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Estimating efficacy of favezelimab plus pembrolizumab relative to pembrolizumab in anti–PD-1–refractory Hodgkin lymphoma

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Key Points

- Favezelimab plus pembrolizumab had a higher response rate and greater reduction in tumor burden vs pembrolizumab alone.
- Results suggest favezelimab contributed substantially to the efficacy observed with favezelimab plus pembrolizumab in MK-4280-003.

Favezelimab plus pembrolizumab had promising efficacy in anti–programmed cell death protein 1 (PD-1)–refractory classical Hodgkin lymphoma in MK-4280-003; however, the contribution of favezelimab was unclear. Here, we assessed the relative contribution of favezelimab by comparison with data from participants treated with only pembrolizumab beyond progression in KEYNOTE-087. Participants in MK-4280-003 had received ≥2 doses of anti–PD-1 therapy and progressed <12 weeks of last dose. Participants eligible from KEYNOTE-087 had received >2 doses of pembrolizumab beyond progression, and progressed <12 weeks of last dose. Participants received pembrolizumab 200 mg plus favezelimab 200 mg or 800 mg, or pembrolizumab 200 mg IV every 3 weeks. Change in target lesion size and response per International Working Group 2007 criteria were assessed. Baseline tumor size was reset at first progression for KEYNOTE-087. A bootstrapping method compared change in target lesion size between groups. Twenty-seven participants from MK-4280-003 and 81 from KEYNOTE-087 were included. Objective response rates were 37% (95% confidence interval [CI], 15-51) for favezelimab plus pembrolizumab, and 2% (95% CI, 0-6) for pembrolizumab alone. A clinically meaningful reduction (≥50%) in target lesion size was observed in 13 (48%) vs 4 participants (5%), respectively. The mean change from baseline in target lesion size was −49% and −0.4%. In the bootstrapping analysis, 99.4% of samples showed greater decrease in tumor burden with favezelimab plus pembrolizumab. Favezelimab plus pembrolizumab had a

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higher response rate and greater reduction in tumor burden vs pembrolizumab alone in anti–PD-1–refractory classical Hodgkin lymphoma, suggesting favezelimab contributed substantially to efficacy in MK-4280-003. The trials were registered at www.clinicaltrials.gov as #NCT03598608 and #NCT02453594.

Introduction

Programmed cell death protein 1 (PD-1) inhibitors, such as pembrolizumab, are a standard of care option for patients with classical Hodgkin lymphoma whose disease has relapsed after or who are refractory to frontline treatment.[1] However, limited treatment options are available for patients whose disease progresses on or after anti–PD-1 therapy.[2] Lymphocyte-activation gene 3 (LAG-3) is an immune checkpoint receptor involved in regulating T-cell activation, proliferation, and homeostasis, which plays a key role in the adaptive immune response.[3] LAG-3 is present on T cells in the classical Hodgkin lymphoma tumor microenvironment, and LAG-3 and PD-1 inhibit T-cell activity via different signaling pathways.[3,4] In preclinical models of cancer, combining anti-LAG-3 and anti–PD-1 antibodies has been shown to have improved antitumor effects,[5] and dual blockade of LAG-3 and PD-1 with relatlimab plus nivolumab has demonstrated efficacy in patients with advanced melanoma.[6,7] We therefore hypothesized that combining LAG-3 and PD-1 blockade may be effective in patients with classical Hodgkin lymphoma, including in those with PD-1–refractory disease.

Favezelimab is a humanized immunoglobulin G4 monoclonal antibody against LAG-3 that is being evaluated in combination with pembrolizumab in patients with hematologic malignancies in the phase 1/2 MK-4280-003 study.[8] Results from cohort 2 showed that the combination of favezelimab plus pembrolizumab provided sustained antitumor activity and acceptable safety in patients with relapsed or refractory classical Hodgkin lymphoma who experienced disease progression after anti–PD-1 therapy.[8] The objective response rate was 31%; however, it remains unclear how much favezelimab contributed to the observed efficacy of the combination, given that continuing or restarting anti–PD-1 therapy after disease progression may also provide a benefit.[8] Furthermore, the objective response rate in patients treated with anti–PD-1 therapy beyond progression is not well characterized, and no prospective clinical trials have been conducted to evaluate the efficacy of single-agent pembrolizumab in patients with anti–PD-1–refractory classical Hodgkin lymphoma. Patients with relapsed or refractory classical Hodgkin lymphoma who received pembrolizumab in the phase 2 KEYNOTE-087 study could receive pembrolizumab beyond disease progression at the discretion of the investigator.[9] These patients can therefore provide a benchmark for the efficacy of single-agent pembrolizumab in patients with anti–PD-1–refractory classical Hodgkin lymphoma and a comparator for combination studies. To estimate the relative contribution of favezelimab to the efficacy of favezelimab plus pembrolizumab, we conducted a post hoc analysis comparing outcomes in participants with anti–PD-1–refractory classical Hodgkin lymphoma who received favezelimab plus pembrolizumab in MK-4280-003 study with those of participants who received pembrolizumab beyond progression in KEYNOTE-087 study.

Methods

Study design and participants

MK-4280-003 (ClinicalTrials.gov, NCT03598608) is a nonrandomized, multicenter, multicohort, open-label, phase 1/2 study designed to investigate favezelimab in combination with pembrolizumab in participants with hematologic malignancies. This analysis included participants from cohort 2 who had relapsed or refractory classical Hodgkin lymphoma that had progressed on treatment with an anti–PD-1 monoclonal antibody, either as monotherapy or in combination with other agents. To be eligible for combination treatment, participants in cohort 2 were required to have received $\geq$2 doses of an anti–PD-1 monoclonal antibody, and have had progressive disease (per International Working Group 2007 revised response criteria[10]) within 12 weeks of the last dose of anti–PD-1 therapy. Intervening therapies between the last dose of anti–PD-1 therapy and enrollment in MK-4280-003 were allowed.

KEYNOTE-087 (ClinicalTrials.gov, NCT02453594) was a nonrandomized, multicenter, multicohort, phase 2 study designed to investigate pembrolizumab monotherapy in participants with relapsed or refractory classical Hodgkin lymphoma, the details of which have been published previously.[9,11,12] For the present analysis, we included participants from KEYNOTE-087 who received pembrolizumab beyond disease progression, which was permitted per protocol if the patient was considered clinically stable. Participants were considered eligible if they had progressive disease per International Working Group 2007 criteria by blinded independent central review within 12 weeks of the last dose of pembrolizumab and confirmed $\geq$4 weeks after initial progression, and had received >2 doses of pembrolizumab beyond progression.

Procedures

Participants in MK-4280-003 received favezelimab 200 or 800 mg plus pembrolizumab 200 mg IV every 3 weeks for up to 35 cycles (~2 years), or until progressive disease, unacceptable toxicity, or other discontinuation criteria were met. Participants in KEYNOTE-087 received pembrolizumab 200 mg IV every 3 weeks for 24 months or until unacceptable toxicity or other discontinuation criteria were met. In MK-4280-003, imaging by computed tomography was performed at baseline and every 12 weeks, or as clinically indicated if relapse or recurrence was suspected. Fluorodeoxyglucose-positron emission tomography (FDG-PET) scans were performed at baseline, week 12, and week 24 to confirm complete response, and as clinically indicated if relapse or recurrence was suspected. In KEYNOTE-087, once progressive disease was confirmed, imaging by computed tomography was performed every 12 weeks from the date of the scan that first showed progression. Response in both studies was assessed per International Working Group 2007 criteria by investigator review.[10]

Statistical analysis

Change in target lesion size, objective response rate, and duration of response were assessed in all participants in cohort 2 of MK-4280-003 who had a baseline and postbaseline assessment available, and in all participants in KEYNOTE-087 who received postprogression pembrolizumab and had postprogression scans available. For participants in KEYNOTE-087, baseline tumor size was reset to the time of first progression after initiating treatment with pembrolizumab, and best change in target lesion size was calculated for the postprogression period. Waterfall plots were derived from best overall change in the sum of the product of the perpendicular diameters of target lesions in the postprogression period. Clinically meaningful growth was defined as a ≥50% increase in target lesion size from the time of initial progressive disease. Clinically meaningful shrinkage was defined as a ≥50% reduction in target lesion size from the time of initial progression. All changes between these values were considered indicative of stable disease.

Objective response rate per International Working Group 2007 criteria was based on change in target lesion size (relative to the initial occurrence of progression), appearance of new lesions, or progression of a nontarget lesion. Participants with progression of a nontarget lesion or nonindexed new lesion at the time of the original progressive disease were assumed to have post-progression progressive disease at the first postprogression time point. New lesions were not measured in KEYNOTE-087, and were thus considered nontarget lesions in the postprogression period. Nontarget lesions were qualitatively assessed throughout the study. Response assessment in nontarget lesions in the pre-progression period was carried over to the postprogression period. Per International Working Group 2007 criteria, bone marrow and FDG-PET assessment should be included in the response criteria; however, in KEYNOTE-087, these assessments were performed at baseline and at the time of censoring, but were not available at the time of initial progression. Hence, bone marrow assessment and FDG-PET findings were not included in the analysis of objective response during the postprogression period of KEYNOTE-087. Duration of response and progression-free survival were evaluated per International Working Group 2007 criteria. The Kaplan-Meier method was used to estimate progression-free survival. Data for participants who were alive and experienced disease progression or who were lost to follow-up were censored for progression-free survival analysis at the time of the last radiographic assessment. Statistical analyses for estimating progression-free survival were performed using R version 3.6 (GNU Project, Boston, MA).

A bootstrapping method with 1000 samples was used to compare the largest change from baseline in target lesion size between participants in MK-4280-003 and KEYNOTE-087.[13] This method randomly selected participants from the historical control arm (participants treated beyond progression in KEYNOTE-087), such that the same number of participants were included as were included in the MK-4280-003 waterfall plot. In general, the historical control arm is selected such that baseline characteristics of the patient population in the trial arm resemble those of the historical control arm. Maximum changes in target lesion size were arranged from worst to best and compared with the waterfall plot from MK-4280-003. For each position in the waterfall plot, a score of 1 was indicated if the depth in MK-4280-003 was greater than that of KEYNOTE-087, a score of 0.5 if depths were equal, or a score of 0 otherwise. This process was repeated 1000 times, and the resulting score was used to assess the degree to which favezelimab contributed to the efficacy observed with favezelimab plus pembrolizumab in MK4280-003.

The study protocols for both trials were approved by the appropriate institutional review board or independent ethics committee at each participating institution. The studies were conducted in accordance with the protocols, Good Clinical Practice guidelines, and the principles outlined in the Declaration of Helsinki. All participants provided written informed consent.

Results

MK-4280-003: favezelimab plus pembrolizumab

Between 20 January 2019 and 14 July 2021, 34 participants were enrolled, and received favezelimab plus pembrolizumab in cohort 2 of the MK-4280-003 study. A baseline scan was available for 33 participants, of whom 27 also had postbaseline scans available. The median time between the last dose of anti–PD-1 therapy and enrollment in MK-4280-003 for the 33 participants with a baseline scan was 17.6 weeks (range, 3.0-131.1). Of the 33 participants, 17 had received treatment other than anti–PD-1 as their most recent line of therapy. Ten participants had received either chemotherapy or an antibody-drug conjugate in the time between the last dose of anti–PD-1 therapy and enrollment. Among the 27 participants with both baseline and postbaseline scans available, the median age was 37 years (range, 25-77); 15 participants (56%) were female, and 18 participants (67%) had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 (Table 1). Participants had received a median of 5 prior lines of therapy (range, 2-5). The best overall response to previous anti–PD-1 therapy was 37% (10/27 participants; 95% confidence interval [CI], 27-61), with 3 participants (11%) achieving a complete response and 7 participants (26%) achieving a partial response (supplemental Table 1).

Among the 27 evaluable participants who received favezelimab plus pembrolizumab, the objective response rate was 37% (10/27 participants; 95% CI, 15-51), with 3 participants (11%) having a complete response and 7 participants (26%) having a partial response (Table 2). All 10 participants with an objective response had a clinically meaningful reduction (≥50%) in target lesion size (Figure 1). In the 10 participants with an objective response, the mean change in target lesion size was −81% (standard deviation [SD], 22%). Overall, 25 of 27 participants (93%) had any reduction in target lesion size, and 13 participants (48%) had a clinically meaningful reduction of ≥50% (Figure 1). The mean change in target lesion size among the 27 evaluable participants was −49% (SD, 39; Figure 2). Among those participants whose disease was nonresponsive, 11 participants (41%) had a best response of stable disease, and 6 participants (22%) had progressive disease (Table 2). Eight additional participants (30%) developed progressive disease after having an initial assessment of stable disease, partial response, or complete response. The median duration of response was 37 weeks (range, 0-84). Median progression-free survival was not reached (supplemental Figure 1).

Table 1. Baseline characteristics

	Favezelimab plus pembrolizumab (MK-4280-003 cohort 2) (N = 27)	Pembrolizumab monotherapy (KEYNOTE-087) (N = 81)
Age, median (range), y	37 (25-77)	39 (20-71)
Sex, n (%)		
Female	15 (56)	34 (42)
Male	12 (44)	47 (58)
Race, n (%)		
Black	2 (7)	3 (4)
White	25 (93)	71 (88)
Asian	0	6 (7)
Missing	0	1 (1)
Region, n (%)		
North America	13 (48)	24 (30)
Europe	4 (15)	49 (60)
Rest of world	10 (37)	8 (10)
ECOG performance status, n (%)		
0	18 (67)	38 (47)
1	9 (33)	43 (53)
Disease subtype, n (%)		
Nodular sclerosing cHL	20 (74)	62 (77)
Mixed cellularity cHL	4 (15)	11 (14)
Data missing	3 (11)	8 (10)
Tumor size at time of randomization (MK-4280-003) or initial progression (KEYNOTE-087), median (range), mm^2	2819 (234-12 863)	866 (37-5550)
Time from initiation of first-line therapy, median (range), mo	61.2 (23.8-252.0)	11.7 (2.3-256.0)
Prior lines of therapy, median (range)	5 (2-5)	4 (2-11)
2, n (%)	1 (4)	12 (15)
3, n (%)	1 (4)	26 (32)
4, n (%)	3 (11)	20 (25)
≥5, n (%)	22 (81)	23 (28)
Time to initial disease progression, median (range), wk	20.4 (7.4-60.3)*	12.0 (4.7-64.9)
Time from last dose of anti–PD-1 therapy to randomization (MK-4280-003) or initial progression event (KEYNOTE-087), median (range), wk	17.6 (3.0-226.1)	2.1 (0-5.6)
Received chemotherapy†/ADC‡ between randomization and prior anti–PD-1 therapy, n (%)	10 (37)	NA
Time from last dose of chemotherapy/ADC, median (range), wk	18.1 (2.9-101.9)	NA
Time from last dose of anti–PD-1 therapy, median (range), wk	62.1 (16.0-131.1)	NA
Prior stem cell transplantation, n (%)	21 (78)	50 (62)

ADC, antibody-drug conjugates; cHL, classical Hodgkin lymphoma; NA, not applicable.

*For participants in MK-4280-003, the median time from enrollment to initial disease progression was 59.4 weeks (range, 36.1-60.3) for participants whose last anti–PD-1 dose was ≤12 weeks prior to randomization (n = 3), and 12.3 weeks (range, 7.4-46.6) for participants whose last anti–PD-1 dose was >12 weeks prior to randomization (n = 10). Fourteen participants did not have disease progression until the time of censoring.

†Included gemcitabine, dacarbazine, doxorubicin, and cyclophosphamide.

‡Included brentuximab vedotin and camidanlumab tesirine.

Among the 27 evaluable participants, 17 (63%) had not received any intervening treatment between prior anti–PD-1 therapy and favezelimab plus pembrolizumab, and 10 participants (37%) had received intervening chemotherapy, antibody-drug conjugates, and kinase inhibitors. The objective response rate was 41% (7/17) among participants who did not receive intervening therapy, and 30% (3/10) among participants who did.

Among the 27 participants from MK-4280-003, 105 target lesions were assessed. Of these, 2 of 105 (2%) exhibited growth (≥50%

Table 2. Best overall response per International Working Group 2007 criteria assessed by the investigator

	Favezelimab plus pembrolizumab (MK-4280-003 cohort 2) (N = 27)	Pembrolizumab monotherapy (KEYNOTE-087) (N = 81)
Objective response rate (95% CI), %	37 (15-51)	2 (0-6)
Best response, n (%)		
Complete response	3 (11)	0
Partial response	7 (26)	2 (2)
Stable disease	11 (41)	23 (28)
Progressive disease	6 (22)	56 (69)

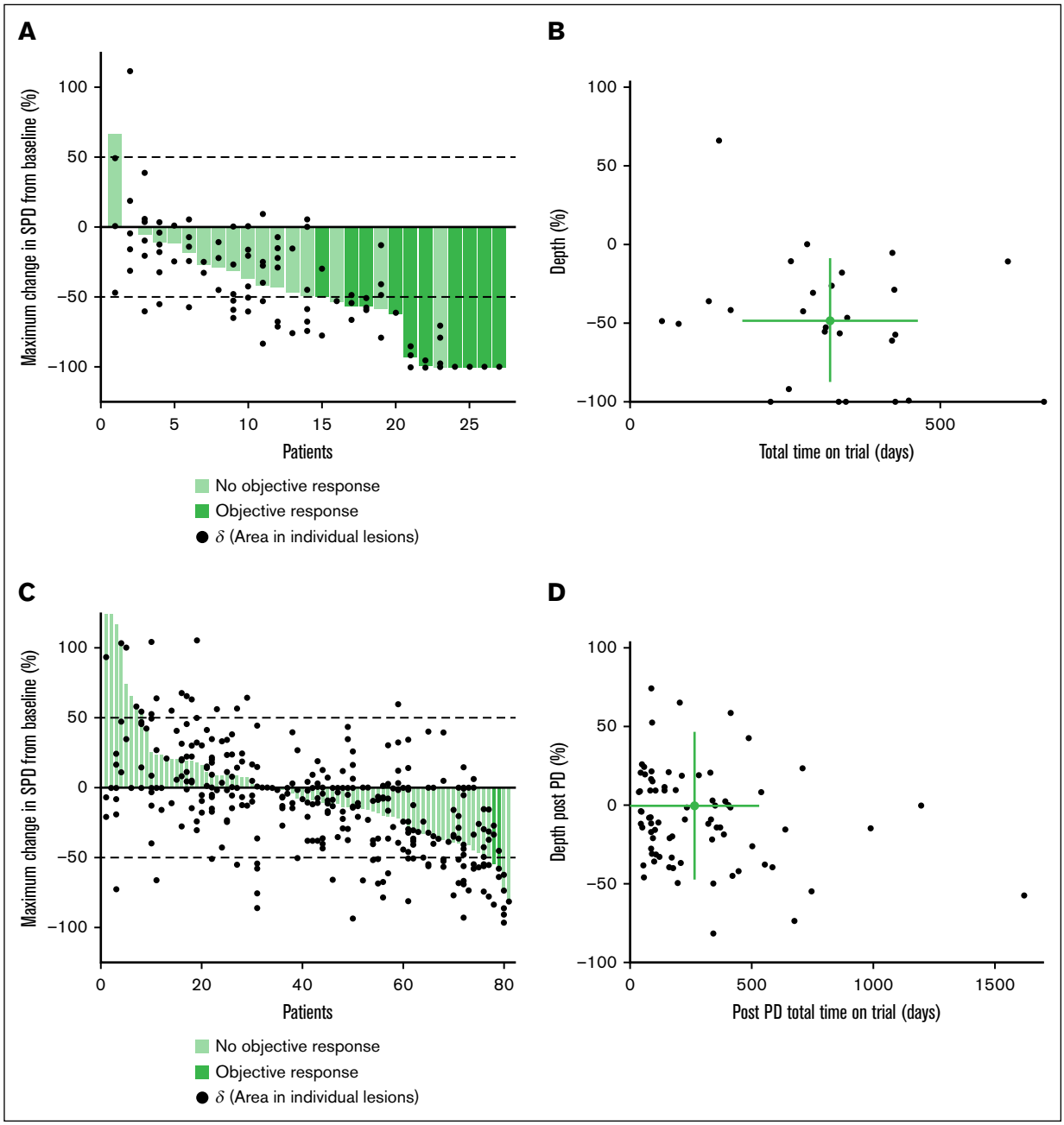

Figure 1. Best percentage change from baseline in target lesion size, and depth and duration of response. (A) Target lesion size, and (B) depth and duration of response of target lesions* in participants treated with favezelimab plus pembrolizumab in MK-4280-003, and best percentage change from baseline in (C) target lesion size, and (D) depth and duration of response of target lesions* in participants who received postprogression pembrolizumab in KEYNOTE-087. *Black dots represent each patient. Green lines show standard deviations from mean data along each axis. PD, progressive disease; SPD, sum of product of perpendicular diameters.

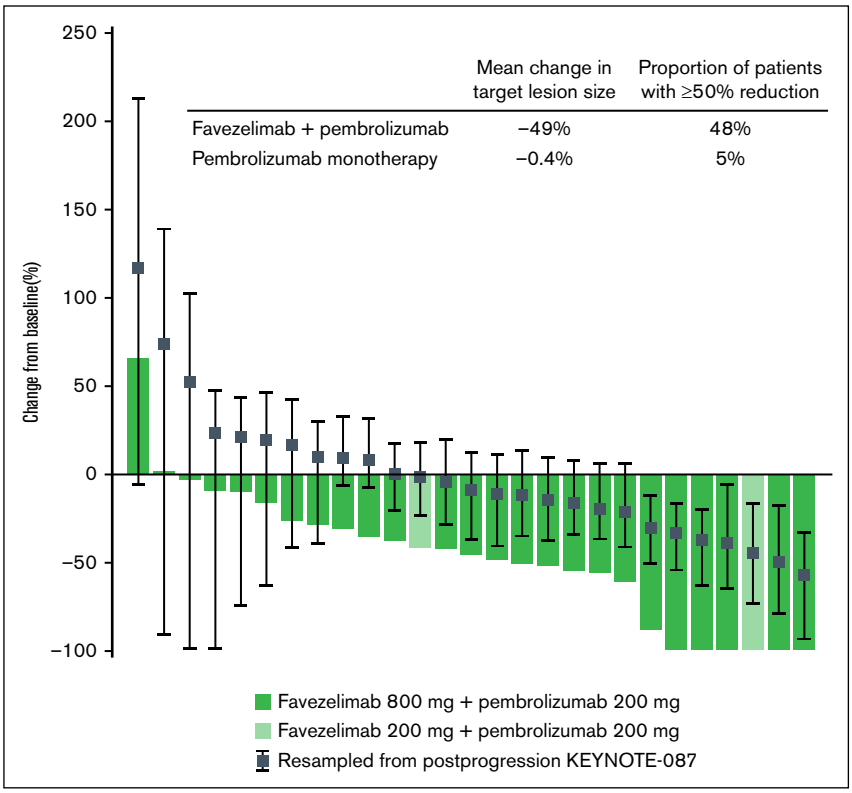

Figure 2. Best percentage change from baseline in target lesion size. Shown for participants treated with favezelimab plus pembrolizumab in MK-4280-003 compared with resampled data from participants who received postprogression pembrolizumab in KEYNOTE-087. Resampled data are median (range) of 1000 random samples obtained from participants who received postprogression pembrolizumab in KEYNOTE-087.

increase from baseline), 47 of 105 (45%) exhibited shrinkage (≥50% reduction from baseline), and 56 of 105 (53%) exhibited stable target lesion size.

KEYNOTE-087: postprogression pembrolizumab

Between 26 June 2015 and 21 March 2016, 210 participants were enrolled and received pembrolizumab in the KEYNOTE-087 study. During the study, 123 participants developed progressive disease per International Working Group 2007 criteria. Of these participants, 81 received postprogression pembrolizumab and were eligible for this analysis. The median time between the last dose of anti–PD-1 therapy and time of the initial progression event was 2.1 weeks (range, 0-5.6; Table 1). Among the 81 participants included in this analysis, the median age was 39 years (range, 20-71), 34 participants (42%) were female, and 38 participants (47%) had an ECOG performance status of 0 (Table 1). Participants had received a median of 4 prior lines of therapy (range, 2-11). The best overall response rate with pembrolizumab during the preprogression period was 51% (41 of 81; 95% CI, 42-63), with 11 participants (14%) achieving a complete response and 30 participants (37%) achieving a partial response (supplemental Table 1).

Among the 81 participants who received postprogression pembrolizumab, the objective response rate was 2% (2 of 81; 95% CI, 0-6), with 2 participants (2%) having a partial response (Table 2). Both participants with a partial response had a clinically meaningful reduction (≥50%) in target lesion size (Figure 1). In the 2 participants with an objective response, the mean change in target lesion size was −56% (SD, 2%). Overall, 50 of 81 participants (62%) had any reduction in target lesion size during the postprogression period, and 4 participants (5%) had a clinically meaningful reduction of ≥50% (Figure 1). The mean change in target lesion size among the 81 participants was −0.4% (SD, 47%; Figure 2). The best response among nonresponders in the postprogression period was stable disease for 23 participants (28%) and progressive disease for 56 participants (69%; Table 2). Fourteen additional participants (17%) developed progressive disease after having an initial response of stable disease, partial response, or complete response. Causes of progression during the postprogression period included growth in ≥1 nontarget lesion (35/81 [43%]), the appearance of new lesions (21/81 [26%]), and progression due to growth or rebound in the target lesions (14/81 [17%]; supplemental Table 2). The median duration of response in the postprogression period was 17 weeks (range, 13-21). Median progression-free survival was 12 weeks (95% CI, 12-13; supplemental Figure 1).

A sensitivity analysis using different assumptions for objective response rate among the 81 participants who received postprogression pembrolizumab in KEYNOTE-087 provided similar results (supplemental Table 3). If the target lesion baseline in the postprogression period was reset at the time of confirmatory scan, the objective response rate was 1.2% (1 of 81); if progression due to nontarget lesion growth was reset to the time point of initial progressive disease, the objective response rate was 3.7% (3 of 81 participants); if progression due to the appearance of new lesions was reset to the time point of initial progressive disease, the objective response rate was 3.7% (3 of 81 participants).

Among the 81 participants who received postprogression pembrolizumab in KEYNOTE-087, 425 target lesions were assessed. Of these, 43 of 425 (10%) lesions exhibited growth (≥50% increase from baseline), 58 of 425 (14%) exhibited shrinkage (≥50% reduction from baseline), and 324 of 425 (76%) exhibited stable target lesion size during the postprogression period. Almost all participants (~99%) had >1 stable or shrinking lesion.

Bootstrapping analysis

Using the bootstrapping method with 1000 random samples obtained from 27 participants from KEYNOTE-087, 26 826 of 27 000 samples (99.4%) showed a greater decrease in tumor burden for favezelimab plus pembrolizumab than for pembrolizumab monotherapy (Figure 2).

Discussion

Favezelimab plus pembrolizumab was shown to have antitumor activity in participants with anti–PD-1–refractory classical Hodgkin lymphoma in the MK-4280-003 study;[8] however, the contribution of favezelimab was unclear. Given that there is currently no benchmark for the response rate to PD-1 blockade alone in such patients, we used data from the KEYNOTE-087 study in this post hoc analysis. The results suggest that favezelimab plus pembrolizumab was associated with a higher objective response rate and deeper response than pembrolizumab alone in patients with anti–PD-1–refractory classical Hodgkin lymphoma. A notable numerical difference was observed in objective response rate (37% favezelimab plus pembrolizumab vs 2% pembrolizumab), and mean change in target lesion size (−49% vs −0.4%, respectively). The bootstrapping method further showed that 99.4% of samples had a greater decrease in tumor burden for favezelimab plus pembrolizumab relative to pembrolizumab alone. These results support the hypothesis that favezelimab contributed substantially to the efficacy observed in participants with anti–PD-1–refractory classical Hodgkin lymphoma in the MK-4280-003 study.

Anti–PD-1 therapies are highly effective and well tolerated in relapsed or refractory classical Hodgkin lymphoma; however, a significant proportion of patients does not achieve long-term disease control.[12,14,15] There are also limited data available regarding treatment options for patients who develop disease progression after anti–PD-(L)1 therapy, and there are no approved drugs or standard of care in this setting. Identifying effective treatment options for use after anti–PD-(L)1 therapy is also of growing importance because anti–PD-1 therapies are being evaluated earlier in the treatment pathway. With recent results from the SWOG S1826 study showing that nivolumab plus doxorubicin, vinblastine, and dacarbazine (AVD) improved progression-free survival compared with brentuximab vedotin plus AVD in patients with newly diagnosed advanced classical Hodgkin lymphoma, PD-1 inhibitors are likely to become more widely used in first-line therapy.[16]

Several studies have evaluated PD-1 inhibitors in patients with disease progression after anti–PD-(L)1–based therapy. In a phase 2 study, treatment with decitabine plus the PD-1 inhibitor camrelizumab resulted in an objective response rate of 60% in patients with relapsed or refractory classical Hodgkin lymphoma who had relapsed or had disease progression after prior anti–PD-1 monotherapy.[17] A phase 1 study has also reported promising response rates with pembrolizumab plus vorinostat, a histone deacetylase inhibitor, in a population of patients with relapsed or refractory classical Hodgkin lymphoma, including patients whose disease was refractory to prior PD-1 blockade.[18] Two small retrospective analyses[19,20] have indicated that PD-1 inhibitors demonstrate efficacy in classical Hodgkin lymphoma that has progressed on anti–PD-L1 therapy, and a third analysis[21] has shown that combination therapy with nivolumab and brentuximab has efficacy after nivolumab monotherapy failure. Retreatment with anti–PD-1 monotherapy beyond progression was also shown to have a benefit in patients with an initial response to anti–PD-1 therapy in the KEYNOTE-087 and CheckMate 205 studies.[12,15] However, these patients differed significantly from those in the current analysis who were required to have primary refractory disease (disease progression <12 weeks of last anti–PD-1 dose). Several retrospective studies have also reported that treatment with checkpoint inhibitor–based therapy may resensitize Hodgkin lymphoma tumor cells to subsequent chemotherapy, with response rates ranging from 60% to 93%.[2,22-24] In CheckMate 205, 51% of patients who underwent allogeneic stem cell transplant after receiving nivolumab achieved a complete response, indicating that they responded to transplant conditioning.[15] While the response rates are impressive, not all these patients had primary refractory disease, as was required for the current analysis.

Dual blockade of LAG-3 and PD-1 has previously shown efficacy in patients with advanced melanoma. In the phase 2/3 RELATIVITY-047 trial, the combination of relatlimab and nivolumab provided a greater benefit than nivolumab alone in patients with previously untreated metastatic or unresectable melanoma, providing a direct indication of the contribution of relatlimab to treatment, albeit in the first-line setting.[6,25,26] A clinical benefit was also observed with relatlimab plus nivolumab in patients with advanced melanoma that had progressed on anti–PD-(L)1 therapy in the phase 1/2a RELATIVITY-020 study; however, the relative contribution of relatlimab in this population was not analyzed.[7] There are currently no other published clinical trial data available regarding dual blockade of LAG-3 and PD-1 in patients with classical Hodgkin lymphoma, although a trial investigating relatlimab plus nivolumab in patients with relapsed or refractory B-cell malignancies is underway (NCT02061761).

This analysis has several limitations. The post hoc nature and the use of data from 2 trials with differing populations provide an indication of the relative efficacy of favezelimab, but prevent the drawing of definitive conclusions. Notably, while participants from KEYNOTE-087 received pembrolizumab without intervening therapy, 37% of evaluable participants from MK-4280-003 had received chemotherapy, antibody-drug conjugates, or kinase inhibitors between prior anti–PD-1 therapy and receiving favezelimab plus pembrolizumab; similarly, the median time from the last dose of anti–PD-1 therapy was longer for participants from MK-4280-003 (17.6 vs 2.1 weeks). Both the receipt of intervening therapy and the longer time from last PD-1 treatment to the restarting of PD-1–based therapy could theoretically have affected the response. A previously presented analysis of MK-4280-003 reported comparable response rates in participants who had anti–PD-1–based therapy as their most recent line of therapy, and in participants who received intervening therapy (objective response rates of 35% vs 23%, respectively).[8] This suggests that these baseline differences between the MK-4280-003 and KEYNOTE-087 populations may be unlikely to significantly affect observed outcomes, although this cannot be ruled out from the present data. A further limitation was that progression due to

nontarget growth or appearance of a new lesion at the time of the original progressive disease in KEYNOTE-087 was carried forward in the analysis, thereby presenting a conservative estimate for objective response rate in the postprogression period; however, results of the sensitivity analysis showed that changing these assumptions had limited impact. Additionally, analysis of response in KEYNOTE-087 was based on computed tomography, whereas FDG-PET scans were available for participants in MK-4280-003, which may have led to some inconsistency in response assessment between the studies. However, this likely had minimal impact on the overall findings, given the magnitude of the difference in response between the groups. Other differences between the populations could have contributed to the results observed, as a higher proportion of participants from MK-4280-003 had an ECOG performance status score of 0 compared with KEYNOTE-087 (67% vs 47%), and the median tumor size at baseline was larger for participants from MK-4280-003 (2819 vs 866 mm^2), but it is not possible to reliably assess the contribution of those differences to the observed outcomes in this study.

The results of this post hoc analysis suggest that favezelimab contributed substantially to the efficacy observed in patients with anti–PD-1–refractory classical Hodgkin lymphoma treated with favezelimab plus pembrolizumab in the MK-4280-003 study. These findings support the further investigation of dual blockade of LAG-3 and PD-1 in classical Hodgkin lymphoma.

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Authorship

Contribution: P.A., J.T., N.A.J., D.L., and A.F.H. were responsible for acquisition of the data; J.T., D.L., K.T., B.G.T., and P.P. analyzed the data; P.A., P.L.Z., J.T., B.G.T., P.P., and A.F.H. interpreted the results; D.L., K.T., B.G.T., and P.P. drafted the manuscript; P.A., P.L.Z., J.T., N.A.J., D.L., P.P., and A.F.H. critically reviewed or revised the manuscript for important intellectual content; and all authors had full access to the primary clinical trial data, and approved the decision to submit the report for publication.

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