Pembrolizumab plus pomalidomide and dexamethasone for patients with relapsed or refractory multiple myeloma (KEYNOTE-183): a randomised, open-label, phase 3 trial

Pembrolizumab combined with pomalidomide and dexamethasone for treatment of relapsed or refractory multiple myeloma: randomised phase 3 KEYNOTE-183 study

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Research in context

Evidence before this study: An initial PubMed search using the search terms “relapsed” and “multiple myeloma” filtered by article type (clinical trial) and publication dates (01/01/2013 to 11/27/2018) yielded 70 articles. Treatment of relapsing/refractory multiple myeloma (RRMM) poses the unique challenge of balancing efficacy and safety in patients who tend to be heavily treated and older. Thus, several ongoing phase 1 and 2 trials are evaluating combinations of the following drugs: bendamustine, tivantinib, bortezomib, carfilzomib, ixazomib, delanzomib, venetoclax, ricolinostat, vorinostat, lenalidomide, pomalidomide, daratumumab, isatuximab, elotuzumab and pembrolizumab. The phase 2 ELOQUENT-3 study by Dimopoulos et al (*New Engl J Med* 2018) in patients with RRMM is noteworthy, demonstrating significantly higher progression-free survival (PFS) in patients treated with immunostimulatory antibody against SLAMF7 (elotuzumab) plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone alone (10·3 months *vs* 4·7 months; HR 0·54; p=0·008). This led to the recent US Food and Drug Administration (FDA) approval of the elotuzumab combination in RRMM.

Narrowing of our search by adding filters for the terms “multiple myeloma” and “PD-1” yielded only two results relevant to RRMM (and a third article on melanoma), both involving a PD-1 inhibitor. Badros et al (*Blood* 2017; phase 2, single arm) reported acceptable safety (grade 3 or 4 adverse events [AEs] in 40% of patients) and promising efficacy (response rate 60% and median PFS 17·4 months) with the combination of pembrolizumab and the immunomodulator pomalidomide and dexamethasone in patients with RRMM. Lesokhin et al (*J Clin Oncol* 2016; phase 1b) demonstrated acceptable safety (drug-related AEs in 63% of patients) and anti-tumour activity (complete response following radiotherapy in one of 27 patients) with nivolumab in patients with RRMM. These results provide a promising backdrop for the KEYNOTE-183 study, which was designed to assess the efficacy and safety of a combination of pomalidomide and dexamethasone with or without pembrolizumab.

Added value of this study: The phase 3 KEYNOTE-183 study (ClinicalTrials.gov identifier, NCT02576977) was conducted to evaluate the efficacy, via analysis of survival outcomes and tumour response, and safety of the checkpoint inhibitor pembrolizumab with pomalidomide and dexamethasone in patients with RRMM. In a phase 2 study (Badros et al *Blood* 2017), this combination provided a response rate of 60%, median response duration of 14·7 months, and manageable safety, supporting its evaluation in KEYNOTE-183. However, an interim analysis conducted at a median follow-up of 8·1 months showed an unfavourable benefit-risk profile of the pembrolizumab-pomalidomide-dexamethasone combination in patients with RRMM. These results led to the FDA decision to halt KEYNOTE-183.

Implications of all the available evidence: Given the unfavourable benefit to risk profile of the pembrolizumab combination with pomalidomide and dexamethasone, KEYNOTE-183 is unlikely to change clinical practice. However, this study may provide valuable information to guide the design of future clinical studies involving checkpoint inhibitors in RRMM.

Abstract

Background: KEYNOTE-183 (ClinicalTrials.gov ID: NCT02576977) evaluated the efficacy and safety of pomalidomide-dexamethasone with or without pembrolizumab in patients with relapsed/refractory multiple myeloma (MM).

Methods: In this phase 3, randomised, open-label, multicentre study (97 medical centres in 11 countries across Europe, North America, the Middle East, Asia and Australasia), 249 patients with active MM treated with at least two prior lines of anti-myeloma therapy (excluding pomalidomide) and refractory to the last line of therapy were randomised 1:1 to receive pembrolizumab 200 mg every 3 weeks plus 4 mg pomalidomide on days 1–21 and 40 mg dexamethasone weekly in 28-day cycles or pomalidomide plus dexamethasone. Randomisation occurred via an interactive voice response system/integrated Web response system; randomised allocation schedules were generated by the sponsor. Dual primary endpoints in patients receiving pembrolizumab-pomalidomide-dexamethasone and pomalidomide-dexamethasone were progression-free survival (PFS; per International Myeloma Working Group 2011 criteria) and overall survival (OS); secondary endpoints in the two treatment arms were overall response and safety. Efficacy was assessed in all randomised patients, and safety in patients who received at least one dose of study treatment. On July 3, 2017 the US Food and Drug Administration (FDA) determined that the risks of the pembrolizumab-pomalidomide-lenalidomide combination outweighed the benefits and that the study should be halted. The findings of the unplanned, ad hoc interim analysis that led to this decision are presented.

Findings: Between January 5, 2016 and June 2, 2017, 125 patients were randomised to the triple-therapy group, and 124 to the double-therapy group, of whom 120 and 121 patients, respectively, were included in the analyses. At data cut-off (June 2, 2017), with median follow-up of 8.1 months (range 0·1–16·2), median PFS was 5·6 months (95% CI 3·7–7·5) with pembrolizumab-pomalidomide-dexamethasone versus 8·4 months (5·9–not reached) with

pomalidomide-dexamethasone, (hazard ratio [HR] 1·53; 95% CI 1·05–2·22; p=0·98). Median time to progression was 8·1 months (95% CI 5·6–not reached) with pembrolizumab-pomalidomide-dexamethasone versus 8·7 months (95% CI 6·6–not reached) with pomalidomide-dexamethasone. Median OS was not reached (95% CI 12·9–not reached) with pembrolizumab-pomalidomide-dexamethasone versus 15·2 months (95% CI 12·7–not reached) with pomalidomide-dexamethasone (HR 1·61; 95% CI 0·91–2·85; p=0·95). Response rates were 34% (95% CI 26–43%) versus 40% (95% CI 32–50%). Overall, 29 (23%) patients (16 progression, 13 adverse events) versus 21 (17%) patients (18 progression, three adverse events) died. Four (3%) deaths were considered by the investigator to be related to pembrolizumab-pomalidomide-dexamethasone (myocarditis, sepsis, Stevens-Johnson syndrome, death of unknown cause); myocarditis and Stevens-Johnson syndrome were attributed to pembrolizumab.

Interpretation: The unfavourable benefit-risk profile of the pembrolizumab-pomalidomide-dexamethasone combination in patients with relapsed/refractory MM reported here led to the decision by the US FDA to halt the KEYNOTE-183 trial. Additional studies are needed to identify patients who would benefit from programmed death 1 inhibition in combination with pomalidomide.

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Introduction

Multiple myeloma, a malignant disorder of clonal plasma cells characterised by monoclonal protein, osteolytic bone lesions, renal disease and immunodeficiency, accounts for approximately 1% of all cancers and 10% of haematological cancers.[1,2] Introduction of the immunomodulatory imide (IMiD) agents lenalidomide and pomalidomide, proteasome inhibitors such as bortezomib and carfilzomib, and effective combination with novel therapies with different mechanisms of action, such as daratumumab, have significantly improved survival in multiple myeloma.[3-10] However, most patients still undergo cycles of remission and relapse until the disease becomes refractory. Prognosis is particularly poor in patients who are refractory to IMiDs or proteasome inhibitors.[11,12] Effective combination of novel therapies with different mechanisms of action remains an unmet need.

Pembrolizumab is a highly selective, humanised monoclonal antibody against programmed death 1 (PD-1) that blocks interaction between PD-1 and its ligands PD-L1 and PD-L2, with anti-tumour activity across multiple tumour types.[13-16] In a phase 1 study, pembrolizumab plus lenalidomide and low-dose dexamethasone had anti-tumour activity with manageable safety in patients with relapsed/refractory multiple myeloma.[17] Moreover, in a phase 2 study, pembrolizumab plus pomalidomide-dexamethasone provided a response rate of 60%, median response duration of 14·7 months, and manageable safety, supporting pembrolizumab-based therapy in patients with relapsed/refractory multiple myeloma.[18]

In KEYNOTE-183, we evaluated the clinical impact of combining pembrolizumab with pomalidomide and dexamethasone (pembrolizumab-pomalidomide-dexamethasone) in patients with relapsed/refractory multiple myeloma. On July 3, 2017, the US Food and Drug Administration (FDA) halted KEYNOTE-183 based on interim data presented to the data monitoring committee, which indicated that the risks associated with the pembrolizumab

combination outweighed the benefits.[19] We present the results of the unplanned, interim efficacy (survival outcomes and tumour response) and safety analyses leading to this decision.

Methods

KEYNOTE-183 was a phase 3, randomised, open-label trial comparing triple therapy with pembrolizumab-pomalidomide-dexamethasone with pomalidomide-dexamethasone alone in patients with relapsed/refractory multiple myeloma (ClinicalTrials.gov ID: NCT02576977). Patients were enrolled at 97 medical centres across 11 countries (Australia, Canada, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Spain and the United States of America). A full account of the trial protocol and key changes made to it after the start of the study is provided in the appendix (table S1).

Patients

Eligible patients were aged ≥18 years; had confirmed diagnosis of active multiple myeloma; measurable disease; received at least two prior lines of anti-myeloma therapy, including IMiDs (lenalidomide or thalidomide) and proteasome inhibitors (bortezomib, ixazomib or carfilzomib); and were refractory to the last line of therapy (primary refractory or documented progression within 60 days of completing IMiD and/or proteasome inhibitor–based treatment; relapsed and refractory [relapse <6 months after stopping treatment with an IMiD or proteasome inhibitor–containing regimen]); pomalidomide-naïve; had Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; and were able to provide bone marrow biopsy or aspirate material for disease assessment and biomarker analysis.

Trial design and treatment

Procedures

Patients were randomised 1:1 to receive intravenous pembrolizumab 200 mg every 3 weeks plus oral pomalidomide 4 mg daily on days 1–21 and oral low-dose dexamethasone 40 mg

(20 mg for patients aged >75 years) on days 1, 8, 15, and 22 in 28-day cycles or pomalidomide and low-dose dexamethasone. Treatment was continued until confirmed progression, unacceptable toxicity, or physician/patient decision. Adverse events were graded according to Common Terminology Criteria for Adverse Events, version 4.0, and monitored throughout the study and for 30 days (90 days for serious adverse events) after treatment end. Patients who discontinued for reasons other than progression had post-treatment follow-up every 4 weeks for disease status until progression, initiation of non-study cancer treatment, withdrawal of consent, or loss to follow-up.

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

Randomisation and masking

Treatment allocation to the pembrolizumab-pomalidomide-dexamethasone and pomalidomide-dexamethasone arms occurred using an interactive voice response system/integrated Web response system (randomised allocation schedules were generated by the sponsor). Randomisation was stratified by number of prior lines (two *vs* at least three) and disease status (lenalidomide-refractory or sensitive). This was an open-label study, and therefore masking was not performed.

Patients were immediately discontinued from pembrolizumab following the FDA decision to halt the trial and were transferred to available standard of care therapies at their individual physician’s discretion and according to local institutional regulations.

Trial oversight

The study was designed by academic advisors and employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. Data were collected by investigators and their site personnel and analysed by statisticians employed by Merck. Results were interpreted by academic authors and authors who were Merck employees. An external data monitoring committee assessed safety and efficacy at interim timepoints and made recommendations regarding patient safety and study integrity. The study was conducted in accordance with the protocol and amendments, Good Clinical Practice Guidelines, and the Declaration of Helsinki. All patients provided written informed consent.

Endpoints and assessments

The dual primary endpoints were progression-free survival per International Myeloma Working Group 2011 (IMWG 2011)[20] criteria by blinded independent central review and overall survival. Progression-free survival was defined as time from randomisation to first documented disease progression or death from any cause, and overall survival as time from randomisation to death from any cause. Secondary efficacy endpoints included overall response rate by central review (at least a partial response per IMWG 2011), duration of response (time from first documented partial response until progression or death), and disease control rate per IMWG 2011 (percentage of patients with confirmed complete response, very good partial response, partial response, minimal response or stable disease for at least 12 weeks before confirmed progression), and the safety and tolerability of both treatments. Complete response was defined as negative immunofixation on serum and urine, disappearance of any soft-tissue plasmacytomas and ≤5% plasma cells in the bone marrow. Very good partial response was defined as serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 hours. Partial response was defined as ≥50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to <200 mg in 24 hours. Patients not meeting the criteria for complete,

very good partial, or partial response or progressive disease were determined to have stable disease. Progressive disease required any one or more of the following criteria: an increase of ≥25% from baseline in serum M-component and/or (the absolute increase must be ≥0.5 g/dL); urine M-component and/or (the absolute increase must be ≥200 mg/24 hours); only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved free light chain levels (the absolute increase must be >10 mg/dL); bone marrow plasma cell percentage (the absolute percentage must be ≥10%); definite development of new bone lesions or soft-tissue plasmacytomas or definite increase in the size of existing bone lesions or soft-tissue plasmacytomas; development of hypercalcaemia (corrected serum calcium >11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder. Because of premature study termination, progression-free survival and response endpoints were evaluated by confirmed investigator assessment. Median time to progression (time from randomisation to first documented progression) was also evaluated. 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 immunologic aetiology, were pre-specified as events of interest.

Efficacy was assessed in the intention-to-treat population of all patients assigned to a treatment group. Safety was assessed in patients who received at least one dose of study treatment. Attribution of adverse events to the study drugs was determined by the site investigators. Disease response assessments were performed every 4 weeks. Patients were contacted for assessment of survival status every 12 weeks after the end of treatment.

Statistical analysis

Hypothesis testing of objective response rate, progression-free survival and overall survival was strongly controlled by a familywise type I error rate of 2·5% (one-sided). A sample size of 300 patients was planned (with approximately 210 subjects at the first interim assessment, the study

would have approximately 88.7% power for detecting a 25% difference in objective response rate [55% vs 30%] at a 0.5% level of significance [one-sided]). For progression-free survival, based on 236 events (estimated to occur approximately 20 months after the first patient enrolled), the study had 90·6% power to detect a hazard ratio of 0·635 with pembrolizumab-pomalidomide-dexamethasone versus pomalidomide-dexamethasone (assuming median progression-free survival of 4·0 months) at a one-sided alpha of 1·5%. For overall survival, based on 182 events (estimated to occur 10 months after progression-free survival analysis), the study had 80·5% power to detect a hazard ratio of 0·6 for pembrolizumab-pomalidomide-dexamethasone versus pomalidomide-dexamethasone (assuming median overall survival of 12·7 months) at one-sided alpha of 0·5%. For overall response rate, based on the first 210 randomly assigned patients, the study had 88·7% power to show a 25% difference for pembrolizumab-pomalidomide-dexamethasone versus pomalidomide-dexamethasone (55% *vs* 30%) at a one-sided alpha of 0·5%. Immune-mediated adverse events were summarized separately by toxicity and grade (including counts, percentages, and 95% confidence intervals). Although two interim analyses were protocol-specified before final analysis (the first a final analysis of objective response rate and the second a final progression-free survival analysis and interim overall survival analysis; details available in the redacted protocol), neither was conducted since the trial was halted prematurely. Statistical analyses were done with SAS (version 9.4).

Multivariable analysis

After study termination, an ad hoc analysis was conducted to identify potential factors associated with the imbalance in deaths in the two treatment arms. Towards that goal, factors associated with prognostic and/or predictive of death were first evaluated by retrospective random forest analysis. A multivariable Cox regression analysis was subsequently used to

calculate differences between groups with factors associated with risk for death identified from the random forest analysis.

Role of the funding source

Merck representatives and academic advisors designed the study. Authors and sponsor representatives analysed and interpreted the data. An external data monitoring committee monitored the interim data and made recommendations to the executive oversight committee about the overall risk and benefit to trial participants. Investigators and site personnel collected data. Authors and Merck representatives analysed and interpreted the data. All authors attest that the study was conducted in accordance with the protocol and all amendments, they had access to the data used for writing of the manuscript and vouch for the accuracy of the data and analyses. The first and last authors wrote the first draft with input from authors who were employees of the sponsor. A medical writer employed by the sponsor assisted with manuscript preparation. All authors reviewed and edited the manuscript and made the decision to submit for publication.

Results

Patients

Between January 5, 2016, and June 2, 2017, 348 patients were screened and 249 were randomly assigned to receive pembrolizumab-pomalidomide-dexamethasone (N=125) or pomalidomide-dexamethasone (N=124). Of these, 120 patients in the pembrolizumab-pomalidomide-dexamethasone group and 121 in the pomalidomide-dexamethasone group were treated. The 20-mg dose of dexamethasone was administered from the start of treatment in 81 patients (37, pembrolizumab-pomalidomide-dexamethasone; 44, pomalidomide-dexamethasone). The most common reasons for screen failure (in ≥10% of patients) were prior treatments did not conform to the inclusion criteria (i.e. patients had not received prior treatment with ≥2 lines of anti-myeloma therapy and had failed the last line or else prior anti-myeloma

treatment did not include an IMiD; n=31/97, 32%), inadequate organ function (n=30, 31%), received prior excluded therapies (i.e. pomalidomide, antibodies or drugs specifically targeting T-cell co-stimulation or checkpoint pathways; monoclonal antibody ≤4 weeks prior to day 1, anti-myeloma therapy ≤2 weeks prior to day 1, n=14, 14%), no confirmed diagnosis of active multiple myeloma and measurable disease (n=12, 12%), lack of informed consent (n=11, 11%), and ECOG performance status >1 (n=10, 10%).

Baseline patient and disease characteristics were generally similar between groups (table 1). More patients in the pembrolizumab-pomalidomide-dexamethasone group had high-risk cytogenetics (28 [22%] versus 17 [14%] with pomalidomide-dexamethasone), including deletion 17p13 in 15 (12%) versus six (5%) patients, and plasmacytoma in 15 (12%; six of 15 [40%] extramedullary) versus six (5%; three of six [50%] extramedullary) patients (table 1). At the time of the unplanned interim analysis, the overall median follow-up was 8·1 months (range 0·1–16·2), and was 7·8 months (range 0·3–16·2) with pembrolizumab-pomalidomide-dexamethasone versus 8·6 months (range 0·1–15·6) with pomalidomide-dexamethasone (table S3). A total of 44 (37%) patients versus 55 (45%) were on treatment; 76 (63%) patients versus 66 (54%) had discontinued (figure 1). Disease progression was the most common reason for study discontinuation in both treatment arms (43 [36%] patients in the pembrolizumab-pomalidomide-dexamethasone arm and 40 [33%] patients in the pomalidomide-dexamethasone arm), followed by adverse events (24 [20%] vs 10 [8%]) (table 2). Eighteen (15%) and five (4%) patients in the pembrolizumab-pomalidomide-dexamethasone and pomalidomide-dexamethasone groups, respectively, discontinued due to treatment-related adverse events.

Efficacy

As of June 2, 2017, median progression-free survival was 5·6 months (95% CI 3·7–7·5) with pembrolizumab-pomalidomide-dexamethasone versus 8·4 months (95% CI, 5·9–not reached) with pomalidomide-dexamethasone; hazard ratio for disease progression or death was 1·53

(95% CI 1·05–2·22; p=0·98; figure 2A). Median time to progression was 8·1 months (95% CI 5·6 months–not reached) with pembrolizumab-pomalidomide-dexamethasone versus 8·7 months (95% CI 6·6 months–not reached) with pomalidomide-dexamethasone. The estimated 6-month progression-free survival rate was 48% (95% CI 37–58%) versus 60% (95% CI 49–69%), respectively (figure 2A). Median overall survival was not reached (95% CI 12·9 months–not reached) with pembrolizumab- pomalidomide-dexamethasone and was 15·2 months (95% CI 12·7 months–not reached) with pomalidomide-dexamethasone; hazard ratio for death was 1·61 (95% CI 0·91–2·85; p=0·95). The estimated 6-month overall survival rate was 82% (95% CI 74–88%) versus 90% (95% CI 82–95%; figure 2B). The hazard ratio for comparison of overall survival was similar among subgroups, except for the ECOG performance status 0, disease stages 1 and 2, and Japan subgroups (figure S1). The hazard ratio for comparison of progression-free survival was similar among subgroups, except for the race (other) and Japan subgroups (figure S2).

The overall response rate with pembrolizumab-pomalidomide-dexamethasone was 34% (95% CI 26·1–43·4), with 43 patients having partial response or better, versus 40% (95% CI 31·6–49·5) with pomalidomide-dexamethasone, with 50 patients having partial response or better. The disease control rate was approximately 85% in both groups (table S4). Median duration of response was 8·2 months (range 0+ to 14·8+) with pembrolizumab-pomalidomide-dexamethasone versus not reached (range 0·9+ to 13·8+) with pomalidomide-dexamethasone. The percentage of patients with response duration ≥6 months was 60% versus 72%, respectively (table S3).

Adverse events

Median duration of study treatment in all treated patients was 123·5 days (range 5–477 days) with pembrolizumab-pomalidomide-dexamethasone versus 127·0 days (range 2–463 days) with pomalidomide-dexamethasone (table S5); at analysis, patients had received a median of 4·4

cycles of treatment. Adverse events of any grade were reported in 119 (99%) patients in the pembrolizumab-pomalidomide-dexamethasone group versus 116 (96%) in the pomalidomide-dexamethasone group (table 2), grade 3 or 4 adverse events were reported in 90 (75%) versus 77 (63%) patients (table 2), and serious adverse events were reported in 75 (63%) versus 56 (46%) patients, respectively (table 3). Grade 5 adverse events were reported in 13 (11%) patients in the pembrolizumab-pomalidomide-dexamethasone group versus three (2%) patients in the pomalidomide-dexamethasone group (table 4). Any-grade adverse events with ≥5% difference in incidence between groups were neutropenia (38% with pembrolizumab-pomalidomide-dexamethasone *vs* 27% with pomalidomide-dexamethasone), pneumonia (23% *vs* 15%), nausea (17% *vs* 12%), headache (13% *vs* 4%), and increased alanine aminotransferase level (10% *vs* 3%). Grade 3 or 4 adverse events with ≥5% difference between groups were neutropenia (34% *vs* 21%) and thrombocytopenia (12% *vs* 7%). There were no serious adverse events with ≥5% difference between groups. Immune-mediated adverse events (most commonly pneumonitis, hyperthyroidism, and rash in 3% of patients each) occurred in 21 (18%) patients in the pembrolizumab-pomalidomide-dexamethasone group (table 2). Of note, only one patient had immune-mediated neutropenia and there were no cases of immune-mediated thrombocytopenia.

Adverse events resulted in treatment discontinuation in 24 (20%) and ten (8%) patients in the pembrolizumab-pomalidomide-dexamethasone and pomalidomide-dexamethasone groups, respectively. The most common (occurring in ≥2 patients in either group) were death (3 [3%] *vs* 3 [1%]), pneumonia (2 [2%] *vs* 3 [1%]), neutropenic sepsis (2 [2%] *vs* 2 [1%]), cerebrovascular accident (2 [2%] *vs* 3 [1%]) and dyspnoea (2 [2%] *vs* 2 [1%]). Of these, neutropenic sepsis (2 [2%] *vs* 2 [1%]), pneumonia (2 [2%] *vs* 2 [1%]) and cerebrovascular accident (2 [2%] *vs* 2 [1%]) were considered by the investigator to be treatment related.

Deaths

As of June 2, 2017, a total of 50 patients had died: 29 (23%) with pembrolizumab-pomalidomide-dexamethasone (16 from progressive disease, 13 from adverse events) versus 21 (17%) with pomalidomide-dexamethasone (18 from progressive disease, three from adverse events). Table 5 summarises the adverse events leading to death. There were four treatment-related deaths with pembrolizumab-pomalidomide-dexamethasone (death of unknown cause, neutropenic sepsis, myocarditis, and Stevens-Johnson syndrome in one patient each). Deaths from myocarditis and Stevens-Johnson syndrome were attributed to pembrolizumab by the investigator. There were three non–treatment-related deaths with pomalidomide-dexamethasone (death of unknown cause, anaemia and pneumonia in one patient each; table 5). A review of disease characteristics among patients who died showed that more patients in the pembrolizumab-pomalidomide-dexamethasone group had International Staging System stage 3 disease (15 [52%]) versus four (19%) in the pomalidomide-dexamethasone group), high-risk cytogenetics (10 [34%] *vs* six [29%]), plasmacytoma (seven [24%] *vs* three [14%]), and ECOG performance status of 1 (21 [72%] *vs* 13 [62%]) at baseline (table S6). The hazard ratio for death was 1·23 (95% CI 0·57–2·66) when patients with high-risk disease characteristics were excluded (figure S3). In the analysis, of 13 deaths in the pembrolizumab-pomalidomide-dexamethasone group, four were from progression and nine were from AEs (myocardial infarction, cardiac failure, pericardial haemorrhage, Stevens-Johnson Syndrome, sepsis [n=3] and unknown death [n=2]); two of those AEs were considered related to pembrolizumab by the investigator (Steven-Johnson Syndrome and unknown death). Of 13 deaths in the pomalidomide-dexamethasone group, 12 were from progression and one was from an AE (unknown death).

In a retrospective random forest analysis, age, ECOG performance status, disease stage, presence of plasmacytoma and double-refractory status were ranked as more relevant contributors to death than treatment (figure S4). A subsequent multivariable analysis showed

that age, ECOG performance status, and plasmacytoma significantly contributed to the risk for death. ECOG performance status was both prognostic and predictive of outcome. ECOG performance status 0 was associated with reduced risk for death (hazard ratio 0·86; 95% Wald confidence limits 0·32–2·29), whereas ECOG performance status 1 was associated with increased risk for death (hazard ratio 2·3; 95% Wald confidence limits 1·11–4·76). The clinical course of patients who died of adverse events in the pembrolizumab-pomalidomide-dexamethasone group is summarised in the appendix (table S7).

Discussion

In this non–protocol-specified interim analysis of KEYNOTE-183, after a median follow-up of 8·1 months, an increased risk for death was observed with pembrolizumab-pomalidomide-dexamethasone versus pomalidomide-dexamethasone alone in patients with relapsed/refractory multiple myeloma. The early mortality signal led to a halt of enrolment by the data monitoring committee and to subsequent study termination by the FDA July 3, 2017.[19] The early study termination resulted in incomplete data collection, and, at analysis, only 27·5% of the protocol-specified events required for evaluation of overall survival (50 of 182 protocol-specified survival events observed) and 48·7% required for analysis of progression-free survival (115 of 236 protocol-specified progression-free survival events observed) had accrued. Treatment exposure was also shortened (median 4·5 treatment cycles in the pembrolizumab-pomalidomide-dexamethasone group [37 (31%) patients with fewer than three cycles] *vs* median 5·0 treatment cycles in the pomalidomide-dexamethasone group [29 (24%) with fewer than three cycles]). Several studies have shown that longer follow-up is necessary to discern efficacy outcomes with immunotherapies given the non-proportional hazard effect that leads to delayed clinical response and late separation of Kaplan-Meier survival curves.[21-23] As such, although the overlapping confidence intervals for both progression-free survival and overall response in this

premature analysis suggest no difference between the two treatment groups, this interpretation is limited by the early termination of the study.

The acknowledged association between severity of disease and degree of immune system dysfunction suggests that PD-1 blockade may be both safer and more effective in patients with a lower burden of disease and less impaired immune system. Thus, the failure of pembrolizumab to improve the outcome in patients with relapsed/refractory multiple myeloma in the present study population may be attributable to the considerable immunodeficiency that exists in these patients.

The incidence of any-grade adverse events was similar between groups, with a higher incidence of grade 3 or 4 and serious adverse events with pembrolizumab-pomalidomide-dexamethasone versus pomalidomide-dexamethasone. All common, non-severe adverse events were manageable, and no specific type led to treatment discontinuation. The most common immune-mediated adverse events reported in the experimental group were pneumonitis, hyperthyroidism and rash in 3% of patients each. There were two grade 5 immune-mediated adverse events of myocarditis and Steven-Johnson syndrome, events expected as per the label for pembrolizumab.[24] Overall, the type and incidence of immune-mediated adverse events in the experimental group were consistent with those reported previously for pembrolizumab[13-16] and with those observed in KEYNOTE-185.

A total of 50 deaths occurred: 29 (23%) deaths with pembrolizumab-pomalidomide-dexamethasone (13 from adverse events) versus 21 (17%) with pomalidomide-dexamethasone (3 from adverse events). However, the number of patients who discontinued (43 *vs* 40) or died from disease progression (16 *vs* 18) was similar between groups, suggesting that the risk for progression was similar between groups. This suggests that progression-free survival in the

pembrolizumab-pomalidomide-dexamethasone group could have been influenced by the imbalance in the number of deaths.

A review of alternatives for the difference in early death observed between the treatment groups showed that the frequency of high-risk features at baseline among patients who died prematurely was higher in the pembrolizumab-pomalidomide-dexamethasone than in the pomalidomide-dexamethasone group, despite the safeguard of randomisation (it should be noted that disease characteristics were generally not balanced between the treatment arms in this study, likely due to the fact that patient enrolment was still ongoing at the time of early study termination and to the unplanned ad-hoc nature of the analysis). Specifically, more patients in the pembrolizumab-pomalidomide-dexamethasone group who died early had stage III disease, high-risk cytogenetics and/or extramedullary plasmacytoma, factors typically associated with poorer prognosis, an imbalance that might account for the difference in early death that led to early termination of KEYNOTE-183. Moreover, when adverse-event–related death was evaluated between the two treatment groups, after removal of patients with these high-risk characteristics, there was no difference in overall deaths between groups with 13 deaths in each group (hazard ratio for death 1·23; p=0·69). A multivariable analysis to identify factors associated with risk for death indicated that only ECOG performance status 1 was predictive and prognostic of risk for death. This might indicate that the performance status evaluation of patients at study entry was underestimated considering that patients with ECOG performance status of 2 are usually included in multiple myeloma clinical studies but was an exclusion criterion in this study. Together, these analyses suggest that the imbalance in the number of deaths observed may be driven by a diverse set of non–treatment-related adverse events and not necessarily by exacerbation of any specific treatment-related safety signal.

The findings of this study are not generalizable to other indications; it is not possible to determine whether the problems encountered in this study population receiving pembrolizumab

in combination with standard of care therapy would be observed in other indications. Moreover, the present findings are limited by the early halting of this study, which rendered completion of prespecified analyses impossible.

In summary, although these data showed an imbalance in the number of deaths between treatment groups, because of the shortened follow-up at termination, the interim analyses were underpowered and inconclusive. Additional studies are needed to optimise identification of patients who would benefit from PD-1 inhibition in combination with pomalidomide. Furthermore, given the efficacy of pembrolizumab combinations demonstrated in the treatment of other diseases, checkpoint inhibitors deserve to be appropriately investigated with other treatment backbones.

Contributors

MVM, JSM, UK, PM, contributed to study design or planning. HB, IA, NB, SZU, SJ, JSM, UK, JL MF, PM, SL contributed to data analysis. FS, AO, DS, AG, HG, AL, ACK, DaS, IA, NB, SI, MM, KS, VR, EO, PRO, JSM, UK, MF, PM, contributed to acquisition of data. MVM, HB, FS, AO, DS, HG, ACK, DaS, IA, SI, MM, VR, SZU, SJ, EO, JSM, UK, MF, PM, SL contributed to interpretation of the results. MVM, HB, AO, KS, JSM, PM, contributed to drafting the manuscript. MVM, FS, AO, DS, AG, HG, AL, ACK, DaS, IA, NB, SI, MM, VR, SZU, SJ, EO, PRO, JSM, UK, MF, JF, PM, SL contributed to critical review or revision of the article drafts. All authors gave final approval for submission. All authors has access to all the relevant study data and related analyses, vouch for the completeness and accuracy of the data and agree to be accountable for all aspects of the work and 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

Dr. Mateos reports receiving consulting fees from Amgen, Celgene, Janssen, and Takeda; Dr Blacklock reports receiving consulting fees from Celgene and Janssen; Dr. Schjesvold reports receiving honoraria from Amgen, Celgene, Takeda, AbbVie, and Janssen, consulting fees from Adaptive, Pfizer, Bristol-Myers Squibb (BMS), Amgen, Celgene, Takeda, and Bayer, research funding from Amgen and Janssen, and reimbursements from Celgene, and Amgen; Dr Oriol reports receiving consulting fees from Amgen, Janssen, and Takeda; Dr. Simpson reports receiving honoraria from Merck Sharp & Dohme (MSD), and honoraria and consulting fees from AbbVie, Celgene, Janssen, and Roche, and research finding from Amgen; Dr. George reports receiving consulting fees and reimbursements from Celgene and Roche; Dr. Goldschmidt reports receiving honoraria from Celgene, Janssen, Novartis, Chugai, BMS, and ArtTempi, consulting fees from Adaptive Biotechnology, Amgen, BMS, Celgene, Janssen, Sanofi, and Takeda, research funding from Amgen, BMS, Celgene, Chugai, Janssen, Sanofi, Takeda, Mundipharma, and Novartis, and reimbursements from Amgen, BMS, Celgene, Janssen, Sanofi, and Takeda; Dr. Larocca reports receiving honoraria from Amgen, BMS, Celgene, and Janssen-Cilag; Dr. Iida reports receiving honoraria from Takeda, Ono, Janssen, Celgene, BMS, and Novartis, and consulting fees from Takeda, Ono, Janssen, Sanofi, and MSD; Dr. Ribrag reports honoraria from Infinity Pharmaceuticals, BMS, Eisai, PharmaMar, and Gilead; Dr. Usmani reports receiving consulting fees from Celgene, Millennium Takeda, Onyx, and Sanofi, speaker's fees from Celgene, Millennium Takeda, and Onyx, and research funding from Array BioPharma, Celgene, Janssen Oncology, Onyx, Pharmacyclics, and Sanofi; Dr. Jagannath reports receiving honoraria from Celgene and Karyopharm, and consulting fees from Celgene, Janssen, Karyopharm, BMS, and Novartis; Dr. Ocio reports receiving honoraria from Novartis, Takeda, AbbVie, PharmaMar, Seattle Genetics, Amgen, Celgene, BMS and Janssen and Research Funding from Array Pharmaceuticals, Mundipharma, Celgene, Amgen and Sanofi; Dr. Rodriguez-Otero reports receiving consulting fees from Celgene, Janssen, and Takeda, speaker's fees from Celgene, BMS, and Janssen, and research funding from BMS, and

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Data-sharing statement

Merck & Co., Inc.'s data sharing policy, including restrictions, is available at http://engagezone.merck.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the EngageZone site or via email to dataaccess@merck.com.

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Figure Legends

***Figure 1*: Randomisation and study disposition**

***Figure 2:* Progression-free survival based on confirmed investigator assessment (A) and median overall survival (B) in the intention-to-treat population**

SOC is pomalidomide and low-dose dexamethasone. SOC=standard of care.

619 ***Table 1:*** Baseline disease and patient characteristics in the intention-to-treat population

Characteristic	**Pembrolizumab + SOC** **N=125**	**SOC** **N=124**
Median age (range), years	65 (45–94)	67 (22–90)
≥70 years	44 (35%)	48 (39%)
ECOG performance status		
0	60 (48%)	60 (48%)
1	65 (52%)	64 (52%)
ISS stage		
I	45 (36%)	45 (36%)
II	46 (37%)	39 (31%)
III	33 (26%)	33 (27%)
Missing	1 (1%)	7 (6%)
Median number of prior recurrences (range)	3 (1–8)	3 (2–7)
High-risk cytogenetics*		
Yes	28 (22%)	17 (14%)
Del17p13	15 (12%)	6 (5%)
t(4;14)	10 (8%)	8 (6%)
t(14;16)	8 (6%)	3 (2%)
Normal	52 (42%)	71 (57%)
Missing	45 (36%)	36 (29%)
Presence of plasmacytoma†	15 (12%)	6 (5%)
Bone, n/N (%)	9/15 (65%)	3/6 (50%)
Extramedullary, n/N (%)	6/15 (40%)	3/6 (50%)
Prior ASCT	77 (62%)	81 (65%)

Prior therapy		
Lenalidomide	119 (95%)	116 (94%)
Thalidomide	48 (38%)	41 (33%)
Bortezomib	121 (97%)	116 (94%)
Carfilzomib	34 (27%)	33 (27%)
Daratumumab	9 (7%)	8 (6%)
Lenalidomide refractory	107 (86%)	107 (86%)
Refractory‡		
Double	51 (41%)	50 (40%)
Triple	23 (18%)	29 (23%)
Quadruple	5 (4%)	2 (2%)

Data are n (%) unless otherwise specified. ASCT=autologous stem cell transplantation**;** SOC=standard of care is pomalidomide and low-dose dexamethasone**;** intention-to-treat population defined as all patients assigned to treatment.

*Baseline cytogenetics was analysed in bone marrow aspirate sample by fluorescence in situ hybridisation (FISH) or by standard karyotyping if FISH is not available, at local laboratories.

†Presence of extramedullary soft tissue plasmacytoma was evaluated by magnetic resonance imaging or computed tomography (CT) or positron emission tomography/CT at screening.

‡Patients were considered refractory if they had failed two (double; lenalidomide/bortezomib), three (triple; lenalidomide/bortezomib/pomalidomide or lenalidomide/bortezomib/carfilzomib) or four (quadruple; lenalidomide/bortezomib/pomalidomide/carfilzomib) prior lines of treatment, defined as documented disease progression during or within 60 days of completing their last anti-myeloma therapy.

633 ***Table 2:*** Adverse events in the as-treated population

Adverse event	**Pembrolizumab + SOC** **N=120**	**SOC** **N=121**
Any adverse event	119 (99%)	116 (96%)
Grade 3 or 4	90 (75%)	77 (63%)
Serious	75 (63%)	56 (46%)
Leading to discontinuation of any drug	24 (20%)	10 (8%)
Leading to death	13 (11%)	3 (2%)
Any-grade adverse events occurring in ≥10% of patients in either arm		
Neutropenia*	46 (38%)	33 (27%)
Anaemia	34 (28%)	43 (36%)
Fatigue	29 (24%)	36 (30%)
Constipation	27 (23%)	24 (20%)
Pyrexia	27 (23%)	23 (19%)
Pneumonia*	28 (23%)	18 (15%)
Thrombocytopenia	25 (21%)	20 (17%)
Diarrhoea	21 (18%)	21 (17%)
Upper respiratory tract infection	20 (17%)	21 (17%)
Dyspnoea	21 (18%)	18 (15%)
Peripheral oedema	19 (16%)	19 (16%)
Cough	18 (15%)	18 (15%)
Nausea*	20 (17%)	14 (12%)
Back pain	13 (11%)	20 (17%)
Neutrophil count decreased	17 (14%)	16 (13%)

Asthenia	14 (12%)	14 (12%)
Dizziness	15 (13%)	13 (11%)
Headache*	15 (13%)	5 (4%)
Muscle spasms	12 (10%)	12 (10%)
White blood cell count decreased	12 (10%)	10 (8%)
Alanine aminotransferase increased*	12 (10%)	3 (2%)
Grade 3 or 4 adverse events with incidence ≥10% in either arm		
Neutropenia*	41 (34%)	26 (21%)
Anaemia	20 (17%)	16 (13%)
Thrombocytopenia*	14 (12%)	8 (7%)
Pneumonia	16 (13%)	15 (12%)
Neutrophil count decreased	15 (13%)	11 (9%)
Any-grade immune-mediated adverse events and infusion reactions		
	Pembrolizumab +SOC **N=120**	
Any event	21 (18%)	
Pneumonitis	5 (4%)	
Hyperthyroidism	3 (3%)	
Rash	3 (3%)	
Hypothyroidism	2 (2%)	
Myopathy	2 (2%)	
Myocarditis	1 (1%)	
Iridocyclitis	1 (1%)	
Hepatitis	1 (1%)	
Anaphylaxis	1 (1%)	

Infusion-related reactions	1 (1%)
Exfoliative dermatitis	1 (1%)
Psoriasis	1 (1%)
Skin necrosis	1 (1%)
Stevens-Johnson syndrome	1 (1%)

Data are n (%). *****Any-grade or grade 3-4 adverse events with ≥5% difference between treatment groups. The as-treated population includes all patients with at least one dose of study treatment. SOC=standard of care (pomalidomide and low-dose dexamethasone)

Table 3: Serious adverse events ≥3% in the as-treated population

Serious adverse event*	**Pembrolizumab + SOC** **N=120**	**SOC** **N=121**
Pneumonia	21 (18%)	17 (14%)
Acute kidney injury	4 (3%)	4 (3%)
Pneumonitis	4 (3%)	0
Febrile neutropenia	3 (3%)	4 (3%)
Death	3 (3%)	0
Pyrexia	3 (3%)	5 (4%)
Sepsis	3 (3%)	3 (3%)
Influenza	1 (1%)	3 (3%)
Upper respiratory tract infection	1 (1%)	3 (3%)

Data are n (%). *****There were no serious adverse events with ≥5% difference between treatment groups. The as-treated population includes all patients with at least one dose of study treatment. SOC=standard of care (pomalidomide and low-dose dexamethasone)

643 ***Table 4:*** Adverse events leading to death in the as-treated population

Adverse event	**Pembrolizumab + SOC** **N=120**	**SOC** **N=121**
Death of unknown cause	3 (3%)*	1 (1%)
Sepsis	3 (3%)	0
Anaemia	0	1 (1%)
Cardiac failure	1 (1%)	0
Myocardial infarction	1 (1%)	0
Myocarditis	1 (1%)*,†	0
Pericardial haemorrhage	1 (1%)	0
Neutropenic sepsis	1 (1%)*	0
Pneumonia	0	1 (1%)
Respiratory tract infection	1 (1%)	0
Stevens-Johnson syndrome	1 (1%)*,†	0

644 Data are n (%). *****Treatment-related in one patient. **†**Attributed to pembrolizumab by investigator.

645 The as-treated population includes all patients with at least one dose of study treatment.

646 SOC=standard of care (pomalidomide and low-dose dexamethasone)

647

Figure 1

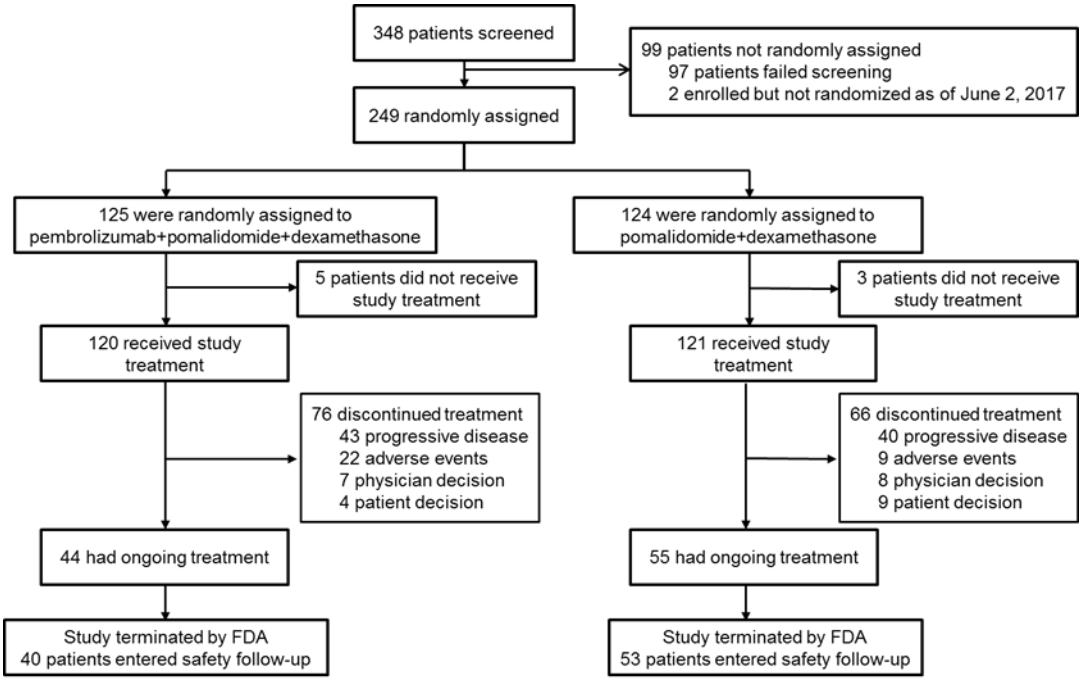
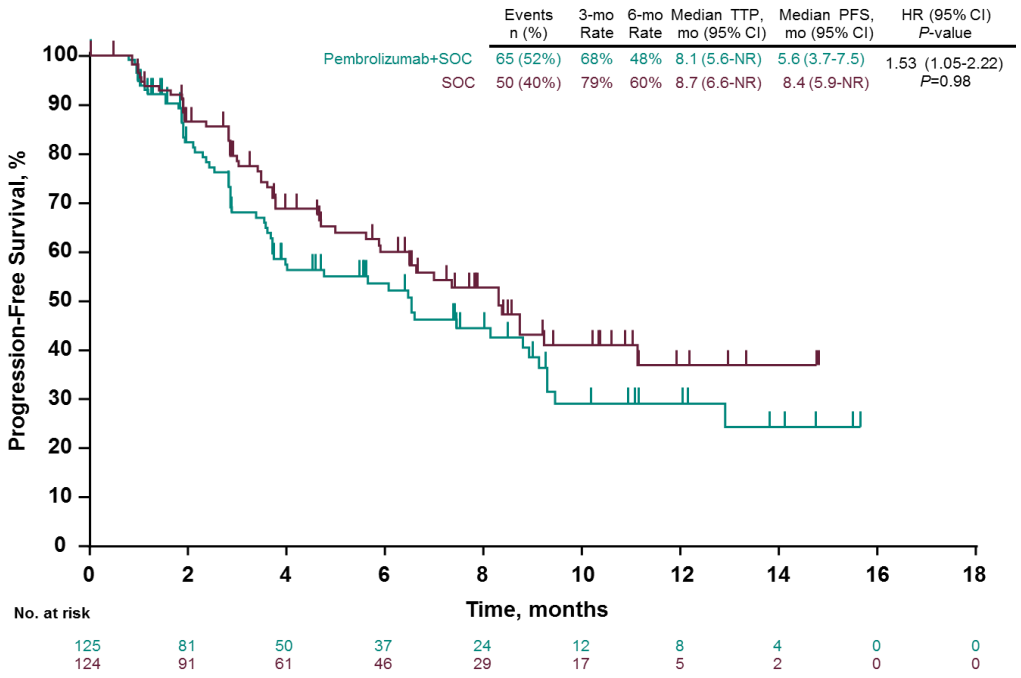
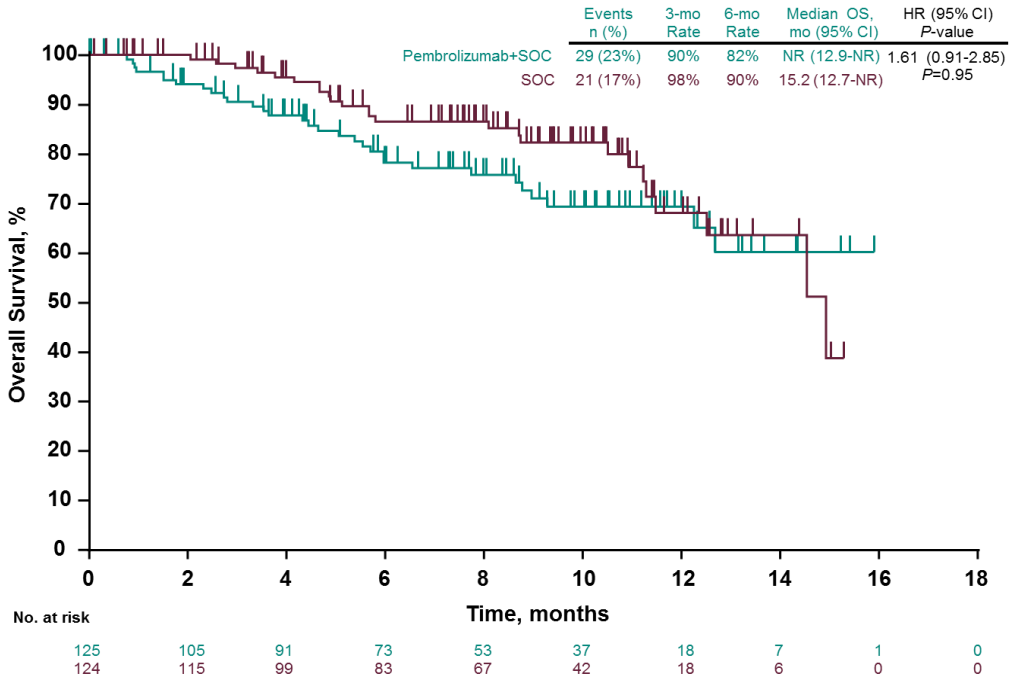

348 patients screened
99 patients not randomly assigned
97 patients failed screening
2 enrolled but not randomized as of June 2, 2017
249 randomly assigned
125 were randomly assigned to pembrolizumab+pomalidomide+dexamethasone
124 were randomly assigned to pomalidomide+dexamethasone
5 patients did not receive study treatment
3 patients did not receive study treatment
120 received study treatment
121 received study treatment
76 discontinued treatment
43 progressive disease
22 adverse events
7 physician decision
4 patient decision
66 discontinued treatment
40 progressive disease
9 adverse events
8 physician decision
9 patient decision
44 had ongoing treatment
55 had ongoing treatment
Study terminated by FDA
40 patients entered safety follow-up
Study terminated by FDA
53 patients entered safety follow-up

Figure 2

A


Events n (%)
3-mo Rate
6-mo Rate
Median TTP, mo (95% CI)
Median PFS, mo (95% CI)
HR (95% CI) P-value
Pembrolizumab+SOC 65 (52%) 68% 48% 8.1 (5.6-NR) 5.6 (3.7-7.5) 1.53 (1.05-2.22) P=0.98
SOC 50 (40%) 79% 60% 8.7 (6.6-NR) 8.4 (5.9-NR)
Progression-Free Survival, %
Time, months
No. at risk
125 81 50 37 24 12 8 4 0 0
124 91 61 46 29 17 5 2 0 0

B


Events n (%)
3-mo Rate
6-mo Rate
Median OS, mo (95% CI)
HR (95% CI) P-value
Pembrolizumab+SOC 29 (23%) 90% 82% NR (12.9-NR) 1.61 (0.91-2.85) P=0.95
SOC 21 (17%) 98% 90% 15.2 (12.7-NR)
Overall Survival, %
Time, months
No. at risk
125 105 91 73 53 37 18 7 1 0
124 115 99 83 67 42 18 6 0 0