Tumor Growth Rate Provides Useful Information to Evaluate Sorafenib and Everolimus Treatment in Metastatic Renal Cell Carcinoma Patients: An Integrated Analysis of the TARGET and RECORD Phase 3 Trial Data

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Abstract

Background: Response Evaluation Criteria in Solid Tumors (RECIST) criteria may not be sufficient to evaluate the response of targeted therapies in metastatic renal cell carcinoma (mRCC). The tumor growth rate (TGR) incorporates the time between evaluations and may be adequate.

Objective: To determine how TGR is modified along the treatment sequence and is associated with outcome in mRCC patients.

Design, setting, and participants: Medical records from all patients prospectively treated at Gustave Roussy (IGR) in the Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGET) (sorafenib vs placebo, n = 84) and the RECORD (everolimus vs placebo, n = 43) phase 3 trials were analyzed. TGR was computed across clinically relevant periods: BEFORE treatment introduction (wash-out), UNDER (first cycle), at PROGRESSION (last cycle) and AFTER treatment discontinuation (washout). The association between TGR and outcome (overall survival [OS] and progression-free survival [PFS]) was computed in the entire TARGET cohort (n = 903).

Intervention: Sorafenib, everolimus, or placebo.

Outcome measurements and statistical analysis: TGR, RECIST, OS, and PFS rates.

Results and limitations: Although nearly all the patients (IGR) were classified as stable disease (RECIST) after the first cycle, the great majority of the patients exhibited a decrease in TGR UNDER compared with BEFORE (sorafenib: \( p < 0.00001 \); everolimus: \( p < 0.00001 \)). In sorafenib-treated but not in everolimus-treated patients (IGR), TGR at PROGRESSION (last cycle) was still lower than TGR BEFORE (washout) (\( p = 0.012 \)), while TGR AFTER progression (washout) was higher than TGR at PROGRESSION (last cycle) (\( p = 0.0012 \)). Higher TGR (first cycle) was associated with worse PFS (hazard ratio [HR]: 3.61; 95% confidence interval [CI], 2.45–5.34) and worse OS (HR: 4.69; 95% CI, 1.54–14.39), independently from the Motzer score and from the treatment arm in the entire TARGET cohort.

Conclusions: Computing TGR in mRCC patients is simple and provides clinically useful information for mRCC patients: (1) TGR is independently associated with prognosis (PFS, OS), (2) TGR allows for a subtle and quantitative characterization of drug activity at the first evaluation, and (3) TGR reveals clear drug-specific profiles at progression.

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1. Introduction

The introduction and recent revision of the Response Evaluation Criteria in Solid Tumors (RECIST) criteria have constituted a major improvement in the standardization of the response to antineoplastic agents in solid tumors [1,2]. In this system, the patient’s tumor burden is estimated by the sum of the longest diameters of the target lesions. The variation of the RECIST sum over a cycle of treatment is then transformed into a categorical variable to standardize the response to therapy (complete response, partial response, stable disease, and progressive disease). However, several authors have discussed the potential inadequacies of the RECIST criteria[3–7]. Those issues appear critical in the metastatic renal cell carcinoma (mRCC) setting, given the widespread use of registered molecular targeted agents (MTAs) such as antiangiogenics (sorafenib, sunitinib) or mammalian target of rapamycin inhibitors (everolimus, temsirolimus)[8–11]. MTAs often induce long-lasting stable disease rather than tumor shrinkage and may even result in “pseudoprogression” images, rendering hazardous the use of RECIST[12,13]. Innovative modalities to assess the drug response in the mRCC setting have been proposed but do not meet the adequate level of evidence to be applied in routine practice[14,15].

The tumor growth rate (TGR) estimates the increase of the tumor volume over time [16,17]. It incorporates the time between the imaging examinations, allowing for a quantitative and dynamic evaluation of the tumor response. However, how TGR is modified along the course of MTA and is associated with outcome in mRCC patients remain unknown. The present study was aimed at assessing whether TGR provides valuable clinical information for the management of mRCC patients as a prognostic factor and evaluating how TGR varies with two registered MTAs (sorafenib and everolimus).

2. Methods

2.1. Patients

The medical records of all patients prospectively enrolled in Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGET) phase 3 [8] (sorafenib vs placebo, n = 84) and in the RECORD phase 3 trial [10] (everolimus vs placebo, n = 43) at Gustave Roussy (IGR) were extracted. Using our institutional cohorts gave us the opportunity to access off-protocol additional imaging examinations performed before baseline or after progression to explore these washout periods (see Supplement). All computed tomography scans were independently reviewed by a senior radiologist (L.R.), blinded to treatment arm. The impact of TGR on the outcome was computed in the entire TARGET phase 3 trial cohort (n = 903) [8]. Such data were not available for the RECORD-1 trial.

2.2. Definition of the tumor growth rate

Tumor size (D) was defined as the sum of the longest diameters of the target lesions, per RECIST[1]. Let t be the time expressed in months at tumor evaluation. Assuming the tumor growth follows an exponential law, \( V_t \) (the tumor volume at time \( t \)) is equal to \( V_0 \exp(TG \cdot t) \), where \( V_0 \) is volume at baseline and \( TG \) is the growth rate. We approximated the tumor volume (V) by \( V = \frac{4}{3} \pi R^3 / 3 \), where \( R \), the radius of the sphere, is equal to \( D / 2 \). Consequently, \( TG = \frac{3 \log(D_t / D_0)}{t} \). To report the TGR results in a clinically meaningful way, we expressed TGR as a percentage increase in tumor volume during 1 mo using the following transformation, in which \( \exp(TG) \) represents the exponent of TGR:

\[
\text{TGR} = 100 \left[ \exp(TG) - 1 \right].
\]

We calculated the TGR across clinically relevant treatment periods (Fig. 1): (1) TGR BEFORE treatment introduction, assessed during the washout period (off therapy) before the introduction of the experimental drug; (2) TGR UNDER, assessed during the first cycle of treatment (ie, between the drug introduction and the first evaluation, on therapy); (3) TGR at PROGRESSION, assessed during the last cycle of treatment before progression while the patients are still receiving the experimental drug (on therapy); and (4) TGR AFTER, assessed during the washout period (off therapy) after the discontinuation of the drug. To compute the TGR BEFORE and AFTER, additional imaging exploring the washout periods (off therapy) immediately before the introduction and immediately after the drug discontinuation were also included, when available. Both TARGET

![Fig. 1 – Hypothetical representation of tumor growth rate (TGR) across specific treatment periods.](image-url)
and RECORD-1 used RECIST 1.0 to assess the tumor response. Patients with nonmeasurable disease at the time of inclusion as per RECIST criteria (eg, patients with fluid effusions only or bone metastases only at baseline) and patients who progressed with new lesions could not be assessed by TGR (Supplemental Table 7).

2.3. Statistical analysis

We performed pairwise comparisons to test the variations of TGR along the treatment sequences using Wilcoxon signed rank tests. Progression-free survival (PFS), overall survival (OS), and tumor response (RECIST [1]) were determined as described earlier [3,4]. To avoid the potential bias introduced by the fact that responders must live long enough for a response to be observed and for TGR to be measured, all associations between survival and TGR were performed using the landmark method [18]. As per the TARGET protocol [8], the patients had to be evaluated within the last 10 d after the 6-wk cycle. Consequently, we set the landmark point at 52 d. Hazard ratios (HRs) were estimated from Cox regression models and were adjusted to the standard clinicopathologic prognostic score (Motzer score [19]). The concordance index and the proportion of variance explained ($R^2$) were computed to assess the prediction performance for survival (PFS, OS). All the analyses were carried out using R statistical software (R v.2.15.0) [20] and the "survival" R package v.2.37.4, and the analyses were controlled by a senior statistician (S.K.).

3. Results

3.1. Description of the cohorts

The Motzer prognostic score, PFS, and OS of the cohorts of patients enrolled in TARGET (both in IGR and in the entire TARGET cohorts) and in the RECORD trial (IGR) are described in Table 1. The distributions of TGR across relevant treatment periods are described in Supplemental Table 1 and 2 and in Supplemental Figure 1.

3.2. Variation of tumor growth rate along clinically relevant treatment periods

At the first evaluation, whatever the treatment delivered (sorafenib or everolimus), nearly all evaluable patients from the IGR cohorts (28 of 29 sorafenib-treated patients and 35 of 36 everolimus-treated patients, respectively) were classified as stable disease according to RECIST criteria (Fig. 2). Such a pattern was also observed in the entire TARGET cohort, in which 261 sorafenib-treated patients (78%) and 186 placebo-treated patients (55%) were classified as stable disease according to RECIST criteria after the first cycle of treatment (Supplemental Fig. 2). This finding suggests that using RECIST criteria is not very informative in the detection of early signs of efficacy of sorafenib or everolimus in mRCC patients. We observed a concomitant decrease in the TGR during the first cycle of treatment (TGR UNDER) as compared with the TGR during the washout period before the treatment introduction (TGR BEFORE) in sorafenib-treated patients (Wilcoxon signed rank test, $p = 1.86 \times 10^{-8}$) (Fig. 2, 3A, 4A) and everolimus-treated patients (Wilcoxon signed rank test, $p = 5.82 \times 10^{-11}$). The latter results reveal clear early signs of antitumor activity of sorafenib and everolimus at the first cycle.

To assess whether the experimental drug still exerts an antitumor effect at the time of progression, we compared the TGR at PROGRESSION with the TGR BEFORE. Most of the Sorafenib-treated patients (17 of 24 patients, IGR cohort) still experienced a decrease in TGR at PROGRESSION as compared with the TGR BEFORE (Wilcoxon signed rank test, $p = 0.0115$) (Fig. 3B). Conversely, there was no significant difference between the TGR at PROGRESSION and the TGR BEFORE in everolimus-treated patients (IGR cohort) (Wilcoxon signed rank test, $p = 0.173$) (Fig. 4B).

To explore the variation of TGR concomitant to the discontinuation of the drug, we compared the TGR of patients at PROGRESSION with the TGR AFTER the drug discontinuation. It is interesting to note that most evaluable patients treated by Sorafenib (11 of 14 patients, IGR cohort) experienced an increase of TGR AFTER comparing to the TGR at PROGRESSION (Wilcoxon signed rank test, $p = 0.0012$) (Fig. 3C). However, such a pattern was not observed in everolimus-treated patients (IGR cohort) (Wilcoxon signed rank test, $p = 0.57$) (Fig. 4C).

3.3. TGR is independently associated with prognosis (progression-free survival and overall survival, multivariate analyses), whatever the treatment arm (sorafenib or placebo), in metastatic renal cell carcinoma patients (entire Treatment Approaches in Renal Cancer Global Evaluation Trial cohort, $n = 903$)

We assessed whether the TGR during the first cycle was associated with survival in the TARGET trial using the
Fig. 2 – Variation of tumor growth rate (TGR) according to the tumor response by Response Evaluation Criteria in Solid Tumors (RECIST) at the first evaluation in (A) sorafenib-treated patients and (B) everolimus-treated patients.

Fig. 3 – Pairwise comparisons of tumor growth rate (TGR) at clinically relevant treatment periods in sorafenib-treated patients (p values are computed from Wilcoxon pairwise tests; n represents the number of samples with pairwise TGR information).
landmark method (Table 2). To be clinically meaningful, HRs were computed for a 10% increase in TGR. Among placebo-treated patients (landmark analysis, \(n = 361\)), TGR was associated with both PFS (adjusted HR: 1.14; 95% confidence interval [CI], 1.10–1.18; \(p < 0.0001\)) and OS (adjusted HR: 1.17; 95% CI, 1.04–1.31; \(p = 0.0068\)), even after adjustment to the standard prognostic score (Motzer score [19]). Practically, every increase of 10% in TGR in placebo-treated patients leads to a 14% and a 17% increase in the progression and the death hazard, respectively. Similarly, among sorafenib-treated patients (landmark analysis, \(n = 422\)), TGR was associated with both PFS (adjusted HR: 1.10; 95% CI, 1.05–1.14; \(p < 0.0001\)) and OS (adjusted HR: 1.14; 95% CI, 1.06–1.22; \(p = 0.0002\)) after adjustment to the Motzer score [19]. The interaction between the assigned treatment arm and TGR was close to significance for PFS (HR: 1.65; 95% CI, 0.98–2.80; \(p = 0.06\)) and not significant for OS (HR: 1.20; 95% CI, 0.32–4.48; \(p = 0.78\)). We consistently observed a larger proportion of explained variance (pseudo-R^2 value) for the TGR and Motzer score combined condition (33–39% for OS) compared with the same variables analyzed alone (TGR: 10–18%; Motzer score: 24–27% for OS) (Supplemental Table 5).

Similar results were observed for the concordance index in all conditions. Similar TGR distributions and associations between TGR and outcome were found in the IGR cohorts of patients enrolled in TARGET and RECORD, although the significance was rarely reached because of the small number of patients tested (Supplemental Table 3 and 4).

Table 2 – Tumor growth rate is associated with overall survival and progression-free survival (multivariate analysis) independent of the treatment arm (sorafenib or placebo) and the Motzer score in the TARGET phase 3 trial (\(n = 903\)) (landmark analysis)

<table>
<thead>
<tr>
<th>TARGET phase 3 trial ((n = 903))</th>
<th>Progression-free survival (multivariate analysis)</th>
<th>Overall survival (multivariate analysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio (95% CI)</td>
<td>Hazard ratio (95% CI)</td>
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<tr>
<td></td>
<td>(p) value</td>
<td>(p) value</td>
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<tr>
<td>Placebo cohort ((n = 361))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGR (first cycle)^*</td>
<td>1.14 (1.10–1.18)</td>
<td>1.17 (1.04–1.31)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.0001</td>
<td>0.0068</td>
</tr>
<tr>
<td>Motzer score (intermediate vs low)</td>
<td>1.68 (1.28–2.20)</td>
<td>3.08 (1.85–5.13)</td>
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<tr>
<td></td>
<td>0.0002</td>
<td>−0.0001</td>
</tr>
<tr>
<td>Sorafenib cohort ((n = 422))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGR (first cycle)^*</td>
<td>1.10 (1.05–1.14)</td>
<td>1.14 (1.06–1.22)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.0001</td>
<td>0.0002</td>
</tr>
<tr>
<td>Motzer score (intermediate vs low)</td>
<td>1.30 (0.99–1.68)</td>
<td>3.18 (1.88–5.42)</td>
</tr>
<tr>
<td></td>
<td>0.051</td>
<td>−0.0001</td>
</tr>
</tbody>
</table>

TARGET = Treatment Approaches in Renal Cancer Global Evaluation Trial; CI = confidence interval; TGR = tumor growth rate.

All the analyses reported are performed with the landmark method (landmark point was set to 52 d).

^* To be clinically meaningful, hazard ratios are computed for 10% variation in TGR.

Fig. 4 – Pairwise comparisons of tumor growth rate (TGR) at clinically relevant treatment times in everolimus-treated patients (\(p\) values are computed from Wilcoxon pairwise tests; \(n\) represents the number of samples with pairwise TGR information).
Finally, adding the tumor volume at baseline (V0, estimated by the RECIST sum) appears to have a very marginal effect on survival: Its HRs are consistently very close to 1 and are not significant or barely significant (Supplementary Table 7), whereas the HR of the TGR and the Motzer score did not vary. These results indicate that the tumor burden at baseline (V0 estimated by the RECIST sum) has no or a marginal effect on the survival when TGR is incorporated into the model (Supplementary Table 6). Finally, combining the Motzer score (intermediate vs low) with a dichotomized TGR variable (high vs low TGR, cut-off empirically set at 15%) reveals a clear segregation of the OS in placebo-treated patients (log-rank test: \( p < 1e^{-5} \) (Supplemental Fig. 3). Together, these findings reveal that the TGR exhibits an independent prognostic value, regardless of the standard prognostic score (Motzer score) or the treatment arm (sorafenib or placebo).

4. Discussion

Although a number of publications have already introduced the TGR in various tumor types, TGR has not yet been translated into clinical use [16,17,19,21–24]. In our opinion, the TGR in various tumor types, TGR has not yet been

A large body of literature has addressed how clinicopathologic features predict prognosis in patients diagnosed with mRCC [25–28]. Most of the published models incorporate both characteristics related to the physical state of the patients (eg, the performance status [PS], the albumin concentration, the degree of anemia) and items attributed to the aggressiveness of the tumor itself (eg, serum lactic dehydrogenase [LDH]). Among the models, the Motzer prognostic score is widely used and is based on the PS, the LDH, the corrected serum calcium concentration, the hemoglobin concentration, and the existence of prior nephrectomy [25]. Our study establishes that both TGR and Motzer score remain strongly associated with prognosis in one of the largest prospective phase 3 trial cohorts of mRCC patients published so far (\( n = 903 \)). Similar results have been reported in mRCC patients treated by sunitinib using more sophisticated models of tumor growth [22–24], as well as in other tumor types [29]. It is interesting to note that we further observed significant differences in terms of OS when stratifying placebo-treated patients into four groups defined by Motzer score and TGR. The latter results have a strong potential for translation at bedside and for guiding the design of future clinical trials but still warrant formal external validation.

The distribution of the TGR assessed before the onset of the treatment reflects the heterogeneity of a group of patients in terms of tumor growth kinetics. Similar to our previous results in the phase 1 setting [17], the present study clearly confirms that early signs of antitumor activity (ie, response evaluation after the first cycle) are not well estimated using the conventional RECIST criteria in mRCC patients treated with sorafenib or everolimus. Conversely, the incorporation of the pretreatment kinetics information in the TGR analyses allows for the precise and quantitative characterization of signs of drug activity at the first evaluation and has potential for changes in practice.

Our study reveals a persistent activity of sorafenib at progression and an apparent flare-up effect after drug discontinuation. Such a pattern was not observed for everolimus-treated patients. These observations are consistent with previous reports on mRCC patients treated by sunitinib [22]. Beyond considerations of the different pharmacokinetic profiles of sorafenib and everolimus, we hypothesize that this observation is related to the existence of contingents of tumor cells that are still sensitive to sorafenib at progression. The recent insights of intratumor heterogeneity in mRCC patients [30] reinforce the assumption that vascular endothelial growth factor–independent or platelet-derived growth factor–independent contingents of cells could emerge at progression under sorafenib, while other cell contingents could remain addicted to this pathway. Our findings suggest that alternative discontinuation schemes could be proposed for sorafenib (eg, similar to corticosteroids or \( \beta \)-blockers). Further studies, however, are warranted to confirm these preliminary results, given the small number of patients in the latter analyses.

Another potential limitation of our study is the fact that patients exhibiting the occurrence of new lesions are classified as progressive disease, and their RECIST sums on the target lesions were not assessable. Although the TGR could not be computed in this case, the great majority of the patients remained assessable for TGR, even at the time of progression (Supplementary Table 7). The difference in the TGR of the target lesions between the patients progressing with the occurrence of new lesions compared with without occurrence of new lesions remains to be further evaluated. Finally, the additional imaging examinations required to explore the specific washout periods may also represent clinical, economic, and ethical limitations for the wide use of the TGR, especially for patients whose tumor is rapidly progressing.

5. Conclusions

The assessment of the TGR is feasible and simple to compute at bedside. Smartphone applications and Internet tools exist (http://www.gustaveroussy.fr/doc/tgr_calculator/index_en.html). Translating the TGR into clinical use could substantially change decision making for mRCC patients in several ways: improving the assessment of the prognosis, allowing for an earlier and more precise evaluation of the response to MTA, and giving an insight into the discontinuation period of the drugs. The TGR method is not restricted to
any tumor type or drugs and deserves to be examined in the broad oncology setting.

This study was previously presented during the 2012 American Society of Clinical Oncology (ASCO) annual meeting at the poster discussion session Genitourinary Cancer. Charles Ferté received an ASCO Merit Award for this work.

**Author contributions:** Bernard Escudier had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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**Acquisition of data:** Ferté, Koscielny, Albiger, Rocher, Soria, Iacovelli, Loriot, Fizazi, Escudier.

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**Appendix A. Supplementary data**

Supplementary data associated with this article can be found, in the online version, at [http://dx.doi.org/10.1016/j.eururo.2013.08.010](http://dx.doi.org/10.1016/j.eururo.2013.08.010).

**References**


