Phase 1b KEYNOTE-200 (STORM): A study of an intravenously delivered oncolytic virus, Coxsackievirus A21 in combination with pembrolizumab in advanced cancer patients

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Disclosures

Charles Rudin, MD PhD

I have the following financial relationships to disclose:

• Consultant:
  • Abbvie, BMS, Celgene, G1 Therapeutics, Novartis

• Scientific advisory board:
  • Harpoon Therapeutics

I will discuss the following off label use and/or investigational use in my presentation: CVA21
CAVATAK® (Coxsackievirus A21) an oncolytic immunotherapeutic agent

- Proprietary formulation of the oncolytic virus, Coxsackievirus A21 (CVA21)
  - Unmodified “common cold” virus
- Targeted to ICAM-1
  - Over-expressed on cancer cells
- High level of patients without pre-existing CVA21 immunity
  - 88% (132/150 pts) lacking anti-CVA21 serum antibody at baseline
- Rapid cytoplasmic replication
  - Kills by oncolytic and immunotherapeutic activity
- Potential application across a range of cancer types
  - Prostate, lung, melanoma, bladder and others
- Potential application as combination with other immunotherapies

Cytoplasmic replication of CVA21 in non-muscle invasive bladder cancer
Preclinical: Intravenous delivered CVA21-induced gene changes in human melanoma

- **Implant human SK-Mel 28**
- **Treatment**: CAVATAK or saline
- **Day 0**: SCID Balb/C
- **Day 14**: CAVATAK or saline IV (tail vein)
- **Sacrifice mice and excise tumor**
  - 3h, 6h, 24h, 72h
- **Excise tumor for viral and cellular gene profiling**
- **Tumor gene profiling**
Preclinical: CVA21-induced up regulation of IFN-γ inducible protein 10 (CXCL10) and PD-L1 in melanoma xenografts

Tumor gene expression

**Saline**

<table>
<thead>
<tr>
<th>Time post-saline administration (h)</th>
<th>Normalised gene fold changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>3h</td>
<td>1.00</td>
</tr>
<tr>
<td>6h</td>
<td>1.00</td>
</tr>
<tr>
<td>24h</td>
<td>1.00</td>
</tr>
<tr>
<td>72h</td>
<td>1.00</td>
</tr>
</tbody>
</table>

**CVA-21**

<table>
<thead>
<tr>
<th>Hours post-CAVATAK administration</th>
<th>Normalised gene fold changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>3h</td>
<td>1.50</td>
</tr>
<tr>
<td>6h</td>
<td>2.00</td>
</tr>
<tr>
<td>24h</td>
<td>2.50</td>
</tr>
<tr>
<td>72h</td>
<td>3.00</td>
</tr>
</tbody>
</table>

Tumor CVA21 replication

<table>
<thead>
<tr>
<th>Time post-CAVATAK administration (h)</th>
<th>Normalised gene fold changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>3h</td>
<td>1.00</td>
</tr>
<tr>
<td>6h</td>
<td>1.00</td>
</tr>
<tr>
<td>24h</td>
<td>1.00</td>
</tr>
<tr>
<td>72h</td>
<td>1.00</td>
</tr>
</tbody>
</table>

**CXCL10**

- Saline: Normalised gene fold changes from 3h to 72h remain constant at 1.00.
- CVA-21: Normalised gene fold changes increase from 3h to 72h, reaching 3.00.

**PD-L1**

- Saline: Normalised gene fold changes from 3h to 72h remain constant at 1.00.
- CVA-21: Normalised gene fold changes increase from 3h to 72h, reaching 3.00.

- Tumor CVA21 replication over time post-CAVATAK administration.
CVA21: Oncolytic immunotherapeutic modes of action in combination therapy
Pre-clinical: Intravenous CVA21 and checkpoint blockade (anti-PD-1) in an immune-competent mouse NSCLC (3LL) model

Tail vein injection 3LL-hICAM-1 cells

Treatment iv CVA21 or saline + ip anti-PD-1 or control mAb

Observation: Sacrifice ≥ 20% weight loss or labored breathing

Day 0

7 10 13 16

3LL-hICAM-1 cells (i.v tail vein)

CVA21

anti-PD-1 mAb

* 3LL-ICAM-1 cells are murine NSCLC 3LL cells stably transfected to express human ICAM-1 to allow CAVATAK binding and cell infection
Preclinical: Combination of intravenous CVA21 and immune checkpoint antibody blockade (anti-m-PD-1): survival

Kaplan-Meier Survival analysis*

- **Control Ab + Saline**
- **Control Ab + CVA21**

*P = NS

- **anti-m-PD-1 + Saline**
- **anti-m-PD-1 + CVA21**

**P = 0.0033

*P = 0.0201

*n=10, sacrifice ≥ 20% weight loss or labored breathing
Part A / CVA21 (Monotherapy)

Advanced melanoma, prostate, NSCLC or bladder cancer, sero-negative

CVA21 days 1,3,5,22,43,64,85,106,127,148

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

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

Cohort 3
1 x 10^9 TCID_{50}
Mandatory lesion biopsy (Day 8) Melanoma, NSCLC, Bladder And Prostate cancer n=3 each

No DLT’s

Part B / CVA21 + pembrolizumab (Combination)

CVA21 days 1,3,5,8,29,50,71,92,113,134,155 + pembrolizumab (200mg) every 3 weeks starting Day 8

Cohort 1 (n=3)
NSCLC or bladder cancer
CVA21 (1 x 10^8 TCID_{50}) + pembrolizumab

Cohort 2 (n=3)
NSCLC or bladder cancer
CVA21 (3 x 10^8 TCID_{50}) + pembrolizumab

Cohort 3 (n=3)
NSCLC or bladder cancer
CVA21 (1 x 10^9 TCID_{50}) + pembrolizumab

Cohort Expansion
NSCLC (~n=40)
CVA21 (1 x 10^8 TCID_{50}) + pembrolizumab

Cohort Expansion
Bladder CA (~n=40)
CVA21 (1 x 10^9 TCID_{50}) + pembrolizumab
KEYNOTE-200 key inclusion criteria

- **Part A**: Histologically-confirmed (1) NSCLC, (2) bladder cancer, (3) castrate-resistant prostate cancer (CRPC) which are metastatic, or (4) Stage IIIC or Stage IV melanoma.

- **Part B**: Histologically or cytologically-confirmed advanced (1) NSCLC, (2) urothelial carcinoma.

- **Part A**: All subjects in Cohort 3 or P2D cohort must have a lesion accessible for FNA or core biopsy or open biopsy on Day 8 of the first treatment cycle.

- **Part B**: All subjects in Cohort 3 or P2D cohort must have either archival tissue available or a lesion accessible for mandatory core biopsy or open biopsy prior to treatment. Day 15 biopsy is requested but optional

- ECOG Performance Scale 0-1 **Part B (Part A: 0-2)**.

- Life expectancy >3 months.

- Measureable disease based on RECIST 1.1.
Primary Objectives

Part A
- To determine if CVA21 given intravenously is capable of tracking to malignant tumors.
- To establish a safe dose schedule of CVA21 for subsequent Phase 2 clinical trials.
- To describe the safety profile for intravenously-administered CVA21.

Part B
- To assess and describe the safety profile of intravenous CVA21 and intravenous pembrolizumab in solid tumors of metastatic bladder cancer and NSCLC.
- To assess efficacy of the combination of CVA21 and intravenous pembrolizumab in solid tumors of metastatic bladder cancer and NSCLC.
### KEYNOTE-200 Part A: CVA21 monotherapy: treatment-related adverse events

<table>
<thead>
<tr>
<th></th>
<th>Related to CVA21 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>4 (22%)</td>
</tr>
<tr>
<td>Flu-like illness</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>1 (6%)</td>
</tr>
</tbody>
</table>
KEYNOTE-200 Part A: CVA21 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: $3 \times 10^8$TCID$_{50}$

Cohort 3: $10^9$TCID$_{50}$

*Area under the curve (AUC) exposure over 48hr following the first infusion of CVA21
KEYNOTE-200 Part A: Systemic CVA21 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 CVA21**

- **Prostate cancer**
  - Bone
  - Lymph Node

- **Melanoma**
  - Soft tissue, chest
  - Thigh
  - Liver

- **NSCLC**
  - Lung
  - Chest Wall

- **Bladder cancer**
  - Iliac node
  - Abdominal Wall

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>CVA21 RNA copies/mg tumour RNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>01-005</td>
<td>Bone</td>
</tr>
<tr>
<td>01-006</td>
<td>Bone</td>
</tr>
<tr>
<td>03-005</td>
<td>Lymph Node</td>
</tr>
<tr>
<td>02-005</td>
<td></td>
</tr>
<tr>
<td>03-006</td>
<td></td>
</tr>
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<td>02-007</td>
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<td>01-010</td>
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<td>03-012</td>
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</tr>
<tr>
<td>01-011</td>
<td></td>
</tr>
<tr>
<td>01-009</td>
<td></td>
</tr>
</tbody>
</table>

**Limit of detection** (1500 copies/mg RNA)
KEYNOTE-200 Part A: CVA21 monotherapy tumor targeting: biopsy viral protein staining* (day 8) – cohort 3, melanoma

*Day 8 biopsy from Cohort 3 patients administered three infusions of 10⁹ TCID₅₀ of CVA21

*irRECIST criteria: Preliminary data, investigator assessed
+First response assessment at Day 42
KEYNOTE-200 Part A: CVA21 monotherapy: Evidence of potential secondary replication – serum CVA21 levels 48-72hr post-infusion
CVA21 monotherapy single-dose and multi-dose pharmacokinetics: serum neutralizing antibody development

**Single IV dose (Phase 1)**

- **Pt 204**
- **Pt 015**
- **Pt 206**
- **Pt 016**

**Multi IV dose (KEYNOTE 200)**

- **03-001**
- **03-002**
- **02-001**
- **02-002**
- **02-003**
- **01-001**

Robust window for multi-IV dosing
Conclusions: KEYNOTE-200 Part A: CVA21 monotherapy

- Enrolment complete

- IV delivery of CVA21 was generally well tolerated
  - no grade 3 or 4 related AE’s with a median of 6 CVA21 infusions per patient
  - no dose-limiting toxicities

- CVA21 tumor targeting in patients with melanoma, NSCLC and bladder cancer patients in Cohort 3 was confirmed
  - detection of CVA21 viral RNA in tumor biopsies at study day 8
  - viral replication by IHC in melanoma tumor biopsies

- Of the 15 patients from Cohorts 1-3 eligible for investigator best overall response assessment, 1 PR, 10 SD and 4 PD were observed

- Serum viral loads suggest potential secondary viral replication events
KEYNOTE-200 Part B: CVA21 in combination with pembrolizumab

- **Cohort 1 (n=3)**
  - NSCLC or bladder cancer
  - CVA21 \(1 \times 10^8 \text{ TCID}_{50}\)
  - pembrolizumab
  - Recruitment complete

- **Cohort 2 (n=3)**
  - NSCLC or bladder cancer
  - CVA21 \(3 \times 10^8 \text{ TCID}_{50}\)
  - pembrolizumab
  - Recruitment complete

- **Cohort 3 (n=3)**
  - NSCLC or bladder cancer
  - CVA21 \(1 \times 10^9 \text{ TCID}_{50}\)
  - pembrolizumab
  - Recruitment complete

- **No DLT’s**

- **Cohort Expansion**
  - NSCLC (\(\sim n=40\) +/- prior checkpoint)
  - CVA21 \(1 \times 10^9 \text{ TCID}_{50}\)
  - pembrolizumab

- **Cohort Expansion**
  - Bladder CA (\(\sim n=40\) +/- prior checkpoint)
  - CVA21 \(1 \times 10^9 \text{ TCID}_{50}\)
  - pembrolizumab

- **Recruitment complete**

*IV CVA21 days 1,3,5,8,29,50,71,92,113,134,155 + IV pembrolizumab (200mg) every 3 weeks starting Day 8*
### KEYNOTE-200 Part B: treatment-related adverse events*

<table>
<thead>
<tr>
<th>N=10</th>
<th>Related to CVA21 n(%)</th>
<th>Related to Pembrolizumab n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1</td>
<td>Grade 2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (30%)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (20%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3 (30%)</td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>2 (20%)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>2 (20%)</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>1 (10%)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (10%)</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (20%)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (10%)</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>1 (10%)</td>
<td></td>
</tr>
<tr>
<td>Chills</td>
<td>1 (10%)</td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td></td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Flu-like illness</td>
<td>1 (10%)</td>
<td></td>
</tr>
<tr>
<td>Malaise</td>
<td>1 (10%)</td>
<td></td>
</tr>
</tbody>
</table>

*Adverse events reported to date

*No DLT’s reported
## KEYNOTE-200 Part B: patient characteristics

<table>
<thead>
<tr>
<th>Cohort</th>
<th>CVA21 Dose (TCID&lt;sub&gt;50&lt;/sub&gt;)</th>
<th>Patient No.</th>
<th>Tumor Type</th>
<th>Age</th>
<th>Gender</th>
<th>Prior Therapy</th>
<th>Response (Day)*</th>
<th>CVA21 Doses</th>
<th>Pembrolizumab Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 x 10&lt;sup&gt;8&lt;/sup&gt;</td>
<td>12001</td>
<td>NSCLC</td>
<td>67</td>
<td>M</td>
<td>surgery (2), chemotherapy (5), radiotherapy</td>
<td>PD (Day 114)</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15001</td>
<td>Bladder</td>
<td>73</td>
<td>M</td>
<td>surgery (11), chemotherapy (2), radiotherapy (2)</td>
<td>PD (Day 118)</td>
<td>9</td>
<td>6</td>
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<tr>
<td></td>
<td></td>
<td>15002</td>
<td>Bladder</td>
<td>58</td>
<td>M</td>
<td>surgery (3), chemotherapy (2)</td>
<td>PD (Day 83)</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>3 x 10&lt;sup&gt;8&lt;/sup&gt;</td>
<td>15003</td>
<td>NSCLC</td>
<td>62</td>
<td>M</td>
<td>surgery, chemotherapy (2), radiotherapy</td>
<td>PD (Day 92)</td>
<td>7</td>
<td>4</td>
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<tr>
<td></td>
<td></td>
<td>15004</td>
<td>Bladder</td>
<td>68</td>
<td>F</td>
<td>surgery (4), chemotherapy (2), immunotherapy (BCG, atezolizumab), other</td>
<td>Withdrawn due to unrelated grade 3 sepsis (Day 19)</td>
<td>4</td>
<td>1</td>
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<tr>
<td></td>
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<td>12002</td>
<td>NSCLC</td>
<td>76</td>
<td>F</td>
<td>chemotherapy (2), radiotherapy</td>
<td>Withdrew consent (Day 25)</td>
<td>3</td>
<td>1</td>
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<tr>
<td>3</td>
<td>1 x 10&lt;sup&gt;9&lt;/sup&gt;</td>
<td>13002</td>
<td>Bladder</td>
<td>80</td>
<td>M</td>
<td>surgery (13), radiotherapy, chemotherapy (5), immunotherapy (BCG, atezolizumab)</td>
<td>PD (Day 29)</td>
<td>4</td>
<td>2</td>
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<tr>
<td></td>
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<td>12003</td>
<td>NSCLC</td>
<td>66</td>
<td>M</td>
<td>chemotherapy (2), radiotherapy (2), immunotherapy (anti-B7H3, anti-PDL1, ipilimumab, nivolumab)</td>
<td>ongoing (Day 44)</td>
<td>5</td>
<td>2</td>
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<tr>
<td></td>
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<td>15005</td>
<td>NSCLC</td>
<td>81</td>
<td>M</td>
<td>chemotherapy, immunotherapy (nivolumab)</td>
<td>ongoing (Day 21)</td>
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<td></td>
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<td>15006</td>
<td>Bladder</td>
<td>61</td>
<td>M</td>
<td>chemotherapy, surgery (2)</td>
<td>ongoing (Day 15)</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

*First response assessment at Day 92; **Clinical progression only
KEYNOTE-200: Relative kinetics of anti-viral responses to CVA21 – serum neutralizing antibody

Part A: CVA21

Part B: CVA21 + pembrolizumab

Reciprocal Log_{10} anti-CVA21 neutralising antibody titer

Study Days
Conclusions: KEYNOTE-200 Parts A and B

- Enrollment in Part A (monotherapy) is complete with no DLTs observed
- Successful systemic CVA21 tumor targeting and findings of potential secondary CVA21 replication (Part A)
- Evidence of tumor stabilization and response (Part A)
- At present, the combination of intravenous CVA21 and pembrolizumab (Part B) has been generally well-tolerated in heavily pre-treated patients with or without prior immune checkpoint therapy
- Enrollment in Part B (combination) Cohorts 1, 2 and 3 complete. Expansion cohort currently recruiting
- One grade 3 CVA21-related hyponatremia with no DLT for the combination of CVA21 and pembrolizumab
- Comparable host anti-CVA21 immune responses in the presence or absence of pembrolizumab
- Intravenous delivery of CVA21 is able to target metastatic lesions with the potential to up-regulate PD-L1 expression during the viral replication process
Acknowledgments

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

• Viralytics R&D and clinical teams

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  • Viralytics Ltd.
  • Merck & Co.