XXXIII SIMPOSIO INTERNACIONAL
INTERNATIONAL SYMPOSIUM
11 - 12 DE DICIEMBRE DE 2025
OVIEDO

¿Cuál es el papel del esquema SEQUENCE-TTD nabpaclitaxel-gemcitabina alternante con FOLFOX en primera línea de cáncer de páncreas?

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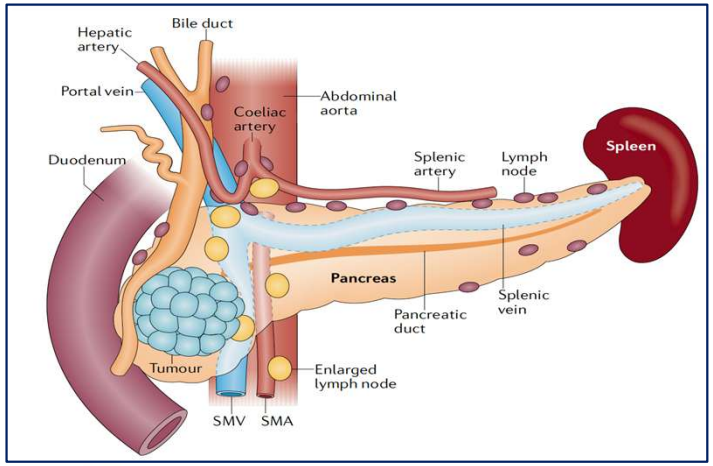
Universidad de Alcalá
Pancreatic Cancer Europe
IRYCIS

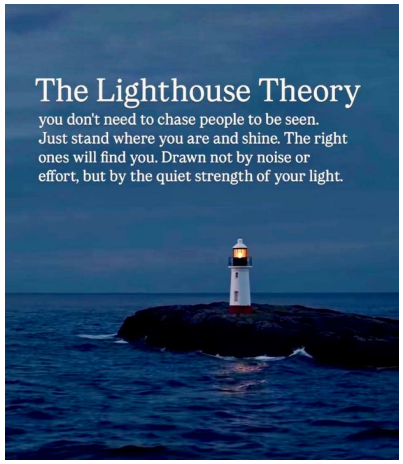
TTD

Disclosure information

- Employment: None
- Consultant or Advisory Role: GoodGut, ProAlt
- Stock Ownership: None
- Research Funding: European Union, ISCIII
- Speaking: Francisco de Vitoria University, ECO Foundation
- Grant support: None
- Other: None

Brief answer: To significantly increase all efficacy parameters of nabP/Gem with a tolerable increase in bone marrow toxicity and improved quality of life





NEJM Evidence

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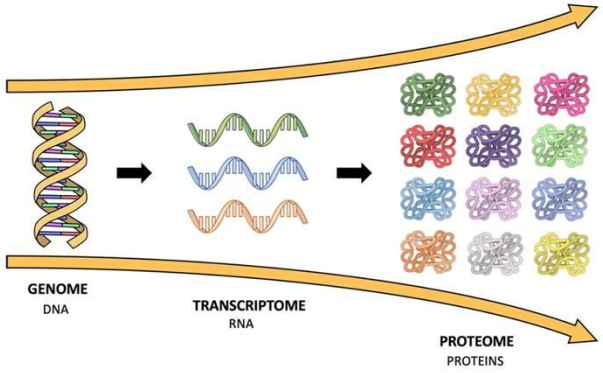
NEJM Evid 2024; 3 (2)
DOI: 10.1056/EVIDoa2300144

ORIGINAL ARTICLE

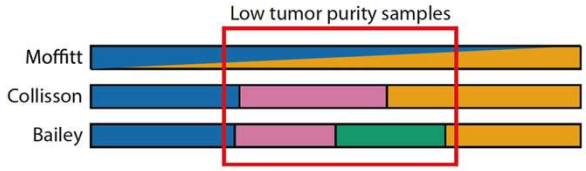
Nab-Paclitaxel plus Gemcitabine and FOLFOX in Metastatic Pancreatic Cancer

Alfredo Carrato, M.D., Ph.D.,[1,2] Roberto Pazo-Cid, M.D., Ph.D.,[3] Teresa Macarulla, M.D., Ph.D.,[4] Javier Gallego, M.D., Ph.D.,[5] Paula Jiménez-Fonseca, M.D., Ph.D.,[6] Fernando Rivera, M.D., Ph.D.,[7] Maria Teresa Cano, M.D.,[8] Mercedes Rodriguez-Garrote, M.D.,[9] Carles Pericay, M.D., Ph.D.,[10] Inmaculada Alés, M.D., Ph.D.,[11] Laura Layos, M.D.,[12] Begoña Graña, M.D., Ph.D.,[13] Vega Iranzo, M.D., Ph.D.,[14] Inmaculada Gallego, M.D.,[15] Rocio Garcia-Carbonero, M.D., Ph.D.,[16] Inmaculada Ruiz de Mena, Ph.D.,[17] Carmen Guillén-Ponce, M.D., Ph.D.,[18] and Enrique Aranda, M.D., Ph.D.[8]

PDAC transcriptomic subtyping & tailor-made treatment



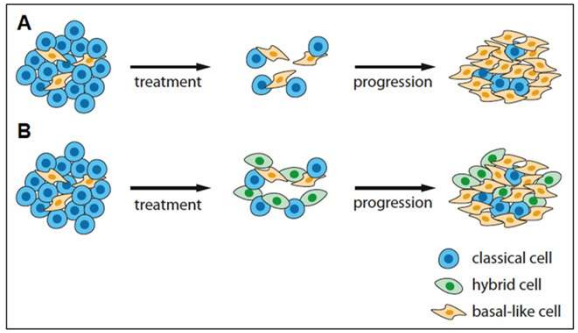
Transcriptional subtypes



Moffitt	Collisson	Bailey
Classical	Classical	Pancreatic progenitor
-	Exocrine-like	ADEX
-	-	Immunogenic
Basal-like	Quasimesenchymal	Squamous

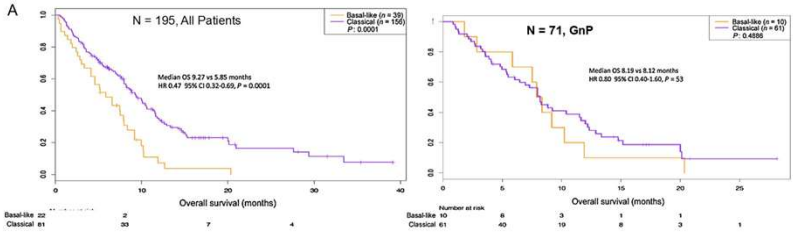
Rashid NU et al. Clin Cancer Res 2020;26:82–92
Lee, Yeh. Surg Clin N Am 2024; 104: 939–50.

The initial subtype can become corrupted due to treatment pressure



Clinical Outcomes by Transcriptional Subtype

The COMPASS Trial: Metastatic pancreatic cancer patients treated with **investigator-choice** first-line mFOLFIRINOX or GnP. Baseline biopsies subtyped by RNAseq.



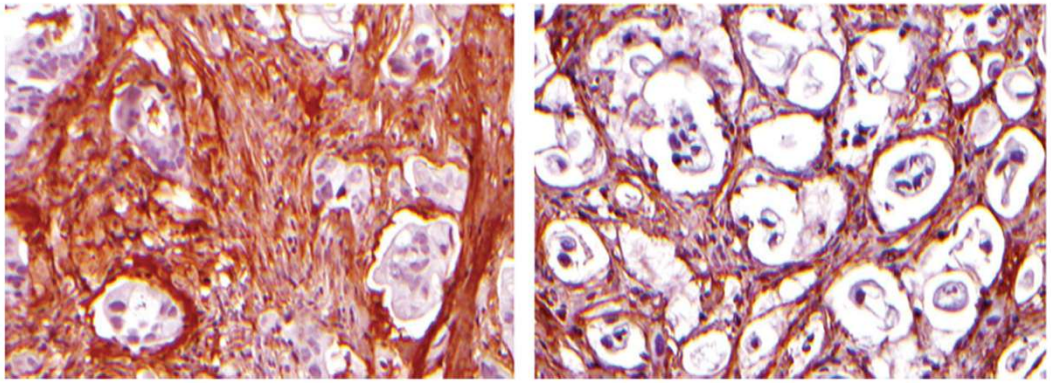
O'Kane G, et al. *Clin Cancer Res* 2020; 26 (18): 4901–10

VOLUME 29 · NUMBER 34 · DECEMBER 1 2011

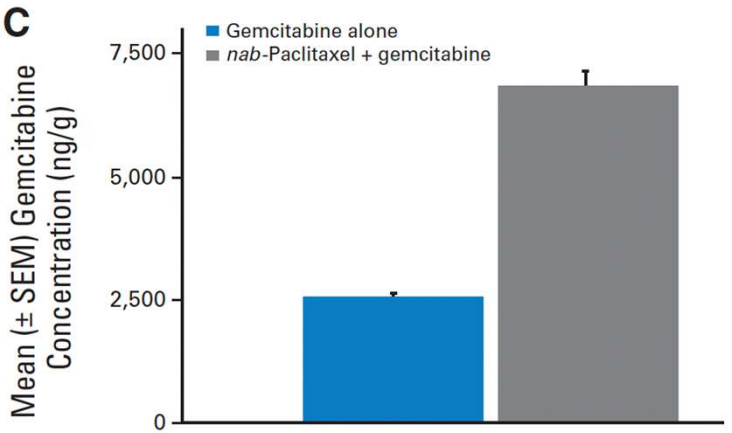
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

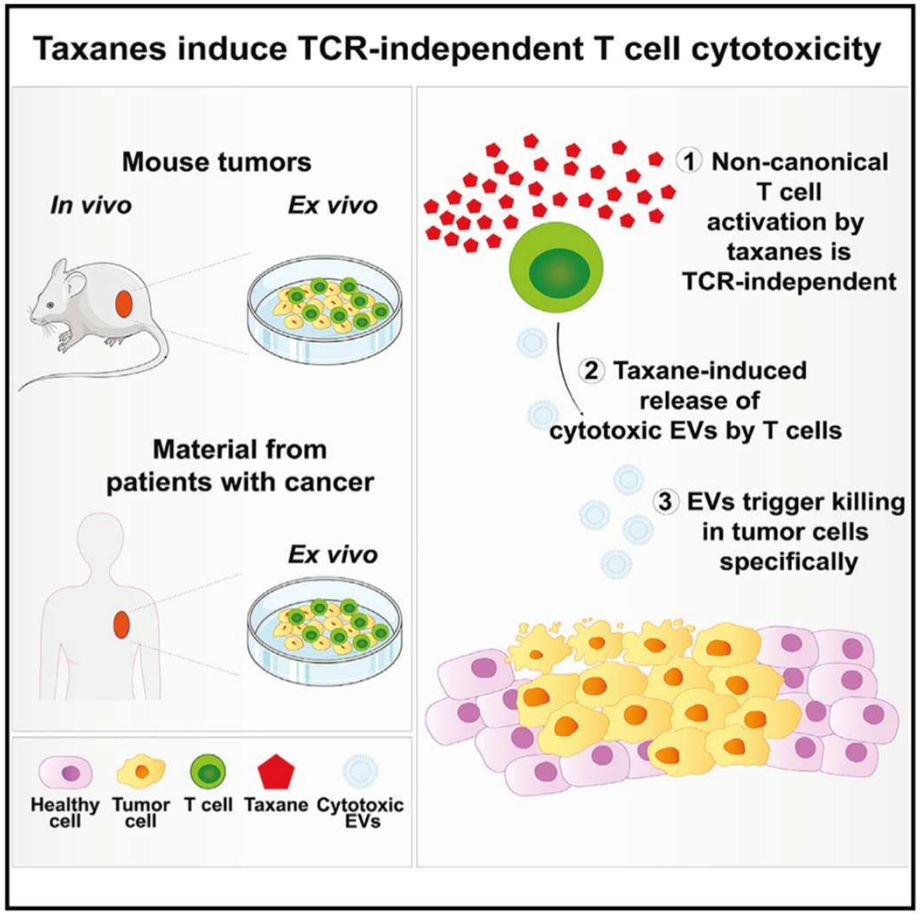
Gemcitabine Plus *nab*-Paclitaxel Is an Active Regimen in Patients With Advanced Pancreatic Cancer: A Phase I/II Trial

Daniel D. Von Hoff, Ramesh K. Ramanathan, Mitesh J. Borad, Daniel A. Laheru, Lon S. Smith, Tina E. Wood, Ronald L. Korn, Neil Desai, Vuong Trieu, Jose L. Iglesias, Hui Zhang, Patrick Soon-Shiong, Tao Shi, N.V. Rajeshkumar, Anirban Maitra, and Manuel Hidalgo



Gemcitabine *nab*-Paclitaxel + gemcitabine





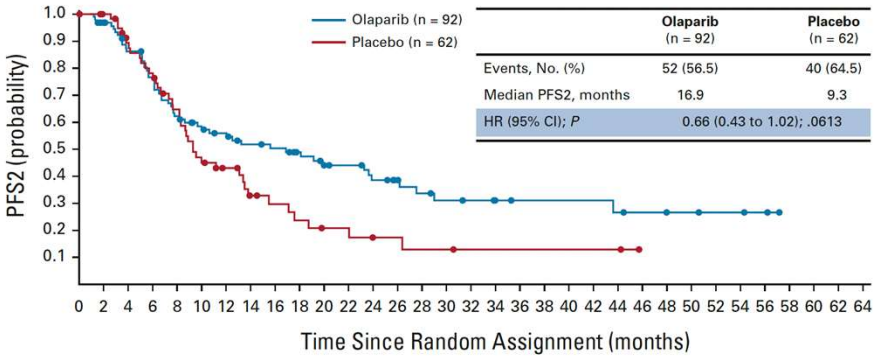
Article

Cancer Cell

Taxanes trigger cancer cell killing *in vivo* by inducing non-canonical T cell cytotoxicity

Claire Vennin, Chiara M. Cattaneo, Leontien Bosch, ..., Dirk M. Pegtel, Emile E. Voest, Jacco van Rheenen

T cells mediate taxane cytotoxicity in vivo
- Taxanes trigger T cells to release cytotoxic extracellular vesicles
- Taxanes increase TCR-independent and TCR-mediated T cell killing
- T cells treated ex vivo with taxanes can eradicate tumors in vivo



	Olaparib (n = 92)	Placebo (n = 62)
Events, No. (%)	52 (56.5)	40 (64.5)
Median PFS2, months	16.9	9.3
HR (95% CI); *P*	0.66 (0.43 to 1.02); .0613	

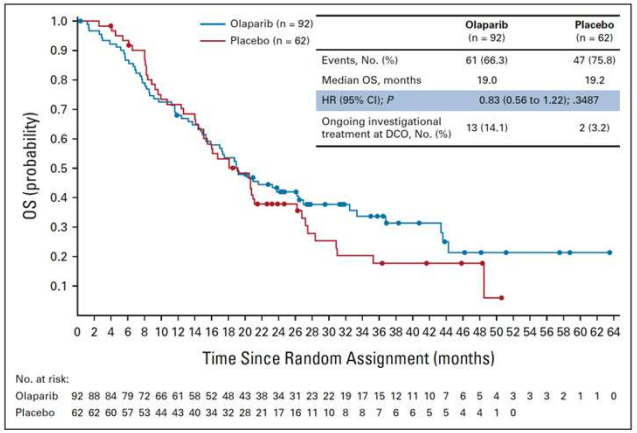
No. at risk:

Olaparib	92	85	73	64	52	45	42	37	35	31	26	25	21	17	14	12	11	8	7	7	7	7	6	5	4	4	3	3	2	0
Placebo	62	58	48	41	33	23	18	12	10	8	6	6	4	4	3	3	2	2	2	2	2	2	2	0						

original reports

Overall Survival Results From the POLO Trial: A Phase III Study of Active Maintenance Olaparib Versus Placebo for Germline BRCA-Mutated Metastatic Pancreatic Cancer

Hedy L. Kindler, MD[1]; Pascal Hammel, MD, PhD[2]; Michele Reni, MD[3]; Eric Van Cutsem, MD, PhD[4]; Teresa Macarulla, MD, PhD[5]; Michael J. Hall, MD[6]; Joon Oh Park, MD, PhD[7]; Daniel Hochhauser, MD, PhD[8]; Dirk Arnold, MD, PhD[9]; Do-Youn Oh, MD, PhD[10]; Anke Reinacher-Schick, MD, PhD[11]; Giampaolo Tortora, MD, PhD[12]; Hana Algül, MD, PhD, MPH[13]; Eileen M. O'Reilly, MD[14]; Sonal Bordia, MD[15]; David McGuinness, MSc[16]; Karen Cui, MD, PhD[17]; Gershon Y. Locker, MD[17]; and Talia Golan, MD[18]



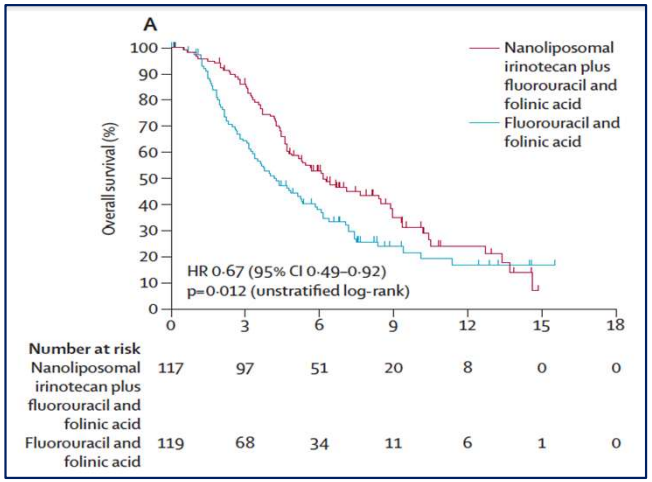
	Olaparib (n = 92)	Placebo (n = 62)
Events, No. (%)	61 (66.3)	47 (75.8)
Median OS, months	19.0	19.2
HR (95% CI); *P*	0.83 (0.56 to 1.22); .3487	
Ongoing investigational treatment at DCO, No. (%)	13 (14.1)	2 (3.2)

No. at risk:

Olaparib	92	88	84	79	72	66	61	58	52	48	43	38	34	31	23	22	19	17	15	12	11	10	7	6	5	4	3	3	3	2	1	1	0
Placebo	62	62	60	57	53	44	43	40	34	32	28	21	17	16	11	10	8	8	7	6	6	5	5	4	4	1	0						

Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial

Andrea Wang-Gillam*, Chung-Pin Li, György Bodoky, Andrew Dean, Yan-Shen Shan, Gayle Jameson, Teresa Macarulla, Kyung-Hun Lee, David Cunningham, Jean F Blanc, Richard A Hubner, Chang-Fang Chiu, Gilberto Schwartsmann, Jens T Siveke, Fadi Braiteh, Victor Moyo, Bruce Belanger, Navreet Dhindsa, Eliel Bayever, Daniel D Von Hoff*, Li-Tzong Chen*, for the NAPOLI-1 Study Group†



Number at risk							
Nanoliposomal irinotecan plus fluorouracil and folinic acid	117	97	51	20	8	0	0
Fluorouracil and folinic acid	119	68	34	11	6	1	0

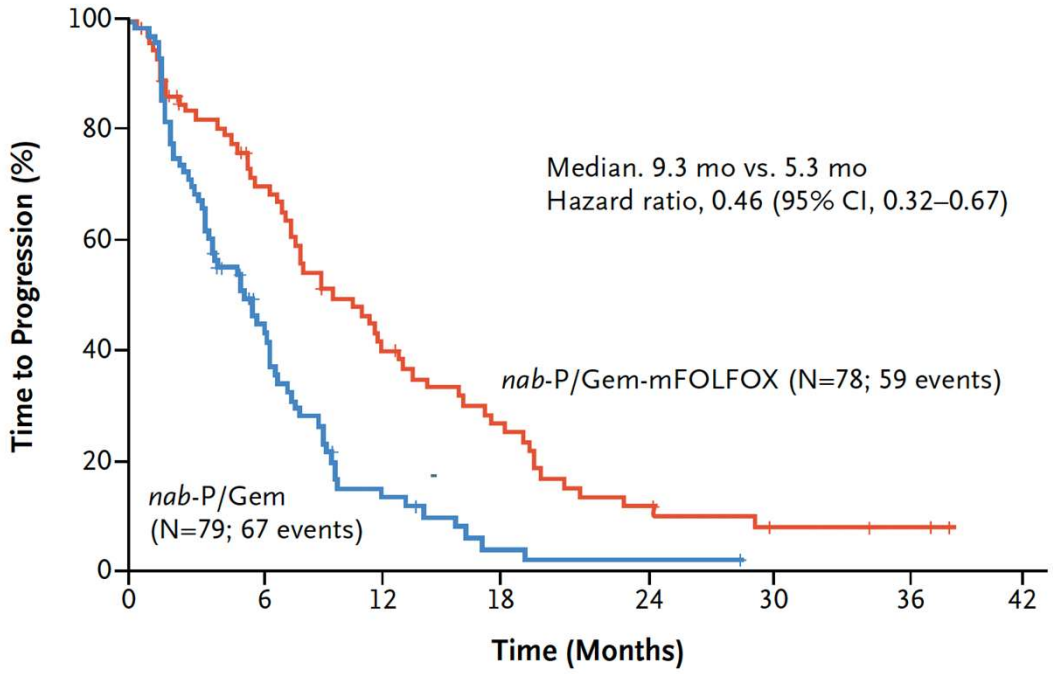
SEQUENCE TRIAL

Best confirmed tumor response

	nab-P/Gem-mFOLFOX (n=78)	*nab*-P/Gem (n=79)	p-value
Best overall tumor response			
Complete response	3 (3·8%)	0 (0·0%)	0·022
Partial response	28 (35·9%)	16 (20·3%)	
Stable disease	31 (39·7%)	38 (48·1%)	
Progressive disease	7 (9·0%)	17 (21·5%)	
Not evaluated	9 (11·5%)	8 (10·1)	
Overall response rate	31 (39·7%) [28·8-51·5%]	16 (20·3%) [12·4-30·8%]	0·009
Disease control rate	62 (79·5%) [68·8-87·8%]	54 (68·4%) [56·9-78·4%]	0·15

SEQUENCE TRIAL

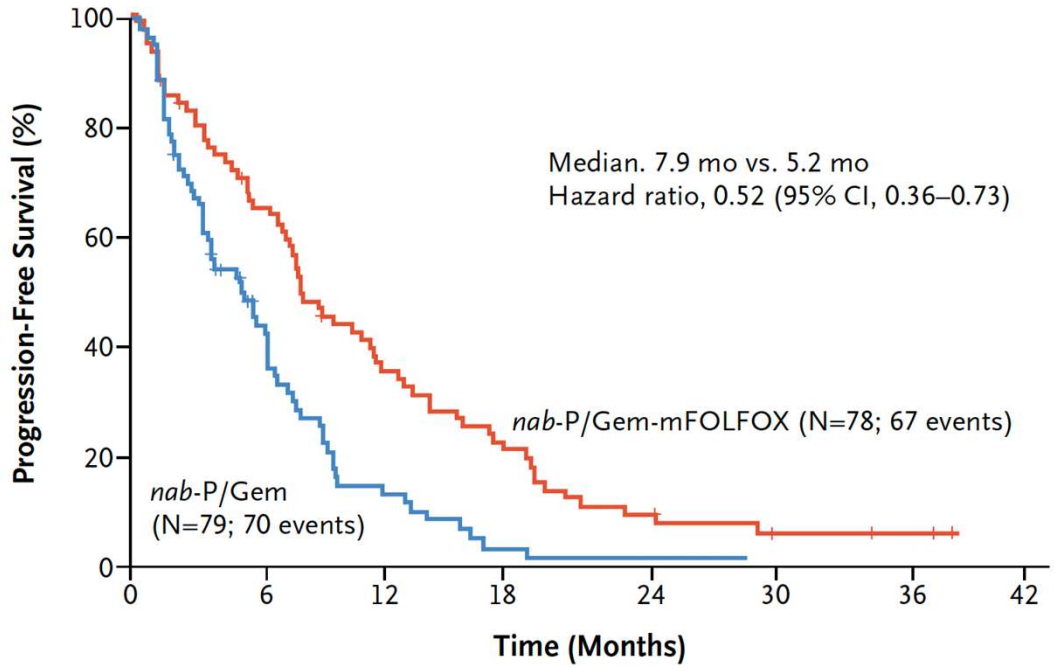
B



No. at Risk							
nab-P/Gem	78	45	25	15	5	3	2
nab-P/Gem-mFOLFOX	79	29	8	2	1	0	0

SEQUENCE TRIAL

C

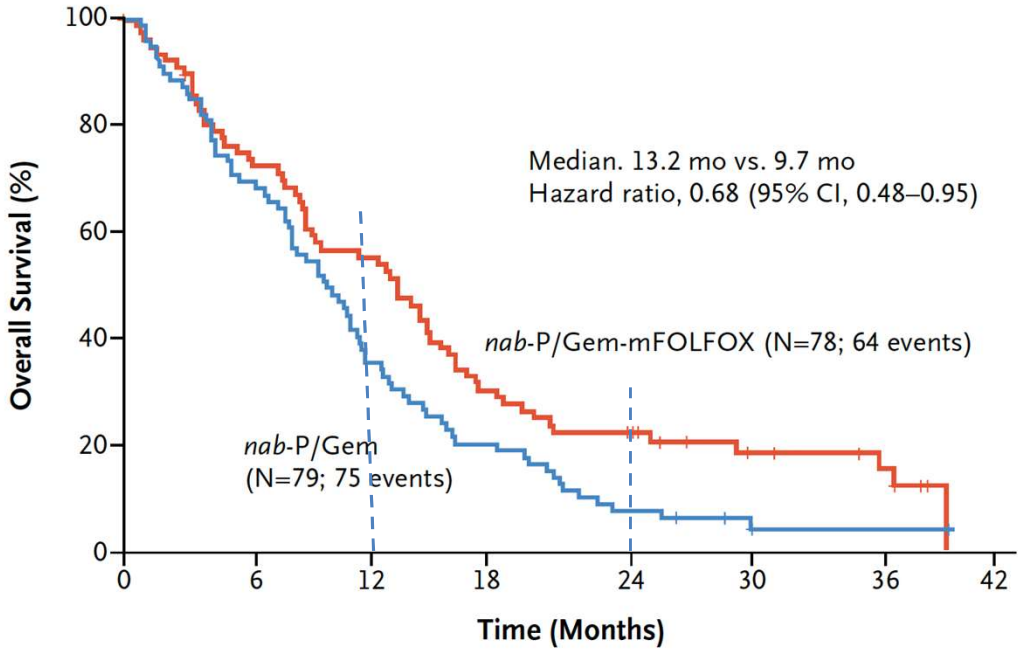


No. at Risk							
nab-P/Gem	78	47	25	15	15	3	2
nab-P/Gem-mFOLFOX	79	29	9	2	1	0	0

SEQUENCE TRIAL

The primary endpoint of **12-month OS** was **55.3%** (95% CI, 44.2 to 66.5) for patients in the nab-P/Gem-mFOLFOX group and **35.4%** (95% CI, 24.9 to 46) for those in the nab-P/Gem group **(p=0.02).**

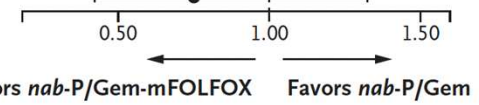
The 24-month OS rates were **22.4%** (95% CI, 13 to 31.8) versus **7.6%** (95% CI, 1.8 to 13.4), respectively



No. at Risk							
nab-P/Gem	78	56	42	22	17	8	5
nab-P/Gem-mFOLFOX	79	55	28	15	6	2	1

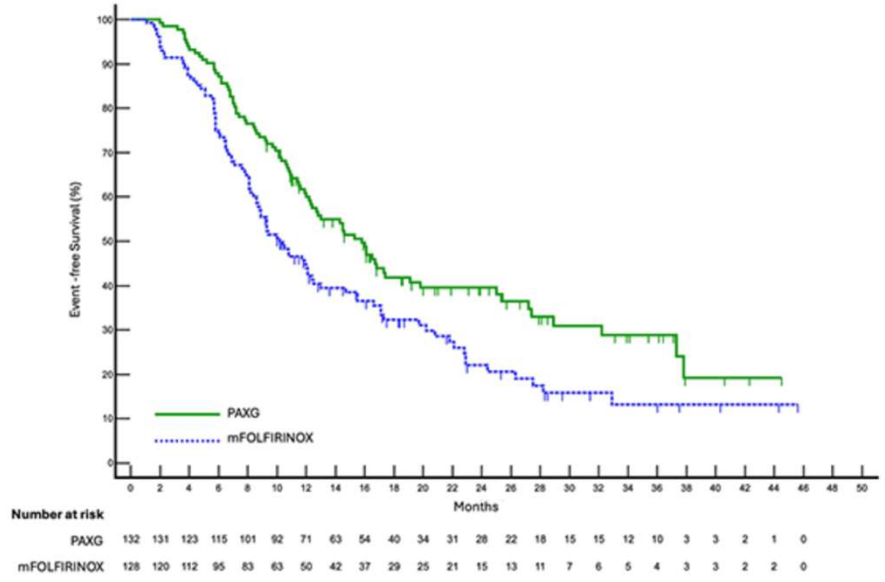
SEQUENCE: Forest plot for overall survival

Subgroup	No. of Patients with Events/Total No. of Patients	Hazard Ratio (95% CI)
Sex		
Male	77/157	0.74 (0.45–1.19)
Female	80/157	0.61 (0.38–0.99)
Age		
Age (≤70 years)	116/157	0.59 (0.40–0.88)
Age (>70 years)	41/157	0.92 (0.48–1.77)
ECOG performance status		
ECOG 0	44/157	0.65 (0.34–1.25)
ECOG 1	113/157	0.68 (0.46–1.01)
Tumor location		
Location of primary tumor: Head of pancreas (Yes)	62/157	0.60 (0.34–1.04)
Location of primary tumor: Other locations: (Yes)	96/157	0.67 (0.44–1.03)
Number of metastatic sites		
2	61/157	0.74 (0.43–1.29)
≥3	91/157	0.73 (0.47–1.14)
Disease state		
Current disease site: Liver (Yes)	119/157	0.63 (0.43–0.93)
Current disease site: Lung (Yes)	47/157	0.80 (0.44–1.48)
CA 19-9 levels		
Normal≤ULN	30/157	0.41 (0.18–0.96)
>ULN* and <59 × ULN	68/157	0.67 (0.39–1.15)
≥59 × ULN	50/157	0.75 (0.43–1.33)



Neoadjuvant PAXG significantly improved EFS compared to mFOLFIRINOX in pts with R/BR PDAC.

Figure. Primary Endpoint: CASSANDRA EFS Results



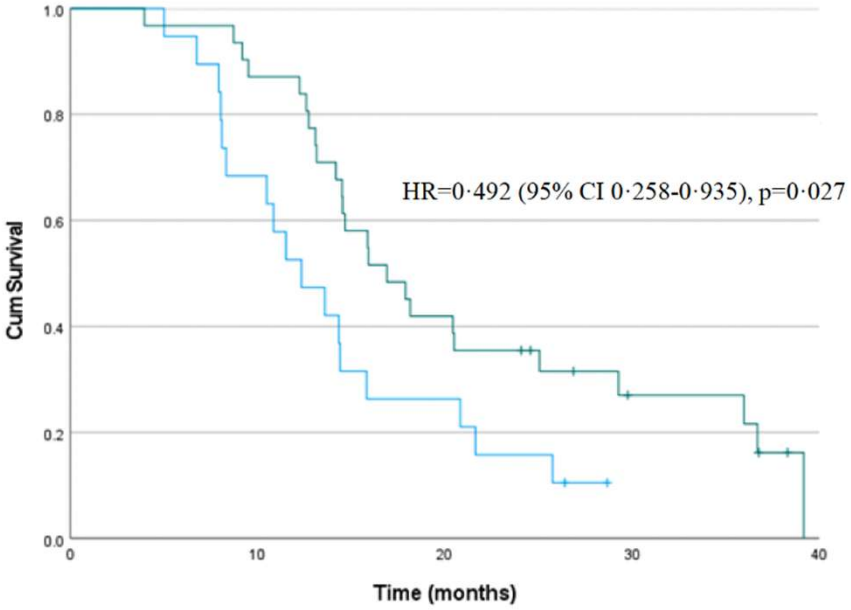
PAXG: oral daily capecitabine 1250 mg/m2 with biweekly cisplatin 30 mg/m2, nab-paclitaxel 150 mg/m2, gemcitabine 800 mg/m2;

At 3 years follow-up, EFS was 31% vs 13%. HR 0.64 (CI 0.48-0.86, p=0.005).

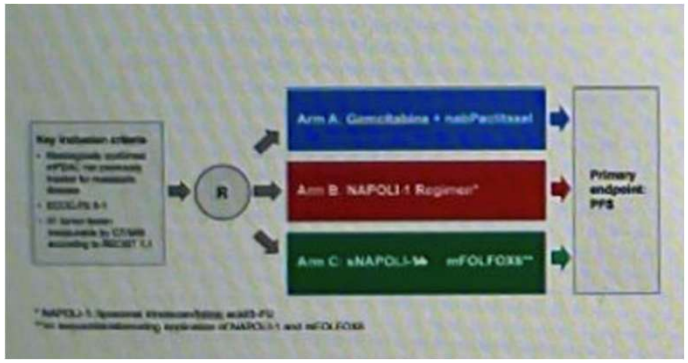
Reni M et al. ASCO 2024 abstract LBA 4004

SEQUENCE TRIAL

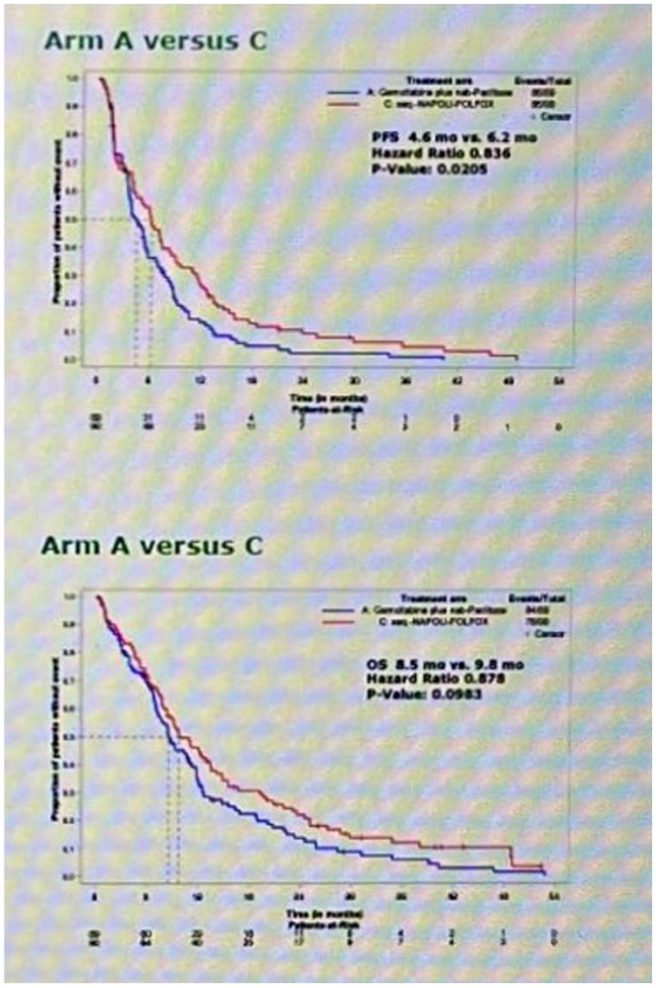
	Events, n	Patients, n	Median overall survival, months (95% CI)
Oxa first line	25	31	16·9 (13·1-20·7)
Oxa subsequent lines	17	19	12·3 (8·4-16·2)



Patients in the nab-P/Gem-mFOLFOX group (which received oxaliplatin in first line with FOLFOX) have a benefit in survival when compared to those patients from the nab-P/Gem that received oxaliplatin-based treatment in subsequent lines (p=0·027).



FOOTPATH TRIAL



Sequential NAPOLI followed by mFOLFOX6 showed a significant improvement in PFS compared to Gem/NabP and a numerically, not significant, longer overall survival.

This regimen may offer an effective treatment option in selected patients with PDAC

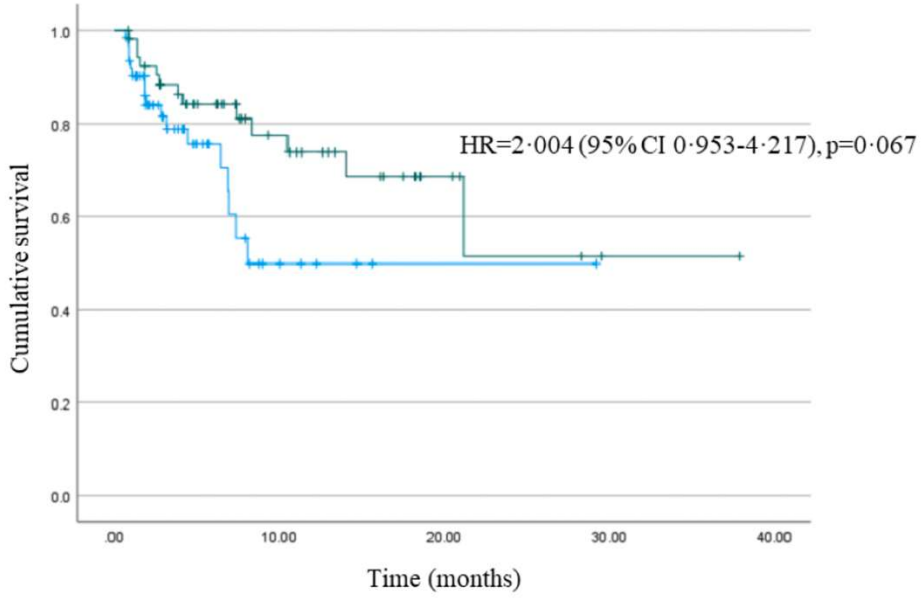
Treatment adverse events

Hematologic events	Grade 3	Grade4
Neutropenia	33 (42)	19 (24)
Thrombocytopenia	27 (34)	6 (8)

- Grade 3 and 4 **neurological** adverse events were similar (18% vs. 16%, p=0.83) in both arms of the study. A previous phase I-II study was performed and published by TTD (EJC).
- **Grade 3 and 4 hematologic toxicity was higher in the experimental arm** (46% vs. 24%, p=0.004), and although the **differences in febrile neutropenia were not significant** (7% vs. 4%, p=0.72), a single patient in the experimental arm died of sepsis with neutropenia.
- **Grade 3 thrombocytopenia was higher in the experimental arm** (24% vs. 8%, p=0.0007), but **no grade 3 or 4 bleeding was reported** in any of the patients in the trial.

SEQUENCE: Time to Quality-of-life deterioration

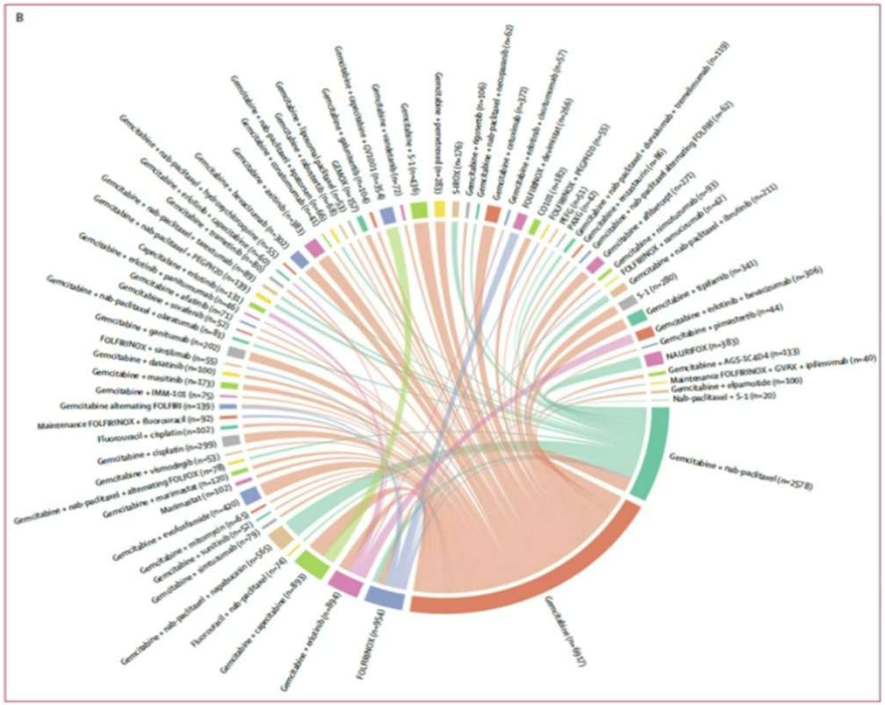
	Events, n	Patients, n	Median time to QoL deterioration, months (95% CI)
nab-P/Gem-mFOLFOX	13	54	NR
nab-P/Gem	17	62	8·1 (NR-NR)



Cox regression analysis showed that a deterioration of more than 10 points (minimal clinically important difference - MCID) was always later in all scale domains.

Figure shows time to deterioration of QoL according to 20-Point MCID for the domain “Global Health Status” in the EORTC QLQ-C30 questionnaire.

First-line chemotherapy: meta-analysis



Comparison of first-line chemotherapy regimens in unresectable locally advanced or metastatic pancreatic cancer: a systematic review and Bayesian network meta-analysis

Luca Mastrantoni, Marta Chiaravalli*, Alexia Spring, Viria Beccia, Armando Di Bello, Cinzia Bagalà, Maria Bensi, Diletta Barone, Giovanni Trovato, Giulia Caira, Giulia Giordano, Emilio Bria, Giampaolo Tortora†, Lisa Salvatore†*

Comparison | PFS | OS

Gemcitabine (PFS=5652, OS=6917 patients)	0·67* (0·59–0·77)	0·66* (0·56–0·78)	0·56† (0·45–0·70)	0·40† (0·25–0·65)	0·46† (0·32–0·66)
0·62* (0·54–0·72)	Gemcitabine plus nab-paclitaxel (PFS=2553, OS=2578 patients)	0·98‡ (0·83–1·16)	0·83§ (0·70–0·98)	0·60* (0·38–0·94)	0·68* (0·48–0·95)
0·55* (0·47–0·65)	0·88‡ (0·75–1·04)	FOLFIRINOX (PFS and OS=954 patients)	0·85‡ (0·66–1·08)	0·61‡ (0·38–0·99)	0·69‡ (0·47–1·01)
0·43* (0·34–0·54)	0·69§ (0·58–0·83)	0·78‡ (0·61–1·00)	NALIRIFOX (PFS and OS=383 patients)	0·72‡ (0·45–1·16)	0·82‡ (0·56–1·20)
0·35† (0·22–0·55)	0·56* (0·36–0·87)	0·63‡ (0·39–1·02)	0·81‡ (0·50–1·30)	PAXG (PFS and OS=42 patients)	1·14‡ (0·65–2·00)
0·32† (0·22–0·47)	0·52* (0·36–0·74)	0·59‡ (0·40–0·87)	0·75‡ (0·51–1·12)	0·93‡ (0·52–1·64)	Gemcitabine plus nab-paclitaxel alternating FOLFOX (PFS and OS=78 patients)

Mastrantoni et al, *Lancet Oncol* 2024

OS (79 trials, 22 104 patients): PAXG (HR 0·40, 95% credible interval 0·25–0·65), **gem plus nab-paclitaxel alternating FOLFOX (0·46, 0·32–0·66),** and NALIRIFOX (0·56, 0·45–0·70**) had the highest benefit**, followed by FOLFIRINOX (0·66, 0·56–0·78) and gem plus nab-paclitaxel (0·67, 0·59–0·77).

SEQUENCE TRIAL STATISTICS

Cualquier **estudio fase III**, con HR de 0,5, y con potencia de 80%, tomando como referencia los 9.7 meses del grupo control, se necesitarían 66 eventos y un tamaño de 90 pacientes totales.

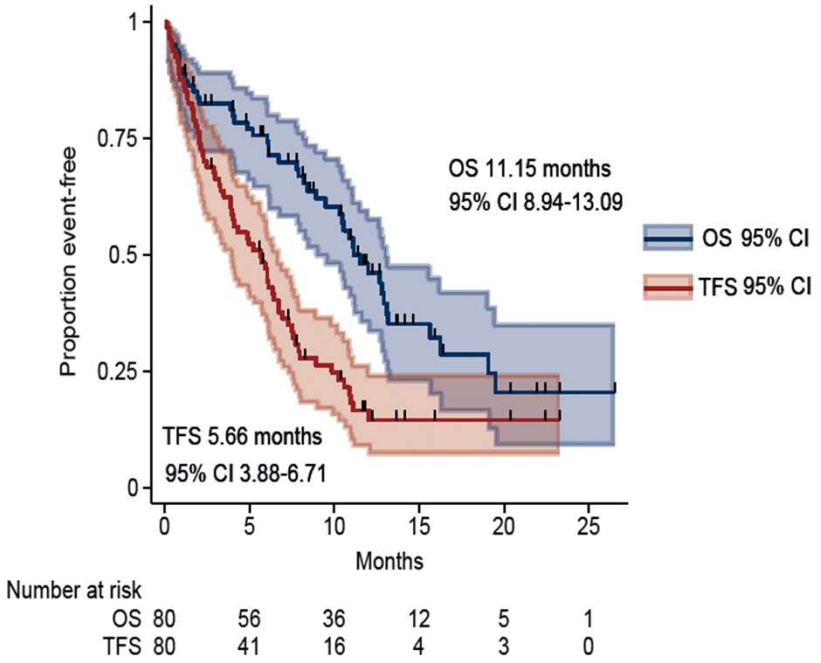
SEQUENCE:
TTP con medianas de 5,3 vs 9,3 meses, HR=0,42, la potencia fue alta, de 0,88.
DFS mostró medianas de 5,2 y 7,9 meses, HR=0,52. La potencia fue del 68%. Para que estos mismos resultados tuvieran una potencia de un 80% necesitaríamos 168 eventos y unos 200 pacientes totales.
OS con medianas de 9,7 vs 13,2 meses, HR=0,68. La potencia fue del 44%. Para una potencia de un 80% necesitaríamos 331 eventos y cerca de 400 pacientes totales.

Probabilidad de que se repitiesen los mismos resultados de OS en un Fase III con:
a. El mismo número de eventos 126 (igual que este ensayo fase II) es de un **57.3%**
b. Si duplicamos el número de eventos:| 252 (≈2×), sería de un **75.2%**

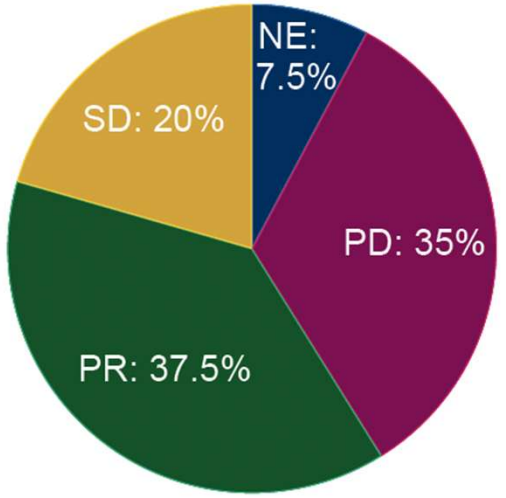
La recogida de datos en la vida real es la mejor opción para poder corroborar estos resultados

ORIGINAL ARTICLE

NALIRIFOX in the treatment of metastatic pancreatic ductal adenocarcinoma: an exploratory analysis of real-world data



B



Reichinger A et al. ESMO Open 2025;10 (10

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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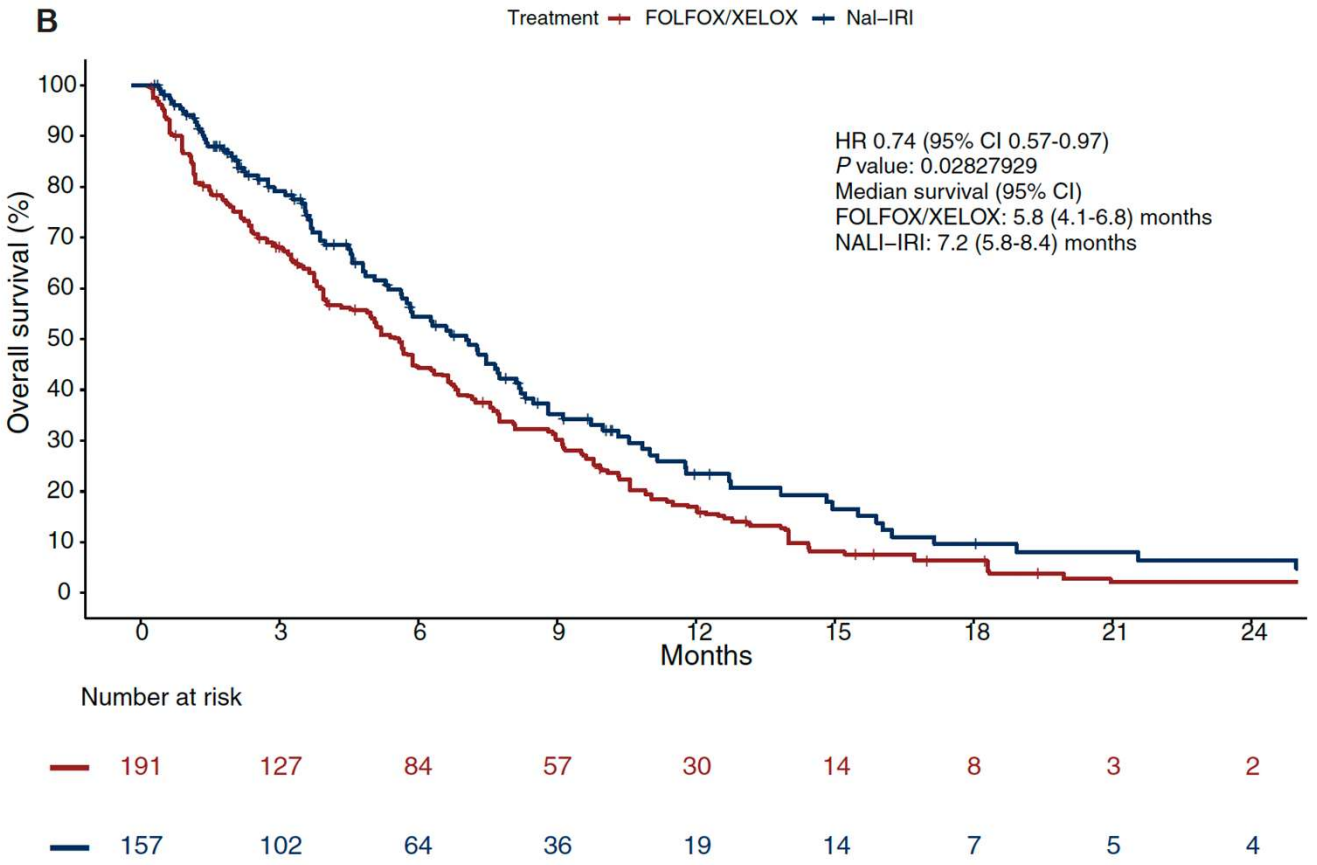
ORIGINAL ARTICLE

Second-line 5-FU plus nanoliposomal irinotecan versus FOLFOX/XELOX in metastatic pancreatic cancer after gemcitabine–nab-paclitaxel failure: a propensity score-matched analysis

G. Trovato[1,2*], D. Rossini[3,4], A. Guidolin[3,4], Y.-Y. Su[5,6,7], Y.-S. Shan[8], N.-J. Chiang[9,10], W.-C. Chou[11,12], L.-Y. Bai[13,14], C. Bagalà[1], M. Bensi[1], M. Niger[15], S. Marchesi[15], S. K. Garattini[16], A. Michelotti[16], A. Pretta[17], M. Scartozzi[17], C. Vivaldi[18,19], L. Bartalini[18,19], L. Procaccio[20], F. Bergamo[20], L. Antonuzzo[3,4], L.-T. Chen[5,6,7], L. Salvatore[1,2] & G. Tortora[1,2]



SEQUENCE was the first **randomised phase II trial** to compare the metastatic PDAC first-line treatment efficacy of **nab-P/Gem-mFOLFOX**, targeting sequentially both subtypes of mPDAC, with the standard control arm nab-P/Gem

The **efficacy** of **nab-P/Gem - FOLFOX** was **significantly greater** than nab-P/Gem in all terms: overall response, TTP, PFS, and overall survival.

The **safety** profile was comparable except for a higher occurrence of grade ≥3 neutropenia and grade ≥3 thrombocytopenia

Time to deterioration of QoL was significantly later in all domains

The whole patient's group of **75 years old or less** (135 patients out of 157) do also significantly benefit in overall survival with this regimen.

¡¡Muchas gracias!!

acarrato@telefonica.net