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ORIGINAL ARTICLE

Management of metastatic melanoma: improved survival in a national cohort following the approvals of checkpoint blockade immunotherapies and targeted therapies

Allison S. Dobry[1,2] · Cheryl K. Zogg[3,4] · F. Stephen Hodi[1,5,6] · Timothy R. Smith[1,7] · Patrick A. Ott[1,5,6] · J. Bryan Iorgulescu[1,6,7,8]

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Abstract

Background Immune checkpoint blockade (ICB) and $BRAF^{V600}$-targeted therapy have demonstrated substantial clinical efficacy for patients with stage 4 melanoma in clinical trials; however, their impact on survival and barriers to treatment in the "real-life" setting remains unknown.

Methods Patients who presented with cutaneous melanoma during 2004–2015 using the National Cancer Database, which comprises > 70% of all newly diagnosed cancers in the U.S., were evaluated for predictors of presenting with stage 4 disease and receiving ICB, and for their associated unadjusted and risk-adjusted overall survival (OS).

Results 17,975 patients presented with stage 4 metastatic cutaneous melanoma. Overall, patients who presented after the FDA's initial approvals (starting in 2011) for ICB and $BRAF^{V600}$-targeted therapy demonstrated a 31% relative improvement in 4-year OS ($p < 0.001$), compared to pre-2011. Following the initial approvals in 2011, improved OS was associated in risk-adjusted analyses with ICB (HR 0.57, 95CI 0.52–0.63). ICB demonstrated improved median and 4-year OS of 16.9 months (95CI 15.6–19.3; vs. 7.7 months, 95CI 7.2–8.4) and 32.4% (95CI 29.5–35.3; vs. 21.0%, 95CI 19.6–22.2, all $p < 0.001$), respectively; improved OS was persistent in unadjusted and risk-adjusted landmark survival analyses. Uninsured patients and management in the community setting were less likely to receive ICB in multivariable analyses.

Conclusions In a national "real-life" treatment population, we show that the wide availability of the novel treatment modalities ICB and $BRAF^{V600}$-targeted therapy has significantly improved the survival of patients with stage 4 melanoma. Our findings additionally suggest that there are opportunities for expanding coverage and access to these novel immunotherapies in community practice.

Keywords Melanoma · Metastasis · Immune checkpoint blockade · Targeted therapy · Immunotherapy

Abbreviations

AJCC	American Joint Committee on Cancer
CDI	Charlson–Deyo comorbidity index
FDA	Food and Drug Administration

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✉ J. Bryan Iorgulescu
jiorgulescu@bwh.harvard.edu

[1] Harvard Medical School, Boston, MA, USA

[2] Department of Dermatology, University of California Irvine, School of Medicine, Irvine, CA, USA

[3] Center for Surgery and Public Health, Brigham and Women's Hospital, Boston, MA, USA

[4] Yale School of Medicine, New Haven, CT, USA

[5] Melanoma Center and Center for Immuno-Oncology, Dana-Farber Cancer Center, Boston, MA, USA

[6] Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

[7] Department of Neurosurgery, Brigham and Women's Hospital, Computational Neuroscience Outcomes Center, Boston, MA, USA

[8] Department of Pathology, Brigham and Women's Hospital, Dana-Farber Cancer Institute, Harvard Medical School, 75 Francis St., Boston, MA 02115, USA

HR	Hazard ratio
ICB	Immune checkpoint blockade
IQR	Interquartile range
NCCN	National Cancer Comprehensive Network
NCDB	National Cancer Database
OR	Odds ratio
RCT	Randomized controlled trial
95CI	95% confidence interval

Introduction

Melanoma incidence rates continue to rise faster than any other solid tumor, with the current lifetime risk for a person developing melanoma in the U.S. estimated to be 1 in 54 [1–3]. Although a majority of cases are diagnosed at an early stage where surgical excision is often curative, treatment of stage 4 melanoma has historically been limited given the low anti-tumor activity of conventional chemotherapies and cytokine therapy, resulting in a median OS time of less than 1 year [4].

However, the approvals of vemurafenib, a $BRAF^{V600}$ inhibitor, and ipilimumab, a monoclonal antibody directed against the inhibitory receptor CTLA-4, by the U.S. Food and Drug Administration (FDA) in 2011 heralded two new classes of drug treatments—oncogene-targeted therapy and ICB—that have drastically changed the systemic therapy of advanced melanoma. Current approved checkpoint immunotherapies include monoclonal antibody inhibitors of PD-1 (nivolumab and pembrolizumab) and CTLA-4 (ipilimumab) as well as the combination of nivolumab and ipilimumab. Approved targeted therapies for MAPK pathway dysregulation by BRAF mutation, which is implicated approximately half of melanomas, include BRAF inhibitors (vemurafenib, dabrafenib, and encorafenib) and MEK inhibitors (trametinib, cobimetinib, and binimetinib) [5–7].

By blocking the CTLA-4 receptor's inhibitory interactions with B7 ligands expressed on antigen-presenting cells, anti-CTLA-4 monoclonal antibodies (e.g., ipilimumab) permit the binding of the costimulatory B7 ligands with T cells' CD28 receptors, thus supplying the secondary activation signals needed for persistent T-cell activation [8]. Separately, expression of PD-1 surface receptors leads to T-cell exhaustion and terminal differentiation; anti-PD-1 monoclonal antibodies (e.g., nivolumab and pembrolizumab) can counteract this T-cell inhibitory mechanism. Thus, anti-CTLA-4 and anti-PD1 immunotherapies enable a robust expansion of tumor-specific T cells that mediate clinical efficacy in advanced melanoma patients. The initial randomized controlled trials (RCTs) of ipilimumab in stage 3 unresectable and stage 4 melanoma patients revealed improved response rates and OS in both previously treated and untreated patients. A substantial proportion of patients developed immune-related adverse events of varying severity on these trials [9–11]. The KEYNOTE-006 RCT comparing pembrolizumab to ipilimumab demonstrated significantly improved progression-free survival and OS, durable objective response rates, and reduced serious adverse effects associated with anti-PD-1 immunotherapy [12, 13]. Combined PD-1 and CTLA-4 blockade in the CheckMate 067 and 069 RCTs demonstrated improved PFS and OS compared to ipilimumab [14, 15]. Targeted agents including small molecules that specifically inhibit downstream effectors of the MAPK pathway, such as mutated BRAF (e.g., vemurafenib, dabrafenib, and encorafenib) and MEK (e.g., trametinib, cobimetinib, and binimetinib) have demonstrated remarkable clinical efficacy in $BRAF^{V600}$ mutant melanoma [3, 5–7, 16–20].

The current National Cancer Comprehensive Network (NCCN, v2.2018) guidelines for the initial treatment of stage 4 metastatic melanoma recommend systemic therapy with ICB and $BRAF^{V600}$/MEK-targeted therapy for patients with *BRAF*-mutant melanoma and ICB for *BRAF*-wildtype melanoma [21]. Specifically, first-line immunotherapy treatment includes anti-PD-1 monotherapy with nivolumab or pembrolizumab or combination anti-CTLA-4/PD-1 therapy with nivolumab/ipilimumab. For patients with *BRAF*-mutant melanoma, first-line-targeted therapy includes combination BRAF/MEK inhibitor therapy with either dabrafenib/trametinib or vemurafenib/cobimetinib, or BRAF inhibitor monotherapy with vemurafenib or dabrafenib. These recommendations have been shaped by the efficacy and safety results from a number of phase 2 and 3 randomized clinical trials [5, 13, 22–27]. With the success of these new therapeutic classes, conventional cytotoxic chemotherapy (e.g., dacarbazine, temozolomide, carboplatin/paclitaxel, and/or fotemustine) and biochemotherapy regimens (including high-dose IL-2 and interferon alfa-2b) no longer have a role in the first-line treatment of stage 4 metastatic cutaneous melanoma.

The introduction of these new therapeutic classes has been exciting for both melanoma patients and providers, given their initial successes in multiple RCTs and retrospective analyses [28]. Although multiple RCTs have rigorously examined the safety and efficacy of novel checkpoint immunotherapies and oncogene-targeted therapies in advanced melanoma, there has yet to be a wide-scale evaluation of OS in stage 4 melanoma following the approval of checkpoint immunotherapies and oncogene-targeted therapies in 2011. In this study, we examine the survival and management of melanoma patients who initially presented with stage 4 disease in the contemporary era of ICB and oncogene-targeted therapies from the National Cancer Database (NCDB), one of the largest cancer databases that include data from the

initial presentation for more than 70% of U.S. cancer patients [29].

Materials and methods

Data source and study design

The NCDB, a hospital-based nationwide cancer registry developed as a joint initiative between the American College of Surgeons and American Cancer Society and comprising more than 70% of newly diagnosed cancers in the United States, was queried for all patients newly diagnosed with cutaneous melanoma from 2004 to 2015 [29]. Cutaneous melanoma was identified by World Health Organization ICD-O3 morphological codes for malignant melanoma (i.e., 8720–8723, 8726, 8730, 8740–8746, 8750, 8760–8761, 8770–8774, and 8780, with behavior codes 2 and 3) and skin topographical codes (i.e., C44.0–44.9); as previously described [30, 31]. Patients were excluded if they were younger than 20 years, previously diagnosed with other cancers (i.e., a sequence of case greater than 1), lacked data on metastases, or only diagnosed at their index institution but were entirely treated elsewhere.

Variable design

Cases were classified as stage 4 (i.e., disseminated metastases) based on American Joint Committee on Cancer (AJCC, 7th ed.) M staging, using NCDB's AJCC variables and metastasis collaborative stage site-specific factors for cutaneous melanoma [30]. Clinicopathologic characteristics at presentation, including age, sex, race, insurance status, Charlson–Deyo comorbidity index (CDI), geographic region and type of treating hospital, year of diagnosis, AJCC pT and pN classification, LDH level, and the primary lesion's characteristics (i.e., site, histologic subtype, ulceration status, and mitotic proliferation index) were summarized and compared. Management characteristics included surgery for the primary lesion (i.e., no surgery, local excision, gross excision, or wide excision), resection of a metastatic lesion, radiotherapy, chemotherapy (including targeted therapy), and immunotherapy. Because the NCDB only encodes the initial first-line therapies for a patient and the NCCN guidelines have relegated both cytotoxic chemotherapeutics and biochemotherapeutics (i.e., interferon alfa-2b and high-dose IL-2) to second-line therapy for stage 4 patients who fail initial checkpoint immunotherapy, the overwhelming majority of immunotherapies and chemotherapies encoded in NCDB following FDA approvals in 2011 for melanoma patients should represent checkpoint immunotherapy and oncogene-targeted therapies, respectively.

Statistical analyses

Clinicopathologic characteristics were compared by χ^2 test and t test between melanoma patients who presented with disseminated metastasis and those who did not, and among the patients with disseminated disease, between those that were treated with immunotherapy vs. those that were not. Data elements missing $\geq 10\%$ of data were excluded from multivariable analyses. If patients were missing any data elements, they were excluded from any analyses of those data elements. Risk-adjusted predictors of presenting with disseminated disease or of receiving immunotherapy were assessed by multivariable logistic regression. For survival analysis in stage 4 melanoma patients, OS was evaluated from the date of diagnosis, with unadjusted OS differences compared by Kaplan–Meier plots and log-rank tests, as previously described [31]. The endpoint was date of death, with patients censored at the date of last follow-up. Due to the limited follow-up, the NCDB does not include survival information for patients diagnosed in the most recent year of the dataset, which for this release was 2015. Estimated OS was compared for stage 4 melanoma diagnosed before and after the start of FDA approvals of checkpoint immunotherapy and oncogene-targeted therapy (i.e., 2011). For stage 4 patients diagnosed after initial FDA approval (i.e., 2011+), OS was compared between those who received immunotherapy vs. those who did not; with additional survival landmark analyses to account for any immortal time bias. Landmark timepoints were selected for the median and mean time from diagnosis to receipt of immunotherapy. Predictors of OS were additionally assessed by multivariable Cox proportional hazards, adjusted for all clinicopathologic variables missing $< 10\%$ of data; and repeated for patients that reached the landmark timepoint. A two-sided p value < 0.05 was considered significant. Statistical analyses were performed with STATA (v14.2, StataCorp).

Results

Characteristics of patients presenting with stage 4 melanoma

A total of 407,386 patients diagnosed with cutaneous melanoma from 2004 to 2015 met inclusion criteria, of whom 4.4% ($n = 17{,}795$) initially presented with distant metastases (i.e., AJCC stage 4 or M1). The presenting characteristics of those with and without distant metastases are shown in Supplemental Table 1, along with multivariable logistic regression results for predictors of presenting with stage 4 disease at the time of first diagnosis. In multivariable logistic regression adjusted for variables with $< 10\%$ missing data, male sex [odds ratio (OR) 1.23, 95% confidence interval (95CI)

1.18–1.30], higher number of co-morbidities (CDI 1 vs. 0: OR 1.36, 95CI 1.27–1.45), black or Hispanic race (vs. white: OR 1.61, 95CI 1.35–1.93 and OR 1.46, 95CI 1.28–1.68; respectively), location of primary lesion, uninsured status (vs. privately insured: OR 2.36, 95CI 2.13–2.61), pT0 (i.e., no evidence of primary tumor) or pT4 (vs. pT1: OR 16.89, 95CI 15.32–18.64 and OR 19.83, 95CI 18.17–21.64; respectively), and nodal metastases (pN1 vs. pN0: OR 1.84, 95CI 1.70–1.98) remained significant independent predictors of presentation with stage 4 disease ($p < 0.001$ in each case). Without treatment, stage 4 patients had a median OS of 6.1 mos (95CI 5.4–6.6).

Improved overall survival of stage 4 melanoma patients following FDA approval of ICB and $BRAF^{V600}$-targeted therapies

Of the stage 4 melanoma patients, 47.1% ($n = 8389$) presented following FDA approval of the checkpoint immunotherapy ipilimumab and BRAF inhibitor vemurafenib in 2011 (i.e., 2011–2015, including the subsequent approvals of PD-1, MEK, and BRAF inhibitors). The median time to death/censorship was 8.4 months pre-approval (interquartile range [IQR] 3.2–24.1, with 84.9% reaching endpoint) and 9.4 months post-approval (IQR 3.3–24.7), with 70.9% reaching the endpoint. Following the FDA approvals, median OS among stage 4 melanoma patients increased to 10.2 months (95CI 9.6–10.7; $p < 0.001$) from 8.6 mos (95CI 8.3–8.9) pre-approval and 4-year OS improved to 23.5% (95CI 22.3–24.8) from 18.0% (95CI 17.2–18.8). Patients presenting with AJCC M1b (i.e., with metastatic lung involvement; 27.5%, 95CI 24.1–31.0; vs. 20.1%, 95CI 17.7–22.6; $p = 0.007$), M1c (i.e., any non-lung visceral metastasis or any distant metastasis with elevated LDH; 18.4%, 95CI 16.6–20.3; vs. 8.3%, 95CI 7.4–9.2; $p < 0.001$) demonstrated improved 4-year OS following FDA approval, as compared to pre-approval; whereas patients with M1a disease did not (45.7%, 95CI 41.9–49.5; vs. 42.6%, 95CI 39.9–45.3; $p = 0.16$).

Characteristics associated with receipt of ICB in stage 4 melanoma patients

The proportion of patients who received ICB rose from 16.1% in 2011 to 37.4% in 2015. The characteristics of post-approval stage 4 melanoma patients who were treated with and without ICB are shown in Table 1. Only 3.1% ($n = 194$) of those who did not receive ICB had additional information encoded about why ICB was not administered; of which, ICB was contraindicated in 25.3%, ICB was refused in 44.9%, and patients died prior to receiving ICB in 21.7%. In multivariable logistic regression adjusted for clinicopathologic variables with < 10% missing data, younger age (50–59 vs. 60–69 years: OR 1.22, 95CI 1.02–1.47), lower number of co-morbidities (CDI 1 vs. 0: OR 0.68, 95CI 0.57–0.82), being insured privately (vs. uninsured: OR 2.62, 95CI 1.89–3.65) or through Medicare (OR 2.14, 95CI 1.50–3.04), more recently diagnosed (2015 vs. 2011: OR 3.04, 95CI 2.47–3.73) at an academic/research hospital (vs. community cancer program: OR 2.07, 95CI 1.56–2.74), receiving radiotherapy (OR 1.59, 95CI 1.38–1.83), not receiving targeted therapy (vs. received targeted therapy: OR 4.86, 95CI 4.05–5.84), and not having brain metastases (vs. only subcutaneous metastasis: OR 0.72, 95CI 0.57–0.90) remained significant predictors of receiving ICB (Table 1). Patient sex, race, and site of the primary lesion, and excision of the primary lesion were not significantly associated with ICB treatment.

Immune checkpoint blockade was associated with improved risk-adjusted overall survival

Following FDA approval in 2011, 25.1% ($n = 2088$) of stage 4 patients received ICB and had significantly improved OS in risk-adjusted analyses (HR 0.57, 95CI 0.52–0.63, $p < 0.001$). ICB was associated with improved median OS (16.9 mos, 95CI 15.6–19.3; vs. 7.7 mos, 95CI 7.2–8.4, $p < 0.001$) and 4-year OS (32.4%, 95CI 29.5–35.3; vs. 21.0%, 95CI 19.6–22.2; Fig. 1). In these patients, the median and mean times to ICB receipt were 2.0 months and 2.5 months, respectively; ICB demonstrated improved median and 4-year OS in all survival landmark analyses using these timepoints as landmarks: in patients who survived at least 2.0 months, ICB resulted in improved median OS (19.3 mos, 95CI 17.1–21.0; vs. 13.0 mos, 95CI 12.2–13.8, $p < 0.001$) and 4-year OS (32.9%, 95CI 29.9–35.9; vs. 25.9%, 95CI 24.4–27.6; Fig. 2a); in patients who survived at least 2.5 months, ICB resulted in improved median OS (19.6 mos, 95CI 17.9–22.0; vs. 14.1 mos, 95CI 13.3–15.1, $p < 0.001$) and 4-year OS (33.6%, 95CI 31.5–37.7; vs. 27.1%, 95CI 25.5–28.8; Fig. 2b).

Overall survival for stage 4 melanoma patients diagnosed from 2011 to 2015 was risk-adjusted for variables with less than 10% of data missing (i.e., sex, age, year of diagnosis, CDI, race, insurance status, site of primary lesion, facility type, facility location, M stage, and treatment by primary excision, resection of metastatic lesion, radiotherapy, targeted therapy, and ICB), for which 4867 patients had complete data and 72.7% ($n = 3538$) reached the endpoint (Table 2 left panel). Clinicopathologically, patients who were female (hazard ratio [HR] 0.89, 95CI 0.83–0.96, $p = 0.002$), younger (≤ 49 vs. 60–69 years: HR 0.88, 95CI 0.77–1.00, $p = 0.04$), without comorbidities (CDI of 1 vs. 0: HR 1.29, 95CI 1.18–1.40, $p < 0.001$), insured privately (HR 0.67 vs. uninsured, 95CI 0.58–0.77, $p < 0.001$), insured through Medicare (HR 0.77 vs. uninsured, 95CI 0.66–0.90, $p = 0.001$), or had M1a disease

Table 1 Characteristics of post-approval stage 4 patients treated with immune checkpoint blockade

	% of stage 4 pts that received ICB				
	Total (*n*)	% received ICB	*Univariate χ2 p value*		
			Multivariable logistic regression		
			OR	95CI	*p* value
Sex					*< 0.001*
Male	5644	24.8	Reference		
Female	2664	25.8	0.99	0.87–1.14	0.92
Age (year)					*< 0.001*
20–29	161	36.7	No observations in multivar		
30–39	403	34.7	No observations in multivar		
40–49	897	30.2	1.61	1.29–2.01	**< 0.001**
50–59	1873	28.6	1.22	1.02–1.47	**0.03**
60–69	2147	26.6	Reference		
70–79	1647	22.7	0.81	0.67–0.98	**0.03**
80–89	999	12.3	0.35	0.27–0.45	**< 0.001**
90+	154	4.6	0.11	0.05–0.27	**< 0.001**
Year of diagnosis					*< 0.001*
2011	1558	16.1	Reference		
2012	1525	16.7	0.99	0.78–1.25	0.93
2013	1703	24.2	1.69	1.36–2.10	**< 0.001**
2014	1701	28.8	2.12	1.72–2.63	**< 0.001**
2015	1821	37.4	3.04	2.47–3.73	**< 0.001**
Comorbidity Index					*< 0.001*
0	6336	27.5	Reference		
1	1388	19.0	0.68	0.57–0.82	**< 0.001**
2	380	17.6	0.64	0.47–0.89	**0.007**
3	204	9.3	0.37	0.22–0.61	**< 0.001**
Race/ethnicity					0.28
White	7788	25.1	Reference		
Black	128	23.4	0.91	0.54–1.55	0.73
Asian/pacific islander	51	23.5	0.96	0.41–2.28	0.93
Hispanic	235	23.4	0.85	0.56–1.28	0.42
Other/unknown	106	34.0	1.08	0.62–1.88	0.78
Primary payer					*< 0.001*
Not insured	490	17.6	Reference		
Private insurance	3226	31.6	2.62	1.89–3.65	**< 0.001**
Medicaid	748	22.5	1.30	0.88–1.93	0.18
Medicare	3537	20.9	2.14	1.50–3.04	**< 0.001**
Other government	135	25.9	2.10	1.15–3.86	**0.02**
Unknown status	172	23.8	1.63	0.88–3.02	0.12
AJCC pT[a]					*< 0.001*
Is	40	7.5			
0	2415	26.6			
1	350	18.9			
2	274	25.9			
3	389	26.5			
4	1315	29.7			
X	1994	21.9			
AJCC pN[a]					*< 0.001*
0	879	20.0			

Table 1 (continued)

	% of stage 4 pts that received ICB				
	Total (*n*)	% received ICB	*Univariate χ2 p value*		
			Multivariable logistic regression		
			OR	95CI	*p* value
1	702	27.5			
2	338	29.9			
3	468	31.6			
X	3289	24.6			
Primary lesion site					*0.01*
Upper limb/shoulder	567	27.0	Reference		
Lower limb/hip	604	27.0	1.19	0.83–1.70	0.35
Trunk	1223	25.2	0.89	0.65–1.22	0.48
Face	219	22.4	0.81	0.49–1.35	0.43
Scalp/neck	465	31.8	1.31	0.90–1.91	0.15
Ear	77	24.7	1.04	0.47–2.31	0.92
Lip	6	33.3	8.31	0.66–104.05	0.10
Eyelid	8	37.5	3.23	0.43–24.52	0.26
Overlapping sites	16	0	Omitted due to 0 events		
NOS	5123	24.3	0.81	0.60–1.09	0.16
Melanoma subtype[a]					0.57
Superficial spreading	258	29.5			
Nodular	808	31.7			
Acral lentiginous	51	23.5			
Lentigo maligna	50	34.0			
Histology ulceration[a]					*0.42*
No	1786	26.1			
Yes	1499	27.4			
LDH level[a]					*< 0.001*
Within normal limits	681	40.5			
< 1.5× normal	666	39.2			
1.5–10× normal	268	27.6			
> 10× normal	99	23.2			
Facility type					*< 0.001*
Community program	610	15.3	Reference		
Cancer center	2979	19.6	1.24	0.93–1.65	0.14
Academic/research	3300	30.6	2.07	1.56–2.74	**< 0.001**
Integrated network	855	23.7	1.64	1.18–2.28	**0.003**
Facility Location					*< 0.001*
New England	396	27.8	Reference		
Middle Atlantic	1107	29.0	1.06	0.78–1.43	0.72
South Atlantic	1785	22.7	0.84	0.62–1.13	0.24
East North Central	1229	24.2	0.87	0.64–1.18	0.38
East South Central	550	23.3	0.81	0.57–1.16	0.25
West North Central	605	24.3	0.93	0.66–1.32	0.70
West South Central	564	17.6	0.60	0.41–0.88	**0.009**
Mountain	469	31.8	1.24	0.87–1.77	0.24
Pacific	1039	22.4	0.91	0.66–1.25	0.54
Metastatic sites					*< 0.001*
M1a (distant skin/LN)	1151	24.0	Reference		
M1b (lung)	1091	26.0	1.38	1.09–1.74	**0.008**

Table 1 (continued)

	% of stage 4 pts that received ICB				
	Total (*n*)	% received ICB	*Univariate χ2 p value*		
			Multivariable logistic regression		
			OR	95CI	*p* value
M1c (other sites)	3220	29.9	1.48	1.22–1.81	**< 0.001**
Brain involvement	2229	20.5	0.71	0.56–0.89	**0.003**
Excision of primary lesion					*0.62*
Gross excision	467	23.1	Reference		
None	5797	24.7	1.31	0.96–1.78	0.09
Local excision	174	26.4	1.48	0.90–2.43	0.12
Wide excision	1105	26.0	1.20	0.88–1.64	0.25
Resection of metastatic lesion					*0.03*
None	5842	24.3	Reference		
Resected	2388	26.6	0.98	0.86–1.13	0.83
Targeted therapy					*< 0.001*
None	5961	30.2	Reference		
Treated	2101	12.0	0.21	0.17–0.25	**< 0.001**
Radiotherapy					*< 0.001*
None	5027	23.6	Reference		
Irradiated	3240	27.7	1.59	1.38–1.83	**< 0.001**

Italicized *p* values refer to the significance of that variable in univariate X2 analysis

Bold *p* values indicate statistical significance in multivariable regression

[a]Variables missing ≥ 10% of data were excluded from multivariable regression

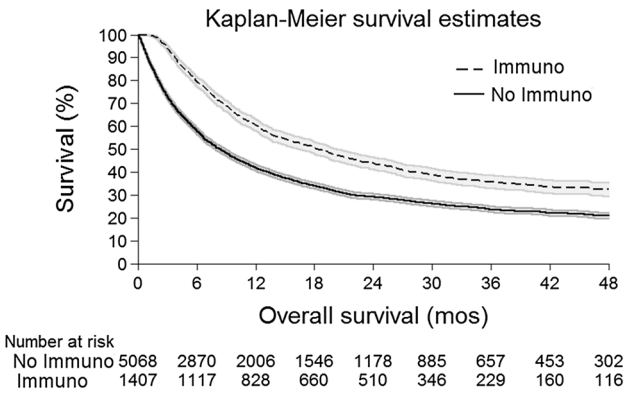

Fig. 1 Kaplan–Meier OS Curves for ICB Treatment in post-approval stage 4 melanoma patients. Survival curve of patients treated with ICB (dashed line, $n = 1407$) demonstrated significantly improved OS compared to no ICB (solid line, $n = 5068$; $p < 0.001$), displayed with the associated number at risk table. 95% confidence interval: gray shading

(reference M1b: HR 0.59, 95CI 0.51–0.68, $p < 0.001$) had significantly improved OS; whereas race had no association with OS. With regards to treatment, resection of a metastatic lesion (HR 0.48, 95CI 0.44–0.52), targeted therapy (HR 0.73, 95CI 0.68–0.79), and ICB (HR 0.57, 95CI 0.52–0.63) were significantly associated with improved OS ($p < 0.001$ in each case). The significant OS improvement associated with ICB persisted in risk-adjusted Cox proportional hazards for patients who reached the landmark timepoints of 2.0 months (HR 0.79, 95CI 0.72–0.88, $p < 0.001$; Table 2 middle panel) and 2.5 months (HR 0.85, 95CI 0.77–0.94, $p = 0.001$; Table 2 right panel).

Discussion

Over the past few decades, melanoma care has been advanced by improved screening, standardized surgical protocols, and increased use of sentinel lymph node biopsy [32]. Stage 4 melanoma has historically been challenging to treat and portended a poor prognosis. In the absence of treatment, median OS for stage 4 melanoma at initial presentation is approximately 6 months in our analyses. Preventative measures such as regular skin exams are increasingly being used to detect melanoma at an earlier stage, yet certain subpopulations continue to be at high risk of presenting with advanced melanoma. Specifically, our multivariable logistic analyses showed that patients who presented with stage 4 melanoma were significantly more likely to be male, non-white, uninsured, afflicted by

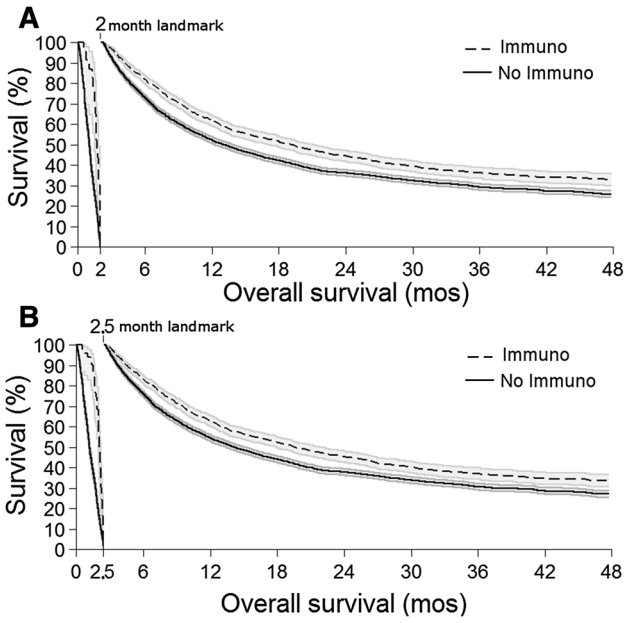

Fig. 2 Kaplan–Meier landmark OS curves for ICB treatment in post-approval stage 4 melanoma patients. Using landmark timepoints of **a** 2.0 and **b** 2.5 months, all survival curves of patients treated with ICB (dashed lines) demonstrated significantly improved OS compared to no ICB patients (solid lines, all $p < 0.001$). **a** There were 23 ICB (1.6%) and 1040 no ICB (20.5%) patients who reached endpoint/censorship before the 2.0 month landmark; and **b** 51 ICB (3.6%) and 1224 no ICB (24.1%) patients who reached endpoint/censorship before the 2.5 month landmark. 95% confidence interval: gray shading

more co-morbidities, diagnosed at community facilities, with AJCC pT0 (i.e., no evidence of primary tumor) or pT4 disease, and positive ulceration status—as compared to those who present at an earlier stage. Less visible or accessible sites of primary melanoma were also associated with significantly higher rates of presenting with stage 4 disease, reinforcing the need for comprehensive skin exams during screening. With the series of FDA approvals for ICB and BRAF-targeted therapies beginning in 2011, new, more effective agents are now available for the first-line treatment of metastatic melanoma.

Our findings are in line with NCCN management recommendations for stage 4 melanoma

The NCDB, by containing more than 70% of all cancer patients newly diagnosed in the U.S., enables the robust examination of melanoma patients' management and survival in the "real-world" setting beyond clinical trials. Our findings are in line with the NCCN guidelines (version 2.2018) for first-line therapy for stage 4 melanoma, in which a multidisciplinary approach including ICB, BRAF-targeted therapy, and resection of metastatic disease is recommended based on improved OS of these approaches in clinical trials. Following FDA approval of ipilimumab and vemurafenib in 2011, and including subsequent approvals of the BRAF inhibitor dabrafenib (2013), the MEK inhibitor trametinib (2013), and the anti-PD-1 monoclonal antibodies pembrolizumab (2014) and nivolumab (2014), we detected a 31% relative increase in 4-year OS of patients with stage 4, as compared to patients diagnosed prior to 2011. Treatment with ICB was associated with improved median and 4-year OS in our unadjusted and risk-adjusted landmark survival analyses.

In our analyses, stage 4 patients treated with ICB were younger, more recently diagnosed, privately insured, treated at academic facilities, had fewer co-morbidities, and were treated with radiotherapy, and less likely to receive targeted therapy, as compared to patients who did not receive immunotherapy. Uninsured patients were significantly less likely to receive immunotherapy than patients insured privately or through Medicare, which translated into worse OS outcomes in risk-adjusted analyses, suggesting that improved coverage and access to these treatments is critical for stage 4 melanoma patients. Additionally, in this "real-world" treatment cohort we observed that stage 4 melanoma patients were significantly more likely to receive immunotherapy at academic centers, even though melanoma care is primarily delivered in the community setting in the U.S. Because ICB provides the best chance for durable disease control, and potentially even a cure, for advanced melanoma patients, our findings suggest that community practice paradigms may trail behind NCCN guidelines.

Clinicopathologic characteristics and overall survival in stage 4 melanoma

In evaluating additional therapeutic modalities for stage 4 patients, we demonstrate that resection of metastatic lesions also conferred a survival advantage. The NCCN recommends resection of non-primary lesions for patients with limited or symptomatic metastases [21]. The surgical debulking of metastatic lesions reduces the overall tumor burden and is hypothesized to synergistically decrease tumor-induced immune suppression [33]. We additionally demonstrated that wide excision of the primary melanoma lesion was associated with improved OS. Radiation therapy is recommended with palliative intent, particularly for brain metastases to reduce tumor size and to ameliorate neurologic symptoms. Despite reports of synergy between checkpoint immunotherapy and radiation therapy via an abscopal effect, a survival advantage was not associated with radiotherapy in our risk-adjusted analyses [34]. Additionally, female sex has long been associated with a favorable prognosis in melanoma patients, particularly in patients with in-transit and

Table 2 Multivariable proportional hazards for OS in post-approval stage 4 melanoma patients, stratified by landmark timepoints

	Multivariable Cox regression								
	All			Landmark = 2.0 mos			Landmark = 2.5 mos		
	HR	95CI	*p* value	HR	95CI	*p* value	HR	95CI	*p* value
Sex									
Female (ref male)	0.89	0.83–0.96	**0.002**	0.87	0.81–0.95	**0.001**	0.86	0.79–0.94	**0.001**
Age (year)									
≤49	0.88	0.77–1.00	**0.04**	0.81	0.70–0.93	**0.003**	0.81	0.70–0.93	**0.004**
50–59	0.97	0.88–1.07	0.57	0.90	0.81–1.01	0.08	0.91	0.81–1.03	0.13
60–69	Reference			Reference			Reference		
70–79	1.11	1.01–1.23	**0.04**	1.09	0.97–1.23	0.14	1.09	0.97–1.23	0.16
80+	1.35	1.21–1.52	**< 0.001**	1.42	1.24–1.62	**< 0.001**	1.45	1.26–1.67	**< 0.001**
Year of diagnosis									
Per year	0.96	0.93–0.99	**0.01**	0.92	0.89–0.96	**< 0.001**	0.92	0.88–0.95	**< 0.001**
Comorbidity Index									
0	Reference			Reference			Reference		
1	1.29	1.18–1.40	**< 0.001**	1.15	1.04–1.27	**0.009**	1.16	1.04–1.29	**0.006**
2	1.54	1.33–1.78	**< 0.001**	1.52	1.27–1.81	**< 0.001**	1.46	1.21–1.76	**< 0.001**
3	1.85	1.54–2.23	**< 0.001**	1.72	1.36–2.18	**< 0.001**	1.64	1.27–2.12	**< 0.001**
Race/ethnicity									
White	Reference			Reference			Reference		
Black	1.12	0.85–1.49	0.42	1.07	0.76–1.52	0.68	1.09	0.77–1.56	0.62
Asian/pacific islander	0.91	0.59–1.41	0.68	0.96	0.59–1.56	0.88	0.96	0.58–1.58	0.87
Hispanic	0.87	0.70–1.08	0.21	0.98	0.77–1.26	0.89	1.02	0.79–1.31	0.90
Other/unknown	0.95	0.71–1.27	0.72	1.07	0.77–1.47	0.70	1.01	0.71–1.42	0.97
Primary payer	Reference			Reference			Reference		
Not insured									
Private insurance	0.67	0.58–0.77	**< 0.001**	0.76	0.63–0.90	**0.002**	0.73	0.61–0.87	**0.001**
Medicaid	0.93	0.78–1.11	0.43	1.02	0.83–1.26	0.86	0.99	0.80–1.23	0.92
Medicare	0.77	0.66–0.90	**0.001**	0.84	0.69–1.01	0.07	0.80	0.65–0.97	**0.02**
Other government	0.65	0.48–0.89	**0.006**	0.81	0.58–1.14	0.22	0.79	0.55–1.12	0.18
Unknown status	0.84	0.62–1.13	0.26	0.89	0.62–1.26	0.51	0.87	0.60–1.25	0.44
Primary lesion site									
Upper limb/shoulder	Reference			Reference			Reference		
Lower limb/hip	1.05	0.86–1.29	0.64	1.11	0.89–1.38	0.36	1.15	0.92–1.45	0.23
Trunk	1.05	0.88–1.26	0.59	1.02	0.84–1.24	0.87	1.07	0.87–1.32	0.50
Face	0.75	0.57–0.98	**0.04**	0.77	0.58–1.04	0.09	0.84	0.62–1.14	0.26
Scalp/neck	0.68	0.54–0.86	**0.001**	0.72	0.57–0.92	**0.01**	0.77	0.60–0.99	**0.04**
Ear	1.41	0.92–2.15	0.11	1.41	0.89–2.24	0.14	1.58	0.99–2.52	0.05
Lip	0.59	0.08–4.24	0.60	0.68	0.09–4.87	0.70	0.74	0.10–5.33	0.77
Eyelid	1.74	0.64–4.72	0.28	2.10	0.66–6.65	0.21	2.58	0.81–8.21	0.11
Overlapping sites	1.43	0.67–3.06	0.36	1.29	0.47–3.50	0.62	1.46	0.54–3.98	0.46
NOS	0.85	0.71–1.01	0.06	0.86	0.71–1.05	0.14	0.92	0.75–1.13	0.42
Facility type									
Community program	Reference			Reference			Reference		
Cancer center	1.03	0.91–1.17	0.64	0.97	0.83–1.12	0.65	0.96	0.82–1.12	0.61
Academic/research	0.81	0.71–0.92	**0.002**	0.80	0.69–0.93	**0.004**	0.79	0.68–0.92	**0.002**
Integrated network	1.02	0.88–1.20	0.76	0.98	0.81–1.17	0.79	0.94	0.78–1.14	0.54
Facility location									
New England	Reference			Reference			Reference		
Middle Atlantic	0.92	0.78–1.10	0.36	1.06	0.87–1.30	0.58	1.09	0.89–1.35	0.41
South Atlantic	0.94	0.80–1.11	0.49	1.06	0.87–1.28	0.59	1.09	0.89–1.33	0.42
East North Central	1.14	0.96–1.35	0.13	1.27	1.04–1.55	**0.02**	1.31	1.06–1.61	**0.01**
East South Central	0.97	0.80–1.17	0.72	1.08	0.86–1.35	0.52	1.13	0.89–1.43	0.31

Table 2 (continued)

	Multivariable Cox regression								
	All			Landmark = 2.0 mos			Landmark = 2.5 mos		
	HR	95CI	*p* value	HR	95CI	*p* value	HR	95CI	*p* value
West North Central	1.14	0.94–1.37	0.18	1.32	1.06–1.63	**0.01**	1.33	1.06–1.67	**0.01**
West South Central	0.98	0.81–1.19	0.85	1.14	0.91–1.44	0.25	1.18	0.93–1.50	0.17
Mountain	0.93	0.76–1.13	0.47	1.08	0.86–1.35	0.54	1.10	0.87–1.39	0.44
Pacific	0.81	0.68–0.97	**0.02**	0.96	0.78–1.18	0.69	0.97	0.78–1.20	0.78
Metastatic sites									
M1a (distant skin/LN)	Reference			Reference			Reference		
M1b (lung)	1.69	1.47–1.95	**< 0.001**	1.63	1.41–1.90	**< 0.001**	1.63	1.40–1.91	**< 0.001**
M1c (other sites)	2.66	2.36–3.00	**< 0.001**	2.26	1.98–2.57	**< 0.001**	2.20	1.93–2.51	**< 0.001**
Brain involvement	3.17	2.77–3.62	**< 0.001**	2.57	2.22–2.97	**< 0.001**	2.50	2.16–2.91	**< 0.001**
Excision of primary lesion									
Gross excision	Reference			Reference			Reference		
None	1.53	1.29–1.81	**< 0.001**	1.21	1.01–1.46	**0.04**	1.19	0.98–1.44	0.08
Local excision	1.10	0.84–1.44	0.47	1.02	0.76–1.37	0.88	1.01	0.75–1.37	0.93
Wide excision	0.84	0.70–1.00	0.05	0.88	0.73–1.06	0.17	0.91	0.75–1.10	0.31
Resection of metastatic lesion									
Yes (ref no.)	0.48	0.44–0.52	**< 0.001**	0.58	0.53–0.63	**< 0.001**	0.60	0.55–0.66	**< 0.001**
Targeted therapy									
Yes (ref no.)	0.73	0.68–0.79	**< 0.001**	1.04	0.95–1.14	0.36	1.13	1.03–1.23	**0.008**
Radiotherapy									
Yes (ref no.)	1.06	0.99–1.15	0.11	1.37	1.25–1.49	**< 0.001**	1.35	1.23–1.48	**< 0.001**
ICB									
Yes (ref no.)	0.57	0.52–0.63	**< 0.001**	0.79	0.72–0.88	**< 0.001**	0.85	0.77–0.94	**0.001**

Bold *p* values indicate statistical significance in multivariable regression

lymph node metastases [35]. We found that female sex was also an independent predictor of improved OS in stage 4 patients.

Limitations

Although the NCDB represents one of the largest cancer registries worldwide, the NCDB only captures data from a patient's initial presentation. Therefore, our findings specifically pertain to patients diagnosed with stage 4 disease at the time of initial diagnosis and do not include the (larger) proportion of patients diagnosed at an earlier stage who later develop disseminated metastasis [29]. Additionally, the NCDB only includes OS data and does not allow for the evaluation of recurrence or progression. The NCDB lacks detailed data about symptomatology and resectability of metastases; as well as granular details about systemic therapy agents, doses, combinations, toxicities, and subsequent courses; and does not rigorously collect data on reasons why patients did not receive immunotherapy. Additionally, in the era of precision oncology where various cancer types are increasingly characterized and categorized by molecular alterations, a key limitation of the NCDB is its lack of molecular data—in particular, BRAF mutational status in melanoma patients. Receipt of targeted therapy was incorporated into multivariable analysis in part as a proxy for BRAF mutational status.

Conclusions

Using a large-scale database analysis of the "real-world" treatment population of melanoma patients, we demonstrate substantial improvement in OS for patients presenting with stage 4 cutaneous melanoma following the 2011 FDA approvals of checkpoint immunotherapy and BRAF-targeted therapies. Our findings are in line with the compelling clinical efficacy found in phase 3 clinical trials, leading to the FDA approvals of the new agents and substantiate the OS benefit that has led to the recommendations delineated in the current NCCN guidelines for first-line management with ICB and BRAF-targeted therapy in stage 4 melanoma. Our results portray the dramatic successes in recent years in the management of metastatic melanoma and suggest that there

are opportunities for expanding coverage and access to these novel agents in community practice.

Author contributions ASD and CKZ contributed to the data analysis and interpretation, and manuscript writing. FSH, TRS, and PAO contributed to the experimental design, interpretation, and manuscript writing. JBI designed and supervised the study, conducted data analysis and interpretation, and wrote the manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval This study was conducted in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments. This study was deemed exempt from Partners Healthcare's IRB review (2018P001413) and for this type of study formal consent is not required. There were no human participants, procedures, animal experiments, or cell line experiments.

References

1. Siegel RL, Miller KD, Jemal A (2016) Cancer statistics, 2016. CA Cancer J Clin 66:7–30. https://doi.org/10.3322/caac.21332
2. Glazer AM, Winkelmann RR, Farberg AS, Rigel DS (2017) Analysis of trends in US melanoma incidence and mortality. JAMA Dermatol 153:225–226. https://doi.org/10.1001/jamadermatol.2016.4512
3. Eggermont AM, Spatz A, Robert C (2014) Cutaneous melanoma. Lancet 383:816–827. https://doi.org/10.1016/S0140-6736(13)60802-8
4. Force J, Salama AK (2017) First-line treatment of metastatic melanoma: role of nivolumab. ImmunoTargets Ther 6:1–10. https://doi.org/10.2147/ITT.S110479
5. Ascierto PA, McArthur GA, Dréno B et al (2016) Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. Lancet Oncol 17:1248–1260. https://doi.org/10.1016/S1470-2045(16)30122-X
6. Sosman JA, Kim KB, Schuchter L et al (2012) Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. N Engl J Med 366:707–714. https://doi.org/10.1056/NEJMoa1112302
7. Dummer R, Ascierto PA, Gogas HJ et al (2018) Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 19:603–615. https://doi.org/10.1016/S1470-2045(18)30142-6
8. Ott PA, Hodi FS, Robert C (2013) CTLA-4 and PD-1/PD-L1 blockade: new immunotherapeutic modalities with durable clinical benefit in melanoma patients. Clin Cancer Res 19:5300–5309. https://doi.org/10.1158/1078-0432.CCR-13-0143
9. Hodi FS, O'Day SJ, McDermott DF et al (2010) Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 363:711–723. https://doi.org/10.1056/NEJMoa1003466
10. Wolchok JD, Neyns B, Linette G et al (2010) Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. Lancet Oncol 11:155–164. https://doi.org/10.1016/S1470-2045(09)70334-1
11. Ascierto PA, Del Vecchio M, Robert C et al (2017) Ipilimumab 10 mg/kg versus ipilimumab 3 mg/kg in patients with unresectable or metastatic melanoma: a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol 18:611–622. https://doi.org/10.1016/S1470-2045(17)30231-0
12. Robert C, Schachter J, Long GV et al (2015) Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med 372:2521–2532. https://doi.org/10.1056/NEJMoa1503093
13. Postow MA, Chesney J, Pavlick AC et al (2015) Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med 372:2006–2017. https://doi.org/10.1056/NEJMoa1414428
14. Larkin J, Chiarion-Sileni V, Gonzalez R et al (2015) Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 373:23–34. https://doi.org/10.1056/NEJMoa1504030
15. Wolchok JD, Chiarion-Sileni V, Gonzalez R et al (2017) Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med 377:1345–1356. https://doi.org/10.1056/NEJMoa1709684
16. Chapman PB, Hauschild A, Robert C et al (2011) Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 364:2507–2516. https://doi.org/10.1056/NEJMoa1103782
17. Long GV, Stroyakovskiy D, Gogas H et al (2015) Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. Lancet 386:444–451. https://doi.org/10.1016/S0140-6736(15)60898-4
18. Long GV, Stroyakovskiy D, Gogas H et al (2014) Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med 371:1877–1888. https://doi.org/10.1056/NEJMoa1406037
19. Larkin J, Ascierto PA, Dréno B et al (2014) Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med 371:1867–1876. https://doi.org/10.1056/NEJMoa1408868
20. Robert C, Karaszewska B, Schachter J et al (2015) Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med 372:30–39. https://doi.org/10.1056/NEJMoa1412690
21. National Comprehensive Cancer Network (2018) NCCN clinical practice guidelines in oncology: Melanoma version 2.2018. National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#melanoma. Accessed 1 Mar 2018
22. Larkin J, Lao CD, Urba WJ et al (2015) Efficacy and safety of nivolumab in patients with BRAF V600 mutant and BRAF wild-type advanced melanoma: a pooled analysis of 4 clinical trials. JAMA Oncol 1:433–440. https://doi.org/10.1001/jamaoncol.2015.1184
23. Atkins MB, Larkin J (2016) Immunotherapy combined or sequenced with targeted therapy in the treatment of solid tumors: current perspectives. J Natl Cancer Inst 108:414. https://doi.org/10.1093/jnci/djv414
24. Ribas A, Puzanov I, Dummer R et al (2015) Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. Lancet Oncol 16:908–918. https://doi.org/10.1016/S1470-2045(15)00083-2
25. Weber JS, D'Angelo SP, Minor D et al (2015) Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a

randomised, controlled, open-label, phase 3 trial. Lancet Oncol 16:375–384. https://doi.org/10.1016/S1470-2045(15)70076-8
26. Weber JS, Gibney G, Sullivan RJ et al (2016) Sequential administration of nivolumab and ipilimumab with a planned switch in patients with advanced melanoma (CheckMate 064): an open-label, randomised, phase 2 trial. Lancet Oncol 17:943–955. https://doi.org/10.1016/S1470-2045(16)30126-7
27. Hodi FS, Chesney J, Pavlick AC et al (2016) Combined nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial. Lancet Oncol 17:1558–1568. https://doi.org/10.1016/S1470-2045(16)30366-7
28. Pasquali S, Chiarion-Sileni V, Rossi CR, Mocellin S (2017) Immune checkpoint inhibitors and targeted therapies for metastatic melanoma: a network meta-analysis. Cancer Treat Rev 54:34–42. https://doi.org/10.1016/j.ctrv.2017.01.006
29. Boffa DJ, Rosen JE, Mallin K et al (2017) Using the national cancer database for outcomes research: a review. JAMA Oncol 3:1722–1728. https://doi.org/10.1001/jamaoncol.2016.6905
30. LeBoit PE, Burg G, Weedon D, Sarasain A (2006) Pathology and genetics of skin tumours, 3rd edn. IARC Press, Lyon
31. Iorgulescu JB, Harary M, Zogg CK et al (2018) Improved risk-adjusted survival for melanoma brain metastases in the era of checkpoint blockade immunotherapies: results from a national cohort. Cancer Immunol Res 6:1–7. https://doi.org/10.1158/2326-6066.CIR-18-0067
32. Shaikh WR, Dusza SW, Weinstock MA et al (2016) Melanoma thickness and survival trends in the United States, 1989–2009. J Natl Cancer Inst 108:1. https://doi.org/10.1093/jnci/djv294
33. Howard JH, Thompson JF, Mozzillo N et al (2012) Metastasectomy for distant metastatic melanoma: analysis of data from the first Multicenter Selective Lymphadenectomy Trial (MSLT-I). Ann Surg Oncol 19:2547–2555. https://doi.org/10.1245/s10434-012-2398-z
34. Barker CA, Postow MA (2014) Combinations of radiation therapy and immunotherapy for melanoma: a review of clinical outcomes. Int J Radiat Oncol Biol Phys 88:986–997. https://doi.org/10.1016/j.ijrobp.2013.08.035
35. Joosse A, de Vries E, Eckel R et al (2011) Gender differences in melanoma survival: female patients have a decreased risk of metastasis. J Investig Dermatol 131:719–726. https://doi.org/10.1038/jid.2010.354