Abstract # 4106: Impact of CTNNB1 Alterations on Outcomes in Patients with Hepatocellular Carcinoma (HCC)
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CTNNB1 mRNA expression, but not CTNNB1 mutation status, is associated with survival in HCC.

• The WNT/beta catenin (CTNNB1) pathway plays an integral role in the development of HCC.
• CTNNB1 has been implicated in HCC progression, metastasis, and drug resistance.
• The impact of CTNNB1 alterations on prognosis and efficacy of immunotherapy and tyrosine kinase inhibitors in HCC is unclear.
• We examined associations between CTNNB1 mutations and mRNA expression and clinical outcomes in a real-world cohort of patients with HCC.

Background
CTNNB1 mRNA expression, but not CTNNB1 mutation status, is associated with survival in HCC.
Patients whose tumors had lower CTNNB1 expression had significantly improved OS, 17.9 vs 12.4 months, Q1 vs Q4 (HR 0.72, CI: 0.58-0.89, p=0.002).
Patients whose tumors had lower CTNNB1 expression appeared to derive more benefit from immune checkpoint inhibitors and TKI therapy in first line.
• CTNNB1 expression is associated with DNA repair, immune, neuronal and angiogenic pathways which may pave the way for potential therapeutic opportunities.
• Further studies are needed to prospectively evaluate CTNNB1 as a biomarker for treatment selection in HCC.

Methods
• 1652 HCC tumors were tested at Caris Life Sciences (Phoenix, AZ) and analyzed with Whole Transcriptome Sequencing (WTS; Illumina Novaseq).
• Whole Exome Sequencing (NovaSeq, WES) and NextGen DNA sequencing (NextSeq, 592 genes). mRNA expression (transcripts per million) was further stratified into top (Q4) and bottom quartiles (Q1).
• Kaplan Meier estimates were calculated for overall survival (OS) in the molecularly defined cohorts and estimated from time of tissue collection to last contact.
• 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).

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Low CTNNB1-expressing tumors (Q1) had more frequent ARID1A mutations (15% vs 8%); less frequent TP53 mutations (31% vs 42%); lower VEGFA, EPHB4, EPHA2, HIF1A, TGFBI/TGFBR3 expression, lower MAPK activation and lower T-Cell inflamed scores vs Q4 tumors (all q < 0.05).

CTNNB1 Mutation Status and Outcomes
All tumors were MSS.
Pathogenic CTNNB1 mutations were present in 32% of HCC and mutation status was not associated with CTNNB1 expression level.
CTNNB1 mutation status (MT vs WT) did not impact survival (OS 17.6 Vs 15.3 mo, CTNNB1-MT vs CTNNB1-WT, HR 1.05, CI: 0.91-1.20, p=0.55).

First Line IO
TKI

Patients whose tumors had lower CTNNB1 expression had significantly improved OS, 17.9 vs 12.4 months, Q1 vs Q4 (HR 0.72, CI: 0.58-0.89, p=0.002).

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This association remained significant in patients who received first-line IO (Q1 vs Q4: OS 16.7 vs 10.6 mo, HR 0.54, CI: 0.32-0.94, q=0.025) or TKI (Q1 vs Q4: OS 27.1 vs 17.6 mo, HR 0.60, CI: 0.38-0.94, q=0.025).

Conclusions
• CTNNB1 mRNA expression, but not CTNNB1 mutation status, is associated with survival in HCC.
• Patients whose tumors had lower CTNNB1 expression appeared to derive more benefit from immune checkpoint inhibitors and TKI therapy in first line.
• CTNNB1 expression is associated with DNA repair, immune, neuronal and angiogenic pathways which may pave the way for potential therapeutic opportunities.
• Further studies are needed to prospectively evaluate CTNNB1 as a biomarker for treatment selection in HCC.

References