



Improvement in Parameters of Hematologic and Immunologic Function and Patient Well-being in the Phase III RESONATE Study of Ibrutinib Versus Ofatumumab in Patients With Previously Treated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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Abstract

In the phase III study RESONATE, ibrutinib reduced the risk of progression and improved overall survival versus ofatumumab in previously treated patients with CLL/SLL. In this novel analysis of patient well-being including patient-reported outcomes, ibrutinib reduced disease burden while preserving parameters of hematologic and immunologic function in RESONATE. These results suggest that ibrutinib can improve quality of life while prolonging survival.

Background: Ibrutinib compared with ofatumumab significantly improves progression-free and overall survival in patients with previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). **Patients and Methods:** Measures of well-being were assessed in RESONATE, where previously treated patients with CLL/SLL were randomized to receive ibrutinib 420 mg/day (n = 195) or ofatumumab (n = 196) for up to 24 weeks. Endpoints included hematologic function, Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F), disease-related symptoms, European Organization for Research and Treatment of Cancer Quality of Life Questionnaires Core 30 (EORTC QLQ-C30), and medical resource utilization. **Results:** With up to 24 months' follow-up (median, 16.4 months), 79% of cytopenic patients showed sustained hematologic improvement (82% with improved platelet count, 69% with

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improved hemoglobin) on ibrutinib versus 43% on ofatumumab ($P < .0001$). Higher rates of clinically meaningful improvement were demonstrated with ibrutinib versus ofatumumab for FACIT-F and EORTC global health. Greater improvement was observed in disease-related weight loss, fatigue, night sweats, and abdominal discomfort with ibrutinib versus ofatumumab. Hospitalizations in the first 30 days occurred less frequently with ibrutinib than ofatumumab (0.087 vs. 0.184 events/patient; $P = .0198$). New-onset diarrhea was infrequent with ibrutinib after the first 6 months (47% at ≤ 6 months vs. 5% at 12-18 months). With ibrutinib, grade ≥ 3 hypertension occurred in 6%, grade ≥ 3 atrial fibrillation in 4%, major hemorrhage in 2%, and tumor lysis syndrome in 1% of patients. **Conclusion:** Ibrutinib led to significant improvements in hematologic function and disease symptomatology versus ofatumumab, and can restore quality of life while prolonging survival in relapsed/refractory CLL/SLL.

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Keywords: Bruton's tyrosine kinase, Disease-related symptoms, Fatigue, Quality of life, Relapsed/refractory CLL/SLL

Introduction

Chronic lymphocytic leukemia (CLL) is a common leukemia in the United States¹; manifestations of progressive disease and indications for treatment include lymphadenopathy, splenomegaly, bone marrow failure (anemia, thrombocytopenia), and significant disease-related symptoms.² CLL complications and toxicities associated with therapy can profoundly impact quality of life (QoL) and well-being, particularly in older patients.^{3,4} Patient-reported outcome (PRO) scores of emotional well-being tend to be lower in patients with CLL than in patients with other malignancies,⁴ and studies have shown significant QoL improvements with effective CLL treatment including chemotherapy, as well as in prior small non-randomized studies with ibrutinib.⁵⁻¹¹

Ibrutinib, an oral, first-in-class, once-daily inhibitor of Bruton's tyrosine kinase, has shown substantial single-agent efficacy and tolerability in CLL/small lymphocytic lymphoma (SLL).¹²⁻¹⁵ In the phase III study (RESONATE) comparing ibrutinib with ofatumumab in previously treated patients with CLL/SLL, ibrutinib reduced risk of progression as assessed by an independent review committee (IRC) by 78% and risk of death by 57% with a median follow-up of 9.4 months at primary analysis.¹⁴ Measures of patient well-being including parameters of hematologic and immunologic function, and QoL are reported from the RESONATE study. These data are the first to show sustained improvements in PRO, hematologic function, and disease symptoms associated with ibrutinib in a randomized study.

Patients and Methods

Patients

Patients with CLL/SLL who had received ≥ 1 prior therapy and had active disease with an indication for therapy per International Workshop on Chronic Lymphocytic Leukemia (iwCLL) guidelines were enrolled.² Eligibility criteria have been described previously.¹⁴ All patients provided written informed consent.

Study Design

Patients were randomized to once-daily oral ibrutinib (420 mg) or intravenous ofatumumab as previously described.¹⁴ Ofatumumab data beyond 6 months were limited by maximum treatment duration (6 months) and a median progression-free survival (PFS) of

8.1 months,¹⁴ affecting the efficacy and safety variables in this updated analysis. Further, 122 patients randomized to ofatumumab had crossed over to ibrutinib after disease progression (PD).

Study Endpoints

PFS, overall survival (OS), and overall response rate (ORR) have been previously reported.^{2,14} Secondary efficacy endpoints include sustained hematologic improvement (see [Supplemental Methods](#) [in the online version] for definition) in patients with cytopenia(s) at baseline, and PRO as measured by Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F). FACIT-F is a validated instrument that assesses tiredness, weakness, and difficulty conducting daily activities owing to fatigue. Scores range from 0 to 52, with high scores indicating less fatigue.¹⁶ A change in FACIT-F score of ≥ 3 points¹⁷ was considered clinically meaningful. FACIT-F forms and other PRO instruments were generally completed by patients prior to any study procedures. Per protocol, patients were not required to complete the questionnaire following PD/crossover or after completing treatment if assigned to the ofatumumab arm.

Prespecified exploratory endpoints included improvement of investigator-assessed disease-related symptoms (National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 [CTCAE] grade decrease of ≥ 1 post-baseline, reported for ≥ 2 consecutive assessments of weight loss, fatigue, fever, night sweats, abdominal discomfort owing to splenomegaly, and/or anorexia), PRO as measured by European Organization for Research and Treatment of Cancer Quality of Life Questionnaires Core 30 (EORTC QLQ-C30; clinically meaningful change defined as > 10 points¹⁸), and medical resource utilization associated with therapy including number of hospitalizations, any blood product transfusions (red blood cells, platelets, whole blood), and use of any hematopoietic growth factors. Compliance rates for FACIT-F and EORTC QLQ-C30 questionnaire completion were monitored (see [Supplemental Table 1](#) in the online version).

To evaluate disease burden, lymph nodes and splenic enlargement were quantified by IRC-assessed computed tomography; reduction was defined per iwCLL criteria.² The effect of ibrutinib versus ofatumumab on white blood cell count and differential was evaluated over time. Lymphocyte subsets (B cells, T cells, natural killer [NK] cells [see [Supplemental Methods](#) in the online version])

were evaluated by flow cytometry for patients with baseline samples. Serum immunoglobulin levels (IgA, IgG, IgM) were quantitated.

Adverse event (AE) severity was graded using CTCAE, except for hematologic toxicities, which were graded based on iwCLL criteria.² The treatment-emergent period for AE collection was defined as the time from the first dose of study drug to 30 days after the last dose of study drug or initiation of subsequent antineoplastic therapy, whichever comes first. Treatment-emergent AEs were summarized by time to event onset and by prevalence. (See [Supplemental Methods](#) in the online version, for details regarding statistical methods used in the study.)

Results

Baseline Characteristics and Patient Disposition

As described previously, 391 patients with previously treated CLL/SLL were randomized to ibrutinib (n = 195; median 3 prior therapies [range, 1-12]) or ofatumumab (n = 196; median 2 prior therapies [range, 1-13]).¹⁴ Baseline characteristics were balanced across both treatment groups and have been previously published.¹⁴ In general, the enrolled population was elderly (over 20% of patients were aged ≥ 75 years), and comorbidities were common (such as reduced creatinine clearance and cytopenias at baseline). The median follow-up was 9.4 months at the time of primary analysis. This analysis reflects data at a median follow-up of 15.0 months (16.4 for ibrutinib, 11.9 for ofatumumab; up to 24 months maximum).

Sustained Hematologic Improvement

In cytopenic patients treated with ibrutinib, 69% showed sustained improvement in hemoglobin, 82% in platelets, and 68% in absolute neutrophil count, all of which were statistically significant versus changes with ofatumumab (Table 1). Of ibrutinib patients with any baseline cytopenia, 79% showed sustained improvement in blood counts with this longer follow-up compared with 69% at the primary analysis, where it was significantly higher versus ofatumumab (43%; *P* < .0001). Figure 1A, B demonstrates early improvement in median hemoglobin and platelet levels, respectively, which were sustained during the first 6 months in patients in both treatment arms with baseline cytopenias, and through 16 months on the ibrutinib arm.

Patient-Reported Outcomes

FACIT-F. Baseline FACIT-F scores for ibrutinib and ofatumumab were similar (mean, 35.7 vs. 34.5, respectively). More patients achieved clinically meaningful improvement in FACIT-F with ibrutinib versus ofatumumab (56% vs. 43%; odds ratio [OR], 1.69; *P* = .0101); clinically meaningful improvement with ibrutinib was sustained through 60 weeks of follow-up (Figure 1C).

EORTC QLQ-C30. At baseline, ibrutinib and ofatumumab patients had similar mean scores for EORTC QLQ-C30 global health status (60.0 vs. 58.3, respectively). Greater improvement in global health status mean score was seen at 24 weeks with ibrutinib versus ofatumumab (9.0 vs. 5.8, respectively) (see [Supplemental Table 2](#) in the online version). Of the 15 EORTC domains assessed at baseline, nausea/vomiting, diarrhea, and constipation had the lowest severity, and global health status had the highest impairment. At week 24, patients treated with ibrutinib improved on 13 (all but nausea/vomiting and diarrhea) versus 12 domains (all but cognitive functioning, pain, or constipation) with ofatumumab (see [Supplemental Table 2](#) in the online version). A significantly greater proportion of patients on ibrutinib compared with ofatumumab reported an improvement in cognitive functioning, including concentration and recall (32% vs. 20%; *P* = .008). Overall, the mean change in scores from baseline to week 24 across the EORTC QLQ-C30 domains appeared comparable between treatment arms. An improvement in the EORTC Fatigue Subscale score from baseline to week 24 was seen with ibrutinib (n = 117; median 11-point improvement), whereas no improvement was seen with ofatumumab (n = 87; median 0-point improvement).

Reduction in Disease Burden

Disease burden was assessed by independent review prior to discontinuation for the primary analysis with 9.4 months median follow-up, similar to the median PFS for the ofatumumab arm (8.1 months). At least a 50% reduction in lymph node size was observed more frequently with patients on ibrutinib versus ofatumumab (92% vs. 14%; *P* < .0001) (Figure 2A); the median time to reduction was 2.6 versus 5.3 months with ibrutinib and ofatumumab, respectively. Reduction in spleen size was more common in ibrutinib-treated than ofatumumab-treated patients (85% vs. 54%;

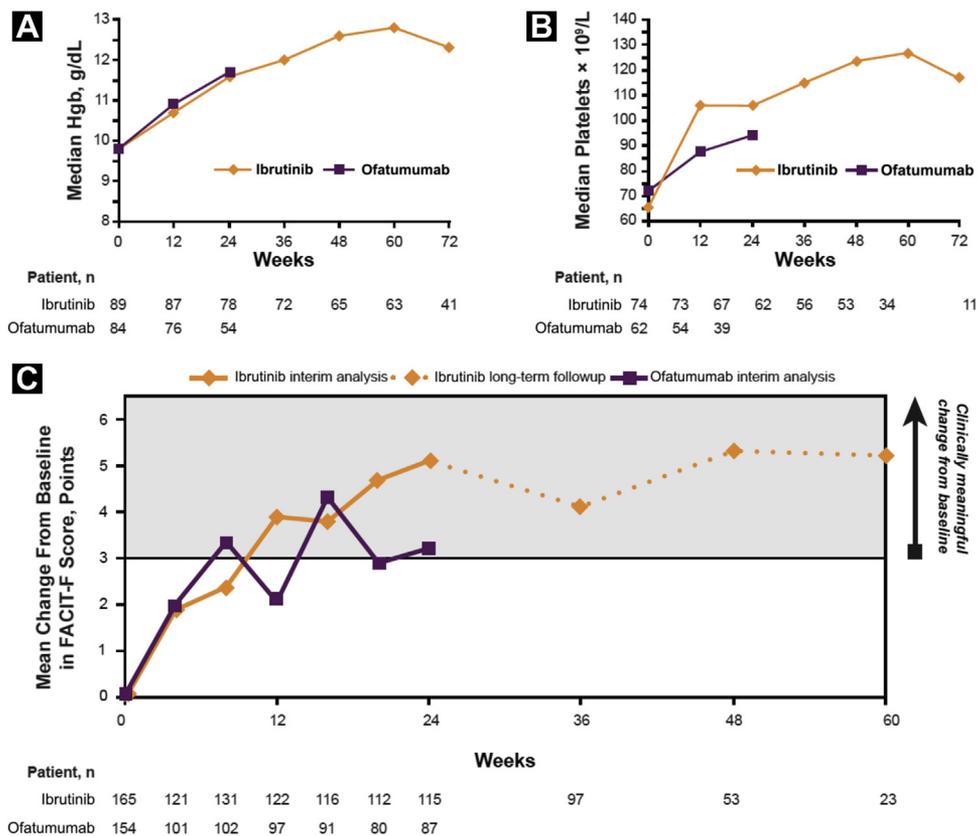
Table 1 Baseline Cytopenias and Sustained Hematologic Improvement^a

	Baseline Cytopenia(s)		Sustained Hematologic Improvement in Patients With Specified Cytopenia(s) at Baseline, n/N (%)		
	Ibrutinib (n = 195)	Ofatumumab (n = 196)	Ibrutinib	Ofatumumab	P Value
Thrombocytopenia, n (%)	74 (38)	64 (33)	61/74 (82)	14/64 (22)	< .0001
Median platelet count, × 10 ⁹ /L (range)	65.5 (20-99)	72 (23-100)			
Neutropenia, n (%)	41 (21)	38 (19)	28/41 (68)	12/38 (32)	.0011
Median neutrophil count, × 10 ⁹ /L (range)	1.1 (0.4-1.5)	1.1 (0.3-1.5)			
Anemia, n (%)	89 (46)	86 (44)	61/89 (69)	32/86 (37)	< .0001
Median hemoglobin, g/dL (range)	9.8 (6.5-11)	9.8 (6.2-11)			
Any cytopenia, n (%)	124 (64)	123 (63)	98/124 (79)	53/123 (43)	< .0001

^aSustained improvement ≥ 56 days without transfusions or growth factors. Blood counts assessed by central laboratory.

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Figure 1 Change Over Time by Treatment Arm in Median Hgb Levels (A), Median Platelet Count (B), and Improvement in FACIT-F Including Long-Term Extended Follow-Up (C)



Abbreviations: FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; Hgb = hemoglobin.

$P < .0001$) (Figure 2B); the median time to reduction was 2.6 months with both ibrutinib and ofatumumab. These improvements are consistent with recently published updates to PFS and OS showing continued benefit for patients randomized to ibrutinib (median follow-up 19 months: PFS, hazard ratio [HR], 0.106; $P < .0001$; 18-month landmark OS, HR, 0.361; 95% confidence interval [CI], 0.208-0.628).^{14,19}

Disease-Related Symptoms and Medical Resource Utilization

Consistent with findings at the primary analysis, improvement in disease-related symptoms were assessed by investigators more frequently with ibrutinib than with ofatumumab for weight loss (100% vs. 87%), fatigue (79% vs. 64%), night sweats (89% vs. 77%), abdominal pain/discomfort (96% vs. 75%), and anorexia (100% vs. 64%), but not fever (88% vs. 100%). Hospitalizations in the first 30 days occurred less frequently with ibrutinib than ofatumumab (0.087 vs. 0.184 events/patient²⁰; $P = .0198$); however, no significant differences were observed through 6 months. Growth factor usage after day 30 occurred slightly more frequently with ofatumumab than ibrutinib (5%-9% vs. 2%-4% each month through month 6, respectively). Transfusion rates with ibrutinib

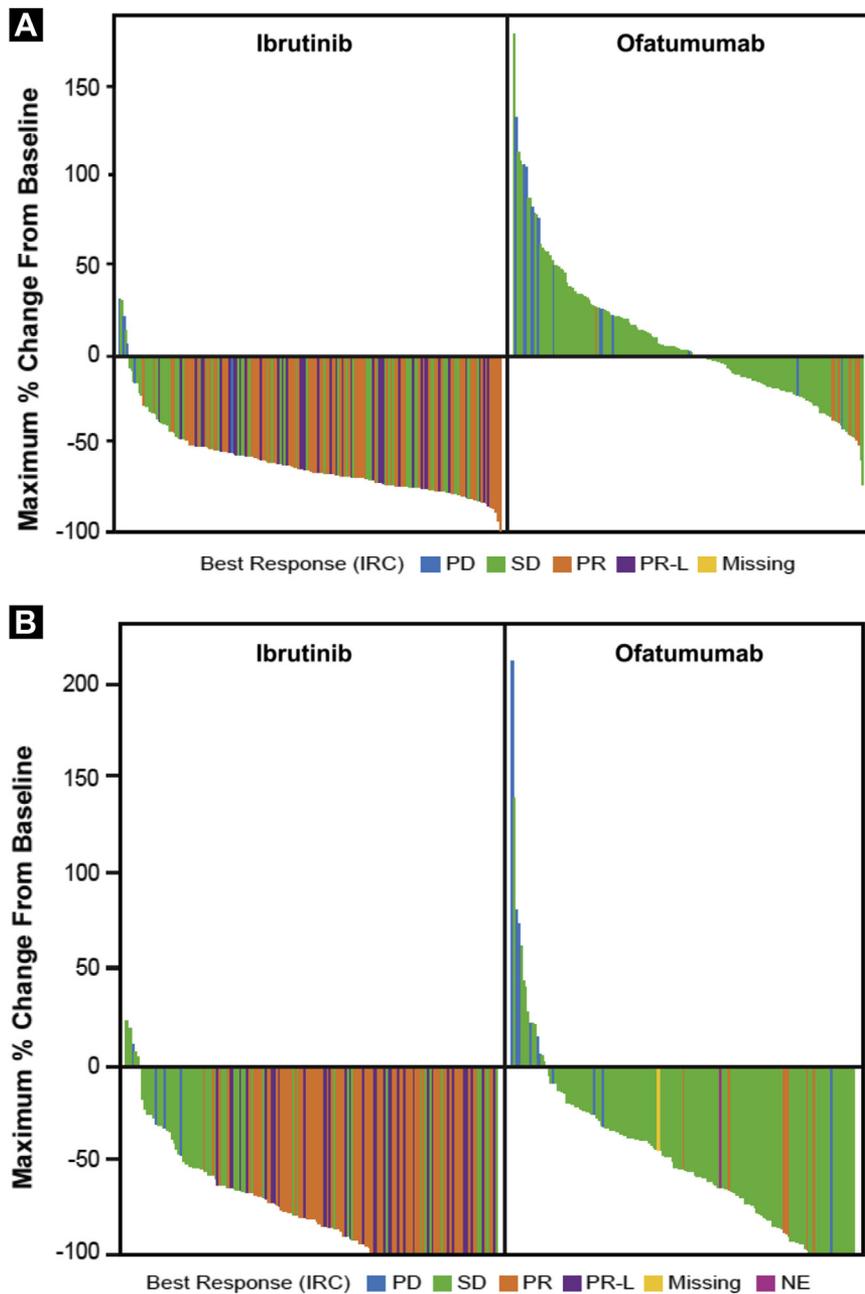
and ofatumumab (30% vs. 24%) were not notably different through 6 months.

White Blood Cell Count, Lymphocyte Counts, and Serum Immunoglobulin Levels

In both arms, the white blood cell differential trended to normal with an increase in the proportion of neutrophils and a decrease in lymphocyte proportions versus baseline (see Supplemental Figure 1A in the online version). In the ibrutinib arm, elevated baseline absolute lymphocyte count (ALC) declined over time to a median of 50% below baseline at 24 weeks and continued to decrease to normal ($< 4 \times 10^9/L$) at later time points (after the expected initial transient increase with ibrutinib) (see Supplemental Figure 1B, C in the online version). Supplemental Table 3 (in the online version) shows distributions of peak ALC in ibrutinib-treated patients relative to baseline ALC.

The primarily malignant B cell counts were stable with ibrutinib and decreased with ofatumumab at week 12 (Figure 3 and Supplemental Figure 2 [in the online version]). After week 12, B cell counts in the ibrutinib arm also decreased significantly over time, with median count approaching the upper limit of normal at week 72. Median T cell (including CD3+, CD4+, and CD8+ subsets)

Figure 2 Reduction in Lymph Nodes* (A) and Splenic Enlargement† (B) (Primary Analysis)



*Sum of the products of multiple lymph nodes (as evaluated by computed tomography scans) or the longest diameter of one target lymph node. †Patients who experienced resolution of splenic enlargement by IRC are considered to have 100% reduction. Abbreviations: IRC = independent review committee; NE = not evaluable; PD = progressive disease; PR = partial response; PR-L = PR with lymphocytosis; SD = stable disease.

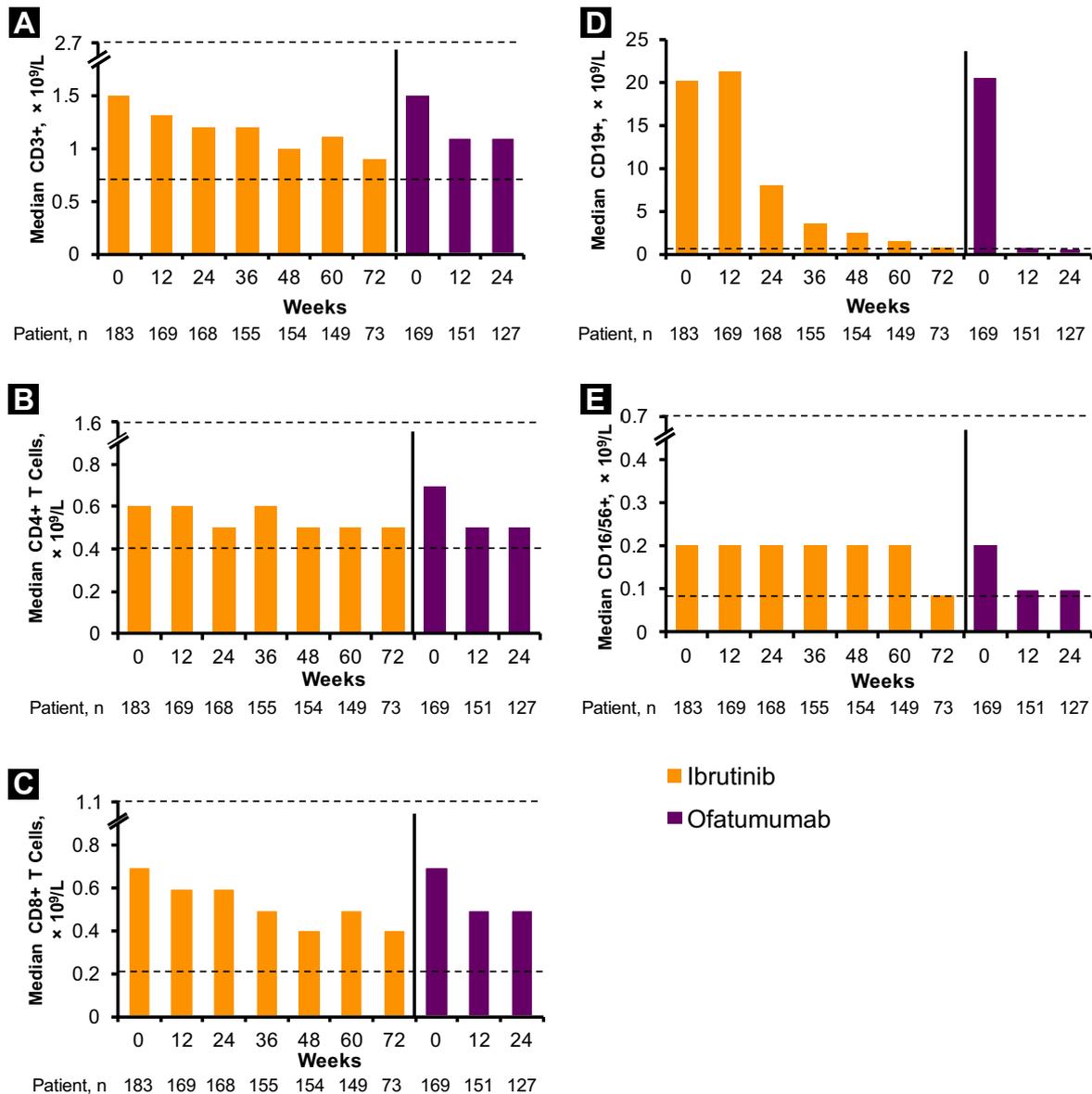
and NK cell counts remained within the limits of normal throughout testing, whereas the relative proportion of T cells (including CD4+ and CD8+ subsets) and NK cells progressively increased over time. For 57 patients with available baseline samples, median counts for CD3+ and CD4+ T cells (but not CD8+) and NK cells were significantly decreased at week 72, remaining above the lower limits of normal (LLN). The median regulatory T cell

counts significantly decreased over time on ibrutinib, dropping from the upper limit of normal to the LLN (see Supplemental Figure 3 in the online version).

Analysis of serum Immunoglobulin levels (excluding the 32% and 22% of ibrutinib and ofatumumab patients on intravenous Immunoglobulin replacement) showed a significant increase in IgA levels with ibrutinib, rising to the LLN at week 12, which was

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Figure 3 Absolute Counts Over Time of CD3+ (A), CD4+ (B), CD8+ (C), CD19+ (D), and CD16/56+ (E) Cells. ULN and LLN ($\times 10^9/L$): CD3+, 0.723-2.737; CD4+, 0.404-1.612; CD8+, 0.22-1.129; CD19+, 0.08-0.724; and CD16/56+, 0.084-0.724. In Each Chart, ULN and LLN are Shown by Dashed Lines (With Axis Breaks); Only ULN is Shown for CD19+ Cells



Abbreviations: LLN = lower limit of normal; ULN = upper limit of normal.

maintained through week 72. Median IgG levels were stable with up to 1.4 years on ibrutinib, rising to the LLN at week 72. Median IgM level changes were nonsignificant and varied over time from just above to just below the LLN from week 36 to week 60 (Figure 4). For those with baseline levels below the LLN, a similar increase was observed for IgA without significant decrement in IgG or IgM over time (data not shown).

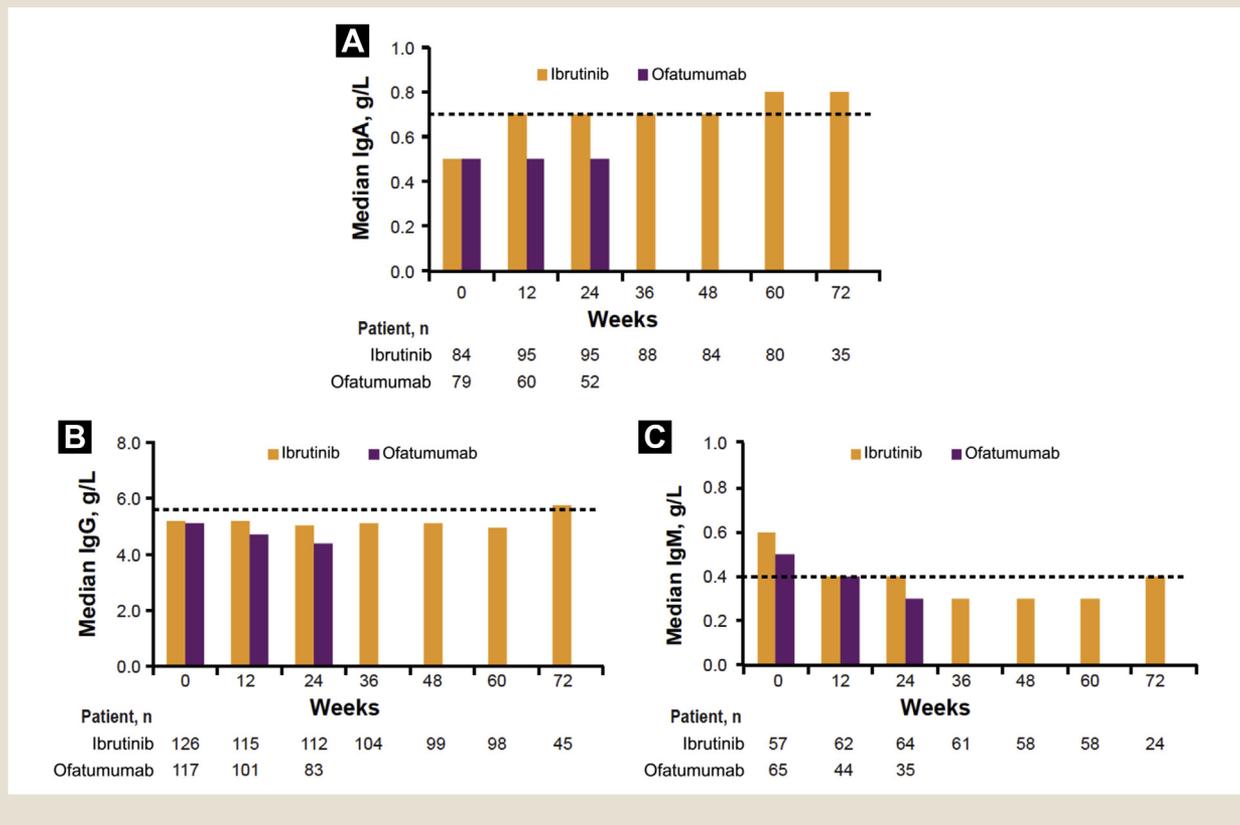
Adverse Events

Most AEs were grade 1 in severity. The most frequently observed AEs among ibrutinib patients at any time were diarrhea (37% grade

1, 10% grade 2, 4% grade 3), fatigue (19% grade 1, 12% grade 2, 3% grade 3), and nausea (24% grade 1, 6% grade 2, 2% grade 3), of which none were grade 4. Except for diarrhea (all grade), rates of common AEs in the first 6 months were similar between the treatment arms (Figure 5A). New onset of these events was less frequent after the first 6 months such as diarrhea (all grades) rates, which declined over time from 47% at 0 to 6 months to 5% at 12 to 18 months (Figure 5B).

With prolonged ibrutinib treatment, the most frequent grade ≥ 3 AEs at any time were neutropenia (18%), pneumonia (11%), hypertension (6%), and thrombocytopenia (6%). The incidences

Figure 4 Median Levels* Over Time of IgA (A), IgG (B), and IgM (C). LLN for Baseline IgA, IgG, and IgM are 0.7 g/L, 5.65 g/L, and 0.4 g/L, respectively, and are shown by dashed lines



*Excluding patients on intravenous Ig. Abbreviations: Ig = immunoglobulin; LLN = lower limit of normal.

of grade ≥ 3 infections and cytopenias were similar for ibrutinib and ofatumumab during the first 6 months of therapy (Figure 5A). Except for hypertension, the incidences of other frequent grade ≥ 3 AEs decreased or were similar over time (Figure 5C). Prevalence of grade ≥ 3 infections at any time was 30% for ibrutinib and 20% for ofatumumab (see Supplemental Figure 4 in the online version). Exposure-adjusted all-grade infection rate with ibrutinib versus ofatumumab was 14.7 versus 18.4 per 100 patient-months (grade ≥ 3 was 2.5 vs. 5.7, respectively). Upper respiratory tract infection was the most common all-grade infection for both the overall ibrutinib cohort (24%) and those with compromised Ig status at baseline (25% for IgA < LLN, 26% for IgG < LLN).

Atrial fibrillation occurred at any time in 13 (7%) patients, including grade ≥ 3 in 7 (4%) patients, resolving in 6 of 7 patients and leading to ibrutinib discontinuation in 1 patient, who was subsequently noted to have PD; the majority of grade ≥ 3 atrial fibrillation events were reported in the first 6 months of ibrutinib therapy. Major hemorrhage occurred in 4 patients (2%): grade 2 subdural hematoma, grade 3 post-procedural hemorrhage, grade 3 spontaneous hematoma, and grade 4 subdural hematoma (see Supplemental Table 4 in the online version). Tumor lysis syndrome occurred 5 and 11 days after ibrutinib discontinuation in 2 patients

with PD (study days 534 and 242, respectively) who had not yet started any next line therapy for CLL.

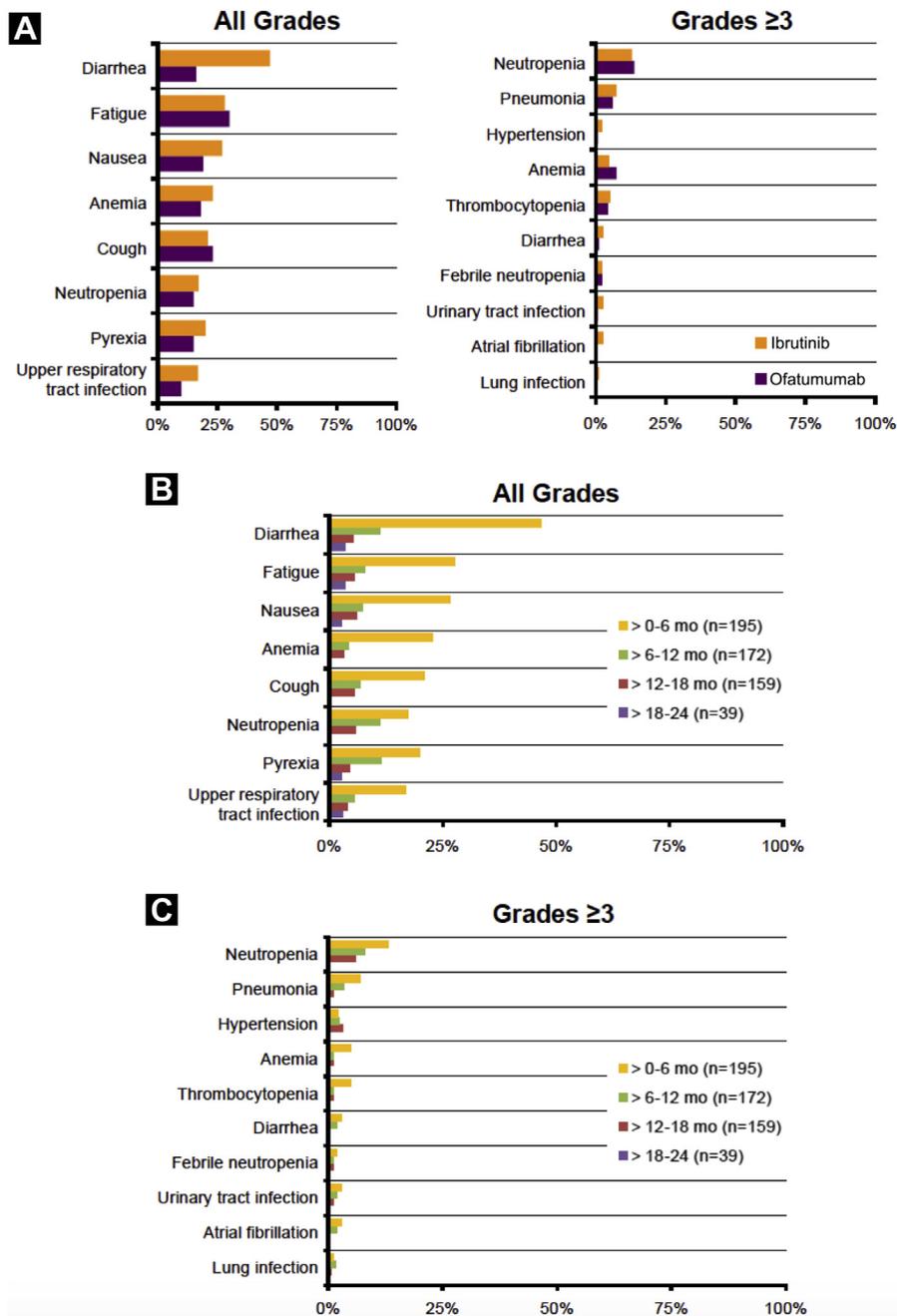
At a median treatment duration of 16 months for ibrutinib versus 5 months for ofatumumab, 13 ibrutinib patients and 7 ofatumumab patients discontinued study drug primarily due to AEs. In total, 23 and 16 patients, respectively, had AEs associated with discontinuation, most frequently pneumonia; among patients who discontinued ibrutinib due to AEs, longer duration of therapy appears to be associated with increased time to progression (see Supplemental Table 5 in the online version). AEs leading to ibrutinib discontinuation occurred in 12 of 195, 9 of 172, 1 of 159, and 1 of 39 patients at 0 to 6, 7 to 12, 13 to 18, and 19 to 24 months, respectively. AEs leading to ibrutinib dose reduction occurred in 7 of 195, 4 of 172, and 2 of 159 patients at 0 to 6, 7 to 12, and 13 to 18 months, respectively.

Discussion

Ibrutinib is a selective first-in-class irreversible inhibitor of Bruton's agammaglobulinemia tyrosine kinase with an important role in multiple cellular functions including B-cell antigen receptor signaling. A high frequency of durable responses and acceptable safety associated with ibrutinib in the previously treated population with CLL has been demonstrated in the RESONATE study with

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Figure 5 Incidence of Common ($\geq 20\%$ for all Grade, $\geq 3\%$ for Grade ≥ 3 at Any Time) Treatment-Emergent Adverse Events that Occurred in the First 6 Months of Treatment in the Ibrutinib and Ofatumumab Arms (A), for all Grades by Time to Event Onset (B), and for Grades ≥ 3 by Time to Event Onset in the Ibrutinib Arm (C). New Events are Presented Only During the Period of Time Where Event Began. Note, No Grade ≥ 3 Events Started at > 18 Months



enhanced PFS, OS, and ORR as compared with ofatumumab, including in high-risk subgroups.^{14,19} This report demonstrates that in addition to its known efficacy, prolonged administration of ibrutinib confers patients additional benefits as assessed by multiple measures of well-being, including preservation of parameters of

hematologic and immunologic function. At a median of 16.4 months follow-up, the present data are among the first reports from a randomized phase III study to demonstrate significant improvement in hematologic and immunologic parameters in parallel with QoL improvements. In the majority of patients with baseline

cytopenias, ibrutinib led to early and sustained platelet and hemoglobin improvements (82% and 69%, respectively), which were markedly better than for the patients randomized to ofatumumab.

With up to 2 years of follow-up, the positive hematologic effects of ibrutinib resulted in sustained normalization of hemoglobin in 69% and of platelet count in 82% of patients with baseline anemia and thrombocytopenia, respectively. Transient increase followed by sustained decrease in percentage of lymphocytes over time is expected given the known pharmacodynamic ‘redistribution’ phenomenon of B-cell receptor inhibitor treatment-related lymphocytosis. Malignant B cell counts decreased dramatically with ibrutinib and approached normal limits by week 72, and median CD4+, CD8+, and NK cell counts remained within normal limits throughout treatment. Reduction in regulatory T cell counts to the LLN was observed in ibrutinib-treated patients consistent with preclinical studies of ibrutinib and other clinical data sets.²¹⁻²³ Future analyses discriminating normal from neoplastic B cells would be beneficial to ascertain any modulatory effects of ibrutinib. An increase in IgA levels was also observed with ibrutinib over time, without significant decrement in IgG or IgM.

In a National Institutes of Health study of patients with CLL ≥ 65 years of age or with *TP53* aberration, the infection rate overall was lower in treatment-naïve (TN) versus relapsed/refractory (R/R) patients, but rates declined over time in both TN and R/R populations²⁴; data that suggest clinically relevant improvement in humoral immunity with ibrutinib treatment. In an integrated analysis of patients from the RESONATE and RESONATE-2 (ibrutinib vs. chlorambucil in older patients with TN CLL/SLL) trials, infection rates were also shown to decrease with time on ibrutinib.²⁵ Although the decreased incidence of various infections over time seen during ibrutinib treatment in this and other reports may reflect these positive hematologic effects on lymphocytes and immunoglobulin levels, future detailed analyses of these infections may be warranted, given recent descriptions of opportunistic infections occurring during ibrutinib treatment.^{26,27}

PROs, including health-related QoL, are increasingly assessed in clinical trials as a measure of effectiveness and to help with decision-making. Analysis of FACIT-F outcomes showed that a clinically meaningful improvement from baseline was reached in < 24 weeks with ibrutinib and ofatumumab, with mean improvement sustained through 60 weeks of follow-up on ibrutinib. Similarly, fatigue was improved as measured with the EORTC fatigue subscale PRO as well as investigator-assessed disease-related symptoms. Additionally, 100% of patients treated with ibrutinib experienced improvements in weight loss and anorexia. The magnitude of improvement (mean change from baseline to week 24) in EORTC QLQ-C30 was greater with ibrutinib compared with ofatumumab for domains including global health status, physical functioning, fatigue, dyspnea, and constipation, whereas the improvement was greater with ofatumumab for role functioning, social functioning, and appetite loss. When considering the threshold for clinically meaningful improvement, only dyspnea was improved with ibrutinib (mean change, -11.0) and appetite loss with ofatumumab (mean change, -13.0). Notably, comparative data between treatment groups are limited due to the ofatumumab arm fixed duration of treatment (maximum 6 months) and relatively short PFS (median,

8.1 months),¹⁴ but the overall effects of ibrutinib on QoL reflect clinically meaningful gains that were sustained throughout the 60 weeks of follow-up. Irrespective of this disparity in drug exposure time, the majority of positive ibrutinib benefits were also observed at the time of the primary analysis when treatment durations were comparable.¹⁴ For safety and medical resource utilization data, this imbalance in follow-up would generally favor ofatumumab. Despite this, medical resource utilization as a prespecified exploratory endpoint, including hospitalizations in the first 30 days and growth factor usage after day 30, was higher in the ofatumumab group versus the ibrutinib group. Cost implications were not analyzed, although one recent real-world analysis of front line CLL treatment showed reduced medical resource utilization and reduced costs of care are incurred with ibrutinib compared with chemoimmunotherapy.²⁸ That analysis did not evaluate pharmacy costs, and it remains unknown how these will contribute to the balance of costs for ibrutinib versus chemoimmunotherapy options. Such evaluations will be of further interest in the real-world setting.

No new safety signals were identified in this study versus earlier phase II studies,¹² and new events of diarrhea, certain infections, and cytopenias, including grade ≥ 3 events, were observed less frequently over time. These data suggest that, except for the appearance of grade 3 hypertension, the likelihood of new onset treatment-emergent AEs may be reduced with long-term ibrutinib therapy.

Conclusion

Clinical data describing psycho-oncologic endpoints in studies of patients with CLL treated with new small targeted molecules or biologics are sparse. These novel RESONATE findings are among the first randomized data to assess multiple measures of overall patient well-being with treatment, including PROs, disease burden, hematologic function, and benefits to patients with regard to disease management and reduced requirement for supportive care. A survival benefit with ibrutinib, together with sustained improvements in hematologic endpoints and patient-reported outcomes, suggest that ibrutinib can improve QoL while prolonging survival.

Clinical Practice Points

- Complications associated with CLL and toxicities of therapy can profoundly affect QoL and patient well-being.
- These analyses of RESONATE are the first to show significant psycho-oncologic improvements with ibrutinib in R/R CLL, in addition to the known benefits of longer PFS, OS, and improved ORR compared with anti-CD20 therapy.
- Sustained hematologic improvement, clinically meaningful improvement in fatigue and overall QoL, and fewer early hospitalizations were observed with ibrutinib compared with ofatumumab while maintaining a reduction in disease burden.
- No new safety signals with ibrutinib were identified in this study, and the onset of treatment-emergent AEs decreased over time.
- Hematologic function, QoL, and overall patient well-being are a vital part of medical decision-making in addition to the clinical benefits of prolonged survival in patients with R/R CLL/SLL.

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Supplemental Data

Supplemental data, figures, and tables accompanying this article can be found in the online version at <https://doi.org/10.1016/j.cml.2018.08.007>.

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Supplemental Methods

Sustained hematologic improvement in cytopenias were defined as hemoglobin > 11 g/dL or $\geq 50\%$ increase over baseline ≤ 11 g/dL, platelet counts $> 100 \times 10^9/L$ or $\geq 50\%$ increase over baseline $\leq 100 \times 10^9/L$, and absolute neutrophil count $> 1.5 \times 10^9/L$ or $\geq 50\%$ increase over baseline $\leq 1.5 \times 10^9/L$, sustained for ≥ 56 days without blood transfusions or growth factors.

The effect of ibrutinib versus ofatumumab on white blood cell count differential and lymphocyte subsets (B cells, T cells, natural killer cells) was also evaluated over time. B cells (CD45bright, SSCLow, CD3-, CD19+), NK cells (CD45bright, SSCLow, CD3-, CD16+/CD56+), T cells (CD45bright, SSCLow, CD3+, \pm CD4 or CD8), and regulatory T cells (CD45bright, SSCLow, CD3+, CD4+, CD127-, CD25bright & FoxP3+) were determined by immunofluorescence. Regulatory T cells were assessed from a subset of 48 patients, representing detected regulatory T cells from available samples at each of the various time points. CD5 immunostaining was not performed.

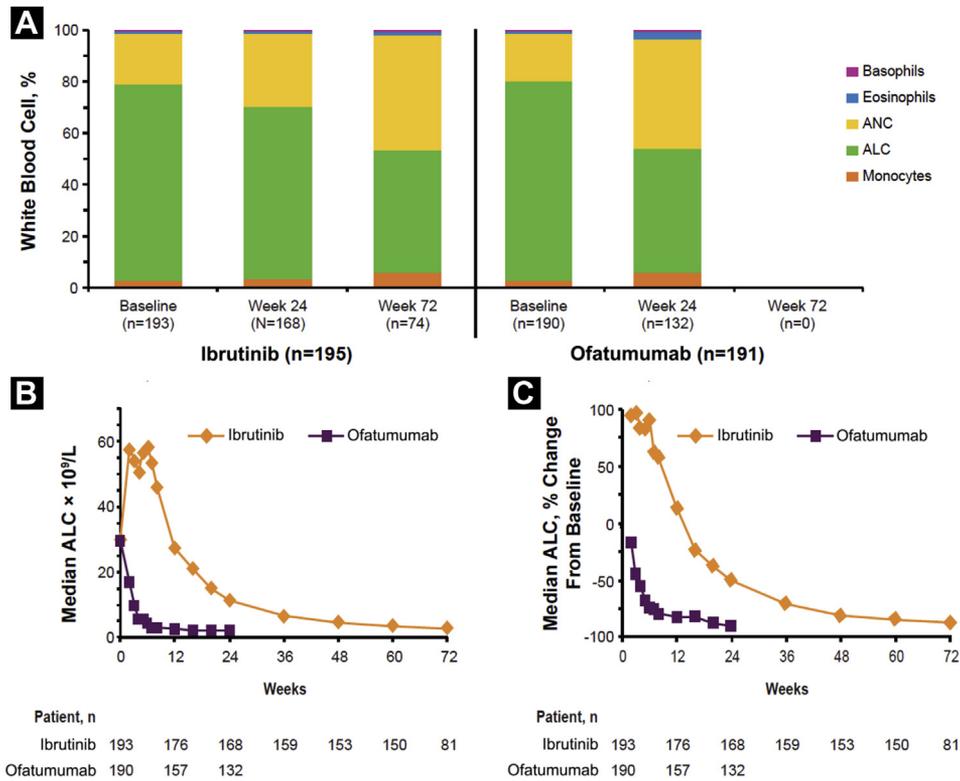
Statistical Analysis

Descriptive statistics were used to summarize findings. Unless specified otherwise, the overall 2-sided significance level of .05 was used as a reference for each statistical comparison without adjusting for multiplicity. Patients with available data were analyzed according to the treatment to which they were randomized for baseline characteristics and efficacy endpoints, whereas those who received ≥ 1 dose of study drug comprised the safety population.

The proportion of patients achieving sustained hematologic improvement was compared between treatment arms using the χ^2 test. Median absolute values for lymphocyte subsets were used due to chronic lymphocytic leukemia-related non-normal distributions.

Patient-reported outcome changes in total score were summarized from baseline to each post-baseline time point with odds ratio (> 1.0 favoring the ibrutinib arm for improvement) assessed between treatment arms. No imputation of missing values was performed. Descriptive statistics were conducted at each scheduled post-baseline assessment by treatment arm.

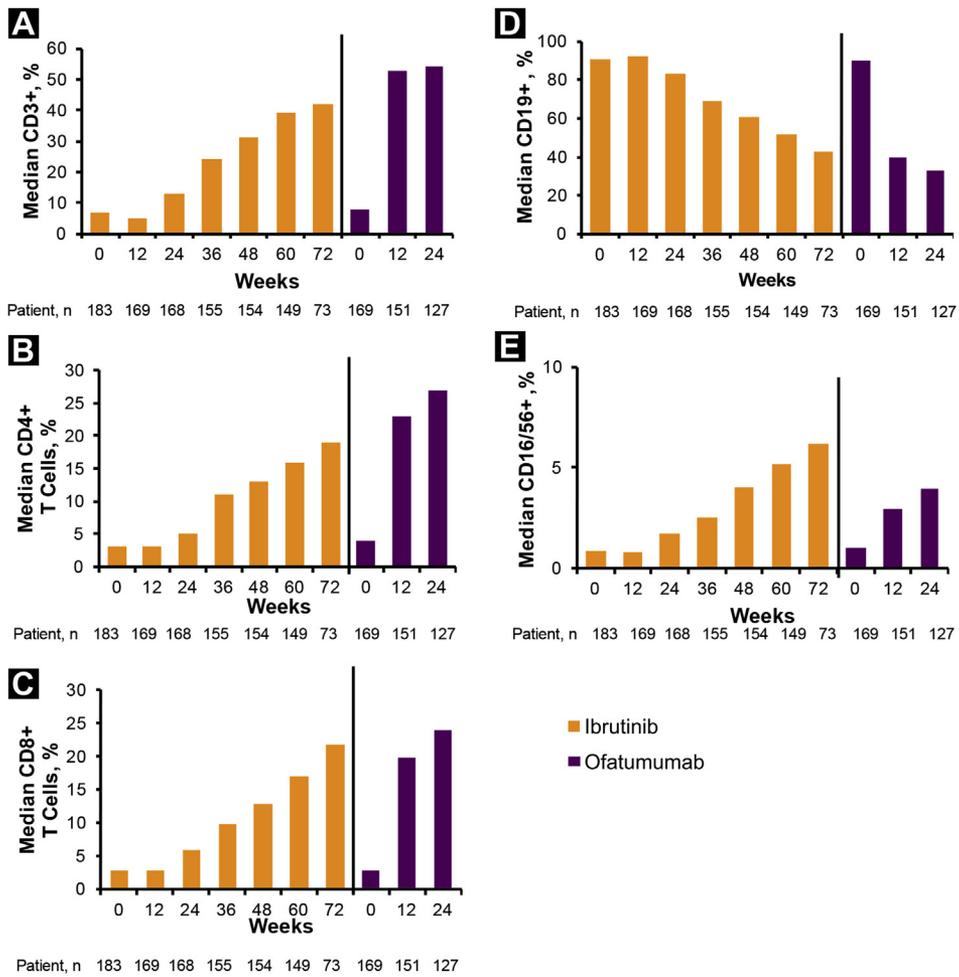
Supplemental Figure 1 Effect of Ibrutinib Versus Ofatumumab Over Time on White Blood Cell Count Differential (A), Median ALC (B), and Percent Change From Baseline in Median ALC (C). ULN and LLN ($\times 10^9/L$) for ALC: 0.91 to 4.28 for Patients < 59 Years (Ibrutinib, n = 41; Ofatumumab, n = 35) and 0.8 to 3.00 for Patients \geq 59 Years (Ibrutinib, n = 152; Ofatumumab, n = 155)



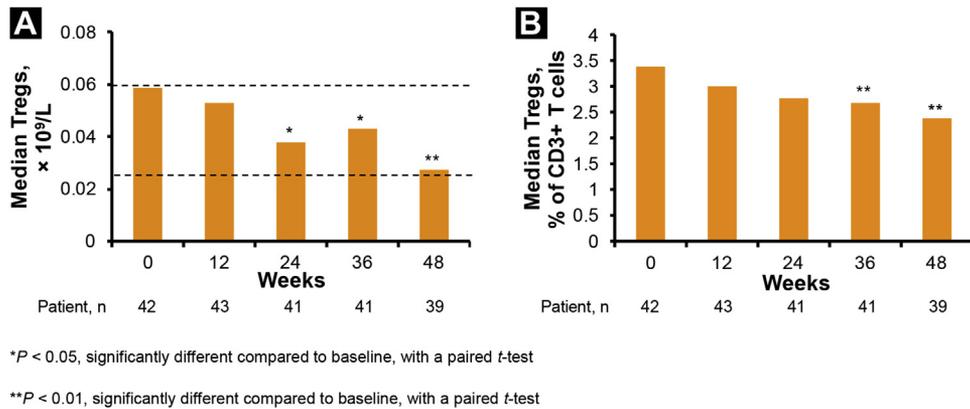
Abbreviations: ALC = absolute lymphocyte count; ANC = absolute neutrophil count; LLN = lower limit of normal; ULN = upper limit of normal.

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Supplemental Figure 2 Percentage Over Time of CD3+ (A), CD4+ (B), CD8+ (C), CD19+ (D), and CD16/56+ (E) cells

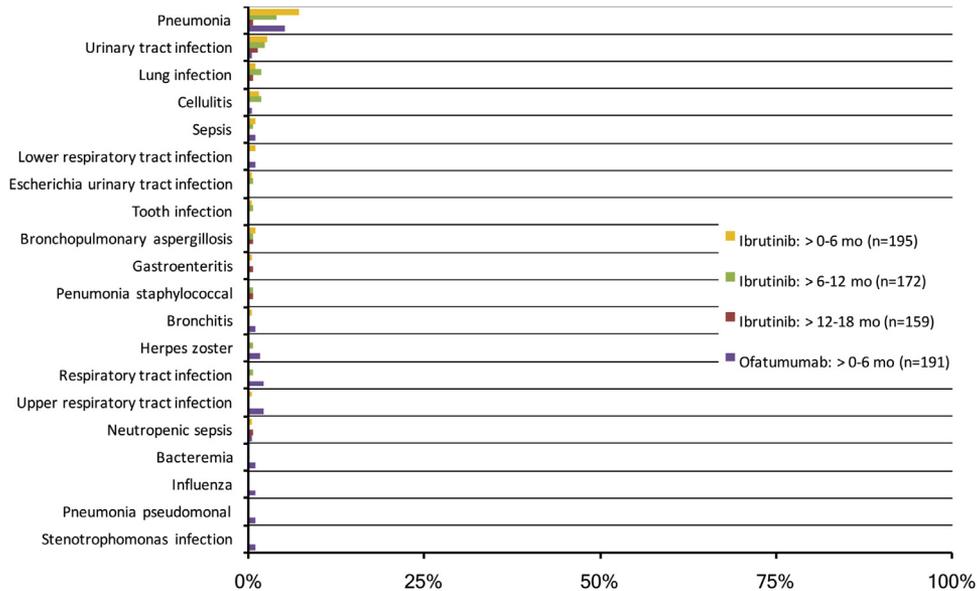


Supplemental Figure 3 Effect of Ibrutinib on Tregs Quantified by Absolute Count by Flow Cytometric Staining (A) and Percentage (B). ULN and LLN ($\times 10^9/L$): 0.025 to 0.06; Shown by Dashed Lines



*P < .05, significantly different compared with baseline, with a paired t test. **P < .01, significantly different compared with baseline, with a paired t test. Abbreviations: LLN = lower limit of normal; Tregs = regulatory T cells; ULN = upper limit of normal.

Supplemental Figure 4 Prevalence Over Time of Grade ≥ 3 Infections Reported in > 1 Patient at Any Time With Ibrutinib (n = 59 of 195; 30%) or Ofatumumab (n = 40 of 196; 20%). Note: Two Ofatumumab-Treated Patients had Grade ≥ 3 Infections > 6 Months (Folliculitis, Tooth Abscess), and 1 Ibrutinib-Treated Patient had Grade ≥ 3 Infections > 18 Months (Urinary Tract infection)



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Supplemental Table 1 Compliance Rates for Patient-reported Outcomes^a

	Ibrutinib, n/N (%)	Ofatumumab, n/N (%)
FACIT-F		
Baseline	165/195 (85%)	154/196 (79%)
Week 12 (day 84)	133/188 (71%)	112/171 (65%)
Week 24 (day 168)	130/178 (73%)	102/134 (76%)
Week 36 (day 252)	112/165 (68%)	—
Week 48 (day 336)	60/158 (38%)	—
Week 60 (day 420)	28/154 (18%)	—
Week 72 (day 504)	6/152 (4%)	—
EORTC QLQ-C30		
Baseline	166/195 (85%)	148/196 (76%)
Week 12 (day 84)	135/188 (72%)	116/171 (68%)
Week 24 (day 168)	131/178 (74%)	107/134 (80%)
Week 36 (day 252)	112/165 (68%)	—
Week 48 (day 336)	60/158 (38%)	—
Week 60 (day 420)	28/154 (18%)	—
Week 72 (day 504)	6/152 (4%)	—

Abbreviations: EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaires Core 30; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue.

^aData for ofatumumab beyond 24 weeks were limited due to the 24-week ofatumumab therapy and allowance of new treatments including crossover to ibrutinib following progression.

Supplemental Table 2 EORTC QLQ-C30 Domains at Baseline and Week 24

Mean ± SD	Ibrutinib (n = 195)			Ofatumumab (n = 196)		
	Baseline (n = 118) ^a	Week 24 (n = 132)	Δ	Baseline (n = 89) ^a	Week 24 (n = 107)	Δ
Global health status ^b	59.8 ± 24.9	68.3 ± 21.3	9.0 ± 24.1	64.9 ± 22.7	69.5 ± 22.1	5.8 ± 21.5
Role functioning	72.9 ± 31.0	75.8 ± 26.8	4.0 ± 28.2	72.3 ± 30.4	76.3 ± 28.0	6.4 ± 27.1
Emotional functioning	76.9 ± 21.1	78.7 ± 23.9	2.4 ± 19.4	80.3 ± 19.3	81.3 ± 22.1	2.6 ± 16.2
Physical functioning	75.6 ± 23.6	80.6 ± 20.5	6.4 ± 18.0	81.4 ± 20.4	82.0 ± 20.2	1.7 ± 15.7
Cognitive functioning	82.2 ± 21.3	82.1 ± 21.0	0.6 ± 16.2	86.1 ± 20.0	82.6 ± 20.7	-3.0 ± 16.8
Social functioning	74.0 ± 28.3	80.2 ± 25.1	7.5 ± 25.4	75.7 ± 27.3	82.4 ± 21.5	8.1 ± 20.6
Fatigue ^c	35.7 ± 27.8	28.7 ± 24.7	-8.1 ± 22.8	31.2 ± 25.8	27.9 ± 24.8	-4.5 ± 23.4
Nausea/vomiting ^c	4.5 ± 12.8	6.3 ± 15.8	0.6 ± 13.4	4.5 ± 8.6	3.4 ± 8.5	-1.5 ± 9.9
Pain score ^c	19.1 ± 26.8	18.8 ± 26.2	-0.7 ± 23.7	14.0 ± 22.2	16.0 ± 24.7	0.2 ± 22.5
Dyspnea ^c	26.3 ± 29.5	15.7 ± 22.7	-11 ± 26.5	23.6 ± 28.1	15.9 ± 24.4	-9.0 ± 27.0
Insomnia ^c	26.3 ± 31.4	21.7 ± 29.7	-5.6 ± 27.7	27.7 ± 27.6	21.8 ± 26.7	-6.0 ± 23.9
Appetite loss ^c	17.2 ± 24.9	10.1 ± 22.5	-8.5 ± 27.3	22.5 ± 29.2	10.0 ± 18.4	-13.0 ± 26.8
Constipation ^c	11.9 ± 23.7	8.8 ± 22.5	-4.5 ± 25.8	8.6 ± 19.2	7.8 ± 18.6	0.4 ± 22.8
Diarrhea ^c	9.6 ± 20.0	15.2 ± 27.4	5.1 ± 29.8	10.1 ± 22.1	10.9 ± 22.8	-0.4 ± 18.5
Financial difficulties ^c	20.1 ± 30.2	18.2 ± 27.1	-3.1 ± 25.0	15.0 ± 28.4	15.6 ± 26.4	-0.7 ± 22.5

Abbreviations: EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaires Core 30; SD = standard deviation.

^aIncludes patients with assessment at both baseline and week 24.

^bWith ibrutinib, n = 117 at baseline and n = 131 at week 24.

^cNegative change is an improvement, for all others a positive change is an improvement.

Supplemental Table 3 Peak ALC in All Patients Treated With Ibrutinib at Any Time

Baseline ALC × 10 ⁹ /L	Post-baseline Peak ALC × 10 ⁹ /L, n (%)			
	< 50	50-100	100-400	≥ 400
< 50 (n = 119)	68 (57.1)	25 (21.0)	25 (21.0)	1 (0.8)
50-100 (n = 36)	2 (5.6)	10 (27.8)	24 (66.7)	0 (0.0)
≥ 100 (n = 37)	1 (2.7)	1 (2.7)	30 (81.1)	5 (13.5)
Total	71 (2.7)	36 (18.8)	79 (41.1)	6 (3.1)

Abbreviation: ALC = absolute lymphocyte count.

Supplemental Table 4 Patient Data for Those Experiencing MH^a

MH Event	Grade 4 Subdural Hematoma	Grade 2 Bilateral Subdural Hematoma	Grade 3 Post-procedural Hemorrhage	Grade 3 Spontaneous Hematoma (in Psoas)
Start of MH, day	321	310	18	508
Use of AC/AP	None reported	Heparin, enoxaparin	None reported	Enoxaparin, clopidogrel
Platelet count	219 × 10 ⁹ /L (central; day 330); 140 × 10 ⁹ /L (local; day 321)	151 × 10 ⁹ /L (central; day 317); 64 × 10 ⁹ /L (local; day 310)	127 × 10 ⁹ /L (central; day 16); 105 × 10 ⁹ /L (local; day 19)	217 × 10 ⁹ /L (central)
Coagulation testing	PT 15.1 sec (11.4-14.0); day 323	PT 11.3 sec and PTT 29.3 sec (both within normal limits); day 310	PT 10.3 sec and PTT 21.3 sec (both within normal limits); day 19	Available from screening only, within normal limits
Inciting events	None reported	None reported	Post-procedural bleeding (removal of skin lesion), related to ibrutinib	None reported ^b
Contributing AEs, other bleeding AEs	Grade 1 thrombocytopenia	Grade 1 petechiae	None reported	Grade 1 right hand hematoma
History of bleeding	Increased tendency to bruise (Grade 1, ongoing)	None reported	None reported	None reported

Abbreviations: AC = anticoagulant; AE = adverse event; AP = antiplatelet; MH = major hemorrhage; PT = prothrombin time; PTT = partial thromboplastin time.

^aAll 4 events deemed possibly related or related to ibrutinib.

^bGrade 3 fall and grade 3 cranial laceration reported on study day 489, unclear if events were contributing AEs.

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Supplemental Table 5 Adverse Events That Led to D/C of Study Drug

Preferred Term	Study Day for Drug D/C	Investigator Response at Time of D/C	Time to Progression, mos	Time to Death/Last Known Alive, mos
Ibrutinib (n = 23 patients)				
Sepsis	6	NA	0.3	0.3
Neutropenic sepsis	23	NA	1.1	1.1
Neutropenia	36	SD	9.4	11.3
Chronic obstructive pulmonary disease	53	PRL	NA	14.6
Pneumonia	55	NA	4.0	4.0
Sepsis	57	NA	2.0	2.0
Pneumonia	69	PRL	2.4	2.4
<i>Pneumocystis jirovecii</i> pneumonia	73	PR	6.7	6.7
Diarrhea	79	SD	4.5	19.0
Lung adenocarcinoma metastatic	88	PRL	2.7	14.3
Gastrointestinal carcinoma	108	SD	5.8	5.8
Pneumonia	177	SD	6.0	6.0
Cardiac arrest	182	PR	6.0	6.0
Atrial fibrillation	229	PD	8.2	16.9
Pneumonia	249	PR	10.8	14.4
Pneumonia	275	SD	9.6	9.6
Myositis	291	SD	13.1	15.0
Subdural hematoma	310	PD	10.7	19.4
Arrhythmia ^a	313	PD	9.9	10.8
Richter syndrome ^a	313	PD	9.9	10.8
Fatigue ^b	316	PR	13.4	15.5
Weight decreased ^b	316	PR	13.4	15.5
Pneumonia	327	PR	11.3	11.3
Sudden death	366	SD	12.1	12.1
Transient ischemic attack	664	PR	21.7	22.2
Ofatumumab (n = 16 patients)				
Infusion related reaction	10	NA	13.4	16.7
Acute myocardial infarction	11	NA	5.9	14.5
Febrile neutropenia	20	PD	0.9	6.9
Nocardiosis	21	NE	3.3	3.3
Bacteremia	29	NA	1.3	1.3
Upper respiratory tract infection	29	NA	1.6	1.6
Pneumonia	30	NA	1.8	1.8
Pneumonia	37	NA	1.7	1.7
Metastatic squamous cell carcinoma	49	NA	3.2	3.2
Herpes zoster	53	NA	8.4	9.7
Influenza	76	NE	3.2	3.2
Pyrexia	94	SD	3.6	3.6
Squamous cell carcinoma	107	SD	4.2	4.2
Pneumonia	112	SD	3.9	3.9
Rash erythematous	141	PR	8.3	9.1
Pneumonia	142	SD	5.5	6.9

Abbreviations: D/C = discontinuation; NA = not assessed; NE = not evaluable; PR = partial response; PRL = PR with lymphocytosis; SD = stable disease.

^aOne patient had 2 adverse events that led to D/C (arrhythmia, Richter syndrome).

^bOne patient had 2 adverse events that led to D/C (fatigue, weight decreased).