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

Kai He, MD, PhD[1#], *Meredith McKean, MD*[2], *Rama Balaraman, MD*[3], *Satish Shah, MD*[4], *Edward Arrowsmith, MD*[5], *Julio A Peguero, MD*[6], *John Hamm, MD*[7], *Aiwu R He, MD, PhD*[8], *Alexander I Spira, MD*[9], *Adriana M. Milillo-Naraine, MD*[10], *Rohit Joshi, MD*[11], *Mark G Goldstein, MD*[12], *David P Carbone, MD, PhD*[1], *Mei Tang, MD, PhD*[13], *Siwen Hu-Lieskovan, MD, PhD*[14], *Zihai Li, MD, PhD*[1], *Dan Chen, MD, PhD*[15], *Hung-Yen Chou, PhD*[15], *John Yang, PhD*[15], *Yang Liu, PhD*[15], *Pan Zheng, MD, PhD*[15], *and Tianhong Li, MD, PhD*[16]

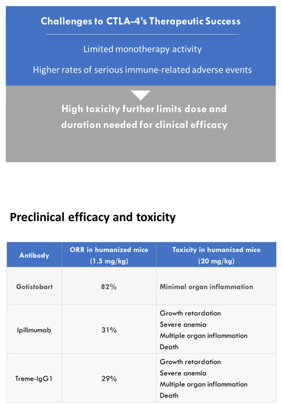
Affiliations: *[1] Pelotonia Institute for Immuno-Oncology, The Ohio State University Comprehensive Cancer Center, Columbus, OH; [2]Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN; [3]Ocala Oncology, Ocala, FL; [4]Pennsylvania Cancer Specialists Research Institute, Gettysburg, PA; [5]Tennessee Oncology, Chattanooga, TN; [6]Oncology Consultants, Houston, TX; [7]Norton Healthcare, Louisville, KY; [8]Ruesch Center for the Cure of Gastrointestinal Cancers, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC; [9]Virginia Cancer Specialists, Fairfax, VA; [10]Memorial Cancer Institute, Pembroke Pines, FL , MD; [11]Cancer Research SA, Adelaide, Australia;[12]Center for Cancer and Blood Disorders, Bethesda; [13]Greater Baltimore Medical Center, Baltimore, MD, [14]Huntsman Cancer Institute/University of Utah Health, Salt Lake City, UT, [15]OncoC4, Inc., Rockville, MD, [16]UC Davis Comprehensive Cancer Center, Sacramento, CA.*

ONC-392/BNT316 is a Target-Preserving Nextgen Anti-CTLA-4 Antibody

Background and Method

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-preservinganti-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.

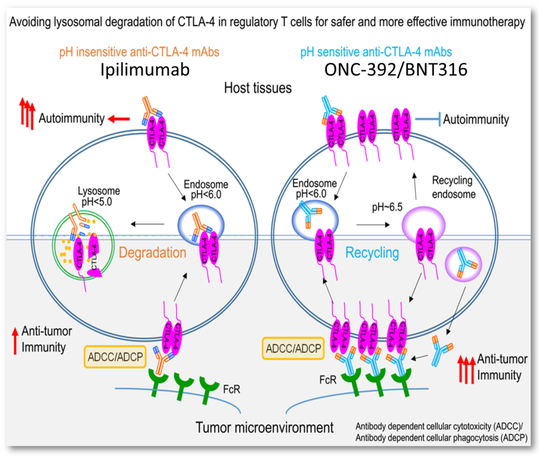
Methods: PD-(L)1 resistant metastatic NSCLC patients were enrolled in dose escalation and dose expansion Arm I in PRESERVE-001 study(NCT04140526). Safety was evaluated based on treatment emergent and treatment-related adverse events, while efficacy was evaluated by investigators using RECIST1.1 criteria. 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.



Preclinical efficacy and toxicity

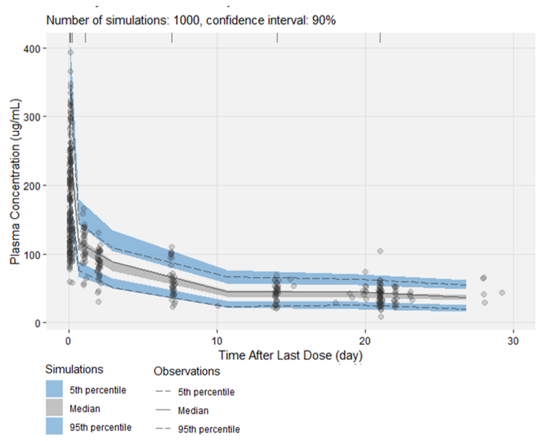
Antibody	ORR in humanized mice (1.5 mg/kg)	Toxicity in humanized mice (20 mg/kg)
Gotistobart	82%	Minimal organ inflammation
Ipilimumab	31%	Growth retardation Severe anemia Multiple organ inflammation Death
Treme-IgG1	29%	Growth retardation Severe anemia Multiple organ inflammation Death

Mechanism of action



Modified from *Trends Pharmacol Sci*. 2020;41(1):4-12 and *Cell Res*. 2018 Apr;28(4):416-432; 2018 Apr;28(4):433-447; 2019 Aug;29(8):609-627

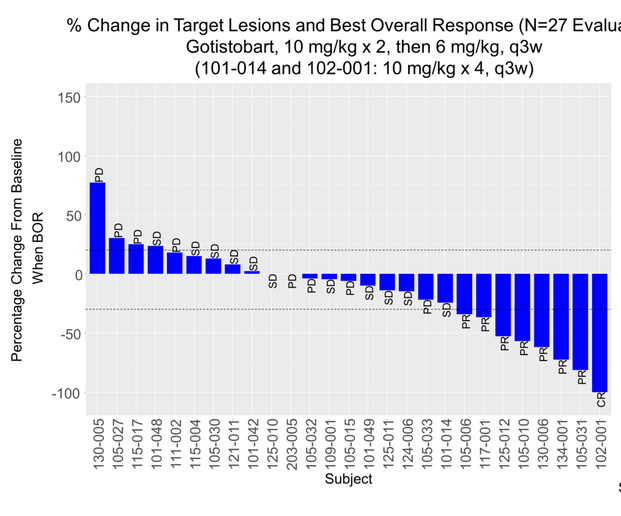
Population PK Data Summary

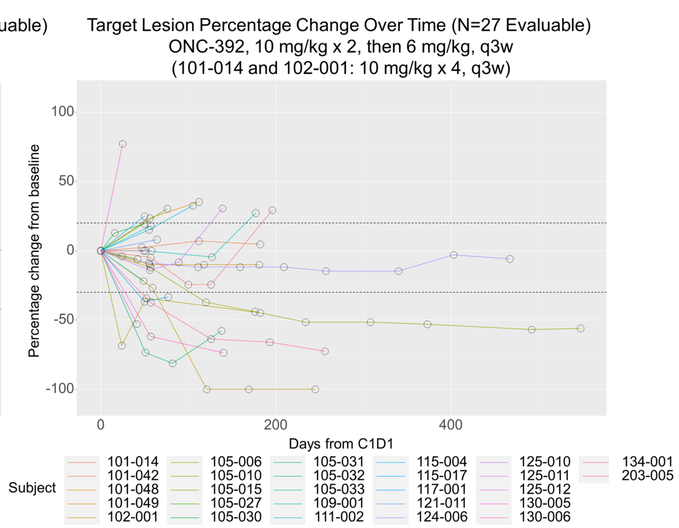


Visual Predictive Check (VPC) Results

- Gotistobart PK was well characterized by a TWO-compartment model with first-order elimination.
- Dose of 10 mg/kg Q3W x 2 + 6 mg/kg Q3W allows the systemic concentration to reach the steady state level after the 2nd dose and maintains high trough levels throughout the dosing period.
- CL was estimated to be 182 mL/day in a typical subject with bodyweight of 70 kg and albumin level of 3.60 g/dL.
- The typical central volume of distribution was estimated to be 2850 mL and the typical peripheral volume of distribution was estimated to be 3340 mL.
- Half life was estimated to be 25.7 days for a typical subject (70kg, Albumin 3.6g/dL).
- Albumin was identified as a significant covariate for CL; increased albumin level is associated with decreased CL.
- Body weight was identified as a significant covariate for volume terms including V1 and V2; increased body weight is associated with increased V1 and V2.
- No effects of age, sex, race, AST, bilirubin, creatinine clearance , and cancer type on ONC-392 PK were detected.

Clinical Activity in PD-(L)1 Inhibitor Resistant NSCLC

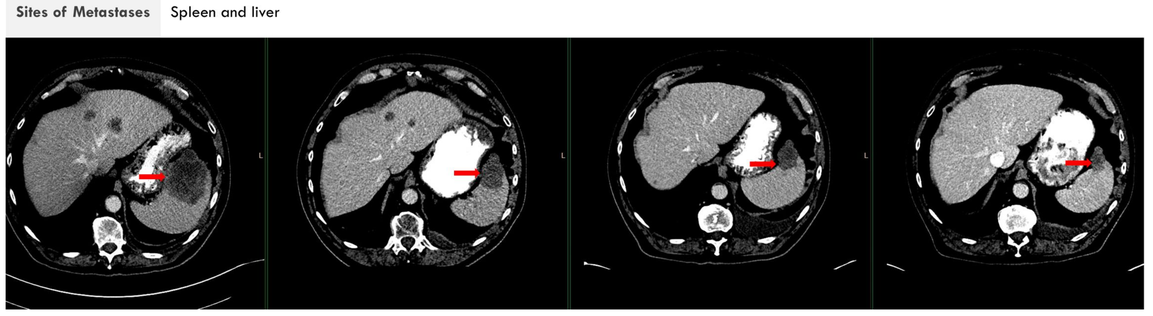




Dada as of Sep. 2023

Clinical Responses to Gotistobart Monotherapy

	Case 64-year-old male
Diagnosis	Squamous cell carcinoma of lung in Aug 2021, 100 pack years smoking history (quit 15 years ago) Tumor PD-L1 <1%. TMB 4. No actionable mutations. Microsatellite status is stable.
Prior Therapy	Initially treated at outside hospital with chemo-RT (weekly paclitaxel and carboplatin), completed in Nov 2021. PET/CT on 12/10/21 showed disease progression with metastases. Started with carboplatin, paclitaxel, ipilimumab and nivolumab; then had progression after 2 cycles of treatment
Sites of Metastases	Spleen and liver



Feb. 2022, baseline	Jul. 2022	Oct. 2022	Sep. 2023

Gotistobart started March 2022; active in treatment cycle 25 as of Sep. 2023

Demographics and Safety Data Summary

Categories	Demographics and basic characteristics
Subject enrolled	35
Median age (range) [Q1, Q3]	66 (43 - 89) [60, 75]
Gender	15F (43%), 20M (57%)
Race (white/Black)	33/2
Ethnicity (Hispanic or Latino)	2
Cohorts	
Part A: NSCLC, PD-1 R/R, 10 mg/kg, q3w	2
Arm I: NSCLC, PD-1 R/R 10 mg/kg x 2, then 6 mg/kg, q3w	33
Non-squamous cell carcinoma	20 (57%)
Squamous cell carcinoma	15 (43%)
ECOG score	
ECOG = 0	9 (26%)
ECOG = 1	26 (74%)
Have Metastatic Lesions	35 (100%)
Safety Data (cutoff date: 03/10/2023)	
ONC-392 related AEs (TRAEs): All grades	26 (74%)
TRAEs: Grade 3-4	15 (43%)
irAEs: All grades	19 (54%)
irAEs: Grade 3-4	12 (34%)
TRAEs leading to dose interruption	9 (26%)
TRAEs leading to dose reduction	1 (3%)
TRAEs leading to study drug discontinuation	7 (20%)

Summary of TRAEs (N=35)			
System Organ Class	All Grade (≥2 cases)	Grade 3	Grade 4
Preferred Term	N (%)	N (%)	N (%)
Gastrointestinal disorders			
Diarrhea	5 (14%)	1 (3%)	0
Colitis	4 (11%)	3 (9%)	0
Nausea	2 (6%)	1 (3%)	0
Vomiting	3 (9%)	1 (3%)	0
General disorders and administration site conditions			
Fatigue	4 (11%)	1 (3%)	0
Chills	4 (11%)	0	0
Pyrexia	3 (9%)	0	0
Skin and subcutaneous tissue disorders			
Rash maculo-papular	0	0	0
Pruritus	2 (6%)	0	0
Rash	2 (6%)	0	0
Injury, poisoning and procedural complications			
Infusion related reaction	7 (20%)	0	0
Investigations			
AST/ALT increased	6 (17%)	1 (3%)	1 (3%)
Musculoskeletal and connective tissue disorders			
Muscular weakness	3 (9%)	3 (9%)	0
Other significant Grade 3 TRAEs: Immune pancreatitis (1), Intestinal perforation (1), Adrenal insufficiency (1), Tubulointerstitial nephritis (1), immune hepatitis (1).			

Summary and Conclusions

- Gotistobart has the PK characteristics typical of clinically used immunotherapy monoclonal humanized antibodies.
- Gotistobart monotherapy at 10 mg/kgx2 followed by 6 mg/kg, Q3W demonstrates a tolerable and manageable safety profile.
- Rate of severe irAE (30%) in dose expansion cohort is relatively lower than that reported rates for other CTLA-4 inhibitors at comparable doses.
- Gotistobart monotherapy shows strong anti-tumor activity in patients with IO-resistant NSCLC.
- These results support initiation of a pivotal study of Gotistobart (ONC-392/BNT316) monotherapy for treating PD-(L)1-resistant NSCLC (NCT05671510).

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sitc 2023 San Diego Nov. 1–5