Phase II CALM Extension study: Intratumoral CAVATAK™ increases immune-cell infiltrates and up-regulates immune-checkpoint molecules in the microenvironment of lesions from advanced melanoma patients


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Coxsackie virus A21: The basic facts

- “Common cold” virus
- Approximately 80-85% patients lack pre-existing neutralizing antibodies
- Non-enveloped *Picornavirus*
- A positive-strand RNA genome, ~7500 nt
- Viral capsid approximately 25 nm diameter
- Major cellular receptor is intercellular adhesion molecule-1 (ICAM-1)
- Rapid lytic cell infection
- Acid-resistant, stable in pH range 3.5-9.5
Coxsackievirus A21 (CVA21) an oncolytic immunotherapeutic agent

- Proprietary formulation of the bio-selected oncolytic virus, Coxsackievirus A 21
- Not genetically modified
- Targeted to specific receptor over expressed on cancer cells (human ICAM-1)
- Does NOT bind rodent ICAM-1
- Rapid cytoplasmic replication
- Kills local and metastatic cells by oncolytic and immunotherapeutic activity
- Potential application across a range of cancer types
  - Prostate, lung, melanoma, bladder and more
- Well tolerated in patients with to date no treatment-related grade 3 or 4 adverse events
- Potential application as monotherapy or with other new agents
Coxsackievirus A21
Oncolytic immunotherapeutic modes of action

CVA21 has limited capacity to infect normal cells due to low levels of ICAM-1 expression.

CVA21 preferentially infects tumor cells expressing high levels of ICAM-1.

CVA21 replicates rapidly, rupturing the tumor cell. Progeny virus and tumor antigens are released.

Adaptive immune response identifies and destroys tumor cells via activated cytotoxic T-cells, even in the presence of anti-CVA21 neutralizing antibody.

Tumor cell lysis leads to cytokine release and immune cells are attracted to tumor sites.

Dendritic cells process and present tumor antigens to mediate a tumor specific immune response.
Phase II CALM study: Study Design*

**Phase 2: CALM study design**

(CAVATAK in Late Stage Melanoma)

- 57 Stage IIIIC and IV melanoma patients at least 1 injectable lesion
- 10 series of multi-intratumoral CVA21 injections (up to $3 \times 10^8$ TCID$_{50}$)
  Day 1,3,5,8,22,43,64,85,106,127
  
Day 169 (w24) irPFS
Primary endpoint (≥ 22.5%)
  [irCR, irPR, irSD]

- If irCR, irPR, irSD or irPD unconfirmed eligible for 9 cycles of multi-intratumoral CVA21 injections q21 days

- Eligible for extension study? Yes/No
  - Yes
  - irPD confirmed
  - Observation only
  - Patient completes or declines extension study or irPD confirmed

- No
**Phase II CALM study: Patient Response Data**

<table>
<thead>
<tr>
<th><strong>Primary endpoint</strong></th>
<th><strong>Secondary endpoints</strong></th>
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<tbody>
<tr>
<td>irPFS 6 months (CR+PR+SD)</td>
<td>Overall response rate* (CR+PR, irRECIST 1.1):</td>
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<tr>
<td></td>
<td>Durable response rate+</td>
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<tr>
<td></td>
<td>Median Time to response onset</td>
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<td>Median irPFS</td>
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<td></td>
<td>Median Overall survival</td>
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<td>1-year survival rate:</td>
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* | 28.1% (16/57 pts) [8CR + 8PR] # |
+ | 21.1% |
| 3.4 months (95% CI: 1.5, 4.2) |
| 5.7 months (95% CI: 2.8, 11.1) |
| 26.7 months (95% CI: 17.4, 34.5) |
| 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
Phase II CALM study: Best Percentage changes in non-injected target lung and liver lesions*

Best percentage change in individual target lung and liver lesions compared to baseline

- Lung lesions
- Liver lesions
- CALM extension cohort

SD or PR = 62.5%
PR = 37.5%
Phase II CALM study: Overall survival
Durable responder versus Non-responder

Study Days

Percent survival

Study Days

Durable responder
Non-responder
Phase II CALM extension study

Phase 2: CALM study design
(CAVATAK in Late Stage Melanoma)

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

10 series of multi-intratumoral CVA21 injections (up to 3x10^3 TCID<sub>50</sub>)
Day 1, 3, 5, 8, 22, 43, 64, 85, 106, 127

Day 169 (w24) iRFDS
Primary endpoint (≥ 22.5%)
[irCR, irPR, irSD]

irCR, irPR, irSD or irPD unconfirmed eligible for 9 cycles of multi-intratumoral CVA21 injections q21 days

Yes

Eligible for extension study?

No

irPD confirmed

Observation only

patient completes/declines extension study or irPD confirmed

Extension Cohort
13 Stage IIIC and IV melanoma patients, Mandatory pre/post Treatment biopsy of at least 1 lesion
Phase II CALM-ext study: Multispectral Analysis

Pt 04-015

Female: Stage IIIC with melanoma to legs
Prior treatment with ipilimumab and pembrolizumab

Pt 03-043

Male: Stage IIIC with melanoma to the feet
Prior treatment with surgery

Day 0: Pre-treatment
Day 8: Post-treatment
CVA21-induces up-regulation of immune response genes in the micro-environment of melanoma lesions: NanoString digital RNA counts are normalized across each experiment relative to the expression of 40 housekeeping genes.
Phase II CALM-ext study: Changes in key immune checkpoint genes in CVA21 injected melanoma lesion (NanoString digital RNA counting)
Phase II CALM-ext study: Best CVA21 injected lesion response*

- Progression
- Disease control (CR + PR+ SD)

Percentage change from baseline to final tumor measurement

Patient Identification

03-045, 03-042, 03-043, 03-044, 03-048

* First response assessment at day 42
Phase II CALM-ext study: Levels of T-cell infiltrates and PD-L1 expression in progressing and disease control injected lesions

![Graph showing CD3+CD8+ and PD-L1+ cells/mm² over different days and treatment groups.](image-url)
Phase II CALM-ext study: Levels of viral RNA response and $\gamma$-interferon induced gene expression in progressing and disease control injected lesions.

**Progression**

- Patients (n=3)

**Disease Control**

- Patients (n=6)
Phase II CALM-ext study: Levels of **immune-checkpoint inhibitory gene expression** in progressing and disease control injected lesions.
Phase II CALM-ext study: Levels of **immune-checkpoint stimulatory gene expression** in progressing and disease control injected lesions

Progression

<table>
<thead>
<tr>
<th>Protein</th>
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<th>Disease Control</th>
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<tbody>
<tr>
<td>CD27</td>
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Change in RNA expression, relative units at Day 8 compared to Day 0
CD122 is the $\beta$-component of the IL-2 receptor complex

Increased expression of CD122, a potential marker for enhanced anti-tumor activity of CTLA-4 blockade

Hannani et al; 2015, Cell Research 25:208–224
VLA-013 MITCI Phase 1b Study Design

(\textit{MELANOMA INTRA-TUMORAL CAVATAK AND IPILIMUMAB})

- **1° end-point**: Safety
- **2° endpoint**: Response (irWHO criteria).

**26 Stage IIIIC and IV melanoma patients at least 1 injectable lesion**

**CVA21** intralesional

\[3 \times 10^8 \text{TCID}_{50} \text{ Day 1,3,5,8 and 22 then Q3W till Day 358}\]

**Ipilimumab** 3 mg/kg IV Q3W x 4

- Day 1
- Day 22
VLA-013 MITCI Phase 1b: Injected lesion Response

Best percentage change in the lesions cross product relative to baseline

ipi-N = ipilimumab naive
ipi-R = ipilimumab refractory
VLA-013 MITCI Phase 1b: Non-injected lesion response

Best percentage change in the lesions cross product relative to baseline

ipi-N
ipi-R
non-injected
VLA-013 MITCI Phase 1b: Best Overall Response

Best percentage change in the lesions cross product relative to baseline irRC

-100 -75 -50 -25 0 25 50 75 100

IIIC IV M1a IV M1b IV M1c

* Prior ipilimumab
+ Prior anti-PD1 or PD-L1
VLA-013 MITCI Phase 1b: Response by stage

- **Study days**: 0, 50, 100, 150, 200, 250, 300
- **Best percentage change in the lesions cross product relative to baseline**

**Graph Legend**
- **IIIc**: Green line
- **IV M1a**: Orange line
- **IV M1c**: Red line

**Ipilimumab**
- **3 mg/kg IV Q3W x 4**
VLA-013 MITCI Phase 1b Study: Partial tumor response Stage IV M1c (Pt 13-12003)
VLA-013 MITCI Phase 1b Study: Complete tumor response Stage IV M1a (Pt 13-04002)

Pre-treatment vs Post-treatment (day 190)
VLA-013 MITCI Phase 1b Study: Complete tumor response Stage IIIC (Pt 13-5001*)

Baseline

1 month

3 months

6 months

* Progression on prior anti-PD1 treatment (nivolumab)
Conclusions and Future Directions

• CVA21 treatment facilitated notable changes within the tumor microenvironment by inducing increases in immune cell infiltrates (CD3+CD8+) and expression of PD-L1, in particular within lesions displaying stable disease or response.

• CVA21 treatment significantly up-regulated a number of interferon-response and immune checkpoint inhibitory genes in injected melanoma lesions, including CXCL10, CXCL11, CTLA-4, PD-L1, LAG-3, TIM-3 and IDO.

• CVA21 treatment can potentially increase the “immunological heat” within the tumor microenvironment.

• The CVA21-ipilimumab combination immunotherapy treatment is generally well tolerated and has displayed anti-tumor activity in local, regional and distant systemic disease.

• The preliminary data confirmed overall response rate (80%) in ipilimumab naïve patients is higher than published rates for either agent used alone.

• Up-regulation of immune cell infiltrates and/or immune checkpoint inhibitory molecules in CVA21-treated lesions may be predictive of future tumor response, particularly in combination with immune checkpoint blockade strategies.
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• The CALM and MITCI study patients and families
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• MITCI study investigators
• CALM and MITCI study Clinical Trials Research Staff
• Viralytics Clinical Development team