An Open-Label, Phase 1B Study of NEO-PV-01 with Pembrolizumab Plus Chemotherapy in Patients With Advanced or Metastatic Nonsquamous Non-Small Cell Lung Cancer

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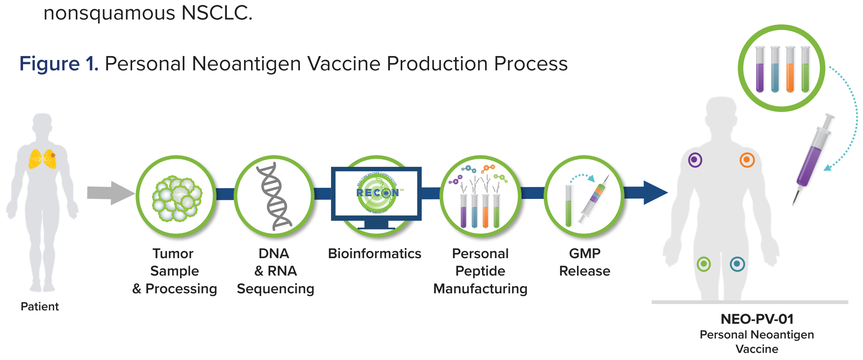
Introduction

- Cancer cells contain unique, somatic DNA mutations that result in altered amino acid sequences known as neoantigens.[1,2]
- Tumor neoantigens are not subject to the immune dampening effects of self-tolerance and are present only in tumors, rendering the neoantigens tumor-specific.[1,2]
- Growing evidence supports a critical role for neoantigens as targets for tumor-directed immune responses.[1,2] Tumor mutational burden, as well as neoantigen load, have been associated with antitumor activity of checkpoint inhibitors.[1,3,4]
- Vaccines targeting neoantigens have been demonstrated to be a highly specific way of inducing de novo T cell reactivity and expanding existing T cell responses.[1,2,5-7]
- The mutational fingerprint of each patient is unique:[7]
  - NEO-PV-01 is a personal neoantigen vaccine custom-designed and manufactured specifically for the mutational profile of each individual's tumor (**Figure 1**).
  - NEO-PV-01 is composed of a mixture of up to 20 unique neoantigen peptides of 14-35 amino acids in length.
- The recent progress with chemotherapy plus anti-PD-1 therapy in front-line NSCLC has demonstrated improved efficacy over chemotherapy alone. This combination reduces the risk of progression during the first 24 weeks of study treatment and may also modulate the tumor microenvironment.[8]
- NT-002 is a Phase 1B trial being conducted in collaboration with Merck & Co., Inc. to investigate the safety and activity of NEO-PV-01 administered with pembrolizumab and carboplatin+pemetrexed in untreated patients with advanced or metastatic nonsquamous NSCLC.

Figure 1. Personal Neoantigen Vaccine Production Process



Objectives

Primary

- To evaluate the safety of NEO-PV-01 administered with pembrolizumab and carboplatin + pemetrexed in untreated patients with advanced or metastatic nonsquamous NSCLC

Secondary

- All secondary objectives will be assessed via RECIST 1.1
  - Post-vaccination responses will be evaluated to determine the RCR (eg, SD to PR)
  - To determine the anti-tumor activity as assessed by ORR and CBR
  - To evaluate the DOR, RCR, PFS, and OS

Exploratory

- To characterize vaccine-induced immune responses by evaluating several criteria, including the antigen-specific $CD8^+$ and $CD4^+$ T cell responses in both peripheral blood and tumor biopsies before, during, and after NEO-PV-01 vaccine treatment
- To correlate patient responses with exploratory biomarkers in peripheral blood and tumor biopsies, such as PD-L1 expression, abundance and phenotypes of TILs and myeloid cells, somatic mutational load, and neoantigen load
- To determine the anti-tumor activity, as assessed by ORR and PFS, by iRECIST

Study Design

- NT-002 is a single-arm, Phase 1B trial designed to evaluate the safety of NEO-PV-01 administered with pembrolizumab and carboplatin+pemetrexed in untreated patients with advanced or metastatic nonsquamous NSCLC (**Figure 2**)
- Target enrollment is 15 patients
- To date, the study is actively enrolling at 5 clinical study sites in the United States

Figure 2. NT-002 Study Design

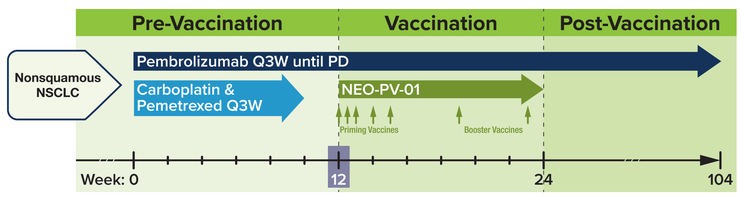


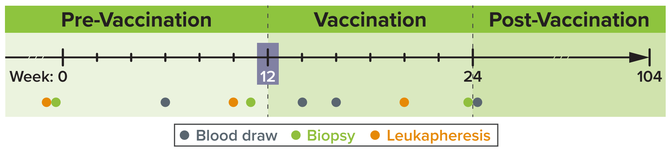
Table 1. Key Patient Eligibility Criteria

Inclusion Criteria
• Have histologically confirmed unresectable or metastatic nonsquamous NSCLC and received no prior systemic therapy for metastatic disease
• Have at least 1 site of disease measurable by RECIST 1.1 that has not been treated with local therapy within 6 months of treatment
• At least 1 site of disease must be accessible to provide repeat biopsies for tumor tissue
• ECOG PS of 0 or 1 with an anticipated life expectancy of > 6 months
Exclusion Criteria
• Received any systemic therapy for cancer treatment including immunotherapeutic agents such as anti-PD-1 or anti-PD-L1 antibody therapy
• Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 30 days prior to Cycle 1, Day 1
• May not have received any radiation therapy to biopsy sites
• Received radiation therapy to the lung > 30 Gy within 6 months of Cycle 1, Day 1
• Active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs)
• Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment

Study Procedures

- During pre-treatment, patients undergo a baseline tumor biopsy and peripheral blood draw
- HLA typing is performed for each patient
- Whole-exome DNA sequencing and RNA sequencing is performed on both the tumor and peripheral blood sample in order to identify the mutations specific to the patient's tumor
- NEO-PV-01 is designed based on computational immunogenicity analysis of the mutations in each patient's tumor using RECON™, Neon Therapeutics' proprietary bioinformatics algorithm
- Patients will receive pembrolizumab with chemotherapy consisting of carboplatin + pemetrexed Q3W for 4 cycles. Beginning with Cycle 5 (Week 12), patients will receive pembrolizumab as monotherapy, Q3W up to Week 103
- NEO-PV-01 is given as follows: 5 vaccinations during the priming phase, on Days 1 and 4 of Week 12, and then weekly for 3 weeks (Weeks 13, 14, and 15); 2 booster vaccinations 4 and 8 weeks following the completion of the priming vaccine (Weeks 19 and 23)

Figure 3. NT-002 Procedure Schedule



Study Assessments

Safety

- Safety assessments will include evaluation of AEs, SAEs, symptom-directed physical examinations, measurement of vital signs, ECOG PS, and safety labs

Efficacy

- Radiographic assessments to evaluate response to treatment (defined by RECIST 1.1) will be conducted at Weeks 8, 12, 24, 36, 52, 63, 75, 87, and 99

Immune Profiling and Monitoring

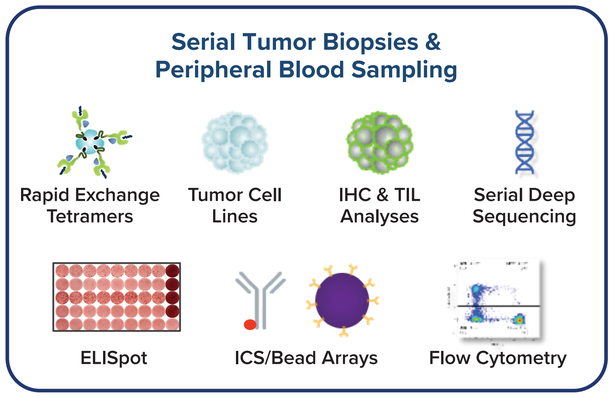
- Profiling immune responses and their correlation with clinical outcome both informs underlying tumor biology and improves future vaccine design and personal programs

References: 1) Yarchoan M, et al. *Nature Reviews Cancer*. 2017;17:209-222. **2)** Martin SD, et al. *Annals of Oncology*. 2015;26:2367-2374. **3)** Farkona S, et al. *BMC Medicine*. 2016;14:73. **4)** van Rooij N, et al. *Journal of Clinical Oncology*. 2013;31:e439-42. **5)** Le DT, et al. *N Engl J Med*. 2015;372:2509-2520. **6)** Rizvi NA, et al. *Science*. 2015;348:124-128. **7)** Ott PA, et al. *Nature*. 2017; 547, 217-221. **8)** Gandhi, et al. N Engl J Med. 2018 Apr 16. doi: 10.1056/NEJMoa1801005. [Epub ahead of print]

Immune Monitoring Tool Kit

- This study aims to characterize immune responses by evaluating several criteria, primarily via assessment of the peripheral T cell response measured by assays such as ex vivo IFN-γ ELISpot (**Figure 4**)
- For patients demonstrating a robust positive response, the precise immunizing peptide(s) are determined in follow-up analyses including evaluation of:
  - The phenotype of T cell subsets (Th1 vs Th2, T effector vs memory cells, cytokine product)
  - The presence and abundance of regulatory cells such as T regulatory cells or myeloid-derived suppressor cells
- Serial tumor biopsies are assessed, including whole exome sequencing, RNA sequencing, and IHC to examine the vaccine-induced activity on tumor cells

Figure 4. Immune Monitoring Tool Kit



Summary

- NT-002 is a Phase 1B trial being conducted in collaboration with Merck & Co., Inc. to investigate the safety and activity of NEO-PV-01 administered with pembrolizumab and carboplatin+pemetrexed in untreated patients with advanced or metastatic nonsquamous NSCLC
- To date, the study is actively enrolling at 5 clinical study sites in the United States

Now Enrolling

For more information:
www.ClinicalTrials.gov
NCT03380871

Abbreviations: AE = adverse event; CBR = clinical benefit rate; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; ELISpot = Enzyme-Linked ImmunoSpot; FACS = fluorescence-activated cell sorting; GMP = good manufacturing processes; Gy = Gray; HLA = human leukocyte antigen; ICS = intracellular cytokine staining; IFN-γ = interferon-γ; IHC = immunohistochemistry; iRECIST = RECIST 1.1 for immune-based therapeutics; MHC = major histocompatibility complex; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PD-1 = programmed cell death protein 1; PD-L1 = programmed death ligand 1; PFS = progression-free survival; PR = partial response; Q3W = every 3 weeks; RCR = response conversion rate; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = significant adverse event; SD = stable disease; TILs = tumor-infiltrating lymphocytes

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