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Pembrolizumab Utilization and Outcomes for Advanced Melanoma in US Community Oncology Practices

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Summary: The programmed death-1 inhibitor pembrolizumab has demonstrated efficacy and safety in clinical trials for treating advanced (unresectable/metastatic) melanoma. We investigated the real-world utilization of pembrolizumab and associated patient outcomes for advanced melanoma in US community oncology practices. This retrospective, observational study used deidentified data from electronic health records for adult patients with advanced melanoma who received pembrolizumab at The US Oncology Network sites from September 2014 through December 2015, with follow-up through September 2016. Patients enrolled in clinical trials were excluded. Overall survival (OS) and physician-stated progression-free survival (PFS) were analyzed from pembrolizumab initiation using Kaplan-Meier, and associations between pembrolizumab therapy and OS/PFS, using multivariable Cox regression. Of 168 patients studied, 110 (65%) were male; the median age was 66 years (range, 26–over 90). Pembrolizumab was prescribed as first-line, second-line, and third-line/later for 39 (23%), 87 (52%), and 42 (25%) patients, respectively. In total, 41 patients (24%) had brain metastases. At pembrolizumab initiation, 21/129 (16%) had Eastern Cooperative Oncology Group performance status (ECOG PS) > 1; 51/116 (44%) had elevated lactate dehydrogenase. Median follow-up was 10.5 months (range, 0–25.1); median OS was 19.4 months (95% confidence interval, 14.0–not reached); median PFS was 4.2 months (95% confidence interval, 2.9–5.3). Brain metastases, ECOG PS > 1, elevated lactate dehydrogenase, and third-line/later (vs. first-line) pembrolizumab were significant predictors ($P < 0.01$) of decreased survival. Treatment-related toxicity was a discontinuation reason for 25% (29/117) of patients, and for 10 of these 29 patients (6% of the full-study cohort) treatment-related toxicity was the only reported reason. The real-world effectiveness and safety of pembrolizumab for advanced melanoma are consistent with clinical trial findings.

Key Words: advanced melanoma, pembrolizumab, real-world utilization, patient outcomes, progression-free survival, overall survival

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Cutaneous melanoma is a common and deadly malignancy with over 76,000 new diagnoses and over 10,000 associated deaths per year in the United States.[1,2] The rate of new melanoma diagnoses has risen consistently over the last several decades at about 1.4% per year,[1] doubling over the last 40 years and projected to include 87,110 new cases in the United States in 2017.[3] In the past, patients with advanced (unresectable or metastatic) melanoma experienced median survival of 6–9 months, with 25% survival at 1 year.[4,5] Fortunately, in the last 7 years we have seen an appreciable increase in effective therapies that are significantly improving clinical outcomes, raising hope of substantial decreases in melanoma-associated mortality.[5–9]

These therapeutic advances have come in 2 general forms, genetic-based and immune-based therapies. Genetic-based approaches comprise treatments that address a common driver mutation seen in ~50% of melanoma tumors, the *BRAF* V600 mutation. The *BRAF* inhibitors dabrafenib and vemurafenib, approved in combination with trametinib and cobimetinib, respectively, for treating *BRAF*-mutant melanoma, have received approval based on randomized trials demonstrating improved overall survival (OS) and progression-free survival (PFS).[10–14] New immunotherapies known as immune checkpoint inhibitors have also played an integral role in advancing outcomes for patients with advanced melanoma in recent years. These drugs are monoclonal antibodies that bind and interfere with negative regulator receptors on T lymphocytes, which in turn allow the lymphocytes to remain active and target melanoma cells. Ipilimumab, a cytotoxic T-lymphocyte antigen-4 inhibitor, was the first to be approved by the US Food and Drug Administration (FDA).[15,16] The programmed death-1 (PD-1) inhibitors, nivolumab and pembrolizumab, are humanized monoclonal antibodies that block the PD-1 receptor, a negative regulator on lymphocytes. These agents are better tolerated than chemotherapy[17] and demonstrate better outcomes, with lower toxicity, than ipilimumab for advanced melanoma.[18,19] Nivolumab is FDA approved for treating advanced melanoma, both as a single agent and in combination with ipilimumab, based on studies demonstrating improved OS.[18,20]

Pembrolizumab was the first PD-1 inhibitor approved by the US FDA for the treatment of advanced melanoma. In the KEYNOTE-001, KEYNOTE-002, and KEYNOTE-006 clinical trials to date, pembrolizumab monotherapy has demonstrated efficacy in treating advanced melanoma, regardless of prior treatment,[21,22] producing superior PFS over chemotherapy for ipilimumab-refractory disease[23] and superior OS and PFS over ipilimumab for advanced melanoma.[19,24] These important clinical trial results support the benefit of pembrolizumab for treating advanced melanoma; however, little is known about real-world utilization and patient outcomes associated with pembrolizumab for advanced melanoma outside of the clinical trial setting. The aim of this retrospective observational study was to investigate the real-world utilization and patient outcomes, including OS and physician-stated PFS,

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of pembrolizumab for patients with advanced melanoma in routine community oncology practice in the United States. In addition, we aimed to describe factors contributing to the discontinuation of pembrolizumab therapy.

MATERIALS AND METHODS

Study Design and Patients

This retrospective observational study of patients with advanced melanoma receiving pembrolizumab (KEYTRUDA, Merck & Co. Inc., Kenilworth, NJ; http://www.merck.com) was part of a larger observational study of treatment patterns for patients initiating first-line systemic therapy for advanced melanoma at The US Oncology Network (USON) sites.[25,26] This substudy included patients initiating pembrolizumab in any line of therapy during the 16-month period from September 1, 2014, through December 31, 2015, with follow-up through September 30, 2016. The analyses were conducted based on deidentified, multicenter clinical data abstracted from the iKnowMed (iKM) electronic health record (EHR) system plus review of longitudinal medical charts.

Eligible patients had newly diagnosed or recurrent unresectable or metastatic (advanced) melanoma and were 18 years or older at the time of initiating first-line therapy for melanoma. Other inclusion criteria were ≥ 2 clinic visits during the study period at a site utilizing the full-iKM EHR capacities. Patients enrolled in a clinical trial during the study period were excluded, as were those who had a previous diagnosis of and treatment for other primary cancer at any time in their medical history (excepting basal cell or squamous cell carcinoma and bladder or cervical carcinoma in situ). Patients initiating pembrolizumab as second-line or third-line (or later) therapy could have received prior systemic therapy initiated before September 1, 2014.

Data used for the study analyses were collected via programmatic queries of the EHRs and by manual chart review and abstraction onto electronic case report forms. These data were supplemented when necessary by vital status from the Social Security Death Master File.[27,28] We followed patients until the earliest of: (1) September 30, 2016; (2) their last clinic visit; or (3) a record of death, thus enabling 9 months' minimum potential follow-up for each patient.

Study data were handled in compliance with the Health Insurance Portability and Accountability Act (HIPAA).[29] All patients within iKM were assigned a unique patient identifier, and working analytic files were stripped of any direct patient identifiers, including all 19 HIPAA identifiers. Approval of the study protocol and statistical analysis plan was obtained from the McKesson Specialty Health Institutional Review Board and Compliance/Privacy Department. Informed consent was not required or possible as the data were deidentified and retrospectively collected.

Data Source

The USON is a physician-led organization comprising a network of integrated, community-based oncology practices. The USON utilizes treatment pathways based on National Comprehensive Cancer Network guidelines; however, there were no pathway restrictions on the use of pembrolizumab during the study period.

The iKM EHR system has been implemented across the USON and captures data on outpatient medical oncology care for patients treated across the United States (19 states) across 350 sites of care. The iKM EHR data represent ~1590 providers in 150 practices across > 550 sites of care and include ~2.4 million patient records documenting > 59 million patient visits. The iKM EHRs capture information including (but not limited to) diagnosis, laboratory tests, therapy administration, line of therapy, staging, comorbidities, and performance status information.

Study Measures

OS was defined as the time from initiation of pembrolizumab until the date of death. PFS was defined as the time from initiation of pembrolizumab until the date of disease progression or death as documented by the physician in the EHR. For the determination of PFS, patients without disease progression and who were still alive were censored on the last visit date available in the database. We investigated these measures for each patient through careful review of radiology reports and physicians' progress notes. Priority was given first to the radiology report. If the scan report was not available, but progression was noted in the physician progress notes, then this fact was captured.

Pembrolizumab and other lines of therapy were identified in iKM structured data and confirmed during chart review. We calculated the duration of pembrolizumab and that of other systemic therapies as the [(end date of index therapy)−(start date of index therapy)+1 d]. Complete cycles were defined as the number of full pembrolizumab cycles completed by the patient without reduction in dose or interruption of therapy within the pembrolizumab cycle.

Information about prior treatments (eg, surgery, radiation, or prior systemic treatment, or adjuvant immunotherapy following complete resection), including those delivered at non-USON sites at prior visits, was collected where available. Information about systemic treatment regimens was assessed up to 3 lines of therapy and included route, dose, units, number of cycles, and regimen start, stop, and discontinuation dates. The first line of therapy was defined as the first systemic treatment regimen beginning either after or <14 days before the advanced/metastatic melanoma diagnosis. Regimen components that began within 28 days of the first episode were considered to be part of a single line of therapy. A treatment line was advanced to the next line when a patient received new combinations of drugs or there was a gap in drug orders or administrations of > 120 days. The line of therapy was not considered as advanced if the chemotherapy combinations were followed by a similar regimen in which ≥ 1 of the component drugs were suppressed for a period of time and then the drug(s) were subsequently reintroduced. Because treatments could change within the first month upon receipt of biomarker results, if patients were switched to BRAF-targeted therapy during the first 28 days of a chemotherapy regimen (monotherapy or combination), the line of therapy was called *BRAF* therapy and the line number was not advanced.

Baseline mutational status and lactate dehydrogenase (LDH) levels used to calculate M1 status were defined as those closest to the initiation of first-line therapy within a 6-month window. Laboratory values closest to pembrolizumab initiation were assessed within a 30-day window. Performance status [Karnofsky performance score (KPS) or Eastern Cooperative Oncology Group performance status (ECOG) PS] was evaluated within a 30-day window of the initiation of pembrolizumab therapy. When only KPS was reported, an algorithm was used to convert KPS to ECOG PS.[30,31]

Possible reasons for treatment discontinuation included disease progression, death, toxicity, decline in ECOG PS, comorbidities, patient choice, and other or unknown. Patients who were lost to follow-up were included in the other or unknown categories and were not censored. The hierarchy for determining date of death was information from the Social Security Death Master File,[27,28] chart review, and programmatic query of the iKM database.

Statistical Analyses

We conducted descriptive analyses to summarize patients' demographic, treatment, and clinical characteristics. Time-to-event outcomes were estimated using the Kaplan-Meier product limit method. We assessed median survival times with 95% confidence intervals (CIs) and survival probabilities (with 95% CIs) at 12 and 24 months. Log-rank statistics were used to evaluate the univariate between-cohort differences in OS and PFS for pembrolizumab lines of therapy and by *BRAF* mutation status, as well as by ECOG PS, LDH level, and presence/absence of brain metastases.

Univariate Cox proportional hazard analyses were conducted to assess the individual associations between variables of interest and time-to-event outcomes (OS and PFS). Selected characteristics included in the univariate assessment were based on clinical relevance and/or best practice. The associations between pembrolizumab therapy and OS and PFS were evaluated by multivariable Cox proportional hazard regression analyses, adjusting for baseline covariates that were either significant in univariate (Cox) analysis or considered clinically relevant by the study team. The multivariable models for OS and PFS included the following potential predictors: age at pembrolizumab initiation (over 65 vs. 65 y or under), body mass index (obese or overweight vs. underweight/normal), brain metastases (yes vs. no), *BRAF* mutation status (positive vs. wild type), ECOG PS at pembrolizumab initiation (2–3 vs. 0–1), LDH level (elevated vs. normal), M1 status (yes vs. no), pembrolizumab line of therapy (second-line or third-line/later vs. first-line), Charlson comorbidity index score (1–2 or ≥ 3 vs. 0), and sex (male vs. female).

Analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Patients

We identified 17,014 patients with melanoma attending The USON sites utilizing the full-iKM EHR capacities from January 1, 2008 through December 31, 2015. A total of 168 patients initiated pembrolizumab during the 16-month period from September 1, 2014, through December 31, 2015, met all eligibility criteria, and were included in the study (Fig. 1). Pembrolizumab was administered as first-line, second-line, and third-line (or later) therapy for 39 (23%), 87 (52%), and 42 (25%) patients, respectively.

The median age of study patients was 66 years, and two thirds (65%) were male (Table 1). At initiation of first-line therapy, 52 of 153 (34%) with recorded laboratory values had an elevated LDH level. At initiation of pembrolizumab therapy, 51 of 116 patients (44%) had an elevated LDH level, 21 of 129 (16%) with documented ECOG PS had a score of >1, and 41 patients (24%) had brain metastases (Table 2). In addition, 83 (49%) patients had metastasis to lung, 45 (27%) to liver, 28 (17%) to bone, and 132 (79%) to other sites.

Therapy for Melanoma

Three quarters of patients [126 (75%)] had undergone surgery for melanoma and one quarter [46 (27%)] had received radiation therapy at some point for their melanoma treatment before initiating pembrolizumab. Of the 41 patients with brain metastases, 34 (83%) had prior treatment, including 30 who had prior surgery and 18 who had prior radiation, of whom 14 had both surgery and radiation.

The most common prior systemic therapy received by the 87 patients who initiated pembrolizumab as second-line therapy was ipilimumab [75 (86%)]. Other common first-line therapies included dabrafenib [9 (10%)], trametinib [9 (10%)], interferon alfa-2b [8 (9%)], and temozolomide [7 (8%)].

Ipilimumab was also the most common prior systemic therapy received by the 42 patients who initiated pembrolizumab as third-line (or later) therapy [39 (93%)]. Other prior therapies for these patients included vemurafenib [18 (43%)]; dabrafenib [17 (40%)], trametinib [17 (40%)], interferon alfa-2b [5 (12%)], and temozolomide [5 (12%)].

The median duration of pembrolizumab therapy captured in the study was 4.7 months (range, 0–23.8 mo). Patients received a median of 7 pembrolizumab cycles (range, 1–35 cycles), with a mean of 10 (SD, 9) cycles. The median cycle length was 3.1 weeks (range, 2.8–11.2 wk), and the mean pembrolizumab dose prescribed over the course of treatment was 1.9 (SD, 0.2) mg/kg.

Overall, 117 patients (70%) discontinued pembrolizumab during the study period, the most common (nonexclusive) reason being physician-documented disease progression [53 (45%) patients; Table 3]. The second most commonly reported reason for discontinuation was treatment-related toxicity [29 (25%)]. For 10 of these 29 patients (6% of the full-study cohort) treatment-related toxicity was the only reported reason, whereas 19 patients also had other reasons for treatment discontinuation.

Time-to-Event Outcomes

The median length of study follow-up for all patients from initiation of pembrolizumab was 10.5 months (range, 0–25.1 mo).

Seventy (42%) patients died during the study period. The overall median OS was 19.4 months, whereas the upper limit of the 95% CI was not reached (Table 3). The survival curves differed by pembrolizumab line of therapy (log-rank P-value = 0.023), as depicted in Figure 2. Survival probabilities at 12 and 24 months were 61% and 44% overall, respectively (Table 3), whereas by pembrolizumab line of therapy, the survival probabilities at 12 months were 68% (95% CI, 49%–81%), 64% (95% CI, 52%–73%), and 49% (95% CI, 32%–63%) for first-line, second-line, and third-line (or later) therapy, respectively.

In multivariable analyses, we identified 4 significant predictors of death in the study population (Fig. 2): the presence of brain metastases [hazard ratio (HR) = 2.45; 95% CI, 1.37–4.36; $P = 0.002$), pembrolizumab line of therapy (initiation as third-line or later vs. first-line, HR = 3.70; 95% CI, 1.65–8.32; $P = 0.002$), ECOG PS of 2–3 (vs. 0–1, HR = 2.85; 95% CI, 1.49–5.47; $P = 0.002$), and elevated (vs. normal) LDH level at pembrolizumab initiation (HR = 3.68; 95% CI, 1.95–6.95; $P < 0.001$). There were no differences in OS or 12-month survival probability by *BRAF* mutation status (Table 3, Fig. 2C) or for male patients (vs. female patients, HR = 0.85; 95% CI, 0.50–1.46; $P = 0.56$).

Overall, 116 (69%) of patients experienced progression or death during the study period (Fig. 2G), with a median time to progression or death of 4.2 months and no

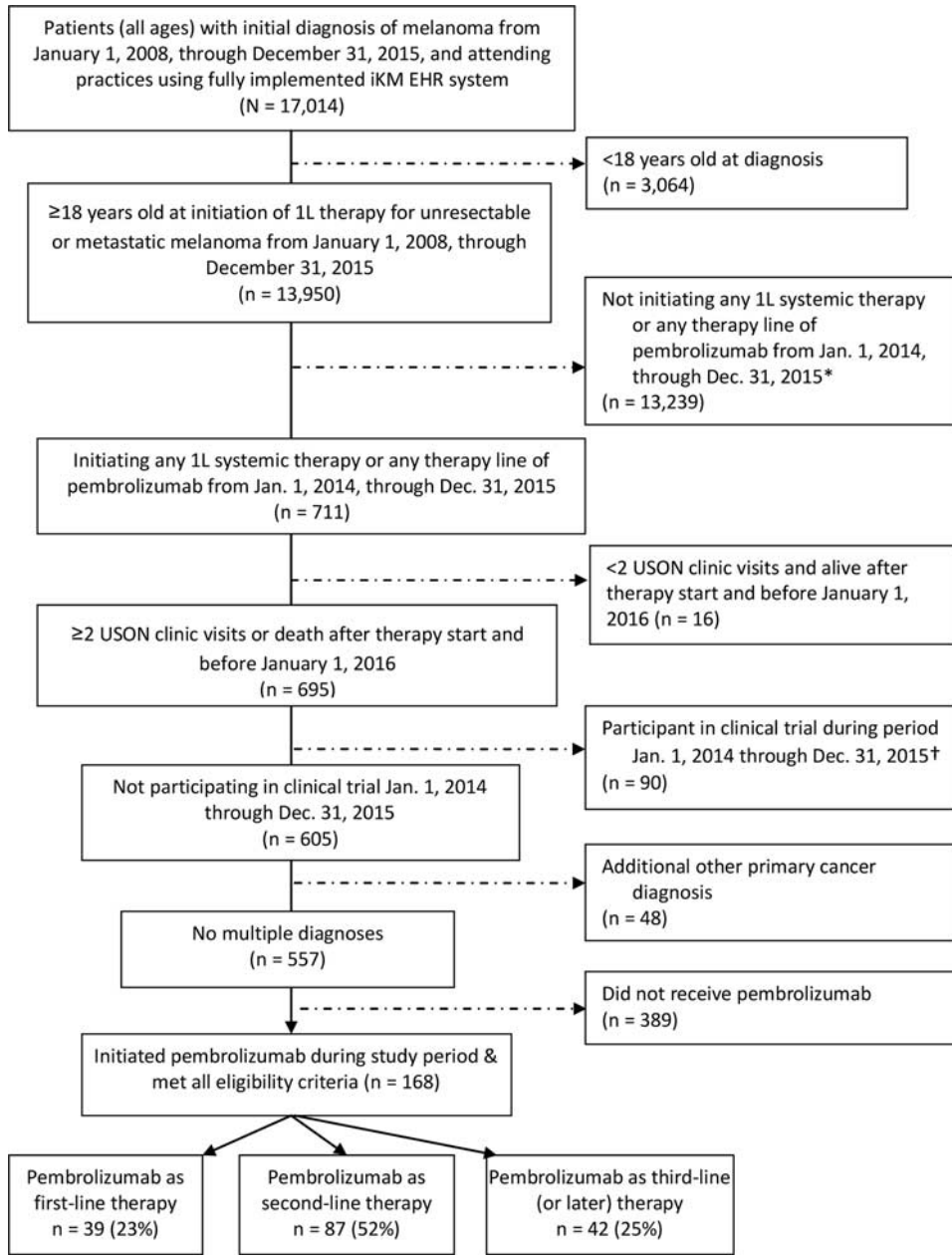

FIGURE 1. Patient flow chart. *Six patients also were in a clinical trial (n = 3) or had another primary cancer (n = 3). †One patient also had another primary cancer. 1L therapy indicates first-line therapy; iKM EHR, iKnowMed electronic health record system; USON, The US Oncology Network.

significant difference among lines of therapy (log-rank P-value = 0.081) or by *BRAF* mutation status (Table 3; log-rank P-value = 0.21). The estimated 12- and 24-month PFS probabilities in the overall population were 32% and 22%, respectively (Table 3). In multivariable analyses, the presence of brain metastases (HR = 2.07; 95% CI, 1.32–3.26; $P = 0.002$) and elevated (vs. normal) LDH level at pembrolizumab initiation were significant predictors of progression in patients still alive at the end of the study period (HR = 2.58; 95% CI, 1.60–4.16; $P < 0.001$). There were no differences by sex (data not shown).

The median length of time to treatment failure was 4.9 months (95% CI, 3.0–7.6 mo). Overall, the 6-month probability of patients still being on pembrolizumab was 46% (95% CI, 38%–53%); the 12-month probability was 31% (95% CI, 24%–38%).

DISCUSSION

We identified 168 patients in US community oncology practices who received pembrolizumab for advanced melanoma between September 1, 2014 and December 31, 2015, approximately half (52%) as second-line therapy, and one quarter as first-line (23%), or third-line or later (25%), respectively. The median OS was 19.4 months (upper limit of the 95% CI not reached) during a median study follow-up

TABLE 1. Patient Demographic Characteristics

Characteristics	All Patients (N = 168)
Male [n (%)]	110 (65)
Age at pembrolizumab initiation	
Median age (range) (y)	66 (26–90+)
≤65 [n (%)] (y)	72 (43)
>65 [n (%)] (y)	96 (57)
White race [n (%)]*	167 (99)
Mean weight (SD) (kg)	86 (17)
Mean height (SD) (m)	1.7 (0.1)
Mean body mass index (SD) (kg/m^2)	29 (6)
Smoking status [n (%)]	
Current smoker	12 (7)
Former smoker	67 (40)
Never smoker	81 (48)
Not recorded	8 (5)
United States Census Bureau region [n (%)]	
South	107 (64)
West	26 (15)
Midwest	24 (14)
Northeast	11 (7)
Charlson comorbidity index score [n (%)]†	
0	52 (31)
1–2	90 (54)
≥3	26 (15)

*One patient was black.
†Charlson comorbidity index scores were calculated without melanoma.

TABLE 2. Clinical Characteristics of Patients at Initiation of First-line Therapy and at Initiation of Pembrolizumab Therapy

Characteristics	All Patients (N = 168) [n (%)]
Stage at initial melanoma diagnosis	
I	17 (10)
II	26 (15)
III	47 (28)
IV	50 (30)
Unknown	28 (17)
M status at 1L therapy initiation	
M1a	24 (14)
M1b	24 (14)
M1c	86 (51)
No M1 status	34 (20)
LDH level at 1L therapy initiation*	
Elevated	52 (31)
Normal	101 (60)
Unknown	15 (9)
Brain metastases at pembrolizumab initiation	41 (24)
ECOG PS at pembrolizumab initiation	
0–1	108 (64)
2	19 (11)
3	2 (1)
Unknown/not documented	39 (23)
LDH level at pembrolizumab initiation*	
Elevated	51 (30)
Normal	65 (39)
Unknown	52 (31)
Albumin level at pembrolizumab initiation*	
Low	39 (23)
BRAF mutation status at melanoma diagnosis	
Positive	58 (35)
Wild type	96 (57)
Unknown/not documented test results	2 (1)
Not tested	12 (7)
NRAS mutation status at melanoma diagnosis	
Positive	11 (7)
Negative	21 (13)
Not tested or unknown†	136 (81)
KIT mutation status at melanoma diagnosis	
Positive	4 (2)
Negative	35 (21)
Not tested or unknown†	129 (77)
PD-L1 tumor expression at melanoma diagnosis	
Positive	1 (0.6)
Not tested or unknown†	167 (99)

*Normal laboratory ranges could differ from clinic to clinic.
†Patients who were tested but had unknown results (not documented) numbered 5 (3%), 7 (4%), and 1 (1%) for NRAS, KIT, and PD-L1, respectively.
1L therapy indicates first-line therapy; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; PD-L1, programmed death ligand-1.

time of 10.5 months; continuous follow-up is ongoing, and analyses will be conducted to update this finding. Survival probabilities at 12 months were best for pembrolizumab as first-line therapy (68%) as compared with third-line and later therapy (49%). Overall, 70 patients (42%) died and 116 patients (69%) experienced progression or death during the study, with a median PFS of 4.2 months and no difference by line of therapy. Estimated 12-month OS and PFS curves did not differ by *BRAF* mutation status in this retrospective observational study.

Clinical trial populations are selected using stringent inclusion and exclusion criteria that exclude many patients in the community who may be appropriate candidates for pembrolizumab, such as those with active brain metastases or poor performance status.[19,23,32,33] Although demographic and many clinical characteristics of our study population were similar to those of patients enrolled in pembrolizumab clinical trials, we also included patients with brain metastases and ECOG score of >1 (24% and 16% of patients, respectively).

Brain metastases develop in 40%–50% of patients with advanced melanoma and are associated with reduced OS,[34] although early evidence in 1 small study suggests that pembrolizumab shows activity in brain metastases in patients with melanoma.[35] An elevated baseline LDH level is also a recognized negative prognostic factor for OS for patients with metastatic melanoma, including those treated with anti-PD-1 therapy[36] and independent of *BRAF* mutation status.[37] In the current study, the presence of brain metastases and an elevated LDH level were both significant predictors of death and of disease progression, which correlates with prior observations that these findings represent a more aggressive cancer pattern. In a recent retrospective observational study, the presence of liver metastases and an elevated LDH level were associated with reduced OS for patients treated with an anti-PD-1 or anti-PD-ligand-1 (anti-PD-L1) agent; notably, tolerability and outcomes were similar regardless of age.[38]

Poor performance status (ECOG PS > 1) in this study was a significant predictor of death, a finding similar to that of a prior observational study of 193 patients with previously treated metastatic melanoma who received ipilimumab, in which the 2-year OS was significantly lower for patients with a poor performance score.[39] However, ECOG PS > 1 was not a significant predictor of disease progression, raising some doubt about the common assumption in oncology therapeutics whereby patients with poor performance status are excluded from clinical trials because of expected poorer outcomes.

TABLE 3. Outcomes and Times To Events From Initiation of Pembrolizumab Therapy, Overall and Stratified by *BRAF* Mutation Status

Characteristics	All Patients (N = 168)	*BRAF* Wild Type (N = 96)	*BRAF* Positive (N = 58)
Discontinued pembrolizumab [n (%)]*	117 (70)	67 (70)	37 (64)
Physician-documented progression	53 (45)	34 (51)	14 (38)
Treatment-related toxicities	29 (25)	17 (25)	10 (27)
Death	22 (19)	13 (19)	8 (22)
Comorbidities	20 (17)	11 (16)	4 (11)
Decline in ECOG PS	11 (9)	5 (7)	4 (11)
Patient choice	5 (4)	2 (3)	2 (5)
Other	24 (21)	11 (16)	9 (24)
Unknown	10 (9)	5 (7)	3 (8)
Death [n (%)]	70 (42)	42 (44)	25 (43)
Overall survival (mo)			
Median (95% CI)	19.4 (14.0–NR)	19.4 (11.2–NR)	19.4 (9.4–NR)
12-month survival probability (%) (95% CI)	61 (53–68)	60 (49–70)	60 (46–72)
24-month survival probability (%) (95% CI)	44 (31–56)	40 (24–56)	48 (31–63)
Disease progression or death [n (%)]	116 (69)	63 (66)	45 (78)
Physician-reported PFS time (mo)			
Median (95% CI)	4.2 (2.9–5.3)	4.1 (2.1–7.6)	3.7 (2.1–5.1)
12-month probability of no progression or death (%) (95% CI)	32 (25–40)	36 (26–46)	26 (16–38)
24-month probability of no progression or death (%) (95% CI)	22 (13–32)	26 (14–39)	NA†

*There could be > 1 reason recorded for pembrolizumab discontinuation.

†There were no patients with *BRAF*-positive status who had 24 months' PFS. The maximum PFS was 20.8 months in the *BRAF*-positive cohort.

CI indicates confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; NA, not applicable; NR, not reached; PFS, progression-free survival.

The probability of survival at 12 months was best for patients who received pembrolizumab as first-line therapy, consistent with findings in the KEYNOTE-001 phase 1b trial.[33] Survival probability at 12 months in the present study was 61% overall, and in KEYNOTE-001, the 12-month survival rate overall was 66% (95% CI, 62%–69%).[33] In a recent report of long-term outcomes (median follow-up duration of 32 mo) for the 655 patients enrolled in KEYNOTE-001, the OS rate was 40% at 36 months and the median OS was 24.4 months.[22] Moreover, treatment outcomes in our study were similar regardless of *BRAF* mutation status, consistent with findings in KEYNOTE-006.[19,24]

The majority of patients (93%) had been tested for tumor *BRAF* mutation status. This is a much higher rate than reported in earlier observational studies from 2008 to 2012 (< 10%–21% tested),[5,40] suggesting a rapid adoption of management guidelines for malignant melanoma,[9] likely at least in part because of the current availability of BRAF-targeted therapies. It would have been of interest to have data regarding PD-L1 tumor expression for all patients, as the level of tumor PD-L1 expression has been positively correlated with response rate, PFS, and OS for patients with advanced melanoma receiving pembrolizumab and other anti-PD-1 and anti-PD-L1 agents.[41,42] However, PD-L1 testing was not standard of care in the melanoma population in the United States over the study period, and we expected to have a low capture. Indeed only 2 tumors were tested for PD-L1, with 1 positive result and 1 indeterminate, during the study period.

Our PFS findings were consistent with those of pembrolizumab clinical trials, albeit with shorter follow-up. The median PFS in this study of 4.2 months was similar to that in KEYNOTE-001 (4.9 mo)[22] and KEYNOTE-006 (5.6 and 4.1 mo for 2 pembrolizumab cohorts).[24] The latest presentation of KEYNOTE-001 findings[22] reports a median time on therapy of 5.6 months, with median follow-up of 32 months, as compared with 4.7 months on therapy in the present study, with median follow-up of 10.5 months. Although the data in this analysis may change as the data mature, if these findings of shorter therapy duration hold true then there may be several explanations. Patients in the community setting may not remain on therapy as long as those enrolled in clinical trials because they lack the close monitoring and support provided in the trial setting. Another reason for an early halt to therapy could be initial evidence of radiographic progression: physicians in the community setting may lack access to the immune-related response criteria used in clinical trials to identify the atypical (delayed) response to therapy accompanying pseudoprogression.[43]

Finally, 29 (25%) of 117 patients in this study discontinued pembrolizumab therapy at least in part because of treatment-related adverse events; however, 19 of them had > 1 reason for discontinuation, leaving 10 patients (6% of the full-study cohort) for whom treatment-related toxicity was the only recorded reason for discontinuation. Treatment discontinuation secondary to adverse events ranged from 7% to 11% in the KEYNOTE trials.[22–24] Common toxicities of pembrolizumab as well as other immune checkpoint inhibitors include fatigue, diarrhea, and immune-related adverse events such as rash.[17,44]

The results of this retrospective observational study should be considered in the context of the strengths and limitations of the data source and study design. Limitations include the possibility of omissions in data entry and errors in physician-reported outcomes. We excluded patients with other prior cancer diagnosis and treatment to reduce confounding of the outcomes associated with pembrolizumab in this study; nonetheless, the existence of unrecognized confounders is always possible in observational studies. Baseline data were incomplete for some patients, and the severities of adverse events and primary reasons for treatment discontinuation were not cataloged; however, data were supplemented with detailed ascertainment of chart review data to reduce errors or missing data. The study cohort was

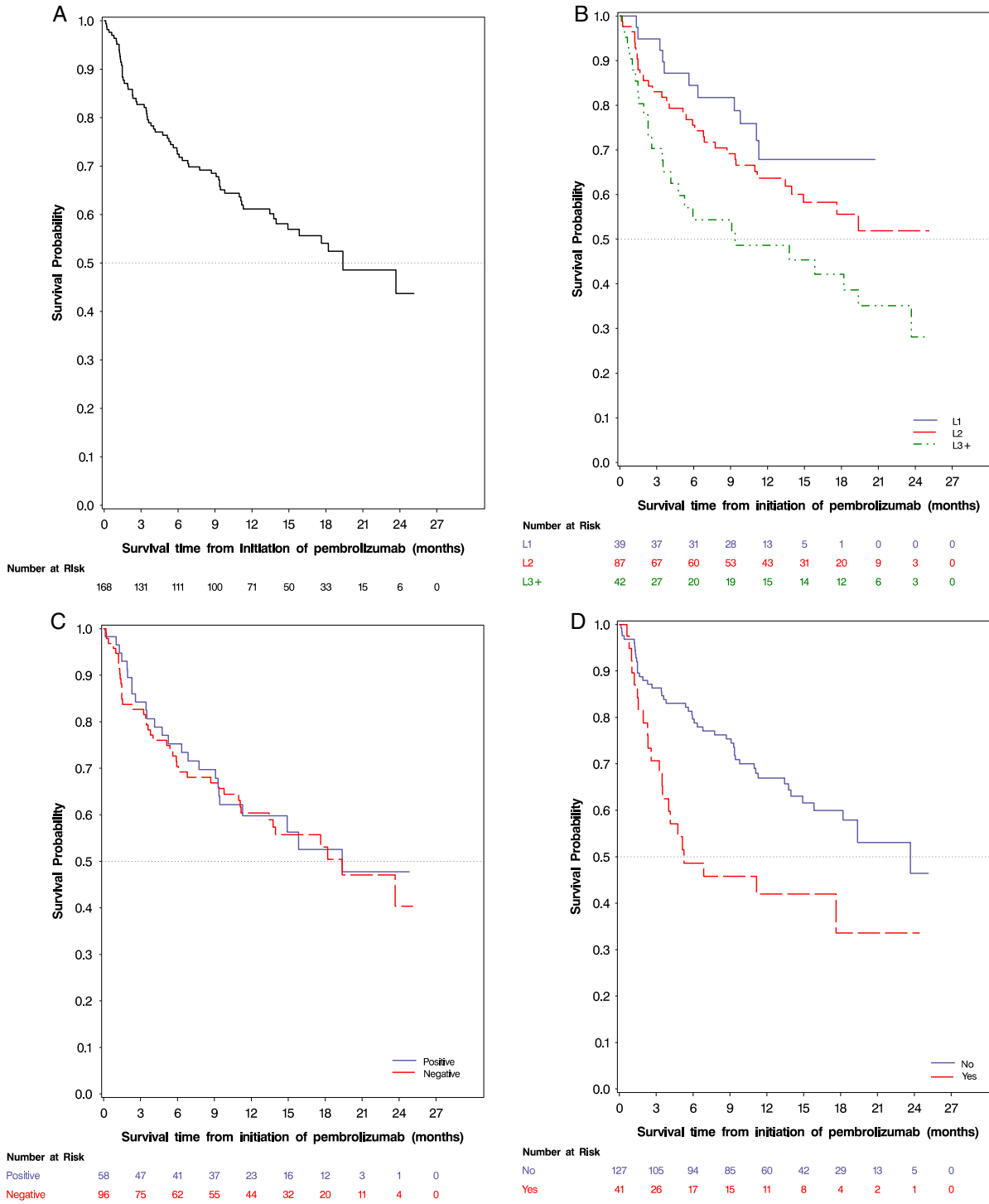

FIGURE 2. *(continued)*

small, and we did not analyze the effects of prior treatment on outcomes for patients with brain metastases. Our findings provide only a snapshot of a narrow window of time in a very rapidly evolving field of therapy, with limited follow-up time for some patients; however, we allowed for a minimum of 9 months of follow-up for all patients utilizing standardized methodology with a finite end point. Although there were no pathway restrictions on the use of pembrolizumab at USON practices during the study period, the USON uses network-wide evidence-based guidelines, which may result in treatment practices different from those used at academic centers or at community practices outside of the network. Despite the aforementioned limitation, USON practices are geographically representative throughout the United States

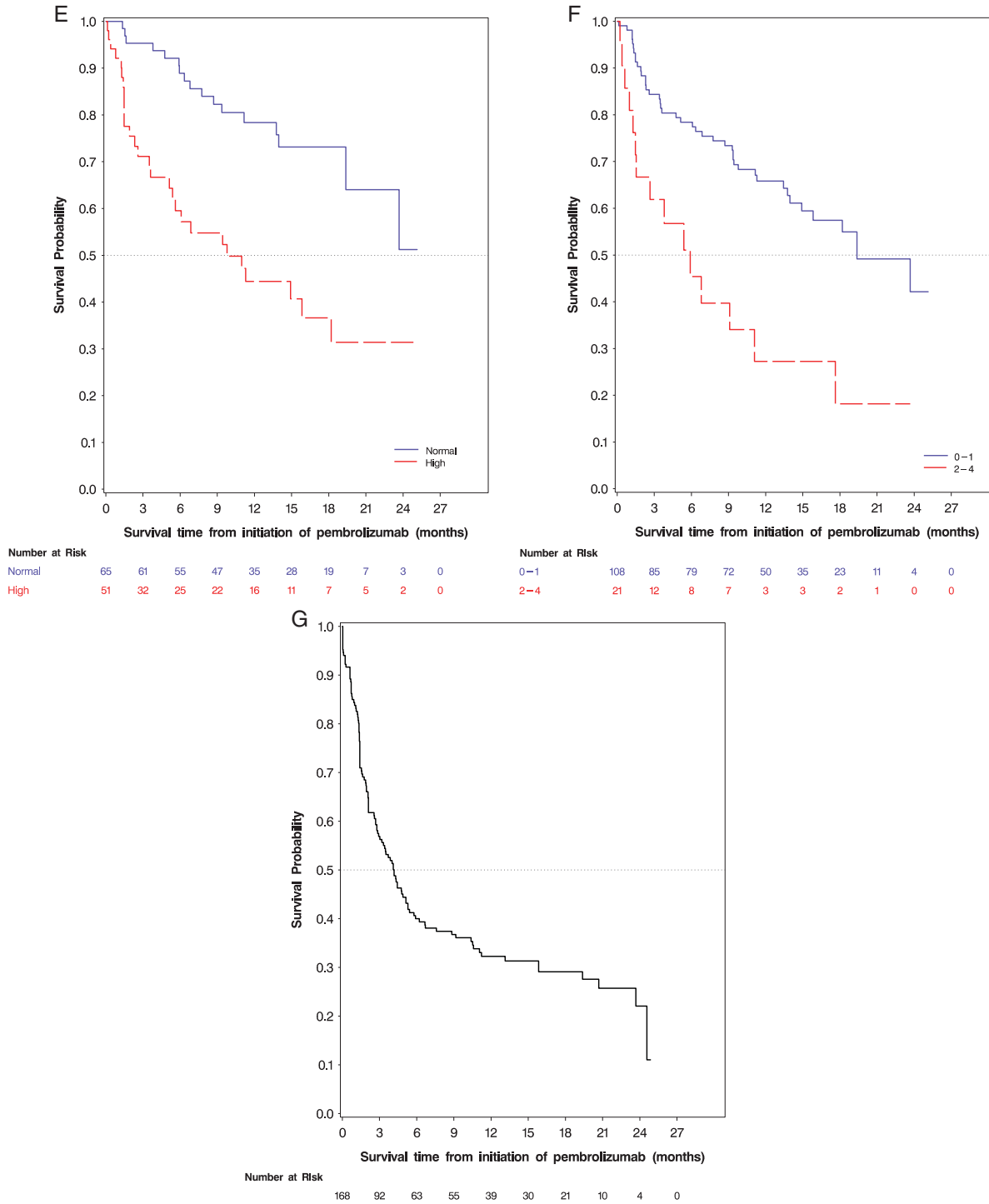

FIGURE 2. Kaplan-Meier plots showing OS from initiation of pembrolizumab (A), OS by line of therapy (B), OS by *BRAF* mutation status (positive vs. wild type) (C), OS by presence of brain metastases (yes vs. no) (D), OS by lactate dehydrogenase level (normal vs. elevated) (E), OS by Eastern Cooperative Oncology Group performance status (0–1 vs. 2–4) at advanced melanoma diagnosis (F), overall progression-free survival from initiation of pembrolizumab (G). L1, L2, L3+ indicate first-line, second-line, and third-line and later therapy; OS, overall survival.

and accurately illustrate treatment patterns in the real-world setting.

Strengths of the study include the use of a well-maintained database that is frequently used in observational research and the inclusion of a wider range of patients than would be eligible for a clinical trial. Observational research is an important tool to translate randomized trial experience to clinical practice, as well as to demonstrate how the

inclusion of patients in the community setting may benefit the design and execution of future clinical trials.

CONCLUSIONS

The efficacy and tolerability of pembrolizumab for treating advanced melanoma have been well described in the pivotal clinical trials. This retrospective observational study provides evidence supporting the effectiveness of pembrolizumab in real-world treatment for patients with advanced melanoma. The results of this study suggest that presence of brain metastases, elevated LDH, poor performance status (ECOG PS > 1), and use of pembrolizumab as third-line or later therapy are associated with worse patient outcomes.

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CONFLICTS OF INTEREST/ FINANCIAL DISCLOSURES

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