Clinical protocol of an open label Phase IA/IB study for safety, pharmacokinetics (PK), and efficacy of ONC-392 as a single agent and in combination with Pembrolizumab in advanced solid tumors

Yang Liu, Ph.D., Kun He, Ph.D . and Pan Zheng, M.D., Ph.D.

[1]OncoC4, Inc., Rockville, MD, USA,

Background: ONC-392 is a highly selective, humanized monoclonal IgG1 antibody against CTLA-4. The parental clone was identified through *in vivo* screening in a humanized CTLA-4 mouse model for high anti-tumor efficacy and low autoimmune toxicity. By preserving CTLA-4 on the cell surface, ONC-392 leaves a higher ligand density for better antibody-dependent cellular cytotoxicity (ADCC), resulting in more efficient in Treg depletion in the tumor microenvironment (TME) and more potent tumor rejection in pre-clinical models. Based on encouraging Phase I dose escalation study, a major revision of the protocol has been performed to expand clinical indications among patients with advanced solid tumors.

Summary of the clinical protocol:

This is a Phase IA/IB, open label, dose-escalation, and dose-expansion study of intravenous (IV) ONC 392 as a single agent and in combination with Pembrolizumab (anti PD-1, marketed as KEYTRUDA® by Merck) in patients with advanced/metastatic solid tumors.

The study consists of three parts:

(1) Part A (Figure 1) is a dose-finding rapid titration study of ONC-392 as a single agent in patients with advanced solid tumors of various histology to define the recommended Phase II dose for ONC-392 monotherapy (RP2D-M).

(2) Part B (Figure 2 and 3) has Part B1 and Part B2 as dose-finding for combination therapy with either pembrolizumab or Osimertinib 80 mg orally once daily to define the recommended Phase II dose for ONC-392 in combination with either drug

(3) Part C (Figure 4) Phase IB expansion cohorts of ONC-392 in monotherapy and in combination therapy with Pembrolizumab to determine safety and initial efficacy. A total of 13 cohorts encompassing monotherapy for Pancreatic Cancer, TNBC, NSCLC, Mel, HNSCC, Ovarian Cancer, Solid Tumors and combination therapy of non-small cell lung carcinoma, melanoma and Markel cell carcinoma.

The primary endpoints for Part A and B are safety and tolerability to observe maximal tolerable dose and recommended doses for Phase II, while that for part C is efficacy as measured by overall response rates. The planned enrollment of up to 468 patients will have the accrual period of 24 months.

Objectives:

Part A: MTD or RP2D-M, safety and tolerability.

Part B: MTD or RP2D-C, safety and tolerability.

Part C: ORR as primary objective. DoR, DCR, PFS, OS as secondary objectives.

Figure 1: Part A Study Diagram

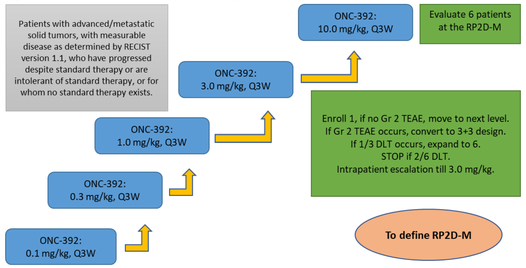


Figure 2: Part B1 Study Diagram

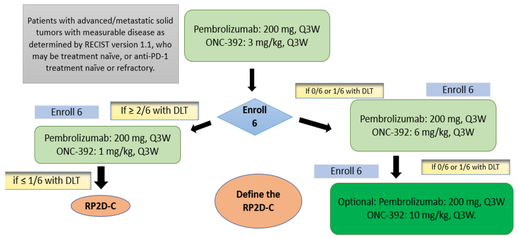


Figure 3: Part B2 Study Diagram

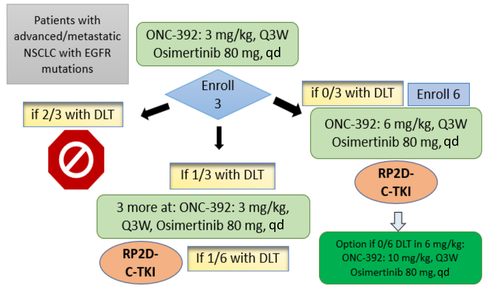
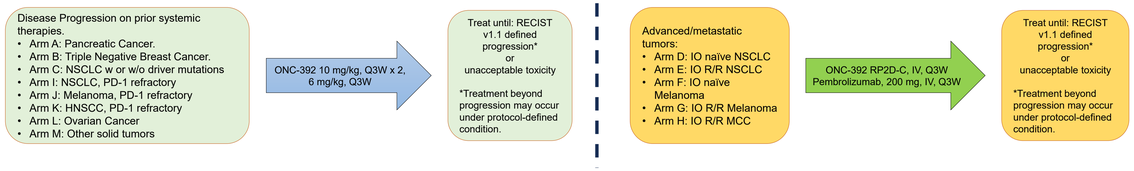


Figure 4: Part C Study Diagram



Eligibility :

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 solid tumors 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. In expansion cohort arms, patient agreement 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 or combined ONC-392 and Pembrolizumab. 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. 8. Patients who are pregnant or breastfeeding. 9. For Part B1 and Part C Arm D to H, patients who are deemed to be not suitable for Pembrolizumab as standard of care treatment.

Clinical Trial In Progress

Poster #533

Related Posters: #231: Molecular insights on ONC-391, #471: ONC-392-001 Part A PK, #949: Late breaking