ARXS17, a Next-Generation Anti-PSMA Antibody Drug Conjugate for the Treatment of Metastatic Castration-Resistant Prostate Cancer, Demonstrates Anti-tumor Activity in Enzalutamide-Resistant and Enzalutamide-Sensitive Models and a Clear Therapeutic Index in a Non-human Primate Model

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INTRODUCTION

Enzalutamide has been approved for the treatment of metastatic castration-resistant prostate cancer (mCRPC), however patients eventually develop resistance and progress. Multiple groups have also reported enzalutamide treatment can upregulate prostate-specific membrane antigen (PSMA) expression in mCRPC patients, providing strong rationale for treating enzalutamide-resistant mCRPC patients with a PSMA-targeted antibody drug conjugate (ADC).

• ARXS17 is a next generation anti-PSMA ADC that employs stable osmine conjugation chemistry and a non-degradable PEG linker to ensure ADC stability and overcome the issues encountered by earlier ADCs.

• ARXS17 is comprised of a humanized anti-PSMA antibody site-specifically conjugated to amphigen 269 (AS269) drug-linker to generate an ADC with a controlled drug-to-antibody ratio (DAR) of 2.

• Here we describe the preclinical characterization of ARXS17 with in vitro and vivo efficacy, PK and stability, and therapeutic index studies.

• Preliminary FIH safety data, from an on-going Phase 1 dose escalation trial (APEX-01), show a favorable safety signal in multiple doses tested, including 2.28 mg/kg.

RESULTS

Figure 1. In Vitro Cytotoxic Activity in Tumor Cells

Figure 2. Efficacy in Enzalutamide-Sensitive and -Resistant Tumor Models, A. TM00298 PDX, B. C4-2 CDX

Figure 3. Stability in Circulation

Figure 4. Minimal Payload Release in Monkey Tox Study

Figure 5. Monkey Toxicology & Therapeutic Index

CONCLUSION

• ARXS17 exhibits anti-tumor activity in preclinical enzalutamide-sensitive and -resistant prostate cancer models, with high stability in circulation.

• ARXS17 demonstrates a clear therapeutic index in IND-enabling studies.

• The upregulation of PSMA by enzalutamide in mCRPC patients and our preclinical combination data provide scientific rationale to investigate the potential benefit of ARXS17 and enzalutamide combination therapy in mCRPC patients.

• ARXS17 is currently being evaluated in a multi-center Phase 1 clinical trial in the US (ARXS17-2011, APEX-01, NCT04646250).

References


Disclosure: Shawn Zhang, PhD, is an employee of Ambrx, Inc.