

Impact of tumor mutational burden on checkpoint inhibitor drug eligibility and outcomes across racial groups

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ABSTRACT

The FDA approval of immune checkpoint inhibitors for cancers with tumor mutation burden (TMB) of at least 10 mut/Mb is postulated to reduce healthcare disparities by broadly expanding treatment eligibility. In a cohort of 39,400 patients with available genomic and race data, black and Asian patients were less likely to have TMB-high cancers in multiple types of malignancies based on the currently approved cut-off. Decreasing TMB thresholds preferentially increased the eligibility of minority patients for immune checkpoint inhibitors while retaining predictive value of treatment benefit in a cohort of immune checkpoint inhibitor treated patients. This study highlights differing distributions of TMB-high cancers between racial groups and provides guidance in developing more rational eligibility criteria for immune checkpoint inhibitors.

INTRODUCTION

Given the transformative impact of immune checkpoint inhibitors (ICIs) on cancer outcomes for a subset of patients, biomarkers to guide selection of patients who benefit from immunotherapies have been intensely investigated. Early observations in melanoma and non-small cell lung cancer demonstrated that ICI activity was associated with tumor mutation burden (TMB), which ultimately contributes to neoantigen load.^{1 2} TMB may explain differences in ICI response rates across different types of cancers, with malignancies associated with high rates of mutagenesis such as skin and lung cancers being among the most ICI sensitive cancers.³ Multiple lines of evidence support an association between TMB and ICI activity within multiple cancer types, though no consensus has been reached in determining how TMB should be applied as a predictive biomarker.⁴

Based on the phase 2 KEYNOTE-158 trial, pembrolizumab was approved by the Food and Drug Administration (FDA) for patients with refractory solid cancers harboring a TMB ≥ 10 mut/Mb.⁵ Such cancers with a TMB ≥ 10 mut/Mb were labeled as TMB-high cancers and associated with greater response

rates.⁶ However, TMB-high cancers were not shown to be associated with longer median progression-free or overall survival.⁶ In addition, cancers with <10 mut/MB had non-trivial response rates and lower TMB cutoffs were not precisely explored, bringing into question the clinical and scientific basis of the FDA approved cut-off.⁶ While the expanded eligibility of patients to immunotherapies is purported to reduce cancer treatment disparities, racial differences in TMB and ICI treatment outcomes have not been investigated.⁷ Here, we demonstrate that cancers in Black and Asian patients were less likely to harbor TMB ≥ 10 mut/Mb across multiple cancer types. Thus, the 10 mut/Mb cut-off may result in fewer non-White patients meeting eligibility for ICIs, although this imbalance would be alleviated by lowering the definition of high TMB. In a large cohort of ICI-treated patients, we show that lower numerical cutoffs for high TMB retain predictive value of ICI benefit regardless of race, which may have implications for determining ICI eligibility.

TMB-high cancers are less frequent in blacks and Asians across two large genomic cohorts

We analyzed data from among the two largest tumor sequencing efforts to date including The Cancer Genome Atlas (TCGA) spanning 30 cancer types (n=8347) and Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) cohorts spanning 49 cancer types (n=31,053). All eligible patients included adults with solid cancers and race data (see online supplemental methods). TMB was calculated as the number of all non-synonymous, somatic mutations identified per Mb of the length of genome sequenced. Using the 10 mut/Mb cut-off, TMB-high cancers (excluding melanomas where a majority of cases would have been classified as TMB-high) accounted for 10.3% and 11.3% of cases in TCGA and MSK-IMPACT cohorts, respectively. Across both



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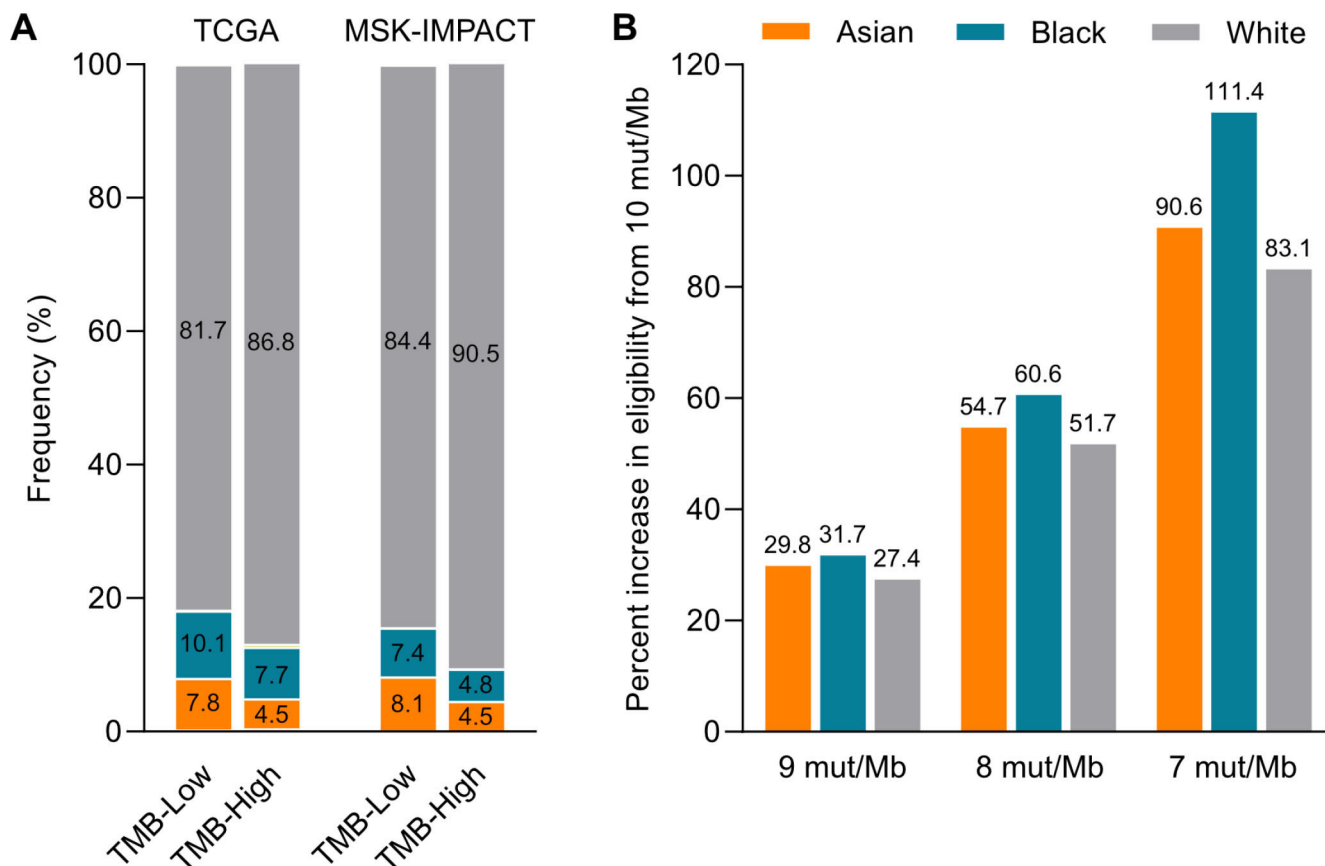


Figure 1 Race of eligible patients for immunotherapies and tumor mutation burden (TMB) cutoffs. (A) Proportions of patients with TMB-high or TMB-low cancers by race across The Cancer Genome Atlas (TCGA) and Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) cohorts. In the TCGA cohort, blacks (OR 0.72; 95% CI 0.55 to 0.93, $p=0.01$) and Asian (OR 0.54; 95% CI 0.39 to 0.76, $p<0.001$) patients were less likely to have cancers with high TMB. Similarly, in the MSK-IMPACT cohort, blacks (OR, 0.61; 95% CI 0.52 to 0.72, $p<0.001$) and Asian (OR, 0.52; 95% CI 0.44 to 0.62, $p<0.001$) patients were less likely to have cancers with high TMB. (B) Percent increase in patients across different race eligible for immunotherapy based on different TMB cutoffs.

cohorts, black (237/2787; OR 0.64; 95% CI 0.55 to 0.73, $p<0.001$) and Asian (198/2789; OR 0.53; 95% CI 0.49 to 0.62, $p<0.001$) patients were less likely to have cancers with high TMB, compared with white patients (3925/29356) (figure 1A and online supplemental table 1). Genetic ancestry could be determined for the TCGA cohort, and categorizing patients by ancestry assignments generated from a prior TCGA Network analysis showed that patients of African (OR 0.77; 95% CI 0.60 to 0.98, $p=0.04$) and Asian (OR 0.62; 95% CI 0.45 to 0.84, $p=0.002$) descent were less likely to have cancers with high TMB, compared with patients of European descent (online supplemental figure 1A).⁸ Even when restricting the analysis to tumor types enrolled in the KEYNOTE-158 trial with at least a 1% prevalence of TMB-high cancers, Black and Asian patients were less likely to have TMB-high cancers (online supplemental figure 1B). Decreasing the TMB cut-off preferentially increased the proportion of eligible black and Asian patients (figure 1B). The sparsity of patients of other races in either cohort precluded analyses of other racial minority groups.

Eligible patient demographics may be affected by differences in the proportion of constituent cancer types, particularly as some cancers may be more frequent in one racial group or associated with higher TMBs. However, logistic regression analysis showed that after adjusting for age, sex, cohort, stage, biopsy site (primary vs metastasis), and cancer type, black (OR 0.76; 95% CI 0.65 to 0.89, $p=0.001$) and Asian (OR 0.65; 95% CI 0.55 to 0.77) patients were less likely to have TMB-high cancers (online supplemental table 2). We repeated the regression analysis after patients were stratified by cancer type which showed a significant or trend association between TMB-high cancers and White patients in multiple cancer types including bladder, colon, breast, unknown primary, and endometrial cancers (online supplemental table 3). Exceptions were found in renal cell carcinomas where TMB-high cancers were enriched in black and Asian patients, and in non-small cell lung cancers where TMB-high cancers were enriched in black patients but reduced in Asian patients.

Neither the TCGA or MSK-IMPACT were designed as population-based studies. To examine the generalizability of the combined TCGA and MSK-IMPACT cohort, we assessed the correlation between the number of cases sequenced per cancer type and US cancer incidence based on Surveillance, Epidemiology, and End Results (online supplemental figure 2). We found a high correlation among 38 cancer types with available incidence data which accounted for 97% of all sequenced cancers ($p < 0.001$). The correlation coefficient of 0.87 indicates that 75% of the variance in cases sequenced across different cancer types is explained by US cancer incidence.

Outcomes among TMB-high and TMB-low cancers are treatment context dependent

To assess whether a TMB cut-off of 10 mut/Mb is associated with clinical outcomes across patients of different race, we analyzed subsets of patients in the MSK-IMPACT cohort with available outcome data who were treated with systemic therapies for advanced cancers. In the non-ICI cohort, 7600 patients comprised of 6396 white, 553 black, and 651 Asian patients received non-ICI systemic agents.⁹ In the ICI cohort, 1867 patients including 1604 white, 128 black, and 135 Asian patients were treated with anti-PD-1/PD-L1/CTLA-4 therapies as any line of therapy.⁹ We used multivariable Cox regression analyses to determine if TMB ≥ 10 mut/Mb was associated with overall survival determined from the time of diagnosis in patients stratified by race and treatment type, noting that statistical power to detect associations may be limited for minorities due to smaller sample sizes.

After adjusting for sex, age, and cancer type, TMB-high cancers in the non-ICI cohort were significantly associated with worse overall survival among white (HR 1.33; 95% CI 1.11 to 1.59) and Asian (HR 2.29; 95% CI 1.22 to 4.29) patients (figure 2A). TMB-high cancers also demonstrated a trend toward worse overall survival among Black patients (HR 1.75; 95% CI 0.90 to 3.40). In contrast, TMB-high cancers in the ICI cohort were associated with improved overall survival among White patients (HR 0.62; 95% CI 0.52 to 0.74) and had no significant association with survival among black (HR 0.99; 95% CI 0.49 to 1.99) and Asian patients ((HR 0.55; 95% CI 0.20 to 1.52) (figure 2A). These results indicate that the association between TMB-high cancers and overall survival is dependent on treatment context regardless of race.

TMB cutoffs less than 10 mut/Mb may be predictive of ICI benefit across racial groups

To assess the predictive value of TMB cutoffs among patients across different racial groups, we assessed the objective response rate (including partial and complete responses) to ICIs among 1594 patients in the ICI-cohort with available response data after stratifying patients by race. By varying cutoffs to define TMB-high cancers, we found that a TMB cut-off of at least 6 mut/Mb was still significantly associated with a higher

probability of objective response in white and black patients (figure 2B). In Asian patients, a trend association towards increased objective responses was observed beginning with a TMB cut-off of 8 mut/Mb (figure 2B). Cox regression analyses adjusting for age, sex, and cancer type showed that progression-free survival, defined as the time from the initiation of an ICI to disease progression or death, was also greater in TMB-high cancers when using cut-off thresholds of at least 8 mut/Mb across all races (online supplemental figure 3A). Cox regression analyses of overall survival did not demonstrate an association between any cut-off threshold and survival for black or Asian patients, but the much smaller sample sizes of minority patients in these analyses does not preclude the possibility of a survival benefit (online supplemental figure 3B). Collectively, these results suggest that a range of TMB thresholds have similar predictive value of ICI benefit across race.

DISCUSSION

Our analyses demonstrate that the distribution of TMB values in tumors may differ among patients of different racial groups, and that the predictive value of high TMB is similar in both ICI and non-ICI contexts. Because of these differences, the use of a single, tissue-agnostic definition of high TMB to define eligibility for anti-PD-1 therapy will not necessarily be a mechanism to alleviate disparities in access to these treatments. To achieve the goal of reducing disparate eligibility for anti-PD-1 therapy under current FDA approvals, the numerical definition of high TMB may need to be set at a lower number. However, the clinical and economic value of doing so remains to be clarified, as it remains to be tested whether such a change would improve survival outcomes or cost-effectiveness. While this study leverages among the largest genomic datasets with available race data and ICI outcomes, the limited sample size of minority patients precludes precise definitions of optimal TMB cutoffs for individual cancer types. Nonetheless, this work underscores a clear need to understand mechanisms of TMB variation across race, and the importance of including minorities within ICI studies to clarify the differential impact of predictive biomarkers.

The biological basis for the differing prevalence of TMB-high cancers between racial groups needs to be clarified, but genomic differences in cancers are known to exist among different racial populations. While we adjusted for age and sex, other clinical factors likely to contribute to TMB such as smoking history and it remains to be investigated whether other patient characteristics may explain a lower frequency of TMB-high cancers in minorities.

There are several limitations to this analysis including the fact that neither the TCGA or MSK-IMPACT cohorts were designed to be representative of the US population and the lack of sufficient data to assess other minority races. Self-reported data on race as used in this study is

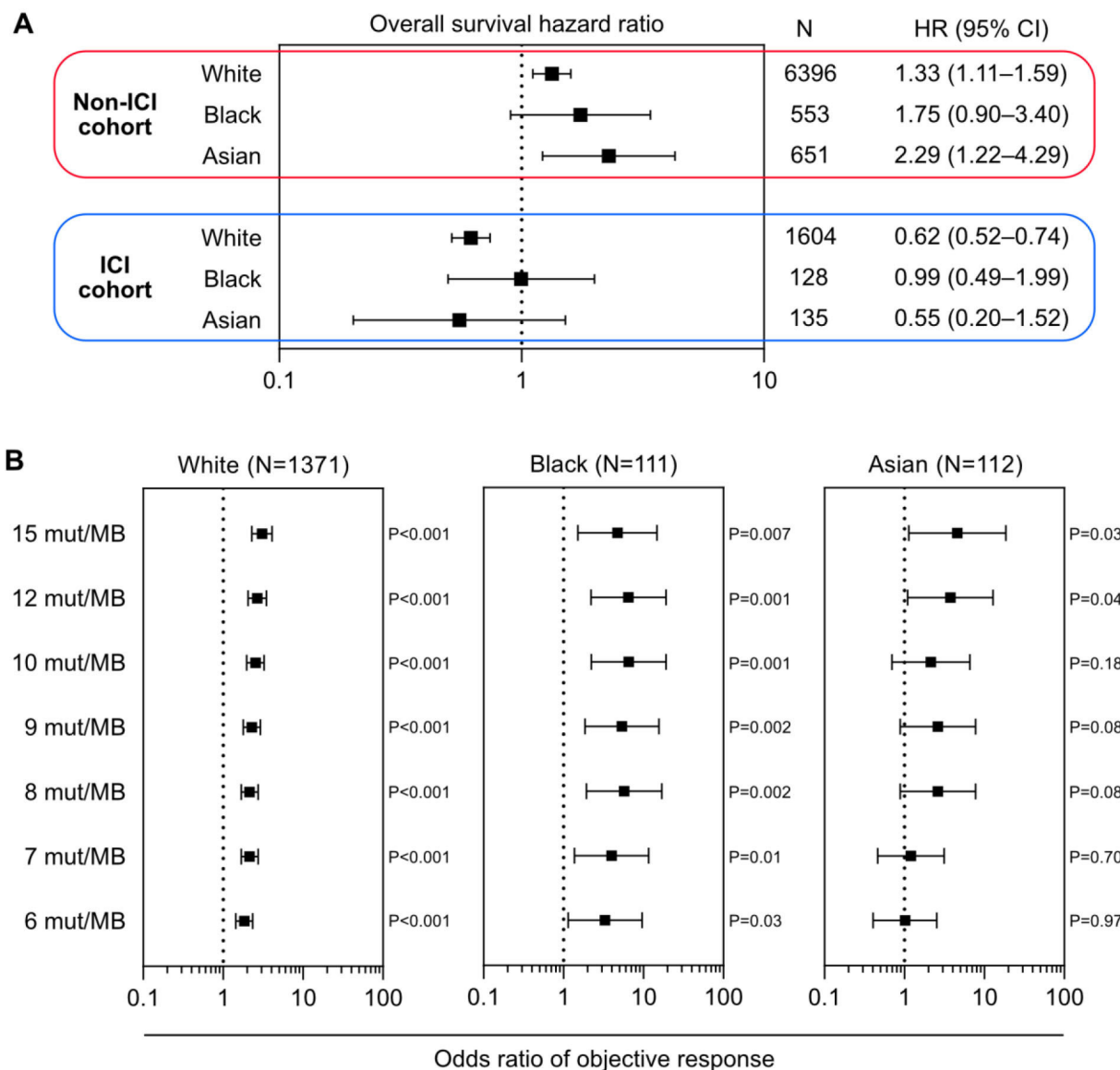


Figure 2 Association between tumor mutation burden and overall survival across race. (A) Multivariable Cox regression analysis of the non-immune checkpoint inhibitor (ICI) cohort and ICI cohort after stratifying patients by race was performed with overall survival as the endpoint. HRs adjusted for age, sex, and cancer type indicate the association between TMB-high or TMB-low status and overall survival. (B), Logistic regression was performed in the ICI cohort after stratifying patients by race using different cutoffs to define TMB-high cancers. ORs indicate the odds of an objective response in TMB-high vs TMB-low cancers. The error bars represent the 95% CIs. All statistical tests were two sided.

the preferred method for collecting race data in most biomedical studies, but is associated with several limitations including a limited relevance to human genetic variation. Estimating race through genetic ancestry is possible with high-density genotyping, but this approach is not applicable to most patients examined in this study and may be less relevant to characterizing healthcare disparities. Nonetheless, analysis of patients categorized by genetic ancestry in the TCGA cohort showed a consistent enrichment of TMB-low cancers in patients of African and Asian descent.

There is conflicting evidence on the use of TMB as a predictive marker across multiple cancer types, and whether TMB cutoffs should be different for specific cancer types remains to be determined. Given the absence

of reliable or validated predictive cancer-specific TMB cutoffs, it remains to be determined how alternative definitions of TMB-high cancers may impact ICI eligibility across racial groups. It should be also noted that the definition of high TMB in the current FDA approval is based on a commercial gene panel companion diagnostic, and whether the current cut-off of 10 mut/Mb can be reliably used in other assays remains to be clarified. In addition, methods used to estimate TMB remain to be standardized, and efforts to harmonize assays, sequencing technologies, and computational algorithms are underway.¹⁰

Given the limited number of minority patients with available treatment data across different cancer types, our conclusions regarding the predictive value of TMB across racial groups requires further study. Limited sample sizes

of minority patients treated with ICIs likely contributed to the lack of a detectable association between overall survival after ICI treatment and TMB-high cancers in Black and Asian patients. Nonetheless, objective response rates and progression-free survival were demonstrated in our study to be greater among TMB-high cancers even when using lower TMB thresholds than the current FDA approval. These results are meaningful given that the FDA approval for the use of a TMB cut-off of 10 mut/Mb was only based on objective response rates.

This work highlights an under-recognized challenge of expanding precision oncology particularly when minorities are under-represented in trials and sequencing datasets used to guide biomarker and treatment approvals. Our work also indicates a need for further race-conscious research particularly in the development of predictive biomarkers and evaluation of cancer treatments. Given a dearth of knowledge on the effect of race on immunotherapy outcomes, additional studies are needed to identify more rationale or equitable strategies to expand immunotherapy eligibility.

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Contributors DH conceived the study. DH, ME, and CA performed data analyses. CV and LGTM contributed data. All authors wrote the paper. DH is the guarantor of the study.

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Data availability statement Genomic and demographic data analyzed in the current study in the TCGA or MSK-IMPACT datasets are available at <https://portal.gdc.cancer.gov> and cbioportal.org.

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Supplemental methods

Genomic data on all eligible adult patients (persons 18 years old or older) with solid cancers and race data from The Cancer Genome Atlas (TCGA) (n=8,347) and MSK-IMPACT (n=31,053) were abstracted from cbiportal.org. We focused our analysis on the MSK-IMPACT and TCGA cohorts because they are among the largest genomic cancer datasets to date using a consistent sequencing platform, provided race data on nearly all cases, and have been used for TMB estimation in prior studies. In our primary and subsequent analyses, skin and uveal melanoma cancers were excluded for the following reasons: 1) a great majority of melanoma already have a TMB greater than 10 mut/Mb, 2) ICIs are already approved and frequently used in unselected patients with this cancer type, and 3) patients with melanoma were excluded in the KEYNOTE-158 trial. Data from whole exome sequencing was analyzed from the TCGA. MSK-IMPACT uses a hybridization capture-based next generation sequencing panel analyzing formalin-fixed, paraffin-embedded tumors and matched peripheral blood for up to 468 cancer associated genes.¹³ We focused this study on adults given that nearly all cases in the TCGA cohort and all cases in the available MSK-IMPACT cohort came from adult patients. Race data was self-reported in both the TCGA and MSK-IMPACT cohorts. TMB was calculated as the number of all non-synonymous, somatic mutations identified per Mb of the length of genome sequenced. For TCGA cases, exome size was estimated at 38 Mb, while the length of genomes sequenced for MSK-IMPACT studies was 0.98, 1.06, and 1.22 Mb depending on the version of the gene panel.¹⁴ Differences in proportions and odds ratios (OR) were analyzed using the Chi-Squared test. To assess the association between race and TMB, logistic regression analysis was performed with TMB greater than 10 mut/Mb as the dependent variable and age, sex, race, ethnicity, and cancer type as indicated. Genetic ancestry assignment of the TCGA cohort was based on consensus calls from a pan-cancer analysis from the TCGA Network.⁸

Approximately 212 different tissue source sites contributed specimens to the TCGA with 95% of sources being in the US. Cancer types included in the TCGA were selected based on those with high public health impact so that common cancer types (breast, colon, gastroesophageal, head and neck, hepatocellular, kidney, glioma, lung, ovarian, pancreatic, prostate, thyroid, and uterine) were studied, though rarer cancer types were also included. The number of cases acquired by the TCGA were not strictly prespecified, but varied significantly between cancer types due to specimen availability partly a result of disease prevalence.^{15,16} For instance, the TCGA cohort included 1084 invasive breast cancers and 1053 lung cancers, but only 255 sarcomas and 36 cholangiocarcinomas. MSK-IMPACT was performed on prospectively enrolled patients with advanced cancers at a large single institution (Memorial Sloan Kettering Cancer Center) as a component of their clinical treatment. No specific patient demographic was excluded from the TCGA or MSK-IMPACT. Given that neither the TCGA or MSK-IMPACT data were designed to be representative of the US population, the number of cases per cancer type in the combined cohort was correlated with cancer type incidence in the US in 2019 based on Surveillance, Epidemiology, and End Results (SEER) data.

A subset of patients in the MSK-IMPACT cohort had available treatment data including those treated with non-ICI systemic agents (N=8,957 patients) for 49 different cancer types and those treated with ICIs (N=1,556 patients) for 10 different cancer types.⁹ The non-ICI cohort included patients who never received ICI therapy at any time, which the ICI cohort included patients who received ICI for any line of cancer therapy. The characteristics of these patients are described in detail elsewhere.^{9,17} Adjusted hazard ratios were determined using Cox regression models including age, sex, and cancer type as

covariates. The proportional hazard assumption was tested by including a time-dependent covariate to each model and results were only reported if the covariate was not significantly associated with outcome indicating that the assumption was not violated. No code was generated in this study. Statistical analysis was performed using SPSS Statistics 20 (IBM). Figures were generated using Prism 9 (GraphPad).

Online supplemental table 1. Absolute numbers of TMB-high and -low cancers in the TCGA and MSK-IMPACT cohorts.

		AI/AN	Asian	Black	NHOPI	White
TCGA	TMB-high	4	39	67	4	752
	TMB-low	22	580	756	8	6115
MSK-IMPACT	TMB-high	2	159	170	2	3173
	TMB-low	57	2209	2031	9	23241

Online supplemental table 2. Logistic regression of TMB-high cancers with race, age, sex, and cancer type as independent variables.

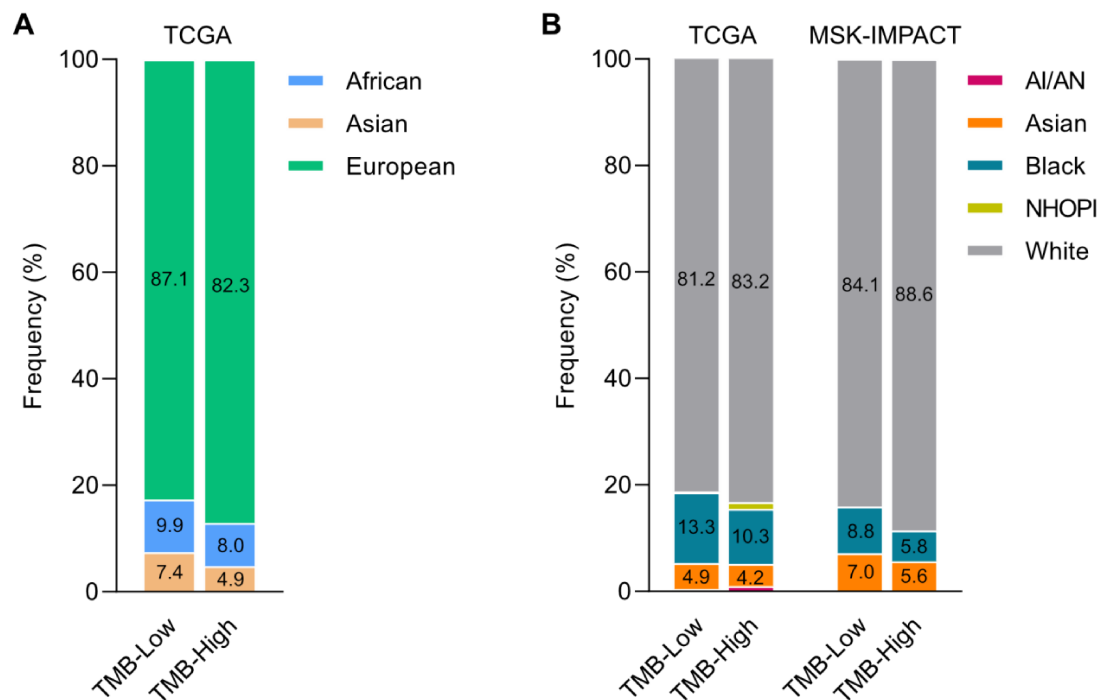
Demographics		Adjusted OR (95% CI)	P value
Cohort	TCGA	1 [Reference]	
	MSK-IMPACT	1.02 (0.87-1.19)	0.80
Race	White	1 [Reference]	
	Black	0.76 (0.65-0.89)	0.001
	Asian	0.65 (0.55-0.77)	<0.001
Sex	Male	1 [Reference]	
	Female	0.82 (0.75-0.89)	<0.001
Age		1.01 (1.01-1.01)	<0.001
Stage	I	1 [Reference]	
	II	1.07 (0.82-1.42)	0.62
	III	0.80 (0.55-1.02)	0.06
	IV	0.73 (0.59-0.91)	0.01
Biopsy site	Primary	1 [Reference]	
	Metastatic	1.15 (1.06-1.26)	0.001

Online supplemental table 3. Logistic regression of TMB-high cancers stratified by cancer type.

	Demographics	N	Adjusted OR (95% CI)	P value
All cancer types				
	White	30945	1 [Reference]	
	Black	2821	0.76 (0.65-0.89)	<0.001
	Asian	2725	0.62 (0.53-0.73)	<0.001
Bladder				
	White	1155	1 [Reference]	
	Black	63	0.59 (0.31-1.12)	0.11
	Asian	76	0.43 (0.22-0.82)	0.01
Breast				
	White	3922	1 [Reference]	
	Black	595	0.56 (0.31-1.00)	0.05
	Asian	356	0.54 (0.25-1.17)	0.12
Cancer of unknown primary				
	White	753	1 [Reference]	
	Black	59	0.34 (0.12-0.94)	0.04
	Asian	58	0.25 (0.08-0.82)	0.02
Colorectal				
	White	2732	1 [Reference]	
	Black	288	0.69 (0.46-1.03)	0.07
	Asian	254	0.70 (0.46-1.07)	0.101
Endometrial				
	White	1395	1 [Reference]	
	Black	241	0.54 (0.38-0.77)	0.001
	Asian	119	1.14 (0.76-1.71)	0.54
Esophagogastric				
	White	1094	1 [Reference]	
	Black	57	0.85 (0.33-2.18)	0.74
	Asian	219	1.09 (0.68-1.74)	0.72
Glioma				
	White	1402	1 [Reference]	
	Black	84	0.79 (0.19-3.32)	0.75
	Asian	94	0.35 (0.05-2.56)	0.3
Head and neck				
	White	754	1 [Reference]	
	Black	73	0.56 (0.19-1.57)	0.27
	Asian	53	0.79 (0.28-1.24)	0.65
Hepatobiliary				
	White	871	1 [Reference]	
	Black	74	0.41 (0.06-3.08)	0.39
	Asian	238	0.52 (0.18-1.48)	0.52
Non-small cell lung cancer				
	White	4398	1 [Reference]	
	Black	326	1.37 (1.04-1.79)	0.03
	Asian	452	0.42 (0.29-0.60)	<0.001
Prostate				
	White	1573	1 [Reference]	
	Black	166	0.78 (0.28-2.20)	0.65
	Asian	70	1.42 (0.43-4.68)	0.56

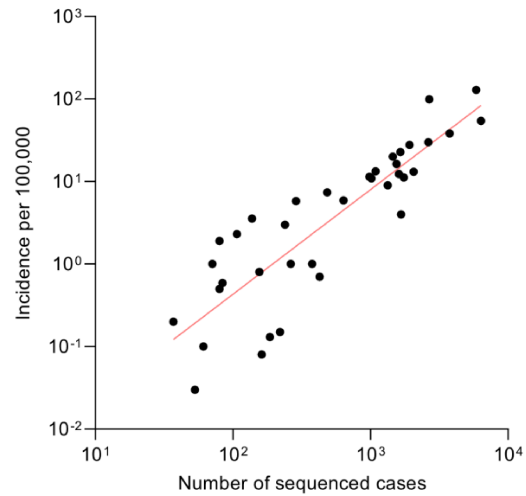
Renal cell				
	White	1032	1 [Reference]	
	Black	161	3.73 (1.08-12.89)	0.04
	Asian	43	3.49 (0.42-28.98)	0.25
Non-melanoma skin				
	White	1675	1 [Reference]	
	Black	29	0.08 (0.02-0.33)	0.001
	Asian	36	0.06 (0.02-0.26)	<0.001

Online supplemental figure 1. Proportion of eligible patients by race for immunotherapies among cancer types enrolled in the KEYNOTE-158 trial.



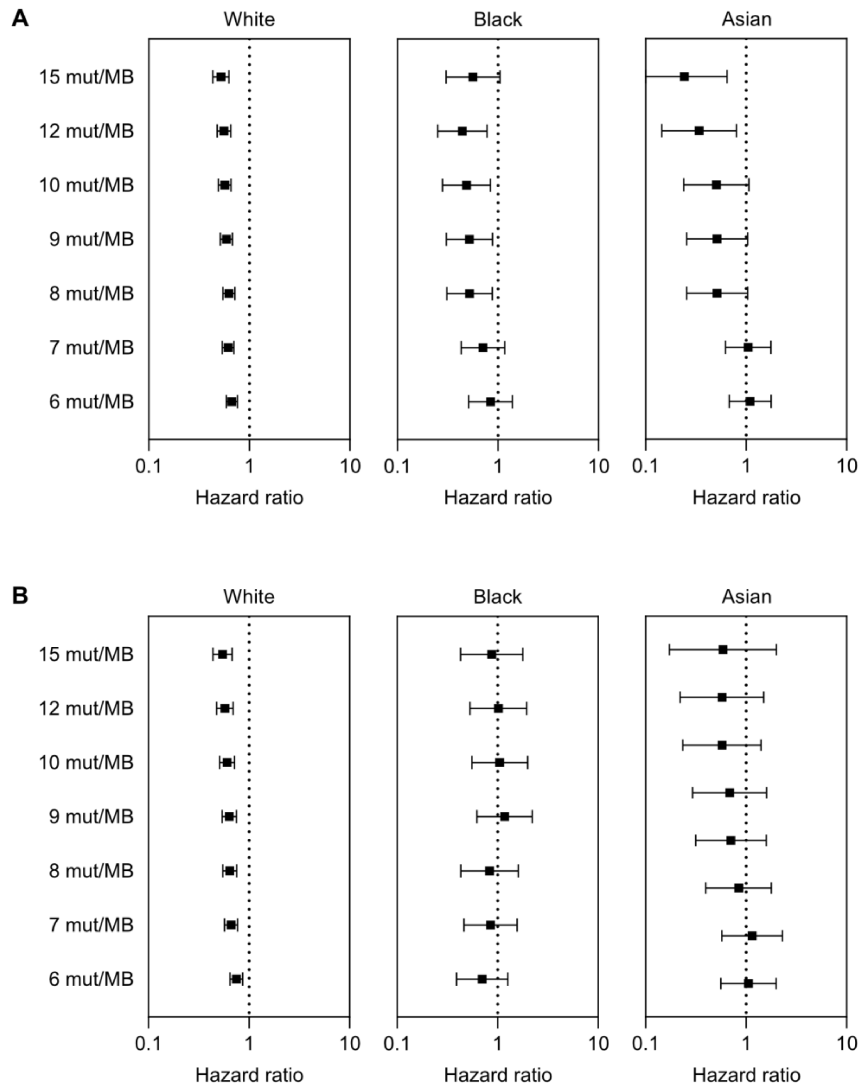
A, Analysis of the TCGA cohort after categorizing patients by genetic ancestry shows that patients of African (OR, 0.77; 95% CI, 0.60-0.98, $p=0.04$) and Asian (OR, 0.62; 95% CI, 0.45-0.84, $p=0.002$) descent were less likely to have cancers with high TMB, compared to patients of European descent. **B**, Analysis of TCGA and MSK-IMPACT cohorts was restricted to patients with adrenocortical, urothelial, cervical, head and neck, breast, prostate, renal, brain, soft tissue, and biliary cancers which demonstrated that Blacks (OR, 0.66; 95% CI, 0.54-0.82) and Asians (OR, 0.78; 95% CI, 0.61-0.98) were less likely to have TMB-high cancers.

Online supplemental figure 2. Association between the number of sequenced cases and US incidence across 38 cancer types.



Scatter plot depicts the relationship between sequenced cases and US incidence based on SEER 21 data which shows a significant correlation (Pearson correlation coefficient=0.87, $P < 0.001$). Data was log transformed due to the right-skewed distribution.

Online supplemental figure 3. Cox regression analysis of progression-free survival and overall survival in the ICI-cohort.



A, Multivariable Cox regression analysis of progression-free survival adjusting for age, sex, and cancer type in the ICI cohort after stratifying patients by race. Hazard ratios indicate the association between TMB-high cancers using different cutoffs and survival. **B**, Multivariable Cox regression analysis of overall survival adjusting for age, sex, and cancer type in the ICI cohort after stratifying patients by race.

