Shelved 4-1BB Antibodies Make Comeback

New formulations may be less toxic, more effective

Scientists have long known about the potential of 4-1BB antibodies to treat a range of cancers, but concerns about liver toxicity stymied previous efforts to bring drugs to market. Now, several trials are testing whether new formulations of the drugs, both alone and in combination with other therapies, can produce an even stronger immune response.

4-1BB antibodies are members of the TNF receptor family that bind to the costimulatory receptor 4-1BB, also known as CD137—which is expressed on CD4 and CD8 T cells, natural killer cells, and other immune cells—thereby promoting survival and proliferation of T cells and enhancing the antitumor immune response. Bristol-Myers Squibb’s antibody urelumab showed promise back in 2008 for treating advanced melanoma, but there were concerns about high liver toxicity.

Urelumab trials are now continuing at lower doses, and researchers have been working on developing other 4-1BB antibodies to boost immune response. In 2014, Pfizer first reported that its 4-1BB antibody PF-05082566 was well tolerated and led to stable disease in some patients with solid tumors [J Clin Oncol 2014;32:55(suppl; abstr 3007)]. The drug showed particularly promising antitumor activity in a patient with Merkel cell carcinoma, says the trial’s lead investigator, Neil H. Segal, MD, PhD, a medical oncologist at Memorial Sloan Kettering Cancer Center in New York, NY.

More recent studies have shown that 4-1BB antibodies may complement the action of other immunotherapies. “Because of their ability to amplify cytotoxic T-cell responses against tumors, 4-1BB antibodies may also make great adjuvants to tumor vaccines—or any kind of intervention that generates an antitumor response,” says Michael Curran, PhD, assistant professor of immunology at The University of Texas MD Anderson Cancer Center in Houston.

At the American Society of Clinical Oncology’s 2015 meeting, investigators reported data from a phase I study combining PF-05082566 with the anti-CD20 monoclonal antibody rituximab (Rituxan; Roche) in 28 patients with non-Hodgkin lymphoma [J Clin Oncol 2015;33(suppl; abstr 3004)]. The overall response rate was 21% for all patients and 38% in patients with rituximab-refractory follicular lymphoma, with no serious adverse events.

“We now have a 20-patient cohort expansion trial to tease out whether 4-1BB works best at making the difference in patients where rituximab was no longer working,” says lead investigator Ajay Gopal, MD, professor of medicine at the University of Washington and a member of the clinical research division at Fred Hutchinson Cancer Research Center, both in Seattle.

Several other phase I trials are testing 4-1BB antibodies in combination with inhibitors of programmed death-1 (PD-1) and its ligand, PD-L1. Blocking PD-L1 expression may free up T cells to mount an immune response, perhaps by stimulating them to enter tumors, where they are most susceptible to anti–PD-L1 therapy.

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“PD-1 blockade works when you have some degree of T-cell infiltration in the tumor microenvironment, but it is much less effective if there are no T cells there in the first place,” says Curran. “Besides acting on T cells inside the tumor, 4-1BB antibodies also have the potential to expand tumor-specific T-cell responses generated outside the tumor.”

Investigators hope that the combination of a PD-L1 inhibitor and a 4-1BB antibody will produce an amplified immune response. One trial is testing PF-05082566 with pembrolizumab (Keytruda; Merck) in patients with a variety of advanced solid tumors; another combines urelumab and nivolumab (Opdivo; Bristol-Myers Squibb) for patients with non-Hodgkin lymphoma.

The drugs may also complement other antibodies that target tumors. Preclinical studies led by Holbrook Kohrt, MD, PhD, at California’s Stanford University School of Medicine, demonstrated that 4-1BB antibodies increase the effectiveness of trastuzumab (Herceptin; Genentech) in HER2-positive breast cancer and cetuximab (Erbitux; Lilly/Bristol-Myers Squibb) in EGFR-mutant head and neck and colorectal cancers [J Clin Invest 2012;122:1066–75; J Clin Invest 2014;124:2668–82]. Those studies laid the foundation for a current phase I trial of urelumab with cetuximab in metastatic colorectal cancer and head and neck cancer.

Other preclinical studies are scrutinizing combinations of 4-1BB agonist antibodies and the CTLA-4 inhibitor ipilimumab (Yervoy; Bristol-Myers Squibb) because previous studies in mice suggest that this combination may be more powerful and less toxic than either drug alone.

“These two therapies seem to have an extremely unique complementary relationship,” Curran says. “Not only do they work better together but they also mutually ameliorate one another’s adverse events.”

Although clinical evidence of the effectiveness of 4-1BB antibodies is limited, findings to date indicate that they may have broad applicability. “We still don’t know what types of tumors will respond best to 4-1BB antibodies but, in mice, almost every type of cancer responds,” he adds. “These drugs have the potential to be extremely therapeutically efficacious.”—Janet Colwell