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

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 [NCT03189991] (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.

Conclusion

- 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).

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.

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>EUS Image grade</th>
<th>Cyst fluid protein</th>
<th>Relative hypointensity to liver</th>
<th>Distance to major blood vessel</th>
<th>Injection 1 (mm)</th>
<th>Injection 1 EUS-FNA</th>
<th>Injection 2 (mm)</th>
<th>Injection 2 EUS-FNA</th>
<th>Cyst Fluid samples</th>
<th>Total imaging follow-up (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Papillae</td>
<td>KRAS, GNAs</td>
<td>Ps choice</td>
<td>4.0</td>
<td>120</td>
<td>4.7</td>
<td>60</td>
<td>KRAS, GNAs</td>
<td>4.4</td>
<td>4.5</td>
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<td>2</td>
<td>Papillae</td>
<td>NA</td>
<td>Morbid Obesity</td>
<td>2.1</td>
<td>15</td>
<td>2.1</td>
<td>30</td>
<td>NA</td>
<td>1.9</td>
<td>1.9</td>
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<tr>
<td>3</td>
<td>Papillae</td>
<td>GNAS, BRAF</td>
<td>Cirrhosis</td>
<td>3.1</td>
<td>67.5</td>
<td>2.7</td>
<td>27.5</td>
<td>No GNAS, BRAF</td>
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<td>NP*</td>
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<tr>
<td>4</td>
<td>Papillae</td>
<td>KRAS, GNAs</td>
<td>Morbid Obesity</td>
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<td>75</td>
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<td>45</td>
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<td>2.2</td>
<td>1.9</td>
</tr>
<tr>
<td>5</td>
<td>Incomplete papillae</td>
<td>KRAS, GNAs</td>
<td>Cirrhosis</td>
<td>4.1</td>
<td>97.5</td>
<td>NP*</td>
<td>NP*</td>
<td>NP*</td>
<td>4.0</td>
<td>20</td>
</tr>
</tbody>
</table>

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).