AACR Special Conference:
Advances in Kidney Cancer Research
June 24-27th, 2023
Poster A002

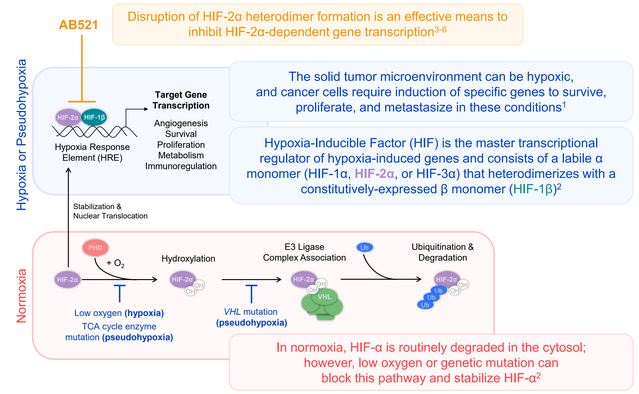
Targeting Hypoxia Inducible Factor (HIF)-2α With AB521, a Novel and Potent Small Molecule HIF-2α Inhibitor, for the Treatment of Clear Cell Renal Cell Carcinoma

Paul G. Foster, Dana Piovesan, Mohammad Ghasemi, Tzuling Cheng, Kai H. Liao, Elaine Paterson, Soonweng Cho, Kenneth V. Lawson, Matthew J. Walters, Kelsey E. Sivick Gauthier

Arcus Biosciences, Hayward, CA, USA

ARCUS BIOSCIENCES

BACKGROUND



Preclinical[3,4] and clinical[7,8] evidence shows that inhibiting HIF-2α is a valid approach to block progression in pseudohypoxic cancers where HIF-2α is a tumorigenic driver.

Here we provide *in vitro*, *in vivo*, and clinical characterization of AB521, a novel and potent small molecule HIF-2α inhibitor in clinical trials.

1) Hockel (2001) J Natl Cancer Inst 10.1093/jnci/93.4.266
2) Triner (2016) JCI 10.1172/JCI84430
3) Wallace (2016) Nature 10.1158/0008-5472.CAN-16-0473
4) Xu (2019) J Med Chem 10.1021/acs.jmedchem.8b00719
5) Li (2019) J Med Chem 10.1021/acs.jmedchem.8b01596
6) Yu (2019) Drug Disc Today 10.1016/j.drudis.2019.09.008
7) Jonasch (2022) JCO 10.1200/JCO.2022.40.16_suppl.4509
8) Jonasch (2022) JCO 10.1200/jco.2022.40.16_suppl.4546
9) Gauthier (2021) Mol Cancer Ther 10.1158/1535-7163.TARG-21-P206*
10) Lawson (2021) Cancer Res 10.1158/1538-7445.AM2021-1206*
11) Gauthier (2019) Mol Cancer Ther 10.1158/1535-7163.TARG-19-C050/
12) Gauthier (2020) JITC 10.1136/jitc-2020-SITC2020.0583
13) Liao (2022) Eur J Cancer 10.1016/S0959-8049(22)00856-5*
14) Choueiri (2023) ASCO TPS 4602
*Available for download at https://arcusbio.com/our-science/publications/

RESULTS

AB521 Inhibits Transcription of Pro-tumorigenic HIF-2α Target Genes in ccRCC Cancer Cells, Primary Endothelial Cells, and M2-polarized Macrophages

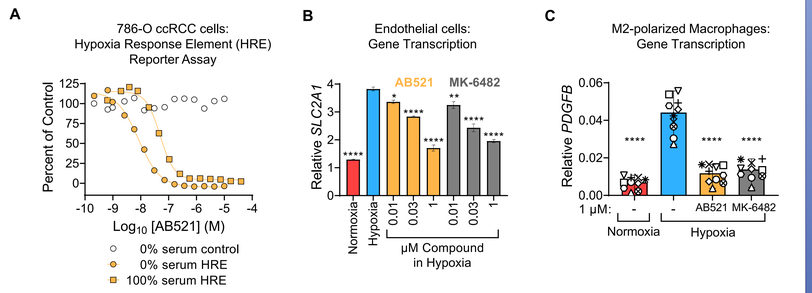


Figure 1. Cells present in the solid renal tumor microenvironment were modeled *in vitro* using: **(A)** 786-O ccRCC cancer cells engineered with a luciferase reporter under control of the HRE, **B)** primary human umbilical vein endothelial cells (HUVECs), and **(C)** primary human CD14+ monocytes differentiated (with M-CSF) and polarized (with IL-4) to M2-like macrophages. (B & C) Cellular changes in gene expression relative to housekeeping gene 24 hours after incubation. (B) Bars and error denote mean ± standard deviation (SD). (C) Bars and error denote median ± range while symbols represent individual donors. MK-6482/belzutifan was synthesized at Arcus according to published methods[4]. *p<0.05, **p<0.01, ****p<0.0001 vs Hypoxia. Normoxia, 21% O_2; Hypoxia, 1% O_2.

RESULTS

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

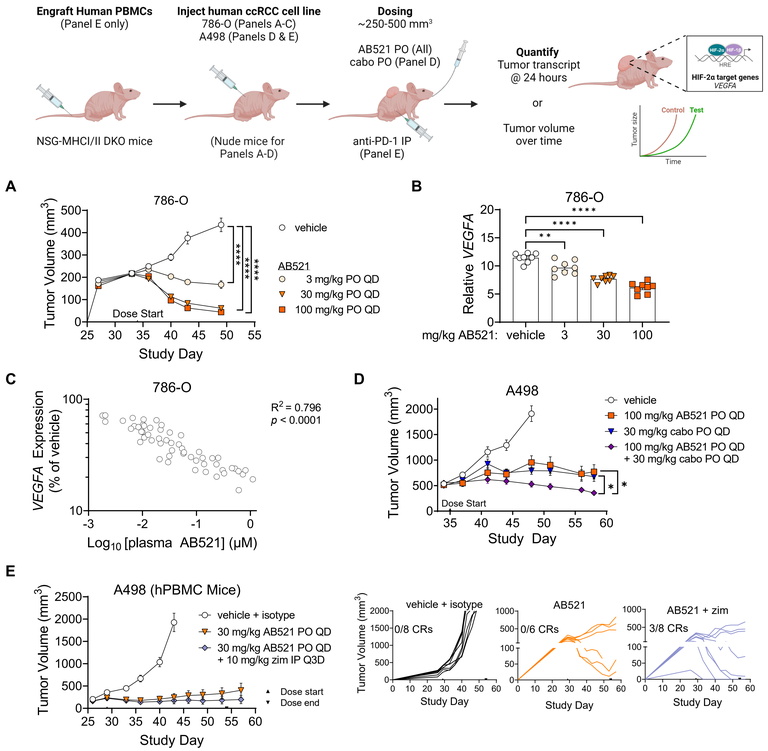


Figure 2. **(A & B)** Vehicle or AB521 administered by oral gavage (PO) once daily (QD) when tumors were ~300 mm3. (A) Group mean ± SD over time. (B) Changes in intratumoral gene expression (*VEGFA* relative to housekeeping gene) 24 hours after the first dose. Bars and error denote mean ± SD while symbols represent individuals. **(C)** Pharmacokinetic (PK)-Pharmacodynamic (PD) correlation plot collated from several studies. Plasma AB521 concentrations after a single dose plotted against relative *VEGFA* tumor transcript levels as a percent of vehicle mean from the corresponding study. Symbols represent individuals. **(D)** Vehicle, 100 mg/kg AB521, 30 mg/kg cabozantinib (cabo), or a combination of 100 mg/kg AB521 + 30 mg/kg cabo administered PO QD when tumors were ~500 mm3. Group mean ± SD over time. **(E)** NSG-MHCI/II double knockout (DKO) mice were engrafted using 10-20x10[6] human PBMCs (hPBMC) from one of two healthy donors. Vehicle, 30 mg/kg AB521, or a combination of 30 mg/kg AB521 + 10 mg/kg anti-PD-1 antibody zimberelimab (zim) intraperitoneally (IP) every three days (Q3D) were administered when tumors were ~275 mm3. Group mean ± SD over time (left) and individual growth curves with number of complete regressions (CRs) (right). *p<0.05, **p<0.01, ****p<0.0001.

RESULTS

AB521 Exhibits Favorable PK and PD Properties in Healthy Human Volunteers (NCT05117554/ARC-14)

- Mean apparent terminal half-life is 18 to 24 hours, supporting once-daily (QD) dosing
- The peak-to-trough ratio is low (~2), which can help minimize potential C_{max}-related toxicity while providing sustained PD effect
- Dose-dependent reductions in serum EPO were observed following a single dose at 10 to 100 mg, with mean maximum reduction from baseline up to 85%
- Following multiple dosing (QD for 7 days), sustained EPO reduction was observed throughout the dosing period, EPO levels recovered rapidly after the end of AB521 dosing

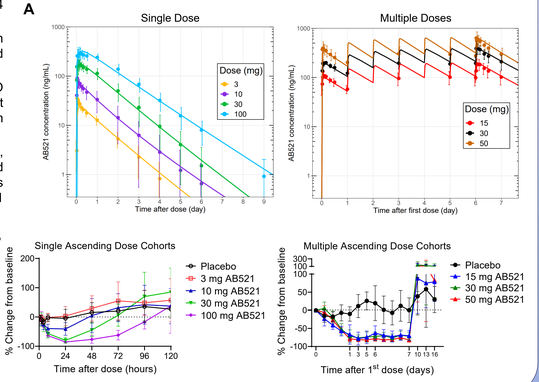


Figure 3. **(A)** Observed (mean ± SD) vs model-predicted (based on a preliminary population PK model) AB521 concentration-time profiles after a single (left) or multiple (right) oral dose(s) of AB521. **(B)** Mean ± SD serum erythropoietin (EPO) reduction-time profiles after a single (left) or multiple (right) oral dose(s) of AB521 or placebo.

SUMMARY

- AB521 is a potent and selective small molecule HIF-2α inhibitor that has been extensively characterized in biophysical, biochemical, and cell-based assays (**Figure 1**). See also[9-12].
- When administered orally in mice, AB521 regressed established 786-O and A498 ccRCC xenograft tumors and decreased tumoral PD markers that correlated with trough plasma 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 PK/PD properties in healthy human volunteers that are consistent with a potential best-in-class HIF-2α inhibitor profile (**Figure 3**). See also[13].
- Phase 1 clinical evaluation of AB521 in subjects with ccRCC and other solid tumors has been initiated using a pharmacologically active dose of AB521 and is ongoing (NCT05536141/ARC-20, **Figure 4**).

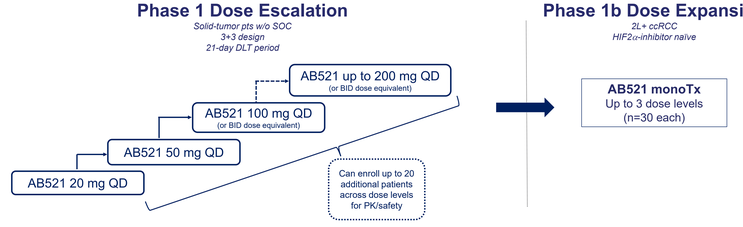


Figure 4. ARC-20 (NCT05536141) is a Phase 1, multicenter, open-label, first-in-patient study that is currently open for enrollment in the United States and South Korea. SOC, standard of care; QD, once-daily; DLT, dose-limiting toxicity; Tx, therapy. See also[14].