Abstract # 4107: Characterizing outcomes of biliary tract cancers (BTC) with β-catenin (CTNNB1) alterations

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Background

- Aberrant Wnt/β-catenin activation has been implicated in tumor formation, progression in BTC.
- CTNNB1 is a key transcriptional co-activator in canonical Wnt signaling.
- The impact of CTNNB1 alterations on outcomes in intrahepatic (IHCC) vs extrahepatic (EHCC) vs gallbladder (GB) tumors and patterns of gene co-expression is unclear.
- We examined the molecular correlates and predictive and prognostic significance of CTNNB1 alterations in a real-world cohort of patients (pts) with BTC.

Methods

- 7450 BTC tumors were analyzed using Next Generation Sequencing (NextSeq), Whole Exome and Whole Transcriptome Sequencing (NovaSeq) at Caris Life Sciences (Phoenix, AZ).
- Tumors were classified by CTNNB1 expression levels in transcripts per million (TPM); top quartile was considered high expressors (Q4), bottom quartile was considered low expressors (Q1) within each subtype. Real-world overall survival (OS) data was obtained from insurance claims.
- Hazard ratio (HR) was calculated using the Cox proportional hazards model, P values were calculated using the log-rank test. Significance was determined to be p <0.05. Chi-square and Mann-Whitney tests determined molecular differences between subgroups and adjusted for multiple comparisons (q<0.05).

Results

- CTNNB1 mutations are rare in BTC (1.3%)
- CTNNB1-mt tumors were more frequently TP53-mt (63% vs 41%), ERBB2-mt (9% vs 2%) and ATM-mt (9% vs 3%). CTNNB1-wt tumors were more likely BAP1-mt (9% vs 0%) and IDH1-mt (10% vs 0%) (all q<0.05).
- CTNNB1-mt tumors had higher median CTNNB1 expression vs wt (154.9 vs 113.4, q<0.009).
- CTNNB1 Q4 tumors were more likely to be TP53-mt (55% vs 34%), PIK3CA-mt (9% vs 5%), KRAS-mt (23% vs 12%) and less likely IDH1-mt (4% vs 14%) compared to Q1 (all q<0.05).
- CTNNB1 Q4 pts had higher ARID1A, CTLA4, LAG3, HIF1A, TGFB1/2/3, EPHA2, EPHA4, VEGFA expression (FC: 2.1-4.2, all q<0.05) and higher T-cell inflamed score and MAPK activation score, as well as lower interferon gamma score vs Q1.

Figure 1: Distribution of Biliary Tract Cancer Subtypes

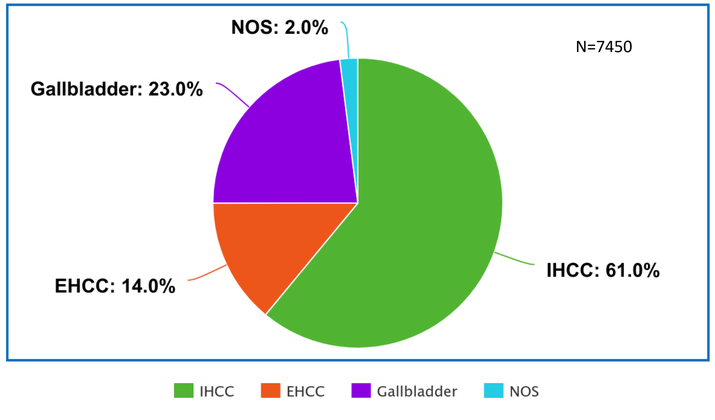
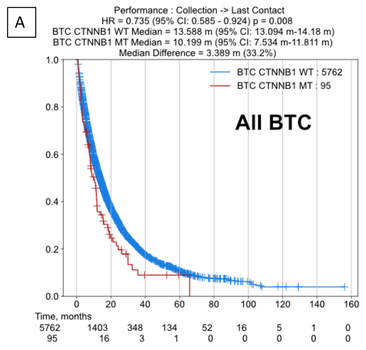
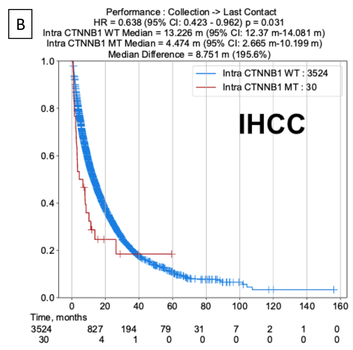
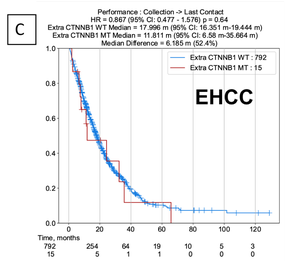
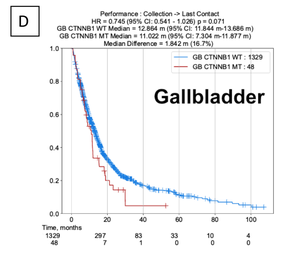


Figure 2: Overall Survival by CTNNB1 Mutation Status in Patients with BTC





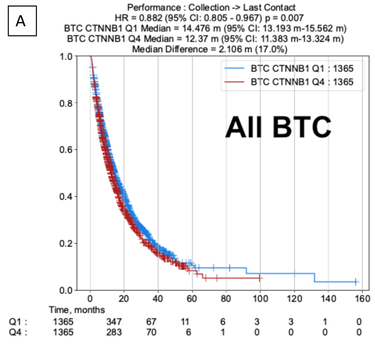


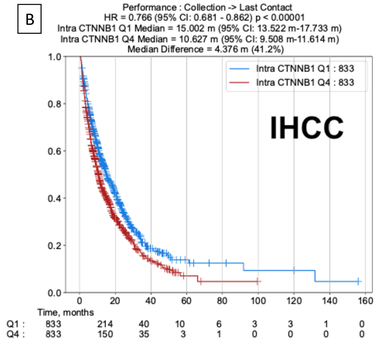


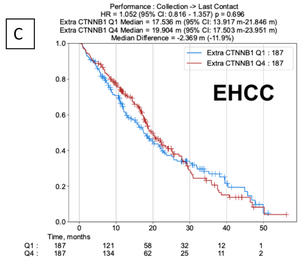
Patients with CTNNB1-wt tumors had significantly better OS vs CTNNB1-mt.
(**A:** 13.6 vs 10.2 mo, HR 0.74, p=0.008). This association remained significant in IHCC (**B:** 13.2 vs 4.5 mo, HR 0.64, p=0.031) but not EHCC (**C:** 18.0 vs 11.8 mo, HR 0.87, p=0.64) or GB (**D:** 12.9 vs 11.0 mo, HR 0.75, p=0.071).

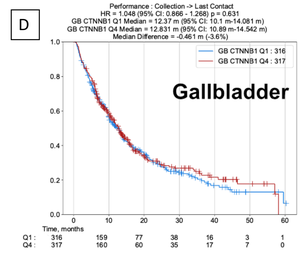
CTNNB1 mutation status and gene expression level is associated with overall survival in patients with BTC, particularly in IHCC.

Figure 3: Overall Survival by CTNNB1 Expression Level in Patients with BTC



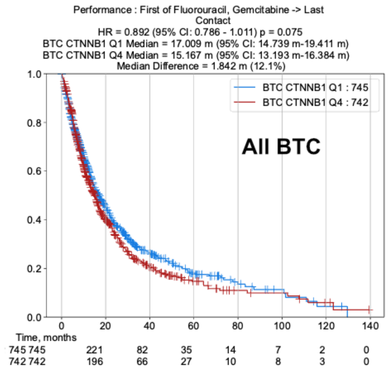


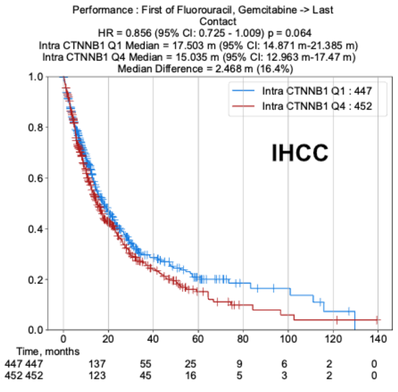




Patients with CTNNB1 Q1 tumors had significantly better OS vs CTNNB1 Q4.
(**A**: 14.5 vs 12.4 mo, HR 0.88, p=0.007). This association held in IHCC (**B:** 15.0 vs 10.6 mo, HR 0.77, p<0.00001) but not EHCC (**C:**17.5 vs 19.9 mo, HR 1.05, p=0.70) or GB (**D:** 12.4 vs 12.8 mo, HR 1.05, p=0.63).

Figure 4: Overall Survival by CTNNB1 Expression Level in Patients with BTC Receiving Chemotherapy





There was a trend towards improved OS in pts with IHCC CTNNB1 Q1 tumors receiving gemcitabine or fluorouracil (17.5 vs 15.0 mo, HR 0.86, p=0.064); no difference in outcomes by CTNNB1 expression in pts receiving immunotherapy.

Conclusions

- CTNNB1 mutations and mRNA expression levels impact survival in BTC, especially IHCC, and may be associated with benefit from chemotherapy.
- CTNBB1 alterations are associated with immunogenic, DNA repair and angiogenic pathways.
- CTNNB1 mutation status and expression levels may serve as predictive and prognostic markers in patients with BTC undergoing systemic therapy and identify novel therapeutic strategies.