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# Economic evaluation for the US of nab-paclitaxel plus gemcitabine versus FOLFIRINOX versus gemcitabine in the treatment of metastatic pancreas cancer

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## Abstract

Background: Nab-paclitaxel plus gemcitabine (NAB-P + GEM) and FOLFIRINOX have shown superior efficacy over gemcitabine (GEM) in the treatment of metastatic pancreatic ductal adenocarcinoma (mPDA). Although the incremental clinical benefits are modest, both treatments represent significant advances in the treatment of a high-mortality cancer. In this independent economic evaluation for the US, the aim was to

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estimate the comparative cost-utility and cost-effectiveness of these three regimens from the payer perspective.

Methods: In the absence of a direct treatment comparison in a single clinical trial, the Bucher indirect comparison method was used to estimate the comparative efficacy of each regimen. A Markov model evaluated life years (LY) and quality-adjusted life years (QALY) gained with NAB-P + GEM and FOLFIRINOX over GEM, expressed as incremental cost-effectiveness (ICER) and cost-utility ratios (ICUR). All costs and outcomes were discounted at 3%/year. The impact of parameter uncertainty on the model was assessed by probabilistic sensitivity analyses.

Results: NAB-P + GEM was associated with differentials of +0.180 LY and +0.127 QALY gained over GEM at an incremental total cost of $25,965; yielding an ICER of $144,096/LY and ICUR of $204,369/QALY gained. FOLFIRINOX was associated with differentials of +0.368 LY and +0.249 QALY gained over GEM at an incremental total cost of $93,045; yielding an ICER of $253,162/LY and ICUR of $372,813/QALY gained. In indirect comparison, the overall survival hazard ratio (OS HR) for NAB-P + GEM vs FOLFIRINOX was 0.79 (95%CI = 0.59–1.05), indicating no superiority in OS of either regimen. FOLFIRINOX had an ICER of $358,067/LY and an ICUR of $547,480/QALY gained over NAB-P + GEM. Tornado diagrams identified variation in the OS HR, but no other parameters, to impact the NAB-P + GEM and FOLFIRINOX ICURs.

Conclusions: In the absence of a statistically significant difference in OS between NAB-P + GEM and FOLFIRINOX, this US analysis indicates that the greater economic benefit in terms of cost-savings and incremental cost-effectiveness and cost-utility ratios favors NAB-P + GEM over FOLFIRINOX.

# Introduction

Pancreatic cancer is the fourth cause of cancer death in the US, and expected to become the second by 2020. More than half of the cases are diagnosed in the advanced/metastatic stage, and 1-year and 5-year survival rates are 15% and 2%, respectively[1]. The standard of care has long been chemotherapy with gemcitabine (GEM), which showed an improvement in overall survival (OS) compared to fluorouracil (5.6 vs 4.4 months, p = .002)[2,3]. Recent evidence indicates that FOLFIRINOX and GEM in combination with nab-paclitaxel (NAB-P + GEM) may have greater efficacy than GEM alone[3,4]. The PRODIGE4/ACCORD11 phase III trial of 342 treatment-naïve metastatic pancreatic ductal adenocarcinoma (mPDA) patients with ECOG score of 0/1 compared FOLFIRINOX (leucovorin 400 mg/m$^2$, 5-fluorouracil 400 mg/m$^2$, irinotecan 180 mg/m$^2$, and oxaliplatin 85 mg/m$^2$ in bolus followed by 2400 mg/m$^2$ as 46-hour continuous infusion Q2W) to GEM. Significant improvements in median OS (11.1 vs 6.8 months, p < .001) and progression-free survival (PFS) (6.4 vs 3.3 months, p < .001) were noted for FOLFIRINOX over GEM[3]. The MPACT phase III trial randomized 861 treatment-naïve mPDA patients with Karnofsky score ≥70 (i.e. ECOG 0-2) to receive either 125 mg/m$^2$ of NAB-P plus 1,000 mg/m$^2$ of GEM Q4W or 1,000 mg/m$^2$ of GEM Q1W for 7 weeks and then Q4W. Significant improvements in median OS (8.5 vs 6.7 months, p < .001) and PFS (5.5 vs 3.7 months, p < .001) were observed for NAB-P + GEM over GEM alone[4]. Pooled grade 3/4 adverse events (AE) for NAB-P + GEM, FOLFIRINOX, and GEM from both studies indicate lower AE rates for GEM and AE rates for NAB-P + GEM and FOLFIRINOX varying by AE type (Table 1)[3,4]. No randomized trials have evaluated these three regimens directly.

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Table 1. Aggregated/pooled grade 3 and 4 adverse event rates reported by Conroy et al. [3] and Von Hoff et al. [4].

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While the incremental survival benefit of these two treatments remains modest, both represent significant advances in treating mPDA[5]. In this independent economic analysis, we estimated the cost-effectiveness and cost-utility of NAB-P + GEM vs FOLFIRINOX vs GEM in the treatment of mPDA from the US payer perspective.

# Model

The model utilized a cohort of patients characterized from the phase III clinical trials[3,4]. In the absence of a single randomized trial directly comparing GEM vs NAB-P + GEM vs FOLFIRINOX, comparative efficacy and safety were estimated using the Bucher et al.[6] method of indirect comparison, a recognized pharmacoeconomic methodology[7] that assumes a valid proportional hazard assumption between treatments. "Pairs" of trials (NAB-P + GEM vs GEM and FOLFIRINOX vs GEM) were compared indirectly by meta-regression using GEM as a common comparator to derive an indirect comparison estimate of NAB-P + GEM vs FOLFIRINOX[8]. AE probabilities were calculated using odds ratios against NAB-P + GEM.

We developed a state-transition model with three disease states reflecting treatment pathway and survival (Figure 1): PFS, survival with disease progression, and death. Patients start at the PFS state with three probabilities: staying in the same health state until the next cycle, progressing to the next disease stage, or death. Patients with disease progression have two probabilities: staying in the disease progression state or death. A full life-time horizon was implemented until 99% of the enrolled patients died. The model did not impose any age ceiling. The primary sources of evidence dictating transitions were the PRODIGE4/ACCORD11[3] and MPACT[4] trials; parametric modeling of survival analysis data; and the indirect comparison of NAB-P + GEM vs FOLFIRINOX. Health outcomes were expressed as life years (LY) and quality-adjusted life years (QALY) gained. The incremental cost-effectiveness (ICER) and cost-utility (ICUR) ratios quantified, respectively, the incremental cost of achieving one extra LY and one extra QALY with a given treatment over another treatment. Consistent with recent economic evaluations in the oncology setting, our approach and assumptions allowed us to model PFS and OS in a manner that reflects the clinical trial data[9,10].



Figure 1. State-transition model.
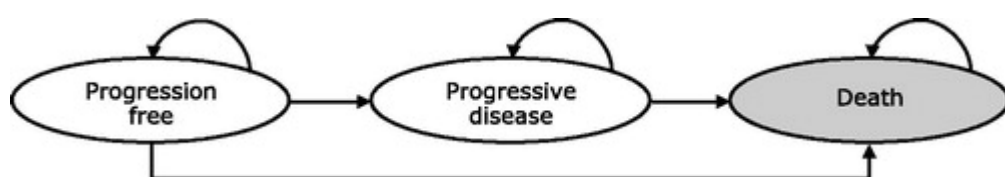
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Analyses were specifically for the US and from the payer's perspective. A bespoke state-transition model was developed in MS Office Excel (Microsoft, Redmond, WA) with proprietary Visual Basic scripts[11]. As survival data for responders and non-responders were not available, we amended utility weights for PFS to reflect the distribution of both groups within this state. The impact of AEs was included within these states and not modeled separately. Limited follow-up and censoring was addressed through parametric Weibull modeling of PFS and OS[12]. The model cycle duration was set to 7 days. We assumed that all drug would be used without wastage, as all regimens are admixtured. Costs and outcomes were discounted at the standard 3%/annum used in US pharmaco-economic evaluations.

## Efficacy

OS and PFS transition probabilities for NAB-P + GEM were calculated from the Kaplan-Meier estimates of the phase III trials[3,4] using a digitizing program (TechDigs 2.2 IUCr, Chester, UK). To generalize the findings from the trials and extrapolate survival beyond the data horizon, Weibull parametric modeling techniques were applied to approximate PFS and OS for NAB-P + GEM for each cycle included within the model's time horizon. The Weibull distribution was chosen over exponential distribution based on a previous publication because of the associated values of the $R^2$ (0.9870 for OS and 0.9858 for PFS) and residual sum of squares statistics (0.312 for OS and 0.218 for PFS)[13] and validation by a clinical expert. The Weibull equation for estimating survival is

where S(t) is the estimate of the survivor function at time t, λ the scale parameter, and γ the shape parameter[12]. λ equalled 0.600 and 0.009 and γ equalled 1.323 and 1.371 for the OS and PFS curves, respectively. OS and PFS for GEM and FOLFIRINOX were estimated by applying the relevant hazard ratio (HR) on the NAB-P + GEM Weibull function for OS and PFS.

## Cost inputs

Costs were expressed in 2015 US dollars (USD; $) (Table 2). Costs not in 2015 USD were inflated using the consumer price index[14]. In the progression-free state, where patients received study or comparator drugs, costs for the following were included: pre-medication, chemotherapy, administration of pre-medication and chemotherapy, disease monitoring and AEs. Upon progression, the model assumed that the study

drugs were no longer provided, and costs included were those for basic supportive care (BSC).

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**Table 2.** Costs and utility input estimates.

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Drug costs were obtained from Red Book 2015[15]. The cost of pre-medications was calculated according to the University of Arizona Cancer Center protocol. The cost of chemotherapy was determined assuming a mean body surface area (BSA) of 1.83 m$^2$ and included dose adjustments that occurred during the reference studies using the relative dose intensity reported (85% for GEM, 81% for NAB-P, 75% for GEM in the NAB-P + GEM arm, 82% for fluorouracil, 81% for irinotecan, and 78% for oxaliplatin). In the base-case analysis, chemotherapy cost was calculated per milligram of chemotherapy. The median numbers of chemotherapy cycles for NAB-P + GEM and FOLFIRINOX were assumed to be four and 10, respectively, as reported in the clinical trials. The cost of drug administration and outpatient physician visit fees were per the 2015 Medicare Physician Fee Schedule using Current Procedural Terminology codes[16]. As the protocols of the phase III clinical trials were unlikely to reflect current clinical practice, resource estimates for disease monitoring were adapted per expert opinion. We included only the cost of managing grade 3/4 AEs; grade 1/2 events were considered manageable within standard patient monitoring. AE costs were obtained from retrospective claims and published literature, including systematic reviews (Table 2)[17–21]. Sensory neuropathy and fatigue were assumed to be managed by dose reduction only. Granulocyte colony-stimulating factor cost was assumed to be included in the cost of neutropenia and febrile neutropenia management reported in the published trials.

## Health-related quality-of-life (HRQoL) utilities

HRQoL estimates based on the EuroQol (EQ-5D) and utility decrements due to adverse events were obtained from published literature[22] (Table 2). The impact utility was assumed to last for 4 days. We chose the EQ-5D because of the availability of validated utilities for the US.

## Sensitivity analyses

Probabilistic (PSA) and one-way sensitivity analyses (OWSA) were conducted to assess the robustness of the deterministic base-case analysis results. PSA was used to evaluate the simultaneous effect of uncertainty relating to all model parameter values and to create the cost-effectiveness acceptability curve (CEAC). This was achieved through repeated sampling of mean parameter values from a series of assigned distribution types, based on the point estimates and the standard error statistics for each average parameter value. Each set of samples from all the parameters generated a single estimate of expected costs, effects and net benefits generated by the model. The analyses were run over 2000 iterations, at which point we evaluated the impact of further simulations on the mean PSA results. The results were used to create the cost-effectiveness acceptability curve (CEAC).

Gamma distributions are constrained on an interval from zero to positive infinity and, therefore, recommended to address uncertainty in costs[23]. Uncertainty in chemotherapy drug costs was addressed by taking into account the vial cost of all generic and branded drugs, applying a gamma distribution to the average cost per milligram, and multiplying these distributions by the BSA estimate. We also applied gamma distributions to the cost of IV administration of chemotherapy agents and to the majority of unit costs used in the estimation of the cost of managing AEs (where base-case was a non-zero cost), patient assessment and support, and BSC.

Beta distributions are indicated for presenting uncertainty in probability parameters constrained between 0–1. We applied beta distributions to the proportions of patients responding to treatment with NAB-P + GEM. Given that confidence limits for RR are calculated on a log scale, we applied log-normal distributions to the RRs of response. Beta distributions were also applied to manage uncertainty about the probability of AEs for those patients treated with NAB-P + GEM, and log-normal distributions to the ORs to derive the probability of AEs in patients treated with GEM and FOLFIRINOX.

In order to address the underlying uncertainty in the probability of a given AE, ORs were applied, where indicated, to the sampled AE relative to NAB-P + GEM. Beta distributions were applied to the HRQoL utility weights and to the disutilities for the toxicities that affect HRQoL.

Assuming that parameters are statistically independent, PSAs sample each parameter independently. However, distributions of PFS and OS times in treatments and

allowed joint distributions to be generated for PFS and OS and used these joint distributions for the coefficients in the parametric models describing OS and PFS.

For both PFS and OS we used Weibull 2-parameter distributions that fitted well to the Kaplan-Meier empirical curves. Data regarding uncertainty in the GEM and FOLFIRINOX HRs applied to the parametric survival models were taken from the trial reports and indirect comparisons, respectively.

OWSAs were conducted on the OS and PFS HRs, NAB-P vial cost, progression-free and progressive disease utility, adverse event management costs, and oxaliplatin vial cost using the upper and the lower 95% CI values. These parameters were chosen on the basis of clinical expert recommendations.

## Secondary analyses

Alternate utility values for each health state have been reported in the literature[24,25]. We performed secondary analyses using these utilities (Table 3).

**Table 3.** Utility estimates used in the secondary analysis

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## Results

Per trial evidence, FOLFIRINOX had superior OS (HR = 0.57, 95% CI = 0.45–0.73) and PFS (HR = 0.47, 95% CI = 0.37–0.59) efficacy over GEM[3]; and NAB-P-GEM had superior OS (HR = 0.72, 95% CI = 0.62–0.83) and PFS (HR = 0.69, 95% CI = 0.58–0.82) efficacy over GEM[4]. Per the indirect comparison calculations, NAB-P + GEM and FOLFIRINOX had similar OS efficacy (HR = 0.79, 95% CI = 0.59–1.05), but FOLFIRINOX had superior PFS efficacy (HR = 0.68, 95% CI = 0.51–0.91).

In the base-case analysis, total cost of treatment with NAB-P + GEM was $25,965 higher and with FOLFIRINOX was $93,045 higher compared to treatment with GEM (Table 4). NAB-P + GEM was associated with an additional 0.180 LYs and 0.127 QALYs gained, and

Compared to GEM, the ICER for NAB-P + GEM was $144,096, and the ICER for FOLFIRINOX was $253,162 per LY gained. The ICUR for NAB-P + GEM was $204,369 and the ICUR for FOLFIRINOX was $372,813 per QALY gained. Compared to NAB-P + GEM, FOLFIRINOX had an ICER of $358,067 per LY and an ICUR of $547,480 per QALY gained.

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Table 4. Base-case and probabilistic sensitivity analysis results.

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As summarized in Table 4, the PSA results confirmed base-case results. NAB-P + GEM and FOLFIRINOX were more expensive but also more effective compared to GEM alone. The ICER for NAB-P + GEM was $136,202 and the ICER for FOLFIRINOX was $252,474 per LY gained. The ICUR for NAB-P + GEM was $190,349, and the ICUR for FOLFIRINOX was $365,530 per QALY gained. Compared to NAB-P + GEM, FOLFIRINOX had an ICER of $363,470 per LY and an ICUR of $544,803 per QALY gained.

All 2000 simulation points for NAB-P + GEM vs GEM were in the upper right quadrant of the cost-effectiveness plane, but FOLFIRINOX had four points in the upper left quadrant (Figure 2). Per the CEAC (Figure 3), NAB-P + GEM has a probability of ~0.25 of being cost-effective at a threshold value of $100,000/QALY. FOLFIRINOX has zero such probability at any threshold value.

Figure 2. Scatter plot of the cost-effectiveness plane generated by the probabilistic sensitivity analyses for NAB-P + GEM and FOLFIRINOX relative to GEM, and NAB-P + GEM and FOLFIRINIX relative to each other.
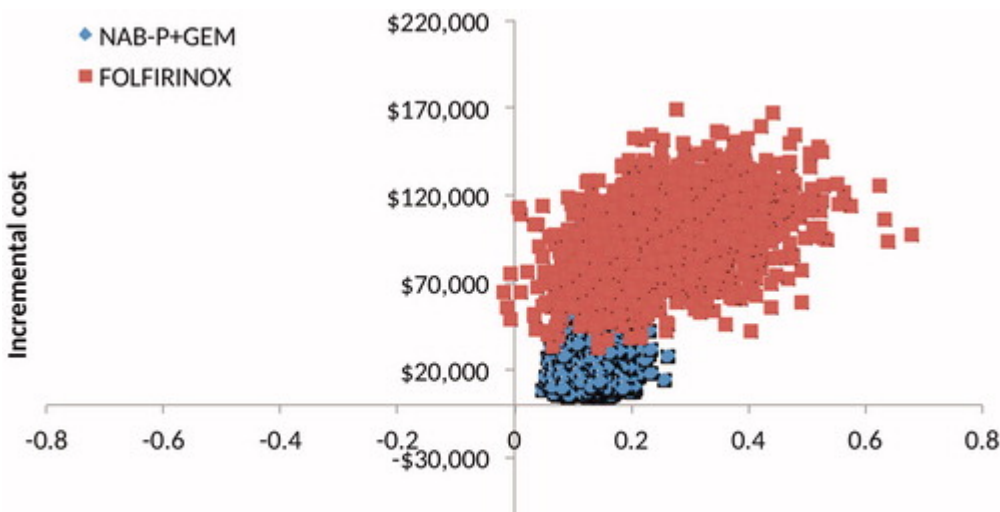
Figure 3. Cost-effectiveness acceptability curves for GEM, NAB-B + GEM and FOLFIRINOX.
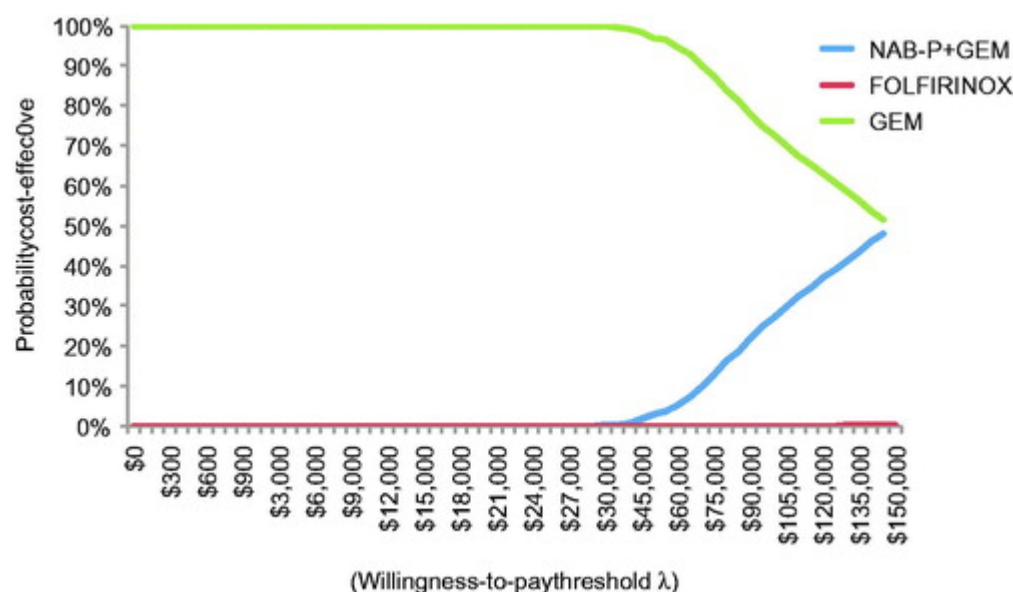
OWSA indicated that, relative to GEM and based on variation in the OS HR, the NAB-P + GEM ICUR varied between $158,812 and $307,552 (Figure 4(A)) and the FOLFIRINOX ICUR between $252,410 to $676,894 per QALY gained (Figure 4(B)). The remaining eight parameters had minimal impact.

Figure 4. Tornado diagrams for the one-way sensitivity analyses for NAB-P + GEM (A) and FOLFIRINOX (B).

(A) NAB-P+GEM vs GEM OWSA

(B) FOLFIRINOX vs GEM OWSA
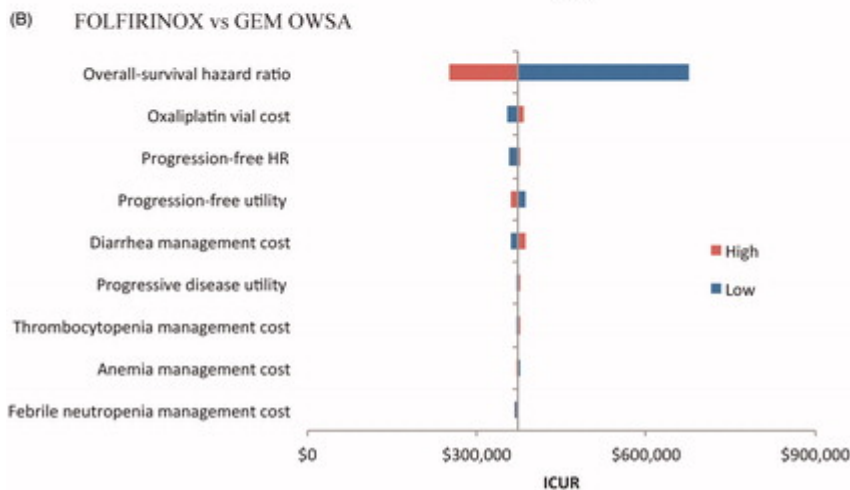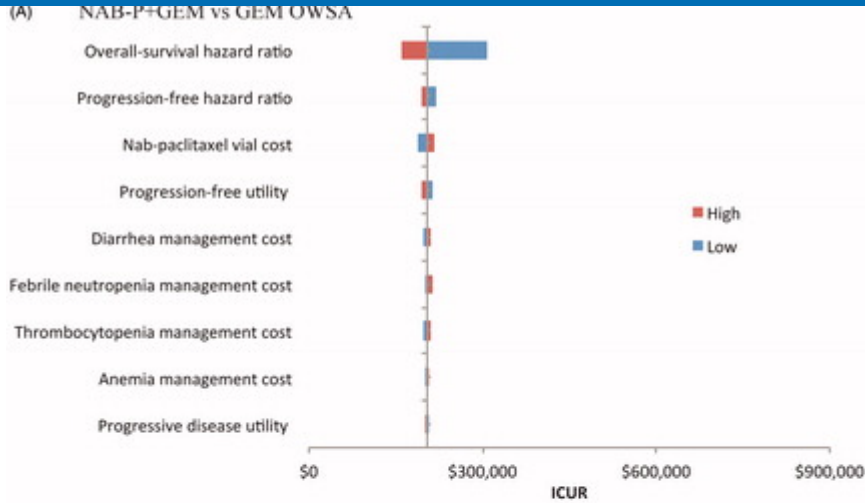
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## Secondary analyses

NAB-P + GEM and FOLFIRINOX were associated with an additional 0.15 and 0.27 QALYs gained, respectively, over GEM. The corresponding ICURs were $171,985 per QALY gained for NAB-P + GEM and $349,079 per QALY gained for FOLFIRINOX over GEM. Compared to NAB-P + GEM, treatment with FOLFIRINOX yielded an ICUR of $580,425 per QALY gained.

Probabilistic sensitivity analyses of these base-case secondary analysis results revealed that, relative to GEM therapy, NAB-P + GEM and FOLFIRINOX treatments were associated with an additional 0.15 and 0.28 additional QALYs, respectively. The corresponding ICURs were $167,112 for NAB-P + GEM and $338,476 for FOLFIRINOX per QALY gained.

## Discussion

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mPDA remains one of the major cancers with high cancer-related mortality rates. Even though their survival benefits remain modest, NAB-P + GEM and FOLFIRINOX represent significant advances in treatment[5]. Our independent economic evaluation used the method of indirect comparison to estimate treatment effects and evaluate the economic implications of GEM, FOLFIRINOX, and NAB-P + GEM. FOLFIRINOX and NAB-P + GEM were found to have a statistically similar OS benefit, with FOLFIRINOX showing a slightly better PFS benefit. Treatment with either regimen was more expensive than with GEM, yet the incremental cost of FOLFIRINOX was 3.6-times higher than that of NAB-P + GEM. With the OS benefit being statistically similar, savings of $67,080 could be achieved by treatment with NAB-P + GEM instead of FOLFIRINOX. These savings were validated by the difference in the ICERs and ICURs for FOLFIRINOX and NAB-P + GEM, which were $159,041 per LY and $188,169 per QALY gained, respectively, in favor of NAB-P + GEM. Even if FOLFIRINOX had a statistically significant better OS benefit over NAB-P + GEM, the ICER of $507,864/LY and the ICUR of $532,560/QALY gained make the incremental gains in survival unjustifiably expensive. Thus, the greater economic benefit in terms of cost-savings and incremental cost-effectiveness and cost-utility favor NAB-P + GEM therapy. Note that this analysis is for the US and should not generalized to other countries, other healthcare systems, or other healthcare financing systems[10].

Three dynamics account for the economic results reported here. First, the higher febrile neutropenia rates associated with FOLFIRINOX impacted this regimen's overall cost and the associated ICER. Likewise, the higher fatigue rates associated with FOLFIRINOX impacted utilities, therefore QALYs, and hence the observed ICURs. Second, the state-transition model underlying our economic analysis recognized the superior PFS efficacy of FOLFIRINOX over NAB-P + GEM. While, per our indirect comparison calculations, the progression-free state may have been maintained longer by FOLFIRINOX-treated than NAB-P + GEM-treated patients, this did not translate into a longer OS benefit and, thus, PFS did not materially impact the economic results. Third, the inclusion criteria for the FOLFIRINOX trial[3] specified an ECOG score of 0 or 1, whereas the NAB-P + GEM trial[4] included patients with a Karnofsky score ≥70. A Karnofsky score of 70 corresponds to an ECOG score of 2, hence there was an (albeit slight) imbalance in performance status between both studies that may have influenced efficacy and safety results.

In our recent economic evaluation for the UK of NAB-P + GEM over GEM[10], we did not apply thresholds to infer the economic benefit of treatments whether the historical

established or validated empirically[26]. Neither have they been adjusted for inflation since the initial valuation of a life year at $50,000 in 1972 as part of the Medicare end-stage-renal-disease legislation or the first use of this estimate in pharmacoeconomic evaluations ~20 years later[27,28]. In our view, pharmacoeconomic analysis intends to inform policy and clinical practice—not set policy or guide clinical practice.

We recognize the accelerating rise in the cost of cancer treatments[29,30]. Although the cost of cancer care is only ~5–6% of healthcare expenditures[31], it is increasing faster than any other field in medicine[32]. The ASCO Value in Cancer Care Task Force has proposed a framework to assess the value of new cancer drugs vs current standard of care treatments[33]. This framework integrates nominal and incremental clinical benefit with toxicity to determine the net health benefit, which then is juxtaposed against the cost of treatment. However, the framework emphasizes the evaluation of one novel treatment against the standard of care and will need to be adapted to accommodate situations, like the one in our analysis, where two alternate treatments have been proposed but not evaluated directly in a head-to-head trial.

The indirect comparative estimate of the survival benefits of NAB-P + GEM, FOLFIRINOX, and GEM is a secondary benefit of our study. Commenting on the Goldstein et al.[34] report on long-term survival in NAB-P + GEM-treated patients, Bekaii-Saab and Goldberg[35] suggested that "historical cross-comparisons seem to give FOLFIRINOX an edge". Our indirect OS estimates for NAB-P + GEM and FOLFIRINOX were not statistically different, indicating relative equivalence of both regimens. Adding the lower probability of AEs, and (febrile) neutropenia in particular, NAB-P + GEM therapy yields more favorable toxicity and economic profiles while assuring similar OS outcomes. We could not use the long-term survival benefits reported by Goldstein et al.[28] because no parallel data were available for FOLFIRINOX.

Our analysis has limitations. The NAB-P + GEM trial did not collect HRQoL data, whereas the FOLFIRINOX study did[3,36]. Although standard pharmacoeconomic practice, we had to impute external utilities and conduct secondary analyses using different published utility estimates to complement the base case analysis. Not uncommon to this method, the Bucher indirect comparison yielded rather wide Confidence intervals (CIs)[37].

## Conclusion

In this independent analysis for the US, the economic benefit in terms of cost-savings and incremental cost-effectiveness and cost-utility favor NAB-P + GEM over FOLFIRINOX therapy in mPDA.

## Transparency

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