Dynamics of tumor response in advanced melanoma patients treated with Coxsvi...}

**Introduction**

CoxsviAK, an oncolytic immunotherapy, is a less-selected strain of Coccsviesv A21 (CVA21). Introduction (IT) of CVA21 induces tumor cell infection, up-regulation of immune checkpoint molecules and increased immune-cell infiltration. The Phase II CALM study investigated the efficacy and safety of IT CVA21 in 57 pts with advanced melanoma resulting in a confirmed ORR of 28.1% and DRR (> 6 months) of 35.7% (9/25). DCR 26.7 months (95% CI: 17.4, 34.5). The CALM extension study (13 pts) investigated CVA21 induced changes in immune-cell infiltration within the tumor-microenvironment (TME). We elected focusing the values of clinical responses in 79 pts with stage IIIC-IV melanomas given IT CVA21.

**Patient Characteristics**

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Race</th>
<th>Stage of screening</th>
<th>Prior RT</th>
<th>Prior chemotherapy</th>
<th>Prior chemotherapy + immuno.</th>
<th>Prior chemotherapy + immuno. + radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>56</td>
<td>M</td>
<td>C</td>
<td>B</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

**Objective endpoints**

- **Overall response rate (ORR):**
  - Before IT: 22% (9/41)
  - After IT: 39.3% (9/23)

- **Durable response rate (DRR):**
  - Median: 26.7 months (95% CI: 17.4, 34.5)
  - 1-year survival rate: 75% (9/12)

- **Change in sum of target lesions:**
  - Median: 39.3% (95% CI: 17.4, 34.5)
  - Change in tumor burden of responding patients:
    - Median: 38.0% (95% CI: 17.4, 34.5)
    - Change in tumor burden of non-responders:
      - Median: 1.6% (95% CI: 0.0, 15.2)

**Secondary endpoints**

- **Progression free survival (irPFS):**
  - Median: 14 months (95% CI: 6.4, 19.1)
  - Median: 3.4 months (95% CI: 2.8, 11.1)

**Changes in tumor burden of responding patients**

<table>
<thead>
<tr>
<th>Pts</th>
<th>Change in RNA expression, relative units (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>5</td>
<td>1.2</td>
</tr>
<tr>
<td>10</td>
<td>2.4</td>
</tr>
<tr>
<td>20</td>
<td>3.6</td>
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</tbody>
</table>

**Summary**

- **Responses were observed in 38% of patients, 6% had complete response, and 32% had partial response.**
- Three patients exhibited progression (≥ 25% by iPLA2) at Day 0.
- A composite ORR was observed in patients receiving prior immunotherapy, 20.7% (95/106) vs 2.6% (10/386) in patients receiving other therapies.
- DCR of the IT CVA21 study was 39.3% (9/23) vs 17.2% (9/52) in patients receiving other therapies.
- A 6-month median was associated with superior ORR (39.3% vs 17.2%), superior DRR (26.7 vs 6.9 months), and greater OS (Log Rank: p = 0.003).
- CVA21 treatment facilitates oncolysis and immune activation, with dose-dependent increases in immune-cell infiltrate (CXCL10+CD8+) and expression of PD-L1, in particular in those exhibiting durable disease response.
- CVA21 treatment significantly up-regulated a number of interferon-response and immune checkpoint inhibitory genes in injected melanoma lesions, including CXCL10, CXCL11, CD40L, LAG-3, TIM-3, and PD-L1.
- CVA21 treatment can potentially reverse the "immunological anergy" within the tumor microenvironment.
- Up-regulation of immune cell infiltration and increased interferon-induced immune responses in CVA21 treated lesions may be predictive of future tumor regressions, particularly in combination with immune checkpoint blockade therapies.

**Conclusions**

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