Phase Ib study of intratumoral oncolytic Coxsackievirus A21 (CVA21) and pembrolizumab in subjects with advanced melanoma

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Background

Coxsackievirus A21 (CVA21, CAVATAK™) is a naturally occurring ICAM-1 targeted oncolytic immunotherapeutic virus. 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, up-regulation of γ-INF response and key immune-checkpoint genes, including PD-L1 (Figure 1). 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 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.

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	Total lesions present (index+non-index)	Number of lesions injected with CVA21	Treatment Discontinuation (relationship to treatment)
1106001	84	M	IIIc	none	3 [1]	6	irSD	2	2	Progressive disease
1106002	75	M	IV M1c	none	11	9 [2]	irPR confirmed	3	3*	
1106004	83	M	IIIb	immunotherapy (T-VEC)	9	11	irSD	3	6*	
1106006	73	F	IV M1c	surgery (2)	2 [3]	5 [3]	not evaluable	10	2	Grade 3 sepsis (unrelated)
1106007	83	M	IV M1c	none	10	7 [2]	irPR confirmed	8	4	
1106008	50	M	IIIc	surgery	8	11	irSD	3	5*	
1106009	94	M	IV M1c	surgery, radiotherapy (1)	5	8	irPR	4	2	
1106010	64	M	IV M1b	surgery (2)	6	9	irPR confirmed	4	1	
1106011	67	M	IV M1c	surgery (3), immunotherapy (ipilimumab)	5	8	irPR confirmed	1	1	
1106013	85	M	IV M1c	surgery	3	6	irPR	4	1	
1106014	69	F	IV M1a	surgery (2)	1	4	not assessed yet	1	1	
1116001	75	M	IV M1a	surgery (3)	5	7 [2]	irPR	3	1	

[1] Pembrolizumab dose held at Day 50 due to AE of grade 2 sinusitis. Subject subsequently withdrawn due to PD.
[2] Further CVA21 inejctions held as no injectable mass
[3] Pembrolizumab and CVA21 dose held after Day 29 due to grade 4 sepsis. Subject subsequently withdrawn.

* includes new lesions
+ T-VEC, talimogene Laherparepvec

Safety*

MedDRA Preferred Term	Related to CAVATAK (n%)					Related to Pembrolizumab (n%)				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhoea	1/(8)	-	-	-	-	2/(15)	1/(8)	-	-	-
Gastro-esophageal reflux disease	1/(8)	-	-	-	-	1/(8)	-	-	-	-
Chills	-	-	-	-	-	-	1/(8)	-	-	-
Fatigue	1/(8)	-	-	-	-	2/(15)	-	-	-	-
Decreased appetite	2/(15)	-	-	-	-	1/(8)	-	-	-	-
Erythema	1/(8)	-	-	-	-	-	-	-	-	-
Rash	-	-	-	-	-	1/(8)	-	-	-	-
Skin mass	1/(8)	-	-	-	-	-	-	-	-	-
Vitiligo	-	-	-	-	-	1/(8)	-	-	-	-

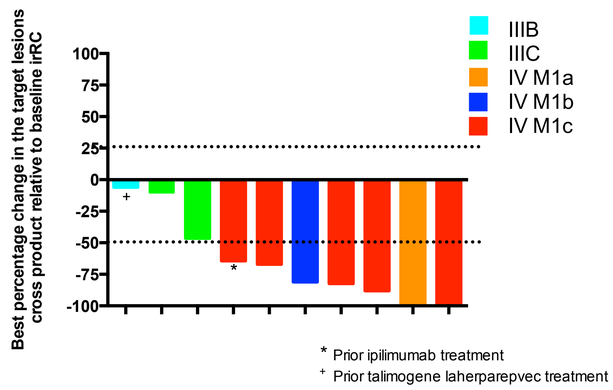
* Preliminary analysis, adverse events from 8 of 12 treated patients using Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0

Tumor Response

Best Overall Response Rate	
BORR (CR+PR, irRC):	70.0% (7/10 pts)* [7PR]
Disease control Rate (CR+PR+SD)	100 % [7PR + 3SD]

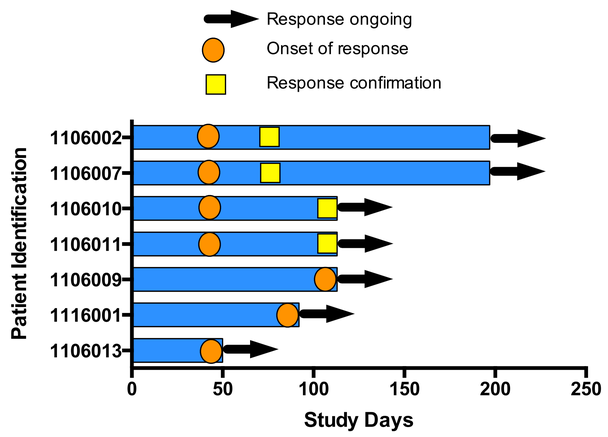
*, Preliminary data, investigator assessed n=10 pts; Pt1106006 terminated study prior to response assessment due to a unrelated-treatment SAE;

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

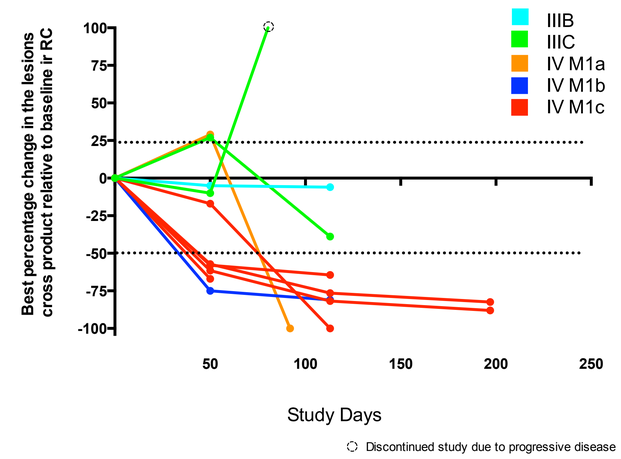


* Prior ipilimumab treatment
+ Prior talimogene laherparepvec treatment

Duration of Response irRC criteria *(Preliminary data, investigator assessed)*

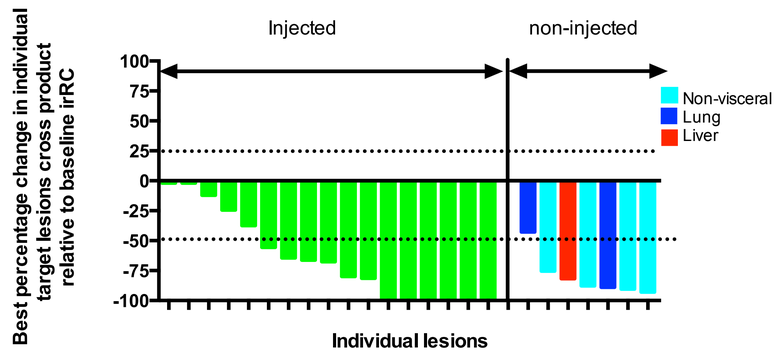


Changes in tumor burden by disease stage*
(Preliminary data, investigator assessed)

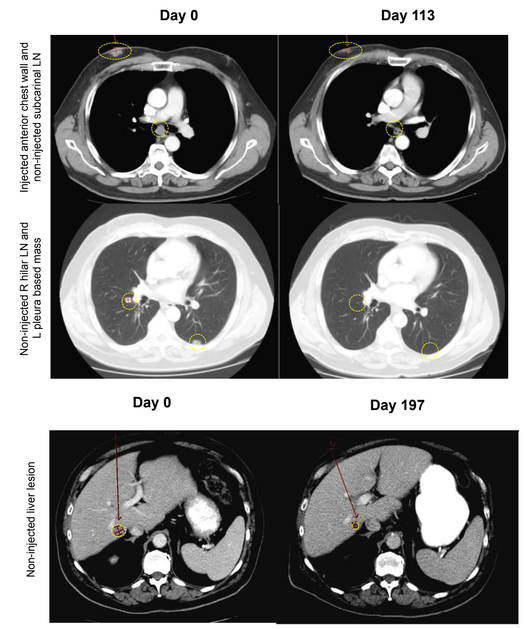


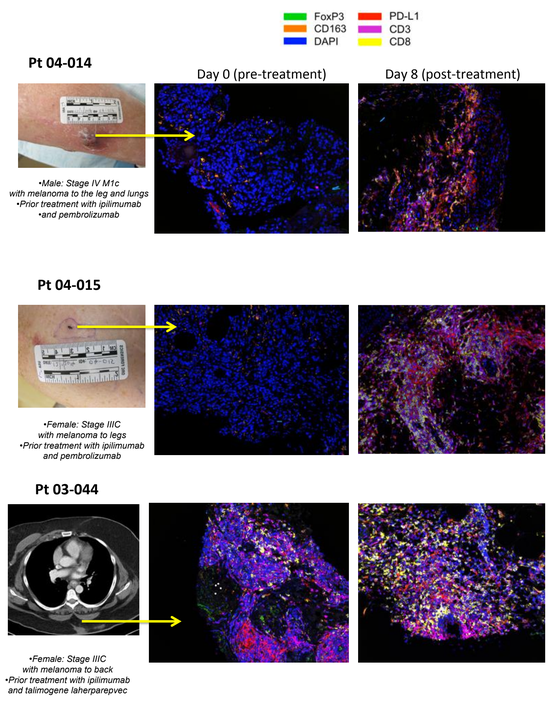
◌ Discontinued study due to progressive disease

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



Individual Patient Response (*investigator assessed)*





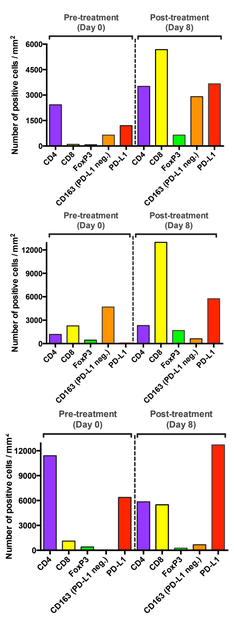
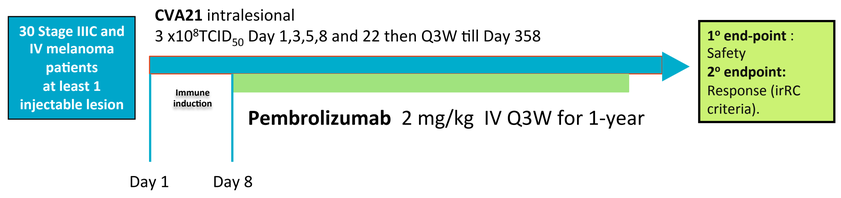


Figure 1. Phase II CALM-extension study: Multispectral imaging of immune-cell infiltrates and PD-L1 expression in day 0 and day 8 tumor biopsies (Multispectral Images obtained and enumerated with PerkinElmer Vectra imaging system and InForm Software) following intratumoral injection of CVA21.

Study Design



Conclusions

- From the first 12 patients enrolled, one patient has left the study with PD and one patient due to a non treatment-related adverse event.
- At present No DLT's have been observed in patients receiving the combination treatment.
- Overall, adverse events have generally been low-grade constitutional symptoms related to CVA21 and standard pembrolizumab-related side effects. No grade 3 or higher treatment-related adverse events have been observed.
- CVA21-pembrolizumab combination therapy was associated with clinical benefit in treated patients.
- Preliminary Best Overall Response Rate (BORR) of 70.0% % (7/10 pts) and 3/10 pts with Stable Disease.
- In patients with stage IV M1b/c disease a BORR of 100% (6/6 pts).
- Preliminary observations have revealed 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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Viralytics Developers of Oncolytic Immunotherapies

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