Phase II CALM extension study: Enhanced immune-cell infiltration within the tumour micro-environment of patients with advanced melanoma following intralesional delivery of Coxsackievirus A21

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**Introduction**

Coxsackievirus A21 (CVA21), following intratumoral (IT) injection, CVA21 preferably infects CTLA4 expressing tumor cells, resulting in viral replication, cell lysis, and a systemic antitumor immune response. The Phase I/CAI study investigated the efficacy and safety of IT CVA21 in a phase with advanced melanoma. The primary endpoint of the study was achieved with 23 of 57 (38.6%) evaluable patients experiencing at least a partial response (CR+PR) or stable disease (SD) at 26 weeks. The results of a phase II extension study detailed in this abstract showed that CVA21 treatment induced notable changes within the tumor microenvironment of patients with melanoma to reconstitute the immune-cell infiltrate within the tumor microenvironment.

**Study Design**

**Preliminary Data**

**Patient Response Data**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Treatment</th>
<th>Follow-up</th>
<th>Time</th>
<th>Best Overall Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt04</td>
<td>Ipilimumab</td>
<td>12 months</td>
<td>23.4</td>
<td>CR</td>
</tr>
<tr>
<td>Pt04</td>
<td>Pembrolizumab</td>
<td>12 months</td>
<td>23.4</td>
<td>CR</td>
</tr>
</tbody>
</table>

**Conclusions**

- CVA21 treatment induced notable changes within the tumor microenvironment by inducing increases in immune cell infiltration and expression of PD-L1.
- CVA21 treatment induces a Th1 gene shift, with increases in interferon-induced genes.
- The observation of CVA21-induced immune cell infiltration in injected melanoma lesions suggests that combination of this treatment with checkpoint inhibitors such as anti-CTLA4 and/or anti-PD1 might result in enhanced antitumor activity, as was shown in preclinical murine models.

**Future Directions**

- Clinical evaluation of the activity of intralesional injection of CVA21 in combination with systemic administration of checkpoint inhibitors in patients with unresectable melanomas is currently underway (Phase II METCO study; ClinicalTrials.gov identifier: NCT03276146).
- CVA21 treatment may be used in a rescue strategy to reconstitute the immune cells within the tumor microenvironment of lesions resistant to immune checkpoint blockade.

**Coxsackievirus A21 reconstitutes immune cells in the micro-environment of melanoma lesions from patients previously treated with multiple lines of immune checkpoint blockade**

**Graphical Abstract**

Image showing the reconstitution of immune cells in the micro-environment of melanoma lesions following CVA21 treatment.