EFFECTIVENESS AND UTILIZATION OF FIRST-LINE IMMUNE CHECKPOINT INHIBITORS FOR PATIENTS WITH EXTRACRANIAL & INTRACRANIAL METASTATIC MELANOMA

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Background We previously demonstrated the effectiveness of 2nd-line immune checkpoint inhibitors (ICI) for stage 4 melanoma patients.¹ In late 2015, ICI was FDA-approved and NCCN-recommended in the 1st-line setting.³ Here we assess the real-world effectiveness and utilization of 1st-line ICI among advanced melanoma patients following 2015.

Methods Patients newly-diagnosed with stage 4 melanoma during 2010–2018 were identified using the U.S. National Cancer Database (comprises >70% of newly-diagnosed cancers).⁵ Post-approval 1st-line ICI's overall survival (OS, estimated by Kaplan-Meier techniques) and utilization were assessed for patients diagnosed in 2016–2018, using multivariable Cox and logistic regression, respectively. To account for immortal time bias in receiving ICI, we only included those patients in regression analyses who survived at least until the landmark timepoint, defined as the median time from diagnosis to ICI initiation (49 days).¹ The more conservative 75th percentile diagnosis-to-ICI-initiation landmark timepoint (80 days) was also evaluated. Analyses were adjusted for patient, tumor, treatment, socioeconomic, and care setting characteristics.

Results Among 14,912 stage 4 melanoma patients, 1st-line immunotherapy utilization increased from 8.4% in 2010 to 39.2% in 2015, and 57.9% in 2018. (Figure 1) Altogether, median OS improved from 8.0 mos (95%CI=7.3–8.8) in 2010 to 16.1 mos (95%CI=14.0–18.5) in 2017. For patients diagnosed in 2016+ who survived at least until the landmark timepoints, OS improved with 1st-line ICI (median OS=33.1 mos, 95%CI=29.4–40.5; vs just 13.6 mos for no ICI, 95%CI=12.1–16.1; HR=0.58, 99%CI=0.50–0.68; padj<0.001) (figure 2A–B)—even after adjusting for patient, disease, and treatment factors, and using either landmark. (Table 1) This included patients with either brain metastases (ICI median OS=16.7 mos, 95%CI=13.1–19.9; vs no ICI=7.8 mos, 95%CI=6.8–9.0; padj<0.001) or lung metastases (ICI median OS=26.0 mos, 95%CI=20.0–33.0; vs no ICI=9.3 mos, 95%CI=8.0–10.5; padj<0.001). (Figure 2C–F) We then used multivariable logistic regression (with landmark timepoints to reduce bias from early mortality) to identify putative barriers to receiving 1st-line ICI in 2016+. Advanced melanoma patients who had more comorbidities or brain metastases, or who were older, uninsured/Medicaid-insured, from the poorest quartile of households, or managed at community hospitals were less likely to receive ICI. (all p<0.05, table 2)

Abstract 246 Figure 1 (A) The percent of stage 4 melanoma patients diagnosed each year who received 1st-line immune checkpoint inhibitor (ICI), with stratification by (B) brain or lung metastatic involvement, and (C) treating hospital type.

Abstract 246 Table 1 Multivariable Cox regression analysis of overall survival among stage 4 melanoma patients in 2016+. To account for immortal time bias, landmark timepoints were utilized, defined by the median (i.e. 49d; panels A, C, E) and 75th percentile (i.e. 80d; panels B, D, F) time from diagnosis to ICI initiation. Patients had to survive at least as long as the landmark timepoint to be included in the analysis. Results are shown for all stage 4 patients, as well as those with brain or lung metastases. p values are only displayed for the primary association of interest.

	Overall			Brain mets			Lung mets			
	Landmark 48d n=2,973	Landmark 80d n=2,750	Landmark 48d n=1,143	Landmark 80d n=993	Landmark 48d n=1,405	Landmark 80d n=1,251				
	HR	95% CI	p val	HR	95% CI	p val	HR	95% CI	p val	
1st-line ICI	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
No	0.58 (0.50-0.68)	<.001	0.72 (0.61-0.85)	<.001	0.48 (0.39-0.6)	<.001	0.57 (0.45-0.73)	<.001	0.45 (0.36-0.55)	<.001
Yes										
Age at diagnosis (yr)										
<50	0.80 (0.65-1)	0.80 (0.64-1)	0.73 (0.54-0.98)	0.69 (0.50-0.95)	0.74 (0.55-1)	0.74 (0.55-1.03)				
50-59	0.91 (0.74-1.1)	0.89 (0.72-1.1)	0.99 (0.75-1.3)	0.94 (0.69-1.28)	0.87 (0.66-1.15)	0.88 (0.65-1.2)				
60-69	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
70-79	1.43 (1.10-1.72)	1.36 (1.11-1.67)	1.45 (1.11-1.89)	1.33 (0.99-1.8)	1.31 (1.01-1.68)	1.28 (0.96-1.7)				
≥80	1.48 (1.36-2.07)	1.77 (1.41-2.22)	1.77 (1.26-2.5)	1.88 (1.28-2.76)	1.45 (1.08-1.94)	1.57 (1.13-2.17)				
Charlson-Deyo comorbidity index										
0	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
1	1.13 (0.91-1.36)	1.10 (0.89-1.35)	1.09 (0.82-1.45)	1.06 (0.77-1.46)	1.01 (0.77-1.32)	1.01 (0.75-1.35)				
≥2	1.33 (1.07-1.65)	1.25 (0.99-1.59)	1.28 (0.93-1.76)	1.29 (0.91-1.83)	1.39 (1.02-1.9)	1.28 (0.88-1.8)				
Chemotherapy										
None	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Single-agent	0.80 (0.68-1.2)	1.00 (0.82-1.21)	0.82 (0.56-1.19)	0.84 (0.62-1.13)	0.67 (0.45-0.99)	0.78 (0.51-1.21)				
Multi-agent	0.77 (0.62-0.95)	none	0.66 (0.40-0.88)	0.83 (0.61-1.15)	0.55 (0.41-0.74)	0.76 (0.51-1.04)				
Radiotherapy (ref no)	1.29 (1.11-1.51)	1.35 (1.13-1.6)	1.34 (1.06-1.68)	1.49 (1.14-1.94)	1.54 (1.23-1.93)	1.62 (1.28-2.09)				
Year of diagnosis	0.97 (0.85-1.11)	0.99 (0.86-1.15)	0.99 (0.82-1.2)	1.03 (0.83-1.29)	0.99 (0.82-1.19)	1.01 (0.82-1.24)				
Metastases (ref no)	0.78 (0.68-0.9)	0.75 (0.63-0.87)	0.82 (0.67-1.01)	0.76 (0.6-0.96)	0.72 (0.6-0.88)	0.69 (0.56-0.85)				
Brain mets (ref no)	1.94 (1.65-2.28)	1.83 (1.55-2.16)	All have brain mets	All have brain mets	1.75 (1.42-2.2)	1.71 (1.35-2.2)				
Lung mets (ref no)	1.25 (1.08-1.45)	1.17 (1.01-1.36)	1.34 (1.08-1.65)	1.33 (1.05-1.68)	All have lung mets	All have lung mets				
Liver mets (ref no)	1.75 (1.49-2.05)	1.58 (1.32-1.88)	1.46 (1.13-1.88)	1.35 (1.01-1.8)	1.51 (1.22-1.87)	1.34 (1.05-1.71)				
Brain mets (ref no)	1.62 (1.38-1.89)	1.60 (1.35-1.9)	1.42 (1.11-1.81)	1.41 (1.07-1.86)	1.70 (1.37-2.1)	1.62 (1.28-2.05)				
Distant LN mets (ref no)	1.12 (0.96-1.29)	1.10 (0.94-1.29)	1.11 (0.93-1.5)	1.11 (0.85-1.46)	1.05 (0.85-1.29)	0.99 (0.78-1.25)				
Other organ mets (ref no)	1.05 (0.92-1.21)	1.03 (0.88-1.19)	1.06 (0.84-1.33)	1.03 (0.81-1.33)	1.08 (0.88-1.32)	1.08 (0.86-1.36)				

ICI = immune checkpoint inhibitor. HR = hazard ratio. CI = confidence interval. LN = lymph node.

Abstract 246 Table 2 Multivariable logistic regression analysis of 1st-line immune checkpoint inhibitor (ICI) receipt among stage 4 melanoma patients in 2016+. To account for bias due to early mortality, landmark timepoints were utilized, defined by the median (i.e. 49d) and 75th percentile (i.e. 80d) time from diagnosis to ICI initiation. Patients had to survive at least as long as the landmark timepoint to be included in the analysis. Results are shown for all stage 4 patients, as well as those with brain or lung metastases. Variables that demonstrate a significant association with ICI receipt are highlighted in yellow.

	Landmark 49d n=3,678			Landmark 80d n=3,459		
	OR	95% CI	p val	OR	95% CI	p val
Age at diagnosis (yr)						
<50	1.33	(0.91-1.94)	0.05	1.34	(0.91-1.97)	0.06
50-59	0.99	(0.74-1.33)	0.958	0.99	(0.74-1.34)	0.96
60-69	Ref			Ref		
70-79	0.78	(0.59-1.03)	0.02	0.54	(0.63-1.13)	0.13
≥80	0.44	(0.32-0.61)	<.001	0.45	(0.32-0.63)	<.001
Sex						
Male	Ref			Ref		
Female	0.91	(0.74-1.12)	0.253	0.90	(0.72-1.11)	0.19
Race/Ethnicity						
White, non-Hispanic	Ref			Ref		
Black, non-Hispanic	1.45	(0.65-3.26)	0.235	1.47	(0.64-3.37)	0.23
Asian/Pacific Islander	0.93	(0.29-2.96)	0.874	0.88	(0.27-2.82)	0.77
Hispanic	0.78	(0.43-1.43)	0.292	0.77	(0.41-1.46)	0.3
Other	1.29	(0.47-3.56)	0.51	1.27	(0.41-3.89)	0.58
n/a	0.77	(0.2-2.99)	0.616	0.72	(0.18-2.82)	0.54
Charlson-Deyo comorbidity index						
0	Ref			Ref		
1	0.91	(0.69-1.19)	0.356	0.91	(0.69-1.21)	0.42
≥2	0.72	(0.53-0.98)	0.007	0.75	(0.54-1.05)	0.03
Year of diagnosis	1.10	(0.98-1.24)	0.039	1.02	(0.9-1.15)	0.72
Primary skin site						
Lip	0.71	(0.05-10.6)	0.741	0.63	(0.04-9.61)	0.66
Eyelid	0.20	(0.02-2.05)	0.074	0.18	(0.02-1.88)	0.06
External ear	1.74	(0.52-5.78)	0.235	2.29	(0.6-8.82)	0.11
Face	0.89	(0.47-1.69)	0.651	0.85	(0.44-1.64)	0.54
Scalp & neck	1.16	(0.73-1.85)	0.406	1.18	(0.73-1.91)	0.38
Trunk	Ref			Ref		
Upper limb & shoulder	0.96	(0.62-1.49)	0.813	0.92	(0.58-1.44)	0.62
Lower limb & hip	1.53	(0.97-2.43)	0.017	1.56	(0.97-2.52)	0.02
Overlapping	2.00	(0.32-12.54)	0.329	3.04	(0.37-25.09)	0.18
Skin, NOS	0.91	(0.64-1.3)	0.498	0.88	(0.61-1.28)	0.37
Liver mets (ref no)	1.03	(0.81-1.31)	0.777	1.08	(0.83-1.4)	0.44
Lung mets (ref no)	1.56	(1.29-1.91)	<.001	1.59	(1.3-1.96)	<.001
Bone mets (ref no)	1.05	(0.83-1.34)	0.584	1.12	(0.87-1.45)	0.25
Brain mets (ref no)	0.55	(0.43-0.7)	<.001	0.57	(0.44-0.74)	<.001
Distant LN mets (ref no)	1.51	(1.21-1.89)	<.001	1.59	(1.26-2.01)	<.001
Other organ mets (ref no)	0.99	(0.81-1.22)	0.945	0.98	(0.8-1.21)	0.82
Primary site surgery						
None	0.96	(0.68-1.35)	0.733	1.00	(0.7-1.43)	0.99
Excisional biopsy	1.02	(0.7-1.48)	0.884	1.07	(0.72-1.57)	0.67
Gross or wide excision	Ref			Ref		
Radiotherapy (ref no)	1.91	(1.5-2.44)	<.001	1.92	(1.49-2.49)	<.001
Chemotherapy						
None	Ref			Ref		
Single-agent	0.19	(0.12-0.32)	<.001	0.18	(0.11-0.3)	<.001
Multi-agent	0.11	(0.07-0.15)	<.001	0.10	(0.07-0.14)	<.001
Metastasectomy (ref no)	1.03	(0.81-1.31)	0.731	1.06	(0.83-1.36)	0.56
Insurance status						
Not Insured	0.60	(0.36-1.01)	0.01	0.63	(0.37-1.09)	0.03
Private insurance	Ref			Ref		
Medicaid	0.57	(0.39-0.84)	<.001	0.56	(0.37-0.84)	<.001
Medicare	0.78	(0.6-1.03)	0.02	0.79	(0.59-1.04)	0.03
Other Government	0.37	(0.18-0.77)	<.001	0.35	(0.17-0.74)	<.001
Unknown	0.62	(0.24-1.6)	0.194	0.70	(0.24-1.99)	0.38
Median household income of patient's ZIP code						
< \$38,227	Ref			Ref		
\$38,227-50,353	1.29	(0.94-1.77)	0.035	1.36	(0.98-1.88)	0.02
\$50,354-63,332	1.14	(0.84-1.57)	0.269	1.15	(0.83-1.59)	0.27
≥\$63,333	1.40	(1.03-1.9)	0.005	1.52	(1.1-2.09)	<.001
Hospital program type						
Community	0.65	(0.43-0.98)	0.007	0.68	(0.44-1.06)	0.02
Comprehensive community	0.58	(0.46-0.72)	<.001	0.57	(0.45-0.72)	<.001
Academic/NCI comprehensive	Ref			Ref		
Integrated Network	0.70	(0.53-0.92)	<.001	0.69	(0.51-0.91)	<.001
Hospital location						
New England	1.46	(0.87-2.43)	0.058	1.47	(0.86-2.5)	0.06
Middle Atlantic	1.20	(0.85-1.71)	0.169	1.25	(0.86-1.79)	0.12
South Atlantic	1.07	(0.79-1.46)	0.56	1.09	(0.79-1.51)	0.47
East North Central	Ref			Ref		
East South Central	1.08	(0.72-1.62)	0.632	1.18	(0.77-1.81)	0.31
West North Central	1.59	(1.03-2.45)	0.006	1.71	(1.08-2.71)	<.001
West South Central	1.20	(0.8-1.81)	0.242	1.19	(0.78-1.82)	0.29
Mountain	1.51	(0.94-2.42)	0.024	1.58	(0.97-2.57)	0.02
Pacific	1.17	(0.82-1.66)	0.259	1.14	(0.79-1.65)	0.36

ICI = immune checkpoint inhibitor. OR = odds ratio. CI = confidence interval. LN = lymph node.

Abstract 246 Figure 2 Overall survival associated with 1st-line immune checkpoint inhibitors (ICI) for stage 4 melanoma patients diagnosed after 2015 (A-B), including patients with brain (C-D) and lung metastases (E-F). To account for immortal time bias, landmark timepoints were utilized, defined by the median (i.e. 49d; panels A, C, E) and 75th percentile (i.e. 80d; panels B, D, F) time from diagnosis to ICI initiation. Patients had to survive at least as long as the landmark timepoint to be included in the analysis.

Conclusions Following FDA-approval in 2015, 1st-line ICI was associated with dramatic improvements in OS for stage 4 melanoma patients—including those with brain or lung metastases. As of 2018, 42% of patients still weren't receiving 1st-line ICI in the U.S.—particularly patients who were underinsured, from the poorest quartile of households, or managed at community hospitals—suggesting that disparities exist in guideline-recommended 1st-line ICI utilization for advanced melanoma patients.

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