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RESEARCH ARTICLE

Nivolumab plus brentuximab vedotin for relapsed/refractory diffuse large B-cell lymphoma

Nathalie A. Johnson[a], Pier Luigi Zinzani[b,c], Eva Domingo-Domenech[d], Joshua Brody[e], Justin Kline[f], Bijal Dinesh Shah[g], Amitkumar Nitinkumar Mehta[h], Herve Ghesquieres[i], Kerry J. Savage[j], Paul M. Barr[k], Armando Santoro[l], Silvia Ferrari[m], David Cunningham[n], Graham P. Collins[o], Michelle Fanale[p], Jennifer Krajewski[q], Alev Akyol[q], Russell Crowe[r]*, Rachael Wen[q] and John Kuruvilla[s]

[a]Department of Medicine, Division of Hematology, Jewish General Hospital, Montreal, QC, Canada; [b]IRCCS Azienda Ospedaliero-Universitaria di Bologna Istituto di Ematologia "Seràgnoli", Bologna, Italy; [c]Dipartimento di Scienze Mediche e Chirurgiche, Università di Bologna, Bologna, Italy; [d]Institut Catala d'Oncologia, Hospital Duran i Reynals, IDIBELL, Barcelona, Spain; [e]Mount Sinai School of Medicine, New York, NY, USA; [f]University of Chicago, Chicago, IL, USA; [g]Moffitt Cancer Center, Tampa, FL, USA; [h]University of Alabama at Birmingham, Birmingham, AL, USA; [i]Hopital Lyon Sud, Pierre-Bénite, France; [j]British Columbia Cancer Agency, Vancouver, BC, Canada; [k]University of Rochester, Rochester, NY, USA; [l]IRCCS Humanitas Research Hospital, Humanitas University, Milan, Italy; [m]Ospedale Papa Giovanni XXIII, Bergamo, Italy; [n]Royal Marsden Hospital, London, UK; [o]Churchill Hospital, Oxford, UK; [p]Pfizer Inc., Bothell, WA, USA; [q]Bristol Myers Squibb, Princeton, NJ, USA; [r]Bristol Myers Squibb, Boudry, Switzerland; [s]Princess Margaret Cancer Centre, Toronto, ON, Canada

ABSTRACT

Aims: Up to 40% of patients with diffuse large B-cell lymphoma (DLBCL) have relapsed or refractory (R/R) disease after first-line treatment with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone, and outcomes are poor after hematopoietic stem cell transplantation failure. CheckMate 436 (NCT02581631) was a phase 1/2 study to evaluate the efficacy and safety of nivolumab, a PD-1/PD-L1 inhibitor, plus brentuximab vedotin (BV) for the treatment of R/R non-Hodgkin lymphoma.

Materials and methods: Adult patients received nivolumab plus BV in 3-week cycles. The primary endpoint was overall response rate (ORR). Here, we report the results from the R/R DLBCL cohort (n = 42).

Results: With a median follow-up of 7.7 months, the ORR was 28.6% (n = 12), and 7.1% (n = 3) of patients achieved a complete response. Median duration of response (95% CI) was 3.6 (1.2–36.5) months. All patients experienced an adverse event (AE), most commonly diarrhea (n = 20, 47.6%). Grade 3/4 and 5 AEs occurred in 24 (57.1%) and 4 (9.5%) patients, respectively. Any-grade treatment-related AEs occurred in 35 (83.3%) patients. No new safety signals were identified.

Conclusions: Overall, the efficacy data from CheckMate 436 do not support the use of nivolumab plus BV for the treatment of R/R DLBCL.

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Diffuse large B-cell lymphoma; nivolumab; brentuximab vedotin; best overall response; immune checkpoint inhibitor; safety

1. Introduction

Approximately 30–40% of patients with diffuse large B-cell lymphoma (DLBCL) have relapsed or refractory (R/R) disease following first-line treatment with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone [1,2]. About half may achieve durable remission with salvage therapy followed by autologous hematopoietic stem cell transplantation (auto-HCT) [3–5]. Outcomes are poor after auto-HCT failure, with a median overall survival (OS) of 4 months and 1-year OS rate of 4% [6]. Therefore, novel and effective treatments are needed for R/R DLBCL.

Programmed death ligand-1 (PD-L1) and CD30 are expressed in 24% and 21% of DLBCL cases, respectively [7–9]. Nivolumab is a fully-human immunoglobulin G4 monoclonal antibody that inhibits programmed death-1 (PD-1)/PD-L1 binding and is indicated for treatment of classical Hodgkin lymphoma [10,11]. Nivolumab monotherapy exhibited modest clinical activity in R/R DLBCL, with an overall response rate (ORR) of 36% [12]; ORR was 10% and 3% for patients in whom auto-HCT had failed and in patients who were ineligible for auto-HCT, respectively [13]. Brentuximab vedotin (BV) is an anti-CD30 antibody–drug conjugate approved for treatment of classical Hodgkin lymphoma and anaplastic large cell lymphoma [14,15]. In a phase 2 trial (NCT01421667) in patients with R/R DLBCL, BV monotherapy resulted in an ORR of 44%, irrespective of CD30 expression [16]. Given the limited activity of nivolumab as monotherapy, one strategy to improve nivolumab efficacy is combining it with BV. BV may deplete immunosuppressive regulatory T cells and induce immunogenic cell death, increasing antigen presentation and augmenting nivolumab checkpoint blockade [17,18]. This analysis of the phase 1/2 CheckMate 436 (NCT02581631) trial evaluates the efficacy and safety of nivolumab plus BV in R/R DLBCL.

CONTACT Nathalie A. Johnson Nathalie.johnson@mcgill.ca Department of Medicine, Division of Hematology, Jewish General Hospital, 3755 Côte Ste-Catherine Road, Montreal, QC H3T 1E2, Canada
*Affiliation at the time of the study.

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Article highlights

- Among adult patients (n = 42) with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) who were treated with nivolumab plus brentuximab vedotin (BV), 28.6% achieved an overall response and 7.1% achieved a complete response.
- With a median 7.7 months of follow-up, the median duration of response was 3.6 months (95% confidence interval, 1.2–36.5).
- Lower cluster of differentiation 30 (CD30) or programmed death ligand-1 expression were both generally associated with worse response outcomes.
- No new safety signals were identified for nivolumab or BV.
- CheckMate 436 does not support the use of combination nivolumab plus BV therapy for the treatment of R/R DLBCL in adult patients.

2. Methods

As described previously [19,20], CheckMate 436 (NCT02581631) enrolled patients in Canada, France, Italy, Spain, the United Kingdom, and the United States who were aged ≥18 years with R/R DLBCL after failure of >1 prior treatment line including auto-HCT or, if transplant ineligible, following ≥2 multi-agent chemotherapy regimens. Eligible patients had Eastern Cooperative Oncology Group performance status scores of 0–1, CD30 expression on ≥1% of tumor cells (by local immunohistochemistry), and ≥1 site of measurable disease according to the Lugano 2014 classification [21]. Epstein–Barr virus status assessment was not mandatory at screening or during treatment. Race and ethnicity were recorded by physician report at the study site. A sample size of 40 patients was selected for a one-sided 90% confidence interval (CI) that excludes ORR of 40%, the null hypothesis ORR rate.

Patients received nivolumab 240 mg intravenously (IV; day 8 of cycle 1, then day 1 of each subsequent 3-week cycle) plus BV 1.8 mg/kg IV (day 1 of all cycles) until disease progression or unacceptable toxicity. Primary endpoints were ORR by investigator and safety. Secondary endpoints included complete response (CR) rate, duration of response (DOR), duration of CR, progression-free survival (PFS) by investigator, and OS. Responses were assessed according to the Lugano 2014 classification [21]. Target lesion reduction by best overall response (BOR) per investigator was defined for ≤6 of the largest dominant nodes or nodal masses measurable by CT or positron emission tomography CT.

ORR and CR were summarized by binomial response rate and its corresponding 2-sided 80% CI using the Clopper–Pearson method. DOR, duration of CR, PFS, and OS were summarized using the Kaplan–Meier product-limit method, and median values, along with 2-sided 95% CI based on log-log transformation were calculated.

This study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki. The trial protocol was approved by the institutional review board and independent ethics committee at each study site. All patients provided written informed consent. Bristol Myers Squibb data sharing policy may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

3. Results

This study was initiated on 11 February 2016 and completed on 7 February 2022. Forty-two patients were enrolled in the R/R DLBCL cohort (data cutoff: 23 July 2018); 17 (40.5%) had relapsed disease, 12 (28.6%) had refractory disease, and 13 (31.0%) had relapsed and refractory disease (Table 1). Median age was 59.0 (range, 24–85) years, 22 (52.4%) patients were male, median CD30 expression (based on central lab analysis) was 30.0% (range, 0–100%) of tumor cells, and 33/41 (80.5%) evaluable patients had ≥5% PD-L1 expression at baseline. Patients had received a median (range) of 3.0 (1.0–5.0) prior lines of systemic therapy. A median (range) of 4.0 (1–80) doses of nivolumab and 4.0 (1–34) doses of BV were received. At database lock (30 March 2022), all patients had discontinued treatment, mostly due to disease progression (n = 29, 69.0%; Supplemental Table S1). Nine (21.4%) patients received a granulocyte-colony stimulating factor (filgrastim) as concomitant medication.

At a median (range) follow-up of 7.7 (0.7–61.4) months, the ORR was 28.6% (95% CI, 15.7–44.6); 3 (7.1%) patients achieved CR and 9 (21.4%) achieved partial response (Table 2). Median DOR was 3.6 months (95% CI, 1.2–36.5). Median PFS was 2.6 months (95% CI, 1.4–2.8; Figure 1) and median OS was 13.3 months (95% CI, 6.6–15.9). Twenty-one (50.0%) patients, including all 12 who responded to treatment, had a measurable reduction in target lesion (Figure 2). Patients with higher CD30 expression generally had better responses (Figure 3). Patients with the lowest PD-L1 expression generally had worse response outcomes compared with patients with higher PD-L1 expression (Supplemental Figure S1).

All patients experienced AEs, most commonly diarrhea (n = 20, 47.6%), fatigue (n = 16, 38.1%), and nausea (n = 16, 38.1%; Table 3). Grade 3/4 AEs occurred in 24 (57.1%) patients, most commonly neutropenia (n = 5, 11.9%), malignant

Table 1. Baseline characteristics.

Characteristic	DLBCL (N = 42)
Median (range) age, years	59.0 (24–85)
<65 years	29 (69.0)
≥65 and <75 years	9 (21.4)
≥75 and <85 years	3 (7.1)
≥85 years	1 (2.4)
Sex	22 (52.4)
Male	22 (52.4)
Female	20 (47.6)
Race	
White	36 (85.7)
Black or African American	3 (7.1)
Asian	3 (7.1)
Disease status	
Relapsed	17 (40.5)
Refractory	12 (28.6)
Relapsed and refractory	13 (31.0)
Number of prior regimens	
Median (range)	3.0 (1.0–5.0)
1	1 (2.4)
2	16 (38.1)
3	19 (45.2)
4	3 (7.1)
≥5	3 (7.1)

Data are n (%) unless otherwise stated.
Abbreviation: DLBCL, diffuse large B-cell lymphoma.

Table 2. Efficacy.

	DLBCL (N = 42)
ORR, n (%)	12 (28.6)
80% CI*	19.4–39.4
95% CI*	15.7–44.6
BOR, n (%)†	
CR	3 (7.1)
PR	9 (21.4)
SD	8 (19.0)
PD	17 (40.5)
UTD	5 (11.9)
DOR, median (95% CI), months	3.6 (1.2–36.5)
DOCR, median (95% CI), months	36.5 (9.9–NR)
PFS, median (95% CI),‡ months‡	2.6 (1.4–2.8)
PFS rate at 12 months, (95% CI)‡	16.2 (6.5–29.7)
PFS rate at 24 months (95% CI)‡	6.5 (1.2–18.3)
PFS by PD-L1 expression, median (95% CI),‡ months‡	
≥5% of tumor cells	2.7 (1.4–3.5)
<5% of tumor cells	1.5 (0.7–2.7)
OS, median (95% CI), months‡	13.3 (6.6–15.9)
OS rate at 12 months (95% CI)‡	56.9 (39.9–70.7)
OS rate at 24 months (95% CI)‡	25.0 (12.3–40.0)
OS by PD-L1 expression, median (95% CI), months‡	
≥5% of tumor cells	12.8 (6.1–15.9)
<5% of tumor cells	14.0 (3.4–NR)

*Confidence intervals based on the Clopper–Pearson method. †Response assessed by Lugano Classification 2014 [21]. ‡Median and rates computed using Kaplan–Meier method.

Abbreviations: BOR, best overall response; CI, confidence interval; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DOCR, duration of complete response; DOR, duration of response; NR, not reached; ORR, overall response rate; OS, overall survival; PD, progressive disease; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, partial response; SD, stable disease; UTD, unable to determine.

neoplasm progression (n = 5, 11.9%), and anemia (n = 4, 9.5%). Grade 5 AEs occurred in 4 (9.5%) patients: malignant neoplasm progression (n = 3, 7.1%) and sepsis (n = 1, 2.4%). Any-grade TRAEs occurred in 35 (83.3%) patients, most commonly peripheral neuropathy (n = 14, 33.3%), diarrhea (n = 11, 26.2%), and fatigue (n = 10, 23.8%). The most common hematologic TRAE was neutropenia (n = 6, 14.3%). Grade 3/4 TRAEs occurred in 15 (35.7%) patients, most commonly neutropenia (n = 5, 11.9%) and anemia (n = 1, 2.4%). There were no cases of grade 3/4 infusion-related reaction and no grade 5 TRAEs; however, the study sponsor's historical grading system for AEs, which was used in this trial, only classified AEs as grade 5 if death occurred within 24 hours of onset of the AE. Thirty (71.4%) patients died, most commonly from disease progression (n = 26, 61.9%). One patient died from study drug toxicity attributed to nivolumab (Stevens–Johnson syndrome, disease progression, toxic epidermal necrolysis; Table 4). Six (14.3%) patients died ≤30 days after their last dose and 14 (33.3%) ≤100 days after their last dose. The most common immune-mediated AE was diarrhea (n = 20, 47.6%; Supplemental Table S2). None of the patients had an allogeneic HCT and 1 patient received high dose chemotherapy followed by auto-HCT.

4. Discussion

In CheckMate 436, ORR was generally comparable with previous studies investigating PD-1 inhibitor monotherapy in patients with R/R DLBCL for whom auto-HCT failed or who were ineligible for auto-HCT. A previous study with nivolumab (NCT02038933) reported an ORR and CR of 10% and 3%, respectively [13], and a study of pembrolizumab monotherapy (NCT01953692) demonstrated an ORR of 12% [22]. In the R/R primary mediastinal B-cell lymphoma (PMBL) cohort of CheckMate 436 (median follow-up, 11.1 months), nivolumab plus BV demonstrated a higher ORR and CR rate (73% and 37%, per investigator) than those reported in this manuscript for patients with R/R DLBCL [19]. However, PMBL exhibits

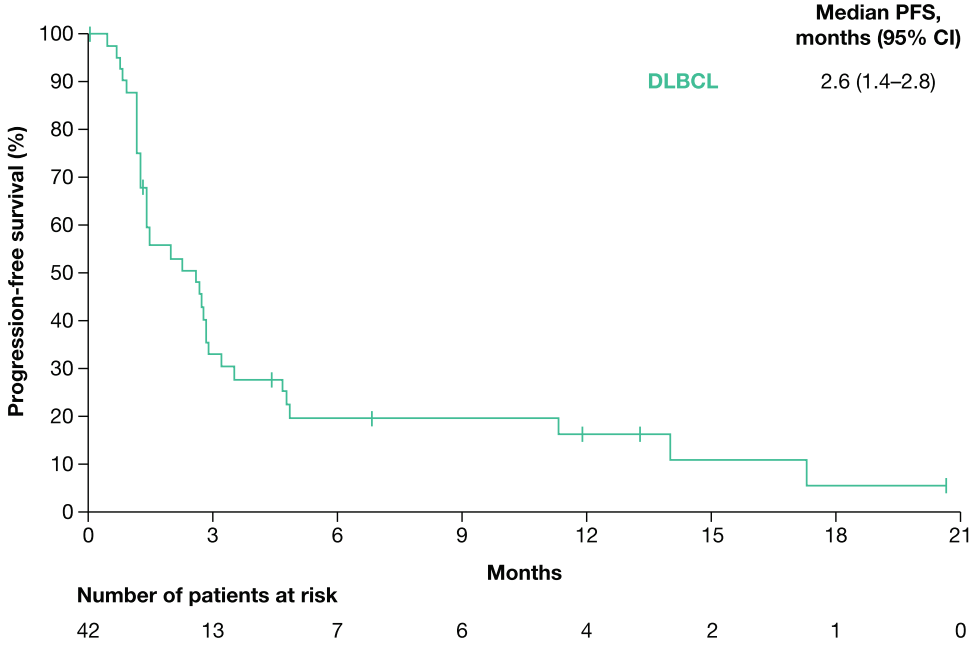

Figure 1. Progression-free survival.

Symbols represent censored observations.

Abbreviations: CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; PFS, progression-free survival.

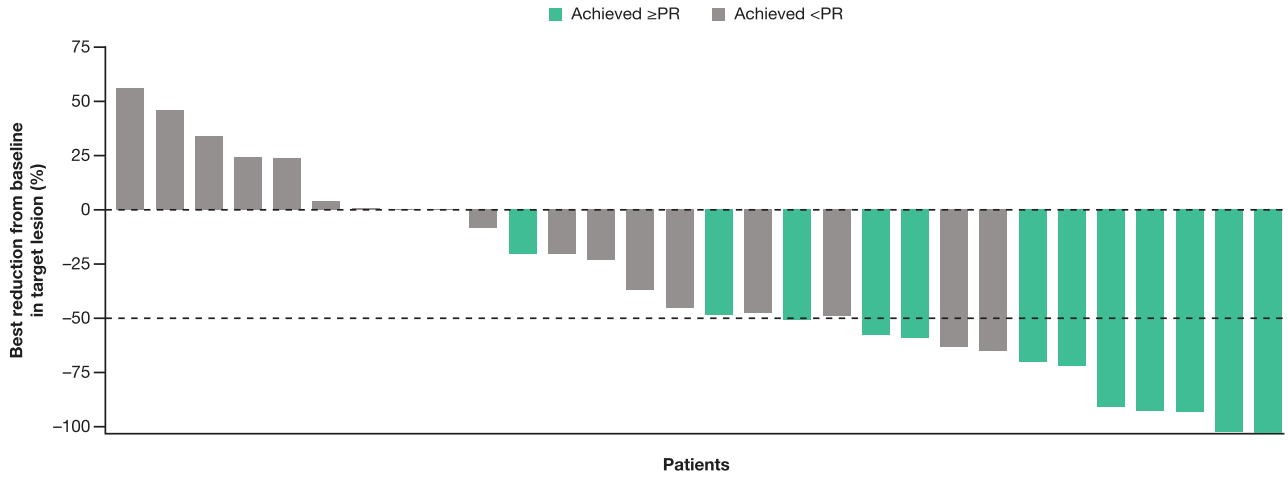

Figure 2. Target lesion reduction by best overall response.

Includes response-evaluable patients with target lesions assessed and at least 1 on-study timepoint with all baseline target lesions assessed. Negative/positive value refers to maximum tumor reduction/minimum tumor increase. Best change is based on evaluable target lesion measurements up to progression or start of subsequent therapy. Horizontal reference line indicates the 50% reduction consistent with a response per Lugano Classification 2014 [21].

Abbreviation: PR, partial response.

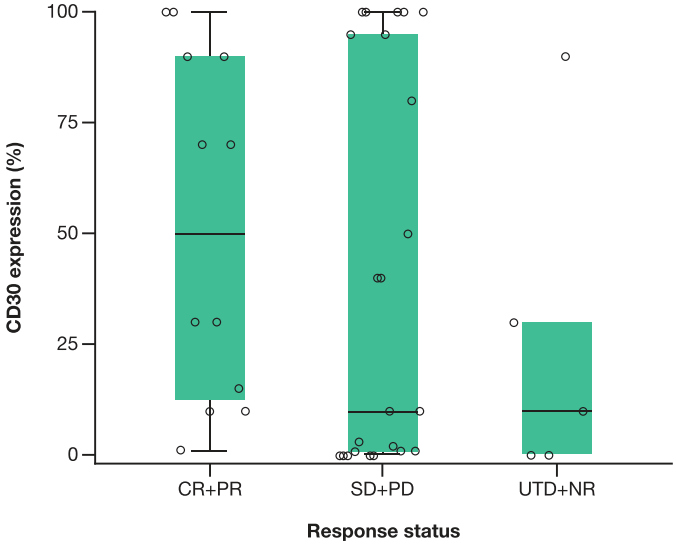

Figure 3. CD30 expression by response status.

The horizontal line within each box represents the median, the lower and upper ends of the boxes represent the 25th and 75th percentiles, and the whiskers indicate the most extreme points within 1.5 of the IQR.

Abbreviations: CR, complete response; IQR, interquartile range; NR, not reported; PD, progressive disease; PR, partial response; SD, stable disease; UTD, unable to determine.

Table 3. Safety summary.

	DLBCL (N = 42)	
	Any grade	Grade 3/4
AEs	42 (100.0)	24 (57.1)*
Non-hematologic AEs in ≥20% of patients		
Diarrhea	20 (47.6)	1 (2.4)
Nausea	16 (38.1)	0
Fatigue	16 (38.1)	1 (2.4)
Peripheral neuropathy	14 (33.3)	2 (4.8)
Pyrexia	13 (31.0)	0
Abdominal pain	11 (26.2)	1 (2.4)
Cough	10 (23.8)	1 (2.4)
Asthenia	10 (23.8)	3 (7.1)
Hypokalemia	9 (21.4)	2 (4.8)
Vomiting	9 (21.4)	1 (2.4)
Constipation	9 (21.4)	0
Malignant neoplasm progression†	9 (21.4)	5 (11.9)
Hematologic AEs	13 (31.0)	11 (26.2)
Neutropenia	6 (14.3)	5 (11.9)
Anemia	5 (11.9)	4 (9.5)
Thrombocytopenia	3 (7.1)	3 (7.1)
Febrile neutropenia	1 (2.4)	1 (2.4)
Lymphadenopathy	1 (2.4)	0
TRAEs	35 (83.3)	15 (35.7)
Non-hematologic TRAEs in ≥10% of patients		
Peripheral neuropathy	14 (33.3)	2 (4.8)
Diarrhea	11 (26.2)	1 (2.4)
Fatigue	10 (23.8)	1 (2.4)
Rash	5 (11.9)	1 (2.4)
Hematologic TRAEs		
Neutropenia	6 (14.3)	5 (11.9)
Anemia	2 (4.8)	1 (2.4)
Thrombocytopenia	1 (2.4)	1 (2.4)

Data are n (%).

*There were also 4 (9.5%) patients who experienced grade 5 AEs. †Defined as progression of the tumor being treated on the study.

Abbreviations: AE, adverse event; DLBCL, diffuse large B-cell lymphoma; TRAE, treatment-related AE.

9p24.1 genetic alterations in 45–63% of patients, resulting in higher PD-L1/2 expression levels than observed in DLBCL, which may explain the difference in response rates [23,24]. While median PFS and duration of response were short, there was a small subset of patients (n = 4) who achieved a remission duration of >1 year.

The combination of nivolumab plus BV resulted in a lower a response rate (28.6%) than a previous study examining BV monotherapy (44%) and was similar to studies examining nivolumab monotherapy (3–36%) in patients with DLBCL [12,13,16]. While direct comparisons between studies cannot be made, potential explanations may include differences in patient populations, such as differences in baseline CD30 or PD-L1 expression, and differences in nivolumab dosing and schedule between studies. Beyond differences in trial design, the reason for the difference in response rates is unclear but may be related to mechanisms of PD-1 resistance [25].

Table 4. Summary of deaths.

	DLBCL (N = 42)
Deaths, n (%)	30 (71.4)
Disease progression	26 (61.9)
Study drug toxicity	1 (2.4)*
Other	3 (7.1)†
Deaths within 30 days of last dose	6 (14.3)
Deaths within 100 days of last dose	14 (33.3)

*This patient's causes of death were Stevens–Johnson syndrome, disease progression, and toxic epidermal necrolysis. This was not considered a grade 5 TRAE as grade 5 TRAEs per protocol assessment criteria were defined as death within 24 hours of the TRAE. †Reasons for death were recurrent infection and pancytopenia (n = 1 [2.4%]), sepsis (n = 1 [2.4%]), and septic shock (n = 1 [2.4%]).

Abbreviations: DLBCL, diffuse large B-cell lymphoma; TRAE, treatment-related adverse event.

The safety profile reported in CheckMate 436 was comparable to studies with BV or nivolumab alone in patients with hematological malignancies, and no new safety concerns were identified [19,20,26].

CheckMate 436 demonstrates nivolumab plus BV has limited efficacy in R/R DLBCL, but a similar safety profile to that observed in PMBL [19]. Since initiation of this study, polatuzumab vedotin with rituximab, cyclophosphamide, doxorubicin, and prednisone has been approved as first-line therapy for adults with DLBCL [27]. Additionally, CD19-targeted chimeric antigen receptor (CAR) T cell therapy with both axicabtagene ciloleucel (the ZUMA-1 trial [NCT02348216] and ZUMA-7 trial [NCT03391466]) and lisocabtagene maraleucel (the TRANSFORM trial [NCT03575351] and TRANSCENT NHL 001 trial [NCT02631044]) have been approved for use in second-line or later DLBCL treatment [28,29]. More recently, CD3/CD20 bispecific antibodies epcoritamab (the EPCORE NHL-1 trial [NCT03625037]) and glofitamab (NCT03075696) have been approved for third-line or later DLBCL treatment [30–33]. Additional therapies are still required for patients with R/R DLBCL who have previously received novel therapies [34].

5. Conclusions

CheckMate 436 demonstrated a safety profile consistent with nivolumab plus BV in the treatment of adults with other lymphoma subtypes; however, this trial does not support the use of nivolumab plus BV in R/R DLBCL treatment. The role of nivolumab and anti–PD-1 therapy in R/R DLBCL treatment is unclear.

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Author contributions

Conceptualization: Nathalie A Johnson, Pier Luigi Zinzani, Eva Domingo-Domenech, Joshua Brody, Justin Kline, Bijal Dinesh Shah, Amitkumar Nitinkumar Mehta, Herve Ghesquieres, Kerry J Savage, Paul M Barr, Armando Santoro, Silvia Ferrari, David Cunningham, Michelle Fanale, Alev Akyol, Graham P Collins, John Kuruvilla

Data curation: Jennifer Krajewski, Alev Akyol, Russell Crowe, Rachael Wen

Formal analysis: Jennifer Krajewski, Alev Akyol, Russell Crowe, Rachael Wen

Funding acquisition: Alev Akyol

Investigation: Nathalie A Johnson, Pier Luigi Zinzani, Eva Domingo-Domenech, Joshua Brody, Justin Kline, Bijal Dinesh Shah, Amitkumar Nitinkumar Mehta, Herve Ghesquieres, Kerry J Savage, Paul M Barr, Armando Santoro, Silvia Ferrari, David Cunningham, Graham P Collins, John Kuruvilla

Methodology: Nathalie A Johnson, Pier Luigi Zinzani, Eva Domingo-Domenech, Joshua Brody, Justin Kline, Bijal Dinesh Shah, Amitkumar Nitinkumar Mehta, Herve Ghesquieres, Kerry J Savage, Paul M Barr, Armando Santoro, Silvia Ferrari, David Cunningham, Michelle Fanale, Alev Akyol, Graham P Collins, John Kuruvilla

Project administration: Jennifer Krajewski, Alev Akyol

Resources: Jennifer Krajewski, Alev Akyol

Software: Jennifer Krajewski, Alev Akyol, Russell Crowe, Rachael Wen

Supervision: Alev Akyol

Validation: Jennifer Krajewski, Alev Akyol, Russell Crowe, Rachael Wen

Visualization: Nathalie A Johnson, Pier Luigi Zinzani, Eva Domingo-Domenech, Joshua Brody, Justin Kline, Bijal Dinesh Shah, Amitkumar Nitinkumar Mehta, Herve Ghesquieres, Kerry J Savage, Paul M Barr, Armando Santoro, Silvia Ferrari, David Cunningham, Graham P Collins, Michelle Fanale, Jennifer Krajewski, Alev Akyol, Russell Crowe, Rachael Wen, John Kuruvilla

Writing – original draft: Nathalie A Johnson, Pier Luigi Zinzani, Eva Domingo-Domenech, Joshua Brody, Justin Kline, Bijal Dinesh Shah, Amitkumar Nitinkumar Mehta, Herve Ghesquieres, Kerry J Savage, Paul M Barr, Armando Santoro, Silvia Ferrari, David Cunningham, Graham P Collins, Michelle Fanale, Jennifer Krajewski, Alev Akyol, Russell Crowe, Rachael Wen, John Kuruvilla

Writing – review and editing: Nathalie A Johnson, Pier Luigi Zinzani, Eva Domingo-Domenech, Joshua Brody, Justin Kline, Bijal Dinesh Shah, Amitkumar Nitinkumar Mehta, Herve Ghesquieres, Kerry J Savage, Paul M Barr, Armando Santoro, Silvia Ferrari, David Cunningham, Graham P Collins, Michelle Fanale, Jennifer Krajewski, Alev Akyol, Russell Crowe, Rachael Wen, John Kuruvilla

Disclosure statement

NAJ has received grants from Gilead, Incyte, and Roche; has received consulting fees from AbbVie, AstraZeneca, BeiGene, Gilead, Merck, and Roche; has received honoraria from AbbVie, AstraZeneca, and BeiGene; and has received payments for expert testimony from Gilead. PLZ has received honoraria from AbbVie, AstraZeneca, BeiGene, Bristol Myers Squibb, Gilead, Incyte, Janssen, Kyowa Kirin, Merck Sharp & Dohme, Novartis, Roche, Sanofi, and Takeda. ED-D has participated in advisory boards with BeiGene and Takeda, and received honoraria and travel support from Bristol Myers Squibb, Kyowa Kirin, and Takeda. JB has received grants, consulting fees, and honoraria from ADC Therapeutics, AstraZeneca, Epizyme, Genentech/Roche, Kite/Gilead, Merck, and Seagen. J Kline has received grants (to institution) from Merck and Verastem; has received consulting fees from Merck and Secura Bio; has received honoraria from Kite/Gilead; and has participated in data safety monitoring or advisory boards for ADC Therapeutics, BeiGene, Daiichi Sankyo, Gilead, and Secura Bio. BDS has received grants (to institution) from Jazz Pharma, Kite, and Servier; has received honoraria from Adaptive Biotech, Amgen, Autolus, BeiGene, Bristol Myers Squibb, Century Therapeutics, Kite/Gilead, Novartis, and Pfizer; has received travel support from Kite/Gilead and Takeda; has participated in data safety monitoring or advisory boards for PeproMene Bio and Takeda; and has held a leadership or fiduciary role for the NCCN. ANM has received grants from Affimed, Bristol Myers Squibb/Celgene/Juno, Forty Seven/Gilead, I-Mab, Incyte, Innate, Kite/Gilead, Merck, Roche/Genentech, Seagen, Takeda, and TG Therapeutics; and has received consultancy fees from AstraZeneca, BeiGene, Bristol Myers Squibb, Gilead, Incyte, Kyowa Kirin, Morphosys/Incyte, Novartis, Pharmacyclics, Seagen, and TG Therapeutics. HG has received consultancy fees from Gilead and Roche and has received honoraria from AbbVie, Bristol Myers Squibb, Gilead, and Roche. KJS has received grants from Bristol Myers Squibb; has received grants (to institution) from Roche; has received honoraria from AbbVie, Bristol Myers Squibb, Janssen,

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Ethical declaration

The trial protocol was approved by the institutional review board and independent ethics committee at each study site. All patients provided written informed consent.

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