

Q&A: Suzanne Topalian on Immune Therapies

What we're learning from striking trial results for immune checkpoint-blocking drugs

"Immunotherapy has finally arrived as one of the mainstays of cancer therapy," says Suzanne Topalian, MD, professor of surgery and oncology and director of the melanoma program at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins in Baltimore, MD. Topalian discussed progress with drugs that inhibit immune-checkpoint receptors and ligands, including PD-1 and PD-L1 inhibitors, with *Cancer Discovery's* Eric Bender.

Why might we think about cancer as an immune disorder?

The tumor microenvironment is immunosuppressive. Our job as cancer immunotherapists is to reverse that phenomenon—basically to restore the ability of the immune system to destroy cancer. Immunotherapy can theoretically take advantage of the hundreds of mutations that can occur in individual cancers, without the need to know exactly what the mutations are. Based on the recent clinical results with anti-CTLA-4, anti-PD1, and anti-PD-L1 drugs, we have more reason to believe that this is indeed the case.

How effective is the PD-1-blocking antibody nivolumab?

In results that were reported at this year's American Society of Clinical Oncology [ASCO] annual meeting, we followed 306 patients who initiated treatment with Bristol-Myers Squibb's nivolumab between 2008 and 2012, and confirmed durable responses in patients with advanced, treatment-refractory lung cancer (17%), melanoma (31%), and kidney cancer (29%). We reported for the first time median overall survivals and landmark survival rates which are very promising. This is especially encouraging since nivolumab is administered in the outpatient setting and has a favorable long-term safety profile. Nivolumab is now in phase III testing for these three cancers simultaneously, which is unprecedented.

What about other immune checkpoint inhibitors?

Our report last year on the anti-PD-L1 drug BMS-936559 [Bristol-Myers Squibb] also showed responses in patients with lung cancer, melanoma, and kidney cancer [N Engl J Med 2012;366:2455–65]. In addition, we reported on a response in ovarian cancer. The message is that you can block PD-1 or you can block PD-L1; they are two sides of the same equation.

We're also hearing very encouraging reports about Genentech/Roche's MPDL3280A anti-PD-L1 drug, and other agents. Promising results with Merck's lambrolizumab anti-PD-1 drug in melanoma were recently published [N Engl J Med 2013 June 2 (Epub ahead of print)].

How well does PD-L1 expression act as a biomarker?

Last year, we reported a robust immunohistochemical assay which gave preliminary evidence, in a subset of the patients treated with nivolumab, that expression of the PD-L1 molecule

in pretreatment tumor samples might correlate with clinical outcomes. This test, performed on paraffin-embedded tissues, was originally developed by Lieping Chen, MD, PhD, now of Yale Cancer Center, who discovered the PD-L1 molecule. Moving forward, PD-L1 expression will be examined in hundreds of patients in randomized trials of PD-1 or PD-L1 blockade, as a potential biomarker of response. Several companies have developed their own anti-PD-L1 antibodies and automated immunohistochemistry tests

to evaluate this. Early results presented at the ASCO 2013 meeting show higher response rates to PD-1 pathway blockade in patients whose tumors express PD-L1.

We and other groups are also looking at other potential biomarkers. However, there's an even larger issue here, which is that the immune system is dynamic and these biomarkers may be dynamic as well. When do you look for the biomarker? Do you need a tumor biopsy just before the patient starts treatment? Sometimes that's difficult to do. This is much more complicated than looking for the *BRAF* V600E mutation in melanoma.

How might we combine these drugs with other therapies?

One promising method is combining multiple immune checkpoint-blocking drugs. Concurrent treatment with the CTLA-4 inhibitor ipilimumab [Yervoy; Bristol-Meyers Squibb] and nivolumab achieved responses in about half of patients with advanced melanoma in a phase I trial reported at the ASCO annual meeting [N Engl J Med 2013 June 2 (Epub ahead of print)]. That makes sense from a scientific standpoint, because even though CTLA-4 and PD-1 are both immune inhibitory molecules, they have distinct properties.

Among other approaches, last year a team led by Jedd Wolchok, MD, PhD, of Memorial Sloan-Kettering Cancer Center, reported on a combination of targeted radiation therapy and ipilimumab in one patient [N Engl J Med 2012; 366:925–31]. They suggested that radiation therapy could have an immune-modulating effect, in essence creating an autologous tumor vaccine, and combining that with checkpoint blockade could be synergistic. Along the same lines as creating an autoimmunization effect via inflammatory tumor lysis, there could be a rationale for combining certain chemotherapies with checkpoint blockade. Then there are the targeted agents. For example, within the past year we've seen some interesting publications about the immune stimulatory properties of vemurafenib [Zelboraf; Genentech/Roche] in melanoma patients. It inhibits mutant *BRAF*, but at the same time, it seems to enhance anti-melanoma T cell responses.

This is just the tip of the iceberg. Many research teams around the world are trying to identify other treatments that may synergize with checkpoint blockade. ■



"Immunotherapy can theoretically take advantage of the hundreds of mutations that can occur in individual cancers," notes Suzanne Topalian, MD.

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