Title (145/165 characters inc spaces): Single-Agent Ibrutinib for Rituximab-Refractory Waldenström’s Macroglobulinemia: Final Analysis of the Substudy of the Phase III iNNOVATE™ Trial

Running title (44/60 characters inc spaces; abbreviations permitted): Single-Agent Ibrutinib for RTX-Refractory WM

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**References:** 20 (limit: 50)

**Translational relevance** (150-word limit): 145

Rituximab resistance is commonly observed in patients with Waldenström’s macroglobulinemia (WM) due to its widespread and repeated use as either monotherapy or in a combination regimen. Results from the first report of the phase III iNNOVATE substudy showed that single-agent ibrutinib was effective and well-tolerated in patients with previously treated, rituximab-refractory WM. Here we present results from the final analysis after up to 5 years of follow-up (median: 58 months [range: 9–61]). Patients were heavily pretreated, receiving a median of four prior lines of therapy. Continuous treatment with single-agent ibrutinib led to sustained response,
durable progression-free survival and overall survival, and an acceptable safety profile. Importantly, sustained improvements in hemoglobin and serum IgM and clinically meaningful improvements in patient-reported outcomes were also demonstrated. Our findings support single-agent ibrutinib as an effective chemotherapy-free treatment option for patients with rituximab-refractory WM, a population with limited treatment options.
Abstract (250-word limit): 250

Purpose: The first report from the open-label substudy of the phase III iNNOVATE study (PCYC-1127; NCT02165397) demonstrated that single-agent ibrutinib was efficacious and well tolerated in patients with heavily pretreated, rituximab-refractory Waldenström’s macroglobulinemia (WM). Results from the final analysis are now reported.

Experimental Design: Ibrutinib 420 mg was administered once daily to patients (N=31) who failed to achieve at least a minor response (MR) or who relapsed <12 months after their last rituximab-containing therapy. Endpoints included progression-free survival (PFS) and overall response rate (ORR; MR or better) per independent review committee, hemoglobin improvement, overall survival (OS), and safety; serum immunoglobulin M (IgM) was also assessed.

Results: After a median follow-up of 58 months (range: 9–61), median PFS was 39 months (95% CI: 25–not evaluable); 60-month PFS rate was 40%. In MYD88L265P/CXCR4WHIM and MYD88L265P/CXCR4WT subtypes, median PFS was 18 months and not reached, respectively. In all patients, ORR was 87%; responses deepened over time with major response (≥ partial response) rates increasing from 61% at 6 months to 77% at 60 months. Median OS was not reached. 17/21 patients (81%) with baseline hemoglobin ≤11.0 g/dL had sustained hemoglobin improvement. Improvements in serum IgM levels were sustained, reaching a maximum median change of −37 g/L at 54 months. Ibrutinib maintained a manageable safety profile, with no new safety signals identified. There were no events of major hemorrhage or atrial fibrillation.
Conclusions: In the final analysis from iNNOVATE, single-agent ibrutinib continued to show sustained efficacy in patients with heavily pretreated, rituximab-refractory WM.
Introduction

Waldenström’s macroglobulinemia (WM) is a rare lymphoproliferative disorder classified as an indolent non-Hodgkin B-cell lymphoma (1). For patients with WM, current treatments include alkylating agents, anti-CD20 monoclonal antibodies, proteosome inhibitors, nucleoside analogues in combination with rituximab, as well as ibrutinib (2). While rituximab-based regimens are most commonly used for the treatment of symptomatic WM, most patients will eventually develop resistance to rituximab (3). For patients with rituximab-refractory WM, effective treatment options are limited (2). Experience with ibrutinib in this patient population remains limited.

Ibrutinib is the only once-daily Bruton’s tyrosine kinase (BTK) inhibitor approved as either a single agent or in combination with rituximab for patients with WM across all lines of therapy and is the only BTK inhibitor approved for the treatment of WM (4). Ibrutinib was originally identified as a potential treatment for WM based on the high prevalence of MYD88 mutations in patients with WM (5). More than 90% of patients carry the MYD88L265P point mutation, and nearly one-third of these patients also have a frameshift or nonsense mutation in CXCR4 (6). Mutations in MYD88 and CXCR4 are associated with important differences in disease presentation, including serum IgM levels and symptoms at diagnosis (5). Mutations in both CXCR4 and MYD88 are associated with constitutive activation of the BTK pathway (7), making BTK inhibitors an attractive therapeutic option (5). Results from a pivotal phase 2 study demonstrated high response rates with single-agent ibrutinib in patients with relapsed WM (8).
In the phase III randomized iNNOVATE study (PCYC-1127; NCT02165397), ibrutinib demonstrated superior progression-free survival (PFS) in combination with rituximab versus single-agent rituximab in patients with WM (9). In the open-label substudy of iNNOVATE for patients with heavily pretreated, rituximab-refractory WM, single-agent ibrutinib demonstrated sustained efficacy and was well tolerated (10,11). With a median follow-up of 18 months, the estimated 18-month PFS rate per investigator assessment was 86%, and the overall survival (OS) rate was 97% (10). Median PFS was still not reached after a median of 39 months of follow-up in a subsequent analysis (11).

Here we present results from the final analysis of the iNNOVATE substudy of single-agent ibrutinib in patients with rituximab-refractory WM, representing up to 5 years of follow-up, an additional 40 months since the first report.

**Methods**

**Study design**

The iNNOVATE substudy was an international, multicenter, single-arm, open-label trial designed to assess the efficacy and safety of single-agent ibrutinib in patients with rituximab-refractory WM. Study design details have been previously published (10). In brief, eligible patients had centrally confirmed WM defined per criteria from the Second International Workshop on Waldenström’s Macroglobulinemia (IWWM) and had failed to achieve at least a minor response to their last rituximab-containing therapy or relapsed <12 months after their last rituximab-containing therapy. Patients received once-daily ibrutinib 420 mg until unacceptable toxicity or progressive disease (PD). iNNOVATE
was approved by institutional review boards or independent ethics committees at each institution and was conducted according to the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines from the International Conference on Harmonization. All patients provided written informed consent prior to enrollment.

Endpoints and assessments

The primary endpoint was PFS per independent review committee (IRC). Other endpoints included response per IRC, hematologic improvement as measured by change in hemoglobin, OS, safety, and patient-reported outcomes (10). Change in serum IgM was also assessed.

Efficacy, safety, and response assessments were conducted as described previously (10). Briefly, responses were assessed according to the modified consensus criteria from the sixth IWWM. The proportion of patients with an overall response was defined as the proportion of patients who achieved a minor response (≥25% but <50% reduction of serum IgM from baseline) or better. Major response was defined as a partial response (PR; ≥50% reduction of serum IgM concentrations from baseline) or better.

Adverse events (AEs), regardless of attribution, were collected by investigators throughout the study and graded per National Cancer Institute Common Terminology Criteria for Adverse Events v4.03.

Genotype analysis
Bone marrow aspirates were collected to assess *MYD88* and *CXCR4* mutational status using the Personalis ACE Extended Cancer Panel (Menlo Park, CA, USA) with >500X mean coverage depth. Calls of somatic variants for *MYD88* and *CXCR4* used the Personalis Cancer Panel DNA pipeline operating in the tumor-only mode with no matched normal samples.

**Patient-reported outcomes**

Patient-reported outcomes and disease-related symptoms were measured according to the Functional Assessment of Cancer Therapy-Anemia (FACT-An) and the EuroQoL 5-Dimension Questionnaire (EQ-5D-5L©; copyright of EuroQol Research Foundation. EQ-5D™ is a trademark of the EuroQol Research Foundation), as previously described (10). A clinically meaningful improvement in FACT-An was defined as an increase of ≥7 points in the total score or ≥6 points in the anemia subscale score. A clinically meaningful improvement in 5Q-5D-5L was defined as an increase of ≥7 points in the visual analog scale (VAS) or ≥0.08 points in the utility score.

**Statistical analysis**

The open-label substudy provided a descriptive analysis of the efficacy, safety, and patient-reported outcomes of single-agent ibrutinib for the treatment of patients with rituximab-refractory WM and was not designed to provide statistical comparisons. Analyses included all patients who received at least one dose of ibrutinib.

Kaplan-Meier estimates of PFS, OS, time to next treatment, and duration of response (DOR) were calculated. For overall response rate (ORR; minor response or better) and
major response rate (PR or better), 95% confidence intervals (CIs) were provided. Sustained hematologic improvement was defined as improvement in hemoglobin of \( \geq 2.0 \text{ g/dL} \) (intent-to-treat population) or an increase to \( >11.0 \text{ g/dL} \) with improvement of \( \geq 0.5 \text{ g/dL} \) (patients with baseline hemoglobin \( \leq 11.0 \text{ g/dL} \)) for \( \geq 56 \) days. DOR was defined as the duration from the date of initial documentation of response to the date of first documented evidence of PD or death for responders.

Results

Patient demographics and characteristics

Thirty-one patients were enrolled; their detailed baseline characteristics were previously reported (10). Patients had received a median four prior lines of systemic therapy (range: 1–7), and more than one-third of patients (39%) had at least five prior treatments (Table 1). Median baseline hemoglobin was 10.3 g/dL (range: 6.4–14.6), and 68% of patients had hemoglobin \( \leq 11.0 \text{ g/dL} \). Mutational data were available for 25 of 31 patients (81%); six were missing due to lack of tumor sample or low tumor yield. Of those with available mutational data, 17 patients (68%) had the \text{MYD88}^{L265P}/\text{CXCR4}^{WT} \text{ genotype}, seven (28%) had the \text{MYD88}^{L265P}/\text{CXCR4}^{WHIM} \text{ genotype}, and one (3%) had the \text{MYD88}^{WT}/\text{CXCR4}^{WT} \text{ genotype}.

Patient disposition

The final analysis was performed at the time of study closure, and the median follow-up was 58 months (range: 9–61). Treatment discontinuations during the study were due to
PD (n=13; 42%), AEs (n=2; 6%), and withdrawal by patient (n=2; 6%). Median duration of treatment was 41 months (range: 0.3–61). At study closure, 14 patients (45%) were still receiving ibrutinib: eight patients opted to enroll in a treatment extension study and six continued to receive commercial ibrutinib. Twelve patients (39%) in total received subsequent treatment; subsequent treatments included alkylating agent (n=7), anti-CD20 antibody therapy (n=6), corticosteroids (n=6), proteasome inhibitor (n=3), vinca alkaloids (n=2), anthracyclines (n=1), immunomodulator (n=1), nucleoside analog (n=1), and other (n=4; including 2 patients who received ibrutinib). Median time to next treatment was not reached (95% CI: 42–not evaluable [NE]).

**Progression-free survival**

At the time of the final analysis, median PFS was 39 months (95% CI: 25–NE); 18 patients had PD or died, and the estimated 60-month PFS rate was 40% (Figure 1). Median PFS was not reached (95% CI: 27–NE) in patients with the MYD88L265P/CXCR4WT genotype (n=17) and was 18 months (95% CI: 3–28) in patients with the MYD88L265P/CXCR4WHIM genotype (n=7). The single patient with the MYD88WT/CXCR4WT genotype progressed at 6 months.

**Response**

At the final analysis, the ORR per IRC was 87%; 29% of patients (n=9) achieved a best response of very good partial response (VGPR), 48% (n=15) achieved a best response of PR, and 10% (n=3) had a best response of minor response. Three patients (10%) had stable disease, and one patient was not evaluable due to a lack of follow-up
assessments after week 1. Over time, a deepening of response was observed with major response rates increasing from 61% at 6 months to 71% at 18 months and 77% at 60 months (Figure 2A). The median time to overall response (minor response or better) was 1 month (range: 1–20), and the median time to major response (PR or better) was 2 months (range 1–52). In patients who achieved a response, the median DOR per IRC was 33 months (range: 2–60+).

ORRs were similar between the MYD88\textsuperscript{L265P}/CXCR4\textsuperscript{WT} (88%) and MYD88\textsuperscript{L265P}/CXCR4\textsuperscript{WHIM} (86%) genetic subtypes (Figure 2B). However, a larger proportion of patients with the MYD88\textsuperscript{L265P}/CXCR4\textsuperscript{WT} genotype achieved a VGPR (41% vs 14%). The one patient with MYD88\textsuperscript{WT}/CXCR4\textsuperscript{WT} genotype had a best response of stable disease. Median time to minor response or better was 1 month (range: 1–4) in patients with the MYD88\textsuperscript{L265P}/CXCR4\textsuperscript{WT} genotype and 1 month (range: 1–2) in those with the MYD88\textsuperscript{L265P}/CXCR4\textsuperscript{WHIM} genotype. Median time to major response (PR or better) was 1 month (range: 1–50) and 4 months (range: 1–7) in patients with MYD88\textsuperscript{L265P}/CXCR4\textsuperscript{WT} and MYD88\textsuperscript{L265P}/CXCR4\textsuperscript{WHIM} genotypes, respectively.

Hemoglobin and IgM levels

At baseline, median hemoglobin was 10.3 g/dL (range: 6.4–14.6). Improvements in hemoglobin were generally rapid (median +1.7 g/dL increase from baseline to week 9) and reached a maximum median change of +3.5 g/dL at 35 months (Figure 3). In patients who had baseline hemoglobin levels ≤11.0 g/dL, the maximum median increase from baseline was +4.3 g/dL (range: 1.2–8.9) at month 50. In total, 22 of 31
patients (71%) exhibited sustained hemoglobin improvement, including 17 of 21 patients (81%) who had baseline hemoglobin levels ≤11.0 g/dL.

Likewise, improvements in IgM were generally rapid and sustained. Median serum IgM was 39 g/L (range: 9–107) at baseline. The median change reached −20 g/L at week 9, and reached the maximum −37 g/L at 54 months (Figure 3).

**Overall survival**

Median OS was not reached (95% CI: NE–NE), and the 60-month OS rate was 73% (Figure 4). Median OS was not reached for all subgroups evaluated by number of prior lines of therapy (Figure 4). When analyzed by genotype, median OS was not reached (95% CI: NE–NE) in patients with the MYD88L265P/CXCR4WT genotype (n=17) and was 50 months (95% CI: 11–NE) in patients with the MYD88L265P/CXCR4WHIM genotype (n=7). The single patient with the MYD88WT/CXCR4WT genotype died at 9 months.

**Safety**

Patients had received single-agent ibrutinib for a median of 41 months (range: 0.3–61). Overall, 30 patients (97%) experienced a treatment-emergent AE (TEAE), and 25 patients (81%) had a grade ≥3 TEAE. The prevalence of TEAEs of clinical interest of any grade (occurring in >2 patients) during the last 2 years of treatment were infections (years 3–4: 47%, 8/17; years 4–5: 50%, 7/14), hypertension (years 3–4: 29%, 5/17; years 4–5: 36%, 5/14), and diarrhea (years 3–4: 24%, 4/17; years 4–5: 7%, 1/14). The prevalence of grade ≥3 AEs of clinical interest generally declined over time with ibrutinib.
treatment (Figure 5). Notably, no patients experienced major hemorrhage or atrial fibrillation. Of three patients with grade ≥3 hypertension during the study, all had hypertension at baseline. Grade ≥3 neutropenia and grade ≥3 thrombocytopenia primarily occurred during the first year of treatment, with one patient each experiencing these AEs in subsequent years. Five patients experienced a total of seven AEs requiring dose reduction (diarrhea, n=2; arthralgia, n=1; maculopapular rash, n=1; nausea, n=1; constipation, n=1; and fecalith, n=1); all seven AEs resolved following dose reduction, and one patient was able to resume treatment at the full ibrutinib dose. Two patients experienced a TEAE leading to discontinuation of ibrutinib (grade 2 diarrhea and grade 3 constipation; n=1 each). No deaths occurred due to TEAEs.

Patient-reported outcomes

Patients reported clinically meaningful improvements in quality-of-life measures. FACT-An score, anemia subscale score, and EQ-5D-5L VAS improved from baseline. At the time of final analysis, most patients had a clinically meaningful improvement in total FACT-An score (77%; n=24) and anemia subscale score (84%; n=26) (Figure S1). Clinically meaningful improvements in EQ-5D-5L VAS and utility score were also reported by 71% of patients (n=22) each.

Discussion

In this final analysis of the open-label substudy of the phase III iNNOVATE trial, once-daily, single-agent ibrutinib demonstrated sustained efficacy in patients with heavily
pretreated, rituximab-refractory WM. With a median follow-up of 58 months, representing approximately 40 months of additional follow-up since the initial analysis, single-agent ibrutinib continued to demonstrate durable clinical benefit. Response deepened over time, driven by an increase in VGPR from 16% at month 6 to 23% at month 18 and 29% at month 60. Additionally, responses were durable with a median DOR of 33 months. After a median 58 months of follow-up and regardless of the number of prior therapies, median OS was not reached. Median hemoglobin increased and serum IgM levels decreased rapidly and were sustained with treatment. Correspondingly, clinically meaningful improvements in patient-reported outcomes were reported by most patients and were sustained over time.

The long-term results of our study suggest that single-agent ibrutinib offers durable clinical benefit for patients with rituximab-refractory WM, a population with few effective treatment options. Other recent trials in previously treated patients with WM have reported similar results to those reported here. In a phase 2 study by Treon et al of 63 patients with relapsed WM treated with single-agent ibrutinib, the median 5-year PFS rate was not reached and the 5-year OS rate was 87% (12). Overall and major response rates were 90.5% and 79.4%, respectively, after a median follow-up of 59 months (12); this is highly concordant with the 87% overall and 77% major response rates reported here after a median follow-up of 60 months. Consistent with previous observations that patients with MYD88-wildtype WM have shorter survival and a lower probability of response than those with a MYD88 mutation (15) and that mutations in CXCR4 are associated with a lower likelihood of achieving a major response compared to patients
with CXCR4-wildtype disease (6), results from Treon et al showed that efficacy responses were genotype dependent. In patients with MYD88-wildtype WM, the median PFS was 0.4 years, whereas those with MYD88\textsuperscript{Mut}/CXCR4\textsuperscript{WT} and MYD88\textsuperscript{Mut}/CXCR4\textsuperscript{Mut} genotypes had a median PFS of not reached and 4.5 years, respectively (12).

In addition to studies with ibrutinib, another BTK inhibitor, zanubrutinib, has been evaluated as a treatment for WM. In the phase 3 ASPEN study investigating ibrutinib versus zanubrutinib in both previously untreated and previously treated patients with MYD88\textsuperscript{L265P} WM, the primary endpoint of superiority of zanubrutinib was not met; 84% of patients treated with ibrutinib and 85% treated with zanubrutinib were progression-free at 18 months, and major response rates were 78% (ibrutinib) and 77% (zanubrutinib) (13). In the ASPEN single-arm cohort conducted in patients with the MYD88-wildtype genotype, estimated 18-month PFS and OS rates were 68% and 88%, respectively, after treatment with zanubrutinib (median PFS and OS were not reached with a median follow-up of 17.9 months) (14). Interestingly, in an earlier report (median 19 months on treatment) of the above study by Treon et al, the overall response rate in patients with MYD88- wildtype genotype was 71% (8), which is similar to the rate reported in the ASPEN study (81%) at 17.9 months of follow-up (14), suggesting that longer follow-up may be needed to clearly observe the impact of genotype on survival benefit.

The impact of genotype status in the current analysis should be interpreted with caution due to small sample sizes of the subgroups, particularly those with the MYD88\textsuperscript{L265P}/CXCR4\textsuperscript{WHIM} (n=7) and MYD88\textsuperscript{WT}/CXCR4\textsuperscript{WT} (n=1) genotypes. Additionally,
indirect comparisons between these studies and our own may be further confounded by differences in patient characteristics and study design. Nonetheless, we did observe lower VGPR rates and shorter median PFS and OS in the subset of patients with the MYD88<sup>L265P</sup>/CXCR4<sup>WHIM</sup> genotype versus those with the MYD88<sup>L265P</sup>/CXCR4<sup>WT</sup> genotype. In contrast to these findings, the double-blind randomized portion of this study in which patients with non–rituximab-refractory WM received ibrutinib or placebo in combination with rituximab demonstrated sustained clinical benefit with ibrutinib-rituximab among all genotypes; patients treated with ibrutinib-rituximab had a PFS benefit over those treated with placebo-rituximab, regardless of genotype (HR [95% CI]: MYD88<sup>L265P</sup>/CXCR4<sup>WT</sup>, 0.18 [0.08–0.43]; MYD88<sup>L265P</sup>/CXCR4<sup>WHIM</sup>, 0.27 [0.12–0.62]; MYD88<sup>WT</sup>/CXCR4<sup>WT</sup>, 0.29 [0.07–1.19]) (16).

Ibrutinib was well tolerated, and no new safety signals emerged over more than 5 years of follow-up. Consistent with observations from other studies, AEs were generally most common during the first year of ibrutinib treatment and decreased over time (17-20). No major hemorrhage or atrial fibrillation events occurred during the entire study. Most AEs were low grade, and few patients (n=2) discontinued treatment due to an AE. Notably, grade ≥3 neutropenia and thrombocytopenia were observed in a small number of patients, primarily during the first year of treatment. This contrasts with a previous report that neutropenia and thrombocytopenia were more common in heavily pretreated patients (12). All AEs that led to an ibrutinib dose reduction resolved following dose reduction, suggesting that many AEs can be managed effectively with dose modification.
In conclusion, single-agent ibrutinib remains an effective treatment for patients with heavily pretreated, rituximab-refractory WM. This regimen provides sustained efficacy, is well tolerated, and provides clinically meaningful improvements in quality of life in a population of patients who have few effective treatment options.

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Data Sharing Statement

Requests for access to individual participant data from clinical studies conducted by Pharmacyclics LLC, an AbbVie Company, can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu
Role of the Funder/Sponsor: Pharmacyclics LLC, an AbbVie Company, sponsored and designed the study. Study investigators and their research teams collected the data. The sponsor confirmed data accuracy and performed analysis of the data. Medical writing support was funded by the sponsor.
References


### Tables and Figures

Table 1. Patient demographics and baseline characteristics

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<td>3–4</td>
<td>10 (32)</td>
</tr>
<tr>
<td>≥5</td>
<td>12 (39)</td>
</tr>
<tr>
<td><strong>Prior autologous stem cell transplant, n (%)</strong></td>
<td>2 (6)</td>
</tr>
<tr>
<td><strong>Types of prior therapy, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Rituximab</td>
<td>31 (100)</td>
</tr>
<tr>
<td>Alkylating agent</td>
<td>28 (90)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>27 (87)</td>
</tr>
<tr>
<td>Purine analog</td>
<td>16 (52)</td>
</tr>
<tr>
<td>Vinca alkaloids</td>
<td>15 (48)</td>
</tr>
<tr>
<td>Proteasome inhibitor</td>
<td>14 (45)</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>12 (39)</td>
</tr>
<tr>
<td>Immunomodulating agent</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Nucleoside analog (cytarabine)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (26)</td>
</tr>
<tr>
<td><strong>Genotype, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>MYD88&lt;sup&gt;L265P&lt;/sup&gt;/CXCR4&lt;sup&gt;WT&lt;/sup&gt;</td>
<td>17 (68)</td>
</tr>
<tr>
<td>MYD88&lt;sup&gt;L265P&lt;/sup&gt;/CXCR4&lt;sup&gt;WHIM&lt;/sup&gt;</td>
<td>7 (28)</td>
</tr>
<tr>
<td>MYD88&lt;sup&gt;WT&lt;/sup&gt;/CXCR4&lt;sup&gt;WT&lt;/sup&gt;</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Most common concomitant medications, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Antibacterials</td>
<td>26 (84)</td>
</tr>
<tr>
<td>Analgesics</td>
<td>17 (55)</td>
</tr>
<tr>
<td>Antivirals</td>
<td>16 (52)</td>
</tr>
<tr>
<td>Anti-inflammatory and antirheumatic agents</td>
<td>14 (45)</td>
</tr>
<tr>
<td>Medications for acid-related disorders</td>
<td>13 (42)</td>
</tr>
<tr>
<td>Antithrombotic agents</td>
<td>12 (39)</td>
</tr>
<tr>
<td>Anti-anemic preparations</td>
<td>12 (39)</td>
</tr>
<tr>
<td>Vitamins</td>
<td>11 (36)</td>
</tr>
<tr>
<td>Ophthalmologicals</td>
<td>10 (32)</td>
</tr>
</tbody>
</table>
### Most common reasons for treatment initiation, n (%)

<table>
<thead>
<tr>
<th>Reason</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>22</td>
<td>71</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>13</td>
<td>42</td>
</tr>
<tr>
<td>Hgb ≤10 g/dL</td>
<td>13</td>
<td>42</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>7</td>
<td>23</td>
</tr>
</tbody>
</table>

*a* Genotype data available for 25 patients; percentages were calculated using 25 as the denominator. Hgb, hemoglobin; IgM, immunoglobulin M; IPSSWM, International Prognostic Scoring System for Waldenström’s Macroglobulinemia.
Figure 1. Progression-free survival as assessed by independent review committee in all patients and by genetic subtype.\textsuperscript{a}
\textsuperscript{a}The single patient with MYD88\textsuperscript{WT}/CXCR4\textsuperscript{WT} genotype is not shown; this patient progressed at 5.6 months.
CI, confidence interval; PFS, progression-free survival.

Figure 2. Overall response rate. A) Cumulative best response over time in all patients. Overall response rates are shown at the top of each bar, and major response rates are shown next to brackets for each bar. B) Best overall response per independent review committee in all patients and by genetic subtype.\textsuperscript{a}
\textsuperscript{a}The single patient with MYD88\textsuperscript{WT}/CXCR4\textsuperscript{WT} genotype is not shown; this patient had a best response of stable disease.
MR, minor response; ORR, overall response rate; PR, partial response; VGPR, very good partial response.

Figure 3. Median immunoglobulin M and hemoglobin levels over time.
Hgb, hemoglobin; IgM, immunoglobulin M.

Figure 4. Overall survival in all patients and by lines of prior therapy.

Figure 5. Prevalence of grade $\geq$3 adverse events of clinical interest by yearly interval.
\textsuperscript{a}Combined terms.
Figure 1

Progression-Free Survival, %

Patients at risk

All patients
MYD88<sup>L265P</sup>/CXCR4<sup>WT</sup>
MYD88<sup>L265P</sup>/CXCR4<sup>WHIM</sup>

Median PFS, mo (95% CI)

All patients 39 (25–NE)
MYD88<sup>L265P</sup>/CXCR4<sup>WT</sup> NR (27–NE)
MYD88<sup>L265P</sup>/CXCR4<sup>WHIM</sup> 18 (3–28)

Months

0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51 54 57 60 63

Progression-Free Survival, %

0 10 20 30 40 50 60 70 80 90 100

Patients at risk

All patients 31 30 27 26 25 23 20 16 15 14 13 12 11 11 11 10 2 0
MYD88<sup>L265P</sup>/CXCR4<sup>WT</sup> 7 6 4 4 4 4 4 3 2 1 1 1 0 1 0 1 0 1 0
MYD88<sup>L265P</sup>/CXCR4<sup>WHIM</sup> 17 17 17 17 16 16 16 15 13 10 9 8 8 8 8 8 8 7 1
Figure 2A

- **Patients, %**
  - 84% 84% 84%
  - 87% 87% 87% 87% 87% 87% 87% 87%
  - 61% 68% 71% 71% 71% 71% 71% 71% 74% 77%

- **Months**
  - 6 12 18 24 30 36 42 48 54 60

- **Bars**
  - MR
  - PR
  - VGPR

- **Values**
  - 16, 16, 23, 29, 29, 29, 29, 48, 16, 16
  - 45, 52, 48, 42, 42, 42, 42, 42, 45, 48
  - 23, 16, 13, 16, 16, 16, 16, 16, 13, 10

- **Author Manuscript Published OnlineFirst on August 11, 2021; DOI: 10.1158/1078-0432.CCR-21-1497**
All patients: N=31

MYD88<sup>L265P</sup>/CXCR4<sup>WT</sup> n=17

MYD88<sup>L265P</sup>/CXCR4<sup>WHIM</sup> n=7

Median time to ORR (≥MR), months (range)

1.0 (1-4)

Median time to major response (≥PR), months (range)

1.4 (1-2)

88%

14

47

86%

14

57

87%

29

48

10

Major response

Figure 2B
Figure 3

Median baseline IgM

Median baseline Hgb

Months

Median IgM, g/L

Hgb

IgM
Clinical Cancer Research

Single-Agent Ibrutinib for Rituximab-Refractory Waldenström's Macroglobulinemia: Final Analysis of the Substudy of the Phase III iNNOVATE™ Trial

Judith Trotman, Christian Buske, Alessandra Tedeschi, et al.

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