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Clinical outcomes in patients receiving three lines of targeted therapy for metastatic renal cell carcinoma: Results from a large patient cohort

Roberto Iacovelli [a], Giacomo Cartenì [b], Cora N. Sternberg [c], Michele Milella [d], Matteo Santoni [e], Giuseppe Di Lorenzo [f], Cinzia Ortega [g], Roberto Sabbatini [h], Riccardo Ricotta [i], Caterina Messina [j], Vito Lorusso [k], Francesco Atzori [l], Fabio De Vincenzo [m], Cosimo Sacco [n], Francesco Boccardo [o], Francesco Valduga [p], Francesco Massari [q], Valentina Baldazzi [r], Saverio Cinieri [s], Alessandra Mosca [t], Enzo Maria Ruggeri [u], Alfredo Berruti [v], Linda Cerbone [c], Giuseppe Procopio [w,*]

[a] *Sapienza University of Rome, Department of Radiology, Oncology and Human Pathology, Rome, Italy*
[b] *Oncology Unit, A. Cardarelli Hospital, Naples, Italy*
[c] *Department of Medical Oncology, San Camillo Forlanini Hospital, Rome, Italy*
[d] *Medical Oncology A, Regina Elena National Cancer Institute, Rome, Italy*
[e] *Department of Medical Oncology, Polytechnic University of the Marche Region, Ancona, Italy*
[f] *Medical Oncology, Genitourinary Cancer Section, University Federico II, Naples, Italy*
[g] *Fondazione del Piemonte per l'Oncologia IRCC, Candiolo, Italy*
[h] *Oncology Division, Department of Oncology and Hematology, University of Modena e Reggio Emilia, Modena, Italy*
[i] *The Falck Division of Oncology, Ospedale Niguarda Ca' Granda, Milan, Italy*
[j] *Oncology Division, Ospedali Riuniti, Bergamo, Italy*
[k] *National Cancer Research Center, Istituto Tumori 'Giovanni Paolo II' Bari, Italy*
[l] *Medical Oncology Unit, Azienda Ospedaliero Universitaria of Cagliari, Italy*
[m] *Oncology and Hematology Unit, Humanitas Cancer Center, Istituto Clinico Humanitas, Rozzano, Italy*
[n] *Oncology Unit, St. Maria della Misericordia Hospital, Udine, Italy*
[o] *University and IRCCS AOU-San Martino-IST, National Cancer Research Institute, Genoa, Italy*
[p] *Medical Oncology, St. Chiara Hospital, Trento, Italy*
[q] *Medical Oncology, 'G.B. Rossi' Academic Hospital, University of Verona, Verona, Italy*
[r] *Department of Medical Oncology, Santa Maria Annunziata Hospital, Florence, Italy*
[s] *Medical Oncology & Breast Unit Department, Sen A. Perrino Hospital, Brindisi, Italy*
[t] *Medical Oncology, Maggiore della Carità University Hospital, Novara, Italy*
[u] *Oncology Unit, Belcolle Hospital, Viterbo, Italy*
[v] *Medical Oncology, University of Brescia, Brescia, Italy*
[w] *Medical Oncology Unit 1, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

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* *Corresponding author:* Address: Istituto Nazionale dei Tumori di Milano, Via G Venezian 1, 20133 Milan, Italy. Tel.: +39 0223902557.
E-mail address: giuseppe.procopio@istitutotumori.mi.it (G. Procopio).

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Third-line

Abstract ***Aim:*** A number of targeted therapies (TTs) are effective in metastatic renal cell carcinoma (mRCC) but clinical outcomes with the sequential use of three TTs have been poorly investigated, this study evaluates their outcome.
Methods: Patients with clear cells mRCC treated with three TTs were retrospectively studied. Therapies were classified as vascular endothelial growth factor (VEGF)/vascular endothelial growth factor receptor (VEGFR) or mammalian target of rapamycin inhibitors (mTORi). Progression free survival (PFS), overall survival (OS) and total PFS (tPFS) – defined as the time from start of first-line to progression on third-line treatment – were estimated using the Kaplan–Meier method and curves were compared with log-rank test.
Results: A total of 2065 patients with mRCC were consecutively treated with first-line TT in 23 centres in Italy. Overall 281/2065 patients (13%) were treated with three TTs. Median OS and tPFS were 44.7 and 34.1 months, respectively and were longer in patients receiving the sequence vascular endothelial growth factor inhibitors (VEGFi)–VEGFi–mTORi compared with those receiving VEGFi–mTORi–VEGFi with a statistical difference in OS (50.7 versus 37.8 months, $p = 0.004$; 36.5 versus 29.3 months, $p = 0.059$, respectively).
Conclusions: Few patients received three lines of TTs. The sequence VEGFi–VEGFi–mTORi was associated with improved survival with respect to VEGFi–mTORi–VEGFi and primary resistance to first-line was a negative predictive and prognostic factor.

1. Introduction

Metastatic renal cell carcinoma (mRCC) is a fatal urological cancer with a 5-year survival rate of approximately 10%.[1,2] During the last decade, five vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) inhibitors (VEGFi) – sorafenib, sunitinib, pazopanib, axitinib and bevacizumab (in combination with interferon) – and two mammalian targets of rapamycin inhibitors (mTORi) – temsirolimus and everolimus – have been approved for the treatment of mRCC. Despite the evident benefits of TTs in terms of increased control of disease and response rate, complete responses are rare, with most patients eventually experiencing progression during treatment, leading to subsequent-lines of therapy in attempts for disease control.[3] Use of sorafenib and sunitinib sequentially is now a common clinical practice due to the growing body of evidence for non-minimal cross-resistance between VEGFR inhibitors. In addition, efficacy has been demonstrated by shifting to a drug with another mechanism of action such as mTOR inhibitors.[4–6] There are to date limited published data on the sequential use of three TTs in the treatment of mRCC.[7–9] Of these, one retrospective study reported that patients who received third-line sorafenib after sunitinib and everolimus or temsirolimus showed a disease control rate (complete responses plus partial responses plus stable disease) of 44% with a favourable toxicity profile.[9]

The aims of this study were to: investigate the numbers of patients receiving three TTs in some of the referral centres in Italy; determine clinical outcomes in those patients receiving three TTs; report outcomes in terms of disease control and overall survival (OS) based on the type of sequences used and assess differences in efficacy between the treatment strategies.

2. Patients and methods

2.1. Patients

We retrospectively reviewed data from patients with mRCC consecutively treated with three TTs at several of the main centres involved in treatment of kidney cancer in Italy. Data were extracted by the database of each centre. Only patients with clear cell histology and measurable disease were included; no other eligibility/exclusion criteria were applied. For each patient the following data were recorded: date of nephrectomy, initial prognostic score based on Motzer criteria,[10] type and length of first-, second- and third-line therapy. Therapies were classified based on the two main mechanisms of action: VEGFi (axitinib, bevacizumab, pazopanib, sorafenib, and sunitinib) or mTORi (everolimus and temsirolimus) or by the specific drug used. Targeted agents were given according to standard recommendation and all drugs were administered orally with the exception of bevacizumab and temsirolimus that were administered intravenously and interferon sub-cutaneously. Standard dose reductions were applied in the case of toxicity. The choice of the sequence of therapy was decided by the clinicians.

Two main sequences were analysed: VEGFi–VEGFi–mTORi and VEGFi–mTORi–VEGFi. Patients treated with a different sequence were not considered in the analysis of clinical outcomes. A supplementary analysis was also performed considering specific molecules from each class and the three most frequently used sequences

Table 1
Baseline characteristic of the patients.

	All patients ($n = 281$)	Sequence		χ^2 test p-Value
		VEGFi–VEGFi–mTORi $N = 152$	VEGFi–mTORi–VEGFi $N = 95$	
Median age (years)	60.6 (IQR = 52.2–68.5)	59.6 (IQR = 51.1–68.1)	60.5 (IQR = 54.6–67.6)	0.53[§]
Male sex	74.2%	72.5%	80.5%	0.45
Metastatic at diagnosis	37.7%	34.9%	41.1%	0.33
MSKCC prognostic group				0.07
Good	46%	50.4%	45.65%	
Intermediate	48%	47.5%	45.6%	
Poor	6%	2.1%	8.8%	
PFS first-line (months)	11.7	12.1	11.3	0.54[*]
Response at first-line				0.42
Partial	45.5%	48%	41%	
Primary resistance	12%	10.7%	15%	

IQR = interquartile range; MSKCC = Memorial Sloan Kettering Cancer Centre; PFS = progression free survival; VEGFRi Vascular endothelial growth factor inhibitors; mTORi mammalian target of rapamycin inhibitors (mTORi).
[*] Log-rank test.
[§] t-Test.

in clinical practice were analysed: sunitinib–sorafenib–everolimus (SuSoEv), sorafenib–sunitinib–everolimus (SoSuEv) or sunitinib–everolimus–sorafenib (SuEvSo).

2.2. Outcome measurements and statistical analysis

Amongst patients who started a first-line of TT we evaluated the proportion of patients who then went on to receive three lines of TTs. Progression free survival (PFS), OS, and total PFS (tPFS) were evaluated. PFS was defined as the time from the beginning of treatment to the first documentation of disease progression or to death by any cause, whichever occurred first. OS was defined as the time from the beginning of treatment to death or last contact. The tPFS was defined as time from the beginning of first-line therapy to the first documentation of disease progression or to death by any cause at third-line. Response to therapy was assessed by computed tomography (CT) or magnetic resonance imaging (MRI) carried out according to local procedures every 8–12 weeks using the Response Evaluation Criteria in Solid Tumours (RECIST) v 1.0.[11] Disease progression was defined as $\geqslant$20% increase of the longer diameter as for RECIST 1.0.[11] Primary resistance was defined as the progression of disease as best response at first evaluation.

2.3. Statistical analysis

Values were expressed as median and interquartile range (IQR). PFS, tPFS and OS were estimated using the Kaplan–Meier method with Rothman's 95% confidence intervals (CIs) and compared across the groups using the log-rank test. The Chi-Square test or t-test was used to assess differences between groups as appropriate. Cox proportional hazards models were applied to explore patient characteristics. Predictors of tPFS and OS in univariate- and multivariable-adjusted analysis were evaluated using a stepwise selection approach with type I error of 0.05 for model entry and 0.10 for elimination. Additional elimination was applied to identify significant variables. A p-value < 0.05 was considered statistically significant. PASW (Predictive Analytics SoftWare) (v 18; IBM SPSS) was used.

3. Results

3.1. Patient characteristics

Only 281 out of 2065 (13.6%) patients with mRCC received three lines of TTs in 23 centres in Italy from August 2006 to June 2011 and were considered for this analysis (Table 1).

Prognosis at the start of first-line was classified as good in 46%, intermediate in 48% and poor in 6% of patients based on Memorial Sloan Kettering Cancer Centre (MSKCC) criteria. Median OS was 44.7 months (95% CI, 39.4–49.9) in the entire cohort and when stratified for MSKCC prognostic criteria was 59.9 months (95% CI, 45.0–74.7) in the good prognosis group, 38.8 months (95% CI, 33.5–44.0) in the intermediate and 24.6 (95% CI, 18.7–30.5) in the poor prognosis group.

Analysis of response rate showed that the number of patients who had a partial response by line of therapy was 45.5% at first-line, 22.7% at second-line and 11.2% at third-line. The percentage of patients who were refractory to therapy increased from 12% at first-line to 27.5% and 30.1% at second- and third-lines, respectively. No difference in terms of partial response or inci-

dence of primary resistance at first-line was found in patients treated with the sequence VEGFi–VEGFi–mTORi or VEGFi–mTORi–VEGFi (Table 1). A the time of analysis 207 out 281 patients progressed and 150 out 281 patients are alive. Median survival was longer in patients who had a partial response compared to stable disease or progression of disease at first-line: 51.4 versus 41.6 versus 32.1 months, respectively ($p < 0.001$).

3.2. Treatment sequences

The percentages of patients who received VEGFi or mTORi were 97.5% and 2.5% at first-line, 62.2% and 37.8% at second-line and 43.9% and 56.1% at third-line, respectively. Of these, 152 (54%) patients received the sequence VEGFi–VEGFi–mTORi and 95 (33%) received the sequence VEGFi–mTORi–VEGFi (Fig. 1). There were no significant differences in terms of demographic and prognostic characteristics between the two groups (Table 1).

Overall 71 (25.3%) patients received the sequence SuSoEv, 56 (19.9%) received the sequence SuEvSo and 44 (15.7%) received SoSuEv. The remaining patients (about 40%) received several combinations with other TTs at first-line, such as bevacizumab, pazopanib or temsirolimus or second-line with temsirolimus. Median PFS rates by line of therapy were: 11.7 months (95% CI, 10.8–12.6) with first-line, 6.7 months (95% CI, 5.8–7.8) with second-line and 6.1 months (95% CI, 5.3–6.9) with third-line (Table 2). Data about PFS for each molecule and line of therapy are reported in Table 2.

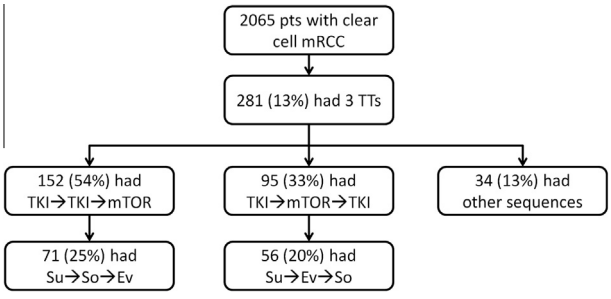

Fig. 1. Flowchart of sequences of therapy received by patients.

3.3. Sequence efficacy

Median tPFS and OS were 36.5 months (95% CI, 30.5–42.6) and 50.7 months (95% CI, 40.6–60.8) for VEGFi–VEGFi–mTORi compared with 29.3 months (95% CI, 23.6–34.9) and 37.8 months (95% CI, 34.2–41.5) for VEGFi–mTORi–VEGFi (Fig. 2). Differences in OS were significant ($p = 0.004$) but differences in tPFS were not ($p = 0.059$). When patients were stratified according to baseline MSKCC prognostic group, tPFS and OS were longer in the good prognosis group treated with VEGFi–VEGFi–mTORi compared with the VEGFi–mTORi–VEGFi group (43.6 versus 42.0 months for tPFS, $p = 0.028$ and 64.9 versus 45.4 months for OS, $p = 0.006$). No significant differences were recorded in the intermediate and poor prognostic groups.

Median tPFS was 42.1 months (95% CI, 31.8–52.4) in patients who received SuSoEv, 30.4 months (95% CI, 26.3–34.5) in patients who received SuEvSo and 46.7 months (95% CI, 42.1–51.2) in the patients who received SoSuEv. No differences in terms of tPFS were detected in patients receiving SuSoEv and SoSuEv. There were significant differences when the sequences SuSoEv or SoSuEv were compared to SuEvSo ($p = 0.006$ and $p < 0.001$ respectively) (Fig. 3). Median OS was not reached in the group treated with SuSoEv compared to 35.6 months (95% CI, 31.6–39.6) in the group treated with SuEvSo and 55.8 months (95% CI, 46.7–64.8) in the group treated with SoSuEv. There were no differences in tPFS when sunitinib or sorafenib were used first, but there were significant differences in OS when SuSoEv or SoSuEv were compared to SuEvSo (both $p < 0.001$) (Fig. 3). When anti-angiogenic inhibitors were followed by an mTOR inhibitor there was an increase in the probability of survival compared to when VEGFi and mTORi were used alternatively (hazard ratio (HR): 1.52, 95% CI, 1.09–2.12; $p = 0.013$) with the sequence SuSoEv doubling the probability of survival compared to the sequence SuEvSo (HR: 2.70, 95% CI, 1.53–4.77).

Table 2
Patients ($n = 281$), type of therapy and progression free survival (PFS) at first, second- and third-line of therapy. PFS was only reported if more than 2% of patients were treated with a drug.

	First line		Second-line		Third-line	
	Patients (%)	PFS (months)	Patients (%)	PFS (months)	Patients (%)	PFS (months)
Sunitinib	62.5	11.0	28.1	11.2	7.5	9.8
Sorafenib	22.9	13.3	33.1	7.7	32.5	5.2
Bevacizumab	9.6	11.4	/	/	/	/
Everolimus	/	/	27.8	4.8	51.1	7.0
Temsirolimus	2.5	7.2	10	3.6	5.0	2.6

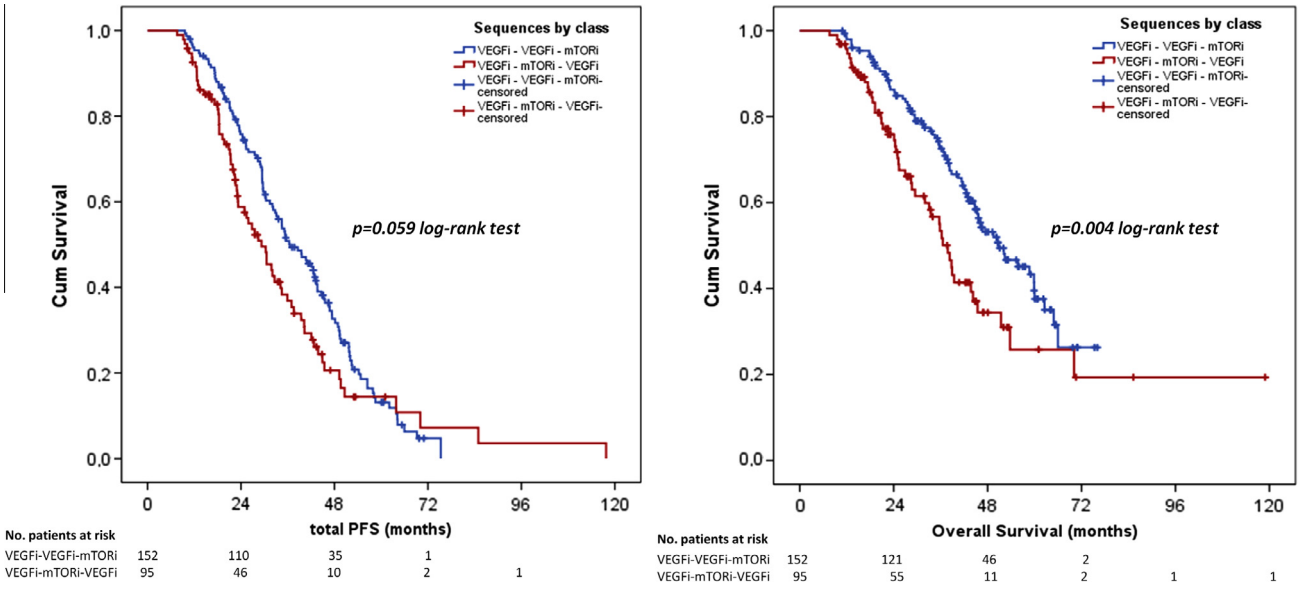

Fig. 2. Total progression free survival (tPFS) and overall survival (OS) considering two sequence classes: vascular endothelial growth factor inhibitors (VEGFi)–VEGFi–mammalian target of rapamycin inhibitors (mTORi) (blue) and VEGFi–mTORi–VEGFi (red). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.4. Univariate and multivariable Cox analyses

The main predictor of tPFS was primary resistance to first-line therapy (HR: 3.15; 95% CI, 1.98–4.99. $p < 0.001$) (Table 3). Factors found to be predictors of OS were initial prognostic group by MSKCC (HR: 2.07; 95% CI, 1.41–3.05. $p < 0.001$), primary resistance at first-line (HR: 2.20; 95% CI, 1.16–4.11. $p = 0.026$) and sequence of therapy (HR: 2.59; 95% CI, 1.59–4.22. $p < 0.001$).

4. Discussion

In recent years the treatment of mRCC has been characterised by results from a number of trials that have increased the possibility of treating kidney cancer. Despite this progress, the majority of new agents have been tested as first-line therapies and only very recently the RECORD1 and AXIS trials have shown efficacy of an mTOR inhibitor and a tyrosine kinase inhibitor (TKi) after failure of first-line treatment with sunitinib.[12,13] The RECORD1 trial, when everolimus (versus placebo) was administered to patients previously treated with one or more therapies, reported an increase in PFS as compared to the placebo. Results in mRCC patients in the third-line setting showed that increased disease control as well as improvements in quality of life are possible by changing the class of agent.[12] Similarly, the AXIS trial recently confirmed the activity of two TKi agents used sequentially as previously demonstrated in a large number of retrospective analyses.[13]

The results of the largest phase III trial (INTORSECT) that compared a VEGFi with an mTORi as second-line therapy after sunitinib progression were recently reported.[14] This study randomised a total of 512 patients to receive temsirolimus or sorafenib after sunitinib progression. The primary end-point was to report an improvement of PFS in favour of temsirolimus, but results showed that there was no significant difference in terms of PFS between the two therapies (4.28 versus 3.91 months; $p = 0.19$). On the contrary, an improvement in OS was reported in favour of sorafenib (16.4 versus 12.3 months, $p = 0.014$).

Unfortunately, these data are not directly transferable in clinical practice considering the lack of data about the comparison between temsirolimus and everolimus. As result of this evidence, entropy in the area of kidney cancer therapy has increased and the optimal treatment sequence dilemma – 'to shift to an mTOR or to persevere on angiogenesis inhibition', is still unresolved.[15,16]

This study, to the best of our knowledge, is the first report of the incidence of patients with mRCC receiving three TTs and as such shows a relatively long median survival of about 44 months compared to the previous large trial which reported a median survival of 22 months.[17] This suggests that patients who receive three lines of TTs have more favourable prognostic characteristics compared to those who did not. The activity of first-line sunitinib and bevacizumab reported in our analysis was comparable to results from the main regulatory phase III trials,[18,19] as well as for PFS of second-line with everolimus.[9] We observed longer PFS rates in patients who received VEGFi in the second- and third-line as evidenced by the particularly good outcomes with sorafenib thus confirming the recent results

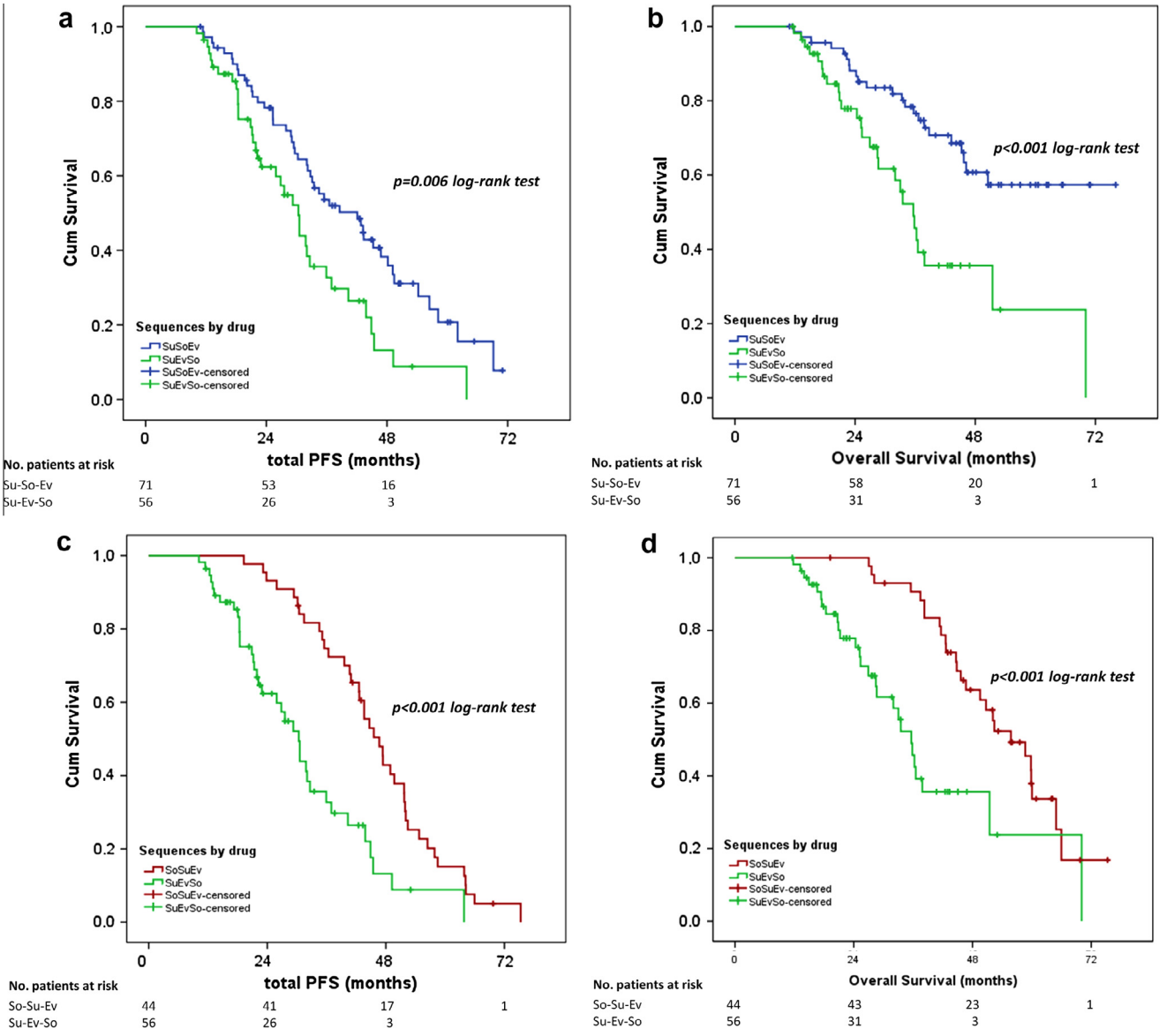

Fig. 3. Total progression free survival (tPFS) and overall survival (OS) of sequence by drugs: (a) tPFS of SuSoEv compared to SuEvSo; (b) OS of SuSoEv compared to SuEvSo; (c) tPFS of SoSuEv compared to SuEvSo; (d) OS of SoSuEv compared to SuEvSo. SuSoEv = sunitinib–sorafenib–everolimus (blue); SuEvSo = sunitinib–everolimus–sorafenib (green); SoSuEv = sorafenib–sunitinib–everolimus (red). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

from AXIS and TIVO 1 trials that have compared the activity of axitinib or tivozanib respectively versus sorafenib.[13,20–22] In fact we observed that the use of two sequential anti-angiogenic inhibitors followed by an mTOR inhibitor increased the probability of survival compared to the alternate use of VEGFi and mTORi. These data were confirmed when single agents were considered with the sequence SuSoEv doubling the probability of survival compared to the sequence SuEvSo suggesting the lack of cross resistance between VEGFi. Our results are in line with the findings of the INTORSECT trial, particularly, we reach a similar result comparing sorafenib with everolimus, the most used mTORi in the second-line. Even if these results are not immediately comparable, we agree that the use of two VEGFis may confer a better outcome in patients with mRCC.[14]

To our knowledge, this is the largest study to date comparing the effects of two sequences of three TTs. Two retrospective studies recently compared the activity of a second VEGF/VEGFR with an mTOR inhibitor after the failure of a first-line anti-angiogenic agent.[23] Busch et al. analysed 108 patients treated with sorafenib or sunitinib as first-line therapy who subsequently received sunitinib or sorafenib (43%) or everolimus (57%).[23] The sequence therapies of TKi/everolimus and TKi/rTKi appeared to be efficacious in terms of PFS and response rate, whereas there was a tendency towards superior survival with the sequence TKi/EV (29.0 versus 43.0 months; $p = 0.034$). Unfortunately

Table 3
Univariate and multivariable analysis of predictors of total progression free survival (tPFS) and overall survival (OS).

	Univariate Cox regression		Multivariable Cox regression	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
tPFS				
Age	0.91 (0.84–0.98)	0.009	0.99 (0.98–1.01)	0.22
Sex	1.09 (0.75–1.59)	0.65		
MSKCC group	12.12 (1.08–135.9)	0.43		
Sequence of therapy*	1.34 (0.99–1.81)	0.06		
Primary resistant first-line	3.11 (1.96–4.92)	<0.001	3.15 (1.98–4.99)	<0.001
OS				
Age	0.99 (0.97–1.00)	0.12		
Sex	1.04 (0.65–1.66)	0.89		
MSKCC group	2.28 (1.67–3.11)	<0.001	2.07 (1.41–3.05)	<0.001
Sequence of therapy*	1.71 (1.19–2.48)	0.004	2.59 (1.59–4.22)	<0.001
Primary resistant first-line	3.04 (1.74–5.31)	<0.001	2.20 (1.16–4.11)	0.026

TTSF = time to strategy failure; OS = overall survival; HR = hazard ratio; CI = confidence interval; MSKCC = Memorial Sloan Kettering Cancer Centre prognostic classification (good versus intermediate versus poor).
* Sequences are: vascular endothelial growth factor inhibitors (VEGFi)–VEGFi–mammalian target of rapamycin inhibitors (mTORi) compared to VEGFi–mTORi–VEGFi.

these data might be negatively influenced by a higher number of patients primarily resistant to first-line in the TKi–TKi group.[23] Similarly, Vickers et al. compared 216 patients treated with a second-line TKi or an mTORi after a first-line TKi.[24] They reported that the time to treatment failure influenced the use of a second TKi therapy compared to the use of an mTORi in second-line but no statistically significant benefit was found in terms of OS.[24] Both studies explored the presence of predictive factors and they found that patient condition at baseline and primary resistance to the first-line agent were the main factors predicting the possibility of receiving a second-line and to have a longer PFS and OS at second-line.[23,24]

Recently, Busch et al. reported the results of a retrospective analysis in 103 patients treated with the sequence VEGFi–mTORi–VEGFi or VEGFi–VEGFi–mTORi. tPFS was 30.4 versus 21.0 months respectively ($p = 0.003$) but no significant differences in terms of OS were reported. Interestingly, PFS at first-line was significantly longer in patients treated with the sequence VEGFi–mTORi–VEGFi compared to VEGFi–VEGFi–mTORi (11.0 versus 8.2 months, $p = 0.016$), and multivariable analysis confirmed the negative predictive role of primary resistance, highlighting the fact that control of disease at first-line may impact on the efficacy of subsequent-lines of therapy.[7]

Primary resistance is a growing problem in the management of mRCC – first-line phase III trials have shown that about 20% of patients are refractory to anti-angiogenic agents and this clearly has a negative effect on survival.[25] In this retrospective study, a lower incidence of primary resistance (12%) was found, suggesting that patients receiving three TTs may have better prognostic characteristics and higher sensitivity to therapy. Despite this, our results confirm its negative predictive and prognostic role also in patients who receive three TTs. In our cohort a sensitivity analysis, performed to evaluate the differences between sequences in non-primary refractory patients, confirmed improved OS in the VEGFi–VEGFi–mTORi group compared to the VEGFi–mTORi–VEGFi (52.1 versus 38.8 months).

The main result of this study is that the sequence VEGFi–VEGFi–mTORi increased survival in patients who received three TTs particularly in those with good prognostic risk at the time of diagnosis of metastatic disease. Unfortunately, the correct sequence of VEGFis remains an unanswered question. In line with a recent pooled analysis and other retrospective analyses[26,27], this study revealed improved disease control when sunitinib was used after sorafenib but the retrospective nature of this and other studies limits the validity of this conclusion. Perhaps the results of the SWITCH trial, in which patients were randomised to receive sorafenib followed by sunitinib or vice versa will provide insight into the optimal sequence of these two VEGFis.

Finally, this study is not without limitations. It is a retrospective study in selected patients who were fit enough to receive three TTs. There is no survival comparison between these patients receiving three TTs with that of the majority of patients in the overall population with mRCC treated with one or two agents over the same period of time. Is important to note that reported sequences may be influenced by the modality of access to second- and third-lines treatment in Italy. Generally, sorafenib and sunitinib may be prescribed as firs as well as second-line and everolimus after one or two previous VEGFis, moreover sorafenib may be prescribed as third-line and the same was for sunitinib as rechallenge in patient with a proved response to first-line. We found that patients treated before the approval of everolimus (June 2010) had major probability to receive a TKI compared to mTOR, but no difference was present in terms of PFS in patients treated with second-line everolimus in

both periods (data not showed). Furthermore, the relatively low numbers of patients included in each sequence group by drug is only hypothesis generating and does not allow definitive conclusions to be made regarding the optimal sequence among those analysed or other possible sequences.

5. Conclusions

Relatively few patients received three TTs compared to the number of patients who started TTs for mRCC in Italy in this time period. Sequential treatment with two anti-angiogenic inhibitors followed by an mTOR inhibitor was associated with improved survival. Resistance to the first-line and Motzer risk group were independent indicators of clinical outcome.

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Conflict of interest statement

Authors report the following conflict of interest:
Iacovelli Roberto: GSK and Bayer.
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Cartenì Giacomo: Pfizer, Novartis, GSK.
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References

1. Lam JS, Leppert JT, Belldegrun AS, Figlin RA. Novel approaches in the therapy of metastatic renal cell carcinoma. *World J Urol* 2005;**23**:202–12.
2. Garcia JA, Rini BI. Recent progress in the management of advanced renal cell carcinoma. *CA Cancer J Clin* 2007;**57**:112–25.
3. Harshman LC, Xie W, Bjarnason GA, et al. Conditional survival of patients with metastatic renal-cell carcinoma treated with VEGF-targeted therapy: a population-based study. *Lancet Oncol* 2012;**13**:927–35.
4. Dudek AZ, Zolnierek J, Dham A, Lindgren BR, Szczylik C. Sequential therapy with sorafenib and sunitinib in renal cell carcinoma. *Cancer* 2009;**115**:61–7.
5. Porta C, Procopio G, Cartenì G, et al. Sequential use of sorafenib and sunitinib in advanced renal-cell carcinoma (RCC): an Italian multicentre retrospective analysis of 189 patient cases. *BJU Int* 2011;**108**:250–7.
6. Calvo E, Ravaud A, Bellmunt J. What is the optimal therapy for patients with metastatic renal cell carcinoma who progress on an initial VEGFr–TKI? *Cancer Treat Rev* 2012 [Epub ahead of print].
7. Busch J, Seidel C, Erber B, et al. Retrospective comparison of triple-sequence therapies in metastatic renal cell carcinoma. *Eur Urol* 2012. http://dx.doi.org/10.1016/j.eururo.2012.09.004, pii: S0302-2838(12)01027-5.
8. Miyake H, Kusuda Y, Harada KI, Sakai I, Fujisawa M. Third-line sunitinib following sequential use of cytokine therapy and sorafenib in Japanese patients with metastatic renal cell carcinoma. *Int J Clin Oncol* 2011 [Epub ahead of print].
9. Di Lorenzo G, Buonerba C, Federico P, et al. Third-line sorafenib after sequential therapy with sunitinib and mTOR inhibitors in metastatic renal cell carcinoma. *Eur Urol* 2010;**58**:906–11.
10. Motzer RJ, Mazumdar M, Bacik J, Berg W, Amsterdam A, Ferrara J. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. *J Clin Oncol* 1999;**17**:2530–40.
11. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;**92**:205–16.
12. Motzer RJ, Escudier B, Oudard S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors. *Cancer* 2010;**116**:4256–65.
13. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet* 2011;**378**:1931–9.
14. Hutson T, Escudier B, Esteban E, et al. Temsirolimus vs. sorafenib as second line therapy in metastatic renal cell carcinoma: results from the INTORSECT trial. *Ann Oncol* 2012;**23**(Suppl. 9), LBA22PR.
15. Porta C. Entropy increases in kidney cancer treatment, but a bit of simplicity may emerge from chaos. *Eur Urol* 2011;**60**:1171–2.
16. Iacovelli R, Palazzo A, Trenta P, et al. Management of metastatic renal cell carcinoma progressed after sunitinib or another antiangiogenic treatment. *Am J Clin Oncol* 2013 [Epub ahead of print].
17. Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. *J Clin Oncol* 2009;**27**:5794–9.
18. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon-alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007;**356**:115–24.
19. Escudier B, Pluzanska A, Koralewski P, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. *Lancet* 2007;**370**:2103–11.
20. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear cell renal-cell carcinoma. *N Engl J Med* 2007;**356**:125–34.
21. Escudier B, Szczylik C, Hutson TE, et al. Randomized phase II trial of first-line treatment with sorafenib versus interferon alfa-2a in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2009;**27**:1280–9.
22. Motzer RJ, Nosov D, Eisen T, et al. Tivozanib versus sorafenib as initial targeted therapy for patients with advanced renal cell

carcinoma: results from a phase III randomized, open-label, multicenter trial. *J Clin Oncol* 2012;**30**(Suppl.; abstr. 4501).
23. Busch J, Seidel C, Kempkensteffen C, et al. Sequence therapy in patients with metastatic renal cell carcinoma: comparison of common targeted treatment options following failure of receptor tyrosine kinase inhibitors. *Eur Urol* 2011;**60**:1163–70.
24. Vickers MM, Choueiri TK, Rogers M, et al. Clinical outcome in metastatic renal cell carcinoma patients after failure of initial vascular endothelial growth factor-targeted therapy. *Urology* 2010;**76**:430–4.
25. Heng DY, MacKenzie MJ, Vaishampayan UN, et al. Primary anti-VEGF-refractory metastatic renal cell carcinoma (mRCC): clinical characteristics, risk factors, and subsequent therapy. *J Clin Oncol* 2011;**29**(Suppl. 7; abstr. 305).
26. Procopio G, Verzoni E, Iacovelli R, Guadalupi V, Gelsomino F, Buzzoni R. Targeted therapies used sequentially in metastatic renal cell cancer: overall results from a large experience. *Expert Rev Anticancer Ther* 2011;**11**:1631–40.
27. Stenner F, Chastonay R, Liewen H, et al. A pooled analysis of sequential therapies with sorafenib and sunitinib in metastatic renal cell carcinoma. *Oncology* 2012;**82**:333–40.