are resistant to PSMA-targeted radioligand therapy with 177Lu-PSMA-617. These data provide a rationale for evaluating AMG 160 in patients with mCRPC who have progressed on 177Lu-PSMA-617. AMG 160 is currently being evaluated in a phase 1 study in patients with mCRPC (NCT03792841).

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Trial Registration

ClinicalTrials.gov Identifier: NCT03792841

Ethics Approval

All animal experimental protocols were approved by the UCLA Animal Research Committee (# 2005-090).

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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

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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 and EWS.

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 other tissues, including the normal prostate. AMG 509 bound to recombinant human CD3ε with a KD of 27.6 nM, and it bound specifically to 293T cells transfected with human STEAP1 with an EC50 of 3.8 nM. AMG 509 triggered potent T cell-redirection lysis of STEAP1-positive cancer cells, with a median EC50 of 37 pM across 19 cancer cell lines that endogenously express various levels of STEAP1. AMG 509-mediated cytotoxicity was specific, as it showed no activity against prostate cancer cells in which STEAP1 was knocked out. 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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The authors acknowledge Micah Robinson, PhD of Amgen Inc. for medical writing support. All animal experimental protocols were approved by an Institutional Animal Care and Use Committee (IACUC protocol number 2015-01243) and were conducted in accordance with the guidelines of the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) (Amgen) or 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).

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CD122-DIRECTED INTERLEUKIN-2 COMPLEXES AND αPD-L1 DIFFERENTIALLY REQUIRE INNATE AND ADAPTIVE IMMUNITY TO TREAT LOCAL AND METASTATIC BLADDER CANCER

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Background αPD-L1 bladder cancer (BC) immunotherapy is effective in <30% of cases.1 To address the large αPD-L1-unresponsive subset of patients, we tested αIL-2/IL-2 complexes (IL-2c) that block IL-2 from binding high-affinity IL-2Rα (CD25) for preferential IL-2β (CD122) binding.2 Immunosuppressive regulatory T cells capture IL-2c alone reduced tumor burden and PD-L1 efficacy in PD-L1 bladder cancer (BC) immunotherapy is effective in <30% of cases.1 To address the large αPD-L1-unresponsive subset of patients, we tested αIL-2/IL-2 complexes (IL-2c) that block IL-2 from binding high-affinity IL-2Rα (CD25) for preferential IL-2β (CD122) binding.2 Immunosuppressive regulatory T cells capture IL-2c alone reduced tumor burden and PD-L1 efficacy in PD-L1 bladder cancer (BC) immunotherapy is effective in <30% of cases.1 To address the large αPD-L1-unresponsive subset of patients, we tested αIL-2/IL-2 complexes (IL-2c) that block IL-2 from binding high-affinity IL-2Rα (CD25) for preferential IL-2β (CD122) binding.2 Immunosuppressive regulatory T cells capture IL-2c alone reduced tumor burden and PD-L1 efficacy in PD-L1 bladder cancer (BC) immunotherapy is effective in <30% of cases.1 To address the large αPD-L1-unresponsive subset of patients, we tested αIL-2/IL-2 complexes (IL-2c) that block IL-2 from binding high-affinity IL-2Rα (CD25) for preferential IL-2β (CD122) binding.2 Immunosuppressive regulatory T cells capture IL-2c alone reduced tumor burden and PD-L1 efficacy in }