pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug-funding decisions. The pCODR process brings consistency and clarity to the cancer drug assessment process by looking at clinical evidence, cost-effectiveness and patient perspectives.

pERC Final Recommendation
Upon consideration of feedback from eligible stakeholders, pERC members considered that criteria for early conversion of an Initial Recommendation to a Final Recommendation were met and reconsideration by pERC was not required.

Drug: Nab-paclitaxel (Abraxane) **Submitted Funding Request:** For the first line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.	
Submitted By: Celgene Inc.	**Manufactured By:** Celgene Inc.
NOC Date: July 16, 2014	**Submission Date:** February 14, 2014
Initial Recommendation: September 5, 2014	**Final Recommendation:** September 23, 2014

pERC RECOMMENDATION

The pCODR Expert Review Committee (pERC) recommends funding nab-paclitaxel (Abraxane) plus gemcitabine for the first line treatment of patients with locally advanced unresectable or metastatic adenocarcinoma of the pancreas. Funding should be for patients with a KPS of 100-70 (or ECOG PS 0-2) conditional on the cost-effectiveness being improved to an acceptable level. The committee made this recommendation because it was satisfied that there was a net overall clinical benefit, there was alignment with patient values and the toxicity profile was manageable. However, the Committee noted that nab-paclitaxel plus gemcitabine could not be considered cost-effective compared with gemcitabine monotherapy at the submitted confidential price and the Economic Guidance Panel's best estimates of the incremental cost-effectiveness ratio.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Pricing Arrangements to Improve Cost-Effectiveness
Given that pERC was satisfied that there is a net clinical benefit of nab-paclitaxel plus gemcitabine in locally advanced unresectable and metastatic adenocarcinoma of the pancreas, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of nab-paclitaxel to an acceptable level.

Time-Limited Need for Nab-paclitaxel plus gemcitabine
At the time of implementing a funding recommendation for nab-paclitaxel plus gemcitabine, jurisdictions may consider addressing the short-term, time-limited need for nab-paclitaxel plus gemcitabine for patients who are currently receiving gemcitabine monotherapy for first line treatment. pERC noted that this time-limited access should be for patients who would otherwise meet the eligibility criteria of MPACT.

No Evidence in Adjuvant or Beyond First-line Use
There is currently no evidence available evaluating the effectiveness of nab-paclitaxel plus gemcitabine in the adjuvant or beyond first-line setting in those patients who progress after receiving FOLFIRINOX. pERC also noted that there is no evidence to support the use of FOFIRINOX in patients whose performance status improves following initial treatment with nab-paclitaxel plus gemcitabine. Therefore, pERC concluded that the optimal sequencing of nab-paclitaxel plus gemcitabine and other treatments in locally advanced, unresectable and metastatic adenocarcinoma of the pancreas is still unknown and pERC was unable to make an informed recommendation on use in these instances.

SUMMARY OF pERC DELIBERATIONS

pERC discussed the burden of illness associated with locally advanced unresectable or metastatic adenocarcinoma of the pancreas and noted that patients typically experience a rapid decline and death soon after diagnosis. pERC noted that patients also have a high burden of illness requiring significant symptomatic and supportive care to manage symptoms and stabilize or improve quality of life. pERC noted that patients with either locally advanced unresectable or metastatic adenocarcinoma of the pancreas are typically treated similarly. Younger and fit patients, without co-morbidities, may be treated with a more intensive, triple drug regimen, FOLFIRINOX. As this regimen is associated with a high level of toxicity, the majority of the patient population with adenocarcinoma of the pancreas would not be expected to be eligible for FOLFIRINOX and would instead likely receive gemcitabine monotherapy. pERC acknowledged that more effective and tolerable systemic therapies are required in this patient population for whom there are very few therapeutic options.

pERC's Deliberative Framework for drug funding recommendations focuses on four main criteria:

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

The pCODR systematic review included one open label, randomized controlled trial, MPACT (Von Hoff 2013), that evaluated nab-paclitaxel plus gemcitabine in patients with previously untreated metastatic adenocarcinoma of the pancreas compared to gemcitabine alone. pERC concluded that there is a net clinical benefit of nab-paclitaxel plus gemcitabine compared to gemcitabine monotherapy based upon a statistically significant improvement in overall survival (1.8 months, HR 0.72 95%CI 0.62 to 0.83) which favoured the nab-paclitaxel plus gemcitabine arm. pERC noted that in a patient population facing rapid decline and a very short life expectancy with few treatment options, an overall survival improvement of 1.8 months was considered to be clinically meaningful. In addition, pERC noted the statistically significant and clinically meaningful improvements in progression free survival and the incremental proportion of patients alive at 1 year (35% vs 22%) and 2 years (9% vs. 4%), proportions which highlight the rapid and lethal course of the disease, further strengthened the significance of the clinical benefit observed with nab-paclitaxel plus gemcitabine versus gemcitabine alone. pERC noted that the majority of patients in the MPACT study had a Karnofsky performance status (KPS) of 100, 90 or 80 while a minority had a score of 70. pERC therefore agreed that, in alignment with the trial population, nab-paclitaxel plus gemcitabine should be made available to patients with Karnofsky performance status (KPS) 100-70, which is similar to an ECOG PS 0-2. pERC noted that the MPACT study excluded patients with locally advanced adenocarcinoma of the pancreas. pERC acknowledged this gap in the evidence and discussed the inclusion of these patients into the funding population. pERC noted that, traditionally, both patient populations receive similar systemic therapies; additionally, the transition from locally advanced to metastatic disease often occurs rapidly. In this context, pERC concluded that treatment should not be limited to the metastatic population alone but should be extended to include patients with locally advanced unresectable disease.

pERC discussed the toxicity profile of nab-paclitaxel plus gemcitabine. It was noted that there were more grade 3 and 4 adverse events in the combination arm compared to the gemcitabine arm (89% vs. 75%, respectively) and similar, number of deaths in both arms (4% in each). Overall, pERC considered that the toxicities associated with nab-paclitaxel and gemcitabine were expected and manageable in the context of the disease and drug. pERC noted that the proportions of patients receiving concomitant medications with growth factors in the MPACT trial is likely not representative of the Canadian context, where access and use of growth factors is generally lower in the palliative setting. pERC further noted that information on the use of growth factors in Canadian patients enrolled in the MPACT study would have been informative, to better understand the rates of neutropenia and febrile neutropenia that could be expected with nab-paclitaxel and gemcitabine. This information was not made disclosable by the submitter. pERC also noted the Health Canada warning regarding the use of nab-paclitaxel in patients ≥ 75 years of age. pERC discussed this concern and noted the higher incidence of serious adverse reactions and adverse reactions leading to treatment discontinuation that were observed in this patient population. pERC acknowledged this concern and discussed the importance of evaluating the overall health of

patients ≥ 75 years of age in determining eligibility for treatment with nab-paclitaxel plus gemcitabine as limiting treatment solely based on age would not be appropriate. Therefore, pERC concluded that, without limiting access to treatment, treating oncologists should assess the overall health of patients and exercise caution when prescribing nab-paclitaxel for patients ≥ 75 years age. pERC noted the safety profiles of FOLFIRINOX and nab-paclitaxel plus gemcitabine and concluded that the two treatment regimens have different toxicity profiles.

pERC deliberated on patient advocacy group input, which indicated that patients with locally advanced and metastatic adenocarcinoma of the pancreas value the efficacy of treatments and the ability to have a choice in treatment, improved side effect profile of drugs and quality of life while on treatment. pERC agreed that nab-paclitaxel plus gemcitabine aligned with patient values based on the improvement in overall survival, progression-free survival and manageable toxicity profile that was observed in the MPACT study. As quality of life data was not measured in the MPACT study, pERC was unable to determine the impact of nab-paclitaxel plus gemcitabine on patient quality of life.

pERC deliberated upon the cost-effectiveness of nab-paclitaxel plus gemcitabine compared with gemcitabine alone. pERC noted that the pCODR Economic Guidance Panel's estimates were less favorable than the manufacturer's estimates. This was primarily because of differences in the estimate of drug wastage, in pharmacy costs associated with drug preparation, in the time horizon and in the estimate of utility values derived from the literature. pERC accepted the EGP's range of estimates and concluded that nab-paclitaxel plus gemcitabine could not be considered cost-effective at the submitted confidential price. Additionally, as the submitted and Economic Guidance Panel`s estimates were based on a confidential price, pERC noted that provinces will need to consider the impact of a change in the drug cost as it could potentially have a substantial impact on the incremental cost effectiveness ratio. pERC also concurred with the Economic Guidance Panels assessment regarding the unreliability of estimates provided using the indirect comparison between FOLFIRINOX and nab-paclitaxel plus gemcitabine.

pERC discussed the feasibility of implementing a funding recommendation for nab-paclitaxel plus gemcitabine. pERC noted that nab-paclitaxel is provided in single use 100mg vials with patients typically requiring 3 vials per course. In most instances, vial sharing will not be feasible, and pERC noted that drug wastage is likely as reconstituted nab-paclitaxel has a short stability and it will be difficult to reuse reconstituted part vials. pERC however acknowledged that the budget impact of drug wastage as addressed in the submitter's analysis was determined to be small in comparison to other factors such as drug price. pERC also noted the increased pharmacy preparation time required to prepare nab-paclitaxel, as it is a drug that is difficult to reconstitute. As an additional systemic therapy to gemcitabine, pERC noted that there will be increased chair time both in terms of treatment administration to patients and the time required for the patient's dose to arrive, as preparation of the drug is only started once the patient arrives at the clinic. pERC also considered that there is no evidence regarding the use of this combination therapy in beyond the first line setting or as adjuvant therapy.

EVIDENCE IN BRIEF

pERC deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report providing clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from pCODR clinical and economic review panels
- input from two patient advocacy groups (Pancreatic Cancer Canada and Craig's Cause Pancreatic Cancer Society)
- input from pCODR's Provincial Advisory Group.

Feedback on the pERC Initial Recommendation was also provided by:

- input from pCODR's Provincial Advisory Group
- the Submitter (Celgene Inc.)

The pERC initial recommendation was to fund nab-paclitaxel (Abraxane) plus gemcitabine for the first line treatment of patients with locally advanced unresectable or metastatic adenocarcinoma of the pancreas. Funding should be for patients with a KPS of 100-70 (or ECOG PS 0-2) conditional on the cost-effectiveness being improved to an acceptable level

Feedback on the pERC Initial Recommendation indicated that the manufacturer and pCODR's Provincial Advisory Group agreed with the initial recommendation.

The pERC Chair and designated pERC members reviewed the feedback and it was determined that the pERC Initial recommendation was eligible for early conversion to a pERC Final Recommendation without reconsideration by pERC because there was unanimous consensus from stakeholders on the recommended clinical population outlined in the pERC Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

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.

Studies included

The pCODR systematic review included one open-label randomised controlled trial, MPACT (Von Hoff 2013), which 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. 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 pCODR review also provided contextual information on a critical appraisal of an indirect comparison of nab-paclitaxel plus gemcitabine with FOLFIRINOX.

Patient populations: KPS 100-70 (or ECOG PS 0-2), locally advanced and metastatic

Baseline characteristics of patients in the MPACT study were well balanced with a median age of 62 and 63 years in the nab-paclitaxel plus gemcitabine and gemcitabine arms, respectively. Patients also 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%), respectively in each arm. Nearly all patients received concomitant medication during the study. Among these, white blood cell (WBC) growth factors were used in 26% vs. 15% of patients in the nab-paclitaxel plus gemcitabine vs. gemcitabine arms, respectively. pERC discussed that the proportions of patients receiving growth factors in the MPACT trial was not representative of the Canadian context, as use of growth factors is generally low in the palliative setting. pERC further noted that although Canadian patients were enrolled in the MPACT study, information on their growth factor use was not made disclosable by the submitter. pERC commented that the availability of this Canadian specific data would have been informative for clinicians, patients and the provinces.

pERC discussed whether or not the results of the MPACT study in patients with metastatic adenocarcinoma of the pancreas could be generalized to the locally advanced disease population. pERC noted that traditionally, both patient populations receive similar systemic therapies; additionally, the transition from locally advanced to metastatic disease often occurs rapidly. In this context, pERC did not consider it appropriate to limit treatment to the metastatic setting and concluded that treatment availability should be extended to include patients with locally advanced disease.

Key efficacy results: statistically significant difference in OS, PFS and 1 and 2 year survival

Key efficacy outcomes deliberated on by pERC included overall survival, which was the primary outcome in this study, as well as PFS. pERC noted that there was a statistically significant improvement in overall survival in favour of the nab-paclitaxel plus gemcitabine arm (1.8 months HR 0.72 95%CI 0.62 to 0.83 p<0.001). These results were maintained in an updated overall survival analysis (May 9, 2013). pERC discussed the magnitude of clinical benefit and noted that it was clinically meaningful in the context of a

disease that is highly and rapidly lethal. pERC also discussed the magnitude of survival benefit achieved over 1 and 2 years along with statistically significant improvements in progression free survival in favour of the nab-paclitaxel plus gemcitabine arm and agreed with the Clinical Guidance Panel that, in a patient population with limited number of treatment options and who otherwise face rapid decline and death, the consistency of the observed effects across major primary and secondary endpoints represented clinically meaningful outcomes for patients.

pERC noted that FOLFIRINOX was also considered as a comparator through a naïve indirect comparison (where the results of individual arms from different trials are compared as if they were from the same randomized trials) provided by the submitter. pERC discussed the critical appraisal of the indirect comparison and noted that, in concurrence with the Clinical Guidance Panel's position, the substantial heterogeneity between the two trials made the results highly unreliable and uncertain.

Quality of life: not measured in the study

pERC noted that quality of life data were not collected in the MPACT study. pERC considered this a very important outcome, given the high burden of illness patients experience with their disease. Although the majority of endpoints evaluated in MPACT are clinically meaningful and highly relevant for the target patient population, patient advocacy group input also indicated that quality of life was important to patients. Because of the lack of data from the pivotal study, pERC was unable to determine the effect of nab-paclitaxel on patient quality of life.

Safety: manageable toxicity profile

pERC discussed the toxicity profile of nab-paclitaxel plus gemcitabine in comparison to gemcitabine alone and noted that overall, patients in the nab-paclitaxel plus gemcitabine arm experienced more grade 3 or higher treatment emergent adverse events (TEAE) (89% vs. 75%). pERC also noted that a similar rate of deaths (4% in both arms) was reported in both arms. Among these, 9 deaths were attributed to the treatment received, with 7 (2%) vs. 2 (<1%) of the treatment related deaths being in the nab-paclitaxel plus gemcitabine vs. gemcitabine arms, respectively. Overall, pERC considered that the toxicities associated with nab-paclitaxel and gemcitabine were expected and manageable in the context of the disease and drug; additionally, no new safety concerns were apparent.

pERC noted the Health Canada warning regarding the use of nab-paclitaxel in patients ≥ 75 years of age and the higher incidence of serious adverse reactions and adverse reactions that led to treatment discontinuation in this patient population. pERC acknowledged this warning and discussed the importance of evaluating the overall health of patients ≥ 75 years of age in determining eligibility for treatment with nab-paclitaxel as limiting treatment solely based on age would not be appropriate. Therefore, pERC concluded that, without limiting access to treatment, treating oncologists should assess the overall health of patients and exercise caution when prescribing in patients ≥ 75 years of age. pERC commented on the safety profiles of FOLFIRINOX and nab-paclitaxel plus gemcitabine and concluded that the two treatment regimens have different toxicity profiles.

Need: few options, patients need more effective and tolerable systemic therapies

pERC noted that 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. With an estimated 4700 new patients being diagnosed in 2013, approximately 4300 are expected to die. The close approximation of incidence and mortality demonstrates the high lethality of the disease, which relates to the fact that the vast majority of patients have unresectable, locally advanced (20-30%) or metastatic disease (~50%) at the time of diagnosis. pERC noted that patients with advanced pancreatic adenocarcinoma are typically ill and require significant symptomatic and supportive care to manage symptoms and stabilize/improve quality of life.

pERC discussed that the standard of care for patients with locally advanced and metastatic adenocarcinoma of the pancreas has been the use of gemcitabine with the more recent introduction of the more intensive, triple drug regimen regimen FOLFIRINOX. Although improvement in objective response rates, progression free survival and overall survival have been demonstrated with FOLFIRINOX, typically this treatment is reserved for younger and fitter patients without co-morbid conditions, and the majority of patients are not expected to be able to tolerate first line FOLFIRINOX. Therefore, pERC

agreed with the pCODR Clinical Guidance Panel that there remains a considerable unmet need for more effective and tolerable systemic therapies in the treatment of advanced pancreatic adenocarcinoma.

PATIENT-BASED VALUES

Experiences of patients with adenocarcinoma of the pancreas: high symptom burden and poor quality of life

pERC deliberated upon patient advocacy group input and discussed the difficult experiences of patients and their caregivers with locally advanced unresectable and metastatic adenocarcinoma of the pancreas. The majority of patients indicated that pain was the most important symptom to control followed by decreased appetite, nausea or vomiting, mal-digestion, diarrhea, fatigue and weakness. Disease consequences such as infection, inflammation of the pancreas, unplanned weight loss and new onset of diabetes were also reported. All of these symptoms and disease consequences significantly impact a patient's quality of life. However, pERC was unable to determine the impact of nab-paclitaxel on quality of life as it was not measured in the MPACT study.

Patient values on treatment: survival benefit, quality of life, improved toxicity profile

pERC deliberated upon patient advocacy group input and discussed the values of patients with locally advanced unresectable and metastatic adenocarcinoma of the pancreas. Input from patient advocacy groups indicated that the main concern for patients is the efficacy of the drug, given the swift decline patients typically experience. Additionally, patients value the availability of treatment options, treatment tolerability and the quality of life that a patient can expect while on treatment. Some patients also indicated that current treatment is not effective in managing the disease. Based upon the improvement in overall survival, progression-free survival and incremental improvements in 1 and 2 year survival rates that were observed in the MPACT study, pERC agreed that nab-paclitaxel aligned with patient values.

pERC also noted that the number one side effect of current treatments reported by patients was nausea followed by tiredness/fatigue, weight loss, diarrhea, loss of appetite, pain, constipation, flu/fever, hair loss, digestive issues and diminished quality of life. While quality of life data was not available, pERC discussed the toxicity profile of nab-paclitaxel plus gemcitabine and noted that although grade 3 and 4 toxicities were higher in the nab-paclitaxel arm, they were considered to be consistent with the known toxicity profiles of nab-paclitaxel plus gemcitabine and were deemed to be manageable. Additionally, pERC noted that some patients are willing to tolerate an increase in toxicity of a new drug if the drug provides a survival benefit.

pERC also noted that patients consider having access to new treatments important, as there are so few options and agreed that nab-paclitaxel provides an additional treatment option with statistically significant and clinically meaningful overall survival and progression free survival benefit.

Based upon these results, pERC overall agreed that nab-paclitaxel plus gemcitabine aligns with patient values.

ECONOMIC EVALUATION

Economic model submitted: cost-effectiveness and cost-utility analysis

The pCODR Economic Guidance Panel assessed the submitter's cost-effectiveness and cost-utility analysis of nab-paclitaxel plus gemcitabine as a first-line treatment of patients with metastatic pancreatic cancer as compared to gemcitabine (MPACT, direct comparison) or FOLFIRINOX (naive indirect comparison, where the results of individual arms from different trials are compared as if they were from the same randomized trials, in this case using data from the PRODIGE 4/ACCORD trial that compared FOLFIRINOX to gemcitabine).

Basis of the economic model: clinical and economic inputs

Costs considered in the analysis included treatment costs, administration costs, second line treatment costs and costs of adverse events.

The clinical effect considered in the analysis was based on overall survival, progression-free survival, time on treatment, the incidence of adverse events and utilities.

Drug costs: confidential price, drug wastage could increase costs

At the list price nab-paclitaxel costs $971.00 per 100mg vial. At the recommended dose of 125 mg/m^2 weekly, for 3 weeks of each 4 week cycle, nab-paclitaxel costs $221.0759 per day and $ 6190.1250 per 28-day course. At the submitted confidential price nab-paclitaxel costs $[redacted] per 100mg vial. At the recommended dose of 125mg/m^2 weekly for 3 of each 4 week cycle, and using the confidential price, nab-paclitaxel costs $[redacted] per day and $[redacted] per 28-day course. *(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed.)* pERC noted that nab-paclitaxel is only available in a single use 100mg vials with patients typically requiring 3 vials per course. In most instances vial sharing will not be feasible and pERC noted that drug wastage will therefore be likely as reconstituted nab-paclitaxel has a short stability and it will be difficult to use up reconstituted vials. pERC however acknowledged that the budget impact of wastage was addressed in the submitter's analysis and determined to be minimal . pERC considered that provinces will need to consider the potential impact of wastage since actual use in clinical practice could increase costs.

Gemcitabine costs $ 0.062 per mg. At the recommended dose of 1000 mg/m2 (3/4 weeks), gemcitabine costs $11.2929 per day and $316.2000 per 28 day course.

FOLFIRINOX costs 10.2 $/mg (Oxaliplatin), 0.5 $/mg (Leucovorin), 0.0033 $/mg (Irinotecan) and 0.0033 $/mg (Fluorouracil). At the recommended dose of 85mg/m^2 Day 1 every 14 days (Oxaliplatin), 400 mg/m^2 Day 1 every 14 days (Leucovorin), 180 mg/m^2 Day 1 every 14 days (Irinotecan), 400 mg/m^2 Day 1 every 14 days (Fluorouracil) and 2400 mg/m^2 Day 1 (continuous intravenous infusion over 46 hours) every 14 days (Fluorouracil), FOLFIRINOX costs $119.6557 per day and $3350.3600 per 28 day course.

Cost-effectiveness estimates: not cost effective at confidential price

pERC deliberated upon the cost-effectiveness of nab-paclitaxel plus gemcitabine compared with other possible therapies. pERC noted that the pCODR Economic Guidance Panel's estimates were less favourable than the manufacturer's estimate. It was also noted that this was primarily because the manufacturer's model underestimated the impact of wastage on the cost effectiveness. pERC agreed that in instances where multiple patients are not treated at the same center, drug wastage is likely. In addition, although nab-paclitaxel is a difficult drug to reconstitute, pERC noted that the submitter did not include some of the pharmacy costs associated with drug preparation into their estimates. pERC also noted the impact time horizon, proportion of patients going onto second line therapies and the utility values derived from the literature had on the submitted model. The EGP conducted reanalyses adjusting for these limitations in the submitted model in order to provide pERC with a range of more plausible incremental cost-effectiveness ratios. pERC also considered that the submitted and Economic Guidance Panel`s estimates were based on a confidential price. pERC therefore noted that provinces will need to consider the potential impact of a change in the drug cost as it could potentially have a substantial impact on the incremental cost effectiveness ratio. Therefore, pERC accepted the EGP's range of estimates and concluded that nab-paclitaxel could not be considered cost-effective at the submitted confidential price.

pERC discussed the cost-effectiveness estimates provided by the submitter comparing FOLFIRINOX and nab-paclitaxel and agreed with the Economic Guidance Panel's assessment. Given the lack of a robust indirect comparison, pERC agreed that the estimates provided by the submitter are highly uncertain and unreliable. pERC further agreed with the Economic Guidance Panel position that any reanalysis estimates that the EGP produced would be extremely uncertain.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: locally advanced disease, pharmacy resources

pERC noted that several factors would be important to consider if a funding recommendation for nab-paclitaxel plus gemcitabine was implemented. First, nab-paclitaxel has a short stability period once reconstituted. pERC noted that since nab-paclitaxel is administered based on body surface area (BSA), in instances where vial sharing is not feasible, such as in small treatment centers, there is a likelihood of

wastage of any excess drug. pERC however noted that the budget impact of wastage as addressed in the submitter's analysis was determined to have small impact on the manufacturer's estimates compared to other factors, such as drug price. pERC also noted that as nab-paclitaxel is a difficult drug to reconstitute prior to administration, jurisdictions will need to consider the potential impact on pharmacy resources for dose preparation. As an additional systemic therapy to gemcitabine, pERC noted that jurisdictions will need to consider increased chemotherapy chair time for the administration of nab-paclitaxel, as well as the additional time the patient will be in the clinic, as preparation of the drug requires more time and is only started once the patient arrives at the clinic.

pERC discussed input from pCODR's Provincial Advisory Group requesting guidance on the use of nab-paclitaxel plus gemcitabine in locally advanced disease. pERC noted that locally advanced patients were excluded from the MPACT study. pERC, however, discussed current treatment patterns and noted that patients with locally advanced unresectable and metastatic adenocarcinoma of the pancreas are typically treated with similar systemic therapies. Additionally, pERC noted that a patient's transition from locally advanced unresectable to metastatic diseases may be rapid. Therefore, pERC agreed that treatment should not be limited to metastatic patients but expanded to include patients with locally advanced unresectable disease. pERC however considered the potential budget impact of a change in the eligible population and noted that the increased incremental costs with the addition of this population could be substantial. pERC also discussed the potential impact of nab-paclitaxel plus gemcitabine in the adjuvant setting and on downstream treatment algorithms. pERC concluded that the impact of using nab-paclitaxel plus gemcitabine in earlier treatment lines is as yet unknown and no evidence is available to evaluate the effectiveness of nab-paclitaxel plus gemcitabine following FOLFIRINOX failure or of a switch to FOLFIRINOX following an improvement in performance status with nab-paclitaxel plus gemcitabine initial treatment.

pERC discussed input from pCODR's Provincial Advisory Group on the potential added cost of growth factor use in supportive therapy. pERC noted that the proportions of patients receiving growth factors in the trial is likely not generalizable to the Canadian context, as use is generally low in the palliative setting.

DRUG AND CONDITION INFORMATION

Drug Information	• Albumin bound formulation of paclitaxel; part of the taxane class of drugs • 100mg vial reviewed by pCODR • Recommended dosage of 125mg/m^2 administered intravenously weekly for three out of four weeks of a 28 day cycle
Cancer Treated	• Locally advanced unresectable or metastatic adenocarcinoma of the pancreas • In combination with gemcitabine
Burden of Illness	• 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 • Incidence to mortality ratio for pancreatic cancer is 0.91, demonstrating high lethality of disease
Current Standard Treatment	• Gemcitabine monotherapy • Triplet combination of 5FU, irinotecan and oxaliplatin (FOLFIRINOX) in selected patients with good performance status (ECOG 0-1) and a normal serum bilirubin, because of superior efficacy to gemcitabine monotherapy
Limitations of Current Therapy	• There remains a considerable need for more effective and tolerable systemic therapies • Many patients ineligible for FOLFIRINOX

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee (pERC)

Recommendations are made by the pCODR Expert Review Committee following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Anthony Fields, Oncologist (Chair)
Dr. Maureen Trudeau, Oncologist (Vice-Chair)
Dr. Chaim Bell, Economist
Dr. Scott Berry, Oncologist
Bryson Brown, Patient Member
Dr. Matthew Cheung, Oncologist
Mario de Lemos, Pharmacist
Dr. Sunil Desai, Oncologist
Mike Doyle, Economist
Dr. Bill Evans, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
Danica Wasney, Pharmacist
Carole McMahon, Patient Member Alternate
Jo Nanson, Patient Member
Dr. Peter Venner, Oncologist
Dr. Tallal Younis, Oncologist

All members participated in deliberations and voting on the initial recommendation except:

- Chaim Bell, Scott Berry, Mario De Lemos and Peter Venner who were not present for the meeting
- Carole McMahon who did not vote due to her role as a patient member alternate

Because the pERC Initial Recommendation met the criteria for early conversion to a pERC Final Recommendation, reconsideration by pERC was not required and deliberations and voting on the pERC Final Recommendation did not occur.

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of nab-paclitaxel for metastatic adenocarcinoma of the pancreas, through their declarations, two members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, none of these members was excluded from voting.

Information sources used

The pCODR Expert Review Committee is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions to inform their deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. Celgene Inc., as the primary data owner, did not agree to the disclosure of economic information, therefore, this information has been redacted in this recommendation and publicly available guidance reports.

Use of this recommendation

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