PRECLINICAL EVALUATION OF ANTI-VISTA ANTIBODY CI-8993 IN A SYNGENEIC HUVISTA-KI MODEL

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Background VISTA (V-domain Ig suppressor of T-cell activation) inhibits anti-tumour immune responses. The Investigational product CI-8993 is a fully human IgG1k monoclonal antibody that binds specifically to this immune checkpoint molecule. Phase I safety has been established in prior trials in patients with advanced cancer (NCT02671955). To assist determining the pharmacokinetics and biodistribution of CI-8993 in patients we aimed to develop a Zirconium-89 (89Zr)-labelled CI-8993 for PET imaging and quantitation, and validate in preclinical models prior to a planned human trial.

Methods Conjugation conditions of CI-8993 to the metal ion chelator desferrioxamine B (Df-) were established by optimisation of Df:mAb ratio, reaction temperature, time and purification method. Conjugates were assessed by SE-HPLC, SDS-PAGE, and ELISA. Radiolabelling was performed with 89Zr and the radioconjugate was tested for specific activity, radiochemical purity and binding affinity for huVISTA. The in-vivo biodistribution and properties of 89Zr-Df-CI-8993 and IgG1 isotype control radioconjugates were assessed in huVISTA knock-in female (C57BL/6N-Vsir< sup >tm1.1(VSIR)Geno</ sup >) or control C57BL/6 mice bearing syngeneic MB49 bladder cancer tumours. Whole body animal PET/CT imaging was performed on day of radioconjugate synthesis and injection and day 1 and day 3 p.i. Biodistribution was assessed by image analyses, and tissue counting, with IHC analyses performed to verify VISTA antigen expression.

Results Conjugation of Df- to CI-8993 for 60 minutes at room temperature followed by purification via gel filtration resulted in stable constructs with an average chelator-to-antibody ratio of 1.81. SDS-PAGE showed integrity of CI-8993 was maintained after conjugation, and ELISA indicated no impact of conjugation on binding to human VISTA. Radiochemical purity (iTLC) and protein integrity (SE-HPLC) at EOS were > 99% and 93%. PET imaging and biodistribution in MB49 tumour-bearing huVISTA knock-in female mice showed specific localisation of 89Zr-Df-CI-8993 to VISTA expressing organs (liver: 14.98 ± 0.50 %ID/g; spleen: 292.00 ± 14.51 %ID/g; n = 3) compared to 89Zr-Df-IgG1 control (liver: 4.615 ± 0.15 %ID/g; spleen: 6.37 ± 0.22 %ID/g; n = 4) or in the presence of competing unlabelled CI-8993 (liver: 8.14 ± 0.50 %ID/g; spleen: 41.14 ± 3.00 %ID/g; n = 5). Tumour-to-blood ratios indicated specific tumour targeting of 89Zr-Df-CI-8993 in the presence of unlabelled CI-8993 (20.47 ± 3.09) compared to trace dose 89Zr-Df-CI-8993 (0.97 ± 0.12 ; P = 0.0001) or 89Zr-Df-IgG1 control (1.75 ± 0.11 ; P < 0.0001).

Conclusions We have validated 89Zr-Df-CI-8993 for specific binding to huVISTA in-vivo. A clinical trial of 89Zr-Df-CI-8993 is planned in solid tumour patients.

Ethics Approval All animal studies were approved by the Austin Health Animal Ethics Committee and were conducted in compliance with the Australian Code for the care and use of animals for scientific purposes.

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