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Guidance for Sponsors
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irRECIST and Immuno-Oncology in Clinical Trials

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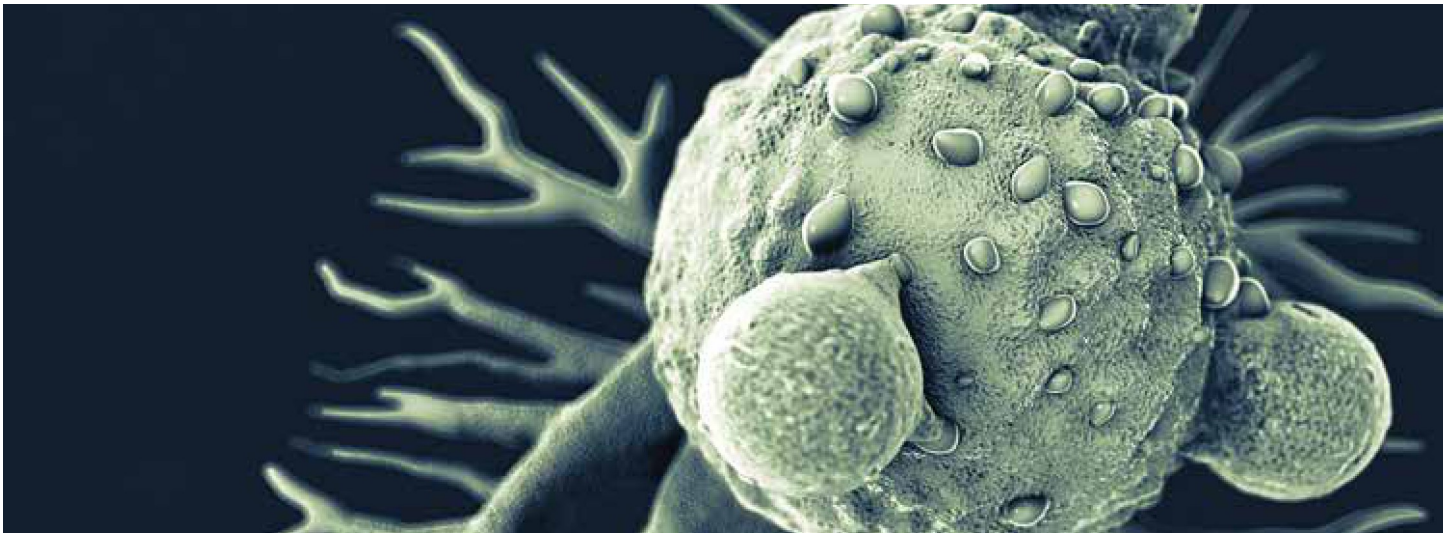

Immunotherapy has changed the practice of oncology, and it has changed the practice of measuring response. Tumors treated with checkpoint inhibitors can enlarge, or show new lesions, before they shrink, a pattern that conventional criteria classify as failure. Over fifteen years, response assessment has moved from the immune-related response criteria of 2009, through unidimensional irRC and irRECIST, to iRECIST, the RECIST Working Group's consensus standard. This issue traces that evolution, compares the criteria and explains how sponsors should apply them so that a working therapy is not mistaken for a failing one.

Immuno-Oncology

Decades of research have shown that the immune system can recognize and destroy tumor cells. Immuno-oncology seeks to harness that capacity to control, stabilize and potentially eradicate disease, with the added promise that immunological memory may prevent recurrence. That promise has been realized. Checkpoint inhibitors targeting CTLA-4, PD-1 and PD-L1 are now standard therapy across melanoma, lung, kidney, bladder, head and neck and many other cancers, and they are joined by cell therapies, bispecific antibodies and cancer vaccines.

Objective, reproducible assessment of tumor response remains the foundation of every oncology trial. Immunotherapy requires that the assessment account for patterns of response that differ fundamentally from those seen with cytotoxic drugs.

RECIST and Its Limits

Except in lymphoma, the Response Evaluation Criteria in Solid Tumors, published in 2000 and revised as RECIST 1.1 in 2009, are the most widely accepted criteria for solid tumors in practice and in trials.[1] RECIST was designed for cytotoxic chemotherapy, however, and it treats an early increase in tumor burden or the appearance of a new lesion as progressive disease. With agents such as ipilimumab, clinicians observed that complete response, partial response or stable disease could still follow an initial increase in tumor burden.

The Immune-Related Response Criteria

Ipilimumab, a fully human monoclonal antibody, blocks CTLA-4, a checkpoint molecule that restrains T-cell activation. The resulting T-cell infiltration can enlarge a tumor, or make occult lesions visible, before regression begins. Observations in melanoma identified four response patterns: immediate shrinkage of baseline lesions; durable stable disease; response after an initial increase in tumor burden; and response in the presence of new lesions.

To capture these patterns, the immune-related response criteria (irRC) were proposed in 2009.[2] Derived from the WHO criteria, irRC used bidimensional measurement, incorporated new measurable lesions into the total tumor burden rather than declaring progression, and required confirmation of progression on a repeat scan at least four weeks later.[2] Bidimensional

measurement proved cumbersome and variable. In 2013, unidimensional irRC was shown to be more reproducible and to correlate closely with the bidimensional version,[3] and this approach, adopted into the irRECIST framework, aligned immune-related assessment with RECIST 1.1 methods.

iRECIST: The Consensus Standard

In 2017, the RECIST Working Group published iRECIST to provide a single, consistent framework.[4] iRECIST retains RECIST 1.1 rules for measurement and adds the concept of unconfirmed progression (iUPD). Progression becomes confirmed (iCPD) only if the next assessment, generally four to eight weeks later, shows further growth or additional new lesions. New lesions are recorded separately rather than added to the target sum. iRECIST was designed for consistent data collection and exploratory analysis, while RECIST 1.1 remains the basis of primary efficacy endpoints.[4]

Feature	RECIST 1.1	irRC (2009)	iRECIST (2017)
Measurement	Unidimensional	Bidimensional	Unidimensional
New lesions	Progression	Added to tumor burden	Recorded separately; unconfirmed progression
Progression confirmation	Not required	Repeat scan ≥4 weeks	Repeat scan at 4–8 weeks
Typical role	Primary endpoint	Historical	Exploratory, alongside RECIST 1.1

How Common Is Pseudoprogression?

A meta-analysis of checkpoint inhibitor trials across solid tumors found an overall incidence of pseudoprogression of 6%, and less than 10% across definitions, cancer types and drugs.[5] The number is modest, but the consequence of misclassification is not: stopping an effective therapy deprives a patient of benefit, and recording false progression biases a trial's results. True hyperprogression, rapid growth during treatment, also occurs, which is why confirmation scans must be scheduled promptly rather than deferred.

Guidance for Sponsors

Applying immune-related criteria

- **Prespecify both criteria.** Name RECIST 1.1 for the primary endpoint and iRECIST for exploratory analysis in the protocol.[1,4]
- **Schedule confirmation.** Build the four-to-eight-week confirmatory scan into the visit schedule.[4]
- **Define treatment beyond progression.** State which patients may continue therapy after unconfirmed progression.
- **Record new lesions rigorously.** Train readers to track new lesions separately.
- **Read centrally.** Use blinded independent central review under a documented imaging charter.[6]

Summary

Immunotherapy has become a pillar of cancer treatment, and response assessment has evolved with it. From irRC to iRECIST, the field has converged on criteria that preserve the rigor of RECIST while recognizing the distinctive behavior of tumors under immune attack. Sponsors who apply these criteria consistently, schedule confirmation scans and rely on expert central review will produce data that regulators and clinicians can trust.

About the Author

Dr. Nisha Sainani, a board-certified radiologist, wrote the original edition of this issue at Intrinsic Imaging. She completed her residency in diagnostic radiology in India and subspecialized in abdominal imaging and intervention at Harvard Medical School's Massachusetts General Hospital and Brigham and Women's Hospital in Boston, where she has held an academic appointment. She has published widely in the *American Journal of Roentgenology*, *Radiology* and *RadioGraphics*, has contributed chapters to radiology textbooks, and is a member of the Society of Gastrointestinal Radiologists, the American Roentgen Ray Society and the Radiological Society of North America.

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