II CURSO
DE RESIDENTES
DE SAOM

13 y 14 DE ABRIL 2018
GRANADA

Organizado por:

Sociedad Andaluza de Oncología Medica

Cáncer de mama localizado Her2 positivo y N negativo.
Opciones de Neoadyuvancia.

Natalia Luque Caro

Complejo Hospitalario de Jaén

DE ENTRADA SÓLO DECIROS…

… QUE NO CREO QUE OS ACLARE NADA

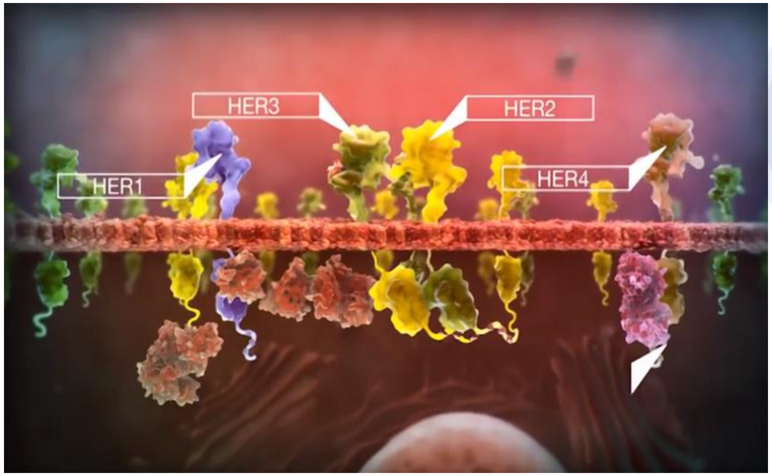
¡PERO A VER SI NO ACABAMOS ASÍ!

Cáncer de mama HER-2+

Organizado por:

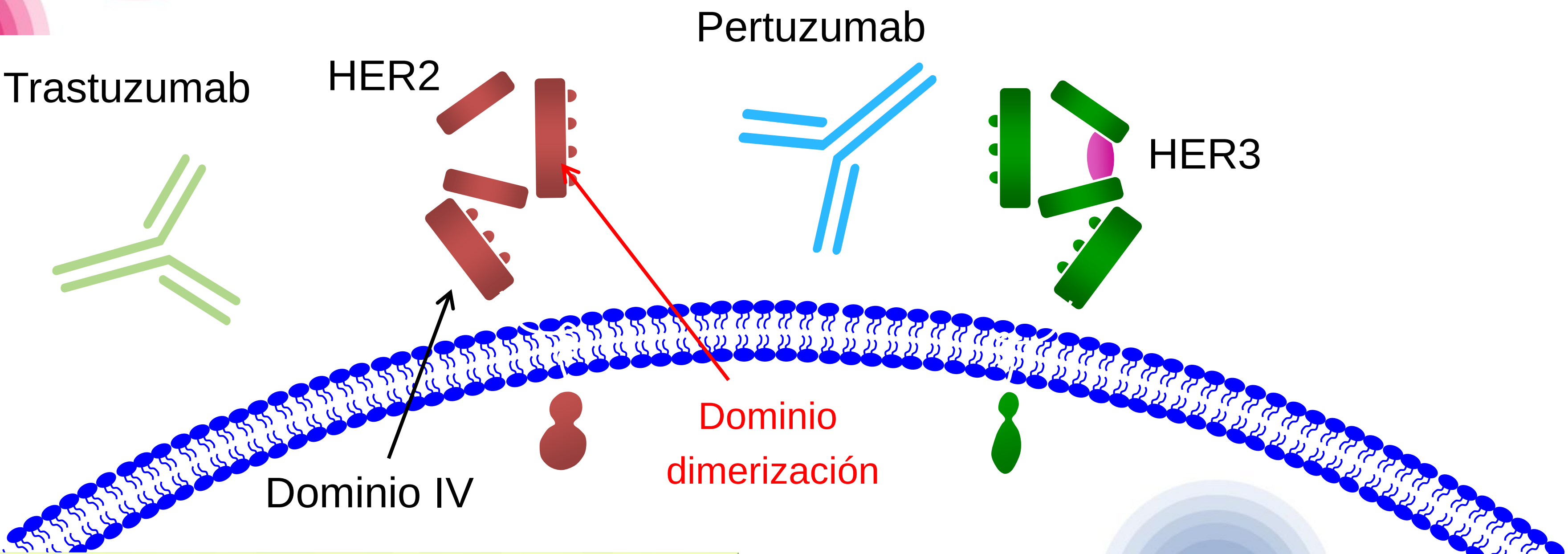
SAOM
Sociedad Andaluza de Oncología Medica

- 20-25% tumores de mama expresan HER-2+:
  - 22% estadio precoz
  - 35% tumores localmente avanzados y metastásicos
  - 40% tumores inflamatorios.
- Amplificación de HER2 es el principal mecanismo para la sobreexpresión de HER2 y es predictivo de respuesta.
- Familia HER2: cuatro receptores forman homo / heterodímeros implicdos en vías de proliferación y supervivencia celular.



Zell JA. Breast Cancer Res 2009.
Yarden Y. Nat Rev Mol Cell Biol 2001.

Terapia anti-HER2: Pertuzumab y Trastuzumab


Pertuzumab
Trastuzumab
HER2
HER3
Dominio dimerización
Dominio IV

Trastuzumab

- Inhibe la señal Her 2 independiente de ligando.
- Previene la formación de receptores truncados.
- Suprime múltiples vias de señalización de Her2.
- Activa el sistema inmunitario:

+

Pertuzumab

- Inhibe la dimerización del Her 2.
- Suprime múltiples vias de señalización de Her2.
- Activa el sistema inmunitario: media en la citotoxicidad celular dependiente de anticuerpos.

Fármacos anti HER-2 en cáncer de mama Neoadyuvante

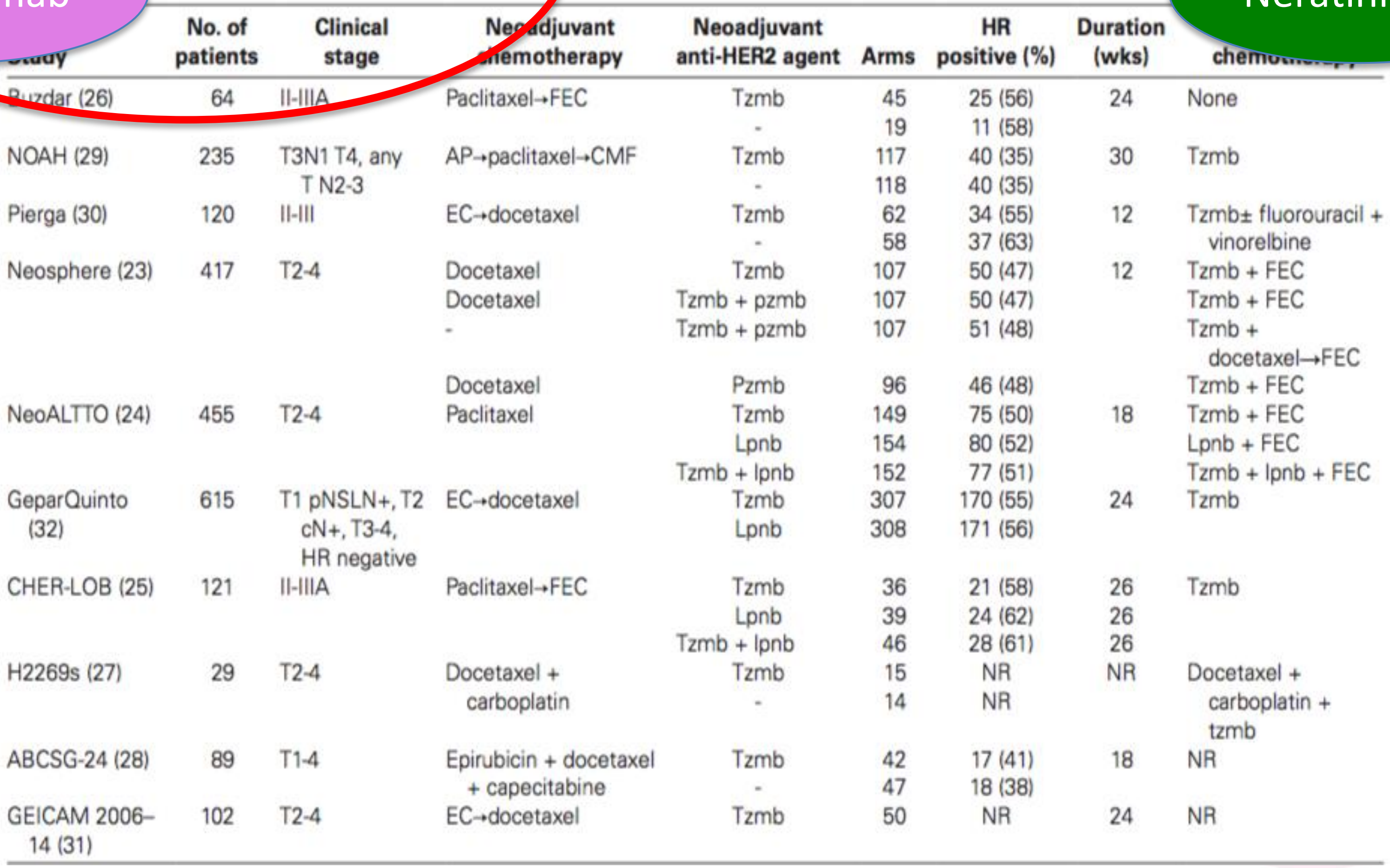
Pertuzumab

Lapatinib

TDM-1

Trastuzumab

Neratinib



Study	No. of patients	Clinical stage	Neoadjuvant chemotherapy	Neoadjuvant anti-HER2 agent	Arms	HR positive (%)	Duration (wks)	chemotherapy
Buzdar (26)	64	II-IIIA	Paclitaxel→FEC	Tzmb	45	25 (56)	24	None
				-	19	11 (58)		
NOAH (29)	235	T3N1 T4, any T N2-3	AP→paclitaxel→CMF	Tzmb	117	40 (35)	30	Tzmb
				-	118	40 (35)		
Pierga (30)	120	II-III	EC→docetaxel	Tzmb	62	34 (55)	12	Tzmb± fluorouracil + vinorelbine
				-	58	37 (63)		
Neosphere (23)	417	T2-4	Docetaxel	Tzmb	107	50 (47)	12	Tzmb + FEC
			Docetaxel	Tzmb + pzmb	107	50 (47)		Tzmb + FEC
			-	Tzmb + pzmb	107	51 (48)		Tzmb + docetaxel→FEC
			Docetaxel	Pzmb	96	46 (48)		Tzmb + FEC
NeoALTTO (24)	455	T2-4	Paclitaxel	Tzmb	149	75 (50)	18	Tzmb + FEC
				Lpnb	154	80 (52)		Lpnb + FEC
				Tzmb + lpnb	152	77 (51)		Tzmb + lpnb + FEC
GeparQuinto (32)	615	T1 pNSLN+, T2 cN+, T3-4, HR negative	EC→docetaxel	Tzmb	307	170 (55)	24	Tzmb
				Lpnb	308	171 (56)		
CHER-LOB (25)	121	II-IIIA	Paclitaxel→FEC	Tzmb	36	21 (58)	26	Tzmb
				Lpnb	39	24 (62)	26	
				Tzmb + lpnb	46	28 (61)	26	
H2269s (27)	29	T2-4	Docetaxel + carboplatin	Tzmb	15	NR	NR	Docetaxel + carboplatin + tzmb
				-	14	NR		
ABCSG-24 (28)	89	T1-4	Epirubicin + docetaxel + capecitabine	Tzmb	42	17 (41)	18	NR
				-	47	18 (38)		
GEICAM 2006–14 (31)	102	T2-4	EC→docetaxel	Tzmb	50	NR	24	NR

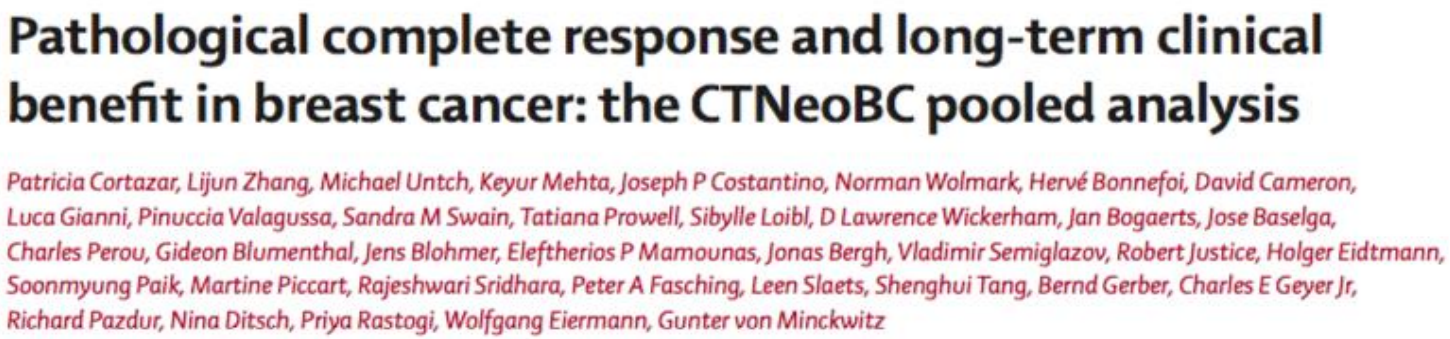
Por qué quimioterapia Neoadyuvante

- Resultados equivalentes si la quimioterapia se administra neo o adyuvante.
- Ventajas del tratamiento Neoadyuvante:
  - Disminución del tamaño tumoral → aumento de cirugías conservadoras
  - Evaluar la eficacia de fármacos
  - Testar "in vivo" la sensibilidad del tumor a un determinado tratamiento.
  - Mayor control sobre la micrometástasis
- Objetivos de los estudios con terapia neoadyuvante:
  - Respuesta completa patológica - pCR
  - Supervivencia global – OS
  - Supervivencia libre de eventos – EFS / PFS

Mauri D. JNCI 2005.
Tagliabue E. Lancet 2003.
Mauri D. J Natl Cancer Inst 2005.

VAMOS SIGUE CONTANDO
QUE ESTO SE PONE INTERESANTE
memegenerator.es

RESPUESTA COMPLETA PATOLÓGICA: pCR



Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis

Patricia Cortazar, Lijun Zhang, Michael Untch, Keyur Mehta, Joseph P Costantino, Norman Wolmark, Hervé Bonnefoi, David Cameron, Luca Gianni, Pinuccia Valagussa, Sandra M Swain, Tatiana Prowell, Sibylle Loibl, D Lawrence Wickerham, Jan Bogaerts, Jose Baselga, Charles Perou, Gideon Blumenthal, Jens Blohmer, Eleftherios P Mamounas, Jonas Bergh, Vladimir Semiglazov, Robert Justice, Holger Eidtmann, Soonmyung Paik, Martine Piccart, Rajeshwari Sridhara, Peter A Fasching, Leen Slaets, Shenghui Tang, Bernd Gerber, Charles E Geyer Jr, Richard Pazdur, Nina Ditsch, Priya Rastogi, Wolfgang Eiermann, Gunter von Minckwitz

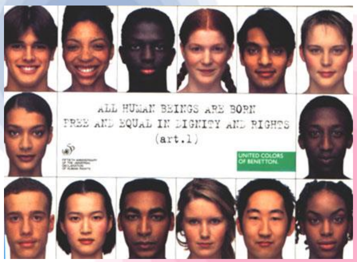
12 estudios / 11955 pacientes

Objetivos:

1 Asociación entre pCR y EFS /OS
2 Definición pCR que se correlaciona mejor con resultado a largo plazo
3 Identificar subtipos de cáncer de mama en los que pCR se correlaciona mejor con un resultado a largo plazo
4 Evaluar que magnitud de mejora de la pCR entre los grupos de tratamiento predice una mejor EFS /OS.

Población

T2: 61%
Inflamatorios: 4%
N+: 46%
RH-: 30%
HER2 +: 17%


ALL HUMAN BEINGS ARE BORN
FREE AND EQUAL IN DIGNITY AND RIGHTS
(art.1)
UNITED COLORS OF BENETTON

Cortazar P. Lancet 2014

Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis

Patricia Cortazar, Lijun Zhang, Michael Untch, Keyur Mehta, Joseph P Costantino, Norman Wolmark, Hervé Bonnefoi, David Cameron, Luca Gianni, Pinuccia Valagussa, Sandra M Swain, Tatiana Prowell, Sibylle Loibl, D Lawrence Wickerham, Jan Bogaerts, Jose Baselga, Charles Perou, Gideon Blumenthal, Jens Blohmer, Eleftherios P Mamounas, Jonas Bergh, Vladimir Semiglazov, Robert Justice, Holger Eidtmann, Soonmyung Paik, Martine Piccart, Rajeshwari Sridhara, Peter A Fasching, Leen Slaets, Shenghui Tang, Bernd Gerber, Charles E Geyer Jr, Richard Pazdur, Nina Ditsch, Priya Rastogi, Wolfgang Eiermann, Gunter von Minckwitz

12 estudios / 11955 pacientes

Objetivos:

1 Asociación entre pCR y DFE /OS

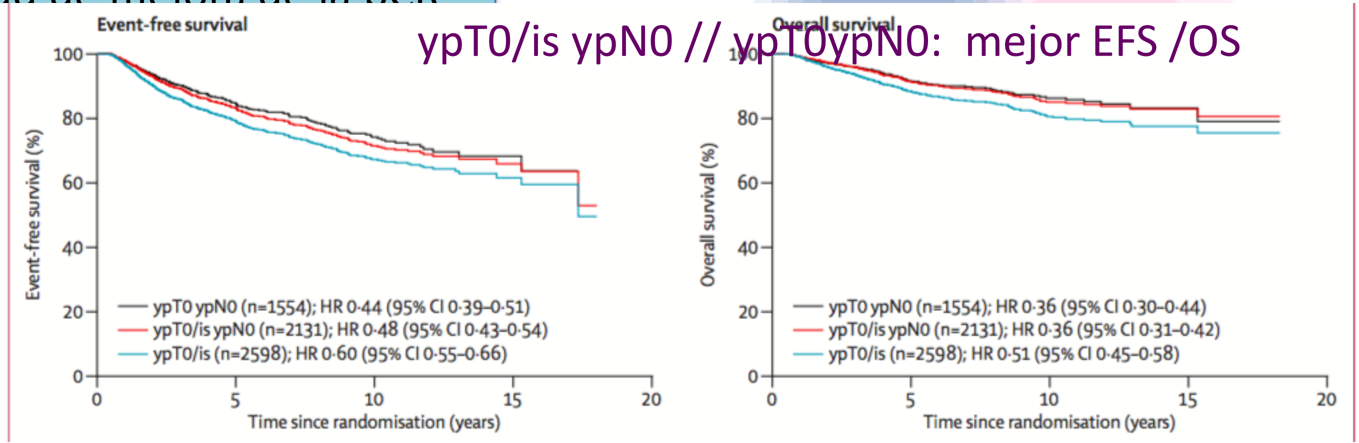
2 Definición pCR que se correlaciona mejor con resultado a largo plazo

3 Identificar subtipos de cáncer de mama en los que pCR se correlaciona mejor con un resultado a largo plazo

4 Evaluar que magnitud de mejora de la pCR entre los grupos de

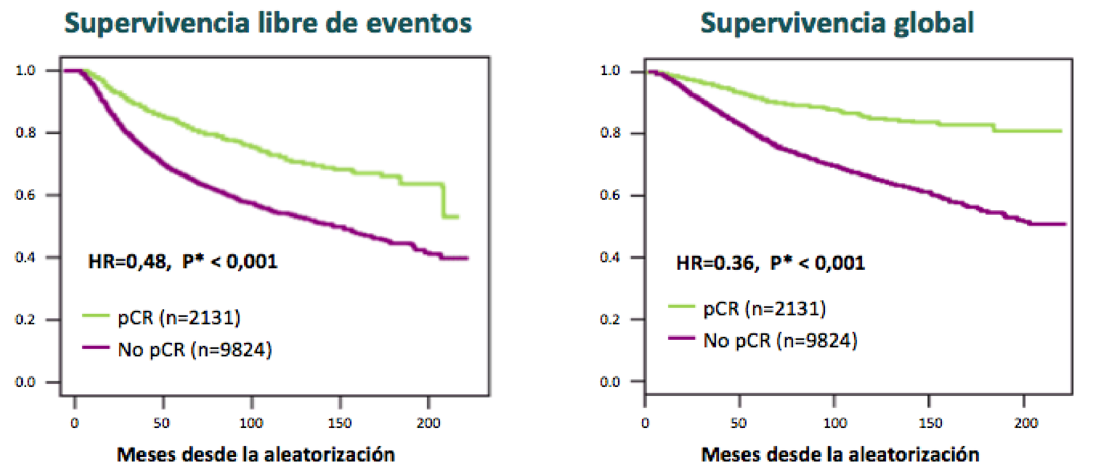
mejor DFE /OS.

pCR:
22% ypT0/is
18% ypT0/is ypN0
13 % ypT0ypN0



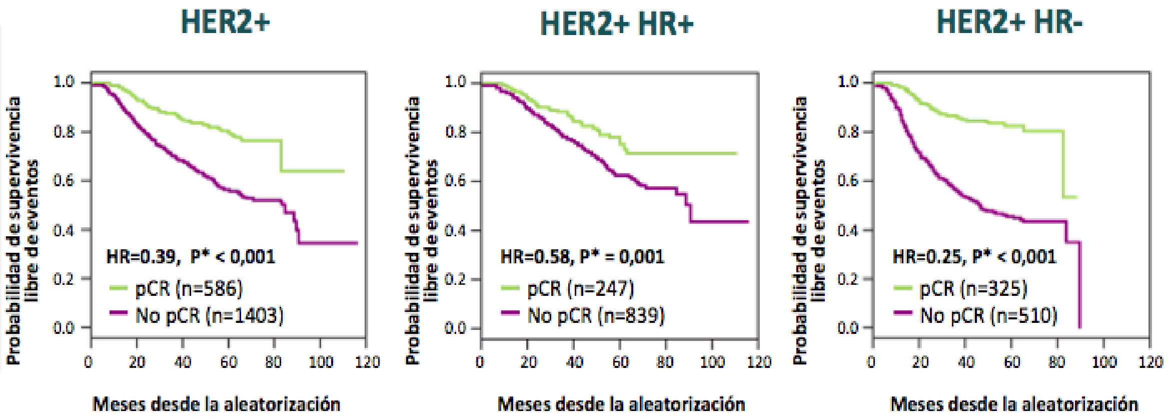
ypT0/is ypN0 // ypT0ypN0: mejor EFS /OS

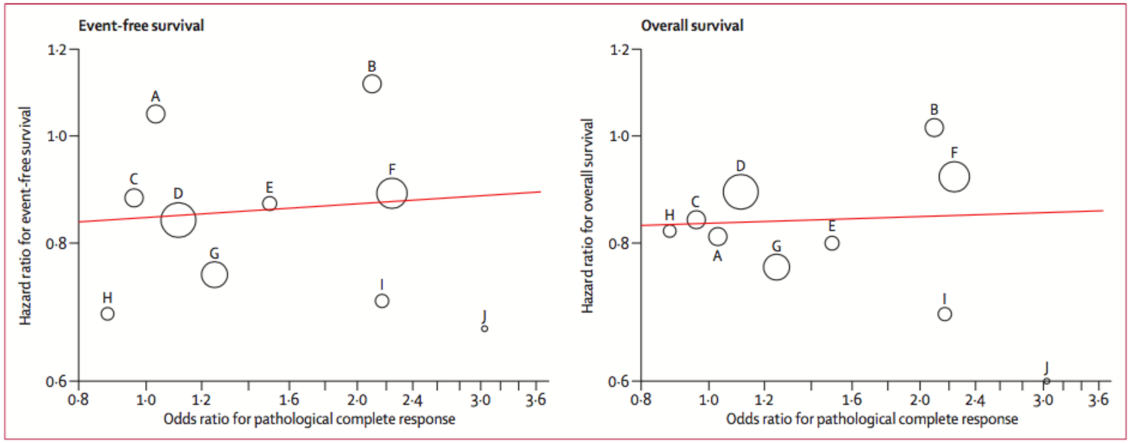
Cortazar P. Lancet 2014



Pacientes que logran una pCR: mejor EFS / OS

Asociación favorable entre pCR y:
HER2+: HR 0.39 EFS / 0.24 OS
HER2+/RH+: 0.58 EFS / 0.57 OS
HER2+/RH-: 0.25 EFS / 0.19 OS

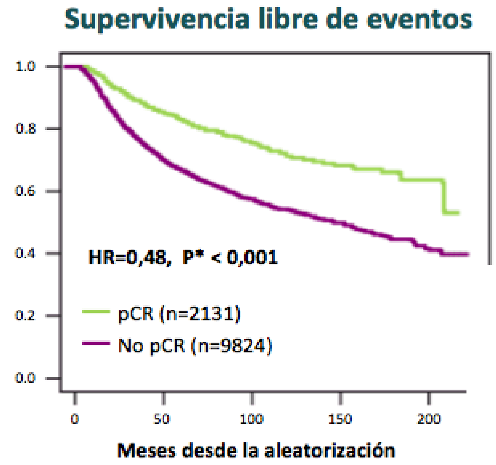


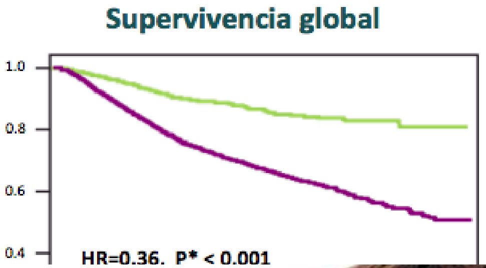


Análisis agrupado **NO** pudo establecer que el incremento en la tasa de pCR en grupos de tratamiento suponga mejor EFS / OS

Cortazar P. Lancet 2014

Pacientes que logran una pCR: mejor EFS / OS



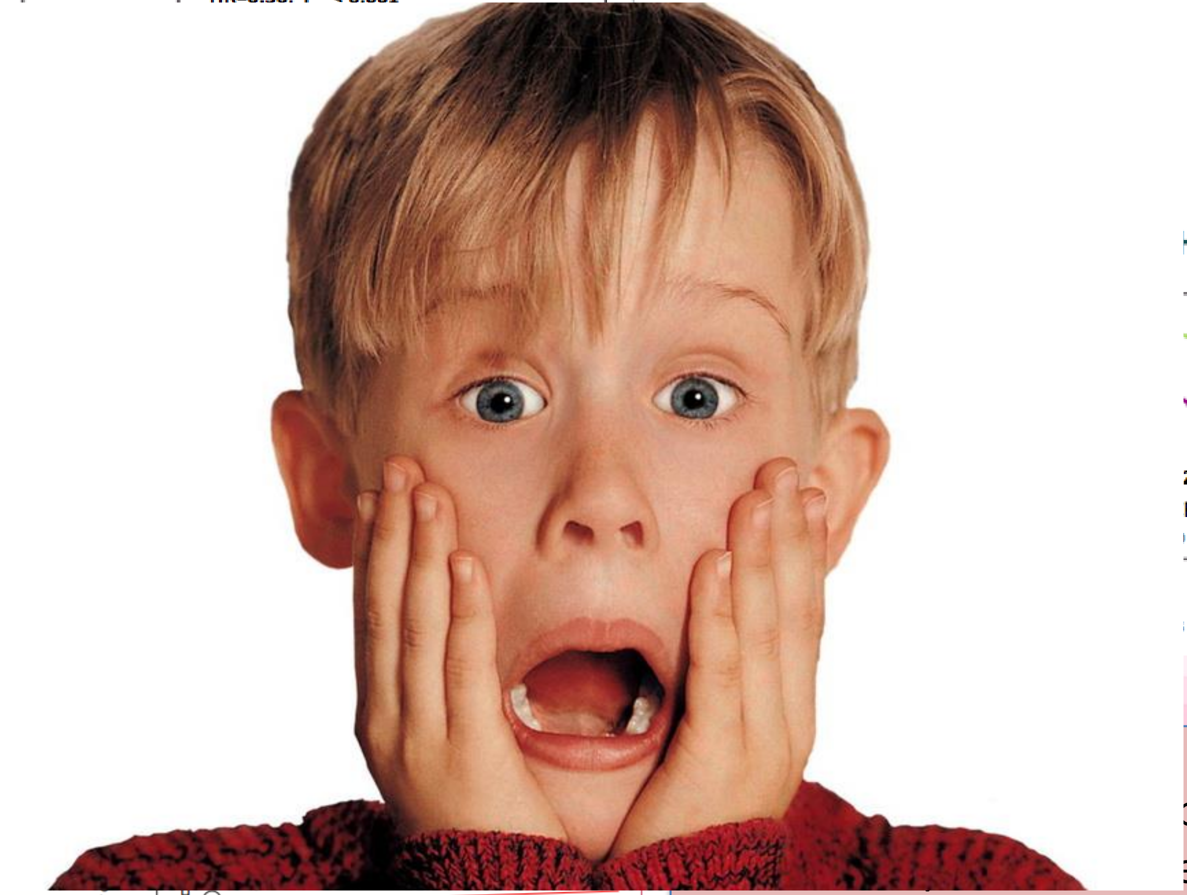


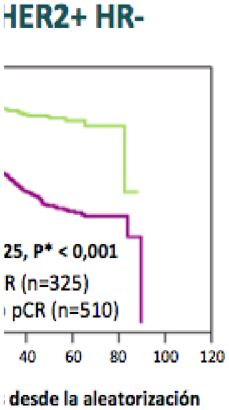
Asociación favorable er

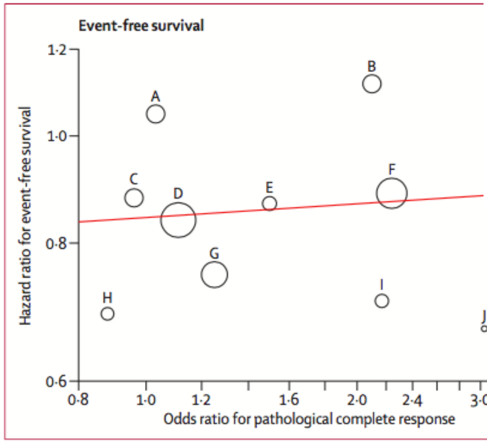
HER2+: HR 0.39 EFS /

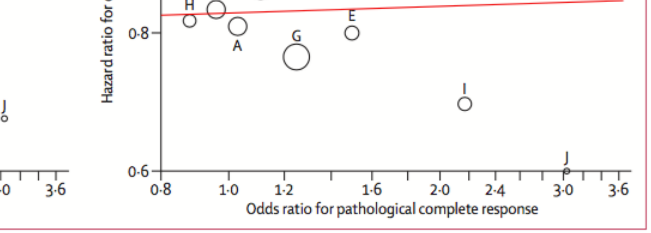
HER2+/RH+: 0.58 EFS

HER2+/RH-: 0.25 EFS









pudo

ento en

la tasa de pCR en grupos de tratamiento predice mejores EFS / OS

Cortazar P. Lancet 2014

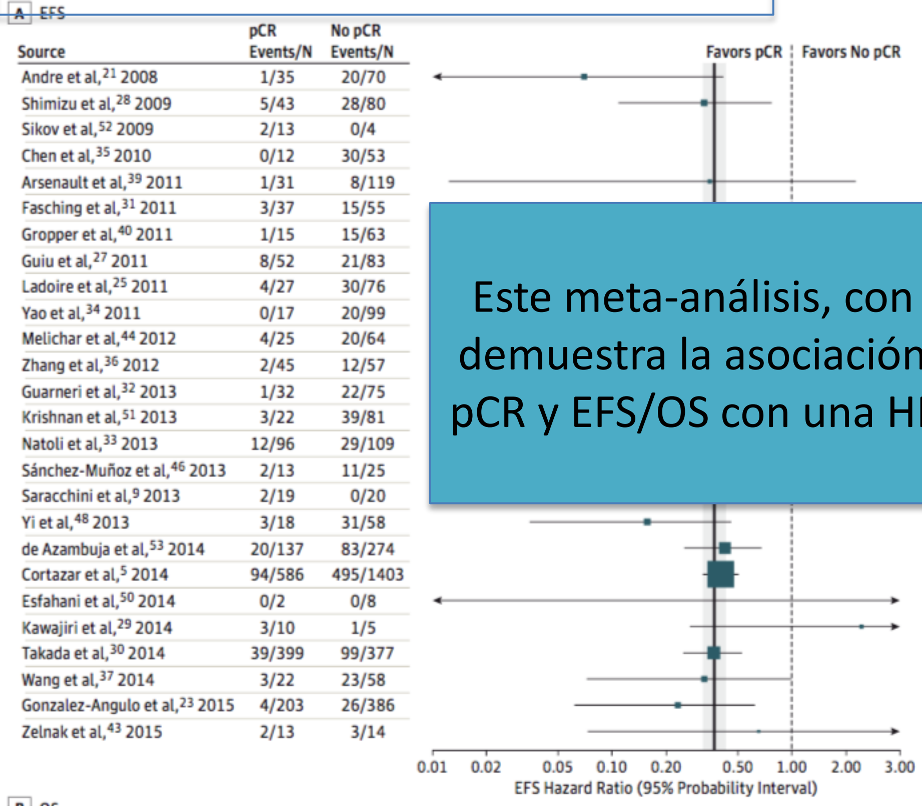
Original Investigation

Association of Pathologic Complete Response to Neoadjuvant Therapy in HER2-Positive Breast Cancer With Long-Term Outcomes

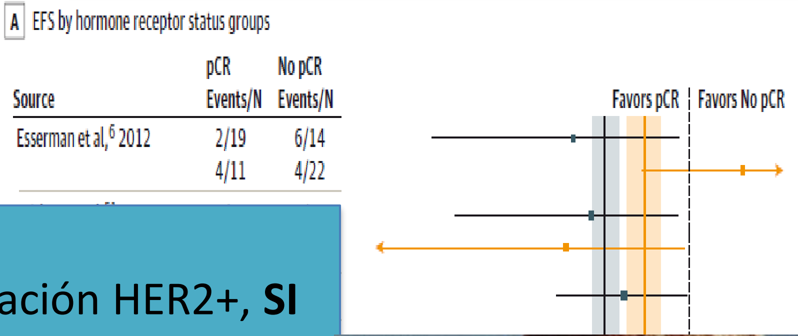
A Meta-Analysis

36 estudios / n:5768
Sólo población HER2+

EFS / pCR: HR, 0,37 (95% 0,32-0,43)
OS / pCR: HR, 0,34 (95% 0,26-0,42)
RH- HR: 0,29 /RH + HR: 0,52


A EFS

Source	pCR Events/N	No pCR Events/N
Andre et al,[21] 2008	1/35	20/70
Shimizu et al,[28] 2009	5/43	28/80
Sikov et al,[52] 2009	2/13	0/4
Chen et al,[35] 2010	0/12	30/53
Arsenault et al,[39] 2011	1/31	8/119
Fasching et al,[31] 2011	3/37	15/55
Gropper et al,[40] 2011	1/15	15/63
Guiu et al,[27] 2011	8/52	21/83
Ladoire et al,[25] 2011	4/27	30/76
Yao et al,[34] 2011	0/17	20/99
Melichar et al,[44] 2012	4/25	20/64
Zhang et al,[36] 2012	2/45	12/57
Guarneri et al,[32] 2013	1/32	22/75
Krishnan et al,[51] 2013	3/22	39/81
Natoli et al,[33] 2013	12/96	29/109
Sánchez-Muñoz et al,[46] 2013	2/13	11/25
Saracchini et al,[9] 2013	2/19	0/20
Yi et al,[48] 2013	3/18	31/58
de Azambuja et al,[53] 2014	20/137	83/274
Cortazar et al,[5] 2014	94/586	495/1403
Esfahani et al,[50] 2014	0/2	0/8
Kawajiri et al,[29] 2014	3/10	1/5
Takada et al,[30] 2014	39/399	99/377
Wang et al,[37] 2014	3/22	23/58
Gonzalez-Angulo et al,[23] 2015	4/203	26/386
Zelnak et al,[43] 2015	2/13	3/14


A EFS by hormone receptor status groups

Source	pCR Events/N	No pCR Events/N
Esserman et al,[6] 2012	2/19	6/14
	4/11	4/22
	43/247	243/839
Takada et al,[30] 2014	35/281	62/158
	11/120	54/214

Este meta-análisis, con población HER2+, **SI** demuestra la asociación a nivel ensayo entre pCR y EFS/OS con una HR EFS: 0,63 y OS:0,29.

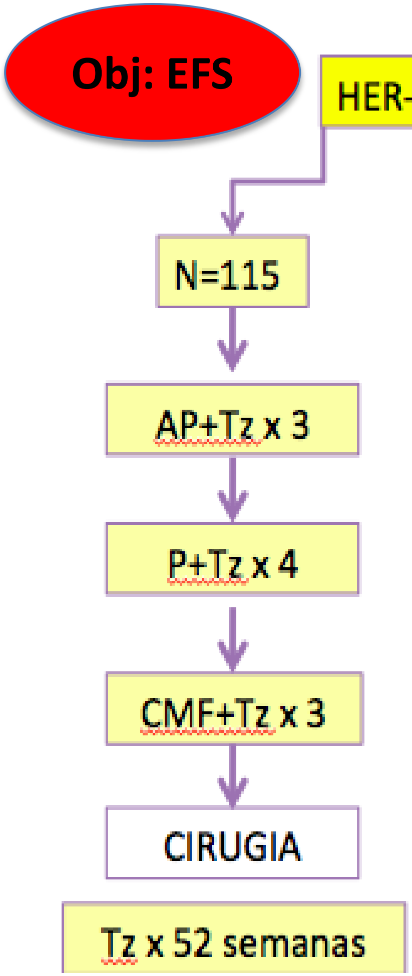
Broglio KR. JAMA Oncol. 2016

¿Por qué tanto hincapié en la pCR?

Mientras encuentras
lo que buscas...
se feliz con lo que tienes.

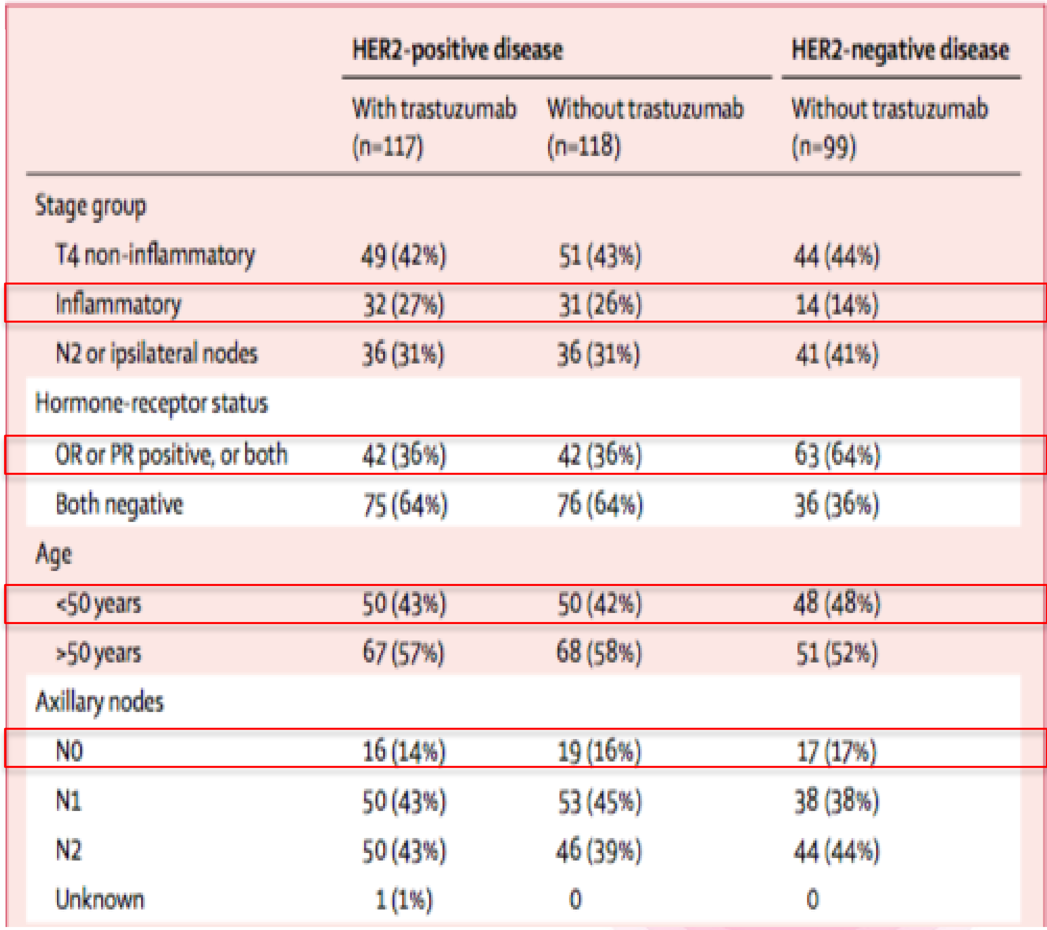
TRASTUZUMAB

Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort


Obj: EFS

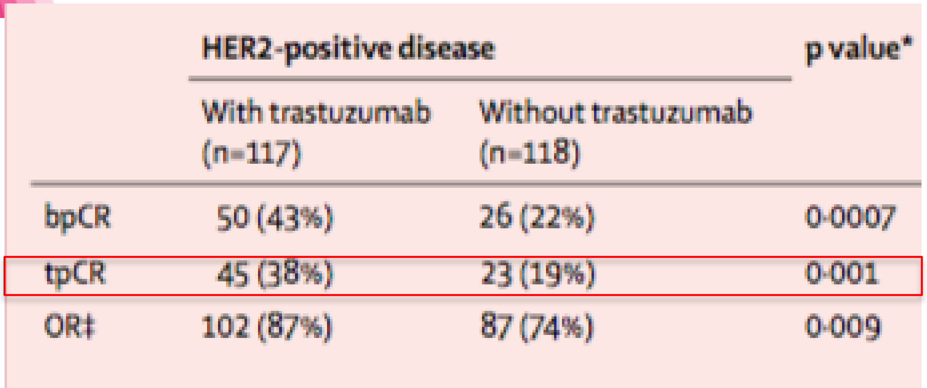
HER-2 pos

N=115	N=113
AP+Tz x 3	AP x 3
P+Tz x 4	P x 3
CMF+Tz x 3	CMF x 3
CIRUGIA	CIRUGIA
Tz x 52 semanas	



	HER2-positive disease		HER2-negative disease
	With trastuzumab (n=117)	Without trastuzumab (n=118)	Without trastuzumab (n=99)
Stage group			
T4 non-inflammatory	49 (42%)	51 (43%)	44 (44%)
Inflammatory	32 (27%)	31 (26%)	14 (14%)
N2 or ipsilateral nodes	36 (31%)	36 (31%)	41 (41%)
Hormone-receptor status			
OR or PR positive, or both	42 (36%)	42 (36%)	63 (64%)
Both negative	75 (64%)	76 (64%)	36 (36%)
Age			
<50 years	50 (43%)	50 (42%)	48 (48%)
>50 years	67 (57%)	68 (58%)	51 (52%)
Axillary nodes			
N0	16 (14%)	19 (16%)	17 (17%)
N1	50 (43%)	53 (45%)	38 (38%)
N2	50 (43%)	46 (39%)	44 (44%)
Unknown	1 (1%)	0	0

Giani L. Lancet 2010



	HER2-positive disease		p value*
	With trastuzumab (n=117)	Without trastuzumab (n=118)	
bpCR	50 (43%)	26 (22%)	0·0007
tpCR	45 (38%)	23 (19%)	0·001
OR‡	102 (87%)	87 (74%)	0·009

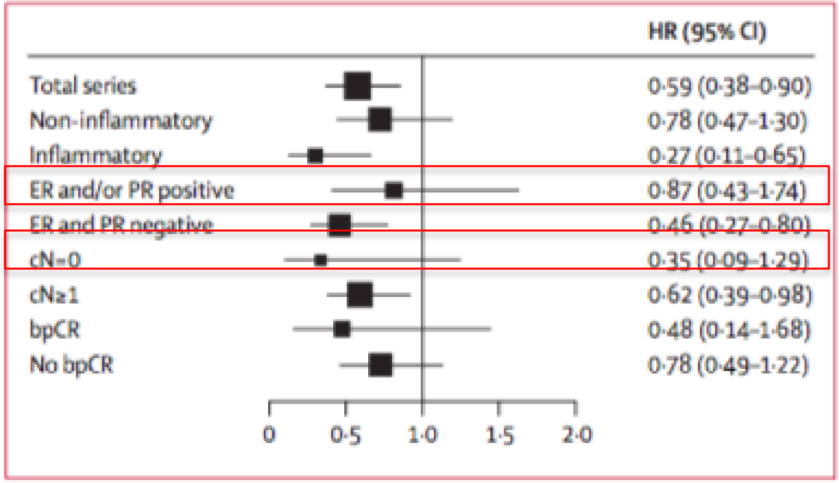
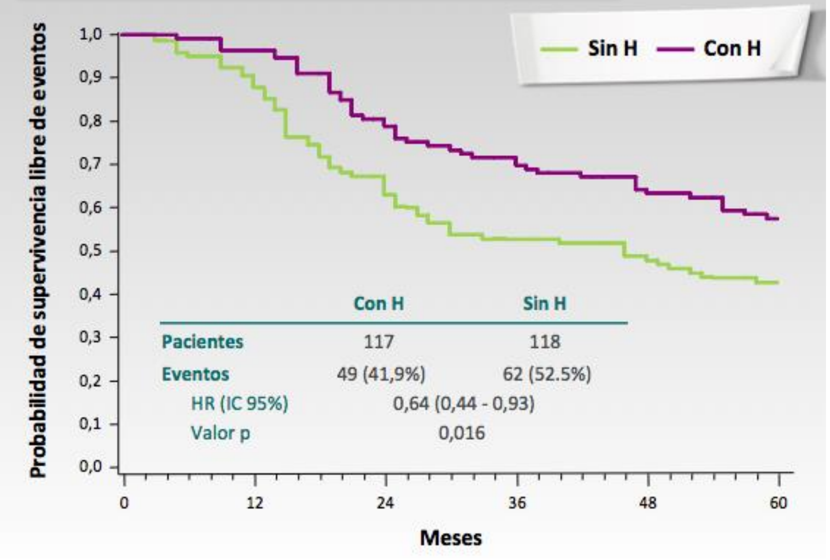


Figure 3: Analyses of event-free survival by subgroup in patients with HER2-positive disease

4.5 años: EFS 58% vs 43%



¡¡CUIDADÍN!!
¡¡CUIDADÍN!!

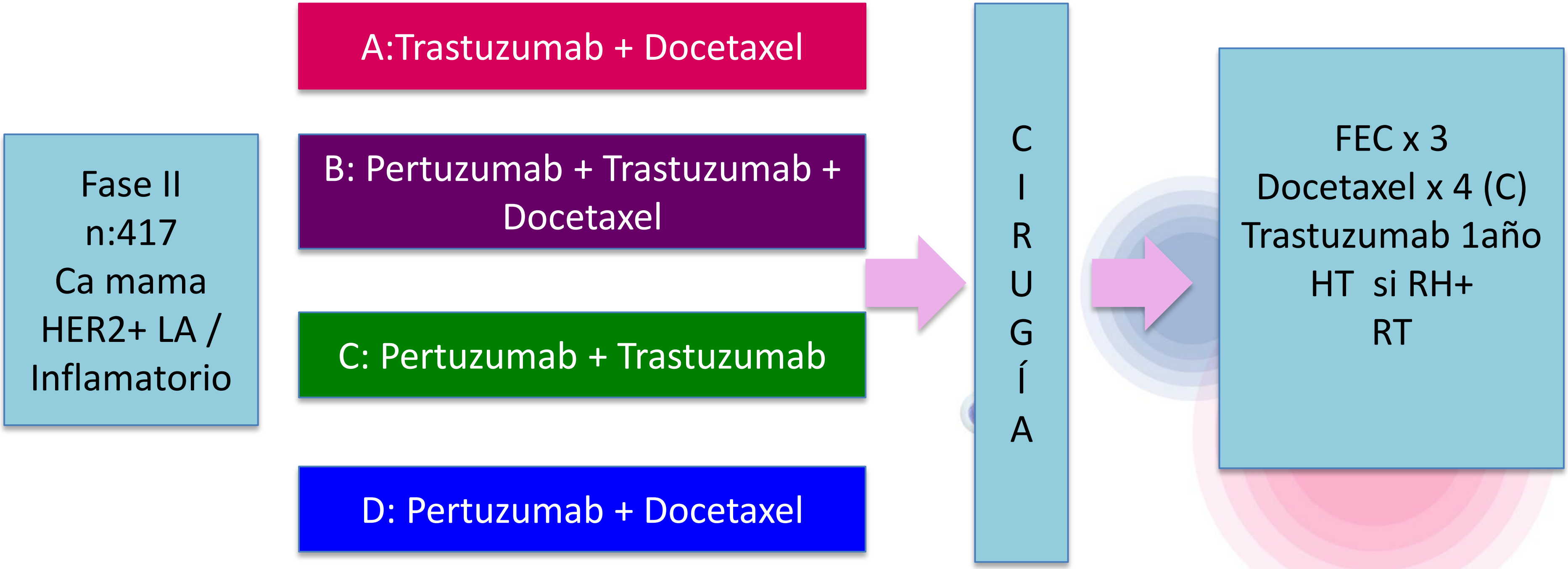
HR para la EFS en pacientes con pCR fue de 0,29

Gianni L. Lancet 2010 // Gianni L. Lancet Oncol 2014

PERTUZUMAB

Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial

Objetivo principal: pCR
Objetivos secundarios: PFS, DFS



Fase II
n:417
Ca mama
HER2+ LA /
Inflamatorio

A:Trastuzumab + Docetaxel

B: Pertuzumab + Trastuzumab + Docetaxel

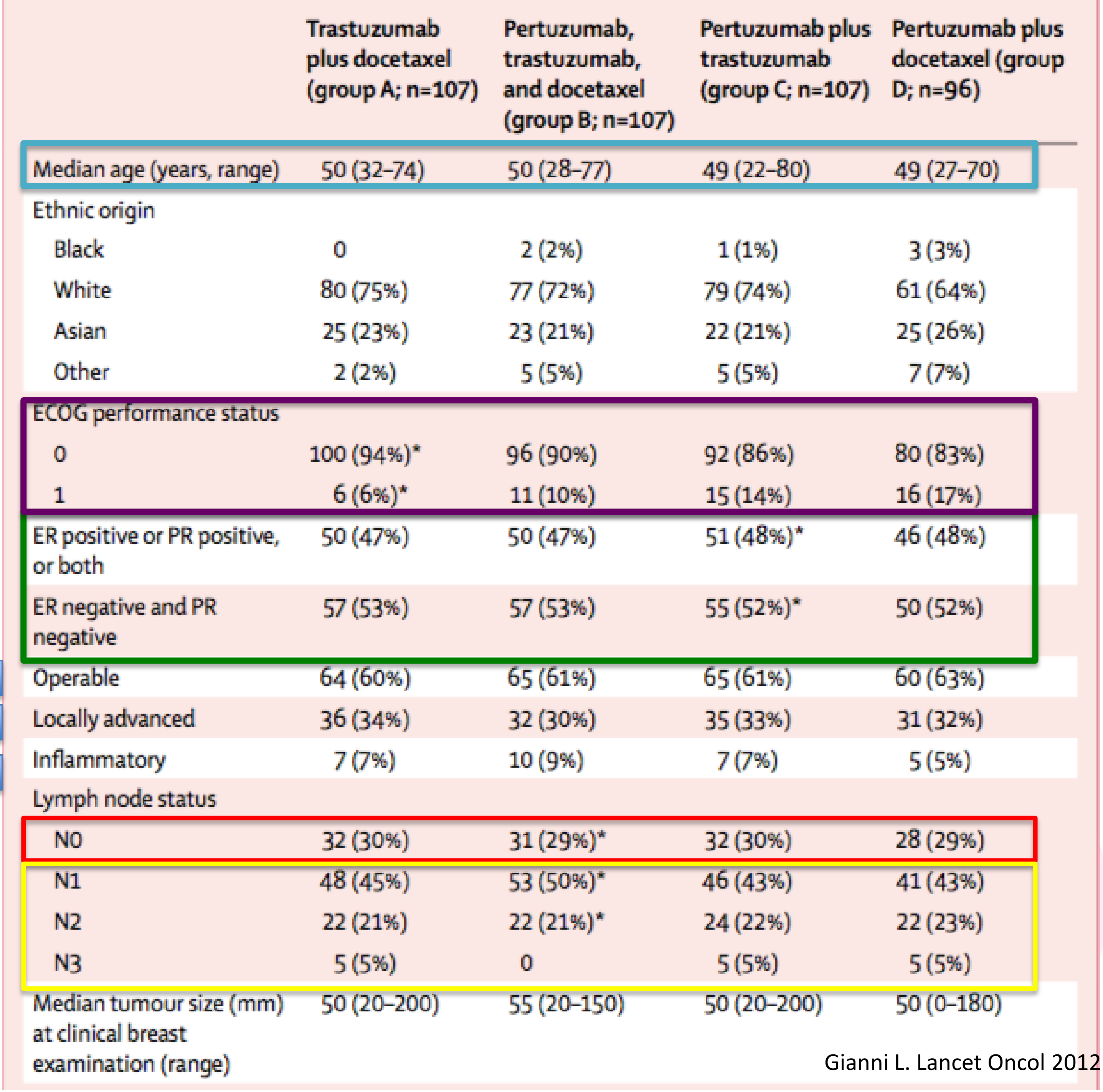
C: Pertuzumab + Trastuzumab

D: Pertuzumab + Docetaxel

CIRUGÍA

FEC x 3
Docetaxel x 4 (C)
Trastuzmab 1año
HT si RH+
RT

Gianni L. Lancet Oncol 2012



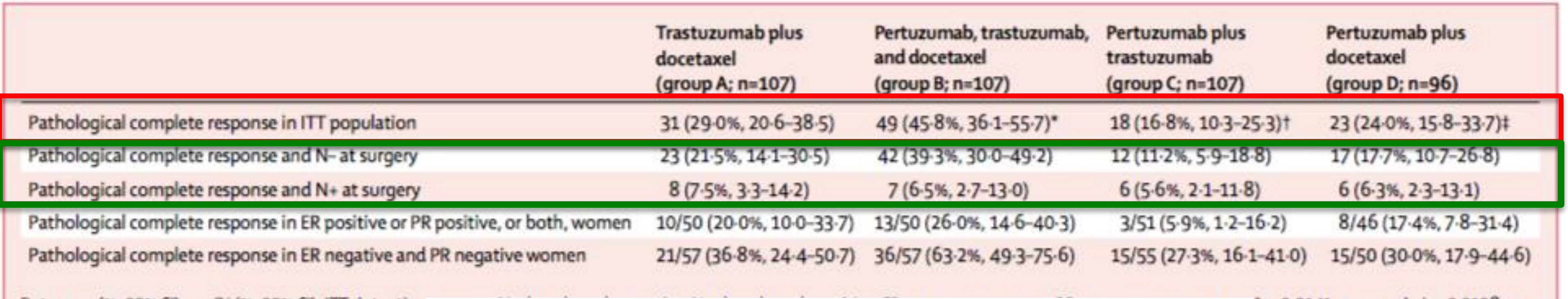
	Trastuzumab plus docetaxel (group A; n=107)	Pertuzumab, trastuzumab, and docetaxel (group B; n=107)	Pertuzumab plus trastuzumab (group C; n=107)	Pertuzumab plus docetaxel (group D; n=96)
Median age (years, range)	50 (32–74)	50 (28–77)	49 (22–80)	49 (27–70)
Ethnic origin				
Black	0	2 (2%)	1 (1%)	3 (3%)
White	80 (75%)	77 (72%)	79 (74%)	61 (64%)
Asian	25 (23%)	23 (21%)	22 (21%)	25 (26%)
Other	2 (2%)	5 (5%)	5 (5%)	7 (7%)
ECOG performance status				
0	100 (94%)*	96 (90%)	92 (86%)	80 (83%)
1	6 (6%)*	11 (10%)	15 (14%)	16 (17%)
ER positive or PR positive, or both	50 (47%)	50 (47%)	51 (48%)*	46 (48%)
ER negative and PR negative	57 (53%)	57 (53%)	55 (52%)*	50 (52%)
Operable	64 (60%)	65 (61%)	65 (61%)	60 (63%)
Locally advanced	36 (34%)	32 (30%)	35 (33%)	31 (32%)
Inflammatory	7 (7%)	10 (9%)	7 (7%)	5 (5%)
Lymph node status				
N0	32 (30%)	31 (29%)*	32 (30%)	28 (29%)
N1	48 (45%)	53 (50%)*	46 (43%)	41 (43%)
N2	22 (21%)	22 (21%)*	24 (22%)	22 (23%)
N3	5 (5%)	0	5 (5%)	5 (5%)
Median tumour size (mm) at clinical breast examination (range)	50 (20–200)	55 (20–150)	50 (20–200)	50 (0–180)

T2-3, N0-1

T2-3, N2-3, T4a-c

T4d, any N

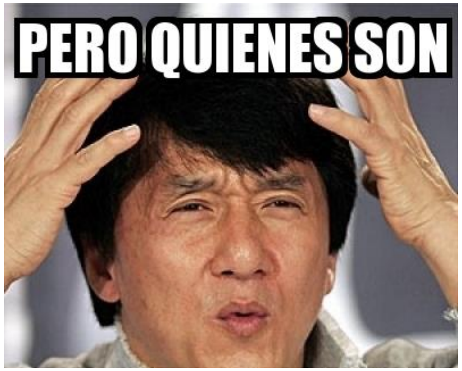
Gianni L. Lancet Oncol 2012

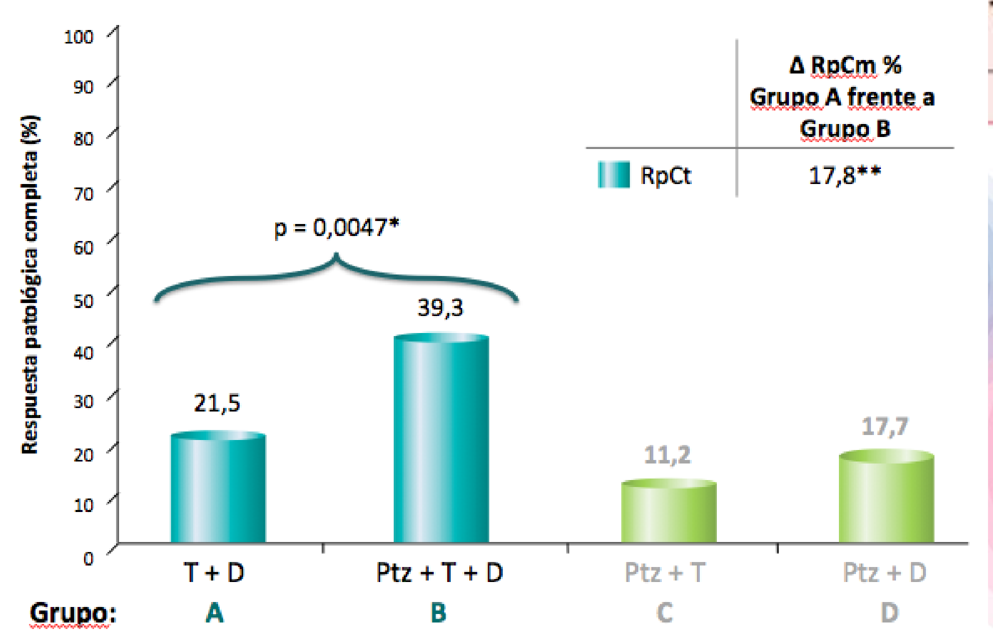


	Trastuzumab plus docetaxel (group A; n=107)	Pertuzumab, trastuzumab, and docetaxel (group B; n=107)	Pertuzumab plus trastuzumab (group C; n=107)	Pertuzumab plus docetaxel (group D; n=96)
Pathological complete response in ITT population	31 (29·0%, 20·6–38·5)	49 (45·8%, 36·1–55·7)*	18 (16·8%, 10·3–25·3)†	23 (24·0%, 15·8–33·7)‡
Pathological complete response and N– at surgery	23 (21·5%, 14·1–30·5)	42 (39·3%, 30·0–49·2)	12 (11·2%, 5·9–18·8)	17 (17·7%, 10·7–26·8)
Pathological complete response and N+ at surgery	8 (7·5%, 3·3–14·2)	7 (6·5%, 2·7–13·0)	6 (5·6%, 2·1–11·8)	6 (6·3%, 2·3–13·1)
Pathological complete response in ER positive or PR positive, or both, women	10/50 (20·0%, 10·0–33·7)	13/50 (26·0%, 14·6–40·3)	3/51 (5·9%, 1·2–16·2)	8/46 (17·4%, 7·8–31·4)
Pathological complete response in ER negative and PR negative women	21/57 (36·8%, 24·4–50·7)	36/57 (63·2%, 49·3–75·6)	15/55 (27·3%, 16·1–41·0)	15/50 (30·0%, 17·9–44·6)

Data are n (%, 95% CI) or n/N (%, 95% CI). ITT=intention
*p=0·0141 vs group A. †p=0·0198 vs
group A. ‡p=0·003 vs group B.

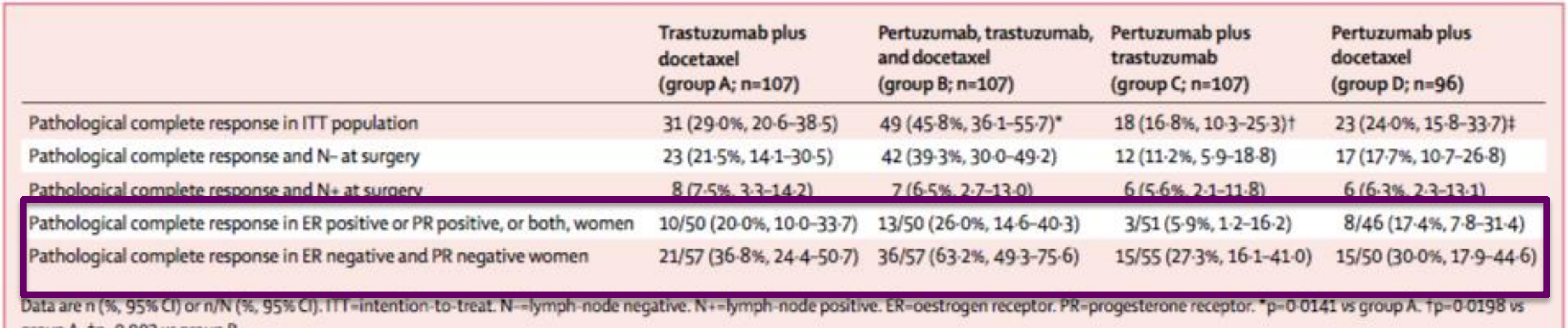
Table 2: **Pathological complete responses in the IT**





Gianni L. Lancet Oncol 2012

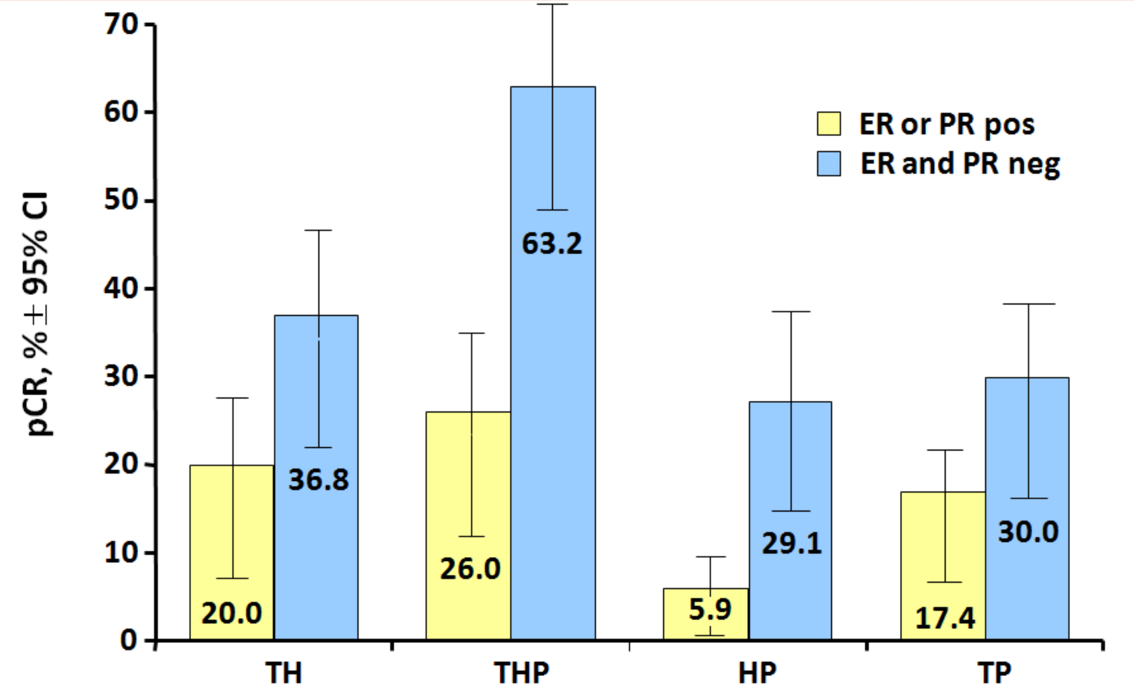
Mayor tasa de rPC: P + T + D
Mayor tasa de rPC en T y N: P + T + D
Mayor tasa de rPC RH- : P + T +D



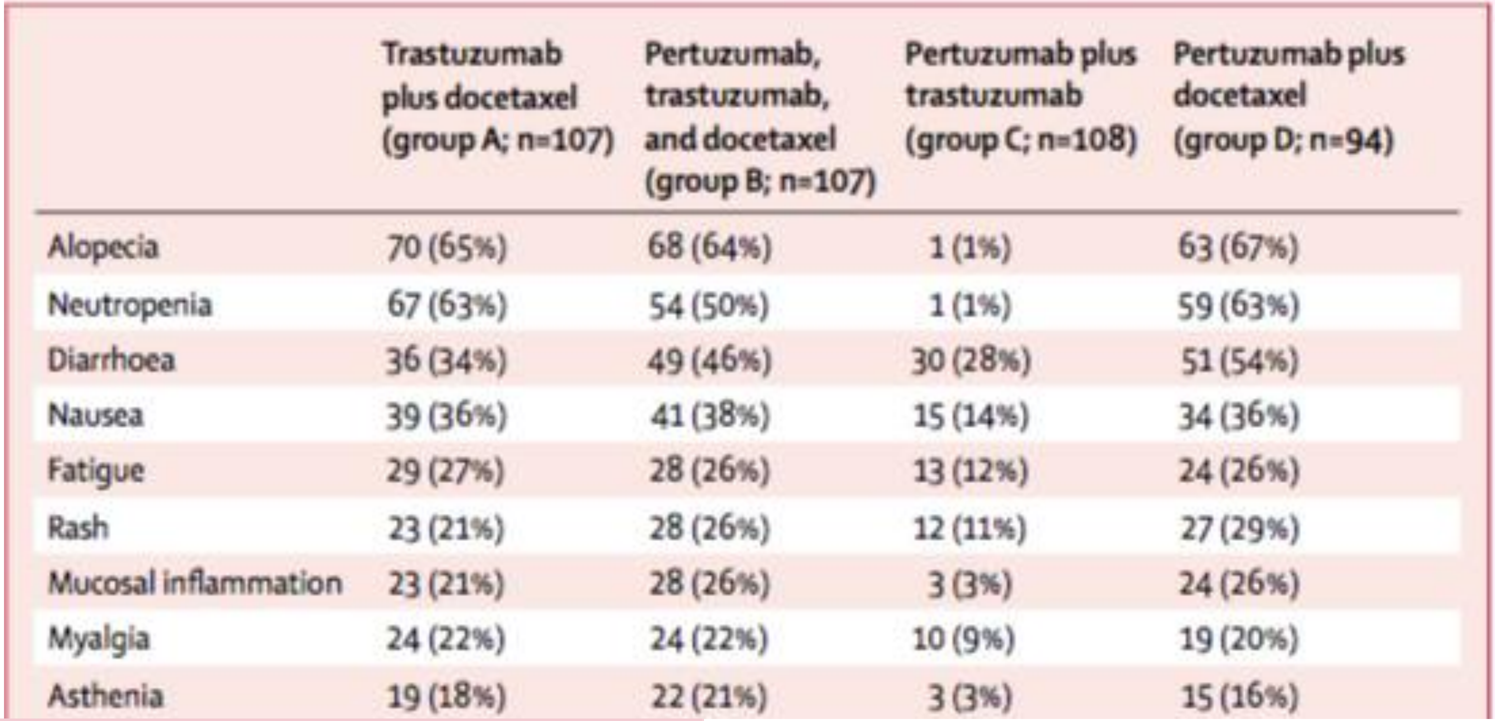
	Trastuzumab plus docetaxel (group A; n=107)	Pertuzumab, trastuzumab, and docetaxel (group B; n=107)	Pertuzumab plus trastuzumab (group C; n=107)	Pertuzumab plus docetaxel (group D; n=96)
Pathological complete response in ITT population	31 (29·0%, 20·6–38·5)	49 (45·8%, 36·1–55·7)*	18 (16·8%, 10·3–25·3)†	23 (24·0%, 15·8–33·7)‡
Pathological complete response and N– at surgery	23 (21·5%, 14·1–30·5)	42 (39·3%, 30·0–49·2)	12 (11·2%, 5·9–18·8)	17 (17·7%, 10·7–26·8)
Pathological complete response and N+ at surgery	8 (7·5%, 3·3–14·2)	7 (6·5%, 2·7–13·0)	6 (5·6%, 2·1–11·8)	6 (6·3%, 2·3–13·1)
Pathological complete response in ER positive or PR positive, or both, women	10/50 (20·0%, 10·0–33·7)	13/50 (26·0%, 14·6–40·3)	3/51 (5·9%, 1·2–16·2)	8/46 (17·4%, 7·8–31·4)
Pathological complete response in ER negative and PR negative women	21/57 (36·8%, 24·4–50·7)	36/57 (63·2%, 49·3–75·6)	15/55 (27·3%, 16·1–41·0)	15/50 (30·0%, 17·9–44·6)

Data are n (%, 95% CI) or n/N (%, 95% CI). ITT=intention-to-treat. N–=lymph-node negative. N+=lymph-node positive. ER=oestrogen receptor. PR=progesterone receptor. *p=0·0141 vs group A. †p=0·0198 vs group A. ‡p=0·003 vs group B.

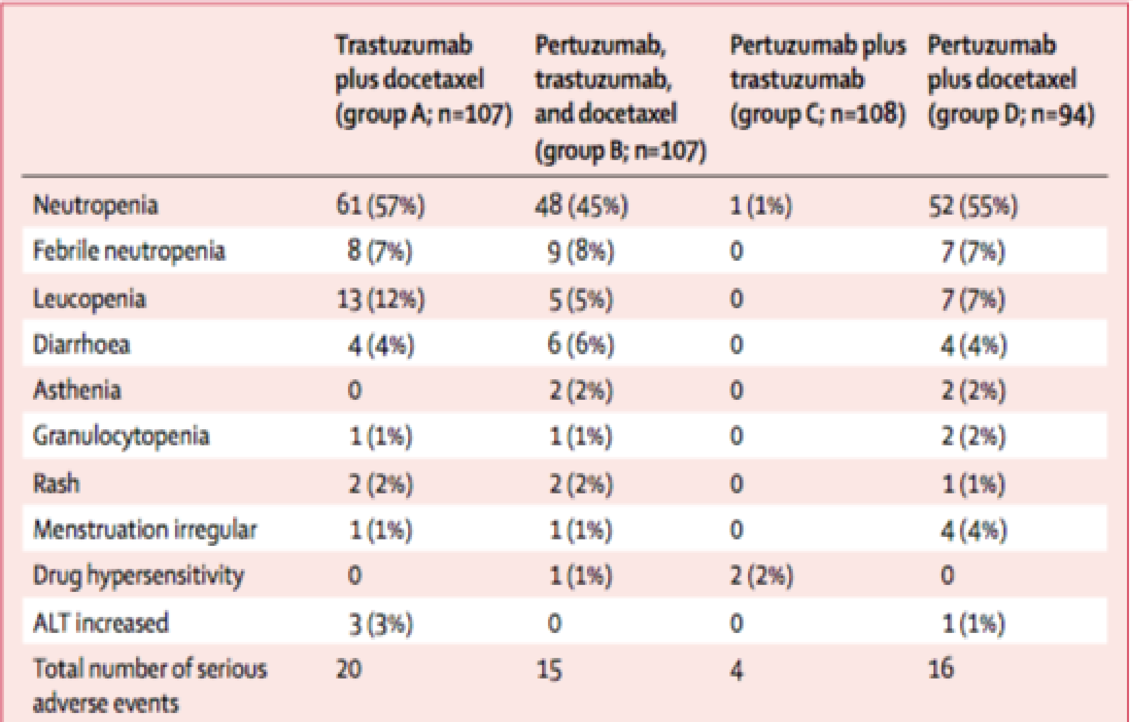
Table 2: Pathological complete



Gianni L. Lancet Oncol 2012



	Trastuzumab plus docetaxel (group A; n=107)	Pertuzumab, trastuzumab, and docetaxel (group B; n=107)	Pertuzumab plus trastuzumab (group C; n=108)	Pertuzumab plus docetaxel (group D; n=94)
Alopecia	70 (65%)	68 (64%)	1 (1%)	63 (67%)
Neutropenia	67 (63%)	54 (50%)	1 (1%)	59 (63%)
Diarrhoea	36 (34%)	49 (46%)	30 (28%)	51 (54%)
Nausea	39 (36%)	41 (38%)	15 (14%)	34 (36%)
Fatigue	29 (27%)	28 (26%)	13 (12%)	24 (26%)
Rash	23 (21%)	28 (26%)	12 (11%)	27 (29%)
Mucosal inflammation	23 (21%)	28 (26%)	3 (3%)	24 (26%)
Myalgia	24 (22%)	24 (22%)	10 (9%)	19 (20%)
Asthenia	19 (18%)	22 (21%)	3 (3%)	15 (16%)



	Trastuzumab plus docetaxel (group A; n=107)	Pertuzumab, trastuzumab, and docetaxel (group B; n=107)	Pertuzumab plus trastuzumab (group C; n=108)	Pertuzumab plus docetaxel (group D; n=94)
Neutropenia	61 (57%)	48 (45%)	1 (1%)	52 (55%)
Febrile neutropenia	8 (7%)	9 (8%)	0	7 (7%)
Leucopenia	13 (12%)	5 (5%)	0	7 (7%)
Diarrhoea	4 (4%)	6 (6%)	0	4 (4%)
Asthenia	0	2 (2%)	0	2 (2%)
Granulocytopenia	1 (1%)	1 (1%)	0	2 (2%)
Rash	2 (2%)	2 (2%)	0	1 (1%)
Menstruation irregular	1 (1%)	1 (1%)	0	4 (4%)
Drug hypersensitivity	0	1 (1%)	2 (2%)	0
ALT increased	3 (3%)	0	0	1 (1%)
Total number of serious adverse events	20	15	4	16

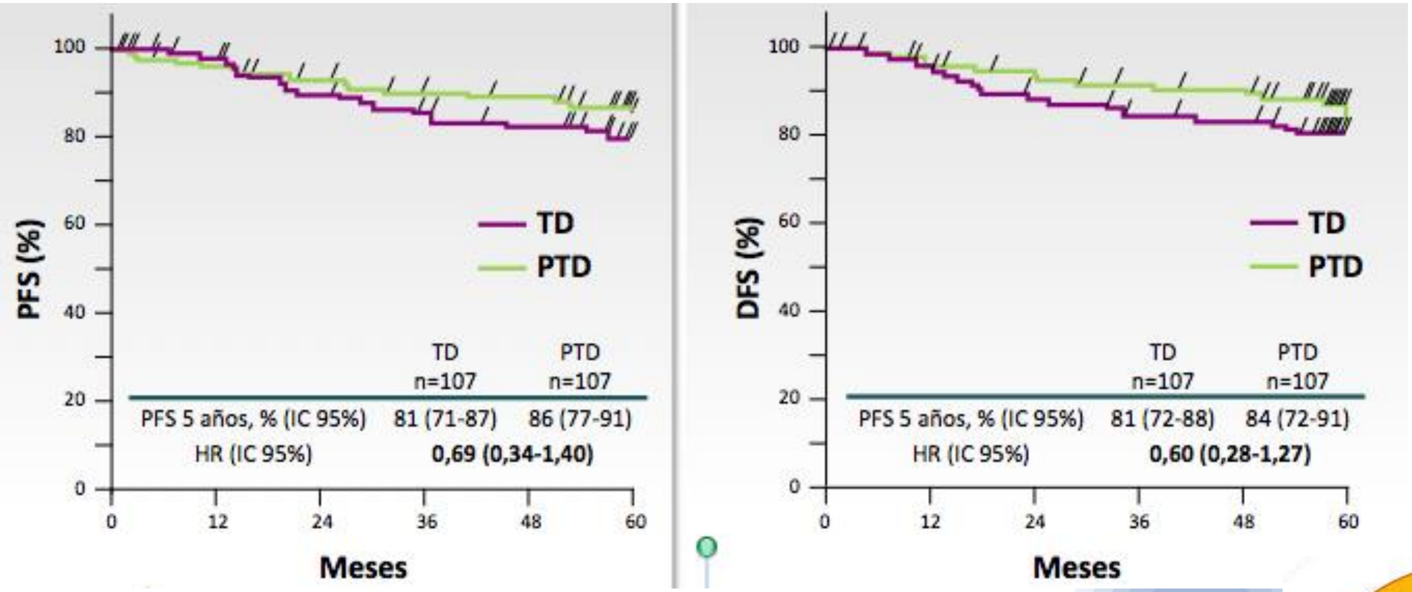
Toxicidad cardiaca:

- Caída FEVI: 4-5 %.
- 3 ptes brazo B caída: 10-15%

Gianni L. Lancet Oncol 2012

5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial

Sociedad Andaluza de Oncología Medica

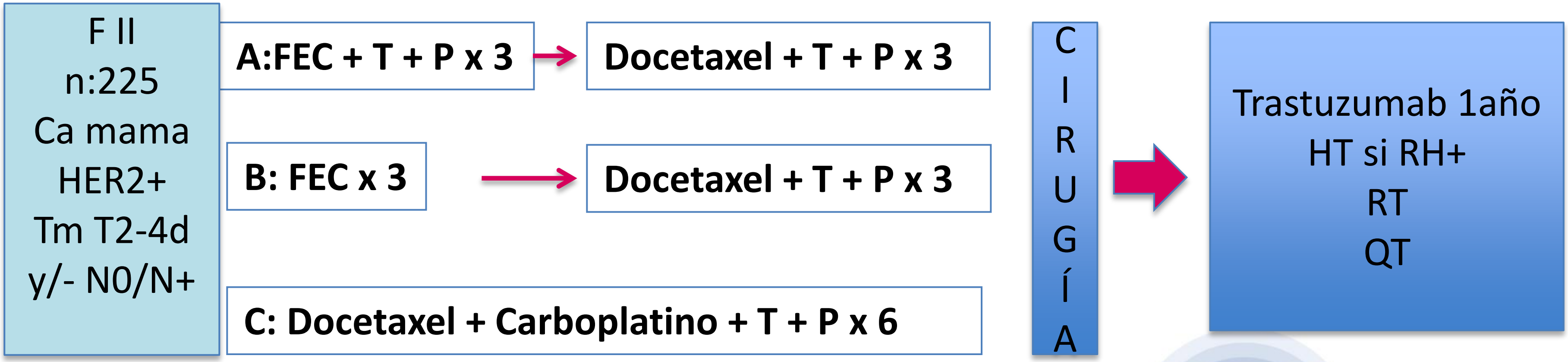


DFS pCR vs no-pCR: 0,68 - IC 95%: 0,36-1,26

PFS pCR vs no-pCR: 0,54 - IC 95%:0,29-1.00

Gianni L. Lancet Oncol 2016

Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA)



F II
n:225
Ca mama
HER2+
Tm T2-4d
y/- N0/N+

A:FEC + T + P x 3 → **Docetaxel + T + P x 3**

B: FEC x 3 → **Docetaxel + T + P x 3**

C: Docetaxel + Carboplatino + T + P x 6

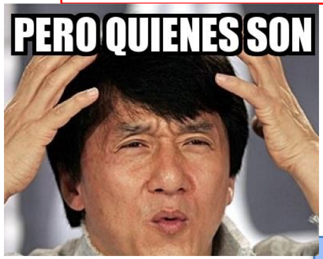
CIRUGÍA

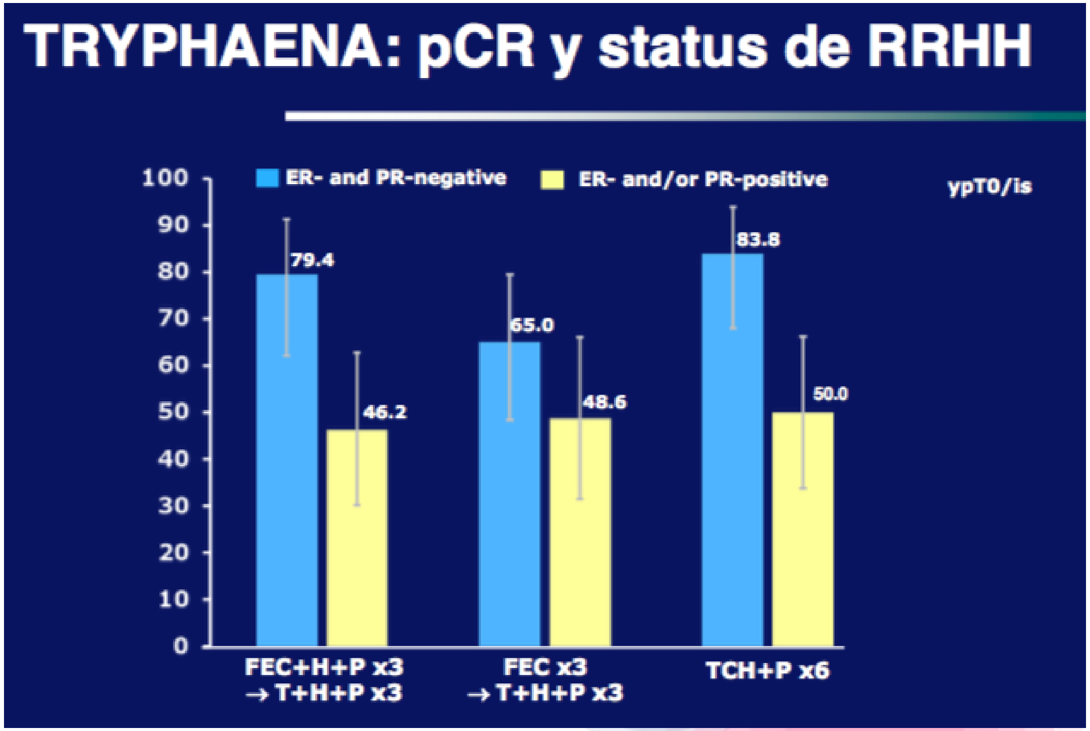
Trastuzumab 1año
HT si RH+
RT
QT

Objetivo principal: seguridad cardiaca
Objetivos secundarios: PFS, DFS, OS

Schneeweiss, *et al. Ann Oncol* 2013

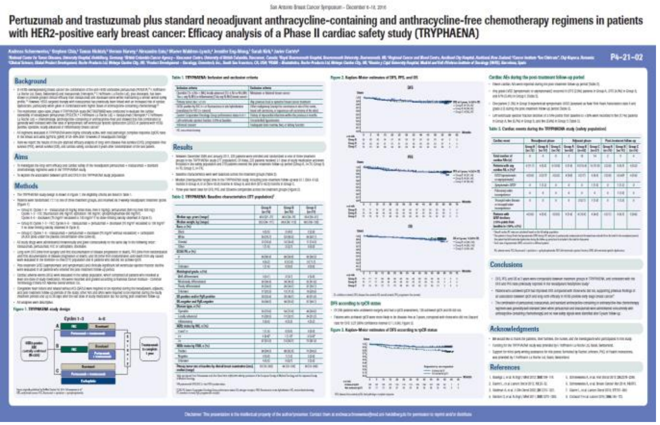
ypT0/is		ypT0/is ypN0
61.6%	A	50.7%
57.3%	B	45.3%
66.2%	C	51.9%




TRYPHAENA: pCR y status de RRHH

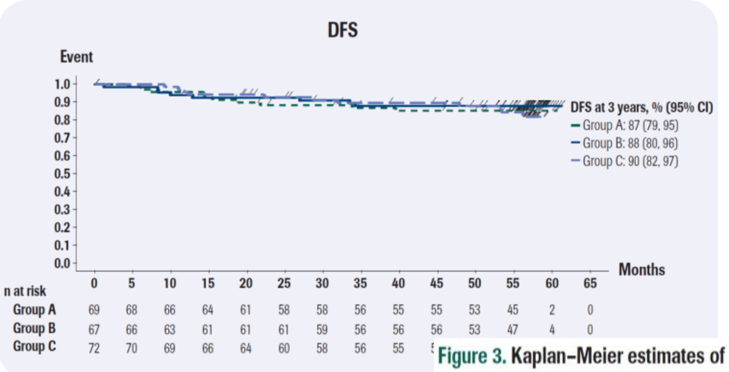
- ↓ Significativa FEVI: baja en todos los brazos.
- ↓ Efectos adversos: C (35,5%) > A (27,8%) > B (20%)

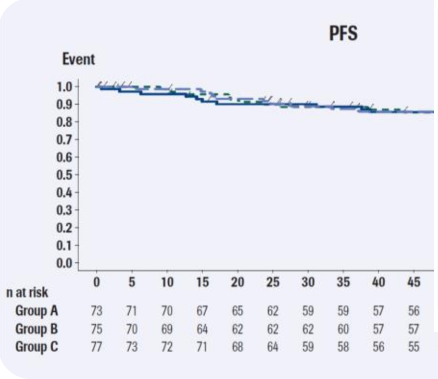
Schneeweiss, *et al. Ann Oncol* 2013



Pertuzumab and trastuzumab plus standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: Efficacy analysis of a Phase II cardiac safety study (TRYPHAENA)

EFS, PFS y OS a 3 años: similares entre brazos y consistentes con NeoSphere





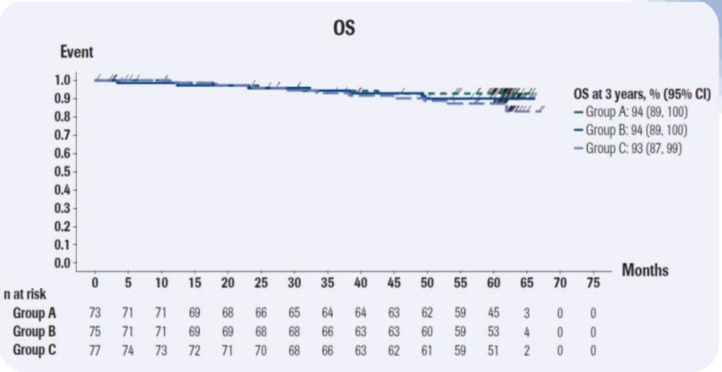
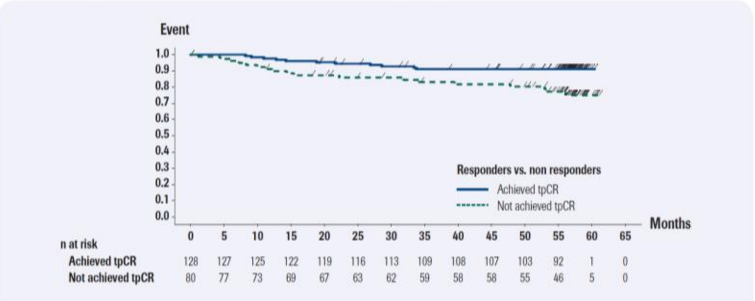


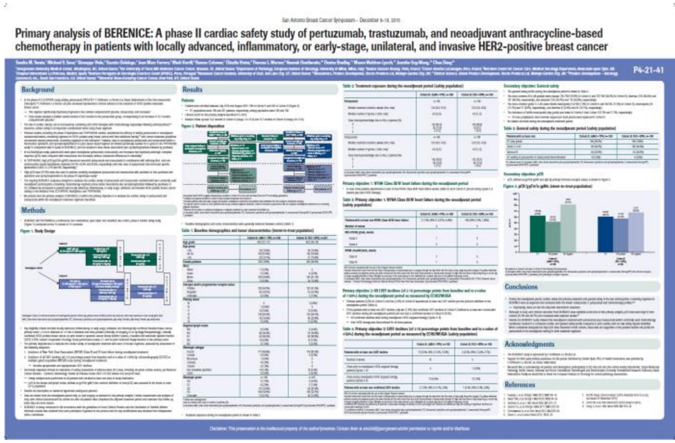
Figure 3. Kaplan–Meier estimates of DFS according to tpCR status



DFS, disease-free survival; tpCR, total pathologic complete response.

Pacientes que alcanzan pCR mejor EFS

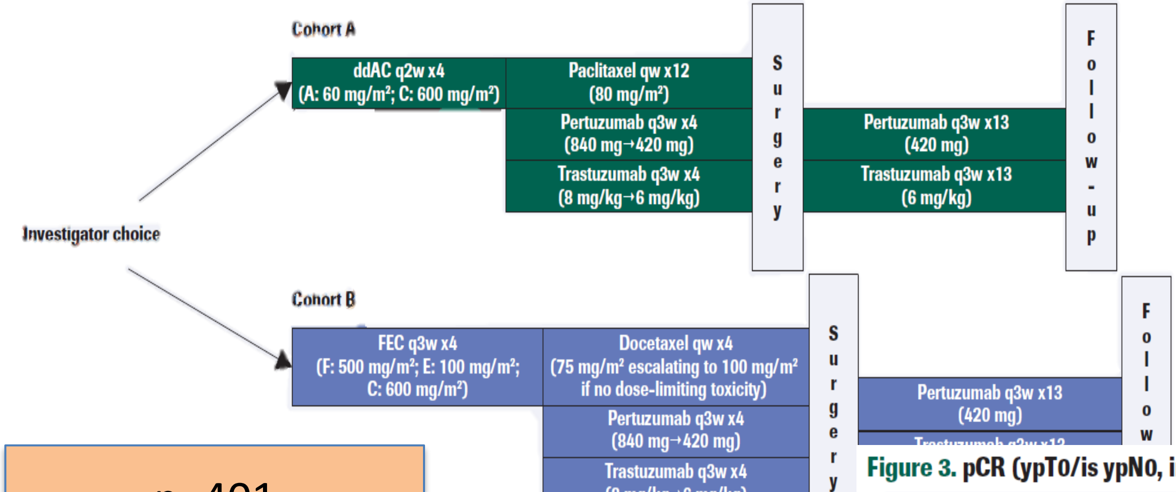
Schneeweiss A. SABCS 2016



San Antonio Breast Cancer Symposium – December 6–10, 2016

Primary analysis of BERENICE: A phase II cardiac safety study of pertuzumab, trastuzumab, and neoadjuvant anthracycline-based chemotherapy in patients with locally advanced, inflammatory, or early-stage, unilateral, and invasive HER2-positive breast cancer

P4-21-41



Investigator choice

Cohort A

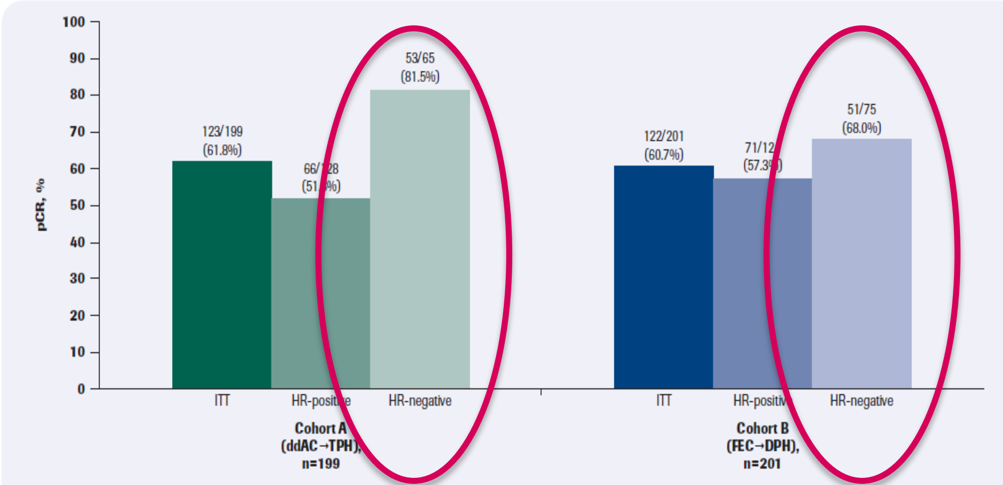
- ddAC q2w x4 (A: 60 mg/m^2; C: 600 mg/m^2)
- Paclitaxel qw x12 (80 mg/m^2)
- Pertuzumab q3w x4 (840 mg→420 mg)
- Trastuzumab q3w x4 (8 mg/kg→6 mg/kg)
- Surgery
- Pertuzumab q3w x13 (420 mg)
- Trastuzumab q3w x13 (6 mg/kg)
- Follow-up

Cohort B

- FEC q3w x4 (F: 500 mg/m^2; E: 100 mg/m^2; C: 600 mg/m^2)
- Docetaxel qw x4 (75 mg/m^2 escalating to 100 mg/m^2 if no dose-limiting toxicity)
- Pertuzumab q3w x4 (840 mg→420 mg)
- Trastuzumab q3w x4 (8 mg/kg→6 mg/kg)
- Surgery
- Pertuzumab q3w x13 (420 mg)
- Follow

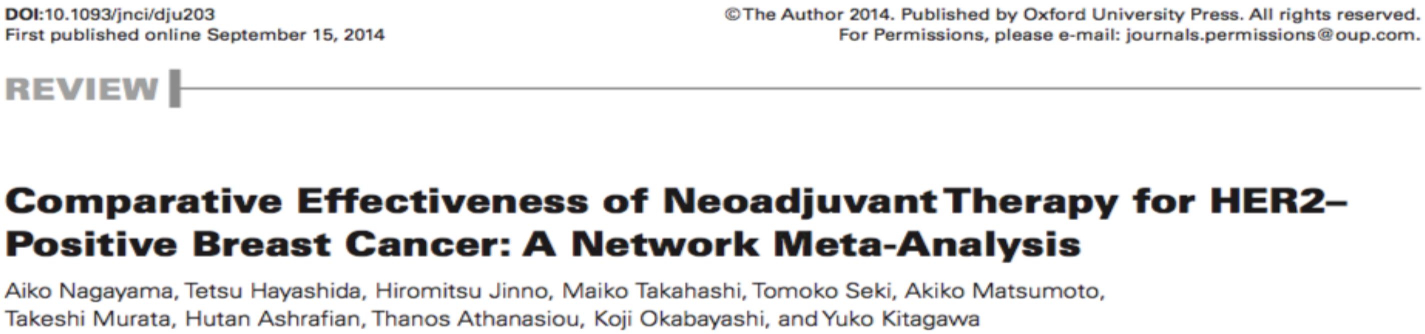
n: 401
Obj 1º: seguridad cardiaca. Obj 2º: pCR.
RH+ 64% // N0: 40%

Figure 3. pCR (ypT0/is ypN0, intent-to-treat population)



Six patients in Cohort A and two in Cohort B had missing HR assessments.
D, docetaxel; ddAC, dose-dense doxorubicin plus cyclophosphamide; FEC, fluorouracil, epirubicin, and cyclophosphamide; H, trastuzumab (Herceptin®); HR, hormone receptor; P, pertuzumab (PERJETA®); T, paclitaxel; pCR, pathologic complete response.

Swain SM. Primary analysis of Berenice, SABCS 2016

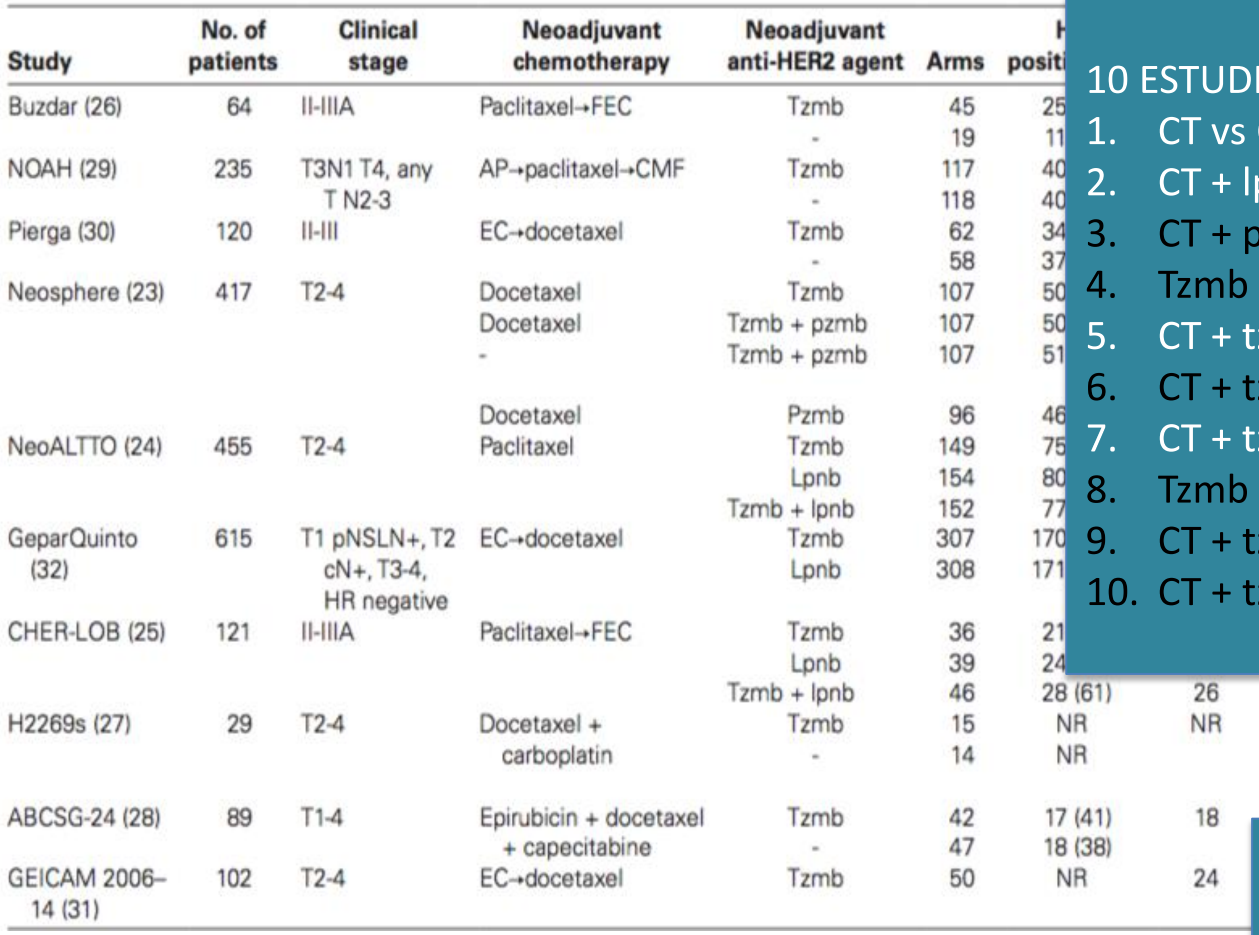


DOI:10.1093/jnci/dju203
First published online September 15, 2014
©The Author 2014. Published by Oxford University Press. All rights reserved.
For Permissions, please e-mail: journals.permissions@oup.com.

REVIEW

Comparative Effectiveness of Neoadjuvant Therapy for HER2–Positive Breast Cancer: A Network Meta-Analysis

Aiko Nagayama, Tetsu Hayashida, Hiromitsu Jinno, Maiko Takahashi, Tomoko Seki, Akiko Matsumoto, Takeshi Murata, Hutan Ashrafian, Thanos Athanasiou, Koji Okabayashi, and Yuko Kitagawa



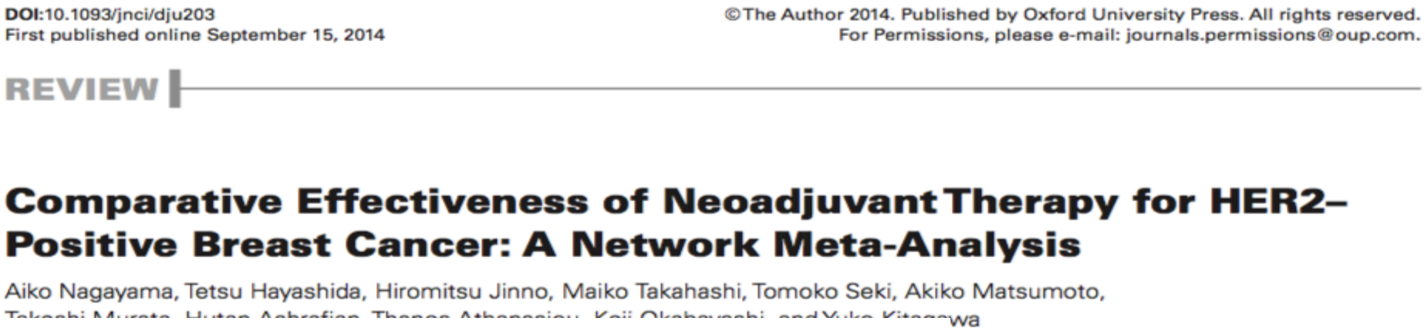
Study	No. of patients	Clinical stage	Neoadjuvant chemotherapy	Neoadjuvant anti-HER2 agent	Arms	H positi		
Buzdar (26)	64	II-IIIA	Paclitaxel→FEC	Tzmb	45	25		
				-	19	11		
NOAH (29)	235	T3N1 T4, any T N2-3	AP→paclitaxel→CMF	Tzmb	117	40		
				-	118	40		
Pierga (30)	120	II-III	EC→docetaxel	Tzmb	62	34		
				-	58	37		
Neosphere (23)	417	T2-4	Docetaxel	Tzmb	107	50		
			Docetaxel	Tzmb + pzmb	107	50		
			-	Tzmb + pzmb	107	51		
			Docetaxel	Pzmb	96	46		
NeoALTTO (24)	455	T2-4	Paclitaxel	Tzmb	149	75		
				Lpnb	154	80		
				Tzmb + lpnb	152	77		
GeparQuinto (32)	615	T1 pNSLN+, T2 cN+, T3-4, HR negative	EC→docetaxel	Tzmb	307	170		
				Lpnb	308	171		
CHER-LOB (25)	121	II-IIIA	Paclitaxel→FEC	Tzmb	36	21		
				Lpnb	39	24		
				Tzmb + lpnb	46	28 (61)	26	
H2269s (27)	29	T2-4	Docetaxel + carboplatin	Tzmb	15	NR	NR	Docetaxel + carboplatin + tzmb
				-	14	NR		
ABCSG-24 (28)	89	T1-4	Epirubicin + docetaxel + capecitabine	Tzmb	42	17 (41)	18	NR
				-	47	18 (38)		
GEICAM 2006–14 (31)	102	T2-4	EC→docetaxel	Tzmb	50	NR	24	

10 ESTUDIOS / n: 2247

1. CT vs CT + tzmb
2. CT + lpnb vs CT + tzmb
3. CT + pzmb vs CT + tzmb
4. Tzmb + pzmb vs CT + tzmb
5. CT + tzmb + lpnb vs CT + tzmb
6. CT + tzmb + pzmb vs CT + tzmb
7. CT + tzmb + lpnb vs CT + lpnb
8. Tzmb + pzmb vs CT + pzmb
9. CT + tzmb + pzmb vs CT + pzmb
10. CT + tzmb + pzmb vs tzmb + pzmb

6 comparaciones basadas en el estudio Neosphere

Nagayama A. J Natl Cancer Inst 2014



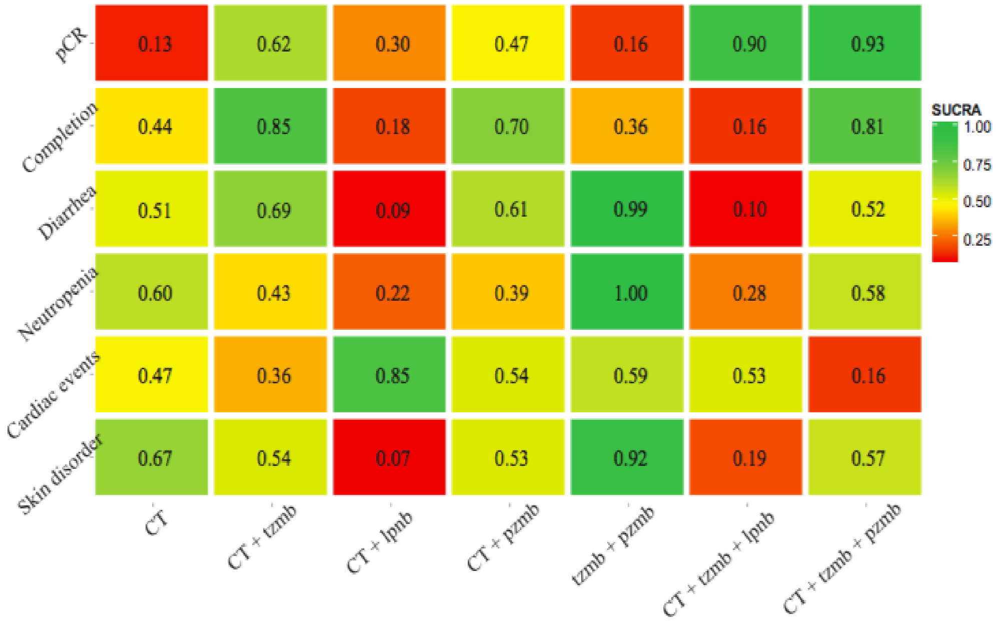
DOI:10.1093/jnci/dju203
First published online September 15, 2014

©The Author 2014. Published by Oxford University Press. All rights reserved.
For Permissions, please e-mail: journals.permissions@oup.com.

REVIEW

Comparative Effectiveness of Neoadjuvant Therapy for HER2–Positive Breast Cancer: A Network Meta-Analysis

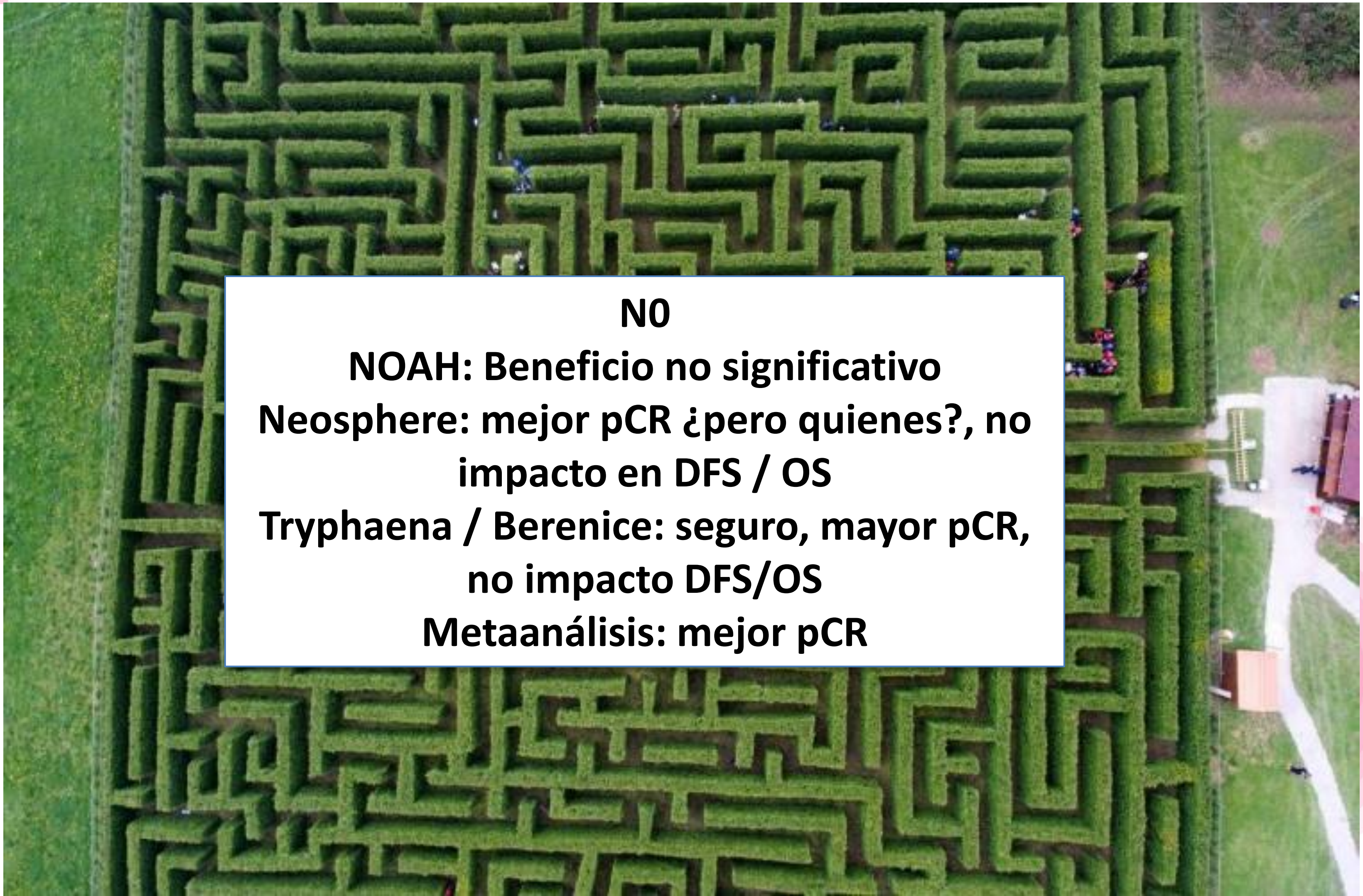
Aiko Nagayama, Tetsu Hayashida, Hiromitsu Jinno, Maiko Takahashi, Tomoko Seki, Akiko Matsumoto,



	CT	CT + tzmb	CT + lpnb	CT + pzmb	tzmb + pzmb	CT + tzmb + lpnb	CT + tzmb + pzmb
pCR	0.13	0.62	0.30	0.47	0.16	0.90	0.93
Completion	0.44	0.85	0.18	0.70	0.36	0.16	0.81
Diarrhea	0.51	0.69	0.09	0.61	0.99	0.10	0.52
Neutropenia	0.60	0.43	0.22	0.39	1.00	0.28	0.58
Cardiac events	0.47	0.36	0.85	0.54	0.59	0.53	0.16
Skin disorder	0.67	0.54	0.07	0.53	0.92	0.19	0.57

- Combinación de 2 anti-HER: >pCR
- Lapatinib: diarrea, neutropenia, < finalizaciones del tto
- QT + tzmb: > finalización del tto
- No diferencias en brazos con CT + 1 anti-HER2
- No diferencias en eventos cardiacos

Nagayama A. J Natl Cancer Inst 2014



N0

NOAH: Beneficio no significativo

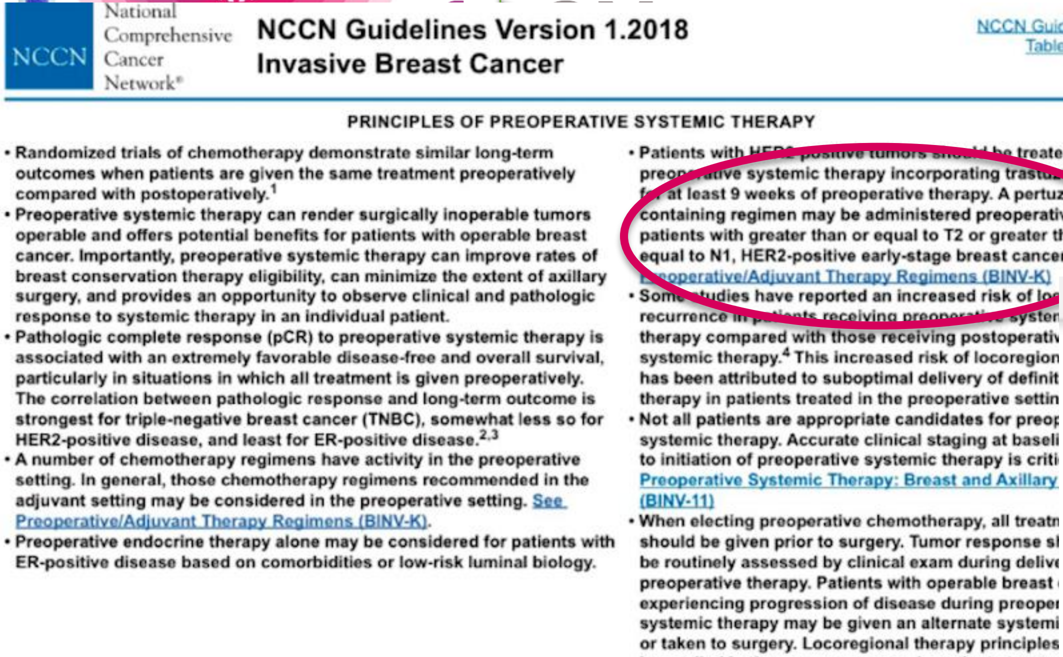
Neosphere: mejor pCR ¿pero quienes?, no impacto en DFS / OS

Tryphaena / Berenice: seguro, mayor pCR, no impacto DFS/OS

Metaanálisis: mejor pCR

Houston tenemos un problema.
Hay que abortar Mision

GUÍAS: HER+ NEOADYUVANCIA-N0



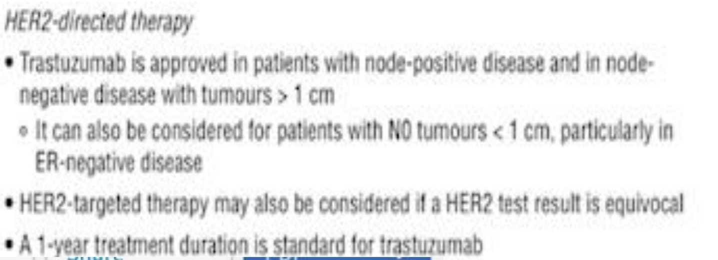
National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF PREOPERATIVE SYSTEMIC THERAPY

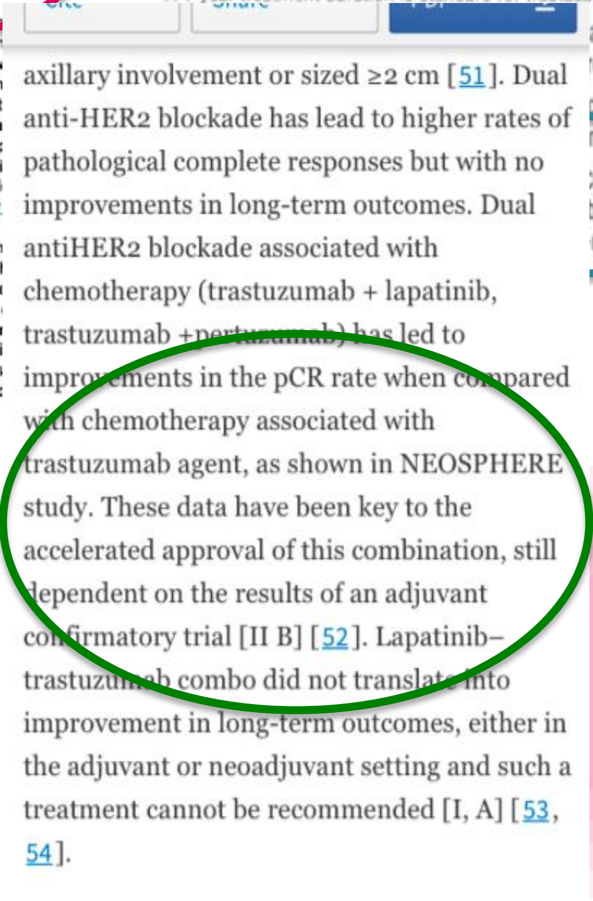
- Randomized trials of chemotherapy demonstrate similar long-term outcomes when patients are given the same treatment preoperatively compared with postoperatively.[1]
- Preoperative systemic therapy can render surgically inoperable tumors operable and offers potential benefits for patients with operable breast cancer. Importantly, preoperative systemic therapy can improve rates of breast conservation therapy eligibility, can minimize the extent of axillary surgery, and provides an opportunity to observe clinical and pathologic response to systemic therapy in an individual patient.
- Pathologic complete response (pCR) to preoperative systemic therapy is associated with an extremely favorable disease-free and overall survival, particularly in situations in which all treatment is given preoperatively. The correlation between pathologic response and long-term outcome is strongest for triple-negative breast cancer (TNBC), somewhat less so for HER2-positive disease, and least for ER-positive disease.[2,3]
- A number of chemotherapy regimens have activity in the preoperative setting. In general, those chemotherapy regimens recommended in the adjuvant setting may be considered in the preoperative setting. See Preoperative/Adjuvant Therapy Regimens (BINV-K).
- Preoperative endocrine therapy alone may be considered for patients with ER-positive disease based on comorbidities or low-risk luminal biology.
- Patients with HER2-positive tumors should be treated with preoperative systemic therapy incorporating trastuzumab for at least 9 weeks of preoperative therapy. A pertuzumab-containing regimen may be administered preoperatively to patients with greater than or equal to T2 or greater than or equal to N1, HER2-positive early-stage breast cancer. See Preoperative/Adjuvant Therapy Regimens (BINV-K)
- Some studies have reported an increased risk of lo
recurrence in patients receiving preoperative system
therapy compared with those receiving postoperativ
systemic therapy.[4] This increased risk of locoregion
has been attributed to suboptimal delivery of definit
therapy in patients treated in the preoperative settin
- Not all patients are appropriate candidates for preop
systemic therapy. Accurate clinical staging at baseli
to initiation of preoperative systemic therapy is criti
Preoperative Systemic Therapy: Breast and Axillary
(BINV-11)
- When electing preoperative chemotherapy, all treatn
should be given prior to surgery. Tumor response sl
be routinely assessed by clinical exam during delive
preoperative therapy. Patients with operable breast
experiencing progression of disease during preoper
systemic therapy may be given an alternate systemi
or taken to surgery. Locoregional therapy principles
be applied in the same manner as in patients treatec
nic therapy.



HER2-directed therapy

- Trastuzumab is approved in patients with node-positive disease and in node-negative disease with tumours > 1 cm
  - It can also be considered for patients with N0 tumours < 1 cm, particularly in ER-negative disease
- HER2-targeted therapy may also be considered if a HER2 test result is equivocal
- A 1-year treatment duration is standard for trastuzumab

ac function and 3–4-monthly
recommended
concomitantly with
nd ET is safe
combination of trastuzumab
b plus pertuzumab may be
risk cases



axillary involvement or sized ≥2 cm [51]. Dual anti-HER2 blockade has lead to higher rates of pathological complete responses but with no improvements in long-term outcomes. Dual antiHER2 blockade associated with chemotherapy (trastuzumab + lapatinib, trastuzumab +pertuzumab) has led to improvements in the pCR rate when compared with chemotherapy associated with trastuzumab agent, as shown in NEOSPHERE study. These data have been key to the accelerated approval of this combination, still dependent on the results of an adjuvant confirmatory trial [II B] [52]. Lapatinib–trastuzumab combo did not translate into improvement in long-term outcomes, either in the adjuvant or neoadjuvant setting and such a treatment cannot be recommended [I, A] [53, 54].

UUUUYYY
MENOS MAL QUE ESTO SE ACABA PRONTO
memegenerator.es

CUANDO ESTÁS PERDIDO LO MEJOR ES VOLVER A CASA

GARY
GARY! I'm Sorry
HAVE YOU
Gary come Home!

En nuestro centro…

Complejo Hospitalario de Jaén

42 pacientes tratadas desde julio/15 a sept/17

Población

Edad 34 – 72

T2: 30 (71%)

N+: 22 (52%)

RH -: 11 (26%)

Ki67 ≤ 25%: 18 (43%)

EC x 4 → Pertuzumab + trastuzumab x 4 + paclitaxel x 12

En nuestro centro: Resultados

- Tumorectomías: 29 (69%)
- Número de pCR: 20 (47%) → 6 pTisN0 / 14 pT0pN0

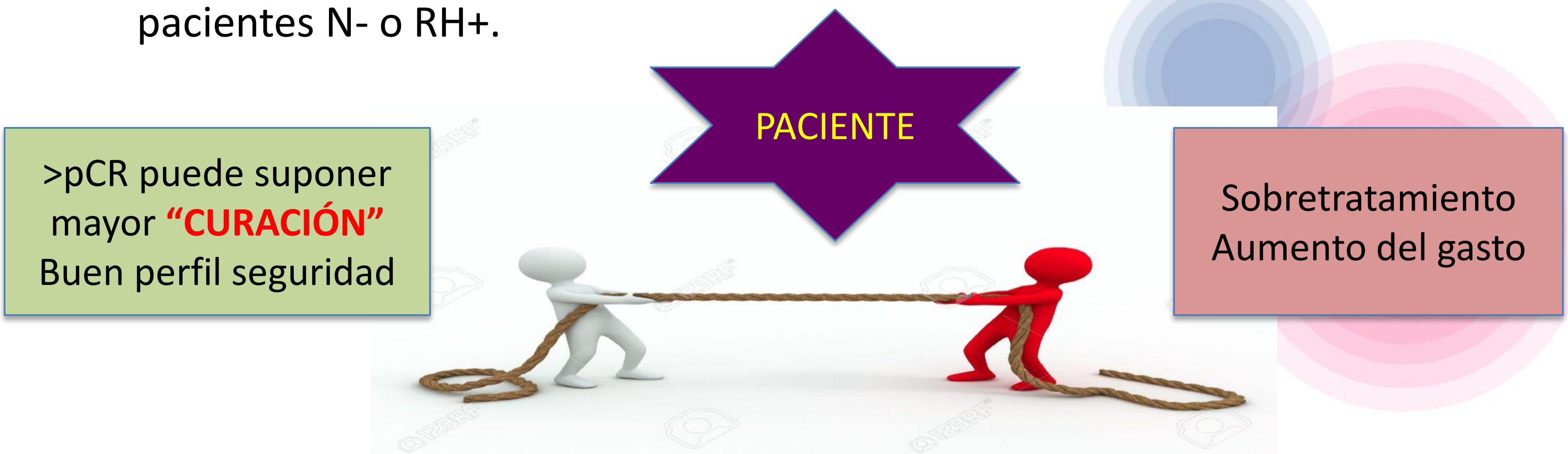
31 pacientes con RH+: 12 pCR (38%)
11 pacientes con RH-: 8 pCR (72%)

22 Pacientes con N+: 12 pCR (54%)
20 pacientes con N-: 8 pCR (40%)

- No “eventos” hasta el momento.

Conclusiones

- La pCR (en T y N) al tratamiento neoadyuvante en cáncer de mama HER2+ parece asociarse con mejor EFS y OS.
- Pertuzumab + trastuzumab + QT se posiciona como tratamiento neoadyuvante en pacientes con cáncer de mama HER2+ con mayor tasa de pCR y perfil de seguridad aceptable.
- La QT no pasa de moda.
- Con los datos actuales no podemos identificar qué pacientes no precisarían tratamiento con Pertuzumab o QT.
- No hay evidencia científica suficiente para no tratar con doble terapia a pacientes N- o RH+.



PACIENTE

>pCR puede suponer mayor **“CURACIÓN”**
Buen perfil seguridad

Sobretratamiento
Aumento del gasto

MUCHAS GRACIAS