#1051PD The MITCI (phase 1b) study: A novel immunotherapy combination of Coxsackievirus A21 and ipilimumab in patients with advanced melanoma

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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-INF response genes, cell lysis and enhancement of a systemic anti-tumor immune response (Figure 1). The Phase II CALM 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 a 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-INF response and key immune-checkpoint genes, including CD122 which may be a potential prognostic marker for anti-tumor activity by anti-CTLA-4 blockade strategies (Figure 1). Presented are the preliminary data of 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.

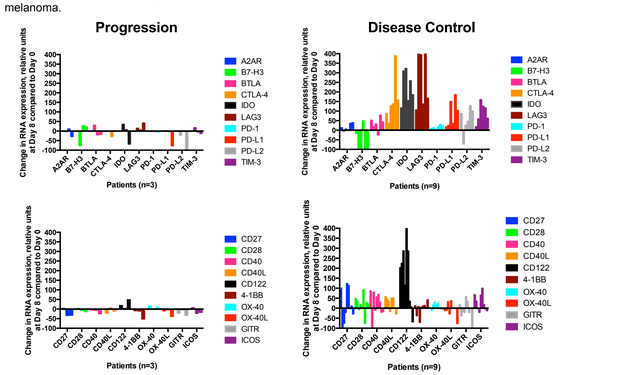


Figure 1: CALM-extension study: CVA21 treatment induced notable up-regulation of key immune-checkpoint genes within the tumor Microenvironment displaying disease control and/or response as assessed by NanoString analysis on a Pan Cancer immune profiling panel .

Study Design

Phase 1b: MITCI study design
(**M**elanoma **I**ntra-**T**umoral **C**avatak and **I**pilimumab)

26 Stage IIIC and IV melanoma patients at least 1 injectable lesion

CAVATAK intratumoral
3 x10^8 $TCID_{50}$ Day 1, 3, 5 ,8 and 22 then Q3W till Day 358

ipilimumab 3 mg/kg IV Q3W x 4

Day 1 Day 22 Day 85

1º end-point : Safety
2º endpoint: Response (irRC criteria)

Key Inclusion Criteria

1. Patients with metastatic or unresectable stage IIIc or IV melanoma for whom treatment with ipilimumab is indicated and who have at least one cutaneous, subcutaneous tumor or palpable lymph node amenable to intratumoral injection. Histological confirmation of melanoma will be required by previous biopsy or cytology.
2. Patients who have received prior ipilimumab treatment for metastatic melanoma are eligible, as long as they did not experience any grade ≥ 3 toxicity and have resolution of any previous toxicity to grade 1 or less.
3. At least one tumor must qualify to be a target lesion for irRC-modified WHO criteria.
4. Patients must be ≥ 18 years of age.
5. ECOG performance status of 0-1

Results

Patient Characteristics

Patient Identification Code	Age	Gender	Melanoma Stage at Baseline	Previous Lines of Treatment	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
1303001	66	M	IIIC	none	4	9 [3]	irCR (irPR confirmed)	1	1
1303003	67	F	IV M1c	immunotherapy (interferon, ipilimumab, pembrolizumab)	0	3	not assessed yet	1	1
1304001	73	M	IIIC	surgery	4	7	irPD	4	1
1304002	64	F	IV M1a	surgery (2), other (vaccine)	4	7 [3]	irCR confirmed	6	2
1304005	36	M	IV M1c	immunotherapy (ipilimumab +nivolumab, nivolumab)	4	12	irPR	19	10 [4]
1304006	60	F	IIIC	surgery (5), other (vaccine)	4	11 [3]	irPR confirmed	4	4
1304009	64	F	IV M1b	hormonotherapy, surgery, radiotherapy, immunotherapy (ipilimumab, pembrolizumab)	4 [1]	10	irSD	2	1
1304010	48	F	IV M1c	surgery	4	7 [3]	irPR confirmed	4	1
1304011	42	M	IV M1c	immunotherapy (ipilimumab, pembrolizumab), surgery (4)	0	2	not assessed yet	3	3
1305001	71	M	IIIC	immunotherapy (nivolumab, BCG)	4	8 [3]	irCR confirmed	5	4 [4]
1305002	28	M	IV M1a	immunotherapy (nivolumab)	4	12	irSD	4	3
1305003	69	M	IV M1c	surgery (2), immunotherapy (nivolumab)	4	10	irPR confirmed	1	1
1312003	67	M	IV M1c	immunotherapy (IL-2)	4	17	irPR confirmed	7	1
1312004	35	F	IIIC	none	4	17	irPR confirmed	3	2
1312007	63	M	IV M1c	surgery (2), immunotherapy (ipilimumab, interferon, galectin, pembrolizumab), radiotherapy	4	18	irSD	8	1
1312009	54	M	IV M1c	none	4	16	irSD	12	3
1312010	81	F	IV M1c	chemotherapy, surgery, immunotherapy (MEDI-6020)	4	12	irSD	8	2
1312011	76	M	IV M1b	radiotherapy, immunotherapy (IL-2)	3 [2]	8	irPD	9	4 [4]
1312012	52	M	IV M1b	surgery (2), radiotherapy (2), immunotherapy (interferon, IL-2, pembrolizumab)	4	9	irPD	16	2
1312013	71	M	IV M1b	surgery (2)	4	8	not assessed yet	6	2

Footnotes:
[1] ipilimumab dose held Day 85 due to ipilimumab-related diarrhea, given Day 106
[2] ipilimumab dose held Day 64 due to ipilimumab-related rash
[3] further CVA21 dose held as clinically injectable mass had resolved
[4] includes new lesions

Safety and Toxicity*

MedDRA System Organ Class	MedDRA Preferred Term	Related to CAVATAK n(%)					Related to Ipilimumab n(%)				
		Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Blood and lymphatic system disorders	Anaemia	-	-	-	-	-	3(17)	-	-	-	-
Endocrine disorders	Hypophysitis	-	-	-	-	-	-	1(6)	-	-	-
	Hypothyroidism	-	-	-	-	-	-	2(11)	-	-	-
Gastrointestinal disorders	Colitis	-	-	-	-	-	1(6)	-	-	-	-
	Constipation	-	-	-	-	-	1(6)	-	-	-	-
	Diarrhoea	-	-	-	-	-	3(17)	2(11)	-	-	-
	Nausea	-	-	-	-	-	1(6)	-	-	-	-
General disorders/administration site conditions	Chills	3(17)	-	-	-	-	1(6)	-	-	-	-
	Fatigue	6(33)	4(22)	-	-	-	7(39)	2(11)	1(6)	-	-
	Inflammation	1(6)	-	-	-	-	-	-	-	-	-
	Inflammatory pain	-	-	-	-	-	1(6)	-	-	-	-
	Influenza like illness	1(6)	-	-	-	-	-	-	-	-	-
	Injection site discomfort	1(6)	-	-	-	-	-	-	-	-	-
	Injection site pain	2(11)	2(11)	-	-	-	-	-	-	-	-
	Injection site pruritus	2(11)	-	-	-	-	-	-	-	-	-
	Injection site reaction	2(11)	-	-	-	-	-	-	-	-	-
	Pain	2(11)	-	-	-	-	-	-	-	-	-
	Pyrexia	4(22)	-	-	-	-	2(11)	-	-	-	-
Investigations	ALT increased	-	-	-	-	-	3(16)	-	-	-	-
	AST decreased	-	-	-	-	-	1(6)	-	-	-	-
	AST increased	-	-	-	-	-	2(11)	-	-	-	-
	Blood ALP increased	-	-	-	-	-	2(11)	-	-	-	-
	Blood bilirubin increased	-	-	-	-	-	1(6)	-	-	-	-
	Lymphocytes decreased	1(6)	-	-	-	-	-	-	-	-	-
	Transaminases increased	-	-	-	-	-	1(6)	-	-	-	-
	Weight decreased	-	-	-	-	-	1(6)	1(6)	-	-	-
Metabolism and nutrition disorders	Decreased appetite	-	-	-	-	-	1(6)	1(6)	-	-	-
Musculoskeletal and connective tissue disorders	Groin pain	-	1(6)	-	-	-	-	-	-	-	-
	Myalgia	1(6)	-	-	-	-	-	-	-	-	-
Neoplasms benign, malignant and unspecified	Tumour necrosis	-	1(6)	-	-	-	-	1(6)	-	-	-
Nervous system disorders	Headache	2(11)	-	-	-	-	-	-	-	-	-
	Neuropathy peripheral	-	-	-	-	-	1(6)	-	-	-	-
Respiratory, thoracic and mediastinal disorders	Dysphonia	1(6)	-	-	-	-	-	-	-	-	-
	Oropharyngeal pain	1(6)	-	-	-	-	-	-	-	-	-
	Rhinorrhoea	1(6)	-	-	-	-	-	-	-	-	-
Skin and subcutaneous tissue disorders	Achromotrichia acquired	-	-	-	-	-	1(6)	-	-	-	-
	Dermatitis	-	-	-	-	-	-	1(6)	-	-	-
	Dermatitis acneiform	1(6)	-	-	-	-	1(6)	-	-	-	-
	Pruritus	3(17)	-	-	-	-	6(33)	2(11)	-	-	-
	Pruritus generalised	-	1(6)	-	-	-	1(6)	3(17)	-	-	-
	Rash	1(6)	-	-	-	-	4(22)	1(6)	-	-	-
	Rash generalised	-	-	-	-	-	-	1(6)	-	-	-
	Rash maculo-papular	-	-	-	-	-	1(6)	-	-	-	-
	Vitiligo	-	-	-	-	-	1(6)	-	-	-	-

* Preliminary analysis, adverse events from 18 treated patients using Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0

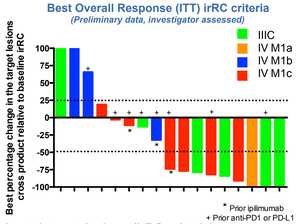
Tumor Response

Response data (preliminary)

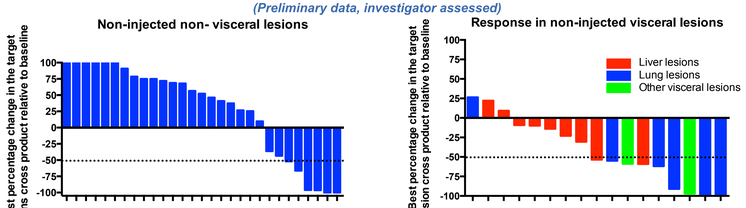
Best Overall response rate	
BORR (CR+PR, irRC):	57.1%* (52.9%+) [3CR + 6PR]
Disease control Rate (CR+PR+SD)	82.4% [3CR + 6PR + 5SD]
Median Time to response	NA

*,ipilimumab naïve patients
+,Intent-to-treat (ITT) population, patients evaluable for tumor assessment n=17, investigator assessed
NA=Not available, all responses have occurred by 4.8 months

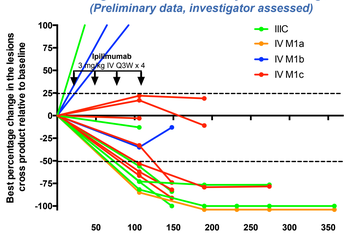
Best Overall Response (ITT) irRC criteria
(Preliminary data, investigator assessed)



Best Percentage changes in individual non-injected target lesions (irRC criteria)
(Preliminary data, investigator assessed)

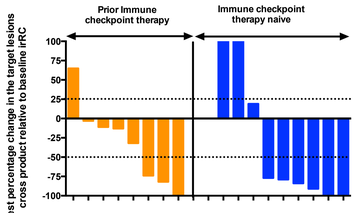


Changes in tumor burden by disease stage*
(Preliminary data, investigator assessed)



* *First tumor response assessment at study day 106*

Best Overall Response in patients with and without prior immune checkpoint therapy
(Preliminary data, investigator assessed)



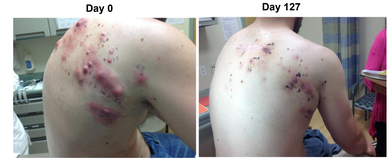
Combination treatments with ipilimumab

	Ipilimumab[1] (phase 3)	Ipilimumab + Nivolumab[1] (phase 3)	Ipilimumab[2] (Prior anti-PD1 treatment)	Ipilimumab + HF10[3] (phase Ib)	Ipilimumab + TVEC[4] (phase Ib)	Ipilimumab + CAVATAK (phase Ib)
Schedule	Ipi 3 mg/kg	Ipi 3 mg/kg + Nivo 1 mg/kg	Ipi 3 mg/kg	Ipi 3 mg/kg + HF10	Ipi 3 mg/kg + TVEC	Ipi 3 mg/kg + CAVATAK
Pts population	315	314	40	43	18	20
≥ 1 Prior systemic treatments (%)	0	0	100	46	0	66
mPFS (months)	2.9	11.5	N/A	NA	10.6	NA
BORR (%)	19*	57.6*	10	49*	50*	57.1* (52.9[+])
BORR (%) Stage IV M1c	NA	NA	NA	33.3 (2/6)	0 (0/5)	57.1 (4/7)
DCR (%)	41	70.7	18	68	73	82.4*
DCR (%) Stage IV M1c	NA	NA	NA	66.3 (4/6)	40 (2/5)	100 (7/7)
Grade 3+ Drug related AE (%)	27	55	35	30	32	6

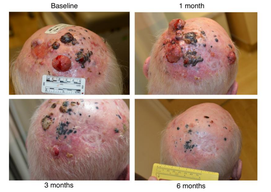
[1] *N Engl J Med. 2015;373(1):23*
[2] *British Journal of Cancer (2016) 114, 1084–1089*
[3] *Andtbacka et al , 2016; ASCO*
[4] *J Clin Oncol. 2016 Aug 1;34(22):2619-26*
* Ipilimumab naïve patients:
+ ITT population, patients evaluable for tumor assessment n=17:
NR=Not reached
NA=Not available

Individual Patient Responses

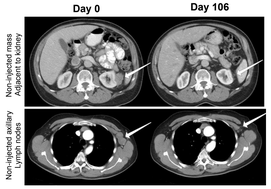
Pt 1304005: Partial response
Stage IV M1c
Prior immune-checkpoint therapy



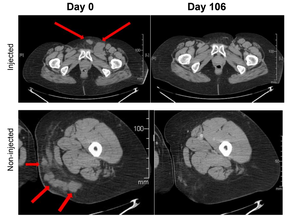
Pt 1305001:Complete response
Stage IIIC
Prior immune-checkpoint therapy



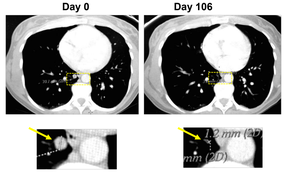
Pt 1312003: Partial response
Stage IV M1c



Pt 1304002: Complete response
Stage IV M1a



Pt 1304010: Partial response
Stage IV M1c



Conclusions

- The CVA21-ipilimumab combination immunotherapy treatment is generally well tolerated and has displayed 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 fatigue) with an overall study Gr 3/4 treatment-related AE rate of 6% (1/18 pts).
- Best Overall Response Rate (BORR) of 57.1% in ipilimumab naïve patients (preliminary data) is higher than published rates for either agent used alone (CVA21: 28.1% and ipilimumab :~15-20%) in advanced melanoma patients.
- DCR of 82.4% (14/17 pts) in patients of which 66% have been administered prior systemic therapy(s).
- In patients with stage IV M1c disease a BORR of 57.1% (4/7 pts) and DCR of 100% (7/7).
- Objective response rate of 52.9% (9/17) and DCR of 94.1% (16/17) in non-injected visceral target lesions.
- While preliminary, the presented response data are encouraging compared to that of other ipilimumab combinations used to treat advanced melanoma patients.

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