0	0.0
Asthenia	13.0 (11.8)	1.0 (0.9)	0.0
Back pain	14.0 (12.7)	0.0	0.0
Constipation	14.0 (12.7)	0.0	
Dyspnea	11.0 (10.0)	3.0 (2.7)	0.0
Hypokalemia	11.0 (10.0)	3.0 (2.7)	0.0
Insomnia	14.0 (12.7)	0.0	0.0
Abdominal pain	11.0 (10.0)	2.0 (1.8)	0.0
Platelet count decreased	10.0 (9.1)	3.0 (2.7)	0.0
Pruritus	12.0 (10.9)	1.0 (0.9)	0.0
Bronchitis	12.0 (10.9)	0.0	0.0
Dizziness	12.0 (10.9)	0.0	0.0
Chills	11.0 (10.0)	0.0	0.0
Dry mouth	11.0 (10.0)	0.0	0.0
Myalgia	11.0 (10.0)	0.0	0.0
Pain in extremity	10.0 (9.1)	1.0 (0.9)	0.0
Pneumonia	3.0 (2.7)	7.0 (6.4)	1.0 (0.9)
Sinusitis	11.0 (10.0)	0.0	0.0

been demonstrated to repolarize $CD4^+$ T cells from Th2 to Th1, possibly by inhibiting ITK, upon which Th2 cells are uniquely dependent for activation.[14] This was confirmed by recent results in patients with CLL that suggested that ibrutinib may promote Th1 selection and switch to an adaptive response.[28]

Similarly, Th1-promoting cytokines, IFN-γ and IL-12, were significantly increased only in patients who achieved a response, which suggests that response to ibrutinib in FL could be related to its T-cell immunomodulatory effects, which have also been observed in the post–allogeneic transplantation setting.[14,29]

Ibrutinib treatment also produced significant decreases in responders in MCP3 (also known as CCL7) and IP-10 (also known as CXCL10), which have been implicated in tumor development.[30] These results, along with a clinical observation of pseudoprogression in some patients, suggest that the immunomodulatory effects of ibrutinib may be linked to a response to therapy. These hypothesis-generating findings must be confirmed by analysis of tumor samples and explained in light of data that indicate that BTK inhibition may be effective in the treatment of graft-versus-host disease.[25,31,32]

This study provides critical insights into the differential biology of BTK inhibition in various B-cell malignancies and raises important questions about the broader effect of this strategy on the immunologic milieu of malignancy. The results of this study do not support ibrutinib monotherapy for patients with relapsed/refractory FL; however, some patients experienced prolonged remission durations and symptom relief with no new safety signals. The relative clinical benefit of ibrutinib in FL will be further defined in ongoing phase III trials of chemoimmunotherapy with or without ibrutinib (ClinicalTrials.gov identifier: NCT01974440) in the relapsed/refractory setting and rituximab-ibrutinib versus rituximab monotherapy in treatment-naïve patients with FL (ClinicalTrials.gov identifier: NCT02947347). Additional biomarker studies may identify patients who may benefit from ibrutinib treatment, and the results of ongoing studies of combination therapies may identify effective treatment regimens. The effect of augmenting the potential immunomodulatory effect of ibrutinib is also being explored in combination with immune checkpoint inhibitors in patients with non-Hodgkin lymphoma (ClinicalTrials.gov identifier: NCT02950220 and NCT02332980). These data provide the foundation for a better understanding of the biology and clinical role of BTK inhibition in B-cell malignancies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Ajay K. Gopal, Stephen J. Schuster, Nathan H. Fowler, Georg Hess, Jing-Zhou Hou, Abdulraheem Yacoub, Michael Lill, Peter Martin, Umberto Vitolo, Wojciech Jurczak, James Morton, Dolores Caballero, Sanjay Deshpande, Gary J. Gartenberg, Shean-Sheng Wang, Michael Schaffer, Sriram Balasubramanian, Jessica Vermeulen, Bruce D. Cheson, Gilles Salles
Provision of study materials or patients: Ajay K. Gopal, Stephen J. Schuster, Nathan H. Fowler, Judith Trotman, Georg Hess, Jing-Zhou Hou, Abdulraheem Yacoub, Michael Lill, Peter Martin, Umberto Vitolo, Andrew Spencer, John Radford, Wojciech Jurczak, James Morton, Dolores Caballero, Sanjay Deshpande, Gary J. Gartenberg, Shean-Sheng Wang, Jessica Vermeulen, Bruce D. Cheson, Gilles Salles
Collection and assembly of data: Ajay K. Gopal, Stephen J. Schuster, Nathan H. Fowler, Judith Trotman, Georg Hess, Jing-Zhou Hou, Abdulraheem Yacoub, Michael Lill, Peter Martin, Umberto Vitolo, Andrew Spencer, John Radford, Wojciech Jurczak, James Morton, Dolores Caballero, Sanjay Deshpande, Gary J. Gartenberg, Shean-Sheng Wang, Rajendra N. Damle, Michael Schaffer, Sriram Balasubramanian, Jessica Vermeulen, Bruce D. Cheson, Gilles Salles
Data analysis and interpretation: Ajay K. Gopal, Stephen J. Schuster, Nathan H. Fowler, Judith Trotman, Georg Hess, Jing-Zhou Hou, Abdulraheem Yacoub, Michael Lill, Peter Martin, Umberto Vitolo, Andrew Spencer, John Radford, Wojciech Jurczak, James Morton, Dolores Caballero, Sanjay Deshpande, Gary J. Gartenberg, Shean-Sheng Wang, Rajendra N. Damle, Michael Schaffer, Sriram Balasubramanian, Jessica Vermeulen, Bruce D. Cheson, Gilles Salles
Manuscript writing: All authors
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Affiliations

Ajay K. Gopal, The University of Washington; **Ajay K. Gopal**, Fred Hutchinson Cancer Research Center, Seattle, WA; **Stephen J. Schuster**, Abramson Cancer Center of the University of Pennsylvania, Philadelphia; **Jing-Zhou Hou**, University of Pittsburgh Medical Center; **Jing-Zhou Hou**, University of Pittsburgh Cancer Institute, Pittsburgh; **Rajendra N. Damle**, **Michael Schaffer**, and **Sriram Balasubramanian**, Janssen Research & Development, Spring House, PA; **Nathan H. Fowler**, The University of Texas MD Anderson Cancer Center, Houston, TX; **Judith Trotman**, Concord Hospital, University of Sydney, Sydney, New South Wales; **Andrew Spencer**, Alfred Hospital-Monash University, Melbourne, Victoria; **James Morton**, Haematology and Oncology Clinics of Australia, Milton, Queensland, Australia; **Georg Hess**, Johannes Gutenberg-University, Mainz, Germany; **Abdulraheem Yacoub**, Kansas University Medical Center, Kansas City, KS; **Michael Lill**, Cedars-Sinai Medical Center, Los Angeles, CA; **Peter Martin**, Weill Cornell Medical College, Cornell University, New York, NY; **Umberto Vitolo**, Azienda Ospedaliero Universitaria Città della Salute e della Scienza di Torino, Turin, Italy; **John Radford**, University of Manchester; **John Radford**, Christie National Health Service Foundation Trust, Manchester Academic Health Science Centre, Manchester, United Kingdom; **Wojciech Jurczak**, Jagiellonian University, Kraków, Poland; **Dolores Caballero**, Hospital Clínico Universitario, Salamanca, Spain; **Sanjay Deshpande**, **Gary J. Gartenberg**, and **Shean-Sheng Wang**, Janssen Research & Development, Raritan, NJ; **Jessica Vermeulen**, Janssen Research & Development, Leiden, the Netherlands; **Bruce D. Cheson**, Georgetown University Hospital, Washington, DC; and **Gilles Salles**, Hospices Civils de Lyon-Université de Lyon, Pierre-Bénite cedex, Lyon, France.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Ibrutinib as Treatment for Patients With Relapsed/Refractory Follicular Lymphoma: Results From the Open-Label, Multicenter, Phase II DAWN Study

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Ajay K. Gopal
Consulting or Advisory Role: Seattle Genetics, Gilead Sciences, Janssen Pharmaceuticals, Brim, Aptevo
Research Funding: Merck (Inst), Janssen Pharmaceuticals (Inst), Spectrum (Inst), Takeda (Inst), Bristol-Myers Squibb (Inst), Pfizer (Inst), Seattle Genetics (Inst), Gilead Sciences (Inst)

Stephen J. Schuster
Honoraria: Celgene, DAVAOncology, Genentech, Gilead Sciences, Merck, Novartis, Pharmacyclics, Janssen Pharmaceuticals, Seattle Genetics
Consulting or Advisory Role: Celgene, Pharmacyclics, Nordic Nanovector, Genentech, Gilead Sciences, Merck, Novartis, Janssen Pharmaceuticals, Seattle Genetics
Research Funding: Novartis (Inst), Janssen Research & Development (Inst), Pharmacyclics (Inst), Celgene (Inst), Genentech (Inst), Merck (Inst), Seattle Genetics (Inst)

Nathan H. Fowler
Consulting or Advisory Role: Pharmacyclics, Janssen Pharmaceuticals
Research Funding: Pharmacyclics (Inst), Janssen Pharmaceuticals (Inst)

Judith Trotman
Consulting or Advisory Role: Janssen Pharmaceuticals, Celgene, Takeda
Research Funding: Janssen Pharmaceuticals (Inst), Genentech (Inst), BeiGene (Inst), Pharmacyclics (Inst), Celgene (Inst)

Georg Hess
Honoraria: Roche, Janssen Pharmaceuticals, Celgene, Novartis, CTI Biopharma
Consulting or Advisory Role: Roche, Janssen Pharmaceuticals, Celgene, Morphosys, Gilead Sciences, CTI Biopharma
Research Funding: Roche (Inst), Pfizer, Celgene, Mundipharma, CTI Biopharma

Jing-Zhou Hou
No relationship to disclose

Abdulraheem Yacoub
Consulting or Advisory Role: Seattle Genetics, Incyte
Speakers' Bureau: Incyte, Seattle Genetics, Novartis, CTI Biopharma

Michael Lill
No relationship to disclose

Peter Martin
Consulting or Advisory Role: Celgene, Janssen Pharmaceuticals, Gilead Sciences, Verastem, Genentech, Pharmacyclics, Acerta Pharma, AstraZeneca, Kite Pharma, Seattle Genetics, BaNot

Umberto Vitolo
Consulting or Advisory Role: Roche, Janssen Pharmaceuticals, Celgene
Speakers' Bureau: Roche, Celgene, Takeda, Gilead Sciences, Janssen Pharmaceuticals Sandoz
Travel, Accommodations, Expenses: Roche, Janssen Pharmaceuticals, Takeda, Celgene, Gilead Sciences

Andrew Spencer
No relationship to disclose

John Radford
Stock or Other Ownership: AstraZeneca, GlaxoSmithKline
Honoraria: Takeda, Seattle Genetics, Novartis
Speakers' Bureau: Takeda, Seattle Genetics, Novartis
Research Funding: Takeda (Inst), Bristol-Myers Squibb, Seattle Genetics, Novartis

Wojciech Jurczak
Research Funding: Pharmacyclics, Janssen Pharmaceuticals

James Morton
No relationship to disclose

Dolores Caballero
No relationship to disclose

Sanjay Deshpande
Employment: Janssen Research & Development
Stock or Other Ownership: Johnson & Johnson

Gary J. Gartenberg
Employment: Janssen Research & Development

Shean-Sheng Wang
Employment: Janssen Research & Development
Stock or Other Ownership: Johnson & Johnson

Rajendra N. Damle
Employment: Janssen Research & Development

Michael Schaffer
Employment: Janssen Research & Development
Stock or Other Ownership: Johnson & Johnson

Sriram Balasubramanian
Employment: Janssen Research & Development, AbbVie
Stock or Other Ownership: Janssen Research & Development

Jessica Vermeulen
Employment: Janssen Research & Development
Stock or Other Ownership: Johnson & Johnson
Honoraria: Johnson & Johnson

Bruce D. Cheson
Consulting or Advisory Role: Acerta, AbbVie, Pharmacyclics, Genentech
Research Funding: Acerta (Inst), AbbVie (Inst), Pharmacyclics (Inst), Genentech (Inst), Gilead Sciences (Inst), TG Therapeutics (Inst)

Gilles Salles
Honoraria: Genentech, Amgen, Janssen Pharmaceuticals, Bristol-Myers Squibb, Celgene, Servier, Gilead Sciences, Novartis, Morphosys, Mundipharma, Merck
Consulting or Advisory Role: Genentech, Gilead Sciences, Janssen Pharmaceutical, Celgene, Novartis, Novimmune, Merck Amgen, Morphysis, Servier
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