

# Neoadjuvant FOLFIRINOX for Patients with Borderline Resectable or Locally Advanced Pancreatic Cancer: Results of a Decision Analysis

JIN G. CHOI<sup>a,b,i,†</sup>, RYAN D. NIPP<sup>c,g,†</sup>, ANGELA TRAMONTANO<sup>a,b</sup>, AYMAN ALI<sup>a,b</sup>, TIANNAN ZHAN<sup>a,b</sup>, PARI PANDHARIPANDE<sup>b,d,g</sup>, EMILY C. DOWLING<sup>a,b</sup>, CRISTINA R. FERRONE<sup>f,g</sup>, THEODORE S. HONG<sup>e,g</sup>, DEBORAH SCHRAG<sup>h</sup>, CARLOS FERNANDEZ-DEL CASTILLO<sup>f,g</sup>, DAVID P. RYAN<sup>c,g</sup>, CHUNG YIN KONG<sup>b,d,g</sup>, CHIN HUR<sup>a,b,g,j</sup>

<sup>a</sup>Gastrointestinal Unit, <sup>b</sup>Institute for Technology Assessment, <sup>c</sup>Department of Medical Oncology, <sup>d</sup>Department of Radiology, <sup>e</sup>Department of Radiation Oncology, and <sup>f</sup>Department of Surgery, Massachusetts General Hospital, Boston, Massachusetts, USA; <sup>g</sup>Harvard Medical School, Boston, Massachusetts, USA; <sup>h</sup>Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, USA; <sup>i</sup>Health Innovations Research and Evaluations Unit and <sup>j</sup>Herbert Irving Comprehensive Cancer Center, Columbia University Medical Center, New York, NY, USA

<sup>†</sup>Contributed equally.

Disclosures of potential conflicts of interest may be found at the end of this article.

**Key Words.** Decision support techniques • Pancreatic neoplasms • Cost-benefit analysis • Computer simulation

## ABSTRACT

**Background.** The effectiveness and cost-effectiveness of using neoadjuvant FOLFIRINOX (nFOLFIRINOX) for patients with borderline resectable or locally advanced pancreatic ductal adenocarcinoma (BR/LA PDAC) are unknown. Our objective was to determine whether nFOLFIRINOX is more effective or cost-effective for patients with BR/LA PDAC compared with upfront resection surgery and adjuvant gemcitabine plus capecitabine (GEM/CAPE) or gemcitabine monotherapy (GEM).

**Materials and Methods.** We performed a decision-analysis to assess the value of nFOLFIRINOX versus GEM/CAPE or GEM using a mathematical simulation model. Model transition probabilities were estimated using published and institutional clinical data. Model outcomes included overall and disease-free survival, quality-adjusted life-years (QALYs), cost in U.S. dollars, and cost-effectiveness expressed as an incremental cost-effectiveness ratio. Deterministic and probabilistic sensitivity analyses explored the uncertainty of model assumptions.

**Results.** Model results found median overall survival (34.5/28.0/22.0 months) and disease-free survival (15.0/14.0/13.0 months) were better for nFOLFIRINOX compared with GEM/CAPE and GEM. nFOLFIRINOX was the optimal strategy on an efficiency frontier, resulting in an additional 0.35 life-years, or 0.30 QALYs, at a cost of \$46,200/QALY gained compared with GEM/CAPE. Sensitivity analysis found that cancer recurrence and complete resection rates most affected model results, but were otherwise robust. Probabilistic sensitivity analyses found that nFOLFIRINOX was cost-effective 92.4% of the time at a willingness-to-pay threshold of \$100,000/QALY.

**Conclusion.** Our modeling analysis suggests that nFOLFIRINOX is preferable to upfront surgery for patients with BR/LA PDAC from both an effectiveness and cost-effectiveness standpoint. Additional clinical data that further define the long-term effectiveness of nFOLFIRINOX are needed to confirm our results. *The Oncologist* 2019;24:945–954

**Implications for Practice:** Increasingly, neoadjuvant FOLFIRINOX has been used for borderline resectable and locally advanced pancreatic cancer with the goal of rendering them resectable and decreasing risk of recurrence. Despite many efforts to show the benefits of neoadjuvant over adjuvant therapies, clinical evidence to guide this decision is largely lacking. Decision-analytic modeling can provide a methodologic platform that integrates the best available data to quantitatively explore clinical decisions by simulating a hypothetical clinical trial. This modeling analysis suggests that neoadjuvant FOLFIRINOX is preferable to upfront surgery and adjuvant therapies by various outcome metrics including quality-adjusted life years, overall survival, and incremental cost-effectiveness ratio.

Correspondence: Ryan D. Nipp, M.D., Massachusetts General Hospital, 55 Fruit St., Boston, Massachusetts 02114, USA. Telephone: 617-726-3252; e-mail: rnipp@mgh.harvard.edu Received February 27, 2018; accepted for publication November 15, 2018; published Online First on December 17, 2018. <http://dx.doi.org/10.1634/theoncologist.2018-0114>

## INTRODUCTION

Pancreatic cancer is among the deadliest forms of cancer and is the fourth leading cause of cancer mortality in the U.S., with an estimated 48,960 new diagnoses and 40,560 deaths in 2015 [1]. Pancreatic ductal adenocarcinoma (PDAC) constitutes the vast majority (>85%) of cancers of the pancreas [2]. The majority of patients with PDAC have metastatic disease at presentation, whereas only 20% of patients present with upfront resectable disease [3, 4]. The remainder of PDAC patients present as either borderline resectable or locally advanced disease, but the definitions for what constitutes borderline resectable and locally advanced PDAC have historically varied across institutions [5–9], and radiographically determined resectability may be unreliable [4].

Survival remains low, even for those who undergo surgery and achieve successful resection with clear margins (R0); estimates suggest 5-year survival rates of 20% for these patients [10]. Furthermore, more than 80% of PDAC tumors recur with distant metastatic disease over the patients' remaining lifetime [11]. Because of the high recurrence rates after surgical resection, oncologists often employ adjuvant chemotherapy with or without radiation therapy with the goal of improving cure rates and survival. Prior studies suggest that adjuvant treatment can improve overall survival in patients with resectable tumors by reducing recurrence [12–15].

With the advent of more effective therapies for metastatic PDAC, efforts to incorporate these agents, such as FOLFIRINOX [16] and gemcitabine/Nab-paclitaxel [17], into the neoadjuvant setting are increasing. More recently, FOLFIRINOX has been used in early-stage and locally advanced patients with the goal of rendering them resectable and allowing patients to undergo curative resection surgery [4, 18, 19]. However, the effectiveness and cost-effectiveness of using neoadjuvant FOLFIRINOX (nFOLFIRINOX) for patients with potentially resectable PDAC is currently unknown.

Although treatment for patients with potentially resectable PDAC is currently experiencing a shift in treatment from adjuvant to neoadjuvant therapies at many institutions, clinical evidence to guide this decision is largely lacking. In circumstances such as these, where trial data are limited, decision-analytic modeling can provide a methodologic platform that integrates the best available data to quantitatively explore clinical decisions by simulating a hypothetical clinical trial between competing strategies. Therefore, we sought to develop and analyze a mathematical decision-analytic model to estimate the long-term clinical outcomes and cost-effectiveness of neoadjuvant FOLFIRINOX compared with surgery followed by adjuvant gemcitabine monotherapy or gemcitabine/capecitabine for patients with borderline resectable or locally advanced PDAC.

## MATERIALS AND METHODS

### Model Overview

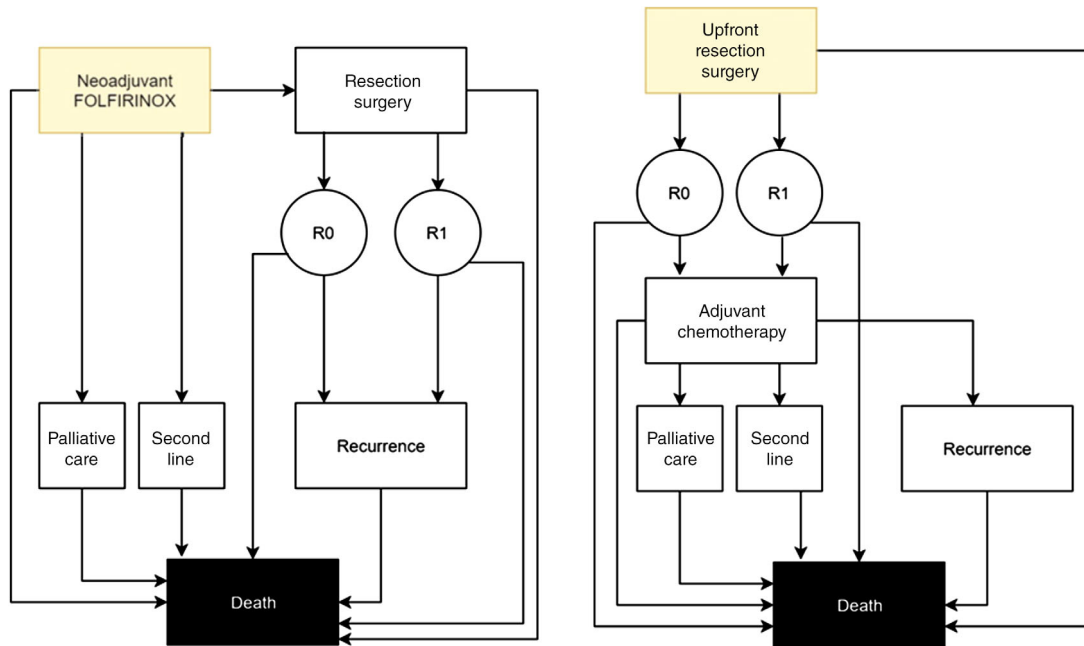
We constructed a decision-analytic state-transition patient-level model, also known as a microsimulation model, in TreeAge Pro (TreeAge, Williamstown, MA). States in the model included the various health states associated with

the two strategies modeled, including cancer undergoing treatment, complete surgical resection, incomplete resection, cancer recurrence, palliative care, second-line chemotherapy, and death (Fig. 1). Possible causes of death included age-related mortality [20], PDAC, surgical mortality, and postsurgical complications. The Markov cycle length or time between state transitions was 1 month. The model simulation began with a hypothetical cohort of 1 million 60-year-old individuals with borderline resectable or locally advanced PDAC who were followed until death. In each cycle (1-month period), the simulated patient could remain in the same state, progress to metastatic cancer, or die from age-related all-cause mortality [20]. We initially estimated transition probabilities between the various health states using data from the literature and then modified or calibrated to achieve good fit to clinical targets. We describe the process of model verification below.

### Neoadjuvant FOLFIRINOX Therapy

Patients in the nFOLFIRINOX strategy were modeled to first receive eight cycles, 2 weeks per cycle, of FOLFIRINOX, prior to surgical resection, consistent with published literature and clinical trials [4, 16, 18, 19, 21–37]. When there were limited published data, we used the Massachusetts General Hospital (MGH) neoadjuvant cohort to inform model inputs. In this group, a proportion (60%) of the cohort received chemoradiation for 6 weeks with low-dose capecitabine; hence, our modeled nFOLFIRINOX strategy represented a hypothetical cohort in which a majority received chemoradiotherapy. Patients in the model could drop out of the neoadjuvant therapy arm (35%) or have minor complications with hospitalization and then resume therapy. For a proportion of those who dropped out, we assumed that they progressed to metastatic disease and thus received second-line gemcitabine/Nab-paclitaxel (65%) [17]. The remainder of those who dropped out were assumed to be unable to tolerate second-line therapy and would receive palliative care alone (35%).

The model included the possibility that simulated patients could experience multiple minor adverse events or complications throughout treatment, consistent with the rates of adverse events in published literature for each chemotherapy regimen. Following completion of all treatment cycles, patients who did not drop out because of adverse events or disease progression underwent surgical resection. We assigned these patients a risk for 30-day surgical mortality as well as surgical complications based on published reports [4, 30, 38]. Patients could receive either a complete or incomplete surgical resection, and would then undergo surveillance for cancer recurrence. We estimated postoperative survival using published data supplemented by estimates from institutional data (Massachusetts General Hospital) of borderline resectable or locally advanced PDAC patients based on resection status and lymph node positivity [22–29]. For all three strategies, those with positive lymph nodes had greater risk of death during the first year after surgery [21], and patients assigned to receive palliative care alone faced a fixed total cost and estimated survival of 4 months [30, 39–42].



**Figure 1.** Simplified schematic of the two strategies in the model. Boxes represent health states. Circles represent temporary transitional states. Black death states are absorbing. Arrows denote transitions.

### Surgery Followed by Adjuvant Gemcitabine Monotherapy or Gemcitabine/Capecitabine

All patients in the adjuvant gemcitabine monotherapy (GEM) or gemcitabine/capecitabine (GEM/CAPE) strategies would undergo upfront resection surgery prior to receiving six cycles, 4 weeks per cycle, of adjuvant chemotherapy. They also faced the same risk of surgical mortality as the nFOLFIRINOX strategy and risks of surgical complications according to published reports [4, 30, 38, 43]. Severe complications due to chemotherapy toxicities could lead to discontinuation of adjuvant therapy (37%). We assumed that a proportion of patients would drop out because of cancer progression and would receive second-line FOLFIRINOX (65%) [16]. The remainder of those who dropped out were assumed to be unable to tolerate second-line therapy and receive palliative care alone (35%). Similar to the other strategies above, simulated patients could have multiple complications due to chemotherapy toxicities throughout treatment, and they could receive either a complete or an incomplete surgical resection. We based patients' postoperative survival on published data for upfront resectable PDAC patients by resection status and lymph node positivity [12, 14, 15, 44, 45].

### Parameter Estimates

Model parameters or inputs were estimated from the literature. For the nFOLFIRINOX strategy, we used MGH patient data when published data were not available. Base-case values and ranges used in sensitivity analyses are summarized in Table 1.

### Costs and Quality of Life Utilities

Costs were estimated from a third-party payer perspective; no indirect costs were included. Chemotherapy drug costs for nFOLFIRINOX, GEM, and GEM/CAPE were based on

2018 average sale price by the Centers for Medicare and Medicaid services (CMS) [46]. Hospitalization costs for grade 3/4 adverse events were based on published sources of Medicare reimbursement rates using the CMS Physician Fee Schedule [47–49]. Rates of grade 3/4 adverse events and subsequent hospitalizations were derived from clinical trial data and two Canadian studies of metastatic PDAC patients [12, 14, 18, 25, 30–32, 45, 50, 51]. Using the aforementioned hospitalization costs and rates, we estimated an average cost of hospitalization per chemotherapy cycle. All costs were inflation-adjusted to 2018 [52].

The nFOLFIRINOX strategy's low-dose capecitabine and radiation therapy and hospitalization for adverse event costs were estimated from a published cost study that used a nationally representative claims and encounter database for upfront resectable PDAC patients [53]. Inpatient costs for PDAC were estimated from a Surveillance, Epidemiology and End Results-Medicare study, which reported monthly direct inpatient medical costs attributable to locoregional resectable and locoregional unresectable pancreatic cancer [54]. Surgical resection costs were estimated from a prospective pancreatoduodenectomy micro-cost analysis, which included equipment, operating room, operating room staff, postanesthesia care, anesthesia, pharmacy, and radiology costs [55]. Second-line chemotherapy costs for FOLFIRINOX and gemcitabine/Nab-paclitaxel in metastatic PDAC patients were estimated from an analysis that sourced drug costs from Medicare average sale prices and Medicare reimbursement rates for administration and adverse event management costs [56].

The model incorporated costs of nFOLFIRINOX and complications, GEM and complications, GEM/CAPE and complications, second-line chemotherapy regimens, resection surgery and complications, inpatient costs, and palliative care. We inflation-adjusted all costs to 2018-year dollars. See references for cost estimates in Table 1.

**Table 1.** Model inputs/parameter estimates

Parameters	Base case	Sensitivity analysis		References
		Low	High	
<b>Common parameters</b>				
Age, years	60	38	88	[4, 25, 31]
PDAC mortality	0.24	0.168	0.57	[4, 50, 57]
Surgical mortality	0.015	0.01	0.053	[30, 38]
Pancreatic fistula mortality	0.093	0	0.24	[38, 43, 58–61]
<b>RR of early mortality</b>				
Lymph node positivity	2.19			[21]
<b>Second-line survival, months</b>				
Gemcitabine/Nab-paclitaxel	9			[17, 56]
FOLFIRINOX	11			[16, 24]
<b>Neoadjuvant FOLFIRINOX</b>				
Chemotherapy cycle length, months	0.5			[16, 25]
Dropout rate	0.35	0.33	0.4	[23, 30]
Toxicity rate	0.75	0.287	0.75	[18, 25, 30–32]
Complete cycles	8			[4, 22, 25, 31]
Surgical complication rate	0.36	0.288	0.432	[4]
Pancreatic fistula rate	0.05	0	0.05	[4]
R0 rate	0.92	0.796	0.94	[4, 21, 30, 32]
PDAC recurrence	0.27	0.26	0.31	[4]
Hospitalization for FOLFIRINOX toxicity	0.1485			[50]
Lymph node positivity	0.557	0.5013	0.6127	[21]
<b>Survival after recurrence, months</b>				
R0	21	19	23	[4, 21]
R1	17	15	19	[4, 21]
N0	22	20	24	[4, 21]
N1	18	16	20	[4, 21]
<b>Adjuvant chemotherapy</b>				
Chemotherapy cycle length, months	1			[12, 45]
Dropout rate	0.37	0.35	0.4	[12, 15]
Toxicity rate (GEM)	0.5355	0.075	0.5355	[12, 14, 50]
Toxicity rate (GEM/CAPE)	0.6295			[45]
Complete cycles	6			[12, 45]
Surgical complication rate	0.36	0.34	0.63	[4, 43]
Pancreatic fistula rate	0.15	0.09	0.285	[4, 43]
R0 rate	0.86	0.4	0.88	[4, 12, 14, 15, 21, 45]
PDAC recurrence	0.31	0.29	0.65	[4, 12, 14, 15, 44, 45]
Hospitalization for toxicity	0.03955			[12, 14, 50]
Lymph node positivity	0.786	0.7074	0.8646	[21, 45]
<b>Survival after recurrence GEM, months</b>				
R0	12	9	15	[12, 15]
R1	9	6	10	[12, 15]
N0	12	9	13	[12, 15]
N1	9	6	10	[12, 15]

(continued)

**Table 1.** (continued)

Parameters	Base case	Sensitivity analysis		References
		Low	High	
Survival after recurrence GEM/CAPE, months				
R0	28	24	28	[45]
R1	12	8	12	[45]
N0	46	42	46	[45]
N1	12	8	12	[45]
Cost (inflation-adjusted to 2018 U.S. dollars)				
FOLFIRINOX per cycle	180	80	240	[62]
Gemcitabine per cycle	160	90	270	[62]
GEM/CAPE per cycle	1,030	515	1,545	[62]
Capecitabine and radiation per month	1,350	700	1,900	[53]
Chemoradiation hospitalization costs	2,800	1,700	3,700	[53]
PDAC costs per month (inpatient)	5,400	3,100	7,300	[54]
Resection surgery (pancreatoduodenectomy)	29,000	15,000	41,000	[55]
FOLFIRINOX toxicity hospitalization per cycle	1,700			[47–50]
Gemcitabine toxicity hospitalization per cycle	600			[47–50]
GEM/CAPE toxicity hospitalization per cycle	700			[45, 47–50]
Cost of palliative care (total)	99,400	91,000	101,000	[63]
FOLFIRINOX second line per month	4,000	3,000	4,800	[64]
Gemcitabine/Nab-paclitaxel per month	12,950	10,000	14,800	[64]
Utility				
Progression-free (stable) PDAC	0.80	0.68	0.88	[50, 51, 65–67]
Progressive disease	0.73	0.62	0.80	[50, 51, 65–67]
Palliative care	0.136	0	0.336	[51]
Recovery from surgery	0.78	0.78	0.81	[68]
Disutilities				
FOLFIRINOX	−0.1199	−0.1369	−0.1012	[50]
FOLFIRINOX toxicity	−0.2382	−0.2823	−0.1941	[50, 51, 66, 69–71]
Gemcitabine monotherapy	−0.0160	−0.0184	−0.0136	[50]
Gemcitabine toxicity	−0.0944	−0.1086	−0.0802	[50, 66, 69–71]
GEM/CAPE	−0.0160	−0.0184	−0.0136	[45, 50]
GEM/CAPE toxicity	−0.1417	−0.1559	−0.1275	[45, 50, 51, 66, 69–71]

Abbreviations: GEM, gemcitabine monotherapy; GEM/CAPE, gemcitabine plus capecitabine; PDAC, pancreatic ductal adenocarcinoma; RR, relative risk.

We incorporated quality of life (QoL) utilities or disutilities for nFOLFIRINOX, GEM, GEM/CAPE and associated toxicities into the model. Because of limited data, we used the disutility value associated with GEM and GEM/CAPE therapy, which likely underestimates the full toxicity of the more aggressive GEM/CAPE strategy. Because utility values for patients with early PDAC were not published or available, the disutility values for nFOLFIRINOX and GEM were largely drawn from studies on metastatic PDAC patients [45, 50, 51]. Resection surgery and recovery periods had QoL decrements applied for 2 weeks. Patients also had QoL adjustments to correspond to either stable disease states or disease progression states (i.e., recurrence to local or distant progression). We derived the QoL utility value for palliative care from published literature on end-of-life care. See references for QoL estimates in Table 1. All costs and QoL estimates were discounted by 3%.

## Outcomes

Our primary outcomes included quality-adjusted life-years (QALYs) and the incremental cost-effectiveness ratio (ICER) to assess the cost-effectiveness when comparing the three strategies using an efficiency frontier. We used a willingness to pay (WTP) of less than \$100,000/QALY as the threshold to classify a strategy as cost-effective. Additional endpoints assessed included life expectancy (unadjusted life-years), total costs, and secondary clinical endpoints frequently reported in oncology clinical trials, such as median disease-free survival and median overall survival.

## Modeling Analysis Performed

We performed a base-case analysis using best estimates for all model parameters to provide the primary results.

We conducted one-way deterministic sensitivity analyses to investigate the effects of changes in model parameters on



**Table 2.** Base case results

Results	FOLFIRINOX	GEM/CAPE	Gemcitabine
Life-years (average survival)	3.95	3.60	3.04
Median OS, months	34.5	28.0	22.0
Median DFS, months	15.0	14.0	13.0
QALYs	2.91	2.61	2.25
Costs	\$174,250	\$160,400	\$130,300
ICER	\$46,200	\$83,600	

Abbreviations: DFS, disease-free survival; GEM/CAPE, gemcitabine plus capecitabine; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALYs, quality-adjusted life-years.

estimated outcomes across a wide range of values, including complete resection rate, surgical mortality, recurrence rate, pancreatic fistula rate, cancer mortality, and utility values. When available, we based the ranges on published data.

Additionally, we performed a probabilistic sensitivity analysis, where model input parameters were varied simultaneously. We first assigned distributions for specific parameters or model input variables and then performed 1,000 iterations of 1,000,000 patients to gain further insight into the optimal strategy under uncertain conditions within our defined WTP threshold.

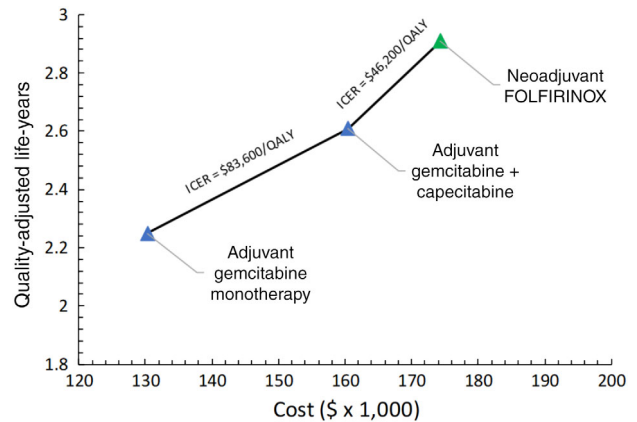
### Model Verification

We calibrated our model by varying model inputs such as recurrence rates, survival after recurrence, chemotherapy dropout rates, and R0 rates within the bounds published in literature. We verified our model outputs by checking them against independent clinical endpoints. For nFOLFIRINOX, our calibration targets were median overall survival of 21.2–37.7 months and median disease-free survival of 13.0–22.6 months [19, 22–29]. Because of limited follow-up data in the published literature, we had broad estimates for median overall survival and median disease-free survival for the nFOLFIRINOX strategy targets. We conducted extensive literature review and chart review of MGH patients to approximate a clinically meaningful calibration target (Institutional Review Board: 2002P000154). For the GEM strategy, our calibration targets were overall survival of 22.8 months and median disease-free survival of 11.6–15.3 months [14]. We also used a Kaplan-Meier survival curve to verify the model outputs (supplemental online Fig. 1). For the GEM/CAPE strategy, our calibration targets were median overall survival of 28.0 months and median disease-free survival of 13.9 months, as shown in the recently published ESPAC-4 study [45]. The survival targets for GEM and GEM/CAPE were largely drawn from studies on upfront resectable cohorts [14, 45].

## RESULTS

### Base-Case Results

The base-case results are presented in Table 2. When the simulated cohorts were followed until death, the nFOLFIRINOX strategy resulted in 0.66 more QALYs than the GEM strategy and 0.30 more QALYs than the GEM/CAPE



**Figure 2.** Efficiency frontier. An efficiency frontier plots the expected return (quality-adjusted life-years) for a defined level of risk (cost in U.S. dollars). The optimal cost-effective strategy is labeled in green. Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years.

strategy, 0.91 more LYs than the GEM strategy and 0.35 more LYs than the GEM/CAPE strategy, and cost \$43,950 more than the GEM strategy and \$13,850 more than the GEM/CAPE strategy, respectively. The nFOLFIRINOX strategy was cost-effective compared with the GEM/CAPE strategy with an ICER of \$46,200 per QALY, the comparator strategy on the efficiency frontier as seen in Figure 2.

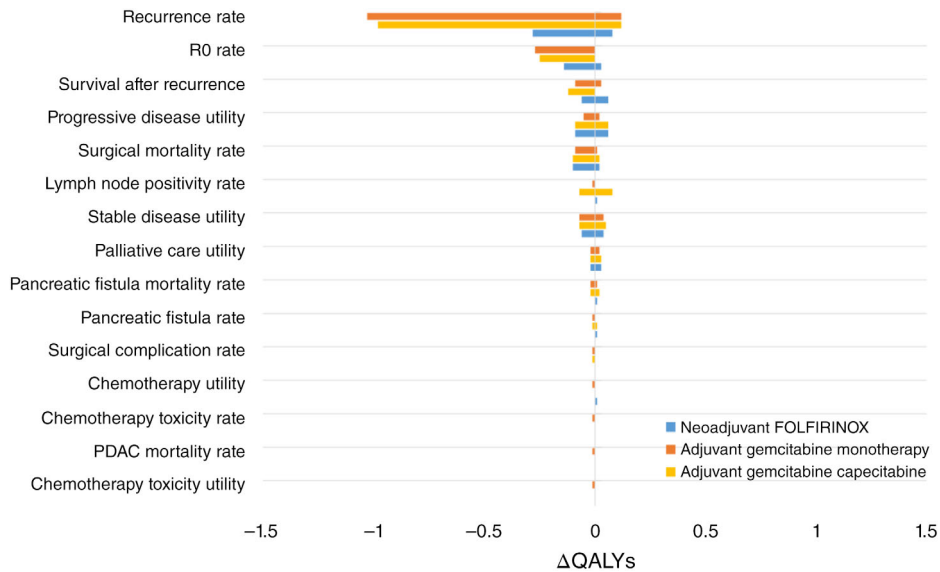
### Survival Results

Median overall survival was 34.5 months for the nFOLFIRINOX strategy, 28.0 months for the GEM/CAPE strategy, and 22.0 months for the GEM strategy. Median disease-free survival was 15.0 months for the nFOLFIRINOX strategy, 14.0 months for GEM/CAPE strategy, and 13.0 months for the GEM strategy.

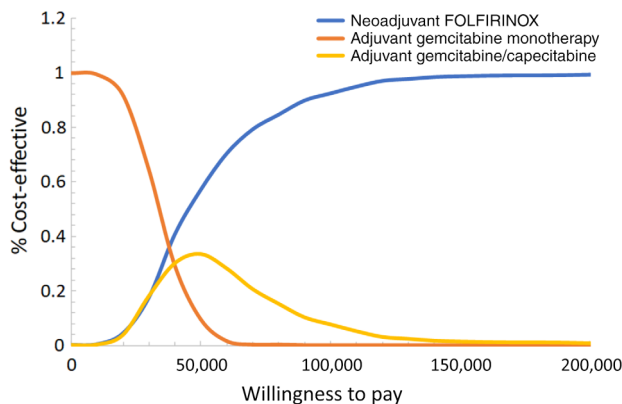
### Sensitivity Analysis

We performed one-way sensitivity analysis to determine the impact of various model inputs on the cost-effectiveness outcomes (Fig. 3) and found that model results were most sensitive to recurrence rate and R0 rate. When we analyzed the model using the upper end of the range or maximum recurrence rate for the nFOLFIRINOX strategy or the minimum R0 rate for the nFOLFIRINOX strategy, the ICER exceeded \$100,000 per QALY and the nFOLFIRINOX strategy was not most cost-effective. Otherwise, the model results were robust with respect to changes in other model parameters including utility values, complete resection rate, chemotherapy toxicity, surgical complications, and mortality.

We also conducted probabilistic sensitivity analyses to assess the impact of model input uncertainty on the cost-effectiveness results. The nFOLFIRINOX strategy was the cost-effective strategy 92.4% of the time with a WTP threshold of \$100,000 per QALY (Fig. 4). The nFOLFIRINOX strategy remained cost-effective 57.0% of the time with a WTP of \$50,000 per QALY, and 98.7% of the time with a WTP of \$150,000 per QALY (Fig. 5). Probabilistic sensitivity analyses results comparing GEM/CAPE versus GEM and nFOLFIRINOX versus GEM at various WTP thresholds are available in supplemental online Figures 2, 3.



**Figure 3.** One-way deterministic sensitivity analyses. The blue bars represent the neoadjuvant FOLFIRINOX strategy, the orange bars represent the gemcitabine monotherapy strategy, and the yellow bars represent the gemcitabine plus capecitabine strategy. Outputs of the lower and upper bounds of parameter inputs are represented as  $\Delta$ QALYs from the base case outputs. Abbreviations: PDAC, pancreatic ductal adenocarcinoma; QALY, quality-adjusted life-years.



**Figure 4.** Cost-effectiveness acceptability curve. Percentage of time each strategy is cost-effective at varying willingness-to-pay thresholds are represented. The orange line represents the percentage of time the gemcitabine monotherapy strategy is cost-effective, the yellow line for the gemcitabine plus capecitabine strategy, and the blue line for the neoadjuvant FOLFIRINOX strategy.

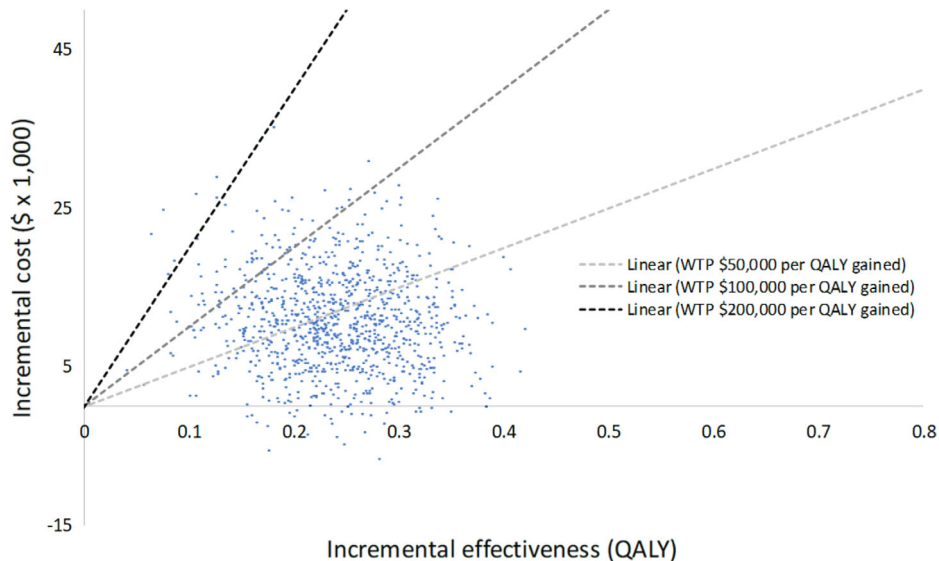
## DISCUSSION

Based on the results of our simulation modeling analysis, we found that neoadjuvant FOLFIRINOX is the optimal strategy of those evaluated for the treatment of borderline resectable or locally advanced PDAC patients by various endpoints. The nFOLFIRINOX was the most cost-effective strategy, as the incremental cost of nFOLFIRINOX per quality-adjusted life-year gained compared with the second most effective strategy (GEM/CAPE) was below the willingness-to-pay threshold. Alternatively stated, the cost of the clinical benefit was not prohibitively expensive. It was also superior by various outcome metrics including quality-adjusted life years and overall survival (unadjusted life-years) compared with the other two treatment strategies.

Our analysis of the cost-effectiveness of neoadjuvant FOLFIRINOX for patients with borderline resectable or locally advanced PDAC provides valuable new information, as prior analyses studied the clinical benefits and cost-effectiveness of FOLFIRINOX in the metastatic stage settings [16, 50, 51]. An older previously published cost-effectiveness analysis studied the quality-adjusted and unadjusted survival benefit of neoadjuvant chemoradiotherapy in upfront resectable PDAC largely as a “thought experiment” and did not include newer, more effective treatments such as FOLFIRINOX or other multimodal systemic therapies [72].

Perhaps even more importantly, the modeling platform we used allows for assessment of endpoints that are not possible even with the results of large, well-designed clinical trials. The incorporation of patient quality of life into the clinical outcome, resource use or cost, and overall survival for the entire cohort until death is particularly important when a subset of patients could achieve cure. When additional trial data become available, we will be able to update many of our model inputs and rerun our analyses.

Our study has limitations. First, when there were no published data to inform model construction, we used a cohort of patients from the MGH who received neoadjuvant FOLFIRINOX therapy. The use of different data sources may introduce bias in the analysis (e.g., the patients treated at MGH may have better outcomes because of self-selection, referral bias, or receiving superior care compared with the average population of pancreatic cancer patients). This relatively small group from a single institution also did not receive uniform treatment. At MGH, after completion of chemotherapy and prior to surgical resection, a multidisciplinary team of surgeons, radiologists, oncologists, and radiation oncologists evaluates results of restaging computed tomography scans to determine if patients should receive a short course or long course of chemoradiotherapy prior to re-evaluation for surgical exploration. In



**Figure 5.** Probabilistic sensitivity analysis. Scatterplot of the probabilistic sensitivity analysis (PSA) comparing neoadjuvant FOLFIRINOX versus gemcitabine plus capecitabine with 1,000 iterations of 1,000,000 hypothetical patients. Each point represents the incremental costs and incremental effectiveness for each iteration in the PSA. Lines on the graph represent various WTP thresholds, and points below each line are considered cost-effective for that WTP threshold. Abbreviations: QALY, quality-adjusted life-years; WTP, willingness to pay.

addition, there were limited data to inform model inputs for costs and the disutilities in quality of life for the nFOLFIRINOX strategy. However, in all instances in which data for the nFOLFIRINOX strategy were limited, we consistently adopted the more conservative estimates by using data from metastatic patient cohorts, thereby theoretically biasing our cost and quality-of-life results against neoadjuvant FOLFIRINOX, or toward the null. It is therefore possible, and arguably even likely, that our model may be underestimating the effectiveness of neoadjuvant FOLFIRINOX, although additional data will be necessary to confirm or refute our assumption. Second, because of the limited data on the different treatment modalities, our study only compared neoadjuvant FOLFIRINOX with adjuvant gemcitabine monotherapy and gemcitabine/capecitabine. We await new data from ongoing clinical studies to further improve and validate our modeling analysis [34, 35, 37, 73]. Results from further investigations involving other therapies such as neoadjuvant gemcitabine/Nab-paclitaxel in the borderline resectable or locally advanced setting will enable additional comparisons of potentially viable treatment strategies [33, 36, 74]. Finally, the limited data for model construction raise concerns about the uncertainty in model outputs or results. However, a critical strength of our model is that we verified that our model outputs were consistent with independent clinically meaningful endpoints related to survival in all three modeled strategies.

## CONCLUSION

Our modeling analysis suggests that neoadjuvant FOLFIRINOX is more effective and cost-effective for patients with borderline resectable or locally advanced PDAC compared with the current standard adjuvant treatment options of gemcitabine or gemcitabine/capecitabine. Although our results provide valuable new insights about the value of

neoadjuvant FOLFIRINOX for patients with potentially resectable PDAC, future clinical trials with sufficient patient recruitment and follow-up duration are needed to confirm our results and further define the long-term efficacy of neoadjuvant FOLFIRINOX for this population.

## ACKNOWLEDGMENTS

This work was presented as a poster at ASCO 2017, Chicago, Illinois. This work was supported by NIH/NCI CA 212086 (to C.H.).

## AUTHOR CONTRIBUTIONS

**Conception/design:** Jin G. Choi, Ryan D. Nipp, Angela Tramontano, Ayman Ali, Tiannan Zhan, Pari Pandharipande, Emily C. Dowling, Cristina R. Ferrone, Deborah Schrag, Carlos Fernandez-Del Castillo, David P. Ryan, Chung Yin Kong, Chin Hur

**Provision of study material or patients:** Jin G. Choi, Ryan D. Nipp, Cristina R. Ferrone, Carlos Fernandez-Del Castillo, Chin Hur

**Collection and/or assembly of data:** Jin G. Choi, Ryan D. Nipp, Cristina R. Ferrone, Carlos Fernandez-Del Castillo, Chin Hur

**Data analysis and interpretation:** Jin G. Choi, Ryan D. Nipp, Angela Tramontano, Ayman Ali, Tiannan Zhan, Pari Pandharipande, Emily C. Dowling, Cristina R. Ferrone, Theodore S. Hong, Deborah Schrag, Carlos Fernandez-Del Castillo, David P. Ryan, Chung Yin Kong, Chin Hur

**Manuscript writing:** Jin G. Choi, Ryan D. Nipp, Angela Tramontano, Ayman Ali, Tiannan Zhan, Pari Pandharipande, Emily C. Dowling, Cristina R. Ferrone, Theodore S. Hong, Deborah Schrag, Carlos Fernandez-Del Castillo, David P. Ryan, Chung Yin Kong, Chin Hur

**Final approval of manuscript:** Jin G. Choi, Ryan D. Nipp, Angela Tramontano, Ayman Ali, Tiannan Zhan, Pari Pandharipande, Emily C. Dowling, Cristina R. Ferrone, Theodore S. Hong, Deborah Schrag, Carlos Fernandez-Del Castillo, David P. Ryan, Chung Yin Kong, Chin Hur

## DISCLOSURES

**Pari Pandharipande:** Medical Imaging and Technology Alliance (RF); **David P. Ryan:** MPM Capital (C/A, OI). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board



## REFERENCES

- American Cancer Society. Cancer Facts and Figures 2015. Atlanta: American Cancer Society, Inc., 2015.
- Tempero MA, Arnoletti JP, Behrman S et al. Pancreatic adenocarcinoma. *J Natl Compr Cancer Netw* 2010;8:972–1017.
- Hidalgo M. Pancreatic cancer. *N Engl J Med* 2010;362:1605–1617.
- Ferrone CR, Marchegiani G, Hong TS et al. Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. *Ann Surg* 2015;261:12–17.
- Varadhachary GR, Tamm EP, Abbruzzese JL et al. Borderline resectable pancreatic cancer: definitions, management, and role of preoperative therapy. *Ann Surg Oncol* 2006;13:1035–1046.
- Katz MH, Marsh R, Herman JM et al. Borderline resectable pancreatic cancer: Need for standardization and methods for optimal clinical trial design. *Ann Surg Oncol* 2013;20:2787–2795.
- Callery MP, Chang KJ, Fishman EK et al. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: Expert consensus statement. *Ann Surg Oncol* 2009;16:1727–1733.
- Tempero MA, Arnoletti JP, Behrman SW et al. Pancreatic adenocarcinoma, version 2.2012: Featured updates to the NCCN Guidelines. *J Natl Compr Cancer Netw* 2012;10:703–713.
- Katz MH, Pisters PW, Evans DB et al. Borderline resectable pancreatic cancer: The importance of this emerging stage of disease. *J Am Coll Surg* 2008;206:833–846; discussion 846–838.
- Wagner M, Redaelli C, Lietz M et al. Curative resection is the single most important factor determining outcome in patients with pancreatic adenocarcinoma. *Br J Surg* 2004;91:586–594.
- Garrido-Laguna I, Hidalgo M. Pancreatic cancer: From state-of-the-art treatments to promising novel therapies. *Nat Rev Clin Oncol* 2015;12:319–334.
- Neoptolemos JP, Stocken DD, Bassi C et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: A randomized controlled trial. *JAMA* 2010;304:1073–1081.
- Neoptolemos JP, Stocken DD, Friess H et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med* 2004;350:1200–1210.
- Oettle H, Neuhaus P, Hochhaus A et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: The CONKO-001 randomized trial. *JAMA* 2013;310:1473–1481.
- Oettle H, Post S, Neuhaus P et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer. *JAMA* 2007;297:267–277.
- Conroy T, Desseigne F, Ychou M et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011;364:1817–1825.
- Von Hoff DD, Ervin T, Arena FP et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013;369:1691–1703.
- Faris JE, Blaszkowsky LS, McDermott S et al. FOLFIRINOX in locally advanced pancreatic cancer: The Massachusetts General Hospital Cancer Center experience. *The Oncologist* 2013;18:543–548.
- Kim SS, Nakamura EK, Wang ZJ et al. Preoperative FOLFIRINOX for borderline resectable pancreatic cancer: Is radiation necessary in the modern era of chemotherapy? *J Surg Oncol* 2016;114:587–596.
- Centers for Disease Control and Prevention. United States Life Tables: National vital statistics report: National Center for Health Statistics. 2011. Accessed August 30, 2016.
- Nipp R, Zanconato A, Zheng H et al. Predictors of early mortality following surgical resection of pancreatic adenocarcinoma in the era of neoadjuvant treatment. *Pancreas* 2017;46:183–189.
- Paniccia A, Edil BH, Schulick RD et al. Neoadjuvant FOLFIRINOX application in borderline resectable pancreatic adenocarcinoma: A retrospective cohort study. *Medicine (Baltimore)* 2014;93:e198.
- Blazer M, Wu C, Goldberg RM et al. Neoadjuvant modified (m) FOLFIRINOX for locally advanced unresectable (LAPC) and borderline resectable (BRPC) adenocarcinoma of the pancreas. *Ann Surg Oncol* 2015;22:1153–1159.
- Sadot E, Doussot A, O'Reilly EM et al. FOLFIRINOX induction therapy for stage 3 pancreatic adenocarcinoma. *Ann Surg Oncol* 2015;22:3512–3521.
- Hosein PJ, Macintyre J, Kawamura C et al. A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline-resectable locally advanced pancreatic adenocarcinoma. *BMC Cancer* 2012;12:1199.
- Marthey L, Sa-Cunha A, Blanc JF et al. FOLFIRINOX for locally advanced pancreatic adenocarcinoma: Results of an AGEO multicenter prospective observational cohort. *Ann Surg Oncol* 2015;22:295–301.
- Suker M, Beumer BR, Sadot E et al. FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis. *Lancet Oncol* 2016;17:801–810.
- Katz MH, Shi Q, Ahmad SA et al. Preoperative modified FOLFIRINOX treatment followed by capecitabine-based chemoradiation for borderline resectable pancreatic cancer: Alliance for Clinical Trials in Oncology Trial A021101. *JAMA Surg* 2016;151:e161137.
- Murphy JE, Wo JY, Ryan DP et al. FOLFIRINOX (F-NOX) followed by individualized radiation for borderline-resectable pancreatic cancer (BRPC): Toxicity, R0 resection, and interim survival data from a prospective phase II study. Abstract 4113 presented at: ASCO; 2017; Chicago, IL.
- Gillen S, Schuster T, Meyer Zum Buschenfelde C et al. Preoperative/neoadjuvant therapy in pancreatic cancer: A systematic review and meta-analysis of response and resection percentages. *PLoS Med* 2010;7:e1000267.
- Christians KK, Tsai S, Mahmoud A et al. Neoadjuvant FOLFIRINOX for borderline resectable pancreas cancer: A new treatment paradigm? *The Oncologist* 2014;19:266–274.
- Petrelli F, Coiu A, Borgonovo K et al. FOLFIRINOX-based neoadjuvant therapy in borderline resectable or unresectable pancreatic cancer: A meta-analytical review of published studies. *Pancreas* 2015;44:515–521.
- Neoadjuvant FOLFIRINOX or Nab-paclitaxel With Gemcitabine for Borderline Resectable Pancreatic Cancer. Available at <https://ClinicalTrials.gov/show/NCT02717091>. Accessed August 3, 2017.
- A Randomized Phase III Trial Comparing FOLFIRINOX to Gemcitabine in Locally Advanced Pancreatic Carcinoma. Available at <https://ClinicalTrials.gov/show/NCT02539537>. Accessed August 3, 2017.
- Neoadjuvant mFOLFIRINOX With or Without Preoperative Concomitant Chemoradiotherapy in Patients With Borderline Resectable Pancreatic Carcinoma (PANDAS-PRODIGE 44). Available at <https://ClinicalTrials.gov/show/NCT02676349>. Accessed August 3, 2017.
- Trial to Investigate Intensified Neoadjuvant Chemotherapy in Locally Advanced Pancreatic Cancer. Available at <https://ClinicalTrials.gov/show/NCT02125136>. Accessed August 3, 2017.
- Randomized Multicenter Phase I/III Study With Adjuvant Gemcitabine Versus Neoadjuvant Adjuvant FOLFIRINOX for Resectable Pancreatic Carcinoma. Available at <https://ClinicalTrials.gov/show/NCT02172976>. Accessed August 3, 2017.
- Veillette G, Dominguez I, Ferrone C et al. Implications and management of pancreatic fistulas following pancreaticoduodenectomy: The Massachusetts General Hospital experience. *Arch Surg* 2008;143:476–481.
- Frey C, Twomey P, Keehn R et al. Randomized study of 5-FU and CNU in pancreatic cancer: Report of the Veterans Administration Surgical Adjuvant Cancer Chemotherapy Study Group. *Cancer* 1981;47:27–31.
- Palmer KR, Kerr M, Knowles G et al. Chemotherapy prolongs survival in inoperable pancreatic carcinoma. *Br J Surg* 1994;81:882–885.
- Glimelius B, Hoffman K, Sjoden PO et al. Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. *Ann Oncol* 1996;7:593–600.
- Huguier M, Barrier A, Valinas R et al. Randomized trial of 5-fluorouracil, leucovorin and cisplatin in advanced pancreatic cancer. *Hepato-gastroenterology* 2001;48:875–878.
- Yeo CJ, Cameron JL, Lillemoe KD et al. Does prophylactic otreotide decrease the rates of pancreatic fistula and other complications after pancreaticoduodenectomy? Results of a prospective randomized placebo-controlled trial. *Ann Surg* 2000;232:419–429.
- Regine WF, Winter KA, Abrams RA et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: A randomized controlled trial. *JAMA* 2008;299:1019–1026.
- Neoptolemos JP, Palmer DH, Ghaneh P et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): A multicentre, open-label, randomised, phase 3 trial. *Lancet* 2017;389:1011–1024.

46. Centers for Medicare & Medicaid Services. 2018 ASP Drug Pricing Files. Available at <https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2018ASPFiles.html>. Accessed July 2, 2018.
47. Caggiano V, Weiss RV, Rickert TS et al. Incidence, cost, and mortality of neutropenia hospitalization associated with chemotherapy. *Cancer* 2005;103:1916–1924.
48. Goldstein DA, Chen Q, Ayer T et al. First- and second-line bevacizumab in addition to chemotherapy for metastatic colorectal cancer: A United States-based cost-effectiveness analysis. *J Clin Oncol* 2015;33:1112–1118.
49. Bilir SP, Ma Q, Zhao Z et al. Economic burden of toxicities associated with treating metastatic melanoma in the United States. *Am Health Drug Benefits* 2016;9:203–213.
50. Attard CL, Brown S, Alloul K et al. Cost-effectiveness of folfinirax for first-line treatment of metastatic pancreatic cancer. *Curr Oncol* 2014;21:e41–e51.
51. Tam VC, Ko YJ, Mittmann N et al. Cost-effectiveness of systemic therapies for metastatic pancreatic cancer. *Curr Oncol* 2013;20:e90–e106.
52. United States Bureau of Labor Statistics: CPI inflation calculator. Available at [https://www.bls.gov/data/inflation\\_calculator.htm](https://www.bls.gov/data/inflation_calculator.htm). Accessed August 3, 2017.
53. Cerullo M, Gani F, Chen SY et al. Assessing the financial burden associated with treatment options for resectable pancreatic cancer. *Ann Surg* 2018;267:544–551.
54. O'Neill CB, Atoria CL, O'Reilly EM et al. Costs and trends in pancreatic cancer treatment. *Cancer* 2012;118:5132–5139.
55. Holbrook RF, Hargrave K, Traverso LW. A prospective cost analysis of pancreatoduodenectomy. *Am J Surg* 1996;171:508–511.
56. Goldstein D, El-Maraghi RH, Hammel P et al. nab-Paclitaxel plus gemcitabine for metastatic pancreatic cancer: Long-term survival from a phase III trial. *J Natl Cancer Inst* 2015;107:dju413.
57. Sener SF, Fremgen A, Menck HR et al. Pancreatic cancer: A report of treatment and survival trends for 100,313 patients diagnosed from 1985–1995, using the National Cancer Database. *J Am Coll Surg* 1999;189:1–7.
58. Alexakis N, Sutton R, Neoptolemos JP. Surgical treatment of pancreatic fistula. *Dig Surg* 2004;21:262–274.
59. Bassi C, Butturini G, Molinari E et al. Pancreatic fistula rate after pancreatic resection. The importance of definitions. *Dig Surg* 2004;21:54–59.
60. Ho HS, Frey CF. Gastrointestinal and pancreatic complications associated with severe pancreatitis. *Arch Surg* 1995;130:817–823.
61. Tsiotos GG, Smith CD, Sarr MG. Incidence and management of pancreatic and enteric fistulas after surgical management of severe necrotizing pancreatitis. *Arch Surg* 1995;130:48–52.
62. Centers for Medicare and Medicaid Services. 2018 ASP Drug Pricing Files. Available at <https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2018ASPFiles.html>. Accessed July 2, 2018.
63. Patnaik A, Doyle C, Oza AM. Palliative therapy in advanced ovarian cancer: Balancing patient expectations, quality of life and cost. *Anticancer Drugs* 1998;9:869–878.
64. Goldstein DA, Krishna K, Flowers C et al. Cost description of chemotherapy regimens for the treatment of metastatic pancreas cancer (mPC). Abstract presented at: Gastrointestinal Cancers Symposium; January 15–17, 2015; San Francisco.
65. Leung HW, Chan AL, Muo CH. Cost-effectiveness of gemcitabine plus modern radiotherapy in locally advanced pancreatic cancer. *Clin Ther* 2016;38:1174–1183.
66. Aballea S, Chancellor JV, Raikou M et al. Cost-effectiveness analysis of oxaliplatin compared with 5-fluorouracil/leucovorin in adjuvant treatment of stage III colon cancer in the US. *Cancer* 2007;109:1082–1089.
67. Romanus D, Kindler HL, Archer L et al. Does health-related quality of life improve for advanced pancreatic cancer patients who respond to gemcitabine? Analysis of a randomized phase III trial of the cancer and leukemia group B (CALGB 80303). *J Pain Symptom Manage* 2012;43:205–217.
68. Huang JJ, Yeo CJ, Sohn TA et al. Quality of life and outcomes after pancreaticoduodenectomy. *Ann Surg* 2000;231:890–898.
69. Lloyd A, Nafees B, Narewska J et al. Health state utilities for metastatic breast cancer. *Br J Cancer* 2006;95:683–690.
70. Lenert LA, Soetikno RM. Automated computer interviews to elicit utilities: Potential applications in the treatment of deep venous thrombosis. *J Am Med Inform Assoc* 1997;4:49–56.
71. Gould MK, Dembitzer AD, Sanders GD et al. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis. A cost-effectiveness analysis. *Ann Intern Med* 1999;130:789–799.
72. de Geus SW, Evans DB, Bliss LA et al. Neoadjuvant therapy versus upfront surgical strategies in resectable pancreatic cancer: A Markov decision analysis. *Eur J Surg Oncol* 2016;42:1552–1560.
73. ESPAC-5F: European Study group for Pancreatic Cancer - Trial 5F. Available at <http://www.isrctn.com/ISRCTN89500674>. Accessed August 3, 2017.
74. S1505: Combination Chemotherapy or Gemcitabine Hydrochloride and Paclitaxel Albumin-Stabilized Nanoparticle Formulation Before Surgery in Treating Patients With Pancreatic Cancer That Can Be Removed by Surgery. Available at <https://ClinicalTrials.gov/show/NCT02562716>. Accessed August 3, 2017.



See <http://www.TheOncologist.com> for supplemental material available online.