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ABSTRACT

Emerging Therapeutic Options for VHL Patients: a tale of three studies

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Background: von Hippel-Lindau (VHL) disease induces vascular neoplasms in multiple organs. We evaluated the safety and efficacy of targeted molecular intervention in VHL patients andexamined the expression of various candidate receptors in the endothelium of archived tissue.

Methods: Patients with genetically confirmed VHL and measurable lesions were enrolled andgiven oral sunitinib. The primary end point was toxicity. Modified RECIST were used for efficacy assessment. We evaluated 20 archival renal cell carcinomas (RCC) and 20 hemangioblastomas(HB) for endothelial biomarker expression levels using laser-scanning cytometry (LSC).

Results: Fifteen patients were treated. Grade 3 toxicity included fatigue in five patients. Eighteen RCC, and 21 HB lesions were evaluable. Six of the RCCs (33%) responded partially, whereas none of the HBs did (P=0.014). LSC revealed mean phosphorylated FRS2 levels in HB endothelium were 12.5 (0.49) vs. 11.9 (0.99) in RCC (P=0.059) and in the whole tumor sample, were 11.45(0.26) for HB vs. 11.26 (0.089) for RCC (P=0.003).

Conclusions: Sunitinib treatment in VHL patients showed acceptable toxicity. We confirmed a significant response to sunitinib in RCC but not in HB. Greater expression of pFRS2 in HB tissue than in RCC raises the hypothesis that treatment with FGF pathway–blocking agents may benefit patients with HB. We will be treating 14 VHL patients with VHL and hemangioblastomas with TKI258, a small molecule inhibitor of FGFR and VEGFR. Additionally, we will be opening a multicenter 40 patient study treating VHL patients with pazopanib, a well tolerated small molecule VEGFR inhibitor.