Canada's Drug and
Health Technology Agency

CADTH Reimbursement Review

Nanoparticle, Albumin-Bound (Nab)-Paclitaxel (in Combination With Gemcitabine)

Nonsponsored Review

Therapeutic area: For the adjuvant treatment of pancreatic cancer

Clinical and Pharmacoeconomic Report

Table of Contents

List of Tables

List of Figures

Abbreviations

AE	adverse event
CI	confidence interval
DFS	disease-free survival
ECOG	Eastern Cooperative Oncology Group
HR	hazard ratio
HRQoL	health-related quality of life
IQR	interquartile range
mFOLFIRINOX	modified leucovorin (folinic acid), fluorouracil, irinotecan, and oxaliplatin
OS	overall survival
PDAC	pancreatic ductal adenocarcinoma
PICOS	population(s), intervention(s), comparator(s), outcome(s), study design(s)
RCT	randomized controlled trial
TEAE	treatment-emergent adverse event

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Table 1: Submitted for Review

Item	Description
Drug product	Nab-paclitaxel powder for injectable suspension, 100 mg/vial
Indication	**Nab-paclitaxel:** The first-line treatment of metastatic adenocarcinoma of the pancreas, in combination with gemcitabine **Gemcitabine:** The treatment of patients with locally advanced (nonresectable stage II or stage III) or metastatic (stage IV) adenocarcinoma of the pancreas to achieve a clinical benefit response (a composite measure of clinical improvement)
Reimbursement request	Nab-paclitaxel in combination with gemcitabine for adjuvant treatment of pancreatic cancer
Health Canada approval status	Off-label
Requester	Provincial Advisory Group

Nab = nanoparticle, albumin-bound; NOC = Notice of Compliance.

Introduction

In Canada, despite being the 11th most commonly diagnosed cancer type, pancreatic cancer is expected to be the third leading cause of death in 2024.[1] It is estimated that 7,100 people in Canada will be diagnosed with pancreatic cancer in 2024 and 6,100 people will die from the disease.[2] More than 60% of cases are diagnosed at a late stage due to a lack of screening tests and the lack of symptoms that people with pancreatic cancer experience until the disease has progressed.[1]

Pancreatic cancer most commonly starts in the cells of the pancreatic duct. This form of cancer is called pancreatic ductal adenocarcinoma (PDAC).[3] It represents 95% of all forms of pancreatic cancer, and it has a poor prognosis.[3] Surgical resection followed by adjuvant chemotherapy is the recommended curative therapy for PDAC, although only 15% to 20% of PDAC patients present with resectable PDAC. Of various adjuvant chemotherapies, the preferred regimens include the modified leucovorin (folinic acid), fluorouracil, irinotecan, and oxaliplatin (mFOLFIRINOX) regimen and gemcitabine plus capecitabine combination therapy.

Nab-paclitaxel in combination with gemcitabine has emerged as another potential option in the adjuvant setting. Nab-paclitaxel is a nanoparticle, albumin-bound formulation containing paclitaxel. Health Canada has approved nab-paclitaxel for the following 2 indications: 1) the treatment of metastatic breast cancer, and 2) the first-line treatment of metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.[4] Nab-paclitaxel is not currently indicated for adjuvant treatment of PDAC.

The objective of this review is to perform a systematic review of the efficacy and safety of nab-paclitaxel in combination with gemcitabine for the adjuvant treatment of PDAC.

Stakeholder Perspectives

The information in this section is a summary of the input provided by stakeholders who responded to CADTH's call for input, and from clinical expert(s) consulted by CADTH for the purpose of this review.

Patient Input

Input for this review was jointly submitted by 2 patient groups, Canadian Cancer Society and Craig's Cause Pancreatic Cancer Society. The perspectives were collected from 2 patients who shared their experiences with the disease, the challenges they faced accessing treatments, and the significant impact that both pancreatic cancer and chemotherapy have had on their quality of life. It is important to note that neither patient has received treatment with nab-paclitaxel in combination with gemcitabine.

Clinician Input

Input From Clinical Experts Consulted by CADTH

Two clinical specialists with expertise in the diagnosis and management of pancreatic cancer provided the following input:

- Roughly 75% of all patients presenting with pancreatic cancer have advanced or unresectable disease, and PDAC is "1 of the most lethal solid tumours."
- A relatively small population of patients have nonmetastatic PDAC eligible for resection compared to those presenting with advanced or unresectable disease.
- The mFOLFIRINOX regimen given for 6 months (or 12 cycles) is currently the preferred adjuvant chemotherapy regimen.
- Combination therapy of gemcitabine plus capecitabine can be used in patients who are not candidates for mFOLFIRINOX.
- Evidence on the combination of nab-paclitaxel plus gemcitabine in the adjuvant treatment of pancreatic cancer is not robust, and the use of the combination therapy of nab-paclitaxel with gemcitabine in pancreatic cancer would be rare.
- The APACT trial did not demonstrate an improvement in disease-free survival (DFS) with the combination therapy of nab-paclitaxel plus gemcitabine compared with gemcitabine monotherapy.
- It is not anticipated that the combination of nab-paclitaxel plus gemcitabine would replace mFOLFIRINOX.

Clinician Group Input

The Ontario Health Gastrointestinal Cancer Drug Advisory Committee provided the following input:

- There are currently no effective options in adjuvant therapy for patients with pancreatic cancer, particularly those intolerable to 5-fluorouracil, those with dihydropyrimidine dehydrogenase deficiency, and those contraindicated for mFOLFIRINOX treatment.
- While the combination of nab-paclitaxel plus gemcitabine is considered as the first-line treatment of metastatic pancreatic cancer, its application in the adjuvant setting could be limited to patients with

an adequate performance status and acceptable laboratory profiles for administration of adjuvant chemotherapy.

- The decision to use the combination therapy of nab-paclitaxel plus gemcitabine after surgery should be made by both patients and their oncologists.

Industry Input

No industry input was provided.

Drug Program Input

The drug programs have provided the following input:

- Adjuvant chemotherapy is recommended for patients with nonmetastatic PDAC who undergo upfront surgery without prior neoadjuvant chemotherapy and are at a high risk of recurrence.
- mFOLFIRINOX would be administered as adjuvant therapy for 6 months in patients with good performance status.
- Gemcitabine in combination with capecitabine would be used in less fit patients.
- Gemcitabine monotherapy would be used in patients with borderline performance status or a comorbidity profile that precludes multiagent therapy.

The drug programs have raised the following questions related to policy and implementation considerations:

- Should the combination of nab-paclitaxel plus gemcitabine be used and funded for the treatment of certain populations pertaining to specific histology, tumour stages, or other subgroups of pancreatic cancer patients?
- What is the appropriate time frame to initiate adjuvant therapy following resection of pancreatic cancer (e.g., 8 to 12 weeks following resection)?
- Can patients who relapse after completing therapy be re-treated with the combination of nab-paclitaxel plus gemcitabine?
- Is there an appropriate disease-free interval for which re-treatment can be pursued in the advanced setting?

Clinical Evidence

Protocol Selected Study

Description of the Study

The APACT trial was a phase III, randomized, open-label, multicentre trial conducted at 160 sites across 21 countries including Canada (5 sites), and the objective of trial was to compare the efficacy and safety of nab-paclitaxel plus gemcitabine (n = 432) with gemcitabine alone (n = 434) as adjuvant therapy in adult patients with surgically resected PDAC. The trial began in April 2014 and patients were eligible for the trial if they had histologically confirmed resected PDAC with macroscopic complete resection (R0 or R1), a lymph node status of N0 or N1, no distant metastasis (M0), and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1.

Patients received either nab-paclitaxel 125 mg/m^2 plus gemcitabine 1,000 mg/m^2, infused intravenously over 30 to 40 minutes, given once weekly for 3 weeks (days 1, 8, and 15) followed by a week of rest (28-day cycle) for 6 cycles, or gemcitabine monotherapy 1,000 mg/m^2 at the same dosing frequency and duration of therapy.

The primary end point was DFS, defined as time from random assignment to disease recurrence or death, which was independently assessed by radiologists blinded to the treatment assignment. Secondary end points included overall survival (OS; defined as the time from the date of randomization to the death of death) and safety outcomes. Investigator-assessed DFS was evaluated in a prespecified sensitivity analysis, and health-related quality of life (HRQoL) was evaluated as an exploratory end point; however, the results of the HRQoL assessment were not reported.

Critical Appraisal

The APACT trial was a randomized, multicentre, open-label trial. The process for randomization was clearly described. However, the open-label design may have resulted in biased estimates for more subjective outcomes such as adverse events (AEs) and HRQoL. The primary end point of DFS was assessed by blinded, independent review, and as such, is less likely to have been impacted by detection bias. OS was evaluated as a secondary end point; however, statistical comparisons were not controlled for type I error. In addition, although it was reported in the trial protocol that HRQoL was to be evaluated in the APACT trial as an exploratory end point, the results of the HRQoL assessments were not reported in the publication. Lastly, the proportional hazards assumption was not evaluated for the DFS and OS analyses. As such, it is unclear whether the proportional hazards assumption was violated, and if so, what the impact of the violation would be on the hazard ratios (HRs) and 95% confidence intervals (CIs) for DFS and OS.

The trial inclusion and exclusion criteria were clinically relevant, and patients from Canada were included in the trial. The administration of nab-paclitaxel plus gemcitabine or gemcitabine alone was consistent with common practice, and the dose modifications were also reasonable based on tolerability. Harms outcomes such as neuropathy and neutropenia were reported. However, hospitalization data were not available.

Efficacy Results

Baseline characteristics were generally balanced between the trial arms. The median age was 64.0 years, and more patients were male (56%). Most patients had an ECOG performance status score of 0 (60%), had R0 resection status (76%), and had N1 lymph node involvement (72%)

Each group received 6 cycles of treatment with a median treatment duration of 24 weeks. At the primary data cut-off, the median follow-up was 38.5 months. Table 2 presents key results from the APACT trial.

For the primary end point of blinded independently assessed DFS, 439 patients (51.0%) had progressed or died at the primary data cut-off. The median independently assessed DFS was 19.4 months in the nab-paclitaxel plus gemcitabine group compared with 18.8 months in the gemcitabine group (HR = 0.88; 95% CI, 0.729 to 1.063; P = 0.18).

For investigator-assessed DFS, 571 of all treated patients (66.0%) had disease progression or died at the primary data cut-off. The median investigator-assessed DFS was 16.6 months in the nab-paclitaxel plus gemcitabine group compared with 13.7 months in the gemcitabine group (HR = 0.82; 95% CI, 0.694 to 0.965; P = 0.02).

At the primary data cut-off, the OS data were 68% mature with 427 of 630 target events. The median OS was 40.5 months in the nab-paclitaxel plus gemcitabine group compared with 36.2 months in the gemcitabine group (HR = 0.82; 95% CI, 0.680 to 0.996; P = 0.045). At the 16-month follow-up, the OS data were based on 511 events with a median follow-up for survival of 51.4 months. The median OS was 41.8 months in the nab-paclitaxel plus gemcitabine group compared with 37.7 months in the gemcitabine group (HR = 0.82; 95% CI, 0.687 to 0.973; P = 0.023). At the 5-year follow-up, the OS data were based on 555 events and the median follow-up for survival was 63.2 months. The median OS was 41.8 months in the nab-paclitaxel plus gemcitabine group compared with 37.7 months in the gemcitabine group (HR = 0.80; 95% CI, 0.678 to 0.947; P = 0.0091).

Harms Results

All treated patients in the nab-paclitaxel plus gemcitabine group and 99% of patients in the gemcitabine monotherapy group had 1 or more treatment-emergent AEs (TEAEs). A TEAE of grade 3 or more was reported in 86% of patients in the nab-paclitaxel plus gemcitabine group and 68% of patients in the gemcitabine group. At least 1 serious TEAE was reported by 41% of patients in the nab-paclitaxel plus gemcitabine group and 23% of patients in the gemcitabine group.

The most frequent TEAEs of grade 3 or higher in the nab-paclitaxel plus gemcitabine group versus the gemcitabine group were neutropenia (49% versus 43%), anemia (15% versus 8%), fatigue (10% versus 3%), and peripheral neuropathy (15% versus 0%).

Table 2: Summary of Key Results From the APACT Trial

Outcome	Nab-paclitaxel + gemcitabine	Gemcitabine
Efficacy (ITT population; 432 vs. 434)		
Blinded, independently assessed DFS (at the primary data cut-off)		
n (%)	226 (52.3)	213 (49.1)
Median DFS, months	19.4	18.8
HR (95% CI)	0.88 (0.729 to 1.063)	
P value	P = 0.1824	
Unblinded, investigator-assessed DFS		
n (%)	282 (65.3)	289 (66.6)
Median DFS, months	16.6	13.7
HR (95% CI)	0.82 (0.694 to 0.965)	
P value	P = 0.0168[a]	
OS (at the primary data cut-off)		

Outcome	Nab-paclitaxel + gemcitabine	Gemcitabine
Death, n (%)	206 (47.7)	221 (50.9)
Median OS, months	40.5	36.2
HR (95% CI)	0.82 (0.680 to 0.996)	
P value	P = 0.045[a]	
OS (at the 16-month follow-up)		
Death, n (%)	248 (57.4)	263 (60.6)
Median OS, months	41.8	37.7
HR (95% CI)	0.82 (0.687 to 0.973)	
P value	P = 0.0232[a]	
OS (at the 5-year follow-up)		
Death, n (%)	268 (62.0)	287 (66.1)
Median OS, months	41.8	37.7
HR (95% CI)	0.80 (0.678 to 0.947)	
P value	P = 0.0091[a]	
Harms (treated population; 429 vs. 423)		
≥ grade 1 TEAE, n (%)	429 (100)	423 (99)
≥ grade 3 TEAE, n (%)	371 (86)	286 (68)
Hematologic		
Neutropenia, n (%)	212 (49)	184 (43)
Anemia, n (%)	63 (15)	33 (8)
Leukopenia, n (%)	36 (8)	20 (5)
Febrile neutropenia, n (%)	21 (5)	4 (1)
Nonhematologic		
Peripheral neuropathy (SMQ)	64 (15)	0
Fatigue, n (%)	43 (10)	13 (3)
Asthenia, n (%)	21 (5)	8 (2)
Diarrhea, n (%)	22 (5)	4 (1)
Hypotension, n (%)	17 (4)	27 (6)

CI = confidence interval; DFS = disease-free survival; HR = hazard ratio; ITT = intention to treat; OS = overall survival; SMQ = Standardized Medical Dictionary for Regulatory Activities Queries; TEAE = treatment-emergent adverse event; vs. = versus.

[a]Comparisons were not adjusted for type I error.

Source: Tempero et al. 2023.[5]

Indirect Comparisons

No indirect treatment comparisons were identified for this review.

Other Relevant Evidence

No long-term extension studies or additional relevant studies were considered to address important gaps in the evidence included in the systematic review.

Cost Information

The economic review included a comparison of the treatment costs of nab-paclitaxel plus gemcitabine and those of comparators deemed to be appropriate based on clinical expert consultations and drug plan feedback.

Based on publicly available list prices, nab-paclitaxel plus gemcitabine is expected to have a 28-day per patient cost of $8,012 when used as dosed in the APACT clinical trial.[5] As the current standard-of-care adjuvant treatments for patients with resected pancreatic cancer include gemcitabine monotherapy, mFOLFIRINOX, and capecitabine plus gemcitabine, this review compared the cost of these regimens with nab-paclitaxel plus gemcitabine. The 28-day per patient cost of mFOLFIRINOX, capecitabine plus gemcitabine, and gemcitabine monotherapy was $4,156, $1,650, and $1,458, respectively.

When comparing nab-paclitaxel plus gemcitabine to mFOLFIRINOX, nab-paclitaxel plus gemcitabine results in per patient incremental costs of $3,856. When comparing nab-paclitaxel plus gemcitabine to capecitabine plus gemcitabine, nab-paclitaxel plus gemcitabine results in per patient incremental costs of $6,362. Lastly, when comparing nab-paclitaxel plus gemcitabine to gemcitabine monotherapy, nab-paclitaxel plus gemcitabine results in per patient incremental costs of $6,554. Costs are based on publicly available list prices and may not reflect actual prices paid by Canadian public drug plans.

Conclusions

In the APACT trial, for the primary end point of independently assessed DFS, the median was 19.4 months in the nab-paclitaxel plus gemcitabine arm and 18.8 months in the gemcitabine monotherapy arm (HR = 0.88; 95% CI, 0.729 to 1.063; P = 0.18). In addition, the combination treatment was associated with a higher incidence of TEAEs including peripheral neuropathy and febrile neutropenia, and patients in this group were more likely to discontinue treatment due to AEs compared to those in the gemcitabine group. Although the OS comparisons between the 2 treatment arms suggested a numerically longer OS with nab-paclitaxel plus gemcitabine compared with gemcitabine monotherapy, the comparisons were not controlled for type I error. As such, it is unclear whether the differences seen in OS were due to a true difference between nab-paclitaxel plus gemcitabine compared to gemcitabine alone or due to type I error.

Results of the cost comparison of drug acquisition costs demonstrate that — when compared to mFOLFIRINOX, capecitabine plus gemcitabine, and gemcitabine monotherapy — nab-paclitaxel plus gemcitabine is expected to increase treatment costs (incremental costs: $3,856, $6,362, and $6,554, per patient, per 28 days, respectively). Based on the clinical review conclusions, nab-paclitaxel plus gemcitabine was associated with a higher incidence of TEAEs and an uncertain OS benefit compared with gemcitabine monotherapy. No randomized controlled trials (RCTs) were identified comparing nab-paclitaxel plus gemcitabine with mFOLFIRINOX or with capecitabine plus gemcitabine; therefore, the comparative efficacy of these treatments is unknown. As such, nab-paclitaxel plus gemcitabine is associated with incremental

treatment costs and uncertain clinical impact. Costs associated with AEs and administration costs were not considered in this cost comparison. However, clinical expert input indicated that nab-paclitaxel plus gemcitabine is anticipated to increase monitoring costs because more chair time is required for patients to receive this treatment.

Introduction

Disease Background

In Canada, despite being the 11th most commonly diagnosed cancer type, pancreatic cancer is expected to be the third leading cause of death in 2024.[1] It is estimated that 7,100 people in Canada will be diagnosed with pancreatic cancer in 2024 and 6,100 people will die from the disease.[2] More than 60% of cases are diagnosed at a late stage due to a lack of screening tests and the lack of symptoms that people with pancreatic cancer experience until the disease has progressed.[1]

Pancreatic cancer most commonly starts in the cells of the pancreatic duct. This form of cancer is called pancreatic ductal adenocarcinoma (PDAC).[3] It represents 95% of all forms of pancreatic cancer, and it has a poor prognosis.[3] It is estimated that PDAC will be the second leading cause of cancer-related death in 2030, with a 5-year survival rate of 5 to 7%.[6,7] Radical resection surgical treatment with tumour-free excision margins (referred to as R0 resection) is the only potential curative approach for PDAC at this time.[8] According to the National Comprehensive Cancer Network (NCCN) Guidelines version 1, 2024, resectability status can be categorized as resectable, borderline resectable, or locally advanced.[9] However, it has been noted that decisions about resectability status should be made in consensus at multidisciplinary meetings or discussion. The criteria for resectability status are listed in Table 3.

Table 3: Criteria Defining Resectability Status at Diagnosis[9]

Resectability status	Arterial	Venous
Resectable	No arterial tumour contact (CA, SMA, or CHA)	No tumour contact with the SMV or PV or ≤ 180° contact without vein contour irregularity
Borderline resectable	**Pancreatic head/uncinate process:** • Solid tumour contact with CHA without extension to CA or hepatic artery bifurcation allowing for safe and complete resection and reconstruction • Solid tumour contact with the SMA of ≤ 180° • Solid tumour contact with variant arterial anatomy (e.g., accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery) and the presence and degree of tumour contact should be noted if present, as it may affect surgical planning	• Solid tumour contact with the SMV or PV of > 180°, contact of ≤ 180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction • Solid tumour contact with the IVC

Resectability status	Arterial	Venous
	Pancreatic body/tail: • Solid tumour contact with the CA of ≤ 180°	
Locally Advanced	**Head/uncinate process:** • Solid tumour contact of > 180° with the SMA or CA **Pancreatic body/tail:** • Solid tumour contact of > 180° with the SMA or CA • Solid tumour contact with the CA and aortic involvement	• Unreconstructible SMV/PV due to tumour involvement or occlusion (can be due to tumour or bland thrombus)

CA = celiac axis; CHA = common hepatic artery; IVC = inferior vena cava; PV = portal vein; SMA = superior mesenteric artery; SMV = superior mesenteric vein.

About 15% to 20% of patients with PDAC have localized and potentially resectable disease at diagnosis.[8] For these patients with curative resection, the rate of postoperative tumour recurrence is high, and many patients will eventually experience a disease relapse.[8] According to guidelines from Ontario[10] and Alberta,[11] adjuvant chemotherapy is recommended for patients with resected PDAC with chemotherapy options.

Standards of Therapy

Currently, various adjuvant chemotherapies are recommended by the NCCN Guidelines following curative resection.[9] The preferred regimens include the mFOLFIRINOX regimen and gemcitabine plus capecitabine combination therapy. Other options include gemcitabine monotherapy as well as options involving 5-flurououracil with leucovorin and with chemoradiation.[9] Based on the European study group for pancreatic cancer (ESPAC)-1 trial, evidence demonstrated that fluorouracil-based adjuvant chemotherapy (median OS: 19.7 months) offered survival benefits compared to surgery alone (median OS: 14.0 months) (HR = 0.66; 95% CI, 0.52 to 0.83, P = 0.0005).[12] Further, the CONKO-001 trial demonstrated an improvement in DFS using gemcitabine-based adjuvant monochemotherapy (median DFS: 13.4 months) when compared to observation (median DFS: 6.7 months) in resected PDAC patients (HR = 0.55; 95% CI, 0.44 to 0.69; P < 0.001).[13]

According to Ontario Health Cancer Care Ontario Guidelines 2 to 23,[10] "adjuvant chemotherapy is recommended for patients with R0 or R1 resected PDAC. mFOLFIRINOX is recommended for appropriately fit patients. If a patient is not suitable for mFOLFIRINOX, alternative options include gemcitabine plus capecitabine or gemcitabine alone." Likewise, the Cancer Care Alberta Clinical Practice Guideline[11] also recommends adjuvant chemotherapy with mFOLFIRINOX, gemcitabine with oral capecitabine or, for patients not suitable for combination chemotherapy, leucovorin with 5-fluorouracil as chemotherapy options for potentially curable adenocarcinoma of the pancreas.

More recently, nab-paclitaxel in combination with gemcitabine has emerged as another potential option in the adjuvant setting.[8]

Drug

Nab-paclitaxel is a nanoparticle, albumin-bound formulation containing paclitaxel. It is a solvent-free formulation, which is associated with fewer infusion-related reactions compared to paclitaxel. Health Canada

has approved nab-paclitaxel for the following 2 indications: 1) the treatment of metastatic breast cancer, and 2) the first-line treatment of metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.[4]

CADTH completed a reimbursement review of nab-paclitaxel in 2014 for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine, and the recommendation from this review was to reimburse with clinical criteria and/or conditions.[14] In 2024, in addition to this review, there are 2 ongoing reviews with nab-paclitaxel: nab-paclitaxel in patients with hypersensitivity reactions and nab-paclitaxel, in combination with gemcitabine, for previously treated advanced (locally advanced unresectable or metastatic) pancreatic cancer.

The Provincial Advisory Group (PAG) and clinical experts consulted by CADTH for this review indicated that there is an interest in clinical practice to use nab-paclitaxel in combination with gemcitabine for adjuvant treatment of pancreatic cancer. PAG requested that CADTH review nab-paclitaxel in combination with gemcitabine for this patient population and provide a reimbursement recommendation.

Stakeholder Perspectives

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups.

The full patient group input will be posted on the nab-paclitaxel landing page. Input for this review was jointly submitted by 2 patient groups, the Canadian Cancer Society and Craig's Cause Pancreatic Cancer Society. The perspectives were collected from 2 patients who shared their experiences with the disease, the challenges they faced accessing treatments, and the significant impact that both pancreatic cancer and chemotherapy have had on their quality of life. It is important to note that neither patient has received treatment with nab-paclitaxel in combination with gemcitabine.

Clinician Input

Input From Clinical Experts Consulted by CADTH

All CADTH review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is being evaluated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The following input was provided by 2 clinical specialists with expertise in the diagnosis and management of pancreatic cancer.

Unmet Needs

The clinical experts noted that the typical treatment landscape in the PDAC adjuvant setting includes mFOLFIRINOX given for 6 months (or 12 cycles) based on the ESPAC-6 trial.[15] If a patient is not a candidate for mFOLFIRINOX due to contraindication(s) to the treatment regimens or because they have comorbidities that would render them unable to tolerate the treatment's harms, combination therapies such as gemcitabine

plus capecitabine or gemcitabine alone would be offered. The main treatment goal is to reduce the chance of recurrence. In their opinion, regimens that include more drugs tend to offer greater benefits as well as harms. The clinical experts also stated that, in their opinion, additional options would be preferred to improve tolerance and potentially reduce the risk of hospitalization.

Place in Therapy

One clinical specialist said that the evidence for nab-paclitaxel in combination with gemcitabine for the adjuvant treatment of PDAC does not appear to be robust. In their current practice, nab-paclitaxel may be prescribed as a palliative chemotherapy before surgery. Following surgery, this clinical specialist indicated their preference would be to prescribe mFOLFIRINOX but that nab-paclitaxel may be used in combination with gemcitabine if the patient cannot tolerate mFOLFIRINOX. This clinical specialist indicated that the use of nab-paclitaxel in combination with gemcitabine would be rare and does not anticipate that this regimen will replace mFOLFIRINOX.

Another clinical specialist highlighted that the evidence from the APACT[5] trial did not demonstrate an improvement in DFS with nab-paclitaxel in combination with gemcitabine compared with gemcitabine monotherapy. Hence, this clinical specialist does not expect nab-paclitaxel in combination with gemcitabine to offer the same effect as mFOLFIRINOX.

Patient Population

The clinical experts indicated that nab-paclitaxel combined with gemcitabine is best suited for patients who cannot tolerate mFOLFIRINOX. However, this combination is unsuitable for patients with contraindications to either drug, comorbidities that preclude chemotherapy in the adjuvant setting, or life-threatening conditions where any treatment is contraindicated.

Assessing Response to Treatment

The clinical specialists highlighted that there is no formal guidance in treatment evaluation in the PDAC adjuvant setting. However, treatment response typically involves imaging, tumour marker monitoring, blood work investigations, and clinical exams.

Discontinuing Treatment

The clinical specialists noted that treatment may be discontinued upon disease progression or related to an adverse event not manageable with supportive medication, dose modifications, or treatment delays.

Prescribing Conditions

A medical oncologist would be typically required to prescribe nab-paclitaxel with gemcitabine. In some community settings, treatment may be recommended by a medical oncologist. However, the administration of care and subsequent follow-ups may be conducted by general practitioners or individuals with supervision by medical oncologists.

Additional Considerations

The clinical experts emphasized that PDAC, being “one of the most lethal solid tumours,” affects a relatively small population of patients with nonmetastatic resected pancreatic cancer compared to those presenting

with advanced or unresectable disease. The clinical specialists also noted that the adjuvant use of nab-paclitaxel with gemcitabine will represent a small population given that mFOLFIRINOX is the preferred regimen. Lastly, roughly 75% of all patients presenting with pancreatic cancers are in the advanced or unresectable disease stage.

Clinician Group Input

This section was prepared by CADTH staff based on the input provided by clinician groups.

The Ontario Health Cancer Care Ontario Gastrointestinal Cancer Drug Advisory Committee submitted input for this review. The clinician group identified several unmet needs in adjuvant therapy for pancreatic cancer, particularly the absence of effective options for patients intolerant to 5-fluorouracil, those with dihydropyrimidine dehydrogenase deficiency, and those with contraindications to mFOLFIRINOX treatment. They noted that while nab-paclitaxel combined with gemcitabine is established in the first-line treatment of metastatic pancreatic cancer, its application in the adjuvant setting could be limited to the aforementioned populations who have adequate performance status and laboratory profiles for administration of adjuvant chemotherapy. The clinician group emphasized that the decision to proceed with nab-paclitaxel in combination with gemcitabine postcurative surgery should involve informed, collaborative decision-making between patients and their oncologists.

Industry Input

No input was provided to CADTH from the pharmaceutical industry.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's reimbursement review processes by identifying issues that may impact their ability to implement a recommendation.

The drug programs have highlighted that adjuvant chemotherapy is recommended for patients with nonmetastatic PDAC who undergo upfront surgery (pancreatectomy) without prior neoadjuvant chemotherapy and are at a high risk of recurrence. It has also been noted that for patients with a good performance status, mFOLFIRINOX would be administered as adjuvant therapy for 6 months. For less fit patients, gemcitabine in combination with capecitabine would be used instead of mFOLFIRINOX. For patients with borderline performance status or a comorbidity profile that precludes multiagent therapy, gemcitabine monotherapy would be used.

The drug programs highlighted policy and implementation considerations and questions. One question relates to the eligibility funding criteria of adjuvant nab-paclitaxel with gemcitabine pertaining to histologies, tumour stages, and subgroups of pancreatic cancer patients to qualify for treatment. In addition, the drug programs would seek guidance on the appropriate time frame to initiate adjuvant therapy following resection of pancreatic cancer (e.g., 8 to 12 weeks following resection). Further, the drug programs would seek clarification on whether nab-paclitaxel in combination with gemcitabine can be given again to patients who relapse after completing therapy, and whether there is an appropriate disease-free interval for which re-treatment can be pursued in the advanced or metastatic setting.

Other implementation questions and corresponding responses from the clinical experts consulted by CADTH are summarized in the Drug Plan Input published on the nab-paclitaxel landing page.

Clinical Evidence

The clinical evidence included in the review of nab-paclitaxel in combination with gemcitabine is presented in 3 sections. The first section, the systematic review, includes studies that were selected according to an a priori protocol. The second section includes indirect evidence from the literature that met the selection criteria specified in the review. The third section includes additional relevant studies that were considered to address important gaps in the evidence included in the systematic review.

Systematic Review (Pivotal and Protocol Selected Studies)

Objectives

To perform a systematic review of the efficacy and safety of nab-paclitaxel in combination with gemcitabine for the adjuvant treatment of PDAC.

Methods

Studies selected for inclusion in the systematic review included those meeting the selection criteria presented in Table 4. Outcomes included in the CADTH review protocol reflect outcomes considered to be important to patients, clinicians, and drug plans.

Table 4: Inclusion Criteria for the Systematic Review

Criteria	Description
Patient population	Patients with resected PDAC
Intervention	Adjuvant nab-paclitaxel 125 mg/m^2 IV followed by gemcitabine 1,000 mg/m^2 IV, both given once weekly for 3 weeks on days 1, 8, and 15 followed by a week of rest (28-day cycle) for 6 cycles.
Comparators	Adjuvant gemcitabine 1,000 mg/m^2 IV, given once weekly for 3 weeks on days 1, 8, and 15, followed by a week of rest (28-day cycle) for 6 cycles. Adjuvant gemcitabine plus capecitabine Adjuvant mFOLFIRINOX
Outcomes	**Efficacy:** • OS • PFS • DFS • HRQoL **Safety:** • AE, SAE, WDAE **Harms of interest:** • Neuropathy

Criteria	Description
	• Febrile neutropenia • Hospitalization
Study Design	Published phase III and IV RCTs

AE = adverse events; DFS = disease-free survival; HRQoL = health-related quality of life; mFOLFIRINOX = modified leucovorin (folinic acid), fluorouracil, irinotecan, and oxaliplatin; OS = overall survival; PDAC = pancreatic ductal adenocarcinoma; PFS = progression-free survival; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Two CADTH clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least 1 reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

An information specialist performed the literature search for clinical studies using a peer-reviewed search strategy according to CADTH's *PRESS Peer Review of Electronic Search Strategies* checklist.[16]

Published literature was identified by searching the following bibliographic databases: MEDLINE via Ovid and Embase via Ovid. All Ovid searches were run simultaneously as a multifile search. Duplicates were removed using Ovid deduplication for multifile searches, followed by manual deduplication in EndNote. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the PICOS framework and research questions. The main search concepts were gemcitabine, nab-paclitaxel, pancreatic cancer, and adjuvant therapy. The following clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, WHO's International Clinical Trials Registry Platform (ICTRP) search portal, Health Canada's Clinical Trials Database, the European Union Clinical Trials Register, and the European Union Clinical Trials Information System (CTIS).

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. Refer to Appendix 1 for the detailed search strategies.

The initial search was completed on March 1, 2024. Regular alerts updated the search until the meeting of the CADTH Formulary Management Expert Committee (FMEC) on July 4, 2024.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from CADTH's Grey Matters: A Practical Tool For Searching Health-Related Grey Literature. Included in this search were the websites of regulatory agencies (US FDA and European Medicines Agency). Google was used to search for additional internet-based materials. Refer to Appendix 1 for more information on the grey literature search strategy.

Findings From the Literature

Of 248 records identified by the searches, 20 were screened by full text, and 1 study (APACT trial) met the selection criteria as described in Table 4 and was included in this review. The flow diagram for study

selection is available in Appendix 2. A list of excluded studies is presented in Appendix 3. Of note, there were no RCTs identified that compared adjuvant nab-paclitaxel plus gemcitabine to the other relevant comparators identified in the protocol, including adjuvant mFOLFIRINOX or adjuvant gemcitabine plus capecitabine.

Protocol Selected Study

Characteristics of the Included Study

The characteristics of the APACT trial are summarized in Table 5.

Table 5: Details of the Included Trial

Detail	APACT 2023[5]
Design and population	
Study design	Phase III, multicentre, open-label, randomized controlled trial
Locations	160 sites across 21 countries including Canada (5 sites), US, UK, Germany, Australia
Patient enrolment dates	Between April 2014 and April 2016
Randomized (N)	866 patients
Inclusion criteria	• 18 years of age and older • Histologically confirmed resected PDAC with macroscopic complete resection (R0 and R1) • PDAC staging T1 to 3, N0 to 1, M0 • Patient should be able to start treatment no later than 12 weeks postsurgery • Male or nonpregnant, nonlactating females who are 18 years of age or older at the time of signing the informed consent form • ECOG PS of 0 or 1 • Acceptable hematology parameters (e.g., ANC ≥ 1,500 cell/mm^3, platelet count ≥ 100,000/mm^3, hemoglobin ≥ 9 g/dL) • Acceptable blood chemistry levels (e.g., AST/SGOT and ALT/SGPT ≤ 2.5 x ULN, alkaline phosphatase ≤ 2.5 x ULN, serum creatinine within ULN or calculated clearance ≥ 50 mL/min/1.73 m^2) • Carbohydrate antigen 19 to 9 < 100 U/mL assessed within 14 days of randomization • Acceptable coagulation studies
Exclusion criteria	• Patients with neuroendocrine (and mixed type) tumours • Prior neoadjuvant treatment, radiation therapy, or systemic therapy for pancreatic adenocarcinoma • Presence of or history of metastatic or locally recurrent PDAC • Any other malignancy within 5 years before randomization • Peripheral neuropathy ≥ grade 2 • Serious medical risk factors involving any of the major organ systems, or serious psychiatric disorders, which could compromise the subject's safety or the study data integrity

Detail	APACT 2023[5]
Drugs	
Intervention	Nab-paclitaxel 125 mg/m^2, IV infusion over 30 to 40 minutes, followed by gemcitabine 1,000 mg/m^2, IV infusion over 30 to 40 minutes, given once weekly for 3 weeks (days 1, 8, and 15) followed by a week of rest (28-day cycle) for 6 cycles
Comparator(s)	Gemcitabine 1,000 mg/m^2, IV infusion over 30 to 40 minutes, given once weekly for 3 weeks (days 1, 8, and 15) followed by a week of rest (28-day cycle) for 6 cycles
Duration	
Follow-up	Disease recurrence was assessed every 8 weeks for the first 24 weeks and then every 12 weeks for the next 2.5 years until 3 years after random assignment. After 3 years, disease recurrence was assessed every 24 weeks up to 5.5 years after random assignment.
Outcomes	
Primary end point	DFS, assessed by blinded independent radiological review[a]
Secondary and exploratory end points	Secondary: Investigator-assessed DFS,[b] OS,[c] and safety (AE, SAE, TEAE) Exploratory: HRQoL[d]
Notes	
Publications	*J Clin Oncol.* 2023;41(11):2007 to 2019

AE = adverse event; ALT = alanine transaminase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; DFS = disease-free survival; ECOG PS = Eastern Cooperative Oncology Group performance status; HRQoL = health-related quality of life; OS = overall survival; PDAC = pancreatic ductal adenocarcinoma; SAE = serious adverse event; SGOT = glutamic-oxaloacetic transaminase; SGPT = serum glutamate pyruvate transaminase; TEAE = treatment-emergent adverse events; ULN = upper limit of normal range.

[a]DFS was defined as the time from the date of randomization to the date of disease recurrence or death, whichever occurred earlier. Disease recurrence was determined by the independent radiological review of CT or MRI scans.

[b]For investigator-assessed DFS, investigators determined recurrence using all available information collected and evaluated using their expert judgment during the usual treatment.

[c]OS was defined as the time from the date of randomization to the date of death.

[d]HRQoL was evaluated using the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-30) and the EORTC QLQ Pancreatic Cancer Module (EORTC QLQ-PAN26).

Source: Tempero et al. 2023.[5]

Study Design

The APACT trial was a phase III, randomized, open-label, multicentre trial conducted at 160 sites across 21 countries including Canada (5 sites), and the objective of trial was to compare the efficacy and safety of nab-paclitaxel plus gemcitabine with gemcitabine alone as adjuvant therapy in adult patients with surgically resected PDAC. Patients were randomly assigned in a 1:1 ratio, using a permuted-block random assignment method and interactive response technology, to receive nab-paclitaxel plus gemcitabine or gemcitabine alone. Patients were stratified on the basis of resection status (R0 [tumour-free margin] or R1 [microscopically positive margin]), nodal status (lymph node-positive [N1] or lymph node-negative [N0]), and region (non-Asian regions [North America, Europe, and Australia], or Asia).

The trial began in April 2014 and the primary data cut-off was on December 31, 2018, at which the analyses for all end points were conducted. In addition to the primary data cut-off analyses, OS analyses were conducted at the 16-month follow-up analysis cut-off (April 3, 2020) and at the 5-year follow-up analysis

cut-off (April 9, 2021). The trial was funded by Bristol Myers Squibb and by Celgene, a Bristol Myers Squibb Company.

Eligibility Criteria

Patients were eligible for the APACT trial if they had histologically confirmed resected PDAC with macroscopic complete resection (R0 or R1), a lymph node status of N0 or N1, M0, an ECOG performance status score of 0 or 1, acceptable hematology parameters, acceptable blood chemistry levels, a carbohydrate antigen 19 to 9 level lower than 100 U/mL assessed within 14 days of randomization, and acceptable coagulation studies.

The trial excluded patients with neuroendocrine (and mixed type) tumours; those who received neoadjuvant treatment, radiation, or systemic therapy for pancreatic cancer; patients with a history of metastatic or locally recurrent PDAC; or those with medical risk factors including peripheral neuropathy of grade 2 or higher.

Interventions

The intervention evaluated in this trial was nab-paclitaxel 125 mg/m^2 plus gemcitabine 1,000 mg/m^2, infused IV over 30 to 40 minutes, given once weekly for 3 weeks (days 1, 8 and 15) followed by a week of rest (28-day cycle) for 6 cycles. The comparison was gemcitabine monotherapy 1,000 mg/m^2 at the same dosing frequency and duration of therapy. Supportive care, such as white blood cell growth factor could be administered for treatment of neutropenic fever or infections associated with neutropenia and for prevention of febrile neutropenia in patients with an absolute neutrophil count of less than 500 cells/mm^3. Two levels of dose modifications were permitted for hematologic or other harms, reducing nab-paclitaxel to 100 mg/m^2 for level 1 and 75 mg/m^2 for level 2, and reducing gemcitabine to 800 mg/m^2 at level 1 and 600 mg/m^2 at level 2. Treatment was discontinued if there was radiologic evidence of disease recurrence and unacceptable harm.

Outcomes

The efficacy end points identified in the CADTH review protocol that were assessed in the included studies are summarized below and are listed in Table 6.

Table 6: Summary of Outcomes of Interest Identified in the CADTH Review Protocol

Outcome measure	APACT
Blinded, independently assessed DFS	Primary
Unblinded, investigator-assessed DFS	Sensitivity analysis
OS	Secondary
Safety	Secondary
HRQoL	Exploratory

DFS = disease-free survival; HRQoL = health-related quality of life; OS = overall survival.

The primary end point was DFS, defined as time from random assignment to disease recurrence or death, and was independently assessed by radiologists blinded to the treatment assignment. Disease recurrence was assessed based on radiologic review (CT or MRI) based on Response Evaluation Criteria in Solid Tumours (RECIST) version 1.[17] After random assignment, disease recurrence was assessed every 8 weeks

for the first 24 weeks, then every 12 weeks for the next 2.5 years until 3 years. After 3 years, disease recurrence was assessed every 24 weeks up to 5.5 years after random assignment. During assessment of disease recurrence, a biopsy was recommended for patients who had suspicious lesions or accumulate ascites, pleural, or other fluids. In case of positive biopsy for disease recurrence, a tumour sample was sent to the central laboratory for confirmation.

Secondary end points included OS (defined as the time from the date of randomization to the death of death) and safety outcomes. TEAEs, defined as any event that begins or worsens in grade after the start of trial treatment until 28 days after the last dose of the trial treatment, were identified and reported. In addition, grade 3 or higher TEAEs; TEAEs leading to dose reduction, dose interruption, or treatment discontinuation; TEAEs leading to death; and serious AEs were reported. AEs were coded using the Medical Dictionary for Regulatory Activities version 21.0 and graded for intensity according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.[18]

Investigator-assessed DFS was evaluated in a prespecified sensitivity analysis; investigators determined recurrence using all available clinical information collected and evaluated it using their expert judgment during the usual treatment of their patients.

HRQoL was evaluated as an exploratory end point using the EORTC QLQ-C30 and EORTC QLQ-PAN26 questionnaires; however, the results of the HRQoL assessment were not reported.

Statistical Analysis

Power Calculation

To achieve the expected median DFS of 13.5 months (gemcitabine) and 18.5 months (nab-paclitaxel plus gemcitabine) equivalent to a HR of 0.73, approximately 438 DFS events were required to allow 90% power to detect a 27% risk reduction in disease recurrence or death at a 2-sided significance threshold of 0.05.

Statistical Tests

All efficacy analyses were conducted in the intent-to-treat population, defined as all randomized patients regardless of whether the patient received any treatment or had any efficacy assessments collected. Supportive analyses of the primary and secondary end points were conducted using the treated population (defined as all randomized patients who received at least 1 dose of treatment) and the per-protocol population (defined as patients who were treated as randomized and who met all eligibility criteria and had no radiological evidence of pancreatic cancer before randomization by independent review).

The distribution of DFS was estimated using the Kaplan-Meier method, and DFS was compared between treatment arms using a stratified log-rank test, based on the stratification factors of resection status, lymph node status, and region. A stratified Cox proportional hazards model was conducted to estimate HRs and 95% CIs comparing nab-paclitaxel plus gemcitabine to gemcitabine monotherapy. Patients were censored if they received a new anticancer therapy or cancer-related surgery before disease recurrence or death, or at the end of the study for patients who were still alive. The same analyses were employed for OS and investigator-assessed DFS. The authors did not report if the proportional hazards assumption was tested before conducting the Cox proportional hazards analyses.

All safety analyses were conducted based on the treated population. The analyses were evaluated by the incidence of TEAEs, serious AEs, AEs of special interest, laboratory abnormalities, and other safety parameters during the treatment.

HRQoL was evaluated using the EORTC QLQ C-30 and QOL-PANC26 questionnaires, which were collected at screening, at cycle 4 day 1 before dosing, end-of-treatment, then on the same days when the CT or MRI was performed until disease recurrence. However, details for the HRQoL analysis were not provided in the current publication.

Statistical comparisons in APACT trial were not controlled for type I error. In addition, details regarding how missing data were managed in the statistical analysis were not reported. All statistical analyses were conducted using SAS v9.2 or higher.

Critical Appraisal

Internal Validity

Study Design, Intervention, and Comparators

The APACT trial was a randomized, multicentre, open-label trial comparing nab-paclitaxel plus gemcitabine to gemcitabine monotherapy. Patients received 6 cycles of study treatment, for approximately 6 months, unless discontinued early due to early evidence of radiologic disease recurrence, death, harms, patient or physician decision, or withdrawal of consent. After treatment, patients were followed until disease recurrence, new cancer therapy, or death, whichever came first, for up to 5 years. Safety data were monitored until 28 days after the last dose of study treatment.

The trial used an open-label design, which may have resulted in biased estimates for more subjective outcomes such as AEs and HRQoL. However, the primary end point of DFS was assessed by blinded, independent review, and as such, is less likely to have been impacted by detection bias. This is further emphasized by the difference seen in the primary DFS end point analysis compared to the sensitivity analysis that evaluated an unblinded assessment of DFS.

Selection, Allocation, and Disposition of Patients

Randomization was completed using a permuted-block random assignment method and interactive response technology. Overall, the baseline characteristics between the 2 treatment arms were balanced.

Details of the patient disposition were reported and are included in Table 7. More patients in the nab-paclitaxel plus gemcitabine group discontinued treatment compared with gemcitabine monotherapy group (33% versus 26%), mainly due to a higher incidence of AEs (16% versus 9%). During the randomization period, 3 and 11 patients in the nab-paclitaxel plus gemcitabine and gemcitabine monotherapy groups, respectively, were randomly assigned but did not undergo complete treatment due to protocol deviation (0 versus 2 patients), patient withdrawal (2 patients versus 9 patients), and AE (1 patient versus 0). The treated populations of the nab-paclitaxel plus gemcitabine and gemcitabine monotherapy groups were, therefore, 429 (99%) and 423 (97%), respectively.

Outcome Measures

The primary end point, independently assessed DFS, was determined by radiologists blinded to the treatment assignment. The authors of the trial justified their use of DFS as a valid and reliable measure of clinical benefit based on the results of phase III adjuvant clinical studies of resected high-risk colon cancer, and meta-analysis of clinical studies involving patients with non–small cell lung cancer, showing a high level of correlation between DFS and improvement in OS. However, whether DFS is a validated surrogate outcome for OS in this patient population is unclear.

AEs were coded using Medical Dictionary for Regulatory Activities version 21.0 and graded for intensity according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. However, reporting of subjective AEs like fatigue and asthenia may have been influenced by the awareness of treatment allocation. In addition, although it was reported in the protocol that HRQoL was to be evaluated in the APACT trial as an exploratory end point, the results of the HRQoL assessments were not reported in the publication.

Statistical Analysis

The statistical analyses of the primary end point used the intention-to-treat population; however, the authors did not describe how patients with missing data were included in the analysis. Another limitation is that a multiplicity adjustment was not applied to the statistical analysis; as such, the possibility of a type I error in the statistically significant difference in OS between the nab-paclitaxel plus gemcitabine group compared to the gemcitabine monotherapy group cannot be ruled out. The authors of the study acknowledged that, since the primary end point was not met, the results of other comparisons such as investigator-assessed DFS and OS are, therefore, considered descriptive. Lastly, the authors did not report whether the proportional hazards assumption was evaluated before conducting the Cox proportional hazards analyses. Based on the visual inspection of the Kaplan-Meier curves for DFS and OS, the proportional hazards assumption may have been violated. As such, it is unclear what the impact of the proportional hazards assumption violation would be on the reported HR and 95% CIs for DFS and OS.

External Validity

Patient Selection, Treatment Regimen, Length of Follow-Up, and Outcome Measures

The trial inclusion and exclusion criteria were clinically relevant and generalizable to patients in Canada given that the trial included 5 sites in Canada. The administration of nab-paclitaxel plus gemcitabine or gemcitabine alone was consistent with common practice, and the dose modifications were also reasonable based on tolerability. The duration of follow-up was adequate for the assessment of DFS and OS. Relevant harm outcomes such as neuropathy and neutropenia were reported. However, hospitalization data were not available.

Table 7: Patient Disposition

Patient disposition	APACT	
	Nab-paclitaxel + gemcitabine	Gemcitabine
Screened, N	1,226	
Randomized, N (%)	866 (70.6)	
Started, N	432	434
Treated, N	429	423
Completed, N	287	310
Randomly assigned but not treated, N	3	11
Discontinued treatment, n	142	113
Reason for discontinuation, n		
Adverse event	71	37
Patient withdrawal	36	27
Disease relapse	28	38
Physician decision	5	4
Death	1	3
Protocol deviation	0	1
Other	1	3
ITT, N	432	434
PP, N	400	403
Safety (treated population), N	429	423

ITT = intention to treat; PP = per-protocol.
Source: Tempero et al. 2023.[5]

Results

Patient Disposition

Among the 866 patients randomized into the study, 93% of each treatment arm completed the study (Table 7). More patients from the nab-paclitaxel plus gemcitabine group discontinued the study treatment (33% versus 26%) and experienced more AEs (16% versus 9%) compared with gemcitabine alone group. During the randomization period, 3 patients in the nab-paclitaxel plus gemcitabine group and 11 patients in the gemcitabine alone group were randomly assigned but were not treated due to the following reasons: protocol deviation (0 versus 2 patients), patient withdrawal (2 patients versus 9 patients), and adverse event (1 patient versus 0).

Baseline Characteristics

The baseline characteristics of the 2 treatment arms are listed in Table 8. They were generally balanced between the 2 arms, although 53% of patients in the nab-paclitaxel plus gemcitabine arm and 58% of patients in the gemcitabine monotherapy arm were male.

Table 8: Summary of Baseline Characteristics

Characteristic	Nab-paclitaxel + gemcitabine (n = 432)	Gemcitabine (n = 434)	Total (n = 866)
Age, years			
Median (range)	64.0 (34 to 83)	64.0 (38 to 86)	64.0 (34 to 86)
< 65, n (%)	221 (51)	225 (52)	446 (52)
≥ 65, n (%)	211 (49)	209 (48)	420 (48)
< 75, n (%)	382 (88)	399 (92)	781 (90)
≥ 75, n (%)	50 (12)	35 (8)	85 (10)
Sex, n (%)			
Female	204 (47)	181 (42)	385 (44)
Male	228 (53)	253 (58)	481 (56)
Race, n (%)			
White	333 (77)	339 (78)	672 (78)
Asian	60 (14)	56 (13)	116 (13)
Black or African American	4 (1)	8 (2)	12 (1)
Others	11 (3)	9 (2)	20 (2)
Not collected or reported	24 (3)	22 (5)	46 (5)
Region, n (%)			
North America	144 (33)	156 (36)	300 (35)
Europe	203 (47)	205 (47)	408 (47)
Australia	30 (7)	20 (5)	50 (6)
Asia Pacific	55 (13)	53 (12)	108 (12)
ECOG PS, n (%)			
0	252 (58)	268 (62)	520 (60)
1	180 (42)	166 (38)	346 (40)
Distance from tumour to the closest margin, mm, n (%)			
< 1	114 (26)	112 (26)	226 (26)
≥ 1	287 (66)	292 (67)	579 (67)
Missing	31 (7)	30 (7)	61 (7)

Characteristic	Nab-paclitaxel + gemcitabine (n = 432)	Gemcitabine (n = 434)	Total (n = 866)
Pancreatic cancer primary location, n (%)			
Head	354 (82)	347 (80)	701 (81)
Body	53 (12)	55 (13)	108 (12)
Tail	50 (12)	62 (14)	112 (13)
TNM classification, n (%)			
T category			
T1	16 (4)	13 (3)	29 (3)
T2	38 (9)	37 (9)	75 (9)
T3	377 (87)	384 (88)	761 (88)
T4	1 (< 1)	0	1 (< 1)
N category			
N0	121 (28)	122 (28)	243 (28)
N1	311 (72)	312 (72)	623 (72)
M category			
M0	432 (100)	433 (> 99)	865 (> 99)
M1	0	1 (< 1)	1 (< 1)
Resection status, n (%)			
R0 (tumour-free margin)	327 (76)	334 (77)	661 (76)
R1 (microscopically positive margin)	105 (24)	100 (23)	205 (24)
Tumour grade, n (%)			
Well differentiated	49 (11)	55 (13)	104 (12)
Moderately differentiated	264 (61)	241 (56)	505 (58)
Poorly differentiated	101 (23)	115 (26)	216 (25)
Undifferentiated	1 (< 1)	2 (< 1)	3 (< 1)
Unknown	9 (2)	5 (1)	14 (2)
Others	8 (2)	16 (4)	24 (3)
CA19 to 9			
n	423	429	852
U/mL, median (IQR)	14.3 (6.9 to 27.4)	12.9 (5.9 to 27.6)	13.6 (6.3 to 27.5)
Level of CA19 to 9, n (%)			
WNL	351 (81)	345 (80)	696 (80)
ULN < 100 U/mL	70 (16)	81 (19)	151 (17)
ULN ≥ 100 U/mL	2 (< 1)	3 (1)	5 (1)

Characteristic	Nab-paclitaxel + gemcitabine (n = 432)	Gemcitabine (n = 434)	Total (n = 866)
Missing	9 (2)	5 (1)	14 (2)

CA19 to 9 = carbohydrate antigen 19 to 9; ECOG PS = Eastern Cooperative Oncology Group performance status; IQR = interquartile range; M = metastasis; N = node; R = resection; T = tumour; ULN = upper limit of normal; WNL = within normal limits.

Source: Tempero et al. 2023.[5]

Exposure to Study Treatments

Patients from both treatment arms had a similar median of duration of treatment (24.0 weeks) and same median number of cycles administered (6.0). More patients from the nab-paclitaxel plus gemcitabine group experienced dose delays (52.4% versus 33.6%) and dose omission (54.5% versus 35.0%) of gemcitabine, when compared to the gemcitabine alone group. Refer to Table 9.

Table 9: Treatment Exposure

Exposure	APACT	
	Nab-paclitaxel + gemcitabine (n = 429)	Gemcitabine (n = 423)
Duration of treatment, median (IQR), weeks	24.0 (19.0 to 24.9)	24.0 (21.1 to 24.1)
Number of cycles administered, median (range)	6.0 (1 to 6)	6.0 (1 to 6)
Percentage of protocol dose, median (range), %		
Nab-paclitaxel	75.11 (11.1 to 186.7)	NA
Gemcitabine	80.00 (11.1 to 186.7)	91.16 (43.1 to 200.0)
Patients with 1 or more dose reduction, n (%)		
Nab-paclitaxel	273 (63.6)	NA
Adverse event	273 (100.0)	NA
Per-protocol	2 (0.7)	NA
Other	3 (1.1)	NA
Gemcitabine	266 (62.0)	213 (50.4)
Adverse event	265 (99.6)	207 (97.2)
Per-protocol	2 (0.8)	1 (0.5)
Other	3 (1.1)	6 (2.8)
Patients with 1 or more dose delay, n (%)		
Nab-paclitaxel	218 (50.8)	NA
Gemcitabine	225 (52.4)	142 (33.6)
Patients with 1 or more dose omission, n (%)		

Exposure	APACT	
	Nab-paclitaxel + gemcitabine (n = 429)	Gemcitabine (n = 423)
Nab-paclitaxel	268 (62.5)	NA
Gemcitabine	234 (54.5)	148 (35.0)

IQR = interquartile range; NA = not applicable.
Source: Tempero et al. 2023.[5]

Efficacy

Only the efficacy outcomes identified in the review protocol are reported below. Refer to Table 10.

The median follow-up was 38.5 months (interquartile range [IQR], 33.8 to 43 months) for the primary data cut-off (December 31, 2018). At the 16-month follow-up OS analysis (cut-off: April 3, 2020), the median follow-up for survival was 51.4 months (IQR, 47.0 to 57.0 months) based on 511 events.

Disease-Free Survival

Blinded, Independently Assessed DFS

A total of 439 patients (51.0%) had progressed or died at the primary data cut-off. The median independently assessed DFS was 19.4 months (95% CI, 16.62 to 21.91) in the nab-paclitaxel plus gemcitabine group versus 18.8 months (95% CI, 13.83 to 20.30) in the gemcitabine monotherapy group (HR = 0.88; 95% CI, 0.729 to 1.063; P = 0.18).

Unblinded, Investigator-Assessed DFS

For the sensitivity analysis of investigator-assessed DFS, 571 of all treated patients (66.0%) had disease progression or died at the primary data cut-off. The median investigator-assessed DFS was 16.6 months (95% CI, 14.55 to 19.29) in the nab-paclitaxel plus gemcitabine group versus 13.7 months (95% CI, 11.24 to 16.00) in the gemcitabine monotherapy group (HR = 0.82; 95% CI, 0.694 to 0.965; P = 0.02).

The concordance between independent and investigator-assessed DFS was 77.0% (nab-paclitaxel plus gemcitabine, 78%; gemcitabine, 76%).

Overall Survival

At primary data cut-off, the OS data were 68% mature with 427 of 630 target events. A total of 207 patients (48%) in the nab-paclitaxel plus gemcitabine treatment arm and 220 patients (51%) in the gemcitabine treatment arm had died. The median OS was 40.5 months (IQR, 20.7 to not estimable) with nab-paclitaxel plus gemcitabine compared with 36.2 months (IQR, 17.7 to 53.3) with gemcitabine (HR = 0.82; 95% CI, 0.680 to 0.996; P = 0.045).

At the 16-month follow-up (April 3, 2020) with a median follow-up for survival of 51.4 months (IQR, 47.0 to 57.0) based on 511 events (81% mature), 246 patients (57%) from the nab-paclitaxel plus gemcitabine group versus 265 (61%) from the gemcitabine group had died. The median OS was 41.8 months (95% CI, 35.55 to 47.28) with nab-paclitaxel plus gemcitabine versus 37.7 months with gemcitabine (HR = 0.82; 95% CI, 0.687 to 0.973; P = 0.023).

At the 5-year follow-up (April 9, 2021, 88% mature), the median follow-up for survival was 63.2 months (IQR, 60.1 to 68.7) based on a total of 268 (62%) and 287 (66%) deaths in the nab-paclitaxel plus gemcitabine group and gemcitabine monotherapy group respectively. The median OS with nab-paclitaxel plus gemcitabine was 41.8 months compared with 37.7 months with gemcitabine group (HR = 0.80; 95% CI, 0.678 to 0.947; P = 0.0091). The OS rates for 5 years or greater were 38% in the nab-paclitaxel plus gemcitabine group and 31% in the gemcitabine group.

HRQoL

HRQoL was not reported in this study.

Table 10: Outcomes From the APACT Trial

Outcome	Nab-paclitaxel + gemcitabine N = 432	Gemcitabine N = 434
Efficacy		
Blinded, independently assessed DFS (at the primary data cut-off)		
n (%)	226 (52.3)	213 (49.1)
Median DFS, months	19.4	18.8
HR (95% CI)	0.88 (0.729 to 1.063)	
P value	P = 0.1824	
Unblinded, investigator-assessed DFS		
n (%)	282 (65.3)	289 (66.6)
Median DFS, months	16.6	13.7
HR (95% CI)	0.82 (0.694 to 0.965)	
P value	P = 0.0168[a]	
OS (at the primary data cut-off)		
Death, n (%)	206 (47.7)	221 (50.9)
Median OS, months	40.5	36.2
HR (95% CI)	0.82 (0.680 to 0.996)	
P value	P = 0.045[a]	
OS (at the 16-month follow-up)		
Death, n (%)	248 (57.4)	263 (60.6)
Median OS, months	41.8	37.7
HR (95% CI)	0.82 (0.687 to 0.973)	
P value	P = 0.0232[a]	
OS (at the 5-year follow-up)		
Death, n (%)	268 (62.0)	287 (66.1)
Median OS, months	41.8	37.7

Outcome	Nab-paclitaxel + gemcitabine N = 432	Gemcitabine N = 434
HR (95% CI)	0.80 (0.678 to 0.947)	
P value	P = 0.0091[a]	

CI = confidence interval; DFS = disease-free survival; HR = hazard ratio; OS = overall survival.

[a]Comparisons were not adjusted for type I error.

Source: Tempero et al. 2023.[5]

Harms

Only those harms identified in the review protocol are reported below. Refer to Table 11 for detailed harms data.

Table 11: Summary of Harms

Outcomes	APACT Nab-paclitaxel + gemcitabine N = 429	APACT Gemcitabine N = 423
≥ Grade 1 TEAE, n (%)	429 (100)	423 (99)
≥ Grade 3 TEAE, n (%)	371 (86)	286 (68)
Hematologic		
Neutropenia, n (%)	212 (49)	184 (43)
Anemia, n (%)	63 (15)	33 (8)
Leukopenia, n (%)	36 (8)	20 (5)
Febrile neutropenia, n (%)	21 (5)	4 (1)
Nonhematologic		
Peripheral neuropathy (SMQ)	64 (15)	0
Fatigue, n (%)	43 (10)	13 (3)
Asthenia, n (%)	21 (5)	8 (2)
Diarrhea, n (%)	22 (5)	4 (1)
Hypotension, n (%)	17 (4)	27 (6)

SMQ = Standardized Medical Dictionary for Regulatory Activities Queries; TEAE = treatment-emergent adverse event.

Source: Tempero et al. 2023.[5]

Adverse Events

- Based on the TEAE data reported from the primary analysis (cut-off: December 31, 2018), all treated patients in the nab-paclitaxel plus gemcitabine arm and 99% of patients in the gemcitabine arm had 1 or more TEAE. Grade 3 or higher TEAEs were reported in 86% of patients from the nab-paclitaxel plus

gemcitabine group and 68% of patients from the gemcitabine monotherapy group. Further, at least 1 serious TEAE occurred in 41% and 23% of patients in each group, respectively.

- In the nab-paclitaxel plus gemcitabine group, 27% of patients discontinued nab-paclitaxel and 17% of patients discontinued gemcitabine because of TEAEs, versus 10% of patients who discontinued gemcitabine in the gemcitabine group.
- Two patients (< 1%) died in each arm because of TEAEs. In the nab-paclitaxel plus gemcitabine group, the patients died from pneumonia (n = 1) and sepsis (n = 1). In the gemcitabine group, the patients died from drug-induced liver injury with hepatic failure (n = 1) and capillary leak syndrome (n = 1).

Notable Harms

The notable harms identified in the review were peripheral neuropathy, febrile neutropenia, and hospitalization. In this study, peripheral neuropathy was reported in 64 patients (15%) in the nab-paclitaxel plus gemcitabine group and none in the gemcitabine group. Febrile neutropenia was reported in 21 patients (5%) in the nab-paclitaxel plus gemcitabine group and 4 patients (1%) in the gemcitabine group. Hospitalization was not a reported harm in this study. Refer to Table 11.

Indirect Evidence

No indirect treatment comparisons were identified for this review.

Other Relevant Evidence

No long-term extension study, or additional relevant study was identified that addressed important gaps in the evidence.

Economic Evidence

The economic review consisted of a cost comparison between nab-paclitaxel plus gemcitabine and appropriate comparators for adjuvant treatment of patients with resected pancreatic cancer.

CADTH Analyses

The comparators presented in Table 12 have been deemed to be appropriate based on feedback from clinical experts and drug plans. Recommended doses were based on each product's respective product monographs unless otherwise indicated and validated by clinical experts. Dosing for nab-paclitaxel plus gemcitabine was sourced from the APACT trial.[5] If discrepancies in dosing between the product monograph and Canadian clinical practice were noted, the dose specified by clinical experts was used. Pricing for comparator products was based on publicly available list prices.

Clinical expert feedback obtained by CADTH indicated that there are 3 distinct comparators: mFOLFIRINOX, capecitabine plus gemcitabine, and gemcitabine alone. Results of the cost comparison demonstrate that, over a 28-day cycle, nab-paclitaxel with gemcitabine is more costly than all comparators. Note that results may differ by jurisdiction if there are differences in their list prices for the drugs under review compared to those presented in Table 12.

Issues for Consideration

- **Generic nab-paclitaxel may be available:** According to the Health Canada Drug Product Database, a generic version of nab-paclitaxel imported by Apotex Inc. is also marketed in Canada in 100 mg vials. No pricing or claims data were available through IQVIA DeltaPA or Pharmastat for this product at the time of this review (as of June 10, 2024).[20,23] If this product is available at a lower cost than Abraxane-brand nab-paclitaxel, then the cost of treatment with nab-paclitaxel may be lower than estimated. If the generic price of nab-paclitaxel is 55% of the reference brand within 3 months after market entry of a single source generic, consistent with the pan-Canadian Pharmaceutical Alliance (pCPA) pan-Canadian Tiered Pricing Framework,[24] then the standardized 28-day drug acquisition cost of nab-paclitaxel would be $2,949 per patient, while the drug acquisition cost of the nab-paclitaxel with gemcitabine regimen would be $4,407 per patient. At these costs, nab-paclitaxel with gemcitabine would continue to be more expensive than all comparators.

Table 12: CADTH Cost Comparison Table for Adjuvant Therapy for Patients With Advanced Pancreatic Cancer

Treatment	Strength/ concentration	Form	Price ($)	Recommended dosage	Daily cost ($)	Average 28-day cost ($)
Nab-paclitaxel (Abraxane)	2 mg/mL	50 mL vial	971.0000	125 mg/m^2 on days 1, 8, and 15 of every 28-day cycle[a]	234.08	6,554
Gemcitabine (generic)	1,000 mg 2,000 mg	Lyophilized powder for injection	270.0000 540.0000	1,000 mg/m^2 on days 1, 8, and 15 of every 28-day cycle[a]	52.07	1,458
Nab-paclitaxel plus gemcitabine					**286.15**	**8,012**
mFOLFIRINOX						
Oxaliplatin (generic)	5 mg/mL	10 mL vial 20 mL vial 40 mL vial	45.0000 90.0000 180.0000	85 mg/m^2 every 2 weeks	9.84	275
Irinotecan (generic)	20 mg/mL	2 mL vial 5 mL vial 25 mL vial	208.3400 520.8500 2,604.2500	150 mg/m^2 every 2 weeks	100.45	2,813
Folinic acid (leucovorin)	10 mg/mL	5 mL vial 50 mL vial	68.9430[b] 350.1900	400 mg/m^2 every 2 weeks	26.58	744
Fluorouracil bolus	50 mg/mL	100 mL vial	160.9000	400 mg/m^2 every 2 weeks	11.58	324
Fluorouracil infusion	50 mg/mL	100 mL vial	160.9000	2,400 mg/m^2 every 2 weeks		
mFOLFIRINOX					**148.45**	**4,156**
Capecitabine plus gemcitabine						
Gemcitabine (generic)	1,000 mg 2,000 mg	Lyophilized powder for injection	270.0000 540.0000	1,000 mg/m^2 on days 1, 8, and 15 every 28 days	52.07	1,458

Treatment	Strength/ concentration	Form	Price ($)	Recommended dosage	Daily cost ($)	Average 28-day cost ($)
Capecitabine (Xeloda)	150 mg 500 mg	Tab	0.4575[c] 1.5250[c]	830 mg/m^2 twice daily from days 1 to 21	6.86	192
Capecitabine plus gemcitabine					**58.93**	**1,650**
Gemcitabine alone						
Gemcitabine (generic)	1,000 mg 2,000 mg	Lyophilized powder for injection	270.0000 540.0000	1,000 mg/m^2 on days 1, 8, and 15 of every 28-day cycle	52.07	1,458

mFOLFIRINOX = modified leucovorin (folinic acid), fluorouracil, irinotecan, and oxaliplatin.

All dosing from the Cancer Care Ontario formulary, unless otherwise specified.[19] All prices are from the IQVIA Delta PA (accessed May 2024)[20] unless otherwise indicated and do not include dispensing fees. Patients are assumed to have a body surface area of 1.8m^2. Treatment is assumed to occur in specialized cancer centres and thus no wastage is included.

[a]Source: APACT trial.[5]

[b]Alberta Health Care Insurance Plan (accessed May 2024).[21]

[c]Ontario Drug Benefit Formulary (accessed May 2024).[22]

- **Health care resource use:** Relative to gemcitabine therapy alone, clinical expert input indicated that nab-paclitaxel plus gemcitabine is anticipated to increase monitoring costs due to greater chair time required when patients are treated with nab-paclitaxel plus gemcitabine. Additionally, clinical expert feedback indicated that there would be no anticipated differences in hospitalizations, outpatient visits, and disease management and health care utilization costs between nab-paclitaxel plus gemcitabine and gemcitabine alone.
- **Limited cost-effectiveness information:** No cost-effectiveness studies conducted in Canada were identified based on a literature search conducted on June 10, 2024. One cost-effectiveness study conducted in the US that compared FOLFIRINOX versus nab-paclitaxel plus gemcitabine for the adjuvant treatment for resected pancreatic cancer was identified.[25] The study concluded that FOLFIRINOX was more effective and more costly than nab-paclitaxel plus gemcitabine. Notably, this conclusion was drawn from a naive comparison of FOLFIRINOX versus nab-paclitaxel plus gemcitabine.

Discussion

Summary of Available Evidence

The main evidence base for this review was the APACT trial, a phase III, multicentre, open-label, randomized study conducted at 160 sites across 21 countries. Nab-paclitaxel plus gemcitabine (n = 432) was compared to gemcitabine alone (n = 434), in patients with resected PDAC. All patients received 6 treatment cycles unless there was radiologic evidence of disease recurrence or unacceptable harms. The median treatment duration was 24 weeks for each arm.

The primary end point was independently assessed DFS. Other end points included OS and safety, and investigator-assessed DFS, which was reported as a sensitivity analysis. Of the randomized patients, 90% were aged 75 years or younger; 48% of randomized patients were aged 65 years or younger. The proportions

of male versus female patients were 56% versus 44%, respectively. The distributions by race were 78% white, 13% Asian, 1% Black or African American, 2% others, and 5% not collected or reported. An ECOG PS of 0 was reported by 60% of patients, and 40% of patients reported an ECOG PS of 1.

Interpretation of Results

Efficacy

In the APACT study, 287 of 432 patients completed 6 treatment cycles with nab-paclitaxel plus gemcitabine, while 310 of 434 patients completed 6 treatment cycles with gemcitabine.

At the primary data cut-off on December 31, 2018, the median follow-up was 38.5 months (IQR, 33.8 to 43). The median blinded, independently assessed DFS was 19.4 months for the nab-paclitaxel plus gemcitabine group versus 18.8 months for the gemcitabine group, translating to an HR of 0.88 (95% CI, 0.729 to 1.063, P = 0.18). Thus, the primary end point was not met.

The median unblinded, investigator-assessed DFS was 16.6 months (95% CI, 14.55 to 19.29) in the nab-paclitaxel plus gemcitabine treatment group versus 13.7 months (95% CI, 11.24 to 16.00) in the gemcitabine monotherapy group (HR = 0.82, 95% CI, 0.694 to 0.965, P = 0.02). This comparison is limited by the lack of type I error control.

At the 5-year follow-up, the median OS based on 555 events was 41.8 months for the nab-paclitaxel plus gemcitabine group versus 37.7 months for the gemcitabine group, translating to an HR of 0.80 (95% CI, 0.678 to 0.947; P = 0.0091). However, this comparison is limited by the lack of type I error control.

Limitations of the APACT trial included lack of control for type I error and the lack of reporting of the HRQoL results.

Harms

- All treated patients in the nab-paclitaxel plus gemcitabine arm and 99% of patients in the gemcitabine arm had 1 or more TEAE. Grade 3 or higher TEAEs were reported in 86% of patients from the nab-paclitaxel plus gemcitabine group and 68% of patients from the gemcitabine group. Further, at least 1 serious TEAE occurred in 41% and 23% of patients, respectively.
- In the nab-paclitaxel plus gemcitabine group, 27% of patients discontinued nab-paclitaxel and 17% of patients discontinued gemcitabine because of TEAEs, whereas 10% of patients discontinued gemcitabine from the gemcitabine group.
- Two patients (< 1%) died in each arm because of TEAEs. In the nab-paclitaxel plus gemcitabine group, patients died from pneumonia (n = 1) and sepsis (n = 1). In the gemcitabine group, patients died from drug-induced liver injury with hepatic failure (n = 1) and capillary leak syndrome (n = 1).

Based on the reported harm outcomes, the nab-paclitaxel plus gemcitabine group had higher incidence of neuropathy (15% versus 0%) and febrile neutropenia (5% versus 1%) when compared with the gemcitabine group.

Cost

- Based on publicly available list prices, nab-paclitaxel plus gemcitabine is expected to have a 28-day per patient cost of $8,012 when used as dosed in the APACT clinical trial.[5] As the current standard-of-care adjuvant treatment for patients with resected pancreatic cancer consists of gemcitabine monotherapy, mFOLFIRINOX, and capecitabine plus gemcitabine, this review compared the cost of these regimens with nab-paclitaxel plus gemcitabine. The 28-day per patient cost of mFOLFIRINOX, capecitabine plus gemcitabine, and gemcitabine monotherapy was $4,156, $1,650, and $1,458, respectively.
- When comparing nab-paclitaxel plus gemcitabine to mFOLFIRINOX, nab-paclitaxel plus gemcitabine results in per patient incremental costs of $3,856. When comparing nab-paclitaxel plus gemcitabine to capecitabine plus gemcitabine, nab-paclitaxel plus gemcitabine results in per patient incremental costs of $6,362. Lastly, when comparing nab-paclitaxel plus gemcitabine to gemcitabine monotherapy, nab-paclitaxel plus gemcitabine results in per patient incremental costs of $6,554. Costs are based on publicly available list prices and may not reflect actual prices paid by Canadian public drug plans.

Conclusions

In the APACT trial, for the primary end point of independently assessed DFS, the median was 19.4 months in the nab-paclitaxel plus gemcitabine arm and 18.8 months in the gemcitabine monotherapy arm (HR = 0.88; 95% CI, 0.729 to 1.063; P = 0.18). In addition, the combination treatment was associated with a higher incidence of TEAEs including peripheral neuropathy and febrile neutropenia, and patients in this group were more likely to discontinue treatment due to AEs compared to those in the gemcitabine group. Although the OS comparisons between the 2 treatment arms suggested a numerically longer OS with nab-paclitaxel plus gemcitabine compared with gemcitabine monotherapy, the comparisons were not controlled for type I error. As such, it is unclear whether the differences seen in OS were due to a true difference between nab-paclitaxel plus gemcitabine compared to gemcitabine alone or due a to type I error.

Results of the cost comparison of drug acquisition costs demonstrate that — when compared to mFOLFIRINOX, capecitabine plus gemcitabine, and gemcitabine monotherapy — nab-paclitaxel plus gemcitabine is expected to increase treatment costs (incremental costs: $3,856, $6,362, and $6,554, per patient, per 28 days, respectively). Based on the clinical review conclusions, nab-paclitaxel plus gemcitabine was associated with a higher incidence of TEAEs and an uncertain OS benefit compared with gemcitabine monotherapy. No RCTs were identified comparing nab-paclitaxel plus gemcitabine with either mFOLFIRINOX or capecitabine plus gemcitabine; therefore, the comparative efficacy of these treatments is unknown. As such, nab-paclitaxel plus gemcitabine is associated with incremental treatment costs and uncertain clinical impact. Costs associated with AEs and administration costs were not considered in this cost comparison. However, clinical expert input indicated that nab-paclitaxel plus gemcitabine is anticipated to increase monitoring costs because more chair time required for patients to receive this treatment.

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Appendix 1: Literature Search Strategy

Note that this appendix has not been copy-edited.

Clinical Literature Search

Overview

Interface: Ovid

Databases:

- MEDLINE All (1946-present)
- Embase (1974-present)
- Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: March 01, 2024

Alerts: Bi-weekly search updates until project completion

Search filters applied: No filters were applied to limit the retrieval by study type.

Limits:

- Publication date limit: 1996-present
- Humans
- Language limit: English- and French-language
- Conference abstracts: excluded

Table 14: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary

Syntax	Description
.kf	Keyword heading word
.dq	Candidate term word (Embase)
.rn	Registry number
.nm	Name of substance word (MEDLINE)

MEDLINE Database Strategy

1. ("gemcitabine/nabpaclitaxel" or "nabpaclitaxel/gemcitabine" or "gemcitabine/nab paclitaxel" or "nab paclitaxel/gemcitabine" or "Gem + nab ptx" or "gem + nabptx" or "gem+nabptx" or GnP or GmAb).ti,ab,kf,ot,hw,rn,nm.
2. Gemcitabine/
3. (gemcitabin* or gemzar* or infugem* or LY188011 or LY 188011 or NSC613327 or NSC 613327 or B76N6SBZ8R).ti,ab,kf,ot,rn,nm.
4. or/2-3
5. Albumin-bound paclitaxel/
6. ((nab or nabs) adj2 paclitaxel*).ti,ab,kf,ot,rn,nm.
7. Nabpaclitaxel*.ti,ab,kf,ot,rn,nm.
8. Abraxane*.ti,ab,kf,ot,rn,nm.
9. (abi-007 or abi007 or QY511JBA21).ti,ab,kf,ot,rn,nm.
10. (paclitaxel* adj2 (protein or albumin or nanoparticle* or nano particle* or nanodeliver* or nano deliver*)).ti,ab,kf,ot,rn,nm.
11. or/5-10
12. exp Pancreatic neoplasms/
13. (pancrea* adj3 (carcin* or cancer* or neoplas* or tumor* or tumour* or growth* or adenocarcin* or malig*)).ti,ab,kf.
14. or/12-13
15. exp Chemotherapy, Adjuvant/
16. adjuvant*.hw.
17. adjuvant*.ti,ab,kf.
18. or/15-17
19. 1 and 14 and 18
20. 4 and 11 and 14 and 18
21. 19 or 20

Embase Database Strategy

1. *gemcitabine plus paclitaxel/

2. ("gemcitabine/nabpaclitaxel" or "nabpaclitaxel/gemcitabine" or "gemcitabine/nab paclitaxel" or "nab paclitaxel/gemcitabine" or "Gem + nab ptx" or "gem + nabptx" or "gem+nabptx" or GnP or GmAb).ti,ab,kf,dq.
3. or/1-2
4. *Gemcitabine/
5. (gemcitabin* or gemzar* or infugem* or LY188011 or LY 188011 or NSC613327 or NSC 613327).ti,ab,kf,dq.
6. or/4-5
7. *Paclitaxel/ and (protein or albumin or nanoparticle* or nano particle* or nanodeliver* or nano deliver*).ti,ab,kf,dq.
8. ((nab or nabs) adj2 paclitaxel*).ti,ab,kf,dq.
9. Nabpaclitaxel*.ti,ab,kf,dq.
10. Abraxane*.ti,ab,kf,dq.
11. (abi-007 or abi007).ti,ab,kf,dq.
12. (paclitaxel* adj2 (protein or albumin or nanoparticle* or nano particle* or nanodeliver* or nano deliver*)).ti,ab,kf,dq.
13. or/7-12
14. exp pancreas tumor/ or pancreatobiliary cancer/
15. (pancrea* adj3 (carcin* or cancer* or neoplas* or tumor* or tumour* or growth* or adenocarcin* or malig*)).ti,ab,kf,dq.
16. or/14-15
17. exp adjuvant therapy/
18. adjuvant*.hw.
19. adjuvant*.ti,ab,kf,dq.
20. or/17-18
21. 3 and 16 and 20
22. 6 and 13 and 16 and 20
23. 21 or 22
24. 23 not (conference abstract or conference review).pt.

Clinical Trials Registries

ClinicalTrials.gov

Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials.

[Search -- Studies with results | gemcitabine AND nab-paclitaxel AND (adjuvant OR resectable) AND Pancreas Cancer]

WHO ICTRP

International Clinical Trials Registry Platform, produced by WHO. Targeted search used to capture registered clinical trials.

[Search terms -- gemcitabine AND nab-paclitaxel AND (adjuvant OR resectable) AND pancreas*]

Health Canada's Clinical Trials Database

Produced by Health Canada. Targeted search used to capture registered clinical trials.

[Search terms -- nab-paclitaxel]

EU Clinical Trials Register

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms -- gemcitabine AND nab-paclitaxel AND pancreas AND adjuvant]

EU Clinical Trials Information System (CTIS)

European Union Clinical Trials Information System, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms -- (gemcitabine AND nab-paclitaxel AND adjuvant) AND (pancreas OR pancreatic)]

Grey Literature

Search dates: March 13, 2024 – March 25, 2024

Keywords: gemcitabine, nab-paclitaxel, adjuvant therapy, respectable, preventative therapy, pancreatic cancer

Limits: Publication years: no date limit

Relevant websites from the following sections of the CADTH grey literature checklist Grey Matters: A Practical Tool for Searching Health-Related Grey Literature were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trials Registries
- Databases (free)

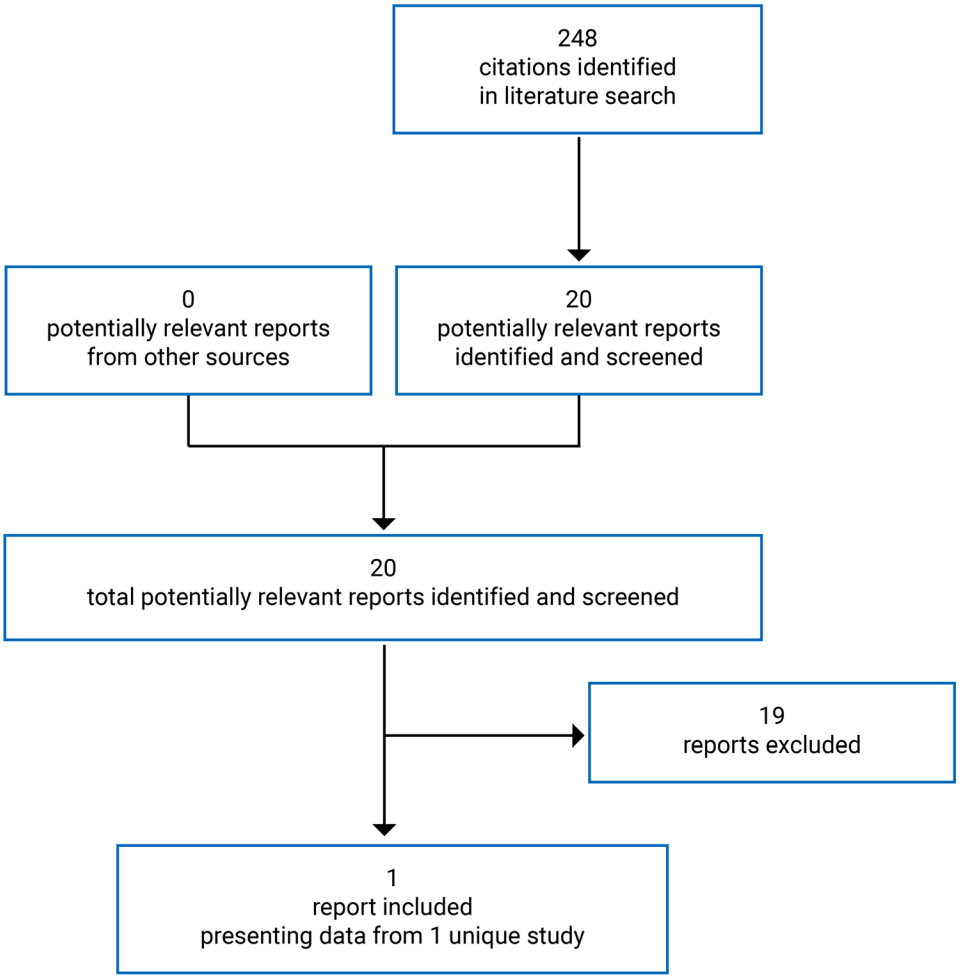
- Internet Search

Appendix 2: Study Selection

Findings From the Literature

A total of 248 studies were identified from the literature for inclusion in the systematic review (Figure 1).

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies



Appendix 3: List of Excluded Studies

Note that this appendix has not been copy-edited.

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