FIRST-IN-HUMAN STUDY OF THE FIRST ACID pH-SENSITIVE AND RECYCLING CTLA-4 ANTIBODY THAT PRESERVES THE IMMUNE TOLERANCE CHECKPOINT TO AVOID IMMUNOTHERAPY-RELATED ADVERSE EVENTS IN CANCER PATIENTS

¹Tianhong Li*, ²Mei Tang, ³Karen Kelly, ³Hui Amy Chen, ³Stacy Joo, ⁴Imaan Khan, ⁴Nicole Do, ⁴Raymond Toumou, ⁴Dan Chen, ⁴Yang Liu, ⁴Pan Zheng. ¹University of California at Davis, Sacramento, CA, USA; ²Berman Cancer Institute at GBMC, Baltimore, MD, USA; ³UC Davis Comprehensive Cancer Center, Sacramento, CA, USA; ⁴OncoC4, Inc., Rockville, MD, USA

Background CTLA-4 is the first immune checkpoint target for cancer immunotherapy. However, the clinical benefit of targeting CTLA-4 has been limited by suboptimal doses and early discontinuation due to immunotherapy-related adverse events (irAE). Our preclinical studies suggest that acid pH-sensitive anti-CTLA-4 antibodies that preserve CTLA-4 recycling and avoid lysosomal degradation are more effective for immunotherapy but largely devoid of immunotherapy-related adverse events (irAE) [1-6]. To test this new hypothesis in human, we initiated first-in-human study evaluating the safety and tolerability of ONC-392 in patients with advanced solid tumors.

Methods ONC-392-001 Part A is a dose finding study of ONC 392, IV infusion, Q3W. Patients (pt) with advanced solid tumors who had progressed to standard of care cancer therapies with ≥ 1 measurable tumor were enrolled. Inpatient dose-escalation were performed for 4 doses (0.1, 0.3, 1.0 and 3.0 mg/kg) and 6 pts for the final dose of 10.0 mg/kg. The primary endpoints are the safety and tolerability of ONC-392 for identifying recommended Phase II dose (RP2D).

Results Ten pts have received 2-11 cycles of ONC-392 treatment at dose levels ranging from 0.1 to 10 mg/kg. Pt characteristics: median age 62 (range 43-81), female/male: 7/3, White/Asian/Black: 6/3/1. Tumor types: 4 ovarian, 4 NSCLC, 1 cervical and 1 GE junction cancer. Prior line of treatment: 2-7. Six pts were in 10 mg/kg dose level and received 2-4 doses of the drug as of this writing. None of the 10 pts experienced dose limiting toxicity (DLT) or Gr 3-4 adverse events (AEs) in DLT period. The RP2D for ONC-392 monotherapy is 10 mg/kg. After the DLT period, 1 patient developed Gr 3-4 elevated amylase/lipase at 10 weeks after 4 cycle of 10 mg/kg. No other treatment-related severe AE was observed. Among eight evaluable pts, 7/8 (87.5%) had stable disease (SD) after three cycle of treatment, and beneficial clinical efficacy activities was observed in 3/8 (37.5%) pts. Among them, a stage 4B ovarian cancer patient had stayed in treatment for 30 weeks till disease progression, and 2/2 evaluable PD(L)-1 antibody-refractory NSCLC patients were either eligible for surgery or had significant tumor shrinkage.

Conclusions ONC-392 monotherapy is well tolerated with very low irAE rate. The RP2D for ONC-392 monotherapy is 10 mg/kg. The acid pH-sensitive anti-CTLA-4 mAb that preserves CTLA-4 recycling and avoids lysosomal degradation was safe and well tolerated. Our work paves the way for significant increase of drug exposure to reach full immunotherapeutic potential of CTLA-4 targeting.

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Trial Registration NCT04140526

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Ethics Approval This study obtained ethic approval from WIRB with Study #20193108. All participants gave informed consent before taking part of the study.

Consent N/A.

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