Journal for ImmunoTherapy of Cancer

Outcomes of stage IV melanoma in the era of immunotherapy: a National Cancer Database (NCDB) analysis from 2014 to 2016

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To cite: Sussman TA, Knackstedt R, Wei W, *et al*. Outcomes of stage IV melanoma in the era of immunotherapy: a National Cancer Database (NCDB) analysis from 2014 to 2016. *Journal for ImmunoTherapy of Cancer* 2022;**10**:e004994. doi:10.1136/jitc-2022-004994

Accepted 08 July 2022

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ABSTRACT

Background To evaluate factors affecting the utilization of immunotherapy and to stratify results based on the approval of ipilimumab in 2011 and programmed death-1 inhibitors in 2014, an analysis of available data from the National Cancer Database (NCDB) was performed.

Methods The NCDB was analyzed to identify patients with stage IV melanoma from 2004 to 2016. Patients were categorized during the time periods 2004–2010, 2011–2014, and 2015–2016. Overall survival (OS) was analyzed by Kaplan-Meier, log-rank, and Cox proportional hazard models; IO status was analyzed using logistic regression.

Results 24,544 patients were analyzed. Overall, 5238 patients (21.3%) who received IO had improved median OS compared with those who did not (20.2 months vs 7.4 months; p<0.0001). Between 2004 and 2010, 9.7% received immunotherapy; from 2011 to 2014, 21.9% received immunotherapy; and from 2015 to 2016, 43.5% received immunotherapy. Three-year OS significantly improved in patients treated with IO across treatment years: 31% (95% CI 29% to 34%) from 2004 to 2010, 35% (95% CI 33% to 37%) from 2011 to 2014, and 46% (95% CI 44% to 48%) from 2015 to 2016 (p<0.0001). Survival was worse in patients who did not receive IO during these treatment years: 16% (15%–17%), 21% (20%–22%), and 27% (25%–28%), respectively. In the overall cohort, age <65 years, female gender, private insurance, no comorbidities, residence in metropolitan area, and treatment at academic centers were associated with better OS (p<0.0001 for all). In the multivariate analysis, receipt of IO from 2015 to 2016 was associated with age <65 years (OR 1.27, 95% CI 1.08 to 1.50), African American race (OR 5.88, 95% CI 1.60 to 28.58), lack of comorbidities (OR 1.43, 95% CI 1.23 to 1.66), and treatment at academic centers (OR 1.44, 95% CI 1.26 to 1.65) (p<0.05 for all).

Conclusions OS improved in patients with stage IV melanoma receiving IO, with the highest OS rate in 2015–2016. Our findings, which represent a real-world population, are slightly lower than recent trials, such as KEYNOTE-006 and CheckMate 067. Significant socioeconomic factors may impact receipt of IO and survival.

INTRODUCTION

Melanoma is the fifth most common cancer in men and women, with an estimate of about 96,000 new diagnoses and about 9000 deaths annually in the USA. Of these cases, about 9% and 4% are stage III and IV, respectively.[1] Although early-stage patients can be treated successfully with surgical resection in the majority, many will develop metastatic disease. Overall 5-year survival of all stages of melanoma is about 92%; however, the 5-year overall survival (OS) for metastatic melanoma is 27%.[2]

Prior to the advent of immune checkpoint inhibitor therapy in 2011, the median OS of metastatic melanoma was 6–8 months, with 5-year OS less than 10% with use of dacarbazine or temozolomide chemotherapy.[3] Additionally, treatment with interferon-alpha or high-dose interleukin 2 during this time period yielded similar survival outcomes.[4 5] Recently, treatment options for patients with advanced melanoma have expanded greatly with the US Food and Drug Administration (FDA) approval in 2011 of the anticytotoxic T-lymphocyte antigen 4 antibody, ipilimumab. In a pooled analysis from 1861 patients who received ipilimumab in clinical trials, the median OS was 11.4 months, with 5-year OS of 20%.[6] Ipilimumab was also later approved in the adjuvant setting for stage III melanoma in 2015.

In September and December 2014, the FDA approved anti-programmed death-1 (PD-1) humanized monoclonal antibodies pembrolizumab and nivolumab for treatment of metastatic melanoma. These agents revolutionized melanoma, with several phase II and III clinical trials reporting a median OS of about 36 months and a 5-year OS of 44%.[7 8]

While options for immunotherapy in melanoma hold promise, the majority of data stem

from clinical trials that have specific inclusion criteria and often exclude important patient populations. In this analysis, we use the National Cancer Database (NCDB) to provide the first real-world evidence of outcomes of patients with stage IV cutaneous melanoma receiving immunotherapy from 2015 to 2017 and interrogate factors associated with receipt of immunotherapy in this population, and compare these outcomes with patients receiving chemotherapy or immunotherapy (likely interferon and interleukin 2) from 2004 to 2010 and immunotherapy (addition of ipilimumab) from 2011 to 2014.

METHODS

Patient cohort

The NCDB is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society (ACS). The data used in the study were derived from de-identified NCDB files. The ACS and CoC have not verified the data files and are not responsible for analytic or statistical methodology employed or the conclusion in this report.

Patients 18 years of age or older diagnosed with stage IV melanoma between January 1, 2004 and December 31, 2016 were identified from the NCDB. Follow-up data for all patients were available through 2017. Patients who did not have data available on analytic staging, survival status (with 3 years or longer follow-up), and treatment details (including type of therapy (surgery, radiation therapy, chemotherapy, immunotherapy) and the time of administration) were excluded from the analyses.

Covariates included age, gender, race, Charlson-Deyo comorbidity score, treatment facility, insurance, tumor site, histology, Breslow depth, and ulceration status. Age at diagnosis was categorized into <40, 40–64, or 65+ years. Race was categorized into Caucasian, African American, other, or unknown. The Charlson-Deyo comorbidity score was defined as previously published.[9] Facility type was categorized into academic/research program, community cancer program, comprehensive community cancer program, and integrated cancer network. This is defined as follows: academic/research hospitals participate in postgraduate medical education in at least four fields, with >500 newly diagnosed cancer cases per year; community cancer programs have 100–500 newly diagnosed cancer cases per year and offer some diagnostic or treatment services; comprehensive community center programs have >500 newly diagnosed cancer cases per year and offer a range of diagnostic and treatment services; and integrated network cancer programs are a joining of multiple facilities to provide comprehensive cancer services. Insurance was categorized into Medicare, Medicaid, private, other, or none. The great circle distance is the spherical distance between the patient's residence and the treatment facilities. Tumor site was categorized into head and neck, upper extremities, trunk, lower extremities, or not specified. Histologic subtypes were superficial spreading, nodular, acral lentiginous, mucosal, desmoplastic, other, or unspecified. Breslow depth was categorized into <1.0, 1.01–2.00, 2.01–4, and >4.00. Ulceration status was classified as present, absent, or unknown. For any patient demographic where more than 50% was listed as unknown, that factor was not analyzed.

Subcohorts were categorized into receipt of immunotherapy or not during the diagnosis years 2004–2010, 2011–2014, and 2015–2017. Detailed information on some important variables was not available in the NCDB and therefore details regarding aspects of chemotherapy or immunotherapy regimens and doses were not analyzed.

Statistical analysis

Categorical variables were summarized using frequencies and percentages, while continuous variables were summarized using median, quartiles, and range. Multivariate logistic regression model was used to associate patient and tumor characteristics with immunotherapy utilization status. OS was estimated using the Kaplan-Meier method and compared using log-rank test between patient groups. Multivariate Cox proportional hazards model was used to identify prognostic factors associated with OS. Interactions between immunotherapy (IO) and other factors (year of diagnosis, age, gender, race, histology, site, comorbidity, insurance, income, and center type) were tested in the Cox model, and a subgroup analysis by year of diagnosis was carried out due to significant interactions. All tests were two-sided and p values of 0.05 or less were considered statistically significant. Statistical analysis was carried out using SAS Studio V.3.7 and R V.4.1 (R Foundation, Vienna, Austria).

RESULTS

Cohort characteristics

The study analyzed 24,544 patients, 10,496 from 2004 to 2010, 8743 from 2011 to 2014, and 5305 from 2015 to 2017. Majority of the patients (63.7%) were 60 years of age or older. There were 13,048 (67.66%) men and 6258 (32.34%) women. Of the patients, 94.1% identified as Caucasian and 75.87% had a Charlson-Deyo score of 0. Most patients (62.63%) received care at a non-academic medical center. In regard to melanoma therapy, only 27.8% received surgery, 36.52% received radiation therapy, and 27.93% received chemotherapy. Patient demographics are presented in table 1.

Factors affecting immunotherapy utilization

Overall, from 2004 to 2017, 21.3% of patients received immunotherapy. Between 2004 and 2010, 9.7% received immunotherapy; from 2011 to 2014, 21.9% received immunotherapy; and from 2015 to 2016, 43.5% received immunotherapy. The median time from diagnosis to immunotherapy initiation was 62 days in 2011–2014 and 49 days in 2015–2016.

In the multivariate analysis for treatment years 2011–2014, patients 65 or older (OR 0.589, 95% CI 0.499

Table 1 Patient demographics and immunotherapy utilization

	Immunotherapy					
	No		Yes		All	
	n	%	n	%	n	%
Primary site						
Skin extremities	2459	77.89	698	22.11	3157	12.86
Skin head and neck &	1785	77.44	520	22.56	2305	9.39
Skin not otherwise specified	12,695	79.57	3260	20.43	15,955	65.01
Skin trunk	2367	75.7	760	24.3	3127	12.74
Histology						
Acral melanoma	93	73.81	33	26.19	126	0.51
Desmoplastic melanoma	128	71.51	51	28.49	179	0.73
Melanoma not otherwise specified	16,601	79.48	4287	20.52	20,888	85.1
Nodular melanoma	1425	73.87	504	26.13	1929	7.86
Melanoma unspecified	256	75.29	84	24.71	340	1.39
Spindle cell melanoma	341	77.32	100	22.68	441	1.8
Superficial spreading melanoma	462	72.07	179	27.93	641	2.61
Age						
18–29	297	68.12	139	31.88	436	1.78
30–39	739	68.43	341	31.57	1080	4.4
40–49	1832	74.11	640	25.89	2472	10.07
50–59	3723	75.64	1199	24.36	4922	20.05
≥60	12,715	81.33	2919	18.67	15,634	63.7
Gender						
Female	6258	78.85	1679	21.15	7937	32.34
Male	13,048	78.57	3559	21.43	16,607	67.66
Race/ethnicity						
Unknown	156	85.71	26	14.29	182	0.74
African American	331	83.38	66	16.62	397	1.62
Asian	108	81.2	25	18.8	133	0.54
Caucasian	18,126	78.49	4966	21.51	23,092	94.08
Hispanic	499	80.48	121	19.52	620	2.53
Unspecified	86	71.67	34	28.33	120	0.49
Stage						
Stage IV	19,306	78.66	5238	21.34	24,544	100
Charlson-Deyo score						
0	14,352	77.07	4270	22.93	18,622	75.87
1	3352	82.66	703	17.34	4055	16.52
2	1004	85.52	170	14.48	1174	4.78
≥3	598	86.29	95	13.71	693	2.82
Primary payer						
Unknown	376	79.66	96	20.34	472	1.92
Government	11,199	81.91	2474	18.09	13,673	55.71
Not insured	1026	85.86	169	14.14	1195	4.87
Private	6705	72.85	2499	27.15	9204	37.5
Cancer center type						
Academic/research center	6749	73.57	2424	26.43	9173	37.37

Continued

Table 1 Continued

	Immunotherapy					
	No		Yes		All	
	n	%	n	%	n	%
Non-academic	12,557	81.69	2814	18.31	15,371	62.63
Residence area						
Unknown	613	74.3	212	25.7	825	3.36
Metro	15,425	78.36	4259	21.64	19,684	80.2
Rural	402	82.89	83	17.11	485	1.98
Urban	2866	80.73	684	19.27	3550	14.46
Surgery						
Unknown	50	86.21	8	13.79	58	0.24
No	13,983	79.17	3680	20.83	17,663	71.96
Yes	5273	77.28	1550	22.72	6823	27.8
Radiation therapy						
Unknown	340	94.44	20	5.56	360	1.47
No	11,943	78.46	3278	21.54	15,221	62.02
Yes	7023	78.36	1940	21.64	8963	36.52
Chemotherapy						
Unknown	623	89.77	71	10.23	694	2.83
No	12,621	74.26	4374	25.74	16,995	69.24
Yes	6062	88.43	793	11.57	6855	27.93
Bone mets						
Unknown	2358	73.37	856	26.63	3214	13.09
No	15,442	79.69	3935	20.31	19,377	78.95
Yes	1506	77.11	447	22.89	1953	7.96
Brain mets						
Unknown	2302	72.83	859	27.17	3161	12.88
No	14,045	79.07	3718	20.93	17,763	72.37
Yes	2959	81.74	661	18.26	3620	14.75
Liver mets						
Unknown	2364	73.26	863	26.74	3227	13.15
No	15,172	79.76	3851	20.24	19,023	77.51
Yes	1770	77.16	524	22.84	2294	9.35
Lung mets						
Unknown	2363	73.23	864	26.77	3227	13.15
No	13,442	80.17	3324	19.83	16,766	68.31
Yes	3501	76.93	1050	23.07	4551	18.54
Lymph node mets						
Unknown	2945	76.12	924	23.88	3869	15.76
No	15,622	79.31	4076	20.69	19,698	80.26
Yes	739	75.64	238	24.36	977	3.98
Palliative care						
Unknown	223	83.21	45	16.79	268	1.09
None	16,447	78.61	4476	21.39	20,923	85.25
Surgery	140	81.4	32	18.6	172	0.7
Radiation therapy	1573	83.36	314	16.64	1887	7.69

Continued

Table 1 Continued

	Immunotherapy					
	No		Yes		All	
	n	%	n	%	n	%
Chemo, hormone, other systemic drugs	390	65.66	204	34.34	594	2.42
Pain management therapy with no other palliative care	221	89.47	26	10.53	247	1.01
Palliative care						
Unknown	223	83.21	45	16.79	268	1.09
No	16,447	78.61	4476	21.39	20,923	85.25
Yes	2636	78.62	717	21.38	3353	13.66
Year of diagnosis						
2004–2010	9481	90.33	1015	9.67	10,496	42.76
2011–2014	6827	78.09	1916	21.91	8743	35.62
2015–2016	2998	56.51	2307	43.49	5305	21.61
Vital status						
Alive	3232	62.13	1970	37.87	5202	21.19
Dead	16,074	83.1	3268	16.9	19,342	78.81
Total	19,306	78.66	5238	21.34	24,544	100

mets, metastasis.

to 0.696, p<0.0001), with Charlson-Deyo score of 1 or higher (OR 0.681, 95% CI 0.578 to 0.800, p<0.0001), with government insurance (vs private; OR 0.807, 95% CI 0.683 to 0.955, p=0.01), treated at a non-academic cancer center (OR 0.675, 95% CI 0.592 to 0.769, p<0.0001), and in the lowest degree of education quantile (vs the highest quantile; OR 0.644, 95% CI 0.519 to 0.797, p<0.0001) had significantly lower chance of receiving immunotherapy.

In the multivariate analysis for treatment years 2015–2016, patients 65 or older (OR 0.788, 95% CI 0.668 to 0.930, p=0.005), Caucasian (vs African American; OR 0.536, 95% CI 0.301 to 0.942, p=0.03), with Charlson-Deyo score of 1 or higher (OR 0.699, 95% CI 0.601 to 0.813, p<0.0001), with government insurance (vs private; OR 0.779, 95% CI 0.657 to 0.924, p=0.004), treated at a non-academic cancer center (OR 0.692, 95% CI 0.607 to 0.790, p<0.0001), and in the lowest degree of education quantile (vs the highest quantile; OR 0.722, 95% CI 0.586 to 0.887, p=0.002) had significantly lower chance of receiving immunotherapy (table 2).

Overall predictors of survival

Overall, receiving immunotherapy improved the median survival (7.36 months vs 20.21 months, p<0.0001). Improved median survival, regardless of immunotherapy utilization, was noted with each subsequent timeframe at 7.95, 9.3, and 13.93 months for diagnosis years 2004–2010, 2011–2014, and 2015–2016, respectively (p<0.0001). The median survival with and without IO from 2004 to 2010 was 17.64 and 7.13, from 2011 to 2014 it was 17.71 and 7.59, and from 2015 to 2016 it was 25 and 7.16 (all p<0.0001) (figure 1). Improved median survival was observed in patients with head and neck (12.45 months) and extremity (12.12 months) melanoma compared with trunk (9.92 months) and not otherwise specified (NOS) (7.92 months) melanoma (p<0.0001). For histology, the greatest median survival was noted in desmoplastic (18.76 months), spindle cell (16.69 months), and superficial spreading (16.43 months) melanoma (p<0.0001).

Improved median survival was noted with each subsequent timeframe at 7.95, 9.3, and 13.93 months for diagnosis years 2004–2010, 2011–2014, and 2015–2016, respectively (p<0.0001). Overall, receiving immunotherapy improved the median survival (7.36 months vs 20.21 months, p<0.0001). In the multivariate analysis, better OS was associated with younger age, female gender, lower Charlson-Deyo score, and receiving treatment at an academic center (all p<0.0001). All multivariate analyses are listed in table 3.

In the multivariate analysis, from 2004 to 2010, improved OS was observed in those who had surgery (HR 0.592 (0.549–0.639), p<0.0001) and those who received radiation therapy (HR 1.195 (1.134–1.259), p<0.0001). Decreased OS was observed in those who did not receive immunotherapy (HR 1.578 (1.45–1.717), p<0.0001), men (HR 1.1 (1.047–1.156), p<0.0002), those with a Charlson-Deyo score of 1 or greater (HR 1.296 (1.277–1.368), p<0.0001), those treated at a non-academic center (HR 1.13 (1.077–1.186), p<0.0001), those receiving palliative care (HR 1.67 (1.556–1.792), p<0.0001), and those with liver or lymph node metastases (HR 1.459 (1.271–1.674), p<0.0001 and HR 0.631 (0.566–0.703), p<0.0001).

Table 2 Multivariate analysis of factors impacting immunotherapy utilization

Year of diagnosis	Factor	Comparison	OR (95% CI)	P value
2011–2014	Age	≥65 vs <65	0.589 (0.499 to 0.696)	<0.0001
	Charlson-Deyo score	≥1 vs 0	0.681 (0.578 to 0.800)	<0.0001
	Primary payor	Private vs government	1.238 (1.048 to 1.463)	0.0122
		Not insured vs government	0.581 (0.403 to 0.821)	0.0027
	Cancer center type	Academic vs non-academic	1.482 (1.300 to 1.689)	<0.0001
	Per cent of no high school degree, quartiles, 2012–2016	≥17.6% vs <6.3%	0.644 (0.519 to 0.797)	<0.0001
		10.9%–17.5% vs <6.3%	0.766 (0.641 to 0.915)	0.0033
		6.3%–10.8% vs <6.3%	0.943 (0.800 to 1.113)	0.4892
	Brain mets	Yes vs no	0.746 (0.644 to 0.861)	<0.0001
	Liver mets	Yes vs no	1.201 (1.028 to 1.400)	0.0204
	Lung mets	Yes vs no	1.364 (1.192 to 1.561)	<0.0001
	Lymph node mets	Yes vs no	1.714 (1.300 to 2.244)	0.0001
2015–2016	Age	≥65 vs <65	0.788 (0.668 to 0.930)	0.0047
	Race/ethnicity	Unspecified vs African American	0.170 (0.035 to 0.624)	0.0131
		Hispanic vs African American	0.612 (0.309 to 1.199)	0.1542
		Caucasian vs African American	0.536 (0.301 to 0.942)	0.0307
		Asian vs African American	0.266 (0.073 to 0.875)	0.0345
	Charlson-Deyo score	≥1 vs 0	0.699 (0.601 to 0.813)	<0.0001
	Primary payor	Private vs government	1.283 (1.082 to 1.522)	0.0042
		Not insured vs government	0.787 (0.519 to 1.183)	0.2545
	Cancer center type	Academic vs non-academic	1.444 (1.266 to 1.647)	<0.0001
	Per cent of no high school degree, quartiles, 2012–2016	≥17.6% vs <6.3%	0.722 (0.586 to 0.887)	0.002
		10.9%–17.5% vs <6.3%	0.924 (0.777 to 1.100)	0.3748
		6.3%–10.8% vs <6.3%	0.981 (0.831 to 1.159)	0.8246
	Brain mets	Yes vs no	0.751 (0.622 to 0.904)	0.0026
	Liver mets	Yes vs no	0.717 (0.572 to 0.896)	0.0037

mets, metastasis.

In the multivariate analysis, from 2011 to 2014, improved OS was observed in those who received surgery (HR 0.712 (0.643–0.788), p<0.0001) or chemotherapy (HR 0.786 (0.732–0.844), p<0.0001). Decreased OS was observed in those who did not receive immunotherapy (HR 1.686 (1.557–1.826), p<0.0001), 65 years of age or older (HR 1.138 (1.051–1.231), p=0.0013), men (HR 1.102 (1.033–1.175), p=0.0032), those with a Charlson-Deyo score of 1 or greater (HR 1.294 (1.21–1.384), p<0.0001), those treated at a non-academic center (HR 1.224 (1.151–1.301), p<0.0001), those receiving palliative care (HR 1.506 (1.384–1.638), p<0.0001), and those with bone, brain, liver, or lung metastases (all p<0.0001).

In the multivariate analysis, from 2015 to 2017, improved OS was observed in those who had surgery (HR 0.596 (0.517–0.688), p<0.0001) or chemotherapy (HR 0.738 (0.661–0.822), p<0.0001). Decreased OS was observed in those who did not receive immunotherapy (HR 1.982 (1.811–2.17), p<0.0001), those 65 years of age or older (HR 1.125 (1.009–1.255), p=0.341), those with a Charlson-Deyo score of 1 or greater (HR 1.285 (1.173–1.408), p<0.0001), those treated at a non-academic center (HR 1.192 (1.094–1.299), p<0.0001), those receiving palliative care (HR 1.545 (1.382–1.727), p<0.0001), those with bone, brain, liver, and lymph node metastases (p=0.058, p<0.0001, p<0.0001, and p=0.01, respectively), and those

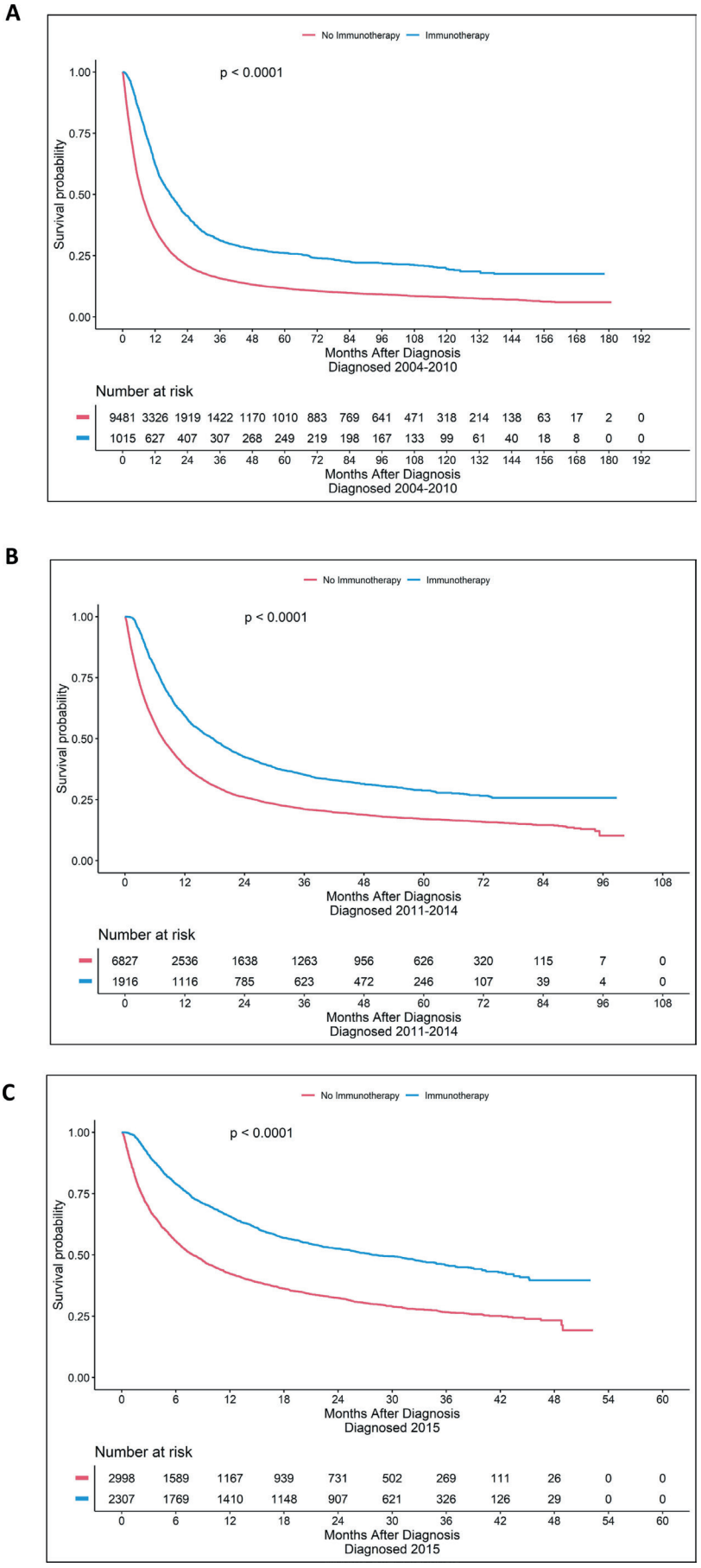

Figure 1 Survival curves with and without immunotherapy: (A) 2004–2010, (B) 2011–2014, and (C) 2015.

Table 3 Multivariant analysis of factors impacting survival

Factor		Total (n)	Events (n)	Median survival in months (95% CI)	Rate at 3 years (95% CI)	P value
All stage IV patients		24,544	19,342	9.13 (8.9 to 9.36)	0.23 (0.23 to 0.24)	
Immunotherapy	No	19,306	16,074	7.36 (7.16 to 7.56)	0.19 (0.19 to 0.2)	<0.0001
	Yes	5238	3268	20.21 (19.19 to 21.52)	0.39 (0.37 to 0.4)	
Year of diagnosis	2004–2010	10,496	9343	7.95 (7.66 to 8.21)	0.17 (0.17 to 0.18)	<0.0001
	2011–2014	8743	6811	9.3 (8.9 to 9.69)	0.24 (0.23 to 0.25)	
	2015–2016	5305	3188	13.93 (12.81 to 15.05)	0.35 (0.34 to 0.36)	
Primary site	Skin extremities	3157	2447	12.12 (11.43 to 12.88)	0.27 (0.25 to 0.28)	<0.0001
	Skin head and neck	2305	1774	12.45 (11.79 to 13.47)	0.27 (0.25 to 0.29)	
	Skin not otherwise specified	15,955	12,578	7.92 (7.62 to 8.15)	0.23 (0.22 to 0.23)	
	Skin trunk	3127	2543	9.92 (9.36 to 10.51)	0.21 (0.19 to 0.22)	
Histology	Acral melanoma	126	103	12.71 (12 to 18.46)	0.24 (0.17 to 0.33)	<0.0001
	Desmoplastic melanoma	179	128	18.76 (15.11 to 25.17)	0.33 (0.27 to 0.41)	
	Melanoma not otherwise specified	20,888	16,530	8.48 (8.25 to 8.74)	0.23 (0.22 to 0.23)	
	Nodular melanoma	1929	1569	11.14 (10.32 to 11.89)	0.22 (0.2 to 0.24)	
	Unspecified	340	249	12.45 (9.86 to 17.38)	0.31 (0.26 to 0.37)	
	Spindle cell melanoma	441	303	16.69 (14.39 to 18.89)	0.35 (0.3 to 0.4)	
	Superficial spreading melanoma	641	460	16.43 (13.86 to 19.68)	0.33 (0.3 to 0.37)	
Age	<65	11,964	9017	10.68 (10.32 to 11.07)	0.26 (0.25 to 0.27)	<0.0001
	≥65	12,580	10,325	7.85 (7.56 to 8.11)	0.21 (0.2 to 0.21)	
Gender	Female	7937	6106	10.4 (9.92 to 10.84)	0.25 (0.24 to 0.26)	<0.0001
	Male	16,607	13,236	8.61 (8.38 to 8.87)	0.22 (0.22 to 0.23)	
Race/ethnicity	African American	397	317	7.26 (6.31 to 8.71)	0.19 (0.16 to 0.24)	0.0739
	Asian	133	105	11.17 (6.54 to 15.97)	0.21 (0.15 to 0.29)	
	Caucasian	23,092	18,248	9.13 (8.9 to 9.36)	0.23 (0.23 to 0.24)	
	Hispanic	620	441	10 (8.71 to 11.73)	0.25 (0.21 to 0.29)	
	Unspecified	120	96	9.36 (6.54 to 14.98)	0.23 (0.16 to 0.32)	
Charlson-Deyo score	0	18,622	14,322	10.28 (9.99 to 10.58)	0.25 (0.25 to 0.26)	<0.0001
	≥1	5922	5020	6.28 (6.01 to 6.6)	0.17 (0.16 to 0.18)	
Primary payor	Government	13,673	11,245	7.62 (7.36 to 7.92)	0.2 (0.19 to 0.21)	<0.0001
	Not insured	1195	979	5.95 (5.36 to 6.67)	0.18 (0.16 to 0.2)	
	Private	9204	6744	12.48 (12 to 12.98)	0.29 (0.28 to 0.3)	
Cancer center type	Academic/research center	9173	6943	11.47 (11.1 to 11.99)	0.27 (0.27 to 0.28)	<0.0001
	Non-academic	15,371	12,399	7.89 (7.62 to 8.11)	0.21 (0.2 to 0.21)	
Residence area	Metro	19,684	15,477	9.23 (8.94 to 9.46)	0.24 (0.23 to 0.24)	0.0002
	Rural	485	393	7.33 (6.28 to 8.64)	0.2 (0.16 to 0.24)	
	Urban	3550	2880	8.54 (7.9 to 9.13)	0.2 (0.19 to 0.22)	
Palliative care	No	20,923	16,062	10.64 (10.35 to 10.91)	0.26 (0.25 to 0.26)	<0.0001
	Yes	3353	3038	4.63 (4.44 to 4.83)	0.1 (0.09 to 0.11)	

Continued

Table 3 Continued

Factor		Total (n)	Events (n)	Median survival in months (95% CI)	Rate at 3 years (95% CI)	P value
Surgery	No	17,663	14,122	7.33 (7.13 to 7.59)	0.21 (0.2 to 0.22)	<0.0001
	Yes	6823	5179	14.06 (13.5 to 14.78)	0.29 (0.28 to 0.3)	
Chemotherapy	No	16,995	12,928	9.26 (8.87 to 9.59)	0.26 (0.26 to 0.27)	<0.0001
	Yes	6855	5886	9 (8.8 to 9.3)	0.16 (0.15 to 0.16)	
Radiation therapy	No	15,221	11,470	11.3 (11.01 to 11.6)	0.27 (0.26 to 0.28)	<0.0001
	Yes	8963	7560	7.23 (7 to 7.46)	0.17 (0.16 to 0.18)	
Immunotherapy (2004–2010)	No	9481	8545	7.13 (6.9 to 7.39)	0.16 (0.15 to 0.17)	<0.0001
	Yes	1015	798	17.64 (15.9 to 19.94)	0.31 (0.29 to 0.34)	
Immunotherapy (2011–2014)	No	6827	5482	7.59 (7.23 to 7.98)	0.21 (0.2 to 0.22)	<0.0001
	Yes	1916	1329	17.71 (15.8 to 19.35)	0.35 (0.33 to 0.37)	
Immunotherapy (2015–2016)	No	2998	2047	7.92 (7.16 to 8.8)	0.27 (0.25 to 0.28)	<0.0001
	Yes	2307	1141	28.32 (25 to 32.72)	0.46 (0.44 to 0.48)	

who received radiation therapy (HR 1.201 (1.092–1.321), p=0.0002). All multivariate analyses are presented in table 4.

DISCUSSION

With advances in immunotherapy options for cancer treatment, the therapeutic options for melanoma have expanded greatly. Immunotherapy has demonstrated promise in improving the OS in melanoma, but the majority of this research stems from trials that may not be representative of all patients.[1–4] Thus, the impact that immunotherapy has on melanoma outcomes outside of clinical trials warrants exploration. Through analysis of the NCDB, real-world utilization and outcomes in melanoma can be analyzed.

From 2004 to 2017, there was an increase in immunotherapy utilization with each subsequent time period analyzed. However, there were several patient factors that impacted immunotherapy utilization. For all time periods analyzed, patients with Charlson-Deyo scores of 1 or greater and those with liver and brain metastases were less likely to receive immunotherapy. As reasons for receiving or not receiving immunotherapy are not included in the NCDB, it is unclear why these patients had lower utilization rates. Clinical trials typically exclude patients with increased comorbidities and higher Charlson-Deyo scores. Thus, this might reflect providers being hesitant to offer patients who were not represented in clinical trials of immunotherapy for fear of increased side effects or intolerability. Alternatively, this could reflect the choice of patients with increased comorbidities to not pursue additional treatment. While patients with higher Charlson-Deyo scores had decreased median survival, as cause of death is not recorded, it is not clear if death was due to melanoma, which could have been prevented with immunotherapy, or due to other comorbidities.

In this cohort, men had worse survival outcomes, regardless of whether immunotherapy was used. Gender-specific outcomes for immunotherapy are not always demonstrated in the literature. A systematic review of 23 studies found that the survival benefit with immune checkpoint inhibitors for advanced cancers was not gender-dependent.[5] However, recent meta-analyses found that males had significantly better responses to immunotherapy compared with females.[6–8] Contradicting this finding, initial in vivo models in mice demonstrated that females had better responses to checkpoint inhibitors than male mice.[10] Future studies should further elucidate if certain immunotherapy options have gender-dependent results for melanoma and the mechanisms at play.

On multivariant analysis, patients who received radiation therapy as part of their treatment for melanoma had decreased survival outcomes, regardless of immunotherapy utilization. Radiotherapy in patients with melanoma is most frequently delivered in the palliative setting, particularly in the management of brain metastases or for nodal, satellite, and in-transit metastases that are unresectable or have progressed despite systemic therapy. Historically, the role of radiation in the treatment of melanoma has been questioned due to perceived radioresistance, but for certain cases it may be appropriate.[11] The Tasman Radiation Oncology Group (TROG) study demonstrated a 36% nodal relapse rate 6 years after lymph node dissection, which was reduced to 21% with postoperative nodal radiotherapy, but there was no

Table 4 Multivariant analysis of factors impacting survival by year

Year of diagnosis	Factor	Comparison	HR (95% CI)	P value
2004–2010	Immunotherapy	No vs yes	1.578 (1.45 to 1.717)	<0.0001
	Primary site	Extremities vs trunk	0.839 (0.766 to 0.92)	0.0002
		Head and neck vs trunk	0.827 (0.75 to 0.912)	0.0001
		Not otherwise specified vs trunk	0.747 (0.683 to 0.816)	<0.0001
	Histology	Acral vs Not otherwise specified	1.073 (0.769 to 1.498)	0.678
		Desmoplastic vs Not otherwise specified	0.838 (0.642 to 1.094)	0.1941
		Nodular vs Not otherwise specified	1.119 (1.019 to 1.23)	0.0189
		Unspecified vs Not otherwise specified	0.732 (0.576 to 0.93)	0.0107
		Spindle cell vs Not otherwise specified	0.8 (0.673 to 0.95)	0.0111
		Superficial spreading vs Not otherwise specified	0.993 (0.852 to 1.158)	0.9296
	Age	≥65 vs <65	1.056 (0.992 to 1.124)	0.09
	Gender	Male vs female	1.1 (1.047 to 1.156)	0.0002
	Charlson-Deyo score	≥1 vs 0	1.296 (1.277 to 1.368)	<0.0001
	Primary payor	Private vs government	0.794 (0.745 to 0.846)	<0.0001
		Not insured vs government	1.106 (0.986 to 1.242)	0.0862
	Cancer center type	Non-academic vs academic/research center	1.13 (1.077 to 1.186)	<0.0001
	Palliative care	Yes vs no	1.67 (1.556 to 1.792)	<0.0001
	Bone mets	Yes vs no	1.122 (0.966 to 1.302)	0.1306
	Brain mets	Yes vs no	1.057 (0.952 to 1.173)	0.2978
	Liver mets	Yes vs no	1.459 (1.271 to 1.674)	<0.0001
	Lung mets	Yes vs no	1.038 (0.942 to 1.143)	0.4493
	Lymph node mets	Yes vs no	0.631 (0.566 to 0.703)	<0.0001
	Surgery	Yes vs no	0.592 (0.549 to 0.639)	<0.0001
	Chemotherapy	Yes vs no	1.037 (0.986 to 1.091)	0.1539
	Radiation therapy	Yes vs no	1.195 (1.134 to 1.259)	<0.0001
2011–2014	Immunotherapy	No vs yes	1.686 (1.557 to 1.826)	<0.0001
	Primary site	Extremities vs trunk	0.881 (0.781 to 0.995)	0.0415
		Head and neck vs trunk	0.785 (0.69 to 0.894)	0.0003
		N vs trunk	0.734 (0.657 to 0.82)	<0.0001
	Histology	Acral vs Noth otherwise specified	1.339 (0.908 to 1.974)	0.1406
		Desmoplastic vs Not otherwise specified	1.069 (0.744 to 1.534)	0.7193
		Nodular vs Not otherwise specified	1.101 (0.973 to 1.246)	0.128
		Unspecified vs Not otherwise specified	0.919 (0.72 to 1.172)	0.4958
		Spindle cell vs Not otherwise specified	0.632 (0.503 to 0.794)	<0.0001
		Superficial spreading vs Not otherwise specified	0.824 (0.667 to 1.018)	0.0722
	Age	≥65 vs <65	1.138 (1.051 to 1.231)	0.0013
	Gender	Male vs female	1.102 (1.033 to 1.175)	0.0032
	Charlson-Deyo score	≥1 vs 0	1.294 (1.21 to 1.384)	<0.0001
	Primary payor	Private vs government	0.801 (0.739 to 0.869)	<0.0001
		Not insured vs government	1.14 (0.986 to 1.319)	0.0774
	Cancer center type	Non-academic vs academic/research center	1.224 (1.151 to 1.301)	<0.0001
	Palliative care	Yes vs no	1.506 (1.384 to 1.638)	<0.0001
	Bone mets	Yes vs no	1.388 (1.283 to 1.502)	<0.0001
	Brain mets	Yes vs no	1.839 (1.704 to 1.985)	<0.0001
	Liver mets	Yes vs no	1.924 (1.783 to 2.074)	<0.0001
	Lung mets	Yes vs no	1.367 (1.284 to 1.454)	<0.0001
	Lymph node mets	Yes vs no	1.038 (0.898 to 1.199)	0.6185
	Surgery	Yes vs no	0.712 (0.643 to 0.788)	<0.0001
	Chemotherapy	Yes vs no	0.786 (0.732 to 0.844)	<0.0001
	Radiation therapy	Yes vs no	0.928 (0.861 to 1.001)	0.052

Continued

Table 4 Continued

Year of diagnosis	Factor	Comparison	HR (95% CI)	P value
2015–2016	Immunotherapy	No vs yes	1.982 (1.811 to 2.17)	<0.0001
	Primary site	Extremities vs trunk	0.828 (0.695 to 0.979)	0.0341
		H&N vs trunk	0.815 (0.678 to 0.979)	0.0289
		NOS vs trunk	0.67 (0.575 to 0.781)	<0.0001
	Histology	Acral vs NOS	1.084 (0.554 to 2.12)	0.8148
		Desmoplastic vs NOS	0.823 (0.499 to 1.357)	0.4452
		Nodular vs NOS	1.167 (0.977 to 1.394)	0.0876
		Unspecified vs NOS	0.975 (0.701 to 1.358)	0.883
		Spindle cell vs NOS	0.72 (0.516 to 1.002)	0.0517
		Superficial spreading vs NOS	0.964 (0.739 to 1.261)	0.7908
	Age	≥65 vs <65	1.125 (1.009 to 1.255)	0.0341
	Gender	Male vs female	1.034 (0.946 to 1.13)	0.4631
	Charlson-Deyo score	≥1 vs 0	1.285 (1.173 to 1.408)	<0.0001
	Primary payer	Private vs government	0.796 (0.71 to 0.893)	0.0001
		Not insured vs government	1.089 (0.845 to 1.402)	0.5099
	Cancer center type	Non-academic vs academic/research center	1.192 (1.094 to 1.299)	<0.0001
	Palliative care	Yes vs no	1.545 (1.382 to 1.727)	<0.0001
	Bone mets	Yes vs no	1.229 (1.061 to 1.422)	0.0058
	Brain mets	Yes vs no	1.316 (1.167 to 1.484)	<0.0001
	Liver mets	Yes vs no	1.865 (1.631 to 2.132)	<0.0001
	Lung mets	Yes vs no	0.94 (0.841 to 1.051)	0.2801
	Lymph node mets	Yes vs no	0.647 (0.465 to 0.902)	0.0101
	Surgery	Yes vs no	0.596 (0.517 to 0.688)	<0.0001
	Chemotherapy	Yes vs no	0.738 (0.661 to 0.822)	<0.0001
	Radiation therapy	Yes vs no	1.201 (1.092 to 1.321)	0.0002

mets, metastasis.

impact on survival.[12] Due to the lack of survival advantage and potential neurocognitive toxicity, whole brain radiation therapy is today viewed as a last resort.[13 14] As the NCDB does not report on location of radiation treatment, it is unclear if the radiation received was for a nodal basin, whole brain, in-transit metastases, etc. Additionally, an inherent limitation of database research is the inability to determine eligibility and reason to pursue radiation. The utility of combining immunotherapy and radiation therapy remains to be further elucidated and demands further research.[15] While some patients benefit from the combination of radiation and immunotherapy, this is not uniformly demonstrated. It is anticipated that the development of reagents to study the immune response to immunotherapy will allow for a better understanding of the mechanism of interaction between radiation therapy and immunotherapy. There are currently numerous ongoing clinical trials investigating the combination of radiotherapy and immunotherapy in melanoma.[16]

Patients who received treatment at academic programs had increased immunotherapy utilization and improved. Similarly, a recent article found that patients treated at high-volume centers had improved 5-year OS for melanoma compared with patients treated at lower-volume facilities.[17] This may reflect readiness of academic institutions to treat advanced melanoma or to intrinsic differences in patient populations in regard to access of care. However, academic centers are often also referral centers for complex patients, which would be expected to bring down survival data. As increasing time passes since the FDA approval of various immunotherapy options for melanoma, utilization at non-academic centers will hopefully increase to that of academic centers and will likely impact survival outcomes.

Older patients (>65) in this cohort were less likely to receive immunotherapy and this correlated with a decreased median survival. There are conflicting data in the literature in regard to the impact that age has on response to immunotherapy, likely due to the limited number of older patients available for analysis and their potential exclusion from clinical trials. In this cohort, patients with increasing comorbidities were less likely to receive immunotherapy, making it unclear if age or comorbidities were more of a determining factor in utilization. Several studies have demonstrated that that toxicity does not depend on age.[18 19] Additionally, our prior study examining the NCDB from 2011 to 2014 demonstrated improved OS in those >65 years of age.[20] Thus, providers must be aware of the potential survival benefit and likely tolerability of immunotherapy in older patients.

The increase in immunotherapy utilization corresponded to an increase in median survival in those receiving immunotherapy (17.64, 17.71, and 28.32 months for 2004–2010, 2011–2014, and 2015–2016, respectively). The median survival in those not receiving immunotherapy remained relatively constant in these time periods (7.13, 7.59, and 7.92 months, respectively). From 2011 to 2014, except for the last few months of 2014 with the approval of the PD-1 inhibitors, the only option for immunotherapy was ipilimumab. However, from 2015 to 2017, patients could be treated with any combination of ipilimumab and PD-1 inhibitors. The survival results of this cohort can be compared with clinical trials that often exclude or have difficulty recruiting certain patient populations. The phase III clinical trial, CheckMate 067, investigated ipilimumab and nivolumab monotherapy, and combination therapy. At a minimum follow-up of 60 months, the median OS had not been reached for the nivolumab plus ipilimumab group (thus more than 60.0 months), and was 36.9 months in the nivolumab group and 19.9 months in the ipilimumab group.[21] The phase II trial, CheckMate 069, compared patients with BRAF wild-type melanoma treated with combination ipilimumab/nivolumab and ipilimumab alone. At a median follow-up of 24.5 months, the median OS had not been reached in either group, implying greater than 24.5 months.[22] In our study, for patients treated from 2015 to 2016, the median OS was 28.32 months. Thus, updated results of CheckMate 069 are required to compare real-world outcomes with this phase II trial. The survival outcomes in these studies improved compared with those of our study, even for 2015–2016, when ipilimumab and PD-1 inhibitors were available and improved results compared with monotherapy trials would be expected. This could be due to numerous factors. Clinical trials often exclude patients with increased comorbidities and Charlson-Deyo scores, patients who are included in the NCDB analysis. Additionally, patients with lower socioeconomic status who may not have the option or access to enroll in a clinical trial are included in the NCDB and have demonstrated to have worse outcomes in melanoma, regardless of stage or race.[23] The median time from diagnosis to immunotherapy initiation in our cohort was 62 days for 2011–2014 and 49 days for 2015–2016. Thus, results may continue to improve with expedited access to immunotherapy.

There are limitations to this study. Only 3-year OS data were available for comparison with clinical trials, which often have longer follow-up. Certain data that have previously been associated with response to immunotherapy, such as body mass index, tumor infiltrating lymphocytes, and lactate dehydrogenase levels, were either not included or had limited availability. The type of immunotherapy received is not available in the NCDB, so it is unknown if patients treated in 2015–2016 were receiving ipilimumab with increased frequency or if the newer PD-1 inhibitors were being prescribed. As providers in academic centers likely have access to and information about newly approved immunotherapy prior to those in non-academic centers, it is possible that the increase reflects improved utilization by providers in non-academic centers in a delayed fashion. It is also unclear if patients in the NCDB were receiving monotherapy or combination therapy. In several clinical trials, such as CheckMate 067 and 069, patients were immunotherapy-naïve, a demographic that is not gathered in the NCDB and could influence response to immunotherapy. Additionally, the number of patients with each location of metastases was limited, preventing subgroup analysis. However, despite these limitations, NCDB analysis has led to very impactful studies that influence medical decision-making.[17 24 25]

This is the first non-clinical trial to examine real-world utilization and outcomes associated with checkpoint immunotherapy in the treatment of advanced melanoma since the FDA approval of ipilimumab and the PD-1 inhibitors. Analysis of patients who are typically difficult to recruit into clinical trials, or are typically excluded, was performed. Utilization increased with each subsequent cohort with a corresponding improved median survival among patients receiving immunotherapy. While the median survival is less than clinical trials, this might be due to lack of combination therapy or inclusion of certain patient populations. As immunotherapy is increasingly available and prescribed, it is anticipated that NCDB survival outcomes will increase to approach that of clinical trials. Future studies should focus on further analyzing disparities with immunotherapy.

Contributors BRG conceptualized and supervised the paper and acted as guarantor, TAS, RK, and WW performed data curation, formal analysis, and writing. PF performed writing - review and editing and supervision.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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