Comparative Effectiveness of FOLFIRINOX vs. Gemcitabine + nab-Paclitaxel in Metastatic Pancreatic Ductal Adenocarcinoma: A Marginal Structural Model Analysis

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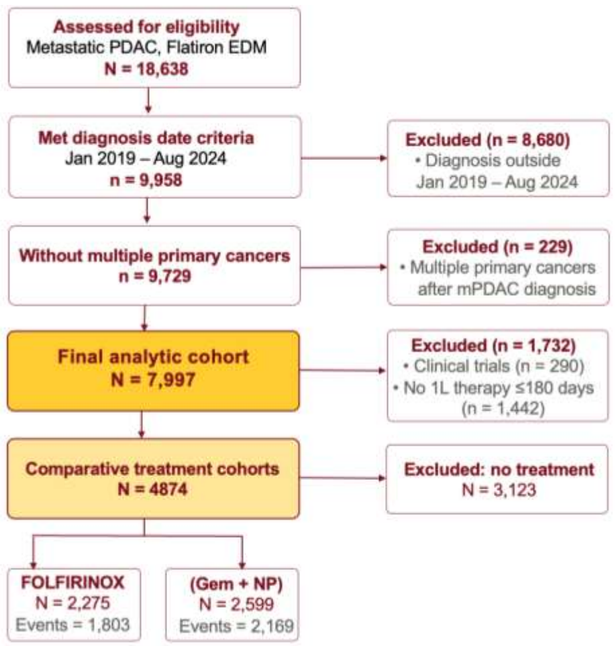
INTRODUCTION

- Pancreatic ductal adenocarcinoma (PDAC) is the 3rd leading cause of cancer mortality in the U.S., with most patients presenting with metastatic disease.[1]
- First-line multi-agent regimens; FOLFIRINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin) and Gemcitabine plus nab-paclitaxel (Gem + NP) demonstrated survival benefits over gemcitabine monotherapy in landmark RCTs (PRODIGE 4/ACCORD 11 and MPACT). [2,3]
- Comparative effectiveness between these regimens in real-world practice remains uncertain.
- The study aims to compare the real-world effectiveness of FOLFIRINOX versus Gem + NP on overall survival using causal inference methods.

METHODS

- Retrospective cohort study design using a nationally representative Flatiron Health Electronic Health Record-derived oncology database (2019-2024).[4]
- Included adults with metastatic PDAC initiating first-line systemic therapy within 180 days of diagnosis.
- Primary outcome was overall survival from treatment initiation to death.
- Treatment effects were evaluated using multivariable Cox regression, outcome regression, and marginal structural models (MSMs) with stabilized inverse probability weighting (IPW) to address baseline confounding bias.[5]
- Covariates included demographic, clinical, and socioeconomic factors: age, sex, race/ethnicity, smoking status, insurance type, practice type, socioeconomic status, ECOG performance status, and de novo metastatic presentation.
- We conducted sensitivity analyses using propensity score matching and conditional Cox regression to assess robustness. Subgroup analyses were performed by smoking status. Propensity score distributions (range: 0.06-0.93; mean: 0.46) showed sufficient overlap to support weighting.

FIGURE 1: COHORT FLOW DIAGRAM



RESULT

Table 1: Baseline Demographics and Clinical Characteristics

Variable	FOLFIRINOX (N=2,275)	Gemcitabine + nab-paclitaxel (N=2,599)	SMD
Age at diagnosis, mean (SD)	64.8 (8.9)	70.4 (9.1)	0.62
Sex n (%)			0.06
Female	990 (44%)	1,207 (46%)	
Male	1,285 (56%)	1,392 (54%)	
Race/Ethnicity n (%)			0.12
Non-Hispanic White	1,148 (50%)	1,270 (49%)	
Non-Hispanic Black	180 (7.9%)	211 (8.1%)	
Asian	41 (1.8%)	30 (1.2%)	
Hispanic/Latino	158 (6.9%)	150 (5.8%)	
Other / Unknown	748 (32.8%)	938 (35.8%)	
Smoking status n (%)			0.02
Never	1,059 (47%)	1,188 (46%)	
Ever	1,214 (53%)	1,409 (54%)	
Unknown	2 (<0.1%)	2 (<0.1%)	
Insurance, n (%)			
Commercial insurance	1,896 (85%)	2,179 (85%)	0.01
Medicare	828 (37%)	1,237 (48%)	0.23
Medicaid	186 (8.3%)	206 (8.0%)	0.01
Self-pay	177 (7.9%)	131 (5.1%)	0.11
Government program	152 (6.8%)	176 (6.9%)	0.00
Patient assistance	373 (17%)	448 (17%)	0.02
Other/Unknown	355 (16%)	421 (16%)	0.02
Practice type n (%)			0.14
Community	552 (24%)	486 (19%)	
Academic	1,723 (76%)	2,113 (81%)	
Socioeconomic status n (%)			0.09
SES Level 1-2 (Low)	657 (29%)	848(33%)	
SES Level 3	449 (20%)	483 (19%)	
SES Level 4-5 (High)	967 (43%)	1046 (40%)	
Unknown	202 (8.9%)	222 (8.5%)	
ECOG performance status n (%)			0.30
ECOG 0-1	1,800 (79.1%)	1,874 (72.1%)	
ECOG 2-4	179 (7.9%)	452 (17.4%)	
Unknown	296 (13.0%)	273 (10.5%)	
De novo metastasis n (%)			0.23
No	76 (3.3%)	295 (11%)	
Yes	1,885 (83%)	1,583 (61%)	
Unknown	314 (14%)	721 (28%)	

*Note: Insurance categories are not mutually exclusive; percentages may sum to >100%.SMD = standardized mean difference; SES = socioeconomic status; ECOG = Eastern Cooperative Oncology Group.

- A total of 7,997 eligible patients were identified; 4,874 received FOLFIRINOX or Gem + NP.
- Patients receiving FOLFIRINOX were younger with better ECOG performance status.

Table 2: Primary Overall Survival and Treatment Outcomes

Regimen	N	Events	Median OS (mo)	95% CI	AHR (95% CI)
FOLFIRINOX	2275	1803	10.35	9.90 -10.90	Reference
GEM + NP	2599	2169	7.48	7.03-7.97	1.21 (1.13 -1.29)

*Adjustment for age, sex, race/ethnicity, smoking status, socioeconomic status, and de novo metastasis. p-value <0.001 in both unadjusted and adjusted hazard ratios (HR)

- Median OS was longer with FOLFIRINOX versus Gem + NP (10.4 vs 7.5 months).
- In adjusted analyses, Gem + NP was associated with increased mortality relative to FOLFIRINOX (adjusted HR 1.21, 95% CI 1.13 - 1.29).

Figure 2: Survival Plot of Overall Survival.

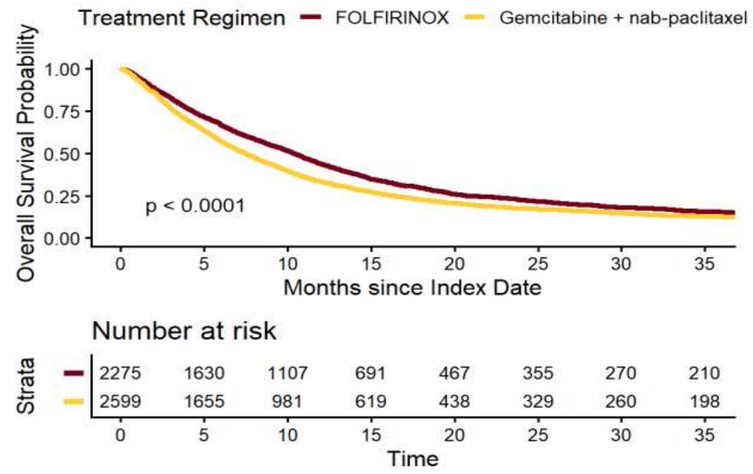


Table 3: Treatment Effects by Analytical Model and Smoking Subgroup

Population / Model Setup	Standard Outcome Regression HR (95% CI)	Marginal Structural Model (IPW) HR (95% CI)
Overall Cohort (Unadjusted)	0.82 (0.77-0.87)	0.82 (0.77-0.87)
Overall Cohort (Adjusted)	0.85 (0.79-0.91)	0.86 (0.80-0.93)
Subgroup: Ever SS	0.80 (0.73-0.88)	0.81 (0.74-0.90)
Subgroup: Never SS	0.90 (0.81-1.00)	0.92 0.82-1.02)

- Marginal structural models demonstrated consistent survival benefit with hazard ratios of 0.86 in the overall cohort, favoring FOLFIRINOX across analytic approaches.
- Among those who smoke, FOLFIRINOX was associated with significantly improved survival (HR 0.81; 95% CI 0.74 - 0.90), whereas among those who do not smoke, the benefit was smaller and not statistically significant (HR 0.92; 95% CI 0.82 - 1.02).

LIMITATIONS

- Residual confounding from unmeasured factors (tumor biology, CA19-9, BRCA, KRAS status, clinician preference).
- A non-randomized design cannot fully replicate randomization.
- Substantial missingness in ECOG (~12%) and socioeconomic status; complete-case and imputation strategies applied.
- Results may not generalize beyond U.S. Flatiron-represented practices.

CONCLUSIONS

- **Across all analytic approaches, FOLFIRINOX was consistently associated with superior overall survival compared to Gem + NP.**
- **Subgroup analyses revealed that those who smoke derived significantly greater survival benefit from FOLFIRINOX, potentially reflecting underlying biological or metabolic heterogeneity rather than a protective effect.**

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