

Abstract 5886

Preclinical characterization of ARX305, a next-generation anti-CD70 antibody drug conjugate for the treatment of CD70-expressing cancers

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Background

CD70 is an attractive tumor target due to its over-expression in numerous solid and hematological cancers and limited expression in healthy cells. In the last decade, multiple anti-CD70 antibody drug conjugates (ADCs) have been developed, but most have been discontinued due to unacceptable toxicity or a narrow therapeutic index. Using an expanded genetic code to create Engineered Precision Biologics, Ambrx has developed ARX305, a CD70-targeted next-generation ADC to potentially overcome the challenges associated with earlier ADCs. ARX305 is comprised of a proprietary, high-affinity, humanized anti-CD70 antibody stably and site-specifically conjugated to AS269, a potent microtubule inhibitor. After binding to CD70 expressed on tumor cells, ARX305 is internalized and catabolized, releasing the cytotoxic payload pAF-AS269 which inhibits cellular proliferation. ARX305 utilizes stable oxime conjugation chemistry, a non-cleavable PEG linker, and a membrane-impermeable payload to minimize premature payload release in circulation and associated off-target toxicity.

Methods

ARX305 was evaluated in multiple pre-clinical pharmacology and toxicology models using standard methodology.

Results

In vitro studies demonstrate that ARX305 selectively induces cytotoxicity of CD70-expressing tumor lines. In multiple *in vivo* xenograft or disseminated models, ARX305 induced significant tumor growth inhibition or regression whereas unconjugated antibody exhibited poor activity. The stable conjugation and cell-impermeable payload of ARX305 led to high serum stability, a long terminal half-life, and a similar exposure profile as unconjugated antibody in rodent pharmacokinetic studies. Repeat dose studies in cynomolgus monkeys demonstrated ARX305 was tolerated at exposures well above therapeutic exposures in mouse pharmacology studies, indicating a wide therapeutic index.

Conclusions

In summary, the highly selective and potent anti-tumor activity in multiple tumor types and wide pre-clinical therapeutic index of ARX305 support clinical evaluation of this next generation anti-CD70 ADC. ARX305 is currently in a Phase 1 dose escalation study in China.

Clinical trial identification

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