

ORIGINAL ARTICLE

Five-year survival outcomes for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001

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Background: Pembrolizumab demonstrated robust antitumor activity and safety in the phase Ib KEYNOTE-001 study (NCT01295827) of advanced melanoma. Five-year outcomes in all patients and treatment-naïve patients are reported herein. Patients whose disease progressed following initial response and who received a second course of pembrolizumab were also analyzed.

Patients and methods: Patients aged ≥ 18 years with previously treated or treatment-naïve advanced/metastatic melanoma received pembrolizumab 2 mg/kg every 3 weeks, 10 mg/kg every 3 weeks, or 10 mg/kg every 2 weeks until disease progression, intolerable toxicity, or patient/investigator decision to withdraw. Kaplan–Meier estimates of overall survival (OS) and progression-free survival (PFS) were calculated. Objective response rate and PFS were based on immune-related response criteria by investigator assessment (data cut-off, September 1, 2017).

Results: KEYNOTE-001 enrolled 655 patients with melanoma; median follow-up was 55 months. Estimated 5-year OS was 34% in all patients and 41% in treatment-naïve patients; median OS was 23.8 months (95% CI, 20.2–30.4) and 38.6 months (95% CI, 27.2–not reached), respectively. Estimated 5-year PFS rates were 21% in all patients and 29% in treatment-naïve patients; median PFS was 8.3 months (95% CI, 5.8–11.1) and 16.9 months (95% CI, 9.3–35.5), respectively. Median response duration was not reached; 73% of all responses and 82% of treatment-naïve responses were ongoing at data cut-off; the longest response was ongoing at 66 months. Four patients [all with prior response of complete response (CR)] whose disease progressed during observation subsequently received second-course pembrolizumab. One patient each achieved CR and partial response (after data cut-off). Treatment-related AEs (TRAEs) occurred in 86% of patients and resulted in study discontinuation in 7.8%; 17% experienced grade 3/4 TRAE.

Conclusions: This 5-year analysis of KEYNOTE-001 represents the longest follow-up for pembrolizumab to date and confirms the durable antitumor activity and tolerability of pembrolizumab in advanced melanoma.

Clinical Trial Registry: ClinicalTrials.gov, NCT01295827.

Key words: pembrolizumab, melanoma, treatment-naïve, long-term follow-up, metastatic, overall survival

Introduction

The incidence of melanoma is increasing, with up to 20% of patients expected to develop advanced/metastatic disease [1]. The historical 10-year survival rate in patients with advanced melanoma was approximately 10% [2–4]; experience with monotherapy directed against cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) [5–7] has increased this survival rate up to 22% [4]. Given the increased response and 1-year survival rates with programmed death (PD-1) inhibitors [8–12], a complementary increase in 5-year survival is expected.

Two PD-1 inhibitors, pembrolizumab and nivolumab, have been evaluated extensively in patients with melanoma; both block the interaction between PD-1 and its ligands, PD-L1 and PD-L2, to reinstate the antitumor immune response [13, 14]. In three separate trials of advanced melanoma (KEYNOTE-001, KEYNOTE-002, and KEYNOTE-006), which included previously treated and treatment-naïve patients, pembrolizumab monotherapy provided durable response rates of 30%–40% [8, 10, 12, 15–18]. Similarly, in the advanced melanoma cohort of patients from the dose-ranging phase I CA209-003 study, treatment with nivolumab resulted in a cumulative response rate of 28% [19] and 5-year overall survival (OS) rate of 34% [20]. Subsequent phase III studies of nivolumab as monotherapy in treatment-naïve and previously treated advanced melanoma yielded durable response rates of 32% and 40%, respectively [9, 11]. Reports of long-term efficacy and safety in patients treated with PD-1 inhibitors for advanced melanoma are limited.

In the large phase Ib KEYNOTE-001 study, pembrolizumab monotherapy provided 3-year OS rates of 41% for patients with ipilimumab-treated and ipilimumab-naïve advanced melanoma and 45% for patients with treatment-naïve advanced melanoma [12]. Median OS was 23.8 months (95% CI, 20.2–29.0) overall and 20.0 (95% CI, 17.8–27.1), and 28.8 (95% CI, 23.1–32.2) months for ipilimumab-treated and treatment-naïve patients, respectively. Five-year follow-up data of patients treated with pembrolizumab are presented, including data on retreatment of patients receiving a second-course of pembrolizumab on disease progression after first course therapy.

Patients and methods

Patients

KEYNOTE-001 (NCT01295827) was an open-label, phase Ib clinical trial that included multiple cohorts of patients with advanced solid tumors, including melanoma and non-small-cell lung cancer. Eligibility criteria for the ipilimumab-treated or ipilimumab-naïve melanoma cohorts are published [8]. Briefly, eligible patients were ≥ 18 years of age with confirmed advanced or metastatic melanoma, measurable disease per immune-related response criteria (irRC) [21], Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1, no history of chemotherapy within 4 weeks of first pembrolizumab dose, and no history of treatment targeting the PD-1/PD-L1 pathway. Patients were recruited between December 2011 and September 2013, and they enrolled in nonrandomized and randomized cohorts.

Study design

The study protocol and amendments were approved by the appropriate institutional review board or independent ethics committee at each

participating institution. The study was conducted in accordance with the protocol, good clinical practice guidelines, provisions of the Declaration of Helsinki, and all local regulations. All patients provided written informed consent to participate.

Treatment and assessments

Patients received pembrolizumab 2 mg/kg every 3 weeks, 10 mg/kg every 3 weeks, or 10 mg/kg every 2 weeks until disease progression, intolerable toxicity, or patient or investigator decision to withdraw. After a protocol amendment, patients who experienced complete response (CR), confirmed by imaging scans ≥ 4 weeks apart, and who received pembrolizumab treatment for ≥ 6 months could, at the discretion of the investigator and if the patient desired, discontinue treatment after receiving ≥ 2 pembrolizumab doses beyond the initial determination of CR. Patients were eligible to receive a second course of pembrolizumab if they stopped initial treatment after attaining investigator-determined CR per irRC, investigator-determined partial response (PR), or stable disease (SD) after 2 years of treatment with pembrolizumab; were treated for ≥ 24 weeks before discontinuing therapy; experienced investigator-determined progression after stopping their initial treatment; had an ECOG status of 0 or 1; and did not receive any cancer treatment since the last dose of pembrolizumab. Tumor response was assessed every 12 weeks by independent central review using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (for determining efficacy) and by investigator review using irRC (for disease management). For all analyses of response rates and PFS, tumor response was assessed by investigator review using irRC; for the biomarker analyses, response was assessed by central review per RECIST v1.1.

Gene expression analysis

The correlation between response to pembrolizumab and gene expression profile (GEP) was explored using the 18-gene T-cell-inflamed GEP [CCL5, CD27, CD274 (PD-L1), CD276 (B7-H3), CD8A, CMKLR1, CXCL9, CXCR6, HLA-DQA1, HLA-DRB1, HLA-E, IDO1, LAG3, NKG7, PDCD1LG2 (PD-L2), PSMB10, STAT1, and TIGIT]; development is described elsewhere [22]. The 18-gene T-cell-inflamed GEP consists of genes related to antigen presentation, chemokine expression, cytolytic activity, and adaptive immune resistance. GEP scores were computed by taking a weighted sum of the housekeeping-normalized values of the 18 genes on the GEP18 signature.

Statistical analysis

All analyses were performed in the treated population, defined as all patients who received ≥ 1 dose of pembrolizumab. The Kaplan–Meier (KM) method was used to estimate the OS curve in each patient population; the nonparametric KM method was used to estimate the progression-free survival (PFS) curve in each treatment and duration of response. Duration of response was calculated from time of first response to time of progression. Patients without a progression event were censored at the date of the last non-PD assessment. Best overall response (BOR) was based on investigator assessment. Analyses were performed using a data cut-off date of September 1, 2017.

Results

KEYNOTE-001 enrolled 655 patients in the melanoma cohorts; of these, 151 were treatment-naïve and 496 were previously treated (205 received 1 prior therapy, 178 received 2 prior therapies, 113 received ≥ 3 prior therapies); 8 patients had uveal melanoma and had received no prior systemic therapy. Baseline characteristics according to treatment group are published and were well balanced [8]. [Supplementary Table S1](#), available at

Annals of Oncology online, presents baseline characteristics in the melanoma cohorts. Median duration of follow-up was 55 months (range: 48–69), and median duration of exposure to pembrolizumab was 5.6 months (range: 1 day–67 months). At data cut-off, 33 (5%) patients, including 2 on second course, were still receiving treatment, and 569 patients (87%) discontinued because of progressive disease (PD; $n = 275$; 42%), adverse events ($n = 166$; 25%), physician decision ($n = 80$; 12%), patient withdrawal ($n = 36$; 5%), protocol violation ($n = 8$; 1%), or lost to follow-up ($n = 4$; <1%) (supplementary Table S2, available at *Annals of Oncology* online).

At data cut-off, 63% ($n = 412$) of all patients and 54% ($n = 81$) of treatment-naive patients had died. The estimated 5-year OS rate was 34% in all patients and 41% in treatment-naive patients. Median OS was 23.8 months (95% CI, 20.2–30.4) in all patients and 38.6 months (95% CI, 27.2–NR) in treatment-naive patients (Figure 1A and B). The 5-year estimated PFS rate was 21% and 29%, respectively. Median PFS was 8.3 months (95% CI, 5.8–11.1)

in all patients and 16.9 months (95% CI, 9.3–35.5) in treatment-naive patients (Figure 1C and D).

Among all 655 treated patients, 104 (16%) achieved CR, 163 (25%) achieved PR, and 156 (24%) achieved SD, for a disease control rate (DCR) of 65% (Table 1; Figure 2). In total, 164 (25%) patients experienced a BOR of PD. Of the 423 patients who contributed to the DCR, 165 (13 CR, 61 PR, 91 SD) experienced subsequent disease progression. Median time to response was 2.8 months (range: 0.5–49.6), and median duration of response was NR (range: 1.3+ to 66.3+ months) (supplementary Figure S1A, available at *Annals of Oncology* online). Of those who achieved CR, median time to response was 2.8 months (range: 0.5–11.0), and median duration of response was NR (range: 3.8+ to 66.3+ months). Response was ongoing in 89% ($n = 93$) of patients who achieved CR. In patients with PR, median time to response was 2.8 months (range: 1.7–49.6), and median duration of response was NR (range: 1.3+ to 63.5+ months). At data cut-off, response was ongoing in 63% ($n = 102$) of patients who achieved PR.

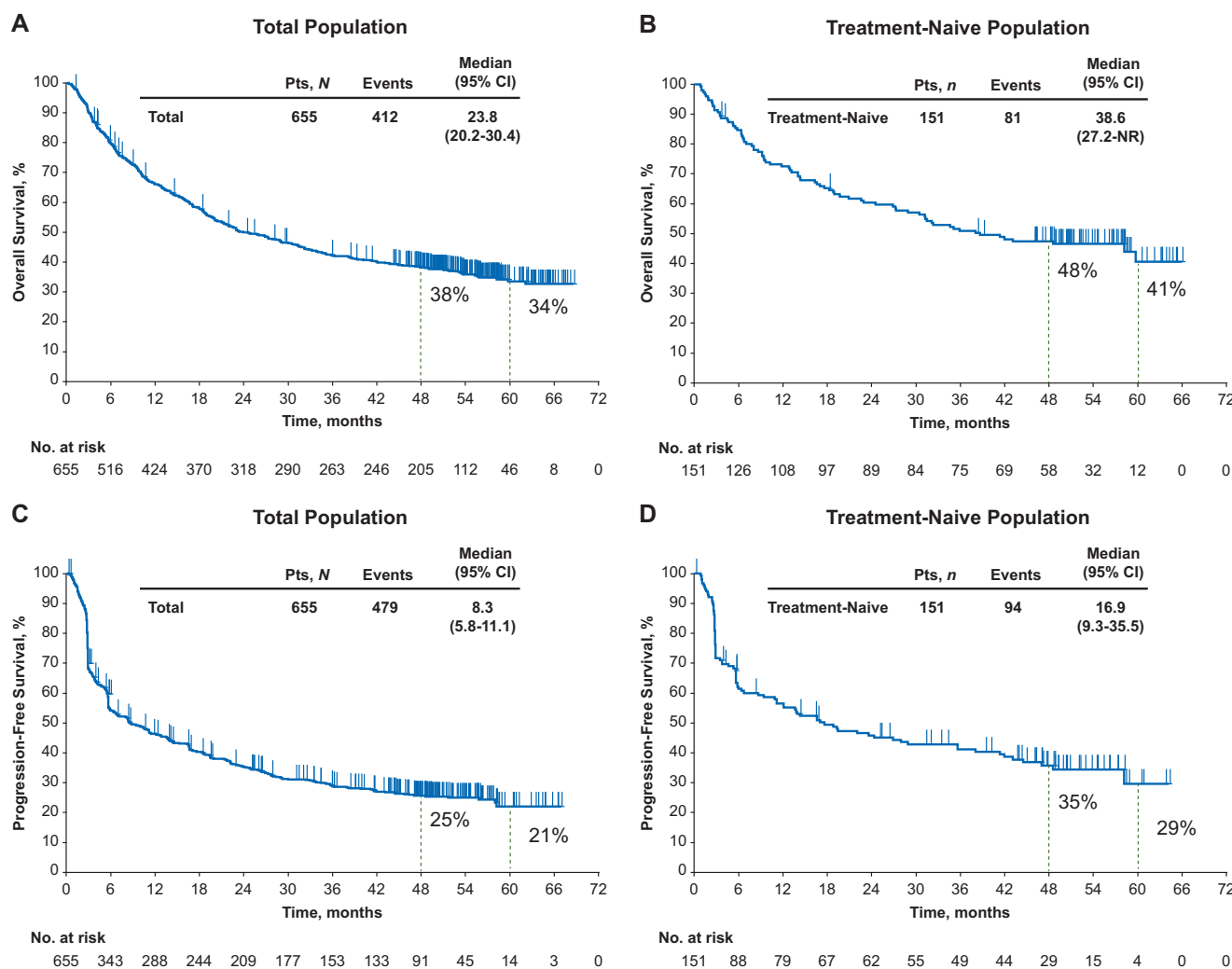


Figure 1. Kaplan–Meier estimates of OS in (A) all patients and (B) treatment-naive patients and estimates of PFS^a based on irRC (investigator review) [21] in (C) all patients and (D) treatment-naive patients. irRC, immune-related response criteria; NR, not reached; OS, overall survival; PFS, progression-free survival. ^aTwo patients who had PD after a first course of pembrolizumab and received a second course of pembrolizumab were not included in this analysis because they did not meet the criteria for confirming progression (i.e. they did not meet the two-image criterion for timepoint overall response of PD).

In the treatment-naïve population, BOR was CR in 38 patients (25%); 40 (27%) achieved PR and 30 (20%) experienced SD, for a DCR of 72% (Table 1). BOR in 32 patients (21%) was PD. Median time to response was 2.8 months (range: 2.5–32.0), and median duration of response was NR (range: 1.3+ to 60.8+ months) (supplementary Figure S1B, available at *Annals of Oncology* online). Of the 38 patients who achieved CR, median time to response was 2.8 months (range: 2.5–8.3), and median duration of response was NR (range: 6.0+ to 60.8+ months). Response was ongoing in 35 patients (92%) at the time of data cut-off. Of the 40 who achieved PR, median time to response was 2.8 months (range: 2.5–32.0), and median duration of response was NR (range: 1.3+ to 51.4+ months). Response was ongoing in 29 treatment-naïve patients (73%) who achieved PR.

Table 1. Best overall responses based on irRC (investigator review) [11] in all patients and treatment-naïve patients^a

Response	Total, % (95% CI) N = 655	Treatment-naïve, % (95% CI) n = 151
ORR	41 (37–45)	52 (43–60)
DCR	65 (61–68)	72 (64–79)
Best response		
CR	16 (13–19)	25 (19–33)
PR	25 (22–28)	27 (20–34)
SD	24 (21–27)	20 (14–27)
PD	25 (22–29)	21 (15–29)
No assessment	10 (8–13)	7 (4–13)

^aOnly confirmed responses.

CR, complete response; DCR, disease control rate; irRC, immune-related response criteria; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Response by prior ipilimumab treatment was also evaluated (supplementary Table S3, available at *Annals of Oncology* online). The overall response rate was slightly higher in ipilimumab-naïve patients (46%) than in ipilimumab-exposed patients (36%); DCR was similar between groups (66% and 64%, respectively).

Seventy-two patients who met eligibility criteria for stopping pembrolizumab discontinued treatment to enter observation, per the protocol. Sixty-seven achieved CR and 5 achieved PR as BOR. Median time to first response for them was 2.8 months (range: 0.5–13.8) after treatment initiation. Seven patients had PD (6 CR, 1 PR) after stopping pembrolizumab; most (90%) responses were maintained (Figure 2). Four patients, all who achieved CR as a first response, received second-course pembrolizumab (Table 2). BOR on second-course treatment was 1 CR and 1 SD (patient achieved a PR of 2 weeks after data cut-off); 2 had subsequent PD.

Analysis of the 18-gene GEP demonstrated an association between GEP score and overall response to pembrolizumab (supplementary Figure S2A, available at *Annals of Oncology* online) in treatment-naïve and treatment-exposed patients (supplementary Figure S2B, available at *Annals of Oncology* online) and in ipilimumab-naïve and ipilimumab-exposed patients (supplementary Figure S2C, available at *Annals of Oncology* online).

Treatment-related AEs occurred in 562 patients (86%) (supplementary Table S4, available at *Annals of Oncology* online); 114 (17%) experienced grade 3–4 treatment-related AEs, 65 (10%) discontinued because of a treatment-related AE and none experienced treatment-related death. Immune-mediated AEs are shown in supplementary Figure S3, available at *Annals of Oncology* online.

Discussion

In this analysis of patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001, the estimated OS rate at

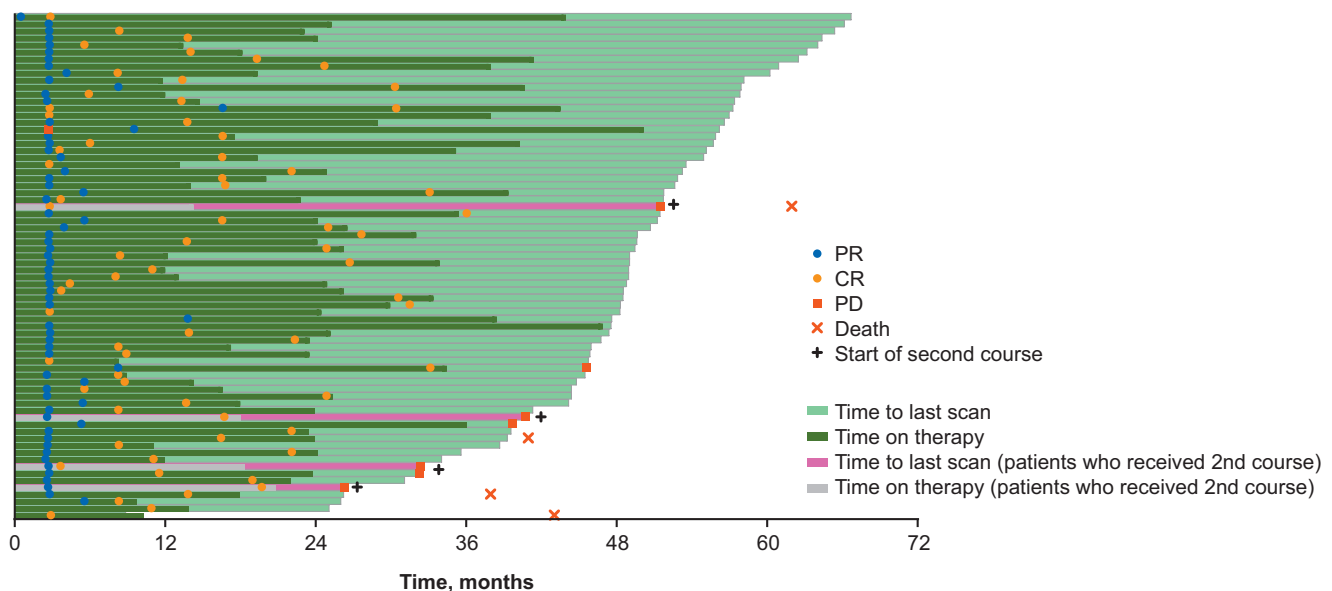


Figure 2. Responders who stopped pembrolizumab during observation ($n = 72$). CR, complete response; PD, progressive disease; PR, partial response.

Table 2. Response with second course of pembrolizumab

Patient	Exposure to first course, months	Best response on first course ^a	Time from start of first course to CR, months	Time from end of first course to PD, months	Exposure to second course, months	Time from start of second course to response ^a (SD or CR), months	Time from start of second course to second course progression, months
1	14.3	CR	2.8	37.3	2.1	NA	2.8 ^c
2	18.0	CR	16.7	22.7	14.8	2.5 (SD ^b)	NA
3	18.4	CR	3.6	14.0	15.0	6.2 (CR)	NA
4	20.8	CR	19.7	5.5	4.2	NA	5.6

^aBased on irRC (investigator review) [21].

^bPR documented 2 weeks after data cut-off.

^cPatient died.

CR, complete response; irRC, immune-related response criteria; NA, not applicable; PD, progressive disease; PR, partial response; SD, stable disease.

5 years in the overall population and in those who were treatment-naïve was comparable to the 4-year OS rate. The percentage of patients with an ongoing response was higher in those who were treatment-naïve than in all patients and numerically higher in patients who achieved CR than in those who achieved PR. DCR was unaffected by prior ipilimumab exposure. These data, which represent the longest follow-up of pembrolizumab published in any cancer histology to date, confirm the durable antitumor activity of pembrolizumab in advanced and metastatic melanoma. The safety profile of pembrolizumab in patients with melanoma has been established partly through KEYNOTE-001; with continued follow-up, no new safety signals have been identified in this study.

Five-year OS rates observed with pembrolizumab in this analysis were significantly higher than those reported for ipilimumab monotherapy (12.3%–28.4%) [23]. They represent the first long-term follow-up data from a trial evaluating pembrolizumab in patients with advanced and metastatic melanoma. As with the results presented here [pembrolizumab, 5-year OS rates: 34% (all patients) versus 41% (treatment-naïve patients)], slightly higher 5-year survival rates were achieved with ipilimumab in treatment-naïve patients [ipilimumab, 5-year OS rates: 12.3%–28.4% (all patients) versus 21.4%–49.5% (treatment-naïve patients)]. Single-agent nivolumab demonstrated an OS rate of 34% and median OS of 17.3 months after ≥45-months' follow-up in heavily pretreated patients with advanced melanoma [20]. A plateau in OS was seen at approximately 48 months, indicative of a long-term benefit in some patients [20]. In the phase III KEYNOTE-006 trial in which a head-to-head comparison of ipilimumab and pembrolizumab was conducted, 48-month OS rates were 42% with pembrolizumab and 34% with ipilimumab (manuscript in preparation), confirming the superiority of anti-PD-1 therapy in the first-line setting over anti-CTLA-4 and other standard therapies. This assertion is further supported by the robust duration of response.

Previous work has demonstrated correlation between pembrolizumab response rate, PFS, and OS and pretreatment PD-L1 expression in tumor biopsies from patients in KEYNOTE-001, although patients with PD-L1-negative tumors may also achieve durable responses [24]. At the molecular level, long-term

responses observed with pembrolizumab in KEYNOTE-001 may be explained by induction of several cytotoxicity-associated and natural killer-associated genes in the tumor through PD-1 [25]. In patients treated with pembrolizumab for advanced/metastatic melanoma, long-term responses may be maintained through prominent expansion of CD8⁺ memory cells [26]. In the present analysis, the distribution of 18-gene GEP scores [22] was higher in responders than in nonresponders, regardless of previous exposure to any treatment, including ipilimumab.

Data are limited describing outcomes in patients who experience disease progress and are retreated with a second course of checkpoint inhibitor therapy. In a retrospective review of 8 patients retreated with nivolumab, response on first-course treatment was 3 CR along with 3 SD before therapy was discontinued (due to PD in 7 patients and grade 3 colitis in 1 patient) [27]. The median nivolumab treatment period was 4.3 months. Following retreatment, 2 patients (25%) achieved PR and 3 (38%) achieved SD, for a response rate of 25% (2 patients) and DCR of 62% (5/8 patients). In another study of nivolumab ($N=107$), all 5 patients who discontinued treatment for ≥100 days and experienced subsequent disease progression achieved durable disease control and were alive at 5 years [20]. In a preliminary analysis of the CA184-025 study evaluating ipilimumab in advanced melanoma ($N=855$), 51 patients (6%) who achieved disease control were retreated on disease progression [28]. Of these, 28 (55%) regained disease control and 42% were alive 2 years after the first induction dose. In a follow-up analysis involving 122 patients, 7 (6%) achieved CR and 21 (17%) achieved PR for a BOR rate of 23%. Another 31 (25%) patients achieved SD for a DCR of 48% [23]. Although patient numbers were low, survival outcomes of patients who received second-course pembrolizumab in KEYNOTE-001 compare favorably with those of other immunotherapies; 1 patient each achieved CR and SD (PR documented 2 weeks after data cut-off). Second-course pembrolizumab treatment was also recently assessed in the phase III KEYNOTE-006 study of patients with ipilimumab-naïve advanced melanoma. Of the eight patients (first-course responses: 3 CR, 4 PR, 1 SD) who received second-course pembrolizumab, 1 achieved CR, 3 achieved PR, 3 had SD, and 1 had PD [29]. This study reports second-course pembrolizumab in patients with advanced

melanoma, and it underscores the role of reinduction as appropriate next-line therapy for patients who experience initial benefit with pembrolizumab therapy.

Conclusions

This 5-year analysis of KEYNOTE-001 confirms the durable and robust antitumor activity and safety of pembrolizumab for treatment-experienced and treatment-naïve patients with advanced/metastatic melanoma. As second-course treatment, pembrolizumab provides additional antitumor activity.

Acknowledgements

The authors thank Maxine Giannotti and Cathie Scalzo for study support, Scott Diede and Scot Ebbinghaus for study design and oversight, and Andrea L. Webber, Michael Nebozhyn (all from Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA), and Robin Mogg for assistance with biomarker analyses. Medical writing and/or editorial assistance was provided by Doyel Mitra, PhD, and Cathy Winter, PhD of the ApotheCom pembrolizumab team (Yardley, PA). This assistance was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. This research was funded in part through the NIH/NCI Cancer Center Support Grant P30 CA0087 48. Funding for this research was provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Data availability: The Merck & Co., Inc. data sharing policy, including restrictions, is available at http://engagezone.merck.com/ds_documentation.php. Requests for access to the study data can be submitted through the EngageZone site or via email to dataaccess@merck.com.

Funding

Funding for this study was provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. No grant number is applicable.

Role of the funding source

Funding for this study was provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA; no grant number is applicable. The sponsor collaborated with academic advisers to design the study and gather, analyze, and interpret the results. All authors had full access to all study data and approved the decision to submit the manuscript for publication.

Disclosure

OH reports personal fees from Merck, during the conduct of the study; personal fees from Amgen, Novartis, Genentech Roche, BMS, and Array Biopharma; and other support from Astra Zeneca, BMS, Celldex, Genentech Roche, Immunocore, Incyte, Merck, Merck Sereno, MedImmune, Novartis, Pfizer,

and Rinat outside the submitted work. CR reports personal fees from BMS, Pierre Fabre, Novartis, Amgen, Merck, and Roche, outside the submitted work. AD reports grants and personal fees from Merck, BMS, personal fees from Amgen, and grants from Incyte, during the conduct of the study. FSH reports clinical trial support to the institution from BMS during the conduct of the study; grants to the institution and personal fees from BMS, and personal fees from Merck, EMD Serono, Novartis, Celldex, Amgen, Genentech/Roche, Incyte, Apricity, Bayer, Aduro, Partners Therapeutics, Sanofi, Pfizer, Pionyr, Seven Hills Pharma, Verastern, Compass Therapeutics, Takeda, and Surface, outside the submitted work. FSH has received personal fees from and holds equity in Torque. FSH holds a patent pending with royalties paid for Methods for Testing MICA Related Disorders (#20100111973), issued patents Tumor antigens and uses thereof (#7250291), and Therapeutic Peptides (#9402905); and patents pending for 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), and Methods of Using Pembrolizumab and Trebananib (#Pending). RK reports other support from Merck during the conduct of the study and other support from BMS, Novartis, Amgen, and Teva outside the submitted work. JDW reports grants and personal fees from Merck during the conduct of the study; personal fees from and stock ownership in BeiGene, Apricity, and Adaptive Biotech; is the cofounder of, has stock ownership in, and has received personal fees from Potenza, Tizona, Imvaq, and Trieza; grants and personal fees from BMS, Genentech, MedImmune, and personal fees from Surface Oncology, Polaris, Polonoma, Array BioPharma, Ascentage, Chugai, FStar, Sellas Life Sciences, Seramatrix, Neon, Eli Lilly, Kleo, Psioxus, Syndax, Recepta, Amgen, Puretech, Elucida, Ono, and Celgene outside the submitted work. JDW holds patents and receives royalties for Xenogeneic DNA vaccines, anti-CTLA4 antibodies, and anti-GITR antibodies and methods of use thereof. JDW has patents pending for Alphavirus, Newcastle Disease Viruses for Cancer Therapy, Genomic Signature to Identify Responders to Ipilimumab in Melanoma, Engineered Vaccinia Viruses for Cancer Immunotherapy, Anti-CD40 agonist mAb fused to Monophosphoryl Lipid A (MPL) for cancer therapy, and CAR+ T cells targeting differentiation antigens as means to treat cancer. RJ reports other support from Merck as a consultant outside the submitted work. JSW reports personal fees from Merck, BMS, Genentech, Celldex, Pfizer, and AstraZeneca outside the submitted work. In addition, JSW is named on a PD-1 biomarker patent issued by Biodesix. TCM reports personal fees from BMS, Aduro, Merck, and Incyte, outside the submitted work. AP reports grants from Merck during the conduct of the study. HZ reports grants from BMS, Merck, Tesaro, and Imcheck outside the submitted work. QZ, EJ, and SA are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. NI is an employee and stockholder of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and a stockholder of GlaxoSmithKline. AR reports financial support from Merck for the conduct of the clinical trial through an institutional

contract with UCLA, during the conduct of the study and personal fees from Merck outside the submitted work. WJH, PH, RD, and AJ have nothing to disclose.

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