Original Investigation

Association of Pembrolizumab With Tumor Response and Survival Among Patients With Advanced Melanoma

Antoni Ribas, MD, PhD; Omid Hamid, MD; Adil Daud, MD; F. Stephen Hodi, MD; Jedd D. Wolchok, MD, PhD; Richard Kefford, MD, PhD; Anthony M. Joshua, MBBS, PhD; Amita Patnaik, MD; Wen-Jen Hwu, MD, PhD; Jeffrey S. Weber, MD, PhD; Tara C. Gangadhar, MD; Peter Hersey, MD, PhD; Roxana Dronca, MD; Richard W. Joseph, MD; Hassane Zarour, MD; Bartosz Chmielowski, MD, PhD; Donald P. Lawrence, MD; Alain Algazi, MD; Naiyer A. Rizvi, MD; Brianna Hoffner, BA, RN, MSN; Christine Mateus, MD; Kevin Gergich, MA; Jill A. Lindia, MS; Maxine Giannotti, BS; Xiaoyun Nicole Li, PhD; Scot Ebbinghaus, MD; S. Peter Kang, MD; Caroline Robert, MD, PhD

IMPORTANCE The programmed death 1 (PD-1) pathway limits immune responses to melanoma and can be blocked with the humanized anti-PD-1 monoclonal antibody pembrolizumab.

OBJECTIVE To characterize the association of pembrolizumab with tumor response and overall survival among patients with advanced melanoma.

DESIGN, SETTINGS, AND PARTICIPANTS Open-label, multicohort, phase 1b clinical trials (enrollment, December 2011-September 2013). Median duration of follow-up was 21 months. The study was performed in academic medical centers in Australia, Canada, France, and the United States. Eligible patients were aged 18 years and older and had advanced or metastatic melanoma. Data were pooled from 655 enrolled patients (135 from a nonrandomized cohort [n = 87 ipilimumab naive; n = 48 ipilimumab treated] and 520 from randomized cohorts [n = 226 ipilimumab naive; n = 294 ipilimumab treated]). Cutoff dates were April 18, 2014, for safety analyses and October 18, 2014, for efficacy analyses.

EXPOSURES Pembrolizumab 10 mg/kg every 2 weeks, 10 mg/kg every 3 weeks, or 2 mg/kg every 3 weeks continued until disease progression, intolerable toxicity, or investigator decision.

MAIN OUTCOMES AND MEASURES The primary end point was confirmed objective response rate (best overall response of complete response or partial response) in patients with measurable disease at baseline per independent central review. Secondary end points included toxicity, duration of response, progression-free survival, and overall survival.

RESULTS Among the 655 patients (median [range] age, 61 [18-94] years; 405 [62%] men), 581 had measurable disease at baseline. An objective response was reported in 194 of 581 patients (33% [95% CI, 30%-37%]) and in 60 of 133 treatment-naive patients (45% [95% CI, 36% to 54%]). Overall, 74% (152/205) of responses were ongoing at the time of data cutoff; 44% (90/205) of patients had response duration for at least 1 year and 79% (162/205) had response duration for at least 6 months. Twelve-month progression-free survival rates were 35% (95% CI, 31%-39%) in the total population and 52% (95% CI, 43%-60%) among treatment-naive patients. Median overall survival in the total population was 23 months (95% CI, 20-29) with a 12-month survival rate of 66% (95% CI, 62%-69%) and a 24-month survival rate of 49% (95% CI, 44%-53%). In treatment-naive patients, median overall survival was 31 months (95% CI, 24 to not reached) with a 12-month survival rate of 73% (95% CI, 65%-79%) and a 24-month survival rate of 60% (95% CI, 51%-68%). Ninety-two of 655 patients (14%) experienced at least 1 treatment-related grade 3 or 4 adverse event (AE) and 27 of 655 (4%) patients discontinued treatment because of a treatment-related AE. Treatment-related serious AEs were reported in 59 patients (9%). There were no drug-related deaths.

CONCLUSIONS AND RELEVANCE Among patients with advanced melanoma, pembrolizumab administration was associated with an overall objective response rate of 33%, 12-month progression-free survival rate of 35%, and median overall survival of 23 months; grade 3 or 4 treatment-related AEs occurred in 14%.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01295827

JAMA. 2016;315(15):1600-1609. doi:10.1001/jama.2016.4059

Editorial page 1573

Author Video Interview and **JAMA Report Video** at jama.com

Supplemental content at jama.com

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Antoni Ribas, MD, PhD, Division of Hematology and Oncology, University of California-Los Angeles, 10833 Le Conte Ave, 11-934 Factor Bldg, Los Angeles, CA 90095-1782 (aribas@mednet.ucla.edu).

Immune checkpoint inhibitors have provided a new treatment approach in cancer immunotherapy.[1,2] One such inhibitor is programmed cell death protein 1 (PD-1), which limits T-cell effector functions against chronic inflammation and cancer by binding to its primary ligand, PD-L1.[1,3-5] Pembrolizumab (MK-3475) is a highly selective, humanized monoclonal IgG4-κ isotype antibody against PD-1 that is approved around the world for the treatment of patients with unresectable or metastatic melanoma with disease progression following ipilimumab and, if *BRAF*^{V600} (NCBI accession number NM_004324.2) mutated, a BRAF inhibitor. Following a phase 1 dose-finding study to determine the recommended phase 2 dose, 1235 patients with advanced solid tumors, melanoma, or non–small cell lung cancer were enrolled into expansion cohorts. With a median follow-up of 11 months among responders, pembrolizumab provided an objective response rate of 25% to 52% in the initial melanoma expansion cohorts of KEYNOTE-001, irrespective of dosing schedule or prior ipilimumab status.[6] In a randomized cohort of patients with ipilimumab-refractory melanoma, the objective response rate was 26% for both pembrolizumab 2 mg/kg and 10 mg/kg every 3 weeks.[7] In patients with ipilimumab-refractory melanoma enrolled in the phase 2 KEYNOTE-002 trial, pembrolizumab (2 mg/kg or 10 mg/kg) every 3 weeks was better tolerated and demonstrated superior progression-free survival compared with chemotherapy, with no clinically meaningful differences noted between pembrolizumab doses.[8] In the randomized phase 3 KEYNOTE-006 study, pembrolizumab had fewer toxicities and significantly improved overall survival compared with ipilimumab.[9]

The current report analyzed pooled data from all 655 patients with advanced melanoma enrolled in KEYNOTE-001 to characterize the association of pembrolizumab administration with antitumor activity and safety and to allow for the assessment of long-term outcomes with therapy.

Methods

Study Design and Conduct

KEYNOTE-001 was an international (Australia, Canada, France, United States), open-label phase 1 study in which pembrolizumab safety and antitumor activity were assessed in multiple cohorts of patients with advanced solid tumors, melanoma, or non–small cell lung cancer. Of the 655 patients with melanoma enrolled in this study, 173 were included in the randomized cohort previously reported by Robert et al,[7] 135 were included in the nonrandomized cohort previously reported by Hamid et al,[6] and 347 were not included in prior reports. Between December 2011 and September 2012, 135 patients with advanced melanoma who were naive to ipilimumab or who had previously received ipilimumab were enrolled in 5 sequential, nonoverlapping treatment groups in a nonrandomized cohort and treated with pembrolizumab, 2 mg/kg every 3 weeks or 10 mg/kg every 2 or every 3 weeks.[6] Between August 2012 and September 2013, 520 patients were enrolled in 3 randomized cohorts: an ipilimumab-naive cohort treated with pembrolizumab, 2 or 10 mg/kg every 3 weeks[10]; an ipilimumab-treated cohort treated with pembrolizumab, 2 or 10 mg/kg every 3 weeks[7,10]; and a cohort that included both ipilimumab-naive[10-13] and ipilimumab-treated patients treated with pembrolizumab, 10 mg/kg every 2 weeks or 10 mg/kg every 3 weeks.[11] The final randomization ratio for all randomized cohorts was 1:1. Pembrolizumab was administered intravenously over 30 minutes and the regimen continued until disease progression or withdrawal was determined by an investigator for intolerable toxicity or protocol violation. The nonrandomized cohorts were dose-confirmation expansion cohorts, in which patients were enrolled at different dose levels in a sequential fashion. For the randomized cohorts, a randomization schedule was generated for the dose assignment.

The study was conducted in accordance with the protocol, Good Clinical Practice standards, and the Declaration of Helsinki. The protocol and its amendments were approved by the relevant institutional review boards or ethics committees of the participating institutions. All patients provided written informed consent.

Patient Eligibility

Common patient eligibility among all cohorts was age 18 years and older; advanced unresectable melanoma with measurable disease per investigator assessment; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; and adequate organ function. Patient-reported race/ethnicity information was collected by the investigator to ensure lack of differences in safety and activity. Common exclusion criteria included chemotherapy within 4 weeks of the first study dose, active infection, active autoimmune disease or history thereof, ongoing systemic corticosteroid therapy at treatment doses, and previous treatment targeting the PD-1 pathway. There was no protocol-mandated baseline magnetic resonance imaging of the brain, but patients with previously treated central nervous system metastases that were clinically stable for at least 8 weeks were eligible.

For all patients naive to ipilimumab, 1 or 2 previous therapies were permitted. For all patients previously treated with ipilimumab, the number of previous therapies was unlimited. For patients previously exposed to ipilimumab and enrolled in the nonrandomized cohort or one of the randomized cohorts, confirmed progression following ipilimumab and resolution of all ipilimumab-related adverse events with no treatment for these adverse events at least 4 weeks prior to start of pembrolizumab were required. Patients previously treated with ipilimumab and enrolled in the randomized cohort previously reported by Robert et al[7] were required to have received at least 2 ipilimumab infusions (minimum dose of 3 mg/kg), have not received ipilimumab for at least 4 weeks, have documented disease progression according to immune-related response criteria within 24 weeks of the last ipilimumab dose, and have resolution of all ipilimumab-related adverse events to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade 0 to 1 with prednisone of as much as 10 mg/day or equivalent for at least 2 weeks before the first pembrolizumab dose. Previous BRAF inhibitor therapy, MEK inhibitor therapy, or both were required for patients with ipilimumab-refractory, *BRAF*^{V600}-mutant melanoma.

Assessments

Tumor response was assessed every 12 weeks by independent central review (primary for calculating objective response rate and progression-free survival) using Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1; the conventional criteria for assessing change in tumor burden)[12] and by investigator review (for treatment management) using immune-related response criteria.[13] Objective response rate, which was the primary end point, was assessable only in patients with measurable disease at baseline (assessed by independent central review using RECIST v1.1). For assessment of response rate, patients without postbaseline disease assessments were counted as nonresponders. A prespecified subgroup analysis of objective response rate was conducted. Secondary end points included objective response rate as assessed by immune-related response criteria by investigators, duration of response, progression-free survival, and overall survival. Best target lesion response was assessed in patients with measurable disease at baseline per central review.

Assessed variables and definitions included the following: (1) objective response rate, the percentage of patients with a best overall response of complete response or partial response; (2) measurable disease, having at least 1 measurable lesion (a lesion that can be measured in at least 1 dimension); (3) complete response, disappearance of all target lesions (all measurable lesions ≤2 lesions per organ and 5 lesions in total) in response to treatment; (4) partial response, a decrease (≥30%) in sum of diameters of target lesions from baseline in response to treatment; (5) stable disease, neither a response nor progressive disease; (6) progressive disease, a 20% increase in the sum of the longest diameter of target lesions from nadir; (7) disease control rate, rate of complete response + partial response + stable disease; (8) duration of response, time from best overall response to first documentation of disease progression; (9) progression-free survival, time from start of treatment to documented disease progression or death due to any cause; and (10) overall survival, time from start of treatment to death due to any cause. Durable responses were defined as responses lasting for at least 1 year.

Adverse events were recorded continuously throughout treatment up to 30 days after treatment (90 days for serious adverse events). All adverse events were graded according to the NCI-CTCAE, version 4.0.[14] Investigators specified whether an adverse event was considered to be treatment related, immune related, or both. Tumor specimens were collected from all patients within 60 days before the start of pembrolizumab for biomarker analysis.

Statistical Analyses

Analysis of objective response rate was performed in the full analysis set, defined as all patients with measurable disease per independent central review at baseline who received at least 1 dose of study treatment. All other analyses were performed in the all-patients-as-treated population, defined as all patients who received at least 1 dose of study treatment. Objective response rates and associated 95% CIs were estimated using the Clopper-Pearson method.[15] Duration of response, progression-free survival, overall survival, and survival rates were estimated using the Kaplan-Meier method; the associated 95% CIs for median survival were estimated using the Greenwood formula. Safety analyses were performed using a data cutoff date of April 18, 2014; analyses of antitumor activity were performed using a data cutoff date of October 18, 2014. SAS software, version 9.3, was used for all analyses.

The study protocol has been previously published.[16]

Results

Study Conduct and Patient Characteristics

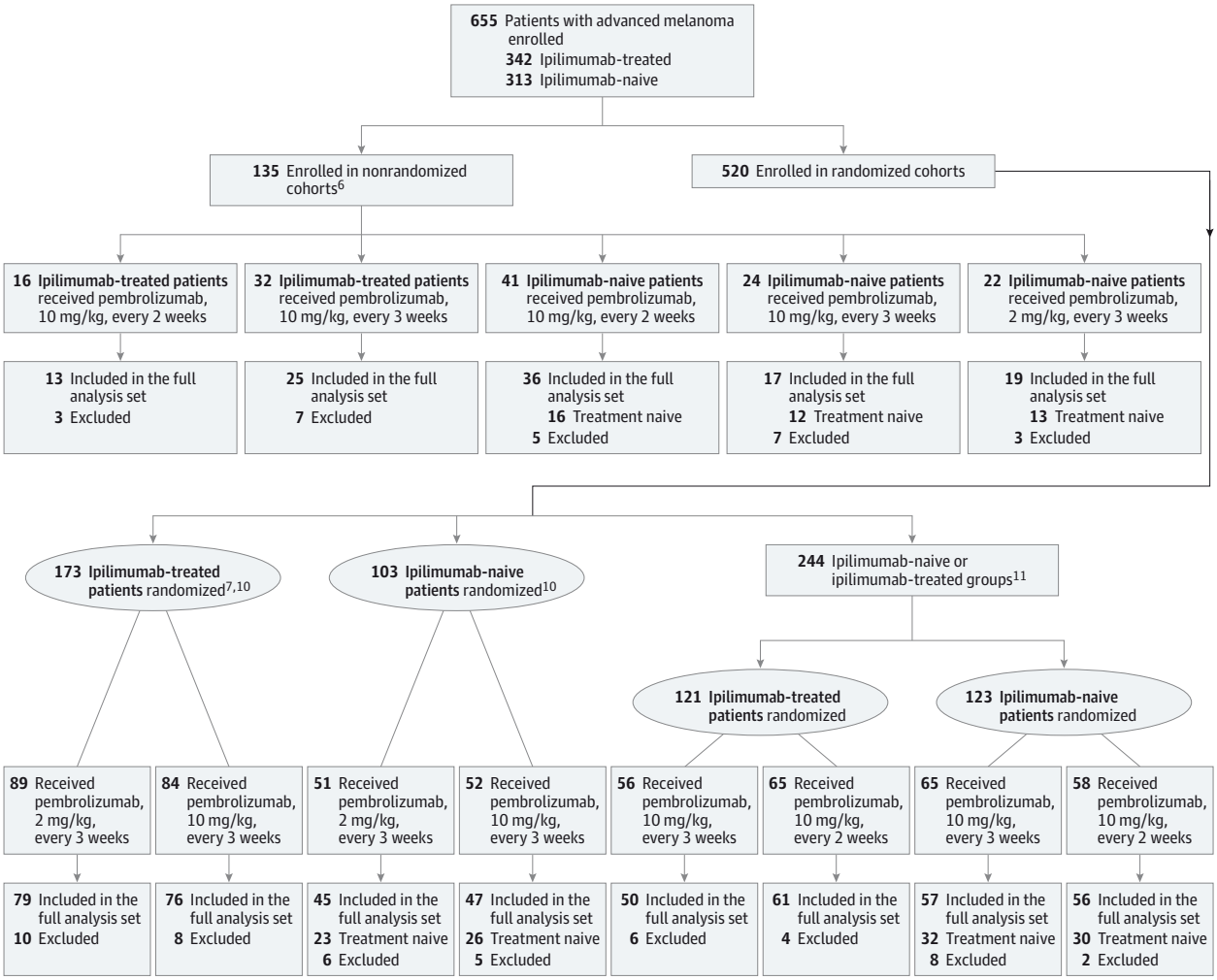
Data were pooled from 655 patients enrolled in 8 cohorts between December 2011 and September 2013 (**Figure 1**). The nonrandomized cohorts included 135 patients who were naive to ipilimumab (n = 87) or who had previously received ipilimumab (n = 48). Randomized cohorts included 520 patients (n = 226 ipilimumab naive and n = 294 ipilimumab treated). Overall, 152 patients had received no prior therapy for advanced disease. Baseline patient characteristics were similar to those observed in most large studies of patients with advanced melanoma (**Table 1**). Median age was 61 years, and there was a higher frequency of men (n = 405; 62%). Five hundred eight patients (78%) had M1c disease, and 250 (38%) had an elevated lactate dehydrogenase level. Only 155 patients (24%) had tumors that contained a *BRAF*^{V600} mutation, likely representing the trend at the time of KEYNOTE-001 enrollment to preferentially offer patients with *BRAF*^{V600} mutations treatment with BRAF inhibitors, MEK inhibitors, or both. Overall, 342 (52%) patients previously received ipilimumab, and 110 (17%) previously received BRAF or MEK inhibitors. Among treatment-naive patients, there were fewer *BRAF*^{V600} mutations (n = 25; 16%) and a smaller median baseline tumor size (87 mm vs 102 mm for the total population). The mean interval between the last ipilimumab and first pembrolizumab doses was 33 weeks (range, 4-248 weeks).

As of April 18, 2014, median duration of follow-up was 15 months (range, 8-29 months), and 244 patients (37%) remained on study treatment. The most common reasons for treatment discontinuation were disease progression (n = 256; 39%) and adverse events (n = 128; 20%). For analyses of antitumor activity, median duration of follow-up was 21 months (range, 14-35 months) at the final data cutoff date of October 18, 2014.

Antitumor Activity

The 581 patients who had measurable disease assessed by central review at baseline (RECIST v1.1) comprised the full analysis set, which was the protocol-defined population for primary analysis of the objective response rate. Confirmed objective response rate assessed by central review (RECIST v1.1) in this population was 33% (95% CI, 30%-37%; n = 194), with a complete response rate of 8% (95% CI, 6%-11%; n = 48), and a disease control rate of 51% (95% CI, 47%-55%; n = 298). Response rates were similar when analyzed by investigator-assessed immune-related response criteria (40% [95% CI, 36%-44%]; n = 260). The majority of subgroup analyses showed

Figure 1. Flowchart of Enrolled Participants and Progress Through the Trial



There was 1 nonrandomized cohort with 5 sequential, nonoverlapping treatment groups,[6] and there were 3 randomized cohorts.[7,10,11] In all 3 randomized cohorts, patients were randomized prior to assignment to a treatment group. The enrolled group consists of patients with and without measurable disease by independent review who received at least 1 dose of pembrolizumab.

The group comprising the full analysis set consists of patients with measurable disease at baseline (per independent review) who received at least 1 dose of pembrolizumab; those without measurable disease at baseline were excluded.

minimal differences in objective response rate and overlapping 95% CIs compared with the total population (**Figure 2**). A smaller median tumor size at baseline was associated with a higher objective response rate. There was no significant difference in antitumor activity among doses in randomized cohorts (eTable 1 in the Supplement). Among the 304 ipilimumab-treated patients, objective response rate was 29% (95% CI, 24%-34%; n = 87) (eTable 2 in the Supplement). Among the 277 ipilimumab-naive patients, objective response rate was 39% (95% CI, 33%-45%; n = 107; eTable 2 in the Supplement). In the 133 evaluable patients with no prior therapy, confirmed objective response rate per RECIST v1.1 by central review was 45% (95% CI, 36%-54%; n = 60), complete response rate was 14% (95% CI, 8%-21%; n = 18), and disease control rate was 61% (95% CI, 52%-69%; n = 81). By investigator-assessed immune-related response criteria, the response rate was 50% (95% CI, 42%-58%; n = 76). Among patients with treatment-naive *BRAF*^{V600}-mutant melanoma, objective response rate per RECIST v1.1 was 50% (95% CI, 28%-72%; n = 11); in patients with *BRAF*^{V600}-wild-type melanoma, objective response rate was 45% (95% CI, 35%-55%; n = 49).

Considering all responders, regardless of whether they had measurable disease per central review at baseline (RECIST v1.1), most responses were durable, with 74% (152 of 205) in the total population and 82% (53 of 65) in the treatment-naive population ongoing at the time of the October 18, 2014, final data cutoff; overall, 90 patients (44%) had a response duration of greater than 1 year. The Kaplan-Meier estimate of median duration of response was 28 months (range, ≥1-28 months) in the total population and was not reached (range, ≥3 to ≥28 months) in treatment-naive patients; however, there were fewer than 5 patients at risk at the time the median was reached (**Figure 3**).

Table 1. Patient Baseline Characteristics

Characteristic	No. (%)[a] Total (N = 655)	Ipilimumab-Treated (n = 342)	Ipilimumab-Naive (n = 313)	Treatment-Naive (n = 152)[b]
Age, median (range), y	61 (18-94)	61 (18-88)	61 (23-94)	63 (26-90)
Sex				
Men	405 (62)	214 (63)	191 (61)	103 (68)
Women	250 (38)	128 (37)	122 (39)	49 (32)
Race				
White	636 (97)	334 (98)	302 (96)	144 (95)
Asian	10 (2)	3 (1)	7 (2)	4 (3)
Black or African American	5 (1)	3 (1)	2 (1)	2 (1)
Other	4 (1)	2 (1)	2 (1)	2 (1)
ECOG performance status				
0	444 (68)	215 (63)	229 (73)	113 (74)
1	210 (32)	126 (37)	84 (27)	39 (26)
Unknown	1 (0.2)	1 (0.3)	0	0
BRAF^{V600} mutation status				
Mutant	155 (24)	64 (19)	91 (29)	25 (16)
Wild type	494 (75)	277 (81)	217 (69)	125 (82)
Unknown	6 (1)	1 (0.3)	5 (2)	2 (1)
Brain metastasis				
Yes	54 (8)	37 (11)	17 (5)	7 (5)
No	600 (92)	305 (89)	295 (94)	145 (95)
Unknown	1 (0.2)	0	1 (0.3)	0
Lactate dehydrogenase level				
Normal[c]	393 (60)	199 (58)	194 (62)	95 (63)
Elevated[d]	250 (38)	139 (41)	111 (35)	50 (33)
Unknown[e]	12 (2)	4 (1)	8 (3)	7 (5)
Baseline tumor size, median (range), mm[f]	102 (10-895)	120 (10-895)	90 (11-752)	87 (11-752)
M category[g]				
M0	8 (1)	2 (1)	6 (2)	3 (2)
M1a	50 (8)	30 (9)	20 (6)	12 (8)
M1b	89 (14)	38 (11)	51 (16)	28 (18)
M1c	508 (78)	272 (80)	236 (75)	109 (72)
Previous systemic therapies				
0	161 (25)	0	161 (51)	152 (100)
1	206 (31)	103 (30)	103 (33)	0
2	174 (27)	128 (37)	46 (15)	0
≥3	114 (17	111 (32)	3 (1)	0
Previous treatments[h]				
Ipilimumab	342 (52)	342 (100)	0	0
Chemotherapy	215 (33)	155 (45)	60 (19)	0
BRAF or MEK inhibitor	110 (17)	63 (18)	47 (15)	0
Other immunotherapy[i]	173 (26)	105 (31)	68 (22)	0
Other therapy	94 (14)	66 (19)	28 (9)	0

Abbreviations: ECOG, Eastern Cooperative Oncology Group; Response Evaluation Criteria in Solid Tumors, version 1.1.

[a] Values are reported as No. (%) unless otherwise indicated.

[b] Indicates patients without any prior systemic treatment for advanced melanoma.

[c] Defined as less than or equal to 100% of the upper limit of normal.

[d] Defined as greater than 100% of the upper limit of normal.

[e] Lactate dehydrogenase level was unknown.

[f] Baseline tumor size was calculated as the sum of the longest diameters of all target lesions for patients with measurable disease by independent central review at baseline (using RECIST v1.1).

[g] The M category indicates extent of metastasis: M0 = no distant metastasis; M1a = metastasis to skin, subcutaneous tissues, or distant lymph nodes; M1b = metastasis to lung; M1c = metastasis to all other visceral sites or distant metastases at any site associated with elevated levels of serum lactate dehydrogenase level.

[h] Excludes neoadjuvant therapies. Patients may have received more than 1 type of previous therapy.

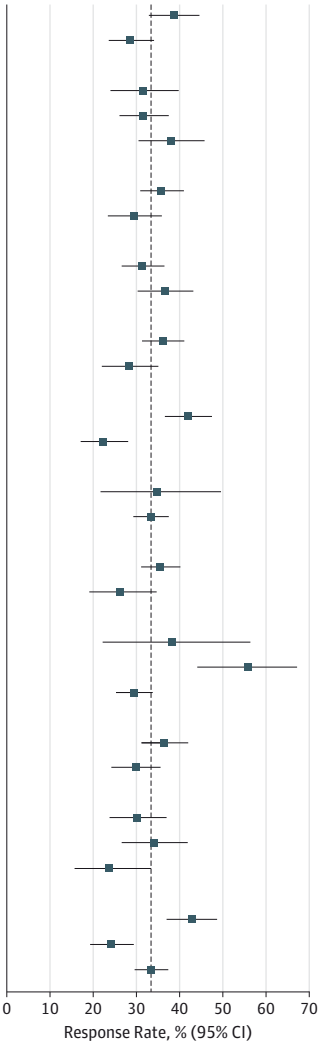
[i] Excludes ipilimumab.

Of the 510 patients with measurable disease per central review and at least 1 postbaseline tumor measurement, 364 (71%) experienced a decrease from baseline in the sum of target lesions, with a median decrease of 36% (**Figure 4**). Similarly, of the 121 treatment-naive patients with measurable disease per central review and at least 1 postbaseline tumor measurement, 96 (79%) experienced a decrease in tumor baseline size, with a median decrease of 54%.

Figure 5 shows the Kaplan-Meier estimates of progression-free and overall survival in the overall and treatment-naive populations. Median progression-free survival was 4 months (95% CI, 3-6 months) in the overall population and 14 months (95% CI, 7-17 months) in treatment-naive patients. The 12-month progression-free survival rates were 35% (95% CI, 31%-39%) in the overall population and 52% (95% CI, 44% to 60%) in treatment-naive patients. Median overall survival was 23

Figure 2. Objective Response Rate Assessed in Patients With Measurable Disease at Baseline in Subgroups (n = 581)

Source	No. With Objective Response	Total No. of Patients	Objective Response Rate, % (95% CI)[a]
Previous ipilimumab			
Naive	107	277	38.6 (32.9-44.6)
Treated	87	304	28.6 (23.6-34.1)
Pembrolizumab dose and schedule			
2 mg/kg, every 3 weeks	45	143	31.5 (24.0-39.8)
10 mg, every 3 weeks	86	272	31.6 (26.1-37.5)
10 mg, every 2 weeks	63	166	38.0 (30.5-45.8)
Sex			
Men	130	363	35.8 (30.9-41.0)
Women	64	218	29.4 (23.4-35.9)
Age, y			
<65	111	354	31.4 (26.6-36.5)
≥65	83	227	36.6 (30.3-43.2)
Eastern Cooperative Oncology Group performance status			
0	139	385	36.1 (31.3-41.1)
1	55	195	28.2 (22.0-35.1)
Lactate dehydrogenase level			
Normal	139	331	42.0 (36.6-47.5)
Elevated (>100% ULN)	53	238	22.3 (17.1-28.1)
Brain metastases			
Yes	17	49	34.7 (21.7-49.6)
No	177	531	33.3 (29.3-37.5)
BRAF			
V600 Wild type	157	442	35.5 (31.1-40.2)
V600 Mutant	35	133	26.3 (19.1-34.7)
M stage			
M1a	13	34	38.2 (22.2-56.4)
M1b	43	77	55.8 (44.1-67.2)
M1c	136	463	29.4 (25.3-33.8)
No. previous therapies			
<2	116	318	36.5 (31.2-42.0)
≥2	78	263	29.7 (24.2-35.6)
Type of previous therapy			
Chemotherapy	59	196	30.1 (23.8-37.0)
Immunotherapy[b]	54	159	34.0 (26.6-41.9)
BRAF or MEK inhibitor	23	97	23.7 (15.7-33.4)
Baseline tumor size			
<Median (<102 mm)	124	290	42.8 (37.0-48.7)
≥Median (≥102 mm)	70	291	24.1 (19.3-29.4)
Overall	194	581	33.4 (29.6-37.4)



Data were assessed by independent central review using RECIST v1.1. ULN indicates upper limit of normal.

[a] Objective response rate was defined as the percentage of patients with a complete or partial response.

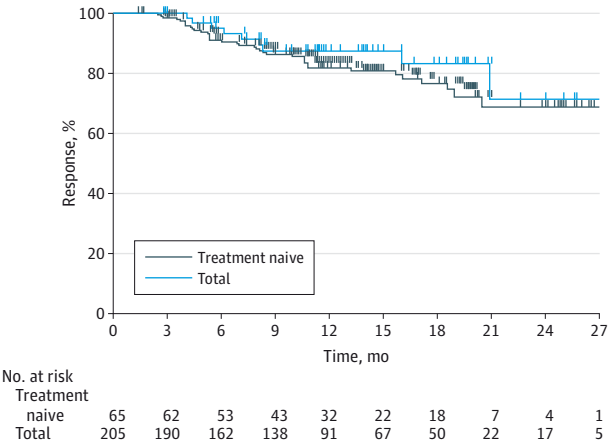
[b] Immunotherapy category excludes ipilimumab.

months (95% CI, 20-29 months) in the overall population, with 12- and 24-month overall survival rates of 66% (95% CI, 62%-69%) and 49% (95% CI, 44%-53%). In patients given pembrolizumab as their initial systemic cancer treatment, median overall survival was 31 months (95% CI, 24 months to not reached), with 12- and 24-month overall survival rates of 73% (95% CI, 65%-79%) and 60% (95% CI, 51%-68%). Progression-free and overall survival were numerically similar regardless of prior treatment with ipilimumab (eFigure; eTable 1 in the Supplement) or dosing regimen (eTable 2 in the Supplement).

Toxicity

Pembrolizumab was generally well tolerated, without clear evidence of a dose- or regimen-related increase in toxicities. As of the April 18, 2014, cutoff date, median time of undergoing therapy was 24 weeks (range, 0.1-123 weeks), and the median number of pembrolizumab doses was 10 (range, 1-59). The most common any-grade toxicities considered to be treatment related by investigators were fatigue, pruritus, and rash (**Table 2**). Grade 3 or 4 treatment-related toxicities occurred in 92 patients (14%). The most common grade 3 or 4 treatment-related toxicity was fatigue, which occurred in 12 patients (1.8%). All other treatment-related grade 3 or 4 toxicities occurred in less than 1% of patients. Treatment-related serious adverse events were noted in 59 (9%) patients: most frequently colitis (n = 9; 1%), pyrexia (n = 6; 1%), and pneumonitis (n = 5; 1%). Discontinuation due to treatment-related adverse events occurred in 27 patients (4%). There were no treatment-related deaths. The pembrolizumab toxicity profile was similar in patients with ipilimumab-naive and ipilimumab-treated melanoma, with no consistent differences observed (eTable 3 in the Supplement).

Figure 3. Duration of Response to Pembrolizumab Among Responders

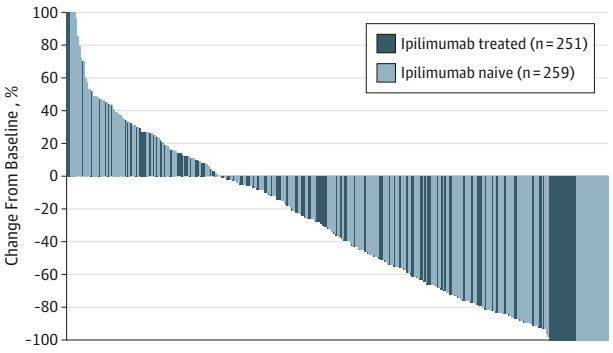


No. at risk

Treatment naive	65	62	53	43	32	22	18	7	4	1
Total	205	190	162	138	91	67	50	22	17	5

Reports estimates of duration of response among responders in the total population (n = 205) and the treatment-naive population (n = 65), as assessed by RECIST v1.1 by independent central review for patients with confirmed response who had at least 1 dose of study treatment, regardless of whether they had measurable disease per central RECIST v1.1 at baseline. Small vertical tick marks represent patients who were censored at that specific time in the analysis. Tick marks appear to be floating when multiple events occurred at the same time.

Figure 4. Maximum Percentage of Change From Baseline in Sum of the Longest Diameter of Each Target Lesion in the Full Analysis Set



Reports maximum percentage change from baseline in the sum of the longest diameter of each target lesion, as assessed by RECIST v1.1 by independent central review for patients who had measurable disease at baseline by the same and at least 1 postbaseline tumor assessment (full analysis set, N = 510). Target lesions were defined as all measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total. Changes greater than 100% were truncated at 100%.

Prespecified toxicities of any grade based on the immune-stimulatory mechanism of action of pembrolizumab occurring in more than 1 patient were hypothyroidism (n = 49; 7%), pneumonitis (n = 18; 3%), hyperthyroidism (n = 15; 2%), colitis (n = 11; 2%), severe skin reactions (n = 11; 2%), thyroiditis (n = 8; 1%), uveitis (n = 6; 1%), hepatitis (n = 4; 1%), hypophysitis (n = 3; 0.5%), hypopituitarism (n = 3; 0.5%), nephritis (n = 3; 0.5%), and myositis (n = 2; 0.3%). All of these events were of grade 1 or 2 severity except for 23 grade 3 events (n = 9 for severe skin reactions, n = 7 for colitis, n = 2 each for hyperthyroidism and pneumonitis, and n = 1 each for hepatitis, hypothyroidism, and nephritis) and 3 grade 4 events (n = 1 each for hepatitis, hypophysitis, and nephritis). There was no effect of prior ipilimumab treatment on immune-mediated adverse events (eTable 4 in the Supplement).

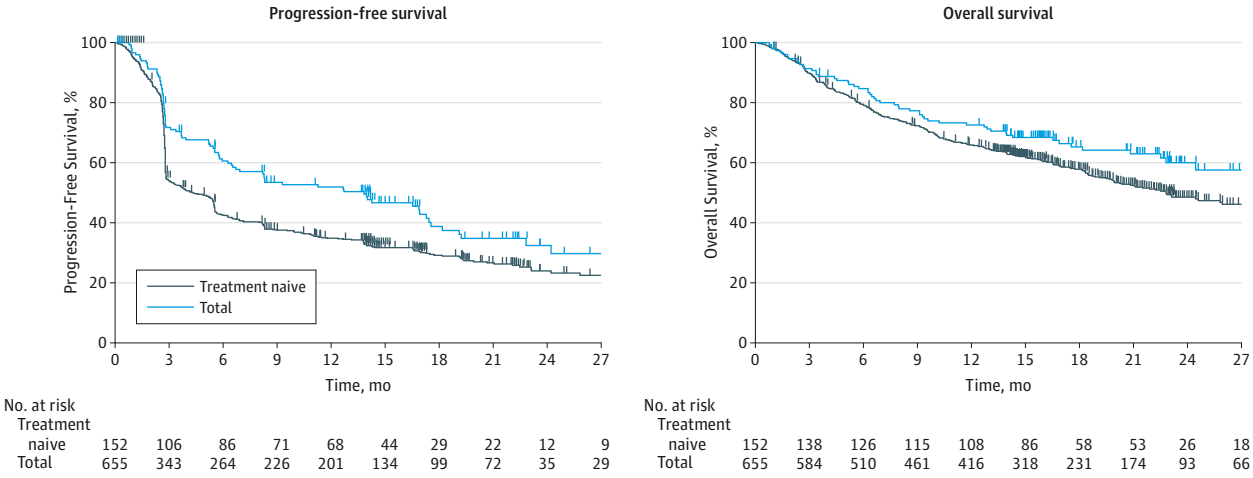
Discussion

In this population of 655 patients, pembrolizumab treatment was associated with an objective response rate of 33%, 12-month progression-free survival rate of 35%, a 23-month median overall survival, and a grade 3 or 4 adverse event rate of 14%, regardless of previous ipilimumab treatment or pembrolizumab dose or schedule. In treatment-naive patients, the overall response rate was 45%, the 12-month progression-free survival rate was 52%, and the median overall survival was 31 months. The observed difference in response rate between ipilimumab-naive (39%) and ipilimumab-treated (29%) melanoma may not be directly linked to ipilimumab treatment history. As shown by Joseph et al,[17,18] previous ipilimumab therapy is not an independent predictor of response to pembrolizumab in patients with melanoma, for whom the sum of target lesions at baseline was the strongest predictor of response. In the population reported in this article, median baseline tumor burden was 90 mm in the ipilimumab-naive population and 120 mm in the ipilimumab-treated population. This imbalance in baseline tumor burden may confound comparisons of pembrolizumab activity in ipilimumab-naive and ipilimumab-treated patients and may have been related to the difference in objective response rate observed in this analysis. The protocol-specified requirement for disease progression on prior BRAF inhibitor therapy in the randomized ipilimumab-refractory cohort may have further skewed the patient population to have a lower response rate independent of the prior therapy with ipilimumab.

The 29% objective response rate reported for the ipilimumab-treated population is similar to the 26% objective response rate reported for the randomized KEYNOTE-001 cohort of patients with ipilimumab-treated melanoma[7] that led to the approval of pembrolizumab by the US Food and Drug Administration (FDA). Differences in objective response rate observed between the cohorts may be due to chance or may be a reflection of different enrollment criteria. All patients in the randomized cohort were required to have received at least 2 ipilimumab doses and have confirmed disease progression within 24 weeks of the last ipilimumab dose and treatment with a BRAF inhibitor (if indicated), whereas the ipilimumab-treated population in this analysis also included patients enrolled under less stringent criteria.

In a subgroup analysis, antitumor activity with pembrolizumab was observed across all clinicopathologic factors examined. Consistent with the aforementioned role of baseline tumor size as a predictor of outcomes,[17,18] patients with a baseline tumor burden below the median, regardless of ipilimumab status, had a higher objective response rate (43%). Patients with category M1b disease also had a higher response rate (43 of 77 patients; 56%). Compared with the total population, the response rates were higher among the 133 patients who were treatment naive (45% for overall response; 14% for

Figure 5. Progression-Free and Overall Survival in Patients Treated With Pembrolizumab in Total and Treatment-Naive Populations



The small vertical tick marks represent patients who were censored at that specific time in the survival analysis. Tick marks appear to be floating when multiple events occurred at the same time. Data were assessed by independent central review using RECIST v1.1.

complete response). Although patients in the total population with *BRAF*^{V600}-mutant melanoma had a lower objective response rate (26%), the 95% CI for *BRAF*^{V600}-mutant melanoma is wide (95% CI, 19%-35%) and overlaps with that seen for *BRAF*^{V600}-wild-type melanoma (response rate 36% [95% CI, 31%-40%]). Of note, in the treatment-naive population, the objective response rate was similar in patients with *BRAF*^{V600}-mutant (50% [95% CI, 28%-72%]) and wild-type (45% [95% CI, 35%-55%]) melanoma. This suggests that the difference observed in the total population may be driven in part by the selection bias of many oncologists to treat patients with *BRAF*^{V600}-mutant melanoma deemed to be more aggressive with BRAF inhibitors,[19] as well as extrinsic confounding factors such as the selection of patients with previous treatment with BRAF inhibitors rather than by the mutational status of the tumor itself.[20-22]

The objective response rate in KEYNOTE-001 is clinically meaningful, with 90 of 205 responders (44%) having a response that lasted more than 1 year at the time of data cutoff and an estimated median duration of response of 28 months. Results of the progression-free survival analysis also support the durability of the clinical benefit associated with pembrolizumab. Collectively, these data suggest that the majority of patients with melanoma treated with pembrolizumab will experience lasting objective responses.

Although there appeared to be slight differences in antitumor activity based on the pembrolizumab dose and schedule, data from the randomized cohorts included in this 655-patient population showed no significant difference in activity between pembrolizumab doses of 2 and 10 mg/kg every 3 weeks[7,10] or 10 mg/kg every 2 or every 3 weeks.[11] In the 540 patients enrolled in KEYNOTE-002, there was a lack of clinically meaningful differences in antitumor activity between pembrolizumab, 2 and 10 mg/kg every 3 weeks.[8] Similarly, there was no dose-response relationship between pembrolizumab, 10 mg/kg every 2 or every 3 weeks in the 834 patients with advanced melanoma from KEYNOTE-006.[9] Taken together, these data support the FDA-approved pembrolizumab dose of 2 mg/kg every 3 weeks.

Table 2. Adverse Events Considered to Be Drug-Related by Investigators That Occurred in ≥5% of Patients Treated With Pembrolizumab[a]

Adverse Event	Grade, No. (%)[b] Any (N = 655)	3-4 (N = 655)
Any	544 (83)	92 (14)
Fatigue	245 (37)	12 (2)
Pruritus[c]	174 (27)	2 (0.3)
Rash[d]	161 (25)	4 (1)
Diarrhea	115 (18)	6 (1)
Arthralgia	107 (16)	0
Nausea	97 (15)	2 (0.3)
Vitiligo	69 (11)	0
Asthenia	63 (10)	4 (1)
Myalgia	60 (9)	0
Decreased appetite	56 (9)	1 (0.2)
Headache	51 (8)	2 (0.3)
Cough	48 (7)	1 (0.2)
Hypothyroidism	46 (7)	1 (0.2)
Pyrexia	42 (6)	1 (0.2)
Dyspnea	41 (6)	4 (1)
Chills	41 (6)	0
Vomiting	33 (5)	3 (0.4)

[a] The Medical Dictionary for Regulatory Activities preferred terms *progressive disease* and *malignant neoplasm progression* not related to study drug were excluded.

[b] Indicates individuals with events.

[c] Includes pruritus generalized.

[d] Includes rash generalized and rash maculopapular.

The safety profile observed in this analysis over a median follow-up duration of 15 months was similar to that reported previously for patients with melanoma treated with

pembrolizumab[7-11] No deaths from treatment-related adverse events were reported, and only 4% of patients discontinued pembrolizumab because of a treatment-related adverse event. Most treatment-related adverse events in the current study were of grade 1 or 2 severity and were reversible. Similar to previous reports,[6,11] there was no difference in safety between the ipilimumab-naive and ipilimumab-treated populations. Although uncommon, severe adverse events of potential immune causality were successfully managed with treatment interruption, immunosuppressive therapy, or both. The safety profile was similar across doses, although a higher frequency of some adverse events was observed in patients treated with 10 mg/kg every 2 weeks. This imbalance could be partially explained by a longer duration of therapy compared with those of 2 other dosing regimens but could also be influenced by the small sample size of the 10-mg/kg every 2 weeks population. No significant between-dose and schedule differences in toxicity were observed in the randomized melanoma cohorts of KEYNOTE-001,[7,10,11] KEYNOTE-002,[8] or KEYNOTE-006.[9]

Results in this study were similar to those reported for nivolumab, another anti-PD-1 inhibitor approved for treating patients with advanced melanoma that progressed following ipilimumab and, if *BRAF*^{V600}-mutated, a BRAF inhibitor. Among 107 patients with advanced melanoma treated with nivolumab, the response rate was 31%, with a 1-year survival rate of 62% and a 2-year survival rate of 43%.[23] In a phase 3 study of treatment-naive patients with melanoma, nivolumab alone or in combination with ipilimumab demonstrated significantly longer progression-free survival and a higher objective response rate (44%-58%) than ipilimumab monotherapy.[24]

Most limitations of this study are a consequence of it being composed of multiple expansion cohorts of a larger phase 1b study. This study accrued very rapidly after there was initial evidence of durable tumor responses in patients with advanced melanoma. Four different cohorts with slightly different eligibility criteria and different doses and schedules were included to help address questions of the optimal dose and schedule, as well as which patients would benefit from pembrolizumab. Besides the known variables derived from the eligibility criteria and treatment plan, it is certainly possible that the initial cohorts may have been biased to patients with a higher likelihood of response, as the prevailing thinking at that time was that only patients with slow-growing and low-volume melanoma would benefit from immunotherapy. As investigators observed significant antitumor activity, it is likely that patients with worse prognostic factors may have enrolled in subsequent cohorts. Regardless, we believe that the large number of patients reported herein and the later randomization of several key factors in the randomized cohorts provide a comprehensive account of the broad activity of pembrolizumab in patients with metastatic melanoma.

Conclusions

Among patients with advanced melanoma, pembrolizumab administration was associated with an overall objective response rate of 33%, 12-month progression-free survival rate of 35%, and median overall survival of 23 months; grade 3 or 4 treatment-related adverse events occurred in 14%.

ARTICLE INFORMATION

Author Affiliations: Division of Hematology and Oncology, University of California-Los Angeles, Los Angeles (Ribas, Chmielowski); Department of Hematology/Oncology, The Angeles Clinic and Research Institute, Los Angeles, California (Hamid, Hoffner); Department of Hematology/Oncology, University of California-San Francisco, San Francisco (Daud, Algazi); Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts (Hodi); Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York (Wolchok, Rizvi); Department of Medical Oncology, Crown Princess Mary Cancer Centre, Westmead Hospital and Melanoma Institute Australia, Sydney, Australia (Kefford); Department of Clinical Medicine, Macquarie University, Sydney, Australia (Kefford); Department of Medical Oncology, Princess Margaret Cancer Centre, Toronto, Ontario, Canada (Joshua); Department of Clinical Research, South Texas Accelerated Research Therapeutics, San Antonio (Patnaik); Department of Melanoma, The University of Texas MD Anderson Cancer Center, Houston (Hwu); Department of Cutaneous Oncology, H. Lee Moffitt Cancer Center, Tampa, Florida (Weber); Division of Hematology and Oncology, Abramson Cancer Center at the University of Pennsylvania, Philadelphia (Gangadhar); Department of Medicine, University of Sydney, Sydney, Australia (Hersey); Division of Medical Oncology, Mayo Clinic, Rochester, Minnesota (Dronca); Department of Hematology/Oncology, Mayo Clinic, Jacksonville, Florida (Joseph); Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania (Zarour); Department of Hematology/Oncology, Massachusetts General Hospital, Boston (Lawrence); Department of Medical Oncology, Gustave-Roussy Cancer Campus and Paris Sud University, Villejuif Paris-Sud, France (Mateus, Robert); Department of Clinical Oncology, Merck & Co, Inc, Kenilworth, New Jersey (Gergich, Lindia, Giannotti, Ebbinghaus, Kang); BARDS, Merck & Co, Inc, Kenilworth, New Jersey (Li).

Author Contributions: Dr Ribas had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr Li conducted and is responsible for the data analysis.
Study concept and design: Ribas, Daud, Wolchok, Hwu, Joseph, Gergich, Li, Ebbinghaus, Kang, Robert.
Acquisition, analysis, or interpretation of data: Ribas, Hamid, Daud, Hodi, Wolchok, Kefford, Joshua, Patnaik, Hwu, Weber, Gangadhar, Hersey, Dronca, Joseph, Zarour, Chmielowski, Lawrence, Algazi, Rizvi, Hoffner, Mateus, Gergich, Lindia, Giannotti, Li, Ebbinghaus, Kang, Robert.
Drafting of the manuscript: Ribas, Kefford, Joshua, Patnaik, Weber, Lindia, Li, Ebbinghaus, Kang.
Critical revision of the manuscript for important intellectual content: Ribas, Hamid, Daud, Hodi, Wolchok, Kefford, Joshua, Patnaik, Hwu, Weber, Gangadhar, Hersey, Dronca, Joseph, Zarour, Chmielowski, Lawrence, Algazi, Rizvi, Hoffner, Mateus, Gergich, Lindia, Giannotti, Li, Ebbinghaus, Kang, Robert.
Statistical analysis: Li.
Obtained funding: Mateus.
Administrative, technical, or material support: Daud, Hodi, Kefford, Joshua, Weber, Chmielowski, Lawrence, Algazi, Gergich, Lindia, Giannotti.
Study supervision: Hamid, Wolchok, Joshua, Weber, Hersey, Algazi, Rizvi, Gergich, Kang.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Drs Gergich, Lindia, Li, Ebbinghaus, Kang, and Ms Giannotti are employees of and/or stockholders in Merck & Co, Inc. Drs Gergich and Kang are named on a patent application related to the use of pembrolizumab for the treatment of cancer. Dr Ribas reports ownership of stock in Acteris, Arcus, CytomX, Compugen, FLX Bio, and Kite Pharma, and consulting for the following companies with honoraria paid to UCLA: Merck & Co, Inc, Amgen, GlaxoSmithKline, Genentech, Novartis, Roche, and Pfizer. Dr Hamid reports receipt of research funding and consulting fees from Merck & Co, Inc. Dr Hodi reports receipt of fees from the following companies for clinical trial support or grants paid to Dana-Farber Cancer Institute: Merck & Co, Inc, Bristol-Myers Squibb, and Genentech; receipt of personal fees from Merck & Co, Inc and Novartis; and having a patent for methods for treating MICA-related disorders

with royalties paid, a patent for therapeutic peptides pending, and a patent for tumor antigens and uses thereof pending. Dr Wolchok reports receipt of consulting fees from Merck & Co, Inc and Bristol-Myers Squibb. Dr Kefford reports receipt of fees from the following companies for travel or honoraria paid to Crown Princess Mary Cancer Centre and/or Macquarie University: Merck & Co, Inc, Bristol-Myers Squibb, GlaxoSmithKline, Roche, and Novartis. Dr Patnaik reports receipt of research funding from Merck & Co, Inc. Dr Hwu reports receipt of research funding and has served on an advisory board for Merck & Co, Inc. Dr Weber reports receipt of personal fees and research funding paid to H. Lee Moffitt Cancer Center from Merck & Co, Inc and Bristol-Myers Squibb. Dr Zarour reports receipt of research funding from Merck & Co, Inc. Dr Chmielowski reports serving on advisory boards for Merck & Co, Inc, Genentech, Bristol-Myers Squibb, Prometheus, Astellas, GlaxoSmithKline, Eli Lilly, and Amgen and receipt of speaker fees from Genentech, Bristol-Myers Squibb, and Prometheus. Dr Rizvi reports serving on advisory boards for Merck & Co, Inc. Ms Hoffner reports serving on an advisory board for and/or receiving speaker fees from Merck & Co, Inc. Dr Robert reports serving on advisory boards for Merck & Co, Inc, Roche, GlaxoSmithKline, Novartis, Amgen, and Bristol-Myers Squibb. No other disclosures were reported.

Funding/Support: This study was supported by Merck & Co, Inc.

Role of the Funder/Sponsor: In collaboration with academic authors, representatives of the sponsor participated in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, and approval of the manuscript. Dr Ribas had control over the decision to submit the manuscript for publication. Medical writing and editorial assistance were provided by Tricia Brown, MS, and Melanie Leiby, PhD (The ApotheCom Merck oncology team, Yardley, Pennsylvania). This assistance was funded by Merck & Co, Inc.

Previous Presentations: Presented in part in Hamid O et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. *N Engl J Med*. 2013;369:134-144; at the 2014 Annual Meeting of the American Society of Clinical Oncology (Ribas A et al. Efficacy and safety of the anti-PD-1 monoclonal antibody MK-3475 in 411 patients with melanoma [abstract]. *J Clin Oncol*. 2014;32(suppl 5):9000); in Robert C et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. *Lancet*. 2014;384:1109-1117; the 11th International Congress of the Society for Melanoma Research (Ribas A et al. Updated clinical efficacy of the anti-PD-1 monoclonal antibody pembrolizumab (pembro, MK-3475) in 411 patients (pts) with melanoma (MEL) [abstract]. *Pigment Cell Mel Res*. 2014;27(6):1222); and the 2015 Annual Meeting of the American Society of Clinical Oncology (Daud A et al. Long-term efficacy of pembrolizumab in a pooled analysis of 655 patients with advanced melanoma enrolled in KEYNOTE-001 [abstr]. *J Clin Oncol*. 2015;33(suppl 15):9005).

Additional Contributions: The authors thank Eric Rubin, MD, and Alise Reicin, MD (Merck & Co, Inc), for critical review of the manuscript and supervision of the research group, and Kellie Celentano, BA, Cong Chen, PhD, Scott Diede, MD, PhD, Linda Gammage, BA, Amanda McDonald, BA, and Andrea Perrone, MD, Merck Research Laboratories, for their contributions to study conduct and critical review of the manuscript. These individuals were not compensated in association with their contributions to this article. The authors thank the patients, their families, and caregivers, as well as all investigators and site personnel.

REFERENCES

1. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer*. 2012;12(4):252-264.

2. Ribas A. Tumor immunotherapy directed at PD-1. *N Engl J Med*. 2012;366(26):2517-2519.

3. Blank C, Brown I, Peterson AC, et al. PD-L1/B7H-1 inhibits the effector phase of tumor rejection by T cell receptor (TCR) transgenic CD8+ T cells. *Cancer Res*. 2004;64(3):1140-1145.

4. Okazaki T, Honjo T. PD-1 and PD-1 ligands: from discovery to clinical application. *Int Immunol*. 2007; 19(7):813-824.

5. Barber DL, Wherry EJ, Masopust D, et al. Restoring function in exhausted CD8 T cells during chronic viral infection. *Nature*. 2006;439(7077): 682-687.

6. Hamid O, Robert C, Daud A, et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. *N Engl J Med*. 2013;369(2):134-144.

7. Robert C, Ribas A, Wolchok JD, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma. *Lancet*. 2014;384(9948):1109-1117.

8. Ribas A, Puzanov I, Dummer R, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002). *Lancet Oncol*. 2015;16(8):908-918.

9. Robert C, Schachter J, Long GV, et al; KEYNOTE-006 investigators. Pembrolizumab vs ipilimumab in advanced melanoma. *N Engl J Med*. 2015;372(26):2521-2532.

10. Hamid O, Robert C, Ribas A, et al. Randomized comparison of two doses of the anti-PD-1 monoclonal antibody MK-3475 for ipilimumab-refractory (IPI-R) and IPI-naive (IPI-N) melanoma (MEL). *J Clin Oncol*. 2014;32(15)(suppl):Abstract 3000.

11. Robert C, Joshua AM, Weber JS, et al. Pembrolizumab (MK-3475) for advanced melanoma: randomized comparison of two dosing schedules. Poster presented at: European Society for Medical Oncology 2014 Congress; September 28-30, 2014; Madrid, Spain. Abstract LBA34.

12. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247.

13. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res*. 2009;15(23):7412-7420.

14. National Institutes of Health. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.3. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. Accessed February 23, 2016.

15. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. *Biometrika*. 1934;26:404-413. doi:10.1093/biomet/26.4.404.

16. Garon EB, Rizvi NA, Hui R; et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med*. 2015;372(21):2018-2028.

17. Joseph RW, Elassaiss-Schaap J, Wolchok JD, et al. Baseline tumor size (BTS) and PD-L1 expression are independently associated with clinical outcomes in patients (pts) with metastatic melanoma (MM) treated with pembrolizumab (pembro; MK-3475). Abstract presented at: Society for Melanoma Research 2014 Congress; November 13-16, 2014; Zurich, Switzerland. *Pigment Cell Melanoma Res*. 2014;27:1188.

18. Joseph RW, Elassaiss-Schaap J, Wolchock JD, et al. Baseline tumor size as an independent prognostic factor for overall survival in patients with metastatic melanoma treated with the anti-PD-1 monoclonal antibody MK-3475. *J Clin Oncol*. 2014;32(15)(suppl):Abstract 3015.

19. Ascierto PA, Simeone E, Grimaldi AM, et al. Do BRAF inhibitors select for populations with different disease progression kinetics? *J Transl Med*. 2013;11:61.

20. Ascierto PA, Grimaldi AM, Acquavella N, et al. Future perspectives in melanoma research: meeting report from the "Melanoma Bridge. Napoli, December 2nd-4th 2012". *J Transl Med*. 2013;11:137.

21. Ackerman A, Klein O, McDermott DF, et al. Outcomes of patients with metastatic melanoma treated with immunotherapy prior to or after BRAF inhibitors. *Cancer*. 2014;120(11):1695-1701.

22. Kluger HM, Sznol M, Callahan MK et al. Survival, response duration and activity by BRAF mutation status in a phase 1 trial of nivolumab (anti-PD-1; BMS-936558,ONO-4538) and ipilimumab concurrent therapy in advanced melanoma (MEL). Abstract presented at: Society for Melanoma Research 2014 Congress; November 13-16, 2014; Zurich, Switzerland. *Pigment Cell Melanoma Res*. 2014;27:1203.

23. Topalian SL, Sznol M, McDermott DF, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. *J Clin Oncol*. 2014;32(10): 1020-1030.

24. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med*. 2015;373(1):23-34.