

A comprehensive review of lenalidomide therapy for B-cell non-Hodgkin lymphoma

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Key message: This review provides a comprehensive overview of the clinical efficacy and safety of lenalidomide as a single agent and in combination therapy for B-cell non-Hodgkin lymphoma (NHL), taking into account recent advances, including the US FDA approval of lenalidomide for relapsed/refractory mantle cell lymphoma, the emergence of lenalidomide/rituximab-based combination regimens, and initiation of numerous trials at varying stages of treatment in NHL.

Keywords: diffuse large B-cell lymphoma, follicular lymphoma, lenalidomide, mantle cell lymphoma, non-Hodgkin lymphoma, rituximab

Abstract

Lenalidomide is an oral non-chemotherapy immunomodulator with direct and indirect effects on non-Hodgkin lymphoma (NHL) cells and with single-agent activity in relapsed/refractory aggressive and indolent B-cell NHL, including mantle cell lymphoma (MCL), diffuse large B-cell lymphoma, and follicular lymphoma. Based on the pivotal phase II MCL-001 trial of lenalidomide in heavily pretreated patients with relapsed/refractory MCL, lenalidomide was approved by the US Food and Drug Administration for the treatment of relapsed/refractory MCL after failure of two prior therapies, one of which includes bortezomib, at a recommended starting dose of 25 mg on days 1-21 of each 28-day cycle. Lenalidomide enhanced the survival benefit in combination with rituximab in preclinical models, prompting clinical evaluation of the lenalidomide-rituximab (R2) combination. In phase II trials, lenalidomide 20 mg on days 1-21 in combination with different standard-dose rituximab schedules exhibited promising activity in both first-line and relapsed/refractory disease across multiple B-cell NHL subtypes. The feasibility of combining lenalidomide with immunochemotherapy, including R-CHOP and rituximab-bendamustine, has been demonstrated in phase I/II trials. These latter regimens are currently being evaluated in ongoing phase II and III trials. The role of lenalidomide monotherapy and R2 in maintenance therapy is also being examined. Based on available evidence, a comprehensive review of lenalidomide in all treatment phases of B-cell NHL—relapsed/refractory disease, first-line, and maintenance—is presented here.

Introduction

It is estimated that in the United States in 2015 there will be ~70,800 new cases of non-Hodgkin lymphoma (NHL) and 18,990 deaths, accounting for a predicted 4% of new cancer diagnoses and 3% of cancer deaths [1]. Approximately 85% of NHL are of B-cell origin; the most common subtypes are aggressive diffuse large B-cell lymphoma (DLBCL), indolent follicular lymphoma (FL), and mantle cell lymphoma (MCL) [2,3]. First-line treatment is usually immunochemotherapy, typically rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or bendamustine/rituximab (BR) [2,4-6]. In MCL patients, induction may be followed by autologous stem cell transplantation (ASCT) or rituximab maintenance [7,8]. Treatment for relapsed/refractory disease has lacked a standard of care with a broad range of chemoimmunotherapy and radioimmunotherapy options [2,4,9]. Subsequent relapses are characterized by progressively shorter durations of response (DOR), underscoring the need for new agents capable of offering longer DORs with improved toxicity profiles.

Lenalidomide is an oral immunomodulator with direct antineoplastic activity and immunologic effects, including blocking tumor cell proliferation and angiogenesis, and stimulating T-cell– and natural killer (NK) cell–mediated cytotoxicity in experimental models [10-17]. Antineoplastic and antiproliferative effects and increased NK cell numbers and activity were observed *in vitro* and *in vivo* against malignant lymphoma B-cells in general [11,15,17-19] and specifically against DLBCL, FL, and MCL cells [14,16,17,20,21]. In activated B-cell (ABC)-subtype

DLBCL preclinical models, lenalidomide induced cytotoxicity required the presence of cereblon to downregulate IRF4 and BCR-NF- κ B and increase interferon- β production [21,22]; low cereblon expression is a possible resistance mechanism to lenalidomide.

This article provides a comprehensive overview of the clinical efficacy and safety of lenalidomide as monotherapy or in combinations for B-cell NHL including recent FDA approval of lenalidomide for relapsed/refractory MCL [23], the emergence of lenalidomide/rituximab-based combination regimens, and initiation of numerous clinical trials.

Lenalidomide monotherapy for relapsed/refractory NHL

Lenalidomide was initially evaluated in several single-arm, multicenter phase II trials in relapsed/refractory NHL including a pilot study in indolent NHL (NHL-001) [24], and two subsequent studies in aggressive NHL (NHL-002 and NHL-003; **Table 1**) [25,26]. Lenalidomide was administered orally (PO) at a dose of 25 mg on days 1-21 of 28-day cycles (d1-21/28) for each trial and continued for 52 weeks (NHL-001, NHL-002) or until disease progression (PD; NHL-003). NHL-001 enrolled 43 patients (mainly FL), including 67% refractory to rituximab and 50% refractory to their last treatment [24]. Overall response rates (ORR) of 23%, including 7% complete response (CR) or unconfirmed CR (CRu) encouraged further study. Median progression-free survival (PFS) overall was 4.4 months

(95% CI, 2.5-10.4), whereas the median DOR for responders was >16.5 months at the time of reporting.

NHL-002 enrolled 49 patients with aggressive relapsed/refractory disease (53% DLBCL, 31% MCL, 10% FL grade 3); 58% refractory to rituximab [25].

Lenalidomide produced a 35% ORR, a median PFS of 4 months, and a 6.2-month median DOR. The activity of lenalidomide was notable in a subset of 15 MCL patients (5 received prior bortezomib, 5 prior ASCT) [27]. MCL patients had an ORR of 53%, including 3 (33%) with CR (1 prior bortezomib, 1 prior ASCT); the median PFS was 5.6 months with a median DOR of 13.7 months with responses ongoing at 12.7-27.6 months in CR patients.

The international NHL-003 study conducted in North America and Western Europe enrolled 217 patients with aggressive relapsed/refractory disease (50% DLBCL, 26% MCL, 9% FL grade 3) [26]. ORR and CR/CRu rates were 35% and 13%, respectively. The median PFS overall was 3.7 months; median DOR was 10.6 months (not reached at 9.2 months for CR/CRu patients). Longer follow-up of 57 MCL patients showed an ORR of 35% and 12% CR/CRu by independent central review [28]. After a median 20-month follow-up, median DOR was 16.3 months (notably not reached at 31.8 months for CR patients). Responses for MCL patients were independent of baseline characteristics, number of prior treatments, and prior ASCT, and paved the way for subsequent clinical study designs in MCL [28]. Retrospective review from NHL-002 and NHL-003 in 87

patients who relapsed after ASCT and were subsequently treated with lenalidomide showed an ORR of 39%, an outcome similar to 179 patients with no prior ASCT (35% ORR) [29].

The prospective, international, single-arm phase II MCL-001 (EMERGE) trial enrolled 134 patients with MCL who had relapsed or were refractory to prior bortezomib [30]. Standard dosing of lenalidomide 25 mg/day, d1-21/28 continued until PD or intolerability. Key patient characteristics included 63% aged ≥ 65 years, 93% stage III-IV, 57% high tumor burden, 33% bulky disease, and 60% bortezomib-refractory. ORR and CR/CRu by independent central review were 28% and 7.5%, respectively, with a median time to response (TTR) of 2.2 months, a median PFS of 4.0 months, and a median DOR of 16.6 months. Lenalidomide treatment demonstrated consistent ORR and DOR across subgroups per demographics, baseline disease characteristics, number of and response to prior therapies [30,31]. Only high baseline lactate dehydrogenase (LDH) levels, a known adverse prognostic factor for MCL, were associated with a significantly weaker response to lenalidomide. Median PFS was 4.0 months, and overall survival (OS) was 19.0 months [30]. On the basis of this study, lenalidomide was approved by the FDA in June 2013 for the treatment of relapsed/refractory MCL after two prior therapies, one of which includes bortezomib [23]. Longer follow-up for MCL-001 [32] and a combined analysis for the NHL-002, NHL-003 and MCL-001 studies have confirmed durable efficacy outcomes and a consistent safety profile for lenalidomide in relapsed/refractory

MCL patients (**Table 1**) [33,34]. An exploratory analysis of Ki-67 in 81/134 evaluable patients from MCL-001 indicated that lenalidomide showed activity in patients with both low and high baseline Ki-67, with the lower baseline Ki-67 (<30% or <50%) associated with better CR rates, DOR and survival than in those with elevated Ki-67 [32].

A multicenter phase II United Kingdom study examined standard dose lenalidomide followed by a lower maintenance dose in relapsed/refractory MCL [35]. Twenty-six patients received lenalidomide 25 mg/day, d1-21/28 for six cycles, after which responders received maintenance lenalidomide 15 mg, days 1-21 until PD. ORR was 31% with a median PFS of 3.9 months and median DOR of 22.2 months. In patients who responded and received maintenance the median PFS was 14.6 months and median OS has not yet been reached. Correlative studies demonstrated that responders had 40%-60% increases in peripheral T- and NK-cells during the first 6 months of treatment, with an initial dip in NK cells, suggesting infiltration into tumor sites.

Efficacy of lenalidomide was also examined within the two major molecular subgroups of DLBCL: germinal center B-cell-like (GCB) and ABC (or non-GCB). In a retrospective analysis of 40 DLBCL of patients treated with single-agent lenalidomide, patients with tumors classified as non-GCB (vs. GCB) by the Hans algorithm using immunohistochemistry achieved significantly higher ORR (53% vs. 9%; $P=0.006$) and CR (24% vs. 4%) and had significantly longer median PFS

(6.2 vs. 1.7 months; $P=0.004$) [36]. Median OS was similar between subgroups (14.0 and 13.5 months, respectively).

In Italy, 157 heavily-pretreated, advanced-stage NHL patients ineligible to receive more intensive regimens were allowed off-label treatment with lenalidomide [37]. Patients comprised 44% DLBCL, 35% MCL, 9% FL, and 6% transformed lymphoma (TL), with a median age of 70 years and median number of 3 prior therapies. Lenalidomide was generally dosed at 25 mg (61%) and as part of combination therapy (58%; 35% with dexamethasone, 10% with rituximab). Overall, 42% of patients responded to lenalidomide-based therapy, including 18% with CR/CRu; median DOR was 7.8 months overall and 14.2 months for CR/CRu patients. By lymphoma subtype, ORR was 45% for DLBCL, 39% MCL, 54% FL, and 33% TL. Overall, median PFS and OS were 5.7 and 21.8 months, respectively.

Lenalidomide combinations

In preclinical studies, lenalidomide enhanced the survival benefit in conjunction with rituximab in a disseminated lymphoma-bearing SCID mouse xenograft model [16,38], which was associated with expansion of circulating NK cells and increased recruitment to tumor sites [16,38,39]. NK-cell expansion by lenalidomide was mediated by stimulation of dendritic cells and alteration of the cytokine microenvironment, contributing to the augmentation of rituximab-associated antibody-dependent cellular cytotoxicity [17,39], without affecting

CD20 density on lymphoma cells [38]. In cultured and freshly prepared MCL cells, lenalidomide enhanced rituximab-induced apoptosis by upregulating phosphorylation of c-Jun N-terminal protein kinases, Fas ligand, and granzyme B, as well as a series of apoptotic proteins [16,17].

R2

Lenalidomide plus rituximab (R2) has been evaluated in multiple phase II trials with variable dosing schedules and in multiple NHL subtypes (**Table 2**). In a phase I/II trial of relapsed/refractory MCL patients, the maximum tolerated dose (MTD) of oral lenalidomide was identified as 20 mg, d1-21/28 with standard-dose rituximab 375 mg/m²/week in cycle 1 [40]. All patients had received rituximab previously, and 27% had received bortezomib. During the phase II part of the study, R2 was highly active, showing a 57% ORR and 36% CR. Median TTR was 2 months, and median DOR was 18.9 months. Median PFS and OS were 11.1 months and 24.3 months, respectively.

R2 was also evaluated in MCL as a first-line therapy in a multicenter phase II study [41]. Induction treatment included 12 cycles of lenalidomide 20 mg/day d1-21/28 plus rituximab 375 mg/m² weekly during cycle 1, and then on day 1 of every other cycle (9 cycles total). R2 maintenance started at cycle 13, with the lenalidomide dose lowered to 15 mg, d1-21/28 plus rituximab every other cycle until PD. After a median follow-up of 24 months, 30/38 patients remain on treatment without PD, including 24 who completed induction and entered

maintenance. ORR was 84% (53% CR/CRu), median TTR was 2.8 months, and median DOR and PFS had not been reached.

In relapsed/refractory DLBCL or grade 3 FL ($n=45$), R2 showed a 33% ORR (22% CR), median DOR of 10.2 months, median PFS of 3.7 months, and median OS of 10.7 months [42]. In an Italian single-center phase II trial, 23 older patients (≥ 65 years) with relapsed/refractory DLBCL received lenalidomide 20 mg/day, d1-21/28 with rituximab 375 mg/m² on days 1 and 21 for four cycles [43]. Patients with stable disease or better responses received lenalidomide maintenance on the same dosing schedule for an additional 8 cycles. At the end of induction, R2 produced a 35% ORR and 30% CR. Of 10 patients eligible for maintenance, 8 achieved CR and a median DOR of 32 months [44].

In a phase II MD Anderson Cancer Center study in previously untreated, advanced-stage indolent NHL (FL, marginal zone lymphoma [MZL], and small lymphocytic lymphoma [SLL]), lenalidomide 20 mg/day, d1-21/28 (10 mg starting dose for SLL) with rituximab 375 mg/m² day 1 of each cycle $\times 6$ cycles were given with optional continued treatment for ≤ 12 cycles in responders [45]. In 103 evaluable patients, 90% responded, including 63% with CR/CRu. ORR was 98%, 89%, and 80% in FL, MZL, and SLL, respectively, with corresponding CR/CRu of 87%, 67%, and 23%. In the FL subset, responses were independent of Follicular Lymphoma International Prognostic Index (FLIPI) score, tumor bulk, or GELF criteria. Of 18/44 patients with detectable *Bcl-2* by PCR at baseline, 89%

achieved molecular response after 6 cycles. Estimated 3-year PFS was 75% overall and 79% for FL.

In a single-center phase II study of relapsed/refractory indolent lymphoma, 27 evaluable patients (22 with FL) with a median of 3 prior therapies responded to R2 (lenalidomide 20 mg/day d1-21/28 plus rituximab 375 mg/m² day 15 cycle 1 and weekly for 4-8 doses, with 4 additional rituximab doses allowed if <CR after cycle 2) [46]. All patients showed a 74% ORR and 44% CR/CRu (77% ORR, 41% CR/CRu in 22 FL patients). At a 43-month median follow-up, median DOR and PFS were 15.4 and 12.4 months, respectively.

The CALGB 50401 phase II study randomized patients with recurrent FL to lenalidomide (15 mg, cycle 1 and 20 mg, cycles 2-12; d1-21/28) alone or with rituximab (375 mg/m² weekly x4 in cycle 1) [47]. All 89 evaluable patients received rituximab-based treatment ≥6 months prior. The R2 regimen was more active than single-agent lenalidomide (ORR 75% vs. 49%; CR 32% vs. 13%) and exhibited significantly longer event-free survival (EFS) (2.0 vs. 1.2 years; *P*=0.0063). Based on these results, the multicenter phase II CALGB 50803 trial with R2 was initiated in patients with previously untreated grade 1-3A FL [48]. R2 was administered for 12 cycles, with lenalidomide 20 mg/day, d1-21/28 (optional dose increase to 25 mg/day in cycles 2-12) plus rituximab weekly in cycle 1, day 1 of cycles 4, 6, 8, and 10. Among 57 evaluable patients, ORR was 93% and CR 72%, with CR independent of FLIPI risk, histologic grade, or bulky disease.

Median time to CR was 10 weeks; 92% of PET-negative CRs were identified by 24 weeks.

Lenalidomide plus dexamethasone

Based on potential synergy between lenalidomide and dexamethasone in MCL cells [20] and established clinical studies in multiple myeloma [49,50], lenalidomide 25 mg, d1-21/28 plus dexamethasone 40 mg weekly for ≤ 12 cycles was evaluated in relapsed/refractory MCL ($n=33$) [51]. Patients received a median of 3 prior treatments; 36% had undergone ASCT, and 24% had received bortezomib. At treatment end, lenalidomide-dexamethasone produced a 52% ORR and 24% CR. Median DOR, PFS and OS were 18, 12, and 20 months, respectively. In another single-center study, 27 patients with relapsed/refractory indolent lymphoma or MCL resistant to rituximab received continuous lenalidomide 10 mg daily \pm dexamethasone 8 mg/week (part I), with rituximab 375 mg/m²/week $\times 4$ added during cycle 3 (part II) [52]. ORR improved from 29% (part I) to 58% ORR (with a 33% CR) after part II; estimated PFS and DOR were 23.7 and 26.6 months, respectively, at a 12.2-month median follow-up. This combination showed activity in rituximab-resistant patients, while also improving tolerability to lenalidomide (with the addition of dexamethasone) manifest by fewer episodes of mild tumor flare and rash than generally experienced with lenalidomide.

Lenalidomide plus bortezomib ± rituximab

Lenalidomide synergistically enhances bortezomib-induced cytotoxicity and apoptosis in B-cell lymphoma and primary cells [53]. The CALGB 50501 phase II study evaluated lenalidomide 20 mg, days 1-14 with bortezomib 1.3 mg/m² IV, days 1, 4, 8, and 11 in eight 3-week cycles in relapsed/refractory MCL (*n*=54) [54]. Responders received maintenance lenalidomide 15 mg, days 1-14 and bortezomib, days 1 and 8 per cycle until PD. Forty percent of patients received ≥2 previous therapies, 85% prior rituximab, and 40% prior ASCT.

Lenalidomide/bortezomib produced a 40% ORR and 15% CR, with 6/8 CRs remaining in remission at a 3.2-year follow-up. Overall, 1-year EFS, PFS, and OS were 25%, 40%, and 68%, respectively. The activity of this combination was considered disappointing given the high single-agent activity of both agents, and future studies using this dosing regimen do not appear to be warranted.

In a phase I study, the MTD of lenalidomide was identified as 10 mg, days 1-14 of a 3-week cycle when combined with bortezomib 1.3 mg/m², days 1, 4, 8, and 11 and rituximab 375 mg/m², days 1, 8, and 15 in cycle 1, and day 1 of cycles 2-6 [55]. This combination was administered to 22 MCL patients (16 first-line, 6 second-line), a majority with stage IV disease at diagnosis (82%). In 18 evaluable patients, the ORR and CR rates were 82% and 32%, respectively. Among previously untreated patients, the ORR and CR rates were 75% and 25%, respectively. Estimated 18-month PFS and OS were 61% and 79%, respectively. Although active, the incidence of neuropathy (18% grade 3/4) associated with

twice-weekly bortezomib infusions necessitated further investigation with a modified dosing schedule for optimal efficacy and safety.

R2-CHOP

Several groups have evaluated lenalidomide with R-CHOP given every 3 weeks (R2-CHOP21; **Table 2**). A phase I Mayo Clinic trial demonstrated that lenalidomide 25 mg, days 1-10 can be combined with standard-dose R-CHOP21 without causing dose delays or increased toxicity in aggressive B-cell lymphomas [56]. A phase II trial of R2-CHOP21 in 60 evaluable patients reported a 98% ORR and 80% CR, with a 24-month PFS of 59% [57]. A contemporary cohort from the Mayo Clinic Lymphoma Database of 87 consecutive DLBCL patients with similar risk characteristics who received R-CHOP21 alone showed a 24-month PFS of 52%. The non-GCB DLBCL subtype (per IHC) had an inferior 24-month PFS with R-CHOP compared with GCB DLBCL (28% vs. 64%, respectively). With R2-CHOP, the negative prognostic impact of the non-GCB phenotype appeared to be overcome with the addition of lenalidomide: 24-month PFS with R2-CHOP21 was 60% non-GCB vs. 59% GCB patients.

A French multicenter phase Ib dose-escalation study examined first-line lenalidomide (5, 10, 15, 20, or 25 mg) with longer dosing on days 1-14 with standard R-CHOP21 in 27 patients with mainly indolent NHL (18 FL, 4 DLBCL, 3 MCL, 2 indolent unclassified) [58]. ORR was 96%, with 74% CR/CRu. On the basis of this study, firstline R2-CHOP21 (with lenalidomide at 25 mg/day, days 1-

14) was evaluated in a multicenter phase II study of 80 patients with FL grade 1-3A and high tumor burden per GELF criteria [59]. R2-CHOP21 produced an ORR of 94% and 74% CR/CRu, with 11% of patients progressing or relapsing during a median follow-up of 13 months.

The Fondazione Italiana Linfomi conducted a phase I study (REAL07) of first-line R2-CHOP21 in elderly patients (median age, 68 years) with DLBCL (including 5% FL grade 3B), where lenalidomide 15 mg/day, days 1-14 was identified as the MTD [60]. Final results from the phase II part of REAL07 showed that first-line R-CHOP21 with lenalidomide 15 mg/day, days 1-14 for six 21-day cycles (R2-CHOP21) was active in 49 DLBCL patients (median age, 69 years) [61]. R2-CHOP21 produced a 92% ORR and 86% CR (positron emission tomography [PET] negative) after six treatment cycles. At a median follow-up of 28 months, 2-year PFS and OS were 80% and 92%, respectively. Patients with low-intermediate and intermediate-high/high risk according to IPI had 2-year PFS of 89% and 74%, respectively. 16 patients each with GCB vs. non-GCB DLBCL (per IHC) demonstrated an 88% ORR in each group and 2-year PFS of 71% vs. 81%, respectively. These studies provide support for the combination of lenalidomide with standard R-CHOP21 in previously untreated NHL, including older patients and those with unfavorable prognostic profiles, in whom lenalidomide was given at 25 mg/day for 10 or 14 days in 2 studies [56,58,59] and 15 mg/day for 14 days of each 21-day cycle [60].

R2-bendamustine

Some lymphoma patients are ineligible for or unable to tolerate anthracycline-based or high-dose chemotherapy. Because the BR combination has shown promising anti-lymphoma activity, the feasibility of combining R2 with bendamustine is under investigation. In the phase I SAKK 38/08 study in aggressive relapsed/refractory B-cell lymphoma, the MTD for lenalidomide was 10 mg, days 1-21 when combined with rituximab 375 mg/m², day 1 and bendamustine 70 mg/m², days 1 and 2 of every 4-week cycle [62]. The Nordic Lymphoma Group MCL4 (LENA-BERIT) phase I/II study evaluated first-line R2-bendamustine for MCL patients aged >65 years. Phase I dose-escalation study identified an MTD for lenalidomide of 10 mg/day, days 1-14 [63]. Unexpected grade 3/4 cutaneous and allergic reactions led to a modified initial dosing schema so that lenalidomide was initiated in cycle 2. Phase II induction treatment consisted of lenalidomide 10 mg/day, days 1-14, cycles 2-6; prednisolone 20 mg/day, days 1-14, cycle 2; and bendamustine 90 mg/m², days 1-2 and rituximab 375 mg/m², day 1 of six 4-week cycles [64]. Following induction, lenalidomide maintenance was provided on days 1-21 at 10 mg in cycles 7-8 and 15 mg in cycles 9-13. Preliminary efficacy data for 29 evaluable patients showed 97% ORR and 79% CR/CRu with 61% of patients MRD-negative after 6 cycles [64]. Estimated 2-year PFS and OS were 74% and 87%, respectively.

Clinical safety of lenalidomide in single-agent and combination therapy

The safety profile of single-agent lenalidomide is predictable and manageable with dose modifications or supportive therapy. **Table 3** presents a broad overview of select clinical studies that have published detailed safety results; studies not presented in **Table 3** have published limited toxicity data to date. Hematologic myelosuppression is the most common grade 3/4 adverse event (AE) encountered overall. Non-hematologic events are predominantly grade 1/2 in severity, with pneumonia and fatigue being the most common grade 3/4 AEs in <10% of patients [30]. Grade 1/2 rash has been effectively managed with antihistamines or low-dose steroids [30]. Prophylaxis for thrombotic events is determined based on individual patient needs. Based on studies in multiple myeloma patients, the incidence of second primary malignancies (SPMs) over long-term treatment is also closely monitored. The SPM incidence was reported from the MCL-001 study was 2.21/100 person-years, similar to the age-adjusted incidence rate of 2.1/100 person years for newly-diagnosed, invasive cancer in individuals ≥65 years from the US SEER program [30,65].

R2 was generally well tolerated, with hematologic AE rates consistent with those for single-agent therapy. The rates of grade 3/4 hematologic toxicity with R2 varied across phase II studies, likely reflecting the different patient populations, NHL subtypes, and lines of therapy: neutropenia ranged from 30%-66% and thrombocytopenia from 6%-23% [40,41,43,45]. Non-hematologic toxicity, mainly grade 1/2, also varied across studies, mostly consisting of fatigue, myalgia, rash

and infusion-related reactions. In the randomized CALGB 50401 trial in recurrent indolent lymphoma, R2 and single-agent lenalidomide exhibited similar toxicity (grade 3/4 events: 52% vs. 49%; 9% grade 4 in each arm), with a trend toward lower thrombotic risk with R2 (4% R2 vs. 16% lenalidomide) [47].

The R2-CHOP safety profile was generally consistent with that expected for R-CHOP. In two phase II trials, grade 4 neutropenia and thrombocytopenia were the most common [57,59]. Febrile neutropenia was reported in <10% of patients in both trials. Other lenalidomide-based combinations (e.g., R2-bendamustine) have only been evaluated in small patient cohorts and require continued evaluation to better characterize their safety profiles.

Dosing recommendations

Lenalidomide is approved by the US FDA for relapsed/refractory MCL at a dose of 25 mg, days 1-21 of each 28-day cycle based on the pivotal MCL-001 study [23,30]. This dose has been modified to 10 mg with the same schedule for patients with renal insufficiency, in the event of significant treatment-related toxicity or when used in maintenance or combination therapy [23,30].

The use of lenalidomide in other NHL types remains investigational but has been evaluated using the same dosing regimen. The optimal use of lenalidomide in maintenance therapy is under active investigation; activity was shown at 15 mg, days 1-21 of each 28-day cycle [35,41]. In combination with rituximab, a phase I

study demonstrated a maximum tolerated dose of 20 mg lenalidomide [40]. The most common schedule of lenalidomide has been 20 mg, days 1-21 every 4 weeks in relapsed/refractory NHL [40,42,44,47] and frontline MCL [41], and 25 mg on days 1-10 [56], 25 mg on days 1-14 [58], or 15 mg on days 1-14 [60] with first-line R-CHOP21.

Numerous clinical studies are planned or ongoing to evaluate the activity of first-line R2±chemotherapy or R2 consolidation/maintenance, as well as the feasibility of R2-bendamustine in elderly patients in first-line therapy and beyond (**Table 4**). Additional studies not shown here are being conducted in T-cell NHL, with initial results demonstrating activity with a similar tolerability profile in relapsed/refractory peripheral T-cell lymphoma and classical Hodgkin lymphoma [66,67]. Results of ongoing studies will help establish optimal dosing for lenalidomide alone, in combination, and by line of therapy, as well as assist with determining the potential role for molecular-based therapeutic options in indolent and aggressive NHL.

Conclusions

The FDA approval of lenalidomide in MCL was first established based on single-agent activity in relapsed/refractory patients. As summarized in this review, it is now apparent that lenalidomide is also active across multiple subtypes of indolent and aggressive NHL other than MCL. Preclinical evidence provided the basis for combining lenalidomide with rituximab, and the clinical activity of R2 led

to ongoing evaluations in combination with chemotherapy. Dosing modifications were made to administer lenalidomide safely in combination—lowering the dose to 20 mg in R2 and adjusting the dose and frequency to the first 10-14 days of 3-week R-CHOP cycles. These studies have now led to large ongoing randomized trials of lenalidomide in all phases of NHL treatment that will determine the optimal use of this novel class of immunomodulatory drugs.

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Table 1. Clinical efficacy of single-agent lenalidomide in relapsed/refractory NHL

Study	Patients/subset	<i>n</i>	Median age, y/ prior therapies, <i>n</i>	ORR, %	CR/CRu, %	Median DOR, months (95% CI)	Median PFS, months (95% CI)
NHL-001 [24]	All patients	43	63/3	23	7	> 16.5 (15.5-NR)	4.4 (2.5-10.4)
	FL grade 1/2	22	—	27	9		
	SLL	18	—	22	6		
NHL-002 [25, 27]	All patients	49	65/4	35	12	6.2 (range, 0-12.8)	4.0 (range, 0-14.5)
	DLBCL	26	—	19	12	—	—
	MCL	15	66/4	53	20	13.7 (4.0-NR)	5.6 (2.6-18.2)
	FL grade 3	5	—	60	20	—	—
NHL-003 [26, 28]	All patients	217	66 /3	35	13	10.6 (7.0-NR)	3.7 (2.7-5.1)
	DLBCL	108	—	28	7	4.6	2.7
	MCL	57	68/3	35	12	16.3 (7.1-NR)	8.8 (5.5-23.0)
	TL	33	—	45	21	12.8	5.4
	FL grade 3	19	—	42	11	NR	8.9
MCL-001 [30]	MCL	134	67/4	28	7.5	16.6 (7.7-26.7)	4.0 (3.6-5.6)
Pooled analyses [33, 34, 68]	MCL	206	67/4	32	10	16.6 (9.2-32.4)	5.4 (3.7-6.7)
	DLBCL	134	66/3	26	9	6.0	—
Lenalidomide lower dose [35]	MCL	26	66/3	31	8	22.2 (0-53.6)	3.9 (0-11.1)

CR, complete response; CRu, unconfirmed CR; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; FL, follicular lymphoma; NHL, non-Hodgkin lymphoma; NR, not reached; ORR, objective response rate; PFS, progression-free survival; SLL, small lymphocytic lymphoma; TL, transformed large B-cell lymphoma.

Table 2. Clinical efficacy of lenalidomide plus rituximab and chemotherapy in NHL

Study	Patients	n	Median age, y/ prior treatments, n	ORR, %	CR/CRu, %	Median DOR, months (95% CI)	Median PFS, months (95% CI)
<i>R2 in MCL</i>							
R2 [40]	R/R MCL	44	66/2	57	36	18.9 (17.0-NR)	11.1 (8.3-24.9)
R2 [41]	First-line MCL	31	65 /0	77	40	NR	NR
<i>R2 in DLBCL</i>							
R2 [42]	R/R DLBCL, grade 3 FL, or TL	45	—/3	33	20	10.2	3.7
R2 [43, 44]	Elderly R/R DLBCL	23	74 /3	35	30	32 (range, 18-34)	1-year DFS: 35%
<i>R2 in Indolent NHL</i>							
R2 [46]	R/R indolent NHL	27	60.5 / 3	74	44	15.4	12.4
CALGB 50401 [47]	Recurrent FL		63 /—				EFS: <i>P</i> = 0.0063
	R2	44		75	32	—	2.0 years
	Lenalidomide	45		49	13		1.2 years
R2 (CALGB 50803) [48]	First-line FL	57	53/0	93	72	> 1.6 years	> 1.6 years
R2 [45]	First-line indolent	103	58 /0	90	63	—	3-year PFS: 75%
	FL	46		98	87		79%
	MZL	27		89	67		87%
	SLL	30		80	23		62%
<i>Lenalidomide plus dexamethasone or bortezomib</i>							
Lenalidomide + dexamethasone [51]	R/R MCL	33	68/3	52	24	18 (12-NR)	12 (5-19)
R2 ± dexamethasone [52]	Rituximab-resistant R/R indolent or MCL	27	60/3	58 ^a	33 ^a	26.6	23.7

Study	Patients	n	Median age, y/ prior treatments, n	ORR, %	CR/CRu, %	Median DOR, months (95% CI)	Median PFS, months (95% CI)
Lenalidomide + bortezomib (CALGB 50501) [54]	R/R MCL	53	67 /—	40	15	—	7 months; 1-year PFS: 40%
R2 + bortezomib [55]	First- and second- line MCL	18	66/—	82	32	—	18-month PFS: 61%
R2-CHOP							
R2-CHOP [57]	First-line DLBCL or grade 3 FL	60	65/0	98	80	NR	2-year PFS: 59%
R2-CHOP [59]	First-line FL with high tumor burden	80	57/0	94	74	—	—
R2-CHOP (REAL 07) [61]	Elderly first-line DLBCL	49	69/0	92	86	—	2-year PFS: 80%
R2-bendamustine							
R2-bendamustine [64]	Elderly first-line MCL	29	72/0	97	79	—	2-year PFS: 74%

CALGB, Cancer and Leukemia Group B; CR, complete response; CRu, unconfirmed CR; DFS, disease-free survival; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; FL, follicular lymphoma; MZL, marginal zone lymphoma; NR, not reached; ORR, objective response rate; PFS, progression-free survival; SLL, small lymphocytic lymphoma; R/R, relapsed/refractory; R2, rituximab-lenalidomide; R2-CHOP, R2 plus cyclophosphamide, vincristine, doxorubicin, and prednisone.

^a24 of 27 patients were evaluable for response.

Table 3. Most common grade 3/4 adverse events in select clinical studies of lenalidomide alone or in combination in NHL

	Lenalidomide alone					R2 in MCL		R2 in DLBCL		Len/dex ± BTZ		R2-CHOP
Study	NHL-001 ^a [24]	NHL-002 ^a [25]	NHL-003 [26]	MCL-001 ^a [30]	Lower maint. ^a [35]	R2 [40]	R2 [41]	R2 [42]	R2 [43]	Len/dex [51]	R2 ± dex [52]	REAL 07 [61]
Patient type	iNHL	NHL	NHL	MCL	MCL	R/R MCL	First-line MCL	R/R NHL	Elderly R/R DLBCL	R/R MCL	R/R iNHL or MCL	Elderly first-line DLBCL
<i>n</i>	43	49	217	134	26	44	31	45	23	33	27	49
Neutropenia	46%	33%	41%	43%	62%	66%	39%	53%	30%	53%	30%	28%
Thrombocytopenia	19%	20%	19%	27%	42%	23%	13%	34%	14%	22%	7%	9%
Anemia	9%	6%	9%	11%	15%	2%	7%	17%	5%	6%	7%	3%
Leukopenia	9%	14%	7%	6%	–	30%	–	27%	–	26%	15%	21%
Febrile neutropenia	2%	6%	2%	–	–	5%	–	11%	–	12%	–	5%
Fatigue	2%	6%	5%	7%	4%	5%	–	7%	–	–	4%	–
Asthenia	5%	–	5%	1%	–	–	–	–	5%	–	–	–
Pneumonia	5%	4%	3%	8%	–	–	–	–	–	12% ^b	4%	–
Diarrhea	2%	2%	–	6%	4%	0	–	0	–	–	4%	–
Dyspnea	2%	–	5%	5%	–	0	–	0	–	–	–	–
Back Pain	–	–	5%	1%	–	–	–	–	–	–	–	–
Rash	–	4%	–	1%	4%	5%	23%	4%	–	–	4%	–
Thrombotic event	2%	4%	2%	5%	–	7%	–	8%	–	–	4%	–

– Denotes AEs that were not reported; BTZ, bortezomib; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; dex, dexamethasone; DLBCL, diffuse large B-cell lymphoma; iNHL, indolent NHL; len, lenalidomide; maint., maintenance; MCL, mantle cell lymphoma; R2, lenalidomide + rituximab.

^aIncluded AEs regardless of causality. ^bReported as infections overall.

Table 4. Planned or ongoing clinical trials with lenalidomide in NHL

Clinical study phase (name)	NCT number	NHL type	N	Primary endpoint	First-line treatment	Maintenance	Relapsed/refractory
First-line							
Phase II (ECOG 1412)	NCT01856192	Stage II-IV DLBCL	300	PFS	R2-CHOP vs R-CHOP	—	—
Phase III RCT (RELEVANCE)	NCT01650701	FL	1,000	10-year CR, PFS	R2 vs R-chemotherapy	R2 (after R2) vs R (after R-chemo)	—
Maintenance							
Phase II (ECOG 1411)	NCT01415752	Age ≥ 60 years MCL	332	2-year PFS	R-benda ± bortezomib	R2 vs R	—
Phase III RCT (MAGNIFY; NHL-008)	NCT01996865	FL, MZL, MCL	500	PFS	R2 induction	Lenalidomide vs R	—
Phase III RCT (LARO R2 elderly)	NCT01865110	Age ≥ 60 years MCL	633	2.5-year PFS	Alternating R-CHOP/ R-HAD vs R-CHOP	R2 vs R	—
Phase III RCT (LARO REMARC)	NCT01122472	Age ≥ 60 years DLBCL	621	PFS	R-CHOP	Lenalidomide vs placebo	—
Phase III RCT (FIL IIL MCL0208)	—	Advanced MCL	250	2-year PFS	R-chemotherapy, to HD chemo/ASCT	Lenalidomide vs observation	—
Relapsed/refractory							
Phase I (NCCTG/Alliance N1088)	NCT01429025	FL, SLL, MZL, WM	26	MTD	—	—	R2-benda
Phase II (FIL R2-B)	NCT01737177	MCL	42	CR, 3-year PFS	—	—	R2-benda to R2 to lenalidomide

ASCT, autologous stem cell transplantation; benda, bendamustine; chemo, chemotherapy; ECOG, Eastern Cooperative Oncology Group; HAD, cytarabine, dexamethasone; HD, high dose; LARO, Lymphoma Academic Research Organisation; NCCTG, North Central Cancer

Treatment Group; NHL, non-Hodgkin lymphoma; R, rituximab; R-CHOP, rituximab plus cyclophosphamide, vincristine, doxorubicin, and prednisone RCT, randomized controlled trial; R2, rituximab-lenalidomide.