Prospective Longitudinal Tumor-Informed ctDNA in Resectable Biliary Tract Cancers

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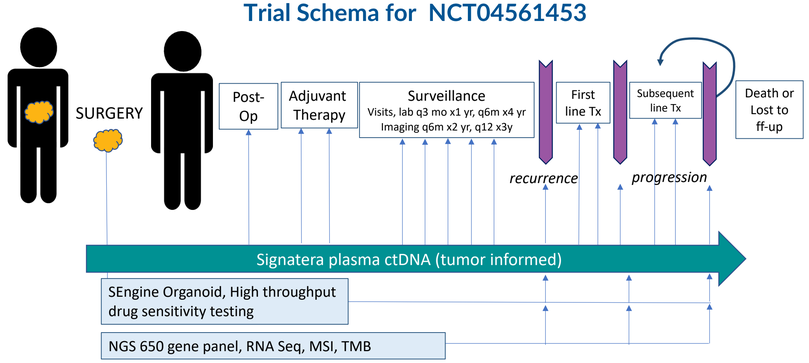
Purpose

- Circulating tumor DNA (ctDNA) has emerged as a prognostic biomarker correlating with risk of recurrence in patients (pts) with resected solid tumors.
- However, there is limited data on the prognostic and predictive utility of longitudinal ctDNA monitoring specifically in biliary tract cancers (BTC)
- Understanding the peri-operative kinetics of ctDNA and its relationship to clinical features and and outcomes can aid in risk stratification and define areas of further investigation for its clinical applicability in BTC.

Methodology

- We conducted a prospective multi-platform profiling study for resectable BTC from 2020 to 2023 (NCT04561453, still open to enrollment).
- Tumor-informed ctDNA testing (Signatera™, Natera, Inc. USA) was conducted on plasma samples collected pre-operatively, within 6 weeks post-operatively prior to adjuvant therapy (MRD window) and, longitudinally every 3 months thereafter until death or last follow-up.
- Herein, we evaluate the relationship between ctDNA and clinical features and outcomes in pts with BTC.

Trial Schema for NCT04561453



Baseline Characteristics N = 12

Patient Demographics		
Median Age	69.5	
Sex (M%:F%)	(50/50)	
BTC subtype		
Intrahepatic	9	75%
Hilar	1	8%
Gallbladder	2	17%
Stage		
I	4	33%
II	6	50%
III	2	17%
Median T size	5.15 cm (range: 2.1-10 cm)	

Treatment Factors		
Resection Margin		
R0	8	67%
R1	4	33%
Neoadjuvant Therapy		
Gemcitabine and Cisplatin	2	17%
Adjuvant Therapy		
Capecitabine	10	80%
Gemcitabine and Cisplatin	1	8%
Adjuvant Chemoradiation*	2	17%

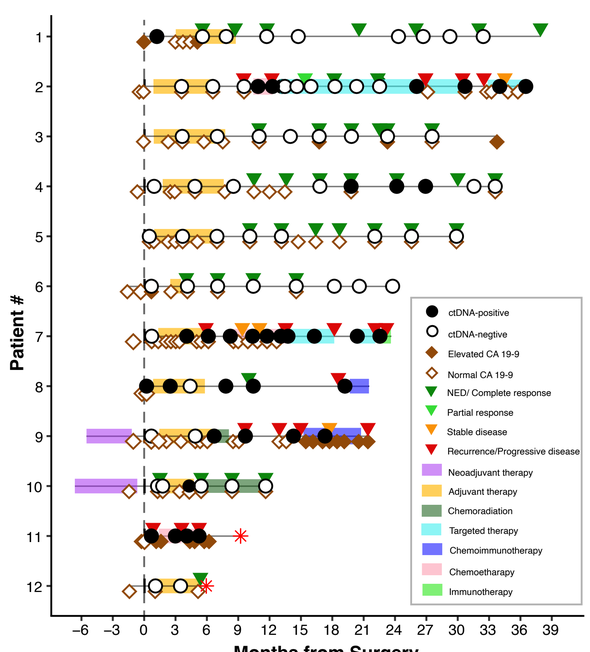
**2 patients completed chemoradiation, followed by 4 months capecitabine monotherapy*

Tumor Characteristics, ctDNA & CA 19-9 status, Treatment Characteristics , Relapse Pattern, and Molecular Profile

								preoperative			*post-operative (MRD)*					
ID	BTC type	pStage	T	T size	N	M	Margin	ctDNA	mt/Mb	CA 19-9	ctDNA	mt/Mb	CA 19-9	Adj Tx	Recurrence	Tissue NGS**
1	GBCA	III	2	2.1	1	0	R0	N/A	18	60	+	0	34	Cape	NTD	TP53 LOF, CCNE1 CNG, ERBB2 CNG, CDK12 CNG
2	iCCA	II	2	10	0	0	R1	+	331	50	N/A	0	N/A	Cape	Pulmonary	FGFR2-SORBS1 RNG, CDKN2A CNL
3	iCCA	II	2	5.2	0	0	R0	+	30	34	N/A	0	N/A	Cape	NTD	TP53 LOF, ARID1A LOF, KRAS G12D GOF
4	eCCA	III	2	4.2	1	0	R1	+	1.06	239	-	0	N/A	Cape	NTD	KRAS pQ61H GOF
5	iCCA	I	1	4.2	0	0	R0	+	10.58	N/A	-	0	17	Cape	NTD	FBXW7 pN21fs LOF
6	iCCA	I	1	6	0	0	R0	+	17.72	13	-	0	16	Cape	NTD	IDH p132C, MTAP LOF, CDKN2A/B CNL, FGFR2 CNG
7	iCCA	I	1	6.6	0	0	R1	+	404.24	10	-	0	15	GemCis	Peritoneum	IDH1 pR132C GOF, ANK3-BRAF RNG, BAP1 LOF, CDKN2A/B CNL
8	iCCA	I	1	5.1	0	0	R0	+	37.04	29	+	0.04	11	Cape	Liver	BAP1 LOF
9*	GBCA	III	3	3	0	0	R0	+	0.53	34	-	0	18	CapeRT	Liver	TP53 LOF, KRAS pG12C GOF, FGFR1 CNG, CUX1 LOF, RASA1 LOF
10*	iCCA	II	2	8.3	0	0	R1	+	4.21	152	-	0	39	Cape	NTD	IDH1 GOF, PBRM1 LOF, KRAS pG12D GOF, BAP1 LOF
11	iCCA	II	2	8.9	0	0	R0	+	483.33	1,224	+	12.1	28	x	Liver	ARID1A LOF, PBRM1 LOF, NF1 LOF, RB1 LOF
12	iCCA	II	2	4.8	0	0	R0	+	112.79	6	N/A	0	N/A	Cape	NTD	BAP1 LOF NRAS pQ61R GOF, CDKN2A/B CNL

Abbreviations: *pStage: pathologic stage, mt/Mb: mutations per megabase, iCCA: intrahepatic cholangiocarcinoma, eCCA: extrahepatic cholangiocarcinoma, GBCA: gall bladder carcinoma, Adj Tx: adjuvant treatment Cape: capecitabine, CapeRT: capecitabine plus radiation, GemCis: gemcitabine cisplatin, NTD: none to date, LOF: loss of function, GOF: gain of function, CNG: copy number gain, CNL: copy number loss . Normal CA 19-9 value 0-40 mg/dl. * received neoadjuvant therapy, ** All patients were microsatellite stable and had low tumor mutation burden (<10mt/Mb).*

Longitudinal ctDNA Relationship to CA 19-9, Radiography, Treatment



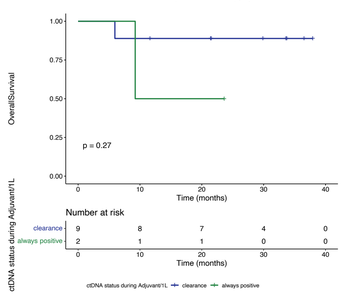
At the time of surgery, all pts tested positive for ctDNA (not depicted in the overview plot) except pt# 1 who lacked this time point. Within the MRD window, 6/12 pts tested negative, 3/12 tested positive, and 3/12 lacked an MRD time point.

Among the 6 pts who were ctDNA negative, 2 converted to positive and the remaining showed serial ctDNA negativity for the length of follow-up up to 18 months post-surgery. Both these events were concordant with radiologic imaging; ctDNA positivity and negativity correlated with recurrence and no evidence of disease (NED), respectively.

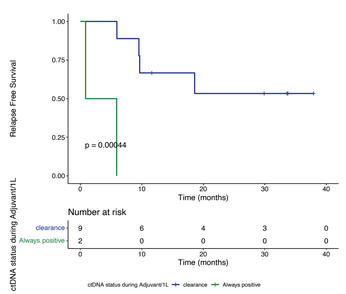
Of the 3 patients who were positive in the MRD window, one pt cleared and remained ctDNA negative and 2 showed persistent ctDNA-positivity correlating with relapse. Of the 3 pts who lacked an MRD time point, subsequent ctDNA testing was concordant with imaging.

Survival Based on ctDNA Clearance At Any Time Point

OS: HR 4.2 95% CI (0.27-68), p=0.27



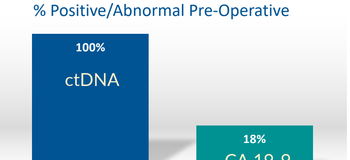
RFS: HR 7.4 95% CI (2.6-4758) p=0.00044



Peri-Operative ctDNA vs CA 19-9

ctDNA + pre-op	11/11	**100%**
ctDNA + post-op	3/9	33%
Abnormal CA 19-9 pre-op	2/11	**18%**
Abnormal CA 19-9 post-op	2/8	25%

% Positive/Abnormal Pre-Operative



Conclusions

- Baseline ctDNA had higher detection rate compared to CA 19-9 prior to resection.
- Persistent ctDNA negativity post resection was associated with improved recurrence free survival.
- Assessing ctDNA levels may have potential utility in evaluating response in the absence of radiographically visible disease.

Disclosure: Dr. King, as presenter, has no significant conflicts of interest to declare for this presentation

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