

# Recentes Avanços no Tratamento do Câncer de Mama HER2 positivo

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1. Tratamento Adjuvante  
Duração da Adjuvância
2. Tratamento NeoAdjuvante
3. *Tratamento da Doença Metastática*

*1 ano*

*versus*

*2 anos*

# HERA TRIAL DESIGN

## ACCRUAL 2001 – 2005 (N=5102)

Women with locally determined HER2-positive invasive early breast cancer

Surgery + (neo)adjuvant CT ± RT

Centrally confirmed IHC 3+ or FISH+ and LVEF ≥ 55%

Randomization

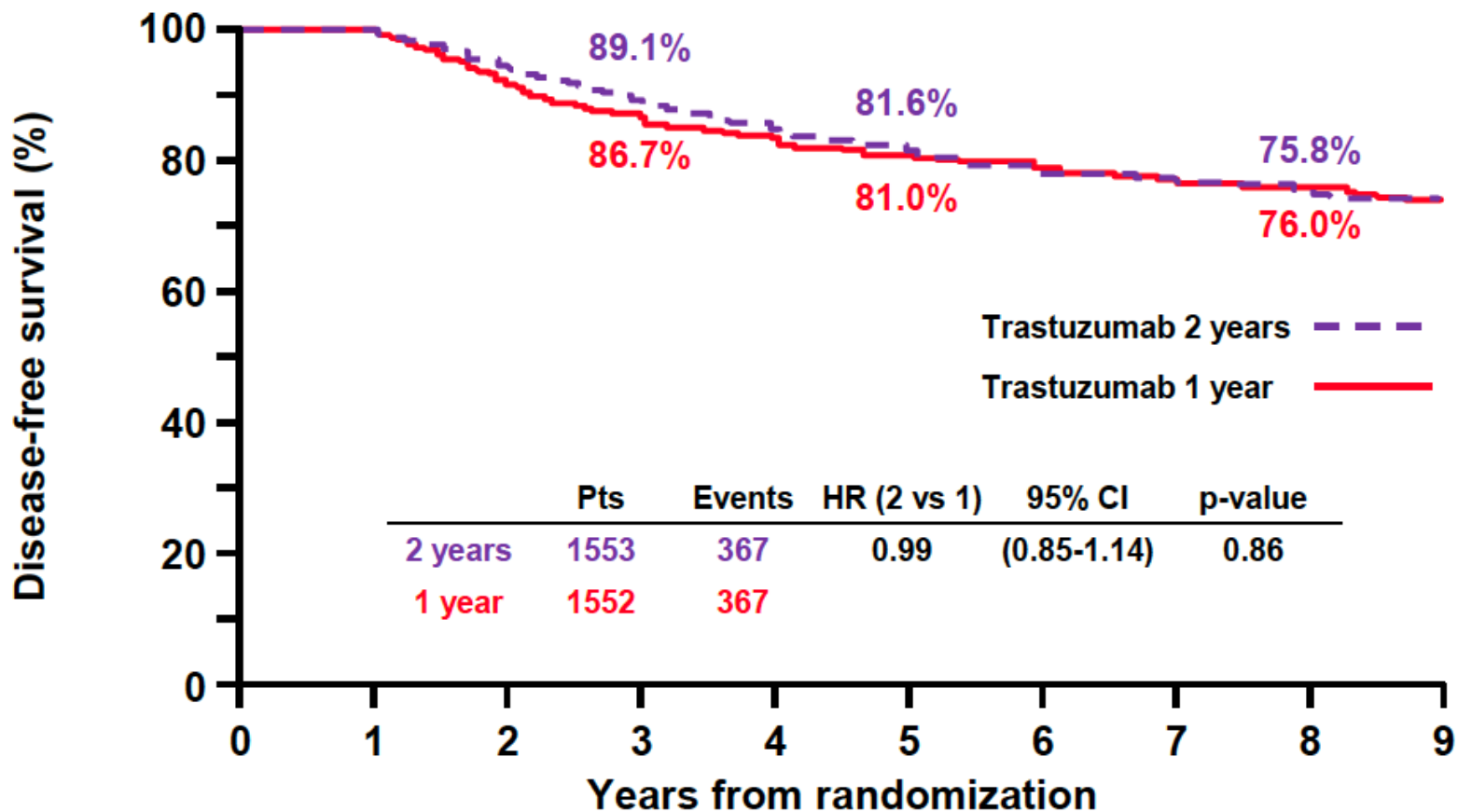
**OBSERVATION**  
n=1698

After ASCO 2005, option of switch to Trastuzumab

1 year Trastuzumab  
8 mg/kg – 6 mg/kg  
3 weekly schedule  
n=1703

2 years Trastuzumab  
8 mg/kg – 6 mg/kg  
3 weekly schedule  
n=1701

# HERA 2 years vs 1 year - DFS



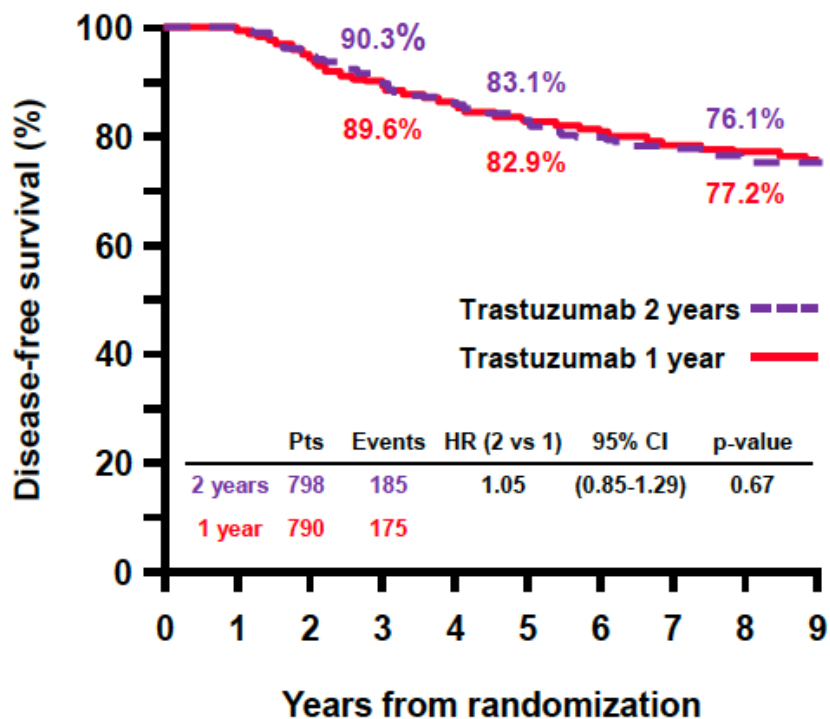
	Pts	Events	HR (2 vs 1)	95% CI	p-value
2 years	1553	367	0.99	(0.85-1.14)	0.86
1 year	1552	367			

## No. at risk

Trastuzumab 2 years	1553	1553	1442	1361	1292	1223	1153	1051	633	194
Trastuzumab 1 year	1552	1552	1413	1319	1265	1214	1180	1071	649	205

# HERA 2 years vs 1 year - DFS

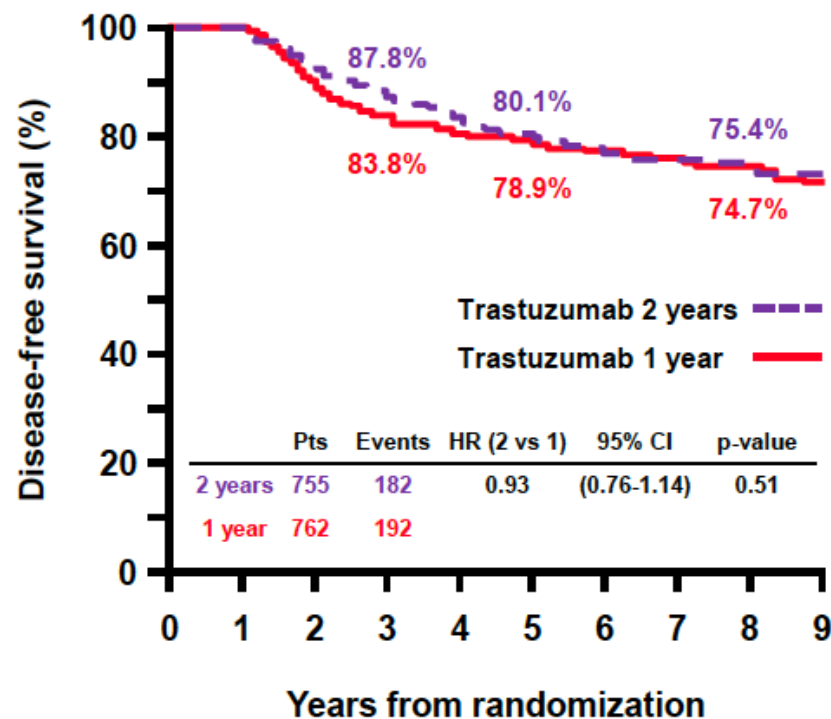
## Hormone receptor positive 92.6% received endocrine therapy



No. at risk

Trastuzumab 2 years	798	798	747	710	673	642	597	544	321	97
Trastuzumab 1 year	790	790	736	691	663	634	617	559	337	106

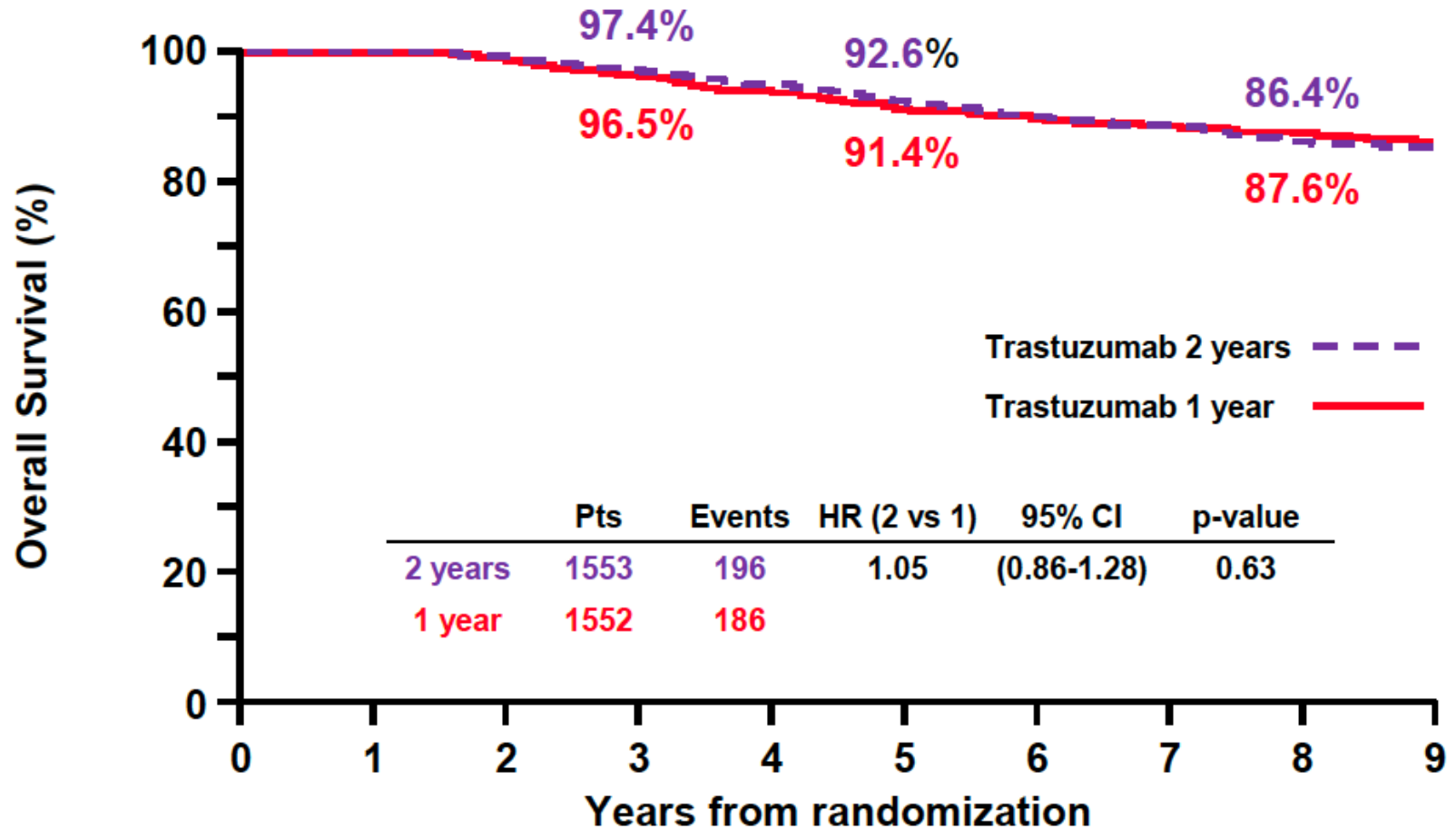
## Hormone receptor negative 2.8% received endocrine therapy



No. at risk

Trastuzumab 2 years	755	755	695	651	619	581	556	507	312	97
Trastuzumab 1 year	762	762	677	628	602	580	563	512	312	99

# HERA 2 years vs 1 year - SG



	Pts	Events	HR (2 vs 1)	95% CI	p-value
2 years	1553	196	1.05	(0.86-1.28)	0.63
1 year	1552	186			


## No. at risk

Trastuzumab 2 years	1553	1553	1525	1485	1438	1382	1317	1193	708	208
Trastuzumab 1 year	1552	1552	1513	1461	1413	1364	1329	1218	732	225

*1 ano*

*versus*

*6 meses*

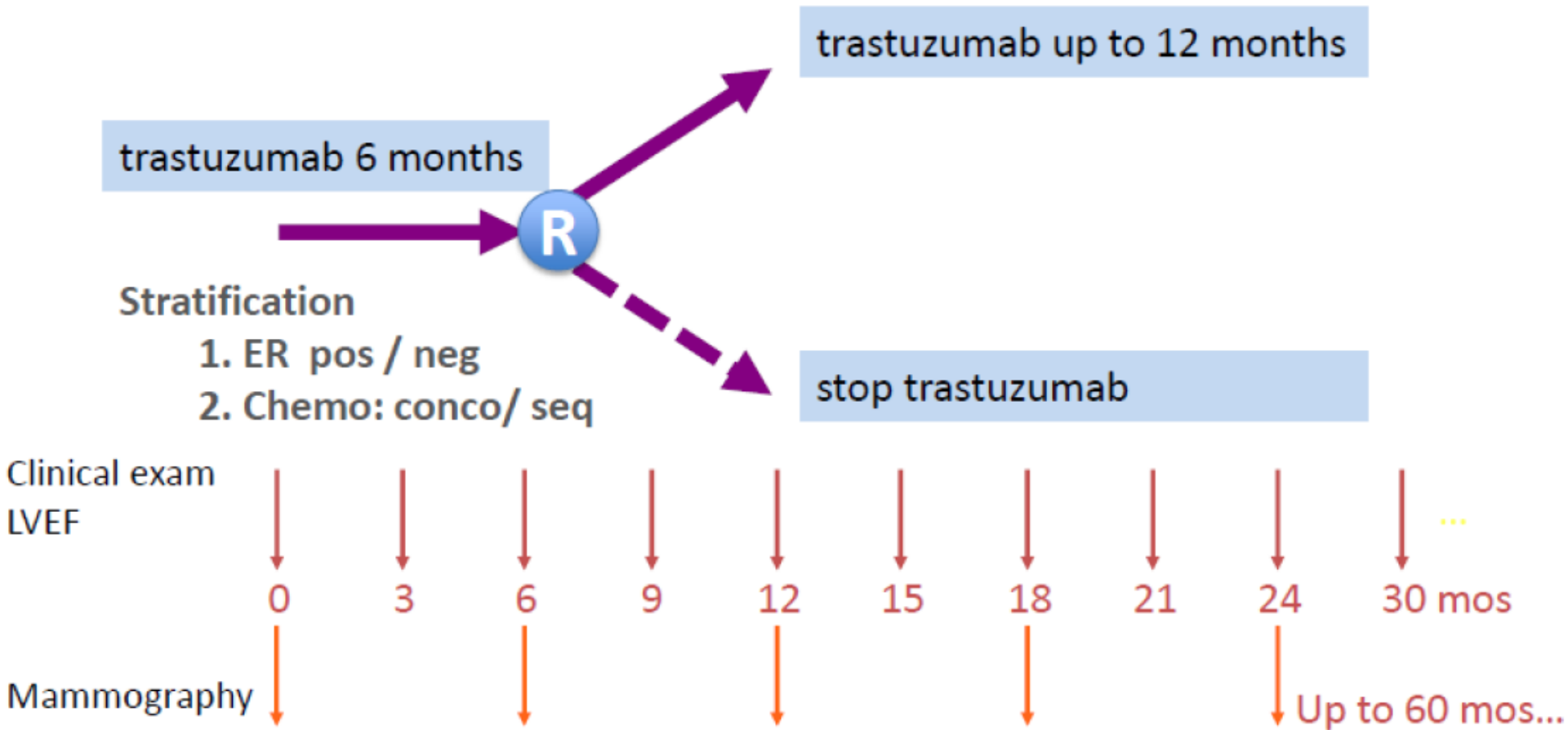


Protocol of  
Herceptin®  
Adjuvant with  
Reduced  
Exposure

## PHARE\* Trial results comparing 6 to 12 months of trastuzumab in adjuvant early breast cancer

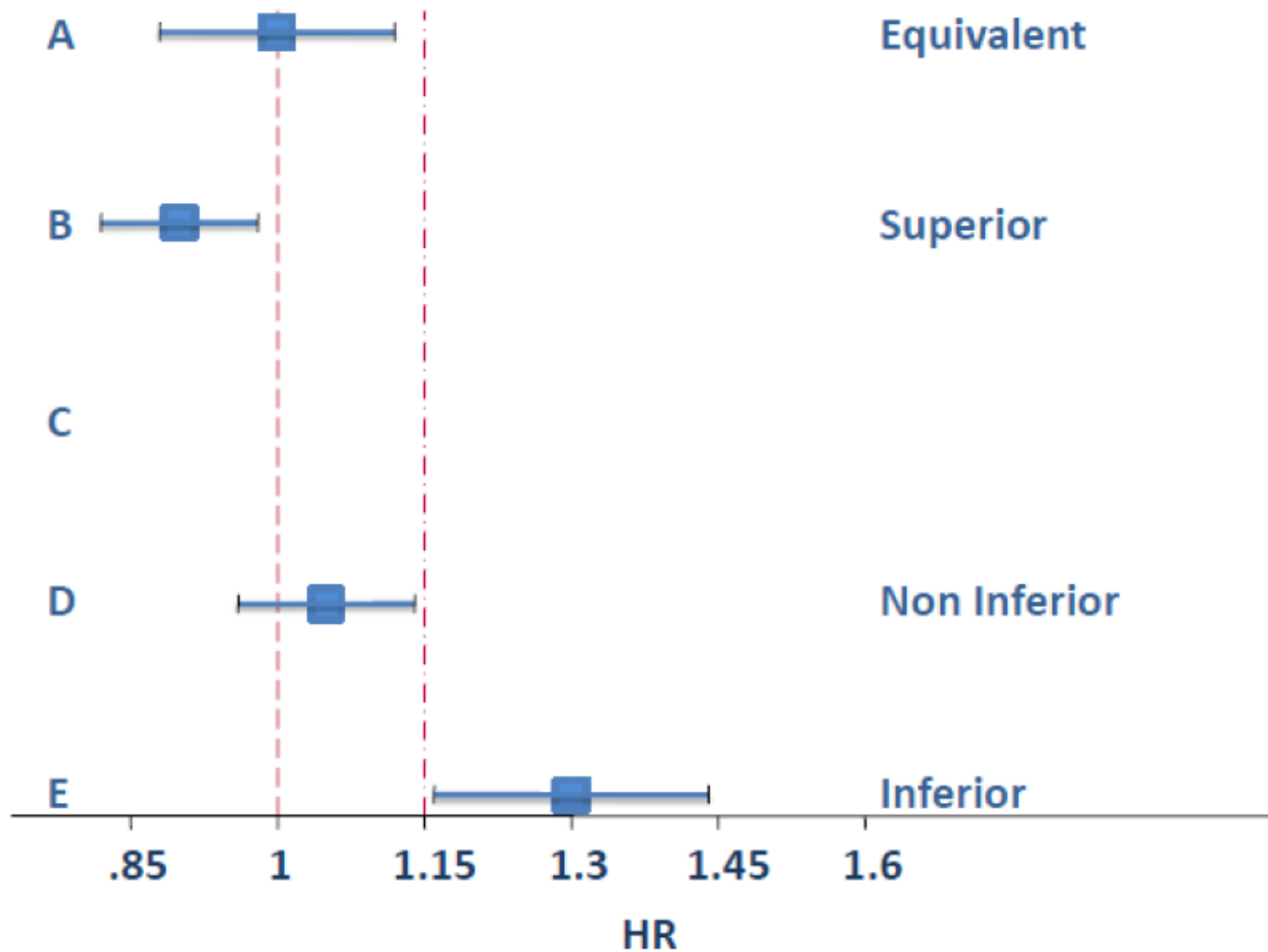
**Xavier Pivot**, Gilles Romieu, Hervé Bonnefoi, Jean-Yves Pierga, Pierre Kerbrat, Thomas Bachelot, Alain Lortholary, Marc Espié, Pierre Fumoleau, Daniel Serin, Jean-Philippe Jacquin, Christelle Jouannaud, Maria Rios, Sophie Abadie-Lacourtoisie, Nicole Tubiana-Mathieu, Laurent Cany, Stéphanie Catala, David Khayat, Iris Pauporté, Andrew Kramar.

# PHARE 1 year vs 6 months

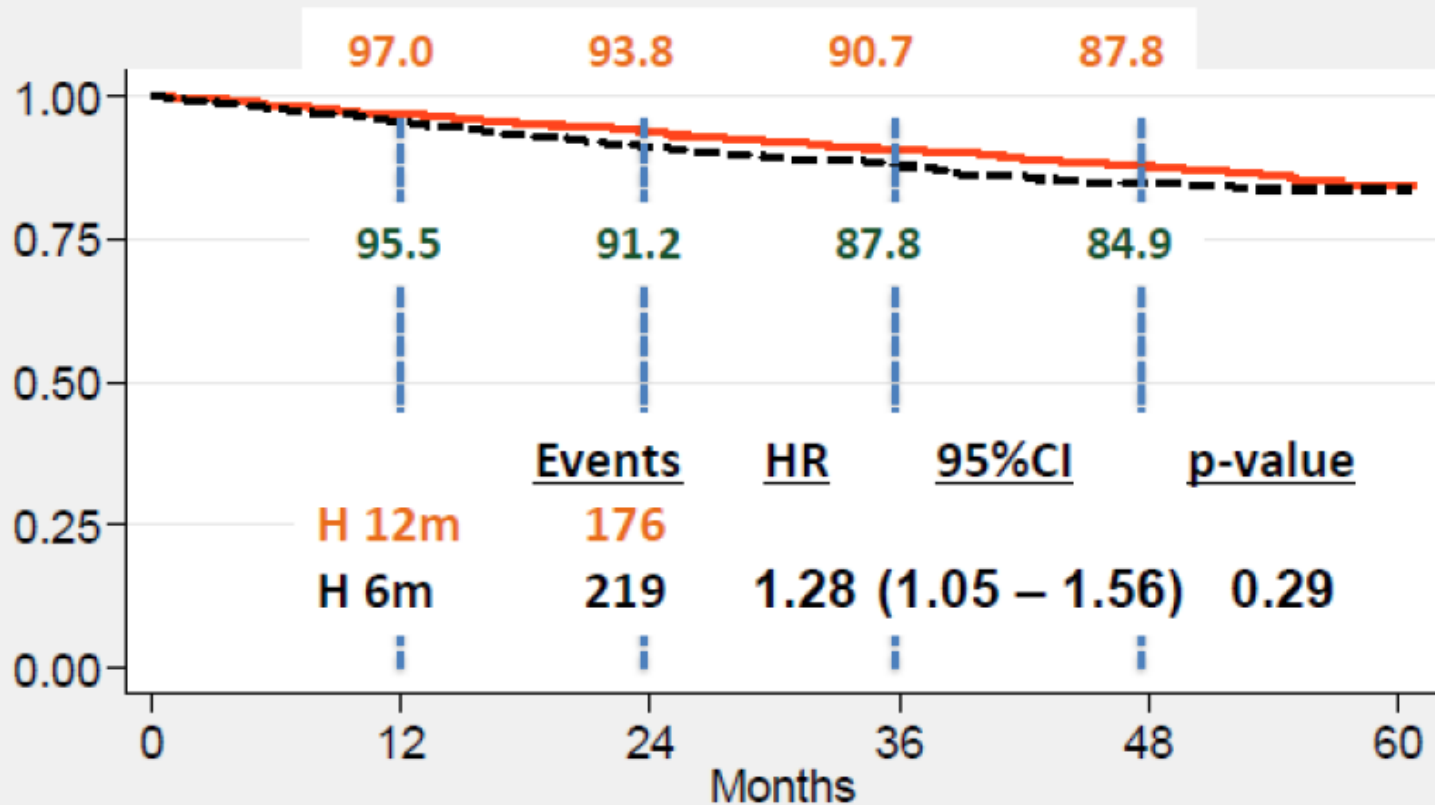


R: Randomization after informed consent

# PHARE 1 year vs 6 months



# PHARE 1 year vs 6 months DFS



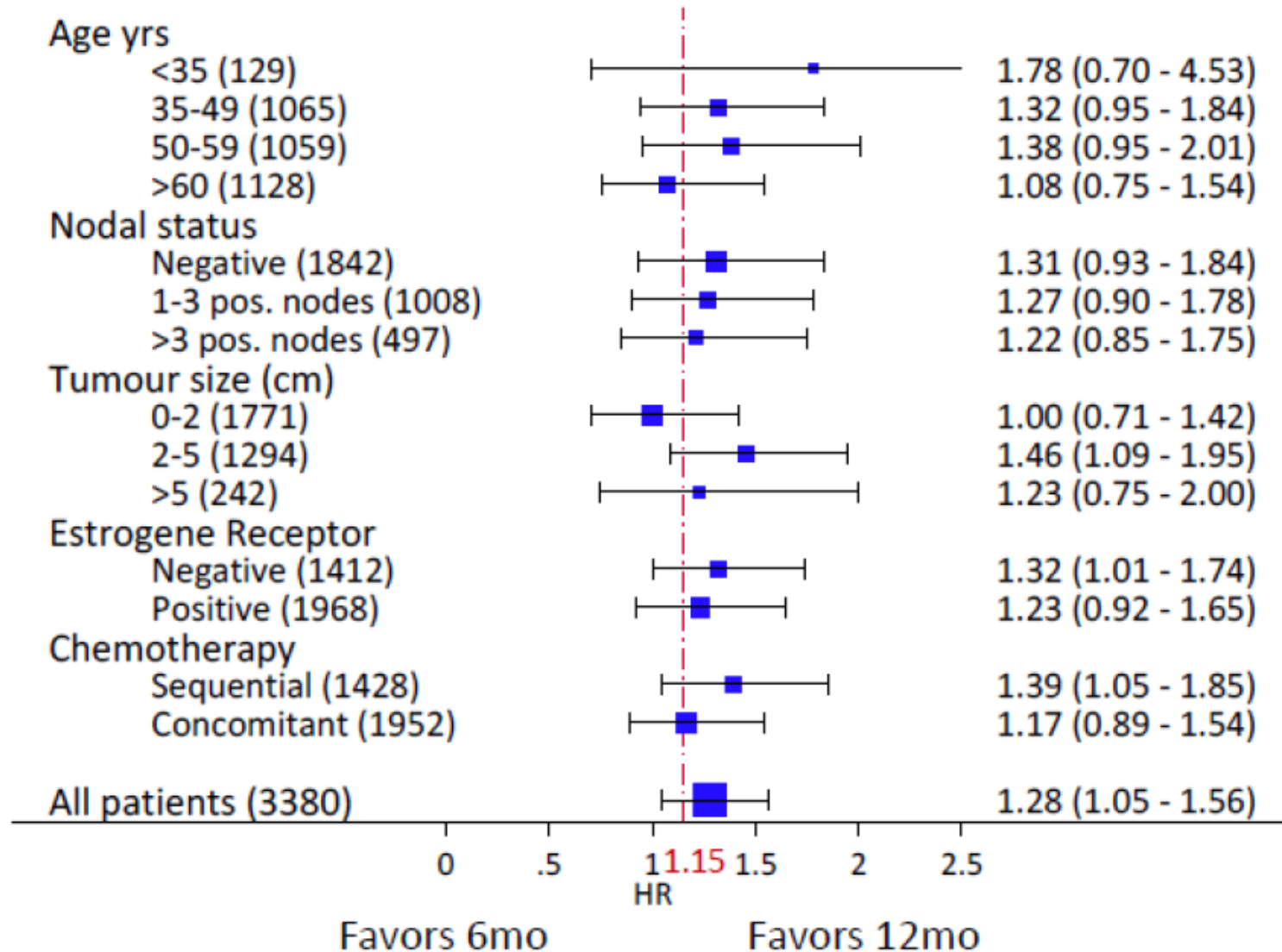
Events      HR      95%CI      p-value  
**176**      **1.28**      **(1.05 – 1.56)**      **0.29**

At risk

H-12m	1690	1613	1390	980	544	18
H 6m	1690	1586	1353	939	526	23

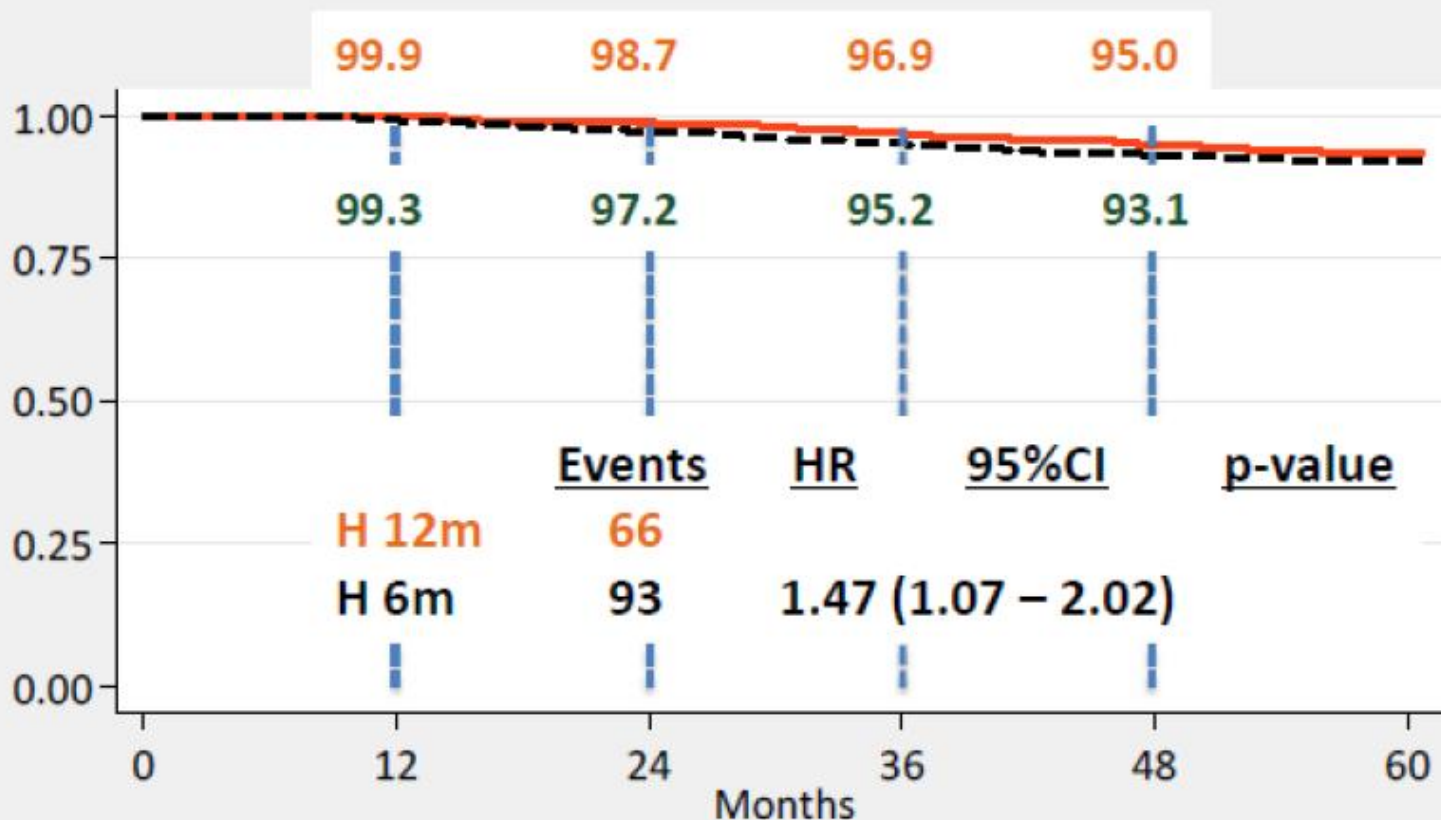
— H-12m      - - - - H-6m

# PHARE 1 year vs 6 months DFS



# PHARE 1 year vs 6 months OS

42.5mos. median FU



H 12m  
H 6m

Events

66

93

HR

1.47 (1.07 - 2.02)

95%CI

p-value

At risk

H-12m 1690

H 6m 1690

1662

1645

1463

1438

1042

1016

583

566

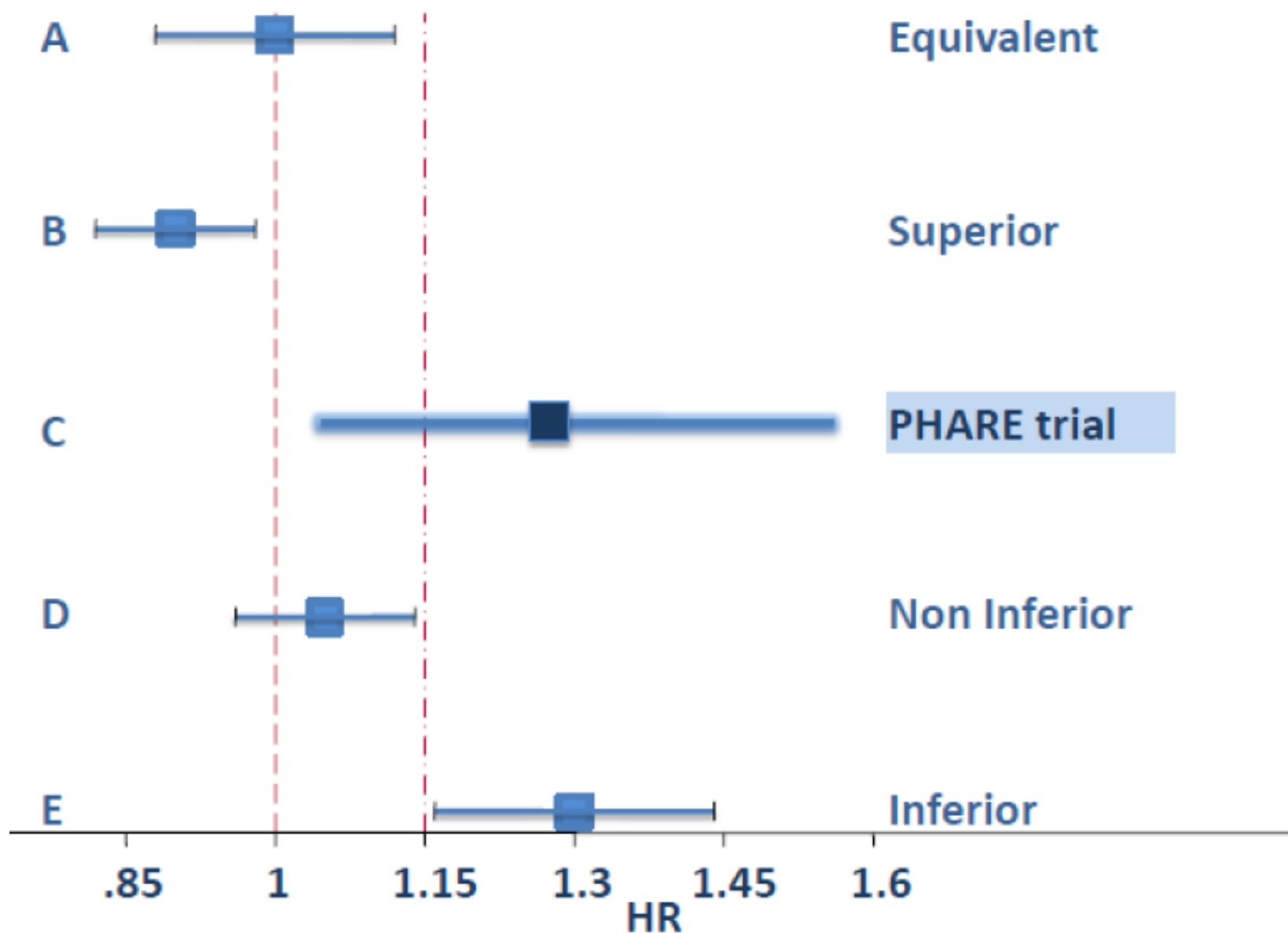
19

25

— H-12m

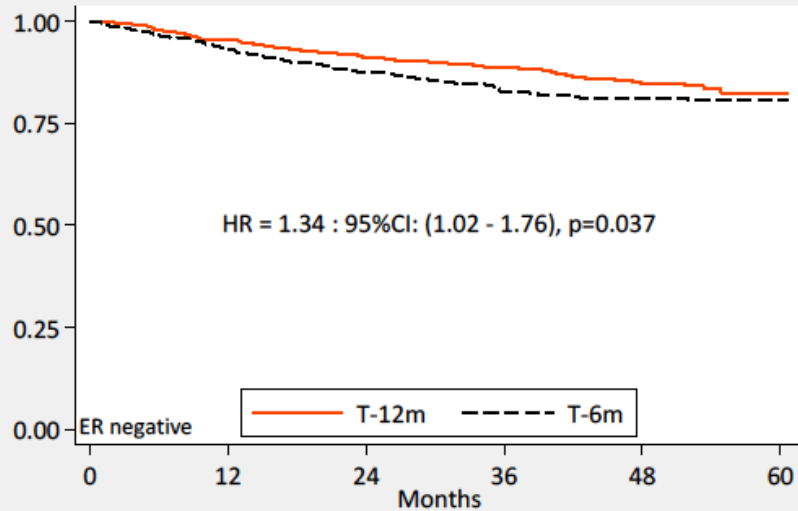
- - - H-6m

# PHARE 1 year vs 6 months OS



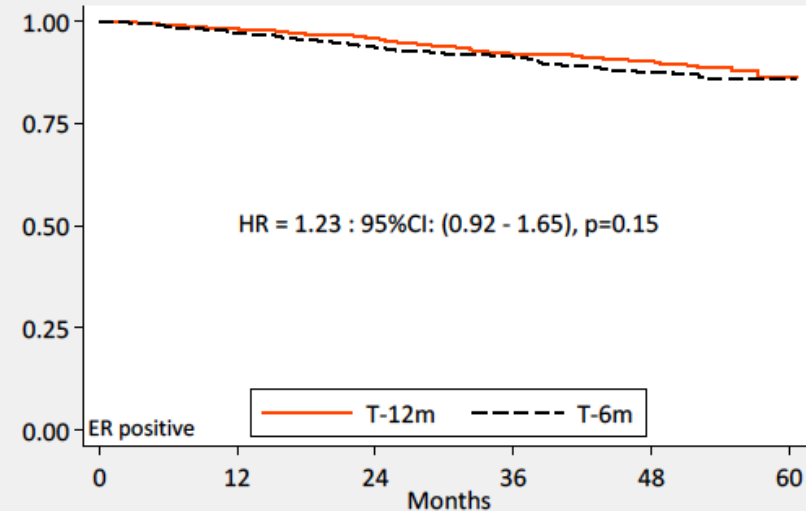
# PHARE 1 year vs 6 months OS

## ER negative



Trastuzumab		0	12	24	36	48	60
T-12m	716	668	568	410	221	6	
T-6m	696	639	544	373	207	8	

## ER positive



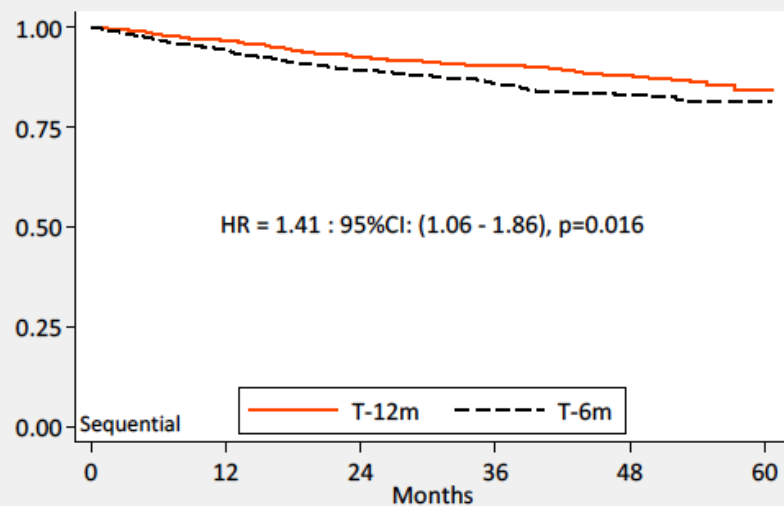
Trastuzumab		0	12	24	36	48	60
T-12m	974	945	822	570	323	12	
T-6m	994	947	809	566	319	15	

	Trastuzumab 12 months			Trastuzumab 6 months		
	Events	N	DFS-3	Events	N	DFS-3
ER negative	92	716	0.888	117	696	0.829
ER positive	83	974	0.920	102	994	0.912

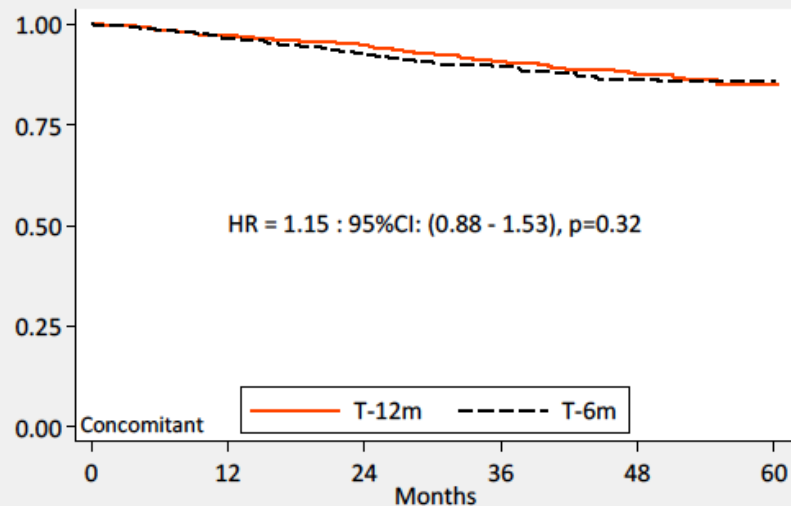
# PHARE 1 year vs 6 months OS

## Sequential

## Concomitant



Trastuzumab						
	0	12	24	36	48	60
T-12m	729	691	616	502	324	17
T-6m	747	692	605	485	309	19



Trastuzumab						
	0	12	24	36	48	60
T-12m	961	922	774	478	220	1
T-6m	943	894	748	454	217	4

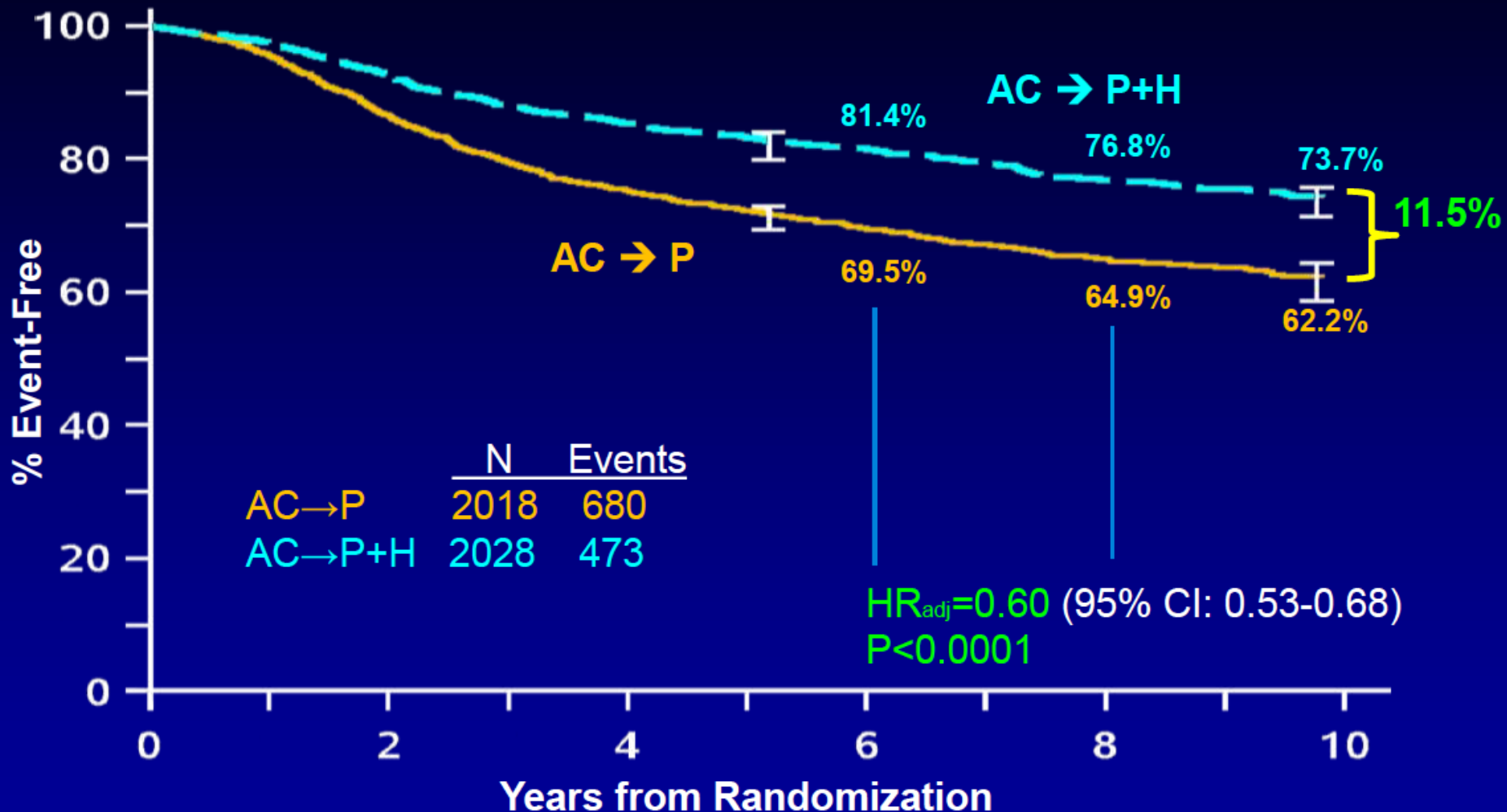
	Trastuzumab 12 months			Trastuzumab 6 months		
	Events	N	DFS-3	Events	N	DFS-3
Sequential	84	729	0.904	117	747	0.857
Concomitant	91	961	0.907	102	943	0.896

***NSABP B31 &***

***NCCTG 9831***

***8 anos seguimento***

# N9831/B-31 Disease-Free Survival

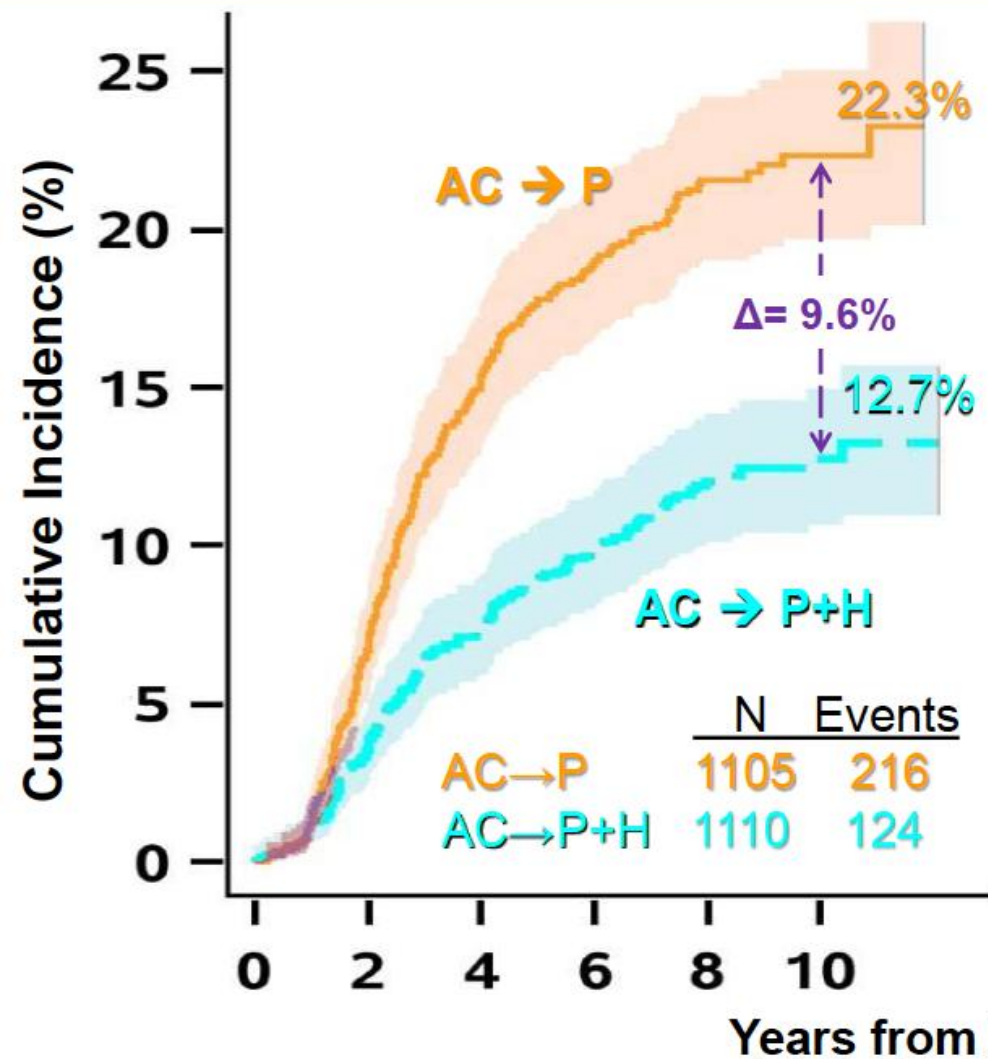


	N	Events
AC → P	2018	680
AC → P+H	2028	473

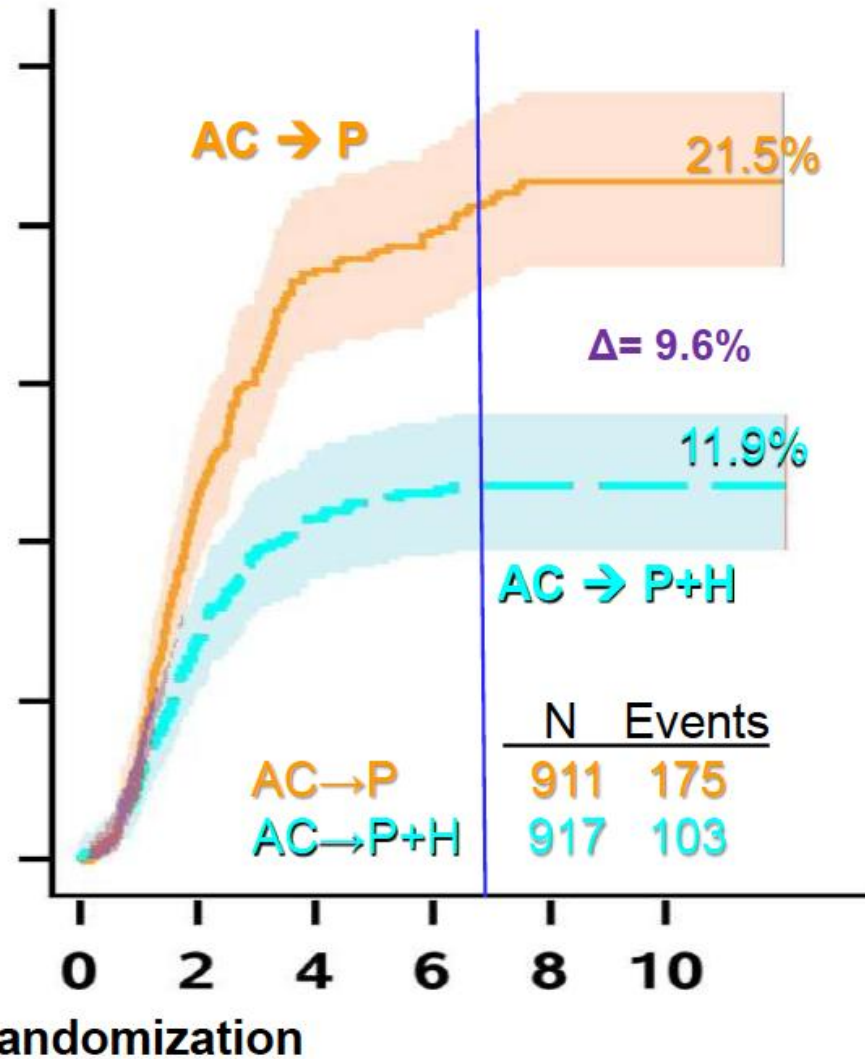
No. at risk

2028	1959	1848	1747	1675	1611	1514	1293	910	619	350
2018	1887	1689	1529	1423	1329	1232	1027	705	449	255

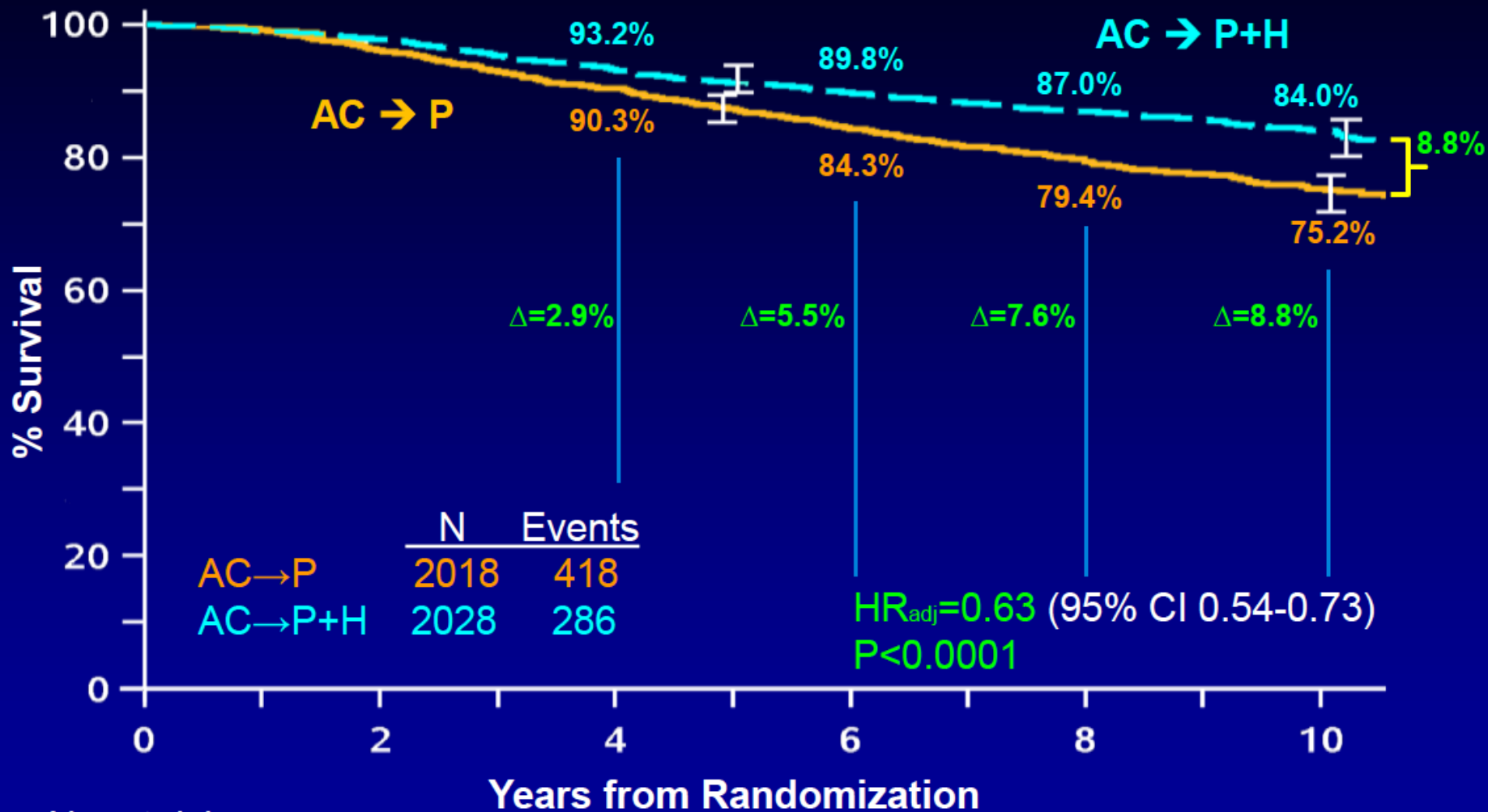
## ER and/or PR Positive



## ER and PR Negative



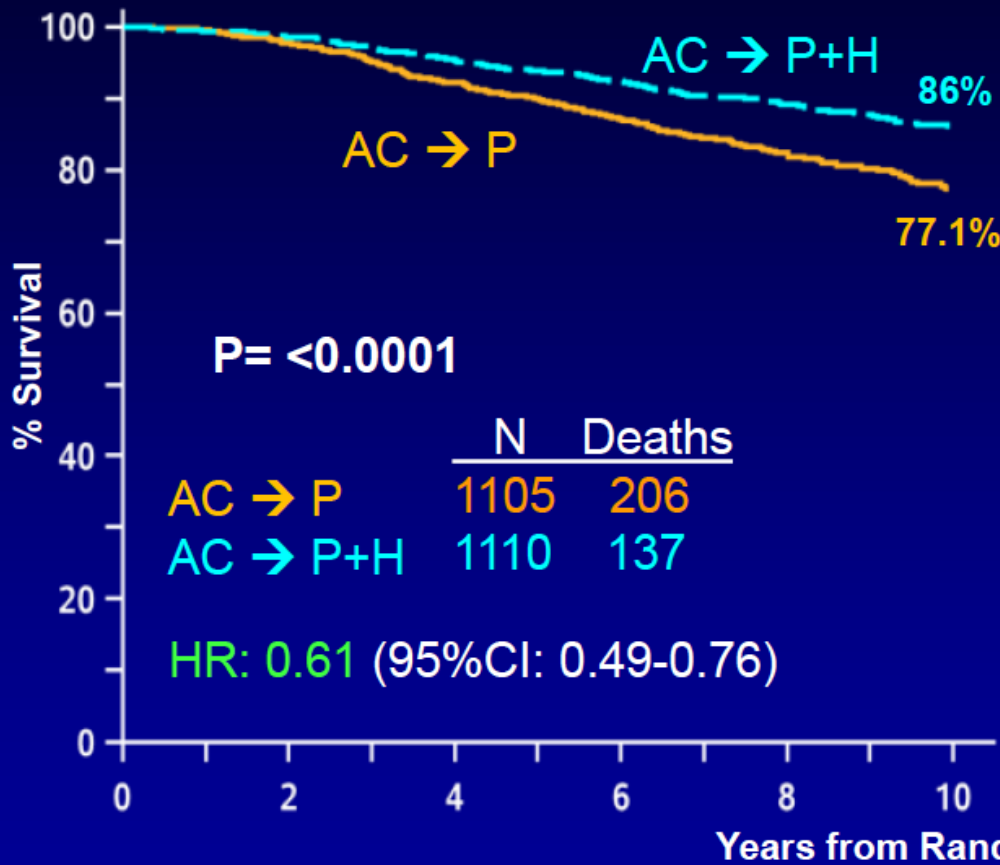
# B-31/N9831 Overall Survival



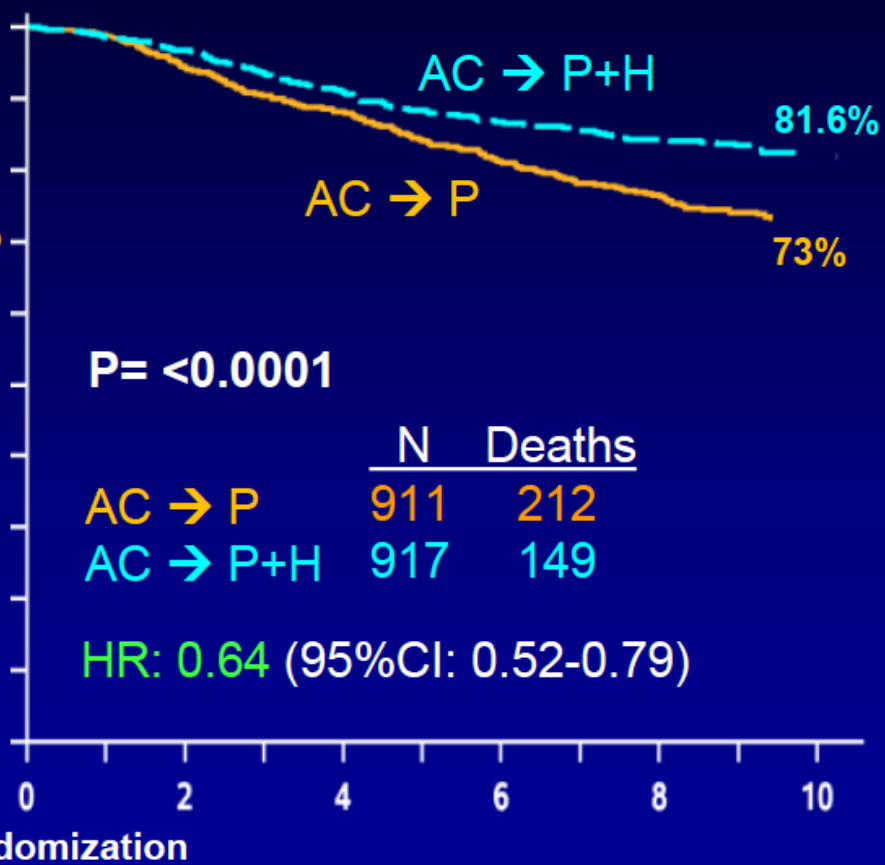
No. at risk

2028	1995	1959	1897	1843	1785	1709	1506	1085	735	439
2018	1962	1883	1806	1730	1640	1534	1336	944	604	353

## ER and/or PR Positive



## ER and PR Negative



No. at risk

Years from Randomization	0	2	4	6	8	10
ER and/or PR Positive - AC → P+H	1110	1002	925	263	917	176
ER and/or PR Positive - AC → P	1105	925	840	204	911	148
ER and PR Negative - AC → P+H	917	782	713	263	917	176
ER and PR Negative - AC → P	911	713	648	204	911	148

Significado da Resposta  
Patológica Completa

*Duplo Bloqueio da via do  
HER2*

# Estudo TECHNO

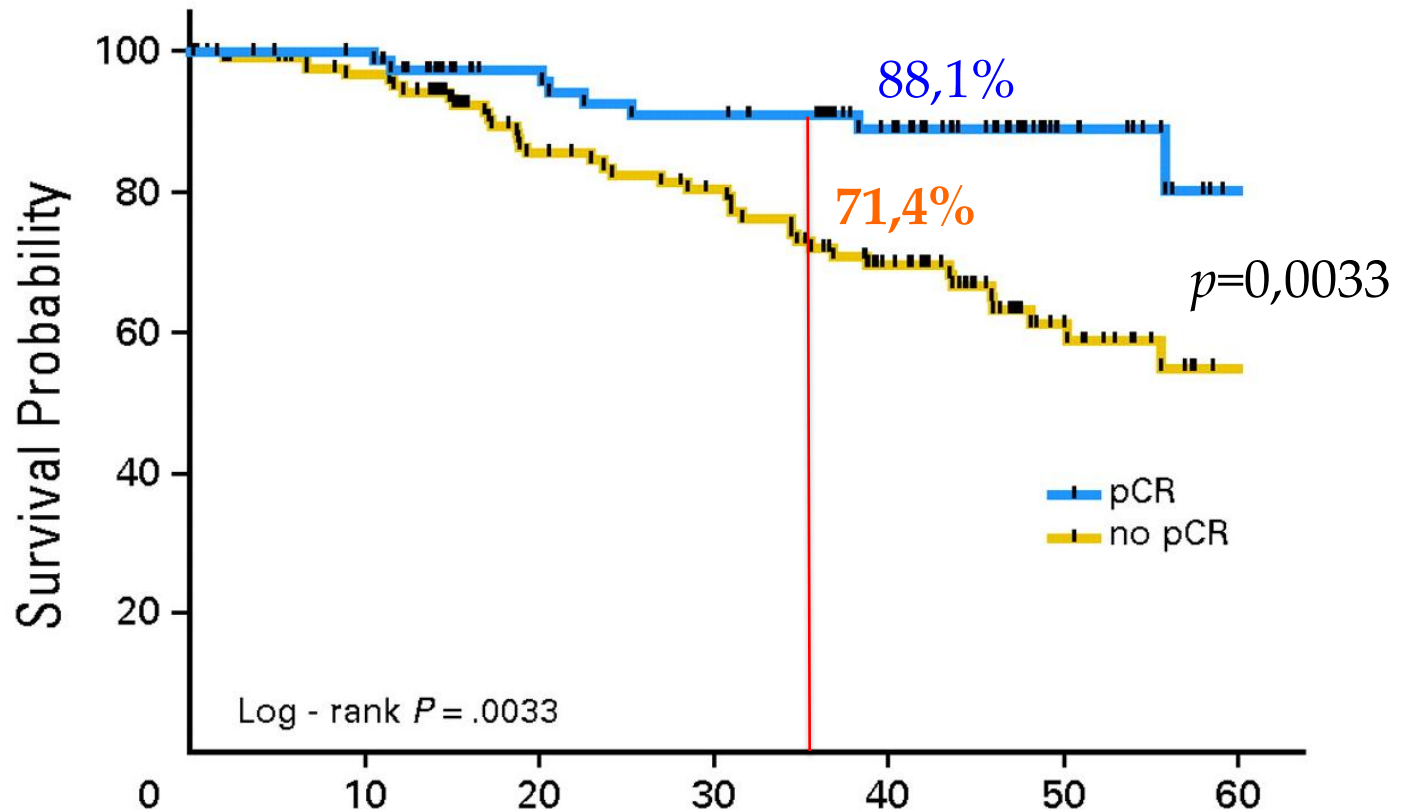
n= 217

$E_{90}C_{600}$  x 4 ciclos

Paclitaxel<sub>175</sub> x 4 + Trastuzumab (1 ano)

RC<sub>patol</sub> 38,7% (22,6%-45,2%)

# Estudo TECHNO

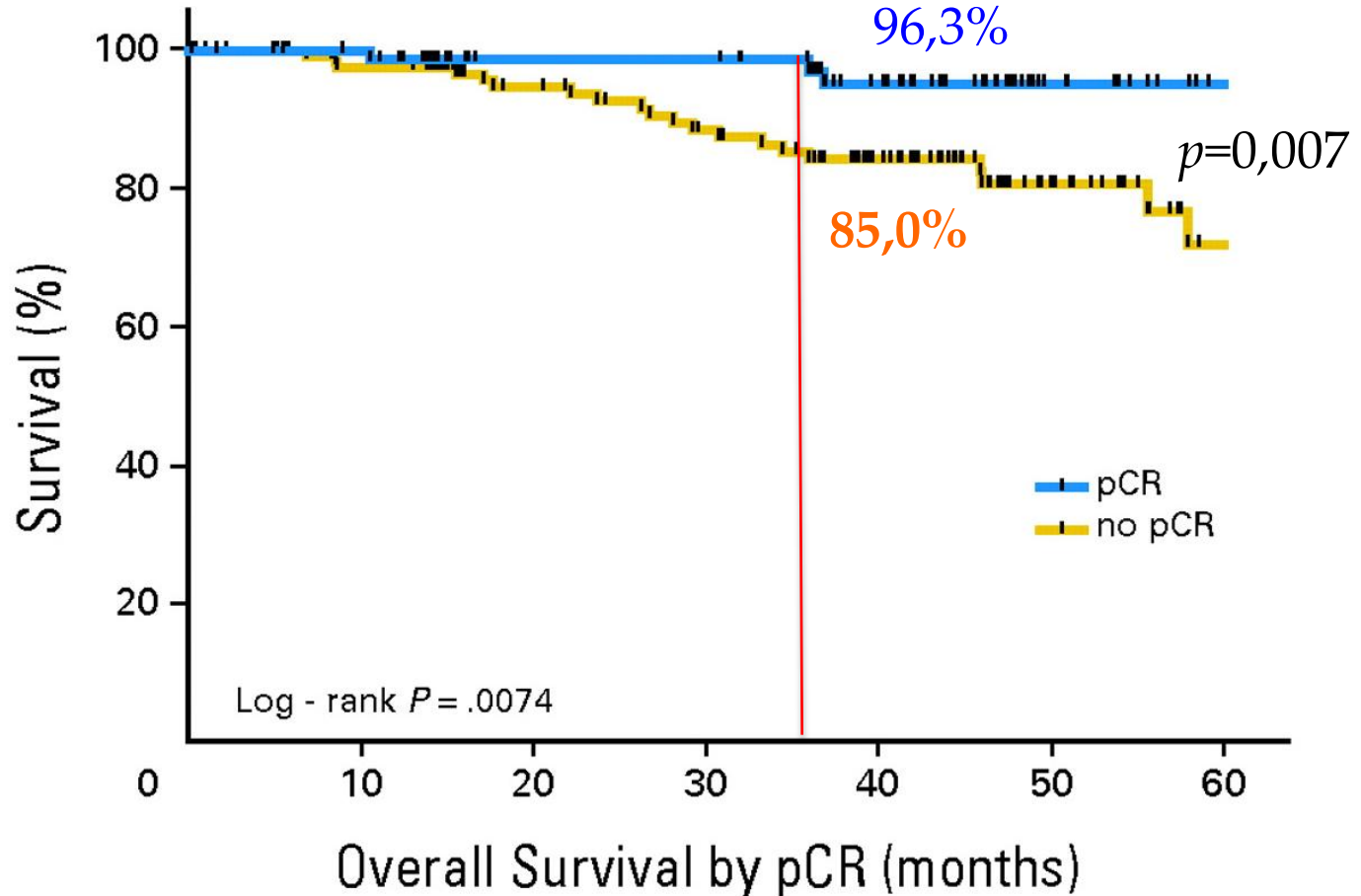


Disease-Free Survival by pCR (months)

No. at risk

pCR	84	79	61	57	43	16	5
no pCR	133	118	86	76	56	27	10

# Estudo TECHNO



No. at risk

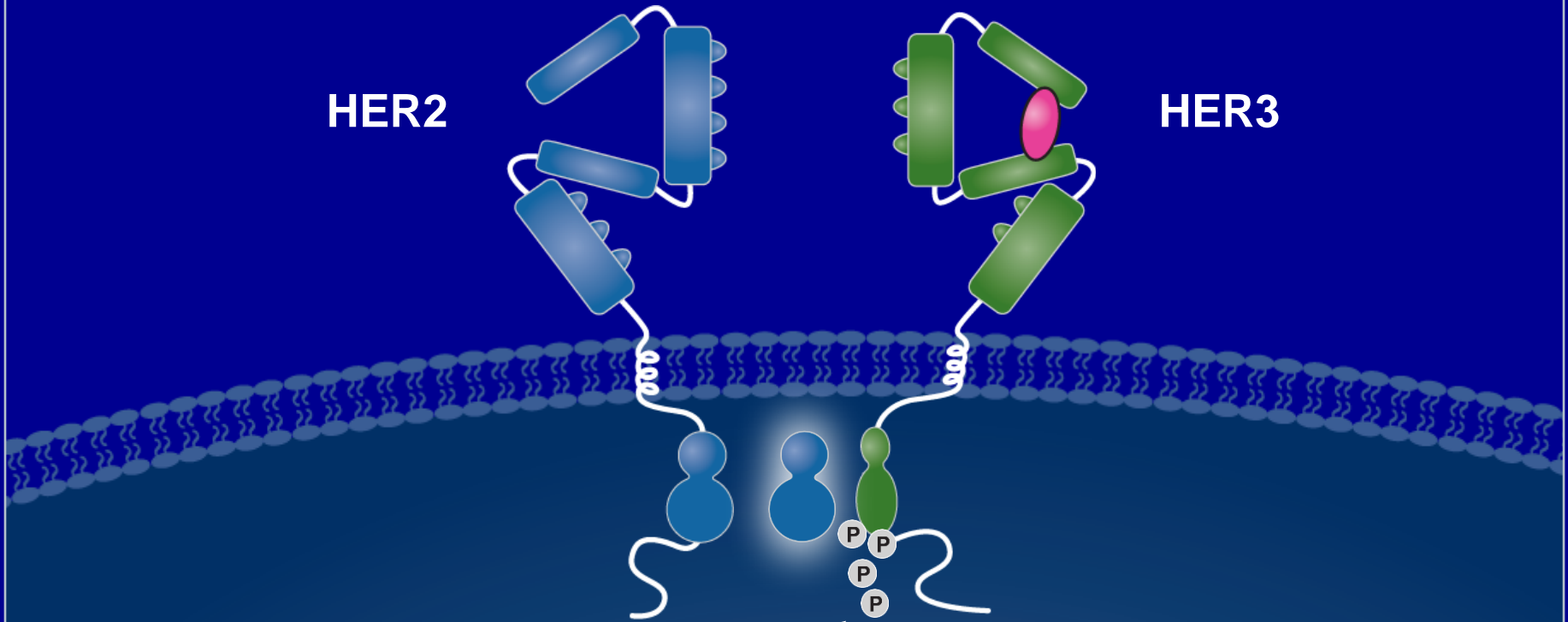
pCR	84	79	62	62	47	17	7
no pCR	133	118	96	84	65	33	14

# Duplo Bloqueio

Ligand-activated HER2:HER3 dimer

HER2

HER3



Phosphorylation of the tyrosine kinase domain initiates intracellular signaling

# *Neoadjuvant Treatment*

<b>Nome</b>	<b>Autor</b>	<b>Data</b>	<b>Esquema</b>	<b>N</b>	<b>Desfecho primário</b>	<b>Resultados</b>	<b>Cardiotoxicidade</b>
<b>NA</b>	Buzdar	2005	<b>Paclitaxel x4 -&gt; 4 FEC +/- Tmab por 24 sem</b>	42	<b>pCR</b>	<b>pCR 65,2% vs 26% (p=0,02)</b>	<b>Nenhum caso de ICC</b>
<b>NOAH</b>	Gianni	2010	<b>Doxo + Paclitaxel x3&gt; Paclitaxel q21d x4 -&gt; CMF x3 +/- Tmab concomitante</b>	235	<b>SLE</b>	<b>tpCR 38% vs 19% (p=0,001). Relação com EFS</b>	<b>2% casos de ICC sintomática</b>
<b>GQuinto</b>	Untch	2012	<b>EC -&gt; Doectaxel + Tmab ou Lapatinib por 24 semanas</b>	620	<b>pCR</b>	<b>pCR 30,3% (Tmab) e 22,7% (Lapatinib)</b>	<b>NI</b>
<b>NeoALTTO</b>	Baselga	2010	<b>Paclitaxel + Lapatinib/Tmab-&gt; Cx -&gt; FEC x 3 -&gt; Lapatinib/Tmab</b>	450	<b>pCR</b>	<b>tpCR 27% (Tmab) 20% (Lapatinib)</b>	<b>Sem toxicidades cardíacas G3 ou 4</b>
<b>GQuattro</b>	Untch	2010	<b>ECx4-&gt;docetaxel x4 + Tmab concomitante 24 sem +/- capecitabina</b>	445	<b>pCR</b>	<b>pCR 31,7%</b>	<b>1 caso ICC sintomática</b>
<b>TECHNO</b>	Untch	2011	<b>ECx4 -&gt; Paclitaxel x4 +Tmab por 12 sem (braço único)</b>	217	<b>pCR</b>	<b>pCR 38,7%. Relação com DFS e OS.</b>	<b>Cardiotox. 3,7% (6 casos de decréscimo de FE)</b>

# Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial

*José Baselga, Ian Bradbury, Holger Eidtmann, Serena Di Cosimo, Evandro de Azambuja, Claudia Aura, Henry Gómez, Phuong Dinh, Karine Fauria, Veerle Van Dooren, Gursel Aktan, Aron Goldhirsch, Tsai-Wang Chang, Zsolt Horváth, Maria Coccia-Portugal, Julien Domont, Ling-Min Tseng, Georg Kunz, Joo Hyuk Sohn, Vladimir Semiglazov, Guillermo Lerzo, Marketa Palacova, Volodymyr Probachai, Lajos Pusztai, Michael Untch, Richard D Gelber, Martine Piccart-Gebhart, on behalf of the NeoALTTO Study Team*

*Lancet* 2012; 379: 633–40

# Trastuzumab & Lapatinib

Invasive operable  
HER2+ BC  
T > 2 cm  
(inflammatory BC  
excluded)  
LVEF  $\geq$  50%  
**N=450**

## Stratification:

- T  $\leq$  5 cm vs. T > 5 cm
- ER or PgR + vs. ER & PgR -
- N 0-1 vs. N  $\geq$  2
- Conservative surgery or not

R  
A  
N  
D  
O  
M  
I  
Z  
E

lapatinib  
paclitaxel

trastuzumab  
paclitaxel

lapatinib  
trastuzumab  
paclitaxel

6 wks

+ 12 wks

S  
U  
R  
G  
E  
R  
Y

F  
E  
C  
X  
3

lapatinib

trastuzumab

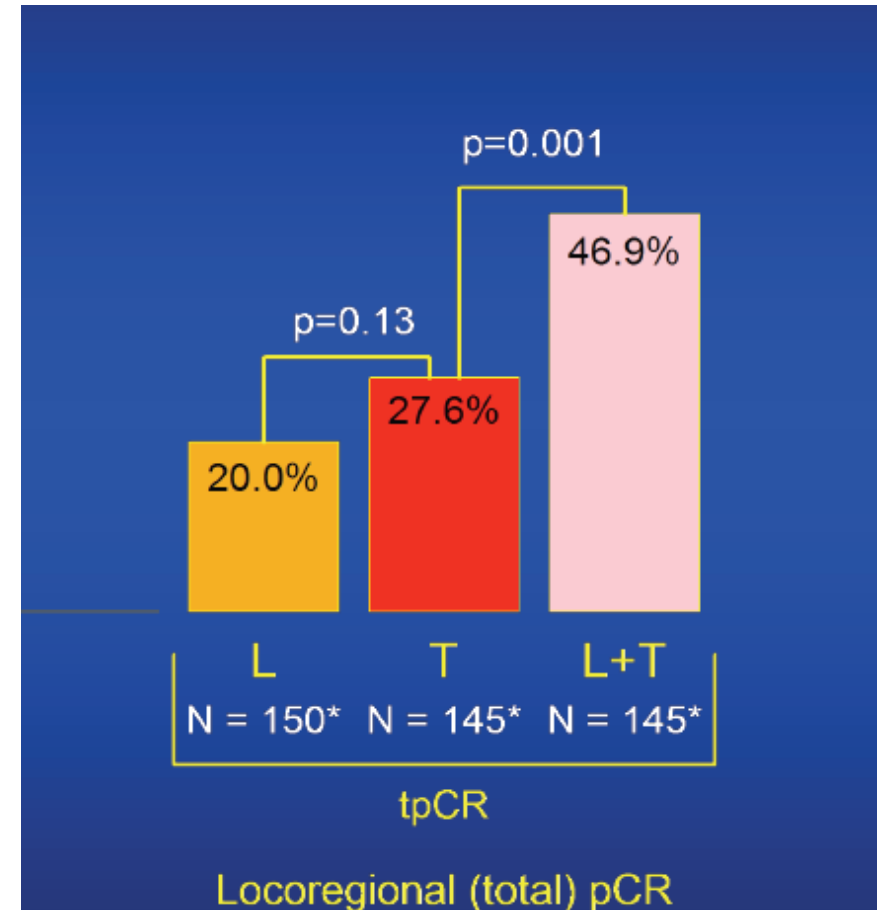
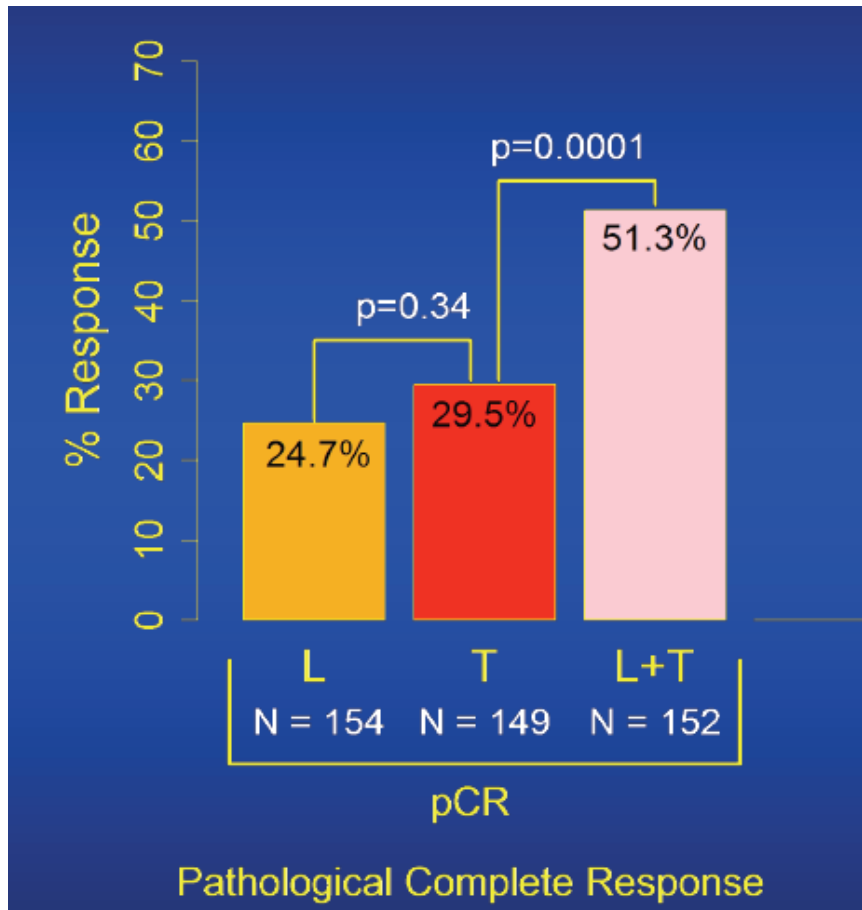
lapatinib  
trastuzumab

34 weeks

52 weeks of anti-HER2 therapy

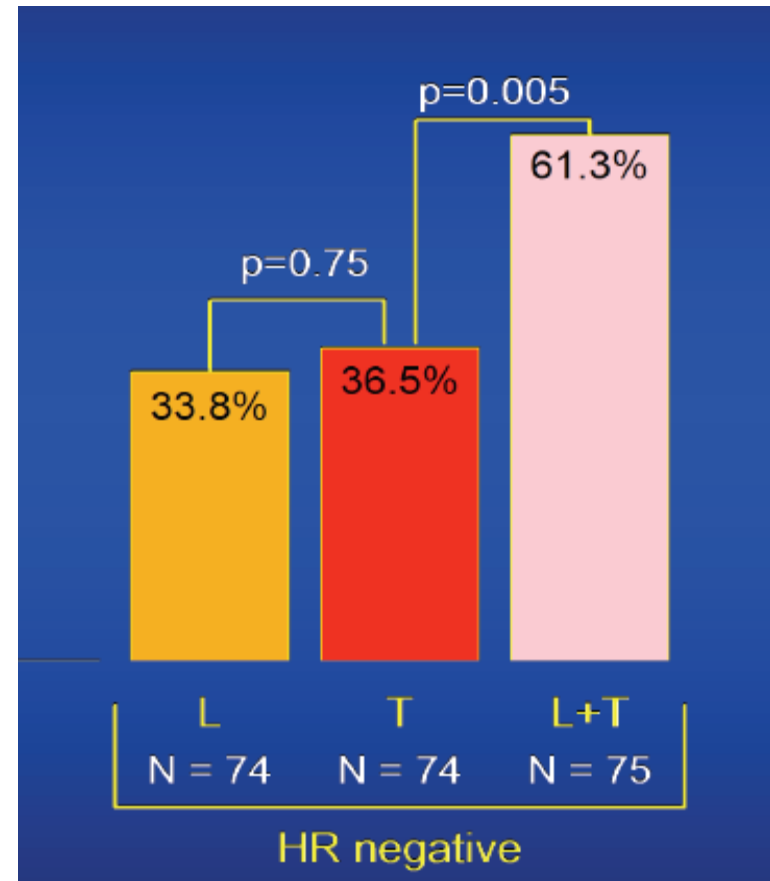
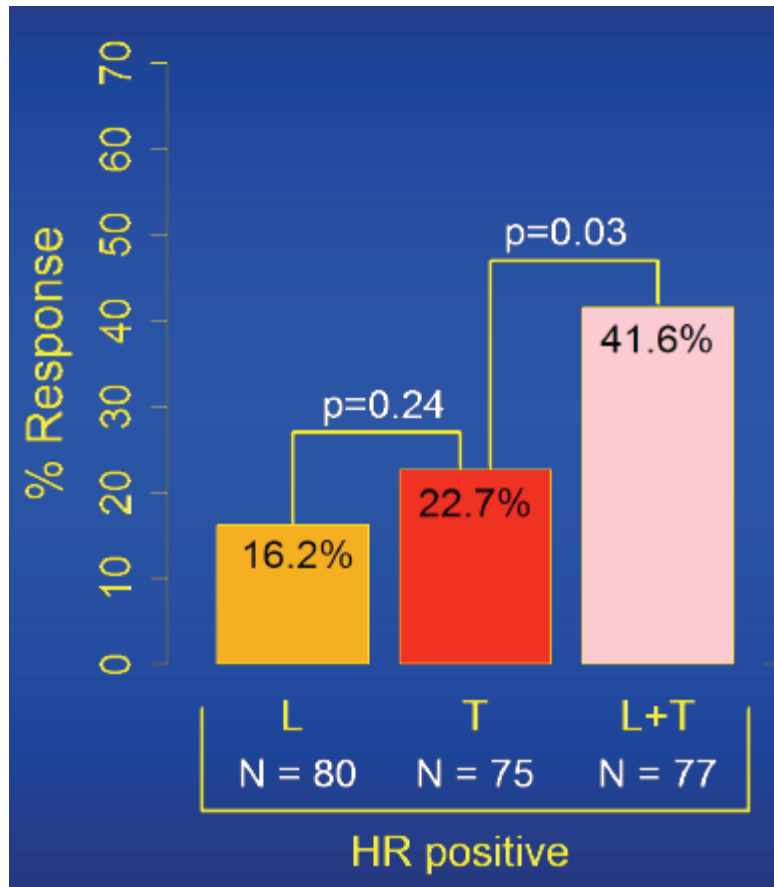
# Trastuzumab & Lapatinib

- Primary endpoint – pCR



# Trastuzumab & Lapatinib

## ■ pCR and ER expression



# Trastuzumab & Lapatinib

Number (%) of patients with AEs at Grade  $\geq$  3

	<b>L</b> <b>(N= 154)</b>	<b>T</b> <b>(N= 149)</b>	<b>L+T</b> <b>(N= 152)</b>
<b>Diarrhea</b>	36 (23%)	3 (2%)	32 (21%)
<b>Hepatic *</b>	20 (13%)	2 (1%)	13 (9%)
<b>Neutropenia</b>	24 (16%)	4 (3%)	13 (9%)
<b>Skin disorders</b>	10 (7%)	4 (3%)	10 (7%)

\* Includes 2 patients with Hy's Law criteria in T, and one patient in L

- No major cardiac dysfunction
- One death in L+T immediately after end of treatment

L: lapatinib; T: trastuzumab; L+T: lapatinib plus trastuzumab

# Trastuzumab & Pertuzumab

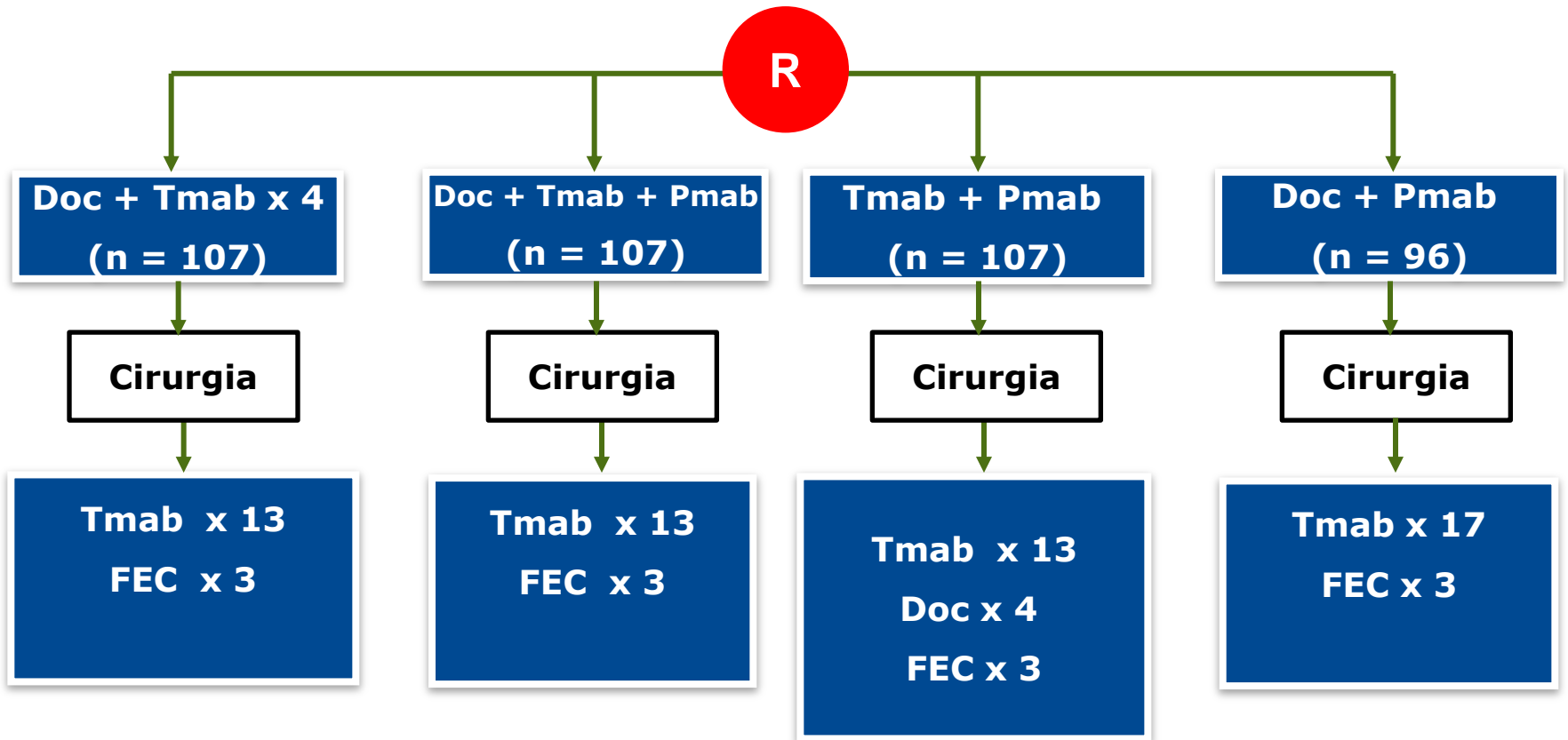
**Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial**

*Luca Gianni, Tadeusz Pienkowski, Young-Hyuck Im, Laslo Roman, Ling-Ming Tseng, Mei-Ching Liu, Ana Lluch, Elżbieta Staroslawska, Juan de la Haba-Rodriguez, Seock-Ah Im, Jose Luiz Pedrini, Brigitte Poirier, Paolo Morandi, Vladimir Semiglazov, Vichien Srimuninnimit, Giulia Bianchi, Tania Szado, Jayantha Ratnayake, Graham Ross, Pinuccia Valagussa*

*Lancet Oncol 2012; 13: 25-32*

- ◆ **Randomized phase II trial**
- ◆ **HER2 positive**
- ◆ **T2-4 N0-3 or inflammatory**

# Trastuzumab & Pertuzumab



Primary endpoint - pCR

# Trastuzumab & Pertuzumab

	Doc + Tmab	Doc + Tmab + Pmab	Tmab + Pmab	Doc + Pmab
pCR in breast	29.0%	45.8%	16.8%	24.0%
pCR in breast and node negative at surgery	21.5%	39.3%	11.2%	17.7%
pCR in breast and node positive at surgery	7.5%	6.5%	5.6%	6.3%

**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**

# Trastuzumab & Pertuzumab

	Doc + Tmab	Doc + Tmab + Pmab	Tmab + Pmab	Doc + Pmab
pCR (ER- or PR-positive)	22.0%	26.0%	5.9%	17.4%
pCR (ER- and PR-negative)	36.8%	63.2%	29.1%	30.0%

**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**

# Trastuzumab & Pertuzumab

	Doc + Tmab	Doc + Tmab + Pmab	Tmab + Pmab	Doc + Pmab
Grade 3-4 neutropenia	57.0%	44.9%	0.9%	55.3%
Febrile neutropenia	7.5%	8.4%	0.0%	7.4%
Grade 3-4 diarrhea	3.7%	5.6%	0.0%	4.3%
Grade 3-4 rash	1.9%	1.9%	0.0%	1.1%
Grade 3-4 increased ALT	2.8%	0.0%	0.0%	1.1%
Serious adverse events	16.8%	10.3%	3.7%	17.0%

**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**

# Cardiotoxicidade

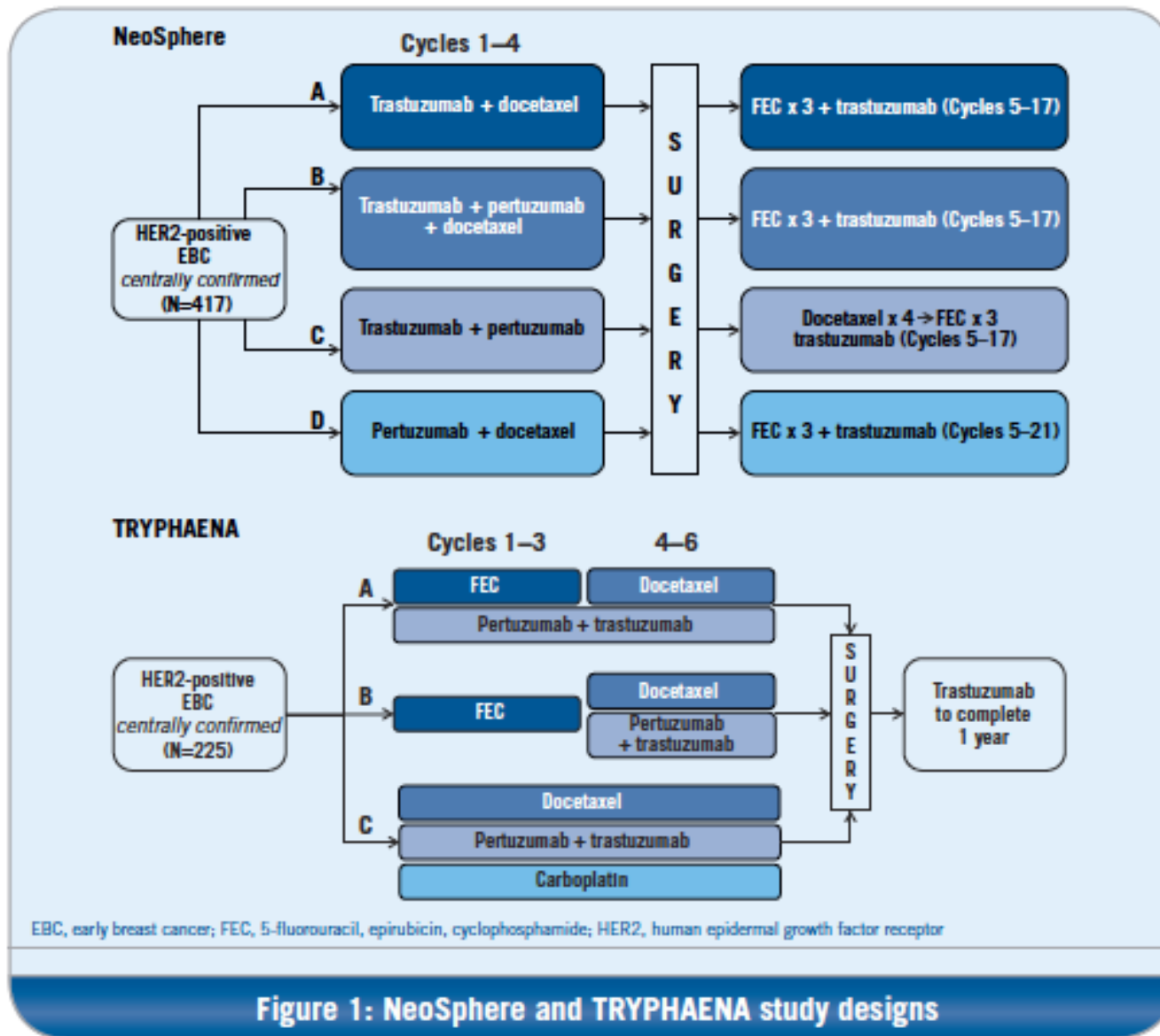
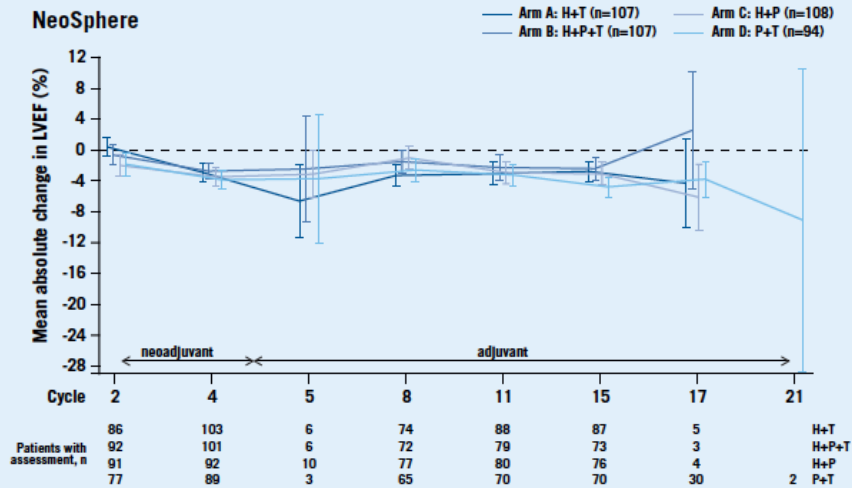
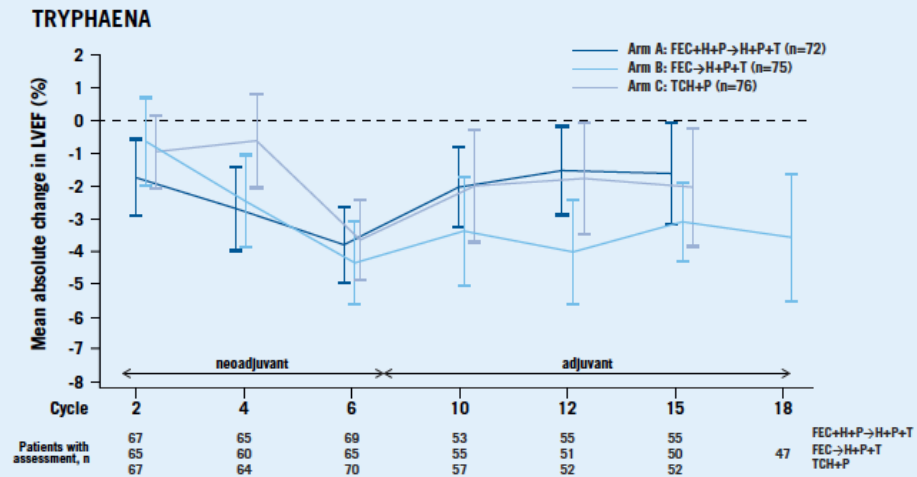


Figure 1: NeoSphere and TRYPHAENA study designs

# Cardiotoxicidade



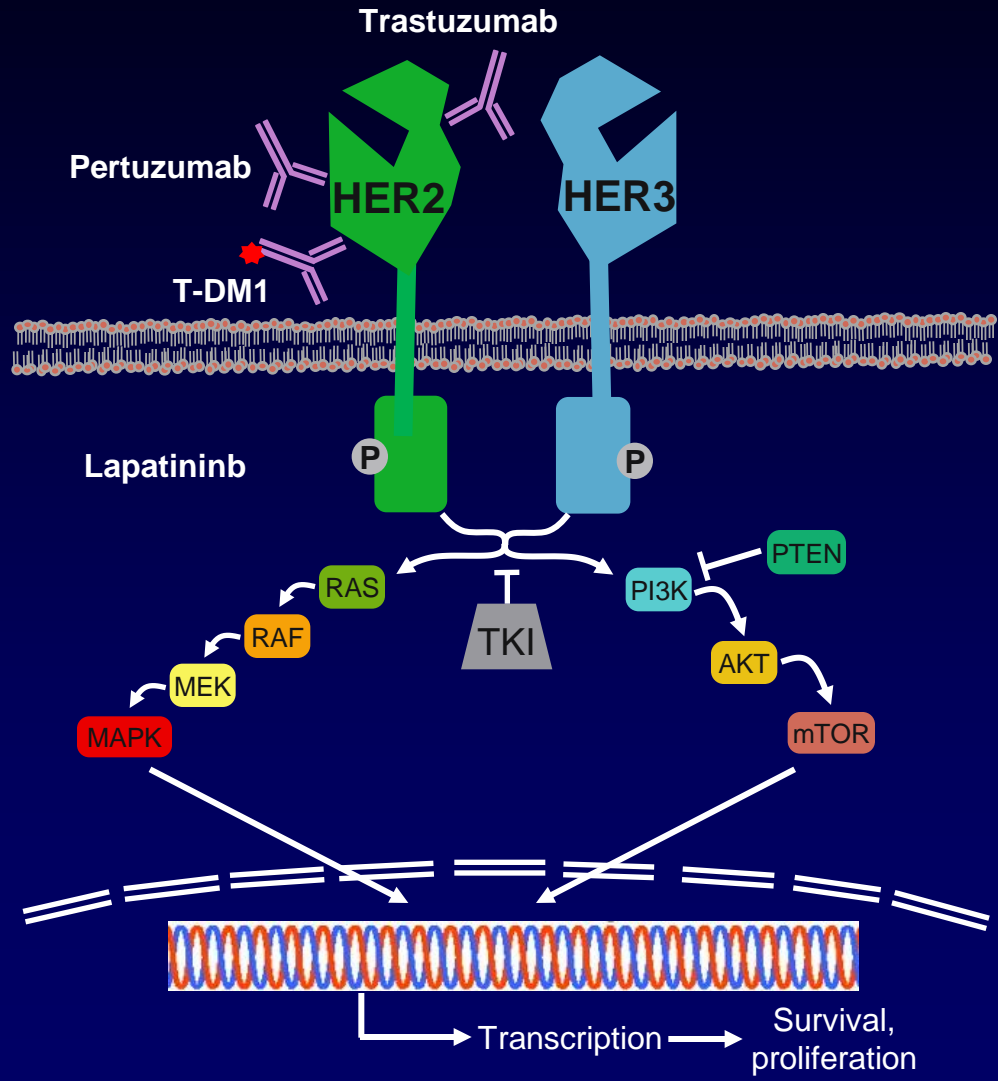
Note that the number of patients with LVEF assessment at Cycles 5, 17 and 21 is low resulting in wide confidence intervals.



Only scheduled visits are presented for both studies.

FEC, 5-fluorouracil, epirubicin, cyclophosphamide; H, trastuzumab; P, pertuzumab; T, docetaxel; TCH, docetaxel, carboplatin, trastuzumab  
LVEF, left ventricular ejection fraction

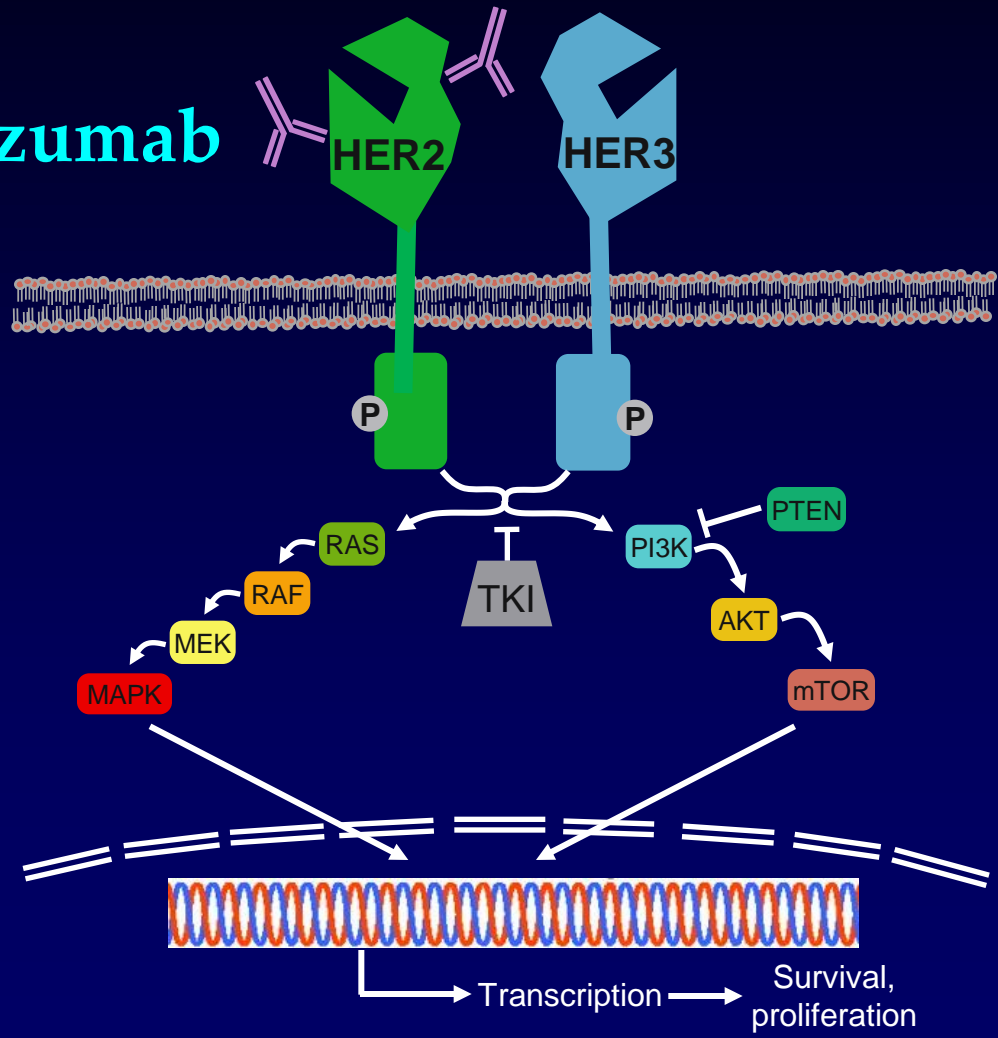
Figure 2: Mean change in LVEF from baseline over the treatment period



Olson EM, et al. J Clin Oncol. 2012;30:1712-1714.

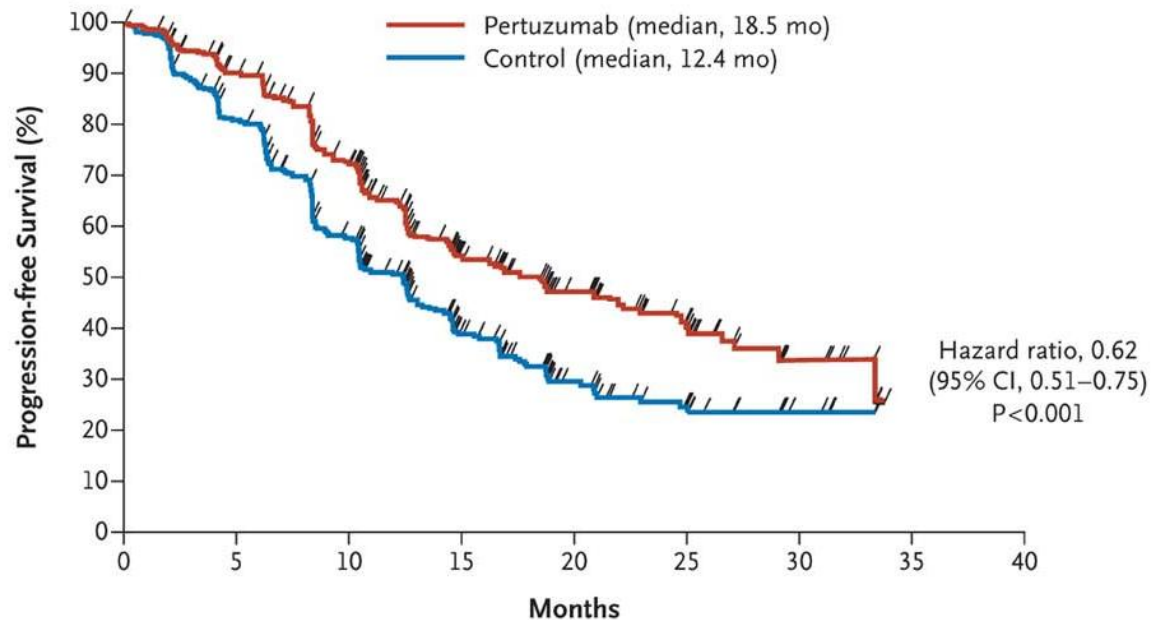
# Trastuzumab

Pertuzumab



# Estudo CLEOPATRA

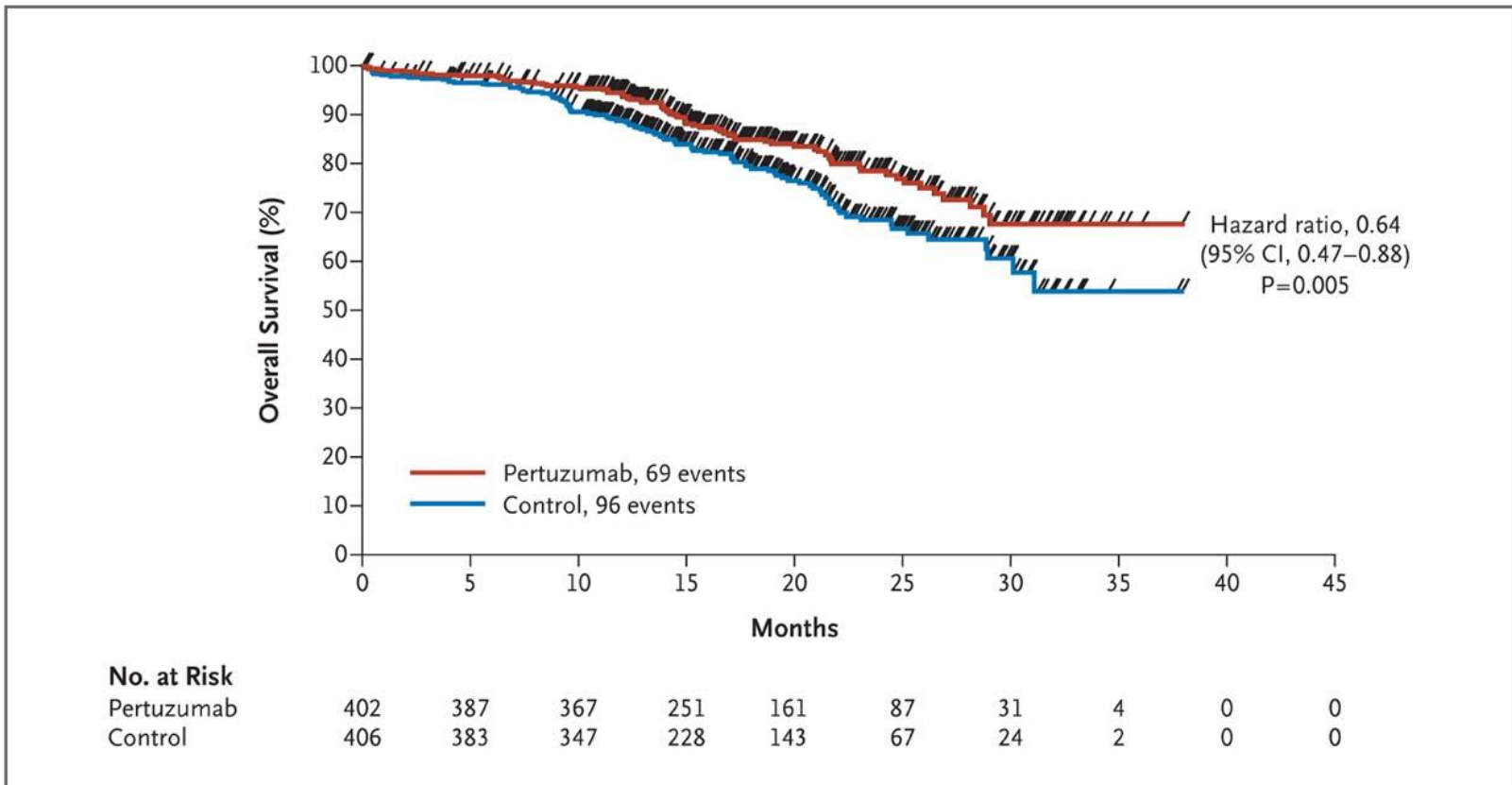
## Independently Assessed Progression-free Survival



### No. at Risk

Pertuzumab	402	345	267	139	83	32	10	0	0
Control	406	311	209	93	42	17	7	0	0

# Estudo CLEOPATRA



# *Bloqueio HER2/HER3 Novo standard*

## CLEOPATRA

The benefit of pertuzumab–trastuzumab–docetaxel therapy with respect to progression-free survival was observed across all predefined subgroups (Fig. 1B). Among the 88 patients who had received adjuvant or neoadjuvant chemotherapy with trastuzumab, the median independently assessed progression-free survival was 10.4 months in the control group, as compared with 16.9 months in the pertuzumab group (hazard ratio. 0.62: 95% CI. 0.35 to 1.07).

# Estudo CLEOPATRA

**Table 2.** Overall Response, as Assessed at an Independent Review Facility.\*

Response	Placebo plus Trastuzumab plus Docetaxel (N = 336)	Pertuzumab plus Trastuzumab plus Docetaxel (N = 343)
	<i>number (percent)</i>	
Objective response	233 (69.3)	275 (80.2)
Complete response	14 (4.2)	19 (5.5)
Partial response	219 (65.2)	256 (74.6)
Stable disease	70 (20.8)	50 (14.6)
Progressive disease	28 (8.3)	13 (3.8)
Not assessable	2 (0.6)	2 (0.6)
No assessment performed	3 (0.9)	3 (0.9)

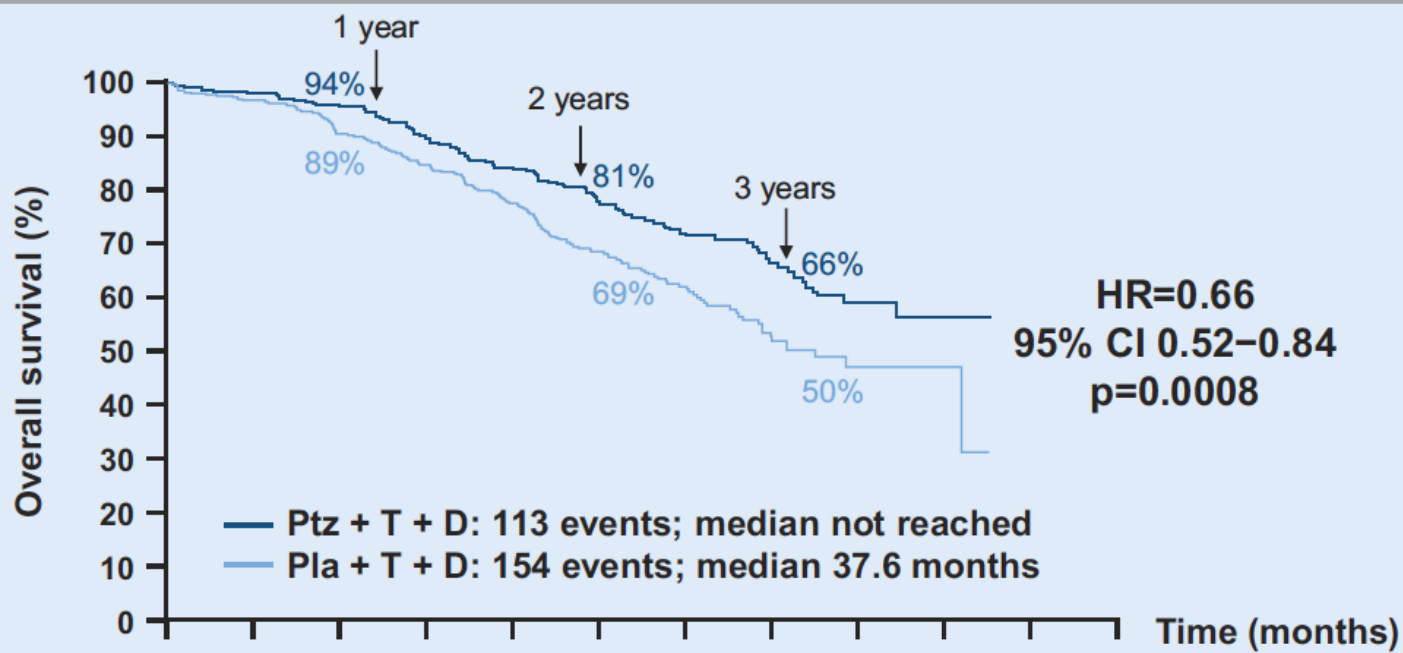
\* Total numbers in the two groups represent the number of patients with measurable disease at baseline, as assessed at an independent review facility.

# Estudo CLEOPATRA

## Grade 3 or higher events‡

Neutropenia	182 (45.8)	199 (48.9)
Febrile neutropenia	30 (7.6)	56 (13.8)
Leukopenia	58 (14.6)	50 (12.3)
Diarrhea	20 (5.0)	32 (7.9)
Peripheral neuropathy	7 (1.8)	11 (2.7)
Anemia	14 (3.5)	10 (2.5)
Asthenia	6 (1.5)	10 (2.5)
Fatigue	13 (3.3)	9 (2.2)
Granulocytopenia	9 (2.3)	6 (1.5)
Left ventricular systolic dysfunction	11 (2.8)	5 (1.2)
Dyspnea	8 (2.0)	4 (1.0)

# Estudo CLEOPATRA



n at risk	0	5	10	15	20	25	30	35	40	45	50	55
— Ptz + T + D	402	387	371	342	317	230	143	84	33	9	0	0
— Pla + T + D	406	383	350	324	285	198	128	67	22	4	0	0

Stopping boundary for concluding statistical significance at this second interim analysis was  $p \leq 0.0138$   
D, docetaxel; Pla, placebo; Ptz, pertuzumab; T, trastuzumab

Figure 2: Kaplan-Meier curves of the confirmatory overall survival analysis

# Estudo CLEOPATRA

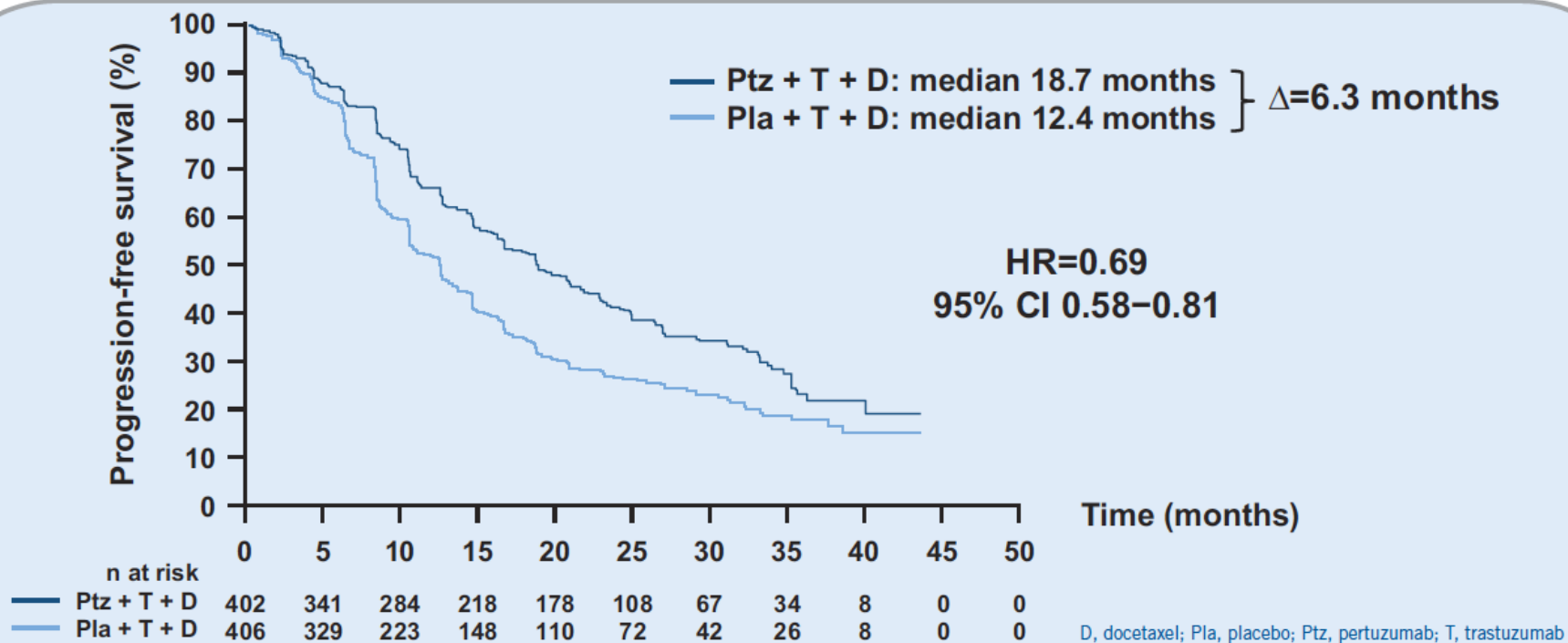


Figure 4: Updated Kaplan-Meier curves of investigator-assessed PFS

# Estudo CLEOPATRA

n (%)	Placebo + trastuzumab + docetaxel (n=396)	Pertuzumab + trastuzumab + docetaxel (n=408)
Neutropenia	182 (46.0)	200 (49.0)
Febrile neutropenia	30 (7.6)	56 (13.7)
Leukopenia	59 (14.9)	50 (12.3)
Diarrhea	20 (5.1)	37 (9.1)

Mucosal inflammation (grade  $\geq 3$ ) was reported in 4 (1.0%) patients in the placebo arm and in 6 (1.5%) patients in the pertuzumab arm.

**Table 4: Grade  $\geq 3$  adverse events (incidence  $\geq 5\%$ )**

# Blocking HER2/HER3 New Standard

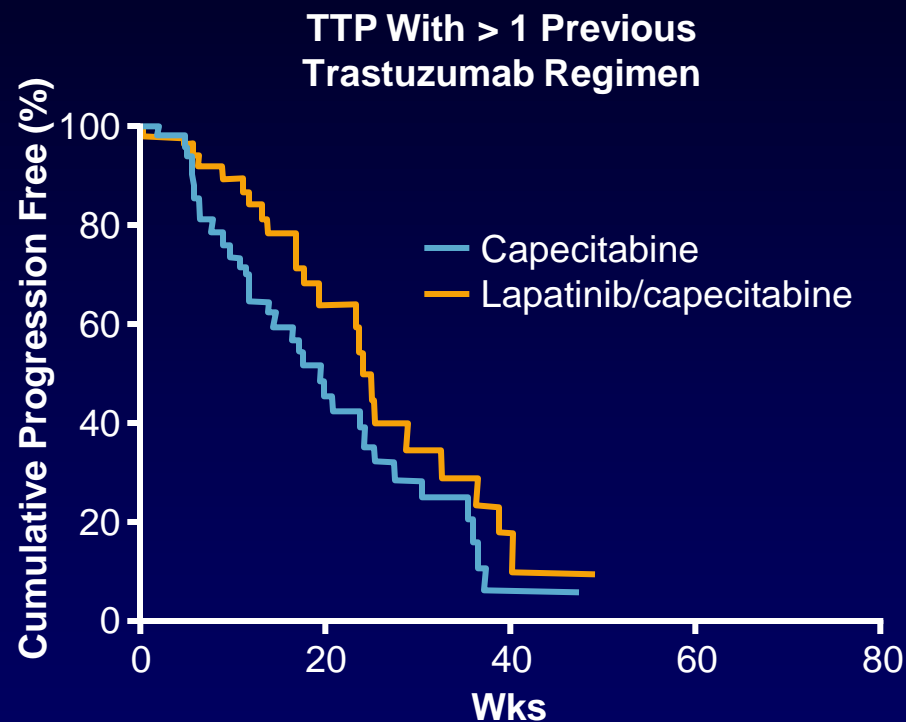
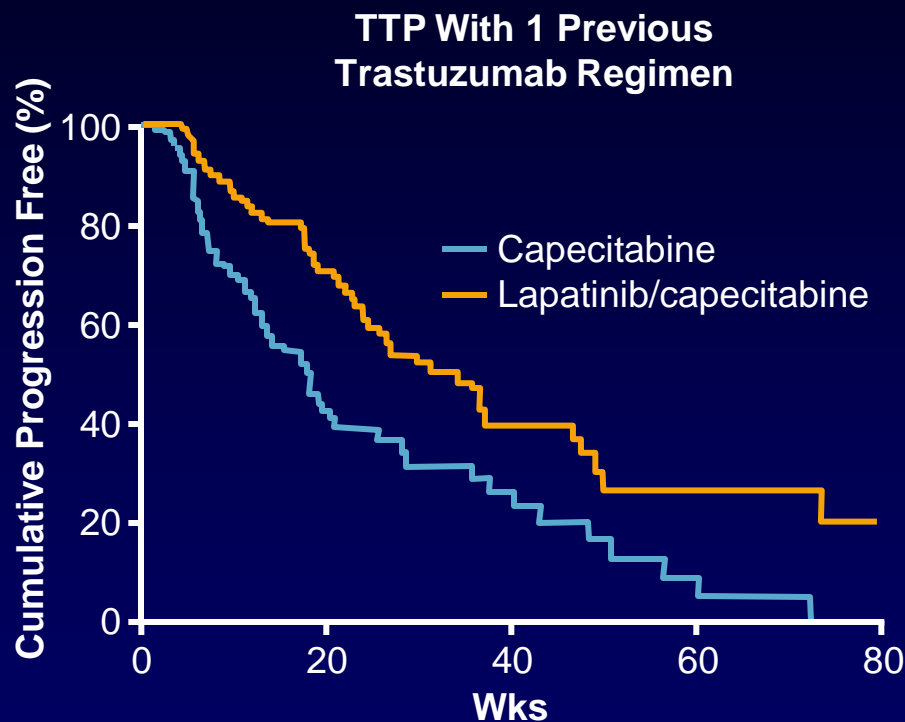
## CLEOPATRA

### Grade 3 or higher events‡

Neutropenia	182 (45.8)	199 (48.9)
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Left ventricular systolic dysfunction	11 (2.8)	5 (1.2)
Dyspnea	8 (2.0)	4 (1.0)

# Mantenha a via do HER2 bloqueada

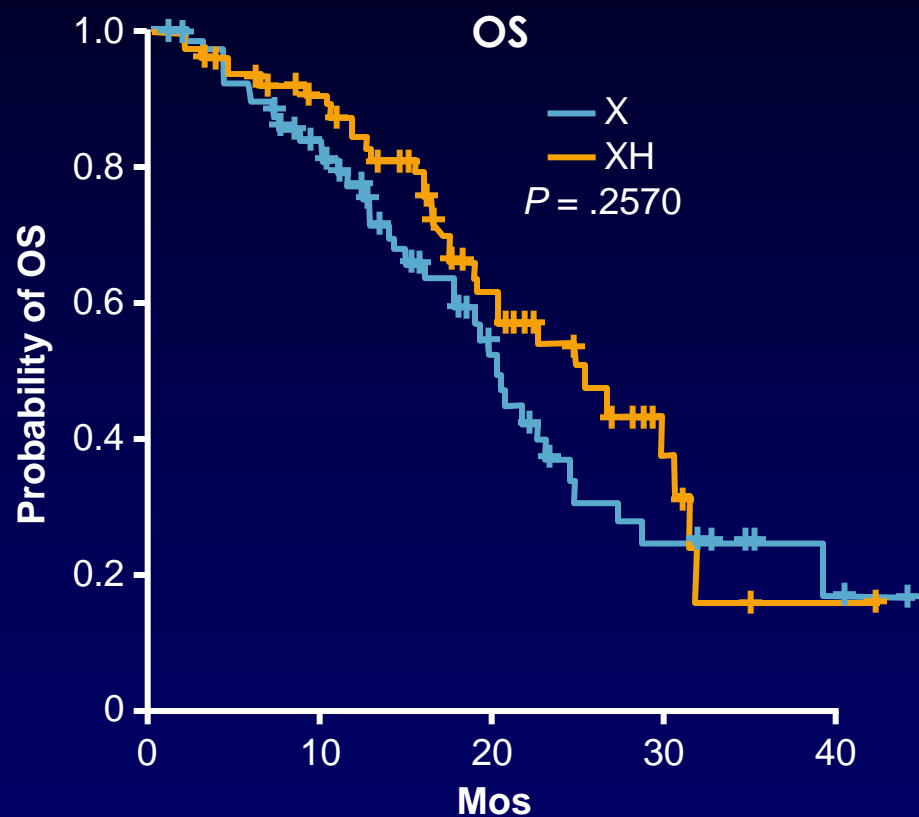
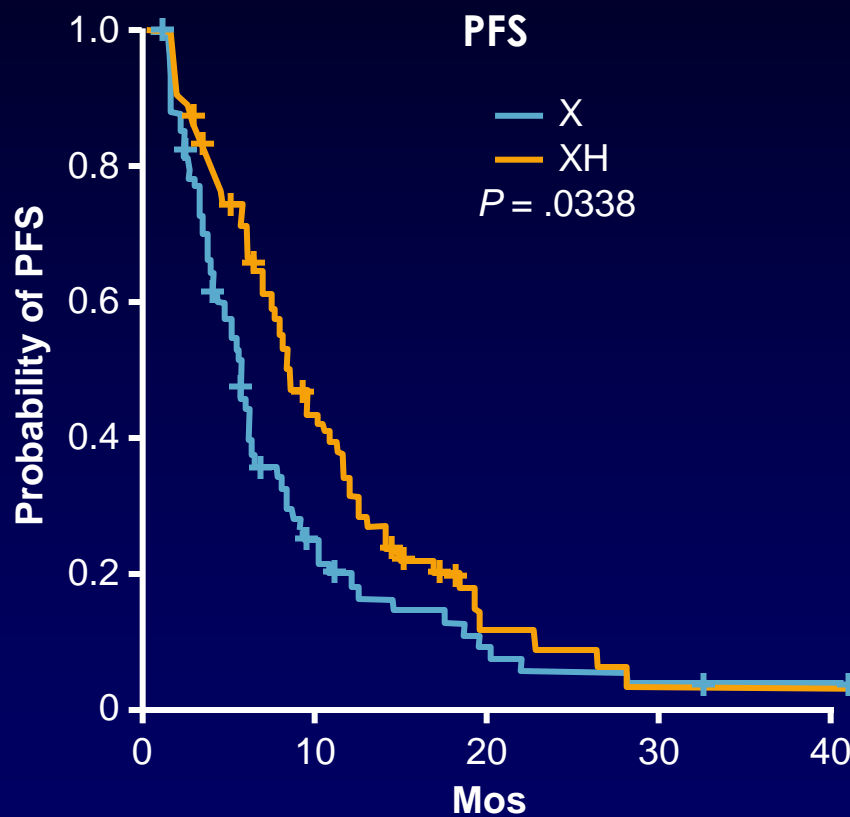
## Lapatinib/Capecitabine: TTP



Patients with HER2-positive progressive MBC or stage IIIB/IIIC LABC with T4 lesion PD after treatment with regimens that included, but were not limited to, a taxane an anthracycline and trastuzumab

# Mantenha a via do HER2 bloqueada

## Xeloda/Trastuzumab: TTP



Pts at Risk, n

X	74	40	15	8	5	3	2	1	1
XH	77	55	29	12	4	3	1	1	1

Pts at Risk, n

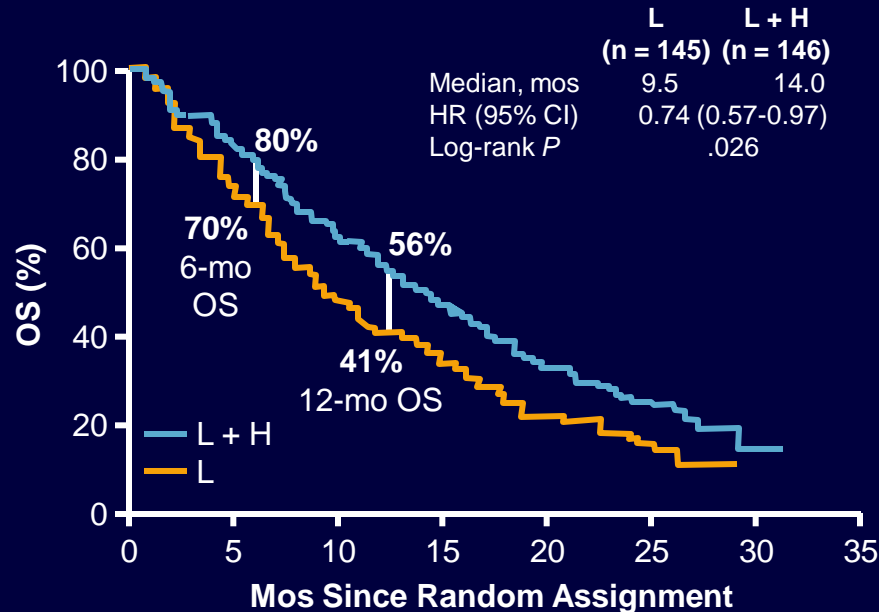
X	74	66	50	33	21	10	3	3	2
XH	77	68	59	47	27	15	6	1	1

# Mantenha a via do HER2 bloqueada

## EGF104900: OS With Lapatinib ± Trastuzumab

OS

(ITT population)

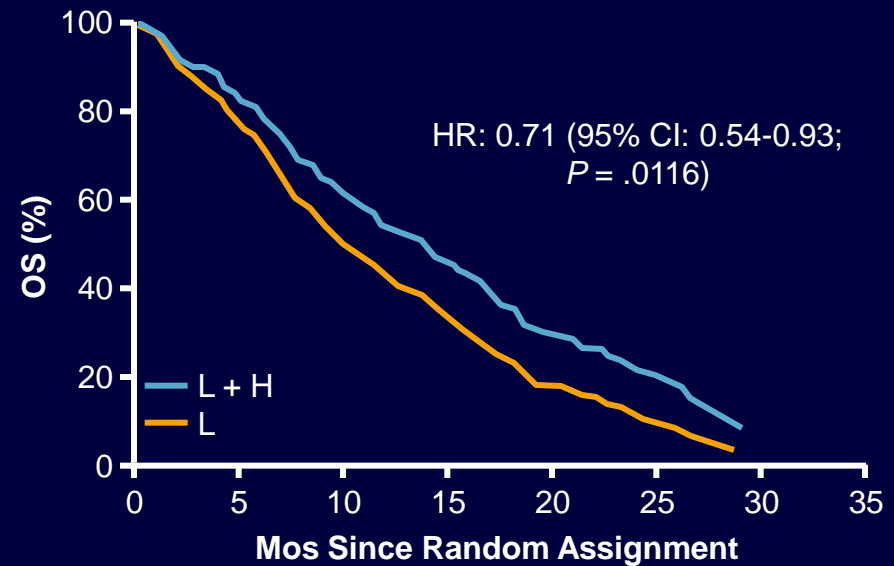


Pts at Risk, n

L + H	146	120	87	63	42	25	1
L	145	100	64	46	28	13	

OS

(Adjusted for ECOG PS, disease site, number of metastatic sites, time from diagnosis to randomization)



Pts at Risk, n

L + H	146	120	87	63	42	25	1
L	145	100	64	46	28	13	

# TD M1

Target expression: HER2

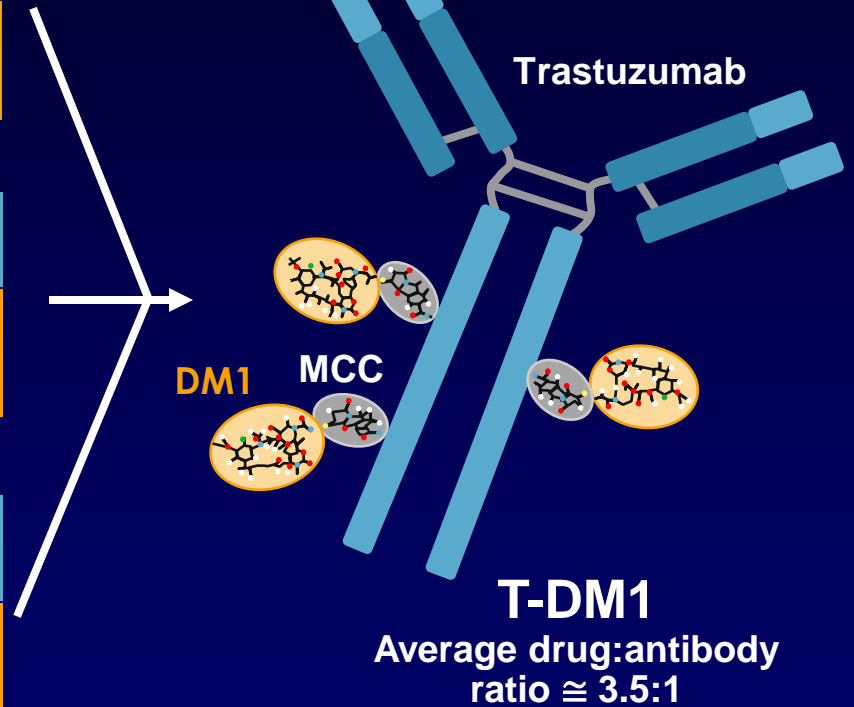
Monoclonal antibody: trastuzumab

Cytotoxic agent: emtansine (DM1)

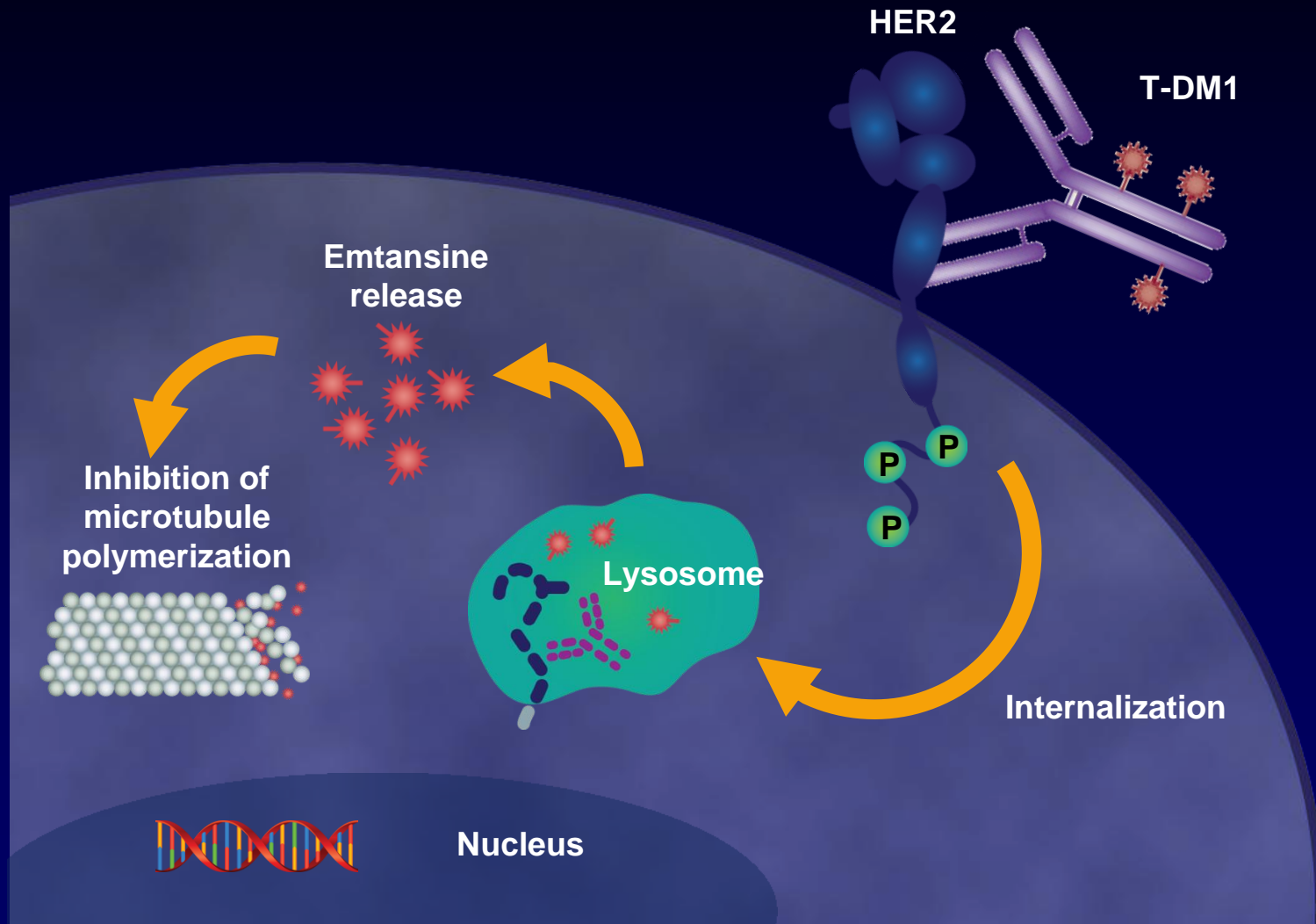
Highly potent cytotoxic agent

Linker: SMCC

Systemically stable



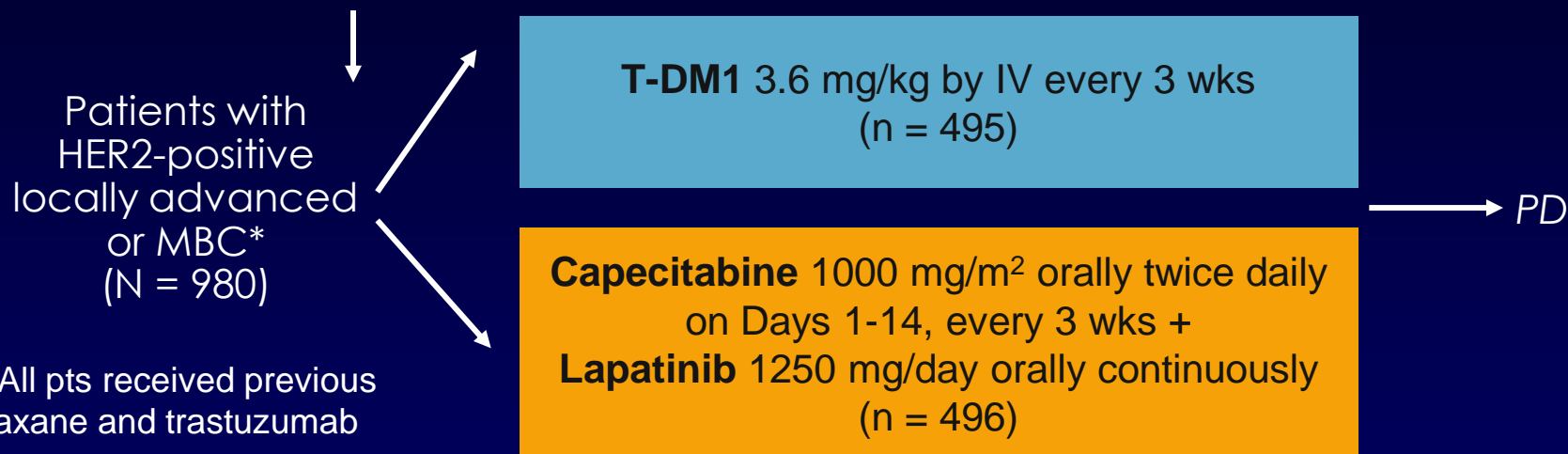
# TD M1



Adapted from LoRusso PM, et al. Clin Cancer Res. 2011;17:6437-6447.

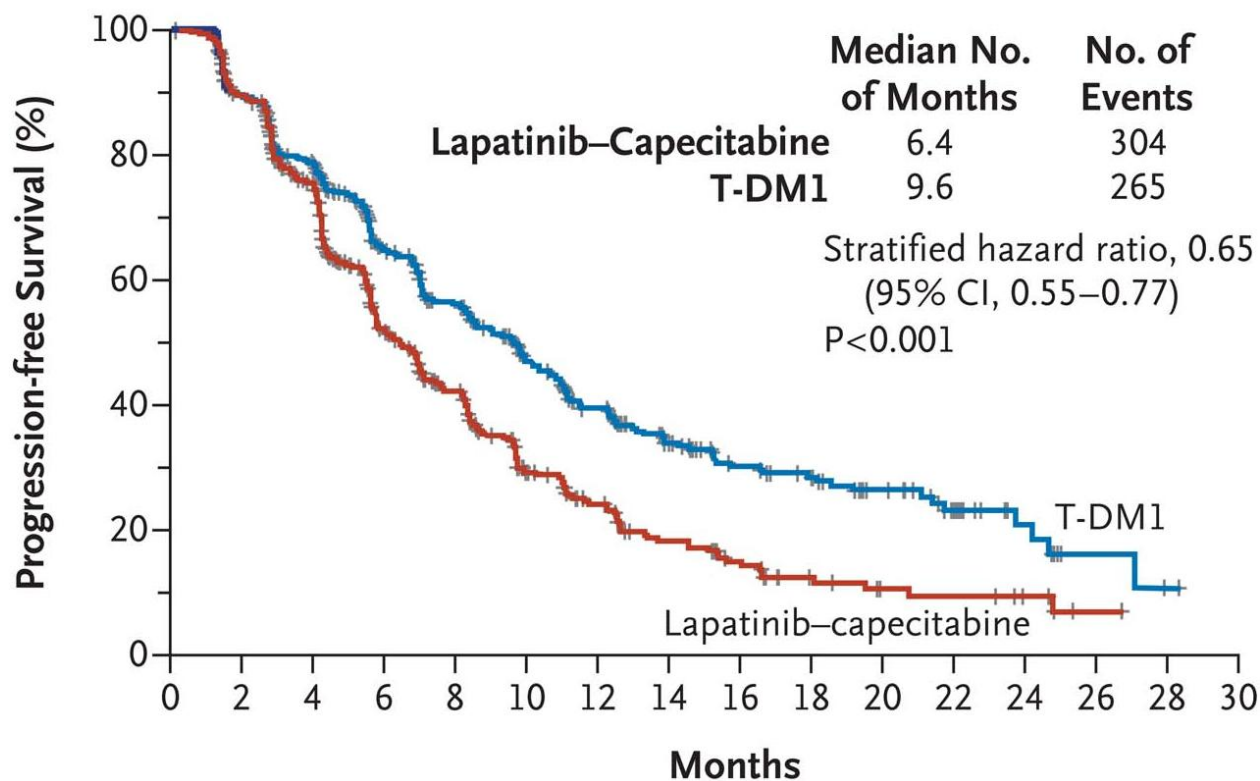
# Estudo EMILIA

*Stratified by world region, number of previous chemotherapy regimens for MBC or unresectable locally advanced breast cancer, presence of visceral disease*



- Primary endpoint: PFS by IRF, OS, safety
- Secondary endpoints: QoL (FACT B), DOR, PFS by investigator assessment

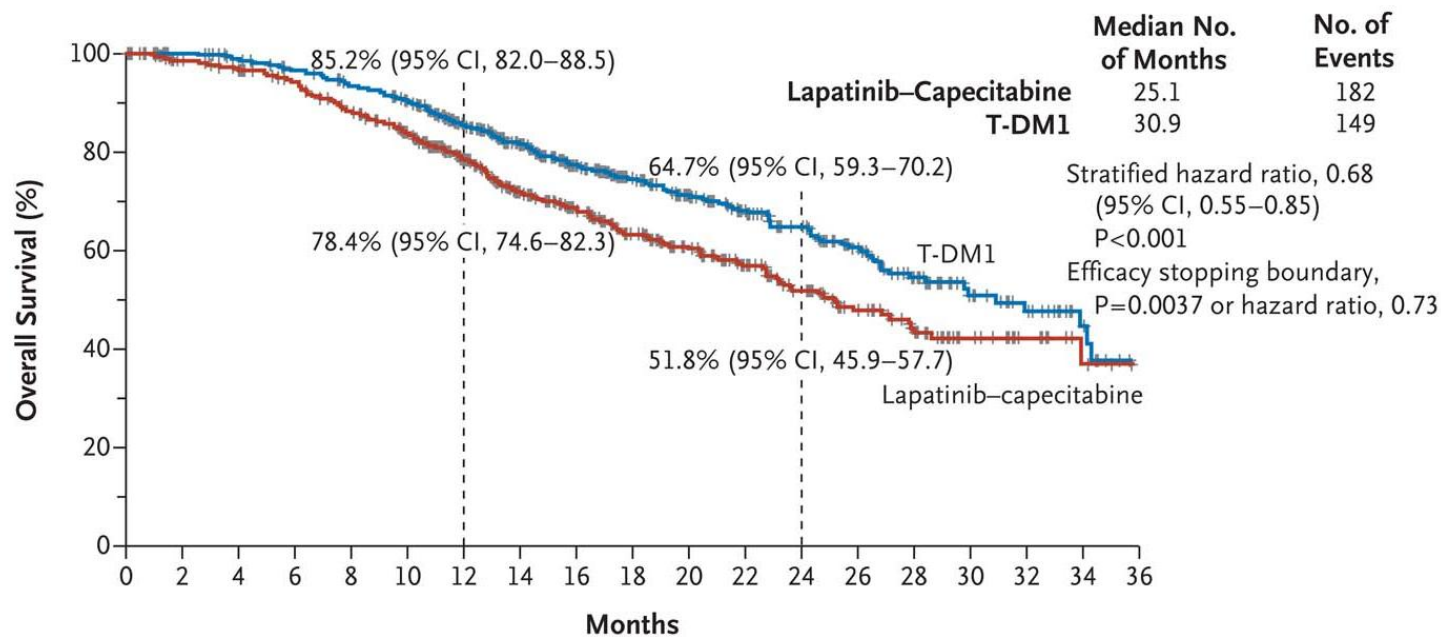
# Estudo EMILIA



## No. at Risk

Lapatinib–capecitabine	496	404	310	176	129	73	53	35	25	14	9	8	5	1	0	0
T-DM1	495	419	341	236	183	130	101	72	54	44	30	18	9	3	1	0

# Estudo EMILIA



## No. at Risk

Lapatinib–capecitabine	496	471	453	435	403	368	297	240	204	159	133	110	86	63	45	27	17	7	4
T-DM1	495	485	474	457	439	418	349	293	242	197	164	136	111	86	62	38	28	13	5