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ORIGINAL ARTICLE

Prognostic factors in second-line targeted therapy for metastatic clear-cell renal cell carcinoma after progression on an anti-vascular endothelial growth factor receptor tyrosine kinase inhibitor

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ABSTRACT

Background: About 40% of metastatic clear-cell renal cell carcinoma (m-ccRCC) patients receive a second-line targeted therapy after failure of anti-vascular endothelial growth factor receptor tyrosine kinase inhibitors (anti-VEGFR-TKI). Efficacy of second-line therapy is usually limited and prognostic and predictive factors at the start of second-line therapy are lacking. To identify the subgroup of patients that will benefit from such treatment remains a challenge.

Methods: We performed a multi-institutional, retrospective study of patients who received a second-line therapy after progression on an anti-VEGFR-TKI. Univariate and multivariate analyses were performed in order to identify prognostic factors for progressive disease (PD) as best response, progression-free survival (PFS) and overall survival (OS) on second-line therapy.

Results: For the whole cohort of 108 patients, mOS from the start of second-line therapy was 8.9 months while mPFS on second-line therapy was 2.8 months. A total of 49/105 (47%) patients had PD, 50/105 (48%) stable disease (SD) and 6/105 (6%) a partial response (PR). On multivariate analysis, the following markers were associated with improved outcome on second-line therapy: a PFS on first-line therapy $\geq$12 months (HR for PFS: 1.961; $p = 0.008$) (HR for OS: 1.724; $p = 0.037$) and Fuhrman grade 1–2 tumors (HR for OS: 2.198; $p = 0.007$). Markers associated with poorer outcome on second-line therapy were: elevated serum lactate dehydrogenase (LDH) levels (HR for PFS: 0.511; $p = 0.04$) (HR for OS: 0.392; $p = 0.017$), low albumin (HR for OS: 0.392; $p = 0.01$) and elevated corrected calcium levels (HR for OS: 0.416; $p = 0.01$). The impact on OS of the Memorial Sloan Kettering Cancer Centre (MSKCC) and International Renal Cell Carcinoma Database Consortium (IMDC) prognostic scores as calculated at start of second-line therapy was validated in our patient series.

Conclusions: Duration of first-line PFS, Fuhrman grade, serum LDH levels, albumin levels, corrected calcium levels and the MSKCC and IMDC scores calculated at start of second-line therapy are prognostic factors for m-ccRCC patients treated with second-line targeted therapy.

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In recent years, several novel therapies targeting the vascular endothelial growth factor (VEGF)- or the mammalian target of rapamycin (mTOR)-pathways have improved the outcome of metastatic clear-cell renal cell carcinoma (m-ccRCC) patients. In the first-line setting, the use of anti-VEGFR-tyrosine kinase inhibitors (TKIs), such as sunitinib [1] or pazopanib [2], or the combination of the anti-VEGF monoclonal antibody bevacizumab with interferon [3], have induced a considerable therapeutic improvement compared to previous standards of care, cytokine therapy with interleukin-2 or interferon-α, leading to an unprecedented median initial duration of disease control of approximately 11 months. Unfortunately, almost all patients eventually experience disease progression and may require subsequent therapies. About 40% of patients progressing on a first-line therapy proceed to a second-line treatment [4,5].

Several compounds, such as axitinib, sorafenib and everolimus, are commonly used in second-line therapy after progression on first-line anti-VEGFR-TKIs. Considering the aggressive behavior of non-treated patients failing VEGF inhibitor treatment, illustrated by the median-progression-free survival (PFS) of only 1.9 months in the placebo-arm of the RECORD-1 trial [6], these drugs seem to show efficacy in a

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Table I. Published efficacy of second-line therapy in metastatic renal cell carcinoma.

	First-line	Second-line	mPFS	mOS	PR	PD
Phase III data						
RECORD-1 [6]	Anti-VEGFR-TKI	Everolimus	5.4 months	NA	NA	NA
AXIS [7]	Sunitinib	Axitinib	4.8 months	15.2 months	NA	NA
		Sorafenib	3.4 months	16.5 months	NA	NA
INTORSECT [8]	Sunitinib	Temsirolimus	4.3 months	12.3 months	8%	23%
		Sorafenib	3.9 months	16.6 months	8%	24%
SWITCH-1 [9]	Sorafenib	Sunitinib	5.4 months	NA	17%	NA
	Sunitinib	Sorafenib	2.8 months	NA	5%	NA
Phase II data						
Rini et al. [11]	Sorafenib	Axitinib	7.4 months	13.6 months	23%	40%
Di Lorenzo et al. [26]	Sunitinib	Sorafenib	3.7 months	7.3 months	9.6%	23%
Rini et al. [27]	Bevacizumab	Sunitinib	6.7 months	10.4 months	23%	8%
RECORD-3 [4]	Sunitinib	Everolimus	2.8 months	NA	NA	NA
Retrospective data						
Levy et al. [5]	All	Anti-VEGFR-TKI	NA	20.8 months	16%	43%
		mTOR-inhibitor	NA	16.6 months		
Vickers et al. [28]	VEGF-targeted therapy	Anti-VEGFR-TKI	4.9 months	14.2 months	NA	NA
		mTOR-inhibitor	2.5 months	10.6 months	NA	NA
Mackenzie et al. [29]	VEGF-targeted therapy	Temsirolimus	3.9 months	11.2 months	5%	30%
Al-Marrawi et al. [22]	VEGF-targeted therapy	VEGF-targeted therapy	3.9 months	NA	11%	>40%
Porta et al. [30]	Sunitinib	Sorafenib	4.2 months	NA	NA	NA
	Sorafenib	Sunitinib	7.9 months	NA	NA	NA
Present study	Anti-VEGFR-TKI	All	2.8 months	8.9 months	6%	47%
		Anti-VEGFR-TKI	2.8 months	8.9 months	6%	47%
		mTOR-inhibitor	2.8 months	9.0 months	5%	47%

Median progression-free survival (PFS) is usually between 3 and 5 months and median OS between 10 and 16 months. Response rate is around 10%. At first evaluation, 23–47% of the patients display progressive disease. Anti-VEGFR-TKI, anti-vascular endothelial growth factor receptor tyrosine kinase inhibitor; mOS, median overall survival; mPFS, median progression-free survival; mTOR-inhibitor, mammalian target of rapamycin inhibitor; NA, not available; PD, progressive disease; PR, partial response; VEGF, vascular endothelial growth factor.

proportion of patients. Nevertheless, the clinical benefit remains modest. In four phase III studies, AXIS [7], INTORSECT [8], SWITCH-1 [9] and RECORD-1 [6,10], mPFS on second-line therapy ranged from 3.4 to 5.4 months, depending on the prescribed drug. Up to 40% of patients will experience PD after the first two months of treatment [5,11]. Partial responses (PR) are rare and only a minority of patients will achieve longer lasting clinical benefit. Table I gives an overview of the modest outcome on second-line therapy in several phase III and II studies as well as in retrospective series. As expected, outcome is better in phase III and II studies compared to retrospective series.

As a consequence, many patients are exposed to the potential side effects of second-line therapy without experiencing clinical benefit. Moreover, the use of ineffective medications is associated with considerable costs. Therefore, beside the question of optimal therapeutic sequence (to continue an anti-VEGFR-TKI in second-line or to switch to an mTOR-inhibitor), there is an urgent need for prognostic and predictive factors prior to the start of second-line therapy, in order to select patients who will (not) benefit from a second-line treatment.

The aim of this retrospective study was to investigate prognostic factors in m-ccRCC patients at the start of second-line therapy after progression on anti-VEGFR-TKIs. Additionally, we aimed to identify a subgroup of patients with limited benefit of second-line therapy and a subgroup with a higher probability of benefit on second-line therapy.

Patients and methods

We performed a multi-institutional, retrospective study conducted in three centers: University Hospitals Leuven in Leuven (Belgium), General Hospital AZ Groeninge in Kortrijk (Belgium) and Centre Hospitalier Régional Universitaire de Strasbourg in Strasbourg (France). We identified all m-ccRCC-patients who started a second-line targeted therapy between March 2006 and February 2015 after progression on an anti-VEGFR-TKI. Patients who received chemotherapy and/or cytokine therapy before the first-line targeted therapy were also eligible. Patients who stopped first-line anti-VEGFR-TKI for toxicity were excluded. The database was closed in July 2015. The study was approved by the ethics committees of the participating hospitals.

The endpoints of our study were response rate (RR) on second-line therapy, mPFS during second-line therapy and mOS from start of second-line therapy. mPFS was calculated as the time between start of therapy until documented progression of disease or death from any cause, whatever occurred first. Patients alive without disease progression were censored at the date of last contact. mOS was calculated as the time from start of second-line therapy until death or last contact, with censoring at last contact. In the vast majority of cases, the radiological evaluation was performed every 8–12 weeks by a thoracic and abdominal computed tomography and assessed according to RECIST 1.0. Best response was assessed in each patient and defined as PD, stable disease (SD) or PR.

We selected clinical and biochemical factors with a validated impact on RR, mPFS and/or mOS in the first-line treatment setting and assessed their prognostic role in patients failing VEGF-targeted therapy. The IMDC and MSKCC prognostic scores were calculated at start of second-line therapy, as well as the different factors that form the basis for these established scores (interval between diagnosis and systemic treatment, performance status, hemoglobin levels, corrected serum calcium levels, serum LDH levels, neutrophil and platelet

Table II. Patient characteristics.

Patient characteristics at diagnosis	
Age, median (range)	59 (30–78)
Male/female ratio	74/34
Renal cell carcinoma at diagnosis	
Fuhrman Grade 1–2	24% (24/102)
Sarcomatoid differentiation ≥25% of tumor volume	9% (9/102)
Treatments	
Nephrectomy	93% (100/108)
Time between diagnosis and systemic therapy <12 months	57% (62/108)
Immunotherapy before first-line anti-VEGFR-TKI	21% (23/108)
First-line anti-VEGFR-TKI	
Sunitinib	70% (76/108)
Pazopanib	17% (18/108)
Sorafenib	13% (14/108)
Second-line therapy	
Everolimus	50% (54/108)
Temsirolimus	4% (4/108)
Axitinib	17% (18/108)
Sorafenib	22% (24/108)
Sunitinib	6% (7/108)
Pazopanib	1% (1/108)
Characteristics at start of second-line targeted therapy	
Site of metastasis	
Presence of bone metastases	44% (47/108)
Presence of brain metastases	15% (16/108)
Presence of glandular metastases (pancreatic, thyroid, adrenal)	18% (19/108)
Baseline CRP-levels ≤5 mg/l	22% (22/101)
Karnofsky PS ≤70	23% (25/108)
Serum albumin ≤3.5 g/dl	24% (25/104)
Neutrophils >4500/mm^3	35% (38/108)
Platelets >400 000/mm^3	10% (11/108)
LDH >1.5xULN	14% (15/107)
Corrected Calcium >10 mg/dl*	17% (18/108)
Low hemoglobin (<13 g/dl for men, <11.5 g/dl for women)	75% (81/108)
MSKCC score at start of second-line therapy	
Good	4% (4/108)
Intermediate	71% (77/108)
Poor	25% (27/108)
IMDC score at start of second-line therapy	
Good	3% (3/107)
Intermediate	68% (73/107)
Poor	29% (31/107)

*For 4 patients, in absence of albumin values, non-corrected calcium was used.

Anti-VEGFR-TKI, anti-vascular endothelial growth factor receptor tyrosine kinase inhibitor; CRP, C-reactive protein. ECOG PS, Eastern cooperative oncology group performance status; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; LDH, lactate deshydrogenase; MSKCC, Memorial Sloan Kettering Cancer Center; mTOR-inhibitor, mammalian target of rapamycin inhibitor; ULN, upper limit of normal.

count), presence of sarcomatoid dedifferentiation in ≥25% of the tumor volume [12], PFS [13] and best response on first-line therapy, the presence of bone metastases [14], brain metastases [15] or glandular metastases (defined as pancreatic, adrenal or thyroid metastases) [16], baseline C-reactive protein (CRP) levels (≤ or > inferior limit of normal, 5 mg/dl) [17] and albumin levels (≤ or > inferior limit of normal, 3.5 g/dl) [18,19] at start of second-line therapy.

Associations between PFS or OS and potential prognostic factors were assessed using Kaplan-Meier estimates and the log-rank test in univariate analysis. Correlations between PD as best response and potential prognostic factors were assessed by Fisher's exact test. A bivariate Cox regression was performed in order to see if the new prognostic markers could add any information to the MSKCC prognostic score. A multivariate Cox regression model was subsequently performed in order to identify independent prognostic factors for PFS and/or OS by using factors with a $p < 0.05$ on univariate analysis. Multivariate analysis was done including the MSKCC or IMDC score and subsequently including the factors composing these scores. The discriminatory power of the models was estimated by the Concordance Probability Estimate (CPE) [20]. Statistical analyses were conducted in GraphPad Prism 6 (GraphPad Software, La Jolla, CA, USA), the XLstat software (Addinsoft, Paris, France) for multivariate analyses, and SAS (version 9.4 of the SAS System for Windows) to calculate the CPE. A p-value of <0.05 was considered significant for the purpose of all statistical analyses.

Results

Included patients

We included 108 patients treated between 2006 and 2015 at three different centers: Leuven ($n = 66$), Kortrijk ($n = 15$) and Strasbourg ($n = 27$). In second-line setting, 58 patients were treated with an mTOR-inhibitor (everolimus in 54 and temsirolimus in four patients) and 50 patients with an anti-VEGFR-TKI (axitinib in 18, sorafenib in 24, pazopanib in one and sunitinib in seven patients). First-line treatment was pazopanib in 18 patients, sorafenib in 14 patients and sunitinib in 76 patients. Median follow-up after start of second-line therapy

Table III. Correlation of scores, previously described factors and potential new factors with early progressive disease, progression-free survival and overall survival.

	Patients with early PD	*p*-value (Fisher Exact)	Median PFS (months)	*p*-value (log-rank) HR	Median OS (months)	*p*-value (log-rank) HR
Scores						
MSKCC score prior to second-line treatment						
Poor	-	-	2.3	0.06	5.5	**<0.0001**
Intermediate	-		2.8		10.2	-
Good	-		10.4		41.9	
MSKCC score prior to second-line treatment						
Poor	62% (16/26)	**0.04**	2.3	**0.04**	5.5	**<0.0001**
Interm/Good	37% (27/73)		3.0	**1.75**	11.0	**3.57**
IMDC score at start of second-line treatment						
Poor	-	-	2.1	0.14	6.2	**0.0003**
Intermediate	-		2.8		10	-
Good	-		10.8		63.4	
IMDC score at start of second-line treatment						
Poor	53% (16/30)	0.52	2.1	0.13	6.2	**0.0001**
Interm/Good	45% (33/74)		2.8		10.2	**2.94**
Factors part of the scores						
Interval diagnosis to systemic therapy						
<12 months	51% (31/61)	0.32	2.7	**0.046**	7.9	**0.01**
>12 months	41% (18/44)		3.5	**0.66**	11.0	**0.58**
Karnofsky PS						
≤70	56% (14/25)	0.28	2.5	0.13	6.1	**0.007**
>70	44% (35/80)		2.8		10.0	**0.45**
Neutrophils						
≤4500/mm^3	43% (30/69)	0.36	3.0	0.29	9.1	0.14
>4500/mm^3	53% (19/36)		2.2		6.8	
Platelets						
>400 000/mm^3	55% (6/11)	0.58	2.7	0.4	7.9	0.45
≤400 000/mm^3	46% (43/94)		2.8		9.0	
Hemoglobin						
Anemia	46% (36/79)	0.69	3.0	0.27	8.1	0.64
No anemia	50% (13/26)		2.8		12.0	
LDH						
>1.5xULN	69% (9/13)	0.08	2.8	**0.009**	4.3	**0.0005**
<1.5xULN	43% (38/89)		2.4	**0.37**	9.9	**0.24**
Corrected calcium						
>10 mg/dl	63% (10/16)	0.17	1.9	0.06	3.5	**<0.0001**
≤10 mg/dl	44% (39/89)		3.0		10.0	**0.14**
Potential new factors						
Fuhrman grade						
1–2	38% (9/24)	0.37	6.0	0.11	13.0	**0.045**
3–4	48% (36/75)		2.7		7.9	**1.59**
Sarcomatoid component						
>25%	66% (6/9)	0.3	1.8	**0.03**	5.2	**0.009**
<25%	46% (41/90)		2.8	**0.33**	10.0	**0.26**
PFS with first-line therapy						
<12 months	51% (34/67)	0.31	2.7	**0.001**	6.5	**0.005**
≥12 months	39% (15/38)		5.3	**2.08**	14.0	**1.82**
Best response during first-line						
PD	43% (9/21)	0.1	3.0	0.96	8.9	0.18
SD	50% (19/38)		2.7		6.1	
PR	48% (21/44)		2.8		12.0	
CRP						
>5 mg/l	51% (39/76)	0.15	2.7	0.3	6.6	**0.04**
≤5 mg/l	32% (7/22)		3.5		14.6	**1.64**
Albumine						
≤3.5 g/dl	60% (15/25)	0.17	2.6	**0.02**	4.1	**<0.0001**
>3.5 g/dl	42% (32/76)		3.5	**0.49**	12.0	**0.14**
Bone metastases						
No	49% (29/59)	0.56	2.8	0.06	9.1	0.68
Yes	43% (20/46)		3.5		8.1	
Brain metastases						
Yes	73% (11/15)	**0.03**	2.0	0.1	5.1	0.06
No	42% (38/90)		3.0		9.1	
Glandular metastases						
No	51% (44/87)	0.08	2.7	**0.03**	7.6	**0.02**
Yes	28% (5/18)		6.0	**0.59**	14.0	**0.56**

CRP, C-reactive protein; HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; LDH, lactate deshydrogenase; MSKCC, Memorial Sloan Kettering Cancer Center; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; PS, performance status; SD, stable disease; ULN, upper limit of normal.

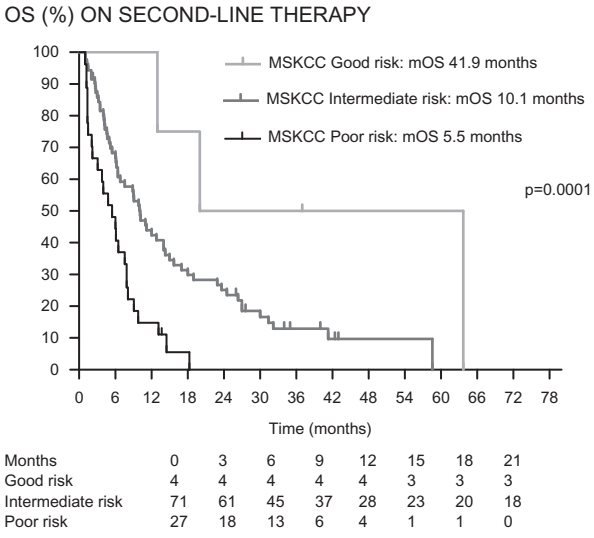
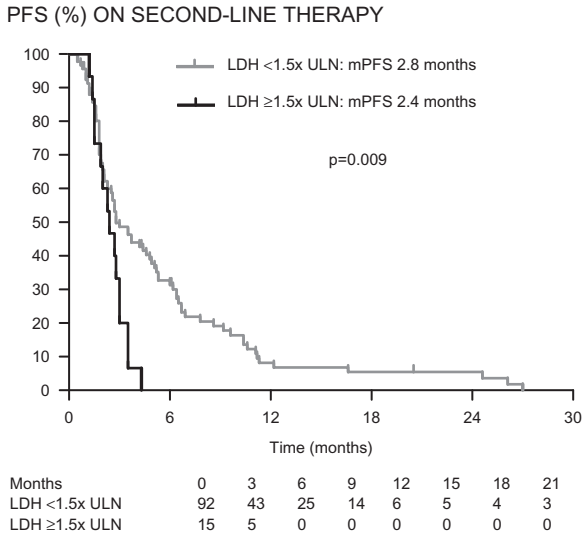


Figure 1. Validation of the impact of the MSKCC score as calculated at start of second-line therapy on overall survival.



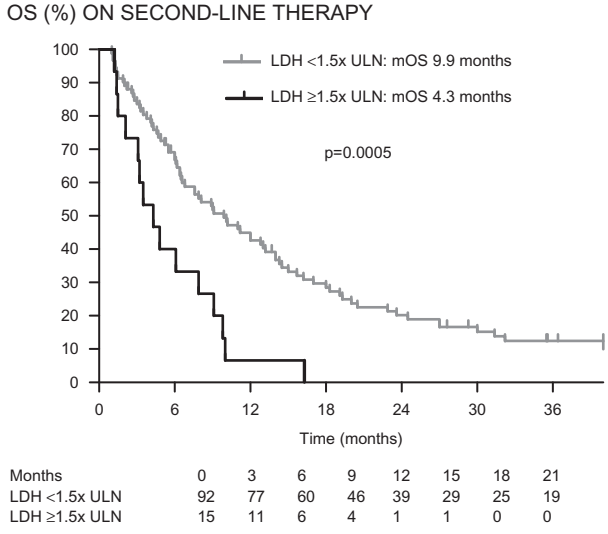


Figure 2. Kaplan-Meier estimates showing the poor outcome on second-line therapy in patients with elevated baseline lactate dehydrogenase.

was 40 months (range 1–64). Median PFS on first-line therapy was 8.3 months and median OS from the start of the first-line therapy 22.9 months. Key patient characteristics are reported in Table II. Global median PFS on second-line therapy was only 2.8 months. Global median OS from start of second-line therapy was 8.9 months. Best response on second-line therapy was as follows: 49/105 (47%) patients had PD, 50/105 (48%) had SD and 6/105 (6%) had a PR. Best response to second-line therapy was not evaluable in three patients. At the time of the analysis 98 of 108 patients (91%) had reached progression and 95 of 108 (88%) patients had died. Three patients remained on second-line therapy for more than 24 months.

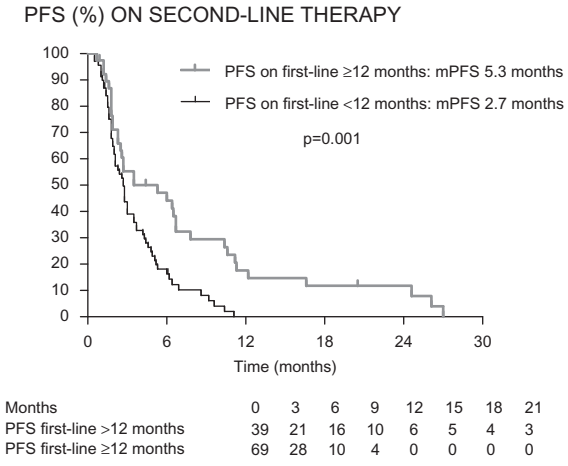
Impact of the MSKCC and IMDC prognostic scores

In the total series, only few patients had an MSKCC ($n = 4$) or IMDC ($n = 3$) good prognosis, as calculated at start of second-line therapy: most had intermediate or poor risk. On univariate analysis (Table III), the MSKCC prognostic score was significantly associated with OS: mOS 41.9 months for good, 10.2 months for intermediate and 5.5 months for poor risk patients ($p < 0.0001$) (Figure 1). Similarly, the IMDC prognostic score was associated with OS (mOS 63.4, 10.0 and 6.2 months, respectively; $p = 0.0003$). The impact of the MSKCC or IMDC scores on PFS was less important. mPFS was 10.4, 2.8 and 2.3 months in MSKCC good, intermediate and poor risk patients ($p = 0.06$) and 10.8, 2.8 and 2.1 months in IMDC good, intermediate and poor risk patients ($p = 0.14$). When comparing MSKCC good and intermediate risk versus poor risk patients, the difference in PFS was statistically significant ($p = 0.04$), but clinically not significant (mPFS 3.0 vs. 2.3 months), although patients with a poor MSKCC risk prognosis had more often (62%) early PD on second-line therapy compared to patients with good or intermediate MSKCC prognosis (37%; $p = 0.04$). Similarly, when comparing IMDC good and intermediate versus poor risk patients, the difference in PFS was statistically nor clinically significant. As a consequence, the MSKCC and IMDC score did not permit us to define a subgroup with a high probability of poor or good PFS on second-line therapy. Moreover, even in the MSKCC or IMDC poor risk subgroups, some patients can have benefited from second-line therapy. Therefore, we intended to define additional prognostic factors besides the MSKCC score and to improve the prognostic value of the MSKCC score in second-line therapy, both for PFS as for OS.

Study of the correlation of factors with PFS

Concerning factors included in the MSKCC and IMDC scores, on univariate analysis (Table III), time between initial diagnosis and start of systemic therapy <12 months ($p = 0.046$) and elevated baseline LDH-activity ($p = 0.009$) were associated with shorter PFS. The PFS-curve shows that all the patients with elevated LDH had a short PFS (Figure 2).

Concerning potential new prognostic factors for PFS, on univariate analysis, the presence of glandular metastases ($p = 0.03$) and a PFS on first-line therapy ≥12 months ($p = 0.001$) (Figure 3) were associated with longer PFS. The presence of sarcomatoid dedifferentiation ≥25% ($p = 0.03$) and low albumin levels ($p = 0.02$) were associated with shorter PFS.



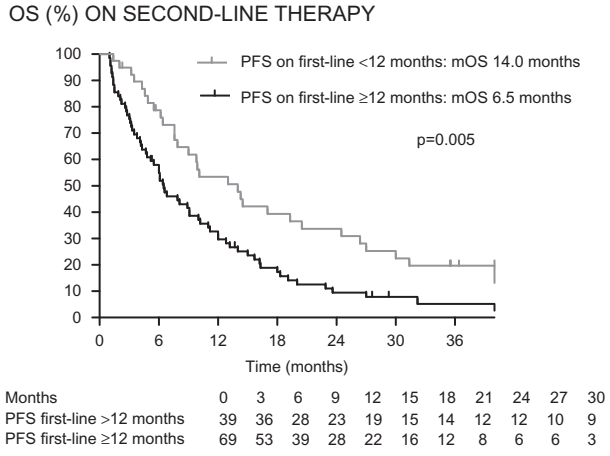
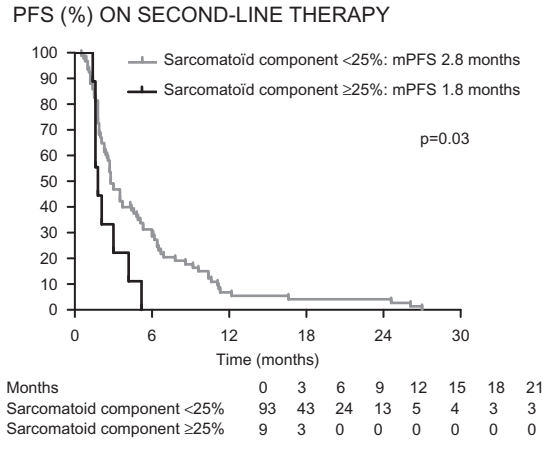


Figure 3. Kaplan-Meier estimates showing the correlation between progression-free survival on first-line therapy and outcome on second-line therapy.



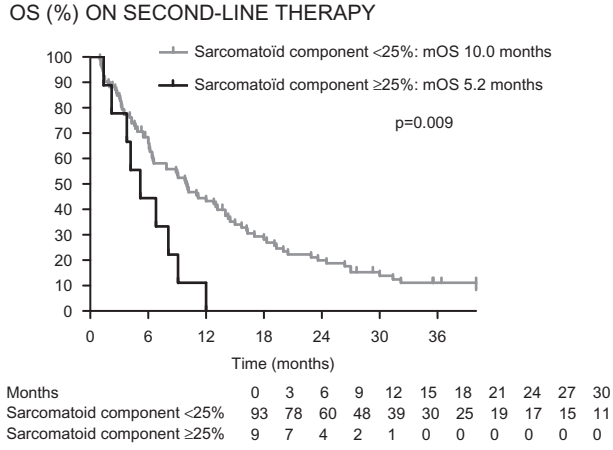


Figure 4. Kaplan-Meier estimates showing the poor outcome on second-line therapy in patients with tumors with an important sarcomatoid component (≥25% of tumor volume).

Figure 4 shows that all patients with a sarcomatoid tumor component of ≥25% had a short PFS. Patients with brain metastases had more often early PD than patients without brain metastases ($p = 0.03$). In a bivariate analysis with the MSKCC score, the presence of a sarcomatoid component ≥25% ($p = 0.047$) and a longer PFS on first-line therapy ($p = 0.002$) remained as independent prognostic factors for PFS (Table IV).

On multivariate analysis including PFS on first-line therapy, sarcomatoid dedifferentiation, the presence of glandular metastases, albumin levels and the MSKCC prognostic score, PFS on first-line therapy ≥12 months ($p = 0.007$) was independently associated with PFS (Table V). On multivariate analysis including PFS on first-line therapy, sarcomatoid dedifferentiation, the presence of glandular metastases, baseline LDH-activity, albumin levels and time between initial diagnosis and start of systemic therapy <12 months, LDH-activity ($p = 0.04$) and PFS on first-line therapy ≥12 months ($p = 0.008$) were associated with PFS (Table VI).

Study of the correlation of factors with OS

Concerning factors included in the MSKCC and IMDC scores, time between initial diagnosis and start of systemic therapy <12 months ($p = 0.01$), elevated baseline LDH-activity ($p = 0.0005$), Karnofsky PS ≤70 ($p = 0.007$) and elevated baseline corrected calcium ($p < 0.0002$) were associated with shorter OS (Table III). Comparing patients with normal LDH to patients with elevated LDH, the HR for survival was as low as 0.14. Moreover the OS-curve shows that all but one patient with elevated LDH died within 10 months after the start of second-line therapy (Figure 2).

On univariate analysis, several new prognostic factors associated with a shorter OS were discovered: the presence of a sarcomatoid component >25% ($p = 0.009$), an elevated CRP ($p = 0.04$), and low albumin levels ($p < 0.0001$). All patients with a sarcomatoid tumor component of ≥25% (Figure 4) or a decreased albumin level (Figure 5) experienced a short survival. Fuhrman grade 1–2 tumors ($p = 0.045$), a PFS on first-line therapy ≥12 months ($p = 0.005$) (Figure 3) and the presence of glandular metastases ($p = 0.02$) were associated with longer OS. In a bivariate analysis with the MSKCC score, Fuhrman grade 1–2 tumors ($p = 0.02$), the presence of sarcomatoid dedifferentiation ≥25% ($p = 0.027$), PFS on first-line therapy ≥12 months ($p = 0.017$), lower albumin levels ($p < 0.0001$) and the presence of glandular metastases ($p = 0.043$) remained as prognostic factor independent of the MSKCC score (Table IV). Four factors were capable to improve the CPE of the MSKCC score, which was 0.587. The addition of albumin levels to the MSKCC score improved the CPE from 0.587 to 0.646, the addition of duration of PFS on first-line therapy to the MSKCC score to 0.626, the addition of Fuhrman grade to the MSKCC score to 0.613 and the addition of the presence of glandular

Table IV. Bivariate analysis with concordance probability estimate.

	p	HR	95% CI	CPE (95% CI)
PFS				
MSKCC Good and intermediate risk	0.075	1.562	0.957–2.552	-
Presence of a sarcomatoid component ≥25%	**0.047**	0.486	0.239–0.990	
MSKCC Good and intermediate risk	**0.049**	1.586	1.001–2.512	-
PFS on first-line ≥12 months	**0.002**	2.083	1.305–3.333	
MSKCC Good and intermediate risk	0.150	1.427	0.880–2.313	-
Low albumin	0.073	0.627	0.376–1.044	
MSKCC Good and intermediate risk	0.054	1.568	0.991–2.479	-
Presence of glandular metastases	0.051	1.742	0.968–3.049	
OS				
MSKCC Good and intermediate risk	**0.000**	2.732	1.623–4.587	0.613 (0.562–0.664)
Fuhrman grade 1–2	**0.020**	1.849	1.103–3.099	
MSKCC Good and intermediate risk	**0.001**	2.408	1.438–4.030	0.594 (0.551–0.637)
Presence of a sarcomatoid component ≥25%	**0.027**	0.443	0.215–0.912	
MSKCC Good and intermediate risk	**0.000**	2.503	1.538–4.072	0.626 (0.575–0.678)
PFS on first-line ≥12 months	**0.017**	1.727	1.105–2.703	
MSKCC Good and intermediate risk	**0.000**	2.495	1.522–4.089	-
Normal CRP-levels	0.145	1.484	0.872–2.526	
MSKCC Good and intermediate risk	**0.005**	2.047	1.235–3.395	0.646 (0.600–0.692)
Low albumin	**<0.0001**	0.293	0.169–0.505	
MSKCC Good and intermediate risk	**0.000**	2.558	1.576–4.152	0.613 (0.566–0.661)
Presence of glandular metastases	**0.043**	1.818	1.019–3.247	

The Concordance Probability Estimate for the MSKCC score was 0.587 (95% CI 0.547–0.628).
CPE, Concordance Probability Estimate; CRP, C-reactive protein; 95% CI, 95% confidence interval; HR, hazard ratio; MSKCC, Memorial Sloan Kettering Cancer Center; OS, overall survival; PFS, progression-free survival.

Table V. Multivariate analysis for progression-free survival and overall survival including the MSKCC or IMDC prognostic score.

	p	HR	95% CI
PFS (MSKCC)			
PFS on first-line ≥12 months	**0.007**	1.964	1.200–3.215
OS (MSKCC)			
Fuhrman grade 1–2	**0.011**	2.025	1.172–3.498
Low albumin	**<0.0001**	0.262	0.141–0.485
MSKCC Good and intermediate risk	**0.011**	2.074	1.179–3.647
OS (IMDC)			
Fuhrman grade 1–2	**0.022**	1.889	1.096–3.257
Low albumin	**<0.0001**	0.251	0.138–0.454
IMDC Good and intermediate risk	**0.015**	1.904	1.135–3.194

95% CI, 95% confidence interval; HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC, Memorial Sloan Kettering Cancer Center; OS, overall survival; PFS, progression-free survival.

Table VI. Multivariate analysis for progression-free survival and overall survival with individual factors.

	p	HR	95% CI
PFS			
PFS on first-line ≥12 months	**0.008**	1.961	1.190–3.226
LDH >1.5xULN	**0.040**	0.511	0.270–0.970
OS			
Fuhrman grade 1–2	**0.007**	2.198	1.235–3.913
PFS on first-line ≥12 months	**0.037**	1.724	1.033–2.882
Low albumin	**0.010**	0.392	0.192–0.800
LDH >1.5xULN	**0.017**	0.392	0.181–0.848
Elevated corrected calcium	**0.010**	0.416	0.214–0.810

95% CI, 95% confidence interval; HR, hazard ratio; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; ULN, upper limit of normal.

metastases to the MSKCC score to 0.613. Nevertheless, the addition of sarcomatoid dedifferentiation to the MSKCC score changed the CPE only from 0.587 to 0.594 (Table IV).

On multivariate analysis including Fuhrman grade, PFS on first-line therapy, sarcomatoid dedifferentiation, the presence of glandular metastases, baseline CRP-levels, albumin levels and MSKCC score, Fuhrman grade ($p = 0.011$), albumin levels ($p < 0.0001$) and the MSKCC score ($p = 0.011$) remained as independently associated with OS (Table V). Results with the IMDC score were similar. On multivariate analysis including PFS on first-line therapy, sarcomatoid dedifferentiation, Fuhrman grade, the presence of glandular metastases, baseline albumin, time between initial diagnosis and start of systemic therapy <12 months, baseline LDH-activity, Karnofsky PS and baseline calcium levels, Fuhrman grade ($p = 0.007$), PFS on first-line therapy ≥12 months ($p = 0.037$), baseline LDH-activity ($p = 0.017$), albumin ($p = 0.01$) and baseline calcium levels ($p = 0.01$) were independently associated with OS (Table VI).

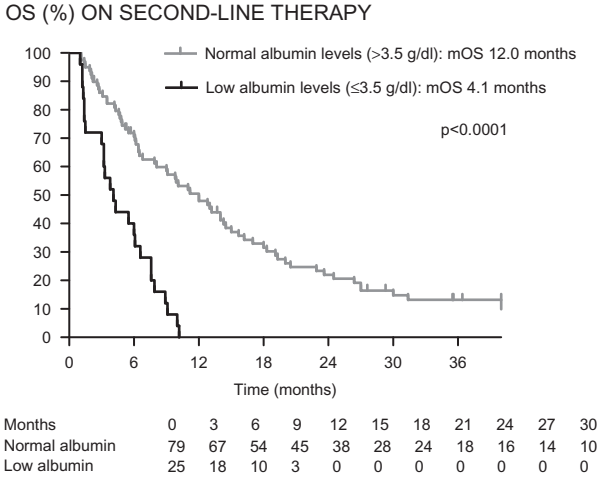
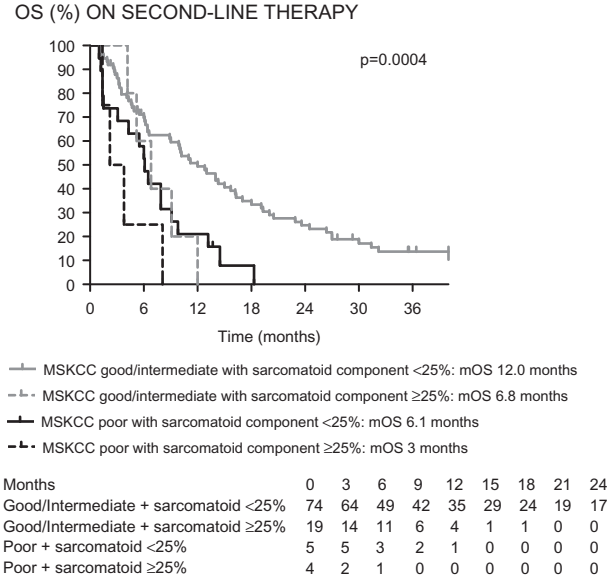


Figure 5. Kaplan-Meier estimates showing the poor overall survival on second-line therapy in patients with low albumin levels.

Table VII. Internal validation.

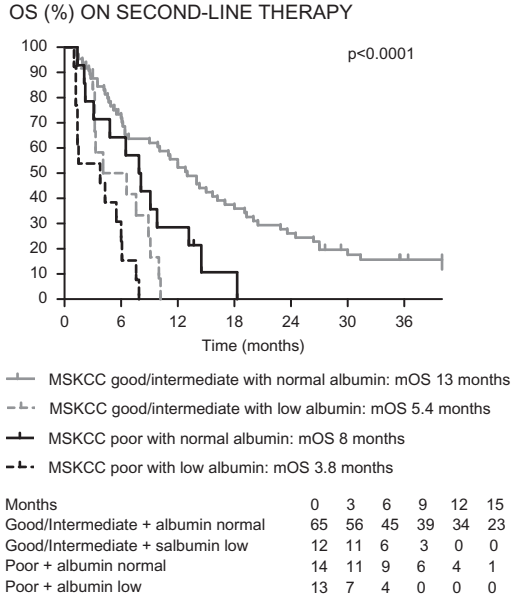
	mTOR-inhibitor		Anti-VEGFR-TKI	
	Months	*p*	Months	*p*
Scores				
MSKCC Poor vs. Intermediate/Good				
OS	**6.3 vs. 11.2**	**0.002**	**2.2 vs. 10.1**	**0.001**
IMDC Poor vs. Intermediate/Good				
OS	**7.1 vs. 10.0**	**0.02**	**4.8 vs. 14.3**	**0.001**
Factors part of the scores				
LDH >1.5xULN vs. ≤1.5xULN				
PFS	2.4 vs. 3.0	0.06	2.4 vs. 2.8	0.11
OS	**6.1 vs. 9.9**	**0.009**	**3.8 vs. 9.1**	**0.04**
Corrected calcium levels > vs. ≤10 mg/dl				
OS	**3.8 vs. 10.0**	**<0.0001**	**3.2 vs. 10.1**	**0.01**
Potential new factors				
PFS on first-line < vs. ≥12 months				
PFS	**2.6 vs. 5.0**	**0.01**	**2.8 vs. 5.3**	**0.03**
OS	**6.3 vs. 13.0**	**0.009**	6.6 vs. 14.3	0.16
Fuhrman grade 1–2				
OS	8.1 vs. 10.2	0.76	**6.8 vs. 24.5**	**0.02**
Low albumin				
OS	**4.8 vs. 11.2**	**<0.0001**	**3.2 vs. 12.6**	**0.002**

IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; LDH, lactate deshydrogenase; MSKCC, Memorial Sloan Kettering Cancer Center; OS, overall survival; PFS, progression-free survival; ULN, upper limit of normal; vs., versus.



Months	0	3	6	9	12	15	18	21	24
Good/Intermediate + sarcomatoid <25%	74	64	49	42	35	29	24	19	17
Good/Intermediate + sarcomatoid ≥25%	19	14	11	6	4	1	1	0	0
Poor + sarcomatoid <25%	5	5	3	2	1	0	0	0	0
Poor + sarcomatoid ≥25%	4	2	1	0	0	0	0	0	0

Figure 6. Kaplan-Meier estimates showing how the addition of sarcomatoid dedifferentiation to the MSKCC score can improve the prognostic value of the MSKCC score.



Months	0	3	6	9	12	15	18	21	24
Good/Intermediate + albumin normal	65	56	45	39	34	23	24	18	16
Good/Intermediate + salbumin low	12	11	6	3	0	0	1	0	0
Poor + albumin normal	14	11	9	6	4	1	0	0	0
Poor + albumin low	13	7	4	0	0	0	0	0	0

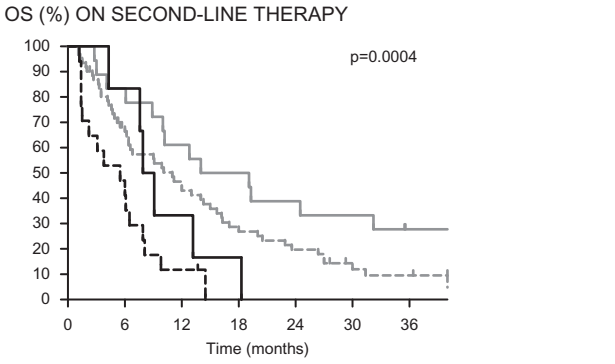
Figure 7. Kaplan-Meier estimates showing how the addition of albumin levels to the MSKCC score can improve the prognostic value of the MSKCC score.

Internal validation: Subgroup of patients treated with second-line anti-VEGFR-TKIs or mTOR-inhibitors

As an internal validation of our findings, the impact on PFS and/or OS of the different factors (MSKCC and IMDC score, PFS on first-line therapy >12 months, Fuhrman grade, LDH, calcium and albumin levels) was analyzed in the subgroups of patients treated in second-line with mTOR-inhibitors or anti-VEGFR-TKIs. Although the subgroups were small, most of these factors were associated significantly with PFS and/or OS in both subgroups, as shown in Table VII. Note that there were no differences in PFS (mPFS 2.8 vs. 2.8 months; $p = 0.45$) and OS (mOS 9.0 vs. 8.9 months; $p = 0.78$) when comparing patients receiving mTOR-inhibitors or anti-VEGFR-TKIs in second-line therapy. Nevertheless, our study was not designed and the sample size too small to detect such differences.

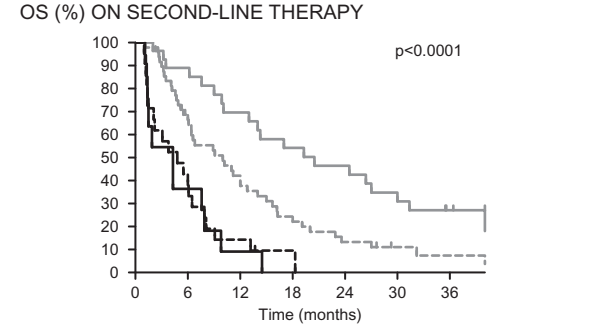
Identification of a subgroup of patients that will probably not benefit from second-line therapy

Overall survival (mOS range 3.5–5.2 months) (HR range 0.14–0.26) was very much reduced in patients with one of the following prognostic markers: elevated corrected calcium levels, low albumin, elevated LDH levels or a sarcomatoid component ≥25%. In total 44% of our patients were part of this unfavorable subgroup and 59% of them displayed early PD. Compared to patients without one of these unfavorable



Months	0	3	6	9	12	15	18	21	24
Good/Intermediate + Fuhrman grade 1+2	18	17	15	13	11	9	9	7	7
Good/Intermediate + Fuhrman grade 3+4	65	52	38	32	26	21	16	13	11
Poor + Fuhrman grade 1+2	6	6	5	3	2	1	1	0	0
Poor + Fuhrman grade 3+4	17	11	8	3	2	0	0	0	0

Figure 8. Kaplan-Meier estimates showing how the addition of Fuhrman grade to the MSKCC score can improve the prognostic value of the MSKCC score.



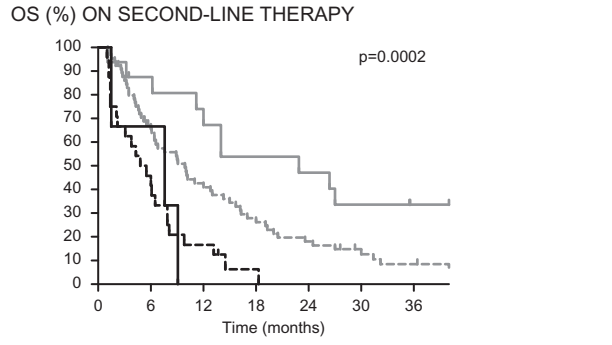
Months	0	3	6	9	12	15	18	21	24
Good/Intermediate + PFS on first-line ≥12M	28	26	23	21	18	15	14	12	12
Good/Intermediate + PFS on first-line <12M	48	44	31	24	19	15	11	8	6
Poor + PFS on first-line ≥12M	11	6	4	2	1	0	0	0	0
Poor + PFS on first-line <12M	21	13	9	4	3	1	1	0	0

Figure 9. Kaplan-Meier estimates showing how the addition of the duration of progression-free survival on first-line therapy to the MSKCC score can improve the prognostic value of the MSKCC score.

markers, one-year survival was 7% versus 60% and two-year survival 0% versus 28%. Patients with poor MSKCC score and low albumin (13/104 patients) had a very short mOS (3.8 months) as shown in Figure 6. Similarly, patients with poor MSKCC score and a sarcomatoid component ≥25% (4/102 patients) had a very short mOS (3 months) as shown in Figure 7. The short mOS of these patients suggest that they will have experienced few or no benefit from second-line therapy.

Identification of a subgroup of patients with higher probability of benefit from second-line therapy

On the opposite, patients with good or intermediate MSKCC score and Fuhrman grade 1–2 tumors (18/102 patients) had a



Months	0	3	6	9	12	15	18	21	24
Good/Intermediate + Glandular metastases	16	15	13	12	11	9	8	8	7
Good/Intermediate + No glandular metastases	65	56	41	33	26	22	17	12	11
Poor + Glandular metastases	3	2	2	1	0	0	0	0	0
Poor + No glandular metastases	24	16	11	5	4	1	1	0	0

Figure 10. Kaplan-Meier estimates showing how the addition of the presence of glandular metastases to the MSKCC score can improve the prognostic value of the MSKCC score.

long mOS (16.6 months) after start of second-line therapy as shown in Figure 8. Four of these patients (22%) displayed a PR on second-line therapy. Patients with good or intermediate MSKCC score and a PFS on first-line therapy ≥12 months (33/108 patients) had a long mOS (20.5 months) after start of second-line therapy (Figure 9). Four of these patients (12%) displayed a PR on second-line therapy. Finally, Figure 10 shows that patients with good or intermediate MSKCC score and glandular metastases (16/108 patients) had a long mOS (22.9 months) after start of second-line. Nevertheless, only one of these patients (7%) displayed a PR on second-line therapy.

Other possible confounding factors

Immunotherapy before the start of first-line anti-VEGFR-TKI (in 21% of the patients) had no impact on outcome of second-line therapy. The type of first-line anti-VEGFR-TKI sunitinib, sorafenib or pazopanib) had no significant impact on outcome on second-line therapy (mPFS: $p = 0.12$; mOS: $p = 0.65$). Nevertheless, our study was not aimed nor powered to detect such differences.

Discussion

Although anti-VEGF-targeted therapies have significantly improved outcome in m-ccRCC, efficacy of second-line targeted therapy after progression on first-line therapy remains disappointing. About one patient out of three will not benefit from second-line therapy. Currently, prognostic and predictive markers at start of second-line therapy are lacking, although they would be very helpful in order to avoid adverse events and costs in patients not benefitting from second-line treatment. Therefore, the aim of this retrospective study was to study prognostic factors in m-ccRCC patients at the start of second-line therapy after progression on anti-VEGFR-TKIs and

to identify subgroups of m-ccRCC patients that will or will not benefit from second-line targeted treatment.

Summary of our results

Our study confirms the poor global outcome on second-line therapy with a median PFS of 2.8 months, a median OS of 8.9 months and a RR of only 6%, similar to the results reported in the literature (Table I).

On multivariate analysis, we confirmed the prognostic impact on OS of the MSKCC and the IMDC score as calculated at start of second-line therapy. On univariate analysis, the MSKCC and IMDC scores were also associated with OS in the subgroups of patients treated with anti-VEGFR-TKIs and mTOR-inhibitors.

On multivariate analysis, the following factors were associated with favorable outcome on second-line therapy: a PFS on first-line therapy $\geq$12 months (associated with longer PFS and OS) and Fuhrman grade 1 and 2 tumors (associated with longer OS). The presence of glandular metastases was associated with longer PFS and OS only on univariate analysis, and not on multivariate analysis, probably because it is associated with other favorable characteristics.

On multivariate analysis, the following factors were associated with unfavorable outcome: elevated LDH-activity (associated with short PFS and OS), low albumin levels (associated with OS) and elevated baseline corrected calcium (associated with OS). The presence of an important component of sarcomatoid dedifferentiation ($\geq$25% of the tumor volume) was associated with short PFS and OS only on univariate analysis, and not on multivariate analysis. This is probably due to the fact that this factor is highly associated with other factors, among them the duration of PFS on first-line therapy [12]. Patients with one of the following prognostic markers: elevated corrected calcium levels, low albumin, elevated LDH levels or a sarcomatoid component $\geq$25% had a very reduced survival after start of second-line therapy.

Similar findings in literature

Consistent with our results, in a retrospective series of 119 patients, Seidel et al. showed that a PFS >6 months with a prior anti-VEGFR-TKI (sunitinib, sorafenib or axitinib) was a prognostic factor for longer OS with a second-line anti-VEGFR-TKI or mTOR-inhibitor [13]. Similarly, in patients who progressed on first-line sunitinib and who were treated consecutively with sorafenib in the AXIS-trial, mOS was longer (19.0 vs. 14.9 months; $p = 0.018$) in patients who had a PFS of $\geq$9.7 months on first-line sunitinib compared to patients with a PFS <9.7 months on first-line sunitinib [21]. This finding was not confirmed in patients switching from sunitinib to axitinib in the same trial. In the same way, a large retrospective database analysis of 464 patients treated successively with two different VEGF targeting therapies did not demonstrate an association between PFS during first- and second-line treatment [22].

Our data show that the MSKCC and IMDC scores, calculated at start of second-line targeted therapy, maintain their prognostic value for OS in this clinical setting. In the RECORD-1 trial, the MSKCC score was associated with PFS and OS on everolimus. Individual factors associated with mPFS were the presence of liver, bone or brain metastases, corrected calcium levels, hemoglobin and neutrophil count. The same six factors were also associated with OS, as well as Karnofsky PS, time from initial diagnosis till systemic therapy, prior radiation therapy and LDH levels. Note that the RECORD-1 study was not a pure second-line study, as patients could have received several lines of targeted therapy before receiving everolimus [10]. On a series of 1.021 m-RCC patients treated with second-line therapy after progression on a first-line targeted therapy, on multivariate analysis, five of the six individual factors composing the IMDC prognostic score (hemoglobin levels, baseline platelets, baseline neutrophil count, Karnofsky PS and the time interval between initial diagnosis and start of systemic therapy), as well as the IMDC score itself, were significantly associated with OS [23].

Glandular metastases

Interestingly, the present study highlights the favorable prognostic value of glandular (pancreatic, thyroid or adrenal) metastases. Previous reports, regarding specifically thyroid or pancreatic metastases, have already described an association with better outcome in terms of survival [16,24]. The diagnosis of involvement of these organs is sometimes difficult, and frequently such lesions are only found after administration of an anti-VEGFR-TKI due to the density changes on computed tomography. Metachronous glandular metastases can appear late after nephrectomy, suggesting a less aggressive tumoral behavior of tumors with this type of metastatic spread. Nevertheless, mechanisms underlying this more indolent evolution remain unclear.

Limitations of our study

Our study suffers from several limitations, due to it retrospective nature and the limited number of patients. As a consequence, we were not capable to find a significant association between baseline neutrophil count, baseline blood platelets count and hemoglobin levels and OS, unlike in the study of Ko et al. [23]. Moreover, the multivariate analysis was done on a reduced number of patients (range 92–98) due to missing data. Response evaluation was done by treating physicians rather than by independent radiologists. There was no central pathology review and second-line therapy was heterogeneous, mixing patients treated with anti-VEGFR-TKIs and mTOR-inhibitors.

Even if we have identified a subgroup of patients with a very short OS on second-line therapy, we cannot exclude that some of these patients experienced a limited benefit of second-line therapy. If our results would be confirmed in an external validation, it would still remain difficult to preclude any patient from a second-line therapy.

However, in patients with one of the favorable prognostic markers, it is not clear if the improved outcome is due to the impact of the therapy or to the more indolent underlying disease. Second-line therapy rarely seems capable to induce clinically relevant tumor shrinkage. Therefore, most of the factors that we have found to be associated with PFS or OS

have most probably a prognostic rather than a predictive value. They are associated with tumor biology or the general shape of the patient, and in part reflect the natural evolution of RCC.

Our results emphasize the need for predictive rather than prognostic markers and the need for new treatment options in the second-line setting, like more potent anti-VEGF-inhibitors or drugs with alternative mechanisms of action, such as immunotherapy or demethylating agents. At this moment, inclusion in clinical trials likely represents the best second-line option. Better insights in tumor biology could probably also help to predict efficacy of second-line therapy with anti-VEGFR-TKIs or mTOR-inhibitors [25].

Declaration of interest: Benoit Beuselinck has received research grants from GlaxoSmithKline and Novartis. He is an investigator of the EudraCT: 2011-006085-40/MetaSun trial supported by Pfizer and received honoraria for educational activities from Pfizer, GlaxoSmithKline and Amgen. Patrick Schöffski received research funding and honoraria for consulting, advisory and educational functions for Glaxo Smith Kline, Novartis and Bayer. Philippe Barthélémy has received research grants from Novartis. He participates in advisory boards for Novartis, Pfizer. Philip R. Debruyne was an investigator in clinical trials of Pfizer, Bayer, Novartis and GlaxoSmithKline. He received an educational research grant of Pfizer. The other authors did not report any conflict of interest.

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