

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Recent Insights Into the Use of Combination Immunotherapy in Solid Tumors



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H&O What are the main targets of immunotherapy?

JL In solid tumors, immunotherapy currently focuses the most on the checkpoint proteins cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed death 1 and its ligand (PD-1/PD-L1; Figure). Antibodies blocking these checkpoints have been effective in clinical trials. Currently, the only anti-CTLA-4 antibody approved by

ing. There is some suggestion that CTLA-4 may deplete T-regulatory cells in the tumor microenvironment. It is hypothesized that PD-1/PD-L1 checkpoint inhibitors function within the tumor microenvironment. Infiltrating T cells drive expression of PD-L1 in tumor cells via interferon- γ secretion, which can then inhibit those infiltrating T cells via the PD-1 receptor.

H&O Is immunotherapy more likely to work in certain types of cancers?

JL The old paradigm in drug development was that certain chemotherapies worked particularly well in certain diseases. That is not the right way to think about immunotherapeutic agents. Rather, with T-cell-based checkpoint antibodies, the goal is to target a productive antitumor immune response. A subset of patients have a spontaneous, antigen-driven T-cell response that causes tumor-infiltrated lymphocytes to be present in the tumor microenvironment. These cells can produce interferon- γ , which drives a number of gene programs, including PD-L1, leading to upregulation of that molecule. Upregulation of PD-L1 eventually leads to anergy of the T cells and apoptosis. This phenomenon is known as the T-cell-inflamed tumor microenvironment. The activity of PD-1 is confined to those tumors infiltrated by T cells, which drive PD-L1 expression. Mechanistically, this makes sense. To block PD-1, it needs to be present.

Patients with T-cell inflammation are likely to be amenable to combination approaches directed toward the inflammation. In patients without T-cell inflammation, it will be necessary to prime an immune response and generate inflammation before treatment with an anti-PD-1

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the US Food and Drug Administration is for melanoma. Additional indications are expected, such as for cancers of the lung, bladder, and kidneys. Anti-PD-1 antibodies have been broadly effective across many different histologies: at least 7 different cancers, with more to come.

CTLA-4 blockade and PD-1 blockade are mechanistically distinct. Anti-CTLA-4 antibodies are thought to inhibit the negative regulatory molecule CTLA-4, which functions at the activation stage of T-cell prim-

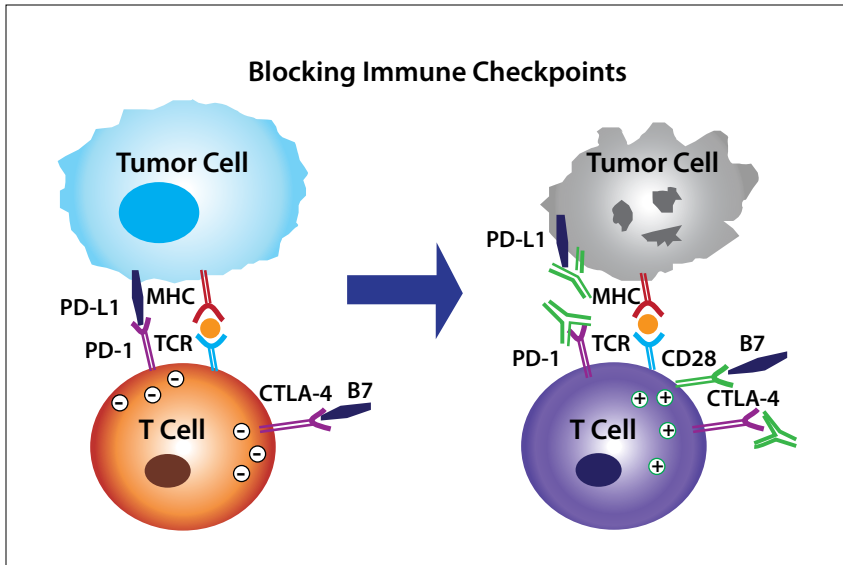


Figure. In solid tumors, immunotherapy currently focuses the most on blocking the checkpoint proteins CTLA-4 and PD-1/PD-L1. Reprinted from *Pharmacological Research*, Volume 120. Sweis RF, Luke JJ. Mechanistic and pharmacologic insights on immune checkpoint inhibitors, Pages 1-9. Copyright 2017, with permission from Elsevier. CTLA-4, cytotoxic T-lymphocyte-associated protein 4; MHC, major histocompatibility complex; PD-1, programmed death 1; PD-L1, programmed death 1 ligand; TCR, T-cell receptor.

antibody. There are several ways to generate inflammation in noninflamed tumors. Perhaps the most interesting way would be to activate type 1 interferons via infection with the oncolytic virus, toll-like receptor (TLR) agonism, or stimulator of interferon genes (STING). Stereotactic radiation is also being explored.

H&O How can biomarkers be used to predict which patients are more likely to benefit from immunotherapy?

JL In the current paradigm, the most robust assay is immunohistochemistry (IHC) to detect PD-L1. The selection of patients via PD-L1 immunohistochemistry is inherently flawed, however, because the presence of PD-L1 in the tumor microenvironment is dynamic. The presence of PD-L1 also fluctuates according to which tumor is biopsied, when the test is performed, and how the assay is reproduced. The biology dictates that the results will be wrong some of the time.

That being said, IHC testing for PD-L1 does enrich for the likelihood of response to PD-1–based agents. Patients with high PD-L1 status are good candidates for immunotherapy with an anti-PD-1 agent. However, patients with low PD-L1 status are not necessarily poor candidates for an anti-PD-1 agent. T-cell inflammation can provide insight into the optimal combination for each patient.

Given the current technical difficulties for community practitioners, IHC testing is sometimes used to determine whether a patient should receive immunotherapy. That is not my approach, and hopefully there will be better biomarkers in the future. Several potential

biomarkers are under investigation. The most robust biomarker in development may be gene-expression profiling of interferon- γ -associated genes. At the University of Chicago, we have termed this a “T-cell–inflamed” gene signature. There are different versions of this approach, which can include anywhere from tens to hundreds of genes. This approach is more robust because measurement includes interferon- γ -associated inflammation, not just PD-L1, thus providing a more holistic sense of what is happening in the tumor microenvironment. Detection of PD-L1 will enrich for response, but its absence does not rule out the possibility of response. In contrast, the interferon- γ -associated gene signature is more robust. If a patient has very low gene expression of the interferon- γ -associated gene signature, it is almost impossible that he or she could respond to therapy with an anti-PD-1 antibody. Low expression means that there are no T cells present and therefore no PD-L1.

Other biomarkers are also in development. The mutational load in the tumor has been associated with the response rate. The biology behind this correlation is unclear, although the predominant hypothesis suggests that neoantigens may play a role. T-cell receptor diversity is another potential biomarker.

H&O Which immunotherapeutic agents are farthest along in development?

JL Ipilimumab (Yervoy, Bristol-Myers Squibb) is the only anti-CTLA-4 antibody that is approved by the FDA. The approved anti-PD-1/PD-L1 antibodies are pembrolizumab (Keytruda, Merck), nivolumab (Opdivo, Bristol-Myers Squibb), atezolizumab (Tecentriq,

Genentech), and, most recently, avelumab (Bavencio, EMD Serono/Pfizer). Ongoing registrational trials are evaluating monotherapy with anti-PD-1/PD-L1 antibodies or combination approaches. The anti-PD-L1 antibody durvalumab (Imfinzi, AstraZeneca) is being combined with the anti-CTLA-4 antibody tremelimumab. The anti-PD-1 antibody PDR001 is also in phase 1 testing.

H&O Are there any other emerging targets of immunotherapy?

JL When interferon- γ is elaborated in the tumor microenvironment, it causes the tumor cells to produce a number of inhibitory molecules, such as PD-L1 and indoleamine-2,3-dioxygenase (IDO). The T cells in the tumor microenvironment then become “exhausted,” and begin to express a number of different molecules that also may be targets for new drugs. Examples include lymphocyte-activation gene 3 (LAG-3) and T-cell immunoglobulin- and mucin domain-containing molecule 3 (TIM-3), as well as activating checkpoints, such as CD137 and OX40. These molecules can work as targets only within the T-cell-inflamed phenotype. The biology does not support the use of these molecules in patients with noninflamed tumors.

Regarding inhibitors of IDO, several molecules are in development. Epcadostat is furthest along, with accrual already completed for a phase 3 registrational trial in melanoma, and several more phase 3 trials launching soon. At least 4 additional IDO inhibitors from other companies are also rapidly coming forward. The use of IDO inhibition appears to be a promising combination partner for patients with inflamed tumors. Several other immune checkpoints are being evaluated in clinical trials, ranging from early, first-in-human studies to phase 2 trials.

H&O Can immunotherapeutic agents be used in combination with targeted therapies?

JL This is an interesting area with potential overlap. There are 2 different ways to think about combining immunotherapy with targeted therapy. The more simple rationale is to achieve an additive benefit, similar to combining different chemotherapies. Targeted therapy is active in patients with certain oncogenes, and the addition of another active drug, such as an anti-PD-1 antibody, might provide additional benefit.

The second rationale would be to identify targeted therapies with an immunologic effect that could be synergistic with immunotherapy. An interesting question is whether there are oncogenic pathways that lead to

immune exclusion. While particular mutations can confer a growth advantage to the tumor, they may also have immunotherapeutic ramifications. In melanoma, the mutant BRAF protein has immunologic properties, so blocking it in combination with immunotherapy makes sense. Other oncogenic pathways that may have an immunologic impact, as suggested by published data, include β -catenin, phosphatase and tensin homolog (PTEN), and fibroblast growth factor receptor 3 (FGFR3).

H&O Can immunotherapy be used in combination with chemotherapy?

JL Chemotherapy clearly has a survival advantage in certain tumors. The appropriate use of chemotherapy with immunotherapy requires nuance because of the associated cytotoxicity to T cells. Among patients with inflamed tumors, the hope would be that the tumor microenvironment is so amenable to immunotherapy that chemotherapy is unnecessary. In patients with noninflamed tumors, administration of chemotherapy up-front might disrupt the immunosuppressive mechanisms and lead to tumor antigen release, which might prime an immune response. Treatment with immunotherapy then might be beneficial. Trials in lung cancer have shown a disproportionate increase in response rates with chemotherapy plus immunotherapy relative to the response rates of either of these therapies alone.

In the future, some patients will receive combination treatment with chemotherapy and immunotherapy. Hopefully, a subset of patients will be able to avoid chemotherapy, at least early in the course of management.

H&O What toxicities can arise from combination immunotherapy?

JL The toxicities associated with checkpoint-blocking immunotherapy are consistent across the entire class of molecules, but they occur with variable frequencies. Inflammatory, autoimmune-like consequences include colitis, pneumonitis, dermatitis, and thyroiditis, among others. With anti-CTLA-4 antibodies, grade 3/4 events occur in approximately 20% to 30% of patients, whereas with anti-PD-1/PD-L1 antibodies, the rate is approximately 10%. The first combination of anti-CTLA-4 and anti-PD-1 antibodies at approved doses was associated with dramatically higher rates of grade 3/4 toxicities of approximately 55%. That toxicity can be mitigated to some degree by varying the dosage of the anti-CTLA-4 antibody. However, it is an important consideration as those combinations move into phase 3 trials.

The combination of an anti-PD-1 antibody plus an IDO inhibitor showed a very high response rate in

early-phase melanoma trials, and the toxicity remained approximately 10%. The rates of toxicities with other immune molecules are unclear, which is why these therapies are under investigation in early-phase trials.

H&O Do you have any recommendations for the use of immunotherapy?

JL At least initially, therapies should be used within their indicated label. Clinicians should follow approved treatment guidelines from compendium bodies, such as the National Comprehensive Cancer Network. When these therapies are considered for use outside of the standard of care, it is not possible to predict which patients will benefit given the current biomarkers. I am an investigator on many early-phase trials, and I strongly advocate that if patients still require treatment after standard-of-care therapy, they consider immunotherapy because we do not yet know for sure who will benefit.

There are patients with very rapidly progressing disease who will have a poor outcome unless they can achieve an immediate benefit from treatment, whether that be radiation, chemotherapy, or another type of treatment. Some of these patients may need chemotherapy rather than immunotherapy, immunotherapy combined with chemotherapy, or chemotherapy followed by immunotherapy. The decision-making process must be nuanced and based on clinical factors.

H&O Are there other immunotherapy combinations under investigation?

JL There are more than 900 immuno-oncology combination strategies under investigation in clinical trials. We are in the infancy of understanding how to best combine therapies, whether that means 2 immunotherapy agents, immunotherapy plus targeted therapy, or immunotherapy plus chemotherapy. Although the recent increased efforts and interest in immunotherapy are welcome, there must be consideration for the levels of evidence supporting these trials. There are not enough patients to complete 900 trials of combination immunotherapy. A combination regimen should have a strong preclinical rationale before it is tested in a clinical trial.

H&O Are there any other areas of research in this field?

JL Beyond PD-1/CTLA-4 or IDO combinations across

many tumor types, several T-cell–based checkpoints—such as LAG-3, TIM-3, and V-domain immunoglobulin-containing suppressor of T-cell activation (VISTA)—seem attractive in combination with PD-1. Beyond these, anti-colony stimulating factor 1 receptor (CSF1R) antibody-targeting macrophages and inhibition of the adenosine axis via the A2A receptor appear to be interesting combination partners for an anti-PD-1 antibody. In patients with noninflamed tumors, it may be beneficial to combine PD-1 with innate immune activators in the tumor microenvironment, such as the oncolytic virus, TLRs, STING agonists, and maybe radiation.

Disclosure

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Suggested Readings

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