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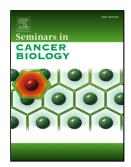
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Abstract

Immune checkpoint inhibition with anti-PD-1 therapy has been notably successful in non-small cell lung cancer (NSCLC) and changed standard practice in multiple settings. However, despite some durable benefits seen, the majority of unselected patients with NSCLC fail to respond to checkpoint inhibitors. Patient selection is crucial and will become even more important in the development of combination therapies with immune checkpoint inhibitors. PD-L1 expression by immunohistochemistry (IHC) has emerged as the most commonly used clinical biomarker of response and overall tumor mutational burden (TMB) is being explored as a clinical biomarker. However, both are hampered by being imperfect predictors of response and both can be dynamic during the course of illness. In this review, we will discuss the development of PD-L1 expression as a biomarker as well as the ongoing emergence of other genomic and proteomic markers that can help refine our use of immunotherapies to maximize benefit in the most patients.

Keywords: PD-1, PD-L1, immunotherapy, checkpoint inhibitors, biomarkers, non-small cell lung cancer, tumor mutational burden, microbiome

Introduction

Signaling via the PD-1 pathway is a tumor cell evasion strategy that inhibits immunity by preventing T-cell chemotaxis, proliferation, and cytokine release(1-4). PD-1 can be expressed on activated T-cells and is often considered a marker of T cell exhaustion. When engaged by its ligand, PD-L1, which can be expressed on both tumor and immune cells, effector T-cell function is inhibited(1, 3, 5). Tumor cell expression of PD-L1 is thought to be a mechanism of tumor escape from a specific T-cell response. PD-L1 is expressed on a variety of tumor types including 53-62% of patients with NSCLC(6-8). Early responses seen in NSCLC on phase I trials of PD-1 or PD-L1 inhibitors led to a rapid expansion of clinical development in this tumor type.

There are currently three monoclonal anti-PD-1/PD-L1 antibodies approved in advanced NSCLC (nivolumab, humanized IgG4 anti-PD-1; Bristol-Myers Squibb Company, pembrolizumab; humanized IgG4 anti-PD-1; Merck & Co, atezolizumab; humanized IgG1 anti-PD-L1; Genentech/Roche) by the US Food & Drug Administration (FDA). Although anti-PD-1/L1 antibodies have been practice-changing in NSCLC, only about 20% of unselected patients will respond to treatment. These responses are sometimes long lasting—approximately 16% of patients treated with single-agent nivolumab have continued benefit after 3 years(9). Although much is made of the relatively lower toxicity profile than chemotherapy (6-8, 10), these agents can be associated with life-threatening and sometime irreversible autoimmune toxicities. Therefore, the accurate selection of patients who will respond to treatment with an anti-PD-L1/PD-1 monoclonal antibody is of paramount importance.

Although PD-L1 expression by immunohistochemistry (IHC) has some predictive value in the use of PD-1/PD-L1 inhibitors in NSCLC, it is an imperfect biomarker, in part because of its dynamic nature (can change over time and with response/exposure to therapy). Similarly, TMB, a potential surrogate

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