Abstracts

765 NG-350A, A TUMOR-SELECTIVE ANTI-CD40 AGONIST EXPRESSING THERAPEUTIC, GEMCITABINE/ Nab-PACLITAXEL AND IPILIMUMAB FOR UNTREATED METASTATIC PANCREATIC ADENOCARCINOMA: COHORT C OF THE REVOLUTION TRIAL

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Background Historically, the treatment of metastatic pancreatic adenocarcinoma (mPDAC) has had limited success. This is particularly true of conventional immunotherapy, largely due to the immunosuppressive and dysregulated nature of the mPDAC tumor microenvironment. However, chemoimmunotherapy approaches combining immune checkpoint blockade (including CTLA-4 inhibition to increase T-cell infiltration) with anti-CD40 agonists have demonstrated tumor control in relevant mPDAC preclinical models. Furthermore, chemoimmunotherapy combinations incorporating anti-CD40 agonists have shown promising initial data in mPDAC clinical trials. However, systemic administration of CD40 agonists and anti-CTLA4 therapy can be limited by toxicity.

NG-350A is a T-SIGn (Tumor-Specific Immuno Gene) therapy designed to combine systemic IV delivery with tumor-selective replication and gene delivery and expression within primary and metastatic epithelial tumor cells. NG-350A encodes a CD40 agonist monoclonal antibody and has shown promising tolerability and functional pharmacodynamics, likely related to tumor localized expression and activity of the encoded anti-CD40 antibody. The mechanism of action of NG-350A (driving tumor localized expression of anti-CD40) should be well-suited to chemoimmunotherapy combinations in mPDAC.

REVOLUTION (NCT04787991) is an adaptive platform trial, designed to assess the activity of parallel, novel chemoimmunotherapy combinations in patients with untreated mPDAC. Here we describe Cohort C, which is designed to explore the following combination as an approach to overcome immune resistance in mPDAC: standard-of-care gemcitabine/nab-paclitaxel to induce immunogenic cell death; NG-350A for antigen presenting cell activation and immune priming; and ipilimumab to enhance T-cell activation, proliferation and tumor infiltration.

Methods REVOLUTION is an open-label, non-randomized, exploratory platform trial enrolling patients with mPDAC. Each cohort utilizes a Simon two-stage design (15 patients per stage), with expansion to Stage 2 based on the safety, efficacy and biomarker analyses.

Patients in Cohort C will receive standard of care gemcitabine/nab-paclitaxel. In addition, NG-350A will be administered a total of 3 times (once at $1 \times 10^{12}$ viral particles [vp]; twice at $3 \times 10^{12}$ vp) and ipilimumab will be administered twice (1 mg/kg; 6 weeks apart). The primary and secondary objectives are safety and clinical activity, respectively. Exploratory endpoints include pharmacodynamics and association of tumor, blood, and stool biomarkers with clinical activity.

Cohort C is enrolling into Stage 1.

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REFERENCES


Ethics Approval This study is approved by the WCG IRB, reference number 20203790.

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