

# Lenalidomide in DLBCL: Are We Past the Cell of Origin?

Mendel Goldfinger, MD,<sup>1</sup> and Dennis L. Cooper, MD<sup>2</sup>

<sup>1</sup>Department of Medical Oncology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York

<sup>2</sup>Rutgers Cancer Institute of New Jersey, New Brunswick, New Jersey

Corresponding author:  
Mendel Goldfinger, MD  
Montefiore Hospital  
111 E 210 St  
Bronx, NY 10467  
Email: mgoldfin@montefiore.org

**Abstract:** Single-agent lenalidomide has modest activity in diffuse large B-cell lymphoma (DLBCL) and is thought to be more potent in activated B-cell (ABC) lymphomas, which are more treatment-resistant. However, the addition of lenalidomide to rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in randomized clinical trials has shown equivocal benefit, despite phase 2 studies that suggested otherwise. These equivocal results suggest that either the cell of origin (COO) has limited importance for prescribing lenalidomide, or that lenalidomide is not the optimal agent for exploiting the vulnerability of ABC lymphomas. As more recent analyses have shown that the genetic landscape of DLBCL is considerably more complex than the binary COO paradigm, the disappointing impact of lenalidomide is less surprising. In contrast to the marginal benefit from the addition of lenalidomide to R-CHOP, recent studies suggest that lenalidomide in combination with novel agents has potent activity. Lenalidomide was recently approved in combination with the anti-monoclonal B-cell antibody tafasitamab for patients with relapsed DLBCL after 1 to 3 previous treatments. This combination has led to surprisingly prolonged progression-free survival rates, along with possible cure in a subset of patients. In addition, early-phase single-arm trials are also showing deep and durable responses in relapsed patients when lenalidomide is combined with the novel agents ibrutinib and venetoclax. Although these drugs have limited single-agent activity in DLBCL, their pronounced activity in combination suggests a possible unique synergistic effect. Overall, recent studies suggest that lenalidomide will continue to be an active player in the treatment for DLBCL but likely in combination with other novel agents rather than in combination with chemotherapy.

## Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma in the United States. With the use of

Keywords  
Cell of origin, DLBCL, lenalidomide

standard chemoimmunotherapy, a cure is achieved in 60% to 70% of patients, and disease progression occurs in 30% to 40%. With the exception of new treatments for double- and triple-hit lymphoma and primary mediastinal lymphoma, the addition of rituximab to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) therapy nearly 20 years ago was the last major change in up-front therapy for DLBCL, and this regimen remains the standard of care for patients with newly diagnosed DLBCL.<sup>1,2</sup>

Clinical trials employing treatment intensification, including high-dose therapy and stem cell transplant, have not shown a consistent benefit from these approaches.<sup>3</sup> In addition, despite encouraging results of single-arm phase 2 trials with continuous infusion chemotherapy consisting of dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine, prednisone, and rituximab (DA-EPOCH-R), a phase 3 trial failed to show superiority over rituximab plus CHOP (R-CHOP).<sup>4</sup> In sum, these results suggest that we have hit a therapeutic ceiling with respect to conventional chemotherapy for most patients with DLBCL, and further advances will require novel strategies.

### Cell of Origin in DLBCL

The variability in outcomes has long suggested that DLBCL is a heterogeneous disease, an observation confirmed by seminal gene expression profiling (GEP) analyses showing that in most cases DLBCL originates from either activated B cells (ABCs) or germinal center B cells (GCBs), with approximately 15% of cases remaining in an indeterminate category.<sup>5</sup> The ABC subgroup has been shown to have a less favorable prognosis with chemoimmunotherapy.<sup>6</sup> The cell of origin (COO) is now officially required as part of the World Health Organization classification of DLBCL<sup>7</sup>; however, it is important to note that although the original COO study was performed with GEP, this approach is impractical in clinical practice, and immunohistochemistry based on the Hans classification is generally used.<sup>8</sup> Nevertheless, fidelity is inconsistent with GEP, and the Hans classification ignores the 15% to 20% of cases that are indeterminate by GEP, so that DLBCL is divided into GCB and non-GCB types.<sup>9</sup>

### Clinical Trials With Lenalidomide

The identification of 2 main COOs for DLBCL encouraged clinical trials with drugs that might exploit pathways unique to each subtype. An initial focus of treatment was the ABC subgroup owing to its aggressive biology and resistance to chemotherapy, which are believed to be due to chronic activation of the B-cell receptor (BCR) and

constitutive activation of the nuclear factor  $\kappa$ B signaling pathway. On the basis of preclinical models showing lenalidomide (Revlimid, Celgene) to have particularly potent cytotoxic activity in ABC cell lines,<sup>10</sup> and the ability of ibrutinib (Imbruvica, Pharmacyclics/Janssen) to block Bruton tyrosine kinase upstream in the BCR pathway, these agents were thought to have activity specific to the ABC lymphomas and therefore to be good candidates for evaluation in clinical trials.

In fact, retrospective analyses of the treatment of DLBCL with lenalidomide seemed to link responses to ABC COO.<sup>11,12</sup> Given that lenalidomide is generally well tolerated, it was an attractive agent to be added to the chemoimmunotherapy backbone of R-CHOP for patients with ABC DLBCL. Nowakowski and colleagues<sup>13</sup> evaluated the addition of lenalidomide to R-CHOP (R2-CHOP) in 64 patients with newly diagnosed DLBCL and concluded that the addition of lenalidomide erased the adverse effect of ABC COO on outcome. Similar findings were confirmed in a longer follow-up that also included patients from an Italian phase 2 trial.<sup>14</sup> However, the small number of patients in these studies and the inherent error rate in assigning COO by immunohistochemistry limited their interpretation. As a result, the results of prospective randomized trials comparing R2-CHOP with R-CHOP were eagerly awaited. The first results of ROBUST and the Eastern Cooperative Oncology Group (ECOG)-ACRIN 1412 trial (E1412) were presented at the 2019 International Conference on Malignant Lymphoma.

ROBUST was a randomized phase 3 registration study<sup>15</sup> that enrolled 570 patients from various countries who had newly diagnosed stage II to IV ABC DLBCL, with ABC COO confirmed by the Lymph2Cx GEP assay. Patients were randomly assigned in a 1:1 ratio either to 6 cycles of lenalidomide at 15 mg/d on days 1 to 14 of a 21-day cycle plus R-CHOP given every 21 days (R-CHOP21) or to placebo plus R-CHOP21. The study did not meet its primary endpoint of progression-free survival (PFS), with a hazard ratio (HR) of 0.85 (95% CI, 0.63-1.14;  $P=0.29$ ). An overall response rate (ORR) of 91% was seen in the 2 arms, with similar complete response (CR) rates of 69% and 65% for R2-CHOP and placebo/R-CHOP, respectively. The 2-year overall survival (OS) rates were also similar in the 2 groups, at 79% for R2-CHOP and 80% for placebo/R-CHOP. A positive trend toward improvement in PFS favoring R2-CHOP was observed in patients who had advanced-stage disease (HR, 0.81; 95% CI, 0.60-1.10) and in patients with an International Prognostic Index (IPI) score of at least 3 (HR, 0.74; 95% CI, 0.53-1.05).

E1412 was a randomized phase 2 trial comparing 6 cycles of R2-CHOP vs R-CHOP21 in previously

untreated DLBCL irrespective of COO.<sup>16</sup> The primary endpoint of PFS was measured in 280 evaluable patients (R2-CHOP, n=145; R-CHOP, n=135). The overall and complete response rates were 92% and 67%, respectively, in the R-CHOP arm and 97% ( $P=.12$ ) and 72% ( $P=.44$ ), respectively, in the R2-CHOP arm. With a median follow-up of 2.4 years, R2-CHOP showed a 33% reduction in the risk for progression or death compared with R-CHOP, and the 2-year OS rates were 87% and 80%, respectively.

Approximately 40% of patients with DLBCL are older than 70 years. Although many of these patients can be treated with standard R-CHOP, patients older than 80 years are often treated with rituximab plus reduced-dose CHOP (R-mini-CHOP), which has produced 2-year survival rates of 59% to 65%.<sup>17</sup> In the recently published SENIOR trial, in which patients older than 80 years were randomly assigned to standard R-mini-CHOP or R2-mini-CHOP, no difference was seen between the 2 arms.<sup>18</sup> Although the outcomes of patients with ABC COO were worse than the outcomes of those with GCB COO, this difference persisted in patients treated with R2-mini-CHOP.

In sum, these studies suggest that if an advantage exists from the addition of lenalidomide to R-CHOP, it is likely to be very small and does not necessarily apply to the ABC subgroup. Similarly, the PHOENIX trial, which compared R-CHOP vs R-CHOP plus the putative ABC inhibitor ibrutinib in patients with ABC DLBCL, also failed to show a significant difference in event-free survival.<sup>19</sup>

Although the results with the 2 best-known ABC-specific targeted agents could be interpreted to mean that COO does not as of yet have any practical application in treatment, subsequent studies have shown a much more complicated genetic landscape of DLBCL, with up to 7 subtypes serving as potential drivers and affecting responses to therapy.<sup>20-23</sup> It is thus possible that any potential benefit of lenalidomide is diluted by the inclusion of subtypes of lymphoma unlikely to be affected.

### Lenalidomide in Central Nervous System Lymphoma

It is more difficult to rationalize the mediocre results with lenalidomide in patients who have primary central nervous system (CNS) lymphoma. Primary CNS lymphoma is considered to be the classic ABC lymphoma, with a high incidence of *MYD88* and *CD79B* mutations<sup>22</sup> that should theoretically be sensitive to lenalidomide. Rubenstein and colleagues described a 64% response rate with lenalidomide monotherapy in 14 patients who had recurrent CNS lymphoma, of whom 6 had primary

CNS lymphoma and 8 had secondary CNS lymphoma.<sup>24</sup> In a much larger study of 50 patients limited to cases of recurrent primary CNS lymphoma (including vitreoretinal lymphoma), lenalidomide plus rituximab produced a 36% CR rate after 4 cycles of treatment. After 8 cycles of treatment, the CR rate had decreased to 29%.<sup>25</sup> This result was only slightly better than that seen in a prior study of systemic DLBCL that was COO-agnostic.<sup>26</sup> The authors concluded that although the combination had activity against primary CNS lymphoma, it could not be recommended as a standard of care because of the short duration of response. Thus, although the National Comprehensive Cancer Network considers lenalidomide alone or in combination with rituximab an acceptable therapy for recurrent primary CNS lymphoma, this stance may reflect the absence of better alternatives.

Recent studies have cast doubt on the efficacy of CNS prophylaxis with either intrathecal or systemic high-dose methotrexate.<sup>27-29</sup> As a result, there has been some hope that because of the activity of lenalidomide in CNS lymphoma, R2-CHOP might fill an important niche for patients with a high CNS IPI score. Ayed and colleagues performed a pooled analysis of 2 trials of R2-CHOP in 136 patients. A CNS relapse occurred in only one of them despite the fact that most of the patients had intermediate or high CNS IPI scores.<sup>30</sup> None of these patients received systemic methotrexate, and only 15% received intrathecal methotrexate. On the other hand, the REMARC study (see below)<sup>31,32</sup> evaluated lenalidomide maintenance after R-CHOP in elderly patients at high risk for recurrence, of whom 35% had a high CNS IPI score. The rate of CNS recurrence was *higher* in the group that received lenalidomide than in the control arm, despite a superior PFS.<sup>33</sup> These data make it uncertain whether lenalidomide has a strong role in CNS prophylaxis.

As previously noted, the REMARC trial showed a statistically significant increase in PFS after lenalidomide maintenance therapy in patients aged 60 to 80 years who achieved a partial response (PR) or a CR after R-CHOP.<sup>31,32</sup> Interestingly and counter-intuitively, the activity of lenalidomide appeared to be greater in GCB lymphoma than in ABC lymphoma. Unfortunately, the lack of a survival benefit in the lenalidomide arm remains unexplained, which has likely muted enthusiasm for this approach. One explanation for the failure to improve survival is that the PFS of the control group was nearly 6 years, indicating that the patients entered in this trial represented a more favorable group. This is further supported by the findings of a retrospective study that analyzed the REMARC cohort and confirmed the independent prognostic effect of total metabolic tumor volume, but the effect was significantly smaller than in other series of patients with DLBCL.<sup>34</sup>

## Lenalidomide in Relapsed DLBCL

Until recently—with the advent of chimeric antigen receptor (CAR) T cells, bispecific antibodies, and antibody-drug conjugates<sup>35</sup>—the treatment of patients with relapsed DLBCL who were ineligible for autologous transplant, or with relapsed disease after autologous transplant, was a critical unmet need. In a single-arm trial by Ferreri and colleagues,<sup>36</sup> 48 patients with relapsed disease who initially had been treated primarily with salvage regimens based on high-dose cytarabine (Ara-C) or ifosfamide, and who achieved a PR or CR, were eligible for indefinite lenalidomide maintenance (a later amendment allowed patients to discontinue treatment at 2 years). At 1 year, 28 of 46 assessable patients were free of progression, a figure that surpassed the 19 patients whom the investigators considered worthy of further study. The results of this trial were recently updated<sup>37</sup> and remain highly encouraging. The 1- and 5-year PFS rates were 68% and 48%, respectively, with 10 of 20 patients in PR and 21 of 28 patients in CR at the time of lenalidomide initiation remaining free of disease progression. None of the patients who completed 2 years of maintenance therapy experienced relapse. Remarkably, 4 of the 6 patients who previously had undergone transplant were alive and without disease at 47 to 91 months from the time of lenalidomide initiation. As in the REMARC trial, no correlation of response with COO was noted, nor was the response rate decreased in the patients who required dose reduction. These results suggest that lenalidomide may be working as an immunomodulatory agent rather than as a cytotoxic agent.

Investigators from Rochester have provided additional evidence for the COO-agnostic efficacy of lenalidomide (with or without rituximab) in relapsed DLBCL.<sup>38</sup> They evaluated 62 patients with relapsed DLBCL or high-grade B-cell lymphoma whose median age was 73 years, including patients with transformed disease and patients with *MYC*, *BCL2*, or *BCL6* translocations. The objective response rate was 43% overall but was 63% in the 18 patients with transformed disease. Objective responses were recorded in 6 of 7 patients with an *MYC* translocation, including 3 CRs, and all 3 patients with high-grade B-cell lymphoma had responses, including 1 CR. The patients with transformed lymphoma had a median PFS of 2 years and a median OS of 4 years. The high response rate in the patients with transformed lymphoma is not completely unexpected, given the effectiveness of lenalidomide in indolent B-cell lymphomas,<sup>39</sup> and perhaps anticipates the activity of lenalidomide plus the anti-CD19 monoclonal antibody tafasitamab (Monjuvi, MorphoSys/Incyte) in transformed lymphomas, as described below. A recent study of GCB DLBCL showed that as many as 27% of cases have a double-hit gene signature,<sup>40</sup> and that

this percentage is undoubtedly higher in patients with recurrent disease. Further studies are clearly required to study the effectiveness of lenalidomide in relapsed GCB lymphoma. Paradoxically, according to the studies mentioned above, lenalidomide may prove to have more activity in relapsed GCB lymphoma than in ABC lymphoma. In any case, these data provide a rationale for considering lenalidomide in patients with transformed or high-grade B-cell lymphoma whose disease has relapsed or who are ineligible for other therapy. In addition, lenalidomide can be considered for patients with transformed lymphoma who require bridging therapy before CAR T-cell therapy. This is especially noteworthy because lenalidomide can be safely combined with radiation, and a recent study showed that CAR T-cell treatment appeared to be more effective when radiation was used as bridging therapy.<sup>41</sup>

Although the results with lenalidomide alone or in combination with initial therapy have been disappointing in ABC lymphomas, recent studies suggest that when combined with other novel agents, lenalidomide has clinically important activity that may be greater in patients with relapsed ABC lymphomas but is not limited to them. In the L-MIND trial, lenalidomide was combined with tafasitamab in transplant-ineligible patients after 1 to 3 previous regimens.<sup>42</sup> The ORR in 80 patients was 60%, with a CR rate of 43%. The response rate and duration of response were greater in patients with ABC COO than in those with GCB COO. Nevertheless, 7 of 7 patients with transformed lymphoma—who classically have a GCB COO—responded to treatment, including 2 with a CR. In addition, 1 patient with double-hit lymphoma had a PR, and another patient with triple-hit lymphoma had a CR. Remarkably, in the 48 responding patients, the median duration of response was nearly 2 years and was not reached in the patients who achieved a CR. On the basis of the latter results, on July 31, 2020, the US Food and Drug Administration approved the combination of tafasitamab and lenalidomide in patients with relapsed or refractory DLBCL, including transformed lymphoma, who are not eligible for autologous transplant.

Lenalidomide/prednisone has also been combined with the novel agents ibrutinib, venetoclax (Venclexta, AbbVie), and obinutuzumab (Gazyva, Genentech) in the ViPOR (venetoclax, ibrutinib, prednisone, obinutuzumab, lenalidomide) regimen, described at the 62nd (2020) American Society of Hematology Annual Meeting by investigators from the National Cancer Institute.<sup>43</sup> Patients received 6 cycles of therapy without maintenance therapy. Among the 31 evaluable patients with aggressive lymphoma, the objective response rate was 55%, including a 35% CR rate. The ORR and CR rate were higher in patients with ABC COO. The overall 1-year PFS rate was 32.8%, including a rate of 43.8% in ABC COO vs



a rate of 23.3% in GCB COO, a borderline-significant result. The potential for unmaintained durable CRs is particularly exciting, and may eventually provide a viable option for patients who either are not candidates for or experience relapse after CAR T-cell therapy.

## Conclusion

Although lenalidomide has activity in a variety of lymphomas, including DLBCL, the results of clinical trials attempting to exploit its putative activity in ABC lymphomas have been disappointing. In contrast, lenalidomide has shown activity in the setting of maintenance and relapsed disease independently of COO. Recent studies of lenalidomide alone or in combination with rituximab, tafasitamab, and other novel agents in relapsed lymphoma have shown excellent and surprisingly durable activity in patients with transformed and high-grade lymphomas. Future clinical trials should therefore focus on combining lenalidomide with novel agents rather than with chemotherapy. In addition, further study is required to assess whether lenalidomide should play a greater role in patients with relapsed GCB DLBCL, especially in those with transformed lymphoma.

## Disclosures

Neither Dr Goldfinger nor Dr Cooper has any conflicts of interest to disclose.

## References

1. 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):235-242.
2. Pfreundschuh M, Trümper L, Osterborg A, et al; MabThera International Trial Group. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MINT) Group. *Lancet Oncol.* 2006;7(5):379-391.
3. Chiappella A, Martelli M, Angelucci E, et al. Rituximab-dose-dense chemotherapy with or without high-dose chemotherapy plus autologous stem-cell transplantation in high-risk diffuse large B-cell lymphoma (DLCL04): final results of a multicentre, open-label, randomised, controlled, phase 3 study. *Lancet Oncol.* 2017;18(8):1076-1088.
4. Bartlett NL, Wilson WH, Jung SH, et al. Dose-adjusted EPOCH-R compared with R-CHOP as frontline therapy for diffuse large B-Cell lymphoma: clinical outcomes of the phase III Intergroup Trial Alliance/CALGB 50303. *J Clin Oncol.* 2019;37(21):1790-1799.
5. Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature.* 2000;403(6769):503-511.
6. Rosenwald A, Wright G, Chan WC, et al; Lymphoma/Leukemia Molecular Profiling Project. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. *N Engl J Med.* 2002;346(25):1937-1947.
7. Beham-Schmid C. Aggressive lymphoma 2016: revision of the WHO classification. *Memo.* 2017;10(4):248-254.
8. Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood.* 2004;103(1):275-282.
9. Czuczman MS, Trnny M, Davies A, 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):4127-4137.
10. Yang Y, Shaffer AL III, Emre NC, et al. Exploiting synthetic lethality for the therapy of ABC diffuse large B cell lymphoma. *Cancer Cell.* 2012;21(6):723-737.
11. Hernandez-Ilizaliturri FJ, Deeb G, Zinzani PL, et al. Higher response to lenalidomide in relapsed/refractory diffuse large B-cell lymphoma in non-germinal center B-cell-like than in germinal center B-cell-like phenotype. *Cancer.* 2011;117(22):5058-5066.
12. Mondello P, Steiner N, Willenbacher W, et al. Lenalidomide in relapsed or refractory diffuse large B-cell lymphoma: is it a valid treatment option? *Oncologist.* 2016;21(9):1107-1112.
13. Nowakowski GS, LaPlant B, Macon WR, 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.* 2015;33(3):251-257.
14. 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.
15. Vitolo U, Witzig TE, Gascoyne RD, et al. ROBUST: first report of phase III randomized study of lenalidomide/R-CHOP (R2-CHOP) vs placebo/R-CHOP in previously untreated ABC-type diffuse large B cell lymphoma. *Hematol Oncol.* 2019;37:36-37.
16. Nowakowski GS, Hong F, Scott DW, et al. Addition of lenalidomide to R-CHOP (R2CHOP) improves outcomes in newly diagnosed diffuse large B cell lymphoma (DLBCL): first report of ECOG-ACRIN1412. A randomized phase 2 US Intergroup study of R2CHOP vs R-CHOP. *Hematol Oncol.* 2019;37:37-38.
17. Peyrade F, Jardin F, Thieblemont C, et al; Groupe d'Etude des Lymphomes de l'Adulte (GELA) investigators. Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. *Lancet Oncol.* 2011;12(5):460-468.
18. Oberic L, Peyrade F, Puyade M, et al. Subcutaneous rituximab-miniCHOP compared with subcutaneous rituximab-miniCHOP plus lenalidomide in diffuse large B-cell lymphoma for patients age 80 years or older. *J Clin Oncol.* 2021;39(11):1203-1213.
19. Younes A, Sehn LH, Johnson P, et al; PHOENIX investigators. Randomized phase III trial of ibrutinib and rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in non-germinal center B-cell diffuse large B-cell lymphoma. *J Clin Oncol.* 2019;37(15):1285-1295.
20. Chapuy B, Stewart C, Dunford AJ, et al. Molecular subtypes of diffuse large B cell lymphoma are associated with distinct pathogenic mechanisms and outcomes. *Nat Med.* 2018;24(5):679-690.
21. Reddy A, Zhang J, Davis NS, et al. Genetic and functional drivers of diffuse large B cell lymphoma. *Cell.* 2017;171(2):481-494.e15.
22. Schmitz R, Wright GW, Huang DW, et al. Genetics and pathogenesis of diffuse large B-cell lymphoma. *N Engl J Med.* 2018;378(15):1396-1407.
23. Wright GW, Huang DW, Phelan JD, et al. A probabilistic classification tool for genetic subtypes of diffuse large B cell lymphoma with therapeutic implications. *Cancer Cell.* 2020;37(4):551-568.e14.
24. Rubenstein JL, Geng H, Fraser EJ, et al. Phase 1 investigation of lenalidomide/rituximab plus outcomes of lenalidomide maintenance in relapsed CNS lymphoma. *Blood Adv.* 2018;2(13):1595-1607.
25. Ghesquieres H, Chevrier M, Laadhari M, et al. Lenalidomide in combination with intravenous rituximab (REVRI) in relapsed/refractory primary CNS lymphoma or primary intraocular lymphoma: a multicenter prospective 'proof of concept' phase II study of the French Oculo-Cerebral Lymphoma (LOC) Network and the Lymphoma Study Association (LYSA). *Ann Oncol.* 2019;30(4):621-628.
26. Wang M, Fowler N, Wagner-Bartak N, 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(9):1902-1909.
27. Eyre TA, Djebbari F, Kirkwood AA, Collins GP. Efficacy of central nervous system prophylaxis with stand-alone intrathecal chemotherapy in diffuse large B-cell lymphoma patients treated with anthracycline-based chemotherapy in the rituximab era: a systematic review. *Haematologica.* 2020;105(7):1914-1924.
28. Orellana-Noia VM, Reed DR, Sen J, et al. CNS prophylaxis during frontline therapy in aggressive non-Hodgkin lymphomas: real-world outcomes a practice patterns from 19 US academic institutions [ASH abstract 478]. *Blood.* 2020;136(1)(suppl).

29. Puckrin R, El Darsa H, Ghosh S, Peters A, Stewart DA. Lack of effectiveness of intravenous high-dose methotrexate for prevention of CNS relapse in patients with high-risk DLBCL: a retrospective analysis from Alberta, Canada [ASH abstract 477]. *Blood*. 2020;136(1)(suppl).
30. Ayed AO, Chiappella A, Pederson L, et al. CNS relapse in patients with DLBCL treated with lenalidomide plus R-CHOP (R2CHOP): analysis from two phase 2 studies. *Blood Cancer J*. 2018;8(7):63.
31. Thieblemont C, Howlett S, Casasnovas RO, et al. Lenalidomide maintenance for diffuse large B-cell lymphoma patients responding to R-CHOP: quality of life, dosing, and safety results from the randomised controlled REMARC study. *Br J Haematol*. 2020;189(1):84-96.
32. 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):2473-2481.
33. Bernard S, Ghesquieres H, Casasnovas R-O, et al. Lenalidomide as maintenance therapy after R-CHOP has no protecting effect for central nervous system relapse in frontline treatment of diffuse large B-cells lymphoma. An ancillary studies of the Remarc Study. *Blood*. 2020;136:3023.
34. Vercellino L, Cottreau AS, Casasnovas O, et al. High total metabolic tumor volume at baseline predicts survival independent of response to therapy. *Blood*. 2020;135(16):1396-1405.
35. Abramson JS, Ghosh N, Smith SM. ADCs, BiTEs, CARs, and small molecules: a new era of targeted therapy in non-Hodgkin lymphoma. *Am Soc Clin Oncol Educ Book*. 2020;40:302-313.
36. 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-e146.
37. Ferreri AJM, Sassone M, Angelillo P, et al. Long-lasting efficacy and safety of lenalidomide maintenance in patients with relapsed diffuse large B-cell lymphoma who are not eligible for or failed autologous transplantation. *Hematol Oncol*. 2020;38(3):257-265.
38. Rodgers TD, Baran A, Reagan PM, et al. Efficacy of lenalidomide in high-risk diffuse large B-cell lymphoma. *Br J Haematol*. 2020;188(4):e33-e36.
39. Leonard JP, Trneny M, Izutsu K, et al; AUGMENT Trial Investigators. 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):1188-1199.
40. Ennishi D, Jiang A, Boyle M, et al. Double-hit gene expression signature defines a distinct subgroup of germinal center B-cell-like diffuse large B-cell lymphoma. *J Clin Oncol*. 2019;37(3):190-201.
41. Pinnix CC, Gunther JR, Dabaja BS, et al. Bridging therapy prior to axicabtagene ciloleucel for relapsed/refractory large B-cell lymphoma. *Blood Adv*. 2020;4(13):2871-2883.
42. Salles G, Duell J, González Barca E, et al. Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study. *Lancet Oncol*. 2020;21(7):978-988.
43. Melani C, Lakhota R, Pittaluga S, et al. Phase 1b/2 study of VIPOR (venetoclax, ibrutinib, prednisone, obinutuzumab, and lenalidomide) in relapsed/refractory, B cell lymphoma: safety, efficacy and molecular analysis. *Blood*. 2020;136:598.