XVI SIMPOSIUM

BASES BIOLÓGICAS DEL CÁNCER E INNOVACIÓN TERAPÉUTICA

MÁS DE 20 AÑOS A LA VANGUARDIA DE LA FORMACIÓN EN LA BIOLOGÍA Y TRATAMIENTO DEL CÁNCER

SALAMANCA, 23 Y 24 DE MAYO DE 2024

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Diseñando juntos el Tratamiento Sistémico del Cáncer de Mama en 2024.
CÁNCER DE MAMA HER2 POSITIVO

César A. Rodríguez
Hospital Universitario de Salamanca-IBSAL

Conflictos de Interés

- Consultant or Advisory Role: Novartis, Lilly, AstraZeneca, Daiichi Sankyo, MSD, Pierre Fabre, Gilead.

- Speaking: Novartis, Pfizer, Lilly, AstraZeneca, Daiichi Sankyo, MSD, Veracyte, Roche, Eisai, Gilead, Seagen.

Diseñando juntos el Tratamiento Sistémico del Cáncer de Mama en 2024.

CÁNCER DE MAMA HER2 POSITIVO

Enfermedad METASTÁSICA

Supervivencia en CMM

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN CANCER HORIZONS

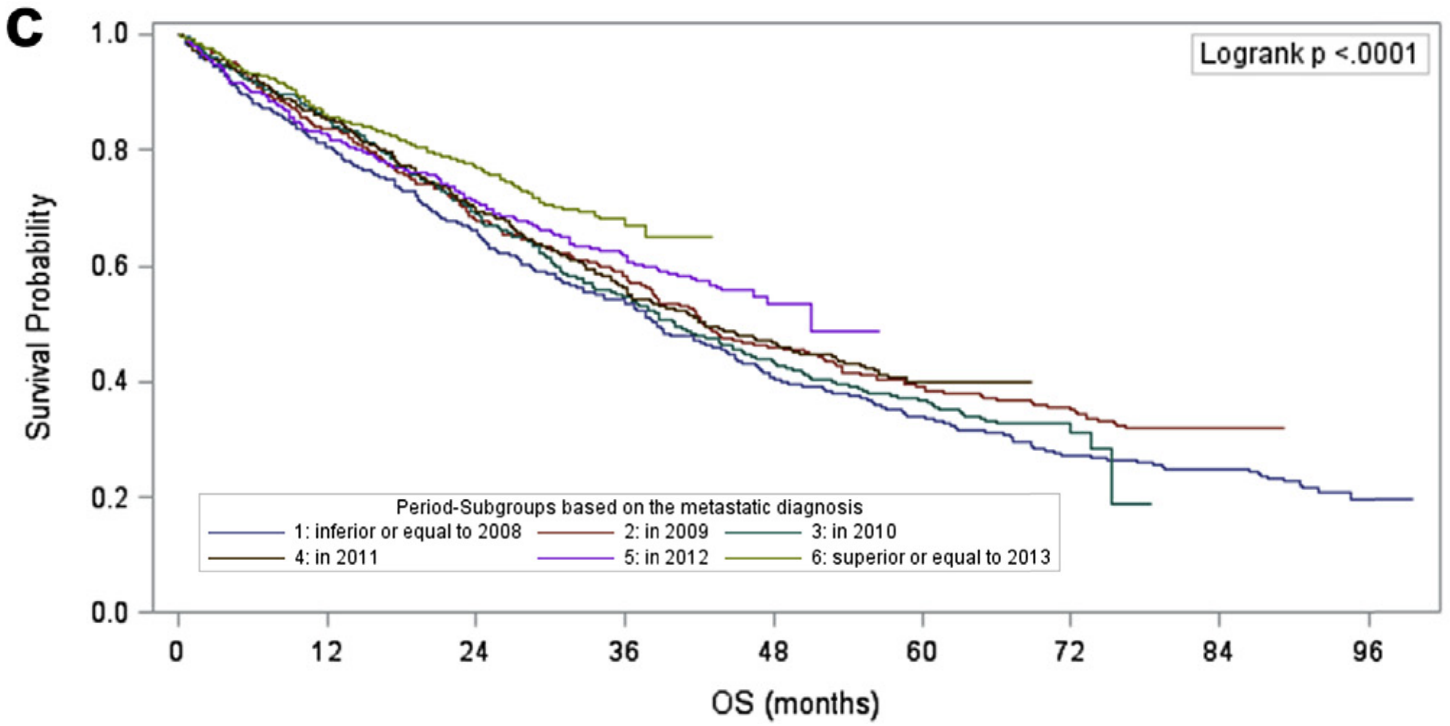
ORIGINAL RESEARCH

Available online 23 April 2021

Evolution of overall survival and receipt of new therapies by subtype among 20 446 metastatic breast cancer patients in the 2008-2017 ESME cohort

T. Grinda[1], A. Antoine[2], W. Jacot[3], C. Blaye[4], P.-H. Cottu[5], V. Diéras[6], F. Dalenc[7], A. Gonçalves[8], M. Debled[3], A. Patsouris[9], M.-A. Mouret-Reynier[10], A. Mailliez[11], F. Clatot[12], C. Levy[13], J.-M. Ferrero[14], I. Desmoulins[15], L. Uwer[16], T. Petit[17], C. Jouannaud[18], M. Lacroix-Triki[19], E. Deluche[20], M. Robain[21], C. Courtinard[21,22,23], T. Bachelot[24], E. Brain[1], D. Pérol[2] & S. Delaloge[1,*]

Overall survival in the HER2+ MBC subcohort by year of diagnosis

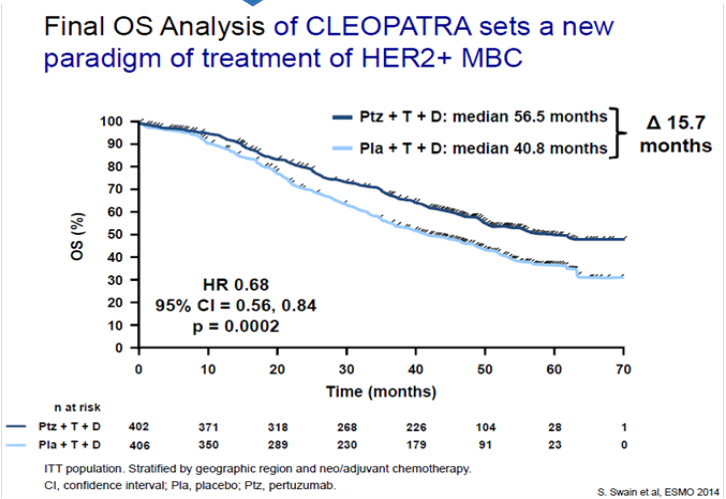


CURRENT STANDARD OF CARE IN 1st LINE HER2-POSITIVE ABC

FIRST LINE

- TAXANE +
- TRASTUZUMAB +
- PERTUZUMAB

Baselga J, et al. NEJM 2012
Swain S, et al NEJM 2015



EVOLUTION OF STANDARD OF CARE IN HER2-POSITIVE ABC

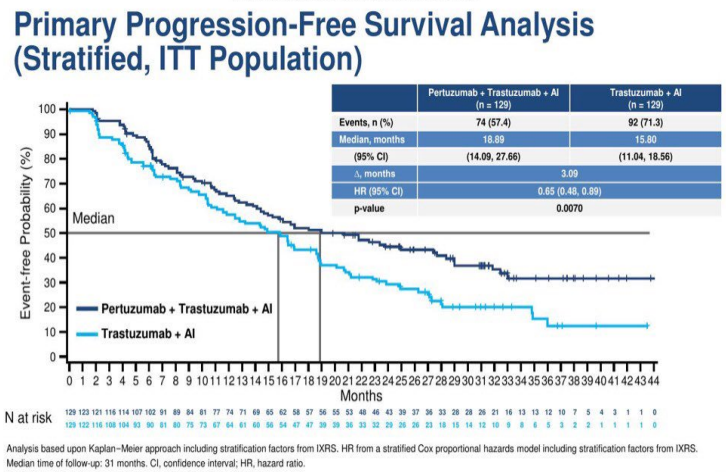
FIRST LINE

- **TAXANE +**
- **TRASTUZUMAB +**
- **PERTUZUMAB**

Baselga J, et al. NEJM 2012
Swain S, et al NEJM 2015

IN PATIENTS WITH HER2+ & ER+ Combination of AntiHER2 ther + ET Must be Considered

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



EVOLUTION OF STANDARD OF CARE IN HER2-POSITIVE ABC until 2022

FIRST LINE

· **TAXANE +**
· **TRASTUZUMAB +**
· **PERTUZUMAB**

Baselga J, et al. NEJM 2012
Swain S, et al NEJM 2015

PROG

2nd LINE

· **T-DM1**
(Trastuzumab/EmtansinE)
Verma S, et al. NEJM 2012.

PROG

BEYOND 2nd LINE

TRASTUZUMAB + LAPATINIB
Blackwell K, el al. JCO 2012

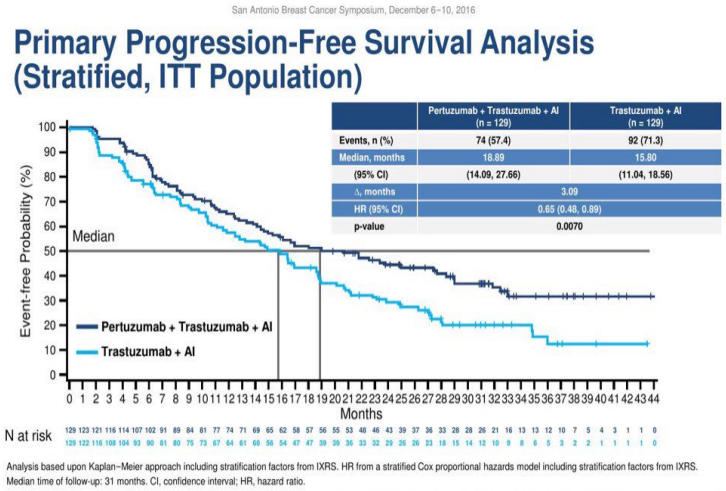
T-DM1
(Trastuzumab/Emtansina)
WHEN PREVIOUSLY NOT USED
Krop IE, et al. Lancet Oncol '14

CAPECITABINE + LAPATINIB Geyer, NEJM '06

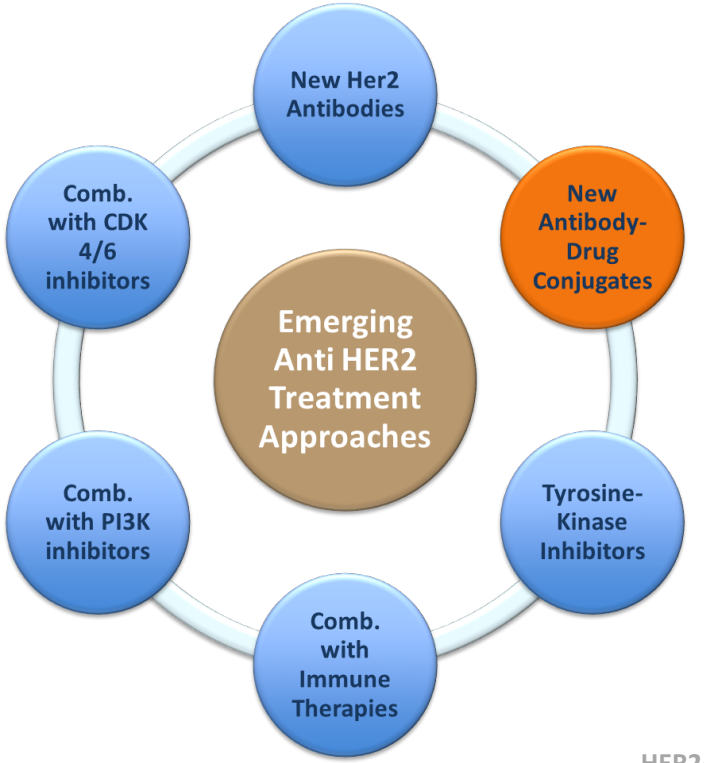
CAPECITABINE + TRASTUZ. V.Minckwitz, JCO'09

VINORELBINE+ TRASTUZ.

IN PATIENTS WITH HER2+ & ER+ Combination of AntiHER2 ther + ET Must be Considered

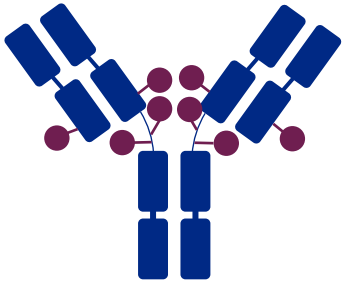


HER2+ ABC
CURRENT STANDARD OF CARE, NEW & EMERGING TREATMENT APPROACHES



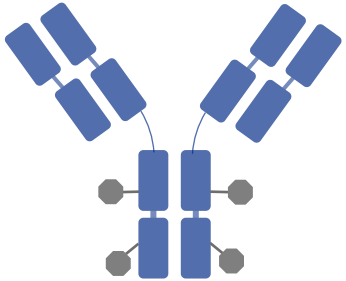
ADC Characteristic Differences Between T-DXd and T-DM1

Trastuzumab deruxtecan (T-DXd)[1]



T-DXd[1-4,a]	ADC Attributes	T-DM1[3-5]
Topoisomerase I inhibitor	**Payload MoA**	Anti-microtubule
~8:1	**Drug-to-antibody ratio**	~3.5:1
Yes	**Tumor-selective cleavable linker?**	No
Yes	**Evidence of bystander anti-tumor effect?**	No

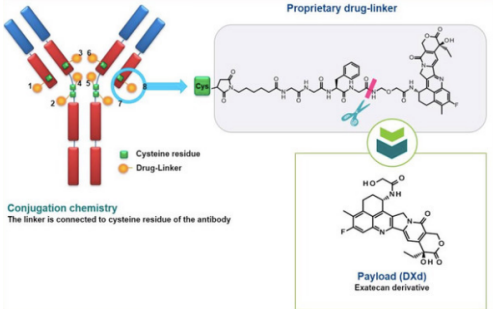
Trastuzumab emtansine (T-DM1)[5]



aThe clinical relevance of these features is under investigation.

1. Nakada T et al. Chem Pharm Bull (Tokyo). 2019;67:173-85. 2. Ogitani Y et al. Clin Cancer Res. 2016;22:5097-108. 3. Trail PA et al. Pharmacol Ther. 2018;181:126-42. 4. Ogitani Y et al. Cancer Sci. 2016;107:1039-46. 5. LoRusso PM et al. Clin Cancer Res. 2011;17:6437-47.

TRASTUZUMAB DERUXTECAN



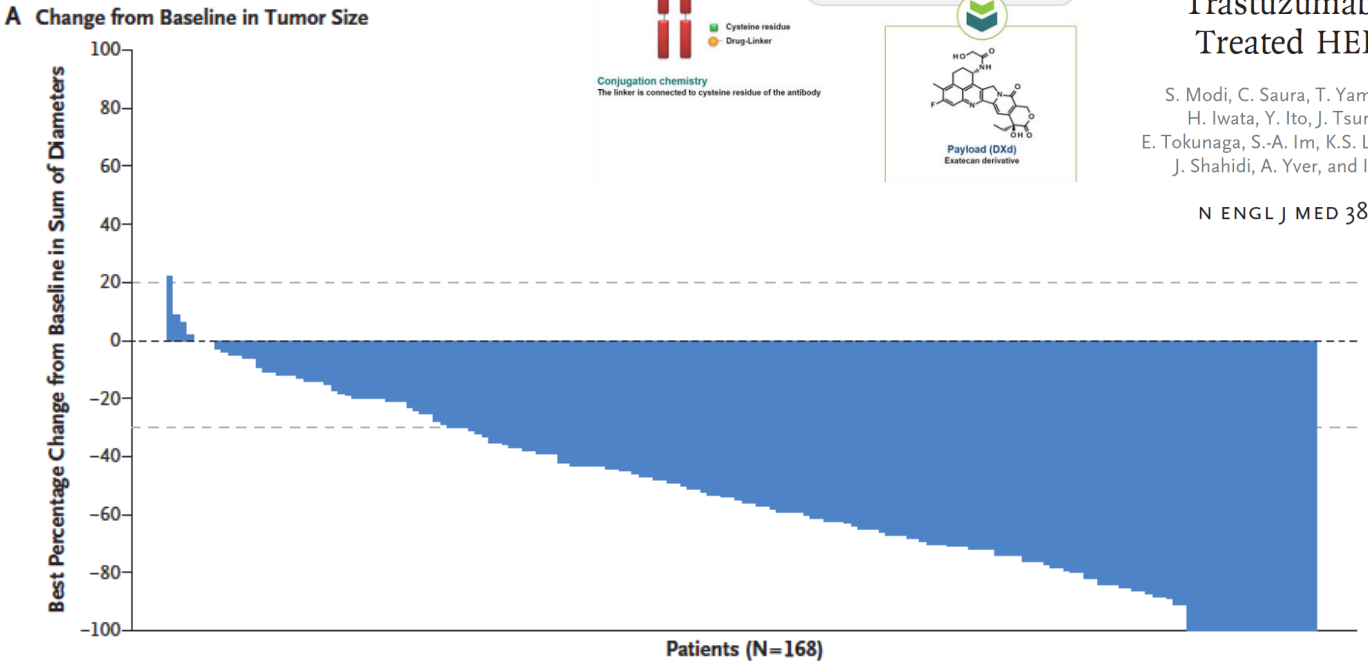
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer

S. Modi, C. Saura, T. Yamashita, Y.H. Park, S.-B. Kim, K. Tamura, F. Andre, H. Iwata, Y. Ito, J. Tsurutani, J. Sohn, N. Denduluri, C. Perrin, K. Aogi, E. Tokunaga, S.-A. Im, K.S. Lee, S.A. Hurvitz, J. Cortes, C. Lee, S. Chen, L. Zhang, J. Shahidi, A. Yver, and I. Krop, for the DESTINY-Breast01 Investigators*

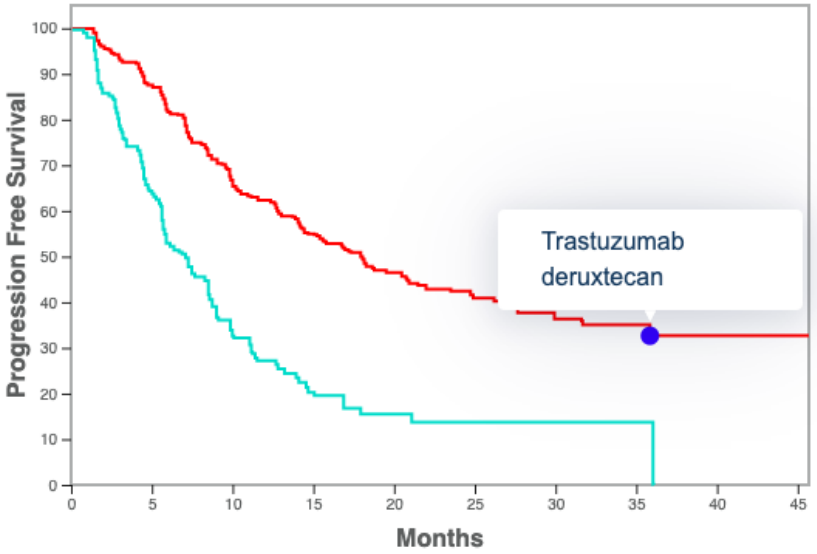
N ENGL J MED 382;7 NEJM.ORG FEBRUARY 13, 2020



DESTINY-Breast02

Randomized phase 3, open-label, multicenter study (NCT03523585)

Progression free survival by BICR



Curves	N	Median (95% CI)
Trastuzumab deruxtecan	406	17.8 (14.3-20.8)
Treatment of physician's choice	202	6.9 (5.5-8.4)

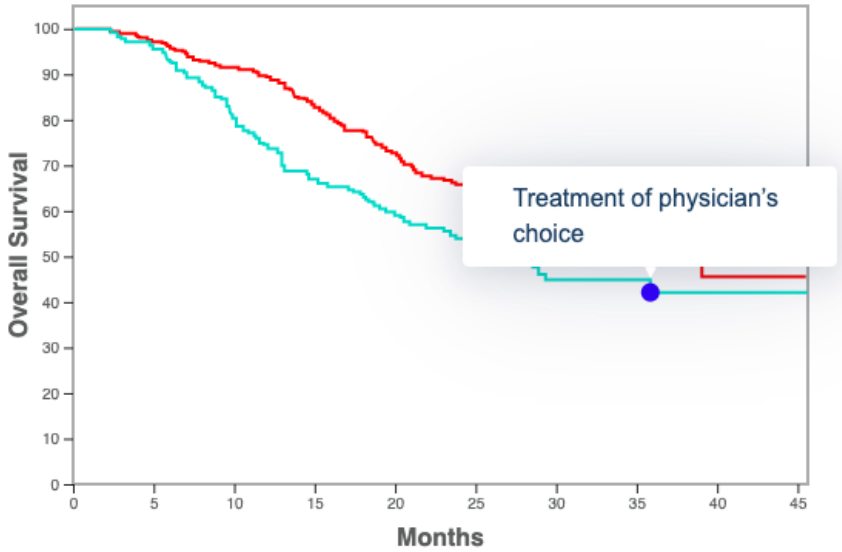
	HR (95% CI)
Trastuzumab deruxtecan vs Treatment of physician's choice	0.36 (0.28 - 0.45)

Krop I, et al. SABCS 2022

DESTINY-Breast02

Randomized phase 3, open-label, multicenter study (NCT03523585)

Overall survival: Secondary end point



Curves	N	Median (95% CI)
Trastuzumab deruxtecan	406	39.2 (32.7-0)
Treatment of physician's choice	202	26.5 (21-0)

	HR (95% CI)	P-value
Trastuzumab deruxtecan vs Treatment of physician's choice	0.66 (0.50 - 0.86)	0.0021

Krop I, et al. SABCS 2022

EVOLUTION OF STANDARD OF CARE IN HER2-POSITIVE ABC until 2022

FIRST LINE

· TAXANE +
· TRASTUZUMAB +
· PERTUZUMAB

Baselga J, et al. NEJM 2012
Swain S, et al NEJM 2015

PROG

2nd LINE

· T-DM1
(Trastuzumab/EmtansinE)

Verma S, et al. NEJM 2012.

PROG

BEYOND 2nd LINE

TUCATINIB + CAPECITABINE + TRASTUZUMAB
Murthy, NEJM '20
↑PFS ↑OS
↑↑CNS

T-DERUXTECAN
Mody, NEJM '19
Krop I, SABCS '22
↑PFS ↑OS

NERATINIB + CAPECITABINE +
Saura, JCO '20
↑PFS ✕OS

MARGETUXIMAB
Rugo, JAMA Oncol 2021
↑PFS ✕OS

TRASTUZUMAB + LAPATINIB

CAPECITABINE + LAPATINIB

CHEMOTHERAPY + TRASTUZUMAB

FIRST LINE*

· AROMATASE inh+
· TRASTUZUMAB +
· PERTUZUMAB

Pertain Trial SABCS 2020

*Upfront (+++) or After Trast + Pert + Chemoth.

IN PATIENTS WITH HER2+ & ER+ Combination of AntiHER2 + ET Must be Considered

LAPATINIB + ENDOCRINE THERAPY

Johnston S, et al. JCO 2009

TRASTUZUMAB + ENDOCRINE THERAPY

Kaufman B, et al. JCO 2009

LAPATINIB + TRASTUZUMAB ENDOCRINE THERAPY

Alternative Trial , JCO 2017

An open-label, multicenter, phase 3 study (NCT03529110)

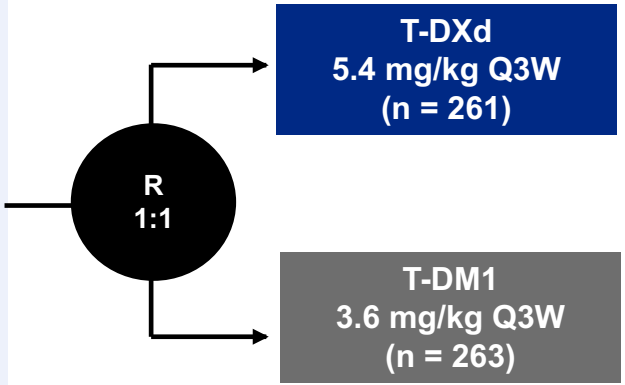
DESTINY-Breast03 - Study Design

Patients

- Unresectable or metastatic HER2 positive[a] breast cancer
- Previously treated with trastuzumab and taxane in advanced/metastatic setting[b]
- Could have clinically stable, treated brain metastases

Stratification factors

- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease



Primary endpoint

- PFS (BICR)

Key secondary endpoint

- OS

Secondary endpoints

- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

Interim analysis for PFS (data cutoff: May 21, 2021)

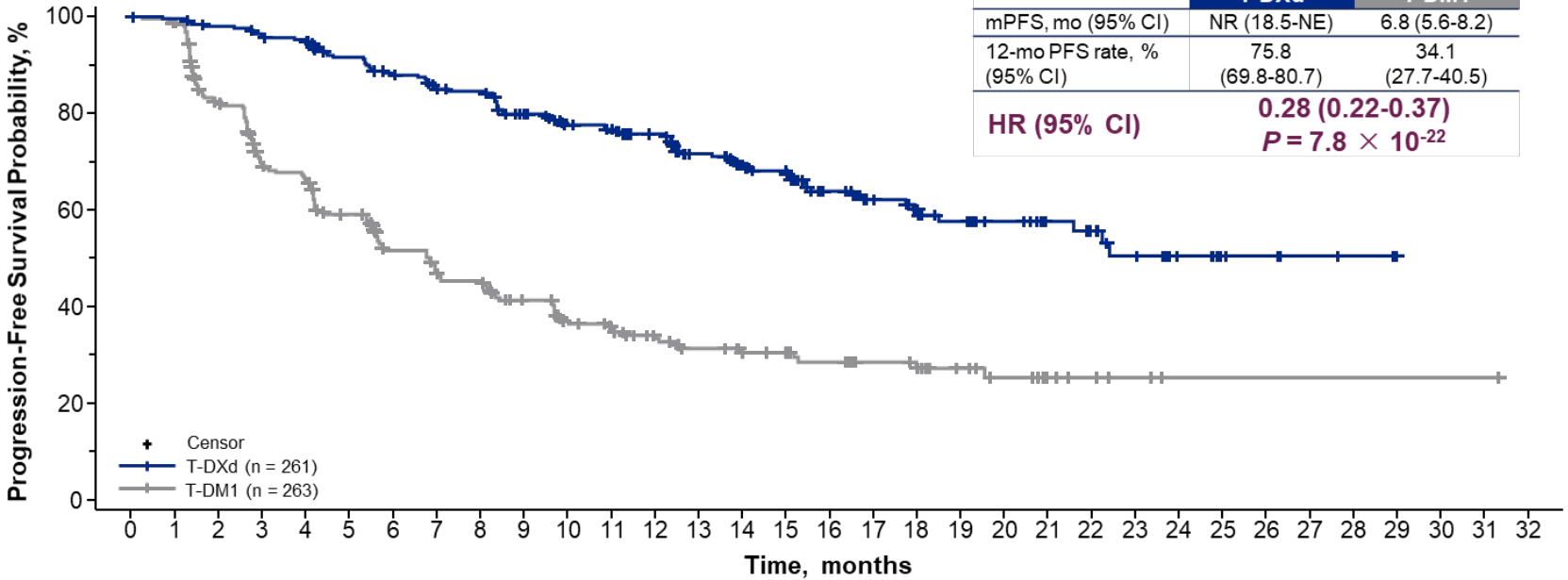
- Efficacy boundary for superiority: $P < 0.000204$ (based on 245 events)
- IDMC recommendation to unblind study (July 30, 2021)

Key secondary endpoint, OS: boundary for efficacy: $P < 0.000265$ (based on 86 events)

aHER2 IHC3+ or IHC2+/ISH+ based on central confirmation. bProgression during or <6 months after completing adjuvant therapy involving trastuzumab and taxane.
Cortés J et al. Presented at: ESMO Virtual Congress 2021; September 17-21, 2021. Presentation 2525.

Primary Endpoint - PFS by BICR

	T-DXd	T-DM1
mPFS, mo (95% CI)	NR (18.5-NE)	6.8 (5.6-8.2)
12-mo PFS rate, % (95% CI)	75.8 (69.8-80.7)	34.1 (27.7-40.5)
HR (95% CI)	**0.28 (0.22-0.37)**	
	***P* = 7.8 × 10^{-22}**	



Patients Still at Risk:

T-DXd (261)	261	256	250	244	240	224	214	202	200	183	168	164	150	132	112	105	79	64	53	45	36	29	25	19	10	6	5	3	2	0
T-DM1 (263)	263	252	200	163	155	132	108	96	93	78	65	60	51	43	37	34	29	23	21	16	12	8	6	4	1	1	1	1	1	1	1	1	0

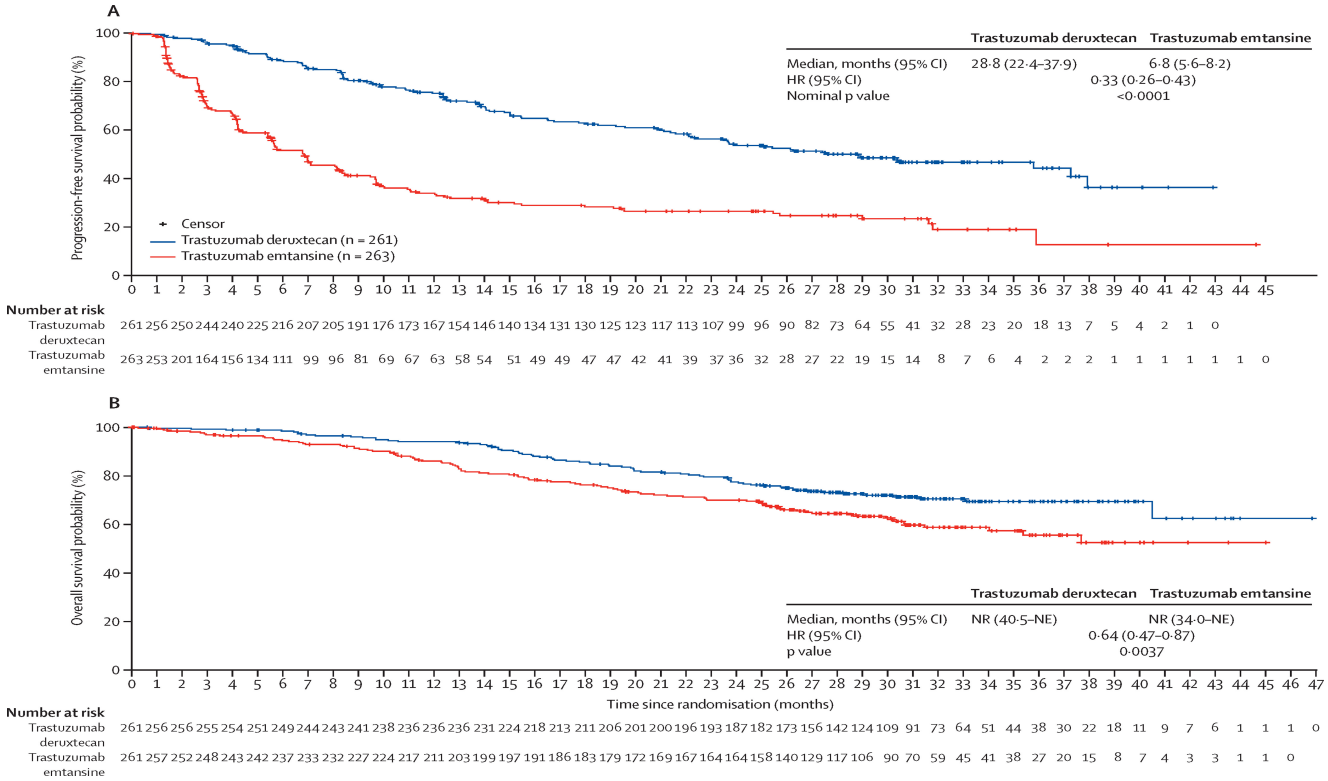
Median PFS follow-up for T-DXd was 15.5 months (range, 15.1-16.6) and for T-DM1 was 13.9 months (range, 11.8-15.1)

Cortés J et al. Presented at: ESMO Virtual Congress 2021; September 17-21, 2021. Presentation 2525.

Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial

Sara A Hurvitz, Roberto Hegg, Wei-Pang Chung, Seock-Ah Im, William Jacot, Vinod Ganju, Joanne Wing Yan Chiu, Binghe Xu, Erika Hamilton, Srinivasan Madhusudan, Hiroji Iwata, Sevilay Altintas, Jan-Willem Henning, Giuseppe Curigliano, José Manuel Perez-Garcia, Sung-Bae Kim, Vanessa Petry, Chiun-Sheng Huang, Wei Li, Jean-Sebastien Frenel, Silvia Antolin, Winnie Yeo, Giampaolo Bianchini, Sherene Loi, Junji Tsurutani, Anton Egorov, Yali Liu, Jillian Cathcart, Shahid Ashfaque, Javier Cortés

Lancet 2023; 401: 105–17
Published Online
December 7, 2022
https://doi.org/10.1016/S0140-6736(22)02420-5



NO FINANCIADO

FIRST LINE

- TAXANE +
- TRASTUZUMAB +
- PERTUZUMAB

Baselga J, et al. NEJM 2011
Swain S, et al NEJM 2015

PROG →

2nd LINE

- T-DERUXTECAN

(Cortés, et al. ESMO 2021, Lancet 2023).

↑PFS ↑OS

PROG →

BEYOND 2nd LINE

TUCATINIB + CAPECITABINE + TRASTUZUMAB — ↑PFS ↑OS; ↑↑CNS
Murthy, NEJM '20

T-DERUXTECAN* — ↑PFS ↑OS
Mody, NEJM '19
Krop I, SABCS '23

* Si no administrado Previamente

FIRST LINE*

- AROMATASE inh+
- TRASTUZUMAB +
- PERTUZUMAB

*Upfront (++) or After Trast + Pert + Chemoth.

Pertain Trial SABCS 2020

TRASTUZUMAB + LAPATINIB

CAPECITABINE + LAPATINIB

CHEMO +TRASTUZUMAB

T-DM1 Krop IE, et al. Lancet Oncol '14

NERATINIB + CAPECITABINE — ↑PFS ✗ OS
Saura, JCO '20

MARGETUXIMAB — ↑PFS ✗ OS
Rugo, JAMA Oncol '21

TRASTUZUMAB DUOCARMAZINA — ↑PFS ✗ OS
Saura, ESMO '21

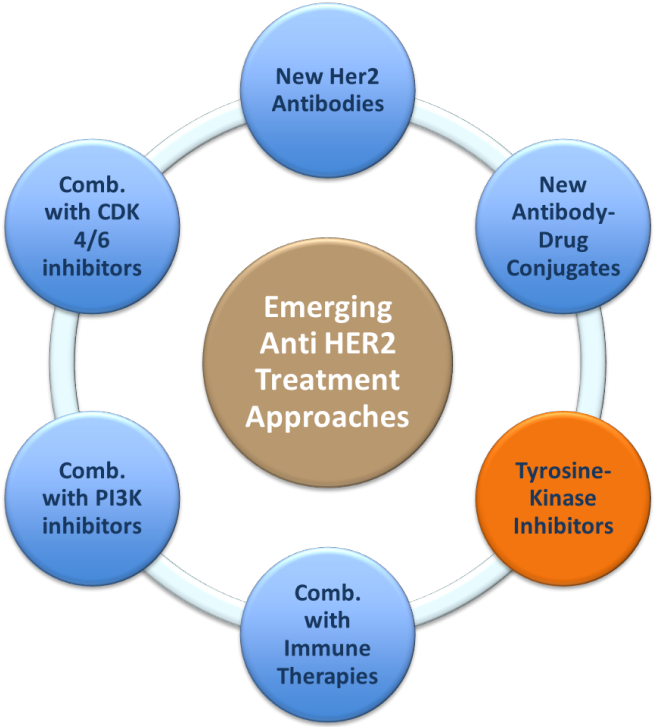
IN PATIENTS WITH HER2+ & ER+ Combination of AntiHER2 + ET Must be Considered

LAPATINIB + ENDOCRINE THERAPY
Johnston S, et al. JCO 2009

TRASTUZUMAB + ENDOCRINE THERAPY

LAPATINIB + TRASTUZUMAB ENDOCRINE THERAPY
Alternative Trial , JCO 2017

HER2+ ABC
CURRENT STANDARD OF CARE, NEW & EMERGING TREATMENT APPROACHES



HER2CLIMB: Phase III Study Design

- Randomized, double-blind, placebo-controlled, active comparator phase III trial at 155 sites in 15 countries (February 2016 to May 2019); data cutoff: September 4, 2019; median f/u: 14.0 mos

Stratified by brain mets (yes vs no), ECOG PS (0 vs 1), and region (US or Canada vs rest of world)

21-day cycles

Patients with HER2+ MBC;
prior trastuzumab, pertuzumab, and T-DM1; ECOG PS 0-1;
brain mets allowed*
(N = 612)

*Including previously treated stable mets, untreated mets not needing immediate local therapy, and previously treated progressing mets not needing immediate local therapy.

Tucatinib 300 mg PO BID +
Trastuzumab 6 mg/kg Q3W (loading dose: 8 mg/kg C1D1) +
Capecitabine 1000 mg/m^2 PO BID, D1-14
(n = 410)

Placebo PO BID +
Trastuzumab 6 mg/kg Q3W (loading dose: 8 mg/kg C1D1) +
Capecitabine 1000 mg/m^2 PO BID, D1-14
(n = 202)

- Primary endpoint: PFS (RECIST v 1.1 by BICR) among first 480 randomized patients
  - 90% power with 288 events at α = 5%, HR: 0.67
- Secondary endpoints (total population): OS, PFS in patients w/ brain mets, ORR in patients w/ measurable disease, safety in patients who received ≥ 1 dose of study tx

Murthy. SABCS 2019. Abstr GS1-01. Murthy. NEJM. 2019;[E-pub].

TUCATINIB

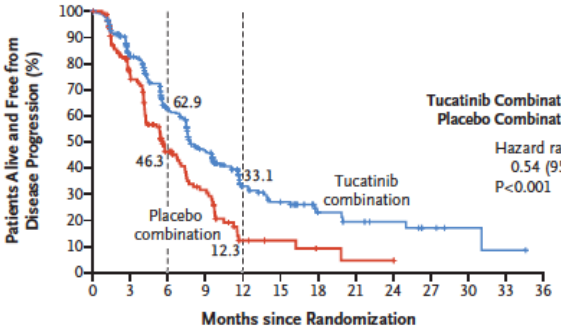
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer

R.K. Murthy, S. Loi, A. Okines, E. Paplomata, E. Hamilton, S.A. Hurvitz, N.U. Lin, V. Borges, V. Abramson, C. Anders, P.L. Bedard, M. Oliveira, E. Jakobsen, T. Bachelot, S.S. Shachar, V. Müller, S. Braga, F.P. Duhoux, R. Greil, D. Cameron, L.A. Carey, G. Curigliano, K. Gelmon, G. Hortobagyi, I. Krop, S. Loibl, M. Pegram, D. Slamon, M.C. Palanca-Wessels, L. Walker, W. Feng, and E.P. Winer

A Kaplan–Meier Estimates of Progression-free Survival



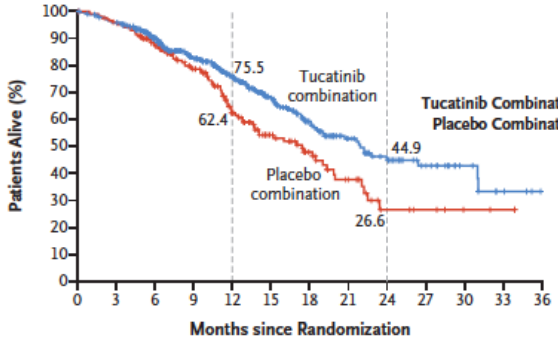
	No. of Events/ No. of Patients	Median Duration (95% CI)
		mo
Tucatinib Combination	178/320	7.8 (7.5–9.6)
Placebo Combination	97/160	5.6 (4.2–7.1)

Hazard ratio for disease progression or death, 0.54 (95% CI, 0.42–0.71)
P<0.001

No. at Risk

Tucatinib combination	320	235	152	98	40	29	15	10	8	4	2	1	0
Placebo combination	160	94	45	27	6	4	2	1	1	0	0	0	0

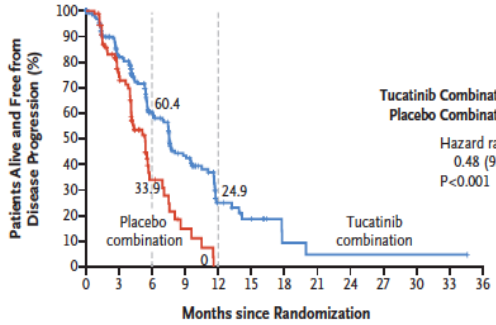
A Kaplan–Meier Estimates of Overall Survival



	No. of Deaths/ No. of Patients	Median Duration (95% CI)
		mo
Tucatinib Combination	130/410	21.9 (18.3–31.0)
Placebo Combination	85/202	17.4 (13.6–19.9)

Hazard ratio for death, 0.66 (95% CI, 0.50–0.88)
P=0.005

A Kaplan–Meier Estimates of Progression-free Survival among Patients with Brain Metastases



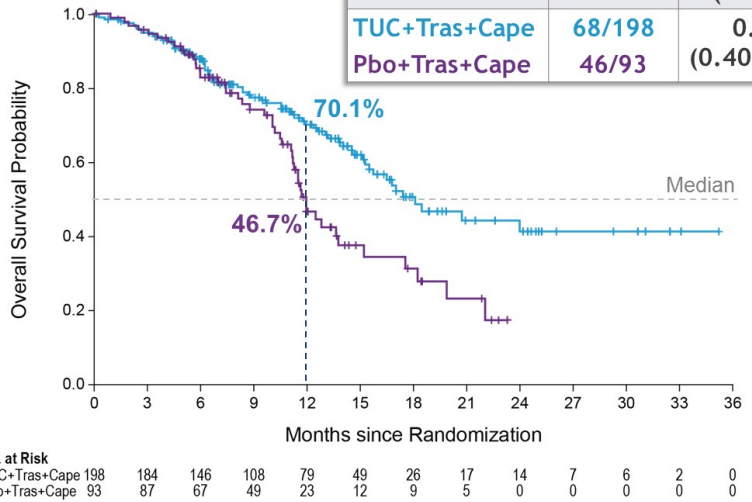
	No. of Events/ No. of Patients	Median Duration (95% CI)
		mo
Tucatinib Combination	106/198	7.6 (6.2–9.5)
Placebo Combination	51/93	5.4 (4.1–5.7)

Hazard ratio for disease progression or death, 0.48 (95% CI, 0.34–0.69)
P<0.001

TUCATINIB

OS Benefit in Patients with Brain Metastases

	Events N=291	HR (95% CI)	P Value
TUC+Tras+Cape	68/198	0.58 (0.40, 0.85)	0.005
Pbo+Tras+Cape	46/93		



No. at Risk

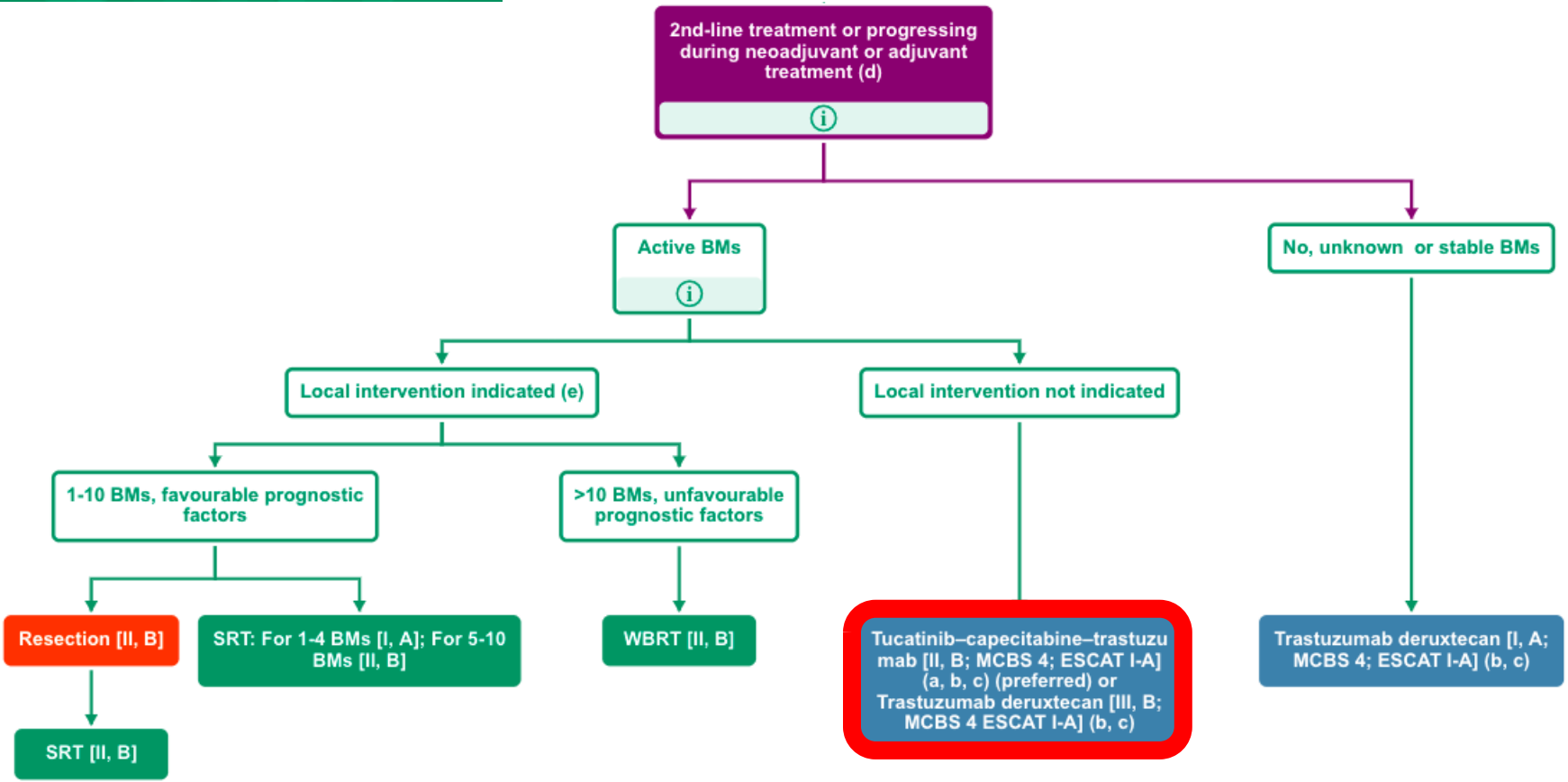
TUC+Tras+Cape	198	184	146	108	79	49	26	17	14	7	6	2	0
Pbo+Tras+Cape	93	87	67	49	23	12	9	5	0	0	0	0	0

Risk of death was reduced by 42% in patients with brain metastases

One-year OS (95% CI):	
TUC+Tras+Cape 70.1% (62.1, 76.7)	Pbo+Tras+Cape 46.7% (33.9, 58.4)
Median OS (95% CI):	
18.1 months (15.5, NE)	12.0 months (11.2, 15.2)

NE: not estimable

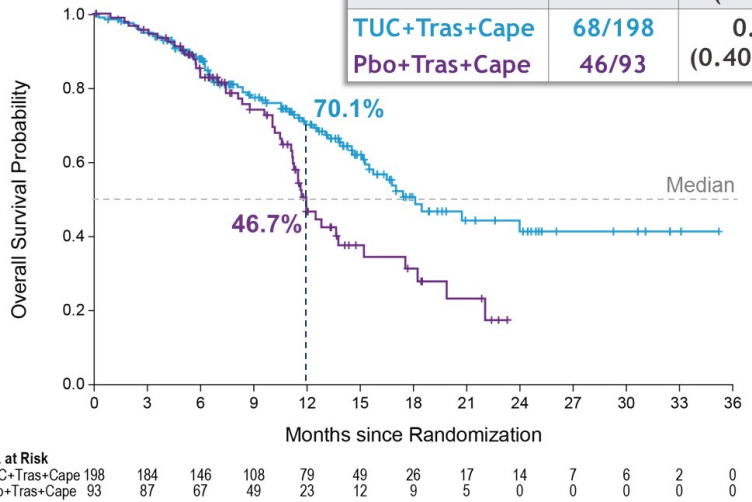
HR: hazard ratio computed from Cox proportional hazards model using stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization. All P values are nominal.


2nd-line treatment or progressing during neoadjuvant or adjuvant treatment (d)
Active BMs
No, unknown or stable BMs
Local intervention indicated (e)
Local intervention not indicated
1-10 BMs, favourable prognostic factors
>10 BMs, unfavourable prognostic factors
Resection [II, B]
SRT: For 1-4 BMs [I, A]; For 5-10 BMs [II, B]
WBRT [II, B]
Tucatinib–capecitabine–trastuzumab [II, B; MCBS 4; ESCAT I-A] (a, b, c) (preferred) or Trastuzumab deruxtecan [III, B; MCBS 4 ESCAT I-A] (b, c)
Trastuzumab deruxtecan [I, A; MCBS 4; ESCAT I-A] (b, c)
SRT [II, B]

TUCATINIB

OS Benefit in Patients with Brain Metastases

	Events N=291	HR (95% CI)	P Value
TUC+Tras+Cape	68/198	0.58 (0.40, 0.85)	0.005
Pbo+Tras+Cape	46/93		



No. at Risk

TUC+Tras+Cape	198	184	146	108	79	49	26	17	14	7	6	2	0
Pbo+Tras+Cape	93	87	67	49	23	12	9	5	0	0	0	0	0

Risk of death was reduced by 42% in patients with brain metastases

One-year OS (95% CI):	
TUC+Tras+Cape 70.1% (62.1, 76.7)	Pbo+Tras+Cape 46.7% (33.9, 58.4)
Median OS (95% CI):	
18.1 months (15.5, NE)	12.0 months (11.2, 15.2)

NE: not estimable

HR: hazard ratio computed from Cox proportional hazards model using stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization. All P values are nominal.

MADRID 2023 ESMO congress

A Pooled Analysis of Trastuzumab Deruxtecan in Patients With HER2-Positive Metastatic Breast Cancer With Brain Metastases (BMs) from DESTINY-Breast01, -02, and -03

Presentation 3770

Sara A. Hurvitz[1], Shanu Modi, Wei Li, Yeon Hee Park, Wei-Pang Chung, Sung-Bae Kim, Javier Cortes, Toshinari Yamashita, Jose Luiz Pedrini, Seock-Ah Im, Ling-Ming Tseng, Nadia Harbeck, Ian Krop, Giuseppe Curigliano, Elton Mathias, Jillian Cathcart, Antonio Cagnazzo, Shahid Ashfaque, Anton Egorov, Fabrice André

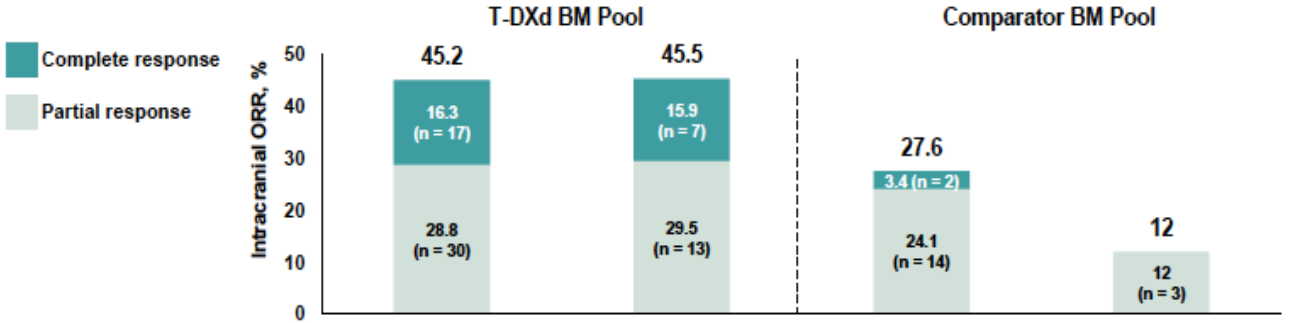
On behalf of the DESTINY-Breast01, -02, and -03 pooled investigators

[1]Fred Hutchinson Cancer Center, University of Washington School of Medicine, Seattle, WA, USA

Madrid, Spain, October 20-24, 2023

Exploratory Best IC Response, ORR, and DoR per BICR

Intracranial ORR[a]



	Treated/stable BMs (n = 104)	Untreated/active BMs (n = 44)	Treated/stable BMs (n = 58)	Untreated/active BMs (n = 25)
Best overall IC response, n (%)				
Stable disease	48 (46.2)	15 (34.1)	28 (48.3)	15 (60.0)
Progressive disease	3 (2.9)	1 (2.3)	7 (12.1)	5 (20.0)
Not evaluable/Missing	6 (5.8)	8 (18.2)	7 (12.1)	2 (8.0)
IC-DoR, median, months (95% CI)	12.3 (9.1-17.9)	17.5 (13.6-31.6)	11.0 (5.6-16.0)	NA[b]

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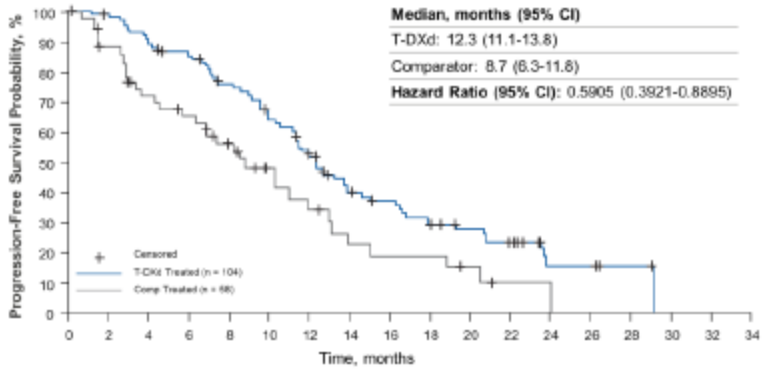
DESTINY-Breast01, -02, and -03

Exploratory CNS-PFS per BICR

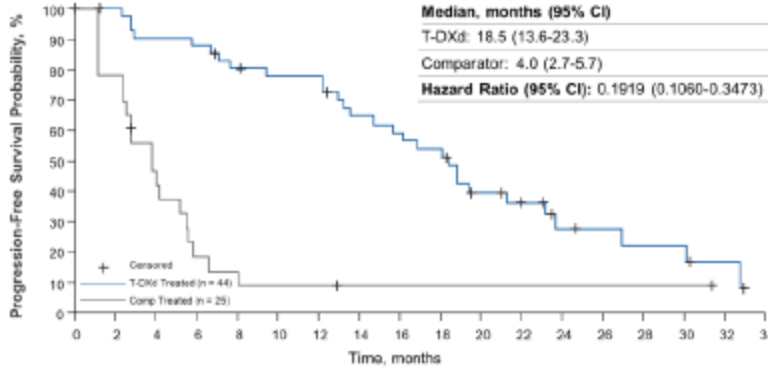
Treated/Stable BMs



Patients still at risk

T-DXd Treated (n = 104)	104	100	89	83	72	58	46	32	28	21	18	12	4	4	2	0	0	0
Comparator Treated (n = 58)	58	44	33	29	22	14	10	6	5	5	3	1	0	0	0	0	0	0

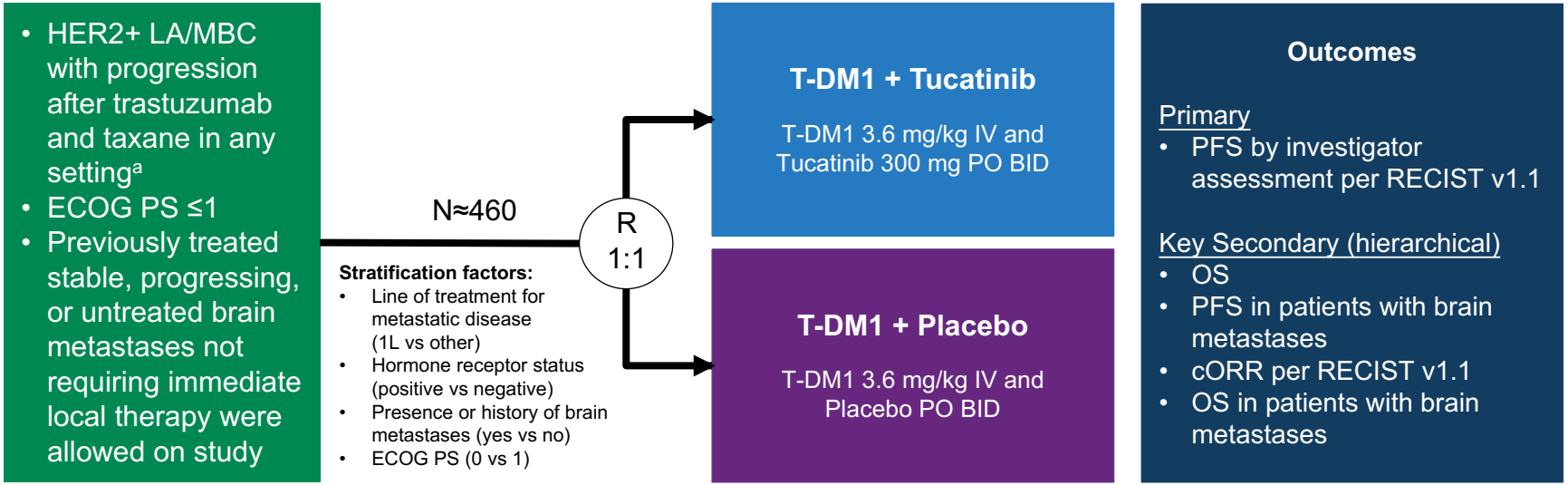
Untreated/Active BMs



Patients still at risk

T-DXd Treated (n = 44)	44	41	37	36	32	30	30	24	22	20	13	11	6	5	4	4	2	0
Comparator Treated (n = 25)	25	18	11	5	3	2	2	1	1	1	1	1	1	1	1	0	0	0

HER2CLIMB-02 Study Design



The primary analysis for PFS was planned after ≈331 PFS events to provide 90% power for hazard ratio of 0.7 at two-sided alpha level of 0.05. The first of two interim analysis for OS was planned at the time of the primary PFS analysis, if the PFS result was significantly positive.[b]

NCT03975647. https://www.clinicaltrials.gov/study/NCT03975647. Accessed Oct 5, 2023.

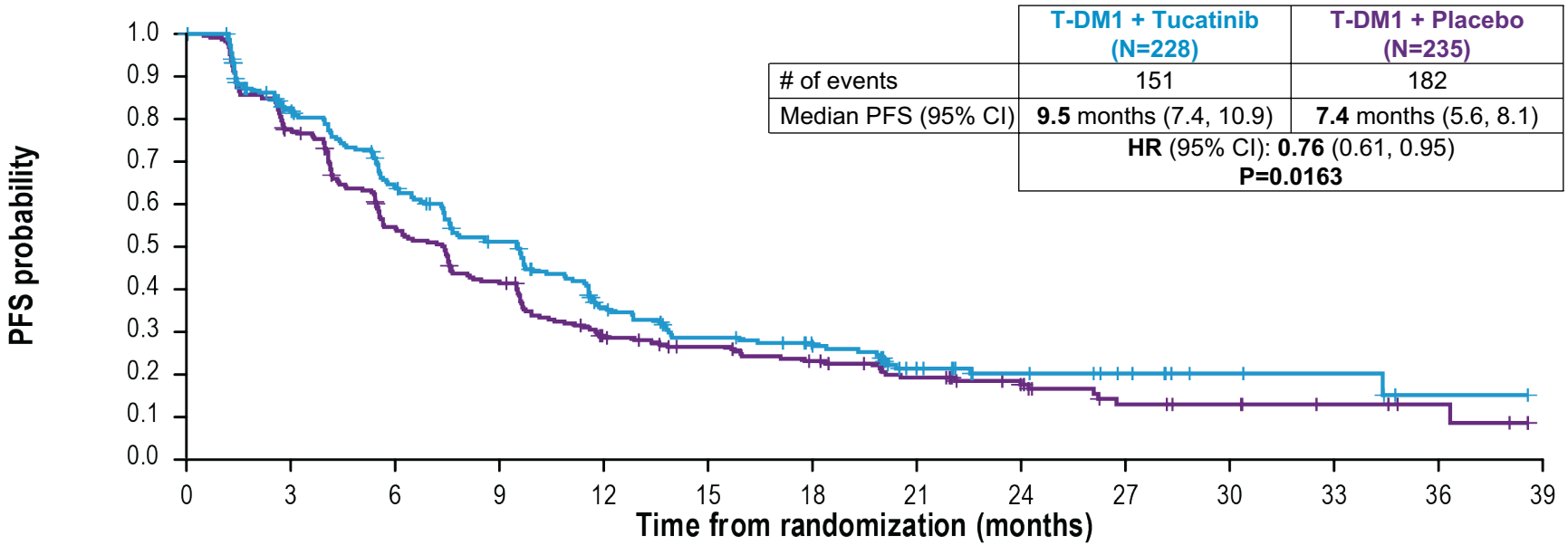
1L: first-line; **BID**: twice daily; **cORR**: confirmed objective response rate; **ECOG PS**: Eastern Cooperative Oncology Group performance status; **HER2**: human epidermal growth factor receptor 2; **IV**: intravenously; **LA/MBC**: locally advanced or metastatic breast cancer; **OS**: overall survival; **PFS**: progression-free survival; **PO**: orally; **R**: randomization; **RECIST**: Response Evaluation Criteria in Solid Tumors; **T-DM1**: trastuzumab emtansine; **T-DXd**: trastuzumab deruxtecan; **TKIs**: tyrosine kinase inhibitors

[a]Patients who received prior tucatinib, afatinib, T-DXd, or any investigational anti-HER2, anti-EGFR, or HER2 TKIs were not eligible. Patients who received lapatinib and neratinib were not eligible if the drugs were received within 12 months of starting study treatment, and patients who received pyrotinib for recurrent or metastatic breast cancer were not eligible. These patients were eligible if the drugs were given for ≤21 days and were discontinued for reasons other than disease progression or severe toxicity.

[b]Subsequent OS analyses are planned upon 80% and 100% of required events for the final OS analysis.

Date of data cutoff: Jun 29, 2023. Patients were enrolled from Oct 8, 2019, to Jun 16, 2022.

Progression-Free Survival



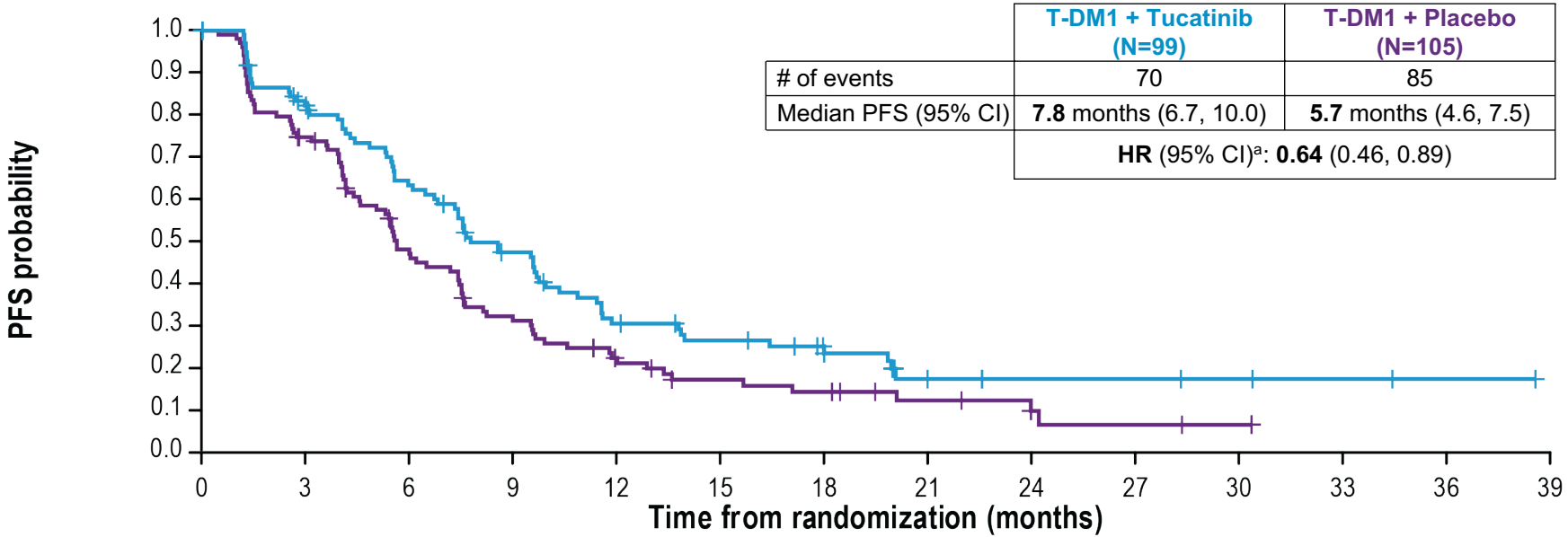
	T-DM1 + Tucatinib (N=228)	T-DM1 + Placebo (N=235)
# of events	151	182
Median PFS (95% CI)	**9.5** months (7.4, 10.9)	**7.4** months (5.6, 8.1)
	HR (95% CI): **0.76** (0.61, 0.95) **P=0.0163**	

Patients at risk

T-DM1 + Tucatinib	228	165	126	96	62	47	40	22	14	10	5	4	1	0
T-DM1 + Placebo	235	177	120	91	58	48	40	29	19	10	8	5	3	0

CI: confidence interval; **HR**: hazard ratio; **PFS**: progression-free survival; **T-DM1**: trastuzumab emtansine
Date of data cutoff: Jun 29, 2023.

PFS in Patients with Brain Metastases



	T-DM1 + Tucatinib (N=99)	T-DM1 + Placebo (N=105)
# of events	70	85
Median PFS (95% CI)	**7.8** months (6.7, 10.0)	**5.7** months (4.6, 7.5)
	HR (95% CI)[a]: **0.64** (0.46, 0.89)	

Patients at risk

T-DM1 + Tucatinib	99	76	57	40	25	20	15	6	4	4	3	2	1	0
T-DM1 + Placebo	105	75	46	30	18	12	10	6	3	2	1	0	0	0

CI: confidence interval; **HR**: hazard ratio; **PFS**: progression-free survival; **T-DM1**: trastuzumab emtansine

[a]The outcome was not formally tested.

Date of data cutoff: Jun 29, 2023

FIRST LINE

· TAXANE +
· TRASTUZUMAB +
· PERTUZUMAB

Baselga J, et al. NEJM 2011
Swain S, et al NEJM 2015

PROG

2nd LINE

· T-DERUXTECAN

(Cortés, et al. ESMO 2021, Lancet 2023).

↑PFS ↑OS

TUCATINIB + CAPECITABINE + TRASTUZUMAB

PROG

BEYOND 2nd LINE

TUCATINIB + CAPECITABINE + TRASTUZUMAB — ↑PFS ↑OS, ↑↑CNS
Murthy, NEJM '20

T-DERUXTECAN* — ↑PFS ↑OS
Mody, NEJM '19
Krop I, SABCS '23

* Si no administrado Previamente

FIRST LINE*

· AROMATASE inh+
· TRASTUZUMAB
+
· PERTUZUMAB

Pertain Trial SABCS 2020

*Upfront (+++) of After Trast + Pert + Chemoth.

TUCATINIB + T-DM1

IN PATIENTS WITH HER2+ & ER+ Combination of AntiHER2 + ET Must be Considered

LAPATINIB + ENDOCRINE THERAPY
Johnston S, et al. JCO 2009

TRASTUZUMAB + ENDOCRINE THERAPY

LAPATINIB + TRASTUZUMAB ENDOCRINE THERAPY
Alternative Trial , JCO 2017

TRASTUZUMAB + LAPATINIB

CAPECITABINE + LAPATINIB

CHEMO +TRASTUZUMAB

T-DM1 Krop IE, et al. Lancet Oncol '14

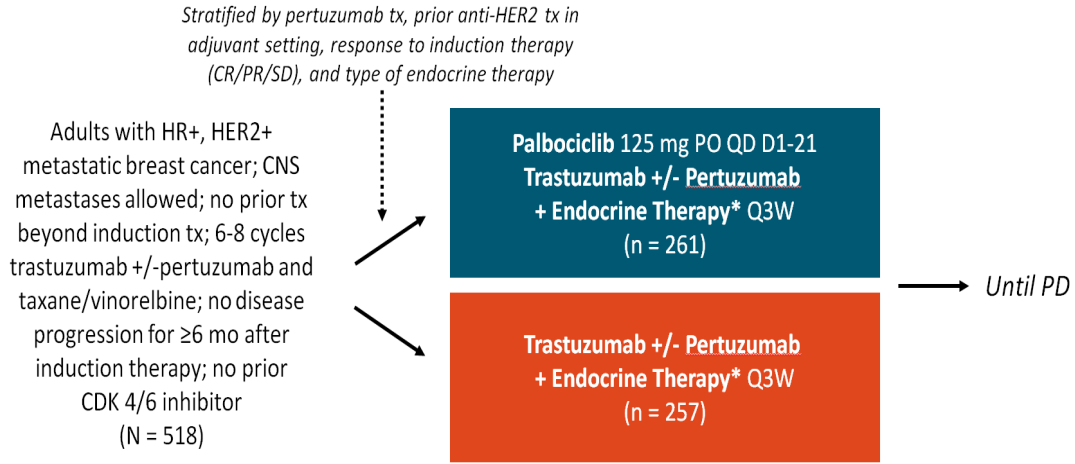
NERATINIB + CAPECITABINE Saura, JCO '20 — ↑PFS ✗OS

MARGETUXIMAB — ↑PFS ✗OS
Rugo, JAMA Oncol '21

TRASTUZUMAB DUOCARMAZINA Saura, ESMO '21 — ↑PFS ✗OS

PATINA: Palbociclib + Anti-HER2 + Endocrine Therapy in Previously Treated HR+/HER2+ MBC

- Randomized, open-label phase III study



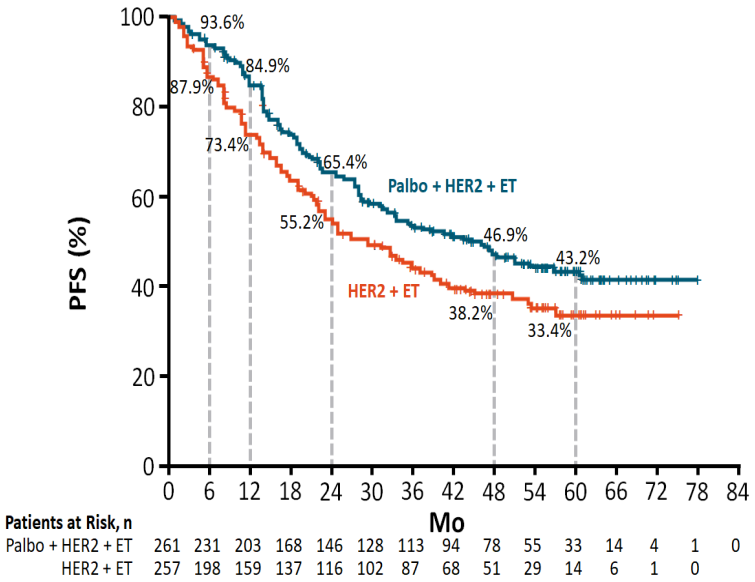
*8 mg/kg trastuzumab (6mg/kg D1 loading dose). Pertuzumab 420 mg Q3W (840 mg loading dose). Endocrine therapy: letrozole, anastrozole, exemestane, or fulvestrant).

- **Primary endpoint:** PFS by investigator
- **Secondary endpoint:** OS, ORR, DoR, CBR, PROs, CNS metastasis incidence, safety

Metzger. SABCS 2024. Abstr GS2-12.

PATINA: PFS and Interim OS

Median follow-up: 52.6 mo



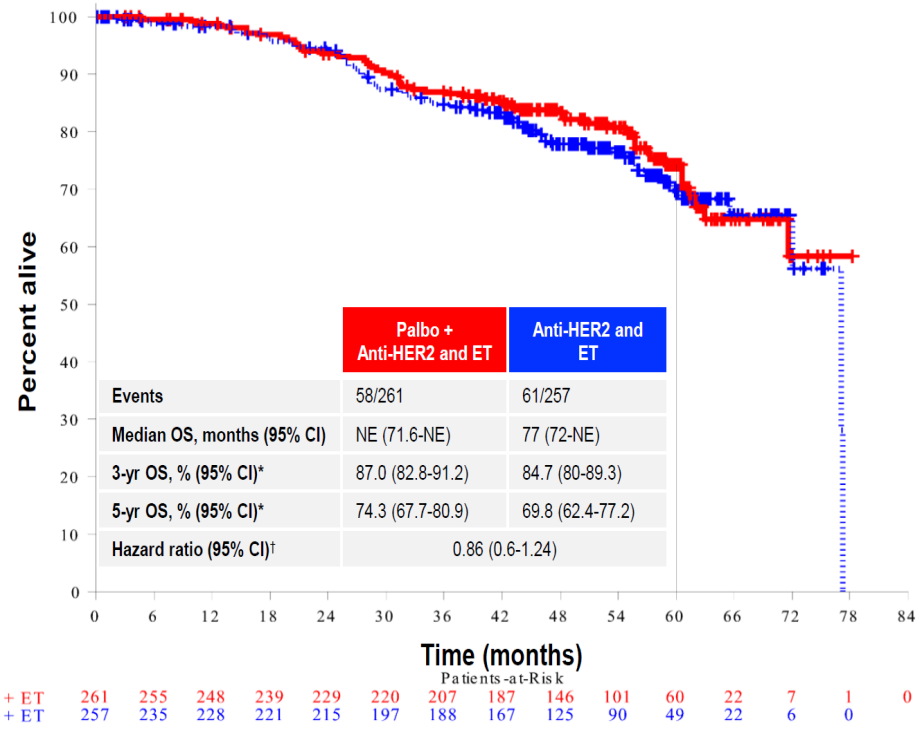
PFS Result	Palbociclib + Anti-HER2 + ET (n = 261)	Anti-HER2 + ET (n = 257)
Events	126	136
mPFS, mo (95% CI)	44.3 (32.4-60.9)	29.1 (23.3-38.6)
HR (95% CI)	0.74 (0.58-0.94)	
P value	.0074	

Stratification Subgroups	n/N	HR (95% CI)
Prior anti-HER2 tx		
▪ Yes	186/372	0.76 (0.57-2.02)
▪ No	76/146	0.68 (0.543-1.07)
Best response to induction		
▪ CR or PR	182/355	0.76 (0.57-1.02)
▪ SD	80/163	0.72 (0.47-1.12)

- mOS: NE (71.6-NE) vs 77 (72-NE) mo

Metzger. SABCS 2024. Abstr GS2-12.

Secondary Endpoint: Overall Survival (Interim Analysis)



	Palbo + Anti-HER2 and ET	Anti-HER2 and ET
Events	58/261	61/257
Median OS, months (95% CI)	NE (71.6-NE)	77 (72-NE)
3-yr OS, % (95% CI)*	87.0 (82.8-91.2)	84.7 (80-89.3)
5-yr OS, % (95% CI)*	74.3 (67.7-80.9)	69.8 (62.4-77.2)
Hazard ratio (95% CI)†	0.86 (0.6-1.24)	

*Kaplan-Meier method.
†Unstratified Cox model.
CI=confidence interval; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; NE=not evaluable; OS=overall survival; palbo=palbociclib.

FIRST LINE

· TAXANE +
· TRASTUZUMAB +
· PERTUZUMAB

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Swain S, et al NEJM 2015

PROG

2nd LINE

ACT

· T-DERUXTECAN

(Cortés, et al. ESMO 2021, Lancet 2023).

↑PFS ↑OS

PROG

BEYOND 2nd LINE

TUCATINIB + CAPECITABINE + TRASTUZUMAB — ↑PFS ↑OS, ↑CNS

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· TRASTUZUMAB
+
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Pertain Trial SABCS 2020

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PALBOCICLIB

TUCATINIB + CAPECITABINE + TRASTUZUMAB — ACT

TUCATINIB + T-DM1

TRASTUZUMAB + LAPATINIB

CAPECITABINE + LAPATINIB

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T-DM1 Krop IE, et al. Lancet Oncol '14

NERATINIB + CAPECITABINE — ↑PFS ✕OS — Saura, JCO '20

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LAPATINIB + TRASTUZUMAB ENDOCRINE THERAPY

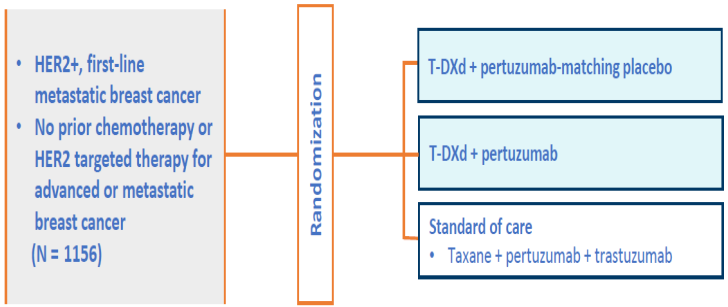
Alternative Trial , JCO 2017

DESTINY-Breast09 (D967UC00001)

Study of Trastuzumab Deruxtecan With or Without Pertuzumab Versus Taxane, Trastuzumab, and Pertuzumab for Patients With HER2 positive Metastatic Breast Cancer

A phase 3 study of trastuzumab deruxtecan (T-DXd) with or without pertuzumab versus taxane, trastuzumab and pertuzumab in HER2 positive, first-line metastatic breast cancer (North America, South America, Europe, Asia, Africa)

Study Design



Stratification by:
- Prior treatment status (de novo vs recurrent)
- HR status (positive vs negative)
- PIK3CA mutation status (detected vs not detected)

Tolaney SM, et al. Presented at San Antonio Breast Cancer Symposium (SABCS) 2021. December 7-10. Poster OT1-14-02.

ClinicalTrials.gov Identifier: NCT04784715
Eudra Clinical Trial Identifier: 2020-004074-21

Primary Endpoint

- Progression-free survival (PFS) by blinded independent central review (BICR)

Secondary Endpoints

- PFS by investigator assessment
- Overall survival (OS)
- Objective response rate (ORR) by BICR and investigator assessment
- Duration of response (DOR) by BICR and investigator assessment
- Time to second progression or death (PFS2) by investigator assessment
- Health-related quality of life (HRQoL)
- Pharmacokinetics (PK)

Diseñando juntos el Tratamiento Sistémico del Cáncer de Mama en 2024.

CÁNCER DE MAMA HER2 POSITIVO

Enfermedad LOCALIZADA

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]

Received: 4 May 2023 / Accepted: 5 May 2023 / Published online: 16 June 2023

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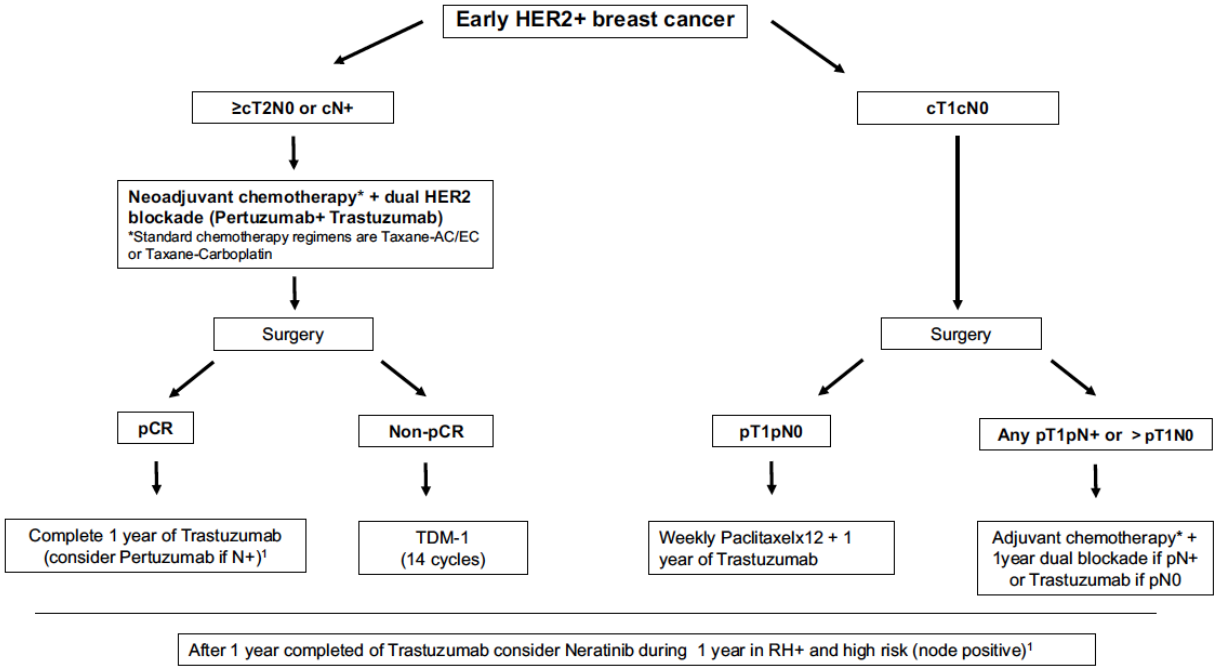

Fig. 2 HER2-positive early breast cancer algorithm. *CT:* chemotherapy. *pCR:* pathologic complete response. (1) This treatment is still awaiting financial approval from the health authorities in Spain

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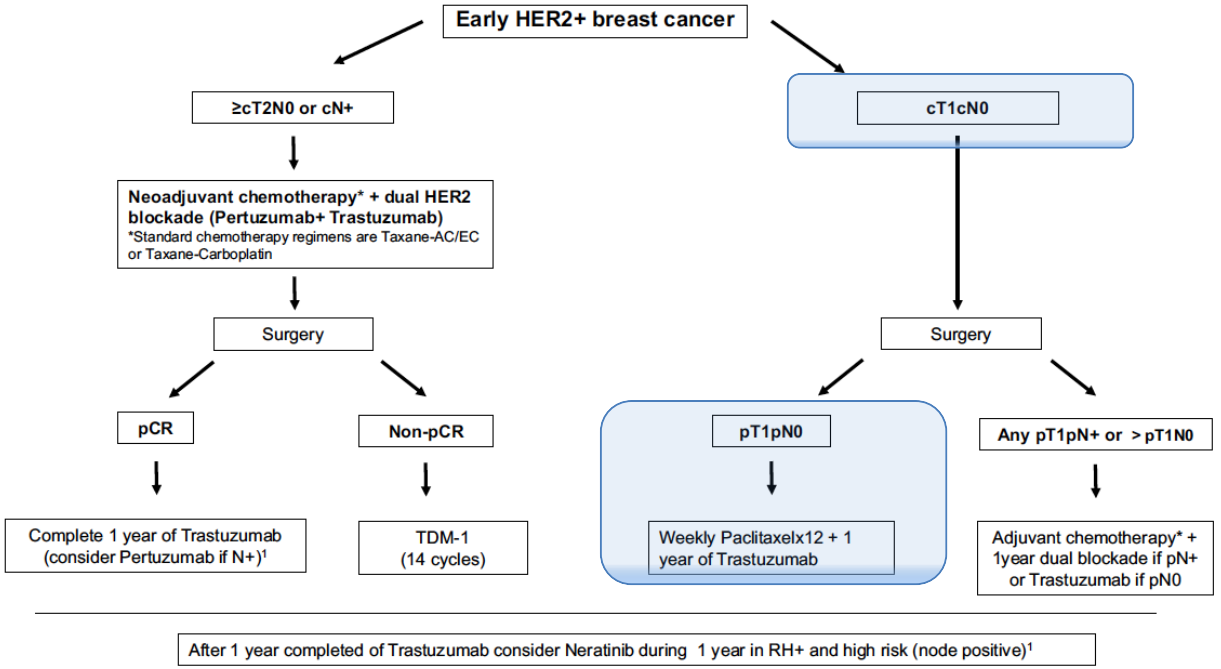

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Seven-Year Follow-Up Analysis of Adjuvant Paclitaxel and Trastuzumab Trial for Node-Negative, Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer

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]

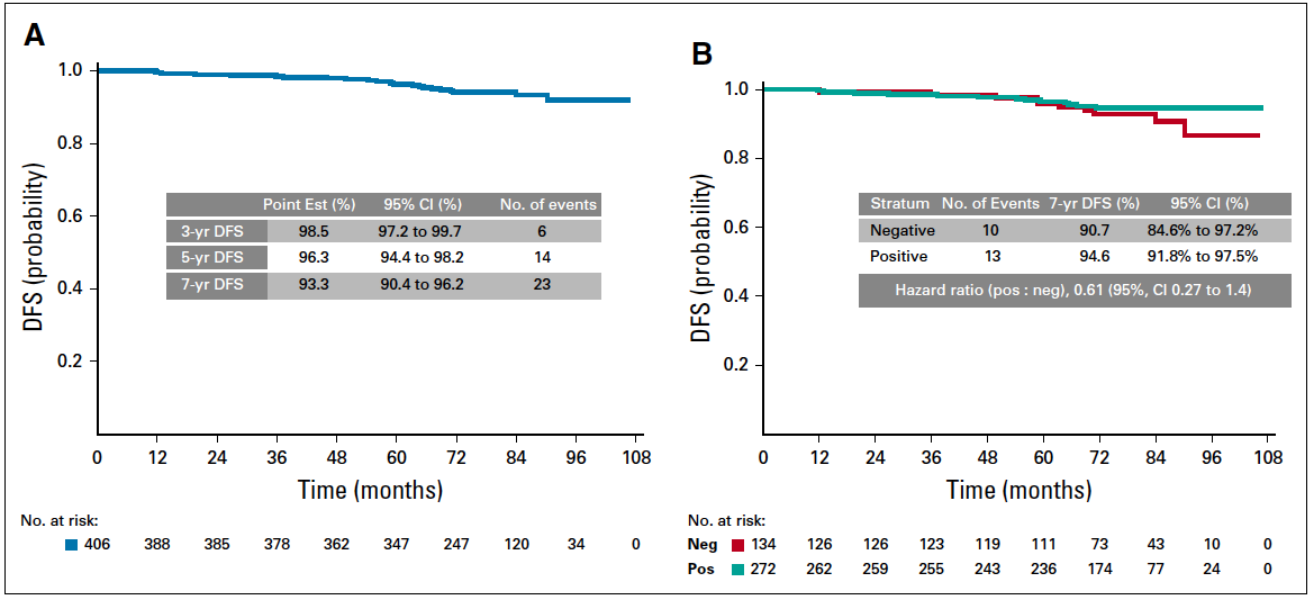

FIG 2. Disease-free survival (DFS). (A) Kaplan-Meier plot of DFS in the intention-to-treat population. (B) DFS according to hormone-receptor status. Abbreviations: neg, negative; Point est, point estimate; pos, positive.

Breast Cancer Research and Treatment (2019) 173:247–254
https://doi.org/10.1007/s10549-018-5001-x

REVIEW

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

Alessandro Inno[1] · Sandro Barni[2] · Antonio Ghidini[3] · Alberto Zaniboni[4] · Fausto Petrelli[2]

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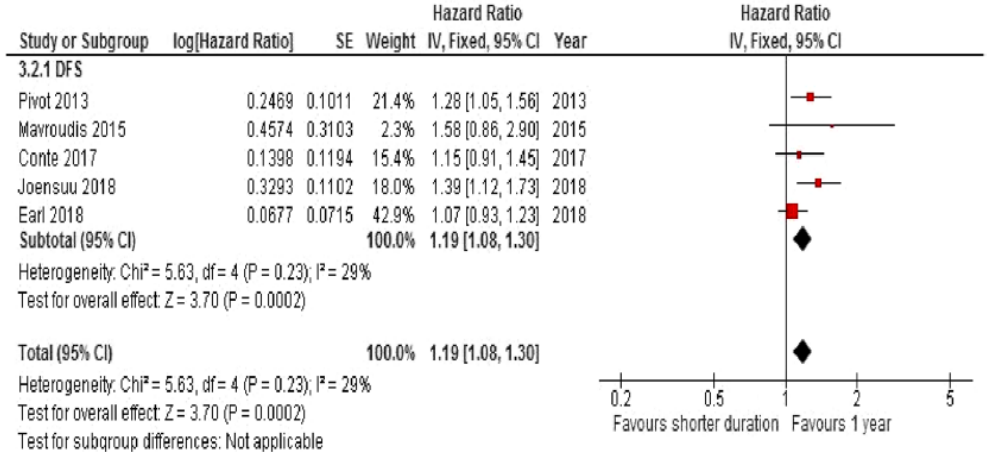
Fig. 4 Meta-analysis of hazard ratios for disease-free survival



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REVIEW

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Alessandro Inno[1] · Sandro Barni[2] · Antonio Ghidini[3] · Alberto Zaniboni[4] · Fausto Petrelli[2]

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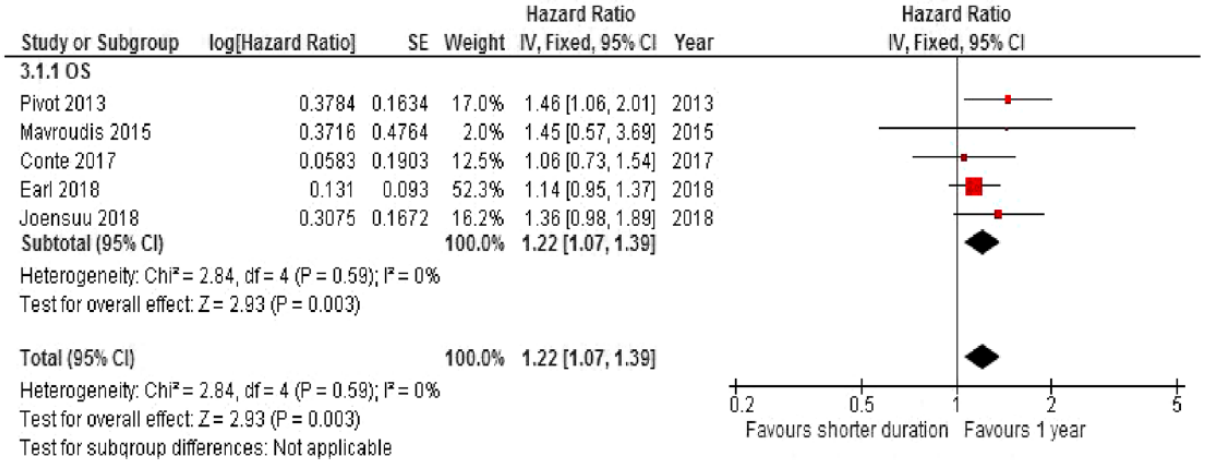
Fig. 2 Meta-analysis of hazard ratios for overall survival



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https://doi.org/10.1007/s10549-018-5001-x

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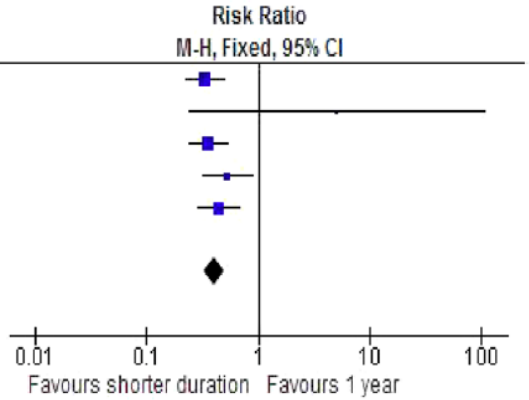
Fig. 5 Pooled results of risk ratios for cardiac events comparing 1 year versus shorter duration of adjuvant trastuzumab

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)



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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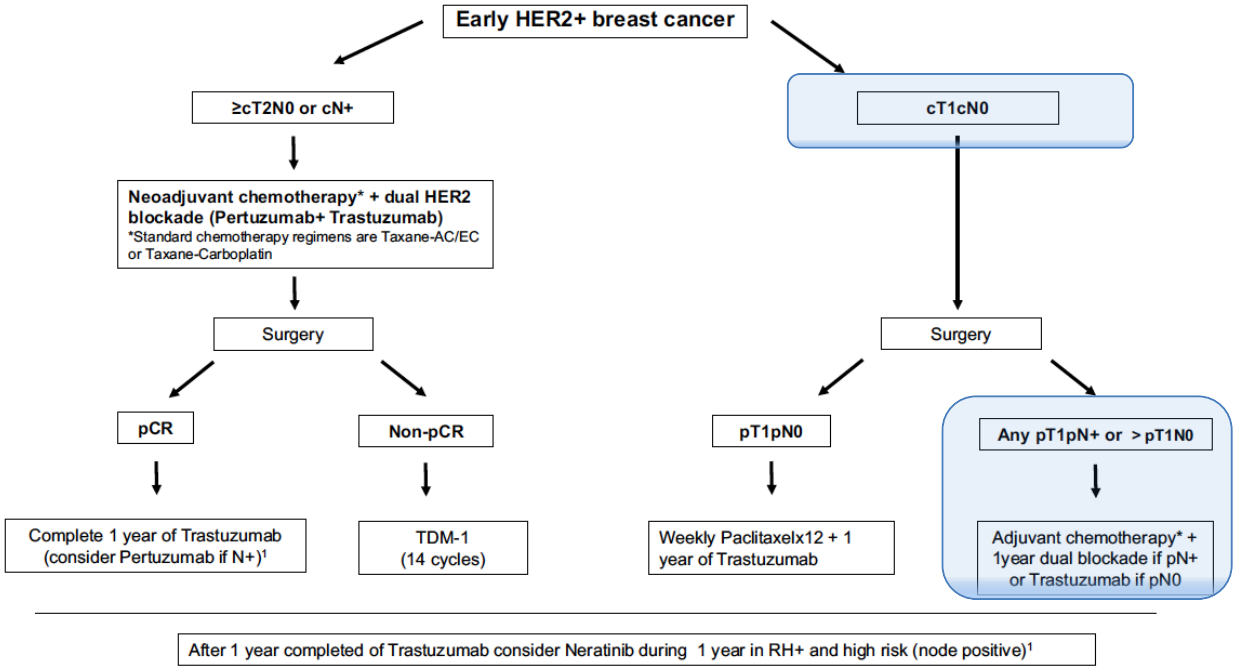


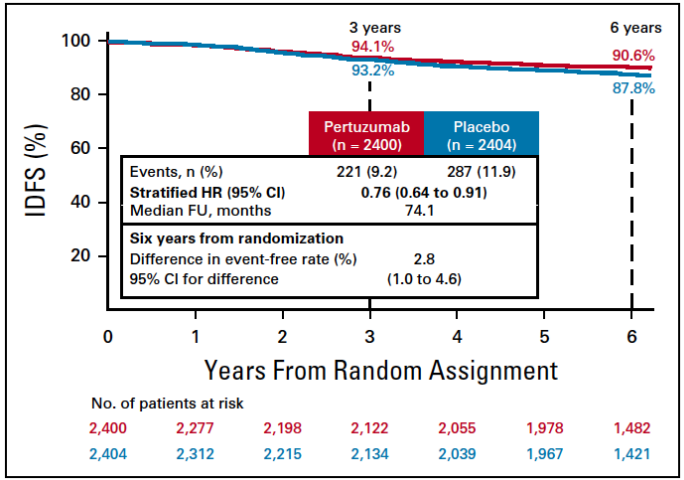
Fig. 2 HER2-positive early breast cancer algorithm. *CT:* chemotherapy. *pCR:* pathologic complete response. (1) This treatment is still awaiting financial approval from the health authorities in Spain

original reports

Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer in the APHINITY Trial: 6 Years' Follow-Up

Martine Piccart, MD, PhD[1]; Marion Procter, PhD[2]; Debora Fumagalli, MD, PhD[3]; Evandro de Azambuja, MD, PhD[1]; Emma Clark, MSc[4]; Michael S. Ewer, MD, JD, PhD[5]; Eleonora Restuccia, MD[6]; Guy Jerusalem, MD, PhD[7]; Susan Dent, BSc, MD[8]; Linda Reaby, AM, PHD[9,10]; Hervé Bonnefoi, MD[11]; Ian Krop, MD, PhD[12]; Tsang-Wu Liu, MD[13]; Tadeusz Pieńkowski, MD, PhD[14]; Masakazu Toi, MD, PhD[15]; Nicholas Wilcken, PhD[16,17]; Michael Andersson, MD, DMSci[19,18]; Young-Hyuck Im, MD, PhD[19]; Ling Ming Tseng, MD[20]; Hans-Joachim Lueck, MD[21]; Marco Colleoni, MD[22]; Estefania Monturus, PhD[6]; Mihaela Sicoe, MSc[3]; Sébastien Guillaume, MSc[1]; José Bines, MD, PhD[23]; Richard D. Gelber, PhD[24]; Giuseppe Viale, MD[25]; and Christoph Thomssen, MD[26] for the APHINITY Steering Committee and Investigators

J Clin Oncol 39:1448-1457. © 2021 by American Society of Clinical Oncology



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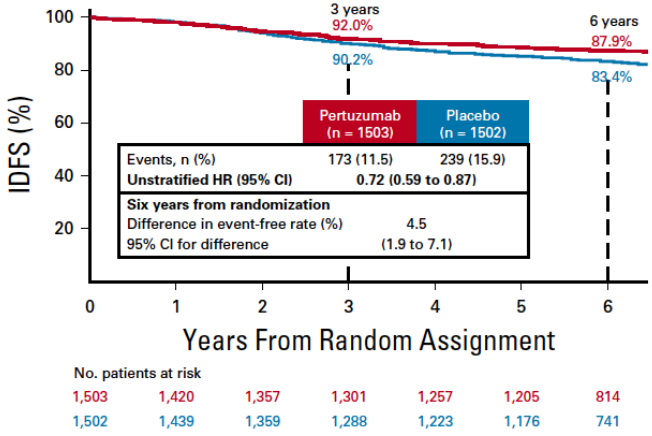

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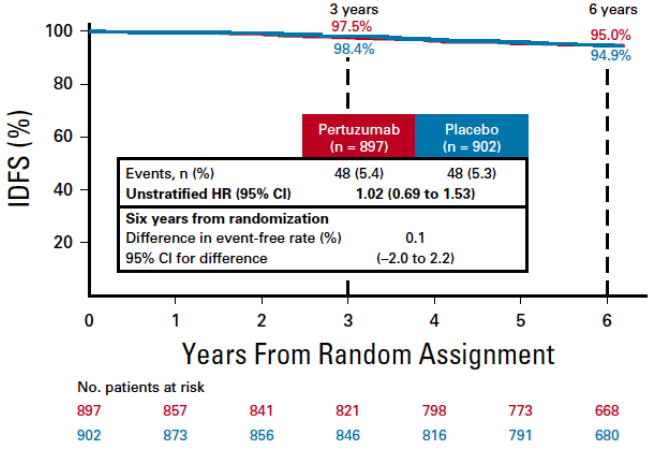

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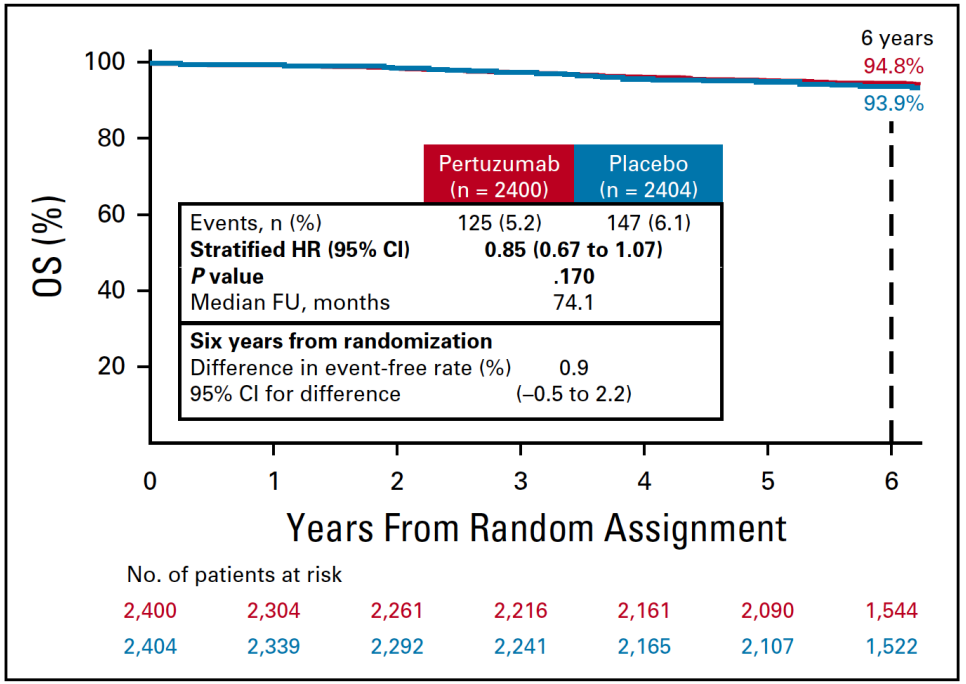
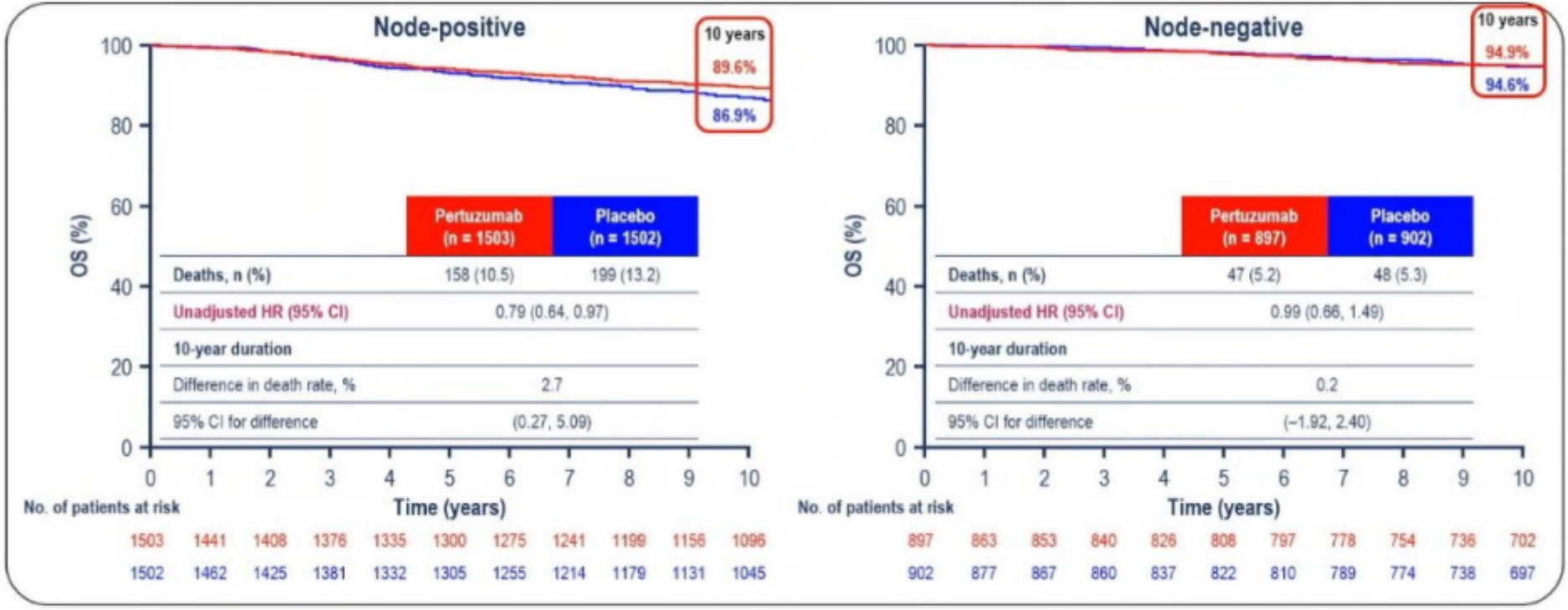


APHINITY FINAL OS ANALYSIS AT 11.3 YEARS' MEDIAN FOLLOW-UP BY TREATMENT REGIMEN AND NODAL STATUS



CI, confidence interval; HR, hazard ratio; OS, overall survival.

Sibylle Loibl, MD, PhD

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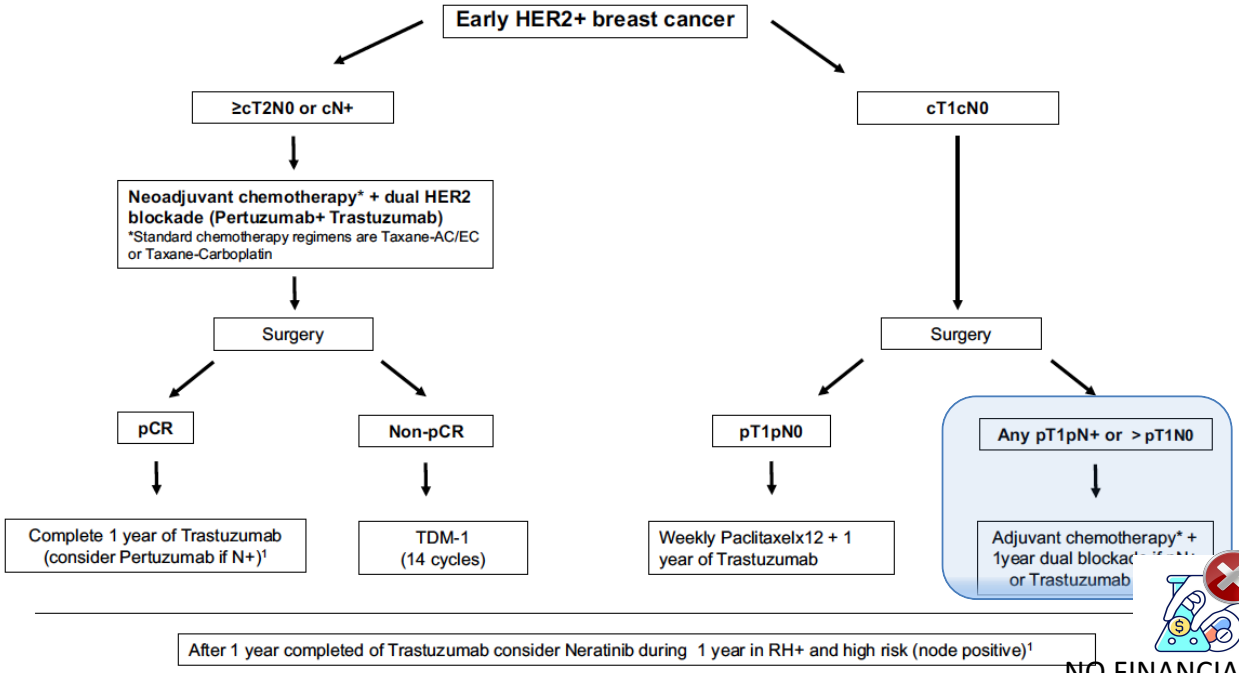

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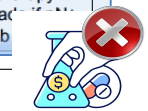

NO FINANCIADO

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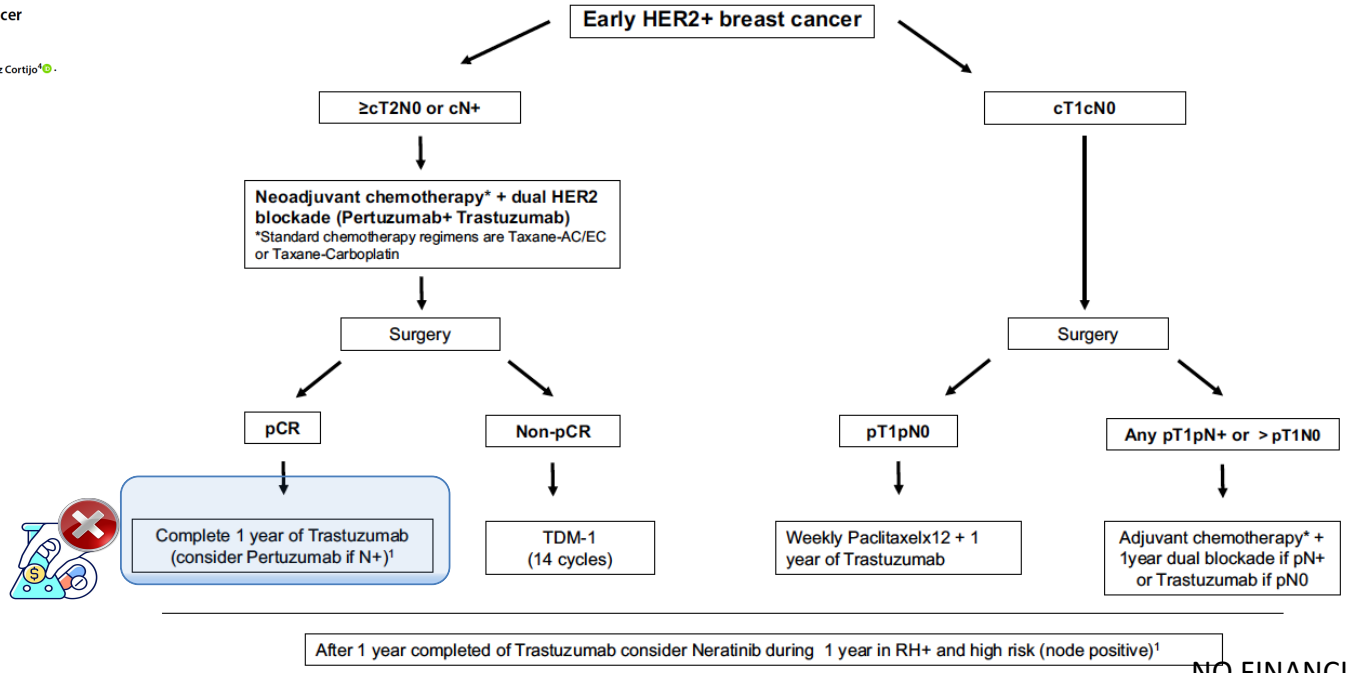

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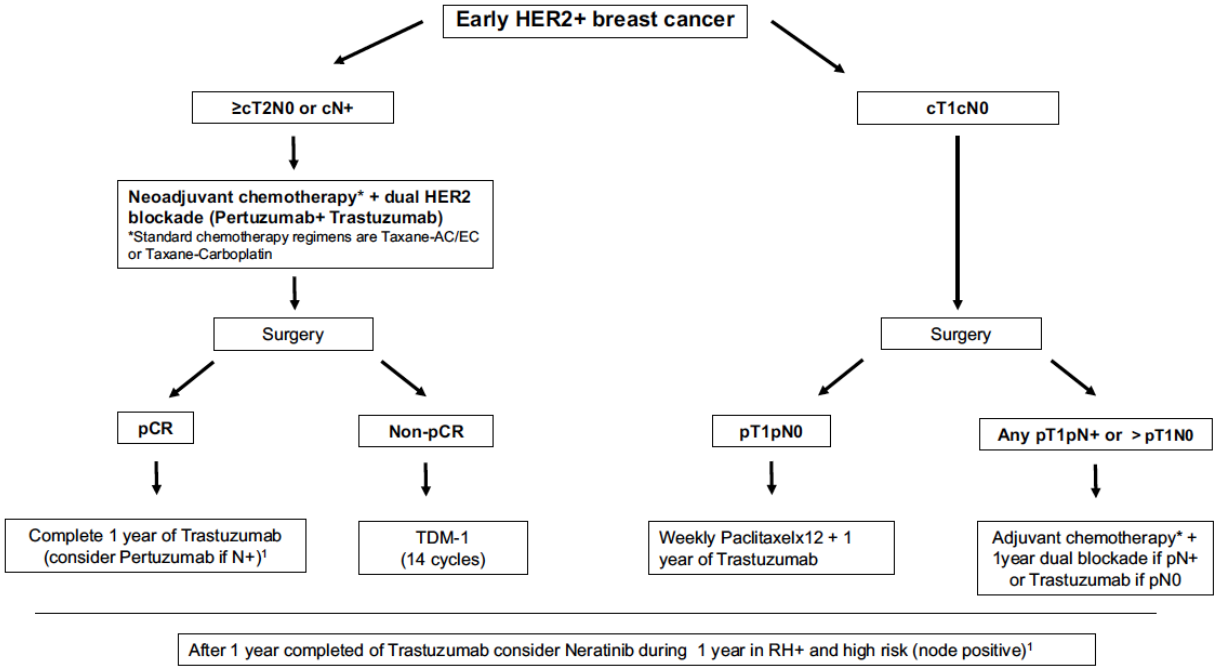

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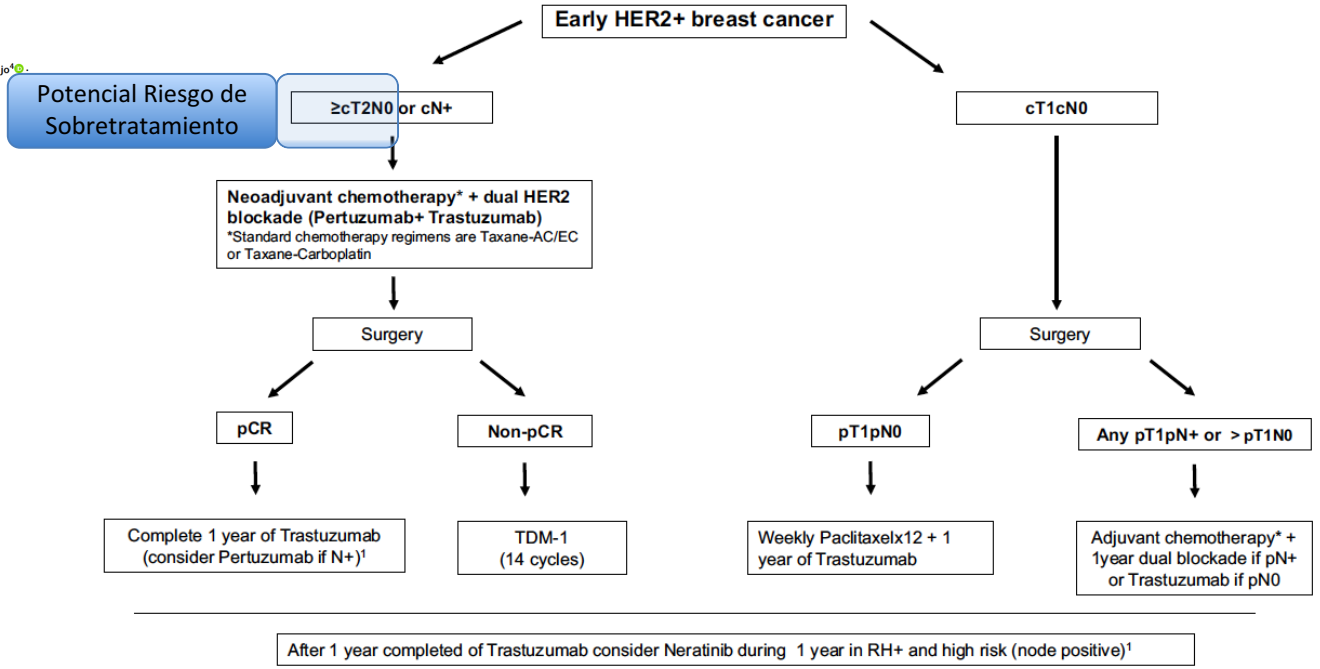

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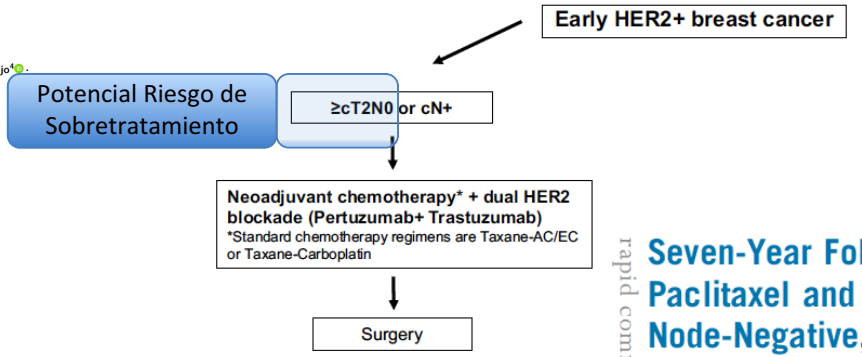

rapid communication

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[6]; 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]

EBioMedicine 2022;75: 103801
Published online xxx
https://doi.org/10.1016/j.ebiom.2021.103801

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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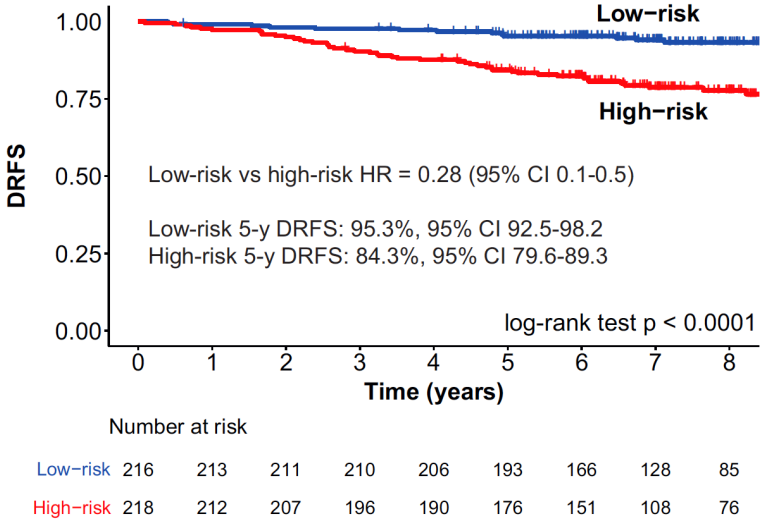
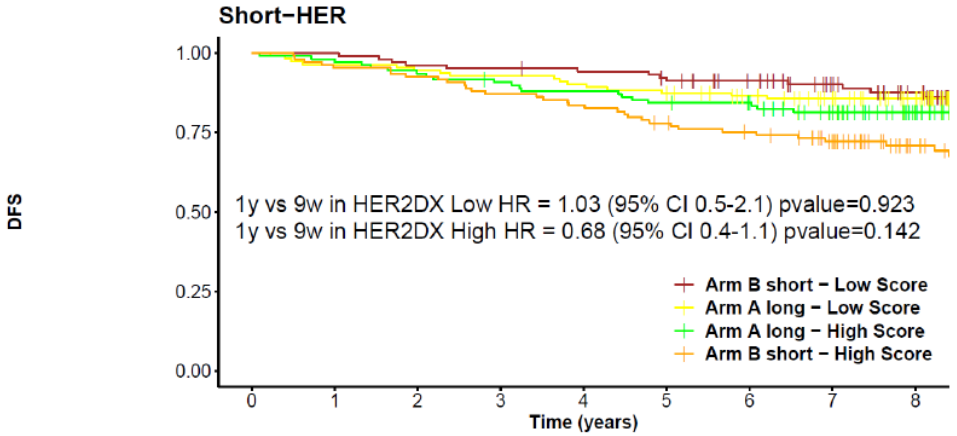
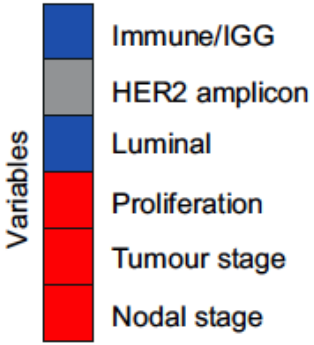
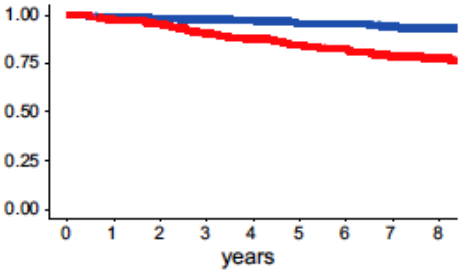




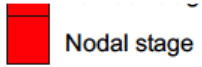
Development and validation of the new HER2DX assay

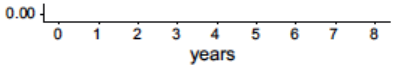
HER2DX risk score





Blue=good outcome
Red=poor outcome





Blue=good outcome
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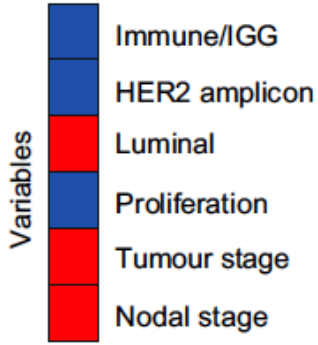
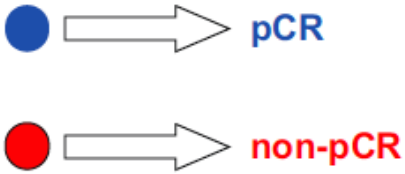
HER2DX pCR likelihood score





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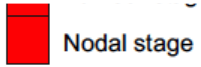

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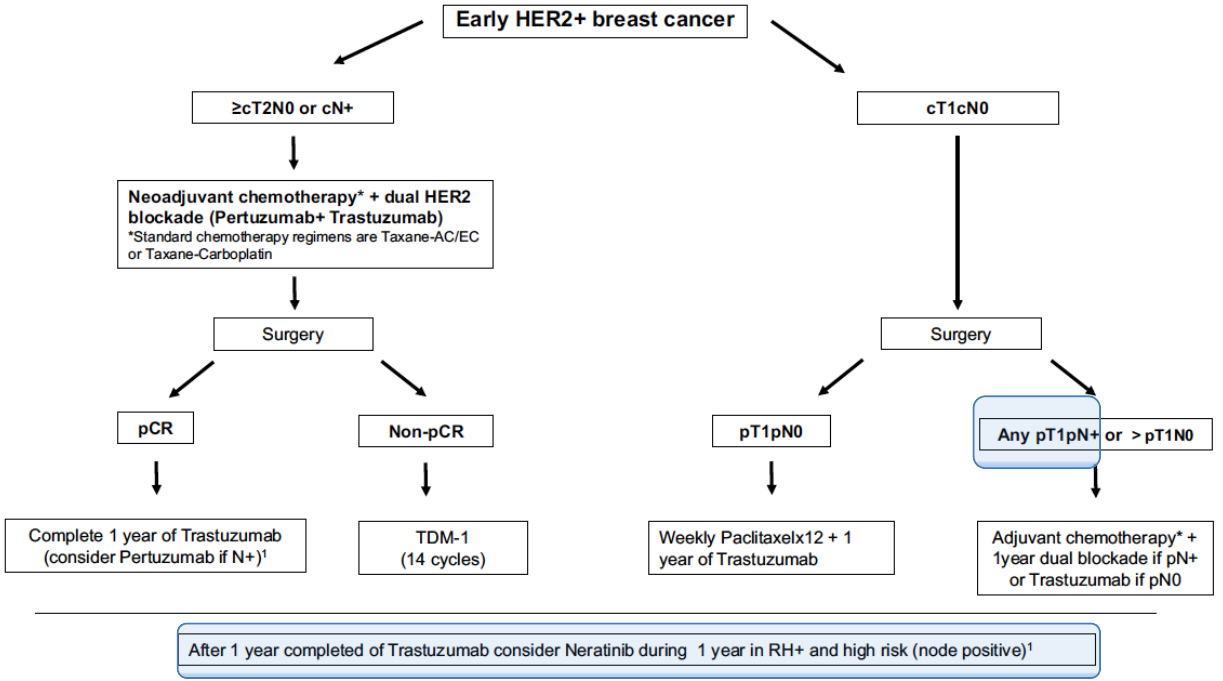

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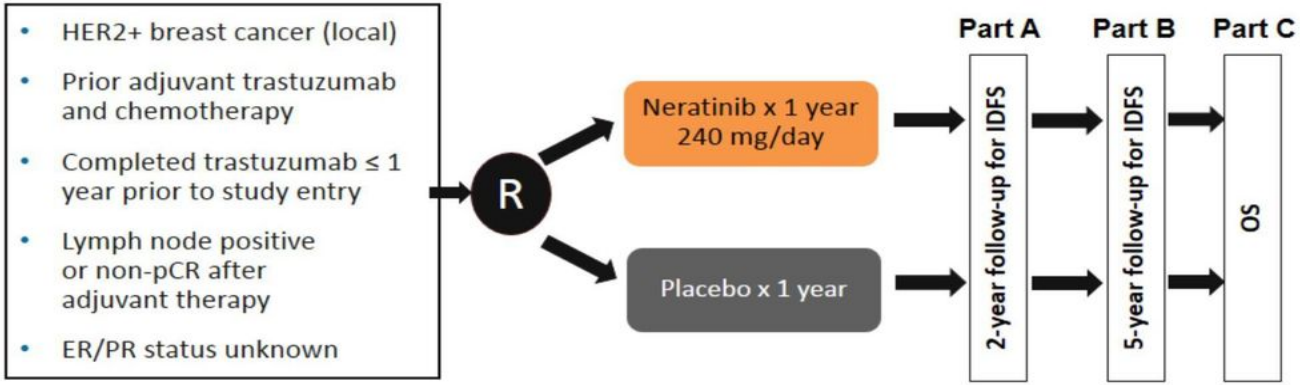
ExteNET Trial: Study Schema



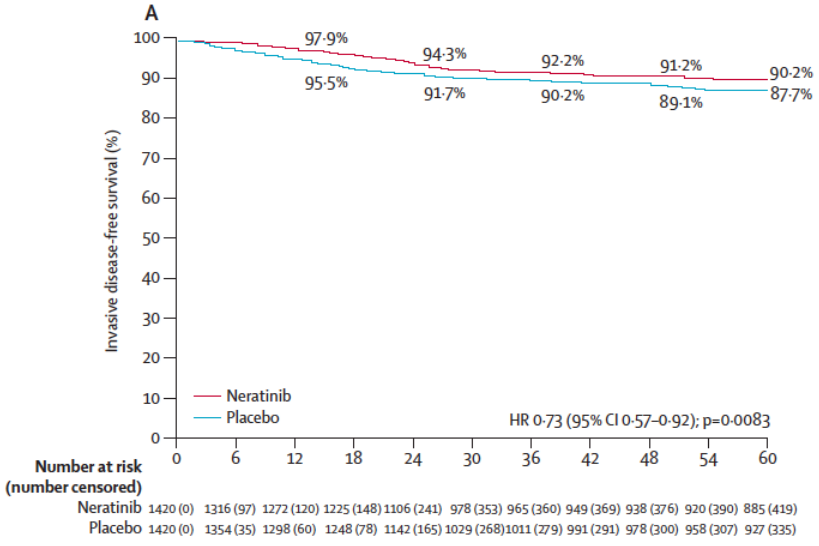
- Primary analysis: IDFS in ITT population (n = 2840)
- IDFS at 2 years: hazard ratio = 0.67 (0.50, 0.91); *P* =.0091
- HR positive (n = 1631, 57.4%); hazard ratio = 0.51; *P* =.0013
- Centrally confirmed HER2-positive 60% (n = 1463; 51%); hazard ratio = 0.51; *P* =.002

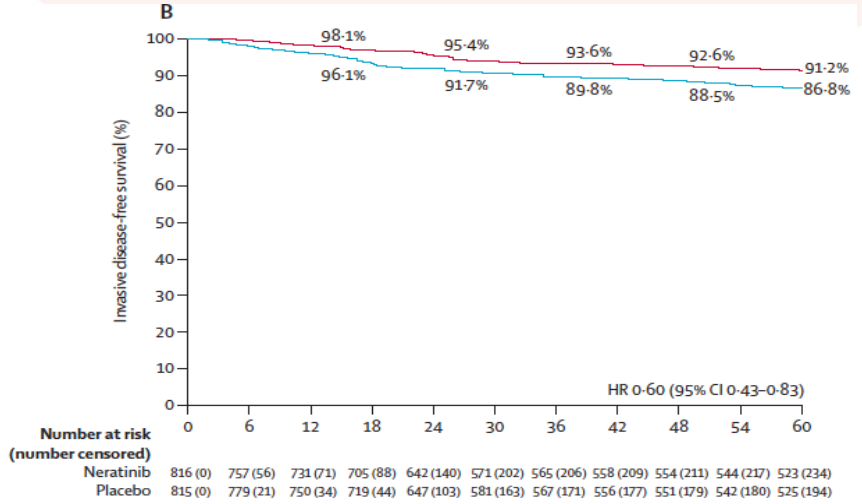
a. Martin M, et al. *Ann Onc*ol. 2017;28(Suppl 5): Abstract 149O. Reproduced with permission from Dr. Miguel Martin.
b. Chan A, et al. *Lancet Oncol*. 2016;17:367-377.

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





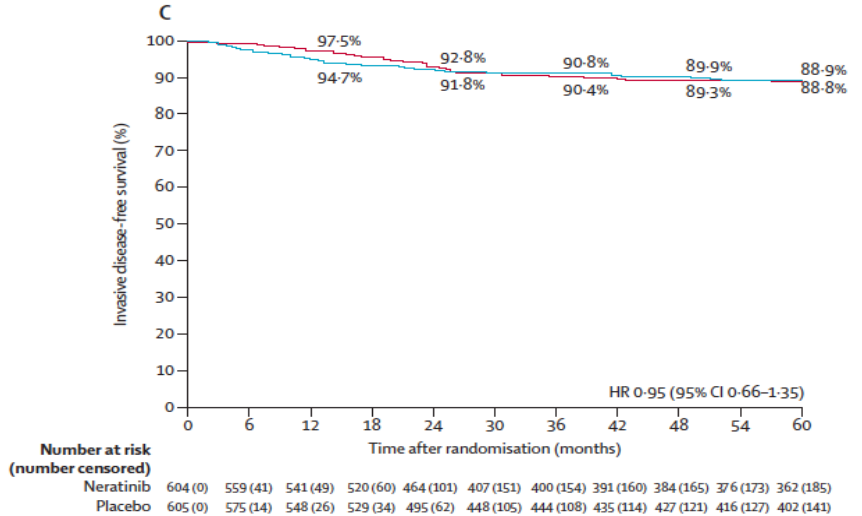
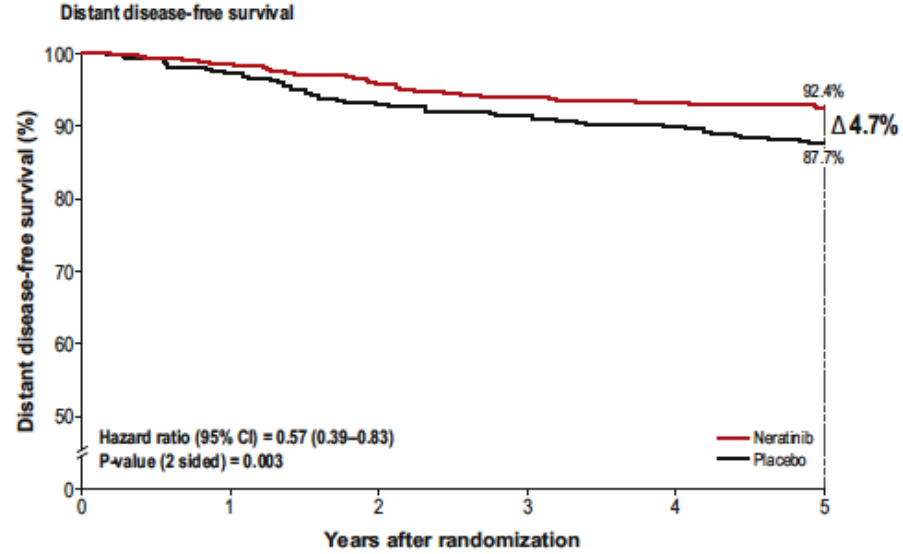


Figure 2: **Invasive disease-free survival in the intention-to-treat population (A), patients with hormone receptor-positive breast cancer (B), and patients with hormone receptor-negative breast cancer (C)**

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

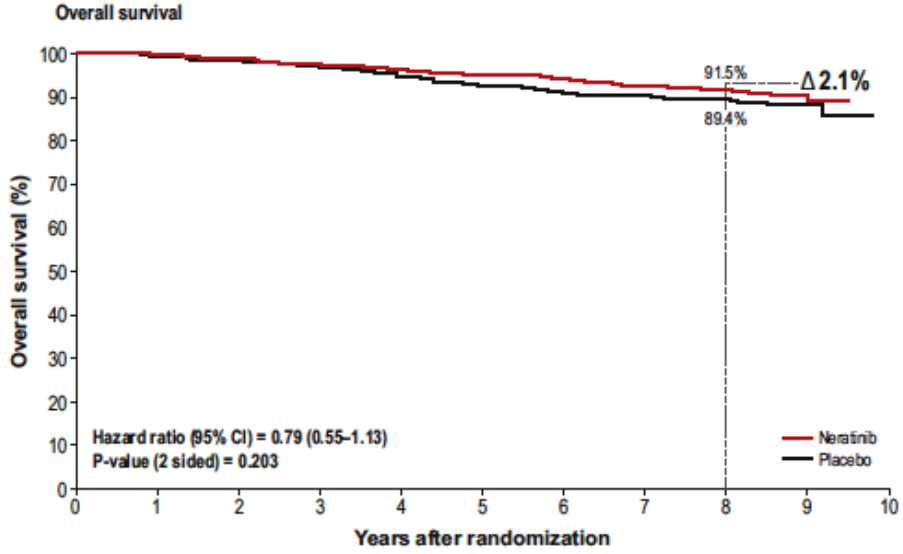
Arlene Chan,[1] Beverly Moy,[2] Janine Mansi,[3] Bent Ejlertsen,[4] Frankie Ann Holmes,[5] Stephen Chia,[6] Hiroji Iwata,[7] Michael Gnant,[8] Sibylle Loibl,[9] Carlos H. Barrios,[10] Isil Somali,[11] Snezhana Smichkoska,[12] Noelia Martinez,[13] Mirta Garcia Alonso,[14] John S. Link,[15] Ingrid A. Mayer,[16] 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

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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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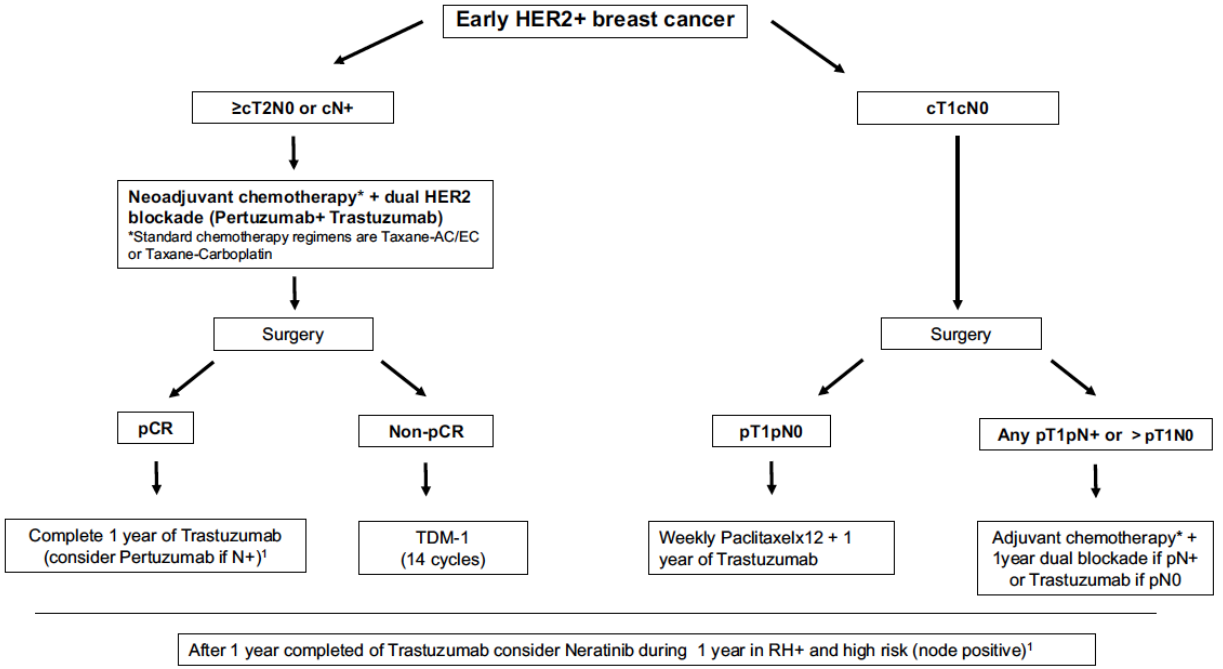

Fig. 2 HER2-positive early breast cancer algorithm. *CT:* chemotherapy. *pCR:* pathologic complete response. (1) This treatment is still awaiting financial approval from the health authorities in Spain

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¡Gracias!