Neoadjuvant CAN-2409 + Prodrug Plus Chemoradiation for Borderline Resectable or Locally Advanced Non-Metastatic Pancreatic Adenocarcinoma (PDAC)

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Background

Effective therapies for PDAC are urgently needed. CAN-2409 is a replication-defective adenovirus encoding the HSV-thymidine kinase gene, administered intratumorally in combination with a prodrug (valacyclovir or acyclovir). Cells transduced with CAN-2409 activate prodrug, resulting in immunogenic cell death and release of tumor necrotic factors within the inflammatory tumor microenvironment. Together, this results in antivaccination against the patient's own tumor. A phase 1 clinical trial in PDAC, previously showed marked infiltration by CD8+ T cells and initial evidence of clinical activity after administration of CAN-2409 + prodigyn [1].

Methods

PaTH2 is a randomized, open-label, phase 2 clinical trial evaluating safety and efficacy of CAN-2409 + prodigyn combined with standard of care (SOC) chemotherapy (CR) and surgery in borderline resectable (BR) or locally advanced (LA) PDAC. Two to 3 courses of CAN-2409 + prodigyn were administered after induction chemotherapy, during CR, and during surgery if performed. Endpoints included overall survival (OS) at 24 months and serial CA 19-9 levels in treatment arm (n=6) versus controls (n=5). Immune profiling of available peripheral blood samples was performed using ULNMe in 4 treatment arm patients compared to 3 control patients. H&E staining and multiplex immunofluorescence were performed on available tissue samples pre- and post-treatment with CAN-2409 + prodigyn from 2 treatment arm patients versus 1 control patient.

Figure 1. PaTH2 study design

Table 1. Baseline characteristics and enrollment summary by disease category

Table 2. Most frequent treatment-related AE on Test Arm

Table 3. Grade 3-4 events per arm

Clinical Results

Figure 3. CAN-2409 induces formation of dense lymphocyte aggregates, disruption of tumor structures, and necrosis in PDAC

Figure 4. Immunological Effect of CAN-2409 in Resected PDAC Tissue

Immunological Effect of CAN-2409 in Resected PDAC Tissue

Immunophenotyping

- CD3+ T cells
- CD8+ T cells
- CD8+Ki67+ T cells
- CD8+Granzyme B+ T cells
- Cytokeratin

Figure 5. Pathway analysis showing increased expression of immune-related markers in post treatment samples compared to pre-treatment samples

Conclusions

- Interim data from the PaTH2 randomized clinical trial showed that treatment with two to three injections of CAN-2409 + prodigyn in patients undergoing SOC treatment for BR PDAC is associated with prolongation of overall survival.
- Administration of CAN-2409 + prodigyn was not associated with significant incremental local or systemic toxicity in patients with non-metastatic PDAC when used in combination with SOC chemoradiation and surgery.
- In patients with progressive disease, there was a CA19.9 and survival response to salvage chemotherapy in the CAN-2409 arm, but not in control arm.
- Resection specimens and biomarker analysis demonstrated CAN-2409 activates immune response in the pancreatic tumor and peripheral blood, potentially altering disease course in PDAC.

Ethics Statement: This investigational Protocol was reviewed by the FDA and the Institutional Review Board at participating institutions. All study patients provided written informed consent prior to study enrollment.

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