Research Highlight

# Identification of biomarkers in pazopanib treated patients with renal cell carcinoma

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Targeted therapy has become the mainstay in the treatment of renal cell carcinoma (RCC). That being said, it is difficult to predict which patients will respond to targeted therapy. A recent article published in *The Lancet Oncology* attempts to identify biomarkers in patients receiving pazopanib that may be helpful in the clinical management of renal cell carcinoma.

Tran and colleagues performed an investigation of prognostic or predictive biomarkers in metastatic RCC patients treated with pazopanib (1). Using a retrospective design in three phases, the authors screened, confirmed, and validated prospective cytokines and angiogenic factor (CAF) biomarkers using previously published data from an open-label phase 2 trial and a randomized, placebo-controlled phase 3 study. From all patients enrolled in the phase 2 trial, 129 samples were selected for initial screening because these individuals had the greatest or least change in tumor length from baselines. The initial screening phase tested for 17 potentially valuable CAFs, although the authors' inclusion criteria for which biomarkers to assess are unclear. During the confirmation phase, the investigators tested promising CAFs in the complete sample of patients from the same phase 2 trial (n=215). Finally, the validation phase used available samples from the phase 3 trial and analyzed pre-treatment levels of 7 CAFs for their relationship to progression-free survival (PFS): interleukin 6, interleukin 8, osteopontin, VEGF, hepatocyte growth factor (HGF), tissue inhibitor of metalloproteinases-1 (TIMP-1), and E-selectin. Of the 435 patients enrolled in the phase 3 trial, 344 (79%) samples were obtained by Tran et al for validation.

After these three phases of analysis, 4 CAFs were found to interact significantly with PFS in metastatic renal-cell cancer patients who received pazopanib treatment. High (relative to median) pre-treatment plasma concentrations of interleukin 8, HGF, osteopontin, and TIMP-1 were correlated with statistically significant reductions in PFS. Median decreases in PFS ranged from 16-17.8 weeks in patients with high concentrations of these biomarkers, compared to patients with low concentrations. In addition, the study authors found that higher levels of interleukin-6, interleukin-8, and osteopontin were stronger negative prognostic markers than standard clinical classifications, including Eastern Clinical Oncology Group, Memorial Sloan Kettering Cancer Center, and Heng methods. Attempts to investigate the relationship of CAFs to overall survival were confounded by the high proportion of patients (55%) in the phase 3 trial who were randomized to receive placebo but were switched to pazopanib therapy upon disease progression.

Renal cell carcinoma is a biologically diverse cancer accounting for approximately 4% of all new cancer diagnoses in the United States (2). Mutations of the von Hippel-Lindau (VHL) gene are involved in most cases of hereditary and sporadic RCC, leading to overexpression of interleukin-8, VEGF and PDGF (1,3). Numerous targeted agents have been approved for use in renal cell carcinoma, including tyrosine kinase inhibitors and mTOR inhibitors. Pazopanib is one of four tyrosine kinase inhibitors used in the treatment of RCC targeting both VEGF and PDGF.

Past research has been done to identify factors that would be useful in guiding a personalized treatment approach to RCC. These factors have focused on clinical features, histology, immunohistochemistry, VEGF levels, gene mutation status and cell cycle and proliferation markers (4). Although there are numerous biomarkers mentioned in the literature, there is currently no standard biomarker routinely

 

used in the therapy management of RCC. As new drugs emerge, it would helpful for practitioners to have guidance on which therapy would be appropriate for an individual patient.

While high-quality prospective trials remain the gold standard for predictive biomarker validation, retrospective analyses of clinical studies represent a more feasible and cost-effective alternative when designed and conducted appropriately. Strengths of the Tran et al study include the prospectively declared techniques and study population, and its use of data from two separate peer-reviewed randomized controlled trials for the identification and validation of CAFs. However, the potential for selection bias of the study samples remains since not all patients from the phase 3 trial were included in the validation phase. In addition, no clear sample size or power calculations were described by the investigators, leaving doubt as to whether the analyses were adequately powered to detect all predictive or prognostic biomarkers.

The authors found a high correlation between the three platforms tested (ELISA, protein array, and multiplex assay), suggesting that results were independent of the CAF testing method. However, concentration cutoffs established on one platform could not be applied to other tests. Therefore, verifiable cutoffs must be established before these results can be applied widely.

The study by Tran and colleagues was a well-designed trial that provides evidence for the use of certain CAF biomarkers in the prediction of outcomes in patients treated with pazopanib. Future research needs to expand on this information in order to identify clinically relevant biomarkers that can be generalized to the entire RCC population.

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## Footnote

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

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