Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006)


Summary
Background Interim analyses of the phase 3 KEYNOTE-006 study showed superior overall and progression-free survival of pembrolizumab versus ipilimumab in patients with advanced melanoma. We present the final protocol-specified survival analysis.

Methods In this multicentre, open-label, randomised, phase 3 trial, we recruited patients from 87 academic institutions, hospitals, and cancer centres in 16 countries (Australia, Austria, Belgium, Canada, Chile, Colombia, France, Germany, Israel, Netherlands, New Zealand, Norway, Spain, Sweden, UK, and USA). We randomly assigned participants (1:1:1) to one of two dose regimens of pembrolizumab, or one regimen of ipilimumab, using a centralised, computer-generated allocation schedule. Treatment assignments used blocked randomisation within strata. Eligible patients were at least 18 years old, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, at least one measurable lesion per Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1), unresectable stage III or IV melanoma (excluding ocular melanoma), and up to one previous systemic therapy (excluding anti-CTLA-4, PD-1, or PD-L1 agents). Secondary eligibility criteria are described later. Patients were excluded if they had active brain metastases or active autoimmune disease requiring systemic steroids. The primary outcome was overall survival (defined as the time from randomisation to death from any cause). Response was assessed per RECIST v1.1 by independent central review at week 12, then every 6 weeks up to week 48, and then every 12 weeks thereafter. Survival was assessed every 12 weeks, and final analysis occurred after all patients were followed up for at least 21 months. Primary analysis was done on the intention-to-treat population (all randomly assigned patients) and safety analyses were done in the treated population (all randomly assigned patients who received at least one dose of study treatment). Data cutoff date for this analysis was Dec 3, 2015. This study was registered with ClinicalTrials.gov, number NCT01866319.

Findings Between Sept 18, 2013, and March 3, 2014, 834 patients with advanced melanoma were enrolled and randomly assigned to receive intravenous pembrolizumab every 2 weeks (n=279), intravenous pembrolizumab every 3 weeks (n=277), or intravenous ipilimumab every 3 weeks (ipilimumab for four doses; n=278). One patient in the pembrolizumab 2 week group and 22 patients in the ipilimumab group withdrew consent and did not receive treatment. A total of 811 patients received at least one dose of study treatment. Median follow-up was 22-9 months; 383 patients died. Median overall survival was not reached in either pembrolizumab group and was 14-6 months with ipilimumab (hazard ratio [HR] 0.68, 95% CI 0.53–0.87 for pembrolizumab every 2 weeks vs ipilimumab; p=0.0009 and 0.68, 0.53–0.86 for pembrolizumab every 3 weeks vs ipilimumab; p=0.0008). 24-month overall survival rate was 55% in the 2-week group, 55% in the 3-week group, and 43% in the ipilimumab group.

Interpretation Substantiating the results of the interim analyses of KEYNOTE-006, pembrolizumab continued to provide superior overall survival versus ipilimumab, with no difference between pembrolizumab dosing schedules. These conclusions further support the use of pembrolizumab as a standard of care for advanced melanoma.

Funding Merck & Co.

Introduction The immune system is an effective target in oncology therapy. Checkpoint pathways, including the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) pathway, which downregulates early T-cell function, and the programmed death 1 (PD-1) pathway, which regulates T-cell activity at the effector phase, can be coopted by tumours to elude an immune response.1 Checkpoint inhibitors restore anti-tumour immune responses, and have become a mainstay in cancer therapy. Several checkpoint inhibitors have been extensively studied, including the anti-CTLA-4 monoclonal antibody ipilimumab and anti-PD-1 monoclonal antibodies pembrolizumab and nivolumab, all of which are approved for the treatment of advanced melanoma.2–4 PD-1 inhibitors are typically associated with better outcomes and fewer grade...
Evidence before this study
In August, 2016, we performed an extensive PubMed search for studies of PD-1, PD-L1, and CTLA-4 inhibitors in advanced cancer using the primary search terms of “PD-1 OR PD-L1 OR pembrolizumab OR MK-3475 OR lambrolizumab OR CTLA-4 OR ipilimumab OR nivolumab OR BMS-936558 OR atezolizumab OR MPDL3280A OR durvalumab OR MEDI4736 OR atezolizumab OR MSB0010718C OR BMS-936559.” Congress abstracts from annual oncology meetings were also included. Our search was not limited by date. The final reference list was generated on the basis of relevance to the scope of this paper.

Added value of this study
KEYNOTE-006 is the first head-to-head comparison of pembrolizumab versus ipilimumab for advanced melanoma.

Research in context
3–4 treatment-related adverse events than is ipilimumab.1,6 Additional immune checkpoint inhibitors in development for various solid malignancies, including advanced melanoma, include the anti-programmed death ligand 1 (PD-L1) antibodies atezolizumab, durvalumab, and avelumab.

KEYNOTE-006 was a randomised, phase 3 trial comparing two dosing schedules of pembrolizumab (10 mg/kg every 2 weeks or every 3 weeks) versus ipilimumab (3 mg/kg every 3 weeks for 4 doses) in patients with ipilimumab-naive unresectable or advanced melanoma. Data from two protocol-specified interim analyses suggested that pembrolizumab provides superior progression-free survival and overall survival compared with ipilimumab, with fewer grade 3–5 treatment-related adverse events.6,7 On the basis of these promising results, the US Food and Drug Administration (FDA) expanded the indication of pembrolizumab to provide first-line treatment of patients with advanced melanoma regardless of BRAFV600 status.8 After the second protocol-specified interim analysis, an external data monitoring committee recommended making pembrolizumab available to patients in KEYNOTE-006 whose disease progressed while in the ipilimumab group, and continuing to follow up all patients for overall survival until the planned final analysis of the study. We present the results of the protocol-specified final analysis to assess long-term survival benefit of pembrolizumab compared with ipilimumab.

Methods
Study design
KEYNOTE-006 was a multi-centre, open-label, randomised, controlled, phase 3 study done at 87 academic institutions, cancer centres, and hospitals in 16 countries (Australia, Austria, Belgium, Canada, Chile, Colombia, France, Germany, Israel, Netherlands, New Zealand, Norway, Spain, Sweden, UK, and USA) and compared pembrolizumab with ipilimumab in patients with ipilimumab-naive unresectable or advanced melanoma. The study protocol and all amendments were approved by the institutional review board or independent ethics committee of each participating institution. The trial complied with the Declaration of Helsinki, Good Clinical Practice guidelines, and all local laws and regulations.

Participants
Eligible patients were aged at least 18 years, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, at least one measurable lesion per Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1), unresectable stage III or IV melanoma (excluding melanoacutal melanoma), and up to one previous systemic therapy (excluding anti-CTLA-4, PD-1, or PD-L1 agents). Additional eligibility criteria included known BRAF status (previous treatment with BRAF inhibitor therapy was not required for patients with normal lactate dehydrogenase [LDH] and no clinically significant tumour-related symptoms or evidence of rapidly progressing disease), and provision of a tumour sample for determination of PD-L1 status by immunohistochemistry using the 22C3 anti-PD-L1 antibody (Merck & Co, Kenilworth, NJ, USA) at a central laboratory. Patients were excluded if they had active brain metastases (patients with previously-treated stable brain metastases without evidence of progression by magnetic resonance imaging at least 4 weeks before the first dose of pembrolizumab were permitted) or active autoimmune disease requiring systemic steroids. All patients provided written informed consent.

Randomisation and masking
Patients were randomly assigned to receive pembrolizumab or ipilimumab using a centralised, computer-generated allocation schedule. Following patient consent, an interactive voice/web response system (IVRS/IWRS) assigned a unique screening number to each patient. Randomisation was stratified by ECOG performance status.
status (0 vs 1), line of therapy (first vs second), and PD-L1 status (positive [defined as ≥1% staining in tumour and adjacent immune cells as assessed by immuno-histochemistry using the 22C3 antibody] or negative). Treatment assignments used blocked randomisation within strata.

Procedures
Patients were randomly assigned 1:1:1 to receive intravenous pembrolizumab 10 mg/kg every 2 or 3 weeks or intravenous ipilimumab 3 mg/kg every 3 weeks for four doses (ipilimumab only). Treatment was given for 2 years (pembrolizumab groups only) or until disease progression, intolerable toxicity, complete response, patient withdrawal of consent, or investigator decision to discontinue treatment. Patients achieving complete response per RECIST v1.1, supported by two scans at least 4 weeks apart, and who received pembrolizumab treatment for at least 6 months were permitted to discontinue treatment. Eligible patients who had disease progression were permitted to remain on treatment until progression was substantiated by imaging at least 4 weeks later.

Outcomes
The pre-specified primary endpoint at the final analysis was overall survival (defined as the time from randomisation to death from any cause); secondary analyses included progression-free survival (defined as the time from randomisation to first documented progressive disease [based on blinded independent central review using RECIST v1.1] or death from any cause, whichever occurs first), objective response rate (defined as the proportion of the patients in the analysis population who have best response as complete response or partial response), and duration of response (defined as the time from the first documented response to radiologic progression according to RECIST v1.1). Response was assessed per RECIST v1.1 by independent central review at week 12, then every 6 weeks up to week 48, and then every 12 weeks thereafter; clinical decisions were based on investigator-assessed immune-related response criteria (irRC). Survival was assessed every 12 weeks during the survival follow-up phase. Adverse events were recorded throughout the study and for 30 days thereafter (90 days for serious adverse events), and were graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Pre-specified immune-mediated adverse events (defined as events of unknown cause associated with drug exposure and consistent with an immune event) were recorded throughout the study.

Statistical analyses
There were two planned interim analyses (first interim analysis data cutoff date: Sep 3, 2014; second interim analysis data cutoff date: Mar 3, 2015), the results of which have been reported.4 5 Although crossover was not allowed per protocol, after the second interim analysis, an external data monitoring committee recommended making pembrolizumab available to patients in KEYNOTE-006 whose disease progressed during treatment with ipilimumab, and continuing to follow all patients for overall survival until the planned final analysis of the study, which was to be done after 435 survival events had occurred or after all patients had at least 21 months of follow-up, whichever occurred first. The primary progression-free analysis was planned for the first interim analysis (after 6 months of follow-up and about 260 progression-free survival events); the study had at least 95% power to detect a true hazard ratio (HR) of 0·5 (comparing each pembrolizumab regimen with ipilimumab), testing each of the two comparisons at α of 0·2%, assuming there were 180 progression-free survival events between the pembrolizumab and ipilimumab groups. At the final analysis, the available α for testing overall survival was expected to be between 1·5% and 2·0%; with 1% available for each pembrolizumab regimen compared with ipilimumab, there was 85% power to detect a true HR of 0·70, provided 300 deaths were observed in the comparison. These criteria are based on random assignment of about 645 patients across the three treatment groups. In actuality, 834 patients were randomly assigned.

Overall survival, progression-free survival, and objective response rate analyses were done in the intent-to-treat population (all randomised patients); safety analyses were done in the treated population (all randomised patients who received at least one dose of study treatment).

The Kaplan-Meier method was used to estimate overall and progression-free survival and duration of response. Treatment differences in survival were assessed using the stratified log-rank test with the Hochberg procedure, using a one-sided α of 0·02 as the superiority threshold for overall survival. The Hochberg procedure controlled for multiple testing and for the planned interim analyses; type 1 error rate was strongly controlled at 2·5% (one-sided). The stratified Cox model1 was used to estimate HRs for progression-free and overall survival, comparing each of the pembrolizumab regimens with ipilimumab, and was used to estimate the HRs for overall survival, comparing the pooled pembrolizumab regimens with ipilimumab within pre-specified subsets of patients. The same stratification factors used for randomisation were applied to the stratified log-rank test and the stratified Cox model. Patients for whom death was not documented at the time of final analysis were censored at the last-known alive date. Treatment differences in objective response rate were assessed using the stratified Miettinen and Nurminen method, which was used to calculate the CI for the difference between the proportions. No α was pre-specified at the final analysis for supportive analyses. Adverse events were summarised by 6-week periods across treatment groups. Time-adjusted and exposure-adjusted comparisons of safety events were...
done to adjust for the decreased reporting period for ipilimumab treatment. The cutoff date for the final analysis was Dec 3, 2015. This trial was registered with ClinicalTrials.gov, number NCT01866319.

Role of funding source
The sponsor collaborated jointly with the senior academic authors to design the study and gather, analyse, and interpret the results. The corresponding author had full access to all study data, and all authors had final responsibility for the decision to submit the manuscript for publication.

Results
Between Sep 18, 2013 and Mar 3, 2014, 834 patients with advanced melanoma were enrolled and randomly assigned to receive pembrolizumab every 2 weeks (n=279), pembrolizumab every 3 weeks (n=277), or ipilimumab every 3 weeks for four doses (ipilimumab only; n=278); 811 received treatment (figure 1). Baseline characteristics were well balanced across treatment groups (table 1). Median age was 62 years and 497 (60%) of 834 patients were male; 270 (32%) of 834 patients had elevated LDH; 302 (36%) of 834 had \( \text{BRAF}^{V600/EK} \) mutations; 671 (80%) of 834 patients had PD-L1-positive tumours; and 549 (66%) of 834 patients had not received previous systemic therapy. Median time on therapy was 28·1 weeks (range 0·1–108·1) for pembrolizumab every 2 weeks, 24·0 weeks (0·1–111·1) for pembrolizumab every 3 weeks, and 9·0 weeks (0·1–13·1) for ipilimumab. At final analysis, median follow-up was 22·9 months; per protocol, all patients had been followed up for at least 21 months.

As of the data cutoff date, treatment was ongoing in 52 (19%) of 279 patients who received pembrolizumab every 2 weeks and in 38 (14%) of 277 patients who received pembrolizumab every 3 weeks; 25 (9%) of 279 patients in the 2-week group and 26 (9%) of 277 patients in the 3-week group completed the protocol-specified maximum 2 years of treatment (figure 1). In the ipilimumab group, 155 (56%) of 278 patients received all four doses of treatment. The most common reasons for discontinuation across treatment groups were progressive disease and adverse events (figure 1). After discontinuing study treatment, more patients given ipilimumab (133 [52%] of 256) started new oncologic therapy than those given pembrolizumab (111 [40%] of 278 patients in the 2-week group and 108 [39%] of 277 patients in the 3-week group); these post-study anti-neoplastic therapies most commonly included immunotherapy (24–35%) and BRAF inhibitor or MEK inhibitors (17–29%, appendix). Patients receiving pembrolizumab were more likely to receive an anti-CTLA-4 agent post-study (127 [23%] of 555), whereas those who received ipilimumab most commonly received anti-PD-1 therapy (76 [30%] of 256), including 30 patients who received pembrolizumab.

At the time of data cutoff, 383 patients had died, representing 88% of the target number of events at final analysis (435 deaths). Median overall survival was not...
reached in either pembrolizumab group (range 22·1 months—not reached for the 2-week group and 23·5 months—not reached for the 3-week group) and was 16·0 months (range 13·5–22·0) for ipilimumab; 24-month overall survival rates were 55% in the 2-week group (95% CI 49·1–61·1), 55% in the 3-week group (95% CI 49·1–61·1), and 43% in the ipilimumab group (95% CI 37·4–49·8; figure 2A). Both pembrolizumab groups were superior to the ipilimumab group (HR 0·68; 95% CI 0·53–0·87; p=0·0009 for the 2-week schedule and HR 0·68; 95% CI 0·53–0·87; p=0·0009 for the 3-week schedule vs ipilimumab; figure 2A). There was no difference between the two pembrolizumab schedules (HR 1·01; p=0·93). Additionally, overall survival was superior in the pooled pembrolizumab groups compared with ipilimumab across subgroups, including in those with typically poor prognosis (eg, patients with elevated LDH and baseline tumour size greater than or equal to the median; figure 3).

Overall, 566 progression-free survival events were reported. 364 (65%) of these 556 events occurred in the pooled pembrolizumab groups. Progression-free survival was longer with pembrolizumab than with ipilimumab (HR 0·61; 95% CI 0·50–0·75; p=0·0001 for both pembrolizumab schedules vs ipilimumab). There was no difference in progression-free survival between the two pembrolizumab schedules (HR 0·95; 95% CI 0·77–1·17; p=0·62). Median progression-free survival was 5·6 months (range 3·4–8·2), 4·1 months (range 2·9–7·2), and 2·8 months (range 2·8–2·9) for pembrolizumab every 2 and 3 weeks and ipilimumab, respectively, with the curves showing a definite separation after the week 12 assessment (figure 2B). Additionally, the 24-month progression-free survival rate was 31% in the 2-week group, 28% in the 3-week group, and 14% in the ipilimumab group.

Objective response was reported in 103 (37%) of 279 patients taking pembrolizumab every 2 weeks, 100 (36%) of 277 patients taking pembrolizumab every 3 weeks, and 37 (13%) of 278 patients taking ipilimumab (table 2). Best overall response was complete response (including complete responses) continued to accrue, and pembrolizumab continued to show superiority over ipilimumab (appendix). Responses were ongoing in approximately 129 (64%) of 203 of patients who were no longer alive at the time of analysis.

<table>
<thead>
<tr>
<th>Pembrolizumab every 2 weeks n=279</th>
<th>Pembrolizumab every 3 weeks n=277</th>
<th>Ipilimumab n=278</th>
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<tr>
<td><strong>Age, median (range), years</strong></td>
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<td>63 (22–89)</td>
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<td><strong>Sex</strong></td>
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<tr>
<td>Male</td>
<td>161 (58%)</td>
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<tr>
<td>Female</td>
<td>118 (42%)</td>
<td>103 (37%)</td>
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<td><strong>ECOG performance status</strong></td>
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<tr>
<td>0</td>
<td>196 (70%)</td>
<td>189 (68%)</td>
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<td>1</td>
<td>83 (30%)</td>
<td>88 (32%)</td>
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<td><strong>LDH</strong></td>
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<tr>
<td>Normal</td>
<td>194 (70%)</td>
<td>175 (63%)</td>
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<tr>
<td>Elevated</td>
<td>81 (29%)</td>
<td>98 (35%)</td>
</tr>
<tr>
<td>Missing</td>
<td>4 (1%)</td>
<td>4 (1%)</td>
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<td><strong>BRAF</strong> status</td>
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<tr>
<td>Wild-type</td>
<td>177 (63%)</td>
<td>178 (64%)</td>
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<tr>
<td>Mutant</td>
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<td>97 (35%)</td>
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<tr>
<td>Undetermined</td>
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<td>2 (1%)</td>
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<td><strong>PD-L1 expression</strong></td>
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<tr>
<td>Positive*</td>
<td>225 (81%)</td>
<td>221 (80%)</td>
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<tr>
<td>Negative</td>
<td>49 (18%)</td>
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</tr>
<tr>
<td>Unknown</td>
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<td>2 (1%)</td>
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<td><strong>M staging of the extent of metastasis†</strong></td>
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<tr>
<td>M0</td>
<td>9 (3%)</td>
<td>8 (3%)</td>
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<td>M1</td>
<td>6 (2%)</td>
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</tr>
<tr>
<td>M1a</td>
<td>21 (8%)</td>
<td>35 (13%)</td>
</tr>
<tr>
<td>M1b</td>
<td>64 (23%)</td>
<td>41 (15%)</td>
</tr>
<tr>
<td>M1c</td>
<td>179 (64%)</td>
<td>189 (68%)</td>
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<tr>
<td><strong>Lines of previous therapy</strong></td>
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<td>0</td>
<td>183 (66%)</td>
<td>185 (67%)</td>
</tr>
<tr>
<td>1</td>
<td>96 (34%)</td>
<td>91 (33%)</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>1 (&lt;1%)</td>
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<td><strong>Previous (neo)adjuvant therapy</strong></td>
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<tr>
<td>Previous chemotherapy</td>
<td>42 (15%)</td>
<td>30 (11%)</td>
</tr>
<tr>
<td>Previous interferon</td>
<td>36 (13%)</td>
<td>41 (15%)</td>
</tr>
<tr>
<td>Previous BRAF or MEK inhibitor</td>
<td>50 (18%)</td>
<td>45 (16%)</td>
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<tr>
<td><strong>Previous immunotherapy</strong></td>
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<tr>
<td>Interferon</td>
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<td>2 (&lt;1%)</td>
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<td>Peg-interferon</td>
<td>1 (&lt;1%)</td>
<td>0</td>
</tr>
<tr>
<td>IL-2</td>
<td>1 (&lt;1%)</td>
<td>3 (1%)</td>
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<td><strong>Baseline tumour size, median (range) mm</strong></td>
<td>58.5 (10–390)</td>
<td>63.4 (11–554)</td>
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</tbody>
</table>

**Table 1: Patient characteristics**

Data are n (%) unless otherwise specified. ECOG-Eastern Cooperative Oncology Group performance status; IL-2-interleukin-2; LDH-lactate dehydrogenase; PD-L1-programmed death ligand 1, "Defined as ≥1% staining in tumour and adjacent immune cells as assessed by immunohistochemistry using the 22C3 antibody. M0=no distant metastasis. M1a=metastasis to skin, subcutaneous tissues, or distant lymph nodes. M1b=metastasis to lung. M1c=metastasis to all other visceral sites or distant metastases at any site associated with elevated serum concentrations of LDH.
Figure 2: Kaplan-Meier plots
(A) overall survival; (B) progression-free survival assessed per RECIST v1.1 by independent central review; and (C) duration of response assessed per RECIST v1.1 by independent central review. p values for progression-free survival are nominal because no α was pre-specified at the final analysis. HR=hazard ratio; NR=not reached; Q2W=every 2 weeks; Q3W=every 3 weeks.
responded to pembrolizumab and in 23 (62%) of 37 of those who responded to ipilimumab, with approximately 70% of responses lasting 78 weeks or longer (figure 2C). Median duration of response was not reached in any treatment group.

Of the 834 patients enrolled, one patient in the pembrolizumab 2-week group and 22 patients in the ipilimumab group withdrew consent and did not receive treatment. A total of 811 patients received at least one dose of study treatment and were included in the safety analysis population. Median time on treatment was 197 days for pembrolizumab every 2 weeks (mean 312 days, SD 260), 168 days for pembrolizumab every 3 weeks (292 days, 264), and 63 days for ipilimumab (50 days, 21). After week 12, almost all patients in the ipilimumab group had completed or discontinued active treatment as planned; consequently, the adverse event reporting period for ipilimumab was shorter than that for pembrolizumab. Any-grade treatment-related adverse events occurred in 229 (82%) of 278 patients in the 2-week group, 213 (77%) of 277 patients in the 3-week group, and 190 (74%) of 256 patients in the ipilimumab group (table 3); most of these treatment-related adverse events were grade 1–2. The most common any-grade treatment-related adverse events were fatigue, pruritus, diarrhoea, and rash. Grade 3–5 treatment-related toxicities occurred in 47 (17%) of 278 patients in the 2-week group and 46 (17%) of 277 patients in the 3-week group, compared with 50 (20%) of 256 patients in the ipilimumab group (table 3). Most grade 3–5 treatment-related adverse events occurred in less than 1% of patients, with the exception of colitis, diarrhoea, fatigue, alanine aminotransferase increase, hypokalemia, and pneumonitis. Treatment-related toxicity resulted in treatment discontinuation for 19 (7%) of 278 patients in the 2-week group, 30 (11%) of 277 patients in the 3-week group, and 23 (9%) of 256 patients in the ipilimumab group. Treatment-related adverse events leading to discontinuation that were reported more than once included colitis (three patients) and autoimmune hepatitis (two patients) in the pembrolizumab every 2 weeks group; colitis (four patients), pneumonitis (three patients), hepatitis (two patients), and tubulointerstitial nephritis (two patients) in the pembrolizumab every 3 weeks group; and colitis (nine patients) and diarrhoea (five patients) in the ipilimumab group. One treatment-related death in the pembrolizumab every 2 weeks group was a result of sepsis. Immune-mediated adverse events occurred across treatment groups and most commonly included thyroid disorders (includes hyperthyroidism, hypothyroidism, and thyroiditis) and colitis (appendix). Adverse events were generally managed with supportive care, withholding treatment, or corticosteroid therapy. There were no differences in the overall safety profile between pembrolizumab treatment schedules.

Serious and treatment-related grade 3–4 adverse events occurred more frequently in the ipilimumab group than in the pembrolizumab groups in each 6-week reporting period between start of treatment and week 18 (appendix). From week 13 through week 18 (when most patients in the ipilimumab group had discontinued treatment), a smaller percentage of patients on pembrolizumab had treatment-related serious adverse events (five [2%] of 236 patients in the pembrolizumab 2-week group, one [<1%] of 232 patients in the pembrolizumab 3-week group, and four [3%] of 160 patients in the ipilimumab group) or treatment-related grade 3–4 adverse events (six [3%] of 236 patients in the 2-week group, three [1%] of 232 patients in the 3-week group, and four [3%] of 160 patients in the ipilimumab group; appendix). Across treatment groups,
adverse events were reported most frequently in the first 3 months of treatment when adjusted for exposure, and then decreased in frequency thereafter (appendix); most immune-mediated adverse events occurred within the first 6 months in all treatment groups (appendix). Colitis occurred more frequently in the ipilimumab group, whereas hepatitis and endocrinopathies occurred more frequently in the pembrolizumab group (appendix). 38 (19%) of 202 patients given pembrolizumab for at least 1 year had grade 3–4 treatment-related adverse events, nine (4%) of these 202 patients discontinued pembrolizumab because of a treatment-related adverse event, and none died of treatment-related toxicity.

### Discussion

KEYNOTE-006 is the first head-to-head comparison of pembrolizumab versus ipilimumab for advanced melanoma. Results of the protocol-specified first and second interim analyses showed that pembrolizumab provided superior progression-free and overall survival, respectively, compared with ipilimumab, with fewer grade 3–4 treatment-related adverse events. The results of this protocol-specified final analysis substantiate the survival advantage for pembrolizumab compared with ipilimumab. The final analysis showed that pembrolizumab treatment resulted in twice the percentage of patients alive and without disease progression compared with ipilimumab (24-month progression-free survival rates of 31% in the pembrolizumab every 2 weeks group, 28% for the pembrolizumab every 3 weeks group, and 8% for the ipilimumab group).

Compared with earlier published results, pembrolizumab continued to provide a greater reduction in risk for death than ipilimumab, with 24-month survival rates approximately 12% higher with pembrolizumab than with ipilimumab. Overall survival for ipilimumab in KEYNOTE-006 is substantially longer than previously reported in other phase 3 studies, probably because more than half the patients in the ipilimumab group of this study received a subsequent efficacious anticancer therapy, including 76 (30%) of 256 patients who received anti-PD-1 therapy after discontinuation of ipilimumab (appendix). Despite this, we observed a significant improvement in survival with pembrolizumab. Importantly, however, it is difficult to draw strict comparisons about longer term survival with ipilimumab between previously published data and the KEYNOTE-006 study.

Response rates at the final analysis, which were consistent with the previously published interim data, remain substantially higher with either pembrolizumab schedule than with ipilimumab, with an approximately three times higher improvement in objective response rate. Most responses were durable and ongoing at the time of data cutoff, regardless of treatment group. Long-term benefit with ipilimumab, including durable responses lasting more than 8 years and survival of up to 10 years, has been reported in patients with advanced melanoma. Here we report durability of response with pembrolizumab and ipilimumab with a 2-year follow-up. Results suggest that the percentage of patients with ongoing response as of the data cutoff date is similar across the three treatment groups.

Our data show that additional objective responses, including complete responses, with pembrolizumab, and to a lesser extent with ipilimumab, can occur after 21 months of follow-up and support the fact that delayed responses or late conversion of partial responses to complete responses are possible with these immunotherapies. Prolonged complete response after pembrolizumab discontinuation was observed in the KEYNOTE-001 study: 59 (97%) of 61 patients maintained response and only two (3%) of 61 patients had progression after 2 years or longer on treatment. As patients continue to have long-term benefits after short duration of treatment, questions regarding the optimal duration of treatment should be further investigated.

The results reported here are similar to those in the phase 3 CheckMate 067 trial in which nivolumab monotherapy provided improved median overall survival (not reached vs 20·0 months), median progression-free survival (6·9 vs 2·9 months), and objective response rate (44 vs 19%) compared with ipilimumab monotherapy in previously untreated patients with advanced melanoma. Differences in eligibility criteria and treatment framework between the two studies might have contributed to the slightly improved responses seen with nivolumab.

In KEYNOTE-006, more patients given ipilimumab than pembrolizumab went on to receive post-study anti-neoplastic therapy, including anti-PD-1 therapy. The tolerability profile of pembrolizumab makes it a promising candidate for combination therapy, which has the potential to further improve outcomes for patients.
with advanced melanoma. In the phase 1 KEYNOTE-029 study of standard-dose pembrolizumab with low-dose ipilimumab, combination therapy provided higher objective response rates and improved survival than those historically reported with either therapy alone, but also led to higher rates of toxicity. As a result, we assessed two additional ipilimumab dosing regimens with standard-dose pembrolizumab. Similarly, the combination of low-dose nivolumab with standard-dose ipilimumab led to higher objective response rates and longer progression-free survival than either therapy alone, but at the expense of higher grade toxicity; as shown by the data that have been reported, the overall survival benefit with the combination was encouraging but not statistically significant. Results from phase 1 and phase 2 studies of pembrolizumab in combination with the indoleamine 2,3-dioxygenase 1 inhibitor epacadostat, or the oncolytic virus talimogene laherparevc, reported an acceptable safety profile and high objective response rates in patients with melanoma; phase 3 trials of these combinations in melanoma are underway.

Although first-line therapy with anti-PD-1 antibodies has shown superiorit to ipilimumab, and combination therapy with anti-PD-1 and anti-CTLA-4 antibodies appears to improve anti-tumour efficacy, optimal sequencing of these agents has not been established. Arguments exist for first line use of BRAF inhibitors because of the rapid responses often observed with these agents, whereas other studies support use of immunotherapy as front line treatment since these agents typically result in more durable anti-tumour responses and might have reduced benefit following targeted therapy. Retrospective studies suggest that patients might benefit regardless of the treatment sequence. Of note, a considerable percentage of patients in this study (71 [26%] of 278 patients in the pembrolizumab every 2 weeks group, 48 [17%] of 277 patients in the pembrolizumab every 3 weeks group, and 74 [29%] of 256 patients in the ipilimumab group) received BRAF or MEK targeted therapy following checkpoint inhibitor therapy. Although no additional data are available, analysis of the clinical activity in this subset of patients would be of interest for sequencing discussions. Clearly, the optimal sequencing strategy remains to be elucidated. Questions also remain as to the effect that LDH and other potential prognostic factors might have on sequencing strategy, and appropriate biomarkers to select for those patients most likely to respond to anti-PD-1 therapy.

In KEYNOTE-006, the prevalence of adverse events and rate of discontinuation for patients receiving pembrolizumab for more than 1 year were similar to those in the overall population, showing that tolerability of pembrolizumab is maintained over time. Additionally, despite a three times longer duration of exposure, pembrolizumab continued to provide a favourable safety profile compared with ipilimumab. As expected from the mechanisms of action of pembrolizumab and ipilimumab, immune-mediated events occurred across treatment groups. As has been previously reported, frequency and type of adverse events differed between pembrolizumab and ipilimumab, owing to their unique targets. Notably, and in line with previous findings, colitis was more frequently reported with use of ipilimumab, whereas thyroid disorders were more prevalent with use of pembrolizumab. The number of pembrolizumab and ipilimumab exposure-adjusted adverse events decreased with time, although the decrease was more pronounced in the ipilimumab group, probably because treatment was completed (after four doses) much earlier in the study. Although it is difficult to directly compare the safety profiles because of the difference in reporting periods across the three groups, the average frequency of grade 3-4, serious, and immune-mediated adverse events leading to discontinuation was slightly higher for patients given ipilimumab than those on either pembrolizumab schedule. No new safety signals or increase in adverse event frequency was seen with longer duration of pembrolizumab therapy.

In conclusion, results of the final analysis from KEYNOTE-006 show that after close to a median of 2 years follow-up, pembrolizumab continues to show a clear and significant superiority compared with ipilimumab for patients with advanced melanoma, and further support the use of pembrolizumab as a standard of care in this patient population.

Contributors
The study was conceived, designed, or planned by JS, AD, HZ, SE, and CR. Acquisition of the data was done by JS, GVL, AA, JG, LM, AD, MSC, CMcN, ML, JL, PL, BN, CB, OH, HZ, and NI. Data analysis was done by JS, AR, GVL, AD, MI, JL, OH, HZ, SE, NI, and CR. Interpretation of the results was done by JS, AR, GVL, AA, JG, LM, AD, MSC, ML, JL, PL, BN, TMP, OH, HZ, SE, NI, and CR. The manuscript was drafted by GVL, SE, and NI. All authors critically reviewed iterations of the manuscript and approved the final draft for submission.

Declaration of interests
JS reports personal fees for advisory board participation and presentations from Merck Sharp & Dohme Corp (a subsidiary of Merck & Co), and Bristol-Myers Squibb outside the submitted work. AR reports grants and honoraria to his institution from Merck & Co outside the submitted work. GVL reports consulting fees from Bristol-Myers Squibb, Amgen, Novartis, Roche, Pierre-Fabre, Array, and Merck Sharp & Dohme Corp, outside the submitted work. AA reports grant support from Merck & Co in support of the submitted work; personal fees from Novartis, Roche, and Bristol-Myers Squibb outside the submitted work; academic board participation from Bristol-Myers Squibb outside the submitted work; and non-financial support from Roche outside the submitted work. LM reports study support from Merck & Co in support of the submitted work. MB reports personal fees for advisory board participation from Merck Sharp & Dohme Corp, Bristol-Myers Squibb, Roche, Novartis, Amgen, Pierre-Fabre, and Merck & Co outside the submitted work; and grant support from Bristol-Myers Squibb outside the submitted work. LM reports study support from Merck & Co in support of the submitted work. MSC reports personal fees for advisory board participation from Merck Sharp & Dohme Corp, Bristol-Myers Squibb, Novartis, and Amgen outside the submitted work. CMcN reports fees for her staff for travel to scientific meetings from Merck Sharp & Dohme Corp, and Bristol-Myers Squibb outside the submitted work; advisory board participation from Bristol-Myers Squibb, Merck Sharp & Dohme Corp, and Roche to her institution outside the submitted work; fees for her institution for presentations from Bristol-Myers Squibb, Merck Sharp & Dohme Corp, Novartis, and Roche outside the submitted work; and grants to her institution from Merck Sharp & Dohme Corp outside the submitted work. PL reports personal fees for advisory board participation, speaker’s bureau, and travel support from Merck Sharp & Dohme Corp outside the submitted work. BN reports personal fees for advisory board participation and public
speaking from Merck Sharp & Dohme Corp outside the submitted work. CB reports personal fees to his institution from Merck Sharp & Dohme Corp, Bristol-Myers Squibb, Roche, Novartis, Lilly, Pfizer, and GlaxoSmithKline outside the submitted work; and grants to his institution from Novartis outside the submitted work. TMP reports grant support and honoraria for advisory board participation from Merck & Co in support of the submitted work; honoraria from Bristol-Myers Squibb, Novartis, and Roche outside the submitted work; and grants from Roche and Bristol-Myers Squibb outside the submitted work. OH reports consulting fees from Amgen, Novartis, Roche, Bristol-Myers Squibb, and Merck & Co outside the submitted work; speaker fees from Bristol-Myers Squibb, Genentech, Novartis, and Amgen outside the submitted work; and contracted research for AstraZeneca, Bristol-Myers Squibb, Celldex, Genentech, Immunocore, Incyte, Merck & Co, Merck Serono, MedImmune, Novartis, Pfizer, Rinat, and Roche outside the submitted work. HZ was an employee of Merck Sharp & Dohme Corp at the time of the study. SE is an employee of Merck Sharp & Dohme Corp and holds stock in the company. NL is an employee of Merck Sharp & Dohme Corp, and holds stock in Merck Sharp & Dohme Corp, and GlaxoSmithKline. CR reports personal fees for advisory board participation from Bristol-Myers Squibb, GlaxoSmithKline, Novartis, Amgen, Merck Sharp & Dohme Corp, and Roche outside the submitted work. AD, ML, and J.R. report no competing interests.

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