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

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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 the associated unadjusted and risk-adjusted overall survival (OS).

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Compliance with Ethical Standards:

Ethical approval and ethical standards: 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.

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

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-yr 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-yr 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

Précis:

Improvement of overall survival was found following the approvals of immune checkpoint blockade and targeted therapies in a “real-life” national cohort of stage 4 melanoma patients.

Keywords

Melanoma; Metastasis; Immune Checkpoint Blockade; Targeted therapy; Immunotherapy

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 one 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-PD-1 immunotherapies enable a robust expansion of tumor-specific T-cells that mediate clinical efficacy in advanced melanoma patients. The initial 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 IF-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 randomized controlled trials (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 includes 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-03 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-old, were previously diagnosed with other cancers (*i.e.* a sequence of case greater than 1), lacked data on metastases, or were 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 versus those that were not. Data elements missing 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 versus 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 2-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 2004–2015 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 comorbidities (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=8,389) 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-yr 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-yr 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 yrs vs. 60–69 yrs: 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% ($n=2,088$) 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-yr OS (32.4%, 95CI: 29.5–35.3; vs. 21.0%, 95CI: 19.6–22.2; **Figure 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-yr 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-yr OS (32.9%, 95CI: 29.9–35.9; vs. 25.9%, 95CI: 24.4–27.6; **Figure 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-yr OS (33.6%, 95CI: 31.5–37.7; vs. 27.1%, 95CI: 25.5–28.8; **Figure 2b**).

Overall survival for stage 4 melanoma patients diagnosed from 2011–2015 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 4,867 patients had complete data and 72.7% ($n=3,538$) 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 yrs vs. 60–69 yrs: 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 (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, 95%CI: 0.72–0.88, $p<0.001$; **Table 2 middle panel**) and 2.5 months (HR 0.85, 95%CI: 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 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 surveillance. 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 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 therapies’ 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

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

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Number at risk

No Immuno	5068	2870	2006	1546	1178	885	657	453	302
Immuno	1407	1117	828	660	510	346	229	160	116

Figure 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=1,407) demonstrated significantly improved OS compared to no ICB (solid line, n=5,068; $p<0.001$), displayed with the associated number at risk table. 95% confidence interval: grey shading.

Figure 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 1,040 no ICB (20.5%) patients who reached endpoint/censorship before the 2.0 month landmark; and (b) 51 ICB (3.6 %) and 1,224 no ICB (24.1%) patients who reached endpoint/censorship before the 2.5 month landmark. 95% confidence interval: grey shading.

Table 1.

Characteristics of Post-Approval Stage 4 Patients Treated with Immune Checkpoint Blockade

	% of Stage 4 Pts that received ICB		<i>univariate χ^2 p-value</i>		
	total (n)	% received ICB	Multivar Logistic regression		
			OR	95%CI	p-value
Sex					<i><0.001</i>
Male	5,644	24.8	<i>Reference</i>		
Female	2,664	25.8	0.99	0.87–1.14	0.92
Age (yr)					<i><0.001</i>
20–29	161	36.7	<i>no observations in multivar</i>		
30–39	403	34.7	<i>no observations in multivar</i>		
40–49	897	30.2	1.61	1.29–2.01	<0.001
50–59	1,873	28.6	1.22	1.02–1.47	0.03
60–69	2,147	26.6	<i>Reference</i>		
70–79	1,647	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					<i><0.001</i>
2011	1,558	16.1	<i>Reference</i>		
2012	1,525	16.7	0.99	0.78–1.25	0.93
2013	1,703	24.2	1.69	1.36–2.10	<0.001
2014	1,701	28.8	2.12	1.72–2.63	<0.001
2015	1,821	37.4	3.04	2.47–3.73	<0.001
Comorbidity Index					<i><0.001</i>
0	6,336	27.5	<i>Reference</i>		
1	1,388	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					<i>0.28</i>
White	7,788	25.1	<i>Reference</i>		
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					<i><0.001</i>

% of Stage 4 Pts that received ICB					
	<i>univariate χ^2 p-value</i>				
	total (n)	% received ICB	Multivar Logistic regression		
			OR	95%CI	p-value
Not insured	490	17.6	<i>Reference</i>		
Private insurance	3,226	31.6	2.62	1.89–3.65	<0.001
Medicaid	748	22.5	1.30	0.88–1.93	0.18
Medicare	3,537	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*					<i><0.001</i>
is	40	7.5			
0	2,415	26.6			
1	350	18.9			
2	274	25.9			
3	389	26.5			
4	1,315	29.7			
X	1,994	21.9			
AJCC pN*					<i><0.001</i>
0	879	20.0			
1	702	27.5			
2	338	29.9			
3	468	31.6			
X	3,289	24.6			
Primary Lesion Site					<i>0.01</i>
Upper limb/Shoulder	567	27.0	<i>Reference</i>		
Lower limb/Hip	604	27.0	1.19	0.83–1.70	0.35
Trunk	1,223	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	<i>omitted due to 0 events</i>		
NOS	5,123	24.3	0.81	0.60–1.09	0.16
Melanoma Subtype*					<i>0.57</i>
Superficial spreading	258	29.5			
Nodular	808	31.7			

	% of Stage 4 Pts that received ICB		<i>univariate χ^2 p-value</i>		
	total (n)	% received ICB	Multivar Logistic regression		
			OR	95%CI	p-value
Acral lentiginous	51	23.5			
Lentigo maligna	50	34.0			
Histology Ulceration *					
No	1,786	26.1			
Yes	1,499	27.4			
LDH Level *					
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					
Community program	610	15.3	Reference		
Cancer center	2,979	19.6	1.24	0.93–1.65	0.14
Academic/Research	3,300	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					
New England	396	27.8	Reference		
Middle Atlantic	1,107	29.0	1.06	0.78–1.43	0.72
South Atlantic	1,785	22.7	0.84	0.62–1.13	0.24
East North Central	1,229	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	1,039	22.4	0.91	0.66–1.25	0.54
Metastatic Sites					
M1a (distant skin/LN)	1,151	24.0	Reference		
M1b (lung)	1,091	26.0	1.38	1.09–1.74	0.008
M1c (other sites)	3,220	29.9	1.48	1.22–1.81	<0.001
Brain involvement	2,229	20.5	0.71	0.56–0.89	0.003
Excision of Primary Lesion					

% of Stage 4 Pts that received ICB					
	<i>univariate χ^2 p-value</i>				
	total (n)	% received ICB	Multivar Logistic regression		
			OR	95%CI	p-value
Gross excision	467	23.1	<i>Reference</i>		
None	5,797	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	1,105	26.0	1.20	0.88–1.64	0.25
Resection of Metastatic Lesion					<i>0.03</i>
None	5,842	24.3	<i>Reference</i>		
Resected	2,388	26.6	0.98	0.86–1.13	0.83
Targeted Therapy					<i><0.001</i>
None	5,961	30.2	<i>Reference</i>		
Treated	2,101	12.0	0.21	0.17–0.25	<0.001
Radiotherapy					<i><0.001</i>
None	5,027	23.6	<i>Reference</i>		
Irradiated	3,240	27.7	1.59	1.38–1.83	<0.001

* Variables missing 10% of data were excluded from multivariable regression.

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	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	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 (yr)									
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	<i>Reference</i>			<i>Reference</i>			<i>Reference</i>		
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	<i>Reference</i>			<i>Reference</i>			<i>Reference</i>		
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	<i>Reference</i>			<i>Reference</i>			<i>Reference</i>		
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									
Not insured	<i>Reference</i>			<i>Reference</i>			<i>Reference</i>		
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	<i>Reference</i>			<i>Reference</i>			<i>Reference</i>		

Multivariable Cox Regression									
	All			Landmark 2.0 mos			Landmark 2.5 mos		
	HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value
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	<i>Reference</i>			<i>Reference</i>			<i>Reference</i>		
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	<i>Reference</i>			<i>Reference</i>			<i>Reference</i>		
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
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)	<i>Reference</i>			<i>Reference</i>			<i>Reference</i>		
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	<i>Reference</i>			<i>Reference</i>			<i>Reference</i>		
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									

Multivariable Cox Regression									
	All			Landmark 2.0 mos			Landmark 2.5 mos		
	HR	95%CI	<i>p-value</i>	HR	95%CI	<i>p-value</i>	HR	95%CI	<i>p-value</i>
Yes (<i>Ref no</i>)	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 (<i>Ref no</i>)	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 (<i>Ref no</i>)	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 (<i>Ref no</i>)	0.57	0.52–0.63	<0.001	0.79	0.72–0.88	<0.001	0.85	0.77–0.94	0.001