II JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN:
A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN
SEVILLA, 6 Y 7 DE FEBRERO DE 2025

INHIBIDORES DE CICLINAS EN CANCER DE MAMA METASTASICO

Blanca Cantos Sánchez de Ibargüen
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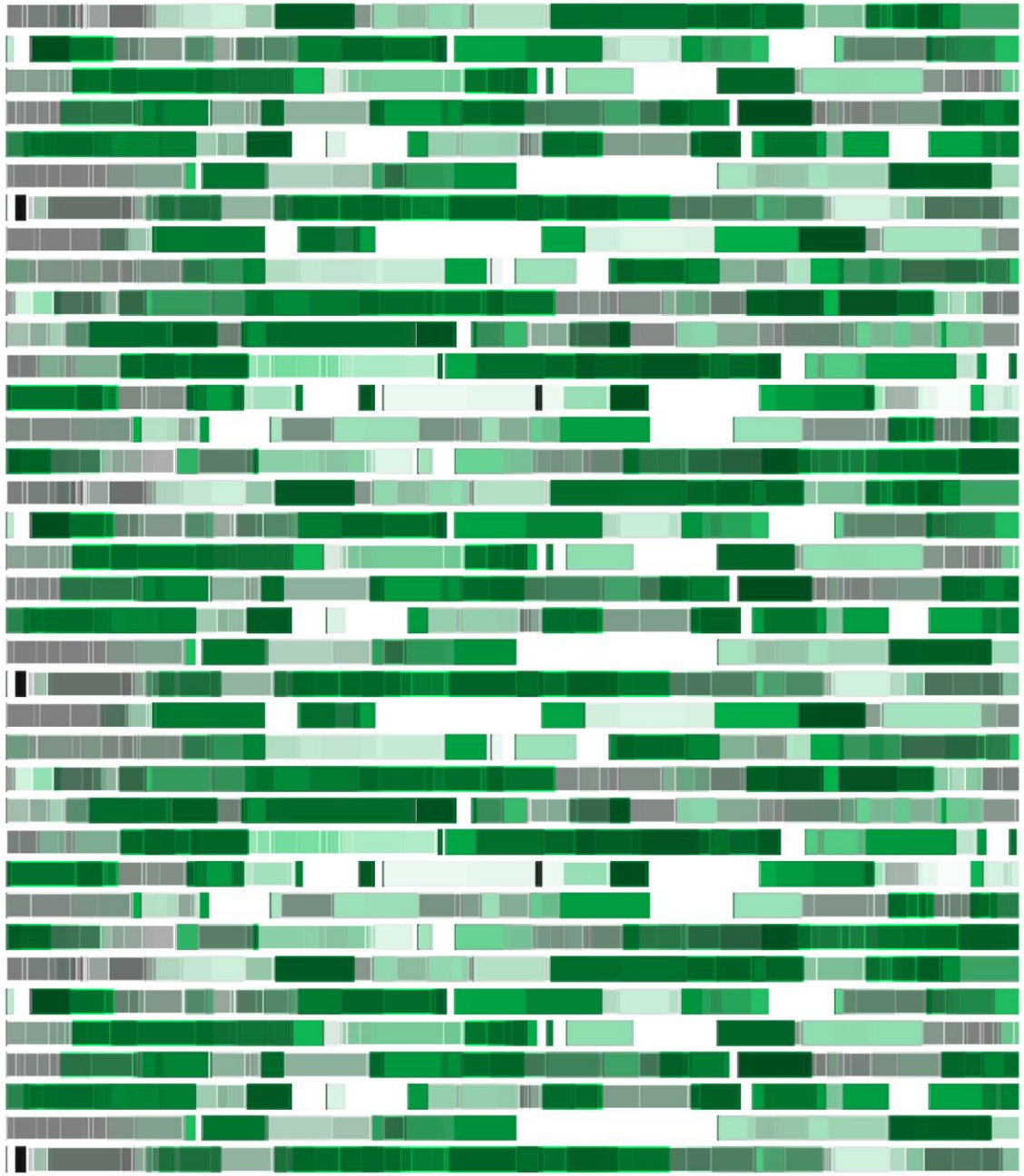
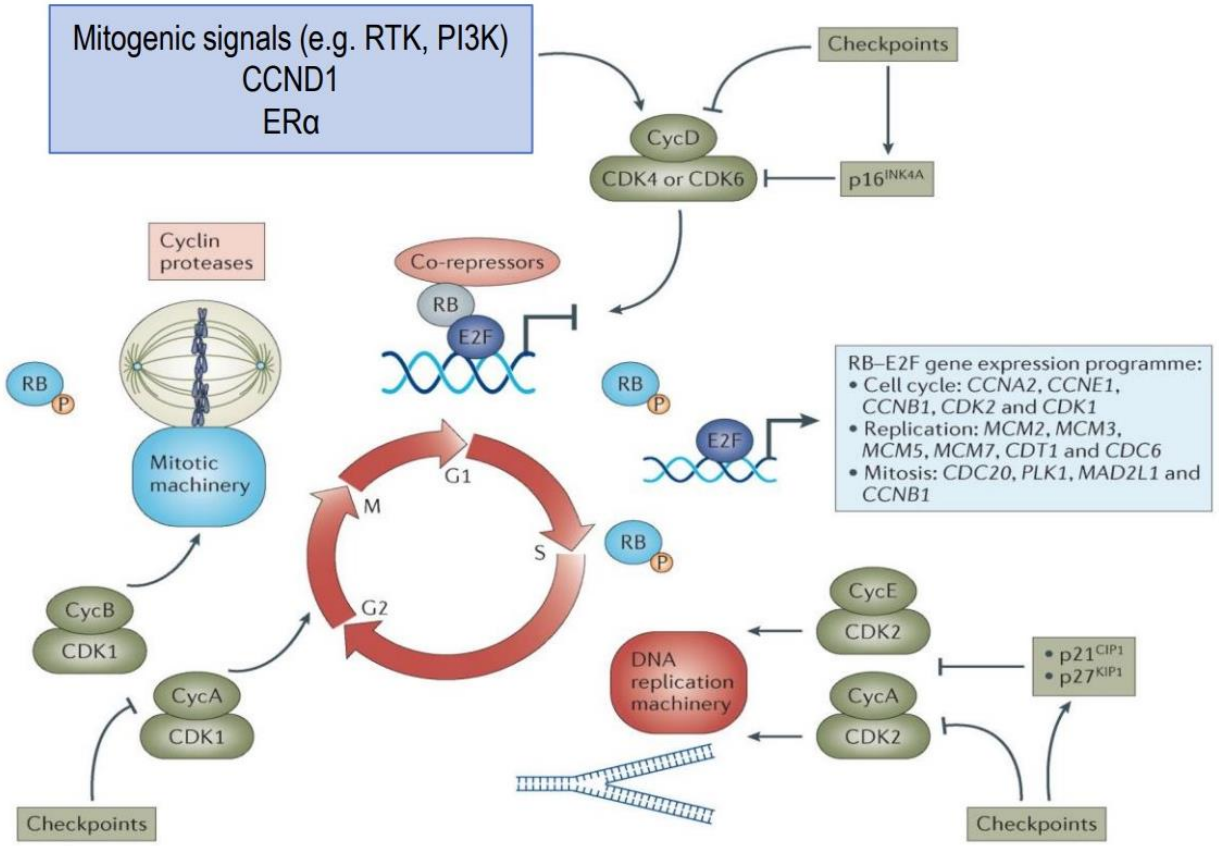
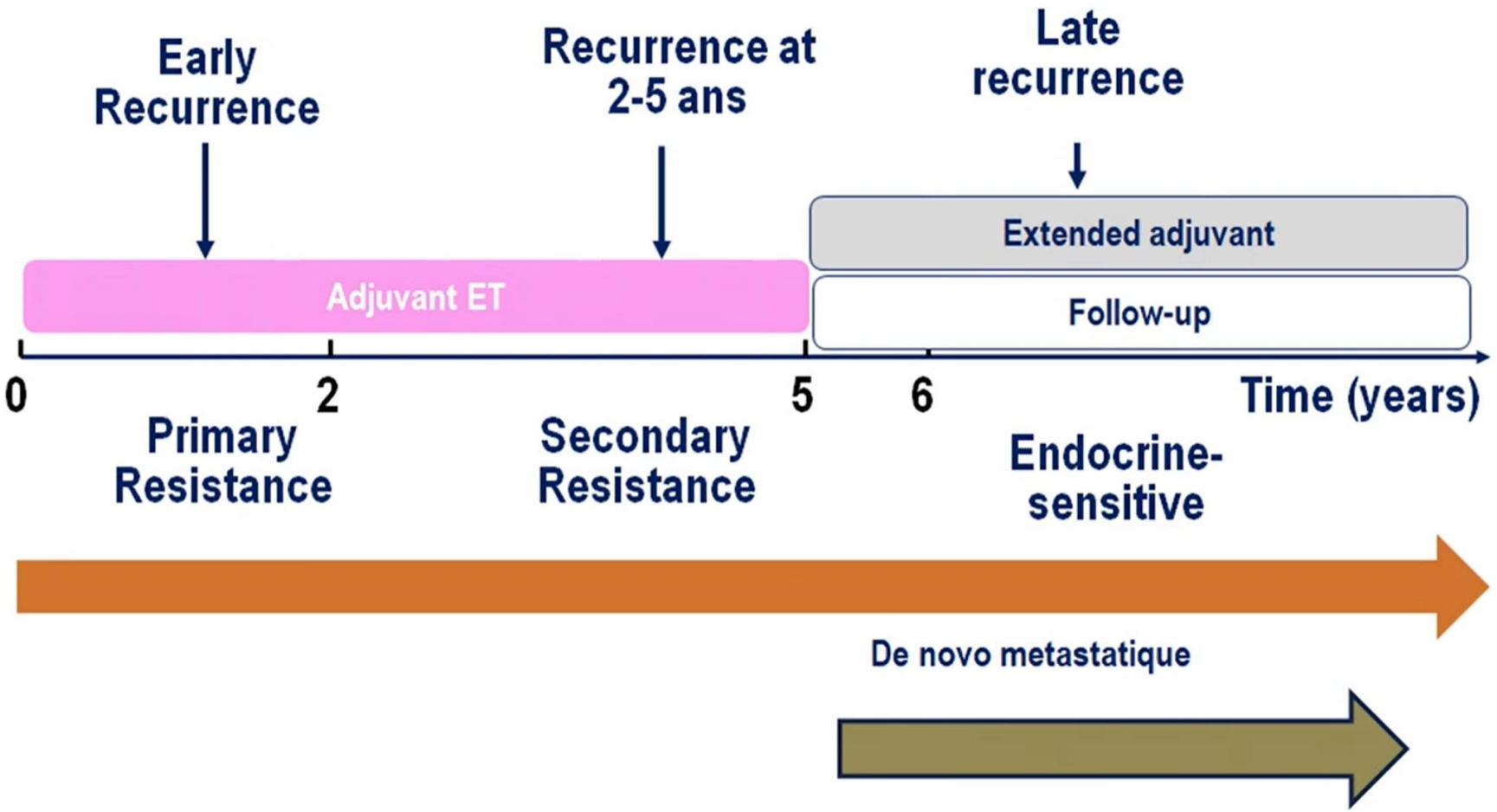


INH CICLINAS. MECANISMO DE ACCION

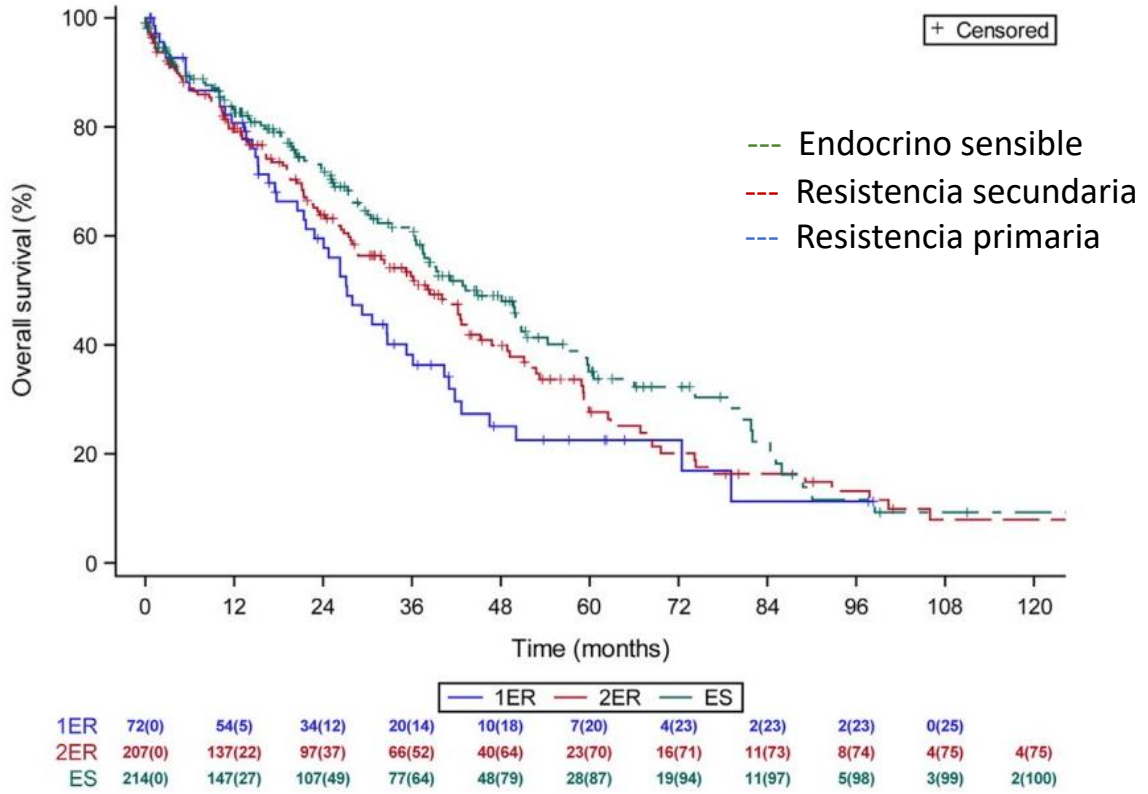


Asghar et al, Nat Rev Drug 2015

INTRODUCCION

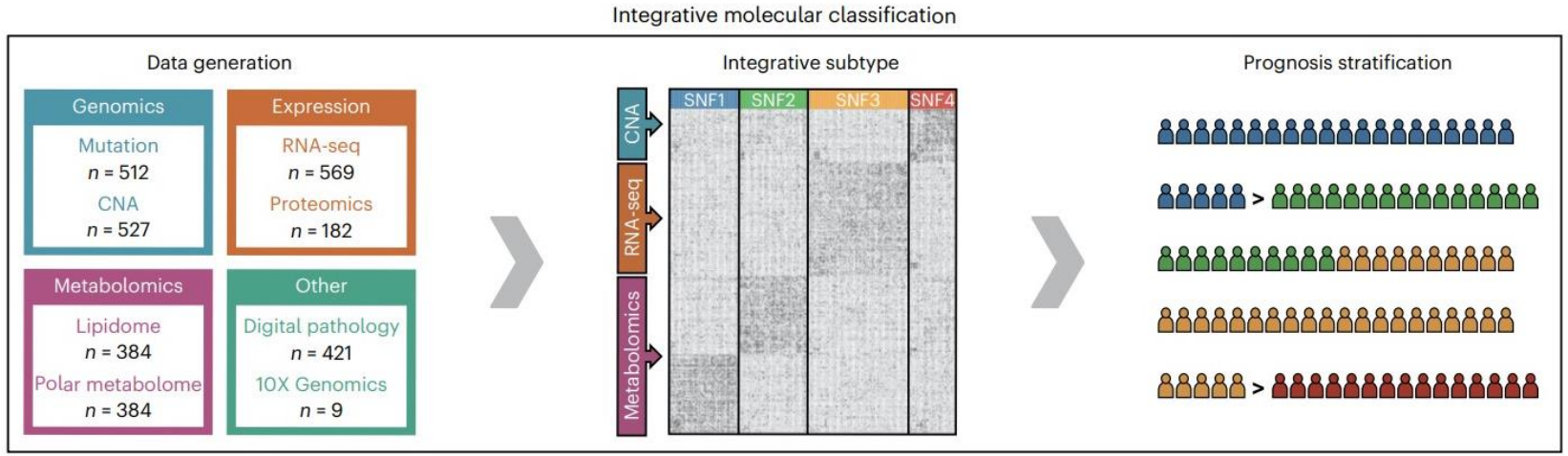


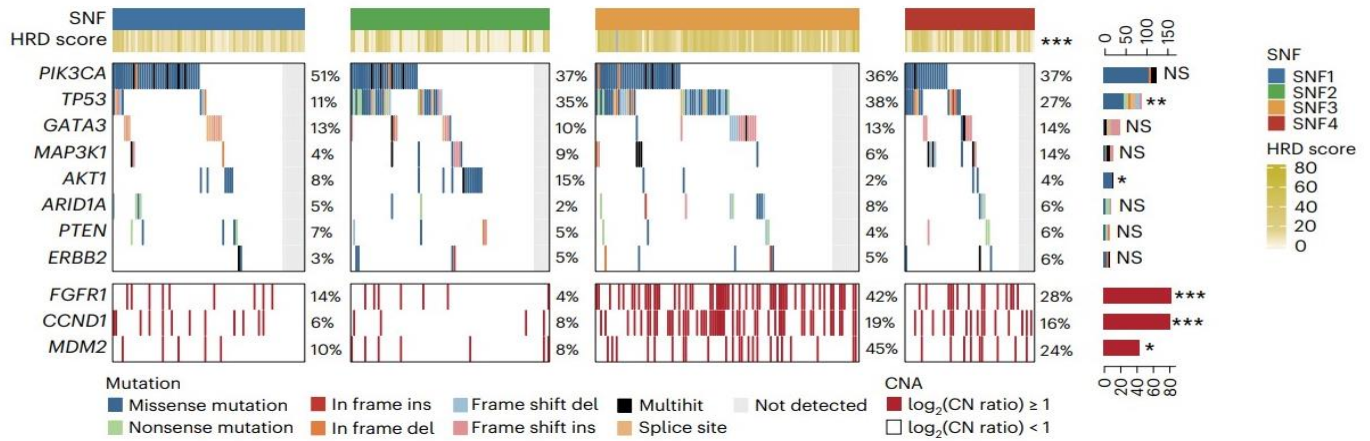
	Primary endocrine resistant cohort (n = 72)	Secondary endocrine resistant cohort (n = 207)	Endocrine sensitive cohort (n = 214)	p
(Continued from previous page)				
Metastatic site				0.003
Brain	6 (8.3%)	14 (6.8%)	8 (3.7%)	
Liver	33 (45.8%)	65 (31.4%)	47 (22.0%)	
Lung	7 (9.7%)	29 (14.0%)	36 (16.8%)	
Bone	25 (34.7%)	81 (39.1%)	100 (46.7%)	
Other	1 (1.4%)	18 (8.7%)	23 (10.8%)	



mOS was 27.2, 38.4 and 43.2 months, in patients with 1ER, 2ER and ES breast cancer, respectively (p = 0.03)

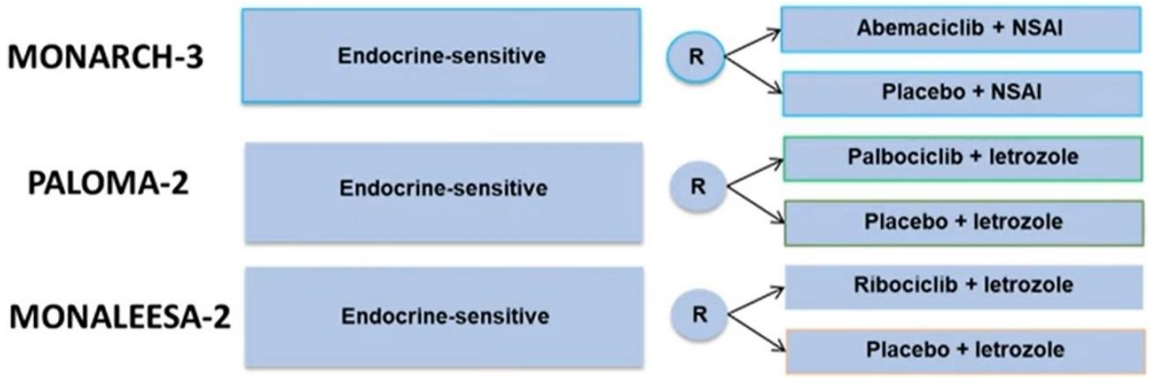
Lambertini et al. Eclinical Medicine 2023



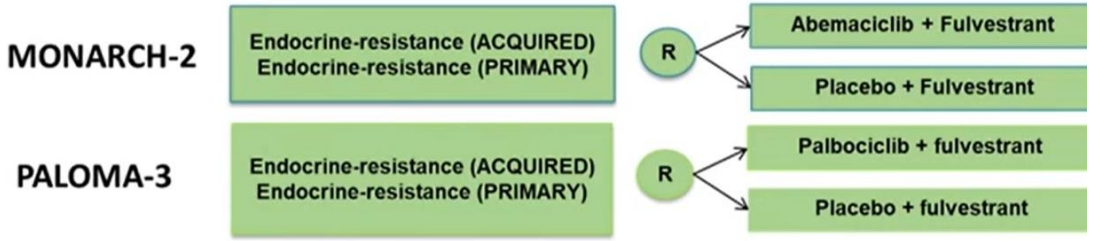


Jin et al. Nature Genetics 2023

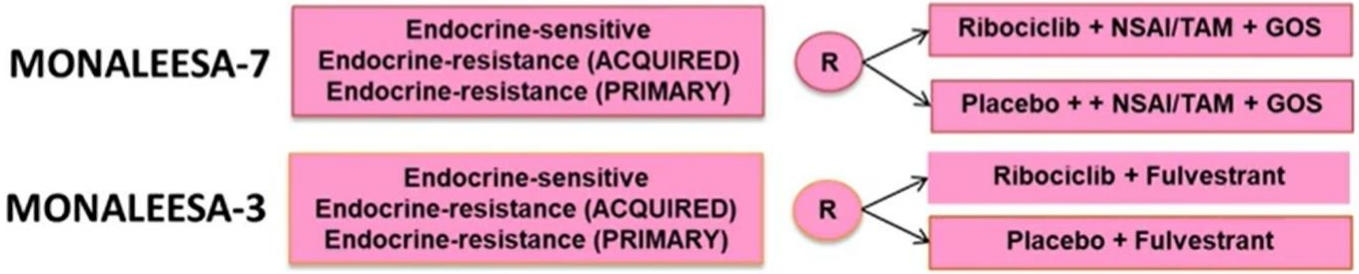
Endocrine sensitive



Endocrine resistant (primary and acquired)



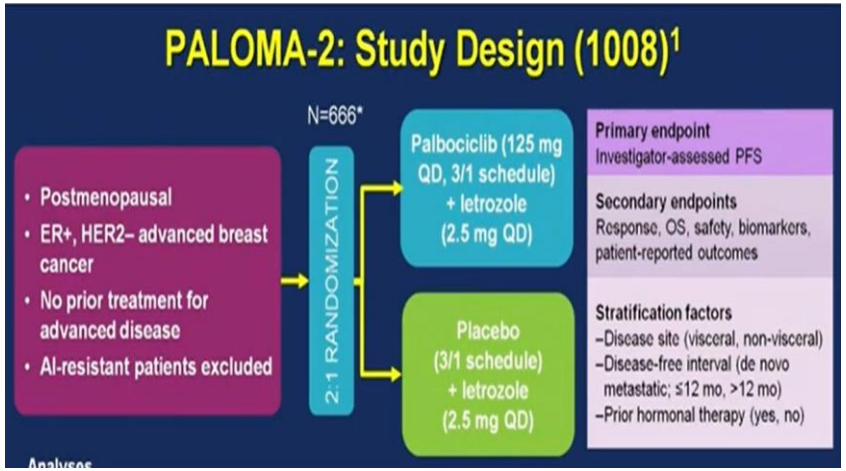
Mixed populations Endocrine sensitive and resistant (primary and acquired)

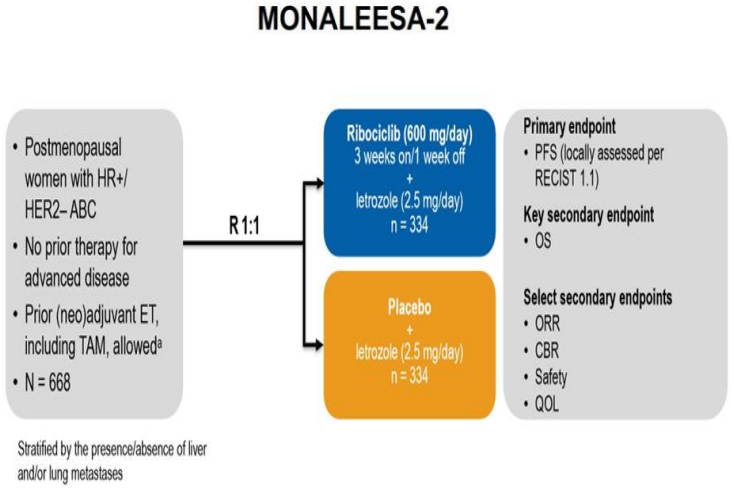


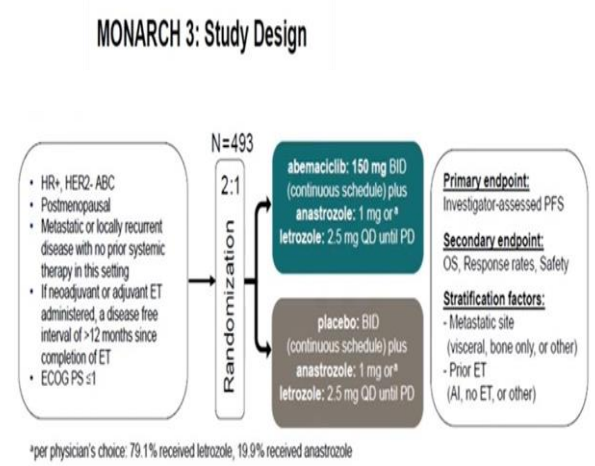
Study	Line	Sensitivity	Primary ET resistance	Secondary ET resistance
PALOMA-2[1]	1°	~100%		
MONARCH-3[2]	1°	~100%		
MONALEESA-2[3]	1°	~100%		
MONALEESA-7[4]	1°	~70%		~30%
MONALEESA-3[5]	1st & 2°	~50%	~50% (% of pts with secondary resistance not provided)	
MONARCH-2[6]	1st & 2nd		~25%	~75%
PALOMA-3[7]	2nd		~21%	~79%

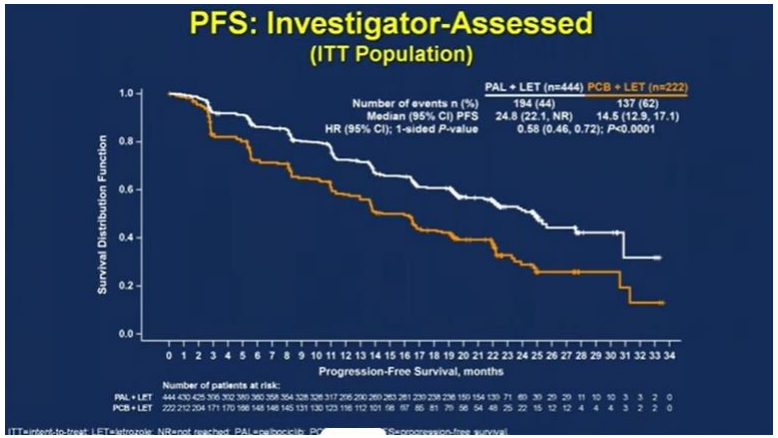
1. *Finn NEJM 2016.*
2. *Goetz JCO 2017*
3. *Hortobagyi NEJM 2016*
4. *Triphaty Lancet Oncol 2018*
5. *Slamon JCO 2018*
6. *Cristofanilli Lancet Oncol 2016*

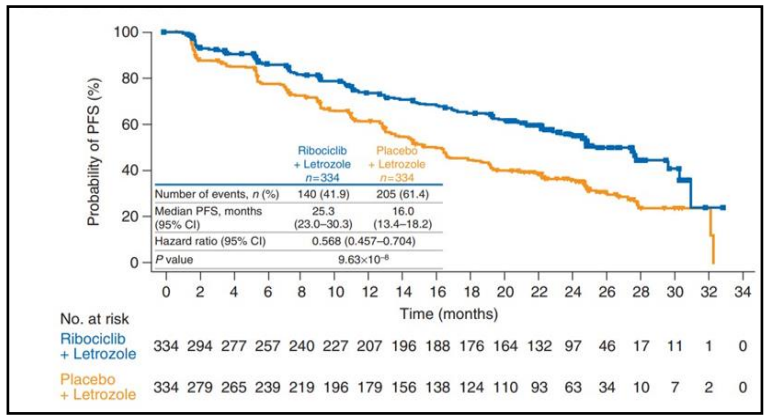
INH DE CDK EN LA PACIENTE HORMONOSENSIBLE. SLP

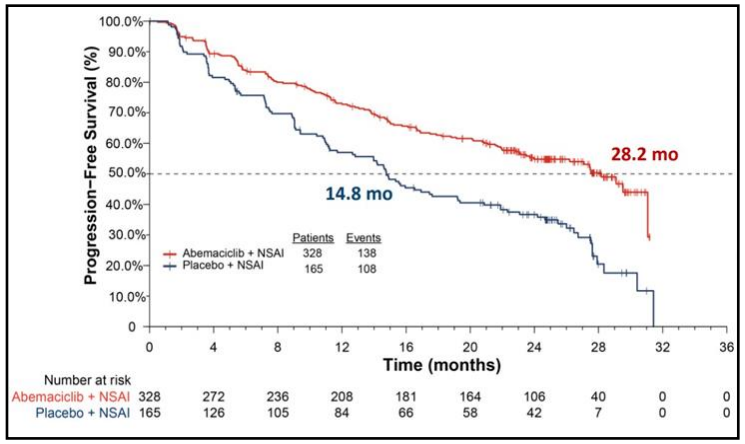








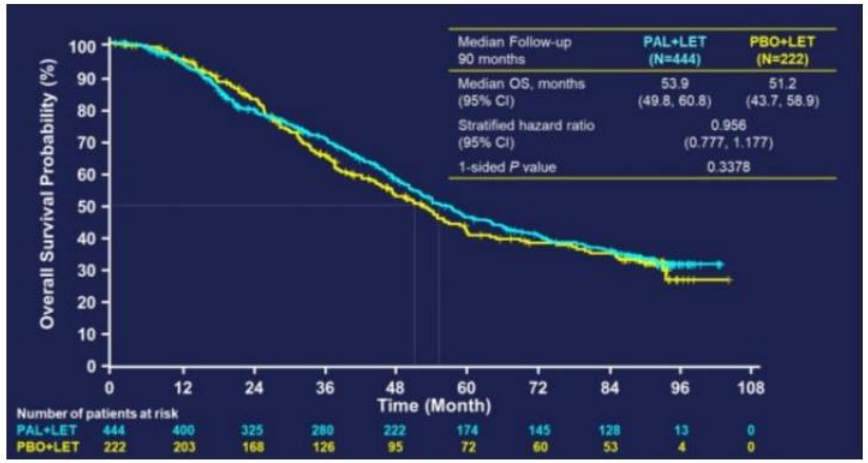




Finn NEJM 2016. Hortobagyi Ann Oncol 2018. Johnston ESMO 2022

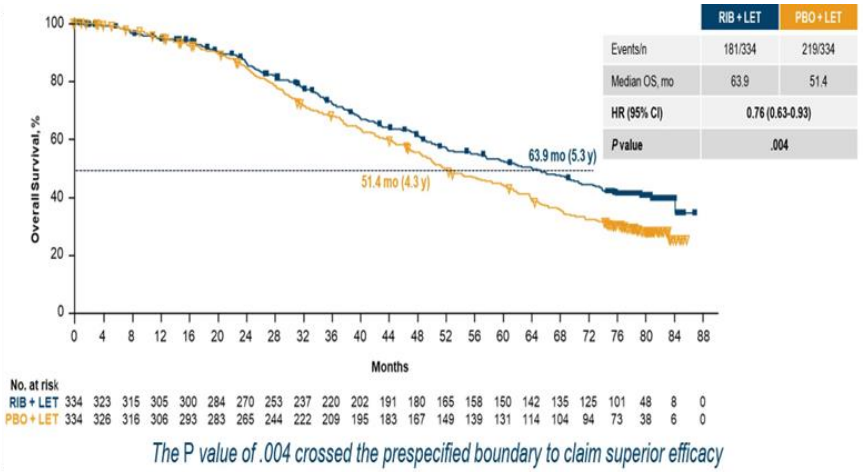
INH DE CDK EN PACIENTES HORMONOSENSIBLES. SG

PALOMA-2



HR 0.96
No significant OS benefit

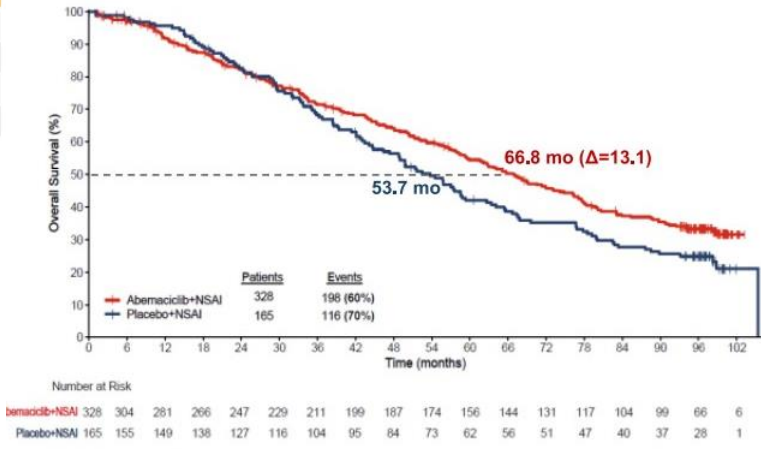
MONALEESA-2



The P value of .004 crossed the prespecified boundary to claim superior efficacy

HR 0.76
Significant OS benefit

MONARCH-3



HR 0.80
No significant OS benefit

Finn ASCO 2022. Slamon JCO 2024. Hortobagyi SABCS 2023

MONALEESA-7 Study Design

First Phase III trial with a CDK4/6 inhibitor exclusively in premenopausal patients

Pre/perimenopausal women[a] with HR+/HER2− ABC

No prior ET for ABC[b]
≤ 1 prior CT for ABC

N = 672

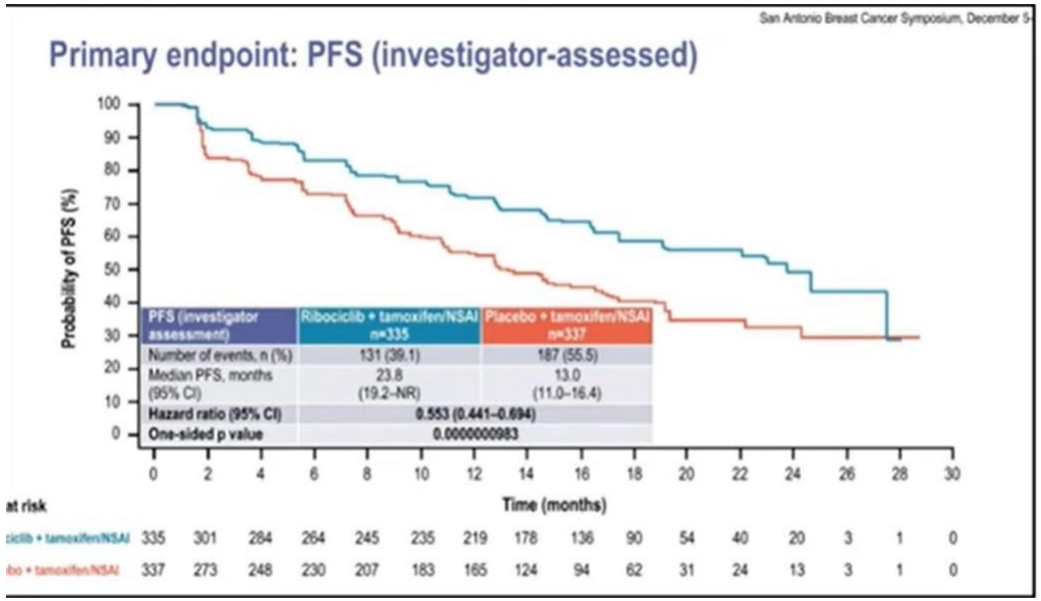
Randomized 1:1

Ribociclib
600 mg/day;
3 weeks on/1 week off
+
NSAI/TAM[c] + GOS[d]
n = 335

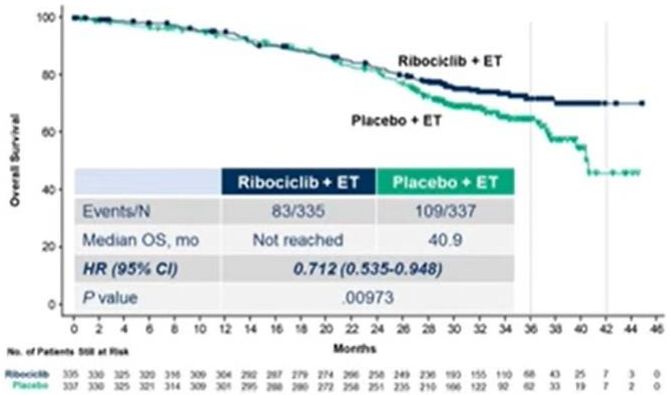
Placebo
3 weeks on/1 week off
+
NSAI/TAM[c] + GOS[d]
n = 337

Stratification Factors
- Liver/lung metastasis (yes/no)
- Prior chemotherapy (yes/no)
- Combination partner (NSAI/TAM)

60% of patients: no prior adjuvant ET
14% of patients: prior chemotherapy for MBC



Overall Survival



	Ribociclib + ET	Placebo + ET
Events/N	83/335	109/337
Median OS, mo	Not reached	40.9
HR (95% CI)	*0.712 (0.535-0.948)*	
P value	.00973	

- ≈ 29% relative reduction in risk of death
- The *P* value of .00973 crossed the prespecified boundary to claim superior efficacy

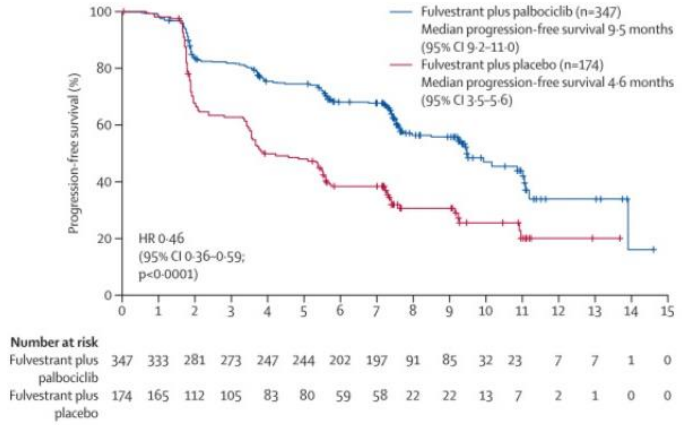
Landmark Analysis

Kaplan-Meier Estimate	Ribociclib + ET	Placebo + ET
36 months	71.9%	64.9%
42 months	***70.2%***	***46.0%***

Hurvitz ASCO 2021. Im et al. NEJM 2019

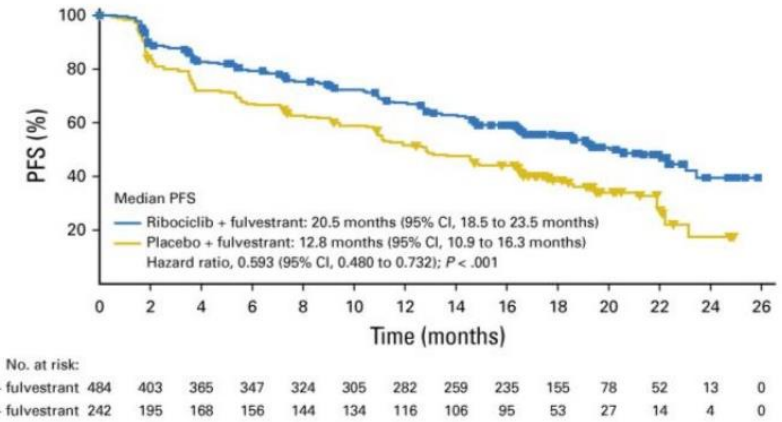
INH CDK EN POBLACION HORMONORESISTENTE. SLP

PALOMA-3



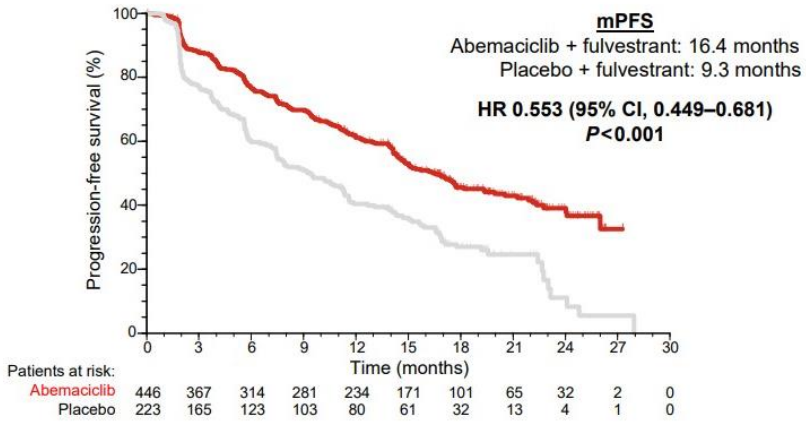
HR 0.46
PFS benefit

MONALEESA-3



HR 0.59
PFS benefit

MONARCH-2

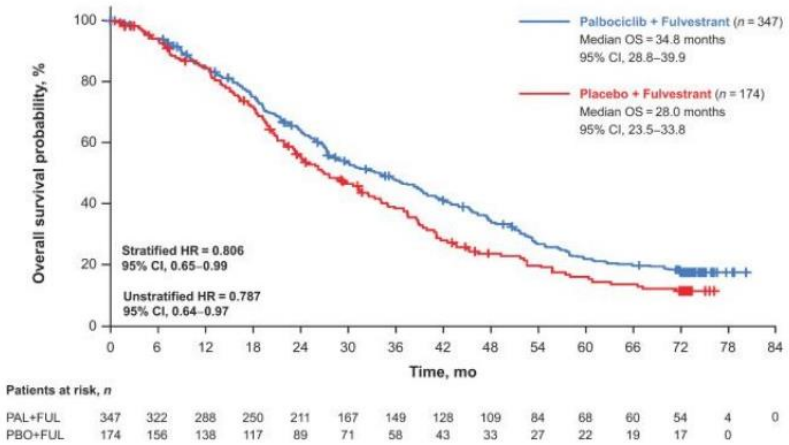


HR 0.55
PFS benefit

Cristofanilli Lancet Oncol 2016. Sledge JCO 2017. Slamon JCO 2017

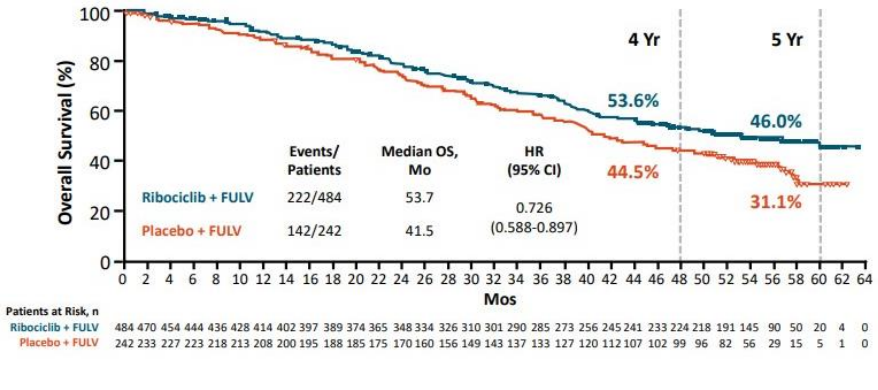
INH CDK EN POBLACION HORMONORESISTENTE. SG

PALOMA-3



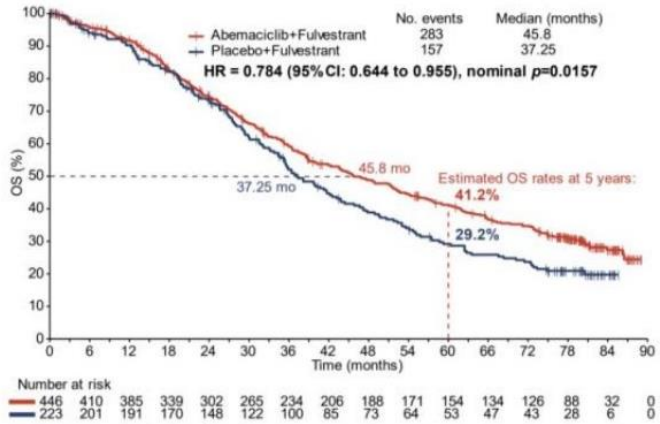
HR 0.80
No significant OS benefit

MONALEESA-3



HR 0.73
Significant OS benefit

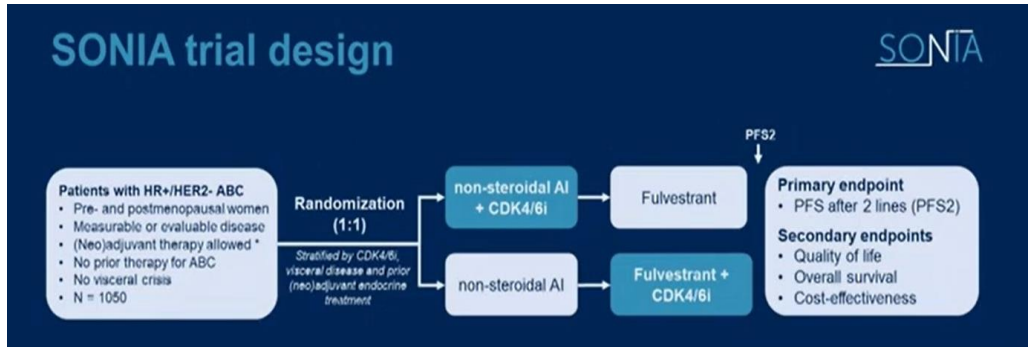
MONARCH-2

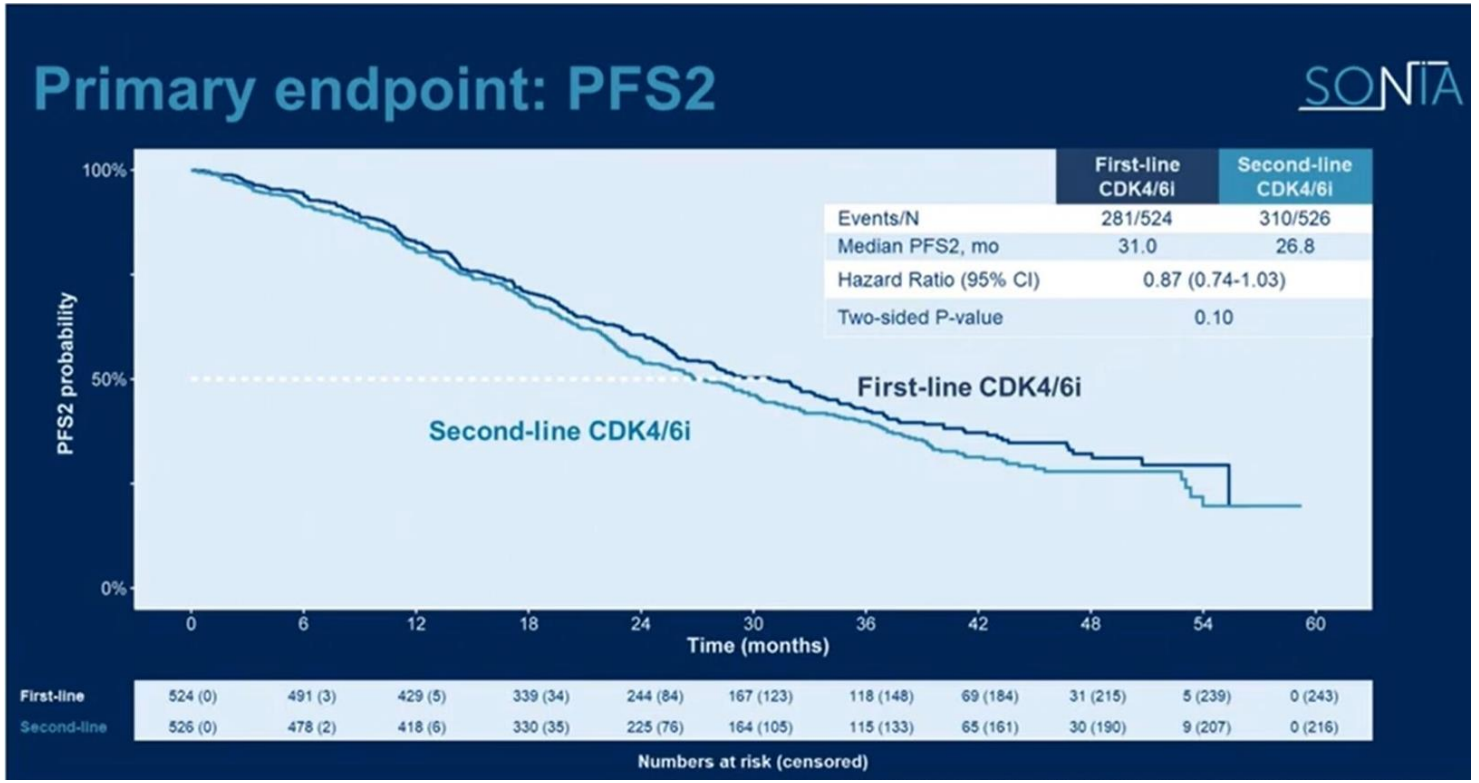


HR 0.78
Significant OS benefit

Cristofanilli Clin Cancer Res 2022. Llombart SABCS 2022. Slamon ASCO 2021

¿NECESITAN TODOS LOS PACIENTES EL INH CDK EN PRIMERA LÍNEA?

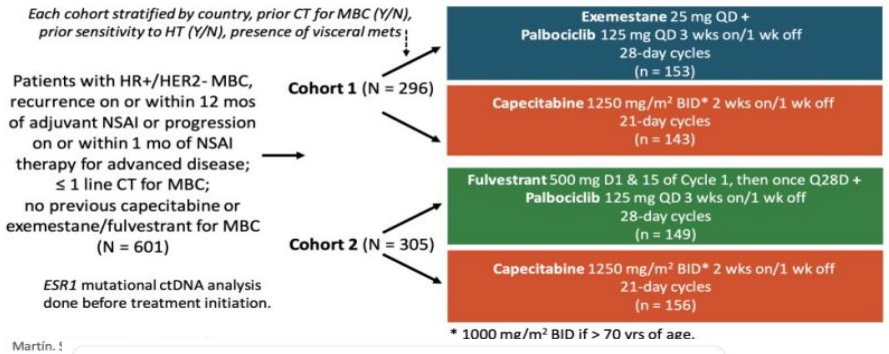


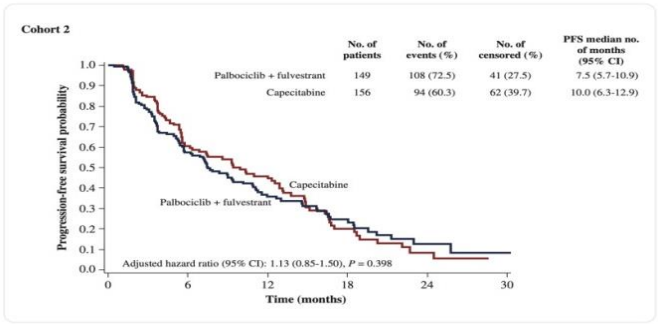


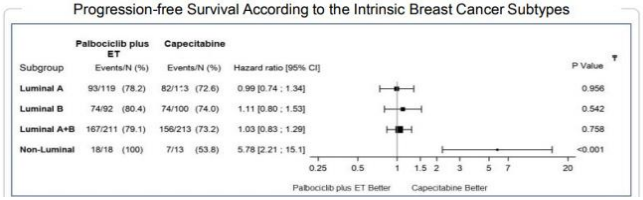
Sonke ASCO 2023

¿ES MEJOR QUIMIOTERAPIA O INH CICLINA EN PRIMERA LINEA?

PEARL - Palbociclib Plus ET vs Capecitabine in AI Resistant MBC







Martin M. Ann Oncol 2021

RIGHT Choice study design

- Pre-/perimenopausal women
- HR+/ HER2– ABC (>10% ER+)
- No prior systemic therapy for ABC
- Measurable disease per RECIST 1.1
- Aggressive disease[a]
  - Symptomatic visceral metastases
  - Rapid disease progression or impending visceral compromise
  - Markedly symptomatic non-visceral disease
- ECOG PS ≤ 2[b]
- Total bilirubin ≤ 1.5 ULN
- N = 222[c]

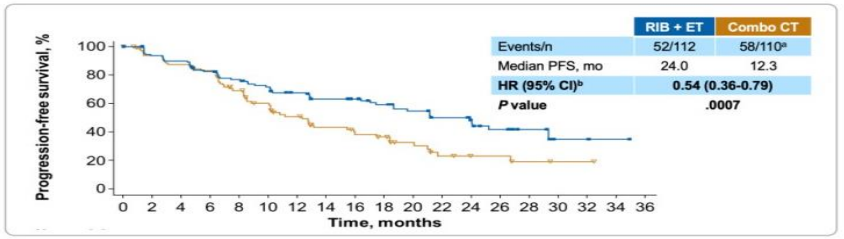
Stratified by (1) the presence or absence of liver metastases and by (2) DFI[d] < or ≥2 years

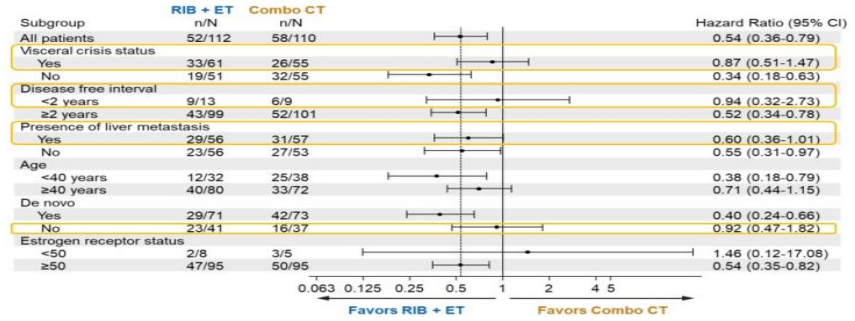
R 1:1

Ribociclib (600 mg, 3 weeks on/1 week off) + **Letrozole or anastrozole + goserelin**

Investigators' choice of combination CT[e]
Docetaxel + capecitabine
Paclitaxel + gemcitabine
Capecitabine + vinorelbine

Tumor imaging evaluation
Q6W for 1st 12 weeks, Q8W for next 32 weeks, then Q12W[f]





Lu Y. SABCS 2022

¿ CUAL ES EL MEJOR TTO ENDOCRINO EN PRIMERA LINEA EN COMBINACION CON INH CDK?

PARSIFAL: Study Design

Key inclusion criteria:
1. ER/PR[+]/HER2[-] MBC
2. No prior therapy for advanced disease
3. Postmenopausal or premenopausal*
4. Endocrine sensitive criteria:
   - Relapse >12 months from the end of endocrine therapy; or
   - Endocrine naïve

Stratification factors:
- Visceral involvement (N/Y)
- *"de novo"*/recurrent

N = 486 **Randomization (1:1)**

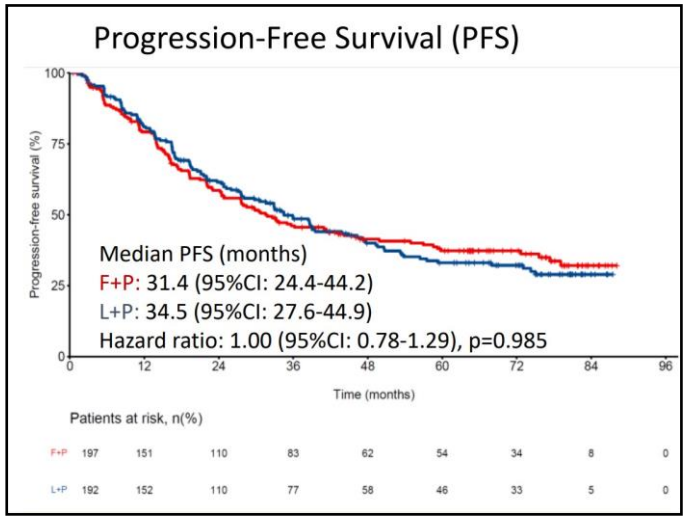
Fulvestrant
500mg IM, on Days 1, 14, 29 & monthly thereafter
+
Palbociclib
125mg PO, once daily, 3 weeks on, 1 week off

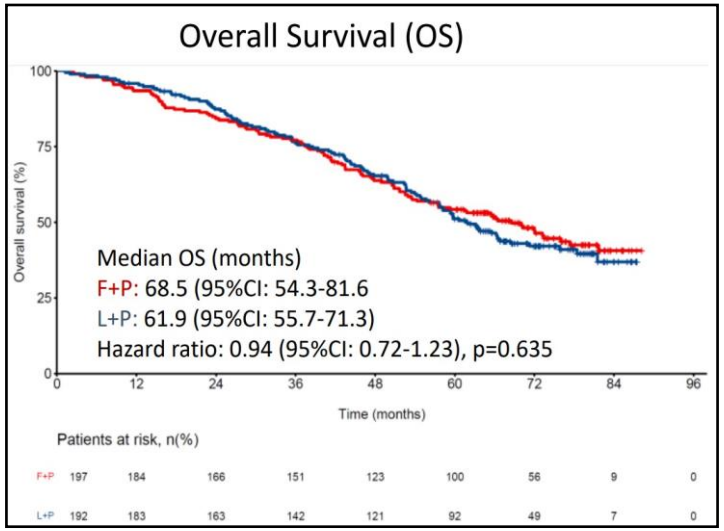
Letrozole
2.5mg PO, once daily, continuously
+
Palbociclib
125mg PO, once daily, 3 weeks on, 1 week off

Treatment until progressive disease per investigator

or

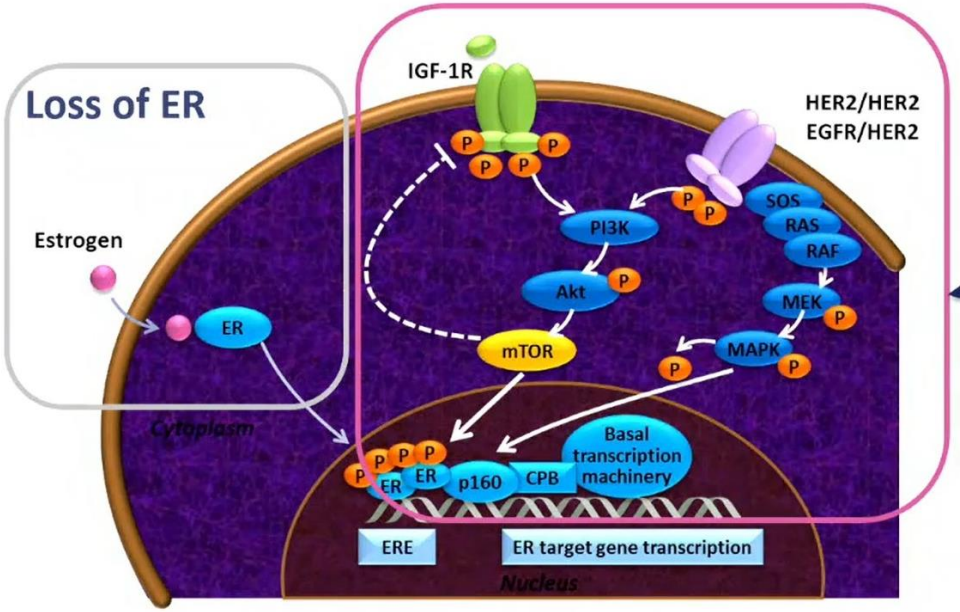
intolerable toxicity





Llombart . ASCO 2020

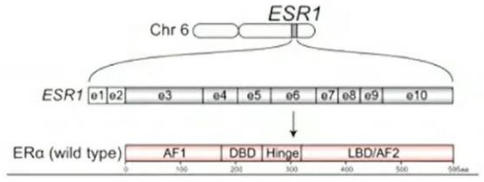
MECANISMOS DE RESISTENCIA A INH CDK



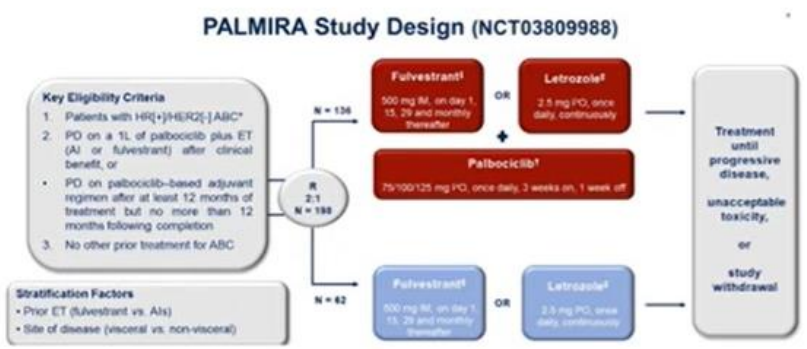
Modified from Di Cosimo. *Nature Rev Clin Oncol* 2009

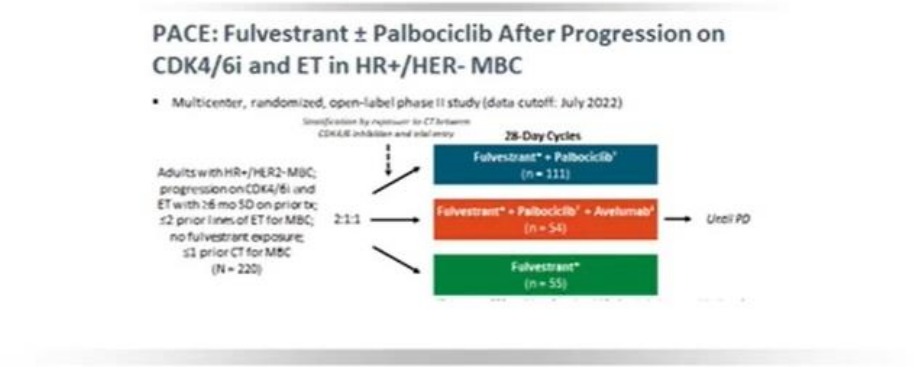
Endocrine-Independent transcriptomal activity of the ER-Pathway

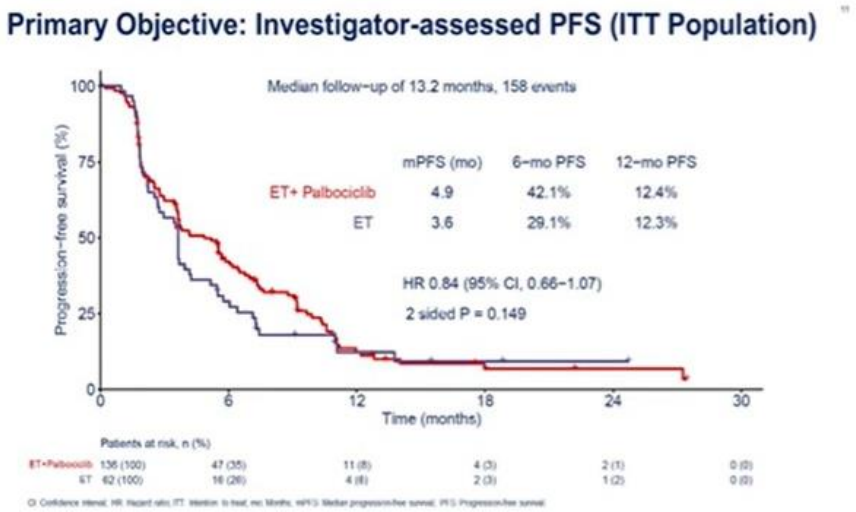
Alterations at ESR1 gene

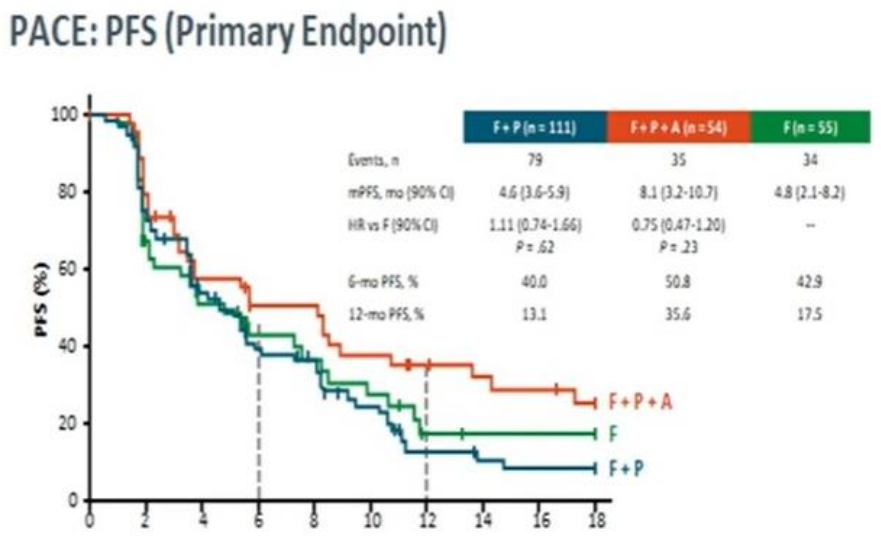


MANTENER EL MISMO CDK Y CAMBIAR EL TTO ENDOCRINO









Llombart ASCO 2023

Mayer SABCS 2022

CAMBIAR EL INH CDK Y EL TTO ENDOCRINO

MAINTAIN study

Key Entry Criteria
- Men or Women age ≥ 18 yrs
- ER and/or PR ≥ 1%, HER2- MBC
- Progression on ET + any CDK 4/6 inhibitor
- ≤ 1 line of chemotherapy for MBC
- Measurable or non-measurable
- PS 0 or 1
- Postmenopausal
  - GnRH agonist allowed if premenopausal
- Stable brain metastases allowed

1:1, N=120

Arm 1: Ribociclib + Switch Endocrine Therapy*

Arm 2: Placebo + Switch Endocrine Therapy*

Primary Endpoint
- Progression free survival
  - Locally assessed per RECIST 1.1

Secondary Endpoints
- Overall response rate
- Clinical benefit rate
- Safety
- Tumor and blood markers, including circulating tumor DNA

postMONARCH Study Design

Eligibility

HR+, HER2- ABC

Men & Pre/post menopausal women

Prior Therapy:
- **ABC**: Disease progression on CDK4/6i + AI as initial therapy
- **Adjuvant**: Disease recurrence on/after CDK4/6i + ET
- No other therapy for ABC

Randomization 1:1

N = 368

Abemaciclib + Fulvestrant

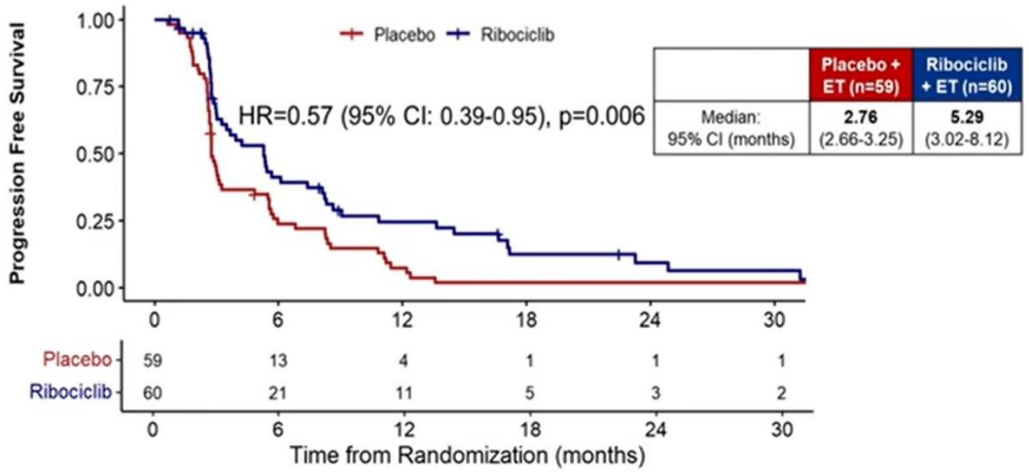
Placebo + Fulvestrant

Primary Endpoint: Investigator-Assessed PFS

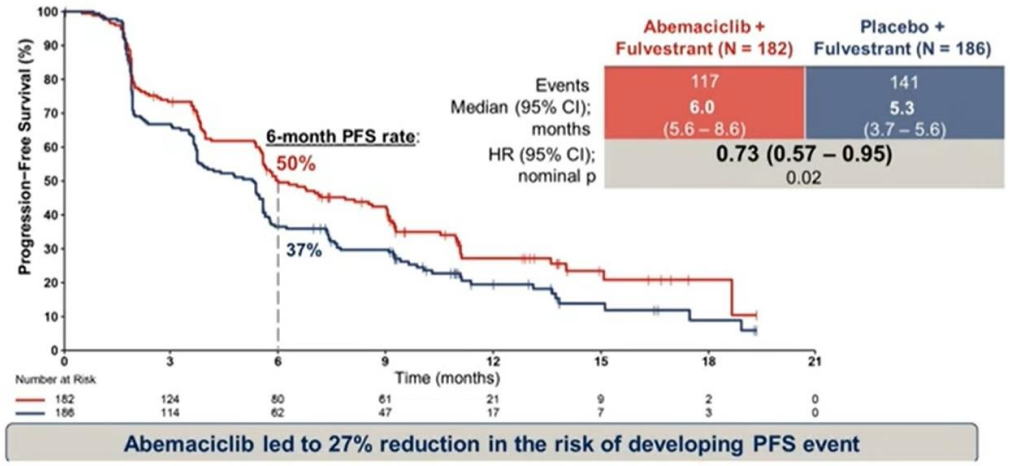
Secondary Endpoints: OS, PFS by BICR, ORR, CBR, DCR, DoR, Safety, PK & PRO

Stratification Factors:
- Duration of prior CDK4/6i
- Visceral metastases
- Geographic region

Primary Endpoint: Progression Free Survival (PFS)



Primary Analysis: Abemaciclib Improved Investigator-Assessed PFS



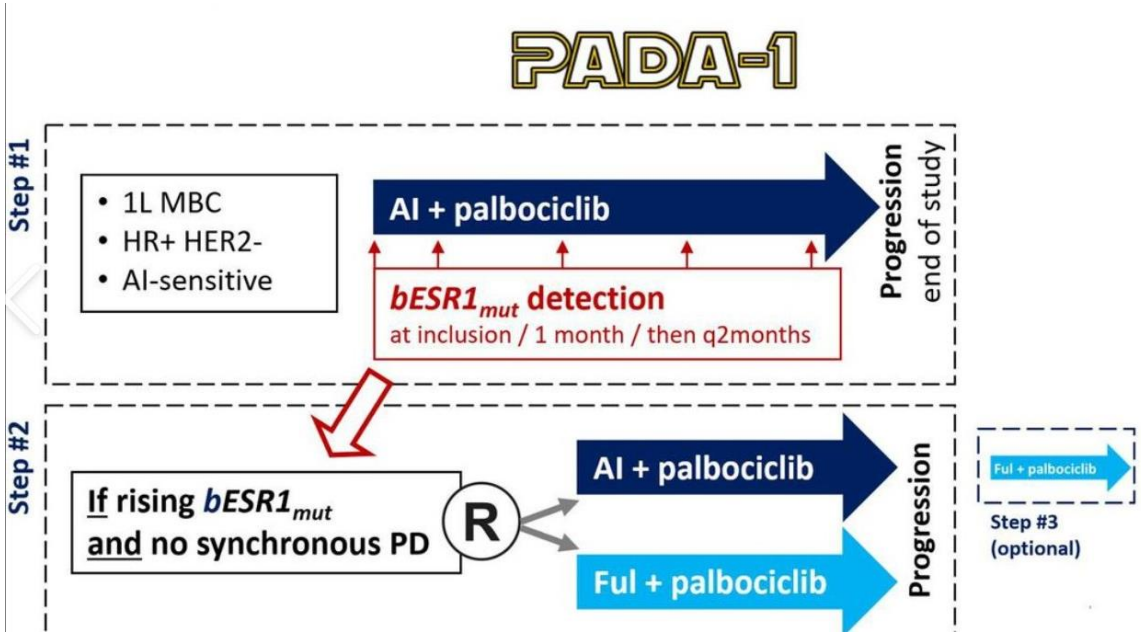
Abemaciclib led to 27% reduction in the risk of developing PFS event

INCIDENCIA DE LA MUTACION DE ESR1 EN PAC CON RESISTENCIA ENDOCRINA

Trial	Tumor characteristics	Timing of test	Test (sample)	*ESR1*m frequency	N, *ESR1*m/total	Reference
MONARCH 3	Endocrine-therapy-naive HR+/HER2- ABC treated with 1L AI monotherapy (control arm)	End of 1L AI treatment	NGS (plasma)	**31%**	NR	Goetz, ASCO 2020]
EMERALD	One or two previous lines of endocrine therapy, at least one in combination with CDK4/6i	Start of 2L or 3L treatment	NGS (plasma)	**48%**	228/477	Bidard, JCO 2022
GuardantINFORM database	At least one previous AI therapy	Post-AI therapy	NGS (plasma)	**31%**	2044/6541	Hanna, SABCS 2020
SoFEA/EFECT	HR+ mBC that had progressed on previous AI monotherapy	Start of 2L treatment	ddPCR (plasma)	**30%**	151/383	Turner, CCR 2020
BOLERO-2	HR+ ABC that had progressed on previous AI monotherapy	Start of 2L or 3L treatment	ddPCR (plasma)	**29%**	156/541	Chandarlapaty, JAMA Oncol 2016
PEARL	AI-resistant HR+/HER2- mBC	Start of 2L or 3L treatment	ddPCR (plasma)	**29%**	164/557	Martin, Ann Oncol 2021
PALOMA-3	HR+/HER2- mBC that had relapsed or progressed on previous AI or tamoxifen monotherapy	Start of 2L or 3L treatment	ddPCR (plasma)	**26%**	114/445	O'Leary, Nat Comm 2018

Turner. Future Oncol 2023

CAMBIAR EL TRATAMIENTO ENDOCRINO



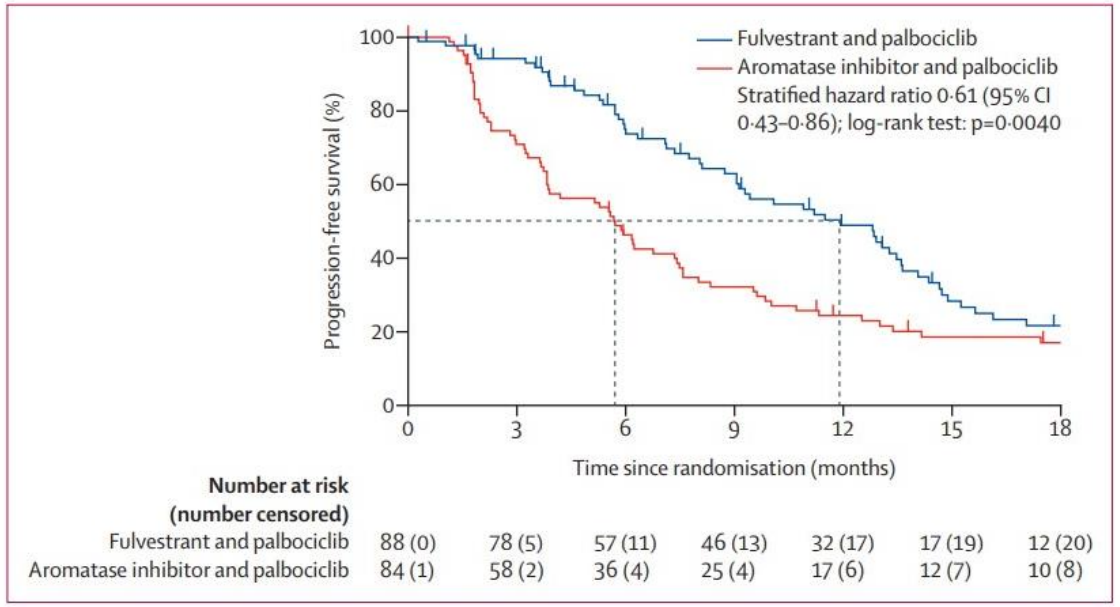


Figure 2: **Progression-free survival in the second step, by treatment group (co-primary endpoint)**

COMBINAR INH CDK + INH PI3KCA + TE

INAVO120 study design

Key eligibility criteria

Enrichment of patients with poor prognosis:

- ***PIK3CA*-mutated, HR+, HER2- ABC** by central ctDNA* or local tissue/ctDNA test
- **Measurable disease**
- **Progression during/within 12 months of adjuvant ET completion**
- **No prior therapy for ABC**
- **Fasting glucose <126 mg/dL and HbA_{1c} <6.0%**

Enrolment period: December 2019 to September 2023

N=325

R 1:1

- **Inavolisib (9 mg QD PO) + palbociclib (125 mg PO QD D1–D21) + fulvestrant (500 mg C1D1/15 and Q4W)****
- **Placebo (PO QD) + palbociclib (125 mg PO QD D1–D21) + fulvestrant (500 mg C1D1/15 and Q4W)****

Until PD or toxicity

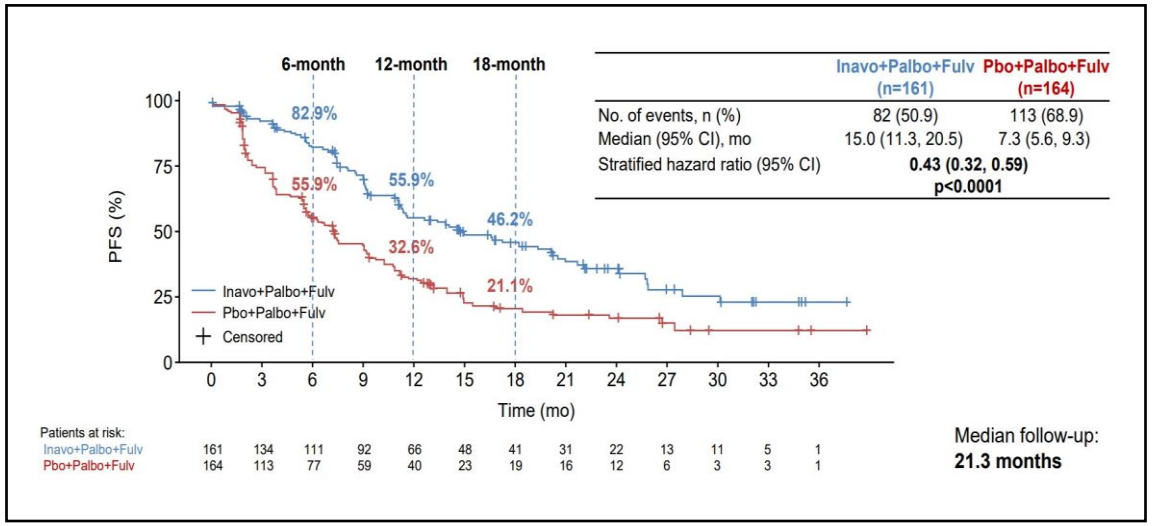
SURVIVAL FOLLOW-UP

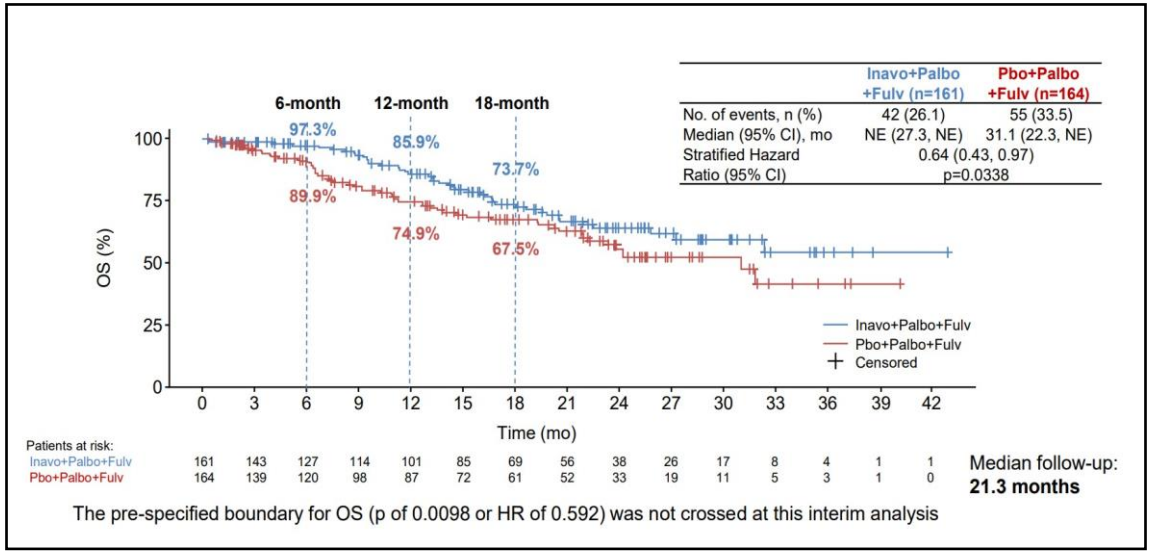
Stratification factors:

- Visceral Disease (Yes vs. No)
- Endocrine Resistance (Primary vs. Secondary)†
- Region (North America/Western Europe; Asia; Other)

Endpoints

- Primary: PFS by Investigator
- Secondary: OS‡, ORR, BOR, CBR, DOR, PROs





Juric. ASCO 2024

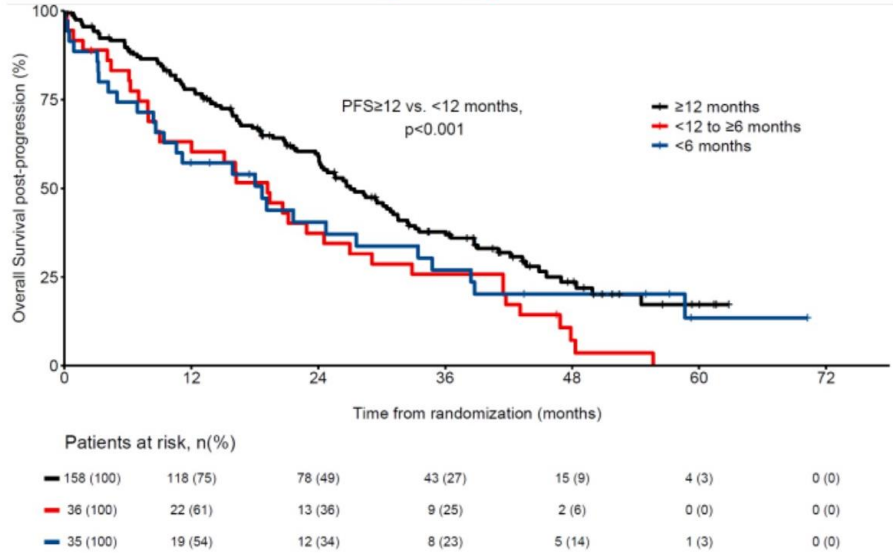
RESISTENCIA PRIMARIA A LOS INH CDK

PATIENTS WHO DON'T BENEFIT FROM CDK4/6 INHIBITORS

	patients without clinical benefit	Early progressors
AI-naive		
PALOMA 2	15%	NR
MONARCH 3	22%	4%
MONALEESA 2	20%	6%
AI-pretreated		
PALOMA 3	33%	17%
MONARCH 2	28%	9%
AI-naive and AI-pretreated		
MONALEESA 3	30%	10%
MONALEESA 7	21%	7%

PARSIFAL:

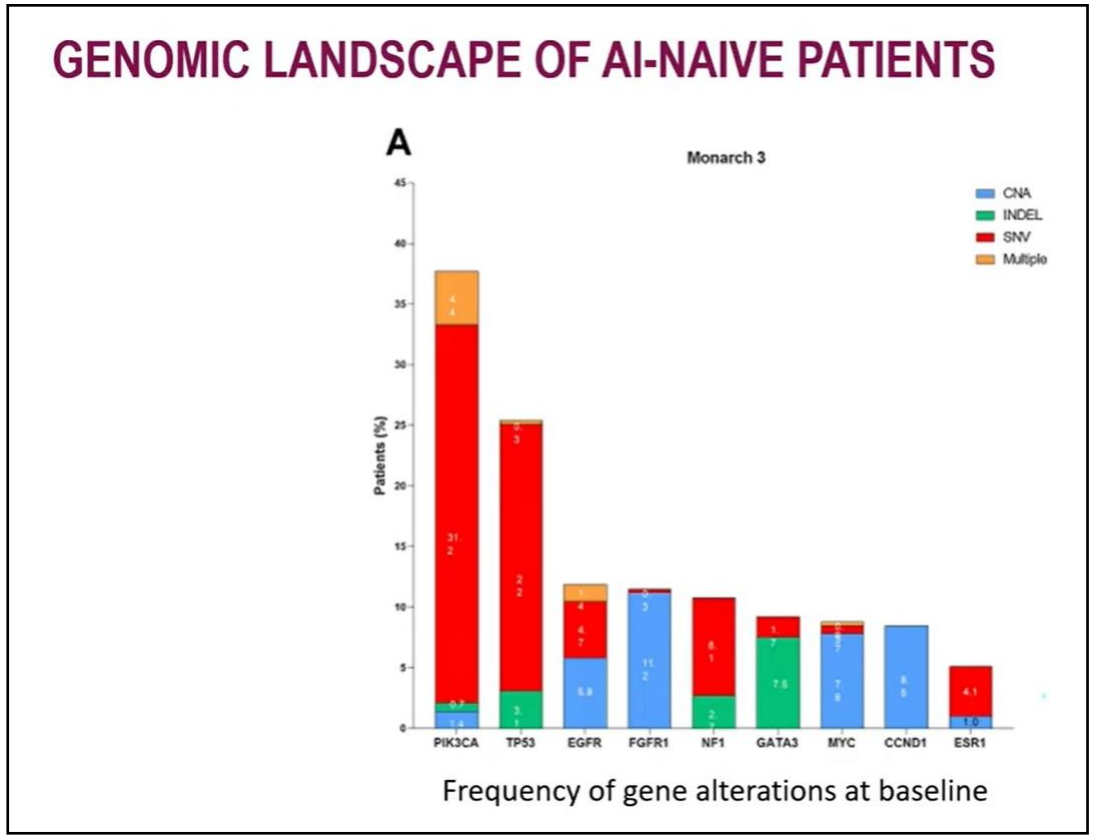
Post-progression Survival by PFS duration (< 6, 6 - 12, and ≥12 months) for progressing patients (n=229)

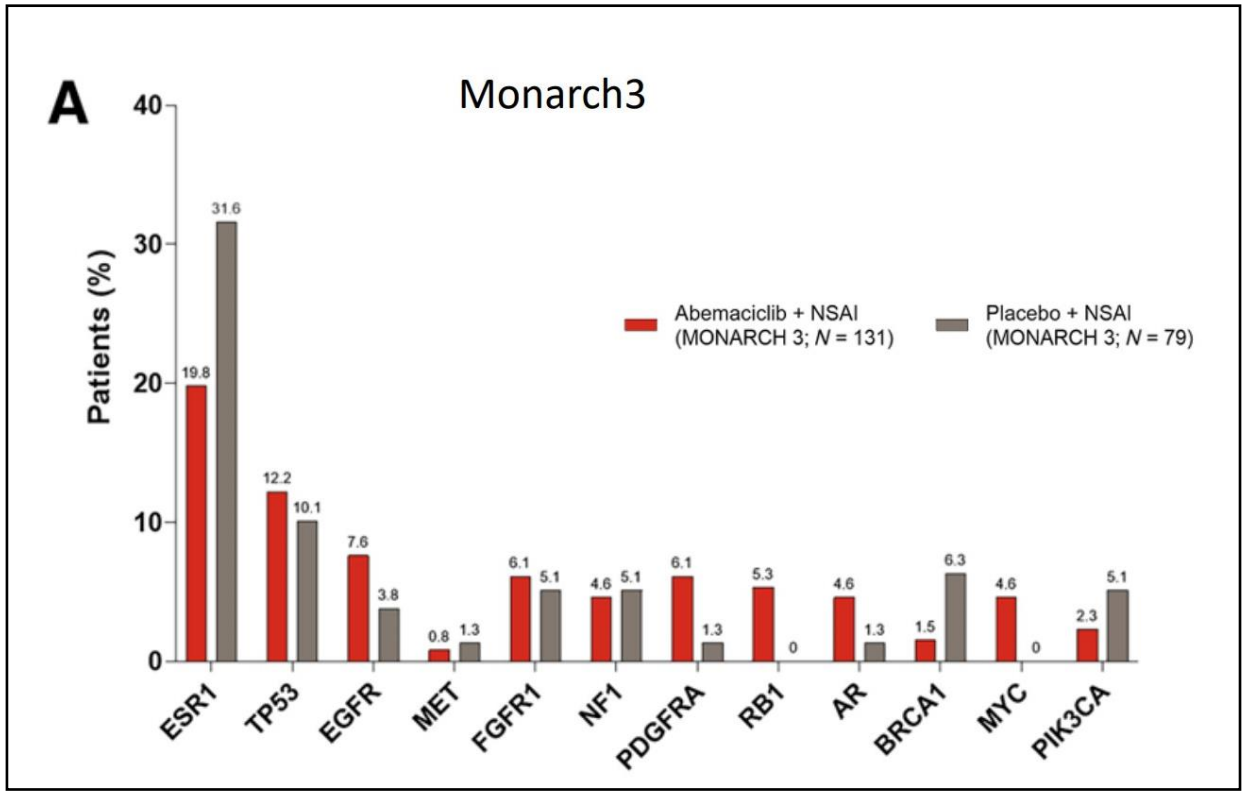


Median OS post-progression:
≥12: 27 mo. (95%CI: 24.1-31.1)
<12 to ≥6: 19.2 mo.(95%CI: 8.6-24.5)
<6: 18 mo. (95%CI: 8.6-24.7)

Llombart-Cussac, et al. SABCS 2023

CAMBIOS EN EL PERFIL MUTACIONAL ANTES Y DESPUES DE CICLINAS



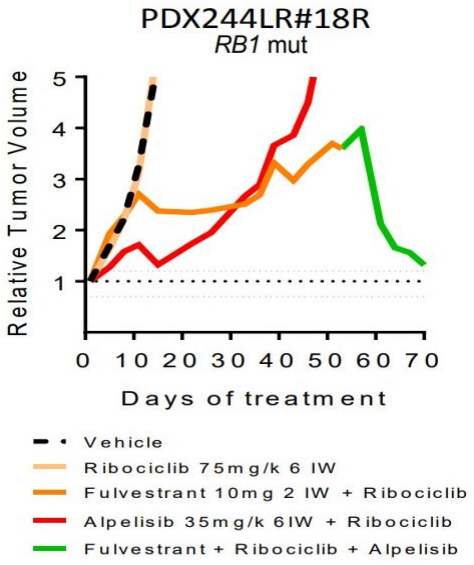


Clin Cancer Res 2024

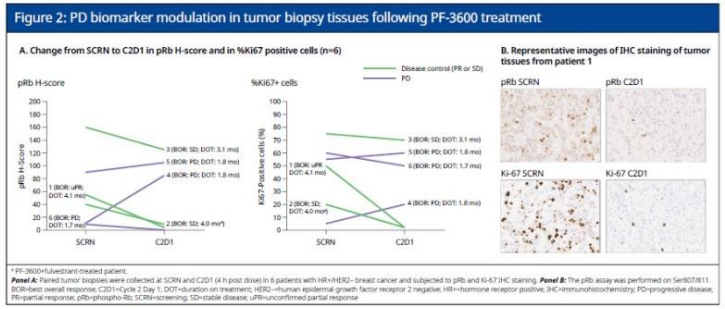
NUEVOS AGENTES

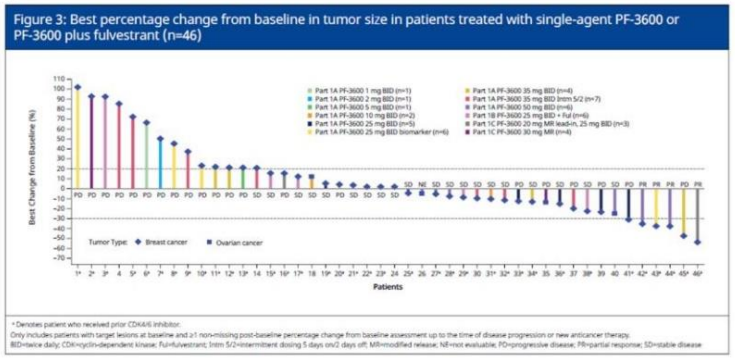
ACQUISITION OF *RB1* MUTATIONS IN 10% TUMORS

***RB1*-ALTERED PDXS ARE SENSITIVE TO CDK4/6I PLUS PI3KI**



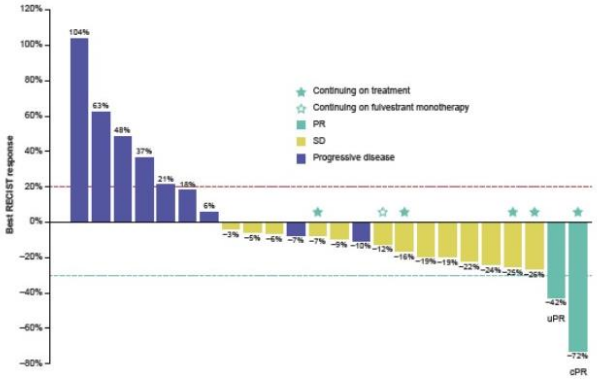
PHASE I OF A CDK2/4/6 INHIBITOR: PF-3600





CDK7 REGULATES CDK4/6 ACTIVATION: SAMURACICLIB (CT7001)

- Phase 1/2 in combination with fulvestrant
- HR+ BC, post CDK4/6i
- CBR of 39%
- ctDNA analysis: p53-WT
- FDA fast track designation Aug'21
- Ongoing combination with SERD (elacestrant



Hower et al, ESMO 2021

CONCLUSIONES

- El cancer de mama metastásico RH+/HER2- se clasifica en Hormonosensible y hormonorresistente en base a un consenso de expertos pero existen tanto características biológicas como genómicas que corroboran esta clasificación y confiere distinto pronóstico .
- La rebiopsia de la enfermedad metastásica puede identificar un subgrupo de pacientes que no se beneficiaran de ciclinas.
- Los inhibidores de ciclinas son el tratamiento estándar de la enfermedad tanto hormonosensible como hormonoresistente.
- Es fundamental realizar un estudio molecular a la progresión a ciclinas para identificar posibles mecanismos de resistencias y determinar la segunda línea de forma más precisa
- Un 10% de las pacientes tienen resistencia primaria a inh de ciclinas . Es importante descifrar estos mecanismos de resistencia primaria y obtener mejores vías de aproximación terapéutica.

GRACIAS!

II JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN: A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN

SEVILLA, 6 Y 7 DE FEBRERO DE 2025