Pembrolizumab combined with lenalidomide and dexamethasone for treatment-naive multiple myeloma: randomised phase 3 KEYNOTE-185 study

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Running title: Pembrolizumab combination in multiple myeloma

Study support: Merck & Co., Inc., Kenilworth, NJ, USA

Previous presentation: Presented at the American Association of Clinical Oncology Annual Meeting, June 1-5, 2018; Chicago, Illinois, USA

Word count and other limits:

Abstract: 376/300 words
Text: 4625/4500 words
Tables/figures: 6 (4 tables, 2 figures)
References: 35/30

Research in context

Evidence before this study: 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" yielded only two results relevant to multiple myeloma (MM) (a third article was on melanoma). They are Badros et al *Blood* 2017 and Lesokhin et al *J Clin Oncol* 2016. Both studies involve a PD-1 inhibitor, pembrolizumab or nivolumab, in patients with relapsed or refractory (RRMM) and show promising efficacy and safety. These results raise a pertinent unanswered question regarding the use of PD-1 inhibitors combined with immunomodulators and dexamethasone in treatment-naive MM.

We then searched PubMed using the keywords "multiple myeloma" and "immunomodulatory" using the same filters mentioned above and found 47 results. Most of these articles involved patients with relapsed or refractory multiple myeloma.

We performed another search of PubMed with the keywords, "multiple myeloma" and "transplantation-ineligible" using the same filters and found six results. One reported updated data from the phase 3 FIRST study of lenalidomide and low-dose dexamethasone (Rd) until disease progression, or Rd for 72 weeks, or melphalan, prednisone and thalidomide (MPT) for 72 weeks in patients with newly diagnosed MM. In the FIRST study, overall survival was longer with continuous Rd than with MPT. These results provide support for the choice of the comparator arm, Rd, in the current KEYNOTE-185 study. In the second article, the alkylator-containing triplet, melphalan-prednisone-lenalidomide, was shown to be not superior to the Rd doublet in transplantation-ineligible MM. The third, fourth, and fifth articles concerned regimens—such as bortezomib-dexamethasone or bortezomib-thalidomide-dexamethasone (VTD) and bortezomib-melphalan-prednisone (VMP)—based on the proteasome inhibitor

bortezomib in newly diagnosed transplantation-ineligible MM. In the phase 3b UPFRONT study in US community practices, all bortezomib-containing regimens showed favourable outcomes; VMP and VTD regimens did not appear to provide additional benefit over the VD regimen. The phase 3 ALCYONE study showed that the addition of daratumumab to VMP led to a lower risk of disease progression or death, but with an increased occurrence of grade 3-4 infections. The sixth article reported results of the phase 3 SWOG SO777 study and showed that the addition of bortezomib to lenalidomide and dexamethasone improved survival outcomes. These searches further consolidate the need for new treatment options for patients with newly diagnosed transplantation-ineligible MM.

Added value of this study: The phase 3 KEYNOTE-185 (ClinicalTrials.gov identifier, NCT02579863) study was conducted to evaluate the efficacy, assessed through survival outcomes and tumor response, and safety of the checkpoint inhibitor pembrolizumab with lenalidomide and dexamethasone in patients with newly diagnosed transplantation-ineligible MM. Pre-clinical evidence suggested that combination of PD-1 blockade with lenalidomide resulted in greater anti-tumour activity in MM (Gorgun 2015). However, an unplanned interim analysis of KEYNOTE-185, conducted at a median follow-up of 6.6 months, showed an unfavourable benefit-risk profile of the pembrolizumab-lenalidomide-dexamethasone combination. Therefore, the US Food and Drug Administration halted KEYNOTE-185.

Implications of all the available evidence: Although KEYNOTE-185 is unlikely to change clinical practice, it is likely to provide valuable information to guide the design of future clinical studies involving checkpoint inhibitors in newly diagnosed MM.

Abstract (372/300)

Background The combination of a PD-1 inhibitor, pembrolizumab, with an immunomodulator, lenalidomide and dexamethasone (lenalidomide-dexamethasone), may provide anti-tumour activity with tolerable safety in patients with newly diagnosed multiple myeloma.

Methods In this adaptive design, open-label, multicentre, phase 3 trial, transplantation-ineligible patients with active multiple myeloma were enrolled from clinical sites across 15 countries (Australia, Canada, France, Germany, Ireland, Israel, Italy, Japan, New Zealand, Norway, Russian Federation, South Africa, Spain, United Kingdom, United States). Patients were randomly assigned 1:1 using an interactive voice response system/integrated Web response system. Patients received intravenous pembrolizumab 200 mg every 3 weeks plus oral lenalidomide 25 mg on days 1 to 21 and oral dexamethasone 40 mg weekly every 28 days (pembrolizumab-lenalidomide-dexamethasone) or lenalidomide-dexamethasone. Primary endpoint was progression-free survival per International Myeloma Working Group 2011 criteria; secondary endpoints included overall survival and safety. Efficacy and safety were analysed in all randomly assigned patients who received at least one dose of study drug. On Jul 3, 2017 the US FDA determined that the risks of pembrolizumab plus pomalidomide or lenalidomide outweighed the benefits and halted the study (ClinicalTrials.gov identifier, NCT02579863) . Results of an unplanned interim analysis that led to the FDA decision are presented.

Findings At database cut-off (Jun 2, 2017), 151 patients received pembrolizumab-lenalidomide-dexamethasone; 150 received lenalidomide-dexamethasone. Median follow-up was 6·6 months (range 0·1–16·9). Neither median progression-free survival (hazard ratio [HR] 1·22; 95% CI 0·67 to 2·22; p=0·75) nor median overall survival (HR 2·06; 95% CI 0·93 to 4·55; p=0·97) was reached in either treatment arm due to the study's short median follow up. Nineteen (13%)

patients (six from progression, 13 from adverse events) died in the pembrolizumab-lenalidomide-dexamethasone arm versus nine (6%) (one from progression, eight from adverse events) in the control arm. Six (4%) (large-intestine perforation, pulmonary embolism, cardiac arrest, pneumonia, myocarditis, and cardiac failure) versus two (1%) (upper intestinal haemorrhage and respiratory failure) treatment-related deaths occurred; cardiac arrest, pneumonia, myocarditis, and cardiac failure were considered related to pembrolizumab.

Interpretation The benefit-risk profile of pembrolizumab-lenalidomide-dexamethasone is unfavourable for newly diagnosed multiple myeloma. Older age and high-risk features for patients who died were more prevalent in the pembrolizumab-lenalidomide-dexamethasone arm. Long-term safety and survival follow-up is ongoing. Additional clinical studies involving programmed death 1 inhibitors are needed.

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

Introduction

Multiple myeloma is a malignancy of plasma cells that predominantly affects elderly patients and is associated with hypercalcemia, renal impairment, anemia, and bone disease.[1,2] Treatment options have evolved considerably over the past decade and include chemotherapy, autologous stem cell transplantation, immunomodulators, proteasome inhibitors, and monoclonal antibodies.[3,4] Treatment combinations are chosen based on patient age, performance status, and co-morbidities.[3,5] Autologous stem cell transplantation improves the depth and duration of response achieved with initial therapy[4] and is the standard of care after primary therapy for eligible patients.[3]

Standard of care for patients with newly diagnosed transplantation-ineligible multiple myeloma in the United States consists of lenalidomide and dexamethasone (lenalidomide-dexamethasone), with or without bortezomib.[3,6-8] The European Society for Medical Oncology clinical practice guidelines recommend a third option in the non-transplantation setting: bortezomib, melphalan, and prednisone.[5,9] For these therapies, median progression-free survival ranges from 21 to 43 months and median overall survival from 49 to 75 months.[6-8] The addition of dexamethasone to bortezomib, melphalan, and prednisone lowered the risk of disease progression and death in this patient population, resulting in another treatment option for this patient population.[10] However, most patients with myeloma eventually experience relapse, and new treatment options are needed.

Plasma cells from most patients with multiple myeloma express programmed death ligand 1 (PD-L1),[11] and PD-L1 up-regulation is associated with disease relapse.[12] Combination of programmed death 1 (PD-1)/PD-L1 blockade and lenalidomide showed enhanced effector cell–mediated multiple myeloma cytotoxicity.[13] Thus, immune checkpoints may play an important role in myeloma resistance and represent an attractive therapeutic target. Combination immune checkpoint inhibition and lenalidomide-dexamethasone might provide synergistic anti-tumour activity in patients with multiple myeloma.[14] Indeed, 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 response rates of 50% and 60%, respectively, in patients with relapsed refractory multiple myeloma.[15-17] Results of a preclinical study showed increased levels of PD-L1 on multiple myeloma cells and enhanced PD-1 expression on exhausted IL-10-producing T cells. Inhibition of the PD-1/PD-L1 pathway increased survival of mice with myeloma from 0% to 40%, suggesting that blocking the pathway may enhance immunotherapy for this disease.[18] We hypothesized that inhibiting the PD-1/PD-L1 pathway in patients with treatment-naïve multiple myeloma may improve efficacy outcomes. The phase 3 KEYNOTE-185 trial was conducted to evaluate the safety and efficacy, assessed through survival outcomes and tumor response, of pembrolizumab-lenalidomide-dexamethasone versus lenalidomide-dexamethasone alone in patients with treatment-naive multiple myeloma. On Jul 3, 2017, the US Food and Drug Administration (FDA) halted this trial based on the interim data presented to the data monitoring committee, which showed an unfavourable benefit-risk profile of pembrolizumab-lenalidomide-dexamethasone.[19] Unplanned interim analysis results that led to the FDA decision are presented.

Methods

KEYNOTE-185 was a phase 3, randomized, open-label study of pembrolizumab with or without lenalidomide and low-dose dexamethasone in newly diagnosed and previously untreated patients with multiple myeloma (ClinicalTrials.gov identifier, NCT02579863). Patients were enrolled from clinical sites across 15 countries (Australia, Canada, France, Germany, Ireland, Israel, Italy, Japan, New Zealand, Norway, Russian Federation, South Africa, Spain, United Kingdom, United States).

Patients

Patients 18 years or older with a confirmed diagnosis of active multiple myeloma with measurable disease, an Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate organ function were enrolled. Patients were required to be ineligible to receive autologous stem cell transplantation because of age (≥65 years) or any significant co-existing medical condition (cardiac, renal, pulmonary, or hepatic dysfunction) likely to have a negative impact on their tolerability of autologous stem cell transplantation. Patients were also required to provide bone marrow biopsy or aspirate material for disease assessment. Women of childbearing potential had 2 negative urine pregnancy tests before the first dose of study medication and were required to use 2 methods of birth control or to abstain from heterosexual activity for 28 days before receiving lenalidomide during the course of the study, during any dose interruptions, and through 28 days after the last dose of lenalidomide. Male patients agreed to use adequate contraception starting with the first dose of study medication through the last dose of lenalidomide or 120 days after the last dose of pembrolizumab. Patients with oligosecretory myeloma, smoldering multiple myeloma, monoclonal gammopathy of undetermined

significance, Waldenström's macroglobulinemia, or a history of plasma cell leukemia were not eligible for participation in the study. Patients with a history of repeated infections, immunosuppression, a history of or current pneumonitis necessitating steroids, and active autoimmune disease or with active infections requiring intravenous systemic, grade ≥2 peripheral neuropathy, known human immunodeficiency virus, active Hepatitis B or Hepatitis C infection, or received a live vaccine within 30 days of the first dose of study medication were excluded. Patients were not permitted to have previously received therapy with an anti-PD-1, anti_PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 antibody. Patients received study treatment until documented confirmed disease progression, unacceptable adverse events, or withdrawal from the study.

Trial design and treatment

Procedures

Patients were randomly assigned 1:1 to receive intravenous pembrolizumab plus oral lenalidomide and oral low-dose dexamethasone or lenalidomide and low-dose dexamethasone. Patients received lenalidomide 25 mg daily on days 1 to 21 and dexamethasone 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 dose of dexamethasone was reduced to 20 mg on days 1, 8, 15, and 22 of each 28-day cycle among patients older than 75 years of age.

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.

Randomization and masking

Treatment allocation occurred using an interactive voice response system/integrated Web response system (randomised allocation schedules were generated by the sponsor). 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 administration in this open-label trial.

Patients were immediately discontinued from pembrolizumab treatment 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 protocol and its amendments were approved by the appropriate institutional review board or independent ethics committee. The trial was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent.

Endpoints and assessments

The primary endpoint was progression-free survival, defined as the time from randomisation to the first documented instance of disease progression, per International Myeloma Working Group

2011 response criteria based on blinded independent central review or death from any cause, whichever occurred first. Secondary endpoints included safety, overall survival, overall response rate, duration of response, and disease control rate. Overall survival was defined as time from randomisation to death from any cause. Overall response rate was defined as the proportion of patients in the analysis population 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. Objective responses were defined per the International Myeloma Working Group 2006 criteria.[21] Complete response was defined as negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and ≤5% plasma cells in bone marrow. Stringent complete response included complete response as defined above plus normal FLC ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence. 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 in 24 hours. Partial response was defined as a ≥50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to <200 mg in 24 hours. Stable disease was defined as not meeting the criteria for complete response, very good partial response, partial response, or progressive 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 FLC 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 hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder.[21] Disease control rate 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.

Progression-free survival and response endpoints were assessed by confirmed investigator review because of premature study termination. Median time to progression (time from randomisation to first documented instance of progression) was assessed. 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 study drug (all-subjects-as-treated population).

Response was assessed by investigator and central review per the International Myeloma Working Group 2011 response criteria[20] every 4 weeks. Response was also assessed using a full myeloma laboratory panel and calcium, creatinine, and haemoglobin laboratory results, radiographical imaging (x-ray or magnetic resonance imaging [MRI] or computed tomography [CT] or MRI/positron emission tomography [PET] or CT/PET as clinically indicated) for patients with extramedullary soft tissue plasmacytomas and bone marrow biopsy specimen or aspirate for confirmation of complete response or disease progression. Low-dose CT and MRI bone surveys were allowed.

Patients were followed up for survival status every 12 weeks after the end of study treatment and were 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. 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.

Statistical analysis

Hypothesis testing of objective response rate, progression-free survival, and overall survival was strongly controlled by a family-wise type I error rate of 2·5% (one-sided α). The boundaries and the alpha level were determined from the actual number of events at the time of the interim analysis using the corresponding alpha-spending function.[22] A step-down approach was used to control the type I error rate for the testing of end points. The primary end point (progression-free survival) was tested first then, if significant, the secondary end point (overall survival) was tested.[22] A sample size of 640 patients was planned. For progression-free survival, based on 227 events, the study had 90% power to detect an HR of 0·65 with pembrolizumab-lenalidomide-dexamethasone versus lenalidomide-dexamethasone at one-sided alpha 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 arm, 2) an enrolment period of 18 months and at least 12 months follow-up, and 3) a cumulative dropout rate of 2% at the end of the first year and 5% at 4 years. 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 experience documented disease progression or did not die were censored for progression-free survival analysis at the last disease assessment. The treatment difference between arms was evaluated using the stratified log-rank test. Hazard ratios and associated 95% CIs between treatment arms 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 (see appendix for details).

Overall response and disease control rates were compared between treatment groups using the stratified Miettinen and Nurminen method[23] 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. SAS software version 9.4 (SAS Institute, Cary, NC, USA) was used for statistical analyses.

One interim analysis was planned when all patients had been enrolled and approximately 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. On July 3, 2017 the US FDA determined that the risks of pembrolizumab plus lenalidomide outweighed any potential benefits for patients with multiple myeloma and immediately halted the study. Based on that decision, all patients stopped study treatment, completed the discontinuation visit, and moved into the long-term safety and survival follow-up per protocol. Full statistical plans to continue or stop the trial are provided in the protocol (3475-P185-07).

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 had access to the data. Medical writing and/or editorial assistance was provided by the ApotheCom pembrolizumab team. This assistance was funded by Merck Sharp & Dohme, Inc., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. All authors reviewed and edited this manuscript, approved the submitted draft, vouch for the completeness and accuracy of the reported data, and attest that the trial was conducted per protocol.

Results

Patients and treatment

Between Feb 2016 and Jun 2017, 400 patients were screened for enrolment at 95 sites in 15 countries. Patients (n=301) were randomly assigned to the pembrolizumab-lenalidomide-dexamethasone (n=151) or lenalidomide-dexamethasone (n=150) arm (figure 1). Of these, 149 received pembrolizumab-lenalidomide-dexamethasone, and 145 received lenalidomide-dexamethasone; most patients discontinued because of adverse events or disease progression (figure 1). The most commonly reported adverse events that led to discontinuation are listed in appendix table S2. Overall, 156 patients started treatment with a dose of 20 mg of

dexamethasone. (78, pembrolizumab-lenalidomidee-dexamethasone; 78, lenalidomide-dexamethasone). The most common reasons for screen failure (in ≥10% of patients) were inadequate organ function (n=25/90, 28%), no confirmed diagnosis of active multiple myeloma and measurable disease (n=12, 13%), ECOG performance status >1 (n=10, 11%), and unknown reasons (n=15, 17%)

At the database cut-off date (Jun 2, 2017), median follow-up was 6.6 months (range 0.1–16.9). Baseline disease characteristics (table 1) showed differences between treatment arms, with numerically higher percentages of patients displaying high-risk cytogenetics, defined as del17p13, t(4;14) and/or t(14;16) (15.9% *vs* 6.7%), anaemia (55.6% *vs* 45.3%), and renal impairment (13.9% *vs* 8.0%) in the pembrolizumab-lenalidomide-dexamethasone arm versus the lenalidomide-dexamethasone arm (table 1). In contrast, the pembrolizumab-lenalidomide-dexamethasone arm had a lower percentage of patients with plasmacytomas (2.6% *vs* 7.3%; extramedullary in zero of four *vs* two of 11) at baseline.

Efficacy

Median progression-free survival (primary end point) was not reached in either arm, and only 44 progression-free survival events had occurred at analysis. The HR for progression-free survival for pembrolizumab-lenalidomide-dexamethasone versus lenalidomide-dexamethasone was 1·22 (95% CI 0·67 to 2·22; p=0·747) (figure 2A). Progression-free survival rates were 88.5% (95% CI 81·3 to 93·0) and 89·3% (95% CI 82·3 to 93·7), respectively, at month 3 and 82·0% (95% CI 73·2 to 88·1) and 85·0% (95% CI 76·8 to 90·5), respectively, at month 6. Median time to

progression was not reached in either arm; there were only 17 progression events, and the HR was 0·55 (95% CI 0·20 to 1·50; p=0·119) (figure 2B).

Median overall survival was not reached in either arm; only 28 overall survival events had occurred, and the HR was 2·06 (95% CI 0·93 to 4·55; p=0·965) (figure 2C). The 3-month overall survival rates were 94.7% (95% CI, 89·3 to 97·5) and 91·8% (95% CI, 85·7 to 95·4), respectively, and the 6-month overall survival rates were 87·2% (95% CI, 79·9 to 92·0) and 93·9% (95% CI, 88·1 to 96·9), respectively.

Overall response rates were comparable between arms: 63·6% (95% CI, 55·4 to 71·2) in the pembrolizumab-lenalidomide-dexamethasone arm and 62·0% (95% CI, 53·7 to 69·8) in the comparator arm; 96 and 93 patients, respectively, achieved partial response or better. Disease control rates (81·5% *vs* 84·7%) were comparable between arms (appendix table S3). Median time to response was 1·1 months in either arm, and median duration of response was not reached in either arm (appendix table S4). Proportions of patients with a response duration ≥6 months were 88·7% in the pembrolizumab-lenalidomide-dexamethasone arm and 93·5% in the lenalidomide-dexamethasone arm.

Adverse events

Median treatment duration was 131·0 days (range 1–485) in the pembrolizumab-lenalidomide-dexamethasone arm and 162·0 days (range 1–467) in the lenalidomide-dexamethasone arm (appendix table S5). At analysis, patients had received a median of 4·6 cycles of treatment.

Adverse events of any grade occurred at similar proportions of patients in the pembrolizumab-lenalidomide-dexamethasone and the lenalidomide-dexamethasone arms (94·0% *vs* 91·7%) (table 2). Grades 3–5 adverse events (71·8% *vs* 50·3%) and serious adverse events (54·4% *vs* 39·3%) occurred more frequently in the pembrolizumab-lenalidomide-dexamethasone arm than in the lenalidomide-dexamethasone arm (table 2). Grade 5 adverse events occurred in 13 (8·7%) and eight (5·5%) patients in the pembrolizumab-lenalidomide-dexamethasone arm and the lenalidomide-dexamethasone arm, respectively. Adverse events that occurred more frequently (≥5% difference) in the pembrolizumab-lenalidomide-dexamethasone arm than in the lenalidomide-dexamethasone arm are presented in table S6 (appendix). Serious adverse events occurred in at least 3% of patients (appendix table S7). No grade 3–5 events or serious adverse events occurred with at least a 5% difference in incidence between arms. Immune-mediated adverse events occurred in 32·2% of patients in the pembrolizumab-lenalidomide-dexamethasone arm; rash (8·7%), hypothyroidism (7·4%), and hyperthyroidism (6·0%) were the most common (table 3). Of note, only two patients had immune-mediated neutropenia and one patient had immune-mediated thrombocytopenia.

Nineteen (12·8%) patients died in the pembrolizumab-lenalidomide-dexamethasone arm (six because of disease progression, 13 because of adverse events), and nine (6%) patients died in the

lenalidomide-dexamethasone arm (one because of disease progression, eight because of adverse events). Six (4·0%) treatment-related deaths occurred in the pembrolizumab-lenalidomide-dexamethasone arm (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 (1·4%) treatment-related deaths occurred in the lenalidomide-dexamethasone arm.

Overall, patients in the pembrolizumab-lenalidomide-dexamethasone arm who died were older than those in the lenalidomide-dexamethasone arm (at least 70 years, 94·7% *vs* 77·8%; at least 80 years, 42·1% *vs* 33·3%) and had high-risk cytogenetics (26·3% *vs* 0) (appendix table S8). A similar trend in age and high-risk cytogenetics was observed among patients who died because of an adverse event (appendix table S9). The clinical courses of patients in the pembrolizumab-lenalidomide-dexamethasone arm who died because of adverse events are summarised in table S9 (appendix).

To evaluate the higher risk for death in the pembrolizumab combination arm, a retrospective, random forest analysis was performed, followed by a multivariable Cox regression analysis; however, this did not lead to conclusive results because of the small number of deaths (n=28; 14·4% information based on the predefined 195 deaths in the protocol) at analysis.

Discussion

The KEYNOTE-185 study evaluated the safety and efficacy of pembrolizumab-lenalidomide-dexamethasone versus lenalidomide-dexamethasone in transplantation-ineligible patients with treatment-naive multiple myeloma. This non–protocol-specified analysis, with a median follow-up of 6·6 months (range 0·1–16·9), showed an increased risk for death with pembrolizumab-lenalidomide-dexamethasone than with lenalidomide-dexamethasone alone. Because of the imbalance in the proportion of death between arms, the data monitoring committee halted enrolment; this was followed by FDA termination of the study on Jul 3, 2017. Consequently, data collection was incomplete, and efficacy analysis was underpowered. Only 19% of the protocol-specified 227 events required for evaluation of progression-free survival and 14% of the protocol-specified 195 events necessary for evaluation of overall survival were reached at analysis. Median progression-free survival (primary endpoint) and median overall survival were not reached in either arm. Response rates were comparable between arms. Treatment exposure was truncated, with patients in either arm receiving a median of six treatment cycles at analysis; 47 (31·5%) and 36 (24·8%) patients in the pembrolizumab-lenalidomide-dexamethasone and lenalidomide-dexamethasone arm, respectively, received fewer than three cycles of treatment. Delayed survival benefit of immunotherapy, as evident from delayed separation of Kaplan-Meier curves, has been reported.[24-26] Such deviation from proportional hazards may reduce the statistical power to detect differences in survival rates,[25,26] particularly in early trial termination scenarios, and longer follow-up may be necessary to determine immunotherapy efficacy outcomes. Although the overlapping Kaplan-Meier curves for progression-free survival or overall survival in the current unplanned interim analysis suggested similar progression-free or overall survival between arms, this interpretation is limited by early study termination. Cancer severity is associated with immune system dysfunction and thus, it is possible that because of the

degree of immunodeficiency associated with multiple myeloma these patients may not have experienced an optimal response to treatment with a PD-1 inhibitor.[27,28] There is increasing evidence of the efficacy of immunotherapy in patients with multiple myeloma; however, patients continue to relapse, which can partly be a consequence of immune blockade.[29] Early intervention may be particularly relevant for patients with multiple myeloma treated with immune-based therapies.

Adverse events of any grade (94·0 % *vs* 91·7%) occurred at a similar proportion between arms. The frequency of grade 3–5 adverse events (71·8% *vs* 50·3%) and serious adverse events (54·4% *vs* 39·3%) was higher in the pembrolizumab-lenalidomide-dexamethasone arm. There were more discontinuations because of adverse events in the pembrolizumab-lenalidomide-dexamethasone arm (34 [22·8%] *vs* 19 [13·1%]) than in the lenalidomide-dexamethasone arm. The immune-mediated adverse event profile was consistent with that previously reported for pembrolizumab in other cancers[30-32] and with those observed with pembrolizumab-pomalidomide-dexamethasone in patients with relapsed, refractory multiple myeloma in the KEYNOTE-183 study[33] and the study by Badros et al.[17] The most common immune-mediated adverse events were rash, hypothyroidism, and hyperthyroidism. A total of 22.8% of patients experienced grade 3-5 immune-mediated adverse events, with rash (8.7%) being the most commonly reported. One patient died because of an immune-mediated adverse event: myocarditis. The 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 or with daratumumab experienced similar percentages of grade 3-4 neutropenia (38.7% vs. 39.9%), thrombocytopenia (37.6% vs. 34.4%) anemia (19.8% vs. 15.9%) and infections (14.7% vs.

23.1%).[10] Patients in the SWOG S0777 study who received lenalidomide and dexamethasone alone or with bortezomib also experienced similar percentages of grade 3/4 blood or bone marrow adverse events (70%/34% vs. 73%/41%), grade 3 infections (29% vs. 29%), and grade 3 neurological adverse events (21% vs. 76%).[8]Of importance, more patients died in the pembrolizumab-lenalidomide-dexamethasone arm (19 [12·8%] *vs* nine [6·2%]) than in the lenalidomide-dexamethasone arm. More deaths occurred because of disease progression (six [4%] *vs* one [0·7%]) in the pembrolizumab-lenalidomide-dexamethasone arm than in the lenalidomide-dexamethasone arm. The presence of high-risk cytogenetics and other unfavourable risk factors in patients in the pembrolizumab combination arm might have contributed to the higher incidence of early progression and subsequent death in that arm. Additionally, the number of deaths attributed to adverse events (13 [8·7%] *vs* 8 [5·5%]) was numerically different between the arms; however, no specific adverse event was exacerbated in patients who received pembrolizumab-lenalidomide-dexamethasone.. It is also possible that age and unfavourable risk factors contributed to increased toxicity and early (3 month) mortality rates of 8% in the pembrolizumab-lenalidomide-dexamethasone arm and 5% in the lenalidomide-dexamethasone arm. These early mortality rates are higher than the 4-month mortality rates reported 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).[34] 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 elderly patients.[34] In the current study the starting dose of dexamethasone was reduced to 20 mg for 156 patients who were older than 75 years of age. Although the

lenalidomide 25 mg dose was determined in the dose-confirmation phase of the KEYNOTE-023 study,[16] reducing the dose to 15 mg in elderly patients should be considered, based on the increased rate of AEs observed in this study.

To understand the imbalance of proportion of deaths between arms, the baseline characteristics were evaluated among patients who died during the study. More patients in the pembrolizumab-lenalidomide-dexamethasone arm who died were older (at least 70 years, 94·7% *vs* 77·8%) and had higher cytogenetic risk (26·3% *vs* 0) than those in the lenalidomide-dexamethasone arm. Furthermore, among all study patients, there was an imbalance of disease severity and manifestation at baseline, whereby patients in the pembrolizumab-lenalidomide-dexamethasone arm, compared with the lenalidomide-dexamethasone arm, had more advanced disease (stage III disease, 29·1% *vs* 20·7%; renal impairment, 13·9% *vs* 8·0%). According to the International Myeloma Working Group recommendations, cytogenetic abnormalities by fluorescence in situ hybridisation, International Staging System (ISS) stage, and renal failure are some of the factors used for risk stratification in patients with newly diagnosed multiple myeloma.[35] It is plausible that the imbalance between arms of risk factors such as ISS stage III and del17p13, t(4;14), t(14;16), which are associated with poor prognosis,[35] 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 the KEYNOTE-185 study. Because of the small number of progression events reached at this protocol-unspecified interim analysis, exclusion of these patients at high risk (seven *vs* four) from the analysis of progression-free survival or overall survival will further reduce the number of events analysed and the statistical power of the analysis. Collectively, these results suggest that the observed imbalance in the proportion of

deaths between arms might have resulted from diverse non–treatment-related adverse events and/or differences in patient baseline characteristics and not necessarily by exacerbation of any specific treatment-related safety signal. Differences in baseline characteristics may have been a result of the early termination of the study, with enrolment still in progress at over 100 sites worldwide, which limited the number of patients.

In conclusion, an imbalance was observed between arms in the number of deaths. However, the shortened follow-up resulting from premature study termination rendered this interim analysis underpowered and inconclusive. Additional studies involving PD-1 inhibitors are necessary to determine the effect of combining PD-1 inhibitors with lenalidomide and dexamethasone in previously untreated, transplantation-ineligible patients with multiple myeloma. Future study design should consider excluding unfit patients, patients older than 75 years of age, and patients with high tumor burden or tumor staging. Other treatment combinations should also be evaluated, and excluding dexamethasone may reduce toxicity, and improve T cell activation. Stratification of patients by renal function and ECOG performance status may also be considered in future study design.

Contributors

JSM, PM, RG contributed to study design or planning. SZU, SL, RG, MZHF, PM, JSM contributed to data analysis. FS, AO, LK, RMR, HAY, RL, NT, RDM, ABML, KS, IA, TF, MZHF, PM, JSM contributed to acquisition of data. SZU, FS, AO, MC, RL, NT, ABML, HK, GG, IA, SJ, SL, MZHF, PM, JSM contributed to interpretation of the results. SZU, AO, KS, PM, JSM contributed to drafting the manuscript. SZU, FS, AO, LK, MC, RMR, HAY, RL, NT, RDM, ABML, HK, GG, IA, TF, SJ, SL, RG, MZHF, PM, JSM 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

AO reports 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; consulting or advisory role at Pfizer, Adaptive, Bristol-Myers Squibb, Amgen, Celgene, Takeda, and Bayer; research funding from Amgen and Janssen; 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 reports consulting or advisory role at Amgen, Bristol-Myers Squibb, Celgene, Janssen, MSD, Novartis, Takeda, Sanofi, and Roche. LK reports employment at Laboratoires Aguettant; honoraria from Celgene, Janssen, Amgen, and Gilead; consulting or advisory role at Celgene, Janssen, and Amgen; 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 Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. SL reports consulting or advisory role at Takeda, Celgene, Novartis, Bristol-Myers Squibb, Amgen, Janssen, and Merck & Co., Inc.; and research support from Takeda, Celgene, Bristol-Myers Squibb, and Janssen. RL reports honoraria from Celgene Canada; consulting or advisory role at Janssen Inc., Takeda Canada, Celgene Canada, Merck Canada, and Amgen Canada; and travel, accommodations, and expenses from Amgen Canada. RMR reports employment at McKeson Specialty Health; stock or other ownership at McKesson Corporation; and 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 role at Celgene, Janssen, Takeda, Sanofi, Amgen, and Karyopharm; and participation in speaker's bureau at Celgene, Janssen, and Takeda. ABML, HK, IA, KS, NT, and RDM have nothing to disclose

Data Sharing

The data sharing policy for Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, 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

Acknowledgments

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

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Figure Legends

Figure 1: Randomisation and follow-up of patients on study

[a]One additional patient had progressive disease in the lenalidomide-dexamethasone arm but is not included in this figure because the discontinuation visit occurred after the database cut-off date. FDA=US Food and Drug Administration.

[b]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.

Figure 2: Survival in the intention-to-treat population in patients receiving pembrolizumab plus lenalidomide plus low-dose dexamethasone or lenalidomide and low-dose dexamethasone

Shown are (A) progression-free survival and (B) time to progression per International Myeloma Working Group 2011, based on confirmed investigator review. (C) Overall survival. HR=hazard ratio.

730 ***Table 1***: **Demographic and baseline characteristics of the intention-to-treat population**

Characteristic	**Pembrolizumab plus lenalidomide plus dexamethasone (n=151)**	**Lenalidomide plus dexamethasone (n=150)**
Age, median (range), years	74·0 (53–89)	74·0 (57–91)
70–79	87 (57·6%)	86 (57·3%)
≥80	32 (21·2%)	31 (20·7%)
Sex		
Male	70 (46·4%)	71 (47·3%)
Female	81 (53·6%)	79 (52·7%)
ECOG performance status*		
0	51 (33·8%)	55 (36·7%)
1	100 (66·2%)	92 (61·3%)
2	0	1 (0·7%)
ISS stage		
I	38 (25·2%)	51 (34·0%)
II	68 (45·0%)	66 (44·0%)
III	44 (29·1%)	31 (20·7%)
Missing	1 (0·7%)	2 (1·3%)

Cytogenetics		
High-risk Del17p13,t(4;14) and/or t(14;16)	24 (15·9%)	10 (6·7%)
del13	13 (8·6%)	17 (11·3%)
t(11;14)	11 (7·3%)	13 (8·7%)
Normal	93 (61·6%)	89 (59·3%)
Missing	34 (22.5%)	51 (34.0%)
Renal impairment†	21 (13·9%)	12 (8·0%)
Plasmacytoma	4 (2·6%)	11 (7·3%)
Bone	4/4 (100%)	9/11 (81·8%)
Extramedullary	0	2/11 (18·2%)
Hypercalcaemia	14 (9·3%)	14 (9·3%)
Anaemia	84 (55·6%)	68 (45·3%)

Data are n (%). ASCT=autologous stem cell transplantation; ECOG=Eastern Cooperative Group Oncology; ISS=International Staging System. *ECOG performance status scores range from 0 to 5, with higher scores indicating greater disability. †Creatinine clearance <40 mL/min or serum creatinine >177 μmol/L (>2 mg/dL).

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

Adverse event	**Pembrolizumab plus lenalidomide plus dexamethasone (n=149)**		**Lenalidomide plus dexamethasone (n=145)**	
	Any Grade	**Grade 3–5**	**Any grade**	**Grade 3–5**
Any	140 (94·0%)	107 (71·8%)	133 (91·7%)	73 (50·3%)
Serious	81 (54·4%)	—	57 (39·3%)	—
Led to death	13 (8·7%)*	—	8 (5·5%)	—
Led to discontinuation	44 (29·5%)	—	20 (13·8%)	—
Occurring in ≥10% of patients in any group†				
Constipation	52 (34·9%)	2 (1·3%)	30 (20·7%)	0
Fatigue	40 (26·8%)	5 (3·4%)	32 (22·1%)	3 (2·1%)
Nausea	36 (24·2%)	3 (2·0%)	29 (20·0%)	1 (0·7%)
Diarrhoea	33 (22·1%)	5 (3·4%)	28 (19·3%)	0

Anaemia	31 (20·8%)	15 (10·1%)	24 (16·6%)	8 (5·5%)
Pyrexia	30 (20·1%)	4 (2·7%)	9 (6·2%)	0
Rash‡	28 (18·8%)	6 (4·0%)	16 (11·0%)	1 (0·7%)
Vomiting	27 (18·1%)	2 (1·3%)	9 (6·2%)	0
Peripheral oedema	24 (16·1%)	1 (0·7%)	22 (15·2%)	0
Decreased appetite	24 (16·1%)	2 (1·3%)	16 (11·0%)	3 (2·1%)
Neutropenia	22 (14·8%)	16 (10·7%)	22 (15·2%)	15 (10·3%)
Insomnia	19 (12·8%)	0	22 (15·2%)	0
Dyspnoea	19 (12·8%)	6 (4·0%)	13 (9·0%)	0
Pneumonia	17 (11·4%)	9 (6·0%)	9 (6·2%)	6 (4·1%)
Hypokalaemia	17 (11·4%)	7 (4·7%)	16 (11·0%)	2 (1·4%)
Back pain	16 (10·7%)	5 (3·4%)	15 (10·3%)	3 (2·1%)
Upper respiratory tract infection	16 (10·7%)	0	10 (6·9%)	0
Cough	15 (10·1%)	0	16 (11·0%)	0

Treatment-related	120 (80·5%)	83 (55·7%)	104 (71·7%)	48 (33·1%)
Led to discontinuation	31 (20·8%)	—	12 (8·3%)	—
Led to death	6 (4·0%)	—	2 (1·4%)	—

Data are n (%). *Included patient who died because of severe sepsis second to health care–associated pneumonia from listing of randomly assigned patients who died. †Adverse events listed in the order of decreasing frequency in the pembrolizumab combination arm. ‡Includes rash and maculopapular rash.

Table 3: **Immune-mediated adverse events in patients treated with pembrolizumab plus lenalidomide and dexamethasone in the all-subjects-as-treated population**

	Pembrolizumab plus lenalidomide plus dexamethasone (N=149)	
Immune-mediated adverse event	**Grade 1/2**	**Grade 3–5**
Any	14 (9·4%)	34 (22·8%)
Rash*	0	13 (8·7%)
Hypothyroidism	11 (7·4%)	0
Hyperthyroidism	6 (4·0%)	3 (2·0%)
Colitis	2 (1·3%)	1 (0·7%)
Myocarditis	0	2 (1·3%)
Adrenal insufficiency	0	1 (0·7%)
Autoimmune thyroiditis	1 (0·7%)	0
Hypersensitivity	2 (1·3%)	0

Infusion-related reaction	0	2 (1·3%)
Drug eruption	0	2 (1·3%)
Pancreatitis	0	1 (0·7%)
Drug-induced liver injury	0	1 (0·7%)
Hepatitis	0	1 (0·7%)
Fulminant type 1 diabetes mellitus	0	1 (0·7%)
Rhabdomyolysis	0	1 (0·7%)
Systemic lupus erythematosus	0	1 (0·7%)
Myasthenia gravis	0	1 (0·7%)
Pneumonitis	1 (0·7%)	0
Dermatitis bullous	1 (0·7%)	0
Dermatitis exfoliative	1 (0·7%)	0
Dry skin	0	1 (0·7%)
Erythema	0	1 (0·7%)

Erythema multiforme	0	1 (0·7%)
Erythematosus rash	0	1 (0·7%)
Pruritic rash	0	1 (0·7%)
Stevens-Johnson syndrome	0	1 (0·7%)

Data are n (%). *Includes rash and maculopapular rash.

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

Adverse events leading to death	**Pembrolizumab plus lenalidomide plus dexamethasone (n=149)**	**Lenalidomide plus dexamethasone (n=145)**
Any	13 (8·7%)	8 (5·5%)
Acute myocardial infarction	0	1 (0·7%)
Cardiac arrest*	1 (0·7%)	0
Cardiac failure*	1 (0·7%)	0
Acute cardiac failure	0	1 (0·7%)
Cardio-respiratory arrest	2 (1·3%)	0
Myocardial infarction	0	1 (0·7%)
Myocarditis*†	1 (0·7%)	0
Intestinal ischaemia	1 (0·7%)	0
Large intestine perforation*	1 (0·7%)	0

Upper intestinal haemorrhage*	0	1 (0·7%)
Unknown cause[‡]	1 (0·7%)	3 (2·1%)
Pneumonia*[†]	1 (0·7%)	0
Completed suicide	1 (0·7%)	0
Pulmonary embolism*	2 (1·3%)[§]	0
Respiratory failure*	0	1 (0·7%)
Sepsis[¶]	1 (0·7%)	0

Data are n (%). *Considered treatment related by investigator. Among cardiac events, cardiac arrest and cardiac failure were considered related to treatment by the 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 listing of randomly assigned patients who died.

Figure 1

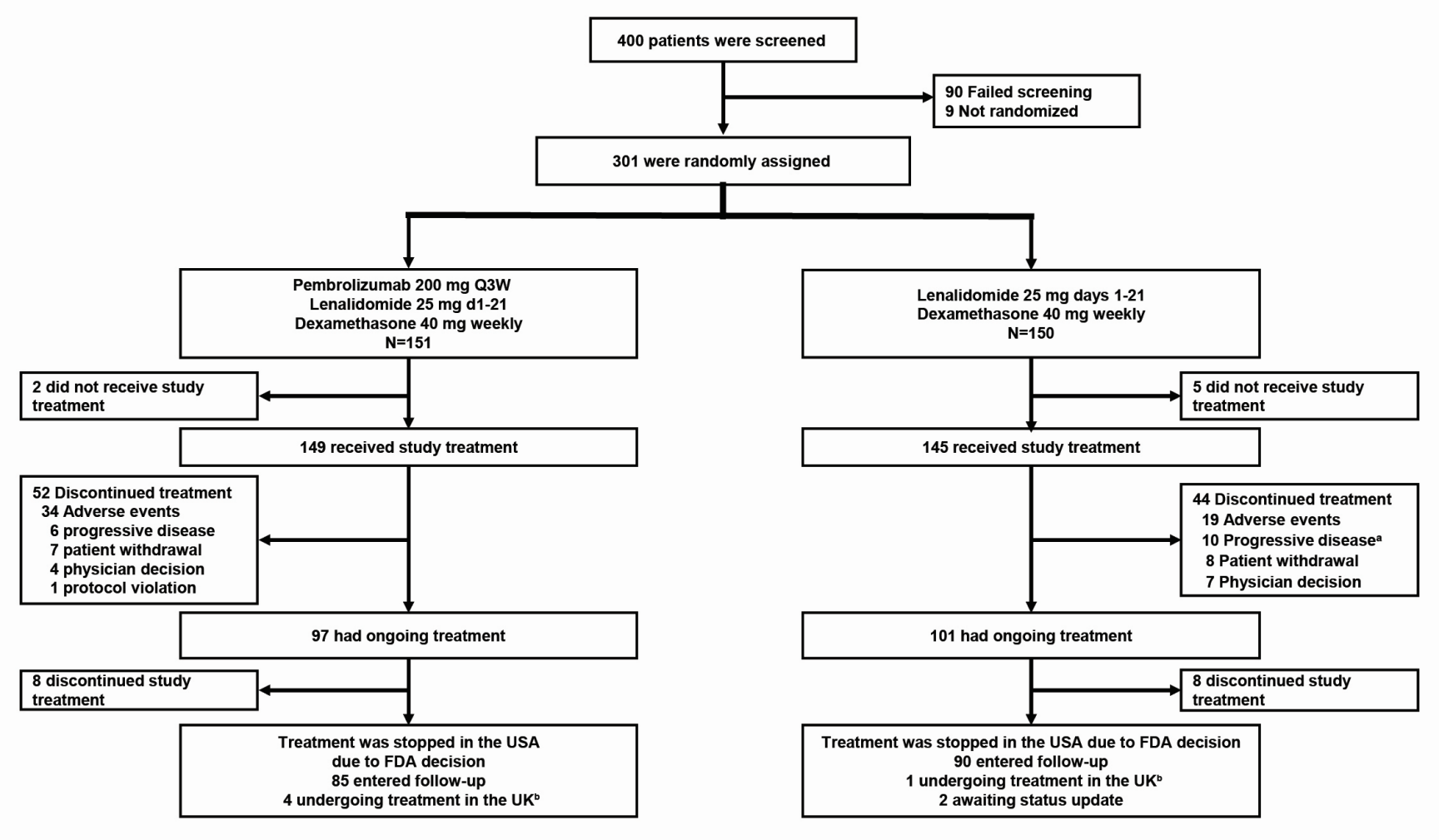
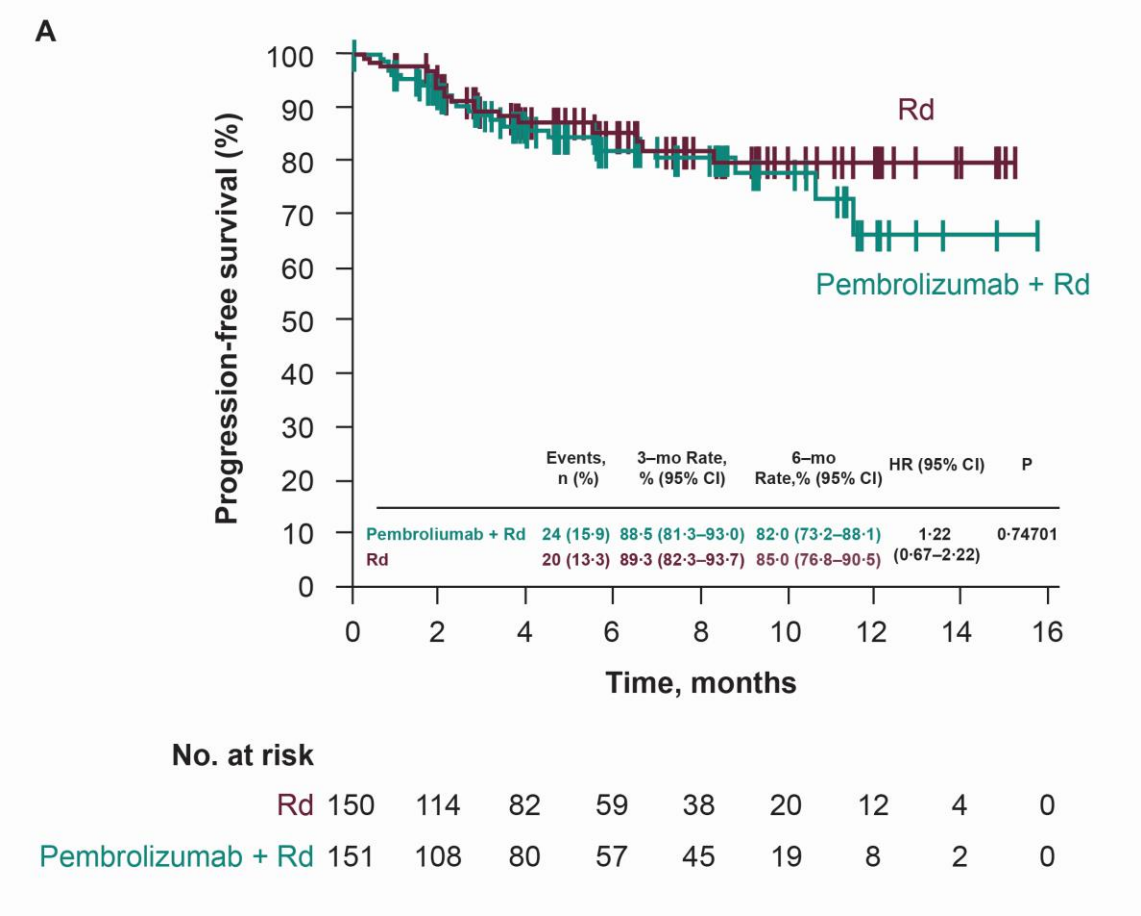
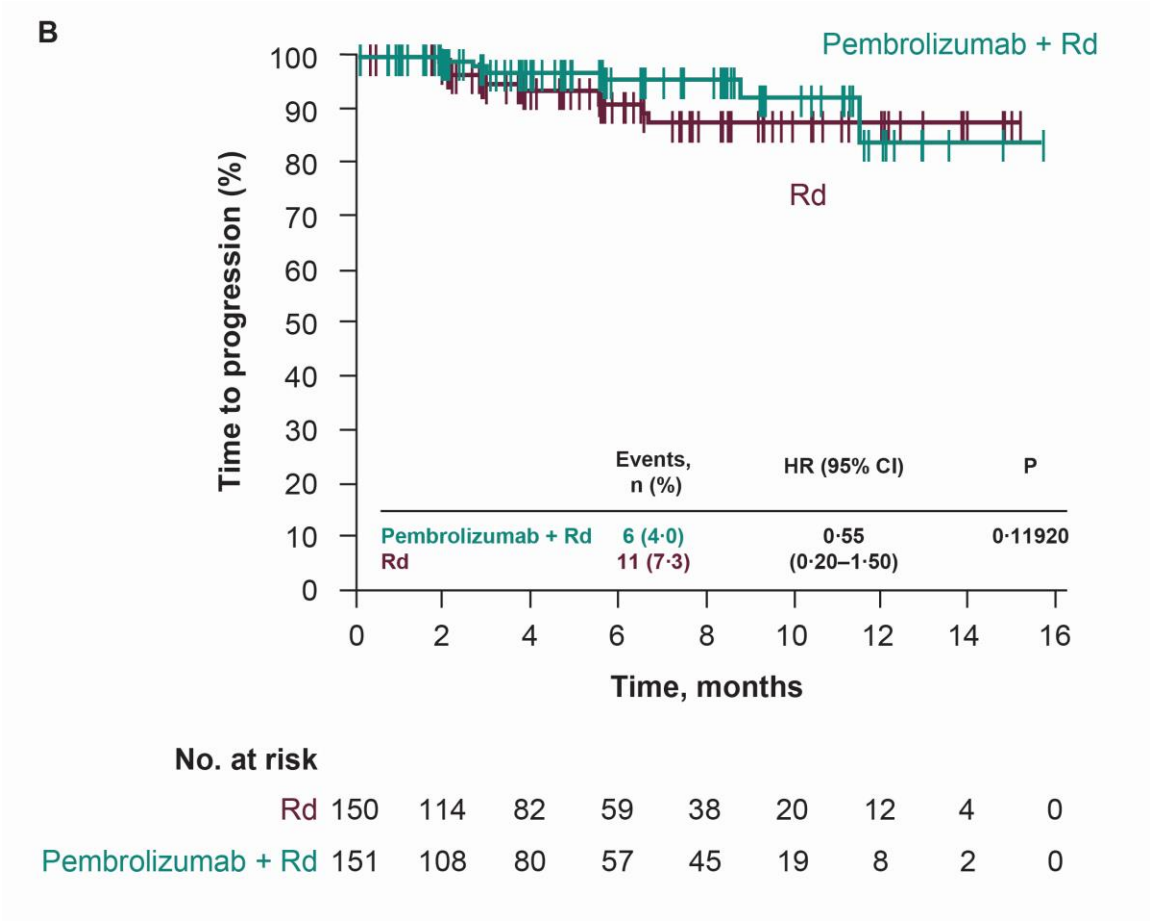
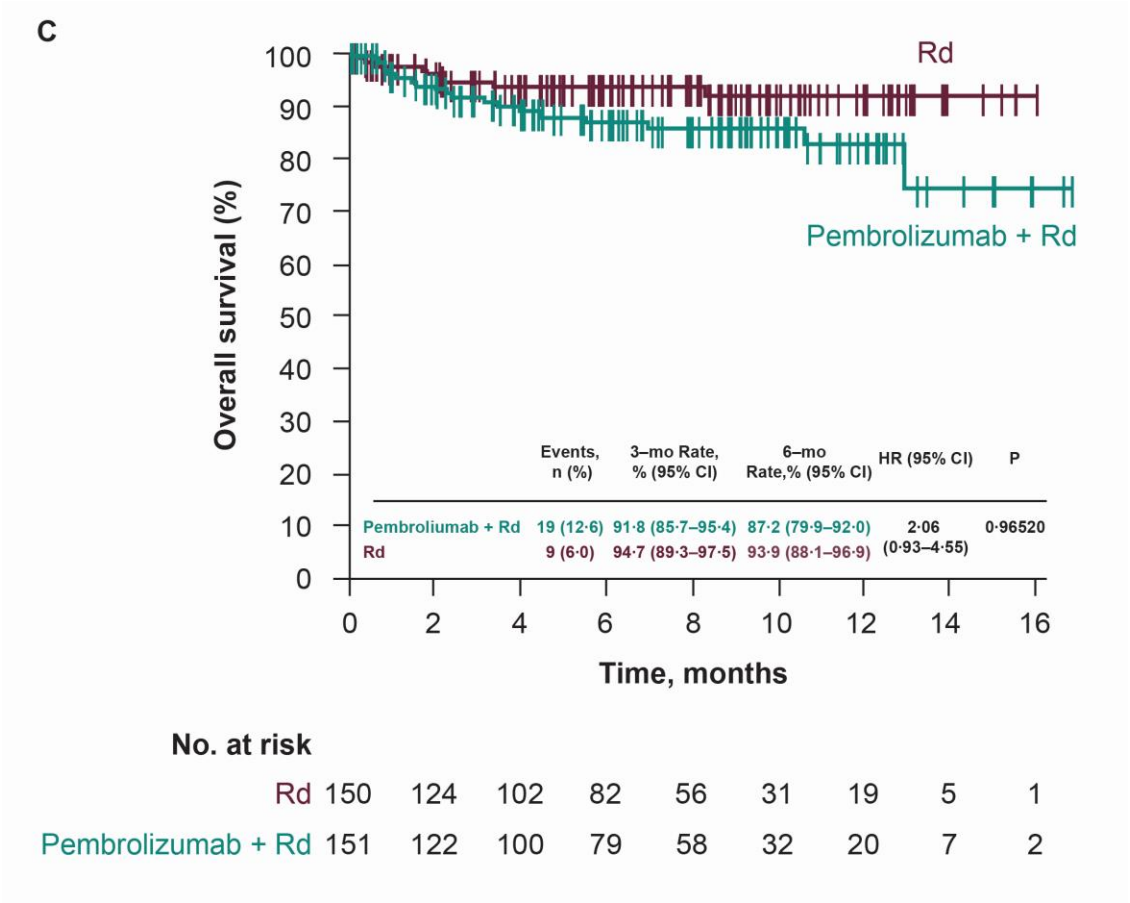

400 patients were screened
90 Failed screening
9 Not randomized
301 were randomly assigned
Pembrolizumab 200 mg Q3W
Lenalidomide 25 mg d1-21
Dexamethasone 40 mg weekly
N=151
Lenalidomide 25 mg days 1-21
Dexamethasone 40 mg weekly
N=150
2 did not receive study treatment
5 did not receive study treatment
149 received study treatment
145 received study treatment
52 Discontinued treatment
34 Adverse events
6 progressive disease
7 patient withdrawal
4 physician decision
1 protocol violation
44 Discontinued treatment
19 Adverse events
10 Progressive disease[a]
8 Patient withdrawal
7 Physician decision
97 had ongoing treatment
101 had ongoing treatment
8 discontinued study treatment
8 discontinued study treatment
Treatment was stopped in the USA due to FDA decision
85 entered follow-up
4 undergoing treatment in the UK[b]
Treatment was stopped in the USA due to FDA decision
90 entered follow-up
1 undergoing treatment in the UK[b]
2 awaiting status update

Figure 2


A
Progression-free survival (%)
100
90
80
70
60
50
40
30
20
10
0
Rd
Pembrolizumab + Rd
Events, n (%)
3–mo Rate, % (95% CI)
6–mo Rate,% (95% CI)
HR (95% CI)
P
Pembroliumab + Rd 24 (15·9) 88·5 (81·3–93·0) 82·0 (73·2–88·1) 1·22 (0·67–2·22) 0·74701
Rd 20 (13·3) 89·3 (82·3–93·7) 85·0 (76·8–90·5)
0 2 4 6 8 10 12 14 16
Time, months
No. at risk
Rd 150 114 82 59 38 20 12 4 0
Pembrolizumab + Rd 151 108 80 57 45 19 8 2 0


B
Pembrolizumab + Rd
Rd
Time to progression (%)
100
90
80
70
60
50
40
30
20
10
0
Events, n (%)
HR (95% CI)
P
Pembrolizumab + Rd 6 (4·0) 0·55 (0·20–1·50) 0·11920
Rd 11 (7·3)
0 2 4 6 8 10 12 14 16
Time, months
No. at risk
Rd 150 114 82 59 38 20 12 4 0
Pembrolizumab + Rd 151 108 80 57 45 19 8 2 0


C
Rd
Pembrolizumab + Rd
Overall survival (%)
100
90
80
70
60
50
40
30
20
10
0
Events, n (%)
3–mo Rate, % (95% CI)
6–mo Rate,% (95% CI)
HR (95% CI)
P
Pembroliumab + Rd 19 (12·6) 91·8 (85·7–95·4) 87·2 (79·9–92·0) 2·06 (0·93–4·55) 0·96520
Rd 9 (6·0) 94·7 (89·3–97·5) 93·9 (88·1–96·9)
0 2 4 6 8 10 12 14 16
Time, months
No. at risk
Rd 150 124 102 82 56 31 19 5 1
Pembrolizumab + Rd 151 122 100 79 58 32 20 7 2