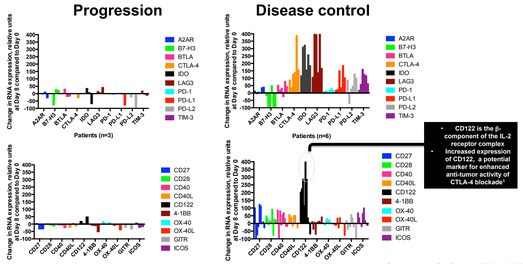
3014 Activity of a novel immunotherapy combination of intralesional Coxsackievirus A21 and systemic ipilimumab in advanced melanoma patients previously treated with anti-PD1 blockade therapy

Brendan Curti[1], Jon Richards[2], Mark Faries[3], Robert H.I. Andtbacka[4], Sigrun Hallmeyer[2], Gregory A. Daniels[5], Mark Grose[6], Roberta Karpathy[6], Darren R. Shafren[6]

[1]Providence Cancer Center, Portland, OR; [2]Oncology Specialists, Chicago, IL; [3]John Wayne Cancer Institute, Santa Monica, CA; [4]Huntsman Cancer Institute, Salt Lake City, UT; [5]UCSD Moores Cancer Center, La Jolla, CA; [6]Viralytics Limited, Sydney, Australia,

Introduction

CAVATAK is a novel bio-selected oncolytic and immunotherapeutic strain of Coxsackievirus A21. Intratumoral (I.T.) CVA21 injection can induce preferential tumor cell infection, tumor immune-cell infiltration, up-regulation of γ-IFN response genes, cell lysis and enhancement of a systemic anti-tumor immune response (Figure 1). The Phase II CALM monotherapy study investigated the efficacy and safety of intratumoral (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-tumor responses. In the CALM-extension study, I.T. CVA21 injection of advanced melanoma lesions that displayed signs of disease control/response resulted in increases in tumor immune-cell infiltration, up-regulation of γ-IFN response and key immune-checkpoint genes at day 8 relative to baseline, including CD122 which may be a potential prognostic marker for anti-tumor activity by anti-CTLA-4 blockade strategies (Figure 1). The open-label, Phase Ib MITCI (***M***elanoma ***I***ntra-***T***umoral ***C***avatak and ***I***pilimumab [anti-CTLA-4]) study of novel immunotherapy combination Coxsackievirus A21 and ipilimumab in patients (pts) with advanced melanoma has currently enrolled 34 subjects with a response rate 67% (8/12) observed in a subset of prior immune checkpoint naïve patients (Figure 2). Presented are preliminary data from 15 of the currently enrolled 34 subjects who have received prior anti-PD1 immune checkpoint therapy.



[1] Hannani *et al., Cell Research* (2015) **25**:208–224.

Figure 1: CALM-extension study: CVA21 treatment induced notable up-regulation of key immune-checkpoint genes within the tumor microenvironment of biopsies taken at baseline and day 8 displaying disease control and/or response as assessed by NanoString analysis on a Pan Cancer immune profiling panel .

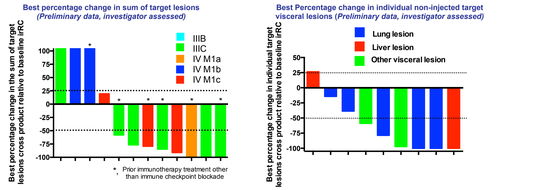
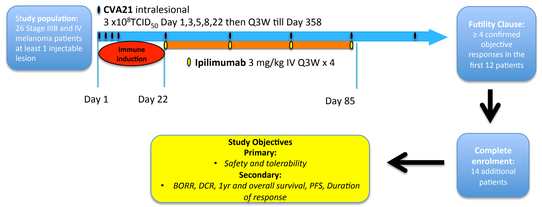


Figure 2: MITCI study: Best percentage change in the sum of target lesions and individual non-injected visceral lesions in immune checkpoint naïve advanced melanoma subjects.

Study Design

MITCI Phase 1b Study Design

(***M***ELANOMA ***I***NTRA-***T***UMORAL ***C***AVATAK AND ***I***PILIMUMAB)



Results

Patient Characteristics

Prior anti-PD1 therapy

Patient Identification Code	Age	Gender	Melanoma Stage at Baseline	Previous Lines of Treatment	Days from Last PD1 Inhibitor to Day 1	Days on prior PD1 Inhibitor	Best Response on prior PD1 Inhibitor	No. of Ipilimumab Doses	No. of CVA21 Doses	Best irRC Overall Response (last visit)	Total lesions present (Index +non-index)	Number of lesions injected with CVA21
1303005	71	M	IV M1c	surgery, immunotherapy (pembrolizumab, T-VEC)	35	146	PD	4	13	irSD	3	1
1305001	71	M	IIIC	immunotherapy (nivolumab, BCG)	34	57	PD	4	8 [1]	irCR confirmed	5	4 [2]
1305002	28	M	IV M1a	immunotherapy (nivolumab)	81	224	PD	4	12	irSD	4	3
1305003	69	M	IV M1c	surgery (2), immunotherapy (nivolumab)	33	112	PR	4	13	irPR confirmed	2	1
1305004	69	M	IV M1c	immunotherapy (BCG, pembrolizumab, T-VEC), radiotherapy (2), chemotherapy	69	126	PD	4	9	irPD	6	2
1305005	84	F	IIIC	immunotherapy (T-VEC, BCG, pembrolizumab)	98	147	PR	3 [3]	8	not assessed yet	2	2
1312012	52	M	IV M1b	surgery (2), radiotherapy (2), immunotherapy (interferon, IL-2, pembrolizumab)	40	83	PD	4	8	irPD	16	2

Prior anti-PD1 and anti-CTLA-4 therapies

Patient Identification Code	Age	Gender	Melanoma Stage at Baseline	Previous Lines of Treatment	Days from Last PD1 Inhibitor to Day 1	Days on prior PD1 Inhibitor	Best Response on prior PD1 Inhibitor	No. of Ipilimumab Doses	No. of CVA21 Doses	Best irRC Overall Response (last visit)	Total lesions present (Index +non-index)	Number of lesions injected with CVA21
1303003	67	F	IV M1c	immunotherapy (interferon, ipilimumab, pembrolizumab), surgery (2), radiotherapy	131	628	not evaluable	4	8	irPD	4	2 [1]
1303008	65	F	IV M1c	surgery, radiation therapy, chemotherapy, immunotherapy (pembrolizumab, HF10/ ipilimumab)	26	384	PD	1	5	irPD	6	2
1304005	36	M	IV M1c	immunotherapy (ipilimumab +nivolumab, nivolumab), surgery	31	205	IPI+Nivo: PR Nivo: PD	4	19	irPR confirmed	19	13
1304009	64	F	IV M1b	hormonotherapy, surgery, radiotherapy, immunotherapy (ipilimumab, pembrolizumab)	56	162	PD	4 [2]	19	irSD	2	1
1304011	42	M	IV M1c	immunotherapy (ipilimumab, pembrolizumab), surgery (4)	83	449	SD	3 [3]	7 [3]	irPD	6	4 [3]
1310001	69	M	IV M1c	immunotherapy (IL2 x2, ipilimumab+nivolumab x2),	37	328	PD	4	8	irSD	5	1
1310002	34	M	IV M1c	immunotherapy (PEG-IFN, TIL, ipilimumab+nivolumab, IL2 x2, SD-101, pembrolizumab)	34	511	PD	2	7	not assessed yet	4	?
1312007	63	M	IV M1c	surgery (2), immunotherapy (ipilimumab, interferon, galectin, pembrolizumab), radiotherapy	3	95	PD	4	19	irSD	8	1

Footnotes:
[1] ipilimumab dose held Day 85 due to ipilimumab-related diarrhea, given Day 106
[2] one ipilimumab dose not given due to ipilimumab-related AE
[3] further CVA21 dose held as clinically injectable mass had resolved
* includes new lesions
[1] CVA21 and ipilimumab held at Day 85 due to grade 3 elevated liver enzymes

Safety and Toxicity*: Treatment Related Adverse Events

Coxsackievirus A21

System Organ Class MedDRA Preferred Term	Grade 2	Grade 3
All Systems	6 (40%)	0 (0%)
General disorders and administration site conditions	3 (20%)	0 (0%)
Fatigue	2 (13%)	0 (0%)
Injection site pain	2 (13%)	0 (0%)
Skin and subcutaneous tissue disorders	2 (13%)	0 (0%)
Pruritus	1 (7%)	0 (0%)
Pruritus generalised	1 (7%)	0 (0%)
Rash generalised	1 (7%)	0 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (7%)	0 (0%)
Tumour exudation	1 (7%)	0 (0%)

Anti-CTLA-4 (ipilimumab)

System Organ Class MedDRA Preferred Term	Grade 2	Grade 3
All Systems	8 (53%)	1 (7%)
General disorders and administration site conditions	2 (13%)	0 (0%)
Fatigue	2 (13%)	0 (0%)
Skin and subcutaneous tissue disorders	3 (20%)	0 (0%)
Pruritus	2 (13%)	0 (0%)
Rash	1 (7%)	0 (0%)
Urticaria	1 (7%)	0 (0%)
Gastrointestinal disorders	2 (13%)	0 (0%)
Diarrhoea	2 (13%)	0 (0%)
Investigations	2 (13%)	0 (0%)
Alanine aminotransferase increased	1 (7%)	0 (0%)
Aspartate aminotransferase increased	1 (7%)	0 (0%)
Weight decreased	1 (7%)	0 (0%)
Endocrine disorders	3 (20%)	0 (0%)
Hypothyroidism	2 (13%)	0 (0%)
Hypophysitis	1 (7%)	0 (0%)
Metabolism and nutrition disorders	1 (7%)	0 (0%)
Hypernatraemia	1 (7%)	0 (0%)
Musculoskeletal and connective tissue disorders	1 (7%)	0 (0%)
Neck pain	1 (7%)	0 (0%)
Nervous system disorders	1 (7%)	0 (0%)
Headache	1 (7%)	0 (0%)
Hepatobiliary disorders	0 (0%)	1 (7%)
Hepatotoxicity	0 (0%)	1 (7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (7%)	0 (0%)
Tumour exudation	1 (7%)	0 (0%)

* *Preliminary analysis, adverse events from 15 treated patients using Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0*

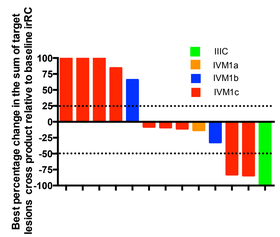
Tumor Response

Best Overall Response (irRC criteria) ***(Preliminary data, investigator assessed)***

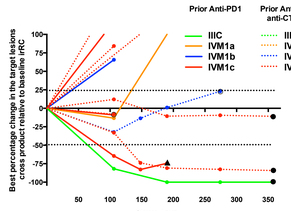
Tumor Response *	Prior anti-PD1 therapy** (n=13)	Prior anti-PD1 therapy without anti-CTLA-4 (n=6)	Both Prior anti-PD1 and anti-CTLA-4 therapy (n=7)
BORR (CR+PR)	23.1% (3/13)	33% (2/6)	14.3% (1/7)
DCR (CR+PR+SD)	62% (8/13)	67% (4/6)	57% (4/7)

*, *First tumor response assessment at study day 106*
**, *Median duration of prior anti-PD1 therapy = 23 weeks*

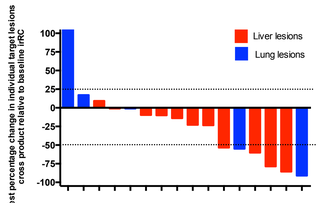
Best percentage change in sum of target lesions ***(Preliminary data, investigator assessed)***



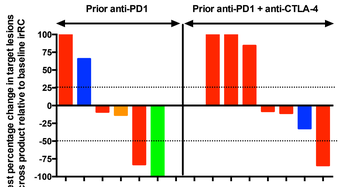
Best percentage change in sum of target lesions by disease stage ***(Preliminary data, investigator assessed)***



Best Percentage change in individual non-injected target visceral lesions ***(Preliminary data, investigator assessed)***

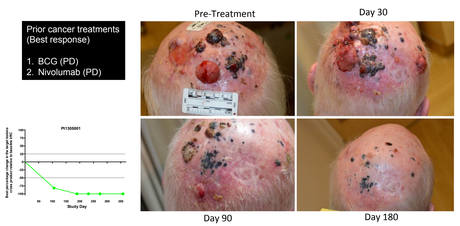


Best percentage change in the sum of target lesions in patients with prior anti-PD1 or anti-PD1 and anti-CTLA-4 therapy ***(Preliminary data, investigator assessed)***



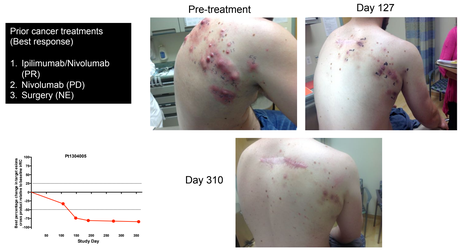
Pt1305001 (Stage IIIC) Complete tumor response

Prior cancer treatments (Best response)
1. BCG (PD)
2. Nivolumab (PD)



Pt1304005 (Stage IVM1c) Partial tumor response

Prior cancer treatments (Best response)
1. Ipilimumab/Nivolumab (PR)
2. Nivolumab (PD)
3. Surgery (NE)



Conclusions

- The CVA21/anti-CTLA-4 (ipilimumab) combination immunotherapy treatment is generally well tolerated and has displayed durable anti-tumor activity in local, regional and distant systemic disease.
- At present no DLT's have been reported, with surprisingly, only 1 Gr 3 treatment-AE (ipilimumab-related elevated liver enzymes) with a Gr 3/4 treatment-related AE rate of 7% in patients administered prior anti-PD1 therapy (1/15 pts).
- Preliminary investigator assessed confirmed Best Overall Response Rates (BORR):
  - 23.1% (3/13 pts) in all patients receiving prior anti-PD1 therapy;
  - 33.3% (2/6 pts) in patients administered prior anti-PD1 therapy without anti-CTLA-4 therapy ;
  - 14.3% (1/7 pts) in patients administered both prior anti-PD1 + anti-CTLA-4 therapies.
- Preliminary investigator assessed Disease Control Rate (DCR):
  - 62% (8/13 pts) in all patients receiving prior anti-PD1 therapy;
  - 67% (4/6 pts) in patients administered prior anti-PD1 therapy without anti-CTLA-4 therapy ;
  - 57% (4/7 pts) in patients administered both prior anti-PD1 + anti-CTLA-4 therapies.
- Promising response activity (38%, 6/16) in individual non-injected visceral target lesions, particularly liver metastases in patients receiving prior anti-PD1 therapy.
- While preliminary, the data suggest that a CVA21-ipilimumab combination may represent a viable treatment option for an unmet need in advanced melanoma patients refractory to prior anti-PD1+/- CTLA-4 therapies.

Future Directions

A focus on an unmet clinical need in advanced melanoma patients refractory to prior anti-PD1 immune checkpoint therapies.

Expansion Cohort
44 Stage IIIB and IV melanoma patients at least 1 injectable lesion, refractory to prior anti-PD1 therapies

Recruitment commenced

Primary study Objective
- *Response rate*