CCR 20th Anniversary Commentary: Immune-Related Response Criteria—Capturing Clinical Activity in Immuno-Oncology

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To evaluate antitumor responses to chemotherapeutic agents, investigators would typically rely upon Response Evaluation Criteria in Solid Tumors (RECIST) or modified WHO criteria, which do not comprehensively capture responses with immunotherapeutic agents. In the December 1, 2009, issue of *Clinical Cancer Research*, Wolchok and colleagues reported their development of novel criteria, designated "Immune-related Response Criteria" (irRC), designed to better capture the response patterns observed with immunotherapies. Broad use of the irRC since then has allowed for a more comprehensive evaluation of immunotherapies in clinical trials, indicating that their concepts can be used in conjunction with either RECIST or WHO, and has shown irRC to be a powerful tool for improved clinical investigation. *Clin Cancer Res; 21(22); 4989–91. ©2015 AACR.*

See related article by Wolchok et al., Clin Cancer Res 2009;15(23) December 1, 2009;7412–20

With the advent of immuno-oncology triggered by the approval of ipilimumab in 2011 (1), a broad wave of new cancer drugs is being developed that function differently than chemotherapies or targeted therapies. While the latter induce direct cytotoxic effects on cancer cells, immunotherapies target the immune system and exert indirect effects on tumors with distinct characteristics in the clinic. Such characteristics include the fact that (i) immune activation can take time and may lead to a delay in onset of clinical effects; (ii) T cells recruited to tumors may increase tumor volume before they can shrink it; and (iii) the interplay between the immune system and the tumor may be a long-term dualistic process with slow and possibly undulating clinical effects.

History

These unique characteristics of immunotherapies brought attention to the need for new criteria by which their effects can be evaluated in the clinic. The concept was introduced by the Cancer Immunotherapy Consortium (CIC; previously Cancer Vaccine Consortium) in 2004, which had been founded to systematically improve the development process for cancer immunotherapies (2). The work of the CIC was based on clinical observations that immunotherapies can create unconventional activity patterns such as responses after progression or "mixed" responses where some lesions shrink but others grow or appear anew. To ensure that new criteria were based on clinical data, the concept was applied to the ipilimumab (anti–CTLA-4) program, which, at the time, represented the largest immunotherapy development program in the pharmaceutical industry (3). The data differed from conventional oncology programs through availability of follow-up imaging to detect response after progression, posttreatment tumor biopsies to demonstrate immune infiltration, and measurement of new lesions to longitudinally include their volume in the total tumor burden assessed from baseline (3–6). The translation of historic observations across the field together with the ipilimumab data enabled a critical set of modifications to standard oncology response criteria [WHO and Response Evaluation Criteria in Solid Tumors (RECIST)] termed "Immune-related Response Criteria" (irRC; ref. 6). Introduced in 2009, irRC detect four clinical activity patterns: (i) conventional rapid responses consistent with those observed after chemotherapy and, in addition, nonconventional responses, including the following: (ii) responses in the presence of new lesions; (iii) growth of existing lesions prior to durable tumor shrinkage (delayed responses); and (iv) prolonged stable disease (6, 7). irRC helped explain why low conventional response rates with ipilimumab of about 10% still translated into long-term survival in 20% to 25% of patients with metastatic melanoma (1), as new patterns of response not captured with standard WHO or RECIST criteria contributed to the survival outcome of patients (6). These new criteria also set the stage for a more accurate evaluation of clinical activity in future immunotherapy trials.

Advances from 2009 to 2015

irRC provide a tool for clinical investigators and treating oncologists to evaluate responses to cancer immunotherapy without a substantial departure from chemotherapy-based clinical practice, thus enabling nearly direct implementation

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Table 1. Concepts and progress of irRC

Concepts of irRC
• Confirmation of progression via a subsequent scan to detect delayed responses
• Measuring new lesions to include them into the total tumor volume
• Accounting for durable stable disease as benefit
• Treating beyond conventional progression if the clinical situation allows
Advances of irRC utility between 2009 and 2015
• Transferability of irRC concepts between WHO (bidimensional) and RECIST (unidimensional)
• Application of irRC to diseases beyond melanoma
• Inclusion of irRC concepts into regulatory guidance documents of the FDA and EMA
• Expansion of irRC concepts beyond the initial implementation
• Demonstration of an irRC-detected class effect across several immunotherapies

(6, 7). irRC focus on central concepts for capturing immunotherapy response patterns: (i) image-based confirmation of progression via subsequent scan(s) to detect delayed responses; (ii) measuring new lesions to include them into the total tumor volume; (iii) accounting for durable stable disease as a benefit; and (iv) treating beyond conventional progression if the clinical situation allows (Table 1). Together, these central concepts allow for assessing immunotherapy clinical activity patterns longitudinally and including them in the design of new clinical endpoints such as overall response rate (ORR), immune-related overall response rate (irORR), immune-related disease control rate (irDCR), or immune-related progression-free survival (irPFS). These endpoints can then be correlated with overall survival (OS) to determine their long-term therapeutic impact.

While irRC concepts are universal, their first implementation was limited by its context, the introduction via the ipilimumab program, a single-drug program using the standard WHO (bidimensional) system for response assessment with an initial focus on metastatic melanoma. Subsequently, irRC required use beyond a single drug, in conjunction with other response systems such as the unidimensional RECIST criteria, and expansion into other diseases. Metastatic melanoma is an aggressive disease, which in 2009 had a 2-month median time to progression using dacarbazine chemotherapy, the standard of care for decades (8). irRC implementation accounted for this course of disease with confirmation of progression requiring a confirmatory scan 4 weeks after first detection of progression. This practice allowed treating physicians to avoid long waiting periods for potentially delayed responses beyond 4 weeks. In diseases with a different (possibly less aggressive) natural course than melanoma, this 4-week interval can be adjusted, for example, to 8 or 12 weeks while still upholding the irRC concept of confirmation of progression. Similarly, other aspects of irRC can be adjusted to the disease or setting under study.

The advancements of irRC utility include five key aspects (Table 1). First, irRC concepts were proven transferrable to the framework of RECIST criteria. The comparison of irRC applied to the bidimensional WHO system and the unidimensional RECIST system indicated a high level of concordance (9). Second, irRC were applied to other cancers outside of melanoma, including non–small cell lung cancer and small cell lung cancer (10, 11). Third, the FDA and the European Medicines Agency (EMA) have included concepts of irRC into regulatory guidance documents pertaining to cancer drug development (12, 13). Fourth, new studies with PD-1/PD-L1 checkpoint blocking antibodies are demonstrating the expansion of irRC concepts via longer follow-up periods beyond progression and describing patterns such as "spikes," "waves," and "blips." These enhancements are supportive of the original tenets of the irRC but still need to be more formally characterized (14). Other expansions are expected as irRC are applied to new diseases such as hematologic malignancies in which immunotherapies are demonstrated to be active (15). Fifth, irRC response patterns have been demonstrated with second-generation immunotherapies, such as pembrolizumab (anti–PD-1; Merck) or atezolizumab (MPDL3280A; anti–PD-L1; Genentech), indicating a class effect (16, 17). The utility for irRC-based endpoints of irORR, irDCR, and irPFS was shown across the CTLA-4, PD-1, and PD-L1 programs of Bristol-Myers Squibb, Genentech, Merck, and AstraZeneca in a workshop of CIC in October 2014. These novel endpoints reflect the biology of immunotherapies and more accurately capture clinical effects than was the case with standard endpoints. The widely demonstrated correlation between novel irRC response patterns and favorable overall survival suggests surrogacy (A. Hoos; manuscript in preparation).

Outlook

Going forward, the expanding spectrum of immuno-oncology modalities under investigation will further increase the complexity of clinical activity patterns. Current modalities are checkpoint modulators (e.g., ipilimumab, pembrolizumab, nivolumab, atezolizumab, and durvalumab), bispecific antibodies (e.g., blinatumomab), oncolytic viruses (e.g., T-vec), various types of cancer vaccines, cytokines, and cellular therapies (e.g., CAR-Ts or TCR-Ts), among others. Some of these agents will induce high conventional response rates and others will not. As was evidenced by ipilimumab, a 10% conventional response rate can translate into 20% to 25% of long-term survival via additional patterns of clinical activity that convey survival benefit (1, 6). Every new modality will likely carry its own clinical activity profile, which can only be understood with tools able to capture them, such as irRC.

irRC will continue to evolve. The advances described here allow for modification of the criteria for clinical protocol applications, as is routine for other criteria (e.g., mRECIST). A next important step will be the adjustment to hematologic malignancies, in which immunotherapies are beginning to demonstrate substantial benefit (15). Throughout this evolution of irRC, particular attention will need to be paid to aspects directly influencing patient management, including (i) selecting time points for disease assessments (especially the first assessment) that align with the natural course of the cancer under investigation; (ii) defining progression and the duration of follow-up for response after progression; (iii) discontinuation criteria for investigational immunotherapy; and (iv) accounting for delayed effects relative to any post-progression therapies. Each of these aspects can be included in subsequent versions of irRC or be specified in clinical trial protocols.

The outlook for cancer patients has never been better since the introduction of immuno-oncology therapies.

Understanding their full potential will depend on new tools such as irRC.

Disclosure of Potential Conflicts of Interest

A. Hoos is a Director on the Board of Imugene. J.D. Wolchok reports receiving commercial research grants from Bristol-Myers Squibb, MedImmune/AstraZeneca, and Merck, and is a consultant/advisory board member for Bristol-Myers Squibb, Genentech, MedImmune/AstraZeneca, and Merck. F.S. Hodi is a consultant/advisory board member for Genentech and Merck, and is listed as a co-inventor on a patent related to methods for treating MICA-related disorders, which is owned by Dana-Farber Cancer Institute. No potential conflicts of interest were disclosed by the other author.

Authors' Contributions

Conception and design: A. Hoos

Writing, review, and/or revision of the manuscript: A. Hoos, J.D. Wolchok, R.W. Humphrey, F.S. Hodi

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