Abstract 5819

Evaluation of ARX517, a next-generation anti-PSMA antibody drug conjugate for prostate cancer treatment, in preclinical enzalutamide-resistant and enzalutamide-sensitive pharmacology models and in toxicology models

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Background

Prostate cancer is the second leading cause of cancer death among men in the United States. Metastatic castration-resistant prostate cancer (mCRPC) is an advanced disease stage in which patients ultimately fail androgen-deprivation therapies and exhibit a poor survival rate. Recently, prostate-specific membrane antigen (PSMA) has been validated as a mCRPC tumor antigen with its over-expression in tumors and low expression in healthy tissues. Using an expanded genetic code to create Engineered Precision Biologics, Ambrx has developed ARX517, a PSMA-targeted antibody drug conjugate (ADC), which is composed of a humanized anti-PSMA antibody site-specifically conjugated to a tubulin inhibitor drug-linker at a drug-to-antibody ratio of 2. After binding to PSMA, ARX517 is internalized and catabolized, leading to cytotoxic payload delivery and cellular apoptosis. To minimize premature payload release and maximize delivery to tumor microenvironments, ARX517 employs a non-cleavable PEG linker and stable oxime conjugation chemistry, enhancing systemic stability.

Methods

ARX517 was evaluated in multiple pre-clinical pharmacology and toxicology models using standard methodology.

Results

In vitro studies demonstrate that ARX517 selectively induces cytotoxicity of PSMA-expressing tumor lines. ARX517 exhibited a long terminal half-life and high serum exposure in mice, and dose-dependent anti-tumor activity in both enzalutamide-sensitive and -resistant CDX and PDX prostate cancer models. Repeat dose toxicokinetic studies in non-human primates demonstrated ARX517 was tolerated at exposures well above therapeutic exposures in mouse pharmacology studies, indicating a wide therapeutic index.

Conclusions

In summary, ARX517 inhibited tumor growth in diverse mCRPC models, demonstrated a tolerable safety profile in monkeys, and had a wide therapeutic index based on preclinical exposure data. Based on strong preclinical data and recent clinical validation of PSMA targeting, ARX517 is being evaluated in a Phase 1/2 clinical trial (NCT04662580).

Clinical trial identification

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