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. Intravenous 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: 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-L1 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.

Acknowledgements The study is sponsored by OncoC4, Inc with the support of NCI SBIR grant R44CA250824.

Trial Registration NCT04140526

REFERENCES

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.

http://dx.doi.org/10.1136/jitc-2021-SITC2021.949