NHS England

Clinical Priorities Advisory Group Summary Report

Agenda item	3.8
Date of Meeting	11/05/26-13/05/26
Title of the Proposition	Gemcitabine and paclitaxel albumin combination chemotherapy for the treatment of locally advanced non-metastatic pancreatic cancer (adults)
Unique Reference Number	2423
Programme of Care	Cancer
Clinical Reference Group	Chemotherapy
Service/treatment status	delegated

Action requested

Support the adoption of the policy proposition

Recommended its relative prioritisation.

Summary of the proposition:

Gemcitabine and paclitaxel albumin combination chemotherapy is recommended to be available as a routine commissioning treatment option for locally advanced non-metastatic pancreatic cancer within the criteria set out in the policy proposition document.

The policy proposition is restricted to adults (age ≥18 years) only as there is insufficient evidence to confirm safety for children (age <18 years). The pancreas is an organ in the abdomen that produces digestive enzymes, which help digest food and hormones, notably insulin which helps the body process sugar (glucose). Pancreatic cancer is the 10th most common cancer in the UK and is more common in older populations with 47% of new cases being diagnosed in people aged 75 years and over (Cancer Research UK, n.d.). Other risk factors include deprivation, ethnicity (more common in Black patients compared to White patients), smoking and obesity (Cancer Research UK, 2023).

Pancreatic cancer has a poor prognosis, with one- and five-year survival being only 21% and 3.3% respectively. This is lower than the European and American average survival rates (Cancer Research UK, n.d; National Cancer Institute, 2024).

Pancreatic adenocarcinoma is the most common type of pancreatic cancer, and this arises from the cells that produce digestive enzymes (exocrine glands) (Rawla et al, 2019).

Symptoms of pancreatic cancer include yellowing of the skin (jaundice), weight loss and abdominal pain. The onset of these is usually gradual and subtle as symptoms only become evident once the tumour is of significant size. As a result, patients usually present as an emergency or at an advanced state.

At presentation, 30-40% of pancreatic adenocarcinomas are locally advanced, inoperable and non-metastatic (Conroy et al, 2023). This is collectively referred to as locally, advanced non-metastatic pancreatic cancer (LANPC). These cancers spread in and around the pancreas, and may obstruct local vital structures, such as blood vessels.

Clinical Panel recommendation:

The Clinical Panel recommended that the policy proposition progress as a routine commissioning policy.

Assurances

The committee is asked to receive the following assurance:		
1.	The Deputy Director of Clinical Effectiveness confirms the proposition has completed the appropriate sequence of developmental and governance steps.	
2.	The Deputy Director of Cancer Programme confirms the proposition is supported by the following documentation (please tick the box where applicable)	
	Draft Clinical Commissioning policy proposition	☒
	Three Paper Evidence Summary	☒
	Public Health Evidence Report	☐
	Evidence to Decision Making (EtD) Summary	☐

	Equalities and Heath Inequalities Assessment (EHIA)	☒
	Prior Approval Form	☒
	Engagement Report	☒
	13Q Assessment and Patient & Public Voice Assurance	☒
	Clinical Panel Report	☒
	Policy Working Group membership	☒
	Other (please state if required)	☐
3.	The Deputy Director of Finance (Specialised Commissioning) confirms that the Impact Assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.	
4.	The Director of Clinical Commissioning (Specialised Commissioning) confirms that the Service and Operational Impact Assessments have been completed.	
5.	The Deputy Director of Quality and Nursing (Specialised Commissioning) confirms that the proposed quality indicators have been adequately defined (where applicable).	

Evidence Review Summary

Three papers included in the summary

Paper 1:
Philip, P.A., Portales, F., Sobrero, A., Pazo-Cid, R., Manzano Mozo, J.L., Kim, E.J., et al. 2020. Nab-paclitaxel plus gemcitabine in patients with locally advanced pancreatic cancer (LAPACT): a multicentre, open-label phase 2 study. The Lancet Gastroenterology & Hepatology, 5(3), pp. 285–294.

- A prospective, single arm, open-label study of 107 adults with previously untreated unresectable, locally advanced, non-metastatic pancreatic cancer treated with induction nab-paclitaxel plus gemcitabine, followed by treatment according to investigator's choice (continued nab-paclitaxel plus gemcitabine, chemoradiation, or surgery). The median follow-up for overall survival was 25.4 months (95% CI 22.4 to 27.2).

Paper 2:
Kunzmann, V., Siveke, J.T., Algül, H., Goekkurt, E., Siegler, G., Marterns, U., et al. 2021. Nab-paclitaxel plus gemcitabine versus nab-paclitaxel plus gemcitabine followed by FOLFIRINOX induction chemotherapy in locally advanced pancreatic cancer (NEOLAP-AIO-PAK-0113): a multicentre, randomised, phase 2 trial. The Lancet Gastroenterology & Hepatology, 6(2), pp. 128–138.

- A randomised controlled trial (RCT) of 165 adults with untreated, locally advanced, non-metastatic pancreatic adenocarcinoma. Patients received induction nab-paclitaxel plus gemcitabine, and were then randomised to receive either two additional cycles of nab-paclitaxel plus gemcitabine or four cycles of sequential fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX). Median follow-up duration of 24.9 months (95% CI 21.8 to 27.6).

Paper 3:

Ozaka, M., Nakachi, K., Kobayashi, S., Ohba, A., Imaoka H., Terashima, T., et al. 2023. A randomised phase II study of modified FOLFIRINOX versus gemcitabine plus nab-paclitaxel for locally advanced pancreatic cancer (JCOG1407). European Journal of Cancer, 181, pp. 135–144. • RCT of 126 adults with untreated, locally advanced, non-metastatic pancreatic cancer who received gemcitabine plus nab-paclitaxel or modified 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (mFOLFIRINOX). Median follow-up duration of 22.2 months (IQR 14.1 to 29.9).	
Outcome	**Evidence statement**
Clinical effectiveness	
Time to treatment failure **Certainty of evidence:** Not assessed for 3 paper summaries	Time to treatment failure was reported in one of the three papers included in the summary. Philip et al (2020; LAPACT) reported that the median time to treatment failure[1] was 9.0 months (90% CI 7.3 to 10.1) in patients with locally advanced, non-metastatic pancreatic cancer who started induction treatment with nab-paclitaxel plus gemcitabine (n=107). The authors reported that this exceeded the protocol-specified target of 6.6 months. **One of the included papers (n=107) reported a median time to treatment failure of 9.0 months in patients with locally advanced, non-metastatic pancreatic cancer who were treated with nab-paclitaxel plus gemcitabine. The authors reported that this exceeded the protocol-specified target of 6.6 months.**
Surgical conversion rate **Certainty of evidence:** Not assessed for 3 paper summaries	Surgical conversion rate was reported in all three papers included in the summary. Philip et al (2020; LAPACT) reported the rate of surgical resection on an ITT basis after induction treatment with nab-paclitaxel plus gemcitabine in patients with locally advanced, non-metastatic pancreatic cancer (n=107). Post-hoc analysis indicated that 20 (18.7%) patients were considered suitable for surgery before completion of induction treatment, while 17 (16%) patients actually underwent surgery after completion of induction treatment: one patient was unresectable at the point of surgery and 16 patients completed surgery (seven had R0 and nine had R1[2]). During the survival follow-up period, an additional 11 patients underwent surgery with the aim of resection (five of whom had received follow-on treatment with chemoradiation before surgery). Kunzmann et al (2021; NEOLAP-AIO-PAK-0113) reported surgical conversion rates (i.e. complete macroscopic resection rate) which was assessable for 82 (63%) patients with locally advanced, non-metastatic pancreatic cancer. The authors reported that of the 165 patients who received induction treatment (two 28-day cycles of nab-paclitaxel plus gemcitabine), 52 (32% [95% CI 24·5 to 39·2]) had complete surgical

[1] Treatment failure was defined as discontinuation of study treatment because of disease progression (assessed by the investigator), death by any cause, or the start of a non-protocol defined anticancer treatment. Patients who did not fail treatment were censored on the last date of tumour assessment.
[2] Resection status was graded according to institutional guidelines, but no further details were provided.

macroscopic resection: 23 patients in the nab-paclitaxel plus gemcitabine group and 29 in the sequential FOLFIRINOX group. Of the 130 patients randomised to follow-on treatment, the conversion rate was 35·9% (95% CI 24·3 to 48·9) in the nab-paclitaxel plus gemcitabine group compared with 43·9% (95% CI 31·7 to 56·7) in the sequential FOLFIRINOX group. The difference between treatment groups was not statistically significant: odds ratio (OR) 0.72, 95% CI 0.35 to 1.45; p=0.38. The authors reported similar non-significant results for subgroup analyses (including age, ECOG performance status, baseline neutrophil to lymphocyte ratio, baseline CA 19-9 U/mL, and baseline tumour size). Histological assessment of resection specimens in patients who had complete surgical macroscopic resection (n=52) indicated no statistically significant difference between treatment groups in terms of R0 resection rate, but statistically significantly fewer patients in the nab-paclitaxel plus gemcitabine group had a lower tumour stage (ypT1 or 2) and no pathological lymph nodes compared to patients in the sequential FOLFIRINOX group (see Table 1).

Table 1: Histological assessment of resection specimens in patients who had complete surgical macroscopic resection after treatment with nab-paclitaxel plus gemcitabine or sequential FOLFIRINOX reported by Kunzmann et al 2021

	Nab-paclitaxel plus gemcitabine (n=23)	**Sequential FOLFIRINOX (n=29)**	**p-value**
Resection margin, n (%)			
R0 R1 *Missing data (%)*	15 (65.2) 5 (21.7) 3 (13.0)	20 (69.0) 8 (27.6) 1 (3.4)	0.99
Tumour stage, n (%)			
ypT1 or ypT2 ypT3 or ypT4 *Missing data (%)*	4 (17.4) 18 (78.3) 1 (4.3)	20 (69.0) 9 (31.0) -	0.0003
Nodal stage, n (%)			
ypN0 ypN1 *Missing data (%)*	4 (17.4) 15 (65.2) 4 (17.3)	15 (51.7) 13 (44.8) 1 (3.4)	0.02

Osaka et al (2023; JCOG1407) reported that five patients with locally advanced, non-metastatic pancreatic cancer in each treatment group, who responded positively to chemotherapy, underwent conversion to surgery (7.8% in the gemcitabine plus nab-paclitaxel group [n=63] versus 8.1% in the mFOLFIRINOX group [n=62]).

One of the included papers (n=107) reported that, following induction treatment with nab-paclitaxel plus gemcitabine, 17 (16%) patients with locally advanced, non-metastatic pancreatic cancer underwent surgical resection. A second included paper (n=82 assessable patients) reported no statistically significant difference in complete macroscopic resection rates between patients treated with additional nab-paclitaxel plus gemcitabine (35.9%) compared to patients treated with sequential FOLFIRINOX (43.9%) following two 28-day cycles of

	nab-paclitaxel plus gemcitabine. However, of the patients who had complete surgical macroscopic resection, a statistically significantly lower proportion of patients treated with additional nab-paclitaxel plus gemcitabine compared to patients treated with sequential FOLFORINOX had tumours of ypT1 or ypT2 tumour stage and of ypN0 nodal stage at resection. The third included paper (n=125) reported that a similar proportion of patients with locally advanced, non-metastatic pancreatic cancer underwent conversion to surgery in the gemcitabine plus nab-paclitaxel group (7.8%) and mFOLFIRINOX group (8.1%).
Progression-free survival **Certainty of evidence:** Not assessed for 3 paper summaries	Progression-free survival was reported in all three papers included in the summary. Philip et al (2020; LAPACT) reported that median progression-free survival was 10.9 months (90% CI 9.3 to 11.6) in patients with locally advanced, non-metastatic pancreatic cancer who started induction treatment with nab-paclitaxel plus gemcitabine (n=107). Kunzmann et al (2021; NEOLAP-AIO-PAK-0113) reported that there was no statistically significant difference in median progression-free survival (hazard ratio [HR] 0.75, 95% CI 0.49 to 1.14; p=0.18) between patients with locally advanced, non-metastatic pancreatic cancer who were treated with additional nab-paclitaxel plus gemcitabine (7.7 months, 95% CI 6.2 to 9.7; n=64) compared to patients treated with sequential FOLFIRINOX (9.5 months, 7.0 to 11.7; n=66) following two 28-day cycles of nab-paclitaxel plus gemcitabine. Osaka et al (2023; JCOG1407) found no statistically significant difference in median progression-free survival between patients with locally advanced, non-metastatic pancreatic cancer who received gemcitabine plus nab-paclitaxel (9.4 months, 95% CI 7.4 to 12.8; n=63) compared to patients treated with mFOLFIRINOX (11.2 months, 95% CI 9.9 to 15.9; n=62); the HR for mFOLFIRINOX compared to gemcitabine plus nab-paclitaxel was 1.36 (95% CI 0.94 to 1.97; p-value not reported). The proportion of patients with 1-year progression-free survival was 40.4% (95% CI 28.2 to 52.2) in the gemcitabine plus nab-paclitaxel group and 48.4% (95% CI 35.5 to 60.1) in the mFOLFIRINOX group; statistical measures were not reported. **One of the included papers (n=107) reported median progression-free survival of 10.9 months in patients with locally advanced, non-metastatic pancreatic cancer who started induction treatment with nab-paclitaxel plus gemcitabine. A second included paper (n=130) reported that there was no statistically significant difference in median progression-free survival between patients with locally advanced, non-metastatic pancreatic cancer treated with additional nab-paclitaxel plus gemcitabine compared to patients treated with sequential FOLFIRINOX, following two 28-day cycles of nab-paclitaxel plus gemcitabine. The third included paper (n=125) found no statistically significant difference in median progression-free survival between patients with locally advanced, non-metastatic pancreatic cancer who**

	received gemcitabine plus nab-paclitaxel compared to patients treated with mFOLFIRINOX.
Overall survival **Certainty of evidence:** Not assessed for 3 paper summaries	Overall survival was reported in all three papers included in the summary. Philip et al (2020; LAPACT) reported that at a median follow-up of 25.4 months (95% CI 22.4 to 27.2), median overall survival was 18.8 months (90% CI 15.0 to 24.0) in patients with locally advanced, non-metastatic pancreatic cancer who started induction treatment with nab-paclitaxel plus gemcitabine (n=107). Kunzmann et al (2021; NEOLAP-AIO-PAK-0113) reported that the median follow-up for survival analysis was 24.9 months (95% CI 21.8 to 27.6). There was no statistically significant difference in median overall survival (HR 0.86, 95% CI 0.55 to 1.36; p=0.53) between patients with locally advanced, non-metastatic pancreatic cancer who were treated with nab-paclitaxel plus gemcitabine (18.5 months, 95% CI 14.4 to 21.5; n=64) compared to patients treated with sequential FOLFIRINOX (20.7 months, 13.9 to 28.7; n=66), following two 28-day cycles of nab-paclitaxel plus gemcitabine. Osaka et al (2023; JCOG1407) reported that for patients with locally advanced, non-metastatic pancreatic cancer, 47 of 63 (74.6%) patients in the gemcitabine plus nab-paclitaxel group and 44 of 62 (70.6%) patients in the mFOLFIRINOX group had died at a median 22.2 months follow-up (IQR 14.1 to 29.9). The median overall survival was 21.3 months (95% CI 18.2 to 24.1) in the gemcitabine plus nab-paclitaxel group and 23.0 months (95% CI 19.3 to 29.3) in the mFOLFIRINOX group. The proportion of patients with 1-year overall survival in the gemcitabine plus nab-paclitaxel group was 82.5% (95% CI 70.7 to 89.9) and 77.4% (95% CI 64.9 to 86.0) in the mFOLFIRINOX group; the HR for mFOLFIRINOX compared to gemcitabine plus nab-paclitaxel was 1.10 (95% CI 0.73 to 1.65); p-value not reported. The proportion of patients with 2-year overall survival was 41.3% (95% CI 29.1 to 53.0) and 46.2% (95% CI 33.4 to 58.0), respectively; no statistical measures were reported. **One of the included papers (n=107) reported a median overall survival of 18.8 months at a median follow-up of 25.4 months in patients with locally advanced, non-metastatic pancreatic cancer who started induction treatment with nab-paclitaxel plus gemcitabine. A second included paper (n=130) reported no statistically significant difference in median overall survival at a median follow-up of 24.9 months in patients with locally advanced, non-metastatic pancreatic cancer treated with additional nab-paclitaxel plus gemcitabine (18.5 months) compared to sequential FOLFIRINOX (20.7 months), following two 28-day cycles of nab-paclitaxel plus gemcitabine. The third included paper (n=125) found no statistically significant difference in median overall survival at a median follow-up of 22.2 months between patients with locally advanced, non-metastatic pancreatic cancer who received gemcitabine plus nab-paclitaxel (21.3 months) compared to patients treated with mFOLFIRINOX (23.0 months).**

<table>
<tr>
<td>Distant metastasis-free survival

Certainty of evidence:
Not assessed for 3 paper summaries</td>
<td>Distant metastasis-free survival was reported in one of the three papers included in the summary.

Osaka et al (2023; JCOG1407; n=125) found no statistically significant difference in median distant metastasis-free survival between patients with locally advanced, non-metastatic pancreatic cancer who received gemcitabine plus nab-paclitaxel group (13.3 months, 95% CI 9.3 to 16.9) compared to patients treated with mFOLFIRINOX (17.4 months, 95% CI 12.3 to 22.1); the HR for mFOLFIRINOX compared to gemcitabine plus nab-paclitaxel was 1.25 (95% CI 0.85 to 1.84); p-value not reported. The proportion of patients with 1-year distant metastasis-free survival in the gemcitabine plus nab-paclitaxel group was 58.2% (95% CI 44.9 to 69.3) and 64.5% (95% CI 51.3 to 75.0) in the mFOLFIRINOX group; statistical measures were not reported.

One of the included papers (n=125) found no statistically significant difference in median distant metastasis-free survival between patients who received mFOLFIRINOX compared to patients with locally advanced, non-metastatic pancreatic cancer treated with gemcitabine plus nab-paclitaxel group.</td>
</tr>
<tr>
<td>Best response to treatment

Certainty of evidence:
Not assessed for 3 paper summaries</td>
<td>Best response to treatment was reported in all three papers included in the summary.

Best response to treatment

Philip et al (2020; LAPACT) reported that during induction treatment with nab-paclitaxel plus gemcitabine, the overall response rate (i.e. complete or partial response) in 107 patients with locally advanced, non-metastatic pancreatic cancer was 33.6% (90% CI 26.6 to 41.5). In 36 of 107 (34%) patients, the best response to treatment was ‘partial response’. The authors reported that 83 patients achieved disease control (when using a definition of stable disease of at least 16 weeks) during induction treatment and the disease control rate was 77·6% (90% CI 70·3 to 83·5). At six months after completion of six cycles of induction therapy, the authors reported that the disease control rate[3] was 60·7% (90% CI 52·8 to 68·2), based on ITT analysis (i.e. n=107). The best response to treatment during induction and at six months after induction treatment are summarised in Table 2.

Table 2: Best response during induction treatment and at six months (after completion of six cycles of induction treatment) reported by Philip et al 2020
<table>
<tr><th></th><th>ITT population (n=107)</th></tr>
<tr><td>Best response during induction phase</td><td></td></tr>
<tr><td>Complete response</td><td>0</td></tr>
<tr><td>Partial response</td><td>36 (34%)</td></tr>
<tr><td>All stable disease
Stable disease ≥16 weeks</td><td>60 (56%)
47 (44%)</td></tr>
</table>
</td>
</tr>
</table>

[3] Disease control rate was based on best response during induction treatment (i.e. complete response, partial response, or stable disease, with stable disease required for ≥16 or ≥24 weeks, and also at six months after induction treatment, but excluding tumour assessments after non-protocol-defined anticancer therapy or surgery).

Stable disease ≥24 weeks	35 (33%)
Progressive disease	5 (5%)
Not evaluable	1 (1%)
No post-baseline evaluation	5 (5%)
Best response at 6 months	
Complete response	0
Partial response	29 (27%)
Stable disease	36 (34%)

Kunzmann et al (2021; NEOLAP-AIO-PAK-0113) reported that there were no statistically significant differences in radiographic partial response or radiographic disease control rate between patients with locally advanced, non-metastatic pancreatic cancer who were treated with nab-paclitaxel plus gemcitabine (n=64) compared to patients treated with sequential FOLFIRINOX (n=66), following two 28-day cycles of nab-paclitaxel plus gemcitabine (week 16 to 18). The response rate and disease control rate are summarised in Table 3.

Table 3: Radiographic partial response and disease control rate in patients receiving follow-on treatment after two 28-day cycles of nab-paclitaxel plus gemcitabine (week 16 to 18) reported by Kunzmann et al 2021

	Additional nab-paclitaxel plus gemcitabine (n=64)	Sequential FOLFIRINOX (n=66)	Odds ratio (95% CI)	p-value
Radiographic partial response*	14 (22%)	11 (17%)	1·40 (0·58 to 3·37)	0.51
Radiographic disease control rate*	50 (78%)	45 (68%)	1·67 (0·76 to 3·66)	0.24

* Response was determined by local investigators according to Response Evaluation Criteria in Solid tumours (version 1.1) after induction treatment was complete (week 16 to 18). Computer tomography (CT) or magnetic resonance imaging (MRI) scans were not performed or were not evaluable in 28 patients (nine patients receiving nab-paclitaxel plus gemcitabine and 19 receiving sequential FOLFIRINOX).

Osaka et al (2023; JCOG1407) reported that during a median follow-up duration of 22.2 months, the tumour response rate[4] in patients with locally advanced, non-metastatic pancreatic cancer treated with gemcitabine plus nab-paclitaxel was 42.1% (95% CI 29.1 to 55.9; n=57) and 30.9% (95% CI 19.1 to 44.8; n=55) in patients treated with mFOLFIRINOX; p-value was not reported. The disease control rate[5] was 96.5% (95% CI 87.9 to 99.6) in patients treated with gemcitabine plus nab-paclitaxel and 87.3% (95% CI 73.3 to 93.5) in patients treated with mFOLFIRINOX; no statistical comparison was reported. Best tumour responses are presented in Table 4.

[4] Tumour response was assessed using the Response Evaluation Criteria in Solid Tumours version 1.1.
[5] Disease control rate: complete response plus partial response plus stable disease.

Table 4: Best tumour response (patients with measurable disease) during median 22.2 months follow-up reported by Osaka et al 2023

	Gemcitabine plus nab-paclitaxel (n=57)	mFOLFIRINOX (n=55)
Complete response	0	1 (1.8%)
Partial response	24 (42.1)	16 (29.1%)
Stable disease	31 (54.4%)	31 (56.4%)
Progressive disease	1 (1.8%)	5 (9.1%)
Not evaluable	1 (1.8%)	2 (3.6%)
Response rate	24 (42.1%)	17 (30.9%)
Disease control rate	55 (96.5%)	48 (87.3%)

One of the included papers (n=107) reported that during induction treatment with nab-paclitaxel plus gemcitabine, 83 patients achieved disease control when using a definition of stable disease of at least 16 weeks (a disease control rate of 77·6%). At six months after completion of six cycles of induction therapy, the disease control rate was 60·7%. A second included paper (n=130) reported that there were no statistically significant differences in radiographic partial response or radiographic disease control rate between patients with locally advanced, non-metastatic pancreatic cancer who were treated with nab-paclitaxel plus gemcitabine compared to patients treated with sequential FOLFIRINOX, following two 28-day cycles of nab-paclitaxel plus gemcitabine. The third included paper (n=112) reported tumour response rates[6] in patients with locally advanced, non-metastatic pancreatic cancer treated with gemcitabine plus nab-paclitaxel or mFOLFIRINOX (42.1% and 30.9%, respectively). The disease control rate[7] was 96.5% in patients treated with gemcitabine plus nab-paclitaxel and 87.3% in patients treated with mFOLFIRINOX; no statistical comparisons were reported.

Serum CA 19-9 concentrations

Certainty of evidence:
Not assessed for 3 paper summaries

Serum CA 19-9 concentrations were reported in all three papers included in the summary.

Philip et al (2020; LAPACT) reported changes from baseline up to 24 weeks in serum CA 19-9 concentrations in 92 evaluable patients with locally advanced, non-metastatic pancreatic cancer during induction treatment with nab-paclitaxel plus gemcitabine. Post-hoc analysis indicated a decrease in serum CA 19-9 concentrations of at least 50% in 68 (74%) patients and a decrease of at least 70% in 51 (55%) patients.

Kunzmann et al (2021; NEOLAP-AIO-PAK-0113) assessed the mean change in CA 19-9 response from baseline to week 16 in patients with locally advanced, non-metastatic pancreatic cancer. There was no statistically significant difference in the response rate between patients treated with nab-paclitaxel plus gemcitabine (-62.4%, range 40.9; n=64) compared to patients treated with sequential FOLFIRINOX (-56.7%, range

[6] Tumour response was assessed using the Response Evaluation Criteria in Solid Tumours version 1.1.
[7] Disease control rate: complete response plus partial response plus stable disease.

	62.7; n=66) following two 28-day cycles of nab-paclitaxel plus gemcitabine (p=0.52). Osaka et al (2023; JCOG1407) reported that the CA 19-9 response rate[8] in patients with locally advanced, non-metastatic pancreatic cancer treated with gemcitabine plus nab-paclitaxel was 85.0% (95% CI 70.2 to 94.3; n=40) and 57.1% (95% CI 41.0 to 72.3; n=42) in patients treated with mFOLFIRINOX; no statistical comparison was reported. **One of the included papers (n=92) reported that post-hoc analysis indicated a decrease in serum CA 19-9 concentrations of at least 50% in 68 (74%) patients with locally advanced, non-metastatic pancreatic cancer and a decrease of at least 70% in 51 (55%) patients during induction treatment with nab-paclitaxel plus gemcitabine. A second included paper (n=130) reported that there was no statistically significant difference in the CA 19-9 response from baseline between patients treated with nab-paclitaxel plus gemcitabine compared to patients treated with sequential FOLFIRINOX (-62.4% and -56.7%, respectively; p=0.52), following two 28-day cycles of nab-paclitaxel plus gemcitabine. The third included paper (n=82) reported that in patients with locally advanced, non-metastatic pancreatic cancer treated with gemcitabine plus nab-paclitaxel, the percent who had a 50% or greater reduction in CA19 9 from baseline was 85.0% and 57.1% in patients treated with mFOLFIRINOX; no statistical comparison was reported.**
Quality of life **Certainty of evidence:** Not assessed for 3 paper summaries	Quality of life was reported in one of the three papers included in the summary. Philip et al (2020; LAPACT) reported on the mean change in global health status/quality of life (GHS/QoL) from baseline (n=99 evaluable patients) to day one of cycle six of induction treatment with nab-paclitaxel plus gemcitabine (n=42 evaluable patients) in patients with locally advanced, non-metastatic pancreatic cancer. GHS/QoL was measured using the European Organisation for the Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) and Quality of Life Questionnaire for pancreatic cancer (QLQ-PAN26). Mean changes in global health status QOL were only presented graphically, but the authors reported that patient global health status was maintained in most patients (i.e. stable or improved) during induction treatment. **One included paper reported that quality of life was maintained in most patients with locally advanced, non-metastatic pancreatic cancer from baseline (n=99 evaluable patients) to day one of cycle six of induction treatment with nab-paclitaxel plus gemcitabine (n=42 evaluable patients).**
Safety	
Safety	Safety was reported in all three papers included in the summary.

[8] CA 19-9 response was assessed for patients with a baseline level >100 U/mL, and a positive response was defined as a >50% reduction from the baseline level.

Certainty of evidence: Not assessed for 3 paper summaries	Philip et al (2020; LAPACT) reported that during induction treatment with nab-paclitaxel plus gemcitabine, 105 of 106 (99%) patients with locally advanced, non-metastatic pancreatic cancer experienced at least one treatment-related adverse event and 85 [80%] patients experienced grade 3 or higher adverse events. The most frequent (≥10% incidence) grade 3 or higher treatment-related adverse events were neutropenia (35 [33%] patients), anaemia (12 [11%]), and fatigue (11 [10%]). The authors reported that there were no deaths due to treatment-related adverse events during induction treatment, but 19 (18%) patients discontinued treatment due to adverse events.[9] Kunzmann et al (2021; NEOLAP-AIO-PAK-0113) reported that 93 of 165 (56%) patients with locally advanced, non-metastatic pancreatic cancer who initially received induction nab-paclitaxel plus gemcitabine experienced treatment-related adverse events of grade 3 or higher and 61 (37%) patients reported serious adverse events. For patients randomised to further treatment, 35 (55%) of 64 patients in the additional nab-paclitaxel plus gemcitabine group and 35 (53%) of 66 patients in the sequential FOLFIRINOX group reported treatment-related adverse events of grade 3 or higher; the most common were neutropenia (18 [28%] patients in the additional nab-paclitaxel plus gemcitabine group and 16 [24%] patients in the sequential FOLFIRINOX group), nausea and vomiting (two [3%] and eight [12%] patients, respectively), and bile duct obstruction with or without cholangitis (six [9%] and seven [11%] patients, respectively). The authors reported that there were no statistically significant differences between treatment groups in the incidence of treatment-related adverse events, but a higher proportion of patients in the sequential FOLFIRINOX group had non-haematological grade 3 or higher adverse events (33 [50%] patients) compared to patients in the additional nab-paclitaxel plus gemcitabine group (19 [30%]). The authors reported that there were no deaths due to treatment-related adverse events during induction chemotherapy, but three patients discontinued treatment due to adverse events during this phase. In addition, eight patients discontinued additional treatment due to adverse events (three in the nab-paclitaxel plus gemcitabine group and five in the sequential FOLFIRINOX group). Osaka et al (2023; JCOG1407) reported that grade 3 or 4 diarrhoea and grade 3 or 4 anorexia were less frequent in patients with locally advanced, non-metastatic pancreatic cancer treated with treated with gemcitabine plus nab-paclitaxel (1.6% and 6.3%, respectively; n=63) compared to patients treated with mFOLFIRINOX (17.7% and 16.1%, respectively; n=62); no statistical measures were reported. By contrast, the following adverse events were more frequent in patients treated with gemcitabine plus nab-paclitaxel compared to patients treated with mFOLFIRINOX: grade 3 or 4 peripheral sensory neuropathy (36.5% versus 25.8%, respectively), decreased white blood cells (44.4% versus 22.6%, respectively), and decreased neutrophil count (79.4% versus 59.7%, respectively); no

[9] One patient was reported as discontinuing induction treatment due to adverse events, but there was no record of any adverse event and they have therefore not been included in the 19 patients reported as discontinuing treatment.

	statistical measures were reported. The authors reported that no treatment-related deaths occurred in either treatment group but did not report whether any patients discontinued treatment due to adverse events. **One of the included papers (n=106) reported that during induction treatment with nab-paclitaxel plus gemcitabine, 99% patients with locally advanced, non-metastatic pancreatic cancer experienced at least one treatment-related adverse event and 80% experienced a grade 3 or higher adverse event. A second included paper (n=130) reported that 55% of patients with locally advanced, non-metastatic pancreatic cancer who received additional nab-paclitaxel plus gemcitabine and 53% of patients who received sequential FOLFIRINOX, following two 28-day cycles of nab-paclitaxel plus gemcitabine, experienced treatment-related adverse events of grade 3 or higher. The third included paper (n=125) reported that grade 3 or 4 diarrhoea and anorexia were less frequent in patients with locally advanced, non-metastatic pancreatic cancer treated with gemcitabine plus nab-paclitaxel compared to patients treated with mFOLFIRINOX. By contrast, grade 3 or 4 peripheral sensory neuropathy, decreased white blood cells, and decreased neutrophil count were more frequent in the gemcitabine plus nab-paclitaxel group compared to mFOLFIRINOX; no statistical measures were reported.**

Patient Impact assessment

The condition has the following impacts on the patient's everyday life:

- **mobility:** Patients have moderate problems in walking about or are unable to walk about
- **ability to provide self-care:** Patients have moderate problems in washing or dressing or are unable to wash or dress
- **undertaking usual activities:** Patients have severe problems in doing their usual activities or are unable to do their daily activities
- **experience of pain/discomfort:** Patients have extreme pain or discomfort
- **experience of anxiety/depression:** Patients are extremely anxious or depressed

Further details of impact upon patients:

Patients with advanced disease often suffer from distressing and difficult to control symptoms such as abdominal pain, nausea and vomiting, and fatigue. As surgery is not possible, treatment options are limited. Current chemotherapy options require multiple hospital appointments and admissions in a single cycle as well to manage chemotherapy complications and maintain the central lines required for chemotherapy infusions. As the survival rate of pancreatic cancer is low, this means patients are unable to spend the little time they do have left at home. This has a significant effect on their mental health.

Further details of impact upon carers:
Carers, often the patients' family members and children, need to assist with personal care, mobilising patients as well as taking patients to numerous hospital appointments. The caring role can affect their relationship with their loved one as well as put significant emotional stress on the carer. They may have to give up their jobs to care which puts financial burden on the family.

Considerations

Equality and Health Inequalities Impact Assessment (EHIA)	
Summary of any potential impacts of the proposal	This policy proposition will make gemcitabine-nab-paclitaxel available for all patients with locally advanced, non-metastatic pancreatic adenocarcinoma and an ECOG performance status of 0 or 1. It will provide an alternative treatment option to the modified FOLFIRINOX regime. It is thought this policy proposition will have a positive impact on individuals from protected characteristic groups and on those experiencing health inequalities.
13Q Assessment	
PPVAG outcome	No consultation required
Were PPVAG assured of the level of stakeholder testing?	Yes
Rare Disease Advisory Group	
Not Applicable	
Pharmaceutical	
Yes The Clinical Commissioning Policy Proposition recommends the use of gemcitabine and paclitaxel albumin as a treatment option for locally advanced non-metastatic pancreatic cancer in adults. This recommendation is outside the marketing authorisations for	

gemcitabine and paclitaxel albumin, so use is off-label. Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

Gemcitabine and paclitaxel albumin are included on the NHS Payment Scheme Annex A, so are high-cost drugs.

National Programme of Care

Cancer Programme of Care

The proposal received the full support of the Cancer National Programme of Care.