Pembrolizumab Utilization and Clinical Outcomes Among Patients With Advanced Melanoma in the US Community Oncology Setting: An Updated Analysis

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Summary: Favorable outcomes have been observed with pembrolizumab among patients with advanced melanoma in clinical trials; however, limited evidence exists on the long-term efficacy in the real-world setting. This was an updated, retrospective observational study of adult patients with advanced (unresectable or metastatic) melanoma who initiated pembrolizumab (in any line of therapy) between January 1, 2014, and December 31, 2016, in The US Oncology Network and were followed through December 31, 2019 [median follow-up: 18.2 mo (range: 0.1–63.1 mo)]. Study data were sourced from electronic health records. Patient demographic, clinical, and treatment characteristics were assessed descriptively. Kaplan-Meier methods were used to evaluate overall survival (OS), time to treatment discontinuation, time to next treatment, physician-assessed time to tumor progression, and physician-assessed progression-free survival (rwPFS). Independent risk factors for OS and rwPFS were identified with multivariable Cox regression models. Of the 303 study-eligible patients, 119, 131, and 53 received pembrolizumab in the first-line, second-line, and third-line or beyond setting, respectively. Median OS across the study population was 29.3 months [95% confidence interval (CI): 20.3–49.7] and was the longest among those who received first-line pembrolizumab [42.8 mo (95% CI: 24.8–not reached)]. Median rwPFS across the study population was 5.1 months (95% CI: 4.0–7.6) and 8.1 months (95% CI: 4.6–14.4) among those who received first-line pembrolizumab. In the multivariable analyses for OS, increased age, worsening performance status, elevated lactate dehydrogenase, brain metastases, and pembrolizumab use in later lines were significantly associated a worse prognosis.

Key Words: advanced melanoma, retrospective observational study, anti-PD1 monotherapy, community oncology, clinical outcomes

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The incidence of malignant melanoma has been steadily rising over the last 2 decades in the United States.[1,2] In 2020, it is estimated that ~100,000 individuals will receive a diagnosis of malignant melanoma and 6850 will die from the disease in the United States.[3] Early-stage melanoma has a favorable prognosis, with a 5-year survival rate of 99%. However, for patients with advanced (unresectable or metastatic) cancer, the current 5-year survival estimate is 27%.[2]

The treatment landscape for advanced melanoma is rapidly evolving.[4] In particular, treatments that inhibit the programmed death receptor (PD-1) pathway, including pembrolizumab and nivolumab, have emerged. These are humanized monoclonal antibodies that block PD-1 receptors on T cells from binding the ligands PD-L1 and PD-L2, thus helping to restore T-cell–mediated antitumor immunity.[5] Given improved survival and favorable tolerability profiles observed in clinical trials, these anti-PD1 monotherapies are the current standard of care for patients with advanced melanoma in the National Comprehensive Cancer Network (NCCN) guidelines (version 3.2020).[4] For patients with BRAF V600 mutations, BRAF/MEK inhibitors have demonstrated clinical benefits with delayed drug resistance.[4–7]

Pembrolizumab was approved by the Food and Drug Administration (FDA) in September 2014 for the treatment of patients with advanced melanoma.[5] Accelerated approval was based on the initial results of the KEYNOTE-001 study, which investigated treatment-naive as well as patients previously treated for unresectable or metastatic melanoma.[8] In a 5-year follow-up analysis of KEYNOTE-001, Hamid et al[9] reported the long-term efficacy of pembrolizumab: the median overall survival (OS) was 23.8 months among all patients and 38.6 months among the treatment-naive group alone.

Two other clinical trials, KEYNOTE-002 and KEYNOTE-006, have affirmed the tolerability and efficacy of pembrolizumab for the treatment of advanced melanoma.[10–13] In KEYNOTE-002, patients with ipilimumab-refractory melanoma were randomized to pembrolizumab 2, 10 mg/kg, or the investigator's choice chemotherapy.[10] At a median follow-up of 28 months, median OS among patients who received pembrolizumab 2 and 10 mg/kg groups were 13.4 and 14.7 months, respectively, compared with 11.0 months with chemotherapy.[11]

KEYNOTE-006 was an open-label, randomized controlled phase 3 trial that compared pembrolizumab 10 mg/kg q2w or q3w regimens were with ipilimumab among patients with advanced melanoma who had up to one previous systemic therapy.[12] At a median follow-up of 5 years, the median OS was 32.7 months among patients who received pembrolizumab compared with 15.9 months among those who received ipilimumab [hazard ratio (HR) = 0.73; 95% confidence interval (CI): 0.61–0.88; *P* = 0.00049].[13] Among patients who received first-line (1L) treatment, median OS was 38.7 months for pembrolizumab and 17.1 months for ipilimumab (HR = 0.73; 95% CI: 0.57–0.92; *P* = 0.0036).

Beyond clinical trials, pembrolizumab has demonstrated comparable outcomes in real-world settings. Liu et al[14] examined the use of pembrolizumab [in any line of therapy (LOT)] among patients treated in community oncology clinics and, at a median follow-up duration of 12.9 months, the median OS for the study population was 21.8 months (95% CI: 16.8–29.1). Similarly, Moser et al[15] evaluated patients who received 1L

pembrolizumab and reported that the median OS among these patients was 22.6 months.

In a previous publication,[16] we reported the patient profiles and outcomes associated with utilization of pembrolizumab in a large network of community oncology practices, The US Oncology Network. This was a retrospective analysis of 168 patients with advanced melanoma who initiated pembrolizumab (in any LOT) from September 1, 2014, through December 31, 2015 in The US Oncology Network. Patients were followed through September 30, 2016 and the median follow-up for the study population was 10.5 months. In this study, we observed that the median OS was 19.4 months (14.0–not reached) across the study population and was not reached among those who were treatment-naive.

As pembrolizumab for advanced melanoma has now been available for over 5 years, it is important to examine how the adoption of this treatment has influenced clinical outcomes in the community oncology setting. The follow-up duration of published real-world studies is limited and, as we observed in our previous study, this may particularly hinder survival estimates. The aim of this study, therefore, was to extend the observation period of our prior analysis in hopes of providing insight into the long-term efficacy of pembrolizumab in the real-world setting.

MATERIALS AND METHODS

Study Design and Data Sources

This was an extension of a retrospective cohort study of US adult patients with advanced (unresectable and/or metastatic) melanoma who initiated pembrolizumab, in any LOT, from January 1, 2014, to December 31, 2016, at practices in The US Oncology Network that utilize the iKnowMed electronic health record (iKM EHR).[17] The US Oncology Network is affiliated with ~1200 physicians in > 470 sites of care across the United States, treating over 1 million patients annually.[17] Patients were followed through December 31, 2019.

While the FDA granted accelerated approval for pembrolizumab in September 2014, the results of the KEYNOTE-001 trial were announced before approval and a rolling submission for the Biologics License Application was filed in early 2014.[18,19] In the community oncology setting, physicians may opt to treat their patients with promising therapies, ahead of FDA approval. To capture potential prelabel use and optimize the number of patients available for analyses, the study identification period was extended to January 2014.

Study data were obtained via programmatic database extraction from the iKM EHR and supplemented with chart review. Supplemental vital status information was provided from the Social Security Administration's Limited Access Death Master File (LADMF). In a study of the iKM EHR database and LADMF, it was observed that 93.3% of all death records were captured in structured fields and 6.7% of death records were solely identified by the LADMF.[20] Among deaths recorded by both structured data and the LADMF, concordance was 88.0%. When both structured and unstructured data are available, 99.4% of death records are captured from these sources, with 0.6% death records solely identified by the LADMF. Between 2015 and 2019, the proportion of death records captured by structured data trended upward (slope = 4.04).

Eligible patients were at least 18 years of age at diagnosis of advanced melanoma and had at least 2 visits in The US Oncology Network or a record of death during the study period. Patients were excluded if they were enrolled in clinical trials at any time during the study observation period or if they had another documented primary cancer diagnosis or receipt of treatment for another primary cancer during the study period (with the exception of basal cell carcinoma, squamous cell carcinoma, bladder carcinoma in situ, or cervical carcinoma in situ). Patients were followed until the last patient record, date of death, or end of the study observation period, whichever occurred first.

The study protocol was granted an exception and waiver of informed consent by the US Oncology Institutional Review Board.

Statistical Analysis

Patient demographic, clinical, and treatment characteristics were descriptively assessed. χ^2 or the Fisher exact test (depending on normality) were used to assess associations between categorical variables. Analysis of variance/t tests or Kruskal-Wallis tests (depending on normality) were used for continuous variables. An α level of 0.05 was the primary criterion for statistical significance.

Time-to-event endpoints were estimated using the Kaplan-Meier method. Patients who did not experience an event within the study observation period were censored on the study end date or the last visit date available in the dataset, whichever occurred first. OS was defined as the duration (months) from initiation of pembrolizumab, in each LOT, until the date of death from any cause. Time to treatment discontinuation (TTD) was defined as the duration (months) from pembrolizumab initiation until discontinuation for any reason. Time to next treatment (TTNT) was defined as the initiation of pembrolizumab until the initiation of a new treatment. If another treatment was added to an ongoing regimen, the resulting combination was defined as the next LOT. Time to physician–assessed tumor progression (rwTTP) was defined as the duration (months) from initiation of pembrolizumab until physician-assessed disease progression. Physician-assessed progression-free survival (rwPFS) was defined as the duration (months) from initiation of pembrolizumab until the date of physician-assessed disease progression or death.

In clinical trials, tumor assessments are generally performed according to Response Evaluation Criteria In Solid Tumors (RECIST) criteria.[21] However, the detailed assessments needed for these classifications are generally unavailable for retrospective real-world evaluations.[22] As such, for this study, tumor assessments were captured as documented by physicians during the routine course of care, and no attempts to mimic RECIST criteria were made.

The following variables were fitted into multivariable Cox proportional hazard regression models to identify independent risk factors for OS and rwPFS while adjusting for the influence of other variables within the models: age, race, practice region, sex, performance status, body mass index, tobacco use, stage at diagnosis, Deyo-adapted Charlson Comorbidity Score, BRAF mutation status, baseline laboratory measurements [albumin, bilirubin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase (LDH)], sites of metastases (bone, brain, liver, lung), prior radiation, prior surgery, and pembrolizumab LOT. A stepwise selection process was used to identify the final covariates for the model, with consideration of multicollinearity.

Analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC) and/or R, version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria) or higher as appropriate.

RESULTS

Patient Characteristics

Study attrition data for the 168 patients derived from the previous phase of the study (January 1, 2014–December 31, 2015 patient identification period) have been previously reported.[16] For this extension, an additional 135 patients were identified by applying the same study eligibility criteria, with an extended identification period. Therefore, in total, 303 patients were included in the analysis: 119 initiated pembrolizumab as 1L treatment, 131 as second line (2L), and 53 patients as third line or beyond (3L+).

Among the overall study population, the median age at initiation of pembrolizumab was 67 years (range: 26–90+ y). Note, ages greater than 90 years were collapsed into a single category to confirm to Health Insurance Portability and Accountability guidelines. Median follow-up duration was 18.2 months (range: 0.1–63.1 mo). The majority of patients had Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1 (69.0%) at pembrolizumab initiation and stage III/IV disease at diagnosis (63.0%). PD-L1 status was not documented for 95% of patients. Lung, brain, and liver were the most commonly reported sites of metastases in the overall study population and among the 1L and the 2L pembrolizumab cohorts, and lung, brain, and bone were the most commonly reported sites of metastases among the 3L+ pembrolizumab cohort (Table 1).

Treatment Characteristics

Among the 1L, 2L, and 3L+ pembrolizumab cohorts, 29.4%, 29.0%, and 18.9% received radiation treatment before initiation of 1L, respectively; 69.7%, 72.5%, and 71.7% of the 1L, 2L, and 3L+ cohorts underwent surgical resection before initiation of 1L, respectively (Table 1).

Median durations of pembrolizumab treatment among the respective LOT cohorts were 5.1, 4.8, and 2.8 months, with median numbers of treatment cycles being 8.0, 7.0, and 4.0. Among the 2L and 3L+ pembrolizumab cohorts, ipilimumab was the most common treatment preceding administration of pembrolizumab (77.1% and 90.6%, respectively). Dabrafenib and trametinib were the second and third most common treatments preceding administration of pembrolizumab among both of those cohorts (Table 1).

Across all LOT cohorts, 96.7% of patients discontinued pembrolizumab treatment by the end of the study observation period, with disease progression as the leading cause of treatment discontinuation. In addition, in the 1L, 2L, and 3L+ cohorts, death was reported as the reason for discontinuation for 8.4%, 7.6%, and 9.4% of patients overall, while treatment-related toxicities were reported as the sole reason for discontinuation among 5.9%, 10.7%, and 1.9%, respectively (Table 1).

Clinical Outcomes

The median OS in the overall study population was 29.3 months (95% CI: 20.3–49.7), with significant differences observed across the pembrolizumab LOT cohorts (log-rank $P = 0.0080$; Table 2, Fig. 1). Median OS was longest among the 1L cohort [42.8 mo (95% CI: 24.8–not reached)], followed by the 2L cohort [30.0 mo (95% CI: 14.9–54.5)], and 3L+ cohort [13.8 mo (95% CI: 4.8–25.7)].

The median TTD in the overall study population was 4.8 months (95% CI: 3.6–5.3) and was similar across the pembrolizumab LOT cohorts (Table 2, Fig. 2). The median TTNT in the overall study population was 10.6 months (95% CI: 7.3–18.8), without differences observed across the pembrolizumab LOT cohorts (Table 2, Fig. 3). Likewise, the median rwTTP was 11.2 months (95% CI: 6.7–20.7), without significant differences across the pembrolizumab LOT cohorts (Table 2, Fig. 4).

The median rwPFS in the overall study population was 5.1 months (95% CI: 4.0–7.6) and was significantly different across the pembrolizumab LOT cohorts (log-rank $P = 0.0193$). The median rwPFS was the longest in the pembrolizumab 1L cohort and the shortest in the pembrolizumab 3L+ cohort (Table 2, Fig. 5).

On the basis of the multivariable Cox regression model for OS, the following significant associations were found: older age (HR = 1.015/year increase; 95% CI: 1.001–1.029; $P = 0.0307$), an ECOG PS score of at least 2 at initiation pembrolizumab (HR = 1.870; 95% CI: 1.198–2.920; $P = 0.0059$), elevated LDH (HR = 3.614; 95% CI: 2.456–5.316; $P < 0.0001$), unknown LDH status (HR = 1.516; 95% CI: 1.001–2.296; $P = 0.0495$), presence of brain metastases (HR = 1.708; 95% CI: 1.190–2.449; $P = 0.0037$), and receipt of pembrolizumab in later lines of therapy (HR = 2.727 for the 3L+ setting; 95% CI: 1.716–4.334; $P < 0.0001$; Table 3).

On the basis of the multivariable Cox regression model for rwPFS, the following significant associations were found: presence of brain metastases (HR = 1.482; 95% CI: 1.090–2.015; $P = 0.0120$), elevated LDH (HR = 3.472; 95% CI: 2.474–4.872; $P < 0.0001$), unknown LDH status (HR = 1.575; 95% CI: 1.128–2.199; $P = 0.0077$), and receipt of pembrolizumab in later lines of therapy (HR = 1.807 for the 3L+ setting; 95% CI: 1.239–2.635; $P = 0.0021$; Table 3).

DISCUSSION

To the best of our knowledge, this study presents the longest follow-up duration of patients with advanced melanoma who received pembrolizumab in the community oncology setting. With a median follow-up of 18.2 months (range: 0.1–63.1 mo), these results provide insight into the treatment patterns and long-term outcomes that can supplement previously published real-world studies, as well as clinical trials.

Observed outcomes in this study may have been influenced by the demographic and clinical characteristics of the community oncology patient population, which vary from the profiles of patients who participate in clinical trials. For example, patients with ECOG PS of 2+ and those with brain metastases were excluded from KEYNOTE-001, KEYNOTE-002, and KEYNOTE-006, whereas 13.5% of the study population in this real-world analysis had ECOG PS of 2+ and 25.4% had brain metastases.[9,11,13] Likewise, 34% tested positive for the BRAF mutation in this study, versus 24% in KEYNOTE-001 (the analysis of pooled treatment-naive, ipilimumab-naive, ipilimumab-refractory), 24% in KEYNOTE-002, and 35.1% in KEYNOTE-006.[10,12,23]

Compared with other real-world studies, the proportions of male patients and those with ECOG 0 or 1 in our study were similar to Moser et al,[15] and the proportions of patients with BRAF-mutant status in all LOT cohorts in our study appeared similar to those in Liu et al.[14] Likewise, Moser and colleagues found a history of brain metastases in 18% of patients overall and 16.2%, 19.1%, and 24.6% in the pembrolizumab 1L, 2L, and 3L+ cohorts, respectively; and our study had 25.4% in the overall study population and 21.0%, 26.7%, and 32.1% in the respective cohorts.

In KEYNOTE-002, OS remained consistent across all covariate subgroups tested (ECOG 0 vs. 1, LDH status, BRAF status, baseline tumor size, type of chemotherapy before study

TABLE 1. Characteristics of the Study Population

	Overall (N = 303) [n (%)]	LOT of Pembrolizumab [n (%)]		
		1L (N = 119)	2L (N = 131)	3L+ (N = 53)
Age at pembrolizumab initiation [median (range)] (y)	67 (26–90+)	70 (26–90+)	66 (29–86)	62 (31–90+)
Race				
White	286 (94.4)	110 (92.4)	124 (94.7)	52 (98.1)
Other	17 (5.6)	9 (7.6)	7 (5.3)	1 (1.9)
Male sex	191 (63.0)	78 (65.5)	82 (62.6)	31 (58.5)
Follow-up time from pembrolizumab initiation [median (range)] (mo)	18.2 (0.1–63.1)	20.6 (0.3–60.5)	18.9 (0.1–63.1)	8.9 (0.2–62.0)
ECOG PS at pembrolizumab initiation				
0 or 1	209 (69.0)	88 (74.0)	87 (66.4)	34 (64.2)
2+	41 (13.5)	16 (13.4)	18 (13.7)	7 (13.2)
Not documented	53 (17.5)	15 (12.6)	26 (19.8)	12 (22.6)
Stage at diagnosis				
Stage I/II	67 (22.1)	27 (22.7)	28 (21.4)	12 (22.6)
Stage III/IV	191 (63.0)	73 (61.3)	82 (62.6)	36 (67.9)
Not documented	45 (14.9)	19 (16.0)	21 (16.0)	5 (9.4)
PD-L1 expression				
Positive	7 (2.3)	4 (3.4)	3 (2.3)	0 (0.0)
Negative	8 (2.6)	7 (5.9)	1 (0.8)	0 (0.0)
Not documented	288 (95.1)	108 (90.8)	127 (96.9)	53 (100.0)
BRAF mutation				
Positive	103 (34.0)	30 (25.2)	40 (30.5)	33 (62.3)
Negative	175 (57.8)	75 (63.0)	83 (63.4)	17 (32.1)
Not documented	25 (8.3)	14 (11.8)	8 (6.1)	3 (5.7)
LDH status at pembrolizumab initiation				
Normal	160 (52.8)	63 (52.9)	73 (55.7)	24 (45.3)
Elevated	62 (20.5)	22 (18.5)	32 (24.4)	8 (15.1)
Not documented	81 (26.7)	34 (28.6)	26 (19.8)	21 (39.6)
Sites of metastases at pembrolizumab initiation				
Bone	62 (20.5)	26 (21.8)	23 (17.6)	13 (24.5)
Brain	77 (25.4)	25 (21.0)	35 (26.7)	17 (32.1)
Liver	72 (23.8)	27 (22.7)	33 (25.2)	12 (22.6)
Lung	142 (46.9)	51 (42.9)	64 (48.9)	27 (50.9)
Other	251 (82.8)	98 (82.4)	111 (84.7)	42 (79.2)
Metastatic status at pembrolizumab initiation				
M1a	40 (13.2)	19 (16.0)	13 (9.9)	8 (15.1)
M1b	50 (16.5)	23 (19.3)	22 (16.8)	5 (9.4)
M1c	151 (49.8)	54 (45.4)	66 (50.4)	31 (58.5)
Mx	62 (20.5)	23 (19.3)	30 (22.9)	9 (17.0)
Time from advanced diagnosis to pembrolizumab initiation [median (range)] (mo)	6.5 (0.1–118.7)	1.7 (0.1–118.7)	8.8 (0.9–99.2)	19.2 (3.9–93.3)
Duration of pembrolizumab therapy [median (range)] (mo)	4.8 (0.0–49.7)	5.1 (0.0–46.6)	4.8 (0.0–49.1)	2.8 (0.0–49.7)
No. cycles [median (range)]	6.0 (1.0–82.0)	8.0 (1.0–73.0)	7.0 (1.0–82.0)	4.0 (1.0–71.0)
Radiation before 1L initiation	83 (27.4)	35 (29.4)	38 (29.0)	10 (18.9)
Ipilimumab use before pembrolizumab initiation	149 (49.2)	0 (0.0)	101 (77.1)	48 (90.6)
Dabrafenib use before pembrolizumab initiation	40 (13.2)	0 (0.0)	20 (15.3)	20 (37.7)
Trametinib use before pembrolizumab initiation	41 (13.5)	0 (0.0)	19 (14.5)	22 (41.5)
Vemurafenib use before pembrolizumab initiation	24 (7.9)	0 (0.0)	4 (3.1)	20 (37.7)
Nivolumab use before pembrolizumab initiation	17 (5.6)	0 (0.0)	10 (7.6)	7 (13.2)
Surgical resection before 1L initiation	216 (71.3)	83 (69.7)	95 (72.5)	38 (71.7)
Patients who discontinued pembrolizumab treatment	293 (96.7)	115 (96.6)	127 (96.9)	51 (96.2)
Reason for pembrolizumab discontinuation				
Not applicable—ongoing pembrolizumab treatment	10 (3.3)	4 (3.4)	4 (3.1)	2 (3.8)
Disease progression	76 (25.1)	25 (21.0)	37 (28.2)	14 (26.4)
Death	25 (8.3)	10 (8.4)	10 (7.6)	5 (9.4)
Toxicity	22 (7.3)	7 (5.9)	14 (10.7)	1 (1.9)
Other single reason	81 (26.7)	38 (31.9)	28 (21.4)	15 (28.3)
Multiple reasons	39 (12.9)	17 (14.3)	13 (9.9)	9 (17.0)
Not documented	50 (16.5)	18 (15.1)	25 (19.1)	7 (13.2)

ECOG PS indicates Eastern Cooperative Oncology Group Performance Status; 1L, first line; 2L, second line; 3L+, third line and beyond; LDH, lactate dehydrogenase; LOT, line of therapy; PD-L1, programmed death receptor ligand 1.

treatment, PD-L1 expression, number of prior lines of therapy, metastatic staging, and liver involvement).[11] In contrast, an association between survival and age, ECOG PS, LDH, and brain metastases was observed with OS. In a similar real-world study, among patients receiving pembrolizumab in the community oncology setting, Liu et al[14] reported that the following

TABLE 2. Summary of Kaplan-Meier Time-to-event Analyses

| Outcome | Overall (N = 303) [Median (95% CI)] | LOT of Pembrolizumab [Median (95% CI) (mo)] | | | Log-rank *P* |
		1L (N = 119)	2L (N = 131)	3L+ (N = 53)	
OS	29.3 (20.3–49.7)	42.8 (24.8–NR)	30.0 (14.9–54.5)	13.8 (4.8–25.7)	0.0080
TTD	4.8 (3.6–5.3)	5.1 (4.0–8.1)	4.8 (3.5–6.0)	2.8 (1.4–6.2)	0.7118
TTNT	10.6 (7.3–18.8)	19.5 (8.5–27.3)	8.9 (5.6–18.8)	6.5 (3.7–19.0)	0.2615
rwTTP	11.2 (6.7–20.7)	18.2 (8.5–43.2)	13.1 (4.4–37.1)	3.4 (2.1–16.4)	0.1875
rwPFS	5.1 (4.0–7.6)	8.1 (4.6–14.4)	5.1 (3.6–13.1)	2.8 (1.4–4.8)	0.0193

CI indicates confidence interval; 1L, first line; 2L, second line; 3L+, third line and beyond; LOT, line of therapy; NR, not reached; OS, overall survival; rwPFS, physician-assessed progression-free survival; rwTTP, physician-assessed time to tumor progression; TTD, time to treatment discontinuation; TTNT, time to next treatment.

covariates were associated with significantly improved survival: ECOG PS of 0 or 1 versus 2+, normal versus elevated LDH, no corticosteroid prescriptions in the prior 3 months.

With 96.7% of the study population having discontinued pembrolizumab by the end of follow-up, discontinuation due to treatment-related toxicities was recorded for 7.3% (n = 22) of the study population. In KEYNOTE-006 at 5 years of follow-up, 10% of patients in the combined pembrolizumab group discontinued due to toxicity.[13] The relatively small sample size of this study may limit comparisons with clinical trials. In addition, given the nature of the retrospective review of records, it was not possible to discern the severity or grading of these toxicities.

The long-term results of the KEYNOTE-001, KEYNOTE-002, and KEYNOTE-006 trials have reported median OS estimates that range from 13.4 months (95% CI: 11.0–16.4) among patients previously treated with ipilimumab who received 2 mg/kg pembrolizumab in the KEYNOTE-002 trial to 38.7 months (95% CI: 27.3–50.7) among treatment-naive patients in the KEYNOTE-006 trial.[9,11,13] Notably, in KEYNOTE-002, 22.2% of patients received 1 prior LOT, 43.9% received 2 prior LOTs, 17.8% received 3 prior LOTs, 6.7% received 4 prior LOTs, and 18.9% received 5 or more prior LOTs.[11] Among patients who received 2L treatment in the KEYNOTE-006 trial, median OS was 23.5 months (95% CI: 8.2–16.4).[13] With an overall median OS of 29.3 months, the survival estimates observed in this real-world study are comparable to those reported in the KEYNOTE trials, with the longest median OS also observed among treatment-naive patients in this study (42.8 mo for the 1L cohort vs. 14.8 among the 3L+ cohort).

Compared with the previous described real-world studies, the observed median OS in this study was ~6 months longer overall. Liu et al[14] reported a median OS of 21.8 months for the overall study, which was not reached among patients who received pembrolizumab in the 1L setting, 13.9 months among those who received it in the 2L setting and 12.5 months among
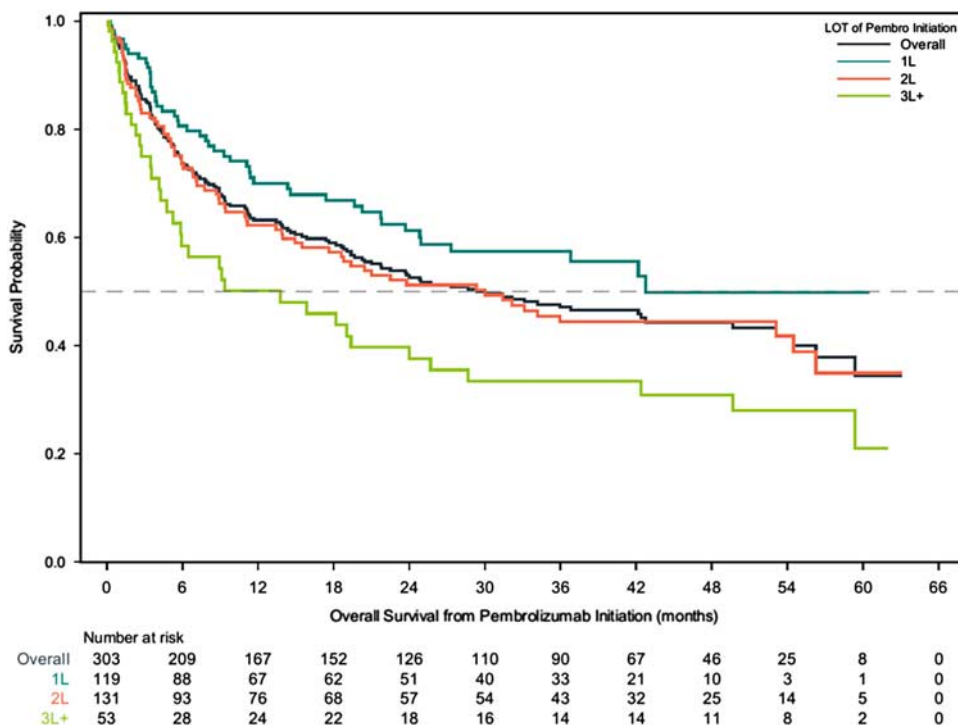

FIGURE 1. Kaplan-Meier curve of overall survival by LOT of pembrolizumab initiation. 1L indicates first line; 2L, second line; 3L+, third line and beyond; LOT, line of therapy; pembro, pembrolizumab.
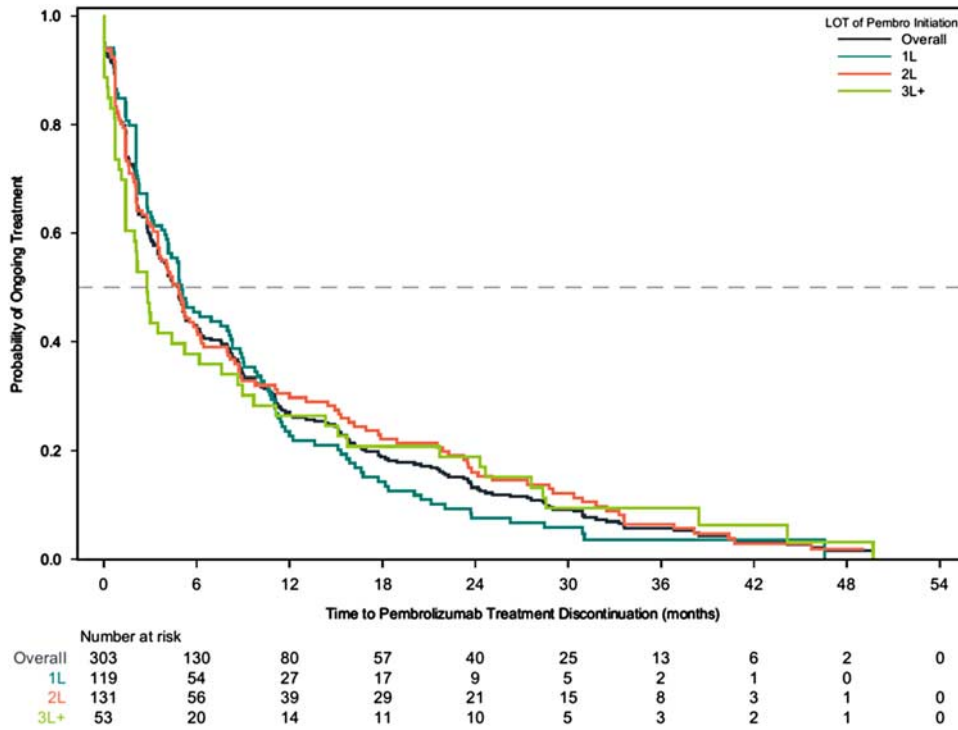
FIGURE 2. Kaplan-Meier curve of time to pembrolizumab treatment discontinuation by LOT of pembrolizumab initiation. 1L indicates first line; 2L, second line; 3L+, third line and beyond; LOT, line of therapy; pembro, pembrolizumab.

those who received it in the 3L setting. Moser et al[15] reported a median OS of 22.6 among all patients who received pembrolizumab in their study. It is hypothesized that longer median OS duration observed in this study may be due underlying differences in the patient populations and/or research methodologies across these 3 studies.[14,15]
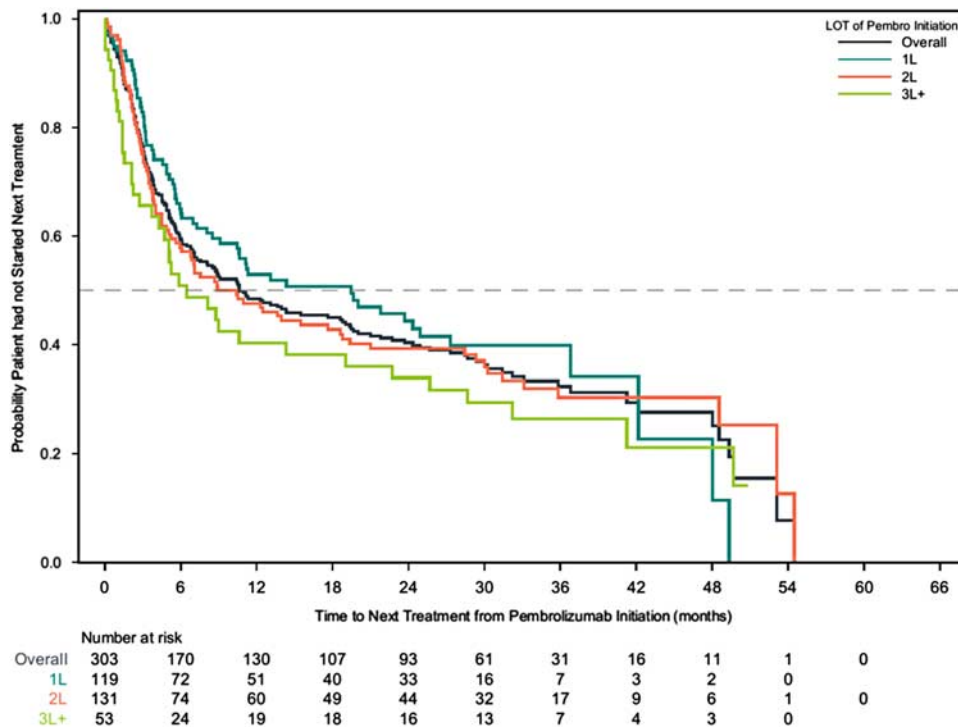

FIGURE 3. Kaplan-Meier curve of time to next treatment from pembrolizumab initiation by LOT of pembrolizumab initiation. 1L indicates first line; 2L, second line; 3L+, third line and beyond; LOT, line of therapy; pembro, pembrolizumab.
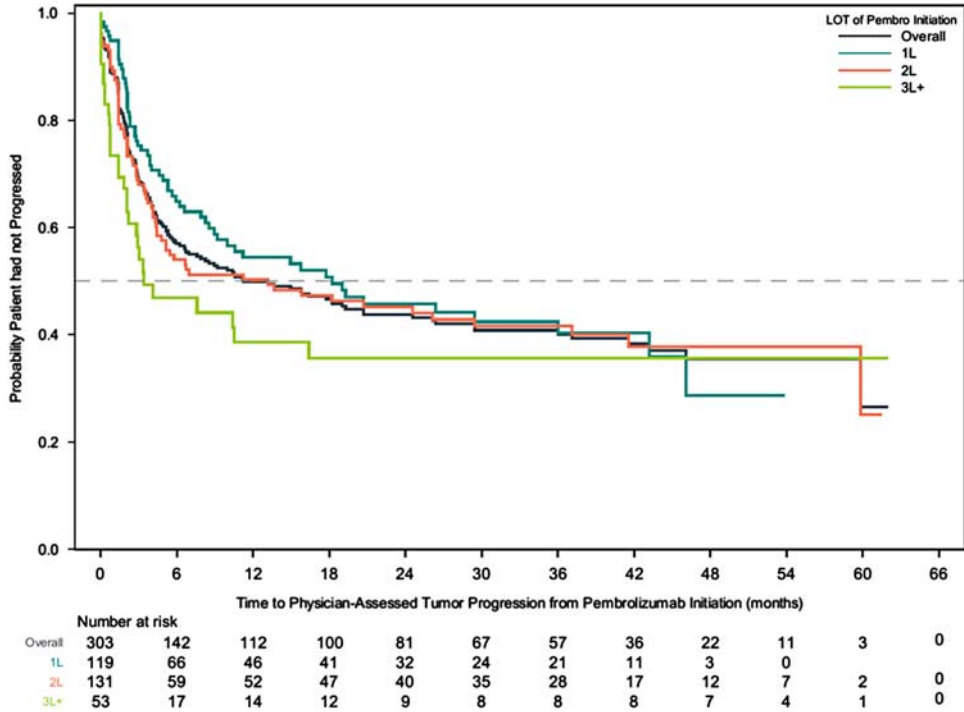
FIGURE 4. Kaplan-Meier curve of real-world (physician-assessed) time to tumor progression by LOT of pembrolizumab initiation. 1L indicates first line; 2L, second line; 3L+, third line and beyond; LOT, line of therapy; pembro, pembrolizumab.

Assessments of survival in the real-world setting may be hindered by incomplete records of death for the study population. In particular, the completeness of death records in the LADMF has decreased since 2011 given limitations on state records in the database.[24,25] Conversely, the completeness of death records in the iKM EHR database has
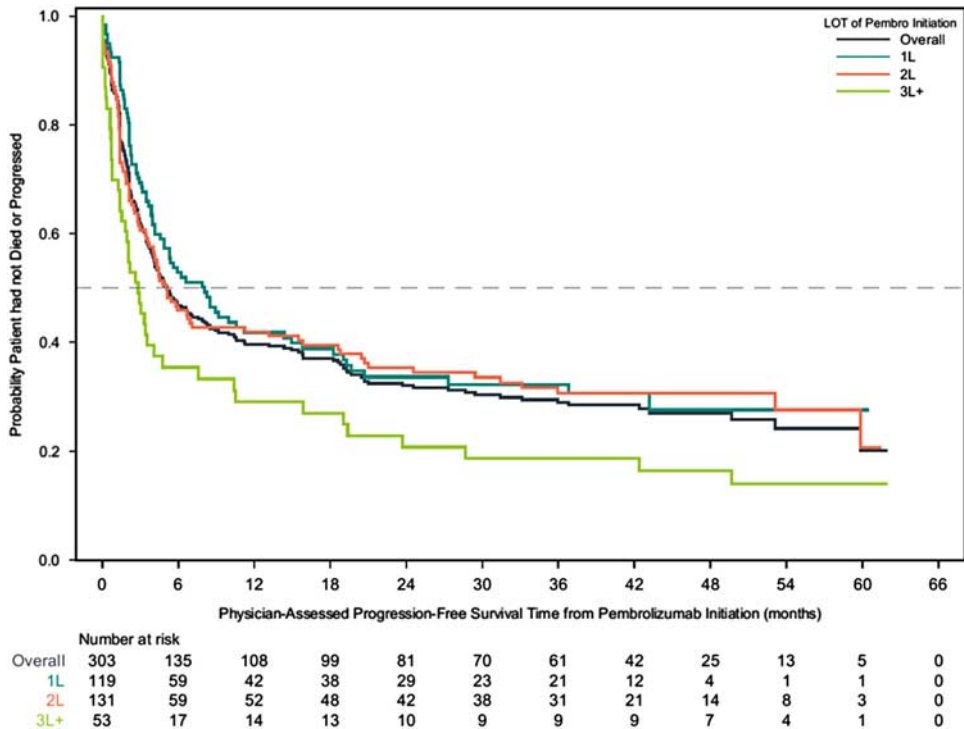

FIGURE 5. Kaplan-Meier curve of real-world (physician-assessed) progression-free survival by LOT of pembrolizumab initiation. 1L indicates first line; 2L, second line; 3L+, third line and beyond; LOT, line of therapy; pembro, pembrolizumab.

TABLE 3. Multivariable Cox Regression Models on Overall Survival and Physician-assessed Progression-free Survival From Pembrolizumab Treatment Initiation

Covariate	Level	Total	Event (Censored) [n (%)]	HR (95% CI)	P
			Overall survival		
Age at pembrolizumab	Per year increase	303	154 (149)	1.015 (1.001–1.029)	0.0307
ECOG at pembrolizumab initiation	0–1 (reference)	209	100 (109)	—	0.0103
	2+	41	27 (14)	1.870 (1.198–2.920)	0.0059
	Not documented	53	27 (26)	0.885 (0.573–1.366)	0.5809
LDH at pembrolizumab initiation	Normal (reference)	160	66 (94)	—	<0.0001
	Elevated	62	51 (11)	3.614 (2.456–5.316)	<0.0001
	Not documented	81	37 (44)	1.516 (1.001–2.296)	0.0495
Presence of brain metastases	No (reference)	226	110 (116)	—	0.0037
	Yes	77	44 (33)	1.708 (1.190–2.449)	0.0037
LOT of pembrolizumab	1L (reference)	119	47 (72)	—	<0.0001
	2L	131	71 (60)	1.378 (0.942–2.016)	0.0986
	3L+	53	36 (17)	2.727 (1.716–4.334)	<0.0001
			Real-world progression-free survival		
Sex	Female (reference)	112	83 (29)	—	0.1162
	Male	191	129 (62)	0.797 (0.601–1.058)	
Brain metastases	No (reference)	226	151 (75)	—	0.0120
	Yes	77	61 (16)	1.482 (1.090–2.015)	0.0120
LDH at pembrolizumab initiation	Normal (reference)	160	96 (64)	—	<0.0001
	Elevated	62	59 (3)	3.472 (2.474–4.872)	<0.0001
	Not documented	81	57 (24)	1.575 (1.128–2.199)	0.0077
LOT of pembrolizumab	1L (reference)	119	78 (41)	—	0.0073
	2L	131	90 (41)	1.142 (0.838–1.556)	0.4019
	3L+	53	44 (9)	1.807 (1.239–2.635)	0.0021

CI indicates confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; 1L, first line; 2L, second line; 3L+, third line and beyond; LDH, lactate dehydrogenase; LOT, line of therapy.

increased over time.[20] This upward trend may potentially due to documentation requirements of quality initiatives, like the Oncology Care Model. Nonetheless, patients whose death dates are not captured in the electronic health record or LADMF may be inaccurately censored for the analysis. Furthermore, variations in OS across different real-world settings may be due to completeness in death information.

In the long-term results of the KEYNOTE-001, KEYNOTE-002, and KEYNOTE-006 trials, median progression-free survival (PFS) ranged from 2.9 months (95% CI: 2.8–3.8) among previously treated patients who received 2 mg/kg every 3 weeks in the KEYNOTE-002 trial to 16.9 months (95% CI: 9.3–35.5) among treatment-naive patients in the KEYNOTE-001 trial.[9,11,13] For assessment of PFS in these trials, RECIST criteria were used, along with investigator-assessed immune-related response criteria for the KEYNOTE-001 and KEYNOTE-001 trials.[8–11,13]

Unlike clinical trials, in the real-world setting, tumor assessments may not be performed according to RECIST criteria or there may incomplete documentation available for research purposes.[22] As such, evaluation of PFS in real-world studies is limited and proxies for PFS may be used. Treatment-based endpoints, TTD and TTNT, can be sourced from structured data alone. For TTD and TTNT, patients may discontinue or start a new treatment for any reason; however, as many patients discontinue treatment due to progression, these endpoints may correlate with PFS.[26,27] Nonetheless, the utility of these endpoints may be limited as they do not account for patients who cease treatment for other reasons, including toxicity. As alternative proxies, rwTTP and rwPFS, are physician-documented progression, which are impressions recorded in progress notes based on scan reports and/or clinical symptoms. The capture of rwTTP and rwPFS usually involves a targeted chart review, as was performed for this study.

For this study, four proxies for PFS were considered: TTD, TTNT, rwTTP, and rwPFS. As with median OS, median rwPFS in this study was significantly different across the LOT cohorts and decreased with the successive LOTs (8.1 mo among the 1L cohort and 2.8 among the 3L+ cohort). In a pooled analysis of 7 retrospective studies performed with The US Oncology Network database, median TTD was observed to be shorter than rwPFS and TTNT.[27] This finding was echoed in the current study, with an observed median rwPFS of 5.1 months, median TTD of 4.8 months, and a median TTNT of 10.6 months.

Median TTD and TTNT in our study were similar across the LOT cohorts and comparable to that reported by other studies. The median TTD found in this study was in the range reported across the KEYNOTE studies (3.7–6.4 mo).[10,23,28] In the community oncology setting, Liu et al[14] observed an overall median time on treatment of 4.9 months.

Liu et al[14] and Moser et al[15] median TTNT to range from 13.6 to 15.7 months, respectively, among patients who initiated 1L pembrolizumab; whereas longer median TTNT and rwTTP were observed in this study (19.5 and 18.2 mo, respectively) among the 1L cohort. Otherwise, the overall median TTNT reported in Liu et al,[14] 11.2 months, was similar to the overall median TTNT and rwTTP estimates across this study population (10.6 and 11.2 mo, respectively). The correlation observed in this study suggests that TTNT may be an appropriate proxy for rwTTP for studies that only include structured data, without a targeted chart review.

As providers navigate an increasingly complex melanoma treatment landscape, understanding the optimal sequence of therapies is important. As adjuvant therapy with anti-PD1 monotherapies becomes a standard of care for patients with stage III resectable disease, further research is needed to understand how this may contribute to long-term outcomes.[4,29] In particular, future studies should consider evaluating outcomes based on what treatments patients receive before and after 1L therapy through adjusted models.

Conclusions about the study results must be drawn in the context of the strengths and limitations of the data source and study design. First, as a retrospective, observational electronic health record–based study, study data were initially recorded for clinical care, not for research, which may result in missing, incorrect, or incomplete data. For example, certain variables of interest, such as PD-L1 status, were not always available for the entire study population. The generalizability of this study may be limited due to the location distribution of The US Oncology Network practices and their use of evidence-based guidelines.

The results of this study show that pembrolizumab was associated with favorable outcomes in real-world patients with advanced melanoma, similar to other real-world studies and to pivotal clinical trials. Notably, the median OS was 43 months among patients who received pembrolizumab in the 1L setting. The study also provides a benchmark for future studies aiming to evaluate treatment sequencing among patients with advanced melanoma who receive pembrolizumab in a real-world setting.

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Conflicts of Interest/Financial Disclosures

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