Molecular characterization of 350 hepatocellular carcinomas identifies biomarker aberrations with potential novel therapeutic options

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Background: Effectiveness treatment strategies for hepatocellular carcinoma (HCC) remain limited. Identification of additional therapies remains paramount as currently available agents have resulted in marginal improvements in overall survival or are not appropriate for this patient population.

Methods: 350 HCC samples were evaluated on a commercial platform, for both genomic and proteomic aberrations. Tissue included Sanger or next generation sequencing (NGS), detection by immunohistochemistry (IHC) and gene amplification by in situ hybridization (ISH).

Results: TP53 was mutated in 34%, CTNNB1 in 20%, and BRCA2 in 18%; other gene mutation rates were <5%. TP53-mutated tumors significantly higher TOP2A (89% vs. 39%, p<0.0001), 75% vs. 32%, p=0.0083) and MDM2 expression (49% vs. 2%, p=0.0017), implying high rates of polyploidy and DNA synthesis. CTNNB1-mutated tumors showed significantly higher SMARCA4 (67% vs. 23%, p=0.001) and AR expression (53% vs. 22%, p=0.025). Changes in protein expression are shown.

Conclusions: The molecular profile in HCC suggests potential therapeutic targets, such as tyrosine kinase inhibitors, anti-PD-1 agents, or PI3 kinase pathway inhibitors. Immuno-modulatory agents may be an option, such as tyrosine kinase inhibitors, anti-PD-1 agents, or PI3 kinase pathway inhibitors. Immuno-modulatory agents may be an option, with potential benefit of targeting WNT pathway in combination with nab-paclitaxel, anti-androgens, anti-PD-1 agents and PARP inhibitors.

Results, ISH: Figure 3A. Either overexpression, reported as percent positive of total cases tested, or loss, reported as percent negative. Therapeutic agents associated with the aberrations observed are listed in parenthesis, 2B: Comparison of protein expression, for those with significant differences between primary and metastatic cases (Stars indicate differences statistically significant by Fisher’s Exact test.)

Results, Molecular Aberrations: Figure 4. Gene alterations. Mutations were found in 22 of 47 (47%) genes tested. Genes with no alterations identified included ALK, BRAF, CDH1, c-KIT, CSF1R, EGFR*, ERBB4, FGFR1, FGFR2, FLT3, GNAS, HNF1A, HRAS, JAK2, MAPK1, NOTCH1, PIM1, POGFRA, RET, SMAD4, SMARCA4 and BRCA1. (* One additional tumor presented an EGFR activating mutation from an external lab.) 43% of cases tested had either a CTNNB1 or a TP53 gene alteration, including 6 cases with both a CTNNB1 and a TP53 gene alteration. No significant differences in gene mutations were found between primary and metastatic cases.

Conclusions: These data suggest potential therapeutic strategies, such as tyrosine kinase inhibitors, anti-PD-1 agents, or PI3 kinase pathway inhibitors. Although no evidence shows that cytotoxic drugs are effective in patients with HCC, immuno-modulatory agents, fluoropyrimidines, anthracyclines, nab-paclitaxel, gemcitabine, or taxanes may be therapeutically relevant in a selected population.

• The unexpected high BRCA2 mutation rate observed highlights a population that may benefit from PARP inhibitors.

• The protein changes associated with CTNNB1-mutated tumors suggest potential benefit of targeting WNT pathway inhibitors in combination with nab-paclitaxel, anti-androgens, anti-PD-1 and PARP inhibitors.

• Significantly higher PD-1+ tumor-infiltrating lymphocytes and TS expression were seen in primary tumors, suggesting increased opportunity for immune checkpoint inhibitors in the metastases and higher likelihood of fluoropyrimidine agents to be effective in the primary tumors.

• Data presented herein and suggestions for therapeutic potential are limited by the lack of clinical outcomes.

References:


