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REGULAR ARTICLE

blood advances

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Key Points

- Atezolizumab consolidation in high-risk patients with DLBCL raised 2-year DFS to 87.9% and OS to 96.3%, surpassing historical outcomes.
- Atezolizumab showed manageable AEs, supporting its potential role as a consolidation tregy in high-risk DLBCL.

The risk of relapse among high-risk patients with diffuse large B-cell lymphoma (DLBCL) in complete metabolic remission (CMR) after rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) therapy is 20% to 25%. Here, we evaluated whether consolidation with the programmed cell death ligand 1 checkpoint inhibitor atezolizumab could reduce the relapse risk. In this phase 2, open-label trial, patients with DLBCL with an International Prognostic Index (IPI) score of ≥3 and CMR after R-CHOP received 1200 mg atezolizumab every 3 weeks for 18 cycles. The primary end point was disease-free survival (DFS) at 2 years, with the aim of improving it to 89% compared to historical 79%. Secondary end points included overall survival (OS) and safety (Common Terminology Criteria for Adverse Events version 4.0). Analyses were on an intention-to-treat principle. Of 109 patients, 65% completed treatment. The cohort was 59% males, with 63% having high-intermediate risk IPI scores. At a median follow-up of 36.4 months, 15 relapses occurred (median, 8.2 months). The 2-year DFS was 87.9% (90% confidence interval [CI], 81.5-92.1), and the 2-year OS was 96.3% (90% CI, 91.7-98.3), meeting the primary objective. Treatment

Submitted 1 November 2024; accepted 7 January 2025; prepublished online on *Blood Advances* First Edition 18 April 2025; final version published online 10 July 2025. https://doi.org/10.1182/bloodadvances.2024015226.

The data presented in this study are available on request; check the HOVON website (www.hovon.nl) for HOVON data sharing policy. The data are not publicly available because of specific conditions extended by the HOVON foundation, as the owner of the data collected in HOVON studies.

The full-text version of this article contains a data supplement.

with salvage chemotherapy resulted in 10 of 13 patients achieving a second CMR. OS was significantly better among atezolizumab-treated patients than in a population-based matched control cohort from the Netherlands Cancer Registry. Adverse events (AEs) affected 79% of patients, with 18% developing immune-related AEs, including 4.5% grade 3 to 4. Atezolizumab consolidation significantly improved DFS in high-risk patients with DLBCL compared to historical cohorts. OS was significantly better than a population-based control cohort. These findings warrant further validation and assessment of immune checkpoint inhibitors as consolidation strategy in DLBCL. This trial was registered at www.clinicaltrials.gov as #NCT03463057.

Introduction

Diffuse large B-cell lymphoma (BCL; DLBCL) accounts for 35% to 40% of all mature B-cell lymphoproliferative diseases. Treatment with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) in patients with low-risk DLBCL with an International Prognostic Index (IPI) score of 0 to 2 typically results in an excellent prognosis. However, patients with DLBCL classified as high risk (IPI score ≥3) often face unsatisfactory outcomes, with a 2-year overall survival (OS) rate of only 59%.[1] Even for patients with a complete metabolic remission (CMR) after R-CHOP, the risk of relapse is high, with a 2-year disease-free survival (DFS) of 78%.[2]

In response to the increased risk of relapse among high-risk patients with DLBCL, various studies have explored consolidation strategies. Autologous stem cell transplantation, rituximab maintenance, and everolimus consolidation did not improve outcomes.[3,4] Conversely, lenalidomide maintenance did significantly improve progression-free survival (PFS), albeit with an increase in toxicity.[5]

During the conceptualization of the study, there was significant optimism about the potential of lymphomas, including DLBCL, as promising candidates for immune checkpoint therapy. This optimism stemmed from their high mutational burden and mechanisms to inhibit the body's antitumor immune response, such as the expression of programmed cell death ligand 1 (PD-L1) and the loss of HLA.[6-8] In DLBCL, both cell surface expression of PD-L1 and soluble PD-L1 in serum are associated with inferior prognosis.[9,10]

Checkpoint inhibitors targeting programmed cell death protein 1 (PD-1) are effective in various lymphomas, such as relapsed Hodgkin lymphoma and primary mediastinal BCL. However, although early clinical data suggested promising results, more mature studies have shown that their effectiveness in relapsed or refractory (R/R) DLBCL has so far been limited.[11,12] In R/R DLBCL, the anti–PD-1 antibody nivolumab and the anti–PD-L1 antibody atezolizumab exhibited modest responses, with overall response rates of 10% and 17%, respectively.[13,14]

Nevertheless, the potential use of checkpoint inhibitor as a consolidation strategy to eradicate minimal residual disease (MRD) in R/R DLBCL is yet unclear, with conflicting results reported when used after salvage chemotherapy.[15,16] In first-line treatment, a single-arm phase 2 study combining R-CHOP with atezolizumab has shown promising efficacy and a safety record consistent with the known toxicities of the individual drugs.[17]

Given that R-CHOP itself could potentially impair T-cell function, we hypothesized that atezolizumab would be more effective as a consolidation strategy to reduce relapse rate by eradicating MRD in high-risk patients with DLBCL who achieve CMR after R-CHOP therapy, rather than being used in combination with R-CHOP. Drawing on principles from similar trial designs, the duration of consolidation was set at 12 months.[18] For MRD assessment, immunoglobulin high-throughput sequencing, published at the time of study initiation, was chosen as the method.

Methods

Study design and participants

The Hemato Oncology Foundation for Adults in the Netherlands (HOVON) trial 151 (registered with www.clinicaltrials.gov; identifier: NCT03463057) was a nonrandomized, investigator-initiated phase 2 trial, conducted in accordance with the Good Clinical Practice guidelines and the principles of the Declaration of Helsinki (Guideline for good clinical practice E6[R2]). Before participation, all patients provided written informed consent. Safety data were reviewed by an independent data and safety monitoring committee during prescheduled interim analyses. The article was authored by academic researchers, with all authors thoroughly reviewing and contributing to its final version. The authors affirm the completeness and accuracy of the data, as well as the trial's adherence to the protocol and statistical analysis plan.

Patients meeting the following criteria were eligible for inclusion: aged between 18 and 75 years; newly diagnosed DLBCL in CMR after R-CHOP treatment; IPI score of ≥3; World Health Organization performance status score of 0 to 2 at the time of study enrollment; and demonstrating adequate hematologic, renal, hepatic, and cardiac function. Key exclusion criteria were a history of indolent lymphoma, presence of *MYC* and *BCL2* and/or *BCL6* rearrangement via fluorescence in situ hybridization (FISH) analysis, known involvement of the central nervous system (CNS), and prior autoimmune disease. PD-L1 positivity by immunohistochemistry (IHC) was not required for enrollment in this study.

Procedures

The treatment regimen consisted of IV infusion of atezolizumab at a fixed dose of 1200 mg, administered once every 3 weeks for 18 consecutive cycles, with a maximum duration of 54 weeks, or until relapse, if earlier. Consolidation therapy was scheduled to commence within 8 to 12 weeks after the completion of the last cycle of R-CHOP. No adjustment of atezolizumab dose was

allowed. Temporary suspension of atezolizumab treatment due to adverse events (AEs) was permitted, with the condition that such suspension should not exceed 12 weeks. If treatment could not be resumed within 12 weeks, atezolizumab was discontinued.

Response assessment. Assessment of response after R-CHOP relied on positron emission tomography–computed tomography (PET-CT) scans, using the Lugano classification response criteria for lymphoma.[19] Response during atezolizumab consolidation and follow-up was assessed by CT scans every 6 months for 2 years.

Central review. Pathology review was performed by 2 expert hematopathologists (A.D. and D.d.J.) according to the standard procedures of the HOVON Pathology Facility and Biobank. All cases were classified according to the World Health Organization classification of Tumours of Haematopoietic and Lymphoid Tissues 2016.[20] FISH analysis to detect *MYC*, *BCL2*, and *BCL6* rearrangements was performed at regional laboratories. PET-CT scans were centrally reviewed by an expert nuclear physician (G.J.C.Z.) from the HOVON Imaging Working Group.

Outcomes

The primary end point of the study was DFS, defined as the duration from study enrollment to relapse or death from any cause. Secondary end points included OS and the incidence of AEs, which were assessed according to the Common Terminology Criteria for AE version 4.0. AEs of special interest were immune-related AEs (irAEs) during checkpoint inhibitor treatment. Exploratory analyses included variables associated with outcomes such as gender, IPI score, cell of origin (COO), and HLA-I and PD-L1 expression, as well as the detection and dynamics of MRD.

Biomarker assessment. As part of the pathology review, COO was determined by IHC and the Hans algorithm.[20] HLA class I and PD-L1 expression were assessed using IHC according to standard procedures on whole tissue sections, using the polyclonal antibody beta-2 microglobuline (B2M) (1:800; DAKO, Glostrup, Denmark) and the monoclonal antibody PD-L1 (clone 22C3; 1:50; DAKO), respectively. Membranous B2M staining of tumor cells was considered positive for HLA class I expression, whereas PD-L1 positivity was defined as expression in >1% of tumor cells. PD-L1 expression was also scored as the percentage of tissue surface positivity, reflecting the abundance of tumor-associated macrophages in the tumor microenvironment.

Assessment for MRD. MRD assessment was performed using high-throughput sequencing of immunoglobulin genes of cell-free tumor DNA (ctDNA) with the clonoSEQ assay (Adaptive Biotechnologies Corporation, Seattle, WA).[21] High-throughput sequencing of immunoglobulin genes operates by amplifying and sequencing the variable, diversity, and joining segments of rearranged immunoglobulin receptor genes to quantify serum ctDNA content. Tumor clonotypes were initially identified in pretreatment tissue biopsy samples or, for relapsed patients, in biopsy samples taken upon relapse when pretreatment biopsies were not available. Subsequently, plasma samples for monitoring ctDNA were obtained after R-CHOP and after every 3 cycles of atezolizumab. During follow-up, samples were collected every 6 months, coinciding with CT scans.

Population-based control cohort. Data from the Netherlands Cancer Registry (NCR) were used to compose a population-based matched control cohort for comparing OS with the study population.[22] In summary, of 5803 patients diagnosed with DLBCL-not otherwise specified (NOS) between 2014 and 2018, a total of 718 patients met the HOVON 151 inclusion and exclusion criteria and were selected from the NCR (supplemental Figure 3). Subsequently, to account for baseline differences between the NCR and HOVON 151 patients, 1:1 propensity-score matching was performed with a caliper of 0.20 × standard deviations of the propensity score. The propensity scores for inclusion in the HOVON 151 trial were calculated, including age (as a continues variable), sex, and IPI score as covariables. Patients were excluded from matching if no matches were available with the same propensity score. Kaplan-Meier estimates were used to compare the 2-year DFS and 3-year OS rates. More detail on the analysis conducted with the population-based control cohort are described in the supplemental Methods.

Statistical analysis

The objective of the study was to determine whether atezolizumab maintenance might result in an improvement in DFS. For the sample size calculation, a 2-year DFS of <79% was considered insufficient, and a 2-year DFS of 89% was needed to warrant further research with atezolizumab in this patient population, corresponding to a hazard ratio of 0.49.[2,23] With 1-sided significance level of α equal to 0.05 and a power of $1 - \beta$ of 0.9, the target number of patients to be enrolled was 109. For the primary analysis of the study, the Kaplan-Meier estimate at 2 years was computed, and the null hypothesis was rejected if this estimate was ≥86%. For the efficacy of the maintenance treatment, OS was also analyzed as a secondary end point. The median and probabilities at 2 years were calculated with 90% and 95% confidence intervals (CIs). The safety of atezolizumab maintenance was evaluated by tabulating the (S)AEs, with special attention to the irAEs. Cox regression analysis and the associated likelihood test were used to explore the predictive value of a number of patient-related factors on survival. *P* values <.05 were considered significant. All analyses performed on the secondary end points had exploratory purposes only. All analyses were according to the intention-to-treat principle. For treatment adherence and toxicity data, it is critical to evaluate the entire cohort to provide a comprehensive understanding of the safety and tolerability of the treatment. For efficacy data, we also used the entire cohort to adhere to the intention-to-treat principle. However, to account for the impact of discordant histology cases, we performed a sensitivity analysis specifically focusing on the subgroup of patients with confirmed large BCL. Data were analyzed using Stata version 17 or higher. More details on statistical analysis are outlined in the supplemental Methods.

Results

From January 2019 to January 2022, a total of 109 patients were enrolled in the study. Upon inclusion, the median age was 64 years (interquartile range [IQR], 54-70), with males constituting 59% of the cohort (Table 1). Notably, most patients (80%) presented with stage IV disease, whereas 63% were classified as high-intermediate risk according to the IPI score. Treatment primarily consisted of 6 cycles of R-CHOP every 3 weeks, with 95% of the patients receiving this regimen and the remaining patients receiving

Table 1. Baseline clinical and treatment characteristics of 109 patients with high-risk DLBCL in CMR receiving atezolizumab consolidation

Baseline variable	No. of patients	%
Total	109	100
Sex		
Male	64	59
Female	45	41
Median age, IQR	64	(54-70)
Ann Arbor stage		
II	1	1
III	21	19
IV	87	80
IPI score		
3	69	63
4-5	40	37
Histology		
Large BCL		
DLBCL NOS	97	89
Transformed FL	4	4
Unclassifiable	3	3
EBV-positive DLBCL	2	2
Follicular lymphoma I-II	2	2
NLPHL	1	1
R-CHOP		
6 cycles	104	95
8 cycles	5	5
CNS prophylaxis		
MTX intrathecally	39	36
No prophylaxis	70	64

EBV, Epstein-Barr virus; FL, follicular lymphoma; MTX, methotrexate; NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma; NOS, not otherwise specified.

8 cycles. CNS prophylaxis was administered to 36% of patients. Upon central review, 89% of cases were confirmed as DLBCL NOS, 56% of which were classified as germinal center B-cell like and 44% as non–germinal center B-cell subtype, based on COO classification. Although 6 cases had an *MYC* rearrangement by FISH analysis, none of these cases harbored a *BCL2* and/or *BCL6* rearrangement. Of the remaining cases, 4% were identified as transformed follicular lymphomas, 2% as Epstein-Bar virus–positive DLBCL, 2% as low-grade follicular lymphoma, 1% as nodular lymphocyte-predominant Hodgkin lymphoma, and 3% were unclassifiable because material was lacking for review (Table 1). Central review of the PET-CT scans at inclusion, after R-CHOP, showed an increased fluorodeoxyglucose uptake (Deauville score, 4 or 5) in 7 of the 99 evaluable scans.

Atezolizumab treatment

The median time from the last cycle of R-CHOP until the start of atezolizumab treatment was 2.1 months (IQR, 1.8-2.5), with patients receiving a median of 14 cycles of atezolizumab (range, 1-18). Of the total cohort, 65% successfully completed the treatment protocol, with patient discontinuation occurring due to AEs (17%), relapse (10%), patients own choice (6%), or death (2%; Figure 1; supplemental Figure 2).

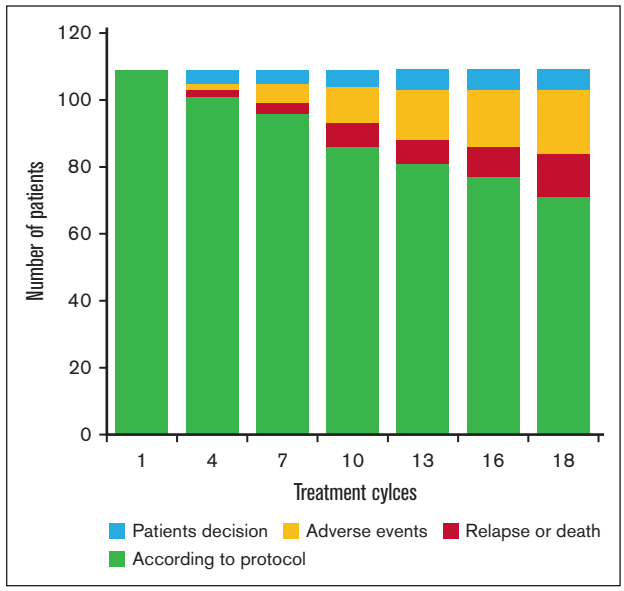

Figure 1. Depiction of adherence to the prespecified treatment protocol and delineation of factors contributing to noncompletion of atezolizumab consolidation in a cohort of 109 patients diagnosed with high-risk DLBCL in complete remission.

Outcomes

The median duration of follow-up for surviving patients was 36.4 months (range, 24-60). During this period, 15 relapses were observed, with a median time to relapse of 8.2 months (range, 0.4-32). Of these, 12 relapses occurred while patients were receiving atezolizumab. Two relapses occurred at immune sanctuary sites (brain and ocular) early during consolidation. Among the 7 patients not in CMR after R-CHOP, 3 relapses were observed. The 2-year DFS was 87.9% (90% CI, 81.5-92.1; Figure 2A). In an exploratory multivariable analysis considering IPI score (3 vs 4-5), age (<60 years vs ≥60 years), and treatment schedule (per protocol vs premature stop), no significant differences were found between patients who did and did not relapse (supplemental Table 1). In a sensitivity analysis in patients with large BCL only, the 2-year DFS was similar at 87.5% (90% CI, 81.0-91.9).

Among patients experiencing relapse, 13 received platinum-based salvage chemotherapy, with 77% achieving a second CMR and 53% receiving an autologous stem cell transplantation. Only 1 of these patients experienced a second relapse and subsequently received chimeric antigen receptor (CAR) T-cell therapy.

The 2-year OS for the entire study population was 96.3% (90% CI, 91.7-98.3; Figure 2B). Only 2 of the 4 deaths recorded were due to lymphoma, whereas the other 2 were attributed to unrelated causes (1 due to COVID-19 and 1 unknown cause).

Toxicity

Of the 109 patients, 79% experienced at least 1 AE, with a total of 257 AEs. AEs were predominantly grade 2 (75%), followed by grade 3 (21%) and grade 4 (3%). Among the most frequently

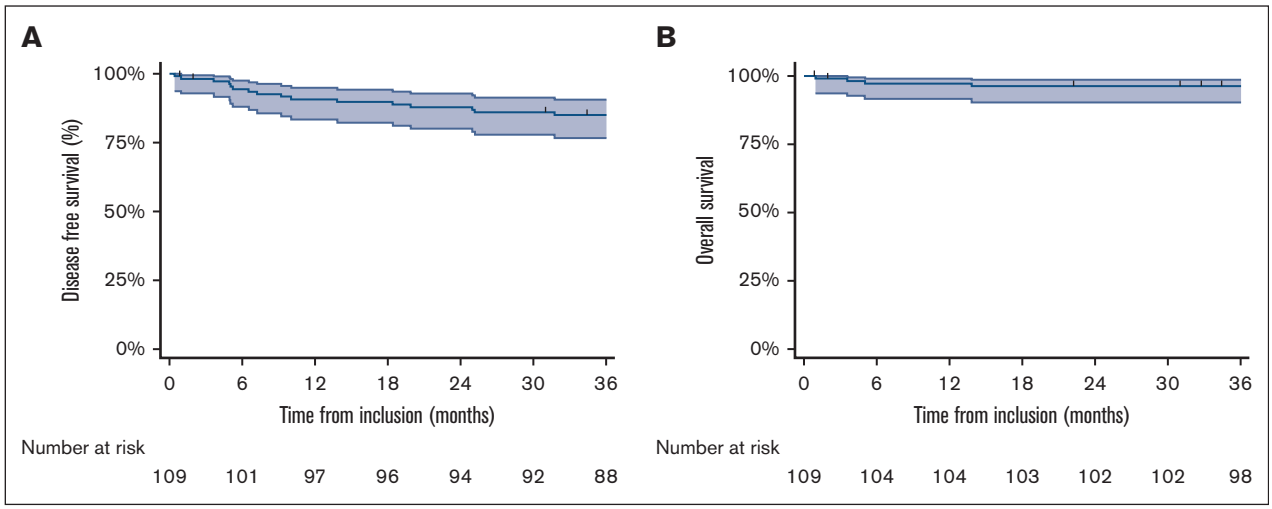

Figure 2. Survival curves for high-risk DLBCL patients treated with atezolizumab consolidation. Disease free survival (A) and overall survival (B) outcomes observed in 109 patients diagnosed with high-risk DLBCL who achieved complete remission and were treated with atezolizumab for up to 54 weeks.

reported AEs, infections, investigations, musculoskeletal/connective tissue disorders, and CNS disorders were prevalent within the System Organ Classes (Figure 3; supplemental Table 2). Atezolizumab was directly associated with 7% of the AEs, whereas an additional 36% were possibly related to its administration. A total of 41 serious AEs (SAEs) were reported among 27 patients, most commonly infections (41.5%). Nearly half of the infections were due to COVID-19.

Among the 109 patients, 18.3% developed an irAE, with a median time to onset of 2.9 months (IQR, 1.4-4.7). The most common irAEs observed were endocrinopathies (9.2%), ocular toxicities (2.8%), cutaneous reactions (1.8%), and colitis (1.8%; Table 2). Although most irAEs were grade 1 to 2, a total of 5 patients (4.5%) experienced a grade 3 to 4 irAE. The median duration of irAEs was 2.7 months (IQR, 0.7-11.3). irAE events resolved in 18 of the 20 patients (90%), with 6 patients (27%) requiring systemic steroids. No relapses were observed among the 6 patients requiring systemic steroids.

Exploratory analysis

Tumor analysis, conducted among a subset of patients with sufficient tumor tissue available for additional IHC (n = 59), revealed membranous PD-L1 and B2M expression on the tumor cells in 6.7% and 27% of patients, respectively (supplemental Figure 3). PD-L1 expression in the tumor microenvironment varied, with 18% showing 0% to 1% expression, 60% exhibiting 1% to 20%

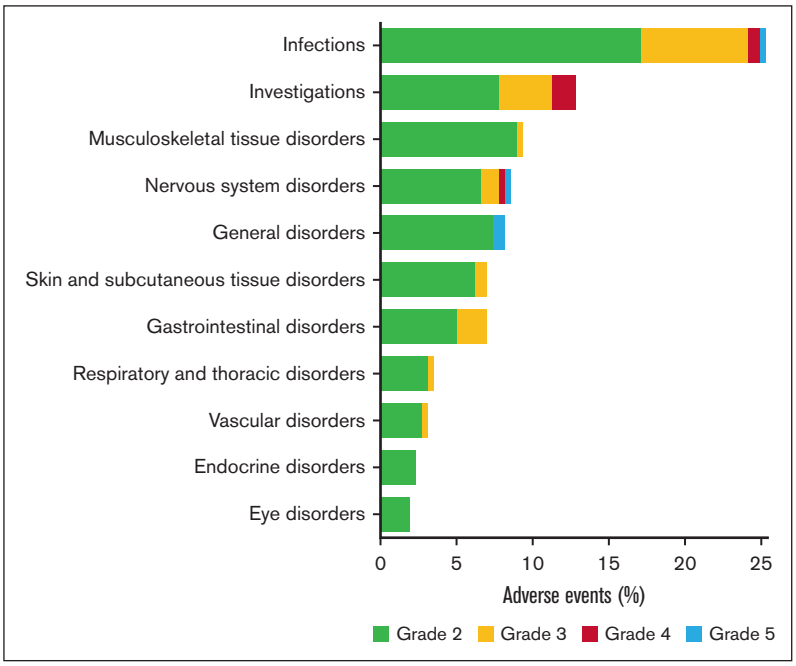

Figure 3. Representation of AEs occurring at a prevalence of >2% among 109 patients diagnosed with high-risk DLBCL in complete remission, treated with atezolizumab for up to 54 weeks.

Table 2. irAEs according to Common Terminology Criteria for AE grading version 5.0 among 109 patients with high-risk DLBCL in CMR receiving atezolizumab consolidation

Organ system	Total n (%)	Grade 1-2 n (%)	Grade 3-4 n (%)
Endocrinopathies	10 (9.2)	7 (6.4)	3 (2.8)
Ocular toxicities	3 (2.8)	3 (2.8)	0 (0)
Colitis	2 (1.8)	1 (0.9)	1 (0.9)
Cutaneous	2 (1.8)	2 (1.8)	0 (0)
Hepatitis	1 (0.9)	1 (0.9)	0 (0)
Pneumonitis	1 (0.9)	1 (0.9)	0 (0)
Neurological	1 (0.9)	0 (0)	1 (0.9)
Total	20 (18.3)	15 (13.8)	5 (4.5)

expression, and 22% having >20% expression. PD-L1 and B2M expression by IHC was not correlated with COO (supplemental Table 3). Neither COO nor PD-L1 and B2M expression was correlated with DFS (supplemental Table 4).

MRD

Of the 109 patients, 70 had sufficient-quality tumor biopsies available for determining tumor clonotypes. In 9 of 70 patients, sequencing of the tumor biopsy failed (n = 3) or plasma samples did not calibrate due to low B-cell count (n = 6), leaving 61 patients (56%) for MRD analysis. Among the 15 patients who eventually experienced relapse, a tumor clonotype (identified in pretreatment biopsies, n = 9; or identified in relapse biopsy, n = 1) was available in 10 patients. After R-CHOP treatment, all 51 patients without a relapse tested negative for MRD. Of the 10 patients with a relapse and a tumor clonotype determined, only 1 patient had a detectable clonotype after R-CHOP. During sequential follow-up sampling of the 10 patients who did relapse, a positive MRD signal was detected in 7 of 10 patients before clinical relapse. These MRD signals were detected as early as 4 to 104 weeks before clinical relapse (Figure 4). In 2 patients, MRD became positive only after clinical relapse, and in 1 patient, MRD could not be detected despite clinical relapse. The median time between MRD signal and relapse was 20 weeks. No additional MRD analysis was performed in patients without a relapse.

Matched population-based control cohort

To delineate the effect of atezolizumab consolidation on OS, a population-based 1:1 matched control cohort analysis was performed. After matching, 5 patients from the HOVON 151 trial were excluded due to no overlap of the propensity scores with NCR patients. In total, 208 patients treated with and without atezolizumab (104 in each arm) were included. Distributions of sex, Ann Arbor stage, and IPI score were similar between the atezolizumab and control cohort (supplemental Table 5). The median follow-up in

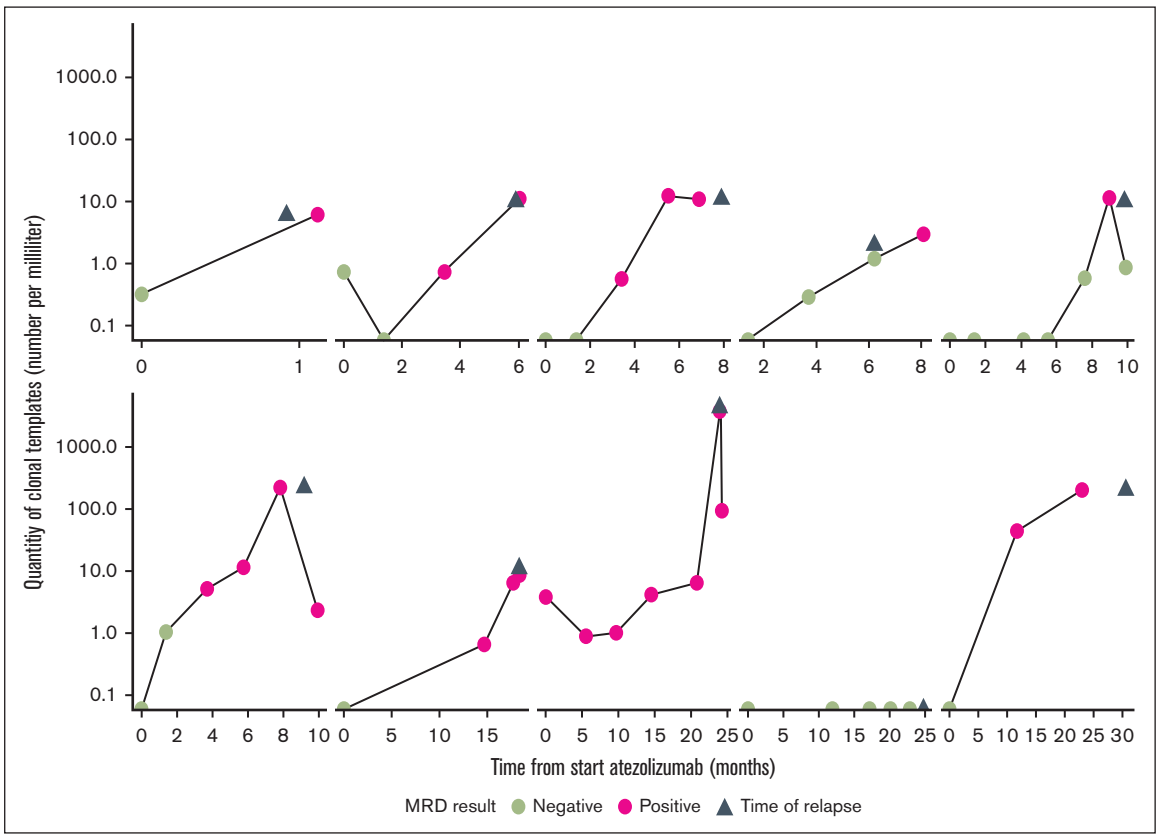

Figure 4. Temporal dynamics of MRD in 10 patients with high-risk DLBCL who experienced relapse during or after atezolizumab treatment. MRD assessment was performed using the clonoSEQ assay on cell-free DNA samples. MRD status is determined as either positive or negative based on the limit of detection (LOD) of the assay, which is individually calculated for each sample. The LOD represents the lowest level of residual tracked templates that can be reliably detected in at least 95% of samples.

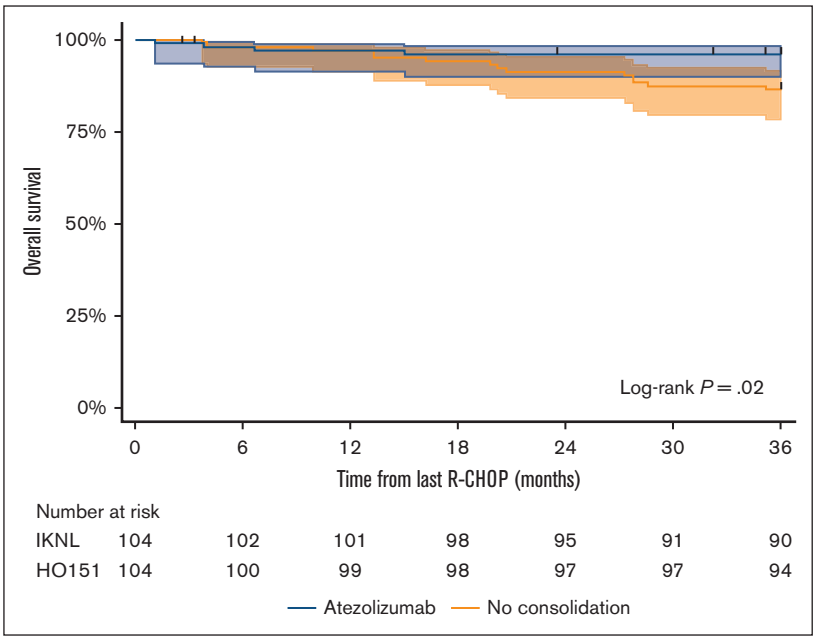

Figure 5. OS of patients diagnosed with high-risk DLBCL treated with atezolizumab consolidation and a 1:1 matched population-based control group from the NCR. IKNL, Netherlands Comprehensive Cancer Organization; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone.

the control group was 80 months (range, 4-118). In this comparison, the 2-year DFS rate did not significantly differ between the atezolizumab cohort (88%; 95% CI, 80-93) and the control cohort (85%; 95% CI, 76-90; $P = .42$; supplemental Figure 5). The atezolizumab cohort had a superior 3-year OS rate of 96% (95% CI, 90-99) compared to 87% (95% CI, 78-92) for the control cohort ($P = .02$; Figure 5).

Discussion

This is, to our knowledge, the first study to assess the utilization of atezolizumab as a consolidation regimen for high-risk patients with DLBCL after first-line R-CHOP therapy. Atezolizumab consolidation showed an encouraging 2-year DFS rate of 87.9%, effectively fulfilling the primary end point of the study. Furthermore, the high 2-year OS rate of 96.3% is remarkable, with most patients responding to salvage chemotherapy in case of relapse. Achieving such a high OS rate is particularly noteworthy for high-risk patients with DLBCL, because this population typically faces a poor prognosis.[24]

Despite major advances in the treatment of R/R DLBCL, including CAR T-cell therapy and bispecific monoclonal antibodies, long-term remissions are achieved in only approximately half of these patients.[25,26] This underscores the pressing need to improve first-line treatments, particularly for high-risk patients. Nonetheless, most first-line studies in DLBCL, involving intensified chemotherapy or the addition of agents such as ibrutinib, bortezomib, and lenalidomide to R-CHOP, have failed to improve outcomes.[27-30] Although the addition of polatuzumab vedotin to R-CHOP and lenalidomide consolidation has shown increased progression-free survival rates, these strategies did not result in OS benefit.[5,31] The findings of this study suggest that atezolizumab consolidation may be a potential strategy for mitigating relapse risk by targeting tumor cells at the MRD level to provoke immune engagement.

The duration of consolidation in this study was set at 12 months, consistent with other consolidation studies with checkpoint inhibition in nonhematologic malignancies.[18] However, a notable proportion of patients did not complete consolidation treatment, with 17% discontinuing prematurely due to AEs. This dropout rate is close to the range of 10% to 15% in the adjuvant use of checkpoint inhibitors in nonhematologic malignancies.[18] The impact of these premature discontinuations on efficacy remains uncertain, given the undetermined optimal duration of checkpoint inhibition consolidation. In the exploratory analysis, the duration of treatment was not associated with outcomes. Across trials, the incidence of checkpoint inhibitor–induced grade 3 to 4 irAEs was 5%.[18] The incidence of grade 3 to 4 irAEs in this study was 4.5%, indicating that treatment-induced side effects are in line with expectations. Most of these irAEs were manageable, with most resolving during treatment. The most common SAEs were infections, with nearly half attributed to COVID-19 infections. Unfortunately, 1 patient succumbed to COVID-19. As a result, the SAE rate in this trial (starting in 2019) was heavily affected by the COVID-19 pandemic.

The encouraging survival rates of patients in this study (compared to a historical and population-based matched control cohort) raise the question of how to identify patients who benefit most from consolidation with checkpoint inhibitors. One aspect of this strategy could involve better patient selection by improved MRD detection without solely relying on PET-CT imaging. The hypothesis of this study was that MRD detection before consolidation treatment could provide such insight. Unfortunately, one of the limitations of the clonoSEQ assay in the study was the inability to determine tumor clonotypes in 40% of patients due to a lack of available tumor tissue or technical failure. Additionally, the assay showed limited sensitivity in detecting MRD after R-CHOP treatment, with only 1 patient testing positive after R-CHOP, including those who eventually experienced relapse. More recently, targeted next-generation sequencing methods of cell free DNA of

lymphoma-associated genes show potential for improved MRD detection at the end of treatment.[21,32] Hence, using ctDNA-based techniques together with PET-CT imaging may better discern which patients derive the most benefit from consolidation strategies and improve the risk-benefit ratio. However, it is essential to note that these plasma-based analyses have yet to undergo validation in prospective clinical trials to inform decision-making.[33]

Moreover, alongside improving MRD detection techniques, another crucial aspect in optimizing consolidation therapy involves selecting patients based on tumor characteristics. Atezolizumab's efficacy may be influenced by biomarkers such as PD-L1 and HLA expression, but the correlation of IHC with outcome in other cancers is generally limited.[34,35] In this study, COO, PD-L1, and HLA expression were not correlated with outcome, although the number of events were low. It remains speculative whether specific DLBCL subtypes, such as the recently described primary mediastinal B-cell lymphoma-like DLBCL, might be more susceptible to checkpoint inhibitors, warranting further investigation.[36]

Most relapses occurred within 12 months: a time frame typically associated with a very poor prognosis and death due to lymphoma.[24] Surprisingly, therefore, the OS in the study was excellent, with only a small proportion of deaths attributable to lymphoma. Most patients experiencing relapse were treated with salvage chemotherapy. Notably, access to CAR T-cell treatment in the Netherlands was still limited at the time of the study. It is remarkable that 90% of relapsed patients achieved a second CMR, with only infrequent secondary relapses. Similar observations have recently been reported in Hodgkin lymphoma, in which checkpoint inhibition after relapse has been shown to resensitize tumors to chemotherapy.[37,38] Nonetheless, the exact mechanism behind this phenomenon remains poorly understood.

This study has several limitations that should be acknowledged. First, the single-arm design lacks a comparator arm, which restricts the ability to directly evaluate the efficacy of atezolizumab consolidation against standard-of-care treatments. To mitigate this, we attempted a 1:1 matching with population-based controls; however, such analyses are inherently limited by potential confounding factors and selection bias. Second, consolidation strategies are not applicable to patients with primary refractory disease, representing an unmet medical need. Third, although MRD assessment was used as a surrogate end point for relapse risk, the prognostic value of MRD in DLBCL is still being validated, and its correlation with long-term clinical outcomes requires further study. Finally, similar to many phase 2 trials in DLBCL, the translation of positive results into a phase 3 setting remains uncertain, given the historical challenges in demonstrating survival benefits in larger, randomized trials. Future studies addressing these limitations are essential to confirm the utility of atezolizumab consolidation in high-risk DLBCL. However, the feasibility of conducting a randomized study faces significant challenges, including reduced commercial interest in atezolizumab and rapid advancements in DLBCL therapy. The therapeutic landscape for DLBCL is evolving, marked by recent provisional approvals of novel therapies such as polatuzumab vedotin, loncastuximab tesirine, tafasitamab, CAR T-cell therapy, and bispecific monoclonal antibodies.[25,26,39-41] As MRD detection techniques advance, consolidation strategies are set to play a more significant role in DLBCL treatment. The potential utility of checkpoint inhibitors as consolidation agents or in combination therapies remains an area of investigation. For instance, atezolizumab is currently under evaluation in combination with glofitamab (ClinicalTrials.gov identifier: NCT03533283) and CAR T-cell therapy (ClinicalTrials.gov identifier: NCT02926833), underscoring the continuous evolution and diversification of treatment strategies in this field.

Conclusion

In summary, the incorporation of atezolizumab consolidation significantly enhanced DFS for patients with high-risk DLBCL compared to historical controls. Additionally, the significantly increased 2-year OS rate of 96%, compared to a population-based matched control cohort, represents one of the most promising outcomes observed for high-risk patients. These findings suggest the potential of atezolizumab as a consolidation regimen after first-line therapy. Further research and clinical trials are necessary to validate these results and reconsider the potential role of checkpoint inhibition in the management of DLBCL.

Acknowledgments

The authors acknowledge all participating patients, their families, the members of the data safety and monitoring board, and Roche for their support. The authors thank HOVON Clinical Operations and the HOVON Pharmacovigilance Department at Erasmus MC, The Netherlands, for their efforts and support to optimize data acquisition and reviewing. The authors offer special thanks to Sumulai Westen, Evelien Drenth, and Liping Fu for their support of the central laboratory.

This trial was sponsored by Hoffmann-La Roche, which provided atezolizumab and supported the study financially.

Hoffmann-La Roche was not involved in the design of the trial, data analysis, or manuscript preparation.

Authorship

Contribution: M.N. and J.M.Z. designed the protocol and were involved in data collection and interpretation, and patient accrual, enrollment, and treatment; D.A.C. provided statistical support and performed statistical analysis; A.D. and D.d.J. conducted central pathology review; G.J.C.Z. conducted central imaging review; J.A.A.B. and M.B. performed the matched-control cohort analysis; J.A.A.B. conducted the analysis of high-throughput sequencing of immunoglobulin genes; E.B. supervised the central laboratory; H.V.-W. performed central study coordination; S.J.v.d.B. handled central data management; D.E.I., D.D., G.J.C.Z., M.R.N., Y.S., V.V., M.O., R.F., R.E.B., R.S.B., K.W., L.N., J.S.P.V., R.J.W.v.K., W.E.T., S.S., M.W.v.d.P., E.d.J., M.F.D., L.S., A.B., A.G., R.S.v.R., O.V., J.K.D., T.J.F.S., and M.H.S. were involved in patient accrual, enrollment, and treatment; R.M. and H.J. served as consulting physicians for immune-related adverse events; M.N., D.A.C., J.M.Z., J.A.A.B., and M.B. directly accessed and verified the underlying data; and all authors had full access to all data in the manuscript and had final responsibility for the decision to submit for publication.

Conflict-of-interest disclosure: M.N. reports research support from Takeda; travel support from AbbVie; and participation in data safety monitoring board or advisory board for AbbVie. M.C. declares research support from Bristol Myers Squibb, Gilead, and

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