Cancer immunotherapy advances spawn calls for new endpoints

The 72-year-old man had tried every approved drug option available to treat the advanced kidney cancer that had spread throughout his body. As a last resort, he signed up for the first clinical trial of nivolumab, an experimental drug from Medarex and Bristol-Myers Squibb (BMS) that inhibits a protein called programmed death-1 (PD-1), which has a role in suppressing the activity of anticancer immune cells. After one dose of the antibody drug, the tumors in the man's lungs and lymph nodes started to recede. At the same time, though, the cancerous lesions in his pancreas and bones enlarged. This mixed response—with progression in some lesions and regression in others—begged the question: was the drug working?

Cancer trial protocols typically require that further treatment be discontinued if it seems to hasten disease progression—and this man's pancreatic and bone lesions were clearly progressing. Fortunately for him, however, the trial sponsors had included a provision in the study design allowing for such nonstandard responses to immunotherapy. After all, they'd witnessed these kinds of responses before with a similar drug that, like nivolumab, targets another key immune 'checkpoint' receptor.

"It was very reminiscent of what I had seen as an investigator on some of the earliest trials of ipilimumab," recalls study lead Suzanne Topalian, a surgical oncologist at the Johns Hopkins University School of Medicine in Baltimore, referring to another Medarex-BMS antibody marketed as Yervoy that blocks CTLA-4, a protein that, like PD-1, is found on the surface of activated T cells. "It didn't seem so unusual the second time around." The man received two more doses of nivolumab, each spaced four weeks apart, and soon enough his pancreatic and bone lesions started to shrink in size, as well. Close to six years later, and without further therapy, he is alive and disease free today.

This type of 'unconventional' response to cancer immunotherapies is actually seen relatively frequently—and shouldn't be ignored, says Axel Hoos, head of Immuno-Oncology & Combinations at GlaxoSmithKline outside of Philadelphia. Hoos has championed the need for alternative endpoints for cancer immunotherapy trials as codirector of the Cancer Immunotherapy Consortium (CIC), a program of the Cancer Research Institute, a New York–based nonprofit focused on such treatments.

"You might see conventional responses with every immunotherapy," Hoos says. "But there are additional patterns that have not been captured with standard approaches, and they are captured with immune-related response criteria"—which incorporate mixed responses and cases in which there was a delayed response (with tumor volume initially increasing before receding). In the follow-up multidose study of nivolumab, for example, Topalian and her colleagues observed standard 'objective' responses in 24% of participants. But they also documented immune-related responses in 5% of trial participants. Similarly, "with the most conservative definition, around 10% of patients in the ipilimumab phase 2 program had evidence of immune-related clinical activity," according to Jedd Wolchok, a CIC member at the Memorial Sloan-Kettering Cancer Center in New York who led the ipilimumab trials.

Notably, stresses Topalian, in nearly all of these unconventional responses, the final result was the same: a durable tumor regression on par with those seen in people who experienced a straightforward decline at all tumor sites.

Clinical stand-in

These days, companies often seek to get early approval of their drug candidates and rarely wait to reach overall survival endpoints. But since established response criteria used to support market applications don't include immune-related activity, existing 'surrogate' trial endpoints—secondary measures that are thought to predict traditional endpoints such as long-term survival—aren't always capturing the totality of the clinical benefit to patients.

Beyond regulatory filings, surrogate endpoints also help drug companies decide at interim analyses whether to continue with clinical development, and many suspect that the failure to account for delayed immune-related responses led Pfizer to prematurely halt a phase 3 trial involving another anti–CTLA-4 antibody called tremelimumab in 2008.

"We are currently in a cookie-cutter mold where we're using clinical trial design that was really intended to test chemotherapies in the twentieth century," Topalian says, "and now we're in the twenty-first century and we're talking about immunotherapies with a completely different biology."

Friends of Cancer Research (FOCR) and the Brookings Institution want to change the paradigm for trials of drugs like nivolumab that act on checkpoint proteins in immune cells. As *Nature Medicine* went to press, experts from industry, academia and the US Food and Drug Administration (FDA) planned to gather at a 7 November meeting in Washington, DC, convened by the two think tanks, to discuss ways to incorporate 'immune-related' responses into surrogate endpoints for cancer immunotherapy trials.

Four potential surrogate endpoints were on the agenda for consideration: one that measures tumor growth dynamics, one that calculates the overall clinical benefit rate (which factors in overall responses and cases of stable disease for six months or more) and one that considers a twist on progression-free survival, with the baseline measurement taken some months out from the initiation of drug therapy (rather than from the get-go) so as to accommodate the time it might take the body to start mounting an anticancer immune response. However, the proposed surrogate endpoint with the most data behind it is one dubbed 'milestone survival'—in effect, the proportion of participants still alive at some interim time point that's late enough to surpass any delayed immune-related response but soon enough to allow for accelerated regulatory approval.

At the meeting this month, Tai-Tsang Chen, a biostatistician from BMS, was slated to present the results of a retrospective analysis from a phase 3 trial involving 500 patients with untreated metastatic melanoma who received the chemotherapy drug dacarbazine alone or in combination with ipilimumab. He showed that the probability of survival once 300 patients had reached two years of follow-up was highly predictive of final overall survival. In the original analysis, overall survival was evaluated after 414 deaths had occurred, 37 months after the last of the 500 participants had enrolled.

Of course, a metric like milestone survival wasn't needed for ipilimumab to gain approval. But, in hindsight, it might have helped avoid the abandonment of tremelimumab. And looking forward, it could help with many of the PD-1 blockers or similar immunotherapies now in various stages development. As FOCR executive director Jeff Allen points out, "What we're trying to lay out here is a model that can be used for future immunotherapies."

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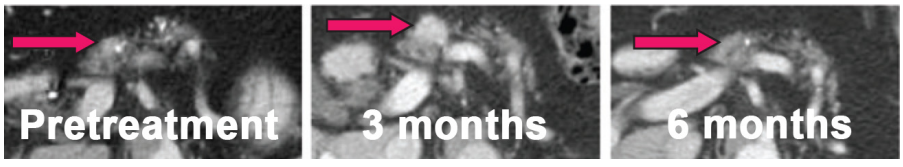

An unconventional response: The 72-year-old's pancreatic lesion following nivolumab treatment.

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