Safety and Clinical Activity of Target Preserving Anti-CTLA-4 Antibody ONC-392/BNT316 as Monotherapy in NSCLC Patients who Progressed on PD-(L)1 targeting Immunotherapy

Abstract # 9024

Kai He, MD, PhD.[1], David P Carbone, MD, PhD[1], Meredith McKean, MD[2], Rama Balaraman, MD[3], Satish Shah, MD[4], Edward Arrowsmith, MD[5], Julio A Peguero, MD[6], Rohit Joshi, MD[7], Aiwu R He, MD, PhD[8], Adriana M. Milillo-Naraine, MD[9], John T Hamm, MD[10], Mark G Goldstein, MD[11], Zihai Li [1], MD, PhD[1], Dan Chen, MD, PhD.[12], Yang Liu, PhD.[12], Pan Zheng, MD, PhD.[12], and Tianhong Li, MD, PhD.[13*]

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]Cancer Research SA, Adelaide, Australia; [8]Ruesch Center for the Cure of Gastrointestinal Cancers, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC; [9]Memorial Cancer Institute, Pembroke Pines, FL; [10]Norton Cancer Institute, Louisville, KY; [11]Center for Cancer and Blood Disorders, Bethesda, MD; [12]OncoC4, Inc., Rockville, MD; [13]UC Davis Comprehensive Cancer Center, Sacramento, CA, *Corresponding Author.

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

Background and Method

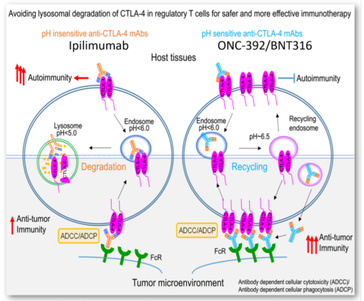
Background

PD-1 or PD-L1 inhibitors have transformed clinical care for NSCLC patients. However, many patients may develop primary or secondary resistance to PD-(L)1 inhibitors. The marketed anti-CTLA-4 mAbs are ineffective as monotherapy for NSCLC. ONC-392/BNT316 is a novel target-preserving anti-CTLA-4 antibody that confers immunotherapeutic efficacy by selective depletion of regulatory T cells (Treg) in the tumor microenvironment. Preclinical studies show that ONC-392/BNT316 is more effective and less toxic for immunotherapy than other clinically used anti-CTLA-4 antibodies. In the first-in-human study in patients with advanced solid tumors, the recommended Phase 2 dose (RP2D) for ONC-392/BNT316 monotherapy was established as 10 mg/kg. In this study, we tested the safety and clinical activities of ONC-392/BNT316 in an expansion chohort NSCLC patients who progressed on PD(L)1-targeted therapy.

Methods:

Metastatic NSCLC patients who lack targetable driver gene mutations and progressed on anti-PD-(L)1 therapy were enrolled as part of PRESERVE-001 study (NCT04140526) Part A dose escalation cohort (10 mg/kg, Q3W, N=2) or the Part C expansion cohort Arm I and treated with 2 cycles of ONC-392/BNT316 10 mg/kg, followed by 6 mg/kg, q3w (N=33), by IV infusion. Safety was evaluated based on treatment emergent and treatment-related adverse events, while efficacy was evaluated by investigators using RECIST1.1 criteria.

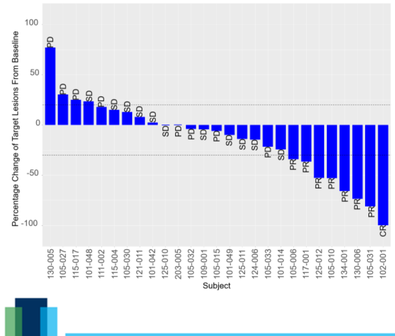
Mechanism of action



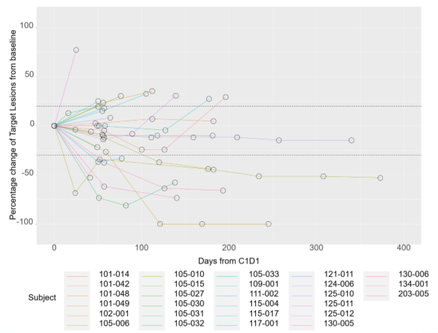
Liu Y, Zheng P. Preserving the CTLA-4 Checkpoint for Safer and More Effective Cancer Immunotherapy. *Trends Pharmacol Sci*. 2020;41(1):4-12. doi:10.1016/j.tips.2019.11.003

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

Target Lesion Best Overall Response (N=27 Evaluable)
ONC-392, 10 mg/kg x 2, then 6 mg/kg, q3w
(101-014 and 102-001: 10 mg/kg x 4, q3w)



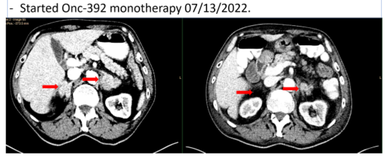
Target Lesion Percentage Change Over Time (N=27 Evaluable)
ONC-392, 10 mg/kg x 2, then 6 mg/kg, q3w
(101-014 and 102-001: 10 mg/kg x 4, q3w)



Response to ONC-392/BNT316 Treatment: Representative Cases

Case 1

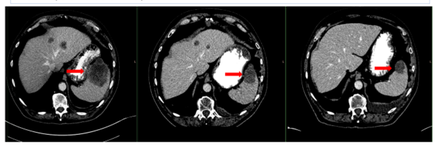
- 75-year-old male was diagnosed a stage IV lung adenosquamous carcinoma in Jan 2019. Tumor PD-L1 25%. TMB 8. No actionable mutations. MMR is proficient
- Since Feb 2019, received 1st line treatment with carboplatin, paclitaxel, and pembrolizumab, followed by pembrolizumab maintenance.
- SBRT for oligo-progression in LUL In Jan 2022
- Systemic cancer progressed with metastases in adrenal glands and brain in May 2022. s/p SRS to brain lesion Jun 2022.
- Started Onc-392 monotherapy 07/13/2022.



Jun. 2022, baseline | Sep. 2022, Right adrenal lesion resolved

Case 2

- 64-year-old male, with 100 pack years smoking history (quit 15 years ago) was diagnosed a squamous cell carcinoma of lung in Sep 2023. Tumor PD-L1 <1%. TMB 4. No actionable mutations. Microsatellite status is stable.
- Initially treated at outside hospital with chemo-RT (weekly paclitaxel and carboplatin), completed in Nov 2022. PET/CT on 12/10/21 showed disease progression with metastases in spleen and liver.
- Started with carboplatin, paclitaxel, Ipilimumab and nivolumab; however, cancer continued to progress after 2 cycles of treatment.
- Onc-392 monotherapy started 03/07/2022. Patient is active in treatment and in cycle 19 as of May 2023.



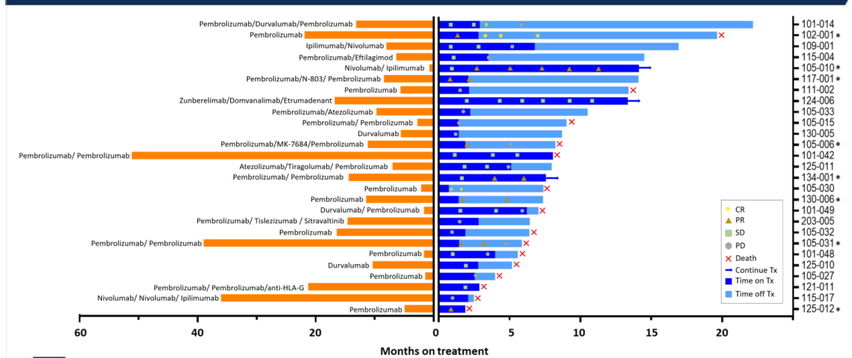
Feb. 2022, baseline | Jul. 2022 | Oct. 2022

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 AE (TRAE): All grades	26 (74%)
TRAE: Grade 3-4	15 (43%)
irAEs: All grades	19 (54%)
irAE: Grade 3-4	12 (34%)
TRAE leading to dose interruption	9 (26%)
TRAE leading to dose reduction	1 (3%)
TRAE leading to study drug discontinuation	7 (20%)

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).			

Prior Anti-PD-1/ PD-L1/CTLA-4 Treatment and ONC-392/BNT316 Treatment



All 27 evaluable patients had prior platinum-based chemotherapy. The * indicates responders to ONC-392 monotherapy.

Summary and Conclusions

Safety Summary (03/10/2023 Datacut)

- ONC-392/BNT316 was tolerated at a dose regimen at 10 mg/kg x 2 then 6 mg/kg, q3w.
  - Longest dosing up to 19 cycles and continuing.
- Grade 3-4 TRAEs were observed in 13 pts (39%) with a follow up period from 7 to 18 months. 10 pts (30%) had Gr 3-4 irAEs. No ONC-392/BNT316 related Gr. 5 AE was observed. Significant irAEs include:
  - 2 immune-mediated colitis.
  - 1 intestinal perforation
  - 1 Gr. 4 ALT/AST increased and immune hepatitis
  - 1 Adrenal insufficiency
  - 1 Tubulointerstitial nephritis

The study is part of an ongoing Phase 1 / 2 study (NCT04140526).
OncoC4 is the sponsor of the study, partially supported by NCI SBIR R44CA250824 to PZ, KH and TL.

Clinical Activity

- Response rate among the evaluable patients is 29.6% (22.2% confirmed and 7.4% unconfirmed).
  - 1 CR and 1 SD in 2 patients with ONC-392/BNT316, 10 mg/kg q3w for 4 doses.
  - 7 PR and 10 SD among 25 evaluable patients in the expansion cohort with ONC-392/BNT316 dose regiment of 10 mg/kg x 2, then 6 mg/kg q3w.
  - Responders include those that failed multiple IO agents targeting PD-(L)1, CTLA-4, and TIGIT.
  - All but 1 responders have been on treatment of PD-(L)1 targeting agents for >12 weeks, which is provisionally defined as PD-(L)1-resistant NSCLC.
- Survival follow up is ongoing.

Conclusions

- ONC-392/BNT316 was generally safe and tolerated at 10 mg/kgx2, followed by 6 mg/kg Q3W. Treatment-related AEs are manageable.
- Severe irAE rate in dose expansion cohort (30%) is considered lower than what was reported for drugs of the similar class of drug at comparable doses.
- Early readout of the expansion cohort shows strong clinical activity in patients with IO-resistant NSCLC.
- These results support initiation of a pivotal study using ONC-392/BNT316 monotherapy for PD-(L)1-resistant NSCLC (Poster TPS#9146, NCT05671510).

Related Poster: #TPS9146
PRESERVE-003 Study Design

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

Background and Method

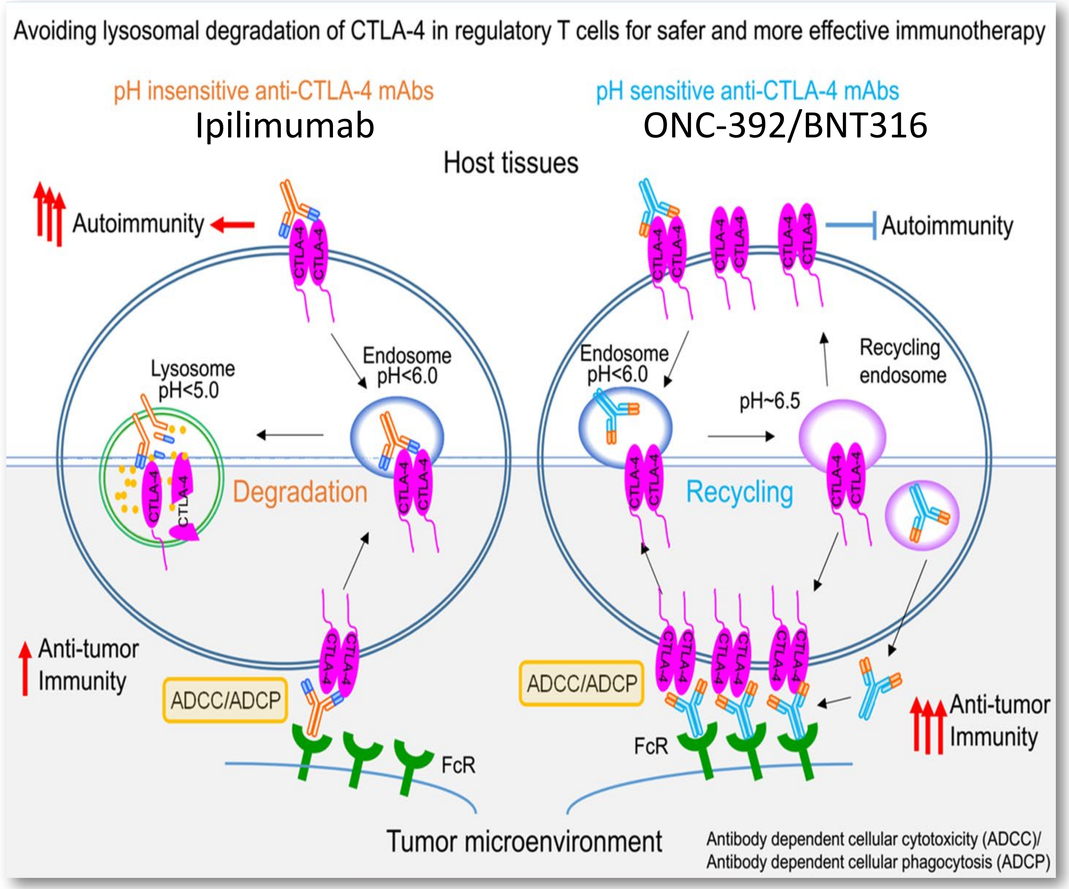
Background

PD-1 or PD-L1 inhibitors have transformed clinical care for NSCLC patients. However, many patients may develop primary or secondary resistance to PD-(L)1 inhibitors. The marketed anti-CTLA-4 mAbs are ineffective as monotherapy for NSCLC. ONC-392/BNT316 is a novel target-preserving anti-CTLA-4 antibody that confers immunotherapeutic effucact by selective depletion of regulatory T cells (Treg) in the tumor microenvironment. Preclinical studies show that ONC-392/BNT316 is more effective and less toxic for immunotherapy than other clinically used anti-CTLA-4 antibodies. In the first-in-human study in patients with advanced solid tumors, the recommended Phase 2 dose (RP2D) for ONC-392/BNT316 monotherapy was established as 10 mg/kg. In this study, we tested the safety and clinical activities of ONC-392/BNT316 in an expansion chohort NSCLC patients who progressed on PD(L)1-targeted therapy.

Methods:

Metastatic NSCLC patients who lack targetable driver gene mutations and progressed on anti-PD-(L)1 therapy were enrolled as part of PRESERVE-001 study (NCT04140526) Part A dose escalation cohort (10 mg/kg, Q3W, N=2) or the Part C expansion cohort Arm I and treated with 2 cycles of ONC-392/BNT316 10 mg/kg, followed by 6 mg/kg, q3w (N=33), by IV infusion. Safety was evaluated based on treatment emergent and treatment-related adverse events, while efficacy was evaluated by investigators using RECIST1.1 criteria.

Mechanism of action



Liu Y, Zheng P. Preserving the CTLA-4 Checkpoint for Safer and More Effective Cancer Immunotherapy. *Trends Pharmacol Sci*. 2020;41(1):4-12. doi:10.1016/j.tips.2019.11.003

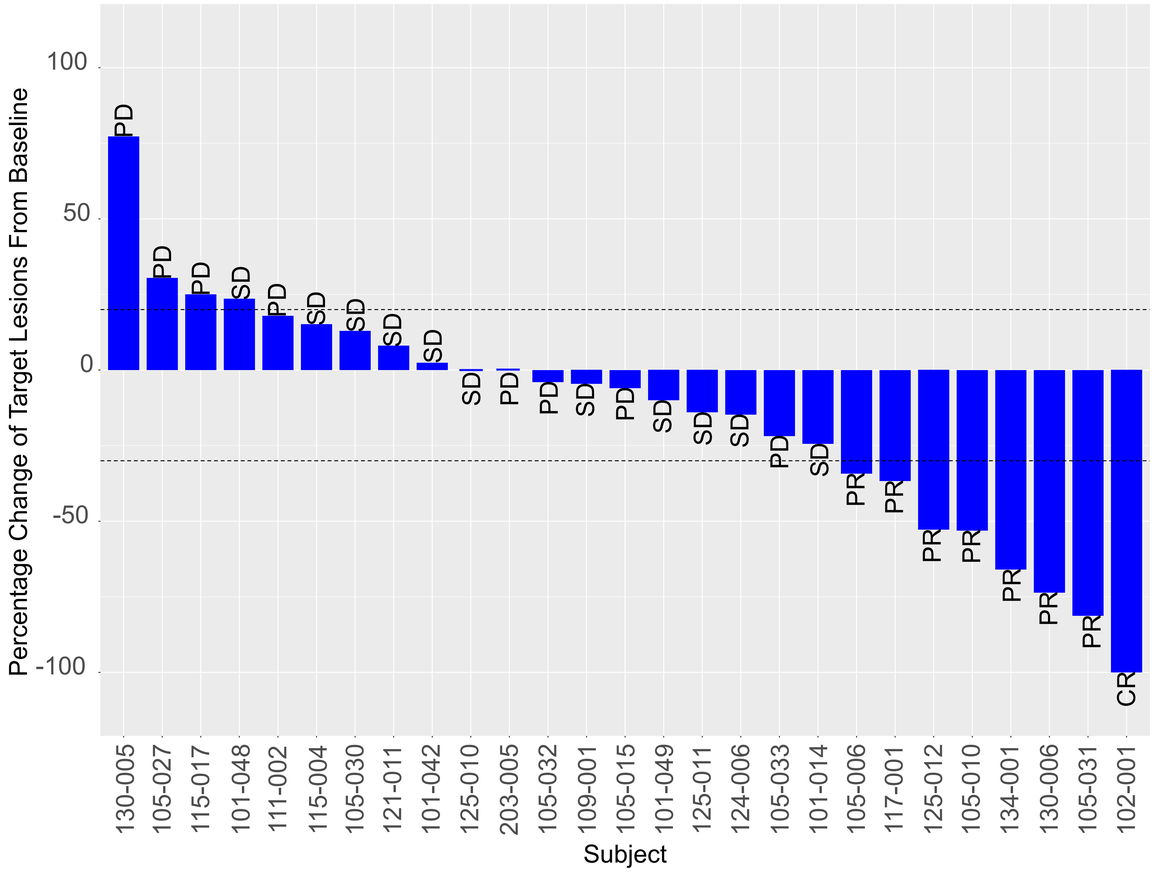
Demographics and Safety Data Summary

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 AE (TRAE): All grades	26 (74%)
TRAE: Grade 3-4	15 (43%)
irAEs: All grades	19 (54%)
irAE: Grade 3-4	12 (34%)
TRAE leading to dose interruption	9 (26%)
TRAE leading to dose reduction	1 (3%)
TRAE leading to study drug discontinuation	7 (20%)

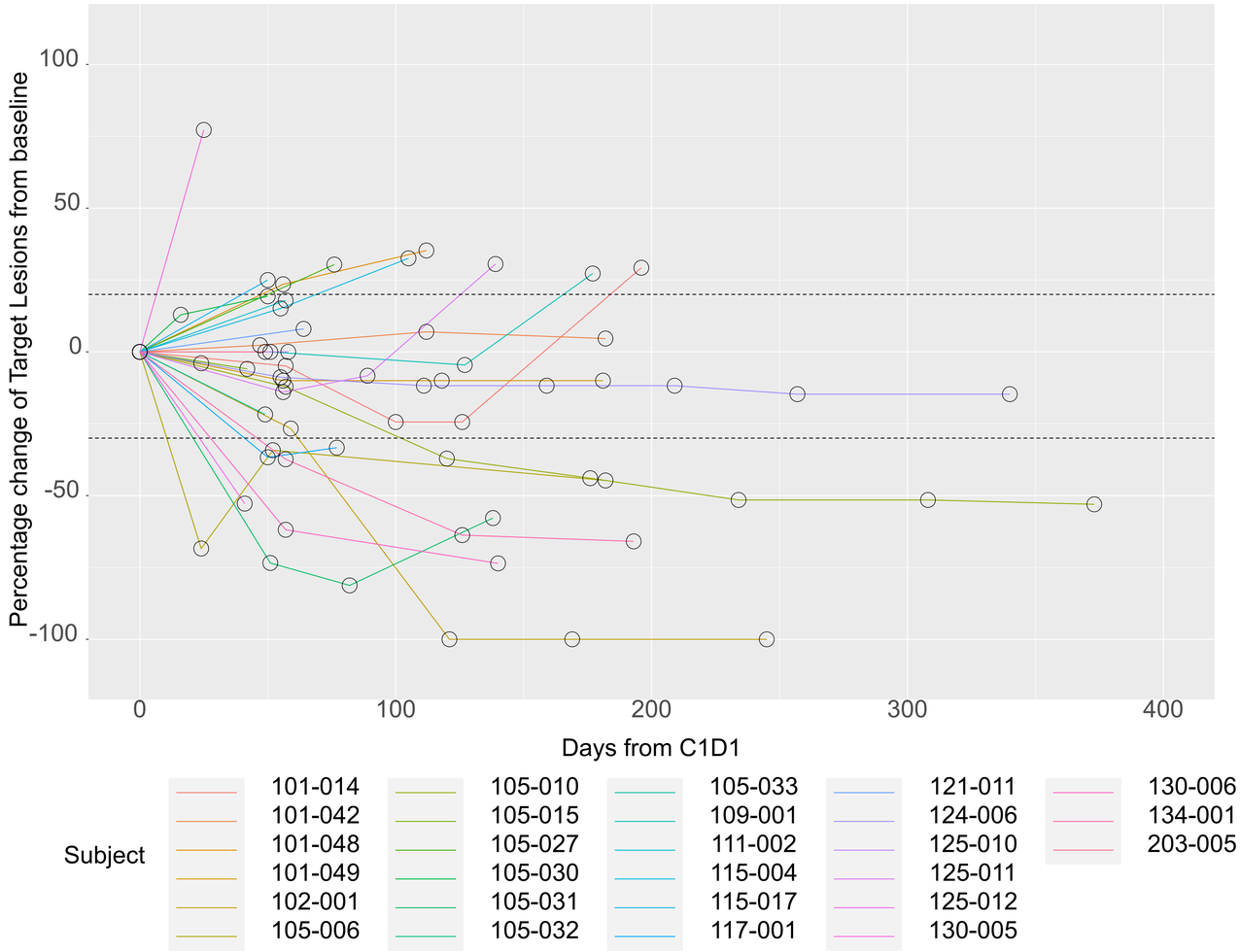
System Organ Class	All Grade (≥2 cases)	Grade 3	Grade 4
Preferred Term	N (%)	N (%)	N (%)
Gastrointestinal disorders			
Diarrhea	5 (14%)	1 (3%)	0
Colitis	4 (11%)	3 (9%)	0
Nausea	2 (6%)	1 (3%)	0
Vomiting	3 (9%)	1 (3%)	0
General disorders and administration site conditions			
Fatigue	4 (11%)	1 (3%)	0
Chills	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).			

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

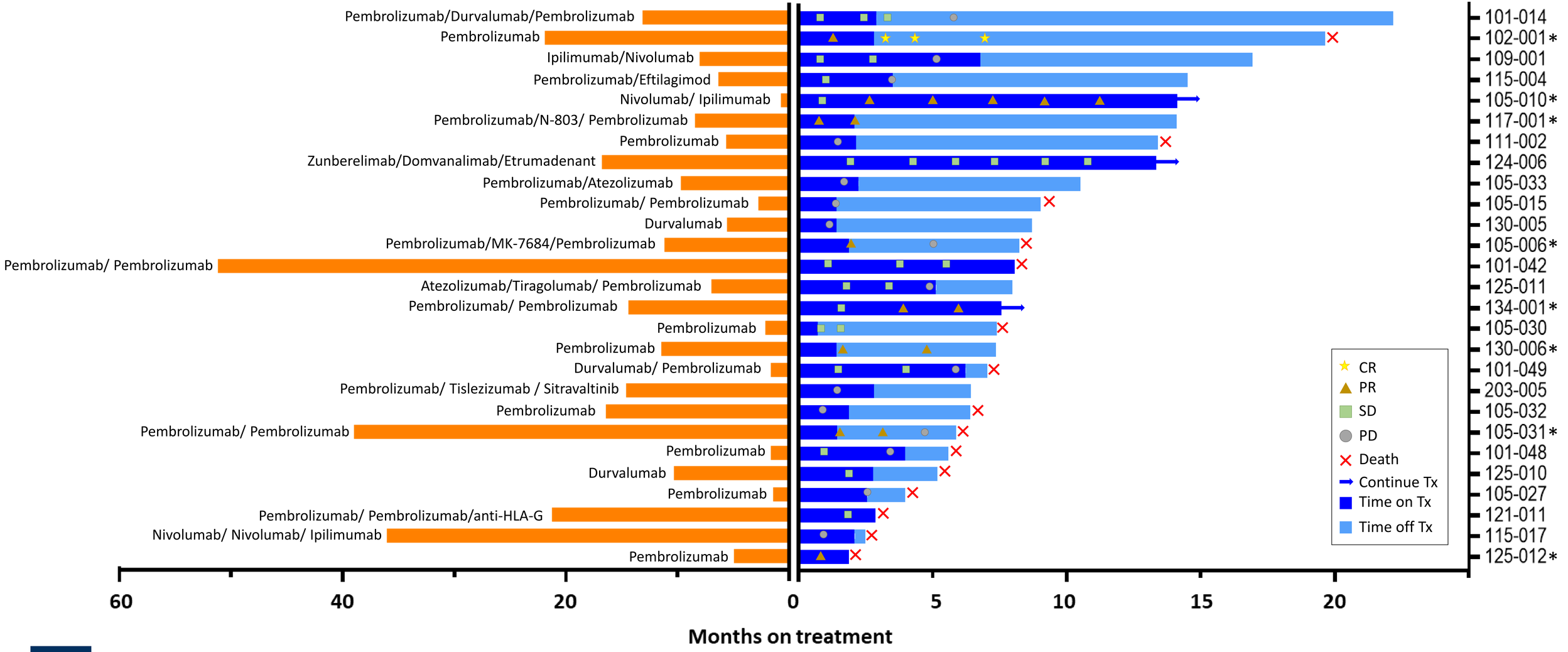
Target Lesion Best Overall Response (N=27 Evaluable)
ONC-392, 10 mg/kg x 2, then 6 mg/kg, q3w
(101-014 and 102-001: 10 mg/kg x 4, q3w)



Target Lesion Percentage Change Over Time (N=27 Evaluable)
ONC-392, 10 mg/kg x 2, then 6 mg/kg, q3w
(101-014 and 102-001: 10 mg/kg x 4, q3w)



Prior Anti-PD-1/ PD-L1/CTLA-4 Treatment and ONC-392/BNT316 Treatment

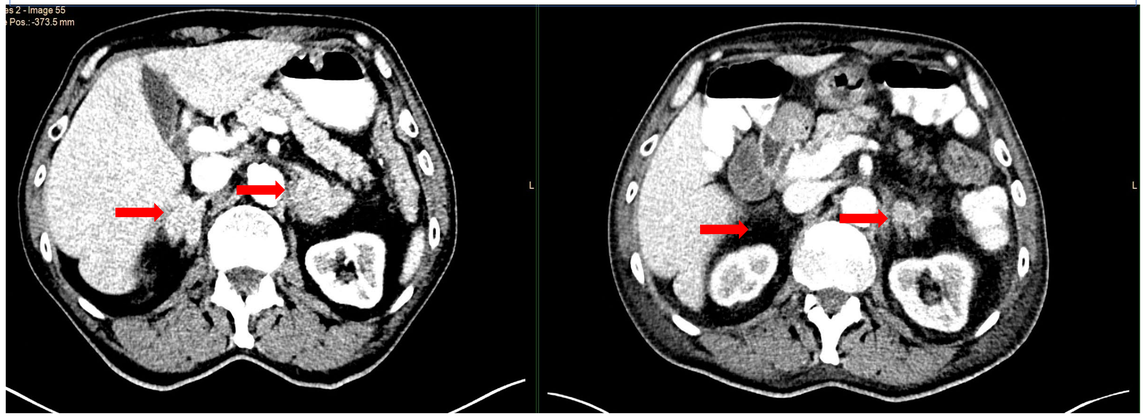


All 27 evaluable patients had prior platinum-based chemotherapy. The * indicates responders to ONC-392 monotherapy.

Response to ONC-392/BNT316 Treatment: Representative Cases

Case 1

- 75-year-old male was diagnosed a stage IV lung adenosquamous carcinoma in Jan 2019. Tumor PD-L1 25%. TMB 8. No actionable mutations. MMR is proficient
- Since Feb 2019, received 1st line treatment with carboplatin, paclitaxel, and pembrolizumab, followed by pembrolizumab maintenance.
- SBRT for oligo-progression in LUL In Jan 2022
- Systemic cancer progressed with metastases in adrenal glands and brain in May 2022. s/p SRS to brain lesion Jun 2022.
- Started Onc-392 monotherapy 07/13/2022.

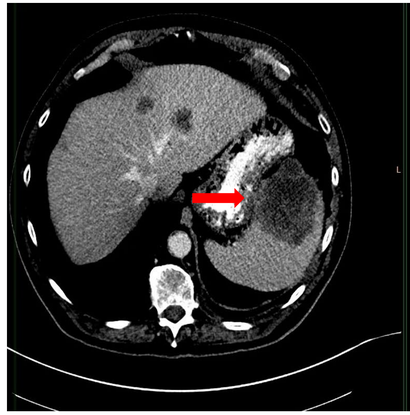


Jun. 2022, baseline

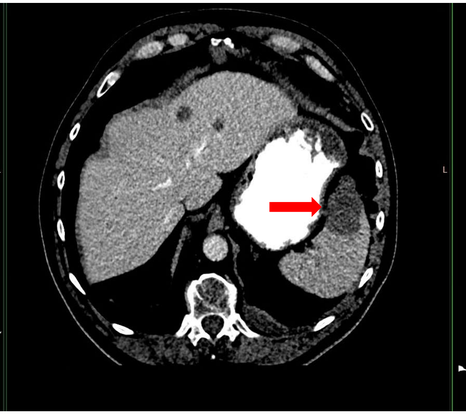
Sep. 2022, Right adrenal lesion resolved

Case 2

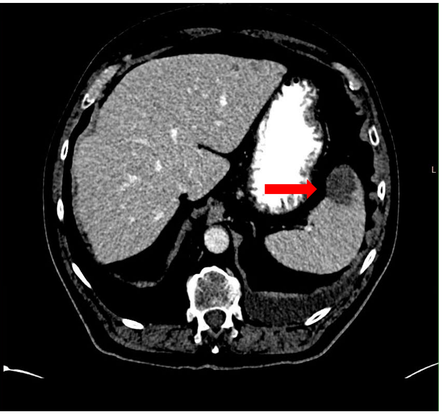
- 64-year-old male, with 100 pack years smoking history (quit 15 years ago) was diagnosed a squamous cell carcinoma of lung in Sep 2023. Tumor PD-L1 <1%. TMB 4. No actionable mutations. Microsatellite status is stable.
- Initially treated at outside hospital with chemo-RT (weekly paclitaxel and carboplatin), completed in Nov 2022. PET/CT on 12/10/21 showed disease progression with metastases in spleen and liver.
- Started with carboplatin, paclitaxel, Ipilimumab and nivolumab; however, cancer continued to progress after 2 cycles of treatment.
- Onc-392 monotherapy started 03/07/2022. Patient is active in treatment and in cycle 19 as of May 2023.



Feb. 2022, baseline



Jul. 2022



Oct. 2022

Summary and Conclusions

Safety Summary (03/10/2023 Datacut)

- ONC-392/BNT316 was tolerated at a dose regimen at 10 mg/kg x 2 then 6 mg/kg, q3w.
  - Longest dosing up to 19 cycles and continuing.
- Grade 3-4 TRAEs were observed in 13 pts (39%) with a follow up period from 7 to 18 months. 10 pts (30%) had Gr 3-4 irAEs. No ONC-392/BNT316 related Gr. 5 AE was observed. Significant irAEs include:
  - 2 immune-mediated colitis.
  - 1 intestinal perforation
  - 1 Gr. 4 ALT/AST increased and immune hepatitis
  - 1 Adrenal insufficiency
  - 1 Tubulointerstitial nephritis

The study is part of an ongoing Phase 1 / 2 study (NCT04140526).
OncoC4 is the sponsor of the study, partially supported by NCI SBIR R44CA250824 to PZ, KH and TL.

Clinical Activity

- Response rate among the evaluable patients is 29.6% (22.2% confirmed and 7.4% unconfirmed).
  - 1 CR and 1 SD in 2 patients with ONC-392/BNT316, 10 mg/kg q3w for 4 doses.
  - 7 PR and 10 SD among 25 evaluable patients in the expansion cohort with ONC-392/BNT316 dose regiment of 10 mg/kg x 2, then 6 mg/kg q3w.
  - Responders include those that failed multiple IO agents targeting PD-(L)1, CTLA-4, and TIGIT.
  - All but 1 responders have been on treatment of PD-(L)1 targeting agents for >12 weeks, which is provisionally defined as PD-(L)1-resistant NSCLC.
- Survival follow up is ongoing.

Conclusions

- ONC-392/BNT316 was generally safe and tolerated at 10 mg/kgx2, followed by 6 mg/kg Q3W. Treatment-related AEs are manageable.
- Severe irAE rate in dose expansion cohort (30%) is considered lower than what was reported for drugs of the similar class of drug at comparable doses.
- Early readout of the expansion cohort shows strong clinical activity in patients with IO-resistant NSCLC.
- These results support initiation of a pivotal study using ONC-392/BNT316 monotherapy for PD-(L)1-resistant NSCLC (Poster TPS#9146, NCT05671510).