New Response Criteria Proposed for Immunotherapies

By Rabiya S. Tuma

Clinical investigators are testing the antitumor activity of several immunotherapies in a variety of malignancies. But new data from trials in melanoma patients suggest that the standard criteria used to define tumor response and progression may not adequately reflect patient responses to immunotherapeutic agents. In a worst-case scenario, researchers say, the disconnect between patient responses and the criteria used to evaluate them could cause active drugs to fail in clinical trials and the regulatory process. With these concerns in mind, a group of academic and industry researchers proposed a modification to the standard response criteria, which they presented at the annual meeting of the American Society of Clinical Oncology.

"This is important to all of us in the field," said Jedd Wolchok, M.D., director of immunotherapy clinical trials at Memorial Sloan-Kettering Cancer Center in New York and a coauthor on the proposal. "We don't want to see drugs discarded because the response criteria are inappropriate."

"This is important to all of us in the field. We don't want to see drugs discarded because the response criteria are inappropriate."

Researchers typically use Response Evaluation Criteria in Solid Tumors (RECIST) criteria or modified World Health Organization (mWHO) criteria to define tumor responses and disease progression. Both systems were developed for the evaluation of cytotoxic chemotherapies and rely on tumor shrinkage to indicate antitumor activity. By contrast, in several recent trials that tested an antibody that inhibits CTLA-4, a key immune system checkpoint, some patients appeared to derive long-term survival benefit from the treatment but showed continued tumor growth initially. By standard criteria, such patients would be classified as having progressive disease and taken off the study drug.

To illustrate the problem more systematically, F. Stephen Hodi, M.D., an assistant professor of medicine at Harvard Medical School and the Dana-Farber Cancer Institute in Boston, presented data from two phase II trials that tested the safety and efficacy of the anti-CTLA-4 antibody ipilimumab in patients with advanced melanoma. A total of 227 patients were enrolled in the trials. Of those, 41 did not have adequate follow-up data and were excluded from the current analysis. On the basis of the first tumor assessment, 12 weeks after the start of therapy, 63 patients had either a partial response or stable disease according to mWHO criteria, and 123 were considered to have progressive disease. With longer follow-up, 45 of the patients with stable disease showed a slow, steady decline in their overall tumor burden.

More important, though, were the long-term outcomes of some patients who appeared to progress initially. Researchers continued to monitor 57 of these patients and reported the following results at the meeting. Two patients eventually developed a partial response on the basis of mWHO criteria, meaning that their index lesions decreased by at least 50% relative to baseline. Eight patients had stable disease according to mWHO criteria with a slow but steady decline in total tumor burden. One patient developed a partial response but only after having an initial increase in total tumor burden, which occurred between the start of treatment and week 12. Finally, three patients who had new lesions arise during the first 12 weeks eventually had sufficient tumor shrinkage in the new lesions and the index lesions to satisfy the mWHO criteria for partial response.

Hodi acknowledged that the analysis was retrospective and included only some of the patients enrolled in the trials but said the data demonstrated the need for amended criteria. "Standard response criteria may not adequately capture the clinical benefit for immunotherapies, such as ipilimumab," he said. "The responses can take time to mature and can occur at variable times."

Paul Chapman, M.D., a physician with the melanoma and sarcoma service at Memorial Sloan-Kettering Cancer Center, who discussed Hodi's abstract, noted that these types of responses have been consistently seen in ipilimumab trials. "These types of late responses have been seen by all of the investigators around the world who have been using ipilimumab. These are real and are going to be important in evaluating this drug and perhaps other drugs as well."

Jedd Wolchok, M.D.

To more accurately reflect the clinical benefit gained from ipilimumab and similar agents, Hodi and colleagues proposed that the mWHO criteria be amended so that new lesions would not immediately be ruled as progressive disease. Under the proposed immune response criteria, the definition of a complete response would remain the same, with all lesions eliminated at the time of evaluation. A partial response would be defined as a 50% or greater decrease in the sum of the perpendicular diameters of index lesions and any new lesions, but the detection of new lesions would be allowed. Progressive disease would be defined as a 25% or greater increase in the sum of the perpendicular diameters of index and new lesions. Stable disease would apply to individuals who do not fit in the other categories, and new lesions would be allowed.

To perform an initial test of the immune response criteria, Hodi separated the 227 patients from the phase II trials into those who had a partial response or stable disease by mWHO criteria (28%), those who had a partial response or stable disease by the new immune response criteria but progressive disease by mWHO (10%), those with progressive disease by both criteria (38%), and those with early progressive disease and no extended follow-up (25%). When he plotted overall survival of the four groups on a Kaplan–Meier survival curve, the patients who achieved a partial response or stable disease by either criterion had noticeably better overall survival than the other two groups.

"While this is retrospective and a small number [of patients], it is intriguing," Hodi said. "The new immune response criteria were established in an attempt to more comprehensively capture those patients with clinical benefit." He added that it would be critical to test the immune response criteria in prospective trials before the new criteria will be ready for use as a trial endpoint. "The [prospective] investigation into the potential association with survival is the most important endpoint and is ongoing."

Hodi said that although he is aware that the proposed criteria will be tested, he did not know any specifics. Similarly, a representative of Bristol-Myers Squibb, one of the companies developing ipilimumab, said that they could not disclose any information about prospective testing at this time.

Not everyone is equally convinced that a redesign of the response criteria will solve the problem, though. "Even if you reclassify WHO and RECIST criteria, we would still have patients that would not fit in that classification," said Antoni Ribas, M.D., associate director of the tumor immunology program area at the University of California Jonsson Comprehensive Cancer Center in Los Angeles, who led a phase III trial with a different anti–CTLA-4 antibody called tremelimumab.

As in the ipilimumab trials, Ribas and colleagues saw some patients with delayed or mixed responses. This finding supports Hodi's contention that the problem will arise in trials other than those testing ipilimumab. The delayed responses "are not common, they are a subset of a subset, but they are there," Ribas said.

For Wolchok, the Memorial Sloan-Kettering oncologist, the key benefit of the new criteria is that they can help physicians manage patient care better. "If a person at week 12 or 16 after starting a therapy like ipilimumab has some lesions that are stable or getting smaller, yet a new lesion appears, by the old criteria that person would be taken off study and labeled a progressor. But under the immune response criteria, if the total tumor burden—regardless of whether the tumors are new or old—is stable or improved that is considered evidence of efficacy."

Nonetheless, Wolchok emphasized the importance of using overall survival as the primary endpoint in the phase III registration trial comparing ipilimumab plus dacarbazine to dacarbazine alone. "The only thing that matters here is overall survival. How they get to that extended lifespan is not as important," he said.

Bristol-Myers Squibb and Mederex, which are codeveloping ipilimumab, have requested that the primary endpoint of the phase III trial be changed from progression-free survival to overall survival, according to a spokesperson for Bristol-Myers Squibb. The companies declined to release further details about the protocol, however.

Wolchok pointed out that no one wants to be seen as changing the criteria to fit the data, which means that using the overall survival endpoint is even more important in this instance. He noted that standard mWHO criteria for progression-free survival will be used in the phase III trial but that he didn't know if the companies had any plans to test the new immune response criteria prospectively with the phase III ipilimumab data.

Although the value of these modified response criteria still need to be proven prospectively, experts agree that the problem of delayed responses is probably not confined to the anti–CTLA-4 antibodies or to melanoma. "It is becoming difficult to have drug development for immunotherapeutics," Ribas said, "because they do not seem to behave like chemotherapeutics, which is what WHO and RECIST criteria were designed for."

 DOI: 10.1093/jnci/djn334