Immune checkpoint inhibitors have been hailed by many as a breakthrough in cancer care. Curative, durable responses are being seen in patients whose cancers would have once been intractable with conventional therapies. New investigational drug development and approval for ever-widening indications in this arena is proceeding at a breakneck pace. Although it was initially hoped that checkpoint blockade alone could be a panacea for many types of cancer—since it works, in essence, by unleashing one’s own immune system to kill tumors—we are now beginning to understand limitations on clinical efficacy of this class of drugs.

Currently-approved checkpoint inhibitors, all of which are monoclonal antibodies, fall into three main classes: ipilimumab, which targets cytotoxic T lymphocyte 4 (CTLA-4); nivolumab and pembrolizumab, which target programmed death 1 (PD-1); and atezolizumab, which targets programmed death ligand 1 (PD-L1). Many other therapeutics directed at these targets, as well as novel immune checkpoint receptors and ligands, are being actively developed. The rapid progress in this field might be attributed to two major factors. First, the mechanism of action implies broad application for many cancers. Second, the clinical effects have been, in many cases, profound. For instance, in a clinical trial for advanced melanoma (NCT01721772), the Response Evaluation Criteria In Solid Tumors (RECIST) objective response rate with nivolumab was 40%, compared to previous standard of care therapy with dacarbazine with a response rate of 13.9%. In a subsequent study, again for advanced melanoma (NCT01844505), combination therapy with ipilimumab and nivolumab resulted in an objective response rate of 57.6%, compared with 43.7% for nivolumab alone and 19% for ipilimumab alone. In many cases, responses are durable, with progression-free and overall survival being extended months to years beyond previous standard of care therapies.

Although these results are encouraging, it is apparent that a large proportion of patients do not respond to checkpoint inhibitors. Similar findings—where only a subset of patients show durable clinical benefit with checkpoint inhibitor therapy—have been reported for hundreds of trials examining various cancers. These findings beg the question: what characteristics define tumors and patients most amenable to checkpoint inhibitor treatments?

There are many factors that could affect the efficacy of checkpoint inhibition. These include, but are not limited to: the patient’s inherent capacity for mounting an anti-tumor response; the ability for cytotoxic T cells or other immune effectors to access the cancerous cells by infiltrating a biophysically and metabolically inhospitable tumor microenvironment (in the case of solid tumors); the presence of inhibitory molecules or cells, including regulatory T cells, that may dampen effector cell responses; and whether the cancerous cells are recognized as foreign and targeted for killing.

Studies suggest that tumor foreignness is highly correlated with response to checkpoint inhibitors. Checkpoint blockade has been found to be particularly effective in cutaneous melanoma and smoking-associated non-small cell lung carcinoma (NSCLC), where ultraviolet rays and combustible tobacco carcinogens, respectively, induce hundreds to thousands of mutations. Cancers with lower mutational loads have been shown to be less responsive to checkpoint inhibitors (e.g., NCT01295827). These findings are likely attributable to the presence of cancer neoantigens—those polypeptides that are absent from the normal human proteome, but rather are expressed only as a result of the unique set of mutations within a cancer cell and thus recognized as non-self antigens.

A new frontier in checkpoint blockade is to increase cancer cell antigenicity through neoadjuvant or adjuvant induction of DNA damage to spur further cancer cell mutations with the hope of inducing highly immunogenic neoantigen expression. Luckily, oncologists are experts at inducing DNA damage. DNA damage is the basis for radiotherapy and many traditional chemotherapeutic drugs, including cisplatin, doxorubicin, etoposide, and others. It is tantalizing to speculate that those cells initially spared from DNA-damaging chemotherapy may accumulate mutations that become neoantigens for subsequent immune surveillance. Recent preliminary studies combining targeted tumor irradiation and dual CTLA-4/PD-1 blockade in melanoma (NCT01497808) look promising, and this approach is being explored in numerous studies for various cancers. Similarly, combination cisplatin and checkpoint blockade has also shown encouraging efficacy as a first-line treatment for NSCLC (NCT00981058, NCT00982111). Hundreds of other trials are ongoing to examine the efficacy of checkpoint inhibitors in combination with other DNA-damaging modalities.

The DNA damage response (DDR) is the endogenous set of pathways governing a cell’s response to DNA lesions. Interestingly, a recent study of colorectal cancer patients (NCT01876511) showed that those with germline loss-of-function mutations in DNA mismatch repair genes involved in DDR showed a roughly four to seven-fold greater response rate to pembrolizumab than patients without DDR loss-of-function. Of note, DDR-deficient patients’ tumors harbored roughly ten to one hundred times as many somatic mutations as DDR-proficient patients’ tumors. Pursuing DDR and replicative stress in cancer has been of interest for some time, including ongoing preclinical and clinical investigation of targets like ataxia telangiectasia and Rad3-related protein (ATR), checkpoint kinase 1 (CHK1), WEE1, Topoisomerases 1 and 2, and poly (ADP-ribose) polymerase (PARP). Among these candidates,
the PARP inhibitor olaparib was recently approved for treatment of breast and ovarian cancers harboring mutations in BRCA1 or BRCA2 (other genes involved in DDR). To assess whether DDR inhibition can augment checkpoint blockade, the MEDIOLA trial (NCT02734004) is currently recruiting participants to study the effects of olaparib in combination with an anti-PD-L1 antibody in advanced solid tumors. Another trial, BISCAY (NCT02546661), will explore olaparib and other PARP inhibitors in combination with another anti-PD-L1 antibody in invasive bladder cancer. A handful of other trials combining various anti-CTLA-4 or anti-PD-1 antibodies with olaparib or other DDR-targeting drugs are also recruiting patients (e.g., NCT02571725, NCT02484404).

Many checkpoint blockade therapeutic strategies to date have relied simply on the antibodies' proposed mechanisms of action: take the reins off exhausted T cells, allowing them to kill again. Now five years on from the first checkpoint inhibitor's approval, with tens of thousands of patients treated in clinical trials and in real-world clinics post-approval, we have learned many lessons that should help us be smarter in our approaches and maximize the potential of checkpoint blockade. Increasing cancer cell antigenicity is but one of several tactics. There are ongoing efforts to develop novel checkpoint inhibitors, to use biomarker-based patient stratification to steer clinical decision making, to limit the prevalence and severity of immune-related adverse events, to overcome resistance that develops in some patients, and to rationally combine checkpoint blockade with existing and emerging therapies—including cancer antigen vaccines, adoptive T cell transfer or chimeric antigen receptor T cell therapy, and treatments to further stimulate immune cells or drive their infiltration into tumors. Given the tremendous hope for checkpoint blockade therapies that has developed over a relatively short time, we eagerly await the next five years—and beyond—of advances in this field.

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