CAPRA: A Phase Ib study of intratumoral oncolytic Coxsackievirus A21 (CVA21) and systemic pembrolizumab in advanced melanoma patients

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Background

Coxsackievirus A21 (CVA21, CAVATAK®) is a naturally occurring ICAM-1 targeted oncolytic immunotherapeutic virus (Figure 1). The Phase II CALM study investigated the efficacy and safety of intratumoral 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, intratumoral CVA21 injection of advanced melanoma lesions that displayed signs of disease control/response resulted in increases in tumor immune-cell infiltration, activation of the RIG-I pathway, up-regulation of γ-INF response and key immune-checkpoint genes, including PD-L1 (Figure 2). Pembrolizumab is a human programmed death receptor-1 (PD-1) blocking antibody that has yielded significant solid tumor responses via reversal of tumor induced T-cell suppression. Preclinical studies in an immune-competent mouse model of melanoma confirmed that combinations of intratumoral CVA21 + anti-PD-1 mAbs mediated survival benefit compared to use of either agent alone. We postulate that the combination of CVA21+pembrolizumab may translate to a similar benefit in the clinic. The presented phase 1b clinical trial evaluates combination CVA21 and pembrolizumab based on increased expression of PD-L1 following virus administration and higher response rates of pembrolizumab in patients with increased tumor PD-L1.

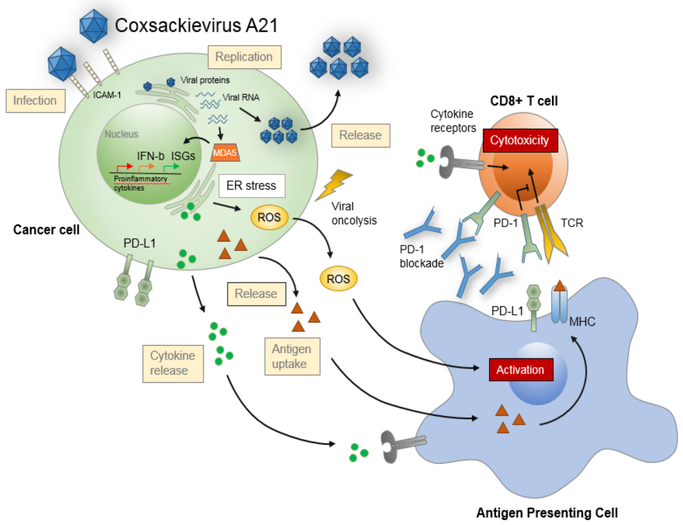


Figure 1. Coxsackievirus A21 (CVA21) mode of action in combination with immune-checkpoint blockade.

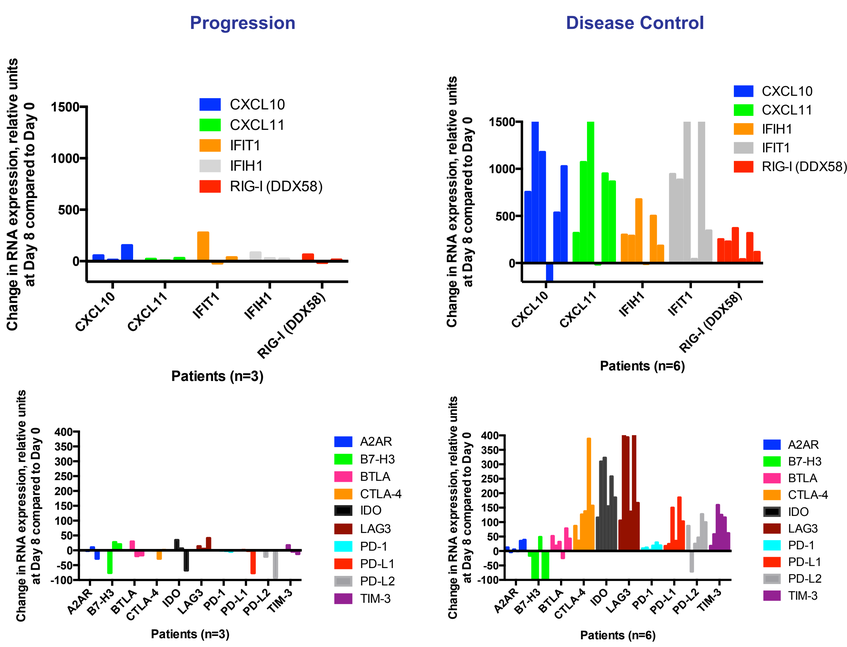
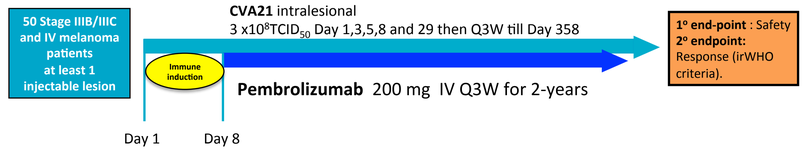


Figure 2. Coxsackievirus A21 treatment induced notable up-regulation of the RIG-I pathway and key immune-checkpoint genes within the tumor microenvironment of biopsies taken at baseline and day 8 displaying disease control and/or response as assessed by NanoString analysis on a Pan Cancer immune profiling panel.

Study Design



Patient Characteristics

Patient Identification Code	Age	Gender	Melanoma Stage at Baseline	Previous Lines of Treatment	No. of Pembrolizumab Doses	No. of CVA21 Doses	Best irRC Overall Response
1105001	76	F	IIIB	surgery (2), vaccine	8 [1]	4 [2]	irCR confirmed
1105003	66	F	IV M1c	surgery (2), vaccine	10	5 [2]	irPR confirmed
1106001	84	M	IV M1a	surgery	3 [1]	6	irSD
1106002	75	M	IV M1c	surgery (2)	22 [1]	11	irPR confirmed (irCR)
1106003	70	M	IIIB	surgery (5)	10 [1]	14	irSD
1106004	83	M	IIIB	Surgery (8), immunotherapy (T-VEC)	14	16	irSD
1106006	73	F	IV M1c	surgery (2)	2 [3]	5 [3]	not evaluable
1106007	83	M	IV M1c	none	19	7 [2]	irPR confirmed
1106008	50	M	IIIC	surgery	19	11 [2]	irPR confirmed
1106009	94	M	IV M1c	surgery, radiotherapy	14 [6]	12 [6]	irPR confirmed
1106010	64	M	IV M1b	surgery (2)	24	10 [2]	irPR confirmed
1106011	67	M	IV M1c	surgery (3), immunotherapy (ipilimumab)	9 [1]	12 [2]	irPR confirmed
1106013	85	M	IV M1c	surgery	20	18 [2]	irPR confirmed
1106014	69	F	IV M1c	surgery (2)	18	19	irSD
1106015	65	M	IV M1b	surgery	5 [5]	8 [5]	irPD
1106016	76	M	IIIC	surgery	15	7 [2]	irPR confirmed
1106017	73	M	IV M1a	surgery (2)	9 [1]	13	irPR confirmed
1106019	53	F	IV M1c	surgery (2), immunotherapy (ipilimumab)	2 [1]	10	irPR confirmed
1106020	77	M	IV M1c	surgery (2)	2	5 [5]	irPD
1106022	78	M	IIIC	surgery	6	9	irPR confirmed
1106023	56	M	IIIB	surgery, immunotherapy (interferon)	2	4 [2]	irPR confirmed
1106024	43	M	IV M1c	surgery (4)	2	5	irPD
1106025	78	M	IIIC	surgery (3)	2	5	irPD
1106026	67	M	IV M1b	none	2	5	Not assessed yet
1106027	67	M	IIIC	surgery	2	5	Not assessed yet
1116001	75	M	IV M1c	surgery (3)	9	7 [2]	irPD

1 Pembrolizumab dose held for one or more days due to AE

2 Further CVA21 injections held as no injectable mass

3 Pembrolizumab and CVA21 dose held after Day 29 due to Grade 4 sepsis. Subject subsequently withdrawn.

4 includes new lesions

5 further treatment held due to progressive disease

6 further treatment held due to unrelated AE.

Safety*

MedDRA Preferred Term	Related to CAVATAK Treatment					Related to Pembrolizumab Treatment				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypothyroidism	-	-	-	-	-	1/(4)	1/(4)	-	-	-
Diarrhoea	1/(4)	-	-	-	-	2/(8)	2/(8)	-	-	-
Dry mouth	-	-	-	-	-	3/(12)	1/(4)	-	-	-
Chills	1/(4)	-	-	-	-	-	1/(4)	-	-	-
Fatigue	2/(8)	-	-	-	-	10/(39)	-	-	-	-
Injection site pain	-	1/(4)	-	-	-	-	-	-	-	-
Pyrexia	1/(4)	-	-	-	-	-	-	-	-	-
Candida infection	-	-	-	-	-	1/(4)	-	-	-	-
Blood alkaline phosphatase increased	-	-	-	-	-	1/(4)	-	-	-	-
Eosinophil count	-	-	-	-	-	1/(4)	-	-	-	-
Hepatic enzyme increased	-	-	-	-	-	-	-	1/(4)	-	-
Thyroid function test abnormal	-	-	-	-	-	-	1/(4)	-	-	-
Weight decreased	-	-	-	-	-	1/(4)	-	-	-	-
Decreased appetite	2/(8)	-	-	-	-	1/(4)	1/(4)	-	-	-
Arthralgia	-	-	-	-	-	1/(4)	-	-	-	-
Myalgia	-	-	-	-	-	1/(4)	-	-	-	-
Keratoacanthoma	-	-	-	-	-	-	-	1/(4)	-	-
Pneumonitis	-	-	-	-	-	-	1/(4)	-	-	-
Erythema	1/(4)	-	-	-	-	-	-	-	-	-
Pruritus	-	-	-	-	-	3/(12))	-	-	-	-
Rash	1/(4)	-	-	-	-	10/(39)	-	-	-	-
Rash maculo-papular	-	-	-	-	-	1/(4)	-	-	-	-
Vitiligo	1/(4)	-	-	-	-	3/(12)	-	-	-	-

** Preliminary analysis, adverse events from 26 treated patients using Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0*

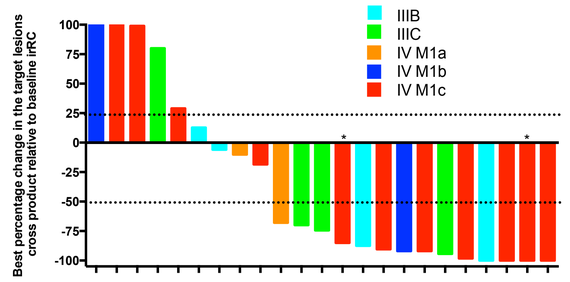
Tumor Response

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

Best Overall Response Rate	
BORR (CR+PR, irRC):	61.0% (14/23 pts)*
Disease control Rate (CR+PR+SD)	78.3 % (18/23 pts)

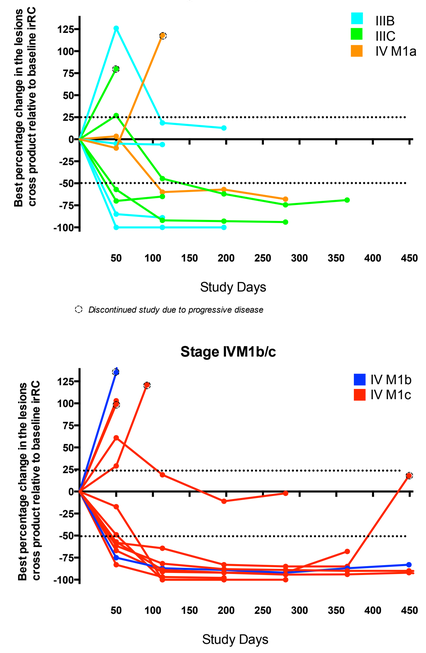
*, Preliminary data, investigator assessed n=23 pts; Pt 1106006 terminated study prior to response assessment due to an unrelated-treatment SAE;

Best percentage change in target lesions irRC criteria
(Preliminary data, investigator assessed)



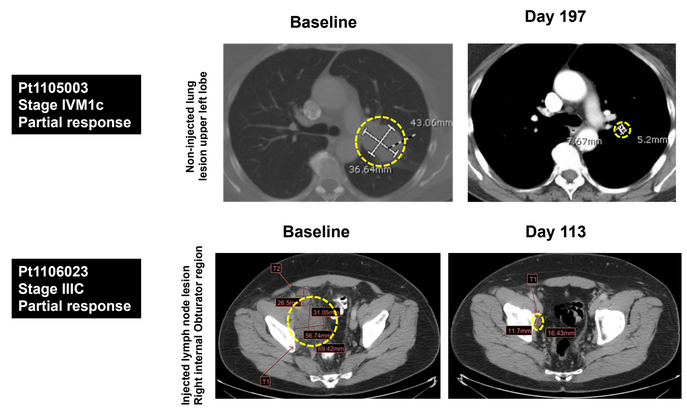
* Prior ipilimumab treatment

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



◌ *Discontinued study due to progressive disease*

Individual Patient Response (*investigator assessed*)



Conclusions

- At present No DLT's have been observed in the first 26 patients receiving the combination treatment.
- Overall, adverse events have generally been low-grade constitutional symptoms related to CVA21 and standard pembrolizumab-related side effects. At present only two Grade 3 adverse events (hepatic toxicity and keratoacanthoma) related to pembrolizumab have been observed.
- CVA21-pembrolizumab combination therapy was associated with clinical benefit in treated patients.
- Preliminary Best Overall Response Rate (BORR) of 61.0% (14/23 pts) and 4/23 pts with Stable Disease.
- In patients with stage IV M1c disease a BORR of 64% (7/11 pts).
- Preliminary observations have revealed durable reductions in a number of injected and non-injected visceral/non-visceral lesions, with a number of patients displaying evidence of post-injection systemic exposure to CVA21.

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