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To interview Neelam Sinha, please contact Julia Gunther at julia.gunther@aacr.org or 770-403-7690. For a photo of Sinha, click here. Visit our newsroom.

Immunotherapy Response Prediction Using Tumor Mutational Burden May Differ Between Men and Women With Melanoma

PHILADELPHIA –Tumor mutational burden (TMB) was an accurate predictor of response to treatment with immune checkpoint inhibitors for female melanoma patients, but not for male patients, according to results of a study presented during Week 1 of the virtual AACR Annual Meeting 2021, held April 10-15.

In June 2020, the U.S. Food and Drug Administration (FDA) approved the use of the immune checkpoint inhibitor pembrolizumab (Keytruda) to treat adult and pediatric patients with advanced solid tumors with a high TMB. The FDA set the threshold for treatment of patients whose tumors have 10 or more mutations per megabase (TMB $\geq$ 10 mut/Mb).

Early research has suggested that high TMB levels may be associated with better response to immune checkpoint inhibition, and that the response may differ between males and females. “This motivated us to examine what are the sex-specific implications, if any, of the TMB $\geq$ 10 mut/Mb threshold for selecting patients to be treated with immune checkpoint inhibitors,” said the study’s lead author, Neelam Sinha, MS, a member of the Cancer Data Science Laboratory at the Center for Cancer Research, part of the National Cancer Institute.

The researchers analyzed data from Memorial Sloan Kettering Cancer Center’s MSK-IMPACT tumor profiling panel. They examined data from 1,286 patients treated with anti-PD1/PD-L1 monotherapy, 99 patients treated with anti-CTLA4 monotherapy, and 255 treated with a combination of the two. They focused on the nine cancer types that had TMB and clinical response data for at least 50 patients.

Consistent with previous reports, they first found that female patients with melanoma had a median of 6.51 mut/Mb, while male patients had a median of 11.81 mut/Mb.

Female patients whose tumors had TMB $\geq$ 10 mut/Mb had 81 percent better overall survival following immune checkpoint inhibition compared with female patients with TMB below the current threshold. In contrast, no significant differences were observed in treatment response between male patients with TMB above and below the 10 mut/Mb threshold.

The researchers did not find any significant sex-dependent differences in the response to anti-CTLA4 therapies, different chemotherapies, or combination therapies, when analyzed using the TMB $\geq$ 10 mut/Mb threshold.

In the analysis of other cancer types, female patients with glioblastoma had a similar trend of better response to immune checkpoint inhibition based on the current TMB threshold; however, the data did not reach statistical significance, possibly due to small sample size, said co-author Sanju Sinha, also a member of the Cancer Data Science Lab at the Center for Cancer Research and a PhD candidate in the Biological Sciences Graduate Program at the University of Maryland.

“First, it is important to note that TMB $\geq$ 10 mut/Mb is not currently required for melanoma patients to receive pembrolizumab. However, as clinicians may still take this threshold into account while considering therapies for a patient, it is important to raise awareness to this bias,” said Sanju Sinha. “Second, in

cancer types like glioblastoma and cancer of unknown primary, the FDA TMB criterion does currently apply. Hence, more data must be gathered to carefully assess whether its usage may induce a sex bias."

The authors said the results of this study suggest that more research is necessary to fully assess the utility of TMB as a predictor of immunotherapy response.

"The overall value of TMB as a predictor of response is quite moderate, as many factors are involved in a patient's response to immunotherapy," said Neelam Sinha. "If the current TMB threshold also induces a sex bias, its usage as a biomarker requires further scrutiny."

Neelam Sinha added that the study results could add to research on cancer health disparities, which encompass sex as well as racial, ethnic, socioeconomic, and cultural differences. "Addressing longstanding sex disparities in health care can help ensure equal treatment opportunities and benefit both sexes," she said.

This research was performed under the supervision of Eytan Ruppin, MD, PhD, chief of the Cancer Data Science Laboratory, and supported by the Intramural Research Program of the National Cancer Institute. The authors, who are siblings, declare no conflict of interest.

Abstract

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Publishing Title: The recently approved high-TMB criteria may introduce a sex bias in response to PD1 inhibitors

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Abstract Body: Motivation and research question: The U.S. Food and Drug Administration recently approved treatment with pembrolizumab, an immune checkpoint inhibitor (ICI) targeting PD1 (anti-PD1), for all advanced solid tumors with high tumor mutational burden (TMB), defined as ≥10 mutations/Megabase (mut/Mb). Recent studies have suggested that strength of immune selection, biomarkers of outcome, TMB levels and response to ICI treatment may differ between male and female cancer patients in some tumor types. This motivated us to examine what are the sex-specific implications, if any, of the ≥10 mut/Mb threshold on selecting patients for ICI treatment.
Data & Methods: We analyzed the largest ICI cohort publicly available to date (Samstein *et al*. 2019), including 1,286 patients treated with anti-PD1/PD-L1 monotherapy, 99 treated with anti-CTLA4 and 255 treated with an ICI combination. We focused on the nine solid tumor types with TMB and clinical response data (median follow-up of 19 months) for at least 50 patients.
Results: We observed a significant difference in the median TMB across sex among melanoma patients (n=130, female vs male median TMB=6.51 vs 11.81, P<0.1), in concordance with previous observations. Notably, we found that the FDA-approved threshold of ≥10 mut/Mb to select patients would result in an unwarranted sex bias in melanoma patients. This threshold successfully identifies female melanoma patients with better overall survival (hazard ratio (HR) =0.19, P<0.03) but fails to

do so in male patients (HR=0.94, P<0.85), resulting in a five times higher HR in males vs females at that threshold level (interaction between sex and TMB P<0.03). This bias is confirmed in two out of three independent melanoma cohorts tested where patients are treated with anti-PD1 (Roh, *et al.*, 2017, N=23, P<0.24; Liu *et al.*, 2016, N=144, P<0.08; Valero *et al.*, 2021, N= 56, P<0.72 and combined P<0.027, weighted Z method). We do not observe this differential effect for anti-CTLA4 treatment (P<0.14, N=174) or for anti-PD1 + anti-CTLA4 combination (P<0.8, N=115) or for non-ICI treatments (P<0.4, N=322). Analysis of additional seven cancer types (Samstein *et al.*, 2019) points to glioblastoma (female vs male HR=0.87 vs 0.5) and cancer of unknown origin (female vs male HR= 1.03 vs 0.15), which show marked differences in the HR between male and female patients when applying the FDA threshold for TMB. However, despite these large effects, they do not achieve statistical significance. A power analysis indicates that the lack of significance observed in these two cancer types is likely to be due to their small cohort sizes and may become significant with larger sample size, warranting further careful testing in larger cohorts.

Conclusions:

The FDA-approved criteria of 10 mutations/Mb could serve as an informative biomarker for stratifying female melanoma patients but is inadequate for stratifying male patients for anti-PD1 treatment. Our results indicate that its usage is likely to introduce a sex bias in additional cancer types, which will be highly important to carefully test further in larger datasets.

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