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

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Summary

Background Pomalidomide and dexamethasone is a standard of care for patients with multiple myeloma in whom bortezomib and lenalidomide treatment has failed. KEYNOTE-183 assessed efficacy and safety of pomalidomide and dexamethasone with or without pembrolizumab in patients with relapsed or refractory multiple myeloma. Here, we present the findings of an unplanned, ad-hoc interim analysis at the request of the US Food and Drug Administration (FDA).

Methods KEYNOTE-183 was a randomised, open-label, phase 3 trial done at 97 medical centres across 11 countries (Australia, Canada, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Spain, and USA). Patients aged at least 18 years with multiple myeloma, an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, previously treated with at least two lines of therapy (excluding pomalidomide) and refractory to the last line were randomly assigned 1:1 to the pembrolizumab plus pomalidomide and dexamethasone group or the pomalidomide and dexamethasone group via an interactive voice response or integrated web response system. Patients received oral pomalidomide 4 mg daily on days 1–21 and oral low-dose dexamethasone 40 mg on days 1, 8, 15, and 22 in 28-day cycles, with or without intravenous pembrolizumab 200 mg every 3 weeks. The dual primary endpoints were progression-free survival and overall survival. Efficacy was assessed in all randomly assigned patients and safety was assessed in patients who received at least one dose of study treatment. The trial is registered at ClinicalTrials.gov, number NCT02576977, and it is closed for accrual.

Findings Between Jan 18, 2016, and June 7, 2017, 249 patients were randomly assigned to either the pembrolizumab plus pomalidomide and dexamethasone group (n=125) or the pomalidomide and dexamethasone group (n=124). On July 3, 2017, the FDA established that risks associated with the triple combination outweighed benefits and halted the study. Median follow-up was 8·1 months (IQR 4·5–10·9). Median progression-free survival was 5·6 months (95% CI 3·7–7·5) in the pembrolizumab plus pomalidomide and dexamethasone group versus 8·4 months (5·9–not reached) in the pomalidomide and dexamethasone group; progression-free survival estimates at 6 months were 48% (95% CI 37–58) versus 60% (49–69) at 6 months (hazard ratio [HR] 1·53; 95% CI 1·05–2·22; p=0·98). Median overall survival was not reached (95% CI 12·9–not reached) versus 15·2 months (12·7–not reached; HR 1·61; 95% CI 0·91–2·85; p=0·95); overall survival estimates at 6 months were 82% (95% CI 74–88) versus 90% (82–95). Serious adverse events occurred in 75 (63%) of 120 patients in the pembrolizumab plus pomalidomide and dexamethasone group versus 56 (46%) of 121 patients in the pomalidomide and dexamethasone group. Four (3%) treatment-related deaths occurred in the pembrolizumab plus pomalidomide and dexamethasone group (one each of unknown cause, neutropenic sepsis, myocarditis, and Stevens–Johnson syndrome); myocarditis and Stevens-Johnson syndrome were considered related to pembrolizumab. No treatment-related deaths were reported in the pomalidomide and dexamethasone group.

Interpretation The results from this unplanned, FDA-requested, interim analysis showed that the benefit–risk profile of pembrolizumab plus pomalidomide and dexamethasone is unfavourable for patients with relapsed or refractory multiple myeloma.

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Introduction

Multiple myeloma, a malignant disorder of clonal plasma cells characterised by osteolytic bone lesions, renal disease, and immunodeficiency, accounts for about 1% of all cancers and 10% of haematological cancers.[1,2] Immunomodulatory imide drugs lenalidomide and

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Research in context

Evidence before this study

We did a PubMed search using the terms "relapsed" and "multiple myeloma" filtered by article type (clinical trial) and publication dates (Jan 1, 2013, to Nov 27, 2018) with no language restrictions, which yielded 70 articles. Treatment of relapsed or refractory multiple myeloma poses the unique challenge of balancing efficacy and safety in patients who tend to have had many previous treatments and are older. Therefore, several ongoing phase 1 and 2 trials are being done to assess 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 in patients with relapsed or refractory multiple myeloma showed improved progression-free survival 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; hazard ratio 0·54; p=0·008). This result led to the recent US Food and Drug Administration (FDA) approval of the elotuzumab combination in relapsed or refractory multiple myeloma.

Narrowing the search by adding filters for the terms "multiple myeloma" and "PD-1" yielded only two results relevant to relapsed or refractory multiple myeloma, both involving a PD-1 inhibitor. One phase 2, single-arm trial reported acceptable safety (grade 3 or 4 adverse events in 40% of patients) and promising activity (response in 60% of patients and median progression-free survival of 17·4 months [95% CI 11·7–18·8]) with the combination of pembrolizumab and pomalidomide and dexamethasone in patients with relapsed or refractory multiple myeloma. A phase 1b study showed acceptable safety (drug-related adverse events in 63% of patients) and antitumour activity (complete response after radiotherapy in one [4%] of 27 patients) with nivolumab in patients with relapsed or refractory multiple myeloma. These results provide a promising backdrop for the KEYNOTE-183 study.

Added value of this study

This phase 3 study was done to assess the efficacy and safety of the checkpoint inhibitor pembrolizumab with pomalidomide and dexamethasone in patients with relapsed or refractory multiple myeloma. Despite positive results in a previous study, an interim analysis done at a median follow-up of 8·1 months (IQR 4·5–10·9) at the request of the US FDA showed an unfavourable benefit–risk profile for the pembrolizumab plus pomalidomide and dexamethasone combination in patients with relapsed or refractory multiple myeloma and KEYNOTE-183 was halted.

Implications of all the available evidence

Although the results of KEYNOTE-183 are unlikely to change clinical practice in light of alternative, efficacious, and safe triplet and quadruplet treatments in this setting, this study might provide valuable information to guide the design of future clinical studies involving checkpoint inhibitors in relapsed or refractory multiple myeloma.

pomalidomide, proteasome inhibitors such as bortezomib and carfilzomib, and effective combination with novel therapies with different mechanisms of action such as daratumumab have improved overall survival in multiple myeloma.[3–9] Most patients still undergo cycles of remission and relapse until the disease becomes refractory. Prognosis is poor in patients who are refractory to immunomodulatory imides or proteasome inhibitors.[10] Effective combination of novel therapies with different mechanisms of action remains an unmet need.

Pembrolizumab is a highly selective humanised monoclonal antibody against PD-1 that blocks interaction between PD-1 and its ligands PD-L1 and PD-L2, with antitumour activity across multiple tumour types.[11–14] In two phase 1 studies, pembrolizumab as monotherapy and in combination with lenalidomide and low-dose dexamethasone had manageable safety and promising antitumour activity in patients with relapsed or refractory multiple myeloma.[15,16] In a phase 2 study, pembrolizumab plus pomalidomide and dexamethasone led to a response in 60% of patients, a median response duration of 14·7 months (95% CI 7·9–17·5), and manageable safety, supporting a randomised trial of pembrolizumab-based therapy in patients with relapsed or refractory multiple myeloma.[17]

See Online for appendix 2

In the KEYNOTE-183 study, we assessed clinical effects of combining pembrolizumab with pomalidomide and dexamethasone in patients with relapsed or refractory multiple myeloma. We present the results of the unplanned, interim efficacy (survival outcomes and tumour response) and safety analyses.

Methods

Study design and participants

KEYNOTE-183 was a randomised, open-label, phase 3 trial of pembrolizumab plus pomalidomide and dexamethasone compared with pomalidomide and dexamethasone alone in patients with relapsed or refractory multiple myeloma. Patients were enrolled at 97 medical centres across 11 countries (Australia, Canada, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Spain, and USA). The trial protocol is available in appendix 2 (pp 1–151). The study was done in accordance with the protocol and amendments, Good Clinical Practice Guidelines, and the Declaration of Helsinki. The protocol and subsequent amendments were approved by the appropriate institutional review board or ethics committee at each participating institution.

Eligibility criteria were age 18 years or older; confirmed diagnosis of active multiple myeloma and measurable disease; at least two previous lines of anti-myeloma therapy, including immunomodulatory imides (lenalidomide or thalidomide) and proteasome inhibitors (bortezomib, ixazomib, or carfilzomib); failure of last line of therapy, defined as refractory (resistant to treatment or documented progression during or within 60 days of completing immunomodulatory imide or proteasome inhibitor-based treatment) or relapsed and refractory (relapse within 6 months of stopping treatment with an immunomodulatory imide or proteasome inhibitor-containing regimen); Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; adequate organ (protocol-defined haematological, renal, hepatic, and coagulation) function; and provision of bone marrow biopsy sample or aspirate material for disease assessment and biomarker analysis. Patients were ineligible if they had non-secretory or oligosecretory myeloma; smouldering multiple myeloma; monoclonal gammopathy of unknown significance; plasma cell leukaemia; Waldenström's macroglobulinaemia; hypersensitivity to thalidomide, lenalidomide, or dexamethasone; previous therapy with pomalidomide; active autoimmune disease necessitating systemic treatment in the past 2 years; evidence of active, non-infectious pneumonitis; active infection requiring intravenous systemic therapy; known psychiatric or substance abuse disorders that would interfere with compliance with trial requirements; history of repeated infections, primary amyloidosis, hyperviscosity, or POEMS syndrome; history of immune suppression or is receiving systemic steroid or immunosuppressive therapy within 7 days of first dose of study drug; previous monoclonal antibody within 4 weeks of study or ongoing adverse events due to drugs administered more than 4 weeks earlier; previous antimyeloma therapy within 2 weeks of study; previous allogeneic haemopoietic stem cell transplantation (SCT) in 5 years before the study; autologous SCT in the 12 weeks before the study; plasmapheresis in the 4 weeks before the study; inability to undergo thromboembolic prophylaxis; peripheral neuropathy grade 2 or worse; another malignancy in the 5 years before the study; previous therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte-associated antigen-4 antibody; HIV, hepatitis B, or hepatitis C infection; received live vaccine in 30 days before first dose of study drug; or if they had an immediate relative who is investigational site or funder staff involved in this trial. All patients provided written informed consent to participate.

Randomisation and masking

Patients were randomly assigned 1:1 to the pembrolizumab plus pomalidomide and dexamethasone group or the pomalidomide and dexamethasone group using an interactive voice response system or integrated web response system (randomised allocation schedules were generated by the funder and provided to site staff as required via an automated telephone system). Randomisation was stratified by number of previous lines of therapy (two *vs* ≥three) and disease status (lenalidomide refractory *vs* sensitive). This was an open-label study; therefore, masking was not performed.

Procedures

Patients received 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, with or without intravenous pembrolizumab 200 mg every 3 weeks. Dose interruptions were permitted in cases of medical or surgical events or for logistical reasons unrelated to study therapy; patients continued with study therapy within 28 days of the scheduled interruption. Dose modification occurred per prespecified protocol guidance for each of the treatment drugs in response to toxicity (details in the redacted protocol). Treatment was continued until confirmed progression, unacceptable toxicity, or physician or patient decision to withdraw.

Disease response was assessed every 4 weeks; patients were considered non-evaluable if they had received at least one dose of study treatment but had not had post-treatment assessment or if they had been assigned to a group but had not received study treatment. Patients who discontinued for reasons other than progression had post-treatment follow-up visits for disease status every 4 weeks until progression, initiation of non-study cancer treatment, withdrawal of consent, or loss to follow-up. Patients were contacted for assessment of survival status every 12 weeks after the end of treatment.

Adverse events were graded per Common Terminology Criteria for Adverse Events, version 4.0, and monitored throughout treatment and for 30 days (90 days for serious adverse events) after treatment end. Immune-mediated adverse events were defined as adverse events—specified by the sponsor (non-serious and serious) and included by the investigator—associated with pembrolizumab exposure that were consistent with immune phenomena and had a potentially immunological cause regardless of attribution to study treatment or immune relatedness. Attribution of adverse events to the study drugs was determined by site investigators.

Patients could withdraw consent at any time for any reason or be excluded from the trial at the investigator's discretion in the event of untoward effects. Patients could also have been withdrawn for the following reasons: documented disease progression, unacceptable adverse events, intercurrent illness preventing further study treatment, confirmed pregnancy, receipt of non-protocol-specified anti-myeloma therapy before documented disease progression, non-adherence to trial treatment or procedures, loss to follow-up, and administrative reasons. The trial was to be terminated prematurely if quality or

quantity of data recording were inaccurate or incomplete, adherence to the protocol and regulatory requirements were poor, plans were made to modify or discontinue development of pembrolizumab, or in response to a request by the US Food and Drug Administration (FDA) or other health authority because of safety concerns.

Outcomes

The dual primary endpoints were progression-free survival, defined as time from randomisation to first documented disease progression or death from any cause per International Myeloma Working Group 2011 criteria[18] by masked independent central review, and overall survival, defined as time from randomisation to death from any cause. Secondary efficacy endpoints were overall response, duration of response, disease control, safety and tolerability of both treatments, and secondary progression-free survival (time from randomisation to subsequent disease progression after initiation of new anticancer therapy or death from any cause, whichever occurs first, based on investigator assessment; not reported here). Overall response was the proportion of patients who achieved at least a partial response, assessed by masked central review.[19,20] Duration of response was defined as the time from first documented partial response until progression or death, assessed by masked central review. Disease control was the proportion 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. The International Response Criteria for multiple myeloma[19] were used to define complete, very good partial, and partial responses, and stable and progressive disease. Full description of these criteria is in appendix 1 (p 4). Median time to progression, defined as time from randomisation to first documented progression, was also assessed.

Statistical analysis

Hypothesis testing of objective response rate, progression-free survival, and overall survival was controlled by a family-wise type I error rate of 2·5% (one-sided α).[21] A sample size of 300 patients was planned. For progression-free survival, based on 236 events (estimated to occur about 20 months after the first patient enrolled), the study had 90·6% power to detect a hazard ratio (HR) of 0·635 with pembrolizumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone (assuming median progression-free survival of 4·0 months) at a one-sided α 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 HR of 0·6 for pembrolizumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone (assuming a median overall survival of 12·7 months) at a one-sided α of 0·5%. For overall response, based on the first 210 randomly assigned patients, the study had 88·7% power to show a 25% difference between the groups (55% for pembrolizumab plus pomalidomide and dexamethasone *vs* 30% pomalidomide and dexamethasone) at a one-sided α of 0·5%.

Progression-free survival was compared between treatment groups using a stratified log-rank test with a stratified Cox regression providing the HR. Proportions of progression events were estimated within treatment groups using the Kaplan-Meier method. Duration of response was assessed descriptively using Kaplan-Meier statistics. Safety was analysed using descriptive statistics overall and a tiered approach. There were no tier 1 events (subject to inferential testing for statistical significance between groups); tier 2 events, which must occur in at least four patients in any treatment group, were assessed using point estimates with 95% CIs for between-group comparisons; tier 3 events (adverse events that are neither tier 1 nor tier 2) were analysed using point estimates only. Immune-mediated adverse events were summarised separately by toxicity and grade (including counts, percentages, and 95% CIs). Two interim analyses were protocol-specified before final analysis: a final analysis of objective response and a final progression-free survival analysis and interim overall survival analysis (appendix 2 p 104). Statistical analyses were done using SAS software, version 9.4.

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 (safety population). An external data monitoring committee assessed safety and efficacy at interim timepoints and made recommendations regarding patient safety and study integrity. This trial is registered at ClinicalTrials.gov, number NCT02576977.

Role of the funding source

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

Results

Between Jan 18, 2016, and June 7, 2017, 348 patients were screened, of whom 97 were not eligible and two were not assigned to a group before the study was halted, and 249 were randomly assigned to either the pembrolizumab plus pomalidomide and dexamethasone group (n=125) or the pomalidomide and dexamethasone group (n=124). Of these, 120 patients in the pembrolizumab plus pomalidomide and dexamethasone group and 121 in the pomalidomide and dexamethasone group were treated (figure 1). Dexamethasone 20 mg was given from the start of treatment in 81 patients (37 in the pembrolizumab plus pomalidomide and dexamethasone group and 44 in the pomalidomide and dexamethasone group). A list of key

changes made to the protocol after the start of the study is in appendix 1 (p 3). On July 3, 2017, the FDA halted KEYNOTE-183 on the basis of interim data presented to the data monitoring committee, which indicated that the risks associated with the pembrolizumab combination outweighed the benefits.[22] Pembrolizumab was immediately discontinued after the FDA decision to halt the trial and patients were transferred to available standard-of-care therapies at their physician's discretion and according to local institutional regulations. Patient-reported outcomes, pharmacokinetic endpoints, and exploratory biomarker endpoints were not analysed and the two preplanned interim analyses were not done because of early trial termination.

Baseline patient and disease characteristics were generally similar between groups (table 1). More patients in the pembrolizumab group had high-risk cytogenetics than in the pomalidomide and dexa-methasone group (28 [22%] of 125 in the pembrolizumab group *vs* 17 [14%] of 124 in the pomalidomide and dexamethasone group), including del17p13 (15 [12%] of 125 *vs* six [5%] of 124) and plasmacytoma (15 (12%) of 125 [six extramedullary] *vs* six [5%] of 124 [three extramedullary]; table 1). At the time of the unplanned interim analysis, median follow-up was 8·1 months (IQR 4·5–10·9) across both groups and 7·8 months (IQR 4·0–10·5) in the pembrolizumab group versus 8·6 months (IQR 5·1–11·1) in the pomalidomide and dexamethasone group (appendix 1 p 5). At data cutoff, 40 (33%) of the 120 patients who started treatment in the pembrolizumab group versus 53 (44%) of the 121 who started treatment in the pomalidomide and dexamethasone group were still on study treatment; 80 (67%) patients versus 68 (56%) had discontinued (figure 1). Disease progression was the most common reason for study discontinuation in both treatment groups (46 [38%] patients in the pembrolizumab group *vs* 41 [34%] patients in the pomalidomide and dexamethasone group), followed by adverse events (22 [18%] *vs* nine [7%]). 18 (15%) patients in the pembrolizumab group and five (4%) in the pomalidomide and dexamethasone group discontinued because of treatment-related adverse events.

Because of premature study termination, progression-free survival and response endpoints were assessed by substantiated investigator assessment. At database cutoff (June 2, 2017), median progression-free survival was 5·6 months (95% CI 3·7–7·5) in the pembrolizumab plus pomalidomide and dexamethasone group versus 8·4 months (5·9–not reached) in the pomalidomide and dexamethasone group; with an HR for disease progression or death of 1·53 (95% CI 1·05–2·22; p=0·98; figure 2A). The number of progression-free survival events was 115 (65 [52%] patients in the pembrolizumab group and 50 [40%] in the pomalidomide and dexa-methasone group). Median time to progression was 8·1 months (95% CI 5·6–not reached) in the pembrolizumab group versus 8·7 months (6·6–not reached) in the pomalidomide and dexamethasone group. Estimated progression-free survival was 48% (95% CI 37–58) versus 60% (49–69) at 6 months and 68% (58–76) versus 79% (70–85) at 3 months (figure 2A). Median overall survival was not reached (95% CI 12·9–not reached) in the pembrolizumab group versus 15·2 months (12·7–not reached) in the pomalidomide and dexamethasone group; the HR for death was 1·61 (95% CI 0·91–2·85; p=0·95). Estimated overall survival was 82% (95% CI 74–88) versus 90% (82–95) at 6 months and 90% (83–95) versus 98% (93–100) at 3 months (figure 2B). The HR for comparison of overall survival was similar among subgroups, except for ECOG performance status 0, disease stages 1 and 2, and patients from Japan (appendix 1 p 19). The HR for comparison of progression-free survival was similar among subgroups, except for the race (other) and Japan subgroups (appendix 1 p 20).

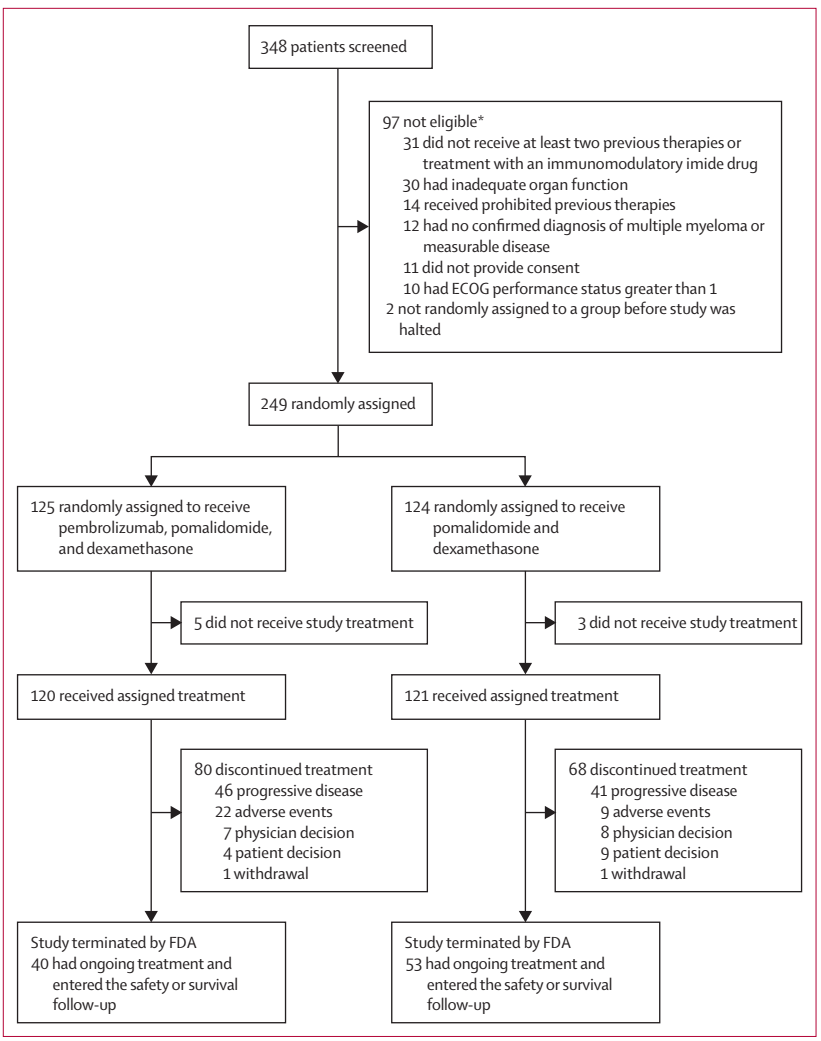

Figure 1: **Trial profile**
ECOG=Eastern Cooperative Oncology Group. FDA=Food and Drug Administration. *Reasons are not exclusive—ie, one patients can meet more than one criteria.

	Pembrolizumab plus pomalidomide and dexamethasone group (n=125)	Pomalidomide and dexamethasone group(n=124)
Age, years	65 (60–72)	67 (60–74)
70–79 years	37 (30%)	38 (31%)
≥80 years	7 (6%)	10 (8%)
Sex		
Female	48 (38%)	46 (37%)
Male	77 (62%)	78 (63%)
ECOG performance status		
0	60 (48%)	60 (48%)
1	65 (52%)	64 (52%)
International Staging System stage		
I	45 (36%)	45 (36%)
II	46 (37%)	39 (31%)
III	33 (26%)	33 (27%)
Missing	1 (1%)	7 (6%)
Number of previous recurrences	3 (1–3)	3 (1–3)
Cytogenetics*		
High-risk del17p13, t(4;14), or t(14;16)	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	9 (7%)	7 (6%)
Renal impairment†	8 (6%)	21 (17%)
Presence of plasmacytoma‡	15 (12%)	6 (5%)
Bone	9/15 (65%)	3/6 (50%)
Extramedullary	6/15 (40%)	3/6 (50%)
Previous autologous stem cell transplantation	77 (62%)	81 (65%)
Previous 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 median (IQR), n (%), or n/N (%). ECOG=Eastern Cooperative Oncology Group. FISH=fluorescence in-situ hybridisation. *Baseline cytogenetics were analysed in bone marrow aspirate sample by FISH or by standard karyotyping if FISH was unavailable, at local laboratories. †Creatinine clearance less than 40 mL/min or serum creatinine more than 177 µmol/L (>2 mg/dL). ‡Presence of extramedullary soft tissue plasmacytoma was assessed by MRI, CT, or PET/CT at screening. §Patients were considered refractory if two (double; lenalidomide and bortezomib), three (triple; lenalidomide, bortezomib, and pomalidomide or lenalidomide, bortezomib, and carfilzomib) or four (quadruple; lenalidomide, bortezomib, pomalidomide, and carfilzomib) previous lines of treatment were ineffective, defined as documented disease progression during or within 60 days of completing their last anti-myeloma therapy.

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

43 (34%; 95% CI 26·1–43·4) of 125 patients in the pembrolizumab group achieved an overall response (partial response or better) compared with 50 (40%; 31·6–49·5) of 124 in the pomalidomide and dexamethasone group (appendix 1 p 6). Disease control was achieved by 106 (85%; 77·3–90·6) patients in the pembrolizumab group and 105 (85%; 77·1–90·5) in the pomalidomide and dexamethasone group. Median duration of response was 8·2 months (95% CI 5·2–not reached) in the pembrolizumab group and was not reached in the pomalidomide and dexamethasone group (appendix 1 p 5).

Median duration of study treatment was 123·5 days (IQR 57·5–225·0) in the pembrolizumab group and 127·0 days (78·0–253·0) in the pomalidomide and dexamethasone group (appendix 1 p 6); at analysis, patients had received a median of 4·4 cycles (2·0–9·0) of treatment.

Adverse events of any grade were reported in 119 (99%) of 120 patients in the pembrolizumab group versus 116 (96%) of 121 in the pomalidomide and dexamethasone group; grade 3 or 4 adverse events were reported in 90 (75%) of 120 versus 77 (64%) of 121 patients; and serious adverse events were reported in 75 (63%) of 120 versus 56 (46%) of 121 patients (appendix 1 p 7). Grade 5 adverse events occurred in 13 (11%) patients in the pembrolizumab group versus three (2%) in the pomalidomide and dexamethasone group (table 2). Any-grade adverse events with an at least 5% difference in incidence between groups were neutropenia, anaemia, fatigue, pneumonia, nausea, headache, back pain, and increase in alanine aminotransferase (table 2). Grade 3 or 4 adverse events with an at least 5% difference between groups were neutropenia (41 [34%] of 120 *vs* 26 [21%] of 121) and thrombocytopenia (14 [12%] of 120 *vs* eight [7%] of 121). No serious adverse events occurred with at least a 5% difference between groups; serious adverse events with at least 3% difference between groups are in appendix 1 (p 7). Data regarding timing of onset of adverse events are not available. Immune-mediated adverse events (most commonly pneumonitis, hyperthyroidism, and rash in 3% of patients each) occurred in 21 (18%) of 120 patients in the pembrolizumab group (table 3). The minimum median time to onset of any immune-mediated adverse event in patients who received pembrolizumab was 10 days (severe skin reaction), with an IQR of 14–65 across all immune-mediated adverse events. 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%) of 120 patients in the pembrolizumab group versus ten (8%) of 121 patients in the pomalidomide and dexamethasone group. The most common (occurring in at least two patients in either group) were death (three [3%] *vs* 0), pneumonia (two [2%] *vs* one [1%]), neutropenic sepsis (two [2%] *vs* 0), cerebrovascular accident (two [2%]

vs one [1%]), and dyspnoea (two [2%] *vs* 0). Of these, the cases of neutropenic sepsis, pneumonia, and cerebrovascular accident were considered by the investigator to be related to treatment. Treatment-related adverse events resulted in treatment discontinuation in 18 (15%) patients in the pembrolizumab group and five (4%) patients in the pomalidomide and dexamethasone group; adverse events resulting in treatment interruption occurred in 72 (60%) and 60 (50%) patients.

As of June 2, 2017, 50 patients had died: 29 (23%) of 125 in the pembrolizumab group (16 from progressive disease and 13 from adverse events) versus 21 (17%) of 124 in the pomalidomide and dexamethasone group (18 from progressive disease and three from adverse events). Four (3%) of 120 patients died as a result of treatment-related adverse events in the pembrolizumab group (one each of unknown cause, neutropenic sepsis, myocarditis, and Stevens–Johnson syndrome; table 4). Deaths from myocarditis and Stevens–Johnson syndrome were attributed to pembrolizumab by the investigator. Three non-treatment-related deaths occurred in the pomalidomide and dexamethasone group (one each of unknown cause, anaemia, and pneumonia; table 4). A review of disease characteristics among patients who died showed that more patients in the pembrolizumab group than the pomalidomide and dexamethasone group had International Staging System stage III disease (15 [52%] of 29 in the pembrolizumab group *vs* four [19%] of 21 in the pomalidomide and dexamethasone group), high-risk cytogenetics (ten [34%] *vs* six [29%]), plasmacytoma (seven [24%] *vs* three [14%]), and ECOG performance status of 1 (21 [72%] *vs* 13 [62%]) at baseline (appendix 1 p 8). The HR for death was 1·23 (95% CI 0·57–2·66; p=0·69) when patients with these high-risk disease characteristics were excluded (appendix 1 p 21). After exclusion of patients with high-risk characteristics, of the 13 deaths in the pembrolizumab group, four were from progression and nine were from adverse events (one each of myocardial infarction, cardiac failure, pericardial haemorrhage, and Stevens–Johnson syndrome, three sepsis, and two unknown cause); two of these adverse events (Stevens–Johnson syndrome and unknown cause) were considered by the investigator to be related to pembrolizumab. Of the 13 deaths in the pomalidomide and dexamethasone group after exclusion of patients with high-risk characteristics, 12 were from progression and one was from an adverse event (unknown death).

After study termination, a post-hoc analysis was done to identify potential factors associated with the imbalance in the number of deaths between the two treatment groups. Factors associated with being prognostic or predictive of death were first assessed by retrospective random forest analysis. A multivariable Cox regression analysis was subsequently done to calculate differences between groups with factors associated with risk for death identified from the random forest analysis. Age, ECOG performance status, disease stage, presence of plasmacytoma, and double-refractory status were more relevant contributors to death than treatment (appendix 1 p 22). 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. An ECOG performance status of 0 was associated with reduced risk for death (HR 0·86; 95% Wald confidence limits 0·32–2·29), whereas ECOG performance status 1 was associated with increased risk for death (HR 2·3; 95% Wald confidence limits 1·11–4·76). The clinical course of patients who died from adverse events in the pembrolizumab group is summarised in appendix 1 (pp 9–18).

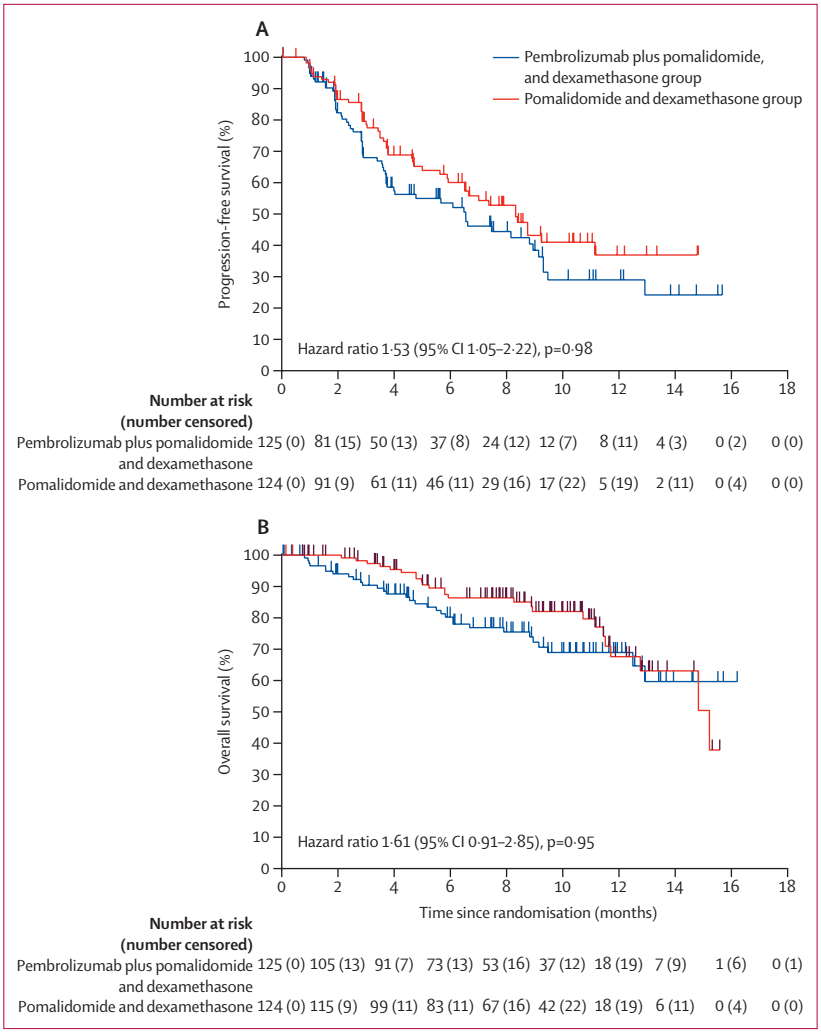

Figure 2: **Progression-free survival by investigator assessment (A) and overall survival (B), in the intention-to-treat population**

Discussion

In this non-protocol-specified interim analysis of KEYNOTE-183, after a median follow-up of 8·1 months (IQR 4·5–10·9), an increased risk for death was observed

	Pembrolizumab plus pomalidomide and dexamethasone group (n=120)				Pomalidomide and dexamethasone group (n=121)			
	Any	Grades 1–2	Grade 3	Grade 4	Any	Grades 1–2	Grade 3	Grade 4
Any	119 (99%)	19 (16%)	58 (48%)	32 (27%)	116 (96%)	37 (31%)	54 (45%)	23 (19%)
Neutropenia*	46 (38%)	5 (4%)	24 (20%)	17 (14%)	33 (27%)	7 (6%)	18 (15%)	8 (7%)
Anaemia*	34 (28%)	14 (12%)	20 (17%)	0	43 (36%)	27 (22%)	13 (11%)	3 (2%)
Fatigue*	29 (24%)	29 (24%)	0	0	36 (30%)	26 (21%)	9 (7%)	1 (1%)
Constipation	27 (23%)	26 (22%)	1 (1%)	0	24 (20%)	24 (20%)	0	0
Pyrexia	27 (23%)	26 (22%)	1 (1%)	0	23 (19%)	19 (16%)	1 (1%)	3 (2%)
Pneumonia*	28 (23%)	12 (10%)	15 (13%)	1 (1%)	18 (15%)	2 (2%)	14 (12%)	1 (1%)
Thrombocytopenia*	25 (21%)	11 (9%)	8 (7%)	6 (5%)	20 (17%)	12 (10%)	6 (5%)	2 (2%)
Diarrhoea	21 (18%)	19 (16%)	2 (2%)	0	21 (17%)	19 (16%)	2 (2%)	0
Upper respiratory tract infection	21 (18%)	17 (14%)	2 (2%)	1 (1%)	21 (17%)	19 (16%)	2 (2%)	0
Dyspnoea	21 (18%)	20 (17%)	1 (1%)	0	18 (15%)	15 (12%)	2 (2%)	1 (1%)
Nausea*	20 (17%)	20 (17%)	0	0	14 (12%)	13 (11%)	1 (1%)	0
Peripheral oedema	19 (16%)	19 (16%)	0	0	19 (16%)	18 (15%)	1 (1%)	
Cough	18 (15%)	18 (15%)	0	0	18 (15%)	17 (14%)	1 (1%)	0
Neutrophil count decreased	17 (14%)	2 (2%)	9 (8%)	6 (5%)	16 (13%)	5 (4%)	6 (5%)	5 (4%)
Dizziness	15 (13%)	14 (12%)	1 (1%)	0	13 (11%)	13 (11%)	0	0
Headache*	15 (13%)	15 (13%)	0	0	5 (4%)	5 (4%)	0	0
Asthenia	14 (12%)	14 (12%)	0	0	14 (12%)	11 (9%)	3 (2%)	0
Back pain*	13 (11%)	13 (11%)	0	0	20 (17%)	15 (12%)	5 (4%)	0
Alanine aminotransferase increased*	12 (10%)	6 (5%)	6 (5%)	0	3 (2%)	1 (1%)	2 (2%)	0
White blood cell count decreased	12 (10%)	4 (3%)	8 (7%)	0	10 (8%)	6 (5%)	3 (2%)	1 (1%)
Muscle spasms	12 (10%)	12 (10%)	0	0	12 (10%)	12 (10%)	0	0

Data are n (%). 13 grade 5 events occurred in the pembrolizumab plus pomalidomide and dexamethasone group (three unknown cause and three sepsis and one each of cardiac failure, myocardial infarction, myocarditis, pericardial hemorrhage, neutropenic sepsis, respiratory tract infection, and Stephens–Johnson syndrome) and three occurred in the lenalidomide and dexamethasone group (one each of unknown cause, anaemia, and pneumonia). *Any-grade or grade 3 or 4 (combined) adverse events with at least 5% difference between treatment groups.

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

	Any	Grades 1–2	Grades 3–4
Any event	21 (18%)	11 (9%)	10 (8%)
Pneumonitis	4 (3%)	3 (3%)	1 (1%)
Hyperthyroidism	3 (3%)	3 (3%)	0
Rash	3 (3%)	0	3 (3%)
Hypothyroidism	2 (2%)	2 (2%)	0
Myopathy	2 (2%)	0	2 (2%)
Myocarditis	1 (1%)	0	0
Iridocyclitis	1 (1%)	1 (1%)	0
Hepatitis	1 (1%)	0	1 (1%)
Anaphylaxis	1 (1%)	1 (1%)	0
Infusion-related reactions	1 (1%)	1 (1%)	0
Exfoliative dermatitis	1 (1%)	1 (1%)	0
Psoriasis	1 (1%)	1 (1%)	0
Skin necrosis	1 (1%)	1 (1%)	0
Stevens–Johnson syndrome	1 (1%)	0	0

Data are n (%). Immune-mediated adverse events of clinical interest are presented. Two grade 5 immune-mediated events occurred (myocarditis and Stevens–Johnson syndrome).

Table 3: **Immune-mediated adverse events and infusion reactions with pembrolizumab plus lenalidomide and dexamethasone (n=120) in the safety population**

with pembrolizumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone alone in patients with relapsed or 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 on July 3, 2017.[22] Early study termination resulted in incomplete data collection; at analysis, only 50 (27%) of the 182 protocol-specified events required for analysis of overall survival and 115 (49%) of the 236 required for analysis of progression-free survival had occurred. Treatment exposure was also shortened, with a median of 4·5 treatment cycles (IQR 2·0–8·0) in the pembrolizumab plus pomalidomide and dexamethasone group (37 [31%] of 120 patients had fewer than three cycles) compared with a median of 5·0 treatment cycles (3·0–9·0) in the pomalidomide and dexamethasone group (29 [24%] of 121 had fewer than three cycles). Longer follow-up is necessary to discern efficacy outcomes with immunotherapies given the non-proportional hazards effect that leads to delayed clinical response and late separation of Kaplan-Meier survival curves.[23–25] As such, although the overlapping CIs for 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 study termination.

The acknowledged association between severity of disease and degree of immune system dysfunction[26,27] suggests that PD-1 blockade is safer and more effective in patients with lower burden of disease and less-impaired immune systems. Therefore, the failure of pembrolizumab to improve the outcomes in patients with relapsed or refractory multiple myeloma in our study population might be attributable to the considerable immunodeficiency that exists in these patients.[28]

The incidence of any-grade adverse events was similar between groups, although grade 3 or 4 and serious adverse events occurred more frequently with pembrolizumab plus pomalidomide and dexamethasone than with pomalidomide and dexamethasone. All common, non-severe adverse events were manageable and no specific type led to treatment discontinuation. The most common immune-mediated adverse events were pneumonitis, hyperthyroidism, and rash (each in 3% of patients) in the pembrolizumab plus pomalidomide and dexamethasone group. Two grade 5 immune-mediated adverse events of myocarditis and Stevens–Johnson syndrome occurred, events expected per the label for pembrolizumab that were attributed to this drug.[29] Overall, the type and incidence of immune-mediated adverse events in the pembrolizumab plus pomalidomide and dexamethasone group were consistent with those reported previously for pembrolizumab[11–14] and those observed in KEYNOTE-185.[30]

More deaths occurred in the pembrolizumab plus pomalidomide and dexamethasone group than in the pomalidomide and dexamethasone group. However, the numbers of patients who discontinued or died from disease progression were similar between groups, suggesting that the risk for progression was similar, implying that progression-free survival in the pembrolizumab plus pomalidomide and dexamethasone group could have been influenced by the imbalance in the number of deaths, two of which were pembrolizumab related. Similarly, in the KEYNOTE-185 study[30] of patients with newly diagnosed multiple myeloma, more deaths occurred in the pembrolizumab plus lenalidomide and dexamethasone group (19 [13%] of 149) than in the lenalidomide and dexamethasone group (nine [6%] of 145).

The frequency of high-risk features at baseline among patients who died prematurely was higher in the pembrolizumab plus pomalidomide and dexamethasone group than in the pomalidomide and dexamethasone group, despite the safeguard of randomisation. Disease characteristics were generally not balanced between the treatment groups in this study, probably because patient enrolment was still ongoing at the time of early study termination and the unplanned ad-hoc nature of the analysis. Specifically, among the patients who died early during the study, a greater proportion of those in the pembrolizumab plus pomalidomide and dexamethasone group than in the pomalidomide and dexamethasone group had stage III disease, high-risk cytogenetics, or extramedullary plasmacytoma (three [43%] of seven *vs* one [33%] of three), factors typically associated with poorer prognosis; this imbalance might account for the difference in early death that led to early termination of KEYNOTE-183. Moreover, when adverse-event-related death was assessed between the two treatment groups, after removal of patients with these high-risk characteristics, there was no significant difference in numbers of deaths between groups. A multivariable analysis to identify factors associated with risk for death indicated that only ECOG performance status 1 was both predictive and prognostic of risk for death. This might indicate that the performance status assessment of patients at study entry was underestimated, considering patients with ECOG performance status of 2 are usually included in multiple myeloma clinical studies but were not (per exclusion criteria) in this study. Together, these analyses suggest that the imbalance in the number of deaths is not only related to treatment (two deaths were pembrolizumab related) but also to non-treatment-related adverse events.

This study was limited by the ad-hoc unplanned nature of the analysis. The trial was terminated during the enrolment period. Early termination also probably affected results of this unplanned analysis because of the absence of longer-term follow-up efficacy data. The findings of this study are not generalisable to other indications; it is not possible to establish whether the problems encountered in the patients who received pembrolizumab in combination with standard-of-care therapy would be observed in other indications.

Our findings are disappointing given the positive outcomes reported in the previous phase 2 study of

	Pembrolizumab plus pomalidomide and dexamethasone group (n=120)	Pomalidomide and dexamethasone group (n=121)
Any	13 (11%)	3 (2%)
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

Data are n (%). *Treatment related in one patient. †Attributed to pembrolizumab by investigator. ‡Death and sudden death were combined as unknown-cause adverse events.

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

pembrolizumab plus pomalidomide and dexamethasone in patients with relapsed or refractory multiple myeloma.[17] In the previous trial, the combination was well tolerated and showed encouraging antimyeloma activity, with a response achieved by 29 (60%) of 48 patients and median progression-free survival of 17·4 months (95% CI 11·7–18·8);[17] median follow-up was longer than in our study.

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

Contributors

M-VM, JSM, UK, and PM contributed to study design or planning. HB, IA, NB, SZU, SJ, JSM, UK, JL MF, PM, and SL contributed to data analysis. FS, AO, DSi, AG, HG, AL, AC-K, DSh, IA, NB, SI, MM, KS, VR, EMO, PR-O, JSM, UK, MF, and PM contributed to acquisition of data. M-VM, HB, FS, AO, DSi, HG, AC-K, DSh, IA, SI, MM, VR, SZU, SJ, EMO, JSM, UK, MF, PM, and SL contributed to interpretation of the results. M-VM, HB, AO, KS, JSM, and PM contributed to drafting the manuscript. M-VM, FS, AO, DSi, AG, HG, AL, AC-K, DSh, IA, NB, SI, MM, VR, SZU, SJ, EMO, PRO, JSM, UK, MF, JF, PM, and SL contributed to critical review or revision of the article drafts. All authors gave final approval for submission. All authors had access to all the relevant study data and related analyses, vouch for the completeness and accuracy of the data 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.

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

Declaration of interests

M-VM reports receiving consulting fees from Amgen, Celgene, Janssen, and Takeda. HB reports receiving consulting fees from Celgene and Janssen. FS 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. AO reports receiving consulting fees from Amgen, Janssen, and Takeda. DSi reports receiving honoraria from Merck Sharp & Dohme (MSD); honoraria and consulting fees from AbbVie, Celgene, Janssen, and Roche; and research funding from Amgen. AG reports receiving consulting fees and reimbursements from Celgene and Roche. HG 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. AL reports receiving honoraria from Amgen, BMS, Celgene, and Janssen; and has served on advisory boards for BMS, Celgene, Janssen, and Takeda. SI reports receiving honoraria from Takeda, Ono, Janssen, Celgene, BMS, and Novartis; and consulting fees from Takeda, Ono, Janssen, Sanofi, and MSD. VR reports a consulting or advisory role for Infinity Pharmaceuticals, BMS, Gilead Sciences, NanoString Technologies, Incyte, MSD, Roche/Genentech, Epizyme, immune design; research funding from arGEN-X BVBA; patents, royalties, and other intellectual property regarding BAY1000394 studies; expert testimony for Servier; travel, accommodations, and expenses from Roche, BMS, and AstraZeneca; principal investigator or subinvestigator of clinical trials for Abbvie, Agios Pharmaceuticals, Amgen, Argen-X Bvba, Arno Therapeutics, Astex Pharmaceuticals, AstraZeneca, Aveo, Bayer Healthcare, Bbb Technologies, Blueprint Medicines, Boehringer Ingelheim, BMS, Celgene Corporation, Chugai Pharmaceutical, Clovis Oncology, Daiichi Sankyo, Debiopharm, Eisai, Eli Lilly, Exelixis, Forma, Gamamabs, Genentech, GlaxoSmithKline, H3 Biomedicine, Hoffmann La Roche, Innate Pharma, Iris Servier, Janssen Cilag, Kyowa Kirin Pharm Dev, Loxo Oncology, Lytix Biopharma, Medimmune, Menarini Ricerche, MSD Chibret, Merrimack Pharmaceuticals, Merus, Millennium Pharmaceuticals, Nanobiotix, Nektar Therapeutics, Novartis Pharma, Octimet Oncology, Oncoethix, Onyx Therapeutics, Orion Pharma, Oryzon Genomics, Pfizer, Pharma Mar, Pierre Fabre, Roche, Sanofi Aventis, Taiho Pharma, Tesaro, and Xencor; and honoraria from Infinity Pharmaceuticals, BMS, Eisai, PharmaMar, and Gilead. SZU 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. SJ reports receiving honoraria from Celgene and Karyopharm; and consulting fees from Celgene, Janssen, Karyopharm, BMS, and Novartis. EMO 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. PR-O reports receiving consulting fees from Celgene, Janssen, and Takeda; speaker's fees from Celgene, BMS, and Janssen; and research funding from BMS and Celgene. JSM reports receiving consulting fees from Amgen, BMS, Celgene, Janssen, MSD, Novartis, Takeda, Sanofi, and Roche. UK, MF, JL, and PM are employees of and report stock ownership in Merck & Co, (Kenilworth, NJ, USA). SL reports receiving consulting and advisory board fees from Amgen, Celgene, Novartis, BMS, Takeda, MSD, and Janssen; and research support from BMS, Janssen, Takeda, and Celgene. All other authors declare no competing interests.

Data sharing

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

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