ARX517, a Next Generation Anti-PSMA Antibody Drug Conjugate (ADC) Demonstrates Stability, Dose-Dependent Exposure, and Long Half-Life

1828P

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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 and off-target delivery of the cytotoxic payload (**Table 1**) (**Figure 1**).
- ARX517 is a novel anti-PSMA ADC designed to overcome the stability challenges with resulting toxicity of other PSMA-targeted ADCs (**Figure 2**).[1-5] Key differentiating features increasing stability include:
  - Unique oxime conjugation chemistry using a genetically encoded and biosynthetically incorporated synthetic amino acid (SAA)
  - Non-cleavable PEG linker
  - Non-cell permeable payload
- APEX-01 is a Phase 1/2 first-in-human trial evaluating ARX517 in patients with mCRPC resistant or refractory to prior therapies (NCT04662580). Pharmacokinetic data from the trial are reported here. Clinical results and details of the study design are presented at ESMO 2023 in poster 1804P.

Figure 1. Conjugation

Conventional conjugation techniques can result in premature release of the cytotoxic payload in circulation, potentially increasing adverse events and reducing amount of payload delivered to target.

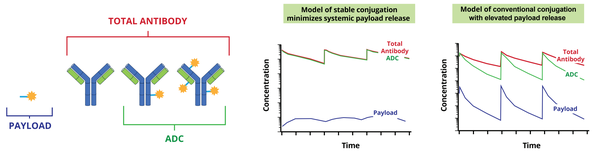


Figure 2. ARX517

ARX517 is comprised of 4 key elements: (**A**) a humanized J591 anti-PSMA antibody; (**B**) a payload covalently conjugated to a SAA, para-acetyl phenylalanine (pAF), genetically encoded and biosynthetically incorporated at amino acid position 114 on the heavy chain of the anti-PSMA antibody; (**C**) a non-cleavable PEG linker; and (**D**) a non cell-permeable cytotoxic payload of a microtubule targeting antineoplastic agent (AS269).

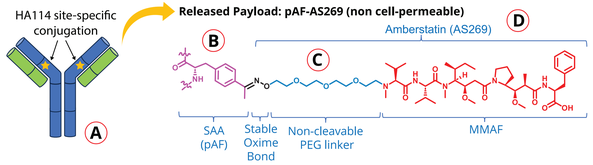


Table 1. PSMA-Targeted ADCs

Name	MLN-2704	PSMA-ADC	MEDI-3726	ARX517
Antibody	J591 (humanized)	fully human IgG1	J591 (humanized)	J591 (humanized)
Payload	DM1	MMAE	PBD dimer (SG3199)	AS269
Payload cell permeability	yes	yes	yes	no
Drug-antibody ratio (DAR)	~4	~4	~1.8	2
Conjugation	Lysine	Cysteine	Cysteine	pAF site-specific, oxime
Linker	cleavable (disulfide)	cleavable (val-cit)	cleavable (val-ala)	non-cleavable
Treatment-Related SAE	peripheral neuropathy	neutropenia, neuropathy, 2 deaths at 2.5 mg/kg	myelosuppression, skin tox, vascular leakage	None
T1/2 (day)	~2.5	~2	<2	~8 days
Highest Dose (mg/kg)	~12.5	2.8	0.3	Currently at 2.88 mg/kg
Reference	Milowsky et al, *Urol Oncol*. 2016, 34(12): 530.e15-530e.21.	Petrylak et al., *Prostate*. 2019, 79(6) 604-613.	de Bono et al, *Clin Cancer Res*. 2021, 27(13):3602-3609.	ESMO 2023

RESULTS

Table 2. Baseline Demographics of the Pharmacokinetic Population (N=32)

	Dose (mg/kg)						
	0.32	0.64	1.07	1.4	1.7	2	2.4
Number of Patients	1	3	3	5	5	9	6
Age (yr)							
Mean (SD)	57.0 (NA)	67.3 (11.5)	73.0 (7.00)	77.8 (12.9)	73.6 (9.84)	67.9 (9.33)	67.5 (10.7)
Median [Min,Max]	57.0 [57.0, 57.0]	67.0 [56.0, 79.0]	70.0 [68.0, 81.0]	72.0 [69.0, 100]	75.0 [62.0, 83.0]	68.0 [50.0, 83.0]	64.5 [56.0, 82.0]
Body Weight (kg)							
Mean	69.3 (NA)	102 (20.3)	83.4 (29.3)	78.6 (17.5)	80.7 (15.9)	88.0 (21.4)	85.3 (18.0)
Median [Min,Max]	69.3 [69.3, 69.3]	108 [80.0, 120]	71.3 [62.0, 117]	80.7 [54.4, 95.0]	78.7 [60.1, 98.6]	92.1 [61.9, 127]	81.7 [64.1, 108]
Creatinine Clearance (mL/min)							
Mean	125 (NA)	142 (49.4)	92.4 (36.0)	76.6 (37.7)	71.0 (26.5)	105 (27.7)	98.1 (37.1)
Median [Min,Max]	125 [125, 125]	123 [105, 198]	112 [50.8, 115]	79.3 [32.0, 132]	63.6 [48.2, 117]	105 [66.2, 153]	107 [41.1, 144]
Hepatic Function							
Normal	1 (100%)	3 (100%)	3 (100%)	3 (60.0%)	5 (100%)	8 (88.9%)	5 (83.3%)
Mild impairment	0 (0%)	0 (0%)	0 (0%)	2 (40.0%)	0 (0%)	1 (11.1%)	1 (16.7%)
PSA (ng/mL)							
Mean	33.8 (NA)	1310 (2190)	51.1 (58.7)	195 (277)	462 (786)	51.4 (43.7)	273 (410)
Median [Min,Max]	33.8 [33.8, 33.8]	63.5 [26.0, 3850]	26.8 [8.50, 118]	101 [8.30, 685]	51.7 [10.6, 1840]	57.0 [2.33, 121]	125 [0.520, 1080]

Figure 3. Low serum concentrations of free payload observed at all doses, with the molar ratio of payload to ADC at 0.06%

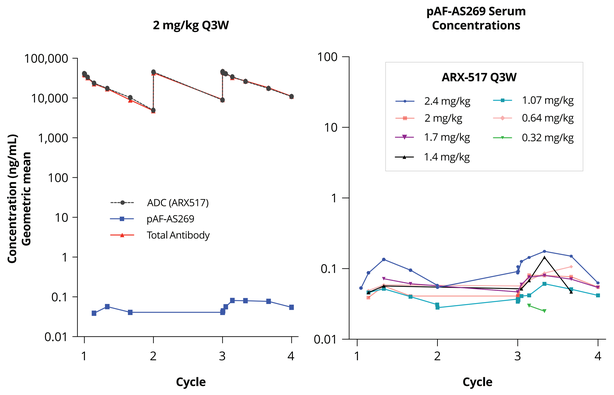


Figure 4. Virtually overlapping TA and ADC PK curves demonstrate strong stability at all dose levels

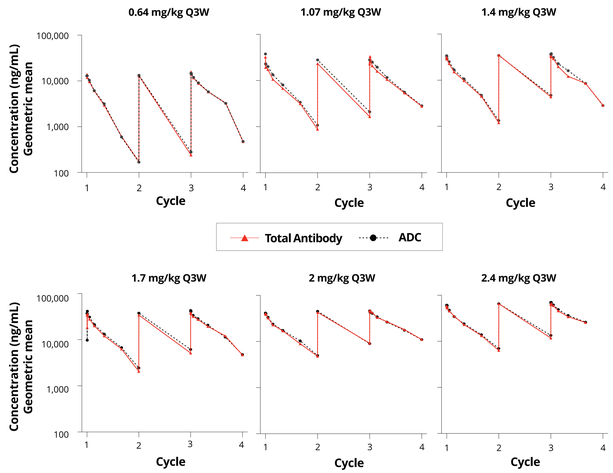
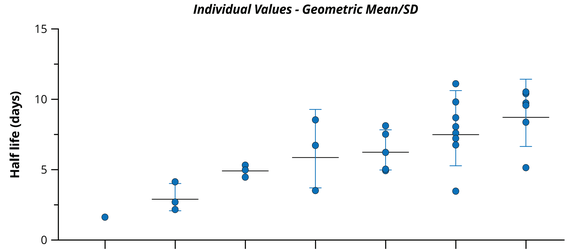
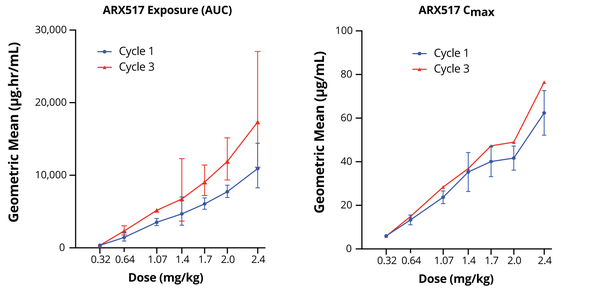


Figure 5. ARX517 exhibits a long half life of ~6–10 days at doses ≥1.4 mg/kg



Dose (mg/kg)	0.32	0.64	1.07	1.4	1.7	2	2.4
Number of Patients	1	3	3	3	5	7	6
Minimum (days)	1.6	2.2	4.5	3.2	4.9	6.2	5.0
Maximum (days)	1.6	4.1	5.3	8.5	8.2	10.4	11.8
Range	0.0	1.9	0.8	5.4	3.3	4.1	6.7
Geometric Mean	1.6	2.9	4.9	5.6	6.0	7.9	8.3
Geometric SD	1.0	1.4	1.0	1.7	1.2	1.2	1.4

Figure 6. Drug exposure increases proportional to ARX517 dose



METHODS

The pharmacokinetics population consisted of 32 patients having received ARX517 at doses ranging from 0.32 to 2.4 mg/kg as an intravenous infusion Q3W.

Patient serum samples were collected at fixed time points and evaluated in validated Total Antibody (TA; sum of deconjugated antibody and conjugated antibody), ADC (conjugated antibody with a DAR of 1 or 2), and payload (pAF-AS269) assays. The lower limit of quantitation for the TA, ADC, and payload assays were 62.5 ng/mL, 7.8 ng/mL, and 0.02 ng/mL, respectively.

Cycle 1 and Cycle 3 pharmacokinetic parameters were determined by noncompartmental analysis using Phoenix WINNONLIN (version 8.4) using serum concentrations of TA, ADC, and payload.

SUMMARY

- 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 (with the molar ratio of payload to ADC at 0.06%)
- Long ADC terminal half-life of ~6-10 days at doses ≥1.4 mg/kg, thereby maximizing drug exposure

CONCLUSION

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

References

1. Petrylak DP et al. *Prostate*. 2020 Jan;80(1):99-108; **2.** Galsky MD et al. *J Clin Oncol*. 2008;26: 2147–54.; **3.** de Bono JSD et al. *Clin Cancer Res*. 202 Jul 1;27(13):3602-3609; **4.** Milowsky MI et al. *Urol Oncol*. 2016 Dec;34(12):530.; **5.** Petrylak DP et al. *Prostate*. 2019;79:604–13.

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Disclosures

Dr. Tagawa is an investigator on the APEX-01 study and his institution (Weill Cornell) receives associated research funding.

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