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ORIGINAL ARTICLE

Safety and efficacy of durvalumab with R-CHOP or R^2-CHOP in untreated, high-risk DLBCL: a phase 2, open-label trial

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Abstract

Patients with high-risk diffuse large B-cell lymphoma (DLBCL) have poor outcomes following first-line cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab (R-CHOP). Evidence shows chemotherapy and immune checkpoint blockade can increase antitumor efficacy. This study investigated durvalumab, a programmed death-ligand 1 inhibitor, combined with R-CHOP or lenalidomide + R-CHOP (R^2-CHOP) in newly diagnosed high-risk DLBCL. Patients received durvalumab 1125 mg every 21 days for 2–8 cycles + R-CHOP (non-activated B-cell [ABC] subtype) or R^2-CHOP (ABC), then durvalumab consolidation (1500 mg every 28 days). Of 46 patients, 43 received R-CHOP and three R^2-CHOP. All patients had the high-risk disease; 14 (30.4%) and eight (17.4%) had double- or triple-hit DLBCL, respectively. Following induction, 20/37 (54.1%) patients receiving durvalumab + R-CHOP achieved complete response (CR), and seven (18.9%) partial response (PR); 25 (67.6% [95% CI 50.2–82.0]) continued to consolidation and were progression-free at 12 months. Among efficacy-evaluable patients with double- or triple-hit DLBCL ($n = 12$), five achieved CR and five PR. Adverse events were generally consistent with R-CHOP. Correlative analyses did not identify conclusive biomarkers of response. Durvalumab + R-CHOP is feasible in DLBCL with no new safety signals, but the combination provided no greater benefit than R-CHOP.

Keywords Durvalumab · Diffuse large B-cell lymphoma · High risk · R-CHOP

Justine Dell'Aringa, Nurgul Kilavuz and Oliver Manzke: At the time of the study.

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Introduction

Patients with high-risk diffuse large B-cell lymphoma (DLBCL) have poor clinical outcomes and limited treatment options. Gene expression profiling subdivides DLBCL into two biologically distinct and prognostically important entities—germinal center B-cell (GCB) DLBCL and activated B-cell (ABC) DLBCL [1]. Patients with ABC-type DLBCL have worse overall survival (OS) than those with the GCB (non-ABC) subtype, regardless of clinical risk status, when treated with standard chemotherapy, including rituximab-containing regimens [1, 2]. A cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab (R-CHOP) regimen containing lenalidomide (R^2-CHOP) has been evaluated in patients with ABC-type DLBCL, but evidence of its efficacy remains inconclusive [3–5]. Therefore, treatment options are limited for patients with DLBCL, and novel treatments that provide improved outcomes are needed in this setting.

Increased activation of the programmed death receptor (PD-1)/programmed death-ligand 1 (PD-L1) immune checkpoint pathway may suppress the antitumor responses in B-cell lymphomas [6]. PD-L1 tumor expression is correlated with worse OS in DLBCL and was found to be an independent prognostic factor based on multivariate analyses [7]. In addition, elevated levels of soluble PD-L1 at diagnosis are an adverse prognostic factor, independent of the International Prognostic Index (IPI), and are associated with inferior OS [8].

Preclinical evidence also suggests that chemotherapy and radiotherapy may upregulate PD-L1 expression on tumor cells [9, 10]; therefore, combining immune checkpoint inhibitors with chemotherapy may enhance tumor-specific immune responses [11, 12]. Durvalumab is a human IgGκ monoclonal antibody engineered to prevent complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity [13]. It has high affinity and selectivity for PD-L1, blocking its interaction with PD-1 and CD80 and inducing T cell-mediated tumor cell killing [14] and has shown promising clinical activity and safety in several tumor types [15].

This phase 2 study (NCT03003520) explored clinical activity and evaluated the safety and tolerability of durvalumab in combination with R-CHOP or R^2-CHOP followed by durvalumab consolidation therapy in previously untreated patients diagnosed with high-risk DLBCL. An exploratory biomarker analysis was performed to assess the expression of PD-L1 and interferon (IFN)-gamma gene signature and the correlation with response to treatment.

Materials and methods

Study design

This phase 2, two-arm, open-label study assessed the activity, safety, and tolerability of durvalumab + R-CHOP (Arm A; non-ABC subtype) or R^2-CHOP (Arm B; ABC subtype), followed by durvalumab consolidation in newly diagnosed patients with high-risk DLBCL (Fig. 1). The study included an initial safety run-in part to determine the tolerability of the durvalumab + R-CHOP combination in the first 10 patients who received at least one cycle of treatment, followed by an expansion phase. A total of 19 sites in the United States and Europe were included. The study was in compliance with the World Medical Association Declaration of Helsinki and the International Council for Harmonisation E6 Guideline for Good Clinical Practice. Approval was obtained from the institutional review board or research ethics board at each site and all patients provided informed consent.

Patient selection criteria

Eligible patients aged ≥ 18 years had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, had received no prior anti-lymphoma treatment, and had a life expectancy ≥ 6 months. Patients had histologically confirmed CD20+ DLBCL with the following World Health Organization subclassifications [16]: not otherwise specified; associated with chronic inflammation; Epstein-Barr virus positive of the elderly; or T-cell/histiocyte rich. Patients were enrolled only if they had high-risk DLBCL, defined as Ann Arbor stage III–IV or stage II with bulky disease (≥ 7.0 cm) and intermediate-high or high disease risk (IPI ≥ 3 or National Comprehensive Cancer Network [NCCN]-IPI ≥ 4).

Study treatment

All patients received one cycle of induction therapy with durvalumab + R-CHOP. Following cell-of-origin (COO) analysis, patients were allocated to Arm A or Arm B from cycle 2 onward based on their DLBCL subtype as determined by the NanoString Lymphoma subtyping test assay, which was based on the NanoString 20-gene assay (NanoString Technologies, Seattle, WA, USA) using formalin-fixed paraffin-embedded (FFPE) tissue [17]. Following a partial clinical hold by the US Food and Drug Administration on trials combining checkpoint inhibitors and immunomodulatory agents in September 2017 due to identified risks associated with these regimens, enrollment of new

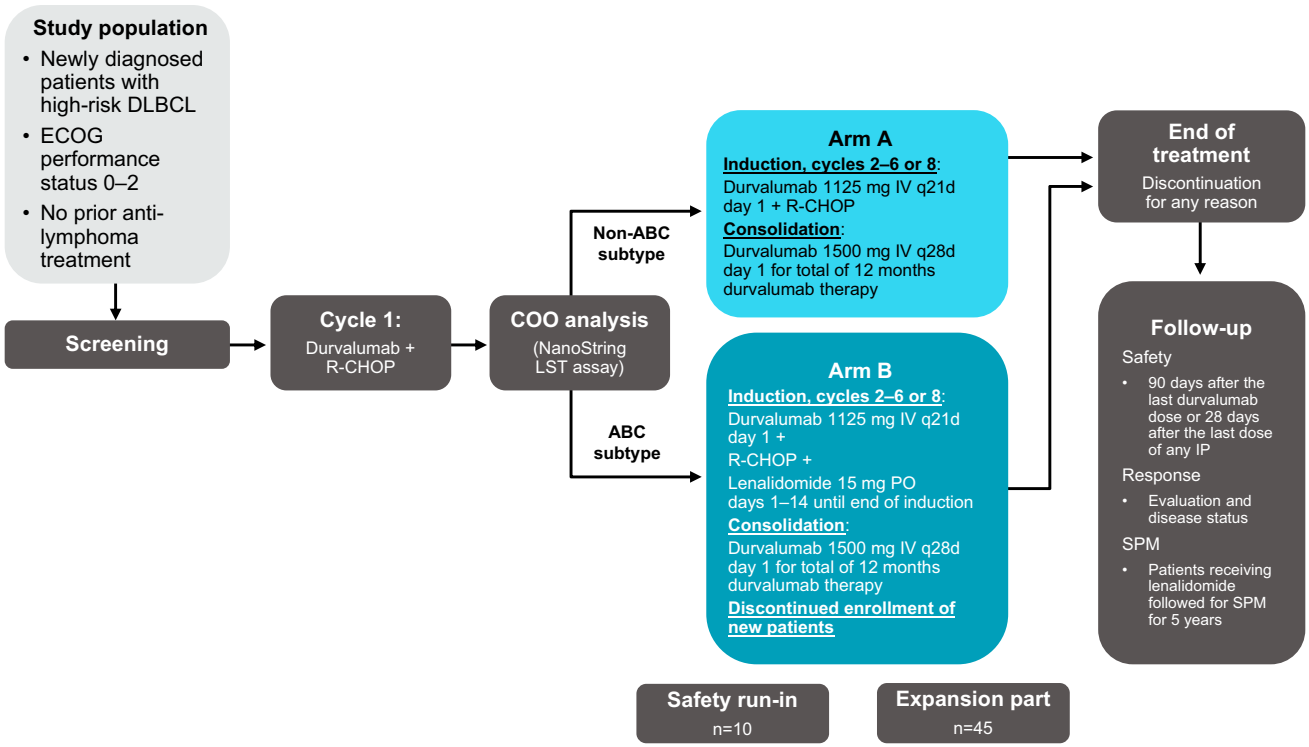

Fig. 1 Study design. After the US FDA partial clinical hold, enrollment of new patients into Arm B was discontinued. If receiving a clinical benefit, at the discretion of the investigator, patients could continue treatment in Arm B after being reconsented. Any newly enrolled patient with DLBCL of ABC COO subtype after US FDA partial clinical hold continued induction therapy on Arm A after cycle 1. *ABC* activated B cell; *COO* cell of origin; *IP* investigational product; *IV* intravenous; *LST* lymphoma subtyping test; *PO* orally; *q21d* every 21 days; *q28d* every 28 days; *R-CHOP* cyclophosphamide, doxorubicin, vincristine, and prednisone in combination with rituximab; *SPM* secondary primary malignancy

patients into the R^2-CHOP arm was discontinued, and newly enrolled patients with the ABC subtype continued induction therapy with R-CHOP after cycle 1. Patients with the ABC subtype who were already treated with R^2-CHOP could continue treatment if, per the judgment of the investigator, they received clinical benefit and after being reconsented.

Study treatment in both arms was administered in 21-day cycles during induction and 28-day cycles during consolidation. Patients in Arm A (durvalumab + R-CHOP) received durvalumab 1125 mg intravenously (IV) on day 1 of each 21-day cycle plus 6–8 cycles of R-CHOP (IV rituximab, doxorubicin, vincristine, and cyclophosphamide on day 1; daily oral/IV prednisone/prednisolone on days 1–5). In Arm B (durvalumab + R^2-CHOP), patients received durvalumab 1125 mg IV on day 1 of each 21-day cycle plus 6–8 cycles of R-CHOP as in Arm A plus daily oral lenalidomide 15 mg on days 1–14 from the cycle following COO determination until end of induction therapy (cycle 6 or cycle 8) or starting from cycle 1 if the ABC subtype was identified before cycle 1, day 1. Consolidation treatment with durvalumab was administered following induction therapy in patients who achieved a complete response (CR) or partial response (PR) and consisted of durvalumab 1500 mg IV administered on day 1 of each 28-day cycle for up to a total of 12 months from the start of induction therapy. Treatment was administered until disease progression, unacceptable toxicity, or treatment completion. Patients at high risk for central nervous system (CNS) involvement received CNS prophylaxis with intrathecal methotrexate or cytarabine. After treatment completion or discontinuation, patients were followed for up to 5 years after the enrollment of the last patient until the first progression or start of new anti-lymphoma therapy.

Endpoints and assessments

Efficacy

The primary efficacy endpoint was complete response rate (CRR) assessed by integrated fluorodeoxyglucose (FDG)-positron emission tomography (PET) scans-computed tomography (CT) at the end of induction therapy (6–8 cycles). Responses were classified per 2014 International Working Group Response Criteria for Non-Hodgkin's Lymphoma [18]. A bone marrow biopsy and aspirate confirmed suspected CRs (within 28 days), except in patients who had no evidence of lymphomatous marrow involvement during

screening. In addition, if FDG-PET-CT was performed and confirmed FDG-negative CR, no bone marrow biopsy/aspirate was required. Secondary endpoints were the percentage of patients who continued consolidation therapy (completing 6–8 induction cycles and at least one consolidation cycle) and response in biomarker-defined subgroups. Other exploratory efficacy endpoints included PFS at 12 and 24 months and CRR at the end of treatment.

Safety

Secondary endpoints included assessment of treatment-emergent adverse events (TEAEs), coded according to the Medical Dictionary for Regulatory Activities and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. Durvalumab-related adverse events (AEs) of special interest involved those with potential inflammatory/immune-mediated mechanism(s), including diarrhea/colitis, pneumonitis/interstitial lung disease, hepatitis and increases in transaminases, endocrinopathies, dermatitis/rash and pruritus, nephritis and increases in serum creatinine, neuromuscular toxicity such as myasthenia gravis and Guillain-Barré syndrome, and pancreatitis. Other AEs of special interest were infusion-related reactions, allergic reactions, tumor lysis syndrome, and myelosuppression.

Biomarker analysis

Prespecified biomarkers of the tumor microenvironment that have been shown to correlate with response to durvalumab were examined [19, 20]. The following cell surface markers or cell types were quantified as continuous values by immunohistochemistry (IHC) analysis of baseline (pretreatment) tumor biopsy specimens: total PD-L1 (percentage of total cells staining for PD-L1), tumor PD-L1 (percentage of tumor cells staining for PD-L1), and CD8 + T cells (percentage of total cells staining for CD8 and CD3). Baseline tumor biopsies were analyzed via whole transcriptome RNA-sequencing, and the IFN-gamma gene expression signature score (IFN-gamma score) [19], a continuous value, was calculated as follows: for each sample, raw sequencing data (in FASTQ format) were aligned to the human transcriptome, and expression values for each gene were summarized as the $\log_2$ of 1 plus the tags per million. The mean of the expression values for four genes (*IFN-gamma*, *CD274*, *CXCL9*, and *LAG3*), which comprise the IFN-gamma gene expression signature described by Higgs et al. were used as the IFN-gamma score for each sample [19].

Biomarker thresholds were defined based on internal reference datasets. For IHC-based biomarkers, a commercial DLBCL cohort of 70 FFPE biopsies was obtained and stained for CD8 and PD-L1. The median value of each biomarker readout was chosen as the threshold between high and low, as follows: 774 CD8 cells/mm^2, 13.8% of total cells positive for PD-L1, 6.2% of tumor cells positive for PD-L1. For the IFN-gamma RNA-sequencing signature, a commercial cohort of 210 DLBCL samples was analyzed using the same library preparation and analysis methods described above; the median IFN-gamma score of 3.28 was used as the threshold between high and low.

IHC was performed by Geneuity Clinical Research Services (Maryville, TN) using CD8 and PD-L1 on separate slides. CD8 was quantified as a cell density as the number of positive cells per mm^2. PD-L1 was quantified as a cell density of the number of PD-L1-positive cells per mm^2, and also a visual estimate of the percent of tumor cells that are positive for PD-L1. The antibodies used were CD8 (4B11) and PD-L1 (SP142; Spring Bioscience, Pleasanton, CA, USA).

Statistical analysis

The efficacy-evaluable population included all patients who received at least one cycle of assigned treatment, had a baseline assessment by CT scan, and had at least one post-baseline tumor-response assessment. The safety population included all patients who received at least one dose of durvalumab. The IHC and RNA biomarker-analysis sets included patients who completed at least four cycles of their assigned treatment, had a baseline assessment by CT scan, tumor-response assessment at or later than the fourth cycle, and pretreatment baseline IHC or RNA-sequencing assessments, respectively. Samples with low-quality IHC data or whole transcriptome data were excluded.

A sample size of 45 patients (with approximately 40 in the efficacy-evaluable population) was based on historical control data of CRR of 55% at completion of induction with R-CHOP and 75% at the end of induction with durvalumab + R-CHOP. A sample of 40 patients provided approximately 71% power to reject the null hypothesis that the CRR at the end of induction is < 55%. Based on a hierarchical testing strategy and the assumption that the rate of continuation to consolidation is 85%, 40 patients provided 43% power to reject the null hypothesis that the rate of continuation to consolidation is < 70%.

The CRR at the end of induction therapy and rate of continuation to consolidation therapy were summarized with two-sided 95% CIs based on the Clopper-Pearson approach. Differences in biomarker expression between responders and nonresponders at the end of induction therapy were analyzed with the area under the receiver operating characteristics curve and *P* value and Fisher's exact test of the contingency table using prespecified biomarker thresholds. All authors had full access to the study data and accept the responsibility to submit it for publication.

Results

Demographics and baseline characteristics

Between March 9, 2017, and March 13, 2018, a total of 46 patients with high-risk DLBCL were enrolled, with 43 receiving R-CHOP and three receiving R^2-CHOP. Patients were enrolled in the United States ($n=22$), Austria ($n=15$), Denmark ($n=8$), and the United Kingdom ($n=1$). All patients had confirmed high-risk disease. The majority had adverse prognostic risk factors, including Ann Arbor stage IV (76.1%), bulky disease (50.0%), high-intermediate/high IPI score (69.6%), and high-intermediate/high NCCN-IPI score (58.7%) (Table 1). The population included patients with low IPI or low NCCN-IPI score because some patients were enrolled based on either a high IPI score or high NCCN-IPI score; however, both scores were not available for all enrolled patients. Double- and triple-hit DLBCL were present in 30.4% and 17.4% of all patients, respectively. The median time from diagnosis with DLBCL to first treatment was 22 (range, 6–67) days in the durvalumab + R-CHOP arm and 16 (range 15–35) days in the durvalumab + R^2-CHOP arm.

Disposition

As of the data cutoff date (August 2, 2018), 19 patients in Arm A were still receiving treatment, one patient had completed treatment, and 23 (53.5%) had discontinued treatment, primarily due to progressive disease ($n=7$, 16.3%) or AEs ($n=6$, 14.0%) (Fig. 2). Of the three patients in Arm B, 2 had completed treatment and one had discontinued treatment due to progressive disease. Among all patients who discontinued treatment, 12 discontinued during induction, six after completing induction, and six during consolidation. Median duration of follow-up was 6.2 months in Arm A and 14.0 months in Arm B.

Table 1 Demographics and baseline characteristics (safety population)

	Durvalumab + R-CHOP ($n=43$)	Durvalumab + R^2-CHOP ($n=3$)	Overall ($n=46$)
Age, median (years)	62.0	66.0	62.5
Male, no. (%)	26 (60.5)	2 (66.7)	28 (60.9)
ECOG performance status, no. (%)			
0	16 (37.2)	2 (66.7)	18 (39.1)
1	19 (44.2)	0 (0)	19 (41.3)
2	8 (18.6)	1 (33.3)	9 (19.6)
Time from diagnosis to first study treatment, median (days)	22	16	22
Ann Arbor stage at diagnosis, no. (%)			
Stage III	9 (20.9)	2 (66.7)	11 (23.9)
Stage IV	34 (79.1)	1 (33.3)	35 (76.1)
Bulky disease (tumor diameter ≥ 7.0 cm), no. (%)	21 (48.8)	2 (66.7)	23 (50.0)
Molecular abnormalities, no. (%)			
Double-hit (BCL2 or BCL6 with MYC rearrangement)	13 (30.2)	1 (33.3)	14 (30.4)
Triple-hit (BCL2 and BCL6 and MYC rearrangement)	7 (16.3)	1 (33.3)	8 (17.4)
IPI score, no. (%)			
Low	0 (0)	0 (0)	0 (0)
Low-intermediate	9 (20.9)	0 (0)	9 (19.6)
High-intermediate	21 (48.8)	0 (0)	21 (45.7)
High	9 (20.9)	2 (66.7)	11 (23.9)
Missing	4 (9.3)	1 (33.3)	5 (10.9)
NCCN-IPI score, no. (%)			
Low	1 (2.3)	0 (0)	1 (2.2)
Low-intermediate	13 (30.2)	0 (0)	13 (28.3)
High-intermediate	21 (48.8)	0 (0)	21 (45.7)
High	4 (9.3)	2 (66.7)	6 (13.0)
Missing	4 (9.3)	1 (33.3)	5 (10.9)

ECOG Eastern Cooperative Oncology Group, *IPI* International Prognostic Index, *NCCN* National Comprehensive Cancer Network

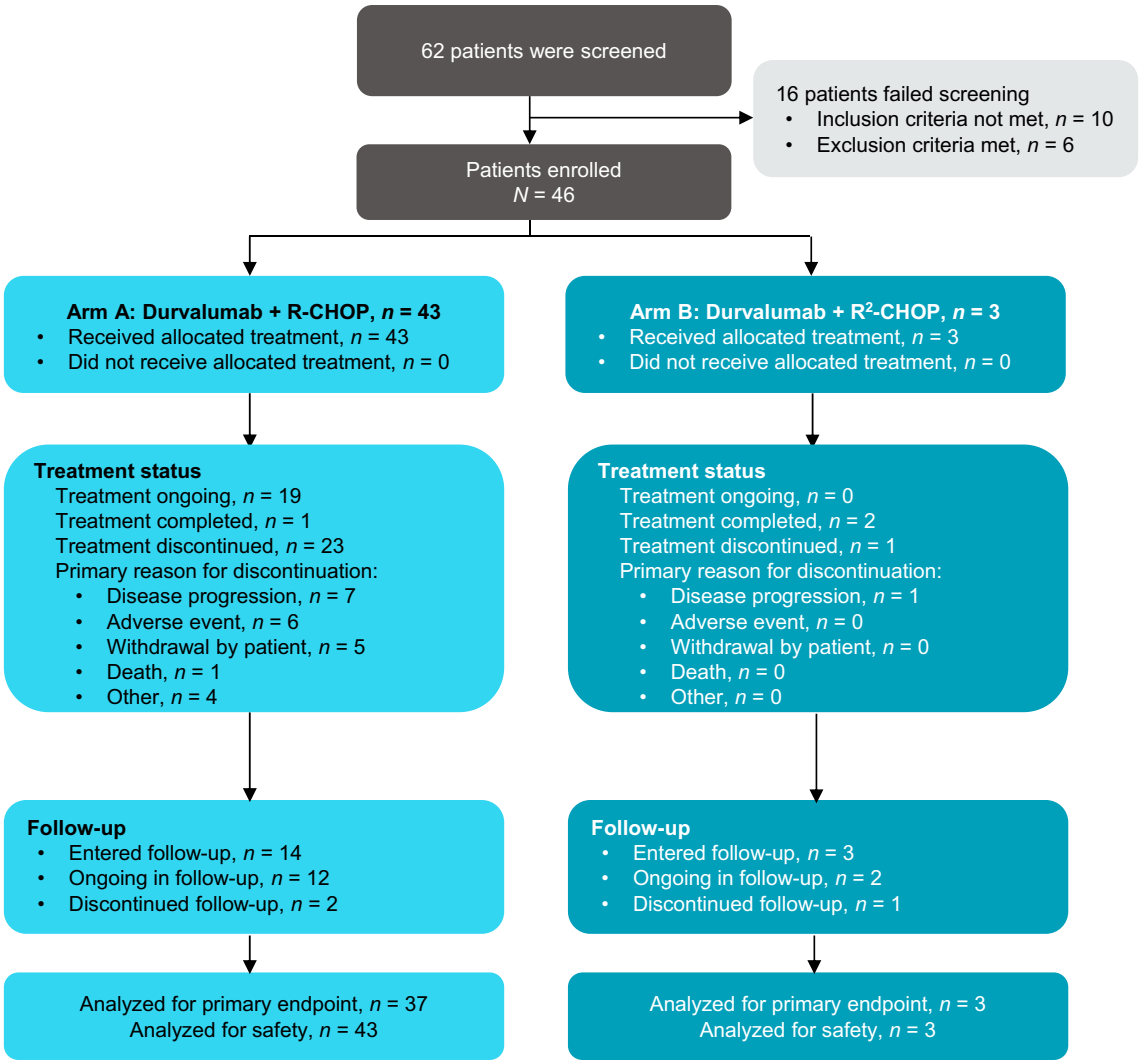

Fig. 2 Patient disposition. Summary of patients enrolled in the trial, treatment status, and discontinuation. *R-CHOP* cyclophosphamide, doxorubicin, vincristine, and prednisone in combination with rituximab; *R^2-CHOP* lenalidomide plus R-CHOP

Efficacy

Durvalumab + R-CHOP

A total of 37 patients in Arm A had a baseline CT and had at least one postbaseline tumor response assessment and were included in the efficacy-evaluable population. Thirty patients completed induction therapy and one completed consolidation therapy. At the end of induction, 20 of 37 patients (54.1% [95% CI 36.9–70.5]) achieved CR and seven patients (18.9%) achieved PR. Twenty-five patients (67.6% [95% CI 50.2–82.0]) receiving durvalumab + R-CHOP continued to consolidation therapy. The overall response rate (ORR) at the end of consolidation, including patients who completed induction only, was 97.3% (36/37 patients; 95% CI 85.8–99.9), with 25 (67.6% [95% CI 50.2–82.0]) achieving a CR and 11 (29.7% [95% CI 15.9–47.0]) achieving PR (Fig. 3a). The 12-month PFS rate was 67.7% (95% CI 42.7–83.6) for the durvalumab + R-CHOP group; the 24-month PFS rate was not estimable. Among 11 evaluable patients with double- or triple-hit DLBCL, five (45.5%) achieved CR and five (45.5%) achieved PR (Fig. 3b).

Durvalumab + R^2-CHOP

All 3 patients in Arm B completed at least one treatment cycle, had a baseline CT, and had at least one postbaseline tumor response assessment and were included in the efficacy-evaluable population. All three patients completed induction and two completed consolidation. Two patients (66.7% [95% CI 9.4–99.2]) receiving durvalumab + R^2-CHOP continued to consolidation therapy and were progression-free at month 12. Across induction and consolidation, a response was observed in all three patients

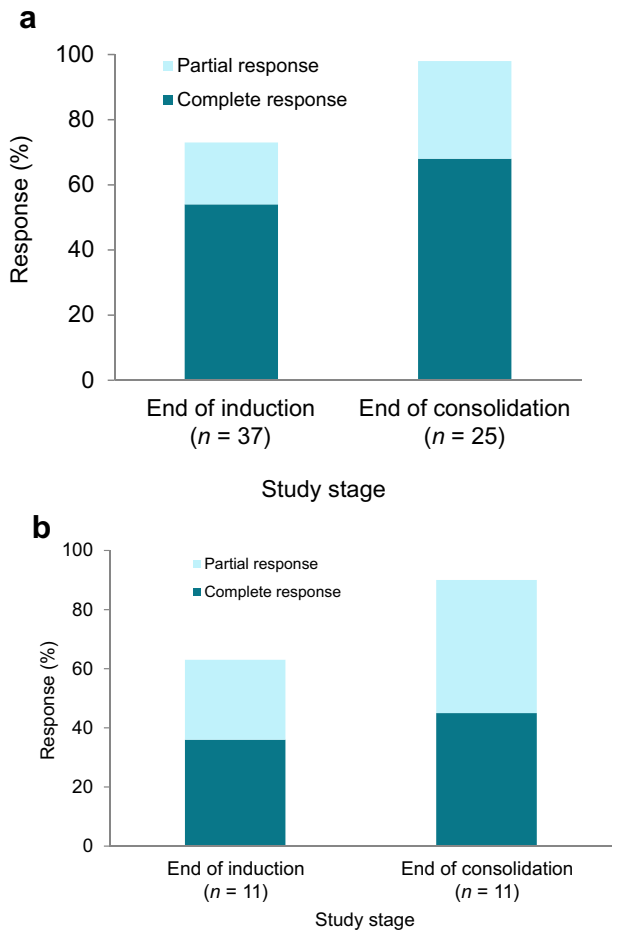

Fig. 3 Response rates. Response rates at end of induction and consolidation in patients receiving durvalumab + R-CHOP in **a** all patients and **b** patients with double-hit or triple-hit lymphoma. *R-CHOP* cyclophosphamide, doxorubicin, vincristine, and prednisone in combination with rituximab; *R^2-CHOP* lenalidomide plus R-CHOP

(two CR and one PR). Twelve-month PFS rate was 66.7% (95% CI 5.4–94.5); 24-month PFS rate was not estimable. Two of the three patients had double- or triple-hit DLBCL and both achieved CR at the end of consolidation. Descriptive analytical methods were used due to the small sample size; results were inconclusive due to the limited number of patients.

Safety

Treatment exposure, safety population

The overall median (range) duration of durvalumab treatment was 26.5 (2–54) weeks across both treatment arms. During induction, median (range) durvalumab treatment duration was 18.7 (3–26) weeks and the dose intensity was 1125 mg/cycle, with a median (range) relative durvalumab dose intensity of 100% (33.3–100) for Arm A and 100% (100) for Arm B. During consolidation, median (range) durvalumab treatment duration was 12.0 (4–36) weeks and the dose intensity was 1500 mg/cycle, with a median (range) relative dose intensity of 100% (0–100) for Arm A and 94.5% (88.9–100) for Arm B.

Table 2 Treatment-emergent adverse events (safety population)

Patients, no. (%)	Durvalumab + R-CHOP ($n = 43$)	Durvalumab + R^2-CHOP ($n = 3$)
TEAEs	43 (100.0)	3 (100.0)
Related TEAEs	41 (95.3)	3 (100.0)
TEAEs grade 3/4	36 (83.7)	3 (100.0)
Related TEAEs grade 3/4	31 (72.1)	3 (100.0)
Serious TEAE	22 (51.2)	1 (33.3)
Related serious TEAE	13 (30.2)	1 (33.3)

TEAE treatment-emergent adverse event

The median duration of R-CHOP treatment was 18.0 weeks. Thirty-four patients in Arm A and all patients in Arm B completed six cycles of treatment; five patients in Arm A completed eight cycles. Median (range) relative dose intensity was 100% (18.8–109.9) for rituximab IV, 100% (100) for rituximab SC, 100% (0–104.4) for cyclophosphamide, 100% (0–104.4) for doxorubicin, 100% (0–139.3) for vincristine, and 100% (20–173.3) for prednisone/prednisolone. In Arm B, median duration of lenalidomide treatment was 18.1 weeks. Median (range) dose intensity was 190 mg/cycle (171–210), and the median (range) relative dose intensity was 90.5% (81.4–100).

A total of 13 patients (30.2%) in Arm A had treatment delays during induction, with eight patients experiencing delays due to AEs for a median 7.5 (range 1–29) days; one patient in Arm B had a treatment delay. TEAEs led to dose reduction or interruption in 18 patients in Arm A (durvalumab, $n = 14$; R-CHOP, $n = 13$) and three patients in Arm B (durvalumab, $n = 2$; R-CHOP, $n = 1$; lenalidomide, $n = 2$).

Durvalumab + R-CHOP

All patients experienced a TEAE; 95.3% were considered related to treatment (Table 2). Figure 4 shows TEAEs occurring in ≥ 20% of patients. A total of 36 (83.7%) patients experienced grade 3/4 TEAEs, with 31 (72.1%) deemed treatment-related. The most common grade 3/4 treatment-related TEAEs related were hematologic events (neutropenia, 46.5%; leukopenia, 16.3%; and febrile neutropenia, 14.0%); other grade 3/4 events were infections (16.3%), fatigue (9.3%), peripheral sensory neuropathy (4.7%), nausea (4.7%), and cardiotoxicity (4.7%). Serious treatment-related TEAEs occurred in 13 (30.2%) patients, most commonly febrile neutropenia ($n = 5$; 11.6%). Of 2 grade 5 AEs

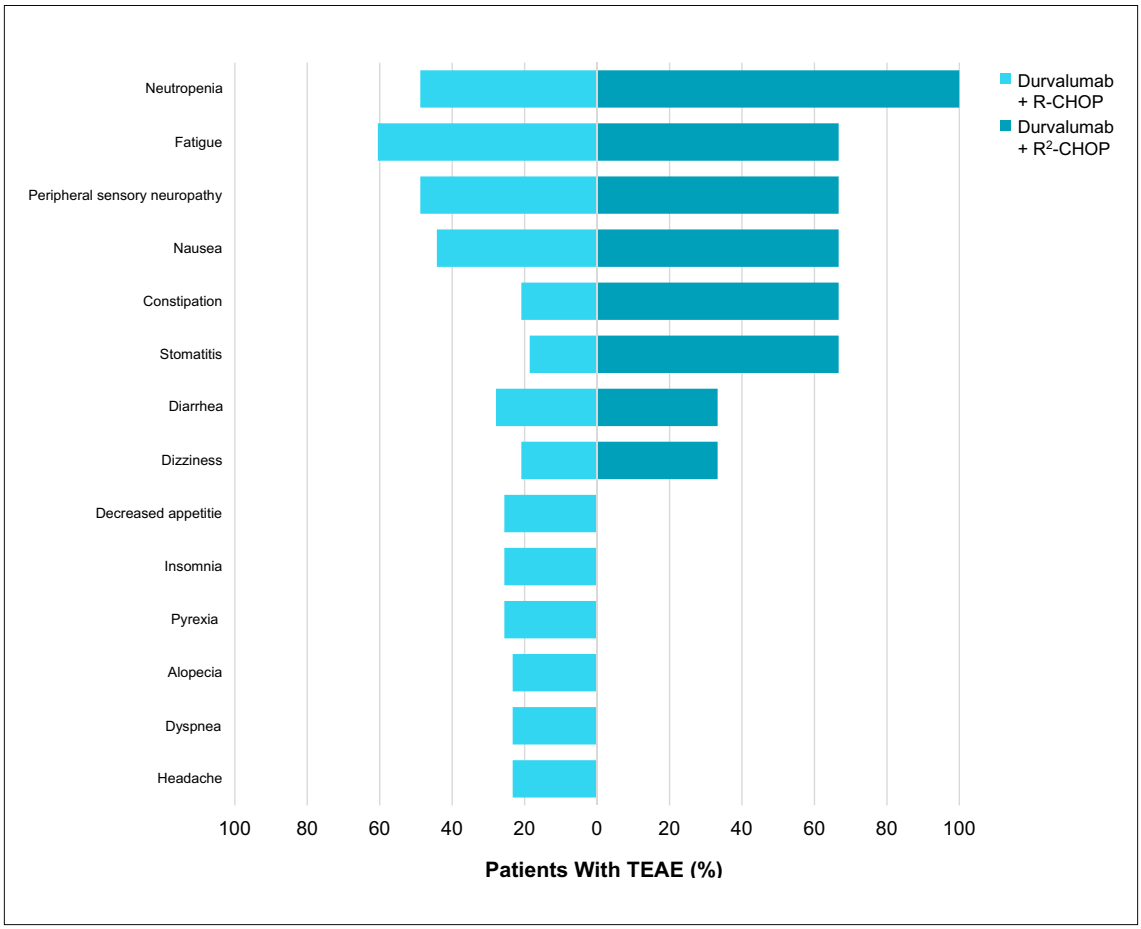

Fig. 4 Treatment-emergent adverse events. Summary of treatment-emergent adverse event in ≥ 20% of the overall safety population. *R-CHOP* cyclophosphamide, doxorubicin, vincristine, and prednisone in combination with rituximab; *R^2-CHOP* lenalidomide plus R-CHOP; *TEAE* treatment-emergent adverse event

(cardiac arrest, acute kidney injury), neither was considered related to treatment. The patient with a fatal acute kidney injury was admitted to the hospital with a grade 3 acute kidney injury and succumbed to acute kidney failure 2 days later. Study drug was discontinued in nine patients who experienced a TEAE, with nine and four patients discontinuing durvalumab and R-CHOP, respectively.

Immune-related and other AEs of special interest occurred in 26 patients and were mainly grade 1 or 2 (Table 3); grade 3 or 4 events occurred in five (11.6%) patients and included infusion-related events ($n = 2$), diarrhea ($n = 1$), hepatitis ($n = 1$), and rash ($n = 1$); no instances of pneumonitis or serious immune-related events were reported.

Durvalumab + R^2-CHOP

All 3 patients experienced grade 3/4 treatment-related AEs, with neutropenia the most frequently reported event ($n = 3$) (Table 2). One death in this group was due to

Table 3 Adverse events of special interest for durvalumab (safety population)

Patients, no. (%)	Durvalumab + R-CHOP, no. (%) ($n = 43$)		Durvalumab + R^2-CHOP, no. (%) ($n = 3$)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any AESI	26 (60.5)	5 (11.6)	3 (100.0)	0
Diarrhea	12 (27.9)	1 (2.3)	1 (33.3)	0
Rash	10 (23.3)	1 (2.3)	1 (33.3)	0
Infusion-related reaction	7 (16.3)	2 (4.7)	1 (33.3)	0
Dermatitis	5 (11.6)	0	1 (33.3)	0
Hypothyroidism	2 (4.7)	0	0	0
Myocarditis	2 (4.7)	0	0	0
Adrenal insufficiency	1 (2.3)	0	0	0
Hepatitis	1 (2.3)	1 (2.3)	0	0

AESI adverse event of special interest

lymphoma progression. All patients experienced an AE of special interest, but none were grade 3/4.

Biomarker analysis

Biomarkers were evaluated without regard to the study arm due to small sample size. As a whole, the biomarker values evaluated did not show a consistent and significant difference between responders and nonresponders (Supplementary Table, Supplementary Figure). Baseline CD8 cell density data were available for 26 patients; 17 were responders. Among responders, 10 (58.8%) patients had high CD8 density and seven had low CD8 density. PD-L1 total expression level was available for 25 patients, 16 of whom were responders. Among responders, 15 (93.8%) patients had high PD-L1 total expression level. A greater proportion of responders had high PD-L1 total expression level versus nonresponders ($P=0.04$, Fisher's test), but the continuous value of total PD-L1 did not have a significant Wilcoxon test when comparing responders with nonresponders (Supplementary Figure). Tumor PD-L1 expression level was available for 20 patients; 12 were responders. Of the 12 responders, seven (58.3%) had high PD-L1 tumor expression level and five had low PD-L1 tumor expression level. Baseline IFN-gamma score was available for 27 patients; 15 were responders. Low IFN-gamma score was observed in 12 of these patients (80.0%).

Discussion

Based on initial studies that suggested promising antitumor activity with PD-1/PD-L1 blockade, studies to evaluate the safety and activity of monotherapy and combination therapy with immune checkpoint inhibitors are ongoing, with some results reported.

In an open-label study of the PD-L1 inhibitor atezolizumab combined with R-CHOP, among 40 evaluable patients, 31 (77.5%) had a CR and four (10.0%) had a PR at the end of induction [21, 22]. When combining the anti-PD-1 antibody pembrolizumab with R-CHOP, among 30 evaluable patients, 23 (77%) achieved a CR and four (13%) achieved a PR at the end of six cycles of R-CHOP; at 24 months, PFS was 83% and OS was 84% [23]. Sequential treatment of previously untreated patients with stage II–IV DLBCL with avelumab, an anti-PD-L1 monoclonal antibody, plus rituximab induction followed by six cycles of R-CHOP and then avelumab maintenance resulted in a high CR rate (89%) and a manageable safety profile, further supporting the potential benefit of immune checkpoint inhibitors as a frontline treatment for high-risk DLBCL [24]. Multiple studies are evaluating the efficacy of nivolumab in combination with agents such as ipilimumab (NCT03305445), rituximab and chemotherapy (NCT03259529), varlilumab (anti-CD27; NCT03038672), epacadostat (indoleamine 2,3-dioxygenase inhibitor; NCT02327078), and lenalidomide (NCT03015896) in patients with DLBCL. A phase 2 study evaluated the efficacy and safety of nivolumab in patients with relapsed or refractory DLBCL after the failure of autologous stem cell transplant (ASCT) or at least two multiagent chemotherapy regimens in patients who were not candidates for ASCT. Among 121 treated patients, the independent radiology review committee–assessed ORR was 10% in the ASCT-failed group (complete remission, 3%; partial remission, 7%) and 3% in the ASCT ineligible group (complete remission, 0%; partial remission, 3%). The median duration of response was 11.4 months in the ASCT-failed group and 8 months in the ASCT-ineligible group [25]. In a phase 1 trial of nivolumab monotherapy in 81 patients with heavily pretreated relapsed or refractory lymphoid malignancies including 11 patients with DLBCL, four (36%) patients with DLBCL had a response (two CR, two PR). The median follow-up for patients with DLBCL was 22.7 weeks; one of four patients had an ongoing response, and two patients continued to be followed [26]. A phase 1 clinical trial of ipilimumab in 18 patients with relapsed or refractory B-cell non-Hodgkin lymphoma included three patients with DLBCL. One patient with DLBCL achieved a response, which was complete and lasted more than 31 months [27]. Although studies show that there is a subgroup of patients who may respond to single-agent immune checkpoint blockade, most patients do not [28]. Therefore, there is a need to find effective combination treatments with multiple therapeutic approaches.

In the present study, durvalumab + R-CHOP resulted in an ORR of 97.3%, with 67.6% achieving CR after consolidation. The 54.1% CRR at end of induction is comparable to that previously reported for R-CHOP (52% CRR) in untreated and unselected DLBCL [29, 30]. Durvalumab + R-CHOP was also effective in patients with double- or triple-hit DLBCL, who have inferior outcomes with R-CHOP [31, 32]. At the end of induction with durvalumab + R-CHOP, 45.5% of these patients achieved CR. The low number of patients with an ABC subtype did not allow for conclusions regarding the activity of durvalumab + R^2-CHOP.

The toxicity of durvalumab + R-CHOP was consistent with the AE profile reported previously with R-CHOP [29]. Durvalumab-related AEs of special interest were mainly grade 1 or 2, and grade 3/4 AEs occurred in five patients. In a study evaluating atezolizumab + R-CHOP, AEs of special interest were reported in 24% of patients. During induction, the most common AEs of special interest were increased lipase, hyperthyroidism, and increased amylase ($n=1$ each), and during consolidation, increased lipase, pancreatitis, and hepatitis ($n=2$ each). These events were generally well managed by discontinuation

of atezolizumab and steroid treatment, and were largely reversible [21]. With pembrolizumab + R-CHOP, four patients experienced potential immune-related AEs; one case each of grade 1 hyperthyroidism, grade 2 colitis, grade 3 rash, and grade 3 pneumonitis [23]. In the current study, TEAEs that led to durvalumab discontinuation were observed in nine patients (20.9%). Two TEAEs (cardiac arrest, acute kidney injury) led to death in the durvalumab + R-CHOP arm.

In patients with the ABC subtype who received durvalumab + R^2-CHOP, the overall safety profile was similar to that observed in patients receiving durvalumab + R-CHOP, and no grade 3/4 AEs of special interest were reported.

Previously reported data suggest that PD-L1 expression is associated with poor prognosis in patients with DLBCL [7]. In patients with non-small cell lung cancer or urothelial cancer receiving durvalumab monotherapy, elevated PD-L1 expression and IFN-gamma scores in baseline tumor biopsy samples were associated with higher ORR or improved survival [19, 20]. In the present study, although there was a trend towards increased response rates in patients with total PD-L1–positive cell density above a predefined threshold, it was not strong. Patients also received background R-CHOP, so some patients may have responded to therapy independent of biomarker status.

In conclusion, despite a strong rationale, the combination of R-CHOP and durvalumab demonstrated activity similar to R-CHOP alone. Thus, this combination does not warrant further study in DLBCL.

As PD-1/PD-L1 combinations continue to be evaluated in patients with non-Hodgkin lymphoma, it will be critical to understand the biological basis for response to those agents to identify target populations for further study. Additional research on the influence of factors such as the tumor microenvironment is warranted to characterize whether a subset of patients with DLBCL may be more likely to respond to PD-L1 blockade, or if earlier use of immunotherapy before intensive chemotherapy may be more effective. As ongoing clinical trials report results on combination therapies, they will undoubtedly offer an understanding of which patients are good candidates for combination therapy, and which combinations result in long-term survival.

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Declarations

Conflict of interest GSN has received grants from Celgene/Bristol Myers Squibb, Curis, Incyte, MorphoSys, Roche, and Seattle Genetics, and personal fees from Debiopharm, Karyopahrm, Kite, Kymera, Selvita, and TG Therapeutics. WW has served on steering and safety committees for Amgen, Celgene, DSMM, and Morphosys; was employed by Oncotyrol (20%); has served on advisory boards and as a consultant for Amgen, Bristol Myers Squibb/Celgene, Gilead, GSK, Incyte, Janssen, Novartis, Merck, Pfizer, Roche, Sandoz, Sanofi, and Takeda; has presented lectures for Amgen, AbbVie, Bristol Myers Squibb/Celgene, Fujimoto, Gilead, GSK, Janssen, Myelom- und Lymphomselbsthilfe Österreich, Novartis, Pfizer, Roche, Sandoz, Sanofi, and Takeda; and has received research funding from Amgen, Bristol Myers Squibb, Celgene, Janssen, Novartis, Roche, Sanofi, Takeda, oncotyrol, European Commission (FP7—*OPTATIO*), and Bundesland Tirol Programm "Translational research." RG has received honoraria, consulting/advisory fees, research funding, and travel fees, accommodations, and/or expenses from AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, Celgene, Daiichi Sankyo, Gilead, Merck, MSD, Novartis, Roche, Sandoz, and Takeda. TSL has served as a consultant and on advisory boards for Bristol Myers Squibb/Celgene, Novartis, Roche, and Gilead. KP has received grants and/or personal fees from AstraZeneca, Bristol Myers Squibb, Genentech, Kite Pharmaceuticals, Pharmacyclics/Janssen, and TG Therapeutics. UJ has served on the advisory board for Bristol Myers Squibb/Celgene, Roche, Novartis, and Janssen; and has served as a consultant for Miltenyi, Takeda, Merck, Incyte, and AbbVie. RFM, LT, and HE have nothing to disclose. NK has received research funding from Celgene and Roche UK, and has served on the advisory board for Bristol Myers Squibb, Gilead, Karyopharm, and Takeda. PB has served on the advisory board for Celgene, Incyte, Takeda, and Roche. JMJ has received personal fees from Bristol Myers Squibb/Celgene, Gilead/Kite Pharma, Novartis, and Roche. DC has received research funding from Amgen, AstraZeneca, Bayer, Celgene, Clovis, Eli Lilly, Janssen, MedImmune, Merck, Merrimack, Sanofi, and 4SC. BF, NDR, NK, and M-LC are employees of and stockholders in Bristol Myers Squibb. JD, NK, and OM were employees of and stockholders in Bristol Myers Squibb at the time of the study. JM has served as a consultant for Pharmacyclics, Bayer, Gilead/Kite Pharma, Pfizer, Janssen, Juno/Celgene, Bristol Myers Squibb, Kyowa, Alexion, Beigene, Fosunkite, Innovent, Seattle Genetics, and Beigene; has received research funding from Bayer, Gilead/Kite Pharma, Celgene, Merck, Portola, Incyte, Genentech, Pharmacyclics, Seattle Genetics, Janssen, and Millennium; has received honoraria from Kyowa and Seattle Genetics; and has served on the speakers bureau for Gilead/Kite Pharma, Kyowa, Bayer, Pharmacyclics/Janssen, Seattle Genetics, Acrotech/Aurobindo, Beigene, Verastem, AstraZeneca, Celgene/Bristol Myers Squibb, Genentech/Roche, and AbbVie.

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