Point–Counterpoint Review

Cancer Research

Reply to Counterpoint

Why RECIST Works and Why It Should Stay

See Counterpoint by Fojo and Noonan, p. 5151

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In their article entitled "Why RECIST Works and Why It Should Stay," Fojo and Noonan argue that alternatives to Response Evaluation Criteria in Solid Tumors (RECIST) definitions of response and progression would not accelerate improvements in patient outcomes. Their case ignores the fact that the RECIST thresholds were never directly validated for their correlation with survival or quality of life and assumes that proposed alternatives would "lower the bar" for efficacy by decreasing the threshold for a response or by increasing the threshold for progression. We agree that revised thresholds for response and progression will not improve the status quo. We therefore proposed an entirely new paradigm that allows "evidence of efficacy" to be tailored to the drug, disease, and patient population.

Fojo and Noonan downplay the flaws of RECIST and declare that RECIST "has been and will continue to be valuable" for "the majority of metastatic solid tumors." However, the question here is not whether RECIST has value but whether it is the best tool in a growing toolbox for assessing effects of cancer therapeutics. Tumor measurements will continue to be important to the evaluation of efficacy. We contend that in many of the settings of early testing of new agents and combinations, longitudinal measurements should be evaluated more precisely (e.g., with volumetrics) and compared on a continuous scale. Other quantitative tools, such as tumor density on computed tomography (e.g., gastrointestinal stromal tumor), metabolic activity on positron emission tomography (e.g., lymphoma), assays for serum biomarkers (e.g., prostate-specific antigen), and symptom or quality-of-life scores on validated scales could further improve upon tumor size as composite endpoints. Moertel and Hanley (1), whose work was instrumental in advancing the field, did not have any of these tools available when they conducted their study of oncologists measuring spheres. In contrast to RECIST, our proposed paradigm would encourage the use of any or all of these tools in randomized blinded efficacy trials.

In the final section of their article, Fojo and Noonan argue that RECIST is "validated" by the data from oncology drugs approved by the U.S. Food and Drug Administration in the past 10 years. While we agree that the data are sobering about our ability to improve patient outcomes, it is erroneous to conclude that these modest gains are proof that RECIST is the best approach and to assume that alternative approaches would lead to more marginal gains. Indeed, an alternative interpretation is that a RECIST-based approach to drug development has failed to make major gains, and there is little to be lost (and potentially much to be gained) by trying something new. The list is even more sobering when one considers that many of these drugs have been approved for the same indication (e.g., 7 drugs for first- or second-line advanced renal cancer) and rarely compared directly. Our proposed paradigm might motivate sponsors of efficacy trials to answer the real question that oncologists and patients want to know: "Which therapy has the greatest evidence of efficacy for a given patient?"

Disclosure of Potential Conflicts of Interest

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Conception and design: M.R. Sharma, M.L. Maitland, M.J. Ratain
Development of methodology: M.R. Sharma
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M.R. Sharma
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M.R. Sharma
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