

Tivozanib: a novel VEGFR inhibitor for kidney cancer

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Abstract: Treatment of kidney cancer has changed over the past 10 years with the approval of several targeted agents. These drugs are given on a long term base and toxicity is an issue for most patients. Despite improvement compared to immunotherapy, most patients will progress on these drugs. There is a need for more potent and better tolerated drugs. Tivozanib is a potent pan VEGFR specific inhibitor. In this phase II trial it gave interesting results with an overall median PFS throughout the study of 11.7 months (95% CI: 8.3-14.3 months) and an overall objective response rate of 24% (95% CI: 19-30%). "Off"-target toxicity was mild.

Keywords: Tivozanib; VEGFR inhibitor; kidney cancer



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Treatment of metastatic kidney cancer is based on targeting the VEGF pathway. Most renal cell carcinomas are clear cell and present a somatic mutation in VHL, leading to the accumulation of HIF and the transcription of HIF inducible genes for instance VEGF (1). Several VEGF tyrosine kinase inhibitors are approved for renal cell carcinoma: sunitinib, pazopanib, sorafenib and axitinib based on data from randomised phase III trials (2-6). However sunitinib, pazopanib and sorafenib are multitarget TKIs that interact with other pathways and therefore have off-target side effects, that impact the tolerance of these treatments (diarrhoea, hand-foot syndrome, haematological toxicity...).

Tivozanib is a selective, potent, pan VEGFR inhibitor that blocks VEGFR1, VEGFR2 and VEGFR3 at picomolar concentrations. It is administered orally.

Nosov et al report here on a phase II randomized trial of discontinuation (7). Patients received 1.5 mg of tivozanib daily for 3 weeks followed by a 1-week break. Tumour assessments were performed every 2 cycles. Patients who had more than a 25% tumour shrinkage at 16 weeks continued on tivozanib, patients who had an increase of 25% or more in tumour size stopped treatment. Patients, who didn't meet either of these criteria, were randomized between receiving 12 weeks of placebo or 12 weeks of

tivozanib. Tumour status was assessed at every cycle during this phase. Patients who progressed during this phase were unblinded. If they were on placebo they were started again on tivozanib. For the other patients, treatment was stopped.

After 12 weeks, all patients were unblinded and patients could continue on tivozanib. Primary objectives were safety, objective response rates at 16 weeks and the percentage of patients who remained progression free after 12 weeks with placebo or tivozanib.

Two hundred and seventy two patients were enrolled. Most patients had clear cell carcinomas (83%), 73% had had a prior nephrectomy. About half of the patients were treatment naive (54%). No prior VEGF pathway targeted therapy was allowed.

At 16 weeks, 29% of patients had tumour shrinkage of $\geq 25\%$. Seventy six patients had stopped treatment: 50 because of disease progression and 26 for other causes. A hundred and eighteen patients were randomized between receiving tivozanib (n=61) and placebo (n=57).

The objective response rate at 16 weeks was 18% (95% CI: 14-23%), all were partial responses. Sixty six percent of patients had stable disease as best response.

In the blinded phase, progression free rates were significantly higher in the patients who continued tivozanib

than in those who switched to placebo [49% (95% CI: 36-63%) vs. 21% (95% CI: 11-34%); P=0.001]. Median PFS (from randomization) was 10.3 months (95% CI: 8.1-21.2 months) in the tivozanib arm versus 3.3 months (95% CI: 1.8-8 months) in the placebo arm (P=0.01). Forty eight patients out of the 57 patients in the placebo arm were restarted on tivozanib: 24 because they progressed on placebo and 24 at the end of the blinded phase as they hadn't progressed on placebo. Ninety four percent of patients who had progressed on placebo had disease control when restarting tivozanib (objective response or stable disease).

The overall median PFS throughout the study was 11.7 months (95% CI: 8.3-14.3 months) (patients on placebo were censored at the time of randomization). The overall objective response rate was 24% (95% CI: 19-30%).

Patients who had clear cell carcinoma and who had undergone previous nephrectomy had better ORR and longer PFS.

The most frequent toxicity was, as expected, hypertension (45%; grade 3-4:12%). Other frequent side effects were dysphonia (22%; no grade 3-4). Diarrhoea occurred only in 12% of patients and asthenia in 10%. Liver toxicity was mild (1% of grade 3-4 elevation of ASAT and ALATs respectively). Lymphopenia (6%), hypokalemia (6%), increased gamma-glutamyl transpeptidase (17%) and increased uric acid (7%) were the most frequent grade 3-4 lab anomalies. Severe adverse events occurred in 13% of patients.

Eight percent of patients required dose reduction due to side effects, 4% had treatment interruptions and 9% stopped treatment because of them. Fifteen patients died on study: 8 because of disease progression and 6 from cardiovascular events. None of these deaths were considered to be treatment related.

This phase II trial shows good results with this selective and potent VEGFR inhibitor. Tolerance was good with less "off-target" side effects, than what is usually seen with less selective VEGFR inhibitors.

These interesting results with tivozanib were confirmed with the first results from a phase III trial presented at ASCO (8).

Tivozanib was compared to sorafenib in a phase III trial that enrolled 517 patients with advanced renal cell carcinoma and prior nephrectomy. Patients were treatment naive or had received no more than 1 prior systemic therapy for metastatic disease. No prior VEGF- or mTOR-targeted

therapy was allowed. Primary endpoint was PFS according to independent review. Patients who progressed on sorafenib were crossed over to tivozanib in a specific trial.

Median PFS was longer in the tivozanib arm: 11.9 months versus 9.1 months in the sorafenib arm (HR=0.797, 95% CI: 0.639-0.993; P=0.042).

In the treatment-naïve stratum (70% of patients enrolled in each arm), the median PFS was 12.7 months with tivozanib versus 9.1 months with sorafenib (HR: 0.756, 95% CI: 0.580-0.985; P=0.037). More patients had an objective response with tivozanib than with sorafenib [ORR=33% vs. 23%; (P=0.014)]. Hypertension (44%, grade 3-4: 24%), dysphonia (21%) and back pain (14%) were more frequent with tivozanib than sorafenib. Diarrhoea, hand-foot syndrome and alopecia were significantly more frequent with sorafenib.

These progression free survival data and favorable toxicity profile may allow tivozanib to become an option for the 1st line treatment of patients with metastatic renal cell carcinoma.

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None.

Footnote

Conflict of Interest: The author has no conflicts of interest to declare.

References

1. Patel PH, Chadalavada RS, Chaganti RS, et al. Targeting von Hippel-Lindau pathway in renal cell carcinoma. *Clin Cancer Res* 2006;12:7215-20.
2. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007;356:115-24.
3. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2009;27:3584-90.
4. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol* 2010;28:1061-8.

5. Escudier B, Eisen T, Stadler WM, et al. Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. *J Clin Oncol* 2009;27:3312-8.
6. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet* 2011;378:1931-9.
7. Nosov DA, Esteves B, Lipatov ON, et al. Antitumor activity and safety of tivozanib (AV-951) in a phase II randomized discontinuation trial in patients with renal cell carcinoma. *J Clin Oncol* 2012;30:1678-85.
8. Motzer RJ, Nosov D, Eisen T, et al. Tivozanib versus sorafenib as initial targeted therapy for patients with advanced renal cell carcinoma: Results from a phase III randomized, open-label, multicenter trial. *J Clin Oncol* 2012;30:abstr 4501.

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