

SINGLE-AGENT SAFETY AND ACTIVITIES OF TARGET-PRESERVING ANTI-CTLA-4 ANTIBODY GOTISTOBART (ONC-392/BNT316) IN PD-(L)1 RESISTANT METASTATIC NSCLC AND POPULATION PK ANALYSIS IN PATIENTS WITH SOLID TUMORS

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Background Although CTLA-4 was the first validated target in immunotherapy, available anti-CTLA-4 monoclonal antibodies (mAbs) have shown very limited therapeutic activity as a single agent. Preclinical studies showed that gotistobart (ONC-392/BNT316), a CTLA-4 target-preserving anti-CTLA-4 mAb, is more effective and less toxic than other clinically used anti-CTLA-4 mAbs. Using samples from a first-in-human study in patients with advanced solid tumors, we evaluated population pharmacokinetics of gotistobart based on samples from the monotherapy and combination therapy arms. The safety and clinical activities of gotistobart as a single-agent in NSCLC patients who progressed on PD-(L)1-therapy were explored.

Methods PD-(L)1 resistant metastatic NSCLC patients were enrolled in dose escalation and dose expansion Arm I in PRE-SERVE-001 study (NCT04140526). Safety was evaluated based on treatment emergent and treatment-related adverse events, while efficacy was evaluated by investigators using RECIST1.1 criteria. A population PK model was constructed with 420 measurable PK observations from 70 patients, including 57 patients receiving ONC-392 monotherapy and 13 patients receiving ONC-392 and pembrolizumab.

Results As of May 15, 2023, 35 PD-(L)1 resistant mNSCLC patients received at least one dose of ONC-392 at 10 mg/kg. Among the patients who received 10 mg/kg x 2, followed by 6 mg/kg, Q3W, Gr 3–4 irAE rate was 30% with a median follow up of 12 months in alive patients. No ONC-392-related Gr 5 AEs were observed. Eight responders (1 CR and 7 PR), including 2 unconfirmed responses were observed among 27 evaluable patients with ORR of 29.6%. The median duration of response is greater than 6 months. Survival data will be presented in the meeting. PK of ONC-392 are best described by a 2-compartment model with first-order elimination. The systemic clearance (CL) of ONC-392 was estimated to be 182 mL/day, and the terminal $t_{1/2}$ was estimated to be 25.7 days. Increased albumin level is associated with decreased CL, while that of body weight is associated with increased V1 and V2. No effects of age, sex, race, AST, bilirubin, creatinine clearance, cancer type and concurrent immunotherapy with pembrolizumab were significant PK covariates.

Conclusions Gotistobart (ONC-392/BNT316) monotherapy at 10 mg/kg x 2 followed by 6 mg/kg, Q3W is safe and tolerable and appears to be the first anti-CTLA-4 mAb with

significant single agent anti-tumor activity in IO-resistant NSCLC. Gotistobart has the desirable PK characteristics of long half-life and delayed clearance for an immunotherapy antibody.

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Trial Registration NCT04140526.

Ethics Approval This study obtained ethic approval from WCG IRB with study #20193108 or the local institutional IRBs. All participants gave informed consent before taking part of the study.

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