19as Jornadas HITOS ONCOLÓGICOS: LO MEJOR DE 2024
MADRID 20 - 21 NOVIEMBRE 2024

Cáncer de mama HER2-positivo precoz: estudios de desescalada terapéutica

Dr. Manuel Ruiz, Hospital Universitario Virgen del Rocío, Sevilla

Descenso o disminución graduales en la extensión, intensidad o magnitud de una situación crítica, o de las medidas para combatirla.

En TERMINOS MEDICOS , describimos la desescalada como una combinación de estrategias, técnicas y métodos destinados a reducir la agresión de un paciente ,a situación crítica, o de las medidas para combatirla.

DESESCALADA

Disminuir

TOXICIDAD

Disminuir Cantidad y Duración del tto

MANTENER EFICACIA

DESESCALADA

QUE?

PORQUE?

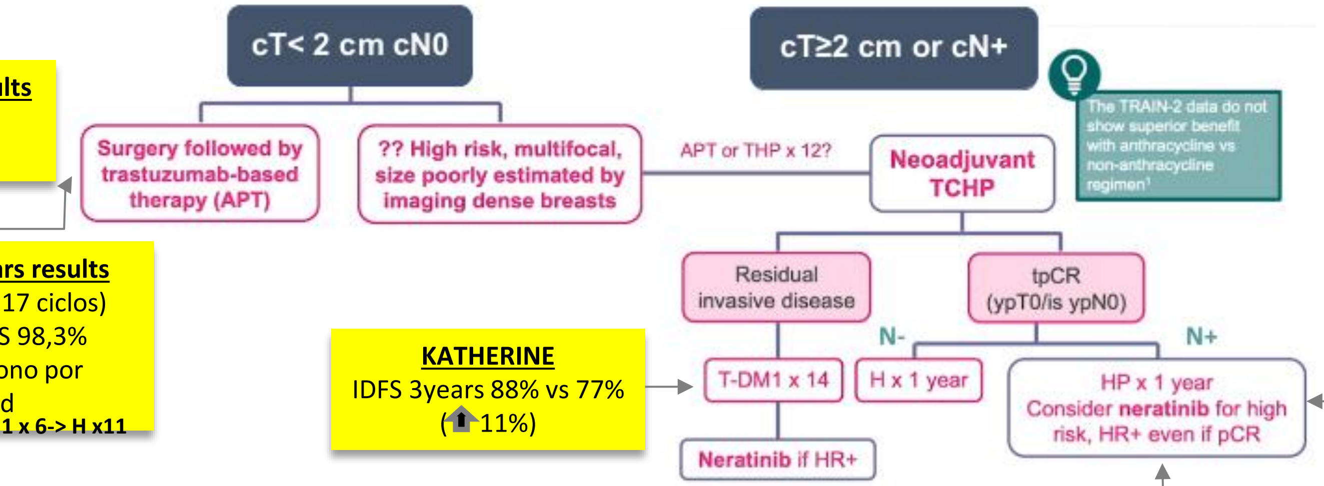
CUANDO?

COMO?

Escalada y desescalada.

APT:10 years results
OS 94,3% / RFS 96,3%

ATTEMPT: 5 years results
(APT vs TDM1 x 17 ciclos)
OS 97,8% / RFS 98,3%
Mayor abandono por toxicidad
***ATTEMP 2.0: TDM1 x 6-> H x11**



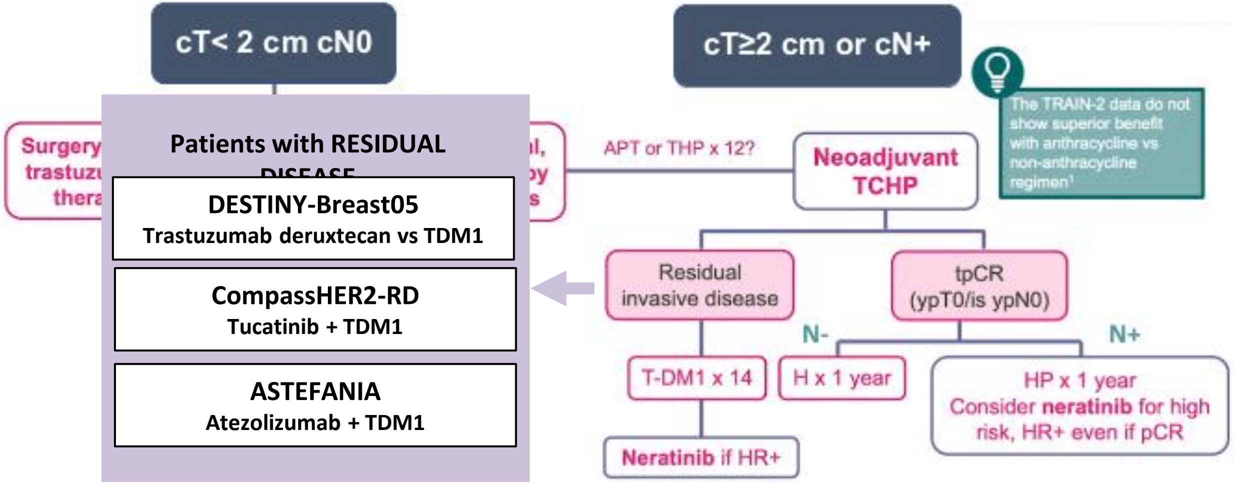
KATHERINE
IDFS 3years 88% vs 77%
(⬆11%)

APHINITY
IDFS 6years 87% vs 83%
(⬆4,5%)

EXTENET
IDFS 5years 85% vs 77%
(⬆7,4%)
Brain protection?

EXTENET
IDFS 5years 90% vs 85%
(⬆5%)

Van der Voort A et al, J Clin Oncol 2020



APT, adjuvant paclitaxel and trastuzumab; H, trastuzumab; HER2, human epidermal growth factor receptor; HP, trastuzumab + pertuzumab; HR, hormone receptor; pCR, pathological complete response; T-DM1, trastuzumab emtansine; TCHP, docetaxel + carboplatin + trastuzumab + pertuzumab; THP, docetaxel + trastuzumab + pertuzumab; tpCR, total pathological complete response.

Van der Voort A et al, J Clin Oncol 2020

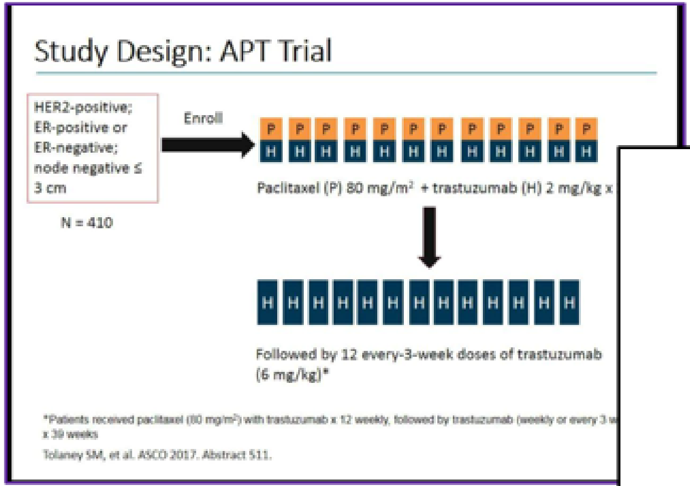
Duración de Trastuzumab adyuvante

TABLE 2. Phase III Studies Evaluating Shorter Duration of Adjuvant Trastuzumab

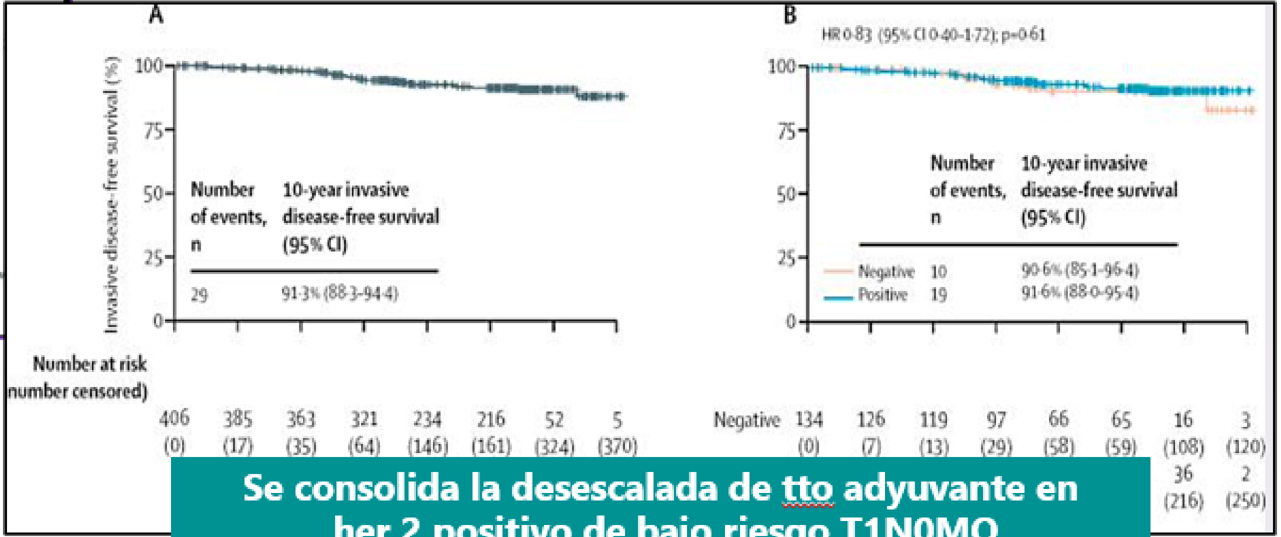
Study	Trastuzumab Duration	N	Results	Comments
SOLD[45]	9 weeks v 1 year	2,174	5-Year DFS 88 v 90.5 HR, 1.39 (two-sided 90% CI, 1.12 to 1.72)	Noninferiority of the 9-week treatment not demonstrated; cardiac tox better with shorter duration
Short-HER[46]	9 weeks v 1 year	1,254	5-Year DFS 85.4 v 87.5 HR, 1.13 (90% CI, 0.89 to 1.42)	Noninferiority of the 9-week treatment not demonstrated; cardiac tox better with shorter duration
HORG[47]	6 v 12 months	481	3-Year DFS 95.7 v 93.3 HR, 1.57 (95% CI, 0.86 to 2.10; P = .137)	Noninferiority of the 6-month treatment not demonstrated
PHARE[48]	6 v 12 months	3,384	7.5-Year DFS 78.8 v 79.6 HR, 1.08 (95% CI, 0.93 to 1.25; P = .39)	Noninferiority of the 6-month treatment not demonstrated; cardiac tox better with shorter duration
PERSEPHONE[44]	6 v 12 months	4,088	4-Year DFS 89.4 v 89.8 HR, 1.07 (90% CI, 0.93 to 1.24; P = .011)	Noninferiority of the 6-month treatment demonstrated with less cardiac cardiotoxicity

- Dados los datos de estos estudios, así como el metaanálisis, 1 año sigue siendo la duración estándar.
- Sin embargo, hay pacientes con enfermedad de bajo riesgo en los que es poco probable que duración < 1año por Tox cardiaca perjudique los resultados a largo plazo

Earl et al. ESMO 2021. Pernas & Tolaney, JCO Oncol Pract 2021



Final 10-year analysis of the open-label, single-arm, phase 2 APT trial



Se consolida la desescalada de tto adyuvante en her 2 positivo de bajo riesgo T1N0MO

91% T1N0M0 (<2cm); 9% >2-3 cm

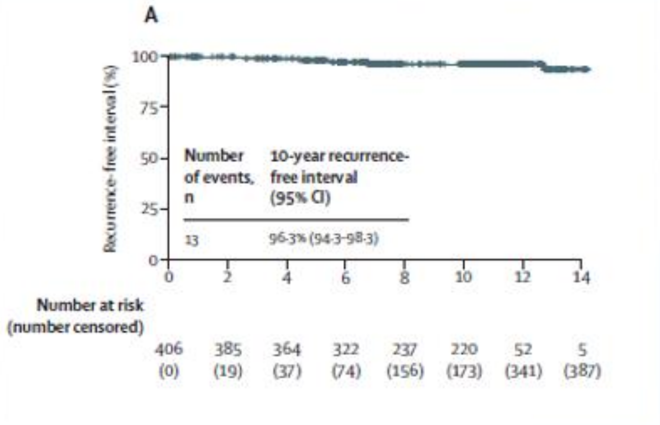
Tolaney SM, Tarantino P, Graham N, et al.. Lancet Oncol. 2023;24(3):273-285. doi:10.1016/S1470-2045(23)00051-7

RH +64%

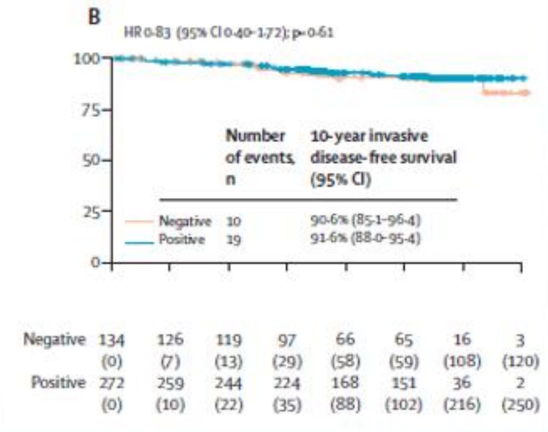
Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer: final 10-year analysis of the open-label, single-arm, phase 2 APT trial

Sara M Tolaney, Paolo Tarantino, Noah Graham, Nabihah Tayob, Laia Parè, Guillermo Villacampa, Chau T Dang, Denise A Yardley, Beverly Moy, P Kelly Marcom, Kathy S Albain, Hope S Rugo, Matthew J Ellis, Iuliana Shapira, Antonio C Wolff, Lisa A Carey, Romualdo Barroso-Sousa, Patricia Villagrasa, Michelle DeMeo, Molly DiLullo, Jorge Gomez Tejeda Zanudo, Jakob Weiss, Nikhil Wagle, Ann H Partridge, Adrienne G Waks, Clifford A Hudis, Ian E Krop, Harold J Burstein, Aleix Prat, Eric P Winer

SLEi 91.3%
ILR 96.3%
Sv espec cáncer 98.8%



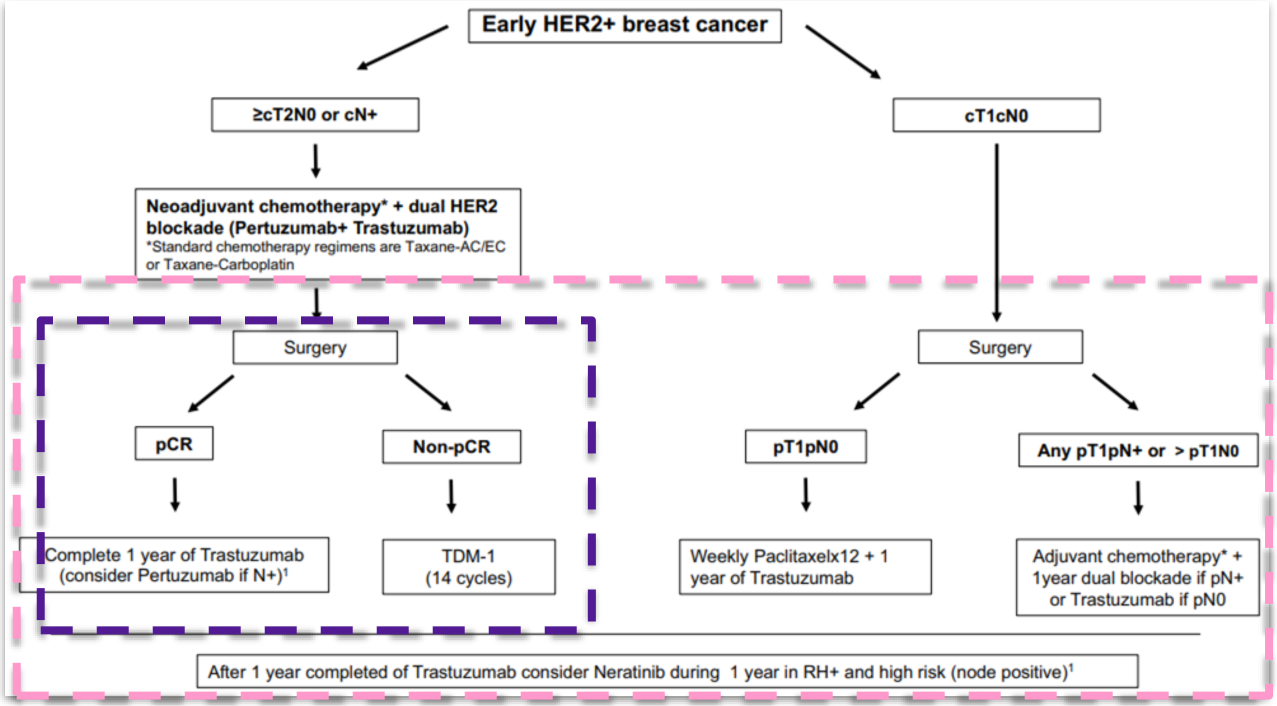
SLEi RH



Tolaney SM et al. Lancet Oncol. 2023

GUÍAS SEOM-GEICAM-SOLTI: ALGORITMO DE TRATAMIENTO PARA CÁNCER DE MAMA PRECOZ HER2 +

ADYUVANCIA



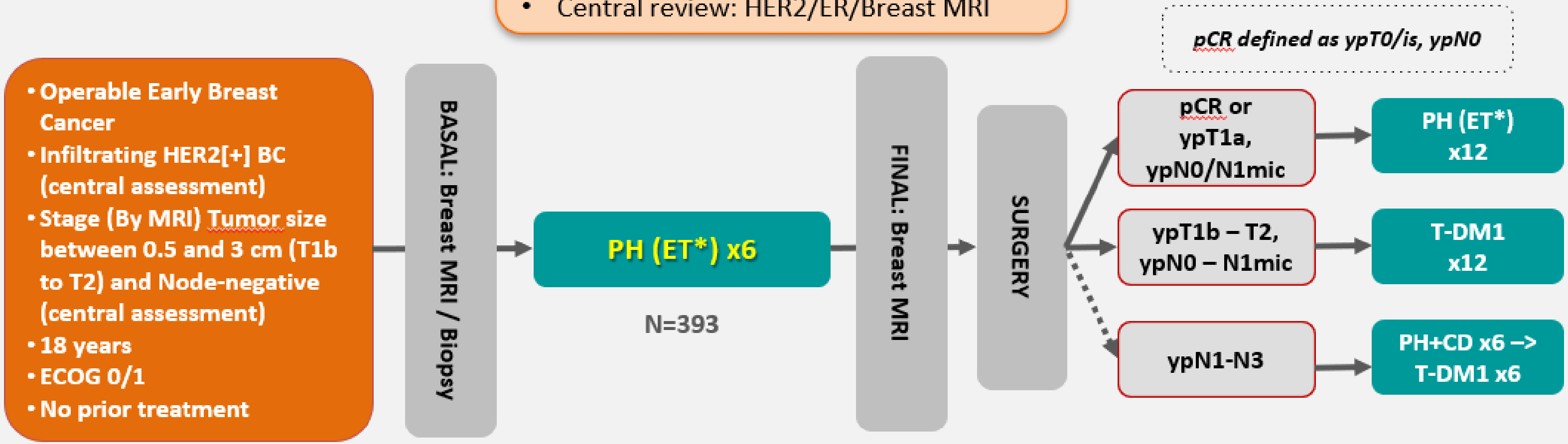
Ayala de la Pena F, *et al.* Clin Transl Oncol. 2023;25:2647-64.

PHERGain-2

Study Design

MedSIR
Medica Scientia Innovation Research

- Stage I – IIA (N0, M0) HER2[+] EBC
- Tumour size (MRI) 5 – 30 mm
- 18 yo - ECOG 0/1 – No prior treatment
- Central review: HER2/ER/Breast MRI



Primary objective:

- 98% 3 years IDFS (Invasive Disease-Free Survival) for the entire population

Secondary objectives:

- Rate of pCR for the whole population and by ER status.
- Correlation between Final MRI and pCR at surgery.
- Molecular.
- 3-years DFS, DDFS, OS, BCSS.
- 5-years IDFS, DFS, DDFS, OS, BCSS.

HER2-enriched subtype as a predictor of pathological complete response following trastuzumab and lapatinib without chemotherapy in early-stage HER2-positive breast cancer (PAMELA): an open-label, single-group, multicentre, phase 2 trial

Antonio Llombart-Cussac, MD [a] · Javier Cortés, MD [b,d] · Laia Paré, PhD [e,f] · Patricia Galván, BS [d,e,f] · Begoña Bermejo, MD [g] ·
Noelia Martínez, MD [b]· et al. Show more

2017

EL SUBTIPO HER-2 ENRICHED PUEDE IDENTIFICAR PACIENTES QUE ALCANZAN RCP SIN QUIMIOTERAPIA

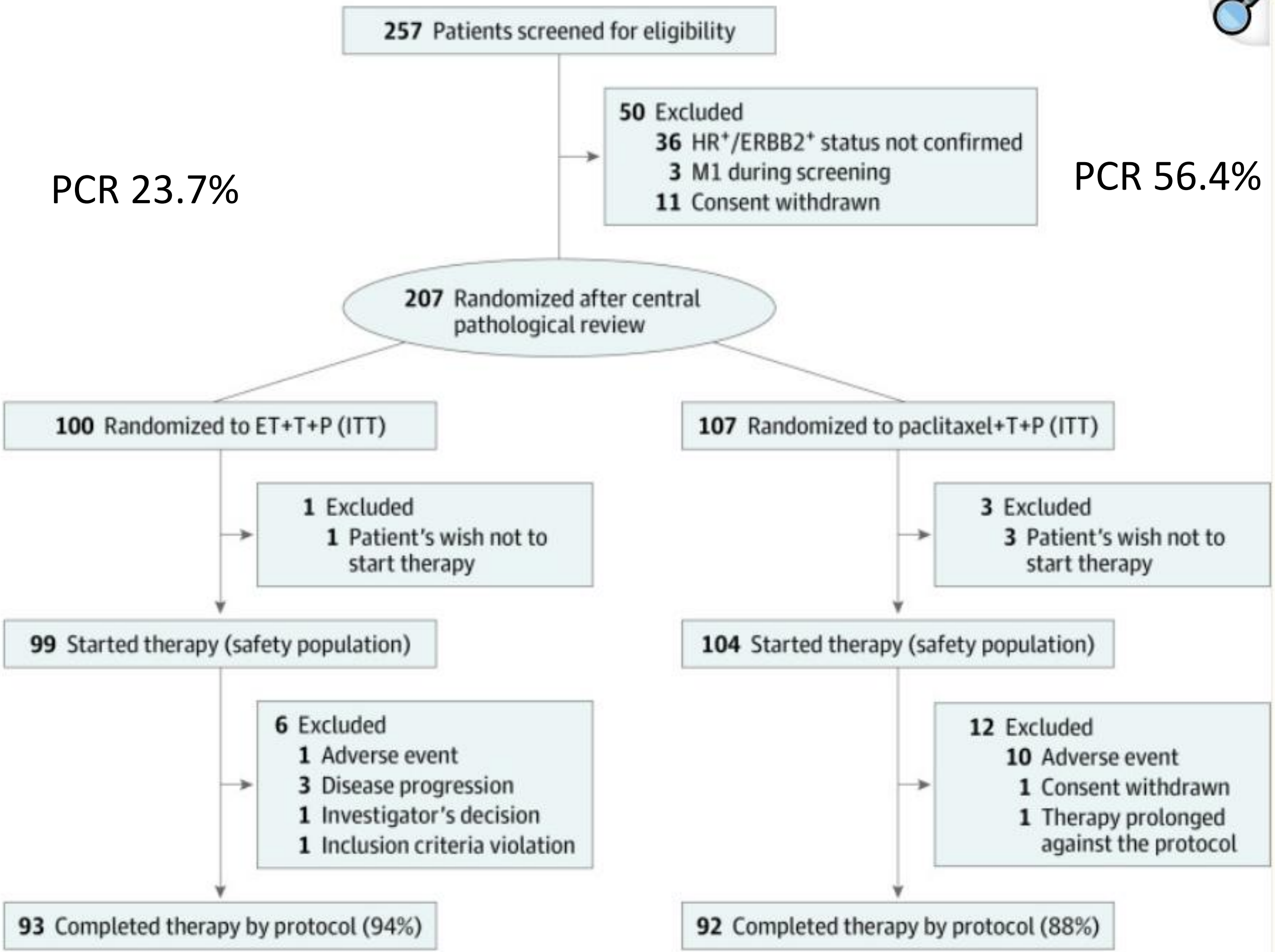
Efficacy of Endocrine Therapy Plus Trastuzumab and Pertuzumab vs De-escalated Chemotherapy in Patients with Hormone Receptor–Positive/*ERBB2*-Positive Early Breast Cancer

The Neoadjuvant WSG-TP-II Randomized Clinical Trial

The WSG-TP-II randomized clinical trial is, to our knowledge, the first prospective trial comparing 2 neoadjuvant de-escalation treatments in HR-positive/*ERBB2*-positive EBC and demonstrated an excellent pCR rate after 12 weeks of paclitaxel plus trastuzumab and pertuzumab that was clearly superior to the pCR rate after ET plus trastuzumab and pertuzumab.

PCR 23.7%

PCR 56.4%



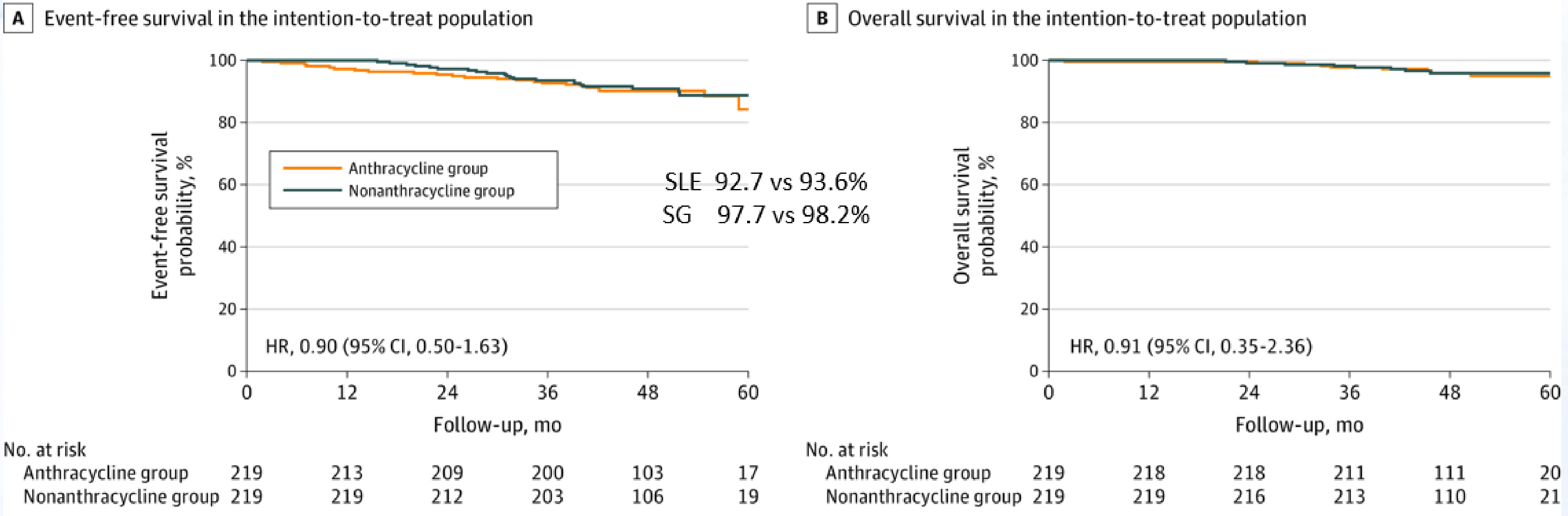
Three-Year Follow-up of Neoadjuvant Chemotherapy With or Without Anthracyclines in the Presence of Dual ERBB2 Blockade in Patients With ERBB2-Positive Breast Cancer: A Secondary Analysis of the TRAIN-2 Randomized, Phase 3 Trial

N 438
Estadios II-III
FECx3 >> Taxol + Carbo x9
Taxol + Carbo x9

+ PT

pCR 67 vs 68%

van Ramshorst MS et al. Lancet Oncol. 2018. van der Voort A et al. JAMA Oncol. 2021



SLE 92.7 vs 93.6%
SG 97.7 vs 98.2%

MRI-guided optimisation of neoadjuvant chemotherapy duration in stage II–III HER2-positive breast cancer (TRAIN-3): a multicentre, single-arm, phase 2 study

Anna van der Voort, Fleur M Louis, Mette S van Ramshorst, Rob Kessels, Ingrid A Mandjes, Inge Kemper, Mariette J Agterof, Wim A van der Steeg, Joan B Heijns, Marlies L van Bekkum, Ester J Siemerink, Philomeen M Kuijer, Astrid Scholten, Jelle Wesseling, Marie-Jeanne T F D Vrancken Peeters, Ritse M Mann, Gabe S Sonke, on behalf of the Dutch Breast Cancer Research Group*

N 438
Estadios II-III
Taxol + Carbo + Trastu + Pertu

30% CR tras 3º ciclo (RM)

van der Voort A et al. Lancet Oncol 2024.

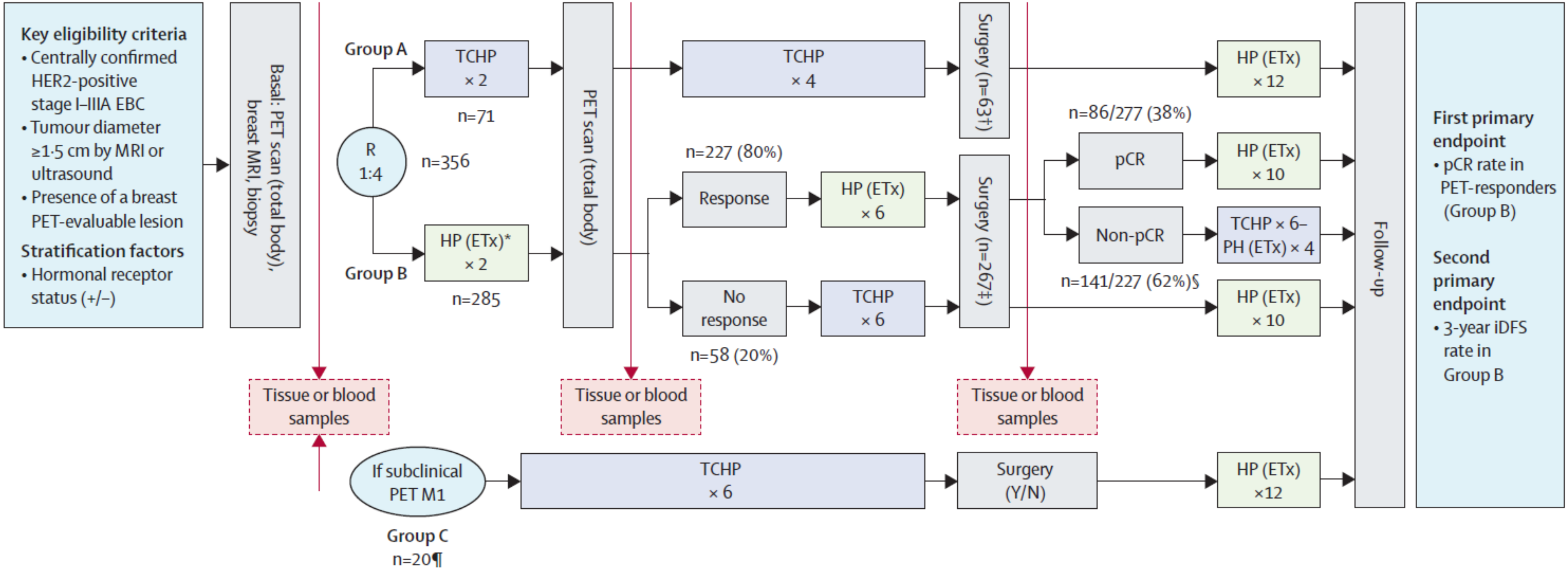
Updated Results of TBCRC026: Phase II Trial Correlating Standardized Uptake Value With Pathological Complete Response to Pertuzumab and Trastuzumab in Breast Cancer

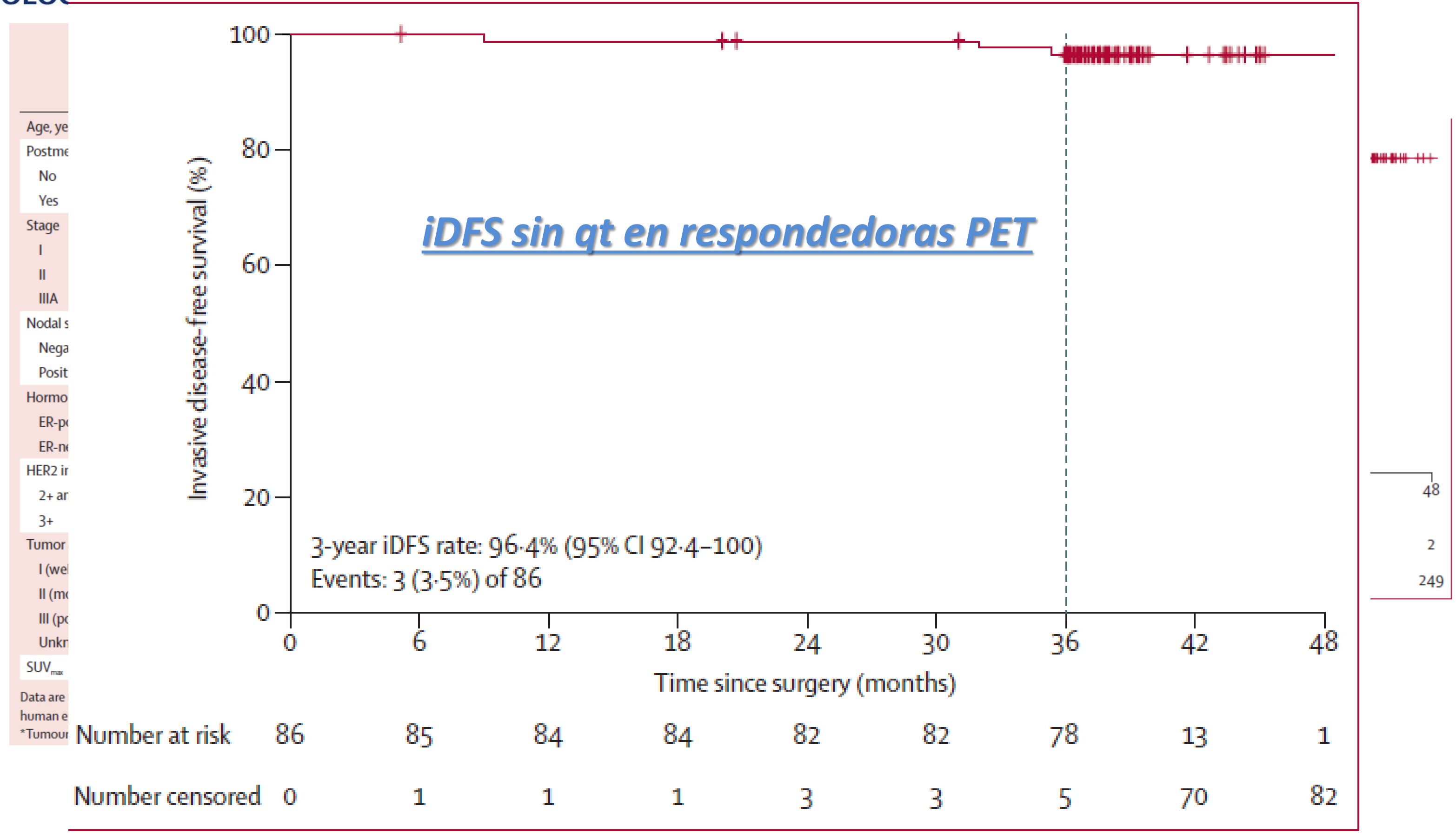
Roisin M. Connolly, MD[1]; Jeffrey P. Leal, BA[1]; Lilja Solnes, MD[1]; Chiung-Yu Huang, PhD[1]; Ashley Carpenter, MA[1]; Katy Gaffney, BSN[1];
Vandana Abramson, MD[2]; Lisa A. Carey, MD[3]; Minetta C. Liu, MD[4]; Mothaffar Rimawi, MD[5]; Jennifer Specht, MD[6];
Anna Maria Storniolo, MD[7]; Vicente Valero, MD[8]; Christos Vaklavas, MD[9]; Ian E. Krop, MD, PhD[10]; Eric P. Winer, MD[10];
Melissa Camp, MD[1]; Robert S. Miller, MD[1]; Antonio C. Wolff, MD[1]; Ashley Cimino-Mathews, MD[1]; Ben H. Park, MD, PhD[1];
Richard L. Wahl, MD[11]; and Vered Stearns, MD[1]

<u>OBJETIVO PRIMARIO NO ALCANZADO PERO CAMBIOS EN SUV (DIA 1 Y DIA 15) PODRIAN DEFINIR LA RESPUESTA A TRASTUZUMAB-PERTUZUMAB.</u>

3-year invasive disease-free survival with chemotherapy de-escalation using an ^{18}F-FDG-PET-based, pathological complete response-adapted strategy in HER2-positive early breast cancer (PHERGain): a randomised, open-label, phase 2 trial

José Manuel Pérez-García, Javier Cortés*, Manuel Ruiz-Borrego, Marco Colleoni, Agostina Stradella, Begoña Bermejo, Florence Dalenc, Santiago Escrivá-de-Romaní, Lourdes Calvo Martínez, Nuria Ribelles, Frederik Marmé, Alfonso Cortés, Cinta Albacar, Geraldine Gebhart, Aleix Prat, Khaldoun Kerrou, Peter Schmid, Sofia Braga, Serena Di Cosimo, Maria Gion, Gabriele Antonarelli, Crina Popa, Emilia Szostak, Daniel Alcalá-López, Petra Gener, Jose Rodríguez-Morató, Leonardo Mina, Miguel Sampayo-Cordero, Antonio Llombart-Cussac, on behalf of PHERGain Trial Investigators†*


Key eligibility criteria
• Centrally confirmed HER2-positive stage I–IIIA EBC
• Tumour diameter ≥1·5 cm by MRI or ultrasound
• Presence of a breast PET-evaluable lesion
Stratification factors
• Hormonal receptor status (+/–)
Basal: PET scan (total body), breast MRI, biopsy
Group A
TCHP × 2
n=71
R 1:4
n=356
HP (ETx)* × 2
Group B
n=285
PET scan (total body)
TCHP × 4
Surgery (n=63†)
HP (ETx) × 12
n=227 (80%)
Response
HP (ETx) × 6
No response
TCHP × 6
n=58 (20%)
Surgery (n=267‡)
n=86/277 (38%)
pCR
HP (ETx) × 10
Non-pCR
TCHP × 6–PH (ETx) × 4
n=141/227 (62%)§
HP (ETx) × 10
Tissue or blood samples
Tissue or blood samples
Tissue or blood samples
If subclinical PET M1
Group C
n=20¶
TCHP × 6
Surgery (Y/N)
HP (ETx) ×12
Follow-up
First primary endpoint
• pCR rate in PET-responders (Group B)
Second primary endpoint
• 3-year iDFS rate in Group B


iDFS sin qt en respondedoras PET
Invasive disease-free survival (%)
100
80
60
40
20
0
3-year iDFS rate: 96·4% (95% CI 92·4–100)
Events: 3 (3·5%) of 86
0 6 12 18 24 30 36 42 48
Time since surgery (months)
Number at risk 86 85 84 84 82 82 78 13 1
Number censored 0 1 1 1 3 3 5 70 82
Age, ye
Postme
No
Yes
Stage
I
II
IIIA
Nodal s
Nega
Posit
Hormo
ER-po
ER-ne
HER2 ir
2+ ar
3+
Tumor
I (wel
II (mo
III (po
Unkn
Data are
human e
*Tumour
48
2
249

Optimal [^{18}F]FDG PET/CT Cutoff for Pathologic Complete Response in HER2-Positive Early Breast Cancer Patients Treated with Neoadjuvant Trastuzumab and Pertuzumab in the PHERGain Trial

Geraldine Gebhart[1], Marleen Keyaerts[2], Thomas Guiot[1], Patrick Flamen[1], Manuel Ruiz-Borrego[3], Agostina Stradella[4], Begoña Bermejo[5], Santiago Escriva-de-Romani[6], Lourdes Calvo Martínez[7], Nuria Ribelles[8], María Fernandez-Abad[9,10], Cinta Albacar[11], Marco Colleoni[12], Laia Garrigos[13], Manuel Atienza de Frutos[14], Florence Dalenc[15], Aleix Prat[16–18], Frederik Marmé[19], Peter Schmid[20,21], Khaldoun Kerrou[22], Sofia Braga[23], Petra Gener[24], Miguel Sampayo-Cordero[24], Javier Cortés[24–26], José Manuel Pérez-García[24,25], and Antonio Llombart-Cussac[24,27]

However, the patients with a ΔSUV_{max} cutoff of at least 77% who avoided neoadjuvant chemotherapy had a pCR rate similar to that of the patients treated with neoadjuvant chemotherapy in arm

Clinicopathological and molecular predictors of [^{18}F]FDG-PET disease detection in HER2-positive early breast cancer: RESPONSE, a substudy of the randomized PHERGain trial

Antonio Llombart-Cussac[1,2,3] · Aleix Prat[4,5,6] · José Manuel Pérez-García[3,7] · José Mateos[8] · Tomás Pascual[4] · Santiago Escrivà-de-Romani[9] · Agostina Stradella[10] · Manuel Ruiz-Borrego[11] · Begoña Bermejo de las Heras[12] · Marleen Keyaerts[13] · Patricia Galvan[6] · Fara Brasó-Maristany[6] · Juan José García-Mosquera[14] · Thomas Guiot[15] · María Gion[16] · Miguel Sampayo-Cordero[3] · Serena Di Cosimo[17] · Jhudit Pérez-Escuredo[3] · Manuel Atienza de Frutos[18] · Javier Cortés[18,2,7] · Geraldine Gebhart[15]

ESTADIO
AFECTACIÓN GANGLIONAR
KI67
GRADO HISTOLÓGICO
EXPRESIÓN DE PROTEINA HER-2

sTILs, PAM50 intrinsic subtyping and ROR scores, and cancer metabolism gene expression according to [^{18}F]FDG-PET status in matched cohorts

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CLINICAL CANCER RESEARCH | PRECISION MEDICINE AND IMAGING

HER2DX Genomic Assay in HER2-Positive Early Breast Cancer Treated with Trastuzumab and Pertuzumab: A Correlative Analysis from the PHERGain Phase II Trial

Antonio Llombart-Cussac[1,2], Jose Pérez-García[2,3], Fara Brasó-Maristany[4,5], Laia Paré[4], Guillermo Villacampa[6], Maria Gion[7], Peter Schmid[8], Marco Colleoni[9], Manuel R. Borrego[10], Patricia Galván[4,5], Joel S. Parker[4,11], Wesley Buckingham[4], Charle
Jose A. Guerrero[2], Miguel Sampayo-Cordero[2], Mario Mancino[2], A
and Javier Cortés[2,3,15]

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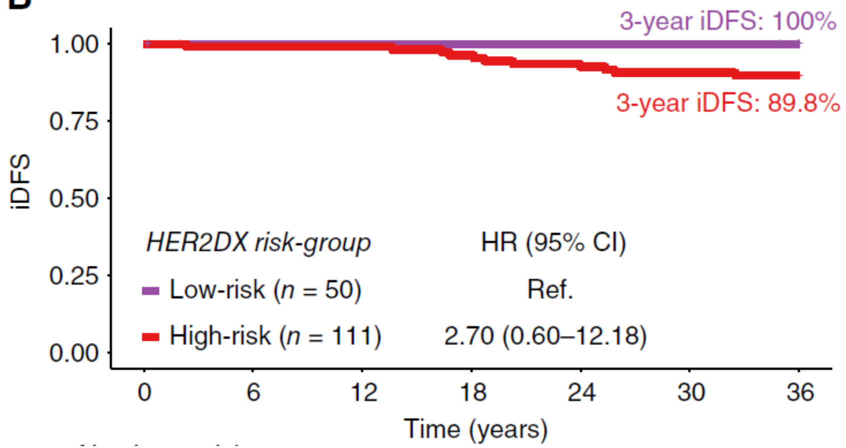


Development and validation of the new HER2DX assay for predicting pathological response and survival outcome in early-stage HER2-positive breast cancer

Aleix Prat,[a,b,c,d,e,1,*] Valentina Guarneri,[f,1] Tomás Pascual,[c] Fara Brasó-Maristany,[a] Esther Sanfeliu,[a,g] Laia Paré,[h] Francesco Schettini,[a,b,c] Débora Martínez,[a] Pedro Jares,[g,i] Gaia Griguolo,[f] Maria Vittoria Dieci,[f] Javier Cortés,[j,k] Antonio Llombart-Cussac,[l] Benedetta Conte,[a,b,c] Mercedes Marín-Aguilera,[h] Nuria Chic,[a,b,c] Joan Anton Puig-Butillé,[i,m] Antonio Martínez,[g] Patricia Galván,[a] Yi-Hsuan Tsai,[h] Blanca González-Farré,[a,g] Aurea Mira,[n] Ana Vivancos,[k] Patricia Villagrasa,[h] Joel S. Parker,[o] Pierfranco Conte,[f,2] and Charles M. Perou[p,2]

Clinical validation of HER2DX in stage 1 HER2+ disease

Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer: final 10-year analysis of the open-label, single-arm, phase 2 APT trial

Sara M Tolaney, Paolo Tarantino, Noah Graham, Nabihah Tayob, Laia Paré, Guillermo Villacampa, Chau T Dang, Denise A Yardley, Beverly Moy, P Kelly Marcom, Kathy S Albain, Hope S Rugo, Matthew J Ellis, Iuliana Shapira, Antonio C Wolff, Lisa A Carey, Romualdo Barroso-Sousa, Patricia Villagrasa, Michelle DeMeo, Molly DiLullo, Jorge Gomez Tejeda Zanudo, Jakob Weiss, Nikhil Wagle, Ann H Partridge, Adrienne G Waks, Clifford A Hudis, Ian E Krop, Harold J Burstein, Aleix Prat, Eric P Winer

N=284 HER2DX

Relapse-free interval
HER2DX low-risk and high-risk
10-year 97.1% vs 90.0%
p=0.030

Tolaney et al. Lancet Oncol 2023

original reports

Adjuvant Trastuzumab Emtansine Versus Paclitaxel in Combination With Trastuzumab for Stage I HER2-Positive Breast Cancer (ATEMPT): A Randomized Clinical Trial

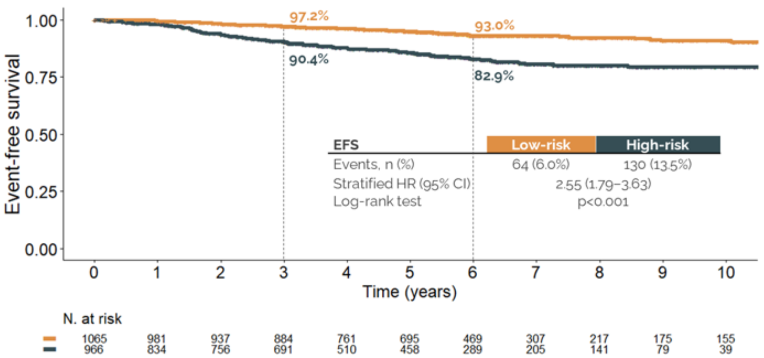
Sara M. Tolaney, MD, MPH; Nabihah Tayob, PhD; Chau Dang, MD; Denise A. Yardley, MD; Steven J. Isakoff, MD, PhD; Vicente Valero, MD; Meredith Faggen, MD; Therese Mulvey, MD; Ron Bose, MD, PhD; Jiani Hu, MSc; Douglas Weckstein, MD; Antonio C. Wolff, MD; Katherine Reeder-Hayes, MD, MBA, MSc; Hope S. Rugo, MD; Bhuvaneswari Ramaswamy, MD; Dan Zuckerman, MD; Lowell Hart, MD; Vijayakrishna K. Gadi, MD, PhD; Michael Constantine, MD; Kit Cheng, MD; Frederick Briccetti, MD; Bryan Schneider, MD; Audrey Merrill Garrett, MD; Kelly Marcom, MD; Kathy Albain, MD; Patricia DeFusco, MD; Nadine Tung, MD; Blair Ardman, MD; Rita Nanda, MD; Rachel C. Jankowitz, MD; Mothaffar Rimawi, MD; Vandana Abramson, MD; Paula R. Pohlmann, MD, PhD, MSc; Catherine Van Poznak, MD; Andres Forero-Torres, MD; Minetta Liu, MD; Kathryn Ruddy, MD; Yue Zheng, MSc; Shoshana M. Rosenberg, ScD, MPH; Richard D. Gelber, PhD; Lorenzo Trippa, PhD; William Barry, PhD; Michelle DeMeo, BS; Harold Burstein, MD, PhD; Ann Partridge, MD, MPH; Eric P. Winer, MD; and Ian Krop, MD, PhD

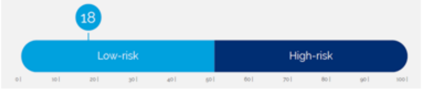
N=187 HER2DX

Relapse-free interval
HER2DX low-risk and high-risk
5-year 98.1% vs 81.8%
p=0.010

HER2DX risk-score: patient-level meta-analysis

Individual-patient level meta-analysis (7 cohorts, 2,031 patients)





HER2DX risk score (continuous variable)		
Type of analysis	**HR (95% CI)**	**p-value**
Univariate	1.21 (1.15-1.27)	<0.001
Multivariable*	1.23 (1.13-1.35)	<0.001

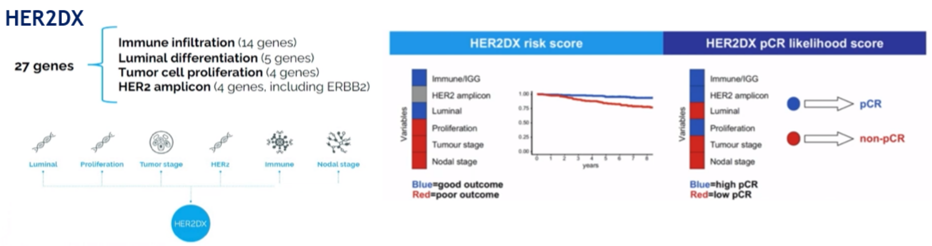
*adjusted by HR status, pCR status, treatment

Villacampa et al. ESMO Breast 2024

- ✓ Randomized clinical trials (ATEMPT[4], PHERGain[5] and CALGB40601[1])
- ✓ Single arm trials (APT[3] and PAMELA[1,2])
- ✓ Observational studies (NEOHER[1,2] and SCAN-B[1,6])

1. *Prat A et al. EBioMedicine 2022*
2. *Martínez-Sáez O et al. ESMO BC 2023*
3. *Tolaney SM et al. Lancet Oncol 2023*
4. *Tarantino P et al. ESMO BC 2023*
5. *Llombart-Cussac A et al. ESMO 2023*
6. *Villacampa G et al. ESMO Open 2024*

HER2+ nuevos BIOMARCADORES para DESESCALADA (PLATAFORMA HER2DX)



HER2DX pCR score predicts pCR independently of HR status and treatment regimen

- **pCR-high** group benefits the most from neoadjuvant dual HER2blockade
- **pCR-medium** group benefits the most from multi-agent CT vs single taxane
- **pCR-low** group shows pCR rates <30% across all therapies

HER2DX**low-risk** is significantly associated with low risk of relapse independently of pCR status

HER2DXhigh-risk and pCR-low group of patients is an unmet need population

Prat EBioMedicine 2022, Villacampa Ann Oncol 2023

HER2DX ERBB2 low-score identifies HER2+ tumors that are not likely to respond to trastuzumab/pertuzumab/T-DM1

In clinically stage 1 disease, **HER2DX risk score** can help identify patients ideal candidates for de-escalation treatments such as TH or H+ET

In clinically stage 2-3 disease, **HER2DX pCR score and/or risk-score** can help identify patients who might be treated with a single taxane (e.g., THP)

EN RESUMEN…

1. LA DESESCALADA EN ADYUVANCIA HER-2 DE PACIENTES DE BAJO RIESGO ES TRATAMIENTO ESTANDAR.

2. EL EMPLEO DE TÉCNICAS DE IMAGEN Y MARCADORES BIOLÓGICOS PERMITE LA DESESCALADA EN NEOADYUVANCIA HER-2.

GRACIAS