The association between tumor immunogenomic features and first line (1L) therapeutic outcomes in advanced biliary tract cancer (BTC)

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INTRODUCTION

- Recent advanced BTC clinical trials reported a ~1.5 mo overall survival (OS) benefit with 1L immunotherapy (ICI) added to gemcitabine + cisplatin (G+C)
- Real world (rw) confirmation of 1L ICI benefit is limited and predictive ICI biomarkers are lacking
- We investigated the relationship between pt outcomes, BTC subtype, immunologic phenotype, and genomic alterations (gAlt) in patients with BTC treated with 1L G+C+ICI

METHODS

We used Tempus Lens to analyze a cohort of de-identified patients with BTC sequenced with xT (DNA seq; 596-648 genes) ± xR (whole-transcriptome RNA-seq). Patients were stratified by subtype (intrahepatic, iCCA; extrahepatic, eCCA; gallbladder, GBC), median %CD8 T cells (%CD8T) High (H)/Low (L), and gAlt: *IDH1*, *KRAS, TP53, ARID1A,* DDR (23 genes) alt, *FGFR2* fusions and MTAP loss. Immunologic phenotype was assessed by TMB (m/MB). Immune infiltration was estimated by quanTIseq (RNA). rwOS was defined as time from the start of 1L G+C±ICI to death from any cause. Median rwOS (mOS) was estimated using the Kaplan-Meier method and hazard ratios (HR) estimated with Cox proportional hazard models.

Table 1: Patient cohort characteristics

Characteristic	Overall	Intrahepatic Cholangiocarcinoma	Extrahepatic Cholangiocarcinoma	Gallbladder Cancer	Cholangiocarcinoma	p-value[1]
	N = 3,529	N = 1,492	N = 537	N = 912	N = 588	
Age at diagnosis						0.001
Median (Q1, Q3)	66 (58, 73)	66 (57, 73)	66 (57, 73)	68 (59, 74)	65 (58, 72)	
Min, Max	18, 88	21, 88	18, 88	26, 88	19, 88	
Unknown	47	9	6	15	17	
Age at sample collection						0.001
Median (Q1, Q3)	67 (59, 74)	67 (58, 74)	67 (59, 74)	69 (60, 75)	66 (59, 73)	
Min, Max	19, 89	23, 89	22, 88	27, 89	19, 89	
Unknown	23	4	5	8	6	
Sex, n (%)						<0.001
Female	1,955 (55%)	778 (52%)	245 (46%)	631 (69%)	301 (51%)	
Male	1,574 (45%)	714 (48%)	292 (54%)	281 (31%)	287 (49%)	
Race, n (%)						<0.001
White	1,573 (77%)	744 (81%)	229 (77%)	349 (69%)	251 (76%)	
Black or African American	233 (11%)	85 (9.2%)	21 (7.0%)	85 (17%)	42 (13%)	
Other Race	143 (7.0%)	50 (5.4%)	25 (8.4%)	49 (9.7%)	19 (5.8%)	
Asian	106 (5.2%)	41 (4.5%)	23 (7.7%)	24 (4.7%)	18 (5.5%)	
Unknown	1,474	572	239	405	258	
Ethnicity, n (%)						0.002
Not Hispanic or Latino	1,251 (82%)	568 (86%)	186 (82%)	297 (77%)	200 (80%)	
Hispanic or Latino	266 (18%)	90 (14%)	40 (18%)	87 (23%)	49 (20%)	
Unknown	2,012	834	311	528	339	
Smoking status, n (%)						<0.001
Never smoker	1,398 (51%)	565 (48%)	207 (52%)	405 (59%)	221 (49%)	
Ex-smoker	1,025 (38%)	472 (40%)	160 (40%)	226 (33%)	167 (37%)	
Current smoker	297 (11%)	146 (12%)	33 (8.3%)	59 (8.6%)	59 (13%)	
Unknown	809	309	137	222	141	
Alcohol consumption, n (%)						0.3
Never or No	140 (54%)	52 (52%)	19 (44%)	41 (62%)	28 (54%)	
Yes	121 (46%)	48 (48%)	24 (56%)	25 (38%)	24 (46%)	
Unknown	3,268	1,392	494	846	536	

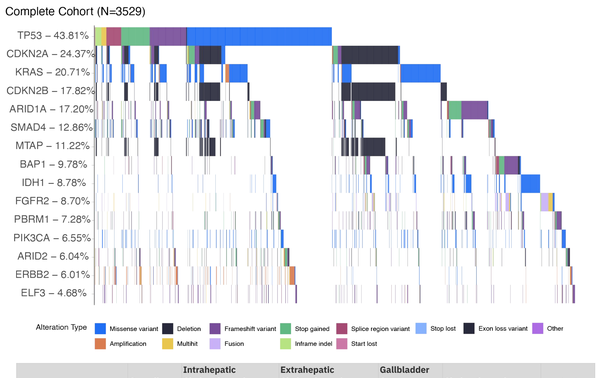
1 Kruskal-Wallis rank sum test; Pearson's Chi-squared test

SUMMARY

- The real world study shows similar rwOS with G+C±ICI in BTC and the gAlts in FGFR2, DDR, TP53 and KRAS genes appeared prognostic
- While there was a modest trend towards improved OS in patients with GBC, a cancer type with a higher proportion of CD8 T cells, the results did not reach statistical significance
- Future immunogenomic analysis in clinical trials is warranted to identify additional prognostic and predictive markers

RESULTS

Figure 1. Somatic landscape overall BTC and actionable alterations across subtypes



Characteristic	Overall N = 3,529[1]	Intrahepatic Cholangiocarcinoma N = 1,492[1]	Extrahepatic Cholangiocarcinoma N = 537[1]	Gallbladder Cancer N = 912[1]	Cholangiocarcinoma N = 588[1]	p-value[2]
KRAS P/LP	683 (19%)	208 (14%)	216 (40%)	94 (10%)	165 (28%)	<0.001
IDH1 P/LP	310 (8.8%)	237 (16%)	10 (1.9%)	3 (0.3%)	60 (10%)	<0.001
FGFR2 fusion	242 (6.9%)	174 (12%)	7 (1.3%)	15 (1.6%)	46 (7.8%)	<0.001
ERBB2 amplification	155 (4.4%)	32 (2.1%)	19 (3.5%)	90 (9.9%)	14 (2.4%)	<0.001
BRAF V600E	46 (1.3%)	31 (2.1%)	3 (0.6%)	1 (0.1%)	11 (1.9%)	<0.001
NTRK1/2/3 fusion	8 (0.2%)	1 (<0.1%)	3 (0.6%)	3 (0.3%)	1 (0.2%)	0.12
RET fusion	4 (0.1%)	2 (0.1%)	1 (0.2%)	1 (0.1%)	0 (0%)	>0.9

Figure 1. The 15 most commonly altered genes across all patients are shown. The table shows the prevalence of targetable drivers across BTC subtypes.

Figure 2. CD8T cell proportions across BTC subtypes

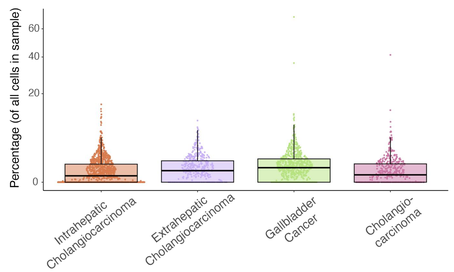
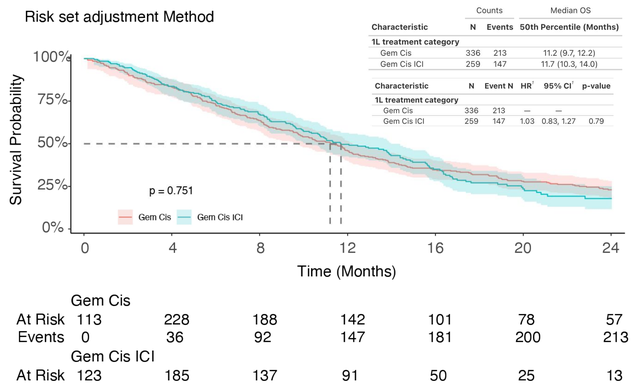


Figure 2. Patients with GBC had the highest proportion of CD8T cells and patients with iCCA had the lowest proportion of CD8T cells (p<0.001).

Figure 3. OS in the BTC patient population treated with G+C±ICI



Characteristic	N	Events	Median OS 50th Percentile (Months)
1L treatment category			
Gem Cis	336	213	11.2 (9.7, 12.2)
Gem Cis ICI	259	147	11.7 (10.3, 14.0)

Characteristic	N	Event N	HR[1]	95% CI[1]	p-value
1L treatment category					
Gem Cis	336	213	—	—	
Gem Cis ICI	259	147	1.03	0.83, 1.27	0.79

Gem Cis							
At Risk	113	228	188	142	101	78	57
Events	0	36	92	147	181	200	213
Gem Cis ICI							
At Risk	123	185	137	91	50	25	13
Events	0	35	70	104	127	142	147

Figure 3. Overall survival was similar in patients with BTC treated with G+C vs G+C+ICI.

Figure 4. OS stratified by BTC subtype

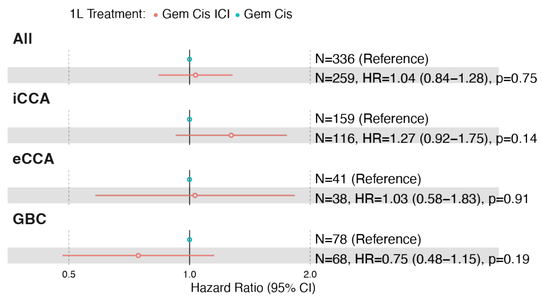


Figure 4. While there was a modest trend towards improved OS in patients with GBC, no subtype showed a statistically significant benefit from G+C+ICI compared to G+C

Figure 5. OS stratified by CD8T cell proportions

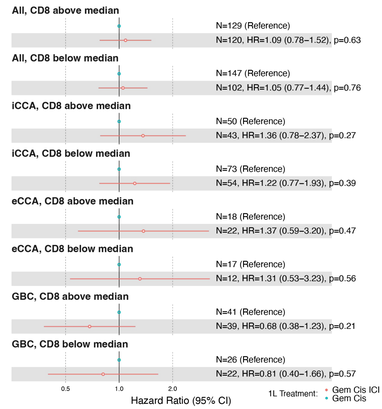


Figure 5. Higher CD8T cell proportions did not enrich for G+C+ICI benefit. However, there was a non statistically significant trend towards improved OS in patients with GBC and CD8T cells above the median.

Figure 6. OS stratified genomic alterations

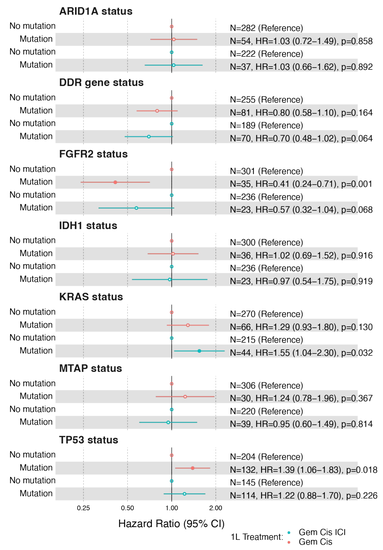


Figure 6. Alterations in DDR, *FGFR2*, *KRAS* and *TP53* genes appeared prognostic but not predictive. Alterations in other genes that were studied did not appear prognostic or predictive.

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