ARX517, an Anti-Prostate-Specific Membrane Antigen (PSMA) Antibody-Drug Conjugate (ADC), Demonstrates Promising Safety and Efficacy in Heavily Pre-Treated Patients With Metastatic Castration-Resistant Prostate Cancer (mCRPC)

1804P

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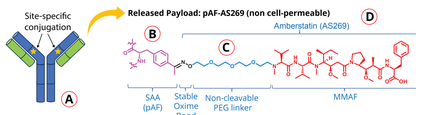
INTRODUCTION

- Previous PSMA-targeted ADCs demonstrated early clinical efficacy, but drug development was discontinued due to intolerable toxicities, resulting from premature release and off-target delivery of the cytotoxic payload.[1–5]
- ARX517 is a novel anti-PSMA ADC designed to overcome the stability and resulting toxicity challenges of other PSMA-targeted ADCs (**Figure 1**). Key differentiating features enabling increased 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). Safety and efficacy from the initial dose escalation and expansion are reported.

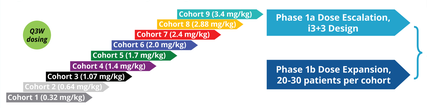
Figure 1. ARX517 structure



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).

STUDY DESIGN

Figure 2. Phase 1 study design



Eligibility

Must have had at least two FDA-approved therapies for mCRPC with at least one being a 2nd generation ARPI (abiraterone, enzalutamide, darolutamide, apalutamide)

- Documented progression by one or more of the following
  - PD by RECIST v1.1
  - PSA progression
  - Radiographic progression in bone

Objectives

- To determine safety and tolerability
- To determine MTD and/or establish recommended phase 2 dose regimen(s)

Table 1. Demographics

	Total (N=65)
Race, n (%)	
Asian	4 (6)
Black or African American	4 (6)
White	53 (82)
Other	4 (6)
Age (years)	
Median	68.0
Min, Max	50, 100
Baseline Weight (kg)	
Median	86.7
Min, Max	54, 133
Prior Lines of Cancer Therapy	
Median	4.0
Min, Max	1, 13
Prior Taxane, n (%)	
Y	43 (66)
N	22 (34)
Prior IO agent, n (%)	
Y	30 (46)
N	35 (54)
Prior PSMA-TRT, n (%)	
Y	11 (17)
N	54 (83)
Number of Prior ARPI treatments	
Median	2.0
Min, Max	1, 5
Prior 2nd generation ARPI, n (%)	
Abiraterone	49 (75)
Enzalutamide	45 (69)
Both Abiraterone and Enzalutamide	31 (48)
Lesion Site, n (%)	
Liver or lung	12 (19)
Lymph node	30 (46)
Bone	52 (80)
Any Measurable Lesions per RECIST, n (%)	
Y	22 (34)
N	43 (66)
Baseline ECOG Performance Status, n (%)	
0	24 (37)
1	38 (59)
2	2 (3)
Missing	1 (2)
Baseline PSA (µg/L)	
Median	47.0
Min, Max	1, 3845
Baseline Alkaline Phosphatase (U/L)	
Median	108.0
Min, Max	30, 848
Baseline LDH (U/L)	
Median	200.0
Min, Max	93, 1492

Data cutoff: 05-Sep-2023

Table 2. Treatment-Related Safety Summary

	Cohort 1 0.32 mg/kg (n=1)	Cohort 2 0.64 mg/kg (n=3)	Cohort 3 1.07 mg/kg (n=3)	Cohort 4 1.4 mg/kg (n=21)	Cohort 5 1.7 mg/kg (n=5)	Cohort 6 2.0 mg/kg (n=20)	Cohort 7 2.4 mg/kg (n=6)	Cohort 8 2.88 mg/kg (n=6)	All Cohorts (N=65)
n (%)									
All AEs	0	2 (67)	3 (100)	12 (57)	5 (100)	15 (75)	6 (100)	5 (83)	48 (74)
Grade 3 AEs	0	0	0	1 (5)	1 (20)	2 (10)	1 (17)	1 (17)	6 (9)
Grade 4 AEs	0	0	0	0	0	0	0	0	0
SAEs	0	0	0	0	0	0	0	0	0
AEs leading to discontinuation	0	1 (33)*	0	0	0	1 (5)†	0	0	2 (3)
Deaths (Grade 5 AEs)	0	0	0	0	0	0	0	0	0

*Patient at dose 0.64 mg/kg experienced Grade 1 platelet count decrease 22 days post C1D1 with no clinical symptoms.
†Patient at dose 2.0 mg/kg experienced Grade 2 decreased appetite and dysphagia 7 days post C2D1.

Table 3. Grade 3 Treatment-Related AEs

	Cohort 1 0.32 mg/kg (n=1)	Cohort 2 0.64 mg/kg (n=3)	Cohort 3 1.07 mg/kg (n=3)	Cohort 4 1.4 mg/kg (n=21)	Cohort 5 1.7 mg/kg (n=5)	Cohort 6 2.0 mg/kg (n=20)	Cohort 7 2.4 mg/kg (n=6)	Cohort 8 2.88 mg/kg (n=6)	All Cohorts (N=65)
n (%)									
Lymphocyte count decreased	0	0	0	0	1 (20)	1 (5)	1 (17)	0	3 (5)
Platelet count decreased	0	0	0	0	0	1 (5)	0	1 (17)	2 (3)
Left ventricular dysfunction	0	0	0	1 (5)	0	0	0	0	1 (2)

Note: 6 patients reported Grade 3 TRAEs, 3 experienced lymphocyte count decrease and 2 experienced transient platelet count decrease that were not clinically significant. At 1.4 mg/kg dose one patient reported transient, asymptomatic left ventricular dysfunction, patient recovered after IV infusion, this event was deemed not serious.

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Abbreviations: AE, adverse event; **ARPI,** androgen receptor pathway inhibitor; **ctDNA**, circulating tumor DNA; **C1D1,** cycle 1 day 1; **DCR,** disease control rate; **DLT,** dose limiting toxicity; **Gr3,** Grade 3; **IO,** immunotherapy; **LDH,** lactate dehydrogenase; **MTD,** maximum tolerated dose; **ORR,** objective response rate; **PD,** progressive disease; **PEG**, polyethylene glycol; **PSA,** prostate-specific antigen; **PSMA,** prostate-specific membrane antigen; **PSMA-TRT,** PSMA-Targeted radionuclide therapy; **SAA,** synthetic amino acid; **SAE,** serious adverse event; **TRAE,** treatment-related adverse event.

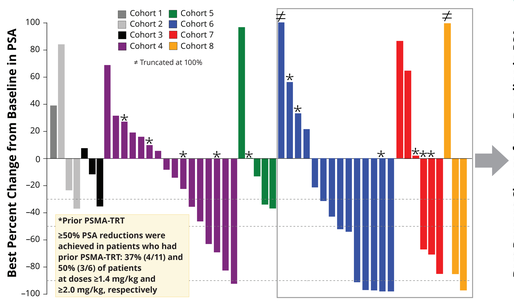
The APEX-01 study is sponsored by Ambrx, Inc.

RESULTS

Table 4. Frequent Grade 1/2 Treatment-Related Adverse Events in ≥10% of Patients

	Cohort 1 0.32 mg/kg (n=1)	Cohort 2 0.64 mg/kg (n=3)	Cohort 3 1.07 mg/kg (n=3)	Cohort 4 1.4 mg/kg (n=21)	Cohort 5 1.7 mg/kg (n=5)	Cohort 6 2.0 mg/kg (n=20)	Cohort 7 2.4 mg/kg (n=6)	Cohort 8 2.88 mg/kg (n=6)	All Cohorts (N=65)
Patients with any Grade 1/2 AE	0	2 (67)	3 (100)	12 (57)	5 (100)	15 (75)	6 (100)	5 (83)	48 (74)
Dry mouth	0	0	1 (33)	3 (14)	3 (60)	6 (30)	2 (33)	3 (50)	18 (28)
Dry eye	0	0	1 (33)	1 (5)	0	6 (30)	4 (67)	2 (33)	14 (22)
Fatigue	0	0	3 (100)	1 (5)	1 (20)	5 (25)	2 (33)	1 (17)	13 (20)
Diarrhoea	0	1 (33)	0	3 (14)	1 (20)	3 (15)	2 (33)	0	10 (15)
Decreased appetite	0	0	1 (33)	2 (10)	1 (20.0)	2 (10)	3 (50.0)	0	9 (14)
Nausea	0	1 (33)	1 (33)	0	0	3 (15)	4 (67)	0	9 (14)
Dysgeusia	0	0	0	1 (5)	1 (20)	3 (15)	3 (50)	0	8 (12)
Vomiting	0	1 (33)	1 (33)	0	0	1 (5)	4 (67)	1 (17)	8 (12)
Aspartate amino-transferase increased	0	0	0	0	1 (20)	4 (20)	1 (17)	1 (17)	7 (11)

Figure 3. Deep PSA reductions with increasing ARX517 dose



PSA waterfall includes patients with at least two on-treatment PSA assessments or discontinued before the second assessment.
Prior to reaching MTD, two dose cohorts (4 and 6) were expanded based on three criteria 1) PSA decline of ≥50%
2) no treatment-related SAEs 3) target lesion reduction or RECIST v1.1 response.

Figure 4. 52% (12/23) of patients experienced a ≥50% PSA reduction at putative therapeutic doses (≥2.0 mg/kg)

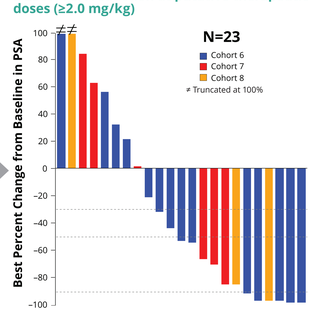
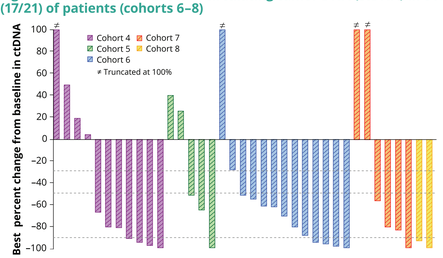


Table 5. Greater Frequency and Depth of PSA Response at Putative Therapeutic Doses (≥2.0 mg/kg)

	C1–3 n=7	C4 n=16	C5 n=5	C6 n=14	C7 n=6	C8 n=3	C6–8 n=23
≥30% PSA	29%	38%	40%,	64%	50%	67%	61%
≥50% PSA	0	25%	0	50%	50%	67%	52%
≥90% PSA	0	6%	0	36%	0	33%	26%

Figure 5. Reductions of ≥50% in circulating tumor DNA (ctDNA) in 81% (17/21) of patients (cohorts 6–8)



On treatment changes in ctDNA have been shown to predict time to progression and survival.[6,7] Serial plasma samples were collected at baseline, C3D1, C4D1 and EOT, best percent change from baseline is shown. ctDNA was measured using GuardantINFINITY test (Guardant Health) with a specificity of 96.9%, a sensitivity of 91.3% and a reported lower limit of detection 0.06%. Samples were processed after passing multiple quality control measurements encompassing DNA yield, GC bias, methylation bias, diversity, and contamination checks. ctDNA changes compared with its baseline level were measured based on aggregated tumor-specific methylation signal scores.

Figure 6. Duration on treatment (Cohorts 4-8)

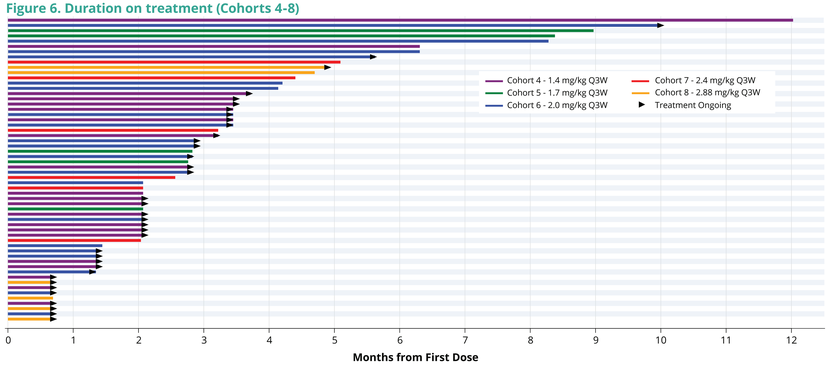
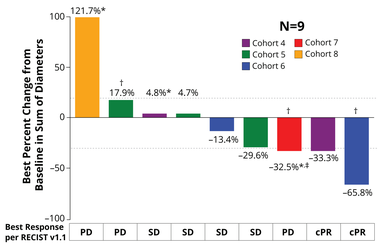


Figure 7. RECIST v1.1 Target lesion reduction was observed in 56% (5/9) of patients (Cohorts 4–8)



Evaluable population includes all patients with measurable target lesion(s) at baseline per RECIST v1.1 who had at least two post baseline tumor assessments or progressed or discontinued treatment prior to the 2nd assessment.
cPR, confirmed partial response per RECIST v1.1
*Patients with lung/liver target lesions
†Patients with prior PSMA-TRT
‡Patient had PR in target lesions; 1 liver lesion reduced in size from 38 to 14mm and 1 lung lesion from 18 to 9mm, but growth in non-target lesion resulted in PD by RECIST v1.1.

SUMMARY

- **ARX517 had a strong safety profile at all doses tested up to 2.88 mg/kg every 3 weeks**
  - No treatment-related SAEs
  - No DLTs
- **At putative therapeutic doses (≥2.0 mg/kg)**
  - 52% (12/23) of patients had a ≥50% PSA reduction
  - 81% (17/21) of patients had a ≥50% ctDNA reduction
- **Target lesion achieved in 56% (5/9) of patients; 2 had confirmed RECIST v1.1 responses**
- **PSA and RECIST v1.1 responses were observed in patients who had prior PSMA-TRT**

CONCLUSIONS

Without PSMA imaging selection, ARX517 monotherapy achieved favorable safety and demonstrated early efficacy, with deep PSA and ctDNA reductions and confirmed RECIST v1.1 tumor response in patients with mCRPC who progressed on multiple FDA-approved treatments.

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Disclosures

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

On-going and Next Steps

- Expansion of Cohort 8
- Escalate into next higher dose, Cohort 9

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.; **6.** Tolmeijer SH et al. *Clin Cancer Res*. 2023 Aug 1;29(15):2835-2844. doi: 10.1158/1078-0432.CCR-22-2998.; **7.** Sartor O. *Clin Cancer Res*. 2023 Aug 1;29(15):2745-2747. doi: 10.1158/1078-0432.CCR-23-1043.

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