foro debate oncología

Zaragoza 26-29 septiembre 2023

INHIBIDORES DE PARP EN CÁNCER DE PÁNCREAS

ESTADO DEL ARTE Y ALTERNATIVAS FUTURAS

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INTRODUCCIÓN

- Ca páncreas se caracteriza por inestabilidad genómica, con elevada tasa de mutaciones activantes en oncogenes e inactivación en genes supresores.

- Escasa sintomatología inicial y la agresividad histopatológica → 80% diagnósticos en enfermedad avanzada.

- Se postula como segunda causa de muerte por cáncer en 2030.

- Tratamientos enfocados a reducir carga tumoral y aumentar supervivencia. **“one-size-fits-all”**

- **No hay estándar de mantenimiento tras 4-6 meses de QT 1L.**

EVIDENCIA PRECLÍNICA Y RACIONAL DE IPARP EN CÁNCER PANCREÁTICO

- Alteraciones genéticas 5–15% .

- Hasta el 20% ca pancreático poseen defectos en HR. La causa más frecuente es por variantes patogénicas BRCA2.

- Actualmente ¿¿¿ **TODOS los pacientes con diagnóstico de ca pancreático deberían tener acceso a estudio genético???**

EVIDENCIA PRECLÍNICA Y RACIONAL DE IPARP EN CÁNCER PANCREÁTICO

- iPARP han demostrado efectividad en tumores sólidos con defectos en recombinación homóloga, y especialmente, en aquellos con sensibilidad aumentada a platino.

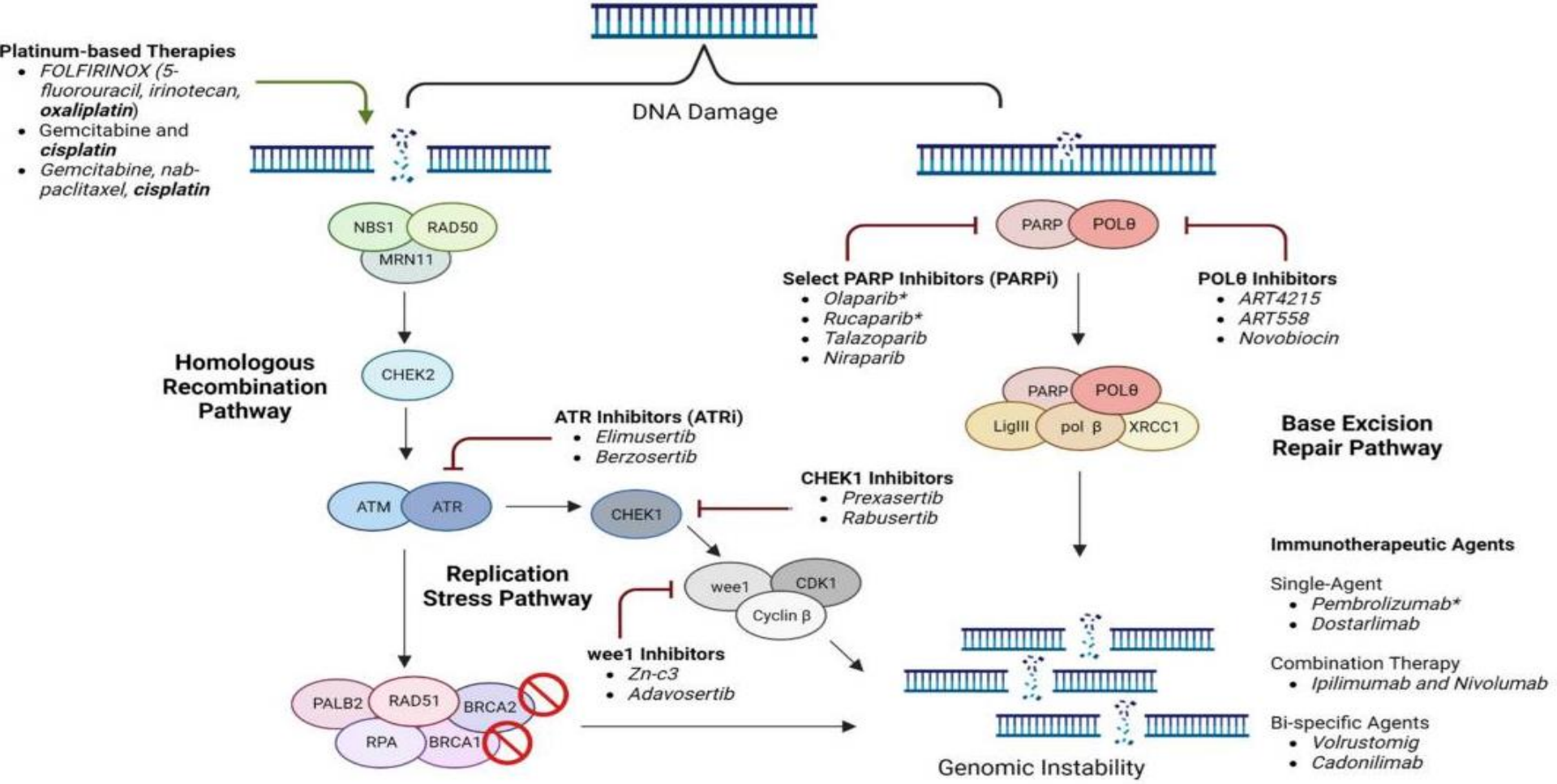
- Estudios prospectivos y retrospectivos demuestran que el tratamiento basado en platino es especialmente efectivo en cancer de pancreas en pacientes portadores de BRCA1, BRCA2 and PALB2, con respuestas mantenidas en el tiempo.

EVIDENCIA PRECLÍNICA Y RACIONAL DE IPARP EN CÁNCER PANCREÁTICO

No test validados para pancreas…

Select Tests to Evaluate for HRD (not specific to pancreatic cancer).

Test	Description
Telomeric Allelic Imbalance (TAI) [28]	Allelic imbalance at the telomere of the chromosome is due to the propensity for inappropriate end joining in HRD, identified by single nucleotide polymorphism (SNP) genotyping.
Large Scale Transitions (LST) [29]	Chromosomal breaks larger than 10 Mb, which arise in HRD cells secondary to erroneous recombination between segments of the chromosome, are identified by single nucleotide polymorphism (SNP) genotyping.
Loss of Heterozygosity (LOH) [30]	Uniparental disomy is owing to inaccurate repair of sister chromatids during S/G2 phase, resulting in the loss of entire genes and the surrounding chromosomal region, as identified by single nucleotide polymorphism (SNP) genotyping.
Genomic Instability Score eg by Myriad Genetics MyChoice Assay	TAI + LST + LOH
Signature 3 (Sig 3) [35]	A single base substitution mutational pattern, associated with microhomology and large deletions, was identified by whole exome sequencing.
HRDetect [36]	A weighted model incorporating a weighted score of base substitution/rearrangement signatures, microhomology-mediated deletions, and an HRD score based on genomic scars identified by whole exome sequencing.



*FDA- and/or guideline-approved for specific indications in pancreas cancer

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Maintenance Olaparib for Germline *BRCA*-Mutated Metastatic Pancreatic Cancer

Talia Golan, M.D., Pascal Hammel, M.D., Ph.D., Michele Reni, M.D.,
Eric Van Cutsem, M.D., Ph.D., Teresa Macarulla, M.D., Ph.D.,
Michael J. Hall, M.D., Joon-Oh Park, M.D., Ph.D., Daniel Hochhauser, M.D., Ph.D.,
Dirk Arnold, M.D., Ph.D., Do-Youn Oh, M.D., Ph.D.,
Anke Reinacher-Schick, M.D., Ph.D., Giampaolo Tortora, M.D., Ph.D.,
Hana Algül, M.D., Ph.D., M.P.H., Eileen M. O'Reilly, M.D.,
David McGuinness, M.Sc., Karen Y. Cui, M.D., Ph.D., Katia Schlienger, M.D., Ph.D.,
Gershon Y. Locker, M.D., and Hedy L. Kindler, M.D.

N Engl J Med 2019;381:317-27. DOI: 10.1056/NEJMoa1903387

A double blind study in patients who have not progressed on first-line platinum-based therapy

- Metastatic pancreatic adenocarcinoma
- gBRCAm
- ECOG PS 0 or 1
- ≥16 weeks of first-line platinum-based chemotherapy for mPAC with no evidence of disease progression. No limit to duration of chemotherapy.
- No persistent CTCAE Grade ≥2 toxicities from current therapy, excluding alopecia and CTCAE Grade 3 peripheral neuropathy

Randomisation
3:2
N=154*

No stratification

Olaparib
300 mg *po* bid
n=92

Placebo
po bid
n=62

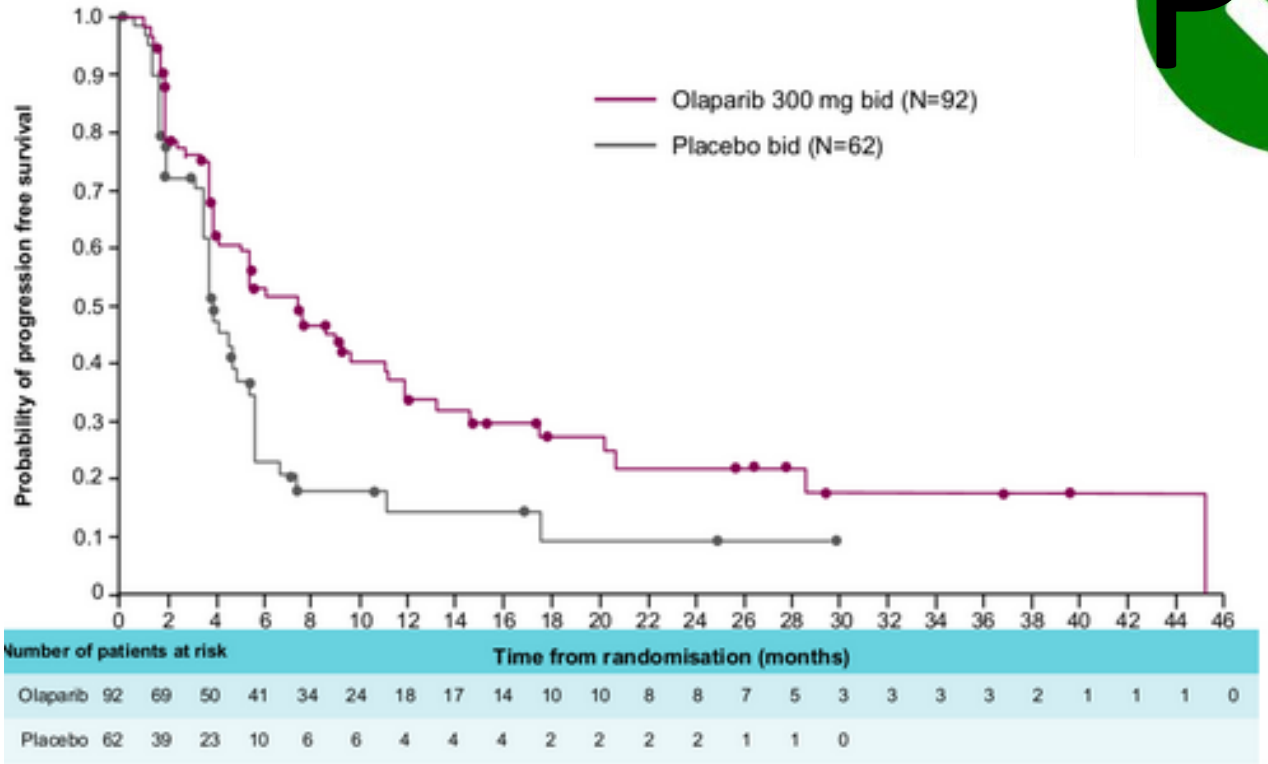
Treatment until progression**

Primary endpoint
- PFS (BICR)†

Secondary endpoints
- OS
- PFS2
- TFST
- TSST
- TDT
- ORR (BICR)†
- DCR (BICR)†
- HRQoL
- Safety and tolerability

ClinicalTrials.gov : NCT02184195

PFS



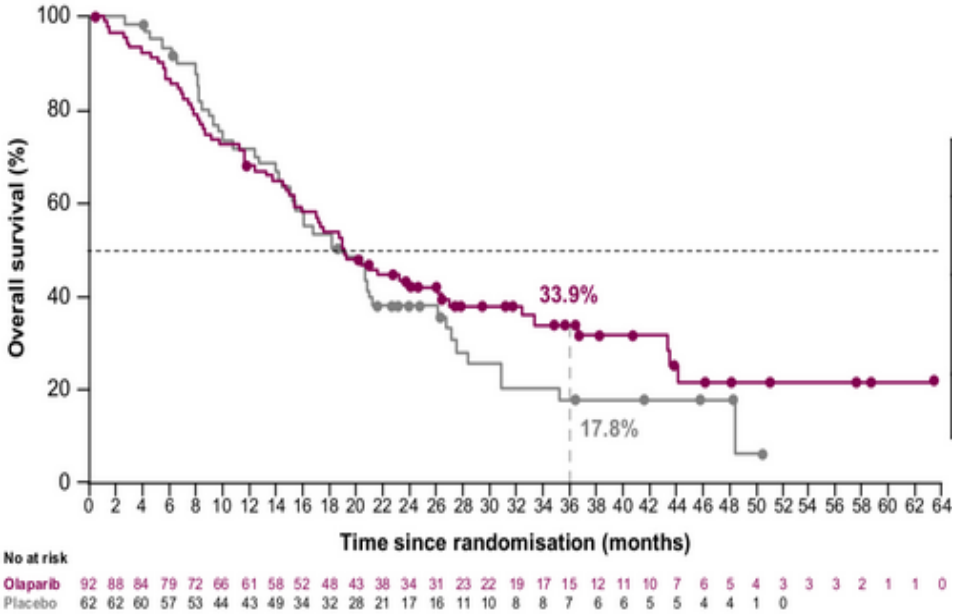
	Olaparib (N=92)	Placebo (N=62)
Events, n (%)	60 (65.2)	44 (71.0)
Median PFS, months (BICR)	**7.4**	**3.8**
Median difference	+3.6	
	HR=0.53 95% CI (0.35-0.82) p=0.004	

Journal of Clinical Oncology > List of Issues > Volume 40, Issue 34 >

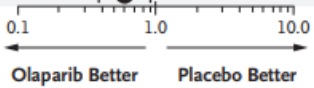
ORIGINAL REPORTS | Gastrointestinal Cancer

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

	Olaparib (n=92)	Placebo (n=62)
Events, n (%)	61 (66.3)	47 (75.8)
Median OS, months	19.0	19.2
Median survival follow-up, months (range)[a]	31.3 (0.3 –63.5)	23.9 (3.9 –50.6)
Hazard ratio (95% CI)	0.83 (0.56, 1.22); p=0.3487	



Subgroup	Olaparib	Placebo	Hazard Ratio (95% CI)
	no. of patients with events/total no. (%)		
All patients	60/92 (65.2)	44/62 (71.0)	0.53 (0.35–0.82)
Previous chemotherapy			
FOLFIRINOX variants	50/79 (63.3)	35/50 (70.0)	0.54 (0.35–0.84)
Other	8/10 (80.0)	6/8 (75.0)	0.76 (0.27–2.32)
Absence of biliary stent	59/91 (64.8)	40/58 (69.0)	0.54 (0.36–0.82)
Type of previous chemotherapy			
Doublet chemotherapy	12/15 (80.0)	8/10 (80.0)	0.59 (0.24–1.50)
Triplet chemotherapy	45/73 (61.6)	33/46 (71.7)	0.51 (0.32–0.82)
Duration of first-line treatment before randomization			
16 wk to 6 mo	42/61 (68.9)	29/40 (72.5)	0.69 (0.43–1.12)
>6 mo	18/30 (60.0)	15/21 (71.4)	0.35 (0.17–0.72)
Best response with first-line treatment			
Partial or complete response	30/46 (65.2)	20/30 (66.7)	0.62 (0.35–1.12)
Stable disease	30/45 (66.7)	24/31 (77.4)	0.50 (0.29–0.87)
Disease at baseline			
Measurable	53/78 (67.9)	39/52 (75.0)	0.57 (0.37–0.88)
Not measurable or no evidence of disease	7/13 (53.8)	5/6 (83.3)	0.45 (0.14–1.57)
Germline *BRCA* mutation type (determined by BRACAnalysis CDx test)			
BRCA1	20/29 (69.0)	12/16 (75.0)	0.40 (0.20–0.85)
BRCA2	38/59 (64.4)	32/45 (71.1)	0.63 (0.39–1.02)
Age at randomization			
<65 yr	39/64 (60.9)	37/49 (75.5)	0.45 (0.28–0.72)
≥65 yr	21/28 (75.0)	7/13 (53.8)	1.02 (0.45–2.60)
Sex			
Male	33/53 (62.3)	23/31 (74.2)	0.46 (0.27–0.80)
Female	27/39 (69.2)	21/31 (67.7)	0.66 (0.37–1.19)
White race	55/82 (67.1)	41/59 (69.5)	0.59 (0.39–0.90)



*Although **no statistically significant OS benefit was observed**, the HR numerically favored olaparib, which also conferred clinically meaningful benefits **including increased time off chemotherapy and long-term survival in a subset of patients.***

LIMITACIONES POLO

- Se comparaba con placebo
- No se estableció una duración máxima límite del régimen de quimioterapia de primera línea previo.
- Los pacientes en los que se había discontinuado el platino por toxicidad eran elegibles si habían continuado con el resto de fármacos y no habían presentado progresión de la enfermedad durante las 4 semanas posteriores a la última dosis de quimioterapia
- El estudio no estaba diseñado con la potencia estadística adecuada para buscar significación estadística en SG.

MANTENIMIENTO TRAS 1L BASADA EN PLATINO

- No hay estándar actual.
- Los estudios dirigidos a evaluar estrategias de mantenimiento han sido escasos y limitados.
- Escaso impacto en SG o SLP de la desescalada tras 4 meses. (PRODIGE-35)

CARACTERÍSTICAS DIFERENCIALES COMPARADAS CON OTRAS ALTERNATIVAS SIMILARES

Nombre	Olaparib	FOLFIRINOX (Leucovorin, Fluorouracilo, Irinotecan, Oxaliplatino)
Presentación	Comprimidos 100 y 150 mg	Leucovorin: Solución inyectable o para perfusión Fluorouracilo: Solución inyectable o para perfusión Irinotecan: Concentrado para solución para perfusión Oxaliplatino: Concentrado para solución para perfusión
Posología	300 mg (2 comprimidos de 150 mg) dos veces al día.	Esquema FOLFIRINOX (6 meses): Oxaliplatino, 85 mg/m2 de superficie corporal; irinotecan, 180 mg/m2; leucovorin, 400 mg/m2; y fluorouracilo, 400 mg/m2 en bolus seguido de 2.400 mg/m2 dado en infusión continua de 46 horas, cada dos semanas
Indicación aprobada en FT o no	Sí	Leucovorin: Sí Fluorouracilo: Sí Irinotecan: No Oxaliplatino: No
Efectos adversos	Anemia, neutropenia, fatiga/astenia, leucopenia, trombocitopenia, otros	Para la combinación FOLFIRINOX: Neutropenia, leucopenia, astenia y neuropatía periférica
Utilización de recursos*	Test BRCA Oral, atención farmacéutica	Administrado en hospital de día
Conveniencia**	Vía de administración oral	Vía de administración iv
Otras características diferenciales	iPARP Solo en gBRCAm	Leucovorin: metabolito activo del ácido folínico Fluorouracilo: Análogo de pirimidinas, antimetabolito Irinotecan: derivado semisintético de la camptotecina, que actúa como inhibidor específico de la ADN topoisomerasa I Oxaliplatino: Derivado de platino

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RR: gem/cisplatin/veliparib-74.1%
vs. gem/cisplatin-65.2% (p = 0.55)

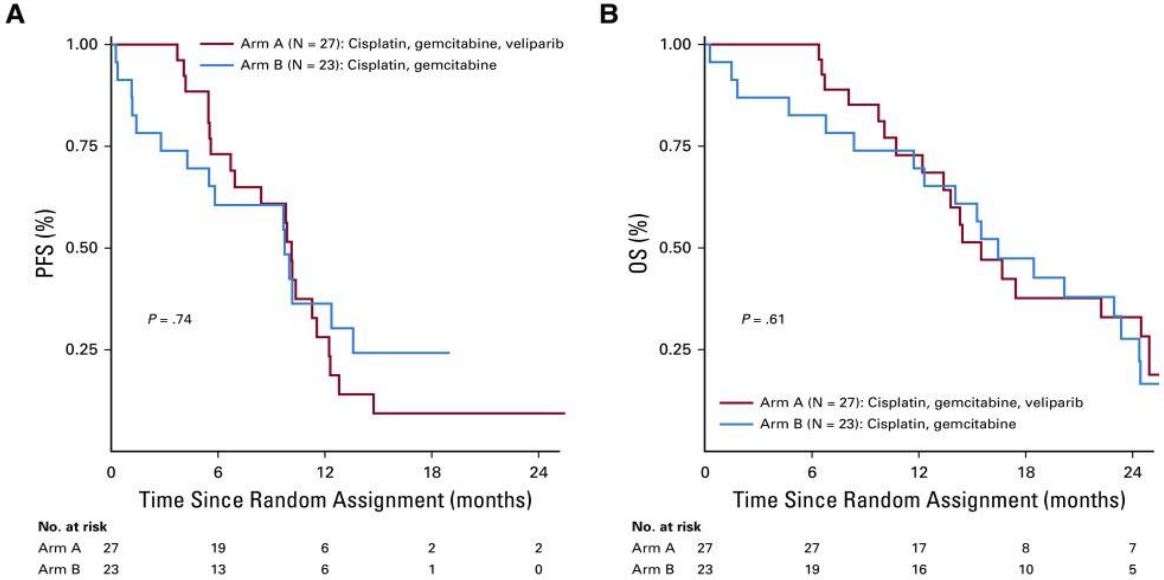
Journal of Clinical Oncology
American Society of Clinical Oncology

Randomized, Multicenter, Phase II Trial of Gemcitabine and Cisplatin With or Without Veliparib in Patients With Pancreas Adenocarcinoma and a Germline *BRCA/PALB2* Mutation

Eileen M. O'Reilly, MD, Jonathan W. Lee, MSc, [...],

and David P. Kelsen, MD

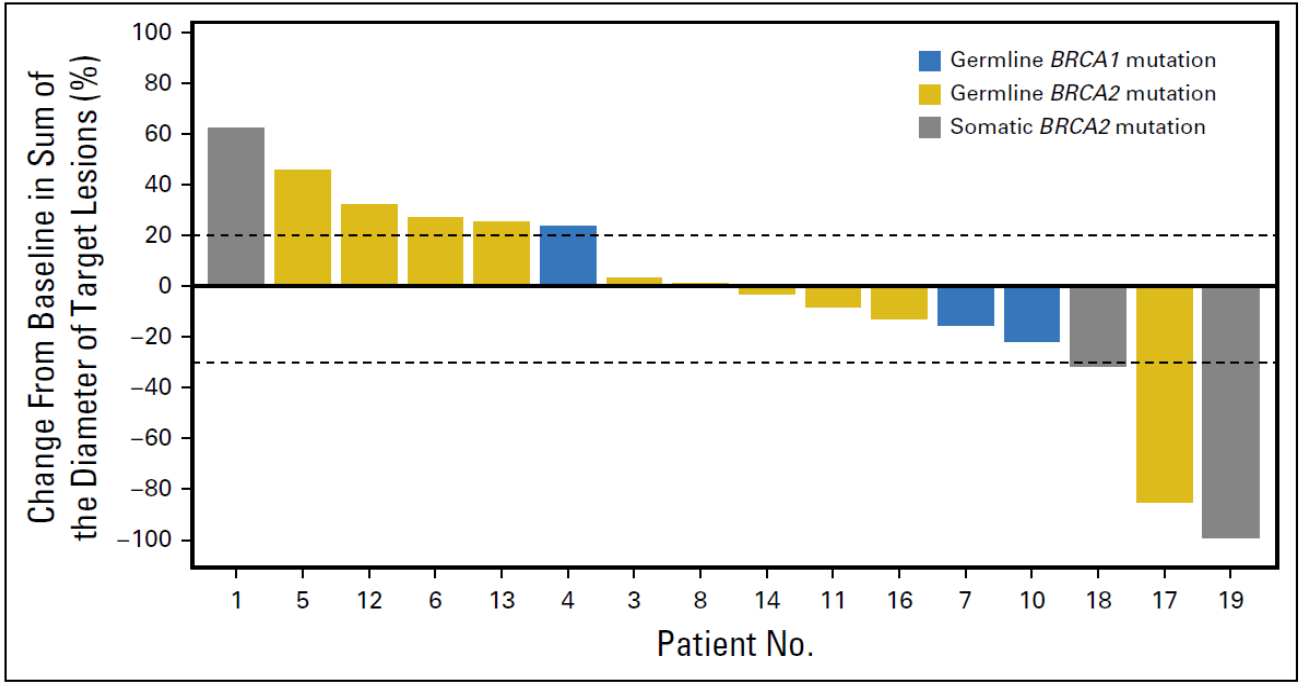
J Clin Oncol. 2020 May 1; 38(13): 1378–1388.



→ *Cisplatin and gemcitabine is an effective regimen in advanced gBRCA/PALB2+ PDAC. Concurrent* ***veliparib did not improve RR****. These data establish cisplatin and gemcitabine as a standard approach in gBRCA/PALB2+ PDAC*

RUCAPANC TRIAL

N= 19 PACIENTES
No randomizado.



→ CONCLUSIÓN: Rucaparib provided clinical benefit to patients with advanced pancreatic cancer and a *BRCA1/2* mutation, and demonstrated an acceptable safety profile.

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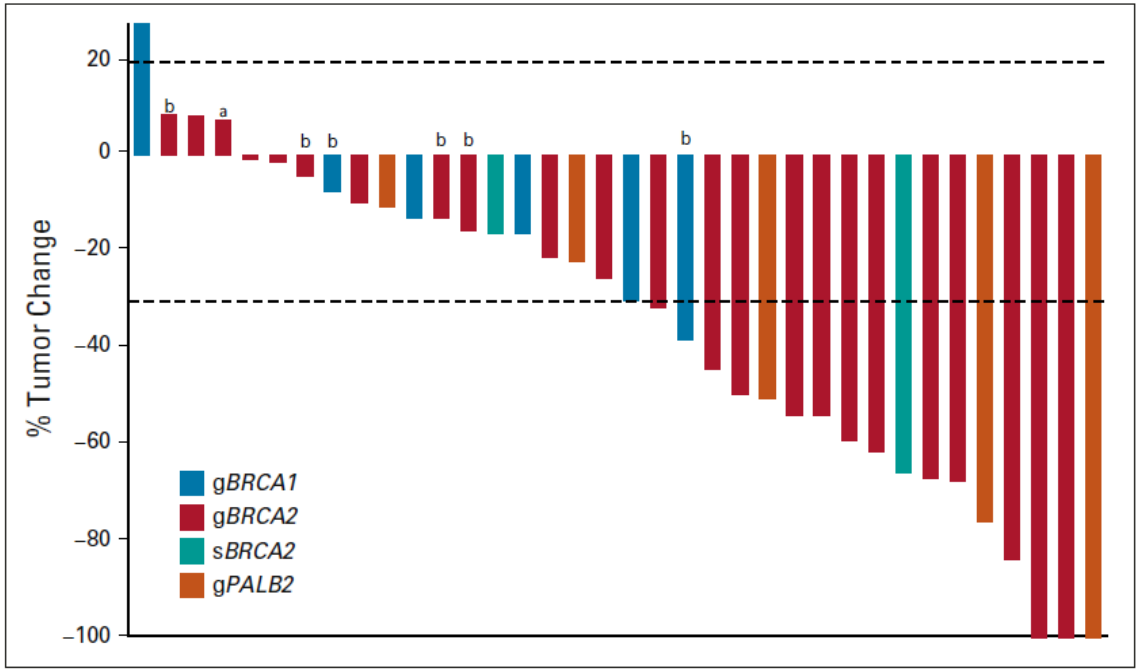
ORIGINAL REPORTS | Gastrointestinal Cancer

Phase II Study of Maintenance Rucaparib in Patients With Platinum-Sensitive Advanced Pancreatic Cancer and a Pathogenic Germline or Somatic Variant in *BRCA1*, *BRCA2*, or *PALB2*



Waterfall plot of best responses of the 36 patients with measurable disease at study start. [a]Clinical progression. [b]New lesion(s).

CONCLUSION

Maintenance rucaparib is a safe and effective therapy for platinum-sensitive, advanced PC with a PV in *BRCA1*, *BRCA2*, or *PALB2*. The finding of efficacy in patients with g*PALB2* and s*BRCA2* PVs expands the population likely to benefit from PARPi beyond g*BRCA1/2* PV carriers.

IPARP + INMUNO RACIONAL

→ *Preclinical studies have demonstrated that PARP inhibitors modulate the immune microenvironment by increasing genomic instability, PD-L1 expression and activating the immune inflammatory stimulator of interferon genes (STING) pathway.*

THE LANCET
Oncology

Niraparib plus nivolumab or niraparib plus ipilimumab in patients with platinum-sensitive advanced pancreatic cancer: a randomised, phase 1b/2 trial

Kim A Reiss, MD • Rosemarie Mick, MSc • Ursina Teitelbaum, MD • Mark O'Hara, MD • Charles Schneider, MD • Ryan Massa, MD • et al. Show all authors

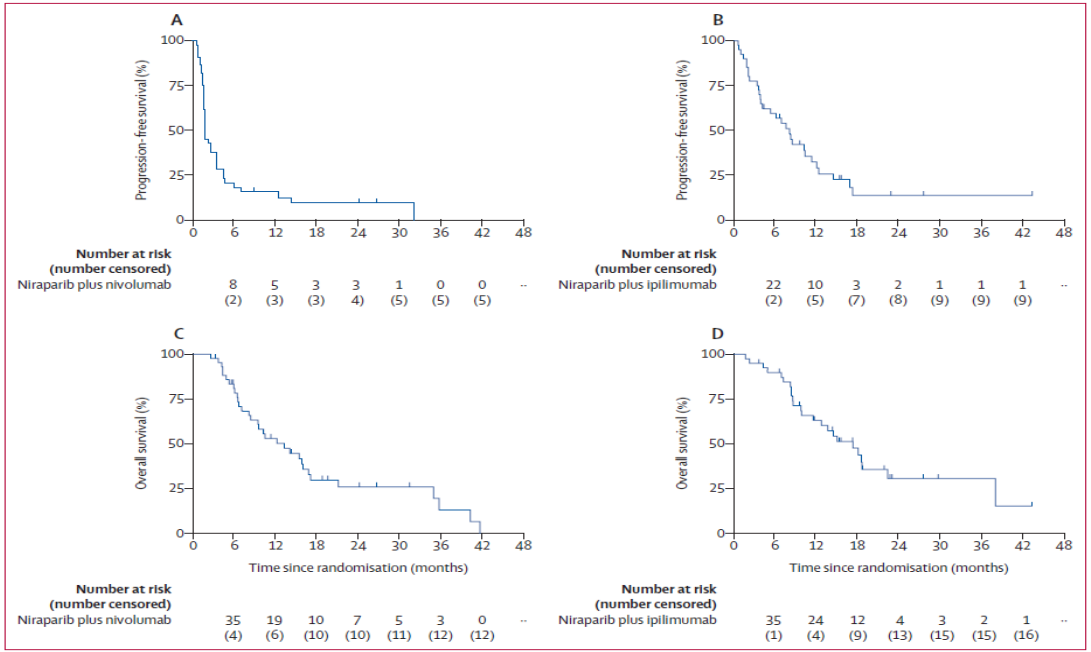


Figure 2: **Kaplan–Meier estimates of progression-free survival and overall survival**
Progression-free survival (centrally assessed) in the niraparib plus nivolumab group (A) and in the niraparib plus ipilimumab group (B). Overall survival in the niraparib plus nivolumab group (C) and niraparib plus ipilimumab group (D).

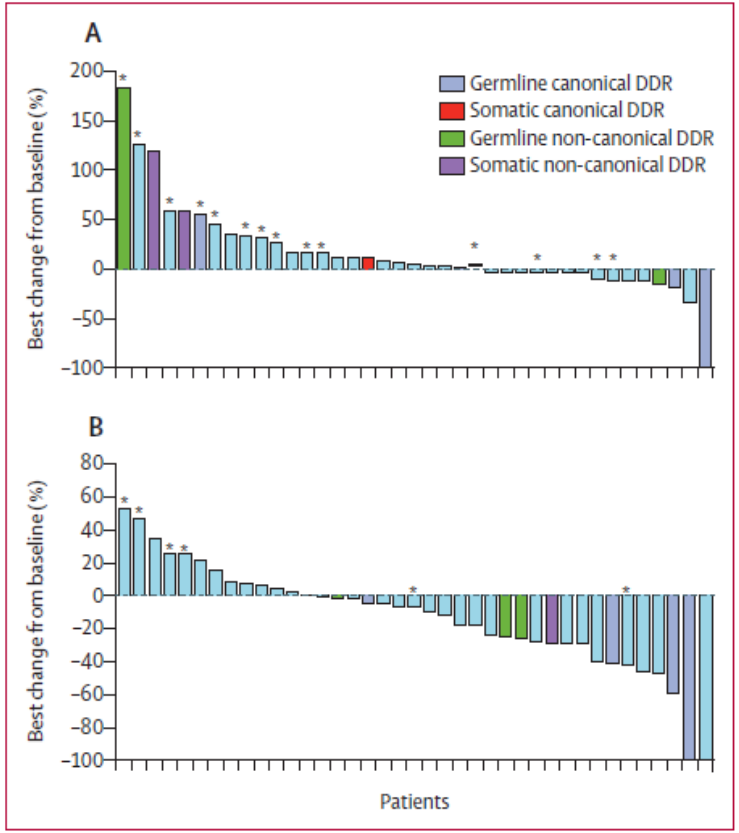


Figure 3: **Waterfall plot of best responses of patients with measurable disease at the start of the study**
(A) Best responses of the 39 patients with baseline measurable disease in the niraparib plus nivolumab group. (B) Best responses of the 39 patients with baseline measurable disease in the niraparib plus ipilimumab group. Canonical variants are those on the *BRCA1*, *BRCA2* or *PALB2* genes. The remaining DDR variants were non-canonical. DDR=DNA damage repair. *New lesions.

ONGOING…

Meeting Abstract | 2021 Gastrointestinal Cancers Symposium

PANCREATIC CANCER

Randomized phase II trial of olaparib + pembrolizumab versus olaparib alone as maintenance therapy in metastatic pancreatic cancer patients with germline BRCA1 or BRCA2 (g*BRCA*1/2+) mutations: SWOG S2001.

- gBRCA1/2 mutations

- No progression after receiving 4 to 6 months of platinum chemotherapy (FOLFIRINOX, FOLFOX or gemcitabine/cisplatin)

-- > **primary objective** of this study is to evaluate the PFS of mPDA pts treated with olaparib + pembrolizumab compared to olaparib alone as maintenance therapy.

ONGOING…
POLAR → Pembro-Olaraparib

- **Cohort A: Core HRD** Patients with either pathogenic germline or somatic alterations of 3 core homologous recombination-genes (HR-genes) - (BRCA1/2, or PALB2) who have stable or responding disease on first-line or second-line platinum therapy in two consecutive imaging assessments over at least 4 months.

- **Cohort B: Non core HRD Patients** with either pathogenic somatic or germline non-core 14 HR-gene alterations (ATM, BAP1, BARD1, BLM, BRIP1, CHEK2, FAM175A, FANCA, FANCC, NBN, RAD50, RAD51, RAD51C, RTEL1) who have stable or responding disease on first-line or second-line platinum therapy in two consecutive imaging assessments over at least 4 months.

- **Cohort C: Platinum sensitive** Patients without any of the above HR-gene who have platinum-sensitivity, which is defined as a partial response (PR) or complete response (CR) for the best overall response (BOR) during at least 4 months on platinum based therapy. Variants of unknown significance of candidate HR-genes from Cohort A or B will be eligible for Cohort C if they meet the partial response to platinum criterion.

ONGOING… iPARP + otros

A phase 2 Study of Cediranib (anti-VEGF) in Combination With Olaparib in Advanced Solid Tumors.

A phase 2 Trial of Ceralasertib (inhibitor of ataxia telangiectasia and Rad3-related kinase) Alone and in Combination With Olaparib or Durvalumab in Patients With Selected Solid Tumor Malignancies who harbor *ARID1A* expression or *ATM* loss/mutations

A phase 1b/2, study of combinations of avelumab, binimetinib and talazoparib patients with metastatic pancreatic ductal adenocarcinoma and other locally advanced or metastatic KRAS- or NRAS-mutant solid tumors.

Pancreas Cancer

EA2192 / APOLLO

APOLLO: A Randomized Phase II Double-Blind Study of Olaparib versus Placebo Following Curative Intent Therapy in Patients with Resected Pancreatic Cancer and a Pathogenic BRCA1, BRCA2 or PALB2 Mutation

STATUS: ACTIVE

→ Patient must have undergone at least 3 combined of perioperative (neoadjuvant, adjuvant or a combination of both) **systemic, multi-agent chemotherapy**. Patients may have had up to 6 months of perioperative systemic therapy as deemed appropriate by their primary treating medical team.

CONCLUSIONES

- EC de mantenimiento con IPARP tras respuesta mantenida a QT basada en platinos son escasos y solo existe un fase III actualmente.
- Rucaparib y Olaparib son los IPARP que tendrían “indicación”/aprobación en las guías
- Combinación IPARP e inmunoterapia puede resultar prometedor. Múltiples ensayos *ongoing*, pero fases precoces.
- *Ongoing* también en adyuvancia y en combinación con otros agentes.

CONCLUSIONES

- Resistencia a iPARP actualmente puede ser una limitación clara
- **Necesidad de identificar más y mejor a los pacientes que se pueden beneficiar de tratamiento con iPARP en cáncer de páncreas**.