SOLCA
NÚCLEO DE QUITO

7 DÉCADAS desde 1954
de atención especializada en cáncer

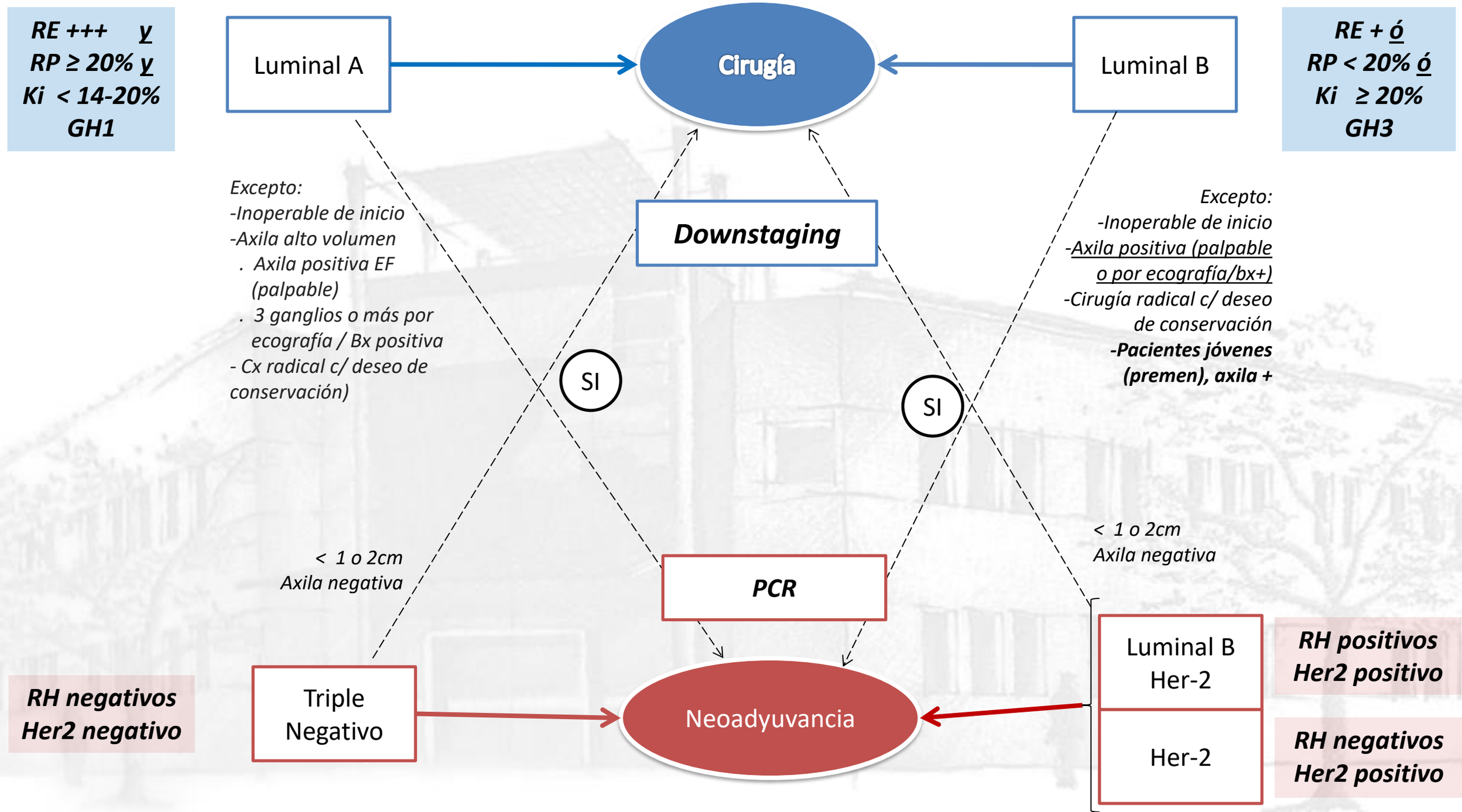
Cáncer de Mama Temprano

"Importancia de la Terapia Dual Anti HER 2 en las Tasas de Respuesta Patológica Completa"

Sergio Rivero

- ONCOLOGIA CLÍNICA, Inst. FLEMING -

20/07/2024


RE +++ y
RP ≥ 20% y
Ki < 14-20%
GH1
Luminal A
Cirugía
Luminal B
RE + ó
RP < 20% ó
Ki ≥ 20%
GH3
Excepto:
-Inoperable de inicio
-Axila alto volumen
. Axila positiva EF (palpable)
. 3 ganglios o más por ecografía / Bx positiva
- Cx radical c/ deseo de conservación)
Downstaging
Excepto:
-Inoperable de inicio
-Axila positiva (palpable o por ecografía/bx+)
-Cirugía radical c/ deseo de conservación
-Pacientes jóvenes (premen), axila +
SI
SI
< 1 o 2cm
Axila negativa
PCR
< 1 o 2cm
Axila negativa
RH negativos
Her2 negativo
Triple Negativo
Neoadyuvancia
Luminal B Her-2
Her-2
RH positivos
Her2 positivo
RH negativos
Her2 positivo

Ca mama Her2 +++ → **ESCENARIO PARA ESTRATEGIA NEOADYUVANTE**

Down staging/
Down sizing →

#Inoperable a operable
(t. inflamatorios)

#Cirugía radical a conservadora
(evitar mastectomía o VAG)

Realizar AGO
y PMG →

Programar cirugías
reductoras de riesgo

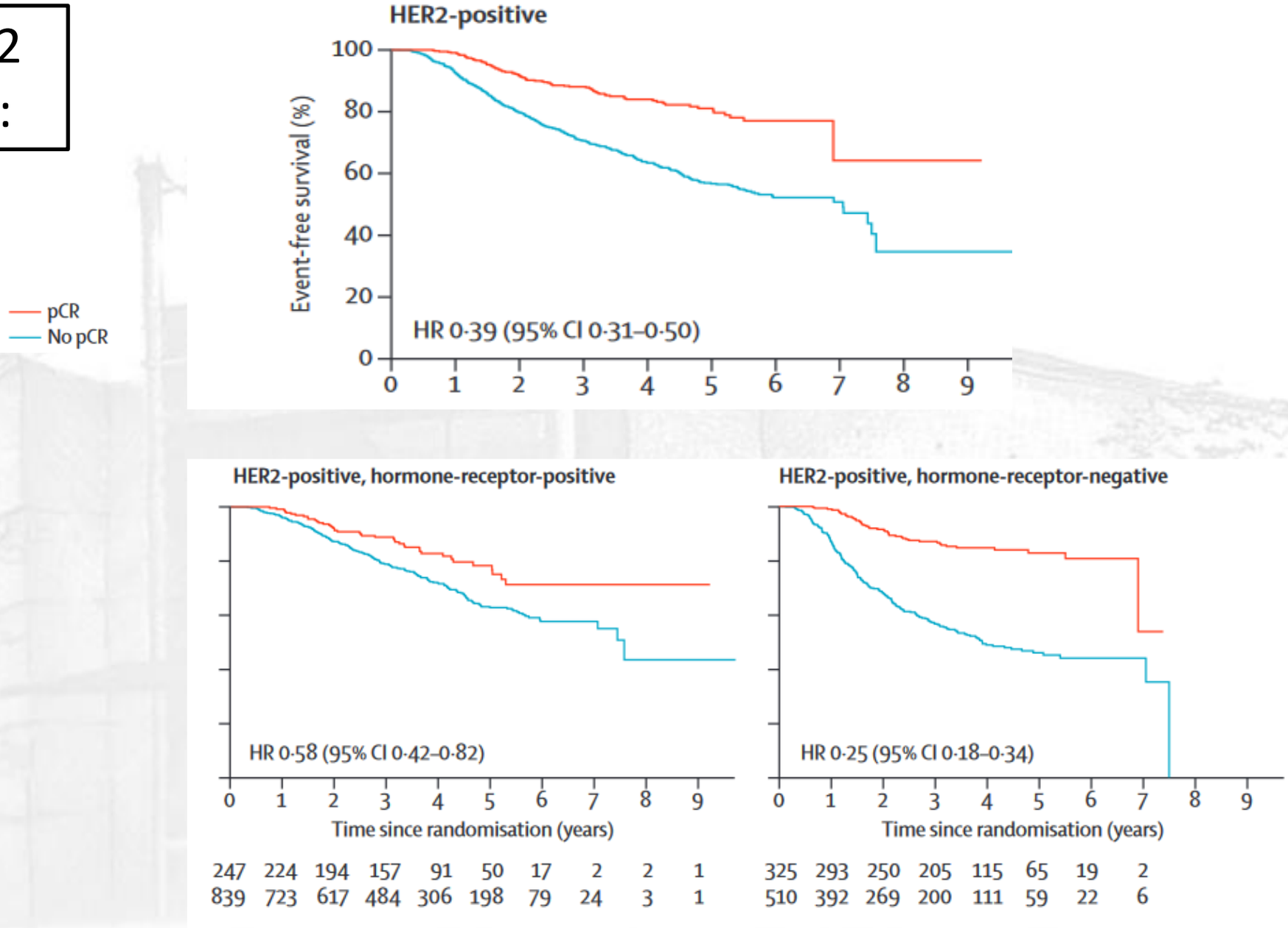
Approximate percentage of patients expressing germline *BRCA* mutations[5]

TNBC	*HR+/HER2–*	*HR–/HER2+*	*HR+/HER2+*
14%	5%	5%	2%

Evaluar sensibilidad al tratamiento sistémico y tratar precozmente eventual enf. micromts →

Factor pronóstico para modificar adyuvancia
(si enf. residual)

Determina 2 escenarios:



Cortazar et al. Lancet. 2019 Mar 9;393(10175):986

Ca mama Her2 +

- ✓ ≥cT1 (1,5-2 cm)
- ✓ ≥cN+

¿Por qué considerar cirugía upfront en tumores menores de 2 cm, axila negativa?

Neoadyuvancia

QT + antiHer2

PCR

Enf residual

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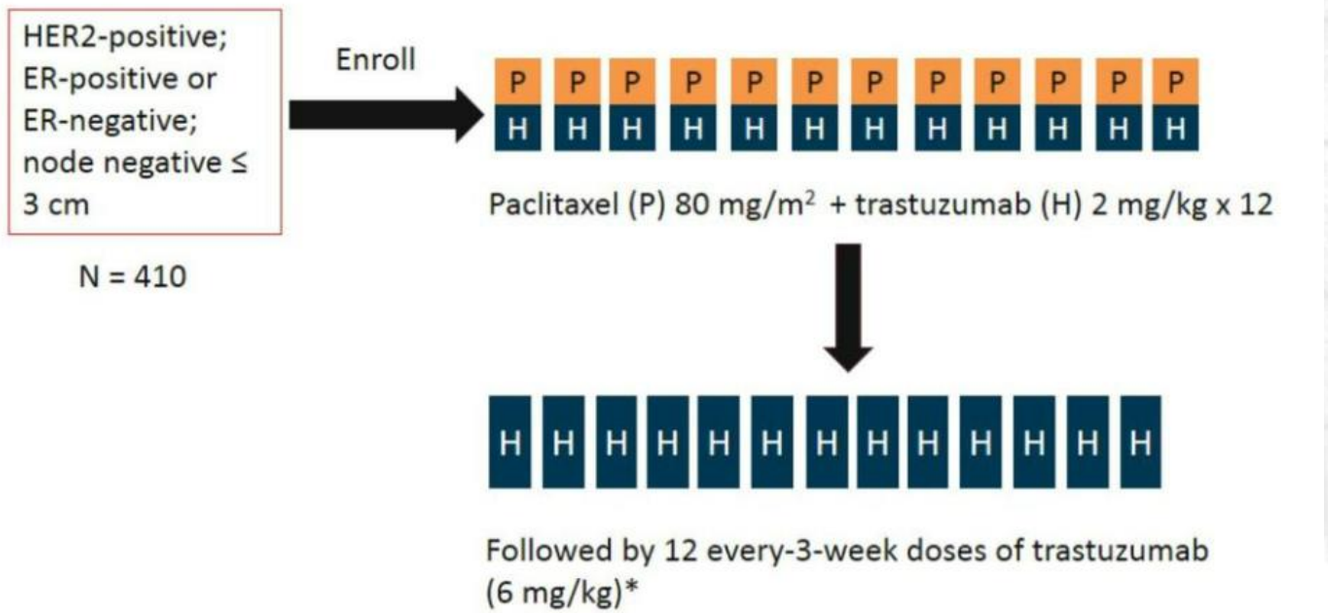
Her2 – Enfermedad Temprana

Considerar neoadyuvancia en todas las pacientes: excepción T <2 cm (3cm), axila negativa

ORIGINAL ARTICLE

Adjuvant Paclitaxel and Trastuzumab for Node-Negative, HER2-Positive Breast Cancer

APT Trial



*Patients received paclitaxel (80 mg/m²) with trastuzumab x 12 weekly, followed by trastuzumab (weekly or every 3 weeks) x 39 weeks

Tolaney SM, et al. ASCO 2017. Abstract 511.

Fase II
1 sola rama 2007-2010

Primary tumor	
Size	
T1mic: ≤0.1 cm	9 (2.2)
T1a: >0.1 to ≤0.5 cm	68 (16.7)
T1b: >0.5 to ≤1.0 cm	124 (30.5)
T1c: >1.0 to ≤2.0 cm	169 (41.6)
T2: >2.0 to ≤3.0 cm	36 (8.9)
Hormone-receptor status	
Positive	272 (67.0)
Negative	134 (33.0)

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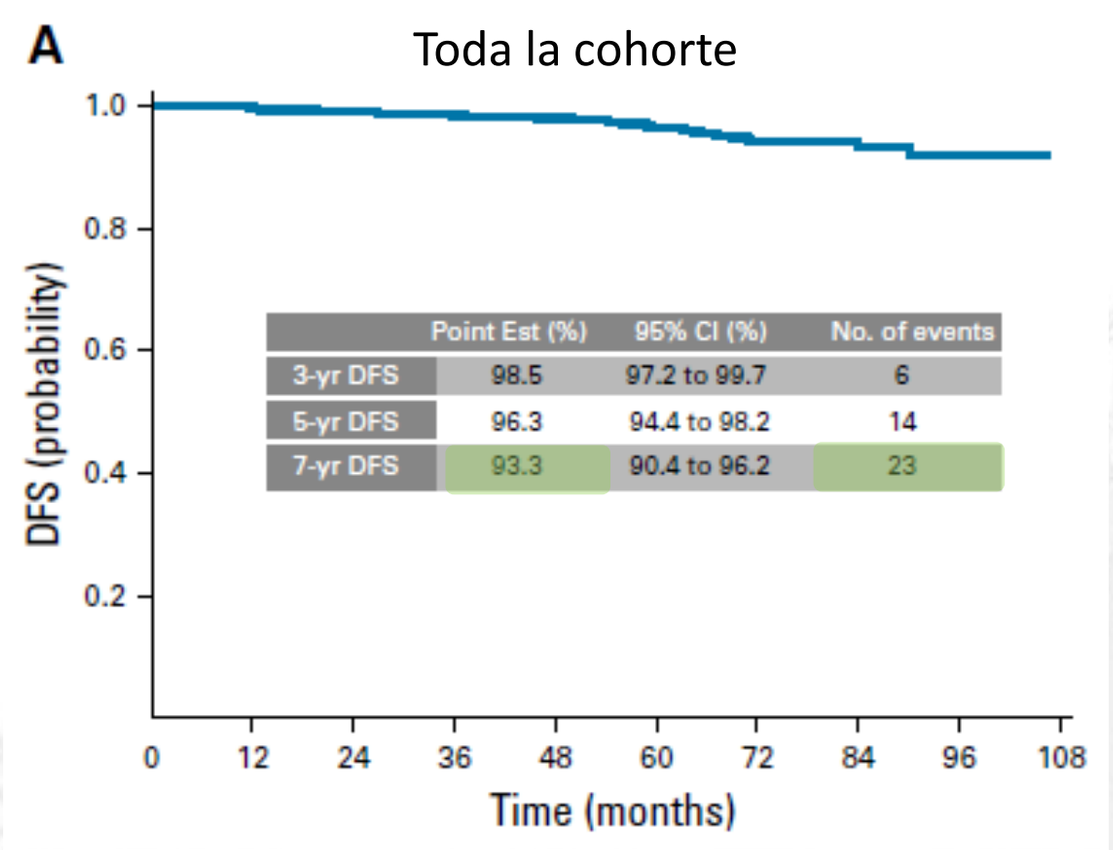
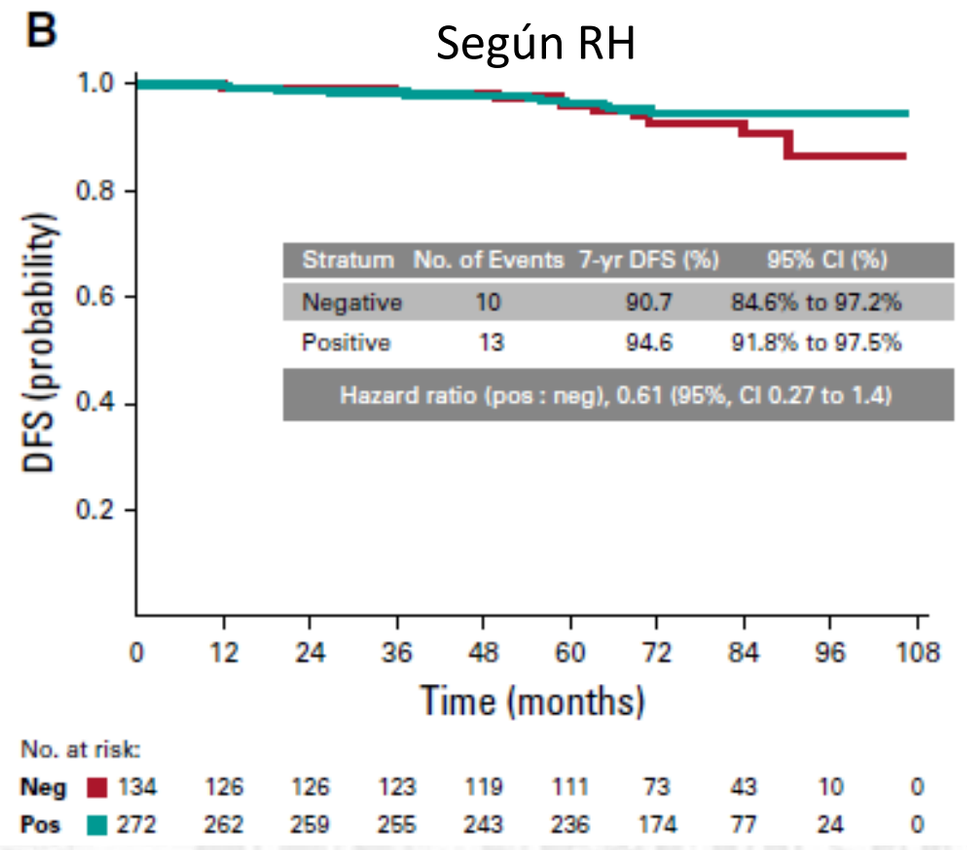




DFS 7 años: 93,3% (1% recurrencia a distancia)
SG 7 años: 95% (95% CI, 92.4 - 97.7)
ILR 7 años: 97.5% (95% CI, 95.9 - 99.1)

FUP 10.8 años → 6 eventos de recurrencia a distancia (n 406)

Tolaney SM, et al. ASCO 2017.

Ca mama Her2 +

- ✓ ≥c T 1,5 - 2 cm
- ✓ ≥c N+

Neoadyuvancia

QT + AntiHer2

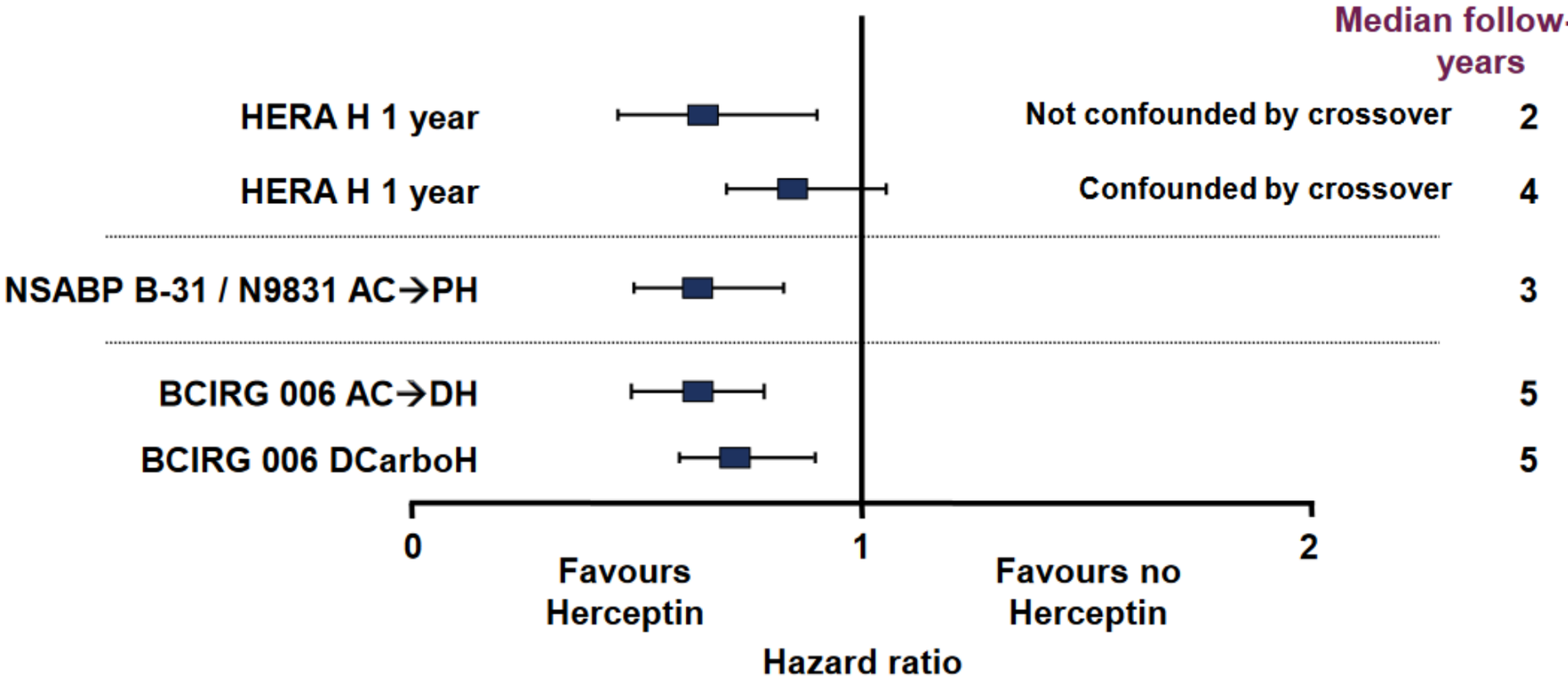
PCR

Enf residual

¿Cuál es la mejor opción?

Diapositiva propia

Trastuzumab for 1 year improves OS in HER2-positive Early Breast Cancer



OS, overall survival; Carbo, carboplatin

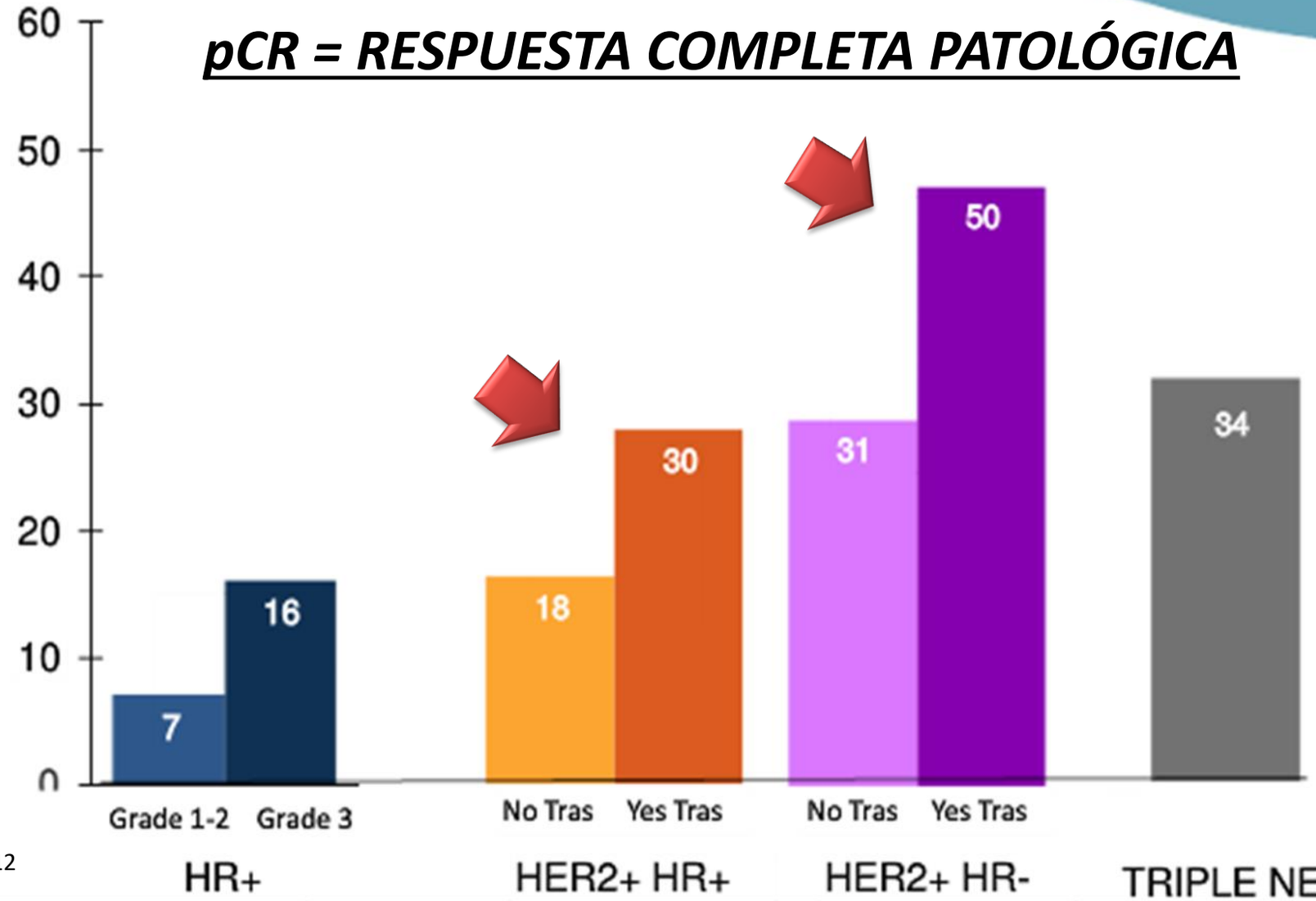
Perez et al 2007; Smith at al 2007; Gianni et al 2009; Slamon et al 2009

San Antonio Breast Cancer Symposium – December 4 - 8, 2012

pCR Rates by Tumor Subtypes

CTNeoBC

pCR = RESPUESTA COMPLETA PATOLÓGICA



Cortazar P, et al: SABCS 2012

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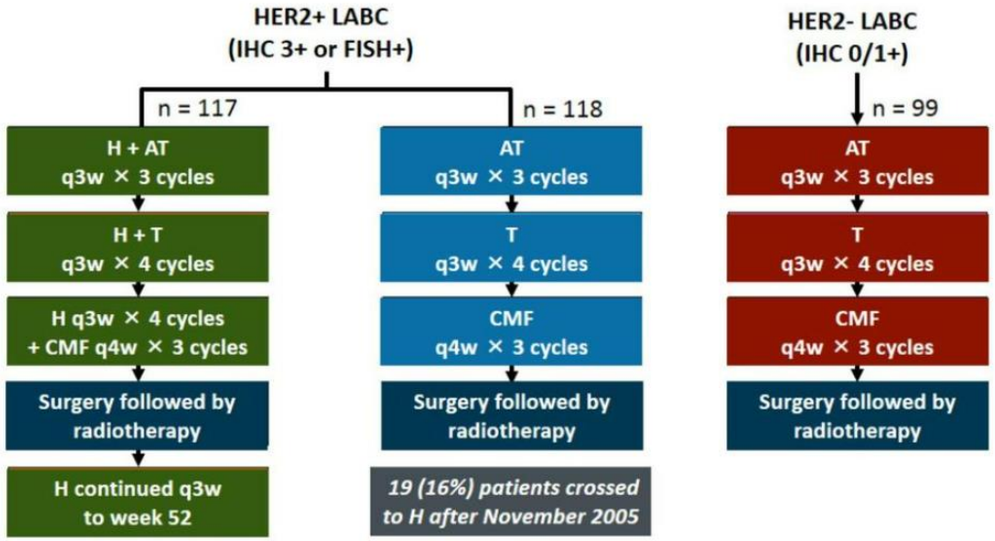
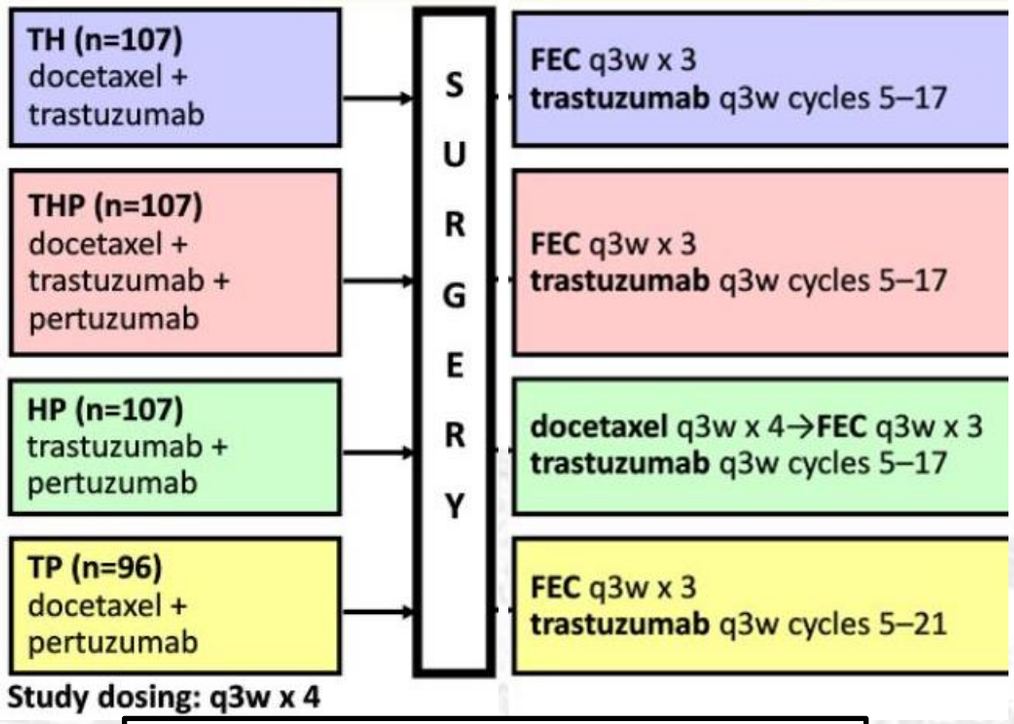
NOAH trial



- Gianni et al. *Lancet.* 2010; 375: 377-384

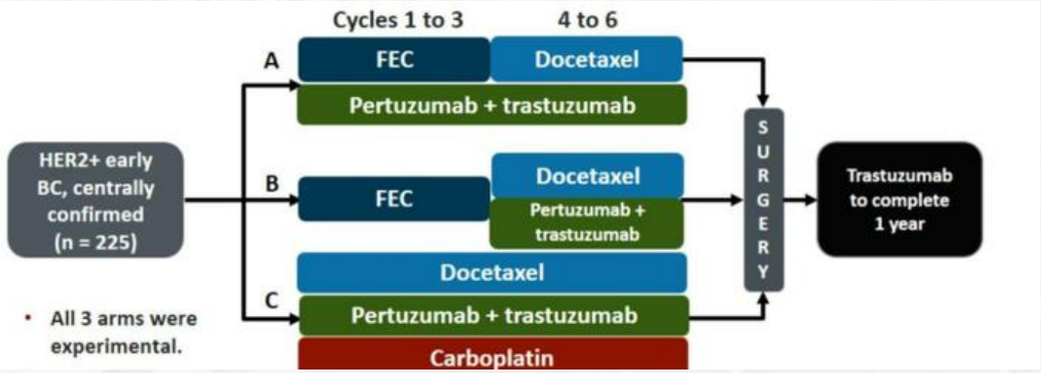
NeoSphere Trial

n=417
(1:1:1:1)
60% operables
45% N1
TTmediana 5 cm
47% RH+



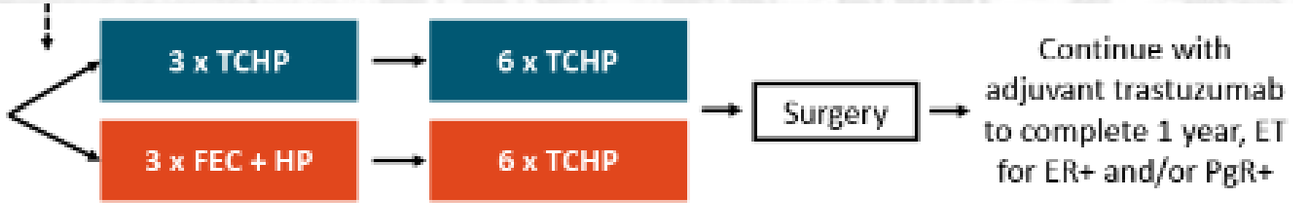
- Gianni et al. *Lancet Oncol.* 2012; 13: 25-32

Tryphaena trial



- Schneeweiss et al. Eur J Cancer. 2018 Jan;89:27-35

Train2 trial



- van Ramshorst et al. Lancet Oncol. 2018 Dec;19(12):1630-1640

Table 1. Rates of pathologic complete response (pCR) in HER2-positive subtypes.

Clinical Trial	Dual HER2 Therapy	pCR Rate with Single Anti-HER2 Agent (%)	pCR Rate with Dual Anti-HER2 Therapy (%)
NeoALTTO [38]	L + T	30 (95% CI, 22.4–37.5) with T 25 (95% CI, 18.1–32.3) with L	51 (95% CI, 43.1–59.5; $p = 0.0001$)
NeoSphere [39]	T + P	29 (95% CI, 20.6–38.5) with T 24 (95% CI, 15.8–33.7) with P	46 (95% CI, 36.1–55.7; $p = 0.0141$)
CALGB 40601 [40]	L + T	40 (95% CI, 32–49) with T 32 (95% CI, 22–44) with L	51 (95% CI, 42–60; $p = 0.11$)
NSABP B-41 [41]	L + T	53 (95% CI, 44.9–59.5) with T 53 (95% CI, 44.4–60.3) with L	62 (95% CI, 54.3–68.8; $p = 0.095$)
TRYPHAENA [36]	T + P	NA	57–66

HER2: human epidermal growth factor receptor; L: lapatinib; T: trastuzumab; P: pertuzumab; pCR: pathologic complete response; NA: not available.

30-50%

50-65%

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Hikmat Abdel-Razeq et al. Curr. Oncol. 2022,29, 5810–5822

pCR Rates Are Lower for ER-Positive HER2-Positive With Chemotherapy and Anti-HER2 Therapy

Trial	pCR in ER+ HER2-Positive	pCR in ER-Negative HER2-Positive
NeoALTTO[a,b]	42%	61%
CALGB 40601[c]	41%	79%
NSABP B-41[d]	56%	73%
NeoSphere[e]	26%	63%
NOAH[f]	30%	51%
Kristine[g]	45%	60%
TRYPHAENA[h]	46%	65%
TRAIN-2[i]	51%	84%

40-50%

60-85%

a. Baselga J, et al. Lancet Oncol. 2017;18:904-916; b. deAzambuja E, et al. Lancet ...37-1146; c. Carey L, et al. J Clin Oncol. 20... Robidoux A, et al. Lancet Oncol. 2013;14:1183-1192; e. Gianni L, et al. Lancet Oncol. 2012;13:25-32; f. Gia... ...010;375:377-384; g. Hurvitz S, et al. La... ...:115-126; h. Schneeweiss A, et al. Ann Oncol. 2013;24:2278-2284; i. Metteet D, et al. J Clin Oncol. 2017;35[illegible]

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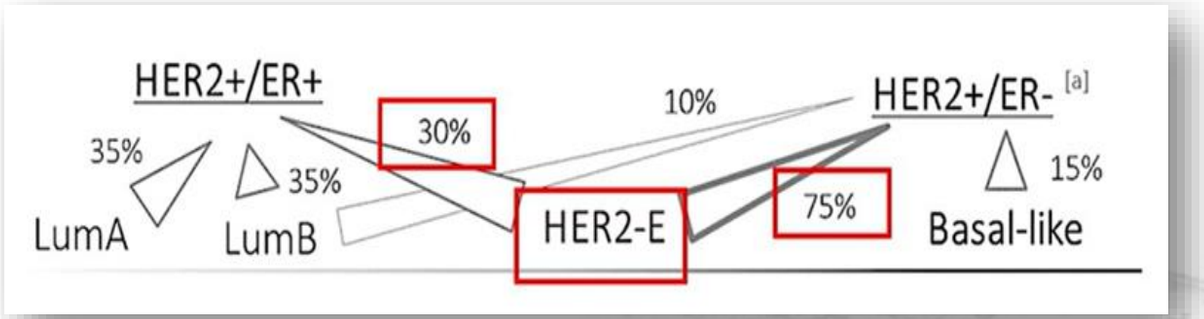
ER-Positive HER2-Positive: Why Lower pCR?

- Less often HER2E
- Lower TILs/ immune activation
- More HER2 heterogeneity
- More often PIK3CA mutated



a. Brandao M, et al. Clin Cancer Res. 2020;26:2783-2788; b. Schettini F, et al. Cancer Treat Rev. 2020;84:101965.

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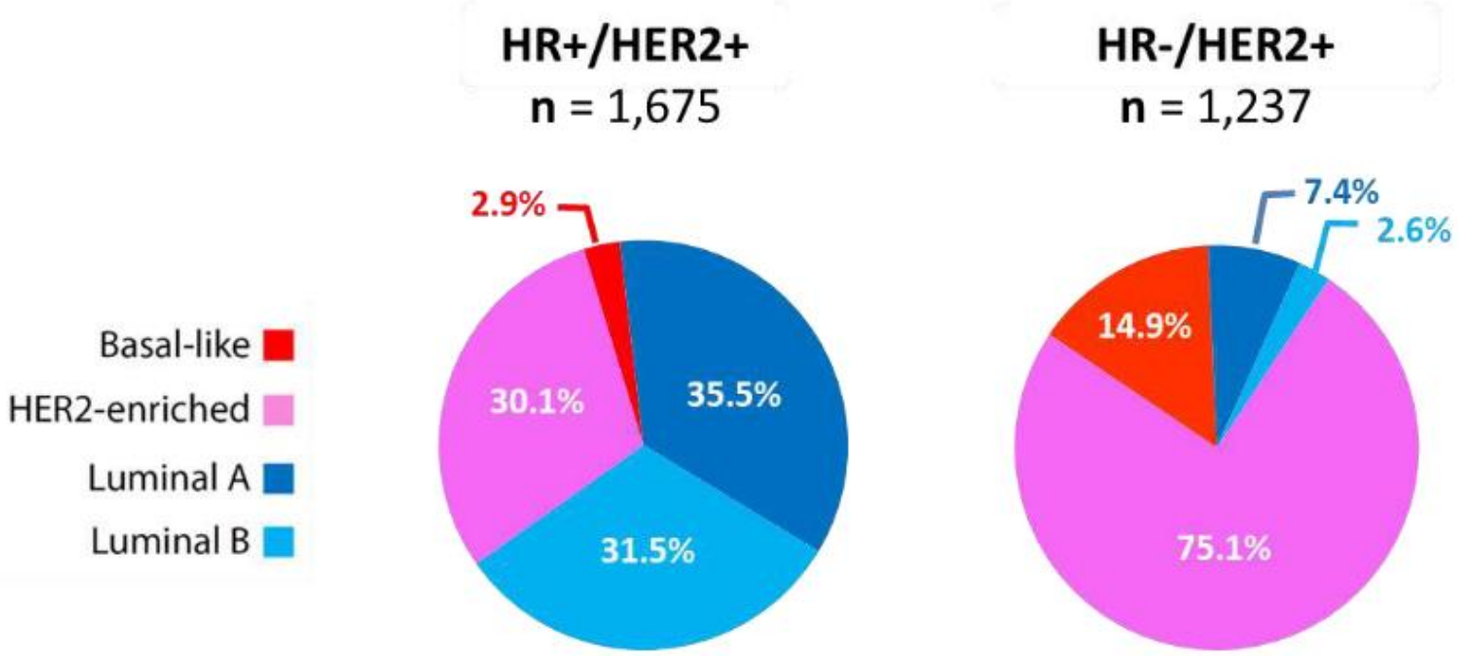
Intrinsic subtypes in HER2+



HR status ≠ intrinsic subtype

Basal-like tumors are rare but exist!

HER2-E subtype represents 50-60% of all HER2+ tumors

1. Cancer Genome Atlas Network Nature 2012; 490:61–70
2. Prat et al. J Natl Cancer Inst. 2014;106 (8)
3. Cejalvo et al. Cancer Treat Rev 2018
4. Cejalvo JM, et al. Ann Oncol. 2017 vol 28 suppl 5

HER2-Enriched Subtype (HER2E) And Association With pCR After Her2-Based Preoperative Chemotherapy

	NOAH[a]	Neo ALTTO[b]	CALGB 40601[c]	CherLOB [d]	ICO+ CLINIC[e]	OPTIHER[f]	KRISTINE [g]	KRISTINE [g]	BERENICE [h]
Therapy	**AT** +H	**T** +L/H/LH	**T** +L/H/LH	**AT** +L/H/LH	**AT** +H	**AT** +H+P	**T-DM1** +P	**DC** +H+P	**A T** +H+P
N	63	254	265	64	154	58	183	171	294
Variable	pCR_{BA}	pCR_{B}	pCR_{B}	pCR_{BA}	pCR_{BA}	pCR_{BA} rate	pCR_{BA}	pCR_{BA}	pCR_{BA}
pCR in HER2E (mean, 63.9%)	52.9%	52.0%	65.8%	50.0%	63.4%	83.3%	62.2%	72.1%	74.2%
pCR in non-HER2E (mean, 29.3%)	34.5%	21.5%	31.1%	17.0%	26.2%	46.43%	26.9%	32.8%	26.9%
***P*-value**	.014	< .001	< .001	.008	< .001	.003	< .001	< .001	< .001

AT, anthracycline/taxane; C, carboplatin; D, docetaxel; H, herceptin; L, lapatinib; P, pertuzumab; T, paclitaxel.

a. Prat A, et al. Clin Cancer Res. 2014;20:511-521; b. Fumagalli D, et al. JAMA Oncol. 2017;3:227-234; c. Carey LA, et al. J Clin Oncol. 2016;34:542-549; d. Dieci MV, et al. Ann Oncol 2019;30:418-423. e. Pernas S, et al. Cancer Res. 2018;78(4 Suppl):P2-09-11; f. Gavilá J, et al. Cancer Res. 2018;78(4 Suppl): P2-09-04. g. Prat A, et al. Cancer Res. 2018;78(4 Suppl):PD3-06; h. Swain SM, Ann Oncol. 2018 ;29:646-653

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- More HER2 heterogeneity
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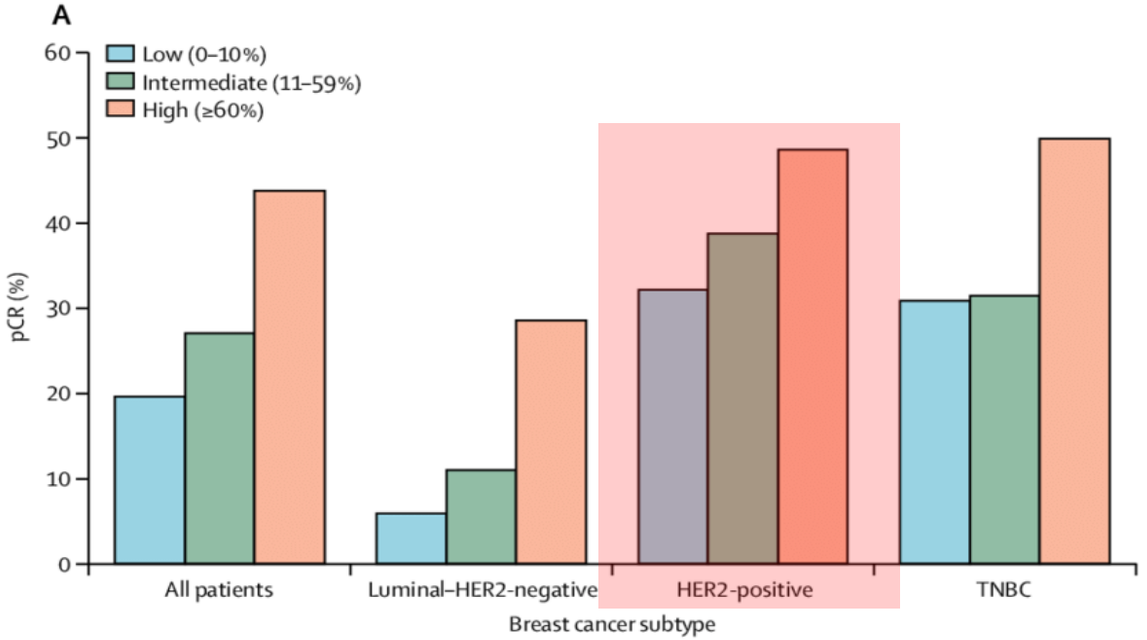
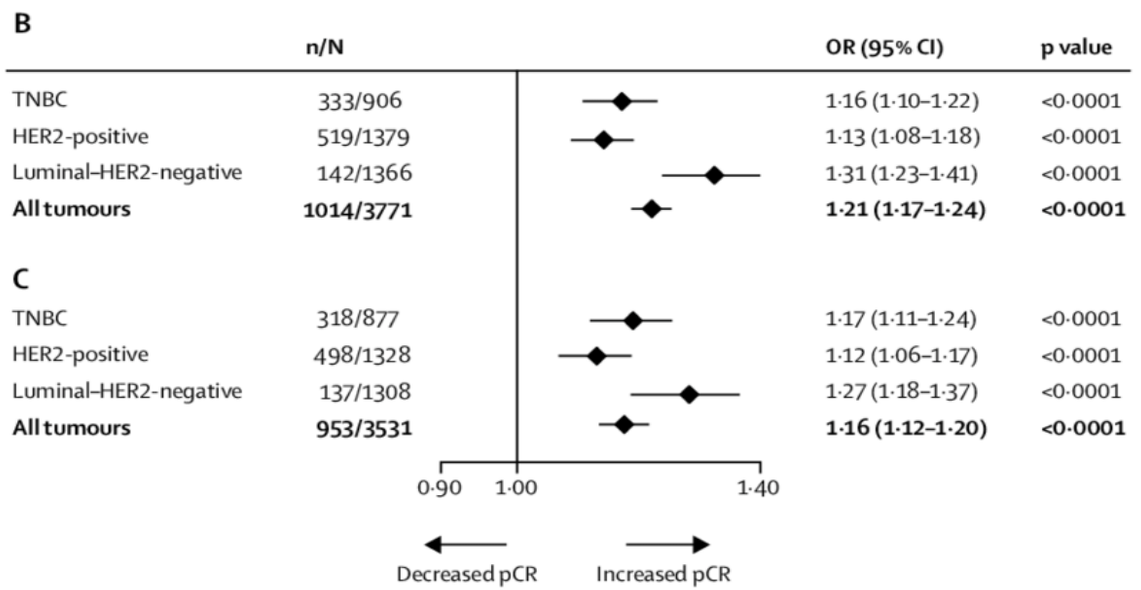
- But despite lower pCR compared with ER-negative HER2-positive tumors, the HR- HER2-positive tumors have better outcome





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Abstract S1-09: Evaluation of tumor-infiltrating lymphocytes (TILs) as predictive and prognostic biomarker in different subtypes of breast cancer treated with neoadjuvant therapy - A metaanalysis of 3771 patients DOI- 10.1158/1538-7445.SABCS16-S1-09 - Cancer Research

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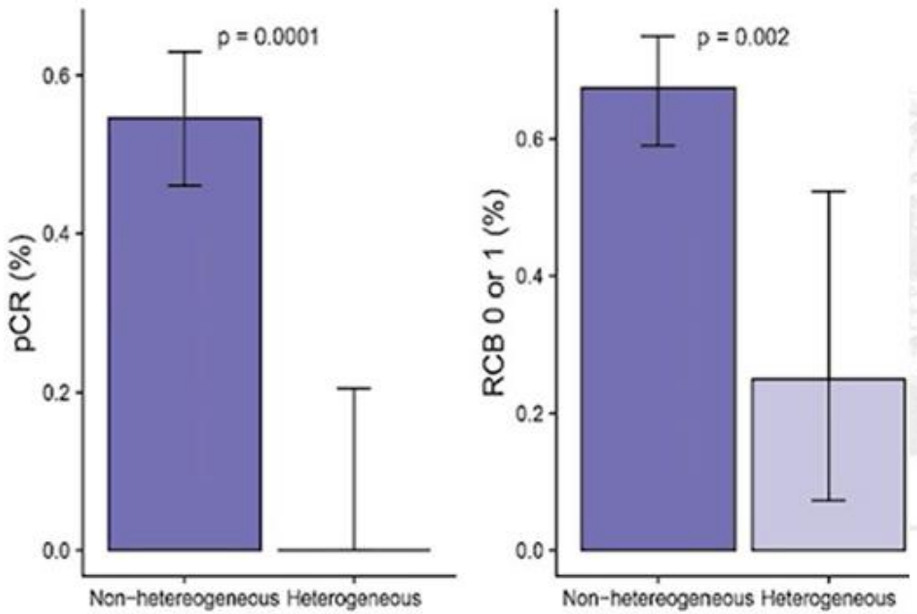
Figure 2[c]



Phase 2 study of neoadjuvant T-DM1 + pertuzumab[c]

- Heterogeneity defined as:
  - HER2-positive (FISH) in > 5% to < 50% tumor cells[a] or
  - An area of tumor that tested HER2-negative
- 10% (16/157) tumors had HER2 heterogeneity[c]
- 81% of tumors (N = 13) with heterogeneity were ER+[b]
- pCR[a]:
  - 0% for heterogeneous tumors
  - 55% for tumors without HER2 heterogeneity[a]

a. Seol H, et al. Mod Pathol. 2012;25:938-948; b. Ohlschlegel C, et al. J Clin Pathol. 2011;64:1112-1116; c. Metzger Filho O, et al. Cancer Discovery. 2021;11:2474-2487.

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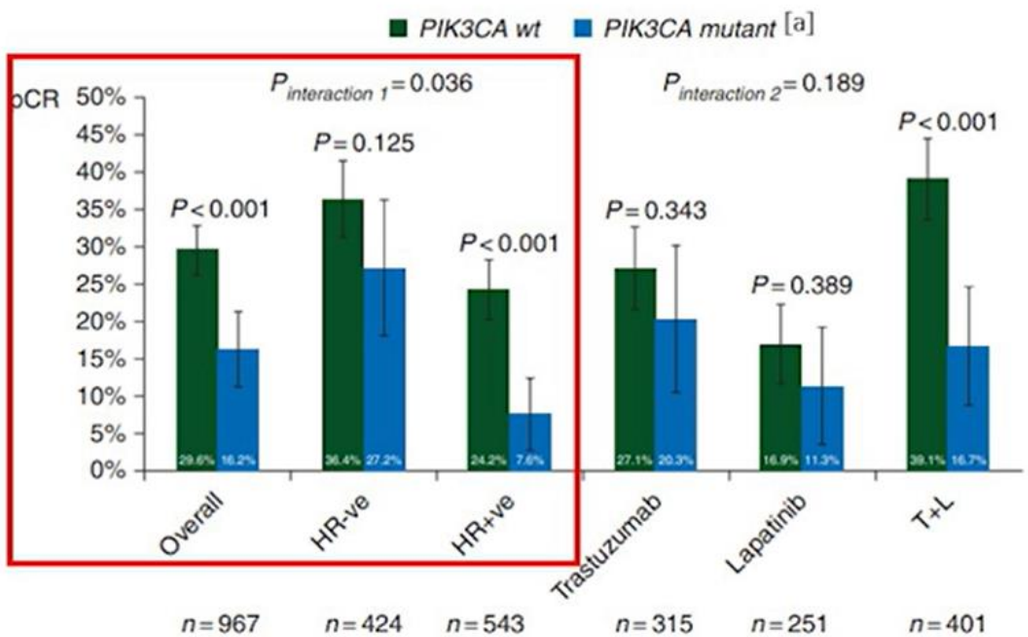
- More often PIK3CA
- But despite lower pC ER-negative HER2-p HER2-positive tumo

PIK3CA Mutations Associated With Lower pCR

- Overall ~22% of HER2-positive BC have a PIK3CA mutation[a]
- In pooled analysis of 5 RCT using taxane, trastuzumab and lapatinib, **PIK3CA mutation predicted for lower pCR, mainly among ER-positive HER2-positive**[b,c]



a. Zardavas D, et al. J Clin Oncol. 2018;36:981-990; b. Loibl S, et al. Ann Oncol. 2016;27:1519-1525; c. Loibl S, et al. Nature. 2012;490:61-70.

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Discrepancy between individual patient's level and trial level

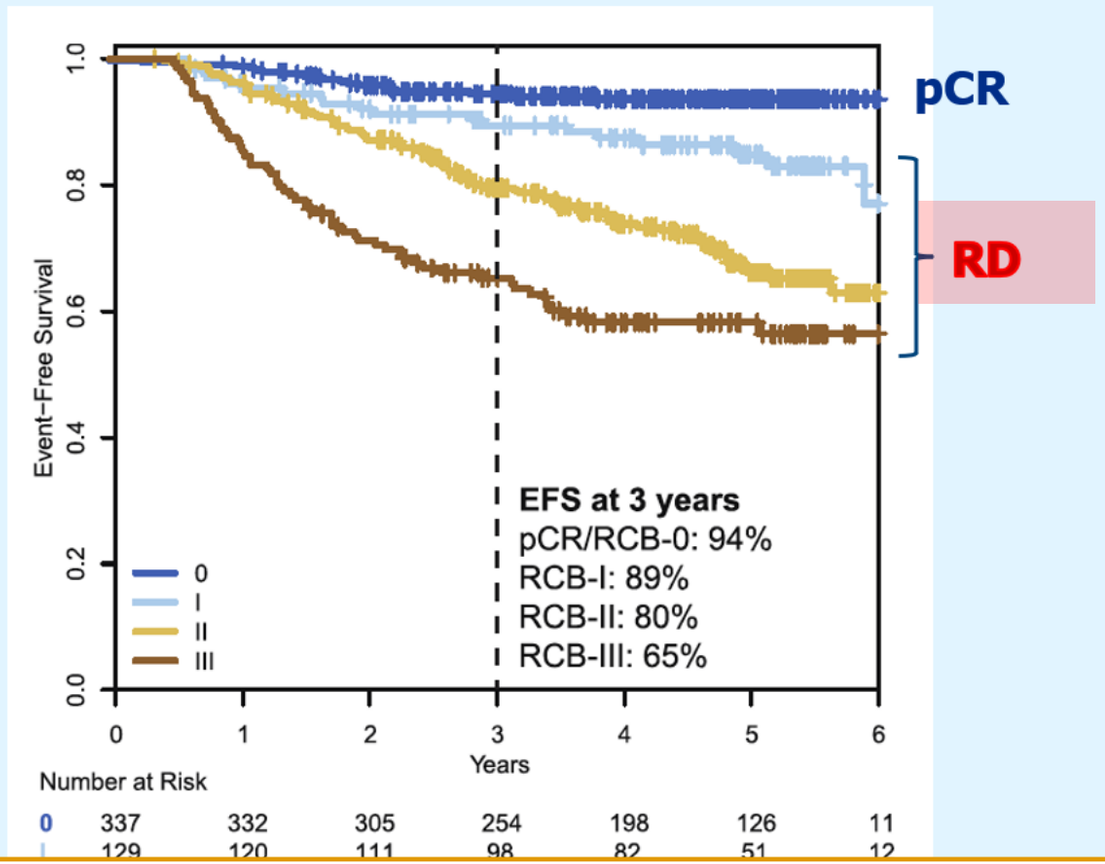
- pCR is a direct measure of treatment effect
- Efficacy measured as EFS and OS depends on:
  - Treatment effect
  - Tumor characteristics not captured by selection criteria (HER2 3+/gene amplification)
  - Intrinsic prognosis of the patient

Not all pCRs are equally "good"

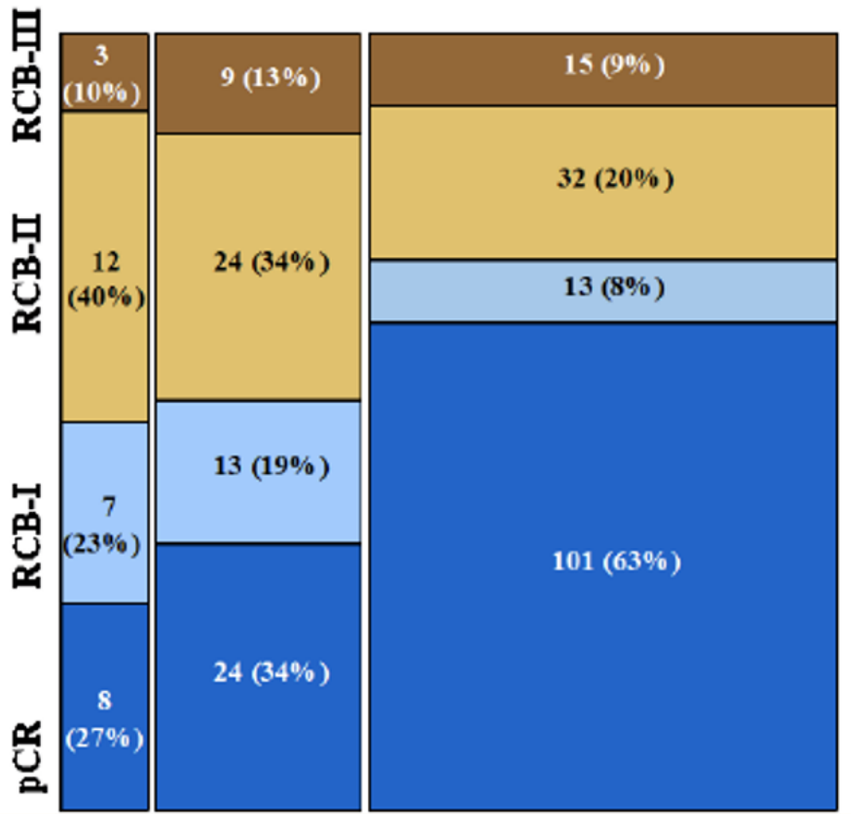
Not all RDs are "bad"

Recurrence Cancer Burden (RCB) in I-SPY2

All patients



HER2+



RCB termina el pronóstico con mayor granularidad respecto al valor dicotómico de pCR vs enf. residual

PERSONALIZING TREATMENT FOR HER2+ EBC

DE-ESCALATION	STANDARD TREATMENT	ESCALATION
	Anthra-tax-based CT + Trastuzumab x 1 y (concurrent to tax → alone to complete 1 y)	

Phergain Trial

Her2Dx

Gold estándar en neoadyuvancia

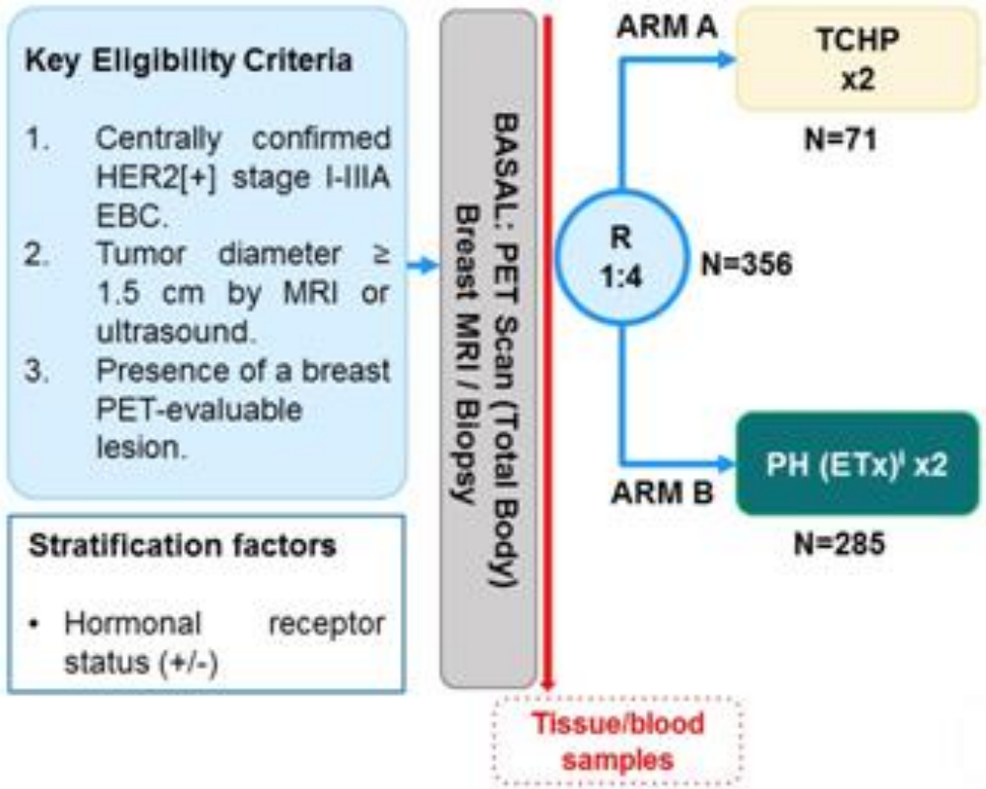
ESMO BREAST CANCER

MEDSIR

Chemotherapy (CT) De-Escalation using an FDG-PET/CT (PET) and Pathological Response-Adapted Strategy in HER2[+] Early Breast Cancer (EBC). PHERGAIN trial

Javier Cortés[1], Geraldine Gebhart[2], Manuel Ruiz Borrego[3], Agostina Stradella[4], Begoña Bermejo[5], Santiago Escrivá-de-Romaní[6], Lourdes Calvo[7], Núria Ribelles[8], Noelia Martinez[9], Cinta Albacar[10], Aleix Prat[11], Florence Dalenc[12], Kerrou Khaldoun[13], Peter Schmid[14], Marco Colleoni[15], Frederik Marmé[16], Noemia Afonso[17], Miguel Sampayo-Cordero[18], José Manuel Pérez-García[19], Antonio Llombart-Cussac[20]

PET respondedores:
SUV reducción ≥40%
posterior a 2 ciclos



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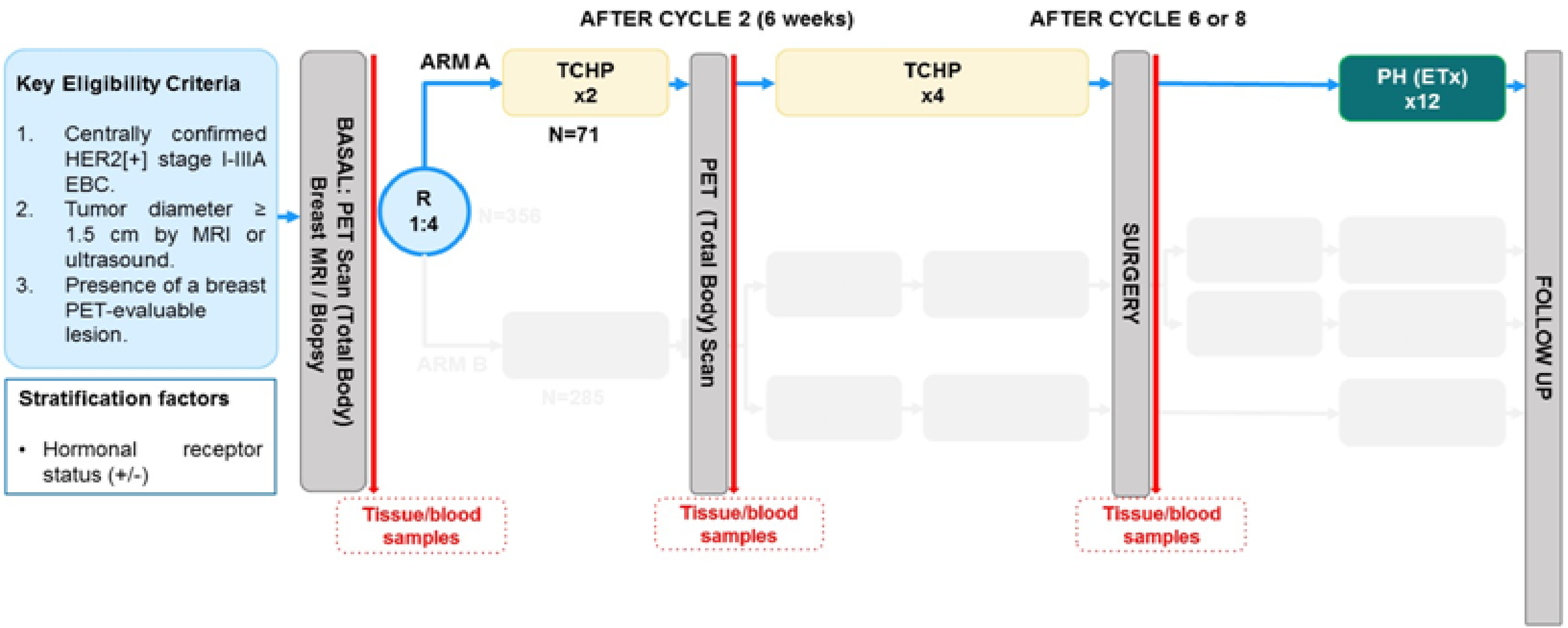

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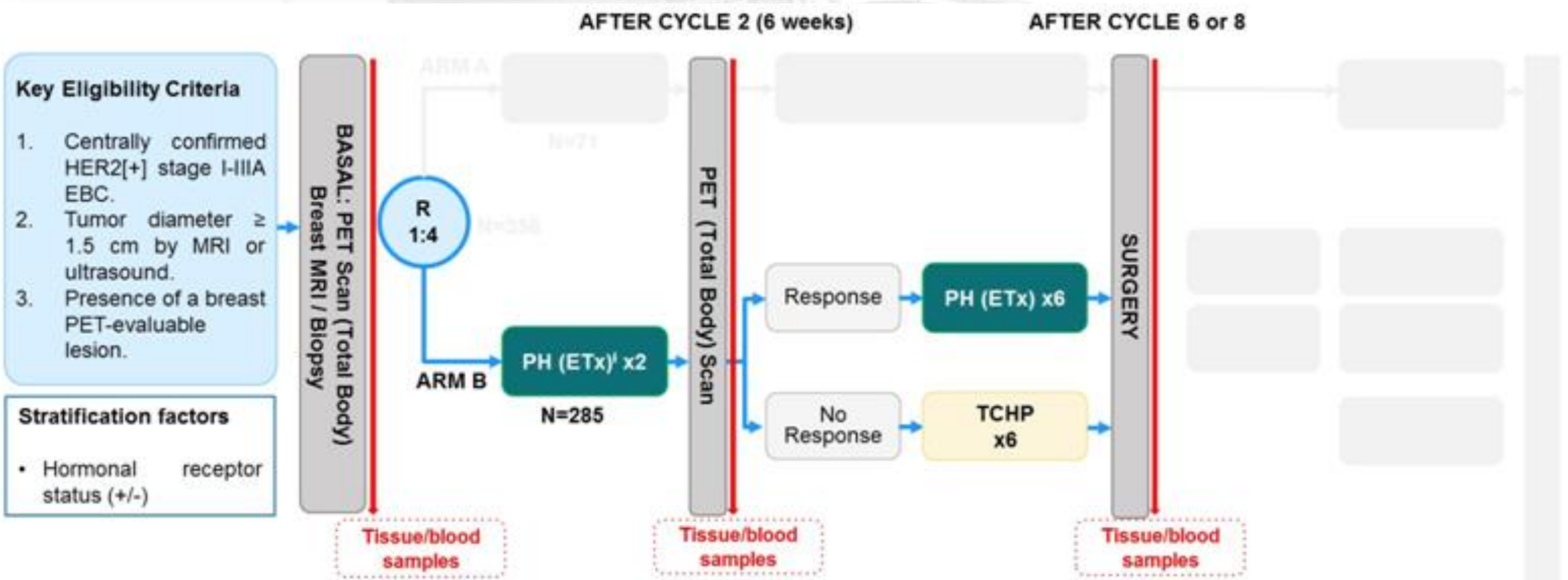

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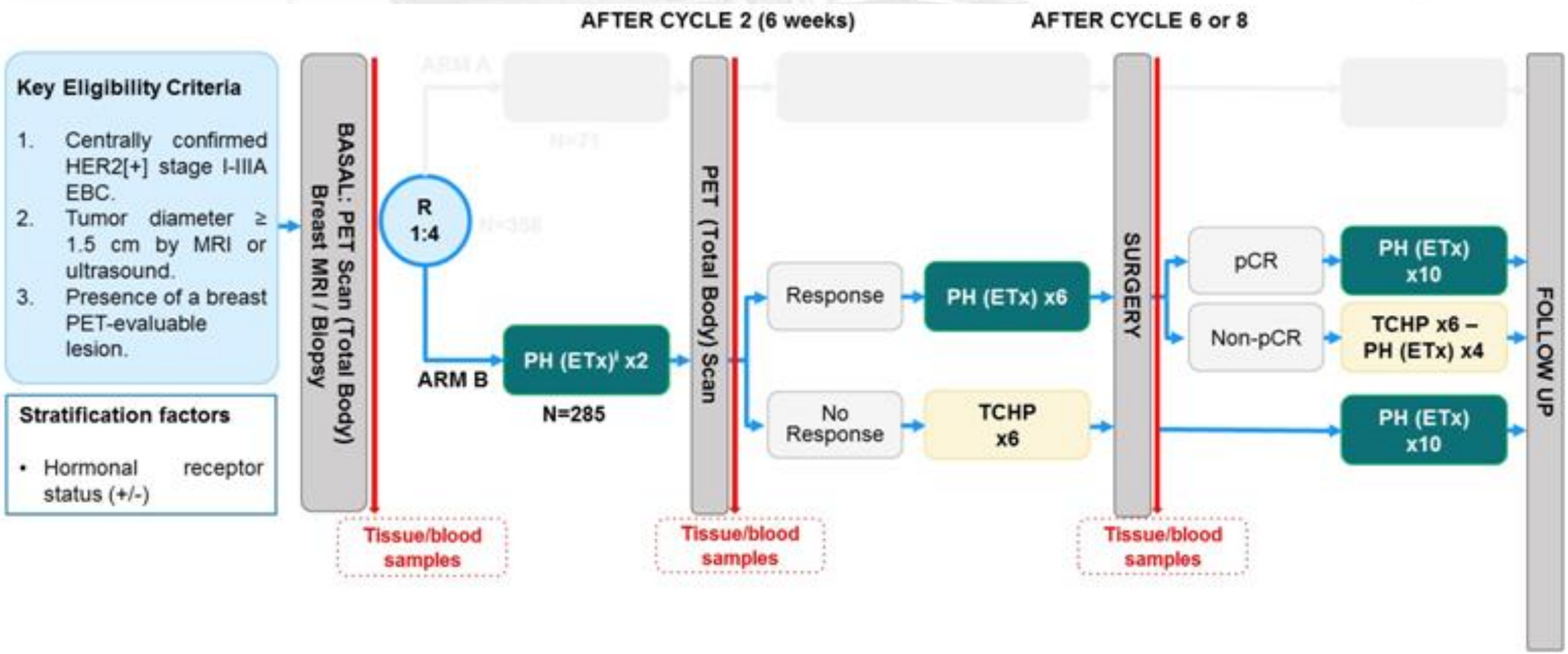
Chemotherapy (CT) De-Escalation using an FDG-PET/CT (PET) and Pathological Response-Adapted Strategy in HER2[+] Early Breast Cancer (EBC). PHERGAIN trial

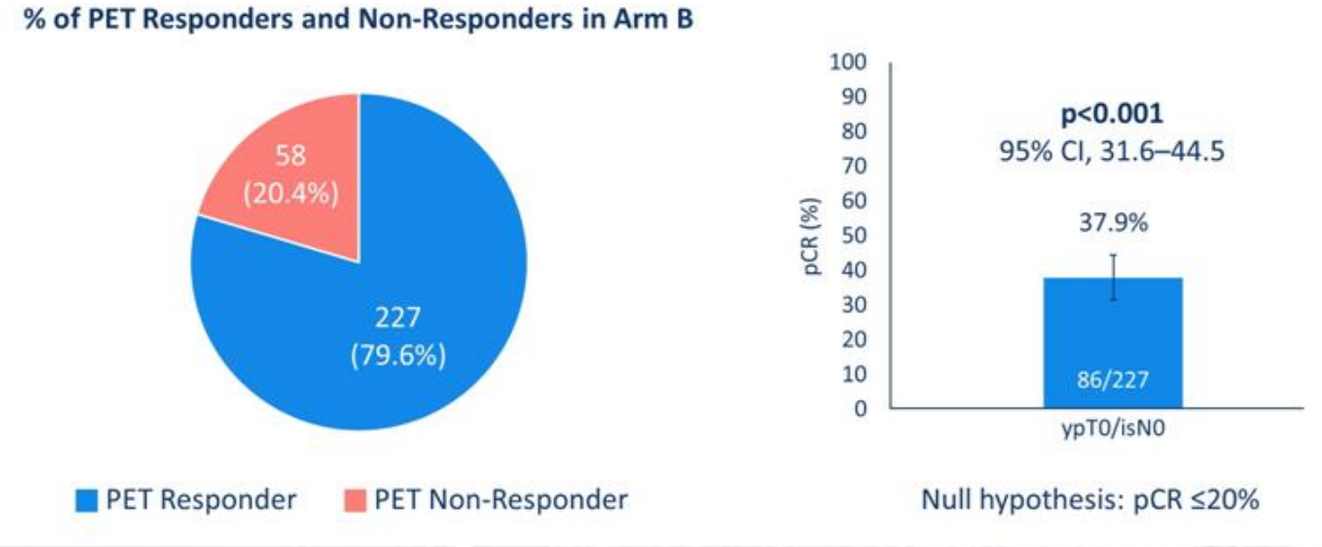
Javier Cortés[1], Geraldine Gebhart[2], Manuel Ruiz Borrego[3], Agostina Stradella[4], Begoña Bermejo[5], Santiago Escrivá-de-Romaní[6], Lourdes Calvo[7], Núria Ribelles[8], Noelia Martinez[9], Cinta Albacar[10], Aleix Prat[11], Florence Dalenc[12], Kerrou Khaldoun[13], Peter Schmid[14], Marco Colleoni[15], Frederik Marmé[16], Noemia Afonso[17], Miguel Sampayo-Cordero[18], José Manuel Pérez-García[19], Antonio Llombart-Cussac[20]

PET respondedores:
SUV reducción ≥40%
posterior a 2 ciclos



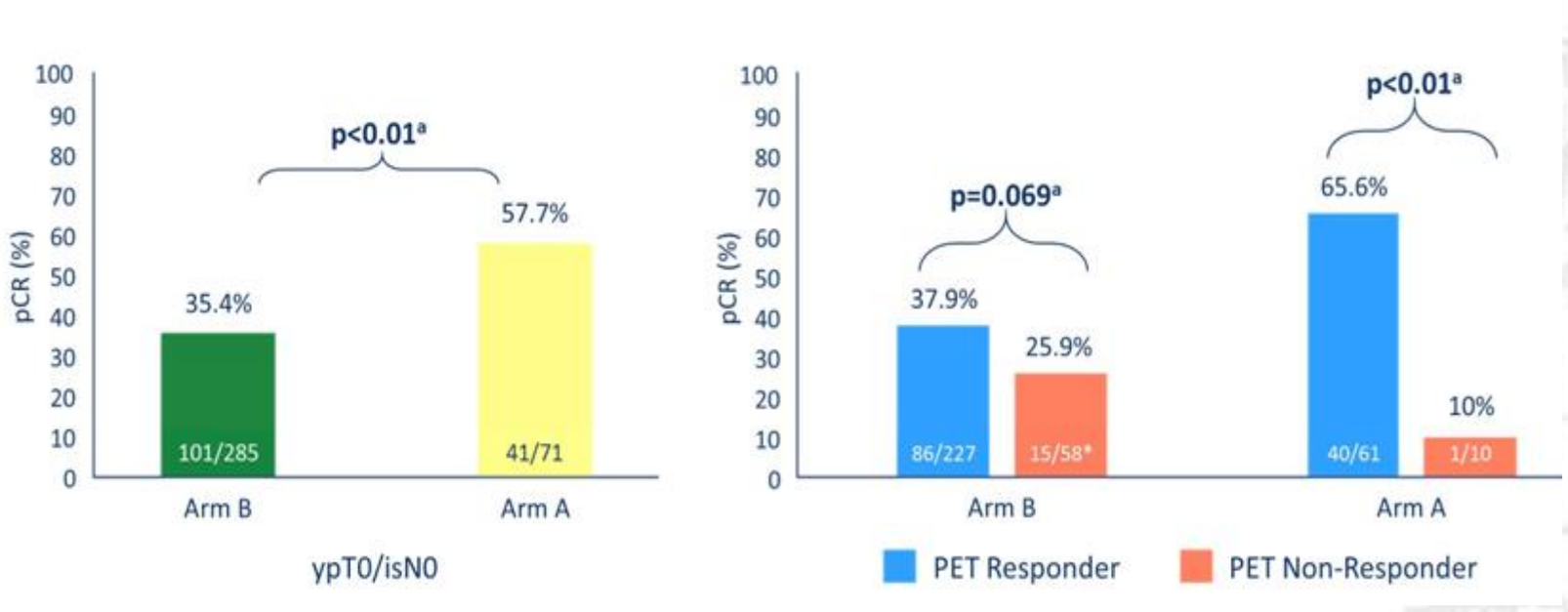
pCR en respondedores por PET (Rama B)

- 80% tuvieron rta por PET.
- Los que tuvieron rta, 38% tuvo pCR (SIN QT)

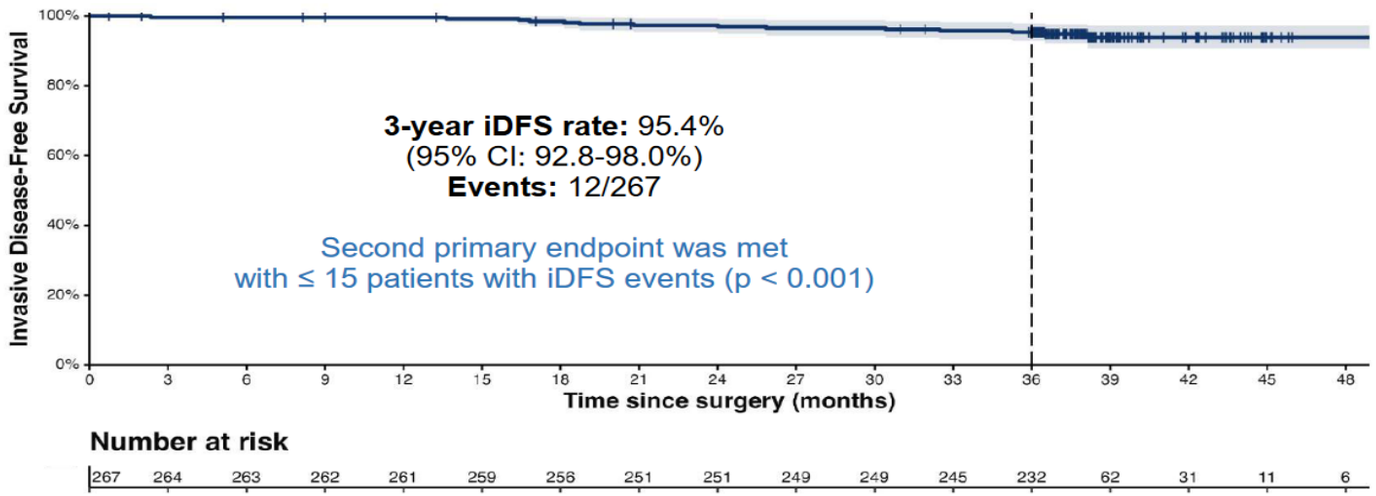


pCR en Rama A y B

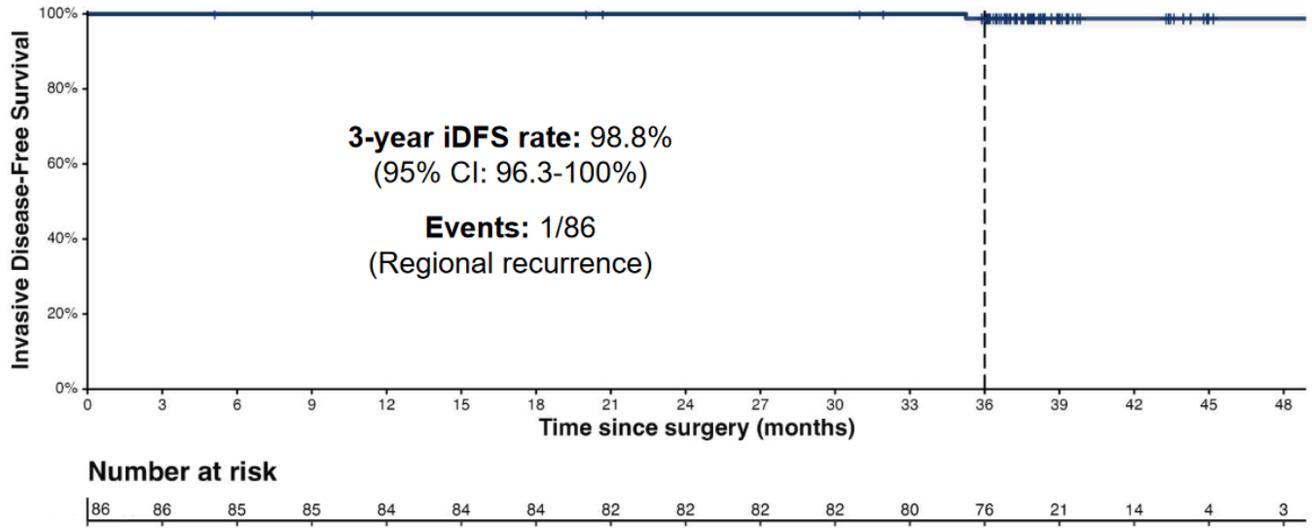
- Los que no respondieron y pasaron a la rama TCHP por 6 tuvieron igualmente baja pCR (26%)



Second Primary: iDFS (Arm B)



Subgroup analysis:
3-y iDFS rate without CT in PET responders with pCR (Group B)



CONCLUSIONES

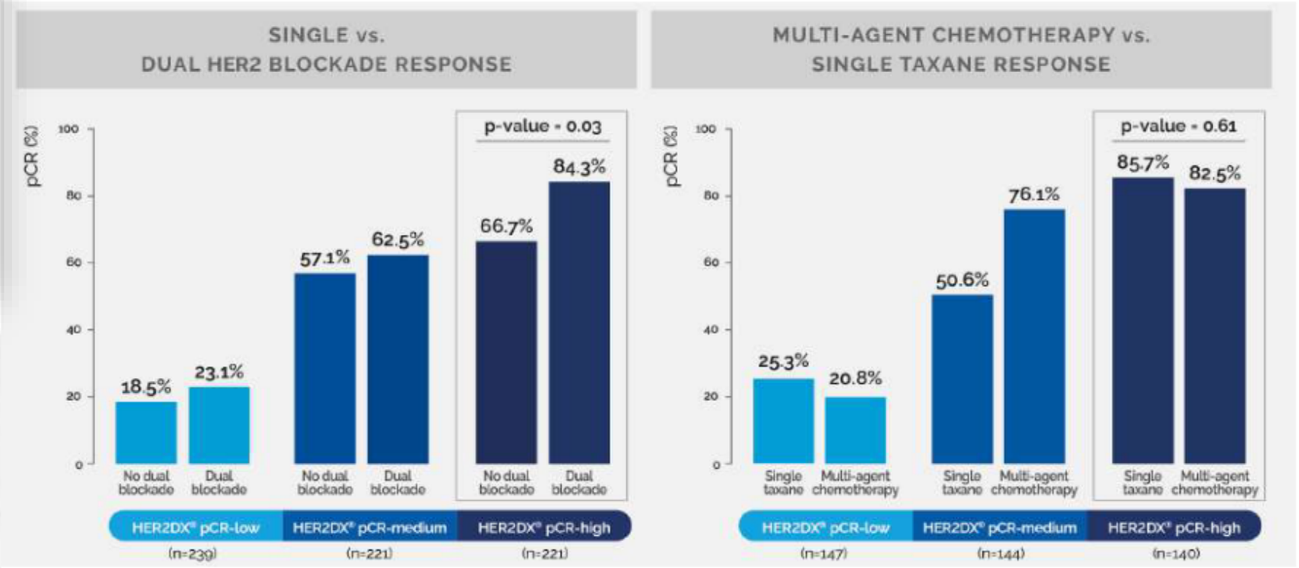
- 37.9% pts que iniciaron T+P (± HT) con respuesta por PET tuvieron pCR
- PET ayuda a determinar aquellos pacientes que lograran pCR con antiHER2 sin QT
- Esta estrategia sin QT no disminuye la posibilidad de cirugías conservadoras
- No impacto de omitir QT en pacientes con rta por PET y que no realizaron QT en neoadyuvancia

Cortes J, et al. ASCO 2023; Perez-Gracia J, et al. Lancet 2024 (in press)

HER2DX pCR score across 7 studies and 765 patients

- 27 genes
- 4 gene signatures
  - IGG/B-cell/plasma (14 genes)
  - Proliferation
  - luminal differentiation
  - HER2 amplicon expression

- **HER2DX risk-score**
- **HER2DX pCR-score**
- **HER2DX ERBB2-score**



80-90% pCR rates in pCR-high group when treated with a single taxane + HP (THP)

1/3 of patients have pCR-high disease

pCR-high and/or low-risk

Consider **single taxane + anti-HER2** instead of **multi-agent chemo + anti-HER2**

Villacampa et al. Ann Oncol 2023
Waks et al. JAMA Oncol 2023
Bueno-Muiño et al. JAMA Oncol 2023

ESMO WEBINAR SERIES

Prat et al. Lancet Oncol 2020
Prat et al. EBioMedicine 2022
Guarneri et al. EBioMedicine 2022
Brasó-Maristany et al. JNCI 2022

The future of ADC in HER2+ eBC

NEOADJUVANT

- **DESTINY-Breast11:** T-DXd +/− sequential THP vs. AC-THP[1] — Ph III
- **ADAPT-HER2-IV:** T-DXd vs. chemo/H/P[2] — Ph II
- **APTneo:** Pertuzumab + trastuzumab + paclitaxel (HPCT) + atezolizumab vs. AC + HPCT + atezolizumab vs. HPCT[3] — Ph III

POST-NEOADJUVANT / ADJUVANT

- **DESTINY-Breast05:** T-DXd vs. T-DM1[4] — Ph III
- **ATEMPT 2.0:** T-DM1 + trastuzumab vs. trastuzumab + paclitaxel[5] — Ph II
- **ADEPT**: Pertuzumab + trastuzumab + ET[6] — Ph II
- **ASTEFANIA:** Atezolizumab + T-DM1 vs. placebo + T-DM1[7] — Ph III
- **COMPASSHER2-RD:** Tucatinib + T-DM1 vs. T-DM1 + placebo[8] — Ph III

- **COMPASSHER2-pCR:** Neoadjuvant trastuzumab + pertuzumab + paclitaxel/nab-paclitaxel or docetaxel -> surgery within 42 days, post-neoadjuvant trastuzumab + pertuzumab ± SOC radiotherapy (if pCR), or T-DM1 ± SOC chemotherapy/hormone therapy (if residual disease)[9] — Ph II
- **PHERGAIN-2:** Neoadjuvant FDC SC trastuzumab + pertuzumab (± ET) followed by post-neoadjuvant FDC SC trastuzumab + pertuzumab or T-DM1 or chemotherapy before adjuvant T-DM1 (± ET)[10] — Ph II
- **DECRESCENDO**: Neoadjuvant FDC SC trastuzumab + pertuzumab + paclitaxel or docetaxel followed by post-neoadjuvant FDC SC trastuzumab + pertuzumab (if RCB=0) or T-DM1 (if RCB ≥1) or anthracycline-based chemotherapy before T-DM1 (if RCB ≥2)[11] — Ph II

Esmo Deep Dive in Breast Cancer. Javier Cortés MD PhD presentation

ESMO DEEP DIVE: BREAST CANCER

HER2+ EBC management algorithm

Dr. Cortés

sergio.rivero84@gmail.com
srivero@alexanderfleming.org
@SergioRiveroMD

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