Background

Coxsackievirus A21 (CVA21) is a naturally occurring (harmless) enterovirus. Intravenous (IV) delivery of CVA21 targets various systemic solid tumours, tumour infection by CVA21 can increase levels of immune biopharmaceuticals, immune-cell infiltration and enhanced immune-checkpoint antitumour immune response (Figure 1). Pembrolizumab is a human monoclonal death receptor (PD-1) blocking antibody that has yielded significant solid tumour responses via reversal of tumour-mediated cell-surface suppression. Preclinical studies in an immune-resistant mouse model of Non-Small Cell Lung Cancer (NSCLC) confirmed that combinations of IV CVA21 + anti-PD-1 antibodies mediated survival benefit compared to use of either agent alone. We postulate that the combination of IV 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: Pts are infused with CVA21 in 100 mL saline in Cohort 1 (n = 6) at a dose of 1 x 10^6 TCID50, in Cohort 2 (n = 5) at a dose of 3 x 10^6 TCID50, and in Cohort 3 (n = 10) at a dose of 1 x 10^7 TCID50 on study days 1,3,5,8,29 and Q3W for 6 additional infusions. Part A enrolment is complete.

Part B: Pts are infused with CVA21 in 100 mL saline + pembrolizumab. In Cohort 1 (n = 3), CVA21 is administered at a dose of 1 x 10^6 TCID50, in Cohort 2 (n = 6) at a dose of 3 x 10^6 TCID50, and in Cohort 3 (n = 8) at a dose of 1 x 10^7 TCID50 at 1 x 10^6 RIU pembrolizumab in 100 mL saline. Pembrolizumab is given in all cohorts at 200 mg IV Q3W from Day 8 up to 2 years. Treatment with CVA21 pembrolizumab will continue until disease progression/pts choose to discontinue therapy or DLT. Part B Cohort 1 enrolment is complete. Cohort 2 enrolment is nearing completion.

Eligibility Criteria

Key Inclusion Criteria

- Part A: Histologically-confirmed (1) NSCLC, (2) bladder cancer, (3) castrate-resistant prostate cancer (CRPC) which are metastatic (III Stage) or Stage IV melanoma.
- Part B: Histologically or cytologically-confirmed (1) advanced NSCLC, (2) urothelial cancer (also known as transitional cell carcinoma), Urothelial carcinoma with variant histological differentiation (e.g. squamous cell differentiation, glandular differentiation, neuroendocrine differentiation) will be eligible provided that the predominant histology is urothelial carcinoma.
- Part A: Patients with advanced disease who are considered candidates for protocol specified pembrolizumab to be used in combination with CVA21.
- Part A: All subjects in Cohort 3 or PDL cohort must have a lesion accessible for PNA or core biopsy or open biopsy on Day 8 or Day 10 of the study. One lesion per site will be selected for biopsy.
- Part B: All subjects in Cohort 3 or PDL cohort must have a lesion accessible for mandatory core biopsy or open biopsy prior to treatment and on Day 15 of the first treatment cycle. PNA is not acceptable for Part B.
- ECOC Performance Scale 0-1.
- Life expectancy > 3 months.
- Measurable disease based on RECIST 1.1 as determined by the site study team. In situ lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

Key Exclusion Criteria

- Part A: 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 (HBV) (e.g. HBsAg or Hepatitis C (HCV) (e.g. HCV RNA (qualitative) is detected).
- Known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, keratinocarcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
- Active infection requiring systemic treatment.
- Has had prior anti-cancer monoclonal antibody within 21 days prior to Study Day 1 or who has not recovered (i.e. Grade 3) 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

- Part A: To determine if CVA21 given intravenously is capable of tracking to malignant tumours.
- 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. Part B: To assess the efficacy and safety of CVA21 and intravenous pembrolizumab in solid tumours of metastatic bladder and non-small cell lung cancer.
- To identify a safe and potentially effective Phase 2 dose for CVA21 in combination with intravenous pembrolizumab. To investigate if CVA21 when given in combination with intravenous pembrolizumab is capable of tracking to remote tumour sites by exhibiting CVA21 RNA in metastatic lesions at biopsy.

Secondary Objectives

- Part B: To assess efficacy via RECIST 1.1 and immune-related RECIST (irRECIST) criteria.
- To correlate C3a and C5a expression with CVA21 RNA in plasma over time.
- CVA21 excretion and shedding studies to assess environmental safety.

Safety

- Enrollment in Part A (monotherapy) is complete with no DLT observed.
- Enrollment in Part B Cohort 1 (combination) is complete with that of Cohort 2 nearing completion.
- At present no DLT for the combination of CVA21 and pembrolizumab has been observed.
- The combination of intravenous CVA21 and pembrolizumab has been generally well-tolerated with no grade 3 or higher treatment-related adverse events observed.

Acknowledgement

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