



18^{as} Jornadas HITOS
ONCOLÓGICOS: LO MEJOR DE 2023

Madrid, 22 y 23 de noviembre de 2023

Fármacos en desarrollo en cáncer de mama metastásico

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Disclosures

Consulting/Advisor: Genentech-Roche, AstraZeneca, Daiichi Sankyo, Ely Lilly, Merck Sharp&Dohme, GSK, Novartis, Gilead, Menarini, Reveal Genomics, Agendia, Pfizer, Guardant health, Piere-Fabre

Honoraria: Roche, Novartis, Pfizer, Ely Lilly, Merck Sharp&Dohme, Daiichi Sankyo, AstraZeneca.

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Patents: HER2 as a predictor of response to dual HER2 blockade in the absence of cytotoxic therapy.
Aleix Prat, Antonio Llombart, Javier Cortés.US 2019/ 0338368 A1.



Fármacos y estrategias, promesas y oportunidades

- De-escalating strategies

First line Long term responders

- New HER2 TKIs
- Bi-specific agents

Pyrotinib, **ZN-1041**
Zanidatamab

- AKT/PI3K pathways
- ESR1/CDK4/6i (ER+)
- Immuno-checkpoint inhibitors
- AntiHER3 strategies

inavolisib
giredestrant, palbociclib
pembrolizumab, atezolizumab
lumretuzumab, patritumab



HER2[+] MBC

T-DXd – DB09 Primera línea HER2[+]

- HER2+ m
cancer
- No prior C
targeted t
advanced
disease

Es altamente probable que T-DXd demuestre un beneficio en SLP con una señal de SG que conlleve la aprobación de la indicación

T-DXd with pertuzumab-matching placebo

b

Standard of care (taxane
[docetaxel or paclitaxel],
trastuzumab and pertuzumab)

Status: Recruiting

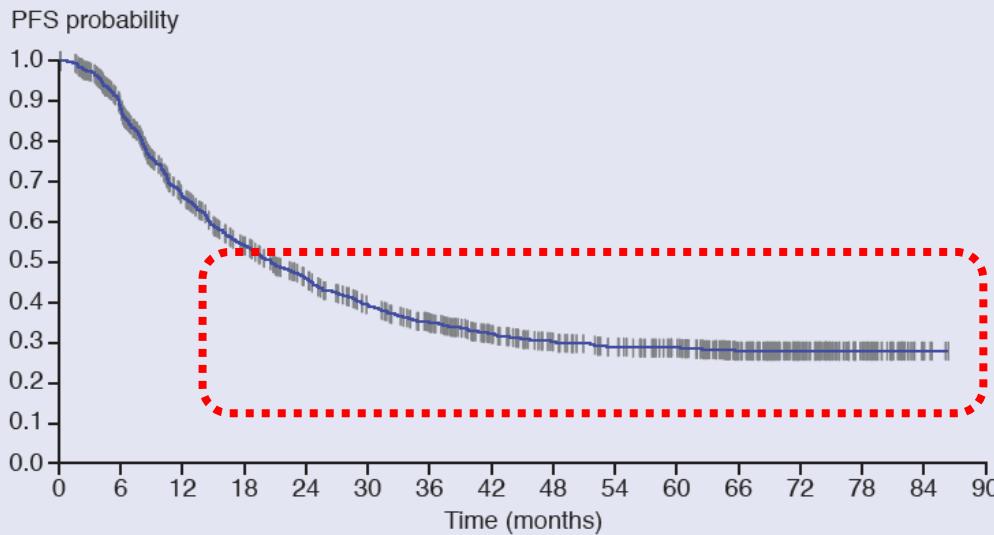
Primary Completion Date: December 2024



HER2[+] MBC

Primera línea – Estudio PERUSE

| Treatment exposure | Median (range) duration, months | Median (range) No. of cycles |
|------------------------------|---------------------------------|------------------------------|
| Taxane (n=1428) ^a | 4.2 (0.0–65.6) | 6 (1–94) |
| Docetaxel (n=790) | 3.8 (0.0–65.1) | 6 (1–90) |
| Paclitaxel (n=613) | 4.2 (0.0–65.6) | 6 (1–94) |
| Nab-paclitaxel (n=73) | 3.9 (0.0–17.3) | 6 (1–25) |



Fenómeno de “largas respondedoras”

Un **32%** de pacientes permanecen libres de enfermedad a partir de los **3-4 años** de tratamiento y sin eventos

Estas pacientes siguen con tratamiento en ausencia de toxicidad inaceptable

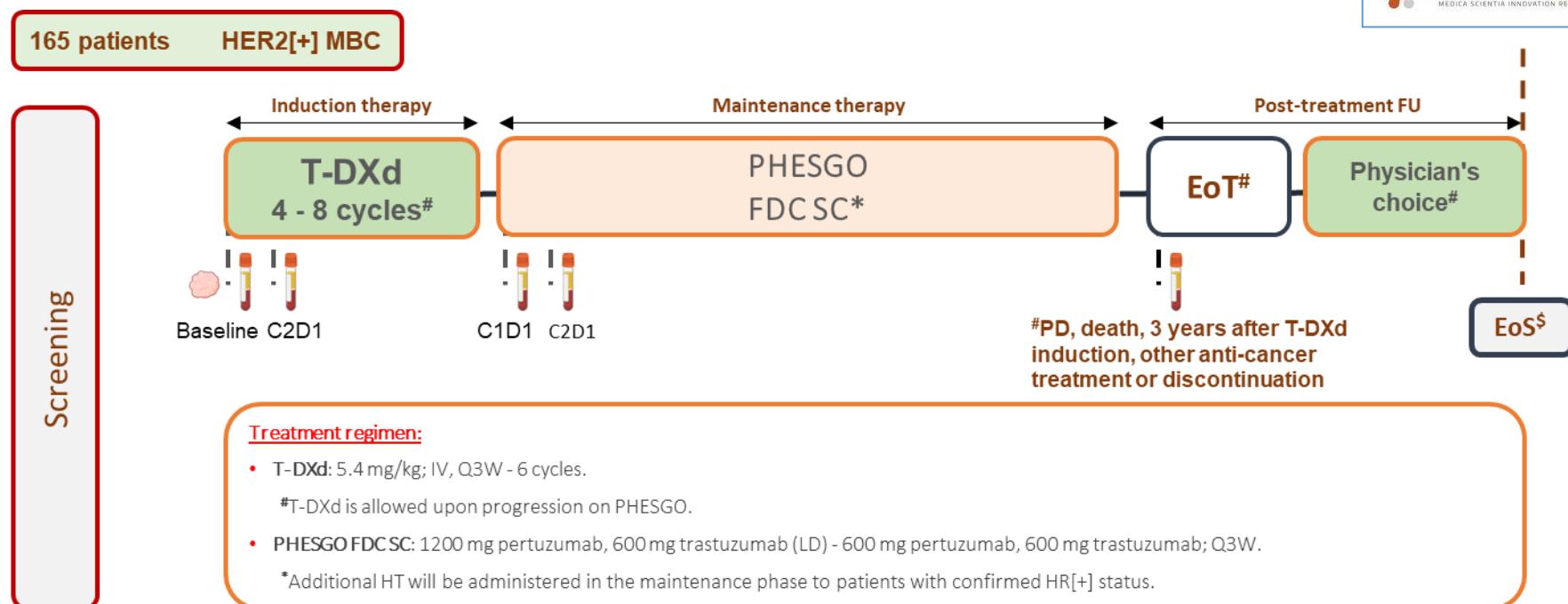
1.- Si con T-DXd aumentamos esta tasa, ¿Cuál será la calidad de vida a dos años o más con esta estrategia?

2.- ¿Podrían algunas de estas pacientes aspirar a la curación?
¿Podemos plantear parar tto?



HER2[+] MBC

T-DXd – DEMETHER: Optimización en Primera línea HER2[+]



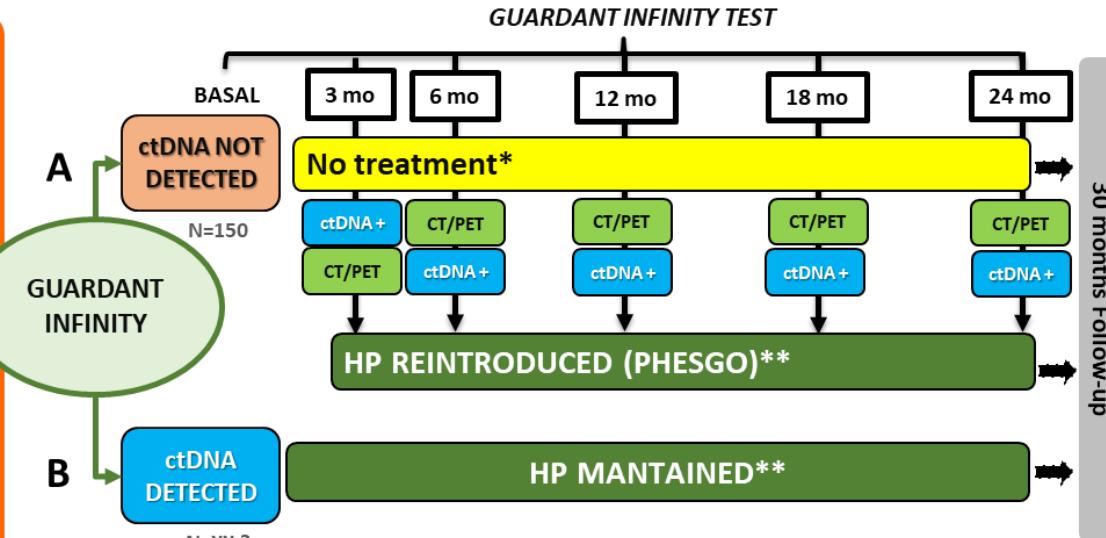
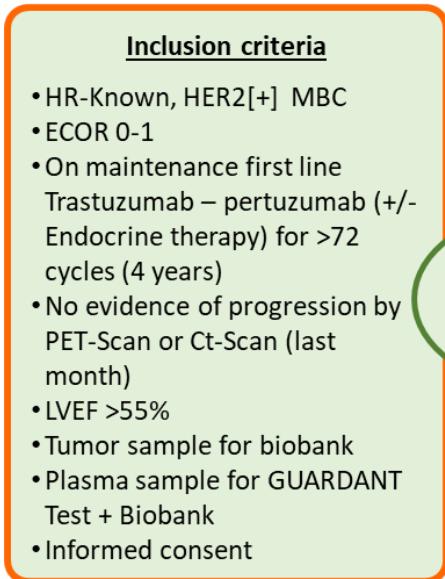


First Line HER2 – Long Responders: PHENIX y PRE-PHENIX

- **PRE-PHENIX:** Determine the prevalence of MRD positive/negative status on Guardant-imphinity) Minimal Residual Disease test from 43 HER2-positive MBC patients on long HP duration (>4 years). Correlate MRD status with clinic-pathological characteristics.
 - Patients collected from 7 Spanish Centers
 - Patients Criteria:
 - ✓ Informed consent for biobank plasma and tumor donation
 - ✓ Metastatic (Stage IV required) BC with confirmed HER2-phenotype
 - ✓ On 1stL trastuzumab + pertuzumab (+/- ET) with a minimum of 72 doses (48 months)
 - ✓ TC or PET/TC showing no evidence of progression over the last 6 months
- *Determinations: 2 plasma samples will be collected in two different cycles (in between 9 weeks)*
 - *Blood analysis including Ca 15.3, CEA and CTCs determination*
 - *Plasma sample for Guardant-Infinity*
 - *Plasma sample for biobanking*
- *Study open in November 2023*

HER2[+] MBC

First Line HER2 – Long Responders: PHENIX y PRE-PHENIX



Patients on arm A require a radiological–clinical – histological evidence of disease by standard methods to be considered as a PFS event (independent of ctDNA result or Phesgo reintroduction)

Primary Clinical Objective

- Arm A – 24 mo. PFS rate
- Co-Primary biological objective:**
- Arm A – ctDNA not-detected rate at 24 mo. test

Secondary Objectives

- Arm A – 24 mo. ctDNA-not detected and HP free PFS rate.
- 24 months PFS rate for groups A vs. B
- 24 mo. QoL test for arm A vs. B



HER2[+] MBC

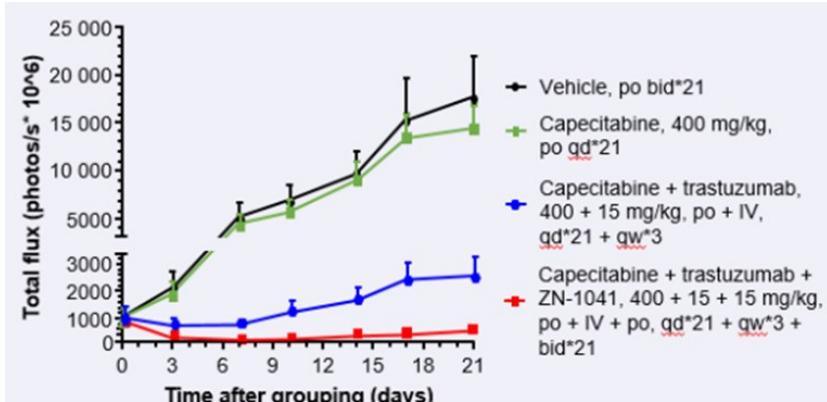
New HER2 – TKIs: ZN-1041

ZN-1041: HER2 – TKI

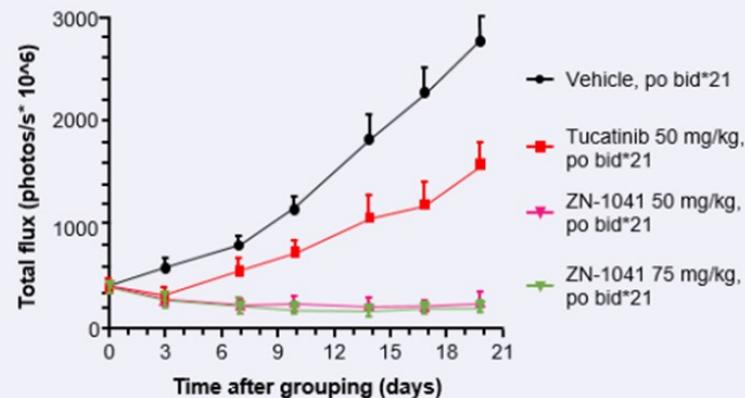
- *Different PK and PD to other TKIs*
- *High CNS penetrance*
- *Potent single activity and synergism in preclinical models*

| Compound | $AUC_{br,u}/AUC_{pl,u}$ | Efflux transporter substrate (P-gp/BCRP) |
|-----------|-------------------------|--|
| Tucatinib | 0.004 | Yes |
| Lapatinib | 0.01 | Yes |
| Neratinib | 0.013 | Yes |
| Pyrotinib | 0.024 | Yes |
| Epertinib | 0.08 | Yes |
| ZN-1041 | 0.47–0.77 | No |

AUC, area under the curve; BCRP, breast cancer resistance protein; P-gp, P-glycoprotein; TKI, tyrosine kinase inhibitor.



bid, twice per day; IV, intravenous; po, by mouth; qd, every day; qw, every week.



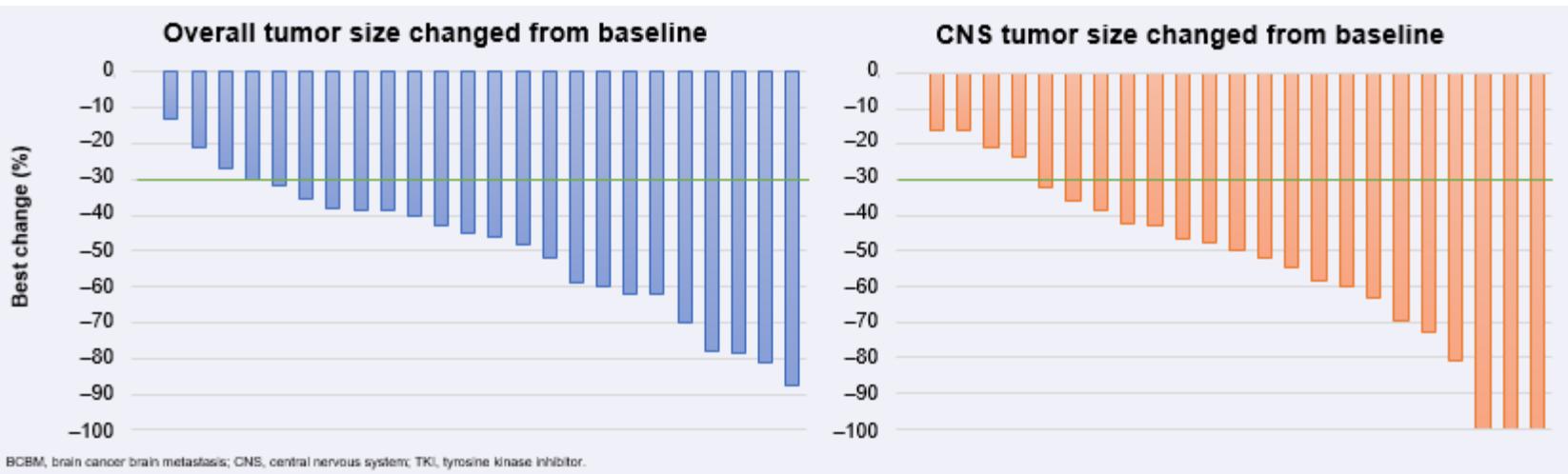
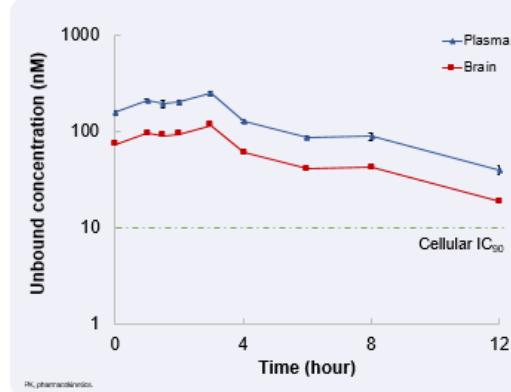


HER2[+] MBC

New HER2 – TKIs: ZN-1041

19 pacientes con HER2[+] M1-BM

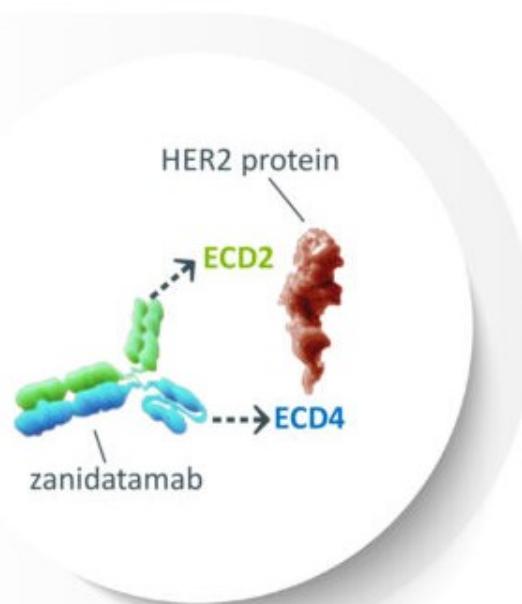
- RO cerebral: 78,9%
- DCR 100%
- 3 RC en SNC (2 confirmadas)
- Niveles en plasma y LCR similares





HER2[+] MBC

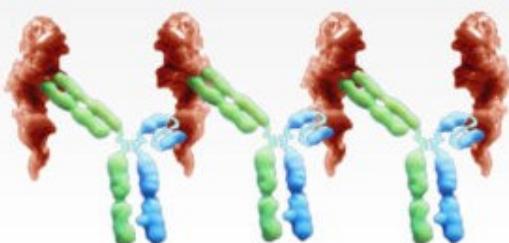
New HER2 – Biespecifics: **zanidatamab**



Zanidatamab's Unique Binding Geometry Promotes:

- Biparatopic – targets two distinct HER2 epitopes and results in HER2 binding across a range of expression levels (low to high)
- HER2-receptor cross-linking, clustering, internalization, and downregulation
 - Enhanced receptor clustering on cell surface (cluster internalization, receptor downregulation)
 - Inhibition of cellular proliferation
- Fc-mediated cytotoxicity: ADCC, ADCP, CDC

Dual HER2-Binding of Zanidatamab Drives Unique MOA



The geometry of zanidatamab prevents it from binding to the same HER2 molecule



HER2[+/-] MBC

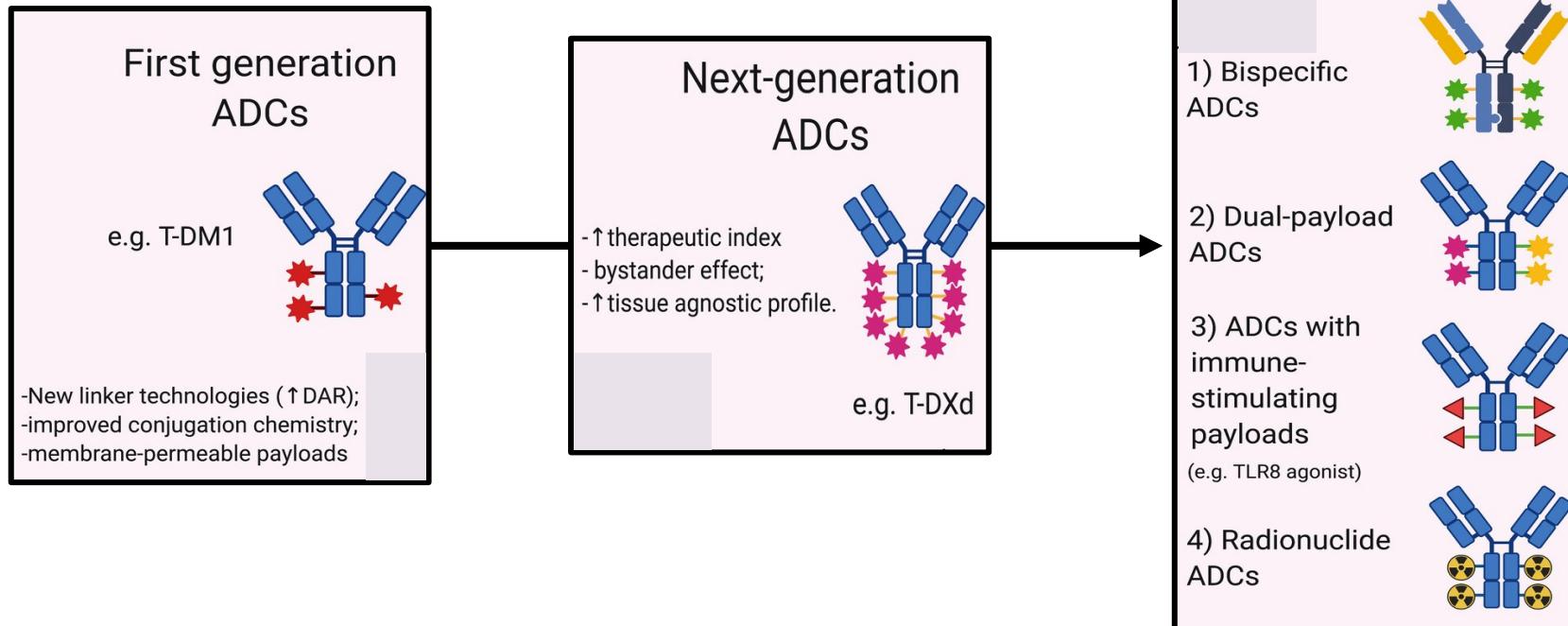
New ADCs

| ADC | Target | Payload | Treatment | Phase, NCTID |
|--|----------|--------------------------------|---|---|
| Ladiratuzumab vedotin (SGN-LIV1a) | LIV1 | MMAE | Monotx SGN-LIV1a+atezo SGN-LIV1a+pembro | Ph 1, NCT01969643 Ph 1/2, NCT03424005 Ph 1/2, NCT03310957 |
| Enfortumab vedotin | Nectin-4 | MMAE | Monotx | Ph 2, NCT04225117 |
| CX2009 | CD166 | DM4 | Monotx and combination | Ph 2, NCT04596150 |
| Patritumab deruxtecan (U3-1402) | HER3 | DXd | Monotx | Ph 1/2, NCT02980341 |
| BA3021-001 (CAB-ROR2 ADC) | ROR2 | Undisclosed | Monotx Monotx and PD-L1 inhibitor | Ph 1/2, NCT03504488 |
| Zilovertamab vedotin (VLS-101/MK-2140) | ROR1 | MMAE | Monotx | Ph 2, NCT04504916 |
| DS-7300 | B7-H3 | DXd | Monotx | Phase 1, NCT04145622 |
| AZD8205 XMT-1660 | B7-H4 | Top1i Microtubule inhibitor | Monotx | Phase 1, NCT05123482 Phase 1, NCT05377996 |



HER2[+/-] MBC

The future of ADCs





HER2[-] MBC

Nuevas dianas y estrategias, el reto de los ADCs

CMTN

- Consolidando estrategias ADCs - ICI
 - Nuevas dianas gpNMB, FGFR2, CDK2, Wee01
 - Viejos conocidos Papel de Bevacizumab

ENF LUMINAL

- SERMs – SERDs El reto de la primera línea
 - Nuevos CDK4i , PI3Ki, AKTi

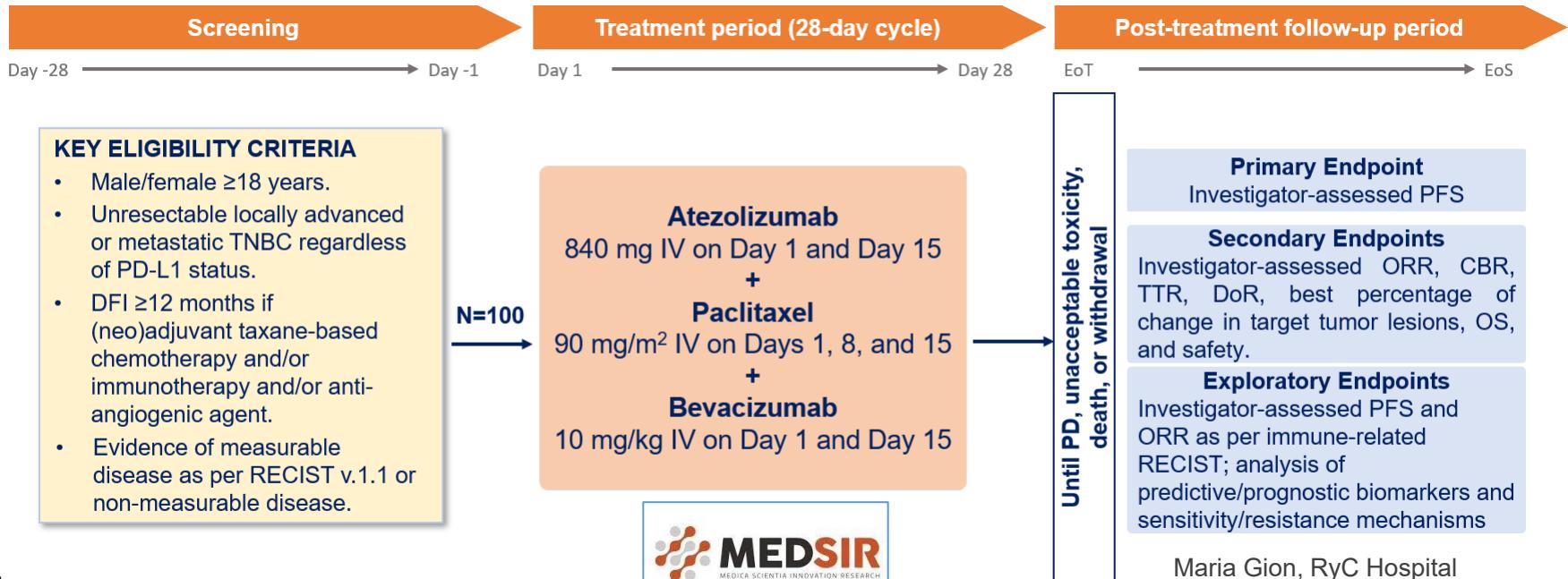
DIANAS COMUNES

- HER2 Low – TROP2 Hay limite a los ADCs (?)



TNBC

ATRACTIB Phase II trial: Atezolizumab – Bevacizumab and paclitaxel in the first line TNBC



*Did n

#Centrally assessed using SP142 (ICs) and 22C3 (CPS) antibodies.

ATZ, atezolizumab; BVZ, bevacizumab; CBR, clinical benefit rate; CPS, combined positive score; DFI, disease-free interval; DoR, duration of response; ICs, tumor-infiltrating immune cells; IHC, immunohistochemistry; IV, Intravenous therapy; ORR, overall response rate; OS, overall survival; PD, progressive disease; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; PTX, paclitaxel; RECIST, Response Evaluation Criteria in Solid Tumors; TNBC, triple-negative breast cancer; TTR, time to response.

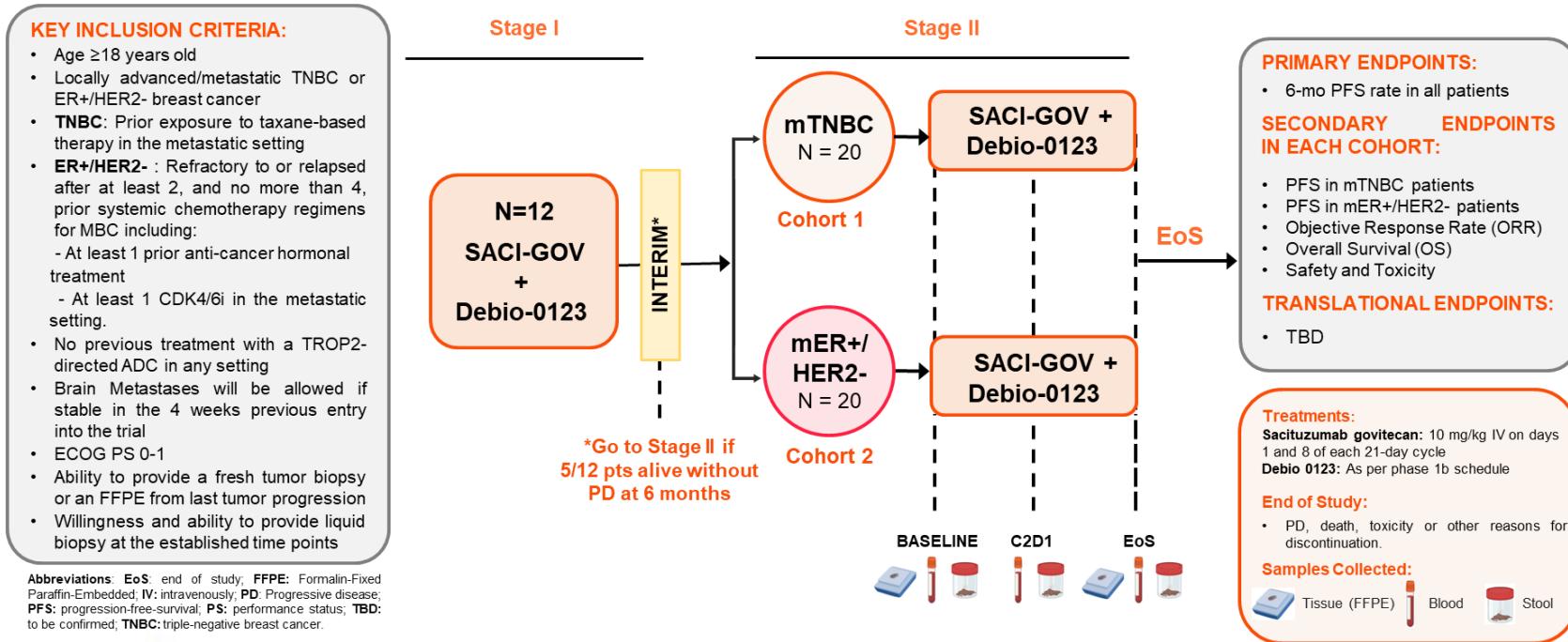


Maria Gion, RyC Hospital



TNBC

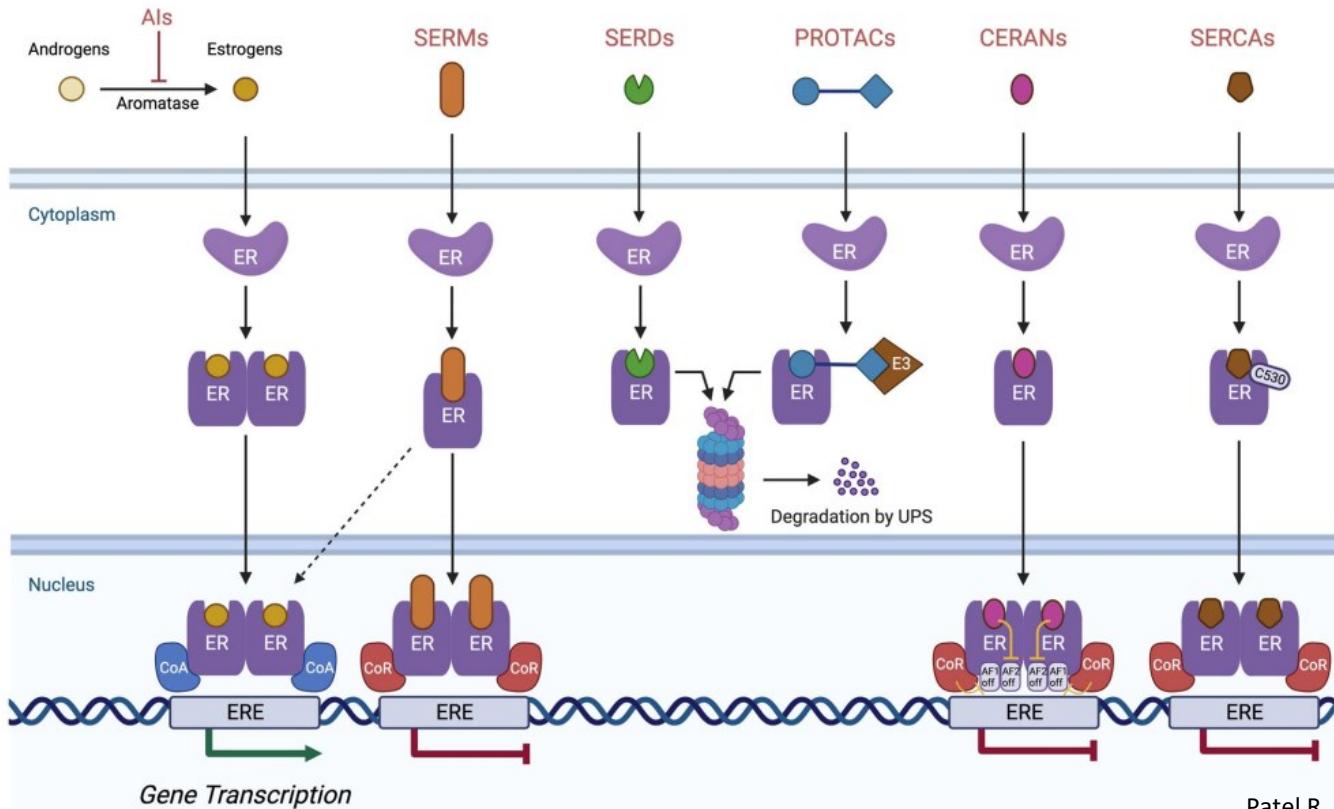
WIN-B study: Phase I - II: Debio0123 (Wee-1i) + Sacituzumab-Govitecan in HER2[-] MBC





ER[+] MBC

Mechanisms of action of new anti-estrogen therapies



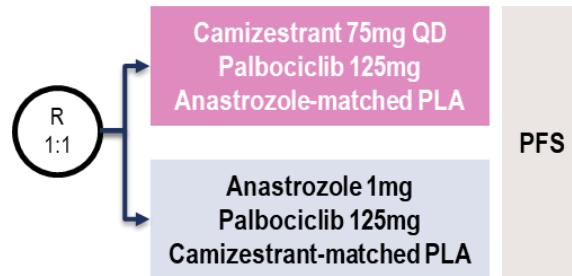
ER[+] MBC

New Anti-estrogens – First Line Studies

SERENA-4

N=1342

- ER+/HER2- LA/ABC
- No prior systemic tx for ABC

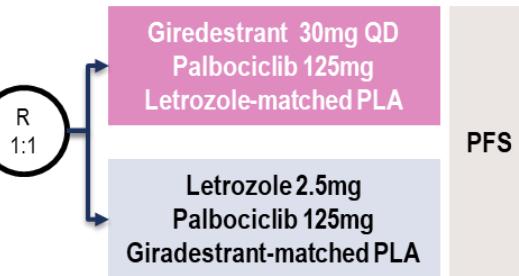


NCT04711252

persevERA

N=978

- ER+/HER2- LA/ABC
- No prior systemic tx for ABC

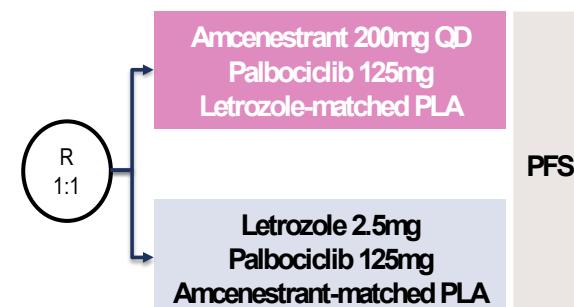


NCT04546009

AMEERA-5

N = 1066

- ER+/HER2- LA/ABC
- No prior systemic tx for ABC

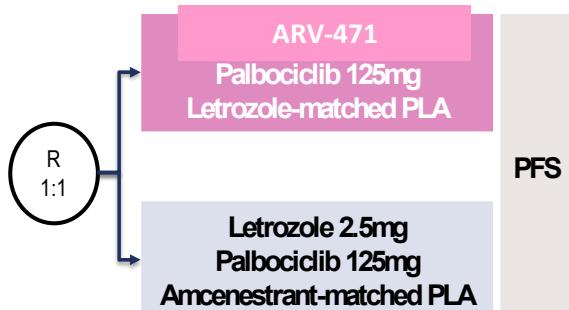


NCT04478266

VERITAC-3

N = 1180

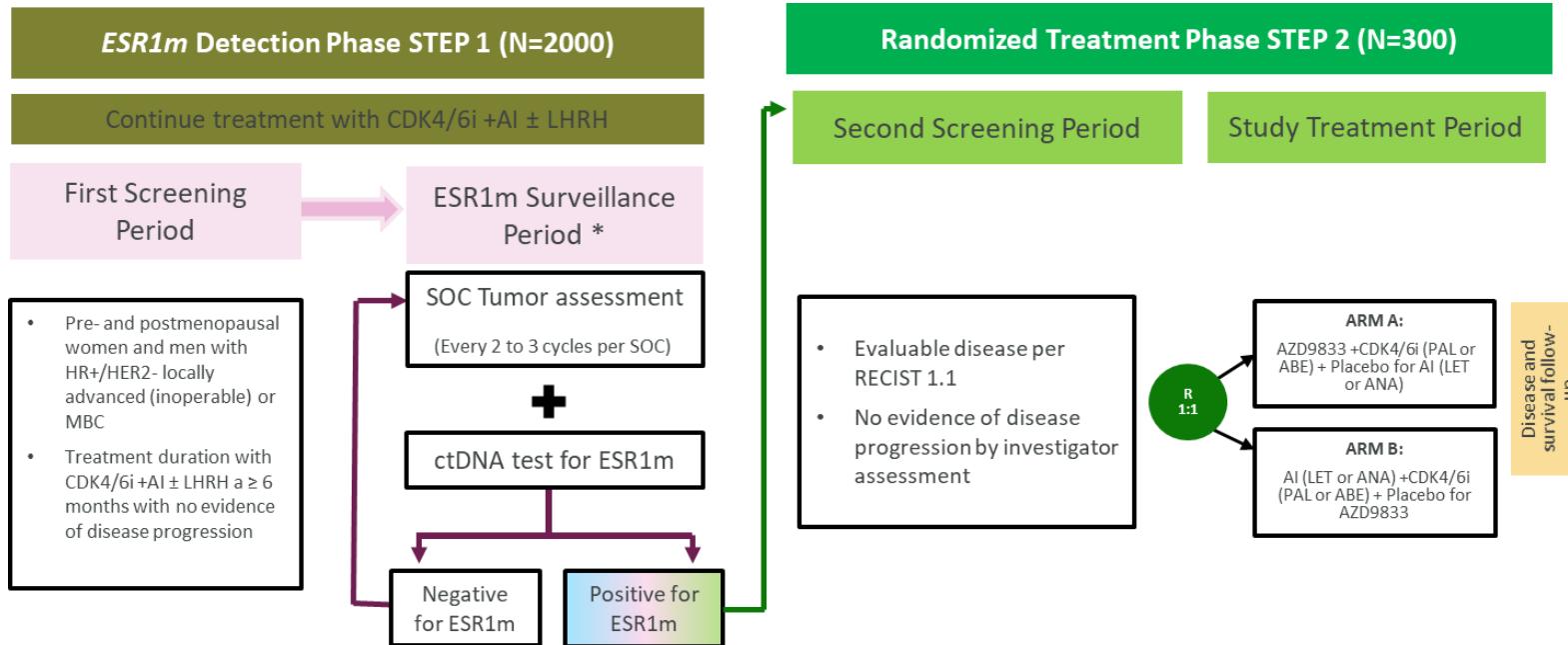
- ER+/HER2- LA/ABC
- No prior systemic tx for ABC



NCT04478266

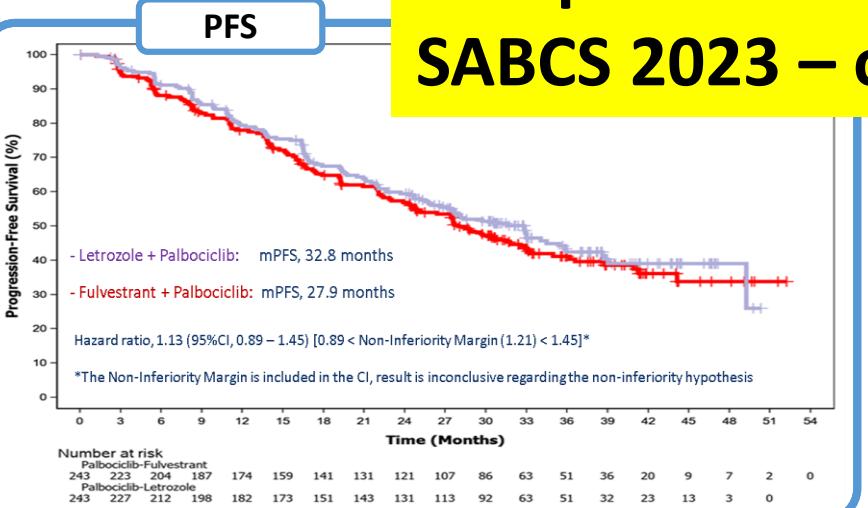
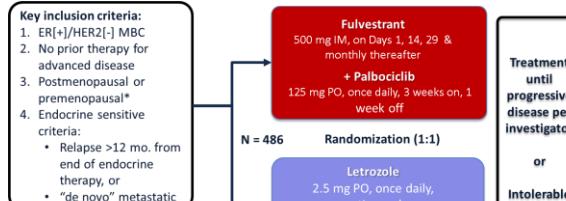
ER[+] MBC

SERENA-6: Camizestrant “First Line” Molecular progression

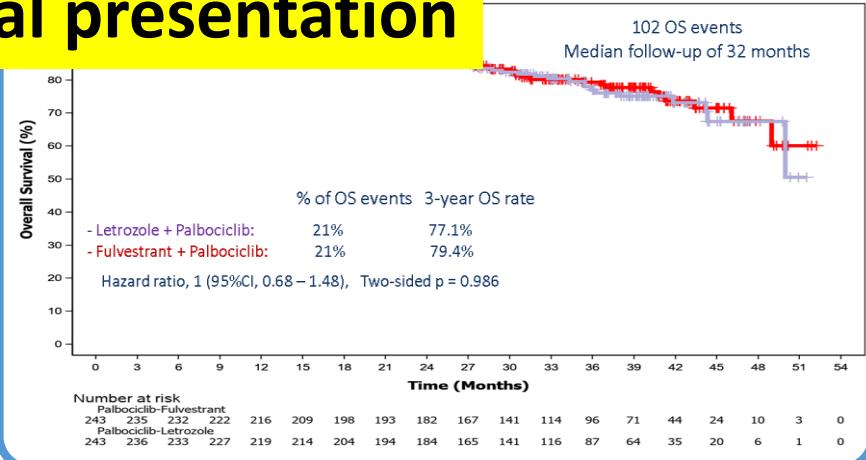


ER[+] MBC

PARSIFAL – First Line Optimal Endocrine Partner for CDK4/6i



Updated Overall Survival SABCS 2023 – oral presentation





ER[+] MBC

PONTIAC: T-DXd vs. CDK4/6i First line in High-Risk ER[+] MBC



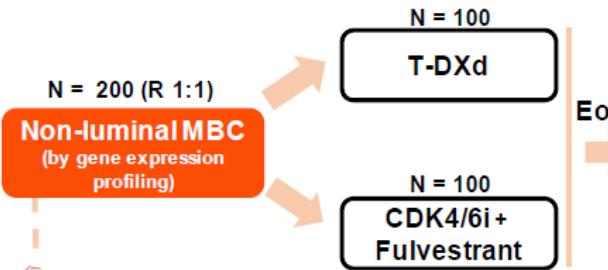
KEY INCLUSION CRITERIA

- Adult patients with HR-positive, HER2-negative BC.
- Locally recurrent inoperable or metastatic disease.
- Biopsy from metastatic site at relapse from the last 90 days classified as non-luminal by gene expression profiling.
- Evaluable and/or measurable disease as defined by RECIST v1.1.
- Patients must have received ET for at least 6 months in the early breast cancer setting.
- Patients must have not received prior treatment with any systemic therapy in the advanced setting.
- Patients must have not received prior treatment with T-DXd and/or fulvestrant. Patients treated with CDK4/6i in the adjuvant setting are allowed if more than 1 year from the last dose.
- LVEF > 50% measured by echocardiogram or MUGA.
- ECOG performance status: 0-1.
- Adequate hematologic and organ function.

Stratification factors:

- Intrinsic subtype (HER2-enriched vs Basal-like)*
- Visceral vs Non-visceral disease
- HER2-0 vs HER2-low (predefined exploratory analysis in HER2-0 population)

*According to gene expression profiling. Sequencing platforms such as HTG.



TREATMENT:

- Fulvestrant: 500 mg, IM, on days 1, 15, 29, and once monthly thereafter
- CDK4/6i: to be determined (TBD)
- T-DXd: 5.4 mg/kg, IV, Q3W
- Pre- and perimenopausal women randomized in the CDK4/6i + fulvestrant arm must receive LHRH agonists*

EoS: Until PD, unacceptable toxicity, discontinuation, or death

Abbreviations – ABC: Advanced breast cancer; BC: Breast cancer; CBR: Clinical benefit rate; CDK4/6i: CDK4/6 inhibitor; CTCAE: Common Terminology Criteria for Adverse Events; DoR: Duration of response; ECOG: Eastern Cooperative Oncology Group; EoS: End of study; ET: Endocrine therapy; HR: Hormone receptor; HRQoL: Health-related quality of life; IM: Intramuscularly; IV: Intravenous; LHRH: Luteinizing hormone-releasing hormone; LVEF: Left ventricular ejection fraction; MUGA: Multigated acquisition; ORR: Overall response rate; OS: Overall survival; PD: Progressive disease; PFS: Progression-free survival; Q3W: Every three weeks; RECIST: Response evaluation criteria in solid tumors; TBD: To be discussed; T-DXd: Trastuzumab deruxtecan.

PRIMARY ENDPOINTS

- PFS at 2y
- in HER2-low patients
- in all comers

SECONDARY ENDPOINTS

- OS
- ORR
- CBR
- DoR
- HRQoL
- Time to first subsequent chemotherapy
- Safety and toxicity (CTCAE 5.0)

EXPLORATORY ENDPOINTS

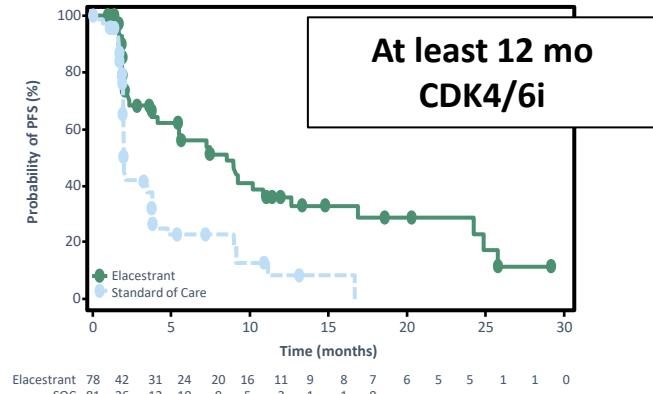
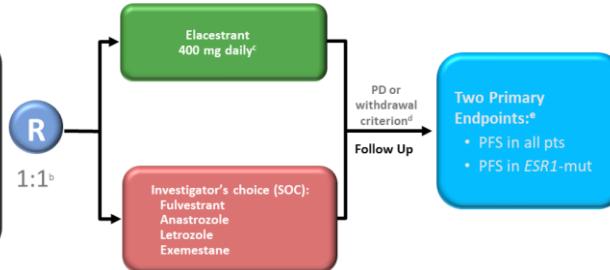
- TBD

ER[+] MBC

Elacestrant – EMERALD: ESR1-mut Tumors: PFS by Duration of CDK4/6i

Inclusion Criteria

- Men and postmenopausal women with advanced/metastatic breast cancer
- ER-positive,^a HER2-negative
- Progressed or relapsed on or after 1 or 2 lines of endocrine therapy for advanced disease, one of which was given in combination with a CDK4/6i
- ≤1 line of chemotherapy for advanced disease
- ECOG PS 0 or 1



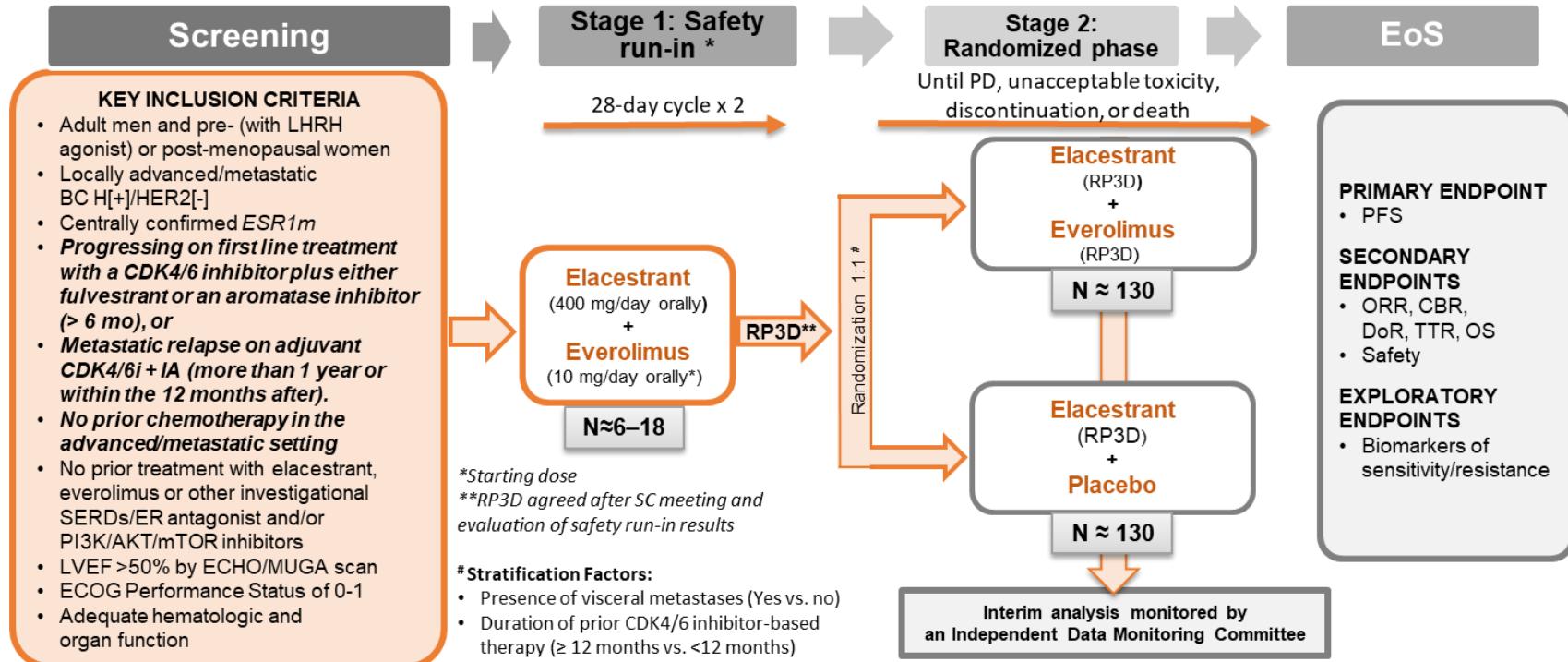
| | At Least 6 Months (92.3%) | | At Least 12 Months (71.6%) | | At Least 18 Months (50.0%) | |
|-----------------------------|---------------------------|------------------------------|----------------------------|-----------------------------|----------------------------|-----------------------------|
| | Elacestrant (n=103) | SOC Hormonal Therapy (n=102) | Elacestrant (n=78) | SOC Hormonal Therapy (n=81) | Elacestrant (n=55) | SOC Hormonal Therapy (n=56) |
| Median PFS, months (95% CI) | 4.14 (2.20 - 7.79) | 1.87 (1.87 - 3.29) | 8.61 (4.14 - 10.84) | 1.91 (1.87 - 3.68) | 8.61 (5.45 - 16.89) | 2.10 (1.87 - 3.75) |
| Hazard ratio (95% CI) | 0.517 (0.361 - 0.738) | | 0.410 (0.262 - 0.634) | | 0.466 (0.270 - 0.791) | |

ER[+] MBC

Elacestrant – ADELA: Second Line in ESR1mut patients

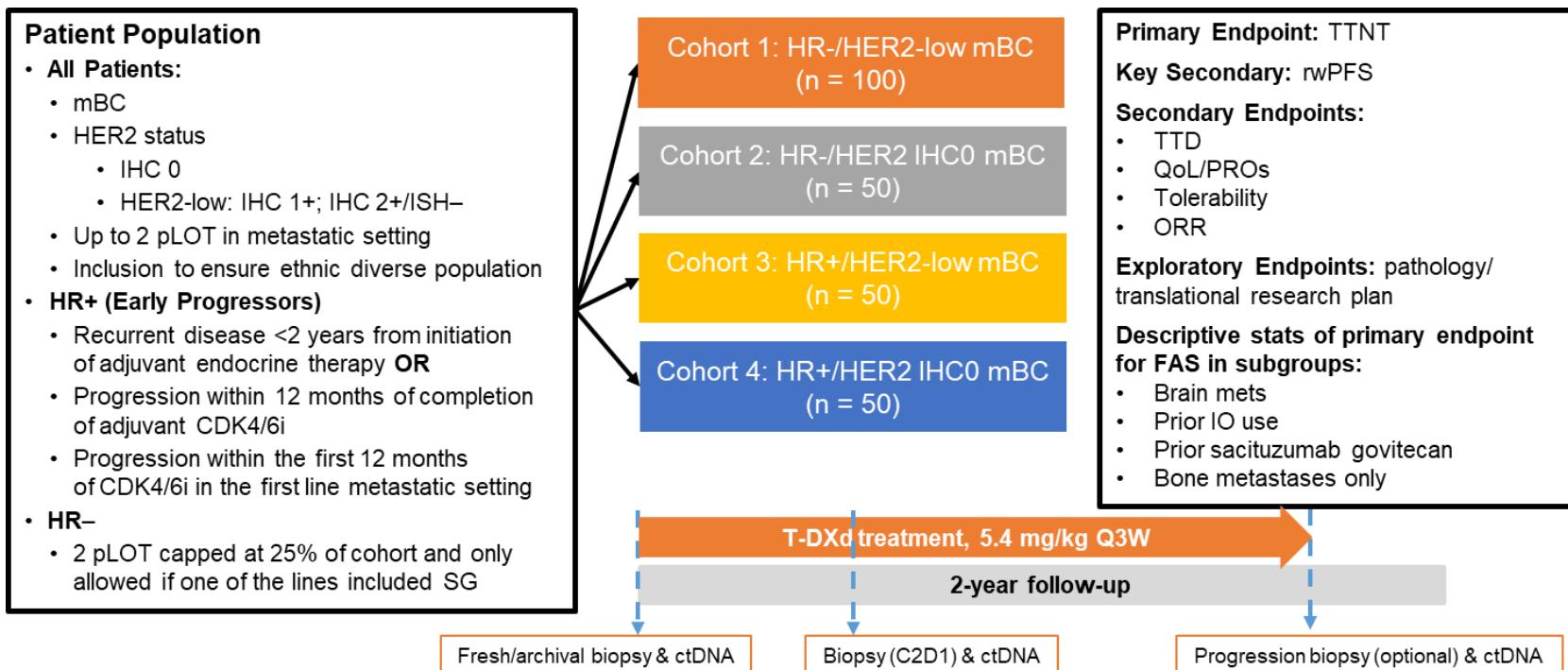


Randomized, double-blind, placebo-controlled, phase III trial



HER2[-]

T-DXd - HER2 0/ultralow - DESTINY-Breast15 Study



ctDNA, circulating tumor deoxyribonucleic acid; FAS, full analysis set; ISH, in situ hybridization; IO, immuno-oncology; ORR, objective response rate; pLOT, prior line of therapy; PROs, patient-reported outcomes; Q3W, every 3 weeks; QoL, quality of life; rwPFS, real-world progression-free survival; SG, sacituzumab govitecan; TTD, time to treatment discontinuation; TTNT, time to next treatment.

DESTINY-Breast15 Study Design (NCT05950945)

Patient Population

- All Patients:**
 - mBC
 - HER2 status
 - IHC 0
 - HER2-low: IHC 1+; IHC 2+/ISH-
 - Up to 2 pLOT in metastatic setting
 - Inclusion to ensure ethnic diverse population
- HR+ (Early Progressors)**
 - Recurrent disease <2 years from initiation of adjuvant endocrine therapy **OR**
 - Progression within 12 months of completion of adjuvant CDK4/6i
 - Progression within the first 12 months of CDK4/6i in the first line metastatic setting
- HR-**
 - 2 pLOT capped at 25% of cohort and only allowed if one of the lines included SG

Cohort 1: HR-/HER2-low mBC
(n = 100)

Cohort 2: HR-/HER2 IHC0 mBC
(n = 50)

Cohort 3: HR+/HER2-low mBC
(n = 50)

Cohort 4: HR+/HER2 IHC0 mBC
(n = 50)

Primary Endpoint: TTNT

Key Secondary: rwPFS

Secondary Endpoints:

- TTD
- QoL/PROs
- Tolerability
- ORR

Exploratory Endpoints: pathology/translational research plan

Descriptive stats of primary endpoint for FAS in subgroups:

- Brain mets
- Prior IO use
- Prior sacituzumab govitecan
- Bone metastases only

T-DXd treatment, 5.4 mg/kg Q3W

2-year follow-up

Fresh/archival biopsy & ctDNA

Biopsy (C2D1) & ctDNA

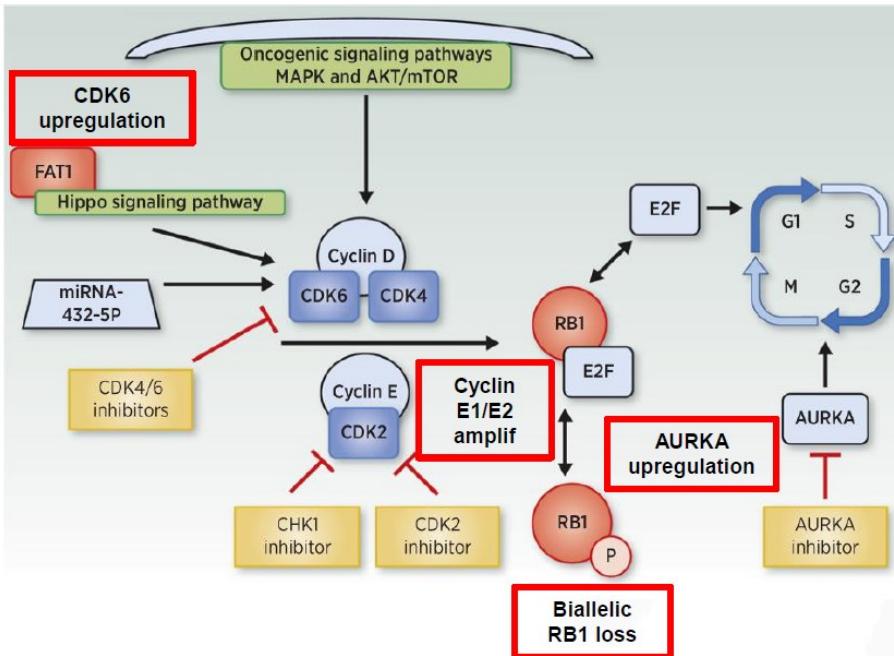
Progression biopsy (optional) & ctDNA

ctDNA, circulating tumor deoxyribonucleic acid; FAS, full analysis set; ISH, in situ hybridization; IO, immuno-oncology; ORR, objective response rate; pLOT, prior line of therapy; PROs, patient-reported outcomes; Q3W, every 3 weeks; QoL, quality of life; rwPFS, real-world progression-free survival; SG, sacituzumab govitecan; TTD, time to treatment discontinuation; TTNT, time to next treatment.

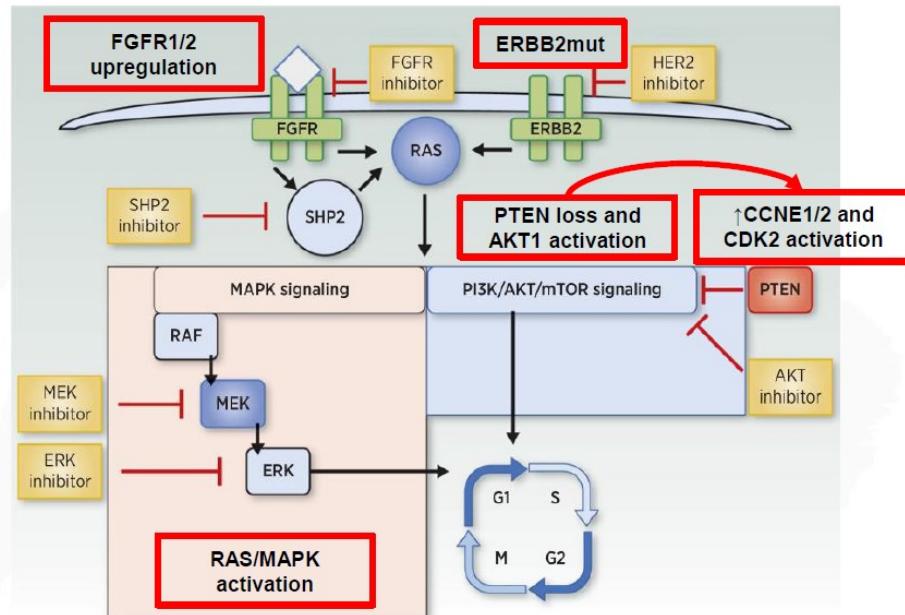
ER[+] MBC

Genetic determinants of resistance to CDK4/6i

Alterations in cell-cycle mediators



Oncogenic signaling pathways activation

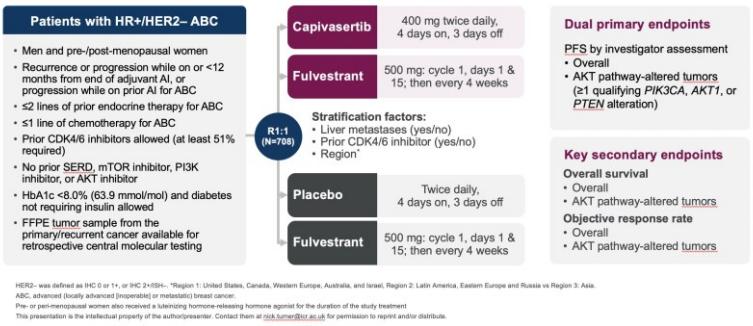


ER[+] MBC

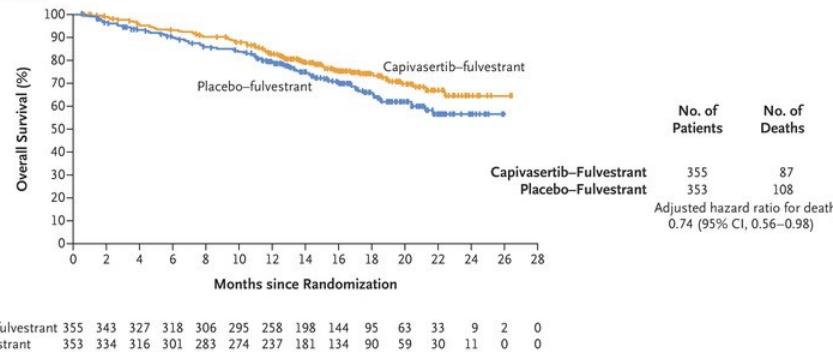
Capitello 291: + Fulvestrant +/- Capivasertib (AKTi)

CAPtello-291: Study overview

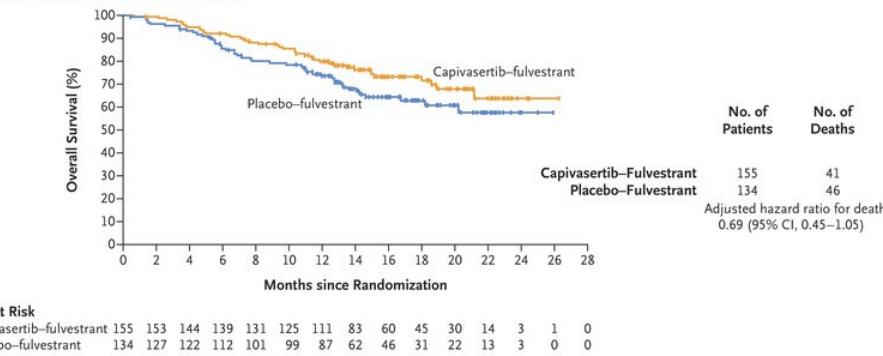
Phase III, randomized, double-blind, placebo-controlled study (NCT04305496)



A Overall Population



B Patients with AKT Pathway-Altered Tumors





HER2[-] MBC



New PI3K inhibitors in clinical development

| Drug | Type of inhibitor | Clinical Trial |
|-------------|--|---|
| Inavolisib | ATP-competitive PI3K α inhibitor | INAVO120 (NCT04191499) INAVO121 (NCT05646862) Phase I with paclitaxel (EudraCT 2020-005057-24) TAPISTRY: multiple PIK3CAmut (NCT04589845) MORPHEUS: Combo with giredestrant (NCT04802759) |
| MEN1611 | ATP-competitive PI3K α , β , γ -selective and δ - sparing | SABINA: combo with eribulin (NCT05810870) |
| Gedatolisib | ATP-competitive pan-class I isoform PI3K and mTOR inhibitor | VIKTORIA-1: Ph 3 combo with palbo + fulv (NCT05501886) |
| RLY-2608 | Allosteric, pan-mutant, isoform-selective PI3K α inhibitor | Ph I single agent or Fulv combo (NCT05216432) |
| RLY-5836 | Allosteric, pan-mutant, isoform-selective PI3K α inhibitor | Ph I single agent and combos (NCT05759949) |
| LOXO-783 | Mutant-selective, brain-penetrant allosteric PI3K α H1047R inhibitor | PIKASSO-01: Ph I single agent (NCT05307705) |
| TOS-358 | Covalent PI3K α inhibitor | FIH (NCT05683418) |



HER2[-] MBC

New CDK inhibitors in clinical development

| Drug | Target | Available and upcoming data | Trial |
|------------------------------|-------------|---|-----------------------------|
| PF-07104091 | CDK2 | ASCO 2023 #3010 (PD) | NCT04553133 |
| PF-07220060 | CDK4 | - | NCT04557449 |
| PF-06873600 | CDK2/4/6 | Hematologic and GI AEs; ORR 8% (Yap T et al, SABCS 2021) | NCT03519178 discontinued |
| PF-07220060 + PF-07104091 | CDK4 + CDK2 | - | NCT05262400 |
| BLU-222 | CDK2 | ASCO 2023 #3095 | NCT05252416 |
| Samuraciclib | CDK7 | Combination with giredestrant Combination with elacestrant Phase II with fulvestrant | NCT04802759 TBD TBD |
| SY-5609 | CDK7 | GI AEs; activity in pancreatic cancer (ESMO 2021) Combo with Fulv in BC: ASCO 2023 #3081 | NCT04247126 |
| XL102 | CDK7 | GI AEs, combos ongoing (Patnaik A et al, SABCS 2022) | NCT04726332 |

Conclusiones

- EL cáncer de mama Avanzado deviene una patología de gran complejidad para la búsqueda de nuevos fármacos o indicaciones
- En HER2[+] el posicionamiento final de T-DXd va a reajustar todas las líneas y escenarios – Oportunidad para estrategias y combinaciones más que nuevos fármacos
- En CMTN las combinaciones de ICLs, ADCs y otras terapias dirigidas (PARPs,...) van a generar oportunidades en la primera línea, pero no se identifica nada radicalmente nuevo en próximos años.
- La incorporación de biomarcadores dinámicos va a permitir generar estrategias más individualizadas, pero complica estrategias de registro y aumenta las necesidades de los clínicos tras aprobaciones regulatorias.