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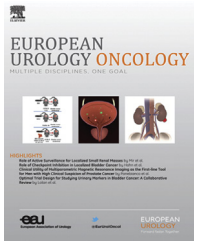

European Association of Urology

Metastatic Renal Cell Carcinoma Rapidly Progressive to Sunitinib: What to Do Next?

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Abstract

Background: From 10% to 26% of patients with metastatic renal cell carcinoma (mRCC) experience rapidly progressive disease (PD) on treatment with sunitinib.

Objective: To investigate the benefit of subsequent treatment with another tyrosine kinase inhibitor (TKI) or a mammalian target of rapamycin (mTOR) inhibitor in such primary refractory patients.

Design, setting, and participants: A total of 150 mRCC patients with rapidly PD on first-line sunitinib (within two cycles, $n = 93$, or four cycles, $n = 57$) were identified: median age 59 yr; nephrectomy 86%; histological subtypes: clear cell (77.8%), papillary (14%), and sarcomatoid features (18%); according to the Memorial Sloan-Kettering Cancer Center and French classifications: good risk (11% and 7%, respectively), intermediate (68% and 63%, respectively), and poor (21% and 29%, respectively).

Outcome measurements and statistical analysis: Data were retrospectively collected by a questionnaire from 19 European oncology centers between March 2005 and March 2011. Progression-free survival (PFS) and overall survival (OS) were calculated (Kaplan-Meier method).

Results and limitations: Median OS from the start of first-line treatment was 7.4 mo. Second-line treatment was administered to 86 (57%) patients (44 mTOR inhibitors: 23 everolimus and 21 temsirolimus; 39 TKIs alone or in combination; three chemotherapy). Second-line PFS was not significantly different between TKIs and mTOR inhibitors (2.0 vs 0.9 mo; $p = 0.536$). Median OS from the start of second-line treatment was 5.0 mo for mTOR inhibitors and 6.6 mo for TKIs ($p = 0.15$).

Conclusions: Treatment with further TKIs or mTOR inhibitors for mRCC patients primarily refractory to first-line sunitinib in the observed time period achieved very minimal benefit, suggesting avoiding TKI rechallenge and possibly preferring alternative strategies, such as immune checkpoint inhibitors, after PD to a treatment line including a TKI in this setting.

Patient summary: The present work collected data about 150 patients affected by metastatic renal cell carcinoma, who received one of the current standard of care as first-line treatment, namely, the antiangiogenic drug sunitinib, and experienced rapid worsening of the disease. We investigated and described the subsequent outcome of such patients treated with two different types of drug, administered as second-line therapy, to better understand the best strategy to adopt for patients who got no benefit from sunitinib and to describe the current therapeutic approach in such cases.

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1. Introduction

Targeted therapy with tyrosine kinase inhibitors (TKIs) has increased overall survival (OS) of patients with metastatic renal carcinoma (mRCC) [1,2]. However, a subgroup of patients treated with such agents never experiences tumor shrinkage, and can be identified as harboring a "primary refractory disease" or a rapidly progressive disease (PD) to TKI therapy [3]. Despite the current availability of new treatment options, such as immune checkpoint inhibitors (CKIs), the sequential use of oral drugs and the rechallenge of further TKIs are still currently indispensable for patients with a longer course of disease, while no data have yet been provided for CKI rechallenge. In this light, it would be useful to understand which type of subsequent mechanism of action (MOA) could be exploited for primary TKI-refractory patients.

Primary refractory disease has no standard definition, and this may partly account for the few studies available on patients with rapidly PD [3–5]. The terms are both commonly used to refer to patients in whom the best response is disease progression according to the Response Criteria in Solid Tumors (RECIST). Two series have been reported to date focusing on this population: Heng et al. [4] identified 272 primary refractory cases among a cohort of 1056 patients receiving TKI (incidence rate, 26%); Busch et al. [5] reported 35 cases with intrinsic resistance to TKIs among a cohort of 189 patients (18.5%).

In large randomized studies reported with vascular-endothelial growth factor receptor (VEGFR) inhibition as first-line treatment, the incidence of PD as the best response was 10.3–12% for sorafenib [6,7], 18% for pazopanib [8], 20% for bevacizumab plus interferon-α [9], 21% for sunitinib [2], 13.1% for tivozanib [10], and 18% for cabozantinib [11].

Owing to of the feeling that primary resistance to sunitinib will apply to other TKIs, the most common treatment strategy for patients with rapidly PD in the pre-CKI era was the use of mammalian target of rapamycin (mTOR) inhibitors, despite the lack of evidence for the efficacy of such switch in this setting. Given the possibility to choose the CKI nivolumab as next-line therapy, the issue would now be simple, if it were not for the current availability of a new multitarget TKI, namely, cabozantinib, which gives the chance to overcome the prior TKI resistance (through MET and AXL inhibition), demonstrating lower rates of primary refractory cases when indirectly compared with nivolumab as second-line therapy (12% vs 35%) [12–14].

Considering the currently ongoing shift of CKIs in the first-line setting of mRCC treatment [15,16] and, on the other hand, the possible applicability of cabozantinib as first-line option in certain subgroups (poor/intermediate-risk patients) [11], what to do in second or subsequent treatment lines after a prior TKI still remains an actuarial issue.

The aim of the present study was therefore to analyze the outcome of second-line treatment of patients rapidly progressing (within 24 wk) on first-line sunitinib therapy, representing the gold standard for mRCC primary treatment at the time of the study planning, to determine whether the TKI rechallenge strategy, or the mTOR-inhibition switch, still has any clinical rationale.

2. Patients and methods

2.1. Patients

We performed a retrospective analysis of data on patients with mRCC who experienced rapidly PD on first-line sunitinib treatment, defined as PD within 24 wk (four cycles) from starting therapy and without tumor shrinkage after two cycles of sunitinib. Data were collected by sending a questionnaire to contact oncologists from the French Kidney Cancer Group, Italian Nephro-Oncology Group, and Royal Marsden Hospital (UK) for distribution to their members. Members had to complete the questionnaire for all patients with mRCC fulfilling all the following criteria: (1) patients with histologically proven mRCC; (2) patients who had been treated with first-line sunitinib between March 2005 and March 2011, according to standard schedule (4 wk on, 2 wk off cycle); (3) patients who had progressed within 24 wk (four cycles) from starting therapy and without tumor shrinkage after two cycles of sunitinib; and (4) patients with documented baseline characteristics and adequate follow-up. In all cases, informed consent must have been obtained for therapy administration.

Data regarding patients and their tumors were retrospectively collected. Patients were classified according to the Memorial Sloan-Kettering Cancer Center (MSKCC) modified criteria [17] and also according to the French prognostic criteria [18,19] (performance status [PS] >0, number of metastatic sites >1, interval between initial diagnosis of mRCC and systemic treatment <1 yr, and presence of liver metastases). The principles outlined in the Declaration of Helsinki have been followed for the present work.

2.2. Statistical analysis

OS was calculated from the start of sunitinib to death or the last follow-up. For patients who received a second-line treatment, second-line survival was also calculated from the start of second line to death or the last follow-up. In addition, progression-free survival (PFS) for second line was defined as the interval from the start of second-line therapy to the first documentation of disease progression or death from any cause, whichever occurred first.

All values were examined as binary variables. Multivariate analysis was performed using the Cox proportional hazard model, and a stepwise selection algorithm that used a type I error of 0.05 for model entry and 0.10 for elimination. Additional elimination was applied to identify significant variables at the level of $p < 0.05$. The chi-square test was used to assess the differences. We used Predictive Analytics SoftWare (PASW, v 18; IBM SPSS).

3. Results

Overall, 150 patients (mean age, 58 yr [range 22–83]) from 19 major European oncology centers were included in this analysis. Their baseline characteristics are presented in Table 1. The mean time from surgery to the diagnosis of metastatic disease was 11 mo, including 78 patients (52%) with synchronous metastatic disease at diagnosis.

3.1. Response to first-line treatment with sunitinib

All 150 patients received sunitinib as first-line therapy; 133 (89%) received a standard dose of 50 mg 4 wk on followed by 2 wk off. Eleven percent of patients started at a lower dose of 37.5 ($n = 13$, 8.7%) or 25 mg/d ($n = 4$; 2.7%).

Two-thirds of the patients ($n = 93$, 62.2%) stopped treatment within the first two cycles of treatment for PD (12 wk), and the remainder ($n = 57$, 37.8%) received up to

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Table 1 – Patient characteristics

Characteristics	Patients
Male/female	115/35
Age (yr)	58 (22–83)
Disease characteristics (%)	
T1	6
T2	14
T3	58
T4	8.7
NA	13.3
N0	26.7
N1	10.7
N2	21.3
NA	41.3
Histology (%)	
Clear cell	77
Papillary	13.5
Pure sarcomatoid	5.4
Sarcomatoid component	13
Others	4
Metastatic at diagnosis (%)	49
Number of metastatic sites (%)	
1	19
2	33
≥3	48
Sites of metastasis (%)	
Lung	70
Lymph node	59
Bone	31
Liver	25
Brain	11
Renal bed	9
MSKCC classification (%)	
Good	10.7
Intermediate	63.7
Poor	18.9
NA	6.7
French classification (%)	
Good	7.7
Intermediate	62
Poor	28.3
NA	2

MSKCC = Memorial Sloan-Kettering Cancer Center; NA = not available.

four cycles (Fig. 1). Assessment of these 57 patients after two cycles identified 29 patients with PD who received two further cycles despite PD on evaluation and 28 with stable disease (SD) according to the RECIST criteria but without any tumor shrinkage, consistent with the inclusion criteria. Median OS in the overall population was 7.4 mo (6.6–8.2; Fig. 2). OS was significantly shorter in the group that received two cycles than in the group receiving four cycles (6.0 [5.2–6.8] vs 9.3 [7.4–11.3] mo; $p = 0.008$).

3.2. *Response to second-line treatments*

Of the 150 patients, 86 (57.3%) received second-line treatment. The reasons for no treatment for the remaining 64 (42.7%) were a poor PS related to disease progression ($n = 55$), diagnosis of brain metastases ($n = 3$), surgery ($n = 1$), patient refusal ($n = 1$), unaffordable treatment ($n = 1$), and unknown ($n = 3$). Second-line response rates were 0% for complete response, 10% for partial response, and 27% for SD. Only 22 patients (25.5%) experienced a clinical benefit lasting for >3 mo.

At the time of analysis, 23/150 patients (15.3%) were alive. Median second-line PFS and second-line survival were 1.6 (0.5–2.7) and 5.9 (4.3–7.4) mo, respectively (Fig. 3). Median OS was significantly longer in patients who received second-line treatment than in those who did not (10.5 [8.0–13.1] vs 4.1 [2.8–5.5] mo; log-rank test, $p < 0.0001$).

Among the 86 patients receiving second-line treatment, 44 received an mTOR inhibitor (21 everolimus and 23 temsirolimus), 39 received a TKI either alone or in combination (35 sorafenib, two axitinib, and two sunitinib plus bevacizumab), and three patients received chemotherapy. The groups receiving mTOR and TKI as second-line targeted therapy had similar baseline characteristics (Table 2). Median second-line survival (6.6 vs 5.0 mo; $p = 0.157$) and second-line PFS (2.0 vs 0.9 mo; log-rank test, $p = 0.536$) were not significantly different between TKI and mTOR inhibitors (Table 3 and Fig. 4).

3.3. *Prognostic variables*

Variables, including Karnofsky performance status (KPS) of <80, absence of nephrectomy, increased baseline value for lactate dehydrogenase (LDH), MSKCC poor-risk group, number of metastatic sites >1, absence of second-line treatment, and number of cycles (2 vs 4 cycles), were associated with worse OS in univariate analyses. In a multivariate analysis, a KPS of <80, high baseline values for LDH, and corrected calcium were found to be independent prognostic factors.

3.4. *Exploratory analysis*

Among the 150 patients, 122 exhibited PD at two-cycle computed tomography scan, while 28 were nonprogressive patients with no tumor shrinkage according to the inclusion criteria (Fig. 5A). Patients who had PD at two-cycle evaluation had median OS of 6.6 mo, while patients with SD at two cycles had median OS of 9.3 mo ($p = 0.12$; Fig. 5B). Among the 122 patients with PD at cycle 2, 93 stopped sunitinib with median OS of 5.9 mo and 29 patients who received two further cycles of sunitinib had 10.0-mo OS ($p = 0.043$; Fig. 5C). It is noteworthy that patients who received a second-line treatment after discontinuation due to progression had OS of 5.2 versus 5.1 mo for patients who stayed on sunitinib despite PD at two cycles ($p = 0.9$; Fig. 5D).

To investigate the impact of PD timing, the population of patients who received four cycles of sunitinib but experienced PD with two cycles ($n = 29$) was compared with those who experienced PD within four cycles while non-PD after two cycles ($n = 28$). There was no difference in OS between these two populations (9.3 vs 10 mo; $p = 0.9$).

4. Discussion

Despite recent advances in the treatment of patients with mRCC, patients with rapidly PD on TKI treatment represent a relatively substantial subset of patients with a very poor prognosis. The rate of primary resistance, defined as PD as

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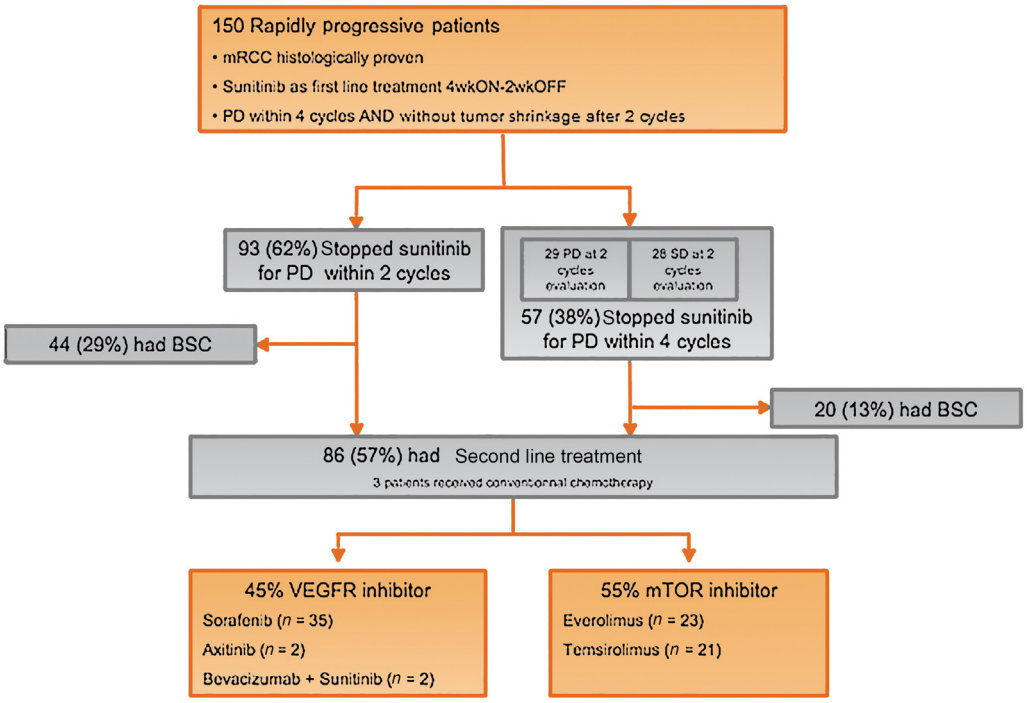

Fig. 1 – Population flowchart. BSC = best supportive care; mRCC = metastatic renal cell carcinoma; mTOR = mammalian target of rapamycin; PD = progressive disease; SD = stable disease; VEGFR = vascular-endothelial growth factor receptor; 4wkON-2wkOFF = 4 wk on, 2 wk off cycle.

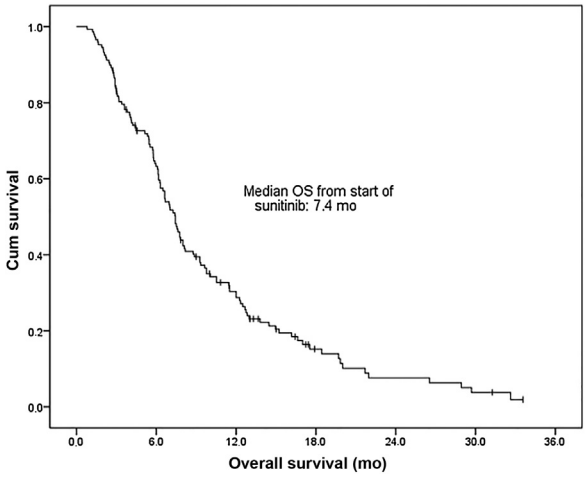

Fig. 2 – Overall survival. Cum = cumulative; OS = overall survival.

the best response, was 21% in the pivotal phase III trial of sunitinib [2], and it was confirmed in the two retrospective studies focusing on this subpopulation by Heng et al. [4] and Busch et al. [5] (rates of 26% and 18.5%, respectively). Since in clinical practice about one patient out of five do not benefit from treatment, the issue of the prognosis and decision of further treatment must be enlightened.

In the present study, which used 24 wk as a time limit to define refractory disease, median OS of the entire cohort of 150 patients was 7.4 mo. These data are consistent with those from Heng et al.'s [4] cohort (6.8 mo). Regarding second-line treatment options, Heng et al. [4] reported a 40% rate of second-line treatment, while we report a 57% rate. In our experience, there was no difference in second-line PFS or OS regardless of the choice of a TKI or an mTOR inhibitor, in line with Heng et al.'s [4] findings. It must be underlined that we provide the most homogeneous comparison between the type of second-line treatments regarding the number of patients (39 vs 44) as well as prognosis characteristics (Table 4).

In our cohort, the overall benefit of a second-line treatment, regardless of its nature, is highly questionable with second-line PFS of 1.6 mo and second-line survival of 5.9 mo, consistent with those previously reported [4].

Furthermore, it is still not possible to predictively identify patients refractory to sunitinib. In our population, the only prognostic element isolated in multivariate analysis was the MSKCC score, with the limitations due to the retrospective design of this study using data from questionnaires.

Of note, the selection of progressive patients within four cycles of treatment provides us with information on three more aspects regarding this subpopulation:

The comparison among patients with PD at two cycles between those who benefit from an alternative second line ($n = 49$) and those who stayed on sunitinib for two more cycles despite progression ($n = 29$) stated no statistical difference in favor of a therapeutic change to an alternative second line (Fig. 5D). It is therefore highly questionable whether switching to another drug rather than staying on sunitinib despite PD is useful. Nevertheless, this finding could be partially related to a selection bias in favor of patients staying on sunitinib therapy, probably identified by the clinicians as individuals with a clinical benefit despite PD.

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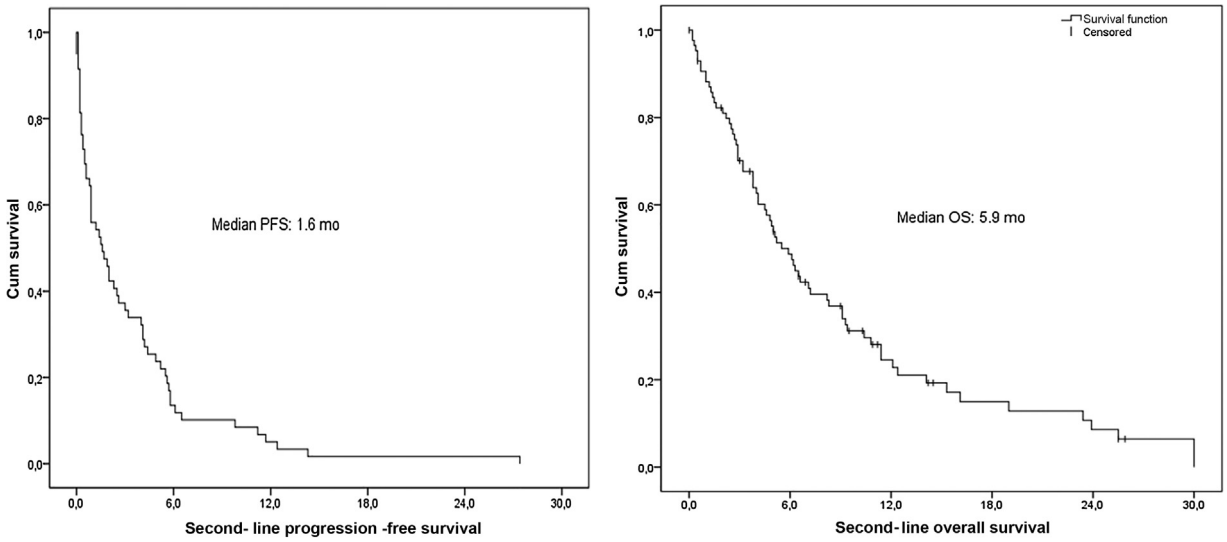

Fig. 3 – Second-line PFS and OS (calculated from the start of second line). Cum = cumulative; PFS = progression-free survival; OS = overall survival.

Table 2 – Comparison between best supportive care (BSC) and second-line treatment

Characteristics	BSC (n = 64)	2nd line (n = 86)	Chi-square test (p value)
Males (%)	73.4	67.4	0.4
Age (yr)	59 (28–83)	57 (23–76)	0.4
Disease characteristics			
Histology (%)			0.6
Cellules clear	79.0	75.6	
Other histologies	21.0	23.4	
Sarcomatoid features (%)	16.1	19.8	0.6
Number of metastatic sites (%)			0.3
1	21.9	17.4	
2	29.7	36.0	
≥3	48.4	46.6	
Sites of metastasis (%)			
Lung	75.0	66.3	0.2
Abdominal nodes	25.0	47.7	0.005
Liver	26.6	24.4	0.8
Bone	31.3	31.4	0.9
Prognostic factors (%)			
Interval diagnosis—sunitinib <1 yr	67.2	77.9	0.1
Karnofsky PS <80%	26.9	7.1	0.001
Ca correct >UNR	11.9	4.8	0.1
Hemoglobin <LNR	61.9	38.1	0.004
LDH 1.5 UNR	21.1	13.4	0.2
MSKCC classification (%)			0.08
Good	10.2	12.2	
Intermediate	59.3	74.4	
Poor	30.5	13.4	
French classification (%)			0.4
Good	7.9	7.1	
Intermediate	55.6	69.1	
Poor	36.5	23.8	

LDH = lactate dehydrogenase; LNR = lower normal rate; MSKCC = Memorial Sloan-Kettering Cancer Center; PS = performance status; UNR = upper normal rate.

Continuing treatment for two extra cycles when PD is diagnosed at first evaluation, we identified that patients receiving four cycles of sunitinib despite a lack of response after two cycles (n = 29) had better OS than those who experienced PD and stopped sunitinib (n = 93; 10.1 vs 5.9 mo, p = 0.049). This comparison is allowed as the percentage of patients who were referred to best supportive care (47.8% vs 41.8%) is similar in both groups (Fig. 5C). Therefore, we hypothesized that the difference in OS may indeed be related to the longer exposure to sunitinib.

The trend in OS between patients who exhibit PD within two cycles (n = 122) versus those who exhibited SD at first evaluation (with no tumor shrinkage; 6.6 vs 9.3 mo) was not significant (p = 0.12; Fig. 5B). About the meaning of developing PD after two or four cycles, there was no difference in OS between patients developing PD at these

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Table 3 – Second-line progression-free survival (PFS) and second-line survival (OS)

Class of second line	*n*	2nd-line survival		*n*	2nd-line PFS	
		Value[a]	95% CI		Value[a]	95% CI
TKI	39	6.6	4.8–8.5	22	2.0	0.3–3.6
mTOR	44	5.0	3.0–7.0	36	0.9	0.1–1.9
Global	83	5.9	4.4–7.4	58	1.6	0.3–2.9

CI = confidence interval; mTOR = mammalian target of rapamycin; OS = overall survival; TKI = tyrosine kinase inhibitor.
[a] Value limited to the maximal time of OS, if censored.

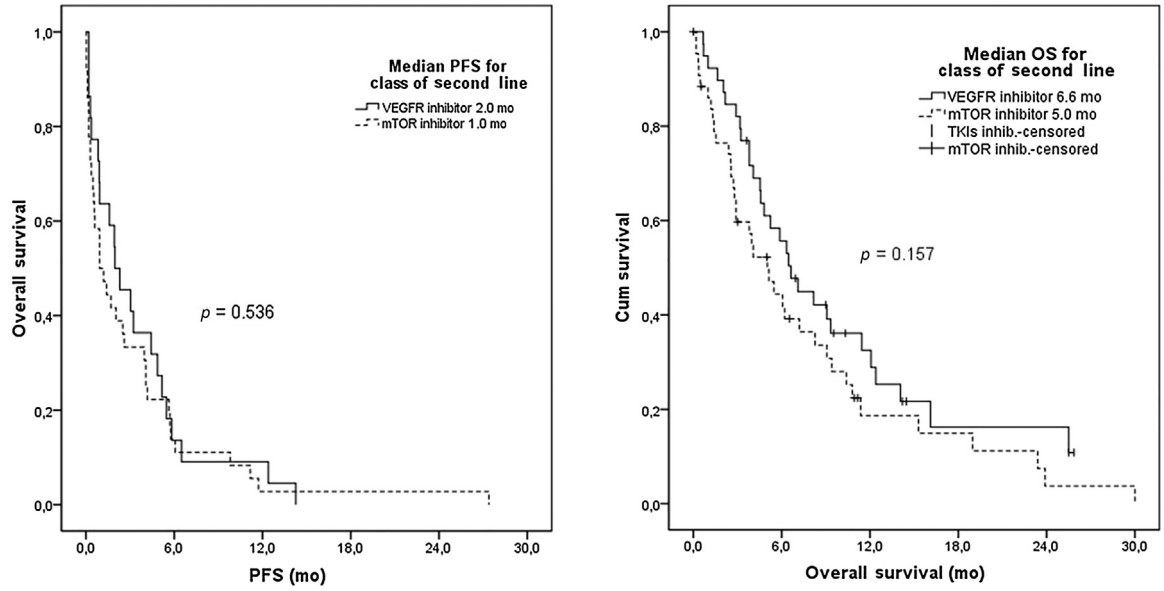

Fig. 4 – Second-line PFS and second-line OS according to the nature of treatment. Cum = cumulative; inhib. = inhibitor; mTOR = mammalian target of rapamycin; PFS = progression-free survival; OS = overall survival; TKI = tyrosine kinase inhibitor; VEGFR = vascular-endothelial growth factor receptor.

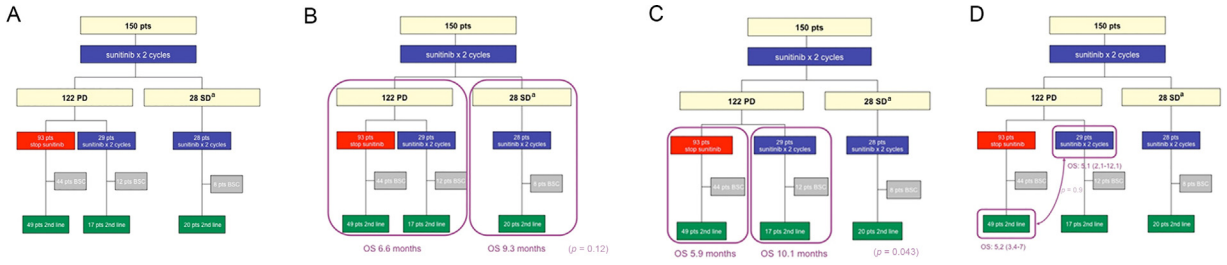

Fig. 5 – Exploratory analysis. (A) Overall population. (B) Prognosis of patients with SD versus PD within two first cycles of sunitinib [a] SD with no tumor shrinkage. (C) Prognosis of patients with PD at two cycles: difference between sunitinib arrest and sunitinib continuation. (D) Patients with PD at two cycles: similar prognosis of patients with second-line treatment versus sunitinib continuation. BSC = best supportive care; OS = overall survival; PD = progressive disease; pts = patients; SD = stable disease. [a] SD with no tumor shrinkage.

two different time points of a four-cycle treatment (9.3 vs 10 mo; $p = 0.9$), raising the hypothesis that whether the PD was occurring earlier or later within the first 6 mo did not impact OS. Furthermore, this observation is in favor of defining primary resistance not only in PD occurring within 3 mo but also extending the definition to the first 6 mo of sunitinib treatment.

The first two highlighted points did not collide with the evidence that the currently available alternative TKI cabozantinib can achieve a benefit irrespective of primary resistance to first-line TKI: in fact, it is uncertain whether the inhibition of MET, RET, or AXL drives the major clinical activity of cabozantinib or whether the benefit is simply due to a VEGFR inhibitory effect [20]. Interestingly, cabozantinib efficacy seems to be independent of MET expression and by its typical "VEGF inhibition–related" toxicity profile. These previous data, together with our current findings, suggest that maintaining "VEGF pressure" can still slow disease progression irrespective of the primary sensitivity to TKI [21].

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Table 4 – Second-line characteristics between mTOR group and VEGFR inhibitor group

Characteristics	VEGFR inhibitor (n = 39)	mTOR inhibitor (n = 44)	Chi-square test (p value)
Males (%)	89.7	70.5	0.03
Age (yr)	57 (31–83)	56 (28–78)	0.5
Histology (%)			0.8
Cellules clear	76.9	75.0	
Other histologies	23.1	25.0	
Sarcomatoid features (%)	15.4	20.5	0.5
Number of sunitinib cycles (%)			0.9
2	54.4	56.8	
4	43.6	43.2	

mTOR = mammalian target of rapamycin; VEGFR = vascular-endothelial growth factor receptor.

Finally, we provided informative observations on pathological characterization: our population included a relatively high proportion of tumors with sarcomatoid features (18%) compared with historical cohorts [22,23], underlining the interest for different therapeutic strategies in these poor-prognosis subtypes, which may benefit from conventional chemotherapy [24] and possibly from the use of CKIs [25].

The design of our study has several caveats. First, the study cohort is outdated, referring to years 2005–2011 and lacking cases treated with second-line nivolumab or cabozantinib; thus, it is limited to providing data about classical therapeutic options (such as "old" TKIs and mTOR inhibitors), beyond the obvious possibility to treat TKI-refractory patients with the new immunotherapy, in case they have not received it previously. Then, the study was retrospective, relied on the analysis of data from questionnaires, and the number of patients did not exceed 150, although the patients were from many oncology centers in three countries. Our study nevertheless has several strengths. We used a reproducible definition for primary refractory disease (progression within four cycles of treatment); the numbers of patients receiving TKIs or mTOR inhibitors as second-line treatment were well balanced; we applied two different classifications for prognosis; details were available on tumor histology.

5. Conclusions

Rapidly progressive mRCC patients can be considered having a similar dismal prognosis to poor-prognosis patients. The TKI or mTOR switch strategy might not be superior to continued treatment with sunitinib in this setting. Nevertheless, given the current rapidly changing treatment landscape for first-line approach in mRCC, the setting represented in this study is going to be outdated. Moreover, the present study only reported data about sunitinib, with no clear applicability for pazopanib, and does not provide data about the new multitarget TKI cabozantinib. Actually, our findings can still be useful to suggest only a change of the MOA, considering immunotherapy as possibly the best management option for primary refractory patients to TKI, in view of their poor prognosis and the lack of efficacy of "old" second-line treatments.

Author contributions: Melissa Bersanelli 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.

Study concept and design: Albiges, Iacovelli, Porta, Escudier.
Acquisition of data: Albiges, Iacovelli, Porta, Houede, Laguerre, Procopio, Lheureux, Fischer, Negrier, Ravaud, Oudard, Escudier.
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