Phase I/II STORM study: Intravenous delivery of a novel oncolytic immunotherapy agent, CAVATAK, in advanced cancer patients

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CAVATAK™ (Coxsackievirus A21) an oncolytic immunotherapeutic agent

• Proprietary formulation of the oncolytic virus, Coxsackievirus A21
• Targeted to specific receptor over expressed on cancer cells (ICAM-1)
• Kills local and metastatic cells by oncolytic and immunotherapeutic activity
• Potential application across a range of cancer types
• Well tolerated in patients with to date no treatment-related grade 3 or 4 adverse events
• Potential intravenous as well as intratumoral and intravesical use
• Potential application as monotherapy or with other new agents
• Manufactured under cGMP at SAFC, California
Coxsackievirus A21 (CVA21)

Oncolytic immunotherapeutic modes of action

Normal cells

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

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

Tumor cells

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

Innate anti-viral defenses within normal cells are able to limit the spread of viral infection.

Replicated viruses repeat the oncolytic process in nearby tumor cells.

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.

\( \text{CVA21} \)

\( \text{ICAM-1} \)

\( \text{Dendritic cell} \)

\( \text{Tumor cell} \)

\( \text{Normal cell} \)

\( \text{Anti-CVA21 antibody} \)

\( \text{Tumor Specific Antigens} \)
Pre-clinical anti-tumor activity of mono-therapy intravenous CVA21 in orthotopic mouse model of Non-small cell lung cancer (NCI-H1299-luc⁺ cells)

Pre-treatment

45 days post-tumor cell administration
VLA-004: Phase I single dose intravenous CAVATAK in subjects bearing ICAM-1 expressing solid tumors

Study Design

10 subjects
advanced melanoma, prostate, breast or colorectal cancer

<1:16 anti-CAVATAK serum antibodies

↓

Single infusion

1 $\times 10^6$ TCID$_{50}$ n=3
1 $\times 10^8$ TCID$_{50}$ n=4
1 $\times 10^9$ TCID$_{50}$ n=2
1 $\times 10^{10}$ TCID$_{50}$ n=1

Study Endpoints

*Primary*

• Patient tolerability
• Determination of MTD

*Secondary*

• Pharmacokinetics of serum viral load and anti-CAVATAK antibodies
• Viral excretion
VLA-004 (Single dose IV study): Pharmacokinetics
Serum viral load (viral RNA)

Pt204: Melanoma (1x10^8)

30min post-CAVATAK infusion

Pt015: Melanoma (1x10^8)

FNA of subcutaneous lesion qRT-PCR positive for CVA21

Pt206: Prostate (1x10^9)

Limit of detection

Pt016: Prostate (1x10^9)

Limit of detection
VLA-004 conclusions

• CAVATAK IV fusion well tolerated
• No SAE related to CAVATAK
• No MTD reached
• Preliminary evidence of CAVATAK tumour targeting
• Preliminary evidence of secondary CAVATAK replication
• Significant levels of neutralising antibodies
• were detected by Day 5 to Day 12
• CAVATAK detected in some excretion samples day 5-20
VLA-009 (STORM study): Phase I/II multi-dose intravenous CAVATAK in subjects with advanced melanoma, prostate, NSCLC or bladder cancer

VLA-009A (Monotherapy)

27 subjects with advanced melanoma, prostate, NSCLC or bladder cancer with <1:16 anti-CAVATAK serum antibodies

IV infusions of CAVATAK on Day 1,3,5,21,43,64,85,106,127,158

Cohort 1
Any cancer
1 x 10^8 TCID_{50}
$n=3$

Cohort 2
Any cancer
3 x 10^8 TCID_{50}
$n=3$

Cohort 3
1 x 10^9 TCID_{50}
Mandatory lesion biopsy
Melanoma, NSCLC, Bladder And Prostate cancer $n=3$ each

VLA-009B (Chemotherapy combination)

IV infusions of CAVATAK Day 1,3,5,21,43,64,85,106,127,158 + Docetaxel or Carbo/Pac every 3 weeks

Cohort 1
Selected cancer
1 x 10^9 TCID_{50}
+ Docetaxel or Carbo/Pac
$n=3$

Cohort 2
Selected cancer
3 x 10^8 TCID_{50}
+ Docetaxel or Carbo/Pac
$n=3$

Cohort 3
Selected cancer
1 x 10^9 TCID_{50}
+ Docetaxel or Carbo/Pac
$n=3$

Study Endpoints

Primary
- Patient tolerability
- Determination of MTD

Secondary
- Pharmokinetics of serum viral load and anti-CAVATAK antibodies
- Viral excretion
- Level of viral replication in tumor
- Virus-induced tumor cell infiltrates and immune checkpoint molecules
## VLA-009 (STORM study): Patient characteristics

<table>
<thead>
<tr>
<th>Cohort</th>
<th>ID</th>
<th>Gender</th>
<th>Cancer Indication</th>
<th>Previous Lines of Treatment</th>
<th>Duration of Treatment (cycles)</th>
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<tbody>
<tr>
<td>1</td>
<td>03-001</td>
<td>Male</td>
<td>NSCLC</td>
<td>Chemotherapy x3, clinical trial (AZD4547), lobectomy (RUL, RML)</td>
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<td>03-002</td>
<td>Male</td>
<td>Melanoma</td>
<td>Chemotherapy x2, resection</td>
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<td>02-001</td>
<td>Male</td>
<td>Bladder</td>
<td>Chemotherapy x3, radiotherapy</td>
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<tr>
<td>2</td>
<td>02-002</td>
<td>Male</td>
<td>Bladder</td>
<td>Immunotherapy, chemotherapy, TUR x 2</td>
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<td>01-001</td>
<td>Male</td>
<td>Prostate</td>
<td>Hormonal therapy x6, clinical trial (ONY-P-1), radiotherapy, chemotherapy</td>
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<tr>
<td></td>
<td>02-003</td>
<td>Male</td>
<td>NSCLC</td>
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<tr>
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<td>01-005</td>
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<td>Hormonal therapy x2, radiotherapy, immunotherapy</td>
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<td>Hormonal therapy x4, radiotherapy</td>
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<td>Radiotherapy, hormone therapy, chemotherapy x2</td>
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<td>Vem, pembro</td>
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<tr>
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<td>03-006</td>
<td>Male</td>
<td>Melanoma</td>
<td>Ip, chemo, RT</td>
<td>2</td>
</tr>
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VLA-009 (STORM study): Product-related Adverse events

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<tr>
<th>AE Terminology</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
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<tbody>
<tr>
<td>Pyrexia</td>
<td>2 (18%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Fatigue</td>
<td>2 (18%)</td>
<td>1 (9%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Flu-like symptoms</td>
<td>2 (18%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Dry skin</td>
<td>1 (9%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bloating</td>
<td>1 (9%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1 (9%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lethargy</td>
<td>1 (9%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tbody>
</table>
VLA-009 (STORM study): Patient anti-viral immune response: Serum neutralizing antibody levels

83% (15/18) sero-negative patients

Reciprocal Log$_{10}$ anti-CVA21 neutralising antibody titer

Pos/Neg (1:16)
VLA-009 (STORM study): Individual patient anti-CAVATAK immune response

Cohort 1

Pt03-001: NSCLC (1x10⁸)

Pt03-002: Melanoma (1x10⁸)

Pt02-001: Bladder (1x10⁹)

Cohort 2

Pt02-002: Bladder (3x10⁸)

Pt01-001: Prostate (3x10⁸)

Pt02-003: NSCLC (3x10⁸)
VLA-004 (single-dose) and VLA-009 (multi-dose): Pharmacokinetics Serum anti-CAVATAK neutralising antibody development

VLA-004 single IV dose

VLA-009 multi IV dose

CAVATAK infusion

Anti-CAVATAK neutralising antibody titre

Days post-CAVATAK infusion
VLA-009 (STORM study): Individual lesion response and Pharmacokinetics of serum viral load (viral RNA): Cohort 1

- Pt03-001: NSCLC (1x10^8)
  
- Pt03-002: Melanoma (1x10^8)
  
- Pt02-001: Bladder (1x10^8)

**Hours post-CAVATAK infusion**

**CVA21 RNA copies/ml serum**

1hr post-CAVATAK infusion

Limit of detection

**Best percentage change in individual lesions compared to baseline**
VLA-009 (STORM study): Individual lesion response and Pharmacokinetics of serum viral load (viral RNA): Cohort 2

Pt02-002: Bladder (3x10^8)

Pt01-001: Prostate (3x10^8)

Pt02-003: NSCLC (3x10^8)

Patient terminated study before the 6-week response assessment

Limit of detection
VLA-009 (STORM study): Target lesion response: Patient 02-002 - Cohort 2

Pt 02-002: Cohort 2
Male with metastatic bladder cancer
Left level III/IV Lymph Node

23% reduction
VLA-009 (STORM study): Individual lesion response and Pharmacokinetics of serum viral load (viral RNA): Cohort 3 - Prostate

Pt01-005: Prostate (1x10⁹)
- Patient terminated study before the 6-week response due to disease progression

Pt01-006: Prostate (1x10⁹)

Pt03-005: Prostate (1x10⁹)
- Patient terminated study before the 6-week response due to disease progression

CVA21 RNA copies/ml serum

Limit of detection

Hours post-CAVATAK infusion
Pt 01-006: Cohort 3
Male with castrate resistant prostate cancer

External ILIAC Lymph Node

Day 0

Day 42

35% reduction
VLA-009 (STORM study): Individual lesion response and Pharmacokinetics of serum viral load (viral RNA): Cohort 3 - Melanoma

Pt02-005: Melanoma (1x10^9)

Waiting 6-week response assessment

Hours post-CAVATAK administration

Best percentage change in individual lesions compared to baseline

CVA21 RNA copies/ml serum

Limit of detection

Hours post-CAVATAK administration

Pt03-006: Melanoma (1x10^9)
VLA-009 (STORM study): CAVATAK tumor targeting: Biopsy Viral RNA levels : Cohort 3: $1.0 \times 10^9$ TCID$_{50}$ – Prostate and Melanoma

- **Prostate cancer**
  - Bone
  - Lymph node

- **Melanoma**
  - Soft tissue, Chest
  - Thigh lesion

Limit of detection qRT-PCR (1500 copies/mg RNA)
Planned biopsy tissue assessment from Cohort 3 patients: $1.0 \times 10^9 \text{TCID}_{50}$ for immune cell infiltrate and NanoString immune profiling.
VLA-009 (STORM Study): Conclusions

• Multi-dose intravenous administration to patients in Cohorts 1, 2 and 3 was well tolerated, with no Grade 3 or 4 product-related AE’s

• A number of patients have exhibited signs of possible tumor specific secondary viral replication

• Evidence of CVA21 tumor targeting with 2 of 2 melanoma patients in Cohort 3 displaying CVA21 RNA in tumor biopsies

• Interim data highlight a robust “multi-dosing-window” in the absence of significant levels of nAb for approximately 7 days post initial viral infusion

• Further clinical evaluation of intravenous delivered CVA21 in combination with immune checkpoint inhibitor strategies
Acknowledgements

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