PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Nab-Paclitaxel (Abraxane) for Pancreatic Cancer

September 23, 2014

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INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
1 University Avenue, suite 300
Toronto, ON
M5J 2P1

Telephone: 416-673-8381
Fax: 416-915-9224
Email: info@pcodr.ca
Website: www.pcodr.ca

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1 GUIDANCE IN BRIEF

1.1 Background

Nab-paclitaxel is an albumin bound formulation of paclitaxel, a member of the taxane class of chemotherapy drugs that causes mitotic arrest in cancer cells by disrupting microtubule function. Nab-paclitaxel has a Health Canada indication for the first-line treatment of metastatic adenocarcinoma of the pancreas, in combination with gemcitabine[1].

The purpose of this review is to evaluate the safety and efficacy of nab-paclitaxel (Abraxane) in combination with gemcitabine as compared to an appropriate comparator for the first line treatment of patients with locally advanced unresectable or metastatic adenocarcinoma of the pancreas. The scope of the pCODR review included patients with locally advanced unresectable disease to account for potential clinical use of nab-paclitaxel in this population.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one open-label randomised controlled trial, MPACT[2] comparing the use of nab-paclitaxel plus gemcitabine (n=431) to gemcitabine alone (n=430) in patients with previously untreated metastatic adenocarcinoma of the pancreas.

Baseline patient characteristics were balanced between groups. In addition, patients entered into the study had a Karnofsky PS score of 100 (16% vs. 16%), 90 (42% vs. 46%), 80 (35% vs. 30%) or 70 (7% vs. 8%) and had metastasis in the liver (85% vs. 84%) or lungs (35% vs. 43%), in the nab-paclitaxel plus gemcitabine vs. gemcitabine arms respectively. Patients were stratified based on performance status, presence or absence of liver metastases and geographic region.

Patients were excluded from the study if they had islet-cell neoplasms, locally advanced disease or if they had prior treatment with cytotoxic doses of gemcitabine or any other chemotherapy in the adjuvant setting.

Efficacy

The primary outcome of the MPACT study was overall survival (OS) with progression free survival (PFS) and overall response rate (ORR) as secondary outcomes.

The study reported statistically significant improvement for the primary outcome of overall survival in favour of the nab-paclitaxel plus gemcitabine arm at the final analysis (8.5 vs. 6.7 months, HR 0.72 95%CI 0.62 to 0.83 p<0.001) and was similar in an updated analysis[3]. One (35 vs. 22% respectively, p< 0.001) and two (9% vs. 4% respectively, p=0.02) year overall survival of patients was also significantly more in the nab-paclitaxel plus gemcitabine vs. gemcitabine arms.[2]

Statistically significant longer independently assessed PFS (5.5 vs. 3.7 months, HR 0.69 95%CI 0.58 to 0.82 p<0.001) and ORR (23% vs 7% of patients achieving objective response) were also reported for patients receiving nab-paclitaxel plus gemcitabine compared to gemcitabine alone, respectively.[2]

Analysis of all major outcomes in the pre-specified subgroups indicated that treatment effect was consistently favoured for nab-paclitaxel plus gemcitabine across most subgroups.

Quality of life was not measured in the study.

Harms

A similar number of deaths were reported in both arms, with 4% in each arm. Among these, 9 deaths were attributed to treatment with 7 (2%) vs. 2 (<1%) being in the nab-paclitaxel plus gemcitabine vs. gemcitabine arms, respectively.[4] Patients in the nab-paclitaxel plus gemcitabine arm experienced more grade 3 or higher treatment emergent adverse events (TEAE) and all grades TEAE's (Table 7). The most frequently occurring (≥10%) grade 3 or higher TEAE in the nab-paclitaxel plus gemcitabine vs. gemcitabine arm were neutropenia, fatigue, peripheral neuropathy, thrombocytopenia and anemia.

1.2.2 Additional Evidence

pCODR received input on nab-paclitaxel (abraxane) for metastatic adenocarcinoma of the pancreas cancer from two patient advocacy groups, Pancreatic Cancer Canada (PCC) and Craig's Cause Pancreatic Cancer Society (Craig's Cause). Provincial Advisory group input was obtained from eight of the nine provinces participating in pCODR.

In addition, one supplemental question was identified during development of the review protocol as relevant to the pCODR review of nab-paclitaxel and is discussed as supporting information:

- Critical appraisal of an indirect comparison of nab-paclitaxel plus gemcitabine with FOLFIRINOX[5].

1.2.3 Interpretation and Guidance

Burden of Illness and need

Pancreatic cancer is the 4th leading cause of cancer death amongst both men and women, after lung, colorectal and prostate cancer in men and lung, breast and colorectal cancer in women. In 2013, it is estimated that 4700 new patients will be diagnosed with the disease and 4300 will die.[6] This symptomatic burden of disease (pain, nausea and vomiting, anorexia/cachexia and general functional decline), experienced by the vast majority of patients with metastatic disease, requires expert management and multiple medical interventions to optimize symptom control.

The vast majority of patients will present with locally advanced (20-30%) or metastatic disease (~50%) at presentation.[7,8] Patients with advanced pancreatic adenocarcinoma are typically ill and require maximal symptomatic and supportive care to control symptoms and stabilize/improve quality of life. Internationally, the standard of care for patients has been the use of gemcitabine. More recently a complex regimen called FOLFIRINOX has been compared to single agent GEM and observed an improvement in objective response rates, progression free survival and overall survival. The majority of patients are however not expected to be able to tolerate first line FOLFIRINOX.

In summary, there remains a considerable unmet need for more effective and tolerable systemic therapies in the treatment of advanced pancreatic adenocarcinoma.

Effectiveness

Both the initial and final analysis, as well as the updated analysis with more event rates, observed a statistically significant OS advantage for the combination arm. One year overall survival of patients was also significantly more in the nab-paclitaxel plus gemcitabine vs.

gemcitabine arms. A statistically significant improvement in PFS as well as objective response rate was also observed favoring the nab-Paclitaxel plus gemcitabine treatment arm. Subgroup analysis observed a favorable treatment effect of the combination therapy in all pre-specified patient subgroups.

The observation of a 2 month improvement in median overall survival coupled with a tripling of ORR and a 13% improvement in 1 year survival represents a group of clinically meaningful outcomes for patients suffering from metastatic pancreatic cancer.

Thus the consistency of the observations across all major primary and secondary endpoints along with the independent confirmation of ORR and PFS strongly supports nab-paclitaxel plus gemcitabine as being an improvement in the therapeutic options available for the palliative treatment of metastatic pancreatic cancer.

Although there was no formal collection of quality of life data in the MPACT trial, information from the patient advocacy input suggests that the major endpoints evaluated in MPACT are clinically meaningful and highly relevant for the target patient population. Based on information from the submitter, patient reported outcomes (PRO) are being collected in 3 other separate trials with data expected over the next 2-3 years. In general, nab-paclitaxel plus gemcitabine would be expected to be better tolerated then FOLIFIRINOX in most cases.

Safety

Safety results were consistent with the known toxicity profile of both nab-paclitaxel plus gemcitabine with no new safety signals apparent. From a clinical viewpoint, this regimen would be considered tolerable for most patients suffering from metastatic pancreatic cancer.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit provided by the addition of nab-paclitaxel to gemcitabine for patients with metastatic adenocarcinoma of the pancreas. This conclusion is based on the final results from a single but the largest randomized phase 3 trial conducted to date for this condition. The combination of nab-paclitaxel plus gemcitabine provided clinically meaningful and statistically significant improvements in all relevant endpoints including OS, PFS, ORR and 1 year OS, compared to gemcitabine alone.

In making this conclusion, the Clinical Guidance Panel also considered that:

- The magnitude of the observed outcomes should be interpreted in the context of the highly morbid nature of the disease and the fact that the nab-paclitaxel plus gemcitabine regimen would be an option offered to the majority of patients who would not otherwise be candidates for FOLFIRINOX, thus potentially improving outcomes for a significant proportion of patients with metastatic disease.
- From a clinical perspective, the magnitude and consistency of the observed incremental benefits across the primary and major secondary endpoints represents a clinically meaningful set of observations that has direct clinical applications for Canadian patients with metastatic pancreatic cancer.
- The safety profile of the combination therapy was consistent with the known safety profiles of both agents administered separately with no new safety signals observed.

2 CLINICAL GUIDANCE

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding nab-paclitaxel (Abraxane) for metastatic adenocarcinoma of the pancreas. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the pCODR website, www.pcodr.ca.

This Clinical Guidance is based on: a systematic review of the literature regarding nab-paclitaxel (Abraxane) conducted by the Gastrointestinal Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on nab-paclitaxel (Abraxane) and a summary of submitted Provincial Advisory Group Input on nab-paclitaxel (Abraxane) are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Nab-paclitaxel has a Health Canada indication for the first-line treatment of metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.[1] Nab-paclitaxel is administered iv and is available as a lyophilized powder in a 100mg single use vial. The Health Canada recommended dose is 125 mg/m^2 administered as an intravenous infusion over 30-40 minutes on days 1, 8 and 15 of each 28-day cycle followed by gemcitabine at 1000 mg/m^2 as an intravenous infusion over 30-40 minutes beginning immediately after the completion of nab-paclitaxel administration on days 1, 8 and 15 of each 28-day cycle.

Nab-paclitaxel is an albumin bound formulation of paclitaxel, a member of the taxane class of chemotherapy drugs that causes mitotic arrest in cancer cells by disrupting microtubule function.[9] The albumin moiety of nab-paclitaxel facilitates the preferential uptake of paclitaxel by pancreatic tumor through gp-60–mediated endothelial transcytosis and binding of SPARC in tumor-associated stroma.[10]

Internationally, the standard of care has been the use of gemcitabine (GEM). More recently a complex regimen called FOLFIRINOX has been compared to single agent GEM.

2.1.2 Objectives and Scope of pCODR Review

The objective of the review is to evaluate the effectiveness of nab-paclitaxel (Abraxane) in combination with gemcitabine for the first line treatment of patients with locally advanced unresectable or metastatic adenocarcinoma of the pancreas. Although the approved indication for nab-paclitaxel is limited to metastatic adenocarcinoma of the pancreas, the scope of the pCODR review included patients with locally advanced unresectable disease to account for potential clinical use of nab-paclitaxel in this population.

2.1.3 Highlights of Evidence in the Systematic Review

This section describes highlights of evidence in the systematic review. Refer to section 2.2 for the clinical interpretation of this evidence and section 6 for more details of the systematic review.

One open-label randomised controlled trial, MPACT[2], met the inclusion criteria for the systematic review. MPACT randomised 861 patients with previously untreated metastatic adenocarcinoma of the pancreas in a 1:1 ratio to receive nab-paclitaxel plus gemcitabine (n=431) or gemcitabine alone (n=430). Patients were stratified based on performance status, presence or absence of liver metastases and geographic region. Baseline patient characteristics are listed in Table 3 and were balanced between groups. The median age of patients was 62 and 63 years in the nab-paclitaxel plus gemcitabine vs. gemcitabine arms, respectively. Patients also had a Karnofsky PS score of 100 (16% vs. 16%), 90 (42% vs. 46%) or 80 (35% vs. 30%) and had metastasis in the liver (85% vs. 84%) or lungs (35% vs. 43%), respectively in each arm. Patients were excluded from the study if they had islet-cell neoplasms, locally advanced disease or if they had prior treatment with cytotoxic doses of gemcitabine or any other chemotherapy in the adjuvant setting.

The study reported statistically significant differences for the primary outcome of overall survival in favour of the nab-paclitaxel plus gemcitabine arm (8.5 vs. 6.7 months in the nab-paclitaxel plus gemcitabine vs. gemcitabine arms HR 0.72 95%CI 0.62 to 0.83 p<0.001). Updated overall survival analysis (May 9, 2013) showed similar results with a median overall survival of 8.7 vs. 6.6 months in the nab-paclitaxel plus gemcitabine vs. gemcitabine arms, respectively (HR 0.72 95%CI 0.620-0.825, p <0.0001). [3] One (35 vs. 22% respectively, p< 0.001) and two (9% vs. 4% respectively, p=0.02) year overall survival of patients was also significantly more in the nab-paclitaxel plus gemcitabine vs. gemcitabine arms.[2] Analysis of OS in the pre-specified subgroups indicated that treatment effect was consistently favoured for nab-paclitaxel plus gemcitabine across most subgroups. Similar trends were observed across the pre-specified subgroups for progression free survival.

Statistically significant longer independently assessed PFS and ORR were also reported for patients receiving nab-paclitaxel plus gemcitabine compared to gemcitabine alone. The median PFS was 5.5 vs. 3.7 months in the two arms respectively (HR 0.69 95%CI 0.58 to 0.82 p<0.001). In the nab-paclitaxel plus gemcitabine vs. gemcitabine arms, 23% vs 7% of patients achieved objective response in each arm, respectively (Response-rate ratio 3.19 95% CI 2.18 to 4.66 p< 0.001, with a HR > 1 favouring the nab-paclitaxel plus gemcitabine arm).

Quality of life was not measured in the study.

A similar number of deaths were reported in both arms, with 4% in each arm. Among these, 9 deaths were attributed to treatment with 7 (2%) vs. 2 (<1%) being in the nab-paclitaxel plus gemcitabine vs. gemcitabine arms, respectively[4]. Patients in the nab-paclitaxel plus gemcitabine arm experienced more grade 3 or higher treatment emergent adverse events (TEAE) and all grades TEAE's (Table 7). The most frequently occurring (≥10%) grade 3 or higher TEAE in the nab-paclitaxel plus gemcitabine vs. gemcitabine arm were neutropenia, fatigue, peripheral neuropathy, thrombocytopenia and anemia.

Potential sources of bias were identified regarding the trial design, administration of concomitant medications and subsequent therapies patients received that may impact the generalizability of the trial results. The Clinical Guidance Panel however confirmed that despite these potential sources of bias, the trial results are generalizable to the general Canadian clinical setting.

2.1.4 Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

2.1.5 Summary of Supplemental Questions

Critical appraisal of an indirect comparison of nab-paclitaxel plus gemcitabine with FOLFIRINOX.

The indirect comparison of nab-paclitaxel plus gemcitabine versus FOLFIRINOX included two studies: the MPACT trial[2] and the PRODIGE 4 / ACCORD 11 trial[11]. The clinical guidance panel were consulted on the comparability between the two study populations and they concluded that they were very different: patients eligible for FOLFIRINOX are generally healthier. As the submitter did not compare the hazard ratios between the two trials, it is not possible to comment on the statistically significant differences for overall survival and progression-free survival. This was a naïve (unadjusted) indirect comparison, as it does not take into account within trial comparisons and therefore is not adjusted for the results of the common control group.[12] Further, in this particular case, there is only one randomized controlled trial to inform each arm of the indirect comparison, limiting the generalizability of the results and increasing any potential risk of bias. The substantial heterogeneity between the two trials also leads to unreliable and highly uncertain results from the indirect comparison.

-See section 7.1 for more information.

2.1.6 Other Considerations

See Section 4 and Section 5 for a complete summary of patient advocacy group input and Provincial Advisory Group (PAG) Input, respectively.

Patient Advocacy Group Input

From a patient perspective, 82% of respondents noted that it was very important to have access to effective treatments for pancreatic cancer. Respondents ranked pain control as the key symptom to control. This was followed by decreased appetite, nausea or vomiting, mal-digestion, infections, diarrhea, inflammation of the pancreas, unplanned weight loss, new onset of diabetes, fatigue and weakness. Based on responses from survey, 127 of respondents stated that they used treatments other than nab paclitaxel to treat their pancreatic cancer. 26% (N=24/92) of respondents had "strongly disagreed" that current treatments were able to manage their pancreatic cancer symptoms; while 12% (11/92) had "strongly agreed" that current treatments were able to manage their pancreatic cancer symptoms. 19% of respondents reported that it was "not at all difficult" to access current treatments; while 18% of respondents reported that it was "extremely difficult" to access current treatments. The majority of respondents indicated that it was very important to be able to have choice of treatment based on each treatment's known side effects. The number one side effect of current treatments was nausea followed by tired/fatigue. Of those respondents who had experienced with nab paclitaxel, the length of treatment ranged between 2-6 months. Respondents reported that nab paclitaxel offered an additional treatment option to choose from, has reduced side effects and improved on quality of life.

PAG Input

From the PAG perspective, nab-paclitaxel is already being used for other tumours and there is familiarity with the preparation and administration of this drug. PAG noted that nab-paclitaxel is add-on therapy for patients who are already receiving gemcitabine alone. The key barriers to implementation are concerns for drug wastage, time to prepare the infusion and the additional chair time for infusion.

Other [1]

The product monograph provided by the manufacturer (Celgene) provides the following serious warnings and precautions:

- Nab-paclitaxel (Abraxane) should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents.
- An albumin form of paclitaxel may substantially affect a drug's functional properties relative to those of drug in solution. Do not substitute with or for other paclitaxel formulations.
- Bone marrow suppression (primarily neutropenia) is dose-dependent and a dose-limiting toxicity of nab-paclitaxel (see CONTRAINDICATIONS and Hematologic section).
- Sepsis with or without neutropenia occurred in patients who received nab-paclitaxel in combination with gemcitabine (see Infection section).
- Pneumonitis, including some cases that were fatal, occurred in patients receiving nab-paclitaxel in combination with gemcitabine (see Respiratory section below).
- Patient's ≥ 75 years of age treated with nab-paclitaxel in combination with gemcitabine experienced more toxicity and no demonstrated survival benefit (see Special Population, Geriatrics section).

Special population

- Nab-paclitaxel can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women using nab-paclitaxel. If nab-paclitaxel is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with nab-paclitaxel.
- It is not known whether paclitaxel is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving nab-paclitaxel therapy.
- The safety and effectiveness of nab-paclitaxel in pediatric patients have not been evaluated.
- Of the 421 patients with metastatic pancreatic adenocarcinoma in the randomized study who received nab-paclitaxel plus gemcitabine, 41% were 65 years or older and 10% were 75 years or older. Diarrhea, decreased appetite, dehydration and epistaxis were more frequent in patients 65 years or older compared with patients younger than 65 years old. In patients 75 years (10% of trial population) and older who received nab-paclitaxel plus gemcitabine, there was a higher incidence of serious adverse reactions and adverse reactions that led to treatment discontinuation.Carefully assess patients 75 years and older for their ability to tolerate nab-paclitaxel in combination with gemcitabine. Give special consideration to performance status, co-morbidities and increased risk of infections.

2.2 Interpretation and Guidance

Burden of metastatic pancreatic cancer

With an estimated 4,700 Canadians diagnosed each year, pancreatic adenocarcinoma is the 4th leading cause of cancer death amongst both the male and female Canadian population.[6] The pancreatic cancer incidence to mortality ratio is 0.91, attesting to the high degree of lethality attributed to the diagnosis. The clinical burden of disease encompasses a wide range of progressive symptoms including pain, nausea and vomiting, anorexia/cachexia and general functional decline. This symptomatic burden of disease, experienced by the vast majority of patients with metastatic disease, requires expert management and multiple medical interventions to optimize symptom control. Improvement in overall survival in the context of symptom control and prolongation of progression free survival are key endpoints of clinical trials for metastatic pancreatic cancer and resonate with patient advocacy groups.

Current Standard of Care in Canada

Gemcitabine monotherapy is the current standard of care for the majority of patients with metastatic pancreatic cancer, who are generally not able or willing to undergo treatment with FOLFIRINOX. This is based upon evidence of clinical benefit for gemcitabine monotherapy (24% vs 5%) and a modest survival gain when compared to 5FU alone (5.6 vs 4.4 mos).[13] For selected patients with good performance status (ECOG 0-1) and a normal serum bilirubin, the triplet combination of 5FU, irinotecan and oxaliplatin (FOLFIRINOX) offers superior efficacy as demonstrated in the ACCORD 11 French trial of 342 patients randomized to first-line FOLFIRINOX vs standard-dose gemcitabine, with a significant overall survival benefit observed of 11.1 mos vs. 6.8 mos. Unfortunately, the number of patients eligible for FOLFIRINOX therapy is limited, and is estimated to be less than 25% of referred cases.[14]

Effectiveness of nab-Paclitaxel plus gemcitabine

The MPACT trial was a randomized, open-label, phase 3 clinical trial comparing the combination of nab-paclitaxel plus gemcitabine to gemcitabine alone for the treatment of biopsy-confirmed metastatic pancreatic cancer. This global trial randomized 861 patients with a Karnofsky performance score of 70-100 (among these 7% vs 8% of patients in the nab-paclitaxel plus gemcitabine vs. gemcitabine arms, respectively had a KPS of 70 which if comparable to an ECOG PS of 2). Eligible patients had not received prior chemotherapy for their disease in either the adjuvant or metastatic setting. The primary endpoint was overall survival (OS) with important secondary endpoints including independently assessed objective response rate (ORR) and progression free survival (PFS). Both the initial final analysis, as well as the updated final analysis with more event rates, observed a statistically significant OS advantage for the combination arm (8.5 m vs 6.7 m; HR 0.72:95%CI 0.62-0.83 p<0.001 and 8.7m vs 6.6m; HR 0.72:95%CI 0.62-0.825 p<0.0001 respectively). A statistically significant improvement in PFS (5.5m vs 3.7 m; HR 0.69:95%CI 0.58-0.82 p<0.001) as well as objective response rate ratio (ORR 23% vs 7%; response rate ratio 3.19, 95%CI 2.18-4.66 p<0.001) was observed favoring the nab-Paclitaxel plus gemcitabine treatment arm. One year OS was also higher in the combination arm (35% vs 22%, p< 0.001). Subgroup analysis observed a favorable treatment effect of the combination therapy in all pre-specified patient subgroups. The consistency of the observations across all major primary and secondary endpoints along with the independent confirmation of ORR and PFS, strongly supports nab-paclitaxel plus gemcitabine as being an

improvement in the therapeutic options available for the palliative treatment of metastatic pancreatic cancer. The observation of a 2 month improvement in median overall survival coupled with a tripling of ORR and a 13% improvement in 1 year survival represents a group of clinically meaningful outcomes for patients suffering from metastatic pancreatic cancer.

Safety of nab-Paclitaxel plus gemcitabine

There were 7 reported treatment related deaths in the nab-paclitaxel plus gemcitabine arm compared to 2 in the gemcitabine alone arm (2% and <1% of study population respectively). There were more grade 3 or higher treatment emergent adverse events in the combination arm (89% vs 75% respectively) with more grade 3 neutropenia and thrombocytopenia in the combination arm (33% vs 21% and 13% vs 8% respectively), but an overall low rate of febrile neutropenia (3% vs 1% respectively). Grade 3 or higher peripheral neuropathy was observed more frequently in the nab-Paclitaxel plus gemcitabine arm (17% vs 1%) and took a median of 29 days to resolve to </= grade 1 in the nab-Paclitaxel arm. Safety results were consistent with the known toxicity profile of both nab-paclitaxel plus gemcitabine with no new safety signals apparent. From a clinical viewpoint, this regimen would be considered tolerable for most patients suffering from metastatic pancreatic cancer. Although there was no formal collection of quality of life data in the MPACT trial, information from the patient advocacy input suggests that the major endpoints evaluated in MPACT are clinically meaningful and highly relevant for the target patient population. Based on information provided from the submitter, patient reported outcomes (PRO) are being collected in 3 other separate trials with data expected over the next 2-3 years. In general, nab-paclitaxel plus gemcitabine would be expected to be better tolerated than FOLIFIRINOX in most cases.

Need

There remains an important unmet medical need for more efficacious systemic therapy for metastatic pancreatic cancer. Until recently, single agent gemcitabine has been the standard of care for this condition based on a single randomized trial published in 1997. Recently, FOLFIRINOX, a complicated and somewhat toxic combination chemotherapy regimen was observed to lead to a significant improvement in OS compared to gemcitabine alone. Due to the complexity and toxicity of the regimen however, it is estimated that only a minority of the Canadian patient population would be eligible or willing to undergo therapy with FOLFIRINOX. It is important to note that there is a large subset of patients who would not be candidates or not willing to undergo therapy with FOLFIRINOX that may be eligible for nab-paclitaxel plus gemcitabine. Factors impacting treatment decisions may include age, co-morbidities, symptom control prior to starting therapy or preference. Thus, both regimens serve an unmet need for different patient subsets of patients with metastatic pancreatic cancer. The clinical guidance panel authors agreed that more patients would meet eligibility criteria and be offered, nab-paclitaxel plus gemcitabine compared to FOLFIRINOX in the Canadian context. Although there were few Canadians included in the MPACT trial (63/823), the CGP, based on information provided regarding subsequent and concomitant therapies as provided by the submitter, felt that the results from the MPACT trial were generalizable to the Canadian population.

2.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit provided by the addition of nab-paclitaxel to gemcitabine for patients with metastatic adenocarcinoma of the pancreas. This conclusion is based on the final results from a single but the largest randomized phase 3 trial conducted to date for this condition. The combination of nab-paclitaxel plus

gemcitabine provided clinically meaningful and statistically significant improvements in all relevant endpoints including OS, PFS, ORR and 1 year OS, compared to gemcitabine alone.

In making this conclusion, the Clinical Guidance Panel also considered that:

- The magnitude of the observed outcomes should be interpreted in the context of the highly morbid nature of the disease and the fact that the nab-paclitaxel plus gemcitabine regimen would be an option offered to the majority of patients who would not otherwise be candidates for FOLFIRINOX, thus potentially improving outcomes for a significant proportion of patients with metastatic disease.
- From a clinical perspective, the magnitude and consistency of the observed incremental benefits across the primary and major secondary endpoints represents a clinically meaningful set of observations that has direct clinical applications for Canadian patients with metastatic pancreatic cancer.
- The safety profile of the combination therapy was consistent with the known safety profiles of both agents administered separately with no new safety signals observed.

3 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Endocrine Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

3.1 Description of the Condition

Adenocarcinomas comprise the vast majority of malignant diagnoses arising within the pancreas and are among the most common gastrointestinal cancers within the Canadian population, second only to colorectal carcinomas. In 2013, it is estimated that 4700 new patients will be diagnosed with the disease, approximately equally divided between males and females. Pancreatic cancer is the 4th leading cause of cancer death amongst both men and women, after lung, colorectal and prostate cancer in men and lung, breast and colorectal cancer in women. Approximately 4300 deaths due to this disease were expected in 2013.[6]

The close approximation of incidence and mortality is a testament to the high lethality of the disease and to the fact that the vast majority of cases are diagnosed with unresectable, locally advanced or metastatic disease. It is commonly quoted that approximately 20% of all patients can undergo an attempt at curative-intent surgery and, of these, only 20% remain alive and disease-free at 5 years leading to a disease specific 5-year survival rate of 5%. Recent data suggests a slight improvement to 8% over the past few years, likely due to a combination of earlier incidental detection, improved peri-operative mortality rates particularly in high volume centres and greater use of adjuvant systemic therapy.[7,8]

Early symptoms of disease are generally non-existent except for small tumours resulting in painless jaundice due to biliary obstruction. More common symptoms include abdominal and/or back pain, intestinal dysmotility, nausea/vomiting, abdominal bloating/distension and anorexia/cachexia, all of which generally indicates advanced disease. Pancreatic cancer is also associated with a hypercoaguable state and a minority of patients present with a thrombotic event as the first indicator of disease.

The vast majority of patients will present with locally advanced (20-30%) or metastatic disease (~50%) at presentation.[7,8] The most common sites of disease involvement include the local-regional lymph nodes with invasion of the celiac plexus, the peritoneum with resultant disturbances in intestinal motility and/or the development of malignant ascites, and the liver. Other possible sites of metastatic involvement include the lungs, bone and brain.

3.2 Accepted Clinical Practice

Patients with advanced pancreatic adenocarcinoma are typically ill and require maximal symptomatic and supportive care to control symptoms and stabilize/improve quality of life. Some of the medications typically employed include narcotic analgesics, prokinetics, corticosteroids, anti-nausea agents and diuretics for malignant ascites. Interventional manoeuvres targeted to specific symptoms can include celiac plexus blockade, paracentesis and gastroduodenal stenting due to gastric outlet obstruction. All of the above are aimed at maximizing comfort in the palliative setting.

Palliative radiation therapy is often considered for unresectable locally advanced disease with goals of treatment including disease control as well as symptom palliation, especially for patients with pain due to celiac plexopathy secondary to local tumor invasion.

Neoadjuvant therapy for borderline resectable disease may include radiation therapy with systemic chemotherapy as a radiosensitizer and may allow consideration of resection in a small minority of selected cases. If resected, overall survival may be similar to patients treated with upfront resection although randomized data and long term follow up information is generally unavailable.[8]

If chosen as an option for locally advanced disease, combined chemo-radiation typically involves external-beam radiation therapy delivered with concomitant radiosensitizing chemotherapy either as infusional 5-FU or oral capecitabine. While there has not been a survival benefit associated with this strategy, it may offer meaningful palliative benefit for symptomatic local disease.

Most patients would be referred to a medical oncologist to consider palliative systemic therapy for locally advanced/metastatic disease. The goals of therapy are to aid in symptom control by stabilizing/improving disease burden and prolong progression-free and overall survival (PFS and OS respectively) with an acceptable or minimal toxicity burden. Ideally, for consideration of systemic therapy, patients would have a reasonable performance status (ECOG PS 0-2), reasonable control of symptoms due to metastatic disease and have recovered from any prior surgical or medical intervention.

Internationally, the standard of care has been the use of Gemcitabine (GEM), typically delivered weekly for 7 weeks out of the first 8 then for 3 out of every 4 weeks subsequently, all as a 30 minute infusion. Results from a pivotal randomized trial which compared GEM to the prior standard of 5-FU demonstrated statistically significant improvement in clinical benefit response (CBR: combination of pain, performance status and weight) with 23.8% of GEM-treated patients experiencing a CBR compared with 4.8% of 5-FU-treated patients; P = .0022). Median survival durations were 5.65 and 4.41 months for GEM-treated and 5-FU-treated patients, respectively (P = .0025) with 1 year survival rates of 18% for GEM and 2% for 5-FU.[13]

A large placebo-controlled, phase 3 trial (n=569, ECOG 0-2) evaluated GEM with or without erlotinib, an oral EGFR inhibitor. Median OS was 6.2m in the erlotinib group versus 5.9m in the placebo group (HR=0.82; 95% CI: 0.69-0.99, p=.038). There was also a significant prolongation of PFS 3.75 v 3.55m (p=0.004) favoring the experimental arm but no difference was observed in tumor response rates. 1 year OS was 23% v 17% favoring the experimental arm (p=0.023). Quality of life was formally assessed with observed differences between treatment arms with the exception of worse diarrhea scores on the erlotinib-containing arm. Despite these statistically significant results, erlotinib is not in routine use in Canada due to lack of funding as a result of relatively marginal absolute differences in OS and PFS between the treatment arms leading to a highly unfavorable cost-effectiveness assessment.[15]

A third large phase 3 trial (n= 533, ECOG 0-2) for advanced pancreatic cancer evaluating the combination of capecitabine + gemcitabine {GEM-CAP} v gemcitabine) has also been reported. Patients randomly assigned to GEM-CAP had a higher response rate compared to GEM (19.1% v 12.4%; p=0.03). The median PFS for GEM-CAP was 5.3 months v 3.8 months for GEM (p=0.004). The 12-month PFS rates were 13.9% for GEM-CAP and 8.4% for GEM. The median survival for GEM-CAP was 7.1 m v 6.2m for GEM (p = 0.08) with 1-year OS rates of 24.3% for GEM-CAP and 22% for GEM. There were no observed differences in assessed quality of life scores between treatment arms.[16]

More recently a complex regimen called FOLFIRINOX has been compared to single agent GEM in a large randomized trial (n=342, ECOG 0-1) for patients with metastatic pancreatic cancer and observed an improvement in objective response rates (31.6% v 9.4%; p<0.001), progression free survival (6.4 m v 3.3 m; p < 0.001) and overall survival (11.1m v 6.8 m; p < 0.001). FOLFIRINOX involves the administration of 4 chemotherapy agents (5-FU, leucovorin, irinotecan, oxaliplatin) delivered q 2 weekly with an infusional component involving 46 hours of 5-FU subsequent to the bolus medications. Due to the complexity and predicted toxicities arising, this trial was restricted

to patients under age 75 and with an with an ECOG PS of 0-1. Statistically significant differences in grade 3 and 4 toxicities were observed for febrile neutropenia (5.4% v 1% with rates of GCSF use being 42.5% v 5.3%, FOLFIRINOX v GEM respectively), thrombocytopenia, diarrhea and sensory neuropathy in the FOLFIRINOX arm. Despite this, a significant increase in the time to definitive deterioration in QOL was observed in the FOLFIRINOX arm (31% v 66% at 6 months favouring FOLFIRINOX).[11]

Most recently, nab-Paclitaxelplus GEM has been compared to single agent GEM in the largest multinational phase 3 trial for advanced pancreatic cancer to date (n=861, ECOG 0-2). Nab-paclitaxel was added to GEM weekly for 3 weeks of each 4 week cycle versus standard single agent GEM administered for 7 out of 8 weeks initially, then for 3 of 4 weeks subsequently. The addition of nab-Paclitaxel plus GEM resulted in improved objective response rates (23% v 7%, independent review; p<0.001), an improved progression-free survival time (5.5 m v 3.7m; p <0.001) and an improved median overall survival time (8.5m v 6.7m; p < 0.001). The primary difference in terms of toxicity was related to grade 3+ peripheral neuropathy in the nab-Paclitaxel plus arm (17% v 1%). Rates of febrile neutropenia were also modestly increased in the experimental arm (3% v 1%) with more patients receiving granulocyte colony stimulating factors in the nab-Paclitaxel plus arm (26% v 15%). There was no formal assessment of quality of life.[2]

In summary, there remains a considerable unmet need for more effective and tolerable systemic therapies in the treatment of advanced pancreatic adenocarcinoma. There are now 5 potential options, supported by level 1 evidence, for palliative-intent first line systemic therapy for advanced adenocarcinoma of the pancreas.[2,11,13,15,16] The current regimen under consideration would be expected to substitute for one of the other discussed options in the appropriate setting. Decisions about optimal option will be individualized and revolve around the individual patient's age and clinical status, performance status and co-morbidities, ease of administration and expected tolerance and patient preference. The majority of patients are not expected to be able to tolerate first line FOLFIRINOX and therefore nab-Paclitaxel could become a preferred first-line therapeutic option for a significant number of patients referred for systemic therapy for advanced disease. Although FOLFORINOX and nab-paclitaxel plus gemcitabine have both been compared to gemcitabine monotherapy, conclusions from a cross trial comparison should be drawn cautiously as the inclusion criteria differed across the two trials.

Paclitaxel and docetaxel have been evaluated as single agents in small Phase II trials as single agents and were only modestly active. Paclitaxel in particular has also been studied in small phase II trials following disease progression on Gem, with difficult to interpret results.[17]

Paclitaxel, in particular, weekly administration at low dose has been evaluated as a radiosensitizer in the context of concurrent radiation for locally advanced disease in small trials, again with somewhat limited results.[18] It is thought that the particular formulation of nab-paclitaxel affords a particular pharmacodynamic advantage given the intense desmoplastic/inflammatory tissue response often observed with metastatic disease. In global practice, neither paclitaxel or docetaxel has ever been incorporated into standard first line therapy and neither have ever been examined in a robust phase 3 trial against a standard of care (Gem).[17,19]

A recent abstract presented by a group from British Columbia reviewed all patients referred to the BCCA between 2001-2011 who initiated palliative gemcitabine for advanced pancreatic cancer and assessed their potential eligibility for either FOLFIRINOX or nab-Paclitaxel plus GEM through chart review. They observed that 24.7% of subjects may have met eligibility criteria for FOLFIRINOX versus 45.2% for nab-Paclitaxel plus GEM. It is important to note that this data does not include clinical examination or patient preferences which would likely result in lower rates of treatment uptake, particularly among those potentially offered FOLFIRINOX.[14]

3.3 Evidence-Based Considerations for a Funding Population

As discussed in section 3.1, the vast majority of patients with pancreatic cancer present with advanced disease or will develop it relatively quickly following curative intent surgery. Adjuvant GEM has been observed to lead to improved overall survival following curative intent surgery and therefore the proportion of patients remaining disease free after surgery may rise modestly over the next few years. Despite this, 80-90% of the 20-25% of patients undergoing curative intent surgery will be expected to relapse with the remainder of those not undergoing surgery having advanced disease at diagnosis. Due to the morbidity of the disease and the often rapid pace of disease progression, a considerable fraction (~ 20-25 %) of the total patient population may not be eligible for systemic therapy due to rapidly progressive symptoms and declining performance status and would be treated with best supportive care (BSC) only.

Most patients will have pathologically confirmed adenocarcinoma of the pancreas although a minority may not have tissue confirmation but have supportive evidence of the disease, typically including a significant elevation of Ca 19-9 (tumour marker) in conjunction with a fine needle aspirate or biliary brushings suggestive of malignancy, in the appropriate clinical setting (symptoms and/or signs of the disease) with supportive radiologic investigation. A smaller minority may not have any tissue submitted for pathologic analysis but be considered to have the disease in the appropriate clinical setting (symptoms and/or signs of the disease), in the context of a significant elevation of Ca 19-9 in conjunction with supportive radiologic investigation. All cases described above would be potentially eligible to receive nab-Paclitaxel plus GEM.

The locally-advanced patient population represents an important patient subset. Extrapolation of the clinical trial results described previously should be made cautiously but, from a clinical perspective, systemic therapies utilized in the metastatic disease setting are often considered for those with locally advanced/unresectable disease. This treatment option would NOT be considered in the context of concurrent radiation therapy.

3.4 Other Patient Populations in Whom the Drug May Be Used

Although each of the large phase 3 trials discussed specified first-line therapy, there would be a proportion of patients in the advanced setting who would remain candidates for second-line therapy and for whom nab-Paclitaxel plus GEM may be an option after disease progression on FOLFIRINOX or in the face of significant and/or treatment-limiting toxicities related to FOLFIRINOX.

As well, those with borderline resectable disease may be considered for neo-adjuvant therapy with nab-Paclitaxel plus GEM, without concurrent radiation therapy, in attempts to render disease resectable.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Two patient advocacy groups, Pancreatic Cancer Canada ("PCC") and Craig's Cause Pancreatic Cancer Society ("Craig's Cause"), collaborated together to provide input on nab paclitaxel (Abraxane) for the first line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine, and their input is summarized below.

PCC and Craig's Cause prepared and disseminated an anonymous online survey directed at individuals with pancreatic cancer as well as their caregivers. A link to the survey was distributed by way of organizational websites, e-mails and by personally reaching out to health care institutions and other pancreatic cancer organizations such as the Pancreatic Cancer Action Network in the United States.

The survey had a combination of multiple choice, rating and open-ended questions. The total number of responses for each question (N) is provided in the analysis of the survey for each question. Certain open responses that reflected the sentiment of a majority of the respondents are included verbatim to provide a deeper understanding of the patient and caregiver perspective.

PCC and Craig's Cause reported a total of 385 respondents who participated in the survey. A number of questions were skipped by the respondents. Of those who responded, a total of 263 respondents were from Canada, with each province represented. There were no responses from the territories. A total of 16 respondents were from outside of Canada. 106 respondents did not provide a response to this question.

According to the survey, a total of 52 respondents were living with pancreatic cancer and 233 were caregivers; 100 respondents had skipped the question. A total of 11 respondents indicated that either they or the person they provided care for used nab paclitaxel to treat their pancreatic cancer.

From a patient perspective, 82% of respondents noted that it was very important to have access to effective treatments for pancreatic cancer. Respondents ranked pain control as the key symptom to control. This was followed by decreased appetite, nausea or vomiting, mal-digestion, infections, diarrhea, inflammation of the pancreas, unplanned weight loss, new onset of diabetes, fatigue and weakness. Based on responses from survey, 127 of respondents stated that they used treatments other than nab paclitaxel to treat their pancreatic cancer. 26% (N=24/92) of respondents had "strongly disagreed" that current treatments were able to manage their pancreatic cancer symptoms; while 12% (11/92) had "strongly agreed" that current treatments were able to manage their pancreatic cancer symptoms. 19% of respondents reported that it was "not at all difficult" to access current treatments; while 18% of respondents reported that it was "extremely difficult" to access current treatments. The majority of respondents indicated that it was very important to be able to have choice of treatment based on each treatment's known side effects. The number one side effect of current treatments was nausea followed by tired/fatigue. Of those respondents who had experienced with nab paclitaxel, the length of treatment ranged between 2-6 months. Respondents reported that nab paclitaxel offered an additional treatment option to choose from, has reduced side effects and improved on quality of life.

Please see below for a summary of specific input received from the patient advocacy groups. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that was reported have also been reproduced as is according to the submission and have not been corrected.

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients Have with Metastatic Pancreatic Cancer

PCC and Craig's Cause reported that pancreatic cancer is the fourth leading cause of all cancer deaths and it remains the cancer with the highest fatality. Moreover, the disease is often referred to as a 'silent killer' because there are generally no symptoms in the early stages and the symptoms are often vague and frequently dismissed by patients and doctors alike.

Respondents were asked to rate the importance of symptom control with 1 as being "not important" and 7 as being "very important". According to the survey, respondents ranked pain control with the highest score. A total of 57% (N=21/40) of the respondents rated this as a "very important". This was followed by decreased appetite with 50% (N=20/40) of respondents who rated this as "very important". All other symptoms based on the order of importance included: nausea or vomiting, mal-digestion, infections, diarrhea, inflammation of the pancreas, unplanned weight loss, new onset of diabetes, fatigue and weakness. Because these other symptoms received an average rating of 5.66 or higher, PCC and Craig's Cause believes this would indicate that all symptoms were considered important to control.

In addition to the above, respondents were asked to consider on how the symptoms impact or limit their day-to-day activities and quality of life. According to the survey, respondents considered the ability to travel was the most impacted with 31% (N=12/39) of respondents who rated this as a "significant impact" and giving this a 7 out of 7. This was followed by ability to work with 28% (N=10/36) of respondents who rated this as a "significant impact". Other activities that were impacted included: ability to exercise (average rating of 4.27), conduct household chores (average rating of 3.82), volunteer (average rating of 3.82), fulfil family obligations (average rating of 3.72), and ability to spend time with family and friends (average rating of 3.59). According to PCC and Craig's Cause, all the day-to-day activities received an average rating of 3.59 or higher, which meant that all responses were slightly closer to "significant impact" than "not at all".

Respondents were also asked to consider on how important it would be to have access to effective treatments for pancreatic cancer. From a patient perspective, 82% (N=36/44) of respondents provided a rating of 7 out of 7, which signified that it was "very important" to have access to effective treatments for pancreatic cancer. The average rating for this question was 6.66

4.1.2 Patients' Experiences with Current Therapy for Metastatic Pancreatic Cancer

PCC and Craig's Cause noted that patients diagnosed with pancreatic cancer receive limited treatment options. PCC and Craig's Cause estimated that 15-20% will be candidates for a potentially life-saving surgery or the majority will be provided with cancer directed therapies.

Based on responses from survey, 127 of respondents stated that they used treatments other than nab paclitaxel to treat their pancreatic cancer. The treatments used were: gemcitabine (n=41),

chemotherapy (n=7), radiation (n=7), surgery (n=5), leucovorin (n=3). Eight (8) respondents indicated that they used alternative or natural therapies.

91 of respondents (patients and caregivers) commented on the side effects of current treatments. The number one side effect was nausea 44% (N=40/91), followed by tired/fatigue 42% (N=38/91), weight loss 25% (N=23/91), diarrhea 19% (N=17/91), loss of appetite 15% (N=13/91), pain 9% (N=8/91), constipation 8% (N=7/91), flu/fever 8% (N=7/91), hair loss 8% (N=7/91), digestive issues 5% (N=5/91), diminished quality of life 3% (n=3/91). A minority of respondents, 15% (N=14/91), indicated that they do not experience side effects with treatment.

Drawing from the responses in the survey, PCC and Craig's Cause reported that 26% (N=24/92) of respondents indicated that they "strongly disagree" that current treatments are able to manage their pancreatic cancer symptoms, and reported with a rating of 1 for "strongly disagree"; while 12% (11/92) provided a rating of 7 for "strongly agree" that current treatments are able to manage their pancreatic cancer symptoms. The largest number, 28% (N=26/92) of respondents, neither disagree nor agree with the statement. The average rating for this question was 3.59.

Respondents were asked to consider on whether or not they found it difficult to access current treatments. Responses were received from Canadian respondents only. It was reported that 19% (N=31/164) of respondents provided a rating of 1 noting that it was "not at all difficult" to access current treatments, while 18% (30/164) of respondents provided a rating of 7 noting that it was "extremely difficult" to access current treatments. This question received an average rating of 3.96, which is reported as slightly more respondents found it difficult to access current treatments than not.

79 Canadian patients and caregivers also provided additional comments concerning the issue of access to current treatments. 34% (N=27/79) of respondents indicated that they had doctor/patient issues, that is, they received the wrong diagnosis and 16% (N=13/79) reported that not all options available were communicated to them. Other comments included: limited options with 19% (N=16/79) of respondents, geographic issues with 19% (N=15/79) of respondents, no option for treatment with 16% (N=13/79) of respondents, unsatisfied with treatment options with 11% (N=9/79) of respondents, clinical trial/drugs unavailable with 11% (N=9/79) of respondents, oncologist unavailable with 7% (N=6/79) of respondents, not covered by insurance with 4% (N=3/79) of respondents.

The following responses represent some of the comments that were provided to help illustrate the difficulties that respondents reported on the issue of accessing current treatments.

> *"We were informed at the time he was given 3 months, that there were other treatments - one that works for stomach cancer and they think it works for pancreatic cancer, but that OHIP wouldn't cover it.*
>
> "N*o treatment was available over Christmas and New Years and then we waited weeks at a time for an appointment watching our chances slip away."*
>
> *"Drugs used caused severe side effects. Drugs used to combat side effects in turn caused their own side effects, constipation, dry mouth etc. My wife survived approx. 1 year from diagnosis. Endured terrible pain despite best attempts of Drs to combat it."*
>
> *"We had access to the current treatments but were hoping for new drugs and clinical trials to become available when the prescribed chemo drugs were no longer effective in controlling the pancreatic cancer."*

"Folfirinox and Gemcitabine were easy to access. Anything beyond that was difficult i.e. abraxane, clinical trials etc. With this disease, time is really critical. Waiting for appointments to get approval for trials was not effective. My Mom passed away before she could even get to an appointment. Also, Abraxane was not offered to her even on a trial basis, which in my opinion is reprehensible."

4.1.3 Impact of Metastatic Pancreatic Cancer and Current Therapy on Caregivers

Respondents were asked to rate on a scale of 1 – 7 on how much the symptoms associated with pancreatic cancer impact or limit the caregiver's day-to-day activity and quality of life, with 1 being "not important", and 7 being "very important".

Caregiver respondents indicated that the most important symptom to control was pain with 89% (N=157/174) of respondents rating this "very important" or 7 out of 7; this was followed by infections with 65% (N=111/171) of respondents rating this "very important". Based on the findings in the survey, each symptom received an average rating of 5.59 or higher, which according to PCC and Craig's Cause, signified that all symptoms were important to control. The order of importance of symptoms was: nausea or vomiting, mal-digestion, fatigue, weakness, decreased appetite, unplanned weight loss, inflammation of the pancreas, diarrhea, and new onset of diabetes.

PCC and Craig's Cause reported that the ability to travel was impacted the most with 59% (N=100/169) of respondents who rated this as 7 in terms of significance of impact. This was followed by ability to work with 42% of respondents rating this as "significant impact" or 7 out of 7. All activities received an average rating of 4.81 or higher, which according to PCC and Craig's Cause, indicated that they are all impacted. The order of importance for other activities included: ability to spend time with family and friends, to fulfil family obligations, to exercise, to volunteer, to conduct household chores.

In addition to the above, 87% (N=95/109) of respondents noted that there were challenges facing caregivers as a result of pancreatic treatment and side effects. 44% (48/109) of caregiver respondents identified emotional/physical challenges related to fear, anxiety, depression, insomnia, fatigue, personal isolation, negative health effects to be the number one challenge. Other challenges included: helping the patient cope with 31% (N=34/109) of respondents, balancing daily routine with 24% (N=26/109) of respondents, getting to appointments with 13% (N=14/109) of respondents, access to doctors/information with 11% (N=12/109) of respondents, aiding pain management with 9% (N=10/109) of respondents, financial stress with 5.5% (N=6/109) of respondents. A minority of 9 respondents indicated that there were minimal challenges and 5 respondents indicated that the question did not apply.

The following responses represent some of the comments that were provided to help illustrate some of the challenges faced by caregivers.

"As a caregiver we face more emotional challenges. The depression, anxiety and helplessness are over- whelming."

"Financial Stress - suffering from financial debt afterwards or not having enough money to pay for all treatments and appointments (gas, parking etc)."

"I was 20 years old at the time and I was the primary caregiver for my mother. Challenges I faced were: - Depression - Ability to care for myself (healthy eating etc.) - A lack of resources caused me to feel lost and uninformed. I wish more information had been

provided - The biggest challenge was financially. My mother could no longer work, so i had to work to support the household while caring for her."

"My relative went into the hospital and never came out. We were at the hospital all the time. There were great financial impacts but we felt we needed to be at the hospital because pain management was not great. General surgical nursing staff did not understand palliative pain management. Surgeons and doctors would not admit the situation was palliative and kept wanting to perform procedures. Surgeons gave false hope and would not deal directly with the topic of death. There was no support for teenage children facing the death of a parent"

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences to Date with Nab Paclitaxel

Respondents were asked if they were to consider taking a new treatment for their pancreatic cancer, how important would it be to bring about improvement in their physical condition. Based on the responses from the survey, 65% (N=120/184) of respondents rated with a 7 out of 7 that it was "extremely important" for a new treatment to bring about improvement in physical condition. The average rating for this question was 6.41.

In addition to the above, 81% (N=149/183) of respondents rated with a 7 out of 7 noting that the expected benefit (for example, lack of disease progression) of taking a new drug was "extremely important". The average rating for this question was 6.64.

18% (N=33/182) of respondents rated with a 7 out of 7 that they would tolerate "significant side effects" if they were to consider taking a treatment proven to be effective for their pancreatic cancer, while 2% (N=4/182) of respondents selected 1 out of 7, "no side effects". The average rating for this question was 4.81.

The survey found that 16% (N=26/166) of respondents rated 7 out of 7 noting that access in their province/territory is "very appropriate fair", with 8% (N=14/166) rated with a 1 out of 7 that it is "very limited." The average rating for this question was 4.53.

Respondents were asked to consider on how important it would be to have a choice of treatments for pancreatic cancer based on each treatment's known side effects. The majority of respondents, 53% (N=94/178) indicated with a rating of 7 out of 7 that it was "very important" to be able to have choice of treatment based on each treatment's known side effects. The average rating for this question was 5.95, which according to the PCC and Craig's Cause, indicated that more respondents thought it was "very important" than "not important" to have choice.

PCC and Craig's Cause reported that 11 respondents had experienced with nab paclitaxel.

Of the eight (8) respondents who replied on the question regarding the length of treatment, six (6) respondents reported that they were on the treatment between 2 – 3 months, and two (2) of the respondents reported that they were on treatment between 4 -6 months.
Of the seven (7) respondents who replied on the question concerning side-effects, four (4) respondents rated with a 1 out of 7 that nab paclitaxel had fewer side effects than other treatments they had taken. One respondent provided a rating of 2, one respondent had a rating of 3 and one respondent had a rating of 7 for greater side effects. The average rating for this question was 2.29.

Respondents were also asked to rate the listed common side effects for nab paclitaxel and their ability to tolerate them. It was reported that the rating average for each side effect ranged between 3 to 7. The rating scale was from 1 for "completely intolerable" to 7 for "able to tolerate". All side-effects listed were tolerable. The least tolerable was neuropathies, which received an average rating of 4.40 and the most tolerable were infections, hair loss and anemia, which received an average rating of 7.00. Others included diarrhea (average rating of 6.50), joint and/or muscle pain (6.25), nausea (6.20), abnormal heart beat (6.00), neutropenia – low white blood cell counts (5.50), changes in liver function (5.00). One respondent noted that "*The Peripheral Neuropathy was the worse. It put him in a wheel chair - that is when they stopped the abraxane*."

Of the seven (7) respondents who replied on the question of overall experience with the drug, three (3) respondents reported that nab paclitaxel was "much better" in terms of overall experience than other drugs for pancreatic cancer and provided a rating of 7 out of 7; three (3) respondents provided a rating of 6, one (1) provided a rating of 2, and one (1) provided a rating of 1 indicating "much worse". The average rating for this question was 5.00.

Of the seven (7) respondents who replied on the question concerning the effectiveness of the drug, one (1) respondent indicated that nab paclitaxel was "extremely effective" in controlling pancreatic cancer and provided a rating of 7 out of 7, three (3) respondents provided a rating of 6, three (3) respondents provided a rating of 5 and one (1) respondent provide a rating of 1 as being "not effective". The average rating for this question was 5.00.

Out of 7 respondents who replied on the question of quality of life, two (2) respondents provided a rating of 6 out of 7 in terms of quality of life, with 1 being "poor quality of life" and 7 being "excellent quality of life". Three (3) respondents provided a rating of 5, one respondent provided a rating of 4 and one respondent provided a rating of 1. The average rating for this question was 4.57.

The following responses represent some of the comments provided that help to illustrate the changes or expected changes in terms of the long-term health and well-being.

> *"It gave my mother 9 precious more months with us and pockets of quality time too - a real gift when one recalls that the initial diagnosis was 3-4 months - we were lucky she was eligible for the trial and she was able to tolerate."*
>
> *"It has given me more time with my family compared to the alternative."*
>
> *"Still waiting to see if it will keep cancer in check. But with fewer side effects it is possible to wait and have a good quality of life."*
>
> *"It reduced (patient's) tumor by 38%. (Patient) was given three months with no treatment and 6-11 months with treatment. He passed 20 months after diagnosis."*
>
> *"Failure. No help and patient died within a few months."*

4.3 Additional Information

Below were additional comments gathered by PCC and Craig's Cause to help illustrate the respondents' experience living with pancreatic cancer, including comments relating to the use of nab paclitaxel.

> *"A diagnosis of pancreatic cancer is like getting a death sentence as there is little hope for survival as there is no known cure and treatment options are not curative they just give us precious extra time with family."*

> *"Imagine going to the doctor with complaints of back pain and being told that you have weeks to live; that was the harsh reality for my mother. In 1996, doctors blindsided my family with her diagnosis of advanced pancreatic cancer and news that there were no approved treatments to help her. Four short weeks later, she was gone and my family left devastated. I have made it my mission to champion this cause and continue the fight my mother so bravely battled. Along with my co-founder, who lost her husband 6 weeks after diagnosis, we are committed to improving overall patient survival. Over the past decade, there has been a significant improvement in cancer survival rates. Sadly, the same cannot be said about pancreatic cancer; incidence and mortality rates continue to rise as there are no reliable methods to detect this disease early on, few effective treatment options and very little hope for those afflicted with this disease."*

> *"During my father's short diagnosis and subsequent surgeries, I remember asking my father "how did we get into such a mess?" He turned his head towards me and sadly responded "Stefanie, I can't even believe I have cancer." I soon came to understand the impact of this statement. Pancreatic cancer does not give a patient time to accept a cancer diagnosis, let alone this particular diagnosis. "Death sentence," "silent killer," and "orphan of cancers," are just a few of the phrases used to describe pancreatic cancer. Phrases that describe a disease with no hope. In addition to our family being devastated by this diagnosis, we were shocked at the lack of treatment options available to patients. Persistent lack of confidence in the available therapies continues to hinder the long term outcomes of PC"*

> *"C'est difficile de faire face à n cancer dont l'issue est la plupart du temps, fatale..."*

> *"My mother was diagnosed at stage four, so she was not able to receive any of the conventional treatments. This lack of hope in terms of prognosis was heartbreaking. I would love to see any advancement in treatment of this deadly disease. Also, I would like to note that I was especially concerned about the fact that my mother was sent home with the news of her diagnosis and poor prognosis without any mental health support."*

> *"I hope that this drug gets approved so that all families can have access to it and will have precious extra time with their loved one."*

> *"Abraxane is not as toxic as other drugs including folfirinox."*

> *"I'm happy with it. I would like to see really good quality drugs for peripheral neuropathy be given at the same time.*

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group as factors that could affect the feasibility of implementing a funding recommendation for Nab-Paclitaxel (Abraxane) for treatment of pancreatic cancer. The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.pcodr.ca).

Overall Summary

Input on nab-paclitaxel (Abraxane) for pancreatic cancer was obtained from eight of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From the PAG perspective, nab-paclitaxel is already being used for other tumours and there is familiarity with the preparation and administration of this drug. PAG noted that nab-paclitaxel is add-on therapy for patients who are already receiving gemcitabine alone. The key barriers to implementation are concerns for drug wastage, time to prepare the infusion and the additional chair time for infusion.

Please see below for more details.

5.1 Factors Related to Comparators

Current treatments for metastatic pancreatic cancer are gemcitabine alone or FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan and oxaliplatin) and are not very effective or well tolerated, respectively. PAG noted that nab-paclitaxel plus gemcitabine has a small overall survival advantage when compared to gemcitabine alone but the difference in overall survival between FOLFIRINOX and gemcitabine alone is greater. PAG also indicated that nab-paclitaxel plus gemcitabine may be better tolerated than FOLFIRINOX.

In some jurisdictions, gemcitabine is the standard of care for pancreatic cancer and PAG noted that nab-paclitaxel plus gemcitabine would become the standard of care in these jurisdictions. In other jurisdiction, either gemcitabine or FOLFIRINOX is used to treat pancreatic cancer and there are no trials comparing nab-paclitaxel plus gemcitabine to FOLFIRINOX.

5.2 Factors Related to Patient Population

Nab-paclitaxel plus gemcitabine provides another treatment option with manageable toxicities for patients with pancreatic cancer, especially for those who are elderly or have poor performance status.

PAG identified barriers related to patient population including the potential for use in the adjuvant setting, in locally advanced disease, or as second-line therapy after FOLFIRINOX. PAG also noted that there may be cases where FOLFIRINOX could be used after nab-paclitaxel plus gemcitabine in patients whose performance status improves with initial treatment. PAG is requesting that use in locally advanced disease and sequencing of therapy with FOLFIRINOX be addressed.

5.3 Factors Related to Accessibility

Nab-paclitaxel is already used in other tumours and is available in most centres, which is an enabler, but PAG noted that nab-paclitaxel may not be used in the smaller outreach or rural centres.

Intravenous chemotherapy is funded for all patients who are eligible in all jurisdictions. However, for some patients, travelling to and from an outpatient infusion clinic can be difficult, especially for those who have to travel far.

5.4 Factors Related to Dosing

Nab-paclitaxel would be administered weekly with gemcitabine. This would be an enabler as these patients would already be at the infusion clinics for weekly gemcitabine.

Since there is only one vial size, PAG has significant concerns for incremental costs due to drug wastage. Vial sharing may be difficult because of the small number of patients and the very short stability of reconstituted vials.

5.5 Factors Related to Implementation Costs

As nab-paclitaxel is an add-on therapy, PAG noted that additional chair time to administer the infusion is required. Other factors that could impact implementation include pharmacy preparation time and concerns for drug wastage. More pharmacy preparation time is required to reconstitute and prepare the infusion solution as nab-paclitaxel takes a long time to go into solution.

5.6 Other Factors

The use of growth factors would be additional cost to the drug plans and to the patients in provinces where supportive therapy is funded through pharmacare.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effectiveness of nab-paclitaxel (Abraxane) in combination with gemcitabine for the first line treatment of patients with locally advanced unresectable or metastatic adenocarcinoma of the pancreas.

Supplemental Questions most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7.

- Critical appraisal of an indirect comparison of nab-paclitaxel plus gemcitabine with FOLFIRINOX.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

[Table 1]. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Randomized controlled trials	First line treatment of patients with (i) metastatic adenocarcinoma of the pancreas (or locally advanced unresectable) † Subgroups: • Karnofsky PS • Locally advanced unresectable vs. metastatic disease	Nab-paclitaxel (Abraxane) (125 mg/m^2 iv, qw 3/4 weeks) + gemcitabine (1000 mg/m^2 iv, qw 3/4 weeks)	• Gemcitabine • FOLFIRINOX • Gemcitabine + erlotinib • Gemcitabine based combination therapy (capecitabine, cisplatin) • Fluoropyrimidine + oxaliplatin (eg. 5FU/leucovorin/oxaliplatin or CapeOx) • Capecitabine or continuous infusion of 5FU • Palliative and BSC • Combined chemotherapy (5-FU or capecitabine) and radiation therapy‡	**OS** PFS Response Rate Time to Progression Rate of disease control (CR+PR+SD) One year overall survival **QoL** **AE's and grade ¾ AE's** • **Nausea/vomiting** • **diarrhea** • **Fatigue** • Febrile neutropenia • Peripheral neuropathy • **Pain** • **Decreased appetite** SAE's WDAE
qw: weekly; **OS**: overall survival; **PFS**: progression free survival; **QoL**: quality of life; **AE**: adverse events; **SAE**: serious adverse events; **WDAE**: withdrawal due to adverse events; **FOLFIRINOX**: folnic acid (leucovorin), fluorouracil, irinotecan, oxaliplatin; **5FU**: fluorouracil; **CapeOx**: capecitabine + oxaliplatin; **CR**: complete response; **PR**: partial response; **SD**: stable disease.				

[†]locally advanced would take lower priority considering that the funding request did not include this patient population. The pivotal trial does not specifically address this population, even as a subset, and thus integrating these patients will be difficult given lack of data.

[‡]comparator for locally advanced population only and not relevant for the metastatic group.

** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.2.2 Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; EMBASE (1980-) via Ovid; The Cochrane Central Register of Controlled Trials (2010, Issue 2) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were nab paclitaxel or nab-paclitaxel or abraxane or ABI-007 or "ABI 007" or abi-007 or "abi 007" or albumin bound paclitaxel or protein bound paclitaxel and carcinoma, neoplasm, pancreas, pancreas tumor, pancreas carcinoma and pancreatic neoplasm.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year. Retrieval was limited to the English language.

The search is considered up to date as of August 8, 2014.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicatrials.gov and Ontario Institute for Cancer Research – Ontario Cancer Trials) and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO) were limited to the last five years. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for information as required by the pCODR Review Team.

6.2.3 Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

6.2.4 Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

6.2.5 Data Analysis

No additional data analyses were conducted as part of the pCODR review.

6.2.6 Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

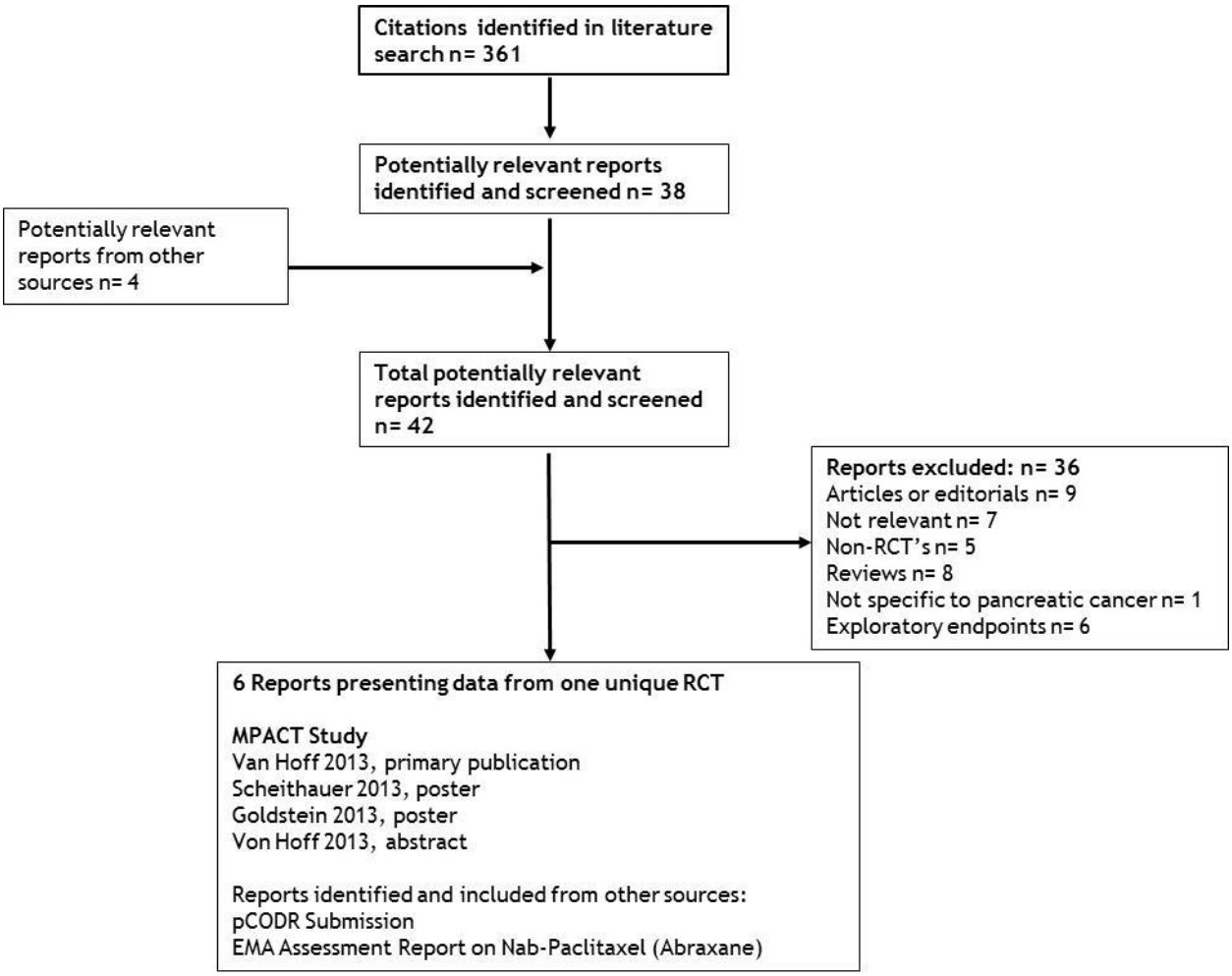
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

6.3 Results

6.3.1 Literature Search Results

Of the 38 potentially relevant reports identified, 6 reports presenting results from one RCT were included in the pCODR systematic review [2,4,5,20-22] and 34 studies were excluded. Studies were excluded because they were articles or editorials[23-29], not relevant [30-36], non-RCT's [37-41], reviews [10,27,42-47], not specific to pancreatic cancer [48] or presented results for exploratory endpoints from the MPACT trial which were not specified as part of the pCODR review protocol. [49-54]

Sample QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to the MPACT study was also obtained through requests to the Submitter by pCODR[55]

6.3.2 Summary of Included Studies

Provide a brief statement summarizing the number and type of included studies.

6.3.2.1 Detailed Trial Characteristics

Table 2. Summary of trial characteristics of the included study, MPACT[2] for patients with metastatic adenocarcinoma of the pancreas.

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
NCT00844649 Funded by: Celgene Randomized: n= 861 Open-label phase 3 RCT Randomized in a 1:1 ratio (nab-paclitaxel plus gemcitabine : gemcitabine) Final analysis-Sept 17, 2012 Updated analysis- May 9, 2013 [3] There is currently an extension study to MPACT (NCT02021500) set to collect data (3 year OS and disease progression) on patients previously enrolled in MPACT. This is a non-randomised observational study. Estimated completion is in March 2015.	Adults (≥18 years of age) Karnofsky PS 70 or more (0 to 100) No prior chemotherapy for metastatic disease Histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas using RECIST Version 1.1 Diagnosed within 6 weeks before randomization. Adequate hematologic, hepatic, and renal function (including an absolute neutrophil count of ≥1.5×10^9 per liter, a hemoglobin level of ≥9 g per deciliter, and a bilirubin level at or below the upper limit of the normal range **Exclusion criteria:** Prior treatment with cytotoxic doses of gemcitabine or any other chemotherapy in the adjuvant setting Patients with islet-cell neoplasms or locally advanced disease	**Intervention:** Nab-paclitaxel 125 mg/m^2 + gemcitabine 1000 mg/m^2 on days 1, 8, 15, 29, 36, and 43 (cycle 1 only). In subsequent cycles, all patients were administered treatment on days 1, 8, and 15 every 4 weeks. **Comparator:** Gemcitabine alone 1000 mg/m^2 weekly for 7 of 8 weeks (cycle 1). In subsequent cycles, all patients were administered treatment on days 1, 8, and 15 every 4 weeks.	**Primary:** OS **Secondary:** Independently assessed PFS and ORR Safety: • Treatment emergent adverse events • Dose reductions interruptions and treatment discontinuation **Exploratory secondary endpoint:** • Rate of disease control All primary and secondary efficacy analyses were carried out in the intention-to-treat population

iv= intravenous; **RECIST**= Response Evaluation Criteria in Solid Tumours; **RCT**= randomized controlled trial; PS= performance status; HR= hazard ratio; **PFS**: progression free survival; **ORR**: objective response rate; **OS**: overall survival

a) Trials

One open-label randomised controlled trial, MPACT[2], met the inclusion criteria for the systematic review. Baseline patient characteristics are listed in Table 3 and were balanced between groups. Patients were excluded from the study if they had islet-cell neoplasms, locally advanced disease or if they had prior treatment with cytotoxic doses of gemcitabine or any other chemotherapy in the adjuvant setting.

The study was funded by Celgene. Patients were enrolled from May 2009 through to April 2012 from 151 community and academic centers in 11 countries. Due to the known toxicities associated with taxanes (alopecia and peripheral neuropathy) and treatment schedule being different between the two arms (in only the first cycle of treatment), blinding of the study was not feasible.[4] Outcomes were however assessed by an independent review committee. Investigator assessed outcomes were also reported.

The method of randomization was generated by a randomization statistician from the sponsor. The randomization was central and implemented via ICON Interactive Voice Response System (IVRS). MPACT randomised 861 patients with previously untreated metastatic adenocarcinoma of the pancreas in a 1:1 ratio to receive nab-paclitaxel plus gemcitabine (n=431) or gemcitabine alone (n=430). Patients were stratified based on performance status, presence or absence of liver metastases and geographic region. The study assessed the superiority of nab-paclitaxel plus gemcitabine compared to gemcitabine alone. Six hundred and eight events were needed from a sample size of 842 patients to have 90% power to detect a HR for death of 0.769 at a two-sided alpha level of 0.049. The power was increased from 80 to 90% in a protocol amendment before any interim analyses were performed. A clarification was requested from the submitter as to why the power calculation was increased. Responses received from the submitter through the checkpoint meeting indicated that the power of the study was increased from 80% to 90% to reduce the likelihood of false negative outcomes in this difficult to treat disease. As a consequence of increasing the power, the sample size was adjusted accordingly. The submitter indicated that this was based on the clinical experience from recent phase 3 pancreatic cancer studies conducted since the approval of gemcitabine. The primary outcome of the MPACT trial was OS. Independently assessed PFS and ORR were secondary outcomes in the trial. PFS and ORR were also assessed by the trial investigators and reported. Additional exploratory secondary efficacy end points included the disease control rate (defined as stable disease for ≥16 weeks, confirmed complete response, or confirmed partial response). The study also reported on treatment emergent adverse events (defined as any AEs that began or worsened in grade after the start of study drug through 30 days after the last dose of study drug or end of treatment, whichever was later), and incidence of dose reductions, interruptions and treatment discontinuations. All efficacy analysis was carried out in the intent to treat population (n=861) while safety analysis was conducted in the treated population only (n=823).[5] Final analysis of the data was carried out in September 17, 2012 and an updated OS analysis was done in May 9, 2013.[3]

b) Populations

MPACT randomised 861 patients with previously untreated metastatic adenocarcinoma of the pancreas in a 1:1 ratio to receive nab-paclitaxel plus gemcitabine (n=431) or gemcitabine alone (n=430). Among the randomised patients, 63 (7%) were Canadian with 33 vs. 30 being in the nab-paclitaxel plus gemcitabine vs. gemcitabine arm, respectively.[5] Baseline patient characteristics were balanced across groups (Table 3). The median age of patients was 62 and 63 years in the nab-paclitaxel plus gemcitabine vs. gemcitabine arms, respectively. Patients also had a Karnofsky PS score of 100 (16% vs. 16%), 90 (42% vs. 46%) or 80 (35% vs. 30%) and had metastasis in the liver (85% vs. 84%) or lungs (35% vs. 43%), respectively in each arm.

Table 3. Baseline Patient Characteristics of all randomised patients in MPACT with previously untreated metastatic adenocarcinoma of the pancreas.[2]		
Characteristic	**Nab-paclitaxel plus gemcitabine, n=431**	**Gemcitabine alone, n=430**
Age (years), n (%)		
Median	62	63
Range	27-86	32-88
Age Distribution, n (%)		
<65 years	254 (59)	242 (56)
≥65 years	177 (41)	188 (44)
Sex, n (%)		
Female	186 (43)	173 (40)
Male	245 (57)	257 (60)
Race, n (%)†		
White	378 (88)	375 (87)
Hispanic	25 (6)	26 (6)
Black	16 (4)	16 (4)
Asian	8 (2)	9 (2)
Other	4 (1)	4 (1)
Region, n (%)		
Australia	61 (14)	59 (14)
Eastern Europe	64 (15)	62 (14)
North America	268 (62)	271 (63)
Western Europe	38 (9)	38 (9)
Karnofsky PS, n (%)‡		
100	69/429 (16)	69/429 (16)
90	179/429 (42)	199/429 (46)
80	149/429 (35)	128/429 (30)
70	30/429 (7)	33/429 (8)
60	2/429 (<1)	0/429 (0)
Site of metastatic disease, n (%)		
Liver	365 (85)	360 (84)
Lung	153 (35)	184 (43)
Peritoneum	19 (4)	10 (2)
Number of metastatic sites, n (%)		
1	33 (8)	21 (5)
2	202 (47)	206 (48)
3	136 (32)	140 (33)
>3	60 (14)	63 (15)
Pancreatic tumour location, n (%)		
Head	191 (44)	180 (42)
Body	132 (31)	136 (32)
Tail	105 (24)	110 (26)
Unknown	3 (1)	4 (1)

Notes: PS= performance status;

† Race or ethnic group was self-reported, ‡ The authors reported that the Karnofsky performance-status scores ranges from 0 to 100, with higher scores indicating better performance status. Two patients in the nab-paclitaxel +plus gemcitabine group had a score of 70 or more at the screening visit but a score of 60 at the baseline visit on day 1 of cycle 1.

c) Interventions

Details of the dose and administration of treatment and control arms for both trials can be found in Table 2 and Table 5. The median duration of therapy were 3.9 vs 2.8 months in the nab-paclitaxel plus gemcitabine vs. gemcitabine arms with 32% and 15% of patients, respectively, receiving treatment for at least 6 months. Treatment continued until patients experienced disease progression or unacceptable toxicity.[2]

The use of granulocyte colony-stimulating factors (G-CSF) was allowed in MPACT for the treatment of neutropenic fever or infections associated with neutropenia and for the prevention of febrile neutropenia in patients with absolute neutrophil count (ANC) < 0.5 x 10^9/L. Patients not experiencing resolution of neutropenia within 21 days, despite uninterrupted G-CSF treatment, were discontinued from study treatment. Supportive care, including but not limited to antiemetic medications, was administered at the discretion of the investigator.[5]

Nearly all patients received concomitant medications of special interest during the study, 91% vs. 83% in the nab-paclitaxel plus gemcitabine vs. gemcitabine arms respectively.[5] Medications of special interest included: narcotics, anti-infectives, WBC growth factors, erythropoietins, blood transfusions and blood products. Concomitant therapies to reduce the extent of myelosuppression were more common in the combination arm than in the gemcitabine arm, i.e. WBC growth factors (26% vs. 15%), erythropoietins (16% vs. 11%), blood transfusions (12% vs. 7%) and blood products (4% vs. 3%) in the nab-paclitaxel plus gemcitabine vs. gemcitabine arms respectively.[4] According to the CGP, the difference in the proportion of patients receiving concomitant medications among the two arms is not expected to have impacted the results. Through the checkpoint meeting, the submitter provided information on the number of Canadian patients that required concomitant medication with growth factors. The CGP confirmed that the proportion of Canadian patients that participated in the MPACT study and which received growth factors is generalizable to the Canadian setting.

d) Patient Disposition

All 861 randomised patients were included in the final efficacy analysis while safety analysis was conducted in the treated population only (n=823). [5] Among the randomised patients, 38 were not treated, primarily because of patient's withdrawal before the study medications were started.[5]

Among the treated population 94% and 97% of patients discontinued treatment in the nab-paclitaxel plus gemcitabine arms, respectively. The majority of patients discontinued treatment due to disease progression or adverse events in the nab-paclitaxel plus gemcitabine and gemcitabine arms. More patients in the gemcitabine arm discontinued treatment due to disease progression (47% vs. 61%) while more patients in the nab-paclitaxel plus gemcitabine arm discontinued treatment due to adverse events (30% vs. 18%). Among patients that discontinued treatment due to adverse events, there were more treatment related adverse events in the nab-paclitaxel plus gemcitabine vs. gemcitabine arms (20% vs. 7%, respectively). All other reasons for treatment discontinuation were similar among the two arms.

Patients were only allowed to crossover following confirmed disease progression.

Table 4. Percentage of patients in the MPACT study that discontinued treatment.[5]		
	Nab-paclitaxel plus gemcitabine	**Gemcitabine**
Patients treated, n (%)	**n=421 (100%)**	**n=402 (100%)**
Patients discontinued	394 (94%)	391 (97%)
Reason for treatment discontinuation		
Progressive disease	196 (47%)	245 (61%)
Adverse events	128 (30%)	73 (18%)
Related to study drug	86 (20%)	29 (7%)
Unrelated to study drug	42 (10%)	44 (11%)
Physicians decision	25 (6%)	18 (4%)
Protocol violation	10 (2%)	6 (1%)
Withdrawal by patient	28 (7%)	39 (9%)
Other	7 (2%)	10 (2%)
Notes:		

e) Limitations/Sources of Bias

- Due to the nature of the intervention used, the MPACT study was designed as an open label study. Although it is reasonable to have an open label design in a study in which the intervention is administered iv, the study design could still potentially introduce bias. Measures were however taken to limit bias for PFS and ORR (secondary outcomes) by having a blinded independent review committee assess the results.
- Patients in the nab-paclitaxel plus gemcitabine arm also received more concomitant medications throughout the trial than those on gemcitabine. Based on clinical input, the increased amount of concomitant medication is however not expected to contribute to differences in patient outcomes.
- Information is not provided regarding the number of patients enrolled into the trial compared to those randomised. As such it is not clear as to whether there was any important difference in patient numbers when comparing patients enrolled vs. patients randomised. If such a difference is present, it may be important to determine the rationale behind why the patients were excluded and rule out any potential for selection bias.
- A potential source of bias was identified regarding the generalizability of the trial results as the patients included in the study were considered to be healthier than patients in the clinical setting. The CGP confirmed that this is typical of recruitment practices into a clinical trial and considered that the patients in the trial are still generalizable to the clinical setting.
- From a methodological perspective the low number of Canadian patient (n= 63) in the study make it uncertain how generalizable results are to the broader Canadian population. The submitter was asked to provide information through the checkpoint meeting on the number of Canadian patients that received concomitant medications and those that went on to receive subsequent therapy. The CGP did however confirm that the proportion of patients that received concomitant medications and went onto subsequent therapy was generalizable to the Canadian clinical setting. [55]
- Disease control rate was reported as an exploratory analysis and, therefore, is subject to bias. Post hoc-analysis of time to progression was requested by pCODR and provided as part of checkpoint responses by the submitter but is subject to bias as it was not a pre-specified analysis.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Table 5. Key efficacy and harms outcomes reported for the MPACT study comparing nab-paclitaxel plus gemcitabine vs. gemcitabine alone in patients with previously untreated metastatic adenocarcinoma of the pancreas.

Efficacy Outcomes[2]

Analysis date	Treatment arms	OS, median (mos)	PFS, median (mos)	Objective response, n (%)
Final analysis (Sept 12, 2012)[2]	Nab-paclitaxel plus gem, n=431 Gem alone, n=430	8.5 6.7 HR 0.72 95%CI 0.62 to 0.83 P<0.001	5.5 3.7 HR 0.69 95%CI 0.58 to 0.82 P<0.001	99 (23%) 31 (7%) HR 3.19 95%CI 2.18 to 4.66 P<0.001

Harms Outcomes[4]

	Nab-paclitaxel plus gemcitabine, n=421	Gemcitabine, n=402
Deaths, n (%)	18 (4%)	18 (4%)
Treatment related deaths	7 (3%)	2 (<1%)
Grade 3/4 adverse events of interest		
Fatigue, n (%)	77 (18)	37 (9)
Diarrhea, n (%)	26 (6)	6 (1)
Nausea, n (%)	27 (6)	14 (3)
Vomiting, n (%)	25 (6)	15 (4)
Peripheral neuropathy, n (%)	70 (17)	3 (1)
Febrile Neutropenia, n (%)	14 (3%)	6 (1%)
Abdominal Pain, n (%)	27 (6)	32 (8%)
Dose Reduction, n (%)	38%/44%	31%
Dose Delay/dose not given*, n (%)	63%/61%	48%
Dose Interruption, n (%) [5]	1%/2%	2%
Withdrawal due to adverse events, n (%)	148 (35%)/126(30%)	95 (24%)

Notes: 95%CI= 95% confidence interval; **Gem**= gemcitabine; **HR**=hazard ratio with HR<1 favouring nab-paclitaxel plus gemcitabine; **mos**=months; **n**=number of patients; **NR**=not reported; **OS**=overall survival; **PFS**=progression-free survival.

Efficacy Outcomes

Overall Survival

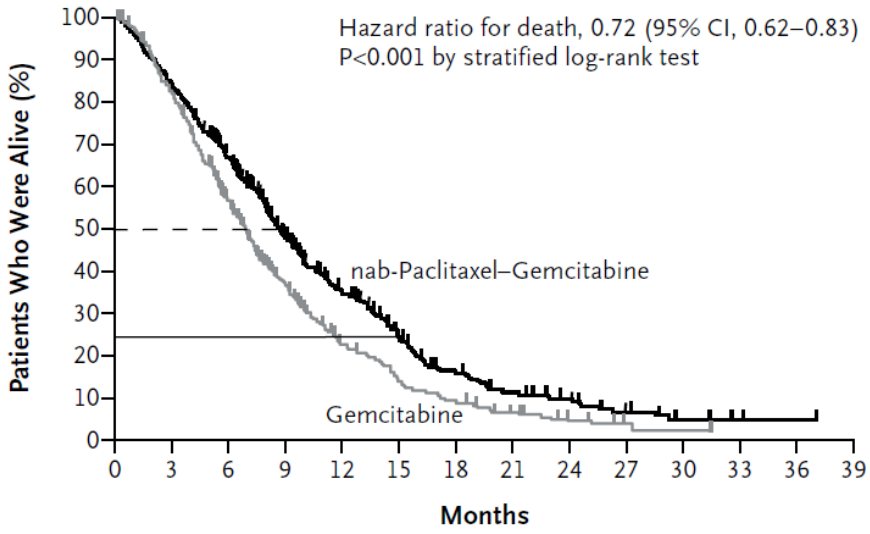
OS was defined as the time from the date of randomization to the date of death from any cause .[4] The MPACT study reported statistically significant differences in overall survival in favour of the nab-paclitaxel plus gemcitabine arm. At the final analysis the median overall survival was 8.5 vs. 6.7 months in the nab-paclitaxel plus gemcitabine vs. gemcitabine arms, respectively (HR 0.72 95%CI 0.62 to 0.83 p<0.001) (Van Hoff 2013). The final analysis (September 12, 2012) was based on 692 (80%) events with 333 (77%) vs. 359 (83%) in the nab-paclitaxel plus gemcitabine vs. gemcitabine arms, respectively. Updated overall survival analysis (May 9, 2013) where 380 (88%) vs. 394 (92%) events had occurred in each arm showed

similar results with a median overall survival of 8.7 vs. 6.6 months in the nab-paclitaxel plus gemcitabine vs. gemcitabine arms, respectively (HR 0.72 95%CI 0.620-0.825, p <0.0001) [3]. One (35% vs. 22% respectively, p< 0.001) and two (9% vs. 4% respectively, p=0.02) year overall survival of patients was also significantly more in the nab-paclitaxel plus gemcitabine vs. gemcitabine arms.[2]

Patients were allowed to receive subsequent therapies following confirmed disease progression (Table 6). OS analysis based on censoring of patients that received subsequent therapy demonstrated similar results favouring the nab-paclitaxel plus gemcitabine arm.[4] The majority of patients that crossed over received other 5-FU/capecitabine based therapy (26% vs. 30%, respectively in the nab-paclitaxel plus gemcitabine vs. gemcitabine arms).[4] In the gemcitabine arm 25 (7%) of patients crossed over to the nab-paclitaxel plus gemcitabine arm following confirmed disease progression.[4]

Figure 1. Overall survival Kaplan-Meier curves from the MPACT study of A[2]: September 17 2012 Final analysis and B[3]: Updated May 9 2013 analysis, comparing nab-paclitaxel plus gemcitabine vs. gemcitabine alone in previously untreated patients with metastatic adenocarcinoma of the pancreas

A



No. at Risk

nab-Paclitaxel–Gemcitabine	431	357	269	169	108	67	40	27	16	9	4	1	1	0
Gemcitabine	430	340	220	124	69	40	26	15	7	3	1	0	0	0

B

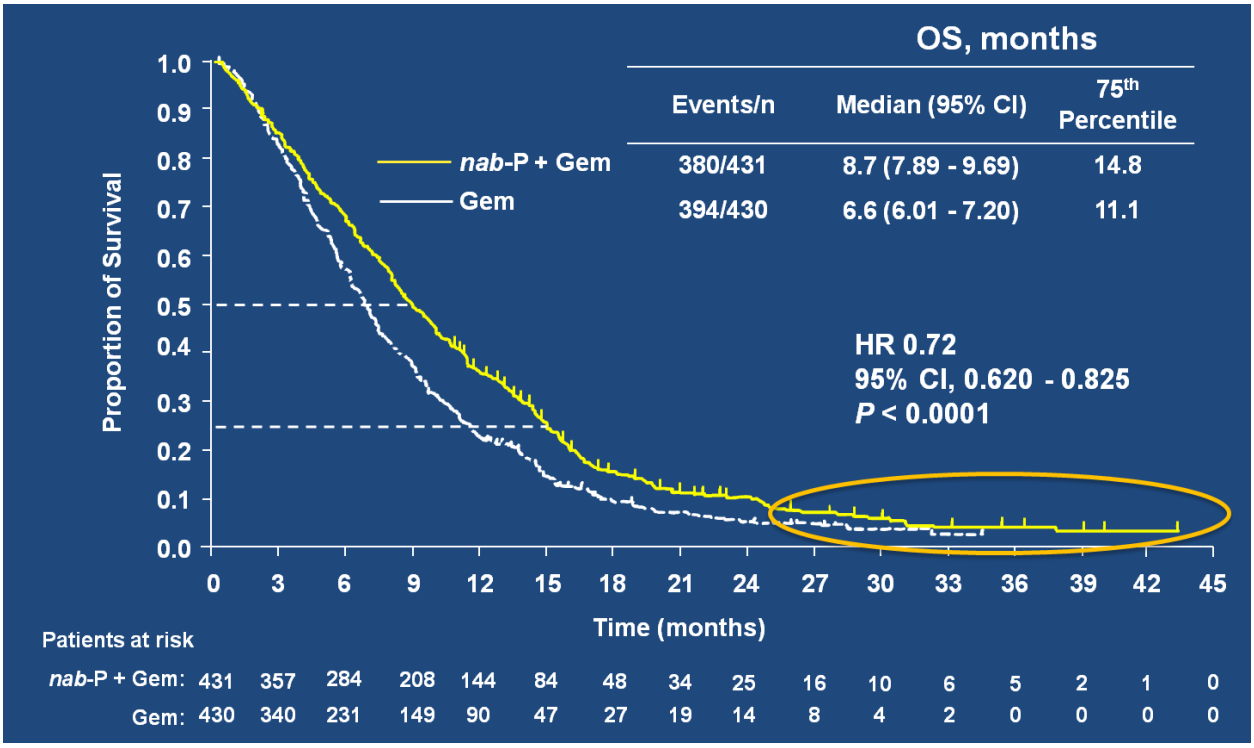


Table 6. Summary of select subsequent therapies used in the ITT population following confirmed progression of disease.[4]

Drug category	Nab-paclitaxel plus gemcitabine, n=431	Gemcitabine, n=430
Patients receiving subsequent therapy	162/431 (38%)	179/430 (42%)
Other 5-FU*/Capecitabine Based	112/431 (26%)	130/430 (30%)
FOLFIRINOX (modified/unmodified**)	19/431 (4%)	25/430 (6%)
Erlotinib Based (Including with other 5-FU)[5]	13/431 (3%)	11/430 (3%)
Other[5]	43/431 (10%)	50/430(12%)

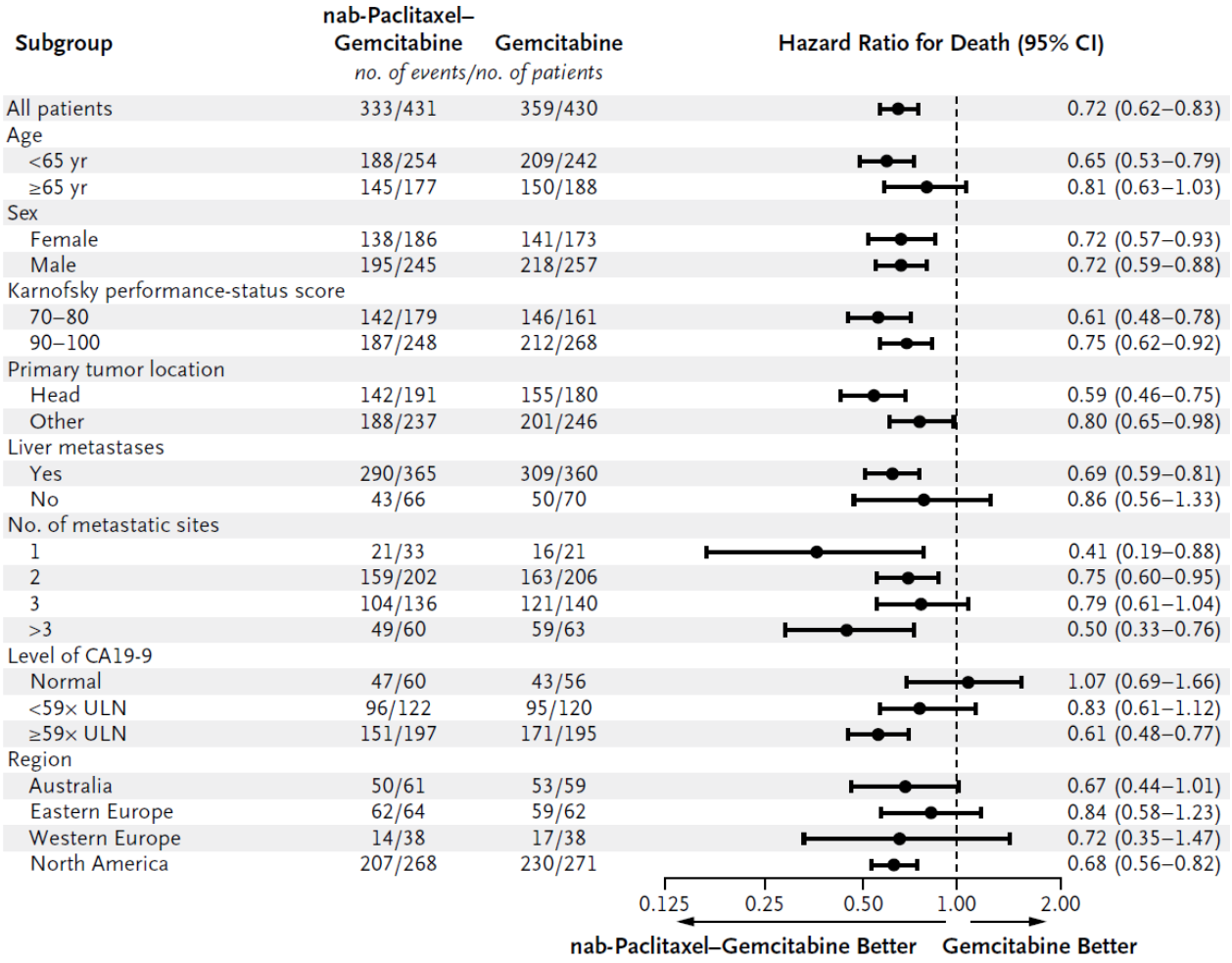
Notes: FOLFIRINOX: Folinic acid (leucovorin), 5-fluorouacil, irinotecan and oxaliplatin; **5-FU:** 5-fluorouracil

*Other 5-FU containing regimen, excluding FOLFIRINOX

**The manufacturer was asked to clarify what constituted modified FOLFIRINOX through the checkpoint meeting. The manufacturer indicated that this information was not collected and so there is no information available on what physicians may have done to modify the FOLFIRINOX dose in second line therapy.

Analysis by stratification factors showed that patients with poorer performance status (Karnofsky performance status score of 70 or 80) and those with the presence of liver metastasis had the greatest reduction in the risk of death (Figure 2). Analysis of OS in the pre-specified subgroups indicated that treatment effect was consistently favoured for nab-paclitaxel plus gemcitabine across most subgroups. Similar trends were observed across the pre-specified subgroups for progression free survival.

Figure 2. Subgroup analyses of overall survival from the MPACT study comparing nab-paclitaxel plus gemcitabine to gemcitabine alone in patients with previously untreated metastatic adenocarcinoma of the pancreas. [2]

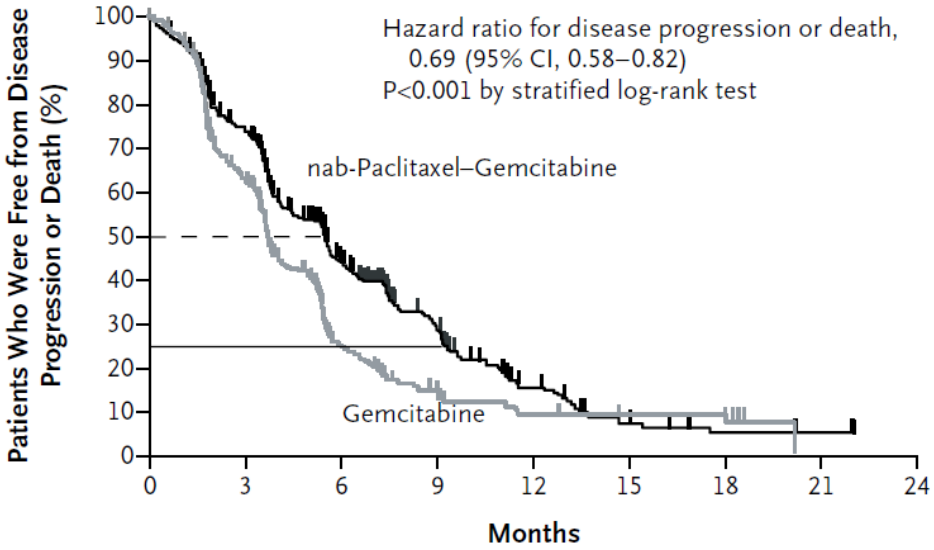


Progression free survival

Progression-free survival was defined as the time from the date of randomization to the date of disease progression or death (any cause) on or prior to the clinical cut-off date, whichever occurred first, based on the blinded IRR of CT or MRI response using RECIST guidelines, v1.0. [4] The MPACT study also reported statistically significant longer independently assessed PFS for patients receiving nab-paclitaxel plus gemcitabine compared to gemcitabine alone. At the time of the analysis, 542 PFS events (progressive disease or death) had occurred with 277 (64%) vs. 265 (62%) in the nab-paclitaxel plus gemcitabine vs. gemcitabine arms, respectively. The median PFS was 5.5 vs. 3.7 months in the two arms respectively (HR 0.69 95%CI 0.58 to 0.82 p<0.001). For the analysis of PFS, a similar amount of patients (36% vs. 38%, respectively) were

censored in each arm.[4] Investigator-assessed progression-free survival was similar to the independently assessed PFS results.

Figure 3. September 17 2012 Final analysis of Independently assessed progression free survival Kaplan-Meier curves from the MPACT study comparing nab-paclitaxel plus gemcitabine vs. gemcitabine alone in previously untreated patients with metastatic adenocarcinoma of the pancreas [2]



No. at Risk									
nab-Paclitaxel–Gemcitabine	431	281	122	62	24	8	4	2	0
Gemcitabine	430	209	51	23	10	6	4	0	0

Objective response rate

ORR was defined as the number and percentage of patients who achieved a confirmed CR or PR as measured by an IRR review of CT and MRI scans.[4] The objective response rate (by independent assessment) was significantly higher in the nab-paclitaxel plus gemcitabine vs. gemcitabine arm with 23% (99/431) vs 7% (31/430) patients achieving objective response in each arm, respectively (Response-rate ratio 3.19 95% CI 2.18 to 4.66 p< 0.001, with a HR > 1 favouring the nab-paclitaxel plus gemcitabine arm) (Van Hoff 2013).[2] One patient (<1%) in the nab-paclitaxel plus gemcitabine arm was confirmed to have complete response while the rest had partial response.[4] Similar objective response rates were observed with investigator assessment.

Disease control Rate

The disease control rate, defined as confirmed response or stable disease for ≥16 weeks, was significantly greater in the nab-paclitaxel plus gemcitabine vs. gemcitabine arms with 48% (206/431) patients vs. 33% (141/430) patients achieving disease control in each arm respectively (Response-rate ratio 1.46 95% CI 1.23 to 1.72, with a HR > 1 favouring the nab-paclitaxel plus gemcitabine arm) (Van Hoff 2013). [2]

Time to Progression

Time to progression was not reported in the MPACT study. Upon further request to the manufacturer through the checkpoint meeting, a post-hoc analysis for time to disease analysis was provided. The results indicated that time to disease progression was statistically significantly improved in patients receiving nab-paclitaxel plus gemcitabine vs gemcitabine.

Quality of Life

Quality of life data was not measured in the MPACT study. Upon further request made to the submitter regarding the availability of quality of life data, the manufacturer confirmed that this data was not collected during the study. The submitter confirmed that patient reported outcomes are currently being collected in 3 separate studies and should be available within the next 2-3 years.[55]

Harms Outcomes

Deaths

A similar number of deaths were reported in both arms 18/421 (4%) and 18/402 (4%). Among these, 9 deaths were attributed to treatment with 7 (2%) vs. 2 (<1%) being in the nab-paclitaxel plus gemcitabine vs. gemcitabine arms, respectively.[4] In the nab-paclitaxel plus gemcitabine arm, 1 patient had acute respiratory distress syndrome and pneumonia, and 1 patient each had diffuse alveolar damage, septic shock, neutropenic sepsis, bacterial sepsis, abnormal hepatic function, and general physical health deterioration that were considered treatment-related. In the gemcitabine arm, 1 patient had a fatal treatment-related AE of large intestine perforation, and 1 patient had fatal treatment-related AEs of acute respiratory failure, hepatic failure, hypovolemic shock and acute renal failure.[5] Overall fatal events that occurred more frequently in the nab-paclitaxel plus gemcitabine arm than in the gemcitabine arm included sepsis (5% vs. 2%) and pneumonitis (3% vs. 1%).[4]

Grade 3 or higher TEAE's

More patients in the nab-paclitaxel plus gemcitabine vs. gemcitabine arm experienced at least one grade 3 or higher treatment emergent adverse events (TEAE), 89% vs. 75% respectively (Table 7). The most frequently occurring (≥10%) grade 3 or higher TEAE in the nab-paclitaxel plus gemcitabine vs. gemcitabine arm were neutropenia (33% vs. 21%), fatigue (19% vs. 9%), peripheral neuropathy (17% vs. 1%), thrombocytopenia (13% vs. 8%) and anemia (12% vs. 8%), respectively. Grade 3 or higher febrile neutropenia was reported in 3% vs. 1% of patients in the nab-paclitaxel plus gemcitabine vs. gemcitabine arms, respectively. Grade 3 or higher abdominal pain was comparable among the two arms (6% vs. 8%, respectively) while decreased appetite was more in patients in the nab-paclitaxel plus gemcitabine vs gemcitabine arms (5% vs. 2%, respectively).[4]

Treatment Emergent Adverse Events (TEAE's)

Nearly all patients experienced at least one treatment emergent adverse event (TEAE) in both arms (Table 7). Overall, patients in the nab-paclitaxel plus gemcitabine arm experienced more TEAE than those in the gemcitabine arm including for the following outcomes of interest: fatigue (59% vs. 46%), diarrhea (44% vs. 24%), nausea (54% vs. 48%), vomiting (36% vs. 28%) and peripheral neuropathy (54% vs. 13), respectively. Febrile neutropenia was reported in 3% vs. 1% of patients in the nab-paclitaxel plus gemcitabine vs. gemcitabine arms, respectively.[4] Abdominal pain (23% vs. 23%), upper abdominal pain (10% vs. 7%) and decreased appetite (36% vs. 26%) were similar among the nab-paclitaxel vs. gemcitabine arms, respectively.

Table 7. Treatment emergent adverse events reported in at least 10% of the treated population in MPACT.[4]		
	Nab-paclitaxel plus gemcitabine, n=421	**Gemcitabine, n=402**
Treatment emergent adverse events	**419 (99%)**	**395 (98%)**
Treatment emergent adverse events of interest		
Fatigue, n (%)	248 (59)	183 (46)
Diarrhea, n (%)	184 (44)	95 (24)
Nausea, n (%)	228 (54)	192 (48)
Vomiting, n (%)	151 (36)	113 (28)
Decreased appetite, n (%)	152 (36%)	104 (26%)
Peripheral neuropathy, n (%)	227 (54)	51 (13)
Febrile Neutropenia, n (%)[5]	14 (3%)	6 (1%)
Abdominal Pain, n (%)	98 (23%)	91 (23%)
Abdominal Pain Upper, n (%)	43 (10%)	28 (7%)
Grade 3 or higher treatment emergent adverse events reported in at least 5% of the population.[4]		
Patients with at least 1 grade 3 or higher TEAE, n (%)	**374 (89)**	**303 (75)**
Blood and lymphatic system disorders, n (%)	**202 (48)**	**128 (32)**
Neutropenia, n (%)	138 (33)	85 (21)
Thrombocytopenia, n (%)	53 (13)	33 (8)
Anemia, n (%)	49 (12)	32 (8)
Leukopenia, n (%)	39 (9)	15 (4)
General disorders and administration site conditions, n (%)	**132 (31)**	**76 (19)**
Fatigue, n (%)	77 (18)	37 (9)
Asthenia, n (%)	29 (7)	17 (4)
Gastrointestinal disorders, n (%)	**114 (27)**	**92 (23)**
Abdominal pain, n (%)	27 (6)	32 (8)
Diarrhea, n (%)	26 (6)	6 (1)
Nausea, n (%)	27 (6)	14 (3)
Vomiting, n (%)	25 (6)	15 (4)
Nervous system disorders, n (%)	**82 (19)**	**19 (5)**
Peripheral neuropathy, n (%)	70 (17)	3 (1)
Metabolism and nutritional disorders, n (%)	**76 (18)**	**48 (12)**
Dehydration, n (%)	31 (7)	10 (2)
Decreased appetite, n (%)	23 (5)	8 (2)
Hypokalemia, n (%)	18 (4)	6 (1)
Respiratory, thoracic and mediastinal disorders, n (%)	**41 (10)**	**45 (11)**
Pulmonary embolism, n (%)	19 (5)	26 (6)
Vascular Disorders, n (%)	**41 (10)**	**39 (10)**
Deep vein thrombosis, n (%)	21 (5)	22 (5)

Dose reductions, dose interruptions and dose delays/dose not given

More patients in the nab-paclitaxel plus gemcitabine arm experienced dose reduction than the gemcitabine arm alone (38%/44% vs. 31%, respectively). In the nab-paclitaxel plus gemcitabine arm the most common (≥ 5% of patients) cause for dose reduction in either the nab-paclitaxel or gemcitabine dose were neutropenia, thrombocytopenia and peripheral neuropathy. In the gemcitabine arm the most common cause for a dose reduction were neutropenia and thrombocytopenia. The dose reductions protocol involved a possible reduction to 100 mg/m^2 (-1) or 75 mg/m^2 (-2) for the nab-paclitaxel dose and 800 mg/m^2 (-1) or 600 mg/m^2 (-2) for the gemcitabine dose. If an TEAE occurred requiring further dose reduction than the -2 level, the treatment was discontinued.[5]

More patients in the nab-paclitaxel plus gemcitabine arm experienced dose delays/not given than in the gemcitabine arm. In the nab-paclitaxel plus gemcitabine arm 63% and 61% of patients had a dose delay/not given, respectively while in the gemcitabine arm 48% of patients had a dose delay/not given. In the nab-paclitaxel arm, the most common (≥ 5% of patients) reported cause for a dose delay/dose not given were neutropenia, thrombocytopenia, fatigue, peripheral neuropathy, peripheral sensory neuropathy, anemia and diarrhea.

Treatment emergent adverse events resulting in dose interruptions were low and similar in the nab-paclitaxel plus gemcitabine and gemcitabine arms.

Withdrawal due to adverse events

Treatment emergent adverse events resulting in permanent discontinuation of therapy occurred more in the nab-paclitaxel plus gemcitabine vs. gemcitabine arms (35%/30% vs. 24%, respectively). The most common cause for permanent discontinuation in the nab-paclitaxel plus gemcitabine arm was peripheral neuropathy, fatigue and thrombocytopenia (Table 7).

6.4 Ongoing Trials

Two ongoing randomized trials investigating the use of nab-paclitaxel plus gemcitabine in patients with previously untreated locally advanced unresectable pancreatic cancer met the eligibility criteria for this review: NCT02043730 and NCT01836432. Details can be found below.

Table 8.

Clinical Trial Design	Patient Population	Intervention and comparator	Outcomes
NCT02043730: Phase II Randomized Trial Comparing a Combination of Abraxane and Gemcitabine Versus Gemcitabine Alone as First Line Treatment in Locally Advanced Unresectable Pancreatic Cancer. GAP (Gemcitabine Abraxane Pancreas) Trial			
Randomized controlled trial Estimated completion: January 2017 Estimated enrolment: n=124 **Sponsor:** Gruppo Italiano per lo studio dei Carcinomi dell'Apparato Digerente **Location**: Italy	Patients with Locally advanced unresectable pancreatic cancer Inclusion Criteria: • Age >18 < 75 years • Histologically/cytologically confirmed locally advanced, unresectable pancreatic cancer • At least one lesion measurable with CT or MRI scan • ECOG PS 0-1 at study entry • Life expectancy of at least 3 months • Adequate marrow, liver and renal function • Effective contraception if the risk of conception exists (in the Informed Consent for the patients the descriptions of possible contraceptives is reported)	Gemcitabine plus nab-paclitaxel (125 mg/mq over 30 min) vs. Gemcitabine alone (1000 mg/mq weekly on days 1, 8 and 15 of a 28-day cycle)	Primary Objective: • Progression rate Secondary Objective: • OS • PFS • TEAE's
NCT01836432: A Phase III Study of Chemotherapy With or Without Algenpantucel-L (HyperAcute®-Pancreas) Immunotherapy in Subjects with Borderline Resectable or Locally Advanced Unresectable Pancreatic Cancer (PILLAR)			
Randomized controlled trial Currently recruiting patients Estimated completion: June 2017 Estimated enrolment: n=280 **Sponsor:**	Patients with borderline resectable or locally advanced unresectable pancreatic cancer Inclusion Criteria: • 18 years or older • A histological confirmed adenocarcinoma of the pancreas • borderline resectable or locally advanced unresectable pancreatic cancer with no metastatic spread • ECOG PS ≤ 1	FOLFIRINOX + algenpantucel-L Immunotherapy FOLFIRINOX Gemcitabine plus nab-paclitaxel + algenpantucel-L Immunotherapy Gemcitabine plus nab-paclitaxel*	Primary Objective: • Overall Survival (Sept 2015 - final data collection date for OS) Secondary Objective: • PFS • All grades AE's • Immune response

Clinical Trial Design	Patient Population	Intervention and comparator	Outcomes
NewLink Genetics Corporation **Location:** United States	• Serum albumin ≥ 2.0 gm/dL. • Expected survival ≥ 6 months • Adequate organ function		
NCT02106884: Randomized Crossover Trial to Assess the Effects and Quality of Life in Patients With Locally Advanced or Metastatic Pancreatic Cancer Treated With Gemcitabine in Combination With Nab-paclitaxel: QOLINPAC			
Phase II Randomized controlled trial, open label Currently recruiting patients Estimated completion: Dec 2016 Estimated enrolment: n=110 **Sponsor:** Celgene Corporation **Location:** Belgium	Patients with locally advanced or metastatic pancreatic adenocarcinoma Inclusion Criteria: • Written informed consent (+ optional for TR) must be given according to ICH/GCP and national/local regulations. • Patient is at least 18 years of age. • Unresectable locally advanced or metastatic pancreatic cancer. • Histologically or cytologically confirmed adenocarcinoma of the pancreas. Islet cell neoplasms are excluded. • Evaluable or measurable disease, not in a previously irradiated area. • Life expectancy of at least 12 weeks. • WHO ECOG performance status ≤ 2 • Adequate organ function. • Adequate bone marrow, hepatic and renal function • Acceptable coagulation (prothrombin time and partial thromboplastin time within +/- 15% of normal limits). • No clinically significant abnormalities in urinalysis. • Effective contraception for both male and female patients if applicable. Women of childbearing potential must have negative blood pregnancy test at screening visit.	Nab-paclitaxel - IV - 125 mg/m2 - 3xq4wks + Gemcitabine - IV - 1000 mg/m2 - 3xq4wks Gemcitabine - IV - 1000 mg/m2 - 3xq4wks	Primary Objective: • Deterioration free rate of quality of life (QOL) scores at three months Secondary Objective: • Safety and tolerability profile • PFS • OS • Overall response and duration of response •
Note: FOLFIRINOX: folnic acid (leucovorin), fluorouracil, irinotecan, oxaliplatin; * No information is provided on the comparison to be made between the 4 arms in the data analysis.			

7 SUPPLEMENTAL QUESTIONS

7.1 Critical appraisal of an indirect comparison of nab-paclitaxel plus gemcitabine with FOLFIRINOX

7.1.1 Objective

To summarize and critically appraise the methods and findings of the manufacturer-submitted indirect comparison of nab-paclitaxel plus gemcitabine versus FOLFIRINOX for the treatment of metastatic pancreatic cancer. FOLFIRINOX is a potential option in the first-line setting in metastatic pancreatic cancer, and is widely funded across Canada.

7.1.2 Findings

The manufacturer submitted an indirect comparison to estimate the efficacy of nab-paclitaxel plus gemcitabine versus FOLFIRINOX in order to inform their economic model to determine the cost-utility. The main analysis for the indirect comparison submitted by the manufacturer was based on the results of two trials: the MPACT[2] trial1 that compared nab-paclitaxel plus gemcitabine to gemcitabine alone and the PRODIGE 4/ACCORD 11[11] trial2 that compared FOLFIRINOX to gemcitabine. No other studies were identified through the systematic review as meeting the eligibility criteria.

This indirect comparison, however, was a naïve (unadjusted) indirect comparison, as it does not take into account within trial comparisons and therefore is not adjusted for the results of the common control group.[12] Further, in this particular case, there is only one randomized controlled trial to inform each arm of the indirect comparison, limiting the generalizability of the results and increasing any potential risk of bias. The clinical guidance panel were consulted on the comparability between the two study populations and they concluded that they were different: patients eligible for FOLFIRINOX are generally healthier. A summary of the two studies is presented in the following table.

Table 1. Study and baseline characteristics of studies included in submitter's indirect treatment comparison

Study	MPACT trial[2]	PRODIGE 4/ACCORD 11 trial[11]
Intervention	Nab-paclitaxel plus gemcitabine	FOLFIRINOX
Comparator	Gemcitabine	Gemcitabine
Location	International	France
Design	Randomized controlled trial	Randomized controlled trial
Method of randomization	N/R	Central randomization
Method of blinding	Open-label	N/R
Cross-over permitted	Yes	N/R
Primary outcome	Overall survival	Overall survival
Secondary outcomes	Progression-free survival, response rate, rate of disease control, time to treatment failure, safety	Progression-free survival, tumor response, safety, quality of life.
Duration of follow-up	N/R	26.6 months
Eligibility criteria	Adults (≥18 years of age); Karnofsky performance-status score of 70 or more; had not previously received chemotherapy for metastatic	Adults (18 -75 years of age); histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas not previously treated

	disease; histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas. Metastatic disease had to have been diagnosed within 6 weeks before randomization. Previous therapy allowed.	with chemotherapy; ECOG performance of 0 or 1; adequate bone marrow, liver function and renal function.
Number of patients in intervention group	431	171
Median age of patients in intervention group	62 (27 – 86)	61 (25-76)
Karnofsky performance status, % 100 90 80 70 60	 16 42 35 7 <1	 N/R
ECOG performance status, % 0 1 2	N/R	 37 62 1
Number of metastatic sites, % 1 2 3 >3	 8% 47% 32% 14%	 See below
Number of metastatic sites, median	See above	2 (1 – 6)
Pancreatic tumor location, % Head Body Tail Unknown Multicentric	 44% 31% 24% 1% N/R	 39% 31% 26% 0 4%
ECOG, Eastern Cooperative Oncology Group; N/R, not reported		

As this was a first-order comparison, no adjusted methods were applied. Hazard ratios for outcomes in the individual trials are presented in the following table:

Table 2. Hazard ratios and 95% confidence intervals for results of studies included for indirect comparison

Study	HR	CI	p-value
Overall survival			
MPACT trial[2]	0.72	0.62 – 0.83	<0.001
PRODIGE 4 /ACCORD 11 trial[11]	0.57	0.45 – 0.73	<0.001
Progression-free survival			
MPACT trial[2]	0.69	0.58 – 0.82	<0.001
PRODIGE 4 /ACCORD 11 trial[11]	0.47	0.37 – 0.59	<0.001

The incidence of adverse events for the two individual trials included in the indirect comparison are presented in the following table:

Table 3. Adverse events (grade 3 or higher) for patients in the studies included for the indirect comparison, n(%)

Study	MPACT trial[2] n (%) or %	PRODIGE 4/ACCORD 11 trial[11] n (%)
Neutropenia	153/405 (38)	75/164 (45.7)
Febrile neutropenia	14 (3)	9/166 (5.4)
Thrombocytopenia	52/405 (13)	15/165 (9.1)
Fatigue	70 (17)	39/165 (23.6)
Diarrhea	24 (6)	21/165 (12.7)
Sensory neuropathy	70 (17)	15/166 (9.0)
Thromboembolism	N/R	11/166 (6.6)

The quality of the trials included is adequate. For the PRODIGE 4 / ACCORD 11 trial, the method of blinding was not detailed, nor was it explicitly specified whether cross-over was allowed or not.

Baseline characteristics of the patients in the intervention arm of the two studies appear similar for age, number of metastatic sites and tumor location. There were more patients with a lower Karnofsky score (Karnofsky score of 70 approximates an ECOG performance status of 2), in the MPACT trial than in the PRODIGE 4 / ACCORD 11 trial.

As there is no pooled data (only two trials, one for each arm), the ISPOR checklist does not apply. However, the substantial heterogeneity between the two trials would lead to unreliable and highly uncertain results from the indirect comparison.

7.1.3 Summary

The indirect comparison of nab-paclitaxel plus gemcitabine versus FOLFIRINOX included two studies: the MPACT trial[2] and the PRODIGE 4 / ACCORD 11 trial[11]. The clinical guidance panel were consulted on the comparability between the two study populations and they concluded that they were different: patients eligible for FOLFIRINOX are generally healthier. As the submitter did not compare the hazard ratios between the two trials, it is not possible to comment on the statistically significant differences for overall survival and progression-free survival. This was a naïve (unadjusted) indirect comparison, as it does not take into account within trial comparisons and therefore is not adjusted for the results of the common control group.[12 15] Further, in this particular case, there is only one randomized controlled trial to inform each arm of the indirect comparison, limiting the generalizability of the results and increasing any potential risk of bias. The substantial heterogeneity between the two trials also leads to unreliable and highly uncertain results from the indirect comparison.

8 ABOUT THIS DOCUMENT

This Final Clinical Guidance Report was prepared by the pCODR Gastrointestinal Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on nab-paclitaxel (Abraxane) for metastatic pancreatic cancer. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.pcodr.ca).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Gastrointestinal Clinical Guidance Panel is comprised of three medical oncologists .The panel members were selected by the pCODR secretariat, as outlined in the *pCODR Nomination/Application Information Package*, which is available on the pCODR website (www.pcodr.ca). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

1. Literature search via OVID platform

Date: Feb 10, 2014

Ovid MEDLINE (R), Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations, and Ovid MEDLINE (R) Daily Update.

(nab: adj paclitaxel:).ti,ot,ab,sh,rn,hw,nm.	258
abraxane.ti,ot,ab,sh,rn,hw,nm.	156
(ABI-007 or "ABI 007" or abi-007 or "abi 007").ti,ot,ab,rn,hw,nm.	71
(paclitaxel: adj2 (protein or albumin)).mp.	450
or/1-4	603
33069-62-4.rn,nm.	29644
5 or 6	29847
exp Carcinoma/	730583
exp Neoplasms/	3736294
or/8-9	3736294
exp Pancreas/	115322
10 and 11	17159
exp Pancreatic Neoplasms/	78158
(Pancrea: adj3 (cancer or carcinoma or tum: or neoplasm:)).mp.	88614
or/12-14	96114
7 and 15	352
exp animals/	24841161
exp animal experimentation/ or exp animal experiment/	8610
exp models animal/	455824
nonhuman/	0
exp vertebrate/ or exp vertebrates/	24330039
or/17-21	24852346
exp humans/	20939551
exp human experimentation/ or exp human experiment/	22790
or/23-24	20940797
22 not 25	3912757
16 not 26	338
limit 27 to english language	299
remove duplicates from 28	194

Ovid EMBASE

(nab: adj paclitaxel:).ti,ab.	450
abraxane.ti,ab.	185
(ABI-007 or "ABI 007" or abi-007 or "abi 007").ti,ab.	54
(paclitaxel: adj2 (protein or albumin)).ti,ab.	342
or/1-4	776
exp CARCINOMA/	848867
exp NEOPLASM/	3693173
or/6-7	3693173
exp PANCREAS/	105677
8 and 9	24007
exp pancreas tumor/	94513
exp pancreas carcinoma/	13135
(pancreas: adj3 (cancer or carcinoma or tum: or neoplasm:)).mp.	91881

or/11-13	105598
5 and 14	131
exp animals/	20335228
exp animal experimentation/ or exp animal experiment/	1759919
exp models animal/	740280
nonhuman/	4233186
exp vertebrate/ or exp vertebrates/	19863813
or/16-20	21556220
exp humans/	15559874
exp human experimentation/ or exp human experiment/	321859
or/22-23	15561374
21 not 24	5995859
15 not 25	127
limit 26 to english language	124
remove duplicates from 27	122

2. Literature search via PubMed

Feb 7 2014		
Search	Query	Items found
#3	Search (#1 AND #2)	22
#2	Search publisher [sb]	443974
#1	Search (nab-paclitaxel OR nab paclitaxel OR ABI-007 OR ABI 007 OR abi-007 OR abi 007 OR nanoparticle albumin bound paclitaxel OR abraxane OR albumin bound paclitaxel)	352

3. Cochrane Library

Date: Feb 12, 2014

nab pactilaxel* or nab-paclitaxel* or abraxane* or ABI-007 or "ABI 007" or abi-007 or "abi 007" or albumin bound paclitaxel or protein bound paclitaxel

4. Grey Literature Search via

Clinical Trial Registries:

U.S. NIH ClinicalTrials.gov
www.clinicaltrials.gov

Ontario Institute for Cancer. Ontario Cancer trials: Nothing found
www.ontariocancertrials.ca

Search terms: nab paclitaxel, nab-paclitaxel, abraxane, ABI-007 or ABI 007 or abi-007 or abi 007, albumin bound paclitaxel (Phase II or III trials), protein bound paclitaxel

Select International Agencies:

Food and Drug Administration (FDA): Nothing found
www.fda.gov

European Medicines Agency (EMA): 1 identified
www.ema.europa.eu

Conference Abstracts (2009-2014)

American Society of Clinical Oncology (ASCO) – Nothing found
European Society for Medical Oncology (ESMO) – 2 identified

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