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Cancer immunotherapy: the quest for better biomarkers

Checkpoint-blockade immunotherapy has transformed cancer therapeutics but still benefits only a subset of patients. The development of more-robust biomarkers of response could change that.

Immune-checkpoint inhibitors (ICIs) that block the immunoinhibitory receptor PD-1 and its ligand PD-L1 or the immunomodulatory receptor CTLA-4 have had a transformational impact on the care of patients with cancer, offering curative potential for patients who until recently had no suitable therapeutic options. Despite the growing number of regulatory approvals for use of these drugs in a number of different malignancies, it is now becoming clear that many patients who receive ICIs do not benefit from treatment but remain at risk for potentially serious immune-related adverse events. Expanding the benefit of ICIs to more patients and limiting the impact of their adverse effects will require better biomarkers of response and toxicity.

Although high tumor mutational burden (TMB), presence of tumor microsatellite instability (MSI) and mismatch-repair-deficient (dMMR) status, as well as high PD-L1 expression, in tumor cells are well established biomarkers, they are not perfect. For example, some patients with PD-L1-negative tumors do respond to ICI treatment. In the CheckMate 227 trial, the combination of nivolumab (anti-PD-1) plus ipilimumab (anti-CTLA-4) yielded comparable overall survival benefits in patients with non–small-cell lung cancer whose tumors were above or below the PD-L1 expression threshold of 1%. Moreover, differences in defining high PD-L1 and TMB thresholds, as well as variability in sensitivity of detection platforms, can influence patient classification. Notably, TMB estimates have recently been shown to be affected by ancestry, with misclassified TMB-high patients not benefiting from ICI treatment.

The US Food and Drug Administration has also approved specific companion diagnostics to determine TMB-high and MSI-high/dMMR status as tumor-agnostic biomarkers of the response to pembrolizumab (anti-PD-1). Although these tests enable more patients to access this drug, the efficacy of these biomarkers in predicting response varies across different tumor types. Multiple analyses suggest that these biomarkers, at least at particular cut-offs, may not be universally associated with response across tumor types and may not necessarily be generalizable for patients with a specific tumor type, and point to the need for tumor-type-specific composite biomarkers that integrate multiple parameters.

As ICIs are tested for more indications, more trial datasets also exist with the potential to both identify and validate potential determinants of response. However, integrating these data has proven challenging due to heterogeneity in trial inclusion criteria, the types of samples collected, workflows for sampling and data processing, as well as assay selection. Dedicated sites managed by research agencies exist for the deposition of sequencing results, but standardizing these data and obtaining the relevant clinical metadata necessary for useful interpretation can be difficult. Repositories for other types of data commonly generated in ICI trials, such as immunohistochemistry and flow cytometry results, are lacking or not consistently used. The Cancer Immune Monitoring and Analysis Centers–Cancer Immunologic Data Commons (CIMAC-CIDC) Network, which was established by the US National Cancer Institute, is one ongoing partnership aimed at harmonizing methods and big data for potential immunotherapy biomarkers.

In addition to trial-intrinsic differences, restricted access to datasets further complicates biomarker-validation efforts. Although many clinical research journals, including *Nature Medicine*, require inclusion of data availability or sharing statements in published papers, data access is still often limited and results that are shared may not be fully clinically annotated, which greatly reduces their utility for analysis and validation. For better leveraging of the correlative big data generated in ICI trials, improved strategies must be developed for efficient sharing and harmonization of all major data types while maintaining patient confidentiality. Portals that aggregate trial datasets and permit query-only analysis could be one option.

Numerous other genomic and non-genomic determinants of ICI response have been proposed, and they are often non-redundant. For example, both an intratumoral T cell–inflamed gene-expression profile and TMB have been shown to independently predict the response to pembrolizumab across multiple types of solid tumors. Prospective validation of some of these biomarkers is already underway. In a recent phase 2 trial, patients with advanced soft-tissue sarcomas and intratumoral tertiary lymphoid structures were shown to have better clinical outcomes after pembrolizumab treatment than those of patients without such structures, which suggests that careful selection of patients with tumor types generally considered less responsive to ICIs could actually lead to clinical benefit. Trials such as this one, ideally randomized with direct comparisons to 'all-comers' arms, and arms focused on different biomarker combinations, could refine the scope of ICIs while also helping to establish standardized approaches for measuring specific biomarkers.

It is critical that future biomarker-driven trials be thoughtfully designed to maximize the types of correlative data that can be reasonably obtained and analyzed from patient samples, as well as the diversity of the patient population, given the potential effect of ancestry. In particular, determinants of response that are less invasive than tumor-based biomarkers, such as blood TMB and serum IL-8, should be a priority for prospective validation.

The future for ICIs is undeniably bright, with promising recent results in the neoadjuvant setting and for inhibitors of targets beyond PD-1–PD-L1 and CTLA-4, as well as approvals for use in combination with other types of therapy. Intensifying efforts to enhance data standardization, sharing of existing trial datasets, and prospective validation of candidate biomarkers in diverse populations will be crucial for the development of more-effective biomarkers of response to and toxicity of ICIs and to expand the impact of immune-checkpoint-blockade therapies to many more patients with cancer.

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