PanCO: An Open-Label, Single-Arm Pilot Study of Oncosil™ in Patients with Unresectable Locally Advanced Pancreatic Adenocarcinoma in Combination with FOLFIRINOX or Gemcitabine+Nab-Paclitaxel Chemotherapies

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Introduction

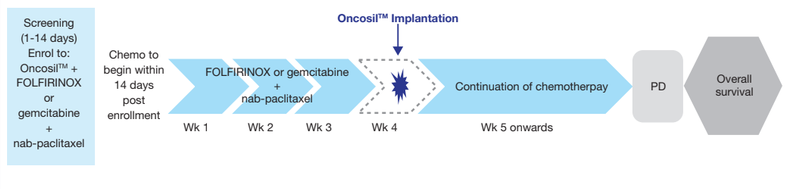
Locally advanced pancreatic cancer (LAPC) accounts for 30% to 40% of all pancreatic cancer presentations[1] and is associated with a poor prognosis with a median survival is 6-10 months.[2] Current standard treatment is limited to chemotherapy or chemo-radiotherapy. Conventional radiotherapy (CRT) has been used to treat patients with this disease and is usually given with gemcitabine or fluoropyrimidine-based chemotherapy. CRT is limited by the amount of radiation that can be delivered to the gastrointestinal tract due to side effects. Novel treatment approaches are crucial in attempting to combat this unmet medical need. Phosphorus-32 (P-32) Microparticles is a brachytherapy device that implants a pre-determined tumouricidal dose of the beta radiation emitting isotope (P-32) directly into cancerous tissue via endoscopic ultrasound (EUS). P-32 has been investigated in combination with gemcitabine monotherapy in 23 patients with LAPC and metastatic disease in two clinical studies which demonstrated that, in combination with gemcitabine chemotherapy, P-32 had an acceptable tolerability and safety profile. Efficacy data showed potential with evidence of a target tumour response rate of 23% and a target disease control rate of 82%. These studies established that EUS-directed implantation of P-32 is an appropriate method of delivery. The presented data are early results from an ongoing international, multi-institutional, single-arm pilot study which is being conducted at 12 sites in Australia, the UK and Belgium.

Objective

The study objective is to further investigate the safety, efficacy, feasibility and performance of the OncoSil™ device when implanted intratumourally using EUS in a patient population undergoing standard chemotherapy for unresectable LAPC. The purpose of this interim analysis is to report on the early observations and experience from the first 25 enrolled and implanted patients up to Week 16 of follow up.

Study design

Figure 1. Study design



Methods

Eligible patients received either gemcitabine + nab-paclitaxel or FOLFIRINOX chemotherapy by physician choice. P-32 implantation took place during the 4th or 5th week following the initiation of chemotherapy. P-32 was implanted directly into the pancreatic tumour via EUS guidance, using a fine needle aspiration (FNA) needle. Each patient's dose was calculated from the tumour volume where the absorbed dose of P-32 to the tumour was calculated to equal 100 Gy. Diffusion pattern of the P-32 suspension following implantation was assessed by EUS and by Bremsstrahlung SPECT/CT imaging within 4 hours and 7 days post implantation. Chemotherapy was continued after the implantation. Safety data was collected weekly and toxicity was graded using the Common Terminology Criteria for Adverse Events (CTCAE). Centrally-read CT scans were conducted every 8 weeks to assess response defined as complete response [CR], partial response [PR], and stable disease [SD]) according to RECIST 1.1 criteria. FDG-PET scans were performed at Baseline and at Week 12. Overall survival (OS) was determined at 8-weekly intervals until subject death or 104 weeks after last subject enrolment. The study will continue to enrol patients until 40 patients have been enrolled and implanted with the P-32 device.

Key eligibility criteria

- Histologically or cytologically proven adenocarcinoma of the pancreas
- Unresectable locally advanced pancreatic carcinoma
- Target tumour diameter 2-6cm
- ECOG Performance Status 0 to 1
- No distant metastases
- No prior radiotherapy or chemotherapy for pancreatic cancer

Primary endpoint:

- Safety and Tolerability

Secondary endpoints: Efficacy

- Local Disease Control Rate at 16 weeks
- Local Progression Free Survival (LPFS), within the pancreas
- Progression Free Survival (PFS), all sites
- Overall Survival (OS)

Results

Baseline patient demographics and characteristics are shown in Table 1 for the first 25 patients implanted with the OncoSil™ device up to the 29th of January 2018. Chemotherapy assignment was per physician choice. Twenty two (22) patients received gemcitabine + nab-paclitaxel and 3 patients received FOLFIRINOX.

Table 1: Patient Demographics and Baseline Characteristics (N=25)

Characteristic	
Age, years Median Range	 65 54-84
Male, n (%) Female, n (%)	17 (68) 8 (32)
Geographical location, n (%) Australia UK	 22 (88) 3 (12)
ECOG PS, n (%) 0 1	 14 (56) 11 (44)
Tumour location within the pancreas, n (%) Head Body	 20 (80) 5 (20)
Longest diameter of target lesion, mm Median Range	 50 32-71
Tumour volume, cc Median Range	 28.9 7.9-52.5
Cancer Antigen 19-9 (CA 19-9), (U/mL) Median Range	 161 1-6576

Safety and Tolerability

A total of 377 AEs were reported by Week 16 of which 55 were ≥ Grade 3 in severity and 25 were reported as SAEs. All SAEs were considered to be causally related to the chemotherapy, underlying disease or comorbidities and not to the device or to the implant procedure. Table 2 lists the most commonly reported AEs. The majority of the AEs of ≥ Grade 3 were AEs of the gastrointestinal and blood System Organ Class (SOC). Twenty nine (29) AEs were considered as possibly or probably related to the device or to the implant procedure, 25 of which also had a possible or probable relationship to the chemotherapy. Table 3 lists the most commonly reported AEs which were considered as possibly or probably related to the device or to the implant procedure. The observed incidence and severity of adverse events compared favourably to that observed in other studies with chemotherapy alone in this patient population.

Table 2. Most commonly reported AEs (N=25)

Adverse Event	Patients, n (%)	Number of AEs	Number of AEs ≥ Grade 3
Total	25 (100)	377	55
Neutropenia	10 (40)	16	10
Thrombocytopenia	5 (20)	11	1
Abdominal pain	10 (40)	12	0
Constipation	10 (40)	12	2
Diarrhoea	11 (44)	19	2
Nausea	12 (48)	22	1
Vomiting	7 (28)	11	3
Fatigue	17 (68)	34	3
Cellulitis	3 (12)	10	1
Decreased appetite	8 (32)	13	0

Table 3. Most commonly reported AEs considered as possibly or probably related to the device or to the implant procedure (N=25)

Adverse Event	Patients, N (%)	Number of AEs
Fatigue/Intermittent fatigue	5 (20)	7
Nausea	3 (12)	7
Indigestion/Reflux	2 (8)	2
Weight loss	2 (8)	2

Efficacy

Radiological response

Table 4 reports the Local Disease Control Rate (LDCR) at Week 8 and Week 16 and Best Response by Week 16 as assessed by central reader review per RECIST 1.1 for 25 patients.

- At Week 8, LDCR was 100%
- At Week 16, LDCR was 84%
- Response Rate (either CR or PR) by Week 16 was 20%

Table 4. Local Disease Control Rate and Best Response Rate, n (%) (N=25)

Week 8 PR SD LDCR at Week 8	 3 22 25 (100%)
Week 16 PR SD PD LDCR at Week 16	 4 17 4 21 (84%)
Best Response by Week 16 per RECIST 1.1 CR PR Overall Response Rate	 0 5 20%

Table 5 reports the LDCR at Week 24 and Best Response by Week 24 for 20 patients.

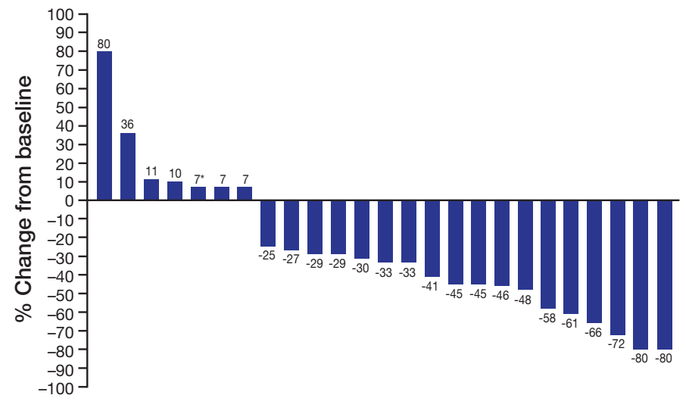
- At Week 24, LDCR was 65%
- Response Rate (either CR or PR) by Week 24 was 25%

Table 5. Local Disease Control Rate and Best Response Rate at Week 24, n (%) (N=20)

PR SD LDCR at Week 24	3 10 13 (65%)
Best Response by Week 24 per RECIST 1.1 CR PR Overall Response Rate	 0 5 25%

Tumour Volume by CT scan assessments reported a median change in tumour volume from Baseline to Week 16 of -33% (range +80% to -80%). Figure 2 shows the volumetric change per patient from Baseline to Week 16.

Figure 2. Percentage change in tumour volume from Baseline to Week 16 (N=25)



*Week 8 assessment

PET scan assessment

PET scans were reported on by a central reader.

20 of 25 patients had evaluable PET scan assessments at Baseline and at Week 12.

Total Lesion Glycolysis (TLG) as measured by PET scan showed a median reduction from Baseline to Week 12 of 56.5% (range +45% to -100%).

Metabolic resolution and absence of defined viable neoplastic disease was reported for three patients at the Week 12 PET scan assessment.

CA 19-9 tumour marker

CA 19-9 serial analysis was carried out. Table 6 outlines the percentage change in CA 19-9 from Baseline to Week 16 for 22* evaluable patients who had assessments at both of these timepoints. Clinically significant reductions were noted for the majority of the patients which were in excess of 80% for thirteen patients.

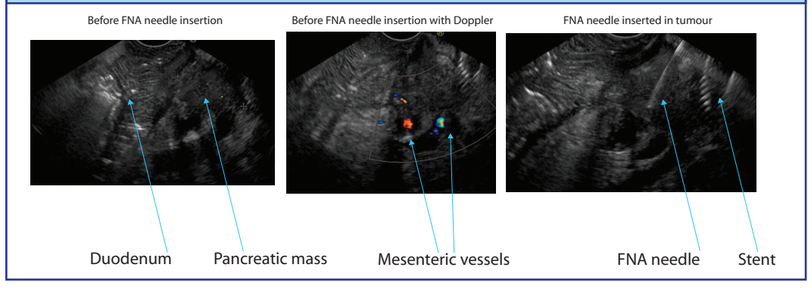
Table 6: Percentage change in CA 19-9 from baseline to Week 16

Cancer Antigen 19-9 (N=22*/25)	Median reduction (%)	87
	Maximum reduction (%)	99.8
	Range of change (%)	+134 to -99.8

OncoSil™ Implantation and Intra-tumoural Localisation

Implantation experience has been satisfactory with the device considered relatively straightforward to implant by operators. No significant or serious procedural complications were reported. Figure 3 shows EUS views of an implantation procedure where tumour access is difficult due to proximity to the duodenum, mesenteric vessels and the bile duct with metallic biliary stent in-situ. This case demonstrates the utility of EUS in accessing tumours even in a difficult location where access is a challenge.

Figure 3.



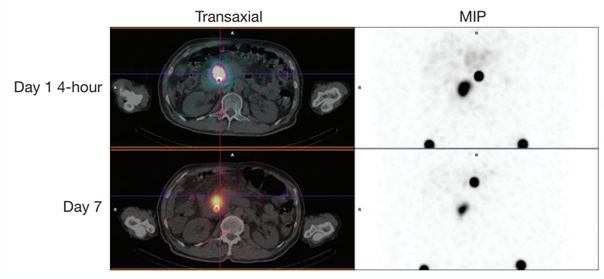
Device localisation as demonstrated by SPECT-CT Bremsstrahlung imaging was acceptable. Table 7 captures this assessment as reported on by the site. Figure 4 is an example of the imaging technique at the two timepoints of assessment.

Table 7. Device performance according to SPECT-CT Bremstrahlung imaging reports (N=25)

	4-Hour Observation Period Post-Implantation	7 Days Post-Implantation
Radiation Localised to the Implant Site	23	22
Radiation Uptake in the Gastrointestinal Tract	11	4
No Radiation Detected	0	1*

*Patient with no detectable radioactivity at Day 7 was reported as having detectable localisation of radioactivity at implantation site at Day 1

Figure 4.



Images show excellent intra-tumoural retention of activity within the pancreatic head at 2 hours post-implantation and at 7 days post-implantation.

MIP = Maximum Intensity Projection

Conclusions

Preliminary findings from the first 25 implanted patients in the PanCO study indicate that:

- The OncoSil™ device has an acceptable safety profile
- Anti-tumour efficacy demonstrated in combination with chemotherapy in LAPC
  - Local disease control rate at 16 Weeks was 84%
  - Partial Response Rate by Week 16 of 20%
- Implantation experience was satisfactory and considered relatively straightforward
- No significant safety concerns or toxicities associated with the device or with the procedure
- Feasibility and tolerability of EUS-guided implantation of Oncosil™ demonstrated
- Utility of SPECT-CT Bremsstrahlung imaging in confirming the satisfactory localisation of the implanted device demonstrated
- The clinical trial is ongoing and additional safety and efficacy data will be presented

References

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Disclosures

M Harris, D Croagh, M Aghmesheh, A Nagrial, N Nguyen, H Wasan, T Ajithkumar & P Ross are participating investigators in the study.
T Maher & A Kraszewski are employees of Oncosil Medical Ltd.

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