Exploratory platform trial to evaluate immunotherapy combinations with chemotherapy for the treatment of patients with previously untreated metastatic pancreatic adenocarcinoma (REVOLUTION)

Background Metastatic pancreatic adenocarcinoma (mPDAC) remains notoriously treatment-refractory, particularly to immunotherapy; however, recent promise has been demonstrated with chemoimmunotherapy combinations. REVOLUTION is an adaptive platform trial, designed to further these advancements by assessing the safety and antitumor activity of parallel, novel chemoimmunotherapy combinations in patients with untreated mPDAC. Coupled with deep immune biomarker profiling, this approach will enable rapid insights from each combination, generating data to be leveraged for future cohorts. REVOLUTION also builds upon the collaborative framework between academic, nonprofit and industry partners, laid by the PRINCE trial.

Methods REVOLUTION is an open-label, non-randomized, exploratory platform trial. Each cohort utilizes a Simon two-stage design: Stage 1 enrolling n=15 patients, expansion to Stage 2 (an additional n=15 patients) based on the totality of safety, efficacy and biomarker analyses.

Key inclusion criteria histologically or cytologically confirmed, treatment-naïve, recurrent or de novo mPDAC, measurable by RECIST 1.1. Primary endpoints: safety, as assessed by the incidence and severity of adverse events. Secondary endpoints: ORR (per RECIST 1.1), DCR, DOR, PFS, and OS. Exploratory endpoints: pharmacodynamics and association of tumor, blood, and stool biomarkers with clinical activity.

Three cohorts are underway, all using a backbone of standard-of-care gemcitabine/nab-paclitaxel (gem/nP).

Cohort A: nivolumab + ipilimumab + gem/nP. We hypothesize chemotherapy will induce antigen release, ipilimumab will enhance T cell activation, proliferation and tumor infiltration, and nivolumab will overcome immunosuppression while re-invigorating therapeutically relevant T cells.

Cohort B: high-dose hydroxychloroquine (HCQ), an autophagy inhibitor, + ipilimumab + gem/nP. The same mechanisms of action for chemotherapy and ipilimumab as Cohort A are hypothesized, with HCQ augmenting T cell priming and cytotoxicity by upregulating MHC-1.

Cohort C: NG-350A, an intravenously administered adenovirus that selectively replicates in tumor cells and expresses a fully human agonistic CD40 monoclonal antibody, + ipilimumab + gem/nP. The same mechanisms of action for chemotherapy and ipilimumab as Cohorts A and B are hypothesized, with NG-350A re-programming the tumor microenvironment, activating antigen-presenting cells, and facilitating immune priming.

In accordance with recent findings, all current cohorts are also testing a novel dosing schedule of ipilimumab (2 doses at 1 mg/kg, Q6W).

Results Cohorts A and B are fully enrolled for Stage 1 and accumulating data to support an expansion decision. Cohort C is in development.

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Trial Registration NCT04787991

REFERENCES

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