Combination of Lenalidomide and Rituximab Overcomes Rituximab Resistance in Patients with Indolent B-cell and Mantle Cell Lymphomas


Abstract

Purpose: Lenalidomide, an immunomodulatory agent that enhances antibody-dependent cell-mediated cytotoxicity, has the potential to synergize with rituximab, an anti-CD20 mAb. We hypothesized that the addition of lenalidomide to rituximab would improve clinical outcomes in patients with B-cell lymphomas who were previously rituximab resistant, defined as no response to or progression of lymphoma within 6 months of rituximab-based therapy.

Experimental Design: We conducted a single-center, phase II trial in patients with indolent B-cell or mantle cell lymphomas who were previously rituximab resistant (ClinicalTrials.gov NCT00783367). Patients received 10 mg lenalidomide daily for 8 weeks, and then received four weekly doses of 375 mg/m² rituximab; lenalidomide continued during and after rituximab. Response to therapy was assessed after 8 weeks of lenalidomide and 12 weeks after first dose of rituximab. The primary endpoint was overall response rate (ORR) after lenalidomide and rituximab.

Results: Fifty patients were enrolled and 43 patients completed both response assessments. ORR after 8 weeks of lenalidomide was 30.2%; 12 weeks after the addition of rituximab to lenalidomide, ORR increased to 62.8% (N = 43). For all patients (N = 50), median progression-free survival (PFS) is 22.2 months (median follow-up, 39.2 months). PFS after lenalidomide–rituximab was significantly longer than the PFS for the antecedent regimen used to define rituximab resistance (22.2 vs. 9.13 months, P = 0.0004).

Conclusions: This trial is the first to show that the combination of lenalidomide and rituximab overcomes prior rituximab resistance in patients with indolent B-cell and mantle cell lymphomas. Clin Cancer Res; 21(8); 1–8. ©2015 AACR.

Introduction

Rituximab, a chimeric mouse–human anti-CD20 IgG1 mAb, is used in most treatment regimens for B-cell non-Hodgkin lymphomas. Despite its efficacy, rituximab-based therapies are not uniformly efficacious. For patients who previously responded to single-agent rituximab, overall response rates (ORR) for retreatment with rituximab are low (40%) and median response duration (RD) is relatively short (16.3 months; ref. 1). Furthermore, many patients who initially respond to rituximab eventually develop rituximab resistance.

FcγRIIIA-158 polymorphisms impact response to rituximab. Specifically, receptors with phenylalanine at position 158 have decreased rituximab binding affinity, which may affect antibody-dependent cell-mediated cytotoxicity (ADCC; refs. 2, 3). Clinically, FcγRIIIA phenylalanine carriers with follicular lymphoma have been reported to have lower ORR and shorter progression-free survival (PFS) compared with FcγRIIIA-158 valine homozygotes after a single course of rituximab (2–4). For previously untreated patients with follicular lymphoma who received a 4-week course of rituximab, some studies found that valine homozygotes have higher ORR (2) and longer event-free survival (4) compared with phenylalanine carriers, although one study failed to confirm this finding in the frontline, low tumor burden setting (5). In the relapsed setting, patients with follicular lymphoma who are FcγRIIIA-158 phenylalanine carriers have a 26% ORR to rituximab and a 14% 2-year PFS (3).

Lenalidomide is an immunomodulatory drug (IMiD) that has demonstrated activity in B-cell non-Hodgkin lymphomas. In vitro and in vivo, lenalidomide enhances ADCC, reverses tumor-induced immunosuppression, and synergizes with rituximab (6–8). We hypothesized that combining lenalidomide with rituximab would overcome resistance to rituximab in patients who were previously rituximab-resistant. To test this hypothesis, we conducted a clinical trial of lenalidomide combined with rituximab in patients with indolent B-cell lymphoma and mantle cell lymphoma (MCL) with demonstrated resistance to prior rituximab monotherapy or rituximab-containing regimens.

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://cincancerres.aacrjournals.org/).

Prior presentation: This work has been presented in part in abstract form as oral presentations at the 2013 and 2011 annual meetings of the American Society of Hematology, and as poster presentations at the 2010 and 2009 annual meetings of the American Society of Hematology, the 2011 and 2010 annual meetings of the American Society of Clinical Oncology, and the 2011 Pan Pacific Lymphoma Conference. Clinical outcome data at one year follow-up for the first cohort was published in part in Cancer 2014;120:222–8.

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doi: 10.1158/1078-0432.CCR-14-2221

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**Translational Relevance**

Rituximab, a chimeric murine-human anti-CD20 mAb, is used for treatment of B-cell lymphomas and improves survival of patients with indolent and aggressive lymphomas. Lenalidomide is an immunomodulatory agent with single-agent therapeutic activity in lymphomas. *In vitro*, lenalidomide enhances antibody-dependent cell-mediated cytotoxicity (ADCC); thus, it has potential to synergize with rituximab via ADCC. This is the first clinical trial to demonstrate that the addition of lenalidomide to rituximab overcomes prior rituximab resistance and prolongs progression-free survival in patients with indolent B-cell and mantle cell lymphomas. Our correlative studies suggest that the immunologic effects of lenalidomide may potentiate the action of rituximab by reducing regulatory T cells. These results suggest pharmacologic immunomodulation to reduce immunosuppression as a new paradigm for augmentation of therapeutic mAb efficacy. This approach may be applicable to any cancer immunotherapy that is enhanced by reduction of immunosuppression, including other monoclonal antibodies, vaccines, and chimeric antigen receptor–modified T cells.

**Materials and Methods**

We conducted a single-center, prospective, open-label, phase II clinical trial examining combination lenalidomide–rituximab in patients with previously treated, rituximab-refractory, or -resistant indolent B-cell lymphoma or MCL. Patients were required to have the following disease characteristics: progressive lymphoma, defined as failure to respond to rituximab, or combination rituximab–chemotherapy or progression of lymphoma within 6 months of rituximab chemotherapy for MCL. Subjects had to have progressive lymphoma, defined as new lesions or ≥50% enlargement of existing lesions, and measurable lymphoma, defined as a lesion ≥2 cm in diameter on imaging. Aspirin, warfarin, or low molecular weight heparin was required as prophylactic anticoagulation for venous thromboembolism. Patients were required to have an absolute neutrophil count ≥1,000/mm³, platelets ≥75,000/mm³, serum creatinine ≤2.0 mg/dL, total bilirubin ≤1.5 mg/dL, and aspartate aminotransferase and alanine aminotransferase ≤2.5× upper limit of normal at study entry. Patients were excluded if they had previously received lenalidomide, had an active infection, or had central nervous system involvement.

Patients received 10 mg lenalidomide by mouth daily, continuously until adverse event, treating physician discretion, or progressive disease after completion of protocol therapy. We chose a lenalidomide dose of 10 mg daily because this dose had been previously reported to have biologic and clinical activity with less toxicity than 25 mg in patients with chronic lymphocytic leukemia (10). One treatment cycle was defined as 28 days of daily oral lenalidomide. After 8 weeks (two cycles) of lenalidomide, patients received a single course of 4 weekly doses of 375 mg/m² rituximab while continuing to receive lenalidomide. Primary response assessments were performed after 8 weeks of lenalidomide monotherapy, and 12 weeks after the addition of rituximab to lenalidomide (i.e., after five 28-day cycles on study with 4 weekly doses of rituximab during cycle 3; Fig. 1).

Per protocol, two cohorts of patients enrolled sequentially: the first cohort received once weekly low-dose (10 mg) dexamethasone (11), given reports of dexamethasone–lenalidomide synergy (12) and to potentially improve tolerance. The second cohort did not receive weekly low-dose dexamethasone. After primary response assessments, patients had follow-up restaging studies at months 12, 18, 24, 36, 48, and 60. CT, MRI, or PET/CT imaging was used for measurement of tumor volume according to anatomic response criteria (13). Patients with stable or responding disease after five 28-day cycles on study (with rituximab during the third cycle only) were permitted to continue lenalidomide with or without dexamethasone; no subject received any additional rituximab. Evaluable patients were defined as patients who remained on trial through week 20 and had the post rituximab response assessment. Adverse events were graded according to the National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

The primary study endpoint was ORR at 12 weeks after addition of rituximab to lenalidomide using the anatomic criteria of the International Workshop Response Criteria for non-Hodgkin lymphoma (13). Functional imaging by 18F-fluorodeoxyglucose-positron-emission tomography (FDG-PET) was not used to assess response given concern regarding the unestablished significance of FDG uptake during immunomodulatory therapy. Assuming 45 evaluable subjects with α = 0.05, we had 87% power to detect an ORR of at least 35%. Secondary endpoints included PFS (13), RD

![Figure 1](image-url)

**Figure 1.** Study schema and ORRs. Rituximab-refractory patients received 8 weeks of lenalidomide alone and then assessed for response to treatment. Patients then received 4 weekly doses of 375 mg/m² rituximab with concurrent lenalidomide. Following rituximab therapy, subjects continued on lenalidomide, until response assessment at week 21 (12 weeks after their first dose of rituximab). ORR for all subjects, follicular lymphoma, MCL, and other indolent lymphoma subtypes is depicted in the bar graphs. Blue represents ORR after lenalidomide alone, and red represents ORR after the addition of four weekly doses of rituximab to lenalidomide.
(13)/time to progression (1), and overall survival (OS; ref. 13). PFS, RD/time to progression, and OS were estimated using Kaplan–Meier survival curves, and the log-rank statistic was used to test statistical differences. Prospectively, additional secondary endpoints included analysis of both cohorts together for primary and secondary endpoints as well as comparison of outcomes based upon whether or not patients received dexamethasone. Univariate analyses with the Fisher exact test were used to analyze the association between response and patient characteristics as well as the association between adverse events and patient variables. Statistical analyses were performed using STATA version 12.1 (StataCorp).

**FcyRIIIA-158F/V and regulatory T cells analysis**

Peripheral blood was collected for planned correlative analyses at enrollment, after 8 weeks of lenalidomide, and at 12 weeks after the first dose of rituximab. Genomic DNA was extracted from whole blood and analyzed for FcyRIIIA-158F/V polymorphism (rs396991) via high-throughput PCR sequencing (Beckman Coulter Genomics, Inc.). Peripheral blood mononuclear cells were obtained by ficoll gradient. Immunophenotyping was performed by flow cytometry to identify regulatory T cells (Tregs), defined as FOXP3+ CD4+ cells. Flow cytometry data were analyzed using FlowJo 8.8.4 (Treestar). Changes were assessed after 8 weeks of lenalidomide and at 12 weeks after the first dose of rituximab for responding [complete response (CR), partial response (PR)] and nonresponding [stable disease (SD), progressive disease] patients using the Wilcoxon rank sum test.

**Results**

**Patient characteristics**

Between July 2008 and July 2012, 50 patients were enrolled and received at least one dose of lenalidomide; 43 of 50 were evaluable for response after lenalidomide and rituximab. Seven patients were not evaluable because they discontinued treatment before completing response assessment (Fig. 2). Data were locked for analysis on November 8, 2013. Twenty-seven patients in the first cohort received lenalidomide with weekly low-dose dexamethasone; 23 patients in the second cohort received lenalidomide without dexamethasone. There were neither statistically significant differences in baseline characteristics (Table 1) between patients nor differences in primary or secondary outcomes between cohorts (Supplementary Table S1). Notably, 48% of patients were rituximab-refractory and 52% of patients had relapsed within 6 months of prior rituximab or rituximab-containing regimens. The median number of prior therapeutic regimens was 3 (range, 1–7).

**Efficacy**

**Overall response.** For all 50 subjects who received at least one dose of lenalidomide, intent-to-treat ORR after 8 weeks of lenalidomide was 26% and ORR after the addition of rituximab to lenalidomide was 54%. For 43 subjects who received both lenalidomide and rituximab, ORR after 8 weeks of lenalidomide was 30.2% [6 CR, 1 complete response unconfirmed (CRu), 6 PR]. The ORR increased to 62.8% [17 CR, 10 PR] after the addition of rituximab to lenalidomide. This improvement in response was most pronounced in follicular lymphoma, in which more than 3-fold increase in ORR was observed [5/26 = 19% (2 CR, 3 PR) after lenalidomide; 17/26 = 65% (9 CR, 8 PR) after lenalidomide–rituximab]. In contrast with follicular lymphoma, MCL had a higher response to lenalidomide monotherapy [6/11 = 55% (3 CR, 1 CRu, 2 PR)]; the addition of rituximab to lenalidomide did not change the ORR, although 2 PR improved to CR. After lenalidomide for 8 weeks, responses for other lymphomas were: MZL, 1/2 (50%; 1 CR); lymphoplasmacytic lymphoma, 1/2 (50%; 1 CR); and primary and secondary outcomes are shown.

**Figure 2.** Flow diagram. Patient outcomes from enrollment to follow-up are shown.
Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Prior autologous stem cell transplant, no differences in ORR after lenalidomide or lenalidomide. Of 22 patients who had SD or PR after rituximab, only 2 patients had a further reduction in tumor volume after the addition of rituximab to lenalidomide. Of 25 patients with decrease in tumor burden on lenalidomide, 13 of these patients who had an increase in tumor volume between enrollment and after lenalidomide and rituximab were responders to the combination of lenalidomide–rituximab. There was no difference in the number of patients who responded based on whether they had rituximab-refractory or rituximab-relapsed disease. We did not detect differences in response rate by gender after 8 weeks of lenalidomide monotherapy or 12 weeks after rituximab was added to lenalidomide (lenalidomide monotherapy: 3/13 women responded vs. 10/30 men responded, \( P = 0.72 \); lenalidomide–rituximab: 9/13 women responded vs. 18/30 men responded, \( P = 0.74 \)).

Overall, the greatest portion of responses to combination lenalidomide and rituximab occurred after the addition of rituximab (Fig. 3). The timing, direction, and magnitude of responses suggest that many patients responded after the addition of rituximab to lenalidomide. Median decrease in tumor volume after lenalidomide alone was 17.0%, whereas after the addition of rituximab to lenalidomide, decrease in tumor volume was 67.2%. Thirty-seven patients (86%) ultimately had reductions in tumor volume between enrollment and after lenalidomide and rituximab. Thirteen of these patients who had an increase in tumor burden after receiving lenalidomide monotherapy had their tumor burden decrease after the addition of rituximab to lenalidomide. Of 25 patients with decrease in tumor burden on lenalidomide, 21 had further reduction in tumor volume after the addition of rituximab to lenalidomide. Of 22 patients who had SD or PR after rituximab, only 2 patients had a further improvement in response status during longer follow-up (both SD to PR at 9 and 31 months). There were instances in which patients had some continued reduction of lymphadenopathy over time; however, these changes did not meet criteria for improvement in response status.

For all patients, median time from last dose of rituximab to first dose of lenalidomide was 8.7 months (range, 1.3–78.3 months). Comparison of patients who received last dose of rituximab ≤6 months before first dose of lenalidomide with those who did not showed no difference between response rates to lenalidomide alone (10/30 nonresponders had lenalidomide within 6 months of last rituximab dose vs. 4/13 responders, \( P = 1.0 \)) or to lenalidomide–rituximab (7/16 nonresponders had lenalidomide within 6 months of last rituximab dose vs. 7/27 responders, \( P = 0.32 \)). There was no correlation between number of months from last dose of rituximab and response to lenalidomide–rituximab (\( R^2 = 0.28 \)).

There was no difference in number of prior therapies between responders and nonresponders to the combination of lenalidomide–rituximab (responders had a median of 3 prior therapies vs. nonresponders had a median of 2 prior therapies, \( P = 0.4 \)). We did not observe any impact of total prior rituximab exposure on response to lenalidomide–rituximab. There was no difference in the number of patients who responded based on whether they had rituximab-refractory or rituximab-relapsed disease (\( P = 0.13 \)). We did not detect differences in response rate by gender after 8 weeks of lenalidomide monotherapy or 12 weeks after rituximab was added to lenalidomide (lenalidomide monotherapy: 3/13 women responded vs. 10/30 men responded, \( P = 0.72 \); lenalidomide–rituximab: 9/13 women responded vs. 18/30 men responded, \( P = 0.74 \)).

**PSF and RD.** Median follow-up (\( N = 50 \)) was 39.2 months (range, 0.47–64.2). At 5 years, OS is 68.3% [95% confidence interval (CI), 51.8%–80.2%]. For all patients who received at least one dose of lenalidomide, the median RD was 24 months (95% CI, 11.4–29.9; range, 0.1–60.4; Fig. 3). For all patients (\( N = 27 \)) who responded to the planned treatment (lenalidomide–rituximab), the median RD was 24 months (95% CI, 12.0–26.0; Fig. 4B), By lymphoma subtype, PFS for follicular lymphoma was 16.5 months and for MCL was 24.4 months (not significantly different, \( P = 0.52 \); Fig. 4C); RD for follicular lymphoma was 19.2 months and for MCL was 22.1 months (\( P = 0.60 \), log-rank; Fig. 4D).

For the 27 patients who continued on daily lenalidomide after the postrituximab response assessment, the average number of cycles received was 22.3.
There was an improvement in PFS relative to prior rituximab resistance–defining regimen. After lenalidomide–rituximab, PFS was significantly longer than PFS after the rituximab-containing regimen to which patients were refractory or had relapsed (22.2 vs. 9.13 months, \( P = 0.0004 \), log-rank; Fig. 4A). There was no difference in PFS between those patients whose rituximab resistance–defining therapy was rituximab–chemotherapy or rituximab maintenance after rituximab–chemotherapy (\( P = 0.5 \)). There was no difference in PFS between men and women, \( P = 0.83 \), log-rank [median PFS, women 18.1 months (95% CI, 7.7–not reached (NR)) vs. men 22.2 months (95% CI, 11.2–30.5)]. There was no difference in RD between men and women, \( P = 0.82 \), log-rank [median RD, women 24.8 months (95% CI, 3.3–NR) vs. men 24 months (95% CI, 6.6–NR)].

**FcyRIIIa analysis.** Of 50 patients enrolled, 42 patients were genotyped, and 40 of them completed response assessments to both lenalidomide and lenalidomide–rituximab. As expected, phenylalanine is the common isoform, and valine is the minor isoform. Nearly all of the patients had at least one phenylalanine allele (39/42; 93%). We then assessed PFS and RD for these 39 patients. Given that there were only 3 patients in our study who had an FcyRIIIa-158 valine/valine genotype, we cannot draw conclusions about differences in response to protocol therapy based on genotype. For the 39 patients with at least one FcyRIIIa-158 phenylalanine allele, median PFS was 20.8 months (range, 0–60 months; 95% CI, 11.4–29.9 months), whereas median PFS for prior rituximab resistance–defining regimen was 10.0 months (95% CI, 7.8–16.1 months; \( P = 0.002 \) log-rank). For responders in this group (\( N = 25 \)), median RD was 24 months (range, 0–55.4).

**Treg analysis.** Changes in peripheral blood Tregs were measured between baseline and after 8 weeks of lenalidomide in 35 patients, and from after lenalidomide to 12 weeks after first dose of rituximab in 32 patients. After 8 weeks of lenalidomide, the number of circulating Tregs was not significantly different between responding and nonresponding patients (0.48 median
fold increase for nonresponders and 0.50 median fold increase for responders; $P = 0.83$). From 8 weeks after lenalidomide mono-
therapy to 12 weeks after the addition of rituximab to lenalido-
mide, Tregs increased in nonresponding patients, whereas the
number of Tregs in responding patients decreased (0.47 median
fold increase for nonresponders and $-0.29$ median fold decrease
for responders; $P = 0.03$). Among responders, we did not observe
a correlation between change in Tregs and RD.

Safety

For all patients enrolled in the trial, we report adverse events that
occurred in $\geq 3$ patients and were considered at least possibly
related to protocol therapy (Table 2). Overall, the regimen was
well-tolerated. The only statistically significant difference in adverse
events between cohorts was insomnia ($N = 10$ with dexameth-
sone vs. $N = 0$ without, $P = 0.001$). The most common toxici-
est events were gastrointestinal complaints (74%), fatigue (62%), grade 3–4
neutropenia (34%), rash (26%), exacerbation of pre-existing
peripheral neuropathy (20%), and myalgias (18%). In 9 cases, adverse
events led to withdrawal from the study (Fig. 2). Two patients
were diagnosed with pulmonary emboli while receiving lenalidomide. One patient developed myocarditis (14) and expired shortly after discontinuing lenalidomide monotherapy.

Dose reductions and interruptions

There was no difference between number of dose interruptions or reductions between cohorts (i.e., low-dose weekly dexameth-
alone vs. no dexamethasone) during lenalidomide alone, combi-
nation lenalidomide–rituximab, or during postrituximab lena-
lidomide (Supplementary Table S2). However, patients who received dexamethasone had fewer dose interruptions for tumor flare and rash during the first 8 weeks of lenalidomide ($P = 0.035$).

Discussion

Our study is the only clinical trial combining lenalidomide and
rituximab for treatment of patients with previously rituximab-
resistant indolent B-cell lymphoma and MCL (11, 15–21). The
unique design of the trial provides new insights into the therapeu-
tic activity of this combination. By treating patients who were
previously rituximab-resistant, we demonstrate that this thera-
peutic combination significantly improves PFS compared with
patients’ prior rituximab resistance–defining regimens, including
rituximab–chemotherapy combinations. The trial design also
allows assessment of response to lenalidomide alone and to
lenalidomide–rituximab with each patient serving as his or
her own control. We observed that the ORR improved from
26% to 54% after the addition of rituximab to lenalidomide.
Taken together, these results provide convincing clinical evidence
of additive activity for the combination of rituximab and
lenalidomide.

The question may be raised that perhaps the improvement in
response observed after the addition of rituximab to lenalidomide
was due to insufficient time to assess best response to lenalido-
mide monotherapy. However, several observations argue against
this possibility. First, the time to achieve best response in our
study is consistent with a response to the combination of lena-
idomide and rituximab. Of 22 patients who had SD or PR at
response assessment 12 weeks after rituximab was added to
lenalidomide, only 2 patients had a further improvement in
response during longer follow-up despite continued lenalido-
mide therapy. In addition, a comparison of change in tumor
volume before and after the addition of rituximab to lenalidomide
shows a significant reduction from a median of 17% reduction before to
67% reduction after rituximab. Responses to rituximab in patients
with apparent progression of disease on lenalidomide alone were
also observed. Finally, our ORR to single-agent lenalidomide,
which was assessed at 2 months, is similar to the reported results
for lenalidomide monotherapy in relapsed/refractory indolent
non-Hodgkin lymphoma and MCL (10, 22–26).

Peripheral blood Tregs decreased after rituximab in patients
responding to lenalidomide–rituximab. Lenalidomide has been
demonstrated to inhibit proliferation and function of peripheral
blood–derived Tregs in vitro (27). Tregs, in turn, have been
demonstrated to inhibit natural killer (NK) cell functions, includ-
ing NK cell–mediated ADCC using another mAb in vitro (28). It is
conceivable that lenalidomide-induced reduction of Tregs num-
ber and function enhances rituximab-induced ADCC by NK cells,
and that this mechanism reverses rituximab resistance in some
patients. Alternatively, it is possible that the reduction in Tregs
reflects decreased tumor burden in patients.

Notably, the patients enrolled in this study were primarily
Fc$\gamma$RIIA-158 phenylalanine carriers, a characteristic associated
with poor outcomes after rituximab treatment. For instance, prior
studies have reported that for patients with relapsed/refractory
follicular lymphoma with at least one Fc$\gamma$RIIA-158 phenylalanine
allele, the 12-month ORR was 26% and 2-year PFS was 14% after
a single 4-week course of rituximab (3). In our trial for our cohort of

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<th>Table 2. Adverse events</th>
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<td><strong>Adverse events</strong> &amp; <strong>Total percentage</strong> &amp; <strong>Grade 1–2</strong> &amp; <strong>Grade 3–4</strong> &amp; <strong>Grade 5</strong> &amp; <strong>$P$ Cohort 1 vs. 2</strong></td>
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<tr>
<td>Abdominal pain &amp; 6% &amp; 2 &amp; 1 &amp; 0.59</td>
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<td>Anemia &amp; 8% &amp; 2 &amp; 2 &amp; 0.12</td>
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<td>Constipation &amp; 32% &amp; 16 &amp; &amp; 1.0</td>
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<td>Cough &amp; 14% &amp; 7 &amp; &amp; 1.0</td>
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<td>Cramping &amp; 24% &amp; 12 &amp; &amp; 1.0</td>
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<td>Diarrhea &amp; 38% &amp; 17 &amp; 2 &amp; 0.56</td>
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<td>Dysgeusia &amp; 6% &amp; 3 &amp; &amp; 1.0</td>
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<td>Erythema &amp; 6% &amp; 3 &amp; &amp; 0.24</td>
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<td>Fatigue &amp; 62% &amp; 31 &amp; 1 &amp; 0.14</td>
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<td>Gerd &amp; 12% &amp; 6 &amp; &amp; 0.67</td>
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<td>Hypophosphatemia &amp; 6% &amp; &amp; 3 &amp; 1.0</td>
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<td>Insomnia &amp; 20% &amp; 10 &amp; &amp; 0.001</td>
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<td>Malagia &amp; 18% &amp; 9 &amp; &amp; 0.48</td>
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<td>Myocarditis &amp; 2% &amp; &amp; 1 &amp; 1.0</td>
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<tr>
<td>Nausea &amp; 18% &amp; 8 &amp; 1 &amp; 0.72</td>
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<td>Neuropathy &amp; 20% &amp; 10 &amp; &amp; 0.74</td>
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<td>Neutropenia &amp; 34% &amp; 17 &amp; &amp; 0.56</td>
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<td>Pruritis &amp; 8% &amp; 4 &amp; &amp; 1.0</td>
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<td>Pulmonary embolism &amp; 4% &amp; &amp; 2 &amp; 0.49</td>
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<td>Rash &amp; 26% &amp; 11 &amp; 2 &amp; 0.25</td>
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<td>Thrombocytopenia &amp; 12% &amp; 2 &amp; 4 &amp; 1.0</td>
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<tr>
<td>Tumor flare &amp; 18% &amp; 7 &amp; 2 &amp; 0.72</td>
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<tr>
<td>Uri &amp; 8% &amp; 4 &amp; &amp; 0.61</td>
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<tr>
<td>Weight loss &amp; 8% &amp; 4 &amp; &amp; 0.61</td>
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*Includes adverse events considered at least possibly related to therapy occurring in $\geq 3$ patients.

Comparison between numbers of adverse events in cohort 1 (weekly low-dose dexamethasone) versus cohort 2 (no dexamethasone) using the Fisher exact test.

$N = 10$ with insomnia (cohort 1) versus $N = 0$ with insomnia (cohort 2).
rituximab-resistant FcγRIIA-F carriers, after lenalidomide–rituximab, ORR for FcγRIIA F carriers was higher at 46% with a 2-year PFS of 44%. These results show that despite previous findings that the phenylalanine form of FcγRIIA is associated with poorer rituximab response, these patients showed improvement with addition of lenalidomide. We also found that responses were durable, with median RD of 24 months. We recognize the possibility that response to the combination of lenalidomide and rituximab may be independent of FcγRIIA-158 genotype; however, our results support the idea that lenalidomide enhances rituximab-mediated ADCC because receptors with phenylalanine at position 158 have decreased rituximab-binding affinity (2).

The most common adverse events were cytopenias, constitutional symptoms, gastrointestinal symptoms, neuropathy, and myalgias, which tended to improve within 1 to 2 cycles of lenalidomide or resolved with dose interruption, dose reduction, or discontinuation of lenalidomide. Dexamethasone did not impact clinical outcomes. Fewer dose interruptions occurred during the first two cycles of lenalidomide in the cohort that received low-dose dexamethasone, due to lower incidence of tumor flare and rash.

Although not directly comparable due to differences in patient selection, dosing, and treatment schedules, our results in a rituximab-resistant patient population are similar to reported outcomes in trials that included rituximab-responsive, relapsed/refractory patients with indolent non-Hodgkin lymphoma and MCL treated with this combination (15–17, 19, 20). This supports our hypothesis that the impact of rituximab resistance is abrogated when rituximab is combined with lenalidomide.

In summary, we treated a group of patients with a poor prognosis for response to retreatment with rituximab. Our data demonstrate that the combination of lenalidomide and rituximab can result in durable responses with an acceptable toxicity profile in this patient population. By enrolling rituximab-resistant patients and treating these patients with lenalidomide monotherapy before retreatment with rituximab, we were able to demonstrate superior response rates and PFS after combining rituximab with lenalidomide using each patient’s past response as their own control. Within the limitations of our study design, our findings suggest that the immunologic effects of lenalidomide potentiate the action of rituximab and may overcome rituximab resistance. Notably, no other clinical trial of lenalidomide–rituximab addresses the ability of this combination therapy to overcome prior rituximab resistance. Finally, our results suggest a new paradigm for augmentation of therapeutic mAb efficacy by pharmacologic immunomodulation to reduce immunosuppression. In addition to mAb-based therapies, this approach may be applicable to any immunotherapy used to treat cancer that is enhanced by reduction of immunosuppression, including therapeutic vaccination, bispecific T-cell engaging antibodies, and chimeric antigen receptor–modified T cells.

Disclosure of Potential Conflicts of Interest

T. Ahmadi is an employee of Janssen R&D. N.A. Aqui, J. Svoboda, and S.J. Schuster report receiving commercial research grants from Celgene. A.R. Mato reports receiving speakers bureau honoraria from Celgene and Genentech, and is a consultant/advisory board member for and reports receiving commercial research grants from Celgene. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions


Acknowledgments

The authors acknowledge the philanthropic support of the Lymphoma Program from Jim and Frannie Maguire and Margarita Louis-Dreyfus. They also thank Dr. Vivian Cheung for her thoughtful review of this article.

Grant Support

This study was supported in part by research funding from Celgene Corporation (to S.J. Schuster and N.A. Aqui). E.A. Chong received support from a 2010 American Society of Hematology Trainee Research Award. T. Ahmadi received a 2010 Special Fellow in Clinical Research Grant from the Leukemia and Lymphoma Society. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received August 26, 2014; revised December 23, 2014; accepted January 19, 2015; published OnlineFirst January 28, 2015.

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Clin Cancer Res  Published OnlineFirst January 28, 2015.