Health Care Resource Utilization and Costs in First-Line Treatments for Patients with Metastatic Melanoma in the United States

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ABSTRACT

BACKGROUND: The treatment landscape for patients with metastatic melanoma has changed dramatically with the introduction of novel therapies, such as targeted therapies and immunotherapies, in recent years. Health care resource utilization (HCRU) and cost data are needed to further evaluate these treatments in a value-based health care system.

OBJECTIVE: To examine HCRU and total cost of care among U.S. metastatic melanoma patients treated with first-line systemic therapies, including immunotherapies, targeted therapies, and chemotherapy.

METHODS: A retrospective observational study was conducted using a U.S. claims database. Adults with ≥ 2 claims for melanoma and ≥ 1 claim for metastasis between January 1, 2012, and June 30, 2017, were identified. Patients had pharmacy and medical enrollment ≥ 6 months before and ≥ 3 months following first-line treatment start. Per patient per month (PPPM) HCRU and costs were calculated by first-line treatment drug class: PD-1 inhibitors, CTLA-4 inhibitors, CTLA-4 + PD-1 combination, BRAF monotherapy, BRAF + MEK combination, and chemotherapy. Adjusted odds ratios (ORs) for HCRU were estimated by logistic regressions and adjusted costs were estimated by generalized linear models using log-link with gamma distribution to control for differences in patient characteristics across groups.

RESULTS: Among 1,599 metastatic melanoma patients (PD-1, $n=255$; CTLA-4, $n=555$; CTLA-4 + PD-1, $n=88$; BRAF, $n=210$; BRAF + MEK, $n=102$; chemotherapy= 389), mean age ranged from 59-68 years, and the majority were male (62%). Any hospitalization during first-line treatment was less frequent among PD-1-treated patients (25.9%) compared with 34.7%-45.5% of all other groups (all $P<0.05$). PPPM hospitalizations were lowest in PD-1 (0.06) compared with 0.09-0.16 across all other groups (all $P<0.05$), and PPPM emergency department (ED) visits were lowest in PD-1 (0.09) compared with 0.13-0.18 across all other groups (all $P<0.05$), except for BRAF + MEK (0.14, $P=0.08$). CTLA-4, CTLA-4 + PD-1, and BRAF + MEK had increased odds of hospitalization compared to PD-1 (adjusted ORs = 2.10, 2.35, 2.15, respectively; all $P<0.05$). Total adjusted PPPM costs were significantly lower for PD-1 (\$13,059) compared with CTLA-4 (\$25,583), CTLA-4 + PD-1 (\$31,310), and BRAF + MEK (\$21,517) and higher compared to BRAF (\$8,158) and chemotherapy (\$6,361).

CONCLUSIONS: Hospitalizations and ED visits represent important HCRU for metastatic melanoma patients and were lowest among PD-1-treated patients compared with any other systemic therapies (except for ED visits when compared with BRAF + MEK). Total monthly costs varied substantially across first-line regimens and were significantly lower in PD-1-treated patients compared with patients treated with CTLA-4, CTLA-4 + PD-1, and BRAF + MEK.

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What is already known about this subject

- Substantial increase in effective therapies for patients with advanced melanoma in the past several years has been significantly improving patient outcomes.
- There is a dearth of data on health care resource utilization (HCRU) and costs of newer agents to treat patients with metastatic melanoma, especially regarding PD-1 antibodies and immunotherapy combinations.

What this study adds

- This retrospective observational study provides insights on HCRU and costs associated with contemporary systemic treatments, including immunotherapies and targeted therapies, for patients with metastatic melanoma in the United States.
- Adjusted odds of hospitalization and emergency department visits across first-line therapies for metastatic melanoma were lowest among patients treated with PD-1 inhibitors.
- Adjusted total monthly costs varied substantially across first-line therapies for metastatic melanoma and were significantly lower in PD-1-treated patients compared with patients treated with a CTLA-4 inhibitor, CTLA-4 + PD-1 combination, and BRAF/MEK combination.

Melanoma is the fifth most common cancer in the United States, representing 5.3% of all new cancer cases.¹ Over the past few years, several new treatment options have emerged for patients with unresectable or metastatic melanoma.² Treatments now include monotherapy and combination and sequential therapies of checkpoint inhibitors and inhibitors targeting the mitogen-activated protein kinase (MAPK) pathway. Ipilimumab, an anti-cytotoxic T-lymphocyte antigen-4 (anti-CTLA-4), was the first checkpoint inhibitor approved by the U.S. Food and Drug Administration (FDA) in 2011; it was followed by FDA approvals of antiprogrammed cell death-1 (PD-1) antibodies pembrolizumab and nivolumab in 2014. Nivolumab in combination with ipilimumab was the first combination of checkpoint inhibitors approved by the FDA in 2015. Targeted therapies include the BRAF inhibitors vemurafenib, dabrafenib, and encorafenib, indicated for patients who test positive for the BRAF V600 mutations, and the MEK inhibitors trametinib, cobimetinib, and binimetinib, which are

administered in combination with BRAF inhibitors.³ The use of these newer immunotherapies and targeted therapies has substantially improved overall survival among patients with metastatic melanoma but at greater economic impacts.⁴⁻¹⁵

Few economic studies exist that evaluate the effect of the newer immunotherapy and targeted therapy agents on the health care resource utilization (HCRU) and costs among patients treated for metastatic melanoma, particularly in a population of patients aged >65 years.^{2,5} Several studies exist that describe resource use and costs before the introduction of immunotherapy agents.² Experience with ipilimumab monotherapy has been reported, although this has been limited to commercially insured populations and/or not limited to the first-line therapy setting.^{16,17} A recent analysis by Ghate et al. (2018), also conducted among commercially insured patients, assessed HCRU and found no difference in inpatient hospitalizations and emergency department (ED) visits between patients treated with first-line dabrafenib plus trametinib and patients treated with first-line nivolumab or pembrolizumab monotherapy (2.3 vs. 2.2 inpatient hospitalizations per patient-year, respectively; 1.6 vs. 2.1 ED visits per patient-year, respectively).¹⁸ While others have modeled U.S. costs among patients with metastatic melanoma treated with immunotherapies, few data exist on a limited set of immunotherapies.¹⁸⁻²¹ Very little information is available on metastatic melanoma patients treated with all currently available immunotherapies and targeted therapies.

Other existing economic studies evaluating specific subsets of patients and costs include the economic burden of metastatic melanoma patients with brain metastases, the economic burden associated with adverse events in patients with metastatic melanoma, and the economic burden in elderly metastatic and high-risk patients.²²⁻²⁴ Further, other studies have addressed the economic burden of metastatic melanoma in European health care settings, which differ greatly from that of the United States.²⁵ However, the total burden of the disease has yet to be described in the current landscape of available systemic therapies.

Given the limitations of the existing literature characterizing the economic burden of metastatic melanoma in specific subgroups and in a period before the introduction of newer immunotherapy agents, this study provides timely data to understand the economic burden, in terms of HCRU and costs of the currently available first-line agents, including the most recently approved PD-1 inhibitors, in both commercial and government payer (Medicare and Medicaid) settings. The analyses that follow represent the first U.S. study to describe patients with metastatic melanoma treated with contemporary immunotherapies and targeted therapies, which include PD-1 inhibitors and CTLA-4 inhibitors, the combination of a CTLA-4 inhibitor and PD-1 inhibitor, targeted monotherapy (BRAF inhibitors), and targeted combination therapy (BRAF inhibitors plus MEK inhibitors), as well as with older agents involving traditional chemotherapy.

Methods

Data Source

This study was a retrospective, observational, cohort study of patients identified from Inovalon's Medical Outcomes and Research for Effectiveness and Economics (MORE²) Registry. The MORE² Registry is a payer database that compiles longitudinal claims data from over 100 U.S. health plans with 129 million unique covered patient lives since 2001, including more than 12 million cancer patients. The database contains adjudicated medical and pharmacy claims from small, medium, and large payers and represents the largest combined managed Medicare/Medicaid dataset in the industry. Approximately 45% of individuals within the dataset are covered by managed Medicare/Medicaid plans, with the remaining 55% covered by nongovernmental, employer-sponsored plans. Data include patient demographic records, hospital discharge records, procedural records, practitioner profiles, eligibility and enrollment status, costs, and laboratory orders and results. Payers contributing data to the database update at least yearly, with approximately 40% updating quarterly. This study received exemption from Western Institutional Review Board because of the use of retrospective deidentified claims data.

Study Population

Patients were selected from the database if they had a melanoma diagnosis (≥ 2 claims with *International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification* [ICD-9/10-CM] codes 172.x/C43.x) between January 1, 2012, and June 30, 2017, had a subsequent diagnosis of metastasis (≥ 1 claim with codes 196.x-198.x/C77.x-C79.x), had a systemic therapy for melanoma, and were aged ≥ 18 years at metastatic melanoma diagnosis date. Patients on active treatment for a second cancer diagnosis, identified as participating in a clinical trial, or diagnosed with AIDS/HIV or a pregnancy during the study period were excluded.

The index date for each patient was set at the earliest date of first-line systemic therapy for melanoma; first-line therapy was identified by the earliest claim for systemic therapy following the diagnosis of melanoma. Patients included in the study cohort were required to have both pharmacy and medical enrollment with ≥ 6 months of continuous medical and pharmacy enrollment before the index date and ≥ 3 months of continuous medical and pharmacy enrollment in the follow-up period, which ended September 30, 2017. Data for each patient included claims until the last date of continuous enrollment or the end of the study period.

Patients were assigned to 1 of 6 treatment groups based on their first-line regimen identified from claims: anti-PD-1 monotherapy (PD-1, which included pembrolizumab or nivolumab), CTLA-4 inhibitor monotherapy (CTLA-4, ipilimumab), CTLA-4 inhibitor plus anti-PD-1 combination therapy (CTLA-4+PD-1, which included ipilimumab plus nivolumab),

FIGURE 1 Patient Attrition

CTLA-4 = cytotoxic T-lymphocyte antigen-4; PD-1 = programmed cell death-1.

BRAF inhibitor monotherapy, BRAF plus MEK inhibitor combination therapy (BRAF+MEK), and other chemotherapies. Patients classified into the CTLA-4+PD-1 treatment group had to have claims for each within a day of each other and could have PD-1 monotherapy following the 16 weeks or less of combination therapy. BRAF inhibitors included vemurafenib and dabrafenib, and MEK inhibitors included trametinib and cobimetinib. Other chemotherapies included the remaining systemic chemotherapies for melanoma not elsewhere classified (e.g., paclitaxel, dacarbazine, temozolomide).

First-line therapy consisted of the time from the start of therapy until a change in regimen, end of continuous enrollment, or end of the study period, whichever occurred first. A gap in claims for the same regimen of >45 days ended the line of therapy, except for CTLA-4 monotherapy given the set number of treatment administrations (i.e., 4 doses over 16 weeks), where follow-up continued until a change in regimen, end of continuous enrollment, or end of the study period.

Study Variables

Patient characteristics (e.g., age at initiation of first-line therapy; sex; commercial insurance; Charlson Comorbidity Index [CCI] score at initiation of first-line therapy; and use of supportive care agents [antiemetics, growth factors, corticosteroids, and infliximab]) were summarized using descriptive statistics.^{26,27} HCRU was reported by all-cause resources during first-line treatment for the following categories: inpatient hospitalization; outpatient visits (composed of ED visits, outpatient office visits, radiation treatment, diagnostic radiology, laboratory services, and other outpatient care); melanoma treatment; and nonsystemic melanoma treatment pharmacy fills. Costs were inflated to 2017 U.S. dollars using the Consumer Price Index for

medical care.²⁸ Standardized costs were used in lieu of paid costs, since the latter were only available for a subset of patients in the study cohort. Standardized costs were derived from the Centers for Medicare & Medicaid Services costs and were applied to observed HCRU for each patient during first-line therapy.^{29,30}

Statistical Analysis

The number and proportion of patients with at least 1 of the resources of interest were calculated, as was the mean (median, standard deviation [SD]) number of the resources of interest among all patients and among patients with at least 1 claim for the resource of interest for each treatment group. HCRU was reported as per patient per month (PPPM) among all patients (whether they had the resource or not) to account for differences in follow-up time.

Comparisons of the proportion of patients with and rates (PPPM) of HCRU of interest across treatment cohorts, using PD-1 monotherapy as the referent, were made on univariate analyses by chi-square tests and t-tests to assess differences in categorical and continuous variables, respectively. To account for differences in baseline patient characteristics (age at initiation of first-line therapy, sex, commercial insurance, CCI score at initiation of first-line therapy, use of supportive care agents, U.S. region, and presence of brain metastases), multivariable logistic regressions were fit to estimate adjusted odds (odds ratios [ORs]) of an inpatient hospitalization and an ED visit during first-line therapy, given a patient's first-line treatment, using PD-1 as the referent. The list of characteristics for which estimates were adjusted were determined a priori, as deemed clinically relevant by clinicians on the study team.

TABLE 1 Demographics and Patient Characteristics (N=1,599)

	PD-1 (n = 255)		CTLA-4+PD-1 (n = 88)		P Value ^a	CTLA-4 (n = 555)		P Value ^a	BRAF (n = 210)		P Value ^a	BRAF + MEK (n = 102)		P Value ^a	Other Chemotherapies (n = 389)		P Value ^a
Male, n (%)	158	(62.0)	54	(61.4)	0.921	369	(66.5)	0.210	126	(60.0)	0.666	58	(56.9)	0.373	226	(58.1)	0.329
Age at treatment initiation in years, mean ± SD	67.6	± 13.4	63.1	± 13.1	0.007	63.1	± 12.8	<0.001	59.0	± 13.6	<0.001	59.3	± 11.9	<0.001	66.2	± 12.2	0.191
Median	68.0		65.0			63.0			59.0			60.0			67.0		
Region, n (%)					0.657			0.142			0.006			0.077			0.392
Northeast	65	(25.5)	17	(19.3)		123	(22.2)		28	(13.3)		13	(12.7)		85	(21.9)	
South	45	(17.6)	14	(15.9)		119	(21.4)		49	(23.3)		20	(19.6)		76	(19.5)	
West	97	(38.0)	40	(45.5)		186	(33.5)		75	(35.7)		42	(41.2)		133	(34.2)	
Midwest	47	(18.4)	17	(19.3)		127	(22.9)		56	(26.7)		27	(26.5)		92	(23.7)	
Unknown	1	(0.4)	0	(0.0)		0	(0.0)		2	(1.0)		0	(0.0)		3	(0.8)	
Insurance status, n (%)					0.024			<0.001			<0.001			<0.001			0.004
Commercial	67	(26.3)	33	(37.5)		262	(47.2)		126	(60.0)		57	(55.9)		139	(35.7)	
Medicare	120	(47.1)	36	(40.9)		188	(33.9)		50	(23.8)		34	(33.3)		187	(48.1)	
Medicaid	36	(14.1)	16	(18.2)		71	(12.8)		25	(11.9)		9	(8.8)		38	(9.8)	
Unknown/other	32	(12.5)	3	(3.4)		34	(6.1)		9	(4.3)		2	(2.0)		25	(6.4)	
CCI at treatment initiation, mean ± SD	2.8	± 1.7	2.9	± 1.9	0.781	2.4	± 1.7	0.006	2.2	± 1.5	<0.001	2.3	± 1.5	0.014	2.6	± 1.8	0.168
Median	2.0		2.5			2.0			1.5			2.0			2.0		
Metastasis in brain and spinal cord, n (%)	57	(22.4)	27	(30.7)	0.117	189	(34.1)	0.001	88	(41.9)	<0.001	49	(48.0)	<0.001	83	(21.3)	0.760
Follow-up period from first-line start to the end of follow-up in months, mean ± SD	10.3	± 6.5	8.8	± 5.1	0.032	14.5	± 12.4	<0.001	13.1	± 12.9	0.005	11.5	± 8.1	0.180	16.4	± 13.9	<0.001
Median	9.1		7.8			10.6			8.4			9.2			11.6		

^aP value calculated by t-test/Wilcoxon or chi-square/Fisher's exact test comparing means or proportions to PD-1 as indicated.

CCI = Charlson Comorbidity Index; CTLA-4 = cytotoxic T-lymphocyte antigen-4; PD-1 = programmed cell death-1; SD = standard deviation.

Costs were calculated by all-cause total health care costs and for each of the HCRU categories previously described during first-line therapy. Mean (median, SD) costs for each HCRU of interest were reported among all patients and among patients with at least 1 claim for the resource of interest. Cost analyses were performed in parallel for all-cause resource use and reported as PPPM costs. Adjusted PPPM costs were estimated by generalized linear models using log-link and a gamma distribution to account for differences in baseline characteristics (age at initiation of first-line therapy, sex, commercial insurance, CCI score at initiation of first-line therapy, use of supportive care agents, U.S. region, and presence of brain metastases).

Results

Baseline Characteristics

There were 6 first-line treatment groups categorized among 1,599 metastatic melanoma patients with ≥6 months of continuous medical and pharmacy enrollment records before and ≥3 months after first-line treatment start (Figure 1): PD-1 (n = 255), CTLA-4 + PD-1 (n = 88), CTLA-4 (n = 555), BRAF (n = 210), BRAF + MEK (n = 102), and other chemotherapies

(n = 389). The majority was male (57%-62%) across treatment groups. On average, those treated with first-line PD-1 were older at treatment initiation (mean = 67.6 years) compared with other first-line treatment groups (range = 59.0-63.1, all $P < 0.05$), except for other chemotherapy, which had a similar mean age of 66.2 years old at metastatic diagnosis ($P = 0.19$; Table 1).

There were regional differences between patients treated with first-line BRAF compared with first-line PD-1: BRAF had a greater proportion of patients in the Midwest (26.7% vs. 18.4%; $P < 0.01$) and a lower proportion of patients in the Northeast (13.3% vs. 25.5%; $P < 0.01$) compared with PD-1. The proportion of commercially insured patients was lower among PD-1 patients (26.3%) compared with other treatment groups (range = 37.5%-60.0%; all $P < 0.05$). The CCI score was higher among PD-1 patients (mean CCI = 2.8) compared with other groups (mean CCI range = 2.2-2.4; all $P < 0.05$), except for CTLA-4 + PD-1 and other chemotherapies, which had similar mean index scores (2.9 and 2.6, respectively). The incidence of brain metastases was more common among CTLA-4 (34.1%), BRAF (41.9%), and BRAF + MEK (48.0%) compared with PD-1

TABLE 2 Unadjusted Health Care Resource Utilization During First-Line

	PD-1 (n = 255)	CTLA-4 + PD-1 (n = 88)	P Value ^a	CTLA-4 (n = 555)	P Value ^a	BRAF (n = 210)	P Value ^a	BRAF + MEK (n = 102)	P Value ^a	Other Chemotherapies (n = 389)	P Value ^a
Hospitalizations, n (%)	66 (25.9)	40 (45.5)	0.001	221 (39.8)	<0.001	78 (37.1)	0.009	42 (41.2)	0.005	135 (34.7)	0.018
Mean PPPM ± SD	0.06 ± 0.13	0.14 ± 0.23	0.001	0.10 ± 0.20	<0.001	0.11 ± 0.20	0.003	0.16 ± 0.32	0.003	0.09 ± 0.21	0.007
Hospitalization length of stay in days,^b mean PPPM ± SD	2.42 ± 1.58	2.33 ± 1.47	0.749	4.13 ± 24.73	0.310	2.49 ± 1.75	0.806	3.29 ± 2.56	0.055	3.70 ± 15.94	0.360
All-cause 30-day readmissions, n (%)	35 (13.7)	16 (18.2)	0.311	106 (19.1)	0.061	48 (22.9)	0.011	22 (21.6)	0.068	76 (19.5)	0.056
ED visits, n (%)	102 (40.0)	44 (50.0)	0.102	261 (47.0)	0.062	91 (43.3)	0.468	47 (46.1)	0.293	169 (43.4)	0.387
Mean PPPM ± SD	0.09 ± 0.18	0.18 ± 0.24	0.004	0.13 ± 0.22	0.014	0.13 ± 0.22	0.030	0.14 ± 0.23	0.083	0.15 ± 0.31	0.006
Clinic/office visits, n (%)	252 (98.8)	88 (100.0)	0.573	555 (100.0)	0.031	208 (99.0)	1.000	100 (98.0)	0.627	385 (99.0)	1.000
Mean PPPM ± SD	2.43 ± 1.42	2.55 ± 1.88	0.604	2.54 ± 1.89	0.360	2.40 ± 1.69	0.813	2.11 ± 1.32	0.051	2.90 ± 2.19	0.001
Pharmacy claims,^c n (%)	239 (93.7)	79 (89.8)	0.219	526 (94.8)	0.545	200 (95.2)	0.480	99 (97.1)	0.205	365 (93.8)	0.957
Mean PPPM ± SD	2.07 ± 1.55	2.21 ± 1.65	0.489	2.17 ± 1.61	0.401	2.25 ± 1.74	0.252	2.25 ± 1.61	0.331	2.32 ± 1.73	0.065

^aP value calculated by t-test/Wilcoxon or chi-square/Fisher's exact test comparing means or proportions to PD-1 as indicated.

^bLength of stay among those hospitalized.

^cExcluded claims for melanoma treatment.

CTLA-4 = cytotoxic T-lymphocyte antigen-4; ED = emergency department; PD-1 = programmed cell death-1; PPPM = per patient per month; SD = standard deviation.

(22.4%; all $P < 0.05$) and was similar to PD-1 in CTLA-4 + PD-1 (30.7%) and other chemotherapies (21.3%; Table 1).

Health Care Resource Utilization

HCRU among patients with metastatic melanoma treated with a first-line PD-1-blocking antibody was compared with the other treatment groups of interest (Table 2). A significantly lower proportion of PD-1 patients had at least 1 hospitalization during first-line treatment (25.9%) compared with 45.5%, 39.8%, 37.1%, 41.2%, and 34.7% of patients treated with CTLA-4 + PD-1, CTLA-4, BRAF, BRAF + MEK, and other chemotherapy, respectively (all $P < 0.05$; Table 2). The rate of hospitalizations PPPM was statistically significantly lower among those treated with PD-1 (mean PPPM = 0.06) compared with all other treatment groups (mean PPPM range = 0.09–0.14; all $P < 0.01$; Table 2).

While not statistically significantly different, 40.0% of PD-1 patients had an ED visit during first-line treatment, while 50.0%, 47.0%, 43.3%, 46.1%, and 43.4% of patients treated with a CTLA-4 + PD-1, CTLA-4, BRAF, BRAF + MEK, and other chemotherapy, respectively, had at least 1 ED visit during first-line treatment (Table 2). PPPM ED visits were statistically significantly lower among PD-1 (mean PPPM = 0.09) patients compared with all other treatments (mean PPPM range = 0.13–0.18; all $P < 0.05$), except for BRAF + MEK, which was similar (mean PPPM = 0.14; $P = 0.08$). Nearly all patients had office visits and pharmacy claims (Table 2).

After adjusting for differences in baseline patient characteristics, patients treated with CTLA-4 + PD-1, CTLA-4, or BRAF + MEK were more than 2 times as likely to have an inpatient hospitalization compared with PD-1 during first-line

treatment (all $P < 0.05$; Table 3). Patients treated with CTLA-4 had adjusted odds that were 1.44 (95% confidence interval [CI] = 1.02–2.04; $P = 0.038$) times as high as PD-1 patients (Table 3).

Total Cost of Care

Overall mean PPPM health care costs during first-line treatment were \$12,424, \$30,558, \$24,945, \$8,068, \$21,444, and \$6,084 among patients treated with PD-1, CTLA-4 + PD-1, CTLA-4, BRAF, BRAF + MEK, and other chemotherapies, respectively (Table 4). These unadjusted costs were all significantly different compared with PD-1: overall mean PPPM costs were higher for CTLA-4 + PD-1, CTLA-4, and BRAF + MEK and lower for BRAF and chemotherapy. Mean PPPM hospitalization costs were statistically significantly lower in PD-1 (mean PPPM = \$371) compared with all other treatment groups (mean PPPM range = \$598–\$1,066; all $P < 0.05$).

Mean PPPM ED visit costs were statistically significantly lower for PD-1 (mean PPPM = \$35) compared with CTLA-4 (mean PPPM = \$49) and CTLA-4 + PD-1 (mean PPPM = \$61; both $P < 0.05$) but similar for all other treatments (mean PPPM range = \$44–\$56). Total monthly health care costs were driven by mean monthly costs for metastatic melanoma treatment (\$8,567, \$26,125, \$21,156, \$5,343, \$16,145, and \$1,160) for patients treated with PD-1, CTLA-4 + PD-1, CTLA-4, BRAF, BRAF + MEK, and other chemotherapies, respectively (Table 4).

Adjusted total PPPM costs (i.e., sum of melanoma treatment, medical costs, and pharmacy costs) were \$13,059, \$25,583, \$8,158, \$21,517, \$6,361, and \$31,310 for PD-1, CTLA-4 + PD-1, CTLA-4, BRAF, BRAF + MEK, and other chemotherapies. Compared with PD-1 patients, those treated with CTLA-4 + PD-1, CTLA-4, BRAF, BRAF + MEK, and other

TABLE 3 Adjusted Odds of Inpatient Hospitalization and ED Visits

	Inpatient Hospitalization			ED Visit		
	OR ^a	95% CI	P Value	OR ^a	95% CI	P Value
First-line treatment						
CTLA-4+PD-1	2.35	1.32-4.18	0.004	1.29	0.74-2.23	0.366
CTLA-4	2.10	1.43-3.07	<0.001	1.44	1.02-2.04	0.038
BRAF	1.45	0.92-2.29	0.107	1.03	0.67-1.57	0.909
BRAF+MEK	2.15	1.24-3.73	0.007	1.32	0.77-2.24	0.310
Other chemotherapies	1.36	0.91-2.05	0.134	0.98	0.68-1.43	0.932

Note: Referent = PD-1.

^aORs adjusted for age at initiation of first-line therapy, sex, commercial insurance, CCI score at initiation of first-line therapy, use of supportive care agents, U.S. region, and presence of brain metastases.

CI = confidence interval; CCI = Charlson Comorbidity Index; CTLA-4 = cytotoxic T-lymphocyte antigen-4; ED = emergency department; OR = odds ratio; PD-1 = programmed cell death-1.

chemotherapies had incremental adjusted PPPM costs of \$18,162, \$12,123, -\$4,706, \$8,273, and -\$6,049, respectively (all $P < 0.01$; Table 4).

Discussion

In the last few years, multiple novel drugs, including immunotherapies, targeted therapies, and their combination therapies, received FDA approval for the treatment of patients with metastatic melanoma—all of which received a first-line indication. As our health care delivery transitions from a volume- to a value-based care design, real-world evidence, which includes the real-world cost of care, will be critical to guide payers and providers in optimal treatment and sequence selection.^{31,32} For those participating in innovative programs such as the Oncology Care Model, understanding respective treatment HCRU and cost is important to consider along with efficacy and toxicity.

There were important differences in HCRU among patients with metastatic melanoma treated with a first-line PD-1 inhibitor compared with the other treatment groups of interest, which may help health care decision makers differentiate first-line therapies. In particular, there were significantly fewer patients (25.9%) treated with a PD-1-blocking antibody who had a hospitalization during first-line treatment, while 35%-46% of patients treated with another first-line regimen had at least 1 hospitalization during this stage of therapy. Rates of PPPM hospitalizations were lower among those treated with first-line PD-1 compared with all other treatment groups. Similarly, while not statistically significantly different, fewer patients (40%) treated with a PD-1-blocking antibody had an ED visit during first-line therapy, while 43%-50% of patients treated with another first-line regimen had at least 1 ED visit during this stage of therapy. Rates of PPPM ED visits were lower among PD-1 patients compared with all other treatments, except BRAF+MEK.

Overall mean adjusted PPPM health care costs during first-line treatment ranged from \$6,361-\$31,310 across all treatment groups analyzed and from \$13,059-\$31,310 among patients treated with an immunotherapy. These total monthly health care costs were driven by mean monthly costs for metastatic melanoma treatment, ranging from \$1,160-\$26,125 across all treatment groups analyzed and from \$8,567-\$26,125 among patients treated with an immunotherapy. Treatment costs of ipilimumab largely occurred in the first 12 weeks, given the fixed maximum duration of ipilimumab monotherapy, while costs for other metastatic melanoma treatments occurred over longer periods, influencing PPPM costs when costs were averaged across the duration of first-line therapy. While all patients were identified as having metastatic melanoma, disease severity within this group may explain some variation in health care costs. Further research is needed to elucidate drivers of higher health care costs in this population, which may include indicators of greater disease severity and/or poorer prognoses.

Comparisons of this study with previous studies are challenging or simply limited due to differences in study design and/or patient populations. However, Reyes et al. (2013) found a mean PPPM of \$11,464 for patients with 1-3 metastases and \$15,662 mean PPPM for patients with ≥ 4 metastasis.³³ They analyzed a younger patient population (mean age 57.2 years vs. 62 years in the current study) and derived data from a commercial payer database, which is likely not generalizable to the broader metastatic melanoma population across payer types where the mean age may be higher. Further, costs estimated by Reyes et al. were before the introduction of more costly melanoma treatments, including ipilimumab. Toy et al. (2015) estimated the mean total costs PPPM at \$35,472 among those treated with ipilimumab and \$17,793 for the vemurafenib cohort, albeit again among a commercially insured population.¹⁶

In the current study, we found a mean adjusted total cost PPPM for those treated with ipilimumab monotherapy to be similar (\$31,310) to the Toy et al. results and a mean total cost PPPM for those treated with BRAF monotherapy (the current study included vemurafenib and dabrafenib, whereas Toy et al. included vemurafenib only; however, variation between these 2 is likely to be substantially lower (\$8,158). Differences in the latter could be partially explained by the different time periods studied and the minimum follow-up period used (1 month vs. 3 months minimum in the Toy et al. and current studies, respectively).

Work by Chang et al. (2015) reports results of systemic therapies for metastatic melanoma before the introduction of nivolumab and pembrolizumab. Unadjusted monthly costs for vemurafenib were \$17,223 per patient and \$65,313 per patient for ipilimumab.¹⁷ It is important to point out that that analysis included any line of therapy, whereas the current study focused on the first-line setting. Further, the cohort analyzed by Chang et al. was limited to a commercially insured population with a

TABLE 4 PPPM Health Care Costs During First-Line Treatment

	PD-1 (n = 255)	CTLA-4+PD-1 (n = 88)	Diff. ^a	P Value ^b	CTLA-4 (n = 555)	Diff. ^a	P Value ^b		
Unadjusted all-cause PPPM cost in dollars, mean ± SD									
Total	12,424 ± 6,429	30,558 ± 21,368	18,134	<0.001	24,945 ± 17,408	12,521	<0.001		
Melanoma treatment related	8,567 ± 4,212	26,125 ± 20,029	17,558	<0.001	21,156 ± 16,028	12,589	<0.001		
Pharmacy ^c	2,061 ± 2,849	2,336 ± 3,063	275	0.445	1,958 ± 2,473	-103	0.619		
Total medical ^d	1,796 ± 3,409	2,097 ± 1,951	301	0.313	1,831 ± 2,594	35	0.884		
Hospitalization	371 ± 885	1,066 ± 1,714	695	<0.001	726 ± 1,630	355	<0.001		
ED	35 ± 75	61 ± 93	26	0.018	49 ± 124	14	0.044		
Clinic/office visits	517 ± 550	488 ± 401	-28	0.604	528 ± 966	12	0.826		
Radiation	48 ± 199	204 ± 512	156	0.007	71 ± 294	23	0.197		
Diagnostic radiology	108 ± 172	92 ± 131	-16	0.353	100 ± 149	-8	0.503		
Laboratory tests	60 ± 68	63 ± 63	3	0.734	56 ± 100	-4	0.520		
Other outpatient visits	795 ± 3,061	720 ± 1,197	-75	0.745	624 ± 1,305	-171	0.392		
Adjusted ^e all-cause total PPPM costs in dollars, mean (95% CI)	13,059 (11,263-15,140)	31,310 (25,890-37,869)	18,162	<0.001	25,583 (22,415-29,199)	12,123	<0.001		
	BRAF (n = 210)	Diff. ^a	P Value ^b	BRAF + MEK (n = 102)	Diff. ^a	P Value ^b	Other Chemotherapies (n = 389)	Diff. ^a	P Value ^b
Unadjusted all-cause PPPM cost in dollars, mean ± SD									
Total	8,068 ± 4,907	-4,356	<0.001	21,444 ± 13,133	9,020	<0.001	6,084 ± 6,226	-6,340	<0.001
Melanoma treatment related	5,343 ± 3,517	-3,224	<0.001	16,145 ± 11,597	7,578	<0.001	1,160 ± 2,344	-7,407	<0.001
Pharmacy ^c	1,711 ± 2,313	-351	0.144	3,534 ± 5,168	1,472	0.008	2,307 ± 3,905	246	0.357
Total medical ^d	1,014 ± 1,317	-782	0.001	1,766 ± 2,189	-30	0.922	2,617 ± 3,956	822	0.005
Hospitalization	598 ± 1,288	227	0.031	1,047 ± 2,016	676	0.001	638 ± 1,728	267	0.010
ED	44 ± 112	9	0.316	56 ± 124	22	0.100	44 ± 105	9	0.212
Clinic/office visits	312 ± 452	-205	<0.001	424 ± 386	-93	0.073	1,079 ± 2,336	562	<0.001
Radiation	21 ± 97	-27	0.057	189 ± 1,202	141	0.241	55 ± 256	7	0.716
Diagnostic radiology	68 ± 163	-40	0.011	113 ± 179	5	0.809	81 ± 154	-28	0.037
Laboratory tests	26 ± 38	-35	<0.001	28 ± 37	-32	<0.001	29 ± 49	-32	<0.001
Other outpatient visits	267 ± 504	-528	0.007	513 ± 769	-282	0.172	986 ± 2,314	191	0.397
Adjusted ^e all-cause total PPPM costs in dollars, mean (95% CI)	8,158 (7,024-9,473)	-4,706	<0.001	21,517 (17,953-25,791)	8,273	<0.001	6,361 (5,560-7,278)	-6,049	<0.001

^aCalculated compared with first-line PD-1 monotherapy (for adjusted costs, difference represents the incremental adjusted costs compared with first-line PD-1 monotherapy).

^bP values calculated by t-tests comparing means of each treatment group compared with first-line PD-1 monotherapy (P values for comparisons of adjusted costs derived from beta coefficients of each treatment group compared with first-line PD-1 monotherapy).

^cPharmacy costs, not including cost of melanoma treatment (i.e., BRAF/MEK).

^dTotal medical costs include all medical claims (excluding pharmacy claims and cost of melanoma treatment).

^eAdjusted costs estimated by generalized linear model using a gamma distribution and log-link to adjust for age at first-line initiation; sex; commercial insurance status; CCI score at first-line initiation; use of supportive care agents (antiemetics, growth factors, corticosteroids, or infliximab); U.S. region; and presence of brain metastases. CCI = Charlson Comorbidity Index; CI = confidence interval; CTLA-4 = cytotoxic T-lymphocyte antigen-4; Diff. = difference; ED = emergency department; PD-1 = programmed cell death-1; PPPM = per patient per month; SD = standard deviation.

mean age of 57.5 years; the current study describes mean ages of 63-68 years across first-line treatment groups.

Outside the United States, hospitalizations for ipilimumab have been reported among 57% of melanoma patients, which was higher than the 40% reported herein.³⁴ Similar to the Chang et al. study, hospitalizations were considered in any line of therapy in which ipilimumab was given, whereas the current study focused on the first-line setting. Another study reported annual costs of hospitalizations in France among patients with melanoma before progression at 5,036 euros (2017), which, in

current 2019 U.S. dollars, is roughly \$5,720.³⁵ This estimate falls within the range of annualized PPPM costs associated with hospitalizations reported in this study across first-line treatment groups (\$4,452-\$12,798). Additional studies in the United States assessing costs of care for metastatic melanoma that consider contemporary, recently approved systemic therapies are needed to make further comparisons to the results of the current study.

There are several important strengths of this current study. There is a dearth of data on the economic burden of

metastatic melanoma in the context of the newer PD-1 inhibitors in commercial and government payer settings. Further, all FDA-approved therapies for metastatic melanoma at the time of this study were included in the analysis. This study begins to fill the economic evidence gap by using medical and pharmacy claims data for patients with metastatic melanoma outside of the clinical trial context. While this often presents methodological challenges, it depicts real use of medications among a population that is likely more diverse than that observed in the clinical trial setting. Differential follow-up time was partially addressed by the use of PPPM units, and odds of hospitalization and ED visits, as well as adjusted costs, were estimated by multivariable analyses to control for potential confounding due to differences in baseline patient characteristics. Results of this study may help quantify the economic burden of treatment for metastatic melanoma and help identify approaches that are less costly in this population.

Limitations

Limitations of this study should be considered to put the results presented into context. The clinical outcome of survival was not available from the dataset, which is an important factor when evaluating available treatments. Adjusted estimates in these analyses controlled for potential confounding, but inherent with any observational study, residual confounding or unobserved confounding may still be present. Standardized costs may differ from paid costs in the real world, since they remove any effect of specific payer reimbursement policies.

While payer claims data do provide valuable insight into real-world use and costs of treatments, they are collected for administrative purposes and not for research. Inherent with all payer claims-based analyses, the identification of metastatic melanoma relies on the accuracy of claims coding; errors of omission or commission are possible. While the follow-up time was up to 3 years following the launch of some of the newer agents, this relatively limited follow-up may result in some right censoring of patients. The costs and resource utilization presented in the current analyses represent those during the period immediately following the index date and may not represent the long-term clinical practice for patients with metastatic melanoma.

Further research is needed that builds upon the current study to characterize the clinical outcomes in this population treated with the newer immunotherapies, as well as with more recently approved regimens (e.g., encorafenib and binimetinib).

Future work should assess HCRU and costs of individual regimens and within-class regimens. With a better understanding of clinical outcomes in the real-world setting, a more complete representation of the overall burden of metastatic melanoma can be realized, ultimately leading to identification of appropriate therapies to treat this population.

Conclusions

Not long ago, the treatment landscape of melanoma drastically changed with the introduction of immunotherapies and the BRAF and MEK inhibitors. Now, the landscape has once again evolved to include the PD-1 inhibitors pembrolizumab and nivolumab in monotherapy, as well as the immunotherapy combination of ipilimumab plus nivolumab. This study provides an early and contemporary investigation into the use of PD-1 monotherapy, CTLA-4 monotherapy, CTLA-4+PD-1 combination therapy, BRAF inhibitor monotherapy, BRAF+MEK inhibitor combination therapy, and chemotherapy in the real-world setting among patients with metastatic melanoma in the United States.

Hospitalizations and ED visits represent important health care resources for patients with metastatic melanoma, and PPPM rates were lowest among PD-1 compared with any other systemic therapies (except for ED visits compared with BRAF+MEK). Total monthly costs varied substantially across first-line regimens and were significantly lower in PD-1 compared with CTLA-4, CTLA-4+PD-1, and BRAF+MEK. Differences in resource use and costs should be considered by health care decision makers in view of a value-based care framework, where cost is weighed alongside clinical effectiveness to inform the selection of the optimal first-line therapy for patients.

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