The Oncologist, 2023, **28**, 268–275
https://doi.org/10.1093/oncolo/oyac219
Advance access publication 27 October 2022
Original Article

Health Care Utilization and Costs in Systemic Therapies for Metastatic Melanoma from 2016 to 2020

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Abstract

Background: Widespread implementation of immune checkpoint inhibitors (ICI) and targeted therapies for metastatic melanoma has led to a decline in melanoma-related mortality but increased healthcare costs. We aimed to determine how healthcare utilization varied by systemic, non-adjuvant melanoma treatment from 2016 to 2020.

Patients and Methods: Adults with presumed stage IV metastatic melanoma receiving systemic therapy from 2016 to 2020 were identified in Optum, a nationwide commercial claims database. Treatment groups were nivolumab, pembrolizumab, ipilimumab+nivolumab (combination-ICI), or BRAF+MEK inhibitor (BRAFi+MEKi) therapy. Outcomes included hospitalizations, days hospitalized, emergency room (ER) visits, outpatient visits, and healthcare costs per patient per month (pppm). Multivariable regression models were used to analyze whether cost and utilization outcomes varied by treatment group, with nivolumab as reference.

Results: Among 2018 adult patients with metastatic melanoma identified, mean (SD) age was 67 (15) years. From 2016 to 2020, nivolumab surpassed pembrolizumab as the most prescribed systemic melanoma therapy while combination-ICI and BRAFi+MEKi therapies remained stable. Relative to nivolumab, all other therapies were associated with increased total healthcare costs (combination-ICI: β = $47 600 pppm, 95%CI $42 200-$53 100; BRAFi+MEKi: β = $3810, 95%CI $365-$7260; pembrolizumab: β = $6450, 95%CI $4420-$8480). Combination-ICI and BRAFi+MEKi therapies were associated with more inpatient hospital days.

Conclusions: Amid the evolving landscape of systemic therapy for advanced melanoma, nivolumab monotherapy emerged as the most used and least costly systemic treatment from 2016 to 2020. Its sharp increase in use in 2018 and lower costs relative to pembrolizumab may in part be due to earlier adoption of less frequent dosing intervals.

Key words: melanoma; immune checkpoint inhibitors; molecular targeted therapy; healthcare cost; administrative claims; healthcare.

Implications for Practice

Immunotherapies and targeted therapies have revolutionized metastatic melanoma treatment over the past decade, and these novel therapeutics have been accompanied by both improved patient survival and higher treatment-related costs. Using administrative claims data, this study found that nivolumab monotherapy emerged as the most used and least costly systemic, non-adjuvant melanoma treatment from 2016 to 2020, an observation that may in part be explained by earlier adoption of reduced dosing intervals. These findings can help providers compare systemic treatment options for metastatic melanoma from an economic and healthcare utilization perspective and facilitate shared decision-making with patients.

Introduction

Melanoma-related mortality rates have declined annually since 2013, following the 2011 United States (US) Food and Drug Administration (FDA) approval of ipilimumab, an immune checkpoint inhibitor (ICI), and vemurafenib, a BRAF inhibitor, for treatment of unresectable melanoma.[1] With the advent of additional ICIs and targeted therapies, often used in combination, health outcomes in advanced melanoma have

Received: 20 June 2022; Accepted: 15 September 2022.

improved compared to previous standard-of-care cytotoxic chemotherapies.[2,3] However, this has been accompanied by significantly increased costs and variable cost effectiveness.[4] Indeed, a recent case-control study reported that for patients with stage IV melanoma, mean first year cancer-attributable costs per patient increased from $46 000 between 2004 and 2010 to $74 000 between 2011 and 2015, which coincided with the adoption of novel treatments.[5]

The increased costs of modern systemic therapies are not solely attributed to direct drug-related expenses. That is, significant indirect costs related to the management of immune-related adverse events (ir-AEs) as well as adverse events particular to targeted therapies (eg, BRAF and MEK inhibitors) have been observed.[6,7] These novel toxicity profiles vary by agent and may be severe in a subset of patients. For instance, in immune checkpoint inhibitors, ir-AEs of any grade may manifest in over 60% of patients on anti-CTLA4 therapy regimens (eg, ipilimumab) but tend to be less frequent and severe for patients on anti-PD1 monotherapy (eg, nivolumab or pembrolizumab).[8,9] Thus, we hypothesized that regimens including anti-CTLA4 therapy (eg, ipilimumab + nivolumab therapy) may be associated with greater ir-AE-related healthcare resource utilization and costs compared with anti-PD1 monotherapies.

While the most recent national characterization of healthcare utilization of systemic therapies for metastatic melanoma analyzed data from 2012 to 2017,[10] there is a paucity of literature describing these trends in recent years. In light of the rapidly evolving landscape of melanoma treatment, the goal of our study was to characterize healthcare costs and utilization for patients with metastatic melanoma undergoing current, first-line systemic therapies in a real-world setting. In so doing, we aimed to build upon existing literature and provide up-to-date information on this topic to help providers compare systemic treatment options for metastatic melanoma from an economic perspective, which may facilitate shared decision-making with patients.

Herein, we analyze medical claims data from a national claims warehouse from 2016 to 2020 to report on trends in utilization and healthcare costs for patients with metastatic melanoma across first-line systemic treatments including anti-CTLA4 ICIs, anti-PD1 ICIs, combination ICIs, and combination BRAF and MEK inhibitors.[2]

Methods

This retrospective cohort study analyzed 5 years of data from the Clinformatics Data Mart Database (OptumInsight, Eden Prairie, MN; "Optum"), a de-identified database from a national claims warehouse that encompasses all 50 states.[11] Optum contains data derived from administrative claims for over 80 million individuals with commercial and Medicare Advantage plans; claims are submitted for billing purposes by providers/pharmacies and verified, adjusted, and de-identified prior to inclusion in the database. Available data points include patient enrollment dates, medical claims, pharmacy claims, inpatient confinement claims, lab results, and provider information.

Using Optum, we interrogated medical claims data for inpatient, outpatient, and pharmacy services in adult patients with metastatic melanoma who received systemic treatment[2] from January 1, 2016, to December 31, 2020. This study period was selected based on the most recent available data and diagnosis code classification (International Classification of Diseases) release. Systemic treatment groups included: (1) nivolumab monotherapy, (2) pembrolizumab monotherapy, (3) combination nivolumab and ipilimumab (combination ICI), and (4) combination BRAF and MEK inhibitor (BRAFi + MEKi) therapy. Diagnosis codes were based on the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM), procedure codes were classified by the Current Procedural Terminology and Healthcare Common Procedure Coding System (HCPCS), and medications were identified by First Databank National Drug Codes (NDC). All data were accessed through the Stanford Center for Population Health Sciences Data Core and fall under Stanford IRB's protocol (PHS-40974) for use of de-identified data in clinical outcomes research.

Patients with metastatic melanoma were identified based on an operational algorithm defined in previous claims-based studies[10] with minor modifications. Inclusion criteria included: at least 1 inpatient or 2+ outpatient diagnoses of invasive cutaneous melanoma (ICD-10-CM, C43), a concomitant diagnosis of secondary malignant neoplasm (ICD-10-CM, C78-C79) less than 30 days before and within 60 days after a melanoma diagnosis, at least 3 months of continuous insurance eligibility before the initiation of therapy, at least 1 month of continuous eligibility after initiation of therapy, and ages 18 years or older. The end of first-line therapy was defined as the initiation of a new drug or drug combination 28 days following the initiation of therapy or a gap of greater than 90 consecutive days in prescription fills or drug administration. Patients were followed from index date until end of first-line therapy, health plan disenrollment, or end of study period (December 31, 2020). In contrast to previous claims-based studies,[3] to isolate Stage IV disease and avoid capturing patients with Stage III melanoma where systemic treatment was given in the adjuvant setting, diagnosis of secondary malignant neoplasm of lymph nodes (ICD-10-CM, C77) was not used as an acceptable inclusion criterion. Exclusion criteria included diagnosis of non-melanoma malignant neoplasm or receipt of systemic therapy within 90 days of study period start date.

Baseline study population characteristics, outcomes of interest, and statistical models were defined before data extraction, based on literature review and author expertise. Healthcare utilization measures included number of hospitalizations, days hospitalized, emergency room (ER) visits, and outpatient visits. Total healthcare costs (adjusted for inflation to real 2020 US Dollars) were extracted and normalized by patient per month. Clinical characteristics such as age, sex, race, healthcare plan, and presence of brain metastasis (ICD-10-CM, C79.31) were also collected. Comorbidity scores were derived using an Elixhauser classification system previously validated in claims data.[12] Multinomial logistic regression models were used to assess differences in baseline characteristics including demographics, comorbidities, presence of brain metastases, baseline (pre-treatment) healthcare utilization, and baseline total healthcare costs across treatment groups with reference group as nivolumab monotherapy. The p-value was adjusted with Bonferroni correction for multiple comparisons. Proportion of the study population on a given therapy by year of treatment initiation was plotted to visualize trends over time. Multivariable linear regression models with standard errors robust to heteroskedasticity were used to assess

healthcare resource utilization and costs across treatment groups, with nivolumab monotherapy as reference. Year of treatment, presence of brain metastasis, healthcare plan, age, comorbidity index, race and baseline utilization of outcome resource were included as covariates if univariable analysis met a threshold of $P < .1$.

Cost analyses focused on 2 measures: (1) total healthcare costs throughout the active study period, which encompassed costs for all claims during the study period and (2) total treatment-related costs, which isolate healthcare costs linked to National Drug Codes and Healthcare Common Procedure Codes per respective treatment group. All costs were standardized by Optum through a methodology that varies across types of services with the purpose of removing variations that may be driven by differences in contractual agreements, locations, timeframes, and providers ("standard cost"); this standardized process provides a uniform and consistent approach to pricing all services. Standardized costs as generated by Optum have been used in recent published cost analysis studies.[13-15] Total standard costs were an estimate of the total amount per patient that the payer contractually agreed to pay for all services received by the patient. All standardized costs were expressed in 2020 USD. All analyses and figures were generated using Stata 16.1 and GraphPad Prism 9.1.

Results

After applying inclusion/exclusion criteria, we identified 2018 patients who received nivolumab monotherapy (811), pembrolizumab monotherapy (670), ipilimumab+nivolumab (combination ICI, 364), or BRAF inhibitor + MEK inhibitor (BRAFi+MEKi, 173) therapy (Table 1). Mean (SD) patient age was 67 (15) years, and the majority were White (1715, 85%) and male (1322, 66%). Those who received pembrolizumab and nivolumab monotherapy tended to be older and have MedicareAdvantage health plans compared to those with combination ICI or BRAFi+MEKi therapy. Brain metastases were observed more frequently in patients who received combination ICI and BRAFi+MEKi therapies. The BRAFi+MEKi group also demonstrated greater baseline hospitalizations and days hospitalized compared to patients in the other treatment groups. Otherwise, baseline demographics, healthcare utilization and costs were similar across treatment groups. Additionally, mean (SD) length of treatment did not differ significantly across therapy groups: 9.3 (7.9) months for nivolumab, 9.5 (9.2) months for pembrolizumab, 8.9 (9.9) months for combination ICI, and 8.6 (7.6) months for BRAFi+MEKi therapy.

Pembrolizumab was the most widely prescribed therapy in 2016 (47% of study population) but decreased by 2018 (24%), which coincided with increased nivolumab use (25 to 51%) (Fig. 1). Combination ICI (20% in 2016 to 18% in 2020) and BRAFi+MEKi (8% to 9%) therapies remained relatively stable.

With nivolumab monotherapy as reference group, pembrolizumab monotherapy was associated with greater treatment-related costs [β = $5553 per patient per month (pppm); 95% CI, $4290 to $6816] and total healthcare costs (β = $6450 pppm; 95% CI, $4423 to $8477). There were no significant differences in number of hospitalizations, days hospitalized, ER visits, or outpatient visits between these treatment groups (Table 2). Combination ICI therapy was associated with

Table 1. Baseline characteristics of study population ($N = 2018$).

	Nivolumab	Pembrolizumab[a]	Ipilimumab + Nivolumab[a]	BRAFi + MEKi[a]
N (%)	811 (40%)	670 (33%)	364 (18%)	173 (9%)
Age (years), mean±SD	69 ± 14	72 ± 13*	64 ± 13*	59 ± 15*
Sex, *n* (%)				
Male	537 (66%)	427 (64%)	253 (70%)	105 (61%)
Female	274 (34%)	243 (36%)	111 (30%)	68 (39%)
Race[b], *n* (%)				
White	679 (89%)	588 (91%)	305 (89%)	143 (87%)
Hispanic, Black or Asian	80 (11%)	55 (9%)	37 (11%)	21 (13%)
Health plan, *n* (%)				
Commercial	268 (33%)	171 (26%)	177 (49%)	96 (55%)
Medicare Advantage	543 (67%)	499 (74%)*	187 (51%)*	77 (45%)*
No. of comorbidities, mean±SD	3.40 ± 2.09	3.61 ± 2.28	3.25 ± 2.00	3.53 ± 2.41
Brain metastasis, *n* (%)	58 (7%)	72 (11%)	82 (23%)*	44 (25%)*
Baseline Healthcare Utilization[c], mean±SD				
Hospitalizations	.06 ± .15	.06 ± .17	.07 ± .17	.10 ± .18*
Days hospitalized	.24 ± 1.03	.34 ± 1.51	.34 ± 1.21	.64 ± 1.80*
ER visits	.07 ± .20	.12 ± .34*	.09 ± .24	.11 ± .30
Outpatient visits	4.00 ± 2.08	3.95 ± 2.35	3.72 ± 1.84	3.62 ± 1.99
Pre-treatment HC cost[c] ($, thousands), mean ± SD	10.41 ± 12.05	9.90 ± 12.66	9.80 ± 9.94	12.18 ± 14.61

[a]* $P < .006$ for multinomial logistic regression model of treatment category with reference as nivolumab, p-value adjusted with Bonferroni correction for multiple comparisons.
[b]Race percentage was calculated based on total reported race per treatment category.
[c]Hospitalizations, days hospitalized, ER visits, outpatient visits, and HC cost are represented per patient per month during the baseline period (90 days before treatment initiation).
Abbreviations: No. of comorbidities, number of Elixhauser comorbidities; pre-treatment HC cost, total healthcare cost during baseline period (real 2020 US dollars in thousands); BRAFi, BRAF inhibitor; MEKi, MEK inhibitor.

greater outpatient visits (β = 0.56 pppm; 95% CI, 0.31 to 0.80), days hospitalized (β = 0.62 pppm; 95% CI, 0.35 to 0.89), increased hospitalizations (β = 0.11 pppm; 95% CI, 0.08 to 0.14), ER visits (β = 0.06 pppm; 95% CI, 0.02 to 0.10), treatment-related costs (β = $41 285 pppm; 95% CI, $36 913 to $45 657) and total healthcare costs (β = $47 622 pppm; 95% CI, $42 190 to $53 054). While BRAFi+MEKi therapy was predictive of greater days hospitalized (β = 0.50 pppm; 95% CI, 0.07 to 0.93), increased treatment-related costs (β = $3455 pppm; 95% CI, $1615 to $5294), and higher total healthcare costs (β = $3813 pppm; 95% CI, $365 to $7261), it was also associated with fewer outpatient visits (β = –0.52 pppm; 95% CI, –0.82 to –0.21).

Discussion

This study used a nationwide administrative claims database to characterize trends in metastatic melanoma treatment and associated healthcare resource utilization and costs in the US from 2016 to 2020. National and regional administrative databases have emerged as powerful tools to assess healthcare utilization, costs and outcomes, and it is important to interpret our results in the context of the strengths and limitations of claims data.[16-18] Administrative databases are typically derived from insurance claims data submitted for the purpose of reimbursement. This permits access to longitudinal medical and financial data from large cohorts of geographically and demographically diverse populations, enabling studies that would be impractical or infeasible with conventional clinical research methods. Claims studies rely on billing codes used to classify diagnoses and procedures, which may lack granularity and be prone to misclassification or clerical errors.[16,17] While various studies have validated billing codes through correlation with medical records,[19-22] study design is critical to optimize internal validity.[16,23,24] Thus, in the present study, we used stringent inclusion criteria (including metastatic melanoma and comorbidity score algorithms previously described in administrative claims data) and limited our study period to years that encompass the most granular diagnosis code set available (ICD-10-CM).

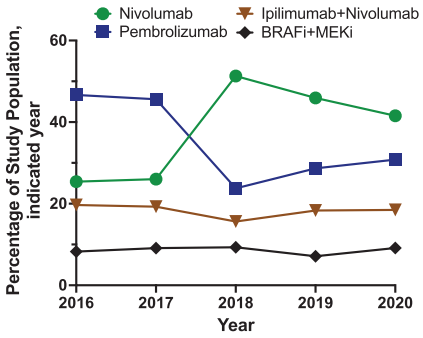

Figure 1. Trends in systemic melanoma treatment over time, 2016 to 2020. Data points are the proportion of the study population represented by each therapy category for the indicated year by year of treatment initiation.

To our knowledge, the findings reported here represent the most up-to-date information regarding the current trends in prescribing patterns, healthcare costs, and healthcare resource utilization associated with first-line systemic treatments for metastatic melanoma. A similar administrative claims-based study of the systemic treatments for advanced melanoma from 2012 to 2017 by van Boemmel-Wegmann et al. reported ipilimumab monotherapy as the most used ICI or targeted therapy (689/1616, 43%) followed by BRAF or MEK inhibitor monotherapy (240/1616, 15%), BRAF + MEK inhibitor combination therapy (214/1616, 13%), combination ipilimumab and nivolumab (185/1616, 11%), pembrolizumab monotherapy (185/1616, 11%), and nivolumab monotherapy (103/1616, 6%), excluding patients receiving chemotherapy.[10] Overall, the aforementioned findings contrast with our results despite 2 years of overlap in our analyses (2016 to 2017), demonstrating the dynamic evolution of systemic treatment utilization in the three additional years reported here. This is not surprising, given the results of several pivotal phase III trials showing the superiority of PD-1 antibodies and nivolumab/ipilimumab to ipilimumab monotherapy.[25,26] Interestingly, when isolating the distribution of therapy

Table 2. Healthcare resource utilization and costs during metastatic melanoma treatment (per month).

	Nivolumab	Pembrolizumab		Ipilimumab + Nivolumab		BRAFi + MEKi	
Healthcare Resource[a]	Mean ± SD	Mean ± SD	β (95% CI)[b]	Mean ± SD	β (95% CI)[b]	Mean ± SD	β (95% CI)[b]
Hospitalizations	.08 ± .21	.10 ± .26	.01 (–.02,.03)	.20 ± .30	.11*** (.08,.14)	.13 ± .28	.04 (–.004,.08)
Days hospitalized	.46 ± 1.74	.57 ± 1.76	–.01 (–.19,.17)	1.14 ± 2.25	.62*** (.35,.89)	1.13 ± 3.98	.50* (.07,.93)
ER visits[c]	.11 ± .29	.16 ± .33	.02 (–.02,.05)	.17 ± .34	.06** (.02,.10)	.11 ± .24	–.004 (–.05,.04)
Outpatient visits	3.89 ± 1.98	3.94 ± 2.20	–.05 (–.26,.15)	4.39 ± 2.02	.56*** (.31,.80)	3.27 ± 1.98	–.52** (–.82, –.21)
Treatment-related cost ($, thousands)	17.2 ± 15.3	21.2 ± 10.6	5.60*** (4.29, 6.82)	59.2 ± 42.7	41.3*** (36.9, 45.7)	22.3 ± 8.7	3.45*** (1.62, 5.30)
Total HC cost ($, thousands)	25.4 ± 22.0	30.5 ± 19.1	6.45*** (4.42, 8.48)	74.5 ± 52.2	47.6*** (42.2, 53.1)	32.5 ± 23.4	3.81* (.365, 7.26)

[a]All outcomes are represented as utilization per patient per month during the study period.
[b]β-coefficients and 95% confidence intervals for multivariable linear regression models of indicated outcome, adjusted for year of treatment, presence of brain metastasis, healthcare plan, age, comorbidity index, and baseline utilization of outcome resource; reference treatment is nivolumab; ***$P < .001$, **$P < .01$, *$P < .05$.
[c]Based on univariable analysis ($P < .1$), the ER visits model was also adjusted for race.
Abbreviations: ER, emergency room; Total HC cost, total healthcare cost during study period (real 2020 US dollars in thousands); BRAFi, BRAF inhibitor; MEKi, MEK inhibitor.

assignment to immunotherapies, one of the drivers of the observed disparity is clarified. Comparing our immunotherapy distribution to van Boemmel-Wegmann et al.'s, respectively, we observe: pembrolizumab monotherapy (670/1845, 36% vs 185/473, 39%), nivolumab monotherapy (811/1845, 44% vs 103/473, 22%), and nivolumab + ipilimumab (364/1845, 20% vs 185/473, 39%). Here, we can appreciate that pembrolizumab distribution was actually quite similar across studies and that the differences in nivolumab utilization can be largely explained by the shift in utilization from combination nivolumab + ipilimumab to nivolumab monotherapy as first-line therapy. This was largely driven by results in the CheckMate 067 trial highlighted in the 2015 ASCO annual meeting with subsequent FDA approval of nivolumab monotherapy in late 2015.[27,28] Otherwise, it is also possible that differences in study design, such as employment of distinct data sources (IBM MarketScan versus Optum) and exclusion criteria contributed to these differences. In the present study, we elected to exclude patients with metastases isolated to lymph nodes (to avoid capturing Stage III disease) and those treated with ipilimumab monotherapy (because ipilimumab monotherapy was no longer recommended as a first-line treatment for advanced melanoma by late 2017[25,26,29-32]).

In our cohort, combination ICI and BRAFi+MEKi therapy use remained relatively stable throughout the study period at just under 20% and 10% of the study population, respectively. Compared to nivolumab, combination ICI demonstrated an increase in totals costs, treatment-related costs, and all measures of healthcare resource utilization including days hospitalized, number of hospitalizations, ER visits, and outpatient visits. These results are consistent with the known treatment-related adverse events and toxicities in ipilimumab-containing (anti-CTLA-4) treatment regimens.[6,33,34] Our baseline characteristics indicated that combination therapy patients had a greater burden of brain metastases, which was adjusted for in cost and utilization analyses. Metastasis to the central nervous system informs provider and patient choice to pursue potent (and simultaneously more toxic) treatment regimens, such as combination ICI and targeted therapies.[35] Patients on BRAFi+MEKi therapy demonstrated greater treatment-related costs, total healthcare costs, and days hospitalized but less outpatient visits versus nivolumab. Consistent with our findings, a previous claims-based analysis showed that the treatment-related cost of combination BRAFi+MEKi therapy was greater than pembrolizumab or nivolumab monotherapy.[10]

A notable observation in our data was the rapid rise in nivolumab use in 2018 and simultaneous decline in pembrolizumab use in 2018, in the context of stable combination ICI and BRAFi+MEKi therapy use throughout the study period. Nivolumab monotherapy was FDA approved for treatment of unresectable or metastatic melanoma in November 2015, and FDA approval of pembrolizumab monotherapy as first-line therapy for unresectable or metastatic melanoma followed shortly thereafter in December 2015.[36] The observed rise in nivolumab use in our data correlated with its FDA-approval to reduce dosing frequency from every 2 weeks to every 4 weeks in March 2018.[28] After a decline in 2018, pembrolizumab monotherapy utilization increased yearly until 2020, the end of the study period, with an associated decrease in nivolumab use. Of note, the 2019 and 2020 increases in pembrolizumab utilization were not as large in magnitude as nivolumab's sharp increase in 2018. This shift may be related to pembrolizumab's FDA approval in April 2020 to reduce dosing frequency from every 3 weeks to every 6 weeks. However, this does not explain pembrolizumab's reclamation of patient share in 2019, which we posit may be accounted for by the landmark KEYNOTE-006 trial's publication in July 2019 demonstrating continued superiority of pembrolizumab monotherapy over ipilimumab monotherapy after 5 years of follow-up with subsequent mention in the 2019 NCCN Melanoma guidelines.[2,26] Conversely, at the time of 2019 NCCN guideline publication, the most recent clinical trials considering nivolumab against other first-line therapies were: January 2015 CheckMate 066 (nivolumab vs dacarbazine), March 2015 CheckMate 037 (nivolumab vs chemotherapy), September 2016 CheckMate 069 (nivolumab + ipilimumab vs ipilimumab), and October 2017 CheckMate 067 (nivolumab + ipilimumab vs nivolumab vs ipilimumab).[36-39] Thus, in 2019, the 2-year gap in relevant nivolumab clinical trials for advanced melanoma in combination with the 2019 KEYNOTE 006's[26] findings of sustained pembrolizumab superiority versus ipilimumab may partially explain the trend we observed. In addition, prescriber patterns may have been impacted by a variety of factors in 2020, including the initiation of a global pandemic. Given pembrolizumab's reduction in dosing frequency at the end of our study, it will be informative to repeat these analyses as additional years of data become available.

Despite our observed fluctuations in anti-PD-1 monotherapy use, published data support similar efficacy and safety between nivolumab and pembrolizumab, although these comparisons are based on retrospective analyses and these drugs have never been directly compared in a clinical trial.[40,41] In line with these previous findings, pembrolizumab and nivolumab monotherapies had similar healthcare resource utilization (including hospitalizations and ER visits) in this cohort. However, pembrolizumab was associated with significantly higher treatment-related and total healthcare costs, even after adjusting for potential confounders including healthcare plan, age, and comorbidity index. Across therapy categories, high treatment-related costs appeared to drive differences in total healthcare costs. Interestingly, no significant differences in treatment-related costs or total healthcare costs were observed in van Boemmel-Wegmann et al.'s 2012-2017 cohort between pembrolizumab and nivolumab.[10] Though unexpected, this variance may be explained by adoption of less frequent dosing intervals for nivolumab (every 2 weeks to every 4 weeks) in 2018 (a year not captured in the previous study) and an associated reduction in infusion-related costs relative to pembrolizumab. Two recent cost-effectiveness analyses comparing pembrolizumab and nivolumab in the treatment of metastatic squamous cell carcinoma of the head and neck found that nivolumab monotherapy provided more cost savings than pembrolizumab monotherapy regimens.[42,43] As pembrolizumab dosing intervals have been approved to extend from 3-week dosing to 6-week dosing as of April 2020, utilization of pembrolizumab monotherapy may be expected to increase while infusion-related costs may decrease due to less frequent infusion sessions. Future studies are needed to clarify the specific contributions of infusion- and facility-related costs to total costs of immunotherapy for metastatic melanoma.

Systemic treatment recommendations for metastatic melanoma depend on numerous factors, including BRAF mutation status, disease burden, patient comorbidities, and

consideration of side effect profiles. In certain cases, therapy usage may be determined by provider and patient preference, including cost and convenience of dosing schedule. This study adds to the repertoire of resources that physicians and patients may use to compare systemic treatment options for metastatic melanoma through a cost and healthcare utilization lens.

Limitations

While our cohort's demographics largely align with the Center for Disease Control's 2012-2016 Melanoma Statistics,[44] our study population may not be nationally representative, as Optum only captures individuals who are commercially ensured. Additionally, because Optum is an administrative claims database limited by available billing codes, we were unable to control for Breslow thickness, TNM stage, or BRAF mutation status. Despite these limitations, it is likely that this study predominantly captured patients with Stage IV metastatic disease due to our inclusion criteria of cutaneous malignant melanoma diagnosis plus concomitant metastasis/secondary malignancy diagnosis (with metastases isolated to lymph nodes not sufficient for inclusion) and receipt of current first-line systemic melanoma therapy.

Conclusions

This study demonstrates fluctuations in the utilization of systemic therapies for metastatic melanoma from 2016 to 2020, with nivolumab monotherapy surpassing pembrolizumab monotherapy in 2018 while other therapies remained stable. Nivolumab monotherapy was associated with lower treatment-related and total healthcare costs compared to all other treatment groups. While combination ICI and BRAFi+MEKi therapies were associated with increased days hospitalized relative to nivolumab monotherapy, utilization outcomes were not significantly different between pembrolizumab and nivolumab monotherapy groups. Nivolumab's sharp increase in use starting in 2018 may be related to earlier adoption of less frequent dosing intervals (from every 2 weeks to every 4 weeks). The data suggests that frequency of administration may be a significant contributor to overall costs and further studies examining less frequent dosing could be justified from a health economic perspective, assuming outcomes remain similar with less frequent dosing (eg, every 8-12 weeks). Given that FDA approval for less frequent dosing of pembrolizumab (from every 3 weeks to every 6 weeks) occurred late April 2020, utilization measures may favor pembrolizumab over nivolumab moving forward. Follow-up studies are also warranted to evaluate cost-effectiveness of these systemic therapies in the setting of metastatic melanoma. Our findings may help physicians compare systemic treatment options for metastatic melanoma from an economic and healthcare utilization perspective and facilitate shared decision-making with patients.

Acknowledgments

Data for this project were accessed using the Stanford Center for Population Health Sciences (PHS) Data Core; specifically, the study used Optum SES (v5.0, Redivis Dataset, DOI: 10.57761/phra-vp46). The PHS Data Core is supported by a National Institutes of Health National Center for Advancing Translational Science Clinical and Translational Science Award (UL1 TR001085) and from Internal Stanford funding. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Conflict of Interest

Evan Hall is a section editor for *The Oncologist* and has received institutional research funding from Bristol-Myers-Squibb, Nektar Therapeutics, Neoleukin Therapeutics, ImCheck Therapeutics, Replimune, and Checkmate Pharmaceuticals. **Sunil Reddy** currently receives institutional research funding from Bristol-Myers-Squibb, Instil Bio, and TriSalus. The other authors have no relevant conflicts of interest or funding sources to disclose. The authors were not assisted by a medical writer.

Author Contributions

Conception/design: M.F.Q., N.J.B., L.C.Z. Provision of study material or patients: M.F.Q., N.J.B., A.P. Collection and/or assembly of data: M.F.Q. Data analysis and interpretation: All authors. Manuscript writing: M.F.Q., N.J.B., A.P. Final approval of manuscript: All authors.

Data Availability

The source data for this study were licensed by Stanford PHS from Optum and are not available for public sharing. However, these data are available through contractual purchase of the Clinformatics Data Mart Database (OptumInsight, Eden Prairie, MN). Stata code used for data analysis (devoid of Optum data) is available upon reasonable request.

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