Recently *BioWorld* called cancer immunotherapy “white hot” based on unprecedented investments in private companies, partnerships between Big Pharma and emerging companies, and the U.S. Food and Drug Administration’s 2014 breakthrough approvals of new agents for chronic lymphocytic leukemia, metastatic melanoma, and B-cell acute lymphoblastic leukemia. This follows *Science’s* 2013 designation of the field as “breakthrough of the year.” Based on the history and ongoing practices we will outline key strategies to consider for accelerating the drug development process in this class of treatment.

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The idea behind cancer immunotherapy—harnessing the immune system to battle cancer—had its origins in the 1890s when William B. Coley injected streptococcal organisms into a patient with inoperable cancer. He theorized the infection produced would shrink the tumor, which it did. Over the next 40 years, Dr. Coley would inject more than 1,000 cancer patients with bacteria or bacterial products, which became known as Coley’s toxins.iii

In the decades that followed, researchers tried multiple approaches to stimulate the immune system to fight cancer. Early therapeutic cancer vaccines resulted in failure after failure in the clinic, and most companies abandoned their cancer vaccine efforts. (The approval of sipuleucel-T for prostate cancer is a notable exception.)

An increased understanding of how the immune system is suppressed by immune checkpoint inhibitors (ICIs), drivers of oncogenic process, and advances in genomics have been used to discover new targets, which in turn has enabled the creation of more targeted immunotherapies that include antibody drug conjugates, chimeric antigen T-cell receptor (CAR-T) therapy and anti-infectives.
Enthusiasm for the field of immunotherapy was reignited by Bristol-Myers Squibb’s ipilimumab. Approved by the U.S. FDA in 2011 for the treatment of metastatic melanoma, ipilimumab targets CTLA-4, a protein on the surface of killer T-cells that prevents their activation and blocks their ability to launch an immune attack on cancer cells. The compound, a monoclonal antibody, keeps T-cells active while destroying melanoma cells.\textsuperscript{iv}

In clinical trials, ipilimumab significantly extended survival in patients with advanced melanoma.\textsuperscript{v} In one study, of 1,800 patients treated with ipilimumab, 22 percent were alive three years later.

CTLA-4 belongs to a superfamily of immune checkpoint inhibitors, which includes programmed cell death protein 1 (PD-1) and its ligand, programmed cell death program ligand [PD-L1]. The PD-1 receptor is expressed on the immune system’s T cells and B cells, while its ligand PD-L1 is expressed on a variety of cells in the body, including many tumor cells. Interaction between PD-L1 and PD-1 results in a dampening of the immune response.\textsuperscript{vi}

Today, PD-1 and PD-L1 immune checkpoint inhibitors are among the most active and important areas of focus in oncology drug development. With different mechanisms of action, they have produced significant response rates in non-small cell lung cancer (NSCLC), as well as in bladder, and head and neck cancers.\textsuperscript{vii}

In 2014, BMS’ anti-PD-1 nivolumab and Merck’s anti-PD-1 pembrolizumab were approved for the treatment of metastatic melanoma. Pembrolizumab was approved two months earlier than expected as a breakthrough therapy following first-line treatment with ipilimumab, or after treatment of ipilimumab and vemurafenib, a BRAF (V-raf murine sarcoma viral oncogene homolog B1) inhibitor in patients with a BRAF mutation. Pembrolizumab has demonstrated high and long-lasting activity in a large Phase I trial in metastatic melanoma. The one-year survival rate across all patient subgroups was 69 percent.\textsuperscript{viii}

Yet some tumor types have shown little response to targeted or precision therapy in early clinical trials, and mutations and resistance remain a challenge. As with combination chemotherapy, a single agent inhibiting a single enzymatic signal transduction pathway may not be adequate to stop disease progression. As a result, novel agents and strategies are being developed and tested in multiple cancers to target different enzymatic pathways using combinations of immune checkpoint inhibitors with first- or second-generation small molecule, tyrosine kinase inhibitors, serine threonine kinase inhibitors, chemotherapy, and vaccines. For example, a recent Phase 1b dose-ranging melanoma trial, combined the PD-1 inhibitor nivolumab with the anti-CTLA-4 monoclonal antibody ipilimumab, and resulted in an unprecedented two-year survival rate of over 80 percent.\textsuperscript{ix}
Examples of pseudo-progression in immunotherapy

The term “flare” or “pseudo-progression” is used in oncology and hematology to describe a phenomenon whereby standard response assessments indicate worsening of the disease on treatment when this may not be the case in many malignancies. For example, treatment-induced lymphocytosis, not related to progression, lead to the adaptation of the 2008 International Working Group CLL (chronic lymphocytic leukemia) criteria. Wolchok, Hoos and Bohnsack recognized that ipilimumab immunotherapy recruited T-cells to the solid tumor sites and this alone could be responsible for “new” lesions becoming visible on CT scans. As a result, the usual solid tumor criteria had to be amended to protect patients from coming off study too soon. Recent pembrolizumab solid tumor data supports that patients on PD-1 and PD-L1 inhibitors and other immunotherapies should continue treatment and derive clinical benefit until disease progression is confirmed.

With the publication of the Lugano Classification in 2014, the response criteria for Hodgkin and most Non-Hodgkin Lymphomas are more strongly imaging-centric, and moves this large group of hematologic malignancies into a predominately functional imaging (PET-based) response assessment. The effect of immune modulating therapies was not specifically addressed in this landmark article. Adaptions to functional imaging response assessment are needed to avoid falsely describing a patient receiving immunotherapy as a progressor.

Immune checkpoint inhibitors appear to offer an advantage compared with standard cytotoxic chemotherapy, in that they produce high response rates, durable response, and survival curves that indicate sustained remissions long after therapy has been completed. Yet, how these therapies work and how long they should be administered is not yet understood. Some tumors continue to grow before disappearing a few months later and predictors of response are lacking. Nor do we understand enough about the late effects of prolonged therapy.

In addition, safety with these new therapies is of concern since the immune system is being suppressed by the cancer but ICIs are turning on a suppressed immune system. Patients treated with ipilimumab for example, have reported autoimmune type adverse events. Skin and gastrointestinal tract are most frequently affected, while hepatic, endocrine, and neurologic events have also been reported but less commonly.

Finally, the costs associated with the new cancer immunotherapies can be very high, making their reimbursement a challenge.
If development continues at its current pace, in ten years there will be better drugs and better strategies to eliminate most cancer cells. Immunotherapies will then be used to keep the disease in check. Here are five strategies to accelerate the field’s progress.

**FIVE STRATEGIES FOR ACCELERATING FUTURE SUCCESSES IN CANCER IMMUNOTHERAPY**

Gene expression profiling is fast becoming the standard of care with many large academic centers already leveraging next-generation sequencing (NGS) technologies to profile newly diagnosed patients. In private industry, for example, Foundation Medicine provides genomic tests for solid tumors and hematologic malignancies and sarcoma. For example, it is known that a small number (five to seven percent) of patients with non-small cell lung cancer patients express the ALK/EML4 mutation that can be inhibited with crizotinib, however most treated patients develop resistance to treatment months after a response is achieved. Second-generation agents that inhibit the ALK/EML4 mutation are being developed. Continued genetic profiling of tumors over time will increase our understanding of secondary mutations and will improve therapy customization.

**CONTINUED GENETIC PROFILING OF TUMORS OVER TIME WILL INCREASE OUR UNDERSTANDING OF SECONDARY MUTATIONS AND WILL IMPROVE THERAPY CUSTOMIZATION.**
Adaptive trial design with dose escalation and other methods to speed up the drug development process allow for rapid identification of active agents and the potential to better identify responsive patients. Well-designed trials accelerate go/no-go decision-making, help minimize financial waste, avoid treatments for patients for whom a compound offers no benefit and even help companies receive approval earlier thus decreasing the cost of drug development. Biomarkers that indicate tumor mutations, predict response/non-response to a drug, or serve as surrogates of survival shorten trial timelines. In addition, the incorporation of medical imaging into trials should be increased since it can lead to earlier, more accurate monitoring of drug effect on disease.

Clinical trials have long relied on intermediate or surrogate endpoints to predict long-term survival, but responses to cancer immunotherapeutics vary greatly. Novel immune-related response criteria that incorporate both early and delayed responses, as well as tumor burden that increases before it recedes should be incorporated into trials. Without accurate endpoints, trials that could be successful might be terminated prematurely.

For the European Society of Medical Oncology (ESMO) 2014 Congress, Bohnsack introduced novel criteria to better capture antitumor activity and reduce immune-related response criteria (irRC). The goal of those modifications (irRECIST) was to provide more objective and reproducible response imaging assessments to meet investigators’ and patients’
needs and to better reflect sponsors’ demands for more reliable and reproducible study data in targeted immuno-oncology studies.

Novel endpoints that should be considered, according to Axel Hoos, M.D., Ph.D., Vice President of Oncology at GlaxoSmithKline, include calculating the overall clinical benefits, taking baseline measurements several months after therapy has been initiated, and "milestone survival,” the proportion of trial participants alive at a designated point late enough to surpass late-onset immune response but early enough for accelerated approval. Others include gated progression-free survival and tumor growth rate.

Regulatory agencies have been under enormous pressure to make the approval process more efficient and less expensive. Oncology drug developers have benefited from the “Breakthrough Therapy” designation for drugs intended to treat a serious or life-threatening disease. As of December 29, 2014, the U.S. FDA had given 16 approvals to drugs designated Breakthrough Therapies. 11 were first-time approvals for novel drugs including pembrolizumab, nivolumab and other immuno-therapies that demonstrated major clinical activity and significant improvement over currently available treatments. The combination of better trial design with the possibility of breakthrough designation allows companies to conduct smaller clinical trials faster with fewer patients, and could lead to accelerated approvals in niche markets.

THE COMBINATION OF BETTER TRIAL DESIGN WITH THE POSSIBILITY OF BREAKTHROUGH DESIGNATION ALLOWS COMPANIES TO CONDUCT SMALLER CLINICAL TRIALS FASTER WITH FEWER PATIENTS, AND COULD LEAD TO ACCELERATED APPROVALS IN NICHE MARKETS.
Thanks to the Internet, today’s cancer patient is better informed than ever; however, less than 10 percent of eligible patients enroll in clinical trials. Few patients want to be placed under the demands of an early phase study nor randomized into the placebo arm of a trial. Patients who understand the benefits of participating in early phase studies and the exceptional quality of care they will receive will be more likely to participate, especially if response rates and durable responses are now being observed in many Phase I studies. It is up to all parties involved in the development process to increase awareness and get more patients into trials. Sponsors also need to be aware that patients and their treating physicians need to be educated that cancer immunotherapies work differently than standard treatments, as response can be delayed and the tumor burden may continue to grow before it decreases and when the treatment shows its effect.

**PATIENTS WHO UNDERSTAND THE BENEFITS OF PARTICIPATING IN EARLY PHASE STUDIES AND THE EXCEPTIONAL QUALITY OF CARE THEY WILL RECEIVE WILL BE MORE LIKELY TO PARTICIPATE, ESPECIALLY IF RESPONSE RATES AND DURABLE RESPONSES ARE NOW BEING OBSERVED IN MANY PHASE I STUDIES.**
Today’s immunotherapies might not help all cancer patients but they are an exciting addition in the fight against this disease. Future successes in cancer immunotherapy are possible through advances in gene expression profiling, better clinical trial design and endpoint selection, more efficient regulatory approval processes, and increased awareness for clinical trials. As our understanding of the immune system and biology of cancer progresses, novel approaches for treating the disease will continue to emerge. If success continues at this pace, the biggest winners will be the patients.

ABOUT THE AUTHORS

Denis R. Miller, M.D., serves as the Global Therapeutic Area Leader, Oncology/Hematology at PAREXEL. Previously, he served as chairman of the Department of Pediatrics at Memorial Sloan-Kettering Cancer Center, and as division head or chief of pediatric hematology/oncology at Strong Memorial Hospital-University of Rochester, New York Hospital-Cornell Medical Center, and Children’s Hospital-Northwestern University in Chicago. Dr. Miller has been involved in the early development of many novel oncology agents including inhibitors of histone deacetylase, cyclin dependent kinases, and other targeted therapies, photodynamic therapy, monoclonal antibodies and erythropoietic stimulating agents (ESA).

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Richard Jacobs, M.D., serves as Senior Vice President, Medical Affairs at PAREXEL Informatics. Through Dr. Jacobs’ leadership, PAREXEL Informatics has become an industry leader in medical imaging and clinical trial technologies and has had more than 30 successful imaging submissions, almost all in to the FDA, more than half of which have led to New Drug Applications. Prior to joining PAREXEL, Dr. Jacobs served as chairman of the Department of Radiology and Diagnostics Imaging at Memorial Health Care.
REFERENCES


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