Immune-checkpoint blockade in combination with a novel oncolytic immunotherapeutic agent, Coxsackievirus A21, significantly reduces tumor growth and tumor rechallenge

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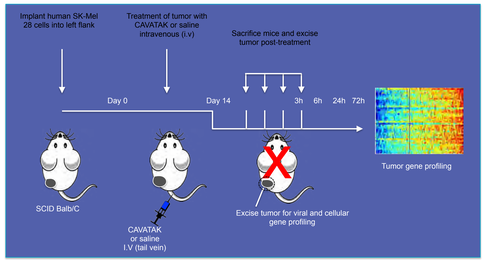
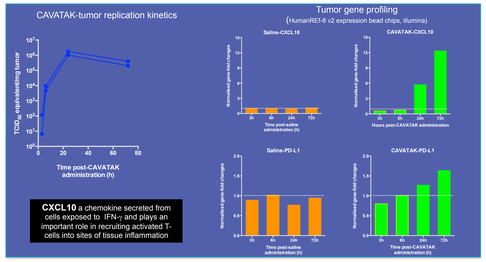
Introduction

Coxsackievirus A21 (CVA21: CAVATAK™) is a naturally occurring "common cold" intercellular adhesion molecule-1 (ICAM-1) targeted RNA virus. Surface ICAM-1 is up-regulated on a number of cancers including melanoma, non-small cell lung, bladder, breast and prostate cancers. Coxsackievirus A21 (CAVATAK™) is a bio-selected oncolytic immunotherapy virus. Following intratumoral (i.t) injection, CAVATAK preferential infects ICAM-1 expressing tumor cell, resulting in tumor cell lysis and a systemic immune-mediated anti-tumor response. A Phase II trial of i.t delivered CAVATAK in advanced melanoma patients has highlighted antitumor activity in both injected and distant non-injected lesions. Blockade of programmed death 1 (PD-1) and CTLA-4 in patients with metastatic melanoma has resulted in substantial tumor responses via a mechanism involving reversal of tumor induced T cell suppression. We hypothesized that combination of CAVATAK and PD-1 or CTLA-4 blockade may enhance antitumor responses, potentially leading to improved clinical activity.

Intravenous delivered CAVATAK-induced gene changes in human melanoma



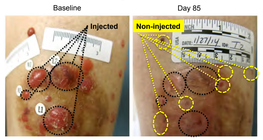
CAVATAK-induced up regulation of IFN-γ inducible protein 10 (CXCL10) and PD-L1 in melanoma xenografts



CXCL10 a chemokine secreted from cells exposed to IFN-γ and plays an important role in recruiting activated T-cells into sites of tissue inflammation

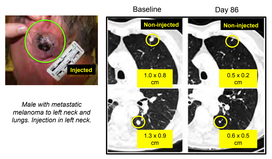
Results

Pt 12-002: Local injected and non-injected lesion responses



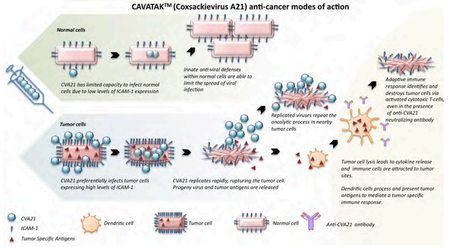
Male with metastatic melanoma to the leg. Injection in leg lesions .

Pt 03-032: Non-injected distant visceral lesion response



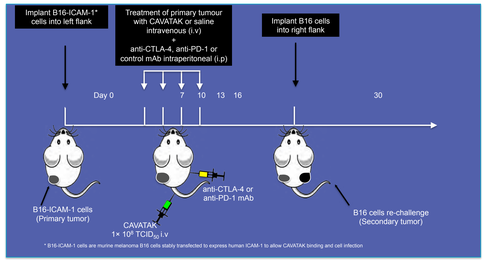
Male with metastatic melanoma to left neck and lungs. Injection in left neck.

Mode of action

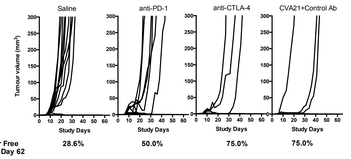


Study Design

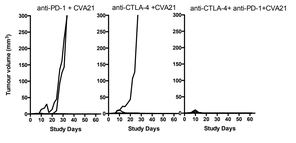
Assessment of combination of intravenous CAVATAK and immune checkpoint antibody blockade (anti-CTLA-4 and/or anti-PD-1) in an immune-competent C57BL mouse melanoma model



Spider plot of Individual primary B16-ICAM-1 tumor growth

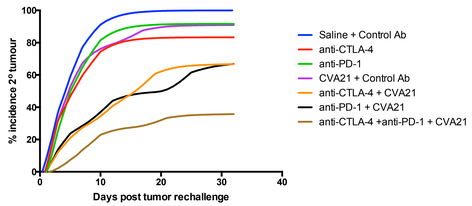


Tumor Free Study Day 62: 28.6% | 50.0% | 75.0% | 75.0%



Tumor Free Study Day 62: 83.3% | 91.7% | 100.0%

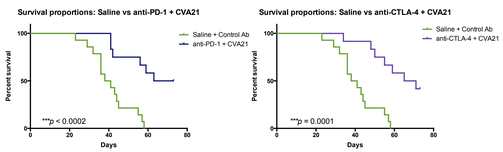
Incidence of palpable secondary B16 tumor

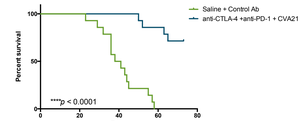


Conclusions

- Following gross examination, CAVATAK and anti-PD-1 or anti-CTLA-4 mAb combination treatment appears to be generally well tolerated
- Significant anti-tumor activity using a combination of CAVATAK (intratumoral or intravenous) and anti-PD-1 or anti-CTLA-4 mAbs in a pre-clinical animal model of melanoma
- The current model provides capacity to assess different sequences of CAVATAK, anti-PD-1 or anti-CTLA-4 mAbs administration.
- Clinical evaluation of a combination of CAVATAK and PD-1 or CTLA-4 blockade in advanced cancer patients with ICAM-1 expression solid tumors is warranted.

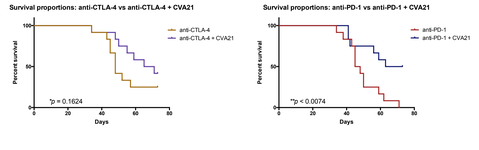
Survival following combination of intravenous CAVATAK and immune checkpoint antibody blockade (anti-CTLA-4 and/or anti-PD-1)

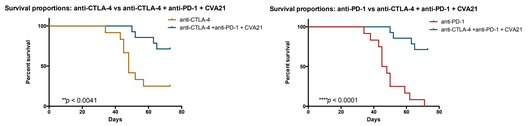




**, mice sacrificed due >20% weight loss, tumor burden >2500mm³, ulceration of primary or re-challenge tumours*

Survival following combination of intravenous CAVATAK and immune checkpoint antibody blockade (anti-CTLA-4 and/or anti-PD-1)





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Future Directions

- The observation of CVA21-induced increases in interferon response genes and PD-L1 expression 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 the presented murine melanoma model
- Clinical evaluation of the activity of intralesional injection of CVA21 in combination with systemic administration of ipilimumab (Phase 1b MITCI study) in patients with unresectable melanoma is currently underway
- Further evaluations of intravenous administration of CVA21 in combination with additional immune checkpoint inhibitors are in planning.

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