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.

OUTCOMES OF STAGE IV MELANOMA IN THE ERA OF IMMUNOTHERAPY: A NATIONAL CANCER DATABASE (NCDB) ANALYSIS FROM 2014 TO 2016

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. 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. 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 cancer 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 |                  | All |                  |
|--------------------------|---------------|------------------|-----|------------------|
|                          | No            | Yes              |     |                  |
|                          | 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
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 0.578 to 0.800, p<0.0001), and in the lowest degree of education quantile (vs the highest quantile; OR 0.664, 95% CI 0.519 to 0.879, 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 0.679 to 0.769, 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.

### 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). 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.

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### Table 1

| Immunotherapy | No       | %       | Yes      | %       | All     | %       |
|---------------|----------|---------|----------|---------|---------|---------|
| 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 |

### Table 1 Continued

| Year of diagnosis | 2004–2010 | 2011–2014 | 2015–2016 |
|-------------------|-----------|-----------|-----------|
| n                 | 9481      | 6827      | 2998      |
| %                 | 90.33     | 78.09     | 56.51     |
| Vital status      | 3232      | 16,074    | 19,306    |
| Alive             | 62.13     | 83.1      | 78.66     |
| Dead              | 37.87     | 16.9      | 21.34     |

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 (1.028 to 1.400), p=0.0204), 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, and 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 (8.36 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
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 multivariate 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 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) |
## 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   |
|                   | 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 Not 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   |
|                   | 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
impact on survival. Due to the lack of survival advantage and potential neurocognitive toxicity, whole brain radiation therapy is today viewed as a last resort. 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. 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.

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. 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 toxicity does not depend on age. Additionally, our prior study examining the NCDB from 2011 to 2014 demonstrated improved OS in those >65 years of age. Thus, providers must be aware of the potential survival benefit and likely tolerability of immunotherapy in older patients.

### Table 4

| 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 | 1.064 (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.
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.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.
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