Do We Need a Different Set of Response Assessment Criteria for Tumor Immunotherapy?

□□ *Commentary on Wolchok et al., p. 7412*

Antoni Ribas,[1,2,3] Bartosz Chmielowski,[1] and John A. Glaspy[1,3]

Tumor shrinkage induced by tumor immunotherapy may be preceded by inflammatory changes. This confounds the assessment of response rates to tumor immunotherapy. In this issue of *Clinical Cancer Research*, Wolchok et al. attempt to address this peculiarity by proposing a new set of criteria termed immune-related response criteria. (Clin Cancer Res 2009;15(23):7116–8)

In this issue of *Clinical Cancer Research*, Wolchok et al. (1) propose a new set of response assessment criteria for tumor immunotherapy, which they termed immune-related response criteria (irRC). It is well known that objective responses defined by the WHO or by the Response Evaluation Criteria in Solid Tumors (RECIST) are infrequent with immunotherapy strategies such as immune activating cytokines, cancer vaccines, or immune modulating antibodies. Tumor immunotherapists have traditionally thought that the benefit may extend beyond this low level of objective response rates and have frequently used terms such as "minor response" or "mixed response" to describe the outcome of some cases that do not meet objective response criteria but have a perceived benefit from immunotherapy. The use of nonconventional response criteria definitions has resulted in skepticism on claims of patient benefit from tumor immunotherapy (2). However, the markedly different mechanism of antitumor activity of immunotherapy compared with cytotoxic drugs suggests that patient benefit may need to be measured by an approach that incorporates the peculiarities of an immune attack to cancer.

In phase II studies aimed at determining an effect of a new agent without a concurrent control group, objective response is the most frequently used primary end point. Tumor shrinkage after dosing when the cancer was previously progressing is an unquestionable drug effect, far more objective than other less well-characterized end points based on time to event compared with historical controls. Objective response criteria measured following the WHO or RECIST approaches were developed primarily to define the effects of cytotoxic drugs, and these criteria may not perform as well for agents with other mechanisms of action. For example, the benefits of antiangiogenic agents may not be well documented in single-arm clinical trials where stable disease induced by the antiangiogenic agent cannot be well differentiated from stable disease due to the natural history of the cancer.

The mechanism of action of tumor immunotherapy, based on harnessing host immune cells to infiltrate tumors and exert a cell-based cytotoxic effect, is quite different from that of cytotoxic chemotherapy. The best documentation of this mechanism of action has been achieved with serial biopsies of regressing metastasis after therapy with anti-CTLA4 antibodies (3, 4). Metastases become infiltrated by $CD8^+$ CTLs, leading to tumor cell killing and eventually regression of melanoma detectable by objective response criteria (Fig. 1). However, tumor regression happens in only a small percentage of patients, around 10% (5, 6), and some cases with long-term disease control may actually represent a drug effect that goes undetected in single-arm clinical trials with response rate as end point. Given this background, it is not surprising that anti-CTLA4 antibody therapy is the basis for the report by Wolchok et al. (1).

The definition of irRC is based on the bidimensional measurement of tumor lesions as done in the WHO criteria, with two major changes. One of them is already used in the RECIST criteria, where the size of individual lesions is added up to a total tumor burden (7). The second one is not to take into account transient increase in size of individual lesions beyond 25% or the transient appearance of new lesions, both of which instances qualify as progressive disease following the standard WHO or RECIST criteria. The irRC approach, as described by Wolchok et al. (1), raises several important issues. Without a prospective validation with the same criteria applied to an experimental tumor immunotherapy arm compared with a concurrent cytotoxic therapy arm, it is unclear how many patients treated with standard chemotherapy would have one of the patterns of response described by Wolchok et al. and would qualify for irRC without an objective response by WHO or RECIST. In addition, it is certainly possible that by using the irRC, patients with a more indolent disease will be assigned to the responder

Authors' Affiliations: [1]Department of Medicine, Division of Hematology/Oncology, [2]Department of Surgery, Division of Surgical Oncology, and [3]Jonsson Comprehensive Cancer Center, University of California, Los Angeles, Los Angeles, California

Received 9/18/09; accepted 9/24/09; published OnlineFirst 11/24/09.

Requests for reprints: Antoni Ribas, Division of Hematology-Oncology, University of California, Los Angeles Medical Center, 11-934 Factor Building. 10833 Le Conte Avenue, Los Angeles, CA 90095-1782. Phone: 310-206-3928; Fax: 310-206-0914; E-mail: aribas@mednet.ucla.edu.

doi:10.1158/1078-0432.CCR-09-2376

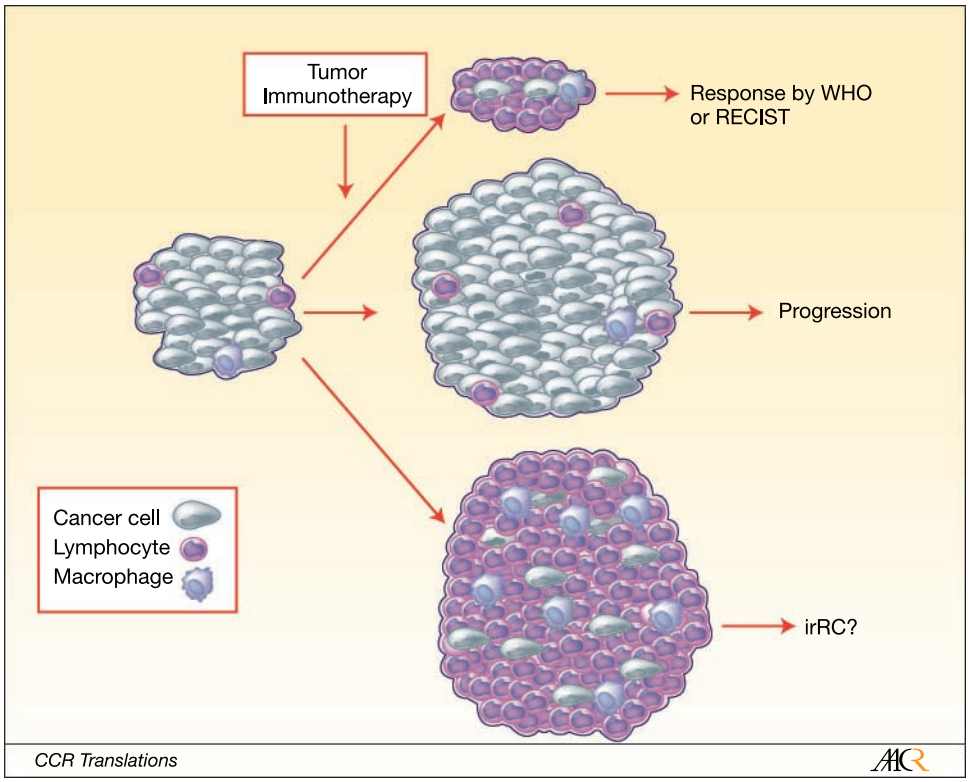

Fig. 1. Metastatic cancer lesions are made up mainly of cancer cells and stromal cells, with a very limited immune and inflammatory infiltrate by lymphocytes and macrophages. After receiving tumor immunotherapy, the size of metastatic lesions may decrease in the few patients that have an objective response, with the tumor being invaded by lymphocytes and later by macrophages; these tumor responses are well captured by the WHO and RECIST criteria. Metastatic tumor lesions will increase in size in cases where the tumor grows progressively, leading to disease progression. However, in some cases, the tumor lesions may become heavily infiltrated by immune and inflammatory cells resulting in an apparent increase in size of lesions, but this is due to infiltration by tumor immunotherapy–recruited cells as opposed to a progressive growth of cancer cells. In this case, the lesion would qualify as progressive disease by WHO or RECIST criteria, but as a responder following the newly proposed irRC.

category, although the experimental drug had no effect on the trajectory of their cancer.

The benefit of using a response assessment that correctly captures patients who benefit from tumor immunotherapy that are missed with RECIST or WHO measurements is important to avoid underestimating the antitumor activity of tumor immunotherapy agents, and it would allow patients who benefit from the intervention to continue on it and not be shifted to another form of therapy. However, this view needs to be counterbalanced by the opposing scenario, where a new set of response criteria wrongly applied to patients receiving tumor immunotherapy may overestimate its benefits and keep patients in futile (or even worse potentially toxic) therapy and withhold the possibility of starting another active therapy.

What would other options be? Some studies have added durable stable disease to partial response and complete response to define a clinical benefit rate, but in single-arm studies it is difficult to conclusively determine that disease stabilization is a direct effect of the experimental agent. Defining the best overall response on study attempts to avoid labeling prematurely the outcome as progressive disease in patients whose tumors initially grew but eventually decreased in size. It would be the best option to perform histological examination of lesions that qualify as progressive disease and see if the increase in size is caused by an inflammatory infiltrate (Fig. 1). However, this is unlikely to be feasible outside pilot experiences. A major hallmark of tumor immunotherapy is a reproducible rate of long-term remissions, which led to the Food and Drug Administration approval of high-dose interleukin-2 for renal cell carcinoma and melanoma based on single-arm studies even though the frequency of this event is very low (8). Therefore, an option would be to prospectively define a delayed time point for objective response critieria that would go beyond the poorly characterized early disease progression or appearance of new lesions of unknown significance. Using this approach, a landmark analysis of responses by RECIST or WHO at 6 or 12 months for patients who continue on therapy may allow bypassing the need for a separate set of response criteria for tumor immunotherapy. However, this approach would leave patients and physicians with little guidance for a significant amount of time and may not be feasible for application in cancers with median survival of months.

In conclusion, the definition proposed by Wolchok et al. of the irRC is a step in the right direction to evaluate the benefit of tumor immunotherapy strategies. The value of irRC can only be fully assessed when it is prospectively validated in a randomized clinical trial including the application of the same response definitions to an adequately sized concurrent control arm. As discussed by the authors, an ongoing randomized clinical trial comparing an experimental arm of the anti-CTLA4 antibody ipilimumab given together with dacarbazine to a control arm of dacarbazine alone may provide the prospective validation for the proposed irRC. Until then, investigators conducting single-arm tumor immunotherapy clinical trials will have a hard time convincing the scientific community that tumor immunotherapy can use a separate set of tumor response criteria.

Disclosure of Potential Conflicts of Interest

A. Ribas, commercial research grants and honoraria, Pfizer, Inc. J.A. Glaspy, speaker's bureau/honoraria, Pfizer, Inc.

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