Phase I STORM study: Intravenous delivery of a novel oncolytic immunotherapy agent, CAVATAK, in advanced cancer patients

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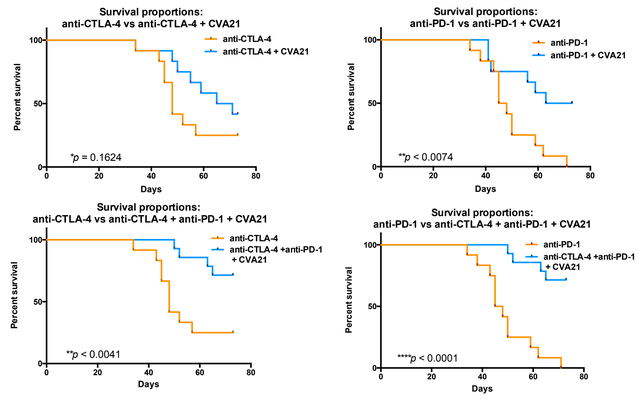
Introduction

Coxsackievirus A21 (CVA21) 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 and prostate cancers. CAVATAK is a novel bio-selected formulation of CVA21, which displays potent oncolytic activity against *in vitro* cultures of cancer cells and *in vivo* xenografts of a number of cancers. In this Phase I/II study advanced cancer patients received multiple intravenous (IV) doses of CAVATAK to assess treatment tolerance, levels of viral replication and viral-induced immune activation within the tumor micro-environment. Intravenous administration of CVA21 in mouse models of melanoma facilitated immune activation within the tumor as evidenced by gene expression increases of CXCL-10 and PD-L1. Furthermore, intravenous delivery of CVA21 in combination with immune checkpoint blockade (anti-PD-1 or anti-CTLA-4) in an immune competent mouse melanoma model mediated significantly greater antitumor activity and survival benefits when compared to use of either agent alone (see below). Of particular interest was the finding that combinations of CAVATAK and anti-PD-1 or anti-CTLA-4 mAbs were able to noticeably delay the onset of palpable tumor development following B16 cell re-challenge when compared to all other single agent treatment regimes.

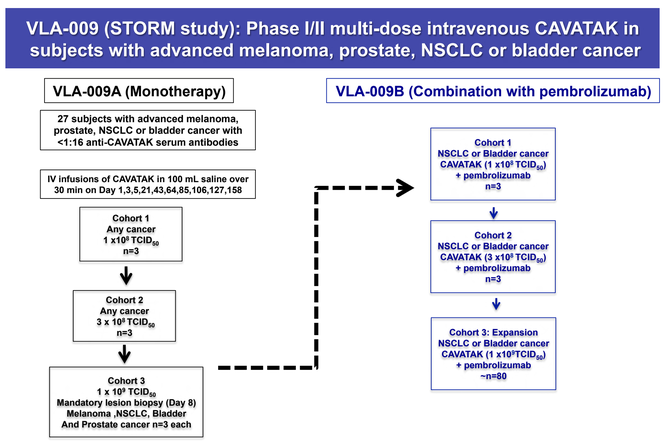


*, mice sacrificed due >20% weight loss, tumor burden >200mm², ulceration of primary or re-challenge tumors

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

Study Design

The Phase I/II STORM (***S****ystemic* ***T****reatment* ***O****f* ***R****esistant* ***M****alignancies:* ***NCT02043665*****)** study is investigating the tolerance of multiple escalating IV doses of CVA21 in approximately 30 advanced cancer patients as a monotherapy and in combination with PD-1 blockade (pembrolizumab) (see design below). Tumor biopsies post-CVA21 infusion are being monitored for levels of virus, immune-cell infiltrates and markers of potential immune activation. Sequential serum samples are being analyzed for viral loads, kinetics of anti-CVA21 neutralizing antibody (nAb) development and immune system activation via relative serum levels of a panel of immune inflammatory cytokines / immune cell subsets.



Preliminary Data

Table 1. Patient treatment Characteristics and response*

Cohort	Patient Identification Code	Gender	Cancer Indication	Previous Lines of Treatment: Surgery	Immunotherapy	Chemotherapy	Radiotherapy	Hormone therapy	Other therapy	Duration of Treatment (cycles)	Best Overall Response	Best target lesion response
1	03-001	Male	NSCLC	1		5			1	4	irPD	SD
	03-002	Male	Melanoma	1	1	1				2	n/a	SD
	02-001	Male	Bladder			7	1			8	irSD	SD
2	02-002	Male	Bladder	1	1	1				4	irSD	SD
	01-001	Male	Prostate	2		1	1	6	1	8	irSD	SD
	02-003	Male	NSCLC			3	1			2	irPD	SD
3	01-005	Male	Prostate		1		1	2		3	irPD	PD
	01-006	Male	Prostate				1	4		8	irPR	PR
	02-004	Female	NSCLC			4	1			1	n/a	n/a
	02-005	Female	Melanoma							3	n/a	n/a
	03-005	Male	Prostate			3	2	1		2	irSD	SD
	03-006	Male	Melanoma	6	1	2	1			4	irSD	SD

*, Investigator assessed

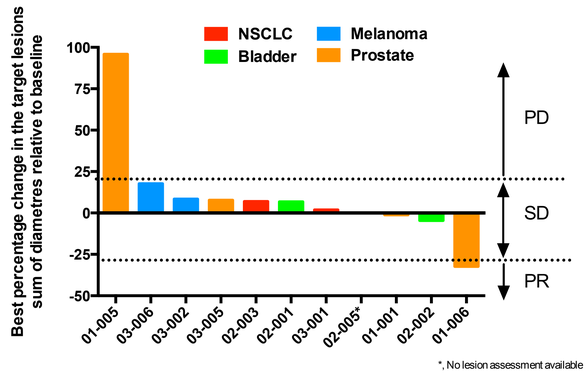
Preliminary Data

Table 2. Product-related Adverse events*

AE Terminology	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Pyrexia	4 (33%)	-	-	-	-
Fatigue	2 (17%)	1 (8%)	-	-	-
Flu-like symptoms/head cold	2 (17%)	-	-	-	-
Lethargy	2 (17%)	-	-	-	-
Dry skin	1 (8%)	-	-	-	-
Arthralgia	1 (8%)	-	-	-	-
Myalgia	1 (8%)	-	-	-	-
Bloating	1 (8%)	-	-	-	-
Diarrhoea	1 (8%)	-	-	-	-
Increased urine WBC	1 (8%)	-	-	-	-

Current treatment-related adverse events [n (% of patients)] for patients in Cohorts 1-3.

Figure 1. Best percentage change in target lesions



*, No lesion assessment available

Figure 2. Tumor Response (Preliminary data: Investigator assessed)

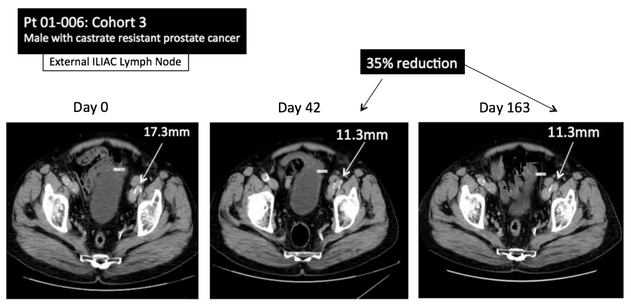


Figure 3. Tumor targeting. CVA21 viral RNA levels in tumor biopsies from Cohort 3 patients at 8 days post-treatment

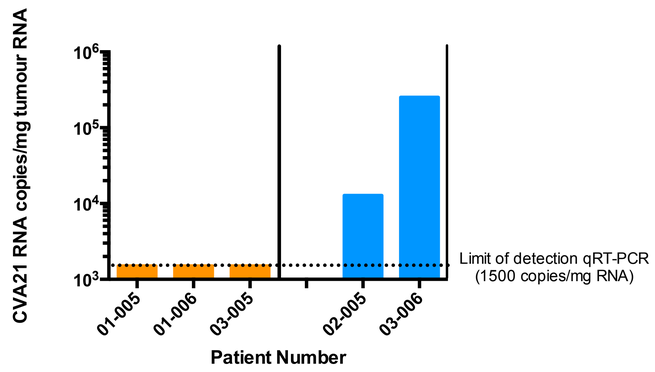


Figure 4. Tumor targeting and viral replication. Cytoplasmic CVA21 viral proteins in biopsies from Cohort 3 Melanoma patients at 8 days post-treatment

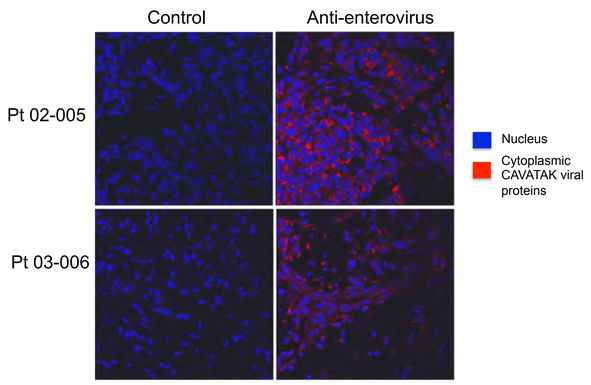


Figure 5. Pharmacokinetics of serum CVA21 viral load (viral RNA)

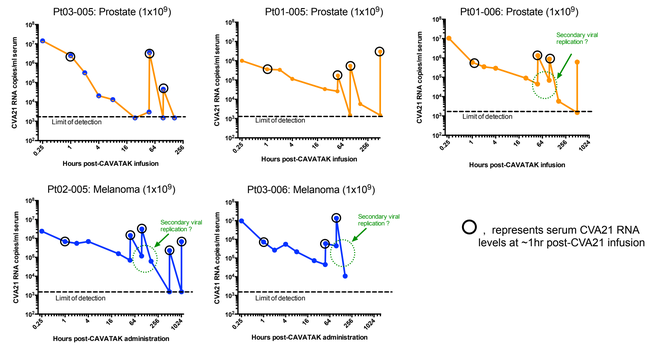
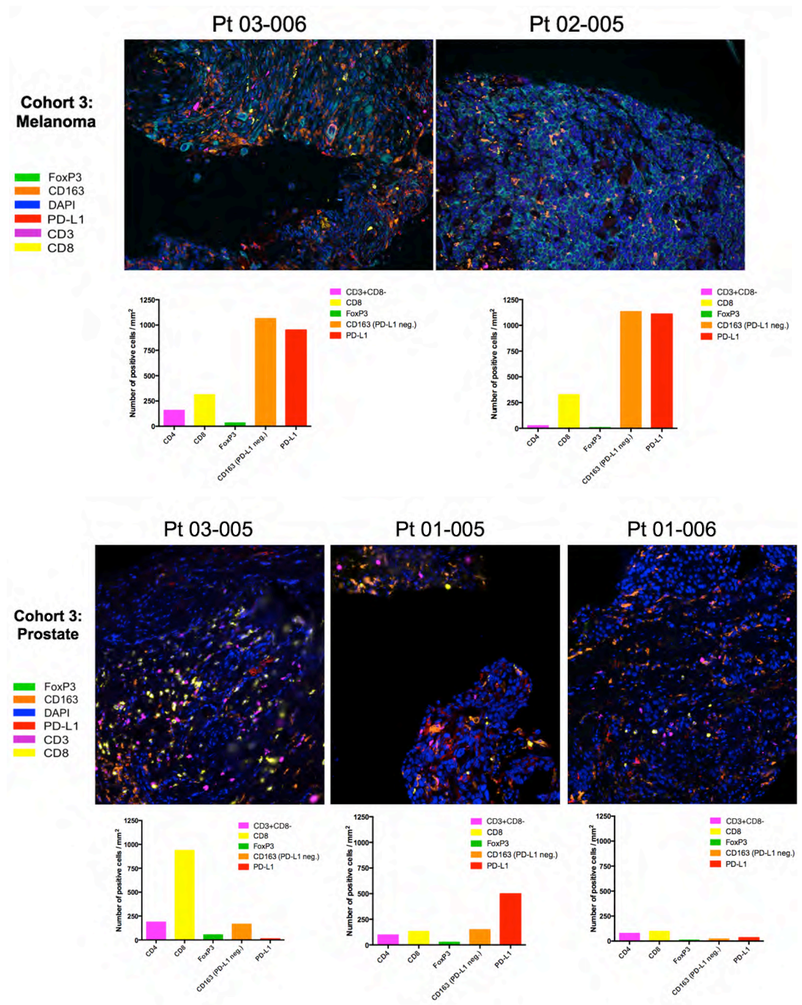


Figure 6. Multi-spectral analysis of immune cell infiltrates in biopsies from Cohort 3 patients at 8 days post-treatment



Conclusions

- Multi-dose intravenous administration to patients in Cohorts 1, 2 and 3 and is generally well tolerated.
- At present no Grade 3 or higher product-related AE's have been observed (Table 2).
- Evidence of CVA21 successful tumor targeting with 2 of 2 melanoma patients in Cohort 3 displaying CVA21 replication and CVA21 RNA in tumor biopsies (Figures 3 and 4).
- A number of patients have exhibited signs of possible tumor specific secondary viral replication *(Figure 5)*
- Multi-spectral analysis revealed the presence of immune cell infiltrates in the Cohort 3 patient day 8 biopsies, with notable levels of PD-L1 staining in both melanoma tumor biopsies
- A number of patients have displayed disease stabilization, with to date, 1 of 5 patients in Cohort 3 displaying a confirmed partial response (Table 1, Figure 1).
- Multi-dosing of patients in the monotherapy Cohort 3 continues.
- Intravenous delivered CVA21 in combination with anti-PD-1 (pembrolizumab) therapy is in late stage planning for clinical evaluation in patients with NSCLC and metastatic bladder cancer.

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Developers of Oncolytic Immunotherapies

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