Intralesional administration of Coxsackievirus A21 (CVA21) oncolytic virus immunotherapy in patients with advanced melanoma induces durable tumour responses

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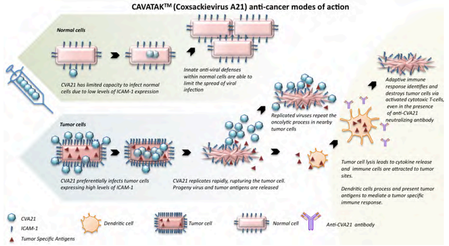
Introduction

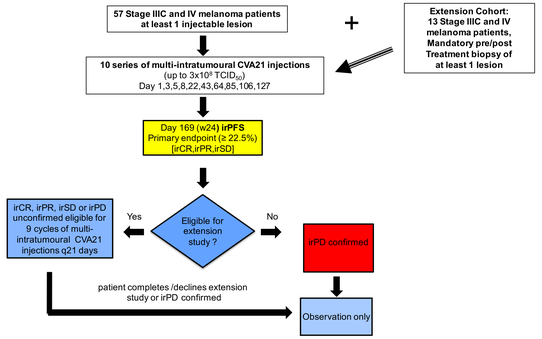
Coxsackievirus A21 (CVA21: CAVATAK™) is a naturally occurring "common cold" intercellular adhesion molecule-1 (ICAM-1) targeted RNA virus. Surface ICAM-1 is up-regulated on a number of cancers including melanoma, non-small cell lung, bladder, breast and prostate cancers. CAVATAK™ is a novel bio-selected formulation of CVA21, which displays potent oncolytic activity against *in vitro* cultures of cancer cells and *in vivo* xenografts of a number of cancers. In addition, *in vivo* tumour challenge studies in immune-competent mouse models have shown that CVA21 lysed tumour cells can induce a secondary systemic host-generated anti-tumour immune response.

Mode of action



Study Design

Phase 2: CALM study design
(CAVATAK in **L**ate **S**tage **M**elanoma)



Results

Patient Characteristics

		Number (n=57)	Percent (%)
Age	Mean (yrs)	57	
	(range)	(28-94)	
ECOG status	0	43	75%
	1	14	25%
Sex	Male	36	63%
	Female	21	37%
Race	Caucasian	56	98%
	Asian	1	2%
Stage at screening	IIIC	22	39%
	IV M1a	14	25%
	IV M1b	9	16%
	IV M1c	12	21%

Safety and Toxicity

Adverse Event†	Grade 1* n (%)	Grade 2 n(%)	Grade 3 n(%)	Grade 4 n(%)
Injection site pain	16 (28%)	2 (4%)		
Tiredness (fatigue)	15 (26%)	2 (4%)		
Chills	15 (26%)			
Pyrexia	7 (12%)			
Injection site erythema	7 (12%)			
Pain	6 (11%)	1 (2%)		
Myalgia	6 (11%)			
Headache	6 (11%)			
Hyperhidrosis	5 (9%)			
Peripheral edema		1 (2%)		
Erythema		1 (2%)		
Musculoskeletal stiffness		1 (2%)		
Rash		1 (2%)		

*only Grade 1 adverse events occurring in 5 or more patients are listed
†AE coded using Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0

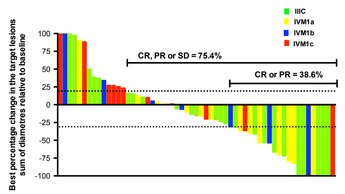
Patient Response Data*

Primary endpoint	
irPFS 6 months (CR+PR+SD)	38.6% (22/57 pts)

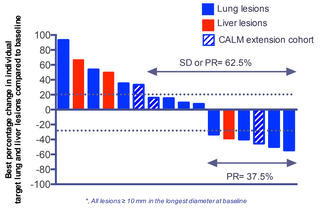
Secondary endpoints	
Overall response rate* (CR+PR, irRECIST 1.1):	28.1% (16/57 pts) [8CR + 8PR] ‡
Durable response rate+	21.1%
Median Time to response onset	3.4 months (95% CI: 1.5, 4.2)
Median irPFS	5.7 months (95% CI: 2.8, 11.1)
Median Overall survival	26.7 months (95% CI: 17.4, 34.5)
1-year survival rate:	75.4% (43/57 pts)

*, Investigator assessed
‡ 3 CR responses unconfirmed at time of data cut-off
+Durable response is a response lasting continuously for ≥ 6 months as assessed by irRECIST 1.1 criteria

Best Percentage changes in Target lesions

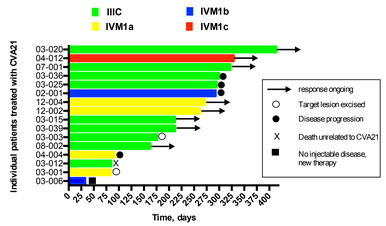


Best Percentage changes in non-injected target lung and liver lesions*



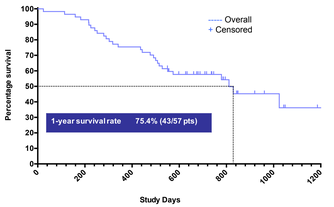
*, All lesions ≥ 10 mm in the longest diameter at baseline

Duration of Response



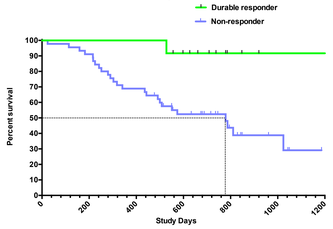
Survival

Kaplan-Meier curve of Interim overall survival

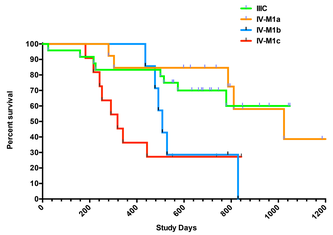


Treatment Group	No. of Subjects	Event (%)	Censored (%)	Median Survival (95% CI)
Overall	57	30 (52.6%)	27 (47.4%)	26.7 months (95% CI: 17.4, 34.5)

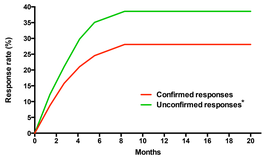
Kaplan-Meier curve of Durable responder versus Non-responder survival



Kaplan-Meier curve of survival based on Stage of disease



Time to Response Onset

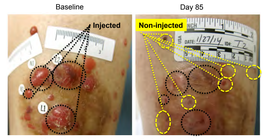


Median time to response onset	
Confirmed responses (n=16)	3.4 months (95% CI: 1.5, 4.2)
Unconfirmed responses (n=22)	3.4 months (95% CI: 1.5, 4.2)

*, Response episode unable to be confirmed 4-6 weeks following onset due to disease progression or patient lost to follow-up

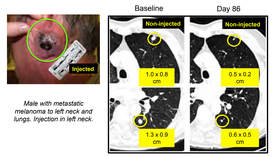
Patient Responses

Pt 12-002: Local injected and non-injected lesion responses



Male with metastatic melanoma to the leg. Injection in leg lesions

Pt 03-032: Non-injected distant visceral lesion response



Male with metastatic melanoma to left neck and lungs. Injection in left neck.

Conclusions

- The CALM study achieved its primary endpoint with 22/57 pts (38.6%) irPFS at 6 months.
- Responses were observed in injected lesions, non-injected non-visceral lesions and in distant non-injected visceral lesions.
- Multi-dose intralesional therapy with CVA21 was generally well tolerated (*No Grade 3 or 4 treatment related AEs*).

Future Directions

- The observation of CVA21-induced immune cell infiltration in injected melanoma lesions (*see Poster P213*) suggests that combination of this treatment with checkpoint inhibitors such as anti-CTLA-4 and/or anti-PD-1 might result in enhanced antitumour activity.
- Clinical evaluation of the activity of intralesional injection of CVA21 in combination with systemic administration of ipilimumab in patients with unresectable melanoma is currently underway (Phase1b MITCI study: *ClinicalTrials.gov Identifier:NCT02307149*) (*see Poster P213*).
- Further evaluations of both intralesional and intravenous administration of CVA21 in combination with additional immune checkpoint inhibitors are in planning.

ESMO 2015, September 25-29, Vienna, AUSTRIA. *Corresponding author, Robert Andtbacka: robert.andtbacka@hci.utah.edu*