Phase I Safety and Biodistribution Study of $^{124}$I-PEG-AVP0458 Diabody in Patients with TAG-72 Positive Ovarian and Prostate Cancer

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Background: The development of antibody therapeutics for imaging and payload delivery is complex, and intact IgG have long half-lives that impact on tumor:blood ratios and tumor penetrance. Smaller molecular weight antibody constructs (eg diabodies) have been developed for improved penetrance into tumor, faster blood clearance, and enhanced tumor: normal tissue uptake, however renal uptake may impact on imaging and therapeutic effects. Through a novel pegylation strategy to surface disulphides, a diabody to TAG-72 (AVP0458) has been generated, and produced under cGMP for a first-in-human clinical trial.

Materials and Methods: We have conducted a Phase I, open label, first-in-human trial of PEG-AVP0458. The primary study objective was the safety of single dose of I-124 PEG-AVP0458 in patients (pts) with TAG-72 +ve relapsed / metastatic prostate or ovarian cancer. Secondary study objectives were evaluation of the biodistribution, tumor targeting, pharmacokinetics (PK) and immunogenicity of I-124 PEG-AVP0458. Pts were infused with I-124 PEG-AVP0458 (3-5mCi) at one of two dose levels (1mg/m² and 10mg/m²), and imaged sequentially over a one week period. Safety, PK, and immunogenicity was assessed up to 30 days post infusion.

Results: Six pts (1F:5M; age range 62-85yrs; 1 ovarian cancer, 5 prostate cancer) were entered into the study, 3 at each dose level. I-124 PEG-AVP0458 was well tolerated, with no infusion-related adverse events, and no serious adverse events observed. There was consistent biodistribution on PET imaging of I-124 PEG-AVP0458, with no normal tissue uptake. High tumor uptake was evident in metastatic disease in liver and lymph nodes, with lesion uptake seen within 1-2 days post injection. PK analysis showed a T½β of 46.8 ± 12.4 hrs. There was no impact of protein dose on biodistribution, tumor uptake or PK. No immunogenicity to PEG-AVP0458 was evident.

Conclusions: I-124 PEG-AVP0458 is safe, and demonstrates excellent, rapid targeting of tumor in-vivo, with no specific normal organ uptake, and high tumor: blood ratios. This data demonstrates the feasibility of using pegylated diabodies for imaging and for delivery of radioisotopes (RIT) or cytotoxic drug payloads (ADC) in cancer patients.