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ORIGINAL ARTICLE

The combination of bevacizumab/temsirolimus after first-line anti-VEGF therapy in advanced renal-cell carcinoma: a clinical and biomarker study

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Abstract

Background Vascular endothelial growth factor (VEGF) targeting represents the standard first-line therapy for metastatic renal-cell carcinoma (mRCC), while blocking the mammalian target of rapamycin (mTOR) is effective in relapsed disease. Since continuing blockade of VEGF may be of value, we studied the combination of bevacizumab with temsirolimus in mRCC patients relapsing after first-line treatment.

Methods A prospective, phase II study of the combination of bevacizumab (10 mg/kg, every 2 weeks) with temsirolimus (25 mg weekly) in patients with mRCC who failed first-line anti-VEGF treatment. 6-month progression-free survival (PFS) rate was the primary end point. The association of VEGFa, VEGFR2, fibroblast growth factor (FGF) b, platelet-derived growth factor receptor (PDGFR) a and PDGFRb with prognostic factors and outcomes were also studied.

Results 39 patients were enrolled. First-line therapy included: sunitinib ($n=16$), bevacizumab/interferon ($n=12$), pazopanib ($n=10$), sorafenib ($n=1$). After a median follow-up of 37 months, 6-month PFS rate was 50.9% [95% confidence interval (CI) 33.8–65.7], median time to progression 6.8 months (95% CI 5.5–9.2) and median overall survival (OS) 18.2 months (95% CI 12.9–27.2). Objective response rate was 27%. The most common AEs were metabolic (33%), renal (8%) and gastrointestinal (GI) (7%). The most common grade 3–5 AEs were GI (18%), infections (14%) and metabolic (25%). Toxicity was the most frequent cause of treatment discontinuation (40%). FGFb levels were associated with OS.

Conclusions In concert with recent data, our study confirms the efficacy of anti-VEGF/anti-mTOR combination in mRCC relapsing after anti-VEGF therapy. Toxicity was considerable leading to high rate of treatment discontinuations.

Trial registration ClinicalTrials.gov: NCT01264341

Keywords Renal cancer · Metastatic · Second-line, temsirolimus · Bevacizumab · FGF

Introduction

Clear-cell renal-cell carcinoma (ccRCC) is characterized by frequent inactivation of the von Hippel Lindau gene [1]. This leads to unrestricted activity of the hypoxia-inducible factor alpha and over production of angiogenic factors, in particular of VEGF and PDGF [2]. Therefore, RCC is an obvious target for anti-angiogenic therapies. The multi-tyrosine kinase inhibitors (TKIs) of VEGF receptor (VEGFR) sunitinib and pazopanib and the combination of the anti-VEGF monoclonal antibody bevacizumab with interferon alfa-2a (IFNa) have been established as a standard first-line treatment for advanced RCC [3–5].

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Despite the undisputed efficacy of these therapies, most patients will relapse and eventually die because of RCC progression. Although several effective agents for relapsed disease exist, the optimal therapy after failure of an anti-angiogenic agent remains undefined, largely because our lack of precise knowledge on the mechanisms leading to the development of resistance to anti-angiogenic therapy. The mammalian target of rapamycin (mTOR) pathway may indirectly increase the production of HIF-a [6] and thus lead to resistance to anti-VEGFR therapies. This notion is supported by the results of a randomized trial, which showed that the mTOR inhibitor (mTORI) everolimus, prolonged PFS compared to placebo following failure of VEGFR TKIs [7]. In addition, preclinical data support the continuous inhibition of the VEGF pathway, since unblocking of VEGF may accelerate disease progression by rapid regrowth of tumor vasculature [8, 9]. In concert, randomized studies in colorectal and lung cancer showed that administration of bevacizumab beyond progression may be beneficial. Finally, a synergistic effect between sunitinib and mTORIs has been shown in experimental models [10]. Taken together, the above data suggest that the combination of an mTORI with anti-VEGF/VEGFR agents may represent an effective strategy in patients failing first-line anti-angiogenic therapy. Selection of patients likely to benefit from targeted therapies is highly desirable. The prediction of outcome should, ideally, be based on molecular factors, which are related to the biological effect of these therapies. Serum levels of VEGF or VEGFR as well as the change of these levels during therapy have been suggested to be of value in this respect [11, 12]. In addition, PDGF and FGF pathways have been implicated in the development of resistance to anti-angiogenic therapy [13–15] and, therefore, the respective levels in the serum may be of predictive value in the treatment of resistant disease.

Considering all the above, we studied the efficacy and safety of a combination of bevacizumab and the mTORI temsirolimus in metastatic ccRCC patients with disease progression after treatment with anti-VEGF/VEGFR therapy. Temsirolimus was preferred instead of everolimus based on the availability of data on the feasibility of this combination [15] at the time of our study design. Furthermore, we studied the predictive value of serum levels of VEGFA, VEGFR2, FGF, PDGFRα and PDGFRβ.

Patients and methods

This was a single-arm, prospective phase II study conducted by the Hellenic Cooperative Oncology Group (HECOG). Patients with metastatic ccRCC, who failed first-line anti-VEGF/VEGFR therapy and had received no second-line therapy were included. Detailed inclusion and exclusion criteria are included in Supplementary material. The study was approved by institutional and national ethics committees and patients gave their written informed consent prior to any procedures related to this protocol. Regarding first-line therapy, initially only the combination of bevacizumab/Interferon-a was allowed. After the enrolment of 9 patients, the protocol was amended due to slow accrual and any anti-VEGF treatment was allowed. In spite of the amendment, accrual remained slow and the completion of the study became difficult due to new therapeutic developments in the field of relapsed mRCC. For these reasons, the study was terminated early after the enrolment of 39 patients.

Treatment

Patients received iv bevacizumab at 10 mg/kg q2w and weekly iv temsirolimus at 25 mg. Treatment was continued until disease progression, intolerable toxicity or consent withdrawal. Tumor assessment was performed every 8 weeks of treatment. Objective responses were confirmed with a second examination, which was performed not earlier than 4 weeks. QoL assessments were performed at baseline and every 2 weeks of treatment.

Treatment with the responsible agent was withheld in case of toxicity grade 3 or 4 and was resumed after resolution to grade 0 or 1, except for the occurrence of special medical conditions (supplemental file) requiring the permanent discontinuation of study drugs. Any temporary discontinuation could last up to 6 weeks. In case of longer discontinuation or two permanent discontinuations of any length, the responsible agent was permanently discontinued. No dose modifications were allowed for bevacizumab. Temsirolimus dose was reduced by 20% in case of treatment interruption. In case of pneumonitis, temsirolimus was reintroduced at 50% of the initial dose after resolution.

ELISA (enzyme-linked immunosorbent assay)

Serum for biomarker studies was obtained prior to the initiation of study treatment. Serum levels of VEGFa, VEGFR2, fibroblast growth factor (FGF) b, platelet-derived growth factor receptor (PDGFR) a and PDGFRb were determined by standard ELISA, as described by the manufacturer, using the following commercial kits: FGF-b (RnD Systems USA), VEGFa, VEGFR2 (E-Biosciences USA), PDGFRa, PDGFRb (Thermo-Scientific, USA).

Statistical design

The primary objective of the study was the evaluation of the efficacy, expressed as 6-month PFS rate. The secondary endpoints of the study were: 12- and 24-month PFS rate, median PFS, OS, RR, safety, and quality of Life

(QoL). Correlative studies of anti-angiogenic parameters and treatment efficacy were also performed. QoL was evaluated using the QLQ C-30 questionnaire (Greek version). Relative dose intensity (RDI) was defined as the ratio of the actual over the anticipated dose intensity (DI) of each drug in the combination. DI was calculated by dividing the administered dose with the duration of therapy in weeks. The anticipated DI for temsirolimus was 25 mg/week, while for bevacizumab 400 mg/kg/week.

Sample size calculation was based on the effectiveness of second-line treatment with the mTOR inhibitor everolimus after previous treatment with anti-angiogenic factors (including bevacizumab) according to the RECORD-1 study, which showed a 6-month PFS rate of 26% for patients receiving monotherapy with everolimus [7]. Assuming that the minimum acceptable value was 30%, a sample of 44 patients was required according to the Fleming's single-stage design to show a clinically relevant absolute increase of at least 20%, when patients are treated with combination bevacizumab/temsirolimus, with a 80% statistical power for a contralateral control type I error $a = 0.05$. Given a withdrawal rate of 5% patients, a total of 47 patients should be included in the study. Methods to assess primary and secondary objectives are depicted in the supplementary material. The prognostic significance of biomarkers was studied by log rank (for categorization around the median value) and regression analysis (as continuous variables).

Results

Patients and treatment exposure

Between Feb 2011 and Apr 2015, 39 patients treated at 7 Greek oncology centers were enrolled. Their baseline characteristics are shown in Table 1.

The median treatment duration was 18 weeks (range 2–65). At the time of analysis, 7 patients were still on treatment. In the remaining 32 patients treatment had been discontinued due to: death ($n = 2$), disease progression ($n = 6$), physician's decision ($n = 3$), toxicity ($n = 13$), while the cause was unknown in 8 cases.

Among 865 scheduled temsirolimus administrations there were 109 (13%) treatment delays or dose reductions due to toxicity reported in 32 (82%) patients. Among 439 scheduled bevacizumab administrations there were 71 (16%) treatment delays due to toxicity reported in 28 (72%) patients. Median RDI for temsirolimus was 79% (37–100) and for bevacizumab 77% (33–100). RDI for both drugs was 100% in only 2 patients who received up to 6 weeks of therapy. RDI of temsirolimus was 100% in another 2 patients.

Efficacy

Median follow-up was 37 months (95% CI 23.5–39.5). The 6-month PFS rate was 50.9% (95% CI 33.8–65.7%). 12 and 24-month PFS rates were: 19.8% (95% CI 8.7–34.1) and 5.7% (95% CI 1–16.6), respectively. The median PFS was 6.8 months (95% CI 5.5–9.2), whereas the median OS was 18.2 months (95% CI 12.9–27.2) (Fig. 1). Thirty-seven patients were evaluable for response. Best responses were: complete-$n = 1$ (2.7%), partial-$n = 9$ (24.3%), stable disease-$n = 20$ (54.1%) and progressive disease-$n = 7$ (18.9%). Neither RR nor PFS or OS were correlated with response to prior anti-VEGFR therapy, pT or Fuhrman grade at nephrectomy.

Toxicity

All patients were assessable for toxicity. Toxicities were reported by all 39 patients. The worst toxicity grade per patient was: 1 (2.5%) grade 1, 20 (51%) grade 2, 15 (39%) grade 3, 1 (2.5%) grade 4 and 2 (5%) grade 5. Four-hundred and fifty-eight adverse events (AEs) were recorded (Table 2). The most common AEs were metabolic (33%), renal (8%) and GI (7%). Twenty-eight grade 3–5 AEs were reported: GI ($n = 5$, 18%), infections ($n = 4$, 14%) and metabolic ($n = 6$, 25%) were the most common. GI toxicity, included one episode of ileus and one of bowel perforation. There were 2 fatal treatment-related events, which were reported as "pneumonia".

Toxicities leading to the 13 treatment discontinuations were: proteinuria ($n = 2$), pulmonary embolism ($n = 1$), pneumonitis ($n = 1$), chest infection ($n = 2$), epistaxis ($n = 1$), GI perforation ($n = 1$), renal toxicity and hypertension ($n = 1$), skin toxicity ($n = 2$), renal toxicity ($n = 1$) and pneumonitis ($n = 1$).

QoL

Two patients did not complete any QoL questionnaire, while 24 patients completed 3 or fewer. Most domains showed no significant changes over time. Specifically, there was no deterioration of most symptoms enquired or of the general health and well-being during therapy. Difficulties in family life due to therapy administered showed a significant increase up to visit 6 ($p = 0.029$), while there was also a significant improvement of weakness between visits 1 and 6 ($p = 0.045$) (Fig. 2).

Correlative biomarker studies

The median serum levels of the biomarkers studied and all correlations with prognostically relevant factors, assessed prior to the initiation of study treatment, are shown in

Table 1 Baseline characteristics of 39 patients enrolled in the study

Characteristic	Median	Range
Age (years)	67	40–80
Duration from initial diagnosis to diagnosis of metastatic disease (months)	2.1	0-98.8
Duration from metastases to start of chemotherapy (months)	9.4	0.3-107.4
	n	%
Sarcomatoid features		
Yes	2	5
No	32	82
Unknown	5	13
Fuhrman grade		
1	1	3
2	6	15
3	15	39
4	9	23
Unknown	8	20
Performance status		
0	27	69
1	10	26
2	2	5
Previous cytokines		
Yes	12	31
No	27	69
First-line therapy		
Sunitinib	16	42
Bevacizumab/interferon-a	12	31
Pazopanib	10	25
Sorafenib	1	2
Best response to first-line		
CR	2	5
PR	6	15
PD	13	33
SD	17	44
NE	1	3
Metastatic sites		
Lung	16	41
Lymph nodes	12	31
Adrenal	5	13
Liver	3	9
Bones	13	33
Renal bed	5	13
Other	4	10
Hgb*		
> 13 for males or > 11.5 for females	21	55
≤ 13 for males or ≤ 11.5 for females	17	45
Calcium*		
> 10	6	16
≤ 10	32	84
ANC*		
> 5000	13	34
≤ 5000	25	66

Table 1 (continued)

	n	%
PLT*		
> 400,000	5	13
≤ 400,000	33	87
IMDC risk stratification*		
Low	5	13
Intermediate	17	45
High	16	42

*Data available for 38 patients

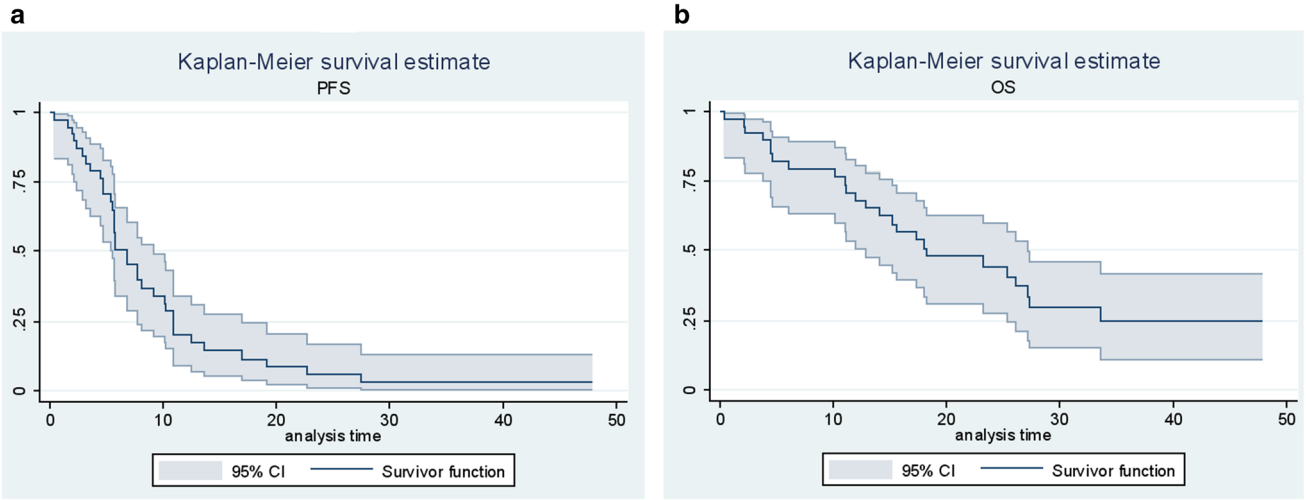

Fig. 1 Kaplan–Meier curves for progression-free (**a**) and overall survival (**b**) of 39 patients with advanced renal-cell carcinoma treated with temsirolimus/bevacizumab after relapse post-first-line anti-VEGF/VEGFR therapy

Table 3. There was no correlation of any biomarker with RR or the IMDC risk stratification. High IL8 levels were associated with poorer PS and anemia, while high FGF levels were also correlated with anemia.

There was no association of any biomarker with PFS or OS when studied as categorical variables. In contrast, when they were studied as continuous variables, there was a significant association of FGF levels and OS: for each unit of FGF increase, there was a 2.4% increase in the risk of death ($p = 0.024$).

Discussion

We showed that the combination of bevacizumab and temsirolimus is active after failure of anti-VEGF/VEGFR therapy. Our results over satisfied our hypothesis of a 20% absolute improvement over RECORD-1 data in spite of the accrual falling short by 8 patients: 6-month PFS rate was 51%, which is almost twofold that of everolimus monotherapy [7]. It should be noted that everolimus was not used in RECORD-1 as a pure second-line therapy as it is the case in our study and therefore, this may have overestimated the increase of our 6-month PFS rate. After the initiation of our study a median PFS of 5.4 months was reported for pure second-line everolimus in a subgroup analysis of RECORD-1 [16]. Still our median PFS of 6.8 months and the RR of 27% (versus 1.8% in the most updated RECORD-1 results [17]) argue for enhanced efficacy by our combination.

Although across-study comparisons cannot lead to definitive conclusions, it is worth noticing that the median PFS (6.8 months) in our study is numerically comparable to those reported for agents which recently emerged and are currently approved for treatment of relapsed disease. In the AXIS trial, axitinib produced a median PFS of 6.5 months after first-line sunitinib [18], while the two most recently approved agents nivolumab and cabozantinib showed respective median PFS of 4.6 and 7.4 months [19, 20]. The median OS in our study (18.2 months) is numerically shorter than those of nivolumab (25 months) and cabozantinib (21.4 months). It

Table 2 Categories and grading of adverse events

Category	Total (%)*	Grade 3–5 (%)**
Hematological		
Anemia	14 (3)	
Neutropenia	15 (3)	2 (7)
Thrombocytopenia	12 (2)	
Biochemical-metabolic		
Hyponatremia	13 (3)	
Hypercholesterolemia	18 (4)	
Hypertriglyceridemia	17 (4)	2 (7)
Hyperglycemia	21 (5)	
Liver toxicity	34 (7)	1 (3)
Metabolic other	49 (11)	3 (11)
Non-hematological, non-biochemical-metabolic		
Gastrointestinal	30 (7)	5 (18)
Pulmonary	20 (5)	2 (7)
Skin	16 (3)	
Renal	38 (8)	1 (3)
Infection	17 (4)	4 (14)
Mucositis	13 (3)	2 (7)
Fatigue	9 (2)	
Hypertension	12 (2)	2 (7)
Neurological	10 (2)	2 (7)
Teeth	7 (1)	1 (3)
Pulmonary embolism	1 (< 1)	1 (3)

*Percentage on total of 458 AEs

**Percentage on total of 28 grade 3 or 4 AEs

should be appreciated that the options for our patients who relapsed after study treatment were more limited than those in the aforementioned studies, since for the longest period of accrual neither axitinib nor nivolumab were available.

Combinations of bevacizumab with both temsirolimus and everolimus, have been studied in first-line [21, 22], but failed to show any superiority compared to the standard bevacizumab/IFN regime. On the contrary, encouraging results with the combination we used, as post-anti-VEGFR treatment failure therapy, were recently reported in two phase II studies [23, 24]. In the first study, the 6-month PFS rate was 40%, median PFS 5.9 months and RR 23%. In the second study a 65% 4-month PFS rate and a median PFS of 5.6 months were reported. These results, combined with ours, suggest that maintaining VEGF/VEGFR blockade may enhance the activity of everolimus. This concept was recently proven in a randomized phase II study, which showed that the combination of the VEGFR TKI lenvatinib with everolimus was superior to everolimus in second-line setting, producing impressive median PFS of 14.6 months and RR of 43% [25]. The higher level of evidence associated with the lenvatinib/everolimus regime together with the convenience offered by an oral combination represents clear advantages compared with the temsirolimus/bevacizumab combination and supports further development and routine use of the former. Nevertheless, taken together, the results of these four studies support the use of anti-VEGFR/mTORI as second-line therapy in mRCC. The reasons for the different results between first and second-line obtained for the combination of VEGFR and mTORIs are not entirely clear. In contrast with its activity in second-line, mTOR inhibition may not be particularly important in first-line, probably due to the dominant role of VEGF in determining tumor behavior. This was suggested by the results of the RECORD-3 study, which showed that the use of everolimus instead of sunitinib in first-line was detrimental. It could, therefore, be speculated that using this

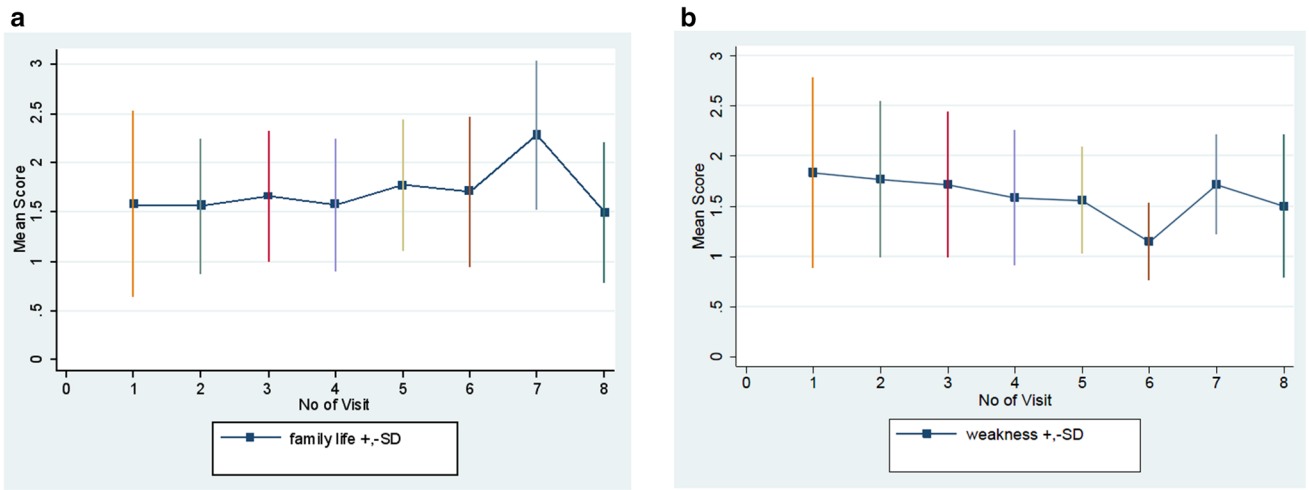

Fig. 2 Changes of family life (**a**) and weakness (**b**) during therapy with temsirolimus/bevacizumab after relapse post-first-line anti-VEGF/VEGFR therapy in 37 patients with advanced renal-cell carcinoma. *X*-axis depicts 2-weekly visits, while bars represent standard deviations

Table 3 Correlations of biomarker serum levels with prognostic characteristics of 36 patients with metastatic renal-cell carcinoma, treated with second-line bevacizumab/temsirolimus

	Medians					
	Il8	VEGFa	VEGFR	FGF	PDGFRa	PDGFRb
Total	12.5	584.8	12764.9	10.1	8.4	2035.7
Response						
CR + PR	9.1	628.9	13371.9	9.5	6.1	2035.7
PD + SD + NE	13.3	584.8	12322.5	10.1	12.2	1955.9
Neutrophils						
≤ 5000	12.2	882.9	12566.2	9.7	12.7	2134.3
> 5000	12.5	575.1	12581.6	9.4	4.3	1953.5
Sex						
Female	11.6	617.5	13385.7	8.2	13.2	2221.5
Male	12.8	576.1	12184.4	11.8	5.3	1799
Age						
≤ 67	12.9	857.5	12,383	13.8	5.7	1979
> 67	12.5	510.4	12968.9	8.1	12.2	2091.9
PS						
0	11.1*	556.7	12643.5	7.9	9.9	2115
≥ 1	19.9	605.5	12792.6	13.6	6	1868.6
Platelets						
≤ 400,000	12.5	605.5	12322.5	8.7	12.2[#]	2091.9
> 400,000	12	325.8	14178.9	17.4	4.3	1938.1
LDH						
Normal	12.7	708.1	12627.1	8.7	8.9	2058.7
Abnormal	10.5	558.9	12338.9	16.2	13.2	2117.1
Ca						
≤ 10	12	605.5	12764.9	10.1	8.4	1945.8
> 10	16.1	576.1	12338.9	3.3	13.8	2156.4
HB						
> limit	10.5[&]	733.4	12948.1	7.6[^]	10.4	2117.1
≤ limit	18.2	584.3	12443.9	16.4	6	1868.6
IMDC risk						
Favorable	12	1223.1	114442.1	6.3	21.8	2582.9
Intermediate	8.1	534.1	13529.9	10	12.2	1890.4
Poor	18.2	584.8	12460.3	12	4.7	1945.8

*$p = 0.024$
[#]$p = 0.026$
[&]$p = 0.015$
[^]$p = 0.022$

combination in second-line is scientifically more rational compared to its use in untreated disease.

In accordance to available data [23–25], toxicity in our study was considerable. Although laboratory abnormalities constituted the most frequent toxicities, clinically more relevant AEs, especially of GI origin, can be of concern. Bowel perforation or bleeding were also reported by Merchan et al. [23] in 4 of 52 patients (8%) who also received bevacizumab/temsirolimus combination. Fatalities attributed to anti-VEGF/mTORI therapy have also been previously reported [25]. We reported two fatal treatment-related events due to pneumonia. Infections have not been frequently reported as SAEs in the aforementioned studies. On the contrary, pneumonitis is a well-known adverse event associated with mTORIs and their combinations. Since differential diagnosis between chest infections and non-infective pneumonitis is not always straightforward, a pneumonitis component cannot be excluded in these two cases. Similarly to other first or second-line studies [21, 23, 24], toxicity resulted in treatment delays in about 80% and permanent discontinuation in 40% of our patients. Toxicity profiles are expected to play an important role in decision-making in the current treatment paradigm in second-line. In this context, discontinuation rates of

nivolumab and cabozantinib have generally been lower than 20% in three reported studies [19, 20, 26].

We found a significant association of FGFb with OS, which is in concert with data from other tumors [27]. FGFb plays a significant role in tumor angiogenesis [28] and it has been implicated in the development of resistance to VEGF pathway inhibition [14]. The value of FGF inhibition in relapsed RCC was studied in a phase III randomized study, which compared the FGF inhibitor dovitinib with the VEGFR TKI sorafenib as third-line therapy [29]. Although dovitinib was not superior to sorafenib, this study confirmed its efficacy. Furthermore, selection based on FGF receptor (FGFR) molecular alterations may increase the efficacy of anti-FGFR agents [30]. We, therefore, believe that our results add to the existing evidence, which suggest that further research on the potential of FGF as a selection biomarker as well as a therapeutic target is warranted.

In conclusion, our study confirms the activity of anti-VEGF/mTORI combinations in advanced ccRCC relapsed after first-line anti-VEGF/VEGFR therapy. The toxicity of these combinations is considerable and this may have an impact in treatment choices in these patients.

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Compliance with ethical standards

Conflict of interest Aristotelis Bamias: Honoraria, Advisory Boards, Research funding: Novartis, Pfizer, Roche, Astra-Zeneca, BMS, Bayer. *Vasilios Karavasilis* Advisory Board: Amgen, Pfizer, Novartis, BI, Lilly, Roche, Astellas, Genesis-Pharma and Janssen. *Gerasimos Aravantinos* Advisory Board: Novartis, BMS, Roche Hellas, Astra Zeneca, Sanofi, Amgen, Genesis Pharma, Merck, Pfizer. Angelos Koutras: Advisory Board: Roche. George Fountzilas. Advisory Board: Pfizer, Sanofi and Roche. Honoraria from Astra-Zeneca. Meletios-Athanassios Dimopoulos: Honoraria, Advisory Board: Janssen, Celgene, Amgen and Takeda.

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