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A PHASE 1B/2 RANDOMIZED STUDY OF AVB-S6-500 IN COMBINATION WITH CABOZANTINIB VERSUS CABOZANTINIB ALONE IN PATIENTS WITH ADVANCED CLEAR CELL RENAL CELL CARCINOMA WHO HAVE RECEIVED FRONT-LINE TREATMENT

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Background In clear cell renal cell carcinoma (ccRCC) the constitutive expression of hypoxia induced factor 1- α leads to increased expression of AXL. AXL overexpression has been associated with the development of resistance to VEGF inhibitors and suppression of the innate immune response through inhibition of macrophage-driven inflammation. AVB-S6-500 (AVB-500) is recombinant fusion protein dimer containing an extracellular region of human AXL combined with the human immunoglobulin G1 heavy chain (Fc), which demonstrates highly potent, specific AXL inhibition. In mouse ccRCC xenograft models, AVB-500 showed significantly more tumor reduction in combination with pazopanib versus pazopanib alone. In a Ph1b study of AVB-500 plus chemotherapy in platinum-resistant ovarian cancer (NCT03639246), no dose limiting toxicity (DLT) or treatment discontinuation due to adverse events was observed. The recommended phase 2 dose (RP2D) of 15 mg/kg was established by a model-informed drug development (MIDD) approach.

eligibility criteria include clear cell histology RCC and at least one prior line of therapy administered in the advanced or metastatic setting.

Results As of July 21, 2021, seven patients have received at least one dose of AVB-500 15 mg/kg and cabozantinib, with six patients ongoing treatment. No DLTs were observed. Trough levels at C1D15 were above the minimally efficacious concentration (MEC) identified from MIDD and GAS6 (AXL ligand) levels were suppressed prior to C2D1. Partial responses were observed in 3 of 5 patients (table 1); all patients demonstrated tumor decrease from baseline.

Conclusions AVB-500 in combination with cabozantinib demonstrates promising preliminary clinical activity and tolerability in patients with ccRCC. AVB-500 15 mg/kg is the presumptive RP2D with C1D15 AVB-500 troughs consistently above MECs observed. Safety, PK/PD and clinical activity will be updated at the time of presentation. (NCT04300140)

Ethics Approval This study has obtained ethics approval from WIRB Institutional Review Board®, Protocol ID #20200159, and all subjects provided informed consent prior to taking part in this study.

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Abstract 424 Table 1 Preliminary clinical activity in NCT04300140

	Prior lines of therapy in the advanced/metastatic setting	# Cycles completed	Best overall response
102-001	1) Nivolumab/ipilimumab 2) Axitinib 3)	1.5, discontinued study	SD
102-002	1) Pazopanib 2) Pembrolizumab/axitinib	3, ongoing	SD
103-001	1) Nivolumab/ipilimumab	4, ongoing	PR, unconfirmed
105-002	1) Sunitinib 2) Nivolumab	2, ongoing	PR, unconfirmed
107-002	1) Pazopanib 2) Everolimus 3) Axitinib 4) Nivolumab/ipilimumab 5) Pembrolizumab/axitinib (Best response to therapy PD)	2, ongoing	PR, unconfirmed

Methods The P1b portion of this trial is a 3+3 dose escalation study to evaluate safety, pharmacokinetics, and pharmacodynamics of AVB 500 in combination with cabozantinib 60 mg daily. Dose levels of AVB-500 may include 15, 20, and 25 mg/kg every two weeks. The primary objective is to evaluate safety and tolerability. Secondary objectives include identification of the RP2D of AVB-500 and clinical activity. Key