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Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: O.H. is a consultant advisor for Aduro, Akeso, Amgen, Array, BeiGene, BMS, Genentech, GSK, Immunocore, Incyte, Janssen, Merck, NextCure, Novartis, Sanofi, Regeneron, Seattle Genetics, Tempus and Zelluna. He is a speaker for Array, BMS, Novartis, Pfizer, Sanofi and Regeneron. He has contracted research for his institution from Aduro, Akeso, Amgen, Arcus, Array, BMS, CytomX, Exelixis, Genentech, GSK, Immunocore, Incyte, Iovance, Merck, Merck Serono, Moderna, NextCure, Novartis, Regeneron, Sanofi, Seattle Genetics, Torque and Zelluna. S.J.D., B.H.M. and E.J. are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and S.J.D. owns stock in Merck & Co., Inc., Kenilworth, NJ, USA. 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His pending patents include Methods for Treating MICA-Related Disorders (#20100111973; includes royalties), Angiopoietin-2 Biomarkers Predictive of Anti-Immune Checkpoint Response (#20170248603), Compositions and Methods for Identification, Assessment, Prevention, and Treatment of Melanoma Using PD-L1 Isoforms (#20160340407), Therapeutic Peptides (#20160046716, #20140004112, #20170022275, #20170008962), Methods of Using Pembrolizumab and Trebananib and Anti-Galectin Antibody Biomarkers Predictive of Anti-Immune Checkpoint and Anti-Angiogenesis Responses (#20170343552). He has been issued patents for Tumor Antigens and Uses Thereof (#7250291), Therapeutic Peptides (#9402905), Vaccine Compositions and Methods for Restoring NKG2D Pathway Function Against Cancers (#10279021) and Antibodies that Bind to MHC Class I Polypeptide-Related Sequence A (#10106611). A.M.J. has received institutional support from MSD. L.M. has no disclosures to report. 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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.08.013.

Long-term outcomes in patients with advanced melanoma who had initial stable disease with pembrolizumab in KEYNOTE-001 and KEYNOTE-006

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Abstract

Objective: Patients with melanoma and early stable disease (SD) with pembrolizumab have unclear prognosis. We present post hoc analyses of long-term outcomes for patients with early SD, partial response (PR) or complete response (CR) with pembrolizumab.

Patients and methods: Patients who received pembrolizumab in the KEYNOTE-001 and KEYNOTE-006 studies and had SD, PR or CR at weeks 12 or 24 were included.

Results: Of 294 patients in the week 12 analysis, 107 (36.4%) had SD at week 12, of whom 7 (6.5%) had a best overall response of CR, 43 (40.2%) had PR and 57 (53.3%) had SD. Forty-eighte–month overall survival (OS) rates were 95.2%, 73.0% and 47.7%, respectively, for patients with CR, PR and SD at week 12. Similar results were observed in the 241 patients in the week 24 analysis. Forty-eight–month OS rates were 72.1% for patients with SD at week 12 followed by subsequent response and 75.0% for patients with PR at week 12 followed by no change in response or progression. Thirty-six–month and 48-month OS rates were 11.6% and not reached, respectively, for patients with SD at week 12 followed by progression before week 24.

Conclusions: A substantial proportion of patients (46.7%) with early (week 12) SD with pembrolizumab achieved subsequent PR or CR. Patients with SD at week 12 and subsequent CR/PR had similar survival to those who maintained PR. In contrast, patients with SD at week 12 and subsequent progression had poor survival outcomes. These findings may guide treatment decisions for patients achieving early SD.

Trial registration: Clinicaltrials.gov: NCT01295827 (KEYNOTE-001); NCT01866319 (KEYNOTE-006).

Keywords

Melanoma; Pembrolizumab; Programmed death 1; PD-1

1. Introduction

Despite increased education and awareness of risk factors for melanoma, the number of cases diagnosed each year continues to rise [1]. Historically, the prognosis for advanced melanoma was poor, but survival has improved significantly with the introduction of targeted therapies and immune checkpoint inhibitors [2]. For patients with advanced *BRAF* wild-type melanoma, the preferred first-line regimens are pembrolizumab, nivolumab or nivolumab with ipilimumab [3]. For the 50–60% of patients with *BRAF*-mutant melanoma, BRAF and MEK inhibitor combination therapy is also an option if early response is needed [1,3]. Although immunotherapy has improved survival in advanced melanoma, predictive factors associated with long-term response remain to be elucidated [4].

Pembrolizumab is a first-line standard of care option for unresectable stage IIIeIV or metastatic melanoma [3,5,6]. Pembrolizumab has shown durable antitumour activity in advanced melanoma in several trials, including KEYNOTE-001 and KEYNOTE-006 [7,8]. KEYNOTE-001, a phase I trial, evaluated pembrolizumab in patients with locally advanced or metastatic solid tumours, including melanoma [7]. The results from the melanoma cohorts showed that pembrolizumab was well tolerated and had durable antitumour activity, including long-term survival benefit, in patients with treatment-naive or previously treated disease. At five-year follow-up, the objective response rate (ORR) in the overall melanoma population was 34%, and the median overall survival (OS) was 23.8 months [7]. A greater proportion of patients with complete response (CR) had ongoing response compared with patients who had partial response (PR) in the total (89% vs. 63%) and treatment-naive (92% vs. 73%) populations [7].

KEYNOTE-006, a phase III trial, evaluated two regimens of pembrolizumab versus ipilimumab in patients with advanced melanoma [9]. The primary analysis showed significant benefit with pembrolizumab and durable benefit on long-term follow-up [9,10]. In the five-year follow-up analysis, the median OS was 32.7 months with pembrolizumab versus 15.9 months with ipilimumab, and the ORR was 42% versus 17% [8]. Of patients who completed two years of pembrolizumab, 76% with CR, 77% with PR and 54% with stable disease (SD) had an ongoing response.

These trials showed that most patients who achieve CR or PR with pembrolizumab experience durable benefit; however, a better understanding of the prognosis for pembrolizumab-treated patients who have an assessment of SD is needed. This analysis evaluates the outcome of patients with melanoma who received pembrolizumab and had an assessment of SD, PR or CR at week 12 or week 24 in the KEYNOTE-001 and KEYNOTE-006 trials.

2. Materials and methods

2.1. Study design and participants

KEYNOTE-001 evaluated pembrolizumab in patients with locally advanced or metastatic carcinoma, melanoma or non-small cell lung carcinoma [7,11]. For the melanoma cohort, eligible patients were required to have ipilimumab-pretreated or ipilimumab-naive melanoma and to have received ≤2 lines of systemic treatment for metastatic or locally advanced melanoma.

KEYNOTE-006 compared two dose schedules of pembrolizumab with ipilimumab in patients with unresectable stage III or IV melanoma who had received ≤1 prior systemic therapy for advanced disease [8,9]. Patients with *BRAF*-mutant melanoma were required to have received prior BRAF inhibitor therapy unless they met specific criteria. Detailed methods for these trials have been reported previously [11,12]. Eligibility criteria, programmed death ligand 1 (PD-L1) status and baseline patient characteristics are listed in the Supplementary Methods.

2.2. Ethics

The KEYNOTE-001 and KEYNOTE-006 studies were conducted in accordance with the protocol, Good Clinical Practice standards, the Declaration of Helsinki and all local regulations. The protocols and amendments were approved by the relevant institutional review boards or ethics committees at each participating institution. All patients provided written informed consent.

2.3. Procedures

In KEYNOTE-001, patients received pembrolizumab 2 mg/kg every 3 weeks (Q3W), 10 mg/kg Q2W or 10 mg/kg Q3W. In KEYNOTE-006, patients received pembrolizumab 10 mg/kg Q2W, 10 mg/kg Q3W or four doses of ipilimumab 3 mg/kg Q3W (for details see Supplementary Methods). In both studies, response at 12, 18 and 24 weeks was assessed as per Response Evaluation Criteria in Solid Tumours v1.1 by independent central review, and the best overall response (BOR) with confirmation was used.

2.4. Statistical analysis

Post hoc analysis of long-term outcomes is presented for patients with an assessment of SD, PR or CR 12 and 24 weeks after randomisation. Patients were included in the week 12 or 24 analysis populations if they had a single time point assessment of CR, PR or SD at week 12 or 24, respectively, and had not experienced disease progression or were censored before week 12 or 24. Patients were not required to have a week 12 assessment for inclusion in the week 24 analysis population.

The analysis included patients with melanoma who were treatment naive or who had received BRAF or MEK inhibitors as their only prior therapy. Patients who had previously received ipilimumab in KEYNOTE-001 were excluded. Data from pembrolizumab dose groups were pooled.

The association of baseline characteristics and clinical response was evaluated using the chi-square test of independence. The data cutoff was 1 September 2017, for KEYNOTE-001, and 4 December 2017, for KEYNOTE-006.

3. Results

3.1. Patients

In KEYNOTE-001 and KEYNOTE-006, there were 643 patients treated with pembrolizumab who had treatment-naive disease or had received BRAF inhibitors as their only prior therapy (Table 1). Of these, 294 (45.7%) were included in the week 12 analysis and 241 (37.5%) were included in the week 24 analysis. Of the 294 patients in the week 12 population, 23 (7.8%) had CR, 164 (55.8%) had PR and 107 (36.4%) had SD (Fig. 1, Supplementary Fig. 1). Of the 241 patients included in the week 24 population, 42 (17.4%) had CR, 160 (66.4%) had PR and 39 (16.2%) had SD.

At baseline, most patients in the week 12 and week 24 populations had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 and M1c disease (Table 2). Most patients (87.1%, week 12; 88.0%, week 24) had treatment-naive disease.

In the week 12 analysis, of the 164 patients with an assessment of PR at week 12, 49 (29.9%) had a BOR of CR, 108 (65.9%) had a BOR of PR and 7 (4.2%) had a BOR of SD. Of the 107 patients with an initial assessment of SD at week 12, 7 (6.5%) had a BOR of CR, 43 (40.2%) had a BOR of PR and 57 (53.3%) had a BOR of SD. The median time for patients with SD at week 12 to evolve into PR or CR was 12.1 weeks (range, 0.1–98.6) and 12.1 weeks (range, 3.9–131.0), respectively. Of patients with SD at week 12, 23 (21.5%) experienced PD by week 24 and 45 (42.1%) experienced PD after week 24.

In the week 24 analysis, of the 160 patients with an assessment of PR at week 24, 32 (20.0%) had a BOR of CR. Of the 39 patients with SD at week 24, 1 (2.6%) had a BOR of CR, 13 (33.3%) had a BOR of PR and 25 (64.1%) had a BOR of SD. The median time for patients with SD at week 24 to evolve into PR or CR was 12.1 weeks (range, 6.1–86.1) and 120.1 weeks, respectively. Of patients with SD at week 24, 20 (51.3%) developed PD after week 24.

3.2. Association between baseline characteristics and response

Baseline tumour size, PD-L1 status, ECOG PS and metastatic stage were associated with week 12 response (Table 3). Patients with small tumours at baseline (<2.5 cm: CR, 73.9%; PR, 19.5%; SD, 16.8%), a baseline ECOG PS of 0 (CR, 95.6%; PR, 71.9%; SD, 72.0%) and stage M0/M1a/M1b disease (CR, 65.2%; PR, 29.9%; SD, 31.8%) were more likely to have CR at week 12 than PR or SD. Patients with positive PD-L1 tumours were more likely to have CR or PR at week 12 than SD (CR, 89.5%; PR, 91.2%; SD, 77.6%). Sex, baseline tumour size, ECOG PS and metastatic stage were associated with week 24 response (Table 3). As observed with week 12 data, patients with small tumours at baseline (<2.5 cm: CR, 66.7%; PR, 16.9%; SD, 15.4%), a baseline ECOG PS of 0 (CR, 90.5%; PR, 70.0%; SD, 76.9%) and stage M0/M1a/M1b disease (CR, 54.82%; PR, 28.79%; SD, 38.5%) were more likely to have CR at week 24 than PR and SD. Patients who were female (CR, 59.5%; PR,

77.5%; SD, 59.0%) and had stage M1c disease (CR, 45.2%; PR, 71.3%; SD, 61.5%) were more likely to have PR at week 24 than CR or SD.

3.3. Survival

In the overall week 12 population, the 24-, 36- and 48-month OS rates were 79.6%, 73.6% and 65.6%, respectively (Table 4). Response at week 12 was correlated with longer subsequent OS than SD at week 12, with 48-month OS rates of 95.2%, 73.0% and 47.7% for patients with CR, PR and SD, respectively (Fig. 2A). In the week 24 population, the overall 24-, 36- and 48-month OS rates were 88.3%, 81.8% and 77.5%, respectively. Response at week 24 was also associated with longer subsequent OS than SD at week 24, with 48-month OS rates of 97.6%, 75.2% and 66.0% for patients with CR, PR and SD, respectively (Fig. 2B).

The OS of patients with SD and PR at week 12 by subsequent response was also assessed. Among patients with a week 12 assessment of SD, followed by subsequent response (PR/CR) or ongoing SD (no subsequent response, no subsequent progression), the estimated 48- month OS rates were 72.1% and 46.9%, respectively (Table 5). Among patients with a week 12 assessment of PR followed by subsequent CR, or ongoing PR, the estimated 48-month OS rates were 93.8% and 75.0%, respectively. The 48-month OS rates for patients with a week 12 assessment of SD or PR followed by progression were not estimable, and ongoing patients were censored before 48 months (Table 5).

Survival outcomes were poorest for patients with a week 12 response of SD who subsequently progressed (Fig. 3). Observational comparisons of baseline characteristics among patients with SD at week 12 by subsequent response showed that patients with subsequent PD were more likely to have *BRAF*-mutant disease (SD followed by response, 41.7%; ongoing SD, 35.4%; SD followed by PD, 60.9%), have received prior BRAF inhibitor therapy only (SD followed by response, 8.3%; ongoing SD, 14.6%; SD followed by PD, 26.1%) and be <65 years (SD followed by response, 44.4%; ongoing SD, 50.0%; SD followed by PD, 69.6%) compared with patients with SD at week 12 and followed by response or ongoing SD (Table 6).

4. Discussion

This retrospective analysis showed distinct outcomes in patients with advanced melanoma who are treated with pembrolizumab and have an early assessment of SD, PR or CR. As expected, the best survival outcomes were observed in patients with a week 12 or week 24 assessment of CR. Notably, however, a significant proportion of patients with early (week 12 or 24) SD went on to have a response with pembrolizumab. Among patients with SD at week 12, almost half (46.7%) achieved a BOR of CR (6.5%) or PR (40.2%) with continued treatment. Similarly, more than one third of patients (35.9%) with SD at week 24 had a BOR of CR (2.6%) or PR (33.3%) with continued pembrolizumab. Interestingly, patients with SD at week 12 had lower 48-month OS compared with patients who had SD at week 24 (47.7% vs. 66.0%); this may partly be due to a greater proportion of patients with primary resistance and/or slow-growing tumours being included in the former group.

Patients with an assessment of SD at week 12 followed by subsequent response had similar survival outcomes to patients with an assessment of PR at week 12 followed by no change in response or progression (48-month OS, 72.1% vs. 75.0%, respectively). Although patients with an assessment of SD at week 12 followed by no response or progression had worse survival outcomes than patients with SD at week 12 with subsequent response, approximately half of patients (46.9%) in the former group were still alive at 48 months. As expected, patients with SD at week 12 who subsequently progressed had the poorest outcomes. Analysis of baseline characteristics among patients with initial SD showed that patients with subsequent progression were more likely to have *BRAF*-mutant disease and to have received prior BRAF inhibitor therapy and were more likely to be younger than those with subsequent response or ongoing SD.

The current treatment paradigm for advanced melanoma involves discontinuation of immune checkpoint inhibitors because of unacceptable toxicity or disease progression [3]. In situations in which patients experience disease progression, switching to an alternative therapy is recommended. However, it is important to confirm disease progression before switching to a different therapy as there are limited effective therapies after checkpoint inhibitor failure [3]. In this analysis, a week 12 or 24 assessment of SD was still predictive of long-term OS benefit for a substantial proportion of patients, with 47.7% and 66.0% of patients, respectively, estimated to be alive at 4 years. These results argue against prematurely switching therapy in patients with early SD with pembrolizumab. An alternative approach may be the addition of other agents to pembrolizumab that may increase the proportion of patients with early SD or elicit response to such combination therapy. Several ongoing clinical trials are investigating the antitumour activity and safety of combinations of various agents with PD-1 inhibitors [13–18]. Alternatively, predictive markers such as circulating tumour DNA or imaging with 18F-fluorodeoxyglucose positron emission tomography can be used to identify early responses to PD-1 inhibitors in metastatic melanoma, which may help differentiate between patients with SD who are likely to gain durable clinical benefit from those whose disease is most likely to progress [19–22].

Our results also demonstrated that baseline tumour size, ECOG PS and metastatic stage were consistently associated with response. Patients with small baseline tumours, an ECOG PS of 0 and less disseminated disease (M0/M1a/M1b) were more likely to have CR at week 12 or week 24 than PR or SD.

This analysis was limited by its retrospective nature and the pooling of results from two trials with differing patient populations and differences in prior treatments between the studies. Approximately 30% of patients included were from KEYNOTE-001, which required patients with *BRAF*-mutant melanoma to have received prior BRAF and/or MEK inhibitors. In contrast, patients with *BRAF*-mutant melanoma in KEYNOTE-006 could be BRAF inhibitor naive if they had normal lactate dehydrogenase, non-symptomatic disease and absence of rapid progression. Furthermore, patients in KEYNOTE-001 could have received ≤2 prior lines of therapy, whereas patients in KEYNOTE-006 could have received 1 prior therapy. Patients in KEYNOTE-001 may therefore have had more advanced disease and differences in tumour biology [23] than those in KEYNOTE-006. KEYNOTE-001 was

also an open-label study with multiple expansion cohorts enrolled without randomisation, which may have confounded this analysis.

Thus, prospective evaluation of outcomes in patients with melanoma who respond early to pembrolizumab is warranted. Earlier intervention with additional or subsequent therapy in patients with SD may provide optimal responses to PD-1 inhibitors, restoring the antitumour activity. In addition, biomarkers are needed to identify responders early during treatment.

5. Conclusions

These results indicate that a substantial proportion of patients who have SD during the first six months of treatment go on to achieve PR or CR with continued pembrolizumab therapy and have promising long-term survival. As expected, the longest survival was observed in patients with CR, followed by patients with early PR who went on to achieve subsequent CR. Patients who had early PR and sustained PR had the next best survival. Notably, patients with SD at week 12 who went on to have PR or CR exhibited similar long-term survival to patients with an early and sustained PR. Patients with SD at week 12 and no subsequent response or progression had poorer outcomes than these groups. The worst outcomes were observed in patients with PR or SD at week 12 who developed progression within 6 months of initiating treatment. The current findings may help guide future trial design and clinical decisions for patients with advanced melanoma who have an initial assessment of SD with pembrolizumab.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data sharing statement

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA (MSD) is committed to providing qualified scientific researchers access to anonymised data and clinical study reports from the company’s clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of

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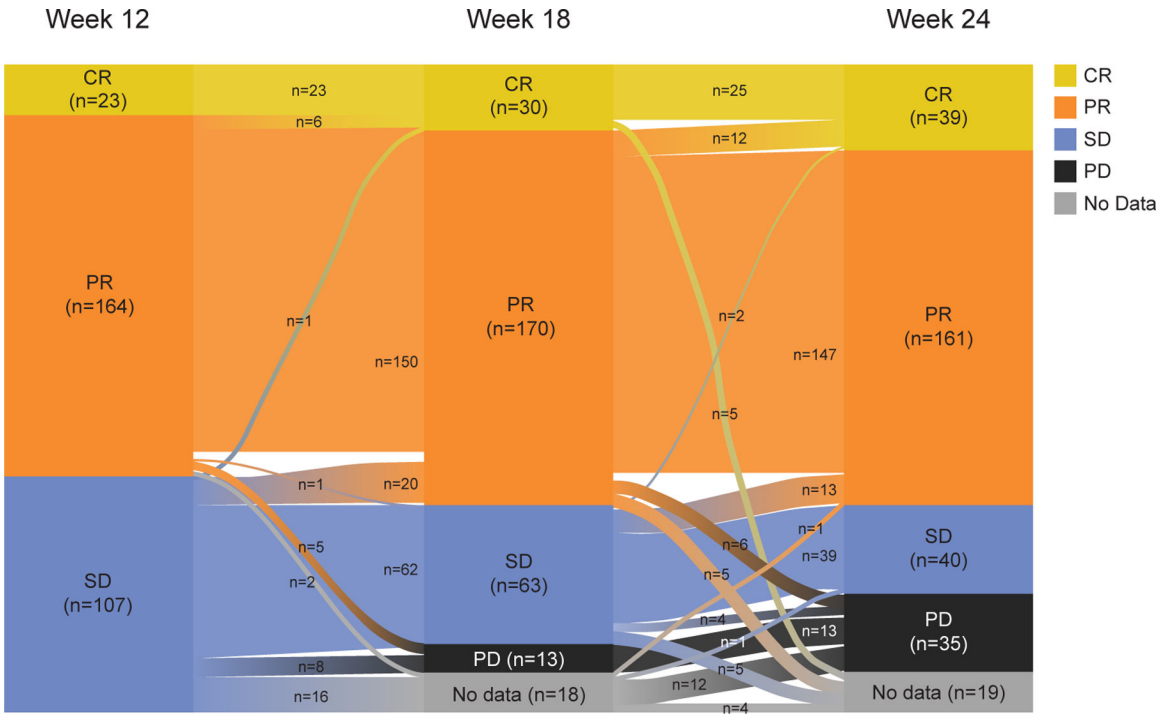

Fig. 1.

Subsequent response for patients with SD, PR or CR at week 12 in the week 12 analysis population. Response was assessed by independent central review in KEYNOTE-001 and in KEYNOTE-006. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

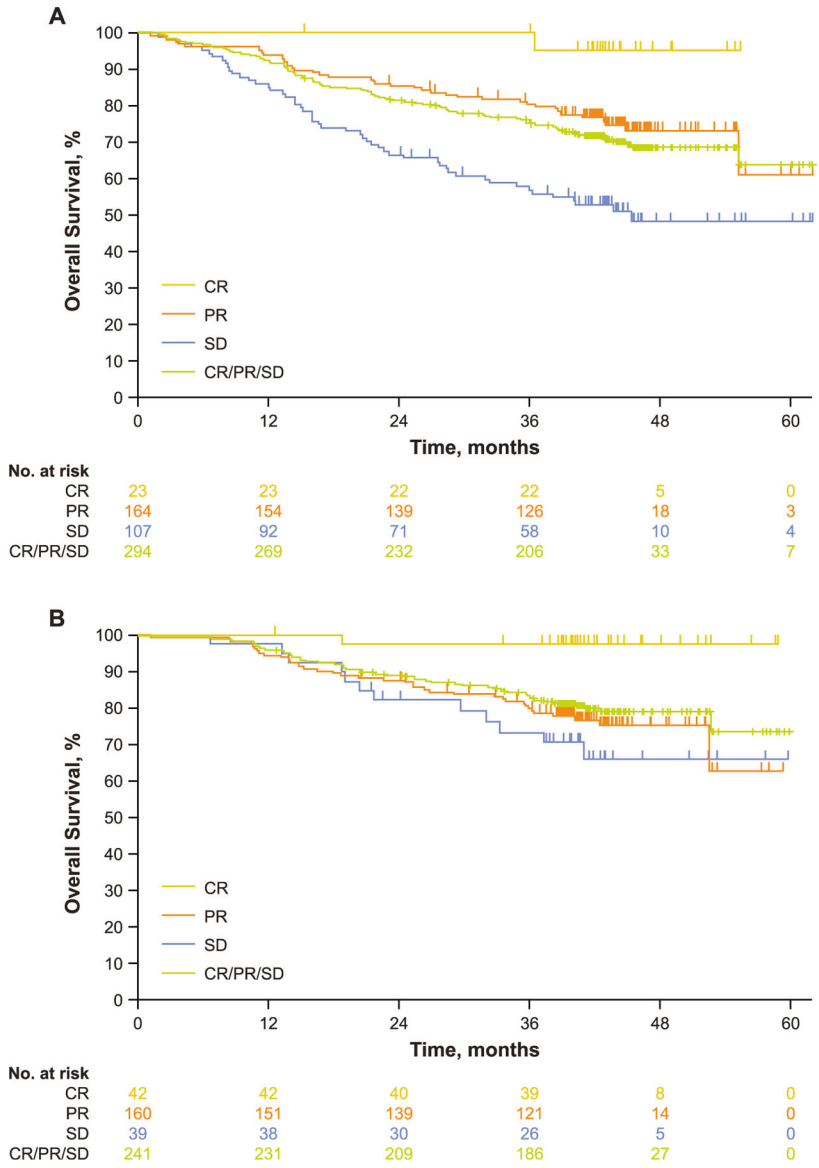

Fig. 2.

Kaplan-Meier estimates of OS (A) by week 12 response in the week 12 analysis population.[a] (B) by week 24 response in the week 24 analysis population.[b] CR, complete response; OS, overall survival; PR, partial response; SD, stable disease. [a]OS rate from week 12. [b]OS rate from week 24.

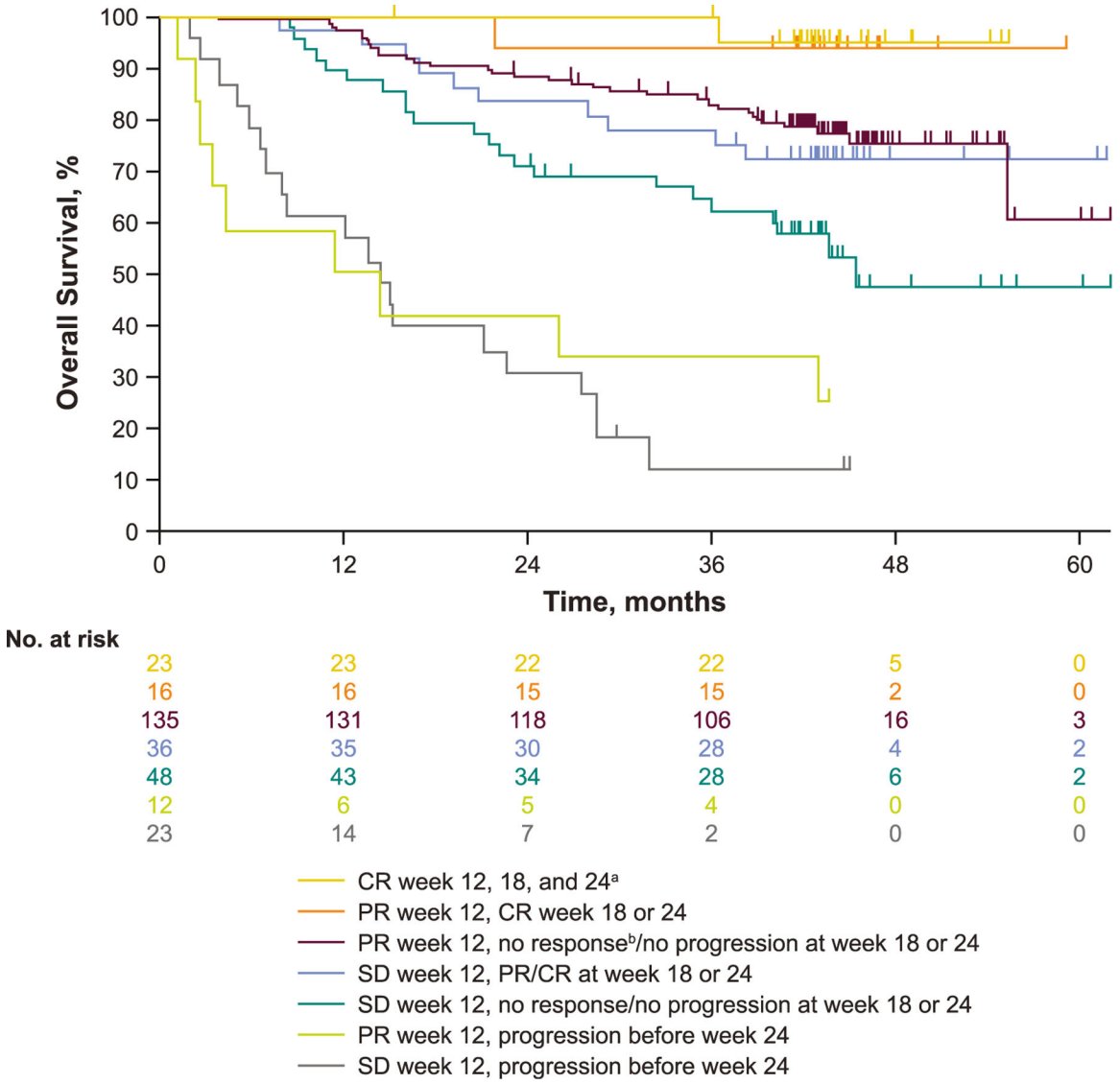

Fig. 3.

Kaplan-Meier estimate of OS from week 12 by subsequent response in patients with PR or SD at week 12 in the week 12 analysis population. CR, complete response; OS, overall survival; PR, partial response; SD, stable disease. [a]All patients with CR at week 12 for whom data were available continued to have CR at weeks 18 and 24. [b]Patients had PR at week 12 and no subsequent change in response and no progression at week 18 or 24.

Table 1

Pembrolizumab-treated patients included in the analysis.

Patients, n	Week 12 analysis			Week 24 analysis		
	KEYNOTE-001	KEYNOTE-006	Total	KEYNOTE-001	KEYNOTE-006	Total
Treatment naive or prior BRAFi	182	461	643	182	461	643
Progressed or censored before time point	82	202	284	97	240	337
Missing response at landmark	7	22	29	9	35	44
Response other than SD, PR or CR[a]	7	29	36	3	18	21
Patients included in analysis, n	**86**	**208**	**294**	**73**	**168**	**241**
Treatment naive	79	177	256	68	144	212
Prior BRAFi only	7	31	38	5	24	29

BRAFi, BRAF inhibitor; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

[a]Included patients with non-CR/non-PD, not available, not done or unconfirmed progression.

Table 2

Baseline characteristics of patients included in the analysis.

Characteristic, n (%)	Week 12 analysis population; n = 294	Week 24 analysis population; n = 241
Sex		
Male	203 (69.0)	172 (71.4)
Female	91 (31.0)	69 (28.6)
Age		
<65 years	150 (51.0)	121 (50.2)
≥65 years	144 (49.0)	120 (49.8)
Tumour size [a]		
<2.5 cm	67 (22.8)	61 (25.3)
2.5 to <5 cm	90 (30.6)	63 (26.1)
5 to <10 cm	69 (23.5)	60 (24.9)
≥10 cm	68 (23.1)	57 (23.7)
***BRAF* status (all patients)**		
Wild type	187 (63.6)	160 (66.4)
Mutant	103 (35.0)	79 (32.8)
Unknown	4 (1.4)	2 (0.8)
***BRAF* status (previously untreated patients)**		
Wild type	185 (72.3)	158 (74.5)
Mutant	68 (26.5)	53 (25.0)
Unknown	3 (1.2)	1 (0.5)
PD-L1 tumour status [b]		
Negative	33 (11.2)	26 (10.8)
Positive	207 (70.4)	168 (69.7)
Unknown	54 (18.4)	47 (19.5)
ECOG PS		
0	217 (73.8)	180 (74.7)
1	77 (26.2)	61 (25.3)
Lactate dehydrogenase level		
Normal	212 (72.1)	179 (74.3)
Elevated	77 (26.2)	57 (23.6)
Unknown	5 (1.7)	5 (2.1)
Metastasis stage		
M0/M1A/M1B	98 (33.3)	84 (34.9)
M1C	196 (66.7)	157 (65.1)

ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death ligand 1.

[a] Baseline tumour size was measured by adding the sum of the longest dimensions of all measurable baseline target lesions.

[b] PD-L1 positivity was defined as membranous staining in at least 1% of tumour cells.

Table 3

Association between baseline characteristics and response in the week 12 and week 24 analysis populations.[a]

Characteristic, n (%)	Week 12 assessment population			Week 24 assessment population		
	SD; n = 107	PR; n = 164	CR; n = 23	SD; n = 39	PR; n = 160	CR; n = 42
Sex						
Male	75 (70.1)	114 (69.5)	14 (60.9)	16 (41.0)	36 (22.5)	17 (40.5)
Female	32 (29.9)	50 (30.5) *p* = 0.673	9 (39.1)	23 (59.0)	124 (77.5) ***p* = 0.01**	25 (59.5)
Tumour size, [b]						
<2.5	18 (16.8)	32 (19.5)	17 (73.9)	6 (15.4)	27 (16.9)	28 (66.7)
2.5 to <5	36 (33.6)	49 (29.9)	5 (21.7)	14 (35.9)	39 (24.4)	10 (23.8)
5 to <10	31 (29.0)	37 (22.5)	1 (4.4)	14 (35.9)	43 (26.9)	3 (7.1)
≥10	22 (20.6)	46 (28.1) ***p* < 0.001**	0	5 (12.8)	51 (31.9) ***p* < 0.001**	1 (2.4)
PD-L1 tumour status [c]						
Positive	66 (77.6)	124 (91.2)	17 (89.5)	22 (75.9)	114 (87.7)	32 (91.4)
Negative	19 (22.4)	12 (8.8) ***p* < 0.05**	2 (10.5)	7 (24.1)	16 (12.3) *p* = 0.17	3 (8.6)
ECOG PS						
0	77 (72.0)	118 (71.9)	22 (95.6)	30 (76.9)	112 (70.0)	38 (90.5)
1	30 (28.0)	46 (28.1) ***p* < 0.05**	1 (4.4)	9 (23.1)	48 (30.0) ***p* < 0.05**	4 (9.5)
Metastatic stage						
M0/M1a/M1b	34 (31.8)	49 (29.9)	15 (65.2)	15 (38.5)	46 (28.7)	23 (54.8)
M1c	73 (68.2)	115 (70.1) ***p* < 0.01**	8 (34.8)	24 (61.5)	114 (71.3) ***p* < 0.01**	19 (45.2)

CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death ligand 1; PR, partial response; SD, stable disease.

[a] Association of baseline characteristics and clinical assessment was evaluated using the chi-square test of independence. *p* values are not adjusted for multiplicity.

[b] Baseline tumour size was measured by adding the sum of the longest dimensions of all measurable baseline target lesions.

[c] Among those with PD-L1eevaluable tumours (week 12: SD, n = 85; PR, n = 136; CR, n = 19. Week 24: SD, n = 29; PR, n = 130; CR, n = 35). PD-L1 positivity was defined as membranous staining in at least 1% of tumour cells.

Table 4

Estimated OS rates by response in the week 12 or week 24 analysis populations.

OS rate, % (95% CI)	Week 12 analysis population[a]			Week 24 analysis population[b]		
	24-month	36-month	48-month	24-month	36-month	48-month
Overall	79.6 (74.5–83.7)	73.6 (68.1–78.3)	65.6 (59.3–71.2)	88.3 (83.6–91.8)	81.8 (76.3–86.2)	77.5 (71.2–82.7)
SD	66.4 (56.6–74.4)	57.5 (47.5–66.3)	47.7 (36.6–58.1)	82.0 (65.9–91.0)	73.5 (56.2–84.8)	66.0 (47.0–79.5)
PR	85.4 (79.0–89.9)	80.4 (73.4–85.7)	73.0 (64.7–79.6)	87.5 (81.3–91.7)	79.7 (72.6–85.2)	75.2 (67.0–81.6)
CR	100.0 (100.0–100.0)	100.0 (100.0–100.0)	95.2 (70.7–99.3)	97.6 (83.9–99.7)	97.6 (83.9–99.7)	97.6 (83.9–99.7)

CI, confidence interval; CR, complete response; OS, overall survival; PR, partial response; SD, stable disease.

[a]OS rate from week 12.

[b]OS rate from week 24.

Table 5

Estimated OS rates by pattern of response in the week 12 analysis population.

OS rate, %[a] (95% CI)	24-month	36-month	48-month
SD at week 12 assessment			
Followed by PR/CR at week 18 or 24	88.3 (66.6–92.1)	77.8 (60.4–88.2)	72.1 (54.4–83.9)
Followed by no response/no progression[b] at week 18 or 24	70.8 (55.8–81.6)	64.1 (48.7–76.0)	46.9 (28.9–63.0)
Followed by progression before week 24	30.4 (13.5–49.3)	11.6 (2.3–29.1)	NE
PR at week 12 assessment			
Followed by CR at week 18 or 24	93.8 (63.2–99.1)	93.8 (63.2–99.1)	93.8 (63.2–99.1)
Followed by no change in response/no progression[b] at week 18 or 24	88.1 (81.4–92.6)	82.8 (75.3–88.2)	75.0 (65.9–82.0)
Followed by progression before week 24	41.7 (15.2–66.5)	33.3 (10.3–58.8)	NE

CI, confidence interval; CR, complete response; NE, not estimable; OS, overall survival; PR, partial response; SD, stable disease.

[a] OS rate from week 12.

[b] Included patients with no subsequent change in response or disease progression, patients with missing subsequent response data and patients censored due to being lost to follow-up.

Table 6

Baseline characteristics of patients with a week 12 response of SD by subsequent response.

Characteristic, n (%)	SD followed by CR/PR; n = 36	SD followed by SD; n = 48	SD followed by PD; n = 23
Prior lines			
Treatment naive	33 (91.7)	41 (85.4)	17 (73.9)
Prior BRAFi only	3 (8.3)	7 (14.6)	6 (26.1)
Sex			
Male	30 (83.3)	30 (62.5)	15 (65.2)
Female	6 (16.7)	18 (37.5)	8 (34.8)
Age			
<65 years	16 (44.4)	24 (50.0)	16 (69.6)
≥65 years	20 (55.6)	24 (50.0)	7 (30.4)
Tumour size,[a] cm			
<2.5 cm	8 (22.2)	6 (12.5)	4 (17.4)
2.5 to <5 cm	10 (27.8)	19 (39.6)	7 (30.4)
5 to <10 cm	10 (27.8)	14 (29.2)	7 (30.4)
≥10 cm	8 (22.2)	9 (18.7)	5 (21.7)
***BRAF* status (all patients)**			
Wild type	21 (58.3)	31 (64.6)	8 (34.8)
Mutant	15 (41.7)	17 (35.4)	14 (60.9)
Unknown	0	0	1 (4.3)
***BRAF* status (previously untreated patients)**			
Wild type	21 (63.6)	31 (75.6)	8 (47.1)
Mutant	12 (36.4)	10 (24.4)	8 (47.1)
Unknown	0	0	1 (5.8)
PD-L1 tumour status [b]			
Negative	7 (19.4)	9 (18.8)	3 (13.1)
Positive	24 (66.7)	27 (56.2)	15 (65.2)
Unknown	5 (13.9)	12 (25.0)	5 (21.7)
ECOG PS			

Characteristic, n (%)	SD followed by CR/PR; n = 36	SD followed by SD; n = 48	SD followed by PD; n = 23
0	26 (72.2)	32 (66.7)	19 (82.6)
1	10 (27.8)	16 (33.3)	4 (17.4)
Lactate dehydrogenase level			
Normal	28 (77.8)	33 (68.7)	18 (78.3)
Elevated	8 (22.2)	14 (29.2)	5 (21.7)
Unknown	0	1 (2.1)	0
Metastasis stage			
M0/M1A/M1B	11 (30.6)	15 (31.3)	8 (34.8)
M1C	25 (69.4)	33 (68.7)	15 (65.2)

BRAFi, BRAF inhibitor; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death ligand 1; PR, partial response; SD, stable disease.

[a]Baseline tumour size was measured by adding the sum of the longest dimensions of all measurable baseline target lesions.

[b]PD-L1 positivity was defined as membranous staining in at least 1% of tumour cells.