ARMORED STEAP2 CAR-T (AZD0754) ALONE AND IN COMBINATION WITH ENZALUTAMIDE DEMONSTRATES ANTI-TUMOR ACTIVITY ACROSS A RANGE OF STEAP2 EXPRESSING PROSTATE CANCER PDX MODELS

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Background Prostate cancer is thought of as immunologically ‘cold’, rendering tumors insensitive to immunotherapy, and limiting treatment options. Prostate cancer ‘coldness’ may be due to multiple factors, including a TGFβ rich immunosuppressive tumor microenvironment, dysfunctional T cells, and lack of tumor associated antigens (TAA). We identified STEAP2 as a highly prevalent prostate cancer antigen, displaying high, homogeneous cell surface expression across all stages of disease, with the potential for superior therapeutic targeting.

Methods A novel lead generation approach facilitated the development of a potent and specific armored STEAP2 CAR-T therapeutic candidate, AZD0754. This 2nd-generation CAR-T product is armored with dominant-negative transforming growth factor beta (TGFβ) receptor II (dnTGFβRII), bolstering activity in the TGFβ-rich immunosuppressive environment of prostate cancer. In a series of in vitro experiments, we evaluated the effect of enzalutamide (androgen receptor (AR) antagonist) on the viability, gene expression and function of AZD0754 and tumor cells alone or in co-culture of AZD0754 and tumor cells. Furthermore, in vivo activity of AZD0754 was tested across a panel of prostate cancer patient derived xenograft models (PDX) alone and in combination with enzalutamide.

Results In vitro experiments demonstrated that the viability and anti-tumor function of AZD0754 was maintained in the presence of enzalutamide. Moreover, AZD0754 CAR-T treatment induced significant anti-tumor efficacy and corresponding IFNγ production in a panel of prostate PDX models that closely mimic the genomic and phenotypic features of human prostate cancer, even in models with low antigen density and stromal derived-TGFβ. Given the correlation between STEAP2 expression and androgen receptor expression, we further investigated the efficacy of AZD0754 in a combination study with the enzalutamide, in prostate cancer PDX models. We found no significant effect of enzalutamide on STEAP2 expression, and our results highlighted the combinatorial activity of enzalutamide and AZD0754 CAR-T therapy.

Conclusions Together, these data underscore the potential therapeutic tractability of STEAP2 in prostate cancer and build confidence in the STEAP2 expression threshold required for AZD0754 activity. Moreover, our study explores potential combination strategies involving standard-of-care therapies.

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