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 second-line standard-of-care (SoC) chemotherapy have poor prognoses with a median OS of less than 2-5 months.2

Immunosuppressive Tumor Microenvironment (TME)

- Pancreatic ductal adenocarcinoma (PDAC) is characterized by a dense fibroinflammatory stroma that is primarily immunosuppressive in nature.3 Increased numbers of immunosuppressive cells in the PDAC TME, such as alternatively-activated (M2a) macrophages and regulatory T (Treg) cells, prevent effective antitumor immunity and are associated with decreased survival.4-6 Furthermore, these cells can have a causative role in carcinogenesis, and have been shown to infiltrate premalignant pancreatitis lesions and increase with disease progression.7 Additionally, the PDAC TME is characterized by poor vasculature and a dense fibrous stroma, which leads to a hypoxic environment that supports tumor cell survival and which also impedes drug delivery and effective immune cell infiltration.

- We hypothesize that effective and sustained response against pancreatic cancer requires a coordinated approach that: 1. reverses the immunosuppressive tumor microenvironment, 2. induces immunogenic cell death (ICD) and 3. re-engages NK and T-cell antitumor responses.

In proof-of-concept trials, the NCV was tested in 10 patients with 3rd-line or greater second-line standard-of-care (SoC) chemotherapy have poor prognoses with a median OS of less than 2-5 months.2

The NCV includes metronomic low-dose nab-paclitaxel and stereotactic body radiation therapy (SBRT) with cryopreserved NK and cytokine NK & T-cell superagonist IL-15R. The NCV is a strategy that uses immunomodulatory doses of chemotherapies, in combination with multifaceted immune-activating investigational agents, in an effort to reprogram the TME towards antitumor immunity (Figure 1).

We believe these results warrant further research, and this poster describes our newly-designed trial.

Table 1: Treatment Components of QUITL 3.080 NANT Pancreatic Cancer Vaccine

<table>
<thead>
<tr>
<th>Component</th>
<th>Description</th>
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<tbody>
<tr>
<td>NANT Cancer Vaccine (NCV)</td>
<td>Contains: 1. Avelumab - inhibits tumor-induced PD-L1 expression on tumor cells and immune-suppressive cells, allowing for ADCC of PD-L1+ tumor cells. 2. Off-the-shelf, high-affinity CD16 natural killer cells (haNK) and cytokine NK &amp; T-cell superagonist IL-15R. 3. off-the-shelf, high-affinity CD16 natural killer cells (haNK) and cytokine NK &amp; T-cell superagonist IL-15R.</td>
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<tr>
<td>NCV - Avelumab</td>
<td>Avelumab is an FDA approved off-the-shelf, high-affinity CD16 natural killer cells (haNK) and cytokine NK &amp; T-cell superagonist IL-15R.</td>
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<tr>
<td>NCV - haNK</td>
<td>haNK cells are administered with IgG1 antibody avelumab.11 PD-L1 can be expressed on tumor cells, as well as immunosuppressive stroma that is primarily immunosuppressive in nature.</td>
</tr>
<tr>
<td>NCV - IL-15R</td>
<td>IL-15R is an FDA approved off-the-shelf, high-affinity CD16 natural killer cells (haNK) and cytokine NK &amp; T-cell superagonist IL-15R.</td>
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<td>NCV - Imaging</td>
<td>Imaging includes PET scans with 18-FDG and CT scans.</td>
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NANT Cancer Vaccine (NCV) to Induce Immunogenic Cell Death

- The NCV includes metronomic low-dose nab-paclitaxel and stereotactic body radiation therapy (SBRT) with cryopreserved NK and cytokine NK & T-cell superagonist IL-15R (N-803) combined with adenovirus (Ad5) & yeast tumor-associated antigen (TAA) vaccines, and checkpoint inhibitors (Table 1).
- Chemotherapies such as nab-paclitaxel, as well as nivolumab, have shown to mitigate immunosuppression in the TME.1,2,3,7,8 Preclinical studies have shown that combined treatments can result in increased NK cell activity and proliferation.9,10 haNK cells have been shown to mediate antibody-dependent cellular cytotoxicity (ADCC) of PD-L1-expressing cells when administered with IgG1 antibody avelumab.11 PD-L1 can be expressed on tumor cells, as well as immunosuppressive stroma that is primarily immunosuppressive in nature.
- Cancer vaccines provide a means to induce immune recognition of TAAs, by conditioning dendritic and CD8+ T cells to present TAAs and to respond to TAA stimulation.

The NCV is non-randomized, open-label, single-arm phase II trial.
- Combination chemotherapy, radiotherapy, CD16 HNK, and immunotherapy administered over a 3-week induction cycle for up to 1 year.
- If long-term disease control or objective response is observed, patient has opportunity to cross into 2-week maintenance cycle, which has reduced therapeutic interventions, 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).
- Exploratory endpoints: CA-19-9 level and correlations with subject outcomes, tumor molecular profiles and correlations with subject outcomes, therapy-induced changes in immune responses and correlations with subject outcomes.

References