SOUNDING BOARD

Immune Checkpoint Inhibitors — The Need for Innovation

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In the field of oncology, clinical investigations of immune checkpoint inhibitors now predominate. These drugs, delivered as antibody therapies that activate T-lymphocyte–mediated antitumor responses, are the result of seminal studies by Freeman et al.,[1] Krummel and Allison,[2] and others. Since the immune checkpoint inhibitor ipilimumab was approved for the treatment of melanoma more than a decade ago, regulatory agencies across the world have granted marketing approval for at least 90 additional uses for the more than 11 different versions of these drugs that are available to oncologists.[3]

These agents have been a major advance for patients with cancer. Their use has moved beyond palliative care for patients with melanoma or lung cancer, and now, with or without chemotherapy, they extend survival among patients with tumor types ranging from non–small-cell lung cancer, melanoma, mismatch repair–deficient colorectal cancer, and bladder cancer to Hodgkin's lymphoma. Recent studies have provided support for extension of their use to adjuvant therapy for patients with resected lung cancer or melanoma. Immune checkpoint inhibitors have also changed neoadjuvant therapy (before surgery) in patients with these same tumor types and others. In patients with mismatch repair–deficient rectal cancer, these agents have delivered remarkable pathological complete remissions and may obviate the need for surgery.[4]

These results justify the enormous investment by the pharmaceutical industry in clinical trials of immune checkpoint inhibitors. As of December 2021, more than 5600 studies were ongoing worldwide, each enrolling tens to hundreds of patients and each seeking a new niche for the multitude of immune checkpoint inhibitors under active investigation.[3] For the pharmaceutical industry, the payoff, even for agents with only minor indications, is generous. At an average yearly cost of $150,000 to $200,000, the total revenue associated with these agents approached $60 billion in 2021. The leader in this competition, pembrolizumab, generated approximately $20 billion in sales, and the minor players returned single-digit billions.[3] Even niche indications for immune checkpoint inhibitors clearly lead to great earning potential for drug companies because most approvals in metastatic cancer require continuous drug administration for an extended period, ranging from 1 to 2 years to indefinite therapy for the duration of the remission. Table 1 highlights the landscape of indications for immune checkpoint inhibitors in lung cancer alone.

Thus, the pharmaceutical industry has an enormous economic incentive to invest in new indications for immune checkpoint inhibitors. But how many of these agents are redundant? And are they distracting from efforts to identify newer and better treatments? Many of the trials evaluating the use of these agents are redundant, with very similar trial designs and statistical assumptions. In addition, the high cost of these agents places patients at risk for financial harm and can lead to inequities between insured patients and uninsured patients and between those with access to health care and those with limited access. For reasons that are unclear, the glut of similar products from many different pharmaceutical companies has not led to competitive pricing.

Despite the impressive results associated with immune checkpoint inhibitors and their return for industry, their use is not a complete victory for patients with cancer. Most responses in patients with metastatic disease are not complete, with the possible exception of long-term remis-

Table 1. Indications for the Use of Immune Checkpoint Inhibitors in the Treatment of Lung Cancer.

Disease and Indication	Checkpoint Inhibitor
Non–small-cell lung cancer	
First-line treatment, metastatic disease	Pembrolizumab alone or combined with chemotherapy Atezolizumab alone or combined with chemotherapy Cemiplimab alone or combined with chemotherapy Nivolumab plus ipilimumab, alone or combined with chemotherapy Tremelimumab plus durvalumab, combined with chemotherapy
Second-line or subsequent treatment, metastatic disease	Pembrolizumab Nivolumab Atezolizumab
Unresectable stage III disease after definitive chemoradiation	Durvalumab
Adjuvant therapy	Atezolizumab Pembrolizumab
Neoadjuvant therapy	Nivolumab combined with chemotherapy
Small-cell lung cancer	
First-line treatment, extensive-stage disease	Atezolizumab combined with chemotherapy Durvalumab combined with chemotherapy

sions in patients with melanoma, non–small-cell lung cancer, Hodgkin's lymphoma, and mismatch repair–deficient tumors of various histologic types. Although numerous indications have emerged for immune checkpoint inhibitors in the treatment of solid tumors, the effect of these therapies in patients with hematologic cancers other than Hodgkin's lymphoma has been limited.

These drugs may have considerable toxic effects in some patients, provoking autoimmunity and a variety of adverse events in the lungs, liver, and skin, with a 1% fatality rate.[5] At one of our institutions and at others, a specific working group meets weekly to deal with the myriad multiorgan toxic effects (e.g., pneumonitis, interstitial lung disease, colitis, hepatitis, and nephritis) resulting from immune checkpoint inhibitors and chimeric antigen receptor (CAR) T-cell therapy. This group addresses questions such as whether patients with underlying and clinically inapparent autoimmune responses are particularly susceptible to the toxic effects of immune checkpoint inhibitors and which countermeasures (e.g., glucocorticoids, anti–interleukin-6 monoclonal antibodies, and anti–tumor necrosis factor therapy) are most effective in treating specific toxic effects in individual patients.

Beyond the clinical issues, the basic nature of immune checkpoint inhibitor therapy poses questions. With the exception of microsatellite instability in mismatch repair–deficient tumors, biomarkers that are sufficiently specific to identify patients who may have a response and to exclude patients who may not have a response are lacking.[6] In the age of precision medicine, the approach of stimulating a global T-cell response, encompassing both normal and mutant antigens, in order to engage a specific target, a cancer antigen, requires refinement.

Ideally, it should be possible to define a tumor antigen and stimulate a response that is limited to a subset of T cells, with strong antitumor specificity and without the global toxicity of immune checkpoint inhibitors. The extraordinary work of Krishna et al.[7] is one example of such an effort. Their group has analyzed the tumor-specific mutant peptide antigens in various solid cancers. They have detected and expanded, ex vivo, antigen-specific, tumor-infiltrating T cells, and they have provided some remarkable, anecdotal, individual case reports. Despite this study, the challenge ahead will be to produce consistent responses with what currently can be regarded only as a complex and costly personalized form of technology that is not easily exported to clinical trials or clinical practice. What is needed is a consistently accurate and clinically usable method to define the antigens and specific epitopes that will evoke a cytotoxic T-cell response in patients. It is encouraging to note the recent progress in defining key epitopes that govern antibody and T-cell responses.[8]

Promising new options in immunotherapy are coming along, despite the failure of current trials to enhance the specificity and reduce the toxicity of checkpoint therapies. For example, the possibility of activating a more tumor-specific and less toxic population of T cells has arisen from the work of Hayday and colleagues at King's College, London. As described by Gulley et al.,[9] Hayday and colleagues have developed antibodies that activate specific variable beta

chain (Vβ) antigens, which are a component of the T-cell antigen receptor. Vβ antigens specify 30 different subsets of T cells. An antibody to a specific Vβ epitope activates and expands an individual subset, eliciting strong antitumor activity and diminished toxicity in murine checkpoint inhibitor–resistant tumors. Clinical trials of Vβ-activating human antibodies are under way.

The Vβ target may prove to be important in new treatments for T-cell lymphoma and cases of leukemia that have clonal Vβ identity. Li et al.[10] developed a CAR T cell against the T-cell receptor Vβ. They found that this CAR T cell had selective antitumor efficacy in vitro and in mouse models of T-cell cancers while simultaneously avoiding global CAR T-cell fratricide and maintaining the integrity of the host T-cell repertoire. This approach has promise for the treatment of T-cell cancers, for which there is a clear unmet need. Another promising example is the work of Liu et al.,[11] who developed a natural killer (NK)–cell therapy modified to express an anti-CD19 CAR. CAR-NK cells appeared to be safe and did not yield the toxic effects seen with CAR T cells, although their durability and efficacy have yet to be determined. Other potential strategies include bispecific antibodies targeting the T-cell receptor β chain.[12]

Numerous other approaches to amplify the effectiveness of immune checkpoint inhibitors are being tested. These approaches include the use of these inhibitors in combination with inhibitors of other repressive T-cell pathways, given that cytotoxic T-lymphocyte–associated antigen 4 (CTLA4) and programmed cell death 1 (PD-1) are not the only inhibitory pathways. These strategies, which are based on the complex regulators of T-cell response, include the following: targeting the innate immune kinase TANK binding kinase 1 and other costimulatory pathways; delivering immune checkpoint inhibitors, toxic cytokines, or both more selectively to the tumor microenvironment (e.g., masking domains that are unmasked by tumor-specific proteases or intratumor approaches to release intratumoral cytokines); developing new vaccine approaches that leverage the messenger RNA technology that was used successfully for vaccination against severe acute respiratory syndrome coronavirus 2; and combining immune checkpoint inhibitors with radiation therapy. However, as of this writing, only inhibition of the anti–lymphocyte-activation gene 3 (LAG-3) has been shown to have increased efficacy with immune checkpoint inhibitors.[13] Our concern is that much of this ongoing immunotherapy research uses antibodies against PD-1 as a foundation, despite their fundamental lack of specificity.

Our expectation moving forward is that the basic and clinical research community will continue to invest time and resources in entirely new approaches that further harness the immense potential of immunotherapy. However, we hope that effort and resources will be focused on developing antigen-specific and less toxic T-cell–based approaches and exploiting T-cell memory for more durable antitumor effects. From a regulatory standpoint, the Food and Drug Administration could consider creating and implementing a standard for approval that is based on bioequivalency. Thus, an anti–PD-1 drug that shows efficacy in preliminary trials could be granted approval for any of the indications for drugs of the same class, and redundancy in clinical trials would decrease. The pharmaceutical industry, which has enjoyed enormous profits from immune checkpoint inhibitors, might be encouraged to spend greater effort on innovative forms of technology that will address the shortcomings of current immune checkpoint inhibitor–based therapies.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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