NANT Cancer Vaccine (NCV): An Orchestration of Immunogenic Cell Death by Overcoming Immune Suppression and Activating Natural Killer (NK) and T Cell Therapy in Patients with Greater than 3rd Line Metastatic Pancreatic Cancer

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Background
Pancreatic Cancer
- Pancreatic cancer is an aggressive and lethal disease. Annually, > 50,000 patients in the US are diagnosed and > 40,000 die from the disease.1
- There is a strong unmet need for novel pancreatic cancer treatments. Patients treated with greater than third-line standard-of-care (SoC) chemotherapy have poor prognoses with a median OS of less than 2-4 months.2

NANT Cancer Vaccine (NCV) to Induce Immunogenic Cell Death
- The NCV includes metronomic low-dose nab-paclitaxel (Abraxane) and low dose radiation therapy with cryopreserved off-the-shelf CD16 targeted natural killer cells (haNK) and cytokine NK & T cell superagonist IL-15RoSuFc (N-803) combined with E2b-deleted adenovirus (Ad) & yeast (Ye) tumor associated antigen vaccines, and checkpoint inhibitors.
- All treatment was administered in the outpatient setting without G-CSF support.
- The NCV is anticipated to reduce immunosuppression in the tumor microenvironment, while increasing immune-mediated cell death, cytotoxic NK and T cell activity, and innate immune responses.3,4
- The ongoing phase 1b/2 study (QUILT-3.070; NCT03387098) seeks to evaluate the overall safety profile of the NCV and to establish preliminary estimates of efficacy. The previously opened, closely related studies QUILT-3.039 and QUILT-3.060 used similar treatment regimens.
- As of October 2018, 171 doses of haNK and NCV Vaccine has been administered in 10 patients (Table 1) have been enrolled.

Methods
Study Design (QUILT-3.070)
- Non-randomized, open-label, single-arm phase 1b/2 trial.
- Combination chemotherapy, CD16 haNK, and immunotherapy administered over a 3-week induction cycle for up to 1 year.

Enrollment Criteria
- Histologically-confirmed metastatic pancreatic adenocarcinoma that has progressed after SoC therapy.
- ≥ 18 years old with ECOG performance status of 0-2.

Endpoints
- Primary endpoint: Incidence of treatment-emergent adverse events (AEs) and serious AEs (SAEs).
- Secondary endpoints: overall response rate (ORR), progression-free survival (PFS), overall survival (OS), duration of response (DOR), disease control rate (DCR), and quality of life (QoL) by patient-reported outcomes (PROs).

Results
Safety
- No DLTs have occurred on study to date.
- Patients received 15.2 ± 7.0 (mean ± SD) doses of haNK per patient, with a total of 152 doses administered with no evidence of cytokine release syndrome (CRS).
- In the NCV treatment regimen, haNK cell therapy was administered concurrently with the PD-L1 IgG1 antibodyavelumab. No immune-related treatment-emergent, haNK-related AEs occurred.
- The most common treatment-emergent, treatment-related grade ≥ 3 AEs were neutropenia (8 of 10 patients) and anemia (6 of 10 patients), consistent with AEs associated with chemotherapy, are summarized in Table 2.

Efficacy
- As of October 2018, the Disease Control Rate (DCR) for the study was 90%, with 9 of 10 patients exhibiting stable disease (SD) for ≥ 8 weeks.
- Median PFS was 5.8 months (95% confidence interval [CI]: 3.3, 8.8) and Median OS was 9.5 months (95% CI: 5.0, upper limit not yet reached).

Table 1: Patient Demographics and Cancer History
<table>
<thead>
<tr>
<th>Mean age (min, max)</th>
<th>53.5 (35, 66)</th>
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<tbody>
<tr>
<td>Gender</td>
<td>6 male 4 female</td>
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<tr>
<td>ECOG status</td>
<td>0 (9 patients) 1 (2 patients)</td>
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<td>Diagnosis to study entry (years)</td>
<td>1.2 (0.2, 2.2)</td>
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<tr>
<td>Line of therapy with NCV</td>
<td>3.7 ± 0.8</td>
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Table 2: AE Incidence by Patient

<table>
<thead>
<tr>
<th>Number of Patients (% Incidence)</th>
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<tbody>
<tr>
<td>All AEs</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>Any AE</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Fatigue</td>
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<tr>
<td>Febrile neutropenia</td>
</tr>
<tr>
<td>Infusion site reaction</td>
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<tr>
<td>Neutropenia</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
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<tr>
<td>Pyrexia</td>
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Conclusions
- The NCV treatment regimen was well tolerated in 10 patients with greater than third line metastatic pancreatic cancer, suggesting that haNK cell therapy given in combination with low-dose chemotherapy, localized radiation, and immune modulators can safely be used to treat patients with advanced cancer.
- Administration of multiple cycles of haNK therapy in combination with a PD-L1 inhibitor did not elicit haNK-related immune AEs, suggesting these therapies may be safely tolerated while promoting patient anticancer immune responses.
- In a highly treatment-refractory patient population, the NCV treatment regimen resulted in a DCR of 90% (SD for ≥ 8 weeks), and a median PFS and OS of 5.8 months and 9.5 months, respectively, suggesting that the NCV shows promise in treating advanced metastatic pancreatic cancer previously targeted with multiple lines of therapy.

The median overall survival of 9.5 months in these patients with greater than 3rd line disease compares favorably with historical median overall survival in 1st line pancreatic cancer patients receiving gemcitabine + Abraxane of 8.7 months.2

Fig. 1: Resolution of a Metastatic Lung Tumor in a Patient with Pancreatic Cancer Refractory to Chemotherapy and Radiation Therapy

January 31, 2018: Baseline imaging assessment. Metastatic lung tumor

April 19, 2018: Resolution of lung tumor after 8 weeks of treatment.

Fig. 2: Patient Treatment Course

Fig. 3: Best Target Lesion Response

References

Acknowledgments
This study is sponsored by NantKwest, Inc. The authors thank Eric Carlson, MS, and Hui Zhang, MS, for data analysis and critical input. Medical writing support was provided by Sharif Taha, PhD.