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## Translating new data to the daily practice in second line treatment of renal cell carcinoma: The role of tumor growth rate

Enrique Grande, Olga Martínez-Sáez, Pablo Gajate-Borau, Teresa Alonso-Gordoa

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cell carcinoma (mRCC) have completely changed during the last ten years. With the sequential use of targeted therapies, median overall survival has increased in daily practice and now it is not uncommon to see patients surviving kidney cancer for more than four to five years. Once treatment fails with the first line targeted therapy, head to head comparisons have shown that cabozantinib, nivolumab and the combination of lenvatinib plus everolimus are more effective than everolimus alone and that axitinib is more active than sorafenib. Unfortunately, it is very unlikely that we will ever have prospective data comparing the activity of axitinib, cabozantinib, lenvatinib or nivolumab. It is frustrating to observe the lack of biomarkers that we have in this field, thus there is no firm recommendation about the optimal sequence of treatment in the second line. In the absence of reliable biomarkers, there are several clinical endpoints that can help physicians to make decisions for an individual patient, such as the tumor burden, the expected response rate and the time to achieve the response to each agent, the prior response to the agent administered, the toxicity profile of the different compounds and patient preference. Here, we propose the introduction of the tumor-growth rate (TGR) during first-line treatment as a new tool to be used to select the second line strategy in mRCC. The rapidness of TGR before the onset of the treatment reflects the variability between patients in terms of tumor growth kinetics and it could be a surrogate marker of tumor aggressiveness that may guide treatment decisions.

**Key words:** Axitinib; Everolimus; Cabozantinib; Kidney cancer; Nivolumab; Renal cell; Sequence; Second line; Sorafenib; Tumor-growth rate

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### Abstract

The therapeutic options for patients with metastatic renal

**Core tip:** The landscape of renal cell carcinoma has dramatically changed in the last decade. Today, at least 6 agents are approved after failure with cytokines,

sunitinib or pazopanib in first line treatment. Lack of reliable biomarkers to select the best treatment in daily practice is somewhat frustrating. Therefore, our decisions in real practice are based on safety profiles, patient' comorbidities and physician experience or preference. Here we debate the pros and cons of the tumor-growth rate as a tool to select second line systemic treatment after failure to a prior tyrosine kinase-inhibitor in patients with advanced renal cell carcinoma.

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## INTRODUCTION

The increased knowledge about the underlying pathogenesis of the metastatic renal cell carcinoma (mRCC) has led to the development of new therapeutic drugs that have completely changed patient prognosis. These drugs are targeting the vascular endothelial growth factor receptor (VEGFR) axis, the mammalian target of rapamycin (mTOR) pathway or the immune system and tumor cell interactions (PD1/PDL1). The number of patients that are candidates for a second line therapy after progressing on a first line varies from 43% to 79%<sup>[1]</sup>. The second line treatment is determinant in mRCC as patients can also benefit from an improvement in overall survival (OS) already achieved with first line choice and expand their chances for a longer therapeutic sequence. In this regard, a large registry-based experience in the United Kingdom has shown that those patients who received a second line treatment lived longer (33 mo; ranging from 30.8-35.2) than those who did not receive further treatment after first line (20.9 mo; ranging from 16.4-25.3)<sup>[2]</sup>. Fortunately, options for second line therapy have multiplied with the recent approval of nivolumab, cabozantinib and the combination of everolimus with lenvatinib<sup>[3-6]</sup>. However, there are no head-to-head comparisons between them and no predictive biomarker has been validated for the second line treatment decision making<sup>[7]</sup>. Besides, the uncertainty regarding the optimal therapeutic sequence, there is an urgent need for developing prognostic and predictive variables, in order to select patients who will benefit from a specific second line treatment<sup>[8]</sup>.

There are some clinical and economic-derived factors coming from the pivotal trials of each agent that could be considered at the time of second line treatment decisions (Table 1). The patient's tumor burden has been suggested from retrospective data as being strongly correlated with the progression free survival (PFS) and OS in patients with mRCC<sup>[9-12]</sup>. The expected response

$$TGR = 100 \times [\exp(TG) - 1]$$

$$TG = \frac{3 \times \log(D2/D1)}{\text{Time (months)}}$$

D1 = tumor size at date 1; D2 = tumor size at date 2;  
and time (months) = (date2 - date1 + 1)/30.44

Figure 1 Tumor growth rate calculation formula. TGR: Tumor-growth rate.

rate from the approved drugs has been reported to be different between cabozantinib, nivolumab and axitinib that achieve an overall response rate (ORR) of 17% to 22%, unlike the combination of everolimus with lenvatinib that has been reported to be of 35% in the phase II pivotal trial<sup>[3-6]</sup>. Moreover, the time required to achieve a tumor response is a major concern for heavily symptomatic patients that need an early tumor control. Prior tolerance and duration of response to first line treatment may identify those patients harboring a kidney tumor that greatly benefits from the angiogenic blockade (angiogenesis addiction), but may limit the decision in primary refractory patients<sup>[13,14]</sup>. Finally, we also propose the assessment of the tumor-growth rate (TGR), as a novel outcome measure that could help in the therapeutic sequence decision in the mRCC setting.

Several authors have discussed that the Response Evaluation Criteria in Solid Tumors (RECIST) may be inadequate to completely evaluate the response of targeted therapies in mRCC as often induce long-lasting stable disease rather than tumor shrinkage<sup>[15-18]</sup>. In addition, these criteria do not take into account tumor growth kinetics, and might not be relevant in slow-growing diseases<sup>[19,20]</sup>. Therefore, alternate modalities to assess the drug response have been proposed to overcome the limitations of the RECIST criteria, such as Choi, SACT, MASS, ETPIC or iRECIST. These approaches include the tumor perfusion evaluation, *via* the use of CT response assessment combining reduction in both, size and arterial phase density, changes in tumor CT texture or metabolism or the immune component evaluation. However, none of them appear to be an adequate surrogate of response or clinical outcome for its application in routine clinical practice<sup>[16,18,21,22]</sup>.

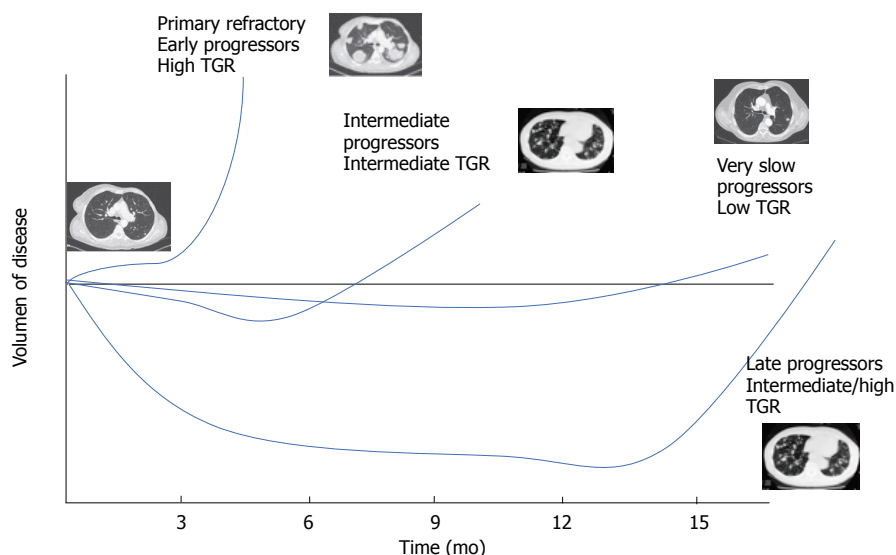
TGR provides a dynamic and quantitative evaluation of tumor kinetics; it estimates the percentage of change in the tumor volume over one month. TGR is usually defined as the ratio between the slope of tumor growth before the initiation of treatment and the slope of tumor growth during treatment, and between the nadir and disease progression<sup>[9,23]</sup>. We can calculate TGR according to the formula shown in Figure 1<sup>[24]</sup>. The tumor size is defined using the sum of the longest diameters (SLD) of target lesions only, without considering non-target and new lesions. However, the assessment of the TGR in clinical practice is easier as there are internet tools available (<http://ec2-54-218-32-173.us-west-2.compute.amazonaws.com:3838/tgrShiny/> or [http://www.gustaveroussy.fr/doc/tgr\\_calculator/index\\_en.html](http://www.gustaveroussy.fr/doc/tgr_calculator/index_en.html)).



**Table 1 Phase III clinical trials evaluating approved drugs in second and subsequent treatment lines for metastatic renal cell carcinoma**

	Axitinib	Cabozantinib	Lenvatinib + Everolimus	Nivolumab
Trial design	Phase III	Phase III	Phase II	Phase III
Size	361	330	51	410
Patient population	2 <sup>nd</sup> Line (100%)	2L- 71% 3L- 29%	2 <sup>nd</sup> Line (100%)	2L- 72% 3L- 28%
MSKCC risk % (Good/int/poor)	28/37/33	45/42/12	24/37/39	35/49/16
Comparator	Sorafenib	Everolimus	Everolimus	Everolimus
ORR% (ICR)	19%	17%	35%	22%
Progression disease (%)	22%	12%	4%	35%
PFS (m)	6.7 (HR 0.66)	7.4 (HR 0.51)	12.8 (HR 0.40)	4.6 (HR 0.88)
PFS (m) in pts with bone mets	NR	7.4 (HR 0.33)	NR	NR
OS (m)	20.1 (HR 0.96)	21.4 (HR 0.66)	25.5 (HR 0.59)	25.0 (HR 0.73)
Dose reductions	30%	60%	71%	N/A
Discontinuations due to AEs	7%	9%	25%	8%
Toxicity G3/4 (%)	56%	68%	71%	19%
Average monthly cost (US basis)	9580\$	10229\$	22461\$	12435\$

MSKCC: Memorial Sloan Kettering Cancer Center Criteria; ORR: Overall response rate; OS: Overall survival; PFS: Progression free survival; AE: Adverse events.

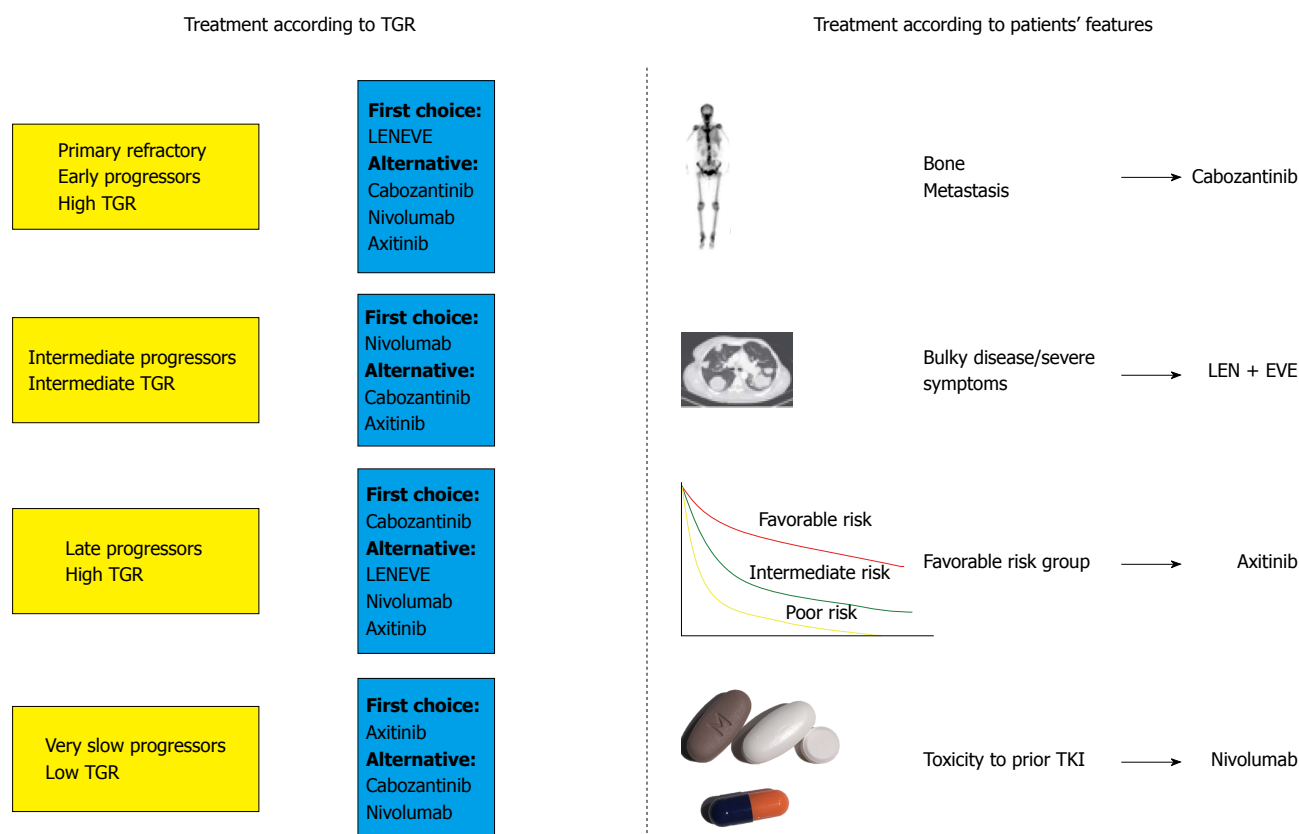


**Figure 2** Hypothetical representation of different groups of patients and their patterns of response to first line treatment: Primary refractory patients with early progression and high tumor growth rate, intermediate progressors with intermediate tumor growth rate, very slow progressors with low tumor growth rate and late progressors with high tumor growth rate. TGR: Tumor-growth rate.

Current evidence from phase I studies in solid tumors and from phase III studies in mRCC (TARGET and RECORD trials) and metastatic neuroendocrine tumors (NETs) (CLARINET trial), although retrospective, show a significant association between prior TGR before the onset of the second line approach with the expected PFS and OS with the later systemic treatment administered<sup>[9,24-28]</sup>. Moreover, TGR could be an important tool in the evaluation of prognosis during treatment and after the discontinuation of VEGFR targeted agents. Iacovelli *et al.*<sup>[29]</sup> showed that those patients with a higher than median TGR during treatment had a significantly shorter OS and, indeed, those patients with lower than the median TGR after discontinuation had longer OS, as compared to TGR after discontinuation greater than or equal to the median. Therefore, it would be possible to use TGR as a possible surrogate for tumor aggressiveness and survival in mRCC patients while on VEGFR-directed TKI in the first line. In the post hoc analysis from the CLARINET trial, TGR

seemed to provide more precise information to predict pretreatment progression regarding actively growing tumors, but considered as stable disease by RECIST criteria, and more sensitive to detect early antitumor activity from treatment compared with RECIST criteria<sup>[28]</sup>. We consider that the addition of TGR in the assessment of individual patients undergoing targeted therapies may help clinicians to know if a given agent is modifying or not the course of the disease and guide the decision of which agent would be preferred in the subsequent line. However, for the use of TGR in the clinical setting, a prospective clinical trial for its validation would be needed<sup>[23]</sup>.

Considering all aspects previously discussed, patients with mRCC that are candidate for a second line treatment could be differentiated into four main subgroups (Figure 2). Patients with florid symptoms, high tumor burden, short time to response to the first line (PFS less than 6 mo, so called, early progressors) and high TGR, in which we would need an early and high response, the



**Figure 3** Adapting the study data to our clinic. A proposed algorithm to treat second line metastatic renal cell carcinoma patients according to tumor growth rate and patients' characteristics. TGR: Tumor-growth rate; TKI: Tyrosine kinase inhibitor; LEN: Lenvatinib; EVE: Everolimus.

combination of everolimus with lenvatinib should be considered, as we will target several mechanisms of action (VEGFR, fibroblast growing factor receptor, FGFR, and m-TOR pathways). In such patients, the expected benefit outweighs the increased toxicity of the combination therapy. In those patients with a long response to first antiangiogenic drug (PFS more than 18 mo, so called angiogenesis addicts) and low or intermediate TGR, the use of cabozantinib may be considered. Regarding those patients that are not responding radiographically but are stable for the advanced disease for a long period with a very low TGR (increase of less than 4% in the sum of the longest diameters per month) and have an adequate tolerability, we propose that axitinib could be a reliable option to prolong the clinical benefit. Finally, for patients with an interval free of progression with first line treatment between 6 and 18 mo, as considered intermediate-progressors, nivolumab may be the treatment of choice as an inhibitor of an actionable immune target by introducing a different mechanism of action against tumor growth.

Lastly, we highlight the upcoming availability of novel immune agents such as ipilimumab, atezolizumab, pembrolizumab either as single agent or in combination that might impact in the first line setting of patients with advanced RCC. Therefore, it is very likely that second line landscape of metastatic RCC may change shortly. Adaptation to the clinic of the amount of new data that are expected in a short term promises to be challenge.

In conclusion, patients with mRCC receiving a second line treatment achieve a median OS of more than 2 years with novel agents. Thus, the optimal treatment selection in this setting allows us to provide the maximal clinical benefit to our patients, but with no definitive biomarker to guide our decision. In this setting, we have considered some relevant clinical parameters before choosing a certain agent such as the patient's tumor burden, the expected response rate to the different drugs and the time to achieve this response, the prior response to previous VEGFR-TKIs, the toxicity profile of each agent and the patient preference. Thus, we propose the employment of the TGR as a new tool that could provide useful information in the management of mRCC patients in addition to clinical features that could better fit with one of the therapeutic alternatives (Figure 3). TGR may represent a surrogate of tumor aggressiveness, a relevant parameter before choosing a treatment and an early biomarker for treatment response and evaluation of the ability to interfere in the natural history of the tumor growth. TGR could be a valuable endpoint for clinical use in treatment decision-making favoring patients with mRCC, with more reliable information about prognosis and evaluation of response to molecular targeted agents.

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