Abstract # TPS9146

PRESERVE-003: Phase 3, Two-stage, Randomized Study of ONC-392 /BNT316 Versus Docetaxel in Metastatic Non-Small Cell Lung Cancers that Progressed on PD-1/PD-L1 Inhibitors (NCT05671510)

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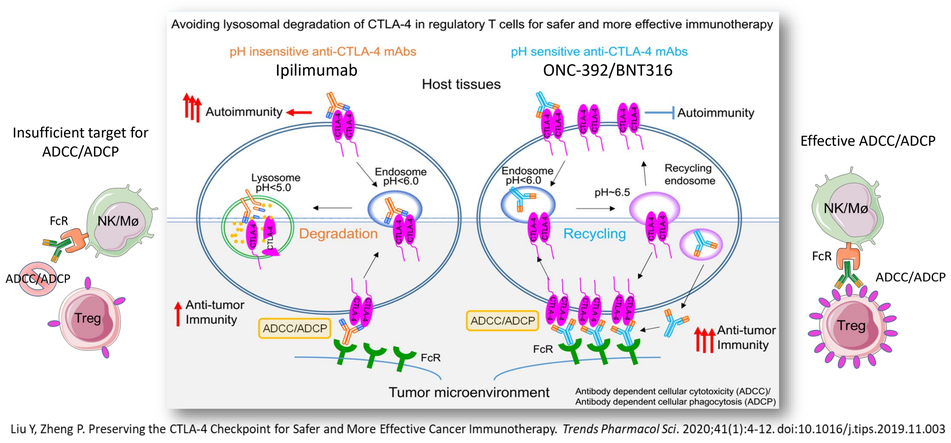
Background:

For NSCLC without driver mutation, the PD-1/PD-L1 inhibitor as the first-line (monotherapy or in combination with platinum-based doublet agents) or second-line therapy after chemotherapy significantly improved overall survival. However, there remain a significant number of patients who do not have response or have an initial response followed by disease progression to PD-1/PD-L1 inhibitor therapy. CTLA-4 is a proven immunotherapy target in solid tumor, unfortunately no monotherapeutic efficacy has been shown in NSCLC by marketed anti-CTLA-4 antibodies, including ipilimumab and tremelimumab. These anti-CTLA-4 mAbs cause severe toxicity that prevents adequate dosing in cancer patients. In contrast, ONC-392/BNT316 keeps high-level CTLA-4 on Treg cells through a recycling mechanism and makes Treg cells a better target for antibody-dependent cellular cytotoxicity, particularly in the tumor microenvironment where macrophages are more abundant (**Figure 1**). The selective elimination of Treg cells in the tumor microenvironment and maintenance of CTLA-4 expression in Treg cells in the peripheral tissues by ONC-392/BNT316 form the cellular and molecular basis for more potent tumor rejection and low toxicity in pre-clinical studies. Our first in human studies have demonstrate safety and clinical activities of ONC-392/BNT316 in patients with NSCLC and other solid tumors.

Summary of the Clinical Protocol:

This is a seamless 2-stage, randomized, open-label, active-controlled, Phase 3 study of ONC-392/BNT316 for treatment of NSCLC patients who progressed on PD-1/PD-L1 inhibitor (NCT05671510). Approximately 600 patients will be enrolled. Stage I, the dose-confirmation stage, will assess the efficacy and safety of two ONC-392/BNT316 dosing regimens of 3 mg/kg Q3W and 6 mg/kg Q3W (preceded by 2 loading doses of 10 mg/kg Q3W) in comparison to docetaxel 75mg/m^2 Q3W. A total of 120 patients will be randomized 1:1:1 in Stage I into one of the two ONC-392/BNT316 dose cohorts or the docetaxel cohort. An interim analysis will be conducted at the end of Stage I when 120 patients are enrolled. Stage 2 will start when ONC-392/BNT316 dose is determined and approximately 480 patients will be randomized 1:1 to receive ONC-392/BNT316 or docetaxel treatment. All enrolled patients who are randomized to the ONC-392/BNT316 arms will receive ONC-392/BNT316 at the randomized dose for up to 17 cycles in approximately 1 year or until discontinuation criteria are met. Patients who are randomized to the docetaxel arm will receive docetaxel 75 mg/m^2 Q3W until disease progression per RECIST 1.1. The primary endpoint is overall survival. The treatment effect will be estimated using a Cox Proportional Hazard model stratified by the randomization stratification factors to calculate the estimated hazard ratio and its 95% CIs. Kaplan-Meier (i.e., product-limit) estimates of median OS time will be presented by treatment arm with two-sided 95% CIs. The analyses will be based on the ITT Population.

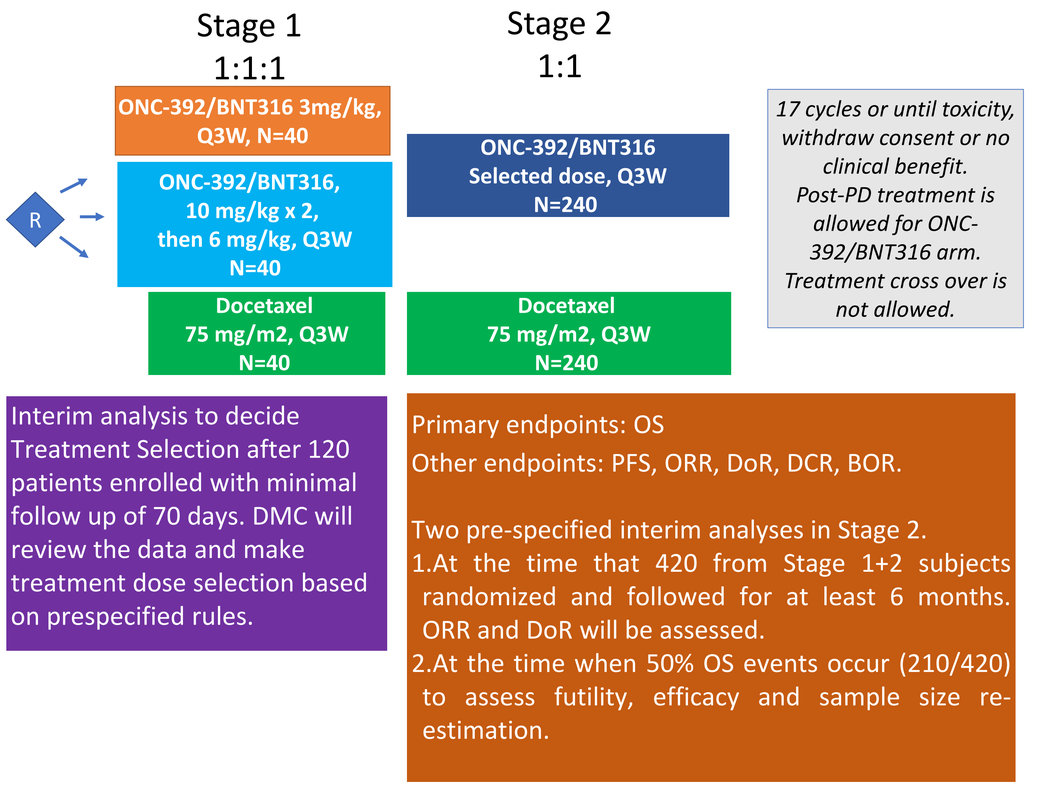
Figure 1: ONC-392/BNT316 Mechanism of Action



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

Seamless two stage, randomized, active controlled, multicenter phase 3 trial

- Adult patients with NSCLC.
- Had systemic platinum-based chemotherapy, either before or in combination with Anti-PD-1/PD-L1 antibodies with at least 12 weeks or 4 cycles of regular doses of anti-PD-1/PD-L1 antibody treatment.
- Disease Progressed on Anti-PD-1/PD-L1 treatment.
- Have RECIST 1.1 measurable lesions.
- ECOG 0/1.
- Adequate organ functions.



Eligibility:

Major Inclusion Criteria	Major Exclusion Criteria
1) Adult (≥ 18 years), all genders, capable of signing informed consent. 2) Histologically- or cytologically- confirmed diagnosis of metastatic NSCLC, metastasis can be regional lymph nodes or distant organs. 3) Radiographic progression after treatment with the most recent line of treatment being either 3a or 3b: a. At least 12 weeks of PD-1/PD-L1 inhibitor in combination with platinum-based chemotherapy; b. Prior treatment with at least 2 cycles of a platinum-based chemotherapy, followed by at least 12 weeks of standard doses of PD-1 or PD-L1 inhibitor-based immunotherapy. Antibodies against CTLA-4, LAG-3, TIGIT, VEGF or VEGFR in combination with PD-1/PD-L1 inhibitor are allowed. 4) At least one measurable tumor lesion according to RECIST 1.1. 5) ECOG score of 0 or 1. 6) Adequate organ functions. Serum LDH level ≤ 2xULN. 7) Life expectancy ≥ 3 months.	1) Cancer treatment related AEs have not recovered to NCI CTCAE grade≤ 1 except endocrinopathy. 2) Last anti-PD-1/PD-L1 dosing within 28 days prior to first dose of study treatment. 3) Receiving systemic steroid therapy with >10 mg/day prednisone or equivalent within 7 days prior to the first dose of study treatment. 4) Having documented targetable mutations or genomic alterations in any of the following genes: EGFR, ALK, ROS1, HER2, MET, BRAF, RET or NTRK. Exception: KRAS mutations are not excluded. 5) Patients who have symptomatic brain metastasis. Palliative radiotherapy or radiosurgery to brain metastasis within 14 days of the first dose of study drug. 6) Active GI disease, including peptic ulcer disease, pancreatitis, diverticulitis, or inflammatory bowel disease. 7) Active interstitial lung disease (ILD) or non-infectious pneumonitis. 8) Active infections with IV antibiotics within 14 days prior to first dose of study treatment. 9) Impaired heart function.

Dose Selection Process:

An independent data monitoring committee (DMC) is planned to review the results and make recommendations to the Sponsor. The first interim analysis will be conducted for Stage I when the 120th randomized patient has the first tumor assessment or 70 days post C1D1. Odds ratios for Arm 1 and Arm 2 of ONC-392/BNT316 vs. Arm 3 of docetaxel will be calculated for ORR and DCR: the dose corresponding to a better odds ratio of (experimental vs. Arm 3) will be selected if the 2 odds ratios for ORR are not equal; else, the dose corresponding to a better odds ratio of (experimental vs. docetaxel) will be selected if the 2 odds ratios for DCR are not equal; else, the dose corresponding to less TEAE/TRAE will be selected. Preliminary exposure-response analyses using key efficacy and safety variables will be performed to help the selection of ONC-392/BNT316 dose regimen for Stage II.

Enrollment Status: being opened globally, starting in the US, Canada, Australia, Europe, South Korea, and China

Related Poster: #9024. Safety and clinical activity of ONC392 /BNT316 as monotherapy in PD-1 resistant NSCLC.