An Open-Label, Phase 1B Study of NEO-PV-01 + CD40 Agonist Antibody (APX-005M) or Ipilimumab with Nivolumab in Patients with Advanced or Metastatic Melanoma

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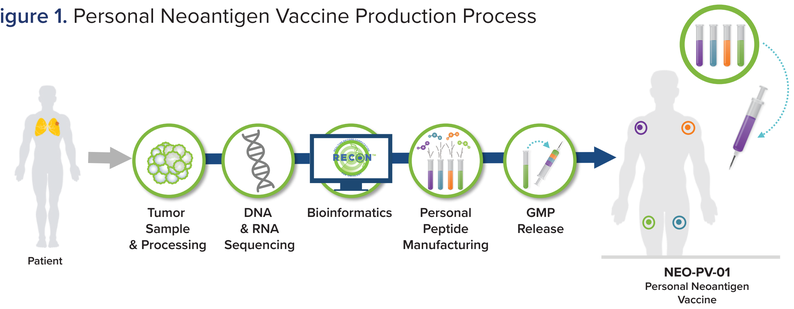
Introduction

- 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.
- Combining the immune-stimulating effects of a neoantigen-targeted vaccine, enhanced immune priming from CD40 agonism or ipilimumab, and the release of immune suppression by an immunomodulator such as nivolumab, a significant improvement in the response rate, the depth of tumor responses, and the durability of responses may be possible.
- NT-003 is a multi-arm, Phase 1B study designed to evaluate the safety of administering NEO-PV-01 using a combination regimens with APX-005M (provided by Apexigen) or ipilimumab + nivolumab in patients with advanced or metastatic melanoma.

Figure 1. Personal Neoantigen Vaccine Production Process



Objectives

Primary

- To evaluate the safety of administering NEO-PV-01 using different regimens as well as in combination with APX-005M or ipilimumab with nivolumab in patients with advanced or metastatic melanoma

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 antigen-specific $CD8^+$ and $CD4^+$ T-cell responses in peripheral blood before, during, and after vaccine treatment
- To evaluate 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

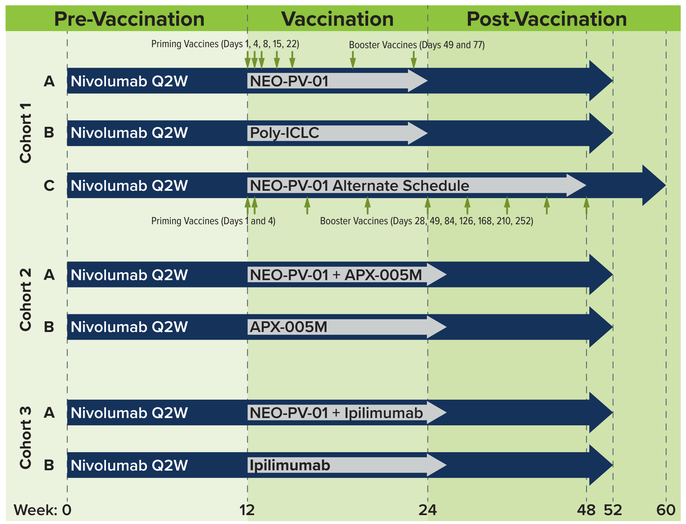
Table 1. Key Patient Eligibility Criteria

Inclusion Criteria
• Have cytologically or histologically confirmed advanced or metastatic melanoma and having 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 advanced or metastatic cancer treatment including immunotherapeutic agents such as anti-PD-1, anti-PD-L1, anti-CD40, or anti-CTLA-4 antibody therapy
• Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 30 days prior to Study Day 1
• May not have received any radiation therapy to biopsy sites
• Has an active infection requiring systemic therapy
• 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 Design

- NT-003 is a multi-arm, Phase 1B trial designed to evaluate the safety of NEO-PV-01 administered either with APX-005M or ipilimumab, and nivolumab, or poly-ICLC and nivolumab for the treatment of advanced or metastatic melanoma (Figure 2)
- Target enrollment is 33 patients

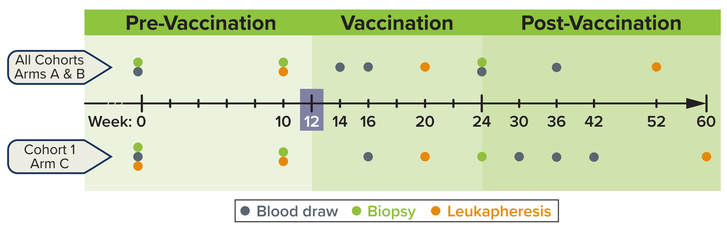
Figure 2. NT-003 Study Design



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

Figure 3. NT-003 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, and 60 (Cohort A, Arm C only)

Immune Profiling and Monitoring

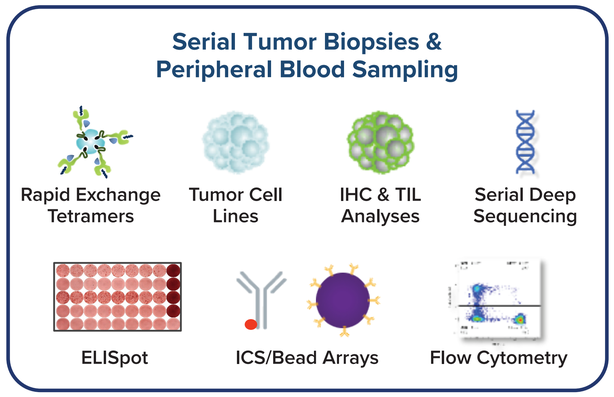
- Profiling immune responses and their correlation with clinical outcome both informs underlying tumor biology and improves future vaccine design and personal programs

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. The New England Journal of Medicine. 2015;372:2509–2520. **6)** Rizvi NA, et al. Science. 2015;348:124–128. **7)** Ott PA, et al. Nature. 2017; 547, 217-221.

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-003 is a Phase 1B trial being conducted to investigate the safety and activity of NEO-PV-01 administered either with APX-005M or ipilimumab, and nivolumab, or poly-ICLC and nivolumab for the treatment of advanced or metastatic melanoma

Now Enrolling

For more information:
www.ClinicalTrials.gov
NCT03597282

Abbreviations: AE = adverse event; CBR = clinical benefit rate; CTLA-4 = cytotoxic t-lymphocyte associated antigen 4; 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; 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; 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; Q2W = every 2 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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