#CT026 Phase Ib study of intratumoral oncolytic Coxsackievirus A21 (CVA21) and systemic pembrolizumab in subjects with advanced melanoma: Interim results of the CAPRA clinical trial

[1]Ann W. Silk, [1]Howard L. Kaufman, [2]Nashat Gabrail, [3]Mark Faries, [1]Janice Mehnert, [1]Jennifer Bryan, [1]Jacqueline Norrell, [1]Daniel Medina, [1]Praveen K. Bommareddy, [4]Darren Shafren, [4]Mark Grose and [1]Andrew Zloza

[1]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ/US; [2] Gabrail Cancer Center, Canton, OH/US; [3]John Wayne Cancer Institute, Santa Monica, CA; [4]Viralytics Limited Sydney, NSW/AU

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-IFN 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 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 the combination of CVA21 and pembrolizumab based on increased expression of PD-L1 following virus administration and higher response rates of pembrolizumab in patients with elevated tumor PD-L1.

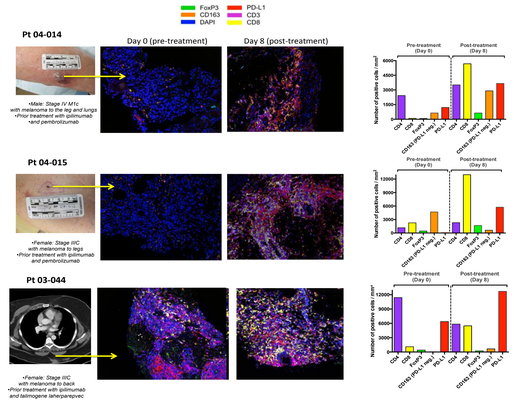
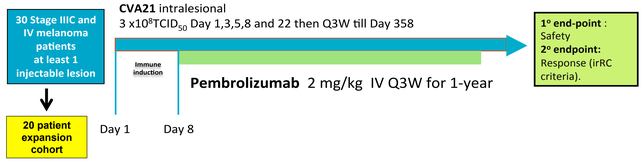


Figure 1. Phase II CALM-extension study: Multispectral imaging of immune-cell infiltrates and PD-L1 expression in day 0 and day 8 tumor biopsies (Multispectral Images obtained and enumerated with PerkinElmer Vectra imaging system and InForm Software) following intratumoral injection of CVA21.

Study Design



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)
1105001	76	F	IIIB	surgery (2)	3	4 [2]	irCR	3	2	
1105003	66	F	IV M1c	surgery (2)	1	4	not assessed yet	5	1	
1106001	84	M	IV M1a	none	3 [1]	6	irSD	2	2	PD Day 99
1106002	75	M	IV M1c	none	14 [1]	11	irPR confirmed	3	4 [4]	
1106003	70	M	IIIB	surgery (5)	2	5	not assessed yet	2	2	
1106004	83	M	IIIB	immunotherapy (T-VEC)	14	15	irSD	3	6*	Index lesions excised Day 279
1106006	73	F	IV M1c	surgery (2)	2 [3]	5 [3]	not evaluable	10	2	Grade 4 sepsis Day 48 (unrelated)
1106007	83	M	IV M1c	none	15	7 [2]	irPR confirmed	8	4	
1106008	50	M	IIIC	surgery	15	11 [2]	irPR confirmed	3	5 [4]	
1106009	94	M	IV M1c	surgery, radiotherapy (1)	12	11 [2]	irPR confirmed	4	2	
1106010	64	M	IV M1b	surgery (2)	14	10 [2]	irPR confirmed	4	1	
1106011	67	M	IV M1c	surgery (3), immunotherapy (ipilimumab)	9 [1]	12 [2]	irPR confirmed	1	1	
1106013	85	M	IV M1c	surgery	11	14	irPR confirmed	4	3	
1106014	69	F	IV M1c	surgery (2)	7	10	SD	3	1	
1106015	65	M	IV M1b	surgery	5	8	irPD	3	8	
1106016	76	M	IIIC	surgery	5	5 [2]	irPR	3	3 [4]	
1106017	73	M	IV M1b	surgery (2)	3	6	irSD	2	8 [4]	
1106019	53	F	IV M1a	surgery (2), immunotherapy (ipilimumab)	1	4	not assessed yet	11	3	
1116001	75	M	IV M1b	surgery (3)	5	7 [2]	irSD	3	1	

[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

Safety*

Treatment-emergent Adverse Events

Preferred Term	Total (N=19) Total N(%)	Total (N=19) Grade 3+ N(%)
Any event	13 (68%)	5 (26%)
Any attributable to CVA21	6 (32%)	0
Any attributable to pembrolizumab	10 (53%)	0
Diarrhoea	5 (26%)	0
Rash	5 (26%)	0
Decreased appetite	4 (21%)	0
Fatigue	4 (21%)	0
Chills	2 (11%)	0
Dry mouth	2 (11%)	0
Erythema	2 (11%)	0
Oedema peripheral	2 (11%)	0
Anaemia	1 (5%)	1 (5%)
Hyperglycaemia	1 (5%)	1 (5%)
Localised infection	1 (5%)	1 (5%)
Pneumonia	1 (5%)	1 (5%)
Sepsis	1 (5%)	1 (5%)

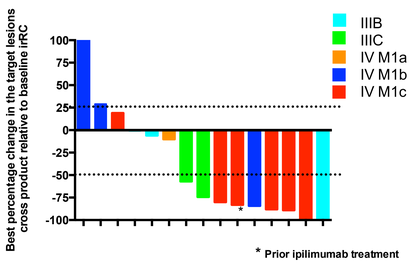
* Preliminary analysis, adverse events from 19 treated patients using Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0

Tumor Response

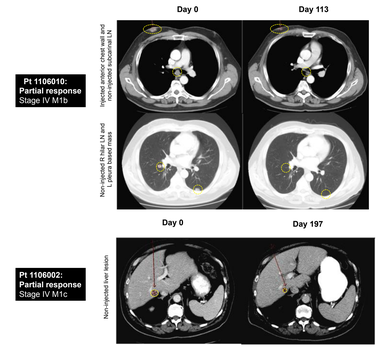
Overall Response	N=15
BORR (CR + PR)	60% (9/15)
DCR (CR + PR +SD)	87% (13/15)

*, Preliminary data, investigator assessed n=15 pts; Pt1106006 terminated study prior to response assessment due to an unrelated-treatment SAE.

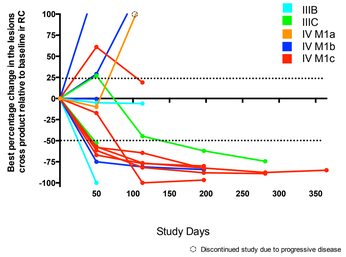
Best Overall Response (ITT) irRC criteria *(Preliminary data, investigator assessed)*



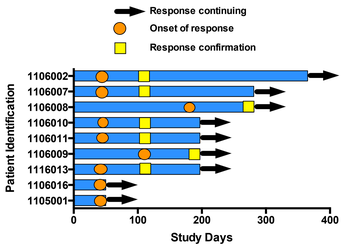
Individual Patient Response (*investigator assessed*)



Change in Tumor Burden by Disease Stage *(Preliminary data, investigator assessed)*



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



Conclusions

- From the first 19 patients, 3 patients have withdrawn from the study, one patient with PD, one patient following excision of index lesions 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.
- From the first 15 patients evaluable for investigator response assessment, we have observed a preliminary Best Overall Response Rate (BORR) of 60% (9/15 pts) and 4/15 pts with Stable Disease.
- In patients with stage IV M1c disease a BORR of 83% (5/6 pts).
- Based on these initial positive results, the sample size has now been expanded to enroll up to 50 patients, including patients refractory to anti-PD1 therapy.
- Combination therapy of CVA21 and pembrolizumab may represent a new approach for the treatment of patients with injectable advanced melanoma.

Viralytics
Developers of Oncolytic Immunotherapies

RUTGERS Cancer Institute of New Jersey
RUTGERS HEALTH

AACR 2017, April 1-5, Washington, DC, USA *Corresponding author: Ann Silk, as2300@cinj.rutgers.edu*