Letter to the Editor

Clinical Cancer Research

TGR Analysis in Phase I Clinical Trials—Response

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We thank Dienstmann and Tabernero for their comments on our article (1). They underscore the high translational potential of using tumor growth rates (TGR) to assess the therapeutic effect independently from the natural course of the disease and ultimately guide the "go - no go decision making" in early drug development setting.

Dienstmann and Tabernero mention that rapid progression may occur at treatment discontinuation after long-term response to anticancer drugs. This has been observed for certain agents such as EGF receptor (EGFR) or VEGF receptor (VEGFR) tyrosine kinase inhibitors (TKI), whereas others do not seem to produce it (e.g., mTOR inhibitors; refs. 2, 3). This may bias the evaluation of the future treatment efficacy if the rapid progression is a transient effect. They suggest that the "previous on-treatment period" would be more appropriate as a "reference period" in this setting. Clearly, rapid progression events warrant to be more clearly defined (i.e., frequency, natural history, predictive factors, prognostic impact, underlying biology, etc.) before addressing definitive conclusions on their potential impact on the treatment efficacy evaluation by TGR. Such data are unfortunately lacking because most clinical research tends to focus on the treatment introduction and neglect the treatment discontinuation. Moreover, when setting the "previous on-treatment period" as the reference period, one cannot exclude a persistent effect of the "previous regimen" on the tumor kinetics. This could also bias the tumor kinetics comparison. As an example, our group previously described that sorafenib still exerts antitumoral activity in patients with mRCC at the time of progression (2), precluding further use of the "previous on-treatment period" as the reference period.

Second, we fully agree with Dienstmann and Tabernero about the management of new lesions. This issue is, however, independent of the TGR method itself but rather secondary to the RECIST system, which assigns any occurrence of novel lesions as "progressive disease." Consequently, dimension measurements of new lesions are mostly lacking from current patient series. Novel evaluation systems such as the immune related response criteria (irRC) take in account the occurrence of new lesions (4). However, they still warrant to be validated for non-immune related drugs.

Finally, Dienstmann and Tabernero point out that the retrieval and the assessment of pretreatment radiologic data is a challenge. This point was already discussed in our article. We were able, retrospectively, to recover and assess pretreatment computed tomography (CT) scans in 79% of the patients (201 out of 253 patients; ref. 1). In our opinion, this is the price to pay to evaluate an experimental therapeutic independently from the natural course of the disease. To this end, we advocate for the creation of a precompetitive consortia on tumor kinetics, comprising both academic and pharmaceutical representatives to prospectively disclose anonymized data and develop more robust treatment evaluation metrics.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Received February 12, 2014; accepted February 22, 2014; published online May 1, 2014.

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doi: 10.1158/1078-0432.CCR-14-0366

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