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

¿Cómo optimizar las líneas de tratamiento en cáncer de páncreas avanzado o metastásico?

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Oviedo, 11 diciembre 2025

TTD

My COIs in the last 5 years

Consultant or advisory role

- GSK, Pfizer, BMS-Celgene, Sanofi, Astra-Zeneca, MSD, Lilly, Servier, Roche, Taiho, Leo Pharma, Regeneron, Jazz Pharmaceuticals.

Research funding

- Leo Pharma.

Speakers' bureau:

- Rovi, Menarini, Stada, Medscape, Incyte.

Patents, Royalties, Other Intellectual Property:

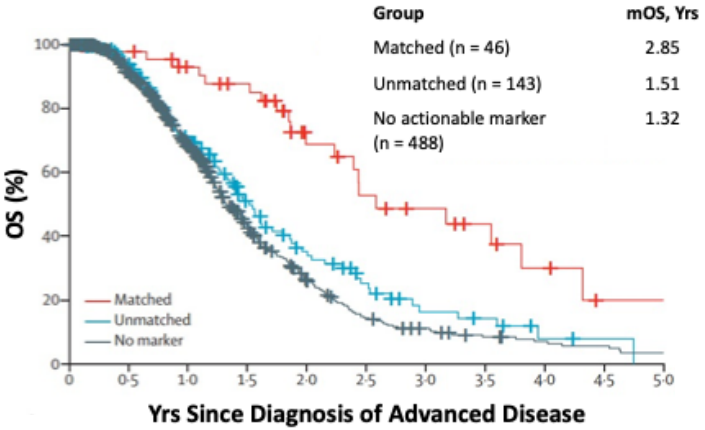
- Risk assessment model in venous thromboembolism in cancer patients (genomic risk score).
- Liquid biopsy developed with Laser technology.

Algunos hechos 2025

- PDAC SG 5 años 13%, 3ª causa de muerte por cáncer en países occidentales y España
- Aunque NO es suficiente:
  - Se ha aumentado la supervivencia global y libre de progresión
  - Se han observado “largos supervivientes” (>5 años) y analizando cirugía de mtx (ALIPANC/CNIO)
  - Se ha triplicado la tasa de respuestas.
  - Se ha consolidado la 2ª línea y 3ª línea (ensayos clínicos aleatorizados PANCRIT-1)
  - Se han introducido nuevos conceptos terapéuticos:
    - **SECUENCIACIÓN TERAPEÚTICA**
    - **MEDICINA PERSONALIZADA**
    - **TERAPIA DE MANTENIMIENTO**

Gold Standard: Overall Survival Benefit

- 1028 pancreatic cancer patients
  - All underwent molecular profiling w/NGS
- 677 patients with outcome information
  - 189 with actionable findings
    - 46 received molecularly matched therapy
    - 143 received "unmatched" therapy
  - 488 with no actionable findings
- Overall survival
  - Matched 1 y > unmatched
  - Matched 1.3 y > no actionable marker

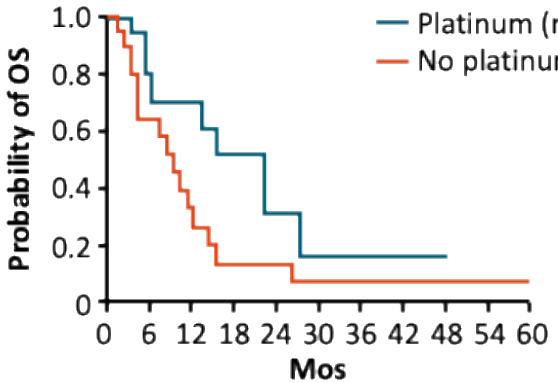


Comparison	HR (95% CI)
Matched vs unmatched (highly actionable)	0.42 (0.26-0.68); *P* = .0004
Matched vs no actionable marker	0.34 (0.22-0.53); *P* < .0001

Pishvaian. Lancet Oncol. 2020;21:508.

BRCA-mutated Pancreatic Cancer

- Germline *BRCA1/2* mutations found in ~ 7% of patients with pancreatic cancer; additional mutations in other DDR genes (eg, *PALB2*, *ATM*)
- Superior OS (22 vs 9 mos; *P* = .039) for patients with *BRCA1/2* mutations and stage 3/4 disease treated with platinum vs non-platinum chemotherapy regimens[1]



- Activity of PARP inhibitors (eg, olaparib) in patients with BRCA mutations; several ongoing/early phase trials
  - PARP inhibitors impair BER, inhibit SSBR/DSBR
  - Phase II study of olaparib for patients with germline *BRCA 1/2* mutation and prior gemcitabine: ORR in 5 of 23 (21.7%) patients[2]

81.7% family history of cancer

1. Golan. Br J Cancer. 2014;111:1132. 2. Kaufman. JCO. 2015;33:244.

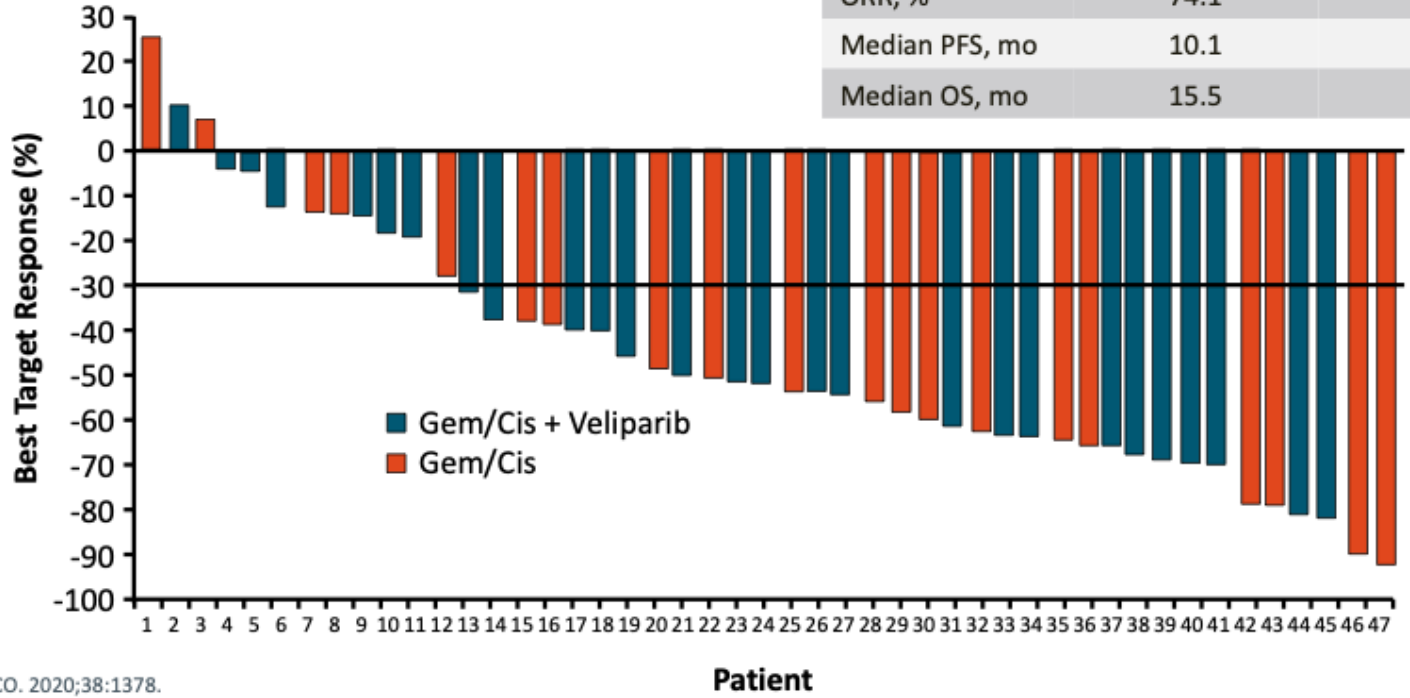
Patient characteristics

		Olaparib (N=92)	Placebo (N=62)
Time from diagnosis to randomization	Median, months (range)	6.9 (3.6–38.4)	7.0 (4.1–30.2)
Duration of first-line chemotherapy	Median, months (range) 16 weeks to 6 months, n (%) >6 months, n (%)	5.0 (2.5–35.2) 61 (66.3) 30 (32.6)	5.1 (3.4–20.4) 40 (64.5) 21 (33.9)
First-line platinum-based chemotherapy, n (%)	FOLFIRINOX variants Gemcitabine/cisplatin Other	79 (85.9) 2 (2.2) 10 (10.9)	50 (80.6) 3 (4.8) 8 (12.9)
Best response on first-line chemotherapy, n (%)	Complete or partial response Stable disease	46 (50.0) 45 (48.9)	30 (48.4) 31 (50.0)
Disease status following platinum-based chemotherapy, n (%)	Measurable Non-measurable or no evidence of disease	78 (84.8) 13 (14.1)	52 (83.9) 6 (9.7)
Site of metastases prior to chemotherapy, n (%)*	Liver Lung Peritoneum Other	61 (66.3) 10 (10.9) 10 (10.9) 14 (15.2)	48 (77.4) 5 (8.1) 5 (8.1) 8 (12.9)

*Patients may be counted in more than one category

Randomized Phase II Trial of Gem/Cis ± Veliparib in Pancreatic Cancer w/Germline *BRCA/PALB2* Mutation

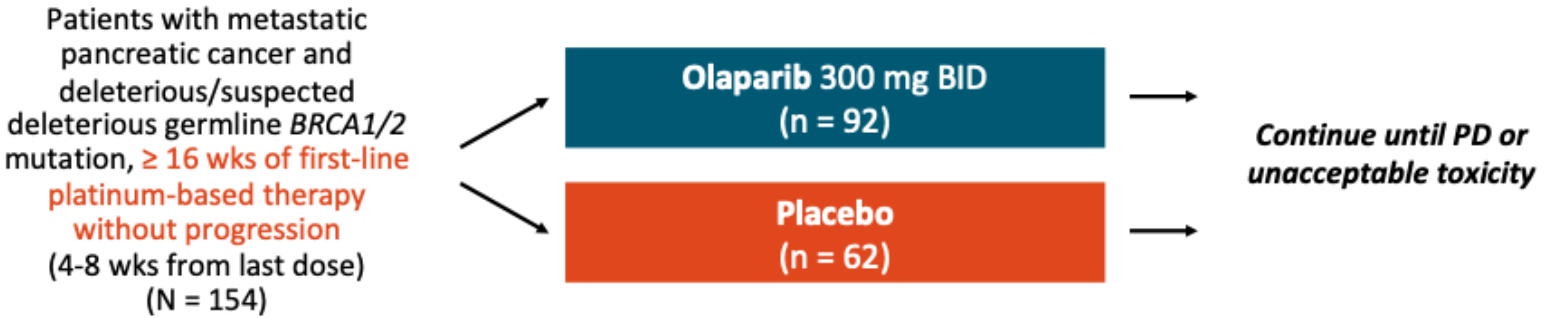
	Gem/Cis + PARPi	Gem/Cis
ORR, %	74.1	65.2
Median PFS, mo	10.1	9.7
Median OS, mo	15.5	16.4



O'Reilly. JCO. 2020;38:1378.

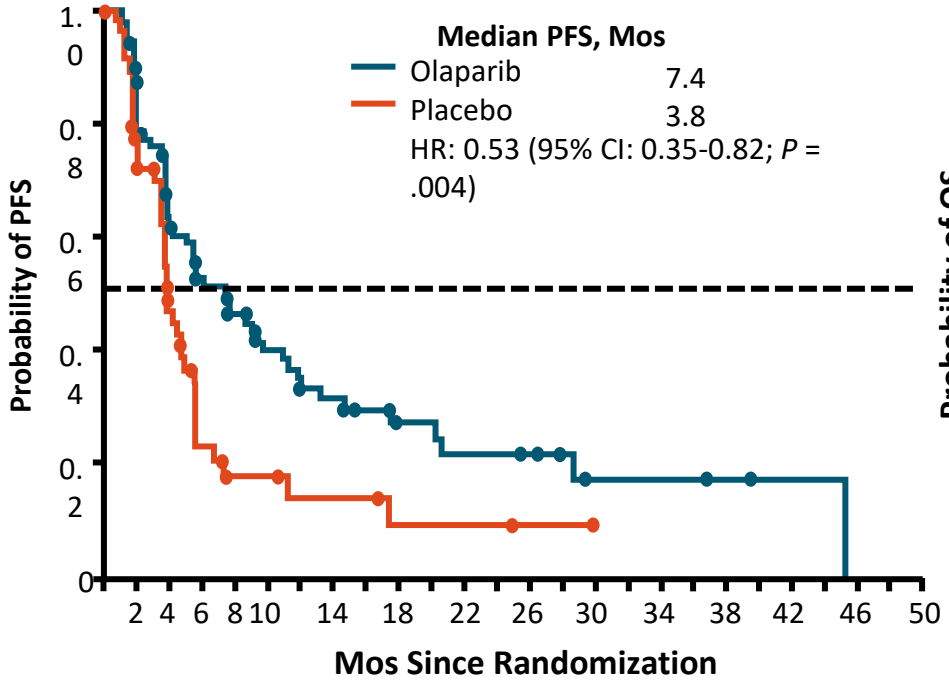
Maintenance Therapy in Advanced Pancreatic Cancer: POLO trial

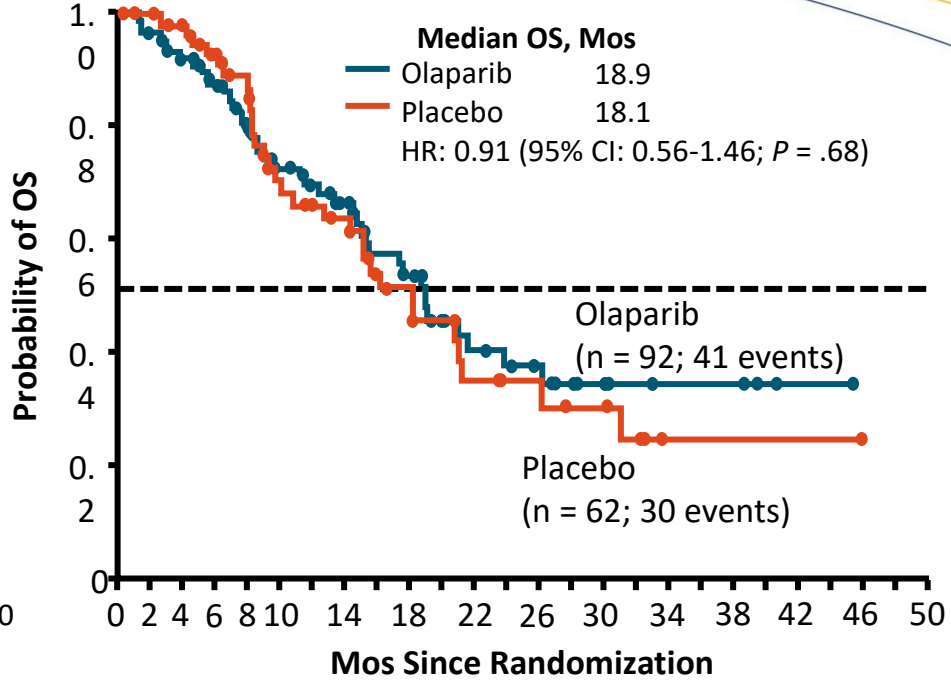
- Rationale for use of PARP inhibitors in HRD-associated cancers: Synthetic lethality
- Phase II trial of olaparib (PARP inhibitor) in patients with germline *BRCA1/2* mutations and advanced solid tumors[1]
  - ORR: 5 of 23 (21.7%) patients with pancreatic cancer
- **POLO-1: International, randomized, double-blind phase III trial[2]**



1. Kaufman. J Clin Oncol. 2015;33:244. 2. Golan. NEJM. 2019;381:317.

POLO: PFS and OS



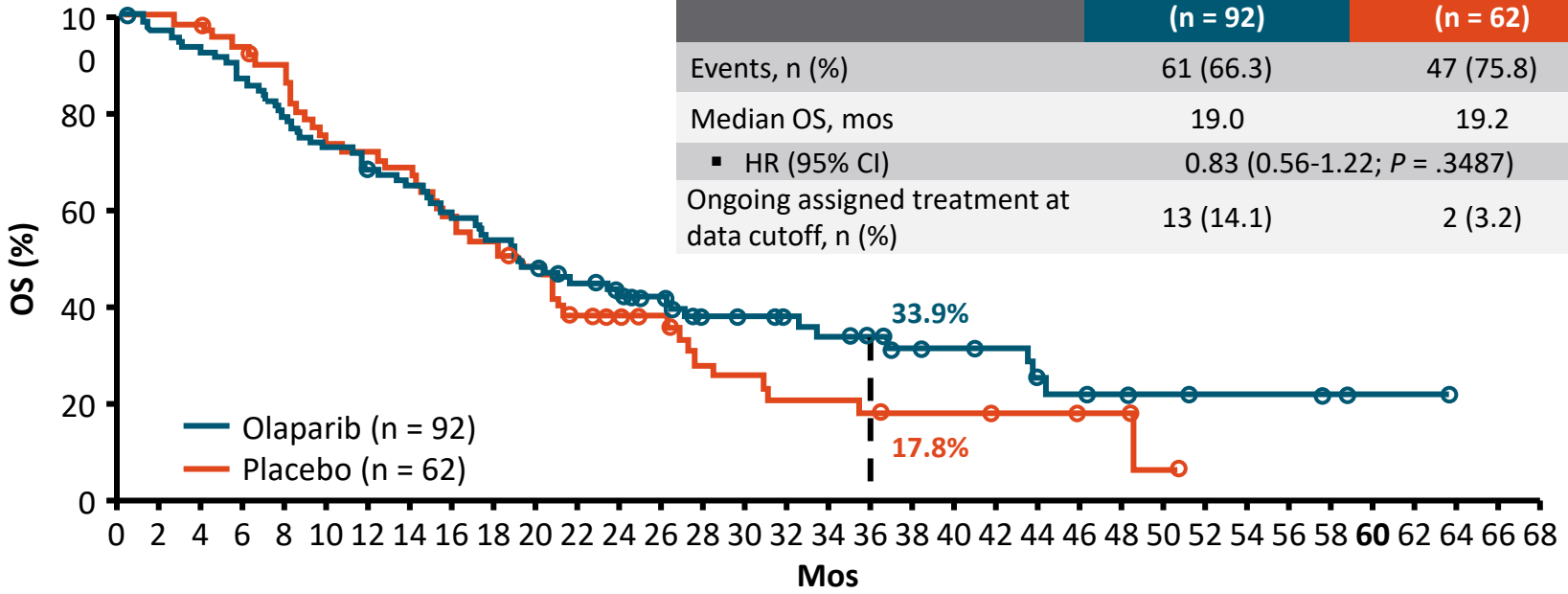


3315 patients screened to identify 154 eligible patients

POLO: Final OS (secondary endpoint)

27% received PARPi after progression

	Olaparib (n = 92)	Placebo (n = 62)
Events, n (%)	61 (66.3)	47 (75.8)
Median OS, mos	19.0	19.2
▪ HR (95% CI)	0.83 (0.56-1.22; *P* = .3487)	
Ongoing assigned treatment at data cutoff, n (%)	13 (14.1)	2 (3.2)



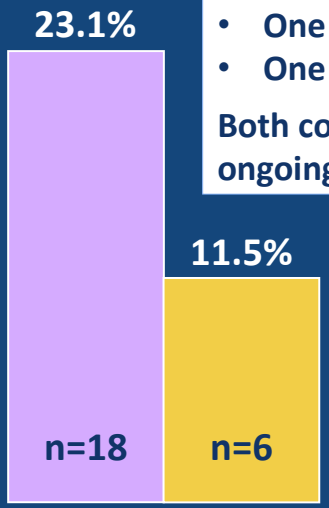
Objective response* in patients with measurable disease by blinded independent central review

Two olaparib arm patients had a complete response to olaparib

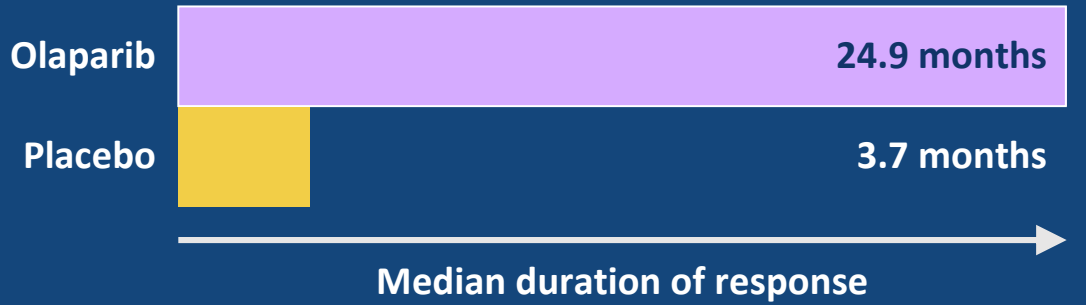
Following first-line chemotherapy:

- One had a partial response
- One had stable disease

Both complete responses were ongoing at the data cut-off†



RR x2



Kindler HL et al. *Proc ASCO* 2019;Abstract LBA4.

*By modified RECIST v1.1. †January 15, 2019

ORIGINAL ARTICLE

Patient-centered outcomes in the POLO study of active-maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer

Hedy L. Kindler MD[1] | Hyun Kyoo Yoo MPH[2] | Robert Hettle MMath[2] | Karen Y. Cui MD, PhD[3] | Seongjung Joo PhD[4] | Gershon Y. Locker MD[3] | Talia Golan MD[5]

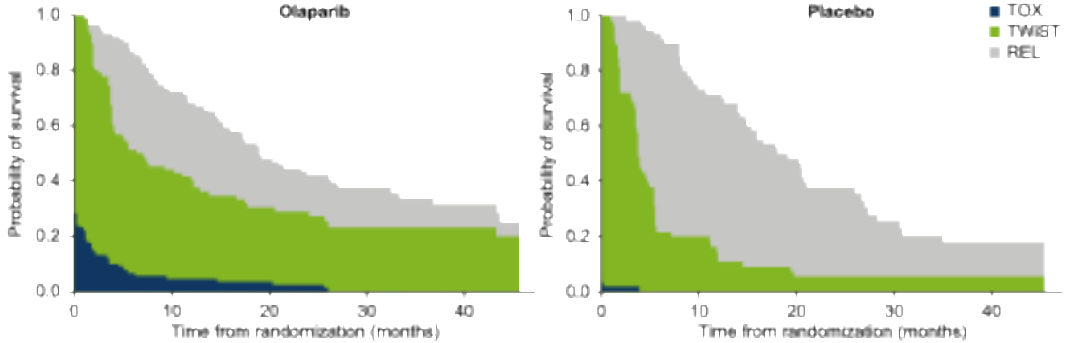


TABLE 2 Restricted mean duration of TWiST, TOX, REL, and Q-TWiST for base-case and sensitivity analyses

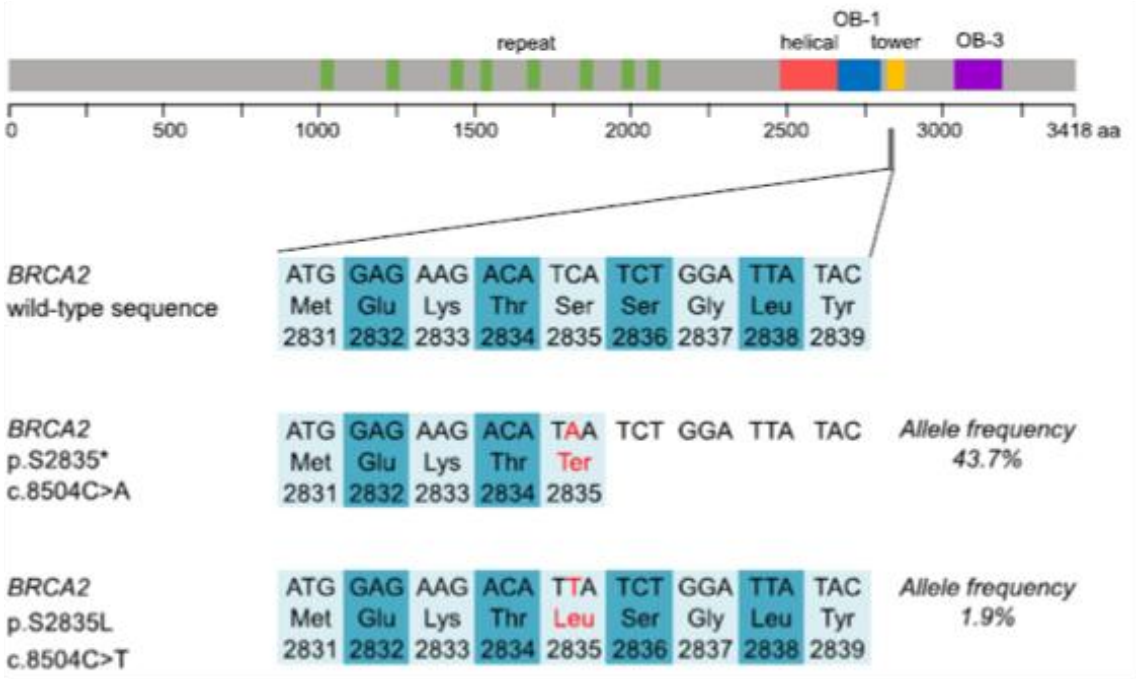
	Base-case analysis[a]			Sensitivity analysis 1[b]		
	Olaparib mean (95% CI)	Placebo mean (95% CI)	Difference (95% CI), *p*	Olaparib mean (95% CI)	Placebo mean (95% CI)	Difference (95% CI), *p*
TWiST	14.6 (10.7–18.5)	7.1 (4.6–9.7)	7.4 (2.9–12.0), .001	14.1 (10.4–17.7)	7.0 (4.5–9.6)	7.0 (2.7–11.3), .001
TOX	1.5 (0.5–2.6)	0.1 (0.0–0.2)[e]	1.5 (0.5–2.5), .005	2.1 (1.0–3.1)	0.2 (0.0–0.4)[e]	1.9 (0.8–3.0), <.001
REL	8.0 (5.6–10.5)	14.7 (11.9–17.4)	−6.7 (−10.4 to −2.9), <.001	8.0 (5.6–10.5)	14.7 (12.0–17.4)	−6.7 (−10.5 to −2.8), .001
Q-TWiST	18.4 (15.8–21.0)	15.9 (13.3–18.4)	2.5 (−1.1 to 6.1), .171	18.4 (15.8–21.0)	15.9 (13.2–18.5)	2.5 (−1.1 to 6.1), .177
	Sensitivity analysis 2[c]			Sensitivity analysis 3[d]		
	Olaparib mean (95% CI)	Placebo mean (95% CI)	Difference (95% CI), *p*	Olaparib mean (95% CI)	Placebo mean (95% CI)	Difference (95% CI), *p*
TWiST	9.9 (6.7–13.2)	4.8 (3.4–6.2)	5.1 (1.5–8.7), .005	14.0 (10.1–17.8)	6.5 (4.2–8.8)	7.5 (3.0–12.0), .001
TOX	6.2 (4.1–8.3)	2.4 (0.7–4.1)	3.8 (1.0–6.6), .007	2.2 (1.0–3.4)	0.7 (0.0–1.8)[e]	1.4 (−0.1 to 3.0), .065
REL	8.0 (5.6–10.5)	14.7 (11.8–17.6)	−6.7 (−10.5 to −2.8), .001	8.0 (5.6–10.4)	14.7 (11.9–17.5)	−6.7 (−10.4 to −2.9), <.001
Q-TWiST	18.4 (15.6–21.1)	15.9 (13.2–18.6)	2.5 (−1.4 to 6.4), .206	18.4 (15.6–21.2)	15.9 (13.2–18.5)	2.5 (−1.4 to 6.4), .209

Mediana de TWiST 14,6 meses vs 7,1 meses (p = 0,001)

Mutaciones de resistencia

Matsumoto et al. Pancreas 2020

BRCA2 Reversion Mutation Identified by Liquid Biopsy After Durable Response to FOLFIRINOX in BRCA2-Associated Pancreatic Cancer

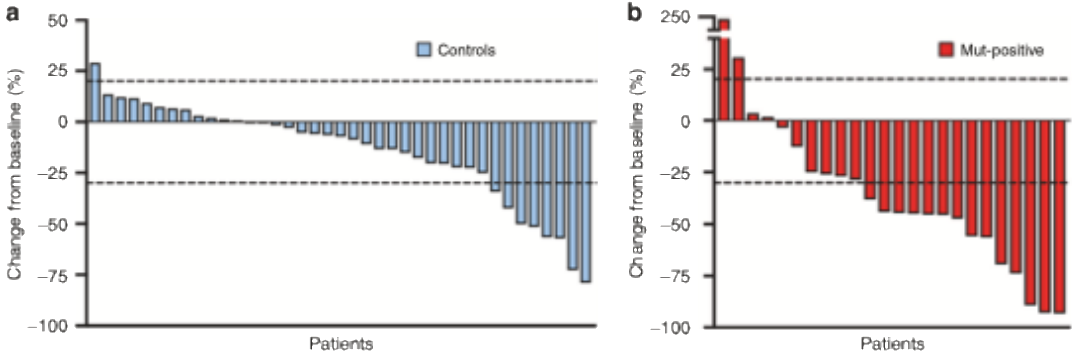


Watenberg et al. BJC 2020: gBRCA/PALB2 vs Control

gPALB2 beneficio similar

Table 3. Summary of efficacy measures

Outcome	Controls ($N = 52$)	Mut-positive ($N = 26$)	*P*-value
Overall survival (mo) **OS**			0.0467
Median	18.8	24.6	–
Real-world progression free survival (mo) **PFS**			0.0068
Median	6.9	10.1	–
Overall response rate—no. (%)[a]	8 (21)	14 (58)	0.0022
Complete response	1	0	–
Partial response	7	14	–
Stable disease	24	5	–
Progressive disease	7	5	–
Disease control rate—no. (%)[b]	42 (81)	21 (81)	> 0.99
Overall response rate by regimen - no. with response/ no. evaluable (%)[a]		–	
FOLFIRINOX	8/29 (28)	6/10 (60)	–
FOLFOX	0 (0)	4/8 (50)	–
Gemcitabine cisplatin	0 (0)	4/6 (67)	–



- **ORR mut-positive 58% vs. 21%** in control group (p = 0.0022)
- **There was no significant difference in ORR between platinum regimens in mut-positive patients** (p = 0.814)
- In control patients, the only observed responses were to FOLFIRINOX.

Table 4. Efficacy Measures Stratified by Line of Therapy

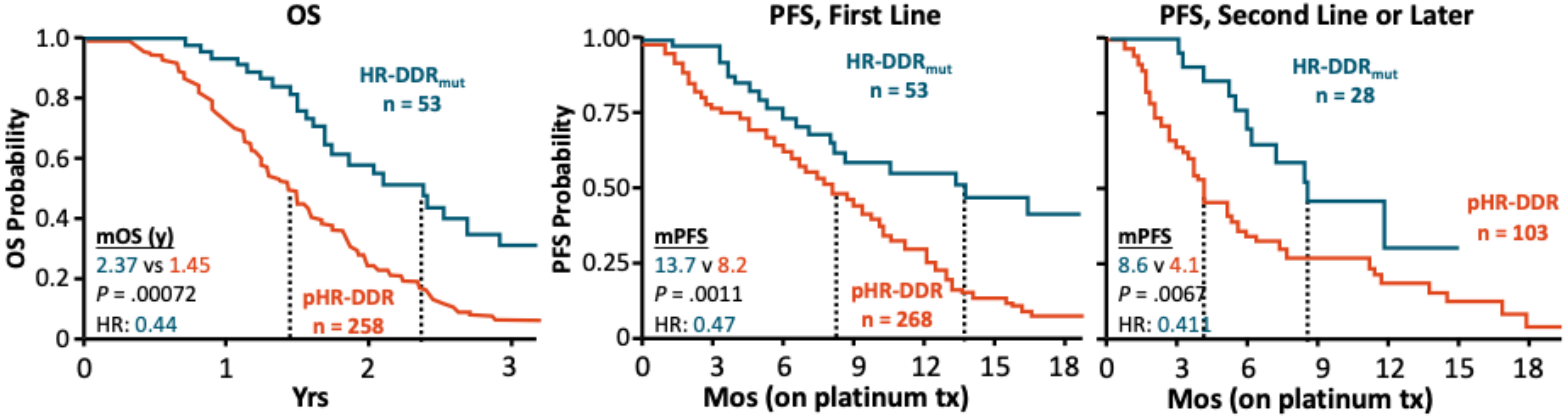
Outcome	Controls ($N = 52$)	Mut-positive ($N = 26$)	*P*-value
Real-world progression free survival by line of therapy (mo) **PFS**			
First	7.9	21.1	0.0046
Second or later	3.4	2.5	0.43
Overall response rate by line of therapy—no. with response/no. evaluable (%)			
First	8/28 (29)	13/19 (68)	0.007
Second or later	0/11 (0)	1/5 (20)	0.12

A subset analysis to compare ORR and rwPFS by line of therapy in which platinum-based treatment was initiated was performed

HRD-Associated Pancreatic Cancer: Survival with Platinum-Based Treatment

g/sBRCA & combo DDR
(ATM/ATR/ATRX/BAP1, BARD1, BRIP1, CHEK1/2, RAD50/51/51/FANCA)

- HRD-associated pancreatic cancer: up to 20% of cases. Pathogenic mutations of somatic or germline origin in *BRCA1/2* or *PALB2* (group 1); *ATM/ATR/ATRX* (group 2); or *BAP1, BARD1, BRIP1, CHEK1/2, RAD50/51/51B,* or *FANCA/C/D2/E/F/G/L*
- Multiple lines of evidence support **platinum-based** therapies in patients with HR-deficient PDAC (improved ORR, PFS, and/or OS)



1. Golan. Br J Cancer. 2014;111:1132. 2. Pishvaian. JCO Precis Oncol. 2019;Oct 23:doi.org/10.1200/PO.10.001 15.
3. Wattenberg. Br J Cancer. 2020;122:333. 4. Park. Clin Cancer Res. 2020;26:3239.

The Oncologist, 2023, **28**, 691–698
https://doi.org/10.1093/oncolo/oyad178
Advance access publication 24 June 2023
Original Article

OXFORD

A Novel HRD Signature Is Predictive of FOLFIRINOX Benefit in Metastatic Pancreatic Cancer

Kuei-Ting Chen[1], Russell Madison[1], Jay Moore[1], Dexter Jin[1], Zoe Fleischmann[1], Justin Newberg[1], Alexa Schrock[1], Neeru Bhardwaj[1], Katherine T. Lofgren[1], Jie He[1], Garrett Frampton[1], Priti Hegde[1], David Fabrizio[1], Michael J. Pishvaian[2], Ericka Ebot[1], Aatur Singhi[1,3], Ethan Sokol[1,3]

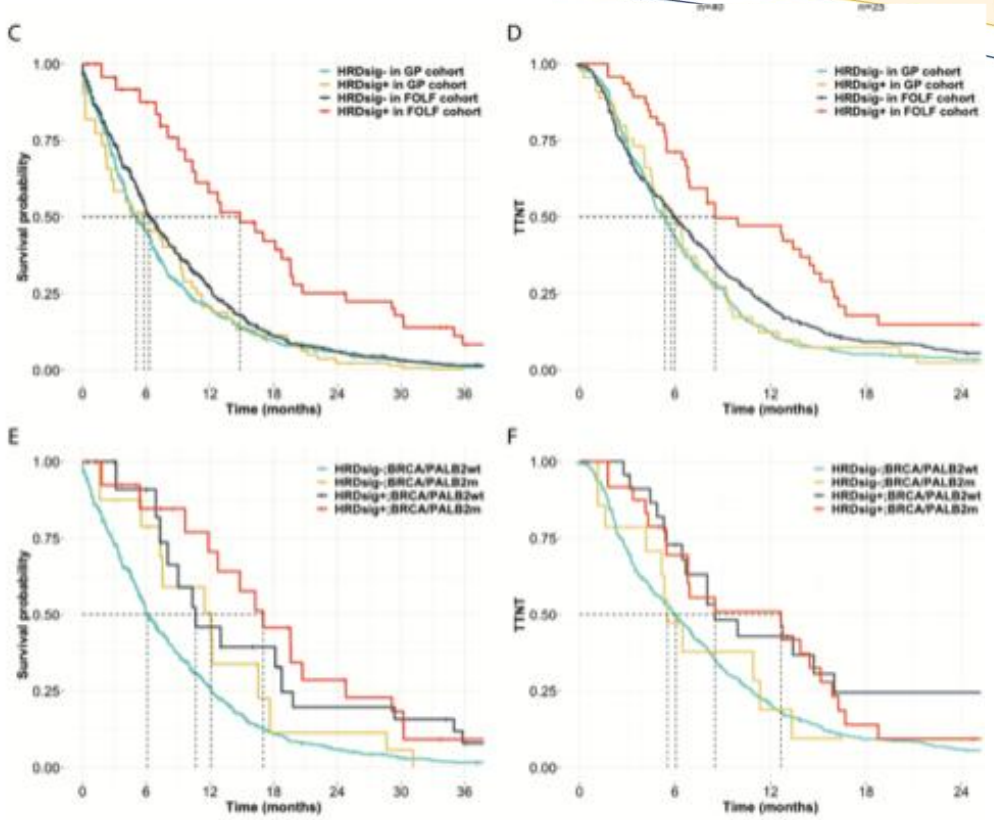


Figure 3. HRDsig is associated with FOLFIRINOX benefit in a clinical cohort. (**A**) Overlap of HRDsig with mutations in *BRCA1/2* or *PALB2* in the CGDB cohort. (**B**) Allelic status for *BRCA1/2*/*PALB2* mutant samples based on overlap with HRDsig. Kaplan-Meier plots for rwOS (**C**) and TTNT (**D**) in HRDsig(+) and HRDsig(−) patients treated with FOLFIRINOX or GP. rwOS (**E**) and TTNT (**F**) for FOLFIRINOX or GP-treated patients based on HRDsig and *BRCA1/2*/*PALB2* mutation status.

Otros biomarcadores 2ª línea

Tabla 1. Otros biomarcadores en cáncer de páncreas.

Biomarcadores	Fármaco	Contexto clínico
KRAS G12C	Sotorasib, adagrasib	1-2% mutaciones en KRAS en cáncer de páncreas. Segunda línea y posterio-res. Tasa de repuestas: 21-33%. SLP: 4-5 meses. SG: 7-8 meses.
Fusión NRG1	Zenocutuzumab	<1% cáncer de páncreas. Segunda línea y posteriores. Tasa de respuesta 42%. Mediana de duración de respuesta 7 meses.
MSI high	Pembrolizumab	1% cáncer de páncreas. Tasa de respuesta segunda línea y posteriores: 18% (ensayo clínico KEYNOTE-158). Duración de respuesta prolongada. Tumores quimiorrefractarios, valorar en primera línea.
Fusión NTRK	Larotrectinib, entrectinib, y repotrectinib.	<1% cáncer de páncreas. Alta tasa de respuestas 50-75%, con duración de respuesta prolongadas. Se sugiere valorar en primera línea por duración de respuesta y buen perfil de toxicidad. En pacientes que progresan a tratamiento inicial con un inhibidor de NTRK se sugiere realizar perfil molecular para eval uar mutaciones de resistencia.
Fusiones en RET	Selpercatinib	<1% cáncer de páncreas. Tasa de respuesta en pacientes previamente tratados 54%, con respuestas duraderas. Se sugiere valorar en primera línea por dura-ción de respuesta prolongada y buen perfil de toxicidad.
Mutaciones BRAF V600E	Dabrafenib más trametinib	Eficacia modesta en cáncer de páncreas previamente tratado, aceptable perfil de toxicidad.
HER-2 positivo	Trastuzumab-deruxtecán	Aprobación agnóstica en HER por inmunohistoquímica 3+ en pacientes previa-mente tratados.

Clasificación molecular

Patrones transcriptómicos

Muñoz TTD ponencias 2025

Tabla 2. Subtipos moleculares classical y basal-like.

	Classical	Basal-like
Histología	Glandular bien diferenciada, arquitectura ductal preservada	Pobremente diferenciada, células escamosas o con fenotipo basal, necrosis frecuente
Biología molecular	Genes epiteliales y de diferenciación pancreática: GATA6, HNF1A, HNF4A, MUC1, PDX1, FOXA2. Alta expresión de GATA6 y programas de diferenciación epitelial → dependencia de vías KRAS-MAPK	Genes de queratinización, EMT y plasticidad: KRT5, KRT6, TP63ΔN, S100A2, lamininas, integrinas Supresión de GATA6, activación de programas MYC, TGFβ y EMT → fenotipo invasivo, quimiorresistente
Esquema de quimioterapia preferencia	Considerar mFFX o FFX	Considerar gemcitabina más nab-paclitaxel, quimiorre-fractariedad a esquemas intensivos basados en 5-FU
Pronóstico	Mejor pronóstico	Peor pronóstico

La determinación de GATA6 por hibridación in situ de RNA o por inmunohistoquímica (método rápido, coste-efectivo y fácilmente disponible en práctica clínica) se correlaciona favorablemente con el subtipo molecular mediante RNA-seq (85-90%).

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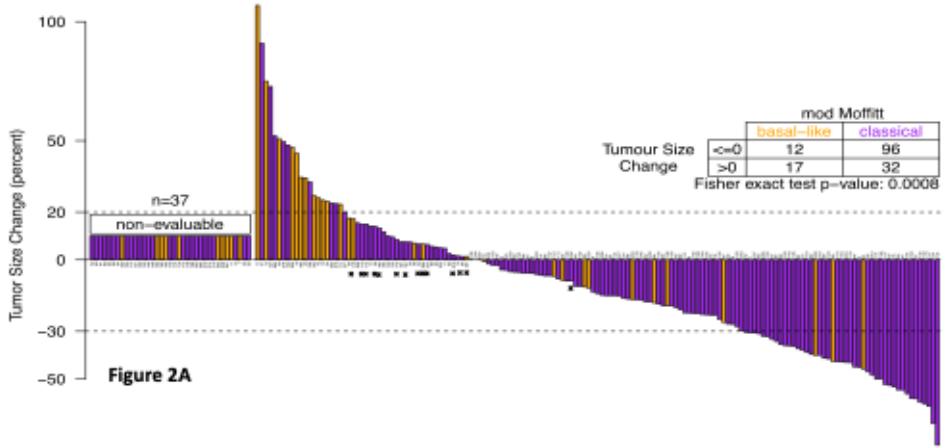
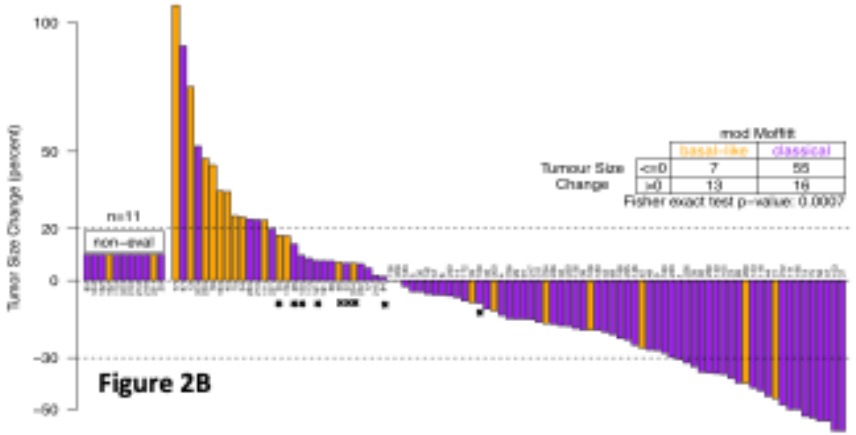
GATA6 Expression Distinguishes Classical and Basal-like Subtypes in Advanced Pancreatic Cancer

Estudio prospectivo, 195 ptes
80% classical, 20% basal



ORR 10% basal-like vs 33% classical (p=0,02)



Progresiones precoces tratados con mFFX (resistencia)
60% basales vs 15% classical (p = 0,0002))

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GATA6 Expression Distinguishes Classical and Basal-like Subtypes in Advanced Pancreatic Cancer

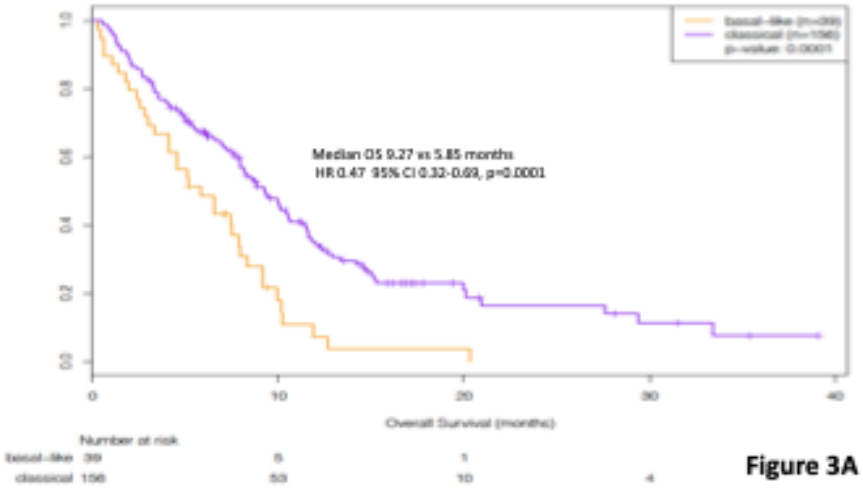


Figure 3A

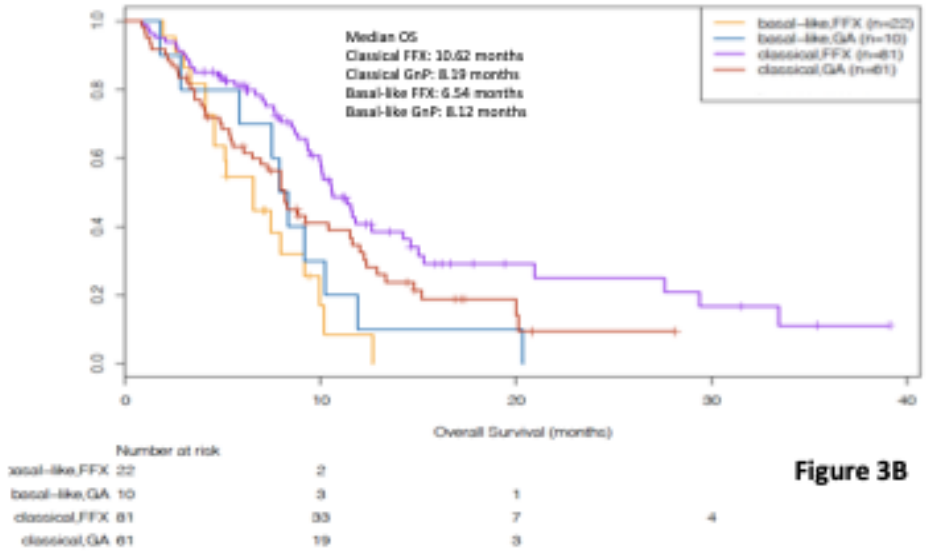


Figure 3B

mSG classical 9,3 vs 5,9 m basal-like
HR = 0,47; IC 95 %: 0,32-0,69; p = 0,0001

Tto FFX mSG basal-like 6,54 m vs classical 10,62 m
Tto GnP mSG basal-like 8,12 m vs classical 8,19 m

GATA6 Expression Distinguishes Classical and Basal-like Subtypes in Advanced Pancreatic Cancer

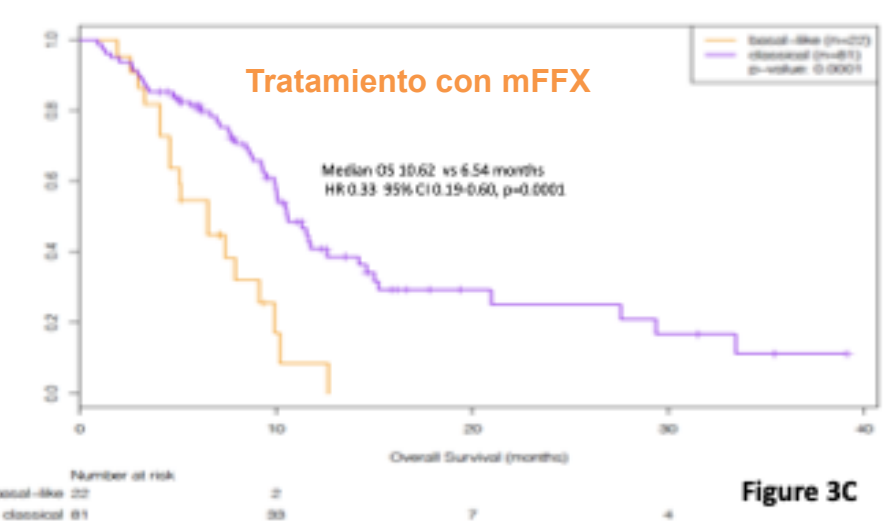


Figure 3C

Figure 3D

Limitaciones a este planteamiento:

1.-Un mismo tumor puede tener poblaciones heterogéneas y

2.-El subtipo puede cambiar con el tratamiento…**SEQUENCE TTD**

O'Kane et al. Clin Cancer Res. 2022

Original Reports | Gastrointestinal Cancer

PASS-01: Randomized Phase II Trial of Modified FOLFIRINOX Versus Gemcitabine/Nab-Paclitaxel and Molecular Correlatives for Previously Untreated Metastatic Pancreatic Cancer

Jennifer J. Knox, MD, MSc[1]; Grainne O'Kane, MD[1]; Daniel King, MD[2]; Daniel Laheru, MD[2]; Amber N. Habowski, PhD[4]; Kenneth Yu, MD[2];

Randomized pase II, de novo mPDAC

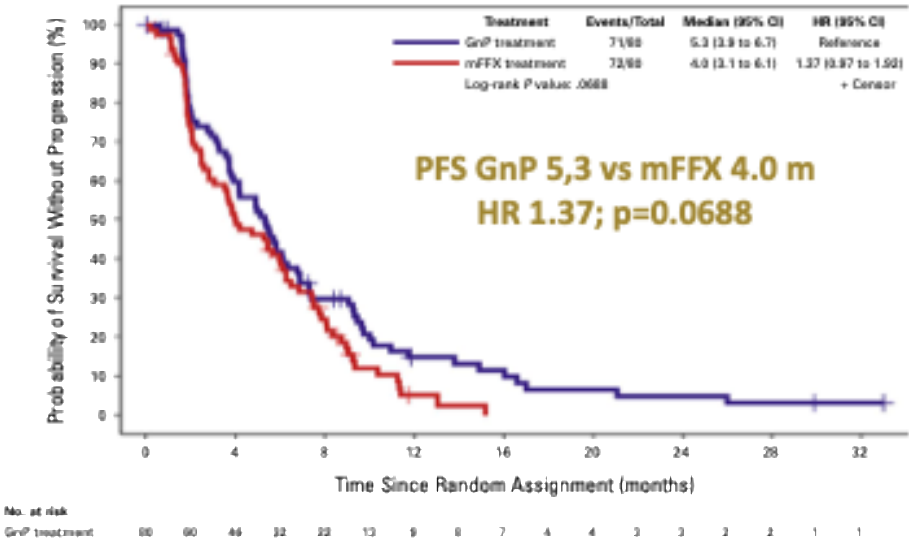
mFFX vs GnP, 160 pts

Exclusion gBRCA1/2 & PALB2

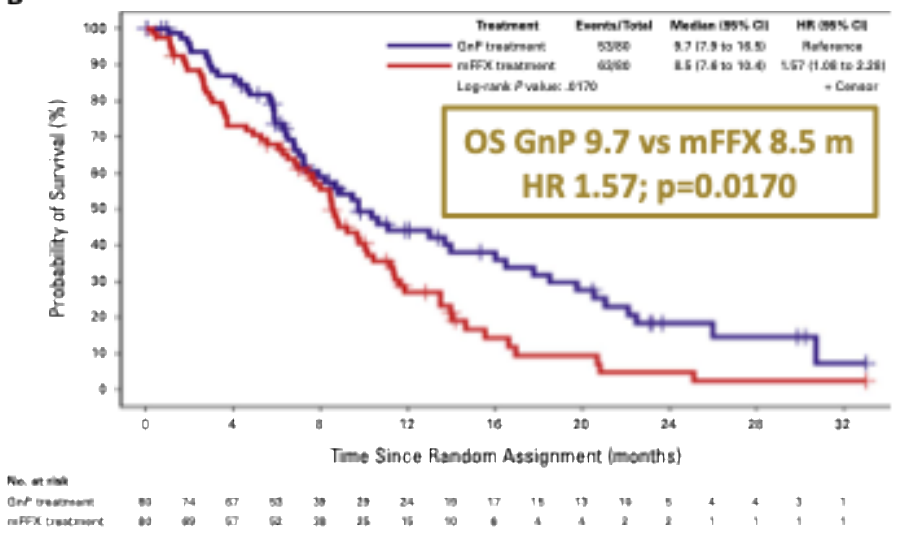
Bulky metastases were needed for biopsies and so patients with low volume or lung-only metastasis, known to have better outcomes, were not accrued

Less chemo-related SAEs for GnP

A



B



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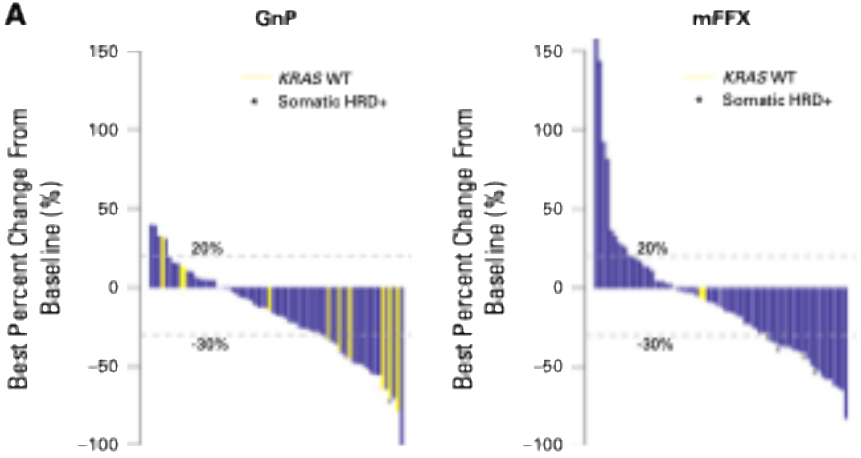
All patients, excluded gBRCA1/2 & PALB2

A



B

	Treatment		
	GnP (n = 69)	*mFFX (n = 71)*	*P*
CR/PR	21 (30.4%)	20 (28.6%)	.07
SD	34 (49.3%)	24 (34.3%)	
PD	14 (20.3%)	26 (37.1%)	
Not evaluable	0 (0.0%)	1 (1.4%)	
DCR (CR/PR/SD)	55 (79.7%)	44 (62.9%)	.028
DOR (months), median (range)	5.9 (1.8-24.1)	4.7 (1.4-7.6)	.025
TTR (months), median (range)	3.5 (1.7-19.0)	3.5 (1.7-7.5)	.30

CR/PR GnP 30.4 vs mFFX 28.6%
p=0.07

DCR (CR/PR/SD)
GnP 79.7 vs mFFX 62.9%
p=0.028

DoR GnP 5.9 vs mFFX 4.7 m p=0.025

Based on signatura stratitication (excluded gBRCA1/2 & PALB2)

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PASS-01: Randomized Phase II Trial of Modified FOLFIRINOX Versus Gemcitabine/Nab-Paclitaxel and Molecular Correlatives for Previously Untreated Metastatic Pancreatic Cancer

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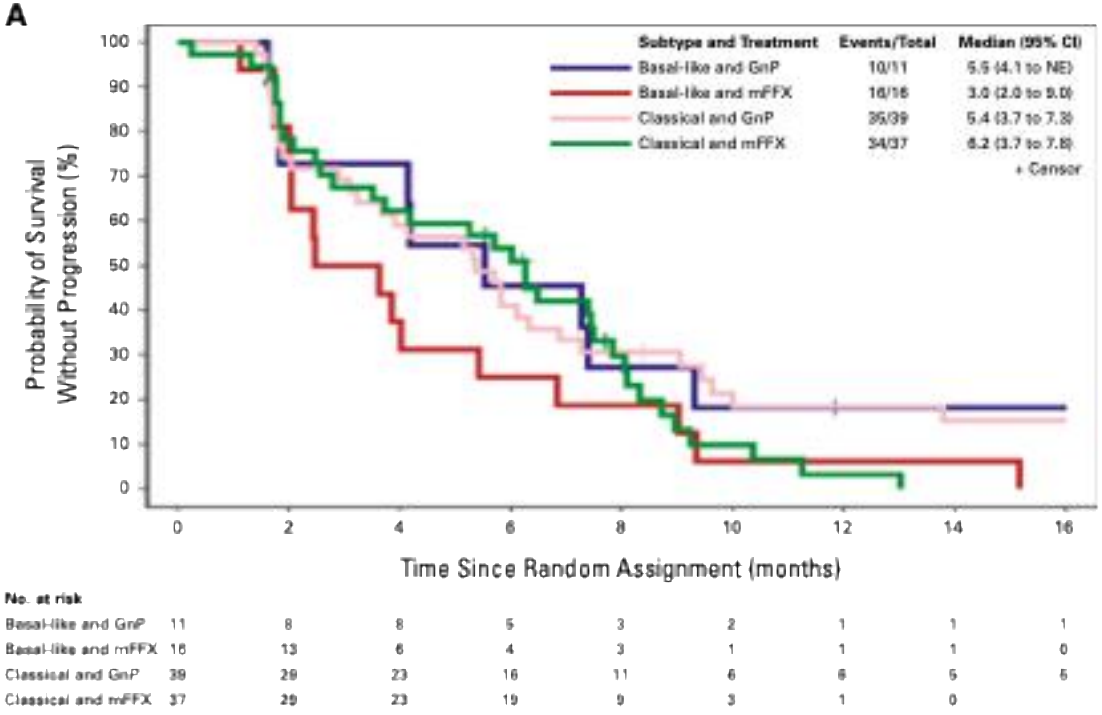

PFS

Basal-like

mPFS mFFX 3.0 m vs GnP 5.5 m; p=0.17

Classical

mPFS mFFX 6.3 m vs GnP 5.4 m; p=0.36

Based on signatura stratitication (excluded gBRCA1/2 & PALB2)

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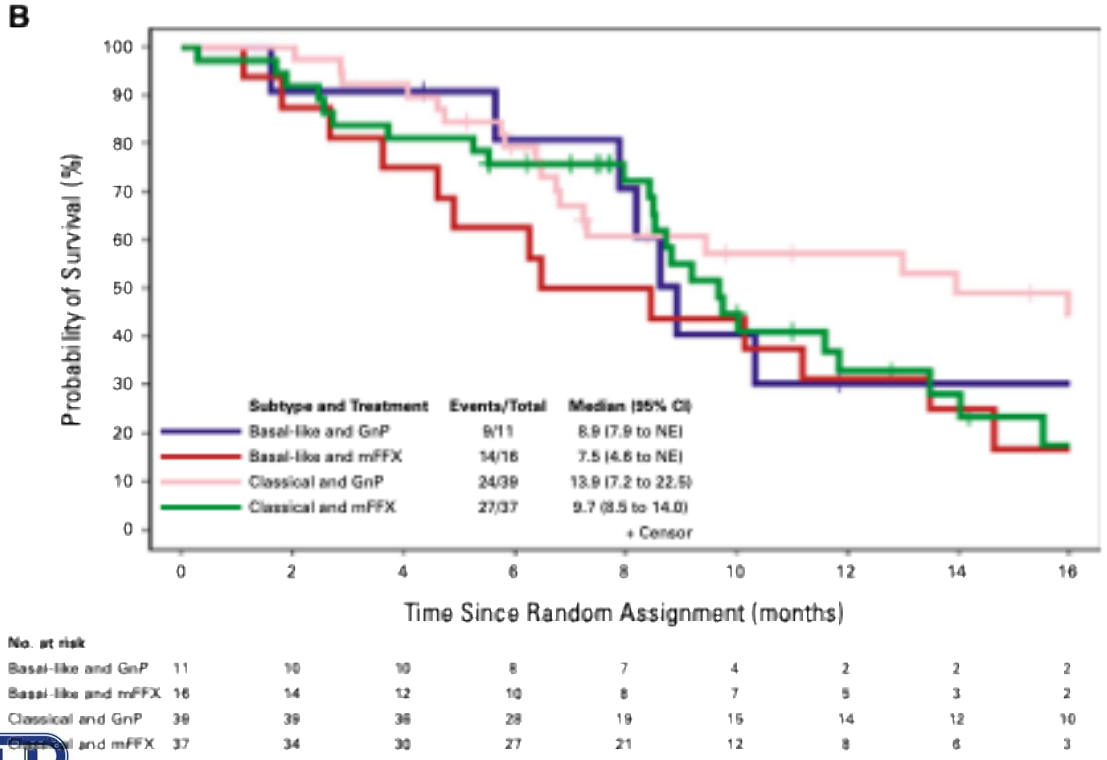


OS

Basal-like

mOS mFFX 7.5 m vs GnP 8.9 m; p=0.75

Classical

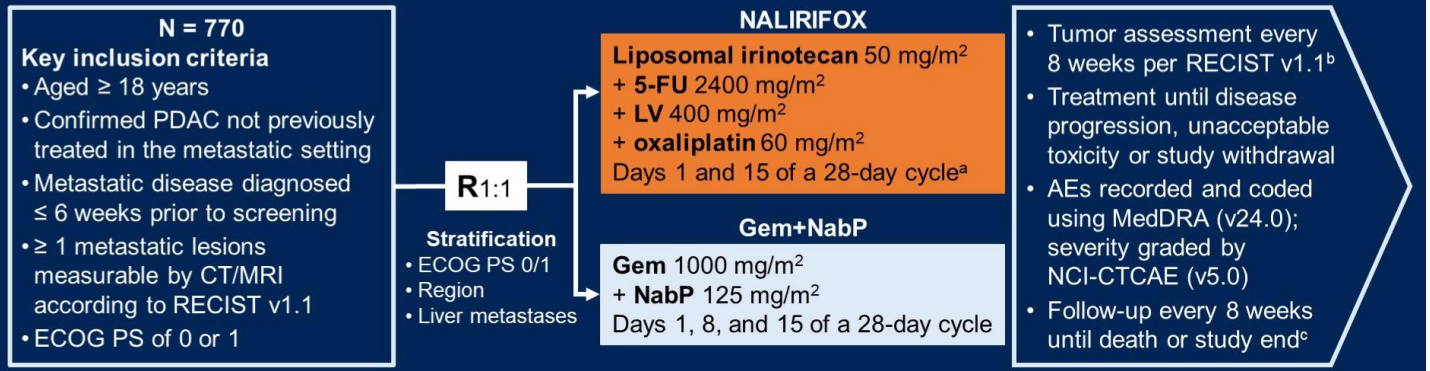
mOS mFFX 9.7 m vs GnP 13.9 m; p=0.047

OS may have been confounded by second-line treatment

Main limitation: small trial, underpowered subgroups

Población no seleccionada

NAPOLI 3: Study design

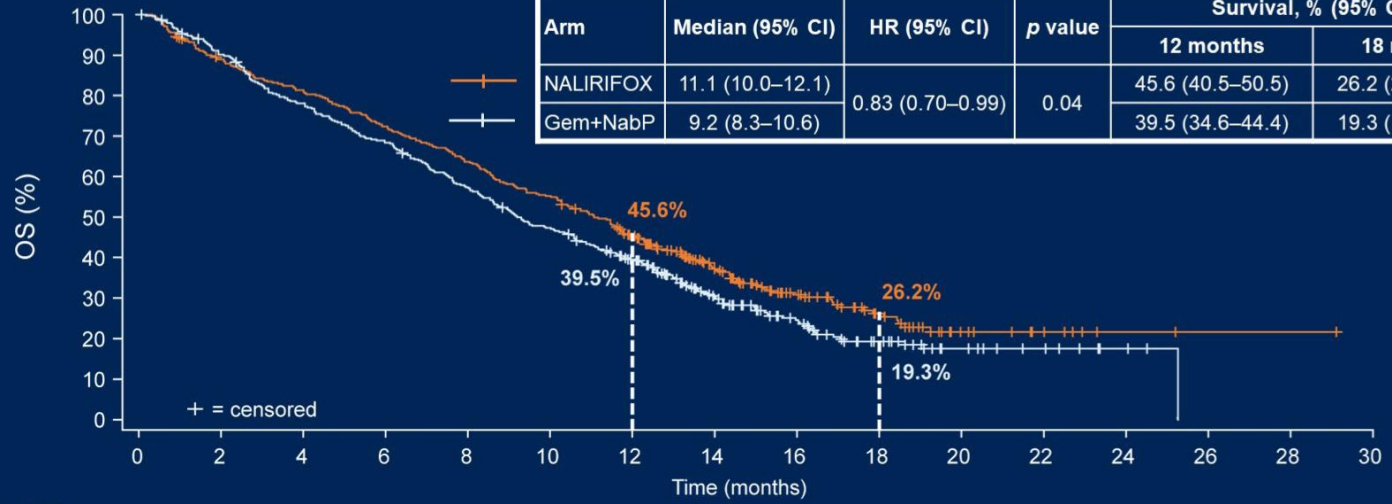


[a]Administered sequentially as a continuous infusion over 46 hours on days 1 and 15 of a 28-day cycle (dose delays and oxaliplatin discontinuation were permitted). [b]Until progressive disease. [c]The study was completed once all patients had discontinued the study treatment and at least 543 OS events had occurred in randomized patients.
5-FU, 5-fluorouracil; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; Gem, gemcitabine; LV, leucovorin; MedDRA, Medical Dictionary for Regulatory Activities; MRI, magnetic resonance imaging; NabP, nab-paclitaxel; NALIRIFOX, liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PDAC, pancreatic ductal adenocarcinoma; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors.

PRESENTED BY: Dr Eileen M O'Reilly

NAPOLI 3: OS (ITT population)

Arm	Median (95% CI)	HR (95% CI)	*p* value	Survival, % (95% CI)	
				12 months	18 months
NALIRIFOX	11.1 (10.0–12.1)	0.83 (0.70–0.99)	0.04	45.6 (40.5–50.5)	26.2 (20.9–31.7)
Gem+NabP	9.2 (8.3–10.6)			39.5 (34.6–44.4)	19.3 (14.8–24.2)



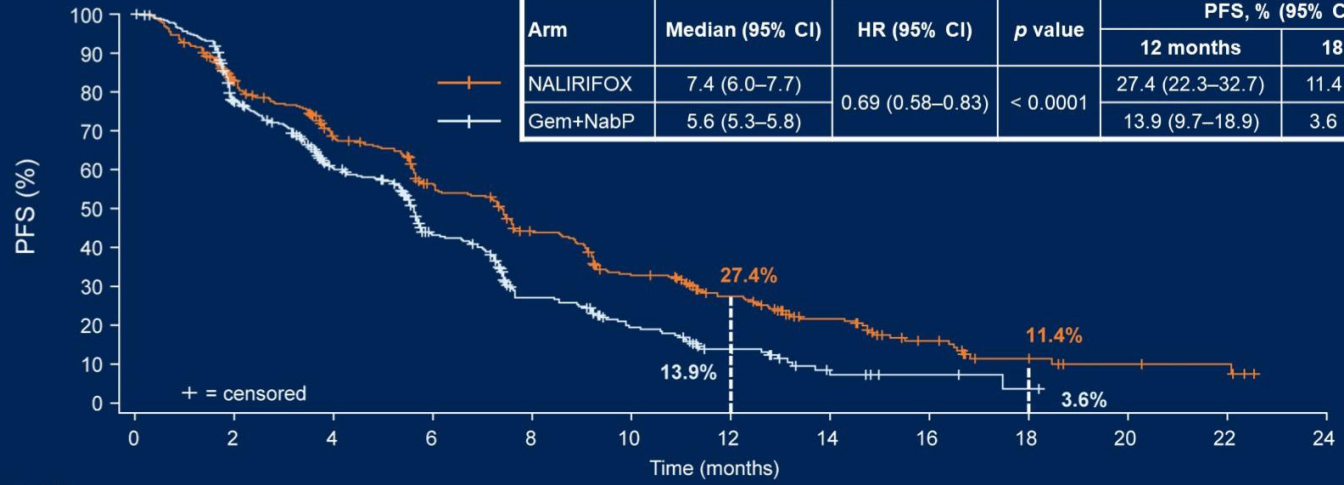
No. at risk:

NALIRIFOX	383	337	308	274	241	209	162	98	59	32	13	7	2	1	1	0
Gem+NabP	387	345	298	261	218	179	140	80	50	28	15	10	3	0	0	0

Hazard ratio and 95% CI based on a Cox proportional hazards regression model, stratified by ECOG PS (0 vs 1), region (North America vs ROW), liver metastases (yes vs no) per IRT. P boundary for efficacy claim *p* value < 0.048.
CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; Gem, gemcitabine; HR, hazard ratio; IRT, interactive response technology; ITT, intention-to-treat; NabP, nab-paclitaxel; NALIRIFOX, liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin; OS, overall survival; ROW, rest of world.

NAPOLI 3: PFS per investigator (ITT population)

Arm	Median (95% CI)	HR (95% CI)	*p* value	PFS, % (95% CI)	
				12 months	18 months
NALIRIFOX	7.4 (6.0–7.7)	0.69 (0.58–0.83)	< 0.0001	27.4 (22.3–32.7)	11.4 (7.1–16.9)
Gem+NabP	5.6 (5.3–5.8)			13.9 (9.7–18.9)	3.6 (0.5–12.3)



No. at risk:

NALIRIFOX	383	271	210	164	122	87	61	39	20	9	5	4	0
Gem+NabP	387	267	182	112	60	38	19	6	3	1	0	0	0

Hazard ratio and 95% CI based on a Cox proportional hazards regression model, stratified by ECOG PS (0 vs 1), region (North America vs ROW), liver metastases (yes vs no) per IRT. P boundary for efficacy claim *p* value < 0.048.
CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; Gem, gemcitabine; HR, hazard ratio; IRT, interactive response technology; ITT, intention-to-treat; NabP, nab-paclitaxel; NALIRIFOX, liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin; PFS, progression-free survival; ROW, rest of world.

NAPOLI 3: Tumor response[a]

	NALIRIFOX (n = 383)	Gem+NabP (n = 387)
Objective response rate (95% CI), %	41.8 (36.8–46.9)	36.2 (31.4–41.2)
Best overall response, %		
Complete response	0.3	0.3
Partial response	41.5	35.9
Stable disease	25.8	26.1
Progressive disease	9.9	14.5
Not evaluable[b]	22.5	23.3
Disease control rate,[c] %	67.6	62.3
Duration of response, median (95% CI), months	7.3 (5.8–7.6)	5.0 (3.8–5.6)

[a]Stratified by ECOG PS (0 vs 1), region (North America vs ROW), liver metastases (yes vs no) per IRT. P boundary for efficacy claim *p* value < 0.048. [b]Included are 68 patients (17.8%) in the NALIRIFOX group and 64 (16.5%) in the Gem+NabP group who did not have an assessment after the baseline visit. [c]Proportion of patients with complete response, partial response and stable disease.
CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; Gem, gemcitabine; IRT, interactive response technology; NabP, nab-paclitaxel; NALIRIFOX, liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin.

Otros ensayos clínicos

Resultados no consistentes

- Fase II aleatorizado SWOG 1505 enfermedad resecable/perioperatorio
  - mFFX versus GnP, mSG sin diferencias
- GENERATE/JCOG1611 (Japón)
  - mSG GnP 17,0 m vs 14 m FFX
  - mSLP GnP 6,7 m vs 5,8 m FFX
- JCOG1407 (Japón)
  - No dif en supervivencia ni tasa de respuesta

Criterios clínicos

Clin Transl Oncol (2017) 19:667–681
DOI 10.1007/s12094-016-1594-x

SPECIAL ARTICLE

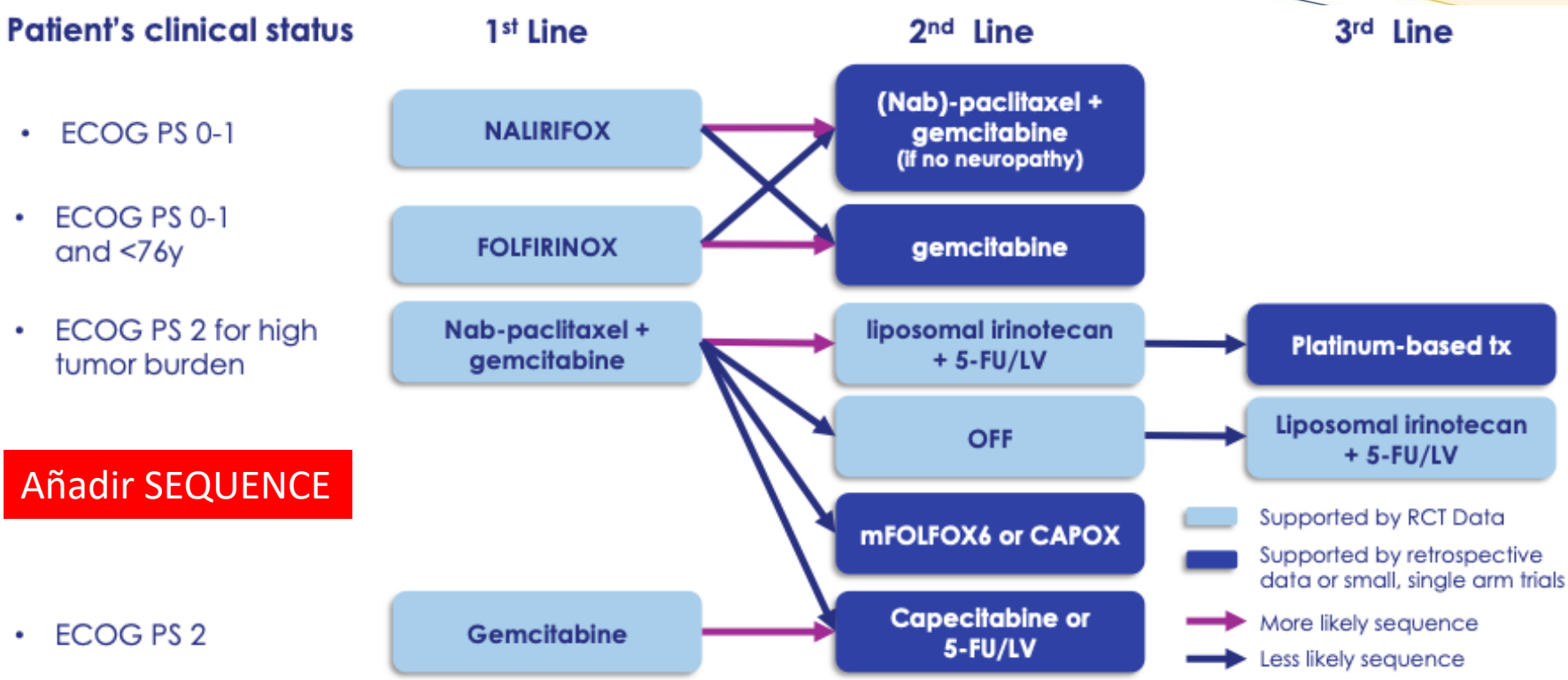
Consensus guidelines for diagnosis, treatment and follow-up of patients with pancreatic cancer in Spain

M. Hidalgo[1,2] · R. Álvarez[3] · J. Gallego[4] · C. Guillén-Ponce[5] · B. Laquente[6] · T. Macarulla[7] · A. Muñoz[8] · M. Salgado[9] · R. Vera[10] · J. Adeva[11] · I. Alés[12] · S. Arévalo[13] · J. Blázquez[14,15] · A. Cabezón[16] · A. Carmona[17] · E. de Madaria[18] · R. Díaz[19] · L. Díez[20] · T. Fernández[21] · B. G. de Paredes[22] · M. E. Gallardo[23] · I. González[24] · O. Hermunds[25,26] · P. Jiménez[27] · A. López[28] · C. López[29] · F. López-Ríos[30] · E. Martín[31] · J. Martínez[32] · A. Martínez[33] · J. Montans[34] · R. Pazo[35] · J. C. Plaza[36] · I. Peiró[36] · J. J. Reina[37] · A. Sanjuanbenito[38] · R. Yaya[39] · Alfredo Carrato[1]

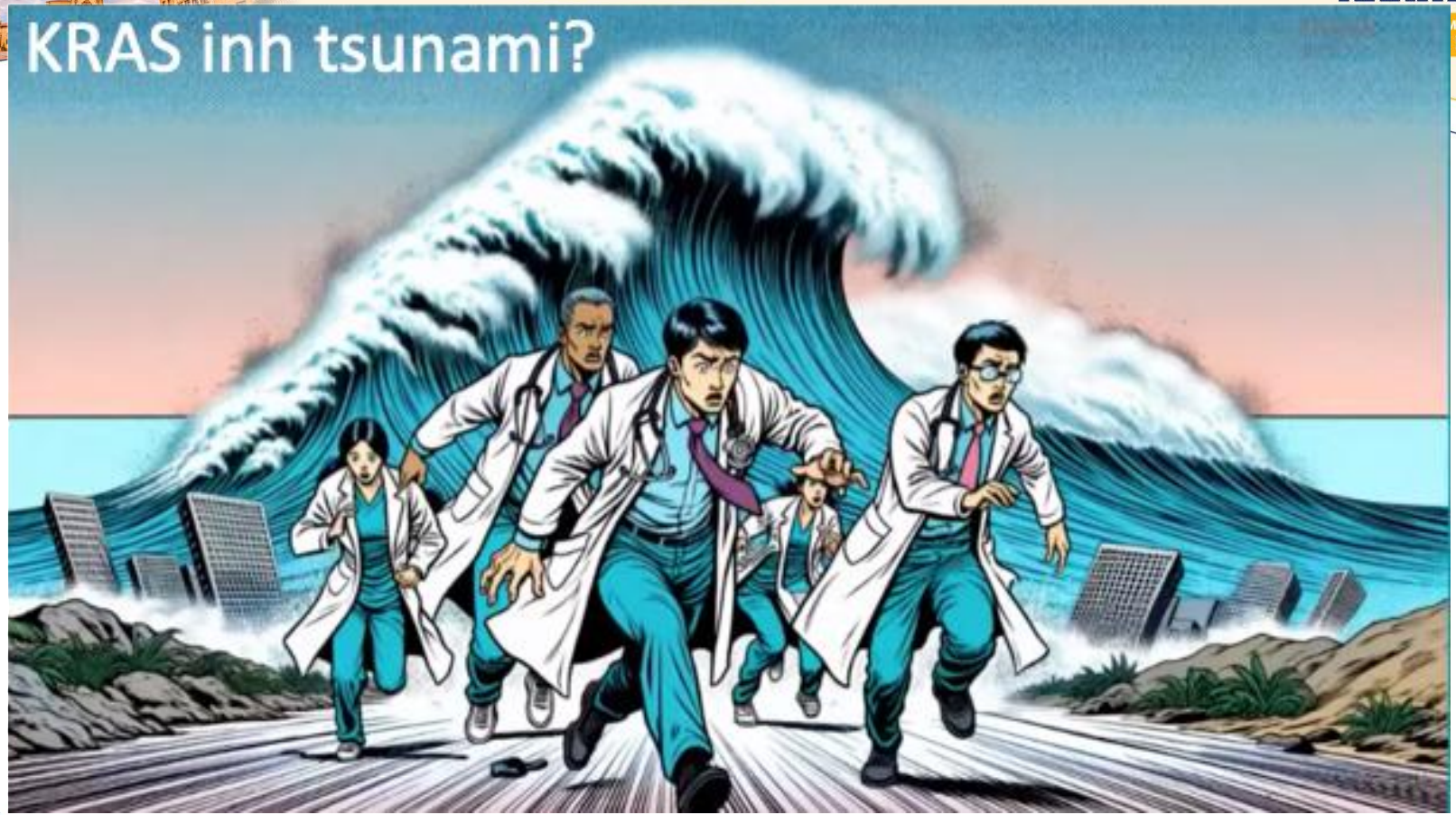
Table 2 Patients' classification, according to treatment perspective (IIIB)

Patients' classification	Factors
Patient suitable for chemotherapy treatment without limitations	The presence of ALL the following factors
	ECOG 0–1
	Age ≤75 years
	Bilirubin ≤1.5 ULN
	Good nutritional status (serum albumin >2.5 mg/dl, weight lost <10% over the last 3–6 months and BMI >20 kg/m^2)
	Lack of co-morbidities
Patient suitable for chemotherapy with limitations	The presence of AT LEAST ONE of the following factors
	ECOG 2 (which can lead to KPS 70%)
	Age >75 years
	Mild to moderate neurological or endocrine-metabolic organ dysfunction; in case of liver dysfunction, hyperbilirubinemia >1.5 × ULN (once optimized if obstructive causes are present, for example with biliary stent) marks the degree of dysfunction. It is considered appropriate to adjust the dose, for example, using GEM at 600–800 mg/m^2 and nab paclitaxel 75–100 mg/m^2) [37]
	Cardiac dysfunction, especially a recent ischemic event; acute, symptomatic, severe TED such as PE with hemodynamic instability or DVT with risk and limb amputation [38]
	BMI <20 kg/m^2 or >10% weight loss in 3–6 months
Patient not suitable for chemotherapy treatment	The presence of AT LEAST ONE of the following factors
	ECOG 3-4 (which may result in KPS ≤ 60%). Active treatment will be initiated in patients with ECOG 3 secondary to the disease (not to their previous comorbidities) without any severe organ dysfunction, thus moving this subgroup of patients to the "candidate for chemotherapy treatment with limitations" group
	Severe organ dysfunction: neurological (e.g., severe cognitive impairment, Alzheimer's type); endocrine-metabolic, infectious (uncontrolled HIV), renal, hepatic dysfunctions, etc

ECOG Eastern Cooperative Oncology Group, *ULN* upper normal limit, *BMI* body mass index, *GEM* gemcitabine, *KPS* Karnofsky performance status, *TED* thromboembolic disease, *PE* pulmonary embolism, *DVT* deep venous thrombosis



Añadir SEQUENCE


KRAS inh tsunami?

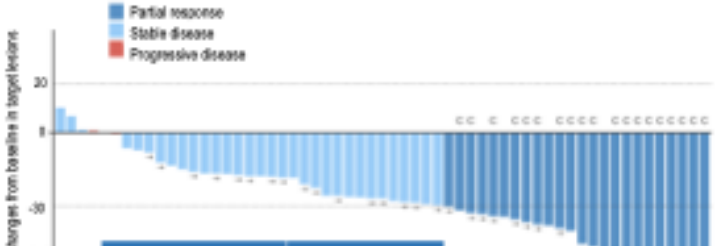
GFH375 is an oral, potent, highly selective inhibitor of *KRAS G12D* in both GDP-bound (off) and GTP-bound (on) status.

Phase I/II GFH375 monotherapy 600 mg QD, 66 PDAC pts, cohort 2, ECOG PS1, 95.5% stage IV, liver mets 78.8%
68.2% of patients had received at least 2 prior lines, 33.3% had previously received ICIs.

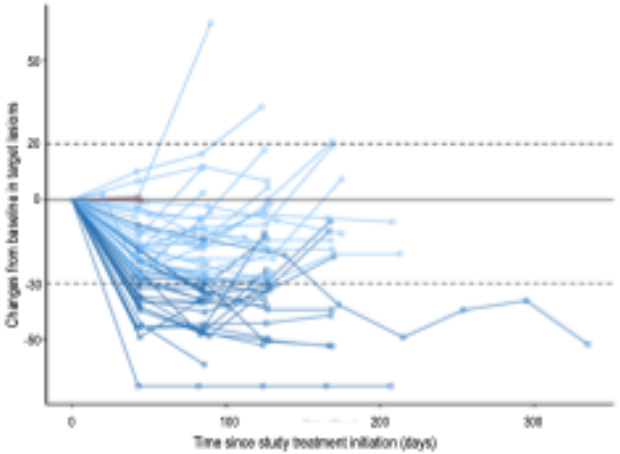
Abstract number: LBA84

Best Overall Response

- ORR was **40.7%** (24/59), 90%CI was [30%, 52%] in the 59 evaluated patients.
- DCR was **96.7%** (57/59), 90%CI was [90%, 99%]; Majority (91.5%) had reduction in target lesions.



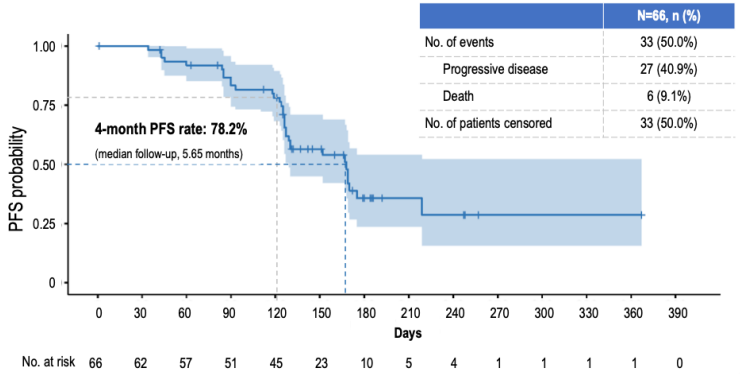
	N=59
ORR [90%CI]	40.7% [30%, 52%]
Best overall response, n (%)	
Partial response	24 (40.7)
Stable disease	33 (55.9)
Progressive disease	2 (3.4)
DCR [90%CI]	96.7% [90%, 99%]



Data cut-off date: September 27, 2025. All patients received first dose of GFH375 for at least 4 months prior to the cut-off date. Seven patients had no post-treatment tumor assessments due to early dropout: 2 due to AEs not related to GFH375 (1 upper gastrointestinal hemorrhage and 1 respiratory failure); 1 started new anticancer therapy; 4 early discontinued due to patient decision. Left figure: "C" represents confirmed responders. Arrows indicate treatment ongoing.
Abbreviations: CI, confidence interval; DCR, disease control rate; ORR, objective response rate.

Progression-Free Survival

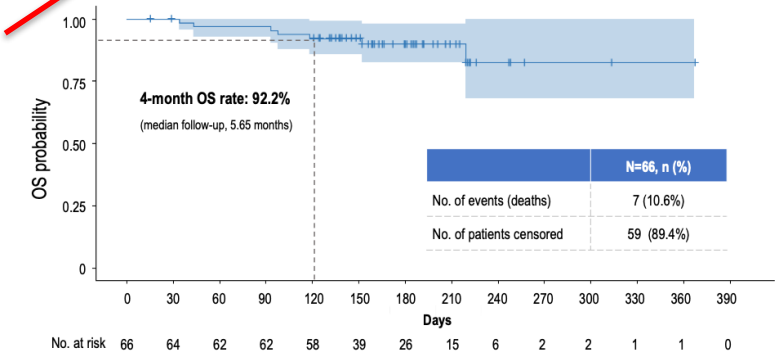
- Median PFS was **5.52 months** (90%CI: 4.27, 7.20), with a median follow-up time 5.65 months (90%CI: 4.96, 6.08).
- 4-month PFS rate was **78.2%** (90%CI: 69.8%, 87.5%).



	N=66, n (%)
No. of events	33 (50.0%)
Progressive disease	27 (40.9%)
Death	6 (9.1%)
No. of patients censored	33 (50.0%)

Overall Survival

- Median OS was not reached with a median follow-up time 5.65 months (90%CI: 5.22, 6.14).
- 4-month OS rate was **92.2%** (90%CI: 86.8%, 97.9%).

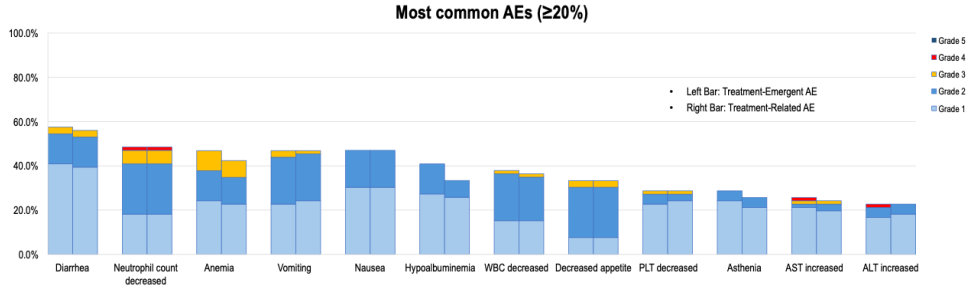


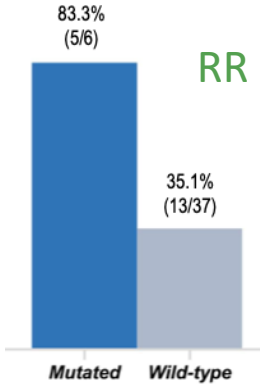
	N=66, n (%)
No. of events (deaths)	7 (10.6%)
No. of patients censored	59 (89.4%)

Common Adverse Events

<10% required dose reduction/discontinuation due to TRAEs

- The safety profile of GFH375 in *KRAS G12D* mutant PDAC patients is consistent with previous report.[1,2]
  - Common TRAEs were gastrointestinal and hematological AEs; most were grade 1 or 2 and manageable with supportive treatment.
  - Most frequent TRAEs (≥20%) were diarrhea (56.1%), neutrophil count decreased (48.5%), vomiting (47.0%), nausea (47.0%), anaemia (42.4%), white blood cell count decreased (36.4%), decreased appetite (33.3%), hypoalbuminaemia (33.3%), platelet count decreased (28.8%), asthenia (25.8%), aspartate aminotransferase increased (24.2%), and alanine transferase increased (22.7%).





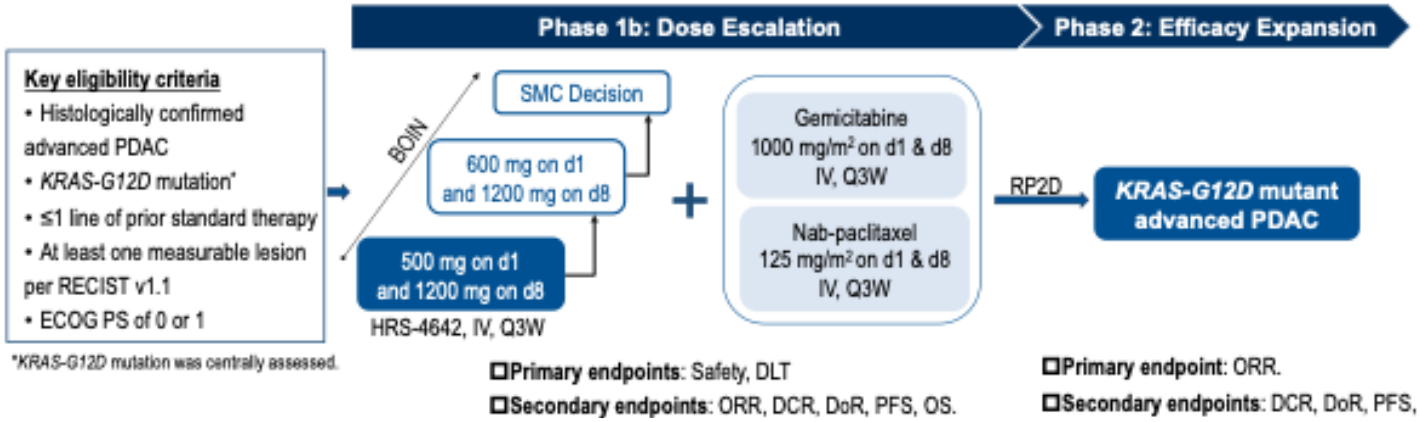
SMAD4

HRS-4642 (liposome): A high affinity, selective, non-covalent KRAS G12D inhibitor

Phase 1b/2 study, HRS-4642 combined with GnP, 31 pts, ECOG 1 90,3%, mtx 87,1%

Study design

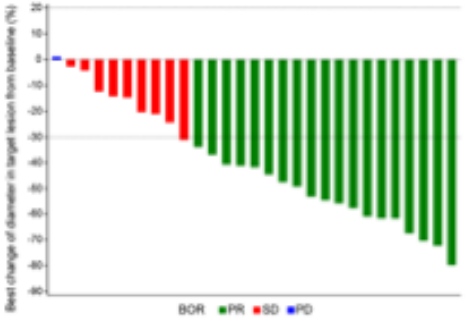
- A phase 1b/2 study to assess HRS-4642 combined with GA in patients with *KRAS-G12D* mutant advanced PDAC (NCT05533463).



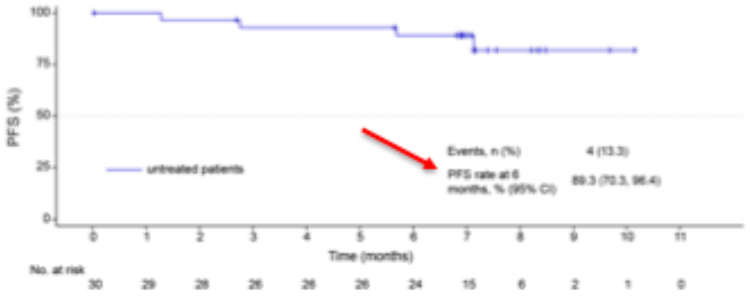
Tumor response in previously untreated patients

	HRS-4642 + GA Previously untreated patients (n = 30)
ORR*, % (95% CI)	63.3 (43.9, 80.1)
DCR, % (95% CI)	93.3 (77.9, 99.2)
BOR, n (%)	
PR*	19 (63.3)
SD	9 (30.0)
PD	1 (3.3)
No post-baseline assessment	1 (3.3)

*Confirmed

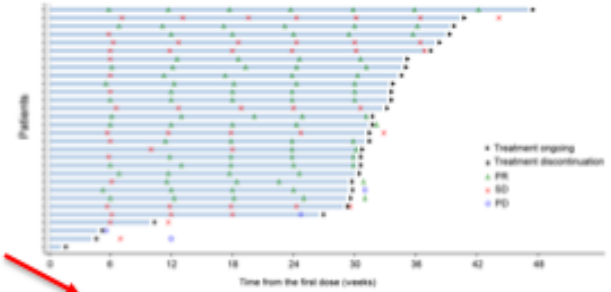


PFS in previously untreated patients



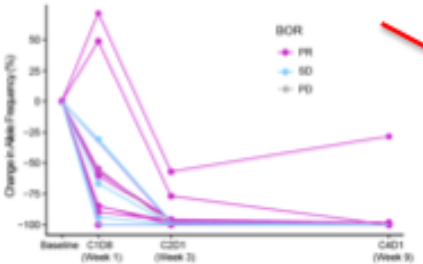
- Most grade ≥ 3 TRAEs were hematologic toxicities;
- No TRAEs led to dose discontinuation or death.

Tumor response over time in previously untreated patients



* Response was ongoing in 18 of the 19 responders; the median duration of response was not reached.

Change in *KRAS-G12D* Variant Allele Frequency in ctDNA



	C2D1 (Week 3) (n = 19*)	C4D1 (Week 9) (n = 18*)
Complete clearance, n (%)	10 (52.6)	16 (88.9)

*30 patients with baseline *KRAS-G12D* ctDNA positivity were evaluable for changes in *KRAS-G12D* variant allele frequency, with 1 patient discontinued treatment prior to week 3 (n = 19) and 1 additional discontinuation by week 9 (n = 18).

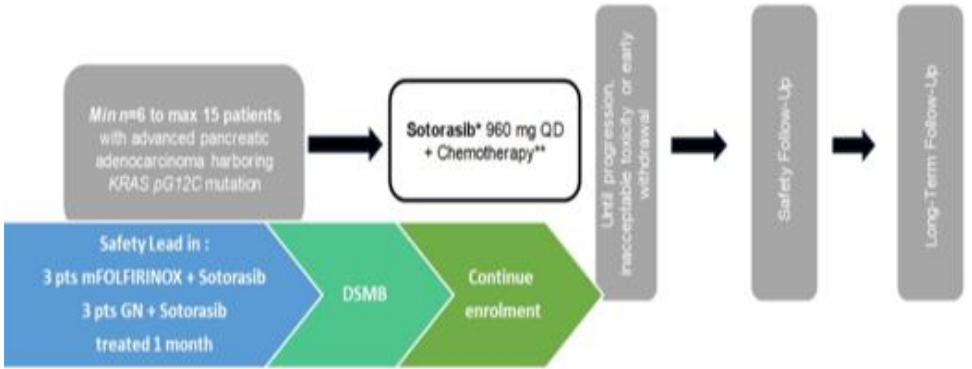
HRS-4642 combined with GA achieved:

- Remarkable and sustained clearance of the *KRAS-G12D* mutant allele;
- A high rate of complete *KRAS-G12D* mutant allele clearance by C4D1.

How we can collaborate…Clinical trials

Sotorasib combined with first-line chemotherapy for advanced pancreatic adenocarcinoma with *KRAS p.G12C* mutation

- Coordinadores: Dra. Macarulla (TTD) and Dr. Hammel (GERCOR)
- Promotor: Grupo TTD
- Centros: TTD (15 Centros) y GERCOR (10 Centros)
- Pacientes: 15
- Periodo de reclutamiento: 3 años
- Determinación local de KRAS pG12C + confirmación central de KRASG12C (VHIO)



Hospital General Universitario Gregorio Marañón
SaludMadrid
Comunidad de Madrid

Muchas gracias por su atención

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