INTRODUCTION

Previous PSMA-targeted ADCs demonstrated early clinical efficacy in metastatic castration-resistant prostate cancer (mCRPC), but drug development was discontinued due to intolerable toxicities, resulting from premature release of the cytotoxic payload (Table 1). AS269 is a novel anti-PSMA ADC designed to overcome the stability challenges with resulting toxicity of other PSMA-targeted ADCs (Figure 1). Differentiating features include stability: Unique oxime conjugation chemistry using a genetically encoded and biosynthetically incorporated synthetic anti-GA.

Table 1. PSMA-Targeted ADCs

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<th>Name</th>
<th>Pharmacokinetic Population (N=32)</th>
<th>Baseline Demographics of the Pharmacokinetic Population (N=32)</th>
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PAYLOAD

- Drug-antibody ratio
- Unique oxime conjugation chemistry using a genetically encoded and biosynthetically incorporated synthetic anti-GA.

Figure 2

- Released Payload: pAF-AS269 (non cell-permeable)
- ARX517 exhibits virtually overlapping total antibody and ADC PK concentration-time curves at all doses, indicating strong stability of the ADC.

Figure 3

- Low serum concentrations of free payload observed at all doses, with the molar ratio of payload to ADC at 0.06%
- Drug exposure increases proportional to ARX517 dose

Figure 4

- Virtually overlapping TA and ADC PK curves demonstrate strong stability at all dose levels.

Figure 5

- ARX517 exhibits a long half-life of ~6–10 days at doses ≥1.4 mg/kg

Figure 6

- Drug exposure increases proportional to ARX517 dose

RESULTS

CONCLUSION

ARX517 is the first anti-PSMA ADC to demonstrate strong stability in circulation. The technology empowered by synthetic amino acid incorporation analogical peptidomimetic chemistry can be employed to create the next generation of truly stable ADCs for the treatment of cancer.

REFERENCES


CONCLUSIONS

- ARX517 exhibited virtually overlapping total antibody and ADC PK concentration-time curves at all dose levels tested, indicating strong stability of the ADC.
- Minimized premature release and minimal concentration of free payload (pAF-AS269) measured in serum (within the molar ratio of payload to ADC at 0.06%).
- Long ADC terminal half-life of ~6-10 days at doses at 1.4 mg/kg, thereby maximizing drug exposure.