Naïve Indirect Treatment Comparison of PanCO, a Pilot Study of OncoSil P-32 Microparticles Combined with Gemcitabine + Nab-Paclitaxelor FOLFIRINOX Chemotherapy, Versus Standard-of-Care Treatment in Unresectable Locally Advanced Pancreatic Cancer

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Background

- Pancreatic cancer is a malignancy with a very poor prognosis and remains an area of high unmet medical need.
- Current standard treatment for patients with unresectable locally advanced pancreatic cancer (LAPC) is limited to chemotherapy (CT-only) or chemoradiotherapy following induction CT (ICT + CCRT).
- International guidelines (e.g. ESMO, ASCO and NCCN) recommend gemcitabine-based regimens or monotherapy as well as regimens containing fluoropyrimidines (capecitabine, 5FU) plus other agents, or ICT + CCRT, for the treatment of unresectable LAPC.[1–3]
- Brachytherapy using beta-emitting phosphorus (P-32) microparticles enables a predetermined radiation dose to be implanted into pancreatic tumours via endoscopic ultrasound (EUS) guidance.
- The results of a prospective, international, multi-centre, interventional, open-label, single-arm pilot study of P-32 microparticles (OncoSil™; OncoSil Medical) in combination with gemcitabine + nab-paclitaxel or FOLFIRINOX chemotherapy demonstrated encouraging safety and efficacy in patients with unresectable LAPC (the PanCO study: NCT03003078).[4]

Objective

- In the absence of a head-to-head randomised controlled trial, a naïve indirect treatment comparison (a universally accepted method to provide a valid categorical and statistical comparison of reported outcomes) was used to assess the results of the PanCO study against 'state-of-the-art' (SOTA) therapy obtained from a systematic literature review (SLR) of published scientific literature from prospective Phase II and III clinical studies.
- This enabled a robust determination as to whether the improvements observed in the PanCO study were due to CT alone or the combination of CT with OncoSil™.

Methods

- A SLR was conducted, based on a previous systematic review and meta-analysis by Chang et al (2018),[5] to identify published clinical data on SOTA/'standard-ofcare' treatments from prospective Phase II and III clinical studies in patients with unresectable LAPC treated with CT-only or ICT + CCRT (excluding borderline resectable LAPC; for inclusion criteria, see Table 1).
- A weighted median of medians method and meta-analysis of proportional outcomes were used to provide summary statistics for SLR outcomes.[6]
- Meta-analysis was performed in the statistical software R and R studio using the R Functions meta,7 metaprop8 and metamedian.[9]
- The SLR outcomes were then compared with the results of the PanCO study in a naïve indirect treatment comparison.
- A binomial test was applied to assess the strength of the PanCO results relative to the SOTA CT-only and ICT + CCRT (comparator) studies of the meta-analysis for overall survival (OS), progression-free survival (PFS), one-year survival, resection rate, disease control rate (DCR) and overall response rate (ORR).

Table 1: Inclusion Criteria for Systematic Literature Search

	Title/Abstract Screening	Full Text Screening
Population	Includes LAPC	Patients with unresectable, non-metastatic LAPC If other populations are included, outcomes are reported separately
Intervention	Any CT or CCRT Trials that include immunotherapy or other biological agents excluded if no chemotherapy control arm	Any CT or ICT and CCRT Trials that include immunotherapy or other biological agents excluded (chemotherapy control arm may be included)
Outcomes		Median OS Median PFS (and LPFS, where available) One-year survival rate DCR (and LDCR where available) ORR Resection rate
Other limits	Phase II or Phase III studies only	Phase II or Phase III studies only

Abbreviations: CCRT, consolidation chemoradiotherapy; CT, chemotherapy; DCR, disease control rate; ICT, induction chemotherapy; ITT, intention-to-treat (enrolled participants); LAPC, locally advanced pancreatic cancer; LDCR, local DCR; LPFS, local PFS; PFS, progression-free survival; ORR, overall response rate; OS, overall survival.

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Results

- The SLR identified clinical outcomes including OS, PFS, one-year survival, resection rate, DCR and ORR. No studies reported LPFS or LDCR.
- In total, there were 46 included studies, comprising 58 study arms and 4,342 patients, 2,398 of whom had unresectable LAPC (see Figure 1 and Table 2).[10–55]

Figure 1: PRISMA Flowchart

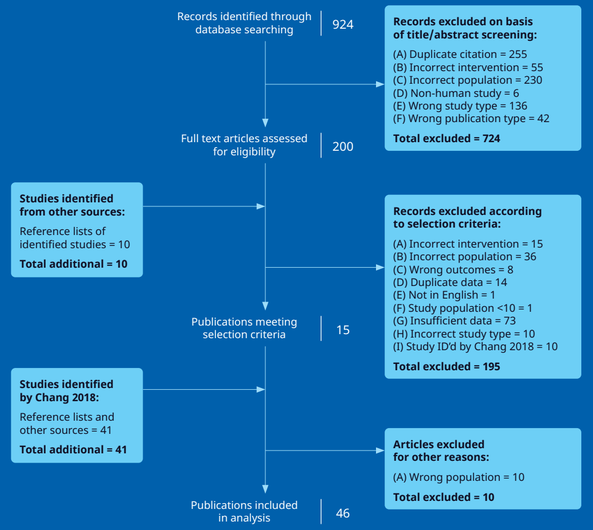

Table 2. Summary of SLR Study Numbers[10–55]

SLR Cohort	Number of Study Arms	Number of Patients	Gem-Based CT (CT or ICT)		FP-Based CT (CT or ICT)		Gem-Based CCRT		FP-Based CCRT	
			Arms	Pts	Arms	Pts	Arms	Pts	Arms	Pts
All Treatments (CT-only and ICT + CCRT)	58	2,398	46	2,034	22	694	7	199	11	371
CT-Only	38	1,690	29	1,418	15	406	–	–	–	–
CCRT-Only	20	708	17	616	7	288	7	199	11	371

Abbreviations: CCRT, consolidation chemoradiotherapy; CT, chemotherapy; ICT, induction CT; FP, fluoropyrimidine (e.g. Fluorouracil [5FU], capecitabine, S-1); Gem, gemcitabine; na, not applicable; Pts, Patients.

- The PanCO study enrolled 50 patients (Intention-to-Treat [ITT] population) of which 42 were implanted with P-32 microparticles (Per Protocol [PP] population), with a median follow-up of 16.1 months.[4]

Overall Survival

- Median OS was significantly longer (p<0.001) in the PanCO study ITT and PP cohorts than CT-only and ICT + CCRT regimens (Tables 3 and 4), representing a ~20% reduction in the risk of death compared to CT-only and ICT + CCRT studies (Hazard Ratio PP: 0.79; ITT: 0.82). The PanCO median OS for ITT and PP cohorts were also significantly longer than the CT-only (p<0.001) and ICT + CCRT subgroups (p=0.0001 or <0.0001).
- One-year survival rates in PanCO were significantly higher than SOTA (p<0.001 for CT-only and ICT + CCRT; see Tables 3 and 4).
- Sensitivity analyses were performed to determine the impact of patient selection and choice of therapy on the median OS. These involved:
  - Substitution of SCALOP1 data in Hurt 2017[10] with defined ITT data in Mukherjee 2013.[56]
  - Substitution of first randomisation LAP07 data with second randomisation LAP07 data from Hammel 2016.[11]
  - Removal of treatment arms containing S-1.
  - Removal of all S-1 studies.
  - Note: base case includes first randomisation LAP07 data from Hammel 2016,[11] SCALOP1 cohort data from Hurt 2017[10] and all S-1 treatment arms.
- This demonstrated that the meta-analyses of the median OS did not differ significantly for all 'state-of-the-art' CT and ICT + CCRT regimens (median OS range: 12.6–13.0 months vs. 12.7 months for the base case) and the subgroups (median OS range for CT-only arms: 12.3–13.0 months *vs.* 12.7 months for the base case; median OS range for ICT + CCRT arms: 12.6–13.4 months vs. 12.6 months for the base case) irrespective of the inclusion of studies and treatment arms that are subject to patient selection bias and confounders.

Table 3: Survival Outcomes for PanCO vs. Meta-Analyses of 'SOTA' Regimens

Cohort	N	Median OS (95% CI)	One-Year Survival (95% CI)
PanCO ITT	50	15.5 months (11.3, nc)	63.4% (47.8%, 75.4%)
PanCO PP	42	16.0 months (11.1, nc)	64.0% (47.5%, 76.5%)
SLR: CT-only and ICT + CCRT	2,350 (54 arms) [OS]	12.7 months (12.2, 13.6)	52.5% (48.7%, 56.3%)
SLR: CT-Only	1,642 (34 arms) [OS]	12.7 months (11.9, 13.6)	50.4% (45.3%, 55.5%)
SLR: ICT + 708 CCRT only	(20 arms) [OS]	12.6 months (12.2, 14.0)	55.2% (49.4%, 60.9%)

Abbreviations: CCRT, consolidation chemoradiotherapy; CI, confidence interval; CT, chemotherapy; ICT, induction chemotherapy; ITT, intention-to-treat (enrolled participants); nc, non-calculable; OS, overall survival; PP, per protocol (enrolled/implanted participants); SLR, study arms identified by Systematic Literature Review.

Table 4: PanCO OS Outcomes vs. 'SOTA' Regimens

Parameter	Naïve Indirect Treatment Comparator	PanCO Cohort	PanCO Outcome	N Comparator Trials	n ≥ PanCO	*p*-value
mOS	CT-only and ICT + CCRT	ITT	15.5 months	54	10	<0.001
		PP	16.0 months	54	6	<0.001
	CT-Only	ITT	15.5 months	34	7	<0.001
		PP	16.0 months	34	4	<0.001
	ICT + CCRT	ITT	15.5 months	20	3	0.001
		PP	16.0 months	20	2	<0.001
One-Year Survival	CT-only and ICT + CCRT	ITT	63.4%	40	8	<0.001
		PP	64.0%	40	7	<0.001
	CT-Only	ITT	63.4%	21	6	0.039
		PP	64.0%	21	5	0.013
	ICT + CCRT	ITT	63.4%	19	2	<0.001
		PP	64.0%	19	2	<0.001

Abbreviations: CCRT, consolidation chemoradiotherapy; CT, chemotherapy; ICT, induction chemotherapy; ITT, intention-to-treat (enrolled participants); n ≥ PanCO, number of comparator trials where the result is the same as or greater than the PanCO study outcome; PP, per protocol (enrolled/implanted participants).

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Surgical Resection

- The rate of surgical resection in PanCO was significantly greater than SOTA (p<0.001; Tables 5 and 6).

Table 5: Resection Rate Outcomes for PanCO vs. Meta-Analyses of 'SOTA' Regimens

Cohort	N	Resection Rate (95% CI)
PanCO ITT	50	20.0% (10.0%, 33.7%)
PanCO PP	42	23.8% (12.1%, 39.5%)
SLR: CT-only and ICT + CCRT	391 (16 arms)	9.9% (6.7%, 13.5%)
SLR: CT-Only	149 (7 arms)	7.7% (3.1%, 13.5%)
SLR: ICT + CCRT only	242 (9 arms)	11.5% (7.4%, 16.2%)

Abbreviations: CCRT, consolidation chemoradiotherapy; C.I., confidence interval; CT, chemotherapy; ICT, induction chemotherapy; ITT, intention-to-treat (enrolled participants); PP, per protocol (enrolled/implanted participants); SLR, study arms identified by Systematic Literature Review.

Table 6: PanCO Resection Rate Outcomes vs. 'SOTA' Regimens

Parameter	Naïve Indirect Treatment Comparator	PanCO Cohort	PanCO Outcome	N Comparator Trials	n ≥ PanCO	*p*-value
Resection Rate	CT-only and ICT + CCRT	ITT	20.0%	16	1	<0.001
		PP	23.8%	16	0	<0.001
	CT-Only	ITT	20.0%	7	1	0.063
		PP	23.8%	7	0	0.008
	ICT + CCRT	ITT	20.0%	9	0	0.002
		PP	23.8%	9	0	0.002

Abbreviations: CCRT, consolidation chemoradiotherapy; CT, chemotherapy; ICT, induction chemotherapy; ITT, intention-to-treat (enrolled participants); n ≥ PanCO, number of comparator trials where the result is the same as or greater than the PanCO study outcome; PP, per protocol (enrolled/implanted participants).

Progression-Free Survival

- Median PFS was significantly longer (p<0.001) than the combined CT-only and ICT + CCRT or CT-only regimens (Tables 7 and 8).

Table 7: PFS Outcomes for PanCO vs. Meta-Analyses of 'SOTA' Regimens

Cohort	N	Median PFS (95% CI)
PanCO ITT	50	9.3 months (5.9, 12.2)
PanCO PP	42	9.3 months (7.2, 12.2)
SLR: CT-only and ICT + CCRT	1,936 (43 arms)	7.6 months (6.6, 7.8)
SLR: CT-Only	1,355 (27 arms)	6.6 months (6.2, 7.8)
SLR: ICT + CCRT only	581 (16 arms)	9.1 months (7.6, 9.3)

Abbreviations: CCRT, consolidation chemoradiotherapy; C.I., confidence interval; CT, chemotherapy; ICT, induction chemotherapy; ITT, intention-to-treat (enrolled participants); PP, per protocol (enrolled/implanted participants); SLR, study arms identified by Systematic Literature Review.

Table 8: PanCO PFS Outcomes vs. 'SOTA' Regimens

Parameter	Naïve Indirect Treatment Comparator	PanCO Cohort	PanCO mPFS Outcome	N Comparator Trials	n ≥ PanCO	*p*-value
mPFS	CT-only and ICT + CCRT	ITT	9.3 months	43	11	<0.001
		PP	9.3 months	43	11	<0.001
	CT-Only	ITT	9.3 months	27	5	<0.001
		PP	9.3 months	27	7	0.010
	ICT + CCRT	ITT	9.3 months	16	6	0.227
		PP	9.3 months	16	6	0.227

Abbreviations: CCRT, consolidation chemoradiotherapy; CT, chemotherapy; ICT, induction chemotherapy; ITT, intention-to-treat (enrolled participants); mPFS, median progression-free survival; n ≥ PanCO, number of comparator trials where the result is the same as or greater than the PanCO study outcome; PP, per protocol (enrolled/implanted participants).

Disease Control and Overall Response Rates

- DCR and ORR were significantly higher than the combined CT-only and ICT + CCRT or CT-only regimens (Tables 9 and 10).

Table 9: DCR and ORR Outcomes for PanCO vs. Meta-Analyses of 'SOTA' Regimens

Cohort	N (DCR/ORR)	DCR (95% CI)	ORR (95% CI)
PanCO ITT	47/47	95.7% (85.5%, 99.5%)	29.8% (17.3%, 44.9%)
PanCO PP	42/42	100.0% (91.6%, 100.0%)	31.0% (17.6%, 47.1%)
SLR: CT-only and ICT + CCRT	751 (19 arms)/ 962 (26 arms)	70.1% (72.9%, 86.4%)	18.2% (13.3%, 23.7%)
SLR: CT-Only	440 (10 arms)/ 640 (16 arms)	71.3% (61.4%, 80.3%)	14.7% (9.0%, 21.3%)
SLR: ICT + CCRT only	311 (9 arms)/ 322 (10 arms)	88.5% (80.4%, 94.9%)	24.2% (15.8%, 33.7%)

Abbreviations: C.I., confidence interval; ITT, intention-to-treat (enrolled participants); DCR, disease control rate (stable disease, partial response or complete response by RECIST v1.1 for best response on imaging); ORR, overall response rate; PP, per protocol (enrolled/implanted participants); SLR, study arms identified by Systematic Literature Review.

Table 10: PanCO Response Outcomes vs. 'SOTA' Regimens

Parameter	Naïve Indirect Treatment Comparator	PanCO Cohort	PanCO Outcome	N Comparator Trials	n ≥ PanCO	*p*-value
DCR	CT-only and ICT + CCRT	ITT	95.7%	19	3	0.002
		PP	100.0%	19	2	<0.001
	CT-Only	ITT	95.7%	10	0	<0.001
		PP	100.0%	10	0	<0.001
	ICT + CCRT	ITT	95.7%	9	3	0.254
		PP	100.0%	9	2	0.090
ORR	CT-only and ICT + CCRT	ITT	29.8%	26	6	0.005
		PP	31.0%	26	6	0.005
	CT-Only	ITT	29.8%	16	2	0.002
		PP	31.0%	16	2	0.002
	ICT + CCRT	ITT	29.8%	10	4	0.377
		PP	31.0%	10	4	0.377

Abbreviations: CCRT, consolidation chemoradiotherapy; CT, chemotherapy; DCR, disease control rate; ICT, induction chemotherapy; ITT, intention-to-treat (enrolled participants); n ≥ PanCO, number of comparator trials where the result is the same as or greater than the PanCO study outcome; ORR, overall response rate; PP, per protocol (enrolled/implanted participants).

Conclusions

- The results from the PanCO study provide a broad and consistently positive outcomes compared to standard-of-care CT-only and ICT + CCRT regimens.
- The naïve indirect treatment comparison to state-of-the-art therapy indicated that P-32 microparticles combined with standard-of-care chemotherapy may provide significant and clinically relevant benefits for patients with unresectable LAPC and a valuable treatment option in an area of high unmet medical need.

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