Background

Coxsackievirus A21 (CVA21, CAVATAK®) is a naturally occurring ICAM-1 targeted oncolytic immunotherapeutic virus. Intravenous (IV) delivery of CVA21 targets various systemic solid tumours. Tumour infection by CVA21 can increase levels of immune-checkpoint molecules, immune-cell infiltration and enhancement of systemic antitumour immune responses 

Study Design

Part A: IV CVA21 (Monotherapy)

Part B: IV CVA21 + pembrolizumab (Combination)

Study Treatment

Part A: Pts are infused with CVA21 in 100 mL saline in Cohort 1 (n = 3), at a dose of 1 x 10^9 TCID_{50} in Cohort 2 (n = 3) at a dose of 3 x 10^9 TCID_{50} and in Cohort 3 (n = 12-18) at a dose of 1 x 10^10 TCID_{50} on study days 1,3,5,22 and Q3W for 6 additional infusions. Part A enrollment 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 10^9 TCID_{50}, in Cohort 2 (n = 3) at a dose of 3 x 10^9 TCID_{50}, and in Cohort 3 (n = 80) at a dose of 1 x 10^10 TCID_{50} on study days 1,3,5,22 and Q3W for 6 additional infusions. Pembrolizumab is given in all cohorts at 200 mg IV Q2W from Day 8 for up to 2 years. Treatment with CVA21 ± pembrolizumab will continue until confirmed CR or PD (whichever comes first) per iRECIST or DLT. Part B has completed enrolment in the dose escalation phase.

Eligibility Criteria

Key Inclusion criteria

- Part A: Histologically-confirmed (1) NSCLC, (2) bladder cancer, (3) castrate-resistant prostate cancer (CRPC) which are metastatic, or (4) Stage IIIIC or IV melanoma.
- Part B: Histologically or cytologically-confirmed (1) advanced NSCLC, (2) urothelial carcinoma (also known as transitional cell carcinoma), (3) squamous cell carcinoma with variant histologic differentiation (e.g. squamous cell differentiation, glandular differentiation, neuroendocrine differentiation) will be eligible provided that the predominant histology is urothelial carcinoma.
- Part B: Patients with advanced disease who are considered candidates for protocol specified pembrolizumab to be used in combination with CVA21.
- Part B: All subjects in Cohort 3 or P2D cohort must have a lesion accessible for FNA or core biopsy or open biopsy on Day 8 of the first treatment cycle.

Safety

- Enrolment in Part A (monotherapy) is complete with no DLTs observed at any of the CVA21 doses tested.
- At present, the combination of intravenous CVA21 and pembrolizumab (Part B) has been generally well-tolerated in heavily pre-treated patients with or without prior immune checkpoint therapy.

Acknowledgement

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Key Exclusion criteria

- Active cardiac disease/insufficiency, 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 period of the trial.
- 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. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
- Active infection requiring systemic therapy.
- Has had prior anti-cancer monoclonal antibody within 21 days prior to Study Day 1 or 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

Part A: To determine if CVA21 given intravenously is capable of tracking to malignant tumours

Part B: To assess and describe the safety profile of intravenous CVA21 and intravenous pembrolizumab in solid tumours of metastatic bladder cancer and non-small cell lung cancer.

Secondary Objectives

Part B: To characterize the pharmaco kinetic profile of CVA21.

To perform CVA21 excetration and shedding studies to assess environmental safety.

To assess the safety of CVA21 in terms of the serum antibody response.