TANDEM EUS-GUIDED FINE NEEDLE INJECTION OF INTRACYSTIC SUBMICRON PARTICLE PACLITAXEL (NANOPAC®) AS A TREATMENT FOR BRANCH-DUCT IPMN: SAFETY, PHARMACOKINETIC, AND PRELIMINARY EFFICACY

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Background and Aims

- Branch duct (BD)-IPMNs with increased risk for malignant transformation are typically treated with surgical resection, and alternate therapies are needed for patients with prohibitive risks for perioperative complications.
- Injection of cysts with paclitaxel may prevent or reverse transformation, but current formulations are not retained in cysts to provide durable benefit.
- A submicron particle formulation of paclitaxel (SPP) has been designed [NanOlogy, Inc] to avoid clearance into the systemic circulation and effectively provides a depot effect releasing the drug at constant saturation levels.
- In this initial study of EUS-guided fine needle injection (FNI) with SPP we evaluated safety, tolerability, pharmacokinetics, and cyst response in BD-IPMNs.
- This report covers 5 of the study subjects enrolled at one site. SPP was administered on two occasions 12 weeks apart in 4/5 subjects and once in 1 subject.
- A diagnosis of BD-IPMNs was confirmed by EUS-guided confocal laser endomicroscopy and cyst fluid next generation sequencing.

Methods

- Subjects received EUS-FNI of SPP (15mg/mL concentration) at volumes equal to the aspirated cyst fluid as part of an ongoing clinical trial [NCT03188991] (Study was interrupted due to COVID-19 pandemic).
- CT Scans were performed at 0, 12, and 24 weeks to assess changes in cyst size.

Results

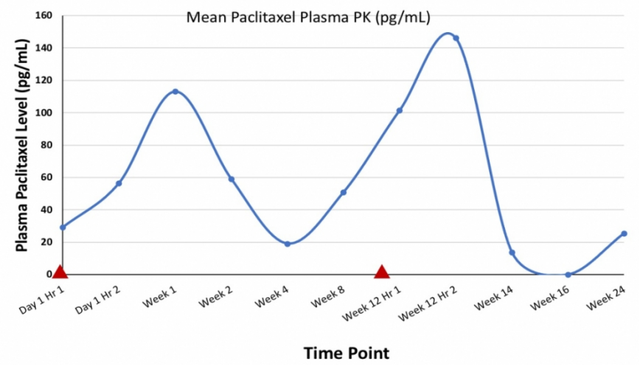
- The mean ± standard deviation duration of follow-up from 1st EUS-FNI was 37.3±19.8 weeks.
- The mean size on CT-Scan of BD-IPMNs at time 0 weeks (*1st EUS-FNI*) was 3.3±0.8 cm, 12 weeks (*2nd EUS-FNI*) was 3.02±1.2 cm, and 24 weeks was 3.15±1.8 cm (Table 1).
- The mean dosage of SPP injected by EUS-FNI was 75±39 mg for 1st dose and 40.6±15.1 mg for 2nd dose.
- No dose limiting toxicities, study-related serious adverse events, or clinically significant changes in blood work were observed.
- The paclitaxel levels (PK) in plasma and cyst fluid are shown in Figure 1. Systemic paclitaxel concentration did not exceed 1 ng/mL at any point post-administration, falling below lower limit of quantitation (25 pg/mL) within 4 weeks. Cyst fluid analysis confirmed sustained presence of SPP for at least 12 weeks.
- At baseline evaluation, 4 of 5 subjects had GNAS mutations in cyst fluid (Table 1). In total, DNA mutations (KRAS or GNAS) were not detectable in two of 4 (50%) subjects after EUS-FNI with SPP (Table 1); both subjects (Figure 1) had a dose-dependent high intracystic concentration (> 1000 ng/mL) of SPP immediately prior to 2nd EUS-FNI (12weeks after the first injection of SPP).

Conclusion

- EUS-FNI of intracystic SPP appears to be safe and well tolerated in patients with BD-IPMNs.
- SPP is likely retained in these cysts up to 12 weeks in a dose-dependent manner and higher doses are associated with regression of mutations that are specific for BD-IPMNs.
- Future studies with additional injections and longer-term follow-up are needed to understand the durability of the benefits observed.

Subject No.	nCLE image pattern	Cyst fluid NGS	Relative contraindication to surgery	Largest dimension (cm, Screen CT)	Injection 1 (mg) 1st EUS-FNA	Largest dimension (12 week)	Injection 2 (mg) 2nd EUS-FNA	Cyst fluid NGS (12 weeks)	Largest dimension (24 weeks)	Largest dimension (50±5 weeks)	EUS follow-up (24-25 week)	EUS follow-up (50-55 week)	Total imaging follow up (weeks)
1	Papillae	KRAS, GNAS	Pt's choice	4.0	120	4.7	60	KRAS, GNAS	4.4	4.5	No KRAS, GNAS	No KRAS, GNAS	50
2	Papillae	NA	Morbid Obesity	2.1	15	2.1	30	NA	1.9	1.9	NA*	KRAS, GNAS	58
3	Papillae	GNAS, BRAF	Cirrhosis	3.1	67.5	2.7	27.5	No GNAS, BRAF	NP*	NP*			13
4	Papillae	KRAS, GNAS	Morbid Obesity	3.2	75	3.1	45	KRAS, GNAS	2.2	1.9			47
5	Incomplete papillae	KRAS, GNAS	Cirrhosis	4.1	97.5	NP*	NP*	NP*	4.0				20

Table 1: Individual subject cyst characteristics pre-and-post EUS-fine needle injection of intracystic submicron particle paclitaxel.*NP – Not performed due to COVID-19 pandemic and/or other unrelated patient morbidity. NA*- Not available.



Week 12 Intracystic Fluid Paclitaxel Concentration	
Subject	(ng/mL)
1	17800
2	270
4	2990

Figure 1. Plasma and pancreatic cyst fluid paclitaxel concentration at different time intervals in relation to the dosing of intracystic submicron particle formulation of paclitaxel (NanoPac).