Clinical evaluation of a novel oncolytic immunotherapy agent, CAVATAK® in combination with immune checkpoint therapy in advanced cancer patients

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CAVATAK®
an oncolytic immunotherapeutic agent

• Proprietary formulation of the bio-selected oncolytic virus, Coxsackievirus A 21
• Not genetically modified positive-strand RNA virus
• Targeted to specific receptor over expressed on cancer cells (human 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
• Potential application as monotherapy or with other new agents
CAVATAK: Oncolytic immunotherapeutic modes of action in combination therapy
CALM study:
Phase II
Monotherapy Intratumoral CAVATAK in late stage melanoma
CALM Phase II Trial 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 \(3 \times 10^6\) TCID\(_{50}\))
Day 1,3,5,8,22,43,64,85,106,127

Day 169 (w24) irPFS
Primary endpoint (\(\geq 22.5\%\))
\([\text{irCR, irPR, irSD}]\)

Extension Cohort
13 Stage IIIC and IV melanoma patients, Mandatory pre/post Treatment biopsy of at least 1 lesion

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Day 1,3,5,8,22,43,64,85,106,127

Day 169 (w24) irPFS
Primary endpoint (\(\geq 22.5\%\))
\([\text{irCR, irPR, irSD}]\)

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
Male with metastatic melanoma to the leg. Injection in leg lesions.
CALM Phase II trial
NON-INJECTED DISTANT VISCERAL LESION RESPONSE

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

Baseline
Injected
Non-injected
Day 86
Non-injected

1.0 x 0.8 cm
1.3 x 0.9 cm
0.5 x 0.2 cm
0.6 x 0.5 cm

Courtesy Dr R Andtbacka, Lead Study Investigator, Huntsman Cancer Institute
Male with metastatic melanoma to lungs and liver.
CALM Phase II Trial: Best percentage change in the sum of target lesions*

Best percentage change in the sum of diameters relative to baseline

CR, PR or SD = 75.4%
CR or PR = 38.6%

<table>
<thead>
<tr>
<th>Best Overall Response* (irRECIST)</th>
<th>Per irRECIST</th>
</tr>
</thead>
<tbody>
<tr>
<td>irPFS 6 months (CR+PR+SD)</td>
<td>38.6% (22/57 pts)</td>
</tr>
<tr>
<td>Overall response rate*</td>
<td>28.1% (16/57 pts)</td>
</tr>
<tr>
<td>(CR+PR):</td>
<td>[8CR + 8PR] ‡</td>
</tr>
<tr>
<td>Durable response rate‡</td>
<td>21.1%</td>
</tr>
<tr>
<td>Median Time to response onset</td>
<td>3.4 months (95% CI: 1.5, 4.2)</td>
</tr>
</tbody>
</table>

* 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
CALM study: Biopsy sub-study
Phase II
Intratumoral CAVATAK in late stage melanoma
Phase II CALM-biopsy sub-study: Best CAVATAK injected lesion response*

Disease control (CR + PR+ SD)

Percentage change from baseline to final tumor measurement

Patient Identification

* First response assessment at day 42
Intratumoral CAVATAK increases immune infiltrates and PD-L1 expression in melanoma lesions

Pt 04-015

Day 0 (pre-treatment)

Day 8 (post-treatment)

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

Pt 04-014

Male: Stage IV M1c with melanoma to the leg and lungs
Prior treatment with ipilimumab and pembrolizumab

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

• Male: Stage IV M1c with melanoma to the leg and lungs
  • Prior treatment with ipilimumab and pembrolizumab
Intratumoral CAVATAK activates RIG-I pathway and increases expression of immune checkpoint target molecules in melanoma lesions

**RIG-I pathway activation**

**Progression**

- CXCL10
- CXCL11
- IFIT1
- IFIH1
- RIG-I (DDX58)

**Immune checkpoint molecules**

- A2AR
- B7-H3
- BTLA
- CTLA-4
- IDO
- LAG3
- PD-1
- PD-L1
- PD-L2
- TIM-3

**Disease Control**

- A2AR
- B7-H3
- BTLA
- CTLA-4
- IDO
- LAG3
- PD-1
- PD-L1
- PD-L2
- TIM-3
Phase II CALM-ext study: Levels of immune-checkpoint stimulatory gene expression in progressing and disease control injected lesions

**Progression**

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
MITCI study: Phase 1b Intratumoral CAVATAK in combination with ipilimumab (anti-CTLA-4) in late stage melanoma
Intratumoral CAVATAK + ipilimumab

*(MITCI study: NCT02307149)*

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

- **CAVATAK** intralesional
  - $3 \times 10^8 \text{TCID}_{50}$ Day 1, 3, 5, 8 and 22 then Q3W till Day 358

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

- **Day 1**
- **Day 22**

- **Immune induction**

- **1º end-point**: Safety
- **2º endpoint**: Response (irWHO criteria)
MITCI Phase Ib trial: Pt1305001 (Stage IIIC) Complete tumor response

Pre-Treatment

Day 30

Prior cancer treatments (Best response)

1. BCG (PD)
2. Nivolumab (PD)

Day 90

Day 180
MITCI Phase Ib trial: Pt1304005 (Stage IVM1c)
Partial tumor response

Prior cancer treatments (Best response)

1. Ipilimumab/Nivolumab (PR)
2. Nivolumab (PD)
3. Surgery (NE)

![Before treatment image](image1)
![Day 127 image](image2)

![Graph showing best percentage change in target lesions cross product relative to baseline irRC](image3)

![Day 310 image](image4)
MITCI Study: Preliminary Best percentage change in the sum of target lesions*

Anti-PD-1 naïve+

<table>
<thead>
<tr>
<th>Best Overall Response* (irRC)</th>
<th>Per irRC n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>8 (50)</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>7 (44)</td>
</tr>
<tr>
<td>Disease control rate (CR+PR+SD)</td>
<td>9 (56)</td>
</tr>
</tbody>
</table>

+, irRC criteria: Preliminary data, investigator assessed
First response assessment at Day 106

11% response rate with ipilimumab alone in advanced melanoma
(Hodi et al., N Engl J Med 2010; 363:711-723)

Anti-PD-1 refractory

<table>
<thead>
<tr>
<th>Best Overall Response* (irRC)</th>
<th>Per irRC n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>4 (45)</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>2 (22)</td>
</tr>
<tr>
<td>Disease control rate (CR+PR+SD)</td>
<td>7 (78)</td>
</tr>
</tbody>
</table>

13% response rate with ipilimumab alone in PD1 refractory advanced melanoma
(Long et al., SMR 2016 Abstract)

*, Preliminary data, investigator assessed
+, 2 patients with clinical progression without post-baseline CT-scans
CAPRA study: Phase 1b Intratumoral CAVATAK in combination with pembrolizumab (anti-PD1) in late stage melanoma
Intratumoral CAVATAK + pembrolizumab

(CAPRA study: NCT02565992)

- **50 Stage IIIIB/C and IV melanoma patients at least 1 injectable lesion**
- **CAVATAK® intralesional** 3 x10⁸ TCID₅₀ Day 1,3,5,8 and 22 then Q3W till Day 358
- **Immune induction**
- **Pembrolizumab** 200 mg IV Q3W for 2-years

Day 1  Day 8

1° end-point: Safety
2° endpoint: Response (irWHO criteria)
CAPRA Phase Ib trial
Non-injected distant lesion responses

Pt1105003
Stage IVM1c
Partial response

Pt1106023
Stage IIIC
Partial response
CAPRA Phase Ib trial
Non-injected distant visceral lesion response
CAPRA Study: Preliminary Best percentage change in the sum of target lesions+

**Best Overall Response** (irRC) | **Per irRC n (%)**
--- | ---
Overall response rate | 16 (59)**
Stable disease (SD) | 6 (22)
Progressive disease (PD) | 5 (19)
Disease control rate (CR+PR+SD) | 22 (81)

* Prior ipilimumab treatment
  *, Preliminary data, investigator assessed
  **, One patient terminated study prior to response assessment due to an unrelated-treatment SAE

33.4% response rate with pembrolizumab alone in advanced melanoma
CANON study: Phase I
Intravesical CAVATAK in non-muscle invasive bladder cancer
Phase I CANON STUDY DESIGN

VLA-012A (Monotherapy)
- 15 subjects with Non-muscle invasive Bladder cancer
  - Intravesicular instillation of CVA21 in 30 mL saline on Day 1 and/or Day 2
  - Transurethral resection (TUR) Day 8-11

Cohort A1
- Day 1
  - CVA21 (1x10^8 TCID<sub>50</sub>)
  - n=3

Cohort A2
- Day 1
  - CVA21 (3x10^8 TCID<sub>50</sub>)
  - n=3

Cohort A3
- Day 1 and 2
  - CVA21 (3x10^8 TCID<sub>50</sub>)
  - n=3

VLA-012B (mitomycin-C combination)

Cohort B1
- Day 1
  - CVA21 (3x10^8 TCID<sub>50</sub>)
  - Day 1 mitomycin C (10 mg)
  - n=3

Cohort B2
- Day 1 and 2
  - CVA21 (3x10^8 TCID<sub>50</sub>)
  - Day 1 mitomycin C (10 mg)
  - n=3

Study Endpoints

**Primary**
- Patient safety and tolerability
- Determination of MTD

**Secondary**
- Evidence of anti-tumor activity
- Virus-induced tumor cell infiltrates and immune response in TUR tissue
- Level of viral replication in TUR tissue
- Pharmacokinetics of serum viral load and anti-CVA21 antibodies
- Viral excretion in blood and urine
CANON Phase I Study: Tumour Response Data

Pre-treatment

Cohort 1:
Pt 01-B001

Post-treatment Day 8

Surface hemorrhage and inflammation of the tumor

Cohort 3:
Pt 01-B008

Complete clinical response (confirmed by histopathology)
CANON Phase I Study: CAVATAK cytoplasmic replication and viral-induced apoptosis in transurethral resection NMIBC tissue

CAVATAK viral proteins, H&E staining, Apoptotic cell staining

Cohort 1: Pt 01-B004

Cohort 2: Pt 01-B007

Cohort 3: Pt 01-B010

CAVATAK viral protein staining, Red=CVA21 proteins; Blue=Nucleus. H&E stain, black arrows indicate apoptotic bodies. Apoptotic cell staining, brown cells represent cleaved caspase-3 staining by IHC.
CANON Study: Intravesicular administration of CAVATAK up-regulates interferon-induced genes and immune checkpoint molecules within the tumour micro-environment of NMIBC tissue.
CANON Phase I Study: Conclusions

• CANON Phase I trial: Proof of concept viral targeting, replication and tumor cell death following a single or multiple intravesicular administrations of CAVATAK was achieved in patients from monotherapy Cohorts 1, 2 and 3.

• Clinical activity of CAVATAK demonstrated by complete tumor response, viral replication (infectious virus increases in urine) and notable signs of viral-induced tumor inflammation.

• No evidence of systemic spread of CAVATAK or development of serum neutralizing antibody.

• Intravesicular administration of CAVATAK was generally well tolerated with no Grade 2, 3 or 4 product-related AE’s.

• The observed tumor targeting and viral replication is likely to provide a strong signal in generating both a strong local and systemic anti-tumor immune response that could potentially enhance that activity of immune checkpoint blockade therapy.
KEYNOTE-200 (STORM) STUDY:  
Phase 1b  
intravenous CAVATAK in combination  
with pembrolizumab in advanced cancer
KEYNOTE-200 Part A: CAVATAK monotherapy: dose escalation – increasing levels of systemic exposure*

AUC 48 hours post-infusion (CVA21 RNA copies/ml serum)

Cohort 1: $10^8$TCID$_{50}$
Cohort 2: $3\times10^8$TCID$_{50}$
Cohort 3: $10^9$TCID$_{50}$

*Area under the curve (AUC) exposure over 48hr following the first infusion of CAVATAK
KEYNOTE-200 Part A: Systemic CAVATAK monotherapy tumor targeting at day 8 post-viral administration – Cohort 3*

*Day 8 biopsy from Cohort 3 patients administered three infusions of $10^9$TCID$_{50}$ of CAVATAK
KEYNOTE-200 Part A: CAVATAK monotherapy tumor targeting: biopsy viral protein staining* (day 8) – cohort 3, melanoma

*Day 8 biopsy from Cohort 3 melanoma patients administered three infusions of $10^9$ TCID$_{50}$ of CAVATAK
KEYNOTE-200 Part B: CAVATAK in combination with pembrolizumab

IV CAVATAK days 1, 3, 5, 8, 29, 50, 71, 92, 113, 134, 155 + IV pembrolizumab (200mg) every 3 weeks starting Day 8

Cohort 1 (n=3)
NSCLC or bladder cancer
CAVATAK ($1 \times 10^8$ TCID$_{50}$) + pembrolizumab

Cohort 2 (n=3)
NSCLC or bladder cancer
CAVATAK ($3 \times 10^8$ TCID$_{50}$) + pembrolizumab

Cohort 3 (n=3)
NSCLC or bladder cancer
CAVATAK ($1 \times 10^9$ TCID$_{50}$) + pembrolizumab

No DLT's

Cohort Expansion
NSCLC (n=43 +/- prior checkpoint)
CAVATAK ($1 \times 10^9$ TCID$_{50}$) + pembrolizumab

Cohort Expansion
Bladder CA (n=35 +/- prior checkpoint)
CAVATAK ($1 \times 10^9$ TCID$_{50}$) + pembrolizumab

Recruitment complete
KEYNOTE-200 Part B: Treatment-related adverse events

• At present the combination of IV CAVATAK and pembrolizumab has been generally well-tolerated with no limiting toxicities;

• 8% (7/85) of patients with Grade 3 treatment-related adverse events;

• No Grade 4/5 treatment-related adverse events have been observed.

*Preliminary analysis, adverse events from 85 treated patients using Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, data cutoff 10 March, 2018.
KEYNOTE-200: Increases in PD-L1 expression levels (IHC) in tumor cells from paired biopsies from NSCLC patients displaying negative/weak positive and Bladder cancer patients displaying negative levels at baseline (Preliminary data)

**CAVATAK® intravenous**
1 x10^9 TCID_{50} Day 1,3,5,8 and 22 then Q3W till Day 155

**1º end-point**: Safety
**2º endpoint**: Response (irRECIST)

**Pembrolizumab 200 mg IV Q3W 2 years**

Day 1 (Biopsy)  Day 8  Day 15 (Optional biopsy)

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**NSCLC**

<table>
<thead>
<tr>
<th>PD-L1 IHC staining intensity level</th>
<th>Baseline (n=8)</th>
<th>Day 15 (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHC PD-L1 Intensity</td>
<td>0= Negative</td>
<td>1= Weak Positive</td>
</tr>
</tbody>
</table>

**Metastatic Bladder Cancer**

<table>
<thead>
<tr>
<th>PD-L1 IHC staining intensity level</th>
<th>Baseline (n=5)</th>
<th>Day 15 (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHC PD-L1 Intensity</td>
<td>0= Negative</td>
<td>1= Positive</td>
</tr>
</tbody>
</table>
KEYNOTE-200 Preliminary data: Best percentage change in the sum of target lesions (irRECIST) +,*

+, Preliminary data, investigator assessment of best percentage change in target and new lesions of combination treatment in checkpoint naive patients (irRECIST). Data cutoff 10 March 2018;
*, Not evaluable due to withdrawal of consent, early disease progression and no early termination scan prior to first response assessment (day 92), 1 NSCLC pts; 1 NSCLC-mutated EGF-R pts; 2 Bladder cancer pts;
●, Patient currently on study;
#, Response not confirmed;
KEYNOTE-200 Preliminary data: Best percentage change in the sum of Metastatic Bladder cancer target lesions (irRECIST) +,*

†, Preliminary data, investigator assessment of best percentage change in target and new lesions of combination treatment in checkpoint naive patients (irRECIST), Data cutoff 10 March 2018;
* , Not evaluable due to withdrawal of consent, early disease progression or no early termination scan prior to first response assessment (day 92), 2 Bladder cancer pts;
●, Patient currently on study;
#, Response not confirmed
KEYNOTE-200 Preliminary data: Best percentage change in the sum of NSCLC target lesions (iriRECIST) +,*

+ Preliminary data, investigator assessment of best percentage change in target and new lesions of combination treatment in checkpoint naïve patients (iriRECIST). Data cutoff 10 March 2018;
* Not evaluable due to withdrawal of consent, early disease progression or no early termination scan prior to first response assessment (day 92), 1 NSCLC pts; 1 NSCLC-mutated EGF-R pts;
• Patient currently on study;
# Response not confirmed;
** EGF-R/ALK mutation status unknown.
KEYNOTE-200: Pt 40001 EGFRmut relapsed TKI Tumor response

Baseline

Day 92

7 x IV CAVATAK
4 x IV pembrolizumab

Response within 3 months
Conclusions: KEYNOTE-200 Parts A and B

- Enrolment in Part A (monotherapy) and Part B is complete with no DLTs observed.

- Successful systemic CAVATAK tumor targeting and findings of potential secondary CAVATAK replication (Part A).

- The CAVATAK/pembrolizumab combination has been generally well tolerated. At present 8% (7 of 85) pts have displayed treatment related Gr 3 adverse events. No grade 4/5 treatment related adverse events (Part B).

- Systemic administration of CAVATAK with pembrolizumab has mediated encouraging clinical signals of activity.

- Prolonged SD have been the best responses observed to date in evaluable patients previously treated with immune checkpoint inhibitors (n=16).

- Preliminary IHC staining demonstrates a notable intratumoral induction of PD-L1 at Day 15 relative to baseline in patients with negative/weak positive baseline PD-L1 treated with CAVATAK and pembrolizumab.
Conclusions CAVATAK® Clinical experience

• CAVATAK administered to advanced cancer patients (>250) via intravenous, intratumoral and intravesicular routes;

• CAVATAK clinical administration: >3000 intratumoral injections; > 600 intravenous infusions; > 20 intravesicular treatments as monotherapy or in combination with immune-checkpoint therapy with no DLT’s;

• Presently, levels of grade 3 or higher treatment-related adverse events when CAVATAK is used in combination with immune-checkpoint therapies are appear to be comparable to levels observed in single agent immune-checkpoint therapy usage;

• Interestingly, clinical studies employing intratumoural, intravesicular and intravenous routes of delivery of CAVATAK have highlighted preliminary data suggesting notable up-regulation of tumour PD-L1 in a number of cancer indications.
Acknowledgments

• The investigators, patients, and study staff who are contributing to these studies;

• Viralytics R&D and clinical teams;

• Support for the CALM, MITCI, CAPRA and CANON studies was provided by Viralytics;

• Support for the STORM (KEYNOTE-200) study was provided by Viralytics Ltd and Merck & Co., Inc., Kenilworth, NJ.