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Original Article

Head-to-head comparison of FOLFIRINOX versus gemcitabine plus nab-paclitaxel in advanced pancreatic cancer: a target trial emulation using real-world data

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ABSTRACT

Purpose: To emulate a hypothetical target trial assessing the effect of initiating 5-fluorouracil, folinic acid, irinotecan, and oxaliplatin (FOLFIRINOX) versus gemcitabine plus nab-paclitaxel (GN) within 8 weeks of diagnosis on overall survival.

Methods: An observational cohort study was conducted using population-level data from Alberta, Canada. Individuals diagnosed with advanced pancreatic cancer between April 2015 and December 2019 were identified through the provincial cancer registry and followed until March 2021. Records were linked to other administrative databases containing information on relevant variables. Individuals were excluded if they did not have adequate hemoglobin, platelet, white blood cell, and serum creatinine measures or if they received prior therapy. The observational analog of the per-protocol effect was estimated using inverse probability weighted Kaplan-Meier curves with bootstrapped 95% confidence intervals.

Results: Four hundred seven individuals were eligible. The weighted median overall survival was 8.3 months (95% CI, 5.7–11.9) for FOLFIRINOX and 5.1 months (95% CI: 4.3 to 5.8) for GN. The adjusted difference in median overall survival was 3.2 months (95% CI, 1.1–7.4) and the mortality hazard ratio was 0.78 (95% CI, 0.61–0.97).

Conclusions: Our estimates favored the initiation of FOLFIRINOX over GN with respect to overall survival.

Introduction

Pancreatic cancer has a 5-year survival of less than 10% [1,2]. Since the vast majority of patients present with locally advanced or metastatic disease, most tumors are not amenable to surgical resection [3–5]. Instead, patients are typically offered systemic therapy [4,6]. Currently, three chemotherapy regimens are considered to provide clinically meaningful benefits: 1) gemcitabine alone; 2) 5-fluorouracil, folinic acid, irinotecan, and oxaliplatin (FOLFIRINOX); and 3) gemcitabine plus nab-paclitaxel (GN) [4,6,7].

Historically, gemcitabine alone was the standard of care based on results from a 1997 trial [8]. In 2011, the ACCORD trial found a 4-month survival improvement for FOLFIRINOX compared with

Abbreviations: cci, canadian classification of health interventions; Ci, confidence intervals; Dad, discharge abstract database; Ecog, eastern cooperative oncology group; Folfirinox, 5-fluorouracil, folinic acid, irinotecan, and oxaliplatin; Gn, gemcitabine plus nab-paclitaxel; HR, hazard ratio; ICD, International Classification of Disease; IP, inverse probability; IQR, interquartile range; NACRS, National Ambulatory Care Reporting System; OS, overall survival; SD, standard deviation.

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Table 1
Specification and emulation of a Target Trial of FOLFIRINOX vs. gemcitabine + nab-paclitaxel in individuals with advanced pancreatic cancer

Protocol Item	Target Trial	Emulation
Eligibility Criteria	- Diagnosis of a pancreatic adenocarcinoma between April 1, 2015 and December 31, 2019 in Alberta, Canada - Metastatic or locally advanced disease - Adenocarcinoma (e.g. neuroendocrine, acinar, or islet cell tumors were ineligible) - Satisfactory laboratory measures taken within 30 days prior to diagnosis (i.e. hemoglobin >80 g/L; platelet count > 100×10^9/L; white blood cell count > 4.0 g/L; serum creatinine <100 umol/L). Individuals who did not have satisfactory laboratory measures at the time of diagnosis were permitted to enter into the study if/when they achieved these laboratory measures up to eight weeks post-diagnosis - No prior surgery, radiation therapy, or chemotherapy for the treatment of advanced pancreatic cancer	Same as target trial, plus availability of baseline variables age, sex, neighbourhood level household income and education, Charlson comorbidity index in previous 6 months, number of emergency room visits in the previous year, cancer stage, tumor location, hemoglobin, platelet count, white blood cell count, and serum creatinine.
Treatment strategies	1) Initiation of gemcitabine + nab-paclitaxel (any dose) within 8 weeks of diagnosis 2) Initiation of FOLFIRINOX (any dose) within 8 weeks of diagnosis Initial dosing and decisions about duration of treatment were left to the discretion of the treating physician	Same as target trial
Treatment assignment	Individuals were randomly assigned to a treatment strategy and were aware of their assignment	Individuals were classified to the treatment strategy compatible with their observed data
Follow-up	Follow-up started at the time of treatment assignment and ended at death, date of last contact with the healthcare system, or administrative end of study (March 31, 2021), whichever occurred first.	Same as target trial
Outcome	Death from any cause as reported to the Vital Statistics database	Same as target trial
Causal contrasts	Intention-to-treat effect and per-protocol effect	Observational analog of the per-protocol effect
Analysis plan	Intention-to-treat analysis: Kaplan-Meier estimator to construct survival curves and a pooled logistic regression model to estimate a proportional hazards ratio Pe-protocol analysis: same as the intention-to-treat analysis except that individuals are artificially censored when they deviate from the assigned treatment strategy. IP weighting is used to adjust for potential selection bias due to artificial censoring.	Same as target trial except that duplication of patients is used to address unknown baseline treatment assignment in the observational dataset.

gemcitabine alone (11.1 vs. 6.8 months), but the risk of grade 3 or 4 neutropenia in the FOLFIRINOX arm was twice that of the gemcitabine alone arm (46% vs. 21%) [9,10]. In 2013, the MPACT trial found a 2-month survival improvement for GN compared with gemcitabine alone (8.5 vs. 6.7 months), but the risk of neuropathy in the GN arm was higher than in the gemcitabine alone arm (17% vs. 1%) [11].

Although the MPACT and ACCORD trials added two therapeutic options for advanced pancreatic cancer, FOLFIRINOX and GN have never been directly compared head-to-head in a randomized trial. Such a trial is unlikely to be conducted due to the high cost and commercial risk barriers for sponsoring firms.

In the absence of a head-to-head trial, a Bayesian network meta-analysis compared the arms of the ACCORD and MPACT trials and found a mortality hazard ratio of 0.79 (95% credible interval: 0.59–1.05) for FOLFIRINOX versus GN [7]. The validity of this comparison is supported by the lack of meaningful imbalances in the distribution of baseline characteristics and the similar median overall survival within the gemcitabine alone arms (6.7 and 6.8 months) [9,11,12]. On the other hand, the validity of the comparison is threatened by the differences in eligibility criteria [12]. For example, the ACCORD trial included individuals aged ≤75 years with an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1 whereas the MPACT trial allowed for the inclusion of individuals over the age of 75 and patients with a Karnofsky score of 70 [9,11,12].

Regardless of their comparability, both trials employed strict eligibility criteria that would have excluded many patients treated in routine clinical practice. Real-world investigations have estimated that 74% and 55% of individuals with advanced pancreatic cancer would be ineligible for inclusion into the ACCORD and MPACT trials, respectively [13,14]. The extent to which the indirect findings from the Bayesian network meta-analysis are applicable to patients treated outside of a clinical trial setting is therefore uncertain.

Here, we estimate the comparative effect of FOLFIRINOX versus GN on the overall survival of patients with advanced pancreatic cancer in a real-world clinical setting. To do so, we used observational data to emulate a randomized trial [15–17].

Methods

This investigation was conducted in two stages. First, we articulated the clinical question by specifying the protocol of a (hypothetical) pragmatic randomized trial – the target trial (Table 1) [18]. Second, we emulated the target trial using observational data.

Target trial specification

The main components of the hypothetical target trial are summarized in Table 1. The target trial would include adult individuals diagnosed with stage III or IV pancreatic adenocarcinoma between April 1, 2015 and December 31, 2019 in Alberta, Canada who had no prior treatment for their tumor. Patients would be considered eligible if they had satisfactory laboratory measures at the time of diagnosis or within 30 days prior to the time of diagnosis, operationalized as follows: 1) hemoglobin > 80 g/L; 2) platelet count

$> 100 \times 10^9$/L; 3) white blood cell count > 4.0 g/L; and 4) serum creatinine <100 umol/L. Individuals who did not have satisfactory laboratory measures at the time of diagnosis would be allowed to enter into the study if and when they achieved those laboratory measures up to 8 weeks post diagnosis. No eligibility restrictions were placed on age or performance status.

Eligible individuals would be randomly assigned to 1) initiation of FOLFIRINOX or 2) initiation of GN within 8 weeks of diagnosis. The 8-week time window was selected in consultation with a senior medical oncologist who treats pancreatic cancer in Alberta and was based on the maximum time window during which individuals are expected to benefit from systemic therapy. Dosing of both regimens and subsequent decisions about treatment continuation were left to the discretion of the treating physician. Eligible participants would be followed from the time they are assigned to a treatment strategy (time zero) to death (the outcome of interest), last contact with the provincial healthcare system, or March 31, 2021, whichever came first.

The causal contrasts of interest would be the intention-to-treat and per-protocol effects. Here, the per-protocol effect refers to the effect of initiating the assigned therapy within the 8-week time-period, regardless of subsequent continuation of treatment, because the protocol only specified the time of treatment initiation.

The intention-to-treat effect would be estimated via an intention-to-treat analysis. The Kaplan-Meier survival curves would be estimated and compared up to 3 years. The difference in median survival, 1-year survival, 2-year survival, and 3-year restricted mean survival would be estimated [19]. The hazard ratio would be estimated using a pooled logistic regression model for death, with day of follow-up (modeled as a restricted cubic spline with four knots placed at the 5th, 35th, 65th, and 95th percentiles) and treatment group as variables in the model [20]. The 95% confidence intervals would be estimated using the bootstrap percentile method with 1000 iterations [21,22]. Due to the reliance upon provincial administrative databases for follow-up information, attrition would be non-informative.

The per-protocol effect would be estimated via a per-protocol analysis that differs from the above intention-to-treat analysis in two ways. First, individuals would be artificially censored at 8 weeks if they had not yet initiated the assigned therapy or if and when they initiated a systemic therapy other than the one to which they were assigned within 8 weeks. Second, time-varying inverse probability (IP) weights would be used to adjust for potential selection bias due to artificial censoring [23–27]. The denominator of the IP weights would be estimated by fitting, separately in each group, a pooled logistic model for the probability of adherence with the following baseline variables: age at diagnosis (years), sex (male/female), median neighbourhood level annual household income (Canadian dollars), proportion of individuals within the neighbourhood who achieved a high school level education or greater (%), Charlson comorbidity index assessed within one-year prior to diagnosis (0, 1, or 2+), any encounters with ambulatory care services within the year prior to diagnosis (yes, no), cancer stage at diagnosis (III vs. IV), tumor topography (pancreatic head vs. other site), hemoglobin (g/L), platelet count (10^9/L), white blood cell count (g/L), and serum creatinine (umol/L), and the time-varying variable surgical placement of a stent before initiation of chemotherapy (yes, no). Continuous variables would be modeled using a restricted cubic spline with knots placed at the 10th, 50th, and 90th percentiles [20]. The numerator of the IP weights would be the estimated by fitting the same model with no covariates. IP weights were truncated at the 99th percentile to address influential observations. These prognostic factors were selected *a priori*, in consultation with a senior medical oncologist, because they are expected to be related to treatment choice.

Target trial emulation

We emulated the above target trial using several observational databases. The Alberta Cancer Registry, which includes information on the date of diagnosis and tumor characteristics, was used to identify individuals diagnosed with advanced pancreatic adenocarcinoma within the province of Alberta, Canada. Data were linked to other provincial administrative databases using a unique lifetime identifier. The date of death was ascertained from vital statistics; receipt of radiation, surgery, and chemotherapy as well as laboratory data from electronic medical records; encounters with ambulatory care services from the National Ambulatory Care Reporting System (NACRS) database; comorbidities and stent placement from the NACRS, hospitalization Discharge Abstract Database (DAD), and the Practitioner Claims databases. The postal code of residence at diagnosis was linked to Statistics Canada Survey census tract data to obtain information on neighborhood level annual household income and the proportion of individuals within the neighbourhood who achieved a high-school level education or greater. Charlson comorbidity index was assessed using International Classification of Disease (ICD) codes [28] and stent placement was assessed using the following Canadian Classification of Health Interventions (CCI) codes: 1.OE.50, 1.OE.25, 1.OE.54.

Analyses were restricted to individuals who met the eligibility criteria in Table 1. We classified eligible individuals into the strategy (initiation of either FOLFIRINOX or GN within 8 weeks) with which their data were compatible at the time of eligibility (time zero) and followed them until death, last contact with the provincial healthcare system, or March 31, 2020, whichever came first.

To estimate the observational analog of the per-protocol effect, we conducted the above per-per-protocol analysis with two modifications. First, because no eligible individuals initiated chemotherapy at exactly the time of eligibility, all individuals had data compatible with both strategies at the time zero. Therefore, we created an expanded database in which each individual was included twice, with one clone assigned to the FOLFIRINOX group and the other to the GN group [17,25]. Then the censoring procedure described for the target trial was applied separately to each clone according to their assigned treatment strategy. Note that an observational analog of the intention-to-treat effect was not estimable because all individuals were included in both groups at baseline.

Second, the time-varying probabilities for the denominator of the IP weights were estimated by fitting a pooled multinomial logit model to the original data. The model had the same covariates as the target trial but the outcome was a three-category variable: 1) initiating FOLFIRINOX, 2) initiating GN, or 3) not initiating either FOLFIRINOX or GN. For each clone, the denominator of the weight was the estimated as the conditional probability of remaining uncensored through each day. For clones assigned to FOLFIRINOX, the probability of being uncensored on each day was the sum of 1) the probability of not initiating FOLFIRINOX or GN and 2) the probability of initiating FOLFIRINOX. On the last day within the 8-week grace period, the probability of remaining uncensored among those who had not yet initiated FOLFIRINOX was solely the probability of initiating FOLFIRINOX. For those assigned to GN, the probability of remaining uncensored was defined similarly except using the probability of initiating GN in place of the probability of initiating FOLFIRINOX.

All statistical analyses were conducted in R version 3.5.2 [21,29]. This study was approved by the Health Research Ethics Board of Alberta (certificate no. HREBA.CC-20–0209).

Comparator analysis

For comparison purposes, we conducted a more conventional observational analysis that did not clearly correspond to any target

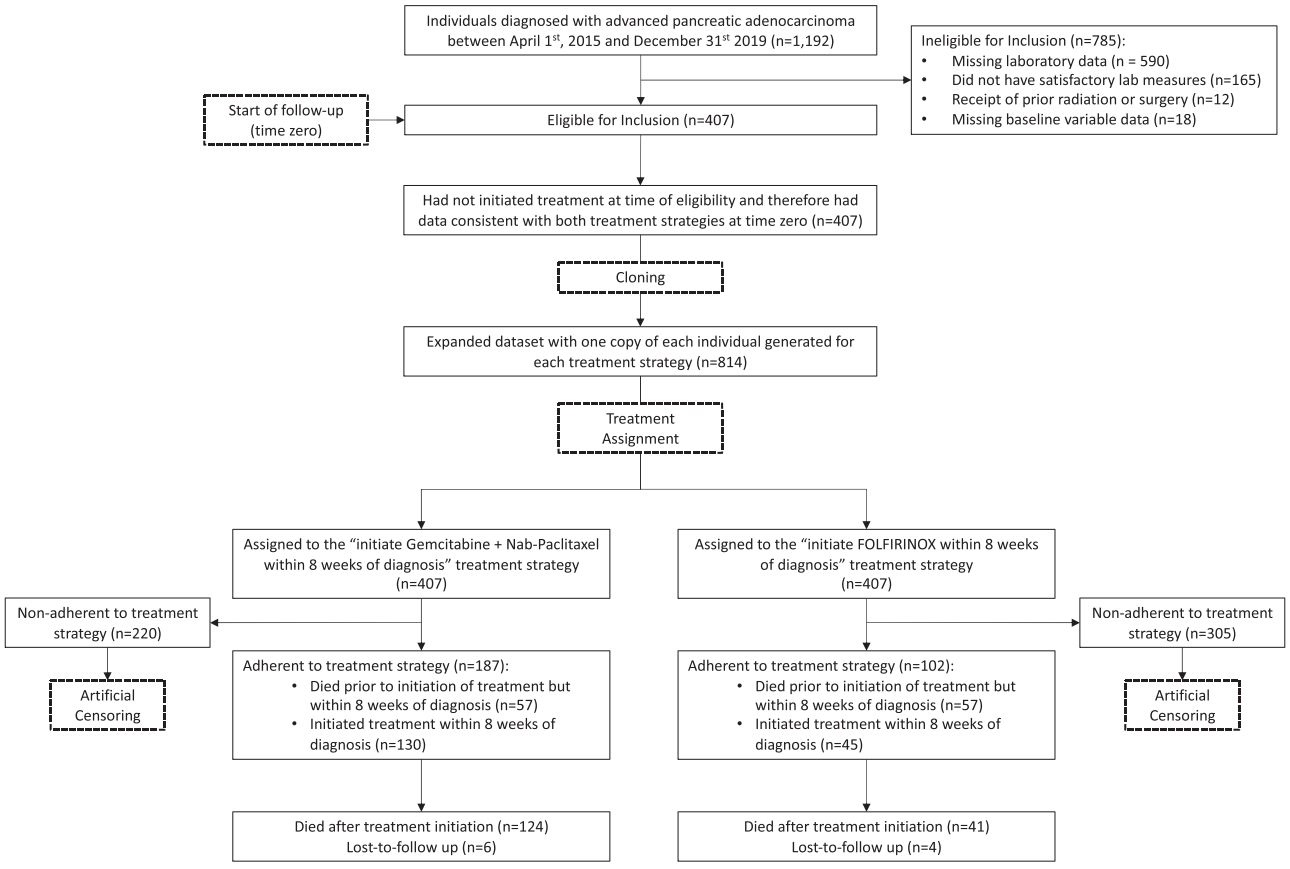

Fig. 1. Flow diagram of individuals with advanced pancreatic cancer diagnosed in Alberta, Canada between 2015 and 2019 included in our emulation of a target trial to estimate the effect of initiating FOLFIRINOX vs. gemcitabine + nab-paclitaxel within 8 weeks of diagnosis
Note: Individuals adhered to their assigned strategy if they started treatment within eight weeks or if they died before having the opportunity to start treatment.

trial. This analysis included the same initial set of individuals as the trial emulation but was further restricted to individuals who initiated either FOLFIRINOX or gemcitabine + nab-paclitaxel at any time. Follow-up started at the time of treatment initiation. Analyses adjusted for the same set of prognostic factors available at the time of treatment initiation used in the trial emulation by including them in a pooled logistic regression outcome model. Variables were modeled using the same parametrization as the trial emulation.

Results

Between April 1, 2015 and December 31, 2019, 1192 individuals had a confirmed diagnosis of advanced pancreatic adenocarcinoma in Alberta, Canada of whom 407 were eligible for inclusion (Fig. 1). The primary reason for exclusion was a lack of laboratory data ($n = 590$). The average age at diagnosis was 66 years (range: 34–91) and 57% were male (Table 2).

Of the 407 eligible individuals, 102 had data consistent with the FOLFIRINOX strategy and 187 had data consistent with the GN strategy in the per-protocol analysis (Fig. 1). The median overall survival (95% CI) was estimated to be 8.3 months (5.7–11.9) for FOLFIRINOX and 5.1 months (4.3–5.8) for GN (Fig. 2; Table 3). The difference in median OS was 3.2 months (1.1–7.4). The mortality HR was 0.78 (0.61–0.97). When the analysis was not adjusted for baseline prognostic factors, the difference in median OS was 3.4 months (1.2–8.1) and the HR was 0.77 (0.61–0.94).

Of the 216 individuals included in the conventional analysis, 58 initiated FOLFORINOX and 158 initiated GN (Supplemental Table 1). A total of 41 individuals in the conventional analysis initiated treatment after 8 weeks (FOLFIRINOX: $n = 13$; GN: $n = 28$). The mortality HR was 0.55 (0.38–0.78). Results in the conventional analysis were similar when a Cox proportional hazards model was used in place of a pooled logistic regression model (HR: 0.55, 0.38–0.80) or when IP weights were used instead of an outcome regression model to adjust for confounding (HR: 0.49, 0.34–0.83).

Discussion

We compared two strategies for cancer treatment by emulating a target trial using observational data. Our estimates suggest that, compared with initiation of GN, initiation of FOLFIRINOX within 8 weeks of diagnosis increases median overall survival by approximately three months for individuals with advanced pancreatic cancer. Our study also confirms the more favorable prognosis of patients enrolled in randomized trials versus those in real-world clinical practice [13,14]. For example, the median overall survival within the FOLFIRINOX arm of the ACCORD trial and the GN arm of the MPACT trial (11.1 and 8.5 months, respectively) were greater than the corresponding estimates in our trial emulation (8.3 and 5.1 months, respectively) [9,11]. Despite these differences in duration of survival, the effect estimate from our investigation was consistent with the indirect comparison of the ACCORD and MPACT trials [7].

Estimates from prior observational studies are conflicting [30]. While this literature has been systematically reviewed, the authors did not present measures of association which makes it difficult to interpret the findings [30]. There have been reports of improved survival with FOLFIRINOX [31,32], whereas other studies have found little survival differences [33–38] or improved survival

Table 2
Baseline Characteristics of Individuals with advanced pancreatic cancer eligible for the emulation of a target trial of FOLFIRINOX vs. gemcitabine + nab-paclitaxel, Alberta, Canada, 2015–2019 (n = 407)

Characteristic	Estimate (n = 407)
Age, years (mean (SD))	65.98 (10.22)
Charlson Comorbidity Index (%)	
0	178 (43.7)
1	141 (34.6)
2+	88 (21.6)
Male (%)	231 (56.8)
Prior Cancer Diagnosis (%)	47 (11.5)
Proportion of Individuals in Neighbourhood who Achieved a High School Diploma or Greater (mean (SD))	0.83 (0.10)
Neighbourhood level household annual income, CAD (median (IQR))	49,340 [39,745, 59,774]
Individuals who had one or more encounters with Ambulatory Services within the year prior to diagnosis (%)	157 (38.6)
Number of Metastases at Diagnosis (%)	
0	97 (23.8)
1	187 (45.9)
2+	123 (30.2)
Tumor located on Pancreatic Head (%)	168 (41.3)
Serum Creatinine, umol/L (median [IQR])	67.00 [55.00, 79.00]
Hemoglobin, g/L (median [IQR])	128.00 [116.50, 139.00]
Platelet Count, 10E9/L (median [IQR])	256.00 [194.00, 322.50]
White Blood Cell Count, 10E9/L (median [IQR])	8.10 [6.43, 10.80]

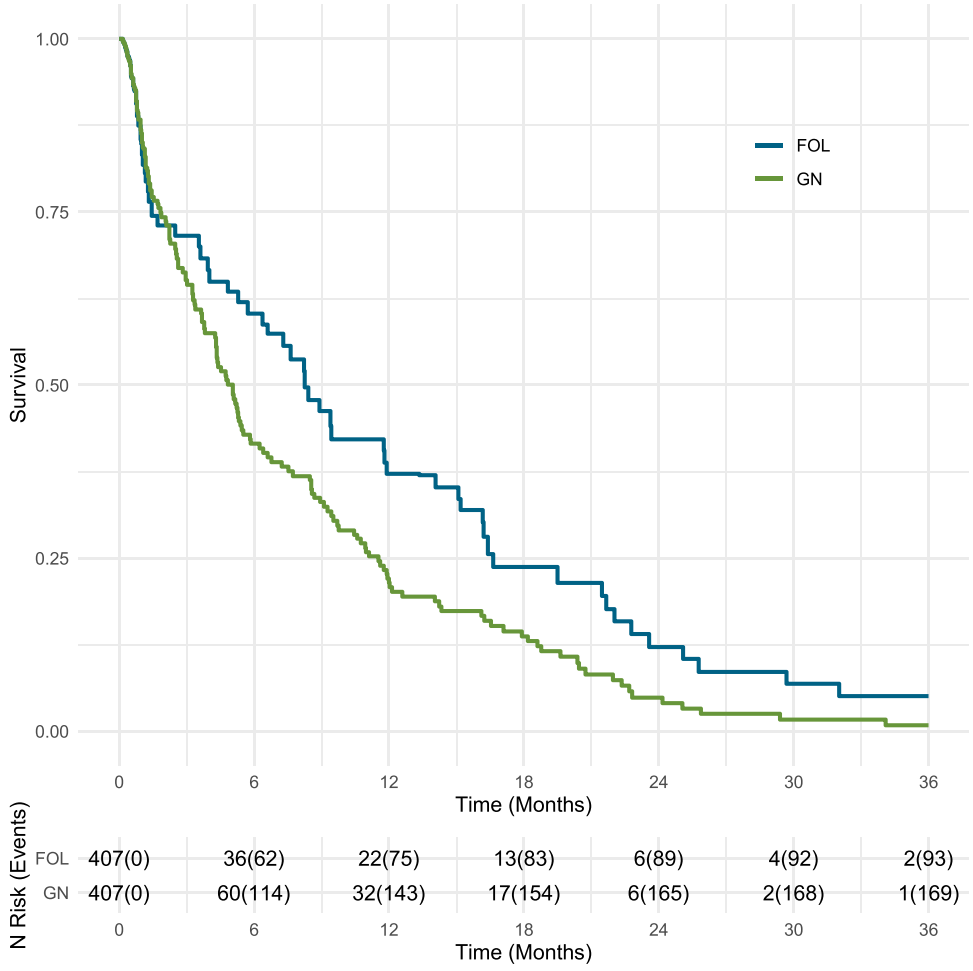

Fig. 2. Weighted Kaplan-Meier Curve Comparing the Overall Survival of Individuals who Initiated 5-fluorouracil, folinic acid, irinotecan, and oxaliplatin (FOL; FOLFIRINOX) or Gemcitabine plus Nab-Paclitaxel (GN) within Eight Weeks of Diagnosis (n = 407)
Notes: FOL = 5-fluorouracil, folinic acid, irinotecan, and oxaliplatin (FOLFIRINOX); GN = gemcitabine plus nab-paclitaxel. N Risk = weighted number of individuals at risk; Events = the weighted cumulative number of death.

Table 3
Adjusted overall survival estimates for FOLFIRINOX vs. gemcitabine + nab-paclitaxel in individuals with advanced pancreatic cancer, Alberta, Canada, 2015–2019 ($n = 407$)

Measure	FOLFIRINOX Estimate (95% CI)	Gem+Nab Estimate (95% CI)	Difference Estimate (95% CI)
Median survival (months)	8.3 (5.7–11.9)	5.1 (4.3–5.8)	3.2 (1.1–7.4)
1-year survival (%)	37.2 (26.2–49.6)	20.8 (14.6–27.3)	16.4 (4.0–30.2)
2-year survival (%)	12.2 (4.0–22.5)	4.8 (1.6–8.6)	7.3 (−1.1 to 18.3)
3-year restricted mean survival (months)	11.3 (9.2–14.1)	7.8 (6.7–9.0)	3.5 (1.2–6.4)

with GN [39,40]. These disparities may be explained by multiple factors, including differences in eligibility, loss to follow-up, and degree of residual confounding.

In an attempt to better understand the direction of bias in previous studies, we re-analyzed our data using a more conventional approach adopted by several prior studies. The conventional hazard ratio estimates were more extreme than ours, but are hard to interpret. First, the conventional analysis was restricted to individuals who initiated either FOLFIRINOX or GN. This restriction can lead to selection bias because of the exclusion of eligible individuals who died before initiating treatment. The risk of such selection bias may be particularly high for fatal conditions such as advanced pancreatic cancer where there are a sizable number of patients who are medically fit for treatment but die shortly after diagnosis without having the opportunity to initiate therapy. In the trial emulation, 57 of the 407 eligible individuals died within eight-weeks without initiating treatment. Unlike in the conventional analysis, the data from these individuals contributed to both treatment strategies in the trial emulation. Excluding these 57 individuals from the trial emulation led to an exaggerated estimate similar to that of the conventional analysis (HR: 0.49; 95% CI, 0.32–0.69). Second, the timing of treatment initiation was not well defined in the conventional analysis. The protocol for our target trial specified that patients must initiate treatment within eight weeks of diagnosis. About 22% of patients who initiated FOLFIRINOX and 18% of patients who initiated GN did so after eight weeks in the conventional analysis, but the time to initiation of therapy after eight weeks was higher among those who initiated GN (mean: 13.7 weeks) than among those who initiated FOLFIRINOX (mean: 11.1 weeks), which might explain the exaggerated estimate. However, when further restricting the conventional analysis to individuals who initiated treatment within eight weeks, the estimate did not meaningfully differ (HR: 0.50; 95% CI, 0.33–0.76) which suggests that selection bias is the primary reason for the exaggerated results. These findings, like those from a previous comparison of gemcitabine plus erlotinib against gemcitabine [41], highlight the utility of the target trial emulation framework to guide clinical practice regarding cancer treatment when randomized trials are not available.

When using observational data to compare treatment strategies for rapidly progressing and highly fatal disease such as pancreatic cancer, the exclusion of eligible individuals who die before starting treatment may result in biased effect estimates. Despite restricting our target trial emulation to relatively healthy individuals fit for either FOLFIRINOX or GN, 57 out of 407 died within 8 weeks before having the opportunity to initiate either therapy. The three-stage cloning, artificial censoring, and inverse probability weighting approach correctly incorporated data from individuals who died prior to initiating therapy by allowing them to contribute data to both treatment strategies. This resulted in an effect estimate that was compatible with available evidence. In contrast, the conventional observational analysis excluded data from eligible individuals who died prior to initiating therapy, which is analogous to removing individuals with early deaths from a randomized trial, and resulted in an estimate that incorrectly suggested a more pronounced effect.

Despite the advantages of an explicit target trial emulation, limitations of our study should be recognized. First, information was not available on potential confounders such as performance status, carbohydrate antigen 19–9 levels, and lifestyle variables and there was potential misclassification of confounders due to our reliance on administrative data algorithms for comorbidities and ecological proxies for socioeconomic status. While there is a risk of bias due to residual confounding, we suspect this risk is small because the adjusted and unadjusted estimates were similar and because our estimate was compatible with the indirect treatment comparison from the ACCORD and MPACT trials [7]. Second, our estimates lacked precision. However, our sample size compares favorably with that of previous studies [30] and the majority of individuals were followed until death. Third, a number of individuals were excluded due to missing laboratory data. The primary reason for this missingness was likely non-referral to an oncology clinic which accounts for an estimated 46% of advanced pancreatic cancer patients in Alberta, Canada [42]. While our findings have high-degree of generalizability due to the reliance on population-level data, they may not be applicable to individuals who are not referred to a cancer center.

To summarize, evidence from this trial emulation supports the superiority of FOLFORINOX over GN for first-line treatment of advanced pancreatic cancer in real-world clinical settings. These findings were compatible with an indirect treatment comparison using data from randomized trials. In the absence of direct head-to-head treatment comparisons from randomized trials, the emulation of a target trial using real-world data may help to generate comparative effectiveness evidence.

Declaration of interests

MAH is data science adviser for ProPublica and a consultant for Cytel. The authors declare that they have no other known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.annepidem.2022.12.005.

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