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## Re: Measure Once or Twice— Does It Really Matter?

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The editorial (1) on our article (2) makes a number of points, and we wish to address these with some further explanation. The first clarification concerns our theoretical section. Our argument is, in fact, more pragmatic rather than mathematical and is indeed the point that the editorial identifies as “largely due to difference in scales.” From its definition as an  $x\%$  reduction, any measure of response entails a proportionate reduction in this measure. Furthermore, since product and diameter are both functions of radius, they may be mathematically transformed from one to the other. As the article specifically mentions, the bidimensional measure can be transformed to have the same re-

lationship to the logarithm of cell number as does diameter simply by taking its square root. Our point was not to dispute the fact that mathematical transformation of product will give the same relationship, rather it was that, *without* the need for transformation, the proportional change in diameter performs well in estimating similar proportional changes in log cell kill.

The more important point made in the article is stronger—the simpler procedure results in the *same* judgments as the more complex one. This implies that any extra information that the product may be thought to contain is redundant to the making of the judgment. The eight trials used in the article were not selected on the basis of any particular criterion, except insofar that they reflected a broad spectrum of tumor types and had serial tumor measurements recorded for comparative analysis of the two criteria. Since the article was published, other data (from Rhone-Poulenc Rorer and Bristol-Myers Squibb databases) confirm that the sum of diameters can replace the sum of the products in determining response. Indeed, the International Working Group on Response Evaluation Criteria in Solid Tumors (RECIST working group) now has data on the two methods for a total of 4613 patients. This larger dataset, of which our data form a subset, continues to show excellent concordance and overlapping response rates determined by unidimensional and bidimensional criteria.

New international response criteria (RECIST criteria) based on these observations will soon be made available. These observations were described in some detail at an educational session at the American Society of Clinical Oncology meeting in Atlanta, GA, in May 1999. These criteria have adopted the unidimensional approach, but they have also addressed many other aspects of response assessment that are not currently standardized between the research groups. This process has involved wide consultation with research groups, industry and regulatory authorities, so it represents an arduous initiative, which we hope will simplify and standardize response assessment in clinical research studies. Unlike the article that we published in March 1999 (2), the RECIST criteria will employ a 20% (rather than a 30%) increase in the sum of diameters as

the criterion for progression. This difference was based on feedback from other groups and investigators who were concerned that the change in volume required to achieve a 30% increase was too high. The RECIST criteria will be published together with appendices that use existing datasets (among them, those contained in our article) to support the change to unidimensional criteria for response and progression.

We do not think that prospective randomized studies of the response criteria, as suggested in the editorial, are likely to add to the argument in view of the further retrospective confirmation by others mentioned above. Indeed, it was not clear what the “randomization” would be between. Prospective assessment of the impact of the change in progression criteria on time-to-progression outcomes will be of interest, but retrospective data to be included in the RECIST publication suggest that there will be no major impact.

It is important to recall that response and progression are norms—conventions encapsulated in a rule—and a good rule should be as simple as possible.

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## REFERENCES

- (1) Hilsenbeck SG, Von Hoff DD. Measure once or twice—does it really matter? [editorial]. *J Natl Cancer Inst* 1999;91:494–5.
- (2) James K, Eisenhauer E, Christian M, Terenzi M, Vena D, Muldal A, et al. Measuring response in solid tumors: unidimensional versus bidimensional measurement. *J Natl Cancer Inst* 1999;91:523–8.

## NOTES

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## RESPONSE

Thank you for the opportunity to reply and clarify.

In our editorial, we pointed out that the authors’ assertion that “diameter is much more nearly proportional to the

logarithm of cell number than is product" is a mathematically incorrect statement. We also pointed out that their Fig. 1, which they use to support their point, is misleading because of differences in the scales of the right- and left-hand axes. In their letter, we feel that they have missed the point of our comments. The mathematics of the situation has not changed. The logarithm of cell number is not linearly related to diameter, bidimensional product, or volume; it is linearly related to the logarithms of these quantities. So the question becomes, "which measure of tumor size is most linearly related to its own logarithm?" and the answer is, "they are all equally unrelated." James et al. go on to state in their letter that "proportional change in diameter performs well in estimating similar proportional changes in log cell kill." By this, we assume that they mean that doubling the diameter is roughly equivalent to doubling the logarithm of cell number. That is, doubling the diameter increases the volume, and therefore the number of cells, by a factor of  $2^3 = 8$ . Doubling the logarithm of cell num-

ber [i.e.,  $2 \cdot \log(\text{cells})$ ] is the same as squaring the number of cells. A 1-cm tumor with  $10^9$  cells would increase by a factor of  $10^9$ , would weigh roughly 1 million kg, and would be the size of 10 blue whales. This assertion, of course, makes no sense. We tried to point this out in the editorial. While there is no theoretical basis for preferring diameter as a measure of tumor size, it is true that any bidimensionally defined response criteria can be translated into equivalent unidimensional criteria. The utility of such a switch from standard practice should be based on quality and reproducibility.

We were very interested to learn of the history of the RECIST working group and of the comparative analyses of several large pharmaceutical databases that confirm the results of James et al. We would, however, feel more comfortable if these analyses were accessible in a peer-reviewed forum and look forward to their publication. As we pointed out in the editorial, the authors' original definition of progression was associated with large increases in tumor

size (30% increase in diameter implies a 120% increase in tumor volume), which might preclude effective second-line therapy. Apparently, the RECIST working group agreed, since they have adopted the more conservative definition of 20% increase in diameter, corresponding to a 73% increase in tumor volume. That is good news.

The authors' last point, implying that we recommended "randomized" studies, is a misrepresentation that we must correct. We recommended "prospective evaluation of their criteria, particularly the criteria for tumor progression." The word randomized was not included and is obviously not applicable.

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## NOTES

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