A Phase 1b Study of AVB-S6-500 in Combination with Cabozantinib In Patients with Advanced Clear Cell Renal Cell Carcinoma Who Received Front-Line Treatment


1Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN, 2Comprehensive Cancer Centers of Nevada, Las Vegas, NV, 3Allegheny Health Network, Pittsburgh, PA, 4Cleveland Clinic Tussing Cancer Center, Cleveland, OH, 5Sidney Kimmel Cancer Center of Prostate and Urologic Cancers, Memorial Sloan Kettering Cancer Center, New York, NY, 6University of Texas, Southwestern, Dallas, TX, 7Massachusetts General Hospital, Boston, MA, 8Beth Israel Deacness Medical Center, Boston, MA, 9Aravive, Inc., Houston, TX, 10The M. D. Anderson Cancer Center, Houston, TX

BACKGROUND

In clear cell renal cell carcinoma (ccRCC), inhibition of the von Hippel Lindau (VHL) gene product in constitutive expression of the hypoxia-inducible factor (HIF-1α), leading to increased expression of aneuploid receptor tyrosine kinase protein (AXL). AXL overexpression has been associated with the development of resistance to targeted agents through endoplasmic reticulum (ER)-induced lipid droplet formation and disruption of growth arrest specific-6 protein (GAS6)-AXL signaling can reverse sensitivity of ccRCC to VEGF receptor pathway inhibitors.

AVB-S6-500 is a recombinant fusion protein dimer, which demonstrates highly potent, specific AXL inhibition (IC50 0.02 nM). The induction of Axl knockdown was evaluated in 786-O in AXL-VRBC. Tumor derived mouse models and mice treated with AVB-S6-500 showed significant reduction of tumor volume compared to controls. AVB-S6-500 demonstrated no significant toxicity in healthy volunteers or in a Phase 1b platinum resistant ovarian cancer (PD) study that identified the recommended phase 2 dose (RP2D) at 15 mg/kg every 2 weeks in the pharmacokinetic (PK) modeling. Influenza reactions and fatigue are the most common adverse events (AE) attributed to AVB-S6-500. Cabozantinib is approved by the FDA for monotherapy treatment for treatment of first- or later-line ccRCC. Phase 3 trials showed an ORR of 17 − 27.8%, with a disease control rate of 83 − 87.9%, a median PFS of 14 − 30 months, and a median OS of 21.4 months.

STUDY DESIGN

To evaluate safety, tolerability, PK, and pharmacodynamics (PD)-data in advanced RCC patients.

- Primary endpoints: safety, tolerability, and identification of the RP2D of AVB-S6-500 in combination with cabozantinib
- Secondary endpoints: assessment of antitumor activity

Exploratory biomarkers: serum soluble AXL and GAS6

Key inclusion criteria by study:

- Age ≥ 18 years
- Histologically confirmed metastatic ccRCC
- Progression on or after at least one prior line of therapy
- Cabozantinib is excluded

INTERIM STUDY RESULTS

Enrollment began in March 2021. As of October 16, 2021, 15 patients have been treated at 15 mg/kg, of whom 10 (66.6%) had IMDC risk: Intermediate and Poor. Median age in years (min/max) 60 (40.0, 76.0). ECOG (0, 1) 10 (66.7), 5 (33.3). Prior VEGF inhibitor therapy: Pazopanib 5 (33.3), Axitinib 4 (26.7), Bevacizumab 3 (20.0), Sunitinib 2 (13.3), Pazopanib/Sunitinib 2 (13.3). The M. D. Anderson Cancer Center, Houston, TX

EFFICACY DATA

In 10 efficacy-evaluable patients, with at least 2 post-baseline scans, 90% (9/10) of patients continue on AVB-S6-500 in combination with cabozantinib; one patient has discontinued treatment and is followed for survival.

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CASE REPORT FOR PATIENT 105-002

- 72-year-old male with a medical history of hypertension, diabetes type II, and chronic kidney disease; ccRCC diagnoses 12 years ago and underwent a nephrectomy.
- Disease recurred in 2016 and treated with sunitinib for 2.5 years, then nivolumab for 2 years.
- AVB-S6-500/RCC-003 Study: AVB-S6-500 (15 mg/kg) in combination with cabozantinib 60 mg/day, Cycle 1 Day 1 April 30, 2021.
- Cabozantinib-related toxicities required dose reduction, including grade 2 palmar plantar erythrodysesthesia.
- The cabozantinib dose intensity throughout the trial has been 35.5 mg/day; AVB-S6-500 dosing, however, has continued without modification.
- Week 8 and 16 imaging showed complete resolution of one of the target lesions in the periaortic lymph node. At week 16 imaging a 76% reduction in target lesions was observed when compared to baseline.

CONCLUSIONS

- AVB-S6-500 15 mg/kg has a manageable safety profile in combination with cabozantinib 80 mg in patients with previously treated ccRCC and no DLTs have been observed.
- Pharmacokinetic analysis indicate that AVB-S6-500 trough levels were above the MEC of 13.8 mg/L prior to C2D1 in 10 efficacy-evaluable patients. The PD marker GAS6 was fully suppressed throughout AVB-S6-500 dosing.
- The safety and tolerability of this combination together with PD/PD data support a phase 2 study.
- Clinical anti-tumor activity is encouraging, with the majority of patients showing tumor disruption of growth arrest specific-6 protein (GAS6)-AXL signaling can restore sensitivity of ccRCC to VEGF receptor pathway inhibitors.

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