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Original Research

Final analysis of a randomised trial comparing pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory advanced melanoma☆

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Survival

Abstract ***Aim:*** To evaluate the protocol-specified final analysis of overall survival (OS) in the KEYNOTE-002 study (NCT01704287) of pembrolizumab versus chemotherapy in patients with ipilimumab-refractory, advanced melanoma.
Methods: In this randomised, phase II study, eligible patients had advanced melanoma with documented progression after two or more ipilimumab doses, previous *BRAF* or MEK inhibitor or both, if $BRAF^{V600}$ mutant-positive. Patients were randomised to pembrolizumab 2 mg/kg or 10 mg/kg every 3 weeks or investigator-choice chemotherapy. Crossover to pembrolizumab was allowed following progression on chemotherapy. The protocol-specified final OS was performed in the intent-to-treat population. Survival was positive if $p < 0.01$ in one pembrolizumab arm.
Results: A total of 180 patients were randomised to pembrolizumab 2 mg/kg, 181 to pembrolizumab 10 mg/kg and 179 to chemotherapy. At a median follow-up of 28 months (range 24.1–35.5), 368 patients died and 98 (55%) crossed over to pembrolizumab. Pembrolizumab 2 mg/kg (hazard ratio [HR] 0.86, 95% confidence interval [CI] 0.67–1.10, $p = 0.117$) and 10 mg/kg (0.74, 0.57–0.96, $p = 0.011$) resulted in a non-statistically significant improvement in OS versus chemotherapy; median OS was 13.4 (95% CI 11.0–16.4) and 14.7 (95% CI 11.3–19.5), respectively, versus 11.0 months (95% CI 8.9–13.8), with limited improvement after censoring for crossover. Two-year survival rates were 36% and 38%, versus 30%. Progression-free survival, objective response rate and duration of response improved with pembrolizumab versus chemotherapy, regardless of dose. Grade III–V treatment-related adverse events occurred in 24 (13.5%), 30 (16.8%) and 45 (26.3%) patients, respectively.
Conclusion: Improvement in OS with pembrolizumab was not statistically significant at either dose versus chemotherapy.

1. Introduction

The introduction of targeted therapy with *BRAF* and *MEK* inhibitors and checkpoint inhibitors improved survival outcomes in patients with advanced, metastatic melanoma [1–4]. Ipilimumab potentiates the antitumour response by blocking signalling through the inhibitory cytotoxic T-lymphocyte-associated (CTLA-4) receptor expressed on activated T cells [5] and improves response rates and survival in patients with advanced melanoma, regardless of the *BRAF* mutation status [6]. At the time of this study, BRAF plus MEK inhibitors (in patients with *BRAF*-mutated melanoma) and ipilimumab were the standard-of-care as front-line therapies for treatment of advanced melanoma [3,4]. When patients progressed after treatment with BRAF or MEK inhibitors or ipilimumab, their systemic treatment options were limited, as no agent had shown survival advantage in this setting.

The monoclonal anti-programmed cell death (PD-1) antibodies, pembrolizumab and nivolumab, have shown clinical efficacy in patients with melanoma [7–13]. Treatment with nivolumab improved objective response but not progression-free survival (PFS) or overall survival (OS) with fewer side-effects versus chemotherapy in patients with ipilimumab-refractory, advanced melanoma in CheckMate 037 [14,15]. In the protocol-specified second interim analysis of the phase II KEYNOTE-002 study of pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory advanced melanoma, pembrolizumab improved objective response and PFS versus chemotherapy with a favourable safety profile. The KEYNOTE-006 study of pembrolizumab versus ipilimumab in patients with advanced melanoma showed that PFS, OS and overall response rates (ORRs) were superior with pembrolizumab versus ipilimumab and led to the approval of pembrolizumab for the treatment of advanced melanoma in the front-line setting [12,13]. Here, we present results of the protocol-specified, event-driven final OS analysis of KEYNOTE-002.

2. Patients and methods

2.1. Study design

KEYNOTE-002 (NCT01704287) was an international, randomised, controlled, phase II study comparing the efficacy and safety of two doses of pembrolizumab with investigator-choice chemotherapy in patients with advanced melanoma refractory to ipilimumab [13]. The study was conducted in accordance with the Declaration of Helsinki. All patients provided written, informed consent. The protocol and amendments were approved by the Institutional Review Board or Ethics Committee at participating institutions.

2.2. Patients and treatment

Study criteria for KEYNOTE-002 were published previously [13]. Briefly, patients were randomly assigned

1:1:1 to pembrolizumab 2 mg/kg or pembrolizumab 10 mg/kg intravenously every 3 weeks (Q3W) or investigator-choice chemotherapy (carboplatin [eliminated with protocol amendment one], carboplatin plus paclitaxel, dacarbazine, paclitaxel alone or oral temozolomide). Randomisation was stratified by the Eastern Cooperative Oncology Group performance status (0 or 1), lactate dehydrogenase (LDH) levels (normal or elevated [≥110% upper limit of normal]) and *BRAF* mutational status (wild type or V600 mutant). Patients and investigators were masked only to the pembrolizumab dose. Additional details in Appendix.

The co-primary efficacy end-point was OS (time from randomisation to death). An updated summary of the co-primary efficacy end-point PFS, (time from randomisation to first documented disease progression [PD] per the Response Evaluation Criteria in Solid Tumours [RECIST], version 1.1 by an independent central review [IRC]), was included as a supportive analysis. Secondary end-points included ORR (proportion of patients with complete response [CR] or partial response [PR] per RECIST, version 1.1 by IRC), duration of response (DOR [time from first CR or PR until PD or death]), safety. Details of all end-points were published previously [13].

2.3. Assessments

Tumour response assessments were performed during screening (baseline), week 12 and then Q6W until week 48. After week 48, assessments were performed every 3 months. During follow-up, survival was assessed Q12W. Additional details in Appendix.

2.4. Statistical analyses

Protocol-specified analysis of OS was to be performed after 370 deaths across all groups. With 370 deaths and assuming a median OS of 6 months with chemotherapy and a hazard ratio (HR) of 0.65 for comparison of pembrolizumab versus chemotherapy, the study had 90% power to detect a difference in OS for at least one pembrolizumab group, using the Hochberg testing procedure at a one-sided alpha of 2% at final analysis [16]. Statistical analyses were done with SAS (version 9.3). Efficacy was assessed in the intent-to-treat population. Safety was assessed in all patients who received ≥1 dose of study treatment. Kaplan–Meier methods were used to estimate PFS, OS and DOR. Additional details in Appendix.

3. Results

From 30th November 2012 to 13th November 2013, 540 patients were randomised to pembrolizumab 2 mg/kg Q3W (n = 180), 10 mg/kg Q3W (n = 181) or chemotherapy (n = 179). Patient characteristics were well balanced, and most patients had two or more prior lines of therapy and visceral metastases (Table 1) [13]. At data cut-off of 16th November 2015, median duration of follow-up was 28 months (range 24.1–35.5) and treatment was ongoing for 17 (9%) patients with pembrolizumab 2 mg/kg and 31 (17%) with pembrolizumab 10 mg/kg; no patients were receiving chemotherapy. Ninety-eight of 179 (55%) patients in the chemotherapy arm crossed over to pembrolizumab (Appendix); median follow-up duration for these patients was 28.1 months (range 24.5–35.5). Including the crossover population, at least one line of subsequent anticancer therapy was received by 80 (44%) patients who discontinued pembrolizumab 2 mg/kg, 54 (30%) who discontinued pembrolizumab 10 mg/kg and 57 (32%) who discontinued chemotherapy, including 34 (6%) who received ipilimumab re-induction, 50 (9%) who were re-treated with BRAF/MEK inhibitors and 61 (11%) patients who received chemotherapy (Appendix). In addition, six (3%) patients who discontinued chemotherapy received subsequent anti–PD-1 or anti–PD-L1 therapy versus nine (5%) and two (1%) patients who discontinued pembrolizumab 2 mg/kg and 10 mg/kg, respectively.

At final analysis 368 patients had died. Survival improved with pembrolizumab 2 mg/kg (HR 0.86, 95% confidence interval [CI] 0.67–1.10; $p = 0.117$) and 10 mg/kg (HR 0.74, 95% CI 0.57–0.96; $p = 0.011$) versus chemotherapy, although the pre-specified threshold for significance of $p < 0.01$ for a single pembrolizumab arm over chemotherapy was not reached. There was no difference in OS between the pembrolizumab doses (HR 0.87, 95% CI 0.67–1.12; $p = 0.290$). Median OS was 13.4 months (95% CI, 11.0–16.4) and 14.7 months (95% CI 11.3–19.5) with pembrolizumab 2 mg/kg and 10 mg/kg, respectively, versus 11.0 months (95% CI 8.9–13.8) with chemotherapy (Fig. 1). Two-year OS rates were 36% (95% CI 28.9–43.0), 38% (95% CI 31.1–45.2) and 30% (95% CI 23.0–36.7) with pembrolizumab 2 mg/kg, 10 mg/kg and chemotherapy, respectively. Adjusting for crossover had limited effect on OS in patients treated with pembrolizumab 2 mg/kg (HR 0.79, 95% CI 0.58–1.08) or 10 mg/kg (0.67, 0.49–0.92; Fig. 2). OS was consistent across all protocol-specified subgroups, including those with 0–1 or ≥2 prior therapies, visceral metastases and regardless of PD-L1 expression (Fig. 3).

With a total of 466 PFS events (RECIST, version 1.1, IRC) at final analysis, PFS improved with pembrolizumab 2 mg/kg (HR 0.58, 95% CI 0.46–0.73; $p < 0.0001$) and 10 mg/kg (0.47, 0.37–0.60; $p < 0.0001$) versus chemotherapy, confirming the PFS benefit reported at the second interim analysis. Estimated 2-year PFS was 16% (95% CI 10.9–22.1) and 22% (95% CI 16.1–28.3) with pembrolizumab 2 mg/kg and 10 mg/kg, respectively, versus 0.6% (95% CI 0.1–3.2) with chemotherapy.

Table 1
Baseline and disease characteristics in the intent-to-treat population.

Characteristic, n (%)	2 mg/kg Q3W n = 180	10 mg/kg Q3W n = 181	Chemotherapy n = 179
Median age, years (range)	62 (15–87)	60 (27–89)	63 (27–87)
≥65 years	78 (43.3)	75 (41.4)	82 (45.8)
Male	104 (57.8)	109 (60.2)	114 (63.7)
ECOG performance status			
0	98 (54.4)	100 (55.2)	98 (54.7)
1	80 (44.4)	81 (44.8)	81 (45.3)
Missing	2 (1.1)	0	0
$BRAF^{V600}$ status			
Mutant	44 (24.4)	40 (22.1)	42 (23.5)
Wild type	136 (75.6)	141 (77.9)	137 (76.5)
Serum lactate dehydrogenase			
Normal	100 (55.6)	106 (58.6)	109 (60.9)
Elevated	78 (43.3)	72 (39.8)	69 (38.5)
Missing	2 (1.1)	3 (1.7)	1 (0.6)
Median tumour size, mm (range)	94.4 (10–428)	98.6 (12–560)	101.3 (11–568)
Metastatic stage			
M0	2 (1.1)	2 (1.1)	2 (1.1)
M1a	8 (4.4)	13 (7.2)	15 (8.4)
M1b	22 (12.2)	17 (9.4)	15 (8.4)
M1c	148 (82.2)	149 (82.3)	147 (82.1)
Number of prior lines of therapy			
0	1 (0.6)	0	0
1	40 (22.2)	55 (30.4)	47 (26.3)
2	79 (43.9)	65 (35.9)	78 (43.6)
3	32 (17.8)	36 (19.9)	32 (17.9)
4	12 (6.7)	18 (9.9)	11 (6.1)
≥5	16 (18.9)	7 (3.9)	11 (6.1)
PD-L1 status			
Positive	99 (55.0)	97 (53.6)	98 (54.7)
Negative	48 (26.7)	46 (25.4)	40 (22.3)
Unknown	33 (18.3)	38 (21.0)	41 (22.9)

Data are n (%). ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death ligand 1.

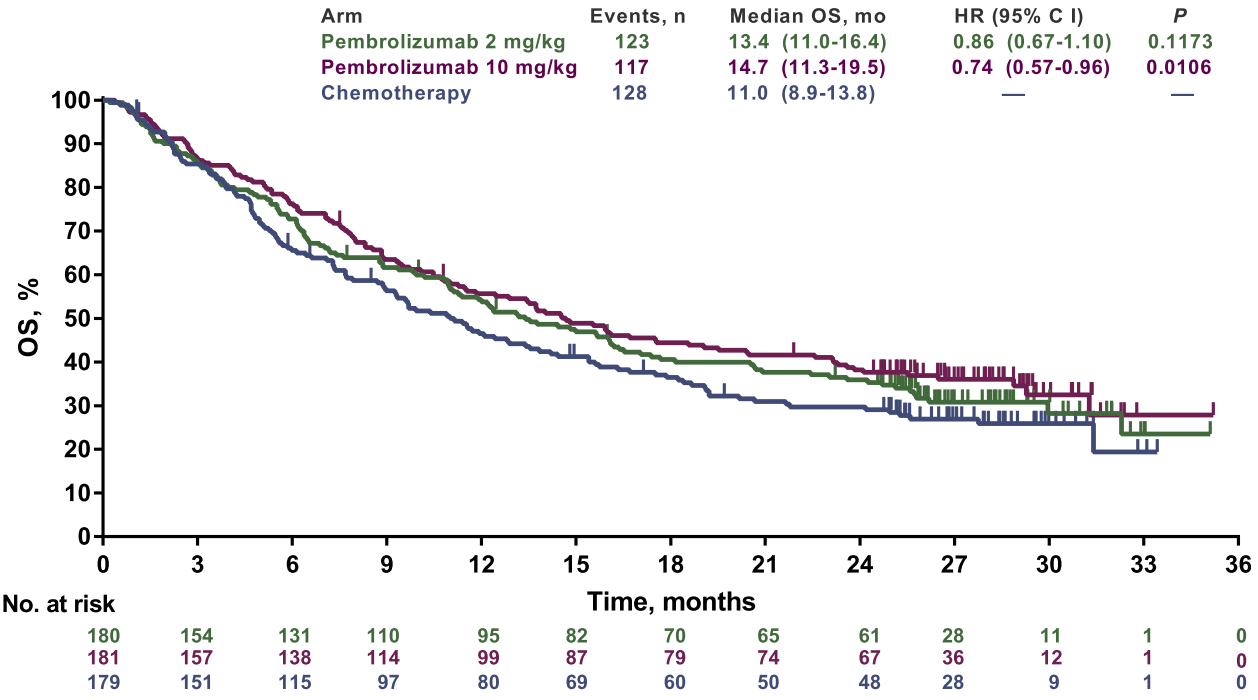

Fig. 1. Kaplan–Meier estimates of OS at final analysis for pembrolizumab 2 mg/kg, 10 mg/kg versus chemotherapy. CI, confidence interval; HR, hazard ratio; OS, overall survival.

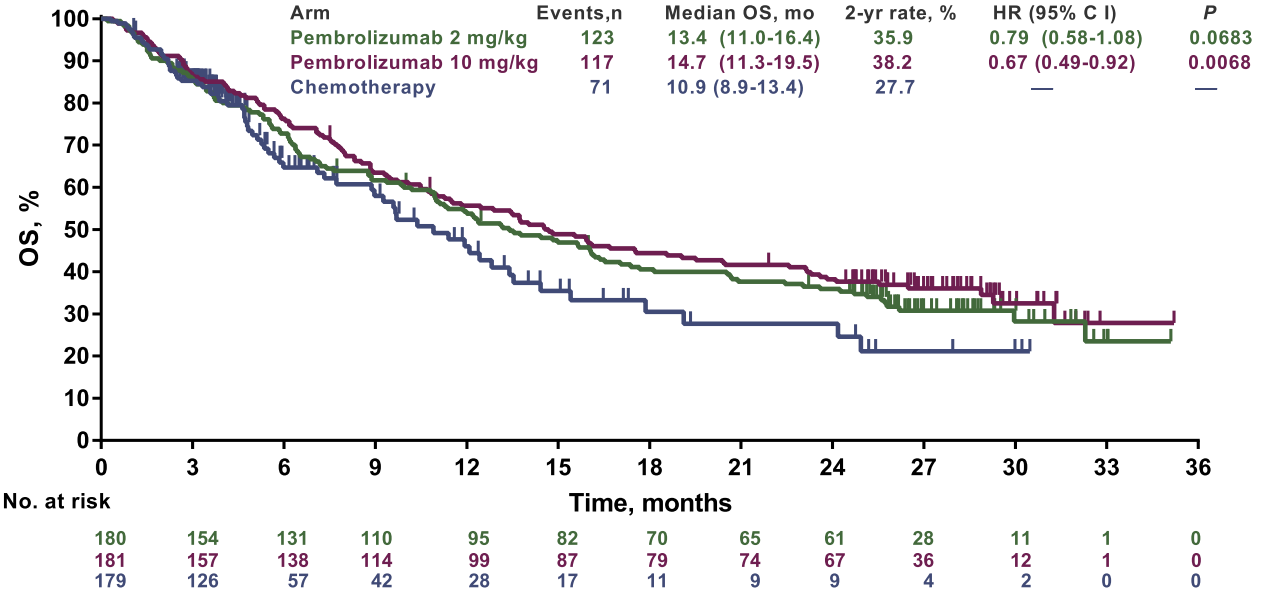

Fig. 2. Kaplan–Meier estimates of OS adjusted for crossover. CI, confidence interval; HR, hazard ratio; OS, overall survival.

The ORR (RECIST, version 1.1, by IRC) was 22% and 28% in 40 and 50 patients receiving pembrolizumab 2 mg/kg and 10 mg/kg, respectively, versus 4% in eight patients receiving chemotherapy ($p < 0.0001$ for both pembrolizumab doses versus chemotherapy). There was no difference between the pembrolizumab doses ($p = 0.214$). At median follow-up of 28 months, 20 (50%) of 40 responders to pembrolizumab 2 mg/kg, 29 (58%) of 50 responders to pembrolizumab 10 mg/kg and one (13%) of eight responders to chemotherapy were alive and progression free, without subsequent anticancer therapy. Median DOR was 22.8 months (range 1.4 + to 25.3+) with pembrolizumab 2 mg/kg and was not reached (range 1.1 + to 28.3+) with pembrolizumab 10 mg/kg, versus 6.8 months (range 2.8–11.3) for chemotherapy. At analysis, eight patients receiving pembrolizumab had response durations greater than 2 years (Fig. 4).

Of the 540 patients enrolled, 528 received ≥1 dose of study treatment and were evaluated for safety. Median time on treatment was 112.5 days (range, 1.0–988.0) and 145.0 days (range, 1.0–967.0) for patients receiving pembrolizumab 2 mg/kg and 10 mg/kg, respectively, versus 62.0 days (range, 1.0–491.0) for chemotherapy. Incidence of any-grade treatment-related adverse events (AEs) was similar among the arms and occurred in 125 (70%) of 178 patients, 136 (76%) of 179 and 138 (81%) of 171 patients treated with pembrolizumab 2 mg/kg, 10 mg/kg and chemotherapy, respectively. Treatment-related grade III–IV AEs were highest with chemotherapy (45 [26%] of 171 patients), versus 24 (13%) of 178 patients with pembrolizumab 2 mg/kg and 29 (16%) of 179 patients with pembrolizumab 10 mg/kg (Table 2). AE profiles of the pembrolizumab doses were similar and consistent with previous reports [13]. Common grade III–IV treatment-related AEs with incidence ≥1% were diarrhoea and fatigue in (n = 4 [1.1%] patients each); vomiting in (n = 2 [<1%] patients) for the combined pembrolizumab doses; anaemia (n = 9 [5.3%]), fatigue (n = 8 [4.7%]), leucopenia (n = 7 [4.1%]), neutropenia (n = 6 [3.5%]), thrombocytopenia, nausea and vomiting in (n = 4 [2.3%] each) and peripheral neuropathy (n = 2 [1.2%]) for chemotherapy. One treatment-related death attributed to a general deterioration in physical health precipitated by grade III diarrhoea, and grade III pneumonia occurred in an 85-year-old patient treated with pembrolizumab 10 mg/kg. Permanent treatment discontinuation due to treatment-related AEs occurred in eight (4%) patients receiving pembrolizumab 2 mg/kg, 15 (8%) receiving pembrolizumab 10 mg/kg and nine (5%) receiving chemotherapy (Table 2).

AEs of an immune nature, regardless of attribution to treatment by investigator, occurred in 32 (18%) patients treated with pembrolizumab 2 mg/kg, 38 (21%) treated with pembrolizumab 10 mg/kg and three (2%) patients treated with chemotherapy (Appendix). The most common immune-mediated AEs were hypothyroidism in 16 (9%) and 15 (8%) patients treated with pembrolizumab 2 mg/kg and 10 mg/kg, respectively; hyperthyroidism in seven (4%) and two (1%), respectively and pneumonitis in four (2% [one grade III event]) and five (3% [three grade III events]), respectively. Grade III treatment-related immune-mediated AEs were 2% and 6% for pembrolizumab 2 mg/kg and 10 mg/kg, respectively. No patients experienced grade IV or V events. Immune-mediated AEs were generally managed by treatment withdrawal, supportive care or corticosteroid therapy. Discontinuations due to immune-mediated AEs occurred in 2% and 6% of patients treated with pembrolizumab 2 mg/kg and 10 mg/kg, respectively.

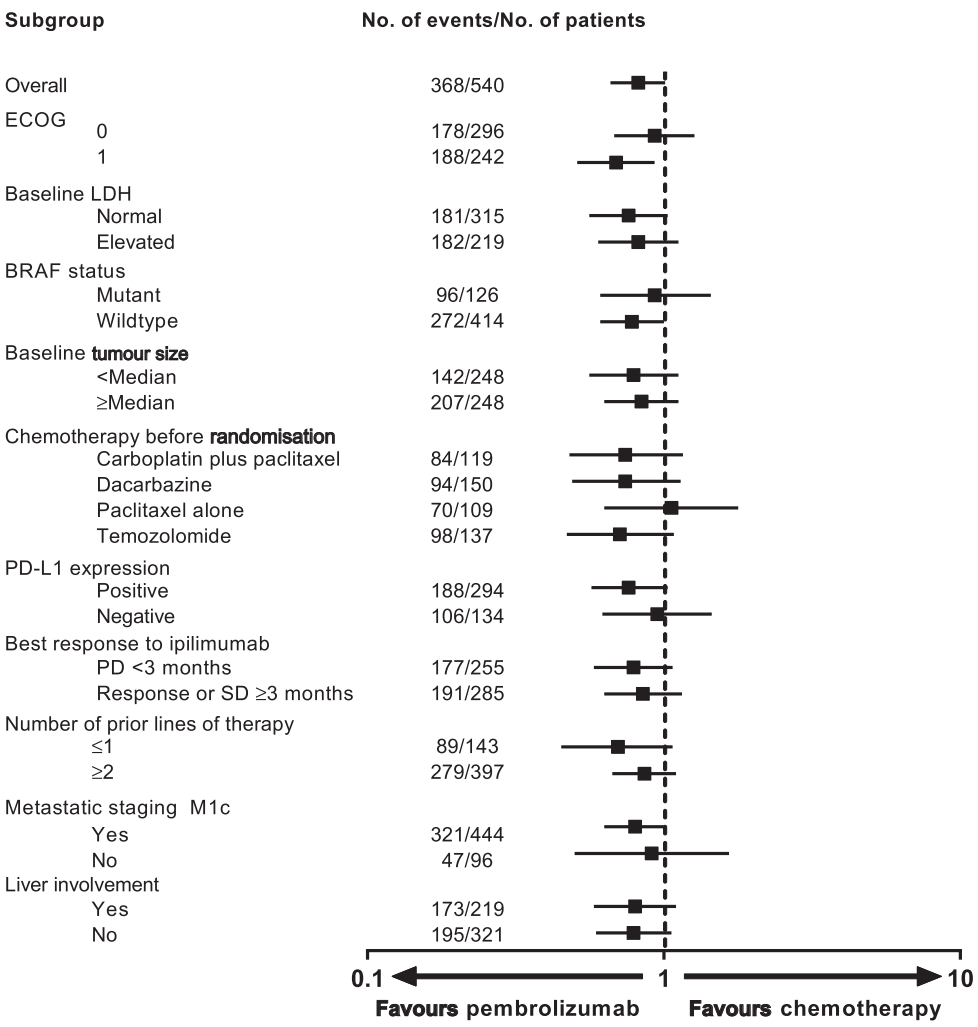

Fig. 3. Overall survival at final analysis in protocol-specified subgroups for pooled pembrolizumab doses versus chemotherapy[a]. [a]Unstratified analysis. ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PD-L1, programmed cell death ligand 1, PD, disease progression; SD; stable disease.

4. Discussion

In this final analysis of KEYNOTE-002, with median follow-up of 28 months, pembrolizumab versus investigator-choice chemotherapy provided numerical but not statistically significant, improvement in OS in patients with heavily pretreated, ipilimumab-refractory, advanced melanoma. With an additional 18 months of follow-up, responses to pembrolizumab continued to be more durable with increased incidence of PR and CR. In addition, the PFS benefit of pembrolizumab was confirmed with approximately 20% of patients alive and progression-free at 24 months. ORR remained five- to six-fold greater with pembrolizumab versus chemotherapy [13]. All analyses favoured pembrolizumab over chemotherapy across all subgroups evaluated, including baseline LDH, tumour size, M-status and hepatic involvement. There were no significant differences in efficacy between pembrolizumab doses, consistent with data from KEYNOTE-001 and KEYNOTE-006 (pembrolizumab versus ipilimumab in advanced, including treatment-naïve melanoma), that showed no significant difference in outcomes based on dose density (2 mg/kg versus 10 mg/kg) and frequency (Q2W versus Q3W).

At final analysis, improvement in median OS was not statistically significant with pembrolizumab versus chemotherapy. This lack of OS benefit is not surprising, given the demanding statistical crossover design of KEYNOTE-002 and baseline patient characteristics. At final analysis, no patients remained on chemotherapy, and over half (98 of 179 [55%]) of the patients had crossed over to pembrolizumab; six patients also received anti–PD-1 therapy off-study, for an effective crossover rate of 58% (104 of 179). These factors may have contributed to an improvement in OS in the chemotherapy arm. Adjusting for crossover provided a numerical, but not statistically significant, benefit in OS with pembrolizumab versus chemotherapy. Moreover, patients were heavily pretreated, (397 [74%] of 540

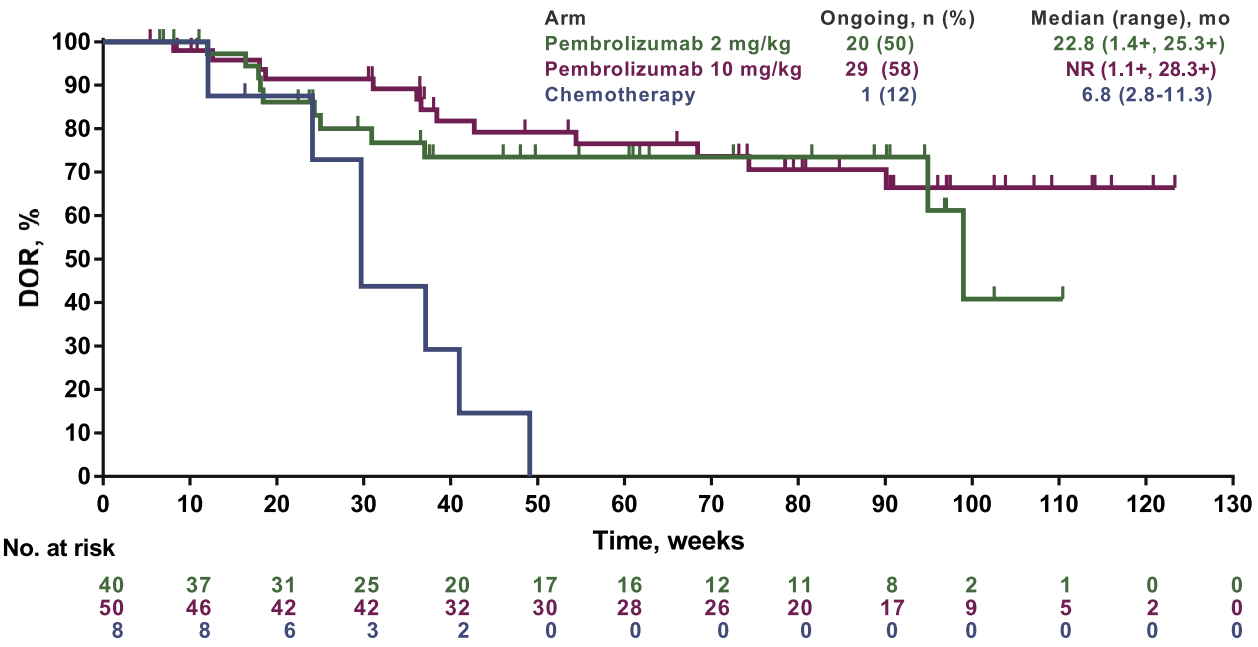

Fig. 4. Kaplan–Meier estimates of duration of response (DOR) at final analysis.

Table 2
Treatment-related adverse events with incidence ≥5% in any treatment group.[a]

Summary	Pembrolizumab 2 mg/kg n = 178			Pembrolizumab 10 mg/kg n = 179			Chemotherapy n = 171		
Events, n (%)	Grade I–II	Grade III–IV	Grade V	Grade I–II	Grade III–IV	Grade V	Grade I–II	Grade III–IV	Grade V
Any	101 (56.7)	24 (13.5)	0	106 (59.2)	29 (16.2)	1 (<1)	93 (54.3)	45 (26.3)	0
Led to discontinuation	2 (1.1)	6 (3.3)	0	4 (2.2)	11 (6.1)	0	5 (2.9)	4 (2.3)	0
Observed in ≥5% of patients in any treatment group									
Fatigue	42 (23.5)	2 (1.1)	0	55 (30.7)	2 (1.1)	0	53 (30.9)	8 (4.6)	0
Pruritus	39 (21.9)	0	0	45 (25.1)	0	0	6 (3.5)	0	0
Nausea	11 (6.2)	0	0	17 (9.5)	1 (<1)	0	55 (32.2)	4 (2.3)	0
Decreased appetite	11 (6.2)	0	0	15 (8.3)	0	0	26 (15.2)	0	0
Anaemia	5 (2.8)	1 (<1)	0	7 (3.9)	0	0	26 (15.2)	9 (5.3)	0
Diarrhoea	18 (10.1)	0	0	18 (10.0)	4 (2.2)	0	11 (6.5)	3 (1.8)	0
Rash	23 (12.9)	0	0	23 (12.8)	0	0	8 (4.7)	0	0
Alopecia	6 (3.4)	0	0	1 (<1)	0	0	36 (21.1)	0	0
Vomiting	3 (1.7)	1 (<1)	0	10 (5.6)	1 (<1)	0	22 (12.8)	4 (2.3)	0
Arthralgia	14 (7.9)	1 (<1)	0	13 (7.2)	1 (<1)	0	8 (4.6)	1 (<1)	0
Constipation	5 (2.8)	0	0	10 (5.6)	0	0	14 (8.2)	0	0
Myalgia	8 (4.5)	2 (1.1)	0	6 (3.4)	0	0	9 (5.2)	1 (<1)	0
Asthenia	6 (3.3)	1 (<1)	0	8 (4.4)	1 (<1)	0	9 (5.2)	1 (<1)	0
Hypothyroidism	14 (7.9)	0	0	13 (7.2)	0	0	0	0	0
Vitiligo	13 (7.3)	0	0	14 (7.8)	0	0	2 (1.2)	0	0
Dry skin	12 (6.7)	0	0	11 (6.1)	0	0	3 (1.8)	0	0
Thrombocytopenia	2 (1.1)	0	0	1 (<1)	1 (<1)	0	12 (7.0)	4 (2.3)	0
Neutropenia	1 (<1)	0	0	0	0	0	9 (5.3)	6 (3.5)	0
Peripheral neuropathy	2 (1.1)	0	0	1 (<1)	0	0	12 (6.0)	2 (1.1)	0
Maculopapular rash	6 (3.3)	1 (<1)	0	12 (6.7)	1 (<1)	0	0	0	0
Leucopenia	0	0	0	1 (<1)	0	0	8 (4.7)	7 (4.0)	0
Paraesthesia	1 (<1)	0	0	2 (1.2)	0	0	10 (5.8)	0	0
Platelet count decreased	0	0	0	1 (<1)	0	0	7 (4.1)	5 (3.0)	0

[a] All patients as treated.

patients with ≥2 prior therapies) with ipilimumab-refractory disease, which may explain why the OS in this study was lower than that seen in the KEYNOTE-001 study of pembrolizumab in a mixed population of patients with treatment-naïve and ipilimumab-refractory melanoma [17,18]. In the latter, median OS was 23 months, with 1- and 2-year OS rates of 66% and 49%, respectively, in the total patient population and was 31 months with 1- and 2-year OS rates of 73% and 60%, respectively, in the treatment-naive population. These data indicate the benefit of initial anti–PD-1 therapy in the first line which is typically greater than

the responses seen in heavily pretreated patient populations.

Prior treatment with CTLA-4 blockade and chemotherapy may affect the tumour microenvironment and impair response to anti–PD-1 therapy. This is suggested by the lower ORR to nivolumab in patients with progression following ipilimumab in CheckMate 037 (32%) [14] compared with ORR in treatment-naïve (40%) patients receiving nivolumab [11]. Similarly, in a pooled analysis of KEYNOTE-001, ORR was 29% in patients with ipilimumab-refractory melanoma versus 39% in the treatment-naïve patients. Differences were seen also in the 1- and 2-year OS rates between patients who were ipilimumab refractory (63% and 46%) versus treatment naïve (71% and 53%). In a longer term follow-up of CheckMate 037, although ORR (27% versus 10%) and DOR (31.9 months versus 12.8 months) remained higher with nivolumab versus chemotherapy, median OS was not significantly improved (15.7 months versus 14.4 months; HR 0.95), and there was no improvement in median PFS (3.1 months versus 3.7 months; HR 1.0) [15]. At the time of initiation of KEYNOTE-002, ipilimumab was among standard-of-care as first-line therapy for advanced melanoma. As currently the clinical standard is PD-1 inhibitor in the first line, few patients can be treated in this sequential fashion. However, the current data support the use of pembrolizumab over chemotherapy for patients who have failed ipilimumab. For patients not treated with PD-1 inhibitor, these data indicate benefit of pembrolizumab over chemotherapy as next-line therapy.

The overall safety of pembrolizumab was tolerable versus chemotherapy, with manageable immune-related AEs. The incidence of treatment-related AEs was similar to that seen at the second interim analysis, with fewer grade III–IV AEs versus chemotherapy, despite an almost two-fold longer treatment exposure. Rates of immune-mediated AEs were similar to those reported at second interim analysis. Most were grade I–II and manageable with supportive care, immunosuppressive therapy or treatment discontinuation. No new immune toxicities were reported.

In summary, these data show that treatment with pembrolizumab improved OS versus chemotherapy in patients with heavily pretreated, ipilimumab-refractory melanoma, but this did not meet statistical significance. The significant PFS benefit, durable response and lower rate of high-grade treatment-related AEs support the benefit of anti–PD-1 therapy in this patient population and pembrolizumab as a standard-of-care for advanced melanoma.

Author contributions

CR, AD, SE conceived, designed or planned the study. OH, IP, RD, JS, LDC, CR, RG, FSH, PAA, KAM, ZW, SE and NI analysed data. OH, IP, RD, AD, CB, LDC, CR, ACP, FSH, KAM and TCG acquired data. OH, IP, JS, DS, CB, LDC, CR, RG, FSH, PAA, KAM, TCG, ZW, SE and NI helped interpret results. OH, IP, JS, DS, LDC, CR, ACP, RG, FSH, PAA, AKS, KAM and TCG provided study materials or patients. OH, SE, NI and AR drafted the manuscript. All authors revised and reviewed this work, and all authors had final approval of the submitted manuscript.

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Role of the funding source

The study sponsor was involved in the study design, protocol development, regulatory and ethics approvals, safety monitoring and reporting, data management and data analysis and also provided writing support. All authors had full access to the study data, reviewed and revised the manuscript and had final responsibility for manuscript submission.

Conflict of interest statement

OH received personal fees as a consultant to Amgen, Novartis, Roche, Bristol-Myers Squib (BMS) and Merck Sharp & Dohme (MSD), as a speaker for Amgen, BMS, Genentech and Novartis and as a support for contracted research from Astra Zeneca, BMS, Celldex, Genentech, Immunocore, Incyte, MSD, Merck Serono, MedImmune, Novartis, Pfizer, Rinat and Roche. RD received personal fees from Amgen, BMS, Roche, Novartis, MSD, Pierre Fabre and Takeda. JS received personal fees and fees as an SAB member from BMS and MSD. DS received fees to institution from MSD, personal and other fees from Amgen, Roche and Novartis and personal fees from Boehringer Ingelheim and Leo Pharma. CB received personal fees from BMS, MSD, Roche, Pfizer, Lilly and GlaxoSmithKline (GSK) and grants and personal fees from Novartis. LDC received personal fees for serving on speakers' bureau from BMS and grants to institution for study conduct from MSD. CR received personal fees as advisory board member for BMS, GSK, Novartis, Amgen, MSD and Roche. ACP received personal fees as a consultant to BMS and MSD. RG received grants and personal fees from Amgen, BMS, Castle BioScience, Novartis and Roche and grants from Array BioPharma, CheckMate Pharma, Celldex, Dynavax, Incyte, Millennium Pharmaceuticals, MSD, Takeda, Reata Pharmaceutical and Syndax. FSH received grants to institution from BMS, personal fees as a consultant to MSD, Novartis, EMD Serono and Genentech and royalties from a pending patent for MICA-related disorders. PAA received grants for research, personal fees as

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2017.07.022.

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