TGR Analysis in Phase I Clinical Trials—Letter

Rodrigo Dienstmann1,2 and Josep Tabernero2

There is considerable current interest in defining more precise measurements of experimental drug efficacy. Ferté and colleagues from Institute Gustave Roussy must be acknowledged for the innovative work on tumor growth rate (TGR) reduction as an early indicator of antitumor efficacy in phase I trials (1). It was remarkable to find out that the majority of patients classified as stable disease or even progressive disease by RECIST criteria are likely deriving benefit from such therapies when assessed with the TGR algorithm.

Biomarker analysis of response magnitude can offer insights into disease biology that go beyond tumor genotyping and matched targeted therapies. Notably, for most kinase inhibitors and VEGF inhibitors approved in solid tumors and hematologic malignancies, impressive early responses were already seen during phase I clinical development, rejecting the widely accepted hypothesis that targeted therapies commonly act by disease stabilization (2). A recent study also suggested that patients who do not exhibit early tumor shrinkage (more than 20% response rate at 8 weeks) are gaining no added benefit from cetuximab therapy compared with chemotherapy alone in the first-line setting of advanced KRAS wild-type colorectal cancer (3). With the plethora of investigational drugs entering genomically driven clinical trials, several with overlapping targets but exhibiting different pharmacokinetic and pharmacodynamic properties, the magnitude of antitumor effects for guiding “go-versus-no go” decisions is further emphasized. Dynamic TGR reduction seems to be a rather lenient criterion for strategic planning of drug development.

Nevertheless, the value of changes in tumor kinetics in the context of stable/progressive disease can be easily translated into “individualized” care of patients included in phase I trials, knowing that delayed time to tumor progression is expected in cases of TGR reduction. As briefly discussed by the authors, it may also be a promising indicator of drug efficacy in specific contexts: (i) when single-agent efficacy is not highly anticipated on the basis of preclinical models, for example HSP90 inhibitors; (ii) for agents without validated predictive biomarkers, such as epigenetic drugs; (iii) and matched targeted therapies in the setting of acquired resistance to approved drugs and combinations. Ferté and colleagues recently presented the value of TGR in evaluating sorafenib and everolimus treatment in advanced renal cell carcinoma, a perfect scenario for biomarker analysis of response magnitude (4). In our opinion, TGR reduction is the strongest argument for continuing therapy "post-progression."

But investigators must be careful when applying TGR calculation to patients enrolled in early clinical trials. First, it is well known that rapid rebound progression is seen in many patients that stop kinase inhibitors after long-term responses (5). Therefore, comparing tumor growth during the "wash-out" period with the 6 to 8 weeks following introduction of the experimental drug can give biased evidence. We wonder whether in this setting, a more adequate comparator could be the TGR during the previous "on-treatment" period right before stopping therapy. Second, we believe that excluding new lesions from the calculation of sum of target lesions and TGR is not appropriate, considering that they probably do not represent completely independent clones with different driver events. Multiple studies have shown that relapsed tumors share mutations with the founder clone seen in the primary site as well as new mutations that likely increase its proliferative advantage (6). In addition, our knowledge on clonal evolution of new metastatic lesions in the refractory setting is still limited. Finally, logistic issues related to the retrieval and radiologic assessment of pretreatment imaging can be challenging even in reference institutions with large phase I units. We would be interested in the authors’ comments on these topics.

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References


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