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CÁNCER DE MAMA LUMINAL METASTÁSICA

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CÁNCER DE MAMA LUMINAL METASTÁSICA

INDICE

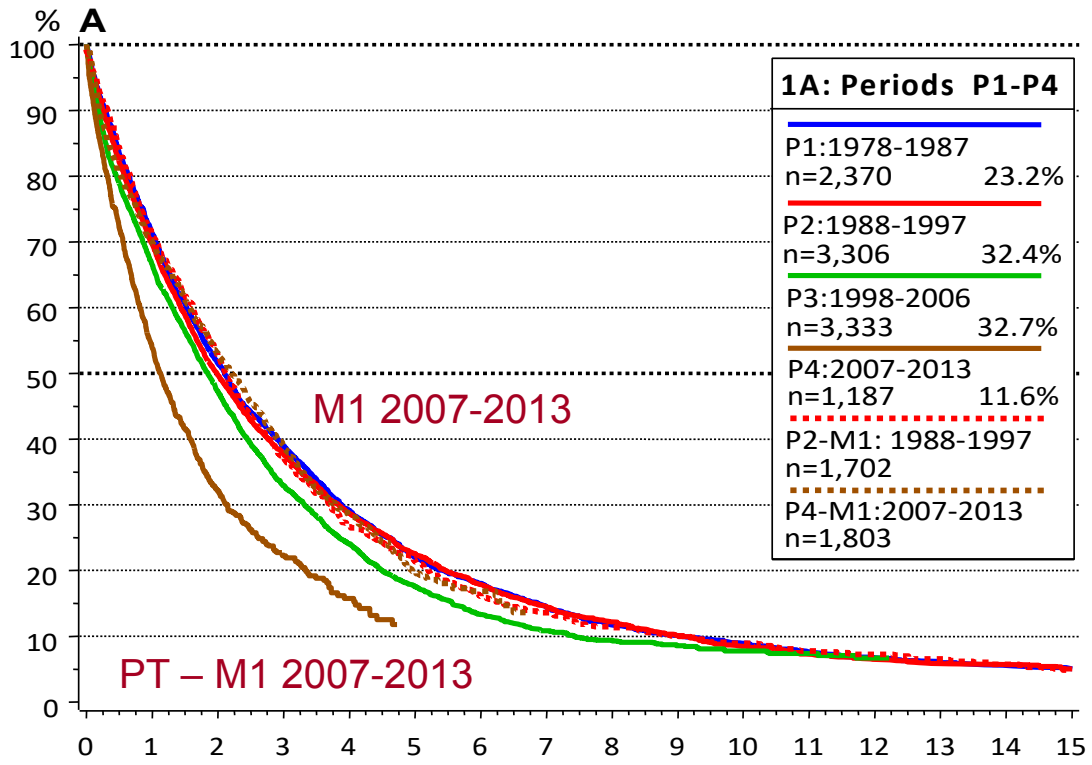
- Generalidades
- Aspectos diagnósticos
- Manejo terapeútico

FUENTES estudio: GUIAS ESMO (ultima actualización 2021 ; pdte de nueva actualización)
GUIAS SEOM (actualizadas 2023)
Libro : Tratamiento multidisciplinar en cáncer de mama. Ed Manuel Ruiz Borrego. Pub 2024.
Aula médica

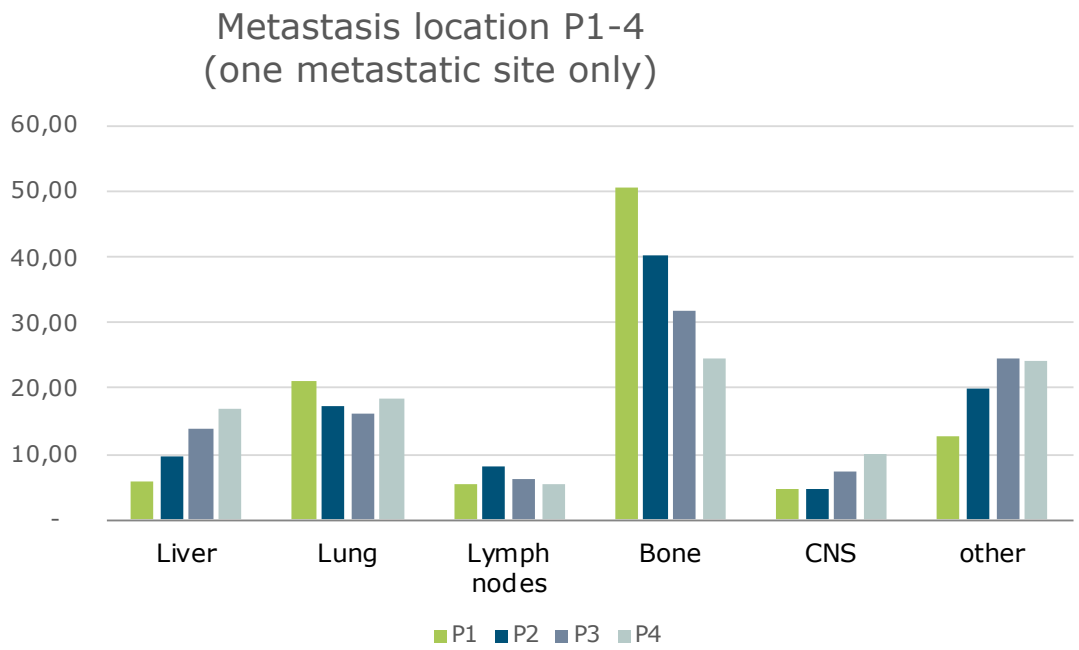
CÁNCER DE MAMA LUMINAL METASTÁSICA: GENERALIDADEES

- El CM Luminal es el subtipo de cáncer de mama mas frecuente representando un 75% del total de los CM , siendo también el subtipo de CMM mas frecuente
- Caracterizado por expresión de Receptores Hormonales (RH) : R estrógeno (RE) y R progesterona (RPg) y ausencia de expresión de Receptor HER2 .
- Dentro de los CMM Luminales al igual que en la enf. precoz podemos diferenciar dos subtipos basándonos en la practica clínica en valor del Ki67 . Luminal A (KI67 < 15%) suelen ser biológicamente menos agresivos ,asociar mayor intensidad de expresión de RH y menor GH y Luminal B (Ki67 ≥ 15%)
- En ambos subtipos el pilar fundamental de tratamiento es la TERAPIA HORMONAL , preferentemente en combinación con terapias dirigidas
- Las Localizaciones de la afectación metastásica han variado en los últimos años

Metastatic Breast Cancer – Impact of improved adjuvant therapies



Overall survival after metastasis (PMS) based on the period (P1–P4) of the primary tumour diagnosis (P<0.0001) (n=10,213) and for primary advanced BC (T-N-M1) from periods P2 and P4 (dotted curves).



Harbeck et al, ABC 4 abstract PO 141 2017)

DIAGNÓSTICO

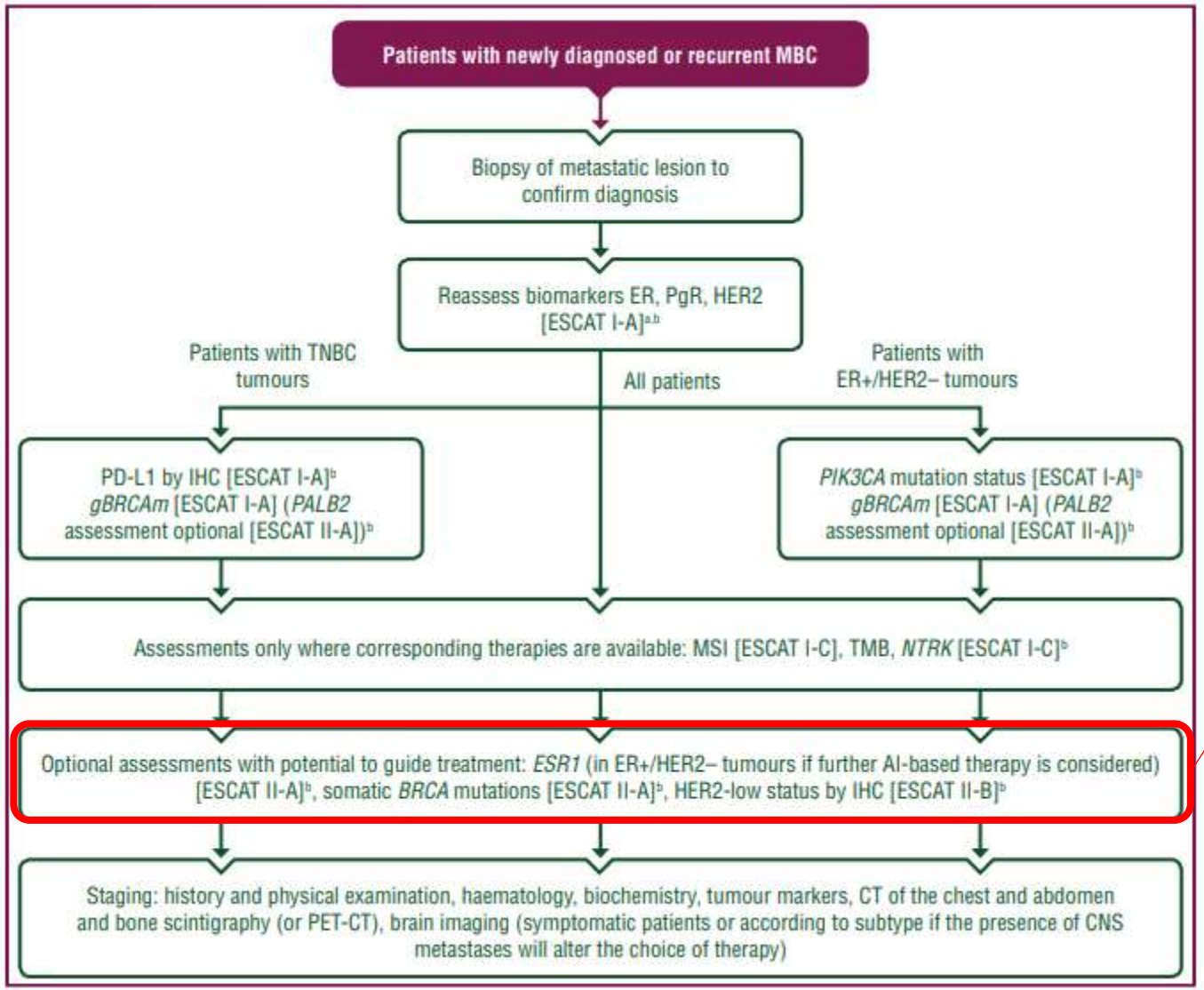
CÁNCER DE MAMA LUMINAL METASTÁSICA: DIAGNÓSTICO

- Si es posible se recomienda biopsiar la recaída para confirmar la misma y definir el subtipo
- Además del estudio de sobreexpresión de RH que confirme el subtipo Luminal , hay que definir la expresión del R Her2 (basado en técnicas de IHQ y de ISH) (ASCOCAP 2018) para identificar al subgrupo HER2 Low *

Otros BIOMARCADORES:

- Mutaciones en PIK3CA (tumor, biopsia liquida) tumor primario o recaída
- Mutaciones ESR1 (tumor , biopsia liquida) recaída (Resistencia a Inhibidores de Aromatasa (IA))
- Mutación germinal en BRCA1/2 (aunque en España no está autorizado el uso de Inhibidores de PARP para el tratamiento del CMM)

CÁNCER DE MAMA LUMINAL METASTÁSICA: DIAGNÓSTICO



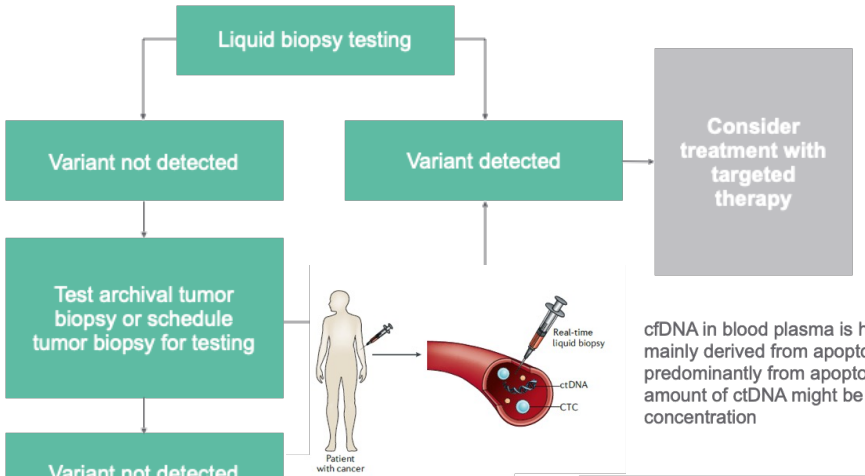
ACTUAL : all patients

ESMO MBC Guidelines, Ann Oncol 2021

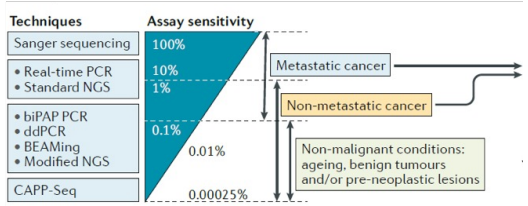
CÁNCER DE MAMA LUMINAL METASTÁSICA: DIAGNÓSTICO PIK3CA

-Per joint recommendations from ASCO-CAP, samples **should be taken at disease progression** for tumor genotyping

-Consider tumor biopsy testing to confirm negative results
-PIK3CA mutation testing can be done on tumor tissue or ctDNA in peripheral blood (liquid biopsy). If liquid biopsy is negative, tumor tissue testing is recommended



cfDNA in blood plasma is highly fragmented DNA mainly derived from apoptotic cells, perhaps predominantly from apoptotic leukocytes. The total amount of ctDNA might be <0.01% of the total cfDNA concentration



Based on Merker JD, et al. *Arch Pathol Lab Med*. 2018;142:1242-1253.

In order to ensure appropriate patient selection for potential alpelisib treatment, patients with HR+/HER2 advanced breast cancer should have **tumors** tested for *PIK3CA* mutations using a **health authority-approved, accurate and validated** test.

PIK3CA mutation testing can be performed on **FFPE tumor specimens** as well as **ctDNA extracted from plasma.**

- Tumor tissue obtained at initial diagnosis or at the most recent biopsy can be used
- Mutations detected in ctDNA should be considered actionable. Mutations "not detected in ctDNA" should reflex to tissue based testing

Initial approval is based on **11 mutations** (C420R, E542K, E545K/A/D/G, Q546E/R, H1047L/R/Y) across exon 7, 9, 20 of *PIK3CA* gene.

PCR and NGS on tissue are generally consistent in detecting the 11 mutations represented in SOLAR-1.

PIK3CA testing can be performed utilizing tumor tissue or ctDNA

ctDNA, circulating tumor DNA; FFPE, Formalin-Fixed Paraffin-Embedded; NGS, Next-Generation Sequencing; PCR, Polymerase chain reaction; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

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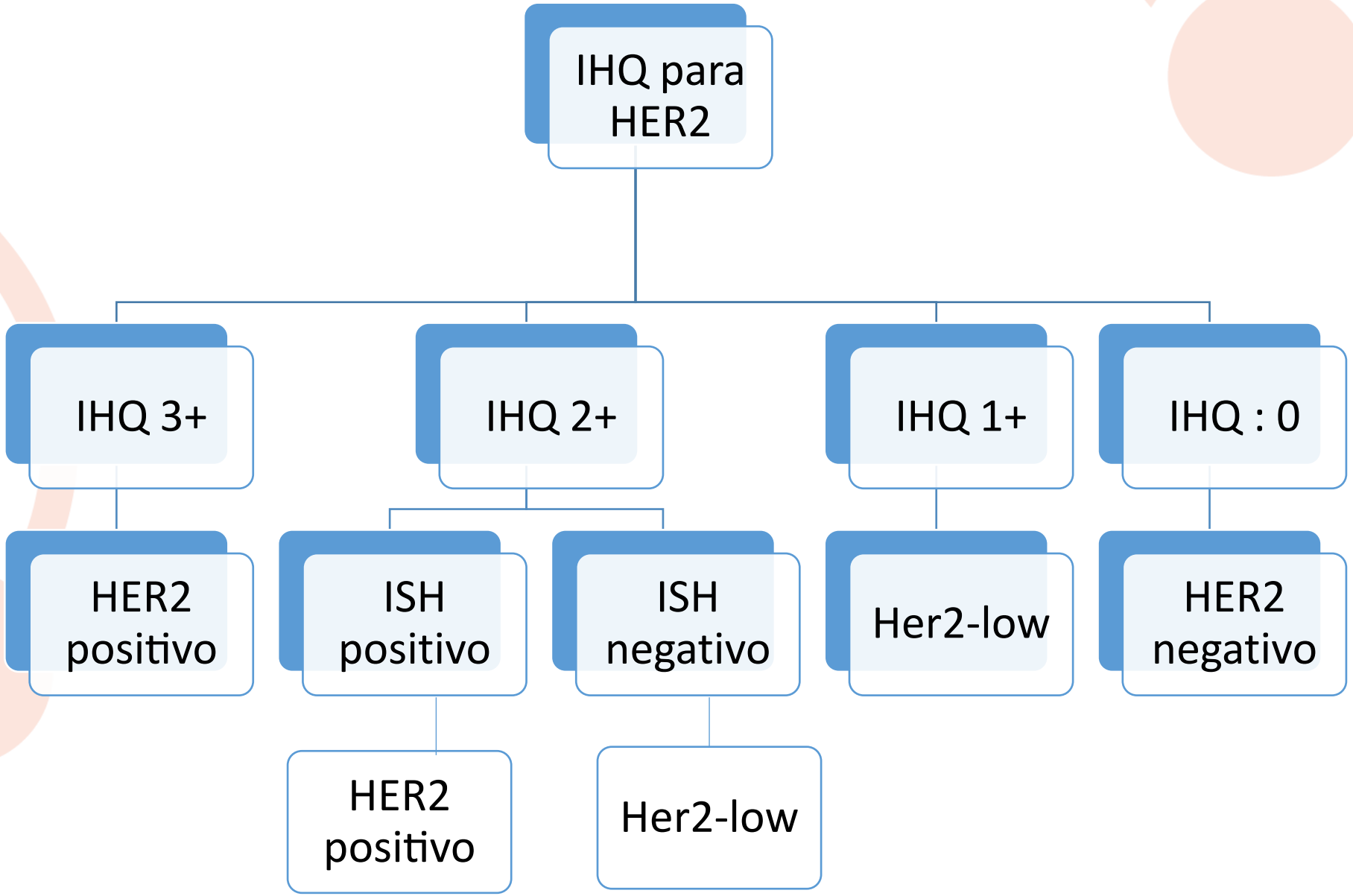
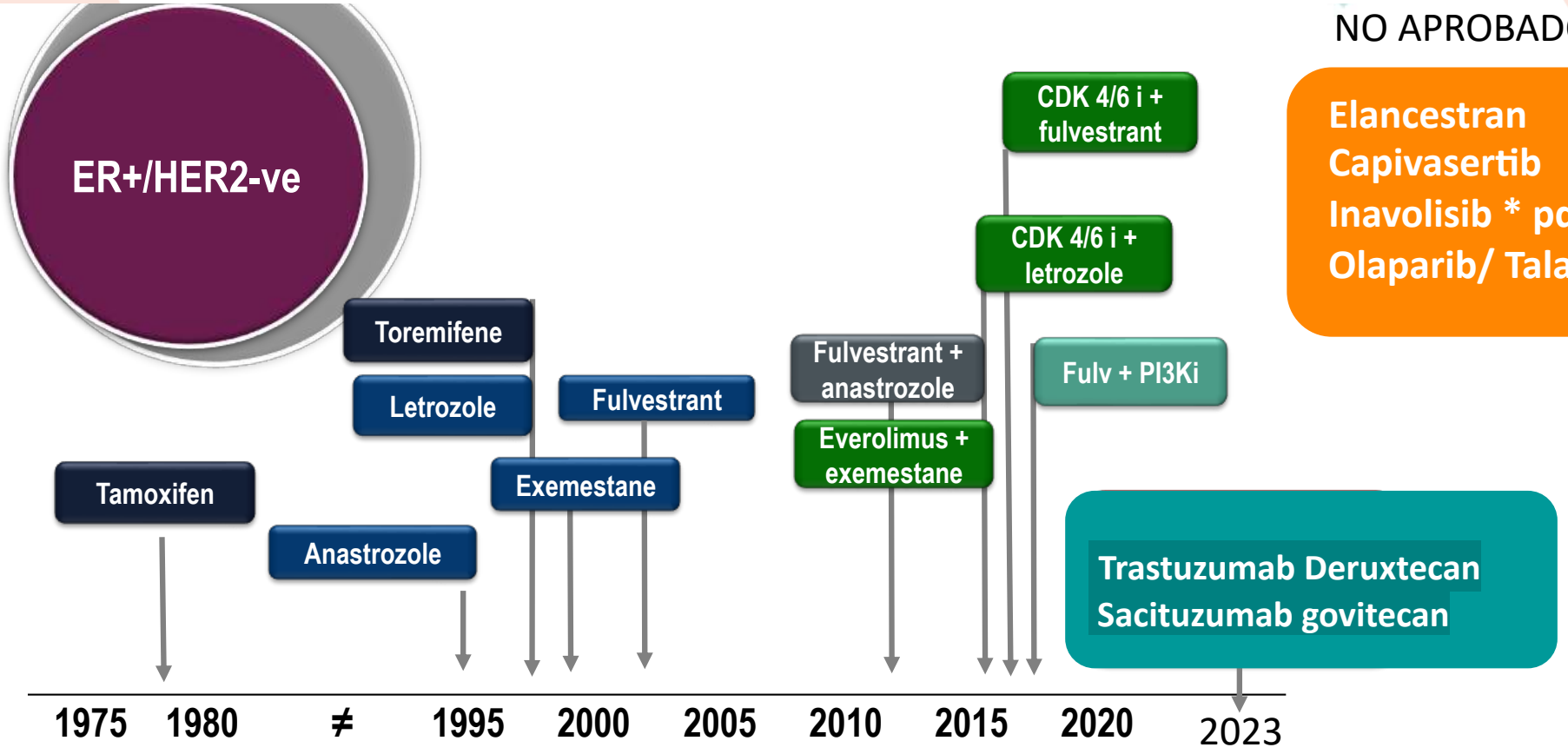


TRATAMIENTO

MILESTONES IN THE TREATMENT OF HR+/HER2- ABC

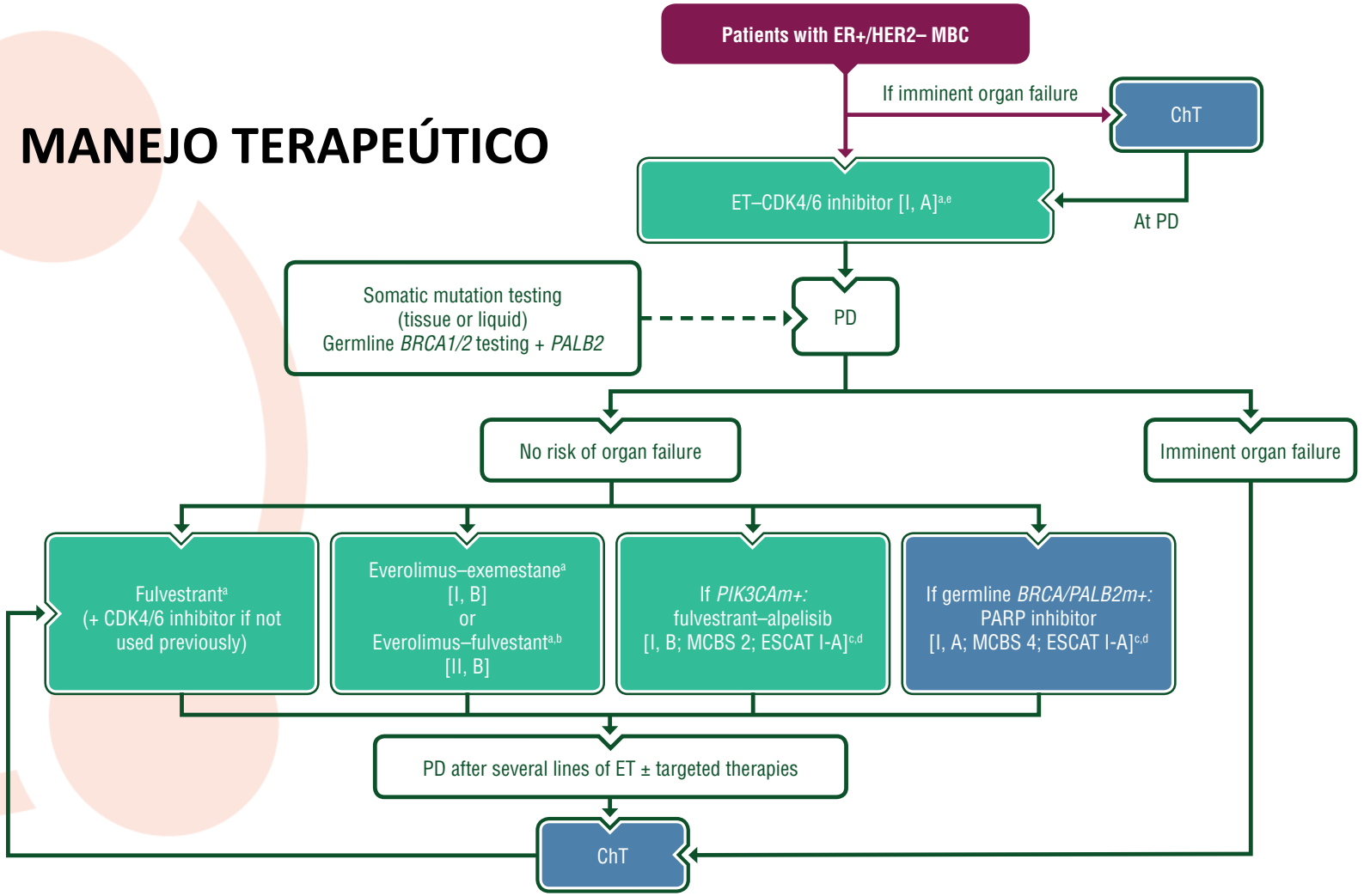


NO APROBADOS EN ESPAÑA

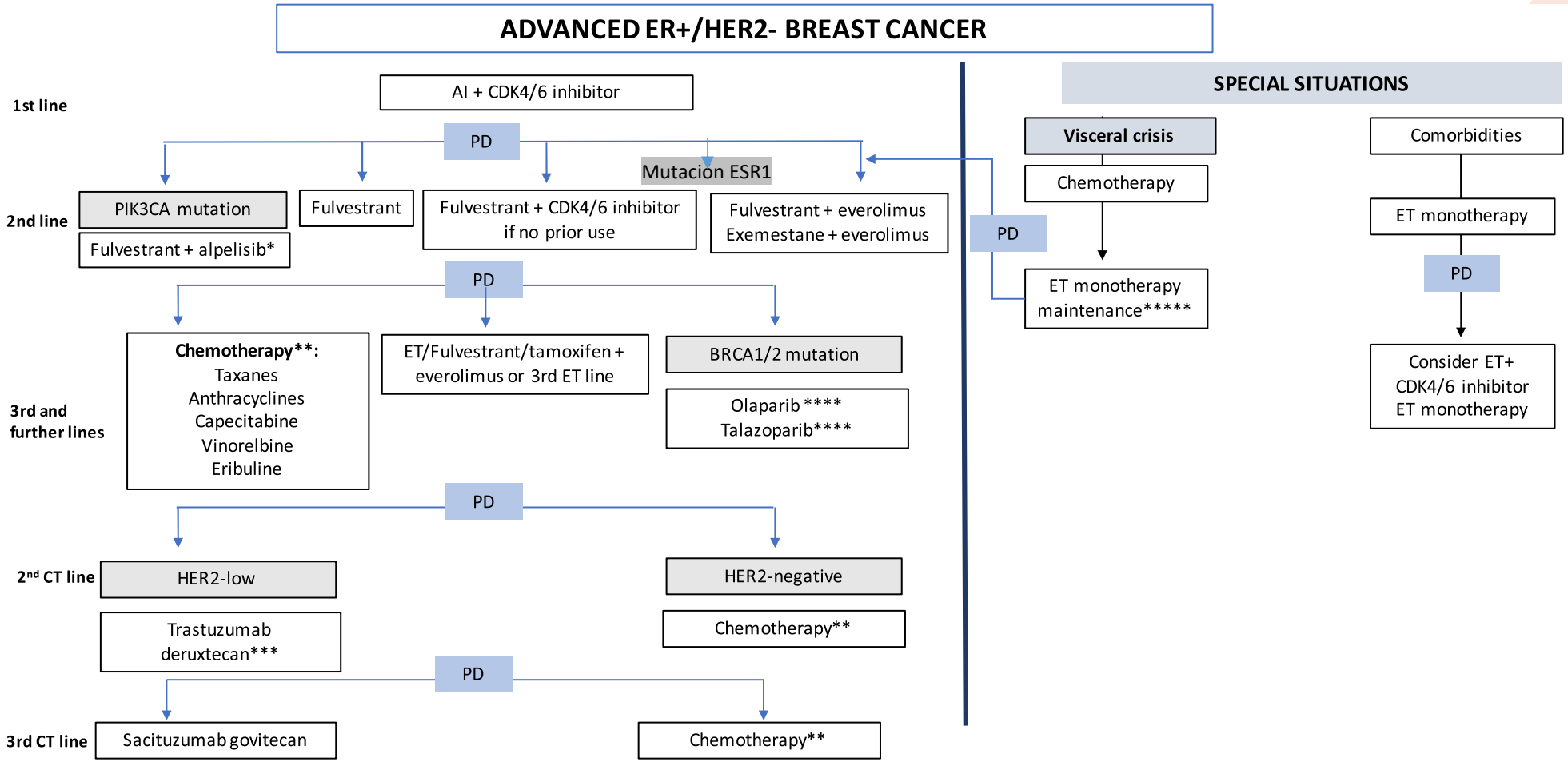
Elancestran
Capivasertib
Inavolisib * pdet aprobación AR
Olaparib/ Talazoparib

CMM LUMINAL :ESTRATEGIAS TRATAMIENTO

MANEJO TERAPEÚTICO

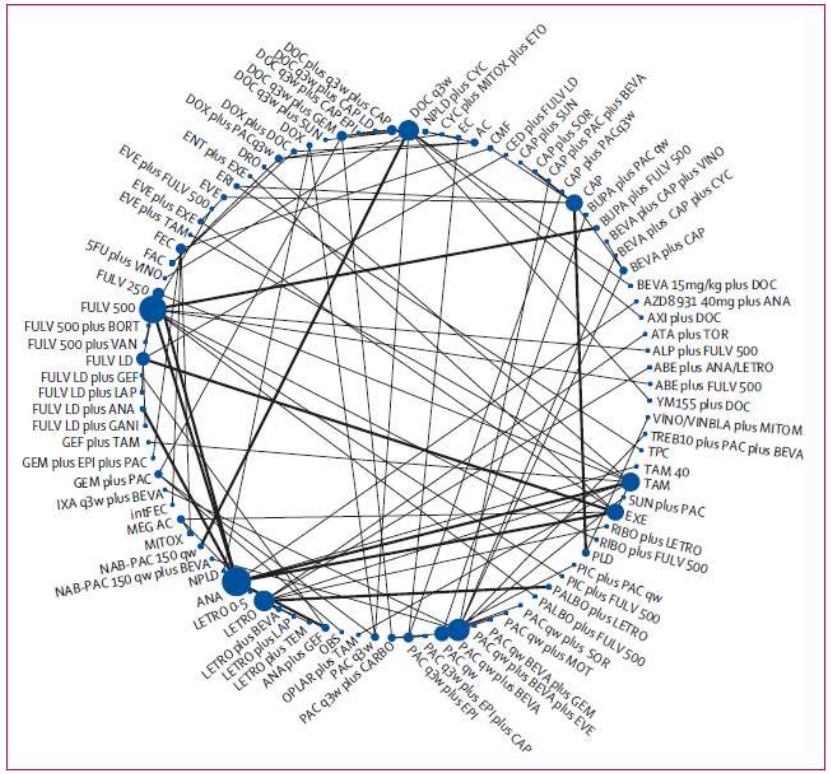


CÁNCER DE MAMA LUMINAL METASTÁSICA: GUIAS SEOM/ GEICAM/ SOLTI



* Currently approved for patients progressing on endocrine monotherapy
** The preferred sequence of chemotherapies is currently unknown, Previous treatments, comorbidities and patient preferences should be taken into account.
*** Still awaiting approval by the EMA and subsequent financial approval from the health authorities in Spain
**** Approved by the EMA but without financial approval from the health authorities in Spain
***** Consider ET + iCDK4/6

1º LINEA CMM LUMINAL



- In the first-line or second-line setting, CDK4/6 inhibitors plus hormone therapies are better than standard hormone therapies in terms of progression-free survival.
- No chemotherapy regimen with or without targeted therapy is significantly better than CDK4/6 inhibitors plus hormone therapies in terms of progression-free survival.

ET plus CDK4/6 inhibition yields similar or better efficacy versus ChT and is associated with less toxicity, making it the preferred treatment unless a patient has imminent organ failure

En pacientes con crisis visceral * seria también una opción a valorar.

1º LINEA CMM LUMINAL

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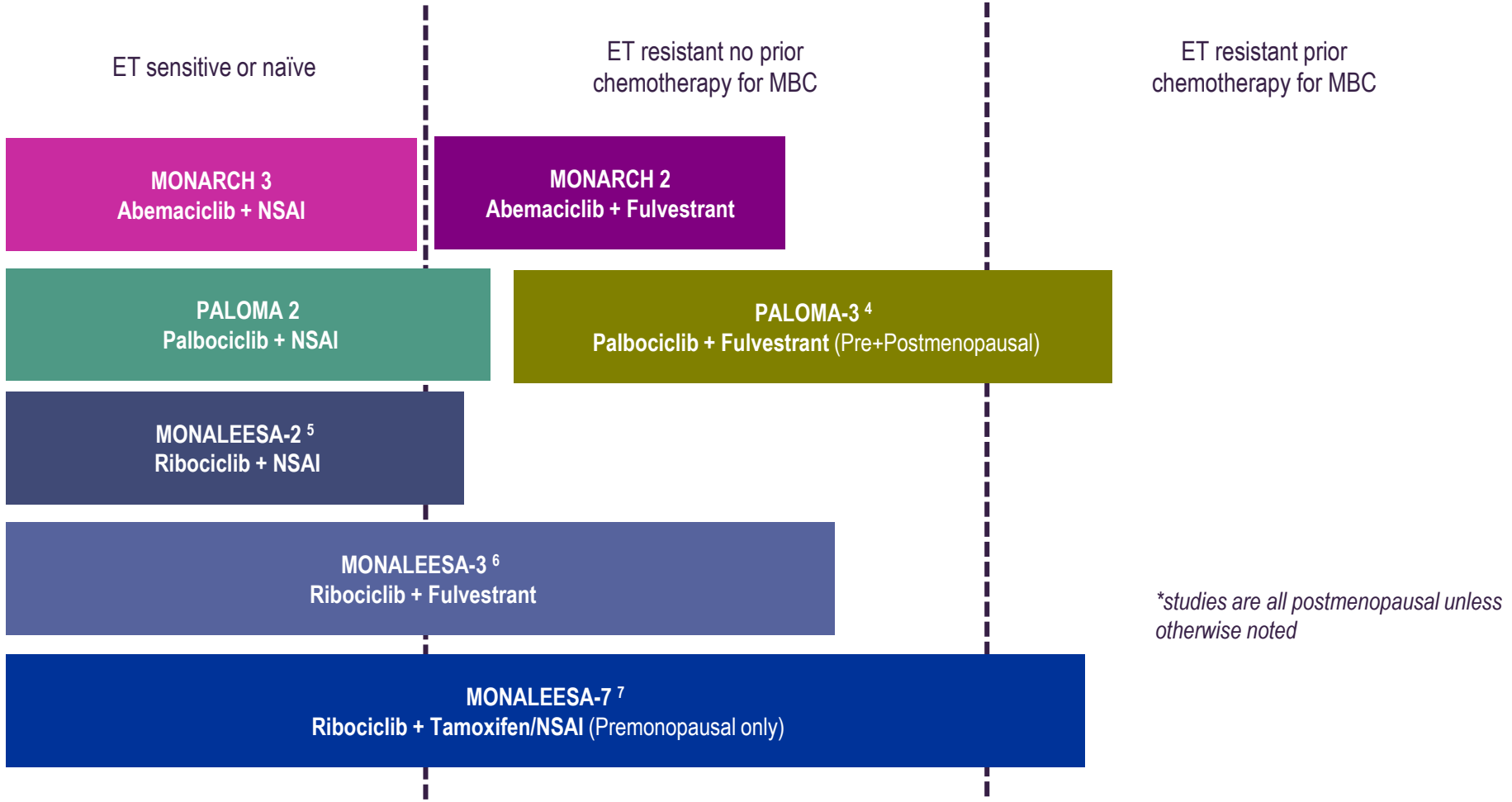
THE ADVANTAGE OF CDK 4/6 INHIBITORS: TRIALS OVERVIEW



*studies are all postmenopausal unless otherwise noted

1. **Goetz et al.** J Clin Oncol 35:3638-3646. **2. Sledge et al.** J Clin Oncol 35:2875-2884. **3. Finn et al.** N Engl J Med 2016. **4. Cristofanilli et al.** Lancet Oncol 2016; **5. Hortobagyi et al.** N Engl J Med 2016. **6. Slamon et al.** J Clin Oncol 36:2465- 2472. **7. Tripathy et al.** Lancet Oncol 2018

1º LINEA CMM LUMINAL

Randomized phase III trials of CDK4/6 inhibitors in the first line setting

	PALOMA-2	MONALEESA-2	MONALEESA-7	MONARCH-3
Regimen	Letrozole +/- **palbociclib** (2:1)	Letrozole +/- **ribociclib** (1:1)	Goserelin + AI or tamoxifen +/- **ribociclib** (1:1)	AI +/- **abemaciclib** (2:1)
Eligibility	Postmenopausal, untreated advanced HR+/HER2- BC	Postmenopausal, untreated advanced HR+/HER2- BC	Pre/perimenopausal, untreated advanced HR+/HER2- BC	Postmenopausal, untreated advanced HR+/HER2- BC
Sample size	666	668	672	493
De novo MBC	38%	34%	41%	20%
Median PFS (CDK vs. placebo)	27.6 vs. 14.5 months (HR 0.56; 0.46-0.69)	25.3 vs. 16 months (HR 0.57; 0.45-0.60)	23.8 vs. 13 months (HR 0.55; 0.44-069)	29 vs. 14.8 (HR 0.53; 0.42-0.66)
Median OS (CDK vs. placebo)	**53.9 vs. 51.2 months** △ **2.7** (HR 0.96; 0.77-1.17)* ✗	**63.9 vs. 51.4 months** △ **12.4** (HR 0.76, 0.63-0.93) ✓	**58.7 vs. 48 months** △ **10.7** (HR 0.76; 0.60-0.95) ✓	**66,8 vs. 53,7 months** △ **13.1** **(HR 0.84; 0.63-1.01** ✗
Toxicities of interest	Neutropenia, leukopenia, fatigue	Neutropenia, leukopenia, fatigue, QTc prolongation, transaminitis	Neutropenia, leukopenia, fatigue, nausea, QTc prolongation, transaminitis	Neutropenia, fatigue, diarrhea, nausea, anemia, abdominal pain

Goetz M et al, SABCS 2023.

1º LINEA CMM LUMINAL

INAVO120 study design

Enrolment period: December 2019 to September 2023

Key eligibility criteria

Enrichment of patients with poor prognosis:

- **Measurable disease**
- ***PIK3CA*-mutated, HR+, HER2- ABC** by central ctDNA* or local tissue/ctDNA test
- **Progression during/within 12 months of adjuvant ET completion**

- **No prior therapy for ABC**
- **Fasting glucose <126 mg/dL and HbA_{1C} <6.0%**

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

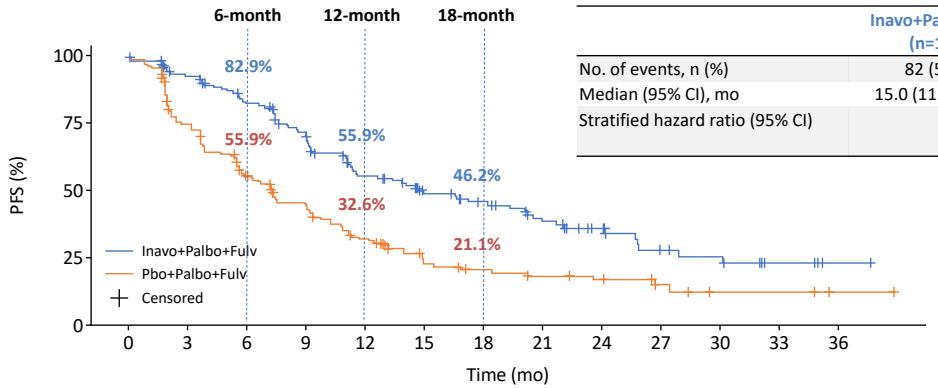
- Primary: PFS by Investigator
- Secondary: OS‡, ORR, BOR, CBR, DOR, PROs

- Central testing for *PIK3CA* mutations was done on ctDNA using FoundationOne®Liquid (Foundation Medicine). In China, the central ctDNA test was the PredicineCARE NGS assay (Huidu). † Defined per 4th European School of Oncology (ESO)–European Society for Medical Oncology (ESMO) International Consensus Guidelines for Advanced Breast Cancer.
- [1] **Primary: relapse while on the first 2 years of adjuvant ET; Secondary: relapse while on adjuvant ET after at least 2 years or relapse within 12 months of completing adjuvant ET.** ‡ OS testing only if PFS is positive; interim OS analysis at primary PFS analysis;
  ** Pre-menopausal women received ovarian suppression. ctDNA, circulating tumor DNA; R, randomized. 1. Cardoso F, *et al. Ann Oncol* 2018;**29:**1634–1657.

1º LINEA CMM LUMINAL

INAVO- 120

Primary endpoint: PFS (investigator-assessed)



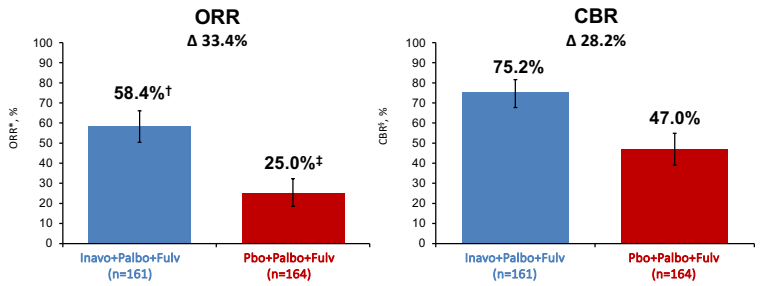
	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
No. of events, n (%)	82 (50.9)	113 (68.9)
Median (95% CI), mo	15.0 (11.3, 20.5)	7.3 (5.6, 9.3)
Stratified hazard ratio (95% CI)	**0.43 (0.32, 0.59) p<0.0001**	

Patients at risk:

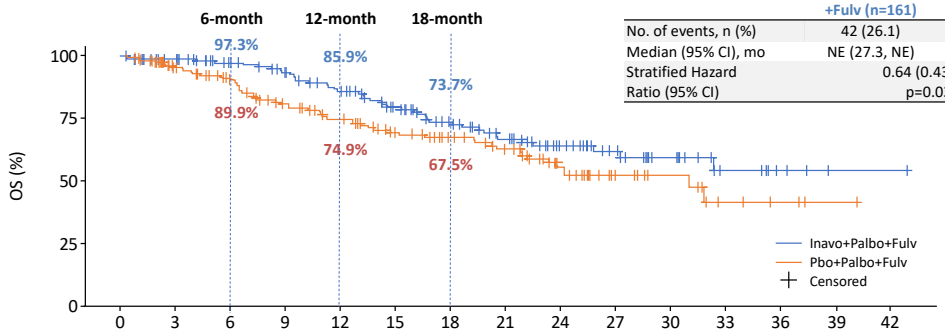
Inavo+Palbo+Fulv	161	134	111	92	66	48	41	31	22	13	11	5	1
Pbo+Palbo+Fulv	164	113	77	59	40	23	19	16	12	6	3	3	1

Median follow-up:
21.3 months

Secondary endpoints: ORR and CBR (investigator-assessed)



Key secondary endpoint: Overall survival (interim analysis)



	Inavo+Palbo +Fulv (n=161)	Pbo+Palbo +Fulv (n=164)
No. of events, n (%)	42 (26.1)	55 (33.5)
Median (95% CI), mo	NE (27.3, NE)	31.1 (22.3, NE)
Stratified Hazard Ratio (95% CI)	0.64 (0.43, 0.97) p=0.0338	

Inavolisib in combination with palbociclib and fulvestrant may represent a new standard of care for patients with *PIK3CA*-mutated, HR+, HER2- ABC

TRATAMIENTO ELECCIÓN PRIMERA LINEA : HT + INHIB CDK4/6

- **SI Hormorrefractaria : PE Durante la HT adyuvancia o en < 12 meses tras fin de la misma:**

  FULVESTRAN + Inhibidor de CDK4/6

  *** Si mutación en PIK3CA : Inavolisib+Fulvestran+ Palbociclib (pdte de aprobación por agencias reguladoras)**

- **Si Hormosensible : IA + Inhib CDK4/6**
- **SI CRISIS VISCERAL ≠ ENFERMEDAD VISCERAL : Según las guias QUIMIOTERAPIA (QT)**
- **¿ QUE INHIB DE CDK4/6 ? : TODOS APROBADOS AL CUMPLIR OBJETIVO PRAL DEL ESTUDIO**

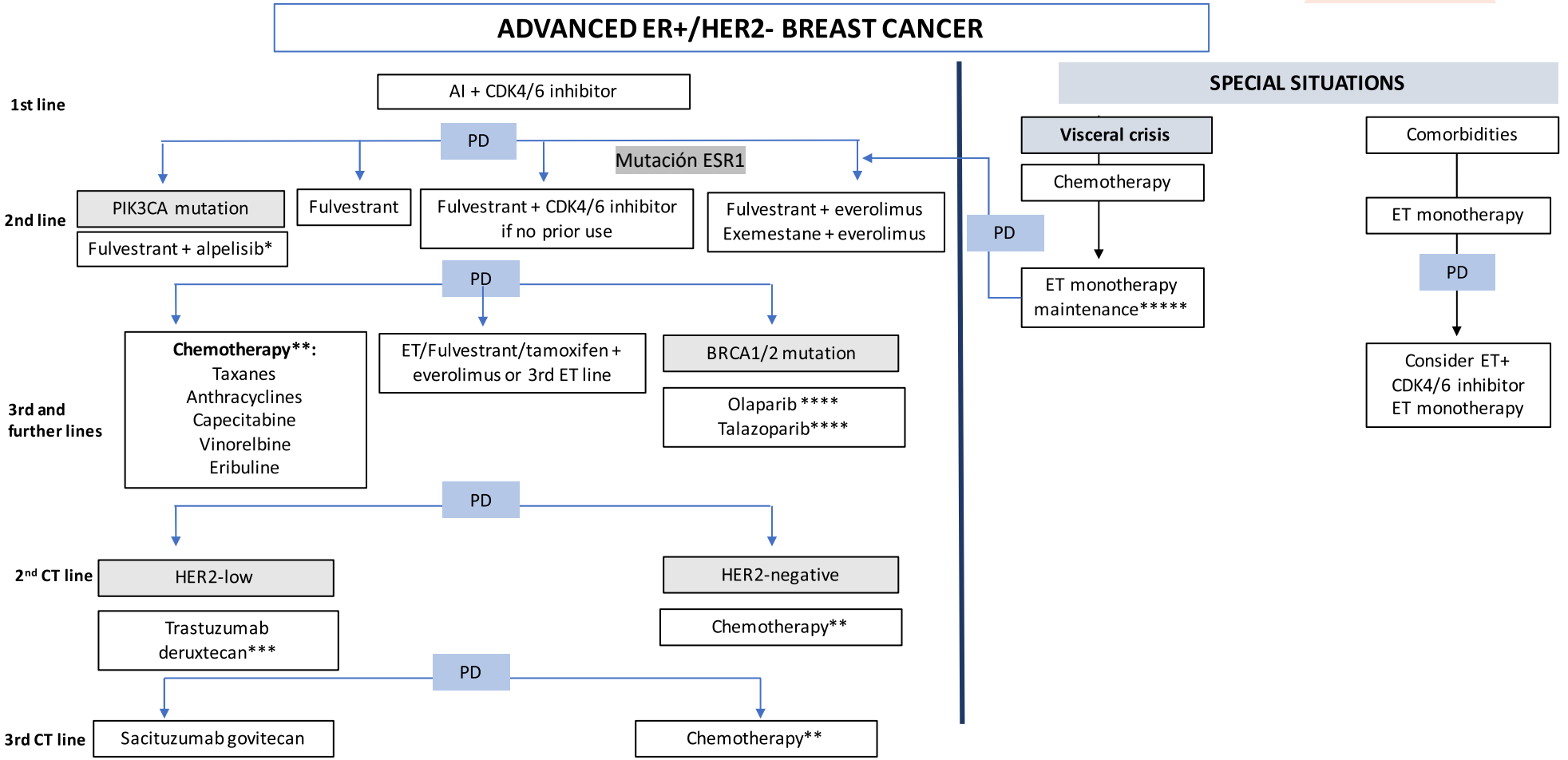
CMM LUMINAL :ESTRATEGIAS TRATAMIENTO

2º LINEA DE TRATAMIENTO TRATAMIENTO DE ELECCIÓN:HORMONOTERAPIA

- Si Mutación en PIK3CA : Alpelisib +Fulvestran * (guias SEOM)
- Sino : Everolimus+Fulvestran / exemestano
  Fulvestran en monoterapia

- FDA ; Aprobacion de Capivasertib (mut PI3K/AKT/ pTEN)
  Aprobacion de Elancestran (mut ESR1)

CÁNCER DE MAMA LUMINAL METASTÁSICA:SEGUNDA LINEA



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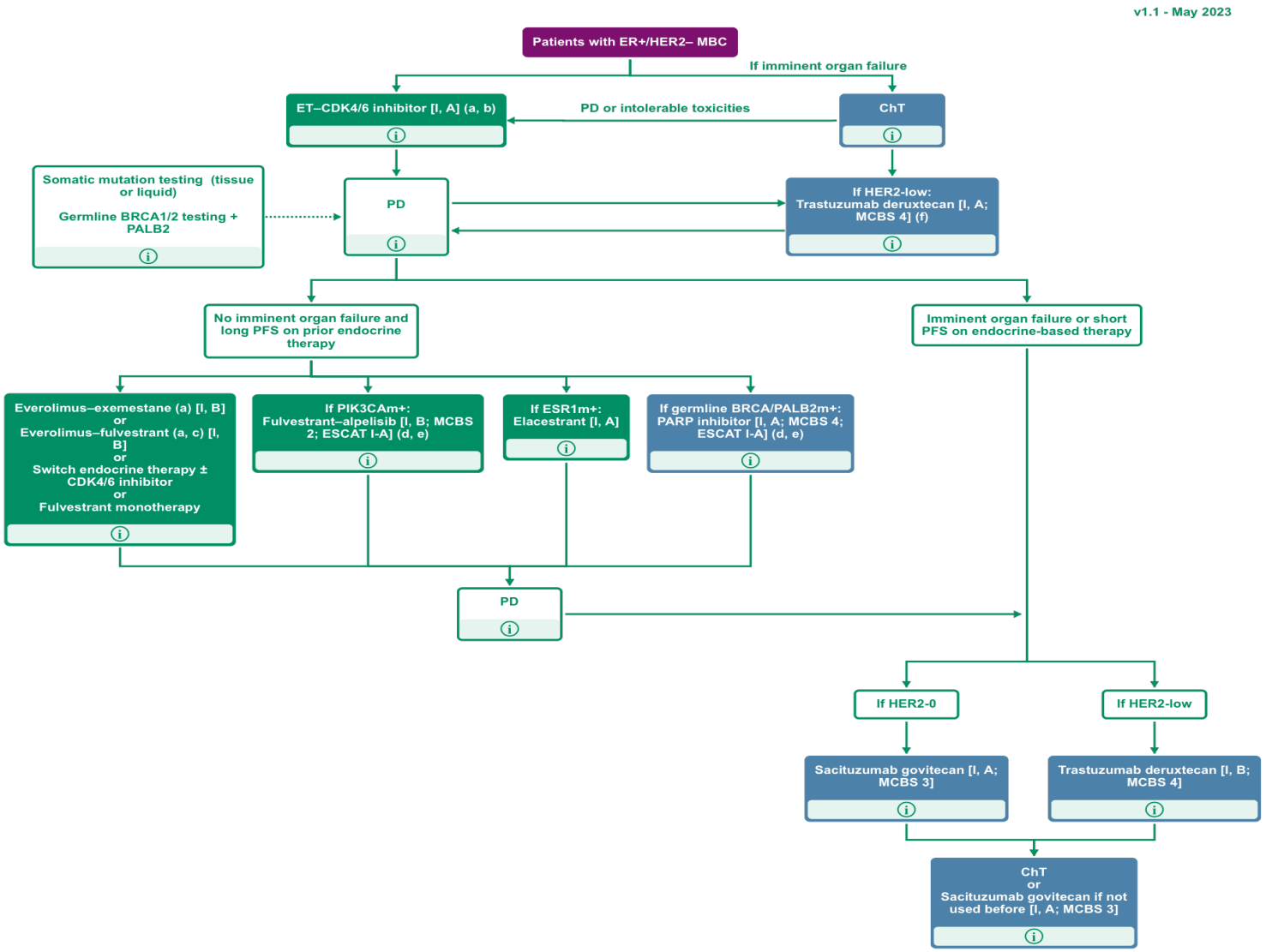
CÁNCER DE MAMA LUMINAL METASTÁSICA: RECOMENDACIÓN ESMO



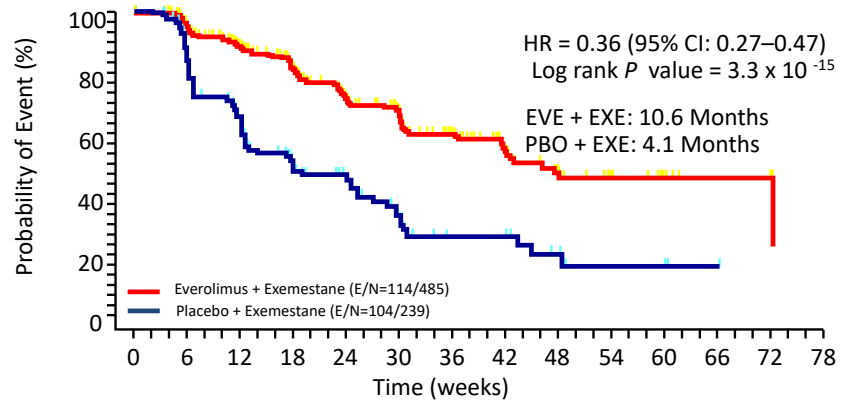
Current drugs approved for the tratment of MBC that inhibit PIK3/AKT/mTOR

	Everolimus (BOLERO-2)	Alpelisib (SOLAR-1)	Capivasertib (Capitello-291)
Mechanism of action	mTOR inhibitor	PI3Kα-specific inhibitor	AKT inhibitor
Design	Postmenopausal women (n=724), randomized 2:1 to exemestane + everolimus or placebo	n=572 (341 with PIK3CAm) randomized 1:1 to fulvestrant +alpelisib or placebo	n=708 (289 with AKT pathway alterations, 489 with prior iCDK4/6) randomized 1:1 to fulvestrant + capivasertib or placebo
Median PFS (months)	**10.6 vs 4.1 mo**	**PIK3CA WT: 7.4 vs. 5.6 mo** **PIK3CAm: 11 vs 5 mo**	**ITT 7.2 vs. 3.6 mo** **altered: 7.3 vs. 3.1**
HR (95%CI)	0.36 (0.27-0.47)	0.65 (0.5-0.85)	Altered 0.50 (0.38-0.65)
US FDA Approval	2012	2019 for patients with PIK3CA altered MBC HR+	2023 for patients with AKT, PTEN, PIK3CA altered HR+ breast cancer

Baselga J el ta, NEJM 2012; Andre F et al NEJM 2029; Turner N et al, NEJM 2023.

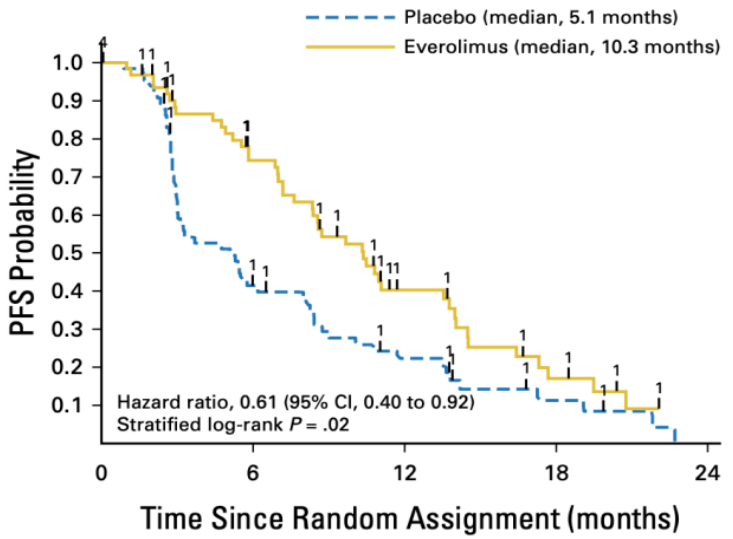
EVEROLIMUS

BOLERO 2: Progression-free survival



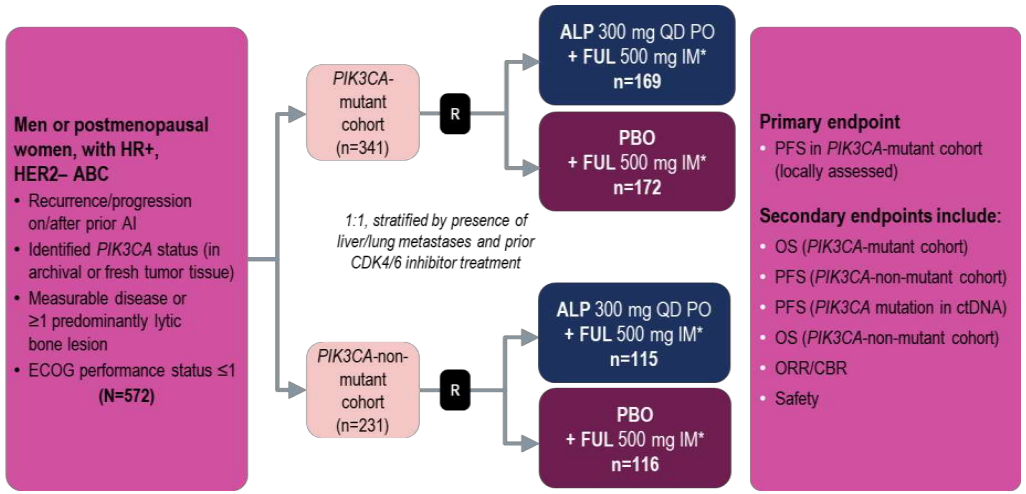
Baselga et al N Engl J Med 2012

PrE0102 fulvestrant ± everolimus: progression-free survival

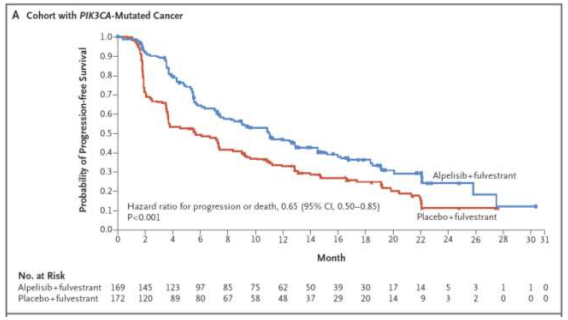


Kornblum et al J Clin Oncol 2018

SOLAR-1:



ALPELISIB



Data cut-off: Jun 12, 2018	Alpelisib + fulvestrant (N=169)	Placebo + fulvestrant (N=172)
Number of PFS events, n (%)	103 (60.9)	129 (75.0)
Median PFS (95% CI)	11.0 (7.5–14.5)	5.7 (3.7–7.4)
HR (95% CI)	0.65 (0.50–0.85)	
p-value	0.00065	

Treatment with alpelisib–fulvestrant prolonged progression-free survival among patients with *PIK3CA*-mutated, HR-positive, HER2-negative advanced breast cancer who had received endocrine therapy previously

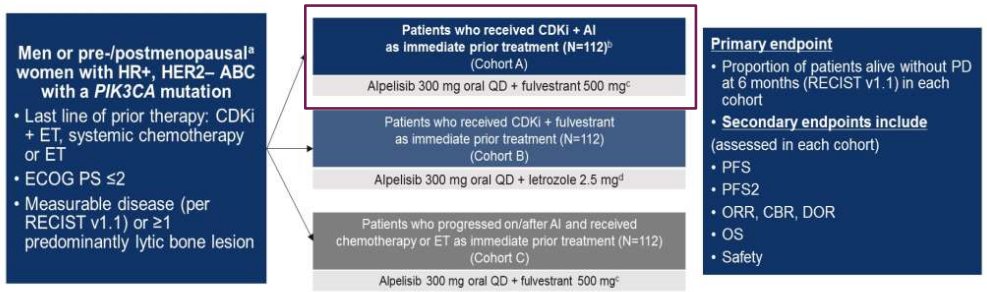
Andrè et al, NEJM 2019

Only a small number of patients (n=20) with HR+, HER2–, PIK3CA-mutated ABC had prior CDK4/6i + AI therapy because the SOLAR-1 enrollment period did not fully overlap with CDK4/6i approvals

BYLieve: A Phase 2, Open-Label, 3-Cohort, Noncomparative Trial (NCT03056755)

BYLieve

Goal: In the post-CDKi setting, assess the efficacy and safety of alpelisib + ET (fulvestrant or letrozole) in patients with *PIK3CA*-mutated HR+, HER2– ABC



Endpoint	Prior CDKi + AI (Cohort A) (n=121)
Primary endpoint: Patients who were alive without disease progression at 6 mo	**50.4%** (n=61; 95% CI, 41.2-59.6)
Secondary endpoint: Median PFS	**7.3 mo** [n=72 (59.5%) with event]; 95% CI, 5.6-8.3)

- In SOLAR-1, 44.4% of patients in the *PIK3CA*-mutant cohort with prior CDKi treated with alpelisib plus fulvestrant were alive without disease progression at 6 months

The primary endpoint for the prior CDKi + AI cohort was met (lower bound of 95% CI was > 30%), with 50.4% of patients alive without disease progression at 6 months

Capitello-291

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

Patients with HR+/HER2– ABC

- Men and pre-/post-menopausal women
- Recurrence while on or <12 months from end of adjuvant AI, or progression while on prior AI for ABC
- ≤2 lines of prior endocrine therapy for ABC
- ≤1 line of chemotherapy for ABC
- Prior CDK4/6 inhibitors allowed (at least 51% required)
- No prior SERD, mTOR inhibitor, PI3K inhibitor, or AKT inhibitor
- HbA1c <8.0% (63.9 mmol/mol) and diabetes not requiring insulin allowed
- FFPE tumor sample from the primary/recurrent cancer available for retrospective central molecular testing

R1:1 (N=708)

Capivasertib	400 mg twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks
Placebo	Twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks

Stratification factors:
- Liver metastases (yes/no)
- Prior CDK4/6 inhibitor (yes/no)
- Region*

Dual primary endpoints

PFS by investigator assessment
- Overall
- AKT pathway-altered tumors (≥1 qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration)

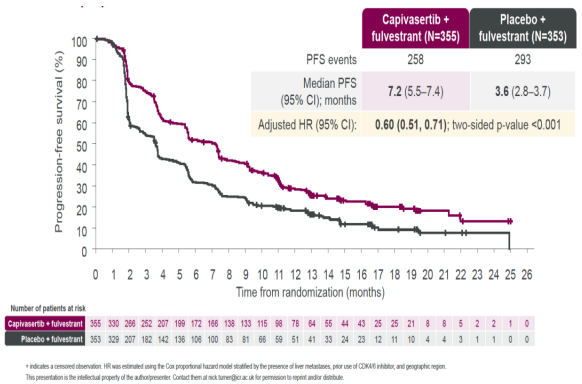
Key secondary endpoints

Overall survival
- Overall
- AKT pathway-altered tumors

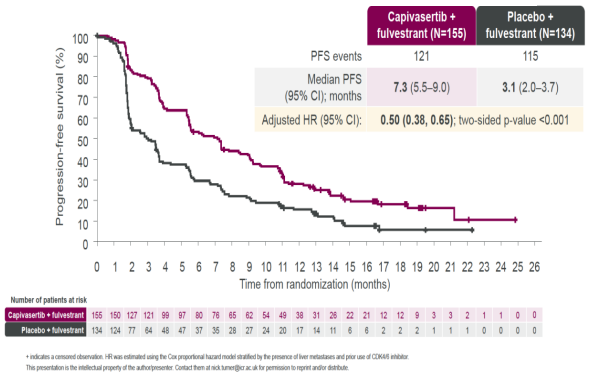
Objective response rate
- Overall
- AKT pathway-altered tumors

Dual-primary endpoint

PFS in overall population



PFS in altered population



CAPIVASERTIB

FDA approves capivasertib with fulvestrant for breast cancer

On November 16, 2023, the Food and Drug Administration approved capivasertib (Truqap, AstraZeneca Pharmaceuticals) with fulvestrant for adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations, as detected by an FDA-approved test, following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.

Content current as of:
11/16/2023

SERD : DEGRADADORES SELECTIVOS DEL RECEPTOR DE ESTRÓGENO

Oral SERD combinations in pretreated HR-positive metastatic breast cancer

	Elacestrant	Giredestrant	Camizestrant	Imlunestrant
Combination with CDK 4/6 Inhibitors	Elevate[1] Electra[2]		Serena-01[5] Serena-06	Ember-01[6]
Combination with PI3K/Akt/ mTOR Inhibitors	Elevate[1]	Morpheus[3] evERA[4]	Serena-01[5]	Ember-01[7]

1 = phase 1b/II SERD + other targeted agents, 2 = phase 1b with abemaciclib in patients with brain mets, 3 = phase Ib/II SERD + targeted agent, 4 = SERD +everolimus, 5 = SERD + targeted agents, 6 = SERD + abemaciclib, 7 = SERD + everolimus or alpelisib

EMERALD: Study Design

Multicenter, Phase III, Randomized, Open-Label Study (NCT03778931)

Objective: To analyse the efficacy and safety of administering elacestrant (once daily) as monotherapy versus fulvestrant or an AI (the current options for SOC) in patients with ER+, HER2- advanced or metastatic breast cancer post at least 1 line of ET (including a CDK4/6i in combination with fulvestrant or an AI)

Inclusion criteria:
- Postmenopausal women/men with ER+(>1%), HER2-neg MBC
- Disease progression or relapse upon/after 1 or 2 lines of ET for advanced disease (one in combination with CDK4/6i)
- ECOG PS 0 or 1
- Administered ≤1 line of chemotherapy for advanced disease

N=478
Randomization (1:1[b])

Stratified by:
Mutation status (*ESR1*)[c],
Presence of visceral metastases, and
Prior treatment with fulvestrant

- Elacestrant Daily, 400 mg[d]
- Investigator's choice for SOC: Fulvestrant / Anastrozole / Letrozole / Exemestane

EOT per investigator's decision based on disease progression or clinically significant AE[e]

Progressive disease/withdrawal criteria[f]

Primary endpoints:
- Progression-free survival (per BICR)
  - All patients
  - Patients with *ESR1* mutations

ELACESTRANT

FDA approves elacestrant for ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer

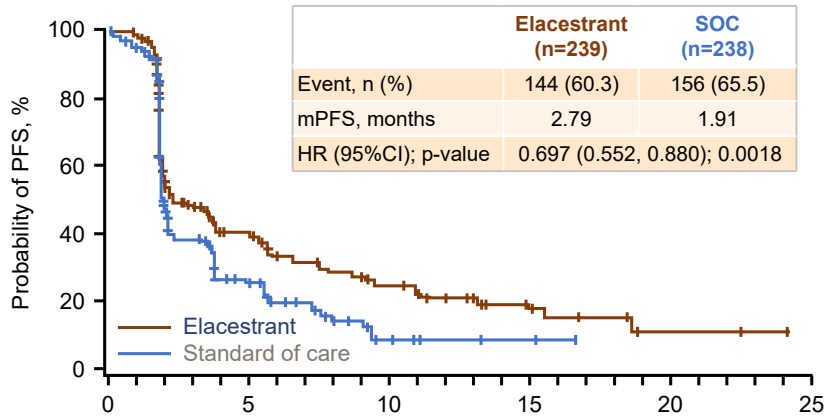
On January 27, 2023, the Food and Drug Administration (FDA) approved elacestrant (Orserdu, Stemline Therapeutics, Inc.) for postmenopausal women or adult men with ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.

FDA also approved the Guardant360 CDx assay as a companion diagnostic device to identify patients with breast cancer for treatment with elacestrant.

Content current as of: 01/27/2023

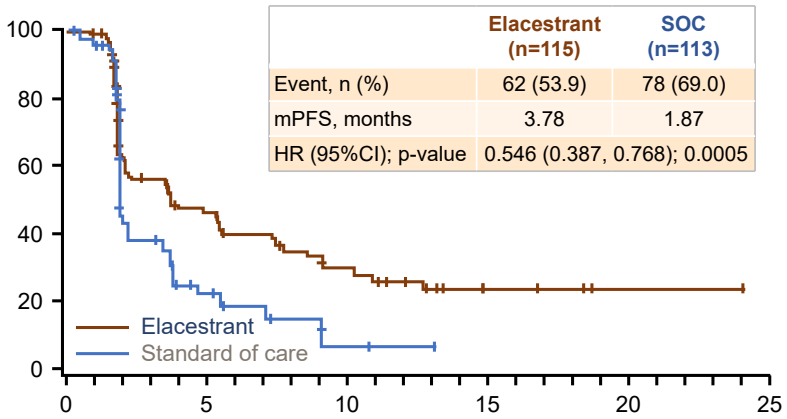
EMERALD: PFS

All patients (ITT)



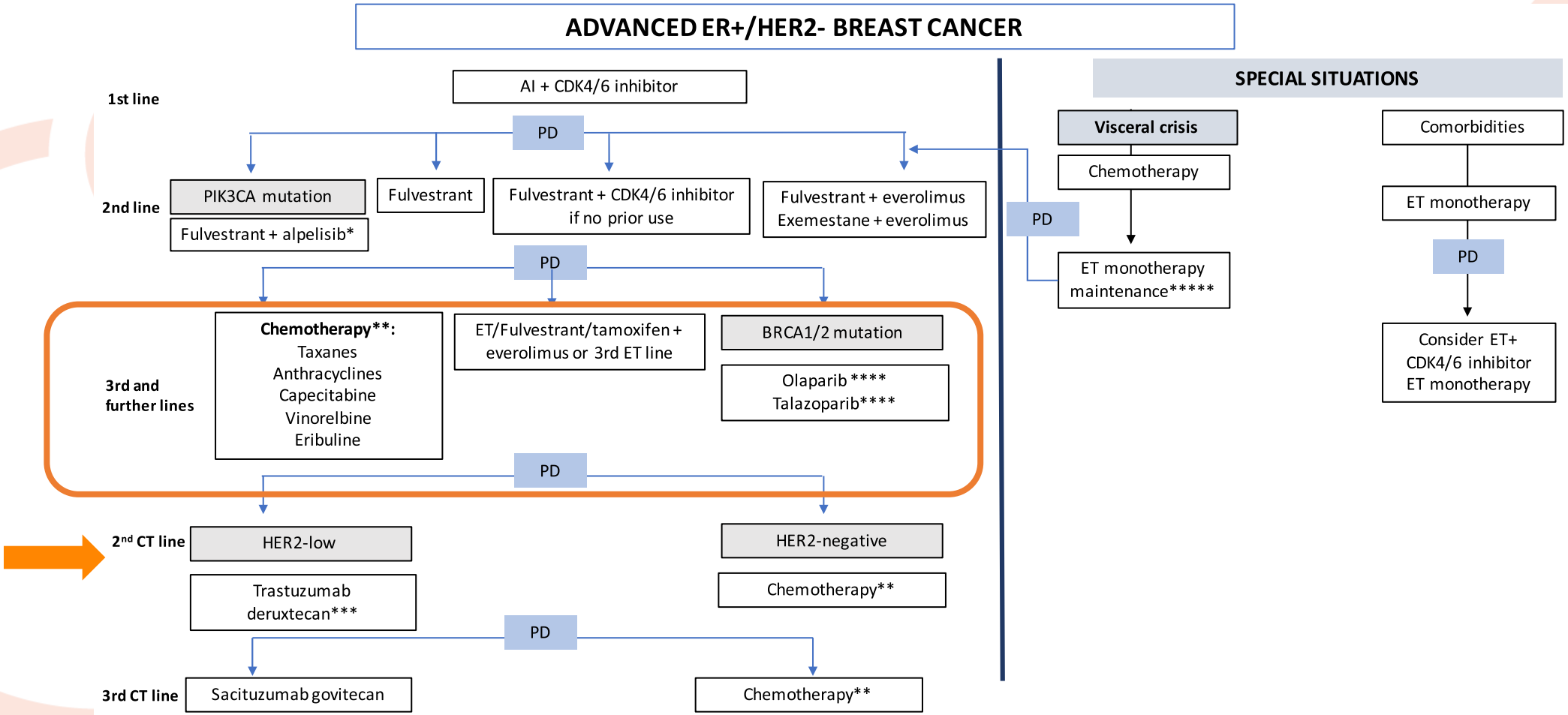
	Elacestrant (n=239)	SOC (n=238)
Event, n (%)	144 (60.3)	156 (65.5)
mPFS, months	2.79	1.91
HR (95%CI); p-value	0.697 (0.552, 0.880); 0.0018	

Patients with tumours harbouring *mESR1*



	Elacestrant (n=115)	SOC (n=113)
Event, n (%)	62 (53.9)	78 (69.0)
mPFS, months	3.78	1.87
HR (95%CI); p-value	0.546 (0.387, 0.768); 0.0005	

CÁNCER DE MAMA LUMINAL METASTÁSICA:



* Currently approved for patients progressing on endocrine monotherapy
** The preferred sequence of chemotherapies is currently unknown, Previous treatments, comorbidities and patient preferences should be taken into account.
*** Still awaiting approval by the EMA and subsequent financial approval from the health authorities in Spain
**** Approved by the EMA but without financial approval from the health authorities in Spain
***** Consider ET + iCDK4/6

CÁNCER DE MAMA LUMINAL METASTÁSICA: TERCERA Y SUCESIVAS LINEA

DIFERENTES OPCIONES :

- QUIMIOTERAPIA
- HORMONOTERAPIA (La que no hemos usado previamente)
- * SI BRCA1/2 mut: OLAPARIB/ TALAZOPARIB (NO APROBADO EN ESPAÑA)

TRAS UNA PRIMERA LINEA DE QT PARA LA ENFERMEDAD AVANZADA EN CMM HER2LOW

TRASTUZUMABDERUXTECAN

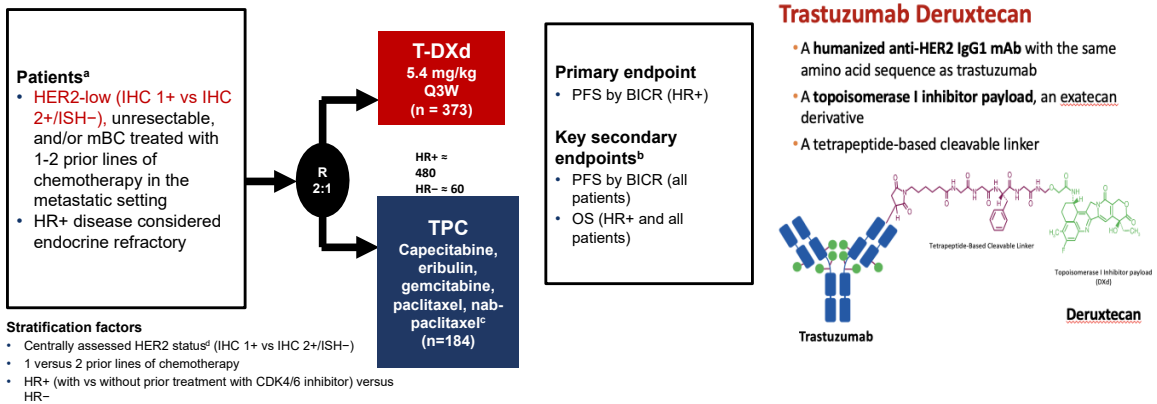
TRAS DOS LINEAS DE QT: SACITUZUMABGOVITECAN

Guideline recommendations of T-DXd in patients with HER2-low mBC

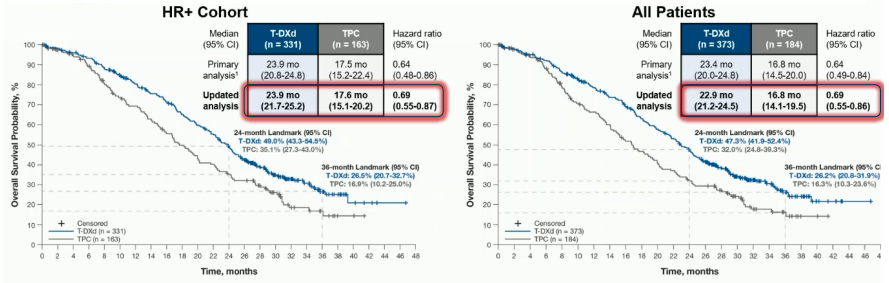
ESMO Guidelines	NCCN Guidelines
The ESMO metastatic breast cancer living guideline for ER-positive HER2-negative breast cancer recommends considering T-DXd for patients with HER2-low mBC after at least 1 line of chemotherapy	The NCCN Guidelines for breast cancer recommend fam-trastuzumab deruxtecan-nxki (T-DXd) as a second line, NCCN Category 1, preferred regimen for HER2 IHC 1+ or 2+/ISH negative (HR+ with visceral crisis or endocrine refractory or HR-negative with no germline *BRCA1/2* mutation) recurrent unresectable (local or regional) or metastatic breast cancer

- **Based on the strength of the DESTINY-Breast04 trial efficacy and safety data reported at ASCO 2022, the NCCN Guidelines for breast cancer were updated to recommend fam-trastuzumab deruxtecan-nxki as a Category 1 preferred second line treatment option for HER2 IHC 1+ or 2+/ISH− mBC**
- **Based on the primary results from DESTINY-Breast04,[3] the ESMO metastatic breast cancer living guideline recommends considering T-DXd for patients with HER2-low mBC after at least 1 line of chemotherapy**
- **Based on the primary results from DESTINY-Breast04, T-DXd was approved for patients with HER2-IHC 1+ or 2+/ISH− unresectable and/or metastatic breast cancer[3,4]**

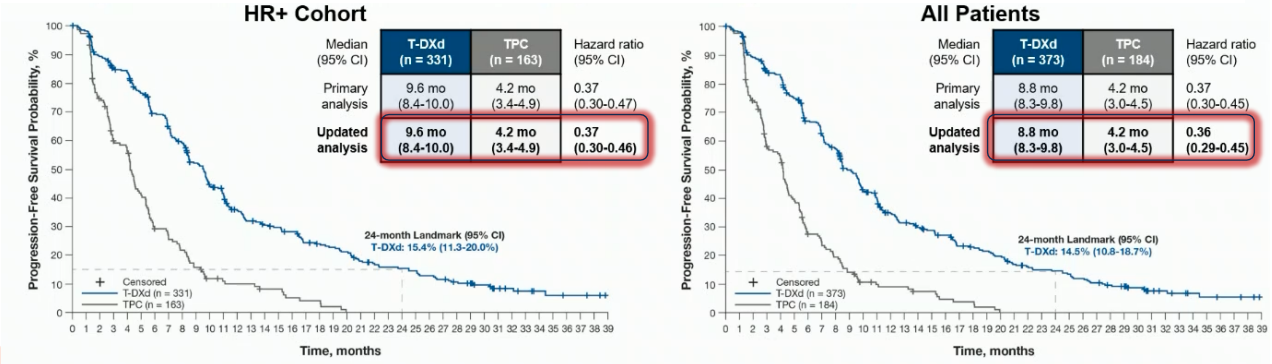
DESTINY-Breast 04



Updated OS (median 32 months) by investigator



Updated PFS (median 32 months) by investigator



Modi S, el at. NEJM 2022

Outcomes from the longer follow-up of DESTINY-Breast04 continue to support the use of T-DXd as the new standard of care after 1L+ chemotherapy in patients with HER2-low mBC²

DESTINY-Breast 04

Patients[a]
- HER2-low (IHC 1+ vs IHC 2+/ISH−), unresectable, and/or mBC treated with 1-2 prior lines of chemotherapy in the metastatic setting
- HR+ disease considered endocrine refractory

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 373)

HR+ ≈ 480
HR− ≈ 60

TPC
Capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel[c]
(n=184)

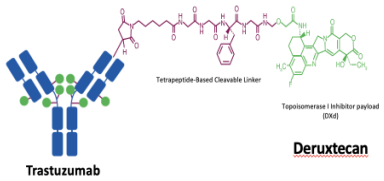
Primary endpoint
- PFS by BICR (HR+)

Key secondary endpoints[b]
- PFS by BICR (all patients)
- OS (HR+ and all patients)

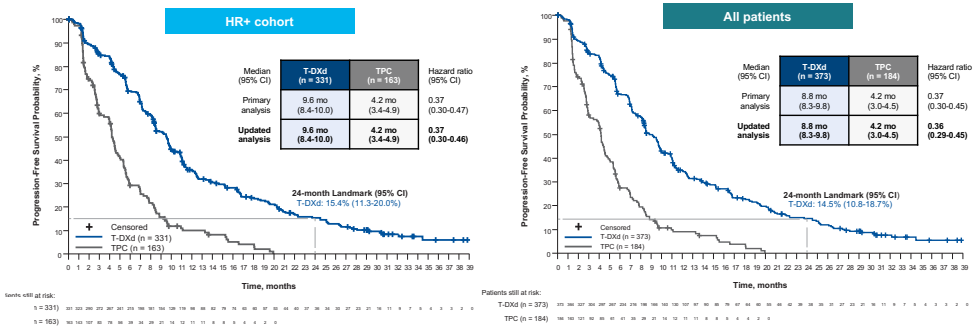
Stratification factors
- Centrally assessed HER2 status[d] (IHC 1+ vs IHC 2+/ISH−)
- 1 versus 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR−

Trastuzumab Deruxtecan

- A **humanized anti-HER2 IgG1 mAb** with the same amino acid sequence as trastuzumab
- A **topoisomerase I inhibitor payload**, an exatecan derivative
- A tetrapeptide-based cleavable linker

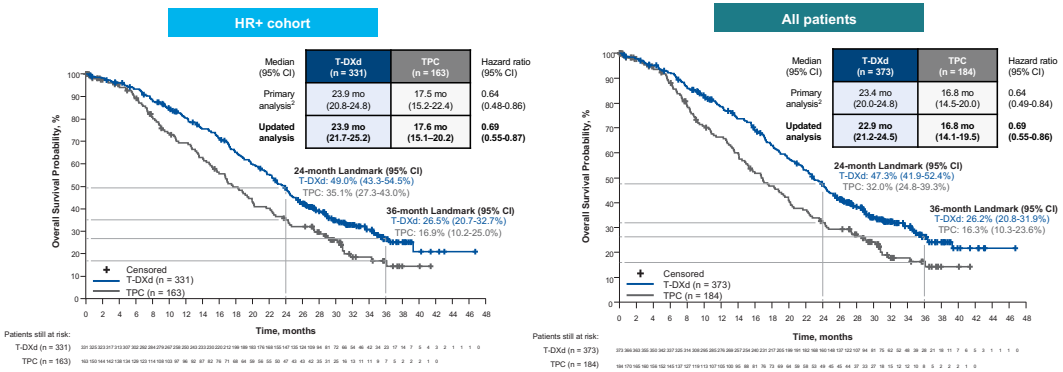


PFS (by investigator) in HR+ all patients



Median PFS was consistent with results from the primary analysis,[2] showing a reduction in risk of disease progression or death of 63% and 64% in the HR+ cohort and all patients, respectively for the T-DXd arm compared with the TPC arm

OS in HR+ and all patients (March 2023)



Outcomes from the longer follow-up of DESTINY-Breast04 continue to support the use of T-DXd as the new standard of care after 1L+ chemotherapy in patients with HER2-low mBC²

TROPiCS-02: A Phase 3 Study of SG in HR+/HER2- Locally Recurrent Inoperable or Metastatic Breast Cancer

NCT03901339

Metastatic or locally recurrent inoperable HR+/HER2− breast cancer that progressed after[a]:

- At least 1 endocrine therapy, taxane, and CDK4/6i in any setting
- At least 2, but no more than 4, lines of chemotherapy for metastatic disease
  - (Neo)adjuvant therapy for early-stage disease qualified as a prior line of chemotherapy if disease recurred within 12 months
- Measurable disease by RECIST 1.1

N=543

R 1:1

Treatment was continued until progression or unacceptable toxicity

- **Sacituzumab govitecan** 10 mg/kg IV days 1 and 8, every 21 days n=272
- **Treatment of physician's choice[b]** (capecitabine, vinorelbine, gemcitabine or eribulin) n=271

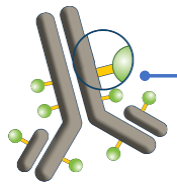
Endpoints

Primary
- PFS by BICR

Secondary
- OS
- ORR, DOR, CBR by LIR and BICR
- PRO
- Safety

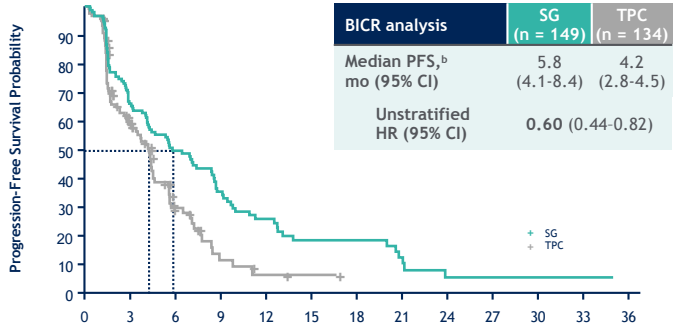
Stratification:
- Visceral metastases (yes/no)
- Endocrine therapy in metastatic setting ≥6 months (yes/no)
- Prior lines of chemotherapies (2 vs 3/4)

SN-38 payload (Topo1 inhibitor) more potent than parent compound, irinotecan



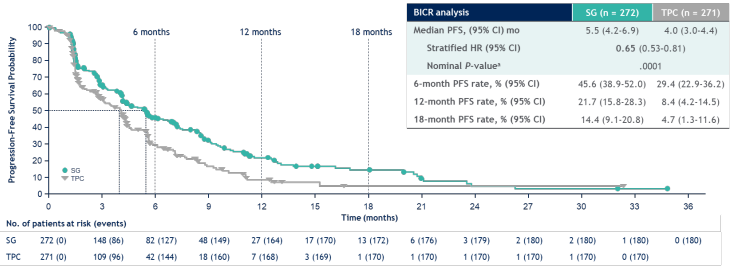
Humanized anti-Trop-2 Ab
- Targets Trop-2, an epithelial antigen expressed on many solid cancers, including mTNBC

HER2-low (IHC1+, IHC2+/ISH-)[a]



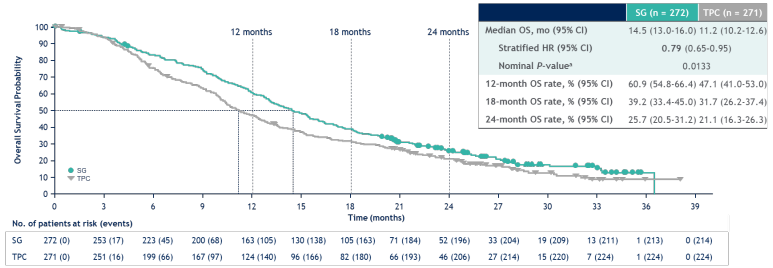
BICR analysis	SG (n = 149)	TPC (n = 134)
Median PFS,[b] mo (95% CI)	5.8 (4.1-8.4)	4.2 (2.8-4.5)
Unstratified HR (95% CI)	0.60 (0.44-0.82)	

Progression-Free Survival



BICR analysis	SG (n = 272)	TPC (n = 271)
Median PFS, (95% CI) mo	5.5 (4.2-6.9)	4.0 (3.0-4.4)
Stratified HR (95% CI)	0.65 (0.53-0.81)	
Nominal *P*-value[a]	.0001	
6-month PFS rate, % (95% CI)	45.6 (38.9-52.0)	29.4 (22.9-36.2)
12-month PFS rate, % (95% CI)	21.7 (15.8-28.3)	8.4 (4.2-14.5)
18-month PFS rate, % (95% CI)	14.4 (9.1-20.8)	4.7 (1.3-11.6)

Overall Survival

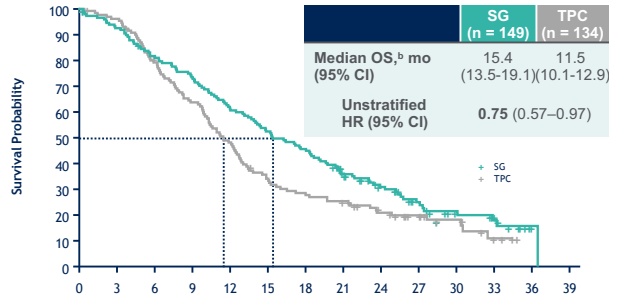


	SG (n = 272)	TPC (n = 271)
Median OS, mo (95% CI)	14.5 (13.0-16.0)	11.2 (10.2-12.6)
Stratified HR (95% CI)	0.79 (0.65-0.95)	
Nominal *P*-value[a]	0.0133	
12-month OS rate, % (95% CI)	60.9 (54.8-66.4)	47.1 (41.0-53.0)
18-month OS rate, % (95% CI)	39.2 (33.4-45.0)	31.7 (26.2-37.4)
24-month OS rate, % (95% CI)	25.7 (20.5-31.2)	21.1 (16.3-26.3)

SG continued to demonstrate improvement in PFS vs TPC at longer follow-up, with 35% reduction in risk of disease progression or death, and a higher proportion of patients remained alive and progression-free at each landmark

SG continued to demonstrate improvement in OS vs TPC at longer follow-up, with 21% reduction in risk of death and a higher proportion of patients remaining alive at each landmark

HER2-low (IHC1+, IHC2+/ISH-)[a]



	SG (n = 149)	TPC (n = 134)
Median OS,[b] mo (95% CI)	15.4 (13.5-19.1)	11.5 (10.1-12.9)
Unstratified HR (95% CI)	0.75 (0.57–0.97)	

1. Tolaney S, et al. Final overall survival (OS) analysis from the phase 3 TROPiCS-02 study of sacituzumab govitecan (SG) in patients (pts) with hormone receptor-positive/HER2-negative (HR+/HER2-) metastatic breast cancer (mBC). Presented at ASCO 2023 Abstract #1003.

Selected studies assessing the role of ADC in of HR+ MBC

	Datopotumab-DXd TROPION-Breast01	Sacituzumab govitecan TROPiCS-02	T-DXd DESTINY Breast-04
Target	**Trop2**	**Trop2**	**HER2**
Payload	**Topo1 inhibitor**	**Topo1 inhibitor (SN38)**	**Topo1 inhibitor**
Linker	Tumor selective, cleavable	Tumor selective, cleavable	Tumor selective, cleavable
Drug:Ab Ratio	4:1	8:1	7-8:1
Bystander effect	Yes	Yes	Yes
Study population	MBC HR+/HER2-, 1-2 prior lines of chemotherapy	MBC HR+/HER2-, ET+CDK4/6 → 2-4 prior lines of chemotherapy	MBC HER2-low with 1-2 prior lines of therapy in the metastatic setting
Sample size	732 (1:1 randomization)	543 (1:1 randomization)	557 (2:1) ~90% HR+
PFS	**6.9 vs 4.5 months (HR 0.64, p<0.001)**	**5.5 vs 4 months (HR=0.65, <0.001)**	**9.6 vs. 4.2 months (HR=0.37, in HR+ group)**
OS	Not mature	15.5 vs. 11.2 m. (HR=0.79, p.013)	23.9 vs 17.6 m. (HR=0.69, in HR+ group)
Follow up	9.7 months	13 months	32 months
Notes	ORR 36 vs 22%. Stomatitis 50%, dry eye 22%, ILD 3%		Nausea/vomiting, ILD
U.S. FDA approval	No	2/2023 → at least 2 prior lines of chemotherapy MBC	8/2022 → at least 1 prior line of chemotherapy MBC

DAR: drug to antibody ratio; DXd: deruxtecan; HER2: human epidermal growth factor receptor 2; HR: hazard ratio, HR+: hormone receptor positive, ILD: interstitial lung disease; ORR: overall response rate; OS: overall survival; PFS: progression free survival; U.S. FDA: United States Food and Drug Administration

TROPION-Breast01 Study Design

Randomized, phase 3, open-label, global study (NCT05104866)

Key inclusion criteria:

- Patients with HR+/HER2– breast cancer* (HER2– defined as IHC 0/1+/2+; ISH negative)
- Previously treated with 1–2 lines of chemotherapy (inoperable/metastatic setting)
- Experienced progression on ET and for whom ET was unsuitable
- ECOG PS 0 or 1

1:1

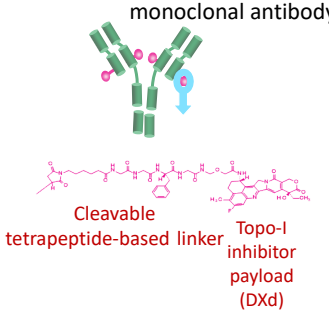
Dato-DXd
6 mg/kg IV Day 1 Q3W
(n=365)

Investigator's choice of chemotherapy (ICC)
as per protocol directions† (eribulin mesylate D1,8 Q3W; vinorelbine D1,8 Q3W; gemcitabine D1,8 Q3W; capecitabine D1–14 Q3W)
(n=367)

Endpoints:

- **Dual primary:** PFS by BICR per RECIST v1.1, and OS
- **Secondary endpoints included:** ORR, PFS (investigator assessed), TFST, safety, PROs

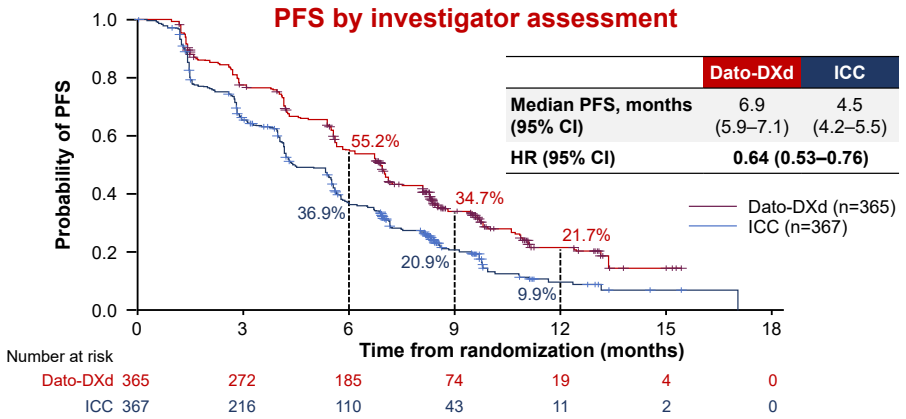
Dato-DXd: Humanized anti-TROP2 IgG1 monoclonal antibody



Randomization stratified by:
- **Lines of chemotherapy** in unresectable/metastatic setting (1 vs 2)
- **Geographic location** (US/Canada/Europe vs ROW)
- **Previous CDK4/6 inhibitor** (yes vs no)

- Treatment continued until PD, unacceptable tolerability, or other discontinuation criteria

Progression-Free Survival

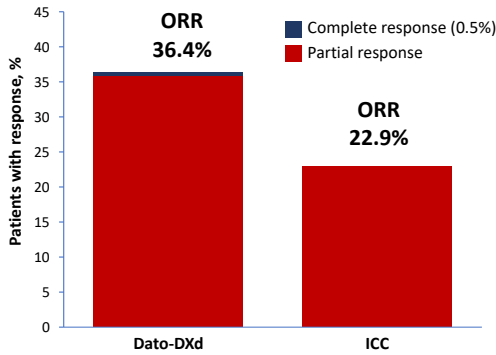


	Dato-DXd	ICC
Median PFS, months (95% CI)	6.9 (5.9–7.1)	4.5 (4.2–5.5)
HR (95% CI)	0.64 (0.53–0.76)	

PFS by BICR (primary endpoint)[1]: Median 6.9 vs 4.9 months; HR 0.63 (95% CI 0.52–0.76); P<0.0001

Response and Interim OS

Response Rate



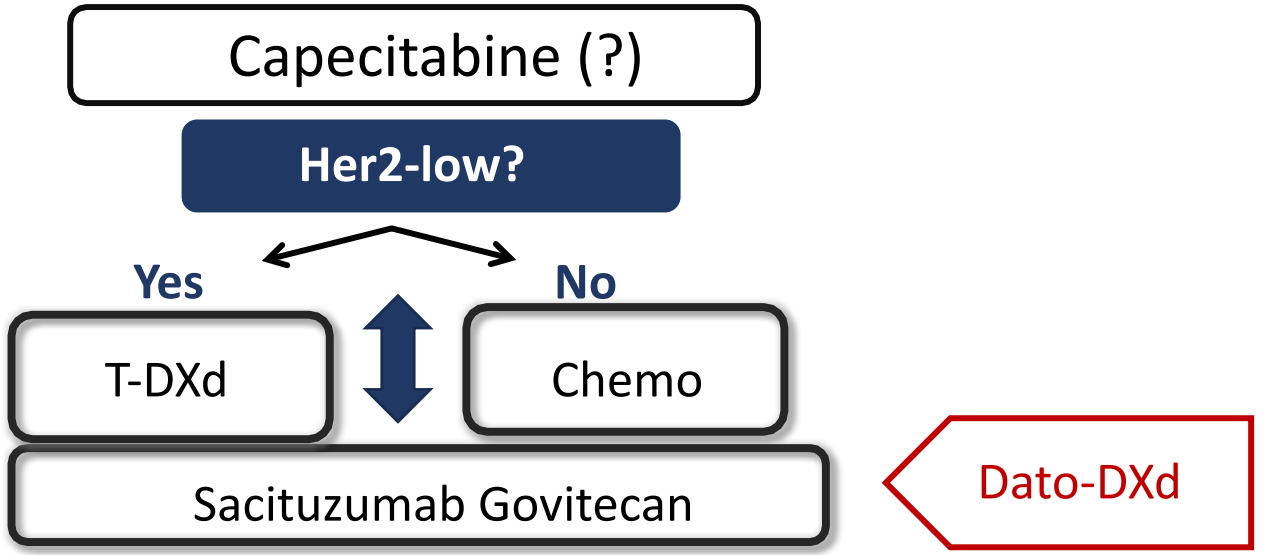
OS: Dual Primary Endpoint

- **OS data not mature**
  - – Median follow-up 9.7 months
- A trend favouring Dato-DXd was observed:
  - – HR 0.84 (95% CI 0.62–1.14)

CÁNCER DE MAMA LUMINAL METASTÁSICA: MAS ALLÁ DE LA 1º LINEA

- Somatic mutations – ESR1, PIK3CA, AKT, PTEN and Germline *BRCA*

g*BRCA*m- iPARP	*ESR1*m Elacestrant	PIK3CA Alpelisib + Fulv	PIK3CA, AKT, PTEN Capivasertib + Fulv	no alterations Exe + Everolimus



Muchas gracias
por vuestra atención

SEOM
Sociedad Española
de Oncología Médica

2L treatment options for metastatic HR+ breast cancer

PI3K, AKT, PTEN, MAPK, mTOR
- **Alpelisib + ET** (BYLieve; PFS: 8.0 months[1])
- **Everolimus + exemestane** (PFS HR, 0.43[2])
- Capivasertib + FUL (PFS HR, 0.5-0.6[3a])

Oral SERDs
- **Elacestrant** (PFS HR, 0.61-0.70[4b])
- Camizestrant (PFS HR, 0.58-0.67[5c])

Antibody-drug conjugates
- **T-DXd in HER2-low** (Destiny Breast 04; HR+ PFS HR, 0.51)[8]
- **Sacituzumab govitecan** (TROPiCS-02; PFS HR, 0.66)[9]

Strategies post CDK4/6i + ET[a]

1L | 2L ET | 3L ET

Continue on CDK4/6i:
- MAINTAIN (mostly RIB + ET after PAL + ET; PFS HR, 0.57[6])
- PACE (mostly PAL + FUL after PAL + ET; PFS HR, 1.11):[7] mostly PAL after PAL
- PADA-1 (if *ESR1*$_{mut}$, switch from PAL+AI to PAL +FUL (PFS HR, 0.61[12])
- Other approaches (eg, + PD-L1 inhibition?)

***BRCA* targeted**
- **Olaparib[d]** (OlympiAD; PFS HR, 0.58[10])
- **Talazoparib** (EMBRACA; PFS HR, 0.54[11])

Hormone refractory

1L CT | 2L CT | 3L CT | 4L CT

Other targeted tx

Approvals by ≥1 global health authority shown in pink

1L, first line; 2L, second line; 3L, third line; 4L, fourth line; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CT, chemotherapy; ET, endocrine therapy; FUL, fulvestrant; HER2, human epidermal growth factor receptor 2; PAL, palbociclib; PFS, progression-free survival; PD-L1, programmed death-ligand 1; RIB, ribociclib; SERD, selective estrogen receptor degrader, T-DXd, trastuzumab deruxtecan; tx, treatment.
[a] HRs are AKT and ITT populations, respectively. [b] HRs are ITT and ^{ESR1} mutant populations, respectively. [c] HRs.are 75mg and 150mg of camizestrant cohorts. [d] Patients with HR+ breast cancer should have been treated with prior ET or be considered inappropriate for ET.

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