A Phase 1b/2 study of Batiraxcept (AVB-S6-500) in combination with cabozantinib in patients with advanced or metastatic clear cell renal cell carcinoma (ccRCC) received front-line treatment (NCT04300140)

Background: AXL is up-regulated by hypoxia-inducible factor-1 signaling in both VHL-deficient and hypoxic tumor cells and plays a critical role in the metastatic phenotype of ccRCC. Batiraxcept is a recombinant fusion protein containing an extracellular region of human AXL combined with the human immunoglobulin G1 heavy chain (Fc), demonstrating highly potent, specific AXL inhibition.

Methods: Batiraxcept at doses of 15 and 20 mg/kg, plus cabozantinib 60 mg daily, was evaluated using a 3+3 dose escalation study design. The primary objective was safety; secondary and exploratory objectives included identification of the recommended phase 2 dose (RP2D), overall response rate (ORR), and duration of response (DOR). Correlation of serum soluble AXL (sAXL)/GAS6 with ORR was evaluated. Key eligibility criteria include previously treated (2L+) ccRCC patients; prior treatment with cabozantanib was not allowed. sAXL/GAS6 was evaluated at baseline.

Results: Data as of 4-February-2022, Phase 1b enrolled 26 patients, 16 patients treated with 15 mg/kg and 10 patients with 20 mg/kg dose of batiraxcept. Baseline characteristics: median age 60 (40-81); male 22 (85%); median prior line of therapy 1 (1-5); IMDC risk group of favorable 6 (23%); prior VEGF inhibitor 15 (58%); 100% with prior immunotherapy.

At median follow up of 4.9 months, 92% (n=24) patients remained on the study. No dose limiting toxicities were observed at either 15 mg/kg or 20 mg/kg dose. Batiraxcept and cabozantinib related adverse events (AEs) occurred in 17 subjects (65%). Most common related AE include decreased appetite 31% (n=8), diarrhea and fatigue 23% (n=6). Grade 3 related AEs occurred in 4 patients (15%) including diarrhea, thromboembolism, hypertension, small bowel obstruction, and thrombocytopenia (n=1, 4% each) being most common. No grade 4 or 5 related AEs were observed.

The ORR was 46% (n=12, partial response [PR], Table 1). No patients had progressive disease as a best response. Among the patients who had baseline sAXL/GAS6 ratio of ≥ 2.3, the ORR was 67% (12/18). Regardless of baseline sAXL/GAS6 ratio, 3-month DOR was 100%; and 6-month progression free survival was 79%. Batiraxcept PK levels were similar across both doses and GAS6 levels suppressed through the dosing period.

Conclusions: Batiraxcept plus cabozantinib is well tolerated. The RP2D of batiraxcept was identified as 15 mg/kg. Early efficacy signals were observed including 100% DOR at 3 months. Baseline sAXL/GAS6 may serve as a potential biomarker to enrich the population.

Table 1	Entire Cohort N=26 (%)	Batiraxcept 15 mg/kg Cohort N=16 (%)	Batiraxcept 20 mg/kg Cohort N=10 (%)
ORR (confirmed + unconfirmed)	12 PR (46)	9 PR (56)	3 PR (30)

DOR (3-month)	26 (100)	26 (100)	Not reached
Any Grade related AEs	17 (65)	11 (69)	6 (60)
Grade ≥3 related AEs	4 (15)	2 (13)	2 (20)