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

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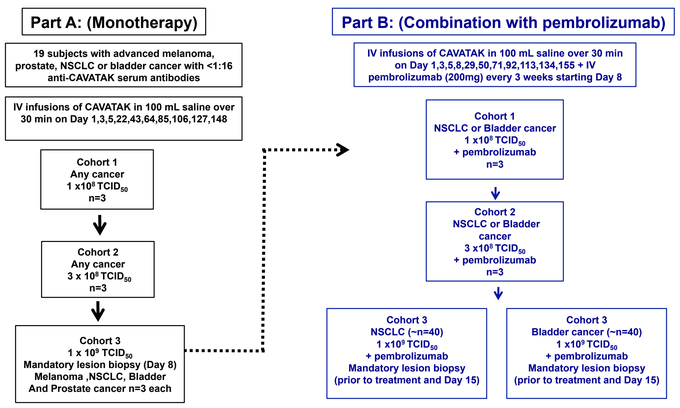
Background

Coxsackievirus A21 (CVA21, CAVATAK™) is a naturally occurring ICAM-1 targeted oncolytic immunotherapeutic virus. Intravenous (IV) delivery of CVA21 targets various systemic solid tumors. Tumor infection by CVA21 can increase levels of immune-checkpoint molecules, immune-cell infiltration and enhancement of systemic antitumor immune response. Pembrolizumab is a human programmed death receptor-1 (PD-1) blocking antibody that has yielded significant solid tumor responses via reversal of tumor induced T-cell suppression. Preclinical studies in an immune-competent mouse model of Non-Small Cell Lung Cancer (NSCLC) confirmed that combinations of IV CVA21 + anti-PD-1 mAbs mediated survival benefit compared to use of either agent alone. We postulate that the combination of CVA21+pembrolizumab may translate to a similar benefit in the clinic. We describe a Phase I study assessing safety and efficacy of IV CVA21 ± pembrolizumab in advanced cancer patients.

Study Design



Study Treatment

Part A*:* Pts were infused with CVA21 in 100 mL saline in Cohort 1 (n = 3), at a dose of 1 x 10^8 $TCID_{50}$, in Cohort 2 (n = 3) at a dose of 3 x 10^8 $TCID_{50}$ and in Cohort 3 (n = 12-18) at a dose of 1 x 10^9 $TCID_{50}$ on study days 1,3,5,22 and Q3W for 6 additional infusions.
Part A enrollment is complete.

Part B: Pts are infused with CVA21 in 100 mL saline + pembrolizumab. In Cohort 1 (n = 3), CVA21 is administered at a dose of 1 x 10^8 $TCID_{50}$, in Cohort 2 (n = 3) at a dose of 3 x 10^8 $TCID_{50}$ and in Cohort 3 (n = ~80) at a dose of 1 x 10^9 $TCID_{50}$ on study days 1,3,5,8,29,and Q3W for 6 additional infusions. Pembrolizumab is given in all cohorts at 200 mg IV Q3W from Day 8 for up to 2 years. Treatment with CVA21 ± pembrolizumab will continue until confirmed CR or PD (whichever comes first) per irRECIST or DLT. Part B Cohort 1 enrollment is complete. Cohort 2 enrollment is nearing completion.

Key Inclusion Criteria

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- *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 (1) advanced NSCLC, (2) urothelial carcinoma (also known as transitional cell carcinoma). Urothelial carcinomas with variant histologic differentiation (e.g. squamous cell differentiation, glandular differentiation, neuroendocrine differentiation) will be eligible provided that the predominant histology is urothelial carcinoma.
- *Part B:* Patients with advanced disease who are considered candidates for protocol specified pembrolizumab to be used in combination with CVA21.
- *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 a lesion accessible for mandatory core biopsy or open biopsy prior to treatment and on Day 15 of the first treatment cycle. FNA is not acceptable for *Part B*.
- ECOG Performance Scale 0-1.
- Life expectancy >3 months.
- Measureable disease based on RECIST 1.1 as determined by the site study team. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

Key Exclusion Criteria

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- Active cardiac disease: unstable angina or onset of angina within last 3 months, myocardial infarction within 6 months, congestive heart failure > class II, cardiac ventricular arrhythmias requiring anti-arrhythmic therapy.
- Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.
- Known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies), known active Hepatitis B (e.g. HBsAg reactive) or Hepatitis C (e.g. HCV RNA [qualitative] is detected).
- Known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
- Active infection requiring systemic therapy.
- Has had prior anti-cancer monoclonal antibody within 21 days prior to Study Day 1 or who has not recovered (i.e. ≤ Grade 1) from adverse events due to agents administered more than 21 days earlier.
- Has known active central nervous system metastases and/or carcinomatous meningitis.

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 to take into subsequent Phase 2 clinical trials.
- To describe the safety profile for intravenously-administered CVA21.

Part B
- To assess the safety and efficacy of intravenous CVA21 and intravenous pembrolizumab in solid tumors of metastatic bladder cancer and non-small cell lung cancer.
- To identify a safe and potentially effective Phase 2 dose for CVA21 in combination with intravenous pembrolizumab.
- To investigate if intravenous CVA21 when given in combination with intravenous pembrolizumab is capable of tracking to remote tumor sites by exhibiting CVA21 RNA in metastatic lesions at biopsy.

Secondary Objectives

Part B
- To assess efficacy via RECIST 1.1 and immune-related RECIST (irRECIST) criteria.
- To correlate ICAM-1 expressivity and DAF expressivity with the ability of CVA21 to reach its target and replicate within tumor cells.
- To assess immune response (e.g. immune cell infiltrates) after the first course of CVA21 via biopsy of an accessible tumor lesion.
- To assess tolerance to intravenous CVA21 for up to 8 courses (21 day cycle) in combination with pembrolizumab.
- To assess the PK/PD of CVA21 as measured by CVA21 RNA in serum over time.
- CVA21 excretion and shedding studies to assess environmental safety.

Part A Monotherapy : Patient Characteristics

Cohort	Patient Identification Code	Gender	Cancer Indication	Prior Lines of Treatment: Surgery	Immunotherapy	Chemotherapy	Radiotherapy	Hormone therapy	Other therapy	Duration of Treatment (cycles)	Best Overall Response	Best target lesion response
1	03-001	Male	NSCLC	1		5			1	4	irPD	SD
	03-002	Male	Melanoma	1	1	1				2	n/a	SD
	02-001	Male	Bladder			7	1			8	irSD	SD
2	02-002	Male	Bladder	1	1	1				4	irSD	SD
	01-001	Male	Prostate	2		1	1	6	1	8	irSD	SD
	02-003	Male	NSCLC			3	1			2	irPD	SD
3	01-005	Male	Prostate		1		1	2		3	irPD	PD
	01-006	Male	Prostate				1	4		8	irPR	PR
	02-004	Female	NSCLC			4	1			1	n/a	n/a
	02-005	Female	Melanoma							3	n/a	n/a
	03-005	Male	Prostate			3	2	1		2	irSD	SD
	03-006	Male	Melanoma	6	1	2	1			4	irSD	SD
	02-007	Female	Melanoma		2	1	1		1	8	irSD	SD
	01-011	Female	Bladder			2				3	irSD	SD
	03-012	Male	NSCLC		1	3				5	irPD	SD
	01-010	Female	NSCLC			3			1	1	n/a	n/a
	01-009	Male	Bladder		1	1	2			8	irSD	SD

Part A Monotherapy : Tumor Response

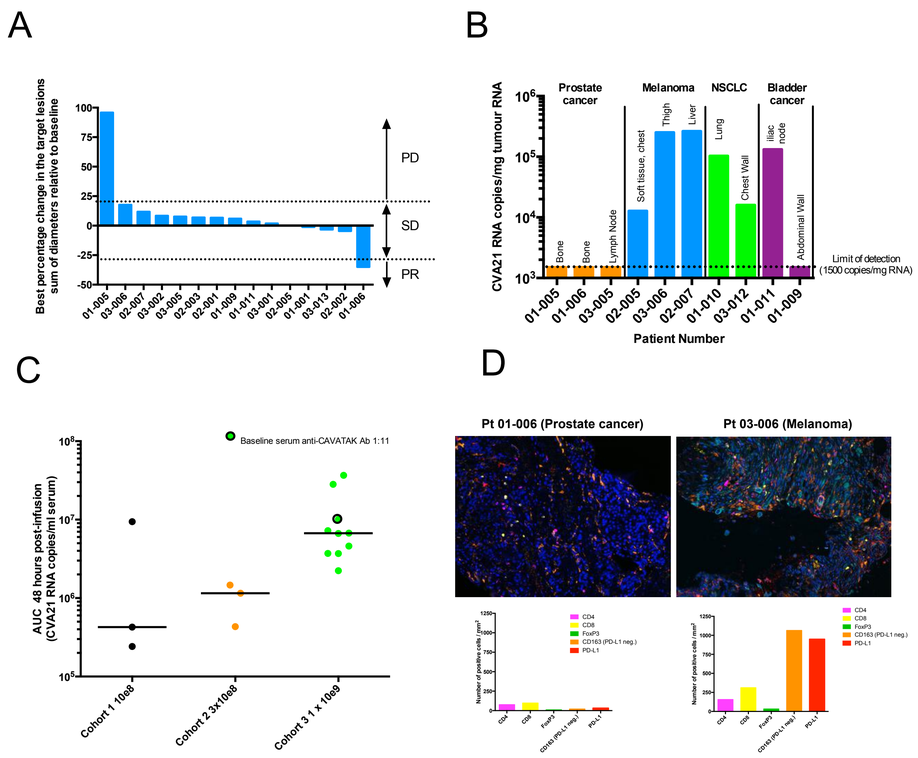

Figure 1. Phase I KEYNOTE 200 study Part A: (A) Best overall tumor response (RECIST 1.1); (B) CVA21 tumor targeting detection by qRT-PCR in tumor biopsies of Cohort 3 patients at study day 8; (C) Systemic exposure to the initial escalating dose of CVA21; (D) Multispectral imaging of immune-cell infiltrates in day 8 tumor biopsies (Multispectral images obtained and enumerated with PerkinElmer Vectra imaging system and InForm Software) from 2 Cohort 3.

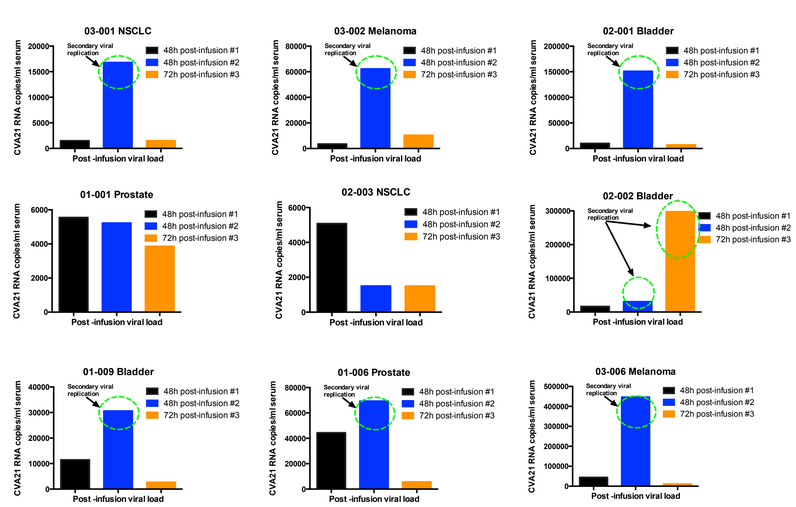

Figure 2. Phase I KEYNOTE 200 study Part A: Potential evidence of secondary viral replication via monitoring of systemic CVA21 RNA levels in the serum at 48-72 hours following the initial three intravenous infusions of CVA21.

Part B: Combination Therapy: Patient Characteristics

Cohort	CVA21 Dose (TCID50)	Patient Identification Code	Tumor Type	Age	Gender	Prior Lines of Treatment	CVA21 Doses	Pembrolizumab Doses
1	1 x 10^8	12001	NSCLC	67	M	surgery (2), chemotherapy (5), radiotherapy	8	5
		15001	bladder	73	M	surgery (11), chemotherapy (2), radiotherapy (2)	8	5
		15002	bladder	58	M	surgery (3), chemomotherapy (2)	7	4
2	3 x 10^8	15003	NSCLC	62	M	surgery, chemotherapy (2), radiotherapy	5	2
		15004	bladder	68	F	surgery (4), chemotherapy (2), immunotherapy (BCG, atezolizumab), other	4	1
		12002	NSCLC	76	F	chemotherapy (2), radiotherapy	3	1

Conclusions

- Enrolment in Part A (monotherapy) is complete with no DLT observed.
- Successful systemic CVA21 tumor targeting and findings of potential secondary CVA21 replication.
- Evidence of tumor stabilization and response (Part A).
- Enrolment in Part B (combination) Cohort 1 is complete with that of Cohort 2 nearing completion.
- The combination of intravenous CVA21 and pembrolizumab has been generally well-tolerated.
- At present one grade 3 CVA21-related hyponatremia (awaiting confirmation) with no DLT for the combination of CVA21 and pembrolizumab being observed.

Acknowledgement

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