Immune-checkpoint blockade in combination of a novel oncolytic immunotherapeutic agent, CAVATAK™ (Coxsackievirus A21) significantly reduces tumor growth and tumor rechallenge.
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Coxsackievirus 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

Cryo-EM CVA21-complexed with ICAM-1
CAVATAK™ (Coxsackievirus A21) 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

Cytoplasmic replication of CVA21 in non-muscle invasive bladder cancer
CAVATAK™ (CVA21)
Oncolytic immunotherapeutic modes of action

Normal cells
- CVA21 has limited capacity to infect normal cells due to low levels of ICAM-1 expression
- Innate anti-viral defenses within normal cells are able to limit the spread of viral infection

Tumor cells
- 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
- 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.

CVA21
ICAM-1
Dendritic cell
Tumor cell
Normal cell
Anti-CVA21 antibody

Tumor Specific Antigens
Current CAVATAK™ (Coxsackievirus A21) clinical trial program

CAVATAK

Intratumoral  Intravenous  Intravesicular

VLA-007/008 (CALM study): Phase II multi-dose intratumoral CAVATAK in subjects with advanced melanoma
n=70, USA *(Dr Andtbacka, Tumor microenvironment, Oral 53)*

VLA-009 (STORM study): Phase I/II multi-dose intravenous CAVATAK in subjects with advanced melanoma, prostate, NSCLC or bladder cancer.
n=30-40, UK *(Dr Pandha, Clinical Trials II, Oral 51)*

VLA-012 (CANON study): Phase I intravesicular CAVATAK in subjects NON-muscle invasive Bladder cancer
n=30-40, UK *(Poster P5)*

VLA-013 (MITCI study): Phase Ib multi-dose intratumoral CAVATAK and intravenous ipilimumab (anti-CTLA-4) in subjects with advanced melanoma
n=30, USA
Oncolytic activity of intravenous and intratumoral CAVATAK in immune-deficient mice bearing pancreatic cancer xenografts

Female Balb-C SCID mice bearing (Panc-1-luc⁺ cells) were administered a single I.V or I.T injection of CAVATAK (~10⁷ TCID₅₀) or saline
Construction a immune-competent mouse model of melanoma (B16 cells) for challenge with Coxsackievirus A21

A

B

C

D

Palpable tumor growth 4 days post-administration of B16-ICAM-1 (2 x 10^6 cells)
Assessment of combination of intralesional CAVATAK and immune checkpoint antibody blockade (anti-PD-1) in an immune-competent C57BL mouse melanoma model

* B16-ICAM-1 cells are murine melanoma B16 cells stably transfected to express human ICAM-1 to allow CAVATAK binding and cell infection
Combination of intralesional CAVATAK and immune checkpoint antibody blockade (anti-PD-1)

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

- **Saline + Control Ab**
- **CVA21 + Control Ab**
- **Saline + anti-PD-1**
- **CVA21 + anti-PD-1**

Study Day 45:
- 0% Tumor-free
- 0% Tumor-free
- 0% Tumor-free
- 75% Tumor-free

B16-ICAM-1 (Primary treated tumor)

*Pseudo-Progression?
Combination of intralesional CAVATAK and immune checkpoint antibody blockade (anti-PD-1)

Incidence of palpable secondary B16 tumor *

- **Study day**
- **% incidence 2o tumor**

- **Saline + Control Ab**
- **Saline + anti-PD-1**
- **CVA21 + Control Ab**
- **CVA21 + anti-PD-1**

B16 cell re-challenge (Secondary tumor Non-treated)
Combination of intralesional CAVATAK and immune checkpoint antibody blockade (anti-PD-1)

Survival*

*, mice sacrificed due >20% weight loss, tumor burden >2500mm³, ulceration of primary or re-challenge tumors
Assessment of combination of intralesional CAVATAK and immune checkpoint antibody blockade (anti-CTLA-4) in an immune-competent C57BL mouse melanoma model

1. Implant B16-ICAM-1* cells into left flank
2. Treatment of primary tumour with CAVATAK or saline intratumoral (i.t) + anti-CTLA-4 or control mAb intraperitoneal (i.p)
3. Implant B16 cells into right flank

Day 0
7 10 13 16
37

B16-ICAM-1 cells (Primary tumor)
CAVATAK 1×10⁸ TCID₅₀ i.t
anti-CTLA-4 mAb 12.5 mg/kg
B16 cells re-challenge (Secondary tumor)

* B16-ICAM-1 cells are murine melanoma B16 cells stably transfected to express human ICAM-1 to allow CAVATAK binding and cell infection
Combination of intralesional CAVATAK and immune checkpoint antibody blockade (anti-CTLA-4)

Spider plot of Individual primary B16-ICAM-1 tumor growth*
Combination of intralesional CAVATAK and immune checkpoint antibody blockade (anti-CTLA-4)

Incidence of palpable secondary B16 tumor *

- **Saline + Control Ab**
- **Saline + anti-CTLA-4**
- **CVA21 + Control Ab**
- **CVA21 + anti-CTLA-4**
Combination of intralesional CAVATAK and immune checkpoint antibody blockade (anti-CTLA-4)

Survival*

* mice sacrificed due >20% weight loss, tumor burden >2500mm³, ulceration of primary or re-challenge tumors
Intravenous delivered CAVATAK-induced gene changes in human melanoma

- **Implant human SK-Mel 28 cells into left flank**

- **Treatment of tumor with CAVATAK or saline intravenous (i.v)**

- **Sacrifice mice and excise tumor post-treatment**

- **Day 0**
- **Day 14**

- **Excise tumor for viral and cellular gene profiling**

- **Tumor gene profiling**
CAVATAK-induced up regulation of IFN-γ inducible protein 10 (CXCL10) and PD-L1 in melanoma xenografts

**CAVATAK-tumor replication kinetics**

**Tumor gene profiling**

(HumanREf-8 v2 expression bead chips, illumina)

CXCL10 a chemokine secreted from cells exposed to IFN-γ and plays an important role in recruiting activated T-cells into sites of tissue inflammation
Assessment of combination of intravenous CAVATAK and immune checkpoint antibody blockade (anti-CTLA-4 and/or anti-PD-1) in an immune-competent C57BL mouse melanoma model

- **Implant B16-ICAM-1* cells into left flank**
- **Treatment of primary tumour with CAVATAK or saline intravenous (i.v) + anti-CTLA-4, anti-PD-1 or control mAb intraperitoneal (i.p)**
- **Implant B16 cells into right flank**

Day 0: 7, 10, 13, 16, 30

* B16-ICAM-1 cells are murine melanoma B16 cells stably transfected to express human ICAM-1 to allow CAVATAK binding and cell infection
Combination of intravenous CAVATAK and immune checkpoint antibody blockade (anti-CTLA-4 and/or anti-PD-1)

Spider plot of Individual primary B16-ICAM-1 tumor growth
Combination of intravenous CAVATAK and immune checkpoint antibody blockade (anti-CTLA-4 and/or anti-PD-1)

Incidence of palpable secondary B16 tumor

Days post tumor rechallenge

% incidence 2° tumour

Saline + Control Ab
anti-CTLA-4
anti-PD-1
CVA21 + Control Ab
anti-CTLA-4 + CVA21
anti-PD-1 + CVA21
anti-CTLA-4 + anti-PD-1 + CVA21

B16 cell re-challenge (Secondary tumor)
Combination of intravenous CAVATAK and immune checkpoint antibody blockade (anti-CTLA-4 and/or anti-PD-1)

Survival proportions: Saline vs anti-PD-1 + CVA21

Survival proportions: Saline vs anti-CTLA-4 + CVA21

Survival proportions: Saline vs anti-CTLA-4 + anti-PD-1 + CVA21

*, mice sacrificed due >20% weight loss, tumor burden >2500mm³, ulceration of primary or re-challenge tumors
Combination of intravenous CAVATAK and immune checkpoint antibody blockade (anti-CTLA-4 and/or anti-PD-1)

Survival proportions: anti-CTLA-4 vs anti-CTLA-4 + CVA21

- Survival proportion: anti-CTLA-4
- Survival proportion: anti-CTLA-4 + CVA21

*p = 0.1624

Survival proportions: anti-PD-1 vs anti-PD-1 + CVA21

- Survival proportion: anti-PD-1
- Survival proportion: anti-PD-1 + CVA21

**p < 0.0074

Survival proportions: anti-CTLA-4 vs anti-CTLA-4 + anti-PD-1 + CVA21

- Survival proportion: anti-CTLA-4
- Survival proportion: anti-CTLA-4 + anti-PD-1 + CVA21

**p < 0.0041

Survival proportions: anti-PD-1 vs anti-CTLA-4 + anti-PD-1 + CVA21

- Survival proportion: anti-PD-1
- Survival proportion: anti-CTLA-4 + anti-PD-1 + CVA21

****p < 0.0001

*, mice sacrificed due >20% weight loss, tumor burden >2500mm$^3$, ulceration of primary or re-challenge tumors
• Following gross examination, CAVATAK and anti-PD-1 or anti-CTLA-4 mAb combination treatment appears to be generally well tolerated

• Significant anti-tumor activity using a combination of CAVATAK (intratumoral or intravenous) and anti-PD-1 or anti-CTLA-4 mAbs in a pre-clinical animal model of melanoma

• The current model provides capacity to assess different sequences of CAVATAK, anti-PD-1 or anti-CTLA-4 mAbs administration.

• Clinical evaluation of a combination of CAVATAK and PD-1 or CTLA-4 blockade in advanced cancer patients with ICAM-1 expression solid tumors is warranted.
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