Editorial

Towards new treatment options for renal cell carcinoma: development and clinical results of tivozanib, a selective VEGFR tyrosine kinase inhibitor

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Clear cell renal cancer (RCC) is the tumor in which the treatment paradigm of locally advanced and metastatic disease has almost completely shifted away from immunotherapy/cytokine treatment towards antiangiogenic therapies.

Apart from a very few selected cases where either interferon-α or (high dose) interleukin-2 is applied, most patients with RCC are nowadays treated with any of the currently registered oral VEGF receptor (VEGFR) tyrosine kinase inhibitors. The rationale to pursue treatment with these VEGF inhibiting agents is found in the biology of RCC where increased Hypoxia Inducible Factor (HIF)1-α leads to increased levels of VEGF ligands, making RCC a predominant angiogenesis driven tumor.

Even though initial clinical studies have demonstrated meaningful antitumor activity of bevacizumab in RCC at the end of the previous millennium, its registration for the treatment of RCC only in combination with interferon-α has somewhat hampered clinical acceptability. Nowadays, and based upon a large randomized phase III clinical study demonstrating superior activity and increased overall survival when compared to interferon-α in fist line treatment, the VEGFR tyrosine kinase inhibitor sunitinib is a global drug of choice for the first line treatment of advanced RCC.

Following the obvious success of sunitinib, many new VEGFR tyrosine kinase inhibitors have been developed. Amongst these new tyrosine kinase inhibitors that have been tested in RCC, most notably sorafenib, pazopanib and axitinib, tivozanib is the latest development.

Tivozanib is a potent and selective VEGFR tyrosine kinase inhibitor with an IC_{50} of 0.21, 0.16, and 0.24 nmol/L for VEGFR-1, -2 and -3 respectively, that inhibits angiogenesis and vascular permeability in tumor tissues and has demonstrated antitumor effects in a wide range of cancer types. Tivozanib is currently being tested in combination with various cytotoxic drug regimens for various indications, but is also, as could be expected, considered to be of interest for the treatment of RCC. Its high selectivity for VEGFR tyrosine kinases could probably mean that apart from activity, tolerability and safety could be an advantage when compared to other, more broad spectrum tyrosine kinase inhibitors, such as sunitinib or sorafenib, both registered for the treatment of RCC.

In the current study (1), Nosov *et al.* applied a randomized discontinuation design which allows for proper activity assessment and a good assessment of safety and tolerability.

Patients with RCC not amenable to surgery were allowed to have received previous systemic therapy, albeit that previous exposure to VEGF- pathway targeted therapy was not allowed. Based upon the data presented in their manuscript, it is clear that the antitumor activity of Tivozanib looks promising, with an absolute increase in Progression Free Survival (PFS) of 7 months (P=0.01) in the randomized double blinded treatment part of this study and an overall median PFS of 11.7 months. Of note is that of the 272 initially enrolled patients, 78 (28%) showed such benefit (response ≥25%) from open-label tivozanib treatment, that they were allowed to continue open label treatment following the first antitumor assessment, whereas only 50 patients (18%) showed disease progression (≥25%) and had to be taken off treatment following the

first antitumor assessment. This observed response rate of tivozanib seems to be comparable with response rates observed in the pivotal phase 3 trial of sunitinib and the (randomized discontinuation) trials performed with sorafenib, pazopanib and axitinib (2-5).

The observed safety profile of tivozanib in this study is well in line with that of the other VEGFR tyrosine kinase inhibitors mentioned and confirms the overall good safety profile observed in the phase I trial of tivozanib with predominantly on-target side effects such as hypertension (6). Cumbersome side effects such as gastrointestinal toxicities and hand-foot skin syndrome and side effects suggestive for increased thromboembolic tendency occurred only infrequently, as did rade 3 or 4 haematological toxicity.

With regard to the 'final' position that tivozanib might reach within the crowded field of VEGFR tyrosine kinase inhibitors available for the treatment of advanced RCC, randomized trials comparing progression free and overall survival are mandatory; if these trials are to be designed for superiority, probably large numbers of patients will be needed when considering the fact that all VEGFR tyrosine kinases discussed here have shown biological and clinical activity. In studies designed to demonstrate non-inferiority, thorough assessment of patient reported outcomes and/or Quality of Life doubtlessly have to be an integral and crucial endpoint. While awaiting the results of the randomized study NCT00720941 comparing first line efficacy of sunitinib *vs.* pazopanib, it is currenly too early to forecast a dramatic shift in the first line treatment preference of advanced RCC.

The fact that some patients cannot tolerate a given VEGFR tyrosine kinase inhibitor, while showing good tolerability for another compound, allows oncologists and patients to make in the very near future an even larger choice between several active compounds now that tivozanib is likely too to find a place and become registered within the armamentarium of VEGFR tyrosine kinase inhibitors available for the treatment of advanced RCC.

Results of the randomized phase 3 trial comparing tivozanib to sorafenib in first line VEGF pathway directed therapy in subjects with advanced RCC (TIVO-1) have been presented at the 2012 ASCO meeting (7).

In conclusion, this phase II randomized discontinuation trial has shown that tivozanib is an active VEGFR tyrosine kinase inhibitor for the treatment of advanced RCC.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. 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.
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. Ratain MJ, Eisen T, Stadler WM, et al. Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. J Clin Oncol 2006;24:2505-12.
4. Hutson TE, Davis ID, Machiels JP, et al. Efficacy and safety of pazopanib in patients with metastatic renal cell carcinoma. J Clin Oncol 2010;28:475-80.
5. Rini BI, Wilding G, Hudes G, et al. Phase II study of axitinib in sorafenib-refractory metastatic renal cell carcinoma. J Clin Oncol 2009;27:4462-8.
6. Eskens FA, de Jonge MJ, Bhargava P, et al. Biologic and clinical activity of tivozanib (AV-951, KRN-951), a selective inhibitor of VEGF receptor-1, -2, and -3 tyrosine kinases, in a 4-week-on, 2-week-off schedule in patients with advanced solid tumors. Clin Cancer Res 2011;17:7156-63.
7. Motzer R, 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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