Aim: Despite significant effort, identifying predictive biomarkers for VEGF-targeted therapies remains a challenge. Using population-based tumor models, we identified a population of infiltrating myeloid cells associated with resistance to tivozanib, a selective VEGF receptor TKI. Myeloid cell biomarkers (immunohistochemistry [IHC] and RNA) from preclinical studies were evaluated in a phase 2 RCC clinical trial.

Methods: Prespecified biomarkers were evaluated in AV-951-10-202 (NCT01297244), a single-arm trial of tivozanib monotherapy in nephrectomized, targeted, therapy-naive RCC. RNA signatures were quantified using averaged qRT-PCR values on available tumor formalin-fixed paraffin-embedded archival tissues. CD68 (+)-infiltrating myeloid cells were quantified by IHC (Aperio Scanscope). RNA signatures were evaluated for prognostic impact in a dataset collected prior to the use of VEGF targeted therapies (Zhao et al. PLoS Med. 2006;3:e13).

Results: Patients (n = 105) were enrolled (90 clear cell [cc] histology): intent-to-treat (ITT) progression-free survival (PFS), 9.7 mo; ccRCC PFS, 9.7 mo). ccRCC samples that passed quality check (RNA, 63; IHC, 66) were analyzed. Low myeloid signature score was associated with significantly longer PFS based on median cutoff (PFS 14.7 vs 8.3 mo, hazard ratio [HR] 0.49, P = .035; 95% CI 0.25-0.96), and as a continuous variable (P = .03; N = 63). The CD68 IHC score exhibited a similar trend but was not significant (median cutoff PFS 13.3 vs 9.2, HR 0.55, P = .067; 95% CI 0.28-1.05; continuous P = .057, N = 66). This gene signature exhibited a prognostic effect in a historical data set (Zhao, 2006).

Conclusions: A preclinically derived myeloid signature identified a ccRCC population with longer PFS on tivozanib and further provides a candidate VEGF pathway resistance mechanism amenable to inhibition. These results warrant the consideration of combination therapies targeting both the VEGF pathway and myeloid cells.

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