Safety and tolerability of CRX100, an NKT cell therapy combined with tumor-specific oncolytic vaccinia virus among patients with recurrent, platinum-resistant ovarian cancer

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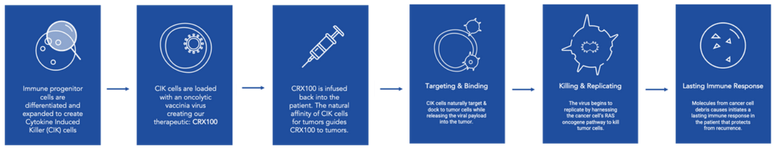
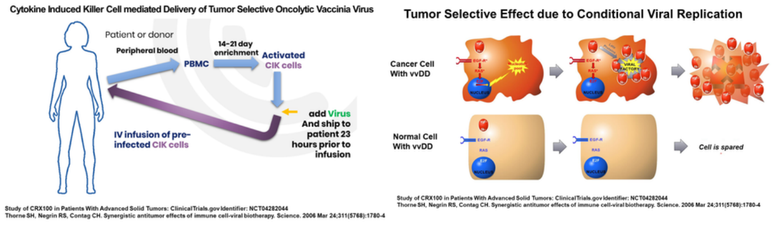
INTRODUCTION

CRX100 is an adoptive Natural Killer-Like T (NKT) cell therapy combined with vaccinia (vvDD), an oncolytic virus. vvDD is a Western Reserve (WR) strain of vaccinia virus (VACV) that is genetically modified with a deletion of viral thymidine kinase (TK) and growth factor genes, and hence does not replicate in normal cells. In contrast, tumor cells express sufficient levels of TK and provide oncogenic signaling for viral replication and lytic activity of vvDD. In preclinical studies using mouse ovarian cancer models, CRX100 eradicated tumor cells and induced an adaptive immune response.



TRIAL DESIGN

Our ongoing phase 1 clinical trial (NCT04282044) began in January 2021 and has enrolled 16 patients with various solid tumors, including seven ovarian cancer patients, seven colorectal cancer patients and two triple negative breast cancer patients. Enrolled subjects underwent leukapheresis to enable the ex vivo generation of autologous cytokine induced killer (CIK) cells, where peripheral blood mononuclear cells (PBMCs) are expanded with interferon-γ (IFN-γ) and anti-CD3 antibody (OKT-3) followed by activation with interleukin-2 (IL-2), which results in the enrichment of CD3+CD56+ cells (NKT cells). Approximately twenty-one (21) days after apheresis, a target dose of 3E9 (range 2-5E9) CIK cells were combined with a specified dose of vvDD. 3E7, 1E8, 3E8, 1E9, and 3E9 pfu/infusion were used to infect CIK cells 24 hours prior to i.v. cell transfer into patients. The cell transfer did not require prior lymphodepletion. Following infusion, subjects were evaluated for adverse events (AEs) for 28 days. Four subjects, two ovarian cancer patients and two CRC patients, had a second infusion based on safety, tolerability, and response of their first treatment cycle.



PATIENT POPULATION

Patients have progressive disease and have failed standard of care in the indications: ovarian cancer, triple negative breast cancer, gastric cancer, colorectal carcinoma (CRC), hepatocellular carcinoma, or osteosarcoma.

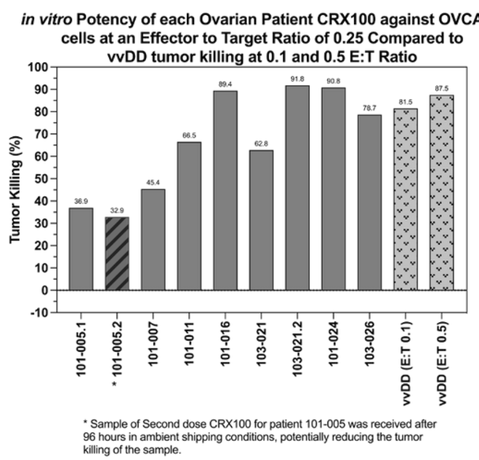
Table 1: Patient Demographics

Patient	Sex	Ethnicity	Race	Disease Type
101-005	F	Not Hispanic or Latino	White	Ovarian
101-007	F	Not Hispanic or Latino	Asian	Ovarian
101-011	F	Not Hispanic or Latino	White	Ovarian
101-016	F	Not Hispanic or Latino	White	Ovarian
103-021	F	Hispanic or Latino	White	Ovarian
101-024	F	Hispanic or Latino	Not reported	Ovarian
103-026	F	Not Hispanic or Latino	White	Ovarian

Table 2: Prior Treatments

Patient	Number of Prior Therapies	Type	Most Recent End Date
101-005	13	Chemotherapy, Hormonal therapy	2020-05-19
101-007	12	Chemotherapy, Immunotherapy	2020-11-23
101-011	10	Chemotherapy, Radiation	2022-08-25
101-016	5	Chemotherapy	2023-02-08
103-021	9	Chemotherapy, Radiation, Surgery	2023-06-27
101-024	7	Chemotherapy, Procedure, Surgery	2023-06-20
103-026	5	Chemotherapy	2023-09-15

CRX100 POTENCY



* Sample of Second dose CRX100 for patient 101-005 was received after 96 hours in ambient shipping conditions, potentially reducing the tumor killing of the sample.

Figure Description: Following manufacturing of CRX100, samples are sent to BioEclipse for analysis of tumor killing potential in OVCAR3 cells. An OVCAR3 cell based in vitro Potency Assay is used to determine tumor killing potential of the manufacturing CRX100 and compared to vvDD. Above is the potency of all Ovarian patients' CRX100 OVCAR3 cell cytotoxicity at an effector to target ratio of one CRX100 cell to four OVCAR3 cells (0.25 E:T Ratio). The patients who received two infusions have their second CRX100 labeled as [patient ID].2 in the figure. 103-021 had an increase in tumor killing from their first infusion of CRX100 to theirCRX100 from their second apheresis. CRC patients who received two doses also had an increase in tumor killing (data not shown). Patient 101-005's sample was compromised during shipping so the tumor killing is not confirmed for their second apheresis CRX100.

SAFETY AND TOLERABILITY

To date, seven heavily pretreated patients with recurrent, platinum resistant ovarian cancer have been treated with CRX100. Ex vivo generation of CD3+CD56+ NK-T cells was successful in all patients. No dose limiting toxicities have been observed. The most common AE was mild fever at 6-12 hours after infusion.

Table 3: Related AEs for Ovarian Cancer Patients

Patient	AE	Action taken with CRX100?	Outcome	SAE	Start Date	Date End	ConMed	Ongoing?	Grade	Expected
101-005	Fever	NA	Resolved	No	6/9/21	6/9/21	Yes	No	1	Yes
101-005	Situational anxiety	NA	Resolved	No	6/15/21	6/15/21	No	No	1	Yes
101-007	Fever	No Change	Resolved	Yes	8/11/21	8/11/21	Yes	No	1	Yes
101-007	headache	NA	Resolved	No	8/11/21	8/11/21	Yes	No	1	Yes
101-007	Abdominal pain	No Change	Resolved	No	8/11/21	8/11/21	No	No	1	Yes
101-007	rigors	NA	Resolved	No	8/11/21	8/11/21	Yes	No	1	Yes
101-007	Fatigue	NA	Resolved	No	8/17/21	9/8/21	No	No	3	Yes
101-011	Fever	NA	Resolved	No	10/22/22	10/22/22	Yes	No	1	Yes
101-016	Fever	No Change	Resolved	No	4/7/23	4/8/23	Yes	No	1	Yes
101-016	cytokine release syndrome (CRS)	No Change	Resolved	No	4/7/23	4/8/23	Yes	No	1	Yes
101-016	Chills/ Rigors	NA	Resolved	No	4/7/23	4/7/23	Yes	No	1	Yes
101-016	Maculopapular rash	No Change	Resolved	No	4/20/23	4/27/23	Yes	No	2	Yes
103-021	Fever	No Change	Resolved	No	8/30/23	8/30/23	Yes	No	2	Yes
103-021	Rigors	No Change	Resolved	No	8/30/23	8/30/23	Yes	No	1	Yes
103-021	Headaches - intermittent	No Change	Not Resolved	No	8/30/23	NA	No	Yes	1	Yes
103-021	Fever - intermittent	No Change	Not Resolved	No	8/31/23	NA	Yes	Yes	1	Yes
103-021	Redness - left side of neck	No Change	Resolved	No	8/31/23	9/1/23	No	No	1	Yes
103-021	Fever	No Change	Resolving	No	11/9/23	11/12/23	Yes	No	1	No
101-024	Fever	NA	Resolved	Yes	12/5/23	12/8/23	Yes	No	2	Yes
101-024	Decreased appetite	NA	Resolved	Yes	12/6/23	12/8/23	Yes	No	2	Yes
101-024	Hypoxia	NA	Resolved	Yes	12/6/23	12/7/23	Yes	No	2	Yes
101-024	Tachycardia	NA	Resolved	Yes	12/6/23	12/7/23	Yes	No	2	Yes
101-024	Body aches	NA	Resolved	Yes	12/7/23	12/8/23	Yes	No	2	Yes
103-026	Vomiting	No Change	Resolved	No	2/2/24	2/2/24	No	No	1	Yes
103-026	Chills	No Change	Resolved	No	2/2/24	2/2/24	No	No	1	Yes
103-026	Nausea	No Change	Resolved	No	2/2/24	2/2/24	No	No	1	Yes

Table 4: ECOG Performance Assessments During Treatment

Patient	Treatment Day	Assessment Performed?	Date of Assessment	Status
101-005	Enrollment	Yes	4/20/21	0
101-005	Day 1 Pre-Infusion	Yes	6/9/21	1
101-005	Day 7	Yes	6/15/21	1
101-005	Day 14	Yes	6/22/21	1
101-005	Day 21	Yes	6/29/21	1
101-005	Day 28 / EOT	Yes	7/7/21	1
101-005	T2: Day 1 Pre-Infusion	Yes	9/3/21	1
101-005	T2: Day 7	Yes	9/9/21	0
101-005	T2: Day 14	Yes	9/17/21	1
101-005	T2: Day 21	Yes	9/23/21	1
101-005	T2: Day 28 / EOT	Yes	9/30/21	1
101-007	Enrollment	Yes	6/21/21	0
101-007	Day 1 Pre-Infusion	Yes	8/11/21	0
101-007	Day 7	Yes	8/17/21	0
101-007	Day 14	Yes	8/24/21	0
101-007	Day 21	Yes	8/31/21	0
101-007	Day 28 / EOT	Yes	9/7/21	0
101-011	Enrollment	Yes	9/14/22	0
101-011	Day 1 Pre-Infusion	Yes	10/21/22	0
101-011	Day 7	Yes	10/27/22	1
101-011	Day 14	Yes	11/3/22	1
101-011	Day 21	Yes	11/10/22	1
101-011	Day 28 / EOT	No	NA	NA
101-016	Enrollment	Yes	3/1/23	0
101-016	Day 1 Pre-Infusion	Yes	4/7/23	0
101-016	Day 7	Yes	4/13/23	0
101-016	Day 14	Yes	4/20/23	0
101-016	Day 21	Yes	4/27/23	0
103-021	Enrollment	Yes	7/27/23	1
103-021	Day 1 Pre-Infusion	Yes	8/30/23	1
103-021	Day 7	Yes	9/5/23	1
103-021	Day 14	Yes	9/12/23	1
103-021	Day 21	Yes	9/19/23	1
103-021	Day 28 / EOT	Yes	9/26/23	0
103-021	T2: Day 1 Pre-Infusion	Yes	11/8/23	1
103-021	T2: Day 7	Yes	11/14/23	1
103-021	T2: Day 14	Yes	11/21/23	1
103-021	T2: Day 21	Yes	11/28/23	0
103-021	T2: Day 28 / EOT	Yes	12/5/23	1
101-024	Enrollment	Yes	10/18/23	0
101-024	Day 1 Pre-Infusion	Yes	12/6/23	1
101-024	Day 7	Yes	12/12/23	1
101-024	Day 21	Yes	12/27/23	1
101-024	Day 14	No	NA	NA
101-024	Day 28 / EOT	No	NA	NA
103-026	Enrollment	Yes	11/30/23	0

Table 3: listed above are the related AEs for the ovarian cancer patients in the clinical trial. The most common AE is a Grade 1 fever. There was only one Grade 3 AE. Only Six AEs were deemed SAEs and none of those SAEs required changes to the CRX100 dosing.

Table 4: Status levels - 0 - Fully active, able to carry on all pre-disease activities without restriction. 1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work. 2 - Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. 3 - Capable of only limited self-care, confined to bed or chair 50% or more of waking hours.

RESPONSE

One patient who received two infusions three months apart at a dose of 1E8 PFU vvDD combined with 2-5E9 NK-T cells since CT imaging showed stable disease after the first dose by iRECIST. 26 weeks following the second CRX100 treatment, the CA125 serum marker level decreased significantly from 20,435 U/ml to 11,538 U/ml with reduced tumor burden by imaging, The patients' follow up treatment using an experimental antibody drug conjugate targeting CD25 on Treg cells combined with pembrolizumab induced a further decrease in CA125 to 296 U/ml.

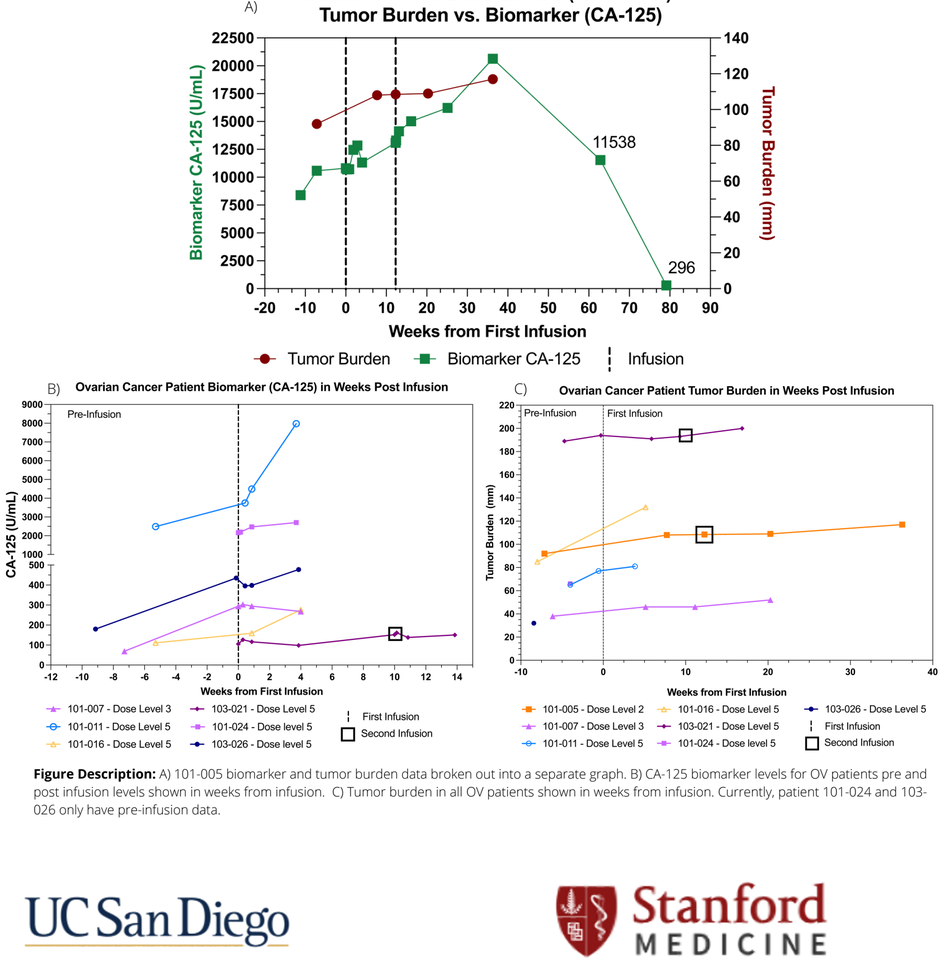
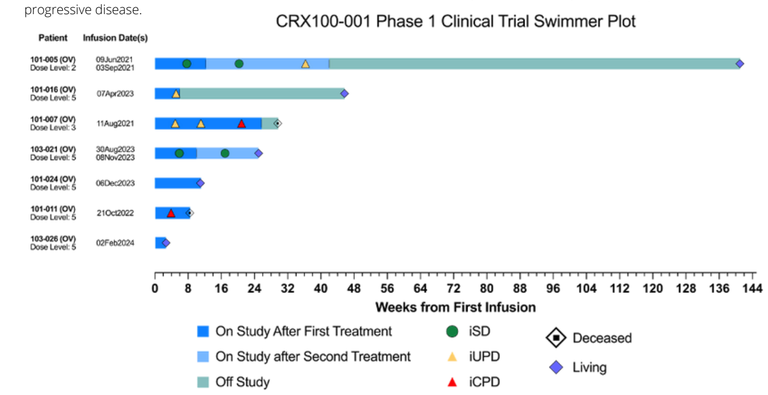


Figure Description: A) 101-005 biomarker and tumor burden data broken out into a separate graph. B) CA-125 biomarker levels for OV patients pre and post infusion levels shown in weeks from infusion. C) Tumor burden in all OV patients shown in weeks from infusion. Currently, patient 101-024 and 103-026 only have pre-infusion data.

SURVIVIAL

Five patients remain alive between 1 and 36 months after cell transfer (CRX100 infusion), while two patients succumbed to progressive disease.



CYTOKINES

Serum IFNγ levels increased on treatment. These observations suggest that CRX100 might induce an inflammatory tumor microenvironment leading to delayed anti-tumor responses and possible improved activity of subsequent immunotherapies.

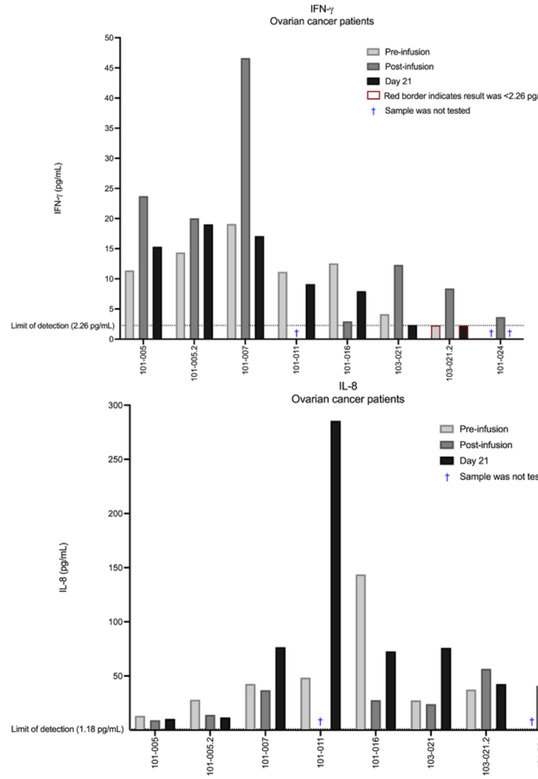


Figure Description: IFN-gamma is a major pro-inflammatory cytokine with known anti-proliferative and pro-apoptotic effects on cancer cells. IL-8 is a pro-angiogenic chemokine proposed as a prognostic biomarker in ovarian cancer. IFN-gamma and IL-8 levels in serum were measured in patients pre-infusion with CRX100 (light gray), 3 hours post-infusion (dark gray), and 21 days post-infusion (black). All patients tested, except 101-016, experienced an increase in serum IFN-gamma levels 3 hours after infusion with CRX100 which then declined by day 21 post-infusion. Only patient 101-005 maintained a higher level of serum IFN-gamma and lower level of IL-8 on day 21 compared to their pre-infusion baseline. IL-8 and IFN-gamma levels are inversely correlated for all patients except 101-016 and 103-021.2. Patients 101-005 and 103-021 received two CRX100 infusions and achieved stable disease while on study. Following their second infusion, patient 101-005 had a larger decrease in IL-8 and patient 103-021 had a smaller increase in IL-8 on day 21 compared to their pre-infusion baseline. This data supports the hypothesis that IL-8 may be a biomarker of cancer progression and response to CRX100.

CONCLUSIONS

This is the first in human trial using adoptive NK-T cell transfer combined with an oncolytic vaccinia virus. The treatment with CRX100 was well tolerated and induced both clinical and immunological responses in patients with recurrent platinum resistant ovarian cancer. Based on our clinical observations and translational data, we are currently developing an expansion protocol that will include lymphodepletion prior to CRX100 treatment, and immune checkpoint inhibition to amplify anti-tumor cellular immune responses in the tumor microenvironment.

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