Phase II CALM extension study: intratumoral Coxsackivirus A21 increases immune-cell infiltrates and up-regulates immune-checkpoint molecules in the microenvironment of lesions from advanced melanoma patients

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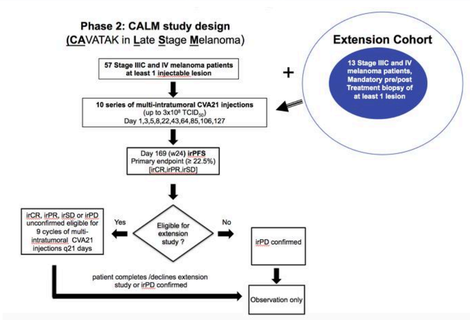
Introduction

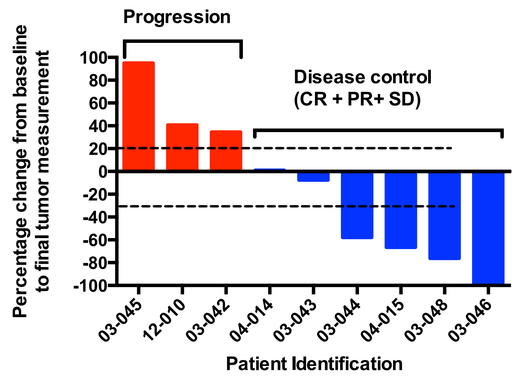
CAVATAK, an oncolytic immunotherapy, is a bio-selected oncolytic strain of Coxsackievirus A21 (CVA21). Following intratumoral (I.T.) injection, CVA21 preferentially infects ICAM-1 expressing tumor cells, resulting in viral replication, cell lysis, and a systemic anti-tumor immune response. The Phase II CALM study investigated the efficacy and safety of I.T. CVA21 in patients with advanced melanoma with durable responses being 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 impact of CVA21 on immune cell infiltrates and immune checkpoint molecules within treated lesions of advanced melanoma patients.

Study Design



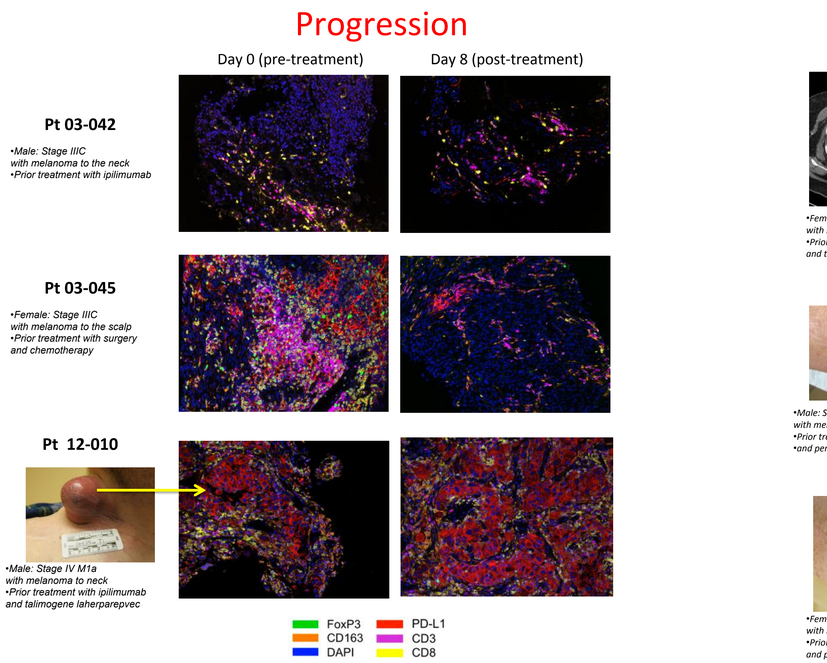
Patient Characteristics and response

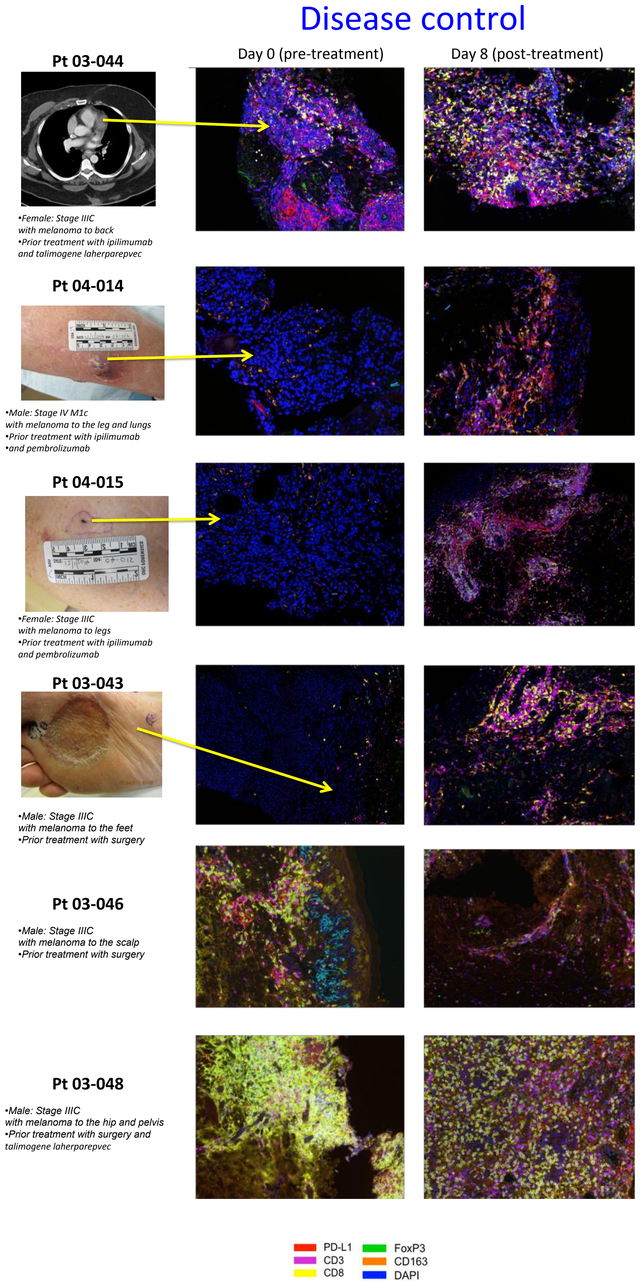
Patient Identification Code	Gender	Melanoma Stage at Baseline	Previous Lines of Treatment	Best irRC Response Overall
03-042	Male	IIIC	Surgery (3), Immunotherapy (ipilimumab)	irPD
03-043	Male	IIIC	Surgery (4)	irSD
03-044	Female	IIIC	Surgery (5), Radiotherapy, Chemotherapy (2), Immunotherapy (ipilimumab/TVEC)	irPR
03-045	Female	IIIC	Surgery (3), Radiotherapy, Chemotherapy	irSD
03-046	Male	IIIC	Surgery (4), Other	irPR
03-048	Male	IIIC	Surgery (3), Immunotherapy (TVEC)	irPR
04-014	Male	IV M1c	Surgery (4), Immunotherapy (ipilummab, pembrolizumab)	irPD (unconfirmed at ET visit)
04-015	Female	IIIC	Surgery (3), Immunotherapy (ipilummab, pembrolizumab)	irPR
12-010	Male	IV M1a	Surgery (3), Radiotherapy, Immunotherapy (IFN, HD-IL2, ipilimumab, TVEC, vemurafenib)	irSD (unconfirmed at ET visit)



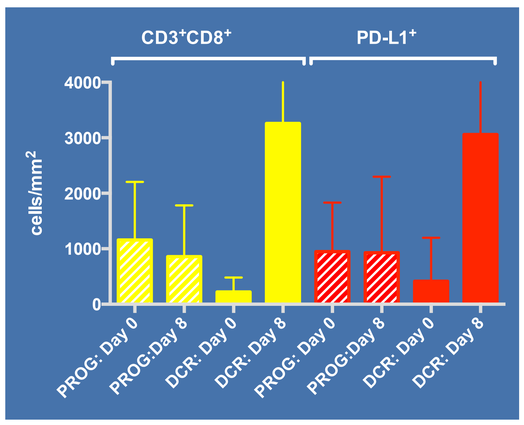
+, Of the 13 patients treated only matched sets of biopsies from 9 patients were analysed
**, Preliminary data, investigator assessed*

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





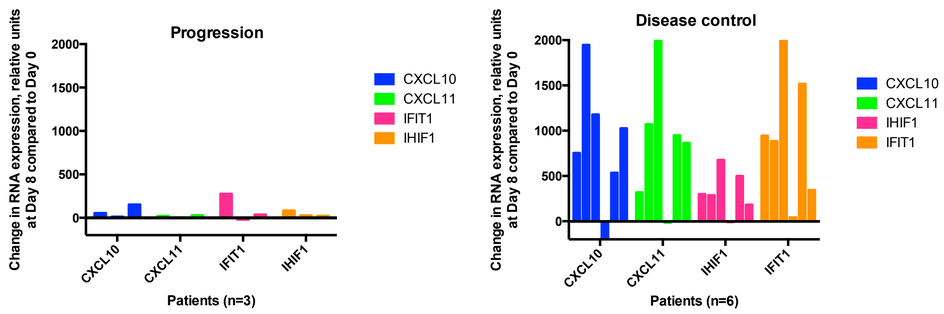
Levels of lesion T-cell infiltrates: Multispectral Images Obtained and Enumerated with PerkinElmer Vectra imaging system and InForm Software



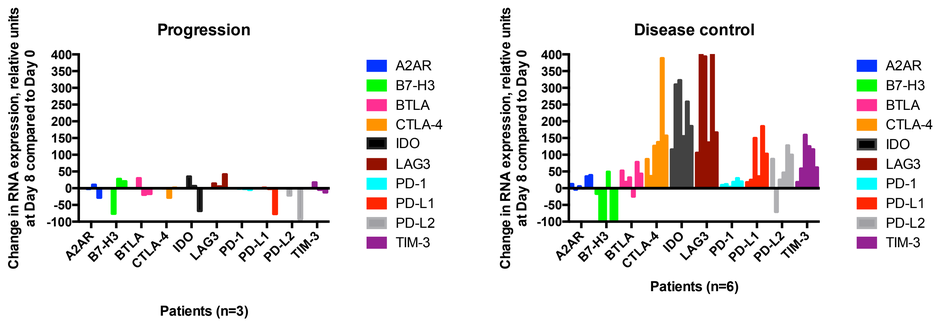
**, Data from Pt 03-048 were excluded for analysis in this section due to cell counts exceeding upper limits of detection.*

Coxsackievirus A21 injection up-regulates in interferon-induced genes and immune checkpoint molecules within the micro-environment of melanoma lesions (*NanoString analysis Pan Cancer Immune Profiling Panel*)

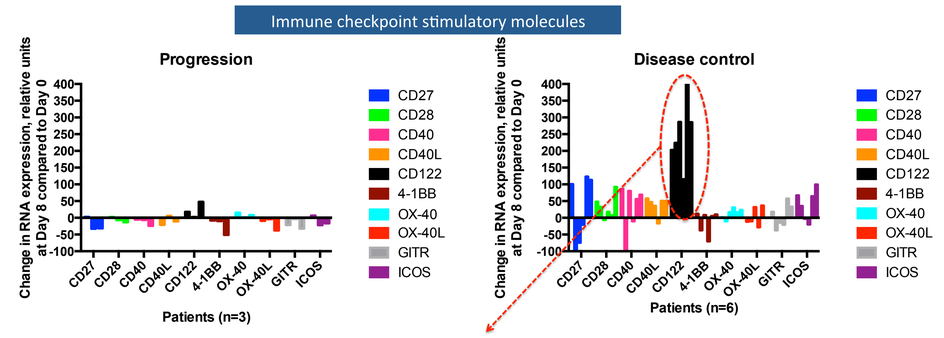
Interferon-induced genes CXCL10, CXCL11 and viral RNA response genes IHIF1, IFIT1

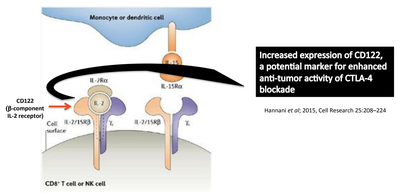


Immune checkpoint inhibitory molecules



Immune checkpoint stimulatory molecules





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Conclusions

- CVA21 treatment facilitated notable changes within the tumor microenvironment by inducing increases in immune cell infiltrates (CD3+CD8+) and expression of PD-L1, in particular within lesions displaying stable disease or response.
- CVA21 treatment induces a Th1-gene shift, with increases in interferon-induced genes.
- CVA21 treatment notably up-regulates many immune checkpoint inhibitory molecules in injected melanoma lesions, including CTLA-4, PD-L1, LAG-3, TIM-3 and IDO.
- CVA21 induced up-regulation of CD122 may potentially increase the clinical activity of anti-CTLA-4 blockade in advanced melanoma patients.
- In general, CVA21 injection appears to facilitate more widespread increased expression of immune checkpoint inhibitory molecules than immune checkpoint stimulatory molecules.
- Up-regulation in immune cell infiltrates and/or immune checkpoint inhibitory molecules in CVA21-treated lesions as early as 7 days post initial viral administration may be predictive of future tumor response.

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*). ***See Poster 140.***
- Clinical evaluation of the activity of intralesional injection of CVA21 in combination with systemic administration of pembrolizumab in patients with unresectable melanoma is currently underway (Phase1b CAPRA study: *ClinicalTrials.gov Identifier:NCT2565992*). ***See Poster 328.***
- CVA21 treatment may be used to reconstitute the immune cells within the tumor microenvironment of cancers that currently respond poorly to immune checkpoint blockade (ie, melanoma liver metastases, colorectal and prostate cancers).

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