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Progression free survival of first line vascular endothelial growth factor-targeted therapy is an important prognostic parameter in patients with metastatic renal cell carcinoma

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Abstract ***Purpose:*** Intrinsic resistance in metastatic renal cell carcinoma (mRCC) was recently associated with poor overall survival (OS), suggesting that VEGF inhibitor sensitivity may represent a valuable prognostic marker. We explored the duration of progression free survival (PFS) in first-line treatment and other variables as prognostic markers in mRCC.
Methods: Medical records from 119 mRCC patients receiving first line treatment with tyrosine kinase inhibitors (TKI) were retrieved retrospectively. Kaplan–Meier and log-rank analyses were employed on PFS and OS and multivariate Cox proportional hazard model analysed clinical parameters for their prognostic relevance.
Results: The median PFS of first line treatment was 8.4 months (95% confidence interval 5.8–11) associated with a median OS of 28.2 months (95% CI 20.9–35.4). Second line therapy with another TKI or mTOR-inhibitor was applied to 81 patients (68%). PFS of any second line therapy was 5.1 and 3.7 months in first line treatment responders and non-responders ($p = 0.3$), respectively. Univariate analyses revealed bone metastases, prior cytokine treatment, Memorial Sloan Kettering cancer centre (MSKCC) score, objective response rate, Eastern Cooperative Oncology Group (ECOG) performance status, first line PFS with 6 months taken as cut-off parameter and second line treatment as prognostic variables. Multivariate analyses proved first line PFS above 6 months (95% CI 0.154–0.641; HR 0.314), second line treatment (95% CI 0.162–0.657; HR 0.326), MSKCC score (95% CI 1.07–3.392; HR 1.905) and objective response rate (95% CI 0.358–0.989; HR 0.595) to be independent prognostic markers.

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Conclusions: The duration of first line PFS is an independent prognostic variable but not predictive for subsequent therapy.

1. Introduction

The systemic treatment of metastatic renal cell carcinoma (mRCC) has dramatically evolved during recent years. The introduction of targeting therapies into the treatment algorithm of mRCC has significantly advanced the field, and these agents either inhibit the vascular endothelial growth factor (VEGF) receptor or the mammalian target of rapamycin (mTOR).

Sunitinib, pazopanib and sorafenib are approved tyrosine kinase inhibitors (TKI), which target numerous kinases, including VEGF receptors.[1–3] VEGF is more selectively inhibited by the monoclonal anti-VEGF antibody bevacizumab, which is applied concomitantly with interferon.[4] Clinical efficacy has been reported for these VEGF targeting agents, and their use has been associated with a median overall survival (OS) of 22.9–26.4 months when applied in first line treatment.[1,2] More recently, the next generation of TKI entered the clinical stage in mRCC treatment.

Despite the significant clinical activity of VEGF targeted therapies, all patients (pts.) will inevitably experience disease progression. Everolimus is an mTOR inhibitor (mTORi) and was the first agent to succeed in a phase III clinical trial in VEGF TKI refractory disease.[5] Based on the explicit sensitivity of mRCC to VEGF inhibition, it remained a matter of debate whether a change of mode of action offered additional clinical benefit compared to a sustained inhibition of the VEGF axis. The first prospective phase III clinical trial addressing this question explored the 2nd generation VEGF receptor TKI axitinib in 2nd line therapy and renders the subsequent use of VEGF TKI effective.[6] Whether another line of therapy can be added to the treatment algorithm is currently under investigation.

Prediction of clinical outcome remains the main translational focus of most contemporary studies. To date, evaluation of the Memorial Sloan Kettering cancer centre (MSKCC) risk category or the modified score by Heng et al. remains the gold standard in order to assess treatments' predictive or prognostic value.[7,8] As a tribute to the solely clinical nature of these scores, intrinsic resistance to VEGF inhibitors may be found in any of these risk groups. Hereby current investigations proved that inadequate response to first line treatment is associated with a devastating prognosis,[9,10] which raises the need for treatment strategies for first line non-responders.

With our analyses we aim to further evaluate prognostic parameters for mRCC patients receiving targeted therapies.

2. Patients and methods

Clinical data of 119 pts. with mRCC treated between November 2005 and October 2011 were gathered. Pts. were required to receive a TKI as first line therapy. No restrictions were made with regard to subtype of RCC, or the MSKCC score. Medical records were retrieved and analysed retrospectively in accordance with the regulatory requirement of the local ethics committee and the Declaration of Helsinki (Table 1).

Treatment outcome was defined by either median OS, which has been calculated from the start of VEGF targeted therapy, or the median progression free survival (PFS) of first line therapy. Tumour response was evaluated as best response according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.0.[11] Pts. with a stable disease (SD), partial remission (PR) and a complete remission (CR) were considered as responders. Computed tomography (CT) scans were performed according to the local standard. For detection of prognostic factors that are significantly associated with the OS and the PFS of first line VEGF-targeted therapy, uni- and multivariate analyses were performed.

3. Treatment regimens

First line VEGF targeted therapy consisted of sunitinib in 91 pts. (76%), sorafenib in 20 pts. (17%) and axitinib in eight pts. (7%). Sunitinib was administered as 50 mg once daily (OD) on 28 consecutive days of a given 6-weeks cycle. Sorafenib was administered continuously 400 mg twice daily (BID) and axitinib was administered according to the protocol, consisting of 5–10 mg BID.

Sunitinib was administered within the 'SU011248 Versus Interferon-Alfa as First-Line Systemic Therapy For Patients With Metastatic Renal Cell Carcinoma' (NCT00083889) ($n = 6$); 'Treatment Use Study With Sunitinib (SU011248) For Patients With Cytokine-Refractory Metastatic Renal Cell Carcinoma' (NCT00130897) ($n = 21$). All pts. received axitinib within the 'Axitinib (AG-013736) with or Without Dose Titration (Increase) In Patients with Kidney Cancer' (NCT00835978) clinical trial.

Second line mTOR-inhibitors were applied within the 'REACT Expanded Access Study of RAD001' (NCT00655252) ($n = 20$) or the RECORD-1 study (NCT00410124) ($n = 8$). Other pts. received their medication by prescription according to the local standard of care.

Fifty-two pts. (44%) received cytokine treatment prior to VEGF targeted treatment according to previous treatment standards.

In case of significant toxicity, dose-reductions were allowed. In sunitinib treated pts. doses were reduced from 50 to 37.5 mg, and further to 25 mg OD if necessary. Sorafenib dose reduction consisted of a decrease to 200 mg BID. Dose reductions of axitinib were according to the protocol.

After failure of first line VEGF-targeted therapy 81 pts. received at least second line treatment with either an mTORi ($n = 51$) or another TKI ($n = 30$).

Of 38 pts. not receiving second line therapy, seven pts. died under first line treatment and eight pts. were still ongoing when these analyses were performed. Twenty-three pts. received best supportive care (BSC) after progression due to a limited performance status. Pts. received between 1 and 6 different treatment lines (median 3).

4. Statistics

The PFS was assessed and defined as time from the initiation of first line VEGF targeted therapy to the day tumour progression was proven or death occurred. Pts. were censored at the date of last follow-up. OS was investigated from initiation of first line VEGF targeted therapy to the time of death or censored at the date of last follow-up. Kaplan–Meier curves comparing PFS and OS between patient characteristics were constructed and log-rank testing was used to compare these censored outcomes. The following patient characteristics were tested as variables: The PFS of first line VEGF targeted therapy with 6 months taken as cut-off. Further factors tested were best objective response to first line TKI treatment, the application of second line treatment, MSKCC risk score prior to first line VEGF targeted therapy, Eastern Cooperative Oncology Group (ECOG) performance status, histology, prior immunotherapy, number of metastatic organ sites prior to TKI therapy, location of metastatic organ sites, e.g. lung, bone, lymph nodes and others. Associations between patient characteristics and the treatment outcome concerning median OS and median PFS were assessed using the log rank test in univariable analysis. Variables were found to be significant if the two sided p-value was <0.05 on univariate testing. We also employed the Cox proportional hazards model for multivariable analysis. The variables that reached statistical significance ($p < 0.05$) in this model were then deemed to be independent predictors of the treatment outcome concerning the OS and PFS. All statistical calculations were performed using the Statistical Package for the Social Sciences (SPSS) 19 (Chicago, United States).

5. Results

5.1. Efficacy of treatment

5.1.1. Outcome of first line treatment with VEGF targeted agents

The median OS from start of first line VEGF targeted therapy was 28.2 months. (95% CI 20.9–35.4). First line VEGF targeted therapy was associated with a median PFS of 8.4 months (95% CI 5.8–11.0).

Pts. with a PFS above 6 months had an OS of 46.8 months compared to 12.1 months for all others, respectively ($p < 0.0001$) (Fig. 1).

Eighty-two pts. (69%) responded to first line VEGF targeted therapy with 53 pts. (45%) achieving SD, 24 pts. (20%) with a PR and five pts. (4%) exerting CR. Thirty-four pts. (29%) had progressive disease at first tumour evaluation and were deemed intrinsic resistant. In three pts. best response was not evaluable due to early permanent treatment interruption based on toxicity.

The clinical response in first line therapy varied among the different TKIs used. Ninety-one pts. received sunitinib of whom 39 pts. (43%) achieved SD, 18 pts. (20%) had PR and five pts. (5%) a CR, while 27 pts. (30%) had PD. Twenty pts. received sorafenib with SD in 10 pts. (50%), PR in four pts. (20%), and five pts. (25%) with PD as best response. Pts. treated with sunitinib reached a median OS of 24.8 months and a median PFS of 8.3 months, compared to 33.4 months and 9.1 months under sorafenib ($p = 0.226$ and $p = 0.559$; respectively).

Only a minority of pts. were treated with axitinib ($n = 8$) in first line, and response consisted of PR in two pts., SD in four pts. and PD in two pts. The median

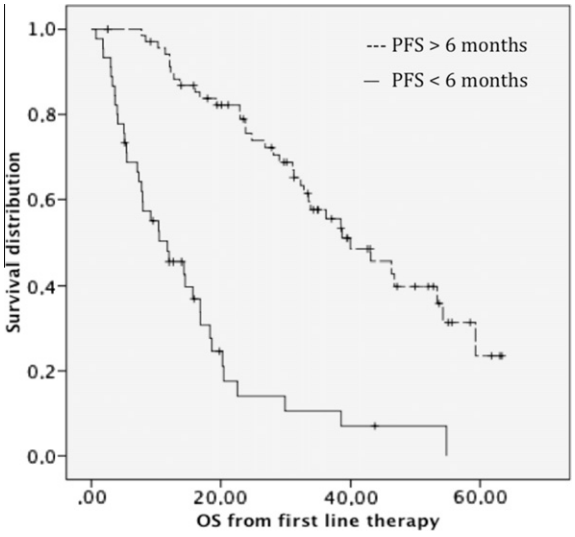

Fig. 1. Patients with first line progression free survival (PFS) above 6 months had a significant superior overall survival (OS) (46.8 months) than others (12.1 months) ($p < 0.0001$).

OS was not reached and the median PFS consisted of 12.8 months.

Dose reductions due to adverse events were required in 30 of all pts. (25%). No difference was seen between the OS of pts. requiring dose reductions compared to pts. receiving the full dose regimen during the entire treatment duration ($p = 0.54$).

5.1.2. Further systemic treatment lines and clinical outcome

Eighty-one pts. (68%) received second line treatment with either an mTORi ($n = 51$) or another TKI ($n = 30$). The median PFS of second line therapy was 4.9 months (95% CI 2.83–7.02). No difference was seen between the PFS of second line treatment with another TKI or an mTORi (4.9 months versus 5.2 months; $p = 0.19$). There were no differences in OS for pts. with either TKI or mTORi as second line treatment, which achieved 30 months and 33.5 months, respectively ($p = 0.74$) (Fig. 2).

Pts. receiving third line therapy were treated with an mTORi after the application of two TKIs (TKI-TKI-mTORi-sequence) or another TKI after the application of an mTORi (TKI-mTOR-TKI-sequence). There was no difference comparing the OS of both groups ($p = 0.43$).

Of 35 pts. with intrinsic resistance (non-responders) to first line TKI therapy, 24 received second line targeted treatment, of whom another TKI or an mTORi was applied in 12 pts., each. In non-responders second line therapy was associated with a median PFS of 3.7 months, compared to 5.1 months in first line treatment responders, which was not significant in univariate analyses ($p = 0.3$) (Fig. 3).

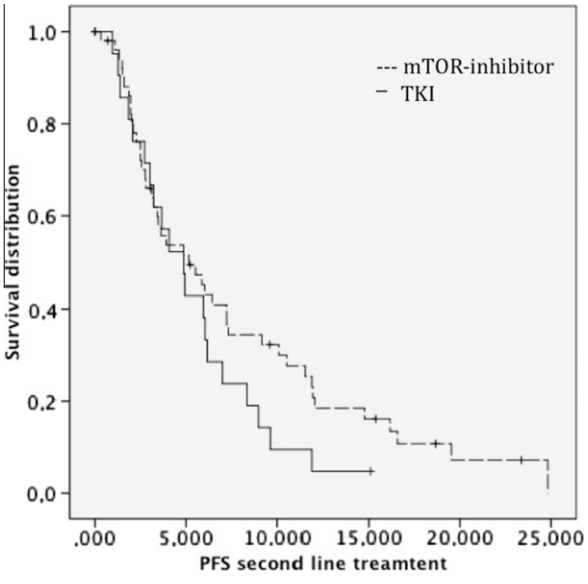

Fig. 2. Median progression free survival (PFS) of second line treatment with either mTOR-inhibitor (5.2 months) or another TKI (4.9 months) ($p = 0.19$).

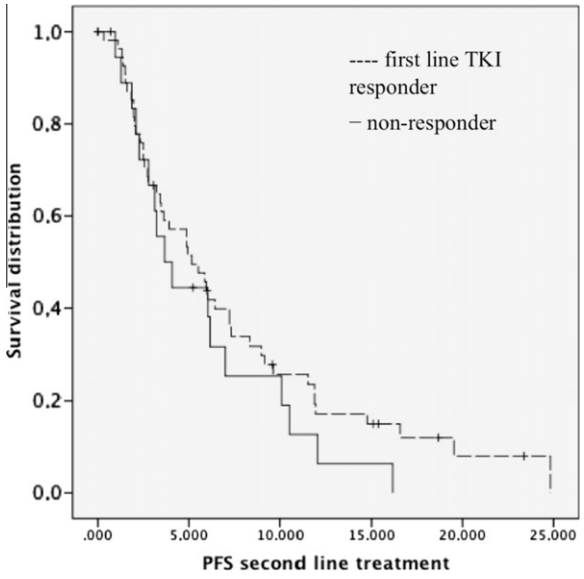

Fig. 3. Median progression free survival (PFS) of second line therapy of first line tyrosine kinase inhibitors (TKI) non-responder (3.7 months) versus responder (5.1 months) ($p = 0.3$).

Pts. receiving best supportive care after progression of first line VEGF targeted therapy had a median OS of 12.1 months, while pts. who received further treatment lines achieved a median OS of 32.8 months ($p < 0.0001$).

5.2. Toxicity analyses

Systemic treatment with first line VEGF targeted therapy had to be permanently interrupted due to toxicity in 15 pts. (13%). Treatment cessation was caused by angina pectoris ($n = 1$); Ulcus cruris ($n = 1$); perforation of the small bowel ($n = 1$); fatigue ($n = 1$); diplopia ($n = 1$); angina pectoris ($n = 1$); limited function of the left ventricle ($n = 1$); proteinuria ($n = 1$); mucositis ($n = 1$); alveolitis ($n = 1$), thrombocytopenia ($n = 1$) and general intolerance ($n = 3$). In one patient the exact reason is not evaluable.

5.3. Prognostic and predictive factors

Patient characteristics that are prognostic for OS were analysed with a univariate and multivariable-adjusted model.

The median OS of pts. with a PFS below versus above 6 months was 12.1 and 46.8 months, respectively ($p < 0.0001$). On univariate analyses second line treatment ($p < 0.0001$), ECOG ($p < 0.0001$), the MSKCC score ($p = 0.002$), prior immunotherapy ($p = 0.21$) and bone metastases ($p = 0.04$) were prognostic factors for the OS. Pts. with a good MSKCC score had a median OS of 43.1 months, compared with 20.3 and 3 months in pts. with intermediate and poor MSKCC score, respectively ($p = 0.002$) (Table 2).

Table 1
Baseline patients' characteristics and evaluation of first line vascular endothelial growth factor (VEGF) targeted-therapy.

		N	%
No. of patients		119	100
Gender	Female	35	29
	Male	84	71
Median age	Years	61	
	Range	27–72	
Histology	Clear cell	106	89
	Mixed	6	4
	Papillary	5	1
	Sarcomatoid	1	1
	Chromophob	1	1
Metastatic organs	Bone	34	29
	Liver	29	24
	Lung	79	66
	Lymph node	65	55
	Others	85	71
Number metastatic organ sites	<3	54	44
	3 and more	65	55
Eastern Cooperative Oncology Group (ECOG)	0	91	76
	1	20	17
	2	1	1
	Not available	7	
Memorial Sloan Kettering cancer centre (MSKCC)	Low	30	29
	Intermediate	76	66
	Poor	8	8
	Not available	5	4
First line treatment	Sunitinib	91	76
	Sorafenib	20	17
	Axitinib	8	7
First line tyrosine kinase inhibitors (TKI) responder		82	69
First line TKI non-responder		34	29
Early interruption		3	
Best response to first line VEGF targeted therapy	Complete remission	5	45
	Partial remission	24	20
	Stable disease	53	4
	Progressive disease	34	29
	Early interruption	3	3
Second line treatment		81	68
Prior immunotherapy		52	44

Multivariate analyses was performed comparing the following factors: first line PFS with 6 months as cut-off, best objective response of first line therapy; availability of second line treatment; MSKCC risk; prior immunotherapy; metastatic organ sites, number of metastatic organ sites with three or more as a cut-off, histology and ECOG.

Multivariate analyses showed that a PFS above 6 months in first line TKI therapy (95% CI 0.154–0.641; Hazard ratio (HR) 0.314) is an independent prognostic marker. Second line treatment (95% CI 0.162–0.657; HR 0.326), the MSKCC risk score (95% CI 1.07–3.392; HR 1.905) and first line treatment best response (95% CI 0.358–0.989; HR 0.595) were also independent prognostic factors.

Pts. with a good MSKCC score also had a beneficial first line PFS of 13.1 months, compared to 8.1 months and 2.3 months with an intermediate and poor score ($p = 0.008$). A prolonged first line PFS was also seen in pts. achieving complete remission with 26.3 months ($p < 0.001$).

Pts. receiving third line therapy had a longer first line PFS then pts. without third line treatment (11.5 versus 6.6 months; $p = 0.045$). In multivariate analyses CR in first line therapy was the only factor significantly associated with first line PFS (95% CI 0.438; 0.303–0.633).

Patient characteristics to predict response to sequential therapy were also evaluated: There were no factors significantly associated with the PFS of second-line targeted therapy.

Table 2
Results of univariate analyses and multivariate Cox proportional hazards model are shown. Multivariate analyses confirm the relevance of the progression free survival (PFS) as a prognostic factor for overall survival (OS). On univariate analysis the PFS of first line vascular endothelial growth factor (VEGF) targeted therapy ($p < 0.0001$), best response according to Response Evaluation Criteria in Solid Tumours (RECIST) ($p < 0.0001$), patients receiving second line treatment ($p < 0.0001$), the Memorial Sloan Kettering cancer centre (MSKCC) score ($p = 0.03$) and interferon therapy prior to VEGF targeted therapy ($p < 0.0001$) correlated with the OS.

Results of univariate analyses for all prespecified prognostic factors

Factor	Value	*P* value of univariate analyses	Median OS in months	95% confidence interval
First line PFS	>6 months versus <6 months	<0.0001	46.8 versus 12.1	21.07–37.05
Best response according RECIST	Complete remission (CR) versus partial remission (PR) versus SD. versus PD	<0.0001	Not reached versus 36.16 versus 38.5 versus 7.96	20.92–35.44
Eastern Cooperative Oncology Group (ECOG)	ECOG 0 versus ECOG 1 versus ECOG 2	<0.0001	29.06 versus 15.68 versus 0.72	20.92–35.43
Second line after 1st line VEGF	Pts. with 2nd line versus without 2nd line	<0.0001	32.7 versus 12.1	20.11–36.25
MSKCC score	Good, intermediate, poor	0.002	43.1 versus 20.1 versus 3.0	19.45–34.26
Interferon prior VEGF treatment	With or without prior interferon	0.02	32.1 versus 20.3	20.92–35.44
Osseus lesions	Pts. without versus with osseus lesions	0.04	31.2 versus 19.3	20.94–35.43
Liver lesions	Pts. without versus with liver lesions	0.685	26.86 versus 38.47	20.92–35.43
Pulmonary lesions	Pts. without versus with pulmonary lesions	0.385	32.75 versus 23.01	20.92–35.43
Lymph node metastases	Pts. without versus with lymph node lesions	0.231	33.47 versus 22.52	20.92–35.43
other organ sites	Pts. without versus with other organs sites	0.231	23.01 versus 31.20	20.92–35.43
Histology	Clear cell versus other histologies	0.735		
Number of metastatic organ sites	<3 versus >3 metastatic organ sites	0.872	26.86 versus 29.95	20.95–35.42

Final multivariate cox proportional hazards models for OS

Factor	Value	*P* value multivariate analyses	HR	95% confidence interval
First line PFS	>6 months versus <6 months	0.001	0.314	0.154–0.641
second line after 1st line VEGF	Pts. with 2nd line versus without 2nd line	0.002	0.326	0.162–0.657
MSKCC score	Good, intermediate, poor	0.029	1.905	1.07–3.392
Best response according RECIST	CR versus PR versus SD. versus PD	0.045	0.595	0.358–0.989
Osseus lesions	With or without prior interferon	0.167	1.664	0.807–3.43
Liver lesions	Pts. without versus with liver lesions	0.244	0.662	0.331–1.324
Pulmonary lesions	Pts. without versus with pulmonary lesions	0.521	0.804	0.413–1.565
Lymph node metastases	Pts. without versus with lymph node lesions	0.065	1.808	0.963–3.393
Other organ sites	Pts. without versus with other organs sites	0.663	0.851	0.413–1.757
Number of metastatic organ sites	<3 versus >3 metastatic organ sites	0.455	0.766	0.381–1.542
ECOG	ECOG 0 versus ECOG 1 versus ECOG 2	0.723	0.865	0.386–1.935
Histology	Clear cell versus other histologies	0.495	0.738	0.309–1.765
Interferon prior VEGF treatment	With or without prior interferon	0.9	0.957	0.481–1.903

6. Discussion

Treatment of metastatic RCC has changed dramatically during recent years. Inhibitors of VEGF or its receptor as well as blockers of mTOR have been implemented in the clinic. Meanwhile overall survival data has matured and is currently available for first generation clinical trials. Current estimates for median OS in mRCC may be expected in the range of 22.9–26.4 months, consistently to the outcome of our cohort.[1,2] The PFS of 8.4 months presented in our analyses may deviate from current expectations. Several just recently published analyses, however, also describe a duration of first line PFS for sunitinib or sorafenib in the range of 8–9 months[13–15] The diverse patient population and the retrospective nature of our work may contribute to the inferior first line PFS in our analyses. Certainly, the proportion of intrinsic resistant patients (29%) in our study population appears to be higher than suggested by current prospective studies, and, hence, may spur inferior clinical outcome.

Based on availability subsequent therapies have been applied to 30–56% of pts. in these trials, whereas the fraction of pts. treated with mTORi remained 3–9%, only. These results spur expectations in regard to a putative OS with the implementation of multiple lines of therapies in the majority of mRCC pts.

In spite of this enthusiastic development prediction of clinical outcome remains the main translational focus of most contemporary studies. To date, evaluation of the MSKCC or Heng-score remains the gold standard in order to assess treatments' predictive or prognostic value.[7,8] As a tribute to the solely clinical nature of these scores, intrinsic resistance to VEGF inhibitors may be still experienced as best response in pts. within any of these risk groups. Recent analyses showed that pts. with insufficient response to first line treatment have dismal prognosis.[9,16] Hereby the PFS of 6 months under first line VEGF-targeted treatment was applied as a cut-off marker and proved to significantly differentiate pts. with beneficial and poor prognosis.[10]

It is our notion that the 6 months cut-off parameter is well applicable in the clinic and was therefore applied for our investigations.

Predictive biomarkers have also been implemented in the majority of recent RCC trials, however, none of these markers provided sound prediction of treatment efficacy that would change clinical practice.[17–28] Hence, these biomarkers may allow early detection of progression or response, to date no available biomarkers are superior to clinical parameters such as those used for the MSKCC score.

Progression free survival of VEGF targeted therapies was thought to represent a putative candidate as a prognostic marker. Our analyses of 119 pts. showed that short term PFS in first line treatment leads to early death in patients with mRCC even though most of the pts. received subsequent treatment lines. Hereby intrinsic resistance to TKI may not preclude benefit from second line therapy to some extent, which renders sensitivity to TKI not a predictive marker for subsequent therapies. This observation is supported by a current analysis of the AXIS trial, where first line PFS of sunitinib above or below 6 months did not predict response to subsequent axitinib therapy.[29] These data challenge the current perception that previous response to a VEGF targeted agent may guide the choice of subsequent therapy.

Lack of susceptibility to VEGF inhibitors reflects an aggressive course of the disease with dismal prognosis and, hence, represents an important cofactor for treatment outcome. These pts. may represent a genetically distinct cohort with poor overall survival. In summary, sensitivity to VEGF targeted therapy is an independent prognostic marker, which reflects tumour behaviour throughout the course of treatment. It is our notion that sensitivity to VEGF inhibitors reflects tumour biology rather than differential response to a given TKI. However, a larger patient cohort is required to detect such differential response to TKIs. Sensitivity to VEGF inhibitors represents a simple and valuable tool in the clinic to assess patients' prognosis and may guide treatment decision in the clinic.

Conflict of interest statement

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Martin Fenner: none
Arnold Ganser: none
Jonas Busch: none
Steffen Weikert: none
Sandra Steffens: none

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