Is PD-L1 Expression a Biomarker of Response?

Some experts say it’s just one predictive factor

Drugs that target the programmed cell death-1 (PD-1) receptor have shown promising antitumor activity in clinical trials, and recent studies suggest that expression levels of PD-1’s ligand, PD-L1, may be a biomarker of patient response. However, experts increasingly say it is more likely that high PD-L1 expression is only one factor among many that affect how patients respond to PD-1 blockade.

“PD-1 is part of an equation that has other variables, and the most important of those is the presence of T cells,” says Antoni Ribas, MD, PhD, a professor of hematology and oncology at the David Geffen School of Medicine at the University of California, Los Angeles. “It is the action of T cells that kills the tumor, and that is what you are unleashing by giving a patient a PD-1 inhibitor.”

Pembrolizumab (Keytruda; Merck) and another PD-1 inhibitor, nivolumab (Opdivo; Bristol-Myers Squibb), are approved to treat both advanced melanoma and advanced non–small cell lung cancer (NSCLC). PD-1 blockade has shown potential to treat other cancers, including renal cell carcinoma and triple-negative breast cancer.

PD-1 inhibitors prevent receptor, found on the surface of activated T cells, from binding to PD-L1 expressed on the surface of tumor cells. When joined, these molecules interfere with the T cells’ ability to mount an immune response. Results from some trials have led investigators to speculate that higher expression of PD-L1 may predict which patients are most likely to respond to the drugs.

For example, in the KEYNOTE 001 trial of pembrolizumab in melanoma and lung cancers, patients who had PD-L1 expression on at least half of their tumor cells had higher response rates and longer progression-free survival (PFS) when treated with pembrolizumab than patients with lower expression levels (N Engl J Med 2015;372:2018–28).

Although response rates are higher in those with elevated PD-L1 expression, high PD-L1 expression does not guarantee response, and low or no PD-L1 expression does not exclude the possibility of response. As a result, investigators are looking at other factors that may affect cancer’s response to PD-1 blockade.

One may be the overall mutation load, says Matthew Hellmann, MD, an oncologist at Memorial Sloan Kettering Cancer Center in New York, NY. To build on an initial finding that smokers with lung cancer often respond better to anti-PD-1 therapy than never-smokers, Hellmann and his colleagues sequenced the tumors of patients with NSCLC who were treated with pembrolizumab (Science 2015;348:124–8).

They found that the overall mutation burden of those who had a durable benefit with pembrolizumab was much higher than those with short or no benefit. Also, those with high mutation burden who responded to the drug often harbored a specific signature of smoking-related DNA damage.

“The next question is ‘why does mutation burden matter?’” says Hellman. “Our hypothesis is that neoantigens, which result from somatic mutations, may direct tumor-specific immune responses. As an initial proof of principle, we identified neoantigen-specific T cells in the peripheral blood of a responder to PD-1 therapy, suggesting that neoantigens may be an important determinant of response.”

The study may explain why PD-1 blockade has been particularly effective for cancers with high mutational loads, such as melanoma or a highly mutated subtype of colon cancer with microsatellite instability, says Ribas. The more mutated the tumor, the more likely it is to trigger a response by preexisting T cells, which are then turned off by PD-L1 expression.

It is not the PD-1 blockade per se, but its ability to spur T cells into action that determines response, notes Ribas. Thus, even if a tumor tests positive for PD-L1 expression, it probably won’t respond to therapy if it doesn’t contain T cells.

As a result, researchers are combining PD-1 inhibitors with CTLA-4 inhibitors, such as ipilimumab (Yervoy; Bristol-Myers Squibb), to activate blocked T cells and allow them to penetrate tumors. In fact, the FDA recently approved the nivolumab–ipilimumab combination to treat BRAF V600 wild-type advanced melanoma (see article, p. 1228).

Other immunotherapies, such as the combination of a 4-1BB antibody and an OX40 inhibitor, may boost the effectiveness of checkpoint inhibitors by unleashing T cells, too. Preclinical studies suggest that activating 4-1BB and OX40, both receptors in the TNF superfamily that activate and promote survival of T cells, leads to a more potent immune response.

“The most important thing going forward will be learning how to prime tumors that are not likely to respond in order to generate a more inflamed environment to promote a response to PD-1 pathway blockade,” says Leisha Emens, MD, PhD, associate professor of oncology at Johns Hopkins Sidney Kimmel Comprehensive Cancer Center in Baltimore, MD. “Combination therapies with PD-L1 inhibitors will likely turn out to be a very important part of the overall strategy for cancer immunotherapy,” she says.—Janet Colwell

TESTING FOR PD-L1 EXPRESSION

When the FDA granted accelerated approval for pembrolizumab (Keytruda; Merck) for non–small cell lung cancer, it also approved the companion diagnostic test PD-L1 IHC 22C3 pharmDx (Dako North America) to assess PD-L1 expression. Despite the debate about using PD-L1 as biomarker of response, the test’s approval was based on an analysis showing that patients with at least 50% of their tumor cells expressing PD-L1 were most likely to respond to the drug.

“Ongoing randomized studies in lung cancer are under way to confirm that patients with the highest PD-L1 expression will have long-term benefit,” says Sarah Peddicord, an FDA spokesperson. Researchers are also testing whether pembrolizumab delays disease progression and extends survival in those with lower PD-L1 expression, she says.