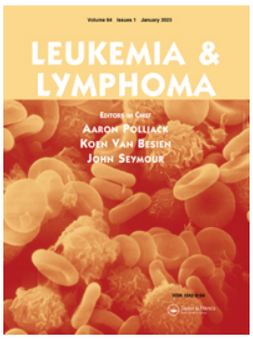

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ORIGINAL ARTICLE

Pembrolizumab for patients with non-Hodgkin lymphoma: phase 1b KEYNOTE-013 study

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ABSTRACT

The multicohort phase 1b KEYNOTE-013 study (NCT01953692) evaluated the safety and efficacy of pembrolizumab in patients with relapsed or refractory NHL who were ineligible for or failed hematopoietic cell transplantation (HCT). Patients received pembrolizumab (cohort 4) or pembrolizumab plus lenalidomide (cohort 5). Primary end points were safety and objective response rate (ORR) per IWG 2007 criteria. Cohort 4 included 89 patients. ORR was 22% (19/86; 90% CI 15–31; 10 CR, nine PR); ORRs by disease type were 48% (10/21), 10% (2/20), 12% (5/41), and 50% (2/4), for PMBCL, FL, DLBCL, and 'other' NHL, respectively. Toxicity was as predicted. Cohort 5 included 19 patients. ORR was 39% (90% CI 20–61; four CR, three PR). Hematologic toxicities were the most common treatment-related AEs. In conclusion, pembrolizumab following HCT ineligibility/failure confirms prior experience in PMBCL but not with NHL subtypes in this study. Additional analyses in DLBCL may not be warranted.

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KEYWORDS
Non-Hodgkin lymphoma; pembrolizumab; B-cell lymphoma; PD-L1

Introduction

Diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) are the two most common types of non-Hodgkin lymphoma (NHL) in the United States [1]; both typically occur at advanced age (mid-60s) but differ in disease aggressiveness and response to treatment [1,2]. Primary mediastinal B-cell lymphoma (PMBCL) is a subtype of DLBCL typically diagnosed in young women; it is aggressive but responds well to available treatments in frontline settings. The frontline standard-of-care for DLBCL with chemoimmunotherapy has largely remained unchanged, and a significant proportion of patients will eventually relapse [1,3]. Most patients with FL will also relapse with available therapies [4]. Thus, new treatments are needed for both diseases, especially in the relapsed or refractory (R/R) setting. Recent treatment advances with chimeric antigen receptor T-cell (CAR-T) therapy have demonstrated significant antitumor activity in R/R NHL [5–8], and immune checkpoint inhibition has shown preliminary activity in PMBCL [9].

Upregulation of programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1) expression may be a mechanism for tumor immune escape in hematologic cancers [10–12]. PD-L1 is located on chromosome 9p24.1, which is amplified in both PMBCL and classical Hodgkin lymphoma (cHL), conferring genetic similarities between the two not shared with other NHL subtypes [13].

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The open-label, multicohort, phase 1b KEYNOTE-013 (NCT01953692) study of the PD-1 inhibitor pembrolizumab investigated the safety and response activity in patients with hematologic malignancies [14–17]. Pembrolizumab demonstrated a manageable safety profile, high response rates, and durable antitumor activity as monotherapy in patients with PMBCL in the phase 1b KEYNOTE-013 ($N=$ 21) and phase 2 KEYNOTE-170 ($N=$ 35) studies [9,18].

The immunomodulatory drug lenalidomide has demonstrated efficacy in various hematologic malignancies as well as efficacy as monotherapy [19,20] and in combination with rituximab [21,22] in R/R DLBCL. Clinical studies of lenalidomide monotherapy in R/R DLBCL reported objective response rates (ORRs) ranging from 19% to 34% [19,20,23]. In comparison, clinical studies on combination therapies with lenalidomide demonstrated ORRs ranging from 28% to 43% [21,22,24], providing a rationale for investigating the efficacy of pembrolizumab and lenalidomide combinations.

PMBCL data from KEYNOTE-013 were initially presented using assessment by independent central review [9]; we present follow-up investigator data with an additional 26 months of follow-up for the PMBCL cohort and data for the other NHL subtypes and the pembrolizumab/lenalidomide combination in DLBCL.

Materials and methods

Study design and participants

Eligible patients were aged ≥18 years with R/R disease categorized as PMBCL (cohort 4A), 'other' PD-L1-positive NHL per independent central review by immunohistochemistry (cohort 4B), FL (cohort 4C), or DLBCL (cohort 4D, cohort 5). Patients with FL or DLBCL were eligible irrespective of PD-L1 status. All patients were ineligible for, experienced failure of, or refused hematopoietic cell transplantation (HCT).

The study protocol was approved by the institutional review board or ethics review committee at each study site and conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. Before enrollment, all patients provided written informed consent to participate. All authors had access to the primary clinical trial data.

Enrolled patients received intravenous pembrolizumab at doses of 10 mg/kg every 2 weeks (Q2W) (cohort 4A and cohort 4B). Following a study amendment, subsequent patients in cohort 4A and all in cohorts 4C and 4D received a fixed dose of 200 mg every 3 weeks (Q3W). Patients in cohort 5 received pembrolizumab 200 mg Q3W plus lenalidomide 25 mg orally daily for the first 21 consecutive days of a 28-day treatment cycle. Treatment began immediately following the day of treatment allocation and continued until confirmed disease progression, unacceptable adverse event (AE), or withdrawal because of patient or investigator decision. For patients receiving pembrolizumab 10 mg/kg Q2W, disease response assessments were performed at week 12 and every 8 weeks thereafter for up to 52 doses. For patients receiving pembrolizumab 200 mg Q3W, disease response assessments were performed at week 6, week 12, and every 9 weeks thereafter for up to 35 doses. Patients in cohort 5 were assessed at week 12 and every 12 weeks thereafter for up to 26 cycles. Survival was assessed every 12 weeks after disease progression or the start of new anticancer treatment. Safety and tolerability were assessed by clinical review of all adverse experiences, laboratory tests, and vital signs. AEs were graded using the Common Terminology Criteria for Adverse Events, version 4.0 [25].

The primary end points were safety of single-agent pembrolizumab as monotherapy and in combination with lenalidomide and ORR by investigator review per International Working Group 2007 criteria for malignant lymphoma by disease subtype [26]. Secondary end points included progression-free survival (PFS), overall survival (OS), duration of response (DOR), and clinical response by PD-L1 expression. Archived formalin-fixed paraffin-embedded biopsy samples or newly obtained core or excisional biopsy samples were obtained at patient screening for PD-L1 immunohistochemistry confirmation by central laboratory. PD-L1 expression status was assessed using the immunohistochemistry *H*-score, which measures the proportion and intensity of tumor cells with membranous staining for PD-L1 [9]. PD-L1-positive status was categorized as absent (*H*-score $=0$), low expression (1–99), and high expression (≥100) [9].

Statistical analyses

The safety analysis population included all patients who received at least one dose of pembrolizumab. Summary statistics were provided for safety end points as appropriate. The efficacy analysis population included all patients assigned who received at least one dose of the study treatment, had a baseline disease assessment, and had a postbaseline assessment or discontinued the study because of drug-related AEs from each disease cohort (cohorts 4 and 5). Patients in the study who did not have disease progression and who received HCT (autologous or allogeneic) following

discontinuation of pembrolizumab treatment were censored for DOR and PFS at the last observed scan before HCT. Patients who started new anticancer therapy were censored for DOR and PFS at the time of initiation of new therapy. For ORR, the point estimate with 90% confidence interval (CI) was calculated based on the exact binomial CI method.

Sample size and power calculations were specific to each cohort. For cohort 4, ~78 patients with NHL were to be included in the study for 80% power to detect a 14% difference in ORR from the null hypothesis of ORR = 25%. For cohort 5, ~30–66 patients were to be included in the study, depending on the number of dose levels of lenalidomide assessed during safety run-in, which assessed lenalidomide at the initial 25-mg dose and reduced in 5-mg increments based on the toxicity probability intervals method [27]. For the final data analysis, patients treated at the confirmed 20-mg recommended phase 2 dose during safety run-in were to be included among the 30 planned participants enrolled in the dose expansion phase. The maximum half-width of the two-sided 90% exact CI was planned as 16%, with a targeted number of 30 patients. However, because of a US Food and Drug Administration hold on studies of immune checkpoint inhibitors plus immunomodulatory imide drugs and dexamethasone due to safety concerns in multiple myeloma studies, the sponsor elected to close cohort 5. A 95% CI based on the exact binomial CI method was used for exploratory analyses. The data cut-off date for this analysis was 26 June 2020.

Table 1. Baseline characteristics and study disposition of all-patients-as-treated population.

	Cohort 4 (NHL) Pembrolizumab $N = 89$	Cohort 5 (DLBCL with combination pembrolizumab + lenalidomide) $N = 19$
Patients, *n* (%)	89 (100)	19 (100)
PMBCL	21 (24)	–
Follicular lymphoma	22 (25)	–
DLBCL	42 (47)	19 (100)
Other PD-L1-positive NHL[a]	4 (4)	–
Male, *n* (%)	50 (56)	11 (58)
Age ≥65 years, *n* (%)	30 (34)	9 (47)
Median, years	60	63
Range, years	22–85	43–87
ECOG PS, *n* (%)		
0	34 (38)	8 (42)
1	54 (61)	11 (58)
2	1 (1)	0
Prior lines of therapy		
Median	3	3
Range	1–14	1–7
PD-L1 status, *n* (%)		
Positive	32 (36)	4 (21)
Negative	37 (42)	9 (47)
Missing	20 (22)	6 (32)
Discontinued treatment	83 (93)	19 (100)
Progressive disease	54 (61)	7 (37)
Clinical progression	13 (15)	4 (21)
Adverse event	7 (8)	1 (5)
Patient decision	6 (7)	1 (5)
Physician decision	3 (3)	0
Study terminated by sponsor	0	6 (32)
Completed ≥2 years of treatment	6 (7)	0

DLBCL: diffuse large B-cell lymphoma; ECOG PS: Eastern Cooperative Oncology Group performance status; NHL: non-Hodgkin lymphoma; PD-L1: programmed death ligand 1; PMBCL: primary mediastinal B-cell lymphoma.
[a]The 'other' PD-L1-positive NHL subcategory includes two patients with gray-zone lymphoma and one patient each with splenic marginal zone lymphoma and mantle cell lymphoma.

Results

Patients

Eighty-nine patients with R/R NHL were treated with pembrolizumab monotherapy (cohort 4) between 27 January 2014 and 15 December 2016, and were included in the safety analysis. The median age was 60 years (range 22–85), with 30 patients (34%) aged ≥65 years. Patients had received a median of three prior lines of therapy (range 1–14), 32 patients (36%) were PD-L1-positive, and one patient (1%) received prior CAR-T therapy. Twenty-one (24%) patients had PMBCL, 22 patients (25%) had FL, 42 patients (47%) had DLBCL, and four patients (4%) had other PD-L1-positive R/R NHL (two patients had gray-zone lymphoma, and one patient each had splenic marginal zone lymphoma and mantle cell lymphoma) (Table 1). Six patients (7%) completed 2 years of study treatment, and 83 patients (93%) discontinued treatment, including 54 patients (61%) who discontinued because of progressive disease (PD), 13 patients (15%) who discontinued because of clinical progression, seven patients (8%) who discontinued because of AEs, and nine patients (10%) who discontinued because of physician or patient decision (Table 1). At the database cutoff date, 63 patients (71%) had died; 49 (55%) were because of PD, 11 (12%) were because of AEs, and three (4%) were because of unknown causes. The median duration of follow-up (time from first dose to date of death or database cutoff date if the patient was still alive) was 10.8 months (range 0.3–76.4). Twelve patients (13%) received study treatment for ≥1 year.

Nineteen patients who had DLBCL were treated with pembrolizumab and lenalidomide (cohort 5) between 14 July 2016 and 24 May 2017, and were included in the safety analysis population. The median age was 63.0 years (range 43–87), with nine (47%) patients aged ≥65 years. Patients had received a median of three prior lines of therapy (range 1–7) (Table 1); four patients (21%) were PD-L1 positive and one patient (5%) had received prior CAR-T therapy. No

Table 2. Treatment-related adverse events occurring in ≥5% of patients in Cohort 4 or ≥10% of patients in Cohort 5.

	Cohort 4, $N = 89$										Cohort 5	
	Overall (NHL)		PMBCL $n = 21$		Follicular lymphoma $n = 22$		DLBCL $n = 42$		Other PD-L1$^+$ NHL $n = 4$		DLBCL with pembrolizumab + lenalidomide $N = 9$	
Adverse event, *n* (%)	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Fatigue	22 (25)	4 (4)	3 (14)	1 (5)	6 (27)	1 (5)	11 (26)	2 (5)	2 (50)	0	3 (16)	0
Nausea	9 (10)	1 (1)	4 (19)	0	1 (5)	1 (5)	3 (7)	0	1 (25)	0	2 (11)	0
Diarrhea	8 (9)	1 (1)	4 (19)	0	3 (14)	1 (5)	0	0	1 (25)	0	3 (16)	0
Decreased appetite	7 (8)	0	3 (14)	0	1 (5)	0	3 (7)	0	0	0	2 (11)	0
Neutropenia	7 (8)	6 (7)	3 (14)	3 (14)	0	0	4 (10)	3 (7)	0	0	8 (42)	7 (37)
Pyrexia	7 (8)	0	2 (10)	0	0	0	4 (10)	0	1 (25)	0	0	0
Anemia	6 (7)	4 (4)	0	0	1 (5)	1 (5)	5 (12)	3 (7)	0	0	2 (11)	1 (5)
Hypothyroidism	6 (7)	0	2 (10)	0	0	0	3 (7)	0	1 (25)	0	3 (16)	0
Pruritus	5 (6)	0	0	0	1 (5)	0	4 (10)	0	0	0	1 (3)	0
Constipation	4 (5)	0	0	0	0	0	2 (5)	0	0	0	3 (16)	0
Thrombocytopenia	3 (3)	2 (2)	0	0	0	0	3 (7)	2 (5)	0	0	5 (26)	3 (16)
Rash	2 (2)	0	0	0	2 (9)	0	0	0	0	0	4 (21)	1 (5)
Hyperthyroidism	1 (1)	0	0	0	0	0	0	0	0	0	2 (11)	0

DLBCL: diffuse large B-cell lymphoma; NHL: non-Hodgkin lymphoma; PD-L1: programmed death ligand 1; PMBCL: primary mediastinal B-cell lymphoma.

patients completed 2 years of study treatments, and all discontinued, including seven patients (37%) who discontinued because of PD, four patients (21%) who discontinued because of clinical progression, one patient (5%) who discontinued because of AEs, one patient (5%) who discontinued because of patient withdrawal, and six patients (32%) who discontinued because the study was terminated by the sponsor (Table 1). At the time of the database cutoff, 12 patients (63%) had died: 11 patients (58%) because of PD and one due to AEs. Median duration of follow-up (time from first dose to date of death or database cutoff date if the patient was still alive) was 17.9 months (range 0.8–46.8). Five (26%) patients received study treatment for ≥1 year.

Safety

Eighty-four of 89 patients (94%) from cohort 4 who were treated with pembrolizumab monotherapy had an AE of any grade; 50 patients (56%) had a treatment-related AE (TRAE), 11 patients (12%) had a serious TRAE, and 19 patients (21%) had a grade 3 or 4 TRAE. The most common TRAEs in cohort 4 were fatigue ($n = 22$ (25%)), nausea ($n = 9$ (10%)), and diarrhea ($n = 8$ (9%)) (Table 2). The most common grade 3 and 4 TRAEs were neutropenia (n = 6 (7%)), anemia (n = 4 (4%), and fatigue (n = 4 (4%)) (Table 2, Supplemental Table 1). Three patients (3%) discontinued from the study because of TRAEs (febrile neutropenia, pneumonitis, and maculopapular rash). Four patients (4%) died because of AEs (grade 5 AEs: intestinal perforation ($n = 1$), sepsis ($n = 1$), pneumonia (n = 2), and veno-occlusive disease (n = 1); one grade 5 AE was considered treatment-related (veno-occlusive disease).

The patient who died due to treatment-related veno-occlusive disease had not undergone allogeneic HCT. On day 101, an ultrasound was performed on this patient with an increased resistive index of 0.88. A high serum-ascites albumin gradient was suggestive of portal hypertension. Hepatitis C polymerase chain reaction and workup for spontaneous bacterial peritonitis were negative. Elevated levels of liver enzymes were deemed multifactorial, and a biopsy could not be performed because of coagulopathy. The patient was diagnosed with grade 4 veno-occlusive disease and died on day 107. The reported cause of death was grade 5 veno-occlusive disease considered related to pembrolizumab.

Eighteen of 19 patients (95%) in cohort 5 who were treated with pembrolizumab and lenalidomide had an

any-grade AE, 16 patients (84%) had a TRAE, two patients (11%) had a serious TRAE, and 10 patients (53%) had a grade 3 or 4 TRAE. The most common TRAEs for patients in cohort 5 were neutropenia (n = 8 (42%)), thrombocytopenia (n = 5 (26%)), rash (n = 4 (21%)), and fatigue, diarrhea, hypothyroidism, and constipation (n = 3 (16%) each) (Table 2). The most common grade 3 and 4 TRAEs were neutropenia (n = 7 (37%)) and thrombocytopenia (n = 3 (16%)) (Table 2, Supplemental Table 1). One patient (5%) discontinued from the study because of treatment-related increases in aspartate aminotransferase and alanine aminotransferase as well as acute kidney injury. No deaths due to AEs or TRAEs were reported.

Efficacy

Eighty-six patients from cohort 4 who were treated with pembrolizumab monotherapy were included in the efficacy analyses. The study did not meet the prespecified clinical response threshold; the ORR from the cohort 4 overall population was 22% (90% CI 15–31), with 10 complete responses (CRs) and nine partial responses (PRs), as presented in Table 3. Of the 10 patients with CR, only one had experienced disease progression at data cutoff, and all were still alive. In patients with PMBCL (*n*= 21), ORR was 48% (90% CI 29–67; six CR, four PR); in patients with FL (*n*= 20), ORR was 10% (90% CI 2–28; one CR, one PR); in patients with DLBCL (*n*= 41), ORR was 12% (90% CI 5–24; three CR, two PR); and in patients with 'other' PD-L1-positive NHL (*n*= 4), ORR was 50% (90% CI 10–90; two PR (gray-zone lymphoma)). The median time to response for the total population of cohort 4 was 2.8 months (range 1.3–19.6), and median DOR was not reached (NR; 95% CI 9.6–NR) (Figure 1). Median DOR for responders in cohort 4 by disease type were: PMBCL (*n*= 10), NR (95% CI 6.9–NR); FL (*n*= 2), NR (95% CI NR–NR); DLBCL (*n*= 5), 13.6 months (95% CI 2.6–NR); and other PD-L1-positive NHL (*n*= 2), NR (95% CI 1.7–NR) (Figure 1). Median PFS for the total population of cohort 4 was 1.7 months (95% CI 1.4–2.7), the 1-year PFS rate was 21%, and the 2-year PFS rate was 16% (Figure 2). The median OS was 12.0 months (95% CI 6.0–22.5), the 2-year OS rate was 38%, and the 4-year OS rate was 29% (Figure 3). For the one patient in cohort 4 who received CAR-T therapy before study treatment, the best overall response was disease progression. Three patients received CAR-T therapy following study treatment with best overall responses of PD in two patients and one stable disease (SD) with pembrolizumab treatment. Eight patients in cohort 4 underwent HCT following study treatment (five allogeneic HCT; three autologous HCT (auto-HCT)). Best overall response to pembrolizumab among these patients was PD in three patients, SD in three patients, and PR in two patients. Three of these patients had died at the time of data cutoff.

Overall, 32 of 86 patients (37%) had PD-L1-positive tumors by immunohistochemistry; in this group, ORR was 19% (95% CI 7–36; two CR, four PR); five patients (16%) had SD, 17 patients (53%) had PD, and four patients were not assessed (Table 3). Thirty-five of 86 patients (41%) had PD-L1-negative tumor status, and ORR was 11% (95% CI 3–27; two CR, two PR). The ORR for 19 patients (22%) with missing PD-L1 expression status was 47% (95% CI 24–71; six CR, three PR).

Eighteen patients from cohort 5 who were treated with pembrolizumab plus lenalidomide were included in the efficacy analyses. Four patients (22%) achieved CR, and three patients (17%) achieved PR; ORR was 39% (90% CI 20–61). Four patients (22%) each had SD and PD (Table 3). Of the four patients with a CR, two were still alive at data cutoff and two had experienced PD and subsequently died. Among the four patients with PD-L1-positive tumors, ORR was 75% (95% CI

Table 3. Responses in all evaluable patients per International Working Group 2007 criteria.

	Cohort 4 (NHL) Pembrolizumab monotherapy							Cohort 5 (DLBCL) Pembrolizumab + lenalidomide		
						PD-L1 status			PD-L1 status	
Response	Overall (NHL) *N*= 86	PMBCL *n*= 21	FL *n*= 20	DLBCL *n*= 41	Other PD-L1$^+$ NHL *n*= 4	Positive *n*= 32	Negative *n*= 35	Overall *N*= 18	Positive *n*= 4	Negative *n*= 8
ORR[a], *n* (%)	19 (22)	10 (48)	2 (10)	5 (12)	2 (50)	6 (19)	4 (11)	7 (39)	3 (75)	2 (25)
90% CI[b]	15–31	29–67	2–28	5–24	10–90[c]	7–36	3–27	20–61	19–99	3–65
CR	10 (12)	6 (29)	1 (5)	3 (7)	0	2 (6)	2 (6)	4 (22)	1 (25)	2 (25)
PR	9 (10)	4 (19)	1 (5)	2 (5)	2 (50)	4 (13)	2 (6)	3 (17)	2 (50)	0
SD, *n* (%)	15 (17)	5 (24)	6 (30)	3 (7)	1 (25)	5 (16)	8 (23)	4 (22)	0	3 (38)
PD, *n* (%)	43 (50)	4 (19)	11 (55)	27 (66)	1 (25)	17 (53)	20 (57)	4 (22)	1 (25)	2 (25)

CI: confidence interval; CR: complete response; DLBCL: diffuse large B-cell lymphoma; ORR: objective response rate; PD: progressive disease; PMBCL: primary mediastinal B-cell lymphoma; PR: partial response; NHL: non-Hodgkin lymphoma; SD: stable disease.
[a]Defined as the sum of CR and PR.
[b]Based on binomial exact confidence interval method.
[c]Both partial responses were in gray-zone lymphoma.

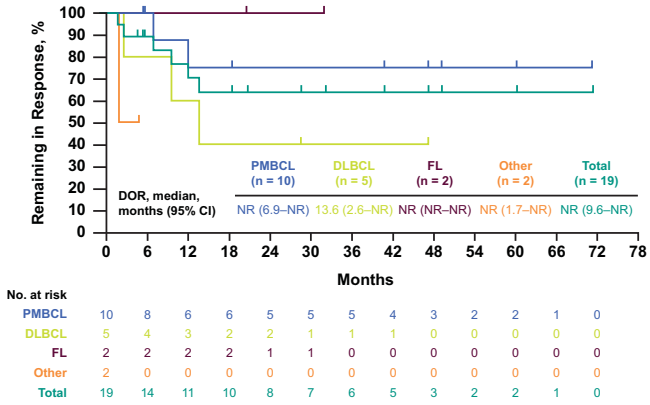

Figure 1. Kaplan–Meier estimates of response duration in cohort 4. DLBCL: diffuse large B-cell lymphoma; DOR: duration of response; FL: follicular lymphoma; NR: not reached; PMBCL: primary mediastinal B-cell lymphoma.

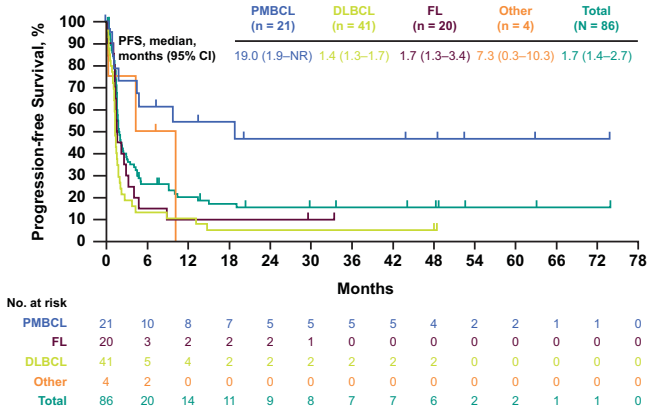

Figure 2. Kaplan–Meier estimates of progression-free survival in cohort 4. DLBCL: diffuse B-cell lymphoma; FL: follicular lymphoma; NR: not reached; PFS: progression-free survival; PMBCL: primary mediastinal B-cell lymphoma.

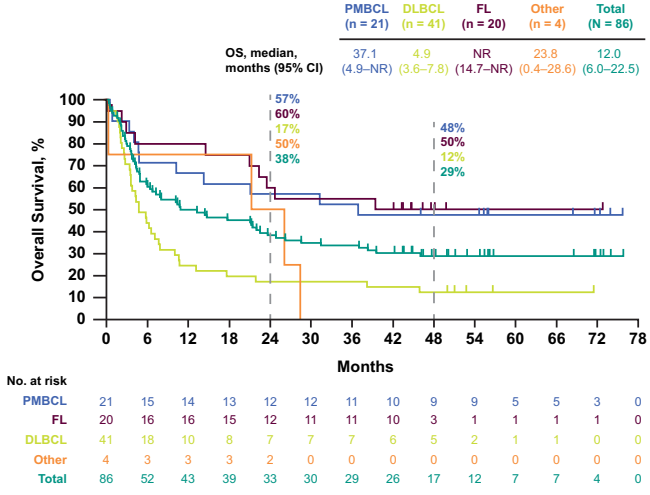

Figure 3. Kaplan–Meier estimate of overall survival in cohort 4. DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; NR: not reached; OS: overall survival; PMBCL: primary mediastinal B-cell lymphoma.

19–99; one CR, two PR). Among the eight patients with PD-L1-negative tumors, ORR was 25% (95% CI 3–65; two CR). Median time to response was 2.8 months (range 2.6–8.2), and median DOR for responders (n= 7) was NR (95% CI 2.8–NR) (Supplemental Figure 1A). Median PFS was 5.5 months (95% CI 2.7–NR), and the PFS rate at 1 year was 36% (Supplemental Figure 1B). Median OS was 23.0 months (95% CI 6.1–NR), and OS rates at 1 and 2 years were 61% and 50%, respectively (Supplemental Figure 1C).

For the one patient in cohort 5 who received CAR-T therapy before study treatment, the best overall response was disease progression. Four patients in cohort 5 received CAR-T therapy following study treatment, with best overall response to pembrolizumab of PD in one patient, SD in two patients, and CR in one patient. Two patients in cohort 5 underwent HCT following study treatment (one allogeneic HCT; one auto-HCT). One of these patients had achieved a CR on study treatment but progressed before auto-HCT and had subsequently died by the time of the data cutoff.

Discussion

Outcomes are generally poor and effective treatment options are limited for patients who have NHL that has progressed or relapsed following multiple therapies. Results from the NHL cohorts of KEYNOTE-013 demonstrated that pembrolizumab was well tolerated across doses and treatment regimens. However, pembrolizumab as monotherapy demonstrated limited antitumor activity outside of PMBCL. Conversely, lenalidomide has shown single-agent activity in R/R DLBCL, with ORRs ranging from 19% to 34% [19,20,23]. Notably, data from the ReMIND study in patients with R/R DLBCL demonstrated improved ORR (34%) compared with prior studies of single-agent lenalidomide in this patient population. The observed activity in DLBCL may be augmented when given in combination with lenalidomide, but given the small cohort size and limited follow-up, assessing the contribution of pembrolizumab in this combination is challenging. As is common with PD-1 blockade therapy, responses were often quite durable, even in lymphoma subtypes in which the response rates were low, including those for FL and DLBCL. Indeed, some responders obtained responses up to 6 years for PMBCL and more than 2 years for other NHL subtypes.

In this study, treatment discontinuations due to AEs and grade 3 or 4 TRAEs were rare across treatment groups. One treatment-related death occurred. The rates of observed TRAEs from the monotherapy cohorts in this study were comparable or lower compared with other phase 1 and 2 pembrolizumab clinical studies for patients with cHL [15,17,28]. However, benefit-risk profile assessments in other disease settings, such as multiple myeloma, were unfavorable for the combinations of immune checkpoint inhibitors plus immunomodulatory imide drugs and dexamethasone [29,30]. The sponsor therefore made the decision to close cohort 5.

In this current study, modest response rates to pembrolizumab monotherapy were observed in patients with R/R DLBCL and R/R FL. Results from this current study were consistent with those seen in phase 1 and phase 2 studies in patients who had R/R DLBCL and R/R FL treated with nivolumab monotherapy [31–33]. In a phase 2 study of nivolumab in patients who had R/R DLBCL and who were ineligible for or for whom treatment with auto-HCT failed (n= 87), response rates were 10% and 3%, respectively [32]. Similar results were seen in the phase 2 CheckMate-140 study in patients with R/R FL (N= 92); the response rate was 4%, and the median DOR was 11 months [33]. In the current analysis, durable responses were observed in some responders with FL and DLBCL treated with pembrolizumab monotherapy, with clinical responses for FL and DLBCL up to 32 and 47 months, respectively.

ORR was 22% (19 of 86 patients) in patients with R/R NHL treated with pembrolizumab monotherapy and thus did not meet the protocol-specified clinical response threshold of 25%. As expected, most responders were from the PMBCL cohort. PMBCL possesses a unique biology, with genetic aberrations at 9p24.1, similar to cHL, which likely underlies its distinct vulnerability to PD-1 blockade, unlike other NHL subtypes. Previous analyses from KEYNOTE-013 and the phase 2 KEYNOTE-170 studies indicated high antitumor activity with pembrolizumab monotherapy, which resulted in the approval of pembrolizumab for the treatment of R/R PMBCL following two or more prior lines of therapy [9,18]. In prior analysis of patients with R/R PMBCL in the KEYNOTE-013 study, ORR by investigator assessment per International Working Group 2007 criteria was 48% (95% CI 21–64; two CR, five PR), and DOR ranged from 2+ to 40+ months [9]. KEYNOTE-170 was a confirmatory study of the preliminary data presented from KEYNOTE-013 and demonstrated durable and effective responses supporting the KEYNOTE-013 data. Data from the current analysis of the PMBCL cohort from KEYNOTE-013 further support previous analyses, with one patient reporting a response duration extending beyond 66 months.

In the present study, patients who had DLBCL and were treated with a combination of pembrolizumab plus lenalidomide in cohort 5 demonstrated higher ORR compared with patients who had DLBCL and were treated with pembrolizumab monotherapy in cohort 4 (39% vs. 12%). However, biologic

predispositions inherent to DLBCL may be the primary contributing factors to observed differences in ORR, and these were not included in the analysis of this study [34]. Thus, we deduced no clear additive or synergistic effect from the combination of pembrolizumab and lenalidomide, particularly when comparing the observed ORR from the combination therapy cohort 5 with reported ORR from the lenalidomide single-agent ReMIND study (39% vs. 34%) [23]. Similar clinical trials on anti-PD-1/PD-L1 combination therapies in DLBCL, including those in combination with CAR-T therapy, have also demonstrated feasibility; however, definitive efficacy results have yet to be reported [30,35–38].

The present analysis was limited by the small sample size of each cohort and their respective subgroups. However, pembrolizumab demonstrated acceptable tolerability when given either as monotherapy or in combination with lenalidomide for patients who have R/R NHL. Modest antitumor activity was demonstrated in this study when pembrolizumab was given as monotherapy, although some patients experienced durable responses. The updated data from the PMBCL cohort support prior analyses and, with additional follow-up, demonstrated improved durability compared with previous results from KEYNOTE-013. The combination of lenalidomide with pembrolizumab also demonstrated acceptable tolerability with no clear signal of additive or synergistic activity for this combination approach.

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Disclosure statement

JK received funding from Merck & Co., Inc.; research funding from Roche, AstraZeneca, and Merck & Co., Inc.; was consultant for AbbVie, Antengene, Bristol Myers Squibb, Gilead, Karyopharm, Medison Ventures, Roche, Seattle Genetics, and Merck & Co., Inc.; received honoraria from AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, Gilead, Incyte, Janssen, Karyopharm, Novartis, Pfizer, Roche, Seattle Genetics, and Merck & Co., Inc.; was a member of a data-safety monitoring board or an advisory board for Karyopharm; and had a leadership role for Lymphoma Canada. PA received research funding from Bristol Myers Squibb, Affimed, Adaptive, Roche, Tensha, Otsuka, Sigma Tau, Genentech, IGM, Kite, and Merck & Co., Inc.; and was a consultant for Bristol Myers Squibb, Pfizer, Affimed, Adaptive, Infinity, ADC Therapeutics, Celgene, Morphosys, Daiichi Sankyo, Miltenyi, Tessa, GenMab, C4, Enterome, Regeneron, Epizyme, AstraZeneca, Genentech, and Merck & Co., Inc. MH received honoraria from Sanofi, Genzyme, AstraZeneca, BeiGene, and ADC Therapeutics; and was a member of a data safety monitoring board or an advisory board for Incyte, ADC Therapeutics, Pharmacyclics, Omeros, Verastem, TeneoBio, MorphoSys, Kite, Genmab, SeaGen, Gamida Cell, and Novartis. JK received research funding from Merck & Co., Inc.; was a consultant for Merck & Co., Inc., received honoraria from Kite, Gilead, and Merck & Co., Inc.; and was a member of a data safety monitoring board or an advisory board for Kite and Gilead. CHM received research funding from Merck & Co., Inc. DA received research funding from Celgene, Pharmacyclics, and Kite; was a consultant for Janssen, Parexel, Takeda, Kite, Sanofi, and Kowa; and was a member of a data safety monitoring board or an advisory board for Celgene, Juno, Partners Therapeutics, Karyopharm, Bristol Myers Squibb, Aviv Med Tech, Takeda, Legend Bio Tech, Chugai, and Kite. AFH received research funding from Bristol Myers Squibb, Genentech, Seattle Genetics, Kite, Gilead, AstraZeneca, ADC Therapeutics, and Merck & Co., Inc., and was a consultant for Bristol Myers Squibb, Genentech, Seattle Genetics, AstraZeneca, Karyopharm, ADC Therapeutics, Takeda, Tubulis, Regeneron, Genmab, and Merck & Co., Inc. FM was a consultant for Roche and Gilead; received honoraria or provided expert testimony from Roche and Janssen; and was a member of a data safety monitoring board or an advisory board for Roche, Gilead, Novartis, AbbVie, Kymera, Bristol Myers Squibb, AstraZeneca, and Epizyme. PLZ received honoraria from Roche, EUSA Pharma, Takeda, Incyte, Kyowa Kirin, Janssen, Gilead, Novartis, and Merck & Co., Inc., and was a member of a data safety monitoring board or an advisory board for Roche, EUSA Pharma, Takeda, Incyte, Kyowa Kirin, Janssen, Gilead, Novartis, and Merck & Co., Inc. HG received honoraria from Gilead, Janssen, Celgene, Mundipharma, Roche, and Takeda. SJS was a consultant for AstraZeneca, Janssen, and Novartis; received honoraria from Incyte, NCCN, and Novartis; and was a member of a data safety monitoring board or an advisory board for BeiGene, Celgene, Bristol Myers Squibb, Genentech, Roche, Incyte, Morphosys, Legend Biotech, Mustang Biotech, Novartis, and Regeneron. MF and PM are employees of Merck & Co., Inc., and hold stock in Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ. NLB received research funding from ADC Therapeutics, Affimed, Autolus, Bristol Myers Squibb, Celgene, Forty Seven, Immune Design, Janssen, Kite, Millennium, Pfizer, Pharmacyclics, Roche, Genentech, Seattle Genetics, and Merck & Co., Inc., and was a member of a data safety monitoring board or an advisory board for ADC Therapeutics, Roche, Genentech, Seattle Genetics, BTG, and Acerta. JDB, VR, AK, and JB have no conflicts of interest to disclose.

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Data availability statement

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD) is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (available at: http://engagezone.msd.com/ds documentation.php) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the US and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

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