



Avelumab in Combination Regimens for Relapsed/Refractory DLBCL: Results from the Phase Ib JAVELIN DLBCL Study

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Abstract

Background Relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) is associated with a poor prognosis despite the availability of multiple treatment options. Preliminary evidence suggests that DLBCL may be responsive to programmed death ligand 1 (PD-L1)/programmed death 1 inhibitors.

Objective The JAVELIN DLBCL study was conducted to assess whether a combination of agents could augment and sustain the antitumor immunity of avelumab, an anti-PD-L1 antibody, in R/R DLBCL.

Methods This was a multicenter, randomized, open-label, parallel-arm study with a phase Ib and a phase III component. Reported here are the results from the phase Ib study, wherein 29 adult patients with DLBCL were randomized 1:1:1 to receive avelumab in combination with utomilumab (an immunoglobulin G2 4-1BB agonist) and rituximab (arm A), avelumab in combination with utomilumab and azacitidine (arm B), or avelumab in combination with bendamustine and rituximab (arm C). The primary endpoints were dose-limiting toxicities and objective response as assessed by the investigator per Lugano Response Classification criteria.

Results Of the seven patients in arm A, one (14.3%) experienced two grade 3 dose-limiting toxicities (herpes zoster and ophthalmic herpes zoster); no dose-limiting toxicities were reported in arms B or C. No new safety concerns emerged for avelumab. One partial response was reported in arm A, three complete responses in arm C, and no responses in arm B. Given the insufficient antitumor activity in arms A and B and the infeasibility of expanding arm C, the study was discontinued before initiation of the phase III component.

Conclusions The low level of clinical activity suggests that PD-L1 inhibitor activity may be limited in R/R DLBCL.

ClinicalTrials.gov Identifier NCT02951156.

Key Points

Avelumab, an anti-programmed death ligand 1 (PD-L1) antibody, was assessed in relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) in combination with therapies hypothesized to augment antitumor immunity.

The low level of clinical activity for avelumab combinations suggests that PD-L1 inhibitor activity may be limited in R/R DLBCL.

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1 Introduction

Diffuse large B-cell lymphoma (DLBCL) is an aggressive and heterogeneous non-Hodgkin lymphoma (NHL) characterized by diverse clinical, pathological, and molecular characteristics [1]. DLBCL accounts for 30–40% of all newly diagnosed cases of NHL [2] and 80% of all aggressive lymphoma types, making it the most common type of lymphoma globally [3]. The first-line standard-of-care treatment for DLBCL is R-CHOP (rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone) [4]. However, \approx 40% of patients with DLBCL are refractory to or relapse following treatment [5].

Patients with relapsed/refractory (R/R) DLBCL may be considered for curative-intent salvage chemotherapy and, if their disease is chemosensitive, for high-dose salvage chemotherapy followed by autologous stem cell transplant (ASCT) [1]. Restrictions associated with age and/or comorbidities mean that only approximately half of patients are eligible for this intensive treatment [4, 6, 7]; of those, only 30–40% respond to therapy and can proceed to ASCT [8]. Approximately 50% of patients who proceed to ASCT relapse after transplant. Patients with primary refractory disease following R-CHOP present the greatest challenge, with < 10% achieving durable remissions with salvage chemotherapy [9]. For patients who are eligible for transplant but do not respond to salvage chemotherapy, anti-CD19 chimeric antigen receptor (CAR) T-cell therapy has been shown to provide complete responses in 40–58% of patients; however, toxicity and accessibility to treatment remain a challenge [4, 5]. Patients who are not eligible for transplant are treated with palliative medications, less-intensive chemotherapy, or newer targeted therapies, including polatuzumab vedotin (an anti-CD79b antibody) and tafasitamab (an anti-CD19 antibody) [4]. Moreover, selinexor, a selective inhibitor of nuclear export, has been approved as a third-line treatment regardless of transplant eligibility. Unfortunately, these targeted therapies have limited single-agent activity and have not provided durable responses, highlighting the need for combinatorial approaches [5]. Despite available treatment options, the prognosis continues to be poor, especially for patients not eligible for ASCT, highlighting an unmet need in this therapeutic area [7].

Avelumab is a human anti-programmed death ligand 1 (anti-PD-L1) immunoglobulin (Ig)-G1 monoclonal antibody (mAb) that may induce innate effector function against tumor cells in vitro [10, 11]. Avelumab has shown activity as monotherapy and in combination treatment of solid tumors [12–20] and is also being investigated in R/R classic Hodgkin lymphoma [21]. Data from in vitro studies and a multicohort study of patients with DLBCL suggested

that DLBCL may be responsive to PD-L1/programmed death 1 (PD-1) inhibitors [22–25]. The combination of avelumab and agents hypothesized to augment antitumor immunity, including chemotherapy, may be a beneficial therapeutic strategy for patients with R/R DLBCL. Current clinical data support concurrent treatment with an immune checkpoint inhibitor and chemotherapy in solid tumors [26] and classic Hodgkin lymphoma [27].

Existing preclinical and clinical data provided a rationale for the combination of avelumab with the following agents hypothesized to augment antitumor immunity: utomilumab (an IgG2 4-1BB agonist) and rituximab, utomilumab and azacitidine, and bendamustine and rituximab. The immunostimulatory effects of 4-1BB (CD137) agonism provided the rationale for the addition of utomilumab, a novel fully human IgG2 mAb agonist of 4-1BB, to anti-PD-L1 therapy. Data suggested that the combination of PD-L1 antagonism and anti-4-1BB agonism may be synergistic [28, 29]. In addition, anti-4-1BB agonist mAbs have been shown to enhance the anti-lymphoma activity of rituximab by enhancing antibody-dependent cell-mediated cytotoxicity [30]. Utomilumab monotherapy has shown clinical activity in advanced solid tumors [31] and in combination with rituximab in B-cell NHL [32]. In an A20 lymphoma model, the combination of all three agents—avelumab, rituximab, and utomilumab—resulted in a higher frequency of tumor-free mice than did these agents alone or corresponding pairs (Pfizer, unpublished data, 2021), thus providing rationale for investigation of this combination in DLBCL. Based on evidence that epigenetic priming by azacitidine (a DNA methyltransferase inhibitor) might sensitize cancer cells to PD-1/PD-L1 axis blockade and preliminary clinical data showing that azacitidine enhances the expression of tumor antigens, a combination of azacitidine and a checkpoint inhibitor may lead to an enhanced antitumor response [33]. Azacitidine has previously shown clinical activity in acute myeloid leukemia [34], myelodysplastic syndromes, and high-risk or previously untreated DLBCL (in combination with R-CHOP) [35, 36]. This, and data previously mentioned for utomilumab, provides a rationale for the combination of avelumab with utomilumab and azacitidine in DLBCL. Given that the combination of bendamustine and rituximab is already recommended for R/R DLBCL by the *National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology* [4], the combination of these two agents with avelumab was also hypothesized as a potentially beneficial strategy for patients with DLBCL.

Here, we report efficacy and safety results from the phase Ib JAVELIN DLBCL trial of avelumab in combination with utomilumab and rituximab (arm A), in combination with utomilumab and azacitidine (arm B), and in combination with bendamustine and rituximab (arm C) in patients with R/R DLBCL.

2 Methods

2.1 Patients

JAVELIN DLBCL (NCT02951156) was a multicenter, randomized, open-label, seamless two-component (phase Ib planned to be followed by phase III), parallel-arm study of avelumab in various combinations for the treatment of R/R DLBCL. Based on the results of phase Ib, a phase III component in which a single avelumab-based combination regimen was to be selected for further investigation was planned. Here, we report the safety and efficacy results of phase Ib.

Key eligibility criteria included histologically confirmed DLBCL in patients who were at least 18 years of age and had R/R disease following two or more and up to four lines of rituximab-based multiagent chemotherapy. Patients who were ineligible for intensive second-line chemotherapy must have received at least one prior rituximab-containing combination chemotherapy regimen. Patients previously treated with bendamustine must have experienced a response duration of ≥ 6 months. Documentation of baseline measurable disease with at least one bidimensional lesion with the longest diameter > 1.5 cm on a computerized tomography scan, which was fluorodeoxyglucose avid on positron emission tomography scan, was required.

Key exclusion criteria included active central nervous system lymphoma, prior organ transplant including prior allogeneic stem cell transplant, and prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-4-1BB (anti-CD137), or anti-CTLA-4 antibody (including ipilimumab and tremelimumab or any other antibody or drug specifically targeting T-cell costimulatory or immune checkpoint pathways). The use of any standard or experimental anticancer therapy within 2 weeks prior to the first dose of study treatment, including cytoreductive therapy and radiotherapy, immunotherapy, or cytokine therapy (except for erythropoietin), was grounds for exclusion, as was the use of any non-drug anticancer therapy (including CAR T-cell therapy).

All patients provided written informed consent. This study was approved by the relevant institutional review boards or ethics committees of all participating centers and conducted in accordance with the principles of the Declaration of Helsinki. All the authors had full access to all data, and the first author had final responsibility for the decision to submit the manuscript for publication.

2.2 Treatment, Endpoints, and Assessments

Patients were randomized 1:1:1 to receive avelumab in combination with utomilumab and rituximab (arm A), in

combination with utomilumab and azacitidine (arm B), or in combination with bendamustine and rituximab (arm C). Doses were selected based on safety results from previous studies, including a study of utomilumab plus rituximab in patients with follicular lymphoma and other CD20+ NHL [32]. In the current study, avelumab 10 mg/kg was administered as a 1-h intravenous infusion every 2 weeks, with a mandatory premedication regimen of an antihistamine and acetaminophen 30–60 min before each dose. For the arm A regimen, intravenous rituximab 375 mg/m² was administered on day 1 of each cycle for a maximum of 8 cycles; intravenous utomilumab 100 mg fixed dose was administered on day 2 of each cycle in cycles 1 and 2 (or if well-tolerated in cycles 1 and 2, then on day 1 in cycle 3 and in all subsequent cycles) at least 1 h after the rituximab infusion was complete, until the patient no longer received clinical benefit. For the arm B regimen, azacitidine 40 mg/m² was administered subcutaneously on days 1 to 5 of each cycle until the patient was no longer receiving clinical benefit; administration of utomilumab and avelumab was identical to arm A. For the arm C regimen, intravenous rituximab 375 mg/m² was administered on day 1 of each cycle for a maximum of 8 cycles; intravenous bendamustine 90 mg/m² was administered on days 2 and 3 of cycles 1 and 2.

If bendamustine was well-tolerated in cycles 1 and 2, bendamustine may have been administered on day 1 and day 2 in cycle 3 (and all subsequent cycles). Bendamustine was administered for a maximum of 6 cycles. Avelumab was administered at least 1 h after the end of bendamustine, following the same administration guidelines as arms A and B. No dose reductions were permitted for avelumab, azacitidine, rituximab, or utomilumab. Patients with documented progressive disease who continued to receive clinical benefit could continue treatment with avelumab and/or utomilumab. Treatment continuation with other agents in the regimen combination with avelumab may have also been considered per investigator's discretion.

The primary endpoints were dose-limiting toxicities (DLTs) and objective response (OR) as assessed by investigator per Lugano Response Classification criteria [37]. Secondary endpoints included PD-L1 expression levels in tumor cells and cells of the tumor microenvironment at baseline, minimal residual disease (MRD) as assessed using serial blood samples, duration of response (DR), time to tumor response (TTR), disease control (DC, defined as the sum of complete response [CR] + partial response [PR] + stable disease [SD]), progression-free survival (PFS; as assessed by the investigator per Lugano Response Classification criteria), overall survival (OS), and safety.

2.3 Biomarker Analyses

Archival or screening formalin-fixed, paraffin-embedded cancer tissue was used for all tumor biomarker analyses. To assess MRD, tumor DNA was extracted and analyzed using the Adaptive ClonoSEQ Clinical Laboratory Improvement Amendments-regulated laboratory-developed test [38] to determine DLBCL clonotypes that could then be followed in serial plasma samples. Cell of origin (COO) was assessed centrally using the HTG EdgeSeq DLBCL Cell of Origin Research Use Only Assay (HTG Molecular Diagnostics, Inc.; Tucson, AZ, USA). Immunohistochemical analysis for PD-L1 (SP263; Ventana), CD4 (SP35; Ventana), CD8 (SP57; Ventana), CD68 (Kp-1; Cell Marque), and 4-1BB/CD137 (TNFRSF9; Cell Signaling) was performed using Ventana UltraView and OptiView DAB Detection kits at Hematogenix Laboratory Services, LLC (Tinley Park, IL, USA).

2.4 Statistical Analysis

DLTs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 and summarized by number and percentage of patients with DLTs, treatment group, primary system organ class (SOC), and preferred term (PT). All primary and secondary endpoints based on radiological assessments of tumor burden (OR, PFS, TTR, DR, DC) were derived using the local radiologist's/investigator's assessment. Objective response rate (ORR) was estimated by dividing the number of patients with OR (CR or PR) by the number of patients randomized to the respective treatment arm; two-sided 95% exact confidence intervals (CIs) were provided by treatment arm using the Clopper–Pearson method. OS, PFS, and DR were analyzed using the Kaplan–Meier method. TTR was summarized using descriptive statistics. DC rate

was summarized by frequency counts and percentages. Pharmacokinetic endpoints were summarized descriptively. Biomarker evaluations (MRD status, activated B-cell-like/germinal center B-cell-like [ABC/GCB] COO, and immunohistochemical analyses) were summarized descriptively.

3 Results

3.1 Patients

A total of 41 patients were screened; among these, eight were excluded from the study as they did not meet the eligibility criteria. Four patients completed screening but discontinued before they could receive study treatment: one withdrew from the study, and three no longer met eligibility criteria. A total of 29 patients were enrolled and randomized between 16 December 2016 and 8 October 2018. At data cutoff (2 December 2019), all patients in the study ($n = 29$) discontinued study treatment (the primary reason for discontinuation was progressive disease) (Table 1); however, one patient transitioned to compassionate use. Baseline patient and disease characteristics are shown in Table 2. The median age was 70 years (range 31.0–86.0), and the majority of patients (82.8%) were male. Of patients with available local COO data, three (33.3%) in arm A and four (36.4%) in arm C had ABC COO. Additionally, two patients (22.2%) in arm A, seven patients (77.8%) in arm B, and three patients (27.3%) in arm C had GCB COO. Two patients in arm B had bulky disease (22.2%).

3.2 Dose-Limiting Toxicities

Seven patients in the avelumab/utomalumab/rituximab treatment arm (arm A), five in the avelumab/utomalumab/azacitidine treatment arm (arm B), and ten in the

Table 1 Patient disposition for study drugs at end of treatment

| Reason for discontinuation | Treatment arm A ($n = 9$) | | | Treatment arm B ($n = 9$) | | | Treatment arm C ($n = 11$) | | |
|--------------------------------------|-----------------------------|-----------|------------|-----------------------------|-------------|------------|------------------------------|--------------|-----------|
| | Avelumab | Rituximab | Utomilumab | Avelumab | Azacitidine | Utomilumab | Avelumab | Bendamustine | Rituximab |
| Death | 0 | 0 | 0 | 2 (22.2) | 2 (22.2) | 2 (22.2) | 1 (9.1) | 1 (9.1) | 1 (9.1) |
| Progressive disease | 8 (88.9) | 7 (77.8) | 8 (88.9) | 5 (55.6) | 5 (55.6) | 5 (55.6) | 5 (45.5) | 5 (45.5) | 5 (45.5) |
| Adverse event | 0 | 1 (11.1) | 0 | 0 | 0 | 0 | 1 (9.1) | 0 | 0 |
| Physician decision | 0 | 0 | 0 | 0 | 0 | 0 | 1 (9.1) | 1 (9.1) | 1 (9.1) |
| No longer meets eligibility criteria | 0 | 0 | 0 | 1 (11.1) | 1 (11.1) | 1 (11.1) | 0 | 0 | 0 |
| Withdrawal by subject | 0 | 0 | 0 | 1 (11.1) | 1 (11.1) | 1 (11.1) | 1 (9.1) | 1 (9.1) | 1 (9.1) |
| Study terminated by sponsor | 0 | 0 | 0 | 0 | 0 | 0 | 1 (9.1) | 0 | 0 |
| Other | 1 (11.1) | 1 (11.1) | 1 (11.1) | 0 | 0 | 0 | 1 (9.1) | 3 (27.3) | 3 (27.3) |

Data are presented as n (%)

Table 2 Select baseline patient and disease characteristics

| Characteristic | Treatment arm A ^a (n = 9) | Treatment arm B ^b (n = 9) | Treatment arm C ^c (n = 11) |
|-----------------------------------|--------------------------------------|--------------------------------------|---------------------------------------|
| Age, years | 71.0 (60.0–78.0) | 70.0 (39.0–79.0) | 70.0 (31.0–86.0) |
| Sex | | | |
| Male | 9 (100) | 6 (66.7) | 9 (81.8) |
| Female | 0 | 3 (33.3) | 2 (18.2) |
| Primary disease type | | | |
| Relapsed | 5 (55.6) | 6 (66.7) | 5 (45.5) |
| Refractory | 4 (44.4) | 3 (33.3) | 6 (54.5) |
| DLBCL stage | | | |
| I | 2 (22.2) | 0 | 3 (27.3) |
| II | 2 (22.2) | 2 (22.2) | 1 (9.1) |
| III | 1 (11.1) | 1 (11.1) | 1 (9.1) |
| IV | 4 (44.4) | 5 (55.6) | 6 (54.5) |
| NR | 0 | 1 (11.1) | 0 |
| DLBCL subtype ^d | | | |
| ABC | 3 (33.3) | 0 | 4 (36.4) |
| GCB | 2 (22.2) | 7 (77.8) | 3 (27.3) |
| NA | 0 | 2 (22.2) | 3 (27.3) |
| Unknown | 4 (44.4) | 0 | 1 (9.1) |
| TNM classification | | | |
| Bulky disease | 0 | 2 (22.2) | 0 |
| Regions of lymph node involvement | 1 (11.1) | 0 | 0 |
| NA | 0 | 2 (22.2) | 3 (27.3) |
| Unknown | 2 (22.2) | 1 (11.1) | 1 (9.1) |
| NR | 6 (66.7) | 4 (44.4) | 7 (63.6) |
| Prior anticancer drug therapies | | | |
| 0 | 0 | 0 | 0 |
| 1 | 3 (33.3) | 1 (11.1) | 2 (18.2) |
| 2 | 4 (44.4) | 5 (55.6) | 4 (36.4) |
| 3 | 1 (11.1) | 1 (11.1) | 2 (18.2) |
| ≥ 4 | 1 (11.1) | 2 (22.2) | 3 (27.3) |
| ECOG PS | | | |
| 0 | 1 (11.1) | 3 (33.3) | 2 (18.2) |
| 1 | 7 (77.8) | 6 (66.7) | 9 (81.8) |
| NR | 1 (11.1) | 0 | 0 |

Data are presented as median (range) or *n* (%)

ABC activated B-cell-like, DLBCL diffuse large B-cell lymphoma, ECOG PS Eastern Cooperative Oncology Group performance status, GCB germinal center B-cell-like, NA not applicable, NR not reported, TNM tumor/node/metastasis

^aAvelumab, utomilumab, and rituximab in combination

^bAvelumab, utomilumab, and azacitidine in combination

^cAvelumab, bendamustine, and rituximab in combination

^dBased on local laboratory assessments

avelumab/bendamustine/rituximab treatment arm (arm C) were evaluable for DLT assessment. One (14.3%) of the seven patients in arm A experienced two grade 3 DLTs (herpes zoster and ophthalmic herpes zoster).

Administration of avelumab and utomilumab was interrupted, and rituximab was discontinued. Both events resolved and were assessed by the investigator as related to rituximab. No DLTs were reported in arm B or C.

3.3 Safety

Table 3 shows the treatment-related adverse events (TRAEs), and Tables 1, 2, and 3 in the electronic supplementary material (ESM) show the TRAEs by SOC, PT, and maximum CTCAE grade during the on-treatment period. In arm A, 50% of patients had a TRAE, and 25% of patients had a grade ≥ 3 TRAE. TRAEs of any grade included neutropenia in 12.5% and chills in 37.5%; grade ≥ 3 neutropenia occurred in 12.5%. In arm B, 55.6% of patients had a TRAE, and 11.1% of patients had a grade ≥ 3 TRAE. TRAEs of any grade included neutropenia in 11.1% and chills in 11.1%; grade ≥ 3 neutropenia occurred in 11.1%. In arm C, 90.9%

of patients had a TRAE, and 72.7% of patients had a grade ≥ 3 TRAE. TRAEs of any grade included neutropenia in 45.5%, decreased lymphocyte count in 27.3%, thrombocytopenia in 27.3%, and chills in 9.1%; grade ≥ 3 TRAEs included neutropenia in 27.3%, decreased lymphocyte count in 27.3%, and thrombocytopenia in 18.2%. No treatment-related deaths occurred.

3.4 Efficacy

Table 4 shows the best overall response, ORR, and disease control rate (DCR), and Fig. 1 shows the TTR and DR. Responses were observed in two of the three treatment arms.

Table 3 Treatment-related adverse events during the on-treatment period

| Treatment-related adverse event | Treatment arm A ^a (<i>n</i> = 8) | | Treatment arm B ^b (<i>n</i> = 9) | | Treatment arm C ^c (<i>n</i> = 11) | |
|---------------------------------|--|----------------|--|----------------|---|----------------|
| | All grades | Grade ≥ 3 | All grades | Grade ≥ 3 | All grades | Grade ≥ 3 |
| Patients with events | 4 (50.0) | 2 (25.0) | 5 (55.6) | 1 (11.1) | 10 (90.9) | 8 (72.7) |
| Neutropenia | 1 (12.5) | 1 (12.5) | 1 (11.1) | 1 (11.1) | 5 (45.5) | 3 (27.3) |
| Decreased lymphocyte count | 0 | 0 | 0 | 0 | 3 (27.3) | 3 (27.3) |
| Thrombocytopenia | 0 | 0 | 0 | 0 | 3 (27.3) | 2 (18.2) |
| Chills | 3 (37.5) | 0 | 1 (11.1) | 0 | 1 (9.1) | 0 |

Data are presented as *n* (%). Any grade in $\geq 30\%$ of patients or grade ≥ 3 in $\geq 15\%$ of patients

^aAvelumab, utomilumab, and rituximab in combination

^bAvelumab, utomilumab, and azacitidine in combination

^cAvelumab, bendamustine, and rituximab in combination

Table 4 Confirmed objective response

| Objective response | Treatment arm A ^a (<i>n</i> = 9) | Treatment arm B ^b (<i>n</i> = 9) | Treatment arm C ^c (<i>n</i> = 11) |
|-------------------------------|--|--|---|
| BOR, <i>n</i> (%) | | | |
| CR | 0 | 0 | 3 (27.3) |
| PR | 1 (11.1) | 0 | 0 |
| SD | 1 (11.1) | 0 | 1 (9.1) |
| PD | 6 (66.7) | 5 (55.6) | 5 (45.5) |
| NE | 1 (11.1) ^d | 4 (44.4) ^e | 2 (18.2) ^f |
| ORR, % (95% CI) | 11.1 (0.3–48.2) | 0 (0–33.6) | 27.3 (6.0–61.0) |
| DCR ^g , % (95% CI) | 22.2 (2.8–60.0) | 0 (0–33.6) | 36.4 (10.9–69.2) |

Based on investigator assessment (Cheson et al. [37] criteria). Data are presented as *n* (%) unless otherwise indicated

BOR best overall response, CI confidence interval, CR complete response, DCR disease control rate, NE not evaluable, ORR objective response rate, PD progressive disease, PR partial response, SD stable disease

^aAvelumab, utomilumab, and rituximab in combination

^bAvelumab, utomilumab, and azacitidine in combination

^cAvelumab, bendamustine, and rituximab in combination

^dNo postbaseline assessments because of other reasons (*n* = 1)

^eNo postbaseline assessments because of early death (*n* = 3); other reasons (*n* = 1)

^fNo postbaseline assessments because of early death (*n* = 1); other reasons (*n* = 1)

^gDefined as the sum of CR + PR + SD

The ORR was 11.1% (95% CI 0.3–48.2) in the avelumab/utomilumab/rituximab arm (arm A; one PR), 0% (95%

CI 0–33.6) in the avelumab/utomilumab/azacitidine arm (arm B), and 27.3% (95% CI 6.0–61.0) in the avelumab/

Fig. 1 Time to and duration of response. Time to tumor response and duration of response are shown for one patient in the avelumab/utomilumab/rituximab arm (partial response) and three patients in the avelumab/bendamustine/rituximab arm (all complete responses). Based on investigator assessment (Cheson et al. [37] criteria)

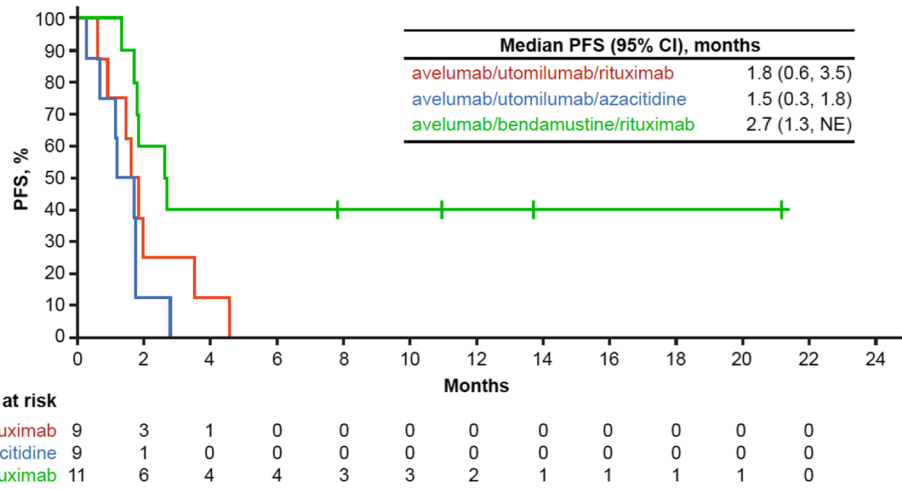
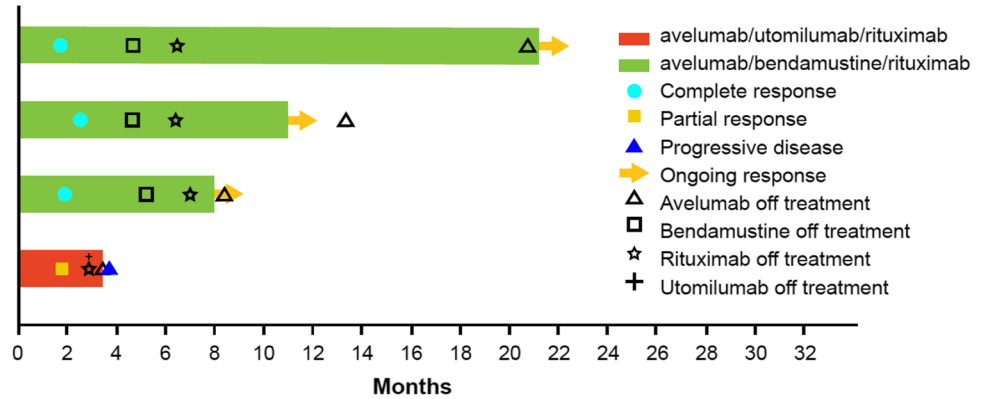


Fig. 2 PFS per investigator assessment based on Cheson et al. [37] criteria. CI confidence interval, NE not evaluable, PFS progression-free survival

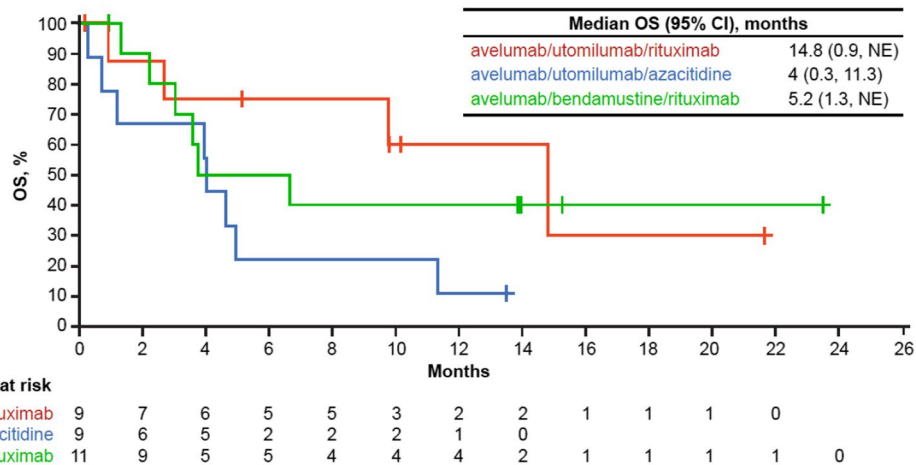


Fig. 3 Overall survival. CI confidence interval, NE not evaluable, OS overall survival

bendamustine/rituximab arm (arm C; three CRs). DR was 1.81 months in arm A. In arm C, all three CRs were still ongoing as of the cutoff date. Duration of CR was ≥ 6 , ≥ 8.4 , and ≥ 19.5 months for each CR, respectively. DC (CR + PR + SD) was observed in two patients (DCR 22.2%; 95% CI 2.8–60.0) in arm A, no patients in arm B (DCR 0%; 95% CI 0–33.6), and four patients (DCR 36.4%; 95% CI 10.9–69.2) in arm C. Figure 2 presents a Kaplan–Meier plot of PFS based on investigator assessment. Median PFS was 1.8 months (95% CI 0.6–3.5) in arm A, 1.5 months (95% CI 0.3–1.8) in arm B, and 2.7 months (95% CI 1.3 to not evaluable [NE]) in arm C. Figure 3 presents a Kaplan–Meier plot of OS. Median OS was 14.8 months (95% CI 0.9–NE) in arm A, 4 months (95% CI 0.3–11.3) in arm B, and 5.2 months (95% CI 1.3–NE) in arm C.

3.5 Biomarker Evaluations

Tables 4, 5, and 6 in the ESM show patient-level biomarker data for each treatment arm. One patient with CR in arm C (avelumab/bendamustine/rituximab) converted to MRD-negative status. COO results were 100% concordant with local laboratory results collected via case report form where both central and local results were available. Two of three patients with CRs had GCB COO, and one had ABC COO. Immunohistochemical analyses of DLBCL biopsies demonstrated a broad range of immunopositivity for various markers pertinent to the mechanism of action of the drug combinations (PD-L1, CD4, CD8, CD68, and 4-1BB [CD137]). The patient who demonstrated a PR in arm A (avelumab/utomalumab/rituximab) exhibited low levels of 4-1BB (1%). Overall, low patient numbers and limited efficacy precluded exploration of correlations between immunohistochemical markers and outcomes.

4 Discussion

This phase Ib trial investigated avelumab in combination with agents hypothesized to augment antitumor immunity, including utomalumab and rituximab (arm A), utomalumab and azacitidine (arm B), and bendamustine and rituximab (arm C), for the treatment of R/R DLBCL. These treatment combinations were selected based on preclinical and clinical data in other tumor types and on preliminary reports suggesting that DLBCL may be responsive to PD-L1/PD-1 inhibitors [22–25]. However, arms A and B showed insufficient antitumor activity, and arm C could not be expanded to meet the minimum number of patients required for this arm because of recruitment difficulties arising from rapidly evolving standards of care for this disease. As such, the study was discontinued.

DLTs were observed in one patient in arm A only (two DLTs). Each treatment regimen was characterized by a manageable safety profile consistent with that for each agent when administered as monotherapy. No new safety concerns emerged for avelumab in any of the treatment arms. One PR occurred in arm A, three CRs occurred in arm C, and no ORs occurred in arm B. Although the results cannot be directly compared, the efficacy observed in this study with avelumab/bendamustine/rituximab (arm C) was similar to that observed in a phase II study, which reported an ORR of 32.5%, PFS of 2.0 months, and median OS of 4.7 months with bendamustine and rituximab [7]. Lymphodepletion with bendamustine may have abrogated any combinatorial effect that could be contributed to avelumab; thus, it is not clear that avelumab contributed to the clinical activity in this study arm [39]. Arm C had the highest ORR; however, this could not be confirmed because of the limited patient population. Of six patients who were evaluable for MRD status, one patient with a CR in arm C converted to MRD-negative status. Conversion was observed on cycle 3 day 1 and sustained through cycle 6 day 1 (last time point tested).

Two of three patients with CRs had GCB COO, and one had ABC COO. The patient with a PR in arm A had ABC COO, which has been reported to be associated with an elevated immune cell component, including 4-1BB (CD137) expression [40], although such an association was not evident in this study. Other ABC tumors did not respond to this combination therapy; thus, it does not appear that ABC COO and/or 4-1BB tumor expression is sufficient to mediate tumor responses in this combination.

The early termination of the trial meant that the most active treatment regimen among the three treatment arms to advance to the phase III component of the study could not be confirmed. The low level of clinical activity observed for these avelumab combinations is consistent with recent published reports [41–44] suggesting that PD-L1 inhibitor activity may be limited in R/R DLBCL. However, selection of combination agents and potentially the timing of administration of those agents, as well as the prior exposure to immunosuppressive chemotherapy, may have impacted the effect of anti-PD-L1 therapy in this study.

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Declarations

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Conflicts of interest EAH has received honoraria for advisory work for Roche, Bristol Myers Squibb, Celgene, MSD, Gilead, Antigene, Janssen, and AstraZeneca; travel expenses and honoraria for speaker work for Roche; and research funding from Roche, Merck, Bristol Myers Squibb, Celgene, MSD, Gilead, Antigene, Janssen, and AstraZeneca. TP has acted in consultancy/advisory roles for AbbVie, ADC Therapeutics, AstraZeneca, Bayer, BeiGene, Bristol Myers Squibb, Celgene, Incyte, Genentech, Gilead, Kite, and Pharmacyclics and has received research funding from AbbVie, Bayer, BMS/Celgene, Genentech, and Incyte. AS has acted in consultancy/advisory roles for Bristol Myers Squibb, Servier, Gilead, Pfizer, Eisai, Bayer, MSD, Arqule, and Sanofi and has undertaken speaker bureau work for Takeda, Bristol Myers Squibb, Roche, AbbVie, Amgen, Celgene, Servier, Gilead, AstraZeneca, Pfizer, Arqule, Lilly, Sandoz, Eisai, Novartis, Bayer, and MSD. NSS has acted in consultancy/advisory roles for Kite, AbbVie, Janssen, and Kyowa Kirin and has undertaken speaker bureau work for Janssen and AbbVie. GPG has acted in advisory roles for Roche, Novartis, Gilead, and Janssen; and has received honoraria from Roche, AbbVie, and Novartis and research funding from MSD, BeiGene, and Janssen. JR has acted in consultancy/advisory roles for Takeda, Bristol Myers Squibb, ADC Therapeutics, and Novartis; owns stock in AstraZeneca and ADC Therapeutics; has received honoraria from Takeda, ADC Therapeutics, and Bristol Myers Squibb; has provided speaker/expert testimony for Takeda and ADC Therapeutics; and has received research funding from Takeda. KG has received honoraria from and served as a consultant for Amgen, AbbVie, BMS/Celgene, Janssen, Sanofi-Genzyme, Takeda, Novartis, Pfizer, Sandoz, and BeiGene and has received research funding from Amgen, AbbVie, BMS/Celgene, Janssen, Sanofi-Genzyme, Takeda, and Novartis. AT, BH, ADL, and RS are employees of and report stock ownership in Pfizer. SMA has received research funding (paid to his institution) for clinical trials from Bristol Myers Squibb, Seattle Genetics, Takeda, AI Therapeutics, Afimed, Pfizer, Trillium, Regeneron, and ADC Therapeutics. LEB, FR, GV, FO, CQ, and DS have no conflicts of interest that are directly relevant to the content of this article.

Availability of data and material Upon request, and subject to certain criteria, conditions and exceptions (see <https://www.pfizer.com/science/clinical-trials/trial-data-and-results> for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the USA and/or EU or (2) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

Code availability Not applicable.

Ethics approval This study was approved by the relevant institutional review boards or ethics committees of all participating centers and conducted in accordance with the principles of the Declaration of Helsinki.

Consent to participate All patients provided written informed consent.

Author contributions EAH, TP, LEB, AS, NSS, FR, GPG, JR, KG, and ADL collected, assembled, analyzed, and interpreted the data. GV

collected and assembled the data. FO, BH, and SMA conceived and designed the study and collected, assembled, analyzed, and interpreted the data. CQ and DS collected and assembled the data. AT conceived and designed the study and analyzed and interpreted the data. RS analyzed and interpreted the data. All authors were involved in writing the article and approved the final version.

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