

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Strategies to Overcome Resistance to PD-1 Inhibitors



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H&O How do programmed death 1 (PD-1) inhibitors work?

TG There is a growing list of antibodies that target either the PD-1 receptor or the ligand in many different types of cancer. PD-1 inhibitors are approved by the US Food and Drug Administration in approximately 15 different cancers. The most frequently used PD-1 inhibitors include pembrolizumab (Keytruda, Merck) and nivolumab (Opdivo, Bristol-Myers Squibb). Nivolumab and pembrolizumab are likely functionally equivalent. Their outcome data and toxicity profiles are similar.

PD-1 inhibitors block the interaction between the PD-1 ligand and the receptor. PD-1 is expressed on activated T cells of the immune system. These drugs block engagement of this receptor, which is an off signal for T cells. Blocking the receptor relieves the off signal, which is thought to reinvigorate T cells that are trying to destroy the tumor. Some patients already have a strong endogenous immune response against the cancer, in which the T cells are activated and expanded, and then traffic into the tumor microenvironment. However, the immune response then stops at this later stage. The main mechanism of action of PD-1 blockade appears to be through restoring function of activated T cells that are already in the tumor microenvironment. These T cells are unable to destroy the tumor in the steady state because they are shut down by inhibitory pathways. At this point, use of the PD-1 inhibitors, either alone or in combination with other therapies, can lead to tumor shrinkage.

Research now shows that a major subset of patients with solid tumors completely lack this endogenous immune response. It is not known at what point the immune response fails. These patients tend to not respond to PD-1 inhibitors because there is no substrate on which

the anti-PD-1 intervention can act. This mechanism is largely linked to the T-cell inflamed tumor microenvironment. Patients with a T-cell inflamed tumor microenvironment are more likely to respond to PD-1 inhibitors. Patients who lack a T-cell inflamed tumor microenvironment are unlikely to respond. The absence of a T-cell inflamed tumor microenvironment is a common mechanism for escape from immune destruction that is seen in multiple cancer types. There is a continuum from one extreme to the other, and patients with a somewhat inflamed microenvironment may respond to treatment.

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H&O What is the difference between primary and secondary resistance to PD-1 inhibitors?

TG Patients with primary resistance do not respond to treatment at all. In these patients, an intrinsic defect along the cascade of immune activation events renders the PD-1 inhibitor ineffective. With secondary resistance, patients experience major, or even complete, tumor regression, but the tumor eventually returns. In patients with multiple sites of metastatic disease, all of the tumors may shrink, but one or more might grow

again. Primary resistance appears to be more common than secondary resistance. Understanding the mechanism of primary resistance would provide clinical benefit to a broad range of patients.

H&O How do the mechanisms behind primary and secondary resistance differ?

TG Researchers are studying the mechanisms of primary and secondary resistance. Both types of resistance appear to partially overlap on a molecular level. Much of primary resistance, however, can be attributed to the lack of a T-cell inflamed tumor microenvironment. Researchers are evaluating the biology of how the T-cell inflamed tumor microenvironment is generated, focusing on the steps that must occur in sequence, which of the steps might be deficient in a certain patient, and then what kind of intervention would be needed to reactivate the immune response to enable checkpoint blockade with PD-1 inhibitors. This question can be considered on a pharmacogenomic level. Some patients naturally have a highly active endogenous immune response against their tumor, and others do not. Why might 2 patients have such different phenotypes? It may be because of differences in the tumor biology. For example, mutations in oncogene pathways might differ. One hypothesis is that there might be oncogenic events in the cancer that block the immune response.

Another hypothesis is that immunotherapy is not acting on the cancer cells directly, but rather on the host's immune response. Host factors that generate interpatient heterogeneity, including germline genetics, might also play a role. There are germline polymorphisms in immunoregulatory genes that predispose patients toward autoimmunity diseases, such as lupus and rheumatoid arthritis, and can lead to greater spontaneous antitumor immunity, similar to autoimmunity. Germline single nucleotide polymorphisms (SNPs) might therefore be important.

A third category is environmental factors, such as the gut microbiota. The constellation of bacteria in the gut can have profound regulatory implications for the entire immune response, not just the mucosal immune response.

These areas are being investigated in prospective and retrospective studies. Tumor oncogenic pathways, germline polymorphisms in immunoregulatory genes, and microbiome differences have all been linked to response vs resistance in patients treated with PD-1 inhibitors.

H&O What is known about the drivers of resistance?

TG It has been suggested that in an individual patient, just one of these categories might drive resistance. For example, a certain patient might have a tumor cell

intrinsic oncogenic event. The first one identified was activation of the WNT/ β -catenin pathway. This pathway is relevant for many human cancers. A patient might lack an immune-potentiating polymorphism in the germline. If these polymorphisms are in druggable targets, it may be possible to mimic them. Another patient might have suboptimal microbiota that do not support a strong systemic immune response against the cancer, and therefore might need a microbiome-based intervention. In the future, elucidation of the different biologic processes that regulate the extent of the endogenous

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immune response against cancer might lead to a distinct set of interventions targeting the dominant defect found in an individual patient. This concept is similar to that of personalized cancer therapy, but in this case targets the dominant mechanism of resistance. Identifying a patient's particular resistance mechanism might lead to combination treatment with another intervention added to a PD-1 inhibitor to restore efficacy.

H&O Have any of the strategies to overcome resistance been used in clinical care?

TG Some of these concepts have moved into the clinic. Strategies to target oncogenic events are the farthest along. Dr Randy F. Sweis, a colleague at the University of Chicago, discovered mutations in the oncogene fibroblast growth factor receptor 3 (*FGFR3*) gene that are associated with lack of an immune infiltrate in bladder cancer. Ongoing trials are evaluating whether blocking *FGFR3* will improve efficacy of PD-1 inhibitors in bladder cancer and other malignancies.

The microbiome effect is also under investigation. Several biotech startups are evaluating ways to restore bacteria that a patient may be missing to improve the component of the immune response that is regulated by the microbiota. Some centers are pursuing fecal transplant from responding patients to nonresponding patients. Fecal transplant is already in use for the treatment of intestinal issues such as

Clostridium difficile infection. This platform is being translated into immuno-oncology.

Researchers are investigating how to provoke a de novo immune response in tumors that lack one. Innate immune system activators have several targets. Agonists against the innate pathways include the stimulator of interferon genes (STING) pathway and the toll-like receptors (TLR) 3 and 9. Oncolytic viruses and viral vectors can be injected into the tumor to ignite an immune response and generate T cells. Treatment with PD-1 inhibitors can then be initiated to maximize efficacy. These concepts are being explored clinically.

H&O Does your research have implications for other types of drug resistance?

TG The focus of these mechanisms is immunotherapy. That being said, an emerging area in the past year is the study of biomarkers to predict durable efficacy of other cancer therapies, such as chemotherapy or kinase inhibitors. Durable benefits from other cancer treatments have also been connected to immune infiltrates. It is conceivable that understanding the factors that regulate an immune infiltrate to make immunotherapy work better could help improve durability of response to other cancer treatments, including chemotherapy, targeted inhibitors, and radiation therapy used in combination regimens.

H&O What is the focus of your work on biomarkers?

TG A large component of multidimensional biomarker work is prospective biobanking. Researchers are performing RNA sequencing of the tumor, analyzing germline SNPs, sequencing bacteria from the gut, and analyzing different proteins and small molecules in the serum. Each of these “omics assays” has millions of data points. We are now trying to integrate all of these dimensions of data into clinical outcome studies, along with data regarding

tumor response and adverse events. This process requires a massive bioinformatic exercise. Some of the existing algorithms and bioinformatic techniques are not fully adequate for this kind of analysis. Researchers are working with experts in computational science to address the important new questions raised by the integration of multiple dimensions of data.

Disclosure

Dr Gajewski is a consultant and/or advisory board member for Merck, Bayer, Jounce, Aduro, FogPharma, Adaptimmune, Five Prime, Sanofi, and Pyxis. He has received research support from Roche/Genentech, BMS, Merck, Incyte, Seattle Genetics, Ono, Evelo, Bayer, and Aduro. He has intellectual property/licensing agreements with Aduro, Evelo, and BMS. He is a cofounder/shareholder of Jounce and Pyxis.

Suggested Readings

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