Comprehensive multiplatform biomarker analysis of 313 hepatocellular carcinoma identifies potential novel therapeutic options


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Abstract

Background: Effective 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.

Methods: 313 HCC samples were evaluated using a multiplatform profiling service (Caris Life Sciences, Phoenix, AZ), including gene sequencing (Sanger, NGS (N=79)), protein expression (IHC) and gene amplification (ISH).

Results: Biomarker changes of interest are shown.

Table 1. Patient demographics. Includes limited documented information of risk factors obtained on a very small subset of cases.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median age</th>
<th>K-RAT (Karyotypic-Ratio)</th>
<th>Known EtOH</th>
<th>Known Viral status</th>
<th>Known mets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age range</td>
<td>61</td>
<td>2.7:1</td>
<td>5%</td>
<td>3=HBV+</td>
<td>36%</td>
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<tr>
<td>Sex</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>M:F ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.7:1</td>
</tr>
</tbody>
</table>

Conclusions: These data suggest potential therapeutic targets, such as tyrosine kinase inhibitors, anti-PD1 agents, or PI3 kinase pathway inhibitors. Although no evidence shows that cytotoxics are effective in patients with HCC, irinotecan, alkylating agents, fluoropyrimidines, anthracyclines, nab-paclitaxel, or taxanes may be therapeutically relevant. The protein changes associated with CTNNB1-mutated tumors suggest potential benefits of targeting WNT pathway in combination with nab-paclitaxel or anti-angiogenic. Immuno-modulatory agents may be a therapeutic option in metastatic HCC, based on the higher levels of PD-1.

Results, FISH

Figure 1. Changes in gene copy number as measured by FISH or CISH were identified for CMET, EGFR, MDR1, and CYP2D6 changes were seen for TOP2A.

Results, Immunohistochemistry (IHC)

Figure 2. Levels of protein expression, A. either overexpression, reported as percent positive of total cases tested, or loss, reported as percent negative (except for PO-1: PO-1+ tumor infiltrating lymphocytes). B. Comparison of protein expression, for those with significant differences between primary and metastatic tumors (PO-1, N:p=12,18; TP, N:p=0,004).

Results, Gene Mutations

Figure 3. Gene alterations. Mutations were found in only 38% of 47 genes tested. Genes with no alterations identified included: ALC, BRAF, CDH1, c-KIT, CSFIR, EGFR, ERBB2, FBW7, FGFR1, FGFR2, FIT3, GNA11, GNAQ, GNAS, HIF1A, HRAS, JAK2, KDR, MEK1, MPL, NOTCH1, NPM1, PDGFRA, RET, SMAD4, SMARCB1, VHL, and BCR. 47% of cases tested had either a CTNNB1 or a TP53 gene alteration, including 4 cases with both a CTNNB1 and a TP53 gene alteration. All CTNNB1 alterations were in exon 3. 2 of the 4 KRAS alterations were G12Q. No significant differences in gene mutations were found between primary and metastatic cases.

Results, Co-incidence

Table 2. Co-incidence of mutations with known pathway members. Co-incidence was defined as a significant change in expression of both genes in a significant subset of cases.

References