#TPS3108 KEYNOTE-200: A phase 1b novel combination study of intravenously delivered Coxsackievirus A21 and pembrolizumab in advanced cancer patients

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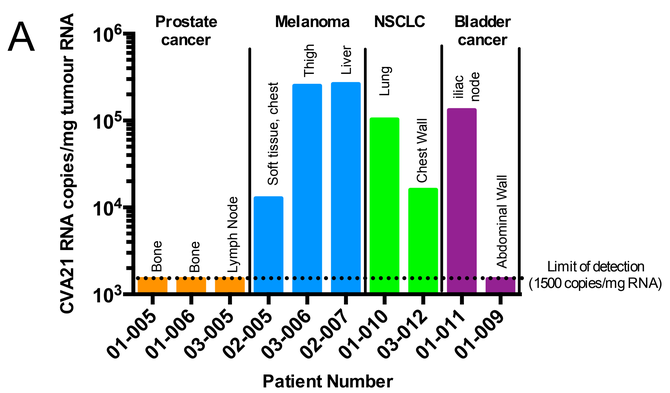
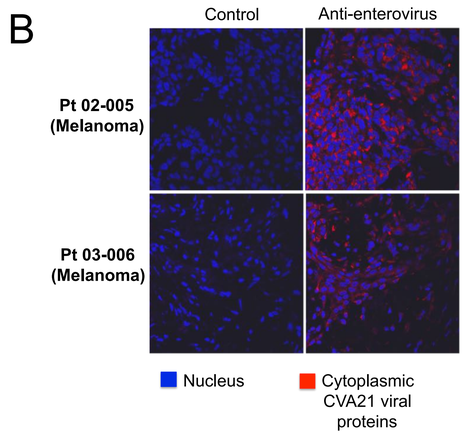
Background

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 response (*Figure 1*). Pembrolizumab is a human programmed death receptor-1 (PD-1) blocking antibody that has yielded significant solid tumour responses via reversal of tumour 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.





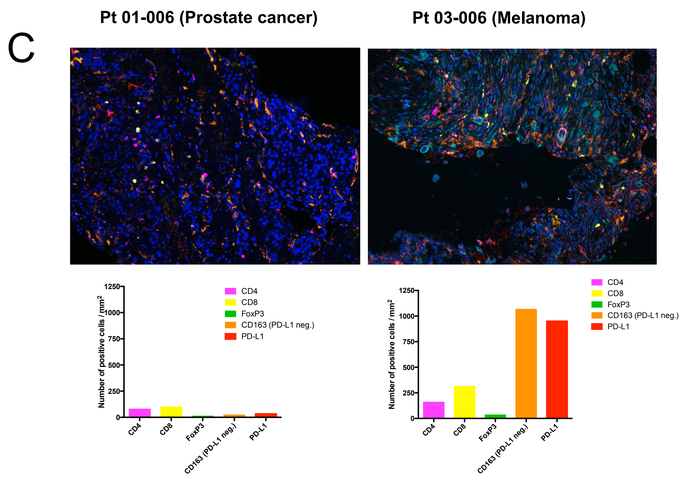
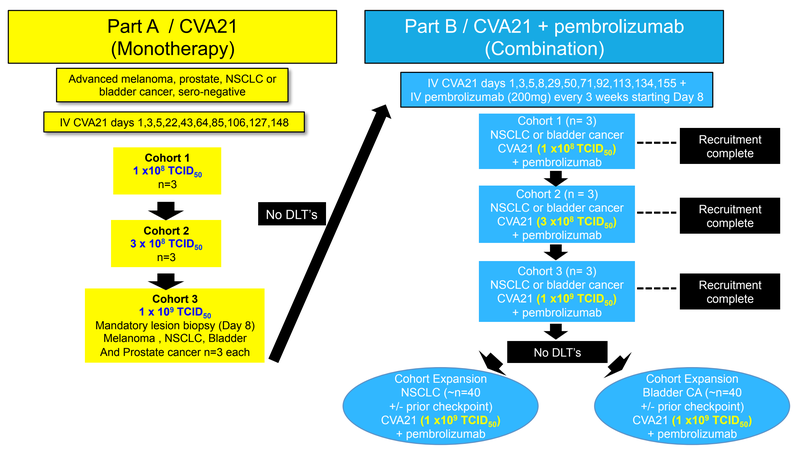


Figure 1. Phase I KEYNOTE-200 study: CVA21 tumour targeting. (A) CVA21 detection by qRT-PCR in tumour biopsies (Part A) at study day 8; (B) IHC detection of active CVA21 replication at study day 8 in tumour biopsies from 2 patients (Part A) with advanced melanoma following 3 intravenous infusions of CVA21 (10^9TCID$_{50}$/infusion); (C) Multispectral imaging of immune-cell infiltrates in day 8 tumour biopsies (Multispectral images obtained and enumerated with PerkinElmer Vectra imaging system and InForm Software)

Study Design



Study Treatment

Part A: Pts are infused with CVA21 in 100 mL saline in Cohort 1 (n = 3), at a dose of 1 x 10^8 TCID$_{50}$, in Cohort 2 (n = 3) at a dose of 3 x 10^8 TCID$_{50}$ and in Cohort 3 (n = 12-18) at a dose of 1 x 10^9 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 10^8 TCID$_{50}$, in Cohort 2 (n = 3) at a dose of 3 x 10^8 TCID$_{50}$ and in Cohort 3 (n = ~80) at a dose of 1 x 10^9 TCID$_{50}$ on study days 1,3,5,8,29,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 irRECIST 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 IIIC or Stage IV melanoma.
- *Part B:* Histologically or cytologically-confirmed (1) advanced NSCLC, (2) urothelial carcinoma (also known as transitional cell carcinoma). Urothelial carcinomas 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 A:* 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.
- *Part B:* All subjects in Cohort 3 or P2D cohort must have either archival biopsy tissue available or a lesion accessible for mandatory core biopsy or open biopsy prior to treatment (baseline). If a biopsy is deemed by the Investigator to not be in the subject's best interest, prior approval must be obtained from the Medical Monitor to waive this requirement. For subject's able to provide a baseline biopsy, a core or open biopsy of an accessible lesion on Day 15 of the first treatment cycle is requested, but optional (FNA is not acceptable for *Part B*).
- ECOG Performance Scale 0-1.
- Life expectancy >3 months.
- Measureable disease based on RECIST 1.1 as determined by the site study team. Tumour lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

Key Exclusion criteria

- Active cardiac diseasmonths, 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. 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
- 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 and describe the safety profile of intravenous CVA21 and intravenous pembrolizumab in solid tumours of metastatic bladder cancer and non-small cell lung cancer.
- To assess preliminary efficacy of the combination of CVA21 and intravenous pembrolizumab in solid tumours of metastatic bladder cancer and non-small cell lung cancer.

Secondary Objectives

Part B

- To characterize the pharmacokinetic profile of CVA21.
- To perform CVA21 excretion and shedding studies to assess environmental safety.
- To assess the safety of CVA21 in terms of the serum antibody response.

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.
- Enrolment in Part B (combination) Cohorts 1, 2 and 3 complete with no DLTs observed at any of the CVA21 doses tested. Expansion cohort currently recruiting.
- Currently only one Grade 3 CVA21-related hyponatremia with no DLT reported for the combination of CVA21 and pembrolizumab.

Acknowledgement

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