Phase II CALM extension study: Enhanced immune-cell infiltration within the tumour micro-environment of patients with advanced melanoma following intralesional delivery of Coxsackievirus A21

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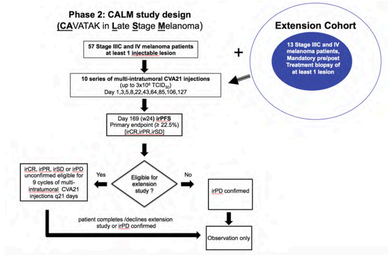
Introduction

CAVATAK, an oncolytic immunotherapy, is a bio-selected oncolytic strain of Coxsackievirus A21 (CVA21). Following intratumoral (IT) injection, CVA21 preferentially infects ICAM-1 expressing tumor cells, resulting in viral replication, cell lysis, and a systemic anti-tumor immune response. The Phase II CALM study investigated the efficacy and safety of IT CVA21 in pts with advanced melanoma. The primary endpoint of the study was achieved with 22 of 57 (38.6%) evaluable pts with durable responses observed in both injected and non-injected melanoma metastases, suggesting the generation of significant host anti-tumor responses. Pre-clinical studies in an immune-competent mouse model of melanoma revealed that combinations of intratumoral CAVATAK and anti-PD-1 or anti-CTLA-4 mAbs mediated significantly greater antitumor activity and compared to use of either agent alone. Here we report on an extension study aimed at understanding the immune mediated effects of CVA21 within the tumour micro-environment.

Study Design



Preliminary Data

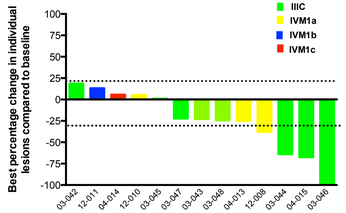
Patient Response Data*

Primary endpoint	
irPFS 6 months* (CR+PR+SD)	41.7% (5/12 pts)

Secondary endpoints	
Overall response rate* (CR+PR, irRECIST 1.1):	30.8 (4/13 % (pts)

*, *Investigator assessed*

Best Percentage changes in Target lesions

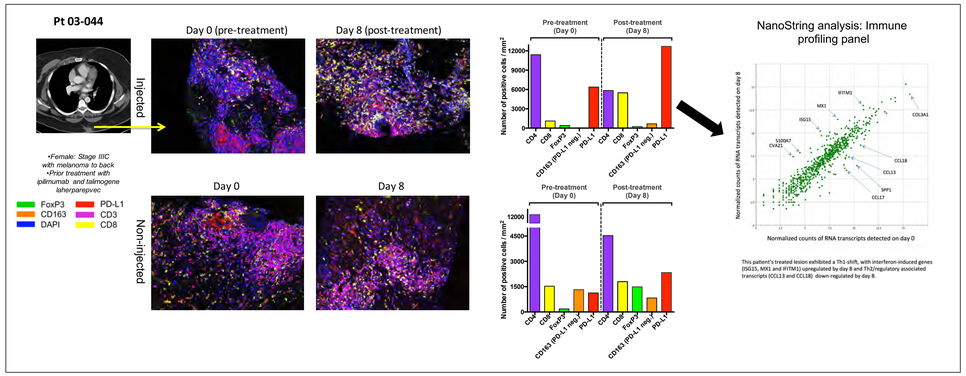


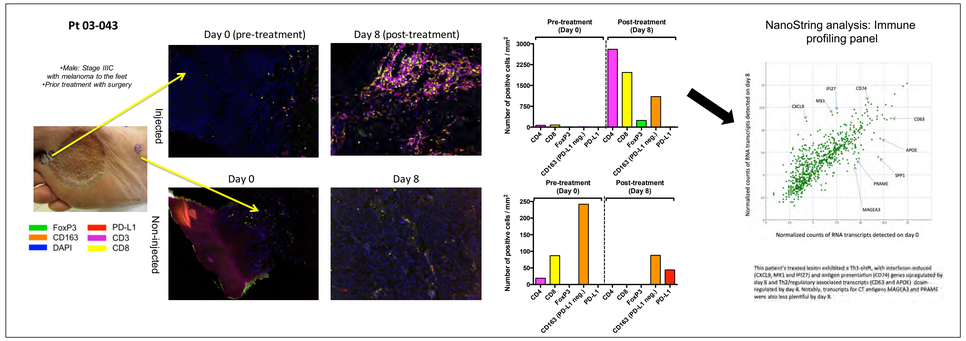
Patient Characteristics and Best Overall Response*

Patient Identification Code	Gender	Melanoma Stage at Baseline	Previous Lines of Treatment	Best irRC Overall Response
03-042	Male	IIIc	Surgery (3), Immunotherapy (ipilimumab)	irPD
03-043	Male	IIIc	Surgery (4)	irPD (unconfirmed at ET)
03-044	Female	IIIc	Surgery (5), XRT (1), chemotherapy (2), Immunotherapy (ipilimumab/TVEC)	irPR
03-045	Female	IIIc	Surgery (3), chemotherapy, XRT	irSD
03-046	Male	IIIc	Surgery (4), other	irPR
03-047	Male	IIIc	Surgery (5), Other (isolated limb perfusion), Immunotherapy (3: pembrolizumab, ipilimumab, Tafinlar/Mekinist)	irSD
03-048	Male	IIIc	Surgery (3), Immunotherapy (TVEC)	irSD
04-013	Male	IV M1a	XRT (2), Immunotherapy (2: HD IL2), other (4)	irSD (unconfirmed at V6)
04-014	Male	IV M1c	Surgery (4), Immunotherapy (2: ipilimumab, pembrolizumab)	irPD (unconfirmed at ET
04-015	Female	IIIc	Surgery (3), Immunotherapy (2: ipilimumab, pembrolizumab)	irPR
12-008	Female	IV M1a	Surgery	irPR
12-010	Male	IV M1a	Surgery (3), XRT, Immunotherapy (5: IFN, HD-IL2, Ipilimumab, Oncovex, vemurafenib)	irSD (unconfirmed) at ET visit
12-011	Male	IV M1b	Surgery	irSD (unconfirmed) at V6

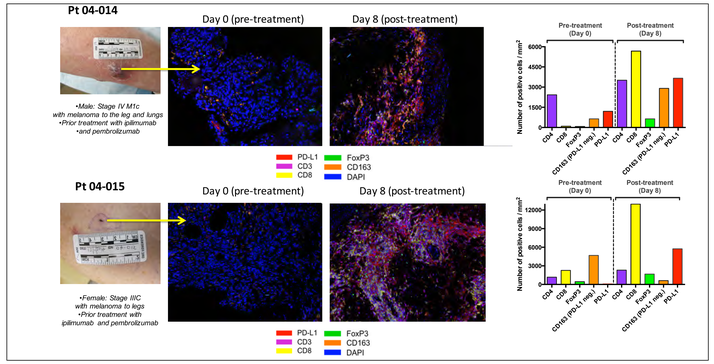
*, *Preliminary data, investigator assessed*

Coxsackievirus A21-induces immune cell infiltration in the micro-environment of melanoma lesions





Coxsackievirus A21 reconstitutes immune cells in the micro-environment of melanoma lesions from patients previously treated with multiple lines of immune checkpoint blockade



Conclusions

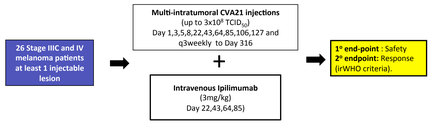
- CVA21 treatment induced notable changes within the tumor microenvironment by inducing increases in immune cell infiltrates and expression of PD-L1)
- CVA21 treatment induces a Th1-gene shift, with increases in interferon-induced genes
- The observation of CVA21-induced immune cell infiltration in injected melanoma lesions suggests that combination of this treatment with checkpoint inhibitors such as anti-CTLA-4 and/or anti-PD-1 might result in enhanced antitumor activity, as was shown in preclinical murine models

Future Directions

- Clinical evaluation of the activity of intralesional injection of CVA21 in combination with systemic administration of ipilimumab in patients with unresectable melanoma is currently underway (Phase1b MITCI study: *ClinicalTrials.gov Identifier:NCT02307149*)
- CVA21 treatment may be used in a rescue strategy to reconstitute the immune cells within the tumor microenvironment of lesions resistant to immune checkpoint blockade

Phase 1b: MITCI study design

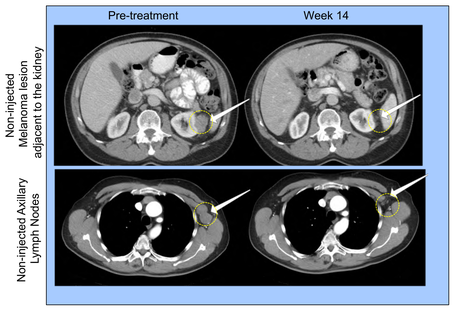
(*M*elanoma *I*ntra*T*umoral *C*AVATAK and *I*pilimumab)



Preliminary Data

- To date no serious adverse advents to the CVA21/ipilimumab combination
- Early signs of anti-tumour activity in metastatic visceral and non-visceral lesions at 14 weeks post-treatment
- Patient treatment and enrolment continues at 3 US clinical sites

*Partial tumour response Stage IV M1c (Pt 13-12003)**



*, *irWHO criteria*

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