#832: Biomarker analysis of neoadjuvant atezolizumab in upper-tract urothelial carcinoma: Results from the ABACUS-2 trial

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Background

High-risk upper-tract urothelial carcinoma (UTUC) is associated with poor clinical outcomes and there are no standard neoadjuvant therapy options currently[1,2]. ABACUS-2 evaluates two cycles of neoadjuvant atezolizumab prior to radical nephroureterectomy (RNU). Here, we report circulating (ctDNA) and urinary tumor DNA (utDNA) findings.

Methods

ABACUS-2 (NCT04624399) is a single-arm phase 2 study of atezolizumab (1200 mg IV Q3W × 2) prior to RNU in patients with high-grade or high-risk (hydronephrosis, tumor > 2 cm, multifocality, variant histology, or prior radical cystectomy for UC) UTUC (cT1-4a N0-1 M0). Co-primary endpoints were pathological complete response (pCR; pT0N0) and predefined biomarker analyses on serial liquid biopsies. For these analyses, baseline genomic profiling was performed using the PredicineWES+ assay to identify somatic variants, followed by longitudinal minimal residual disease (MRD) monitoring with the PredicineBEACON platform. Correlations were explored between pCR, relapse-free survival (RFS) and overall survival (OS) with ctDNA/utDNA dynamics.

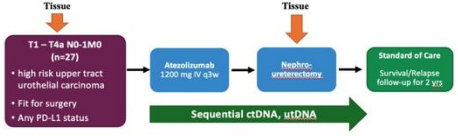
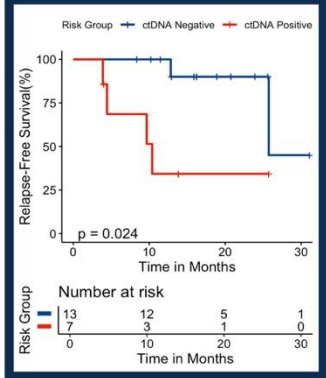
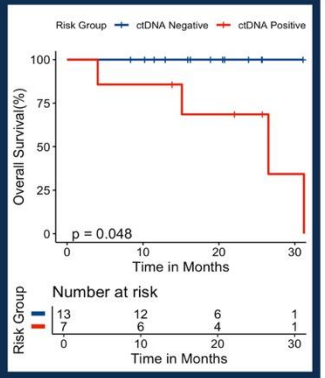


Fig. 1 – ABACUS-2 trial design

Fig. 2 – Patient disposition and treatment exposure





Conclusion

Neoadjuvant atezolizumab was feasible and well tolerated in patients with high-risk UTUC, but pathological complete responses were infrequent. Post-operative liquid biopsy analyses revealed that ctDNA and utDNA provide complementary information on systemic and local disease, respectively.

Persistent or recurrent ctDNA positivity post-RNU was strongly associated with metastatic relapse and inferior survival, while utDNA positivity during follow-up correlated with intravesical recurrence. These findings support the utility of plasma and urine MRD monitoring for risk stratification and early relapse detection in UTUC.

Results

Table 1 – Baseline characteristics

	UTUC cohort (N=27)
Age (years), median (range)	71 (49 – 86)
Sex, n (%)	
Male	17 (62.96)
Female	10 (37.04)
Race, n (%)	
Asian (Indian)	1 (3.7)
Asian (Other)	1 (3.7)
White	23(85.19)
Other	1 (3.7)
Not Specified	1 (3.7)
Received BCG vaccination, n (%)	
Yes	3 (11.11)
No	9 (33.33)
Unknown	15 (55.56)
T Stage diagnosis	
T1	5(19.2)
T2	2(7.6)
T3	1(3.8)
Ta	16(61.5)
TX	2(7.69)
Smoking status, n (%)	
Never	14 (51.85)
Ex-smoker	10 (37.04)
Current smoker	3 (11.11)
ECOG, n (%)	
0	17 (62.96)
1	10 (37.04)
Haemoglobin, median, IQR	132 (126 -148.5)
eGFR, median, IQR	100 (80 – 125.5)
Charlson comorbidity index, median, IQR	5 (4-6)

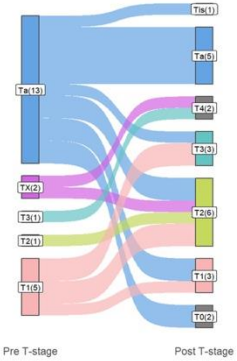


Fig. 3 – T-stage discordance between biopsy and final pathology in UTUC

pCR occurred in 7% (2/27). After a median follow-up of 18.9 months (95% CI 13.9 –25.6), disease recurrence was observed in 26% (6/27) and 15% (4/27) had died. Treatment was well tolerated, with no surgery delays reported.

24 pts had successful MRD tests in at least one of the time points from screening to end of follow-up and were included in this biomarker evaluable subset. At baseline 25% (5/20) of pts were ctDNA(+) and all pts (100%, 14/14) were utDNA(+). After neoadjuvant atezolizumab and RNU, 80% (4/5) pts had ctDNA clearance. Only 1 pt demonstrated utDNA clearance following neoadjuvant atezolizumab, which correlated with pCR on RNU. Post-RNU, 3 pts were ctDNA(+) and subsequently developed metastatic disease. Among 17 pts with post-RNU utDNA monitoring, 29% (5/17) showed repeated utDNA positivity at multiple follow-up timepoints, correlating with bladder tumour recurrence. ctDNA(-) status post neoadjuvant atezolizumab correlated with significantly longer RFS (p = 0.024) and OS (p = 0.048).