Elsevier Editorial System(tm) for Value in Health

Manuscript Draft

Manuscript Number: VIH-2015-689

Title: Network Meta-Analysis-based Cost-Effectiveness Analysis of Systematic Therapies in Advanced Pancreatic Cancer.

Article Type: Original Research

Section/Category: Economic Evaluation

Keywords: Chemotherapy; Cost-Effectiveness Analysis; Economic Evaluation; Gemcitabine

Corresponding Author: Dr. Kelvin K.W. Chan, MD MSc MSc

Corresponding Author's Institution: Division of Medical Oncology and Hematology, Sunnybrook Odette Cancer Centre

First Author: Doug Coyle , MA, MSc, PhD

Order of Authors: Doug Coyle , MA, MSc, PhD ; Yoo-Joung Ko, MD ; Kathryn Coyle , BSc, MSc ; Ronak Saluja, BSc; Keya Shah, BSc ; Kelly Lien, BSc ; Henry Lam; Kelvin K Chan, MSc, MSc, MD

Abstract: Introduction
In this analysis we utilized data from a recently published Bayesian network meta-analysis (NMA) to assess the cost effectiveness of gemcitabine (G), G + 5-fluorouracil (GF), G + capecitabine (GCap), G + cisplatin (GCis), G + oxaliplatin (GOx), G + erlotinib (GE), G + nabpaclitaxel (GnP) and FOLFIRINOX in advanced pancreatic cancer from a Canadian public health payer's perspective.

Methods
Analysis was conducted through a three-state Markov model and uses data on the progression of disease with treatment from the gemcitabine arms of RCTs combined with estimates from the NMA for the newer regimens. Estimates of heath care costs were obtained from local providers and utilities were derived from the literature. The model estimates the effect of treatment regimens on costs and quality adjusted life years (QALYs) discounted at 5% per annum. Detailed sensitivity analyses were conducted.
Results
At a willingness-to-pay (WTP) threshold greater than $30,666, FOLFIRINOX would be optimal. Based on a $50,000 WTP, the probability that FOLFIRINOX would be optimal was 57.3%. There was no price reduction for nab-Paclitaxel where GnP was optimal.
Conclusion
From a Canadian public health payer's perspective at the current time and drug prices, FOLFIRINOX is the optimal regimen based on both clinical efficacy and cost-effectiveness. GnP is not cost-effective regardless of WTP threshold.

***Key Points**

Highlights

i) What is already known about the topic?

- For advanced pancreatic cancer, the following 3 regimens have shown statistically significant improvements in survival when compared to gemcitabine monotherapy: Gemcitabine + Erlotinib, Gemcitabine + nab-paclitaxel and FOLFIRINOX.
- Our previously conducted Bayesian network meta analysis revealed that FOLFIRINOX has the highest probability of being the most effective regimen for advanced pancreatic cancer.

ii) What does the paper add to existing knowledge?

- This is the first study to simultaneously evaluate the cost-effectiveness of all currently available chemotherapy treatments for advanced pancreatic cancer.
- Based on a Canadian public health payer's perspective, this analysis found FOLFIRINOX to be the most cost-effective treatment at willingness-to-pay thresholds greater than $30,666 per quality adjusted life year.
- At very low thresholds (less than $30,666 per quality adjusted life year) either Gemcitabine, Gemcitabine + Cisplatin or Gemcitabine + 5-Fluorouracil would be considered the most cost-effective regimen for advanced pancreatic cancer.

***Title Page [including author details]**

Cost-Effectiveness Analysis of Systemic Therapies in Advanced Pancreatic Cancer

Doug Coyle MA, MSc, PhD [1,2] Yoo-Joung Ko MD [3,4]

Kathryn Coyle BSc, MSc[2]

Ronak Saluja BSc[3]

Keya Shah BSc, MD[5]

Kelly Lien BSc, MD[3]

Henry Lam MSc[3]

Kelvin K. Chan MSc, MSc, MD[3,4]

1. University of Ottawa, Ottawa, ON, Canada
2. Health Economics Research Group, Brunel University, Uxbridge, UK
3. Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada
4. University of Toronto, Toronto, ON, Canada
5. Queen's University, Kingston, ON, Canada

Address for Correspondence
Dr. Kelvin K. Chan
Sunnybrook Health Sciences Centre
2075 Bayview Ave. Room T2-058
Toronto, Ontario, Canada M4N 3M5
Tel: 416 480 4928
Fax: 416 480 6002
Email: kelvin.chan@sunnybrook.ca

Keywords: Chemotherapy; Cost-Effectiveness Analysis; Economic Evaluation; Gemcitabine; Advanced pancreatic cancer; Bayesian network meta-analysis.

Running title: Cost-effective pancreatic cancer therapies

An abstract of this work was presented at the 2015 American Society of Clinical Oncology annual meeting. No significant financial support was received for this work. DC, YK and KKC conceived the idea and designed this study. RS, KL, KS and HL were involved in the collection and assembly of the data. DC, KC, KKC and RS analyzed the interpreted the data. All authors contributed in the writing of this manuscript and approved the final draft. YK has previously received honorariums from Sanofi-Aventis Canada Inc. All other authors have no conflicts of interest to declare.

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Abstract

Introduction

In this analysis we utilized data from a recently published Bayesian network meta-analysis (NMA) to assess the cost effectiveness of gemcitabine (G), G + 5-fluorouracil (GF), G + capecitabine (GCap), G + cisplatin (GCis), G + oxaliplatin (GOx), G + erlotinib (GE), G + nab-paclitaxel (GnP) and FOLFIRINOX in advanced pancreatic cancer from a Canadian public health payer's perspective.

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Results

At a willingness-to-pay threshold (WTP) greater than $30,666, FOLFIRINOX would be the most optimal regimen. Based on a $50,000 WTP, the probability that FOLFIRINOX would be optimal was 57.3%. There was no price reduction for nab-Paclitaxel where GnP was optimal.

Conclusion

From a Canadian public health payer's perspective at the current time and drug prices, FOLFIRINOX is the optimal regimen based on cost-effectiveness criterion. GnP is not cost-effective regardless of WTP threshold.

Introduction

Pancreatic cancer is the fourth leading cause of cancer-related deaths in Canada, with a median overall survival (OS) of 3-5 months without treatment for those with metastatic disease.[1] With fewer than 5% of patients surviving five years, prognosis remains poor as mortality rates in pancreatic cancer closely reflect the incidence rates.[2] However, the availability of new drugs and combinations have significantly improved the outcome of metastatic pancreatic cancer (MPC) patients, increasing the median OS to 8-12 months.

For over a decade, Gemcitabine (G) alone has been considered the standard of care for the treatment of MPC due to the promising results of a landmark phase III randomized control trial (RCT) that compared G with 5-Fluorouracil (5-FU)[3]. Since the publication of this study, many cytotoxic and targeted agents have been tried in combination with G[4-8]. Among these trials, only 3 have shown statistically significant improvements in median OS and survival rates compared to G monotherapy [3,4,9]. Consequently, G + Erlotnib (GE), FOLFIRINOX, and G + nab-paclitaxel (GnP) have emerged as alternatives to G monotherapy for the treatment of chemotherapy-naïve patients with MPC.

Despite the success of these treatments in improving life expectancy of patients with MPC, they are also associated with greater side effects and higher costs than G alone. Furthermore, there is currently a lack of direct pairwise comparisons between these combination therapies. Thus, in a previous study we performed a Bayesian network meta analysis (NMA) to determine the most effective treatment for advanced pancreatic cancer, taking into account the efficacy and safety profiles of each regimen.[10] A Bayesian NMA, an extension of the traditional pairwise meta-analysis, is used to simultaneously compare multiple interventions even in the absence of direct evidence (randomized controlled trials). In our previous study, we found that FOLFIRINIOX had the highest probability of being the best regimen (83%) followed by GnP (11%), based on overall survival (OS) data[10]. In addition, both these regimens had no significant differences in toxicities and the OS hazard ratio for FOLFIRINOX versus GnP was 0.79 [0.50-1.24][10].

For optimal resource allocation, decisions makers require both efficacy and relative cost data to evaluate trade-offs when choosing between multiple interventions. Since many of the therapies included in this analysis have not been directly compared in head to head RCTs, our previously conducted NMA synthesized effectiveness evidence from all sources (direct and indirect) for use in this cost-effectiveness model. The objective of this study is to assess the incremental cost effectiveness of the alternative

treatment options for advanced pancreatic cancer. This was achieved through the development of a decision analytic model populated with data from our previously conducted Bayesian NMA.

Methods

Analytical Framework

We used decision analytic modelling to simulate the lifetime outcomes with different chemotherapeutic regimens in the treatment of advanced pancreatic cancer. A time horizon of ten years was adopted for this analysis. Given the extremely poor prognosis of patients with advanced pancreatic cancer, a ten-year time horizon effectively equates to a lifetime horizon.[2] Outcomes were assessed in terms of cost and quality adjusted life years (QALYs) with cost effectiveness assessed through estimation of incremental cost effectiveness ratios. Optimal treatment options can be inferred through the conduct of a sequential cost effectiveness analysis. For this study, the Canadian public health payer's perspective was adopted.[12]

Patient Population

Analysis was conducted for a patient cohort representing patients receiving first-line treatment for advanced pancreatic cancer or adenocarcinoma. In the base case analysis, the age of the cohort was 63 with 60% of the cohort being male.

Comparators

Comparators were G alone– the previous standard of care, G + 5-Fluorouracil (GF), G + capecitabine (GCap), G + cisplatin (GCisp), G + oxaliplatin (GOx), G + erlotinib (GE), G + nab-paclitaxel (GnP) and FOLFIRINOX

Model

We developed a Markov model to estimate the costs and quality adjusted life years associated with therapies for advanced pancreatic cancer (Figure 1). The model consists of three primary states; pre-progression, post-progression and death. However, during the pre-progression state patients can experience side effects from therapy. This can be characterized as having multiple pre progression states (sub-states) – one relating to the absence of side effects and others relating to the presence of neuropathy, fatigue, diarrhea, febrile neutropenia and/or rash.

The cycle length was assumed to be four weeks. Side effects are assumed to commence at the

onset of treatment – within the first cycle – with patients remaining in the relevant health state for a period of time based on the duration of the side effect. Patients in the pre-progression state can transition either to the post progression state or death or remain in the pre-progression state. Patients in the post progression state can transition to death or remain in the post progression state – patients cannot return to the pre-progression state.

Transition Probabilities

The detailed methods for determining transition probabilities are provided in an online appendix. In brief, we adopted the methodology of Guyot et al. to estimate transition probabilities for gemcitabine using data from a published clinical trial for which there were sufficient data to derive individual data elements.[13-15] We then applied data from the NMA to estimate transitions for all therapies. To incorporate the impact of side effects into this analysis, pooled estimates of the incidence of each side effect were derived from available trials of gemcitabine and then odds ratios were applied from the NMA to estimate incidence for other therapies. For sensitivity analysis, this approach was repeated using data from 5 alternative clinical trials. [9,16-19]

Costs

Costs for individual therapies were derived from current funding arrangements under the New Drug Funding Program of the Ontario Public Drug Plan which covers hospital administered drugs; for drugs not covered under this program, current costs from the Princess Margaret Hospital in Toronto were applied. Costs were based upon target dosage of the drug therapies (mg/m^2/cycle), dose intensity in clinical practice, wastage, administration costs, medical management costs, pharmacy costs and concomitant medications. Analysis assumed an average body surface area of 1.8m^2. Sensitivity analysis assessed the impact of assuming incremental management costs in the pre-progression state of $200 per month. Both costs for patients in the post progression state and the costs of individual side effects were derived from previous Canadian cost effectiveness analyses or from Ontario based cost estimates using administrative data.[20-22] All costs are presented in 2016 Canadian dollars.

Utilities

Utility values for patients in the pre-progression (0.81) and post progression states (0.73) were obtained from analysis of EuroQol data from advanced pancreatic cancer patients participating in a

multicenter, double-blind, randomized trial.[23] Utility decrements associated with side effects were derived from a recent study where values were obtained from a survey of Canadian oncologists with experience in managing patients with non-colorectal gastrointestinal malignancies.[20]

Analysis

The results are reported as both expected values of outcomes (costs and QALYs) and as incremental cost-effectiveness ratios (ICERs) (i.e., the difference in expected costs between two alternatives divided by the difference in expected outcomes). As there are more than two alternatives being compared, the expected costs and outcomes of the alternatives and the relevant ICERs were calculated sequentially; identifying all comparators which were either dominated or subject to extended dominance.[24]

Deterministic Sensitivity Analyses

One-way sensitivity analyses were conducted to evaluate the sensitivity of the base case results to changes in assumptions. The following scenarios were considered under sensitivity analyses. For adverse events: extreme analysis was conducted both excluding adverse events and assuming the duration of 3 months. For form of survival function; analysis was conducted based on the two alternate parametric forms for progression free survival (exponential and Gompertz). For baseline progression free survival with Gemcitabine: analysis was conducted based on data from the other clinical trials. For mortality during the pre progression stage; analysis was codnucted assuming higher mortality based on a relative risk of mortality in the pre-progression state of 2. For costs, analysis was conducted assuming an incremental management cost of $200 per month in the pre-progression state.

Further analysis assessed the degree of price reduction required for the more effective therapies to be considered cost effective based on commonly cited willingness to pay thresholds of $50,000 and $100,000 per QALY.

Probabilistic Sensitivity Analyses

A probabilistic sensitivity analysis (PSA) was conducted in which each model input parameter was represented by a standard probability distribution (Table 1).[25] Within the PSA, values were randomly drawn from the distribution for each parameter to obtain estimates of the costs and utilities for each

treatment strategy. This procedure was repeated 5000 times. The results of the PSA are presented by cost effectiveness acceptability curves that depict the probability of each treatment strategy being most cost effective given different threshold values for a QALY (Figure 2).

Results

Base Case Analysis

G is associated with both the least costs and lowest QALYs, whilst FOLFIRINOX is associated with the greatest QALYs. The results of the sequential analysis find that GCap, GE, GOx and GnP were subject to either dominance (was both more costly and had less QALYs than one of the alternative) or extended dominance (would not be cost effective regardless of a decision maker`s willingness to pay for a QALY). The incremental cost per QALY gained is $3,744 for GCis versus G, %19,574 for GF versus GCis and $30,666 for FOLFIRINOX versus GF. Thus, if a decision maker is willing to pay at least $30,666 for a QALY, FOLFIRINOX can be considered optimal.

Deterministic Sensitivity Analysis

Deterministic sensitivity analyses found the results to be robust in that the original conclusions concerning FOLFIRINOX hold (Appendix B). In all studies based on a decision maker's willing to pay for a QALY being some value greater than $40,000, FOLFIRINOX is optimal. There was no price reduction associated with nab-Paclitaxel which would make GnP optimal – that is, if nab-Paclitaxel had a cost of $0, GnP would be subject to extended dominance, in that G, GCis or GF would be optimal if the WTP for a QALY was less than $30,666 and FOLFIRINOX would be optimal for values greater than $30,666.

Probabilistic Sensitivity Analysis

The probabilistic sensitivity analysis reports similar expected values for costs, QALYs and incremental ratios than in the base case. G, GCap, GF, GE, GOx and GnP remain subject to either dominance or extended dominance. At a WTP of $50,000 per QALY, the probability that FOLFIRINOX is optimal is 57.3%, compared to 26.5% for GF, 9.3% for GCisp, 5.8% for GCap, 0.8% for GOx and 0.4% for G and 0% for all other treatment regimens (Figure 2). At a WTP of $100,000, the probabilities are 72.2% for FOLFIRINOX, 17.4% for GF, 5.2% for GCap, 3.9% for GCis, 0.6% for GOx, 0.6% for GE and 0% for all other treatment regimens. Thus, the probability that FOLFIRINOX is optimal is high inferring a degree of certainty around the result.

Discussion

To our knowledge, this is the first study to simultaneously evaluate the cost-effectiveness of all currently available treatments for advanced pancreatic cancer. Our analysis found FOLFIRINOX to be optimal for all WTP thresholds greater than $30,666. This finding is robust as demonstrated by the results of both the deterministic and probabilistic sensitivity analyses. GOx, GE, GCap and GnP were subject to dominance and GF was subject to extended dominance – that is, regardless of a decision maker's WTP for a QALY GF would not be the optimal therapy..

Due to the recent genericization of oxaliplatin, a significant price reduction was observed for this drug. Consequently, FOLFIRINOX has become a lot more cost effective and is the most optimal treatment for advanced pancreatic cancer over a range of WTP thresholds (see Figure 2). This is a similar finding to the recently conducted Bayesian NMA, as FOLFIRINOX had the highest probability (83%) of being the best treatment.[10] Given that FOLFIRINOX was the clinical standard of care prior to the introduction of GnP, it is important to note that GnP was found to be dominated by FOLFIRINOX in that it was more costly and was associated with lower QALYs.

Our study was limited due to the lack of access to individual patient data. To facilitate indirect comparison across the alternative treatment options we had to make the assumption of proportional hazards with respect to progression free survival. This is based on the published data from which the network meta analysis is based had a made such an assumption. If the proportional hazards assumption does not hold then analysis comparing multiple treatment strategies based in indirect comparisons would be exceptionally difficult to conduct thus precluding access to the necessary information required by decision makers.

Our study adopted utility values for pre-progreession and psot proression froma a previous study suing the US algorithm for estimating utility values from the EQ-5D. Although Canadian data or adoption of the Canadian algorithm would have been preferred, this is unlikely to have affected our results.

No other previous studies have simultaneously compared the cost-effectiveness of all currently available therapies for advanced pancreatic cancer. However, this analysis does have a few limitations. For instance, by taking a public health payer perspective, our analysis was unable to capture any indirect costs related to the loss of productivity that patients or caregivers may experience due to the toxicities of the treatments. Another limitation was the lack of true individual patient data (IPD). The IPD

reconstruction method used in this analysis is a novel application to this area but it does have a number of limitations as indicated by Guyot et al.[13] For instance, without access to IPD for each study included in the NMA, we are unable to test whether the proportional hazards assumption holds. Furthermore, our analysis relied on indirect comparisons to obtain relative efficacy data for a number of treatments due to the absence of head-to-head trials. Lastly, variation in drug pricing among different countries and the availability of generic alternatives can limit the generalizability of our findings. For our results to be applicable in other jurisdictions, the relative cost of drugs should ideally be similar to those in Ontario, Canada.

In conclusion, FOLFIRINOX was considered the most cost effective treatment at WTP thresholds greater than $30,666 per QALY. Only at very low WTP thresholds (less than $30,666 per QALY) G, GCis or GF would be considered the most cost-effective regimen for advanced pancreatic cancer. FOLFIRINOX was identified as the most efficacious treatment,[10] the most cost-effective and it continues to be one of the most commonly prescribed treatments for advanced pancreatic cancer.[26]

Lastly, to reduce the uncertainty around the survival data currently available, future head-to-head clinical trials that directly evaluate the efficacy of the various regimens (particularly, GnP vs. FOLFIRINOX) should be considered.

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Figure 1 - Markov Model

Figure 1. Simplified Schematic of the Markov model.

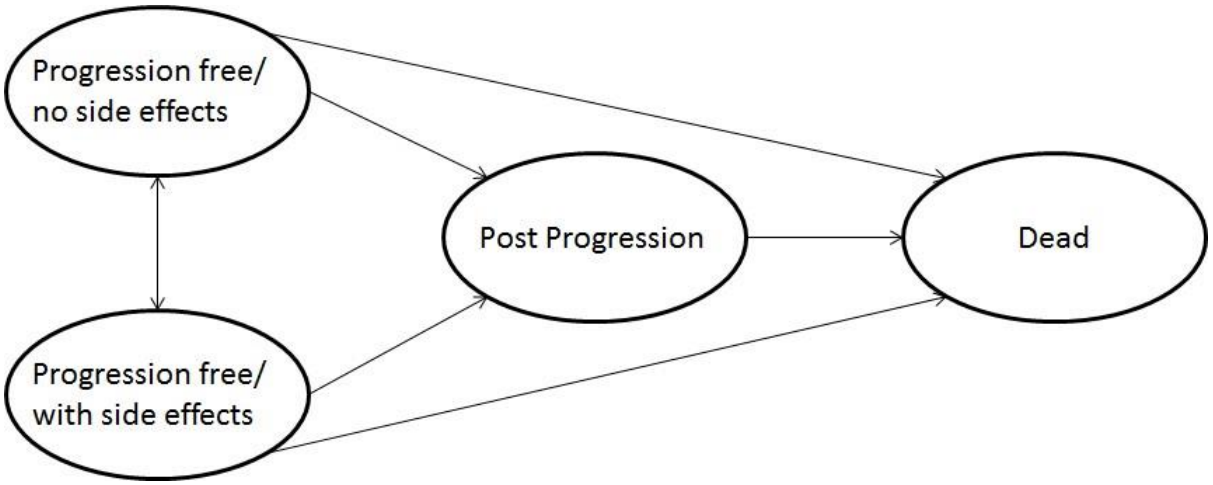

Figure 1. Markov model to estimate the costs and quality adjusted life years associated with therapies for advanced pancreatic cancer. The model consists of three primary states; pre-progression, postprogression and death. Within the pre-progression state patients can either have an absence or presence of side effects, Patients in the pre-progression state can transition either to the post progression state or death or remain in the pre-progression state (transition between progression free/with side effects and progression free/with no side effects). Patients in the post progression state can transition to death or remain in the post progression state – patients cannot return to the pre-progression state. Death is an absorbing state.

Figure 2 - Cost-effectiveness acceptability curve

Figure 2. Cost-effectiveness acceptability curve.

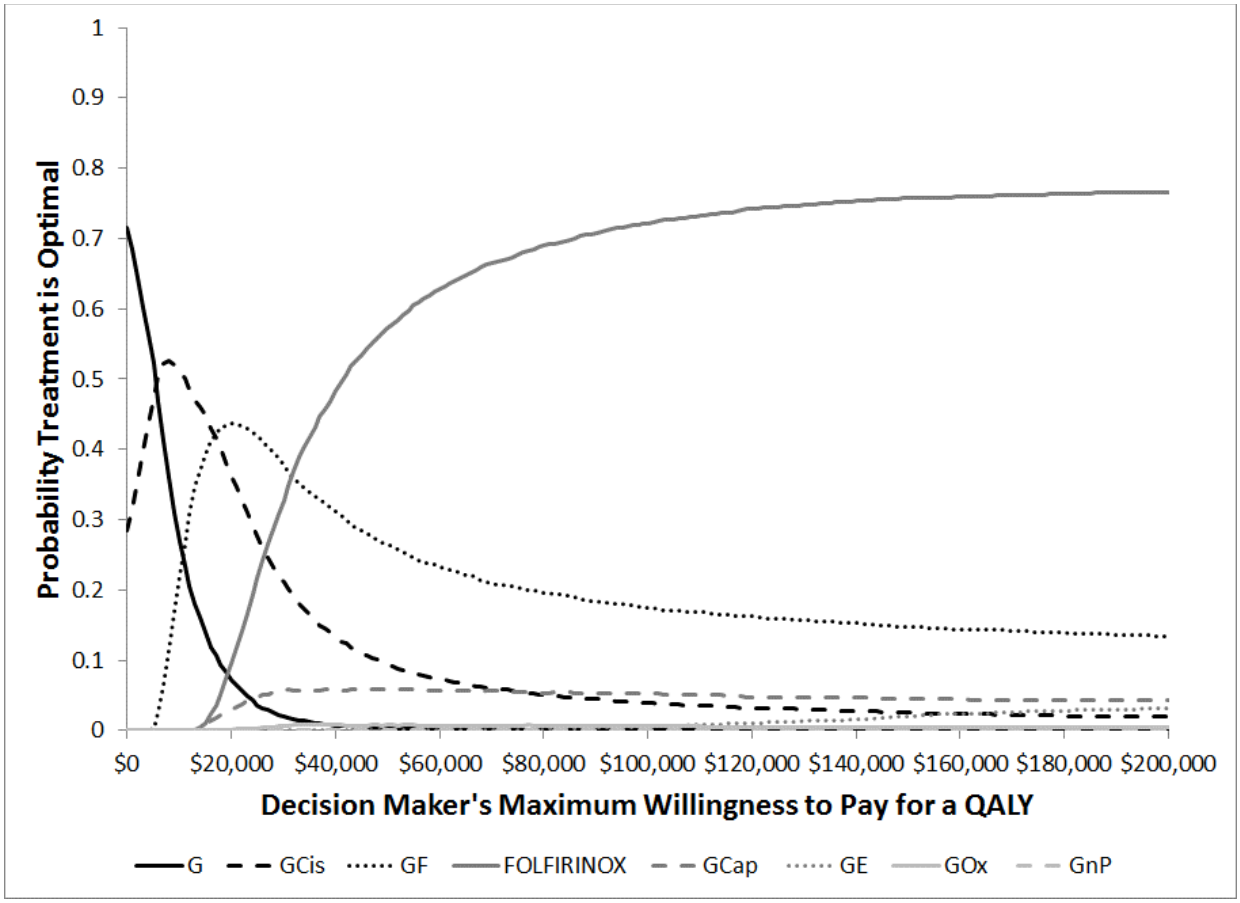

Figure 2. Cost-effectiveness acceptability curve. This graph depicts the results of the probabilistic sensitive analysis, showing the probability of each regimen being optimal at different willingness-to-pay thresholds. G, Gemcitabine monotherapy; GCis, Gemcitabine + Cisplatin; GCap, Gemcitabine + Capecitabine; GE, Gemcitabine + Erlotinib; GOx, Gemcitabine + Oxaliplatin; GnP, Gemcitabine + nabpaclitaxel.

Table 1 - Input parameters

Table 1. Input Parameters for the Markov Model

PARAMETER	VALUE	PROBABILITY DISTRIBUTION	SOURCE
Base Event Rates			
Weibull Parametric Survival Function			
Constant	-2.18	Normal (-2.18, 0.114)	14
ln gamma	0.25	Normal (0.25, 0.044)	14
Correlation coefficient	-0.004		14
Mortality Data			
Probability patient dies rather than progresses	0.006	Beta (1.7, 282.0)	14
Probability of death post progression per cycle	0.404	Beta (284.0, 418.2)	14
Probability of Adverse Event with Gemcitabine			
Neuropathy	0.15	Beta (210, 1446)	10
Fatigue	0.13	Beta (234, 1791)	10
Diarrhea	0.05	Beta (145, 2652)	10
Febrile neutropenia	0.02	Beta (32, 1469)	10
Rash	0.01	Beta (4, 402)	10
Duration of Adverse Events (weeks)			
Neuropathy	13	Gamma (4, 3.25)	Expert opinion
Fatigue	4	Gamma (4, 1)	Expert opinion
Diarrhea	1	Gamma (4, 0.25)	Expert opinion
Febrile neutropenia	1	Gamma (4, 0.25)	Expert opinion
Rash	4	Gamma (4, 1)	Expert opinion
Utility Values			
Utility with Stable Disease	0.81	1-Lognormal (0.783, 0.834)	23
Utility with Progressive disease	0.73	1-Lognormal (0.679, 0.776)	23
Disutility from Neuropathy	0.226	Normal (0.226, 0.031)	20
Disutility from Fatigue	0.473	Normal (0.473, 0.042)	20
Disutility from Diarrhea	0.212	Normal (0.212, 0.036)	20
Disutility from Febrile neutropenia	0.131	Normal (0.131, 0.03)	20
Disutility from Rash	0.094	Normal (0.094, 0.029)	20
Costs			
Treatment Regimen Costs averaged over 4 weeks			
Gemcitabine	$295	Fixed	Ontario Public Drug Programs
Gemcitabine + 5-Fluorouracil	$331	Fixed	Ontario Public Drug Programs
Gemcitabine + capecitabine	$586	Fixed	Ontario Public Drug Programs
Gemcitabine + oxaliplatin	$520	Fixed	Ontario Public Drug Programs

Gemcitabine + cisplatin	$262	Fixed	Ontario Public Drug Programs
FOLFIRINOX	$549	Fixed	Ontario Public Drug Programs
Gemcitabine + erlotinib	$2,058	Fixed	Ontario Public Drug Programs
Gemcitabine + nab-paclitaxel	$4,431	Fixed	Ontario Public Drug Programs
Palliative care	$7,265	Gamma (652, 2176)	22
Costs of Adverse Events			
Fatigue	$4,909	Gamma (401.6, 12.2)	21
Diarrhea	$5,380	Gamma (132.9, 40.5)	21
Febrile neutropenia	$8,220	Gamma (545.1, 15.1)	21
Rash	$326	Gamma (14, 20.4)	20
HR for Progression Free Survival			
Gemcitabine + 5-Fluorouracil	0.77	Lognormal (0.49, 1.2)	10
Gemcitabine + capecitabine	0.77	Lognormal (0.54, 1.07)	10
Gemcitabine + oxaliplatin	0.84	Lognormal (0.63, 1.11)	10
Gemcitabine + cisplatin	0.85	Lognormal (0.63, 1.1)	10
FOLFIRINOX	0.47	Lognormal (0.3, 0.74)	10
Gemcitabine + erlotinib	0.77	Lognormal (0.5, 1.18)	10
Gemcitabine + nab-paclitaxel	0.68	Lognormal (0.45, 1.06)	10
OR for Fatigue			
Gemcitabine + capecitabine	0.98	Lognormal (0.001, 702.8)	10
Gemcitabine + oxaliplatin	0.88	Lognormal (0.566, 1.38)	10
Gemcitabine + cisplatin	1.45	Lognormal (0.708, 3.07)	10
FOLFIRINOX	1.43	Lognormal (0.837, 2.46)	10
Gemcitabine + erlotinib	0.99	Lognormal (0.621, 1.57)	10
Gemcitabine + nab-paclitaxel	2.77	Lognormal (1.77, 4.47)	10
OR for Neuropathy			
Gemcitabine + 5-Fluorouracil	1.38	Lognormal (0.726, 2.66)	10
Gemcitabine + capecitabine	7.72	Lognormal (0.014, 535.9)	10
Gemcitabine + oxaliplatin	175.4	Lognormal (31.5, 4119)	10
Gemcitabine + cisplatin	3.21	Lognormal (0.298, 109.6)	10
FOLFIRINOX	66.8	Lognormal (5.93, 26780)	10
Gemcitabine + nab-paclitaxel	30.38	Lognormal (10.9, 124.4)	10
OR for Diarrhea			
Gemcitabine + 5-Fluorouracil	2.83	Lognormal (1.15, 7.9)	10
Gemcitabine + capecitabine	1.5	Lognormal (0.803, 2.82)	10
Gemcitabine + oxaliplatin	2.47	Lognormal (1.29, 4.97)	10
Gemcitabine + cisplatin	0.75	Lognormal (0.25, 2.14)	10
FOLFIRINOX	8.76	Lognormal (2.85, 41.27)	10
Gemcitabine + erlotinib	3.03	Lognormal (1.22, 8.64)	10
Gemcitabine + nab-paclitaxel	6.74	Lognormal (2.55, 23.98)	10

OR for Febrile Neutropenia				
FOLFIRINOX	5.6	Lognormal	(1.32, 43.6)	10
Gemcitabine + nab-paclitaxel	3.37	Lognormal	(1.15, 12.5)	10
OR for Rash				
Gemcitabine + nab-paclitaxel	5.97	Lognormal	(2.06, 17.3)	10

Lognormal and 1-Lognormal distributions specified by 2.5% and 97.5%tile. Normal distributions specified by mean and standard error of the mean. Beta distribution specified by alpha and beta. Gamma distribution specified by shape and scale. As the duration of treatment cycles vary by regimen, costs were standardized to represent the average cost per four-week cycle of the Markov model. Grade 3 and 4 adverse events were considered for this analysis.

Table 2 - Base case results

Table 2. Base Case Results

	Costs	QALYs	ICER vs G	Sequential ICER
G	$20,460	0.507		
GCis	$20,594	0.543	$3,744	$3,744
GF	$21,452	0.586	$12,459	$19,574
FOLFIRINOX	$26,443	0.749	$24,683	$30,666
GOx	$22,376	0.514	$273,365.64	Dominated by GF and GCis
GCap	$22,836	0.565	$40,486.02	Dominated by GF
GE	$33,145	0.589	$154,365.22	Dominated by FOLFIRINOX
GnP	$54,043	0.587	$36,412.26	Dominated by FOLFIRINOX and GE

ICER, Incremental cost-effectiveness ratio. G, Gemcitabine monotherapy; GCis, Gemcitabine + Cisplatin; GCap, Gemcitabine + Capecitabine; GE, Gemcitabine + Erlotinib; GOx, Gemcitabine + Oxaliplatin; GnP, Gemcitabine + nabpaclitaxel.

Appendix A

Methods for Deriving Transition Probabilities

Model

We developed a Markov model to estimate the costs and quality adjusted life years associated with therapies for advanced pancreatic cancer (Figure 1). The model consists of three primary states; pre-progression, post-progression and death. During the pre-progression state patients can experience side effects from therapy – therefore the pre progression state is really a collection of health states relating to the absence of side effects or the presence of neuropathy, fatigue, diarrhea, febrile neutropenia and/or rash.

The cycle length was assumed to be four weeks. Side effects are assumed to commence at the onset of treatment – within the first cycle – with patients remaining in the relevant health state for a period of time based on the duration of the side effect. Patients in the pre-progression state can transition either to the post progression state or death or remain in the pre-progression state. Patients in the post progression state can transition to death or remain in the post progression state – patients cannot return to the pre-progression state. Death is an absorbing state.

Disease Progression with Gemcitabine

The probabilities that a patient in the pre-progression state receiving gemcitabine would progress – i.e. enter the post progression or death state – was derived through the following approach.

First, we recreated the individual patient data for progression free survival from clinical trials. To do this we adopted the methodology of Guyot et al.[1] For this study, we digitized the published K-M curves relating to progression-free survival within the gemcitabine arms from six clinical trials for which there were sufficient data to derive individual data elements.[2-7] We then took readings at each point along the curve and derived individual patient data which replicated both these readings and the original sample size, number at risk at each time point and the number of censored cases. For our primary analysis we used data from the clinical trial comparing Gemcitabine to FOLFIRINOX – primarily due to greater generalizability to the Canadian context – due to it being the most recent, that the patients had a similar clinical profile to a Canadian population and that it had a high proportion of patients treated in North America and Western Europe.[3] We conducted five individual sensitivity analyses using the data

from each of the five other clinical trials. Data pertained to the time to progression or censoring and an indicator variable relating to whether the individual patient data were censored.

Secondly, we conducted parametric survival analysis on the von Hoff data set to determine the probability that an individual patient would be in the pre-progression state at each time point. A number of standard alternate forms of parametric models (exponential, Weibull, Gompertz) were considered which facilitated the use of the proportional hazards assumption relating to modeling the progression for all candidate drug therapies. The choice of model was based on the fit to observed data using both Bayesian information criteria and Akaike information criteria.[8] Within the base case a Weibull parametric form was chosen based on fit with uncertainty derived from the standard error of the relevant coefficients (*alpha* and *sigma*) incorporating correlation through a Cholesky decomposition matrix. Sensitivity analysis employed the estimated model based on each of the other individual trials as well as alternate parametric forms for the von Hoff dataset. For three of the five datasets considered in sensitivity analysis, the Weibull form was appropriate (for the other two an exponential form was adopted).

Thirdly, the probability that an individual patient would transition from the pre-progression to post progression or death (*pProgression*) at point *t* was estimated as 1 minus ratio of the probability of progression free survival at point *t* divided by the probability of progression free survival at point *t-1*.

Fourthly, the probability that a patient would die rather than progress (*pDie*|*Progression*) after leaving the pre-progression state was estimated as the product of the mean progression free survival and the underlying probability of death based on the age-gender related mortality rate for the general population. This was based on the clinical assumption that elevated mortality would occur only in the post progression state. This latter assumption was tested in sensitivity analysis.

Finally, the probability of transition from pre-progression to death was the product of *pProgression* and *pDie*|*Progression* and the probability of transition from pre-progression to post-progression was the product of *pProgression* and *1-pDie*|*Progression*.

Disease Progression with Other Therapies

The probability that a patient in the pre-progression state receiving therapies other than gemcitabine would progress was derived first by adjusting the *alpha* coefficient from the parametric survival analysis based on the gemcitabine data by the hazard rate for progression free survival for each therapy derived from the recent network meta analysis.[9] We adopted a proportional hazards assumption

based on the published studies which facilitated the network meta analysis all adopting this approach. From here, we derived the probability that an individual patient would be in the pre-progression state at each time point. We then adopted the same approach as for gemcitabine to determine the probability of transition from pre-progression to death and the probability of transition from pre-progression to post-progression

Mortality post Progression

For the probability of death post progression in a given cycle based on expert clinical judgment we made the assumption that this would not vary by treatment option given that first line therapy would not continue after progression and that mortality post progression would not be affected by the choice of drug strategy pre-progression. A constant probability of death per cycle was employed with the estimate derived to replicate the underlying median overall survival as well as overall survival at six, twelve, eighteen and twenty four month from the von Hoff trial. This procedure was repeated within sensitivity analysis for the five other gemcitabine trials.

Side effects from Treatment

We derived the probability of side effects with gemcitabine from the available clinical trials within the network meta-analysis.[9] We applied the odds ratio for side effects from the network meta-analysis to derive probabilities for the other therapies. For those instances where no data was available for a particular side effect, we took the conservative assumption that treatment had the same side effect profile as gemcitabine. Sensitivity analysis adopted an alternate assumption whereby when no data were available for a particular therapy, the highest probability of side effects across all therapies for which data were available was adopted. The duration of side effects were estimated by eliciting opinion from experts. Side effects were assumed to commence at onset of treatment. Sensitivity analysis adopted alternate durations.

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Appendix B - Sensitivity Analyses

Appendix B

Sensitivity Analysis: Sequential Incremental Cost per QALY Gained

	Source of Baseline Clinical Data for Gemcitabine				
	Colluci	Schiethaeur	Conroy	Ozaka	Nakai
G	Reference (least costly)	Reference (least costly)	Reference (least costly)	Reference (least costly)	Reference (least costly)
GCis	$5,707	$3,181	$5,489	$2,500	$1,881
GF	$17,649	$21,361	$20,656	$16,220	$15,910
FOLFIRINOX	$27.649	$39,457	$40,763	$21,878	$20.,261
GCap, GE, GOx, GnP	Subject to Dominance or Extended Dominance				

	Alternate parametric forms for progression free survival	
	Exponential	Gompertz
G	Reference (least costly)	Reference (least costly)
GCis	$3,117	$3,427
GF	$16,593	$18,126
FOLFIRINOX	$22,008	$26,475
GCap, GE, GOx, GnP	Subject to Dominance or Extended Dominance	

	Inclusion of Adverse Events		Relative risk of mortality in pre-progression state =2	Additional $200 monthly management cost in progression free state
	Excluded	3 month duration		
G	Dominated by GCis	Reference (least costly)	Reference (least costly)	Reference (least costly)
GCis	Reference (least costly)	$3,828	$3,752	$7,864
GF	Subject to extended dominance	$13,136	$19,577	$21,831
FOLFIRINOX	$14,719	$32,797	$30,671	$34,476
GCap, GE, GOx, GnP	Subject to Dominance or Extended Dominance			

G, Gemcitabine; GCis, Gemcitabine + Cisplatin; GF, Gemcitabine + 5-fluorouracil; GCap, Gemcitabine + Capecitabine; GE, Gemcitabine + Erlotinib; GOx, Gemcitabine + Oxaliplatin; GnP, Gemcitabine + nab-Paclitaxel