XXIV Simposio de Revisiones en Cáncer
"Tratamiento médico del cáncer en el año 2022"

Incorporando medicina de precisión en cáncer de páncreas

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Epidemiology

Ten Leading Cancer Types for the Estimated New Cancer Cases and Deaths by Sex, United States, 2022

Estimated New Cases

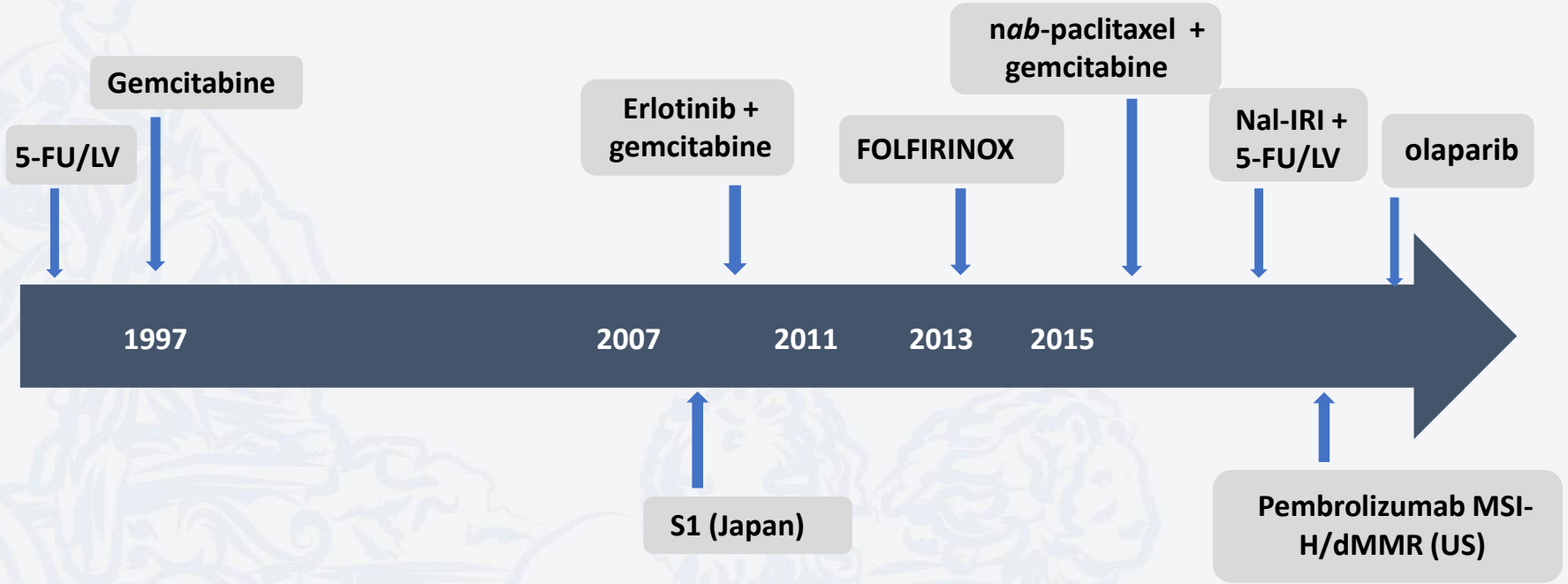
Males			Females		
Prostate	268,490	27%	Breast	287,850	31%
Lung & bronchus	117,910	12%	Lung & bronchus	118,830	13%
Colon & rectum	80,690	8%	Colon & rectum	70,340	8%
Urinary bladder	61,700	6%	Uterine corpus	65,950	7%
Melanoma of the skin	57,180	6%	Melanoma of the skin	42,600	5%
Kidney & renal pelvis	50,290	5%	Non-Hodgkin lymphoma	36,350	4%
Non-Hodgkin lymphoma	44,120	4%	Thyroid	31,940	3%
Oral cavity & pharynx	38,700	4%	Pancreas	29,240	3%
Leukemia	35,810	4%	Kidney & renal pelvis	28,710	3%
Pancreas	32,970	3%	Leukemia	24,840	3%
All Sites	**983,160**	**100%**	**All Sites**	**934,870**	**100%**

Estimated Deaths

Males			Females		
Lung & bronchus	68,820	21%	Lung & bronchus	61,360	21%
Prostate	34,500	11%	Breast	43,250	15%
Colon & rectum	28,400	9%	Colon & rectum	24,180	8%
Pancreas	25,970	8%	Pancreas	23,860	8%
Liver & intrahepatic bile duct	20,420	6%	Ovary	12,810	4%
Leukemia	14,020	4%	Uterine corpus	12,550	4%
Esophagus	13,250	4%	Liver & intrahepatic bile duct	10,100	4%
Urinary bladder	12,120	4%	Leukemia	9,980	3%
Non-Hodgkin lymphoma	11,700	4%	Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	10,710	3%	Brain & other nervous system	7,570	3%
All Sites	**322,090**	**100%**	**All Sites**	**287,270**	**100%**

- Siegel et al, CA Cancer J Clin 2022

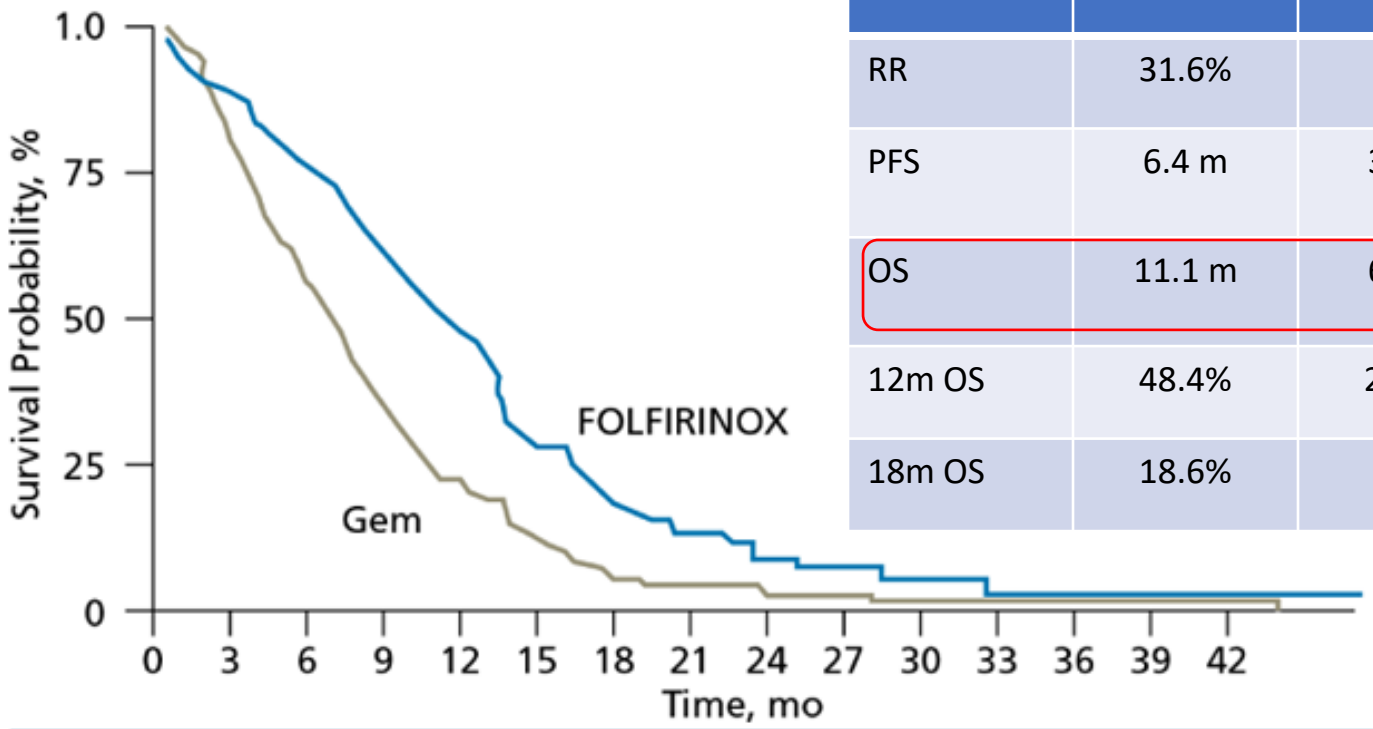
Evolution of Treatment of Metastatic Pancreatic Cancer
The Story So Far



5-FU, 5-fluorouracil; dMMR, mismatch repair deficient; LV, leucovorin; mPCA, metastatic pancreatic adenocarcinoma; MSI-H, microsatellite instability-high; Nal-IRI, nanoliposomal irinotecan

Glimelius B, et al. *Ann Oncol.* 1996;7(6):593-600. Burris HA 3rd, et al. *J Clin Oncol.* 1997;15(6):2403-2413. Ueno H, et al. *J Clin Oncol*. 2013;31(13):1640-1648. Moore MJ, et al. *J Clin Oncol.* 2007;25(15):1960-1966. Conroy T, et al. *N Engl J Med.* 2011;364(19):1817-1825. Von Hoff DD, et al. *N Engl J Med.* 2013;369(18):1691-1703. Wang-Gillam A, et al. *Lancet*. 2016;387(10018):545-557. Le DT, et al. *N Engl J Med*. 2015;372(26):2509-2520.

FOLFIRINOX: Phase II/III study (PRODIGE 4 - ACCORD 11)



Outomes	FOLFIRINOX	Gemcitabine	HR p
RR	31.6%	9.4%	<0.001
PFS	6.4 m	3.3 m	0.47 <0.001
OS	11.1 m	6.8 m	0.57 <0.001
12m OS	48.4%	20.5%	
18m OS	18.6%	6%	

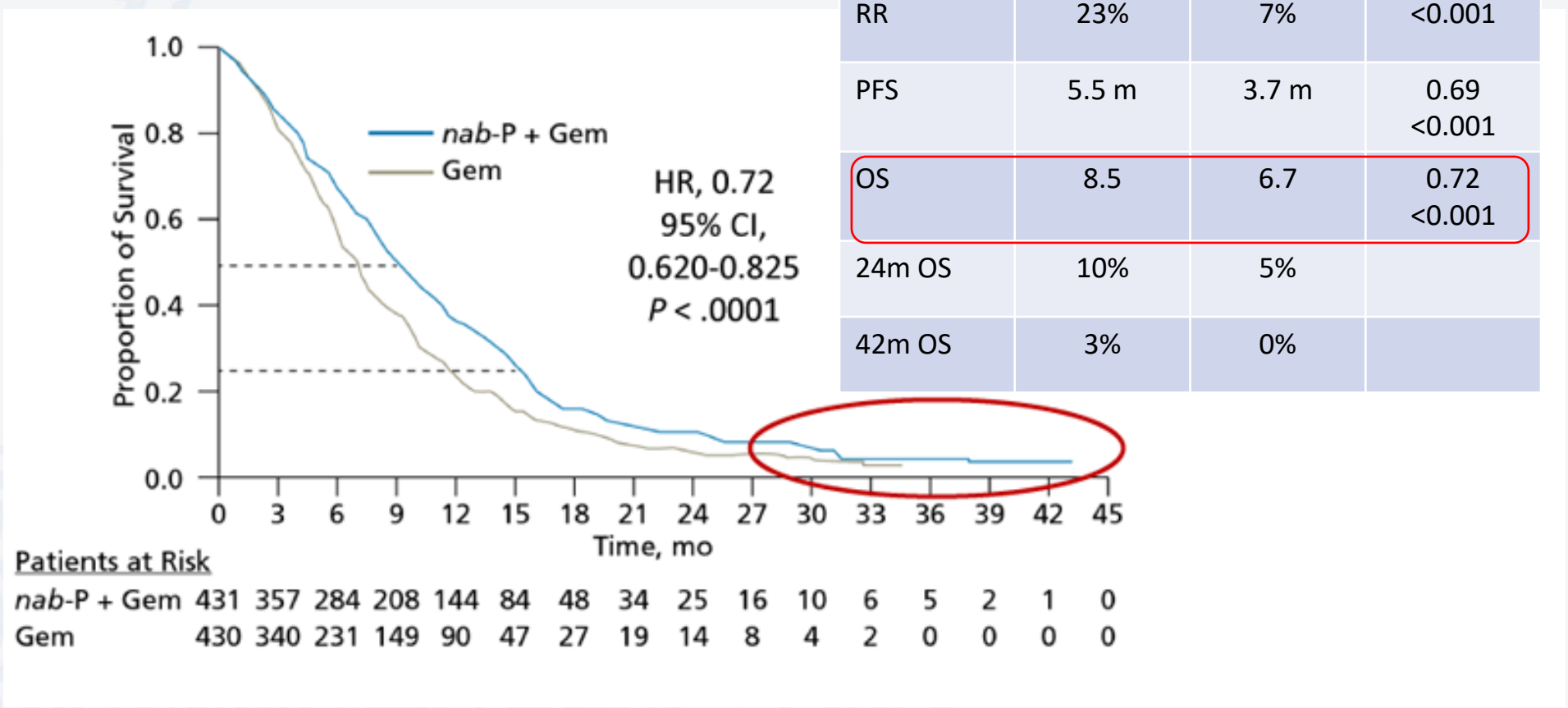
- Median follow-up 26.6 mo (95% CI, 20.5-44.9)
- OS analysis based on 273 deaths among 342 patients (79.8%)

[a] Investigator assessment.

Conroy T et al. NEJM. 2011

Nab-Paclitaxel + Gemcitabine: phase III study (MPACT): Overall Survival

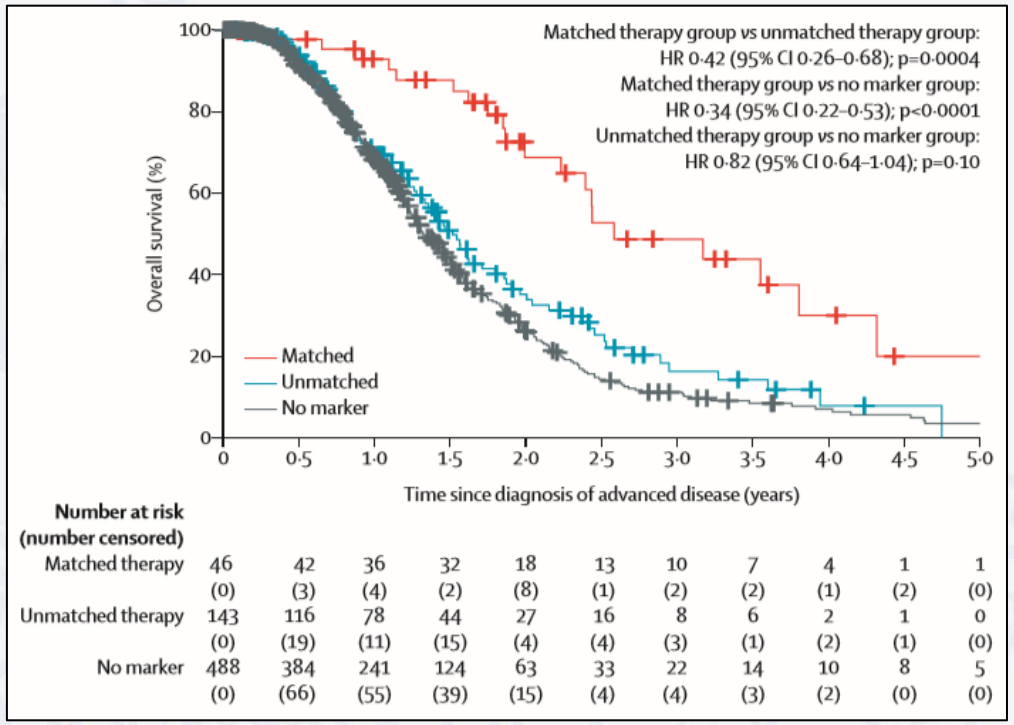
Outomes	Gemci-nab	Gemcitabine	HR, p
RR	23%	7%	<0.001
PFS	5.5 m	3.7 m	0.69 <0.001
OS	8.5	6.7	0.72 <0.001
24m OS	10%	5%	
42m OS	3%	0%	



Von Hoff D et al. NEJM. 2013

Papel de la medicina de precision en cáncer de páncreas

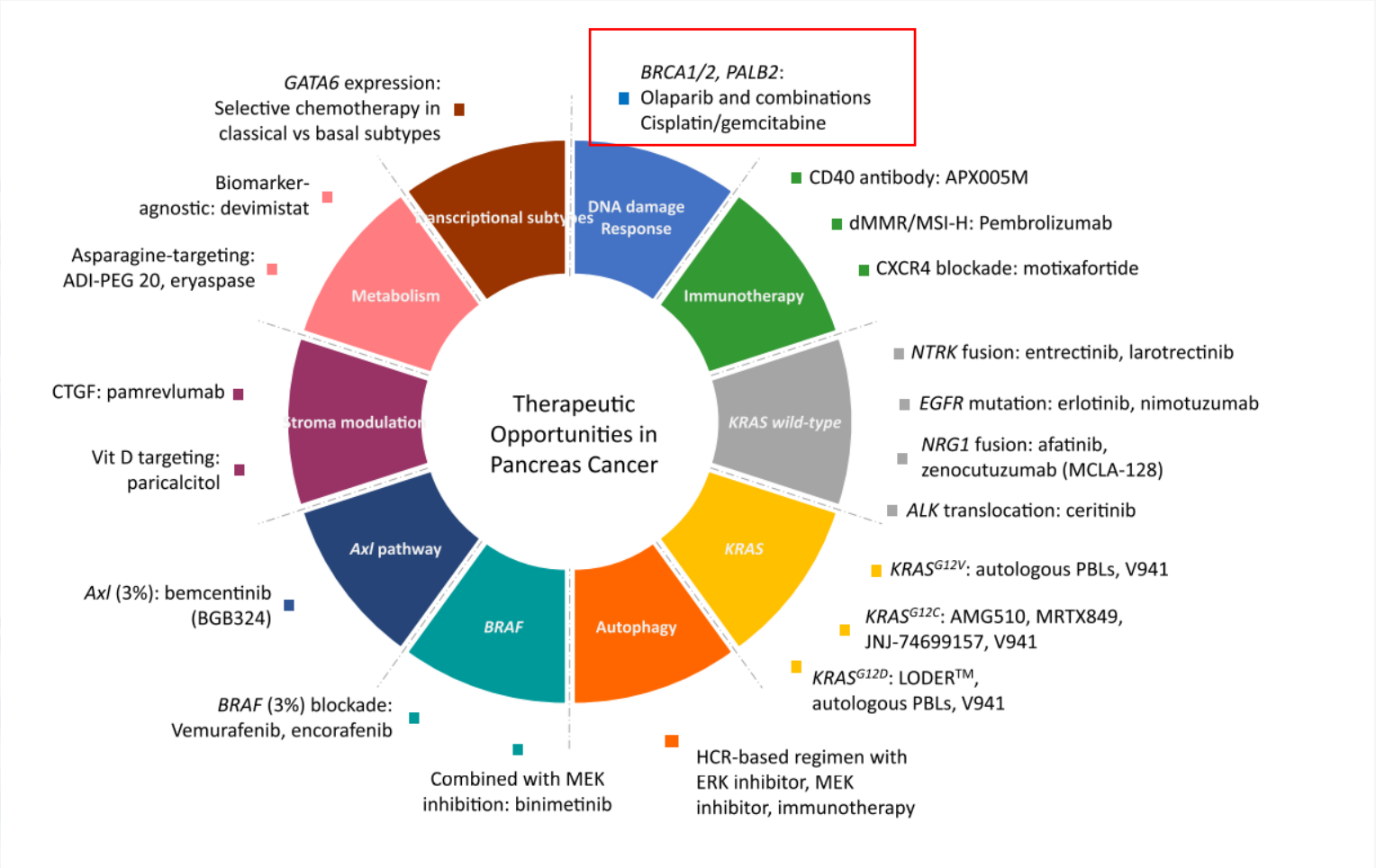
Is there any role for molecular profiling in mPDAC?



Pishvaian M et al, Lancet Oncology 2020

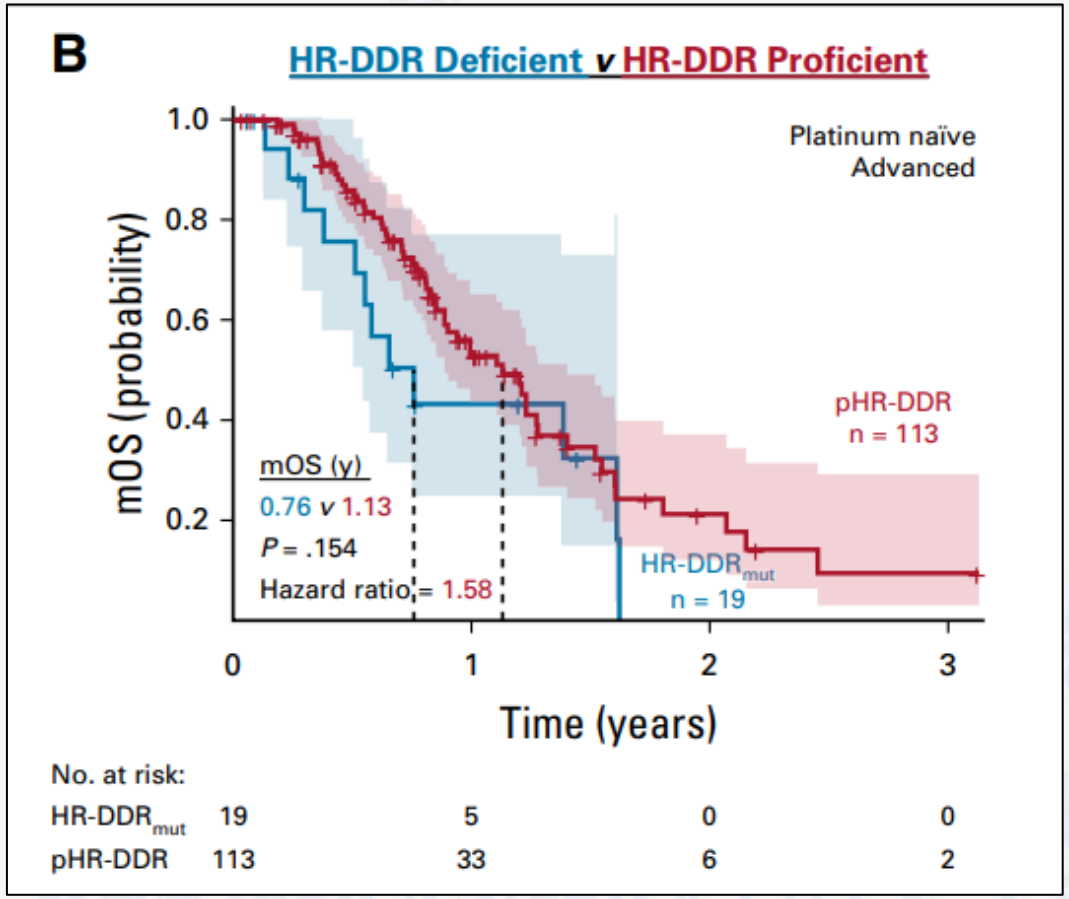
- **677 patients in the analysis and 189 (27%) with actionable mutation.**
- **46 (24%) patients received matched therapy.**
- **mOS matched vs no matched: 2.58 years vs 1.51 years, HR 0.42.**

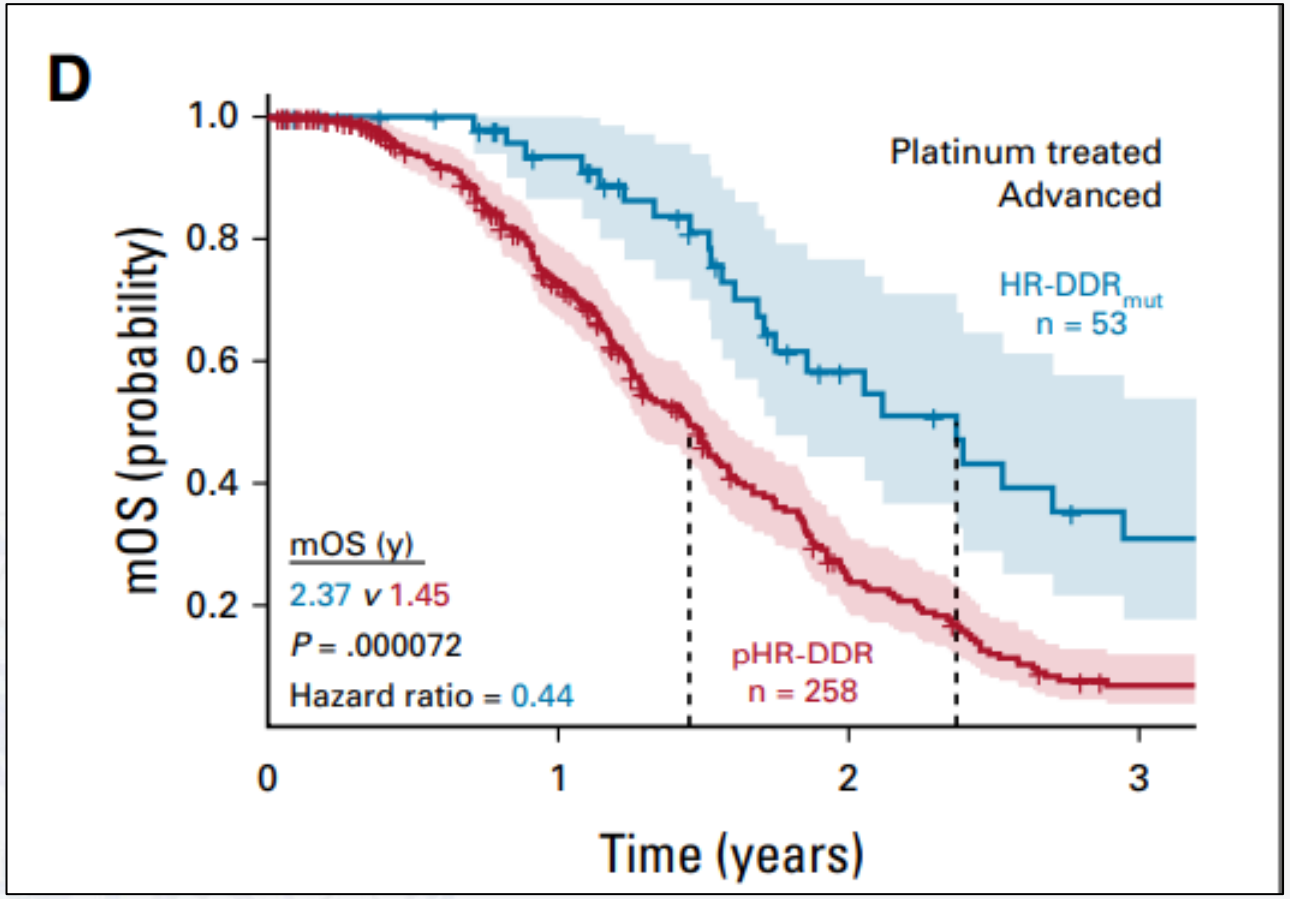
Potential actionable pathways implicated in pancreatic tumorigenesis



Zheng-Lin et al. Seminars in Oncology 2021

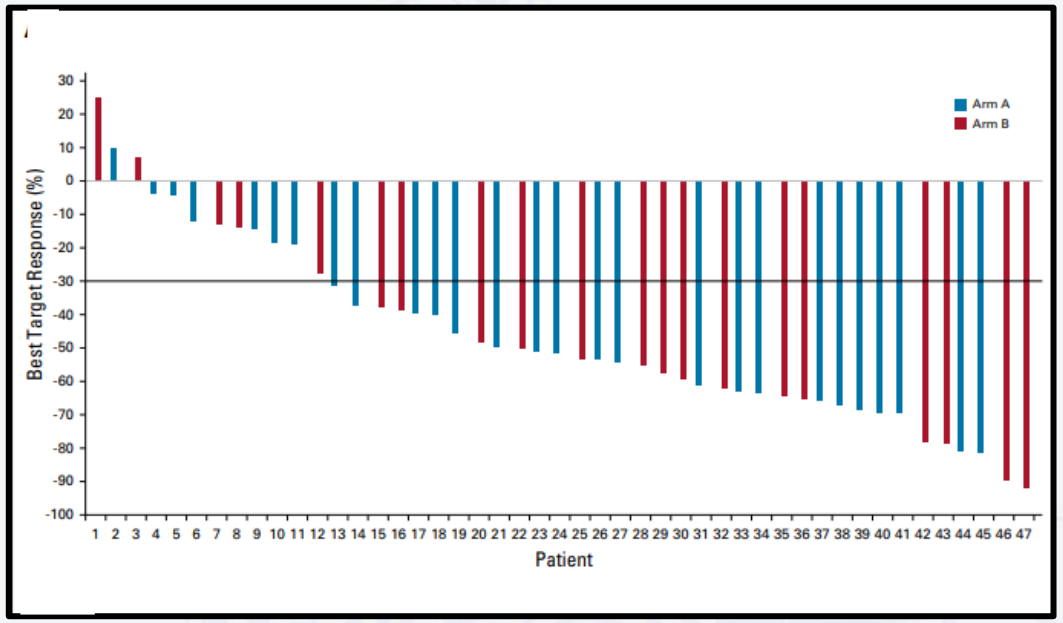
How we have to treat g*BRCA* mutated advanced PDAC patients?



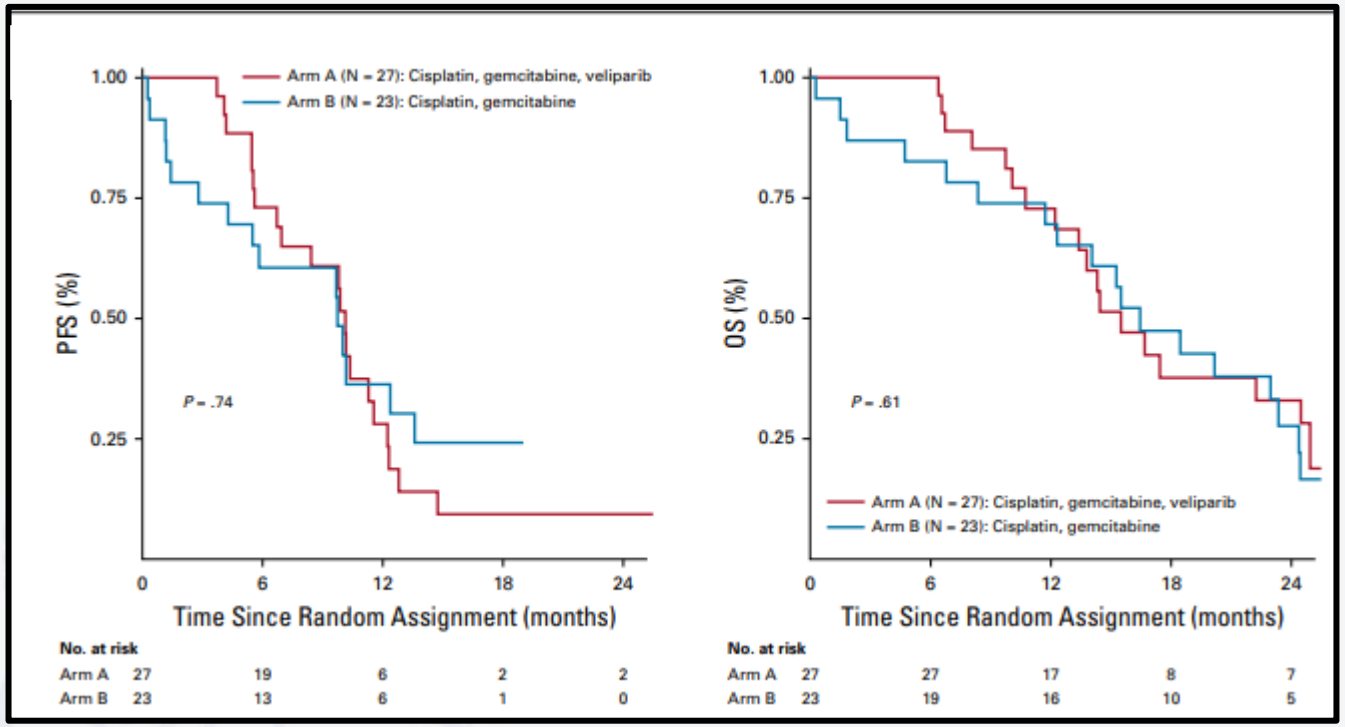


Pishvaian M, *et al*. *JCO Precis Oncol*. 2019.

Gemcitabine and cisplatin: An active regimen in DDR mut population



A: cisplatin 25 mg/m^2 + gemcitabine 600 mg/m^2+ veliparib 80 mg bid
B: cisplatin + gemcitabine



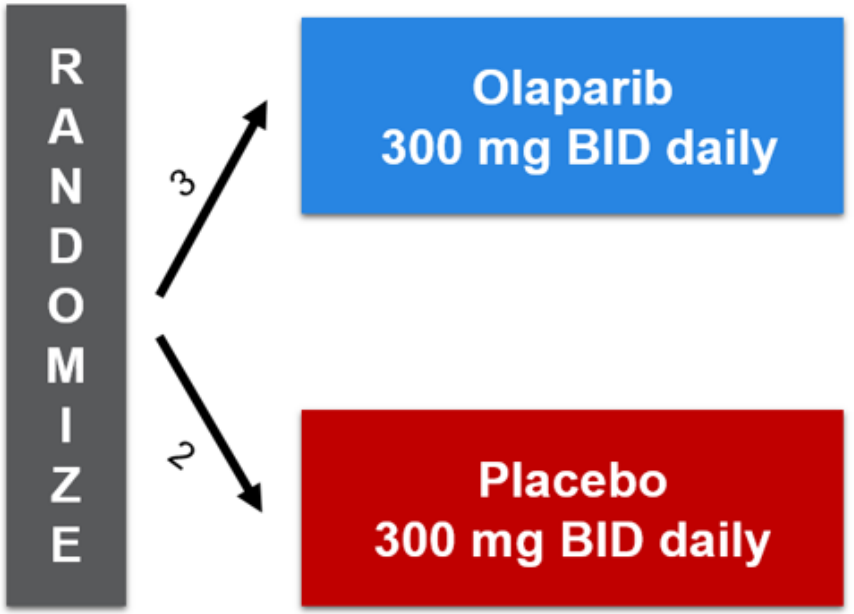
RR: 74% vs 65.2%
PFS: 10.1 m vs 9.7 m
OS: 15.5 m vs 16.4 m

O´Reilly et al, J Clin Oncol 2020; 38:1378-1388

POLO: A phase 3 International PARPi Maintenance Study in Patients who are gBRCA Mutated

- mPCA
- Prior platinum therapy
- Germline *BRCA* mutated
- ECOG 0-1

N = 154
Primary endpoint = PFS

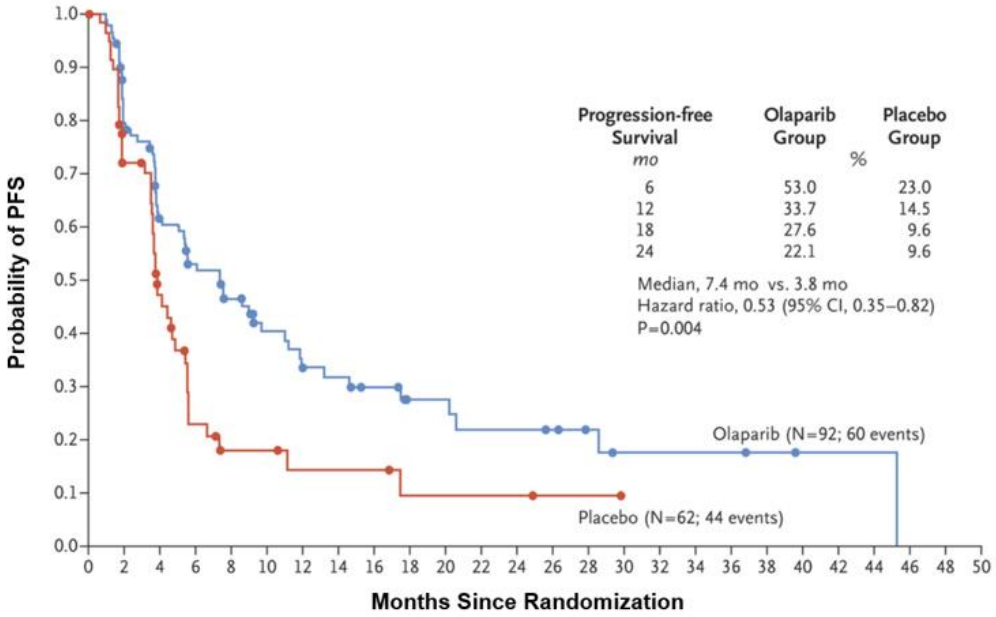


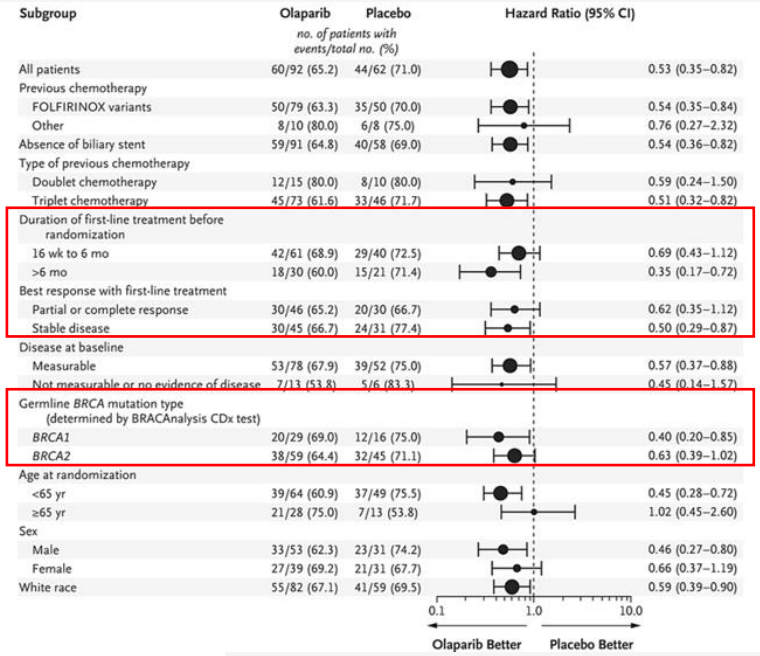
38% of gBRCAm patients had disease progression, were ineligible, or declined randomization

Golan et al, N Engl J Med 2018

Polo trial: Efficacy

Progression free survival



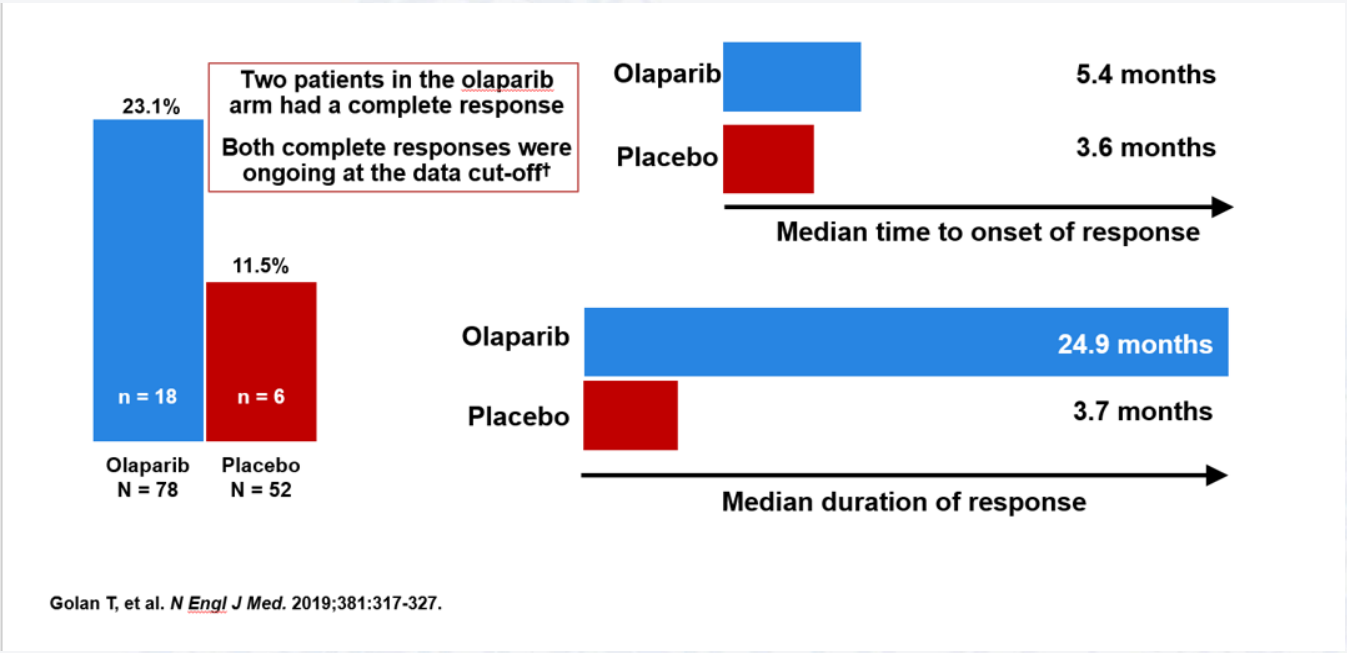


- Olaparib arm: Reduction in risk of progression of 47%
- This benefit was observed in all subgroups irrespectively of *BRCA* mutation, best response of induction treatment or duration of this treatment.

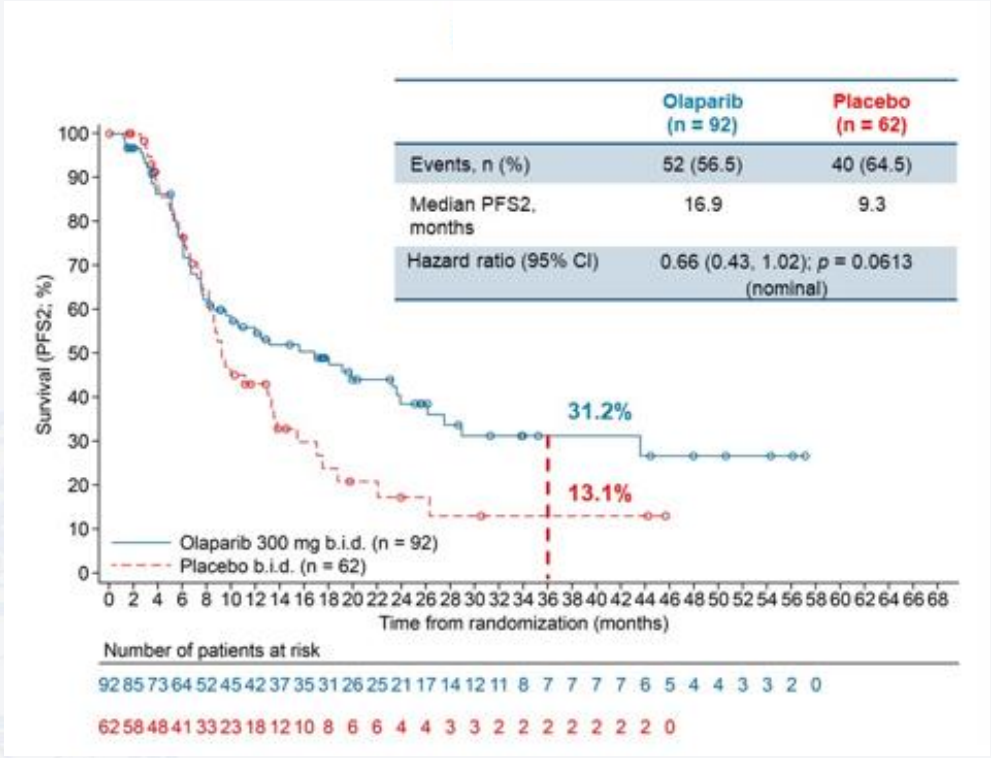
Golan et al, N Engl J Med 2018

Polo trial: Efficacy

Response Rate[1] and time to second progression (PFS2)[2]



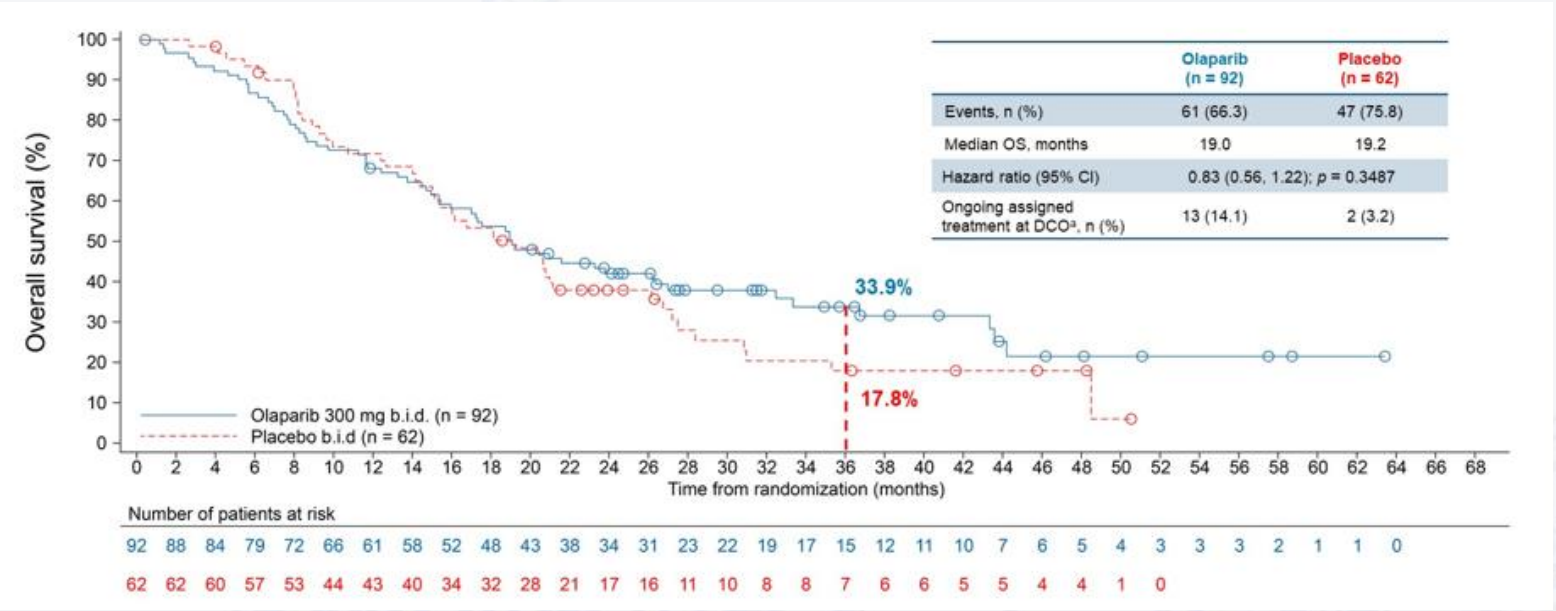
Golan T, et al. *N Engl J Med.* 2019;381:317-327.



1- Golan et al, N Engl J Med 2018
2- Presented By Talia Golan at 2021 Gastrointestinal Cancers Symposium

Polo trial: Efficacy

Overall Survival



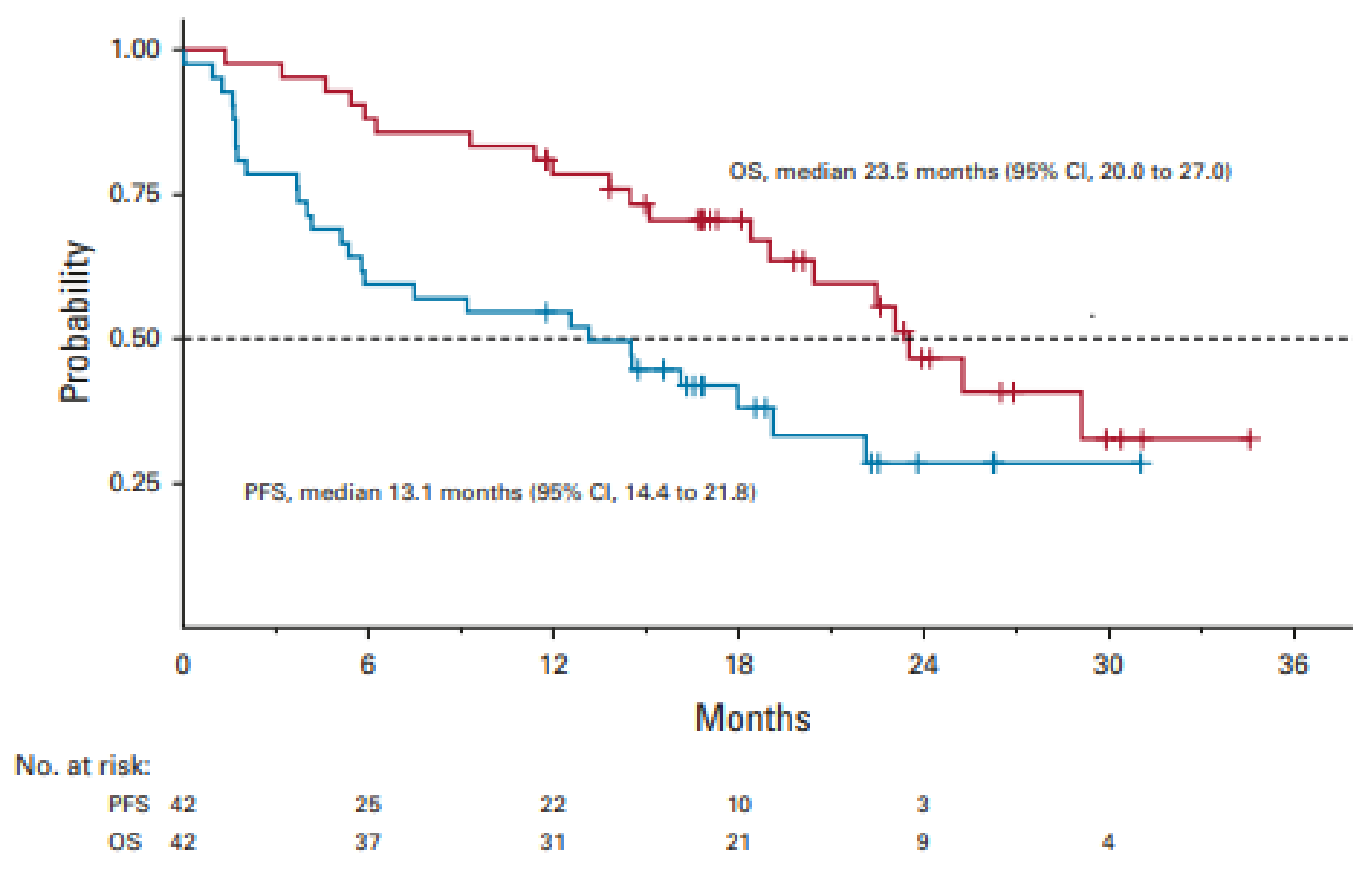
	Olaparib (n = 92)	Placebo (n = 62)
Events, n (%)	61 (66.3)	47 (75.8)
Median OS, months	19.0	19.2
Hazard ratio (95% CI)	0.83 (0.56, 1.22); $p = 0.3487$	
Ongoing assigned treatment at DCO[a], n (%)	13 (14.1)	2 (3.2)

At 3 years:
-17.2% of patients remained on Olaparib treatment vs 3.3% on placebo.
-21.5% in the Olaparib arm remained free of subsequent therapies vs 3.6% in placebo arm
-33.9% of patients receiving Olaparib were alive vs 17.8% on placebo

-Subsequent chemotherapy (≥2L): Olaparib cohort 35.3%, placebo cohort 64.7%
Olaparib
-Subsequent PARP inhibitor treatment: One patient in the olaparib group and 9 patients in the placebo group

Presented By Talia Golan at 2021 Gastrointestinal Cancers Symposium

Phase II maintenance Rucaparib

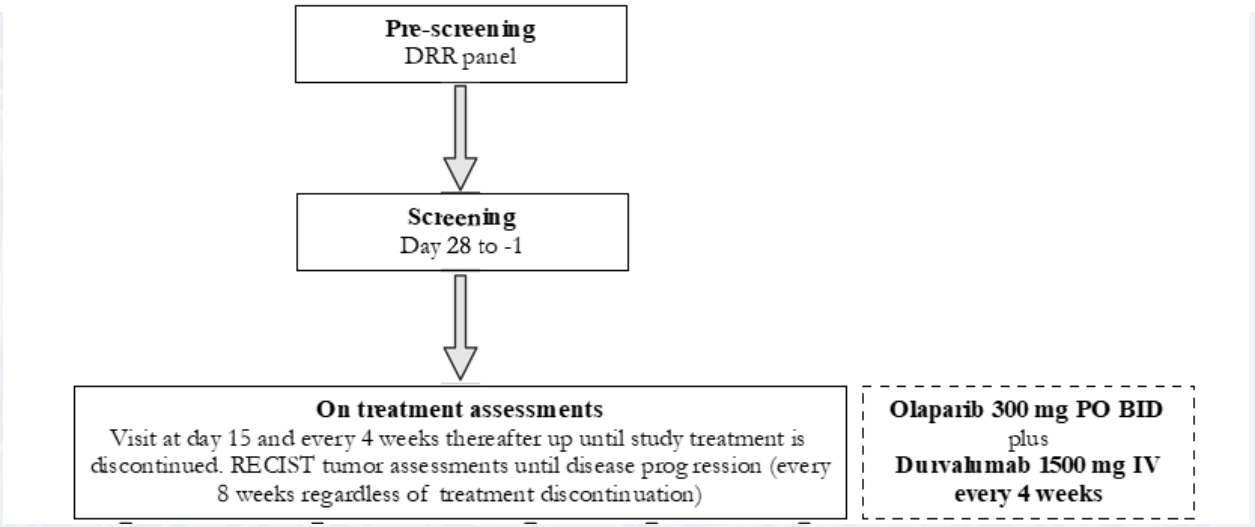


RR 41.7% (3CR, 12 PR)

N 46 germline or somatic mutations in BRCA 1, 2 or PALB2 and received at least 16 weeks of platinum based chemotherapy

Reiss et al, J Clin Oncol 2021

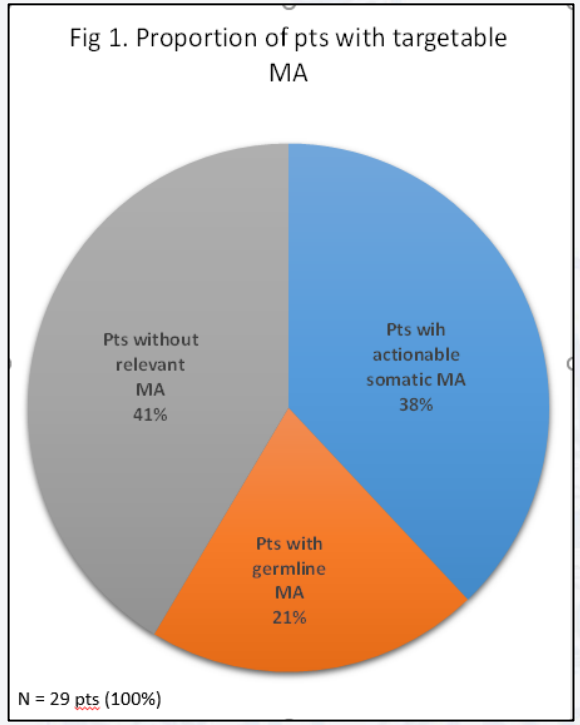
Olaparib and durvalumab (MEDI4736) in patients with metastatic pancreatic cancer and DNA Damage Repair genes alterations



- Open-label, single-arm, multicentric phase II clinical trial of a combination of durvalumab and olaparib
- Somatic and germline BRCA1, BRCA2, PALB2, RAD51C, RAD51D and other functional DDR genes.
- Patients have received up to 2 lines of chemotherapy and who have had benefit from platinum-based chemotherapy.
- Primary objective ORR

KRAS wild-type pancreatic cancers

VHIO: *KRAS* Wild-Type (N= 29)



Molecular alteration	%	n
ATM	9,5%	2
BRAF	4,8%	1
BRCA1	9,5%	2
BRCA2	19,0%	4
*CCDC6/RET **	4,8%	1
CDKN2A del	4,8%	1
*ENOX2/BRAF**	4,8%	1
ERBB3	4,8%	1
NOTCH1	4,8%	1
*NOTCH2/NRG1**	4,8%	1
PALB2	4,8%	1
PIK3CA	4,8%	1
PMS2	4,8%	1
RNF43	9,5%	2
STK11	4,8%	1
Total	100%	21

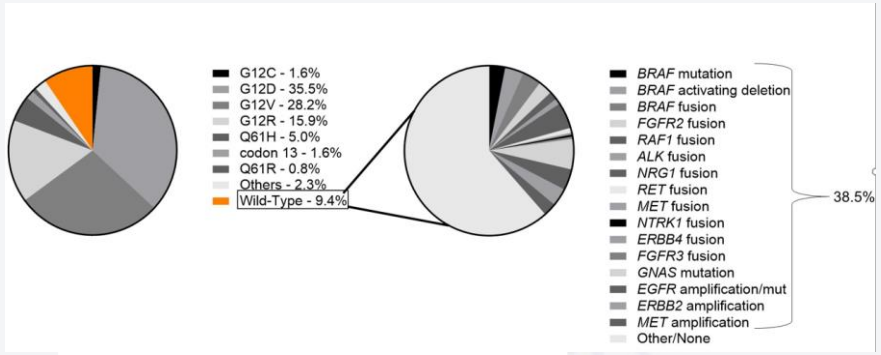
Germline event
Somatic alteration
DNA damage repair related

Most MA are mutations unless otherwise indicated
* Fusion

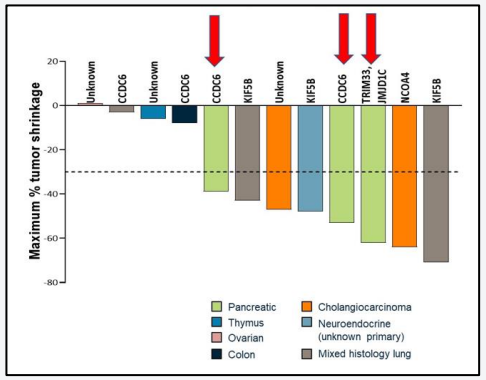
KRAS WT tumours are enriched in younger patients (under age 50 up to 20% _KRAS_ WT)

Presented in ESMO 2020 by Acosta D. et al.

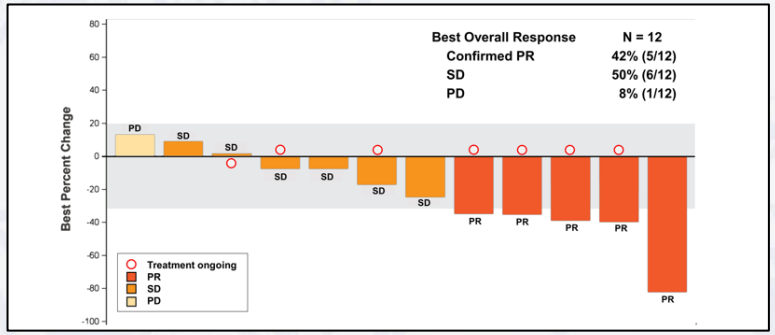
KRAS wild-type pancreatic cancers



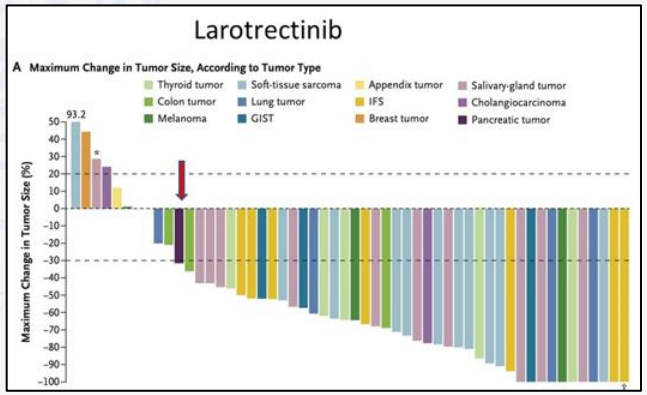
Pralsetinib in RET fusioned PDAC[1]



Zenocutumab in NRG1+ PDAC fusioned[2]

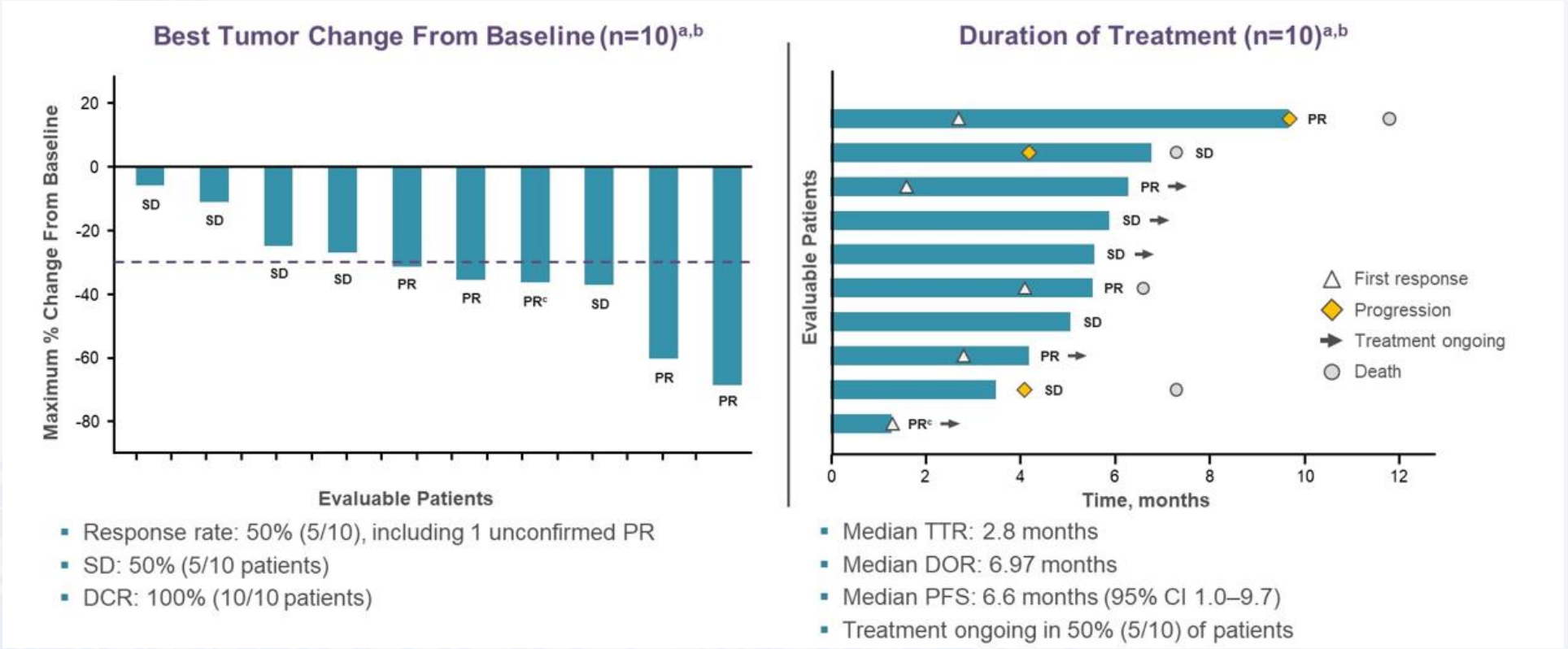


Larotrectinib approved by FDA[3]



1- Subbiah et al, ASCO 2020. 2-Schram et al, ASCO 2021, 3-Hong et al, Lancet Oncol 2020

Adagrasib in patients with advanced PDAC



- Response rate: 50% (5/10), including 1 unconfirmed PR
- SD: 50% (5/10 patients)
- DCR: 100% (10/10 patients)

- Median TTR: 2.8 months
- Median DOR: 6.97 months
- Median PFS: 6.6 months (95% CI 1.0–9.7)
- Treatment ongoing in 50% (5/10) of patients

Adagrasib (MRTX849) selective inhibitor KRAS G12C

Bekaii-Saab et al, presented in 2022 GI ASCO Meeting

Leukemia Inhibitory Factor (LIF) and PDAC

FRANK MCCORMICK

ARTICLE

https://doi.org/10.1038/s41467-019-11844-9 OPEN

nature COMMUNICATIONS

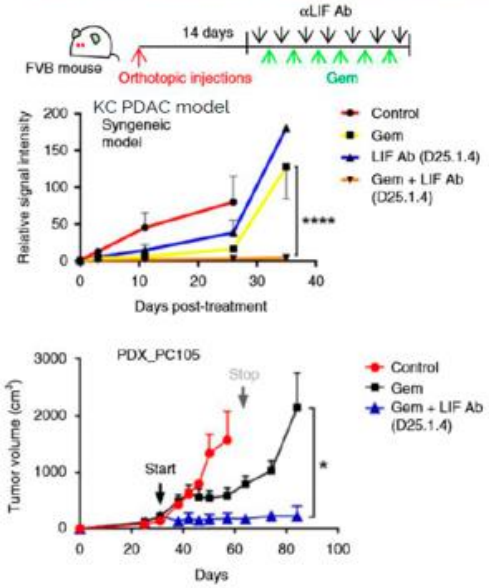
Blockade of leukemia inhibitory factor as a therapeutic approach to KRAS driven pancreatic cancer

KEY CONCLUSIONS

- LIF expression is induced by oncogenic KRAS (90% of PDAC)
- Anti-LIF treatment augments pancreatic tumor cell sensitivity to gemcitabine
- Downstream effects of LIF mediated by YAP and effects on the Hippo pathway

KC: LSL-Kras$^{G12D/+}$-Pdx-1-Cre. GEM: Genetically engineered mouse model

Wang MT. et al 2019 Nature Communications



MSC-1 STUDY DESIGN

MONOTHERAPY DOSE ESCALATION: DOSE LEVELS AND NUMBER OF PATIENTS TREATED

OBJECTIVES

- **Primary**: Safety, tolerability and recommended doses for future studies
- **Secondary**: Preliminary efficacy, PK, PD
- **Exploratory**: Impact of MSC-1 treatment on exploratory biomarkers

PATIENTS

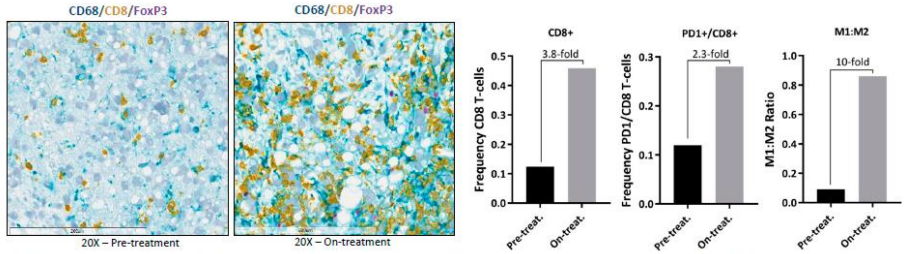
- All-comers, advanced solid tumor
- Multiple lines of therapy (median 3, range 1-9)
- Majority had rapidly progressed on their prior therapies

DOSE ESCALATION
Accelerated Titration / 3+3 Design
(n = 41)

ESCALATION	ESCALATION EXPANSIONS
1500 mg Q3W (n = 6)	1500 mg Q3W (n = 12)
1125 mg Q3W (n = 3)	1125 mg Q3W (n = 7)
750 mg Q3W (n = 3)	750 mg Q3W (n = 7)
225 mg Q3W (n = 1)	
75 mg Q3W (n = 2)	

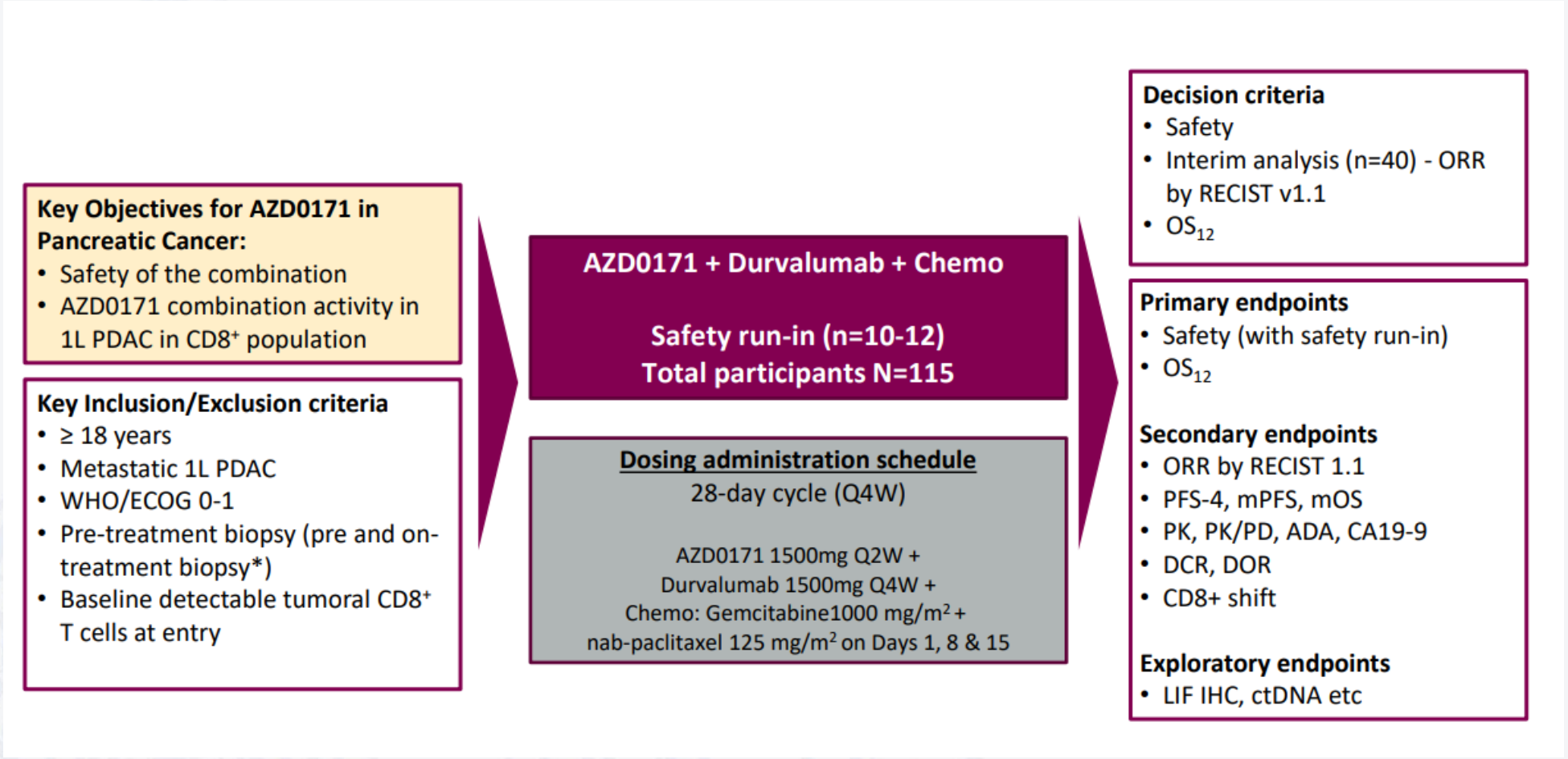
ESCALATION EXPANSION

- Additional PK/LIF stabilization data
- LIF levels by IHC in biopsies
- Assessment of PD modulation by multiplex IHC in biopsies:
  - CD206/CD163/CCL22 & CD68/MHCII (LIF biology)
  - pSTAT3 (LIF signaling)
  - CD8/FoxP3/CD68 & CD8/PD1 (Anti-tumor immune response)



- Potent increase in CD8 T-cell frequency and dramatic increase in the M1:M2 ratio observed in on-treatment relative to pre-treatment biopsies

Leukemia Inhibitory Factor (LIF) and PDAC



AZD0171 is a first-in class humanized monoclonal IgG1 antibody

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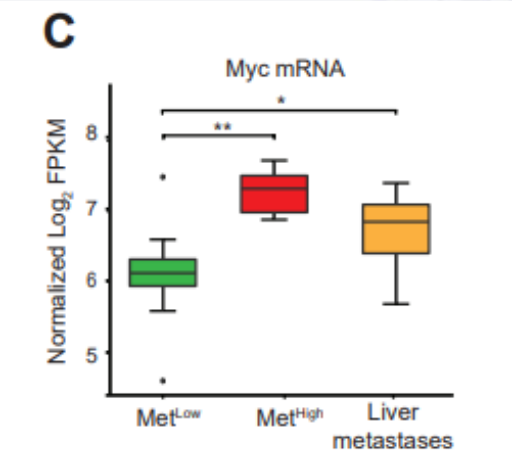
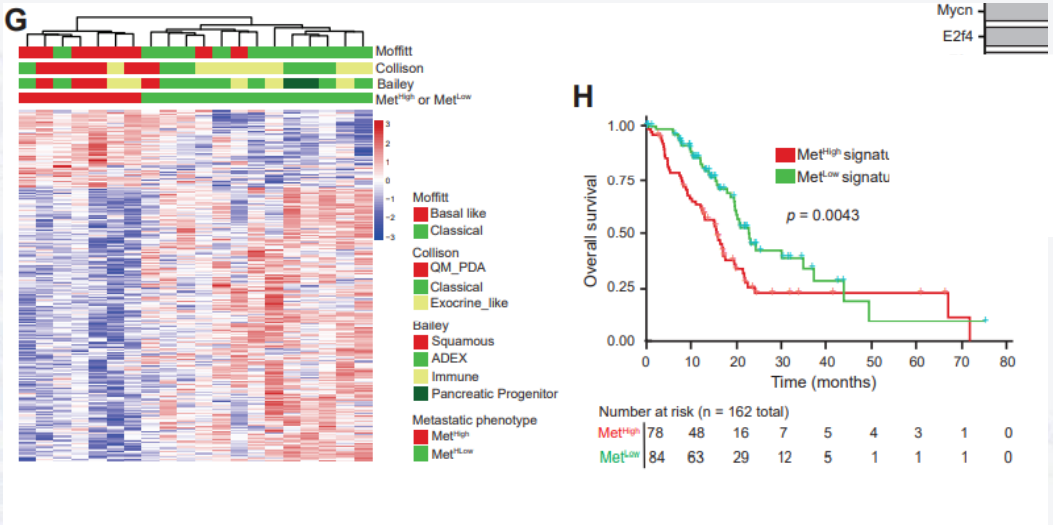
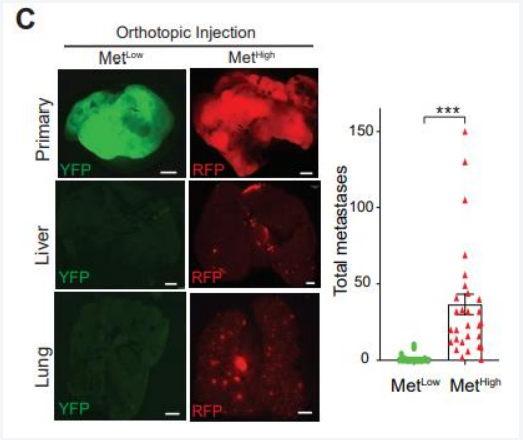
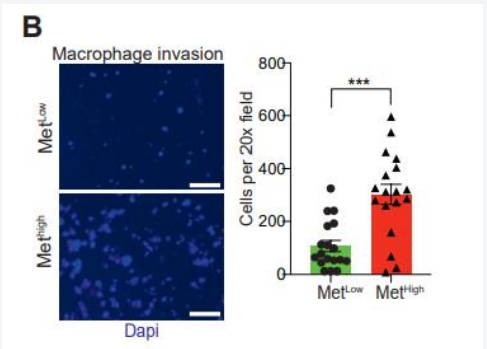
MYC as a potential driver of metastatic PDAC









VHIO Vall d'Hebron Institute of Oncology

First-in-human Phase I/II clinical trial with its first compound - a disruptive Myc inhibitor, Omomyc (OMO-103).

Maddipati et al, Cancer discovery 2021

Conclusiones

- El cáncer de páncreas es uno de los tumores con menos avances en supervivencia en la última década.
- Los pacientes portadores de mutación germinal de *BRCA* se benefician de una quimioterapia basada en platino y de un tratamiento con olaparib de mantenimiento.
- La población PDAC *KRAS* WT presenta un mayor porcentaje de alteraciones diana.
- En la población menor de 50 años la incidencia de KRAS WT incrementa.
- Adagrasib, un inhibidor de KRAS G12C demuestra prometedora actividad en PDAC.
- Debemos seguir en el esfuerzo de la investigación en PDAC para mejorar la disponibilidad de armas terapéuticas.

Muchas gracias por su atención