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Phase II study of the oral HIF-2α inhibitor MK-6482 for Von Hippel-Lindau (VHL) disease-associated clear cell renal cell carcinoma (ccRCC): Update on RCC and non-RCC disease

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Background

The autosomal dominant hereditary disorder VHL disease is characterized by germline inactivating mutations in the *VHL* gene and constitutive activation of the HIF-2α transcription factor, which drives tumor growth. MK-6482, a potent, selective, small molecule HIF-2α inhibitor, was evaluated for efficacy for treatment of VHL-associated tumors in this open-label phase II study (NCT03401788).

Methods

Eligible patients (pts) were aged ≥18 yrs and had a VHL diagnosis based on germline *VHL* alteration, ≥1 measurable solid RCC tumor, no prior systemic anticancer therapy, and ECOG PS 0 or 1. Pts received MK-6482 120 mg orally once daily until progression, intolerable toxicity, or investigator/pt decision to withdraw. Primary end point: ORR of VHL-associated ccRCC tumors per RECIST v1.1 by independent review committee (IRC). Secondary end points: ORR in non-RCC tumors, DOR, and safety.

Results

As of June 1, 2020, 56 of 61 (92%) enrolled pts remain on treatment with a minimum of 60 wks follow-up. All pts had ccRCC, 100% had pancreatic lesions, 70% had CNS hemangioblastomas, and 26% had retinal lesions evaluable by IRC. For ccRCC, ORR was 36% (95% CI, 24-49%) and an additional 7 (11%) unconfirmed responses (documented at single time point and pending confirmation at data cutoff) were reported by IRC; all responses were PRs. DOR in confirmed responses was not reached (NR; range, 12-62 wks). The PFS rate at 52 wks was 98% (95% CI, 89-100%). For non-RCC tumors, per IRC, the ORR was 64% (4 CRs) in pancreatic lesions and 30% (5 CRs) in CNS hemangioblastomas; median DOR was NR (range, 11-71 wks) in pts with pancreatic lesions and NR (range, 12-72 wks) in pts with central nervous system hemangioblastomas. Of 16 pts with evaluable retinal lesions at baseline, 11 (69%) showed improvement per IRC. Treatment-related AEs were reported by 98% of pts; 13% had grade 3 TRAEs. There were no grade 4-5 TRAEs. Five pts discontinued treatment (patient decision [n=3], treatment-related adverse event [n=1; grade 1 dizziness], and death [n=1; acute fentanyl toxicity]).

Conclusions

MK-6482 continued to demonstrate promising antitumor activity against VHL-associated RCC and non-RCC tumors and was well tolerated.

Clinical trial identification

NCT03401788.

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