Association Between Beta-Catenin (CTNNB1) Mutations and Clinical Outcomes of Pembrolizumab in Advanced Hepatocellular Carcinoma: Exploratory Analyses From KEYNOTE-240

Background
• CTNNB1 mutations (CTNNB1mut) occur in approximately 30% of hepatocellular carcinoma (HCC) tumors1.
  – Mutations may result in constitutive activation of CTNNB1, leading to the transcription of genes that regulate cell survival and proliferation via the WNT pathway2.
  – In a small, single-center study (N = 35), patients with HCC harboring CTNNB1mut treated with immune checkpoint inhibitors were shown to have poor outcomes3,4.
  – The global, randomized, phase 3 KEYNOTE-240 study (NCT02702104) evaluated the safety and efficacy of second-line pembrolizumab plus best supportive care (BSC) versus placebo plus BSC in patients with advanced HCC5–7.
  – At the first interim analysis (data cutoff: March 26, 2018), the HR for progression-free survival (PFS) was 0.775 (95% CI, 0.609-0.987; P = 0.0174), which did not meet pre-specified criteria for statistical significance (1-sided P = 0.020).
  – At the final analysis (data cutoff: January 2, 2019), the HR for overall survival (OS) was 0.783 (95% CI, 0.611-0.998; P = 0.0223), which also did not meet pre-specified criteria for statistical significance (1-sided P = 0.0174).
  – HRs for PFS: 0.75 (95% CI, 0.607-0.940; P = 0.0022)
  – A favorable risk-benefit ratio for pembrolizumab was observed.

Objectives
• To evaluate the concordance between ctDNA-derived and tissue-derived CTNNB1mut status.
• To evaluate the association between CTNNB1mut status and clinical outcomes.

Methods
• The analysis population included patients with previously treated advanced HCC enrolled in KEYNOTE-240 who had available ctDNA data.
• ctDNA-derived CTNNB1mut status was evaluated using the Guardant360® assay (Guardant Health, Palo Alto, CA).
• Clinical data were also available for 2:1 randomization to pembrolizumab or placebo.
• The association between ctDNA- and tissue-derived CTNNB1mut status was assessed in patients with HCC who had evaluable clinical outcomes in patients with advanced HCC enrolled in KEYNOTE-240.

Results

Table 1. Prevalence of CTNNB1 mutation status and mutation location by ctDNA versus WES

<table>
<thead>
<tr>
<th>Exon</th>
<th>ctDNA</th>
<th>WES</th>
<th>Patients with evaluable CTNNB1mut status (N = 243)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exon 3</td>
<td>25/137 (18.3)</td>
<td>22/137 (16.1)</td>
<td>119 (77.8) 59 (65.6) 24 (66.7) 54 (76.1)</td>
</tr>
<tr>
<td>Exon 7</td>
<td>3/137 (2.2)</td>
<td>1/137 (0.7)</td>
<td>9 (5.9) 13 (15.2) 1 (2.8) 6 (9.1)</td>
</tr>
<tr>
<td>Exon 13</td>
<td>1/137 (0.7)</td>
<td>0/137 (0)</td>
<td>0 13 (15.2) 98 (23.7)</td>
</tr>
</tbody>
</table>

Table 2. Prevalence of CTNNB1 mut status and clinical outcomes of pembrolizumab vs placebo

<table>
<thead>
<tr>
<th>Pembrolizumab</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS, median</td>
<td>11.0</td>
<td>8.0 (6.0-9.0)</td>
</tr>
<tr>
<td>PFS, %</td>
<td>50</td>
<td>40</td>
</tr>
</tbody>
</table>

Table 3. Concordance for ctDNA-derived and tissue WES concordance

<table>
<thead>
<tr>
<th>Exon</th>
<th>ctDNA mut status</th>
<th>Tissue WES mut status</th>
<th>Data are n (%) unless otherwise specified. WT, wild type.</th>
</tr>
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Table 4. Values of the association analysis between ctDNA-derived CTNNB1 mut status and clinical outcomes

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<th>Pembrolizumab</th>
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Conclusions
• The prevalence of CTNNB1mut was 153/371 (41.3%) by ctDNA and 154/371 (41.6%) by tissue WES.
  – Most CTNNB1mut mutations were located in exon 3 and exon 13.
  – ctDNA- and tissue-derived CTNNB1mut were assessed in tumor tissue and matched germline DNA from blood to assess germline variants using WES for a subset of patients with available data.
  – Concordance between ctDNA- and tissue-derived CTNNB1mut was assessed in tumor tissue and matched germline DNA from blood to assess germline variants using WES for a subset of patients with available data.
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References

Image captions:
1. Association Between Beta-Catenin (CTNNB1) Mutations and Clinical Outcomes of Pembrolizumab in Advanced Hepatocellular Carcinoma: Exploratory Analyses From KEYNOTE-240

2. Evaluation of clinical utility of CTNNB1 mut status: (A) ORR, (B) PFS for CTNNB1 WT, (C) ORR for CTNNB1mut, (D) OS for CTNNB1 WT, and (E) OS for CTNNB1mut

3. Table 1. Prevalence of CTNNB1 mut status and clinical outcomes of pembrolizumab vs placebo

4. Table 2. Prevalence of CTNNB1 mut status and clinical outcomes of pembrolizumab vs placebo

5. Table 3. Concordance for ctDNA-derived and tissue WES-derived CTNNB1 mut status

6. Table 4. Values of the association analysis between ctDNA-derived CTNNB1 mut status and clinical outcomes

7. Figure 2. Evaluation of clinical utility of CTNNB1 mut status: (A) ORR, (B) PFS for CTNNB1 WT, (C) ORR for CTNNB1mut, (D) OS for CTNNB1 WT, and (E) OS for CTNNB1mut

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