Observational Study

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Real-world experience with pembrolizumab in patients with advanced melanoma

A large retrospective observational study

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Abstract

Pembrolizumab has been approved in the United States for treating advanced melanoma for >4 years. We examined real-world pembrolizumab use and associated outcomes in US oncology clinical practices, including patients who would not be eligible for clinical trials.

Flatiron Health longitudinal database was used to identify adult patients with advanced melanoma initiating ≥1 dose of pembrolizumab from September 4, 2014, through December 31, 2016, with follow-up through December 31, 2017. Patients in any clinical trial during the study period were excluded. Overall survival (OS) and time on treatment from pembrolizumab initiation were analyzed using the Kaplan–Meier (KM) method. Subgroup analyses were conducted to examine OS for several patient characteristics including Eastern Cooperative Oncology Group (ECOG) performance status >1, brain metastases, and corticosteroids before pembrolizumab initiation.

Pembrolizumab was administered to 315 (59%), 152 (29%), and 65 (12%) patients as first-, second-, and third-line/later therapy. Median age at pembrolizumab initiation was 68 years (range, 18–84); most patients were male (66%) and white (94%). Of those with available data, 38% had *BRAF*-mutant melanoma, 21% had elevated lactate dehydrogenase (LDH) level, and 23% had ECOG >1. Overall, 18% had brain metastases, and 23% were prescribed corticosteroids <3 months before initiating pembrolizumab. Median study follow-up was 12.9 months (range, 0.03–39.6). Median OS was 21.8 months (95% confidence interval [CI] 16.8–29.1); KM 1-year and 2-year survival rates were 61% and 48%, respectively; and median time on pembrolizumab treatment was 4.9 months (95% CI 3.7–5.5). Median OS for first-line pembrolizumab was not reached, and for second-line and third-line/later was 13.9 and 12.5 months, respectively (log-rank $P = .0095$). Significantly better OS (all $P \leq .0014$, log-rank test) was evident for patients with ECOG performance status (PS) of 0 to 1 (vs >1), normal (vs elevated) LDH level, and no (vs yes) corticosteroid prescription <3 months before. No difference was recorded in OS by brain metastases (log-rank $P = .22$) or *BRAF* mutation status (log-rank $P = .90$).

These findings support effectiveness of pembrolizumab in the real-world clinical setting and provide important insights into patient characteristics and outcomes associated with pembrolizumab therapy for a heterogeneous patient population with advanced melanoma, including patients who would not be eligible for clinical trials.

Abbreviations: CCI = Charlson comorbidity index, CI = confidence interval, ECOG PS = Eastern Cooperative Oncology Group performance status, EHR = electronic health record, FDA = Food and Drug Administration, KM = Kaplan–Meier, LDH = lactate dehydrogenase, OS = overall survival, PD-1 = programmed cell death 1 protein, PD-L1 = PD-ligand 1.

Keywords: antineoplastic therapy, community oncology practice, immuno-oncology, advanced melanoma, pembrolizumab, overall survival, observational study, real-world clinical practice

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1. Introduction

The available treatment options and prognosis for patients with advanced melanoma have improved dramatically over recent years with the development of new immunotherapies. This new era began with the approval of ipilimumab in 2011, followed by approvals of the immune checkpoint inhibitors of programmed cell death 1 protein (PD-1) pembrolizumab and nivolumab.[1–3] Results of clinical trials with these agents indicate significant improvements in overall survival (OS) for patients with advanced melanoma,[4–6] and from 2014 to 2017 the prescribing of PD-1 inhibitors for advanced melanoma has increased substantially, regardless of *BRAF* mutation status, at oncology practices in the United States (US).[7]

Pembrolizumab was the first PD-1 inhibitor approved by the US Food and Drug Administration (FDA; in September 2014) for treating advanced melanoma. Clinical trial findings have demonstrated the efficacy of pembrolizumab[4,8] and established it as standard of care for advanced melanoma.[9] Recently published long-term results of advanced melanoma trials report estimated 4-year OS rate of 42% with pembrolizumab as first- or second-line therapy[10] and estimated 5-year OS rate of 41% with pembrolizumab as first-line therapy.[11] These findings can be contrasted with historical 1-year OS rates of 25% for advanced melanoma in the pre-immunotherapy era.[12]

In real-world clinical practice, however, both patient population and the setting of care are different from those in clinical trials.[13,14] Pivotal melanoma clinical trials, including the KEYNOTE trials for pembrolizumab, typically exclude patients with Eastern Cooperative Oncology Group performance status (ECOG PS) of >1, as well as patients with active or untreated brain metastases or active autoimmune disease.[6,8,15,16] A recent study of patients included in a Danish metastatic melanoma registry determined that 55% of patients would not have been eligible for a clinical trial, most commonly because of ECOG PS >1 and/or active/untreated brain metastases.[17] In addition, while no upper age limit is imposed for these clinical trials, older patients may be under-represented in the trials.[18]

A strong need exists therefore to understand characteristics and outcomes of patients treated for advanced melanoma with PD-1 inhibitors such as pembrolizumab outside of clinical trials. In a prior observational study of 168 patients with advanced melanoma, Cowey et al[19] identified ECOG PS >1, elevated lactate dehydrogenase (LDH) level, the presence of brain metastases, and third-line/later (vs first-line) pembrolizumab therapy, but not *BRAF* mutation status, as significant predictors of decreased survival. Overall, the results of their study and of 2 other small observational studies suggested real-world effectiveness of PD-1 inhibitors for advanced melanoma[19–21]; however, larger studies with longer follow-up are needed to evaluate patient characteristics and the outcomes of PD-1 inhibitor therapy for advanced melanoma outside of the clinical trial setting.

The aims of this retrospective observational study were to examine the real-world utilization pattern of pembrolizumab, patient characteristics, and associated outcomes for patients with melanoma treated at US oncology clinical practices, including OS, time on treatment, and time to next line of treatment. We paid particular attention to the characteristics and outcomes of patients not eligible for or under-represented in clinical trials.

2. Methods

2.1. Data source

We used de-identified data contained in the Flatiron Health cloud-based longitudinal database containing electronic health record (EHR) data from cancer clinics and selected academic centers.[22] Flatiron Health's database is a longitudinal, demographically and geographically diverse database that includes data from over 265 cancer clinics (~800 sites of care) throughout the US. The Flatiron Health EHR data include both structured data and unstructured data, such as physician's notes, captured using technology-enabled abstraction, as previously described.[23] The EHR data in the Flatiron Health dataset are refreshed monthly; and the study dataset was updated through December 31, 2017.

Approval of the study protocol was obtained through Flatiron procedure and approved by the Copernicus Group Institutional Review Board before study conduct and included a waiver of informed consent. Data provided to third parties were de-identified and provisions were in place to prevent re-identification in order to protect patients' confidentiality.

2.2. Patient population and study design

Patients eligible for this retrospective observational study were 18 years or older, with a confirmed diagnosis of advanced melanoma and who initiated and received ≥1 dose of pembrolizumab during the period from September 4, 2014 (the date of first FDA approval of pembrolizumab for melanoma) through December 31, 2016. Patients were drawn from the Flatiron Health advanced melanoma dataset, which has the following additional eligibility requirements: at least 2 documented clinical visits on or after January 1, 2011, and cutaneous melanoma at pathologic stage III or IV, either at initial diagnosis or at local or distant recurrence, confirmed by review of pathology reports (International Classification of Diseases, Ninth Revision, Clinical Modification codes [ICD-9-CM] 172.x or ICD-10 diagnosis codes C43x or D03x[24]). Patients with non-cutaneous melanoma (e.g., ocular, subungual, mucosal, palmar, plantar) are excluded from the dataset. In addition, we excluded patients with recorded participation in any clinical trial during the study period.

The index date was defined as the date of pembrolizumab initiation. We followed patients from pembrolizumab initiation through December 31, 2017, or until death, if earlier.

2.3. Study variables

The primary outcome measures were OS beginning with the first dose of pembrolizumab, time on treatment with pembrolizumab (treatment duration), and time to next line of treatment. Time on treatment was calculated as [(the date of the last pembrolizumab administration minus the index date) +1 day]. The time to next line of treatment was calculated as [(date of initiation of next treatment line or death minus index date) + 1 day].[25,26] The last encounter was identified as the last possible date in the visit table of the Flatiron database, which includes office visits, laboratory visits, and treatment-related visits. Mortality data were captured through a combination of unstructured EHR data, structured EHR data, and Social Security Death Index and a commercial death dataset.

Demographic variables available from the Flatiron database included age, sex, race, and US region of the clinical practices. Disease-related variables included melanoma stage at diagnosis,

dates of initial melanoma and advanced melanoma diagnoses, *BRAF* biomarker testing and test results, ECOG PS, LDH level, and presence of brain metastases, and date. The normal range of LDH level was 105 to 333 U/L, and LDH levels >333 U/L were defined as elevated. The Charlson comorbidity index (CCI) score was derived from ICD-9 and ICD-10 diagnostic data,[27] and the CCI was scored without consideration of melanoma diagnosis since that was an entry criterion. Baseline autoimmune diseases recorded during the 2 years before the index date were captured by using a list of autoimmune conditions reported in 2 recent publications (ICD-9 and ICD-10 codes listed in Supplemental digital content 1, Supplementary Table S1, http://links.lww.com/MD/D130).[28,29]

Treatment-related variables available in the database included drug names, route, dose, and units. The lines of therapy were determined by applying predefined algorithms, as previously described.[7]

2.4. Statistical analysis

Descriptive analyses were conducted to describe the patient population and treatment patterns, overall and according to line of therapy in which pembrolizumab was received. We determined frequencies and percentages for categorical variables and mean, standard deviation, median, and range for variables measured on the continuous or interval scale.

The observed follow-up time was reported by summary statistics. The Kaplan–Meier (KM) method was used to determine OS, time on treatment, and time to next line of treatment, with associated 95% confidence intervals (CIs). Patients who did not die were censored in the KM estimate of OS on the date of their last recorded encounter in the database. Patients who did not die and did not have a recorded next line of therapy, and whose last visit date was within 120 days of the last pembrolizumab administration day, were considered still on therapy and were censored in the KM estimate for time on treatment. For time to next line of treatment, patients who did not die nor initiate a next line of therapy were censored on the date of their last recorded encounter.

We conducted several subgroup analyses of OS by line of therapy (first line and second line/later) and for all patients within the following subgroups: age (<55, 55–74, ≥75 years), ECOG PS (0–1, 2–4), brain metastasis (yes/no), LDH level (normal, elevated), *BRAF* mutation status (wild-type, *BRAF*-mutant), history of corticosteroid prescription(s) within 3 months (yes/no) before the index date, and diagnosis of autoimmune condition(s) within 2 years before the index date (yes/no). We plotted the KM curves for each subgroup, using the log-rank test to compare univariate between-cohort differences in OS for pembrolizumab lines of therapy and (for patients with available data, excluding "unknowns") by age group, ECOG PS, LDH level, *BRAF* mutation status, brain metastasis, prior corticosteroid prescription(s), and prior autoimmune condition(s).

Statistical analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC).

3. Results

3.1. Patients

Of 6543 patients with a confirmed diagnosis of advanced melanoma in the database, 532 patients received pembrolizumab, including 498 as monotherapy (94%) and 34 as combination therapy (6%), and were eligible for the analyses. Overall, 59%, 29%, and 12% received pembrolizumab as first-, second-, and third-line (or later) therapy (Table 1; Supplemental digital content 1, Supplementary Fig. S1, http://links.lww.com/MD/D130); and 297 (94%) received pembrolizumab monotherapy in first line, 146 (96%) in second line, and 55 (85%) in third line or later.

Baseline demographic characteristics of all patients and by pembrolizumab treatment line are summarized in Table 1. Overall, at the time of pembrolizumab initiation, the median age was 68 years (range 18–84 years), two-thirds of patients (66%) were male, and 94% of patients were white. The median Charlson comorbidity index score overall was 6 (range 0–15).

Of the patients with known ECOG PS, 23% had a score of >1 (n = 51/219; Table 2), including 35 patients (16%), 14 (6%), and

Table 1

Patient demographic characteristics at the index date (initiation of pembrolizumab).

Variable	Pembrolizumab treatment line			All patients (*N* = 532)
	First line (*n* = 315)	Second line (*n* = 152)	Third line & later (*n* = 65)	
Male sex, n (%)	214 (67.9)	93 (61.2)	46 (70.8)	353 (66.4)
Age, median (range), yr	71 (18–84)	67 (29–84)	61 (27–84)	68 (18–84)
<55 years, n (%)	56 (17.8)	31 (20.4)	22 (33.8)	109 (20.5)
55–74 years, n (%)	143 (45.4)	72 (47.4)	31 (47.7)	246 (46.2)
≥75 years, n (%)	116 (36.8)	49 (32.2)	12 (18.5)	177 (33.3)
Race data available, n (%)	*288 (91.4)*	*142 (93.4)*	*59 (90.8)*	*489 (91.9)*
White, n (%)*	265 (92.0)	134 (94.4)	58 (98.3)	457 (93.5)
Other, n (%)*	23 (7.9)	8 (5.6)	1 (1.7)	32 (6.5)
US CB region, data available, n (%)	*224 (71.1)*	*111 (73.0)*	*47 (72.3)*	*382 (71.8)*
Northeast, n (%)*	38 (17.0)	16 (14.4)	12 (25.5)	66 (17.3)
Midwest, n (%)*	46 (20.5)	38 (34.2)	15 (31.9)	99 (25.9)
South, n (%)*	76 (33.9)	46 (41.4)	11 (23.4)	133 (34.8)
West, n (%)*	64 (28.6)	11 (9.9)	9 (19.1)	84 (22.0)
Adjusted CCI score, mean (SD)	4.2 (3.6)	5.3 (3.5)	5.0 (3.8)	4.6 (3.6)
Median (range)	6 (0–14)	6 (0–15)	6 (0–15)	6 (0–15)

CCI = Charlson comorbidity index, US CB = United States Census Bureau.
* Patient percentages for race and region refer to those with available data.

Table 2

Clinical characteristics of patients at the index date (initiation of pembrolizumab).

Variable	Pembrolizumab treatment line			
	First line (n=315)	Second line (n=152)	Third line & later (n=65)	All patients (N=532)
ECOG PS data available, n (%)	*137 (43.5)*	*62 (40.8)*	*20 (30.8)*	*219 (41.2)*
ECOG 0–1, n (%)[*]	109 (79.6)	45 (72.6)	14 (70.0)	168 (76.7)
ECOG 2–4, n (%)[*]	28 (20.4)[†]	17 (27.4)	6 (30.0)	51 (23.3)
LDH level data available, n (%)	*198 (62.9)*	*109 (71.7)*	*52 (80.0)*	*359 (67.5)*
Elevated LDH level, n (%)[*,‡]	36 (18.2)	26 (23.9)	14 (26.9)	76 (21.2)
Stage available at first diagnosis, n (%)[§]	240 (76.2)	115 (75.7)	51 (78.5)	406 (76.3)
II or lower, n (%)[*]	88 (36.7)	33 (28.7)	25 (49.0)	146 (36.0)
III, IIIA, IIIB, n (%)[*]	56 (23.3)	23 (20.0)	12 (23.5)	91 (22.4)
IIIC, n (%)[*]	24 (10.0)	11 (9.6)	2 (3.9)	37 (9.1)
IV, n (%)[*]	72 (30.0)	48 (41.7)	12 (23.5)	132 (32.5)
Tested for *BRAF* mutation, n (%)	284 (90.2)	143 (94.1)	64 (98.5)	491 (92.3)
BRAF mutation positive[*]	90 (31.7)	46 (32.2)	39 (60.9)	175 (35.6)
BRAF wild-type[*]	174 (61.3)	88 (61.5)	23 (35.9)	285 (58.0)
Unsuccessful/indeterminate/pending[*]	20 (7.0)	9 (6.3)	2 (3.1)	31 (6.3)
History of brain metastases, n (%)	51 (16.2)	29 (19.1)	16 (24.6)	96 (18.0)
Corticosteroid <3 months before index date	34 (10.8)	56 (36.8)	30 (46.2)	120 (22.6)
Autoimmune condition, n (%)[‖]	20 (6.3)	13 (8.6)	10 (15.4)	43 (8.1)

ECOG PS = Eastern Cooperative Oncology Group performance status, LDH = lactate dehydrogenase, mo months.

[*] Patient percentages for ECOG PS, LDH level, stage at first diagnosis, and *BRAF* test results refer to those with available data.

[†] Two patients who received pembrolizumab as first-line therapy had ECOG PS of 4.

[‡] Included were 27 patients (7.5%) with LDH levels ≥2 times the upper limit of normal. The normal range for LDH levels was 105 to 333 U/L; LDH levels >333 U/L were defined as elevated.

[§] Stage was a variable abstracted from the charts by trained abstractors; when missing, it was because of inadequate information available in the charts to determine stage (including inadequate information in the doctor's handwritten notes, pathology reports, etc).

[‖] Diagnosis of autoimmune condition recorded within 2 years before index date.

2 (1%) with ECOG PS of 2, 3, and 4, respectively. The LDH level was available for two-thirds of patients, of whom 21% (n = 76/359) had an elevated LDH level. The tumors of most patients had been tested for *BRAF* mutation status (Table 2), and of the 460 patients with melanoma of known *BRAF* mutation status, 175 (38%) had *BRAF*-mutant melanoma.

A history of brain metastases was recorded for 96 patients (18%), including 45 patients (47%) with brain metastasis diagnosis recorded within 3 months of the index date (Supplemental digital content 1, Supplementary Table S2, http://links.lww.com/MD/D130). Of these 45 patients, 18 patients (40%) also had a history of corticosteroid prescription(s) within 3 months before the index date.

Almost 1-quarter of patients (23%) had been prescribed corticosteroids during the 3 months before the index date; 8% had a recorded diagnosis of an autoimmune condition during the prior 2 years; and 10 of 43 patients (23%) with an autoimmune condition had been prescribed corticosteroids during the 3 months before the index date (Table 2; Supplemental digital content 1, Supplementary Table S1, http://links.lww.com/MD/D130).

3.2. Treatment summary

The observed follow-up time from the index date to the earliest of death or the last encounter in the database ranged from 0.03 to 39.6 months (median 12.9 months; Table 3).

Treatment regimens for the 34 patients who received pembrolizumab as part of combination therapy are summarized in Supplemental digital content 1, Supplementary Table S3, http://links.lww.com/MD/D130.

Of the 152 patients overall who received pembrolizumab as second-line therapy, most had received an ipilimumab-based regimen as first-line therapy (104; 68%), while 26 (17%) had received BRAF or BRAF/MEK inhibitors, 14 (9%) had received nivolumab or PD-1 combination therapy, and 8 (5%) had received platinum-based therapy or another agent.

Table 3

Length of study follow-up and Kaplan–Meier estimates of survival, time on treatment, and time to next line of treatment.

	Pembrolizumab treatment line			
	First line (n=315)	Second line (n=152)	Third line or later (n=65)	All patients (N=532)
Follow-up from index date,[*] median (range), mo	13.6 (0.03–38.6)	12.1 (0.07–39.6)	10.1 (0.30–39.2)	12.9 (0.03–39.6)
Kaplan–Meier estimates:				
OS, median (95% CI), mo	NR (21.2–NR)	13.9 (10.7–22.7)	12.5 (8.2–24.8)	21.8 (16.8–29.1)
1-year survival (95% CI)	65.6% (59.9–70.7%)	56.1% (47.6–63.7%)	52.8% (39.6–64.4%)	61.3% (56.9–65.4%)
2-year survival (95% CI)	52.8% (46.0–59.1%)	41.6% (33.2–49.8%)	39.0% (26.2–51.5%)	47.9% (43.0–52.6%)
Time on treatment, median (95% CI), mo	4.9 (3.7–5.9)	4.9 (3.5–6.0)	4.2 (2.4–6.2)	4.9 (3.7–5.5)
Time to next line of treatment, median (95% CI), mo	13.6 (9.8–19.0)	9.2 (6.3–12.8)	6.3 (4.9–10.1)	11.2 (8.6–13.3)

mo = months, NR = not reached, OS = overall survival.

[*] Index date defined as date of first pembrolizumab administration.

For the 65 patients who received pembrolizumab in third line or later, ipilimumab was the most common agent received as first- or second-line therapy (by 29 [45%] in first line and 21 [32%] in second line), followed by a BRAF or BRAF/MEK inhibitor (23 [35%] and 21 [32%], respectively), other agents (9 [14%] and 14 [22%], respectively), and nivolumab monotherapy or combination therapy (4 [6%] and 9 [14%], respectively).

3.2.1. Kaplan–Meier estimates of overall survival, time on treatment, and time to next line of treatment. We report outcomes as determined for all 532 patients in the study. The findings were similar when restricted to the 498 study patients (94%) who received pembrolizumab as monotherapy (data not shown).

The overall median OS was 21.8 months, with estimated 1- and 2-year survival rates of 61% and 48%, respectively. For the 315 patients who received pembrolizumab as first-line therapy, the median OS was not reached, and estimated 1- and 2-year survival rates were 66% and 53%, respectively, better than for patients receiving pembrolizumab in second or third line (Table 3). Figure 1 displays the KM results for OS, time on treatment, and time to next line of treatment for all patients and by treatment line. Statistically significant differences in univariate analyses were seen among treatment lines in OS (log-rank $P = .0095$), with longer OS for patients treated with pembrolizumab as first-line therapy (Fig. 1a).

As estimated by KM, the median time on treatment with pembrolizumab was 4.9 months (95% CI 3.7–5.5), including 4.9, 4.9, and 4.2 months in first-, second-, and third-line (or later) therapy, respectively (Table 3). Using an assumption of 2-year maximum pembrolizumab exposure for those still on treatment at data cutoff, the restricted mean treatment duration was 8.0 months (95% CI 7.3–8.7).

The overall median time to next line of treatment was 11.2 months (95% CI 8.6–13.3; Table 3).

3.2.2. Subgroup analyses. The Kaplan-Meier results for OS comparing subgroups of patients with available data (i.e., excluding those with no ECOG PS score, LDH level, or *BRAF* mutation status) are depicted graphically in Figure 2 and Supplemental digital content 1, Supplementary Figs. S2–S5, http://links.lww.com/MD/D130, together with a summary by treatment line and overall in Supplemental digital content 1, Supplementary Table S4, http://links.lww.com/MD/D130. Statistically significant differences in univariate analyses based on the log-rank test were seen for several patient subgroups, with significantly better OS evident for patients with an ECOG PS of 0–1 (vs 2–4), normal (vs elevated) LDH level, and no corticosteroid prescription <3 months before pembrolizumab initiation (Fig. 2). Differences among age groups just reached statistical significance (log-rank $P = .0459$) with slightly longer survival for the middle age group (55–74 years), followed by the youngest age group (<55 years), and lowest survival for patients ≥75 years (Fig. 2a). Most statistically significant differences seen overall were limited to patients who received pembrolizumab in first line, with no significant differences recorded between subgroups of patients receiving pembrolizumab in second-line/later except with regard to LDH level, perhaps in some cases because of small sample size (Supplemental digital content 1, Supplementary Table S4, http://links.lww.com/MD/D130 and Supplementary Fig. S2, http://links.lww.com/MD/D130).

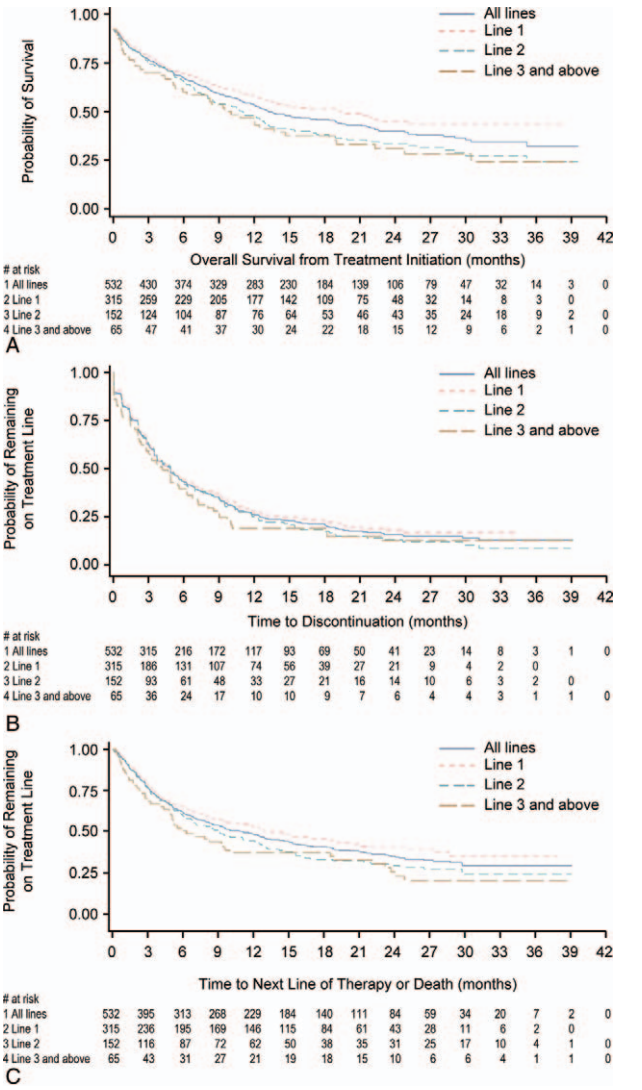

Figure 1. Kaplan–Meier plots, overall and by pembrolizumab line of therapy, of (a) overall survival (OS): all lines median, 21.8 months (95% CI 16.8–29.1); first line (L1) median, not reached (21.2–NR); second line (L2) median, 13.9 (10.7–22.7); third line/later (L3+) median, 12.5 (8.2–24.8; log-rank $P = .0095$), (b) time on treatment with pembrolizumab: overall median, 4.9 months (95% CI, 3.7–5.5); L1 median, 4.9 (3.7–5.9); L2 median, 4.9 (3.5–6.0); L3+ median, 4.2 (2.4–6.2;log-rank $P = .33$), and (c) time to next line of treatment: overall median, 11.2 months (95% CI, 8.6–13.3); L1 median, 13.6 (9.8–19.0); L2 median, 9.2 (6.3–12.8); L3+ median, 6.3 (4.9–10.1;log-rank $P = .021$).

There was no significant difference in univariate analyses of OS by *BRAF* mutation status (log-rank $P = .90$; Supplemental digital content 1, Supplementary Fig. S3, http://links.lww.com/MD/D130), with brain metastasis (log-rank $P = .22$; Supplemental digital content 1, Supplementary Fig. S4, http://links.lww.com/MD/D130), or by presence/absence of an autoimmune condition in the 2 years before pembrolizumab initiation (log-rank $P = .49$; Supplemental digital content 1, Supplementary Fig. S5, http://links.lww.com/MD/D130).

4. Discussion

This large, retrospective observational study at US oncology clinical practices followed 532 patients with advanced melanoma

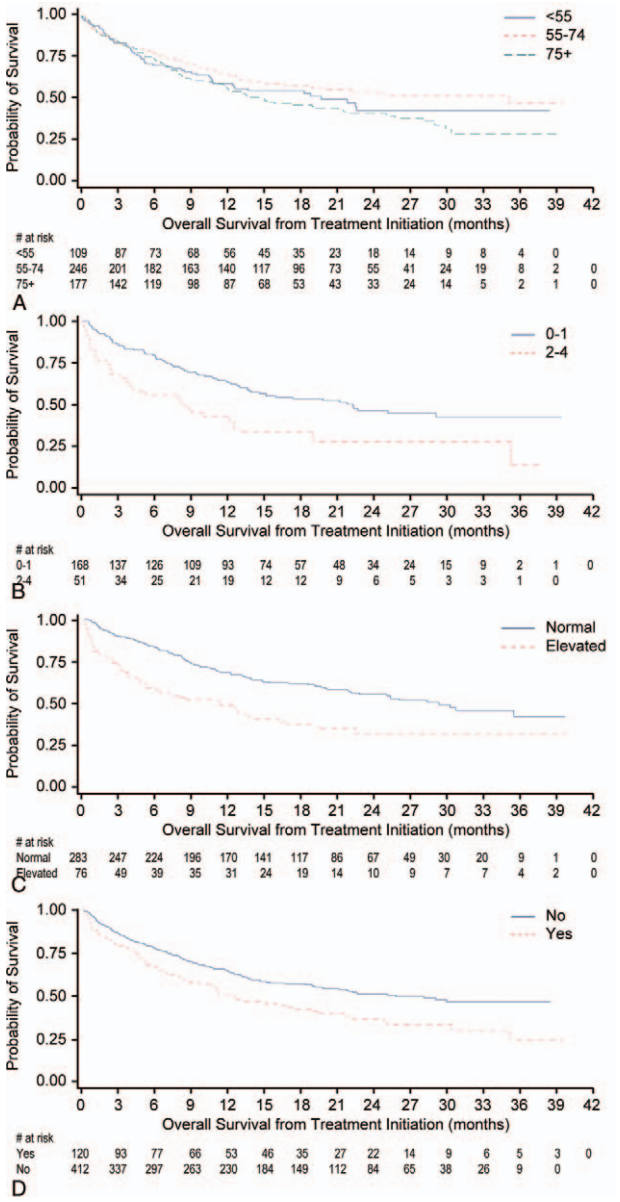

Figure 2. Kaplan–Meier plots of overall survival (OS) for subgroups, including only patients with no missing data (a) by age group: <55 years median, 19.8 months (10.8–NR); 55 to 74 years median, 35.3 months (19.4–NR); ≥75 years median, 15.1 (11.9–21.8; log-rank $P = .0459$), (b) by ECOG PS: of 0–1 median, 22.3 months (13.7–NR); ECOG PS of 2–4 median, 8.2 (3.6–12.5) (0–1 vs 2–4; log-rank $P < .001$), (c) by LDH level: normal LDH median, 29.1 months (21.9–NR); elevated LDH median, 11.2 (5.1–16.8) (normal vs elevated; log-rank $P < .001$), (d) by corticosteroid prescription within 3 months before pembrolizumab initiation: no, median, 25.9 months (95% CI, 19.2–NR); yes, median 12.2 (8.4–19.4) (no vs yes; log-rank $P = .0014$).

for up to 3.3 years (median of 13 months) from initiation of pembrolizumab as monotherapy or combination therapy. We found that pembrolizumab was associated with a median OS of 21.8 months overall and a 2-year survival rate of 48%. As estimated by the KM method, the median time on pembrolizumab treatment was almost 5 months, and median time to next line of treatment was 11.2 months. We did not specifically determine the percentage of patients who would have been ineligible for pembrolizumab clinical trials; however, substantial numbers of patients would not have met 1 or more trial inclusion criteria, namely, those with ECOG PS >1 (n=51), brain metastases (n=96), pretreatment systemic corticosteroid prescriptions (n=120), and pre-existing autoimmune conditions (n=43).

We found statistically significant differences in OS among pembrolizumab treatment lines (first-, second-, and third-line or later). The majority of patients received pembrolizumab as first-line therapy, and these patients experienced longer OS, with a median that was not reached during the study and estimated 2-year survival rates of 53%. Similarly, prior small observational studies found significantly better OS for patients with fewer previous lines of therapy before initiating pembrolizumab.[19,21]

Overall survival and survival rates at 1 and 2 years were consistent with those recorded in the study of Cowey et al,[19] who also studied a broad, real-world population of patients, albeit much smaller (n=168) than our study population, prescribed pembrolizumab for advanced melanoma at US community oncology practices. Our study utilized a different database to cross-validate their findings by using a larger sample size and longer follow-up. Similar to their results, we found significant differences in OS for ECOG PS >1 (vs 0–1) and elevated LDH (vs normal), and no difference in OS according to *BRAF* mutation status. Different from their results,[19] we found no difference in OS with presence of brain metastases (vs no brain metastases). With regard to several additional characteristics studied, we found there were significant differences in OS among 3 age groups and for corticosteroid prescription (vs no prescription) within 3 months before pembrolizumab initiation, while there was no difference in OS for patients with (vs without) pre-existing autoimmune disease.

The finding that patients with ECOG PS >1 had worse survival than those with ECOG PS 0 to 1 was not surprising or unexpected, as reported in other observational studies,[21] and because performance status is generally accepted as a prognostic indicator.[30] Similarly, others have reported significantly worse OS in association with elevated baseline LDH level in both observational studies and clinical trials of PD-1 and PD-ligand 1 (PD-L1) inhibitors.[31–33]

Our results also align with preliminary work in trials and observational studies examining response to anti-PD-1/PD-L1 agents in patients with advanced melanoma and brain metastases. While the majority of these studies were small (18–94 patients) and often conducted in academic or institutional rather than community practice, therapy with PD-1/PD-L1 inhibitors demonstrated activity against untreated and pretreated brain metastases and appeared safe for patients with brain metastases treated concurrently with radiation therapy,[34–38] although in 2 studies patients with symptomatic brain metastases[37] or those not pretreated[36] had worse outcomes. Nonetheless, in a recent open-label trial of 94 patients with untreated brain metastases but no neurologic symptoms, the combination of nivolumab and ipilimumab produced intracranial benefit in line with extracranial benefit that was judged by the authors to be clinically meaningful.[38] The results of future studies examining PD-1/PD-L1 inhibitor therapy for patients with brain metastases will be of great interest.

In their retrospective study, Parakh et al[37] found that patients with symptomatic brain metastases who were receiving corticosteroids concomitant with anti-PD-1 therapy had a significantly shorter OS than those not on corticosteroids. Of note, we found that patients prescribed corticosteroid therapy within 3 months

before initiating pembrolizumab had worse outcomes: a statistically significant difference in OS with vs. without corticosteroid therapy before the index date was evident overall and for patients initiating pembrolizumab as first-line therapy, but not for those initiating pembrolizumab in second- or third-line/later. This finding could be confounded by the large numbers of patients initiating first-line pembrolizumab who were not pretreated with corticosteroids (281; 89%), nonetheless, we believe this finding requires further investigation as potentially important and highly relevant to clinical practice. We did not, however, evaluate corticosteroid therapy after the index date during treatment with pembrolizumab.

Active autoimmune disease is a common exclusion criterion in PD-1 inhibitor clinical trials,[4,8] and the prevalence of autoimmune comorbidities is reportedly high among patients with melanoma. Examination of a large US claims database from 2004 to 2014 found that the prevalence rate of pre-existing autoimmune comorbidities was 28% among 1177 patients with newly diagnosed metastatic melanoma in 2014, a prevalence higher than that in patients with non-metastatic melanoma and in the general population.[39] In our study, we found no significant difference in OS with regard to the presence or absence of an autoimmune condition (8% of patients had pre-existing autoimmune diagnoses). A recent systematic review of case reports and observational studies of patients with cancer found no differences in adverse events between those who had active vs. inactive autoimmune disease and who were prescribed an immune checkpoint inhibitor (ipilimumab or a PD-1/PD-L1 inhibitor); nonetheless, the authors[28] and others[40] have called for more research to establish the risk:benefit ratio of checkpoint inhibitors in this patient population.

Our study found that older patients (≥75 years) experienced slightly worse outcomes than the other 2 age groups, with longer OS recorded for patients 55 to 74 years old. Instead, in a study at 2 academic centers, comparable effectiveness was recorded across age groups for 254 patients with metastatic melanoma treated with a PD-1 or PD-L1 inhibitor,[32] although the latter study included only 47 patients (19%) who were 75 years and older, as compared with 177 patients (33%) in our study. A small French study looking at age used a different cut-point, reporting better OS and PFS for 38 patients >65 years (vs 54 patients ≤65) with metastatic melanoma treated with ipilimumab, nivolumab, or pembrolizumab,[41] and a non-comparative single-center study reported that immunotherapy was effective and well-tolerated by older patients (n=99; all >75 years).[42] Common immune-related adverse effects were similar in different age groups in prior studies, suggesting that older patients can safely tolerate PD-1/PD-L1 inhibitors,[32,41] nonetheless, more studies are needed in future to examine the associations between age and the effectiveness and safety of immunotherapy.

Findings in our study differed in several ways from those of pembrolizumab clinical trials, in addition to including patients who would have been excluded from those trials, such as those with ECOG PS >1. Overall, 18% of patients had a record of brain metastases in our database as compared with 8% to 10% of those enrolled in clinical trials, which according to trial eligibility criteria had to be previously treated and stable brain metastases,[4,8] whereas we had no such requirement. Moreover, the patients in our study (median age of 68) were older than those enrolled in pembrolizumab clinical trials (medians of 61–63 years[4,8]). In the US, the median age at diagnosis of cutaneous melanoma is 64 years.[43] Data from clinical trials of PD-1/PD-L1 inhibitors in a recent meta-analysis that included 2 melanoma trials[6,15] suggest comparable efficacy of PD-1/PD-L1 inhibitors in adults <65 versus ≥65 years.[44]

The outcomes in our study were similar to results of pooled data from patients with advanced melanoma in a pembrolizumab clinical trial (KEYNOTE-001), of whom 151 were treatment-naïve and 504 had received 1 or more prior lines of therapy[8]: the median follow-up was slightly longer (15 months vs 13 months in our study), while median OS was 23 months versus 22 months in our study and 2-year survival rates were 49% versus 48%, respectively. With longer follow-up in KEYNOTE-001, the estimated 5-year OS rate for all patients was 34%.[11] Instead, survival was numerically lower in our study compared with that in KEYNOTE-006 (median OS not reached; 2-year survival 55%).[4] In the latter study, patients received pembrolizumab as first- or second-line therapy (not in later lines).

In summary, our results support the conventionally accepted factors of good performance status (ECOG PS 0–1) and normal LDH level as being prognostic for better survival of patients with advanced melanoma. Moreover, in our study, no current corticosteroid therapy and first-line use of pembrolizumab appeared also to confer better survival. Of course, as for all indications, the potential risk of therapy-related adverse events must also be taken into consideration when selecting a therapeutic course.

We acknowledge several limitations that should be considered in interpreting our findings. Information on several key variables was incomplete or not available in the dataset. For example, baseline ECOG PS was available for only 41% of patients and LDH level for 68% of patients. Moreover, detailed information regarding the management of brain metastases was not available, so we could not determine whether brain metastases had been pretreated, and neither the status of the autoimmune diagnoses nor the indications for corticosteroid therapy pre-index date were available. While 40% of patients with brain metastasis diagnosis within 3 months of the index date also had 1 or more recorded corticosteroid prescription(s) during that time, we cannot be certain there was a connection. In addition, information was not available regarding baseline tumor size or PD-L1 tumor expression, both shown to be prognostic factors,[45,46] nor for number and location of sites of metastasis, disease progression, treatment response, progression-free survival, or patient adherence to oral therapies.

Furthermore, temporal occurrence and characterization of the incidence and types of adverse effects associated with PD-1/PD-L1 inhibitors remain important and clinically relevant areas of study as these agents become more commonly prescribed in real-world practice.[47] However, we were not able, using the available dataset, to assess the incidence of adverse effects of pembrolizumab therapy experienced by patients in this study. A review of common adverse events associated with PD-1/PD-L1 inhibitors was published in 2015.[48]

This study has several strengths, including a large patient population and long follow-up to record outcomes in the real-world clinical setting. At the time of this writing, we were unable to identify another observational study of PD-1 inhibitor therapy for advanced melanoma of similar size or length of follow-up. Most of the patients in this study had tumors that were tested for the *BRAF* mutation, as currently recommended for advanced melanoma.[9] Our patient population was heterogeneous, similar to that encountered in clinical practice, including patients with poor ECOG performance status, who are not eligible for clinical

trials, and patients who are under-represented in clinical trials, such as elderly patients.

It would have been of interest to compare outcomes between the patients who would be ineligible for a clinical trial and those who would meet trial eligibility criteria but instead were treated in real-world clinical settings. This comparison remains an important topic for future research.

5. Conclusions

This study provides important insights into real-world treatment patterns, patient characteristics, and outcomes associated with pembrolizumab therapy for a heterogeneous patient population with advanced melanoma, including patients who would not be eligible for a clinical trial. The median OS of 22 months and estimated 2-year survival rate of 48% are based on real-world clinical decision-making and support effectiveness of pembrolizumab in the real-world clinical setting. These findings illustrate continuing gains in melanoma survival rates with the availability of PD-1 inhibitor therapy and provide valuable insights to guide future research.

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