A combination study of an intravenously delivered oncolytic virus, Coxsackievirus A21 in combination with pembrolizumab in advanced cancer patients: phase Ib KEYNOTE 200 (STORM study)

Hardev S. Pandha1, Kevin J. Harrington2, Christy Ralph3, Alan Melcher2, Brendan Curti3, Rachel Sanborn4, David Mansfield2, Emmett Schmidt5, David Kaufman5, Mark Grose6, Bronwyn Davies6, Roberta Karpathy6, Darren Shafren6

1 University of Surrey, Surrey, UK; 2 Institute of Cancer Research and Royal Marsden Hospital, London, UK; 3 Institute of Oncology, St. James’s University Hospital, Leeds, UK; 4 Earle A. Chiles Research Institute, Providence Cancer Center, Portland, OR; 5 Merck & Co., Inc., Kenilworth, NJ; 6 Viralytics Limited, Sydney, Australia

Background

Coxsackievirus A21 (CVA21, CAVATAK™) is a naturally occurring ICAM-1 targeted oncolytic immunotherapeutic virus. Intravenous (IV) delivery of CVA21 targets various systemic solid tumors. Tumor infection by CVA21 can increase levels of immune-checkpoint molecules, immune-cell infiltration and enhancement of systemic antitumor immune response. Pembrolizumab is a human programmed death receptor-1 (PD-1) blocking antibody that has yielded significant solid tumor responses via reversal of tumor induced T-cell suppression. Preclinical studies in an immune-competent mouse model of Non-Small Cell Lung Cancer (NSCLC) confirmed that combinations of IV CVA21 + anti-PD-1 mAbs mediated survival benefit compared to use of either agent alone. We postulate that the combination of CVA21+pembrolizumab may translate to a similar benefit in the clinic. We describe a Phase I study assessing safety and efficacy of IV CVA21 + pembrolizumab in advanced cancer patients.

Study Design

**Part A** (Monotherapy)
- Pts will be infused with CVA21 in 100 ml saline in Cohort 1 (n = 3), at a dose of 1 x 10^8 TCID50, in Cohort 2 (n = 3) at a dose of 3 x 10^8 TCID50, and in Cohort 3 (n = 12-18) at a dose of 1 x 10^9 TCID50 on study days 1,5,8,22, and Q3W for 6 additional infusions.

**Part B** (Combination with pembrolizumab)
- Cohort 1: 100 ml saline
- Cohort 2: IV pembrolizumab 200 mg Q3W starting Day 8
- Cohort 3: pembrolizumab 200 mg Q3W and CVA21 as in Cohort 2

**Part C**: Pembrolizumab is given in all cohorts at 200 mg IV Q3W from Day 8 for up to 2 additional infusions.

**Part D** (Mandatory lesion biopsy)
- Histologically-confirmed (1) NSCLC, (2) bladder cancer, (3) castrate-resistant prostate carcinoma (also known as transitional cell carcinoma).

Key Inclusion Criteria

- Active cardiac disease: unstable angina or onset of angina within last 3 months, myocardial infarction within 6 months, congestive heart failure + class II, cardiac ventricular arrhythmias requiring anti-arrhythmic therapy.
- Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.
- Known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies), known active Hepatitis B (e.g. HBsAg reactive) or Hepatitis C (e.g. HCV RNA [qualitative] is detected).
- Known additional malignancy that is progressing or requires active treatment.
- Active infection requiring systemic therapy.
- Has had prior anti-cancer monoclonal antibody within 21 days prior to Study Day 1 who has not recovered (i.e. ≤ Grade 1) from adverse events due to agents administered more than 21 days earlier.
- Has known active central nervous system metastases and/or carcinomatous meningitis.

Key Exclusion Criteria

- Any cancer, with advanced disease who are considered candidates for surgery, chemotherapy (2), radiotherapy (2), surgery (5), chemotherapy (5), radiotherapy (5) (prior to treatment and Day 15)
- Post-infusion viral load
- Post-infusion viral load
- Secondary viral pathogen
- Known additional malignancy that is progressing or requires active treatment.
- Active infection requiring systemic therapy.
- Has had prior anti-cancer monoclonal antibody within 21 days prior to Study Day 1 who has not recovered (i.e. ≤ Grade 1) from adverse events due to agents administered more than 21 days earlier.
- Has known active central nervous system metastases and/or carcinomatous meningitis.

Study Objectives

**Primary Objectives**
- To determine if CVA21 given intravenously is capable of tracking to malignant tumors.
- To establish a safe dose schedule of CVA21 to take into subsequent Phase 2 clinical trials.
- To describe the safety profile for intravenously-administered CVA21.

**Secondary Objectives**
- To assess the safety and efficacy of intravenous CVA21 and intravenous pembrolizumab in solid tumors of metastatic bladder cancer and non-small cell lung cancer.
- To identify a safe and potentially effective Phase 2 dose for CVA21 in combination with pembrolizumab.
- To investigate if intravenous CVA21 when given in combination with intravenous pembrolizumab is capable of tracking to remote tumor sites by exhibiting CVA21 RNA in metastatic lesions at biopsy.

Part A Monotherapy : Patient Characteristics

Table 1. Table showing patient characteristics for Part A monotherapy.

<table>
<thead>
<tr>
<th>Code</th>
<th>Tumor</th>
<th>Sex</th>
<th>Age</th>
<th>Histology</th>
<th>PD-L1</th>
<th>PD-L2</th>
<th>CD4</th>
<th>CD8</th>
<th>CD163</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>01-001</td>
<td>Prostate</td>
<td>M</td>
<td>70</td>
<td>NSCLC</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>1</td>
</tr>
<tr>
<td>01-002</td>
<td>Prostate</td>
<td>F</td>
<td>75</td>
<td>Melanoma</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>1</td>
</tr>
<tr>
<td>01-003</td>
<td>NSCLC</td>
<td>M</td>
<td>65</td>
<td>NSCLC</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>1</td>
</tr>
</tbody>
</table>

Part B: Combination Therapy: Patient Characteristics

Table 2. Table showing patient characteristics for Part B combination therapy.

<table>
<thead>
<tr>
<th>Code</th>
<th>Tumor</th>
<th>Sex</th>
<th>Age</th>
<th>Histology</th>
<th>PD-L1</th>
<th>PD-L2</th>
<th>CD4</th>
<th>CD8</th>
<th>CD163</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>01-004</td>
<td>Prostate</td>
<td>M</td>
<td>70</td>
<td>NSCLC</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>1</td>
</tr>
<tr>
<td>01-005</td>
<td>Prostate</td>
<td>F</td>
<td>75</td>
<td>Melanoma</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>1</td>
</tr>
<tr>
<td>01-006</td>
<td>NSCLC</td>
<td>M</td>
<td>65</td>
<td>NSCLC</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>1</td>
</tr>
</tbody>
</table>

Conclusions

- Enrolment in Part A (monotherapy) is complete with no DLT observed.
- Successful systemic CVA21 tumor targeting and findings of potential secondary CVA21 replication.
- Evidence of tumor stabilization and response (Part A).
- Enrolment in Part B (combination) Cohort 1 is complete with that of Cohort 2 nearing completion.
- The combination of intravenous CVA21 and pembrolizumab has been generally well-tolerated.
- At present one grade 3 CVA21-related hyponatremia (awaiting confirmation) with no DLT for the combination of CVA21 and pembrolizumab being observed.

Support for this study was provided by Viralytics Limited and Merck & Co., Inc.

Acknowledgement

These are included for personal use only through Quick Response (QR) code links. The code are for personal use only.