Next Steps for Cancer Immune Therapy

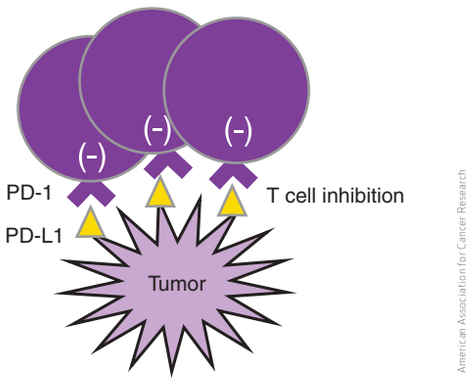
Checkpoint inhibitors hold promise, but more work is needed to determine who may benefit

Each new study seems to augment the good news about checkpoint inhibitors. Second-generation versions of these drugs, which lift the brake that tumor cells put on T-cell activation, have gained approval for recurrent melanoma and shown some activity against advanced non–small cell lung cancer (NSCLC), bladder cancer, kidney cancer, and refractory Hodgkin lymphoma. Patients can do remarkably well on these agents; for example, in melanoma, doctors now often talk about survival in terms of years instead of months.

But not every patient benefits, and additional hurdles stand between the drugs' potential and wide clinical use. Finding predictive biomarkers has been tricky, as some of the most promising molecular signatures don't definitively forecast which tumors will respond. Even when the agents work, tumors can grow—worrying both doctor and patient—before eventually shrinking. Furthermore, serious side effects often accompany these therapies, and the drugs have whopping price tags—around $100,000 per course for melanoma—so the stakes for patients and insurance companies are high.

"It's a great time for understanding immune therapy and its applications to patients, and hopefully we'll continue to find a way to improve efficacy, decrease side effects, and help patients live longer with a good quality of life," says F. Stephen Hodi, MD, director of the Melanoma Treatment Center and the Center for Immuno-Oncology at Dana-Farber Cancer Institute in Boston, MA. "Things are moving very fast."

A series of recent studies published in some of the most prominent medical journals—*Nature*, *The Journal of the American Medical Association*, and *The New England Journal of Medicine*, among others—have strengthened the idea that this family of drugs can combat cancers other than melanoma.



Activated PD-1$^+$ T cells can be inhibited by encountering PD-1 ligand expressed by tumor cells. (Originally published in Brahmer JR, Pardoll DM. Cancer Immunol Res 2013;1:85-91.)

The second-generation drugs pembrolizumab (Keytruda; Merck & Co.) and nivolumab (Opdivo; Bristol-Myers Squibb) prevent PD-1, a protein on the surface of activated T cells, from binding to its ligand, PD-L1. Association of these two molecules obstructs T cell activity, and blocking the ligand's attachment allows T cells to continue fighting the tumor.

Pembrolizumab won FDA approval for treating advanced or unresectable melanoma in September 2014, and nivolumab followed in December. In January, Bristol-Myers Squibb stopped a phase III trial in NSCLC early because participants receiving nivolumab fared so much better than those getting the standard of care, docetaxel.

In most cancers, checkpoint inhibitors used as a monotherapy work in only a subset of patients. Drug companies are therefore testing whether the compounds might prove more reliable if combined with other agents.

MUTATION BURDEN

Researchers and drug companies are also looking for biomarkers that would help them identify patients who are especially likely to benefit from checkpoint inhibitors. So far, one promising indicator seems to be the number

CHECKPOINT INHIBITORS FOR LUNG CANCER

In January, Bristol-Myers Squibb called an early halt to a phase III trial in squamous cell non–small cell lung cancer (NSCLC) because participants who received its second-generation checkpoint inhibitor, nivolumab (Opdivo), fared much better than those who got the standard-of-care drug, docetaxel.

The results have not been published, although the company says it is planning to do so. However, the results so far suggest that nivolumab could become a new standard of care, says Pasi Jänne, MD, PhD, director of the Lowe Center for Thoracic Oncology at Dana-Farber Cancer Institute and professor of medicine at Harvard Medical School, both in Boston.

"It will change the way we treat the disease, and hopefully is one of many [new treatments] to come for lung cancer," he says.

Jänne says he was particularly excited about the trial because so few advances have surfaced in squamous cell NSCLC, which accounts for 20% to 30% of lung cancers, largely among current or former smokers.

Nivolumab blocks the physical association between PD-1 and its ligand, PD-L1, which normally restrains the immune system. Consequently, T cells can attack tumors.

In the phase III, open-label CheckMate -017 trial, 272 patients were randomized to receive either 3 mg/kg of nivolumab every 2 weeks or 75 mg/m^2 of docetaxel every 3 weeks. An independent data monitoring committee concluded that the study met its endpoint of extending overall survival.

With this result, Bristol-Myers Squibb jumps ahead of Merck & Co., which had won FDA approval for its PD-1 inhibitor pembrolizumab (Keytruda) for advanced melanoma, a few months ahead of nivolumab. The NSCLC market is considered more important because of its much larger patient population.

Merck is conducting large-scale trials of pembrolizumab in patients with NSCLC as well.

of mutations in a tumor. Cancers with a large mutation burden, such as the subset of NSCLCs that are caused by smoking, respond better than those with fewer mutations, says Jedd Wolchok, MD, PhD, chief of the Melanoma and Immunotherapeutics Service and associate director of the Ludwig Center for Cancer Immunotherapy, both at Memorial Sloan Kettering Cancer Center in New York, NY.

"The more of these passenger mutations that exist, the more the tumor might look less like a normal cell and more like something foreign," such as a bacterium or virus, Wolchok says. Four cancers that respond well to checkpoint inhibitors—melanoma, head and neck cancers, NSCLC, and bladder cancer—carry heavy mutation loads, he says.

In a November study in *The New England Journal of Medicine* (N Engl J Med 2014;371:2189–99), Wolchok and other researchers analyzed the exomes of tumors from 64 patients with melanoma who were treated with the first-generation checkpoint blockers ipilimumab (Yervoy; Bristol-Myers Squibb) or tremelimumab (Pfizer, AstraZeneca). These agents inhibit CTLA-4, another T-cell surface protein that also dampens the immune response, and they cause more severe side effects than the PD-1 inhibitors. Most, but not all, of the patients with many mutations responded well to the therapy, says Wolchok. This work raises doubts about the usefulness of mutation load as a biomarker in the near term, as an ideal tool would predict responsiveness with close to 100% accuracy, he says.

PD-L1 EXPRESSION

PD-L1 quantities also have potential to indicate which individuals are likely to benefit from particular drugs—in this case, the ones that impede the PD-1/PD-L1 interaction. In one of three November *Nature* papers that address this issue, researchers including Hodi examined tumor tissue from 175 patients with NSCLC, melanoma, renal cell carcinoma, and other cancers, who were treated with the Genentech compound MPDL3280A, which targets PD-L1 (Nature 2014;515:563–7). Overall, 18% of patients showed partial or complete responses; those whose tumor cells and tumor-infiltrating immune cells carried large amounts of PD-L1 were overrepresented in that group.

Similar results emerged from a recent trial of patients with relapsed or refractory Hodgkin lymphoma. Sixty-five percent of participants responded to pembrolizumab and 21% experienced a complete and continuing response, says Eric Rubin, vice president and therapeutic area head for oncology at Merck & Co., citing a presentation at the American Society of Hematology Annual Meeting in San Francisco, CA, in December. Virtually all patients with Hodgkin lymphoma have tumors with abundant PD-L1, he added.

However, it's not yet clear how useful tumor PD-L1 expression levels will be for determining who should receive a PD-1 inhibitor, Rubin says, because some patients without detectable quantities of the ligand respond. Researchers might need to refine their techniques for measuring PD-L1, he says.

The next step, Wolchok says, is to connect the dots among these recent discoveries and devise ways to exploit the findings. In one potential strategy, clinicians might induce mutations in tumors to sensitize them to checkpoint inhibitors, he says. For example, patients could undergo planned radiation treatments or chemotherapy, both of which are mutagenic, before receiving checkpoint inhibitors.

Another possible approach, Wolchok says, would deploy oncolytic viruses to promote inflammation and thus render tumors vulnerable to checkpoint inhibitors. A small study presented last year at the annual meeting of the American Society of Clinical Oncology showed a high response rate when researchers administered the oncolytic virus T-VEC with a checkpoint-blocking antibody, he says. This and other work will help address the key challenge, he says, which is to determine "what drives those immune cells into some tumors… and not others."—*Karen Weintraub* ■

SEEKING SYNERGY WITH SARGRAMOSTIM

Drugs that enhance the immune system in different ways can synergize, and when researchers recently added the immune-system booster sargramostim (Leukine; Sanofi-Aventis) to the CTLA-4 inhibitor ipilimumab (Yervoy; Bristol-Myers Squibb), they hit on a somewhat successful combination.

Sargramostim is a whole-cell vaccine that secretes granulocyte-macrophage colony-stimulating factor (GM-CSF), a growth factor that fosters proliferation and differentiation of multiple hematopoietic lineages—and that fights tumors. The cytokine has shown activity against prostate and ovarian cancers and is being tested in melanoma, but a 2009 study suggested that the drug may dampen T-cell activity. Perhaps, researchers reasoned, a checkpoint inhibitor would counteract that effect.

In the recent study, patients with metastatic melanoma who received the sargramostim–ipilimumab regimen experienced a median overall survival nearly 5 months longer than those treated with ipilimumab alone—17.5 months versus 12.7—and fewer patients had severe side effects, such as gastrointestinal distress (JAMA 2014;312:1744–53). However, the combination did not increase the patients' response rate, and progression-free survival did not improve, as many of the tumors grew before they shrank. The randomized phase II study included 245 patients.

The research team now wants to launch a confirmatory trial and test sargramostim in combination with an anti–PD-1 drug, a second-generation checkpoint inhibitor, which has fewer side effects than ipilimumab, says F. Stephen Hodi, MD, director of the Melanoma Treatment Center and the Center for Immuno-Oncology at Dana-Farber Cancer Institute in Boston, MA, the study's first author.

Overall, the results will help expand the use of checkpoint inhibitors, predicts Sapna Patel, MD, an assistant professor in the department of Melanoma Medical Oncology at The University of Texas MD Anderson Cancer Center in Houston.

Oncologists without highly specialized expertise might hesitate to offer their patients immunotherapy because it's unfamiliar, Patel says. Reducing serious adverse events with this combination could encourage more doctors to prescribe such therapy, she adds.

For more news on cancer research, visit *Cancer Discovery* online at http://CDnews.aacrjournals.org.