Multiomic characterization of early and metastatic biliary tract cancer (BTC)

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INTRODUCTION

Immunogenomic characterization between early and metastatic (met) biliary tract cancer (BTC) is limited, yet paramount for clinical trial strategies. We evaluated the immunogenome in BTC to inform trial designs in the perioperative and metastatic settings.

METHODS

We selected de-identified BTC patients (pts) from the Tempus database sequenced by xT (DNA seq) and a subset with whole transcriptome analysis by xR (RNA-seq). Pts were stratified by stage: I-III (early) or IV (met) and subtype: intrahepatic (iCCA) n=1492, extrahepatic (eCCA), n=537 and gallbladder (GBC), n=912. Targetable driver alterations (dAlts) included SNVs/indels in *IDH1* and *KRAS; BRAF* p.V600E variants; *FGFR2, RET,* and *NTRK1-3* fusions (if present in ≥4% of pts); *ERBB2* amps; or no dAlt. Immune cell (IC) proportions (%) were estimated by quanTIseq; TMB (mt/Mb) was analyzed. Significance (p<0.05) was assessed using χ^2 or Wilcoxon/Kruskal-Wallis rank sum.

Table 1. Cohort Characteristics

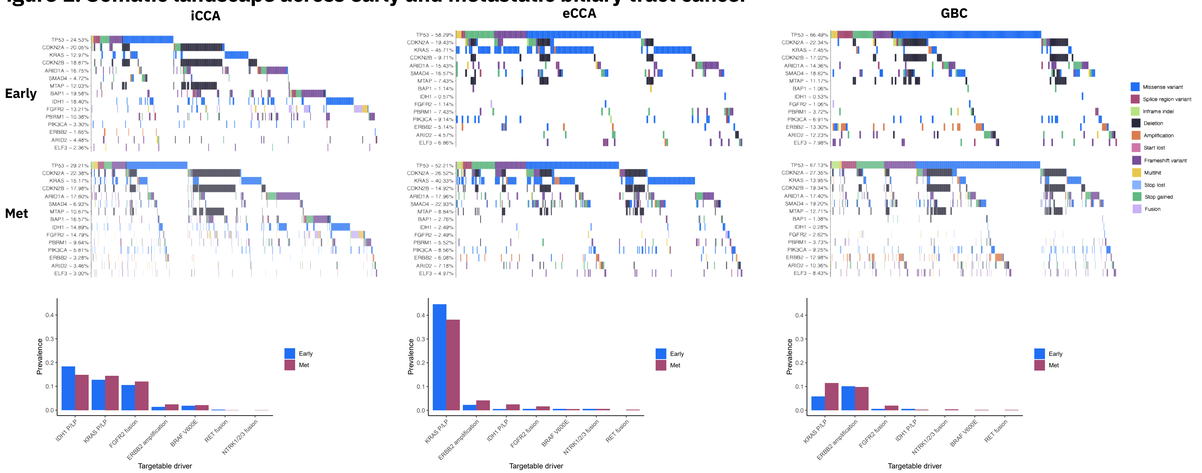
Characteristic	Overall N = 2,941	Extrahepatic Cholangiocarcinoma N = 537	Gallbladder Cancer N = 912	Intrahepatic Cholangiocarcinoma N = 1,492	p-value[1]
Age at Diagnosis					0.002
Median (Q1, Q3)	66 (58, 73)	66 (57, 73)	68 (59, 74)	66 (57, 73)	
Min, Max	18, 88	18, 88	26, 88	21, 88	
Unknown					
Sex (%)					<0.001
Female	1,654 (56%)	245 (46%)	631 (69%)	778 (52%)	
Male	1,287 (44%)	292 (54%)	281 (31%)	714 (48%)	
Race, n (%)					<0.001
White	1,322 (77%)	229 (77%)	349 (69%)	744 (81%)	
Black or African American	191 (11%)	21 (7.0%)	85 (17%)	85 (9.2%)	
Other Race	124 (7.2%)	25 (8.4%)	49 (9.7%)	50 (5.4%)	
Asian	88 (5.1%)	23 (7.7%)	24 (4.7%)	41 (4.5%)	
Unknown	1,216	239	405	572	
Smoking status, n (%)					<0.001
Never smoker	1,177 (52%)	207 (52%)	405 (59%)	565 (48%)	
Ex-smoker	858 (38%)	160 (40%)	226 (33%)	472 (40%)	
Current smoker	238 (10%)	33 (8.3%)	59 (8.6%)	146 (12%)	
Unknown	668	137	222	309	
Alcohol consumption, n (%)					0.2
Never or No	112 (54%)	19 (44%)	41 (62%)	52 (52%)	
Yes	97 (46%)	24 (56%)	25 (38%)	48 (48%)	
Unknown	2,732	494	846	1,392	
Stage within 90 days of sample collection, n (%)					<0.001
Stage 4	2,154 (73%)	362 (67%)	724 (79%)	1,068 (72%)	
Stage 3	412 (14%)	94 (18%)	131 (14%)	187 (13%)	
Stage 2	245 (8.3%)	67 (12%)	51 (5.6%)	127 (8.5%)	
Stage 1	130 (4.4%)	14 (2.6%)	6 (0.7%)	110 (7.4%)	

SUMMARY

- Targetable driver alterations (dAlt) were similar by BTC stages but differed by subtypes
- Immunogenicity was unique among dAlt, and across stage and BTC subtype
- Future trials should analyze how these immunogenomic findings impact the efficacy of targeted and immunotherapy across BTC stages

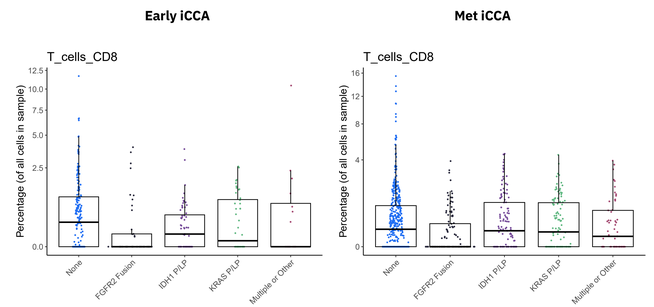
RESULTS

Figure 1. Somatic landscape across early and metastatic biliary tract cancer



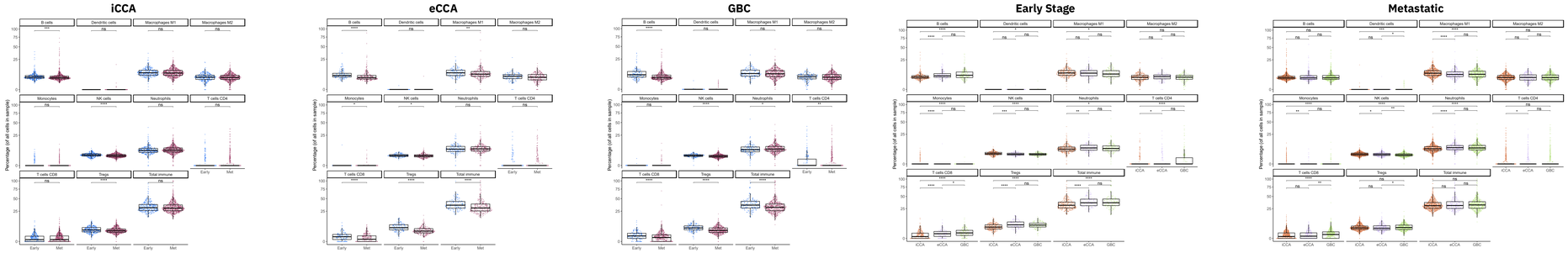
dAlt prevalences were similar between early and met within each subtype, except KRAS in GBC (5.9 vs 11%, p=0.024). Significant differences in dAlt rates between iCCA, eCCA, and GBC included IDH1 (16%, 1.9%, 0.3%; p<0.001); KRAS (14%, 40%, 10%; p<0.001); FGFR2 fusions (12%, 1.3%, 1.6%; p<0.001); and ERBB2 amplifications (2.1%, 3.5%, 9.9%; p<0.001).

Figure 2. CD8 T cell percentages across driver alterations in early and metastatic iCCA



In early and met iCCA, patients with FGFR2 fusions had the lowest % of CD8 T cells, while patients without dAlt had the highest (early, p-global=0.011, met, p-global=0.003).

Figure 3. Immune cell proportions across early and metastatic biliary tract cancer



There was a higher percentage of adaptive and total IC in early vs met BTC: B cells and Tregs in iCCA; B cells, CD8 T cells, Tregs and total IC in eCCA; and B cells, CD4 T cells, CD8 T cells, Tregs and total IC in GBC. Early eCCA and GBC had a higher percentage of adaptive and total IC vs. early iCCA. Met GBC had a higher percentage of CD8 T cells compared to met iCCA or met eCCA. ****: p≤0.0001, ***: p≤0.001, **: p≤0.01, *: p≤0.05, ns: p>0.05.

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