Abstract # 4106: Impact of CTNNB1 Alterations on Outcomes in Patients with Hepatocellular Carcinoma (HCC)

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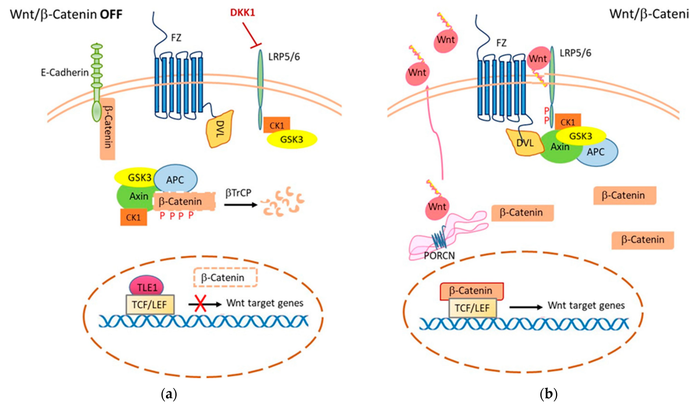
Background

- 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.



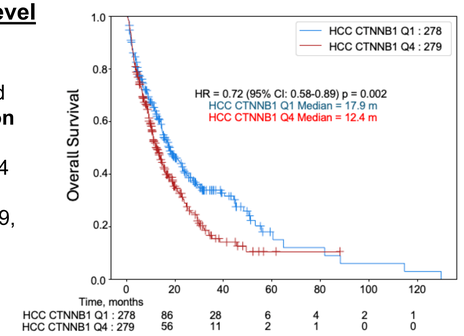
Methods

- 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).

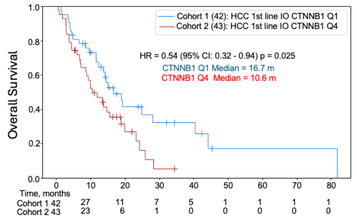
Results

CTNNB1 Expression Level and Outcomes

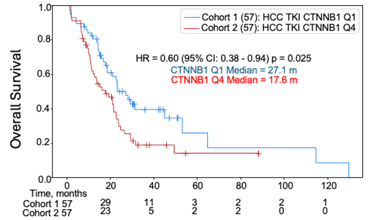
Patients whose tumors had **lower CTNNB1 expression had significantly improved OS,** 17.9 vs 12.4 months, Q1 vs Q4 (HR 0.72, CI: 0.58-0.89, p=0.002)



First Line IO



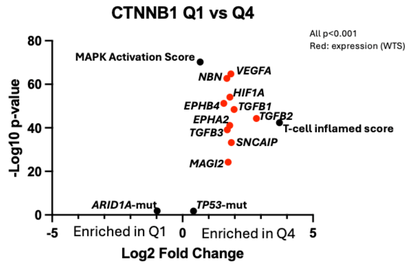
TKI



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, p=0.025) or **TKI** (Q1 vs Q4: OS 27.1 vs 17.6 mo, HR 0.60, CI: 0.38-0.94, p=0.025).

CTNNB1 mRNA expression, but not CTNNB1 mutation status, is associated with survival in HCC.

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, TGFB1/2/3 expression, lower MAPK activation and lower T-cell inflamed scores vs Q4 tumors (all q < 0.05).

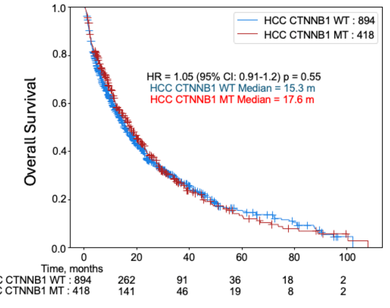


CTNNB1 Mutation Status and Outcomes

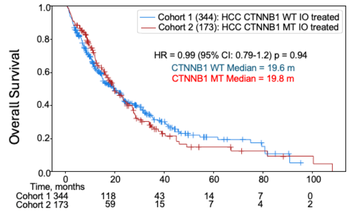
All tumors were MSS.

Pathogenic CTNNB1 mutations were present in 32% of HCC and mutation status was not associate with CTNNB1 expression level.

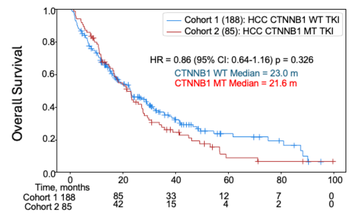
CTNNB1 mutation status (MT vs WT) did not impact survival (OS 17.6 vs 15.3 mo, CTNNB1-MT vs CTNNB1-WT, HR 1.05, CI: 0.91-1.20, p=0.55).



First Line IO



TKI



CTNNB1 mutation status (MT vs WT) did not impact OS in pts treated with IO (19.8 vs 19.6 mo, HR 0.99, p=0.94) or TKI (23.0 vs 22.0 mo, HR 0.86, p=0.33).

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

Selvaggi F, Catalano T, Cotellese R, Aceto GM. Targeting Wnt/β-catenin pathways in primary liver tumours: from microenvironment signaling to therapeutic agents. Cancers (2022) 14(8):1912. doi: 10.3390/cancers14081912