Coxsackievirus A21 (CAVATAK™) - mediated oncolytic immunotherapy in advanced melanoma patients

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I have the following financial relationships to disclose:
Grant/Research support from: Viralytics

I will discuss the following off label use and/or investigational use in my presentation: CVA21 – this product is still investigational and not yet approved by the FDA
Melanoma intralymphatic metastasis

Spectrum of disease (AJCC IIIB/IIIC)

- 3 – 10% of primary melanoma develop local / in-transit recurrences
  - High risk groups: thick, ulcerated, positive SLN, lower extremity
- Source of significant morbidity
- Greater than 50% risk of distant disease and death

AJCC, American Joint Committee on Cancer; SLN, sentinel lymph node
Injectable intralesional therapy

Goals

• Locally ablative therapy for local disease control
  – High local concentration
  – Palliation / local symptom control

• Induction of systemic host immune anti-tumor activity
  – Response in un-injected regional and distant metastases
  – Limited systemic toxicity

• Systemic neoadjuvant effect
  – Preventing stage IIIB / IIIC patients from developing stage IV melanoma
Coxsackievirus A21 (CVA21)
Oncolytic immunotherapeutic modes of action
**CALM Phase II study Design**

**CAVATAK in Late stage Melanoma**

54 Stage IIIC 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 ($\geq 22.5\%$)

Eligible for Extension study
9 cycles of multi-intratumoral CVA21 injections
(up to $3 \times 10^8$ TCID$_{50}$) q21 days

Planned Interim DMC analysis: 35 patients

6 Weeks later, confirm Disease progression

Observation only
CALM Phase II trial
Local-injected lesion responses

Baseline

Day 127

Male with cutaneous melanoma on the chest. Injection in chest lesions.

Histopathological analysis confirmed complete melanoma regression.
CALM Phase II trial

Local injected and non-injected lesion responses

Baseline

Day 85

Male with metastatic melanoma to the leg. Injection in leg lesions.
CALM Phase II trial

Non-injected deep thigh lesion response

Female with metastatic melanoma to the thigh. Injection in left leg cutaneous lesion

Baseline 1.0 cm

Day 127 (18 wks) 0 cm
**CALM Phase II trial**

*Non-injected regional lymph node response*

- **Baseline**
  - 1.7 cm LN
- **Day 80 (11 wks)**
  - 1.0 cm LN

*Male with metastatic melanoma external iliac lymph node. Injection in external iliac lymph node. Response in non-injected common iliac lymph node.*
CALM Phase II trial
Non-injected chest wall distant lesion response

Male with metastatic melanoma to the chest. Injection in cutaneous metastatic arm lesion

<table>
<thead>
<tr>
<th>Date</th>
<th>Measurement</th>
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<tbody>
<tr>
<td>Screening</td>
<td>0.6 cm</td>
</tr>
<tr>
<td>Day 130 (18 wks)</td>
<td>Injection 10 1.1 cm</td>
</tr>
<tr>
<td>Day 262 (37 wks)</td>
<td>Ext. Injection 5 0 cm</td>
</tr>
</tbody>
</table>
CALM Phase II trial
Non-injected distant visceral lesion response

Baseline

Day 86

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

Injected

Non-injected

Baseline:
- Injected: 1.0 x 0.8 cm
- Non-injected: 1.3 x 0.9 cm

Day 86:
- Injected: 0.6 x 0.5 cm
- Non-injected: 0.5 x 0.2 cm
CALM Phase II trial
Investigating mechanism driving CVA21-mediated anti-tumor activity

• Assess host immune competence with regard to developing anti-viral serum response

• Assess the appearance of tumor response with regard to time of developing anti-viral serum response

• Assess serum levels of cytokines that are regarded as being involved in host-mediated anti-tumor responses
CALM Phase II trial

Patient anti-viral immune response:
Serum neutralizing antibody levels *

- All objective tumor responses started in the presence of high level of anti-CVA21 neutralizing antibody and absence of circulating infectious virus
- 96.5% of patients developed significant anti-CVA21 antibody levels (>1:16) by study day 22

* Preliminary on-going analysis
CALM Phase II trial

Patient serum* cytokine levels to CVA21 treatment +

* Serum prior to CVA21 injection from patients with CR, PR or SD
* Preliminary on-going analysis
CALM Phase II trial

Preliminary analysis: Serum cytokine activity
(Patients with objective responses)
CALM Phase II trial

Interim analysis: Conclusions

- Multi-dose intralesional therapy with CVA21 is generally well tolerated (No Grade 3 or 4 treatment-related AEs)
- Achieved Primary endpoint
- Tumor responses observed in both injected lesions, non-injected non-visceral lesions and in distant non-injected visceral lesions at times of high level of anti-CVA21 neutralizing antibody and in the absence of circulating infectious CVA21
- Preliminary evidence of bio-marker activity (IL-8, γ-IFN) indicates possible host anti-tumor immune activity related to response
- Oncolytic and immunotherapeutic activities of CVA21 warrant further clinical evaluation of CVA21 in combination with other immunotherapeutic agents (e.g., immune checkpoint inhibitor strategies anti-CTLA-4 or anti-PD-1)
Assessment of combination of intralesional CVA21 and immune checkpoint antibody blockade (anti-PD-1) in an immune-competent C57BL mouse melanoma model

Implant B16-ICAM-1* cells into left flank

Day 0

Treatment with CVA21 or saline intratumoral (i.t) + anti-PD-1 or control mAb intraperitoneal (i.p)

Day 6 9 12 15

Day 19 26

Implant B16 cells into right flank

Day 31 33 40

Treatment with i.t CVA21 or saline

• B16-ICAM-1 cells are murine melanoma B16 cells stably transfected to express human ICAM-1 to allow CVA21 binding and cell infection

CVA21

1 × 10^8 TCID_{50} i.t

anti-PD-1 mAb 12.5 mg/kg

B16 cells re-challenge (Secondary tumor)
Combination of intralesional CVA21 and immune checkpoint antibody blockade (anti-PD-1)

Spider plot of Individual primary B16-ICAM-1 tumor growth*

Study Day 45

Saline + Control Ab

CVA21 + Control Ab

Saline + anti-PD-1

CVA21 + anti-PD-1

0% Tumor-free

0% Tumor-free

0% Tumor-free

75% Tumor-free

* Preliminary on-going analysis
Combination of intralesional CVA21 and immune checkpoint antibody blockade (anti-PD-1)

*Incidence of palpable secondary B16 tumor*

- **B16 cell re-challenge** (Secondary tumor Non-treated)

<table>
<thead>
<tr>
<th>Condition</th>
<th>% Incidence palpable 2° tumor</th>
<th>Tumour volume (mm³)</th>
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<tbody>
<tr>
<td>Saline + Control Ab</td>
<td>100% (6/6)</td>
<td>50</td>
</tr>
<tr>
<td>CVA21 + Control Ab</td>
<td>81.3% (5/6)</td>
<td>40</td>
</tr>
<tr>
<td>Saline + anti-PD-1</td>
<td>100% (9/9)</td>
<td>30</td>
</tr>
<tr>
<td>CVA21 + anti-PD-1</td>
<td>33.3% (4/12)</td>
<td>10</td>
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Study Day 42

*Preliminary on-going analysis*
Pre-clinical CVA21 and anti-PD1 blockade

Summary and Future Directions

• Following gross examination, CVA21 and anti-PD-1 mAb combination treatment appears to be generally well tolerated

• Significant anti-tumor activity using a combination of CVA21 and anti-PD-1 mAb in a pre-clinical animal model

• Clinical evaluation of a combination of CVA21 and PD-1 blockade in advanced melanoma patients is warranted
Acknowledgements

Many thanks to:

• The CALM study patients and families

• CALM study investigators
  Robert Andtbacka
  Brendan Curti
  Howard Kaufman
  Gregory A. Daniels
  Stephen Schultz
  Lynn E. Spitler
  Jose Lutzky
  Sigrun Hallmeyer
  Eric D. Whitman
  John J. Nemunaitis

• CALM study Clinical Trials Research Staff

• Viralytics Clinical Development team
  Roberta Karpathy
  Leanne Stootman
  Bronwyn Davies
  Gough Au
  Jackie Burgess
  Rebecca Ingham
  Erin Green
  Susanne Johansson
  Penny Yates
  Robert Herd
  Eric Chan
  Min Quah
  Yvonne Vern Vee
  Richard Barry