
# Avances en 1° Línea de Cáncer de mama HER-2 positivo metastásico

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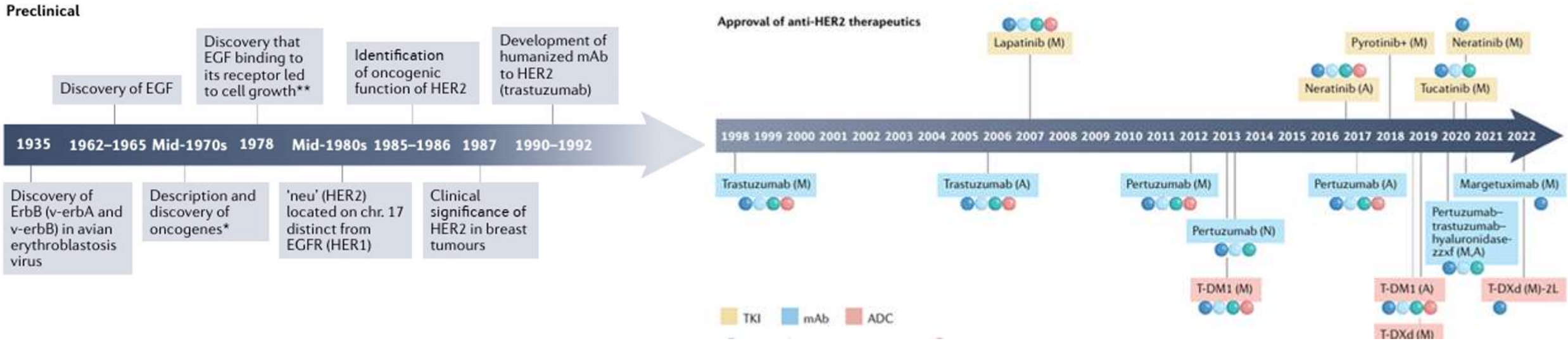
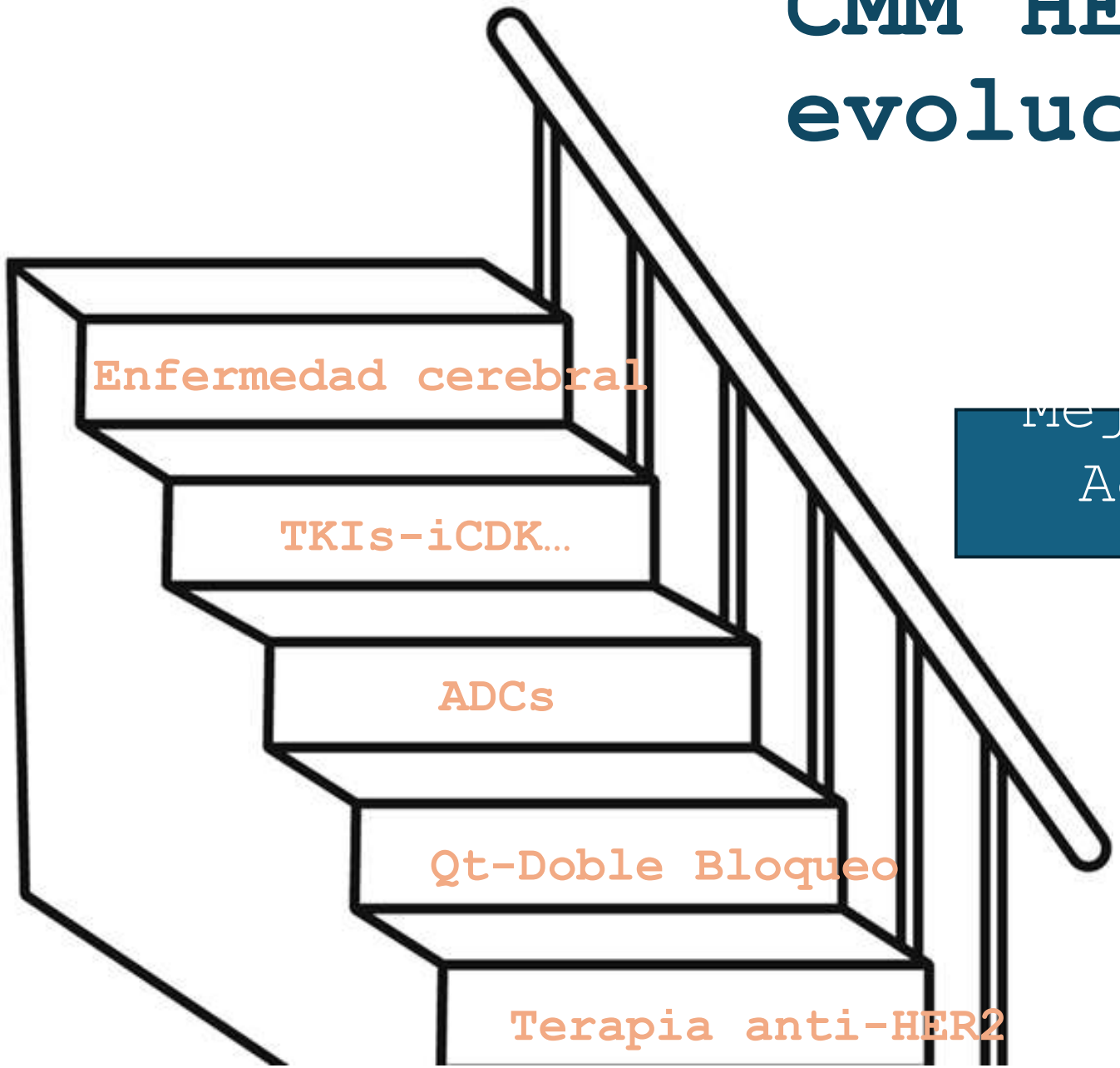

Preclinical
Discovery of EGF
Discovery that EGF binding to its receptor led to cell growth**
Identification of oncogenic function of HER2
Development of humanized mAb to HER2 (trastuzumab)
1935
1962–1965
Mid-1970s
1978
Mid-1980s
1985–1986
1987
1990–1992
Discovery of ErbB (v-erbA and v-erbB) in avian erythroblastosis virus
Description and discovery of oncogenes*
'neu' (HER2) located on chr. 17 distinct from EGFR (HER1)
Clinical significance of HER2 in breast tumours
Approval of anti-HER2 therapeutics
Lapatinib (M)
Pyrotinib+ (M)
Neratinib (M)
Neratinib (A)
Tucatinib (M)
1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022
Trastuzumab (M)
Trastuzumab (A)
Pertuzumab (M)
Pertuzumab (A)
Margetuximab (M)
Pertuzumab (N)
Pertuzumab–trastuzumab–hyaluronidase-zzxf (M,A)
T-DM1 (M)
T-DM1 (A)
T-DXd (M)-2L
T-DXd (M)
TKI
mAb
ADC

# CMM HER2 +: evolución




Mejorando supervivencia
Adelantando opciones terapéuticas

# SITUACIÓN ACTUAL CMM HER-2 POSITIVO

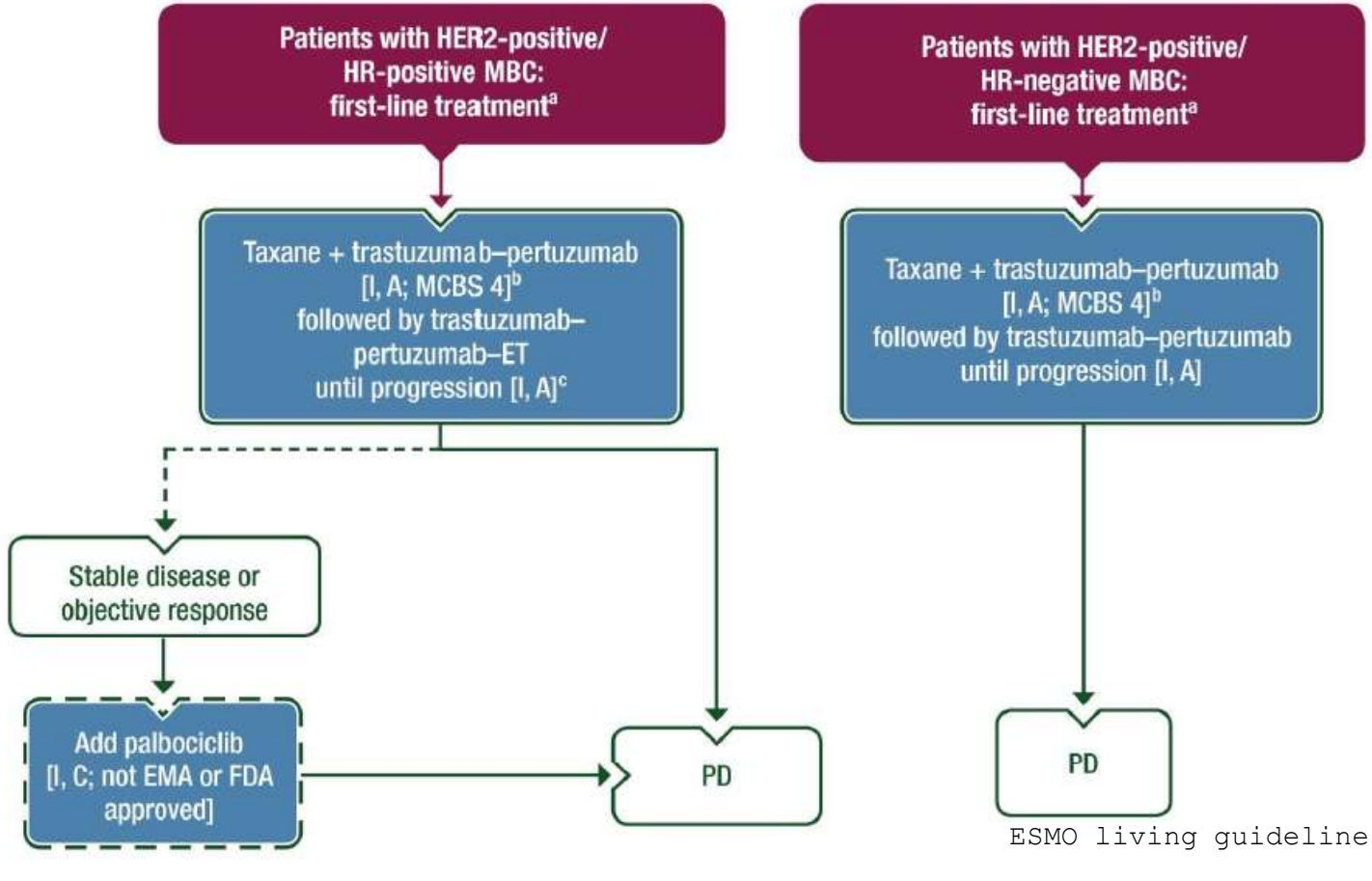
¿Podemos optimizar el mantenimiento en 1° línea?

¿Qué papel juegan los ADCs en 1° línea?

¿La curación es una opción?

¿Es adecuada una primera línea de quimiterapia + doble bloqueo?

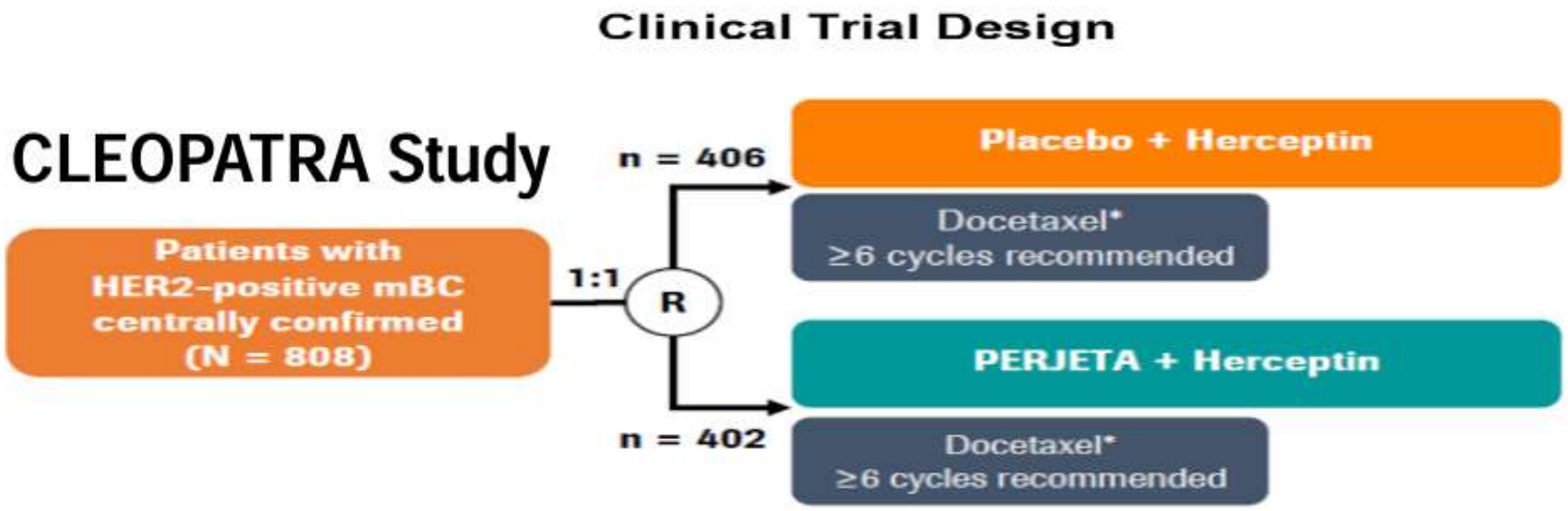
¿Debemos diferenciar entre RH+ y RH -?




ESMO living guidelines v.1.2 abril 2

# **DE ELECCIÓN** desde hace más de 10 años

¿Es adecuada una primera línea de quimiterapia + doble bloqueo?

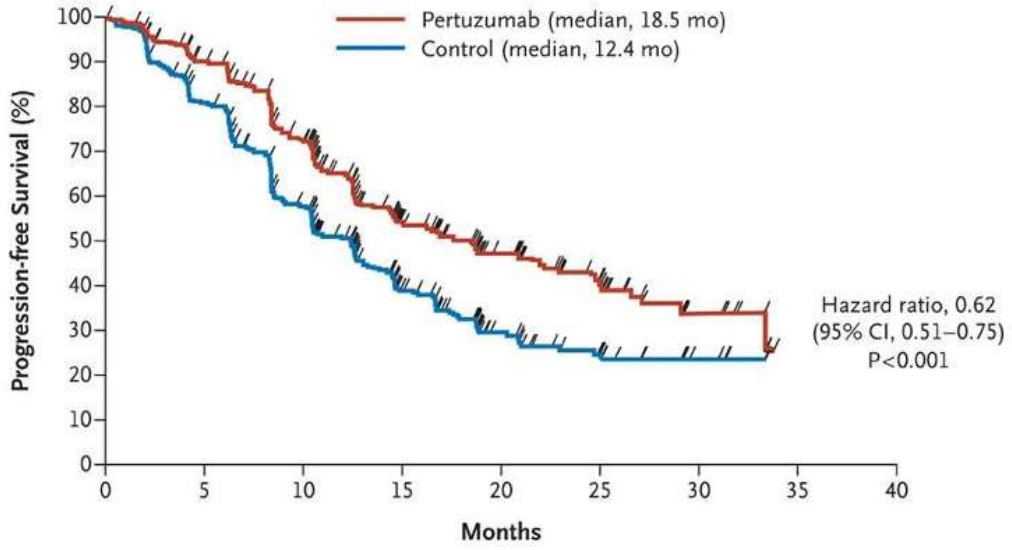



HER2 positivo
Primera línea
**Docetaxel + Trastuzumab + Pertuzumab vs Docetaxel + trastuzumab**

**Características del estudio**

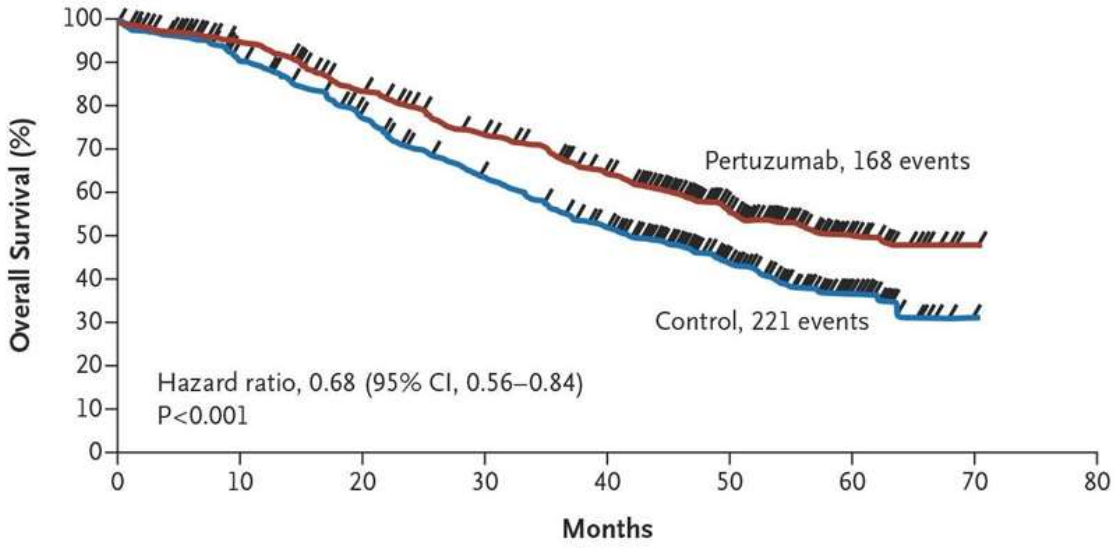
- 808 pacientes randomizados (1196 screening)
- Aleatorización 1:1
- 12 meses de intervalo entre fin de adyuvancia y recidiva

# **DE ELECCIÓN** desde hace más de 10 años: datos no vistos previamente.



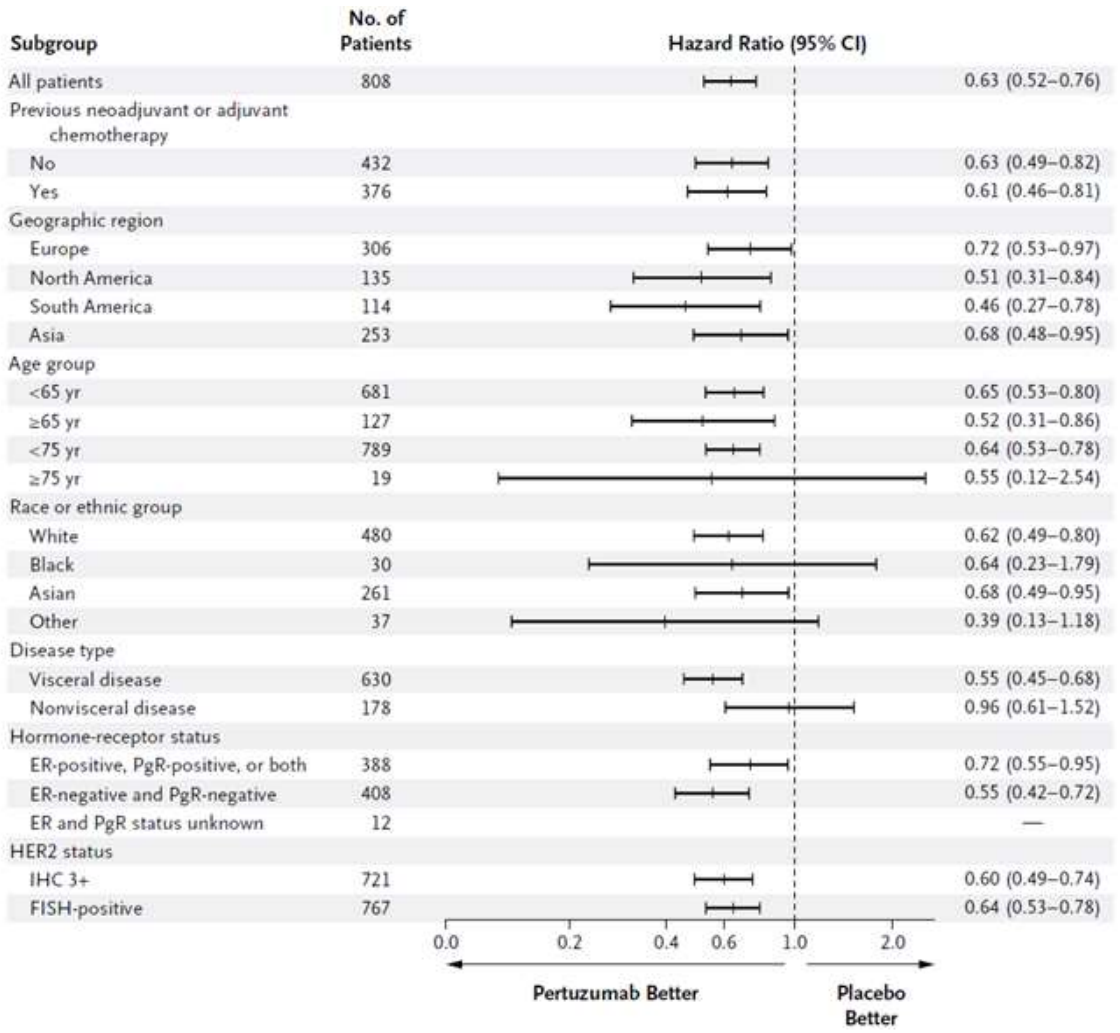

| No. at Risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Pertuzumab | 402 | 345 | 267 | 139 | 83 | 32 | 10 | 0 | 0 |
| Control | 406 | 311 | 209 | 93 | 42 | 17 | 7 | 0 | 0 |

PFS by BICR




| No. at Risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Pertuzumab | 402 | 371 | 318 | 268 | 226 | 104 | 28 | 1 | 0 |
| Control | 406 | 350 | 289 | 230 | 179 | 91 | 23 | 0 | 0 |

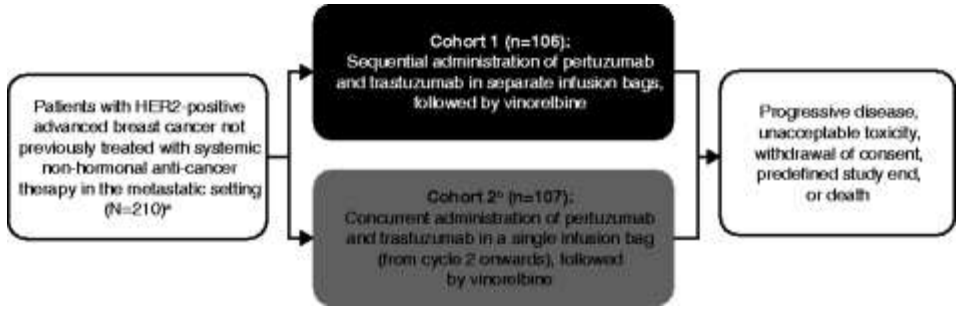
OS: 56.5 *vs.* 39.6 months



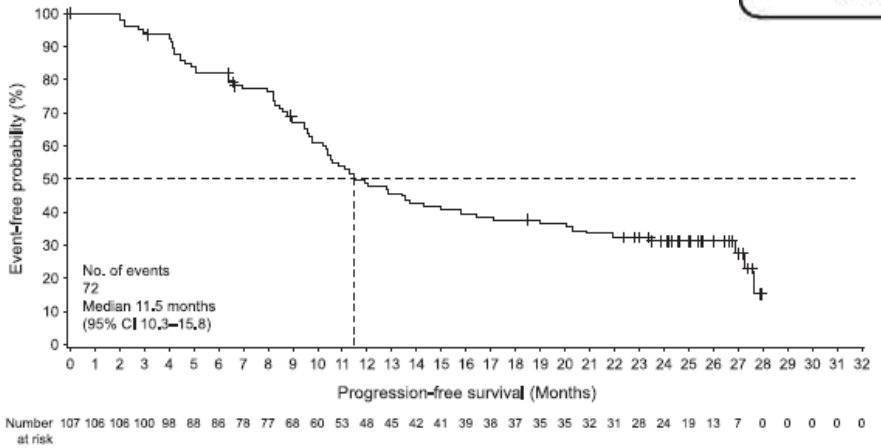

| Grade ≥ 3 Events | Placebo + Trastuzumab + Docetaxel n = 396 | Pertuzumab + Trastuzumab + Docetaxel n = 408 |
|---|---|---|
| **Neutropenia** | 46.2% | 49.0% |
| **Febrile neutropenia** | 7.6% | 13.7% |
| **Leukopenia** | 14.9% | 12.3% |
| **Diarrhea** | 5.1% | 9.3% |
| **Peripheral neuropathy** | 1.8% | 2.7% |
| **Anemia** | 3.5% | 2.5% |
| **Asthenia** | 1.8% | 2.7% |
| **Fatigue** | 3.3% | 2.2% |
| **Granulocytopenia** | 2.3% | 1.5% |
| **Left ventricular dysfunction** | 3.3% | 1.5% |
| **Dyspnea** | 2.0% | 1.0% |
| **Hypertension** | 1.8% | 2.0% |
| **Pneumonia** | 2.0% | 1.0% |

- Significativo aumento de PFS y OS no visto previamente.
- Excelente tolerancia tras finalizar inducción de quimioterapia
- Posibilidad de mantenimiento

# Vinorelbina



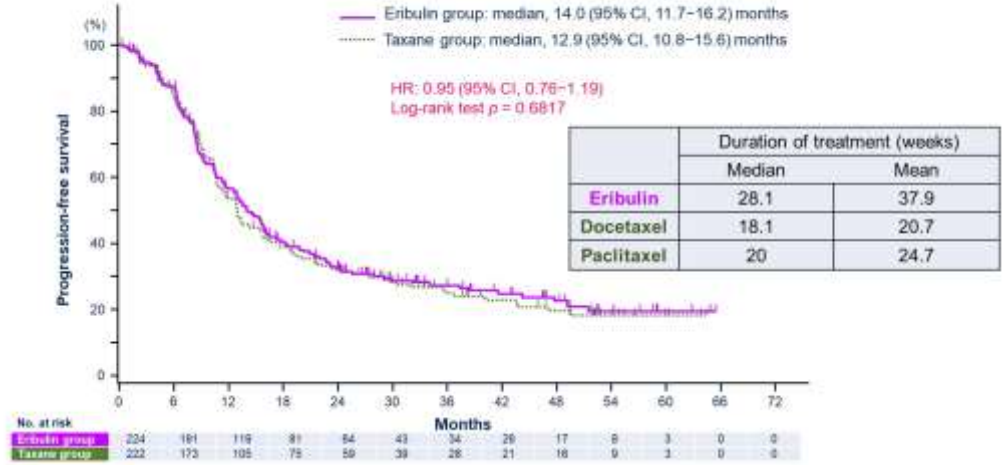

¿Es adecuada una primera línea de quimiterapia + doble bloqueo?



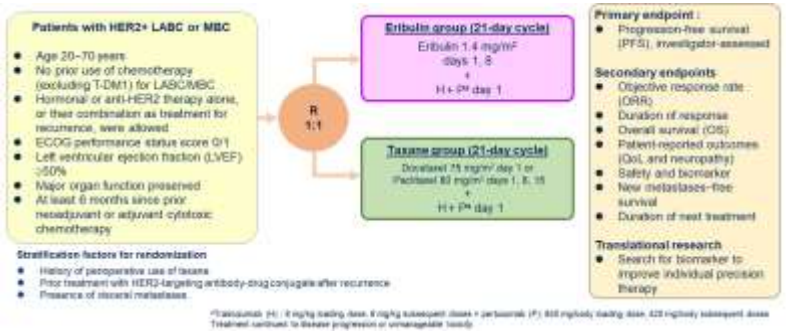

# Eribulina

Otras alternativas modestas…

## PFS (primary endpoint)




| | Duration of treatment (weeks) | |
|---|---|---|
| | Median | Mean |
| Eribulin | 28.1 | 37.9 |
| Docetaxel | 18.1 | 20.7 |
| Paclitaxel | 20 | 24.7 |



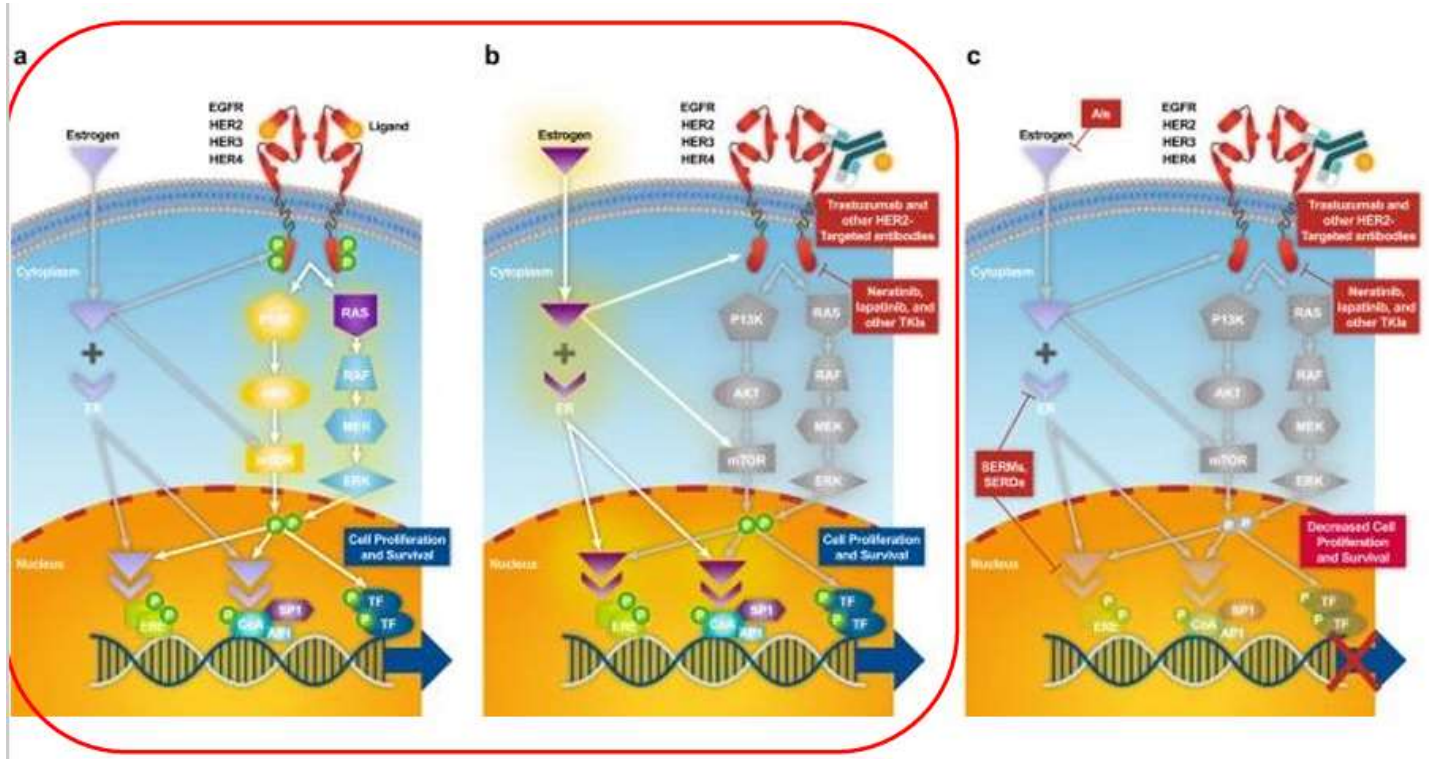

EA Perez. Breast Cancer Res. 2016. Yamashita et

# ¿Qué ocurre en RH+ HER-2 +? ¿Es posible optimizar el mantenimiento tras quimioterapia?

- La vía ER como mecanismo de escape a la inhibición de HER2.
- La señalización de HER2 regula a la baja la transcripción regulada por ER: resistencia a la terapia endocrina.
- La inhibición de HER2 da lugar a la activación de la regulación de ER: mecanismo compensatorio para el crecimiento y la supervivencia del tumor.
- Mejor inhibición del

¿Podemos optimizar el mantenimiento en 1° línea?

¿Debemos diferenciar entre RH+ y RH -?




1 Pegram M et al. npj breast cancer 2023:34.

# PERTAIN

¿Podemos optimizar el mantenimiento en 1° línea?

¿Debemos diferenciar entre RH+ y RH -?

Randomised Phase 2, AI + trastuzumab *vs*. AI + trastuzumab + pertuzumab
Induction chemotherapy allowed (docetaxel, paclitaxel), >50% of all patient
Primary endpoint: PFS

Postmenopausal patients with HER2-positive and hormone receptor-positive MBC/LABC, not previously treated with systemic nonhormonal anticancer therapy in the advanced setting (N=258)

Choice of chemotherapy must be specified before randomisation

R

**Pertuzumab + trastuzumab**
- Aromatase inhibitor
- OR
- Docetaxel or paclitaxel (18-24 weeks)† → Aromatase inhibitor

**Trastuzumab**
- Aromatase inhibitor
- OR
- Docetaxel or paclitaxel (18–24 weeks)[a] → Aromatase inhibitor

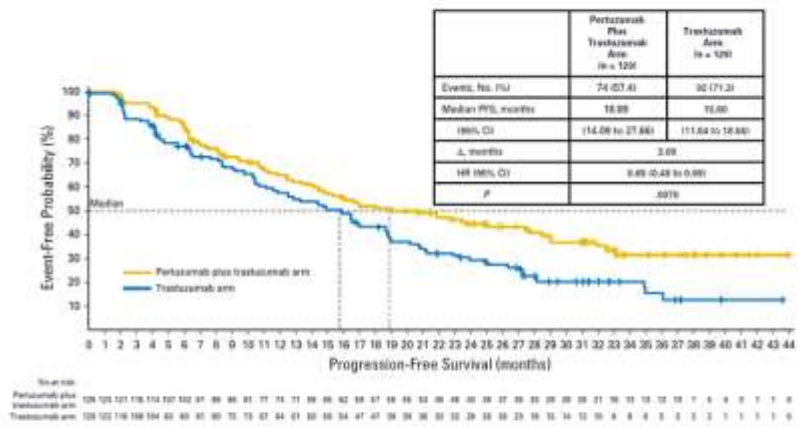
**Stratification factors**
- Chemotherapy (yes/no)
- Time since adjuvant hormone therapy (<12 months / ≥12 months / no prior therapy)

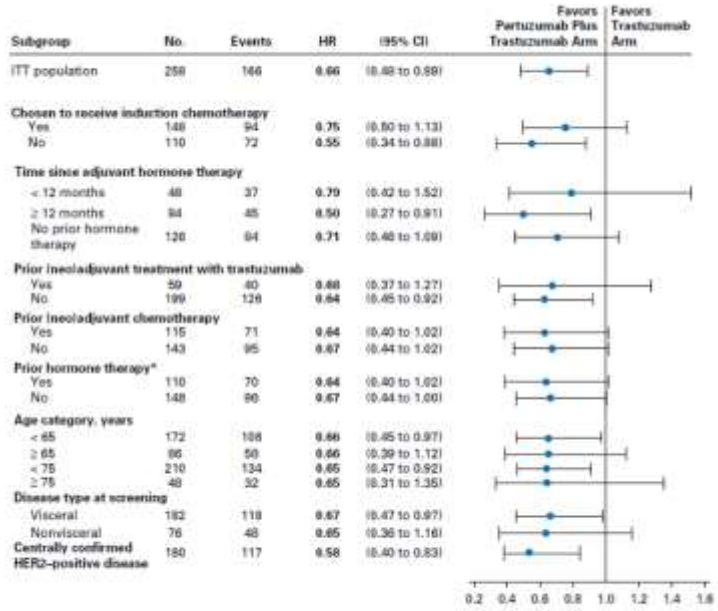
AI, aromatase inhibitor; [a]Choice of chemotherapy specified before randomization.
Rimawi M, *et al.* J Clin Oncol 2018;36:2826–35.

Beneficio de añadir IA al doble bloqueo.

Incremento de PFS 3 meses.

## Results



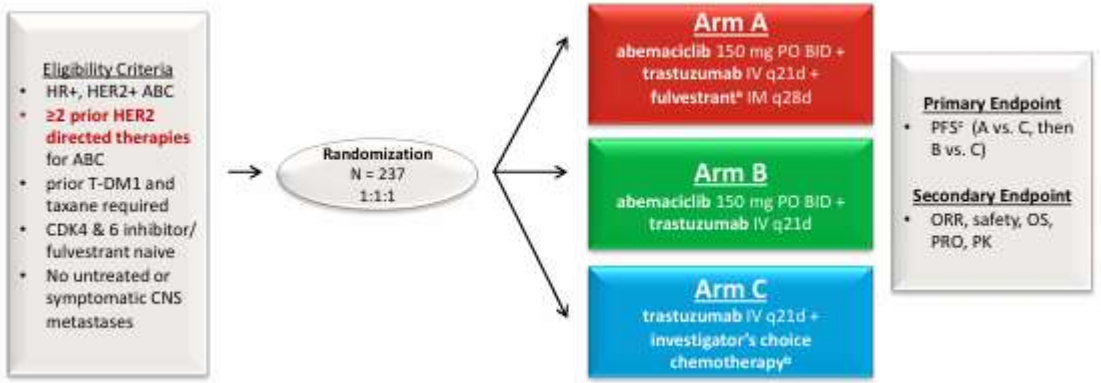



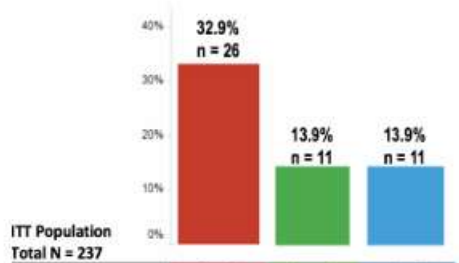

Rimawi M, *et al.* First-Line Trastuzumab Plus an Aromatase Inhibitor, With or Without Pertuzumab, in Human Epidermal Growth Factor Receptor 2-Positive and Hormone Receptor-Positive Metastatic or Locally Advanced Breast Cancer (PERTAIN): A Randomized, Open-Label Phase II Trial. J Clin Oncol 2018;36:2826–35. Available at: https://ascopubs.org/doi/full/10.1200/JCO.2017.76.7863 ; accessed Jan 2023. © 2018 American Society of Clinical Oncology.

# Monarc-HER

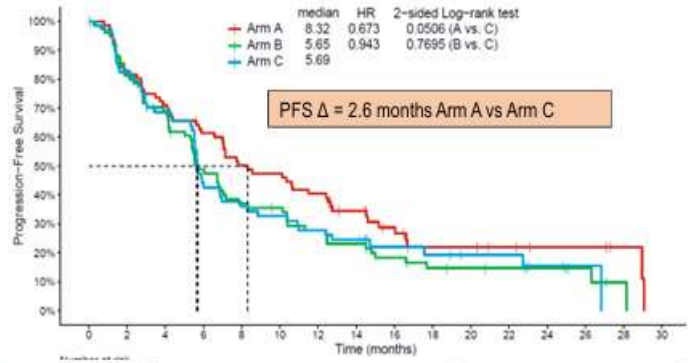
¿Podemos optimizar el mantenimiento en 1° línea?

¿Debemos diferenciar entre RH+ y RH -?



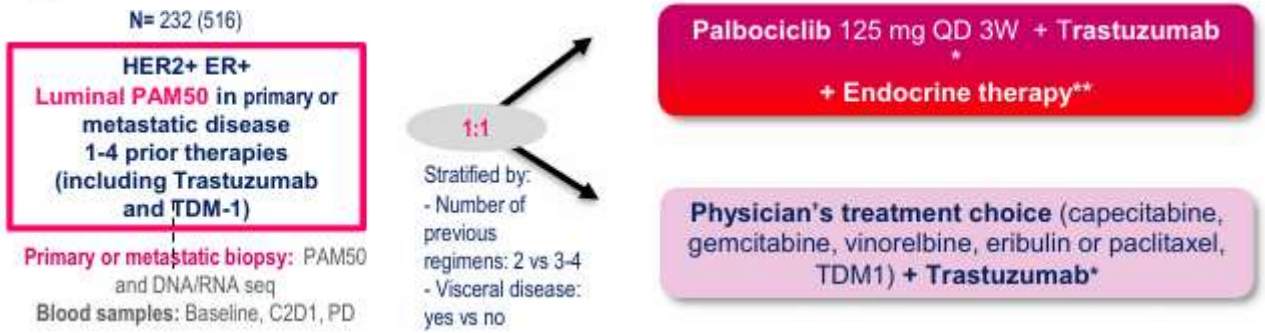




| ITT Population Total N = 237 | Arm A N=79 | Arm B N=79 | Arm C N=79 |
|---|---|---|---|
| 95% CI (%) | (22.5-43.3) | (6.3-21.6) | (6.3-21.6) |
| Stratified 2-sided p-value (vs Arm C) | 0.0042 | 1.0000 | - |
| Duration of Response, months | 12.5 | 9.5 | not reached |

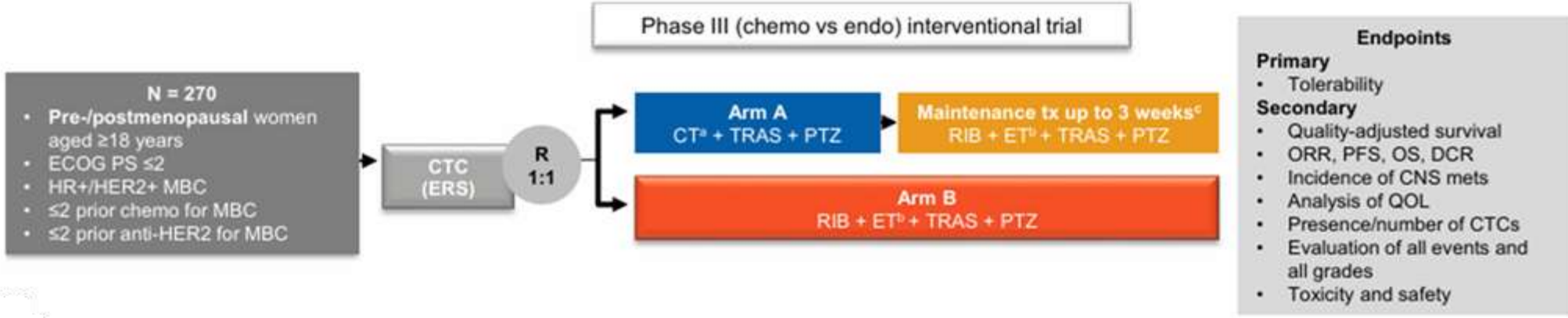



- Abema/Tz ± FUL mOS 31.1 and 29.2 vs CT 30.7 (NS)

# PATRICIA-2




# DETECT-V

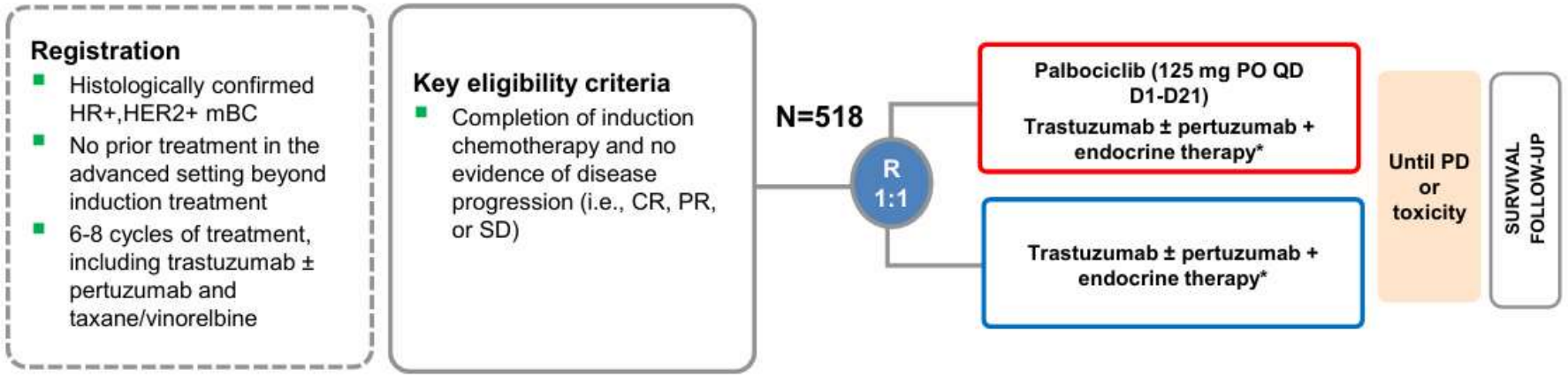



Tolaney et al ESMO 2019 & Lancet Oncol 2020; Ciruelos et al CCR 2020;

# PATIN A

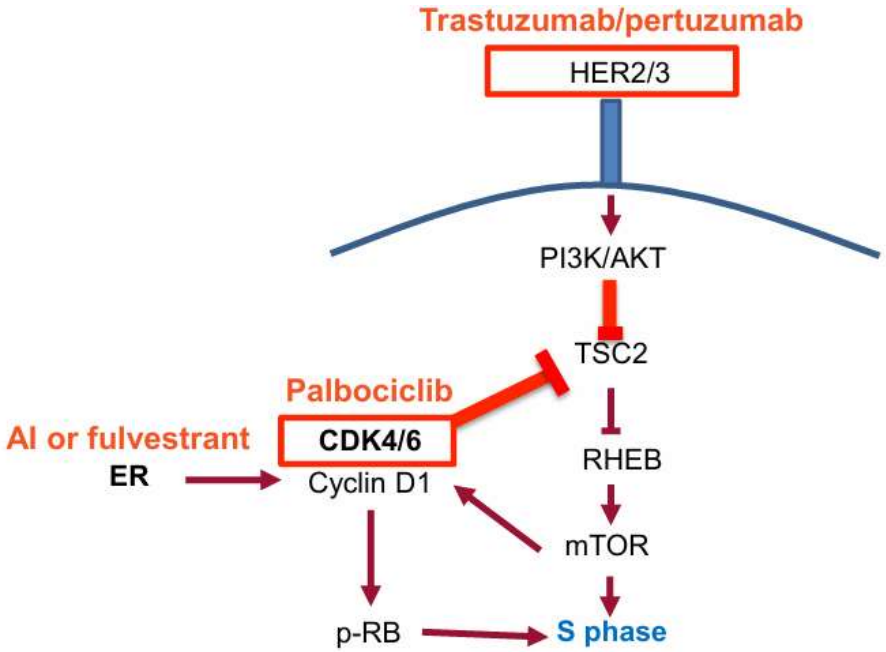
¿Podemos optimizar el mantenimiento en 1° línea?

¿Debemos diferenciar entre RH+ y RH -?



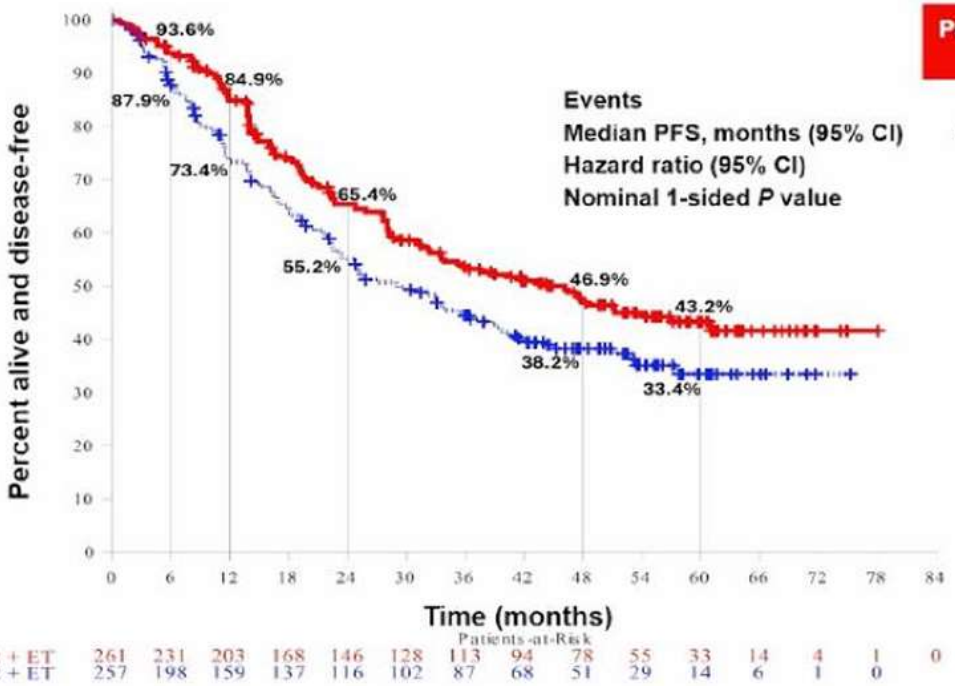

**Stratification factors**

- Pertuzumab use (yes vs no)
  - The non-pertuzumab option is limited to up to 20% of the population
- Prior anti-HER2 therapy in the (neo)adjuvant setting (yes vs no, including de novo)†
- Response to induction therapy (CR or PR vs SD) by investigator assessment†
- Type of endocrine therapy (fulvestrant vs aromatase inhibitor)




- Las vías HER2 y CDK4/6 convergen en la proteína supresora tumoral TSC2.
- La combinan los inhibidores CDK4/6 y HER2, se produce una potente supresión de la fosforilación de RB y la actividad de mTORC1, lo que potencia los efectos antiproliferativos en las células tumorales.

## PFS

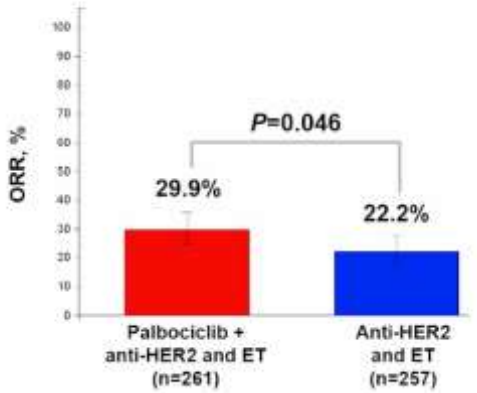



| | Palbo + anti-HER2 and ET | Anti-HER2 and ET |
|---|---|---|
| Events | 126/261 | 136/257 |
| Median PFS, months (95% CI) | **44.3** (32.4-60.9) | **29.1** (23.3-38.6) |
| Hazard ratio (95% CI) | 0.74 (0.58-0.94) | |
| Nominal 1-sided *P* value | 0.0074 | |

Median follow-up on patients who are alive and disease-free, 52.6 months

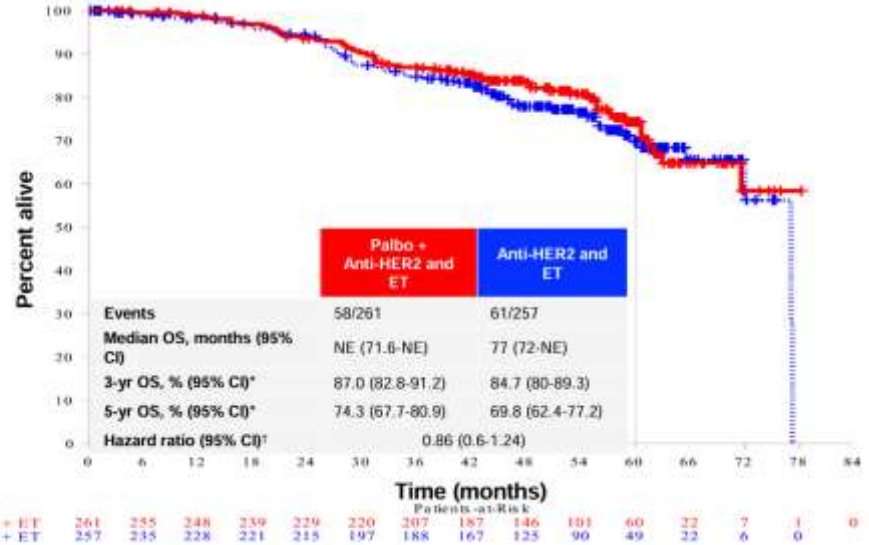
CI=confidence interval; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; palbo=palbociclib.

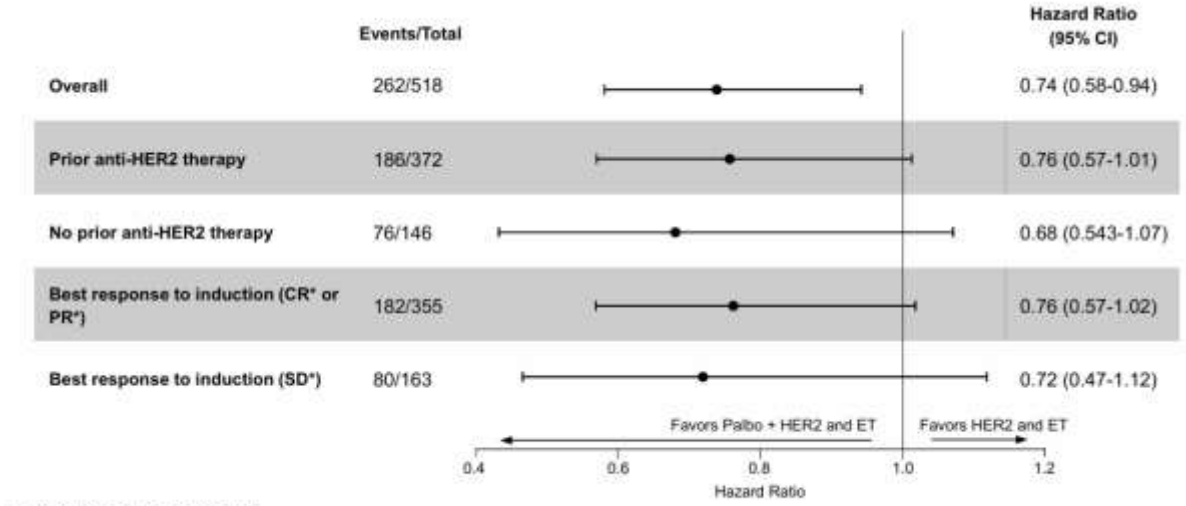
ORR: 29.9% *vs.* 22.2%; *p*=0.046




1 Metzger O et al. Abstr. GS2-12: SABCS 2024.

## OS

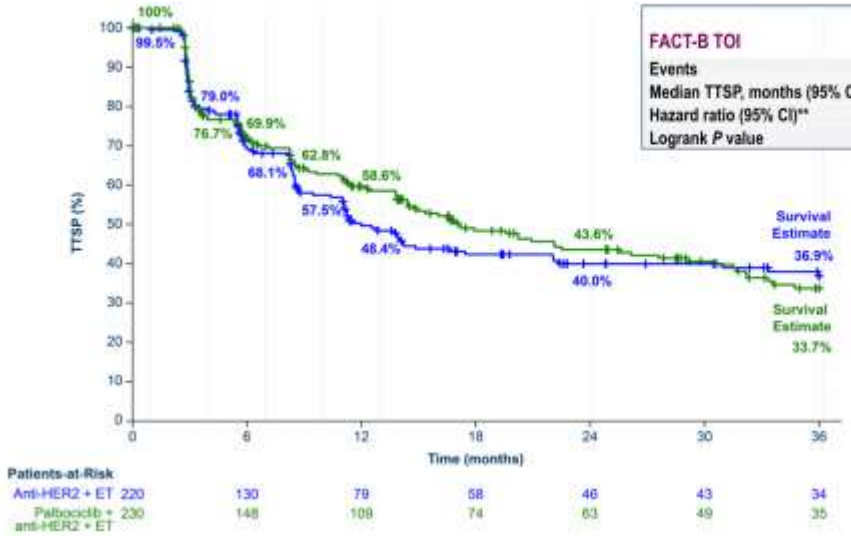



*Factors used in stratified analyses.
CR=Complete Response; Palbo=palbociclib; PR=Partial Response; SD=Stable Disease

Metzger. O et al. SABCS 2024

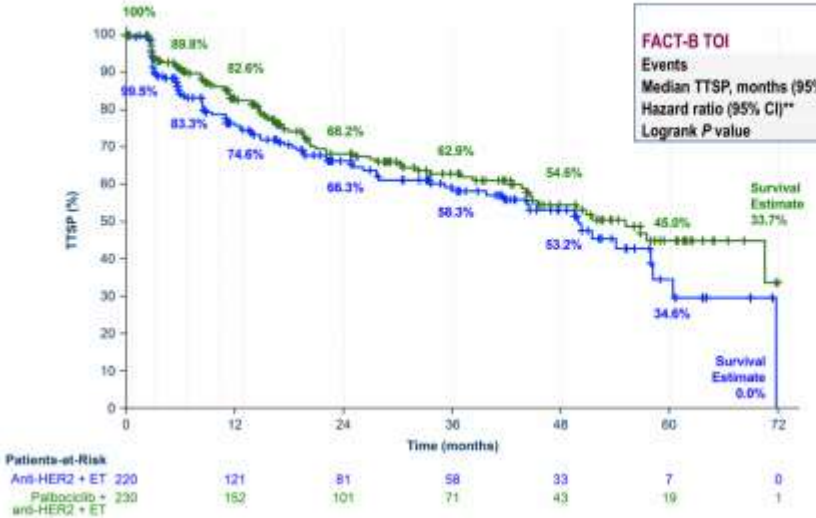
# Time to First Symptom Progression or Death




| FACT-B TOI | Palbociclib + anti-HER2 + ET | Anti-HER2 + ET |
|---|---|---|
| Events | 123/230 | 114/220 |
| Median TTSP, months (95% CI)* | **17.2** (13.9–27.6) | **12.0** (11.1–22.0) |
| Hazard ratio (95% CI)** | 0.93 (0.72–1.20) | Reference |
| Logrank *P* value | 0.5904 | |

There was **no difference observed** between treatment arms in the time to first symptom progression or death.

# Time to Definitive Symptom Progression or Death




| FACT-B TOI | Palbociclib + anti-HER2 + ET | Anti-HER2 + ET |
|---|---|---|
| Events | 81/230 | 83/220 |
| Median TTSP, months (95% CI)* | **55.2** (44.7–NE) | **49.9** (39.8–60.4) |
| Hazard ratio (95% CI)** | 0.80 (0.59–1.08) | Reference |
| Logrank *P* value | 0.1484 | |

There was **no difference observed** between treatment arms in the time to definitive symptom progression or death.

## TTSP

| | Palbociclib + anti-HER2 + ET | Anti-HER2 + ET |
|---|---|---|
| Events | 123/230 | 114/220 |
| Median TTSP, months (95% CI)* | **17.2** (13.9–27.6) | **12.0** (11.0–22.0) |
| Hazard ratio (95% CI)** | 0.93 (0.72–1.20) | Reference |
| Logrank *P* value | 0.5904 | |

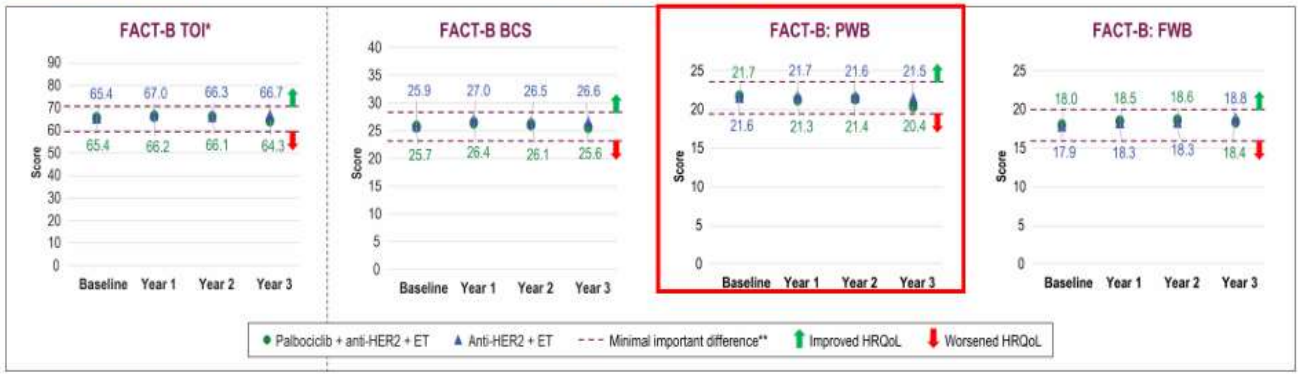
**Definitive TTSP:** sustained deterioration of ≥ 5-point worsening since baseline on the FACT-B TOI that does not improve until the final FACT-B evaluation or death

| | Palbociclib + anti-HER2 + ET | Anti-HER2 + ET |
|---|---|---|
| Events | 81/230 | 83/220 |
| Median TTSP, months (95% CI)* | **55.2** (44.7–NE) | **49.9** (39.8–60.4) |
| Hazard ratio (95% CI)** | 0.80 (0.59–1.08) | Reference |
| Logrank *P* value | 0.1484 | |

**Definitive TTSP provides a more comprehensive characterization of PROs**

FACT-B

## HRQoL scores




PWB is the most strongly correlated with overall QoL

**What is the impact of treatment on QoL in the subgroup of symptomatic patients?**

## PROs completion rates

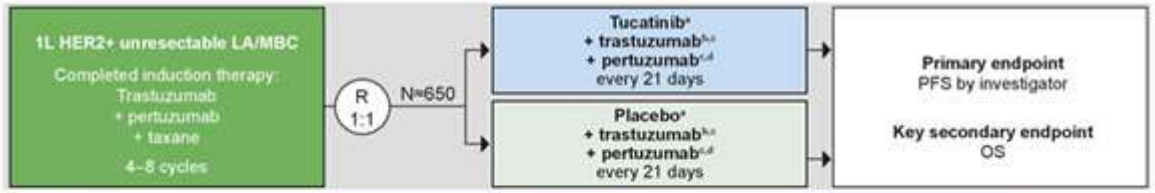
| Treatment arm, n/N (%) | Baseline | Year 1 | Year 2 | Year 3 |
|---|---|---|---|---|
| Palbociclib + Anti-HER2 + ET | 248/261 (95.0) | 187/218 (84.8) | 139/156 (89.1) | 107/119 (89.9) |
| Anti-HER2 + ET | 239/256 (93.4) | 152/180 (84.4) | 113/129 (87.6) | 80/98 (81.6) |

Patient adherence remained ≥81% across all planned timepoints
82%-90% of patients reported PRO measures at year 3

- La mediana de la PFS aumenta de 29,1 a 44,3 meses (Δ15,2 meses).
- Toxicidad manejable.
- Perfil beneficio-riesgo clínico favorable, y respaldan la incorporación del palbociclib en el tratamiento de mantenimiento de primera línea para pacientes con CMH HR+/HER2+

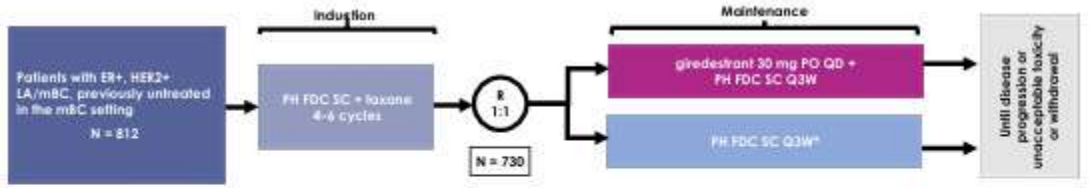
# Otros estudios de mantenimiento en marcha…

## HER-2CLIMB-5




| Primary Objective | Endpoints |
|---|---|
| Evaluate antitumor activity of tucatinib in combination with trastuzumab and pertuzumab | Primary endpoint: PFS by investigator per RECIST v1.1<br>Key secondary endpoint: OS |
| **Other Secondary Objectives** | **Endpoints** |
| Evaluate overall PFS and PFS in the brain | PFS by BICR per RECIST v1.1, and CNS PFS by investigator per RECIST v1.1 |
| Assess the change in HR-QOL | Time to deterioration of HR-QOL, defined as time to 10-point decrease in the global health status/QOL scale of the EORTC QLQ-C30 |
| Evaluate the safety and tolerability of tucatinib in combination with trastuzumab and pertuzumab | • AEs<br>• Clinical laboratory assessments<br>• Incidence of dose holding, dose reductions, and discontinuations of tucatinib<br>• Incidence of dose holding and discontinuations of trastuzumab and pertuzumab |

## heredERA




**Stratification factors**

- Site of disease (visceral vs nonvisceral)
- Type of stage IV presentation (de novo metastatic† vs recurrent metastatic disease)
- Intention to give ET of investigator's choice (yes vs no)
- CR during the induction therapy phase (PR/CR vs SD [or non-CR/non-PD for participants with nonmeasurable disease])

**Primary endpoint**

- Progression-free survival (as determined by the investigator according to RECIST v1.1, time from randomization to the first occurrence of disease progression or death)

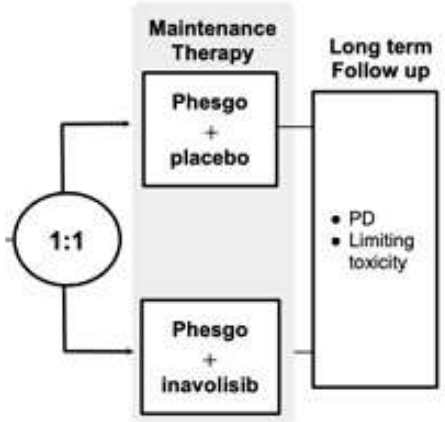
**Secondary endpoints**

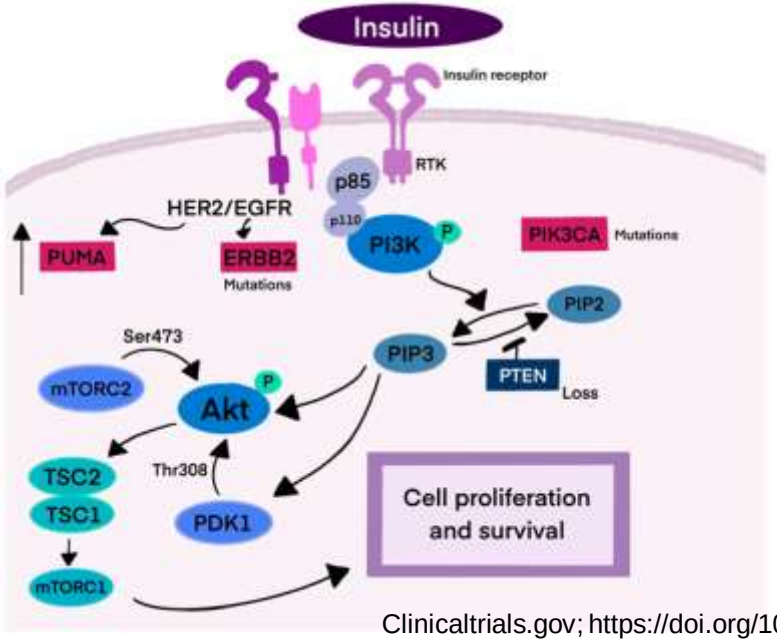
- Overall survival
- Objective response rate
- Duration of response
- Clinical benefit rate
- Patient-reported outcomes
- Safety

## INAVO-122

Untreated HER2+ ABC and completed Induction therapy (4-8 cy taxane Pz/Tz)

- HER2+ and PIK3CA mut




Clinicaltrials.gov; https://doi.org/10.3390/biomedicines13051151

# ¿Y con la llegada de TDM1? ¿Tuvo algún papel en 1

¿Qué papel juegan los ADCs en 1° línea?

¿Es adecuada una primera línea de quimiterapia +/- doble bloqueo?

# MARIANNE

- HER2-positive (central) LABC[a] or MBC
- No prior chemotherapy for LABC/MBC
- >6 months from prior neo-/adjuvant vinca alkaloid or taxane chemotherapy

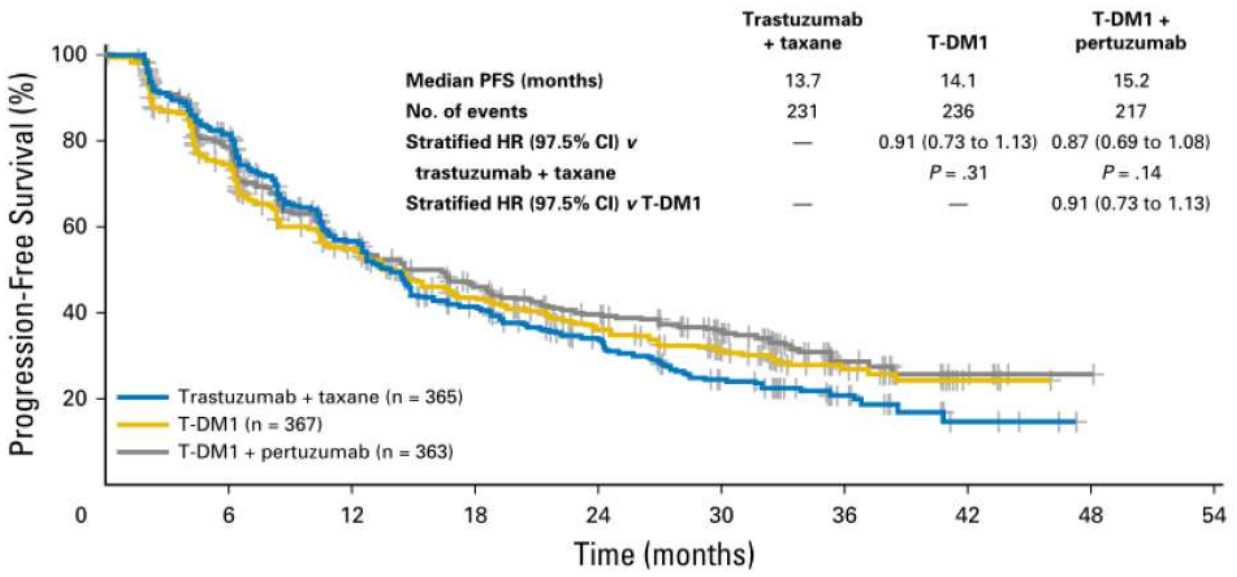
N = 1095

**Trastuzumab + docetaxel**
(8 mg/kg LD then 6 mg/kg + 100 or 75 mg/m² q3w) **OR**
**Trastuzumab + paclitaxel**
(4 mg/kg LD then 2 mg/kg + 80 mg/m² qw)

**T-DM1 + placebo[b]**
(3.6 mg/kg + 840 mg LD then 420 mg q3w)

**T-DM1 + pertuzumab**
(3.6 mg/kg + 840 mg LD then 420 mg q3w)

- **Stratification factors:** World region, Prior neo-/adjuvant therapy (if Yes: prior trastuzumab/lapatinib), Visceral disease
- **Primary end point:** PFS by independent review facility (IRF), non-inferiority and superiority assessed
- **Key secondary end points:** OS, PFS by investigator, ORR, Safety, Patient-reported outcomes




TDM1 +/- pertuzumab no demostraron beneficio frente a taxano-trast

# TRAS RESULTADOS CON EL 1º ADC… qué ocurriría si es Trastuzumab-Deruxtecan

**3L+** **T-DXd, DESTINY-Breast01:** mPFS = 19.4 months[2,7]

- T-DXd demonstrated robust activity following T-DM1 in a phase 2, single-arm study, leading to regulatory approvals globally[2,7,8]
- Prior to approval of T-DXd based on DESTINY-Breast01, SoC in later-line setting was not well defined[9]

| Study Name | Population | Design | Results |
|---|---|---|---|
| **DESTINY-Breast02**[1] | HER2+ metastatic breast cancer previously treated with SoC including T-DM1; 3rd line | Phase 3, multicenter, 2-arm, randomized, open-label, active-controlled Vs. Investigator's Choice (Trastuzumab + Capecitabine or Lapatinib + Capecitabine) | **mPFS T-DXd 17.8 months**, mPFS TPC 6.9 months; HR, 0.3589; P < 0.000001<br><br>**mOS T-DXd 39.2 months**, mOS TPC 26.5 months; HR, 0.6575; P = 0.0021 |
| **DESTINY-Breast03**[2] | HER2+ metastatic breast cancer previously treated with trastuzumab and a taxane; 2nd line | Phase 3, multicenter, 2-arm, randomized, open-label, active-controlled Vs. T-DM1 | **mPFS T-DXd 28.8 months,** mPFS T-DM1 6.8 months; HR, 0.33; P < 0.0001<br><br>**OS rate at 24 months, 77.4% for T-DXd** and 69.9% for T-DM1; HR, 0.64; P=0.0037 |

Swain SM et al. N Engl J Med. 2015;372:724-734. 2. Perez J et al. Expert Opin Biol Ther. 2021;21:811-824. 3. ClinicalTrial.gov. NCT04784715. https://www.clinicaltrials.gov/ct2/show/ NCT04784715.
Accessed August 29, 2023. 4. Hurvitz SA et al. Lancet. 2023;401:105-117. 5. Cortés J et al. N Engl J Med. 2022;386:1143-1154. 6. Verma S et al. N Engl J Med. 2012;367:1783-1791. 7. Saura C et al. ESMO 2021. Poster 279P 8. Modi S et al. N Engl J Med 2020;382:610-621. 9. Tarantino

# DESTINY-BREAST 09

¿Qué papel juegan los ADCs en 1° línea?

## Eligibility criteria

- HER2+ a/mBC
- Asymptomatic/inactive brain mets allowed
- DFI >6 mo from last chemotherapy or HER2-targeted therapy in neoadjuvant/ adjuvant setting
- One prior line of ET for mBC permitted
- **No other prior systemic treatment for mBC†**

R 1:1:1

- n=387: **T-DXd‡ + placebo** — Blinded until final PFS analysis
- n=383: **T-DXd‡ + pertuzumab§**
- n=387: **THP** — Taxane (paclitaxel or docetaxel)¶ + trastuzumab‖ + pertuzumab§

## Endpoints

***Primary***

- PFS (BICR)

***Key secondary***

- OS

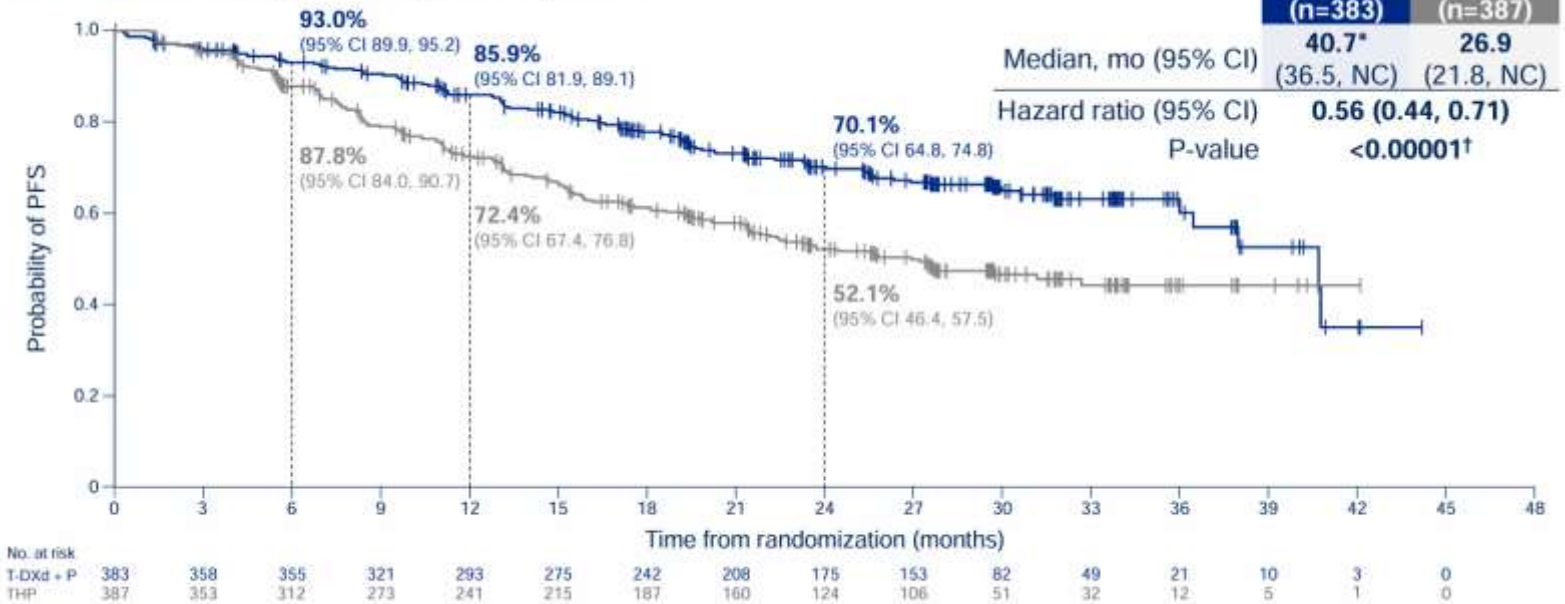
***Secondary***

- PFS (INV)
- ORR (BICR/INV)
- DOR (BICR/INV)
- PFS2 (INV)
- Safety and tolerability

## Patient demographics and key baseline characteristics

| | T-DXd + P (n=383) | THP (n=387) |
|---|---|---|
| **Age, median (range), years** | 54 (27–85) | 54 (20–81) |
| **Female, n (%)** | 383 (100) | 387 (100) |
| **Geographical region, n (%)** | | |
| Asia | 188 (49.1) | 191 (49.4) |
| Western Europe and North America | 87 (22.7) | 78 (20.2) |
| Rest of World | 108 (28.2) | 118 (30.5) |
| **ECOG performance status, n (%)** | | |
| 0 (normal activity) | 256 (66.8) | 246 (63.6) |
| 1 (restricted activity) | 127 (33.2) | 141 (36.4) |
| **HER2 score by central test, n (%)** | | |
| IHC 3+ | 318 (83.0) | 315 (81.4) |
| IHC <3 / ISH+ | 62 (16.2) | 71 (18.3) |
| IHC NR / ISH+ | 3 (0.8) | 1 (0.3) |
| **HR status, n (%)** | | |
| Positive* | 207 (54.0) | 209 (54.0) |
| Negative | 176 (46.0) | 178 (46.0) |
| **De-novo disease at diagnosis, n (%)** | 200 (52.2) | 200 (51.7) |
| ***PIK3CA* mutations detected, n (%)** | 116 (30.3) | 121 (31.3) |
| **Brain metastases, n (%)†** | 25 (6.5) | 22 (5.7) |
| **Visceral metastases, n (%)** | 281 (73.4) | 268 (69.3) |

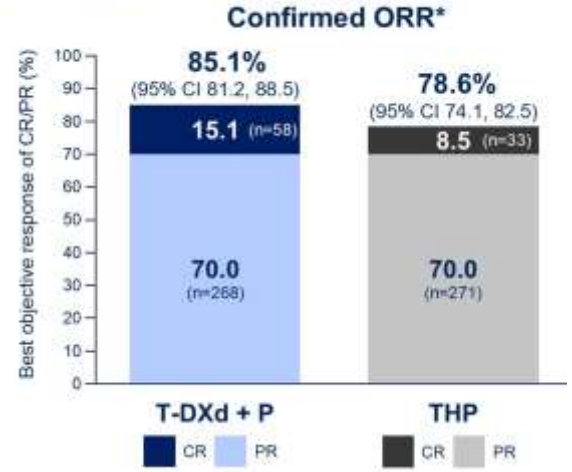
# PFS (BICR): primary endpoint



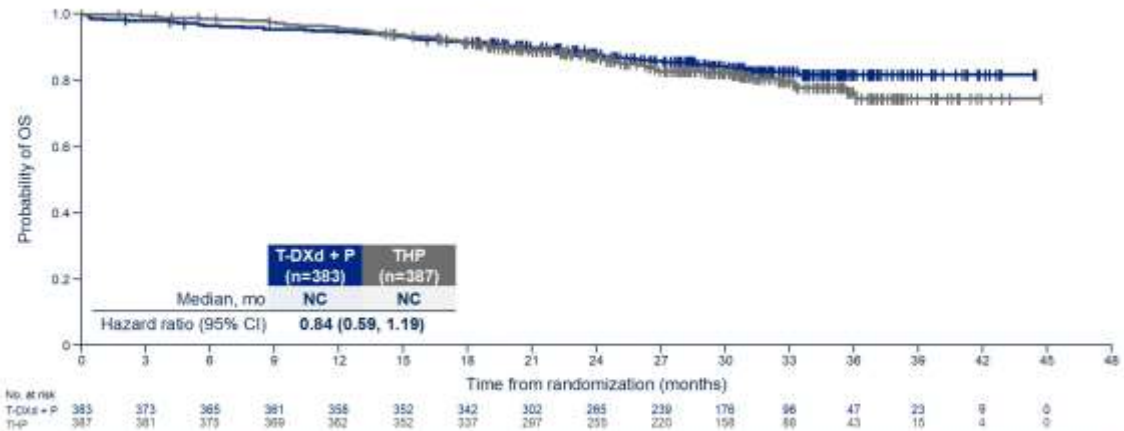

| | T-DXd + P (n=383) | THP (n=387) |
|---|---|---|
| Median, mo (95% CI) | 40.7* (36.5, NC) | 26.9 (21.8, NC) |
| Hazard ratio (95% CI) | 0.56 (0.44, 0.71) | |
| P-value | <0.00001† | |

**Statistically significant and clinically meaningful PFS benefit with T-DXd + P (median Δ 13.8 mo)**

## ORR and DOR (BICR)




## Overall survival (~16% maturity)

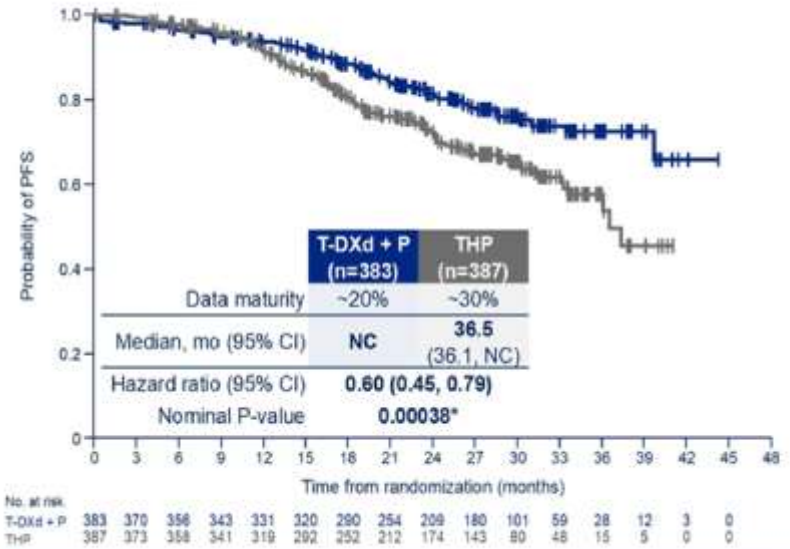



| | T-DXd + P (n=383) | THP (n=387) |
|---|---|---|
| Median, mo | NC | NC |
| Hazard ratio (95% CI) | 0.84 (0.59, 1.19) | |

**Early OS data suggest a positive trend favoring T-DXd + P over THP**

| | T-DXd + P (n=383) | THP (n=387) |
|---|---|---|
| Median DOR, mo (95% CI) | 39.2 (35.1, NC) | 26.4 (22.3, NC) |
| Remaining in response at 24 mo (%) | 73.3 | 54.9 |
| Stable disease, n (%) | 38 (9.9) | 56 (14.5) |

# PFS2 (investigator assessment) and post-trial treatments

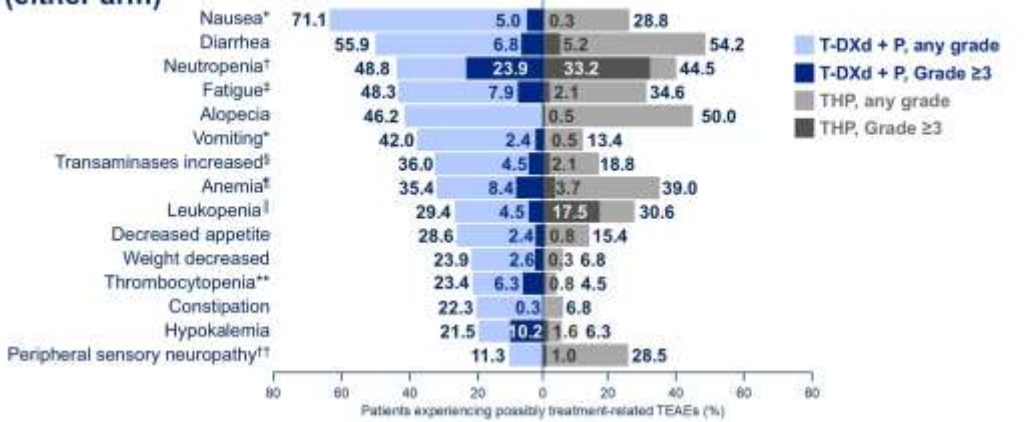



| | T-DXd + P (n=383) | THP (n=387) |
|---|---|---|
| Data maturity | ~20% | ~30% |
| Median, mo (95% CI) | NC | 36.5 (36.1, NC) |
| Hazard ratio (95% CI) | 0.60 (0.45, 0.79) | |
| Nominal P-value | 0.00038* | |

| | T-DXd + P (n=383) | THP (n=387) |
|---|---|---|
| **Received post-discontinuation therapy in second line, n (%)†** | 124 (32.4) | 181 (46.8) |
| **Targeted therapy, n (%)†** | 111 (29.0) | 166 (42.9) |
| T-DXd | 6 (1.6) | 39 (10.1) |
| T-DM1 | 7 (1.8) | 47 (12.1) |
| Trastuzumab-containing regimen‡ | 78 (20.4) | 51 (13.2) |
| Pertuzumab-containing regimen‡ | 53 (13.8) | 34 (8.8) |
| **Chemotherapy, n (%)†** | 68 (17.8) | 57 (14.7) |
| Docetaxel | 24 (6.3) | 8 (2.1) |
| Paclitaxel | 18 (4.7) | 4 (1.0) |
| Capecitabine | 24 (6.3) | 35 (9.0) |
| **Endocrine therapy, n (%)†** | 19 (5.0) | 13 (3.4) |

**Clinically meaningful improvement in PFS2 with T-DXd + P vs THP**

## Possibly treatment-related (investigator assessed) TEAEs in ≥20% of patients (either arm)




# Overall safety summary

| | Safety analysis set* | |
|---|---|---|
| | T-DXd + P (n=381) | THP (n=382) |
| **Total exposure, patient years** | 659.7 | 564.0 |
| **Any TEAE, n (%)** | 380 (99.7) | 378 (99.0) |
| **Possibly treatment-related TEAEs (investigator assessed), n (%)** | 373 (97.9) | 369 (96.6) |
| Grade ≥3 | 209 (54.9) | 200 (52.4) |
| **Serious TEAEs, n (%)** | 103 (27.0) | 96 (25.1) |
| **TEAEs associated with any treatment discontinuation,† n (%)** | 79 (20.7) | 108 (28.3) |
| **TEAEs associated with any dose interruptions,† n (%)** | 262 (68.8) | 187 (49.0) |
| **TEAEs associated with any dose reductions,† n (%)** | 175 (45.9) | 76 (19.9) |
| **TEAEs with outcome of death, n (%)** | 13 (3.4) | 3 (0.8) |
| Possibly treatment related (investigator assessed)‡ | 5 (1.3) | 1 (0.3) |

**Median total treatment duration:**
- **T-DXd + P: 21.7 mo (range 0.3–44.5)**
  - T-DXd: 20.0 mo§
- THP: 16.9 mo (range 0.7–41.7)

**Median treatment duration for taxanes**
- Docetaxel: 5.5 mo (range 0.7–37.4)
- Paclitaxel: 4.4 mo (range 0.2–30.7)

**Median number of cycles for taxanes:**
- Docetaxel: 8 (range 1–51)
- Paclitaxel: 6 (range 1–42)

# Adverse events of special interest

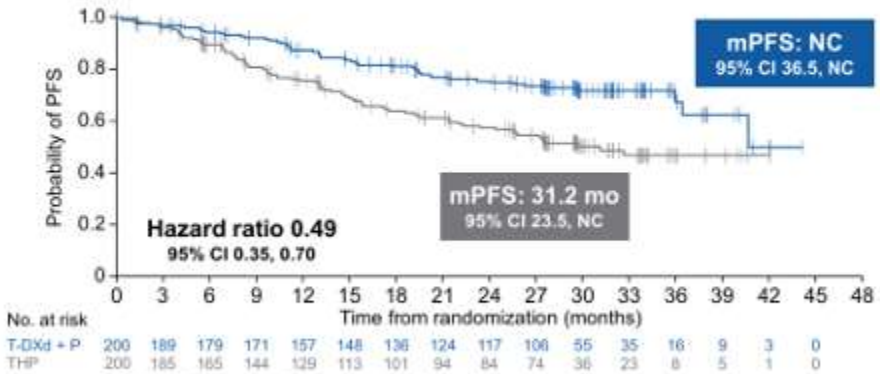
### Adjudicated drug-related ILD/pneumonitis*

| n (%) | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 | Any grade |
|---|---|---|---|---|---|---|
| T-DXd + P (n=381) | 17 (4.5) | 27 (7.1) | 0 | 0 | 2 (0.5) | 46 (12.1) |
| THP (n=382) | 2 (0.5) | 2 (0.5) | 0 | 0 | 0 | 4 (1.0) |

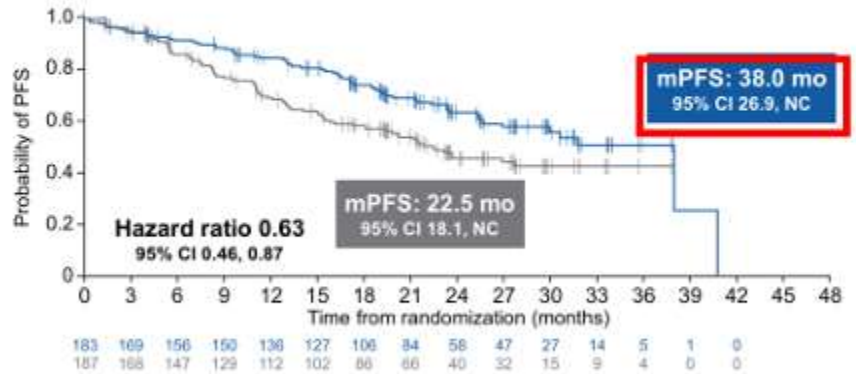
### Left ventricular dysfunction†

| n (%) | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 | Any grade |
|---|---|---|---|---|---|---|
| T-DXd + P (n=381) | 4 (1.0) | 30 (7.9) | 7 (1.8) | 1 (0.3) | 0 | 42 (11.0) |
| THP (n=382) | 1 (0.3) | 19 (5.0) | 7 (1.8) | 0 | 0 | 27 (7.1) |

## PFS:* *de novo*

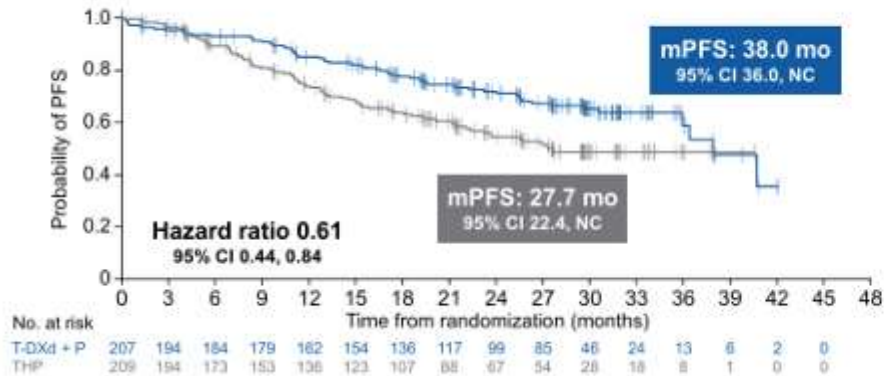



## PFS:* recurrent

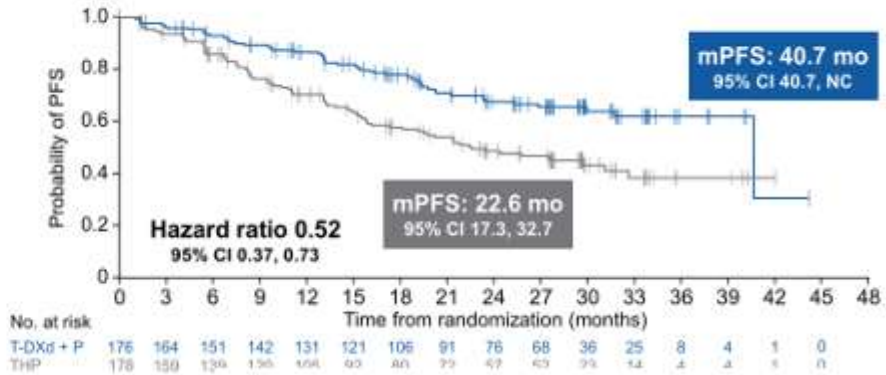



## PFS:* HR−

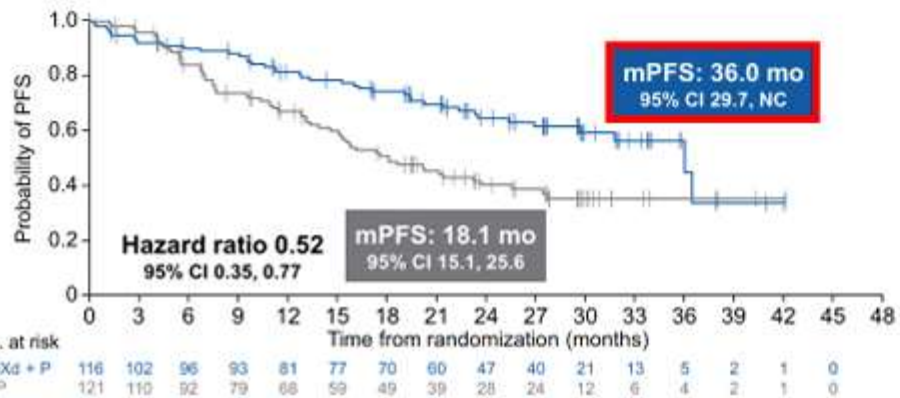
## PFS:* HR+



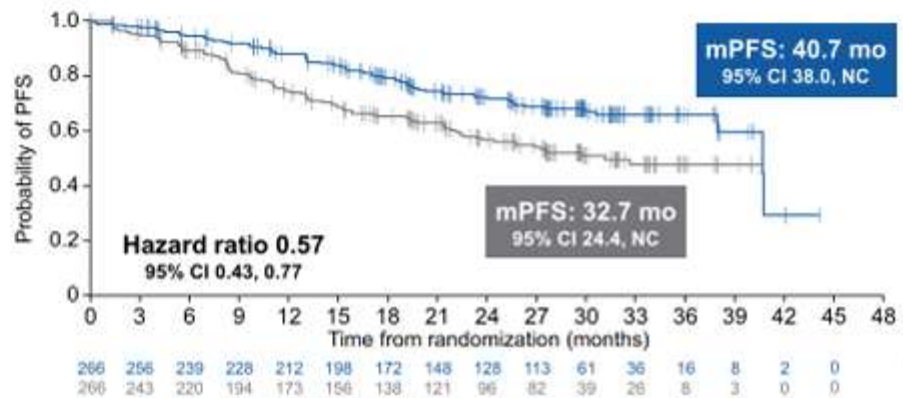

## PFS:* HR−




## PFS:* *PIK3CA*m detected

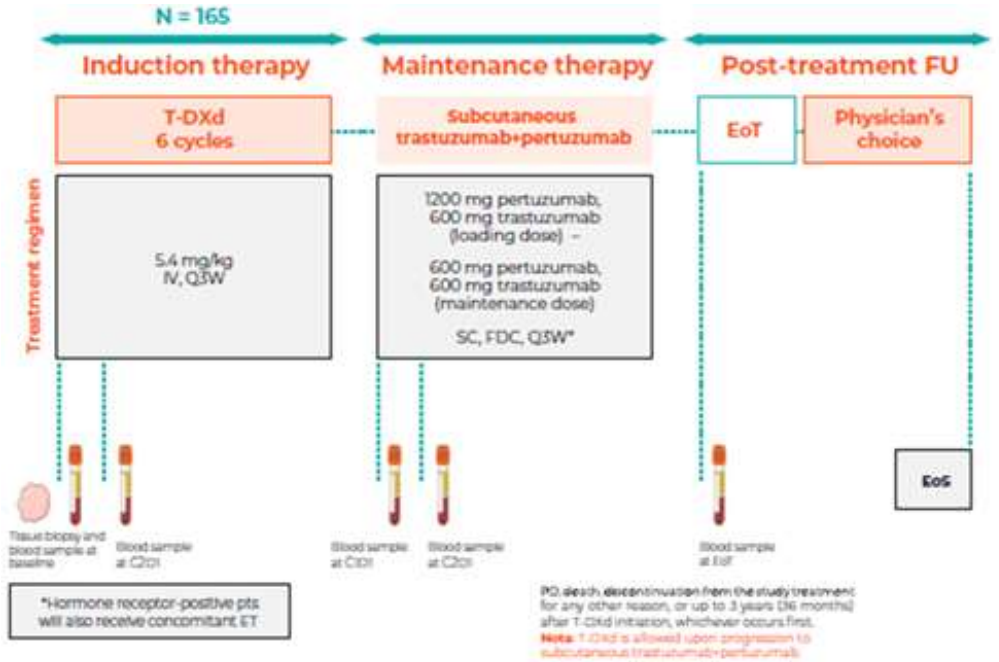



## PFS:* *PIK3CA*m undetected

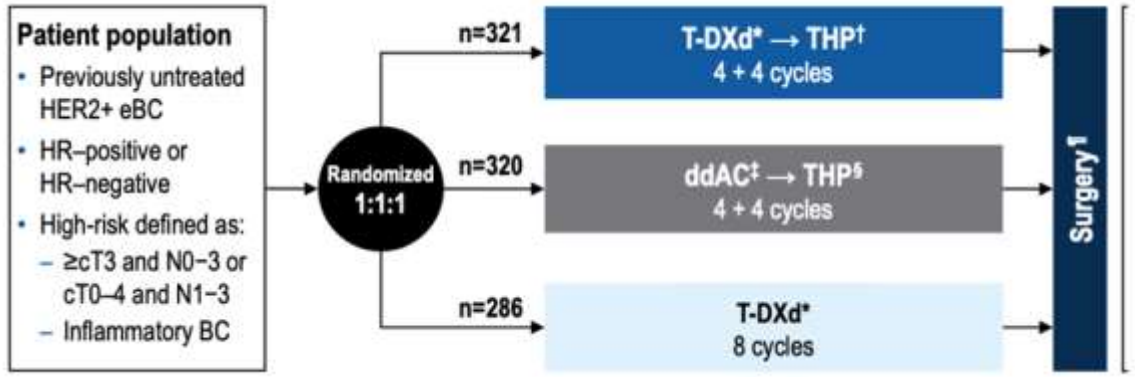



Loibl S et al. LBA 18; ESMO 2025.


## DEMETHER




## DESTINY-BREAST-11




- DXd: 20,0 meses con prolongación de la toxicidad inducida.
- ¿Duración óptima del tratamiento con T-DXd?
- ¿Estrategias de mantenimiento?
- ¿Biomarcadores estáticos basales/factores de riesgo que indiquen un beneficio específico del T-DXd en

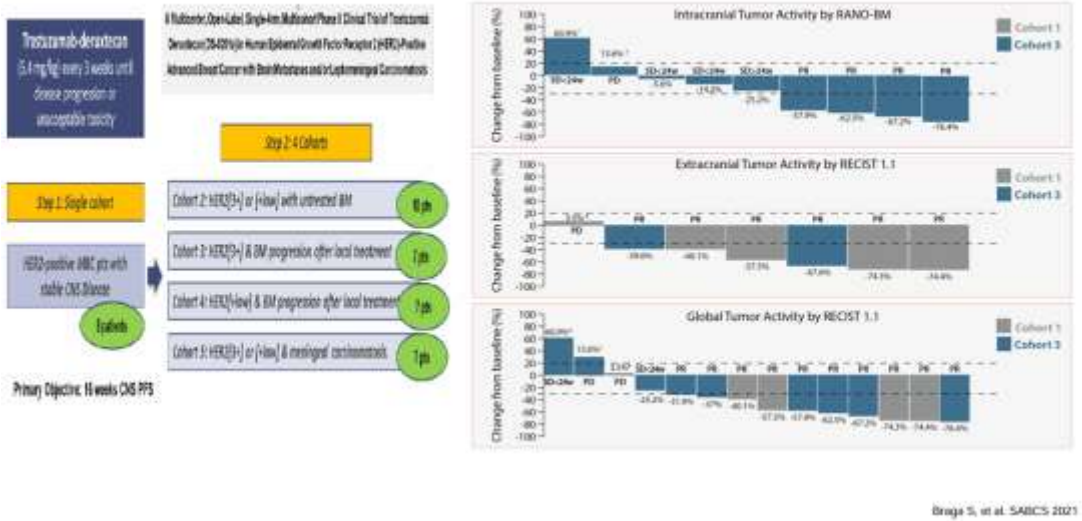
# Metástasis cerebrales

| | T-DM1[1] | T-DXd[2, 7] | Lapatinib[3] | Neratinib[4,5] | Tucatinib[6] |
|---|---|---|---|---|---|
| **Regimen** | T-DM1 (KAMILLA) n=2002 | T-DXd (DB-03) (DB-12) | Cape + Lapa (RANDSCAPE) | Cape + Nera (NALA) (TBCRC 022) | Cape + T + Tucatinib (HER2CLIMB) |
| **Brain Mets status** | Stable or Active | (DB-03) Stable and Treated (DB-12) Active and Stable | Active | (NALA) Stable and Treated (TBCRC 022) Active | Stable or Active |
| **% of patients with brain mets** | 17% | (DB-03) 15% (DB-12) 100% | 100% | (NALA) 16% (TBCRC 022) 100% | 48% (Active 58%) |
| **ORR** | 21.4% | (DB-03) 64% (DB-12) 71.7% | 65.9% | (TBCRC 022) 49% Post-Lapa 33% | 47% |

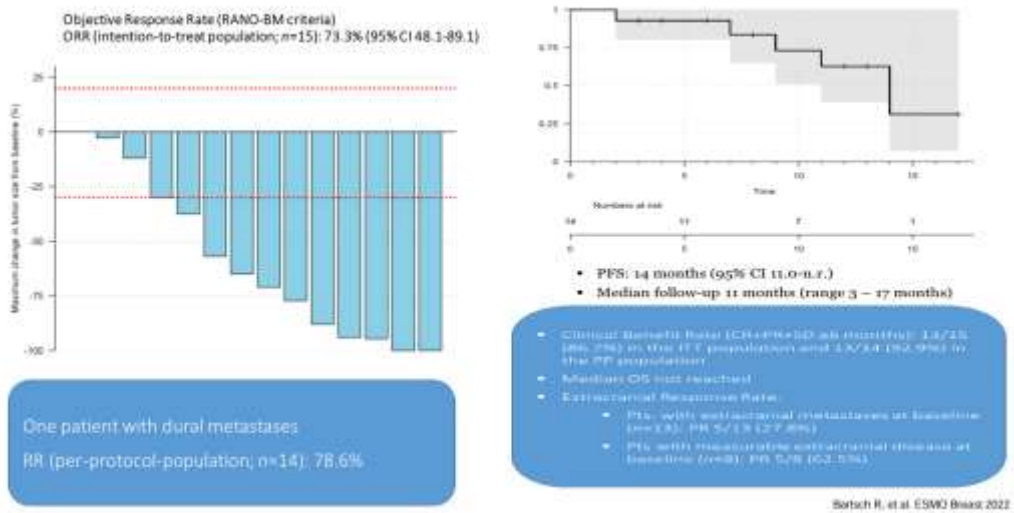
1) Montemurro Delaloge et al. Ann Oncol 2020 2)Hurvitz SABCS 2021 3)Bochelot T, et al. Lancet Oncol 2013
4)Saura. JCO 2020 5)Rachel A Freedman JCO 2019 6)Nancy L ASCO 2020 7) Herbeck N Nature Med 2024

6% metástasis cerebrales
2% vs 3% recaída cerebra

**DS8201- DEBBRAH study**




**TUXEDO-1 study**

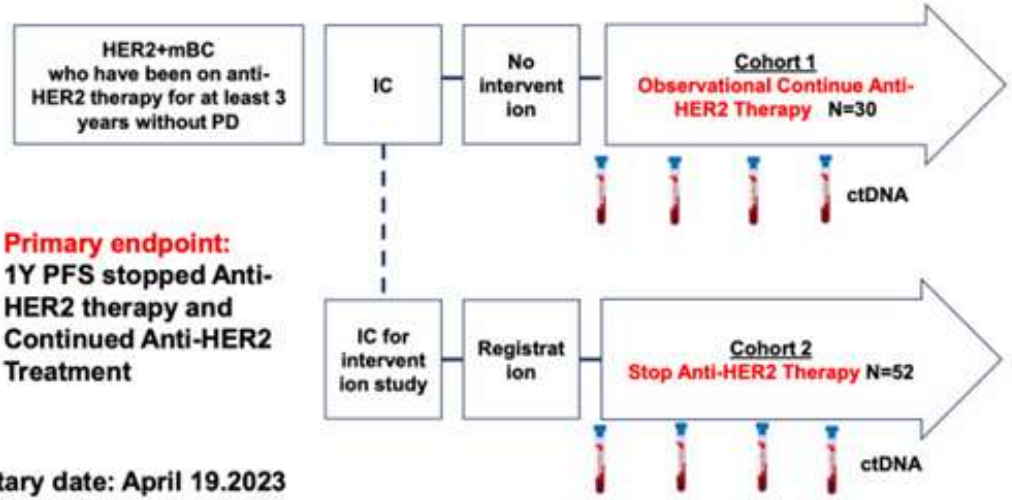


# ¿Podremos hablar de curaci

¿La curación es una opción?

## Abstract PO2-20-01: The STOP-HER2 Trial: A Phase 2 Study of Stopping Trastuzumab - Outcomes in Patients with HER2+ Metastatic Breast Cancer (TBCRC 062) FREE

Heather Parsons; Kathryn Ruddy; Stefania Morganti; Karen Smith; Victoria Attaya; Eliza Kallfelz; Michelle DeMeo; Jamie LaScala; Shirley Mertz; Teri Pollastro; Patricia Spears; Adam Brufsky; Chau Dang; Susan Dent; Ahmed Elkhanany; William Gwin; Ciara O'Sullivan; Kathy Miller; Sara Nunnery; Elaine Walsh; Anna Maria Storniolo; Sara Tolaney; Nabihah Tayob; Antonio Wolff; Eric Winer; Mothaffar Rimawi; Ian Krop; Nancy Lin




**Stary date: April 19.2023**

HA Parsons (PI)

Pts must be receiving 1L anti-HER2 therapy (any regimen) for MBC and must have been on this therapy for at least 3 years without evidence of PD

Pts with history of brain-only PD previously treated with local therapy (surgery and/or radiation therapy) are eligible if asymptomatic, no evidence of interim PD, minimun 24 mo between completion CNS-directed therapy and study start

Pts with oligo-PD outside CNS treated locally or with ET change (with exceptions)

## Treatment of HER2 positive stage 4 breast cancer: When to stop anti-HER2 agents.

**Authors**: Yoshihiko Kamada, Naoko Takigami, Kanou Uehara, Kentaro Tamaki, and Nobumitsu Tamaki AUTHORS INFO & AFFILIATIONS

*J Clin Oncol* 42, e13027(2024) • Volume 42, Number 16_suppl • DOI: 10.1200/JCO.2024.42.16_suppl.e13027

- CMM HER2 positivo estadio IV con CCR en los 6m siguientes al inicio del tratamiento anti-HER2.
- Tratamiento antiHER-2 x 2-3 años adicionales.
- La biopsia líquida podría facilitar la toma de decisiones.

| Subtype | Luminal A | Luminal B | Her2-enriched | Luminal HER2 | Triple Negative |
|---|---|---|---|---|---|
| 5 year survival rate | 74.0% | 52.4% | 53.5% | 76.0% | 0% |
| 10 year survival rate | not assessable | 52.4% | 53.5% | 60.8% | not assessable |

Kamada Y et al. ASCO 2024

# UPCI 99-058

Oncologist. 2023 Sep 19;28(11):e1123-e1126. doi: 10.1093/oncolo/oyad258

**Twenty-Year Follow-Up of a Phase II Trial of Taxotere/Carboplatin/Herceptin in Patients With Metastatic HER2-Positive Breast Cancer**

Juan Luis Gomez Marti [1], Azadeh Nasrazadani [2], Ying Ding [3], Daniel Normolle [4], Adam M Brufsky [5,✉]

| | *N* | Mean | Median | Range |
|---|---|---|---|---|
| Complete or partial response | 29 | 404.3 | 245 | 116.0, 1741.0 |
| Complete response | 17 | 467.8 | 284 | 117.0 1741.0 |

- Un 10 % de pacientes estaban vivos y en seguimiento a los 20 años de seguimiento.
- La causa de la muerte se atribuyó a una enfermedad maligna en 18 participantes (50 %), a otras causas en 3 pacientes (8,3 %) y se desconoce en 15 (42 %) pacientes.

# CLEOPATRA

Tras 8 años de seguimiento, el 16 % de las pacientes del grupo Doce-Pertu/Tz siguen vivas y sin progresión, con una meseta en la curva de supervivencia libre de progresión (PFS).

# PERUSE

1/3 de las 1436 pacientes tratadas con taxano de primera línea Pertu/Tz no presentaron progresión tras 5,7 años de seguimiento.

# CONCLUSIONES

| | |
|---|---|
| ¿Es adecuada una primera línea de quimiterapia + doble bloqueo? | Sí, incrementa SLP y OS, estándar durante más de 10, con posibilidad de mejora. |
| ¿Debemos diferenciar entre RH+ y RH -? | Sin duda, incremento en SLP, adecuada tolerancia, entidades diferenciales. |
| ¿Podemos optimizar el mantenimiento en 1° línea? | Sí, con hormonoterapia +iCDK en RH+ HER-2 +, pendiente de nuevos estudios con TKIs y tratamiento dirigido. |
| ¿Qué papel juegan los ADCs en 1° línea? | Claro beneficio en PFS, datos inmaduros (OS…) |
| ¿La curación es una opción? | Probablemente SÍ en casos concretos grandes respondedoras. |

# MUCHAS GRACIAS…

## ITACA

Cuando emprendas tu viaje a Itaca
pide que el camino sea largo,
lleno de aventuras, lleno de experiencias.
No temas a los lestrigones ni a los cíclopes
ni al colérico Poseidón,
seres tales jamás hallarás en tu camino,
si tu pensar es elevado, si selecta
es la emoción que toca tu espíritu y tu cuerpo.
Ni a los lestrigones ni a los cíclopes
ni al salvaje Poseidón encontrarás,
si no los llevas dentro de tu alma,
si no los yergue tu alma ante ti.

Pide que el camino sea largo.
Que muchas sean las mañanas de verano
en que llegues -¡con qué placer y alegría!-
a puertos nunca vistos antes.
Detente en los emporios de Fenicia
y hazte con hermosas mercancías,
nácar y coral, ámbar y ébano
y toda suerte de perfumes sensuales,
cuantos más abundantes perfumes sensuales
puedas.
Ve a muchas ciudades egipcias
a aprender, a aprender de sus sabios.

Ten siempre a Itaca en tu mente.
Llegar allí es tu destino.
Mas no apresures nunca el viaje.
Mejor que dure muchos años
y atracar, viejo ya, en la isla,

enriquecido de cuanto ganaste en el camino
sin aguantar a que Itaca te enriquezca.

Itaca te brindó tan hermoso viaje.
Sin ella no habrías emprendido el camino.
Pero no tiene ya nada que darte.

Aunque la halles pobre, Itaca no te ha
engañado.
Así, sabio como te has vuelto, con tanta
experiencia,
entenderás ya qué significan las Itacas.

**KAVAFIS**

- Viaje a ÍTACA lleno de aventuras
- Muchas serán las mañanas que lleguemos a sitios nunca vistos.
- Ten siempre en tu mente la idea de ÍTACA, porque es tu destino.
- Y si la encuentras pobre, no es que ÍTACA te haya engañado, como sabio que te habras convertido… sabrás qué significan las ÍTACAS