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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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

Day 0

SCID Balb/C

Treatment CAVATAK or saline

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

Tumor CVA21 replication

<table>
<thead>
<tr>
<th>Saline-CXCL10</th>
<th>CVA21-CXCL10</th>
</tr>
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<tbody>
<tr>
<td>3h</td>
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<tr>
<td>6h</td>
<td>1.0</td>
</tr>
<tr>
<td>24h</td>
<td>2.0</td>
</tr>
<tr>
<td>72h</td>
<td>3.0</td>
</tr>
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<table>
<thead>
<tr>
<th>Saline-PD-L1</th>
<th>CVA21-PD-L1</th>
</tr>
</thead>
<tbody>
<tr>
<td>3h</td>
<td>0.5</td>
</tr>
<tr>
<td>6h</td>
<td>1.0</td>
</tr>
<tr>
<td>24h</td>
<td>1.5</td>
</tr>
<tr>
<td>72h</td>
<td>2.0</td>
</tr>
</tbody>
</table>
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

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

CVA21

anti-PD-1 mAb
Preclinical: Combination of intravenous CVA21 and immune checkpoint antibody blockade (anti-m-PD-1): survival

Kaplan-Meier Survival analysis*

*%n=10, sacrifice ≥ 20% weight loss or labored breathing
Phase 1b: KEYNOTE-200 study design

Part A / CVA21 (Monotherapy)

- Cohort 1
  - 1 x 10^8 TCID<sub>50</sub>
  - n=3

- Cohort 2
  - 3 x 10^8 TCID<sub>50</sub>
  - n=3

- Cohort 3
  - 1 x 10^9 TCID<sub>50</sub>
  - Mandatory lesion biopsy (Day 8)
  - Melanoma, NSCLC, Bladder And Prostate cancer n=3 each

Part B / CVA21 + pembrolizumab (Combination)

- Cohort 1 (n=3)
  - NSCLC or bladder cancer
  - CVA21 (1 x 10^8 TCID<sub>50</sub>) + pembrolizumab

- Cohort 2 (n=3)
  - NSCLC or bladder cancer
  - CVA21 (3 x 10^8 TCID<sub>50</sub>) + pembrolizumab

- Cohort 3 (n=3)
  - NSCLC or bladder cancer
  - CVA21 (1 x 10^9 TCID<sub>50</sub>) + pembrolizumab

- Cohort Expansion
  - NSCLC (~n=40)
  - CVA21 (1 x 10^8 TCID<sub>50</sub>) + pembrolizumab

- Cohort Expansion
  - Bladder CA (~n=40)
  - CVA21 (1 x 10^8 TCID<sub>50</sub>) + pembrolizumab

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

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

No DLT's

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

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>N=18</th>
<th>Related to CVA21 n (%)</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4-5</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>3 (17%)</td>
<td>2 (11%)</td>
<td></td>
<td></td>
<td>5 (28%)</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>4 (22%)</td>
<td>1 (6%)</td>
<td></td>
<td></td>
<td>5 (28%)</td>
<td></td>
</tr>
<tr>
<td>Flu-like illness</td>
<td>2 (11%)</td>
<td>1 (6%)</td>
<td></td>
<td></td>
<td>3 (17%)</td>
<td></td>
</tr>
<tr>
<td>Lethargy</td>
<td>3 (17%)</td>
<td></td>
<td></td>
<td></td>
<td>3 (17%)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td>1 (6%)</td>
<td></td>
<td></td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>1 (6%)</td>
<td></td>
<td></td>
<td></td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (6%)</td>
<td></td>
<td></td>
<td></td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>1 (6%)</td>
<td></td>
<td></td>
<td></td>
<td>1 (6%)</td>
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</tr>
<tr>
<td>Arthralgia</td>
<td>1 (6%)</td>
<td></td>
<td></td>
<td></td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>1 (6%)</td>
<td></td>
<td></td>
<td></td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td>Dry skin</td>
<td>1 (6%)</td>
<td></td>
<td></td>
<td></td>
<td>1 (6%)</td>
<td></td>
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</table>
KEYNOTE-200 Part A: CVA21 monotherapy: dose escalation – increasing levels of systemic exposure*

*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 $10^9$ ICID$_{50}$ of CVA21
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

Best percentage change in the target lesions sum of diameters relative to baseline  

-50  -25  0  25  50  75  100  

Melanoma  
Castrate-resistant prostate cancer  
NSCLC  
Metastatic bladder cancer  

PD  SD  PR  

*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
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

IV CVA21 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
  - CVA21 (1 x10^8 TCID_50) + pembrolizumab
  - Recruitment complete

- **Cohort 2 (n=3)**
  - NSCLC or bladder cancer
  - CVA21 (3 x10^8 TCID_50) + pembrolizumab
  - Recruitment complete

- **Cohort 3 (n=3)**
  - NSCLC or bladder cancer
  - CVA21 (1 x10^9 TCID_50) + pembrolizumab
  - Recruitment complete

- **Cohort Expansion**
  - NSCLC (~n=40 +/- prior checkpoint)
  - CVA21 (1 x10^9 TCID_50) + pembrolizumab
  - No DLT’s

- **Cohort Expansion**
  - Bladder CA (~n=40 +/- prior checkpoint)
  - CVA21 (1 x10^9 TCID_50) + pembrolizumab
  - Recruitment complete
KEYNOTE-200 Part B: treatment-related adverse events*

<table>
<thead>
<tr>
<th></th>
<th>Related to CVA21 n(%)</th>
<th>Related to Pembrolizumab n(%)</th>
<th>• No DLT's reported</th>
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<tbody>
<tr>
<td></td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (30%)</td>
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<tr>
<td>Nausea</td>
<td>2 (20%)</td>
<td>1 (10%)</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3 (30%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>2 (20%)</td>
<td></td>
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</tr>
<tr>
<td>Headache</td>
<td>2 (20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>1 (10%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (10%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (20%)</td>
<td></td>
<td></td>
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<tr>
<td>Vomiting</td>
<td></td>
<td>1 (10%)</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>1 (10%)</td>
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<td></td>
</tr>
<tr>
<td>Chills</td>
<td>1 (10%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flu-like illness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malaise</td>
<td>1 (10%)</td>
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</table>

*Adverse events reported to date
**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>
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</thead>
<tbody>
<tr>
<td><strong>1</strong></td>
<td><strong>1 x 10&lt;sup&gt;8&lt;/sup&gt;</strong></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>
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<tr>
<td></td>
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<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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<td></td>
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<td>15002</td>
<td>Bladder</td>
<td>58</td>
<td>M</td>
<td>surgery (3), chemotherapy (2)</td>
<td>PD (Day 83)</td>
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<td></td>
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<td>15003</td>
<td>NSCLC</td>
<td>62</td>
<td>M</td>
<td>surgery, chemotherapy (2), radiotherapy</td>
<td>PD (Day 92)</td>
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<td>4</td>
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<tr>
<td><strong>2</strong></td>
<td><strong>3 x 10&lt;sup&gt;8&lt;/sup&gt;</strong></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>
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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>
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<td>1</td>
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<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><strong>3</strong></td>
<td><strong>1 x 10&lt;sup&gt;9&lt;/sup&gt;</strong></td>
<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>
<td></td>
<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>
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</table>

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