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

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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 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.

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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INTRODUCTION

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

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.

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 ≥ 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

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 ≤ 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.

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
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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 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.

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 patients with prescribed dose reductions 1.0 (0.9) as a reason for dose reduction. Neutropenia 1.0 (0.9) was the most common adverse event 7.0 (6.4) with ORR of 21% (20 of 94) among patients who did not achieve 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.
87 patients who did not achieve a response (SD + PD). T-cell subset analysis revealed significant downregulation of CD4+CD25+CD127+ regulatory T-cells (Tregs) 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-\( \gamma \) and IL-12 were significantly increased in responders but not in nonresponders (Fig 2B). Specifically, IFN-\( \gamma \) 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-\( \gamma \)-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-\( \gamma \) 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).
**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; \( \geq 10\% \) of patients) are summarized in Table 4. Grade 3 or worse AEs occurred in 68 patients (62%; Data Supplement). AEs that occurred in \( \geq 5\% \) 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 (\( \geq 2\% \) 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 \( \geq 3 \) infections and infestations occurred in...
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<sub>regs</sub> 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<sub>regs</sub> 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

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**Table 3. Percent Change From Baseline in Selected Cytokines and Chemo-

kines Among Responders, Nonresponders, and Pseudo-PD Patients**

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Responders (n = 21)</th>
<th>Nonresponders (n = 29)</th>
<th>Pseudo-PD Patients (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-γ</td>
<td>19.4 (61.8)</td>
<td>−18.1 (26.6)</td>
<td>−19.7 (17.5)</td>
</tr>
<tr>
<td>IL-4</td>
<td>15.2 (55.7)</td>
<td>−7.9 (14.1)</td>
<td>31.3 (103.0)</td>
</tr>
<tr>
<td>IL-12</td>
<td>7.2 (22.5)</td>
<td>−6.1 (12.8)</td>
<td>0.7 (30.5)</td>
</tr>
<tr>
<td>TGF-β1</td>
<td>1.0 (16.7)</td>
<td>−8.1 (12.0)</td>
<td>−11.7 (11.7)</td>
</tr>
<tr>
<td>IP-10</td>
<td>−13.1 (31.4)</td>
<td>42.2 (142)</td>
<td>−17.3 (31.2)</td>
</tr>
<tr>
<td>MCP-3</td>
<td>−10.6 (18.5)</td>
<td>10.8 (40.7)</td>
<td>−10.6 (23.5)</td>
</tr>
<tr>
<td>TNF-α</td>
<td>−3.6 (20.6)</td>
<td>10.0 (25.1)</td>
<td>11.2 (7.0)</td>
</tr>
<tr>
<td>IL-6</td>
<td>−3.2 (55.7)</td>
<td>27.1 (150.0)</td>
<td>20.8 (85.6)</td>
</tr>
<tr>
<td>IL-10</td>
<td>−3.2 (12.4)</td>
<td>3.6 (13.1)</td>
<td>4.0 (13.1)</td>
</tr>
<tr>
<td>IL-27</td>
<td>−8.5 (12.2)</td>
<td>2.0 (13.2)</td>
<td>−10.1 (18.5)</td>
</tr>
<tr>
<td>IFN-αA</td>
<td>0.2 (7.2)</td>
<td>6.0 (9.2)</td>
<td>4.7 (8.1)</td>
</tr>
<tr>
<td>IL-17</td>
<td>1.1 (11.3)</td>
<td>4.8 (14.2)</td>
<td>9.5 (4.5)</td>
</tr>
<tr>
<td>IL-1α</td>
<td>10.5 (20.0)</td>
<td>9.8 (19.9)</td>
<td>20.1 (26.0)</td>
</tr>
</tbody>
</table>

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.
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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

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