Study finds high tumor mutation burden predicts immunotherapy response in some, but not all, cancers

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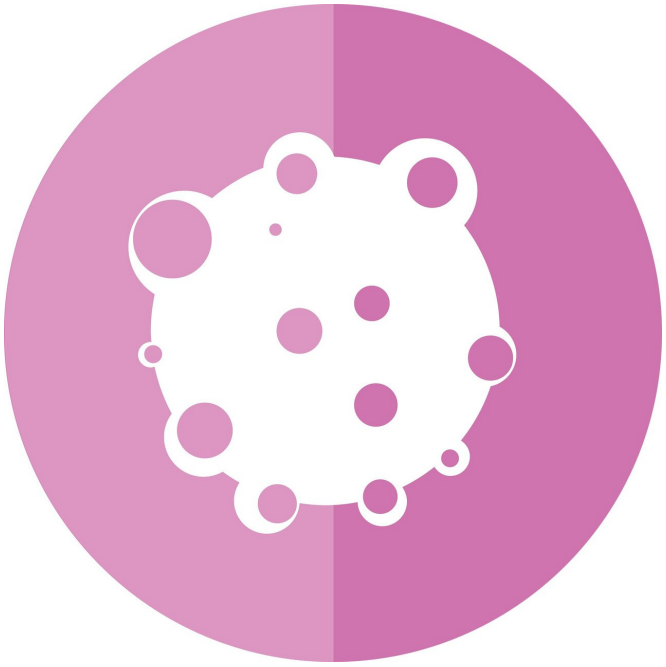

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A high rate of genetic mutations within a tumor, known as high tumor mutation burden (TMB), was only useful for predicting clinical responses to immune checkpoint inhibitors in a subset of cancer types, according to a new study led by researchers from The University of Texas MD Anderson Cancer Center.

The findings, published today in *Annals of Oncology*, suggest that TMB status may not be reliably used as a universal biomarker for predicting immunotherapy response. While TMB status was capable of successfully predicting response to checkpoint blockade in certain cancers, such as melanoma, lung and bladder cancer, there was no association with improved outcomes in others, including breast, prostate and brain cancers.

"This study represents the most comprehensive analysis to date of TMB as a biomarker for response to immune checkpoint blockade," said lead author Daniel J. McGrail, Ph.D., postdoctoral fellow in Systems Biology. "Our results do not support applying high TMB status as a universal biomarker for immunotherapy response, suggesting that additional tumor type-specific studies are needed to clarify how best to apply TMB status in cancer types where it does not appear to be associated with outcomes."

Gene mutations within a tumor lead to the production of mutant proteins, or neoantigens, which can be recognized as abnormal by the immune system. It follows that a high TMB would render tumors more immunogenic, which is why TMB status has become a leading candidate biomarker for predicting immunotherapy response, McGrail explained.

In June 2020, the U.S. Food and Drug Administration approved the anti-PD-1 therapy pembrolizumab for treating patients with advanced and refractory cancers with a high TMB, as indicated by a defined threshold level of mutations. The approval was based on results from the Phase II KEYNOTE-158 study, which found improved overall responses in patients with a high TMB. However, the trial did not include several cancer types, such as breast, prostate and brain cancers, which have not typically responded to immune checkpoint blockade therapy.

"The FDA approval of pembrolizumab for patients with high TMB certainly provides an important option for many patients," said senior author Shiaw-Yih Lin, Ph.D., professor of Systems Biology.

"However, we felt that it was important to look more closely at TMB status in a broader group of cancer types and establish approaches to harmonize TMB across various assays to enable clinicians to best utilize the recent FDA approval."

The researchers analyzed over 10,000 tumors across 31 cancer types from The Cancer Genome Atlas (TCGA) to study the relationship between TMB status and tumor immunogenicity, measured by the infiltration of immune cells (CD8+ T cells) into the tumor. They identified two classes of tumors—those with and without a strong correlation between TMB status and T cell infiltration.

The authors predicted that TMB status would not be able to predict immunotherapy response equally in these two groups. They evaluated this using previously published studies and MD Anderson patient cohorts.

For cancers with a strong correlation between TMB status and T cell infiltration, patients with a high TMB had improved clinical outcomes. Across all cancer types in this category, patients with a high TMB had a 39.8% overall response rate to checkpoint inhibitors, which was significantly higher than those with a low TMB.

In contrast, TMB status was not predictive of outcome in the second class of tumors. Within this category, patients with a high TMB had a 15.3% overall response rate, which was actually lower than the response rate for patients with low TMB.

"While TMB status does show value in predicting response to immune checkpoint blockade in several cancer types, this was not generalizable across all cancers," McGrail said. "For those cancer types where a high TMB does not appear to increase immunogenicity, additional prospective studies are needed to determine if TMB status can be an effective clinical biomarker and at what threshold."

Additionally, the researchers found that evaluating TMB status by sequencing a targeted panel of cancer-related genes may overestimate TMB when compared to whole exome sequencing, which offers an unbiased approach. While whole exome sequencing is not feasible in a clinical setting, the threshold for defining high TMB status may need to be evaluated in a cancer type-specific manner, McGrail explained.

The authors note that this study is limited by retrospective analyses across various DNA sequencing approaches, as well as variations in the immune checkpoint inhibitors and clinical outcomes reported across the different cohorts included.

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