Background

- Cancer cells contain unique, somatic DNA mutations that result in altered amino acid sequences known as neoantigens. 
- Neoantigens are not subject to the immune dampening effects of central tolerance and are expressed only in tumors, rendering them an attractive target for therapy.
- Growing evidence supports a central role for neoantigens as targets for tumor-directed immune responses. Neoantigen mutational burden, as well as neoantigen load, have been associated with antitumor activity of checkpoint inhibitors.
- Immune responses to neoantigens depend on the ability of major histocompatibility complex molecules to effectively bind a small peptide (epitope) containing the altered amino acid sequence and present it to a T cell. Such an epitope can be generated synthetically and used in a vaccine.
- Vaccines targeting neoantigens offer a highly specific way of inducing de novo, and expanding existing, tumor-specific T-cell responses.

Figure 1. NEO-PV-01 Personalized Neoantigen Vaccine Mechanism of Action

Objectives

Primary
- To evaluate the safety of NEO-PV-01 + adjuvant (a personalized neoantigen vaccine) with nivolumab in patients with unresectable or metastatic melanoma, smoking-associated non-small cell lung cancer (NSCLC), or RCC.
- To determine antitumor activity at Week 24, assessed by RECIST for the trial.
- To determine the response duration, defined as time from response until disease progression or death.
- To determine progression-free survival, overall survival, and duration of response.

Secondary
- To determine antitumor activity at Week 24, assessed by overall response rate and clinical benefit rate.
- To determine the response conversion rate, defined as improvement in response category at Week 24 vs Week 12.
- To determine tumor-related adverse events.

Exploratory
- To characterize immune responses including evaluation of antigen-specific CD4+ and CD8+ T-cell responses in the peripheral blood and tumor.
- To correlate patient responses with exploratory biomarkers, such as programmed death-ligand 1 (PD-L1) expression and somatic mutations.

Study Design

- NEO-PV-01 + adjuvant is a personalized neoantigen vaccine custom designed specifically for the molecular profile of each individual’s tumor.
- The vaccine is composed of a set of up to 20 neoantigens of 14–35 amino acids in length, designed based on DNA mutations present in each patient’s tumor.
- Peptides are pooled together in four groups of up to five peptides each, and mixed with the adjuvant polyinosinic-polycytidylic acid-polynucleotidemonophosphate (poly-ICLC) at the time of administration.

Table 1. Key Patient Eligibility Criteria

<table>
<thead>
<tr>
<th>Key Inclusion Criteria</th>
<th>Key Exclusion Criteria</th>
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<tbody>
<tr>
<td>Histologically confirmed disease having received ≤1 prior systemic therapy</td>
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<tr>
<td>Unresectable or metastatic Stage IV melanoma</td>
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<tr>
<td>Unresectable or metastatic Stage IV lung cancer treated with associated NSCLC</td>
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<tr>
<td>Unresectable or metastatic TCC of the bladder, urethra, ureter, or renal pelvis</td>
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<tr>
<td>Measurable disease not treated with locoregional therapy</td>
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<td>&gt;18 years of age</td>
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<td>Adequate hematologic, hepatic, and renal function</td>
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<td>Prior treatment with immunotherapeutic agents including any anti-CTLA-4 or anti-PD-1/PD-L1 antibodies or any other immunotherapeutic agents</td>
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<td>Systemic antineoplastic therapy in past 28 days of first dose of study therapy</td>
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<tr>
<td>Treatment for non-renal cancer within 12 months of study therapy</td>
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<tr>
<td>Treatment for infectious diseases</td>
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<tr>
<td>During the 4-week period prior to first dose of nivolumab</td>
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<tr>
<td>During the period of NEO-PV-01 + adjuvant administration and until &gt;8 weeks after the last dose of the booster vaccine</td>
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<tr>
<td>Condition requiring systemic treatment with other immunosuppressive medications within 12 months prior to the first dose of nivolumab</td>
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<td>Active or history of autoimmune disease</td>
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<tr>
<td>Malignant melanoma and unanalyzed melanoma</td>
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Study Assessments

- Safety
  - Safety assessments include evaluation of adverse events (AEs), serious AEs, symptom-directed physical examinations, measurement of vital signs, Eastern Cooperative Group performance status, and safety laboratory assessments.

- Efficacy
  - Radiographic assessments to evaluate response to treatment (defined by Response Evaluation Criteria in Solid Tumors) will be conducted at Weeks 8, 12, and 24.

Immune Profiling and Monitoring

- Detailed analysis of robust neoantigen peptide T-cell responses detected by ELISPOT will be performed (Figures 5 and 6), including:
  - Determination of the precise epitope specificity of T cells
  - Assessment of the phenotype of T-cell subsets
  - T-effector vs memory cells, cytokines
  - Evaluation of presence and abundance of regulatory cells such as T-regulatory cells or myeloid-derived suppressor cells

- Tumor-specific biomarkers will be assessed, including whole exome sequencing, RNA sequencing, and immunochemistry.

Figure 2. NEO-PV-01 Product Process

Figure 3. NT-001 Study Schema

Figure 4. Treatment and Assessment Schedule

Figure 5. Immune Profiling: Informers and Improvers

Figure 6. Immune Monitoring Questions and Key Assays

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References