AMG 509, A STEAP1 X CD3 BISPECIFIC XmAb® 2+1 IMMUNE THERAPY, EXHIBITS AVIDITY-DRIVEN BINDING AND PREFERENTIAL KILLING OF HIGH STEAP1-EXPRESSING PROSTATE AND EWING SARCOMA CANCER CELLS

Background Metastatic castration-resistant prostate cancer (mCRPC) and Ewing sarcoma (EWS) are diseases for which immune therapies could potentially provide benefit. STEAP1 (Six Transmembrane Epithelial Antigen of the Prostate 1) is a cell surface protein with elevated expression in mCRPC 1 and EWS.2

Methods We designed AMG 509, a novel, half-life extended, STEAP1 x CD3 XmAb® 2+1 bispecific antibody to induce T cell-mediated cytotoxicity against STEAP1-expressing cancer cells. AMG 509 contains two identical anti-STEAP1 Fab domains, an anti-CD3 scFv domain, and an effectorless Fc domain that extends serum half-life. We characterized STEAP1 expression in normal and tumor tissues by immunohistochemistry, and we assessed the pharmacological properties of AMG 509 including binding, T cell-mediated redirected lysis, and in vivo antitumor activity.

Results We detected high STEAP1 surface expression on 80% of primary prostate tumors (n=88), 89% of mCRPC lesions (n=114), including 84% of mCRPC bone metastases (n=31), and 63% of EWS samples (n=35). In contrast, in normal tissues (n=72), low STEAP1 expression was detected in only six tissues, including the normal prostate. AMG 509 bound specifically to 293T cells transfected with human STEAP1 with an EC50 of 3.8 nM. AMG 509 triggered potent cell-mediated cytotoxicity against STEAP1-expressing cancer cells. AMG 509 was 65-fold more potent in inducing the redirected lysis of prostate cancer cells in vitro than an XmAb® molecule with a single anti-STEAP1 Fab domain. AMG 509 had greater cytotoxic activity against high STEAP1-expressing cancer cells than against low STEAP1-expressing cancer cells, and it had minimal activity against normal cells. This preferential killing of high STEAP1-expressing cells is likely driven by the avidity conferred by the dual STEAP1-binding domains, a feature that may help reduce off-target effects in the clinic. In vivo, AMG 509 induced robust anti-tumor activity in prostate cancer and EWS mouse xenograft models, with concomitant CD8+ T-cell activation and expansion in tumors.

Conclusions AMG 509 is a specific, first-in-class T cell-recruiting antibody with avidity-driven activity against STEAP1-positive malignancies. AMG 509 is currently being evaluated for safety, pharmacokinetics, and efficacy in a phase 1, first-in-human study in patients with mCRPC (NCT04221542).

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Ethics Approval All animal experimental protocols were approved by the UCLA Animal Research Committee (# 2005-1810).

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Ethics Approval All animal experimental protocols were approved by an Institutional Animal Care and Use Committee (IACUC) and the standards of the Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals (IACUC protocol number 15015x) in a facility certified with an Office of Laboratory Animal Welfare (OLAW) (UTHSA).