Biomarkers for Checkpoint Inhibition and Their Clinical Utility

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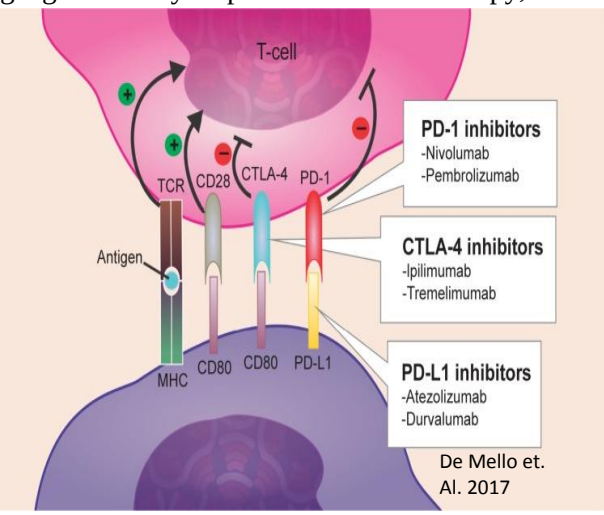
In the past decade, perhaps the most promising breakthroughs for cancer treatment have been made in the realm of immunotherapy. Evidenced by the thousands of ongoing clinical trials, the field has endeavored to treat the 38.8% of Americans who will develop cancer in their lifetimes[1,2]. The goal of immunotherapy is to both harness and restore the immune system's inherent ability to fight cancer[3]. In addition to inhibiting apoptosis and promoting angiogenesis, cancerous cells throughout disease progression evade detection from, or inhibit, the immune system. Checkpoint-based immunotherapy (CBT) can disinhibit the immune system to enable the host to fight cancer. With ongoing efforts to bolster methods of monitoring patients' early treatment response, tumor immunity, and toxicity, CBT can still be improved and catered to treat the individual.

Cancerous cells may inhibit the immune system by promoting an immune-suppressive microenvironment that prevents effector T-cell infiltration, promoting/attracting immunomodulatory cell types, and by expressing immunosuppressive mediators to prevent the host's antitumor immunity[3]. Such mediators like PD-1, PDL-1, and CTLA-4, known as checkpoints, are intended to regulate an immune response by altering T-cell activity to prevent an over-stimulated immune response or an immune attack on healthy cells[4]. Recent efforts have been directed towards designing and improving checkpoint inhibitor therapy to restore antitumor immunity. While checkpoint inhibitors have already proven to be useful cancer therapeutics, not all tumors or cancer types respond favorably. Doctors need to be able to gauge who may respond well to this therapy, what drugs to use, and their toxicity and efficacy.



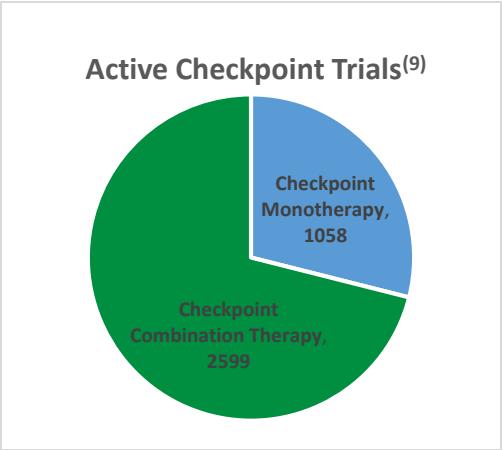
De Mello et. Al. 2017

Before utilizing CBT, doctors assess whether the tumor may be sensitive to an immune response. Inflamed tumors, characterized by PD-L1 positivity, high $CD8^+$ T-cell density, and high INF-γ expression, indicate a preexisting antitumor immune response that may be revived by immune checkpoint modulators (ICM)[4,5]. Profiling the T-cell receptor (TCR) repertoire, T-cell infiltration, expression of checkpoints and other T-cell regulators, and the tumor microenvironment as a whole provides necessary insight for identifying CBT candidates. While this process typically involves invasive biopsies, assessment of circulating biomarkers provides the advantages of monitoring immune and pharmacodynamics activity over time in response to therapy non-invasively, before other methods may indicate if a treatment is effective.

There are multiple methods employed to quantify circulating biomarkers (such as antigen specific T-cells), including tetramer staining, FACS, mass cytometry, and gene expression profiling[5]. Yet, immunoassays for quantifying tumor-associated proteins, cytokines, chemokines, and checkpoints themselves are increasingly useful in clinical studies. Circulating levels of certain cancer biomarkers, such as CEA, LDH, CRP, and sCD25, have already been found to be predictive of patient response to

CBTs[5]. Further studies examining circulating cytokines response to CBTs find that INF-γ correlates to checkpoint expression and may help characterize the early treatment response, while TGF- β can serve as a predictive marker of Pembrolizumab efficacy[5,6]. Studies such as this that quantify checkpoints, downstream TCR effectors, and cytokines in the periphery during treatment may provide useful information regarding compensatory upregulation of other checkpoint molecules, which counter the effect of an ICM. This allows doctors to identify effective drugs to use in combination to an ICM monotherapy[7]. Circulating cytokine assays are also extremely useful to monitor the toxicity of CBT, where immune-related adverse events are reported.

To date, there are 15 identified T-cell regulating targets for therapy, with 7 drugs already on the market to target PDL-1, PD-1, and CTLA-4[1, 8]. With 3305 more clinical trials underway globally investigating CBT and therapies in combination with CBTs[9] , researchers urgently need more options for measuring checkpoint expression and associated biomarkers of treatment efficacy and toxicity in the blood. This is especially crucial as the field continues to develop checkpoint inhibitors, investigate promising combination therapies, and individualize patient treatments to harness humans' inherent antitumor immunity.



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