Abstract 1421

APEX-01: First-in-human phase 1/2 study of ARX517, an anti- prostate-specific membrane antigen (PSMA) antibody-drug conjugate (ADC), in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC)

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Background

ARX517 is a novel ADC composed of a fully humanized anti-PSMA mAb conjugated to amberstatin-269, a potent tubulin inhibitor. ARX517 was designed to reduce off-target ADC instability-related toxicity issues observed in earlier anti-PSMA ADCs by using site-specific synthetic amino acids and stable oxime conjugation chemistry to minimize premature payload release in the human circulation.

Methods

An i3+3 dose escalation design was used. Eligible pts had ≥ 2 FDA-approved treatments for mCRPC with progression by Prostate Cancer Working Group criteria. Key objectives include safety, PK and clinical efficacy. Baseline PSMA PET expression was not required for eligibility, but was evaluated as a biomarker.

Results

24 pts received ARX517 q3w at escalating doses (Table). Pts had a median of 4 prior lines of therapy; 100% received ≥ 1 androgen pathway inhibitor, 50% received taxane, and 12.5% received PSMA-targeted radionuclide. Grade (Gr) 1/2 treatment-related adverse events (TRAEs) were dry mouth (41.7%), fatigue (33.3%), diarrhea and platelet count decrease (20.8% each). Four Gr3 TRAEs were reported at 1.7, 2.4, and 2.88 mg/kg (two lymphopenia, two platelet count decrease). No DLTs, treatment-related serious AEs (SAEs), or ≥ Gr 4 AEs were reported. At higher doses (Cohorts 4-8), median duration on-treatment was 6.3 months (range 0.7+, 11.8+). Additionally, > 50% PSA and ctDNA decline were observed (Table); 2/7 pts had confirmed RECIST v1.1 responses. PK profiles for total antibody and ADC were similar, suggesting strong stability of ARX517 with minimal premature payload release.

PSA and ctDNA decline, confirmed responses, DLTs, and Grade 3/4/5 TRAEs by dose level

	Cohort 1 **0.32 mg/kg**	**Cohort 2** **0.64 mg/kg**	**Cohort 3** **1.07 mg/kg**	**Cohort 4** **1.4 mg/kg**	**Cohort 5** **1.7 mg/kg**	**Cohort 6** **2.0 mg/kg**	**Cohort 7** **2.4 mg/kg**	**Cohort 8** **2.88 mg/kg**

Best % change from baseline*								
PSA > 30%	0/1	1/3	1/3	2/3	2/5	3/3	2/3	2/3
PSA > 50%	0/1	0/3	0/3	1/3	0/5	3/3	2/3	2/3
PSA > 90%	0/1	0/3	0/3	0/3	0/5	2/3	0/3	0/3
ctDNA > 50%	0/1	1/2	2/3	1/3	3/5	3/3	2/2	n/d
Confirmed RECIST v1.1 response	0/1	0/1	0/0	1/2	0/3	1/1	0/1	n/d
DLT	0/3	0/3	0/3	0/3	0/5	0/3	0/3	0/3
Gr3 TRAE	0/3	0/3	0/3	0/3	1/5	0/3	1/3	2/3
Gr4/5 TRAE	0/3	0/3	0/3	0/3	0/5	0/3	0/3	0/3
*Data cut-off 03May23; n/d = no data available								

Conclusions

ARX517 treatment resulted in PSA declines and RECIST v1.1 responses without treatment-related SAEs. Dose expansion has begun, additional safety, PD, efficacy, and PSMA PET data will be presented.

Clinical trial identification

NCT04662580

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