Blood Spotlight

LYMPHOID NEOPLASIA

Lenalidomide in Non-Hodgkin Lymphoma: Biologic Perspectives and Therapeutic Opportunities

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ABSTRACT

Lenalidomide is an immunomodulatory analog (IMiDs™) with activity in lymphoid malignancies occurring primarily through immune modulation (e.g., T-cell immune synapse enhancement and NK-cell/T-cell effector augmentation) and anti-proliferative effects. FDA approved for bortezomib-resistant, relapsed/refractory mantle-cell lymphoma, lenalidomide has demonstrated efficacy in several additional lymphoma subtypes. There are a multitude of ongoing clinical trials examining lenalidomide alone or in combinatorial therapy. It will be important in these studies to delineate reliable, predictive biomarkers to most optimally integrate lenalidomide into lymphoma treatment paradigms.
Introduction

Lenalidomide is an immunomodulatory drug (IMiD™) that has been studied extensively in non-Hodgkin lymphoma (NHL). There have been a multitude of pre-clinical and clinical studies that have helped define the role of lenalidomide in NHL.

Mechanisms of Action

The most prominent mechanisms of action of lenalidomide in lymphoid malignancies appear to be immunomodulatory, anti-proliferative, and anti-angiogenic (Figure 1).

Immunomodulatory

Elegant pre-clinical studies showed that T-cell immune synapse dysfunction in follicular lymphoma (FL) can be “repaired” with lenalidomide. Tumor-infiltrating T-cells from FL patients had significant reduction in formation of the F-actin immune synapse versus healthy donor cells. Lenalidomide reversed these abnormalities by enhancing the immune synapse, an important finding also demonstrated in chronic lymphocytic leukemia (CLL). Additionally, lenalidomide has been shown to reduce Tregs, activate CD8 T-cells, and skew T-helper (TH) subsets with TH1 > TH2 response.

In other NHL experiments, lenalidomide combined with rituximab resulted in anti-tumor effects via increased NK-cell function, enhanced antibody-dependent cellular cytotoxicity, improved NK-cell-mediated synapse formation, and CD20 capping. Further, Zhu et al reported that induction of apoptosis in Burkitt lymphoma (BL) and CLL cells occurred primarily through NK-cell activation.

Anti-proliferative effects

A significant discovery in the mechanism of lenalidomide was identification of the
importance of Cereblon (encoded by *CRBN* gene). Ito et al initially showed that *CRBN* was required for the teratogenic effects of thalidomide leading to down-regulation of fibroblast growth factor. Subsequent research have shown that silencing of *CRBN* diminishes the effect of lenalidomide and results in resistant cancer cells. Gene expression studies via *CRBN* knockdown showed that many of the affected genes were targets of critical transcription factors (e.g., *MYC*, *SP1*, and *TP53*). Interferon regulatory factor 4 (*IRF4*) was significantly decreased with initial *CRBN* knockdown, but returned to normal levels in *CRBN*-depleted (and lenalidomide-resistant) cells. *IRF4* is vital for B-lymphocyte maturation and light chain rearrangement.

Lenalidomide directly binds *CRBN*, reduces *IRF4* and *MYC* expression, increases P21WAF-1 expression, and changes the immunomodulatory activity of T-cells in myeloma models. Subsequent investigations in diffuse large B-cell lymphoma (DLBCL) cells identified that direct tumoricidal effect of lenalidomide was associated with downregulation of *IRF4* and *SPIB* transcription factors, which required *CRBN* expression. Moreover, this effect was preferentially noted in non-germinal center (non-GC) DLBCL, which are more dependent on *IRF4* and NF-κB than GC-DLBCL due to oncogenic mutations in CARD11 and MYD88.

Cereblon has also been shown to be vital in lenalidomide-induced T-cell stimulation. Kronke et al showed that lenalidomide enhanced CRL4<sup>CRBN</sup> binding to Ikaros (IKZF1) and Aiolos (IKZF3) in myeloma and T-cell lines, causing their ubiquitination and degradation. Gandhi et al subsequently demonstrated in NHL that lenalidomide induced CRL4 interaction with Ikaros and Aiolos, both transcriptional repressors of IL-2 expression. The resultant IL-2 expression induced T-cell co-
stimulation. Lenalidomide also exerts direct antiproliferative activity in mantle-cell lymphoma (MCL)\textsuperscript{18} and CLL cells, the latter occurring in a cereblon- and p21-dependent, but p53-independent manner.\textsuperscript{19}

\textbf{Anti-angiogenic}

Reddy et al showed that lenalidomide diminishes angiogenesis (decreased microvessel density (MVD)) in NHL xenograft models.\textsuperscript{5} Related data in MCL mouse models revealed that lenalidomide inhibited tumor growth and dissemination by depleting monocytes and macrophages associated with lymphangiogenesis.\textsuperscript{20} Lenalidomide has also been shown to up-regulate the tumor suppressor gene SPARC, which has antiproliferative, anti-adhesive, and anti-angiogenic properties in 5\textsuperscript{q}- syndrome;\textsuperscript{21} similar preliminary findings were noted in NHL,\textsuperscript{22} though it’s true importance remains to be validated.

\textbf{Clinical Data}

Phase I, II, and III clinical trials have defined the safety and efficacy of lenalidomide in several NHL subtypes including MCL, FL, DLBCL, and T-cell lymphoma (\textit{Table 1}).

\textbf{Mantle-cell lymphoma}

\textbf{Relapsed/refractory}

In a single-agent study (NHL-002)\textsuperscript{23} of relapsed/refractory aggressive NHL histologies, the overall response rate (ORR) of lenalidomide in MCL was 53\% with 14\% complete remission (CR) (\textit{Table 1}). Mature follow-up of NHL-002 showed median duration of response (DOR) of 13.7 months.\textsuperscript{24} Eve et al treated 26 relapsed/refractory MCL with maintenance lenalidomide in responding patients to lenalidomide induction (\textit{Table 1}).\textsuperscript{25} In NHL-003, 57 relapsed/refractory MCL patients had an ORR of 42\%.\textsuperscript{26}
Collectively, adverse effects (AEs) were primarily hematologic with 5% of patients having thromboembolic events. Notably, the risk of thromboembolism in NHL does not appear different compared with myeloma. Longer-term follow-up of NHL-003 (median 20 months) showed DOR of 16.3 months and PFS of 8.8 months in this heavily pretreated group of patients. Second malignancies were noted in 4/57 patients (2 shortly after starting lenalidomide). Continued follow-up of this and other lenalidomide studies are needed to examine risk of second cancers and other late effects.

A prospective, single-arm, phase II International clinical trial (EMERGE, MCL-001) of 134 bortezomib-resistant, relapsed/refractory MCL patients showed meaningful clinical benefit across multiple prognostic groups to single-agent lenalidomide. Grade 3-4 AEs were similar to prior trials (43% neutropenia, 28% thrombocytopenia, 11% anemia). Grade 3 non-hematologic AEs included 7% fatigue, 6% diarrhea, 5% dyspnea. These data led to FDA approval of lenalidomide June 2013 for MCL patients whose disease relapsed or progressed after two prior therapies, one of which included bortezomib.

In an update to MCL-001, median time to CR was 4.1 months and median overall survival (OS) was 20.9 months. Dose reductions or interruptions due to AEs occurred in 40% and 58% of patients, respectively, and the average lenalidomide dose intensity was 20mg/day. Additionally, lower Ki67 levels (<30%) appeared to correlate with improved CR, DOR, and OS.

Untreated

There are ongoing clinical trials incorporating lenalidomide into treatment paradigms for untreated MCL (Supplemental Tables 1 and 2). Jerkeman et al
evaluated lenalidomide combined concurrently with bendamustine and rituximab (BR) in newly-diagnosed older MCL patients. The phase 1 study identified an unexpected high rate of grade 3-4 allergic reactions and cutaneous toxicity and there were 3 treatment-related deaths (Table 1). The study was amended to omit lenalidomide from cycle 1 (i.e., starting cycle 2). Ruan et al presented data using lenalidomide combined with rituximab for first-line treatment of MCL. Treatment was well tolerated with grade 3-4 toxicities of 39% neutropenia, 13% thrombocytopenia, 7% anemia, 23% rash, and 7% tumor flare. Preliminary efficacy data were promising (Table 1).

**Follicular lymphoma**

*Relapsed/refractory disease*

NHL-001 documented the single-agent efficacy of lenalidomide for relapsed/refractory indolent NHL (Table 1); ORR was modest, however responding patients had durable remissions. Tuscano et al reported results with lenalidomide and rituximab in relapsed/refractory indolent NHL half of whom were rituximab-refractory (Table 1). Additionally, UPenn published results of a carefully planned and well-done phase II study in rituximab-refractory FL and MCL showing that lenalidomide had activity as a single-agent and that lenalidomide/rituximab combination therapy may overcome rituximab resistance. There is an ongoing phase III trial ("AUGMENT" study) evaluating lenalidomide combined with rituximab versus single-agent lenalidomide in relapsed/refractory indolent NHL (Supplemental Table 2).

*Untreated patients*

Fowler et al evaluated lenalidomide and rituximab in 110 untreated FL patients.
Responses were high, and at completion of therapy, most patients demonstrated molecular response. There are several ongoing randomized studies examining lenalidomide as part of front-line therapy for FL patients. This includes a randomized phase 2 study examining lenalidomide therapy following immuno-chemotherapy induction ("BIONIC" trial) and a phase 3 study comparing the efficacy of rituximab plus lenalidomide versus rituximab plus chemotherapy in untreated FL ("RELEVANCE" trial) (Supplemental Figure 1).

**DLBCL**

*Relapsed/refractory*

Lenalidomide has activity in relapsed/refractory DLBCL (Table 1). In NHL-002 and NHL-003, the ORRs in DLBCL were 19% and 28%, respectively.\(^{23,35}\) The differential efficacy of lenalidomide in DLBCL based on cell of origin was evaluated by Hernandez et al;\(^{36}\) lenalidomide appeared more effective in non-GC DLBCL with ORR of 53% versus 9% for GC subtype.

Zinzani et al reported data on 23 elderly DLBCL patients treated with rituximab and lenalidomide (with lenalidomide maintenance)\(^{37}\) and Wang et al confirmed the clinical activity of lenalidomide/rituximab in relapsed/refractory de-novo and transformed DLBCL (Table 1).\(^{38}\) Feldman et al studied the addition of lenalidomide to standard salvage chemotherapy for relapsed/refractory DLBCL prior to autologous stem cell transplantation followed by lenalidomide maintenance.\(^{39}\) Ongoing studies are assessing lenalidomide combined with other chemotherapy backbones (Supplemental Table 2).

*Untreated*

The addition of lenalidomide to rituximab, cyclophosphamide, doxorubicin, oncovin,
and prednisone (R2-CHOP) was evaluated in older, untreated DLBCL patients (Table 1). Efficacy appeared high, although ~70% of patients had grade 3-4 hematological AEs. Nowakowski et al added modified lenalidomide to R-CHOP, which was well tolerated and it appeared to overcome the negative prognostic impact of non-GC phenotype in DLCBL. A large, randomized phase II trial randomizing untreated DLBCL patients to R2-CHOP versus R-CHOP (Supplemental Figure 1) and a similarly designed industry-led study (only ABC-type DLBCL; ROBUST study), are underway.

The role of lenalidomide in the post-chemotherapy setting is also being investigated as maintenance therapy alone or combined with rituximab. Early results from a randomized phase II trial of lenalidomide +/- rituximab in intermediate-high/high risk DLBCL have been presented (Table 1).

**T-cell lymphoma**

*Relapsed/refractory*

The EXPECT phase II trial studied patients with relapsed/refractory peripheral T-cell lymphoma (PTCL) treated with single-agent lenalidomide (Table 1). The majority of patients (85%) had angioimmunoblastic (AITL) and PTCL-not otherwise specified histologies. Efficacy was documented, though serious AEs were seen in 54% of patients with 6 deaths unrelated to progression. In additional single-agent studies, Tournishey et al reported results in untreated and relapsed/refractory PTCL, while Querfeld et al showed clinical activity in relapsed/refractory mycosis fungoides/sezary syndrome (Table 1). In the latter study, tumor flare was seen in many patients, which prompted an amendment for lower initial lenalidomide dosing.

*Untreated*
There are limited data examining lenalidomide in the front-line setting for PTCL. A trial investigating the efficacy of lenalidomide combined with CHOP in AITL is ongoing and another study is evaluating romidepsin and lenalidomide in untreated PTCL (Supplemental Table 2).

Future Directions

Biomarkers

Clinical studies have examined potential biomarkers of lenalidomide efficacy and pivotal studies are ongoing in distinct NHL subsets (e.g., non-GC DLBCL). In relapsed/refractory MCL, Zaja et al showed that MVD, macrophage and NK cell counts were altered with lenalidomide and Ki67 is being studied as a biomarker. Despite breakthrough studies that identified CRBN as a critical lenalidomide target, there are challenges in utilization as a biomarker (e.g., messenger RNA/protein correlation). The CRBN-associated transcription factors, Ikaros/Aiolos, may serve as more functional biomarkers as well as downstream substrates (e.g., IRF4 and MYC). Other potential lenalidomide-related biomarkers include components of PI3K signaling (e.g., GSK3β) and the T-cell immune synapse with granzyme B expression.

Novel combinations

In DLBCL cells, azacytidine and lenalidomide increased CRBN expression and enhanced cytotoxicity while ibrutinib and lenalidomide synergistically suppressed IRF4. In vitro FL and MCL studies confirmed synergistic activity with bortezomib and lenalidomide. In T-cell lymphoma models, romidepsin combined with lenalidomide resulted in increased oxidative stress and alteration of PI3K and MAP kinase/ERK signaling pathways. Conversely, preclinical studies in CLL suggests that the PI3Kδ...
inhibitor, idelalisib, antagonizes the immune-modulating properties of lenalidomide.

It will be important to translate these findings in clinical studies to confirm efficacy as well as safety. The latter was highlighted in two phase I studies combining lenalidomide with the PI3Kδ inhibitor, idelalisib, (and rituximab) where prohibitive toxicities suggestive of severe cytokine release syndrome (e.g., rash, fevers, hypotension) were seen. Other clinical studies combining lenalidomide with novel/targeted agents have shown good tolerability and encouraging efficacy, while additional novel combinatorial trials are underway (e.g., obinutuzumab, romidepsin, everolimus, ibritinib) (Supplemental Table 2).

In addition, translational study of new cereblon binding agents (e.g., CC-122) are eagerly anticipated. CC-122 is a first-in-class, pleiotropic pathway modifier that binds cereblon and induces Aiolos and Ikaros degradation in DLBCL and T-cells. In DLBCL, it results in depression of interferon-stimulated genes/proteins ultimately resulting in apoptosis. Furthermore, CC-122 appears to have distinct activity from lenalidomide in that it is active in both GC and non-GC DLBCL.

Conclusions

Owing to its unique immunomodulatory and antiproliferative activity as well as relative ease of use, lenalidomide has garnered clinical consideration in multiple NHL subtypes. Durable responses with manageable side effects have moved lenalidomide into the front-line setting of randomized clinical trials for various NHL subtypes. In addition, combinatorial therapy with novel/targeted therapeutic agents is of particular interest. Finally, continued understanding of the biologic mechanisms and the associated validation of predictive biomarkers will be critical in optimally integrating
lenalidomide into NHL treatment paradigms.

**Author Contributions:** AK: designed research, performed research, analyzed data, and wrote the paper; MC: designed research, performed research and wrote the paper; JS: performed research and wrote the paper; AME: designed research, performed research, analyzed data, and wrote the paper.

**COI Disclosure:** AME: Celgene advisory board and speakers bureau (with honorarium).
Table 1. Lenalidomide Clinical Study Results in Lymphoma.

<table>
<thead>
<tr>
<th>Series/Author</th>
<th>Year</th>
<th>No. Patients</th>
<th>Arms</th>
<th>Conclusions^</th>
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<td><strong>Mantle-Cell: Untreated</strong></td>
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<tr>
<td><em>Jerkeman et al</em></td>
<td>2011</td>
<td>12</td>
<td>BR + lenalidomide (dose escalation) induction; len maint 10-15mg d1-21 x 5mo</td>
<td>Lenalidomide MTD 10mg d 1-14; (cycle 1 tox: allergic/cutaneous), ORR 100%, CR 90% 2-yr PFS 74%, 2-yr OS 87%</td>
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<td><em>Ruan et al</em></td>
<td>2013</td>
<td>38</td>
<td>lenalidomide (20mg d 1-21 q 28 d) + rituximab; len maint 10mg d 1-21 until PD</td>
<td>ORR 84%, 53% CR DOR: NR; 2-yr PFS 84%</td>
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<td><strong>Mantle-Cell: Relapsed/Refractory</strong></td>
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<tr>
<td>Wang et al</td>
<td>2012</td>
<td>52</td>
<td>Lenalidomide (dose escalation) + rituximab</td>
<td>Lenalidomide MTD 20mg, ORR 57%, CR 36%, DOR 19 mo, PFS 11mo, OS 24 mo</td>
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<tr>
<td>Habermann et al</td>
<td>2009</td>
<td>15</td>
<td>Lenalidomide (25mg d 1-21 q 28 d)</td>
<td>ORR 53%, CR 20% DOR 13.7 mo, PFS 5.6 mo</td>
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<td>Witzig et al (NHL-003)</td>
<td>2011</td>
<td>57</td>
<td>Lenalidomide (25mg d 1-21 q 28 d)</td>
<td>ORR 42%, CR 21% DOR: NR, PFS 5.7 mo</td>
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<td>Zaja et al</td>
<td>2012</td>
<td>33</td>
<td>lenalidomide (25mg d 1-21 q 28 d) + dexamethasone</td>
<td>ORR 52%, CR 24% DOR 18 mo, PFS 12 mo, OS 20 mo</td>
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<tr>
<td>Eve et al</td>
<td>2012</td>
<td>26</td>
<td>lenalidomide (25mg d 1-21 q 28 d) x 6 cycle; then len maint</td>
<td>ORR 31%, CR 8% DOR 22 mo, PFS 3.9 mo; maint len PFS 14.6 mo</td>
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<td>Goy et al (MCL-001)</td>
<td>2013</td>
<td>134</td>
<td>Lenalidomide (25mg d 1-21 q 28 d) (all pts pre-treated with bortezomib)</td>
<td>ORR 28%, CR 8%, DOR 17 mo, PFS 4 mo, OS 19 mo</td>
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<td><strong>Indolent NHL: Untreated</strong></td>
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<tr>
<td>Fowler et al</td>
<td>2014</td>
<td>50 FL, 30 MZL, 30 SLL</td>
<td>Lenalidomide (20mg d 1-21 q 28 d) + rituximab</td>
<td>ORR 98%, PFS 89%</td>
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<td><strong>Indolent NHL: Relapsed/Refractory</strong></td>
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<td>Witzig et al. (NHL- 001)</td>
<td>2009</td>
<td>22</td>
<td>Lenalidomide (20mg d 1-21 q 28 d)</td>
<td>ORR 27% DOR: NR (&gt; 17 mo), PFS 4.4 mo</td>
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<tr>
<td>Tuscano et al</td>
<td>2014</td>
<td>22 FL</td>
<td>Lenalidomide (20mg d 1-21 q 28 d) + rituximab</td>
<td>ORR 77% PFS (all) 12.4 mo</td>
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<tr>
<td>Study</td>
<td>Year</td>
<td>Sample Size</td>
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<td>Response</td>
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<tr>
<td>Chong et al&lt;sup&gt;13&lt;/sup&gt;</td>
<td>2015</td>
<td>30 FL, 14 MCL, 4 SLL, 2 MZL (all rituximab-refractory)</td>
<td>Lenalidomide 10mg daily (x five 28-d cycles) and 4 weeks rituximab (cycle 3)</td>
<td>ORR with len: 30%; after len + ritux: 63%; DOR len + ritux: 25 mo, PFS 22 mo</td>
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<td><strong>Aggressive B-Cell NHL: Untreated</strong></td>
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<td>Reddy et al&lt;sup&gt;14&lt;/sup&gt;</td>
<td>2013</td>
<td>43 DLBCL</td>
<td>Maint lenalidomide (25mg d 1-21) vs lenalidomide (20mg d 1-21) + rituximab</td>
<td>len vs len + ritux: 2-yr PFS: 90% vs 86%; 2-yr OS: 95% vs 81%</td>
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<td>Vitolo et al&lt;sup&gt;15&lt;/sup&gt; (REAL-07)</td>
<td>2014</td>
<td>45 DLBCL</td>
<td>Lenalidomide (15mg d 1-14) + RCHOP</td>
<td>CR 86%, PR 6%; 2-yr PFS 80%</td>
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<tr>
<td>Nowakowski et al&lt;sup&gt;11&lt;/sup&gt;</td>
<td>2014</td>
<td>60 DLBCL</td>
<td>Lenalidomide (25mg d 1-10) + RCHOP</td>
<td>ORR 98%, CR 80%, EFS 59% OS 78%</td>
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<td><strong>Aggressive B-Cell NHL: Relapsed/Refractory</strong></td>
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<tr>
<td>Feldman et al&lt;sup&gt;19&lt;/sup&gt;</td>
<td>2014</td>
<td>16 DLBCL</td>
<td>Lenalidomide (dose escalation) + RICE; then maint len 25mg d 1-21 q28 d x 12 mo</td>
<td>MTD: 25mg d1-4 q 14 d ORR 73%, CR 60%</td>
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<tr>
<td>Wiernick et al&lt;sup&gt;23&lt;/sup&gt; (NHL-002)</td>
<td>2008</td>
<td>5 FLG3, 26 DLBCL, 3 TL</td>
<td>Lenalidomide (25mg d 1-21 q 28 d)</td>
<td>ORR: FL 60%, DLBCL, 19% TL 33% PFS (all) 4 mo</td>
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<tr>
<td>Hernandez et al&lt;sup&gt;26&lt;/sup&gt;</td>
<td>2011</td>
<td>DLBCL 23 GCB, 17 non-GCB</td>
<td>Lenalidomide (25mg d 1-21 q 28 d)</td>
<td>ORR: Non-GCB: 53%, GCB 9% PFS 6.2 mo vs 1.7 mo OS 14 mo vs 13.5 mo</td>
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<tr>
<td>Witzig et al&lt;sup&gt;25&lt;/sup&gt; (NHL-003)</td>
<td>2011</td>
<td>19 FLG3, 108 DLBCL, 33 TL</td>
<td>Lenalidomide (25mg d 1-21 q 28 d)</td>
<td>ORR: FL 42%, DLBCL 28%, TL 45% PFS: FL 8.9 mo, DLBCL 2.7 mo, TL 5.4 mo</td>
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<tr>
<td>Zinzani et al&lt;sup&gt;27&lt;/sup&gt;</td>
<td>2013</td>
<td>23 DLBCL</td>
<td>Lenalidomide (20mg d 1-21 q 28 d) + rituximab</td>
<td>ORR 35%; DOR 32 mo</td>
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<tr>
<td>Wang et al&lt;sup&gt;28&lt;/sup&gt;</td>
<td>2013</td>
<td>4 FLG3, 32 DLBCL, 9 TL</td>
<td>Lenalidomide (20mg d 1-21 q 28 d) + rituximab</td>
<td>ORR: FL 25%, DLBCL 28%, TL 56% DLBCL: PFS 2.8 mo, OS 10.2 mo, TL: PFS 4.3 mo, OS 11.5 mo</td>
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<tr>
<td><strong>Aggressive T-Cell NHL: Relapsed/Refractory</strong></td>
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<td>Zinzani et al&lt;sup&gt;20&lt;/sup&gt;</td>
<td>2011</td>
<td>10 PTCL NOS</td>
<td>Lenalidomide (25mg d 1-21 q 28 d)</td>
<td>ORR 30%</td>
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<td>Morschhauser et al&lt;sup&gt;43&lt;/sup&gt; (EXPECT)</td>
<td>2013</td>
<td>54 PTCL</td>
<td>Lenalidomide (25mg days 1-21 q 28 d)</td>
<td>ORR 22%, DOR 3.6 mo, PFS 2.5 mo (4.6 mo in AITL)</td>
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<td>Querfeld et al*</td>
<td>2013</td>
<td>32 MF /Sezary</td>
<td>Initially Lenalidomide 25mg days 1-21; amended to 10mg with incremental (5mg) dose escalation</td>
<td>ORR 28%, DOR 10 mo, PFS 8 mo, OS 43 mo</td>
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<tr>
<td>Toumishey et al**</td>
<td>2014</td>
<td>40 TCL</td>
<td>Lenalidomide (25mg days 1-21 q 28 d)</td>
<td>Rel/ref PTCL: ORR 24%, DOR 5 mo, PFS 4 mo, OS 12 mo Untreated PTCL: ORR 50%, DOR 21 mo, PFS 4 mo, OS 12 mo</td>
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</table>

*Indicates abstract data.

^All survival times are medians, unless otherwise specified.

Abbreviations: FL, follicular lymphoma; MZL, marginal zone lymphoma; SLL, small lymphocytic lymphoma; ORR, overall response rate; PFS, progression-free survival; DLBCL, diffuse large B-cell lymphoma; Len, lenalidomide; R, rituximab; CHOP, cyclophosphamide, doxorubicin, oncovin, and prednisone; CR, complete remission; PR, partial remission; yr, year; OS, overall survival; ICE, ifosfamide carboplatin, etoposide; rel/ref: relapsed/refractory; pts, patients; maint, maintenance; PD, progressive disease; autoSCT, autologous stem cell transplantation; FLG3, follicular lymphoma grade 3; TL, transformed lymphoma; TCL, T-cell lymphoma; GCB, germinal center B-cell; mo, months; d, days; PTCL NOS, peripheral T-cell lymphoma not otherwise specified; AITL, angioimmunoblastic T-cell lymphoma; MF, mycoses fungoides; NR, not reached.
References


Figure 1. Mechanisms of Action of Lenalidomide in Lymphoid Malignancies. **Direct antitumor effects** primarily mediated by lenalidomide binding CRL4^{CRBN}, altering affinity for E3-ubiquitin ligase substrates. Lymphoid transcription factors IKZF1 (Ikaros) and IKZF3 (Aiolos) are preferentially ubiquitinated and degraded rapidly with lenalidomide, causing decreased NF-κB, decreased MYC and IRF4, increased p21^{WAF1} and suppression of cell cycle via degradation of cyclin-dependent kinases. There is also increased interferon production via decreased IRF4 (suppresses IFN response), which promotes cellular death. Other CRL4^{CRBN} substrates may be affected, but are less defined. **Immunomodulatory properties:** Improvement in T-cell and NK-cell anti-tumor activity is seen with lenalidomide, including IL-2 driven co-stimulation of T cells (via increased degradation of IKZF1 and IKZF3 in T-cells). Regulatory T cells are suppressed and there is a skewing towards Th1 population with lenalidomide. The NK- and T-cell effects of lenalidomide in lymphoma are synergistically enhanced with rituximab in preclinical studies. **Anti-angiogenic properties:** lenalidomide decreases angiogenesis in part via decreased microvessel density and it inhibits tumor growth and dissemination of disease through depletion of monocytes and macrophages associated with lymphangiogenesis.

Abbreviations: CRL4^{CRBN}=Cullen 4 ring- E3 ubiquitin ligase-Cereblon complex; IKZF1= Ikaros; IKZF3=Aiolos; IRF4= Interferon regulatory factor 4; IFN= interferon; His H3-Me= Histone H3 methylation; ADCC= Antibody dependent cell-directed cytotoxicity; FL, follicular lymphoma; CLL, chronic lymphocytic leukemia; TCR, T-cell receptor; MHC, major histocompatibility complex; LFA-1, Lymphocyte function-associated antigen 1; ICAM-1, Intercellular Adhesion Molecule 1; Cdc42, Cell division control protein 42; WASp, Wiskott–Aldrich Syndrome protein.
Lenalidomide

**Antiproliferative effects:**
- Binds CRL4<sup>CRBN</sup>
- ↓IKZF1 and IKZF3
- ↓NF-κB
- ↓MYC
- ↑IFNγ
- ↓IRF4
- Changes in His H3-Me
- ↑p21<sup>WAF1</sup>
- ↓cell cycle and ↑apoptosis

**Anti-angiogenic:**
- ↓microvessel density
- ↓Endothelial cell migration

**Immunomodulation:**
- ↑NK/T-cell response
- Activation/expansion CD8 T-cells
- ↑DC (priming to CD8 T-cells)
- T-cell immune synapse repair
- ↑T-helper differentiation (TH1 > TH2)
- Suppression of Treg
- ↑ADCC
- ↑co-stimulation of T cells

Tumor Cell

Tumor Cell binds CRL4<sup>CRBN</sup>
Lenalidomide in non-Hodgkin lymphoma: biologic perspectives and therapeutic opportunities

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