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Zaragoza 26-29 septiembre 2023

Tratamiento quirúrgico inicial y adyuvancia según riesgo. ¿Una alternativa?

Dr. César A. Rodríguez, Hospital Clínico Universitario de Salamanca

IBSAL Instituto de Investigación Biomédica de Salamanca

Sacyl Hospital Universitario de Salamanca

Universidad de Salamanca

Clinical and Translational Oncology (2023) 25:2647–2664
https://doi.org/10.1007/s12094-023-03215-4

CLINICAL GUIDES IN ONCOLOGY

SEOM-GEICAM-SOLTI clinical guidelines for early-stage breast cancer (2022)

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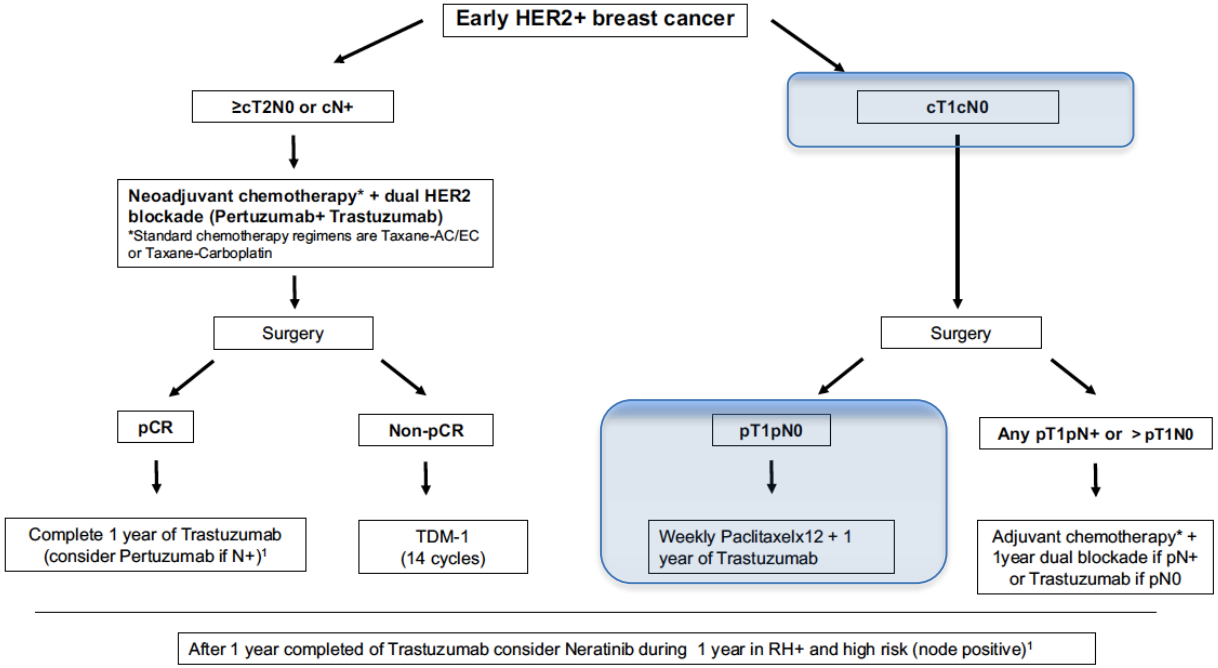

Fig. 2 HER2-positive early breast cancer algorithm. *CT:* chemotherapy. *pCR:* pathologic complete response. (1) This treatment is still awaiting financial approval from the health authorities in Spain

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Neoadjuvant and adjuvant systemic treatment of HER2 breast cancer

Patients with HER2-positive tumors > 2 cm tumor size and/or node-positive disease should be treated with NST including dual HER2 blockade with trastuzumab and pertuzumab and CT with sequential taxanes/anthracyclines or taxane/carboplatin combinations	I, A
Selection of neoadjuvant regimens without anthracyclines may be used if seeking to avoid cardiotoxicity	II, B
HER2Dx may be used to provide estimates of the likelihood of achieving pCR and of the risk of recurrence	II, B
Addition of standard 12-month adjuvant trastuzumab to CT is recommended for HER2 positive breast cancer both in node-positive and in node-negative tumors with a tumor size > 1 cm	I, A
Addition of adjuvant trastuzumab to CT may be considered in cases of node-negative HER2 positive breast cancer with tumor size of 0.5–1.0 cm	II, B
For adjuvant CT of HER2 positive breast cancer, 4 cycles of AC or EC followed by 3 months of paclitaxel (P) or docetaxel (D) or both in combination with trastuzumab (AC/EC P/D + H) or docetaxel, carboplatin and trastuzumab (TCH) are the preferred regimens	I, A
In node-negative, stage I, HER2-positive tumors single-agent weekly paclitaxel and trastuzumab for 12 weeks followed by single-agent trastuzumab (to complete one year) should be considered	II, B
Adjuvant dual HER2 blockade with trastuzumab and pertuzumab for 18 cycles may be considered in patients with node-positive, HER2-positive breast cancer. In clinically node-positive patients that have received neoadjuvant treatment, up to 18 cycles of pertuzumab may be continued after surgery	II, B
Extended adjuvant treatment with neratinib after one year of trastuzumab may be considered in patients with node positive and HR-positive HER2-positive breast cancer	I, B

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Seven-Year Follow-Up Analysis of Adjuvant Paclitaxel and Trastuzumab Trial for Node-Negative, Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer

Sara M. Tolaney, MD, MPH[1]; Hao Guo, MS[1]; Sonia Pernas, MD, PhD[1,2]; William T. Barry, PhD[1]; Deborah A. Dillon, MD[3]; Lauren Ritterhouse, MD, PhD[3,4]; Bryan P. Schneider, MD[5]; Fei Shen, MD[5]; Kit Fuhrman, PhD[6]; Michele Baltay, MS[3]; Chau T. Dang, MD[7,8]; Denise A. Yardley, MD[9]; Beverly Moy, MD, MPH[10]; P. Kelly Marcom, MD[11]; Kathy S. Albain, MD[12]; Hope S. Rugo, MD[13]; Mathew J. Ellis, MB, BChir, PhD[14]; Iuliana Shapira, MD[15,16]; Antonio C. Wolff, MD[17]; Lisa A. Carey, MD[18]; Beth Overmoyer, MD[1]; Ann H. Partridge, MD, MPH[1]; Clifford A. Hudis, MD[7,8,19]; Ian E. Krop, MD, PhD[1]; Harold J. Burstein, MD, PhD[1]; and Eric P. Winer, MD[1]

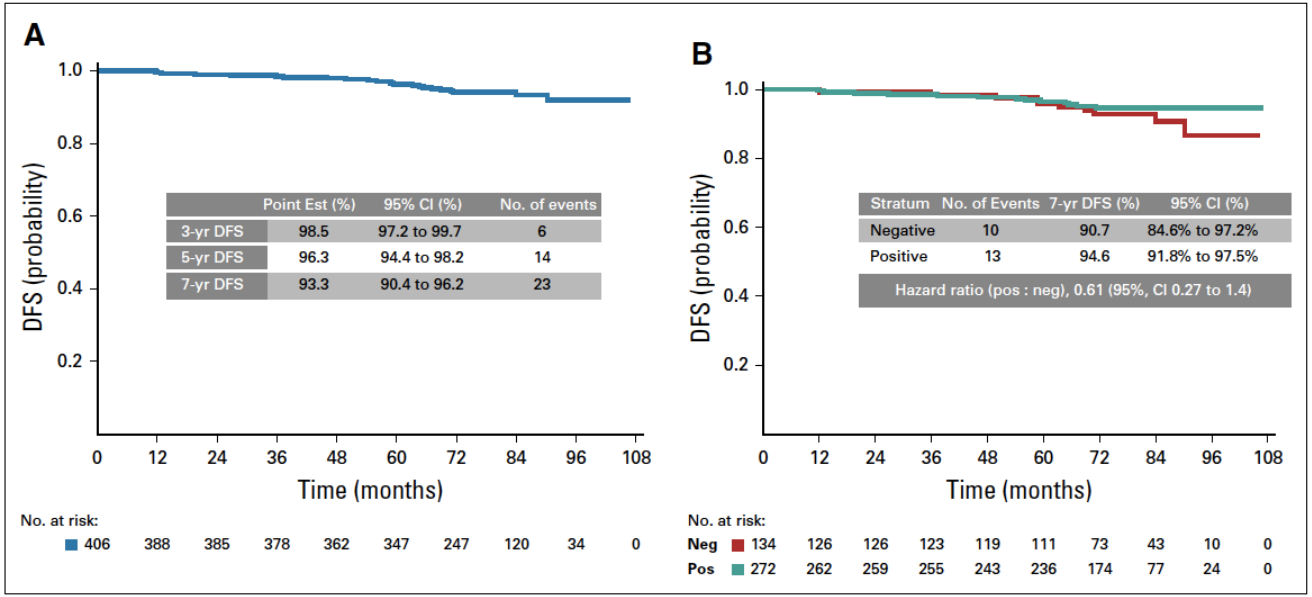

FIG 2. Disease-free survival (DFS). (A) Kaplan-Meier plot of DFS in the intention-to-treat population. (B) DFS according to hormone-receptor status. Abbreviations: neg, negative; Point est, point estimate; pos, positive.

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REVIEW

One year versus a shorter duration of adjuvant trastuzumab for HER2-positive early breast cancer: a systematic review and meta-analysis

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Fig. 4 Meta-analysis of hazard ratios for disease-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI	Year
3.2.1 DFS					
Pivot 2013	0.2469	0.1011	21.4%	1.28 [1.05, 1.56]	2013
Mavroudis 2015	0.4574	0.3103	2.3%	1.58 [0.86, 2.90]	2015
Conte 2017	0.1398	0.1194	15.4%	1.15 [0.91, 1.45]	2017
Joensuu 2018	0.3293	0.1102	18.0%	1.39 [1.12, 1.73]	2018
Earl 2018	0.0677	0.0715	42.9%	1.07 [0.93, 1.23]	2018
Subtotal (95% CI)			**100.0%**	**1.19 [1.08, 1.30]**	
Heterogeneity: Chi² = 5.63, df = 4 (P = 0.23); I² = 29%					
Test for overall effect: Z = 3.70 (P = 0.0002)					
Total (95% CI)			**100.0%**	**1.19 [1.08, 1.30]**	
Heterogeneity: Chi² = 5.63, df = 4 (P = 0.23); I² = 29%					
Test for overall effect: Z = 3.70 (P = 0.0002)					
Test for subgroup differences: Not applicable					

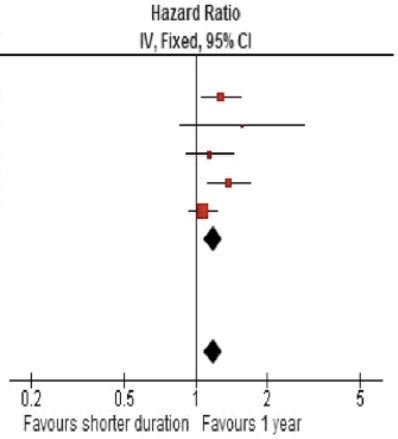

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Fig. 2 Meta-analysis of hazard ratios for overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI	Year
3.1.1 OS					
Pivot 2013	0.3784	0.1634	17.0%	1.46 [1.06, 2.01]	2013
Mavroudis 2015	0.3716	0.4764	2.0%	1.45 [0.57, 3.69]	2015
Conte 2017	0.0583	0.1903	12.5%	1.06 [0.73, 1.54]	2017
Earl 2018	0.131	0.093	52.3%	1.14 [0.95, 1.37]	2018
Joensuu 2018	0.3075	0.1672	16.2%	1.36 [0.98, 1.89]	2018
Subtotal (95% CI)			**100.0%**	**1.22 [1.07, 1.39]**	
Heterogeneity: Chi² = 2.84, df = 4 (P = 0.59); I² = 0%					
Test for overall effect: Z = 2.93 (P = 0.003)					
Total (95% CI)			**100.0%**	**1.22 [1.07, 1.39]**	
Heterogeneity: Chi² = 2.84, df = 4 (P = 0.59); I² = 0%					
Test for overall effect: Z = 2.93 (P = 0.003)					
Test for subgroup differences: Not applicable					

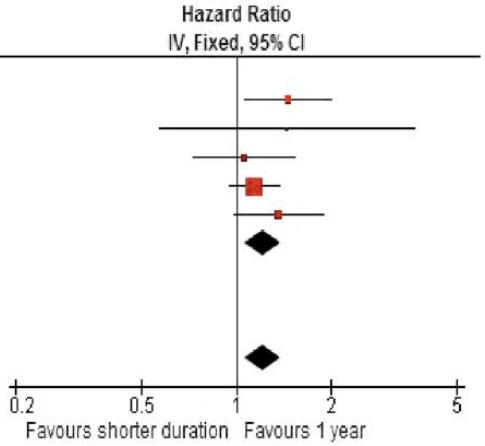

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Fig. 5 Pooled results of risk ratios for cardiac events comparing 1 year versus shorter duration of adjuvant trastuzumab

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Pivot 2013	32	1690	96	1690	32.7%	0.33 [0.22, 0.49]	2013
Mavroudis 2015	2	240	0	241	0.2%	5.02 [0.24, 104.03]	2015
Conte 2017	32	626	90	627	30.6%	0.36 [0.24, 0.52]	2017
Joensuu 2018	22	1085	42	1089	14.3%	0.53 [0.32, 0.87]	2018
Earl 2018	29	1035	66	1046	22.3%	0.44 [0.29, 0.68]	2018
Total (95% CI)		4676		4693	100.0%	0.40 [0.32, 0.49]	
Total events	117		294				

Heterogeneity: Chi² = 5.18, df = 4 (P = 0.27); I² = 23%
Test for overall effect: Z = 8.58 (P < 0.00001)

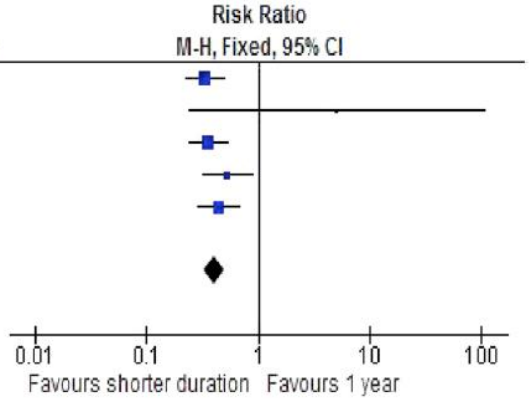

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Table 3 Subgroup analysis for OS and DFS in 1 year versus shorter duration of adjuvant trastuzumab

Subgroups	Number of studies	HR (95% CI)	I^2(%)	*P* for heterogeneity	Test for interaction
Overall survival	5	**1.22 (1.07–1.39)***	0	0.59	***P* = 0.003**
Duration of exp arm	2	1.22 (0.95–1.56)	0	0.39	0.99
9 weeks	3	**1.22 (1.04–1.42)***	0	0.33	
6 months					
Disease-free survival	**5**	**1.19 (1.08–1.3)***	**29**	**0.23**	***P* < 0.001**
Duration of exp arm	2	**1.27 (1.09–1.49)***	26	0.24	0.3
9 weeks	3	**1.15 (1.03–1.9)***	36	0.2	
6 months					
ER status	4	1.14 (0.99–1.3)	22	0.28	0.29
ER+	4	**1.25 (1.11–1.4)***	50	0	
ER−					
Nodal status	4	1.2 (0.99–1.47)	17	0.31	0.32
pN0	4	**1.37 (1.17–1.6)***	0	0.81	
pN+					
Stage	2	1.18 (0.87–1.62)	54	0.14	0.54
I	2	**1.32 (1.09–1.6)***	1	0.39	
II–III					
Grade	1	-	–	–	–
1–2	1				
3					
Histology	1	–	–	–	–
Ductal	1				
Lobular					
Menopausal status	1	–	–	–	–
Premenopausal	1				
Postmenopausal					
Tumour size	1	–	–	–	–
< 2 cm	1				
> 2 cm					
Age	4	**1.36 (1.15–1.61)***	0	0.43	0.34
> 50	4	**1.21 (1.02–1.44)***	0	0.71	
< 50					
Sequence of treatment	2	1.08 (0.65–1.79)	88	0.004	0.48
Sequential	2	**1.33 (1-1.76)***	51	0.15	
Concomitant					

Bold indicate statistically significant values

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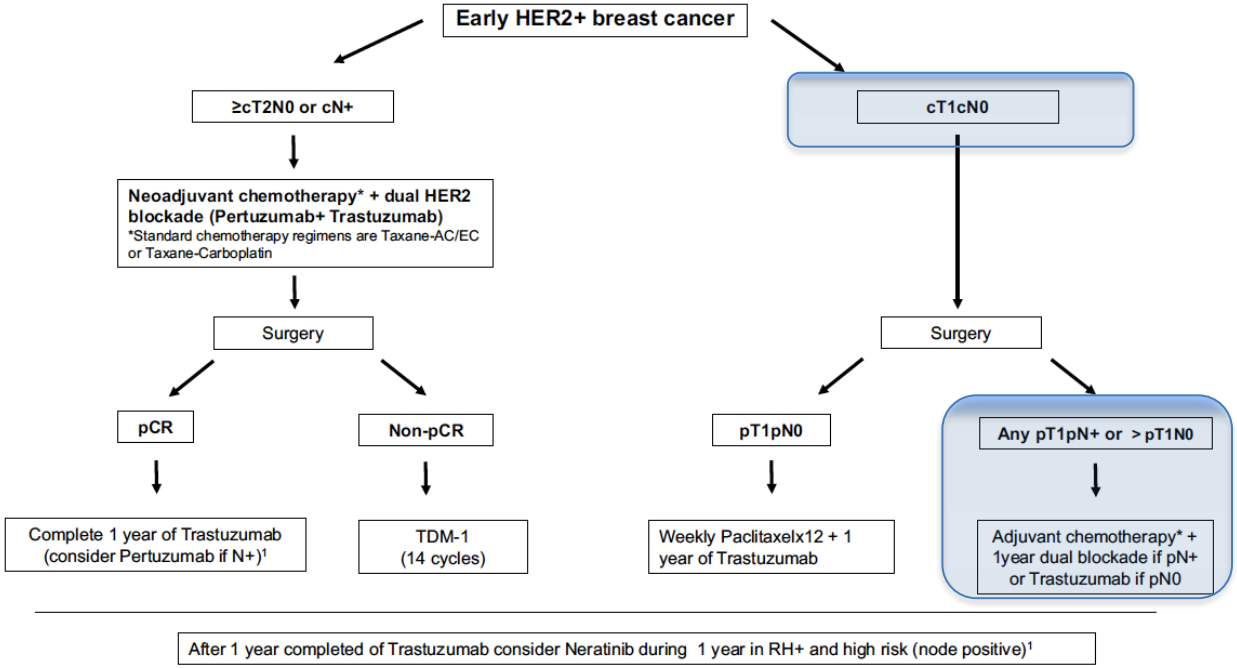

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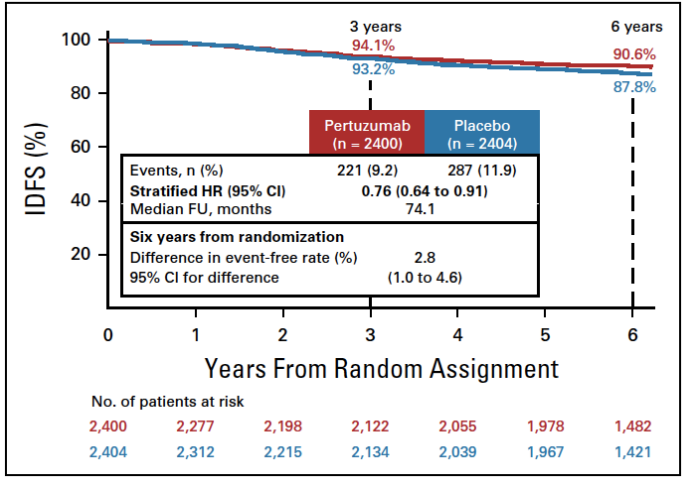

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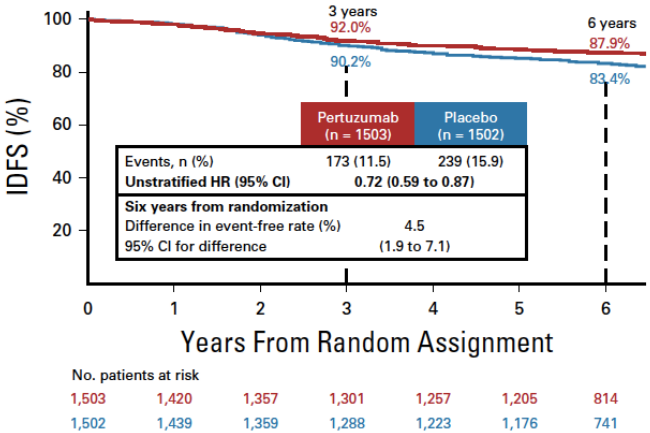

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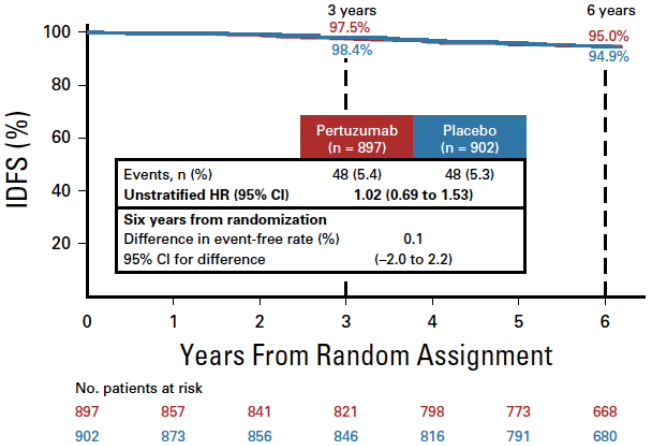

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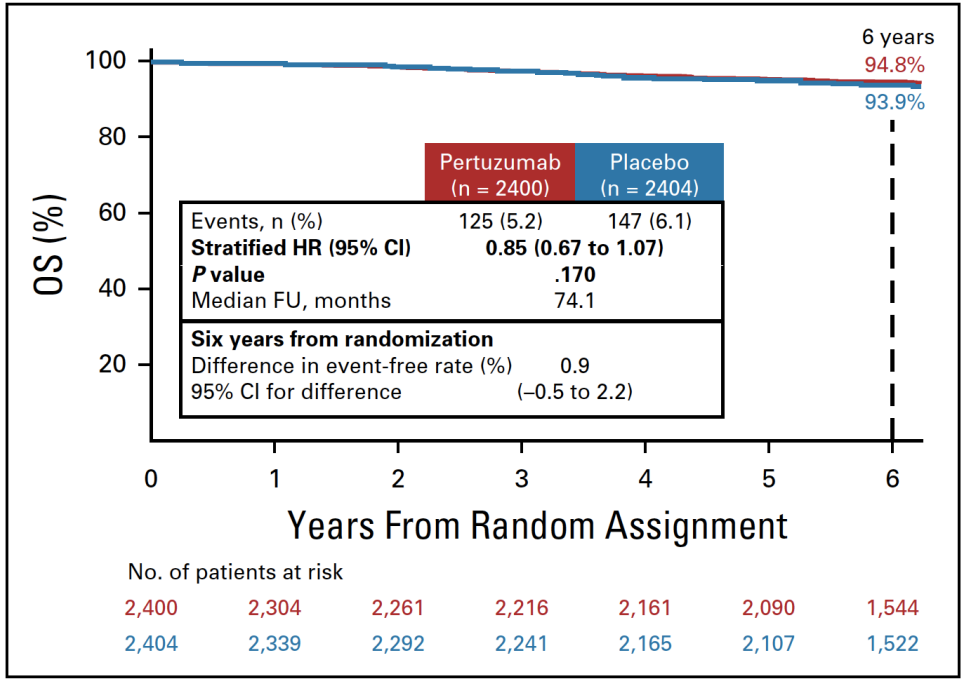

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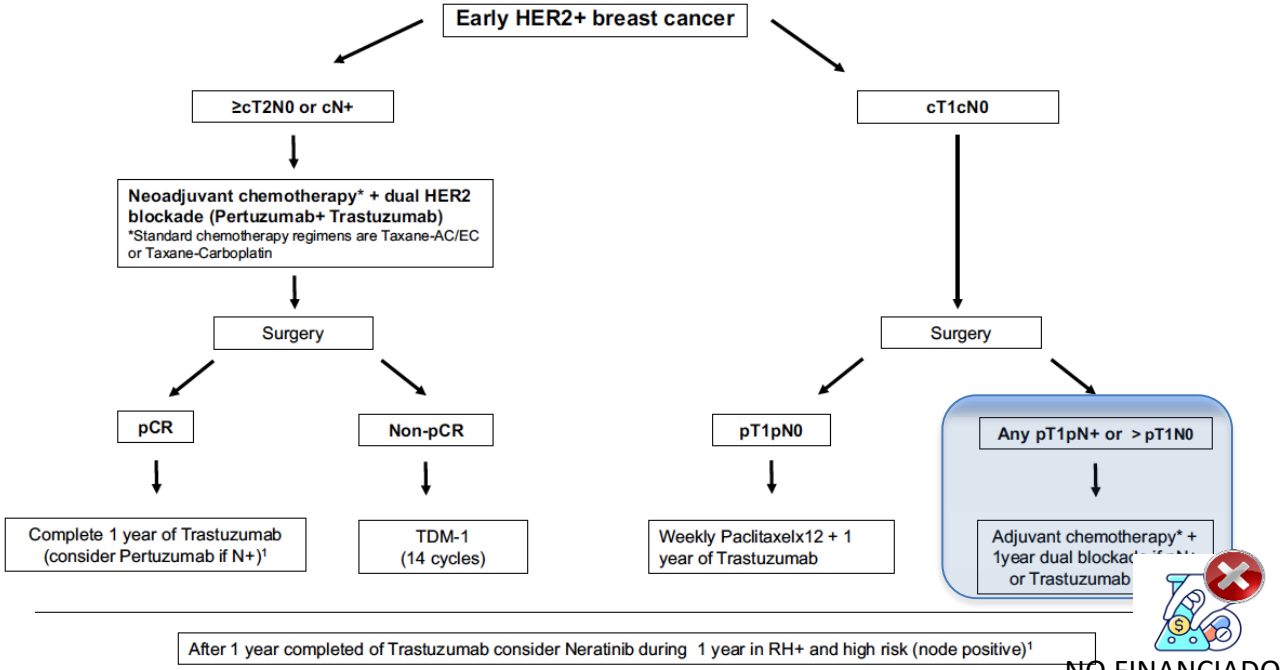

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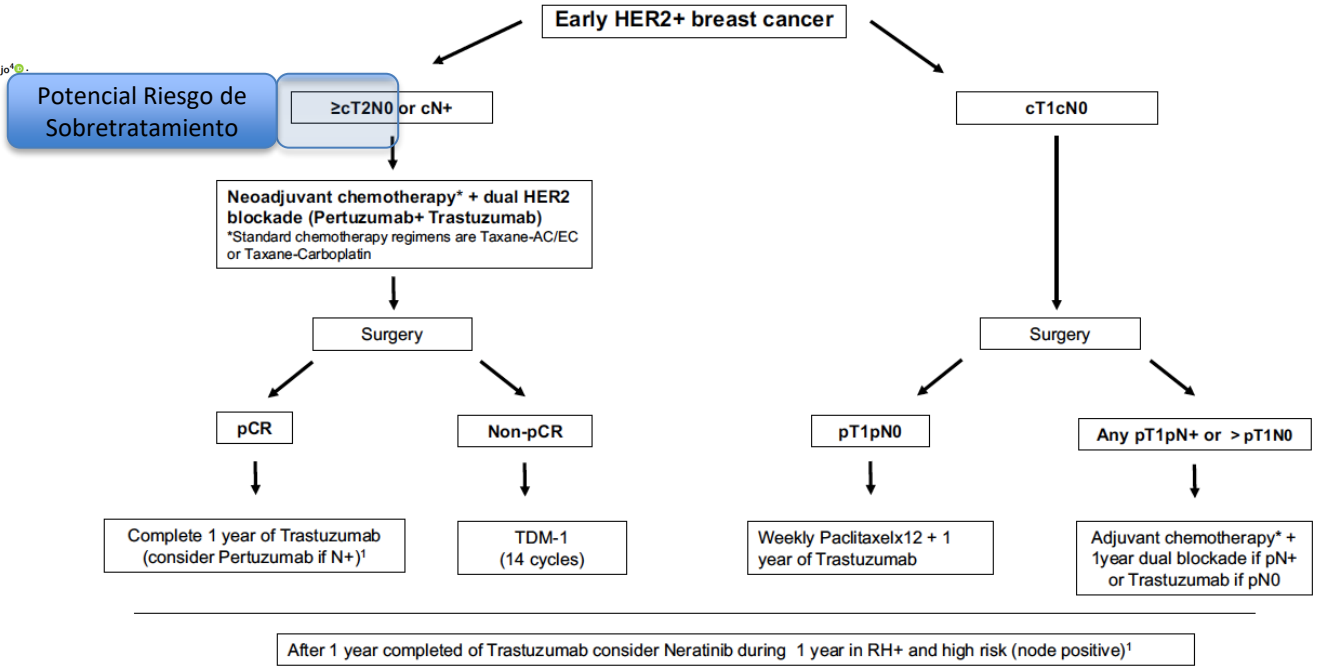

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Early HER2+ breast cancer

Potencial Riesgo de Sobretratamiento

≥cT2N0 or cN+

Neoadjuvant chemotherapy* + dual HER2 blockade (Pertuzumab+ Trastuzumab)
*Standard chemotherapy regimens are Taxane-AC/EC or Taxane-Carboplatin

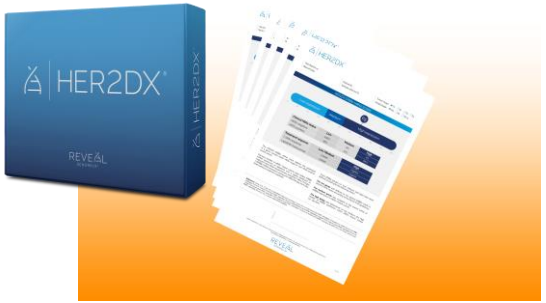
Surgery

rapid communication

Seven-Year Follow-Up Analysis of Adjuvant Paclitaxel and Trastuzumab Trial for Node-Negative, Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer

Sara M. Tolaney, MD, MPH[1]; Hao Guo, MS[1]; Sonia Pernas, MD, PhD[1,2]; William T. Barry, PhD[1]; Deborah A. Dillon, MD[3]; Lauren Ritterhouse, MD, PhD[3,4]; Bryan P. Schneider, MD[5]; Fei Shen, MD[5]; Kit Fuhrman, PhD[6]; Michele Baltay, MS[3]; Chau T. Dang, MD[7,8]; Denise A. Yardley, MD[9]; Beverly Moy, MD, MPH[10]; P. Kelly Marcom, MD[11]; Kathy S. Albain, MD[12]; Hope S. Rugo, MD[13]; Mathew J. Ellis, MB, BChir, PhD[14]; Iuliana Shapira, MD[15,16]; Antonio C. Wolff, MD[17]; Lisa A. Carey, MD[18]; Beth Overmoyer, MD[1]; Ann H. Partridge, MD, MPH[1]; Clifford A. Hudis, MD[7,8,19]; Ian E. Krop, MD, PhD[1]; Harold J. Burstein, MD, PhD[1]; and Eric P. Winer, MD[1]

Size of primary tumor, cm				
T1mi (≤ 0.1)	9 (2)	1 (< 1)	8 (6)	< .001
T1a (0.1 to ≤ 0.5)	68 (17)	29 (10)	39 (30)	
T1b (> 0.5 to ≤ 1.0)	124 (31)	81 (29)	43 (34)	
T1c (> 1.0 to ≤ 2.0)	169 (42)	137 (49)	32 (25)	
T2 (> 2.0 to ≤ 3.0)	36 (9)	30 (11)	6 (5)	



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]

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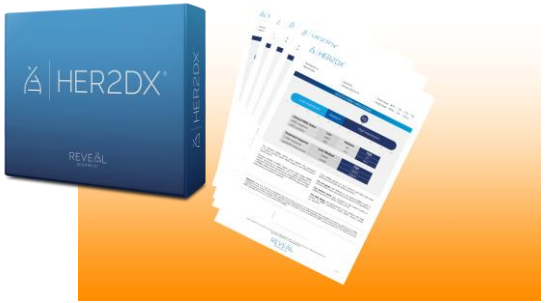
HER2DX 27-gene test

	HER2DX risk score	HER2DX pCR likelihood score	ERBB2 mRNA assay
Training	**Short-HER HER2+** cohort (n=434) (chemotherapy and trastuzumab)	**H.Clinic HER2+** cohort (n=116) (trastuzumab-based chemotherapy)	Combined **Short-HER HER2+** cohort (n=434) and **H.Clinic HER2-** cohort (n=203)
Validation	Combined **H.Clinic/Padova/PAMELA HER2+** cohort (n=268) (trastuzumab-based chemotherapy)	**PAMELA HER2+** cohort (n=91) (trastuzumab and lapatinib without chemotherapy) **H.Clinic/Padova HER2+** cohort (n=67) (trastuzumab-based chemotherapy)	Combined **H.Clinic/Padova/PAMELA HER2+** cohort (n=268) and **SOLTI HER2-** cohort (n=85)
Exploratory	**TCGA** (n=196) **METABRIC** (n=236) **SCAN-B** (n=378) **CALGB-40601** (n=263)	**CALGB-40601** (n=263) **ISPY-2** (n=127)	



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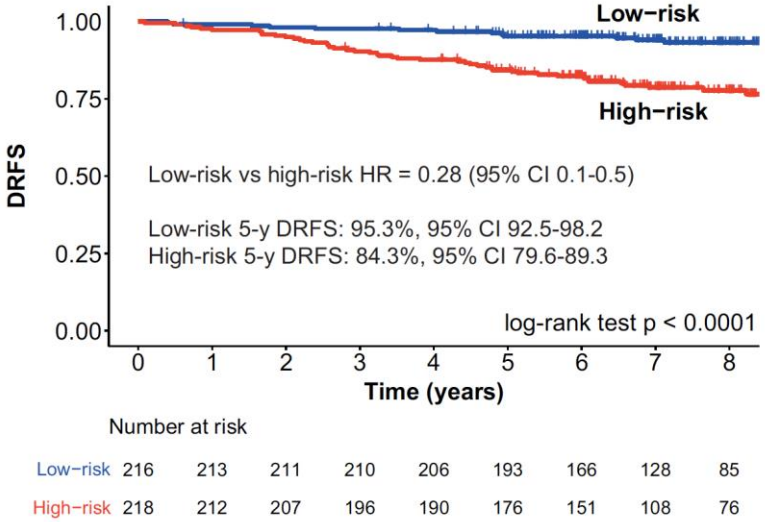

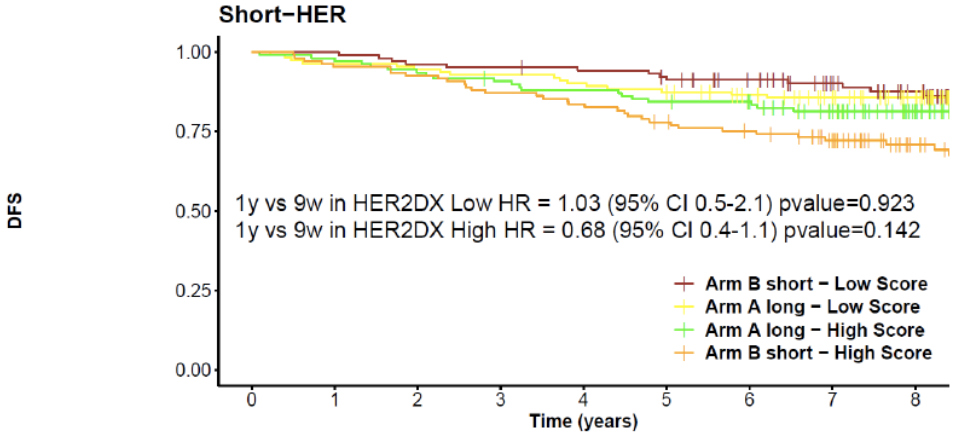

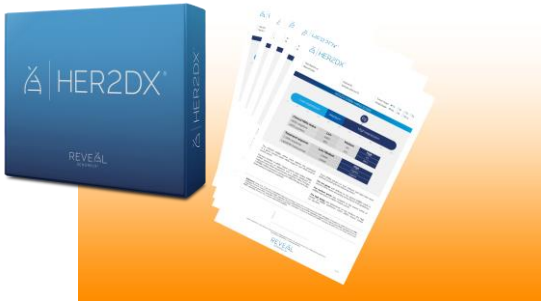

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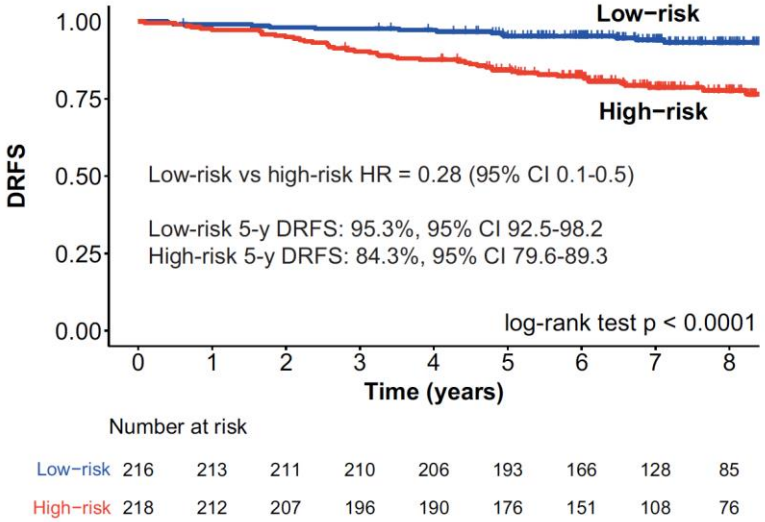
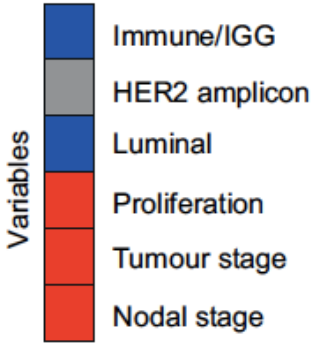
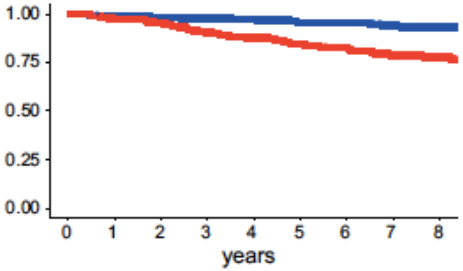


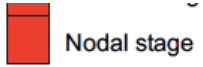
Development and validation of the new HER2DX assay

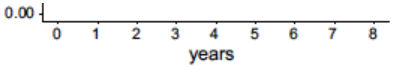
HER2DX risk score





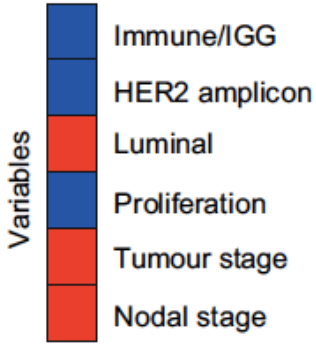
Blue=good outcome
Red=poor outcome

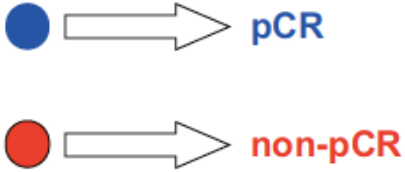




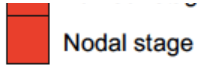
Blue=good outcome
Red=poor outcome

HER2DX pCR likelihood score





Blue=high pCR
Red=low pCR



Blue=high pCR
Red=low pCR

JAMA Oncology | Brief Report

Assessment of a Genomic Assay in Patients With *ERBB2*-Positive Breast Cancer Following Neoadjuvant Trastuzumab-Based Chemotherapy With or Without Pertuzumab

Coralia Bueno-Muiño, MD; Isabel Echavarría, MD; Sara López-Tarruella, MD; Marta Roche-Molina, MD; María del Monte-Millán, MD; Tatiana Massarrah, MD; Yolanda Jerez, MD; Francisco Ayala de la Peña, MD; José Ángel García-Sáenz, MD; Fernando Moreno, MD; Álvaro Rodríguez-Lescure, MD; Diego Malón-Giménez, MD; Ana Isabel Ballesteros García, MD; Mercedes Marín-Aguilera, PhD; Patricia Galván, PhD; Fara Brasó-Maristany, PhD; Adrienne G. Waks, MD; Sara M. Tolaney, MD, MPH; Elizabeth A. Mittendorf, MD, PhD; Ana Vivancos, PhD; Patricia Villagrasa, PhD; Joel. S. Parker, PhD; Charles M. Perou, PhD; Laia Paré, PhD; Guillermo Villacampa, PhD; Aleix Prat, MD, PhD; Miguel Martín, MD, PhD

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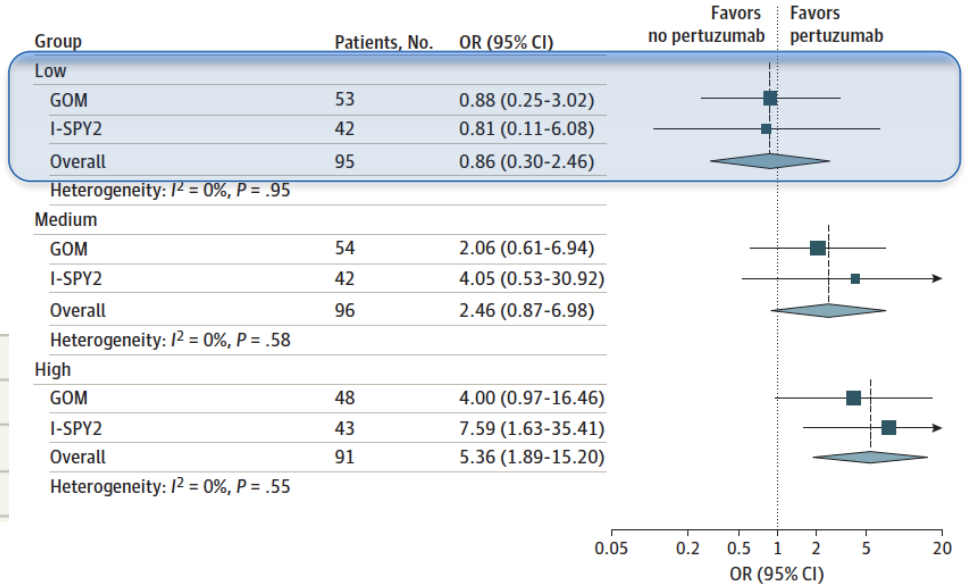
HER2DX pCR score groups		
Low	53	28.3%
Medium	54	70.4%
High	48	75.0%

Figure. Association of HER2DX Pathologic Complete Response (pCR) Groups With Response to Pertuzumab in a Combined Patient-Level Analysis (N = 282)



Clinical and Translational Oncology (2023) 25:2647–2664
https://doi.org/10.1007/s12094-023-03215-4

CLINICAL GUIDES IN ONCOLOGY

SEOM-GEICAM-SOLTI clinical guidelines for early-stage breast cancer (2022)

Francisco Ayala de la Peña[1] · Silvia Antolín Novoa[2] · Joaquín Gavilá Gregori[3] · Lucía González Cortijo[4] · Fernando Henao Carrasco[5] · María Teresa Martínez Martínez[6] · Cristina Morales Estévez[7] · Agostina Stradella[8] · María Jesús Vidal Losada[9] · Eva Ciruelos[10]

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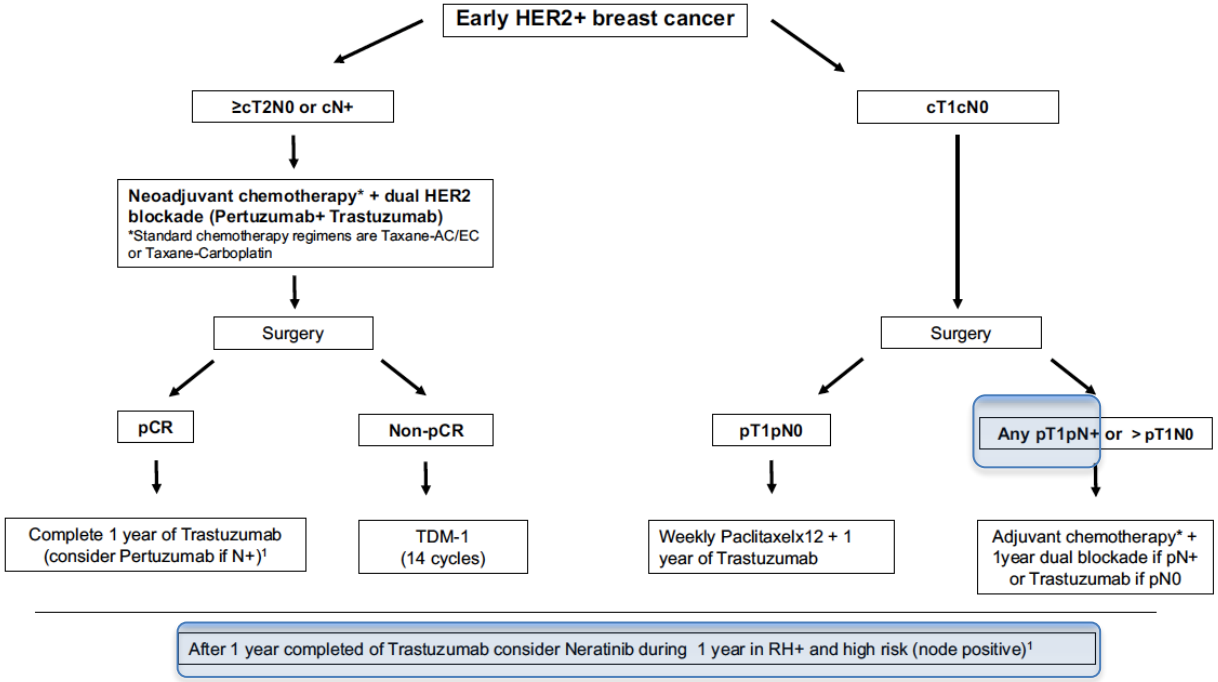
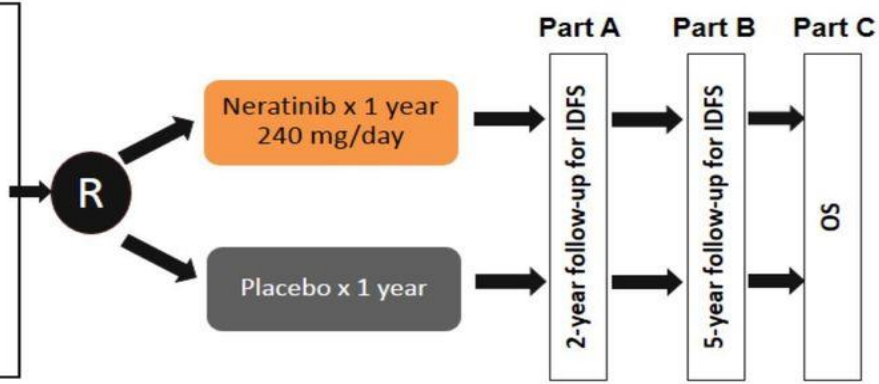


Fig. 2 HER2-positive early breast cancer algorithm. *CT:* chemotherapy. *pCR:* pathologic complete response. (1) This treatment is still awaiting financial approval from the health authorities in Spain

ExteNET Trial: Study Schema

- HER2+ breast cancer (local)
- Prior adjuvant trastuzumab and chemotherapy
- Completed trastuzumab ≤ 1 year prior to study entry
- Lymph node positive or non-pCR after adjuvant therapy
- ER/PR status unknown



- Primary analysis: IDFS in ITT population (n = 2840)
- IDFS at 2 years: hazard ratio = 0.67 (0.50, 0.91); *P* =.0091
- HR positive (n = 1631, 57.4%); hazard ratio = 0.51; *P* =.0013
- Centrally confirmed HER2-positive 60% (n = 1463; 51%); hazard ratio = 0.51; *P* =.002

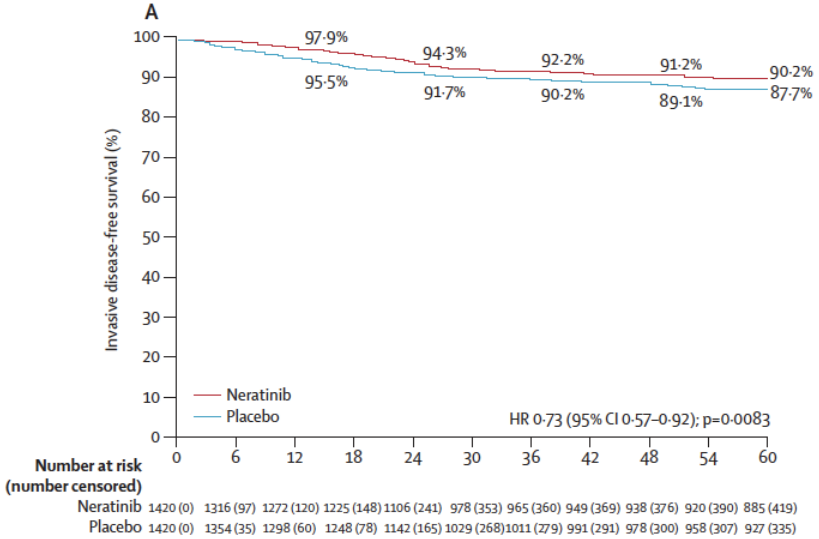
a. Martin M, et al. *Ann Oncol*. 2017;28(Suppl 5): Abstract 149O. Reproduced with permission from Dr. Miguel Martin.
b. Chan A, et al. *Lancet Oncol*. 2016;17:367-377.

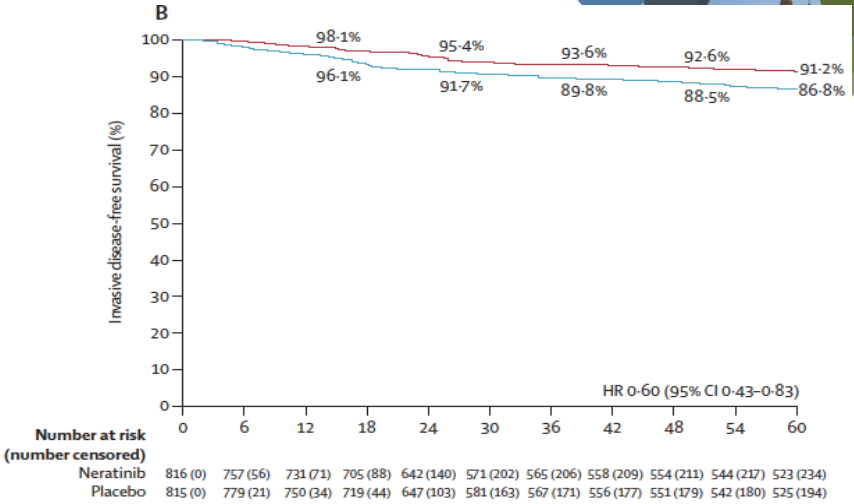
foro debate oncología

Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial

Miguel Martin, Frankie A Holmes, Bent Ejlertsen, Suzette Delaloge, Beverly Moy, Hiroji Iwata, Gunter von Minckwitz, Stephen K L Chia, Janine Mansi, Carlos H Barrios, Michael Gnant, Zorica Tomašević, Neelima Denduluri, Robert Šeparović, Erhan Gokmen, Anna Bashford, Manuel Ruiz Borrego, Sung-Bae Kim, Erik Hugger Jakobsen, Audrone Ciceniene, Kenichi Inoue, Friedrich Overkamp, Joan B Heijns, Anne C Armstrong, John S Link, Anil Abraham Joy, Richard Bryce, Alvin Wong, Susan Moran, Bin Yao, Feng Xu, Alan Auerbach, Marc Buyse, Arlene Chan, for the ExteNET Study Group*

Lancet Oncol 2017; 18: 1688–700





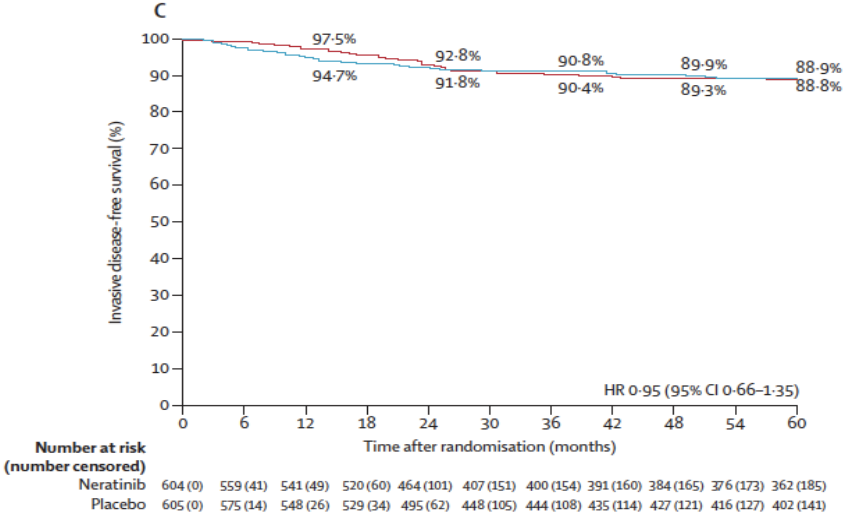


Figure 2: Invasive disease-free survival in the intention-to-treat population (A), patients with hormone receptor-positive breast cancer (B), and patients with hormone receptor-negative breast cancer (C)

foro debate oncología

Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 tria

Miguel Martin, Frankie A Holmes, Bent Ejlertsen, Suzette Delaloge, Beverly Moy, Hiroji Iwata, Gunter von Minckwitz, Stephen K L Chia, Janine Mansi, Carlos H Barrios, Michael Gnant, Zorica Tomašević, Neelima Denduluri, Robert Šeparović, Erhan Gokmen, Anna Bashford, Manuel Ruiz Borrego, Sung-Bae Kim, Erik Hugger Jakobsen, Audrone Ciceniene, Kenichi Inoue, Friedrich Overkamp, Joan B Heijns, Anne C Armstrong, John S Link, Anil Abraham Joy, Richard Bryce, Alvin Wong, Susan Moran, Bin Yao, Feng Xu, Alan Auerbach, Marc Buyse, Arlene Chan, for the ExteNET Study Group*

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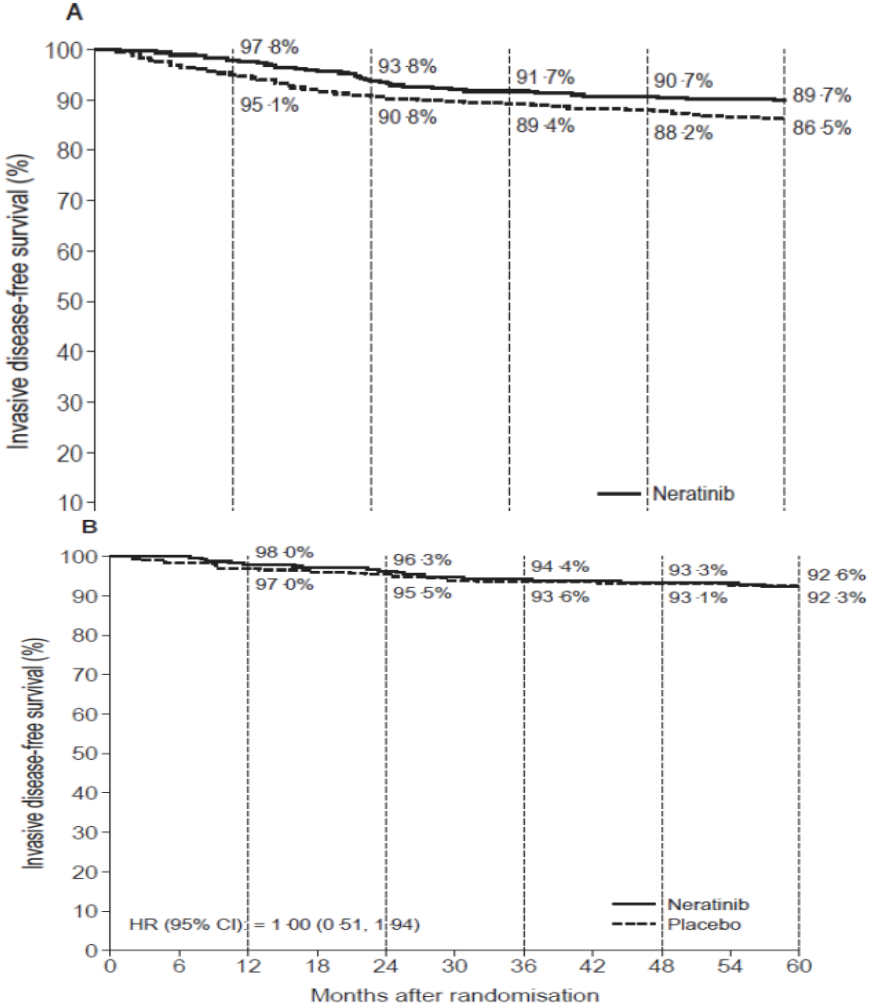


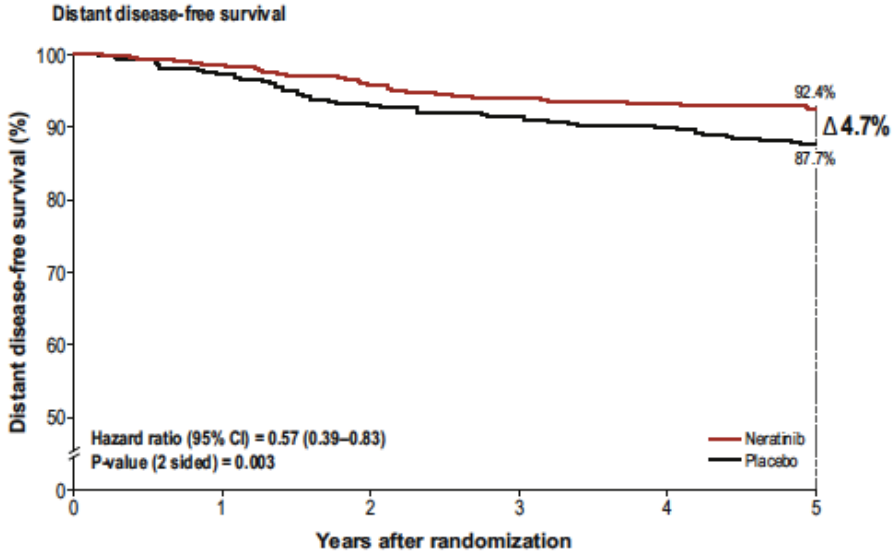
Figure S4. Kaplan-Meier curves for invasive disease-free survival according to time from completion of prior adjuvant trastuzumab to randomisation, showing patients who had received prior trastuzumab within 1 year of randomisation (A) and patients who had received prior trastuzumab more than 1 year before randomisation (B)

foro debate oncología

Final Efficacy Results of Neratinib in HER2-positive Hormone Receptor-positive Early-stage Breast Cancer From the Phase III ExteNET Trial

Arlene Chan,[1] Beverly Moy,[2] Janine Mansi,[3] Bent Ejlertsen,[4] Frankie Ann Holmes,[5] Stephen Chia,[6] Hiroji Iwata,[7] Michael Gnant,[8] Sibylle Loibl,[9] Carlos H. Barrios,[10] Isil Somali,[11] Snezhana Smichkoska,[12] Noelia Martinez,[13] Mirta Garcia Alonso,[14] John S. Link,[15] Ingrid A. Mayer,[16] Søren Cold,[17] Serafin Morales Murillo,[18] Francis Senecal,[19] Kenichi Inoue,[20] Manuel Ruiz-Borrego,[21] Rina Hui,[22] Neelima Denduluri,[23] Debra Patt,[24] Hope S. Rugo,[25] Stephen R.D. Johnston,[26] Richard Bryce,[27] Bo Zhang,[27] Feng Xu,[27] Alvin Wong,[27] Miguel Martin,[28] for the ExteNET Study Group

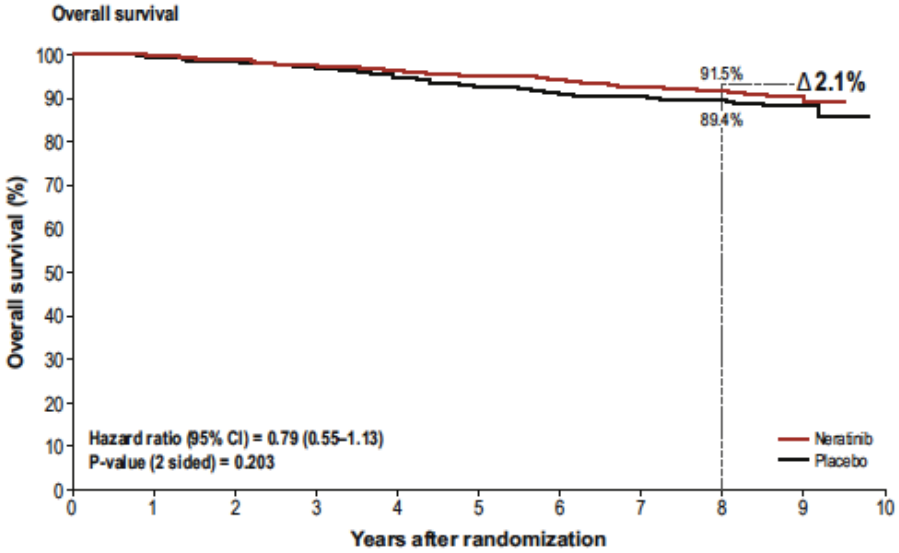
C



No. at risk

Neratinib	670	620	602	580	526	473	469	464	461	454	434
Placebo	664	639	616	594	546	489	480	469	467	457	438

D



No. at risk

Neratinib	670	640	620	578	567	556	534	490	315	78	0
Placebo	664	645	630	589	574	560	537	497	335	78	0

CONCLUSIONES

La Cirugía inicial seguida de una adyuvancia basada en Paclitaxel x 12 semanas y Trastuzumab x 12 meses continúa siendo el abordaje estándar en pacientes con Cáncer de Mama HER2-positivo T1 N0.

En los casos de afectación axilar (N+) evidenciada tras la cirugía, la administración adyuvante de Pertuzumab + Trastuzumab ha demostrado que disminuye de manera significativa el riesgo de recaida (no financiado)

En los casos de afectación axilar (N+) y Receptores Hormonoales positivos, debe considerarse la adyuvancia extendida con Neratinib.

Es necesario identificar pacientes (especialmente T2 N0) en las que el uso de Neoadyuvancia con doble bloqueo puede suponer un sobretratamiento y que pueden seguir estrategias de Cirugía primaria y adyuvancia en desescalada

→ Utilidad de herramientas Genómicas (HER2DX) en la valoración del riesgo de recaída y la probabilidad de alcanzar pCR en neoadyuvancia.

¡Gracias!

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