

CLINICAL TRIALS AND OBSERVATIONS

Pembrolizumab in relapsed or refractory Hodgkin lymphoma: 2-year follow-up of KEYNOTE-087

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KEY POINTS

- Pembrolizumab provided durable and deep responses with acceptable tolerability in a broad spectrum of RRcHL.
- Pembrolizumab was also effective in difficult-to-treat chemorefractory cHL.

Programmed death-1 inhibitors are approved for patients with relapsed or refractory classic Hodgkin lymphoma (RRcHL). We present the 2-year follow-up of the phase 2 KEYNOTE-087 study of pembrolizumab in 210 patients, based on HL progression after autologous stem cell transplantation (ASCT) and subsequent brentuximab vedotin (BV; cohort 1); salvage chemotherapy and BV, with ineligibility for SCT owing to chemorefractory disease (cohort 2); and progression after SCT without BV (cohort 3). With a median follow-up of 27.6 months, the objective response rate (ORR) by blinded independent central review was 71.9% (95% CI, 65.3-77.9), the complete response rate (CRR) was 27.6%, and the partial response (PR) rate was 44.3%. Median duration of response was 16.5 months (range, 0.0+ to 27.0+ [+ , no progressive disease at last assessment]) in all patients, 22.1 months in cohort 1, 11.1 months in cohort 2, and 24.4 months in cohort 3. Median progression-free survival was not reached in

all patients with CR: 13.8 months (95% CI, 12.0-22.1) for patients with PR and 10.9 months (95% CI, 5.6-11.1) for patients with stable disease. Median overall survival was not reached in all patients or in any cohort. Treatment-related adverse events (TRAEs) of any grade occurred in 153 (72.9%) patients; grades 3 and 4 occurred in 25 (12.0%) patients; none resulted in death. Results confirmed effective antitumor activity, durability of response, and manageable safety of pembrolizumab monotherapy in RRcHL, regardless of prior treatment and including chemoresistant cHL. This trial was registered at www.clinicaltrials.gov as #NCT02453594. (*Blood*. 2019; 134(14):1144-1153)

Introduction

The inhibitors of programmed death 1 (PD-1)—nivolumab and pembrolizumab—showed effective antitumor activity and tolerable safety in patients with classic Hodgkin lymphoma (cHL) that progressed after autologous stem cell transplantation (ASCT) and/or brentuximab vedotin (BV).¹⁻⁴ PD-1 inhibitors can be considered for the treatment of patients with refractory cHL who are ineligible for ASCT because of comorbidity or failure of first salvage chemotherapy or relapsed disease after ASCT, with or without BV.⁵ Both drugs were approved with limited follow-up by the US Food and Drug Administration based on phase 1 and

2 studies.^{6,7} Pertinent outstanding questions are the durability of response with PD-1 inhibitors and whether durable remission can be achieved in patients with a broad spectrum of relapsed or refractory cHL (RRcHL).

Previously, we reported the safety and efficacy of pembrolizumab in patients with RRcHL from the phase 2 KEYNOTE-087 study.⁴ With a median follow-up of 10.1 months, pembrolizumab showed excellent antitumor activity, with an overall response rate (ORR) of 69.0% and a complete response (CR) rate of 22.4% in all patients; 75.6% of patients had responses lasting at

least 6 months. Here, we present results with an additional follow-up of ~17.5 months, to evaluate the durability of response to pembrolizumab. We also present exploratory efficacy analyses in patient subgroups by prior treatment, such as BV naive, BV before ASCT, and BV after ASCT. Last, we present efficacy and safety data of a second course of pembrolizumab. Results of a second course may lead to the use of pembrolizumab as an additional treatment option for patients whose disease progresses after CR with pembrolizumab.

Patients and methods

KEYNOTE-087 was a multicenter, single-arm, multicohort, non-randomized phase 2 study of pembrolizumab in patients with RRcHL. Patients were enrolled in 3 cohorts based on cHL progression after ASCT and subsequent BV (cohort 1); salvage chemotherapy and BV, with ineligibility for ASCT owing to chemorefractory disease (cohort 2); and progression after ASCT without subsequent BV (cohort 3). In cohort 2, chemorefractory was defined as failure to achieve CR or partial response (PR) to salvage therapy. Cohort 3 included BV-naive and BV-treated patients; some had received BV as part of primary treatment or salvage therapy. Detailed methods have been published.⁴

Eligible patients were aged ≥18 years, had measurable disease (Eastern Cooperative Oncology Group performance status of 0 or 1) and adequate organ function and were able to provide a new or archival evaluable core or excisional lymph node biopsy sample at screening for biomarker analysis. All patients provided written informed consent before study entry. The protocol and all amendments were approved by the independent institutional review board or ethics committees for each site. The study was conducted in accordance with the guidelines of the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki.

Study design and treatment

Patients were treated with pembrolizumab 200 mg intravenously every 3 weeks for up to 2 years or until documented confirmed disease progression, occurrence of intolerable toxicity, or patient or investigator decision to withdraw from the study. Based on investigator decision, patients achieving CR could stop pembrolizumab after receiving a minimum of 24 weeks of treatment if at least 2 doses of pembrolizumab were received after confirmation of CR per 2007 International Working Group Revised Response Criteria for Malignant Lymphomas (RRC).⁸ Patients who met this criterion were permitted to receive additional pembrolizumab treatment of up to 12 months upon relapse, if the patient had not received any anticancer treatment since the last dose of pembrolizumab and continued to meet eligibility criteria for study.

Assessments

Response was assessed by computed tomography every 12 weeks per RRC.⁸ Positron emission tomography was performed at weeks 12 and 24, to confirm CR or progressive disease (PD), and as clinically indicated. Primary end points were safety and overall response rate (ORR), defined as the proportion of patients who had response (CR or PR), by blinded independent central review (BICR) per RRC⁸ in all patients and in the 3 cohorts. Secondary end points were CR rate by BICR, progression-free survival (PFS) and duration of response (DOR) by BICR per RRC,

Table 1. Best overall response by blinded independent central review

	Cohort 1 (n = 69): after ASCT/BV		Cohort 2 (n = 81): ineligible for ASCT and treatment failure with BV therapy		Cohort 3 (n = 60): no BV after ASCT		All patients (N = 210)	
	n (%)	95% CI*	n (%)	95% CI*	n (%)	95% CI*	n (%)	95% CI*
ORR	53 (76.8)	65.1-86.1	54 (66.7)	55.3-76.8	44 (73.3)	60.3-83.9	151 (71.9)	65.3-77.9
CR†	18 (26.1)	16.3-38.1	21 (25.9)	16.8-36.9	19 (31.7)	20.3-45.0	58 (27.6)	21.7-34.2
PR	35 (50.7)	38.4-63.0	33 (40.7)	29.9-52.2	25 (41.7)	29.1-55.1	93 (44.3)	37.5-51.3
SD	9 (13.0)	6.1-23.3	7 (8.6)	3.5-17.0	7 (11.7)	4.8-22.6	23 (11.0)	7.1-16.0
PD	5 (7.2)	2.4-16.1	18 (22.2)	13.7-32.8	9 (15.0)	7.1-26.6	32 (15.2)	10.7-20.8
No assessment	2 (2.9)	0.4-10.1	2 (2.5)	0.3-8.6	0 (0)	—	4 (1.9)	0.5-4.8

*Based on binomial exact CI method.

†For complete remission, a residual mass was permitted for patients who had negative results, as seen on positron emission tomography.

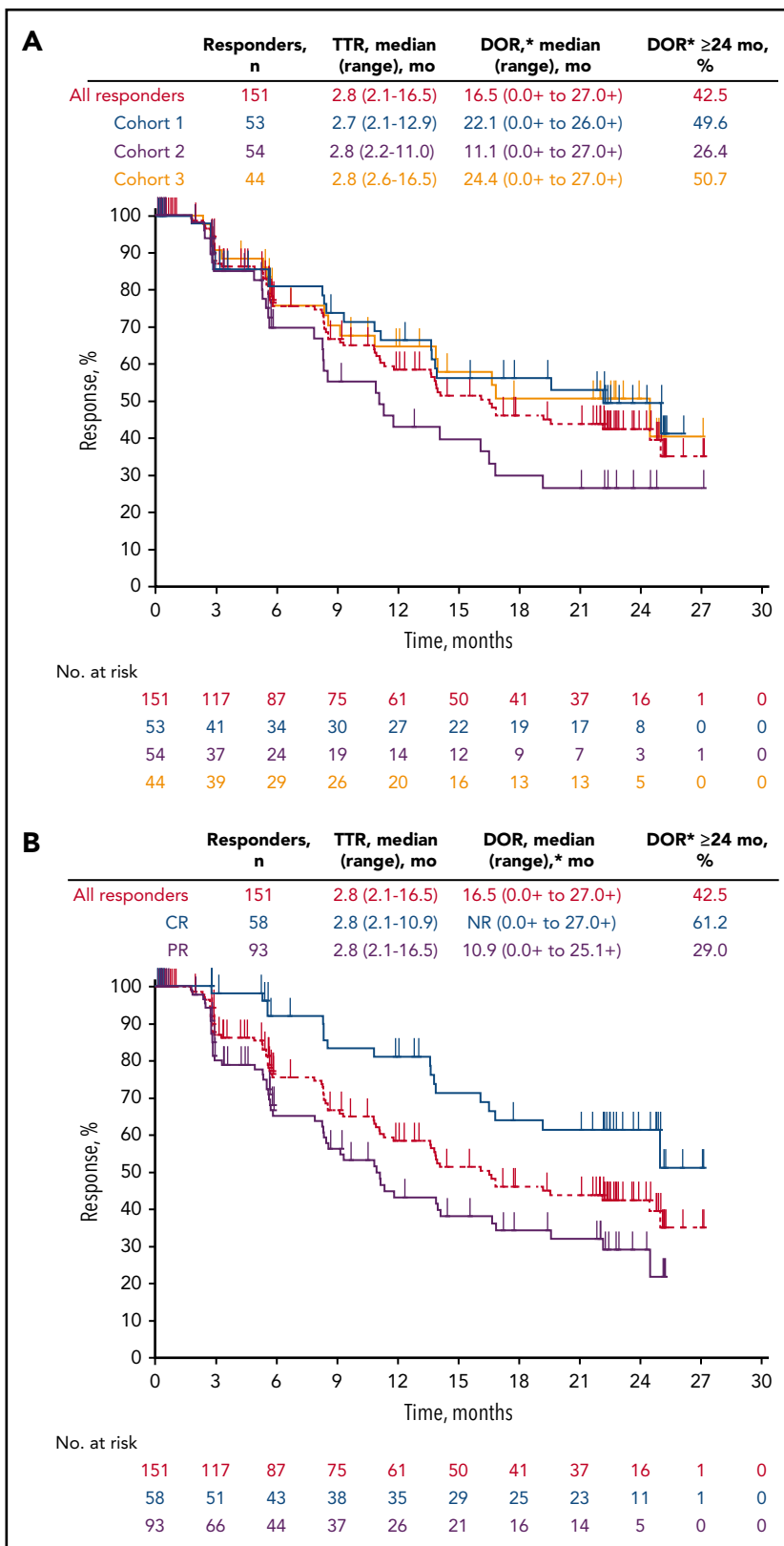


Figure 1. Kaplan-Meier estimate of duration of response. Responders by cohort (A) and by best response (B). *Based on Kaplan-Meier estimate.

and overall survival (OS). Exploratory objectives included ORR, complete response rate (CRR), PFS, DOR, and OS for patients in subgroups based on prior BV use: BV naive, BV before ASCT, and BV after ASCT. Additional exploratory analyses involved ORR, CRR, PR rate (assessed by investigator review), and DOR by

investigator review in patients treated with a second pembrolizumab course.

Patients were monitored for adverse events (AEs), serious AEs, and immune-mediated AEs. AEs were graded per National Cancer

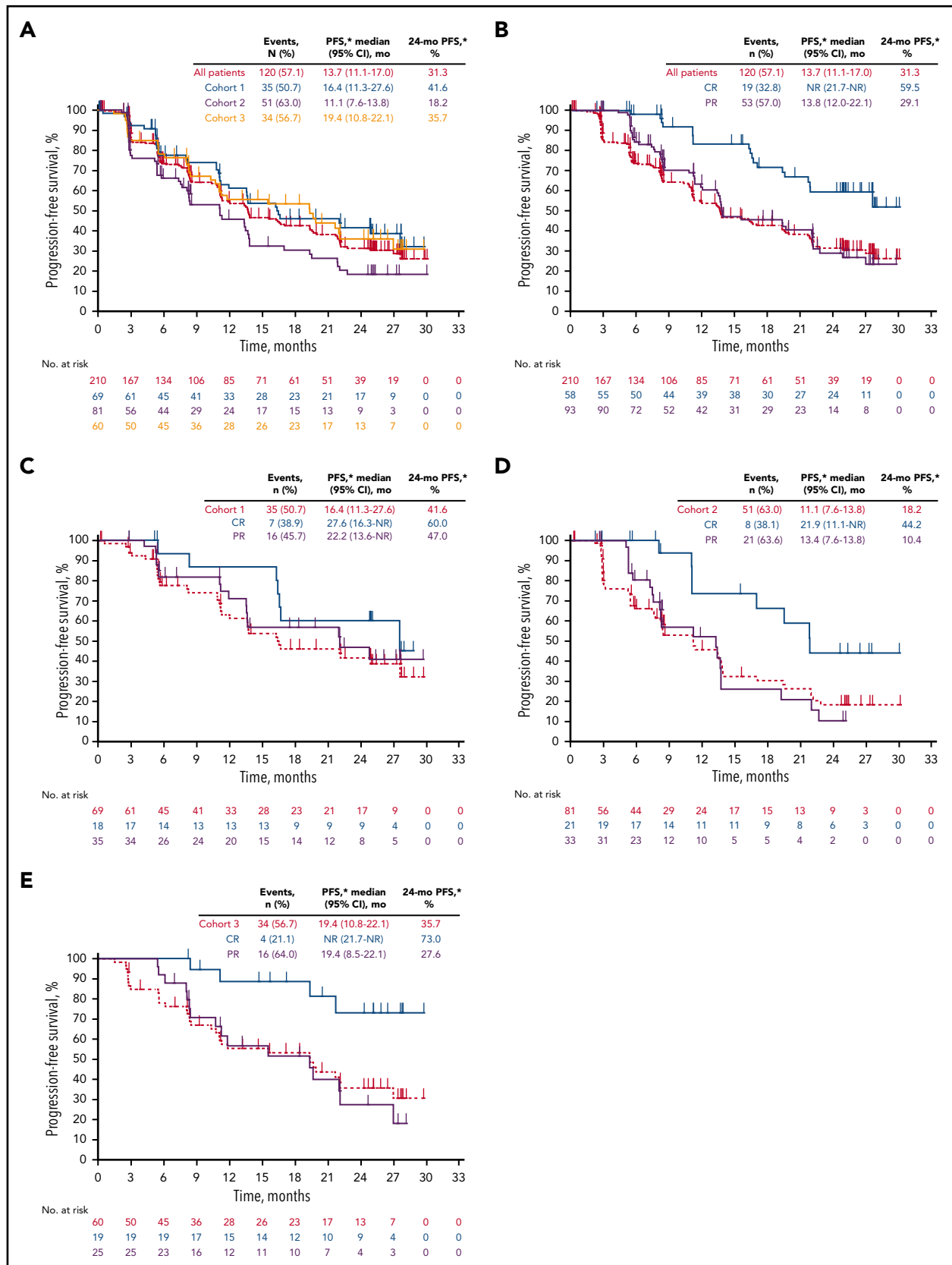


Figure 2. Kaplan-Meier estimate of PFS. In all patients and by cohort (A) and patients with complete or PR in all patients (B), cohort 1 (C), cohort 2 (D), and cohort 3 (E). *Based on Kaplan-Meier method for censored data.

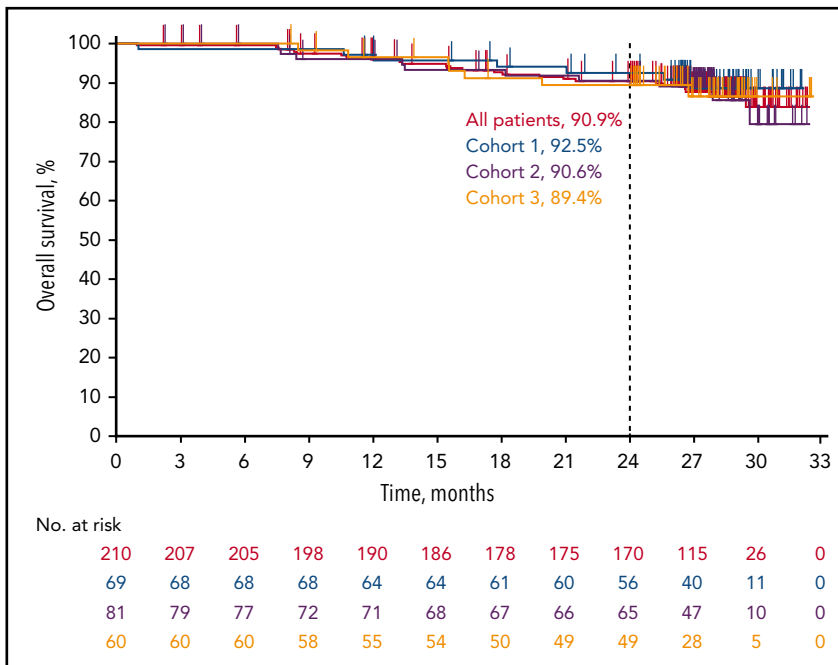


Figure 3. Kaplan-Meier estimate of overall survival, in all patients and by cohort.

Institute Common Terminology Criteria for Adverse Events, version 4.0. Immune-mediated AEs were based on a list of terms specified by the sponsor and included by the investigator regardless of attribution to study treatment or immune relatedness.

Statistical analysis

Efficacy and safety were analyzed in the all-subjects-as-treated population of all patients who received at least 1 dose of study drug. ORR and CR were assessed for the overall population and by each cohort. The ORR assessment involved the point estimate and 95% 2-sided binomial exact confidence interval using the Clopper-Pearson method. PFS, OS, and DOR were estimated using the Kaplan-Meier method.

Results

Patients and disposition

At data cutoff (21 March 2018), of the 210 patients enrolled and treated in the 3 cohorts, 39 (18.6%) had completed treatment, and 5 (2.4%) were still receiving treatment. Of the 166 (79.0%) patients who discontinued treatment, the most common cause of discontinuation across all cohorts was disease progression (n = 86, 41.0%), followed by CR (n = 28, 13.3%) and AEs (n = 18, 8.6%; supplemental Figure 1, available on the *Blood* Web site). Median age was 35 years (range, 18-76). Patients had received a median of 4 prior lines of therapy (range, 1-12; supplemental Table 1). All patients in cohorts 1 and 2 had received prior BV, per study design, and 25 (41.7%) patients in cohort 3 had received prior BV.⁴ Median follow-up was 27.6 months (range, 1.0-32.9). Patients received a median of 21, 12, and 19.5 doses in their first course of pembrolizumab in cohorts 1, 2, and 3, respectively.

Objective responses in all patients

ORR by BICR in all patients was 71.9% (95% CI, 65.3-77.9) with a CRR of 27.6% and PR rate of 44.3% (Table 1). ORR was 76.8% in cohort 1, 66.7% in cohort 2, and 73.3% in cohort 3 (Table 1).

Among patients who achieved CR (n = 58), 84.5% did so after ≥6 months of treatment and 63.8% did so after ≥12 months of treatment. Median time to response (TTR) was 2.8 months (range, 2.1-16.5) in all patients and was similar in patients in each cohort (supplemental Table 2). Median DOR was 16.5 months (range, 0.0+ to 27.0+ months [+ , no progressive disease at last assessment]) in all responders (Figure 1A; supplemental Table 2). Median DOR was 22.1 months in cohort 1, 11.1 months in cohort 2, and 24.4 months in cohort 3 (Figure 1A; supplemental Table 2). Of 151 responders, 37 (24.5%) had ongoing responses. By Kaplan-Meier estimates, 61 (58.5%) had responses lasting ≥12 months, and 16 (42.5%) had responses lasting ≥24 months (Figure 1A). Sixteen (30.2%) patients in cohort 1, 8 (14.8%) in cohort 2, and 13 (29.5%) in cohort 3 had ongoing responses.

Of the 58 patients who achieved CR, median TTR was 2.8 months (range, 2.1-10.9). For all patients with CR, median DOR was not reached (Figure 1B) and was 25.0 months in cohort 1, 19.2 months in cohort 2, and not reached in cohort 3 (supplemental Table 2).

Of the 93 patients who achieved PR, TTR was 2.8 months. Median DOR was 10.9 months in all patients who had PR (Figure 1B; supplemental Table 2), 19.5 months in cohort 1, 7.9 months in cohort 2, and 13.9 months in cohort 3.

PFS in all patients

Median PFS was 13.7 months (95% CI, 11.1-17.0) in all patients, 16.4 months in cohort 1, 11.1 months in cohort 2, and 19.4 months in cohort 3 (Figure 2A). Median PFS was not reached in patients with CR (Figure 2B, supplemental Table 3) and was 13.8 months in all patients with PR (supplemental Table 3). Median PFS in patients with PR by cohort was 22.2 months in cohort 1 (Figure 2C), 13.4 months in cohort 2 (Figure 2D), and 19.4 months in cohort 3 (Figure 2E). In the 23 patients who had stable disease (SD), median PFS was 10.9 months (95% CI, 5.6-11.1) in the total patient population, 10.9 months (95% CI, 5.4-11.0) in cohort 1,

Table 2. Response characteristics and immune-mediated AEs and infusion reactions in patients treated with second pembrolizumab course

Cohort/patient no. *	DOR, 1st course	BOR, 2nd course†	DOR, 2nd course	Response on 2nd course	Reason for 2nd course discontinuation	Immune-mediated AEs and infusion reactions‡	
						1st course	2nd course
Cohort 1							
1	23.5	NA§	—	—	—	Uveitis	—
3	14.5	PR	5.6	Ongoing	—	—	—
4	18.0	NA§	—	—	—	—	—
6	10.8	PR	6.9	—	Clinical progression	—	—
8	8.3	CR	11.3	Ongoing	Completed	Infusion reactions	—
7¶	11.0	PD	5.3	—	PD	—	—
Cohort 2							
2	5.0	CR	8.3	Ongoing	—	Sarcoidosis	Sarcoidosis
10	8.3	CR	0.7	—	AE	Pancreatitis	—
9	5.3	CR	11.2	Ongoing	Completed	Colitis	—
Cohort 3							
5	7.1	SD	11.0	—	Completed	—	—

BOR, best overall response; NA, not applicable.

*Per duration of response graph (Figure 4).

†By site review per International Working Group Revised Response Criteria for Malignant Lymphoma.

‡Based on a list of terms specified by the sponsor and included by the investigator, regardless of attribution to study treatment or immune relatedness; related terms are included.

§At data cutoff, 2 patients had recently started a second course of pembrolizumab, and response assessment had not yet occurred.

¶Patient had an AE of pericarditis during the first course of pembrolizumab treatment that also occurred during the second course of treatment and was considered by the investigator to be immune-related.

13.3 months (95% CI, 5.3 to not reached [NR]) in cohort 2, and 10.3 months (95% CI, 5.6-19.9) in cohort 3.

OS in all patients

Median OS was not reached in all patients or in any cohort (Figure 3). The 24-month OS rate in patients with CR was 100.0% in all 3 cohorts. Among patients who achieved PR, the 24-month OS rates were 91.1% in all patients, 94.3% for patients in cohort 1, 90.4% in cohort 2, and 87.7% in cohort 3. The 24-month OS rates were 84.2% in all patients who had SD, 85.7% in cohort 1, and 83.3% in cohorts 2 and 3. Among patients who experienced PD, the 24-month OS rate was 60.0% in cohort 1, 82.4% in cohort 2, and 77.8% in cohort 3.

Efficacy outcomes in subgroups by prior treatment

In subgroups by BV use, ORR was 77.1% in BV-naive patients (n = 35), 70.6% in patients who received BV before ASCT (n = 17), and 80.0% in patients who received BV after ASCT (n = 25; supplemental Table 4). Median TTR was 2.8 months in BV-naive patients, 4.2 months in patients who received BV before ASCT, and 2.7 months in patients who received BV after ASCT (supplemental Table 4). Median DOR was 24.4 months in BV-naive patients, 13.9 months in patients receiving BV before ASCT, and not reached in patients who received BV after ASCT. Median PFS was 19.4 months (95% CI, 8.1-NR) in BV-naive patients, 19.7 (95% CI, 5.5-22.1) in patients who received BV before ASCT, and 24.9 months (95% CI, 10.9-NR) in patients who received BV after ASCT. Median OS was not reached in BV-naive patients; the 24-month OS rate was 91.2%. The 24-month OS rate was 86.2% in patients who received BV before ASCT and 96.0% in patients who received BV after ASCT.

Response characteristics of patients treated with a second course of pembrolizumab

Ten patients (6 in cohort 1, 3 in cohort 2, and 1 in cohort 3) were treated with a second course of pembrolizumab (Table 2). Eight of 10 patients were evaluable for response (had reached the week 12 second-course assessment or discontinued before it). The ORR, per investigator review, was 75% (6 of 8). Of the 6 patients in cohort 1, 1 had CR with a response duration of 11.3 months and completed a second course of pembrolizumab treatment. Two patients had PR: 1 had a response duration of 5.6 months and was still on treatment at database cutoff, and the other had a response duration of 6.9 months and discontinued treatment because of disease progression (Figure 4). All 3 patients in cohort 2 had CR, 1 had a response duration of 8.3 months and was still on treatment, 1 had a response duration of 0.7 months and discontinued treatment because of an AE, and 1 completed a second course of treatment, with a response duration of 11.2 months. The cohort 3 patient had SD with a duration of 11.0 months.

Safety

Treatment-related AEs occurred in 153 (72.9%) patients; most were mild to moderate: 60.9% had grades 1 and 2, and 11.0% had grade 3 treatment-related AEs (Table 3). None led to death. The most common grade 3 treatment-related AEs were neutropenia and diarrhea. Two patients had grade 4 treatment-related AEs (increased lipase and myocarditis, 1 each). Immune-mediated AEs were reported for 33.8% of patients: most were low grade (grades 3-5, 2.9%; Table 3). The most commonly reported immune-mediated AEs were hypothyroidism (15.7%), pneumonitis (4.8%), and hyperthyroidism (3.8%). Infusion-related

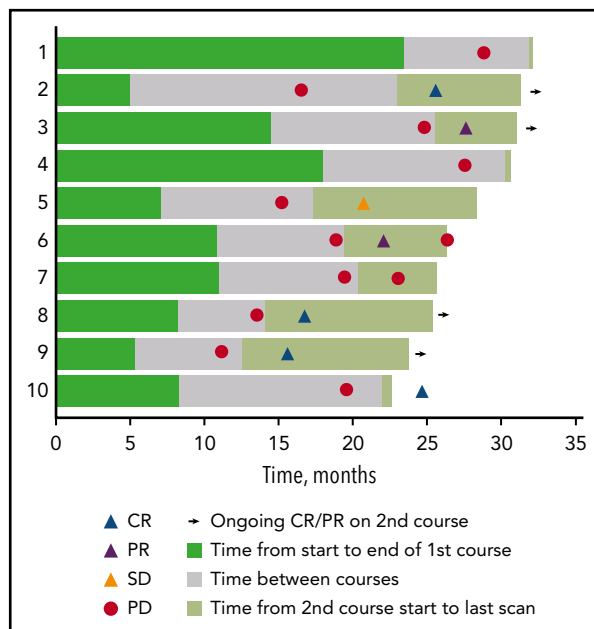


Figure 4. Duration of response in first course and second course in patients treated with a second pembrolizumab course. Patient 10 discontinued the second course because of an adverse event.

reactions were reported in 5.2% of patients. Median time to onset of the first immune-related AE was 85 days (range, 1-787 days). Most immune-related AEs resolved without sequelae (67.6%); 21.1% of events were not resolved. The immune-mediated AE sarcoidosis occurred in 1 patient; this patient experienced the AE during the first course as well (Table 2). One patient had an AE of pericarditis during the first course of pembrolizumab treatment that also occurred during the second course of pembrolizumab treatment and was considered by the investigator to be immune-related. Treatment-related AEs led to discontinuation in 14 (6.7%) patients; the most common causes were pneumonitis in 7 (3.3%) and infusion-related reactions in 2 (1.0%), followed by myocarditis, cytokine release syndrome, myelitis, myositis, epilepsy, and organizing pneumonia in 1 patient each.

Discussion

Treatment options are needed to improve outcomes in patients with RRcHL that has progressed after ASCT.⁵ With more than 2 years of follow-up, pembrolizumab continued to show effective antitumor activity (71.9%) in the overall population of patients with RRcHL and in each cohort. Importantly, responses were durable in all patients, with a median DOR of 16.5 months, and a quarter of the responders had ongoing response at database lock. The ranges for median DOR and the 95% CIs for median PFS in the 3 cohorts overlapped, suggesting that the DOR and PFS are in the same range across cohorts. Complete responders had numerically longer median DOR (NR [0.0+ to 27.0+ months]) than partial responders (10.9 months [0.0+ to 25.1+]) but had overlapping ranges. A longer duration of pembrolizumab treatment may be necessary for patients with RRcHL to achieve CR. In the current study, 63.8% of patients required 1 year or more of treatment before achieving CR. Data were comparable to those reported in prior studies with comparable cohorts.²

Table 3. Treatment-related AEs occurring in ≥5.0% of the total study population and immune-mediated AEs and infusion-related reactions occurring in ≥1 patient

AEs				
	Grade 1 or 2	Grade 3	Grade 4	Any grade
Treatment-related AEs, n (%)*				
Any AE	128 (60.9)	23 (11.0)	2 (1.0)	153 (72.9)
Hypothyroidism	30 (14.3)	0 (0)	0 (0)	30 (14.3)
Pyrexia	23 (10.9)	1 (0.5)	0 (0)	24 (11.4)
Rash	23 (11.0)	0 (0)	0 (0)	23 (11.0)
Fatigue	22 (10.5)	1 (0.5)	0 (0)	23 (11.0)
Headache	16 (7.6)	0 (0)	0 (0)	16 (7.6)
Diarrhea	15 (7.1)	3 (1.4)	0 (0)	18 (8.6)
Nausea	15 (7.1)	0 (0)	0 (0)	15 (7.1)
Cough	13 (6.2)	1 (0.5)	0 (0)	14 (6.7)
Pruritus	13 (6.2)	0 (0)	0 (0)	13 (6.2)
Arthralgia	11 (5.2)	1 (0.5)	0 (0)	12 (5.7)
Infusion-related reaction	11 (5.2)	0 (0)	0 (0)	11 (5.2)
Neutropenia	6 (2.9)	5 (2.4)	0 (0)	11 (5.2)
Immune-mediated AEs and infusion-related reactions, n (%)†				
Any AE	65 (31.0)	5 (2.4)	1 (0.5)	71 (33.8)
Hypothyroidism	33 (15.7)	0	0	33 (15.7)
Infusion-related reactions	11 (5.2)	0	0	11 (5.2)
Pneumonitis	10 (4.8)	0	0	10 (4.8)
Hyperthyroidism	8 (3.8)	0	0	8 (3.8)
Cytokine release syndrome	5 (2.4)	1 (0.5)	0	6 (2.9)
Hypersensitivity	5 (2.4)	1 (0.5)	0	6 (2.9)
Colitis	1 (0.5)	1 (0.5)	0	2 (1.0)
Myositis	1 (0.5)	1 (0.5)	0	2 (1.0)
Myocarditis	0	0	1 (0.5)	1 (0.5)
Autoimmune thyroiditis	1 (0.5)	0	0	1 (0.5)
Iridocyclitis	1 (0.5)	0	0	1 (0.5)
Iritis	1 (0.5)	0	0	1 (0.5)
Enterocolitis	1 (0.5)	0	0	1 (0.5)
Autoimmune hepatitis	0	1 (0.5)	0	1 (0.5)
Drug hypersensitivity	1 (0.5)	0	0	1 (0.5)
Sarcoidosis	1 (0.5)	0	0	1 (0.5)
Encephalitis	1 (0.5)	0	0	1 (0.5)
Organizing pneumonia	1 (0.5)	0	0	1 (0.5)
Pruritus	0	1 (0.5)	0	1 (0.5)

N = 210.

*No grade 5 AEs occurred.

†Immune-mediated AEs were based on a list of terms specified by the sponsor and included by the investigator, regardless of attribution to study treatment or immune relatedness.

Pembrolizumab showed effective antitumor activity in patients with RRcHL who were BV naive and those treated with BV before or after ASCT. A direct comparison of the efficacy and safety of pembrolizumab and BV in patients with RRcHL will be performed in the ongoing phase 3 KEYNOTE-204 study (ClinicalTrials.gov, #NCT02684292) and will provide insight on the choice of treatment.⁹

Pembrolizumab showed promising antitumor activity, with an ORR of 75% and CRR of 50% in patients treated with a second pembrolizumab course who were evaluable for response. Strikingly, all 3 patients in cohort 2 had CR in the second course. At database cutoff, 4 patients were still on treatment, 3 had

completed second-course treatment, and 3 had discontinued because of disease progression and AEs. The only immune-mediated AE that occurred in the second course was sarcoidosis in a patient who had also experienced sarcoidosis in the first course. Longer follow-up will allow better characterization of response during a second course of pembrolizumab as more patients in the current study are treated with a second course. Immune-mediated AEs occurred in only 1 patient treated with a second course of pembrolizumab.

The safety profile of pembrolizumab continued to be consistent with that of previous reports and with that of nivolumab.^{1,2,4} At 2 years of follow-up, no new toxicities or treatment-related deaths

occurred with pembrolizumab. Similarly, no new toxicities or treatment-related deaths were reported after 1.5 years of follow-up with nivolumab.² Low-grade hypothyroidism was the most commonly reported immune-related AE with long-term nivolumab (grades 1 and 2, 9.0%)² and with long-term pembrolizumab (grades 1 and 2, 15.7%). Extended follow-up confirmed the acceptable safety, confirmed the robust antitumor activity, and showed durability of response of pembrolizumab in patients with RRcHL. In addition, response was generally deep and durable regardless of BV use or sequence of BV use. Thus, pembrolizumab has manageable safety and effective antitumor activity in a broad range of patients with RRcHL and may confer additional antitumor activity in patients treated with a second course.

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Authorship

Contribution: R.C., P.A., B.v.T., A.B., and C.H.M. contributed to conception, design, and planning of the study; R.C., V.R., M.A.S., J.L., E.K., A.N., A.B., and C.H.M. contributed to analysis of the data; R.C., P.A., N.A.J., P.B., H.J.L., J.R., V.R., D.M., T.P.V., A.T., B.v.T., A.B., and C.H.M. contributed to acquisition of the data; R.C., P.L.Z., P.A., J.R., V.R., D.M., T.P.V., A.T., B.v.T., M.A.S., J.L., A.N., A.B., and C.H.M. contributed to interpretation of the results; R.C., A.B., and C.H.M. contributed to drafting of the manuscript; and R.C., P.L.Z., H.J.L., P.A., N.A.J., P.B., J.R., D.M., T.P.V., A.T., B.v.T., M.A.S., J.L., E.K., A.N., A.B., and C.H.M. contributed to critically reviewing or revising the manuscript for important intellectual content.

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Footnotes

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