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

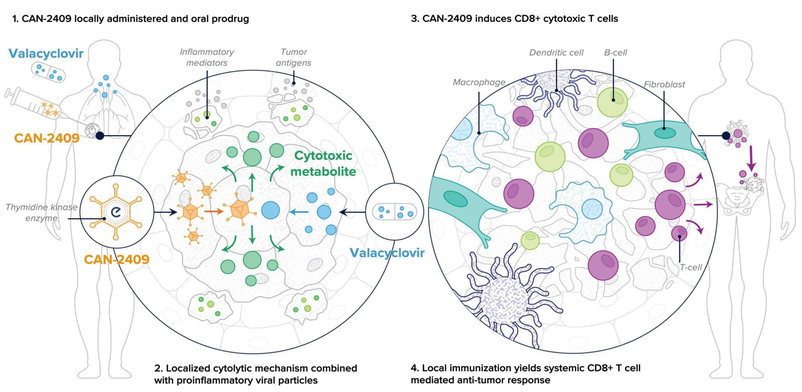
Garrett Nichols[1], Mark Bloomston[2,3], David Huitzil[4], Vanessa Rosas-Camargo[4], Armando Gamboa-Dominguez[4], Elizabeth Webber[1], Marcos Ramirez-Marquez[1], Alejandra Murillo-Cordova[1], Randy Swan[1], Jessica Dwyer[1], Francesca Barone[1], Paul Peter Tak[1]
[1]Candel Therapeutics, Inc., Needham, MA, USA, [2]The Ohio State University, Columbus, OH, USA, [3]Lee Health Regional Cancer Center, Fort Myers, FL, USA, [4]INCMNSZ, México

Abstract #653
Presented at the 2023 Society for Immunotherapy of Cancer (SITC) Annual Meeting
ClinicalTrials.gov no. NCT02446093

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 neoantigens within the inflammatory tumor microenvironment. Together, this results in in situ vaccination 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 + prodrug [1].

CAN-2409 Mechanism of Action



Methods

PaTK02 is a randomized, open-label, phase 2 clinical trial evaluating safety and efficacy of CAN-2409 + prodrug combined with standard of care (SOC) chemoradiation (CR) and surgery in borderline resectable (BR) or locally advanced (LA) PDAC. Two to 3 courses of CAN-2409 + prodrug 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 OLINK in 4 test 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 + prodrug from 2 test arm patients versus 1 control patient.

Figure 1. PaTK02 study design

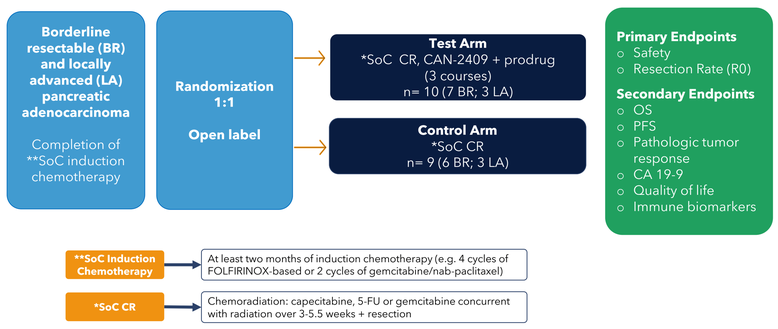
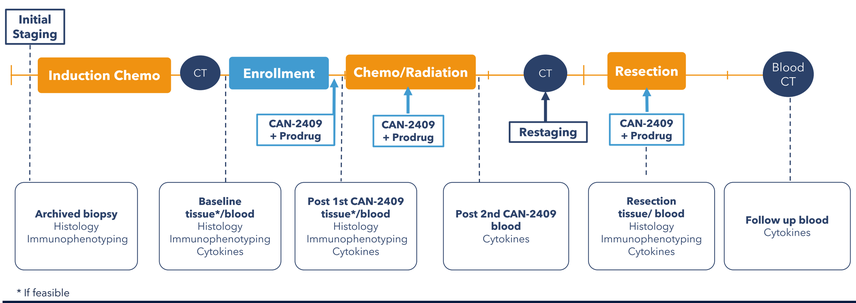


Figure 2. Treatment schema: SoC and timing of CAN-2409 injections



Clinical Results

Table 1. Baseline characteristics and enrollment summary by disease category

Patient population*	Borderline resectable (n=13)		Locally advanced (n=5)	
	Test (n=7)	Control (n=6)	Test (n=3)	Control (n=2)
Demographics				
Age median (range) – yr	63 (56 - 74)	63 (54 - 77)	60 (55 - 73)	60 (48 - 72)
Male sex - no. (%)	2 (29)	5 (83)	2 (66)	1 (50)
Female sex - no. (%)	5 (71)	1 (17)	1 (33)	1 (50)
White not Hispanic ethnicity* - no. (%)	3 (43)	3 (50)	2 (66)	1 (50)
Hispanic ethnicity - no. (%)	4 (57)	3 (50)	1 (66)	1 (50)
ECOG 0 - no. (%)	6 (85)	5 (83)	1 (33)	2 (100)
ECOG 1 - no. (%)	1 (15)	1 (17)	2 (66)	0 (0)
Tumor location				
Head - no. (%)	6 (85)	3 (50)	3 (100)	2 (100)
Other - no.(%)	1 (15)	3 (50)	0 (0)	0 (0)
Induction chemotherapy duration (mo)				
≥ 4 months of induction chemo no. (%)	6 (85)	4 (67)	2 (66)	2 (100)
Induction chemotherapy regimen				
FOLFIRINOX based induction chemo no. (%)	5 (71)	4 (67)	1 (33)	2 (100
Other induction chemo regimen no. (%)	2 (29)	2 (33)	2 (66)	0 (0)

*19 patients were enrolled: 10 in test arm (7 BR, 3 LA) and 9 in control arm (6 BR, 3 LA), one control arm patient with LA disease withdrew consent while undergoing chemoradiation due to an issue with insurance coverage.

Table 2. Most frequent treatment-related AEs on Test Arm *(n=10; 7 BR and 3 LA)*

SOC/Adverse Event (>10%)	Grade 1 n(%)	Grade 2 n(%)	Total patients (n=10)
Gastrointestinal disorders			
Abdominal pain	1(10)	1(10)	2(20)
Nausea	1(10)	3(30)	4(40)
General disorders and administration site conditions			
Fatigue	2(20)	2(20)	4(40)
Fever	2(20)		2(20)
Flu-like symptoms		2(20)	2(20)
Metabolism and nutrition disorders			
Anorexia		2(20)	2(20)
Nervous system disorders			
Dizziness	2(20)		2(20)

Table 3. Grade ≥3 lab events per arm
(n=19; 13 BR and 6 LA)

Lab Abnormalities	Test (n=10)		Control (n=9)	
	Grade 3	Grade 4	Grade 3	Grade 4
Elevated Alk Phospatase	1*	0	0	0
Elevated AST/ALT	1*	0	0	0
Elevated creatinine	1*	0	0	0
Low Hemoglobin	2	0	0	0
Low Leukocytes (WBC)	4	0	0	0
Low Lymphocytes	4*	3	1	0
Low Neutrophils	2	0	2	0
Low Platelets	2	0	0	0

*Related to CAN-2409 + prodrug

- The majority of adverse events and laboratory abnormalities reported were grade 1 and 2.
- The most common adverse events reported in more than one patient included fatigue, fever, flu-like symptoms, abdominal pain, nausea, anorexia, and dizziness.
- One serious adverse event (SAE) of acute kidney injury possibly related to prodrug and one SAE of grade 1 fever related to study drug were reported.
- No dose-limiting toxicities (DLTs) were reported.**

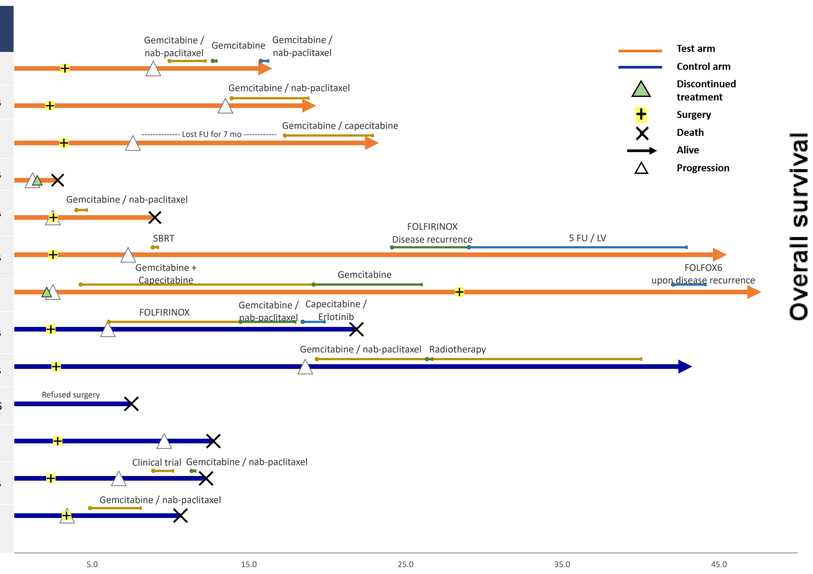
**Any unexpected and possibly related grade 4 toxicity and any unexpected possibly related grade 3 toxicity that delays SoC treatment for more than 2 weeks

Data Cutoff Date: *21AUG2023*

Clinical Results

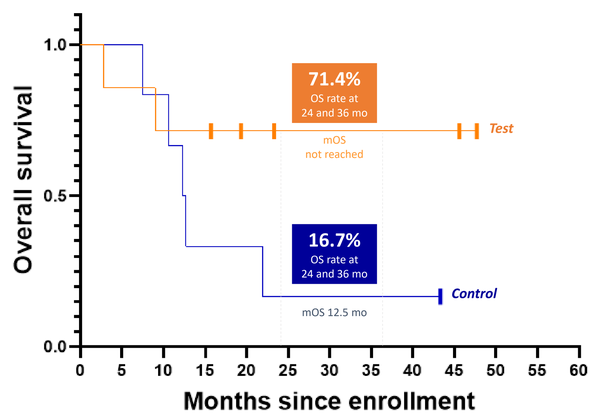
Figure 3. Swimmer's plot – Borderline Resectable patients (n=13)

Induction chemo	Duration (mo)	Surgical result	pT stage (post-surgical resection)	PCN
FOLFIRINOX	4	R0-IA	T1N0M0 Stage IA	2192PIN
FOLFOX	5	R0-IB	T2N0M0 Stage IB	2182PLB
FOLFIRINOX	4	U	N/A	2172PIN
FOLFIRINOX	4	No Surgery	N/A	2162PLB
FOLFIRINOX	3.5	U-IV	TXNXM1 Stage IV	2102PLB
FOLFIRINOX	4	R0-IA	T1N0M0 Stage IA	2082PLB
FOLFOX + 5FU/FA	4	U-IV	TXNXM1 Stage IV	2042PIN
FOLFIRINOX	4	R0-IIB	T2N1M0 Stage IIB	2152PLB
Gemcitabine + Abraxane	4	R0-PanIN 2	N/A	2112PLB
FOLFIRINOX	2	Refused Surgery	N/A	2092POS
FOLFIRINOX + FOLFOX	2.3	U	N/A	2072PIN
FOLFIRINOX	4	R0-IIA	T3N0M0 Stage IIA	2052PLB
FOLFIRINOX	4	U-IV	T2NXM1 Stage IV	2022PIN



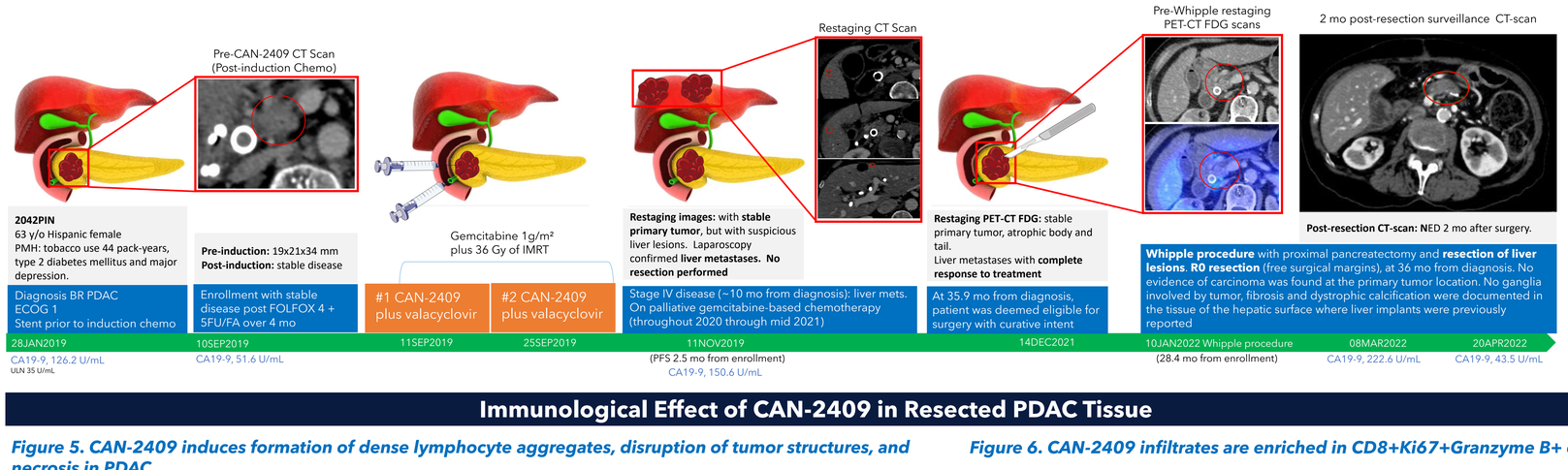
- In the LA patient population, OS in the 3 test arm patients were 6.3 mo, 5.6 mo, and 14.4 mo; OS in the 2 control arm patients were 12.7 mo and 24.6 mo.
- Due to the small number of patients and variability in the data, no statistical significance was reached.

Figure 4. Overall Survival – Borderline Resectable patients (n=13)



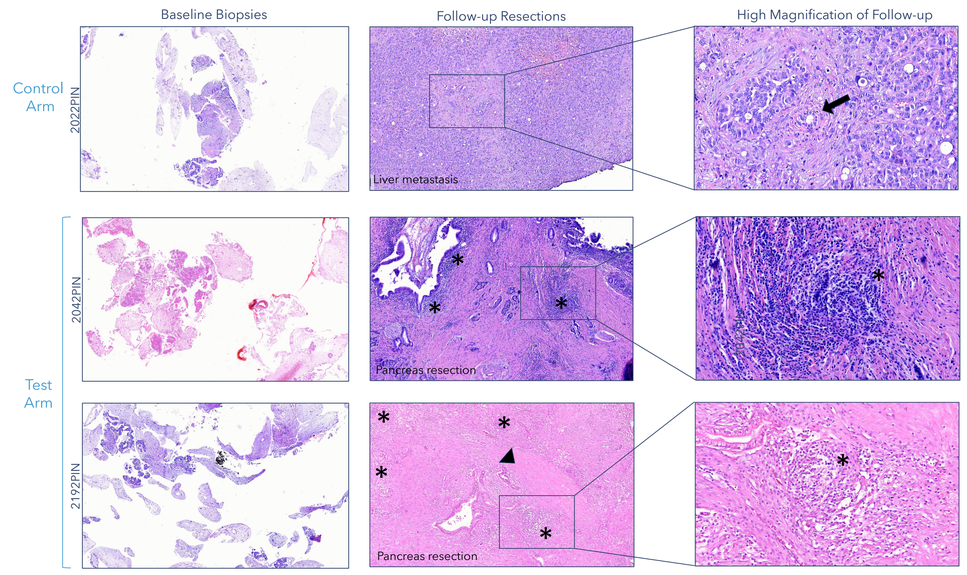
Censored = alive, still under follow-up

Figure 5. Case of Special Interest – From metastatic disease to R0 resection and complete pathologic response with prolonged overall survival



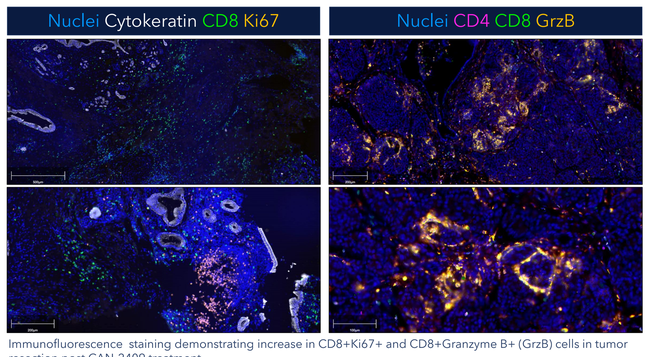
Immunological Effect of CAN-2409 in Resected PDAC Tissue

Figure 5. CAN-2409 induces formation of dense lymphocyte aggregates, disruption of tumor structures, and necrosis in PDAC



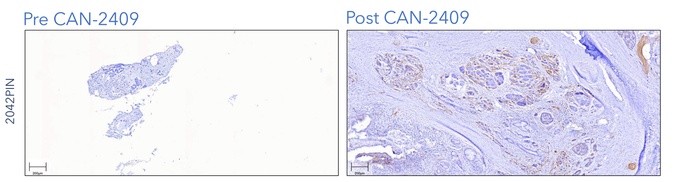
Arrow: cancer cells; Arrowhead: disrupted tumor structures and tumor necrosis; Asterisks: immune cells

Figure 6. CAN-2409 infiltrates are enriched in CD8+Ki67+Granzyme B+ cells



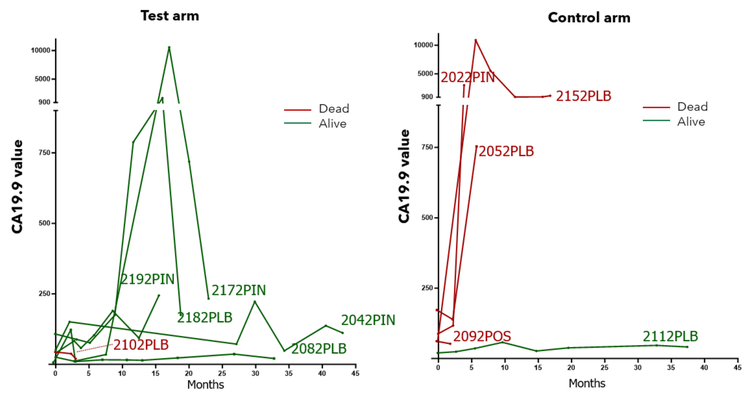
Immunofluorescence staining demonstrating increase in CD8+Ki67+ and CD8+Granzyme B+ (GrzB) cells in tumor resection post CAN-2409 treatment

Figure 7. CAN-2409 increases the level of PDL-1 in post treatment samples



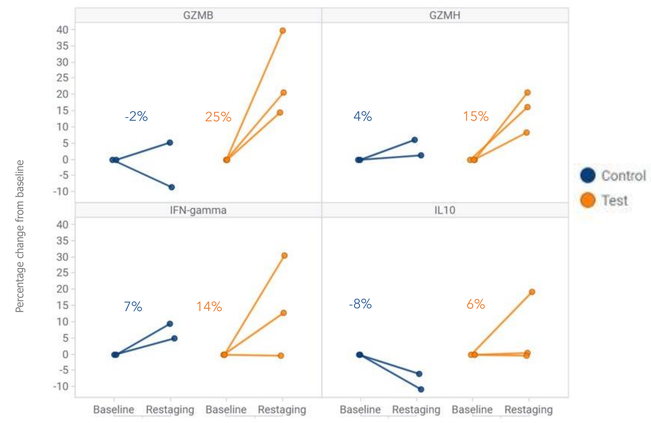
Immunohistochemistry staining (brown) for PDL-1 in pre and post treatment samples demonstrating increase staining around tumor structures and infiltrating cells

Figure 8. Disease course altered with salvage chemotherapy with ongoing survival in CAN-2409 arm, but not in the control arm



- **Test arm** cases 2172PIN, 2182PLB recurred with spike in CA19-9 (sensitive marker of tumor volume), but CA19-9 responded to salvage chemotherapy and patients are alive and under follow-up
- **Control arm** cases 2022PIN, 2152PLB, 2052PLB recurred, but CA19-9 did not respond to salvage chemo and patients died

Figure 9. Increase in plasma levels of granzymes B and H, IFNγ, and IL10 in borderline resectable patients after CAN-2409 administration (but not the control arm)



Olink Target 96 IO panel

Conclusions

- Interim data from the PaTK02 randomized clinical trial showed that treatment with two to three injections of CAN-2409 + prodrug in patients undergoing SOC treatment for BR PDAC is associated with prolongation of overall survival.
- Administration of CAN-2409 + prodrug 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 participated provided written informed consent prior to study enrollment.*

Acknowledgements: *We would like to thank all participating patients, patients' families and friends, and research institutions.*

Contact: info@candeltx.com