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

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BACKGROUND

In clear cell renal cell carcinoma (ccRCC), inactivation of the von Hippel Lindau (VHL) gene results in constitutive expression of hypoxia-inducible factor 1-α (HIF1-α), leading to increased expression of anexelekto receptor tyrosine kinase protein (AXL). AXL overexpression has been associated with the development of resistance to vascular endothelial growth factor (VEGF) receptor inhibitors and disruption of growth arrest specific-6 protein (GAS6)-AXL signaling can restore sensitivity of ccRCC to VEGF receptor pathway inhibitors.

AVB-S6-500 is a recombinant fusion protein dimer, which demonstrates highly potent, specific AXL inhibition (93-324 fM affinity). The impact of AVB-S6-500 was evaluated in 786-O or M62 ccRCC tumor derived mouse models and mice treated with AVB-S6-500 showed significant reduction of tumor size compared to the control.

AVB-S6-500 has demonstrated no significant toxicity in healthy volunteers or in a Phase 1b platinum resistant ovarian cancer (PROC) study that identified the recommended phase 2 dose (RP2D) at 15 mg/kg every 2 weeks (Q2W) by pharmacokinetic (PK) modelling. Infusion reactions and fatigue are the most common adverse events (AE) attributed to AVB-S6-500.

Cabozantinib is approved by the FDA as monotherapy for treatment of second-line or later ccRCC. Phase 3 trials showed an ORR of 17 – 27.8%, with a disease control rate of 83 – 87.9%, a median PFS of 7.4 – 9.3 months, and a median OS of 21.4 months.

STUDY DESIGN

Phase 1b
3 + 3 Dose Escalation

AVB-S6-500 + Cabozantinib 60 mg (N = 9 - 18)
AVB Dose Levels:
DL 1: 15 mg/kg Q2W
DL 2: 20 mg/kg Q2W
DL 3: 25 mg/kg Q2W

To evaluate safety, tolerability, PK, and pharmacodynamic (PD) data in advanced ccRCC 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 eligibility criteria:

- Age ≥ 18 years
- Histologically confirmed metastatic ccRCC
- Progression on or after at least one prior line of therapy
- Prior 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. 10 patients had at least one post-baseline response assessment and are included in the efficacy analyses. Three patients experienced resolution of one or more target lesions.

All patients continue study treatment except for one patient who discontinued due to toxicity related to AVB-S6-500 and cabozantinib (grade 2 diarrhea combined with the lack of caregiver support).

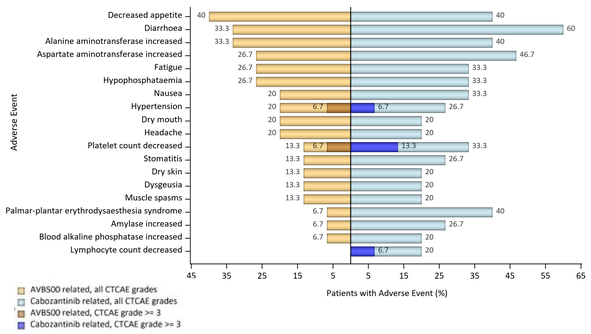
80% (12/15) of patients required cabozantinib dose reductions; median dose intensity was 47.1 mg/day (78.5%), range 10 – 60 mg/day.

AVB-S6-500 Q2W suppressed serum GAS6 to below the level of quantitation in all patients, showing a clear PK/PD relationship. The AVB-S6-500 minimally efficacious concentration (MEC) of 13.8 mg/L was achieved in 10 efficacy-evaluable patients by C2D1.

DEMOGRAPHICS	N = 15 (%)
Median age in years (min/max)	60 (40.0, 76.0)
Sex (Male, Female)	12 (80.0), 3 (20.0)
ECOG (0, 1)	10 (66.7), 5 (33.3)
1 or 2 lines of prior therapy	12 (80.0)
3 or 4+ lines of prior therapy	3 (20.0)
IMDC risk: Favorable	5 (33.3)
IMDC risk: Intermediate and Poor	10 (66.6)
Prior VEGF inhibitor	9 (69.2)
Prior Immunotherapy (PD-1 or PD-L1)	15 (100.0)

PATIENT ID	PRIOR THERAPY(IES) (BEST RESPONSE)	IMDC RISK GROUP	AVB-S6-500 PK PRE-CYCLE 2 TROUGH LEVELS (mg/L) MEC 13.8 mg/dL
101-004	1) nivolumab/ipilimumab (PD)	Intermediate	Data pending
102-001	1) nivolumab/ipilimumab/axitinib (Unknown)	Intermediate	45.2
102-002	1) pazopanib 2) pembrolizumab/axitinib (SD)	Favorable	36
103-001	1) nivolumab/ipilimumab (SD)	Intermediate	55.2 (C3D1 sample)
104-001	1) nivolumab/ipilimumab (PD)	Favorable	Data pending
105-002	1) sunitinib 2) nivolumab (SD)	Intermediate	45.2
105-003	1) sunitinib 2) nivolumab 3) atezolizumab/ciforadenant 4) talazoparib/axitinib (SD)	Intermediate	Data pending
105-004	1) nivolumab/ipilimumab (PR)	Poor	Data pending
106-001	1) pembrolizumab/axitinib 2) belzutifan (PD)	Intermediate	59.7
107-002	1) oncophage vaccine 2) pazopanib 5) nivolumab 3) everolimus 6) nivolumab/ipilimumab 4) axitinib 7) pembrolizumab/axitinib (SD)	Favorable	23.9
107-004	1) nivolumab/ipilimumab (PD)	Favorable	25.7
107-005	1) atezolizumab/eganelisib/bevacizumab (SD)	Intermediate	22.1
107-006	1) nivolumab/ipilimumab (SD)	Intermediate	83.6
107-007	1) sunitinib 3) Pegylated IL-10 2) nivolumab/Peg IL-10 4) ARO-HIF2 (PD)	Intermediate	Data pending
109-001	1) pembrolizumab/axitinib (PD)	Favorable	15.9

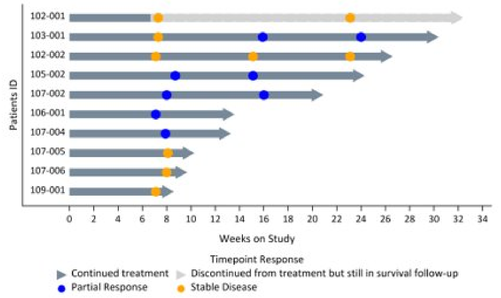
RELATED ADVERSE EVENTS (≥ 20%)

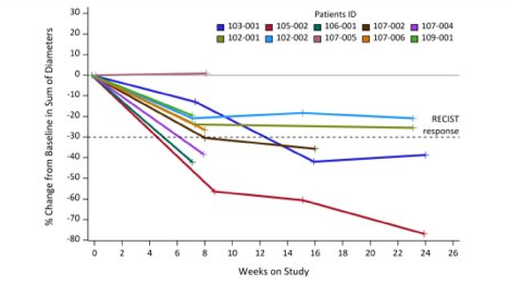


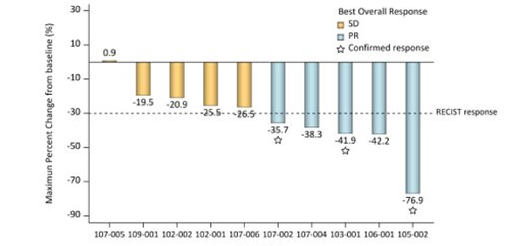
AVB-S6-500 RELATED ADVERSE EVENTS	N = 15 (%)
All Grade Related AE	(86.7)
Grade 3	2 (13.3)
Grade 4 and 5	0 (0)
All Grade SAE	0 (0)
AE of Special Interest: Infusion Reactions	2 (13.3)

EFFICACY DATA

90% (9/10) of patients continue on AVB-S6-500 in combination with cabozantinib; one patient has discontinued treatment and is followed for survival.





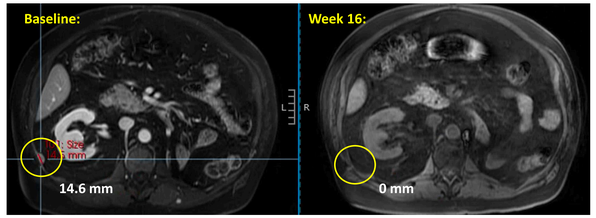


90% (9/10) of patients who had at least 1 post baseline response assessment had a reduction in target lesions. Of the patients with at least 2 post-baseline scans, the confirmed response rate was 60% (3/5).

CASE REPORT FOR PATIENT 105-002

- 72-year-old male with a medical history of hypertension, diabetes type II, and chronic kidney disease; ccRCC diagnosis 21 years ago and underwent a nephrectomy.
- Disease recurred in 2016 and treated with sunitinib for 2.5 years, then nivolumab for 2 years
- AVB500-RCC-003 Study: AVB-S6-500 (15 mg/kg) in combination with cabozantinib 60 mg, Cycle 1 Day 1 April 30, 2021
- Cabozantinib related toxicities required dose reduction, including grade 2 palmar-plantar erythrodysaesthesia
- 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 peritoneum (see image). At week 24 imaging a 76.8% reduction in target lesions was observed when compared to baseline

	Baseline	C2	C4	C6
Sum of target lesions (mm)	37.6	16.4	14.8	8.7
% Change		-56.3%	-60.6%	-76.8%



CONCLUSIONS

- **AVB-S6-500 15 mg/kg has a manageable safety profile in combination with cabozantinib 60 mg in patients with previously treated ccRCC and no DLTs have been observed**
- **Pharmacokinetic analyses 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 PK/PD data support a RP2D of 15 mg/kg**
- **Clinical anti-tumor activity is encouraging, with the majority of patients showing tumor decrease relative to baseline and a best overall response of partial response observed in 50% (5/10) of efficacy-evaluable patients. This clinical activity was observed despite cabozantinib dose reductions in 80% of patients**
- **Targeting the underlying pathology of the disease through combination AXL and VEGF inhibition may be an effective treatment for patients with ccRCC**
- **Enrollment is ongoing to further evaluate the efficacy and safety of this combination in patients with previously treated ccRCC**

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AVB500-RCC-003 **NCT04300140**
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