Predictive Biomarkers and Personalized Medicine

Prespecified Candidate Biomarkers Identify Follicular Lymphoma Patients Who Achieved Longer Progression-Free Survival with Bortezomib–Rituximab Versus Rituximab

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Introduction

The goal of treatment for patients with follicular lymphoma, a generally incurable, common indolent subtype of non-Hodgkin lymphoma (NHL; refs. 1, 2), is to prolong progression-free survival (PFS) and improve overall survival (OS). Follicular lymphoma is a highly heterogeneous
### Translational Relevance

Given the heterogeneity of follicular lymphoma and range of possible therapeutic options for patients with relapsed/refractory disease, the use of selected biomarkers based on mechanistic rationales to identify patient subgroups most likely to benefit from specific therapies is important. Candidate proteins and target gene polymorphisms were prespecified as potential prognostic markers for exploratory biomarker analyses in the phase III LYM-3001 study of bortezomib–rituximab versus rituximab in patients with relapsed/refractory follicular lymphoma. Comprehensive pairwise analyses, with genetic model testing, identified a biomarker pair, PSMB1 P11A (C/G-G/G) plus low CD68 expression, associated with a significant progression-free survival benefit, improved response rates, and longer overall survival with bortezomib–rituximab versus rituximab.

The benefit with bortezomib–rituximab was substantially greater than seen in the overall, unselected study population. The two biomarkers identified, for which a mechanistic hypothesis is provided for the reported efficacy benefit, would be feasible and practical to screen for in the clinical setting.

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**disease, as evidenced by variability in disease course, responsiveness to treatment, and outcomes (3–5). Therefore, to optimize treatment for individual patients, identification of subgroups that are most likely to benefit from a specific therapy is important.**

The anti-CD20 monoclonal antibody rituximab is the mainstay of treatment for follicular lymphoma (1). Additional treatment options may enhance the activity of rituximab-based therapy in the relapsed setting. The proteasome inhibitor bortezomib has shown single-agent activity in follicular lymphoma and other indolent NHL subtypes (6–8), as well as promising activity in combination with rituximab, with or without other agents, in patients with relapsed/refractory follicular lymphoma (9–12).

Results from the international, multicenter, randomized, phase III LYM-3001 study (13) showed improved PFS with bortezomib–rituximab versus rituximab alone in patients with relapsed/refractory rituximab-naive or rituximab-sensitive follicular lymphoma (median 12.8 vs. 11.0 months, HR 0.822, \(P = 0.039\)). The combination resulted in a significantly greater overall response rate (ORR; 63% vs. 49%, \(P = 0.0004\)), complete response (CR) rate (25% vs.18%, \(P = 0.035\)), and durable (≥6 months) response rate (50% vs. 38%, \(P = 0.002; \) ref. 13). After a median follow-up of 33.9 months, there was no difference in OS between arms (13).

The LYM-3001 protocol included as an exploratory end point a biomarker analysis aimed at identifying patient subgroups that derived a longer PFS benefit with, and were more likely to respond to, bortezomib–rituximab or rituximab alone. Candidate proteins and target gene polymorphisms were specified on the basis of prior studies of prognostic and/or response markers for lymphoma and of target or response markers for bortezomib or rituximab. Here, we present the findings of this exploratory biomarker analysis.

### Materials and Methods

**Patients and clinical study design**

The LYM-3001 (ClinicalTrials.gov trial registration ID: NCT00312845) study design has been reported previously (13). Eligible patients were aged 18 years or more with relapsed/refractory, rituximab-naive, or rituximab-sensitive (13) grade 1/2 follicular lymphoma. Patients with grade ≥2 peripheral neuropathy or clinical evidence of transformation to aggressive lymphoma were excluded. Patients were randomized (1:1) to receive five 5-week cycles comprising bortezomib (1.6 mg/m², days 1, 8, 15, and 22; all cycles) plus rituximab (375 mg/m², days 1, 8, 15, and 22, cycle 1, and day 1, cycles 2–5), or rituximab alone. Randomization was stratified according to Follicular Lymphoma International Prognostic Index (FLIPI; ref. 14) score, previous rituximab treatment, time since last dose of antilymphoma treatment, and region.

The primary end point was PFS. Secondary efficacy end points included ORR, CR rate, time to progression, and 1 year OS. Response was assessed using modified International Working Group response criteria (15). Time to next antilymphoma treatment (TTNT; time from randomization to first dose of next treatment) was an additional predefined efficacy end point.

All patients provided written informed consent. Review boards at all participating Institutions approved the study, which was conducted according to the provisions of the Declaration of Helsinki, the International Conference on Harmonization, and the Guidelines for Good Clinical Practice.

### Biomarker analysis study design

This prespecified focused analysis of potential biomarkers of sensitivity to bortezomib–rituximab or rituximab was an exploratory objective. All patients were required to provide consent for biomarker testing, and were included in the biomarker study if they had evaluable biomarker data and data for at least one clinical end point. Archived tumor tissue (samples requested from diagnosis) was collected at baseline, and samples were forwarded to a central laboratory as paraffin-embedded, formalin-fixed blocks or 6-micron slides. Whole blood samples for DNA analysis were collected at baseline. Serum samples were collected at multiple time points and stored for optional exploratory protein analysis.

### Prespecified candidate biomarkers

Protein candidates were NF-κB p65, proteasome subunit α-5 (PSMA5), p27, and CD68. These were chosen based on their attenuation by bortezomib (NF-κB, PSMA5, p27; refs. 16–20), and associations with poor prognosis in lymphoma (CD68; refs. 21, 22) and rituximab activity (CD68; ref. 22).
Drug target candidate genes were included for both bortezomib and rituximab. The proteasome subunit β (PSMB) genes 1, 2, and 5 interact with bortezomib and variation in these and in PSMB 6, 7, and 8 may be important for interindividual variation in responses (23–25). Variation in FCGR2A (26, 27) and FCGR3A influences affinity of immunoglobulin G antibodies for the Fcγ immune cell surface receptor (28, 29); and an association has already been shown between FCGR3A genotype and response to rituximab-based therapy (30, 31).

Assay methods

Validated immunohistochemistry tests were used for protein analysis at a central laboratory; a single pathologist evaluated all samples, averaging counts over 3 high-powered fields for each marker. Assays used included: CD68, DakoCytomation (#M0184; average macrophage counts overall and for the follicular and perifollicular spaces were calculated; CD68 correlated directly with the number of infiltrating macrophages); NF-kB, Cell Signaling (#C22B4); PSA5, Biomol International (#PW8125); and p27, Transduction Laboratories (BD Biosciences, #K25020). Point for protein markers used in the analyses are summarized in Supplementary Table S1. When insufficient sample was available for testing all biomarkers, immunohistochemistry analyses were prioritized; CD68 had the lowest priority.

TaqMan single-nucleotide polymorphism (SNP) assays (Applied Biosystems) and custom PCR/ligase detection reaction were used for genotyping (see Supplementary Materials and Methods). Alleles from PSMB subunit and FCGR2A/3A genes with sufficient variation (>10%) included PSMB1 P11A (rs12717), PSMB5 R24C (rs11543947), PSMB8 G8R (rs114772012), PSMB9 R60H (rs17587) and V32I (rs241419), FCGR2A H131R (rs1801274), Q62R (rs9427398), and Q62X (rs9427397) and FCGR3A V212F (rs396991).

Statistical analysis

The primary single-marker association analysis was aimed at identifying differentially expressed proteins or genotypes associated with clinical study end points (PFS, ORR, CR, TTNT, OS). For single-marker association analyses and pairwise comparisons, the log-rank test and Cox proportional hazard model were used for assessments of PFS, TTNT, and OS with bortezomib–rituximab and rituximab subgroups, including calculation of HRs and 95% CIs. The log-rank test was used for comparisons of outcomes with bortezomib–rituximab and rituximab subgroups according to genotype.

In the absence of independent datasets to validate findings, all LYM-3001 patients with no missing biomarker values were assigned (7:3 ratio) to discovery and confirmation test sets using simple randomization. The discovery set was used for identification of biomarkers significantly associated with a significant PFS benefit. The discovery set was used for independent validation; patients with missing data were included in the confirmation set provided data were available for significant biomarkers identified in the discovery phase. All markers and covariates were treated as categorical variables; protein biomarkers were dichotomized by staining pattern and frequencies of patients within score groups (Supplementary Table S1). PFS after treatment with bortezomib–rituximab and rituximab biomarker subpopulations was compared using the log-rank test, with 5-fold cross-validation for the biomarker pair, PSMB1 P11A (dominant C/G + G/G) and CD68 follicular expression ≤50, in the discovery set, and subsequently tested in the confirmation set.

Results

Patient characteristics

In total, 336 and 340 patients were randomized to treatment with bortezomib–rituximab and rituximab, respectively, and 334 and 339 received treatment (13). Patients providing evaluable samples and included in the biomarker analyses are summarized in Supplementary Fig. S1.

Single-marker associations and pairwise comparisons

Initial analyses focused on single-marker associations. Significant (P < 0.05) differences in PFS in patients treated with bortezomib–rituximab versus rituximab were seen in patient subgroups defined by biomarkers including
CD68 positivity, NF-xB p65 cytoplasmic signal, and PSMB1 P11A, FCGR2A/H166R, and FCGR3A/V212F genotypes; however, the PFS benefit in these patient subgroups (the difference in median PFS in patients treated with bortezomib–rituximab versus rituximab) was generally less than 5 months or population frequencies were low (Supplementary Fig. S2).

In pairwise analyses (1,140 comparisons), in which genotypes of SNP markers were used individually in combination with other biomarkers, 102 biomarker pairs were identified as defining a patient subgroup in which there was a significant ($P < 0.05$) difference in PFS in patients treated with bortezomib–rituximab versus rituximab. Of these, the difference in median PFS in patients treated with bortezomib–rituximab versus rituximab was 6 months or more for 14 biomarker pairs (Table 1). Following FDR correction to control for multiple comparisons (32), this PFS difference remained significant for one biomarker pair (PSMB1 P11A C/G heterozygote, $\leq 50$ CD68-positive cells). The population frequency of this biomarker pair was 33%. This biomarker pair was subsequently tested under different genetic models.

The biomarker pair of PSMB1 P11A and CD68 follicular expression was evaluated for association with PFS and OS under dominant (PSMB1 P11A C/C vs. C/G + G/G), recessive (C/C + C/G vs. G/G), and additive (C/C vs. C/G vs. G/G) genetic models, stratified by CD68 follicular expression ($0$–$50$ vs. $>50$ CD68-positive cells). By Cox regression analysis, among all evaluable patients, significant association with PFS was only seen under the dominant genetic model in patients with low CD68 expression. PSMB1 P11A C/G + G/G was significantly associated with PFS in the rituximab arm ($P = 0.0238$), and there was a trend of significant interaction between PSMB1 P11A genotype and treatment ($P = 0.0647$; Supplementary Table S2 and Supplementary Fig. S3), indicating that the association of the marker pair with PFS may be different between treatment arms. No significant associations with OS were seen, although there was a trend for association with OS in the bortezomib–rituximab arm with low CD68 expression and PSMB1 P11A under both the dominant ($P = 0.0801$; Supplementary Fig. S3) and additive ($P = 0.0888$) models. In subsequent analyses, the dominant model (G allele: C/G + G/G) was adopted for PSMB1 P11A in the significant biomarker pair.

Clinical outcomes in patients with/without significant biomarker pair

A total of 376 patients (186 bortezomib–rituximab treated, 190 rituximab treated) were evaluable for both PSMB1 P11A and CD68. There were 164 (43.6%) patients positive for the biomarker pair (PSMB1 P11A G allele, low CD68 expression, hereafter referred to as “biomarker-positive” patients; 78 bortezomib–rituximab treated, 86 rituximab treated). The PSMB1/CD68-evaluable population (total, and by treatment arm) was representative of the overall population in terms of demographics and baseline characteristics (Table 2), with no significant differences (except region and race, likely due to lower collection rate of tumor blocks/slides in China compared with the rest of the world). In addition, there was a similar distribution in baseline characteristics (Table 2), with no significant differences (except region and race, likely due to lower collection rate of tumor blocks/slides in China compared with the rest of the world).

### Table 1. Significant biomarker pairs identified by pairwise analysis$^a$

<table>
<thead>
<tr>
<th>Marker A</th>
<th>Marker B</th>
<th>Bortezomib–rituximab</th>
<th>Rituximab</th>
<th>Δ PFS, mo</th>
<th>Log-rank $P$</th>
<th>FDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSMB5 R24C C/T</td>
<td>NF-xB p65 cytoplasmic signal intensity $\leq 1$</td>
<td>5</td>
<td>27.0</td>
<td>7</td>
<td>10.4</td>
<td>16.6</td>
</tr>
<tr>
<td>PSMB1 P11A C/G</td>
<td>PSMA5-positive cytoplasmic signal $&gt;90$%</td>
<td>50</td>
<td>18.9</td>
<td>50</td>
<td>9.5</td>
<td>9.4</td>
</tr>
<tr>
<td>PSMB1 P11A C/G</td>
<td>CD68 positive (follicular) $\leq 50$</td>
<td>57</td>
<td>16.6</td>
<td>61</td>
<td>9.1</td>
<td>7.5</td>
</tr>
<tr>
<td>PSMB1 P11A C/G</td>
<td>Time since last treatment $&gt;1$ year</td>
<td>72</td>
<td>18.2</td>
<td>74</td>
<td>10.7</td>
<td>7.5</td>
</tr>
<tr>
<td>PSMB1 P11A C/G</td>
<td>CD68 positive (perifollicular) $&gt;50$</td>
<td>24</td>
<td>16.5</td>
<td>28</td>
<td>9.2</td>
<td>7.4</td>
</tr>
<tr>
<td>PSMB9 R60H G/G</td>
<td>NF-xB p65 nuclear positive $&gt;90$%</td>
<td>35</td>
<td>16.2</td>
<td>28</td>
<td>9.5</td>
<td>6.7</td>
</tr>
<tr>
<td>PSMB5 R24C C/T</td>
<td>CD68 positive (follicular) $\leq 50$</td>
<td>18</td>
<td>13.7</td>
<td>21</td>
<td>7.2</td>
<td>6.5</td>
</tr>
<tr>
<td>PSMB1 P11A C/G</td>
<td>Age $&lt;65$ years</td>
<td>86</td>
<td>15.3</td>
<td>96</td>
<td>9.2</td>
<td>6.1</td>
</tr>
<tr>
<td>Race group ‘other’</td>
<td>CD68 positive (follicular) $\leq 50$</td>
<td>63</td>
<td>18.2</td>
<td>69</td>
<td>9.3</td>
<td>8.9</td>
</tr>
<tr>
<td>High tumor burden: No</td>
<td>PSMA5 nuclear staining $&gt;20$%</td>
<td>11</td>
<td>14.4</td>
<td>7</td>
<td>3.8</td>
<td>7.6</td>
</tr>
<tr>
<td>Male sex</td>
<td>CD68 positive (overall) $&lt;50$</td>
<td>64</td>
<td>22.8</td>
<td>68</td>
<td>16.0</td>
<td>6.8</td>
</tr>
<tr>
<td>High tumor burden: No</td>
<td>CD68 positive (follicular) $\leq 50$</td>
<td>64</td>
<td>20.5</td>
<td>66</td>
<td>13.8</td>
<td>6.7</td>
</tr>
</tbody>
</table>

NOTE: The shaded biomarker pair was determined to remain significant following FDR correction for multiple testing (32).

$^a$Samples from China were not included in these initial pairwise biomarker assessments but were included in the subsequent genetic model analyses.
Table 2. Comparison of baseline demographics and disease characteristics between the overall study population and the PSMB1 P11A G allele/CD68 biomarker-evaluable population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall population</th>
<th>Biomarker-evaluable population</th>
<th>P*  overall vs. biomarker population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Btz-R (n = 336)</td>
<td>R (n = 340)</td>
<td>Total (N = 676)</td>
</tr>
<tr>
<td>Median age, y (range)</td>
<td>57 (24–83)</td>
<td>57 (21–84)</td>
<td>57 (21–84)</td>
</tr>
<tr>
<td>Age &gt;65 years, n (%)</td>
<td>81 (24)</td>
<td>87 (26)</td>
<td>168 (25)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>172 (51)</td>
<td>137 (40)</td>
<td>309 (46)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>249 (74)</td>
<td>257 (76)</td>
<td>506 (75)</td>
</tr>
<tr>
<td>Region, RoW, n (%)</td>
<td>183 (55)</td>
<td>182 (54)</td>
<td>365 (54)</td>
</tr>
<tr>
<td>High FLIPI (≥3), n (%)</td>
<td>138 (41)</td>
<td>140 (41)</td>
<td>278 (41)</td>
</tr>
<tr>
<td>High tumor burden, n (%)</td>
<td>185 (55)</td>
<td>179 (53)</td>
<td>364 (54)</td>
</tr>
<tr>
<td>Prior rituximab, n (%)</td>
<td>147 (44)</td>
<td>147 (43)</td>
<td>294 (44)</td>
</tr>
<tr>
<td>&gt;1 prior therapy, n (%)</td>
<td>192 (57)</td>
<td>202 (60)</td>
<td>394 (59)</td>
</tr>
</tbody>
</table>

Abbreviations: Btz, bortezomib; R, rituximab; RoW, rest of the World, excluding USA, Canada, and Europe.

*Fisher’s exact test or Mann–Whitney test.

**Significant differences likely due to lower collection rate of tumor blocks/slides in China (30%) compared with the rest of the world (80%).

Validation of these findings with the significant biomarker pair, using LYM-3001 patient discovery and confirmation test sets, is summarized in Supplementary Tables S3 and S4. Treatment exposure and safety profiles of bortezomib–rituximab and rituximab in the overall safety population and in biomarker-positive and biomarker-negative patients are summarized in Table 4. Among patients treated with bortezomib–rituximab, the proportion receiving all 5 cycles of bortezomib appeared higher, and rates of grade ≥3 adverse events and serious adverse events appeared numerically lower, in biomarker-positive patients versus biomarker-negative patients and the overall safety population. Conversely, among rituximab-treated patients, rates of grade ≥3 adverse events and serious adverse events appeared numerically higher in biomarker-positive patients.

Discussion

The findings of our analyses of protocol-specified biomarkers in the LYM-3001 study suggest that subgroups of patients with relapsed/refractory follicular lymphoma can be identified that experience significantly longer PFS benefit together with improved OS with addition of bortezomib to rituximab. Our results can be considered robust, being derived from one of the largest prospective randomized studies conducted in this setting. Per protocol, there was mandatory collection of archival tumor samples and whole blood samples, enabling substantial sample collections for these exploratory analyses of prespecified candidate biomarkers. The biomarker subgroup that we identified had a high population frequency (43.6%). There was also a sub- stantially greater efficacy benefit with bortezomib–rituximab versus rituximab in biomarker-positive patients than that seen in the overall, unselected study population (13). These findings indicate the usefulness of such biomarker...
analyses for identifying specific patient subgroups that benefit from bortezomib–rituximab (33) and the potential of such analyses for optimizing treatment for individual patients with follicular lymphoma.

Using pairwise analyses, we identified one biomarker pair that showed a significant PFS benefit with bortezomib–rituximab versus rituximab in biomarker-positive patients after multiple comparison correction. This pair was tested under different genetic models, and the presence of PSMB1 P11A G allele and low CD68 expression (<50 CD68-positive cells) was associated with a median PFS of 1.74 months in the biomarker-positive group and 1.58 months in the biomarker-negative group (P = 0.0013). The OS benefit in patients treated with bortezomib–rituximab appeared comparable with that in the overall study population. It should be noted that this was an exploratory analysis and, in the absence of an independent dataset with which to validate the results with the significant biomarker pair, we split our data from LYM-3001 patients into discovery and confirmatory test sets. The data from these analyses supported our findings. Nevertheless, independent validation studies are required for confirmation.

Important to note, the two biomarkers in this pair would be feasible and practical to screen for in the clinical setting, if these findings are confirmed in independent studies.

CD68 has established prognostic value in lymphoma and with rituximab-based treatment (21, 22, 34), and readily available assays enable measurement using methodology that is likely reproducible in laboratories with experience in lymphoma diagnosis. In addition, because we used a relatively straightforward genotyping assay for PSMB1 P11A, a validated assay could potentially be developed for clinical use.

There are currently no published data on the functional consequence of the PSMB1 P11A variant. The prognostic significance of variants in PSMB genes and in some proteasome α-subunits (PSMA) may be hypothesized to be associated with reduced cellular levels of functional proteasomes (35). Sequence changes such as a G allele in the PSMB1 P11A leader sequence may interfere with the assembly or function of proteasomes (36) and could translate into greater bortezomib activity. Such greater activity could be related to a reduction of active proteasome sites and a consequent requirement for fewer bortezomib molecules to sufficiently inhibit proteasome function, leading to cell death (37). This hypothesis is supported by previous findings suggesting that low PSMA5 levels are associated with longer PFS with bortezomib in mantle cell lymphoma (18). In addition, recent RNAi screens showed that silencing of individual proteasome genes including PSMA5 and PSMB2/3/7 sensitized multiple myeloma cells to bortezomib (37, 38).

The proteasome also regulates CD20, the target of rituximab; therefore, functional mutations in proteasome subunits such as PSMB1 P11A may influence the activity of...
rituximab in patients. In the presence of rituximab, there is upregulation of both the ubiquitin and proteasome systems (39). In patients with lower levels of functional proteasomes at baseline, alternative proteolytic systems (e.g., autophagy) may be used for degradation of ubiquitinated CD20 (40). Autophagy is less efficient than degradation through the proteasome (41), and this may translate into less efficacy for patients treated with rituximab when these proteasome subunit anomalies are present. For such patients, as shown in this report, treatment with bortezomib is more effective than in patients without these anomalies; this may be due to direct inhibition of the proteasome, which leads to control of other survival signaling pathways such as NF-κB.

It has been reported previously that patients with high levels of tumor-associated macrophages (TAM) have favorable outcomes when treated with rituximab but poorer outcomes when treated with chemotherapy alone (22, 42). Our findings (Supplementary Fig. S2A) confirm the relatively poorer outcome of patients with low CD68 expression treated with rituximab alone (22). The antitumoral activity of rituximab is dependent on Fc-receptor-mediated interactions with effector cells including neutrophils, natural killer cells, and macrophages. Macrophages can eliminate B-lymphocytes by direct Fc-receptor–mediated phagocytosis (43), or they may secrete cytolytic factors or release cytokines, thereby recruiting other effector cells to amplify the inflammatory response (44, 45), inferring a direct relationship between CD68 TAM content and efficacy of rituximab. Patients with PSMB1 P11A (G allele), which may indicate lower proteasome levels, and low CD68 TAM did much worse on rituximab alone compared with bortezomib–rituximab, presumably due to less elimination of B-lymphocytes by direct Fc-receptor–mediated phagocytosis and slower clearance of ubiquitinated CD20 protein through

Figure 1. Kaplan–Meier distributions of (A) PFS, (B) OS, and (C) TTNT with bortezomib–rituximab and rituximab in biomarker-evaluable patients (N = 376) who were positive or negative for the biomarker pair PSMB1 P11A (G allele) and low CD68 expression (<50 CD68-positive cells).
autophagy. For these patients, addition of bortezomib overcame this inefficiency, presumably by controlling other survival signaling pathways such as NF-κB.

In conclusion, these findings suggest that prespecified biomarker combinations can identify follicular lymphoma patient subgroups deriving substantial clinical benefit from bortezomib–rituximab versus rituximab, without a notable impact on safety. Further confirmation in independent cohorts of similar patients, and in patients treated with other bortezomib–rituximab–based combination regimens showing activity in relapsed/refractory follicular lymphoma (9, 11, 12), would be warranted.
Table 4: Treatment exposure and safety with bortezomib–rituximab and rituximab in biomarker-positive and biomarker-negative patients in the biomarker-evaluable population (N = 376) and in the overall safety population (N = 673)

<table>
<thead>
<tr>
<th></th>
<th>Overall safety population</th>
<th>Biomarker positive</th>
<th>Biomarker negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Btz-R (n = 334) R (n = 339)</td>
<td>Btz-R (n = 78) R (n = 86)</td>
<td>Btz-R (n = 108) R (n = 104)</td>
</tr>
<tr>
<td>Treatment exposure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycles received, median (range)</td>
<td>5 (1–5) 252 (74)</td>
<td>5 (1–5) 62 (72)</td>
<td>5 (1–5) 74 (85)</td>
</tr>
<tr>
<td>Patients receiving all 5 cycles, n (%)</td>
<td>232 (69)</td>
<td>63 (81)</td>
<td>74 (85)</td>
</tr>
<tr>
<td>Rituximab relative dosing intensity, mean %</td>
<td>96</td>
<td>97</td>
<td>90</td>
</tr>
<tr>
<td>Bortezomib relative dosing intensity, mean %</td>
<td>88</td>
<td>92</td>
<td>90</td>
</tr>
<tr>
<td>Safety profile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any AE, n (%)</td>
<td>316 (95) 265 (78)</td>
<td>74 (95) 71 (83)</td>
<td>105 (97) 85 (82)</td>
</tr>
<tr>
<td>Any treatment-related AE, n (%)</td>
<td>290 (87) 156 (46)</td>
<td>69 (88.5) 48 (56)</td>
<td>93 (86) 39 (37.5)</td>
</tr>
<tr>
<td>Related to rituximab</td>
<td>206 (62) 156 (46)</td>
<td>45 (58) 48 (56)</td>
<td>69 (64)</td>
</tr>
<tr>
<td>Related to bortezomib</td>
<td>276 (83) –</td>
<td>67 (86) –</td>
<td>88 (81) –</td>
</tr>
<tr>
<td>Any grade ≥3 AE, n (%)</td>
<td>152 (46) 70 (21)</td>
<td>26 (33) 20 (23)</td>
<td>47 (43.5) 20 (19)</td>
</tr>
<tr>
<td>Any serious AE, n (%)</td>
<td>59 (18) 37 (11)</td>
<td>9 (11.5) 13 (15)</td>
<td>21 (19) 12 (11.5)</td>
</tr>
<tr>
<td>AE leading to treatment discontinuation, n (%)</td>
<td>19 (6) 5 (2)</td>
<td>3 (4) 2 (2)</td>
<td>6 (6) 2 (2)</td>
</tr>
<tr>
<td>Deaths due to AEs, n (%)</td>
<td>6 (2) 2 (&lt;1)</td>
<td>0 1 (1)</td>
<td>2 (2) 1 (1)</td>
</tr>
</tbody>
</table>

Abbreviation: AE, adverse event; Btz-R, bortezomib

Data shown for cycles of bortezomib therapy; an additional 12 patients in the overall safety population, and an additional 2 and 4 patients in the biomarker-positive and biomarker-negative populations, respectively, received all 5 cycles of R.

Disclosure of Potential Conflicts of Interest

W. Li is employed as a senior scientist in Janssen Research & Development. J. Karkera is employed as a principal research scientist in Janssen Research & Development. R. Favis is an employee of Johnson & Johnson. Y. Elsayed is employed as a vice president, hematology, and has ownership interest (including patents) in Johnson & Johnson. H. van de Velde is employed as a senior director oncology, Research & Development, in Janssen and has ownership interest (including patents) in Johnson & Johnson. M. Schaffer has ownership interest (including patents) in Johnson & Johnson. J. Mayer has commercial research grant from Janssen. S.A.J. Rule has commercial research support for a Cancer Research UK randomized trial and is a consultant/advisory board member of Johnson & Johnson. S. de Vos is a consultant/advisory board member of Millennium. O. Shpilberg has a commercial research grant from Janssen. A. Cakana is an employee of Janssen and has ownership interest (including patents) in Janssen & Johnson. S. de Vos is involved in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.


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Prespecified Candidate Biomarkers Identify Follicular Lymphoma Patients Who Achieved Longer Progression-Free Survival with Bortezomib–Rituximab Versus Rituximab

Bertrand Coiffier, Weimin Li, Erin D. Henitz, et al.


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