Point–Counterpoint Review

Reply to Point

RECIST: No Longer the Sharpest Tool in the Oncology Clinical Trials Toolbox

See Point by Sharma et al., p. 5145

Antonio T. Fojo and Anne Noonan

We agree with many of the points made by Sharma, Maitland, and Ratain in their well-reasoned opinion. But we also disagree with several.

We agree when they conclude that "RECIST... falls short of the ideal as an assessment of efficacy for cancer therapeutics in development." We are not arguing that Response Evaluation Criteria in Solid Tumors (RECIST) is ideal or perfect.

We agree with their negative assessment of "disease control rate" or "clinical benefit" as endpoints, as such endpoints include patients "who may... simply have relatively indolent disease." These "measures" have never been shown to confer a survival benefit. Clinical researchers should not report them and journals should not accept them. They are neither meaningful nor validated.

We agree that "RECIST-based endpoints do not consistently correlate with the important clinical endpoints of survival or improved quality of life, the outcomes of greatest importance" but would underscore that do not consistently correlate means that they very often do correlate with these endpoints and in meaningful ways.

We agree with Sharma and colleagues that efficacy is "best established by randomized comparisons between investigational arms and control arms," but worry about their advocacy of "evidence of efficacy" to evaluate therapies. They acknowledge that in "evidence of efficacy" they have chosen an "intentionally vague term," and we worry that vague terms lead to vague evidence and vague results. They note that "as of December 2011, (they) are aware of at least 4 drugs in 5 indications with evidence of efficacy as monotherapy leading to U.S. Food and Drug Administration (FDA) approval despite RECIST response rates ≤10% in phase III trials." We would note we are aware of the marginal benefits leading to those FDA approvals.

And in arguing that "from a practical point of view, the oncologist wants to know which therapy to start for a given patient and when to discontinue that therapy in favor of an alternative," Sharma and colleagues miss a point. In nearly 30 years at a referral center, one of the authors of this Reply (T. Fojo) has never seen a referral letter that talked about progression based on World Health Organization or RECIST criteria. Oncologists in private practice do not use these measures to assess drug efficacy, relying rather on clinical intuition or on a written radiology report. Indeed, what Sharma and colleagues advocate already happens in clinical practice today: "there (are) no lines at all; efficacy (is) viewed on a continuous (rather than a categorical) scale." RECIST is not about what the practicing oncologist uses. It is about a common language of efficacy for research purposes. While imperfect, RECIST allows efficacy assessments across studies around the globe. RECIST prevents the use of clinical intuition in guiding drug development—witness the intuitions about bone marrow transplant in breast cancer.

Should we replace RECIST? Why not? Provided we can replace it with a validated method that can be widely used and uniformly applied, with assessments that can be readily made in the practice of clinical research. And of course, any modification of RECIST must improve how we value drugs lest we let our efficacy bar decrease lower and it begins to hit the ground.

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No potential conflicts of interest were disclosed.

Authors' Contributions

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