REVIEW

Maintenance therapy following induction chemoimmunotherapy in patients with diffuse large B-cell lymphoma: current perspective

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Background: Maintenance therapy has proven efficacy in indolent non-Hodgkin lymphoma (NHL), yet its role in diffuse large B-cell lymphoma (DLBCL) is an area of ongoing investigation. While DLBCL is potentially curable, >30% of patients relapse following front-line therapy and have a poor prognosis, especially those with refractory disease. Maintenance therapy holds promise to maintain response post-induction.

Patients and methods: Keyword searches were carried out in PubMed and congress abstracts of ‘diffuse large B-cell lymphoma’ and ‘maintenance’ and focused on phase II/III studies of maintenance following front-line induction.

Results: Although used in indolent forms of NHL, studies of maintenance therapy with rituximab in patients with DLBCL responding to front-line R-CHOP (rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone) have not improved efficacy and are not recommended. Targeted agents enzastaurin and everolimus reported results from the phase III studies PRELUDE and PILLAR-2, respectively, both of which showed no proven maintenance benefit following front-line chemoimmunotherapy induction. Overall, the reported efficacy results with these agents in the maintenance setting do not outweigh the risks. Lenalidomide for maintenance has been reported in three studies. Results from two phase II trials on lenalidomide maintenance revealed positive outcomes in higher-risk patients following induction, resulting in improved progression-free survival in relapsed DLBCL patients who were ineligible for transplantation. First analysis from the phase III REMARC trial showed a significant improvement in progression-free survival for lenalidomide versus placebo, with no difference in overall survival, following front-line R-CHOP induction in elderly patients.

Conclusions: Based on currently available studies of DLBCL maintenance therapies, initial results in front-line, as well as the relapsed setting, with immunomodulators such as lenalidomide show promise for further research to identify appropriate patients who would most benefit. Overall, this review of maintenance studies underscores the need for additional analyses of patient subtypes, clinical risk status, and molecular profiles, with careful consideration of study end points.

Key words: diffuse large B-cell lymphoma, induction, lenalidomide, maintenance, non-Hodgkin lymphoma, rituximab

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL), accounting for approximately 25% of all mature NHL [1]. Initial treatment selection for patients diagnosed with DLBCL is based on patient prognosis according to stage of disease, age, and feasibility to tolerate a dose-intensified regimen, commonly comprising a chemoimmunotherapy combination, which may be followed by radiation therapy [2]. Subsequent treatment is based on response to the front-line therapy and imaging-based assessments by [18F]2-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (FDG-PET/CT) [2]. In indolent NHL, maintenance with rituximab is associated with improved outcomes. In patients with
DLBCL who received front-line chemoimmunotherapy such as R-CHOP (rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone), rituximab maintenance is not recommended [2].

While DLBCL is potentially curable, >30% of patients will relapse, and prognosis is extremely poor for those who relapse following the front-line therapy [2]. In DLBCL cases reviewed by the International Lymphoma Study Group, 5-year overall survival (OS) was 46%, and 5-year failure-free survival (FFS) was 41% [3]. Numerous factors influence patient survival; patients with limited disease show improved 5-year progression-free survival (PFS) of 80%–85% compared with 50% in those with advanced disease [4]. DLBCL subtypes have distinct pathobiology and involve B cells at various stages in their differentiation [5], illustrating the potential need for treatments targeted to key molecular processes and determination of additional DLBCL subtypes or prognostic factors to guide personalized treatment options.

Three main therapeutic perspectives/treatment phases can be considered for lymphoma patients: induction, consolidation, and maintenance. During induction in DLBCL, the goal with R-CHOP–based therapy is to obtain the best possible initial response. The objective of consolidation is to avoid relapse by offering high-dose therapy (HDT) and autologous stem cell transplantation (ASCT) in eligible patients. Young patients with high-risk disease based on International Prognostic Index (IPI) may be considered for consolidative HDT/ASCT [2] although this is still a controversial issue [6]. In noneligible patients, the consolidation phase will be the same regimen as induction. Third is maintenance, where a longer improvement in the complete response (CR) rate may ultimately mean a cure for the patient. Maintenance therapy has been studied in previously untreated follicular lymphoma (FL) and mantle cell lymphoma patients [7, 8], with overall goals to reduce the presence of residual disease following induction treatment, prolong PFS, and improve or maintain patient quality of life (QoL). The main objectives for this review are to discuss DLBCL studies of maintenance following front-line chemoimmunotherapy and provide an overview of what has been learned to date.

### Patients and methods

References for this review were identified through initial searches of PubMed and congress abstracts with the search terms ‘diffuse large B-cell lymphoma’ and ‘maintenance’, published in English and focused on phase II/III clinical studies. The final references were decided based on manual evaluation to ensure that maintenance therapy was received after initial induction treatment (versus combination regimen), along with relevance to the broad scope of this review.

### Patients with DLBCL eligible for maintenance

All DLBCL patients have a high risk for relapse following induction, which generally occurs within 2 years. For patients who are refractory to induction therapy (i.e. stable disease or progressive disease), <10% will respond to salvage therapy [9]. Factors associated with refractoriness are further described, including: clinical features [e.g. central nervous system (CNS) involvement]; immunophenotypic biomarkers and molecular characteristics; gene expression profiling; and response to induction.

Among the several factors associated with refractoriness, IPI is an important prognostic tool because it identifies specific groups of patients who are likely to be cured with standard therapy. The risk categories for IPI are based on age, tumor stage, serum lactate dehydrogenase, performance status, and extranodal disease involvement at diagnosis [10, 11]. Age-adjusted IPI stratifies younger (<60 years) patients, along with stage, serum lactate dehydrogenase, and performance status [10]. Multiple IPI-based clinical tools have been shown to accurately predict patient outcomes.

Immunophenotypic biomarkers such as high CD5 expression (>75%) and high Ki67 proliferation index (70%–75%) have strong inverse prognostic value for OS in patients with DLBCL [12, 13]. Molecular characteristics in the form of double/triple hits and coexpression of BCL6, BCL2, and MYC may be present in patients with an inferior response to R-CHOP [14–17]. Endothelial markers and angiogenesis factors in the tumor microenvironment may also provide guidance for future treatment strategies [18].

Gene expression profiling (GEP) in DLBCL has identified two main molecular subtypes as defined by cell-of-origin (COO) [19], which include a germinal center B-cell-like (GCB) subtype and an activated B-cell-like (ABC) subtype [20]. A third type 3, or unclassifiable group, represents a minority of patients [19, 21]. Immunohistochemistry (IHC) can also identify COO subtypes, specifically GCB and non-GCB (ABC and type 3) [22]; however, the IHC method has shown variability compared with GEP and issues with reproducibility [2, 23]. Prognostic evaluations based on COO classification show better outcomes for GCB-type patients over the ABC subtype of DLBCL [19, 21]. Following front-line R-CHOP, ABC-type patients have inferior survival versus the GCB subtype [19]. Thus, it has been hypothesized that ABC-type patients may be the best candidates for maintenance therapy following the front-line treatment [19, 21].

Patients with DLBCL who achieve partial response (PR) to induction have an improved response to salvage therapy compared with primary refractory patients (i.e. stable disease or progressive disease) [9]; yet, patients with PR post-induction often have limited therapeutic options due to advanced age and/or poor PS. In a study of 90 patients with aggressive lymphoma (94% DLBCL), FDG-PET after two induction cycles of combination chemotherapy ≥ rituximab was shown to predict event-free survival (EFS) in lower- and higher-risk IPI patients [24]. Additionally, later imaging (after four induction cycles) attained statistical significance for both EFS and OS. In contrast, interim FDG-PET following four induction cycles of accelerated R-CHOP did not predict outcomes for 98 patients with advanced DLBCL; PFS was identical for patients irrespective of positive or negative FDG-PET [25]. Since a goal of maintenance is to improve or maintain patient QoL, it is important to consider tolerability when identifying treatment options following front-line therapy. Risk–benefit assessments should be carefully constructed for each patient with this goal in mind, alongside extending survival. Prespecified dose modifications may help improve patient discontinuation rates, especially for dose-dependent adverse events, and possibly result in improved tolerability and response over time in patients who would otherwise discontinue an effective treatment.
Flexibility in treatment strategies from multiple molecular targets and therapeutic combinations could allow for optimization of care for patients of varied molecular and clinical profiles. The survival of tumor cells in a dormant state, either by escaping an immune-mediated cell killing or creating a favorable, protective microenvironment, may explain disease relapse following an initial response to standard therapy [26]. Targeting the microenvironment and altering the cytokine milieu with novel drugs exhibiting unique mechanisms of action, different from agents used in the induction phase to eliminate resistant clones, is an exciting avenue in therapy.

End points in DLBCL

The goal of clinical studies in NHL is to improve OS, with PFS, EFS, FFS, and disease-free survival (DFS) as important time-to-event end points that allow for earlier results. The timing of end points varies by study. Since most DLBCL relapses are expected to arise in the first 2 years, tracking a patient’s response during this time frame are crucial [27]. When analyzing EFS after 2 years for patients in remission, half of any events will be from deaths not related to DLBCL [27]. One assessment of 767 patients with newly diagnosed DLBCL (median age, 63 years) compared EFS12 versus EFS24 and examined DLBCL-related events versus death from other causes. The study showed 70% of relapses were within 1 year, and if EFS12 was achieved, the 5-year relapse risk was only 13%; when EFS24 was reached, this risk decreased to 8%. After achieving EFS24, OS matched the risk of death from unrelated causes based on age and sex. The results indicated that patients with DLBCL who are event-free after 2 years have the same survival expectations as non-DLBCL patients in the general population [27]. Considering the age of most patients diagnosed with DLBCL, 2-year end points such as EFS24 are appropriate when evaluating novel agents in the maintenance/consolidation phase for newly diagnosed DLBCL.

DLBCL: a heterogenous disease with multiple oncogenic pathways

DLBCL is a disparate group of malignancies with common morphology and immunohistochemical markers. Phenotypically, it follows an aggressive clinical course; morphologically, DLBCL is composed of large cells (mixed centroblasts and immunoblasts) with nuclei ≥2 times larger than small lymphocytes and generally larger than tissue macrophages [4]. Gene rearrangements identified in DLBCL include BCL6 in 30%–40% of cases, BCL2 in 20% of de novo cases (most transformed from FL), and MYC in approximately 10% of cases [4].

DLBCL is a diverse disease characterized by recurrent somatic mutations in multiple genes controlling the nuclear factor (NF)-κB pathway, histone acetylation, and other cancer genes that affect cell regulation and proliferation. Each of the mutation patterns, however, only affect a minority of patients, making it a genetically heterogeneous malignancy [28]. While COO phenotype for DLBCL has major prognostic implications, the role of subtype in guiding treatment decisions awaits further investigation [2].

Lenalidomide in lymphoma

Lenalidomide is an oral, IMiD® immunomodulatory agent whose activity is evident across multiple lymphoma subtypes. Its mechanism of action is multitargeted, including B-, T-, natural killer, and dendritic cells in the tumor microenvironment [29–31]. Considering B cells, early preclinical studies showed that while lenalidomide did not affect normal B cells, it had anti-neoplastic and antiproliferative activity on malignant lines [32]. The activity profile of lenalidomide against malignant lymphoma B cells has been confirmed by in vitro and in vivo studies [29, 32–36].

The E3 ubiquitin ligase protein cereblon is a direct target for thalidomide and lenalidomide [29, 37]. Lenalidomide binding to cereblon activates ligase activity to the specific B- and T-cell targets Ikaros and Aiolos, ultimately leading to selective degradation of these transcription factors [38–40]. In vitro data with activated T cells has also shown that lenalidomide promotes the aforementioned selective sequence of events in a concentration- and time-dependent manner within hours of drug treatment [40].

The targeted mechanisms of lenalidomide elucidated via preclinical studies have translated in the clinical setting and can be further realized when used in combination with other therapies [29]. A constitutively active NF-κB signaling pathway is representative of ABC-type DLBCL, a pathway inhibited by lenalidomide in a cereblon-dependent manner [41, 42]. For patients with DLBCL, lenalidomide has previously shown preferential activity in the non-GCB/ABC subtype, and its activity across COO has been demonstrated to be significant [30, 43]. These known mechanisms for lenalidomide in DLBCL provide a basis for evaluating lenalidomide’s potential in DLBCL maintenance, as will be further discussed in the context of other maintenance studies.

Outcomes of clinical studies evaluating maintenance in DLBCL

Rituximab. Table 1 outlines prospective trials that have examined the use of maintenance therapy after front-line induction with chemoimmunotherapy, starting with rituximab. Before rituximab maintenance studies, a study on patients with high- or high-intermediate-risk DLBCL demonstrated that interferon alpha yielded insignificant results compared with observation when used after CR to R-CHOP–bleomycin induction (data not shown) [44]. Several years following this study, ECOG 4494 examined patients who responded to induction therapy of CHOP or R-CHOP, followed by rituximab maintenance or observation [45]. The maintenance arms were stratified by PI risk factor, response (PR or CR), and induction therapy (CHOP or R-CHOP). Rituximab maintenance achieved a statistically significant improvement in 2-year FFS only among those patients who exhibited a PR/CR with CHOP. No FFS benefit was observed in patients receiving R-CHOP induction, the current mainstream treatment, followed by rituximab maintenance.

The AGMT NHL13 phase III randomized study of patients with DLBCL and FL grade 3 evaluated responders with CR/CR unconfirmed (CRu) following R-chemotherapy (mainly R-CHOP) who received rituximab maintenance or observation [46]. The primary end point EFS included unacceptable toxicity as a component. No significant difference was observed in EFS,
Table 1. Prospective clinical studies of maintenance therapy following the front-line chemoimmunotherapy in DLBCL

<table>
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<tr>
<th>Study name</th>
<th>Select inclusion parameters</th>
<th>IPI/Risk</th>
<th>Induction therapy</th>
<th>Status before MT</th>
<th>MT arms</th>
<th>MT, y</th>
<th>Overview of results following maintenance</th>
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<tr>
<td>ECOG 4494 (phase III)</td>
<td>Prev. untreated DLBCL, ≥60 y</td>
<td>1–4 (PS 0–3)</td>
<td>CHOP or R-CHOP</td>
<td>PR/CR</td>
<td>Rituximab (n = 207) or observation (n = 208)</td>
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<td>2-year FFS</td>
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<td>0.43–1.27; P = 0.27</td>
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<td>AGMT NHL13 (phase III)</td>
<td>Prev. untreated DLBCL/FL3B</td>
<td>0–5</td>
<td>R-CHOP–like</td>
<td>CR/CRu</td>
<td>Rituximab (n = 338) or observation (n = 345)</td>
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<td>3-year EFS (MR versus Obs) 80% versus 77%; P = 0.0670</td>
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<td>5-year RFS (MR versus Obs) 87% versus 84%; P = 0.35</td>
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<td>Men, 88% versus 74%; P = 0.047</td>
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<td>HD2002 (phase III)</td>
<td>Prev. untreated and R/R DLBCL</td>
<td>0–5</td>
<td>R-CHOP or other</td>
<td>CRf</td>
<td>Rituximab (n = 77) or observation (n = 75)</td>
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<td>5-year RFS (MR versus Obs) 90% versus 94%; P = 0.65</td>
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<th>Overview of results following maintenance</th>
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<tr>
<td>REMARC (phase III) [59]</td>
<td>Prev. untreated DLBCL, 60–80 years</td>
<td>aaIPI &gt;1 (PS 0–2)</td>
<td>R-CHOP</td>
<td>PR/CR</td>
<td>Lenalidomide (n = 323) or placebo (n = 327)</td>
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aPatients with FL3B (n = 21) were also randomized to maintenance arms.
bThe study included patients with untreated or relapsed/refractory CD20(+) B-cell lymphoma (ITT; N = 321); 90.7% of patients in the DLBCL subgroup (137/151) were receiving front-line treatment at study entry. Table reports on subgroup of DLBCL patients.

cPR/CR was included at randomization for indolent lymphoma.

dNumber of patients at enrollment; 139 patients (92%) entered the study after front-line treatment.

ePatients 60–70 years were also eligible if they had ≥1 of the following: ECOG PS 2, cardiac contraindication to anthracycline therapy, or severe medical problems or general frailty.

f47% represented 27 of 45 patients entering the study.

gPatients had stage II bulky or stage III/IV DLBCL.

aaIPI, age-adjusted International Prognostic Index; Abbrev., abbreviated; AGMT, Arbeitsgemeinschaft Medikamentöse Tumorthérapie; CHOP, cyclophosphamide/doxorubicin/vincristine/prednisone; CI, confidence interval; CR, complete response; CRu, complete response unconfirmed; DFS, disease-free survival; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; FFS, failure-free survival; FL3B, follicular lymphoma grade 3 b; HR, hazard ratio; IPI, International Prognostic Index; ME, maintenance enzastaurin; MEv, maintenance everolimus; ML, maintenance lenalidomide; mo, month; MR, maintenance rituximab; MR², maintenance rituximab + lenalidomide; MT, maintenance therapy; NA, not available; NHL, non-Hodgkin lymphoma; NR, not reached; NS, not significant; Obs, observation; Pbo, placebo; PFS, progression-free survival; PR, partial response; Prev., previously; PS, performance status (Eastern Cooperative Oncology Group [ECOG]); R², lenalidomide + rituximab; R-CHOP, rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone; R-CNOP, rituximab/cyclophosphamide/mitoxantrone/vincristine/prednisone; R-CVP, rituximab/cyclophosphamide/vincristine/prednisone; R-EPOCH, rituximab/etoposide/cyclophosphamide/doxorubicin/vincristine/prednisone; RFS, relapse-free survival; RR, relapsed/refractory; SD, stable disease; y, year.
PFS, or OS. The phase III, randomized, prospective trial HD2002 also evaluated rituximab maintenance, which included a subgroup analysis of DLBCL patients, most of whom were in the front-line setting [47]. In both studies, preferential improvements in survival were shown in men (versus women) with rituximab maintenance (Table 1).

Rituximab maintenance has also been studied in elderly, higher-risk patients with stage II-IV DLBCL who received an abbreviated induction regimen (N = 51) [48]. Those who did not progress received a planned 2 years of rituximab maintenance (Table 1). Further assessment is needed regarding this maintenance strategy for very elderly and higher-risk patients.

While not the focus of the review, rituximab maintenance has also followed high-dose consolidative front-line therapy with ASCT. In the LNH 98-3 study, patients were randomized to induction with doxorubicin/cyclophosphamide/etoposide, or doxorubicin/cyclophosphamide/vincristine/bleomycin/prednisone [49]. Responders received HDT/ASCT, and patients with ≥PR were re-randomized to maintenance rituximab (n = 139) or observation (n = 130). At 4 years post-randomization to maintenance, the trend toward increased EFS with rituximab maintenance was nonsignificant, regardless of age-adjusted IPI or induction therapy. Yet, patients with a CR following HDT experienced statistically significant EFS compared with those having no consolidative therapy (86% versus 68%, respectively; P = 0.023).

Notably, a retrospective nonrandomized study of 207 Chinese patients with DLBCL analyzed rituximab maintenance following a response to R-CHOP14 induction [50]. The study stratified patients by IPI status (<2 or ≥2) and showed a significant 5-year PFS benefit with rituximab maintenance for both IPI groups. Yet, rituximab maintenance did not show a significant difference in OS for either risk category compared with observation.

A meta-analysis evaluated the use of rituximab maintenance in 1546 patients from four studies [51]: three studies of previously untreated patients and one study of relapsed/refractory patients. Although rituximab showed improvement over observation only, the main findings of the meta-analysis showed no EFS benefit when rituximab was used as part of induction therapy and in patients who had prior ASCT.

Another meta-analysis included seven studies of 1470 patients with DLBCL who received maintenance rituximab (three studies following response of ≥PR to chemoimmunotherapy induction) and in the salvage setting (three studies following relapse) [52]. Rituximab following induction improved OS and FFS, although there was only statistical significance with FFS, not with OS. The results suggested a benefit for rituximab although a limited number of studies were relevant to the evaluation and considerable variability among studies existed (e.g. patient risk status and response to the front-line treatment).

**Other targeted agents.** Enzastaurin is a selective inhibitor of protein kinase C θ (PKCθ) [53], and everolimus is an mTORC1 inhibitor [54]. To date, no maintenance benefit has been confirmed for these agents (Table 1). Enzastaurin was studied in PRELUDE, a phase III, global, double-blind study of 758 patients with higher-risk DLBCL with a CR/CRu following R-CHOP [53]. Patients were randomized 2:1 to enzastaurin or placebo maintenance for 3 years. Only 26% of patients had overexpression of the PKCθ protein. Nonetheless, 4-year DFS (primary end point), EFS, and OS showed no difference between maintenance arms or within COO subgroups (GCB versus non-GCB).

PILLAR-2 was a phase III randomized study of adjuvant everolimus versus placebo for 1 year in higher-risk patients with DLBCL and a CR to R-CHOP induction [54]. No 2-year DFS benefit (primary end point) was shown between arms. Trends favoring improved survival with everolimus were observed in select patient subgroups (<65 years of age, male, Asian, IPI 4-5), supporting the antilymphoma activity of everolimus. As an alternate treatment approach, everolimus was combined with R-CHOP during induction, and the feasibility of this combination was recently shown by Johnston et al. [55, 56].

**Lenalidomide.** Results from two phase II studies showed positive outcomes for lenalidomide maintenance in the DLBCL setting for higher-risk patients responding to salvage therapy (discussed below) or the front-line induction (Table 1) [57, 58]. The former phase II multicenter study was the first prospective trial to show a maintenance benefit in relapsed DLBCL. Patients (69% after first relapse) had chemosensitive, relapsed DLBCL and were not eligible for or had experienced relapse after ASCT [57]. After a median follow-up of 25 months, 1-year PFS was 70% (primary end point), surpassing the pre-determined efficacy threshold of 41%. Based on Hans’ algorithm, lenalidomide maintenance showed benefit in GCB (n = 20) and non-GCB (n = 19) COO subtypes (1-year PFS, 64% versus 67%); GEP with Nanostring technique also showed similar PFS figures. The 1- and 3-year OS were 81% and 71%, respectively.

In the phase II study of patients responding to R-CHOP induction, 44 patients with intermediate- to high- or high-risk DLBCL were randomized to lenalidomide or lenalidomide + rituximab (R2) maintenance for 1 year (Table 1) [58]. At a median follow-up of 3.64 years in the intent-to-treat maintenance population, 2-year DFS (primary end point) and OS were improved compared with historical controls (no maintenance). Assessment of PFS and OS based on COO revealed no significant differences between the two maintenance arms. Similar findings in both arms indicated that lenalidomide monotherapy demonstrated significant activity. The addition of rituximab did not appear to provide additional benefit.

More recently, REMARC, a phase III, randomized, double-blind, placebo-controlled trial, examined maintenance lenalidomide versus placebo in patients who responded with PR/CR to R-CHOP induction (Table 1) [59]. Lenalidomide maintenance significantly improved PFS (primary end point; hazard ratio 0.71; P = 0.0135), but similar 2-year OS (87% lenalidomide; 89% placebo), with a median that was not reached in either arm. REMARC phase III results are the first to show an immunomodulatory maintenance therapy that prolongs PFS in DLBCL following the front-line R-CHOP induction.

Front-line consolidation with lenalidomide (REVLIMID®) maintenance for DLBCL patients aged 60–80 years is a category 2B recommended option within the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) [11]. In the relapsed/refractory setting, lenalidomide ± R-CHOP has shown potential for DLBCL patients, specifically in the non-GCB subtype [43, 60, 61]. Lenalidomide (REVLIMID®) ± rituximab is a recommended option within NCCN Guidelines® for relapsed/refractory patients with non-GCB DLBCL who are not candidates.
for HDT [11]. In the front-line setting, lenalidomide is being investigated in combination with R-CHOP in a phase III study in the ABC subtype only [DLC-002 (ROBUST), NCT02285062] [62], whereas REMARC enrolled both ABC and GCB subtypes.

Safety of maintenance therapies in DLBCL

When considering the studies shown in Table 1, rituximab maintenance was well tolerated with generally mild grade 1/2 toxicities; grade 3/4 toxicities, including myelosuppression and infection, were observed in a low percentage of patients [45–48]. A meta-analysis evaluating rituximab maintenance following front-line or salvage therapy indicated that rituximab was associated with a significantly higher incidence of neutropenia (P = 0.026) and a nonsignificant higher risk of infection (P = 0.21) compared with observation alone [51]. The phase III PRELUDE trial with enzastaurin maintenance showed neutropenia as the most common grade 3/4 toxicity, occurring at a similar rate to the placebo arm (6% each) and including grade 3/4 febrile neutropenia in 2% of patients taking enzastaurin (1% in the placebo group) [53]. Grade 3 QT prolongation was also reported for enzastaurin in 3% of patients compared with 2% of patients taking placebo. The PILLAR-2 trial reported >3% differences in grade 3/4 toxicities with everolimus versus placebo as neutropenia, stomatitis, decrease in CD4 lymphocytes, lymphopenia, and anemia [54]. Overall, the reported efficacy results with these agents in the maintenance setting do not outweigh the risks.

Table 2 provides an overview of baseline patient parameters and safety results from the lenalidomide maintenance trials [57–59]. The most common grade 3 or 4 adverse event in phase II and III studies was neutropenia. In REMARC, the proportion of patients with secondary primary malignancies was similar in the placebo and lenalidomide arms [41 (13%) versus 32 (10%) patients, respectively]. The risks and possible benefit must be carefully weighed when considering lenalidomide maintenance.

Discussion

While maintenance therapy has proven activity in indolent NHL, the role of maintenance in DLBCL requires continued investigation. There are many variables when considering maintenance therapy following induction in DLBCL. Based on the maintenance trials reviewed, Figure 1 shows key considerations for assessing lack of efficacy in certain studies. The duration of maintenance therapy has varied in studies; however, the implications have yet to be determined.

Important considerations for study design include induction criteria (type and required response) and primary end points. Induction response criteria, for instance, can include PR/CR. For trials including only CR, it may be more difficult to show an advantage of maintenance versus observation/placebo; patients exhibiting CR will likely have higher survival rates and more durable responses following chemoimmunotherapy. Moreover, choice of primary end point (e.g. PFS, EFS, DFS) and associated time frames can greatly influence the study conclusions. While several survival rates may exhibit similar trends, statistical significance may not be achieved in all end points. When choosing EFS as a primary end point, as in the case of the AGMT NHL13 study of rituximab maintenance [46], a toxicity component of EFS may attenuate overall conclusions on the efficacy of the drug.

Study design can also help to refine other key factors such as patient demographics (i.e. age, sex, race), clinical risk status, and molecular profiles. As seen in several subset analyses, there are cases when male sex, younger age, Asian race, and higher IPI score positively impacted the results [46, 47, 54]. The latter is promising for patients, given that higher IPI status predicts substantially lower survival rates and higher risk of relapses.

Yet, even within each prognostic subgroup, a range of clinical outcomes indicates the presence of molecular variables that may not be addressed solely on clinical parameters [63]. Specific gene rearrangements have been identified in DLBCL, including double or triple hits, which can show a worse prognosis and response to R-CHOP induction [2, 4]. Moreover, the two main molecular subtypes revealed by GEP, ABC and GCB, often provide drastically different prognostic implications [19, 21]. By comparison, GCB subtype have superior survival suggesting ABC-type patients may be the best candidates for maintenance. Ongoing investigations in post-induction strategies are warranted for higher-risk patients and corresponding biological markers [53].

Several DLBCL therapies were reviewed for maintenance following front-line induction. Rituximab maintenance has produced nonsignificant results, rejecting its broad use, although preferential survival was found for men (versus women) [46, 47]. Meta-analyses have supported the lack of EFS or OS benefit when rituximab was used as part of induction therapy and in patients who had prior ASCT [51, 52].

Lenalidomide maintenance has shown survival benefit for higher-risk patients and a consistent tolerability profile in several DLBCL patient types. In relapsed patients (most with IPI ≥ 2), 1-year PFS and OS was 70% and 81%, respectively [57]. Lenalidomide as a monotherapy and R2 after CR to front-line R-CHOP showed comparable results in intermediate/high- and high-risk patients [58]. The phase III REMARC study showed 2 years of lenalidomide maintenance following PR/CR to R-CHOP significantly improved PFS versus placebo [59]. Lack of OS benefit despite the positive PFS data is not yet clearly understood and is being explored. It is clear that it is not due to excessive toxicity in the experimental arm, but rather may be due to differences in patient outcomes after progression or another unrecognized reason.

There are ongoing DLBCL phase II/III trials of other agents for maintenance following front-line chemoimmunotherapy; these trials include bortezomib following a CR to R-CHOP in non-GCB, high-risk patients (phase III, NCT01965977) and ibritinib for elderly, responding patients with primary CNS lymphoma (phase II, NCT02623010). Bortezomib with R-CHOP was previously shown to possibly improve outcomes in non-GCB and GCB-DLBCL [64], suggesting effectiveness in the NF-kB-dependent ABC-DLBCL [65]. B-cell receptor signaling is also important in ABC pathogenesis, and ABC-DLBCL expression is a putative biomarker for an enriched response to ibritinib based on phase I/II results in relapsed/refractory DLBCL [66]. Further investigation of ibritinib in the maintenance setting (post-ibrutinib + immunochemotherapy) includes relapsed/refractory non-GCB DLBCL (phase II, NCT02692248 and NCT02955628).
### Table 2. Baseline parameters and safety results of lenalidomide maintenance in DLBCL

<table>
<thead>
<tr>
<th>Study description</th>
<th>Select baseline parameters</th>
<th>Maintenance treatment</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response status</strong></td>
<td>IPI</td>
<td>Median age, y (range)</td>
<td>Male: female</td>
</tr>
<tr>
<td>Multicenter, phase II [57]</td>
<td>Relapsed patients; PR (n = 20) or CR (n = 26) to salvage therapy&lt;sup&gt;a&lt;/sup&gt;</td>
<td>≥2 (83%)</td>
<td>61% &gt;70 years</td>
</tr>
<tr>
<td>Randomized, phase II [58]</td>
<td>CR to R-CHOP ± RT induction (n = 44)</td>
<td>aaIPI=3</td>
<td>59.6 (19–85)</td>
</tr>
<tr>
<td>REMARC: phase III RCT [59]</td>
<td>PR/CR to R-CHOP induction (n = 645)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>58% high aaIPI</td>
<td>68 (58–80)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Patients who experienced relapse after transplantation were also included; 46 of 48 enrolled patients were assessable. All patients were previously treated with rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone (83%) or rituximab/etoposide/doxorubicine/cyclophosphamide/vincristine/prednisone/bleomycin/ rituximab/methotrexate/doxorubicine/cyclophosphamide/vincristine/prednisone/bleomycin (17%), plus ASCT in six patients. Salvage chemotherapy contained rituximab in addition to either high-dose cytarabine based (50%), high-dose ifosfamide based (17%), anthracycline based (13%), bendamustine (11%), or gemcitabine-oxaliplatin (9%).

<sup>b</sup>A total of 556 lenalidomide courses were given (average of 12 courses per patient; range of 3–41). A protocol amendment allowed for discontinuation of maintenance after 2 years; 19 patients were still in treatment or completed 2 years of maintenance at a median follow up of 25 months.

<sup>c</sup>Patients treated with lenalidomide in cycles 2–5 of 12-month treatment.

<sup>d</sup>The safety population included 645 patients who had at least one dose of maintenance treatment.

<sup>e</sup>aIPI, age-adjusted International Prognostic index; AE, adverse event; ASCT, autologous stem cell transplantation; CR, complete response; DLBCL, diffuse large B-cell lymphoma; IPI, International Prognostic Index; ML, maintenance lenalidomide; MR, maintenance rituximab; NA, not applicable; Pbo, placebo; PR, partial response; R<sup>2</sup>, lenalidomide + rituximab; RCT, randomized, controlled trial; RT, radiotherapy.
Conclusion

The DLBCL landscape is heterogeneous, with evolving variables inherent to the disease and within each patient. Maintenance strategies benefit from careful consideration of therapeutic agents' study methods, in addition to patient demographics, clinical risk status, and molecular profiles. Based on currently available studies of maintenance following front-line chemoimmunotherapy, male sex, younger age, and higher-risk status resulted in preferential outcomes in select studies. Patient preference for tolerability and QoL are also important considerations when formulating a possible maintenance strategy. Molecular characterization of patients is evolving, including COO phenotyping and markers related to resistance such as double/triple hit DLBCL. These molecular factors may have key therapeutic implications for maintenance after induction. How DLBCL mechanisms of action alongside molecular testing will personalize medicine in the maintenance setting is an exciting prospect.

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