A novel EUS-guided Intratumoral Delivery of Submicron Particle Paclitaxel for the Treatment of Locally Advanced Pancreatic Cancer

A Prospective Safety, Tolerability and Preliminary Efficacy Study

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Sponsored by NanOlogy, LLC

CEDARS-SINAI

Pancreatic Cancer Prognosis

SEER Stage	5-year Relative Survival Rate
Localized	34%
Regional	12%
Distant	3%
All SEER stages combined	9%

American Cancer Society

Presenting Lesions and Treatments

- Early stage/resectable
  - 10% - 15%
  - Treat with surgery +/- neoadjuvant Rx
- Metastatic
  - 45% - 55%
  - Treat with chemotherapy, plus a variety of radiation, endoscopic or surgical palliation
- Borderline resectable/locally advanced
  - 35% - 40%
  - What's the best course of treatment?
  - May be a good group to try locally delivered targeted therapy

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ASCO website

“Advantages” of tumor-targeted Rx

- Minimal systemic (side) effects
- Concentrated dosing with more effective outcomes
- Many potential forms of treatment (chemo agent, radioisotope, ablating agent, immuno, thermal or cryo treatment)
- Possibly better patient experience
- Potential for simultaneous systemic therapy

What targeted Rx have been tried?

Type	Route(s)	Morbidities	Overall Survival
Surgical resection	Open	Extensive	Longer OS; cheaper
RFA (radiofrequency)	Open; Perc.	Liver failure, sepsis, duod perf, pancreatitis, panc fistula	19-26 months
Microwave	Open; perc	Pancreatitis, pseudoaneurysm	NA
Cryoablation	Open	Pancreatic/bile leak, GI bleeding	No added benefit
HIFU (ultrasound)	External	Skin burn, GI upset/pain, pancreatitis	6-14 months (80% pain improvement)
SBRT	External	Pain, nausea, gastroenteritis	10-20 months
I^{125} implant	Open	Enteritis, seeds migration	10 months (94% pain control)
IRE (electroporation)	Open, lap, perc	Pain, GI upset, leaks, pancreatitis, abscess	15-27 months
PDT	Perc, EUS	Pain , steatorrhea	16 months
EUS guided therapies			

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Ruarus. Cancers (Basel) 2018

EUS guided Intratumoral Therapies

- Allogenic mixed lymphocyte culture (cytoimplant)
- ONYX-015 (dl1520), an E1B-55kD gene-deleted replication-selective adenovirus
- TNFerade, a second-generation adenovector
- Tumor antigen-loaded dendritic cells immunotherapy
- Oncolytic virus, HF10
- Radiofrequency ablation
- Photodynamic therapy
- Brachytherapy
- Ethanol injection

Nakai. GI Endo Clinc NA 2012; Guo. Endosc Ultrasound 2013

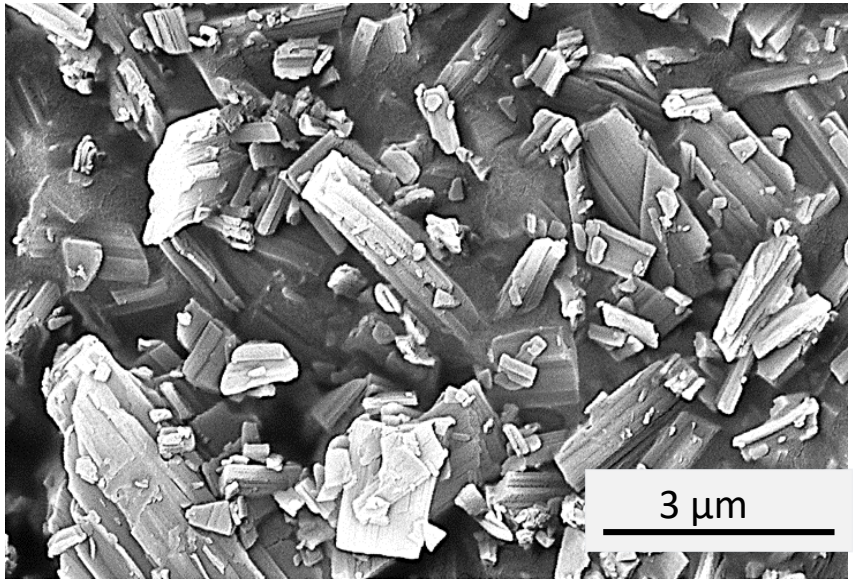
Considerations in local drug delivery

- Volume of fluid injection
  - Tolerated by patient (pain, etc)
  - Compression of the vital structures around the HOP
- Would it cause acute tissue necrosis?
  - Cavity formation
  - Tendency to abscess formation
- Distribution of fluid
  - Does it matter?
  - Multiple vs single spot delivery
  - Could it enter the pancreatic duct or vasculature and what would be the outcome?
- Would it disseminate the cancer by disturbing it?

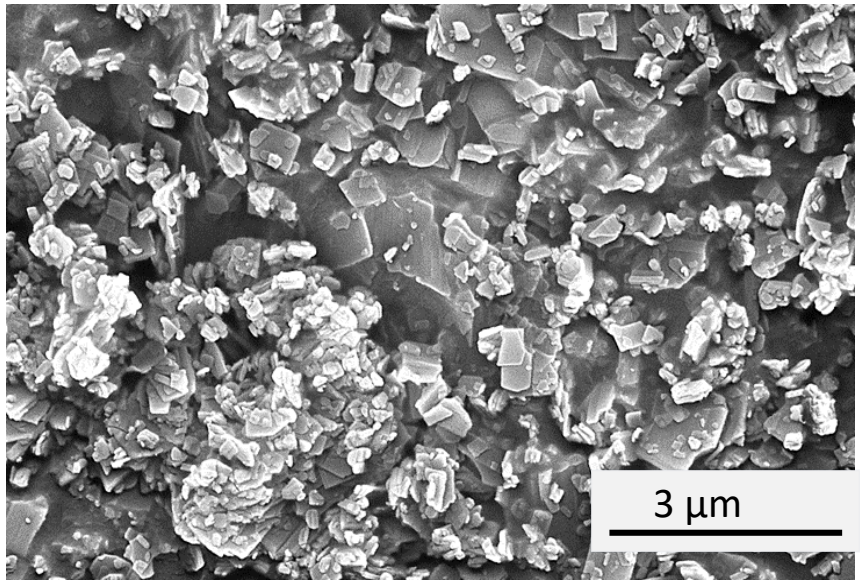
Submicron Particle Paclitaxel

- Stable submicron particles (0.8 µm mean) of pure paclitaxel without additives or coatings with large surface area to size ratio.
- Small particles with good tissue penetration and distribution to get through dense tumor stroma; large enough surface area for sustained drug release.

Unprocessed paclitaxel



Submicron particle paclitaxel



EUS-guided paclitaxel submicron particles injection

- Locally advanced pancreatic cancer
- Direct tumor injection
- IV chemotherapy prior/concurrent

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Drug Safety Study Objectives

PRIMARY OBJECTIVE:

- To evaluate the safety and tolerability of NanoPac injected directly into pancreatic cancer by endoscopic ultrasound-guided injection

SECONDARY OBJECTIVES:

- To describe the PK of NanoPac when administered into the tumor within the pancreas
- To determine whether any of the NanoPac cohorts (6, 10, or 15 mg/mL) show signs of preliminary efficacy
- To determine if two injections of NanoPac (one month apart at the determined dose for this cohort) shows signs of preliminary efficacy

Study Design

Dose Escalation:

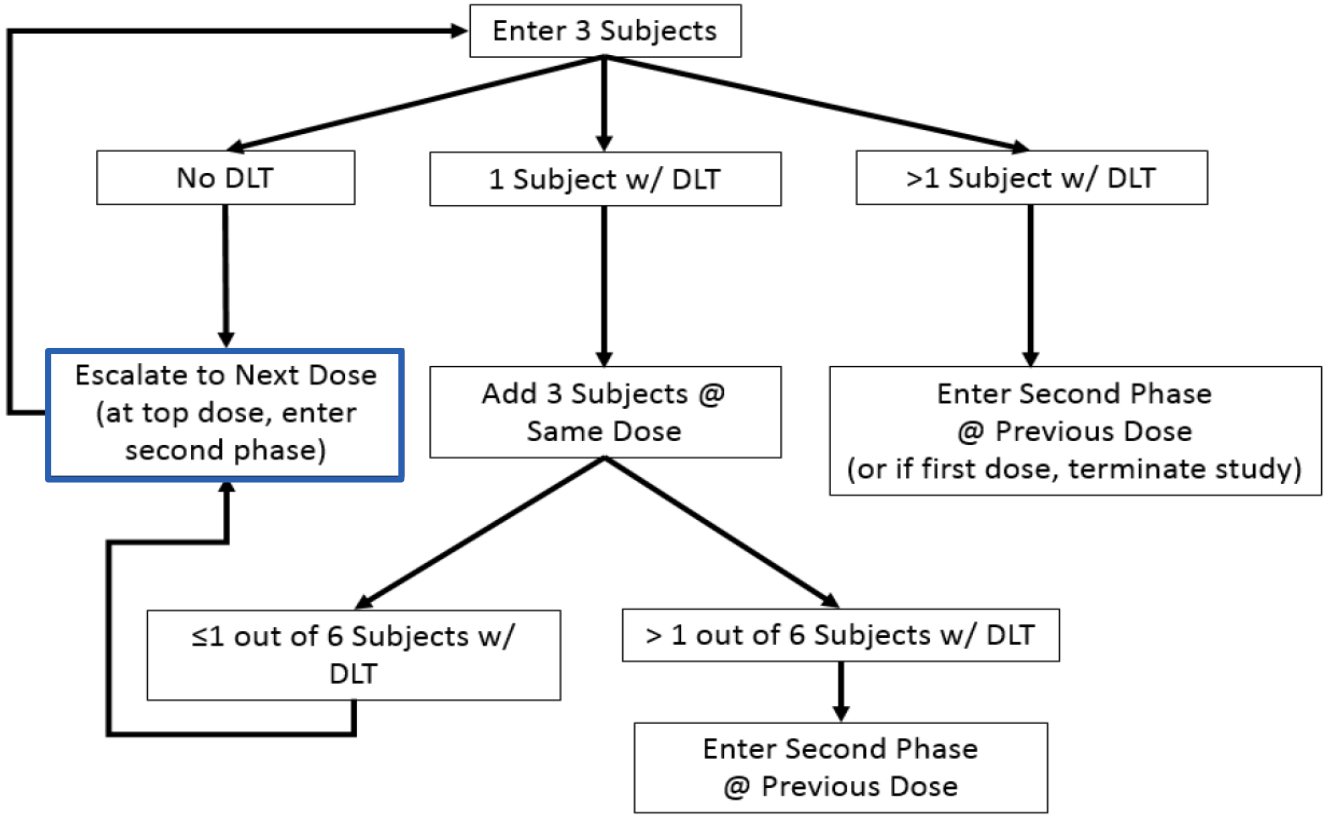
- Standard 3 + 3 design
  - Doses of 6mg/mL, 10mg/mL and 15mg/mL
  - Single injection; imaging at 3- and 6-months post injection
  - CA19-9 and CEA
  - PK (systemic assessment)

Double Injection Phase:

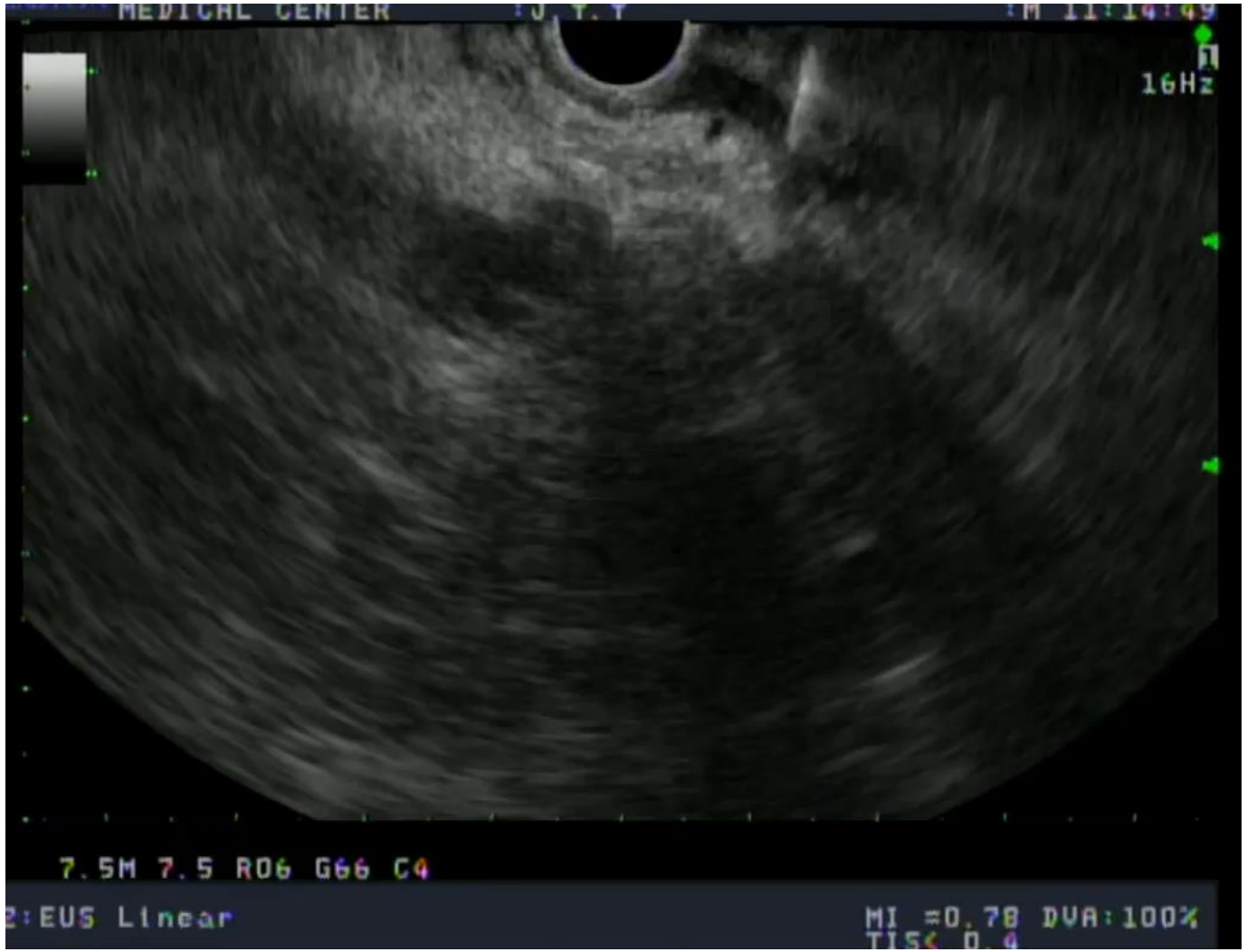
- Additional 12 subjects dosed at highest safe/tolerable dose (15mg/mL) (allowed to add 10 more patients recently)
  - Two injections, one month apart
  - Imaging, CA19-9, CEA, and PK

Drug Safety Study Design (2)

Sequential cohorts of NanoPac 6, 10, and 15 mg/mL at up to 20% of the calculated tumor volume (with a maximum injection volume of 5 mL/Subject)



Pancreatic Body Cancer
Nanopac Injections



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Patient Enrollment & Status

- 10 dose escalation subjects (3 at 6 mg, 3 at 10 mg, 4 at 15 mg/mL):
  - 7 completed the 6m study
  - 1 died just prior to the 6m visit
  - 2 withdrew due to disease progression
- As of Sept 30th, 13 subjects enrolled in double injection phase, 9 have had both injections; 2 have withdrawn due to disease progression
- 9/13 have completed 3m follow-up, 4 of whom have completed 6m
- Study is ongoing; FDA allowed additional 10 subjects for a total of 22 to complete double injection phase

Adverse Events

- Transient mild/moderate abdominal pain was noted in 4 subjects
- Bradycardia, nausea, back pain, bloating, and pancytopenia were also recorded
- Acute pancreatitis has not been encountered
- Systemic toxicity has not been reported
- No Serious Adverse Events considered due to the study agent have been reported

CA 19-9 following single injections

	Subject	Total Drug	CA19-9 (U/mL)							% Change in Biomarker[b]
		Injection 1	Day 1[a]	Week 2	Week 4	Week 6	Week 8	Week 12	Week 24	
Cohort 1 (6 mg/mL)	03001	12.6	74[a]	154	245	N/A[c]	410	282	953	**1188%**
	03002	18	524[a]	448	606	N/A[c]	DNA[e]	W/D	W/D	**W/D**
	02001	30	248	513	3126	N/A[c]	>12000	86580	40480	**16223%**
Cohort 2 (10 mg/mL)	03003	43	51	93	140	N/A[c]	393	576	118	**131%**
	02002	7	5	5	4	N/A[c]	4	5	5	**WNL**
	05001	50	16	17	18	N/A[c]	25	17	25	**WNL**
Cohort 3 (15 mg/mL)	03004	75	1628	2504	W/D	N/A[c]	W/D	W/D	W/D	**W/D**
	02003	75	157	DNA[f]	293	N/A[c]	659	567	DNA[g]	**261%[b]**
	02004	75	>12000	113,630	>12000	N/A[c]	>9999	>9999	DNA[h]	**DNA**
	05002	12	48	123	189	N/A[c]	223	152	2359	**4815%**

CA 19-9 following two injections, one month apart

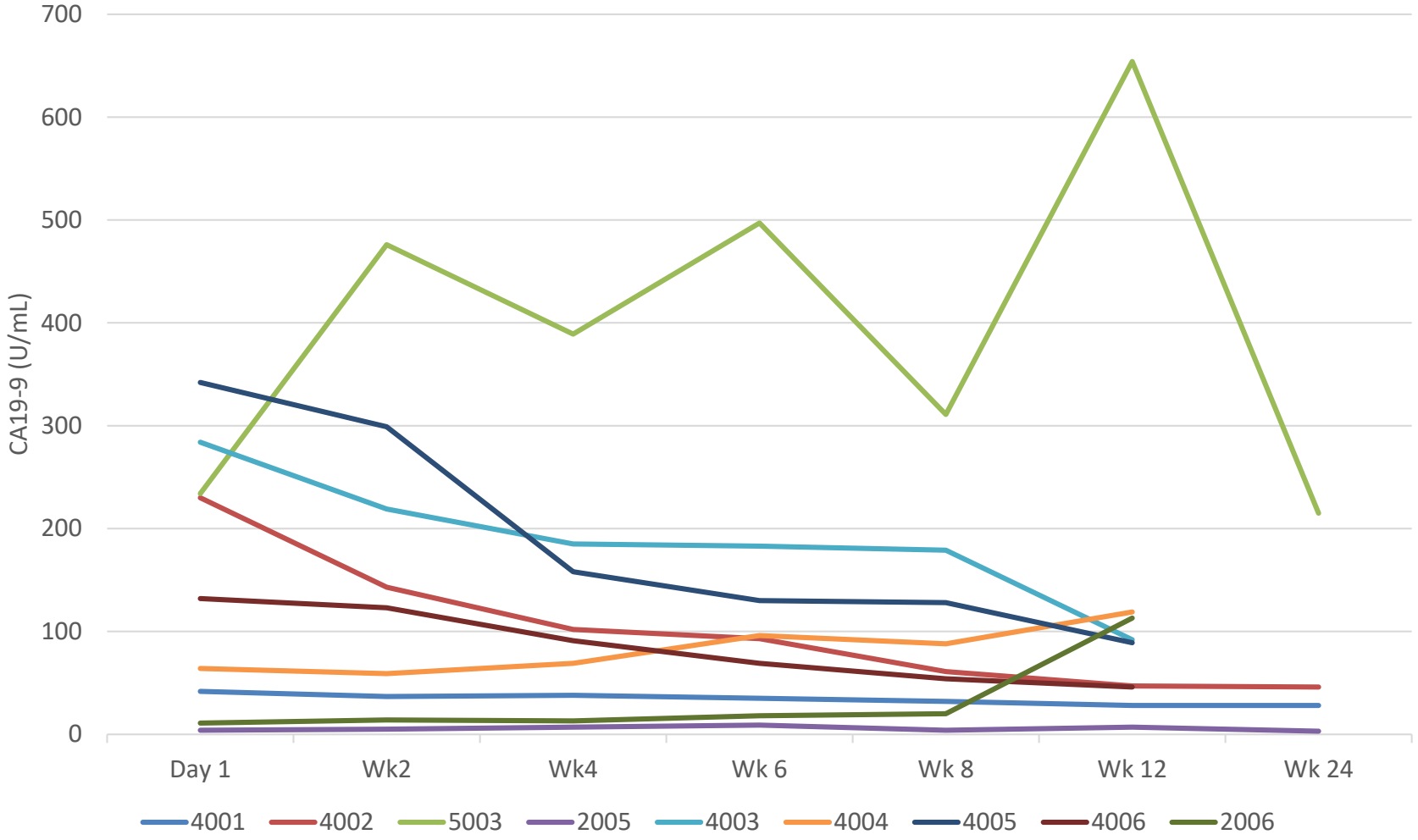
	Subject	Total Drug Given (mg)		CA19-9 (U/mL)							% Change in Biomarker[b]
		Injection 1	Injection 2	Day 1[a]	Week 2	Week 4	Week 6	Week 8	Week 12	Week 24	
Second Phase (2 x 15 mg/mL)	04001	16.5	16.5	41.8	36.8	38	35	32	28	28	**-33%**
	04002	46.5	42	230	143.5	102	93	61	47	46.1	**-80%**
	05003	75	75	234	476	389	497	311	654	215	**-8%**
	03005	75	W/D	4985	W/D	W/D	W/D	W/D	W/D	W/D	**W/D**
	02005	75	75	4	5	7	9	4	7	3	**WNL**
	04003	75	75	284	219	185	183	179	92	Oct 2019	**-68%[b]**
	02007	67.5	W/D	3747	W/D	W/D	W/D	W/D	W/D	W/D	**W/D**
	04004	57	57	64[a]	59	69	96	88	119	Nov 2019	**86%[b]**
	04005	27	27	342[a]	299	158	130	128	89	Nov 2019	**-74%[b]**
	04006	31.5	31.5	132	123	91	69	54	46	Dec 2019	**-65%[b]**
	02006	75	75	11	14	13	18	20	113	Jan 2019	**927%**

[a]Screening data used if Day 1 data not available

[b]Latest available data if Week 24 data is not available

W/D = subject withdrew; WNL = within normal limits at all timepoints

CA19-9 patterns in double injection phase



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Tumor volumes following single injections

	Subject	Total Drug Given (mg)	Tumor Volume (cc)			Change in Tumor Volume (Screening - Week 24)[a]
		Injection 1	Screening	Week 12	Week 24	
Cohort 1 (6 mg/mL)	03001	12.6	DNA[b]	DNA[b]	DNA[b]	**DNA[b]**
	03002	18	W/D	W/D	W/D	**W/D**
	02001	30	23.88	28.05	30.13	**26%**
Cohort 2 (10 mg/mL)	03003	43	12.3	41.6	14.9	**21%**
	02002	7	5.93	25.09	4.7	**-21%**
	05001	50	48.6	100.9	103	**112%**
Cohort 3 (15 mg/mL)	03004	75	W/D	W/D	W/D	**W/D**
	02003	75	DNA[c]	75	DNA[d]	**DNA[d]**
	02004	75	24.19	47	DNA[e]	**94%[a]**
	05002	12	3.5	3.2	3.3	**-6%**

[a]Latest available data if Week 24 data is not available

[b]Tumor volume for Subject 03001 is not available; only tumor dimensions were provided for this subject

[c]Data unavailable as no sample was procedure occurred offsite and results were not obtained

[d]Subject 02003 died prior to Week 24

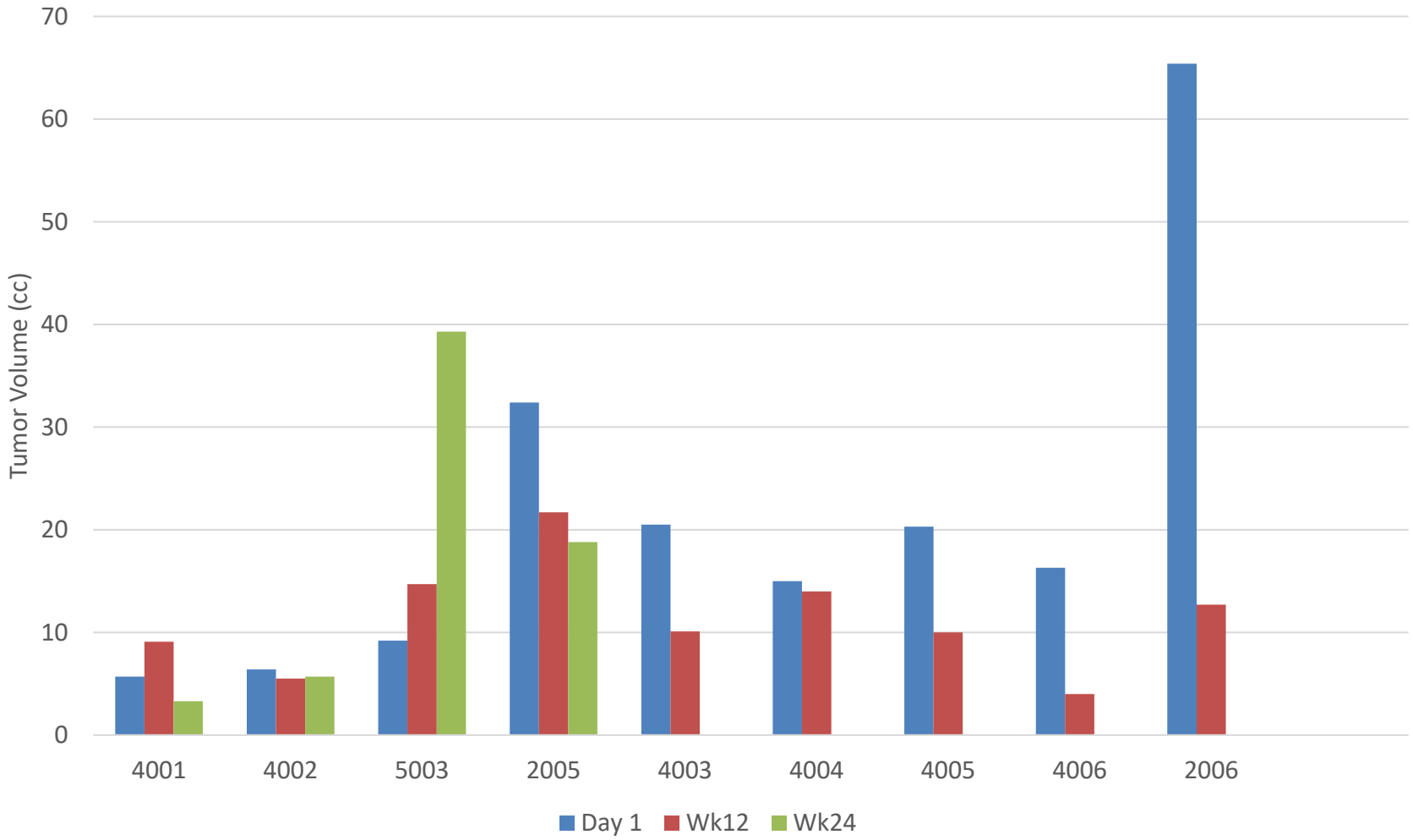
[e]Subject 02004 was lost to follow-up

Tumor volumes following two injections, one month apart

	Subject	Total Drug Given (mg)		Tumor Volume (cc)			Change in Tumor Volume (Screening - Week 24)[a]
		Injection 1	Injection 2	Screening	Week 12	Week 24	
Second Phase (2 x 15 mg/mL)	04001	16.5	16.5	5.7	9.1	3.3	**-42%[a]**
	04002	46.5	42	6.4	5.5	5.7	**-11%**
	05003	75	75	9.2	14.7	39.3	**327%**
	03005	75	W/D	W/D	W/D	W/D	**W/D**
	02005	75	75	32.4	21.7	18.8	**-42%**
	04003	75	75	20.5	10.1	Oct 2019	**-51%[a]**
	02007	67.5	W/D	W/D	W/D	W/D	**W/D**
	04004	57	57	15	14	Nov 2019	**-7%[a]**
	04005	27	27	20.3	10	Nov 2019	**-51%[a]**
	04006	31.5	31.5	16.3	4	Dec 2019	**-76%[a]**
	02006	75	75	65.4	12.7	Jan 2019	**-81%**

[a]Latest available data if Week 24 data is not available

Tumor Volume Change – 2 Injection Phase



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Subject - Eligible for Surgery

59 yr old woman, with T4N0M0 Stage III adenocarcinoma of the pancreas.

Staging a composite of EUA and CT scans – 2.7 x 2.2 cm mass with concern for degree of SMA abutment from pancreatic head mass limiting ability for R0 resection.

Treatment Schedule

- 9/2018 Neoadjuvant mFOLFIRINOX x4 cycles
- 12/2018 SBRT completion (5 fractions)
- 1/8/2019 NanoPac injection #1
- 1/2019 Gemcitibine/Abraxane (Days 1, 8, 15) with Neulasta support (day 15)
- 2/4/2019 NanoPac injection #2
- 3/2019 Gemcitibine/Abraxane cycle 2

Subject - Eligible for Surgery

- NanoPac injections 8 January and 4 February 2019
- EUS performed 4 May 2019 (18 weeks after first injection)
  - Reduction of mass from 2.7 x 2.2 cm to 2.2 x 1.6 cm
  - Less involvement of SMA
  - T4 down to T2; Patient scheduled for Whipple
- Surgery performed 7 June 2019
  - Final pathology 2.2 x 1.8 cm adenocarcinoma of the pancreas with high grade dysplasia, 0/14 nodes involved, negative surgical margins

Conclusions

- Submicron particle paclitaxel appears to be safe and tolerable when administered by intratumoral EUS injection at up to 15 mg/mL on two occasions 4-wks apart
- One subject was down-staged and has undergone surgical resection
- These are encouraging results and warrant further investigation of this novel treatment approach