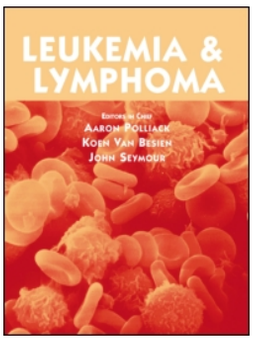

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LETTER TO THE EDITOR

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The efficacy of lenalidomide combination therapy in heavily pretreated non-Hodgkin lymphoma patients: an Italian observational, multicenter, retrospective study

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Non-Hodgkin lymphoma (NHL) is a heterogeneous group of cancers that comprise ~90% of lymphomas, the majority (85%–90%) originating from B lymphocytes;[1] NHL includes indolent forms (e.g. follicular lymphoma [FL]), as well as aggressive forms (e.g. diffuse large B-cell lymphoma [DLBCL]). Although NHL is highly responsive to standard front-line immunochemotherapy, which includes the anti-CD20 antibody, rituximab, with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP),[2] many patients will relapse, develop refractory disease, or develop rituximab resistance.[2,3] Despite clear improvements in outcome in the post-rituximab era, prognosis for patients in the relapsed/refractory setting remains poor, with one study reporting a median overall survival (OS) of only 0.7 months in DLBCL patients with progressive disease following initial R-CHOP therapy.[2] In addition, chemotherapy regimens are highly aggressive and the associated side effects can reduce efficacy and quality of life in some patients, making less toxic agents desirable.

In many lymphoid malignancies, the immunomodulatory agent (IMiD®) lenalidomide exhibits versatile antitumor properties that include immunomodulatory, antiproliferative, and antiangiogenic effects.[4] Lenalidomide, in combination or as single-agent therapy, has demonstrated clinical activity in both treatment-naive and relapsed/refractory NHL patient populations, including DLBCL, FL, mantle cell lymphoma (MCL), marginal zone lymphoma, small lymphocytic lymphoma, and T-cell lymphoma (covered in detail by Witzig et al.).[5] Patients with relapsed/refractory indolent and aggressive NHL have achieved 23%–35% overall response rates (ORR) with lenalidomide monotherapy.[6–8] A retrospective analysis reported clinical benefit from single-agent lenalidomide in relapsed/refractory DLBCL (ORR 28%), with preferential activity in patients with non-germinal center B-cell (non-GCB) versus GCB disease (ORR 53% versus 9%, respectively, $p = 0.006$).[9] Lenalidomide plus rituximab (R^2) has demonstrated activity in multiple phase 2 studies across various NHL subpopulations in the relapsed/refractory setting. For example, R^2 treatment resulted in 74% ORR (44% complete response [CR]) and 12.4 months' median progression-free survival (PFS) in patients with indolent lymphoma,[10] and 33% ORR (22% CR) and 3.7 months' and 10.7 months' median PFS and OS, respectively, in patients with aggressive lymphoma.[11] A recent study in rituximab-resistant NHL and MCL patients showed that addition of rituximab to lenalidomide monotherapy significantly increased response (63% ORR) compared with lenalidomide alone (30% ORR), with a more pronounced response in the FL subpopulation (65% ORR and 19% ORR, respectively).[12] Based on established efficacy in multiple myeloma, lenalidomide in combination with the anti-inflammatory agent dexamethasone (LenDex) was

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Supplemental data for this article can be accessed here.

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Table 1. Demographics and patient characteristics at study entry.

Characteristic	R^2 ($n = 24$)	LenDex ($n = 68$)	Total ($n = 92$)
Median age, years (range)	63 (42–92)	72 (37–91)	69 (37–92)
Males, *n* (%)	19 (79.2)	38 (55.9)	57 (62.0)
Bulky disease (>7 cm), *n* (%)	6 (25.0)	21 (30.9)	27 (29.4)
Median time from diagnosis to first dose of lenalidomide, years (range)	2 (0.4–9.9)	3.2 (0.5–14.6)	3.1 (0.4–14.6)
Prior treatment regimens, median (range)	3.5 (1–9)	3 (0–14)	3 (0–14)
Refractory to rituximab,[a] *n* (%)	15 (62.5)	30 (44.1)	45 (48.9)
NHL histological subtype, *n* (%)[b]			
Follicular lymphoma	4 (16.7)	5 (7.4)	9 (9.8)
Diffuse large B-cell lymphoma	10 (41.7)	38 (55.9)	48 (52.2)
Mantle cell lymphoma	6 (25.0)	18 (26.5)	24 (26.1)
Transformed lymphoma	0 (0.0)	5 (7.4)	5 (5.4)
Lymphocytic	3 (12.5)	1 (1.5)	4 (4.4)
Other	1 (4.2)	3 (4.4)	4 (4.4)

LenDex: lenalidomide + dexamethasone; NHL: non-Hodgkin lymphoma; R^2: lenalidomide + rituximab.
[a]Refractory patients were defined per protocol as patients who had less than a partial response or had disease progression within six months after completion of a prior therapy.
[b]Patients can be classified in more than one histological subtype.

investigated in patients with heavily pretreated, relapsed/refractory MCL ($N = 33$).[13] At final assessment, ORR was 52% (24% CR) and median PFS and OS were 12 and 20 months, respectively.[13]

We have previously reported results from a subset of patients who received lenalidomide monotherapy in a multicenter, retrospective, observational study that investigated the efficacy and safety of off-label lenalidomide use in patients with NHL.[14] Here, we present data from a subset of patients with NHL who received R^2 or LenDex. Eligible patients included those with FL, DLBCL, MCL, T-cell lymphoma or other types of NHL with histology not specified (NHL-NOS) who received lenalidomide combination therapy through the Named Patient Program (NPP) active in Italy from April 2008 to November 2010.[14] A detailed description of the study methodology has been described previously,[14] and all work from this study was conducted in accordance with the International Conference on Harmonisation and Declaration of Helsinki guidelines (the REVEAL Study, AIFA id224). Combination treatments and lenalidomide doses used reflect local clinical practice guidelines and participating investigators' preferences. All treatments were planned until progression or toxicity. Key primary endpoints included ORR, duration of response, PFS, OS, time to response, and abnormalities in laboratory data and adverse events (AEs). Descriptive statistics are presented as means, medians, standard deviations, or ranges for continuous variables and as counts or percentages for categorical variables. Time-to-event variables (i.e. PFS and OS) were summarized with Kaplan–Meier estimates at various time points along with the standard errors, but were limited by the censoring of the variable, and included time to event or last known date without an event.

Out of 180 total patients, patients receiving lenalidomide monotherapy were the subject of an earlier publication;[14] this report focuses on the 92 patients with NHL who were treated with either R^2 ($n = 24$) or LenDex ($n = 68$). The median number of treatment cycles was 4 in the R^2 group and 3 in the LenDex group. The median number of previous treatments was three. Almost half (49%) of patients were refractory to rituximab therapy (Table 1). The majority of the population was composed of patients with DLBCL (52%) and MCL (26%). Median duration of follow-up was 12.4 and 6.9 months for the R^2 and LenDex treatment groups, respectively. Overall response rates (Table 2) in this heavily pretreated population were similar between patients treated with R^2 (42%) or LenDex (40%), and stable disease was observed in 42% and 32% of patients, respectively. In patients who responded to previous therapy, ORRs were higher compared with those who were refractory to previous therapies in both the R^2 (50% and 33%) and LenDex (50% and 30%) groups (Supplemental Table I). When analyzed by NHL histological subtype, following R^2 therapy, the highest ORRs were observed in patients with FL (75%), lymphocytic (67%), transformed lymphoma (40%), and DLBCL (30%; data not shown). In patients treated with LenDex, the highest ORRs were observed in patients with DLBCL (50%), FL (40%), and MCL (28%; data not shown). Duration of response appeared to vary among different NHL histological subtypes (data not shown) and lenalidomide dose levels (Supplemental Figure 1) in both treatment groups. Median duration of response was 8.1 ± 14.1 months and 3.7 ± 9.0 months in patients treated with R^2 and LenDex, respectively. Median PFS (95% CI) was 8.0 months (2.3–12.7 months) in patients receiving R^2 and 5.3 months (2.8–10.9 months) in patients receiving LenDex (Supplemental Figure 2a). Median OS (95% CI) was 8.0 months (3.9–15.8 months) in patients receiving R^2 and 7.9 months (4.3–12.8 months) in patients receiving LenDex (Supplemental Figure 2b). At 12 months, PFS and OS were 49% and 60%, respectively, in patients treated with R^2, and 43% and 52%, respectively, in those treated with LenDex. PFS and OS remained consistent at two and three years for both treatment groups (Table 2).

Observed AEs in patients treated with R^2 and LenDex (Supplemental Table II) included neutropenia ($n = 12$ and $n = 15$), leukopenia ($n = 8$ and $n = 4$), thrombocytopenia

Table 2. Efficacy of lenalidomide-containing therapies in patients with NHL.

Treatment	R^2 ($n = 24$)	LenDex ($n = 68$)	Overall ($n = 92$)
ORR, *n* (%, 95% CI)[a]	10 (41.7, 22.1–63.4)	27 (39.7, 28.0–52.3)	37 (40.2, 30.1–51.0)
CR, *n* (%, 95% CI)	3 (12.5, 2.7–32.4)	9 (13.2, 6.2–23.6)	12 (13.0, 6.9–21.7)
CRu, *n* (%, 95% CI)	0 (0, 0–14.3)	1 (1.5, 0–7.9)	1 (1.1, 0–5.9)
PR, *n* (%, 95% CI)	7 (29.2, 12.6–51.1)	17 (25.0, 15.3–37.0)	24 (26.1, 17.5–36.3)
SD, *n* (%, 95% CI)	10 (41.7, 22.1–63.4)	22 (32.4, 21.5–44.8)	32 (34.8, 25.2–45.4)
PD, *n* (%, 95% CI)	4 (16.7, 4.7–37.4)	19 (27.9, 17.8–40.2)	23 (25.0, 16.6–35.1)
PFS, months (95% CI)	8.0 (2.3–12.7)	5.3 (2.8–10.9)	–
1-year PFS, %	49	43	–
2-year PFS, %	49	37	–
3-year PFS, %	49	37	–
OS, months (95% CI)	8.0 (3.9–15.8)	7.9 (4.3–12.8)	–
1-year OS, %	60	52	–
2-year OS, %	60	44	–
3-year OS, %	60	44	–

[a]Including complete, unconfirmed, and partial responses.

($n = 7$ and $n = 12$), anemia ($n = 6$ and $n = 11$) and pyrexia ($n = 5$ and $n = 7$), which are consistent with other published reports of R^2 or LenDex regimens in pretreated NHL populations.[10,12,13] There were no reports of rash in the R^2 group versus 2 reports in the LenDex group. Serious AEs included thrombocytopenia ($n = 0$ and $n = 2$) and pyrexia ($n = 1$ and $n = 1$) in patients treated with R^2 and LenDex, respectively.

This study suggests that R^2 and LenDex are viable treatment options for patients with relapsed/refractory NHL in real-world clinical practice, a conclusion similar to that reported from large-scale clinical trials. The effectiveness and safety of lenalidomide-containing therapies in relapsed/refractory NHL have been demonstrated in numerous phase 2 trials.[10,12,13] Although patient numbers were small in this retrospective study, favorable response rates were observed with R^2 (42%) and LenDex (40%) therapies, and both regimens were well-tolerated with safety profiles similar to that reported in other clinical trials. Although the overall results appear promising, there were limitations to this retrospective analysis. The small population size and variability of NHL subtypes made it difficult to perform rigorous statistical analysis. Therefore, the effect of R^2 and LenDex therapies on individual NHL subtypes could not be evaluated in depth.

More recently, several phase 2 studies have suggested that lenalidomide can function synergistically with rituximab to overcome rituximab-resistance in patients with indolent NHL and MCL. In patients with rituximab-resistant NHL and MCL ($N = 50$), the ORR increased from 30% in those treated with lenalidomide monotherapy to 63% after the addition of rituximab.[12] An additional trial in patients with FL, MCL, marginal zone lymphoma, and small lymphocytic lymphoma treated with LenDex ($N = 27$) demonstrated an increase in ORR from 29% to 58% after the addition of lenalidomide.[15] In this study, both the R^2 and LenDex regimens demonstrated clinical activity in this highly pretreated population, many of whom (49%) were refractory to previous rituximab therapy. Although patients who responded to previous treatments achieved better responses in both groups (ORR ~50%), patients who relapsed still responded to both lenalidomide-containing therapies (ORR ~30%). Further analysis is warranted to determine the efficacy of either regimen in a rituximab-resistant population.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at http://dx.doi.org/10.1080/10428194.2016.1184755.

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