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Editorial

EDITORIAL

Predictive Biomarkers: Progress on the Road to Personalized Cancer Immunotherapy

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Immune checkpoint blockade (ICB) has transformed cancer care over the last 10 years, inducing durable tumor responses that translate into long-term survival. This success has allowed many patients across a variety of tumor types to live well with cancer. However, not all tumor types have the same capacity to respond to ICB, and not all patients with a given type of tumor known to be responsive to ICB will benefit from it. In this issue of the Journal, Fountzilas and colleagues' review (1) provides an overview of currently approved and emerging genomic biomarkers for ICB that may predict response or resistance to therapy.

Robust predictive biomarkers that allow physicians to select the patients most likely to derive clinically meaningful benefit from ICB will allow for its most effective use in the clinic. Predictive biomarkers that have been approved by the US Food and Drug Administration (FDA) to guide the use of immunotherapy include expression of the protein biomarker programmed death ligand-1 (PD-L1) in the tumor microenvironment (2) and two genomic biomarkers thought to reflect a high neoantigen load, deficient DNA mismatch repair or microsatellite instability-high (dMMR/MSI-high), and tumor mutation burden-high (TMB-high) (3). The broad value of a robust biomarker for ICB is best illustrated by the development of pembrolizumab for dMMR/MSI-high tumors, where a 53% objective response rate (ORR) across 12 diverse histologic cancer types was observed in the initial trial (4). This led to the first-ever tissue-agnostic FDA drug approval in 2017, when pembrolizumab was approved to treat patients with advanced dMMR/MSI-high tumors regardless of histology. This was based on an ORR of 39.6% in a pooled analysis of 5 clinical trials involving 149 patients with dMMR/MSI-high tumors of diverse histologies (5). Polymerase chain reaction and immunohistochemistry were noted to be acceptable assays for defining dMMR/MSI status, so no companion diagnostic was approved for defining dMMR/MSI status. Nivolumab has also now been FDA approved as monotherapy and with ipilimumab for dMMR/MSI-high metastatic colorectal cancer (6,7). A second tissue agnostic biomarker also gained clinical traction in June 2020, when the FDA granted accelerated approval for pembrolizumab to treat advanced TMB-high (TMB $>$ 10 mut/Mb) tumors based on a 29% ORR across diverse tumor histologies (8). The FoundationOneDx assay was approved as a companion diagnostic.

This is good progress, but multiple challenges remain. First, PD-L1 is a dynamic biomarker that can be expressed by tumor cells, immune cells, and other host stromal cells that may vary depending on tumor context, stage, and host factors and with time (9). Moreover, PD-L1 may be assessed by several immunohistochemistry assays, each of which has distinct characteristics related to the antibody, procedure, platform, and scoring algorithm. Thus, these assays may not give concordant results and are not interchangeable. Finally, there are some PD-L1–negative tumors in some histologies that may respond to ICB (10). Second, the value of both dMMR/MSI-high and TMB-high as biomarkers may also be context dependent and variable by tumor type, tumor stage, or other host factors. For example, some noncolorectal MSI-high tumors have comparatively low response rates to pembrolizumab, with pancreas cancers and central nervous system tumors having ORRs of 18.2% and 0%, respectively (4). Similarly, not all TMB-high tumors respond equally well to ICB (11). In tumors such as melanoma, lung, and bladder cancers, where neoantigen load correlates with CD8+ T-cell levels, the ORR of TMB-high tumors was 39.8% and statistically significantly higher than the ORR in TMB-low tumors (odds ratio [OR] = 4.1, 95% confidence interval [CI] = 2.9 to 5.8; $P < 2 \times 10^{-16}$). In contrast, in tumors such as glioma, breast, and prostate cancers where there was no correlation between CD8+ T-cell levels and neoantigen load, the ORRs of TMB-high tumors was only 15.3% and actually lower than the ORRs of TMB-low tumors (OR = 0.46, 95% CI = 0.24 to 0.88; $P = .02$). It is clear that developing robust predictive biomarkers that most reliably reflect the heterogeneity of this complex treatment landscape is a high priority for the field.

MHC class I and II molecules play a key role in antigen presentation and T-cell priming, and the MHC genotype likely plays a key role in determining the response of a given patient to ICB. The interaction between the variables of: 1) the types of

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(neo)antigens present in a patient's tumor, 2) the nature of the binding of the (neo)antigen epitopes to the patient's MHC molecules, and 3) the population of T cells present that can recognize the presented MHC: peptide complex will have an impact on the patient's response to ICB. Accordingly, expression of MHC class I and II molecules and T-cell receptor diversity has been associated with response to ICB (12-15). Not surprisingly, loss of function in genes involved in antigen presentation and T-cell function have been associated with resistance to immunotherapy. These include loss of beta-2 microglobulin, which compromises antigen presentation (16,17), and *JAK1/2* mutations, which limits the generation of interferon-gamma (16). *Wnt/beta-catenin* mutations have also been associated with resistance to ICB through a distinct mechanism (17,18). These mutations are associated with impaired immune cell recruitment into the tumor.

Other emerging genomic biomarkers potentially associated with responsiveness to ICB include genes that regulate chromatin structure through the SSWitch/Sucrose Non-Fermentable (WI/SNF) complex (*ARID1A*, *PBRM1*, and *SMARCA4* and *SMARCB1*) (1). Some of the data in this area are contradictory, again suggesting that a complete assessment of the overall epigenetic, genomic, and immune contexture of a patient's cancer is required to fully understand the contribution of genomic biomarkers to the overall potential for response to ICB. Furthermore, it is likely that the epigenetic landscape will impact the clinical activity of investigational cancer immunotherapy strategies that combine ICB and epigenetic modifying drugs.

An emerging area of importance is the development of biomarkers to identify patients who may be at higher risk for immune-related toxicity prior to the initiation of ICB therapy (19) to enable better assessment of the benefit-risk profile of ICB for a given patient. Of interest are cellular biomarkers (neutrophil to lymphocyte ratio, lymphocyte counts, regulatory T cells), cytokines and chemokines (interleukin-6, interleukin-8, interleukin-18, and cytokine and/or chemokine panel scores), and auto-antibodies (for example, antibodies specific for thyroid antigens, thyroid dysfunction), bullous pemphigoid 180 (BP180, dermatitis), guanine nucleotide-binding protein G subunit alpha (GNAL, hypophysitis), and CD74 (pneumonitis). Investigators are also evaluating single nucleotide polymorphisms and MHC haplotypes, particularly those MHC haplotypes associated with autoimmune disease. To date, these studies evaluating biomarkers of immune-related toxicity are hypothesis generating and typically limited by small sample size.

In summary, 3 FDA-approved biomarkers currently guide physicians in selecting patients for cancer immunotherapy with ICB. Although they represent a meaningful step forward, they remain imperfect biomarkers, and each individually captures only a small component of immune responsiveness. The tumor immune microenvironment is a multidimensional, interconnected network of genes, proteins, immune and stromal cells, and other systemic host factors that together determine the immunological status of the host-tumor interaction. Given this complexity, a composite biomarker that more effectively captures and integrates these elements into an immune responsiveness score should more effectively select patients for cancer immunotherapy and set the stage for highly active personalized immunotherapies.

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