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Immune Checkpoint Therapy as a Weapon against Cancer

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The lunar landing of 1969 made it clear that we can accomplish great things with the appropriate infrastructure and teams in place. Similarly, the establishment of a cancer Moon Shots Program, first at the University of Texas MD Anderson Cancer Center in 2013 by Dr. Ron DePinho, and now a Cancer Moonshot on a national level as called for by President Obama and Vice President Biden, provides an opportunity to take a giant leap forward by applying cutting-edge science and technology in our fight against cancer. Great strides have been made already as we witnessed a revolution in genomic medicine, which led to our understanding of genetic mutations that initiate tumor development and the creation of drugs to target certain mutations for the benefit of cancer patients. In the past decade we also witnessed a paradigm-shift in cancer immunotherapy as we learned to unleash anti-tumor immune responses to eradicate tumors.

Jim Allison's seminal paper on immune checkpoint therapy was published in 1996, which demonstrated that blockade of a T cell inhibitory pathway, CTLA-4, could lead to enhanced anti-tumor immune responses and tumor rejection with long-term survival of mice. As a result, clinical trials ensued and the first FDA-approval of a drug to help patients came in 2011.

Anti-CTLA-4 (ipilimumab, BMS) was the first drug in a randomized Phase 3 clinical trial to demonstrate an overall survival benefit for patients with metastatic melanoma. More importantly, a subset of patients who received ipilimumab has durable responses lasting more than a decade, which drives optimism that a cure may truly be possible. As a result of the clinical success of anti-CTLA-4 therapy, the field of immune checkpoint therapy has taken off exponentially, with many other immune inhibitory pathways being identified, which are either under development for clinical testing or currently being tested in clinical trials.

Anti-PD-1 is another immune checkpoint therapy that has led to significant clinical responses in melanoma, lung cancer and renal cell carcinoma, which led to FDA-approval of agents to treat these cancers. Even the skeptics who thought of immunotherapy as "black magic" started to pay attention as so many different tumor types responded to immune checkpoint therapy. And, as emerging data indicated superior responses with combination therapy, anti-CTLA-4 (ipilimumab) plus anti-PD-1 (nivolumab, BMS) was evaluated and approved as a combination treatment for patients with metastatic melanoma.

With the identification of other immune inhibitory and co-stimulatory pathways, which may also be targeted for combination strategies, and the concept that immune checkpoint therapy can potentially be combined with other treatments such as radiation therapy and genomically-targeted agents, there is a potentially endless list of clinical trials that can be undertaken. This issue will provide an overview of where we are in the field of immune checkpoint therapy as we attempt to provide effective therapies for even more of our patients.

We must also remember that it was basic science that led to the clinical success of immune checkpoint therapy. Although the field has exploded recently to include hundreds of new clinical trials, it is important to note that we need to circle back to careful scientific studies on patients' samples to: 1) determine why some patients respond to treatment while others do not; 2) understand how best to identify immune related toxicities and learn how to predict and treat them; and 3) choose rational combination therapies that will make it possible to provide potentially curative treatments to all cancer patients.

We are clearly in an exciting time as physicians, scientists, pharmaceutical partners, political leaders and patients as we build the appropriate infrastructure and teams to advance our fight against cancer.