# *First-in-human* study of the first acid pH-sensitive and recycling CTLA-4 antibody ONC-392 that preserves the immune tolerance checkpoint to avoid immunotherapy-related adverse events in patients with advanced solid tumor (PRESERVE-1, NCT04140526)

Tianhong Li, M.D., Ph.D.[1*], Karen Kelly, M.D.[1], Hui Amy Chen, M.D.[2], Stacy S. Joo[3], Mei Tang, M.D.[4], Paul Celano, M.D.[4] Imaan Khan, M.D.[5], Nicole Do, M.S.[5], Raymond Touomou, M.S.[5], Hung-Yen Chou, Ph.D[5], Martin Devenport, Ph.D[5], Dan Chen, M.D. Ph.D.[5], Yang Liu, Ph.D.[5], and Pan Zheng, M.D., Ph.D.[5]

**Affiliations:** [1]Division of Hematology and Oncology, Department of Internal Medicine, UC Davis Comprehensive Cancer Center, Sacramento, CA, USA, [2]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, UC Davis Comprehensive Cancer Center, Sacramento, CA, USA, [3]Office of Clinical Research, UC Davis Comprehensive Cancer Center, Sacramento, CA, USA, [4]Sandra & Malcolm Berman Cancer Institute, Greater Baltimore Medical Center, Baltimore, MD, USA, [5]OncoC4, Inc., Rockville, MD, USA.

## CTLA-4 in Cancer Immunotherapy: Introduction

- **The first approved immunotherapeutic antibody (Ipilimumab)**
  - **Clinical efficacy in melanoma as monotherapy**
  - **Low dose in combination with Nivolumab approved in NSCLC, RCC, HCC, Colon cancer**
  - **Long lasting remission in some patients who have responded**
- **Limitations: High toxicity limits doses and duration needed for clinical efficacy**
  **Approved doses significantly lower than what is needed for optimal clinical response:**
- **ONC-392, a new anti-CTLA-4 mAb, aims to overcome both limitations**
  - **Preclinical studies showed intrinsic lower toxicity and higher efficacy**
  - **Early clinical data supports safety of longer dosing and clinical activity among patients with stage IV solid tumors**
  - **See Poster #231 for more details on MOA, Poster #533 for trial design, Poster #471 for PK**
- **Safety and clinical efficacy data of Part A of the PRESERVE-1 clinical study (NCT04140526) in patients with refractory, metastatic solid tumors are presented in this poster**

## ONC-392-001: Demographics and Safety Data Summary

| Demographics | |
|---|---|
| **Category** | **Number** |
| Patients | 10 |
| Gender (F/M) | 7/3 |
| White/Asian/Black | 6/3/1 |
| Median age (range) | 62 (43-81) |
| **Cancer type** | **N/Stage** |
| NSCLC | 4/IV |
| Ovarian cancer | 4/IV |
| GE junction cancer | 1/IV |
| Cervical cancer | 1/IV |
| **Prior lines of treatment** | **4 (2 – 7)** |

**Summary of Treatment-Emergent Adverse Events (TEAEs)**

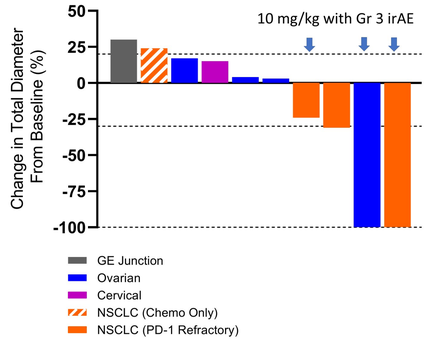
| | Any TEAEs | | | Treatment-Related AEs | | |
|---|---|---|---|---|---|---|
| | 3 mg/kg (N=4) | 10 mg/kg (N=6) | Total (N=10) | 3 mg/kg (N=4) | 10 mg/kg (N=6) | Total (N=10) |
| Any TEAEs | 4 (100%) | 6 (100%) | 10 (100%) | 2 (50%) | 6 (100%) | 8 (80%) |
| Gr1/2 | 4 (100%) | 6 (100%) | 10 (100%) | 2 (50%) | 5 (83%) | 7 (70%) |
| Gr3/4* | 1 (25%) | 4 (67%) | 5 (50%) | 0 | 3 (50%) | 3 (30%) |
| Gr5 | 0 | 0 | 0 | 0 | 0 | 0 |
| DLT | 0 | 0 | 0 | 0 | 0 | 0 |

* The irAEs (all Gr 3) are pancreatitis (1) and colitis (2) after 3 or 4 cycles of 10 mg/kg treatment.

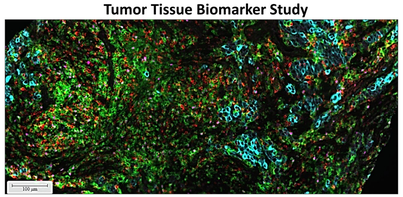
- ONC-392 at all doses was generally well-tolerated. Gr3 irAEs of pancreatitis and colitis were reversible and manageable.
- Recommended Phase II Dose (RP2D) for monotherapy is 10 mg/kg, q3w.

## ONC-392-001 Part A Monotherapy: Best Response and Biomarker Study

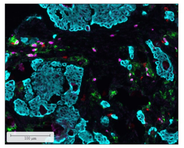
**Best Overall Response pending confirmation CT scan**



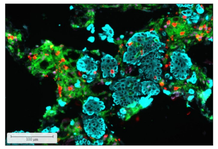

**Tumor Tissue Biomarker Study**



NSCLC patient, 3 mg/kg, 7 cycles, . Red: CD8, Green: CD4, Pink: Foxp3, Cyan: CK (tumor cells)



Ovarian Cancer patient. Biopsy before treatment.

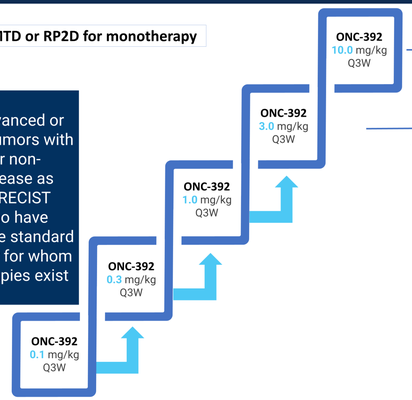


Ovarian Cancer patient. 10 mg/kg, 4 cycles, Biopsy. Red: CD8, Green: CD4, Pink: Foxp3, Cyan: CK (tumor cells)

## ONC-392-001 Part A Monotherapy: Dose Finding

**Objective: To estimate MTD or RP2D for monotherapy**

Patients with advanced or metastatic solid tumors with measurable or non-measurable disease as determined by RECIST version 1.1, who have progressed despite standard of care therapy, or for whom no standard therapies exist




**6 patients dosed at 10 mg/kg dose level**

**2 patients dosed at 3 mg/kg dose level**

**2 pts dose escalated to 3 mg/kg dose level**

## ONC-392-001 Part A Monotherapy: Dosing and Preliminary Outcomes

| | Weeks 3 | 6 | 9 | 12 | | | 24 | | | | 36 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **#1:** Ovarian cancer | 0.1 | 0.3 | 1.0 SD | 3.0 | 3.0 | 3.0 SD | 3.0 | 3.0 | 3.0 SD | 3.0 | 3.0 | PD | |
| **#2:** Cervical cancer | 0.3 | 1.0 | 3.0 SD | 3.0 | 3.0 | PD | | | | | | | |
| **#3:** Gastroesophageal cancer | 3.0 | 3.0 | 3.0 PR | 3.0 | PD | | | | | | | | |
| **#4:** NSCLC | 3.0 | 3.0 | 3.0 SD | 3.0 | 3.0 | 3.0 PD# | 3.0 | Surg# | 3.0 SD | 3.0 | PD | | |
| **#5:** NSCLC | 10.0 | 10.0 | 10.0 PD | 10.0 | PD | | | | | | | | |
| **#6:** NSCLC | 10.0 | 10.0 | 10.0 SD | 10.0 CR | CR* | | | | | | | | |
| **#7:** Ovarian cancer | 10.0 | 10.0 | 10.0 SD | 10.0 | | | | | | | | | |
| **#8:** Ovarian cancer | 10.0 | 10.0 | 10.0 SD | PD | | | | | | | | | |
| **#9:** NSCLC | 10.0 | 10.0 | 10.0 SD | 10.0 | | | | | | | | | |
| **#10:** Ovarian cancer | 10.0 | 10.0 | 10.0 PR | CR* | | | | | | | | | |

*Unconfirmed as of 10/13/21.
#Surgical tissue IHC demonstrated heavy $CD4^+$ and $CD8^+$ T cell infiltration into tumor (biomarker top image).

## Summary and Conclusions

### Safety Summary

- ONC-392 monotherapy was well tolerated.
  - Two patients dosing at 3 mg/kg for 8 or 9 cycles.
  - No DLT or Grade 3/4 AEs during the DLT observation period at any dose.
  - MTD has not been reached; RP2D for monotherapy: 10 mg/kg Q3W.
- Grade 3 immunotherapy-related AEs occurred in 3 patients after 3 or 4 cycles treatment at 10 mg/kg dose – colitis/hypokalemia (2) and pancreatitis (1); 2 of these 3 patients had unconfirmed CR, one had SD with shrinking tumor burden.
- Other TEAEs were grade 1/2. Those occurred in ≥2 patients included infusion-related reactions, pruritus, fatigue, and TSH increase.

### Clinical Activity (pending confirmatory CT scans)

- As of October 13th, 2021, beneficial clinical activity were observed in 4/10 patients
  - At 10 mg/kg, 2/6 had CR pending CT confirmation
  - At 3 mg/kg, 2/4 had SD > 7 months
- At the first tumor assessment after 8 weeks with 3 cycles of treatment, SD in 7/10, and PR in 1/10 patients.
- Activity was seen in 3 mNSCLC patients who failed PD-(L)1 treatment (1 CR, 1 >24 wks disease control and becoming eligible for surgery, and 1 SD at 8 wks with continued treatment) and 3 ovarian cancer patients.

### Conclusions

- ONC-392 monotherapy was safe and well-tolerated; TRAEs were managed. MTD has not been reached. RP2D is 10 mg/kg Q3W.
- ONC-392 monotherapy has demonstrated promising anti-tumor activities in patients with refractory NSCLC and ovarian cancer.
- As the first pH-sensitive mAb that preserves CTLA-4 recycling and avoids lysosomal degradation (see poster No. 231), ONC-392 may fundamentally alter the risk/benefit ratio of CTLA-4 targeting by conferring improved efficacy with reduced toxicity.

The clinical trial is sponsored by OncoC4, Inc, partially supported by NIH grant R44CA250824. The tumor tissue biomarker study was carried out by Ultivue, Inc (Cambridge, MA). We would like to thank the patients, their families and caregivers, and site personnel from UCD and GBMC.

Late Break Poster #949

UC DAVIS HEALTH | COMPREHENSIVE CANCER CENTER

GBMC | SANDRA AND MALCOLM BERMAN CANCER INSTITUTE

OncoC4

Related Posters: #231: Molecular insights on ONC-392, #471: PK results in ONC-392-001 Part A, #533: ONC-392-001 trial design.