Pembrolizumab plus lenalidomide and dexamethasone for patients with treatment-naive multiple myeloma (KEYNOTE-185): a randomised, open-label, phase 3 trial

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Summary

Background Lenalidomide and dexamethasone has been a standard of care in transplant-ineligible patients with newly diagnosed multiple myeloma. The addition of a third drug to the combination is likely to improve treatment efficacy. KEYNOTE-185 assessed the efficacy and safety of lenalidomide and dexamethasone with and without pembrolizumab in patients with previously untreated multiple myeloma. Here, we present the results of an unplanned interim analysis done to assess the benefit–risk of the combination at the request of the US Food and Drug Administration (FDA).

Methods KEYNOTE-185 was a randomised, open-label, phase 3 trial done at 95 medical centres across 15 countries (Australia, Canada, France, Germany, Ireland, Israel, Italy, Japan, New Zealand, Norway, Russia, South Africa, Spain, UK, and USA). Transplantation-ineligible patients aged 18 years and older with newly diagnosed multiple myeloma, Eastern Cooperative Oncology Group performance status of 0 or 1, and who were treatment naive were enrolled, and randomly assigned 1:1 to receive either pembrolizumab plus lenalidomide and dexamethasone or lenalidomide and dexamethasone alone using an interactive voice or integrated web response system. Patients received oral lenalidomide 25 mg on days 1–21 and oral dexamethasone 40 mg on days 1, 8, 15, and 22 of repeated 28-day cycles, with or without intravenous pembrolizumab 200 mg every 3 weeks. The primary endpoint was progression-free survival, which was investigator-assessed because of early trial termination. Efficacy was analysed in all randomly assigned patients and safety was analysed in all patients who received at least one dose of study drug. This trial is registered at ClinicalTrials.gov, number NCT02579863, and it is closed for accrual.

Findings Between Jan 7, 2016, and June 9, 2017, 301 patients were randomly assigned to the pembrolizumab plus lenalidomide and dexamethasone group (n=151) or the lenalidomide and dexamethasone group (n=150). On July 3, 2017, the FDA decided to halt the study because of the imbalance in the proportion of death between groups. At database cutoff (June 2, 2017), with a median follow-up of 6·6 months (IQR 3·4–9·6), 149 patients in the pembrolizumab plus lenalidomide and dexamethasone group and 145 in the lenalidomide and dexamethasone group had received their assigned study drug. Median progression-free survival was not reached in either group; progression-free survival estimates at 6-months were 82·0% (95% CI 73·2–88·1) versus 85·0% (76·8–90·5; hazard ratio [HR] 1·22; 95% CI 0·67–2·22; p=0·75). Serious adverse events were reported in 81 (54%) patients in the pembrolizumab plus lenalidomide and dexamethasone group versus 57 (39%) patients in the lenalidomide and dexamethasone group; the most common serious adverse events were pneumonia (nine [6%]) and pyrexia (seven [5%]) in the pembrolizumab plus lenalidomide and dexamethasone group and pneumonia (eight [6%]) and sepsis (two [1%]) in the lenalidomide and dexamethasone group. Six (4%) treatment-related deaths occurred in the pembrolizumab plus lenalidomide and dexamethasone group (cardiac arrest, cardiac failure, myocarditis, large intestine perforation, pneumonia, and pulmonary embolism) and two (1%) in the lenalidomide and dexamethasone group (upper gastrointestinal haemorrhage and respiratory failure).

Interpretation The results from this unplanned, FDA-requested, interim analysis showed that the benefit–risk profile of pembrolizumab plus lenalidomide and dexamethasone is unfavourable for patients with newly diagnosed, previously untreated multiple myeloma. Long-term safety and survival follow-up is ongoing.

Funding Merck Sharp & Dohme, a subsidiary of Merck & Co, Inc (Kenilworth, NJ, USA).

Introduction

Multiple myeloma, a malignancy of plasma cells, predominantly affects older patients and is associated with hypercalcaemia, renal impairment, anaemia, and bone disease.[1,2] Treatment options have evolved over the past decade and include chemotherapy, autologous stem-cell transplantation, immunomodulators, proteasome inhibitors, and monoclonal antibodies.[3]

Lancet Haematol 2019

Published Online July 18, 2019 http://dx.doi.org/10.1016/S2352-3026(19)30109-7

See Online/Comment http://dx.doi.org/10.1016/S2352-3026(19)30149-8

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See **Online** for appendix 1

Research in context

Evidence before this study

We did a PubMed search using the keywords "multiple myeloma" and "PD-1" filtered by "article type: clinical trial" and "publication dates: 01/01/2013 to 11/27/2018" with no language restrictions, which yielded only two results relevant to multiple myeloma (a third article was on melanoma). Both studies involved a PD-1 inhibitor, pembrolizumab or nivolumab, in patients with relapsed or refractory multiple myeloma and showed promising efficacy and safety. These results raise a pertinent unanswered question regarding the use of PD-1 inhibitors combined with immunomodulators and dexamethasone as first-line treatment in patients with multiple myeloma. We did another search of PubMed on Nov 27, 2018, with the keywords, "multiple myeloma" and "transplantation-ineligible" using the same filters and found six results. In the phase 3 FIRST study of lenalidomide and low-dose dexamethasone until disease progression, or lenalidomide and low-dose dexamethasone for 72 weeks, or melphalan, prednisone, and thalidomide for 72 weeks in patients with newly diagnosed multiple myeloma, overall survival was improved with continuous lenalidomide and dexamethasone compared with with melphalan, prednisone, and thalidomide. In the second article, the alkylator-containing triplets, melphalan, prednisone, and lenalidomide, were shown to be not superior to the alkylator-free lenalidomide and low-dose dexamethasone doublet in patients with transplantation-ineligible multiple myeloma. These results provide support for the choice of the comparator group in this study, KEYNOTE-185. The third, fourth, and fifth articles concerned regimens—such as bortezomib and dexamethasone or bortezomib, thalidomide, and dexamethasone and bortezomib, melphalan, and prednisone—based on the proteasome inhibitor bortezomib in newly diagnosed transplantation-ineligible multiple myeloma. In the phase 3b UPFRONT study in US community practices, all bortezomib-containing regimens showed favourable outcomes. The phase 3 ALCYONE study showed that the addition of daratumumab to bortezomib, melphalan, and prednisone led to a lower risk of disease progression or death but an increased occurrence of grade 3 or 4 infections. The sixth article reported results of the phase 3, SWOG S0777 study and showed that the addition of bortezomib to lenalidomide and dexamethasone improved survival outcomes.

Added value of this study

The phase 3 KEYNOTE-185 study was done to assess the efficacy and safety of the checkpoint inhibitor pembrolizumab with lenalidomide and dexamethasone in transplantation-ineligible patients with newly diagnosed multiple myeloma. Preclinical evidence reported by Gorgun and colleagues in 2015 suggested that combination of PD-1 blockade with lenalidomide resulted in greater antitumour activity in multiple myeloma. However, an unplanned interim analysis of KEYNOTE-185, done at a median follow-up of 6·6 months at the request of the US FDA, showed an unfavourable benefit–risk profile for the pembrolizumab plus lenalidomide and dexamethasone combination and KEYNOTE-185 was halted.

Implications of all the available evidence

Although KEYNOTE-185 is unlikely to change clinical practice in light of alternative, efficacious, and safe triplet and quadruplet treatments in this setting, it is likely to provide valuable information to guide the design of future clinical studies involving checkpoint inhibitors in newly diagnosed multiple myeloma.

Standard of care for patients with transplantation-ineligible newly diagnosed multiple myeloma in the USA consists of lenalidomide plus dexamethasone, with or without bortezomib.[3,4] The European Society for Medical Oncology clinical practice guidelines recommend another option in the non-transplantation setting: bortezomib, melphalan, and prednisone.[5,6] Addition of daratumumab to bortezomib, melphalan, and prednisone lowered the risk of disease progression and death in patients in the first line setting, resulting in another efficacious and safe treatment option.[7] Most patients with myeloma relapse; so new treatment options for subsequent lines of therapy are needed.

Plasma cells from most patients with multiple myeloma express PD-L1,[8] and PD-L1 upregulation is associated with disease relapse.[9] Combination PD-1 and PD-L1 blockade and lenalidomide showed enhanced effector cell-mediated multiple myeloma cytotoxicity.[10] Thus, immune checkpoints might be important in myeloma resistance and are an attractive therapeutic target. Combination of immune checkpoint inhibition and lenalidomide plus dexamethasone might provide synergistic antitumour activity in patients with multiple myeloma.[11] The PD-1 inhibitor pembrolizumab as monotherapy or combined with lenalidomide and low-dose dexamethasone or pomalidomide and low-dose dexamethasone had shown acceptable safety and promising antitumour activity in 50% (monotherapy) and 60% (in combination) of patients with relapsed refractory multiple myeloma.[12–14] We hypothesised that inhibiting the PD-1 and PD-L1 pathway in patients with treatment-naive multiple myeloma might improve efficacy outcomes. This KEYNOTE-185 trial was done to assess safety and efficacy of pembrolizumab plus lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with treatment-naive multiple myeloma. Here, we present the results of an unplanned interim analysis done to assess the benefit–risk profile of the combination therapy at the request of the US Food and Drug Administration (FDA).

Methods

Study design and participants

KEYNOTE-185 was a randomised, open-label, phase 3 trial of pembrolizumab with lenalidomide and low-dose dexamethasone versus lenalidomide and low-dose dexamethasone in newly diagnosed and previously untreated patients with multiple myeloma. Patients were enrolled at 95 medical centres across 15 countries (Australia, Canada, France, Germany, Ireland, Israel, Italy, Japan, New Zealand, Norway, Russia, South Africa, Spain, UK, and USA; appendix 1 pp 3–5). The protocol and its amendments were approved by the appropriate institutional review board or independent ethics committee. The trial was done in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent.

Patients aged 18 years or older with newly diagnosed, treatment-naive, active multiple myeloma with measurable disease, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate organ function were enrolled. Patients had to be ineligible for autologous stem cell transplantation because of age (≥65 years) or any clinically significant co-existing medical condition (cardiac, renal, pulmonary, or hepatic dysfunction) likely to have a negative effect on their tolerability of autologous stem cell transplantation. Patients also had to provide bone marrow biopsy samples or aspirate material for disease assessment. Measurable disease was defined as at least 10% bone marrow plasma cell percentage, biopsy proven bony, or extramedullary plasmacytoma; serum monoclonal protein concentration of at least 5 g/L, urine monoclonal protein concentration of at least 200 mg per 24 h or, if monoclonal protein is not measurable, an abnormal serum free light chain ratio with involved free light chain concentration of at least 100 mg/L; and presence of hypercalcaemia, renal impairment, anaemia, or bone disease. Adequate organ function was assessed as absolute neutrophil count more than 1000 per µL, platelets at least 75 000 per µL, haemoglobin of at least 75 g/L, creatinine maximum 1·5 times the upper limit of normal (ULN) or creatinine clearance at least 30 mL/min, total bilirubin maximum 1·5 times the ULN, aspartate transaminase and alanine transaminase maximum 2·5 times the ULN, and international normalized ratio or prothrombin time maximum 1·5 times the ULN. Exclusion criteria were oligosecretory myeloma; smouldering multiple myeloma; monoclonal gammopathy of unknown significance; Waldenström's macroglobulinaemia; history of plasma cell leukaemia; history of repeated infections or immunosuppression; history of or active pneumonitis necessitating steroids; active autoimmune disease requiring systemic treatment in the past 2 years; active infections necessitating intravenous systemic treatment; grade 2 or worse peripheral neuropathy; known HIV, active hepatitis B, or active hepatitis C infection; and live vaccine within 30 days of the first dose of study medication. Other exclusion criteria were previous therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte-associated antigen-4 antibody; previous anti-myeloma therapy, previous or current participation in another anti-myeloma therapy study; previous allogeneic haemopoietic stem cell transplantation in the past 5 years; known hypersensitivity to any of the study drugs; known additional malignancy requiring active treatment in past 5 years; known psychiatric or substance abuse disorders that would interfere with study compliance; pregnant or breastfeeding or expecting to conceive within projected duration of the trial; unable or unwilling to undergo thromboembolic prophylaxis; lactose intolerance; invasive fungal infection; and immediate relative who is investigational site or funder staff involved in this trial.

Randomisation and masking

Patients were randomly assigned 1:1 to the pembrolizumab plus lenalidomide and dexamethasone group or the lenalidomide and dexamethasone group using an interactive voice or integrated web response system (randomised allocation schedules were generated by the funder). Randomisation was stratified by age (<75 *vs* ≥75 years) and International Staging System stage (I or II *vs* III). There was no masking of treatment allocation in this open-label trial.

Procedures

Patients received intravenous pembrolizumab plus oral lenalidomide and oral low-dose dexamethasone or lenalidomide and low-dose dexamethasone. Lenalidomide was given as 25 mg daily on days 1–21 and dexamethasone as 40 mg daily on days 1, 8, 15, and 22 of repeated 28-day cycles with or without pembrolizumab 200 mg intravenously every 3 weeks. The dexamethasone dose was 20 mg for patients older than 75 years. Patients received study treatment until documented confirmed disease progression, unacceptable adverse events, or withdrawal from study.

Progression-free survival and response endpoints were investigator-assessed. Every 4 weeks, response was assessed per International Myeloma Working Group 2011 response criteria.[15] Response was also assessed using a full myeloma laboratory panel and calcium, creatinine, and haemoglobin laboratory results, radiography (x-ray or MRI or CT or MRI with PET or CT with PET as clinically indicated) for patients with extramedullary soft tissue plasmacytomas and bone marrow biopsy specimen or aspirate material for confirmation of complete response or disease progression. Low-dose CT and MRI bone surveys were allowed.

Cytogenetic analyses were done locally and not assessed centrally; CD138 selection was not done at all centres. Analysis of baseline lactate dehydrogenase concentrations was not available.

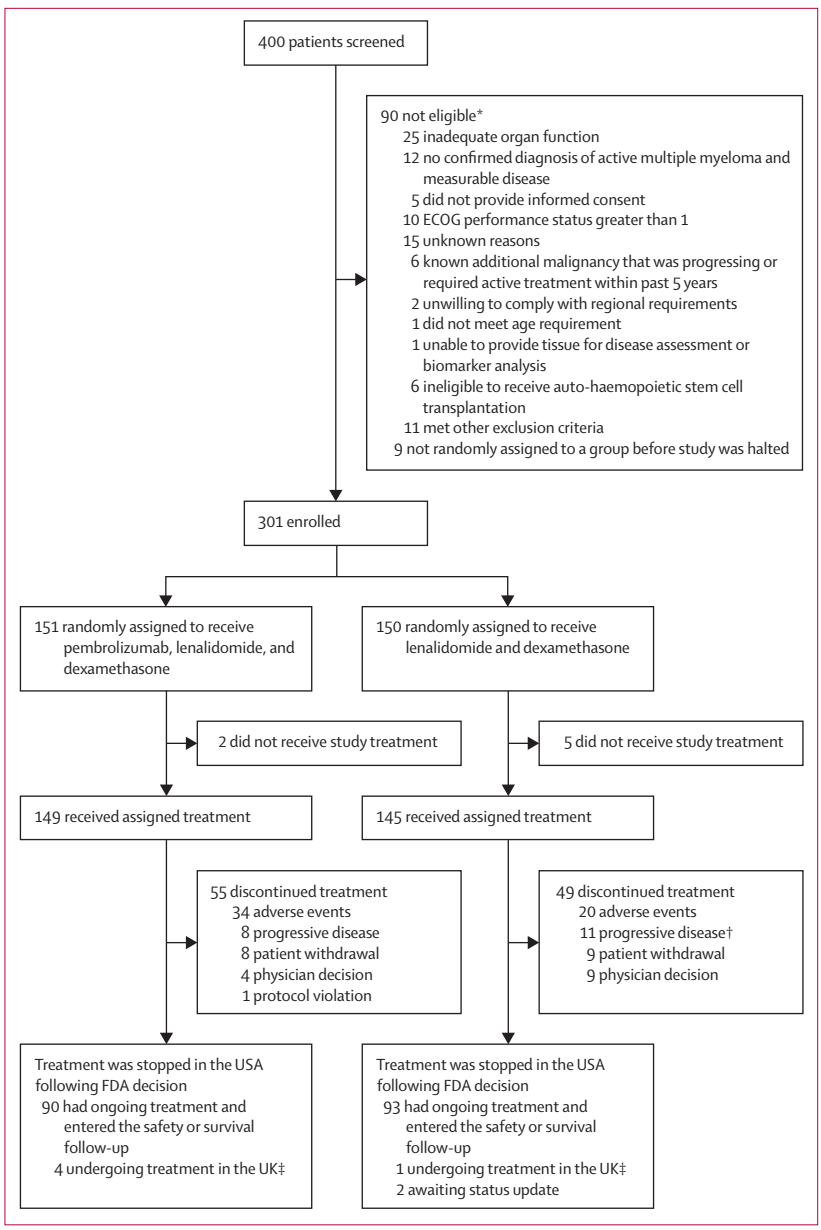

Figure 1: **Trial profile**
FDA=US Food and Drug Administration. *Reasons are not exclusive—ie, one patient can meet more than one criterion. †One additional patient had progressive disease in the lenalidomide-dexamethasone group but is not included in this figure because the discontinuation visit occurred after the database cutoff date. ‡All UK patients discontinued pembrolizumab and continued standard of care treatment. The sponsor agreed to supply lenalidomide to those patients who did not have access to it.

Patients were followed up for survival status every 12 weeks after end of study treatment and monitored for adverse events until 30 days (90 days for serious adverse events) after the end of study treatment. Adverse events were graded per National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

The trial was to be terminated prematurely if quality or quantity of data recording was inaccurate or incomplete, adherence to protocol and regulatory requirements was poor, there were plans to modify or discontinue development of pembrolizumab, or in response to a request by the FDA or other health authority because of safety concerns.

Outcomes

The primary endpoint was progression-free survival, defined as the time from random group assignment to the first documented instance of disease progression or death from any cause, whichever occurred first. Secondary endpoints were safety, overall survival, overall response, duration of response, disease control, and secondary progression-free survival (time from randomisation to subsequent disease progression after initiation of new anti-cancer therapy or death from any cause, whichever occurs first, based on investigator assessment; not reported here). Overall survival was defined as time from randomisation to death from any cause. Overall response was defined as the proportion of patients who achieved at least a partial response per International Myeloma Working Group 2011 criteria based on central review. Duration of response was defined as the time from first documented evidence of at least a partial response by central review until disease progression or death. Overall responses (complete response, very good partial response, partial response, stable disease, and progressive disease) were defined per the International Myeloma Working Group 2011 criteria (appendix 1 p 15). Disease control was defined per International Myeloma Working Group 2011 criteria as the percentage of patients who achieved confirmed stringent complete response, complete response, very good partial response, partial response, minimal response, or stable disease per central review for at least 12 weeks before any evidence of progression. Median time to progression (time from randomisation to first documented instance of progression) was assessed. Immune-mediated adverse events, defined as adverse events (non-serious and serious) associated with pembrolizumab exposure that were consistent with immune phenomena and that had a potentially immunological cause, were prespecified as events of interest.

Statistical analysis

A sample size of 640 patients was planned. For progression-free survival, based on 227 events, the study had 90% power to detect a hazard ratio (HR) of 0·65 with pembrolizumab plus lenalidomide and dexamethasone versus lenalidomide and dexamethasone at a one-sided α of 2·5%. The sample size calculation was based on the following assumptions: (1) progression-free survival follows an exponential distribution with a median of 25·5 months in the control group; (2) enrolment period is 18 months with at least 12 months' follow-up; and (3) cumulative dropout of participants is 2% at the end of the first year and 5% at 4 years.

Hypothesis testing of objective response, progression-free survival, and overall survival was strongly controlled by a family-wise type I error rate of 2·5% (one-sided α). Boundaries and the α level were established from the actual number of events at the time of the interim analysis using the corresponding α-spending function.[16] A stepdown approach was used to control the type I error rate for the testing of endpoints. The primary endpoint (progression-free survival) was tested first; then, if significant, the secondary endpoint (overall survival) was tested.[16] Patients were censored for overall survival analysis at the last date they were known to be alive.

Progression-free survival and overall survival were estimated using the Kaplan-Meier method. Patients who did not have documented disease progression or did not die were censored for progression-free survival analysis at the last disease assessment. Treatment difference between groups was assessed using the stratified log-rank test. HRs and associated 95% CIs between treatment groups were calculated using a stratified Cox proportional hazards model with the Efron method of tie handling. Age and International Staging System were used in the stratified log-rank test and the stratified Cox model. Additional details are in appendix 1 (p 2).

Overall responses and disease control were compared between treatment groups using the stratified Miettinen and Nurminen method[17] and were stratified by age and International Staging System stage. Duration of response was estimated by the Kaplan-Meier method. To analyse duration of response, patients with missing data were censored at the last assessment date if they responded at the time of analysis.

One interim analysis was planned when all patients had been enrolled and about 115 progression-free survival events had been observed. The interim analysis was planned for potential early detection of superiority (with group sequential boundaries) or futility (with non-binding bounds) of pembrolizumab plus standard of care versus standard of care alone.

Efficacy was analysed in all randomly assigned patients (intention-to-treat population). Safety was analysed in all randomly assigned patients who received at least one dose of their assigned study drug (safety population). SAS software, version 9.4, was used for statistical analyses. Full statistical plans to continue or stop the trial are provided in the protocol available in appendix 2 (pp 102–15). An external data monitoring committee monitored interim data and made recommendations to the executive oversight committee about overall risk and benefit to trial participants. This study is registered with ClinicalTrials.gov, number NCT02579863.

Role of the funding source

The funder was involved in study design, data analysis data interpretation, and writing of the report, but not data collection. All authors had access to all the data and had final responsibility for the decision to submit for publication.

	Pembrolizumab plus lenalidomide and dexamethasone group (n=151)	Lenalidomide and dexamethasone group (n=150)
Age, years	74 (70–79)	74 (70–78)
70–79	87 (58%)	86 (57%)
≥80	32 (21%)	31 (21%)
Sex		
Female	81 (54%)	79 (53%)
Male	70 (46%)	71 (47%)
ECOG performance status*		
0	51 (34%)	55 (37%)
1	100 (66%)	92 (61%)
2	0	1 (1%)
Missing	0	2 (1%)
International Staging System stage		
I	38 (25%)	51 (34%)
II	68 (45%)	66 (44%)
III	44 (29%)	31 (21%)
Missing	1 (1%)	2 (1%)
Cytogenetics		
High-risk del17p13, t(4;14), or t(14;16)	24 (16%)	10 (7%)
del13	13 (9%)	17 (11%)
t(11;14)	11 (7%)	13 (9%)
Normal	93 (62%)	89 (59%)
Missing	3 (2%)	16 (11%)
Renal impairment†	21 (14%)	12 (8%)
Plasmacytoma	4 (3%)	11 (7%)
Bone	4/4 (100%)	9/11 (82%)
Extramedullary	0	2/11 (18%)
Hypercalcaemia	14 (9%)	14 (9%)
Anaemia	84 (56%)	68 (45%)

Data are median (IQR) and n (%). ECOG=Eastern Cooperative Group Oncology. *Statuses range from 0 to 5, with higher scores indicating greater disability. †Creatinine clearance less than 40 mL/min or serum creatinine more than 177 μmol/L (>2 mg/dL).

Table 1: **Baseline characteristics of the intention-to-treat population**

Results

400 patients were screened for enrolment at 95 sites in 15 countries. 90 were ineligible and nine were not assigned to a group before the study was halted (figure 1). Between Jan 7, 2016, and June 9, 2017, 301 patients were randomly assigned to the pembrolizumab plus lenalidomide and dexamethasone group (n=151) or the lenalidomide and dexamethasone group (n=150) group. Of these, 149 in the pembrolizumab plus lenalidomide and dexamethasone group and 145 in the lenalidomide and dexamethasone group received their assigned treatment. In the pembrolizumab plus lenalidomide and dexamethasone group, 34 patients discontinued because of adverse events and eight

See Online for appendix 2

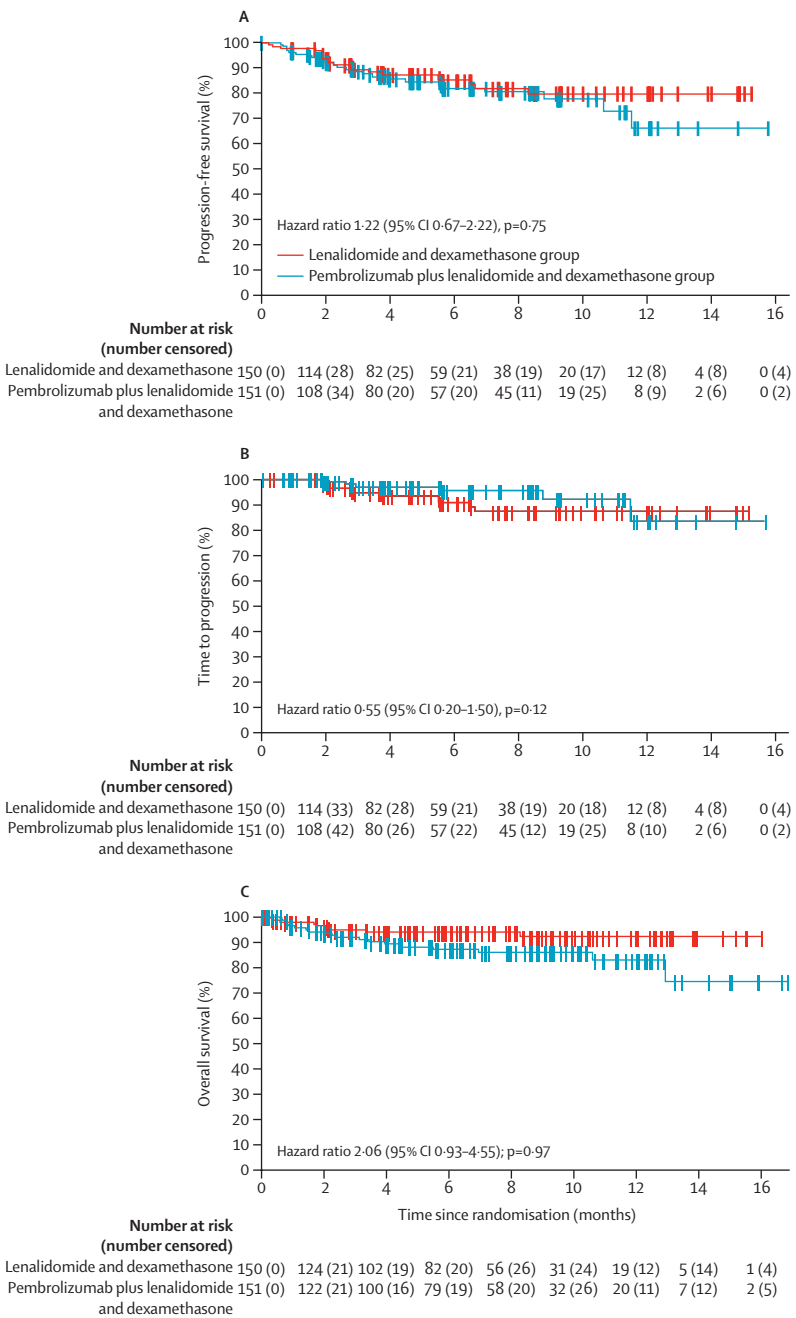

Figure 2: **Survival outcomes in the intention-to-treat population**
(A) Progression-free survival and (B) time to progression per International Myeloma Working Group 2011, based on confirmed investigator review. (C) Overall survival.

because of disease progression; in the lenalidomide and dexamethasone group, 20 discontinued because of adverse events and 11 because of progression (figure 1). The most commonly reported adverse events that led to discontinuation are in appendix 1 (p 16). 156 patients started treatment with a dose of 20 mg of dexamethasone (78 in each group).

Changes made to the trial protocol after the start of the study are in appendix 1 (pp 6–14). On July 3, 2017, the FDA halted this trial on the basis of interim data presented to the data monitoring committee, which showed an unfavourable benefit–risk profile of pembrolizumab plus lenalidomide and dexamethasone.[18] Based on that decision, all patients stopped study treatment, completed the discontinuation visit, and moved into the long-term safety and survival follow-up period per protocol; a long-term survival analysis is planned. Per the FDA decision, no long-term efficacy data will be collected. Quality-of-life assessments will not be reported because of early trial termination. Subsequent treatment decisions were made by the physicians per standard of care; data will not be collected.

At database cutoff (June 2, 2017), median follow-up was 6·6 months (IQR 3·4–9·6). Baseline characteristics were mostly similar between the groups, except high-risk cytogenetics (24 [16%] of 151 in the pembrolizumab plus lenalidomide and dexamethasone group *vs* ten [7%] of 150 in the lenalidomide and dexamethasone group), anaemia (84 [56%] *vs* 68 of [45%]), and renal impairment (21 [14%] *vs* 12 [8%]; table 1).

The primary endpoint of median progression-free survival was not reached in either group; 24 (16%) patients in the pembrolizumab plus lenalidomide and dexamethasone group and 20 (13%) patients in the lenalidomide and dexamethasone group had had a progression-free survival event at analysis. The HR for progression-free survival was 1·22 (95% CI 0·67–2·22; p=0·75; figure 2A). Progression-free survival was 88·5% (81·3–93·0) in the pembrolizumab plus lenalidomide and dexamethasone group versus 89·3% (82·3–93·7) in the lenalidomide and dexamethasone group at 3 months and 82·0% (73·2–88·1) versus 85·0% (76·8–90·5) at 6 months. Median time to progression was not reached in either group; six (4%) in the pembrolizumab plus lenalidomide and dexamethasone group versus 11 (7%) in the lenalidomide and dexamethasone group had progression events, and the HR was 0·55 (0·20–1·50; p=0·12; figure 2B).

Median overall survival was not reached in either group; 19 (13%) patients in the pembrolizumab plus lenalidomide and dexamethasone group versus nine (6%) in the lenalidomide and dexamethasone group died, and the HR was 2·06 (95% CI 0·93–4·55; p=0·97; figure 2C). 3-month overall survival was achieved by 94·7% (89·3–97·5) of patients in the pembrolizumab plus lenalidomide and dexamethasone group versus 91·8% (85·7–95·4) in the lenalidomide and dexamethasone group; 6-month overall survival was achieved by 87·2% (79·9–92·0) versus 93·9% (88·1–96·9).

Overall responses were similar between groups: 96 (64%; 95% CI 55·4–71·2) patients in the pembrolizumab plus lenalidomide and dexamethasone group and 93 (62%; 53·7–69·8) in the lenalidomide and dexamethasone group achieved an overall response

	Pembrolizumab plus lenalidomide and dexamethasone group (n=149)				Lenalidomide and dexamethasone group (n=145)			
	Any grade	Grades 1–2	Grade 3	Grade 4	Any grade	Grades 1–2	Grade 3	Grade 4
Any	140 (94%)	33 (22%)	76 (51%)	19 (13%)	133 (92%)	60 (41%)	52 (36%)	13 (9%)
Constipation	52 (35%)	50 (34%)	2 (1%)	0	30 (21%)	30 (21%)	0	0
Fatigue	40 (27%)	35 (23%)	5 (3%)	0	32 (22%)	29 (20%)	3 (2%)	0
Nausea	36 (24%)	33 (22%)	3 (2%)	0	29 (20%)	28 (19%)	1 (1%)	0
Diarrhoea	33 (22%)	28 (19%)	5 (3%)	0	28 (19%)	28 (19%)	0	0
Anaemia	31 (21%)	16 (11%)	14 (9%)	1 (1%)	24 (17%)	16 (11%)	8 (6%)	0
Pyrexia	30 (20%)	26 (17%)	4 (3%)	0	9 (6%)	9 (6%)	0	0
Rash†	28 (19%)	22 (15%)	6 (4%)	0	16 (11%)	15 (10%)	1 (1%)	0
Vomiting	27 (18%)	25 (17%)	2 (1%)	0	9 (6%)	9 (6%)	0	0
Peripheral oedema	24 (16%)	23 (15%)	1 (1%)	0	22 (15%)	22 (15%)	0	0
Decreased appetite	24 (16%)	22 (15%)	2 (1%)	0	16 (11%)	13 (9%)	3 (2%)	0
Neutropenia	22 (15%)	6 (4%)	13 (9%)	3 (2%)	22 (15%)	7 (5%)	12 (8%)	3 (2%)
Insomnia	19 (13%)	19 (13%)	0	0	22 (15%)	22 (15%)	0	0
Dyspnoea	19 (13%)	13 (9%)	6 (4%)	0	13 (9%)	13 (9%)	0	0
Pneumonia	17 (11%)	8 (5%)	8 (5%)	0	9 (6%)	3 (2%)	6 (4%)	0
Hypokalaemia	17 (11%)	10 (7%)	7 (5%)	0	16 (11%)	14 (10%)	1 (1%)	1 (1%)
Back pain	16 (11%)	11 (7%)	5 (3%)	0	15 (10%)	12 (8%)	3 (2%)	0
Upper respiratory tract infection	16 (11%)	16 (11%)	0	0	10 (7%)	10 (7%)	0	0
Cough	15 (10%)	15 (10%)	0	0	16 (11%)	16 (11%)	0	0

Data are n (%). 13 grade 5 events occurred in the pembrolizumab plus lenalidomide and dexamethasone group (one each of pneumonia, cardiac arrest, cardiac failure, myocarditis, intestinal ischaemia, large intestine perforation, unknown cause, completed suicide, sepsis, and two each of cardiorespiratory arrest and pulmonary embolism) and eight occurred in the lenalidomide and dexamethasone group (one each of acute myocardial infarction, acute cardiac failure, myocardial infarction, upper intestinal hemorrhage, and respiratory failure, and three of unknown cause). *Adverse events listed in the order of decreasing frequency in the pembrolizumab combination group. †Includes rash and maculopapular rash.

Table 2: **Adverse events occurring in at least 10% of patients in either treatment group* in the safety population**

(partial response or better). Disease control results were also similar between groups: 123 (82%; 95% CI 74·3–87·3) patients in the pembrolizumab plus lenalidomide and dexamethasone group versus 127 (85%; 77·9–90·0) in the lenalidomide and dexamethasone group achieved disease control (appendix 1 p 17). Median time to response was 1·1 months (95% CI 1·0–1·9) in the pembrolizumab plus lenalidomide and dexamethasone group versus 1·1 months (1·0–1·3) in the lenalidomide and dexamethasone group, and median duration of response was not reached in either group (appendix 1 p 18). Kaplan-Meier estimates for response duration of at least 6 months were 89% of patients in the pembrolizumab plus lenalidomide and dexamethasone group and 94% in the lenalidomide and dexamethasone group.

Median treatment duration was 131·0 days (IQR 44·0–253·0) in the pembrolizumab plus lenalidomide and dexamethasone group and 162·0 days (83·0–246·0) in the lenalidomide and dexamethasone group (appendix 1 p 19). At analysis, patients had received a median of 5·0 cycles (IQR 2·0–9·0) of treatment in the pembrolizumab plus lenalidomide and dexamethasone group and 6·0 cycles (3·0–9·0) in the lenalidomide and dexamethasone group.

Adverse events of any grade occurred in similar proportions of patients in the pembrolizumab plus lenalidomide and dexamethasone group (140 [94%] of 149) and the lenalidomide and dexamethasone group (133 [92%] of 145; table 2). Grade 3–5 adverse events (107 [72%] in the pembrolizumab plus lenalidomide and dexamethasone group *vs* 73 [50%] in the lenalidomide and dexamethasone group) and serious adverse events (81 [54%] *vs* 57 [39%]) occurred more frequently in the pembrolizumab plus lenalidomide and dexamethasone group than in the lenalidomide and dexamethasone group. Adverse events led to death in 13 (9%) patients in the pembrolizumab plus lenalidomide and dexamethasone group versus eight (6%) patients in the lenalidomide and dexamethasone group and to discontinuation in 44 (30%) versus 20 (14%); treatment-related adverse events led to discontinuation in 31 (21%) versus 12 (8%) patients; adverse events resulting in treatment interruption occurred in 91 (61%) versus 61 (42%) patients. Adverse events that occurred more frequently in the pembrolizumab plus lenalidomide and dexamethasone group than in the lenalidomide and dexamethasone group (≥5% difference) and serious adverse events in at least 3% of patients are in appendix 1 (pp 20, 21). No grade 3–5 events or serious adverse events occurred with at least a 5% difference in incidence between groups. Immune-mediated adverse events occurred in 48 (32%) of 149 patients in the

	Grades 1–2	Grades 3–4
Any	14 (9%)	34 (23%)
Rash*	0	13 (9%)
Hypothyroidism	11 (7%)	0
Hyperthyroidism	6 (4%)	3 (2%)
Colitis	2 (1%)	1 (1%)
Myocarditis	0	1 (1%)
Adrenal insufficiency	0	1 (1%)
Autoimmune thyroiditis	1 (1%)	0
Hypersensitivity	2 (1%)	0
Infusion-related reaction	0	2 (1%)
Drug eruption	0	2 (1%)
Pancreatitis	0	1 (1%)
Drug-induced liver injury	0	1 (1%)
Hepatitis	0	1 (1%)
Fulminant type 1 diabetes mellitus	0	1 (1%)
Rhabdomyolysis	0	1 (1%)
Systemic lupus erythematosus	0	1 (1%)
Myasthenia gravis	0	1 (1%)
Pneumonitis	1 (1%)	0
Dermatitis bullous	1 (1%)	0
Dermatitis exfoliative	1 (1%)	0
Dry skin	0	1 (1%)
Erythema	0	1 (1%)
Erythema multiforme	0	1 (1%)
Erythematosus rash	0	1 (1%)
Pruritic rash	0	1 (1%)
Stevens–Johnson syndrome	0	1 (1%)

Data are n (%). Immune-mediated adverse events of clinical interest are presented. One grade 5 myocarditis was reported. *Includes rash and maculopapular rash.

Table 3: **Immune-mediated adverse events in patients treated with pembrolizumab plus lenalidomide and dexamethasone (n=149) in the safety population**

	Pembrolizumab plus lenalidomide and dexamethasone group (n=149)	Lenalidomide and dexamethasone group (n=145)
Any	13 (9%)	8 (6%)
Acute myocardial infarction	0	1 (1%)
Cardiac arrest*†	1 (1%)	0
Cardiac failure*†	1 (1%)	0
Acute cardiac failure	0	1 (1%)
Cardiorespiratory arrest	2 (1%)	0
Myocardial infarction	0	1 (1%)
Myocarditis*†	1 (1%)	0
Intestinal ischaemia	1 (1%)	0
Large intestine perforation*	1 (1%)	0
Upper gastrointestinal haemorrhage*	0	1 (1%)
Unknown cause‡	1 (1%)	3 (2%)
Pneumonia*†	1 (1%)	0
Completed suicide	1 (1%)	0
Pulmonary embolism*	2 (1%)§	0
Respiratory failure*	0	1 (1%)
Sepsis¶	1 (1%)	0

Data are n (%). *Considered treatment related by investigator. †Attributed to pembrolizumab by the investigator. ‡Death and sudden death were combined as unknown-cause adverse events. §Only one pulmonary embolism was related to treatment. ¶Based on randomly assigned patients who died.

Table 4: **Adverse events leading to death in the safety population**

pembrolizumab plus lenalidomide and dexamethasone group; rash (13 [9%]), hypothyroidism (11 [7%]), and hyperthyroidism (nine [6%]) were the most common (table 3). The minimum median time to onset of immune-mediated adverse events was 14 days. Only two patients had immune-mediated neutropenia and one patient had immune-mediated thrombocytopenia.

19 [13%] of 149 patients died in the pembrolizumab plus lenalidomide and dexamethasone group (six because of disease progression and 13 because of adverse events), and nine [6%] of 145 patients died in the lenalidomide and dexamethasone group (one because of disease progression and eight because of adverse events). Six (4%) treatment-related deaths occurred in the pembrolizumab plus lenalidomide and dexamethasone group (table 4). Of these deaths, cardiac arrest, cardiac failure, myocarditis, and pneumonia were considered by the investigator to be related to pembrolizumab (table 4). Two (1%) treatment-related deaths occurred in the lenalidomide and dexamethasone group.

Patients in the pembrolizumab plus lenalidomide and dexamethasone group who died were older than those in the lenalidomide and dexamethasone group (18 [95%] of 19 in the pembrolizumab plus lenalidomide and dexamethasone group *vs* seven [78%] of nine in the lenalidomide and dexamethasone group were aged ≥70 years; eight [42%] of 19 *vs* three [33%] of nine were aged ≥80 years) and had high-risk cytogenetics (four [21%] of 19 *vs* none; appendix 1 p 22). A similar trend in age and high-risk cytogenetics was observed among patients who died because of an adverse event (appendix 1 p 23). The clinical courses of patients in the pembrolizumab plus lenalidomide and dexamethasone group who died because of adverse events are in appendix 1 (pp 24–38).

To assess higher risk for death in the pembrolizumab plus lenalidomide and dexamethasone group, a retrospective, random forest analysis was done, followed by a multivariable Cox regression analysis; however, this did not lead to conclusive results because of the small number of deaths (28 [14%] of the predefined 195 deaths required) at analysis.

Discussion

Results of this non-protocol-specified analysis, with a median follow-up of 6·6 months (IQR 3·4–9·6), showed an increased risk for death with pembrolizumab plus lenalidomide and dexamethasone than with lenalidomide and dexamethasone alone. Because of the imbalance in

the proportion of death between groups, the data monitoring committee halted enrolment; this was followed by FDA termination of the study on July 3, 2017. Consequently, data collection was incomplete and the efficacy analysis was underpowered. 19% of the protocol-specified 227 events required for analysis of progression-free survival and 14% of the protocol-specified 195 events necessary for analysis of overall survival occurred by the time of analysis. Median progression-free survival (primary endpoint) and median overall survival were not reached in either group. Proportions of patients with a response were similar between groups. Treatment exposure was truncated, with patients in either group receiving a median of six treatment cycles at analysis; 47 [32%] of 149 patients in the pembrolizumab plus lenalidomide and dexamethasone group and 36 [25%] of 145 patients in the lenalidomide and dexamethasone group received fewer than three cycles of treatment. Although overlapping Kaplan-Meier curves for progression-free survival or overall survival in this unplanned interim analysis suggested similar progression-free or overall survival between groups, this interpretation is limited by early study termination. Cancer severity is associated with immune system dysfunction; therefore, it is possible that, because of the degree of immunodeficiency associated with multiple myeloma, these patients might not have had an optimal response to treatment with a PD-1 inhibitor.[19,20] Evidence of efficacy of immunotherapy in patients with multiple myeloma is increasing; however, patients continue to relapse, which can partly be a consequence of immune blockade.[21] Early intervention might be particularly relevant for patients with multiple myeloma treated with immune-based therapies.

The frequencies of grade 3–5 adverse events and serious adverse events were higher in the pembrolizumab plus lenalidomide and dexamethasone group than the lenalidomide and dexamethasone group. More patients discontinued because of adverse events in the pembrolizumab plus lenalidomide and dexamethasone group than in the lenalidomide and dexamethasone group. The immune-mediated adverse event profile was consistent with that previously reported for pembrolizumab in other cancers[22–24] and with those observed with pembrolizumab plus pomalidomide and dexamethasone in patients with relapsed, refractory multiple myeloma in the KEYNOTE-183 study[25] and the study by Badros and colleagues.[14] The most common immune-mediated adverse events were rash, hypothyroidism, and hyperthyroidism. 34 (23%) patients had grade 3–5 immune-mediated adverse events, with rash most commonly reported. One patient died because of an immune-mediated adverse event (myocarditis).

Safety profiles of standard of care therapies have included similar percentages of grade 3–5 adverse events. In the ALCYONE study, patients who received bortezomib, melphalan, and prednisone alone versus with daratumumab had similar percentages of grade 3 or 4 neutropenia (137 [39%] of 354 *vs* 138 [40%] of 346), thrombocytopenia (133 [38%] *vs* 119 [34%]), anaemia (70 [20%] *vs* 55 [16%]), and infections (52 [15%] *vs* 80 [23%]).[7] Patients in the SWOG S0777 study who received lenalidomide and dexamethasone alone versus with bortezomib also had similar percentages of grade 3 or 4 blood adverse events (70% *vs* 73%) or bone marrow adverse events (34% *vs* 41%), grade 3 infections (29% *vs* 29%), and grade 3 neurological adverse events (21% *vs* 76%).[26] Notably, in our study, more patients died in the pembrolizumab plus lenalidomide and dexamethasone group than in the lenalidomide and dexamethasone group. More deaths occurred because of disease progression in the pembrolizumab plus lenalidomide and dexamethasone group than in the lenalidomide and dexamethasone group. Additionally, number of deaths attributed to adverse events was numerically different between groups; however, no specific adverse event was exacerbated in patients who received pembrolizumab plus lenalidomide and dexamethasone. Age and unfavourable risk factors might have contributed to increased toxicity and early (3-month) mortality of 8% of patients in the pembrolizumab plus lenalidomide and dexamethasone group and 5% in the lenalidomide and dexamethasone group. These early mortality results are higher than the 4-month mortality results reported in a previous study for patients with myeloma who were treated with lenalidomide 25 mg on days 1–21 plus dexamethasone 40 mg on days 1–4, 9–12, and 17–20 of a 28-day cycle (high dose, 5% mortality) or lenalidomide on the same schedule and dexamethasone 40 mg on days 1, 8, 15, and 22 of a 28-day cycle (low dose, <1% mortality).[27] The authors noted that the increased percentage of deaths in the high-dose cohort, especially in the first 4 months, might have been related to toxicity in older patients.[27] In our study, the starting dose of dexamethasone was reduced to 20 mg for 156 patients who were older than 75 years. Although the lenalidomide 25 mg dose was established in the dose-confirmation phase of the KEYNOTE-023 study,[13] reducing the dose to 15 mg in older patients should be considered, based on the increased frequency of adverse events observed in this study.

To understand the imbalance of proportion of deaths between groups, baseline characteristics were assessed among patients who died during the study. More patients who died in the pembrolizumab plus lenalidomide and dexamethasone group than in the lenalidomide and dexamethasone group were aged at least 70 years (95% in the pembrolizumab plus lenalidomide and dexamethasone group *vs* 78% in the lenalidomide and dexamethasone group) and had high cytogenetic risk (21% *vs* 0). Furthermore, among all study patients, there was an imbalance of disease severity and manifestation at baseline, whereby patients in the pembrolizumab plus lenalidomide and dexamethasone group had more

advanced disease than those in the lenalidomide and dexamethasone group (29% had stage III disease *vs* 21% in the lenalidomide and dexamethasone group; 14% *vs* 8% had renal impairment). According to the International Myeloma Working Group recommendations, cytogenetic abnormalities by fluorescence in-situ hybridisation, ISS stage, and renal failure are some of the factors used for risk stratification in patients with newly diagnosed multiple myeloma.[28] It is plausible that the imbalance between groups of risk factors such as ISS stage III and high cytogenetic risk, which are associated with poor prognosis,[28] contributed to the incidence of early progression and subsequent death. These risk factors might have led to the observed differences in treatment-related adverse events and deaths in this study. These results suggest that the observed imbalance in proportion of deaths between groups might have resulted from diverse non-treatment-related adverse events or differences in patient baseline characteristics. This study was limited by the ad-hoc unplanned nature of the analysis. Enrolment was ongoing at more than 100 international sites at the time the trial was prematurely terminated. Subsequent longer-term follow-up efficacy data were not collected, probably leading to imbalances in the reported results.

In conclusion, an imbalance was observed between groups in the number of deaths. However, the shortened follow-up time resulting from premature study termination rendered this interim analysis underpowered and inconclusive. Future study designs testing PD-1 inhibitors with lenalidomide and dexamethasone in multiple myeloma should consider excluding unfit patients, patients older than 75 years, and patients with high tumour burden or tumour staging. Other treatment combinations should also be assessed and excluding dexamethasone might reduce toxicity and improve T-cell activation. Stratification of patients by renal function and ECOG performance status could also be considered in future study designs.

For the **MSD data sharing policy** see http://engagezone.msd.com/ds_documentation.php

Contributors

JS-M, PM, RUG contributed to study design or planning. SZU, SL, RUG, MZHF, PM, and JS-M contributed to data analysis. FS, AO, LK, RMR, HAY, RL, NT, RDM, ABML, KS, IA, TF, MZHF, PM, and JS-M contributed to acquisition of data. SZU, FS, AO, MC, RL, NT, ABML, HK, GG, IA, SJ, SL, MZHF, PM, and JS-M contributed to interpretation of the results. SZU, AO, KS, PM, and JS-M contributed to drafting the manuscript. SZU, FS, AO, LK, MC, RMR, HAY, RL, NT, RDM, ABML, HK, GG, IA, TF, SJ, SL, RUG, MZHF, PM, and JS-M contributed to critical review or revision of the article drafts. All authors gave final approval for submission. All authors had access to all the relevant study data and related analyses, vouch for the completeness and accuracy of the data, agree to be accountable for all aspects of the work, will ensure that questions related to accuracy or integrity of any part of the work are appropriately investigated and resolved, and have reviewed the final version of the manuscript to be submitted and agree with the content and submission.

Declaration of interests

AO reports a consulting or advisory role and participation in speaker bureaus at Amgen, Janssen, and Takeda outside the submitted work. FS reports honoraria from Amgen, Celgene, Takeda, AbbVie, and Janssen; a consulting or advisory role at Pfizer, Adaptive, Bristol-Myers Squibb, Amgen, Celgene, Takeda, and Bayer; research funding from Amgen and Janssen; and travel, accommodations, or expenses from Celgene and Amgen. GG reports honoraria from Janssen; fees for serving on advisory boards from Amgen, Celgene, and Specialised Therapeutics; and grant support to his institution from Novartis, Silence Therapeutics, and Janssen. HAY reports stock or other ownership from Bellicum Pharmaceuticals and Puma Biotechnology; consulting or advisory role at Celgene and Epizyme; and participation in speaker bureaus from Janssen and AstraZeneca. JS-M reports a consulting or advisory role at Amgen, Bristol-Myers Squibb, Celgene, Janssen, Merck Sharp & Dohme (MSD), Novartis, Takeda, Sanofi, and Roche. LK reports that his wife is employed at Laboratoires Aguettant; honoraria from Celgene, Janssen, Amgen, and Gilead; a consulting or advisory role at Celgene, Janssen, and Amgen; and travel, accommodations, and expenses from Janssen and Amgen. MC reports honoraria from Janssen, Celgene, Amgen, Bristol-Myers Squibb, and Takeda. MZHF, PM, and RUG report employment and stock or other ownership at MSD, a subsidiary of Merck & Co (Kenilworth, NJ, USA). SL reports consulting or advisory roles at Takeda, Celgene, Novartis, Bristol-Myers Squibb, Amgen, Janssen, and Merck & Co; and research support from Takeda, Celgene, Bristol-Myers Squibb, and Janssen. RL reports honoraria from Celgene Canada; a consulting or advisory role at Janssen, Takeda Canada, Celgene Canada, Merck Canada, and Amgen Canada; a research grant from Celgene as a co-investigator; and travel, accommodations, and expenses from Amgen Canada. RMR reports employment at McKeson Specialty Health; stock or other ownership at McKesson Corporation; and a consulting or advisory role at Amgen, Celgene, and Takeda. SZU reports grants and consulting fees from Merck; grants and consulting and speaking fees from Amgen; consulting fees from AbbVie, Bristol-Myers Squibb, and Sanofi; and grants and consulting and speaking fees from Celgene, Amgen, Janssen, and Takeda. SJ reports honoraria from Celgene and Karyopharm; and consulting or advisory role at Celgene, Janssen, Karyopharm, Bristol-Myers Squibb, and Novartis. TF reports consulting or advisory roles at Celgene, Janssen, Takeda, Sanofi, Amgen, and Karyopharm; and participation in speaker's bureau at Celgene, Janssen, and Takeda. HK reports personal fees from Chugai Pharmaceutical, Celgene KK, Novartis Pharma, Bioverative Japan, MSD, Takeda, Janssen, Japan Blood Products Organization, Bristol-Myers Squibb, and Ono Pharmaceutical outside the submitted work. ABML, IA, KS, NT, and RDM declare no competing interests.

Data sharing

The data sharing policy of Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc (Kenilworth, NJ, USA), including restrictions, is available on the EngageZone website. Requests for access to the clinical study data can be submitted through the EngageZone website or via email to dataaccess@merck.com.

Acknowledgments

Funding for this study was provided by Merck Sharp and Dohme Corp (MSD), a subsidiary of Merck & Co, Inc (Kenilworth, NJ, USA). We thank the patients and their families and caregivers; all primary investigators and their site personnel; Beth Friedmann, Deborah Wolfe, and Caryn Hampton for clinical analysis; Michelle Gallion for data management; Yeliz Kiziltan for clinical trial analysis and operations; and Jason Liao for statistical analysis. Medical writing and editorial assistance was provided by Matthew Grzywacz and Doyel Mitra of the ApotheCom pembrolizumab team (Yardley, PA, USA). This assistance was funded by MSD, a subsidiary of Merck & Co, Inc (Kenilworth, NJ, USA).

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