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Cost Effectiveness and Resource Allocation

RESEARCH

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Economic evaluation of NALIRIFOX vs. nab-paclitaxel and gemcitabine regimens for first-line treatment of metastatic pancreatic ductal adenocarcinoma from U.S. perspective

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Abstract

Background The cost-effectiveness of NALIRIFOX as a potential new standard of care for patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) has yet to be established. Our objective was to evaluate the cost-effectiveness of NALIRIFOX vs. nab-paclitaxel and gemcitabine in this indication from the perspective of U.S. public payers.

Methods A partitioned survival model was constructed from the perspective of U.S. public payers, drawing on baseline patient characteristics and vital clinical data from the NAPOLI-3 trial. Costs and utilities were sourced from publicly accessible databases and literature. A lifetime horizon was applied, with an annual discount rate of 3%. We calculated and compared cumulative costs, life years, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICER). To evaluate the model's robustness, sensitivity analyses, scenario analyses, and subgroup analyses were carried out. Additionally, a price simulation for the costly liposomal irinotecan was conducted to inform the pricing strategy at the given willingness to pay (WTP) threshold.

Results In the base-case analysis, NALIRIFOX provided an additional 0.29 QALYs with an ICER of $206,340.69 / QALY compared to nab-paclitaxel and gemcitabine, indicating it is not cost-effective at a $150,000/QALY threshold. Sensitivity analysis showed the model was most sensitive to the costs of liposomal irinotecan, capecitabine, and post-progression care. Probabilistic sensitivity analysis indicated a 17.66% probability of NALIRIFOX being cost-effective at $150,000/QALY, rising to 47.48% at $200,000/QALY. Pricing simulations suggested NALIRIFOX could become cost-effective at $150,000/QALY if the price of irinotecan liposome drops to $53.24/mg (a 14.8% reduction).

Conclusions NALIRIFOX may not be cost-effective at its current price as a first-line treatment for patients with mPDAC in the long term. The cost of liposomal irinotecan has the greatest impact. It may become cost-effective only if its cost is reduced by 14.8%, with a WTP threshold of $150,000 /QALY.

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Keywords Metastatic pancreatic ductal adenocarcinoma, Cost-effectiveness analysis, NALIRIFOX, Nab-paclitaxel, Gemcitabine

Introduction

Metastatic pancreatic ductal adenocarcinoma (mPDAC) remains one of the most lethal forms of cancer, with a 5-year survival rate below 10% [1] It is the fourth leading cause of cancer-related mortality in the United States, with projections placing it as the second leading cause by 2030 [2, 3]. This alarming trend underscores the imperative need for novel and more efficacious treatment strategies. Despite significant advancements in the understanding of the pathophysiology of mPDAC over recent decades, breakthroughs in clinical treatment strategies are still lacking, with the therapeutic effects of existing regimens being relatively limited. Currently, two combination chemotherapy regimens are the standard first-line treatments for mPDAC: the FOLFIRINOX, which is a combination of fluorouracil, leucovorin, irinotecan, and oxaliplatin, and the doublet regimen of nab-paclitaxel with gemcitabine [4].

Liposomal irinotecan represents an innovative approach in cancer treatment, encapsulating the topoisomerase I inhibitor irinotecan within a lipid bilayer vesicle to prolong its circulation time before it is converted to its active metabolite [5]. A phase 1/2 trial (NCT02551991, which was initially registered on ClinicalTrials.gov on September 16, 2015) that explored the combination of liposomal irinotecan with fluorouracil, leucovorin, and oxaliplatin, known as NALIRIFOX, demonstrated promising antitumor activity in treatment-naive patients with mPDAC [6]. The subsequent international randomized phase III trial, NAPOLI-3 [7], assessed the efficacy and safety of NALIRIFOX in comparison to the standard doublet regimen of nab-paclitaxel and gemcitabine for patients who had not previously received treatment for metastatic PDAC. The survival analysis revealed a median overall survival of 11.1 months with NALIRIFOX, which was significantly longer than the 9.2 months recorded for the doublet chemotherapy group. The risk of death was reduced by 17% for patients receiving NALIRIFOX, with progression-free survival times of 7.4 months compared to 5.6 months for the doublet regimen. Building upon the observed superior efficacy, the NALIRIFOX regimen was formally incorporated into the first-line treatment recommendations for pancreatic cancer in the 2023 V2 edition of the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines [8]. In February 2024, the U.S. Food and Drug Administration (FDA) approved NALIRIFOX regimen as a potential first-line treatment for mPDAC [9].

Despite these promising clinical outcomes, the cost of liposomal irinotecan, at $62.485 for 1 mg, is substantially higher than that of regular irinotecan, which is $2.064 for 20 mg, raising concerns about its cost-effectiveness [10, 11]. To date, there has been an absence of pharmacoeconomic evaluations concerning this issue. Therefore, our study aimed to compare the cost-effectiveness of NALIRIFOX versus the combination of nab-paclitaxel and gemcitabine as first-line therapy for previously untreated mPDAC patients, from the perspective of U.S. public insurance payers.

Methods

Study design

This study adhered to the Consolidated Health Economic Evaluation Reporting Standards reporting guideline (Supplement 1) [12]. The target population comprised adult patients in the United States with pancreatic ductal adenocarcinoma who were previously untreated in the metastatic setting. It was assumed that these patients shared similar baseline characteristics with those enrolled in the NAPOLI-3 trial (baseline information is detailed in Supplement 2 Table S1). Additionally, our model presumed a body surface area of 1.79m^2 for the hypothetical patient cohort [13].

Patients were allocated to either the NALIRIFOX regimen or the standard chemotherapy regimen. The NALIRIFOX arm consisted of liposomal irinotecan at a dose of 50mg/m^2, oxaliplatin at 60mg/m^2, leucovorin at 400mg/m^2, and fluorouracil at 2400mg/m^2, administered sequentially as a continuous intravenous infusion over 46 h on days 1 and 15 of a 28-day cycle. The comparator arm was treated with nab-paclitaxel at a dose of 125mg/m^2 and gemcitabine at 1000 mg/m^2. The proportions of the subsequent treatments as reported in the NAPOLI-3 trial, and the first-line progressive treatment protocol was reference to NCT00112658 [14]. It was assumed that patients in the NALIRIFOX arm, upon disease progression, would be treated with monotherapy gemcitabine at a dose of 1000 mg/m^2 administered via injection on days 1, 8, and 15 throughout four consecutive cycles. In contrast, patients in the nab-paclitaxel and gemcitabine arm, upon progression, would receive the FOLFIRINOX regimen, which includes oxaliplatin at 85 mg/m^2 administered intravenously over 2 hours, leucovorin at 400 mg/m^2 also administered intravenously over 2 hours, irinotecan at 180 mg/m^2, followed by a 400 mg/m^2 bolus of fluorouracil.

Model structure

We developed a partitioned survival model to compare the cost and effectiveness of the NALIRIFOX regimen

versus the Nab-paclitaxel and Gemcitabine regimens as first-line treatments for mPDAC. The model delineated three mutually exclusive health states: progression-free survival (PFS), progressed disease (PD), and death (Fig. 1). The time horizon of the model was established from a lifetime perspective, meaning that 99% of the patients would have transitioned to the death state. The cycle length was defined as one treatment cycle, which was 28 days. This analysis was conducted from the perspective of U.S. public payers (Medicare).

The primary outcomes of the model were costs, life years (LYs), equal value of life years gained (evLYG), quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICER). Both costs and utilities were discounted at an annual rate of 3%. The willingness-to-pay (WTP) threshold considered the common U.S. benchmark of $150,000 /QALY gained, as well as a higher threshold of $200,000 /QALY for metastatic cancer [15]. The modeling and analysis were carried out using R version 4.3.0, available at R Project for Statistical Computing, and Microsoft Excel. Within the R environment, we used the"flexsurv" and "survHE" packages to reconstruct individual patient data (IPD) and extrapolate survival outcomes.

Effectiveness

Probabilities of PFS and OS were extracted from Kaplan-Meier curves from NAPOLI-3 through Engauge Digitizer (version 4.1) by Guyot's method to reconstruct estimates of IPD [16]. Reconstructed IPD comprised event and censor times and were almost equal in number to the initial number at risk, which closely reproduced the digitized Kaplan-Meier curves. The reconstructed IPD was then used to fit the following survival functions: exponential, Weibull, Gompertz, gamma, log-logistic, log-normal, generalized gamma, fractional polynomial, restricted cubic spline models, and Royston-Parmar spline models. The goodness of fit was evaluated through the Akaike information criterion (AIC) and visual inspection. Lower AIC value combined with practical visual effect indicated a better fit of the selected model. Further information on the methodology of the goodness of fit and external validation can be found in Supplement 2 Table S2 and Figure S1.

Cost and utility

The economic model considered direct medical costs such as the cost of acquiring drugs, cost of follow-up, cost of treatment of adverse events (AEs), best supportive care, and end-of-life care. The drug costs were based on prices from Medicare Part B [17]. Given the potential overlap in the statistical categorization of AEs at different levels, to avoid double, and the model specifically considered AEs (Grade 3 or higher) with incidence rates exceeding 2%. The associated costs and durations of these AEs were extracted from data reported in published literature. To ensure the cost estimations were current and reflective of the study's time frame, all prices were adjusted for inflation to October 2023 values using the Consumer Price Index Inflation Calculator [17, 18].

The utility values for PFS and PD were obtained from a U.S. economic evaluation of systemic chemotherapy as a first-line treatment for metastatic pancreatic cancer [15]. The disutilities due to AEs considered in this analysis were extracted from other studies. All AEs were assumed to be incurred during the first cycle; the

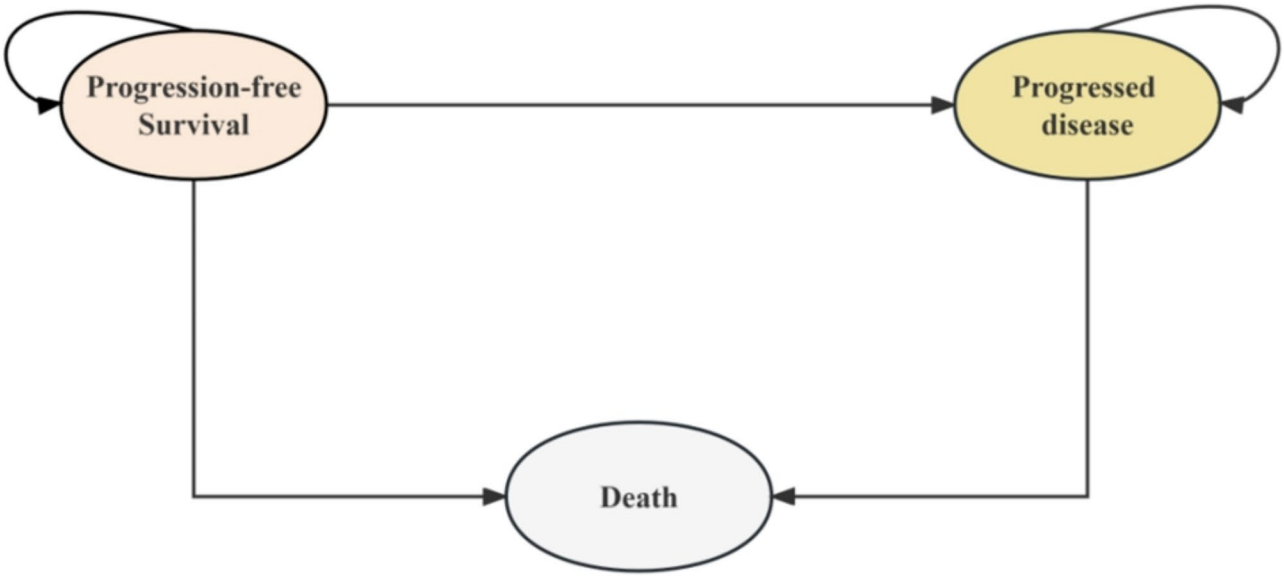

Fig. 1 Partitioned survival model structure

duration-adjusted disutilities were subtracted from the baseline values. The parameters of model input are shown in Table 1.

Sensitivity analysis

To evaluate the stability of the outcomes from the base-case analysis, sensitivity analyses were executed. The deterministic sensitivity analysis (DSA) involved modulating all parameters within their 95% confidence intervals or by ranging plausible variations (±20%) from the base-case estimates. For the cost parameters, a gamma distribution was chosen, while a beta distribution was applied to the probability, proportion, and utility estimates. The probabilistic sensitivity analysis (PSA) was then carried out for the stipulated price point by undertaking 10,000 Monte Carlo simulation iterations. The cost-effectiveness acceptability curve (CEAC) was utilized to determine the cost-effectiveness of each treatment regimen across a range of WTP thresholds.

Scenario analysis

Due to the significant cost variability and associated uncertainty that subsequent treatment may influence the outcomes, we conducted a scenario analysis for second-line therapy approaches. We incorporated second-line treatment regimens for pancreatic cancer as recommended by the NCCN and European Society for Medical Oncology guidelines [19], as well as those reported in NAPOLI-3 (Supplement 2 Table S3). To account for different patient scenarios in subsequent lines of therapy and to minimize the uncertainty of the results, we selected the highest and lowest cycle cost scenarios from the second-line treatment options for the NALIRIFOX group and the Nab-paclitaxel and gemcitabine group. This approach allowed us to construct an analysis consisting of four distinct scenarios. The scenarios are as follows, Scenario 1: NALIRIFOX followed by gemcitabine with nab-paclitaxel and gemcitabine followed by FOLFIRINOX. Scenario 2: NALIRIFOX followed by gemcitabine with nab-paclitaxel and gemcitabine followed by 5-FU, leucovorin, and liposomal irinotecan. Scenario 3: NALIRIFOX followed by mFOLFOX with nab-paclitaxel and gemcitabine followed by FOLFIRINOX. Scenario 4: NALIRIFOX followed by mFOLFOX with nab-paclitaxel and gemcitabine followed by 5-FU, leucovorin, and liposomal irinotecan.

Subgroup analysis

In the subgroup analysis, the ICER was calculated using the subgroup-specific HRs for PFS and OS obtained from NAPOLI-3. Subgroup analyses were conducted under WTP thresholds of $200,000 and $150,000 for the US scenarios. We considered the subgroups of patients of different age (<65 or ≥65), sex (male or female), Eastern Cooperative Oncology Group performance status score (0 or 1), white race, region (North America or rest of the world), number of metastatic sites (1, 2 or ≥3), presence of liver metastases at baseline (yes or no), main pancreatic tumor location (head or other), and baseline CA 19−9 (<37 U/ml or ≥37 U/ml).

Price simulation

Considering the high cost of liposomal irinotecan, we conducted a price simulation by varying the price of irinotecan liposome (1 mg) between $10 and $63 to analyze the possibility of cost-effectiveness of the NALIRIFOX regimen at U.S. willingness-to-pay thresholds of $150,000/QALY and $200,000/QALY.

Results

Base case analysis

The base-case analysis results, presented in Table 2, revealed that the lifetime treatment cost for NALIRIFOX is $216,397.03, which was substantially higher than the lifetime costs for the regimen of nab-paclitaxel and Gemcitabine, calculated at $156,558.23. The NALIRIFOX regimen resulted in an increase of 0.44 evLYG and 0.29 QALYs compared to the nab-paclitaxel and Gemcitabine regimen. However, the ICER for NALIRIFOX in comparison to nab-paclitaxel and Gemcitabine was determined to be $206,340.69 /QALY, which was higher than the chosen WTP threshold of $150,000 /QALY.

Sensitivity analysis

The results of the DSA are shown in Fig. 2. The primary factors influencing the ICER were determined to be the cost of liposomal irinotecan, the cost of capecitabine, and the follow-up cost post-progression per cycle. This is attributed to the fact that liposomal irinotecan is a key component of the NALIRIFOX regimen and carries a relatively high baseline price. Consequently, fluctuations in the price of liposomal irinotecan have the most significant impact on the ICER results. In addition to the cost of liposomal irinotecan, the cost of capecitabine and the follow-up costs after progression emerged as critical determinants of the ICER. These factors are significant components of the second-line treatment and have a substantial impact on the overall cost of the treatment regimen. Given that capecitabine and carboplatin are significant components of the primary treatment options for patients after first-line therapy progression, variations in their costs also had a considerable effect on the ICER. Overall, after accounting for parameter variations within their specified ranges, it was concluded that NALIRIFOX was rarely cost-effective at the WTP threshold of $200,000 /QALY or $150,000 /QALY.

The cost-effectiveness density scatter plot is shown in Fig. 3A. The PSA results indicated that the average

Table 1 Model input parameters

Name	Baseline value	Low	Upper	Distribution	Source
Cost ($)					
Leucovorin calcium injection (50 mg)	4.46	3.57	5.35	gamma	[17]
Fluorouracil injection (500 mg)	2.84	2.27	3.41	gamma	[17]
Oxaliplatin (0.5 mg)	0.07	0.06	0.08	gamma	[17]
Inj irinotecan liposome (1 mg)	62.49	49.99	74.98	gamma	[17]
Paclitaxel protein bound (1 mg)	14.79	11.83	17.74	gamma	[17]
In gemcitabine hcl nos (200 mg)	3.93	3.15	4.72	gamma	[17]
Capecitabine oral (500 mg)	1.17	0.94	1.40	gamma	[17]
Carboplatin injection (50 mg)	2.76	2.21	3.31	gamma	[17]
Irinotecan injection (20 mg)	2.06	1.65	2.48	gamma	[17]
Magnetic Resonance Imaging	308.35	95.47	539.54	gamma	[17]
Chemo iv infusion for 1 h	134.90	113.09	181.29	gamma	[17]
Sequential infusion each additional hour	28.25	25.43	31.08	gamma	[17]
Premedication cost for nab-paclitaxel and gemcitabine	152.92	122.34	183.50	gamma	[15]
Premedication cost for NALIRIFOX	1236.13	988.90	1483.36	gamma	[15]
follow up cost before progression	519.04	415.23	622.85	gamma	[15]
follow up cost after progression	1064.65	851.72	1277.58	gamma	[15]
Best supportive care/cycle	2137.11	1709.69	2564.53	gamma	[23]
End-of-life/patient	21747.14	17397.71	26096.57	gamma	[24]
Clinical input					
Weibull model for NALIRIFOX PFS (shape)	1.22	1.10	1.34	gamma	Model fitting results
Weibull model for NALIRIFOX PFS (scale)	10.47	9.45	11.61	gamma	Model fitting results
Utility					
PFS	0.74	0.73	0.76	beta	[13]
PD	0.67	0.65	0.69	beta	[5]
Disutility of adverse events					
Diarrhoea	0.21	0.17	0.25	beta	[15]
Nausea	0.05	0.04	0.06	beta	[25]
Vomiting	0.05	0.04	0.06	beta	[5]
Decreased appetite	0.0020	0.0018	0.0024	beta	[26]
Fatigue	0.2040	0.1836	0.2244	beta	[27]
Asthenia	0.2040	0.1836	0.2244	beta	[13]
Neutropenia	0.0900	0.0620	0.1220	beta	[25]
Anaemia	0.2040	0.1836	0.2244	beta	[13]
Peripheral neuropathy	0.2260	0.2034	0.2486	beta	[28]
Abdominal pain	0.0510	0.0200	0.1000	beta	[29]
Mucosal inflammation	0.2690	0.2421	0.2959	beta	[30]
Constipation	0.1700	0.1530	0.1870	beta	[31]
Ascites	0.1700	0.1530	0.1870	beta	[31]
Increased γ-glutamyltransferase	0.1700	0.1530	0.1870	beta	[31]
Time duration of adverse events (days)					
Diarrhoea	5.57	5.013	6.127	normal	[5]
Nausea	11.18	10.0611	12.2969	normal	
Vomiting	5.85	5.2668	6.4372	normal	
Decreased appetite	22.04	19.8378	24.2462	normal	
Fatigue	19.89	17.8965	21.8735	normal	
Asthenia	17.63	15.8661	19.3919	normal	
Neutropenia	9.547	8.5923	10.5017	normal	
Anaemia	12.40	11.16	13.64	normal	
Peripheral neuropathy	26.917	24.2253	29.6087	normal	
Abdominal pain	10.452	9.4068	11.4972	normal	
Cost for adverse events treatment per cycle					
Diarrhea	7332.19	5865.75	8798.63	gamma	[15]

Table 1 (continued)

Name	Baseline value	Low	Upper	Distribution	Source
Nausea	7660.29	6128.23	9192.35	gamma	[32]
Vomiting	830.60	664.48	996.72	gamma	[32]
Neutropenia	13656.00	10924.80	16387.20	gamma	[33]
Anemia	7941.00	6352.80	9529.20	gamma	[33]
Asthenia	8099.62	6479.70	9719.54	gamma	[34]
Peripheral Neuropathy	30734.00	24587.20	36880.80	gamma	[35]
Decreased appetite	160.00	128.00	192.00	gamma	[36]
Increased γ-glutamyltransferase	5584.70	4467.76	6701.64	gamma	[31]
Abdominal pain	6538.09	5230.47	7845.71	gamma	[30]
Ascites	10191.85	8153.48	12230.22	gamma	[31]
Constipation	6749.29	5399.43	8099.15	gamma	[31]
Mucosal inflammation	10797.87	8638.30	12957.44	gamma	[30]
Fatigue	2668.76	2135.01	3202.51	gamma	[31]
Risk of adverse events in NALIRIFOX					
Diarrhoea	0.20	0.18	0.22	beta	[7]
Nausea	0.12	0.108	0.132	beta	
Vomiting	0.07	0.063	0.077	beta	
Decreasaed appetite	0.09	0.081	0.099	beta	
Fatigue	0.06	0.054	0.066	beta	
Asthenia	0.09	0.081	0.099	beta	
Neutropenia	0.14	0.126	0.154	beta	
Anaemia	0.11	0.099	0.121	beta	
Abdominal pain	0.04	0.036	0.044	beta	
Peripheral neuropathy	0.03	0.027	0.033	beta	
Ascites	0.03	0.027	0.033	beta	
Constipation	0.02	0.018	0.022	beta	
Mucosal inflammation	0.02	0.018	0.022	beta	
Increased γ-glutamyltransferase	0.06	0.054	0.066	beta	
Risk of adverse events in nab-paclitaxel and gemcitabine					
Diarrhoea	0.05	0.045	0.055	beta	[7]
Nausea	0.03	0.027	0.033	beta	
Vomiting	0.02	0.018	0.022	beta	
Decreasaed appetite	0.03	0.027	0.033	beta	
Fatigue	0.05	0.045	0.055	beta	
Asthenia	0.05	0.045	0.055	beta	
Neutropenia	0.25	0.225	0.275	beta	
Anaemia	0.17	0.153	0.187	beta	
Peripheral neuropathy	0.06	0.054	0.066	beta	
Increased γ-glutamyltransferase	0.06	0.054	0.066	beta	
Other					
Body Surface Area (m^2)	1.79	1.78	1.80	normal	[13]
discount	0.03	0	0.08	beta	
Proportions of subsequent treatment					
NALIRIFOX	0.505	-	-	-	[7]
nab-paclitaxel and gemcitabine	0.544	-	-	-	

cost for NALIRIFOX was $211,568, while that for nab-paclitaxel and gemcitabine was $153,426. The average health outcomes were quantified as 0.94 and 0.65 QALYs for these respective treatments. At a WTP threshold of $150,000 /QALY, the probability of NALIRIFOX being cost-effective was 17.66%. When the threshold increased to $200,000 /QALY, this probability rose to 47.48% (Fig. 3B).

Scenario analysis

The scenario analysis compared the ICER of NALIRIFOX and nab-paclitaxel and gemcitabine under different combinations of subsequent treatment regimens (Supplement

Table 2 Results of base-case analysis

Treatment	Cumulative cost ($)	Cumulative life years (Years)	Cumulative effectiveness (QALY)	Incremental cost ($)	Incremental effectiveness (QALY)	ICER ($/QALY)
NALIRIFOX	216,397.03	1.51	0.94	59,838.80	0.29	206,340.69
Nab-paclitaxel and Gemcitabine	156,558.23	1.07	0.65			

Abbreviation: ICER incremental cost-effectiveness ratio, QALY quality-adjusted life year

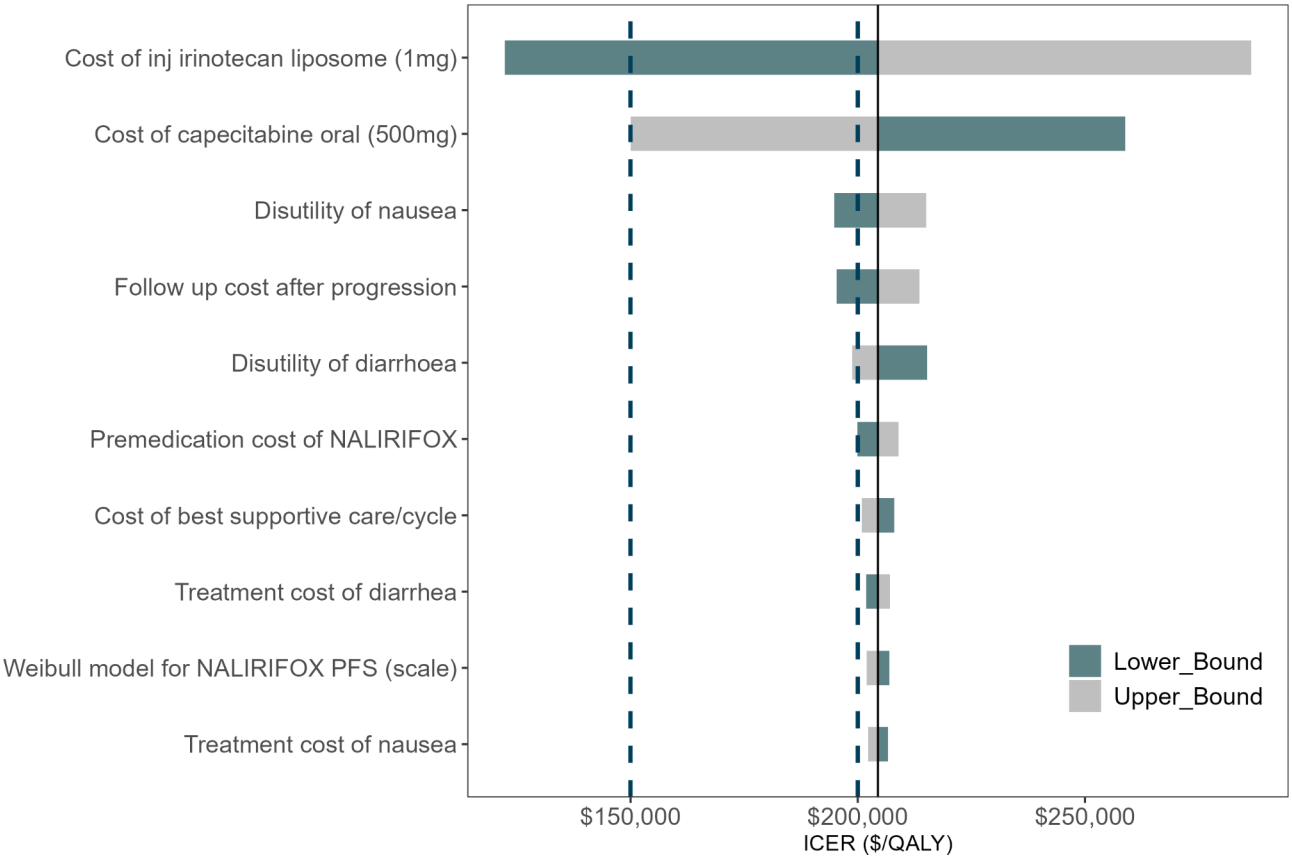

Fig. 2 Tornado diagram shows the association of variables with the ICER of NALIRIFOX vs. nab-paclitaxel and gemcitabine. Abbreviation: ICER incremental cost-effectiveness ratio, QALY quality-adjusted life year

2 Table S4). The scenario analysis showed that scenario 1 and scenario 3 resulted in an ICER of $206,340 /QALY and $248,519 /QALY, respectively. This means that even the higher WTP threshold of $200,000 /QALY would not be cost-effective. This outcome may be because the most expensive subsequent treatment regimen was chosen for use after the NALIRIFOX protocol, while the least expensive subsequent treatment regimen was utilized following the nab-paclitaxel and gemcitabine protocol, resulting in the lack of cost-effectiveness for NALIRIFOX. In the other scenarios, NALIRIFOX was found to be cost-effective. Therefore, the choice of subsequent treatment regimens had a significant impact on the cost-effectiveness of the frontline treatment strategies.

Subgroup analysis

Summary results of the subgroup analysis are presented in Supplement 2 Table S5. At a WTP threshold of $150,000 /QALY, the subgroup with the highest probability of being cost-effective was the North America subgroup (17.4%), followed by the subgroup with a baseline ECOG performance status of 1 (17.0%). A similar trend was observed at a WTP threshold of $200,000 /QALY.

Price simulation

The results of the price simulation are presented in Supplement 2 Figure S2. As the price of irinotecan liposome (1 mg) fluctuated between $10 and $63, the ICER increased in tandem with the rising cost of irinotecan liposome. NALIRIFOX becomes cost-effective at an irinotecan liposome price of $53.24/mg (a 14.8% reduction)

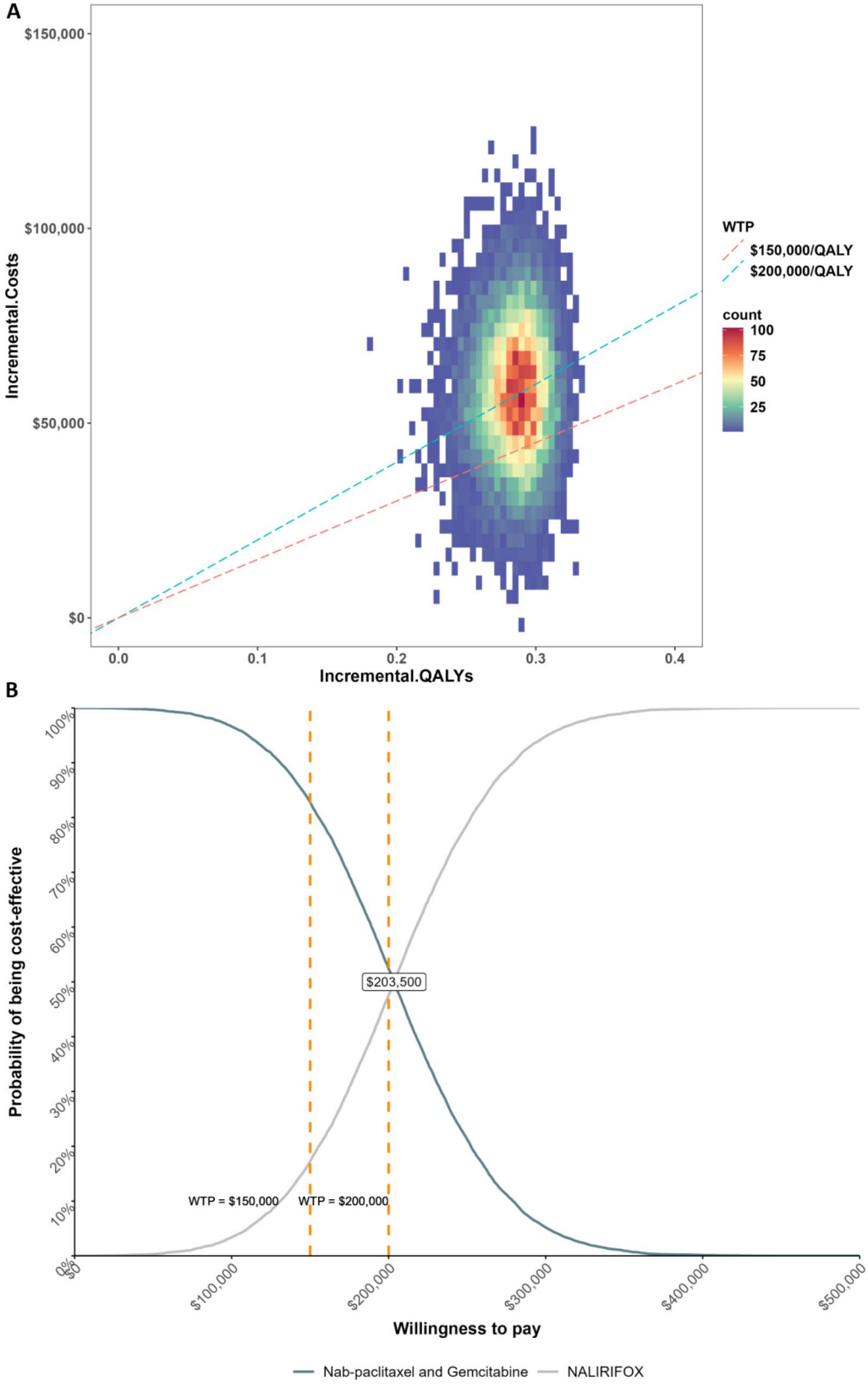

Fig. 3 Results of the probabilistic sensitivity analysis (**A**. Cost-effectiveness scatter plot; **B**. Cost-Effectiveness Acceptability Curve). Note: Different colors in the cost-effectiveness scatter plot represent point density in that area

when considering a WTP threshold of $150,000 /QALY. For a WTP threshold of $200,000 /QALY, the irinotecan liposome price of $60.83/mg (a 2.7% reduction) is required for cost-effectiveness.

Discussion

With the rising costs of healthcare, the emphasis on value in oncology care is becoming increasingly pertinent. The NAPOLI-3 trial's promising results suggest that NALIRIFOX may represent a significant advancement in the treatment of metastatic pancreatic ductal adenocarcinoma (mPDAC), offering potential therapeutic gains and an improved safety profile compared to the existing nab-paclitaxel and gemcitabine regimen. Recognizing its therapeutic promise, the FDA granted approval to NALIRIFOX in February 2024 as a primary treatment option for mPDAC. However, the lack of comprehensive pharmacoeconomic evaluations has left clinicians and patients uncertain about the cost-effectiveness of NALIRIFOX.

Previous research in the U.S. context has been limited. For instance, Bin Wu et al. [20] analyzed the cost-effectiveness of olaparib maintenance therapy for metastatic pancreatic cancer with BRCA mutations, using a partitioned survival model. The study concluded that olaparib was cost-effective at a $200,000 /QALY WTP threshold, based on PFS benefits alone, given no OS advantage over placebo. Similarly, Mahdi Gharaibeh's evaluation [15], using a Markov model, found that combination therapies for mPDAC, including oxaliplatin+gemcitabine, capecitabine+gemcitabine, FOLFIRINOX, and nab-paclitaxel+gemcitabine, surpassed gemcitabine monotherapy ineffectiveness at the same WTP threshold, with nab-paclitaxel+gemcitabine being the most cost-effective. However, there has been a lack of recent evidence on the cost-effectiveness of NALIRIFOX.

To the best of our knowledge, this is the inaugural evaluation of the cost-effectiveness of NALIRIFOX as a first-line therapy for mPDAC from the standpoint of U.S. public payer. The strength of this research lies in its comprehensive approach, which includes evaluating various second-line treatment scenarios and conducting extensive sensitivity analyses. Moreover, we performed pricing simulations for irinotecan liposome, furnishing policymakers with more comprehensive evidence. Finally, we included economic information from 18 subgroups according to the NAPOLI-3, offering insights into tailoring treatment choices in the era of precision medicine.

Despite these strengths, there are several limitations to our study. First, due to constraints in the original clinical trial, our analysis may be subject to inherent biases. For example, the proportions of subsequent treatments were only reported as single agents, which could introduce errors in calculating subsequent treatment costs. Additional clinical data would be necessary to enhance the accuracy of this study. Second, the utilities used in our model were not derived from the NAPOLI-3 trial but were instead sourced from a published health technology assessment. We assumed identical utilities for patients in both groups, which may have introduced bias into the results. Utilizing utility values from other related RCTs rather than directly from NAPOLI-3 presents several potential issues. Patient populations in different trials often have varying baseline characteristics, disease severities, and responses to treatment, all of which can significantly influence health-related quality of life. As a result, utility values from these external RCTs may not fully reflect the specific experiences of patients in the NAPOLI-3 trial. Additionally, differences in study design—such as variations in follow-up duration, assessment tools, and health state definitions—can lead to inconsistencies in utility values, potentially resulting in estimates that are not entirely comparable or representative of the outcomes within the context of NAPOLI-3. While the use of external utility values is sometimes necessary, it is important to acknowledge these limitations and carefully consider the potential biases they may introduce when interpreting the model's results. Furthermore, one concern that arose during the modeling process was the potential for overfitting, particularly given the high mortality rate associated with mPDAC. While our analysis ensured that the fitted survival curves did not fall below the prevailing age-specific all-cause mortality rate, this criterion alone may not be sufficient to completely rule out overfitting. Finally, in the context of our scenario analysis, it is important to note that the NAPOLI-3 clinical trial has limitations, particularly in that post-progression survival outcomes are already established. While we acknowledge that simplifying the post-treatment scenario may appear reductive, adjusting the survival curves to reflect these changes is unfortunately not feasible within the scope of our current analysis.

It is also essential to address the limitations of using QALY as a measure. One of the primary concerns is its potential to be discriminatory, particularly in the context of diseases with limited survival benefits, such as metastatic cancer. QALY has been criticized for potentially undervaluing the lives of individuals with chronic conditions or disabilities, as it combines both the quantity and quality of life into a single metric. This can lead to biases in health economic evaluations, especially when comparing treatments for populations with different baseline health states [21]. Moreover, recent developments, such as the rules outlined in the Inflation Reduction Act, have highlighted the potential discriminatory nature of QALY, and the Act has ruled out QALY as a relevant metric in certain contexts, reflecting growing concerns about its use in healthcare decision-making.

However, despite these limitations, QALY remains a widely recognized and utilized tool in health economics, particularly when applied with careful consideration of its constraints. We understand that in the oncology setting in the United States, the cost-effectiveness threshold for each QALY typically ranges between $150,000 and $300,000, reflecting the country's distributed healthcare financing systems [22]. Specifically, in cases of metastatic cancer and other diseases where the survival benefit is limited—resulting in a relatively small ICER denominator—thresholds closer to $300,000/QALY have been observed. Therefore, while it is crucial to acknowledge the limitations of QALY, particularly its potential for discrimination, it still serves as a valuable measure in evaluating the cost-effectiveness of medical interventions when used judiciously within the appropriate context. Recognizing its limitations allows for a more nuanced application, ensuring that it remains a relevant tool in health economic assessments.

Conclusion

In conclusion, our model's estimation reveals that, NALIRIFOX is not cost-effective at a WTP threshold of $150,000 /QALY. However, pricing simulations suggest that NALIRIFOX could achieve cost-effectiveness at a WTP threshold of $150,000 per QALY if the price of irinotecan liposome were reduced to $53.24 / mg, which represents a 14.8% decrease.

Abbreviations

AEs	Adverse events
CEAC	Cost-effectiveness acceptability curve
DSA	Deterministic sensitivity analysis
ECOG	Eastern Cooperative Oncology Group
ICER	Incremental cost-effectiveness ratios
IPD	Individual patient data
mPDAC	Metastatic pancreatic ductal adenocarcinoma
NCCN	National Comprehensive Cancer Network
PD	Progressed disease
PFS	Progression-free survival
PSA	Probabilistic sensitivity analysis
QALYs	Quality-adjusted life years
WTP	Willingness to pay

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable, this study does not involve human participants or animal subjects.

Consent for publication

All authors agreed to the publication of this manuscript.

Competing interests

The authors declare no competing interests.

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