Safety and Clinical Activities of ONC-392, a target preserving anti-CTLA-4 mAb, in Ovarian Cancer Patients Who Have Failed Multiple Lines of Systemic Therapies

John Hays, MD[1], Tianhong Li, MD, PhD[2], Hui A. Chen, MD[2], George Zahrah, MD[3], Mei Tang, MD[4], Paul Celano, MD[4], Richard Frank, MD[3], John Hamm, MD[5], Merry-Jennifer Markham, MD, Thomas George, MD[6] Eric D. Whitman, M.D., FRCP[7], Mark G. Goldstein, MD[8], Kai He, MD, PhD[1], Rohit Joshi, MD[9], Dan Chen, MD, PhD[10], Yang Liu, PhD[10], Pan Zheng, MD, PhD[10], and David O'Malley, MD[1].

Affiliations: [1]The Ohio State University James Comprehensive Cancer Center, Columbus, OH,[2]UC Davis Comprehensive Cancer Center, Sacramento, CA, [3]Nuvance Health, Norwalk, CT. [4]Sandra & Malcolm Berman Cancer Institute, GBMC, Baltimore, MD, [5]Norton Cancer Institute, Louisville, KY, [6]University of Florida Cancer Center, Gainesville, FL [7]Atlantic Heath, Morristown, NJ [8]Center for Blood Disorder and Cancer, Bethesda, MD. [9]Cancer Research SA, Adelaide, Australia, [10]OncoC4, Inc., Rockville, MD, USA.

Background

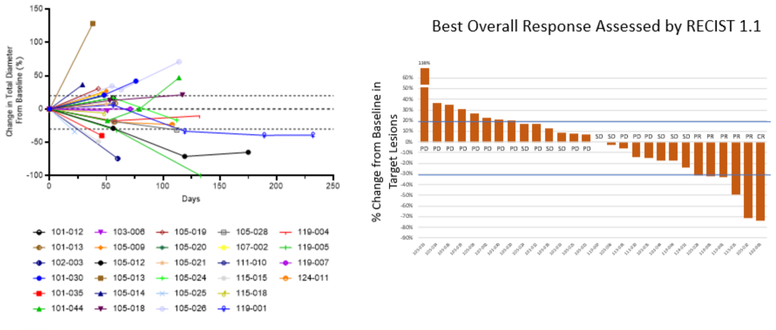
- Despite extensive effort, no immunotherapeutic has been approved for ovarian cancer.
- Ovarian cancer patients who failed multiple lines of systemic therapeutic have extremely poor outcomes.
- ONC-392, the first acidic pH-sensitive anti-CTLA-4 mAb, is being tested in patients with solid tumor who failed multiple lines of systemic therapy.
  - Preclinical studies showed better therapeutic index in both monotherapy and combination.
  - Early clinical data supports safety of prolonged dosing and clinical activity in monotherapy among patients with stage IV solid tumors, including tumor types that are resistant to immunotherapy (See poster #594 for combination therapy data).
  - RP2D for monotherapy is 10 mg/kg.
  - Dose expansion studies (Part C) are ongoing in multiple cancer indications.
- Safety and clinical efficacy data for ovarian cancer patients in the PRESERVE-001 clinical study (NCT04140526) who received at least one dose of ONC-392 at 10 mg/kg are presented.

Arm L, Ovarian Cancer: Demographics and Safety Data Summary

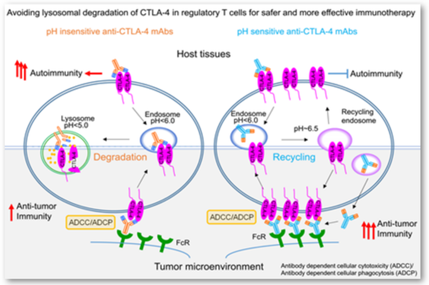
Inclusion Criteria	Exclusion Criteria
1. Age ≥ 18 yrs old. 2. Male or Female; Female must have negative pregnancy test. 3. Must have ECOG score ≤ 1. 4. A histological or cytological diagnosis of ovarian cancer and progressive metastatic disease or progressive locally advanced disease 5. Adequate organ function as determined by laboratory tests 6. Voluntary agreement to participate as evidenced by written informed consent. 7. Female patient: agreement on contraceptive methods. 8. Male patient: agreement on contraceptive methods. 9. Patient agrees to grant study team the access to archival diagnostic tissue (recut slides or tumor biopsy).	1.Patients who have not recovered to NCI CTCAE ≤ 1 from an adverse event (AE) due to cancer therapeutics. The washout period for cancer therapeutic drugs should be 21 days for chemotherapy, radiation, or targeted therapy or 28 days for monoclonal antibody therapy. Best supportive care, such as replacement treatment and therapy for non-cancer conditions are allowed. 2.Patients who are currently enrolled in any other clinical trial testing an investigational agent or device or with concurrent other systemic cancer therapeutics. 3.Patients who are on chronic systemic steroid therapy at doses higher than 10 mg/day prednisone or equivalent. 4.Patients who previously had a severe infusion reaction to another mAb. 5.Patients who have an active infection requiring systemic IV antibiotics within 14 days prior to administration of ONC-392. Regular treatment of urinary tract infection (UTI) and/or topical treatment are allowed. 6.Patients who, in the opinion of the treating Investigator, have a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study, or make study participation not in the best interest of the patient. Investigator should discuss with Sponsor and/or study leaders. 7.Patients with known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

Categories	Data
Subject enrolled	32
Race (white/Ascian/Black)	27/3/2
Ethnicity (Hispanic or Latino)	5 (16%)
Median age (range)	67.5 (40-82)
Cancer type	
High grade serous OC	30
Carcinosarcoma	1
Peritoneal Adenocarcinoma	1
ECOG score	
ECOG = 0	13 (41%)
ECOG = 1	19 (59%)
Tumor Burden at Baseline Median (Q1, Q3), mm	87.5 (39, 126)
Have Metastatic Lesions	29 (91%)
ONC-392 related AE (TRAE): all grades	81% (26/32)
TRAE: Grade 3	31% (10/32) Diarrhea or colitis (6) Myocarditis (1), Hepatitis (1) Fatigue (1), AKI (1).
TRAE: Grade 4	3% (1/32) shock
TRAE: Grade 5	0

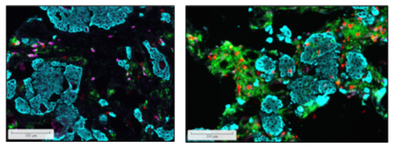
Clinical activity: best of response among evaluable patients (N=28)



PRESERVE-001 Study - Monotherapy



Tumor biopsy before and after ONC-392 treatment



Ovarian Cancer patient. Biopsy before treatment.

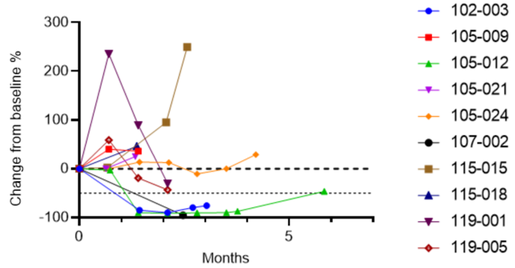
Ovarian Cancer patient, 10 mg/kg, 4 cycles. Biopsy

Red: CD8, Green: CD4, Pink: Foxp3, Cyan: CK (tumor cells)

Monotherapy dose expansion cohorts

Arm A: Pancreatic Cancer	Arm K: HN Cancer
Arm B: TNBC	Arm L: Ovarian Cancer
Arm C: NSCLC w driver mutations	Arm M: Other Solid Tumors
Arm I: NSCLC, PD-1 R/R	

Tumor marker CA-125 responses (N=10)



Summary And Conclusions

Safety Summary

- The safety data set consists of 32 patients. The median age is 67.5 (range 40- 82), White/Asian/Black: 27/3/2, and 5 Hispanic. The median follow up is 6.7 months.
- Treatment related AEs (TRAEs) were observed in 26 (81%) patients.
- Grade 3 TRAEs were observed in 10 pts (31%): myocarditis (1), diarrhea (2), immune-mediated colitis or colitis (4), immune hepatitis (1), fatigue (1), AKI (1).
- Grade 4 TRAE in 1 patient with hypotensive shock (3%).
- No grade 5 AE was observed.

Clinical Activity

- Twenty-eight patients who received at least one doses of 10 mg/kg of ONC-392 were evaluable for tumor response.
- The CR/PR/SD/PD numbers are 1/5/8/14 (ORR=21%, DCR=50%).
- 3/10 patients achieved >50% reduction in CA125 tumor marker

Conclusions

- The safety profile of 10 mg/kg x 2, followed by 6 mg/kg Q3W is comparable to patients who received substantially lower doses other CTLA-4-targeting drug in the ovarian cancer patients.
- While the number of evaluable patients is small, the preliminary assessment suggests ONC- 392 monotherapy has clinical activity among patients who failed multiple lines of systemic therapy. The available data support continued clinical testing of ONC-392 in ovarian cancer.
- A new Phase 2 study with ONC-392 in combination with pembrolizumab will initiate in Q4 2022 (PRESERVE-004, MK3475-E24, GOG-3081, NCT05446298).

Poster #564