AB521 Blocks HIF-2α Target Gene Transcription in a Dose-dependent Manner and Controls Tumor Burden Alone or in Combination with TKI or anti-PD-1 in ccRCC Xenograft Models

**BACKGROUND**

Hypoxia inducible factor (HIF-2α) is a master transcription factor that regulates genes essential for survival, angiogenesis, and immune escape in ccRCC. HIF-2α expression is a driver in ccRCC and is a therapeutic target. Preclinical3,4 and clinical trials using HIF-2α inhibitors have demonstrated efficacy in ccRCC.

**RESULTS**

AB521 is a novel, orally available, potent, and selective HIF-2α inhibitor that has been extensively characterized in biophysical, biochemical, and cellular assays. AB521 demonstrated PK/PD properties in healthy human volunteers that are consistent with a potential best-in-class HIF-2α inhibitor. AB521 up to 200 mg QD was well tolerated in healthy volunteers, and a phase 1 study is ongoing (NCT05117554/ARC-14). When administered orally in mice, AB521 regressed established 786-O and A498 ccRCC xenograft tumors and decreased tumor PD markers that correlated with reduced p-VEGFA concentrations of AB521. Enhanced tumor control was observed in combination with TKI cabozantinib in the standard A498 xenograft model and with anti-PD-1 in a humanized PBMC A498 xenograft model (Figure 2). AB521 demonstrated PFS properties in healthy human volunteers that are consistent with a potential lead in dose HIF-2α inhibitor profile (Figure 3). See also13.

**SUMMARY**

AB521 is a potent and selective small molecule HIF-2α inhibitor that has been extensively characterized in biophysical, biochemical, and cellular assays. AB521 demonstrated PK/PD properties in healthy human volunteers that are consistent with a potential best-in-class HIF-2α inhibitor. When administered orally in mice, AB521 regressed established 786-O and A498 ccRCC xenograft tumors and decreased tumor PD markers that correlated with reduced p-VEGFA concentrations of AB521. Enhanced tumor control was observed in combination with TKI cabozantinib in the standard A498 xenograft model and with anti-PD-1 in a humanized PBMC A498 xenograft model (Figure 2). AB521 demonstrated PFS properties in healthy human volunteers that are consistent with a potential lead in dose HIF-2α inhibitor profile (Figure 3). See also13.