Phase 2 Study of the Efficacy and Safety of Pembrolizumab for Relapsed/Refractory Classical Hodgkin Lymphoma

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*A complete list of investigators in the KEYNOTE-087 trial is provided in the Supplementary Appendix, available at NEJM.org.

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- European Hematology Association (EHA) annual meeting, June 9-12, 2016, Copenhagen, Denmark
- Pan Pacific Lymphoma Conference, July 18-22, 2016, Koloa, Hawaii
- 10th International Symposium on Hodgkin Lymphoma October 22-25, 2016 Cologne, Germany
- American Society of Hematology (ASH) Annual Meeting; December 3-6, 2016: San Diego, CA.
ABSTRACT (248; maximum, 275)

Purpose: Hodgkin Reed-Sternberg cells harbor alterations in chromosome 9p24.1, leading to overexpression of PD-L1 and PD-L2. Pembrolizumab, a PD-1–blocking antibody, demonstrated a high overall response rate (ORR) in patients with relapsed or refractory classical Hodgkin lymphoma (rrHL) in phase I testing.

Patients and Methods: KEYNOTE-087 (ClinicalTrials.gov identifier: NCT02453594) was a single-arm phase II study of pembrolizumab in 3 cohorts of patients with rrHL, defined based on lymphoma progression after: (1) autologous stem cell transplantation (ASCT) and subsequent brentuximab vedotin (BV); (2) salvage chemotherapy and BV, and thus ineligible for ASCT because of chemoresistant disease; and (3) ASCT but had not received BV after transplantation. Patients received pembrolizumab 200 mg once every 3 weeks. Response was assessed every 12 weeks. Primary end point was ORR by central review.

Results: A total of 210 patients were enrolled and treated (69 in cohort 1, 81 in cohort 2, and 60 in cohort 3). At the time of analysis, patients received a median of 13 treatment cycles. Per central review, the ORR was 69.0% (95% CI, 62.3% to 75.2%) and the complete response rate was 22.4% (95% CI, 16.9% to 28.6%). By cohort, ORRs were 73.9% for cohort 1, 64.2% for cohort 2, and 70.0% for cohort 3. Thirty-one patients had a response ≥ 6 months. The safety profile was largely consistent with previous pembrolizumab studies.

Conclusions: Pembrolizumab was associated with high response rates and an acceptable safety profile in patients with rrHL, offering a new treatment paradigm for this disease.
INTRODUCTION

Classical Hodgkin lymphoma (cHL) is a highly curable malignancy with conventional chemotherapy or chemoradiotherapy, but treatment is suboptimal for relapsed or refractory cHL (rrHL).\(^1,2\) The standard of care for patients with rrHL is salvage chemotherapy followed by autologous stem cell transplantation (ASCT) if the disease is chemosensitive.\(^3,4\) Brentuximab vedotin (BV) is indicated after failure of these therapies and was recently approved as consolidation treatment after ASCT in patients at high risk of relapse.\(^5,6\) Although BV demonstrates an overall response rate (ORR) of 75% after ASCT failure,\(^7\) median duration of response (DOR) is only 6.7 months. In a retrospective analysis of two phase I studies with 20 transplantation-naive patients, 18 of whom refused or were ineligible for ASCT because of chemoresistant disease, the response rate of BV was 30%.\(^8\)

cHL is characterized by malignant Hodgkin Reed-Sternberg (HRS) cells dispersed within an extensive inflammatory/immune cell infiltrate.\(^9,10\) HRS cells frequently harbor alterations in chromosome 9p24.1, leading to overexpression of PD-L1 and PD-L2, ligands of the programmed death 1 (PD-1) immune checkpoint receptor.\(^11,12\) rrHL may thus be genetically susceptible to blockade of the PD-1 pathway.

Pembrolizumab is a highly selective, humanized monoclonal Ig G4/κ antibody that blocks the interaction between PD-1 and its ligands; it has shown robust antitumor activity and a favorable safety profile and is approved in multiple tumor types.\(^13,14\) A flat exposure-response relationship has been found in the dose range 2 to 10 mg/kg across clinical studies,\(^15\) and based on population pharmacokinetic models, the fixed dose of pembrolizumab 200 mg once every 3 weeks (Q3W) is within this range.
In a phase Ib trial (ClinicalTrials.gov identifier: NCT01953692), pembrolizumab demonstrated an ORR of 65% in patients with heavily pretreated rrHL. Because of the high unmet need for improved treatments for patients with rrHL in whom ASCT and subsequent therapies failed or who are ineligible for transplantation, a phase II study was designed to evaluate the clinical activity of pembrolizumab in 3 separate cohorts, representing the spectrum of relapsed or refractory disease with varying degrees of prior therapies and transplantation status. Efficacy and safety results from all 3 cohorts are presented.

METHODS

Patients

KEYNOTE-087 (ClinicalTrials.gov identifier: NCT02453594) is a multicenter, single-arm phase II study of pembrolizumab in 3 cohorts of patients with rrHL. Cohorts were defined based on lymphoma progression after: (1) ASCT and subsequent BV; (2) salvage chemotherapy and BV, and thus ineligible for ASCT because of chemoresistant disease; and (3) ASCT but had not received BV after transplantation. Patients in cohort 3 could have received BV as part of primary treatment or as salvage treatment or could have been BV naive. The multicohort design allowed contrast in clinical activity among the 3 main subgroups of patients, defined according to the permutation of relevant previous therapies.

Eligibility criteria for all cohorts included age \( \geq 18 \) years, measurable disease, Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate organ function (hematologic, renal, hepatic, coagulation) as determined by laboratory testing within 7 days of first pembrolizumab dose. Exclusion criteria included diagnosis of immunosuppression or receipt of immunosuppressive therapy within 7 days before first study dose; treatment with a monoclonal antibody within 4 weeks before first study dose; prior chemotherapy, targeted small
molecule therapy, or radiation therapy within 2 weeks before first study dose; prior allogeneic hematopoietic stem cell transplantation within the past 5 years; known clinically active CNS involvement; active autoimmune disease requiring systemic treatment in past 2 years; active, noninfectious pneumonitis; prior therapy targeting T-cell costimulation or checkpoint pathways; and known HIV or active hepatitis B or C infection.

All patients provided written informed consent. The study protocol (number MK-3475-087-02) and all amendments were approved by the independent institutional review boards or ethics committees for each study site and conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice.

**Study Design and Treatment**

Patients received pembrolizumab 200 mg intravenously Q3W without premedication for a maximum of 24 months or until documented confirmed disease progression, intolerable toxicity, or investigator decision. Patients attaining a complete remission (CR) could consider stopping pembrolizumab after a minimum of 6 months of treatment, with ≥2 doses received after documented CR. Continuation of treatment beyond the first assessment of progressive disease (PD) was permitted if the patient was clinically stable and agreed upon by investigator and sponsor. Response was assessed by computed tomography every 12 weeks according to the Revised Response Criteria for Malignant Lymphomas (RRC; see Supplementary Methods). Positron emission tomography (PET) was performed at weeks 12 and 24, to confirm CR or PD, and as clinically indicated.

**End Points and Assessments**

Primary end points were ORR by blinded independent central review (BICR) according to RRC and safety. Secondary end points were ORR by investigator review according to RRC; complete
remission rate (CRR) by BICR and investigator assessment according to RRC; progression-free survival (PFS) and DOR by BICR and investigator assessment according to RRC; and overall survival (OS). For assessment of CR, a posttreatment residual mass of any size was permitted if it was negative on PET imaging.

Safety was assessed descriptively by monitoring all adverse events (AEs), treatment-related AEs, immune-related AEs, and serious and fatal AEs. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Patient-reported outcomes were an exploratory end point assessed every cycle for the first 5 cycles, then every 12 weeks, with the EQ-5D questionnaire followed by the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire-Core 30 (EORTC QLQ-C30; Supplementary Methods).

Statistical Analyses

Efficacy and safety were assessed in all patients who received ≥1 dose of pembrolizumab. Relapsed disease was defined as disease progression after response to most recent therapy; refractory cHL was defined as failure to achieve CR or partial response (PR) to most recent therapy. ORR was defined as the proportion of patients who achieved CR or PR using RRC criteria at any time during the study. Best overall response was defined as best ORR during the period between first dose and first documented PD, death, or, in the absence of PD, last efficacy assessment before subsequent therapy. DOR was defined as time between first response and date of first documented PD, death, or, in the absence of PD, last disease assessment.

ORR and CRR were assessed for all patients and by cohort, using the point estimate and 95% two-sided exact CI; ORR was calculated using the Clopper-Pearson method. An exact binomial test was conducted versus a fixed control rate for each cohort. The nonparametric Kaplan-Meier
method was used to estimate PFS and OS curves and rates. Kaplan-Meier estimates were used for analysis of DOR. A prespecified interim analysis, based on investigator-assessed response, was performed after 30 patients reached the first response assessment in all cohorts.

With 60 patients/cohort in the primary analysis population, the design had ≥93% power (one-sided 2.5% alpha) to detect an ORR of ≥35% in cohorts 1 and 3 compared with a fixed control rate of 15%, and an ORR of ≥20% in cohort 2 compared with a fixed control rate of 5%, using the exact binomial test (nQuery version 2.0 software). Additional exploratory subgroup analyses of ORR based on previous lines of therapy and by relapsed or refractory status were conducted across cohorts.

**Biomarker Assessment**

PD-L1 expression was determined as previously described,16 using fresh or archival formalin-fixed, paraffin-embedded pretreatment tissue sectioned at 4 to 5 microns, with a proprietary immunohistochemical assay developed at QualTek Molecular Laboratories (Newtown, PA) in collaboration with Merck & Co., Inc. (Kenilworth, NJ). PD-L1 expression was scored by a board-certified pathologist. Three scores were reported separately: intensity score (0 to 3), membrane staining score (percentage of tumor cells with membrane staining, 0%, >0 to <50%, ≥50 to <100%, or 100%), and histiocyte score (1 to 3; semiquantitative assessment of histiocytes/macrophages staining positive) ([Supplementary Methods](#)). Delineation of histiocyte staining from HRS cell staining was performed by cytomorphologic assessment by the pathologist.

**Role of the Funding Source**

This study was designed by representatives of the study sponsor, Merck Sharp & Dohme, a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and by academic advisors. The principal
investigators and the sponsor were responsible for study oversight. The sponsor was responsible for the collection and maintenance of data. The first and last authors and authors from the study sponsor wrote the first draft of the manuscript with the support of a medical writing team funded by the sponsor; medical writing and editorial assistance was provided by the ApotheCom oncology team (Yardley, PA). All authors participated in reviewing and editing the manuscript, approved the submitted draft, had full access to the data used to write the manuscript and vouch for their accuracy, and attest that the study was conducted in accordance with the protocol.

RESULTS

Patients and Treatment

A total of 210 patients were enrolled and treated (69 in cohort 1, 81 in cohort 2, and 60 in cohort 3) between June 26, 2015, and March 21, 2016, at 51 study sites (Table S1). As of the September 25, 2016, data cutoff date, 90 discontinued, and 120 were still on study treatment (Fig 1). Median exposure to pembrolizumab was 8.3 months (range, 0.03 to 14.99 months), and median duration of follow-up was 10.1 months (range, 1.0 to 15.0 months). At the time of analysis, patients received a median of 13 treatment cycles (range, 1 to 21 in cohorts 1 and 2, and 3 to 21 in cohort 3). Baseline characteristics are shown in Table 1. Median age was 35 years (range, 18 to 76), and patients received a median of 4 previous lines of therapy (range, 1 to 12), with 86.7% of patients having received at least 3 previous lines. By design, all patients in cohorts 1 and 2 had failed prior BV treatment, and in cohort 3, 41.7% of patients had received BV treatment before ASCT.

Clinical Activity

Rates of Response. Per BICR, the ORR across all cohorts was 69.0% (95% CI, 62.3% to 75.2%) and the CRR was 22.4% (95% CI, 16.9% to 28.6%) (Table 2). For the protocol-prespecified
primary analysis by cohort per BICR, the ORR was 73.9% (95% CI, 61.9% to 83.7%) for cohort 1, 64.2% (95% CI, 52.8% to 74.6%) for cohort 2, and 70.0% (95% CI, 56.8% to 81.2%) for cohort 3 (Table 2). For each cohort, the protocol H0 hypothesis ($P \leq .20$ versus $P > .20$) was rejected ($P < .001$). ORR by investigator review was similar to ORR by BICR (Table S2). Across all cohorts, >90% of patients experienced a decrease in tumor burden (Fig 2). Most responses were observed at the first assessment (Fig S1), and no cases of pseudoprogression (clinical response after initial increase in tumor burden) were observed.

**Additional Subgroup Analysis**

*Rates of Responses Based on Prior Lines of Therapy.* ORRs were similar between patients who received <3 prior lines of therapy versus those who received $\geq$3 lines (71.4% v 68.7%, Table S3).

*Rates of Response in Relapsed or Refractory Subgroups Across Cohorts.* In an analysis of the 73 patients who were refractory to first-line therapy (primary refractory, n = 73), ORR was 79.5% (95% CI, 68.4% to 88.0%), which was higher than the ORR in patients with disease refractory to front-line, salvage therapy, and BV (cohort 2, ORR, 66.7%; 95% CI, 55.3% to 76.8%; Tables S4 and S2). In addition, a high ORR was reported in patients who were refractory to all previous lines of therapy (n = 23), with an ORR of 56.5% (95% CI, 34.5% to 76.8%; Table S4). The ORR in patients who had not previously received BV (n = 35) was 71.4% (95% CI, 53.7% to 85.4%) (Table S4).

For patients whose lymphoma relapsed after $\geq$3 prior lines of therapy (n = 146) and in patients with rrHL refractory to at least 1 previous line (n = 170), ORRs were 67.8% (95% CI, 59.6% to 75.3%) and 71.2% (95% CI, 63.7% to 77.9%), respectively (Table S5). These subgroups were not mutually exclusive, with all 210 patients falling under at least one of these two categories.
Fourteen patients in this study went on to receive a stem cell transplantation; 10 allogeneic and 4 autologous.

*Duration of Response.* A Kaplan-Meier plot of duration of response is presented in Figure 2A. Median DOR was not reached in all cohorts (Figs 2B, 2C, and 2D). At 6 months, the rate of OS was 99.5%, and the rate of PFS was 72.4%. Thirty-one patients (75.6%) had a response ≥6 months. Median OS were not reached, with only four deaths occurring.

*Patient-reported outcomes (PRO).* The majority of patients experienced maintenance and/or improvement in disease-related symptoms, functioning, and health status, particularly among patients who responded to pembrolizumab (Tables S6-S8). There was a net improvement in the EORTC QLQ-C30 global health status/quality of life score and EQ-5D visual analog and utility scores from baseline to week 12 across all cohorts (Tables S6-S8).

*Biomarker Analysis*

One hundred and sixty-one patients had evaluable pretreatment tumor tissue (archival or obtained for study) for immunohistochemistry, and 160 samples tested positive for PD-L1. Figure 3 shows the distribution of the three PD-L1 expression scores (tumor cell staining intensity, membrane staining of tumor cells, and histiocyte staining) and response to pembrolizumab across all cohorts. Notably, 90.7% had the highest intensity staining, 87.6% were 100% by membrane staining, and 70.8% had maximum histiocyte staining. Additionally, 103 patients (64.0%) had the maximum score across all three PD-L1 expression scores (intensity of 3, histiocyte score of 3, and tumor membrane staining of 100%).

*Safety*

With a median of 13 treatment cycles, the most common treatment-related AEs (TRAEs) were hypothyroidism (12.4%) and pyrexia (10.5%). The most common grade 3/4 TRAEs were
neutropenia (2.4%), dyspnea (1%), and diarrhea (1%) (Table 3). Immune-mediated AEs (events with potentially drug-related immunologic causes regardless of treatment attribution) and infusion-related reactions were reported in 60 patients (28.6%), most commonly hypothyroidism (13.8%) (Table S9). Nine patients (4.3%) discontinued because of TRAEs (myocarditis, myelitis, myositis, pneumonitis, infusion-related reactions, cytokine release syndrome) and 26 patients (12.4%) experienced TRAEs resulting in treatment interruptions. Two patients died during follow-up as a result of septic shock and acute graft versus host disease, respectively; neither of these deaths were considered to be treatment-related.

DISCUSSION

New therapies are needed for patients with cHL, in particular for transplantation-ineligible patients and those who relapse after ASCT. In the current study, PD-1 blockade with pembrolizumab demonstrated substantial clinical activity in subsets of heavily pretreated patients with cHL, with most responses observed at the first disease assessment and ongoing at the time of data cutoff. There was a high degree of agreement between response rates per BICR and those per investigator review, both in the whole population and in each cohort. ORRs and CRRs were consistent between the multiple subanalyses of relapsed and refractory patients. This study had two unique patient populations, those with transplantation-ineligible cHL secondary to failure of salvage therapy and BV (cohort 2: 81/210 [39%]) and those with primary refractory disease (73/210 [35%]). Notably, high response rates were achieved with pembrolizumab in the chemoresistant population, which is known to have a poor prognosis and few available therapeutic options, and in patients with primary refractory disease. Moreover, the clinical activity of pembrolizumab clearly indicates there is no cross-resistance with cytotoxic agents.
Pembrolizumab also demonstrated a high response rate (71.4%) in patients who had not previously received BV.

Our results contribute to the increasing evidence of the role of PD-1 inhibition in cHL. The anti–PD-1 antibody nivolumab has shown a high response rate in cHL after failure of both ASCT and BV. Several aspects of our study were different from the nivolumab study, including the use of a fixed dose of pembrolizumab and administration every 3 weeks versus every 2 weeks with nivolumab. The nivolumab study did not include a separate cohort of patients in which salvage chemotherapy and BV failed and who were ineligible for ASCT (ie, cohort 2 in the current study) and did not report on patients whose disease progressed after ASCT but who were not treated with BV after ASCT (cohort 3). In addition, although similar ORRs were reported between the two studies, the CRR by independent central review was higher for pembrolizumab (22%) compared with nivolumab (9%). Additionally, the safety profile of pembrolizumab in this study was at least comparable with that of nivolumab in patients with rrHL, but with markedly lower frequencies of infusion-related reactions.

Responses were seen early with pembrolizumab, without cases of early pseudoprogression.

Fourteen patients in this study went on to receive a stem cell transplantation (10 allogeneic and four autologous). In addition, of the 10 patients who received allogeneic transplantation, one died because of GVHD, and the remaining nine are in survival follow-up.

The existing data suggest 200 mg Q3W as the optimal dose for pembrolizumab. This fixed dose is associated with a very low rate of discontinuation due to AEs and an acceptable safety profile, which differs from the safety profile of current cytotoxic therapies for cHL and BV.

Because of the known genetic alterations in the PD-L1 pathway in patients with cHL, PD-L1 positivity was not a requirement for enrollment in this study. However, the majority of patients
in this study were PD-L1 positive by intensity, membrane staining, and histiocyte score. Clinical activity was seen across all groups, including the minority of patients with low expression. Study limitations include the short duration of follow-up, which precluded the accurate estimation of OS and PFS. The patients in this study are being followed-up to assess the durability of response.

Overall, pembrolizumab showed excellent results in both relapsed and refractory patients and was well tolerated at a fixed dose, consistent with prior pembrolizumab clinical experience in oncology patients. A randomized phase 3 study to compare pembrolizumab with BV in patients with rrHL has been initiated (ClinicalTrials.gov identifier: NCT02684292).

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AUTHOR CONTRIBUTIONS

1. **Conception and design**: Robert Chen, Philippe Armand, Bastian von Tresckow, Alejandro D. Ricart, Arun Balakumaran, Craig H. Moskowitz

2. **Provision of study materials or patients**: Michelle A. Fanale, Pauline Brice, John Radford, Theodoros P. Vassilakopoulos, Bastian von Tresckow, Alejandro D. Ricart


4. **Data analysis and interpretation**: Robert Chen, Michelle A. Fanale, Philippe Armand, Vincent Ribrag, Theodoros P. Vassilakopoulos, Bastian von Tresckow, Margaret A. Shipp, Yinghua Zhang, Alejandro D. Ricart, Arun Balakumaran, Craig H. Moskowitz


6. **Final approval of manuscript**: Robert Chen, Pier Luigi Zinzani, Michelle A. Fanale, Philippe Armand, Nathalie A. Johnson, Pauline Brice, John Radford, Vincent Ribrag, Daniel Molin, Theodoros P. Vassilakopoulos, Akihiro Tomita, Bastian von Tresckow, Margaret A. Shipp, Yinghua Zhang, Alejandro D. Ricart, Arun Balakumaran, Craig H. Moskowitz

7. **Administrative support**: Bastian von Tresckow, Alejandro D. Ricart, Arun Balakumaran
REFERENCES


Table 1. Baseline Characteristics by Cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cohort 1 (n = 69)* After ASCT/BV</th>
<th>Cohort 2 (n = 81)* Ineligible for ASCT and failed BV therapy</th>
<th>Cohort 3 (n = 60)* No BV after ASCT</th>
<th>All Patients (N = 210)</th>
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<td>Age, years, median (range)</td>
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<td>0 (0)</td>
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<td>4 (1–11)</td>
<td>3 (2–10)</td>
<td>4 (1–12)</td>
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<td>Prior lines of therapy, no. (%)</td>
<td>Cohort 1</td>
<td>Cohort 2</td>
<td>Cohort 3</td>
<td>Total</td>
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<tr>
<td>≥3</td>
<td>68 (98.6)</td>
<td>78 (96.3)</td>
<td>36 (60.0)</td>
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<td>Refractory disease or relapsed after ≥3 lines of therapy, no. (%)</td>
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<td>B symptoms at baseline, no. (%)</td>
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<td>26 (32.1)</td>
<td>19 (31.7)</td>
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<td>Previous BV therapy, no. (%)</td>
<td>69 (100)</td>
<td>81 (100)</td>
<td>25 (41.7)</td>
<td>175 (83.3)</td>
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</tbody>
</table>

Abbreviations: ASCT, autologous stem cell transplantation; BV, brentuximab vedotin, ECOG, Eastern Cooperative Oncology Group.

*Cohort 1: Failed ASCT and subsequent BV therapy. Cohort 2: Failed salvage chemotherapy, ineligible for ASCT and failed BV therapy. Cohort 3: Failed ASCT and did not receive BV after ASCT.

†The patient had ECOG performance status of 1 at screening and ECOG performance status of 2 at cycle 1, day 1.
‡Bulky disease was defined as a mass larger than one-third of transthoracic diameter at any level of thoracic vertebrae, or single site of disease in any area that was 10 cm or greater in diameter.

§B symptoms include unexplained weight loss of >10% in the past 6 months; unexplained, persistent, or recurrent fever with temperatures >38°C during the previous month; or recurrent drenching night sweats during the previous month.

¹Patients received BV therapy before transplantation.
**Table 2.** Best Overall Response by Blinded Independent Central Review

<table>
<thead>
<tr>
<th>Cohort 1 (n = 69) After ASCT/BV</th>
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<th>Cohort 3 (n = 60) No BV after ASCT</th>
<th>All Patients (N = 210)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
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<tr>
<td>95% CI †</td>
<td>95% CI †</td>
<td>95% CI †</td>
<td>95% CI †</td>
</tr>
<tr>
<td>Overall response rate</td>
<td>51 (73.9) 61.9–83.7</td>
<td>52 (64.2) 52.8–74.6</td>
<td>42 (70.0) 56.8–81.2</td>
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<tr>
<td>Complete remission*</td>
<td>15 (21.7) 12.7–33.3</td>
<td>20 (24.7) 15.8–35.5</td>
<td>12 (20.0) 10.8–32.3</td>
</tr>
<tr>
<td>Partial remission</td>
<td>36 (52.2) 39.8–64.4</td>
<td>32 (39.5) 28.8–51.0</td>
<td>30 (50.0) 36.8–63.2</td>
</tr>
<tr>
<td>Stable disease</td>
<td>11 (15.9) 8.2–26.7</td>
<td>10 (12.3) 6.1–21.5</td>
<td>10 (16.7) 8.3–28.5</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>5 (7.2) 2.4–16.1</td>
<td>17 (21.0) 12.7–31.5</td>
<td>8 (13.3) 5.9–24.6</td>
</tr>
<tr>
<td>Unable to determine</td>
<td>2 (2.9) 0.4–10.1</td>
<td>2 (2.5) 0.3–8.6</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Abbreviations: ASCT, autologous stem cell transplantation; BV, brentuximab vedotin; CI, confidence interval.

*For complete remission, a residual mass was permitted for patients who were negative on PET scanning.

†Based on binomial exact confidence interval method.
<table>
<thead>
<tr>
<th></th>
<th>All-Cause Adverse Events</th>
<th>Treatment-Related Adverse Events</th>
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<tbody>
<tr>
<td></td>
<td>(N = 210)</td>
<td>(N = 210)</td>
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<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td></td>
<td>Grade 1 or 2</td>
<td>Grade 3</td>
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<tr>
<td>Pyrexia</td>
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<tr>
<td>Cough</td>
<td>44 (21)</td>
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<tr>
<td>Fatigue</td>
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<tr>
<td>Diarrhea</td>
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<td>3 (1.4)</td>
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<td>Vomiting</td>
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<td>Nausea</td>
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<td>Hypothyroidism</td>
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<td>Neutropenia</td>
<td>7 (3.3)</td>
<td>4 (1.9)</td>
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<td>Upper respiratory tract infection</td>
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<tr>
<td>Rash</td>
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<tr>
<td>Pruritus</td>
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<td>Headache</td>
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<td>Arthralgia</td>
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<td>Constipation</td>
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<tr>
<td>Nasopharyngitis</td>
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<tr>
<td>Dyspnea</td>
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<td>Back pain</td>
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<tr>
<td>Condition</td>
<td>Incidence</td>
<td>Grade 1</td>
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<tr>
<td>----------------------------</td>
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<tr>
<td>Oropharyngeal pain</td>
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<tr>
<td>Asthenia</td>
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<td>Sinusitis</td>
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<td>Urinary tract infection</td>
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<td>Insomnia</td>
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<td>Nasal congestion</td>
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<td>Bronchitis</td>
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<tr>
<td>Chills</td>
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<tr>
<td>Anemia</td>
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<tr>
<td>Muscle spasms</td>
<td>11 (5.2)</td>
<td>1 (0.5)</td>
</tr>
</tbody>
</table>

Adverse events of any grade occurring in ≥5% of patients are shown. Two patients died as a result of graft versus host disease and septic shock, respectively, which were unrelated to treatment.
Fig 1. Patient disposition.

Cohort 1
- 69 patients started treatment
  - Completed: n = 0
  - Treatment ongoing: n = 43 (62.3%)
  - Discontinued: n = 26 (37.7%)
    - Adverse event, n = 4 (5.8%)
    - Bone marrow transplant, n = 2 (2.9%)
    - Clinical progression, n = 2 (2.9%)
    - Complete response, n = 5 (7.2%)
    - Death, n = 1 (1.4%)
    - Lost to follow up, n = 0
    - Physician decision, n = 3 (4.3%)
    - Progressive disease, n = 10 (14.5%)
    - Patient withdrawal, n = 0

Cohort 2
- 81 patients started treatment
  - Completed: n = 0
  - Treatment ongoing: n = 36 (44.4%)
  - Discontinued: n = 45 (55.6%)
    - Adverse event, n = 3 (3.7%)
    - Bone marrow transplant, n = 2 (2.5%)
    - Clinical progression, n = 1 (1.2%)
    - Complete response, n = 7 (8.6%)
    - Death, n = 1 (1.2%)
    - Lost to follow up, n = 1 (1.2%)
    - Physician decision, n = 7 (8.6%)
    - Progressive disease, n = 20 (24.7%)
    - Patient withdrawal, n = 3 (3.7%)

Cohort 3
- 60 patients started treatment
  - Completed: n = 0
  - Treatment ongoing: n = 41 (68.3%)
  - Discontinued: n = 19 (31.7%)
    - Adverse event, n = 2 (3.3%)
    - Bone marrow transplant, n = 0
    - Clinical progression, n = 1 (1.7%)
    - Complete response, n = 1 (1.7%)
    - Death, n = 0
    - Lost to follow up, n = 0
    - Physician decision, n = 2 (3.3%)
    - Progressive disease, n = 13 (21.7%)
    - Patient withdrawal, n = 0
**Fig 2.** Decrease from baseline in tumor burden (left) and Kaplan-Meier estimates of objective response duration (right) based on central review in patients with response. (A) All cohorts; (B) cohort 1; (C) cohort 2; (D) cohort 3.
Fig 3. Distribution of PD-L1 expression scores and response to pembrolizumab across all cohorts. A total of 161 patients across all cohorts had evaluable pretreatment tumor tissue. Three scores were reported separately: (A) intensity score (0–3), (B) membrane staining score (percentage of tumor cells with membrane staining 0%, >0 to <50%, ≥50 to <100%, or 100%), and (C) histiocyte score (1-3; semiquantitative assessment of histiocytes/macrophages staining positive for PD-L1).
AUTHOR DISCLOSURES

Robert Chen: Personal fees (consultancy) from Merck & Co., Inc.

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Michelle A. Fanale: Advisory board for Merck & Co., Inc.

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Yinghua Zhang: Employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.,
Kenilworth, NJ

Alejandro D. Ricart: Employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co.,
Inc., Kenilworth, NJ; ownership interest in Pfizer, Inc.

Arun Balakumaran: Employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co.,
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