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The Next Frontier for Cancer Immunotherapy Trials

by

With its measurable impact on patient survival, there's no denying that immunotherapy is already causing momentum in ways that cancer is treated. Drug researchers and developers are identifying new candidates in their growing pipelines and exploring combinations of immunotherapies, while regulatory agencies are providing expedited review and approval of these therapies for new indications at an unprecedented rate.

With checkpoint inhibitors from ipilimumab (*Yervoy*) to nivolumab (*Opdivo*) to pembrolizumab (*Keytruda*) to the most recently approved atezolizumab (*Tecentriq*), each breakthrough has provided new insights on how the immune system can be activated and manipulated to fight a variety of cancers.

Newly Released Research

Ongoing research strives to understand the longer-term potential of these therapies. For example, pembrolizumab, which may be prescribed when the disease relapses or fails to respond to ipilimumab, has recently shown to outperform ipilimumab as a first-line therapy. A third of patients treated with pembrolizumab showed an overall response when treated for melanoma; 73% of those responders had an ongoing response lasting as least two years.

Response durations ranged from >1.3 to >38.8 months, suggesting that the immune system retained its cancer-fighting abilities in those patients, and provided a durable response. Furthermore, in a separate, direct comparison to ipilimumab as a first-line monotherapy, two-year overall survival of metastatic melanoma patients increased from 43% to 55% on pembrolizumab.

Bristol-Myers Squibb also released the results of its two-year overall survival data comparing nivolumab to docetaxel in previously treated metastatic non-small cell lung cancer (NSCLC)

patients, demonstrating improved overall survival: 29% vs. 16% for non-squamous NSCLC and 23% vs. 8% for squamous NSCLC.

More clinical research is needed to determine how the duration of treatment affects a patient's response. It's unknown if periodic treatments are needed long term after the tumor completely shrinks or if the immune system will naturally retain its anticancer activity, although some patients in earlier studies have remained cancer-free without further therapy for more than 5 years.

Expanding the Scope

The FDA has approved many new or expanded indications for immunotherapies, such as nivolumab, for the treatment of patients with classical Hodgkin's lymphoma (cHL) who have relapsed or progressed after autologous hematopoietic stem cell transplantation (auto-HSCT) and post-transplantation brentuximab vedotin.

Beyond a better understanding and expansion of current therapies, potential opportunities exist for re-examining treatment strategies. While the approval of ipilimumab, nivolumab, pembrolizumab and atezolizumab for various indications validates immunotherapies as a valid treatment approach, different strategies in the administration of these drugs should now be considered.

For example, adjusting the timing of a treatment from advanced to earlier stages of the disease may attack a tumor more effectively. Treatments could also be expanded beyond their focus and current indications, to see if similar results may be seen in different tumor types.

Combinations of multiple immunotherapies are also being evaluated to see if they may provide greater efficacy potential, as has been noted in melanoma with the combination of ipilimumab and nivolumab, which increases the two-year overall survival in melanoma from 54% to 64% compared to ipilimumab alone. However, combinations will need to be carefully evaluated not only for efficacy, but also for adverse events due to the potential for increased toxicity. Other immunotherapies are approaching cancer from a different angle than checkpoint inhibitors, such as cancer vaccines, oncolytic viruses and adoptive cell transfer. In the latter, rather than trying to stimulate the T cells in the body through the use of checkpoint inhibitors, a patient's own T cells can be manipulated to seek specific antigens on the patient's tumor cells and kill them. This process involves isolating the patient's own T cells from the blood and then genetically engineering a chimeric antigen receptor (CAR) into the cells.

After those T cells are multiplied, they are re-infused into the patient where they become directed at and destroy the tumor cells. Initial results have shown the potential of this approach for adults with certain advanced blood cancers – including pediatric acute lymphoblastic leukemia – when other treatments are no longer an option.

Focusing on Responders

Regardless of the immunotherapy target or approach, auto-immune adverse events remain a concern when the immune system may also attack healthy cells. Obtaining preclinical data and combining it with clinical data might allow for a better understanding of specific mechanisms of action causing autoimmune response. This perspective may then be valuable in establishing strategies to prevent or reduce these adverse events, and help guide the design and effective monitoring of a clinical trial. Despite these side effects, physicians have become adept at recognizing and treating them early in the course of therapy.

Biomarkers could also be used to better target patients more likely to respond and thus increase the therapeutic window by stratifying and treating patients according to their biomarker profile. This would potentially improve treatment response by treating only patients with the best chances to respond. Currently, the PD-L1 biomarker has been used in such evaluations, and while correlated with potential response in a number of tumor types, it is not the only relevant biomarker for immune-based therapies. Other promising immunotherapy biomarkers include genomic markers, such as the determination of mutational burden and production of neo-antigens, along with blood-based biomarkers of the immune response.

Retrospective and prospective analyses in clinical trials will hopefully lead to further novel biomarker discoveries and applications, and enable earlier phase screening of patients. However, much more work is required to define the most predictive biomarker or combination of biomarkers for immunotherapies.

Considerations for Clinical Success

With more drug candidates, possible targets, approaches and mechanisms to explore, the immuno-oncology field holds great promise for the industry and patients, yet has distinct development needs quite unlike any other oncology treatment.

Drug developers must consider strategies for identifying patients in an increasingly competitive trial landscape, training and supporting investigators, providing adequate site and patient monitoring and bioinformatic needs to better support the increasing complexity of biomarker studies. Suitable site selection also factors into the equation, in that a site must be able to handle the unique volume, complexity and timeline requirements of an immunotherapy trial.

Past performance in previous trials and relevant oncology experience are key factors to consider when considering suitable sites. With a proprietary knowledgebase that has visibility to more than 40% of the world's trials, Covance can apply its Xcellerate Informatics Suite to identify the best sites and investigators for performing these specialized trials. Finding patients is also optimized with access to 75 million de-identified patient test results in the LabCorp database to get these trials optimally designed and placed closer to relevant patient populations.

At the most granular level, it's important to note the unique staffing requirements for an immunotherapy trial. Investigators and clinical research associates must understand how immune-related response criteria differ from those of other oncology treatments. The therapy may take more time to generate a response or the tumor may swell ("pseudo" disease progression) before it shrinks.

To ensure trial compliance, a well-documented plan should outline when to continue or end treatment based on specific response patterns. And from the safety perspective, site staff should be well versed in recognizing, reporting and treating any immune-related adverse events (iRAEs) that appear during the study.

A strong clinical strategy is only one part of the complex equation. With new indications, combination therapies, alternative treatment approaches as well as the response criteria defined by biomarkers, our field has great capacity for discovery and improvement of immunotherapies and their administration. These very unique characteristics pose an immense and imminent challenge, yet it is these same attributes that offer tremendous potential to transform cancer therapy and improve patient survival outcomes.

¹<http://www.news-medical.net/news/20160530/Oncologists-combine-two-different-types-of-immunotherapy-to-successfully-treat-metastatic-melanoma.aspx>