A randomised, double-blind phase II study evaluating cediranib vs cediranib and saracatinib in patients with relapsed metastatic clear cell renal cancer (COSAK)

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ABSTRACT

Background: Preclinical work suggests Src proteins have a role in the development of resistance to vascular endothelial growth factor (VEGF) targeted therapy in metastatic clear cell renal cancer (mRCC). This hypothesis was tested in this trial using the SRC inhibitor saracatinib and the VEGF inhibitor cediranib.

Patients and methods: Patients with disease progression after ≥1 VEGF targeted therapy were eligible to participate in this double-blind, randomised (1:1) phase II study. The study compared the combination cediranib 30mg once daily (OD) and saracatinib 175mg OD (CS) (n=69) or cediranib 45mg OD and placebo OD (C) (n=69). Archived tissue was used for biomarker analysis (SRC, FAK, VHL, PTB1b and HIF2α: n=86).The primary endpoint was progression free survival (PFS) by RECIST v1.1.

Results: Between 2010 and 2012, 138 patients were randomised across 16 UK sites. The characteristics of the two groups were well balanced. Partial responses were seen in 13.0% for C and 14.5% for CS respectively (*P*>0.05). There was no significant difference in PFS [5.4 months (3.6-7.3 months) for C and 3.9 (2.4-5.3 months) for CS; Hazard Ratio (HR) 1.18 (0.94-1.48)], or overall survival (OS) [14.2 months (11.2-16.8 months) for C and 10.0 (6.7-13.2 months) for CS; [HR 1.28 (1.00-1.63)]. There was no significant difference in the frequency of key adverse events, dose reductions or drug discontinuations. None of the biomarkers were prognostic for PFS or OS. Focal adhesion kinase (FAK) overexpression correlated with an OS benefit [HR 2.29 (1.09-4.82) p>0.05], but not PFS, for CS.

CONCLUSIONS: Saracatinib did not increase the efficacy of a VEGF targeted therapy (cediranib) in this setting. Biomarker analysis did not identify consistent predictive biomarkers.

ClinicalTrials.gov number NCT00942877.

KEY WORDS: Renal cell carcinoma; tyrosine kinase inhibitor; biomarker; SRC; VEGF.

INTRODUCTION

Second line vascular endothelial growth factor (VEGF) targeted therapy is less active than first line VEGF targeted therapy in metastatic clear cell renal cancer (mRCC) [1]. There appears to be significant cross resistance between these drugs rendering subsequent therapy less active than the previous treatment. This has been described as a 'law of diminishing returns' [1, 2].

The mechanism of resistance to VEGF targeted therapy in mRCC is unknown. Alternative pathways such as SRC may play a role in progression of disease [3-5]. Preclinical data shows Src may be involved in stability of the von Hippel-Lindau (VHL) gene and overexpression is associated with poor outcomes in RCC. Further data show that the combination of VEGF targeted therapy and the Src inhibitor, saracatinib, are synergistic in renal cancer cell lines [4]. Therefore, saracatinib may enhance the activity of VEGF targeted therapy. Preclinical work also points towards the potential for a personalised approach with this combination. Overexpression of protein tyrosine phosphatase 1b (PTB1b) and focal adhesion kinase (FAK) appeared to be relevant in determining outcome [4].

Cediranib is a potent VEGF tyrosine kinase inhibitor (TKI) with significant activity in renal cancer patients who have not previously received VEGF targeted therapy, with comparable progression-free survival (PFS) results to those seen with sunitinib, pazopanib and axitinib [1, 6-8]. It was not further developed in mRCC due to established alternatives in this arena. Cediranib was used as it was the only VEGF agent with phase I data in combination with saracatinib. Phase I data showed that cediranib monotherapy was well tolerated and efficacious at a dose of 45mg once daily (OD) [6, 9]. However, a dose reduction for cediranib to 30mg OD was required when used in combination with saracatanib 175mg OD due to a dose-limiting toxicity

(hypertension) [10]. The combination was well tolerated with manageable and largely non-overlapping side effect profiles [10].

Preclinical animal model work suggests PTB1b and FAK may be relevant in predicting response to Src inhibition [4]. It is conceivable that the SRC inhibition is only active in biomarker driven subsets of patients. For this reason a number of relevant biomarkers (SRC, FAK, VHL and hypoxia-inducible factor 2α (HIF2α)) were measured from archived tissue.

The aim of this study was to determine if the addition of a SRC inhibitor (saracatinib) to a VEGF TKI (cediranib) led to an improved PFS compared to VEGF inhibition alone in mRCC patients who have already failed VEGF-targeted therapy. We also explored the predictive nature of PTB1b, FAK and other biomarkers in this setting.

MATERIALS AND METHODS

Patient population and study drug

Inclusion criteria included histopathologically-confirmed, measurable (by Response Evaluation Criteria in Solid Tumours (RECIST) v1.1) metastatic clear cell RCC. Patients were required to have progressive disease on VEGF targeted therapy and be naïve to mammalian Target of Rapamycin (mTOR) inhibitors. Prior immune therapy and >1 line of VEGF targeted therapy was permitted. Adequate end organ function was required. Patients with Eastern Co-operative Oncology Group (ECOG) performance status (PS) of 0-2 were permitted. Exclusion criteria focused on the standard exclusion criteria for VEGF targeted therapy studies, such as untreated brain metastases, uncontrolled hypertension/cardiac disease, bleeding, excessive proteinurea and concurrent alternative malignancies.

Patients were randomised (1:1) in a double blinded fashion. They received either cediranib 30mg PO OD + saracatinib 175mg PO OD or cediranib 45mg PO OD + placebo PO OD. Doses were based on single agent and combinations data from phase I-II studies [6, 10]. Dose interruptions (28 days) or reductions were permitted [(i) cediranib 20mg and saracatinib 175mg: (ii) cediranib 15mg and saracatinib 125mg].

Endpoints and assessment.

The primary outcome was to investigate the progression free survival (PFS) of the combination of cediranib and saracatinib compared to cediranib and placebo. Secondary objectives included response rates (RR), overall survival (OS), adverse events (AEs) and specific biomarker analysis from archived tissue [SRC, VHL, FAK, HIF2α, PTB1b].

Patients were randomised to receive study drug until progression of disease, death, excess toxicity or discontinuation for another reason. Radiological assessment (RECIST v1.1) occurred eight weekly until progression. No central radiological review occurred. Clinical assessment occurred on a four weekly basis. AEs were graded according to the National Cancer Institute's Common Terminology Criteria for AEs, version 3.0 (CTCAE v3.0). Stratification factors included performance status, duration on first line VEGF targeted therapy (<6 months) and Memorial Sloan Kettering Cancer Centre (MSKCC) prognostic score [11]. Screen failure rate was high (32%). The 3 commonest reasons for this was the presence of brain metastasis, worsening performance status and inadequate end-organ function.

Statistical analysis and ethical considerations

The study was designed to detect a 50% improvement (from four months to six months) in median PFS by adding saracatinib to cediranib with 90% power at the

20% 1-sided level of statistical significance. The efficacy was estimated from previous studies in this area [1, 12]. The primary analysis required 110 PFS events. Approximately 130 patients (65 per arm) were required to achieve this. All analyses were conducted on an intention-to-treat basis. Progression-free survival was compared between the study arms in the context of a Cox model incorporating the baseline stratification factors. The study had appropriate regulatory and ethical approval: ClinicalTrials.gov number NCT00942877.

Statistical methods

The primary end point was PFS defined as the time from randomisation to disease progression, as defined by RECIST v1.1 criteria, or death, whichever came first. Secondary endpoints included overall survival and radiological response. The strength of the relationship between radiological response and survival (OS and PFS) was tested using Pearson's correlation test. Baseline characteristics and potential prognostic factors were explored using a Cox proportional-hazards model. Progression free survival and overall survival was compared between the two groups using survival analysis methods including Kaplan-Meier plots and Lo-rank tests. The study was designed to detect a 50% improvement (from 4 months to 6 months) in median PFS by adding saracatinib to cediranib with 90% power at the 20% 1-sided level of statistical significance. This required 110 PFS events and 130 patients (65 per arm). All statistical analyses were performed using SPSS version 21.0.

Biomarker analysis

A tissue microarray (TMA) was constructed from biopsy tissue samples from 78 patients. 4µm thick sections were deparaffinised and rehydrated using xylene and alcohol, and incubated with 0.3% hydrogen peroxide to block endogenous peroxidise activity. Heat-mediated antigen retrieval was performed in citrate buffer (pH 6.0). The following antibodies were used to assess protein expression: VHL (1:200; BD

Pharmingen), FAK (1:100; Cell Signalling), SRC (1:200; Cell Signalling), PTB1b (1:2500; Abcam), HIF2α (1:3000, Novus Biologicals). The TMA was then processed using either EnVision Kits (DAKO) or VECTASTAIN ABC Kit (Vector Labs) according to manufacturer's instructions. A single pathologist scored the immunohistochemical (IHC) expression. The immunohistochemical scoring was performed independently and blinded to patient outcome data using the weighted histoscore method. Expression was scored by staining intensity (0, negative; 1+, weakly positive; 2+, moderately positive; 3+, strongly positive), then multiplying with the percentage of tumour cells seen within each section.

RESULTS

Patient population

Between 2010 and 2012, 138 patients were randomised into this study across 16 sites in the UK. Median age for the population was 60 years (interquartile range 54-67 years). Eighty-two percent of patients previously received sunitinib. Overall 96% received only one previous VEGF targeted therapy, the remainder received two previous lines of VEGF therapy. Twenty percent of patients had previously received immune therapy as initial treatment for metastatic disease prior to subsequent VEGF targeted therapy. Overall 15%, 70%, 15% had MSKCC good, intermediate or poor risk disease respectively at the time of randomisation. The characteristics of the two groups (n=69 for each) were well balanced (Table 1). A consolidated standards of reporting trials (CONSORT) diagram summarises the trial in Figure 1. Sixty-six patients (32%) failed during screening. There were no specific exclusion criteria unique to this study. It was felt that the screen failure rate reflects the advanced nature of the cancer. The presence of brain metastases, worsening performance status and inadequate organ function were common reasons for exclusion.

Efficacy analysis

The median progression free and overall survival for the whole group was 4.1 months (95% confidence interval (CI): 3.1-5.1 months) and 12.0 months (95% CI: 8.5-15.6 months) respectively. Partial responses were seen in 13.0% for cediranib and 14.5% for cediranib and saracatinib respectively (P>0.05). Progression of disease as best response occurred 29% for cediranib and 20% for cediranib/saracatinib (P>0.05). There was no significant difference in PFS [5.4 months (3.6-7.3 months) for cediranib and 3.9 (2.4-5.3 months) for cediranib/saracatinib: Hazard Ratio (HR) 1.18 (0.94-1.48) P>0.05] or OS [14.2months (11.2-16.8 months) for cediranib and 10.0 (6.72-13.2 months) for cediranib/saracatinib: HR 1.28 (1.00-1.63) P>0.05] for the two cohorts (Fig. 2 and Fig. 3). Forest plot analysis showed no consistent subsets that benefited from the combination with the exception of patients with PS 0 (compared to 1 or more) (Fig. 4). Due to the small numbers in this group the results may be artefact. Median follow up was 12 months in line with the short OS of the patients. Subsequent targeted therapies (VEGF or mTOR) were given in 25 (36%) cediranib and 33 (47%) cediranib/saracatinib patients.

Adverse events

There were no significant differences in the frequency of key AEs (Table 2). Lethargy and diarrhoea were the most common AEs in both arms (>75% for all grades in both arms and >10% grade 3/4 for both arms). Dose reductions and discontinuation due to AEs with cediranib and cediranib/saracatinib occurred in 13% and 8% vs. 19% and 18% respectively (P>0.05). The commonest reason for dose reduction with the combination was diarrhoea (n=4).

Biomarker analysis and exploratory endpoints

Archived tissue was available from 86 (62%) patients. High levels (IHC 2+/3+) of FAK, SRC, PTB1b and HIF2α were present in 48%, 31%, 38% and 15%

respectively. High levels of VHL were seen in 65% of patients. None of these biomarkers were prognostic in terms of PFS or OS (Table 3). FAK expression was predictive of OS [HR: 2.29 (95% CI: 1.09-4.82) $P<0.05$] but not PFS [HR: 0.85 (95% CI: 0.58-2.40) $P>0.05$] (Table 3).

DISCUSSION

The aim of this study was to determine if the addition of a SRC inhibitor (saracatinib) to a VEGF TKI (cediranib) overcame VEGF resistance in patients who progressed after prior VEGF targeted therapy. Preclinical work suggests the combination of cediranib and saracatinib are more active than cediranib alone in mRCC [4]. Our clinical results show this was not the case in VEGF resistant mRCC. Therefore further evaluation of the combination in this setting is not recommended.

The combination was tolerable and comparable in the two study arms. Adverse events were dominated by the toxicity seen with cediranib, with diarrhoea, lethargy, nausea/vomiting and hand/foot syndrome being most prominent. However 18% of patients discontinued the combination due to toxicity compared to 8% with cediranib alone. This figure (18%) is numerically higher than those seen with axitinib or everolimus in the pivotal trials and may have been relevant in the efficacy results [1, 12]. While indirect comparisons across trials are not valid, the discontinuation rate in this study is high. There are a number of factors which may have contributed to this, ranging from co-morbidities to treatment related toxicity. It underlines the importance of management of toxicity.

Patients' characteristics in the two groups were balanced and in line with previous studies [1, 12]. Most patients had MSKCC intermediate risk disease having failed one line of therapy (96%) (pazopanib or sunitinib in >95%). Forest plot analysis

showed the only subgroup of patients which appeared to gain advantage with the combination were those with PS <1. There is no scientific rationale why this may be the case, although previous work with axitinib also suggested PS may be relevant in predicting response to targeted therapy [13].

Cediranib was used as it was the only VEGF agent with phase I data in combination with saracatinib. Had the trial been positive, the correct competitor for the randomised phase III trial would have been axitinib. Pharmacokinetic data from the phase I saracatinib study suggested 175mg OD is an active dose, while 30mg OD of cediranib has activity and was the optimal dose for combinations. This dose of cediranib has resulted in positive studies in other tumours [14, 15]. Overall the doses in this study tested the optimal doses of both arms to best interrogate the efficacy of the combination. However, in our study, it is possible that cediranib at 45mg in the control arm resulted in additional activity compared to 30mg in the combination arm. Nevertheless, these effects are likely to be subtle and it is hard to justify taking either arm forward at this stage. The relatively high discontinuation rate with the combination (18%) suggests further dose adjustments to improve efficacy are not worthwhile.

The activity of single agent cediranib at 45mg (RR=13% PFS 5.4 months [investigator assessed]) was in line with other agents tested in VEGF refractory disease (axitinib RR=19% PFS 6.5 months [investigator assessed] and sorafenib RR=10% PFS 4.5 months [investigator assessed]) [1]. Cediranib is not being further investigated in mRCC largely due to the competitive landscape. However it has positive results and is being developed in other tumours such as ovarian cancer [14].

The overall survival of 12 months in our trial is modest, especially as most patients were being treated in the second line setting. However, this is within the range of the

OS seen in other randomised trials in this setting (14.8 months) [16]. Shorter survival may in part be due to patient selection and limited access to therapies for RCC in the UK, although a significant proportion received further therapy in this study (36-47%). Recent advances with immune therapy showed prolonged survival with nivolumab in VEGF resistant disease [17]. The median overall survival was over 25 months with this agent. This reflects the rapid progress of treatment development in renal cancer.

Preclinical work suggests FAK, which is downstream of SRC, and PTB1b, which is linked to tumour growth in breast cancer, may be important in the identification of patients who benefit from saracatinib and cediranib combination therapy [4, 18]. Our biomarker analysis was unable to confirm this although FAK overexpression predicted survival (but not PFS) to the drug combination. Further exploration of this may be warranted in other settings. It is unclear why FAK was predictive for OS, but not PFS. Given its role in co-ordinating integrin signalling and cell migration, one possibility is that FAK inhibition reduces metastatic spread without affecting local growth of the tumour [19]. Further evaluation is required. It is possible that biomarker expression from archived tissue was not representative of biomarker expression at the time of randomisation. This questions the validity of this exploratory endpoint. Collection of fresh tissue in randomised trails has proved challenging.

While SRC inhibition may be promising theoretically and preclinically, targeting single tyrosine kinases in VEGF resistant patients may not be optimal due to the tumour heterogeneity seen clinical setting. To support this, similar results were seen with dovitinib (a FGF-2 inhibitor) in VEGF refractory disease [20]. Other resistance pathways may also be involved (reviewed by [21])

In addition to the limitations discussed above, the lack of independent radiology review to determine PFS is a weakness of this study. Although cediranib is not a

licensed treatment in renal cell carcinoma, similarities in the mechanism of action mean that it is uncertain if a different outcome would have been found if axitinib had been used. Therefore, further evaluation in the VEGF resistant setting is not recommended. However, it remains an open question as to whether the combination in a first line setting may be more efficacious by potentially preventing the development of VEGF resistance. Biomarker analysis was carried out on archival tissue. It is possible that biomarker expression from archived tissue was not representative of biomarker expression at the time of randomisation. This questions the validity of these exploratory endpoint. Collection of fresh tissue in randomised trails has proved challenging. This may have limited the ability to analyse the predictive value of some of the biomarkers in the VEGF resistant setting.

CONCLUSIONS

Together these data suggest that cediranib has activity in this setting, as one might expect in view of its mechanism of action. While direct comparisons with other trials are not possible, indirectly there is nothing from this study to suggest the single agent cediranib would be superior to other agents such as axitinib or everolimus in this setting. The addition of saracatinib to cediranib was relatively well tolerated, but did not improve efficacy. This suggests the preclinical hypothesis is flawed rather than an inability to give the drugs together. We were also unable to robustly replicate the preclinical biomarker data which pointed towards a personalised approach with these drugs. However, further exploration of FAK may be warranted.

DISCLOSURES

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Table 1: Patients' characteristics at baseline

VEGF = vascular endothelial growth factor; MSKCC = Memorial Sloan Kettering Cancer Centre; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.

Table 2: Most common adverse events (CTCv3.0)

Table 3: Biomarker analysis (prognostic and predictive evaluation)

*of statistical significance. PFS = progression free survival; OS = overall survival; CI = confidence interval; FAK = focal adhesion kinase; VHL = von Hippel-Lindau; PTB1b = protein tyrosine phosphatase Ib; HIF2α = hypoxia-inducible factor 2α.

Figure 1: Consolidated standards of reporting trials (CONSORT) flow diagram

Figure 2: The progression free survival of cediranib and placebo vs. cediranib and saracatinib

Figure 2 legend: Kaplan-Meier analysis for PFS

Cediranib and Saracatinib = 3.9 months (95% CI: 2.4-5.3)

Cediranib and Placebo = 5.4 months (95% CI: 3.6-7.3)

HR = 1.18 (95% CI: 0.94-1.48)

Figure 3: The overall survival of cediranib and placebo vs. cediranib and saracatinib

Figure 3 legend: Kaplan-Meier analysis for OS

Cediranib and Saracatinib = 10.0 months (95% CI: 6.7-13.3)

Cediranib and Placebo = 14.2 months (95% CI: 11.2-17.3)

HR = 1.28 (1.00-1.63)

Figure 4: Forest plot analysis comparing cediranib and placebo vs. cediranib and saracatinib for pogression free survival

Figure 4 legend: Forest Plot subset analysis comparing cediranib with cediranib and saracatinib. The dots represent the hazard ratio value and the lines the 95% confidence intervals. LDH = lactate dehydrogenase; CRP = C-reactive protein; MSKCC = Memorial Sloan Kettering Cancer Centre risk score.

Enrollment

Assessed for eligibility (n=204)

Excluded (n=66)
- Not meeting inclusion criteria (n=66)

Randomised (n=138)

Allocation

Allocated to cediranib and placebo (n=69)
- Received allocated intervention (n=69)

Allocated to cediranib and saracatinib (n=69)
- Received allocated intervention (n=69)

Follow-Up

Discontinued intervention (n=68)
- Disease progression (n=50)
- Toxicity (n=9)
- Withdrawal of consent (n=3)
- Death (n=2)
- Investigators choice (n=3)
- Other (n=1)

Discontinued intervention (n=66)
- Disease progression (n=47)
- Toxicity (n=13)
- Death (n=3)
- Investigators choice (n=2)
- Other (n=1)

Analysis

Analysed (n=69)
- Excluded from analysis (n=0)

Analysed (n=69)
- Excluded from analysis (n=0)

Time from treatment start (years)

Time from start of treatment (years)

	n		HR (95% CI)
Platelets (below median)	69		1.212 (0.877-1.433)
Platelets (above median)	69		0.956 (0.746-1.226)
Haemoglobin (below median)	73		1.033 (0.815-1.309)
Haemoglobin (above median)	65		1.039 (0.806-1.338)
LDH (below median)	65		1.330 (1.025-1.726)
LDH (above median)	64		0.691 (0.526-0.908)
CRP (below median)	66		0.932 (0.722-1.202)
CRP (above median)	65		1.032 (0.838-1.399)
Performance Status =0	27		1.502 (1.046-2.156)
Performance Status >=1	101		0.879 (0.718-1.076)
No Immunotherapy	109		0.975 (0.803-1.184)
Immunotherapy	29		1.257 (0.837-1.889)
No Previous sunitinib	28		1.191 (0.800-1.774)
Previous sunitinib	110		0.977 (0.805-1.186)
No Liver or Lung mets	43		0.929 (0.680-1.271)
Liver or Lung mets	95		1.053 (0.854-1.298)
MSKCC = 2	20		0.737 (0.447-1.215)
MSKCC = 1	99		1.034 (0.843-1.269)
MSKCC = 0	19		0.975 (0.588-1.616)
Female	30		1.027 (0.701-1.503)
Male	108		1.045 (0.860-1.270)
Age (below median)	69		1.060 (0.827-1.357)
Age (above median)	69		0.990 (0.774-1.265)

00   05   10   15   20   25

← Favours cediranib + placebo   Favours cediranib + saracatinib →

Table 1: Patients' characteristics at baseline

		Cediranib + placebo	Cediranib + saracatinib
Gender	male	51 (74%)	57 (83%)
Previous immune therapy	Yes	17 (24%)	12 (17%)
Performance status	0	19 (28%)	18 (26%)
	1	40 (58%)	43 (62%)
	>1	10 (14%)	8 (12%)
MSKCC risk	low	10 (14%)	9 (13%)
	intermediate	48 (70%)	51 (73%)
	high	11 (16%)	9 (13%)
Nephrectomy	yes	53 (77%)	58 (84%)
Site of disease	bone	11 (16%)	9 (13%)
	liver	8 (11%)	5 (7%)
	lung	46 (67%)	46 (67%)
	lymph nodes	32 (46%)	33 (47%)
First line VEGF targeted therapy.	sunitinib	55 (82%)	54 (80%)
	pazopanib	8 (12%)	9 (13%)
	sorafenib	1 (2%)	3 (4%)
	bevacizumab	3 (5%)	1 (2%)
Best response to first line targeted therapy	CR	2 (3%)	0 (0%)
	PR	11 (15%)	14 (20%)
	SD	27 (39%)	26 (37%)
	PD	25 (36%)	24 (34%)

VEGF = vascular endothelial growth factor; MSKCC = Memorial Sloan Kettering Cancer Centre; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.

Table 2: Most common adverse events (CTCv3.0)

	Cediranib and placebo		Cediranib and saracatinib	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Lethargy	64%	11%	64%	16%
Diarrhoea	62%	15%	68%	16%
Mucositis	38%	2%	35%	0%
Nausea	35%	4%	52%	2%
Hand and foot syndrome	29%	4%	22%	2%
Hypertension	26%	6%	20%	1%
Vomiting	25%	3%	27%	4%
Rash	25%	3%	14%	0%
Shortness of breath	13%	1%	12%	0%
Transaminitis	3%	0%	0%	3%

Table 3: Biomarker analysis (prognostic and predictive evaluation)

| | Prognostic significance of baseline levels of biomarker expression | | | | Baseline levels of biomarker expression predicting benefit with the combination | | | |
| | PFS | | OS | | PFS | | OS | |
	Hazard Ratio	95% CI	Hazard Ratio	95% CI	Hazard Ratio	95% CI	Hazard Ratio	95% CI
FAK	0.88	0.42-1.85	1.90	1.09-3.30	0.85	0.58-2.40	2.29*	1.09-4.82
SRC	1.17	0.70-1.94	1.21	0.70-2.09	0.71	0.30-0.40	1.10	0.51-2.36
VHL	0.907	0.54-1.53	1.32	0.75-2.33	1.19	0.58-2.43	0.78	0.36-1.70
PTB1B	1.08	0.64-1.79	1.33	0.76-2.33	1.27	0.62-2.58	1.09	0.51-2.35
HIF2α	0.75	0.45-1.25	1.05	0.60-1.83	1.03	0.51-2.06	1.03	0.49-2.16

*of statistical significance. PFS = progression free survival; OS = overall survival; CI = confidence interval; FAK = focal adhesion kinase; VHL = von Hippel-Lindau; PTB1b = protein tyrosine phosphatase Ib; HIF2α = hypoxia-inducible factor 2α.