Systemic Therapies for VHL

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Current standard of care for patients with von Hippel Lindau (VHL) disease include regular surveillance followed by organ targeted intervention if threatening lesions are observed. Effective systemic therapy is an unmet need in this patient population.

VHL loss results in an inability to downregulate hypoxia inducible factor 1 alpha and 2 alpha (HIF1 and HIF2), with subsequent upregulation of vascular endothelial growth factor (VEGF) transcription and the formation of highly angiogenic tumors. A number of agents targeting VEGF or VEGF receptors (VEGFR) have been developed and approved for advanced clear cell renal cell carcinoma (ccRCC), which shows frequent somatic mutations in the *VHL* gene. Antiangiogenic agents have been tested in patients with VHL disease, based on the hypothesis that formation and progression of renal, CNS, pancreatic and adrenal lesions in patients with VHL disease is primarily driven by excess angiogenesis. Sunitinib, a small molecule VEGFR inhibitor, demonstrated a 33 percent objective response rate (ORR) in VHL disease related ccRCC in a small phase II study, but did not induce any objective response in hemangioblastomas. Pazopanib, another small molecule VEGFR inhibitor, produced a 52 percent ORR in VHL disease related ccRCC, and a 4 percent ORR in hemangioblastomas in a 31 patient study. In both of these studies, patients experience significant treatment emergent side effects, which resulted in a number of patients coming off study for this reason.

Recently, MK6482, a small molecule inhibitor of HIF2, was tested in a pivotal 61 patient phase II study. In this study, a confirmed ORR of 36 percent was observed in VHL disease related ccRCC and a 30 percent ORR was seen in CNS lesions, with an 11 percent complete response rate. Additional responses were seen in pancreatic lesions and in retinal lesions. This agent was well tolerated, and most patients remain on study. MK6482 was granted Breakthrough Therapy designation for VHL disease related ccRCC. Further follow up and study of MK6482 in VHL disease appears warranted, and provides hope for patients with this devastating disease.