AB521 is a Novel and Potent Clinical-stage HIF-2α Inhibitor for the Treatment of Renal Cell Carcinoma


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Abstract

Background. The transcription factor Hypoxia-inducible Factor (HIF)-2α is an oncogenic driver in clear cell renal cell carcinoma (ccRCC). HIF-2α protein levels are regulated post-translationally in an oxygen-dependent manner. Hypoxic or pseudohypoxic conditions promote HIF-2α stabilization and transcription of pro-tumorigenic genes. Inhibition of HIF-2α has significant potential to mitigate tumor growth, particularly in cancers like ccRCC that have a high prevalence of molecular alterations associated with pseudohypoxia, namely mutations or epigenetic silencing of the Von Hippel-Lindau (VHL) protein. Herein we report findings associated with bioinformatic gene signature analyses and characterize AB521, a novel small molecule HIF-2α inhibitor.

Methods. Published and novel gene signatures were applied to publicly available datasets. Potency and specificity of AB521 was evaluated using biochemical and cell-based assays. Efficacy, pharmacokinetics, and toxicity of AB521 were evaluated in preclinical species and a healthy volunteer study is ongoing.

Results. Evaluated signatures related to hypoxia and HIF-2α were associated with therapeutic response to HIF-2α inhibition in preclinical models. Binding assays and crystal structure elucidation demonstrated that AB521 avidly binds the HIF-2α PAS-B domain. AB521 potently inhibited HIF-2α-dependent reporter transcription and VEGF protein secretion in 786-O cells. AB521 also selectively inhibited HIF-2α, but not HIF-1α, regulated gene expression in Hep3B hepatocellular carcinoma cells. In vivo, AB521 significantly regressed mouse ccRCC xenograft tumors and decreased on-target pharmacodynamic markers in a dose-dependent manner. Additionally, AB521 enhanced anti-tumor activity of a VEGF-targeting tyrosine kinase inhibitor. AB521 had a favorable pharmacokinetics (PK) in vitro and in vivo, resulting in a profile suitable for once-daily oral dosing in humans. Recent healthy volunteer data confirms both the predicted PK profile as well as modulation of erythropoietin (EPO) in a dose dependent manner.

Conclusions. Transcriptional data can be further applied to understand the therapeutic potential of HIF-2α inhibition. AB521 is a novel and selective HIF-2α inhibitor with profound anti-tumor activity, and clinical evaluation of this molecule is underway.

HIF-2α Biology and Therapeutic Rationale

Figure 1. HIF-2α drives physiological changes to adapt to low oxygen that are hijacked by the tumor. HIF-2α is a transcription factor comprised of two proteins: a stably-expressed β subunit (HIF-2αβARNT) and an oxygen-sensitive α subunit (HIF-2αo). In hypoxic or pseudohypoxic conditions, HIF-2α is stabilized and drives transcriptional programs that promote tumor progression. AB521 is a novel, potent, and selective allosteric small molecule inhibitor that can prevent HIF-2α-dependent gene transcription and block tumor progression.

In vitro Profile of AB521

Table 1. Characterization of AB521 and MK-6482 in Arcus biochemical and cell-based assays. Cellular assays: HIF luciferase (Luc) reporter and VEGF secretion in 786-O ccRCC cells; erythropoietin (EPO) transcription in Hep3B hepatocellular carcinoma cells. Binding Assays performed with the HIF-2α PAS-B domain: TSHA, Thermal Shift Assay; MST, Microscale Thermophoresis; ITC, Isothermal Calorimetry; SPA, Scintillation Proximity Assay. MK-6482/betalutin was synthesized at Arcus according to published methods.

Characterization of AB521 in Xenograft Models

Figure 2. AB521 alone or in combination with the tyrosine kinase inhibitor (TKI) cabozantinib (cabo), showed enhanced anti-tumor activity in the A498 ccRCC xenograft model. (A and B) Vehicle or AB521 administered once daily by oral gavage (PO-QD) when tumors were ~300 mm³. (A) Group averages over time. (B) Pharmacodynamic changes in intratumoral gene expression (confluent) and plasma protein levels (VEGF) 24 hours after vehicle or 100 mg/kg AB521 treatment. (C) Vehicle, 100 mg/kg AB521, 30 mg/kg cabozantinib (cabo), or a combination of the two agents administered PO QD when tumors were ~500 mm³. Shown are group averages over time. Pharmacokinometric parameters in preclinical species, including mice, has been disclosed previously3, not significant.

Application of HIF-2α-Specific Gene Signatures

Table 2. Average percent reduction in erythropoietin (EPO) levels observed at 24 hours after a single dose of AB521, relative to pre-dose, in each treatment cohort. Each SAD cohort evaluated was comprised of at least 4 human subjects.

Clinical Evaluation of AB521: ARC-14

Figure 4. AB521 is currently under clinical evaluation in healthy volunteers (ARC-14) to assess the tolerability, pharmacokinetics, and pharmacodynamic properties of orally administered AB521. Based on data from the initial single ascending dose (SAD) cohorts, the predicted pharmacokinetic profile of AB521 confirms a once-daily dosing in humans. In vitro potency reference values are indicated next to the dashed and dotted lines.

Summary and References

AB521 has been extensively characterized in a suite of biochemical and cell-based assays and demonstrates a high affinity for the HIF-2α PAS-B domain and potent inhibition of HIF-2α-dependent transcription (Table 1).

In ccRCC xenograft models, AB521 significantly inhibits tumor growth, and enhanced anti-tumor activity was observed when administered in combination with the TKI cabozantinib (Figure 2).

Arcus-derived HIF-2α signatures are correlated with HIF-2α protein expression in VHL wild type ccRCC and high scores are associated with poorer PFS, PDX models sensitive to HIF-2α inhibition express higher signature scores and downregulate these signatures upon HIF-2α inhibition, ccRCC responding to sunitinib express higher levels of HIF-2α RNA and hypoxia HIF-2α signatures (Figure 3).

We project a dose of 45-60 mg once daily AB521 will match the potency-corrected saturation observed with belzutifan (9) and demonstrates a high affinity for the HIF-2α PAS-B domain and potent inhibition of HIF-2α-dependent transcription (Table 1).

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Reference