Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study

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Summary

Background Pembrolizumab improved progression-free survival and overall survival versus ipilimumab in patients with advanced melanoma and is now a standard of care in the first-line setting. However, the optimal duration of anti-PD-1 administration is unknown. We present results from 5 years of follow-up of patients in KEYNOTE-006.

Methods KEYNOTE-006 was an open-label, multicentre, randomised, controlled, phase 3 study done at 87 academic institutions, hospitals, and cancer centres in 16 countries. Patients aged at least 18 years with Eastern Cooperative Oncology Group performance status of 0 or 1, ipilimumab-naive histologically confirmed advanced melanoma with known *BRAF*^{V600} status and up to one previous systemic therapy were randomly assigned (1:1:1) to intravenous pembrolizumab 10 mg/kg every 2 weeks or every 3 weeks or four doses of intravenous ipilimumab 3 mg/kg every 3 weeks. Treatments were assigned using a centralised, computer-generated allocation schedule with blocked randomisation within strata. Exploratory combination of data from the two pembrolizumab dosing regimen groups was not protocol-specified. Pembrolizumab treatment continued for up to 24 months. Eligible patients who discontinued pembrolizumab with stable disease or better after receiving at least 24 months of pembrolizumab or discontinued with complete response after at least 6 months of pembrolizumab and then progressed could receive an additional 17 cycles of pembrolizumab. Co-primary endpoints were overall survival and progression-free survival. Efficacy was analysed in all randomly assigned patients, and safety was analysed in all randomly assigned patients who received at least one dose of study treatment. Exploratory assessment of efficacy and safety at 5 years' follow-up was not specified in the protocol. Data cutoff for this analysis was Dec 3, 2018. Recruitment is closed; the study is ongoing. This study is registered with ClinicalTrials.gov, number NCT01866319.

Findings Between Sept 18, 2013, and March 3, 2014, 834 patients were enrolled and randomly assigned to receive pembrolizumab (every 2 weeks, n=279; every 3 weeks, n=277), or ipilimumab (n=278). After a median follow-up of 57·7 months (IQR 56·7–59·2) in surviving patients, median overall survival was 32·7 months (95% CI 24·5–41·6) in the combined pembrolizumab groups and 15·9 months (13·3–22·0) in the ipilimumab group (hazard ratio [HR] 0·73, 95% CI 0·61–0·88, p=0·00049). Median progression-free survival was 8·4 months (95% CI 6·6–11·3) in the combined pembrolizumab groups versus 3·4 months (2·9–4·2) in the ipilimumab group (HR 0·57, 95% CI 0·48–0·67, p<0·0001). Grade 3–4 treatment-related adverse events occurred in 96 (17%) of 555 patients in the combined pembrolizumab groups and in 50 (20%) of 256 patients in the ipilimumab group; the most common of these events were colitis (11 [2%] *vs* 16 [6%]), diarrhoea (ten [2%] *vs* seven [3%]), and fatigue (four [<1%] *vs* three [1%]). Any-grade serious treatment-related adverse events occurred in 75 (14%) patients in the combined pembrolizumab groups and in 45 (18%) patients in the ipilimumab group. One patient assigned to pembrolizumab died from treatment-related sepsis.

Interpretation Pembrolizumab continued to show superiority over ipilimumab after almost 5 years of follow-up. These results provide further support for use of pembrolizumab in patients with advanced melanoma.

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Introduction

Historically, advanced melanoma had a poor prognosis, with 5-year survival of less than 10% before the era of targeted therapy and immunotherapy.[1] Approved treatment options for advanced melanoma have improved survival and include BRAF or MEK inhibitors, or both, for patients with *BRAF*^{V600}-mutant disease, and immunotherapy with checkpoint inhibitors directed against cytotoxic T-lymphocyte-associated antigen 4 (CTLA4; ipilimumab) and PD-1 (pembrolizumab and nivolumab) for patients irrespective of their *BRAF* mutation status.[1]

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Research in context

Evidence before this study

Immunotherapy using the PD-1 inhibitors pembrolizumab and nivolumab and the cytotoxic T-lymphocyte-associated antigen-4 inhibitor ipilimumab has improved survival in patients with advanced melanoma. For reports of clinical trials involving checkpoint inhibitors with long-term follow-up of patients with advanced melanoma, we searched PubMed on Feb 5, 2019, for papers published since database inception using the search terms "nivolumab AND melanoma", "pembrolizumab AND melanoma", and "ipilimumab AND melanoma", without any language restrictions. We narrowed the search results to include reports of prospective trials in advanced melanoma with overall survival as a study endpoint. We found a phase 3 study of ipilimumab plus dacarbazine versus placebo plus dacarbazine showing 5-year overall survival of 18·2% and 8·8%, respectively. A report of the 4-year follow-up of the CheckMate 067 trial showed 4-year overall survival of 53% for nivolumab plus ipilimumab, 46% for nivolumab alone, and 30% for ipilimumab alone, respectively. We did not find any reports of 5 years of follow-up in a randomised controlled trial of nivolumab or pembrolizumab in advanced melanoma. We also searched PubMed for reports of second-course treatment or re-treatment in patients with advanced melanoma using the search terms "nivolumab AND re-treatment AND melanoma", but we found no articles presenting results from randomised controlled trials of patients re-treated with nivolumab. We found a pooled analysis of six trials with different patient populations (previously treated or treatment naive) and doses of ipilimumab (3–20 mg/kg), which limited interpretation of results. The proportion of patients with an overall response was 23%. Grade 3–4 immune-related adverse events occurred in 5·9–25·0% of re-treated patients, depending on ipilimumab dose.

Added value of this study

This report of 5 years' follow-up of KEYNOTE-006 is, to our knowledge, the longest follow-up to date in a randomised phase 3 trial of pembrolizumab in patients with advanced cancer. Pembrolizumab continued to show superiority over ipilimumab, irrespective of line of therapy, *BRAF*^{V600} status, or exposure to previous BRAF or MEK inhibitors for those patients with *BRAF*^{V600E}-mutant or *BRAF*^{V600K}-mutant disease. We present outcomes in patients who completed 2 years of pembrolizumab treatment. Additionally, we present an exploratory analysis of best overall response in patients treated with a second course of pembrolizumab.

Implications of all the available evidence

Our results show that median overall survival in patients treated with pembrolizumab versus ipilimumab continued to show superiority in the overall population after almost 5 years of follow-up. Pembrolizumab conferred sustained disease control over a long period, whereby 78% of patients who completed 2 years of pembrolizumab treatment with at least stable disease remained progression free 24 months after pembrolizumab completion. The safety profile of pembrolizumab remained consistent with previous reports. Preliminary findings suggest that re-treatment with pembrolizumab after disease progression can provide additional antitumour activity and second-course pembrolizumab was generally well tolerated.

In an initial study with ipilimumab, 15 (11%) of 137 patients with metastatic melanoma achieved an objective response, and median overall survival was 10·1 months (95% CI 8·0–13·8).[2] First-line nivolumab led to an objective response in 43% or 45% of patients with advanced melanoma[3,4] and in 27% after progression on ipilimumab.[5] Median overall survival was 36·9 months (95% CI 28·3–not reached) or 37·5 months (25·5–not reached) with first-line nivolumab, with 3-year survival and 4-year survival of 51% and 46%, respectively.[3,4] In patients with advanced melanoma, median overall survival with second-line nivolumab was 15·7 months (95% CI 12·9–19·9).[5] In the phase 1b KEYNOTE-001 trial of pembrolizumab in patients with advanced melanoma, 194 (33%) of 581 patients in the overall population and 60 (45%) of 133 treatment-naive patients achieved an objective response, and median overall survival was 23 months (95% CI 20–29) and 31 months (24–not reached), respectively.[6] 5-year overall survival in the overall population was 34%.[7] Despite the substantial progress brought by these therapies on overall survival, long-term survival rates are unknown, as are outcomes after treatment discontinuation.

In the protocol-specified final analysis of the phase 3 KEYNOTE-006 study in advanced melanoma, median overall survival was not reached with pembrolizumab 10 mg/kg every 2 weeks or every 3 weeks and was 16·0 months (95% CI 13·5–22·0) with ipilimumab after a median follow-up of 22·9 months.[8] Median progression-free survival was 5·6 months (95% CI 3·4–8·2) for pembrolizumab every 2 weeks and 4·1 months (2·9–7·2) for pembrolizumab every 3 weeks, compared with 2·8 months (2·8–2·9) for ipilimumab. The proportion of patients who achieved an objective response was also improved with pembrolizumab every 2 weeks or every 3 weeks, compared with ipilimumab (33·7% and 32·9% *vs* 11·9%).[9] Pembrolizumab was associated with a lower frequency of grade 3–5 treatment-related adverse events compared with ipilimumab. Both efficacy and safety were similar between the pembrolizumab dose regimens.[8,9] On the basis of these results, pembrolizumab is now considered a standard of care for advanced melanoma.[1] Health-related quality of life was also better maintained with pembrolizumab than with ipilimumab in patients with advanced melanoma in KEYNOTE-006.[10]

We report outcomes from KEYNOTE-006 after long-term follow-up of almost 5 years, including outcomes by line of therapy, *BRAF*^{V600} status, and previous treatment with BRAF or MEK inhibitors. Outcomes are also presented for patients who completed 2 years of pembrolizumab treatment and for those who had progression after completion of protocol-specified treatment and received second-course pembrolizumab.

Methods

Study design and participants

KEYNOTE-006 was an open-label, multicentre, randomised, controlled, phase 3 study done at 87 academic institutions, hospitals, and cancer centres in 16 countries that compared pembrolizumab with ipilimumab in ipilimumab-naive patients with histologically confirmed unresectable stage III or IV melanoma. The study protocol is available in the appendix (pp 26–167), and the methods have been published previously.[8,9] Eligible patients were aged 18 years or older, with an Eastern Cooperative Oncology Group performance status of 0 or 1, and had received up to one previous systemic therapy for advanced disease with known *BRAF*^{V600} status (see appendix p 1 for additional eligibility criteria).

The study protocol was approved by the appropriate institutional review board or independent ethics committee at each participating institution. The study was done in accordance with the protocol, Good Clinical Practice guidelines, the provisions of the Declaration of Helsinki, and all local regulations. All patients provided written, informed consent.

Randomisation and masking

As previously described,[8,9] patients were randomly assigned (1:1:1) to one of two dose regimens of pembrolizumab, or one regimen of ipilimumab, using a centralised, computer-generated allocation schedule with blocked randomisation within strata (see appendix p 2 for further details). All group assignment was open label and neither investigators nor patients were masked to allocation.

Procedures

Patients were randomly assigned to receive intravenous pembrolizumab 10 mg/kg every 2 weeks, pembrolizumab 10 mg/kg every 3 weeks, or four doses of intravenous ipilimumab 3 mg/kg every 3 weeks, as described previously.[9] Dose reduction of pembrolizumab was not allowed; dose interruptions were allowed for up to 12 weeks for the management of immune-mediated adverse events (appendix pp 1, 3). Treatment was given for 24 months (pembrolizumab groups only) or until disease progression, intolerable toxicity, or patient or physician decision to discontinue treatment. Patients with a confirmed complete response who received pembrolizumab for at least 6 months could discontinue therapy if they received two or more doses beyond the determination of complete response. Patients could withdraw at any time or be discontinued from the study at the discretion of the investigator with occurrence of untoward effects. Additionally, patient withdrawal at the discretion of the investigator or sponsor was allowed for violation of the study plan or for administrative or safety reasons. Per protocol, patients could interrupt pembrolizumab for up to 12 weeks before discontinuation was required. On the basis of these parameters, patients who completed 2 years (a cutoff of ≥94 weeks was used for this analysis to account for treatment interruptions or holds; this cut-off was decided post-hoc) of pembrolizumab treatment and had at least stable disease were considered to have completed the protocol-specified time on pembrolizumab; patients who had progressive disease within 1 month of the end of pembrolizumab treatment were excluded.

A second course (≤1 year) of pembrolizumab (see eligibility criteria in appendix pp 1–2) was available for patients who achieved stable disease or better with the first course of pembrolizumab and had documented disease progression after stopping therapy. Completion of second-course treatment was defined as receipt of 17 cycles of pembrolizumab. Second-course pembrolizumab was administered at 200 mg every 3 weeks.

See Online for appendix

All protocol-prespecified response assessments were done according to Response Evaluation Criteria in Solid Tumors, version 1.1[11] by blinded independent central review; subsequent analyses reported here were per immune-related response criteria by investigator review. Response (for first and second pembrolizumab courses) was assessed by CT or MRI at baseline, week 12, every 6 weeks until week 48, and then every 12 weeks thereafter. Patients were considered assessable for objective response and progression-free survival if they had measurable disease and at least one follow-up imaging.

Adverse events were collected throughout the study and until 30 days (90 days for serious adverse events) after the last dose of study drug or before the initiation of a new anticancer treatment, whichever occurred first, and were graded per National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Laboratory tests such as complete blood count, serum or plasma chemistry, hepatitis, urinalysis, pregnancy test (at screening and during study when clinically indicated), prothrombin time or activated partial thromboplastin time (at screening, at the safety follow-up visit, and during the study when clinically indicated), and thyroid function were performed at screening and throughout the study (appendix p 1).

Immune-mediated adverse events (prespecified and defined as events of unknown cause associated with exposure to drug and consistent with an immune event) were recorded throughout the study.

Outcomes

Progression-free survival (defined as the time from randomisation to first documented disease progression

based on immune-related response criteria by investigator review or death from any cause) and overall survival (defined as time from randomisation to death from any cause) were co-primary endpoints. Secondary endpoints based on immune-related response criteria by investigator review were the proportion of patients who achieved an objective response, and safety. Duration of response was a prespecified exploratory outcome.

Statistical analysis

In this report, we present post-hoc exploratory analyses (not prespecified in the protocol) of the efficacy and safety of pembrolizumab or ipilimumab in patients with 5 years of follow-up, efficacy of pembrolizumab in patients who received 2 years of treatment, and efficacy and safety of second-course pembrolizumab. These analyses were done to obtain long-term efficacy and safety data and to asses durability of response, progression-free and overall survival, and differences in safety profiles with long-term treatment. No formal statistical power calculations were done for these analyses.

Efficacy was analysed in the intention-to-treat population (all randomly assigned patients) and safety was analysed in all randomly assigned patients who received at least one dose of study treatment. Efficacy and safety data from the two pembrolizumab dosing schedules (10 mg/kg every 2 weeks and every 3 weeks) were combined based on the similar efficacy and safety reported previously;[8,12] however, combination of these data was not prespecified in the protocol. Median progression-free survival and median overall survival of the two pembrolizumab dosing schedules were compared using the stratified log-rank test, and two-sided p values were calculated. Progression-free survival, overall survival, and duration of response were estimated using the Kaplan-Meier method. Data for patients who did not have disease progression or who were lost to follow-up were censored at the time of last tumour assessment for progression-free survival. Overall survival was assessed up to 5 years, whereas progression-free survival was not assessed up to 5 years because imaging was performed per protocol and therefore imaging scans were not available for all patients up to 5 years. Treatment differences for survival were assessed using the stratified log-rank test. Hazard ratios (HRs) and associated 95% CIs were assessed by a stratified Cox proportional hazards model with Efron's method of handling ties. The proportion of patients with an objective response was compared across study groups using the stratified Miettinen and Nurminen method.[13] We also analysed the proportion of patients who achieved disease control (complete response + partial response + stable disease) and analysed progression-free survival, overall survival, and overall response according to patients who received first-line treatment, patients who received second-line treatment, *BRAF* status, BRAF inhibitor treatment, and patients who had completed 2 years of pembrolizumab, which were not prespecified in the protocol. Additionally, we analysed treatment exposure and overall response in patients who progressed after completing the first course of pembrolizumab but were not re-treated with pembrolizumab on study; duration of response and safety were also analysed in patients who received the second course of pembrolizumab. Statistical analyses were done with SAS software (version 9.4). The data cutoff for this analysis was Dec 3, 2018. Recruitment is closed; the study is ongoing. This study is registered with ClinicalTrials.gov, number NCT01866319.

Role of the funding source

The sponsor collaborated with the senior academic authors to design the study and collect, analyse, and interpret the data. The sponsor funded medical writing and editorial assistance for this report. All authors had full access to all the data in the study and had final responsibility for the decision to submit the manuscript for publication.

Results

Between Sept 18, 2013, and March 3, 2014, 834 patients were enrolled at 87 sites in 16 countries (appendix pp 5–7) and were randomly assigned to receive pembrolizumab (n=556) or ipilimumab (n=278; figure 1). Of these, 811 patients received at least one dose of study treatment (figure 1). 368 (66%) patients in the combined pembrolizumab groups and 181 (65%) patients in the ipilimumab group received the study drug as first-line therapy for advanced disease, and 195 (35%) and 107 (38%), respectively, had *BRAF*^{V600E}-mutant or *BRAF*^{V600K}-mutant disease. Previous BRAF or MEK inhibitor therapy was received by 95 (17%) of 556 patients in the combined pembrolizumab groups and 56 (20%) of 278 patients in the ipilimumab group. Baseline characteristics were well balanced across the treatment groups (appendix p 8). Median follow-up of surviving patients was 57·7 months (IQR 56·7–59·2).

Neither median overall survival (31·1 months [95% CI 22·1–45·9] for the 2-week group *vs* 34·2 months [23·5–42·7] for the 3-week group; HR 1·00 [95% CI 0·80–1·25], p=0·99) nor median progression-free survival (8·4 months [5·6–13·7] *vs* 9·7 months [5·8–12·0]; HR 0·99 [95% CI 0·81–1·20], p=0·92) differed between the two pembrolizumab dose groups (appendix p 9). Because of the similar efficacy of the two pembrolizumab dosing schedules observed in the present long-term follow-up and previously in the final analysis,[8] although not prespecified in the protocol, results for the two dosing schedule groups were combined.

At data cutoff for this analysis (Dec 3, 2018), 324 (58%) of 556 patients had died in the combined pembrolizumab groups and 172 (62%) of 278 had died in the ipilimumab group (figure 2). Median overall survival was 32·7 months (95% CI 24·5–41·6) in the combined pembrolizumab groups and 15·9 months (13·3–22·0) in

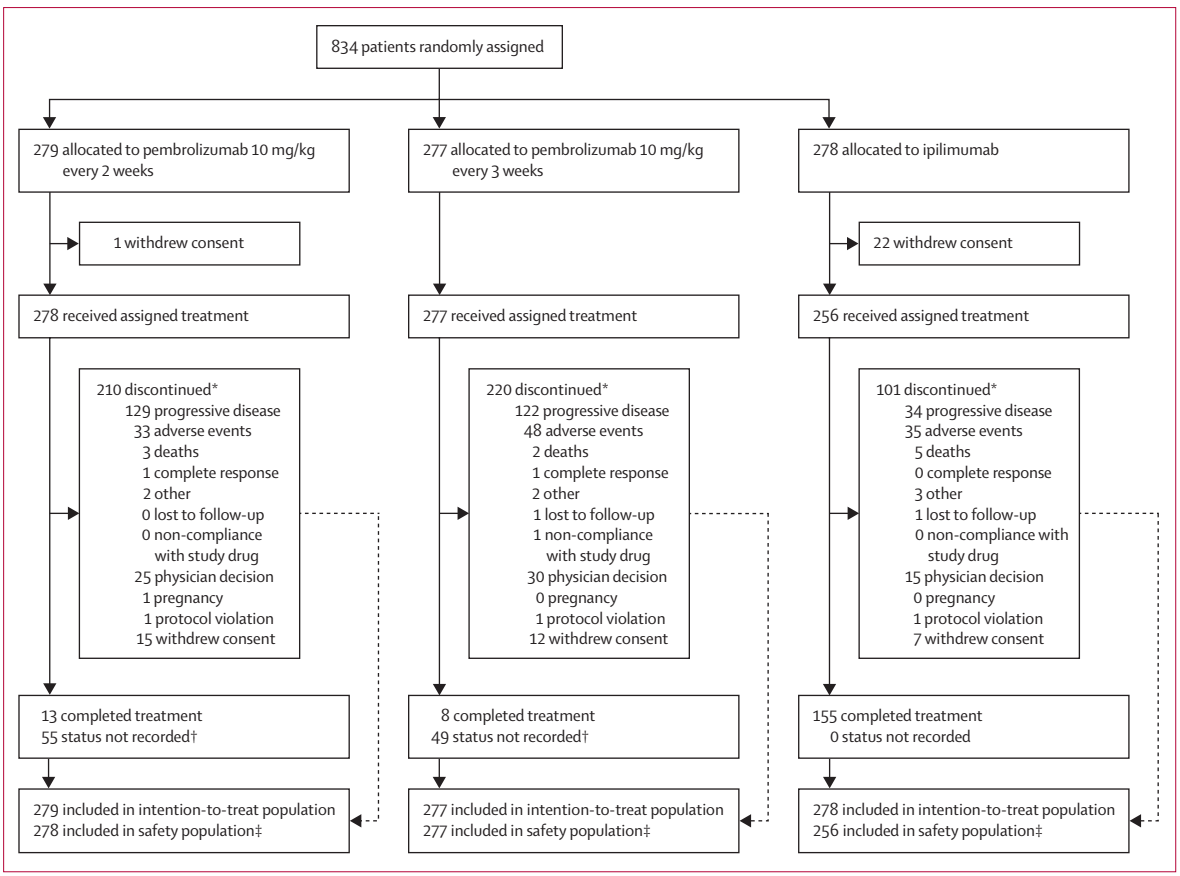
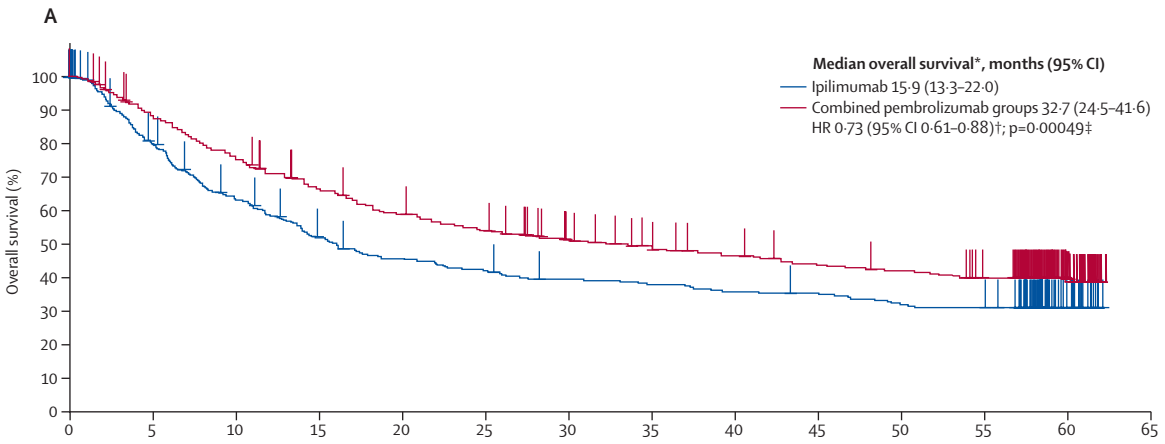


Figure 1: **Trial profile**
*Discontinued study. †Patients were eligible for or receiving second-course pembrolizumab. ‡The intention-to-treat population included all randomly assigned patients. The safety population included in all randomly assigned patients who received at least one dose of study treatment.

the ipilimumab group (HR 0·73, 95% CI 0·61–0·88, p=0·00049). 5-year overall survival was 38·7% (95% CI 34·2–43·1) in the combined pembrolizumab groups and 31·0% (25·3–36·9) in the ipilimumab group. There were 628 progression-free survival events; 411 (74%) in the combined pembrolizumab groups and 217 (78%) in the ipilimumab group (figure 2). Median progression-free survival was 8·4 months (95% CI 6·6–11·3) in the combined pembrolizumab groups versus 3·4 months (2·9–4·2) in the ipilimumab group (HR 0·57, 95% CI 0·48–0·67, p<0·0001). 48-month progression-free survival was 23·0% (95% CI 19·1–27·1) in the combined pembrolizumab groups and 7·3% (3·3–13·3) in the ipilimumab group.

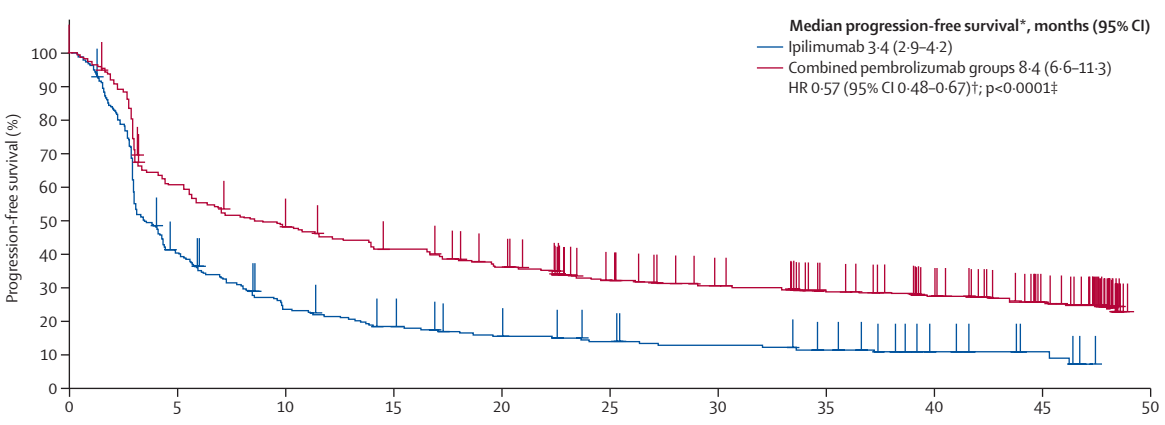
In subgroup analyses, median overall survival in patients who received first-line treatment was 38·7 months (95% CI 27·3–50·7) for pembrolizumab and 17·1 months (13·8–26·2) for ipilimumab (HR 0·73, 95% CI 0·57–0·92, p=0·0036; figure 2). Patients excluded from this subgroup had previously received chemotherapy (77 [14%] in the combined pembrolizumab groups *vs* 29 [10%] in the ipilimumab group), BRAF or MEK inhibitor (95 [17%] *vs* 56 [20%]), or immunotherapy (15 [3%] *vs* 12 [4%]). In patients who received first-line treatment, median progression-free survival was 11·6 months (95% CI 8·2–16·4) in the combined pembrolizumab groups versus 3·7 months (2·8–4·3) in the ipilimumab group (HR 0·54, 95% CI 0·44–0·67, p<0·0001; figure 2). Overall survival at 24, 36, 48, and 60 months and progression-free survival at 24, 36, and 48 months are presented in the appendix (p 10). Median overall survival and progression-free survival for patients receiving first-line pembrolizumab did not differ between patients assigned to pembrolizumab every 2 weeks and those assigned to pembrolizumab every 3 weeks (appendix p 9).

In patients receiving second-line treatment, median overall survival was 23·5 months (95% CI 16·8–34·2) in the combined pembrolizumab groups versus 13·6 months (10·7–22·0) in the ipilimumab group (HR 0·75, 95% CI 0·55–1·03, p=0·036; appendix p 21). In patients with *BRAF*^{V600} wild-type disease, median overall survival was 28·1 months (95% CI 21·1–42·7) in the combined pembrolizumab groups versus 13·9 months (10·7–24·8) in the ipilimumab group (HR 0·73, 95% CI 0·58–0·93, p=0·0048; appendix p 21).



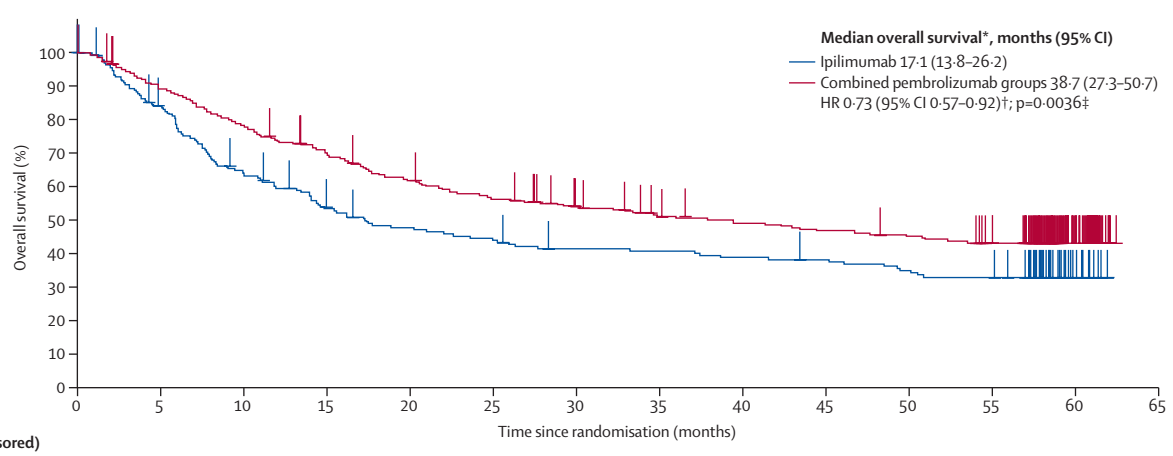
Number at risk (number censored)

Ipilimumab	278 (24)	202 (26)	158 (29)	127 (30)	111 (30)	102 (32)	94 (32)	90 (32)	85 (33)	83 (33)	75 (34)	72 (87)	19 (106)	0 (106)
Combined pembrolizumab groups	556 (7)	481 (7)	416 (12)	357 (14)	317 (15)	289 (24)	264 (30)	245 (32)	233 (34)	217 (35)	208 (40)	194 (185)	47 (232)	0 (232)



Number at risk (number censored)

Ipilimumab	278 (31)	97 (35)	55 (38)	40 (41)	31 (44)	25 (45)	22 (47)	18 (54)	10 (58)	6 (61)	0 (61)
Combined pembrolizumab groups	556 (9)	328 (11)	260 (13)	222 (18)	190 (33)	154 (40)	140 (49)	123 (62)	105 (78)	81 (127)	26 (145)



Number at risk (number censored)

Ipilimumab	181 (13)	140 (14)	105 (17)	86 (18)	76 (18)	70 (20)	64 (20)	63 (20)	60 (21)	58 (21)	52 (22)	49 (63)	8 (71)	0 (71)
Combined pembrolizumab groups	368 (4)	324 (4)	284 (7)	248 (9)	221 (9)	201 (17)	184 (22)	170 (23)	163 (23)	155 (24)	149 (29)	137 (135)	31 (166)	0 (166)

(Figure 2 continues on next page)

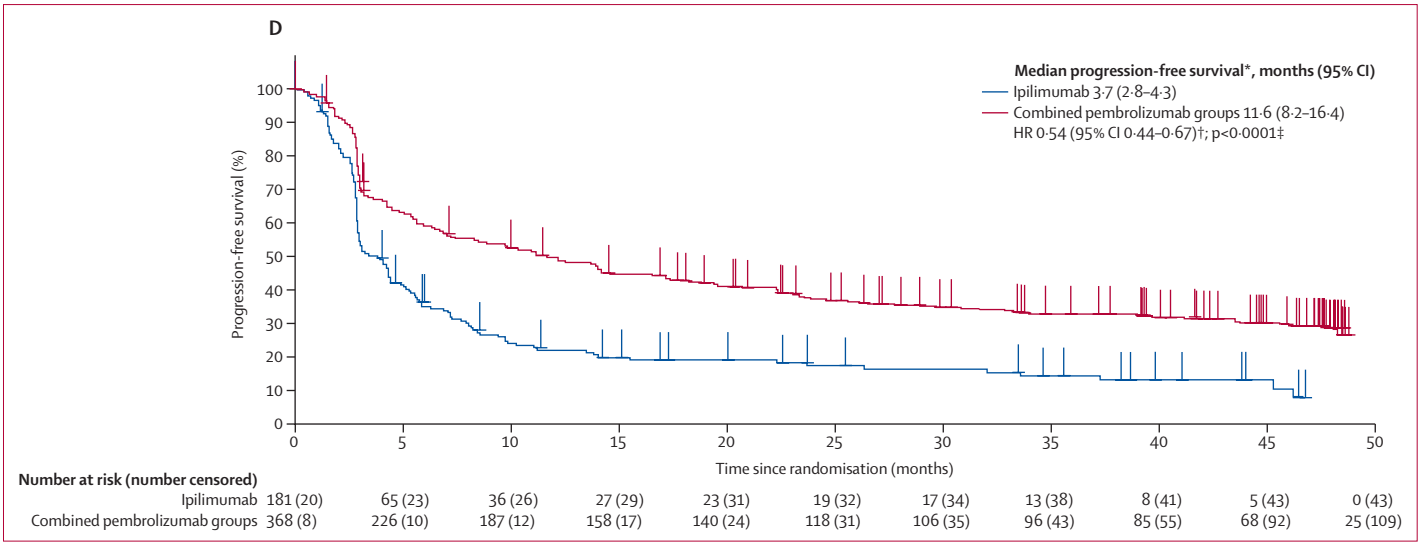


Figure 2: **Survival outcomes in the total study population and in patients receiving first-line treatment**
(A) Overall survival in the total study population; (B) progression-free survival in the total study population per immune-related response criteria by investigator review; (C) overall survival in patients receiving first-line pembrolizumab or ipilimumab for advanced disease; (D) progression-free survival in patients receiving first-line pembrolizumab or ipilimumab for advanced disease. HR=hazard ratio. *From product-limit (Kaplan-Meier) method for censored data. †Based on Cox regression model with treatment as a covariate stratified by line of therapy (first *vs* second), PD-L1 status (positive *vs* negative), and Eastern Cooperative Oncology Group performance status (0 *vs* 1). If no patients are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison. ‡One-sided p value based on log-rank test. Overall survival at 24, 36, 48, and 60 months and progression-free survival at 24, 36, and 48 months in patients in the total study population and in patients receiving first-line treatment are presented in the appendix (p 10).

In patients with *BRAF*^{V600E}-mutant or *BRAF*^{V600K}-mutant disease treated with a previous BRAF or MEK inhibitor, or both, median overall survival was 20·4 months (95% CI 12·8–35·6) in the combined pembrolizumab groups versus 11·9 months (6·0–17·8) in the ipilimumab group (HR 0·71, 95% CI 0·46–1·08, p=0·054; appendix p 22). In patients with *BRAF*^{V600E}-mutant or *BRAF*^{V600K}-mutant disease not treated with a previous BRAF or MEK inhibitor (and as per protocol, therefore patients with a normal baseline concentration of lactase dehydrogenase), median overall survival was not reached (95% CI 36·1–not available) in the combined pembrolizumab groups and 26·2 months (16·0–not available) in the ipilimumab group (HR 0·70, 95% CI 0·44–1·11, p=0·065; appendix p 22).

At data cutoff, 235 (42%; 95% CI 38·1–46·5) of 556 patients in the combined pembrolizumab groups and 46 (17%; 12·4–21·4) of 278 in the ipilimumab group had achieved an objective response (table 1). The best overall response was complete response in 77 (14%) patients in the combined pembrolizumab groups and nine (3%) patients in the ipilimumab group; an additional 158 (28%) and 37 (13%) patients, respectively, had partial response. Responses lasted for at least 42 months in 62 (26%) of 235 patients in the combined pembrolizumab groups and two (4%) of 46 patients in the ipilimumab group. Median duration of response was 53·5 months (95% CI 50·99–not available) in the combined pembrolizumab groups and not reached (20·96–not available) in the ipilimumab group (appendix p 23). Stable disease was achieved in 117 (21%) patients in the combined pembrolizumab groups and in 70 (25%) patients in the ipilimumab group. Disease control was observed in 352 (63%) patients in the combined pembrolizumab groups and in 116 (42%) patients in the ipilimumab group. 163 (29%) patients in the combined pembrolizumab groups and 107 (38%) in the ipilimumab group had progressive disease. Table 1 shows the proportion of patients achieving an objective response in subgroup analyses according to line of therapy, *BRAF*^{V600} status, and exposure to previous BRAF or MEK inhibitors for those patients with *BRAF*^{V600E}-mutant or *BRAF*^{V600K}-mutant disease.

Of the 834 patients enrolled, 811 were included in the safety analysis population (pembrolizumab, n=555; ipilimumab, n=256). Median time on treatment was 6·0 months (IQR 2·8–20·3) for pembrolizumab and 2·1 months (1·4–2·1) for ipilimumab. The overall summary of adverse events was similar between the combined pembrolizumab groups and the ipilimumab group (table 2, appendix pp 11–16), and between the two pembrolizumab dosing regimen groups, as reported previously.[8] Any-grade and grade 3–5 treatment-related adverse events occurred in 442 (80%) and 96 (17%) patients in the combined pembrolizumab groups, respectively. Any grade and grade 3–4 treatment-related adverse events occurred in 190 (74%) and 50 (20%) patients in the ipilimumab group, respectively (table 2). The most common grade 3–4 treatment-related adverse events were colitis (11 [2%] in the combined pembrolizumab groups *vs* 16 [6%] in the ipilimumab group), diarrhoea

	Patients with objective response/total patients	Proportion, % (95% CI)	Difference, % (95% CI*)
All patients			
Combined pembrolizumab groups	235/556	42% (38·1–46·5)	26% (19·5–31·5)
Ipilimumab	46/278	17% (12·4–21·4)	..
Patients receiving first-line pembrolizumab or ipilimumab			
Combined pembrolizumab groups	170/368	46% (41·0–51·4)	29% (21·0–36·1)
Ipilimumab	31/181	17% (11·9–23·4)	..
Patients receiving second-line pembrolizumab or ipilimumab			
Combined pembrolizumab groups	64/187	34% (27·5–41·5)	19% (8·7–28·6)
Ipilimumab	15/97	15% (8·9–24·2)	..
Patients with *BRAF*^{V600} wild-type disease			
Combined pembrolizumab groups	154/355	43% (38·2–48·7)	27% (18·9–34·3)
Ipilimumab	28/170	16% (11·2–22·9)	..
Patients with *BRAF*^{V600E}-mutant or *BRAF*^{V600K}-mutant disease			
Combined pembrolizumab groups	79/195	41% (33·6–47·8)	23% (12·5–32·5)
Ipilimumab	17/107	16% (9·5–24·2)	..
Patients with *BRAF*^{V600E}-mutant or *BRAF*^{V600K}-mutant disease who received previous BRAF or MEK inhibitor, or both			
Combined pembrolizumab groups	28/87	32% (22·6–43·1)	18% (3·4–31·6)
Ipilimumab	7/52	13% (5·6–25·8)	..
Patients with *BRAF*^{V600E}-mutant or *BRAF*^{V600K}-mutant disease who did not receive previous BRAF or MEK inhibitor			
Combined pembrolizumab groups	51/108	47% (37·5–57·1)	26% (10·9–39·9)
Ipilimumab	10/55	18% (9·1–30·9)	..

*Based on the Miettinen and Nurminen[13] method stratified by line of therapy (first *vs* second), PD-L1 status (positive *vs* negative), and Eastern Cooperative Oncology Group performance status (0 *vs* 1); if no patients are in one of the treatment groups involved in a comparison for a particular stratum, that stratum is excluded from the treatment comparison.

Table 1: **Proportion of patients who had objective response per immune-related response criteria by investigator review**

	Combined pembrolizumab group (n=555)				Ipilimumab group (n=256)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any	436 (79%)	90 (16%)	12 (2%)	1 (<1%)	183 (71%)	48 (19%)	6 (2%)	0
Diarrhoea	92 (17%)	10 (2%)	0	0	55 (21%)	7 (3%)	0	0
Nausea	73 (13%)	1 (<1%)	0	0	23 (9%)	1 (<1%)	0	0
Asthenia	68 (12%)	2 (<1%)	0	0	14 (5%)	2 (<1%)	0	0
Fatigue	141 (25%)	4 (<1%)	0	0	40 (16%)	3 (1%)	0	0
Arthralgia	70 (13%)	3 (<1%)	0	0	12 (5%)	1 (<1%)	0	0
Pruritus	111 (20%)	1 (<1%)	0	0	65 (25%)	2 (<1%)	0	0
Rash	92 (17%)	0	0	0	38 (15%)	1 (<1%)	1 (<1%)	0
Vitiligo	71 (13%)	0	0	0	4 (2%)	0	0	0

Data are n (%). Treatment-related adverse events as designated by the investigator. Grade 1–2 events that occurred in at least 10% of patients. Grade 3–5 events are listed for only those grade 1–2 treatment-related adverse events that occurred in at least 10% of patients. A given patient may be counted in more than one toxicity grade category.

Table 2: **Treatment-related adverse events**

(ten [2%] *vs* seven [3%]), and fatigue (four [<1%] *vs* three [1%]; appendix pp 11–14). Any-grade serious treatment-related adverse events occurred in 75 (14%) patients in the combined pembrolizumab groups and in 45 (18%) patients in the ipilimumab group; the most common were colitis (11 [2%] in the combined pembrolizumab groups *vs* 16 [6%] in the ipilimumab group), diarrhoea (eight [1%] *vs* nine [4%]), autoimmune hepatitis (six [1%] *vs* two [<1%]), and pneumonitis (eight [1%] *vs* two [<1%]). Treatment-related adverse events led to discontinuation for 55 (10%) patients in the combined pembrolizumab groups and 23 (9%) patients in the ipilimumab group. 13 (3%) patients in the combined pembrolizumab groups and three (1%) in the ipilimumab group died from adverse events; one death (sepsis) in the pembrolizumab group was treatment-related (appendix p 16). Similar to the previous report,[8] immune-mediated endocrinopathies were more common in the combined pembrolizumab groups whereas colitis was more common in the ipilimumab group (appendix p 15).

103 (19%) of 556 patients completed 2 years of pembrolizumab, of whom 21 (20%) achieved a best overall response of complete response, 69 (67%) achieved partial response, and 13 (13%) had stable disease (appendix p 24). Responses were ongoing in 16 (76%) of 21 patients with a complete response, 53 (77%) of 69 patients with a partial response, and seven (54%) of 13 patients with stable disease. Eight (8%) patients with a previous best overall response of partial response converted to complete response after cessation of pembrolizumab. After a median follow-up of 34·2 months (IQR 33·3–36·1) from completion of pembrolizumab in surviving patients, the estimated 24-month progression-free survival from completion of pembrolizumab for all 103 patients was 78·4% (95% CI 68·3–85·6); 24-month overall survival was 95·9% (89·4–98·4) and 36-month overall survival was 93·8% (86·7–97·2). Estimated 24-month progression-free survival was 85·4% (95% CI 61·3–95·1) for patients with complete response, 82·3% (70·3–89·8) for patients with partial response, and 39·9% (8·1–71·4) for patients with stable disease (figure 3). 23 patients with complete response who stopped pembrolizumab treatment early, as allowed by the protocol (received at least 6 months of pembrolizumab showing complete response and two additional doses after the first scan showing complete response), and who did not complete 2 years of pembrolizumab, had 24-month progression-free survival of 86·4% (95% CI 63·4–95·4), which is similar to that in patients with complete response who did complete 2 years of pembrolizumab.

Patients who completed 2 years of pembrolizumab with stable disease progressed earlier than did those with complete response or partial response (figure 3). Of the seven patients who had ongoing stable disease, six had stable lymph node metastases (four combined with stable lung metastases and one with stable liver metastases), and one had stable lung, kidney, and breast metastases.

In an exploratory analysis of the 103 patients who completed 2 years of pembrolizumab, 76 (74%) were progression free and 27 (26%) progressed, with a median time to progression of 33·3 months (IQR 26·0 months–not available; figure 3) from the end of pembrolizumab

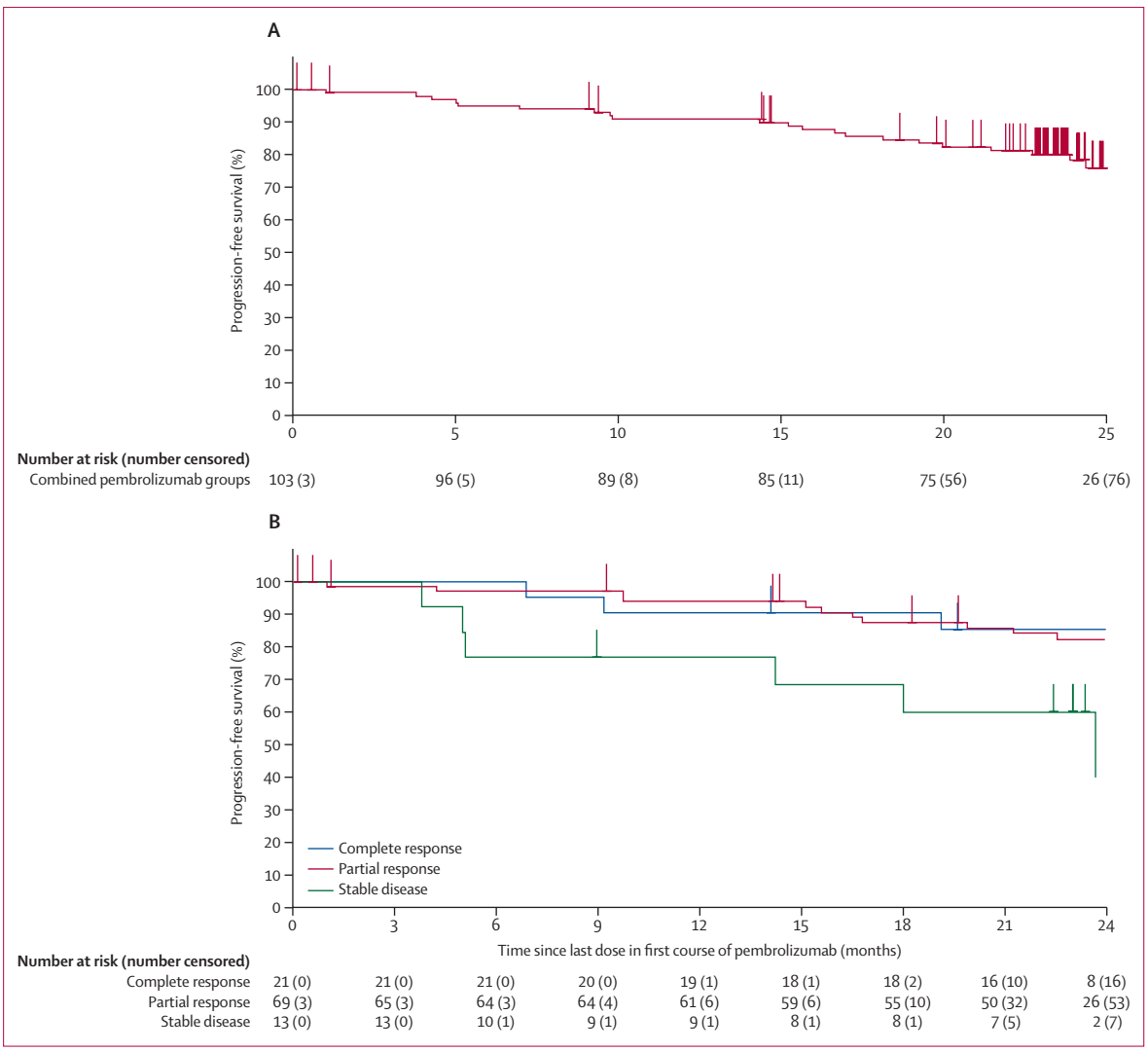


Figure 3: **Progression-free survival from cessation of pembrolizumab in patients who completed 2 years of treatment**
Progression-free survival from cessation of pembrolizumab per immune-related response criteria by investigator review in (A) patients who completed 2 years of pembrolizumab (n=103) and (B) by best overall response in first course of treatment in patients who completed 2 years of pembrolizumab.

treatment. The most common sites of progression were the lymph nodes (n=13), liver (n=4), and lungs (n=3). Of the 27 patients with progression, 12 (44%) received second-course pembrolizumab and 15 (56%) did not receive second-course pembrolizumab in the present study. Of the 15 patients who did not receive second-course pembrolizumab, ten received immunotherapy as their next line of treatment, including pembrolizumab (n=6; outside this study), combined ipilimumab and nivolumab (n=2), and ipilimumab (n=2; appendix p 17). Five patients died (four of progressive disease; one from unknown cause; appendix p 17).

Second-course pembrolizumab was given to 13 patients, including one patient who discontinued early in the first course with complete response (not included in the 103 patients who completed pembrolizumab treatment) and then progressed; best overall response in first-course treatment was six complete responses, six partial responses, and one stable disease (appendix p 24). For patients receiving second-course pembrolizumab, the dose and frequency of the first course of pembrolizumab is described in the appendix (p 4). Median follow-up in these patients was 14·3 months (IQR 8·7–33·8); four patients discontinued before completing 1 year of second-course therapy (two because of progressive disease, one because of grade 2 interstitial pneumonia, and one because of physician decision), four completed second-course pembrolizumab, and five had ongoing treatment. Median duration of second-course pembrolizumab was 9·0 months (IQR 4·2–10·6). Exploratory analysis of efficacy of second-course pembrolizumab in these 13 patients showed best overall response of complete response in three patients (two patients had surgical complete response before the start of the

	First-course best overall response	Site of disease at time of progressive disease	Surgery after first-course progressive disease and before second course	Second-course best overall response	Second-course ongoing response	Second-course duration of response (months)	Reason for second-course discontinuation
Patient 1	Complete response	1 lymph node*	None	Complete response	Complete response	>8·5	NA
Patient 2	Partial response	Lung, 5 lymph nodes, soft tissue*	None	Partial response	Progressive disease†	8·9	NA
Patient 3	Complete response	Brain*	Yes, surgical resection of brain metastasis	Complete response‡	Complete response‡	>3·0	NA
Patient 4§	Complete response	4 lymph nodes*	None	Partial response	Progressive disease	8·0	Progressive disease
Patient 5	Partial response	1 lymph node, 2 lymph nodes*	None	Partial response	Partial response	>8·3	Completed 17 cycles
Patient 6	Complete response	1 lymph node*	Yes, lymph node resection	Complete response‡	Complete response‡	>7·5	Completed 17 cycles
Patient 7	Partial response	Lung, skin*	None	Stable disease	Stable disease	NA	Grade 2 interstitial pneumonia
Patient 8	Partial response	Kidney (56% increase)	None	Partial response	Partial response	>3·7	Physician decision
Patient 9	Stable disease	Lung, 2 iliac lymph nodes, paratracheal node (17% increase)	None	Stable disease	Stable disease	NA	Completed 17 cycles
Patient 10	Complete response	1 lymph node*	Yes, lymph node resection	Stable disease	Stable disease	NA	Completed 17 cycles
Patient 11	Partial response	1 lymph node (39% increase)	None	Progressive disease	Progressive disease	NA	Progressive disease
Patient 12	Partial response	2 lung, 3 soft tissue, 1 lymph node, 2 lymph nodes*	None	NA	NA	NA	NA
Patient 13	Complete response	Liver*	None	NA	NA	NA	NA

NA=not available. *New metastasis. †Progressive disease was not confirmed and patient continued treatment beyond progression. ‡Patient achieved surgical complete response after surgery. §Patient did not complete 2 years of first-course pembrolizumab.

Table 3: **Treatment exposure and duration of response in patients re-treated with pembrolizumab (second course)**

second course), partial response in four patients, stable disease in three patients, and progressive disease in one patient (table 3, appendix p 25). Response assessment was pending for two patients (table 3, appendix p 25). Six patients had treatment-related adverse events during second-course pembrolizumab; there were no grade 3–4 treatment-related adverse events or deaths, and four patients had immune-mediated adverse events (appendix p 18).

Discussion

Consistent with previous analyses with shorter follow-up,[8,9] the estimated 5-year survival outcome of KEYNOTE-006 presented here continued to show superiority of pembrolizumab over ipilimumab in patients with ipilimumab-naive advanced melanoma. Patients who were given pembrolizumab had longer overall survival and progression-free survival than did those given ipilimumab. These results were observed irrespective of *BRAF*^{V600} status, or exposure to previous BRAF or MEK inhibitors for those patients with *BRAF*^{V600E}-mutant or *BRAF*^{V600K}-mutant disease, with a median follow-up of 57·7 months in surviving patients. The safety profile of pembrolizumab also continued to be consistent with previous reported analyses.[8,9] In this 5-year follow-up, overall survival and progression-free survival curves of the two dosing schedules of pembrolizumab, every 2 weeks and every 3 weeks, were similar, as reported previously.[8] Therefore, although not prespecified in the study protocol, data from the two pembrolizumab groups were pooled. Such pooling of safety results is unlikely to have influenced conclusions because progression-free survival and overall survival were similar in the two dosing groups.

In a pooled analysis (n=1861) of phase 2 and 3 ipilimumab trials, 3-year overall survival was 22%; the survival curve began to plateau at around year 3 and was independent of previous therapy or ipilimumab dose.[14] Together with our results, these data suggest that checkpoint inhibitor therapy offers durable antitumour activity in patients with advanced melanoma. The 4-year overall survival in ipilimumab-naive patients treated with pembrolizumab reported here (42·3%, 95% CI 38·1–46·5; appendix p 10) compares more favourably with those treated with ipilimumab in a previous study (30%, 95% CI 25–35).[3,14] The 5-year overall

survival (38·7%) in pembrolizumab-treated patients in KEYNOTE-006 is similar to that in KEYNOTE-001 (34%); however, it should be noted that KEYNOTE-001 (n=655) included treatment-naive (n=151) patients and those previously treated with ipilimumab (n=342) or other therapies, whereas KEYNOTE-006 did not include patients previously treated with ipilimumab.[7] Survival outcome was also favourable for patients receiving pembrolizumab in the first-line setting in KEYNOTE-006 (4-year overall survival of 45·7%). Longer patient follow-up will be necessary to determine whether there is a plateau in overall survival for pembrolizumab. PD-1 blockade is associated with changes in genes involved in cytolysis and natural killer cell function in vivo,[15,16] as well as an increased frequency of CD8 T-effector memory cells[17] and tissue-resident memory T cells[18] in patients who respond to anti-PD-1 therapy, supporting the durable responses observed in patients treated with pembrolizumab in KEYNOTE-006.

The results of the present study also provide an early indication of outcomes following a second course of pembrolizumab. Re-treatment with a second course pembrolizumab in patients who had stable disease or better after the first course of pembrolizumab showed antitumour activity and acceptable safety. Immune-mediated adverse events during the second course were mild to moderate. These data are consistent with real-world data of patients with advanced melanoma who discontinued anti-PD-1 therapy (n=169) in the absence of disease progression and treatment-limiting toxicities and were treated again (n=4) after progression, leading to renewed response in three patients.[19] Study limitations for these exploratory analyses include the small number of patients treated with second-course pembrolizumab and the duration of follow-up. Responses were not confirmed by central review, and surgical resection was permitted with disease recurrence after the first course, thereby limiting interpretation of response to second-course pembrolizumab.

The optimal duration of anti-PD-1 therapy is unknown, and duration of response in patients discontinuing immunotherapy is not well known. In a post-hoc pooled analysis[20] of CheckMate 069, CheckMate 066, and CheckMate 067, 18% of patients treated with nivolumab plus ipilimumab, 16% treated with nivolumab monotherapy, and 4% treated with ipilimumab monotherapy achieved a complete response; and 41%, 28%, and 14%, respectively, achieved a partial response. After a median follow-up of approximately 31 months, 77% of patients were off treatment, the median duration of complete response was not reached, and 84% remained in response.[20] In the aforementioned report, data were pooled from three studies with varying durations of treatment, and patients might have discontinued treatment for a variety of reasons. A recent analysis of patients with advanced melanoma in a real-world setting showed that discontinuing anti-PD-1 therapy (pembrolizumab or nivolumab) in the absence of progressive disease or adverse events was associated with a low risk of short-term recurrence.[21] Four patients were also re-treated with pembrolizumab, resulting in one complete response, one instance of stable disease, and one instance of progressive disease.[21] Our analysis is more rigorous and only included patients who completed the protocol-specified treatment of 2 years with at least stable disease. Results showed that 74% of these patients had ongoing disease control (16 with complete response, 53 with partial response, and seven with stable disease). Furthermore, those patients completing first-course pembrolizumab with a complete response had 24-month progression-free survival from treatment cessation of 85·4%, which is consistent with the durable responses observed in KEYNOTE-001 (24-month disease-free survival of 90% for patients who discontinued pembrolizumab after achieving complete response).[22] Responses were also durable in patients who achieved complete response early and stopped pembrolizumab treatment after receiving at least 6 months of pembrolizumab.

Although KEYNOTE-006 was not designed to specifically determine the optimal duration of pembrolizumab administration, these results provide valuable insight towards understanding underlying factors influencing optimal treatment duration. The findings of long-term benefit following discontinuation of pembrolizumab are further supported by a study evaluating the utility of fluoro-deoxyglucose PET to assess complete metabolic response in patients with metastatic melanoma treated with anti-PD-1-based therapy.[23] Ongoing response was observed in 99% of these patients after a median follow-up of 21 months; 60% of these patients had discontinued treatment with a median post-discontinuation follow-up of 9·9 months.[23] In the present analysis, 24-month progression-free survival from treatment cessation of patients completing first-course pembrolizumab with stable disease (39·9%) was lower than that in patients with complete response (85·4%) or partial response (82·3%). Additional work is necessary to inform treatment cessation decisions; however, additional assessment of stable disease by PET might help guide such decisions. In advanced non-small-cell lung cancer, an ongoing randomised trial, CheckMate 153 (NCT02066636), is being done to assess the clinical benefit of a fixed duration (1 year) of nivolumab versus continuous treatment in patients with previously treated disease.[24] Recent results show lower 1-year progression-free survival (40% *vs* 65%; HR 0·42, 95% CI 0·25–0·71) and 1-year overall survival (81% *vs* 88%) with 1 year of nivolumab treatment compared with continuous treatment and argue against treatment discontinuation after 1 year in patients with non-small-cell lung cancer.[25]

To date, no definitive predictors of response to checkpoint inhibition have been identified in patients with advanced melanoma. Nonetheless, in an analysis of KEYNOTE-001, tumour size and PD-L1 status were

among the baseline factors independently associated with complete response by univariate analysis.[16] When combining tumour burden and PD-L1 expression in multivariate analysis, the proportion of patients with small tumour size (1–5 cm) and PD-L1-positive tumours who had a complete response was 42·7% versus 1·9% in patients with large tumour size (>5 cm) and PD-L1-negative tumours.[22]

Pembrolizumab administration can be an effective long-term therapy for advanced melanoma, with few grade 3–4 toxicities. However, the underlying factors that determine response as well as the standard recommendation of immunotherapy cessation remain unknown. Although the KEYNOTE-006 study was not designed to investigate the optimal duration of pembrolizumab treatment in patients with advanced melanoma, our data suggest that pembrolizumab confers sustained disease control over a long period of time whereby 78·4% of patients who completed 2 years of pembrolizumab treatment with at least stable disease remained progression free at 24 months following pembrolizumab completion. Approximately 86% of patients who achieved complete response and who stopped pembrolizumab treatment early after at least 6 months also remained progression free at 24 months. Because treatment with targeted therapies is typically continued indefinitely,[1] the finding of durable responses following pembrolizumab discontinuation is encouraging. Finally, preliminary findings suggest that re-treatment with pembrolizumab on disease progression can provide additional antitumour activity with acceptable safety.

Contributors

This study was conceived, designed, or planned by CR, AD, and JS. Study materials or patients were provided by GVL, PL, AA, and ML. Data were acquired by CUB, GVL, CK, CMM, BN, TMP, AR, CR, OH, AD, MSC, JMGL, ML, J-JG, NI, LM, and JS. Data were analysed by GVL, CK, CR, S-CS, OH, AD, JMGL, NI, and JS. Results were interpreted by CUB, GVL, CK, PL, TMP, AR, CR, OH, MSC, J-JG, NI, LM, and JS. The manuscript was drafted with contribution from all authors by CUB, CK, CMM, CR, JMGL, NI, and JS. All authors critically reviewed or revised the manuscript for important intellectual content.

Declaration of interests

CR reports personal fees for advisory boards from Bristol-Myers Squibb (BMS), Pierre Fabre, Novartis, Amgen, Merck, and Roche, outside the submitted work. AR reports personal fees from Amgen, Chugai, Novartis, and Merck, outside the submitted work. Additionally, AR has received personal fees from, and is a senior advisory board member and stockholder in Arcus, Bioncotech, Compugen, CytomX, Five Prime, FLX-Bio, Merus, Rgenix, PACT Pharma, and Tango Therapeutics. AA reports personal fees from BMS, Merck Sharp & Dohme (MSD), Novartis, Roche, Pierre Fabre, Amgen, and Merck, outside the submitted work. Additionally, AA has received reimbursement for travel, accommodation, and expenses from BMS, MSD, Roche, and Merck, outside the submitted work. J-JG reports personal fees from MSD, BMS, Amgen, Novartis, Roche, Pierre Fabre, Sanofi, Merck, and Pfizer, outside the submitted work. LM reports personal fees from Roche, BMS, Novartis, and MSD, outside the submitted work. AD reports grants and non-financial support from Merck, BMS, and Roche, and grants from Checkmate during the conduct of the study. MSC reports personal fees from MSD, BMS, Novartis, and Pierre Fabre, outside the submitted work. CMM reports personal fees from MSD during the conduct of the study, and personal fees from MSD outside the submitted work. ML reports personal fees from Merck and BMS, outside the submitted work. JMGL reports grants and personal fees from Achilles Therapeutics, BMS, MSD, Nektar, Novartis, Pfizer, Roche/Genentech, Covance, and Immunocore, and personal fees from AstraZeneca, Boston Biomedical, Eisai, EUSA Pharma, GlaxoSmithKline (GSK), Ipsen, Imugene, Incyte, iOnctura, Kymab, Merck Serono, Pierre Fabre, Secarna, Vitaccess, Aveo, and Pharmacyclics, outside the submitted work. PL reports personal fees and other from BMS, Novartis, GSK, Amgen, and Chugai, and personal fees from Merck, outside the submitted work. BN reports grants from Pfizer, grants and personal fees from Novartis, and personal fees from BMS, Pierre Fabre, Amgen, Roche, MSD, and eTheRNA, outside the submitted work. CUB reports research grants from Novartis and BMS, and personal fees paid to the institute from BMS, MSD, Roche, Novartis, Lilly, and Pfizer, outside the submitted work. TMP reports grants and personal fees from Merck, Novartis, and BMS; a grant from Roche; and personal fees from Incyte, Sanofi-Genzyme, and Polynoma. OH reports personal fees from Merck during the conduct of the study, and personal fees from Amgen, Novartis, Roche, BMS, Genentech, Array, and Sanofi/Regeneron, and contracted research support from AstraZeneca, BMS, Celldex, Genentech Roche, Immunocore, Incyte, Merck, Merck Serono, MedImmune, Novartis, Pfizer, Amgen, CytomX, Iovance, Regeneron, and Polynoma, outside the submitted work. S-CS, CK, and NI report employment with Merck Sharp & Dohme, a subsidiary of Merck & Co, Kenilworth, NJ, USA, and stock ownership in Merck & Co, Kenilworth, NJ, USA. GVL reports personal fees from Aduro, Array, BMS, OncoSec, MSD, Novartis, Pierre Fabre, and Roche, outside the submitted work. JS declares no competing interests.

Data sharing

Merck Sharp & Dohme (MSD), a subsidiary of Merck & Co, Kenilworth, NJ, USA is committed to providing qualified scientific researchers access to anonymised patient-level data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. The company is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The process includes submission of data requests to the MSD data sharing website (http://engagezone.msd.com/ds_documentation.php). Data will be made available for request after product approval in the US and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing the requested data.

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