Impact of claudin-1 (CLDN1) expression on molecular correlates and clinical outcomes in patients with advanced biliary tract cancers (BTCs)

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INTRODUCTION

The tight junction protein CLDN1 is a potential therapeutic target in many cancers where its dysregulation is associated with invasiveness and migration. The effect of *CLDN1* expression on outcomes in BTC is unknown. We examined the molecular and clinical correlates of *CLDN1* expression in a real-world cohort of patients with advanced BTCs, including across subtypes.

METHODS

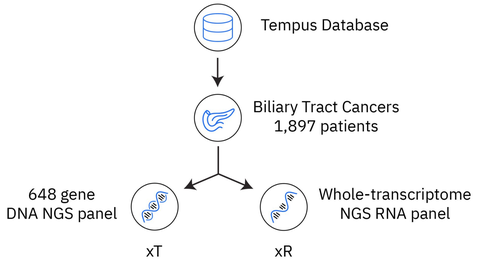
The Tempus Lens Database was used to identify 1,897 pts with BTCs (intrahepatic cholangiocarcinoma [IHCC}, extrahepatic cholangiocarcinoma [EHCC], gallbladder cancer [GC]), whose tumors were tested with Tempus xT and xR panels. Tumors not classified by location were referred to as cholangiocarcinoma NOS. Patients must have received first-line platinum-based chemotherapy +/- IO (PD1-inhibitor).

RNA-seq data were normalized by computing transcripts per million (TPM) and transforming them by log2(TPM+1). PD-L1 status was assessed with the 22C3 clone and immune cell infiltration was estimated using quanTIseq.

Tumors were classified into *CLDN1*-high (*CLDN1*-H) vs *CLDN1*-low (*CLDN1*-L) by median *CLDN1* expression. P-values were calculated by either $\chi 2$ or Fisher's exact tests.

Real-world overall survival (rwOS) was defined as the time from the initiation of first-line (1L) treatment with chemotherapy (chemo) +/- immunotherapy (IO) (N = 919) to the earliest of death, last known follow-up, or max 5 years. Patients must have received a platinum based chemo(cisplatin, carboplatin, or oxaliplatin) +/- IO (durvalumab or pembrolizumab).

Median rwOS (mOS) was estimated with Kaplan-Meier curves and log-rank p-value. Statistical significance was set at p≤0.05; all tests were two-sided.



SUMMARY

- In patients with advanced BTC receiving first-line chemo-immunotherapy, *CLDN1*-H expression is associated with improved rwOS
- *CLDN1*-H expression is more frequent in patients with IHCC versus EHCC and gallbladder cancer.
- *CLDN1*-H expression is associated with immune cell infiltration in advanced BTC.
- Clinically relevant molecular alterations are significantly different in *CLDN1*-H vs *CLDN*-L BTC.

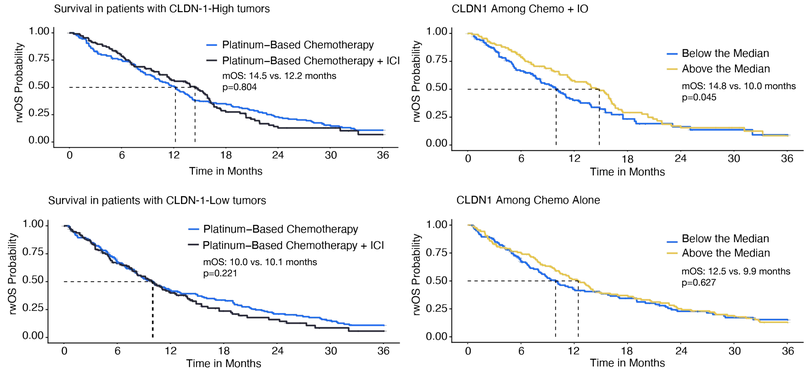
PATIENT CHARACTERISTICS (N = 1,897)

	CLDN-L (N = 948)	CLDN-H (N = 949)	ALL PATIENTS (N = 1,897)
Age at diagnosis, median (range)	65 (21-87)	65 (23-88)	65 (21-88)
Gender			
Female	493 (52%)	521 (55%)	1,014 (53%)
Male	455 (48%)	428 (45%)	883 (47%)
Race / Ethnicity			
White	471 (75%)	510 (82%)	981 (78%)
African American	65 (10%)	41 (6.6%)	106 (8.5%)
Asian	38 (6.0%)	27 (4.3%)	65 (5.2%)
Other	55 (8.7%)	45 (7.2%)	100 (79.9%)
Unknown	319	326	645
ECOG at treatment start (%)			
0 | 1 | 2+	34% | 47% | 19%	28% | 50% | 22%	31% | 49% | 20%

TUMOR CHARACTERISTICS | CLINICAL OUTCOMES

	CLDN-L	CLDN-H	OVERALL	p-value
Biliary Tract Cancer (BTC) Subtype				
IHCC	294 (31%)	680 (72%)	974 (51%)	<0.001
EHCC	212 (22%)	50 (5.3%)	262 (14%)	
Gallbladder	324 (34%)	93 (9.8%)	417 (22%)	
Cholangiocarcinoma NOS	118 (12%)	126 (13%)	244 (13%)	
First-Line Therapy				
Chemotherapy	167 (50%)	171 (53%)	338 (52%)	0.448
Chemotherapy + IO	165 (50%)	150 (47%)	315 (48%)	
Best Response (by 90 Days)				
Complete Response	6 (3.1%)	0 (0%)	6 (1.6%)	0.056
Partial Response	61 (31%)	45 (26%)	106 (29%)	
Stable Disease	44 (23%)	49 (29%)	93 (26%)	
Progressive Disease	83 (43%)	76 (45%)	159 (44%)	
Median Overall Survival (OS) (months)				
	10.2 mths	12.2 mths		0.094

ASSOCIATION BETWEEN *CLDN1* EXPRESSION AND OVERALL SURVIVAL BASED ON FIRST-LINE THERAPY



Among pts receiving 1L chemo + IO, *CLDN1*-H expression was associated with significantly improved mOS (14.8 vs 10.0 mths, p = 0.0461).

No difference in outcomes by *CLDN1* expression was seen in pts receiving chemo alone.

Independent of treatment, patients with *CLDN1*-H tumors had a trend towards improved mOS vs. those with *CLDN1*-L tumors. (12.2 vs. 10.2 mths, p=0.094)

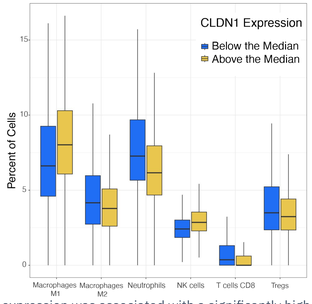
ASSOCIATION BETWEEN *CLDN1* EXPRESSION AND CLINICALLY RELEVANT ALTERATIONS

	OVERALL	CLDN1-L	CLDN1-H	p-value
***TP53*, N (%)**	802 (42%)	566 (60%)	236 (25%)	**<0.001**
***CDKN2A*, N (%)**	472 (25%)	244 (26%)	228 (24%)	0.388
***CDKN2B*, N (%)**	353 (19%)	157 (17%)	196 (21%)	**0.022**
***KRAS*, N (%)**	317 (17%)	239 (25%)	78 (8.2%)	**<0.001**
***ARID1A*, N (%)**	308 (16%)	135 (14%)	173 (18%)	**0.018**
***BAP1*, N (%)**	228 (12%)	50 (5.3%)	178 (19%)	**<0.001**
***FGFR2*, N (%)**	222 (12%)	35 (3.7%)	187 (20%)	**<0.001**
***MTAP*, N (%)**	221 (12%)	104 (11%)	117 (12%)	0.357
***SMAD4*, N (%)**	216 (11%)	186 (20%)	30 (3.2%)	**<0.001**
***IDH1*, N (%)**	204 (11%)	29 (3.1%)	175 (18%)	**<0.001**
***PBRM1*, N (%)**	158 (8.3%)	46 (4.9%)	112 (12%)	**<0.001**
***TERT*, N (%)**	134 (7.1%)	66 (7.0%)	68 (7.2%)	0.863
***ARID2*, N (%)**	126 (6.6%)	88 (9.3%)	38 (4.0%)	**<0.001**
***PIK3CA*, N (%)**	125 (6.6%)	76 (8.0%)	49 (5.2%)	**0.012**
***ERBB2*, N (%)**	108 (5.7%)	92 (9.7%)	16 (1.7%)	**<0.001**
***CKS1B*, N (%)**	101 (5.3%)	37 (3.9%)	64 (6.7%)	**0.006**
***ELF3*, N (%)**	85 (4.5%)	55 (5.8%)	30 (3.2%)	**0.005**
***ATM*, N (%)**	80 (4.2%)	53 (5.6%)	27 (2.8%)	**0.003**
***STK11*, N (%)**	74 (3.9%)	73 (7.7%)	1 (0.1%)	**<0.001**
***APC*, N (%)**	70 (3.7%)	62 (6.5%)	8 (0.8%)	**<0.001**
***KMT2D*, N (%)**	70 (3.7%)	49 (5.2%)	21 (2.2%)	**<0.001**
***NRAS*, N (%)**	67 (3.5%)	13 (1.4%)	54 (5.7%)	**<0.001**
***IDH2*, N (%)**	60 (3.2%)	4 (0.4%)	56 (5.9%)	**<0.001**
***CCNE1*, N (%)**	59 (3.1%)	52 (5.5%)	7 (0.7%)	**<0.001**

CLDN1-H tumors had more frequent *FGFR2* alterations (20% vs 3.7%) as well as *IDH1* (18% vs 3.1%), *PBRM1* (12% vs 5%) and *BAP1* mutations (19% vs 5.3%) (all p < 0.05).

CLDN1-L tumors had more frequent *KRAS* (25% vs 8.2%) and *TP53* mutations (60% vs 25%) and *ERBB2* alterations(9.7% vs 1.7%) (all p < 0.05).

ASSOCIATION BETWEEN *CLDN1* EXPRESSION AND IMMUNE CELL INFILTRATION



CLDN1-H expression was associated with a significantly higher percentage of M1 macrophages and NK cells and lower M2 macrophages, CD8 T-cells, Tregs and neutrophils (all p < 0.001).
There was no difference in *PDL1* (*22c3*) status by *CLDN1* expression.