#1157TiP - Phase Ib study of intratumoural oncolytic coxsackievirus A21 (CVA21) and pembrolizumab in subjects with advanced melanoma

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Background

Coxsackievirus A21 (CVA21, CAVATAK™) is a naturally occurring ICAM-1 targeted oncolytic immunotherapeutic virus. The Phase II CALM study investigated the efficacy and safety of intratumoural (I.T.) CVA21 in patients with advanced melanoma. The primary endpoint of the study was achieved with 22 of 57 (38.6%) evaluable patients with irPFS at 6 months, the confirmed response rate was 28.1% (16 of 57), with responses observed in both injected and non-injected melanoma metastases, suggesting the generation of significant host anti-tumour responses. In a CALM-extension study, I.T. CVA21 injection of advanced melanoma lesions that displayed signs of disease control/response resulted in increases in tumour immune-cell infiltration, up-regulation of γ-INF response and key immune-checkpoint genes, including PD-L1. 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 melanoma confirmed that combinations of I.T. 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. The presented phase 1b clinical trial evaluates combination CVA21 and pembrolizumab based on increased expression of PD-L1 following virus administration and higher response rates of pembrolizumab in patients with increased tumour PD-L1.

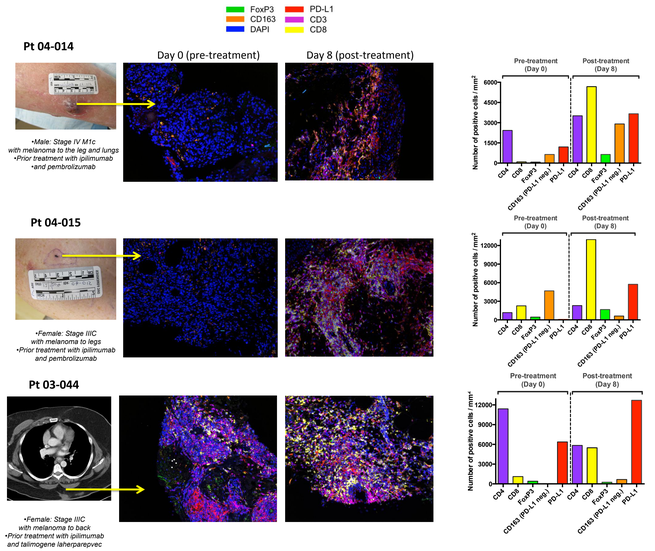
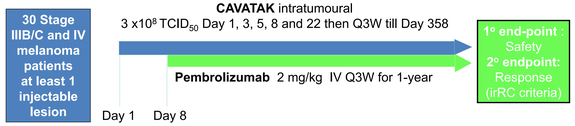


Figure 1. Phase II CALM-extension study: Multispectral imaging of immune-cell infiltrates and PD-L1 expression in day 0 and day 8 tumour biopsies (Multispectral Images obtained and enumerated with PerkinElmer Vectra imaging system and InForm Software) following intratumoural injection of CVA21.

Study Design

Phase 1b: CAPRA study design

(**CA**vatak and **P**emb**R**olizumab in **A**dvanced melanoma)



Eligibility Criteria

Inclusion Criteria:

- Subjects with metastatic or unresectable stage IIIB/C or IV melanoma for whom treatment with pembrolizumab is indicated and who have at least one cutaneous, subcutaneous tumour or palpable lymph node amenable to intratumoural injection.
- At least one tumour must qualify to be an index lesion for modified WHO criteria.
- Subjects must have adequate hematologic, hepatic and renal function.
- ECOG performance status of 0 or 1.
- Anticipated lifespan greater than 12 weeks

Exclusion Criteria:

- Mucosal or ocular primary tumours.
- Presence of any central nervous system tumour that has not been stable for at least 4 weeks off corticosteroids.
- Tumours lying in mucosal regions or close to an airway, major blood vessel or spinal cord.
- Subjects with active, known or suspected autoimmune or immunosuppressive disease.
- Subjects previously treated with CVA21 or anti-PD-1/ PD-L1 agents.
- Subjects requiring systemic treatment with corticosteroids or other immunosuppressive medications within 14 days prior to the first treatment.
- Subject has received chemotherapy within the last 4 weeks prior to first treatment.
- Clinically significant cardiovascular disease.
- Females of childbearing potential must have negative serum or urine pregnancy test.
- Subjects requiring or using other investigational agents while on treatment in this trial.
- History of other malignancy within the last 3 years (with exceptions).
- Active infection requiring systemic therapy.
- Known history of HIV disease, active hepatitis B or hepatitis C.
- History or evidence of other clinically significant disorders that would pose a risk to subject safety.
- Inability to give informed consent and comply with the protocol.

Study Objectives

- Single-arm, multi-institutional open-label phase I clinical trial of I.T. CVA21 and pembrolizumab for treated or untreated unresectable Stage IIIC-IVM1c melanoma.
- Patients receive up to 3 x 10^8 $TCID_{50}$ CVA21 I.T. on days 1,3,5,8 and 22, and then every 3w for up to 19 injections.
- Patients also receive pembrolizumab (2mg/kg) I.V. every 3w starting d8.

Primary Endpoint

- The primary endpoint is safety/tolerability by incidence of dose-limiting toxicity.

Secondary Endpoints

- Response rate
- Immune-related progression-free survival at 12m,
- PFS hazard ratio,
- One-year and overall survival.
- Quality-of-life
- Time to initial response
- Durable response rate

Exporatory Endpoints

- Changes in melanoma-specific T cells, PD-L1 expression and Th1/Th2 gene expression profiles.

Safely Evaluation

- Safety will be assessed using NCI CTCAE, version 4.0.

Statistical Design

- Clinical response will utilize Simon's two-stage design.
- In the first stage, 12 subjects will be accrued. If there are 2 or fewer responses in these subjects within 12m of starting treatment, the study will be stopped due to futility of treatment. Otherwise, 18 additional subjects will be accrued.

Safety

- From the first 10 patients enrolled, one patient has left the study with PD and another patient due to a non treatment-related adverse event.
- Overall, adverse events have generally been low-grade constitutional symptoms related to CVA21 and standard pembrolizumab-related side effects. No grade 3 or higher treatment-related adverse events have been observed.
- Preliminary observations have revealed reductions in a number of injected and non-injected visceral/ non-visceral lesions, with a number of patients displaying evidence of post-injection systemic exposure to CVA21.

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Developers of Oncolytic Immunotherapies

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