The Value of Survival Gains in Pancreatic Cancer from Novel Treatment Regimens

Joanna P. MacEwan, PhD; Wes Yin, PhD; Satyin Kaura, MS, MBA; and Zeba M. Khan, PhD

ABSTRACT

BACKGROUND: Metastatic pancreatic cancer (mPC) is associated with low survival, with less than 10% of patients surviving 5 years. Recent therapies improve survival outcomes where few alternative therapies exist, but few economic analyses measure the value of survival gains attributable to new therapies.

OBJECTIVE: To estimate the value of survival gains in advanced or mPC attributable to the introduction of novel treatment regimens.

METHODS: Multivariate Cox proportional hazards models were used to estimate real-world survival gains associated with the introduction of gemcitabine (GEM) for patients diagnosed with stage IV or unstaged mPC in the Surveillance, Epidemiology, and End Results Program cancer registries. Then, evidence from clinical trials was used to evaluate the survival gains associated with nab-paclitaxel + gemcitabine (nP+GEM) and FOLFIRINOX (FFX) relative to GEM. The survival estimates and clinical trial evidence were used to calibrate an economic model and assess the cumulative value of survival gains in mPC to patients. Costs of treatment were calculated based on published cost-effectiveness studies.

RESULTS: We estimated that the introduction of GEM in 1996 was associated with a hazard ratio of 0.920 ($P < 0.05$) and an increase in median survival from 3.1 to 4.5 months. Results suggested that the value of survival gains attributable to GEM equaled about \$71,000 per patient, while the value attributable to nP+GEM was an additional \$56,700. Estimates for the value of survival gains per patient, net of total incremental lifetime treatment costs (drugs, adverse events, and other costs), were \$50,294 for GEM and an additional \$31,900 for nP+GEM. Clinical trials and cost-effectiveness studies reported an overall survival gain from FFX that was larger than, but statistically similar to, nP+GEM and had greater risk of adverse events and total incremental costs. We estimated that the total value of survival gains to mPC patients, net of total costs, associated with GEM was up to \$47.6 billion, and the additional values attributable to nP+GEM and FFX were up to \$39.0 billion and \$26.3 billion, respectively.

CONCLUSIONS: Historically, mPC patients have faced high disease burden and had few treatment options. Treatments introduced since 1996 have led to improved survival, with varying costs associated with treatment and adverse events. Accounting for total incremental costs, the majority of the value of survival gains from GEM and nP+GEM was retained by mPC patients, highlighting the value of innovation in settings where survival is low and few alternative therapies exist.

J Manag Care Spec Pharm. 2017;23(2):206-13

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What is already known about this subject

- Few economic analyses specifically measure the value of survival gains in metastatic pancreatic cancer (mPC) attributable to new cancer therapies using real-world data.
- Previous studies have shown that nearly all of the gains in life expectancy for mPC patients from 1988 to 2000 were attributable to improvements in treatment rather than earlier cancer detection.

What this study adds

- This study builds on the literature and estimates the value of survival gains in mPC attributable to the introduction of novel treatment regimens.
- This study estimates survival gains in the community—as opposed to clinical trials—associated with the introduction of gemcitabine.
- This study estimates the value of survival gains attributable to recently introduced therapies nab-paclitaxel and FOLFIRINOX, which were approved after gemcitabine.

Since the 1970s, innovation in cancer detection and cancer treatment has contributed to improved survival rates.^{1,2} Dramatic gains have been seen in several tumor types, including breast cancer,³ colon cancer, chronic myeloid leukemia,^{4,5} and non-Hodgkin's lymphoma, due in part to the introduction of targeted therapies such as tyrosine kinase inhibitors, vascular endothelial growth factor-targeted drugs, and proteasome inhibitors, among others.^{6,7}

In advanced or metastatic pancreatic cancer (mPC), however, survival remains low, even in relation to other difficult-to-treat cancers, such as lung cancer, with less than 10% of patients surviving 5 years.⁸ Moreover, relatively few treatments for mPC exist. The chemotherapy gemcitabine (GEM) was approved by the U.S. Food and Drug Administration in May 1996 for the treatment of nonresectable (stage III and stage IV) mPC and has been the standard first-line treatment for metastatic disease since 1997.^{9,10} Since its approval, only 3 of numerous phase III trials for new therapies have demonstrated any significant improvements in overall survival in mPC relative to GEM.^{9,11-14} Several other chemotherapy regimens (e.g., capecitabine + GEM and S-1 with or without GEM) are used outside the United States as alternatives to treatment guideline “preferred” regimens for mPC patients with good performance status and among patients with poorer performance status.¹⁵⁻¹⁷

Nab-paclitaxel (nP) was approved as a first-line treatment for nonresectable mPC in September 2013,¹⁸ after a phase III clinical trial demonstrated an increase in median survival from 6.6 months to 8.7 months for patients treated with nP+GEM, compared with treatment with GEM alone.^{9,11} In 2011, the results of a phase II-III trial comparing FOLFIRINOX (FFX) with GEM monotherapy demonstrated significant improvements in overall survival, progression-free survival, and overall response, as well as a higher incidence of grade 3/4 adverse events.¹³ To date, there are no head-to-head trials of FFX and nP+GEM. However, a recent indirect comparison reports that treatment with FFX (relative to GEM monotherapy) is associated with a statistically similar increase in overall survival as the nP+GEM regimen (hazard ratio [HR] = 1.26, 95% confidence interval [CI] = 0.95-1.67), although FFX was more favorable in terms of progression-free survival (HR = 1.47, 95% CI = 1.10-1.96).¹⁹ In clinical trials, the FFX regimen had significantly higher toxicity than GEM. Both FFX and nP+GEM are “preferred” regimens for mPC patients with good performance status in widely used patient treatment guidelines.¹⁶

mPC represents an area where therapeutic innovation has the potential to offer tremendous value to patients and society as a whole by improving life expectancy where survival is very low and where a limited number of alternative therapies exist.²⁰ Few economic analyses specifically measure the value of survival gains in mPC attributable to new cancer therapies,²¹ and few studies measure survival gains in the real world, where benefits may differ from those observed in clinical trials. Using Surveillance, Epidemiology, and End Results Program (SEER) registry data from 1988 to 2000 (capturing the introduction of GEM in 1996), Lakdawalla et al. (2010) estimated that the lifetime value of the increase in survival for mPC patients during this time period equaled \$25,705 per patient (in U.S. 2006 dollars) and that nearly all of the estimated increase in life expectancy (0.46 years) was attributable to improvements in treatment rather than earlier cancer detection.²¹ According to recent economic assessments of first-line regimens for pancreatic cancer, the albumin-bound (nab) paclitaxel plus GEM (nP+GEM) and FFX (combination of fluorouracil, oxaliplatin, leucovorin, and irinotecan) regimens demonstrated similar increases in overall survival relative to GEM monotherapy at total incremental costs (including nonpharmacy costs) of \$24,751 and \$93,941, respectively.^{15,19}

This study builds on this literature and estimates the value of survival gains in mPC attributable to the introduction of novel therapies. Particularly, the purpose of this study was to estimate the survival gains in mPC since the introduction of GEM, using more recent data through 2013, and assess the value of survival gains attributable to the introduction of nP and FFX for patients diagnosed in 2015 and beyond. This type of economic evaluation of innovative treatments informs payers, policymakers, and other stakeholders about the economic value of novel therapies relative to their costs and the overall benefits they provide to patients and society.

Methods

Survival Analysis

For the survival analysis, we used SEER registry data for patients diagnosed with stage III, IV, or unstaged mPC between 1990 and 2013. Cox proportional hazards models were used to estimate the increase in real-world survival attributable to the introduction of GEM in 1996. The key variable in the hazard model was the post-1996 indicator ($YEARS_{Post1996}$) that captured the increase in survival associated with the introduction of GEM. The model also included a post-2005 ($YEARS_{Post2005}$) indicator to capture any effects from the introduction of erlotinib. We restricted the sample to nonresectable (stage III, IV, or unstaged) mPC patients to minimize the possibility of confounding the impact of resection surgery with the effect of the introduction of GEM on changes in mPC survival.

The HR associated with the $YEARS_{Post1996}$ variable is the primary estimate of the effect of GEM on mPC survival and is the key input in our economic model of the value of survival gains. This indicator captures changes in survival associated with being diagnosed after 1996 (the year in which GEM was introduced). A set of diagnosis-year fixed effects were included to capture the secular trend in mPC survival that is unrelated to the launch of new therapies or other unobserved changes in the standard of care for mPC. In the case that other changes were timed with GEM's introduction, the model captured the joint effect on survival. We also included a broad set of patient characteristics, such as age at diagnosis, gender, stage at diagnosis, race, and insurance status to control for changes in survival as a result of changes in the mPC case mix over time.

SEER data do not include information on which specific therapies patients used. Thus, the hazard model was restricted to only those mPC patients who were diagnosed at stage III, IV, or who were unstaged and most likely to be treated with GEM and/or erlotinib and not treated with surgery. Even so, our estimated HR in the post-1996 time period was interpreted as a measure of the intent-to-treat (ITT) effect of the introduction of GEM. Thus, we scaled the ITT effect by the average annual share of patients diagnosed with pancreatic cancer (*International Classification of Diseases, Ninth Revision, Clinical Modification* codes 157.0-157.4, 157.8, and 157.9) from 2005 to 2013 with a claim for GEM in the Ingenix data (29%) to calculate the treatment-on-the-treated (TOT) effect for GEM. Particularly, we calculated the TOT effect as the ITT survival effect divided by 0.30.

At the time of this analysis, the SEER data did not contain data beyond 2013, so we could not directly estimate any effects from the introduction of nP and FFX in the real world. However, we had evidence from clinical trials on the efficacy of nP+GEM and FFX relative to GEM alone. Thus, we used the relative increase in median survival measured in the clinical trial to infer the shift in the post-1996 survival curve—which represents the state of the world where only GEM is used, or

the control group—to estimate the expected survival gains in the community associated with nP+GEM and FFX.

The nP+GEM clinical trial reported a 2.1 month (32%) increase in median overall survival, from 6.6 in the GEM arm to 8.7 months in the nP+GEM arm (HR=0.72, 95% CI=0.62-0.83).^{9,11} The FFX clinical trial demonstrated a 4.3-month (63%) increase in median overall survival, from 6.8 months in the GEM arm to 11.1 months in the FFX arm (HR=0.57, 95% CI=0.45-0.73).¹³ Separately for nP+GEM and FFX, we used these survival increases to extrapolate the post-GEM survival curve, which we previously estimated from SEER using Cox proportional hazard analysis. To do so, in the case of nP+GEM, we scaled the effect of GEM assuming that the median overall survival for nP+GEM in the real world would be 1.32 (=6.6/8.7) times the estimated median overall survival for GEM estimated using SEER. An analogous approach was applied for FFX, scaling the effect of GEM assuming that the median overall survival for FFX in the real world would be 1.63 (=11.1/6.8) times the estimated median overall survival for GEM estimated using SEER. This approach incorporated the survival gains measured in the real world relative to those measured in the clinical trial setting, as observed when comparing the SEER-based and clinical trial evidence for GEM.

An indirect comparison study of nP+GEM and FFX by Gharaibeh et al. (2016) showed larger but statistically insignificant survival benefits of FFX, as well as larger costs associated with adverse events.¹⁹ For consistency, the valuation of FFX was based on the survival benefits reported in Conroy et al. (2011), who directly compared FFX to GEM, which is the same approach we used to value gains attributable to nP+GEM.¹³

Value of Survival Gains

We calibrated an economic model (BPS) developed by Becker et al. (2005) to estimate the value patients place on increased longevity.²² The model essentially calculates the amount of money that would, all else being equal, make mPC patients facing the baseline lower survival curve as well off as patients who face the improved survival curve. As in Becker et al. and Lakdawalla et al.,^{21,22} we interpreted this amount as the value of survival gains. This framework explicitly allows patients to place greater value on a given increase in survival when baseline survival is low. This is consistent with surveys that reveal higher marginal valuation on survival in end-of-life settings, as well as in settings where few treatment options exist²³—sources of value that have been explicitly codified in some health technology assessment regimes.²⁴

The economic model used patient income level as a key input because patient utility is determined by consumption of goods and services, including health care, which depends on patient income level. We used the Medical Expenditure Panel Survey (MEPS) data from 2009 to 2011 to estimate the earned income of patients who were at least aged 18 years and reported

a diagnosis of pancreatic cancer. We calculated full income as double of the earned income. Adjusting for the complex survey design, the average age of pancreatic cancer patients in the MEPS sample was 67.2 years. The estimated full income for mPC patients equaled approximately \$59,000 per year (2015 U.S. dollars).

Treatment Costs

We used 2015 wholesale acquisition costs (WAC) from Wolters Kluwer Clinical Drug Information Medi-Span database to estimate annual incremental costs of treatment with nP (the WAC per 100 mg vial of nP equaled \$1,035). The annual incremental costs of treatment with GEM and FFX were based on the unit prices reported in Gharaibeh et al., assuming that patients received 2 doses per 28-day cycle for 6 cycles in both regimens.¹⁹ All incremental drug regimen costs were consistent with dose intensities and durations observed in phase III FFX and nP+GEM clinical trials.^{9,13} We used the estimated incremental total cost for the GEM, nP+GEM, and FFX regimens of \$20,440, \$24,751, and \$93,941, respectively.¹⁹ Note that these incremental costs include nonpharmacy costs such as supportive care, drug administration, and cost associated with adverse events.

Estimating Present Discounted Value of Treatment Costs and Survival Gains

Using the estimated annual values of survival gain and treatment costs, we calculated the present discounted value (PDV) of the increase in survival for a single patient over his or her lifetime, weighting values and costs in later years by the estimated survival probability in the given year. Then, we calculated the PDV of the incremental lifetime value and costs for all future patient cohorts, that is, the present value of an infinite stream of lifetime survival benefits to mPC patients diagnosed in 2015 and beyond, assuming that all eligible mPC patients used the regimen. Therefore, our estimates represent the total potential value of survival benefits attributable to a specific treatment regimen. When estimating the total PDV of the lifetime survival gains and costs, we considered the current and future mPC incident cohorts, assuming a 3% discount rate, and accounted for patent expiry (the nP patent expires in 2024).²⁵ We estimated the eligible mPC patient cohort size as the share of incident cases of mPC expected to have an Eastern Cooperative Oncology group (ECOG) score of 0, 1, or 2, using literature that reported survival rates by performance status.^{26,27} Patients with an ECOG score of 3 or more had a median survival rate of less than 3 months; therefore, we assumed patients in the SEER sample who survived at least 3 months had good performance status and were good candidates for treatment with FFX or nP+GEM. In the SEER data, 62.75% of mPC patients survived 3 or more months; therefore, we estimated that the eligible incident mPC patient cohort size

TABLE 1 Summary Statistics for mPC Patients

	Diagnosed 1990-1995	Diagnosed 1996-2013
Age at diagnosis	69.7 (12.22)	68.9 (12.67)
Female	52.2% (0.50)	49.2% (0.50)
Married at diagnosis	55.4% (0.50)	54.0% (0.50)
Hispanic	5.5% (0.23)	9.3% (0.29)
White	81.2% (0.39)	80.6% (0.40)
Black	12.0% (0.33)	12.0% (0.33)
Asian/Pacific Islander	6.8% (0.25)	7.2% (0.26)
Stage IV at diagnosis	69.8% (0.46)	81.9% (0.39)
Unstaged at diagnosis	30.2% (0.46)	18.1% (0.39)
Observations	9,443	71,809

Note: Standard errors are shown in parentheses. There were no individuals in the databases with stage III mPC that met our inclusion criteria.

mPC=metastatic pancreatic cancer.

equaled 28,408 ($=0.6725 \times 42,242$) based on an overall annual incidence of 46,420 cases of mPC in 2014 and 9% of incidence cases diagnosed at a localized (resectable) stage.²⁸ Note that the individual incremental lifetime and total future net value of nP and FFX are *in addition* to the net value generated by GEM, but the therapies themselves substituted for the eligible incident mPC patient population in the valuation model so that the net values we estimated for nP and FFX should not be summed.

To calculate the PDV of costs, we factored in the effect of patent expiry on future prices. The extent to which prices decline following patent expiry depends on several factors, including the number of generic manufacturers that enter the market, the complexity of producing the molecule, outpatient rather than pharmacy benefit coverage, the number of competing therapies, and the length of time since patent expiry.²⁹ A recent study estimated that prices for intravenous specialty drugs, such as nP, decline by 34% after expiration.²⁹ We used this price decline to forecast future costs of nP treatment in mPC. All of the component drugs of the FFX regimen are off patent in the United States; therefore, we did not adjust the future price of the FFX regimen.

Sensitivity Analysis

We also used an alternative method to value increases in life expectancy based on estimates of the value of a life year to society, that is, the value of a statistical life year (VSLY). We used a range of VSLYs that are most commonly used to value changes in quality and length of life.³⁰⁻³³ Estimates for the VSLY range between \$100,000 and \$300,000 in the literature,³⁴ so we reported sensitivity analyses based on midpoints of this range.

Results

Summary Statistics

The sample of patients diagnosed with stage IV, or unstaged mPC, between 1990 and 2013 from the SEER cancer registry

TABLE 2 Effect of Introduction of Novel mPC Therapies

	Hazard Ratio
Hazard ratio associated with post-1996 = 1	0.920 ^a (0.032)
Hazard ratio associated with post-2005 = 1	0.892 ^b (0.024)
Observations	81,252

Source: SEER registry data for 1990-2013 and authors' calculations.

Note: Standard errors are shown in parentheses. The table reports the hazard ratio associated with the post-2005 variable. Demographic controls include sex, age at diagnosis, marital status, race, health insurance, and stage at diagnosis. An annual fixed-effect time trend was included.

^aP<0.05.

^bP<0.01.

mPC=metastatic pancreatic cancer; SEER=Surveillance, Epidemiology, and End Results.

database included 81,252 individuals (Table 1). There were no patients diagnosed with stage III mPC in the SEER database. Eighty-eight percent of these patients in the final sample were diagnosed after 1996. Patients diagnosed in 1996 or later were more likely to be Hispanic and have stage IV disease at diagnosis and less likely to have unstaged disease at diagnosis than patients diagnosed before 1996.

Change in mPC Survival Curves Attributable to New Therapy

Using a Cox proportional hazards model, we estimated that the introduction of GEM was associated with an HR of 0.920 ($P<0.05$; Table 2). That is, we estimated that mPC patients diagnosed in 1996 or later had an approximately 8.0% lower chance of dying within a year (conditional on surviving to that year) than under the counterfactual that GEM and erlotinib were not introduced (Table 2). Note that the counterfactual survival rate in 2013 (plotted in Figure 1) is the estimated survival in 1996 (the final pre-introduction year), adjusted for the estimated secular increase in survival between 1996 and 2013. The estimated 10.8% decrease in mortality after the introduction of erlotinib is also significant. However, small measured increases in survival in the erlotinib clinical trials, changes in the use of adjuvant therapy and screening for high risk patients in the mid-2000s, and low use of erlotinib by pancreatic patients in the Ingenix claims data from 2005 to 2013 make it less clear that all of this change was attributable to the use of erlotinib.^{12,35}

Next, we extrapolated the post-GEM current year survival curve using the relative survival gains in median overall survival for nP+GEM and FFX based on clinical trials for the 2 therapies relative to GEM monotherapy, as previously described (see Figure 1). For nP+GEM, we estimated a median survival increase from 4.5 to 5.9 months (32% increase), and for FFX, we estimated a median survival increase from 4.5 to 7.3 months (63% increase).

TABLE 3 Value of Survival Gain Attributable to Novel mPC Treatment Regimens

	Lifetime Value per Person, ^a \$	PDV Lifetime Value (Billions), ^b \$
GEM		
Benefits	70,734	66.98
Drug-only costs	790	0.75
Total costs	20,440	19.36
Benefits net of drug costs	69,944	66.23
Benefits net of total costs	50,294	47.62
nP+GEM		
Benefits	56,651	53.64
Drug-only costs	10,417	4.99
Total costs	24,751	14.64
Benefits net of drug costs	46,234	48.65
Benefits net of total costs	31,900	39.01
FFX		
Benefits	121,748	115.29
Drug-only costs	13,488	12.77
Total costs	93,941	88.96
Benefits net of drug costs	108,259	102.51
Benefits net of total costs	27,807	26.33

Sources: SEER registry data for 1990-2013, Gharaibeh et al. (2016),¹⁹ Becker et al. (2005),²² and authors' calculations.

Note: Drug and total costs are based on Gharaibeh et al. (2016)¹⁹ and dosing schedules used in nP+GEM and FFX clinical trials (Conroy et al. 2011¹³ and Goldstein et al. 2015¹¹). Drug prices adjusted for patent expiry in PDV of lifetime value calculation are based on Conti and Berndt (2014)²⁹ and reported in 2015 U.S. dollars.

^aThis column reports the present value over a single patient's expected life following Becker et al. (2005).²²

^bThis column reports the present discounted lifetime value for all current and future incident cohorts. We estimated that the incidence cohort size was 28,408 and assumed a 3% annual discount rate.

FFX = FOLFIRINOX; GEM = gemcitabine; mPC = metastatic pancreatic cancer; nP+GEM = nab-paclitaxel + gemcitabine; PDV = present discounted value; SEER = Surveillance, Epidemiology, and End Results.

Value of Survival Gains Attributable to New Therapies

Table 3 compares the estimated value of survival gains to drug-only costs and total costs. We estimated that the lifetime value of survival gains attributable to the introduction of GEM was approximately \$70,734 per patient. The estimated lifetime value of the additional survival gains attributable to the introduction of the nP+GEM regimen was \$56,561—which equals the estimated amount an mPC patient would pay for the higher survival profile associated with the new therapy. This value reflects not only the value of increased survival, but also the greater value patients place on survival when the baseline likelihood of survival is low, as discussed in the Methods section. The estimated value of survival gains attributable to GEM exceeded the drug-only cost of therapy, with lifetime *net* benefit per patient estimated to equal \$69,944 (Table 3, column 1, row 4). The estimated value of survival gains attributable to nP+GEM exceeded the drug-only cost of therapy, with lifetime

TABLE 4 Comparison of Values of Survival Gain for mPC Patients

	LE gain (years)	Lifetime Value of Survival Gains (2015 U.S. \$)		
		VSly \$100K (\$)	VSly \$300K (\$)	BPS ^a (\$)
GEM	0.20	20,000	60,000	70,734
nP+GEM	0.25	25,000	75,000	56,561
FFX	0.40	40,000	120,000	121,748

^aBPS = economic model used based on Becker et al. (2005).²²

FFX = FOLFIRINOX; GEM = gemcitabine; LE = life expectancy; mPC = metastatic pancreatic cancer; nP+GEM = nab-paclitaxel + gemcitabine; VSly = value of a statistical life year.

net benefit per patient estimated to equal \$46,234 (Table 3, column 1, row 9). Accounting for the cost associated with supportive care and adverse events as well, the lifetime *net* benefit per patient attributable to GEM equals \$50,294, and the additional net value of nP+GEM equals \$31,900.

We estimated the lifetime value of the FFX regimen to be \$121,748 per patient, based on Conroy et al., who reported the relative benefits of FFX versus GEM.¹³ A more conservative estimate, assuming the statistical equivalence of the benefits of FFX and nP+GEM, as reported in Gharaibeh et al.,¹⁹ would imply lifetime value of survival gain of approximately \$56,600 per patient, similar to that of the nP+GEM regimen. While the incremental lifetime drug costs of FFX are fairly low at \$13,488, the total incremental costs are higher than nP+GEM because of increased adverse event costs with FFX. Based on the estimated lifetime value of survival gains of \$121,748, the benefit to mPC patients net of total incremental costs equals \$27,807 for FFX.

Assuming an incidence of 28,408 new mPC patients per year and that all mPC patients receive the treatment, we estimated that a cumulative net value (accounting for the total costs of treatment) to all future cohorts of mPC patients equals up to \$47.6 billion for the GEM regimen (Table 3, column 2, row 5) and up to an additional \$39.0 and \$26.3 billion for the nP+GEM and FFX regimens (Table 3, column 2, rows 10 and 15), respectively.²⁸ This value reflects the survival gains and the higher value associated with a given survival gain when baseline survival is low. To the extent that pancreatic cancer incidence has been increasing, this estimate understates the value of this innovative therapy.²⁸

Sensitivity Analysis

Table 4 compares our estimates of value of survival gains attributable to the introduction of GEM, nP+GEM, and FFX with estimates based on the increase in life expectancy (discounted expected survival) and the VSly. Note that our life expectancy gains for nP+GEM (0.25 years) and FFX (0.40 years) relative to GEM are similar to those of Gharaibeh et al. (0.18 years and 0.37 years, respectively).¹⁹ The estimated lifetime value of

FIGURE 1 Estimated Survival Curves for Pancreatic Cancer Patients Before and After Introduction

Sources: SEER registry data for 1990-2013 and authors' calculations.

Note: Cox proportional hazards model predicted survival curves. Model includes age, sex, race, health insurance, tumor stage, and time trend covariates. Sample excludes patients diagnosed at stage I or II.

FFX = FOLFIRINOX; GEM = gemcitabine; nP + GEM = nab-paclitaxel + gemcitabine; SEER = Surveillance, Epidemiology, and End Results.

survival gains attributable to GEM based on the BPS framework is higher than those based on VSLYs and life expectancy gains (Table 4, row 1, columns 2-4) in part because in the BPS framework a given increase in life expectancy is more highly valued when baseline life expectancy is low—as is the case with mPC before the introduction of GEM—which we estimated to equal approximately 0.65 years or 7.8 months. The estimated lifetime value of survival attributable to nP+GEM falls between that implied by a VSLY of \$100,000 and \$300,000, and the estimated lifetime value of survival gains from FFX are slightly larger than the value implied by a VSLY of \$300,000. The greater value placed on survival when survival is low to begin with is consistent with preference surveys and with recent reimbursement policies adopted by agencies conducting health technology assessments (e.g., the National Institute for Health and Care Excellence in the United Kingdom).²⁰ Note that we do not have estimates of the VSLY for mPC patients, specifically. In the BPS framework, we did, however, specifically use mPC patient income to calibrate the model to derive the value of survival gains. This is yet another reason why the BPS figures are our preferred estimates. However, the nearness in the estimates using both methods is reassuring.

Discussion

In this study, we measured the value of survival gains in mPC for patients from the introduction of GEM, FFX, and nP + GEM for patients with mPC. Our Cox proportional hazards model estimated the shift in the probability of survival associated with the introduction of GEM, while controlling for secular time trends and patient characteristics in patients diagnosed with stage IV or unstaged pancreatic cancer. Next, we extrapolated from the nP and FFX clinical trial results and our Cox proportional hazards model to estimate the shift in the survival curve attributable to the introduction of nP. The calibrated BPS economic model (developed by Becker et al.²²) allowed us to calculate the amount that cancer patients would be willing to pay for discrete increases in the probability of survival associated with the increase in survival estimated in the SEER data. We compared the value of these survival benefits to the drug-only and total incremental costs of treatment with the GEM, nP + GEM, and FFX regimens. We estimated that the cumulative value of survival gains attributable to GEM and nP will exceed the cost of therapy by up to \$47.6 billion and \$39.0 billion, respectively, for mPC patients diagnosed in 2015 or later. To the extent that the FFX regimen offers statistically similar survival benefits as nP + GEM relative to GEM monotherapy, the per patient lifetime value of survival gains attributable to the FFX regimen are similar to those of nP. For mPC patients with higher performance status who can tolerate the toxicity of the FFX regimen and realize larger overall survival benefits, the lifetime value of the survival gain may reach up to \$26.3 billion for all future mPC cohorts. The value generated from the nP + GEM and FFX regimens is in addition to that generated by GEM.

The estimates by Lakdawalla et al.²¹ capture the effect of the introduction of GEM and other changes in mPC treatment on survival for all mPC cancer patients (e.g., improvements in imaging and staging),³⁵ whereas our estimates captured the effect of specific drugs for patients diagnosed with nonresectable, advanced mPC. As such, it is not surprising that our estimated increase in life expectancy from the introduction of GEM is lower than that implied by Lakdawalla et al. (0.46 years).²¹ Our estimates also differ in that we estimated income for mPC patients, and Lakdawalla et al. estimated income for cancer patients in general.²¹

One strength of this study is that we used rigorous methods to estimate gains in survival in the real world, rather than a small patient sample such as in a trial, using a large sample of cancer patients from the SEER registry database. The large sample size in the SEER cancer registry data allowed us to detect significant and meaningful survival gains. SEER is the most comprehensive and detailed data available on cancer incidence and survival in the United States. Second, we used

a sound economic framework for valuing survival gains for patients with mPC. Lastly, we assumed that the real-world efficacy of the nP+GEM and FFX regimens would be equivalent to that observed in pivotal clinical trials. To the extent that the real-world efficacy of these regimens is actually higher, our estimates understate the value of survival gains associated with these regimens. Evidence from Canadian cancer registries and 1 small U.S. study suggests that despite frequent dose modifications, real-world mPC patients using the FFX regimen see similar overall survival benefits as patients in clinical trials.^{36,37}

Limitations

This study also has some limitations. The SEER data are not nationally representative and do not include information on the specific treatments used by mPC patients. We addressed this limitation by restricting our analysis to those mPC patients most likely to use GEM, erlotinib, FFX, and nP+GEM, that is, patients with stage III, stage IV, or unstaged pancreatic cancer. The restriction to mPC patients also limited the potential for advances in pancreatic cancer detection to bias our results, since these advances would likely increase the rate of stage I-II pancreatic cancer diagnoses and improve outcomes for these patients. However, to the extent that improved diagnosis, medication adherence, or other factors coincided with the introduction of GEM and influenced overall survival in the post-1996 period, our estimates would overstate the benefits of GEM. Also, at the time of this analysis, the SEER data were only available through 2013, before the introductions of nP and FFX; therefore, we did not observe or estimate the real-world effect of the introduction of these drugs. In addition, our analysis captured the value of increases in progression-free survival associated with the novel treatment regimens, which may have value above and beyond their contribution to extending overall survival. Also, our estimated value of novel treatments for mPC was underestimated to the extent that new treatments decrease the indirect costs of treatment (i.e., productivity losses and caregiver burden) not captured in the total indirect cost estimates from Gharaibeh et al. used in this analysis.¹⁹ Novel treatments that have fewer side effects, are administered orally rather than intravenously, or that have to be taken less frequently, for example, may also decrease the indirect costs of treatment.

Several clinical characteristics account for the large value of survival attributable to innovative therapies for mPC. First, the value of gains in mPC survival attributable to nP and FFX are large because few alternative and comparable therapies exist. Second, baseline survival expectancy is low, so even small discrete gains in survival are highly valuable to patients near the end of life.²³ Finally, our estimated proportional shift in real-world survival attributable to the introduction of GEM was very similar to that observed in the clinical trial.¹⁰

Conclusions

This study demonstrates that the value of innovative treatments to society for mPC has been large and that the vast majority of value accrues to patients. The results of this study and others like it consistently highlight the significant net patient value generated by innovative therapies and that improving patient access to novel and beneficial therapies is warranted.

Authors

JOANNA P. MACEWAN, PhD, Precision Health Economics, Los Angeles, California, and WES YIN, PhD, University of California, Los Angeles. SATYIN KAURA, MS, MBA, and ZEBA M. KHAN, PhD, Celgene, Summit, New Jersey.

AUTHOR CORRESPONDENCE: Joanna P. MacEwan, PhD, Precision Health Economics, 11100 Santa Monica Blvd., Ste. 500, Los Angeles, CA 90025. Tel.: 310.984.7718; E-mail: Joanna.MacEwan@PHEconomics.com.

DISCLOSURES

Support for this research was provided by Celgene. Precision Health Economics was compensated by Celgene for work on this study. MacEwan is an employee of, and Yin is a consultant to, Precision Health Economics. Kaura and Khan are employees of Celgene.

Study concept and design were contributed primarily by Yin and MacEwan, along with Kaura and Khan. MacEwan collected the data, and data interpretation was performed primarily by MacEwan and Yin, along with Kaura and Khan. The manuscript was written and revised by MacEwan, Yin, Kaura, and Khan.

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