Metastatic Melanoma: Treatment and Survival in the US after the Introduction of Ipilimumab and Vemurafenib

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Keywords

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Summary

Introduction: The 5-year survival of metastatic melanoma is < 18%. Historically, treatment options were limited. In 2011, 2 new agents were approved. **Methods:** We re-abstracted the medical records of a random sample (n = 520) of metastatic melanoma patients who had been diagnosed in 2011 and reported to population-based registries in the U.S. We also queried their treating physicians. Factors associated with treatment and survival were assessed using logistic and Cox proportional hazards regressions, respectively. **Results:** 21.4% of patients received no treatment, 20.8% received ipilimumab and 57.5% of patients with BRAF-positive tumors received vemurafenib/dabrafenib. Receipt of ipilimumab was less likely among patients of 75 years or older (vs. < 55 years: odds ratio (OR) 0.32; 95% confidence interval (CI) 0.15–0.66) and patients without private/military insurance. 46.8% of patients received BRAF testing. Receipt of BRAF testing was less likely among patients of 65 years or more and uninsured patients (OR 0.22; 95% CI 0.07–0.65). Receipt of ipilimumab was associated with better survival during the first 18 months after diagnosis (hazard ratio (HR) 0.66; 95% CI 0.51–0.84) and vemurafenib/dabrafenib with better survival during the first 10 months after diagnosis (HR 0.51; 95% CI 0.36–0.73). **Conclusion:** The initial dissemination of ipilimumab and vemurafenib/dabrafenib was limited. Additional research is needed to investigate the apparent lack of long-term survival benefit from these agents.

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Introduction

The incidence of melanoma of the skin is steadily increasing; approximately 76,000 patients will be diagnosed in 2016 and more than 10,000 patients will die from the disease [1]. Overall, the mortality rate has also increased slightly from 2.07/100,000 in 1975 to 2.66/100,000 in 2013 [2]. Metastatic melanoma, which is present in about 4% of melanoma patients at diagnosis, is a devastating disease. The 5-year survival for patients diagnosed between 2006 and 2012 with distant disease was 17.9% [2].

Despite hundreds of clinical trials and attempts to unlock the therapeutic potential of a wide variety of agents, until recently only 2 agents were approved to treat metastatic melanoma and their effectiveness was limited. For decades dacarbazine (DTIC), an alkylating agent, was the standard systemic therapy for melanoma, despite the fact that it has never been shown to convey a survival benefit [3]. Tumor-infiltrating lymphocytes are often present in melanoma lesions and melanomas have been observed to spontaneously regress [4]; thus, many efforts have been made to identify effective immunotherapies. In 1998, interleukin-2 (IL-2) was approved to great fanfare. Unfortunately, IL-2 proved extremely toxic and was generally administered only in specialized centers with experienced personnel, and even then, it was associated with limited benefit [3, 5, 6]. Given the dearth of options, physicians treating melanoma often resorted to non-standard therapies based on case reports or personal experience.

Then in 2011, 2 promising new agents, ipilimumab and vemurafenib, were approved. Approval was granted in March 2011 for ipilimumab, a human monoclonal antibody that enhances the immune response by blocking cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), which is a negative regulator of T cells. 2 phase III randomized clinical trials indicated that receipt of ipilimumab was associated with improved median survival among patients with advanced melanoma [7, 8]. Meanwhile, multiple oncogenic activating mutations had been identified in melanoma and therapies targeted to inhibit cells with these mutations began to be de-

veloped. 1 of the most promising targets was the *BRAF* gene, specifically the codon 600 driver mutations, which are present in up to 60% of patients with melanoma and often occur early in the pathogenesis and are maintained through progression [9, 10]. Vemurafenib, a *BRAF* inhibitor, was approved to treat advanced melanomas with the *BRAF*^{V600E} mutation in August 2011. Results from a phase III randomized clinical trial indicated improved survival among patients treated with vemurafenib [9, 11].

The primary aims of this study were to identify factors associated with the treatment received and with survival of a population-based sample of patients with metastatic melanoma who were diagnosed during the first year of ipilimumab and vemurafenib approval. In order to carry out this research we analyzed data collected by the National Cancer Institute (NCI), which included patients diagnosed in 2011 with histologically confirmed metastatic melanoma who were ascertained through the Surveillance, Epidemiology and End Results (SEER) program.

Methods

The SEER program consists of population-based registries that collect demographic, tumor, diagnostic and treatment characteristics, as well as vital status on all cases of cancer occurring within a defined geographic region [12]. SEER covers about 28% of the US population. The primary data collection is hospital-based; therefore, treatment is often underreported. Because of this, the NCI annually conducts patterns of care studies on a sample of patients diagnosed with specific cancer types. Briefly, after obtaining institutional review board approval, as required by the registries, a central training is conducted annually to assure consistent abstracting and coding of the data. Data are then re-abstracted from hospital medical records, and the patients’ treating physicians were contacted to verify all treatment given; data ascertainment are completed at least 1-year post-diagnosis for all included patients. Each physician is also asked for the names and addresses of others who might have treated the patient and these individuals are then contacted.

Patients diagnosed in 2011 with a new, histologically confirmed metastatic melanoma were eligible for inclusion in the patterns of care study data that were used for the current analyses. Patients were ineligible if they were younger than 20 years old or had metastatic melanoma with a primary site other than skin. Patients were stratified by registry and a random sample of eligible patients was selected. Information on personal and family history of melanoma, *BRAF* mutation status, primary lesion ulceration, presence of positive clinical nodes, insurance status, and treatment, including specific agents given and participation in a clinical trial, were available from the patterns of care study. Hospital characteristics, including bed size and presence of an approved residency training program were also available. All comorbidities recorded in the hospital record were abstracted and centrally coded before being analyzed using the Charlson comorbidity index [13], excluding melanoma. Insurance was categorized as any private or military insurance, any Medicaid, Medicare only, no insurance and all other insurance, including unknown. Age, sex, race/ethnicity, marital status and vital status up to 31 December 2013 were available in the SEER data. Patient-level socioeconomic variables were not available, but residential census tract median household income and percentage of individuals aged 25 years or older with at least a high school education were available, based on the Census 2000 data.

Weighted percentages of patient characteristics and the treatments given were calculated with stratum-specific sample weights to account for the complex survey design. The percentages reported are weighted to reflect the population from which the sample was drawn. Sample weights were calculated as the inverse of the sampling proportion for each sampling stratum. Standard errors were obtained from the Taylor linearization method for variance estimation.

Stratum-specific sample weights were used in logistic regression models to examine factors associated with receipt of ipilimumab and *BRAF* testing. Variations in Kaplan-Meier all-cause survival curves stratified by receipt of ipilimumab and vemurafenib/dabrafenib were assessed using the log-rank test. (Although dabrafenib, another *BRAF* inhibitor, was not approved until May 2013 to treat patients with the *BRAF*^{V600E} mutation, a few patients (n < 5) included in the current data had received it; therefore, due to small sample size concerns vemurafenib and dabrafenib were combined in all analyses.) Cox proportional hazards models were then constructed to examine factors associated with all-cause mortality. Factors identified as being associated with the outcomes of interest during bivariate analyses (p < 0.15) were included in initial multivariate models. To obtain the most parsimonious models, factors that were no longer significant (p > 0.05) were then excluded from the final models. Violations of the Cox proportional hazards assumption were assessed by comparing Kaplan-Meier survival curves stratified by covariate categories. Spline functions were included if the relationship of the survival curves by covariate level were inconsistent over time (e.g. if the survival curves converged or crossed); inclusion of spline functions in a Cox proportional hazards regression model allows for the estimation of separate hazard ratios (HRs) before and after the placement of the spline [14]. Analyses were conducted using SAS version 9.3 (SAS Institute, Cary, North Carolina) and SUDAAN version 11.0.1 (Research Triangle Institute, Raleigh, NC). All statistical tests were 2 sided.

Results

The current study included 520 patients with metastatic melanoma. At diagnosis the majority of the patients were older than 65 years (53.4%), male (70.9%), non-Hispanic white (92.4%) and married (56.8%; table 1). Most of the patients had a Charlson Score of zero (68.2%) and no personal (88.2%) or family history of melanoma (94.3%). The majority of the patients had private or military

Table 1. Demographic and clinical characteristics of patients with metastatic melanoma diagnosed in 2011, NCI’s Patterns of Care Study

Characteristic	n ^a	% ^b
Age, years		
< 55	121	23.4
55–64	119	23.1
65–74	133	25.4
75+	147	28.0
Sex		
Male	370	70.9
Female	150	29.1
Race/ethnicity		
NHW	480	92.4
Hispanic	24	4.6
API	10	1.9
Other	6	1.1
Marital status		
Married, living as	295	56.8
Other	225	43.2
Charlson score		
0	354	68.2
1+	166	31.8
Personal history of melanoma		
Yes	62	11.8
No, unknown	458	88.2

Table 1. Continued on next page

Table 1. *Continued*

Characteristic	n ^a	% ^b
Family history of melanoma		
Yes	29	5.7
No, unknown	491	94.3
Income (quartiles) ^c		
\$15,769–41,350	124	24.6
\$41,351–55,155	128	24.7
\$55,156–73,178	130	24.7
\$73,179–163,393	133	24.9
Missing	5	1.1
Education, % (quartiles) ^d		
28.30–77.38	126	24.5
77.39–86.14	126	24.9
86.15–91.26	133	24.8
91.27–100.00	130	24.8
Missing	5	1.1
Insurance		
Private/military	338	65.0
Any Medicaid	82	15.9
Medicare only	69	13.4
No insurance	25	4.6
Other/unknown	6	1.0
Hospital bed size		
OPD/unknown	15	2.9
< 200 beds	90	17.2
200–299 beds	81	15.3
300–399 beds	120	23.6
400–499 beds	69	13.3
500+ beds	145	27.7
Residency training program		
Yes	290	54.8
No/unknown	230	45.2
Clinical trial participation		
Yes	38	7.3
No/unknown	482	92.7
Clinical nodes present		
Yes	156	29.7
No/unknown	364	70.4
Ulceration		
Yes	75	14.8
No/unknown	445	85.2
<i>BRAF</i> mutation		
Not performed	219	42.1
Negative for mutation	139	26.8
Positive for mutation	87	16.9
Performed, results unknown	16	3.1
Unknown if performed	59	11.1
Vital status as of 31 December 2013		
Alive	118	22.9
Dead	402	77.1

^aUnweighted sample size.^bWeighted percentages.^cMedian household income for the census tract where the patient resided at the time of cancer diagnosis.^dPercentage of individuals age 25 or older with at least a high school education in the census tract where the patient resided at the time of cancer diagnosis. API = Asian Pacific Islander, NCI = National Cancer Institute, NHW = Non-Hispanic white, OPD = outpatient department.**Table 2.** Treatment received by patients with metastatic melanoma diagnosed in 2011, NCI's Patterns of Care Study

	n ^a	% ^b
Treatment, mutually exclusive		
No treatment	111	21.4
Surgery only	64	12.6
Radiation only	70	13.4
Systemic therapy only	81	15.5
Surgery and radiation	21	3.9
Surgery and systemic	58	11.1
Radiation and systemic	89	17.2
Surgery, radiation and systemic	26	4.9
Type of systemic therapy, not mutually exclusive		
Chemotherapy, any	121	23.3
Carboplatin	25	4.7
Cisplatin	12	2.3
Dacarbazine	24	4.4
Paclitaxel	29	5.5
Temozolomide	71	13.8
Other	23	4.5
Immunotherapy		
Ipilimumab	109	20.8
Other antibody therapy ^c	11	2.1
Other immunotherapy ^d	30	6.0
Targeted therapy		
Vemurafenib or dabrafenib	66	12.5
Among <i>BRAF</i> +	51	57.5
Among <i>BRAF</i> - or unknown	15	3.4
TKI inhibitor ^e	10	2.0

^aUnweighted sample size.^bWeighted percentage of patients receiving each treatment.^cRituximab, bevacizumab, denosumab, pidilizumab, pembrolizumab, and farletuzumab.^dHigh-dose IL-2, IL-2, interferon α , Peginterferon α -2b.^eImatinib, axitinib, pazopanib, and nilotinib.

TKI = tyrosine-kinase inhibitor, IL = interleukin.

insurance (65.0%) and were treated in hospitals that had 300 or more beds (64.6%) and in a facility with a residency training program (54.8%). At diagnosis, 29.7% of the patients had clinical nodes present, 14.8% had a primary lesion ulceration and 16.9% were known to be *BRAF*-positive. Slightly more than 7% of the patients participated in a clinical trial and 77.1% were deceased by the end of 2013.

Overall Treatment

While almost a quarter (21.4%) of the patients did not receive any treatment, 32.5% of the patients received surgery, 39.4% received radiation, and 48.7% received systemic therapy (not mutually exclusive; table 2). Among patients who received radiation and/or systemic therapy in addition to surgery, approximately 90% received surgery first (data not shown).

When systemic therapy was further categorized it was estimated that 20.8% of patients received ipilimumab and 12.5% received vemurafenib or dabrafenib. (As mentioned above, only a few ($n < 5$) patients received dabrafenib; therefore, vemurafenib and dab-

rafenib were combined in all analyses.) Utilization of vemurafenib/dabrafenib varied by *BRAF* mutation status. Roughly half of the patients with *BRAF*-positive tumors (n = 51; 57.5%) and 3.4% (n = 15) of patients with *BRAF*-negative or -unknown tumors received vemurafenib/dabrafenib. (The small sample size of patients receiving vemurafenib/dabrafenib precluded assessing factors associated with the receipt of these agents.) It was also estimated that 23.3% of patients received chemotherapy; 2.1% received another antibody; 6.0% received other immunotherapy and 2.0% received a tyrosine-kinase inhibitor.

Ipilimumab

In bivariate analyses, receipt of ipilimumab was less likely among patients who were older, not married, and did not have private or military insurance, and/or had clinical nodes present, a primary lesion ulceration, surgery or chemotherapy (table 3). Receipt

Table 3. Factors associated with receipt of ipilimumab among patients with metastatic melanoma diagnosed in 2011, NCI's Patterns of Care Study

Characteristic	% ^a	pb	OR ^c	95% CI
Age, years				
< 55	24.7	< 0.01	1.00	reference
55–64	27.2		1.02	0.55–1.88
65–74	23.5		0.94	0.49–1.82
75+	9.8		0.32	0.15–0.66
Sex				
Male	20.2	0.57		
Female	22.4			
Race/ethnicity				
NHW	20.9	0.80		
Hispanic	16.8			
API	31.3			
Other	15.6			
Marital status				
Married, living as	25.0	< 0.01		
Other	15.3			
Charlson score				
0	20.0	0.52		
1+	22.5			
Personal history of melanoma				
Yes	19.2	0.74		
No/unknown	21.0			
Family history of melanoma				
Yes	19.9	0.90		
No/unknown	20.9			
Income (quartiles)				
\$15,769–41,350	17.5	0.22		
\$41,351–55,155	16.2			
\$55,156–73,178	23.4			
\$73,179–163,393	25.1			
Missing	42.2			
Education, % (quartiles)				
28.30–77.38	19.1	0.41		
77.39–86.14	17.5			
86.15–91.26	20.5			
91.27–100.00	25.2			
Missing	42.2			

Characteristic	% ^a	pb	OR ^c	95% CI
Insurance				
Private/military	25.4	< 0.01	1.00	reference
Any Medicaid	16.5		0.50	0.26–0.96
Medicare only	9.8		0.37	0.15–0.90
No insurance	4.5		0.10	0.01–0.78
Other/unknown	17.2		0.97	0.06–15.60
Hospital bed size				
OPD, unknown	25.9	0.16		
< 200 beds	20.8			
200–299 beds	12.0			
300–399 beds	18.1			
400–499 beds	21.8			
500+ beds	27.1			
Residency training program				
Yes	26.6	< 0.01	1.00	reference
No/unknown	13.8		0.47	0.29–0.76
Clinical trials participation				
Yes	45.5	< 0.01	1.00	reference
No/unknown	18.9		0.35	0.16–0.75
Clinical nodes present				
Yes	28.2	< 0.01		
No/unknown	17.7			
Ulceration				
Yes	30.3	0.03	1.00	reference
No/unknown	19.2		0.54	0.30–0.97
Surgery				
Yes	26.5	0.03		
No/unknown	18.1			
Radiation				
Yes	23.3	0.26		
No/unknown	19.2			
Vemurafenib or dabrafenib				
Yes	25.7	0.31		
No/unknown	20.1			
Chemotherapy, any				
Yes	27.6	0.04		
No/unknown	18.8			
Other antibody therapy ^d				
Yes	27.8	0.57		
No/unknown	20.7			
Other immunotherapy ^e				
Yes	32.0	0.12		
No/unknown	20.1			
TKI inhibitor ^f				
Yes	19.9	0.95		
No/unknown	20.8			
Vital status as of 31 December 2013				
Alive	23.4	0.63		
Dead	20.3			

^aWeighted percentage of patients in each row that received ipilimumab.

^bBivariate chi² p value.

^cOR from a logistic regression model adjusted for the variables that were found to have a bivariate Chi² p ≤ 0.15 and remained significant in multivariate model.

^dRituximab, bevacizumab, denosumab, pidilizumab, pembrolizumab, and farletuzumab.

^eHigh-dose IL-2, IL-2, interferon α, and Peginterferon α-2b.

^fImatinib, axitinib, pazopanib, and nilotinib.

API = Asian Pacific Islander, CI = confidence interval, NCI = National Cancer Institute, NHW = non-Hispanic white, OPD = outpatient department, OR = odds ratio, TKI = tyrosine kinase inhibitor.

of ipilimumab was also less likely among patients who obtained care at a hospital without a residency program and did not participated in a clinical trial. When included in a multivariate logistic regression model, receipt of ipilimumab remained less likely among patients who were older (> 75 vs. < 55 years: odds ratio (OR) 0.32; 95% confidence interval (CI) 0.15–0.66); did not have private or military insurance; obtained care at a hospital without a residency program (OR 0.47; 95% CI 0.29–0.76); did not participated in a clinical trial (OR 0.35; 95% CI 0.16–0.75) and did not have a primary lesion ulceration (OR 0.54; 95% CI 0.30–0.97).

BRAF testing

Bivariate analyses showed that *BRAF* testing was less likely among patients who were older, not married, uninsured, treated in a hospital without a residency program and among patients without clinical nodes and primary lesion ulceration (table 4). *BRAF* testing was also less likely among patients who had a personal history of melanoma and had not participated in a clinical trial. When included in a multivariate logistic regression model, *BRAF* testing remained less likely among patients who were older (65–74 vs. < 55: OR 0.54; 95% CI 0.30–0.95 and ≥ 75 vs. < 55: OR 0.50; 95% CI 0.29–0.86), not married (OR 0.66; 95% CI 0.45–0.97), uninsured (vs. private or military insurance: OR 0.22; 95% CI 0.07–0.65), treated in a hospital without a residency program (OR 0.64; 95% CI 0.44–0.93) and who had not participated in a clinical trial (OR 0.30; 95% CI 0.14–0.66).

Survival

Receipt of ipilimumab was associated with a significant improvement in median survival (12 vs. 7 months; $p < 0.01$) compared to patients who did not receive ipilimumab, and receipt of vemurafenib/dabrafenib was associated with a non-significant improvement in median survival (11 vs. 7 months; $p = 0.18$; fig. 1, table 5). The survival curves converged at around 18 months of follow-up by receipt of ipilimumab status and at approximately 10 months of follow-up by receipt of vemurafenib/dabrafenib sta-

Table 4. Factors associated with *BRAF* testing among patients diagnosed with metastatic melanoma in 2011, NCI's Patterns of Care Study

Characteristic	% ^a	p ^b	OR ^c	95% CI
Age, years				
< 55	50.8	0.11	1.00	reference
55–64	53.8		0.97	0.56–1.70
65–74	44.3		0.54	0.30–0.95
75+	40.0		0.50	0.29–0.86
Sex				
Male	48.7	0.19		
Female	42.2			
Race/ethnicity				
NHW	47.2	0.76		
Hispanic	39.9			
API	51.0			
Other	31.1			

Characteristic	% ^a	p ^b	OR ^c	95% CI
Marital status				
Married, living as	51.8	< 0.01	1.00	reference
Other	40.2		0.66	0.45–0.97
Charlson score				
0	46.2	0.67		
1+	48.2			
Personal history of melanoma				
Yes	38.0	0.14		
No, unknown	48.0			
Family history of melanoma				
Yes	51.0	0.64		
No, unknown	46.5			
Income (quartiles)				
\$15,769–41,350	41.8	0.70		
\$41,351–55,155	47.9			
\$55,156–73,178	49.0			
\$73,179–163,393	47.7			
Missing	63.7			
Education, % (quartiles)				
28.30–77.38	40.0	0.46		
77.39–86.14	47.7			
86.15–91.26	49.0			
91.27–100.00	49.7			
Missing	63.7			
Insurance				
Private/ military	49.5	0.06	1.00	reference
Any Medicaid	41.5		0.73	0.43–1.24
Medicare only	49.8		1.47	0.83–2.59
No insurance	21.5		0.22	0.07–0.65
Other/ unknown	31.0		0.95	0.18–4.98
Hospital bed size				
OPD, unknown	55.5	0.32		
< 200 beds	39.0			
200–299 beds	39.9			
300–399 beds	49.0			
400–499 beds	49.3			
500+ beds	51.4			
Residency training program				
Yes	52.5	< 0.01	1.00	reference
No/unknown	39.9		0.64	0.44–0.93
Clinical trials participation				
Yes	75.0	< 0.01	1.00	reference
No/unknown	44.6		0.30	0.14–0.66
Clinical nodes present				
Yes	53.0	0.07		
No/unknown	44.2			
Ulceration				
Yes	55.9	0.09		
No/unknown	45.2			

^aWeighted percentage of patients in each row that received *BRAF* testing.

^bBivariate Chi² p value.

^cOR from a logistic regression model adjusted for the variables that were found to have a Chi² $p \leq 0.15$ and that remained significant $p \leq 0.05$ in the multivariate model.

API = Asian Pacific Islander; CI = confidence interval; NCI = National Cancer Institute; NHW = non-Hispanic white; OPD = outpatient department; OR = odds ratio.

Fig. 1. Kaplan-Meier survival curves by receipt of (A) ipilimumab and (B) vemurafenib or dabrafenib, among patients diagnosed with metastatic melanoma in 2011, NCI's Patterns of Care Study. Survival up to 31 December 2013.

Table 5. Factors associated with all-cause survival up to 31 December 2013 among patients diagnosed with metastatic melanoma in 2011, NCI's Patterns of Care Study

Characteristic		Bivariate			Multivariate	
		HR	95% CI	p ^a	HR ^b	95% CI
Age, years						
	< 55	1.00	reference	0.04		
	55–64	1.38	1.03–1.86			
	65–74	1.31	0.98–1.75			
	75+	1.49	1.13–1.97			
Sex						
	Male	1.00	reference	0.21		
	Female	0.86	0.69–1.08			
Race/ethnicity						
	NHW	1.00	reference	0.45		
	Hispanic	1.07	0.71–1.62			
	API	1.13	0.74–1.72			
	Other	0.43	0.14–1.32			
Marital status						
	Married, living as	1.00	reference	< 0.01	1.00	reference
	Other	1.41	1.16–1.70		1.39	1.14–1.70
Charlson score						
	0	1.00	reference	0.09	1.00	reference
	1+	1.19	0.97–1.44		1.23	1.00–1.51
Personal history of melanoma						
	No/unknown	1.00	reference	0.87		
	Yes	1.02	0.77–1.36			
Family history of melanoma						
	No/unknown	1.00	reference	< 0.01	1.00	reference
	Yes	0.44	0.28–0.70		0.48	0.28–0.79
Income (quartiles)						
	\$15,769–41,350	1.00	reference	0.06		
	\$41,351–55,155	0.95	0.73–1.24			
	\$55,156–73,178	0.78	0.59–1.02			
	\$73,179–163,393	0.71	0.54–0.93			
	Missing	1.25	0.61–2.54			
Education % (quartiles)						
	28.30–77.38	1.00	reference	0.09		
	77.39–86.14	0.96	0.73–1.27			
	86.15–91.26	1.03	0.80–1.34			
	91.27–100.00	0.74	0.57–0.97			
	Missing	1.35	0.66–2.76			
Insurance						
	Private/military	1.00	reference	0.12		
	Any Medicaid	1.35	1.05–1.75			
	Medicare only	1.23	0.92–1.65			
	No insurance	1.47	0.83–2.62			
	Other/unknown	1.17	0.46–2.93			

Table 5. Continued on next page

Table 5. Continued

Characteristic		Bivariate			Multivariate	
		HR	95% CI	p ^a	HR ^b	95% CI
Hospital bed size						
	OPD, unknown	1.00	reference	0.20		
	< 200 beds	1.55	0.87–2.77			
	200–299 beds	1.33	0.75–2.38			
	300–399 beds	1.06	0.59–1.88			
	400–499 beds	1.4	0.77–2.52			
	500+ beds	1.23	0.70–2.14			
Residency training program						
	No/unknown	1.00	reference	0.29		
	Yes	1.11	0.91–1.35			
Clinical trials participation						
	No/unknown	1.00	reference	< 0.01		
	Yes	0.64	0.47–0.85			
Clinical nodes present						
	No/unknown	1.00	reference	0.53		
	Yes	1.07	0.87–1.30			
Ulceration						
	No/unknown	1.00	reference	0.22		
	Yes	1.15	0.92–1.45			
Surgery						
	No/unknown	1.00	reference	< 0.01	1.00	reference
	Yes	0.65	0.53–0.80		0.70	0.57–0.86
Radiation						
	No/unknown	1.00	reference	< 0.01	1.00	reference
	Yes	1.36	1.12–1.64		1.23	1.00–1.51
Ipilimumab						
< 18 months	No/unknown	1.00	reference	< 0.01	1.00	reference
	Yes	0.64	0.51–0.81		0.66	0.51–0.84
> 18 months	No, unknown	1.00	reference	0.08	1.00	reference
	Yes	1.86	0.94–3.71		1.66	0.82–3.35
Vemurafenib or dabrafenib						
< 10 months	No/unknown	1.00	reference	< 0.01	1.00	reference
	Yes	0.51	0.36–0.72		0.51	0.36–0.73
> 10 months	No/unknown	1.00	reference	< 0.01	1.00	reference
	Yes	2.13	1.37–3.33		2.27	1.39–3.69
Chemotherapy, any						
	No/unknown	1.00	reference	0.85		
	Yes	1.02	0.84–1.24			
Other antibody therapy ^c						
	No/unknown	1.00	reference	0.11		
	Yes	0.61	0.33–1.11			
Other immunotherapy ^d						
	No/unknown	1.00	reference	< 0.01	1.00	reference
	Yes	0.43	0.29–0.65		0.46	0.29–0.73
TKI inhibitor ^e						
	No/unknown	1.00	reference	0.77		
	Yes	0.96	0.72–1.27			

^aWald F-test p value.^bCox proportional hazard regression model adjusted for the variables that were found to be associated with survival during bivariate analyses ($p \leq 0.15$) and remained significant ($p \leq 0.05$) in multivariate analyses.^cRituximab, bevacizumab, denosumab, pidilizumab, pembrolizumab, farletuzumab.^dHigh-dose IL-2, IL-2, interferon α and Peginterferon α -2b.^eImatinib, axitinib, pazopanib, and nilotinib.

API = Asian Pacific Islander; CI = confidence interval; HR = hazard ratio; NCI = National Cancer Institute; NHW = non-Hispanic white; OPD = outpatient department; TKI = tyrosine kinase inhibitor.

tus. Therefore, to estimate the association between receipt of these agents and all-cause survival more accurately, assessments were made before and after these respective time points.

During bivariate analyses, all-cause survival was found to vary by age, marital status, comorbidity level, family history of melanoma, residential income, education level and clinical trial participation. Survival was also found to vary according to treatments received. When included in a multivariate Cox proportional regression model, all-cause survival was found to be poorer among patients who were not married (HR 1.39; 95% CI 1.14–1.70), had a Charlson Score of 1 or higher (HR 1.23; 95% CI 1.00–1.51) and had received radiation (HR 1.23; 95% CI 1.00–1.51); survival was better among patients who had a family history of melanoma (HR 0.48; 95% CI 0.28–0.79), or had received surgery (HR 0.70; 95% CI 0.57–0.86) and other immunotherapy (HR 0.46; 95% CI 0.29–0.73). The association between all-cause mortality and receipt of ipilimumab and vemurafenib or dabrafenib varied over time. During early follow-up, receipt of ipilimumab (≤ 18 months: HR 0.66; 95% CI 0.51–0.84) and vemurafenib/dabrafenib (≤ 10 months: HR 0.51; 95% CI 0.36–0.73) were associated with better survival. During later follow-up, the survival benefits associated with receipt of ipilimumab and vemurafenib/dabrafenib were no longer apparent. Moreover, receipt of vemurafenib/dabrafenib was found to be associated with significantly worse survival after 10 months of follow-up (HR 2.27; 95% CI 1.39–3.69).

Discussion

The findings from this study indicate that nearly a quarter of metastatic melanoma patients diagnosed in 2011 received no treatment, approximately a quarter received ipilimumab and only half of the patients who were known to have a *BRAF* mutation received vemurafenib/dabrafenib. The findings also indicate that there were disparities in the treatment of metastatic melanoma, particularly by age and insurance status. Finally, there were indications that the survival benefit associated with receipt of ipilimumab and vemurafenib/dabrafenib diminished over time.

Overall, the results are somewhat troubling, especially the finding that nearly a quarter of patients received no treatment. However, given that this study was focused on patients with metastatic disease, it is likely that many patients were deemed too sick or opted not to receive any treatment. Evidence of poorer health status among the patients who did not receive any treatment was suggested when comparing median survival times, which was 3 months among patients who received no treatment and 9 months among patients who received any treatment ($p < 0.01$; data not shown).

Nonetheless, the relatively low uptake of ipilimumab and vemurafenib/dabrafenib was surprising. In the case of ipilimumab, one would have thought that the uptake of what was suddenly the new standard of care with an established overall survival advantage would have been swifter. After all, while IL-2 was still a potentially relevant treatment option for a small subset of potentially ‘curable’

patients, ipilimumab had shown an overall survival advantage over dacarbazine [8]. Again, however, concerns regarding the health status of the patients and how well ipilimumab would be tolerated likely were not trivial, especially given there were serious immune-related adverse events observed during the clinical trials [7, 8]. Thus, the findings from this study seem to indicate that physicians and patients may have been apprehensive about utilizing this new modality of therapy. Receipt of vemurafenib/dabrafenib was also lower than expected, in part because *BRAF* testing was not as widespread as one might have expected. Medical oncologists should have already been well practiced in ordering genetic testing. For example, screening for trastuzumab therapy based on HER2 over-expression during the same time period was being completed for nearly all breast cancer patients [15]. The current study is, however, not the first to suggest slow uptake of genetic testing for therapeutic screening [16]. It is also worth mentioning that the current study also suggests that some patients who were found not to have a *BRAF* mutation were still treated with *BRAF* inhibitors, which is concerning.

Similar factors were associated with receipt of both ipilimumab and *BRAF* testing, including insurance status, age and place of care. Patients who did not have private or military insurance were less likely to receive ipilimumab. It is possible that the co-pay for ipilimumab, which has been estimated to be \$120,000 for a course of 4 doses [17], was prohibitively expensive for patients with other types of insurance or that these insurance carriers did not cover this particular agent. Likewise, having no insurance may have resulted in a cost barrier to receiving the *BRAF* test. Other studies have found that patients without private insurance are less likely to receive chemotherapy or immunotherapy [18–20]. Older patients were also less likely to receive ipilimumab and *BRAF* testing. Again, this might have resulted from concerns about how elderly patients would tolerate treatment. Finally, patients treated in facilities that had an approved residency training program were more likely to receive ipilimumab and a *BRAF* test, which likely is a reflection of the facilities being more aware of the latest advances in therapy. Nearly 70% of the patients who were enrolled in a clinical trial were treated in a facility with an approved residency training program (data not shown).

Factors associated with survival included being married, having a Charlson score of zero, having a family history of melanoma and receipt of certain therapies, all of which are likely related to having better overall health and/or support systems. Most notably the results from this study indicated that the benefits of ipilimumab and vemurafenib/dabrafenib were not sustained after 18 and 10 months, respectively. The reason for these findings is likely multifactorial. Melanoma is often aggressive and can quickly develop drug resistance [21, 22]. Median response durations have been estimated to be 19.3 months for ipilimumab [8] and 6.7 months for vemurafenib [23]. Additionally, although this study entailed treatment verification, misclassification of treatment cannot be ruled out, especially since some patients may have initiated a given therapy after their data were ascertained for this study. Data ascertainment occurred at least 1-year post diagnosis for all patients. Finally, because treat-

ment was not randomized in this study, it is possible that the untreated patients who did not succumb quickly to their disease ended up being a heartier group than their treated counterparts.

This study had strengths, namely it was population-based, had physician verified treatment information and was conducted during a year that new therapies were introduced. This study also had limitations, i.e. this was an observational study. Therefore, although we were able to investigate treatment patterns and predictors of therapy among patients representative of those seen in the general population, we cannot rule out that observed variations, particularly with regard to survival, were not due to confounding by indication. For example, because the severity of comorbidity and/or functional status were not known, these factors might have influenced therapy selection and also survival. Additionally, small sample size with respect to receipt of vemurafenib/dabrafenib also precluded the ability to identify factors associated with the receipt of these therapies.

In conclusion, dissemination of these new agents into community practice was limited during their first year of FDA approval. Over time the utilization of these agents may have increased. However, it will be imperative to conduct additional research to investigate the relatively slow uptake of new therapies to treat melanoma

and the apparent lack of long-term survival benefits associated with ipilimumab and vemurafenib/dabrafenib in the community setting.

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Disclosure Statement

The authors have disclosed that they have no financial interests, arrangements, affiliations, or commercial interests with the manufacturers of any products discussed in this article or their competitors. This article was produced by employees of the US government as part of their official duties and, as such, is in the public domain in the United States of America. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health. The authors declare that they have no conflict of interest.

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