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How Should We Assess Benefit in Patients Receiving Checkpoint Inhibitor Therapy?

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In recent years, immunotherapy has revolutionized the treatment of cancer. Immunotherapy has been used for decades (vaccines, interferon, high-dose interleukin 2), but only since the introduction of checkpoint inhibitors has it had a significant impact on the survival of patients with a variety of cancers. Currently, checkpoint inhibitors involving two specific targets are approved by the US Food and Drug Administration: cytotoxic T-cell lymphocyte-4–blocking antibodies (ipilimumab, approved by the US Food and Drug Administration for patients with melanoma) and programmed cell death protein 1/programmed death ligand 1–blocking antibodies (atezolizumab, avelumab, durvalumab, nivolumab, and pembrolizumab for patients with melanoma, renal cell carcinoma, non–small-cell lung cancer, head and neck cancer, bladder cancer, Merkel cell carcinoma, Hodgkin lymphoma, and others). As clinical trials with checkpoint inhibitors were ongoing, it was noted that occasionally atypical patterns of responses (a transient increase in the size of lesions or even appearance of new lesions) were seen, and therefore the most commonly used response criteria, namely Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, may not capture all patients who received benefit from these therapies.

In the article that accompanies this editorial, Hodi et al[1] present their efforts in refining the assessments of the clinical benefit of immunotherapy. Immune-related response criteria and immune-related RECIST (iRECIST) have been adapted for use in multiple clinical trials as a part of the assessment of overall response rate, but in this study, the authors attempt to use immune-modified RECIST (imRECIST) in the assessment of progression-free survival and overall survival. As the experimental group, patients with non–small-cell lung cancer and urothelial carcinoma treated with atezolizumab in three different clinical trials were selected. When imRECIST, and not RECIST, was used, the best overall response rate was increased by 1% to 2%, and progression-free survival was longer by 0.5 to 1.5 months. The analysis of the overall survival is especially intriguing. Among patients with lung cancer who were alive at 90 days, the survival was 1.4 to 4 months longer; 8-month survival rate was 9% to 28% higher in patients who had progressive disease by RECIST and not by imRECIST when compared with patients who had progressive disease by both RECIST and imRECIST. Interestingly, there was no difference in survival among patients with urothelial carcinoma. A 4.4-month improvement in overall survival was noted in urothelial carcinoma at the 180-day time point. Further subgroup analysis revealed that overall survival in patients with an initial increase in the target lesion(s) followed by reversion was similar to patients with a classic response, but survival of patients who developed new lesions was significantly shorter.

This work represents a meticulous mathematical effort to identify patients with a favorable survival on the basis of the patterns of response to therapy. We have learned that the development of new lesions gives especially unfavorable prognosis; too few patients with progression of nontarget lesions were included in the analysis to obtain a reliable result. This research showed we should strive to better understand the patterns of response; it also showed that the same rules may not apply to all histologies.

Nonetheless, the implications of this research must be interpreted with caution. The results of research might be influenced by various types of bias. It remains a gold standard to test new drugs in the setting of double-blind, placebo-controlled trials, so the bias introduced by the physician or patient knowledge of the treatment arm is eliminated. In modern immunotherapy clinical trials, physicians can make a decision to continue immunotherapy when, on the basis of the assessment by an investigator, patients experience a clinical benefit and their performance status has not worsened. The clinical benefit is poorly defined and open to different interpretations by different investigators. This decision obviously separates patients with more aggressive disease from ones with more indolent disease, and it possibly introduces a bias. We must not attribute the fact the patients stay longer on therapy only to the therapy they receive. It should be also entertained that imRECIST partially serves as a tool to identify patients with less-aggressive disease. Interestingly, the authors reported the patients with lung cancer treated with docetaxel, a traditional chemotherapeutic agent, had a similar pattern of survival, with a better survival when an initial progression of target lesions was seen rather than when new lesions appeared. One must also consider whether the use of imRECIST might occasionally be detrimental to patients. The general principle of imRECIST is to allow patients who otherwise would have to discontinue therapy to continue, despite appearance of new lesions or increase in the size of nontarget lesions. The assumption is that patients benefit from this approach, but this approach unintentionally prevents patients who do not benefit from the therapy from switching to the next-line treatment. The fact that survival curves of patients with urothelial carcinoma who experienced progression by RECIST and imRECIST and patients who experienced progression by RECIST but not by imRECIST overlap supports this notion.

It is possible that an important message regarding the traditional and new response criteria is not fully appreciated by

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practicing oncologists. These criteria were created to guide clinical trials and not necessarily to help with decision making in clinical practice. Clinical trials are medical experiments that on occasion lead to the development of new drugs, but more frequently they fail to prove clinical benefit. Therefore, it is critical that patients who volunteer to participate in a clinical trial who do not benefit from the tested drug be exposed to the experimental therapy for the shortest time possible. At the same time, it is critical that patients' participation in a clinical trial help us to address the tested hypotheses and lead to progress in clinical research (ie, patient's voluntary consent to participate in research becomes a researcher's responsibility that the contribution does not go to waste). It would be ideal that the clinical practice mirrors the stringent settings of the clinical research and that patients are exposed to drugs only for the period needed to assess benefit. The research response criteria are based on detailed measurements and description of target and nontarget lesions; the new criteria often require bidimensional measurements. Despite growing understanding of the tools for the assessment of response, the everyday radiologic reports often do not contain detailed measurements, and they just state that the disease burden worsened or improved. Such limited information is not sufficient to apply the research response criteria. In addition, positron emission tomography scans without a diagnostic computed tomography scan are still frequently ordered, and the clinical decisions in these cases are made on the change of standardized uptake value, which is not a reliable, established tool for most cancers. On the basis of these results, clinicians still have to use clinical judgment to continue or discontinue therapy rather than established algorithms. Modern oncologists and radiologists are extremely busy in their practices, and they are given less and less time to make clinical decisions. It appears that the use of time-consuming research response criteria may not be feasible in the clinical setting; clinicians should be offered simplified tools. These days it is common that physicians continue the treatment with checkpoint inhibitors, at least until the next radiologic assessment, when scans do not show massive progression of the disease and the patient's clinical condition has not worsened. It will be important for researchers to evaluate this simplified, more user-friendly concept against the results of the available clinical trials.

The introduction of immune-related response criteria also has had a significant impact on the conduct of clinical research, and it might not be an entirely positive one. All clinical researchers know how challenging the clinical research environment currently is. The regulatory requirements, the overzealous work of clinical research organizations, collection of unnecessary data, and the amount of paperwork that has to be processed require a lot of time and effort of investigators and research staff members. Immune-related response criteria assessment, in addition to RECIST, is a requirement in most immune therapy trials: radiologists have to spend more time on measuring lesions, including nontarget lesions; investigators and staff double their time on preparing the response assessments; and sponsors must hire additional expert radiologists. It is a costly and time-consuming addition to clinical research. It is all done, as the authors of this study note, to detect a difference in best overall response of 1% to 2%.

The field of immunotherapy is extremely exciting for clinical scientists, for clinicians, and more importantly for patients. Because this therapeutic area is relatively new, additional challenges emerge, including development of reliable methods of the assessment of benefit. The article by Hodi et al[1] is an important contribution to understanding of the field, and we hope that it will stimulate further research. It also indirectly suggests that we still need new computational tools to assess the benefit of cancer immunotherapy.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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1. Hodi FS, Ballinger M, Lyons B, et al: Immune-modified response evaluation criteria in solid tumors (imRECIST): Refining guidelines to assess the clinical benefit of cancer immunotherapy. J Clin Oncol doi:10.1200/JCO.2017.75.1644

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