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B-CELL NHL, T-CELL NHL, AND HODGKIN LYMPHOMA (J AMENGUAL, SECTION EDITOR)

# IMiDs New and Old

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## Abstract

**Purpose of Review** IMiDs are a class of biologic agents with immunomodulatory, anti-angiogenic, and direct anti-cancer activities. This review summarizes current data on clinical development and application of IMiDs in non-Hodgkin lymphoma (NHL) subtypes, focusing primarily on lenalidomide, with additional discussion on managing common side effects.

**Recent Findings** Improved upon the prototype thalidomide, the second-generation compound lenalidomide has enhanced immunological and anti-cancer properties with fewer side effects, while next-generation small molecule cereblon/E3 ubiquitin ligase modulator CC-122 is in early clinical studies. Lenalidomide is FDA-approved for treatment of relapsed/refractory mantle cell lymphoma as a single agent, as well as in combination with rituximab for R/R follicular lymphoma and marginal zone lymphoma. In addition, numerous clinical trials of lenalidomide, as single agent, in combination with anti-CD20 antibodies, or in combination with chemoimmunotherapy regimens, have shown promise in aggressive and indolent NHL in both the upfront and relapsed/refractory setting.

**Summary** As clinical trials with lenalidomide continue to find success in both indolent and aggressive lymphomas, IMiDs are poised to be important building blocks for combinatorial strategies with antibodies, chemotherapy, novel target agents, and emerging immunotherapy involving immune checkpoint inhibitors and chimeric antigen receptor T cell (CAR-T) therapy. Delineation of treatment-specific and disease-specific biomarkers is an important research objective to gain insight into potential mechanisms of action, and to guide future clinical development.

**Keywords** Immunomodulation · Lymphoma · Lenalidomide · Thalidomide · Avadomide

## Introduction

The emergence of immunomodulatory drugs (IMiDs) in the treatment of hematologic malignancies represents one of the most remarkable comeback stories in modern medicine. After thalidomide was infamously banned in 1961 for its teratogenic effects in pregnant women, it gained a new life 40 years later when its anti-angiogenic [1] and anti-tumor [2] effects were discovered, and the development of safer, more efficacious analogues began in earnest for therapeutic gain.

IMiDs are a series of synthetic compounds that have been developed based on the glutamate-derivative backbone of the prototype drug thalidomide. Thalidomide has wide-ranging functions including anti-inflammatory, immunomodulatory, anti-angiogenic, and direct anti-cancer activities [3]. The anti-angiogenic function of thalidomide was thought to be mediated partially via inhibition of basic fibroblast growth factor (bFGF)-induced angiogenesis [1]. The second-generation compounds, lenalidomide and pomalidomide, have enhanced immunological and anti-cancer properties with fewer side effects, consequently dominating the clinical development in hematologic diseases.

Lenalidomide was the first thalidomide analogue developed, and it quickly showed clinical efficacy in a variety of hematologic malignancies. Lenalidomide is FDA-approved for the treatment of multiple myeloma, myelodysplastic syndrome with a 5-q deletion, and relapsed/refractory mantle cell lymphoma (MCL). Recently, it has also received approval in combination with rituximab for relapsed/refractory follicular

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and marginal zone lymphomas. In addition, numerous clinical trials of lenalidomide have shown promise in aggressive and indolent non-Hodgkin lymphoma (NHL) in both the upfront and relapsed/refractory setting.

While pomalidomide, another thalidomide analogue, has shown efficacy in multiple myeloma, there is little data supporting its use in lymphomas. CC-122, a novel, small-molecule therapeutic agent that modulates cereblon E3 ubiquitin ligase and exhibits potent antitumor and immunomodulatory activities, is currently in phase I trials.

## Mechanism of Action

IMiD compounds have both immunomodulatory and anti-angiogenic properties which could confer antitumor and antimetastatic effects [3]. Thalidomide analogues have been shown to increase the production of anti-inflammatory cytokine IL-10 and decrease levels of IL-1b, IL-6, IL-2, and TNF-α, all pro-inflammatory factors [4]. Lenalidomide has demonstrated anti-angiogenic activity through inhibition of bFGF, VEGF, and TNF-alpha-induced endothelial cell migration, due at least in part to inhibition of Akt phosphorylation in response to bFGF [1, 5]. Lenalidomide has also been shown to inhibit vascular endothelial growth factor (VEGF)-mediated lymphangiogenesis in a murine model of mantle cell lymphoma through depletion of macrophages and monocytes [6].

In addition, lenalidomide has a variety of immunomodulatory effects [7]. Lenalidomide stimulates T cell proliferation, and modulates cytokine production [4]. Lenalidomide has been shown to modulate T cell function by repairing T cell immunologic synapse dysfunctions that are associated with follicular lymphoma and chronic lymphocytic leukemia/small lymphocytic lymphoma [8, 9]. When combined with rituximab in vitro, lenalidomide augmented antibody-dependent cell-mediated cytotoxicity (ADCC) by enhancing rituximab-induced lymphoma cell apoptosis, and activation of NK cell-mediated cytotoxicity [10]. In a human lymphoma severe combined immunodeficiency mouse model, lenalidomide in combination with rituximab demonstrated synergistic in vivo anti-lymphoma activity mediated via recruitment of dendritic cells and NK cells, supporting further evaluation of this combination in clinical setting [11, 12].

The direct molecular target of thalidomide and lenalidomide that produces its immunomodulatory activity is cereblon, a component of the E3 ubiquitin ligase complex [13]. Cereblon selectively binds two important transcription factors for T and B cell development, Aiolos and Ikaros, and activation of cereblon by lenalidomide leads to ubiquitination and degradation of these two factors [14••]. This upregulates levels of p21WAF-1 which regulate cyclin-dependent kinases (CDKs), leading to CDK inhibition and cell cycle arrest. Interestingly, these cytotoxic effects were seen only in malignant B cell lines, while protection from apoptosis was seen in normal B cells [15].

## Clinical Studies of Thalidomide in Lymphomas

Thalidomide has demonstrated clinical activity in both CLL and MCL. Single-agent thalidomide demonstrated a limited and modest overall response rate of 12.5% when given at 200 mg daily escalating to a maximum 800 mg daily to patients with relapsed/refractory indolent NHL (SLL and FL) [16]. In combination with fludarabine, thalidomide was associated with significant therapeutic efficacy in CLL [17, 18]. In treatment-naïve patients, the combination of thalidomide (100–300 mg daily) and fludarabine (standard monthly dosing) achieved a 100% OR and 55% CR rate [17]. In fludarabine-refractory patients, an OR rate of 31% was observed with the FR regimen [18]. The combination of thalidomide and rituximab was studied in a small phase II trial for patients with relapsed/refractory MCL [19]. Thirteen of 16 evaluable subjects demonstrated objective responses (5 CR, 8 PR, ORR of 81%, and CR of 31%), with median time to progression (TTP) at 20 months. When thalidomide was combined with rituximab and metronomic oral therapy PEPC, to comprise the RT-PEPC regimen for relapsed/refractory MCL [20], overall response rate was 73% with CR rate of 32%, and median PFS of 10 months.

Recently, a phase II trial utilized thalidomide in combination with cyclophosphamide and prednisone for patients with idiopathic multicentric Castleman disease, a rare lymphoproliferative disorder [21]. Thalidomide was administered for 2 years or until treatment failure. Twenty-five patients were included in the study, with 12 (48%) achieving a durable response for at least 24 weeks and an additional 3 with stable disease. One-year PFS and OS were 60% and 88%, respectively. The main toxicities of thalidomide include fatigue, somnolence, neuropathy, and thromboembolic events, which limits thalidomide's clinical appeal.

## Clinical Development of Lenalidomide in Lymphomas

The vast majority of evidence for IMiD use in lymphomas involves lenalidomide. While currently only FDA-approved for use in relapsed/refractory MCL, lenalidomide is being investigated in clinical trials in a variety of lymphoma subtypes in relapsed and refractory setting, and being moved up to incorporate into the upfront setting (Table 1).

### Mantle Cell Lymphoma: Relapsed/Refractory

Mantle cell lymphoma (MCL) is an uncommon B cell lymphoma defined by the overexpression of cyclin D1 and cell cycle dysregulation. It occurs most in the elderly with a 3:1 male predominance. MCL is unusual in that its clinical course

**Table 1** Clinical application of lenalidomide in non-Hodgkin lymphomas

| | Disease | Agent | Phase | *N* | ORR (CR%) | PFS | OS | Grade 3/4 non-hematologic AEs | Grade 3/4 hematologic AEs | Reference |
|---|---|---|---|---|---|---|---|---|---|---|
| R/R | | | | | | | | | | |
| MCL | MCL | Lenalidomide | II | 134 | 28% (8%) | 4.0 months | 19.0 months | Pneumonia (8%), fatigue (7%), diarrhea (6%), dyspnea (5%) | Neutropenia (43%), thrombocytopenia (27%), anemia (11%), leukopenia (6%) | [22] |
| | MCL | Lenalidomide | II | 170 | 40% (5%) | 8.7 months | 27.9 months | Pneumonia (6%), diarrhea (6%) | Neutropenia (77%), thrombocytopenia (30%), anemia (14%), leukopenia (13%) | [23] |
| | MCL | Lenalidomide + rituximab | II | 44 | 57% (36%) | 11.1 months | 24.3 months | Fatigue (14%), non-neutropenic infections (14%), hyperuricemia (14%) | Neutropenia (86%), thrombocytopenia (36%), leukopenia (36%), lymphopenia (21%) | [24] |
| | MCL | Lenalidomide + rituximab + bendamustine | II | 75 | 75% (55%) | 20.0 months | 67% (2-year) | Pulmonary toxicity (7%), nephrotoxicity (5%) | Neutropenia (71%), thrombocytopenia (14%), febrile neutropenia (10%), anemia (5%) | [25] |
| | MCL | Lenalidomide + rituximab + Ibrutinib | II | 50 | 76% (56%) | 16.0 months | 22.0 months | Infections (22%), cutaneous symptoms (14%), GI symptoms (12%) | Neutropenia (38%), thrombocytopenia (12%) | [26] |
| Indolent | Follicular, MZL | Lenalidomide | II | 43 | 23% (7%) | 4.4 months | – | Pneumonia (5%), abdominal pain (5%) | Neutropenia (36%), thrombocytopenia (19%), anemia (9%), leukopenia (9%) | [27] |
| | Follicular, MZL, MALT, SLL | Lenalidomide + rituximab | II | 27 | 74% (44%) | 12.4 months | – | Fatigue (23%), hyponatremia (9%) | Neutropenia (55%), lymphopenia (45%) | [28] |
| | Follicular, MCL, SLL, MZL | Lenalidomide + rituximab + low-dose dexamethasone | II | 24 | 58% (33%) | 23.7 months | Not reached | Hypokalemia (15%), hypophosphatemia (7%) | Neutropenia (30%), leukopenia (15%), anemia (7%) | [29] |
| | Follicular | Lenalidomide | III | 45 | 53% (20%) | 1.1 year | 4.5 years | Fatigue (9%), thrombosis (16%) | Neutropenia (16%) | [30] |
| | Follicular | Lenalidomide + rituximab | III | 46 | 76% (39%) | 2 years | Not reached | Fatigue (13%), rash (4%), thrombosis (4%) | Neutropenia (20%), thrombocytopenia (4%) | [30] |
| | Follicular, MZL | Lenalidomide + rituximab | III | 178 | 78% (34%) | 39.4 months | 93% (2-year) | Pneumonia (3%), thrombosis (2%) | Neutropenia (50%), leukopenia (7%), anemia (5%) | [31] |
| Aggressive | DLBCL, FL-III, MCL, transformed | Lenalidomide | II | 49 | 35% (12%) | 4.0 months | – | Fatigue (6%), dyspnea (4%), pneumonia (4%) | Neutropenia (33%), thrombocytopenia (20%), leukopenia (14%) | [32] |
| | DLBCL, FL-III, MCL, transformed | Lenalidomide | II | 217 | 35% (13%) | 3.7 months | – | Dyspnea (6%), fatigue (5%), back pain (5%) | Neutropenia (41%), thrombocytopenia (19%), anemia (9%) | [33] |
| | DLBCL | Lenalidomide | II/III | 102 | 28% (14%) | 13.6 weeks | 31.0 weeks | Infections (19%), pulmonary symptoms (18%), GI symptoms (17%) | Neutropenia (43%), anemia (19%), thrombocytopenia (18%) | [34] |
| | DLBCL, FL-III, transformed | Lenalidomide + rituximab | II | 45 | 33% (22%) | 3.7 months | 10.7 months | | Neutropenia (53%), lymphopenia (40%), | [35] |

**Table 1** (continued)

| | Disease | Agent | Phase | *N* | ORR (CR%) | PFS | OS | Grade 3/4 non-hematologic AEs | Grade 3/4 hematologic AEs | Reference |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Hypophosphatemia (9%) thrombosis (8%), fatigue (7%) | thrombocytopenia (33%), leukopenia (27%), anemia (18%) | |
| | DLBCL, FL-III, MCL, transformed | Lenalidomide + rituximab + bendamustine | II | 41 | 61% (37%) | 4.8 months | 14.5 months | Fatigue (6%), rash (6%) | Neutropenia (46%), thrombocytopenia (10%), anemia (6%) | [36] |
| Frontline MCL | MCL | Lenalidomide + rituximab | II | 36 | 92% (64%) | 64% (5-year) | 77% (5-year) | Rash (29%), secondary primary malignancies (16%), fatigue (11%), tumor flare (11%) | Neutropenia (42%), thrombocytopenia (11%), anemia (8%) | [37] |
| | MCL | Lenalidomide + rituximab + bendamustine | II | 51 | 80% (64%) | 42 months | 53 months | Secondary malignancies (16%), infection (42%), rash (18%), allergic reaction (12%) | Neutropenia (51%), thrombocytopenia (20%), anemia (6%) | [38] |
| Indolent | FL, MZL, SLL | Lenalidomide + rituximab | II | 103 | 90% (64%) | 53.8 months | 96% (3-year) | Pain (9%), dyspnea (7%), fatigue (5%) | Neutropenia (35%), thrombocytopenia (6%) | [39] |
| | FL | Lenalidomide + rituximab | II | 66 | 95% (72%) | 75% (5-year) | 100% (5-year) | Infection (9%), rash (8%), fatigue (6%) | Neutropenia (21%), lymphopenia (9%) | [40] |
| | FL | Lenalidomide + rituximab | III | 513 | 86% (59%) | 77% (3-year) | 94% (3-year) | Cutaneous reactions/rash (11%) | Neutropenia (32%), thrombocytopenia (2%) | [41] |
| | FL | Lenalidomide + R-CHOP | II | 80 | 94% (74%) | 79% (3-year) | 95% (3-year) | Diarrhea (5%), vascular event (5%) | Neutropenia (76%), leukopenia (57%), thrombocytopenia (33%) | [42] |
| Aggressive | DLBCL | Lenalidomide + R-CHOP | II | 60 | 98% (80%) | 59% (2-year) | 78% (2-year) | Infection (12%) | Neutropenia (88%), leukopenia (80%), thrombocytopenia (44%), anemia (16%), febrile neutropenia (9%) | [43] |
| | DLBCL | Lenalidomide + R-CHOP | II | 49 | 92% (86%) | 80% (2-year) | 92% (2-year) | Thrombosis (4%), neurologic (4%) | Neutropenia (69%), leukopenia (59%), thrombocytopenia (30%) | [44] |

is highly variable, with some patients presenting with aggressive disease while others have a much more indolent course [45]. MCL is generally responsive to therapy but is marked by relatively short remissions.

The best-studied data for lenalidomide in MCL is in the relapsed/refractory setting, which is currently the only FDA-approved indication for lenalidomide in lymphoma, gaining approval in 2013. The first major trial examining lenalidomide therapy in MCL was a subset analysis of the NHL-002 trial, which examined lenalidomide monotherapy in aggressive lymphomas. Of the 15 patients in the study with MCL, the overall response rate (ORR) was 53%, with 20% achieving complete response (CR) [46]. After the success of this study, the dedicated MCL-001/EMERGE trial studied single-agent lenalidomide in 134 patients with MCL with relapsed or refractory disease after treatment with bortezomib. ORR in this trial was 28%, with 8% with a CR, and a median duration of response of 16.6 months [22•]. Subsequently, the MCL-002 trial randomized patients with relapsed/refractory MCL to receive either lenalidomide monotherapy or investigator's choice. Lenalidomide significantly improved progression-free survival; PFS was 8.7 months versus 5.2 months in the investigator's choice arm with a hazard ratio of 0.61 [23].

Other trials have used lenalidomide in combination with rituximab ("$R^2$") in relapsed/refractory MCL. Wang and colleagues enrolled 44 patients with relapsed/refractory MCL who were treated with $R^2$, and found an ORR of 57% with a 36% rate of CR, with a median duration of response of 18.9 months [24]. Another trial combined $R^2$ with bendamustine, producing an ORR of 75% with 55% CR, as well as 51% progression-free survival at (PFS) 24 months [25]. More recently, the combination of lenalidomide, ibrutinib, and rituximab (PHILEMON study) also showed promising results in relapsed/refractory MCL, with a 76% ORR and 56% CR at a median follow-up of 18 months [26].

## Mantle Cell Lymphoma: Upfront

Newer data suggests that there is significant efficacy of lenalidomide in the frontline treatment of mantle cell lymphoma as well. A cohort of 38 patients received a combination of lenalidomide and rituximab ($R^2$) up front, with rituximab administered weekly for the first 4 weeks and then every other cycle until disease progression. The initial results showed an ORR of 92% with 64% CR and a PFS of 85% at 24 months [37]. A subsequent 5-year follow-up showed that at a median follow-up of 64 months, 3-year PFS and overall survival (OS) were 80% and 90%, with a 5-year estimated PFS and OS of 64% and 77%, respectively [47•]. Eighty-seven percent of subjects in this study had evaluable Ki67, including 21% with Ki67 > 30%. There was no difference in PFS or OS based on Ki67 proliferation index using a cutoff of 30%. These progression-free and overall survival rates were striking in that they were comparable to historical data of more intensive chemotherapy regimens while reducing toxicity, suggesting that a lenalidomide-based approach warrants further clinical investigation in frontline setting [48].

Another trial added lenalidomide to the bendamustine-rituximab (BR) combination in untreated MCL, achieving a 64% ORR with 62% CR. However, the authors observed a high degree of severe infections and second primary malignancies (SPMs) in 16% of patients, which limited its clinical application [38].

Studies are ongoing combining lenalidomide with other therapeutic regimens in the upfront treatment of MCL. For example, lenalidomide is combined with R-CHOP as induction followed by high-dose cytarabine and rituximab consolidation, followed by 6-month maintenance with lenalidomide and rituximab. Preliminary results show a 92% CR rate in patients who completed lenalidomide maintenance, although median follow-up is currently only 9 months [49].

## Indolent Lymphomas: Relapsed/Refractory

Indolent lymphomas include follicular (SLL), marginal zone (MZL), small lymphocytic (SLL), and lymphoplasmacytic lymphoma, with follicular lymphoma as the most common subtype. Indolent lymphomas typically respond well to frontline therapy, but almost always recur, despite their slow-moving nature.

Lenalidomide has been studied extensively in the relapsed/refractory setting in indolent lymphomas. The NHL-001 study was the first major trial of lenalidomide in indolent lymphomas and included 43 patients with relapsed/refractory FL and MZL treated with single-agent lenalidomide, and achieved an ORR of 23% (27% of patients with follicular histology) with CR rate of 7% [27].

Following NHL-001, several trials studied the combination of lenalidomide and rituximab ($R^2$) in relapsed/refractory indolent lymphomas [28], some adding dexamethasone to the regimen [29]. The largest of these studies was CALGB 50401, which randomized patients with relapsed/refractory FL to receive either lenalidomide monotherapy or $R^2$, allowing for a direct comparison of the two regimens. ORR was significantly higher in the $R^2$ arm (76% versus 53%, $p = 0.029$) and time to progression was significantly longer (2 years versus 1.1 years, $p = 0.0023$) [30].

More recently, the phase III AUGMENT trial randomized 358 patients with relapsed/refractory FL and MZL to either rituximab plus placebo or $R^2$. The study's primary endpoint, progression-free survival, showed an impressive difference with a PFS of 39.4 months with $R^2$ versus 14.1 months in the control arm, a hazard ratio of 0.46 (95% CI 0.34–0.62, $p < 0.0001$). Other endpoints included ORR, 78% in $R^2$ versus 53% with rituximab monotherapy ($p < 0.0001$), and CR rate, 34% and 18% respectively ($p = 0.001$). The duration of

response was 36.6 months in the $R^2$ arm versus 21.7 months in the rituximab arm [31•]. The AUGMENT trial has established the combination of lenalidomide and rituximab as an effective option in the treatment of relapsed/refractory follicular lymphoma and MZL.

Given the exciting results with $R^2$, a recent phase I trial combined lenalidomide with obinutuzumab, a type II anti-CD20 monoclonal antibody that increases antibody-dependent cellular cytotoxicity relative to rituximab. Nineteen patients received the GALEN regimen (obinutuzumab + lenalidomide), and after 6 cycles, ORR was 63% with 58% achieving CR and a 3-year PFS of 52% [50]. Further studies are indicated to determine its efficacy as compared with $R^2$.

## Indolent Lymphomas: Upfront

There is also data for the use of lenalidomide as first-line treatment in indolent lymphomas. Fowler and colleagues studied the $R^2$ regimen in untreated follicular lymphoma, MZL, and SLL. ORR was 90% with 64% achieving a CR (98% and 87% respectively in the follicular lymphoma population), with a 78% PFS at 36 months [39].

The $R^2$ regimen has been subsequently evaluated in the untreated follicular lymphoma population in two recent trials. CALGB 50803 enrolled 66 patients with untreated follicular lymphoma, and yielded an ORR of 92% with 72% CR, a 5-year PFS of 70% with a 5-year overall survival of 100%, comparable with the chemotherapy-based regimens [40].

The $R^2$ regimen was also recently evaluated in a phase III randomized control trial of 1030 patients with untreated follicular lymphoma. Patients were randomized to receive $R^2$ or chemotherapy with one of the three rituximab-based regimens (R-chemo) of the investigator's choice. At 120 weeks, the rate of ORR was similar between the two groups (86% and 92% in the $R^2$ and R-chemo arms respectively), as were the rates of CR (48% and 53% respectively). The rates of progression-free survival were also similar (77% and 78% respectively) [41]. This data suggests that $R^2$ may be a reasonable alternative to chemotherapy in the upfront treatment of follicular lymphoma without compromising outcomes.

A recent phase I trial combined ibrutinib with lenalidomide and rituximab in untreated follicular lymphoma. Of 22 patients in the cohort, 95% of patients responded with 36% achieving a CR, and another 32% experiencing resolution of hypermetabolic activity on PET-CT without confirmatory bone marrow biopsy [51]. At 12 months, progression-free survival was 80%.

The combination of lenalidomide and R-CHOP ($R^2$-CHOP) has also been studied in untreated follicular lymphoma. Following a 2013 phase I trial [52], Tilly and colleagues recently published a study of 80 patients with untreated high tumor burden follicular lymphoma treated with 6 cycles of $R^2$-CHOP with a primary endpoint of CR. At end of induction, 74% of patients achieve CR, with 69% maintaining CR at 30 months [42]. Further evaluation with comparative study comparing survival to a standard R-CHOP regimen is warranted.

## Diffuse Large B Cell Lymphoma

In contrast to indolent lymphomas, the aggressive lymphomas have a much more rapidly progressive clinical course but are potentially curable. The most common aggressive lymphoma is diffuse large B cell lymphoma (DLBCL). The standard of care for DLBCL is R-CHOP given every 3 weeks [53]. DLBCL can be further subdivided into at least two subtypes by gene expression profiling: germinal center B cell-like (GCB) and activated B cell-like (ABC, or non-GCB). ABC phenotype DLBCL is associated with a significantly worse prognosis with R-CHOP than the GCB phenotype [54]. Given these differences, attempts have been made in particular to improve upon R-CHOP in patients with ABC-type DLBCL.

## Aggressive Lymphomas: Relapsed/Refractory

Several studies have examined lenalidomide monotherapy as treatment for relapsed/refractory aggressive lymphomas. The NHL-002 and NHL-003 studies each used lenalidomide monotherapy in patients with aggressive lymphomas, including DLBCL, MCL, follicular grade 3 (FL-III), and transformed lymphomas (TL). NHL-002 included 49 total patients, and 29 patients with either DLBCL or TL (26 and 3, respectively). While ORR was 35% for the entire study, only 19% of DLBCL patients responded and only 33% of patients with TL had a response [32]. The subsequent NHL-003 trial included 217 patients, including 108 patients with DLBCL and 33 patients with TL (the remainder were FL-III and MCL). NHL-003 showed comparable findings to NHL-002: while the ORR for all patients was 35%, DLBCL patients only had a 28% ORR, while response rates were 42%, 42%, and 45% for MCL, FL-III, and TL respectively [33].

Following NHL-002 and NHL-003, lenalidomide monotherapy was compared with investigator's choice (single-agent gemcitabine, oxaliplatin, etoposide, or rituximab) for relapsed/refractory DLBCL. Of patients treated with lenalidomide, 27% achieved a response versus 11% of the patients in the investigator's choice arm, which approached but did not reach statistical significance ($p = 0.08$). There was also no difference in response rates for GCB versus non-GCB patients in this study [34].

$R^2$ was evaluated in 45 patients with aggressive lymphomas, including 39 patients with DLBCL and 9 with transformed lymphoma. The overall response rate for the whole cohort was 33%, including 28% for DLBCL and 56% for the transformed lymphomas. Median PFS and OS for the

whole cohort were 3.7 and 10.7 months, respectively; in the DLBCL subgroup, PFS and OS were 2.8 and 10.2 months, and in the transformed lymphoma group, PFS and OS were 4.3 and 11.5 months [35].

A phase I study evaluated the combination of ibrutinib, rituximab, and lenalidomide ($iR^2$) in relapsed/refractory DLBCL. On a 15-mg dose of lenalidomide, ORR was 44% with 17% CR; in the non-GCB subgroup, ORR was 50% with 25% achieving a CR [55]. A phase II study of this regimen exclusively in patients with non-GCB DLBCL is ongoing. Preliminary results show a 55% ORR with 30% achieving a CR; median PFS was 5 months with a 12-month PFS of 28%. Final results from this trial may shed light on whether the $iR^2$ regimen is an effective outpatient option for relapsed/refractory non-GCB DLBCL [56].

There have also been several trials incorporating lenalidomide into salvage chemotherapy regimens for aggressive lymphomas. The phase II portion of the SAKK 38/08 trial combined $R^2$ with bendamustine in 41 patients with aggressive lymphomas who were either relapsed/refractory to first-line treatment or were ineligible for first-line anthracycline therapy. In the subgroup of relapsed/refractory patients, ORR was 54% with 32% CR and a median PFS of 3.2 months [36]. A phase I trial combined lenalidomide with rituximab, etoposide, cisplatin, cytarabine, and methylprednisolone (LR-ESHAP) for patients with relapsed/refractory DLBCL, followed by autologous stem cell transplant (autoSCT) for patients who responded. For the 19 patients in the trial, ORR was 78.9% with 47.4% CR; 2-year PFS and OS were 44% and 63%, respectively [57]. Lenalidomide was also combined with rituximab, ifosfamide, carboplatin, and etoposide (RICER) in a phase I trial for first relapse or primary refractory DLBCL followed by autoSCT. Of the 15 patients in the study, 11 responded, with 9 achieving a CR (73% ORR and 60% CR) [58].

## Diffuse Large B Cell Lymphoma: Upfront

In xenograft models of ABC-subtype DLBCL, lenalidomide showed clinical activity via cereblon-mediated inhibition of transcription factor IFR-4, leading to downregulation of B cell receptor-dependent NF-kB [59]. The promising pre-clinical activity of lenalidomide in ABC-type DLBCL led to two studies: the MC078E trial [43] and the FIL REAL07 study [44] of lenalidomide combined with R-CHOP ($R^2$-CHOP) in untreated DLBCL. Long-term follow-up data from both trials combined was recently published, including data from 112 patients (63 from MC and 49 from FIL) with untreated DLBCL of both GCB and non-GCB subtypes. Endpoints were stratified by cell of origin, with a 5-year PFS of 52.8% in GCB type versus 64.5% in non-GCB type, 5-year overall survival (OS) 68.6% versus 74.1%, respectively, and 5-year time to progression of 61.6% versus 69.6% respectively [60].

These trials suggest that the addition of lenalidomide to the standard R-CHOP regimen in the upfront setting may mitigate the associated negative prognosis of non-GCB DLBCL, and meta-analyses appear to corroborate this hypothesis [61]. The phase III ROBUST study is currently underway attempting to confirm these results, randomizing patients with untreated ABC-type DLBCL to receive either $R^2$-CHOP or placebo-R-CHOP [62]. The first interim report of the ROBUST study at a median follow-up of 27 months showed no significant difference in 2-year PFS (67% for $R^2$-CHOP and 64% for R-CHOP, $p = 0.29$), suggesting potential heterogeneous responses within ABC subtype of DLBCL [63]. Interestingly, the contemporaneous randomized phase 2 US intergroup study E1412, which compares $R^2$-CHOP to R-CHOP in patients with all subtypes of DLBCL as well as ABC subtype of DLBCL, showed a 34% risk reduction of PFS in the $R^2$-CHOP arm for all-comers of DLBCL, suggesting potential therapeutic advantage of adding lenalidomide to R-CHOP for both GCB and ABC subtypes [64].

## DLBCL: The Role of Lenalidomide Maintenance

The role of lenalidomide maintenance in DLBCL has been under investigation, both after frontline R-CHOP or after second-line chemotherapy. The large phase III REMARC study randomized DLBCL patients who had achieved a CR or PR after upfront R-CHOP to receive lenalidomide maintenance or placebo. At the time of primary analysis, with a median follow-up of 39 months, the median PFS was not yet reached for the lenalidomide arm versus 58.9 months in the placebo arm (hazard ratio 0.708, CI 0.537–0.933, $p = 0.01$). However, with a longer follow-up of 52 months, overall survival was similar between the two arms [65].

Another study by Ferreri and colleagues examined the role of lenalidomide maintenance after salvage chemotherapy. Forty-six patients with DLBCL received lenalidomide maintenance after responding to rituximab-containing salvage chemotherapy. One-year PFS was 70%, above the determined threshold for efficacy, but the study was complicated by one death from acute toxicity (intestinal infarction) and another due to secondary myelodysplastic syndrome [66]. Importantly, a large percentage of patients in both the REMARC and the Ferreri study had transformed lymphoma, complicating the ability to extrapolate these results to de novo DLBCL patients [32, 67].

## T Cell Lymphomas

T cell lymphomas are a clinically diverse group of malignancies that can arise from mature or immature T cells. T cell lymphomas include both systemic and cutaneous form of non-Hodgkin lymphomas, with the most common subtypes being peripheral T cell lymphoma, NOS, angioimmunoblastic

T cell lymphoma, and anaplastic large cell lymphoma (ALCL) [68]. In the last several years, data emerged suggesting that lenalidomide may play a role in T cell lymphoma therapy as well.

ATLL typically has dismal outcomes with few treatment options after relapse. The phase I ATLL-001 [69] and subsequent phase II ATLL-002 trials treated patients with relapsed or recurrent ATLL with lenalidomide monotherapy. ATLL-002 treated 26 patients and achieved a 42% ORR, with 19% achieving CR, and a median PFS and OS of 3.8 and 20.3 months respectively [70]. For a disease often accompanied by a bleak prognosis, these findings in a small study may indicate that lenalidomide is a promising option for ATLL in the relapsed setting [71].

Lenalidomide has also been studied as a single agent in other T cell lymphomas. The EXPECT trial treated 54 patients with relapsed/refractory peripheral T cell lymphomas with lenalidomide monotherapy, including AITL, systemic and cutaneous ALCL, and PTCL unspecified. Overall, 22% of patients responded with an 11% rate of CR; 33% had progressive disease. Of note, there was a 31% ORR in the AITL subpopulation and 20% ORR in the PTCL unspecified [72]. Another study of 39 patients with either untreated or relapsed/refractory T cell lymphoma including PTCL unspecified, angioimmunoblastic TCL, enteropathy-type TCL, hepatosplenic TCL, and lymphoblastic TCL also treated with lenalidomide. In the aggregate, ORR was 26%, with an 8% CR rate, and 33% of those with angioimmunoblastic TCL responded. [73]. These results indicate that there may be a role for lenalidomide monotherapy in relapsed/refractory PTCL, in particular, angioimmunoblastic subtype.

The role of lenalidomide in cutaneous T cell malignancies was examined in a phase II trial-evaluated lenalidomide monotherapy in advanced refractory mycosis fungoides/Sezary syndrome. A total of 32 heavily pre-treated patients were enrolled; partial response was achieved in 28% of patients with no CRs. Median progression-free survival was 8 months [74]. Lenalidomide maintenance after debulking in CTCL was studied in the phase III EORTC 21081 study which randomized patients to receive lenalidomide maintenance versus observation after surgical debulking. Median PFS was 5.3 months in the lenalidomide group versus 2.3 months in the observation group, although given the small sample size, it was underpowered to detect statistical significance [75].

## Clinical Development of CC-122 (Avadomide) in Lymphomas

While the vast majority of data for IMiDs in lymphoma is with lenalidomide, there is emerging phase I data for the use of CC-122 (avadomide) in DLBCL and follicular lymphoma. While lenalidomide has shown preferential anti-proliferative activity for cell lines of ABC subtype of DLBCL, CC-122 has shown ability to induce apoptosis in cell lines independent of subtype [76].

Early phase I trials of CC-122 in lymphoma are underway. The current CC-122-NHL-001 study combines CC-122 with obinutuzumab in relapsed/refractory FL, DLBCL, and MZL. At the most recent update, 38 patients with follicular lymphoma achieved an ORR of 68% with 42% in CR [77]. The DLBCL subgroup at last update showed an ORR and CR rate of 47% and 11% respectively [78]. The ongoing CC-122-DLBCL-001 combines CC-122 with rituximab in relapsed/refractory FL and DLBCL patients. At most recent updates, 37 patients with FL had been enrolled and 26 patients with DLBCL. The FL group achieved an ORR of 65% with 22% CR; interestingly, there was no difference between patients previously treated with lenalidomide and those that were not [79]. The cohort as a whole had an ORR of 39% with 15% CR; stratified by subgroup, the transformed lymphoma group had an ORR of 29% while the primary DLBCL patients had an ORR of 42% [80].

## Clinical Considerations in Managing Common Side Effects

Lenalidomide, while significantly less toxic than chemotherapy, requires careful clinical monitoring. By far the most common grade 3/4 toxicities in studies of lenalidomide in lymphoma were hematologic, with neutropenia and thrombocytopenia more common than anemia. Growth factor such as GCSF is commonly used for management of febrile neutropenia and prolonged neutropenia, along with appropriate dose adjustment [81]. Grade 1/2 rash, myalgias, and fatigue were quite common but generally did not limit therapy [82].

Given its derivation from thalidomide, the teratogenic effects of lenalidomide are directly mediated by its activity with cereblon [83]. Birth control and careful monitoring for pregnancy is of great importance if lenalidomide is to be considered in women of childbearing age.

Lenalidomide also carries a black box warning for thrombotic events associated with dexamethasone use in multiple myeloma. The current ASCO guidelines suggest outpatient prophylaxis for the prevention of venous thromboembolism (VTE) in multiple myeloma patients receiving lenalidomide, but make no recommendations with regard to lenalidomide use in lymphoma [84]. A recent meta-analysis showed that VTE rates are similar in patients with lymphoma treated with lenalidomide and with multiple myeloma treated with lenalidomide [85], suggesting that lymphoma patients receiving lenalidomide may benefit from VTE prophylaxis as well. Most trials of lenalidomide in lymphoma routinely require VTE prophylaxis. While there is no consensus or prospective data regarding which agents should be used as VTE

prophylaxis, most studies used aspirin alone as VTE prophylaxis for standard-risk patients.

## Correlative Studies and Potential Biomarkers

Several studies have attempted to identify possible markers of response to lenalidomide. Pre-clinical studies have identified Aiolos, one of the cereblon-associated transcription factors, as a possible marker for lenalidomide activity. In healthy subjects dosed with lenalidomide, Aiolos levels were shown to be decreased in peripheral T cells, mirroring results obtained in vitro [86]. It has been suggested that peripheral Aiolos levels could be used as a marker of response, although its clinical feasibility is unclear.

MCL-001 studied Ki-67 as a potential biomarker in MCL treated with lenalidomide. While patients treated with lenalidomide showed similar ORR regardless of Ki-67 expression, lower levels of Ki-67 showed superior durations of response and survival outcomes [87]. However, Ki-67 has been shown to be correlated with survival outcomes regardless of treatment, so it is unclear if these findings are specific to lenalidomide treatment rather than reflection of MCL disease property [88]. Another pre-clinical study in MCL showed decreased microvessel density after treatment with lenalidomide, with a trend toward an increase in NK cell and macrophage counts, but are of questionable clinical utility [89].

## Conclusions

Immunomodulatory agents target tumor cells as well as the tumor microenvironment, exerting pleotropic therapeutic effects through interaction with intracellular effector cereblon in diverse cell types, including activation of T cells, expansion of NK cells, inhibition of tumor-associated angiogenesis and lymphangiogenesis, and induction of tumor cell apoptosis by interception of crucial proliferative pathways within lymphoma cells. As clinical trials with lenalidomide continue to find success in both indolent and aggressive lymphomas, IMiDs are poised to be important building blocks for combinatorial strategies with chemotherapy, novel biologics, and emerging immunotherapy involving immune checkpoint inhibitors and chimeric antigen receptor T cell (CAR-T) therapy.

### Compliance with Ethical Standards

**Conflict of Interest** Samuel Yamshon declares that he has no conflict of interest. Jia Ruan reports grants and personal fees from Celgene, grants from Pharmacyclics, grants and personal fees from AstraZeneca, grants from Seattle Genetics, personal fees from Juno Therapeutics, and personal fees from Kite Pharma.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

## References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance


1. D'Amato RJ, Loughnan MS, Flynn E, Folkman J. Thalidomide is an inhibitor of angiogenesis. Proc Natl Acad Sci U S A. 1994;91(9):4082–5.
2. Verheul HM, Panigrahy D, Yuan J, D'Amato RJ. Combination oral antiangiogenic therapy with thalidomide and sulindac inhibits tumour growth in rabbits. Br J Cancer. 1999;79(1):114–8.
3. Bartlett JB, Dredge K, Dalgleish AG. The evolution of thalidomide and its IMiD derivatives as anticancer agents. Nat Rev Cancer. 2004;4:314–22.
4. Corral LG, Haslett PAJ, Muller GW, et al. Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF-alpha. J Immunol. 1999;163:380–6.
5. Dredge K, Horsfall R, Robinson SP, Zhang LH, Lu L, Tang Y, et al. Orally administered lenalidomide (CC-5013) is anti-angiogenic in vivo and inhibits endothelial cell migration and Akt phosphorylation in vitro. Microvasc Res. 2005;69(1–2):56–63.
6. Song K, Herzog B, Sheng M, Fu J, Mcdaniel J, Chen H, et al. Lenalidomide inhibits lymphangiogenesis in preclinical models of mantle cell lymphoma. Cancer Res. 2013;73:7254–64.
7. Knight R. IMiDs: a novel class of immunomodulators. Semin Oncol. 2005;32:24–30.
8. Ramsay AG, Clear AJ, Kelly G, Fatah R, Matthews J, MacDougall F, et al. Follicular lymphoma cells induce T-cell immunologic synapse dysfunction that can be repaired with lenalidomide: implications for the tumor microenvironment and immunotherapy. Blood. 2009;114(21):4713–20.
9. Ramsay AG, Johnson AJ, Lee AM, et al. Chronic lymphocytic leukemia T cells show impaired immunological synapse formation that can be reversed with an immunomodulating drug. J Clin Invest. 2008;118(7):2427–37.
10. Zhang L, Qian Z, Cai Z, Sun L, Wang H, Bartlett JB, et al. Synergistic antitumor effects of lenalidomide and rituximab on mantle cell lymphoma in vitro and in vivo. Am J Hematol. 2009;84(9):553–9.
11. Hernandez-Ilizaliturri FJ, Reddy N, Holkova B, Ottman E, Czuczman MS. Immunomodulatory drug CC-5013 or CC-4047 and rituximab enhance antitumor activity in a severe combined immunodeficient mouse lymphoma model. Clin Cancer Res. 2005;11(16):5984–92.
12. Reddy N, Hernandez-Ilizaliturri FJ, Deeb G, Roth M, Vaughn M, Knight J, et al. Immunomodulatory drugs stimulate natural killer-cell function, alter cytokine production by dendritic cells, and inhibit angiogenesis enhancing the anti-tumour activity of rituximab in vivo. Br J Haematol. 2008;140(1):36–45.
13. Lopez-Girona A, Mendy D, Ito T, Miller K, Gandhi AK, Kang J, et al. Cereblon is a direct protein target for immunomodulatory and antiproliferative activities of lenalidomide and pomalidomide. Leukemia. 2012;26:2326–35.
14. •• Gribben JG, Fowler N, Morschhauser F. Mechanisms of action of lenalidomide in B-cell non-Hodgkin lymphoma. J Clin Oncol.

2015;33(25):2803–11 **Comprehensive review on mechanism of action of lenalidomide and its clinical relevance as therapeutic agent in B-cell non-Hodgkin lymphoma.**

15. Verhelle D, Corral LG, Wong K, Mueller JH, Moutouh-de Parseval L, Jensen-Pergakes K, et al. Lenalidomide and CC-4047 inhibit the proliferation of malignant B cells while expanding normal CD34+ progenitor cells. Cancer Res. 2007;67:746–55.
16. Smith SM, Grinblatt D, Johnson JL, Niedzwiecki D, Rizzieri D, Bartlett NL, et al. Thalidomide has limited single-agent activity in relapsed or refractory indolent non-Hodgkin lymphomas: a phase II trial of the Cancer and Leukemia Group B. Br J Haematol. 2008;140:313–9.
17. Chanan-Khan A, Miller KC, Takeshita K, et al. Results of a phase 1 clinical trial of thalidomide in combination with fludarabine as initial therapy for patients with treatment-requiring chronic lymphocytic leukemia (CLL). Blood.
18. Furman RR, Leonard JP, Allen SL, Coleman M, Rosenthal T, Gabrilove JL. Thalidomide alone or in combination with fludarabine are effective treatments for patients with fludarabine-relapsed and refractory CLL. J Clin Oncol. 2005 ASCO Annual Meeting Proceedings 2005;23(supplement):6640.
19. Kaufmann H, Raderer M, Wohrer S, et al. Antitumor activity of rituximab plus thalidomide in patients with relapsed/refractory mantle cell lymphoma. Blood. 2004;104:2269–71.
20. Ruan J, Martin P, Coleman M, Furman RR, Cheung K, Faye A, et al. Durable responses with the metronomic rituximab and thalidomide plus prednisone, etoposide, procarbazine, and cyclophosphamide regimen in elderly patients with recurrent mantle cell lymphoma. Cancer. 2010;116:2655–64.
21. Zhang L, Zhao AL, Duan MH, Li ZY, Cao XX, Feng J, et al. Phase 2 study using oral thalidomide-cyclophosphamide-prednisone for idiopathic multicentric Castleman disease. Blood. 2019;133(16):1720–8.
22.• Goy A, Sinha R, Williams ME, et al. Single-agent lenalidomide in patients with mantle-cell lymphoma who relapsed or progressed after or were refractory to bortezomib: phase II MCL-001 (EMERGE) study. J Clin Oncol. 2013;31(29):3688–95 **First registration trial of lenalidomide in mantle cell lymphoma, which leads to FDA approval of lenalidomide for R/R MCL.**
23. Trněný M, Lamy T, Walewski J, Belada D, Mayer J, Radford J, et al. Lenalidomide versus investigator's choice in relapsed or refractory mantle cell lymphoma (MCL-002; SPRINT): a phase 2, randomised, multicentre trial. Lancet Oncol. 2016;17(3):319–31.
24. Wang M, Fayad L, Wagner-bartak N, et al. Lenalidomide in combination with rituximab for patients with relapsed or refractory mantle-cell lymphoma: a phase 1/2 clinical trial. Lancet Oncol. 2012;13(7):716–23.
25. Zaja F, Ferrero S, Stelitano C, et al. Second-line rituximab, lenalidomide, and bendamustine in mantle cell lymphoma: a phase II clinical trial of the Fondazione Italiana Linfomi. Haematologica.
26. Jerkeman M, Eskelund CW, Hutchings M, Räty R, Wader KF, Laurell A, et al. Ibrutinib, lenalidomide, and rituximab in relapsed or refractory mantle cell lymphoma (PHILEMON): a multicentre, open-label, single-arm, phase 2 trial. Lancet Haematol. 2018;5(3):e109–16.
27. Witzig T, Wiernik P, Moore T, Reeder C, Cole C, Justice G, et al. Lenalidomide oral monotherapy produces durable responses in relapsed or refractory indolent non-Hodgkin's lymphoma. J Clin Oncol. 2009;27:5404–9.
28. Tuscano J, Dutia M, Chee K, Brunson A, Reed-Pease C, Abedi M, et al. Lenalidomide plus rituximab can produce durable clinical responses in patients with relapsed or refractory, indolent non-Hodgkin lymphoma. Br J Haematol. 2014;165:375–81.
29. Ahmadi T, Chong E, Gordon A, Aqui N, Nasta S, Svoboda J, et al. Combined lenalidomide, low-dose dexamethasone, and rituximab achieves durable responses in rituximab-resistant indolent and mantle cell lymphomas. Cancer. 2014;120:222–8.
30. Leonard J, Jung S, Johnson J, Pitcher B, Bartlett N, Blum K, et al. Randomized trial of lenalidomide alone versus lenalidomide plus rituximab in patients with recurrent follicular lymphoma: CALGB 50401 (alliance). J Clin Oncol. 2015;33:3635–40.
31.• Leonard JP, Trneny M, Izutsu K, Fowler NH, et al. AUGMENT: a phase III study of lenalidomide plus rituximab versus placebo plus rituximab in relapsed or refractory indolent lymphoma. J Clin Oncol. 2019;37(14):1188 **The registration trial that led to FDA approval of Len+R for R/R FL+MZL.**
32. Wiernik PH, Lossos IS, Tuscano JM, Justice G, Vose JM, Cole CE, et al. Lenalidomide monotherapy in relapsed or refractory aggressive non-Hodgkin's lymphoma. J Clin Oncol. 2008;26(30):4952–7.
33. Witzig TE, Vose JM, Zinzani PL, Reeder CB, Buckstein R, Polikoff JA, et al. An international phase II trial of single-agent lenalidomide for relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma. Ann Oncol. 2011;22(7):1622–7.
34. Czuczman MS, Trněný M, Davies A, Rule S, Linton KM, Wagner-Johnston N, et al. A phase 2/3 multicenter, randomized, open-label study to compare the efficacy and safety of lenalidomide versus investigator's choice in patients with relapsed or refractory diffuse large B-cell lymphoma. Clin Cancer Res. 2017;23(15):4127–37.
35. Wang M, Fowler N, Wagner-Bartak N, Feng L, Romaguera J, Neelapu S, et al. Oral lenalidomide with rituximab in relapsed or refractory diffuse large cell, follicular and transformed lymphoma: a phase II clinical trial. Leukemia. 2013;27:1902–9.
36. Hitz F, Zucca E, Pabst T, Fischer N, Cairoli A, Samaras P, et al. Rituximab, bendamustine and lenalidomide in patients with aggressive B-cell lymphoma not eligible for anthracycline-based therapy or intensive salvage chemotherapy - SAKK 38/08. Br J Haematol. 2016;174(2):255–63.
37. Ruan J, Martin P, Shah B, Schuster SJ, Smith SM, Furman RR, et al. Lenalidomide plus rituximab as initial treatment for mantle-cell lymphoma. N Engl J Med. 2015;373(19):1835–44.
38. Albertsson-Lindblad A, Kolstad A, Laurell A, Räty R, Grønbæk K, Sundberg J, et al. Lenalidomide-bendamustine-rituximab in patients older than 65 years with untreated mantle cell lymphoma. Blood. 2016;128(14):1814–20.
39. Fowler N, Davis R, Rawal S, Nastoupil L, Hagemeister F, Mclaughlin P, et al. Safety and activity of lenalidomide and rituximab in untreated indolent lymphoma: an open-label, phase II trial. Lancet Oncol. 2014;15:1311–8.
40. Martin P, Jung SH, Pitcher B, et al. A phase II trial of lenalidomide plus rituximab in previously untreated follicular non-Hodgkin's lymphoma (NHL): CALGB 50803 (Alliance). Ann Oncol. 2017;28(11):2806–12.
41. Morschhauser F, Fowler NH, Feugier P, Bouabdallah R, Tilly H, Palomba ML, et al. Rituximab plus Lenalidomide in advanced untreated follicular lymphoma. N Engl J Med. 2018;379(10):934–47.
42. Tilly H, Morschhauser F, Casasnovas O, Molina TJ, Feugier P, Gouill SL, et al. Lenalidomide in combination with R-CHOP (R2-CHOP) as first-line treatment of patients with high tumour burden follicular lymphoma: a single-arm, open-label, phase 2 study. Lancet Haematol. 2018;5(9):e403–10.
43. Nowakowski GS, LaPlant B, Macon WR, Reeder CB, Foran JM, Nelson GD, et al. Lenalidomide combined with R-CHOP overcomes negative prognostic impact of non–germinal center B-cell phenotype in newly diagnosed diffuse large B-cell lymphoma: a phase II study. J Clin Oncol. 2014;33:251–7. https://doi.org/10.1200/JCO.2014.55.5714.
44. Vitolo U, et al. Lenalidomide plus R-CHOP21 in elderly patients with untreated diff use large B-cell lymphoma: results of the REAL07 open-label, multicentre, phase 2 trial. Lancet Oncol. 2014;15:730–7. https://doi.org/10.1016/S1470-2045(14)70191-3.

45. Vose JM. Mantle cell lymphoma: 2017 update on diagnosis, risk-stratification, and clinical management. Am J Hematol. 2017;92:806–13.
46. Habermann TM, Lossos IS, Justice G, Vose JM, Wiernik PH, McBride K, Wride K, Ervin-Haynes A, Takeshita K, Pietronigro D, Zeldis JB, Tuscano JM (2009) Lenalidomide oral monotherapy produces a high response rate in patients with relapsed or refractory mantle cell.
47.• Ruan J, Martin P, Christos P, Cerchietti L, Tam W, Shah B, et al. Five-year follow-up of lenalidomide plus rituximab as initial treatment of mantle cell lymphoma. Blood. 2018;132(19):2016–25 **Long-term follow-up of the first chemo-free regimen (R2) as initial treatment for MCL.**
48. Maddocks K. Chemotherapy-free induction in MCL: ready for prime time? Blood. 2018;132(19):2001–2.
49. Kumar A, Zelenetz AD, Batlevi CL, Caron P, Dogan A, Drullinsky P, et al. Initial results of a phase II study of sequential chemotherapy and lenalidomide followed by rituximab and lenalidomide maintenance for untreated mantle cell lymphoma. Blood. 2018;132(Suppl 1):2880.
50. Morschhauser F, Salles G, Le Gouill S, Tilly H, Thieblemont C, Bouabdallah K, et al. An open-label phase 1b study of obinutuzumab plus lenalidomide in relapsed/refractory follicular B-cell lymphoma. Blood. 2018;132(14):1486–94.
51. Ujjani CS, Jung SH, Pitcher B, Martin P, Park SI, Blum KA, et al. Phase 1 trial of rituximab, lenalidomide, and ibrutinib in previously untreated follicular lymphoma: Alliance A051103. Blood. 2016;128(21):2510–6. https://doi.org/10.1182/blood-2016-06-718106.
52. Tilly H, Morschhauser F, Salles G, Casasnovas R, Feugier P, Molina T, et al. Phase Ib study of lenalidomide in combination with rituximab-CHOP (R2-CHOP) in patients with B-cell lymphoma. Leukemia. 2013;27:252–5.
53. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med. 2002;346(4):235–42.
54. Rosenwald A, Wright G, Chan WC, Connors JM, Campo E, Fisher RI, et al. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. N Engl J Med. 2002;346(25):1937–47.
55. Goy A, Ramchandren R, Ghosh N, Munoz J, Morgan DS, Dang NH, et al. A multicenter open-label, phase 1b/2 study of ibrutinib in combination with lenalidomide and rituximab in patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL). Blood. 2016;128(22):473.
56. Ramchandren R, Johnson P, Ghosh N, Ruan J, Ardeshna KM, Johnson R, et al. The iR2 regimen (ibrutinib, lenalidomide, and rituximab) is active with a manageable safety profile in patients with relapsed/refractory non-germinal center-like diffuse large B-cell lymphoma. Blood. 2018;132(Suppl 1):402.
57. Martín A, Redondo AM, Dlouhy I, Salar A, González-Barca E, Canales M, et al. Lenalidomide in combination with R-ESHAP in patients with relapsed or refractory diffuse large B-cell lymphoma: a phase 1b study from GELTAMO group. Br J Haematol. 2016;173:245–52.
58. Feldman T, Mato AR, Chow KF, Protomastro EA, Yannotti KML, Bhattacharyya P, et al. Addition of lenalidomide to rituximab, ifosfamide, carboplatin, etoposide (RICER) in first-relapse/primary refractory diffuse large B-cell lymphoma. Br J Haematol. 2014;166(1):77–83.
59. Zhang LH, Kosek J, Wang M, Heise C, Schafer PH, Chopra R. Lenalidomide efficacy in activated b-cell-like subtype diffuse large B-cell lymphoma is dependent upon IRF4 and cereblon expression. Br J Haematol. 2013;160:487–502.
60. Castellino A, Chiappella A, LaPlant BR, et al. Lenalidomide plus R-CHOP21 in newly diagnosed diffuse large B-cell lymphoma (DLBCL): long-term follow-up results from a combined analysis from two phase 2 trials. Blood Cancer J. 2018;8(11):108. Published 2018 Nov 8. https://doi.org/10.1038/s41408-018-0145-9.
61. Fang C, Zhu D, Dong H, et al. Lenalidomide alone or in combination with chemotherapy treatment for subtypes of diffuse large B cell lymphoma: a systematic review and meta-analysis. Int J Clin Exp Med. 2015;8(7):10705–13 Published 2015 Jul 15.
62. Nowakowski GS, Chiappella A, Witzig TE, Spina M, Gascoyne RD, Zhang L, et al. ROBUST: Lenalidomide-R-CHOP versus placebo-R-CHOP in previously untreated ABC-type diffuse large B-cell lymphoma. Future Oncol. 2016;12(13):1553–63.
63. Vitolo U, Witzig T, Gascoyne R, et al. ROBUST: first report of phase III randomized study of lenalidomide/R-CHOP ($R^2$-CHOP) vs placebo/R-CHOP in previously untreated ABC-type diffuse large B-cell lymphoma. Hematol Oncol. 2019;37:36–7.
64. Nowakowski G, Hong F, Scott D, et al. Addition of lenalidomide to R-CHOP ($R^2$CHOP) improves outcomes in newly diagnosed diffuse large b-cell lymphoma (dlbcl): first report of ECOG-ACRIN1412 a randomized phase 2 US intergroup study of $R^2$CHOP vs R-CHOP. Hematol Oncol. 2019;37:37–8.
65. Thieblemont C, Tilly H, Gomes da silva M, et al. Lenalidomide maintenance compared with placebo in responding elderly patients with diffuse large B-cell lymphoma treated with first-line rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol. 2017;35(22):2473–81.
66. Ferreri AJ, Sassone M, Zaja F, et al. Lenalidomide maintenance in patients with relapsed diffuse large B-cell lymphoma who are not eligible for autologous stem cell transplantation: an open label, single-arm, multicentre phase 2 trial. Lancet Haematol. 2017;4(3):e137–46.
67. Dada R. Lenalidomide maintenance after R-CHOP therapy in diffuse large B-cell lymphoma: can it be a standard of care. Acta Haematol. 2017;138(4):216–20.
68. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127:2375–90.
69. Ogura M, Imaizumi Y, Uike N, Asou N, Utsunomiya A, Uchida T, et al. Lenalidomide in relapsed adult T-cell leukaemia-lymphoma or peripheral T-cell lymphoma (ATLL-001): a phase 1, multicentre, dose-escalation study. Lancet Haematol. 2016;3(3):e107–18.
70. Ishida T, Fujiwara H, Nosaka K, Taira N, Abe Y, Imaizumi Y, et al. Multicenter phase II study of lenalidomide in relapsed or recurrent adult T-cell leukemia/lymphoma: ATLL-002. J Clin Oncol. 2016;34(34):4086–93.
71. Mehta-shah N, Horwitz SM. Lenalidomide in adult T-cell leukemia/lymphoma. J Clin Oncol. 2016;34(34):4066–7.
72. Morschhauser F, Fitoussi O, Haioun C, Thieblemont C, Quach H, Delarue R, et al. A phase 2, multicentre, single-arm, open-label study to evaluate the safety and efficacy of single-agent lenalidomide (Revlimid) in subjects with relapsed or refractory peripheral T-cell non-Hodgkin lymphoma: the EXPECT trial. Eur J Cancer. 2013;49(13):2869–76.
73. Toumishey E, Prasad A, Dueck G, Chua N, Finch D, Johnston J, et al. Final report of a phase 2 clinical trial of lenalidomide monotherapy for patients with T-cell lymphoma. Cancer. 2015;121(5):716–23.
74. Querfeld C, Rosen ST, Guitart J, Duvic M, Kim YH, Dusza SW, et al. Results of an open-label multicenter phase 2 trial of lenalidomide monotherapy in refractory mycosis fungoides and Sézary syndrome. Blood. 2014;123(8):1159–66.
75. Bagot M, Hasan B, Whittaker S, Beylot-Barry M, Knobler R, Shah E, et al. A phase III study of lenalidomide maintenance after debulking therapy in patients with advanced cutaneous T-cell lymphoma - EORTC 21081 (NCT01098656): results and lessons learned for future trial designs. Eur J Dermatol. 2017;27(3):286–94.

76. Hagner PR, Man HW, Fontanillo C, Wang M, Couto S, Breider M, et al. CC-122, a pleiotropic pathway modifier, mimics an interferon response and has antitumor activity in DLBCL. Blood. 2015;126(6):779–89.
77. Michot J, Bouabdallah R, Doorduijn JK, Vitolo U, Kersten MJ, Chiappella A, et al. Avadomide (CC-122), a novel cereblon modulating agent, in combination with obinutuzumab (GA101) in patients with relapsed or refractory B-cell non-Hodgkin lymphoma. Blood. 2018;132(Suppl 1):449.
78. Michot J, Bouabdallah R, Doorduijn JK, Vitolo U, Kersten MJ, Chiappella A, et al. CC-122, a novel cereblon modulating agent, in combination with obinutuzumab (GA101) in patients with relapsed and refractory (R/R) B-cell non-Hodgkin lymphoma (NHL). Blood. 2017;130(Suppl 1):411.
79. Nastoupil LJ, Bijou F, Ribrag V, Chavez JC, Witzig TE, Andorsky DJ, et al. Avadomide (CC-122), a novel cereblon modulating agent, plus rituximab in patients with relapsed or refractory follicular lymphoma. Blood. 2018;132(Suppl 1):1602.
80. Ribrag V, Chavez JC, Vitolo U, Kaplan JB, Chandler JC, Santoro A, et al. CC-122 DLBCL-001: phase Ib study of CC-122 plus rituximab in patients with chemo-refractory diffuse large B-cell lymphoma (DLBCL). Blood. 2017;130(Suppl 1):1551.
81. Ruan J, Shah B, Martin P, Schuster SJ. Clinical experience with lenalidomide alone or in combination with rituximab in indolent B-cell and mantle cell lymphomas. Ann Oncol. 2016;27(7):1226–34.
82. Witzig TE, Nowakowski GS, Habermann TM, Goy A, Hernandez-Ilizaliturri FJ, Chiappella A, et al. A comprehensive review of lenalidomide therapy for B-cell non-Hodgkin lymphoma. Ann Oncol. 2015;26(8):1667–77.
83. Ito T, Ando H, Suzuki T, et al. Identification of a primary target of thalidomide teratogenicity. Science. 2010;327:1345–50.
84. Lyman GH, Bohlke K, Khorana AA, Kuderer NM, Lee AY, Arcelus JI, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update 2014. J Clin Oncol. 2015;33(6):654–6.
85. Yamshon S, Christos PJ, Demetres M, Hammad H, Leonard JP, Ruan J. Venous thromboembolism in patients with B-cell non-Hodgkin lymphoma treated with lenalidomide: a systematic review and meta-analysis. Blood Adv. 2018;2(12):1429–38.
86. Gandhi AK, Kang J, Havens CG, et al. Immunomodulatory agents lenalidomide and pomalidomide co-stimulate T cells by inducing degradation of T cell repressors Ikaros and Aiolos via modulation of the E3 ubiquitin ligase complex CRL4(CRBN). Br J Haematol. 2013;164(6):811–21.
87. Goy A, Kalayoglu Besisik S, Drach J, Ramchandren R, Robertson MJ, Avivi I, et al. Longer-term follow-up and outcome by tumour cell proliferation rate (Ki-67) in patients with relapsed/refractory mantle cell lymphoma treated with lenalidomide on MCL-001(EMERGE) pivotal trial. Br J Haematol. 2015;170(4):496–503.
88. Determann O, Hoster E, Ott G, Wolfram Bernd H, Loddenkemper C, Leo Hansmann M, et al. Ki-67 predicts outcome in advanced-stage mantle cell lymphoma patients treated with anti-CD20 immunochemotherapy: results from randomized trials of the European MCL Network and the German Low Grade Lymphoma Study Group. Blood. 2008;111:2385–7.
89. Zaja F, De Luca S, Vitolo U, et al. Salvage treatment with lenalidomide and dexamethasone in relapsed/refractory mantle cell lymphoma: clinical results and effects on microenvironment and neo-angiogenic biomarkers. Haematologica. 2012;97(3):416–22.