Current Status of the Treatment of Her-2/neu Positive Breast Cancer
(C. Zielinski)

Javier Cortes Md PhD
Vall d´Hebron Institute of Oncology (VHIO),
Ramon y Cajal University Hospital, Madrid, Spain

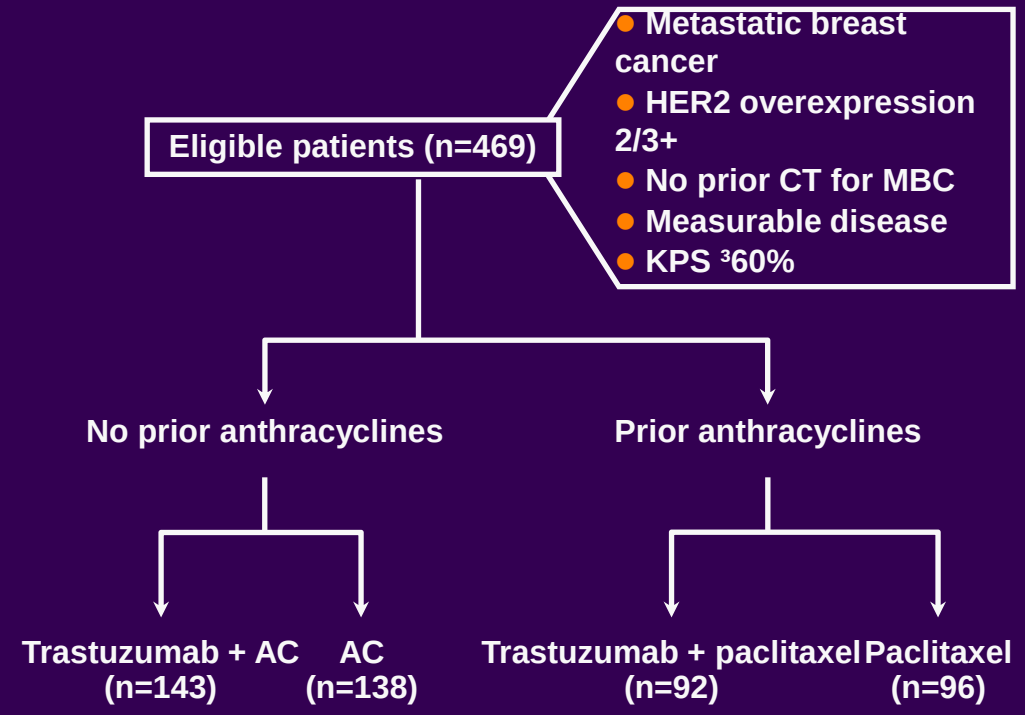
Disclosures

- Advisor
  - Roche, Novartis, Celgene
- Honoraria
  - Roche, Novartis, Celgene, Eisai

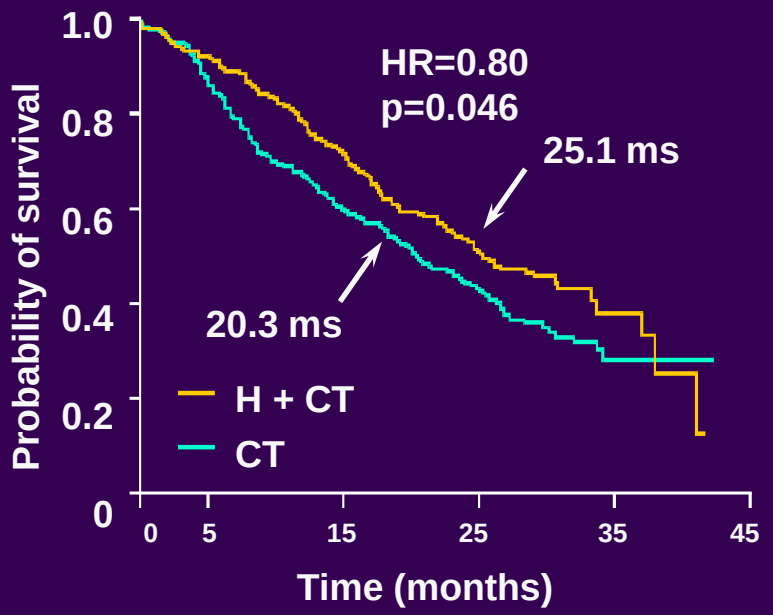
- Partner
  - MedSIR ARO

Trastuzumab with chemotherapy in HER2 positive MBC

Study Design



Overall survival



Slamon DJ et al. NEJM 2001

Efficacy: Capecitabine ± Lapatinib

End point	Lapatinib plus capecitabine (N = 163)	Capecitabine alone (N = 161)	Hazard ratio (95% CI)	P value
Median time to progression - mo	8.4	4.4	0.49 (0.34 - 0.71)	<0.001*
Median progression-free survival - mo	8.4	4.1	0.47 (0.33 - 0.67)	<0.001 †
Overall response % (95% CI)	22 (16 - 29)	14 (9 - 21)		0.09 ‡
Clinical benefit - no (%)	44 (27)	29 (18)		
Death - no (%)	36 (22)	35 (22)		

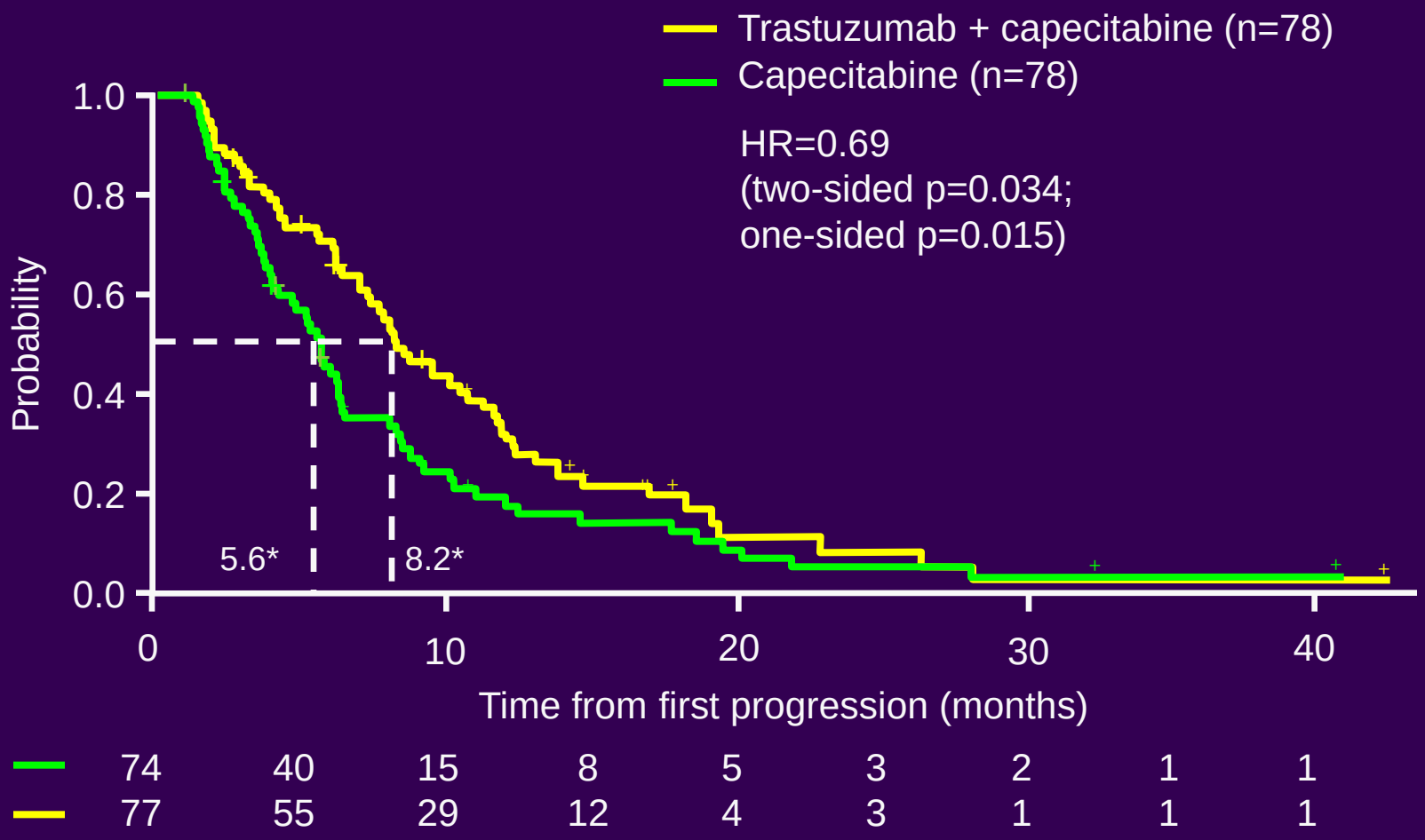
*End points are based on evaluation by the independent review committee under blinded conditions

†The p value was calculated with the log-rank test

‡The p value was calculated with Fisher's exact test

Geyer CE, et al. N Engl J Med 2006

Continuation of trastuzumab prolongs median TTP in the GBG-26 study

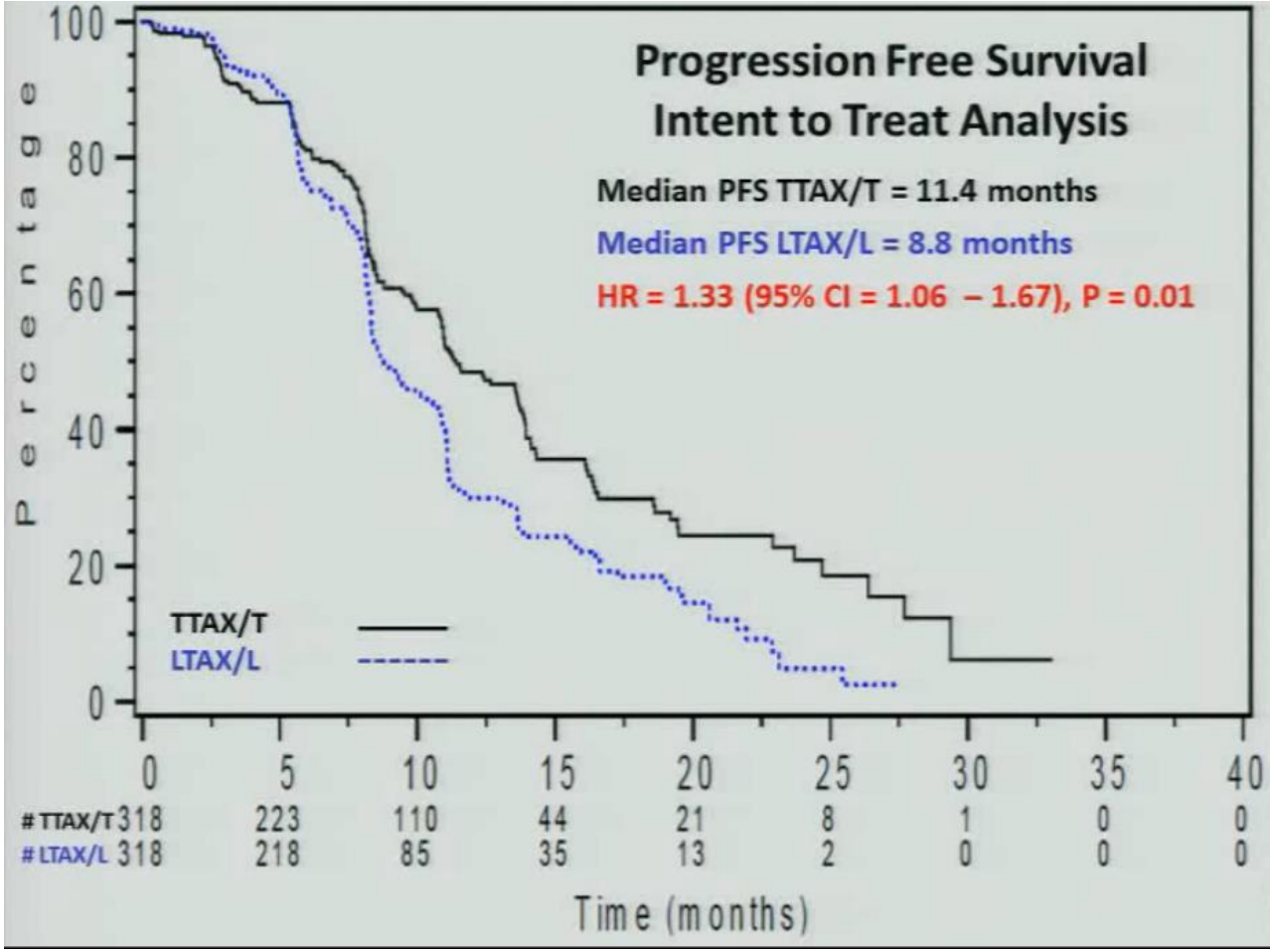


*Median TTP in months

von Minckwitz, et al. JCO 2009

Lapatinib or trastuzumab-based therapy as first-line?

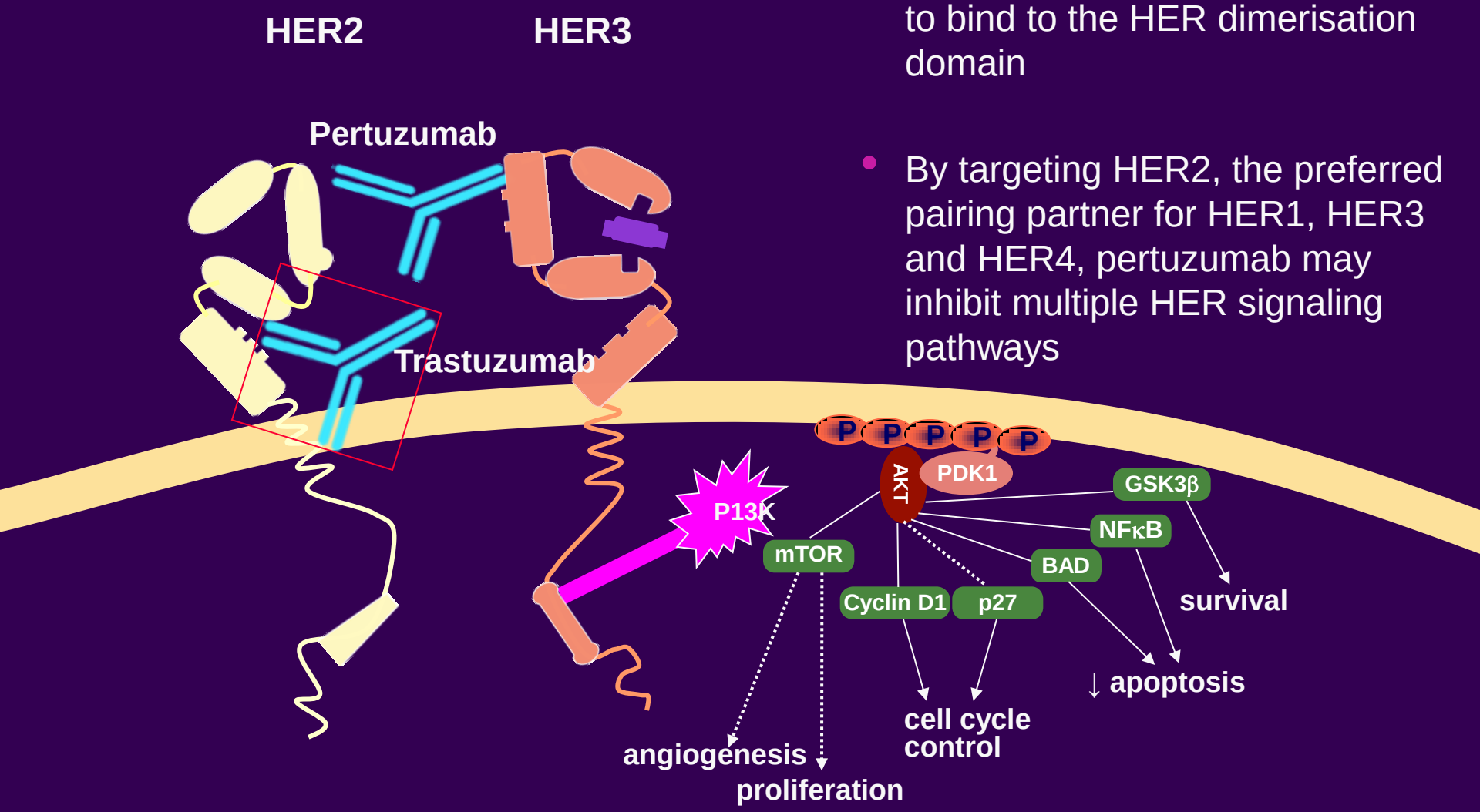
MA 31 Trial



Gelmon K, et al. JCO 2015

Pertuzumab: A HER dimerisation inhibitor

- A mechanism of action designed to bind to the HER dimerisation domain
- By targeting HER2, the preferred pairing partner for HER1, HER3 and HER4, pertuzumab may inhibit multiple HER signaling pathways



HER2 is activated in two different ways

- **Overexpression:**
  - Arising from gene amplification which results in constitutive activation of HER2 (ligand independent)
  - Antagonized by trastuzumab
- **Co-receptor:**
  - For other HER family members especially HER3 (ligand dependent)
  - Antagonized by pertuzumab

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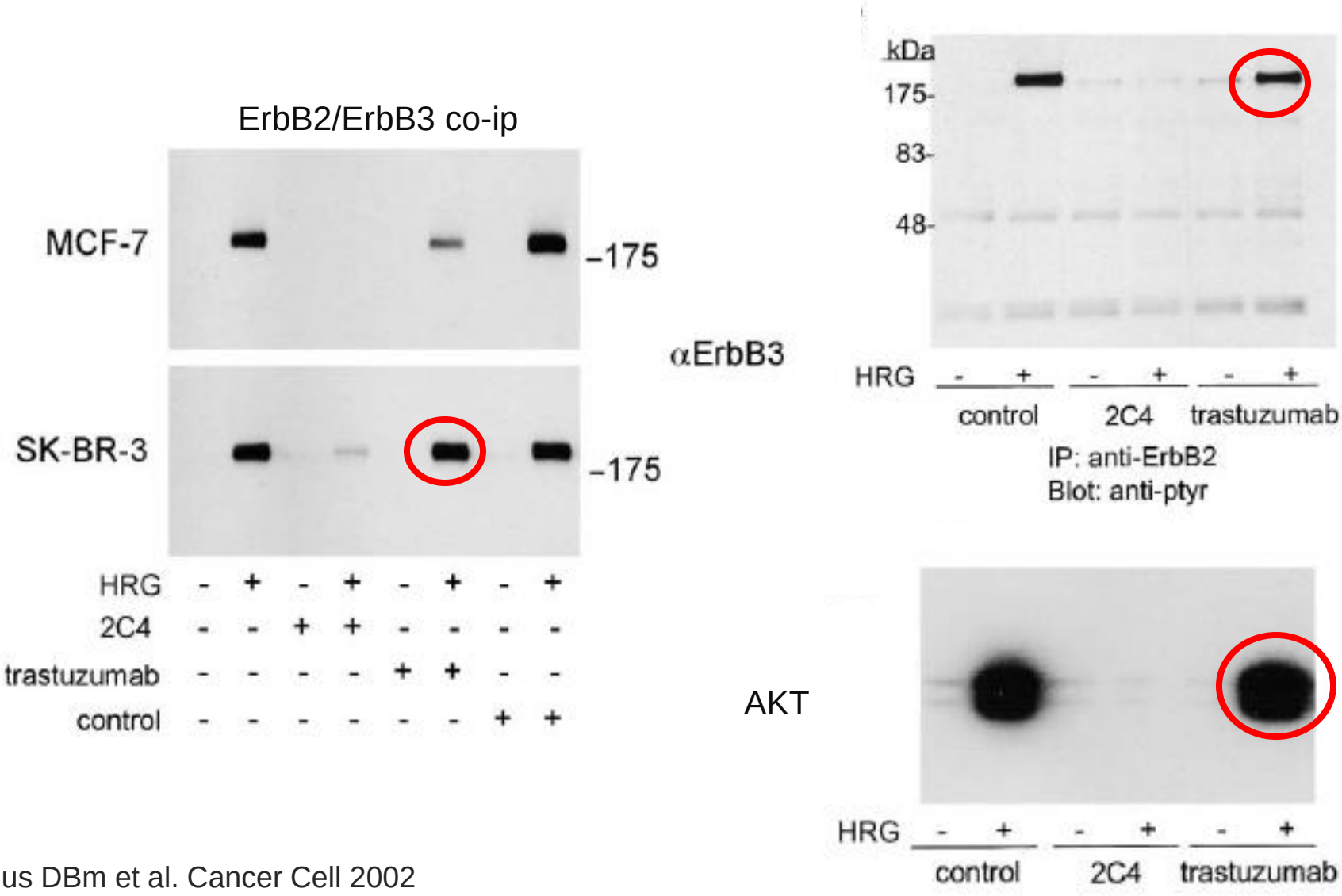
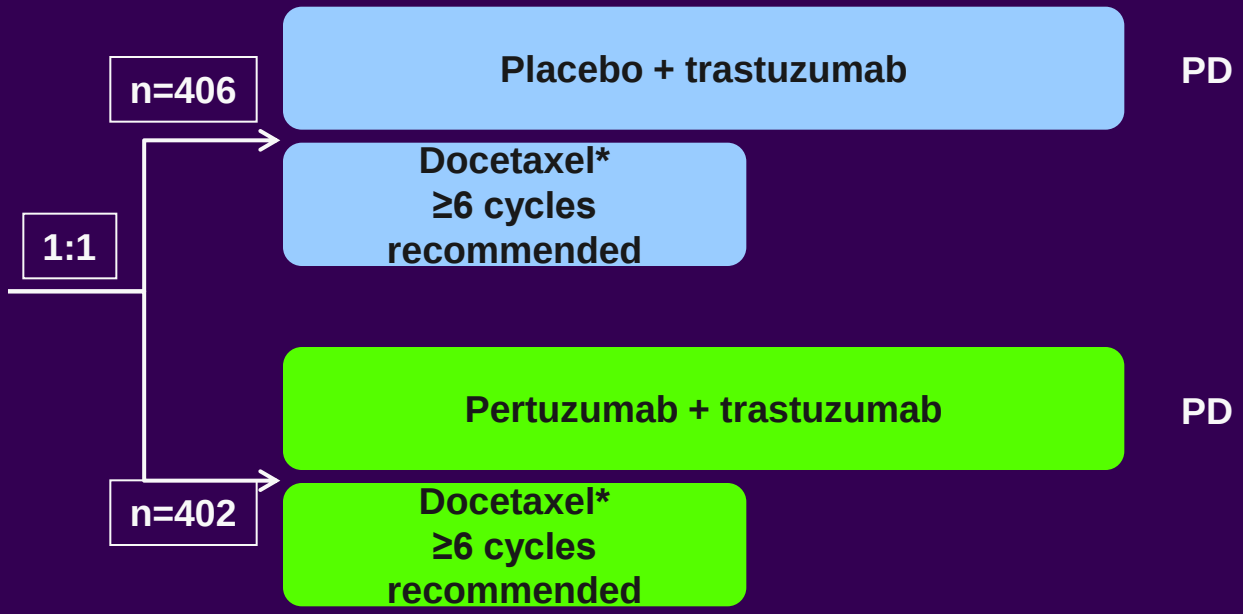
In contrast to trastuzumab, pertuzumab inhibits HRG-mediated HER2 signaling



Agus DBm et al. Cancer Cell 2002

CLEOPATRA Study



- Randomization was stratified by geographic region and prior treatment status (neo/adjuvant chemotherapy received or not)
- Study dosing q3w:
  - Pertuzumab/Placebo: 840 mg loading dose, 420 mg maintenance
  - Trastuzumab: 8 mg/kg loading dose, 6 mg/kg maintenance
  - Docetaxel: 75 mg/m^2, escalating to 100 mg/m^2 if tolerated

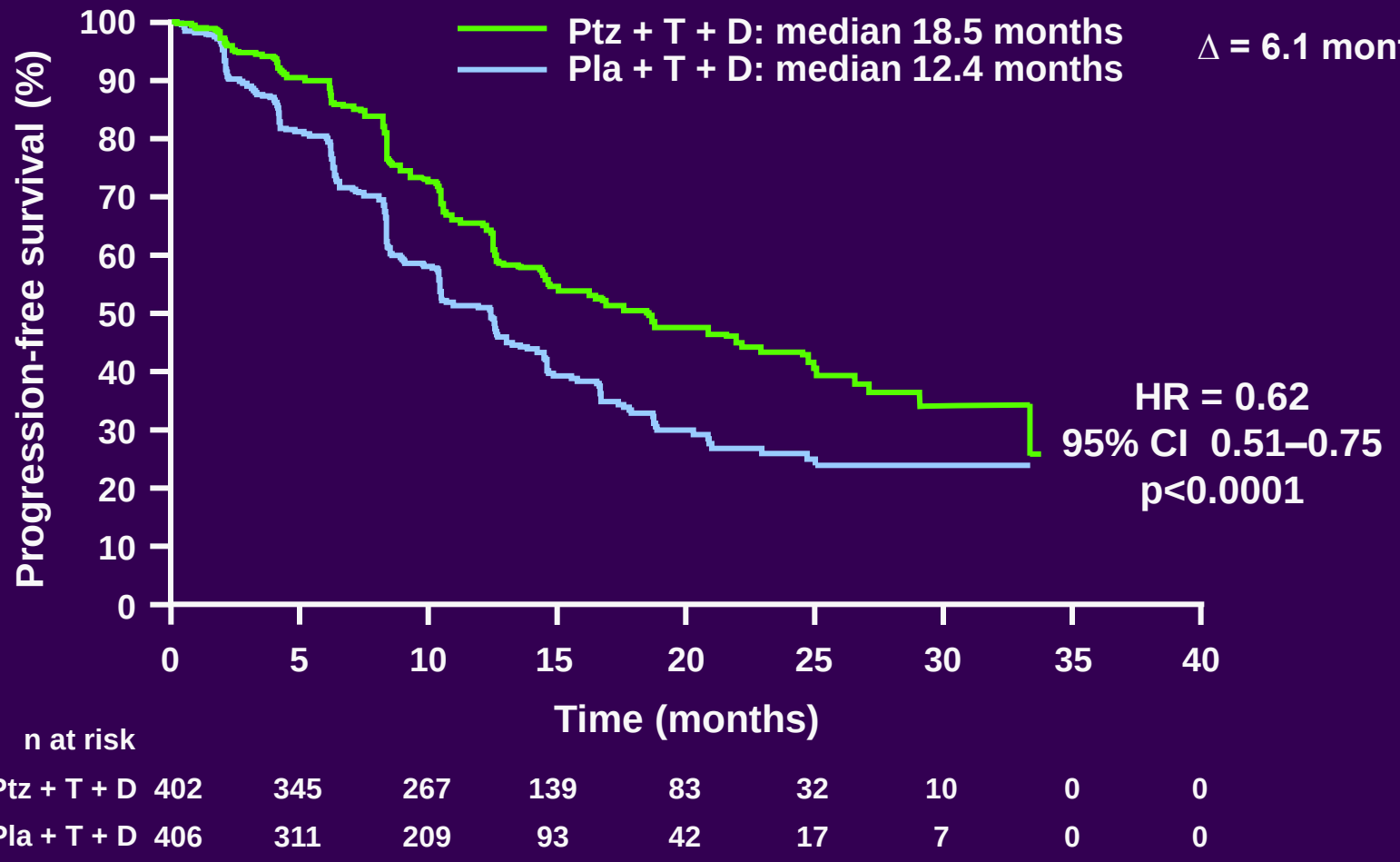
*<6 cycles allowed for unacceptable toxicity or PD; >6 cycles allowed at investigator discretion

MBC, metastatic breast cancer; PD, progressive disease

Baselga J, et al. NEJM 2012

Independently assessed PFS

Median follow-up: 19.3 months, n = 433 PFS events



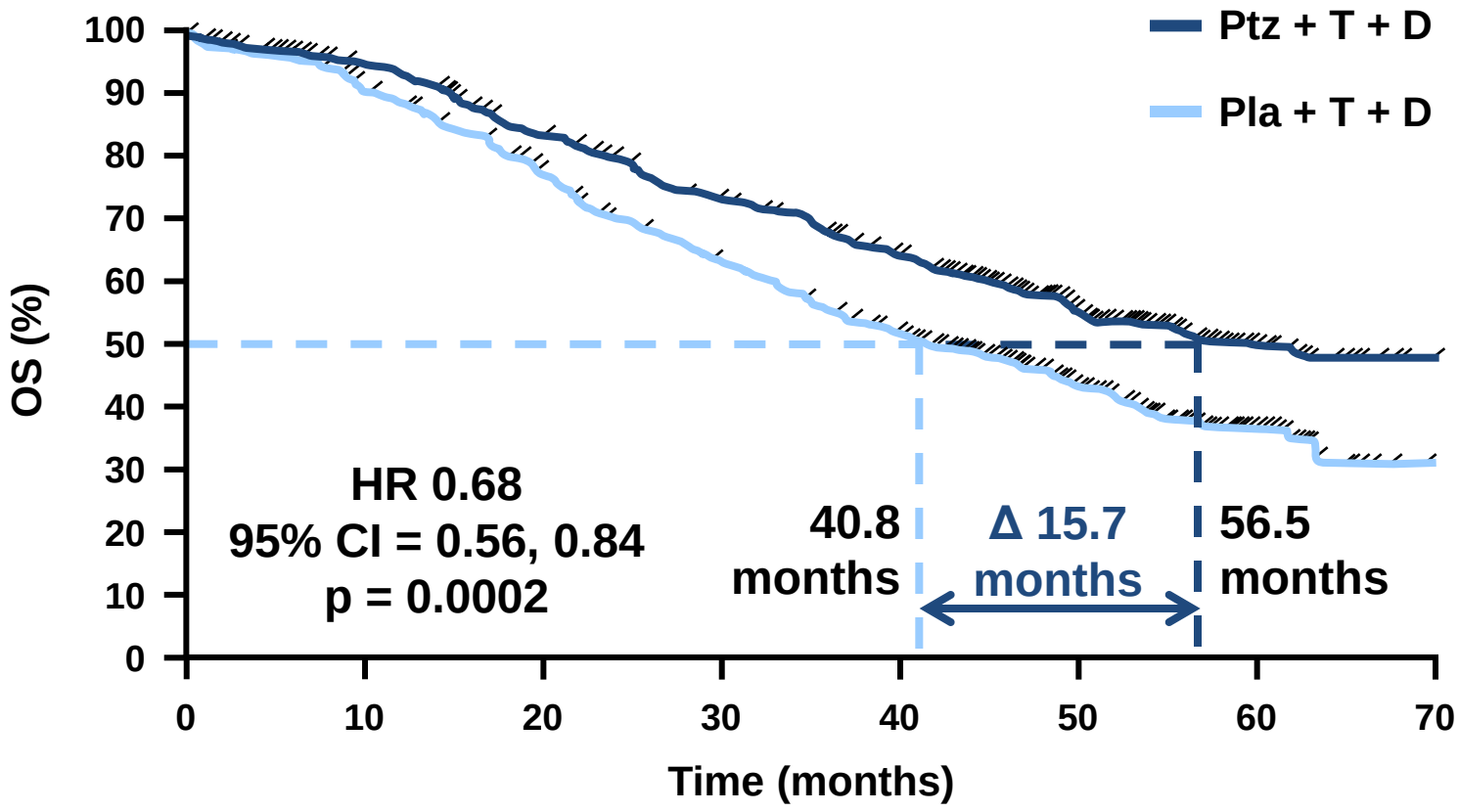
Stratified by prior treatment status and region

D, docetaxel; PFS, progression-free survival; Pla, placebo; Ptz, pertuzumab; T, trastuzumab

Baselga J, et al. NEJM 2012

Final OS Analysis

Median follow-up 50 months (range 0–70 months)



n at risk								
Ptz + T + D	402	371	318	268	226	104	28	1
Pla + T + D	406	350	289	230	179	91	23	0

ITT population. Stratified by geographic region and neo/adjuvant chemotherapy.
CI, confidence interval; Pla, placebo; Ptz, pertuzumab.

Swain S, et al. NEJM 2015

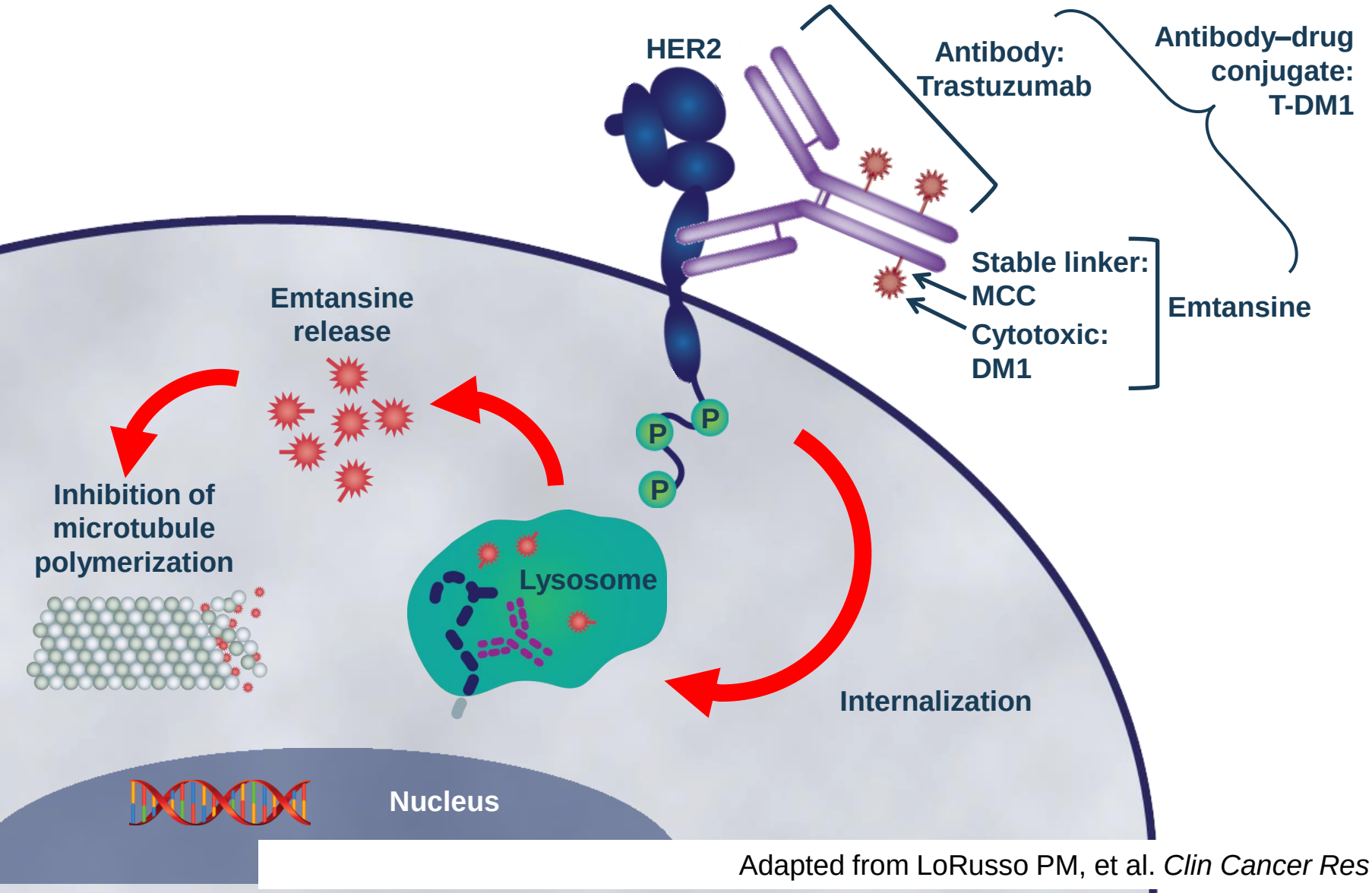
Cardiac Safety

Safety population	Placebo + T + D (n = 396), %	Pertuzumab + T + D (n = 408), %
sLVD	1.8	1.5
LVEF decline to < 50% and by ≥ 10% points from baseline*	7.4	6.1

- One new sLVD event in the pertuzumab group after 40 months (resolved)
- LVEF declines reversed in 88% of pertuzumab patients

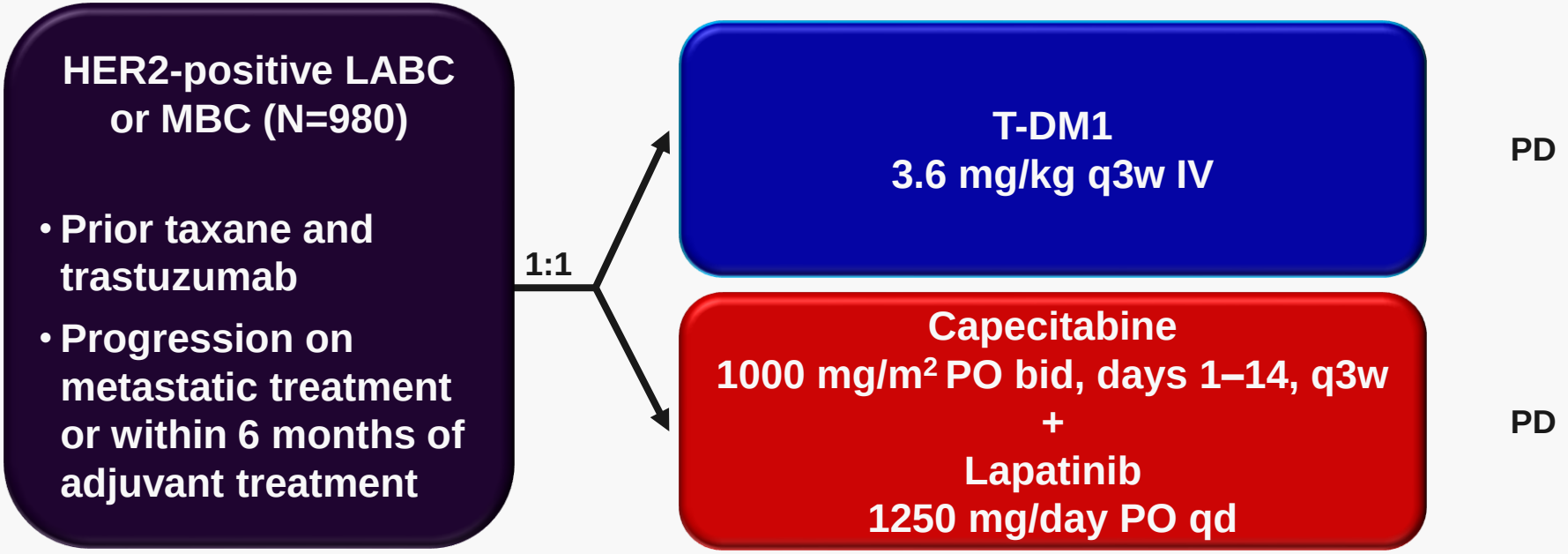
Swain S, et al. NEJM 2015

Trastuzumab Emtansine (T-DM1): Mechanism of Action



Adapted from LoRusso PM, et al. *Clin Cancer Res* 2011

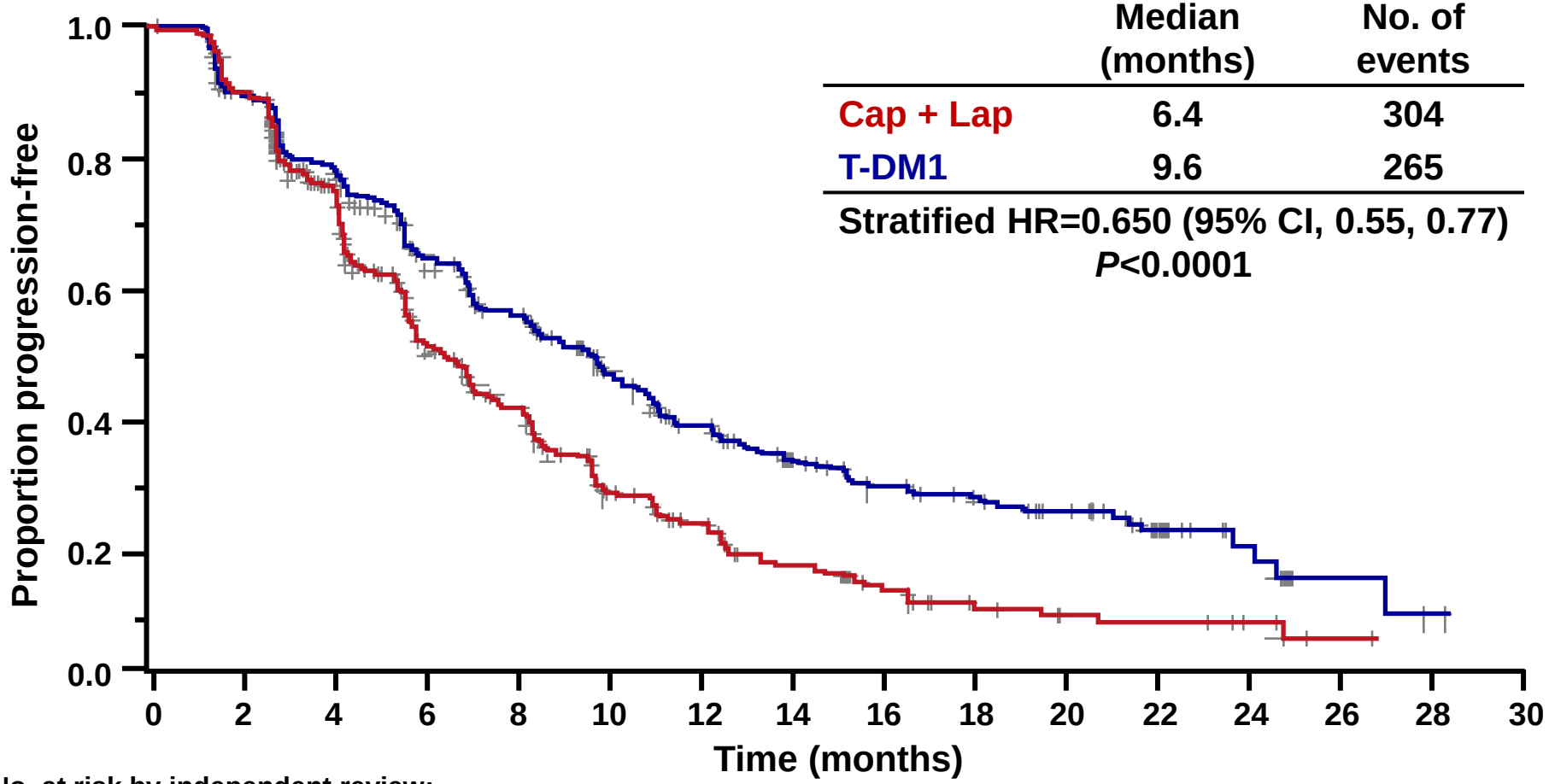
EMILIA Trial



- Primary endpoints: PFS by independent review, OS, and safety
- Key secondary endpoints: PFS by investigator, ORR, DOR
- Statistical considerations: Hierarchical statistical analysis was performed in pre-specified sequential order: PFS by independent review → OS → secondary endpoints

Verma, et al. NEJM 2012

Progression-Free Survival by Independent Review



	Median (months)	No. of events
Cap + Lap	6.4	304
T-DM1	9.6	265

Stratified HR=0.650 (95% CI, 0.55, 0.77)
P<0.0001

No. at risk by independent review:

Cap + Lap	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

Unstratified HR=0.66 (*P*<0.0001).

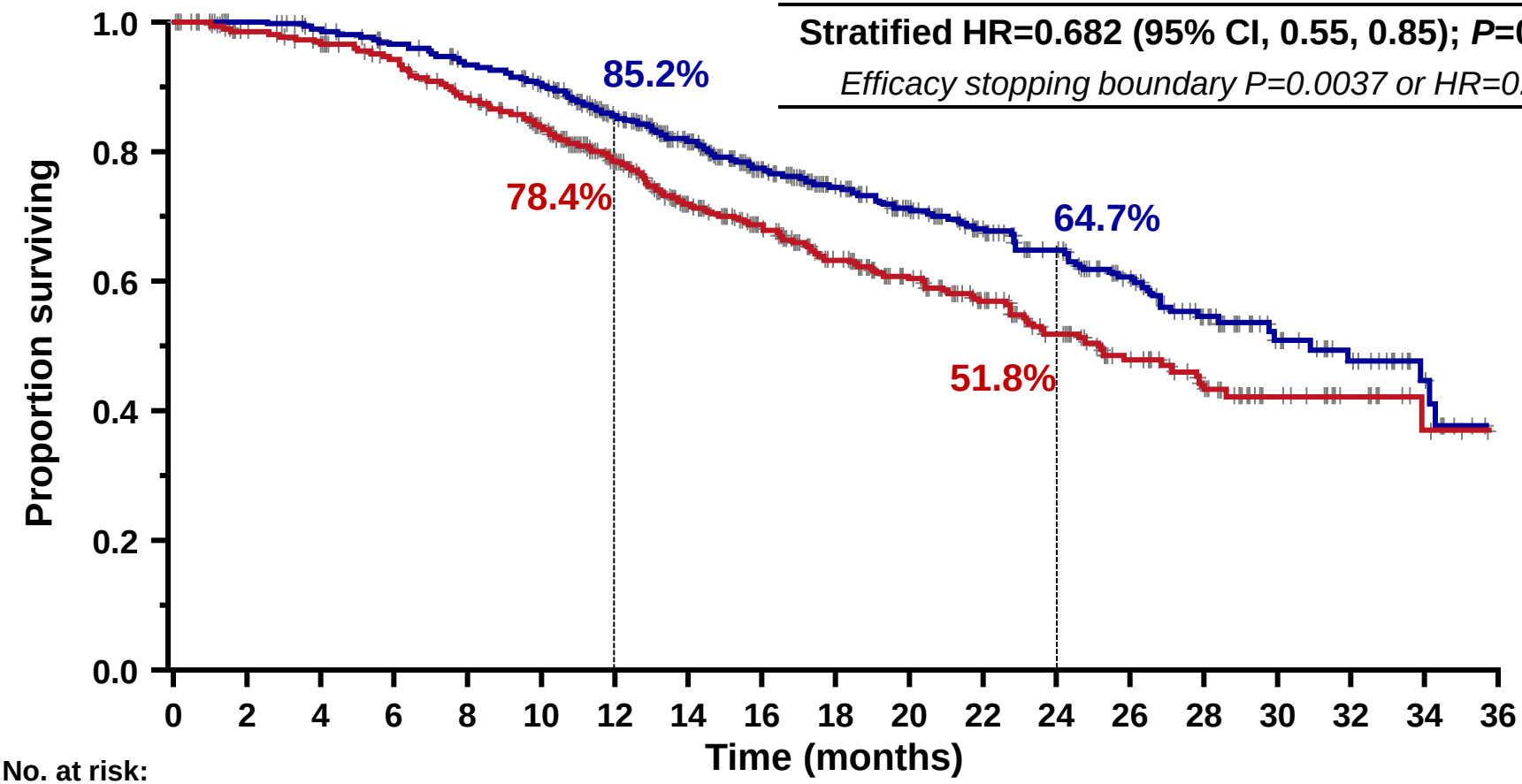
Verma, et al. NEJM 2012

Overall Survival: Confirmatory Analysis

	Median (months)	No. of events
Cap + Lap	25.1	182
T-DM1	30.9	149

Stratified HR=0.682 (95% CI, 0.55, 0.85); *P*=0.0006

Efficacy stopping boundary P=0.0037 or HR=0.727



No. at risk:

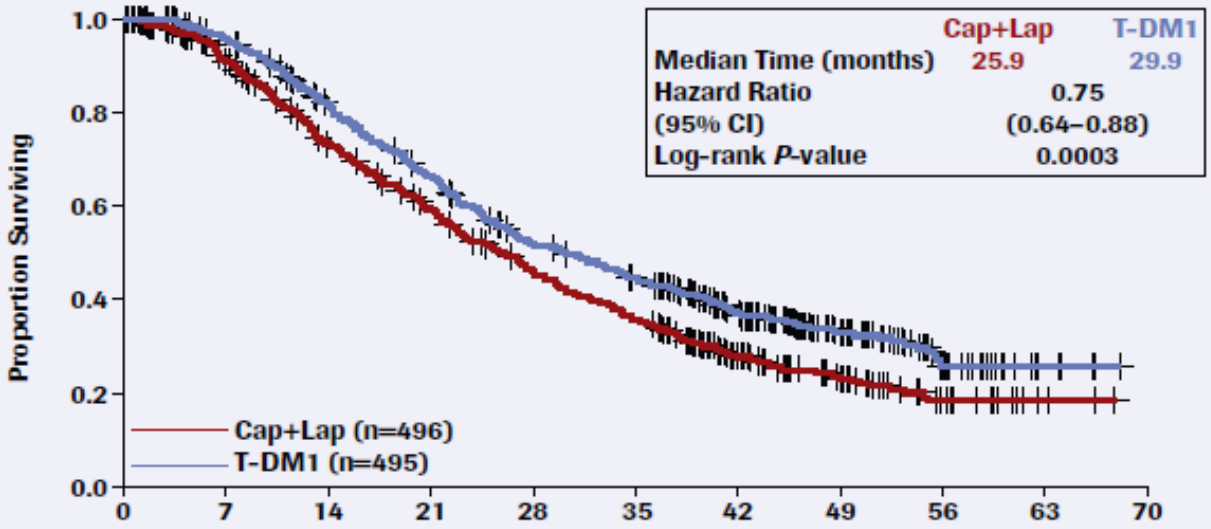
Cap + Lap	496	471	453	435	403	368	297	240	204	159	133	110	86	63	45	27	17	7	4
T-DM1	495	485	474	457	439	418	349	293	242	197	164	136	111	86	62	38	28	13	5

Data cut-off July 31, 2012; Unstratified HR=0.70 (*P*=0.0012).

Verma, et al. NEJM 2012

Updated / post hoc / Exploratory new data from the EMILIA Trial

Figure 3. Final overall survival in the intent-to-treat population

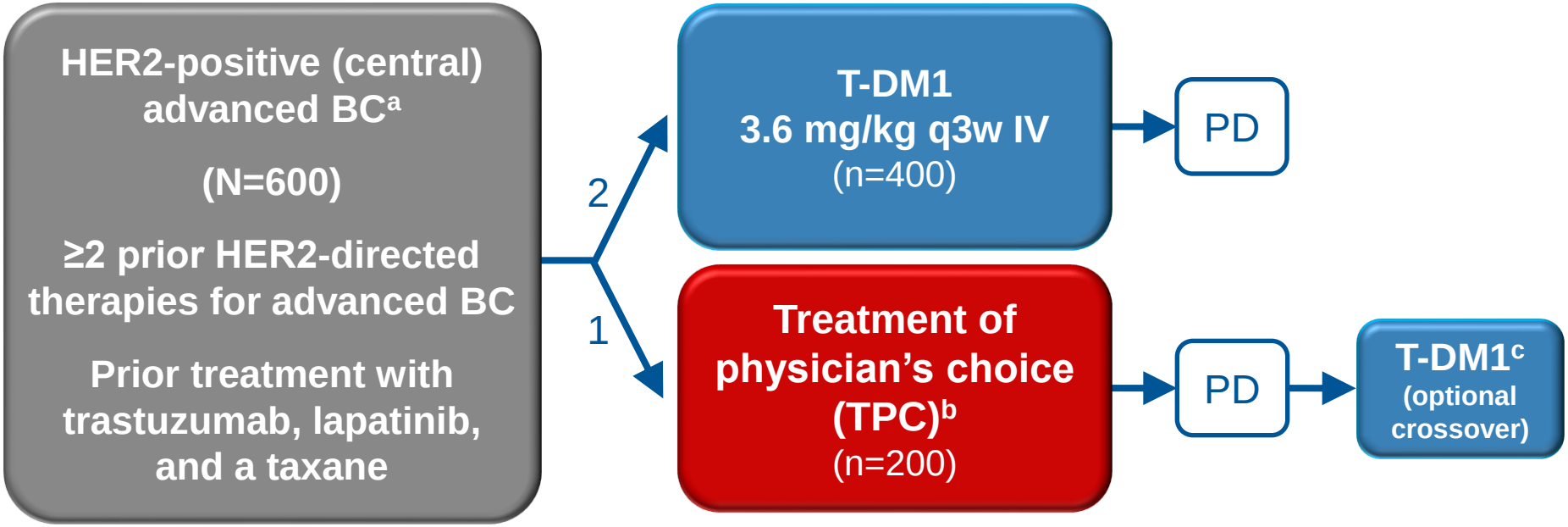


Number at Risk:											
Cap+Lap	496	418	326	258	195	153	82	48	19	3	0
T-DM1	495	451	374	302	231	194	127	68	23	5	0

Cap+Lap, capecitabine plus lapatinib; CI, confidence interval; T-DM1, trastuzumab emtansine.

Dieras V, et al. SABCS 2015

TH3RESA Study Schema



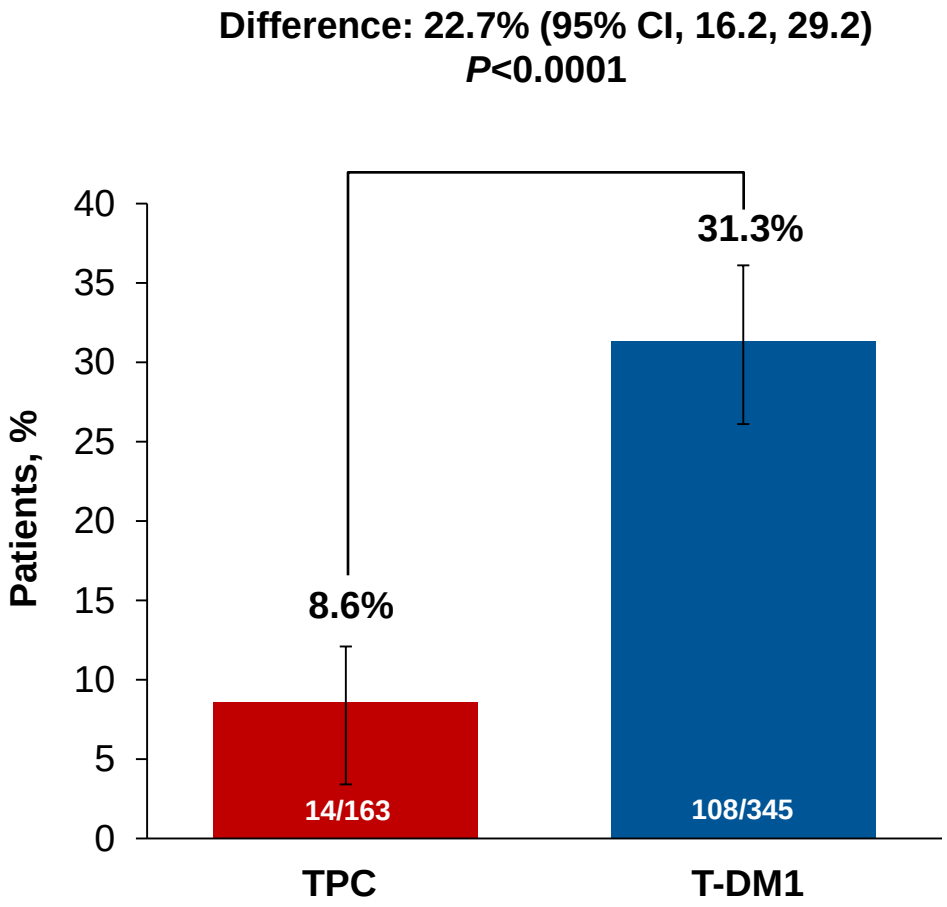
- **Stratification factors:** World region, number of prior regimens for advanced BC,[d] presence of visceral disease
- **Co-primary endpoints:** PFS by investigator and OS
- **Key secondary endpoints:** ORR by investigator and safety

[a] Advanced BC includes MBC and unresectable locally advanced/recurrent BC.
[b] TPC could have been single-agent chemotherapy, hormonal therapy, or HER2-directed therapy, or a combination of a HER2-directed therapy with a chemotherapy, hormonal therapy, or other HER2-directed therapy.
[c] First patient in: Sep 2011. Study amended Sep 2012 (following EMILIA 2nd interim OS results) to allow patients in the TPC arm to receive T-DM1 after documented PD.
[d] Excluding single-agent hormonal therapy.

Krop I, et al. Lancet Oncol 2014

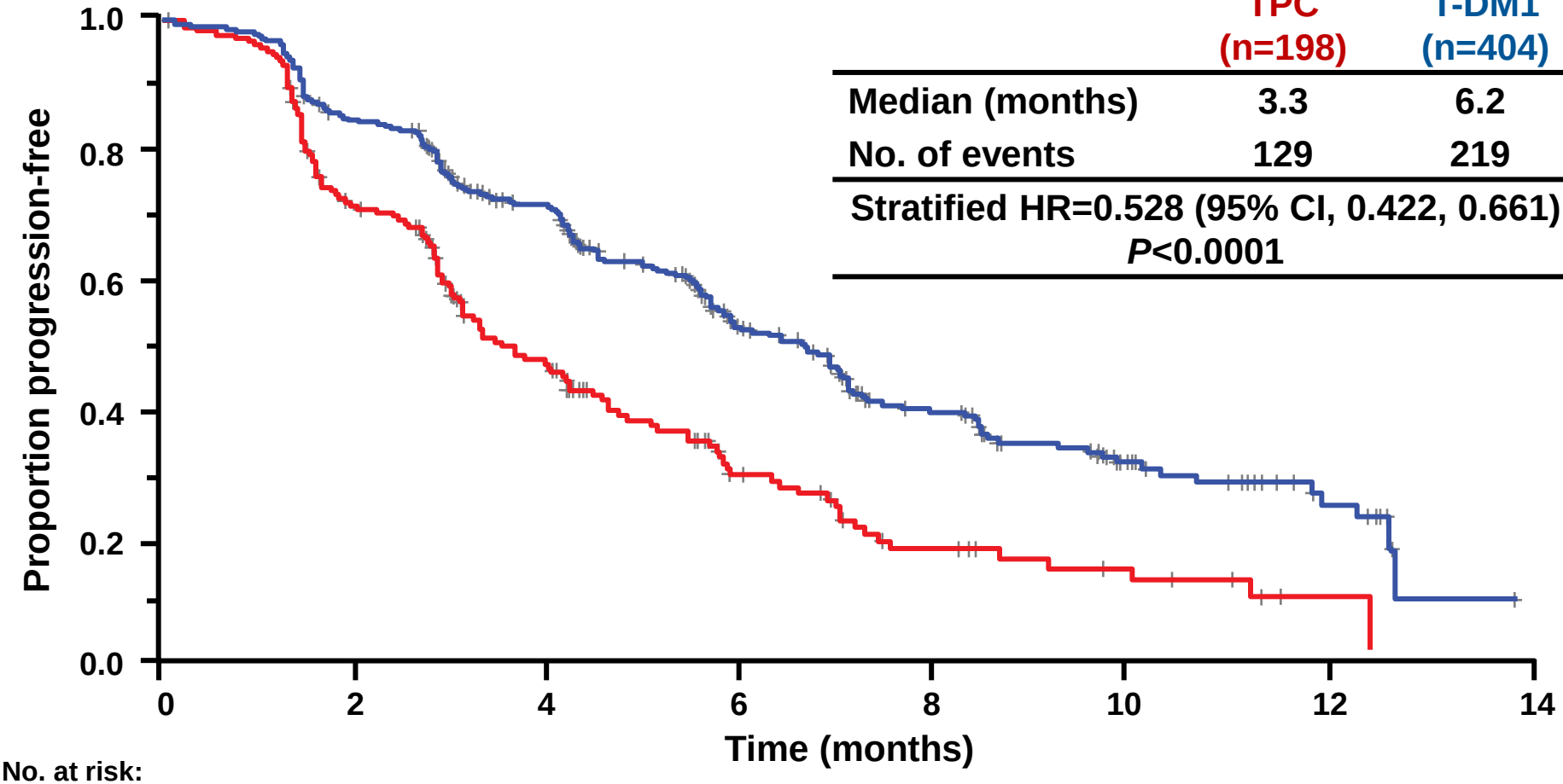
ORR in Patients With Measurable Disease

By Investigator Assessment



Krop I, et al. Lancet Oncol 2014

PFS by Investigator Assessment



	TPC (n=198)	T-DM1 (n=404)
Median (months)	3.3	6.2
No. of events	129	219

Stratified HR=0.528 (95% CI, 0.422, 0.661)
P<0.0001

No. at risk:								
TPC	198	120	62	28	13	6	1	0
T-DM1	404	334	241	114	66	27	12	0

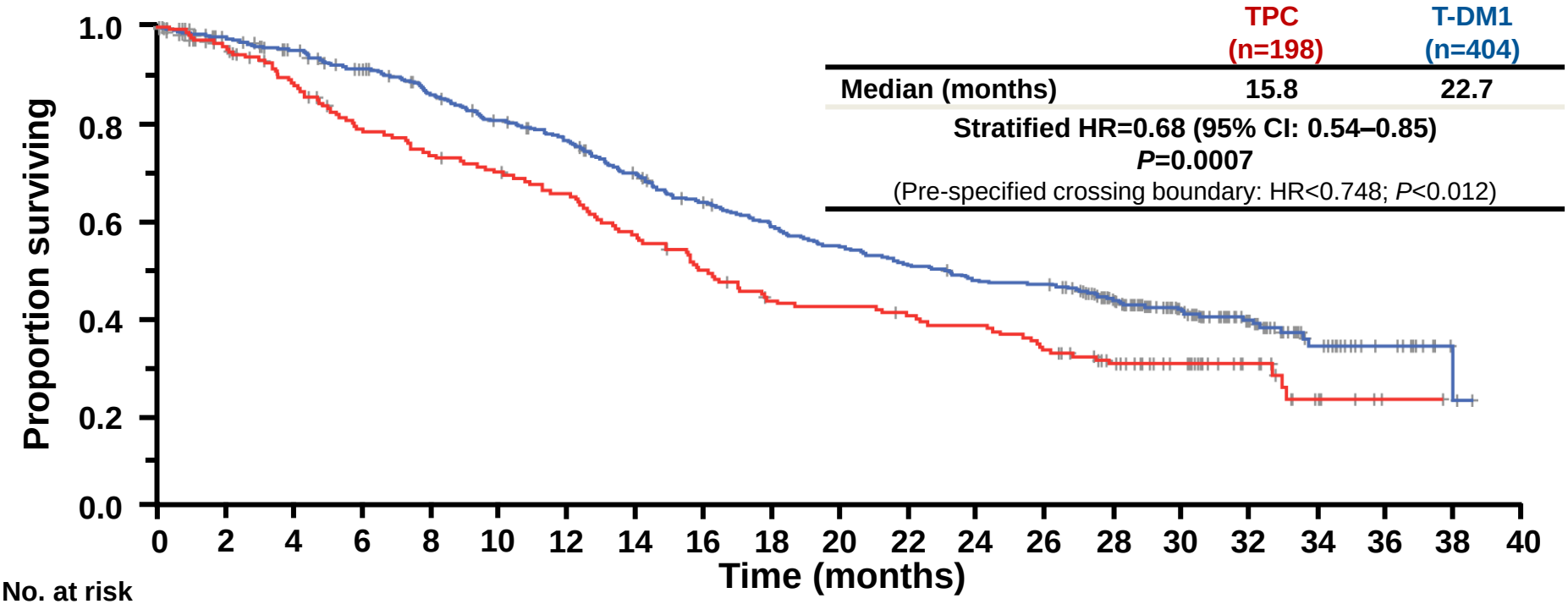
Median follow-up: TPC, 6.5 months; T-DM1, 7.2 months.
Unstratified HR=0.521 (*P*<0.0001).

Krop I, et al. Lancet Oncol 2014

Final OS Results

Second Interim OS Analysis
(cut-off date February 13, 2015)

- Planned: 330 (67%) of 492 targeted events
- Actual: 338 (69%) events; median follow-up 30.5 months
- Pre-specified stopping boundary HR<0.748 or *P*<0.012
- **If stopping boundary is crossed, this will be the final OS analysis**



	TPC (n=198)	T-DM1 (n=404)
Median (months)	15.8	22.7

Stratified HR=0.68 (95% CI: 0.54–0.85)
***P*=0.0007**
(Pre-specified crossing boundary: HR<0.748; *P*<0.012)

No. at risk																					
TPC	198	168	150	131	122	115	107	93	80	68	66	62	59	51	39	28	16	6	1	0	0
T-DM1	404	388	368	347	321	298	280	251	226	207	192	179	167	164	132	84	54	25	12	2	0

Wildiers H, et al. SABCS 2015

MARIANNE Study Design

- **HER2-positive (central) LABC[a] or MBC**
- **No prior chemotherapy for LABC/MBC**
- **>6 months from prior neo-/adjuvant vinca alkaloid or taxane chemotherapy**

N = 1095

Trastuzumab + docetaxel
(8 mg/kg LD then 6 mg/kg + 100 or 75 mg/m^2 q3w) **OR**
Trastuzumab + paclitaxel
(4 mg/kg LD then 2 mg/kg + 80 mg/m^2 qw)

T-DM1 + placebo[b]
(3.6 mg/kg + 840 mg LD then 420 mg q3w)

T-DM1 + pertuzumab
(3.6 mg/kg + 840 mg LD then 420 mg q3w)

- **Stratification factors:** World region, Prior neo-/adjuvant therapy (if Yes: prior trastuzumab/lapatinib), Visceral disease
- **Primary end point:** PFS by independent review facility (IRF), non-inferiority and superiority assessed
- **Key secondary end points:** OS, PFS by investigator, ORR, Safety, Patient-reported outcomes

LD, Loading dose. [a]Locally progressive or recurrent and not amenable to resection with curative intent; [b]Pertuzumab placebo.

Ellis P, et al. ASCO 2015

Statistical Considerations

- Statistical analyses were conducted independently for T-DM1 vs HT and for T-DM1+P vs HT
- Hierarchical statistical testing was performed in pre-specified sequential order

Two-sided alpha = 2.5%

T-DM1 vs HT

1. PFS non-inferiority
2. PFS superiority
3. OS superiority
4. Other secondary end points

Two-sided alpha = 2.5%

T-DM1+P vs HT

1. PFS non-inferiority
2. PFS superiority

T-DM1+P vs T-DM1

3. PFS superiority
4. OS superiority
5. Other secondary end points

% power for target HR=0.75 (T-DM1/T-DM1+P vs. HT) and target HR=0.73 (T-DM1+P vs. T-DM1

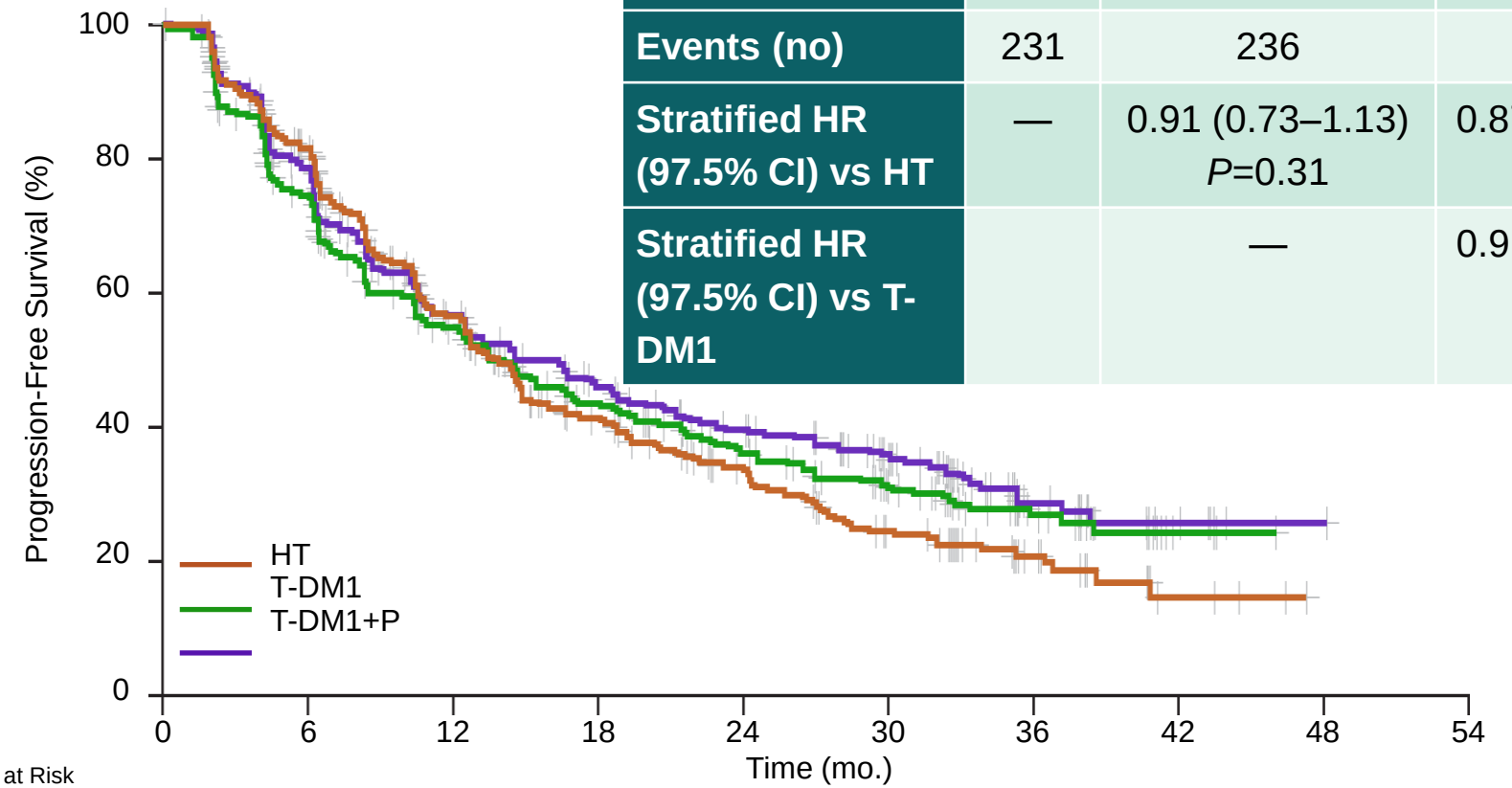
Primary end point of PFS by IRF:

- Trial was powered at 80% for both non-inferiority and superiority analyses of PFS
- Non-inferiority: Established if the upper limit of the 97.5% CI for the HR is below 1.1765 (non-inferiority margin)
- Superiority: Target HR = 0.75 (T-DM1/T-DM1+P vs HT) and target HR = 0.73 (T-DM1+P vs T-DM1). Established if $P \leq 0.025$

Ellis P, et al. ASCO 2015

Progression-Free Survival by IRF

	HT	T-DM1	T-DM1+P
Median PFS (mo)	13.7	14.1	15.2
Events (no)	231	236	217
Stratified HR (97.5% CI) vs HT	—	0.91 (0.73–1.13) *P*=0.31	0.87 (0.69–1.08) *P*=0.14
Stratified HR (97.5% CI) vs T-DM1		—	0.91 (0.73–1.13)

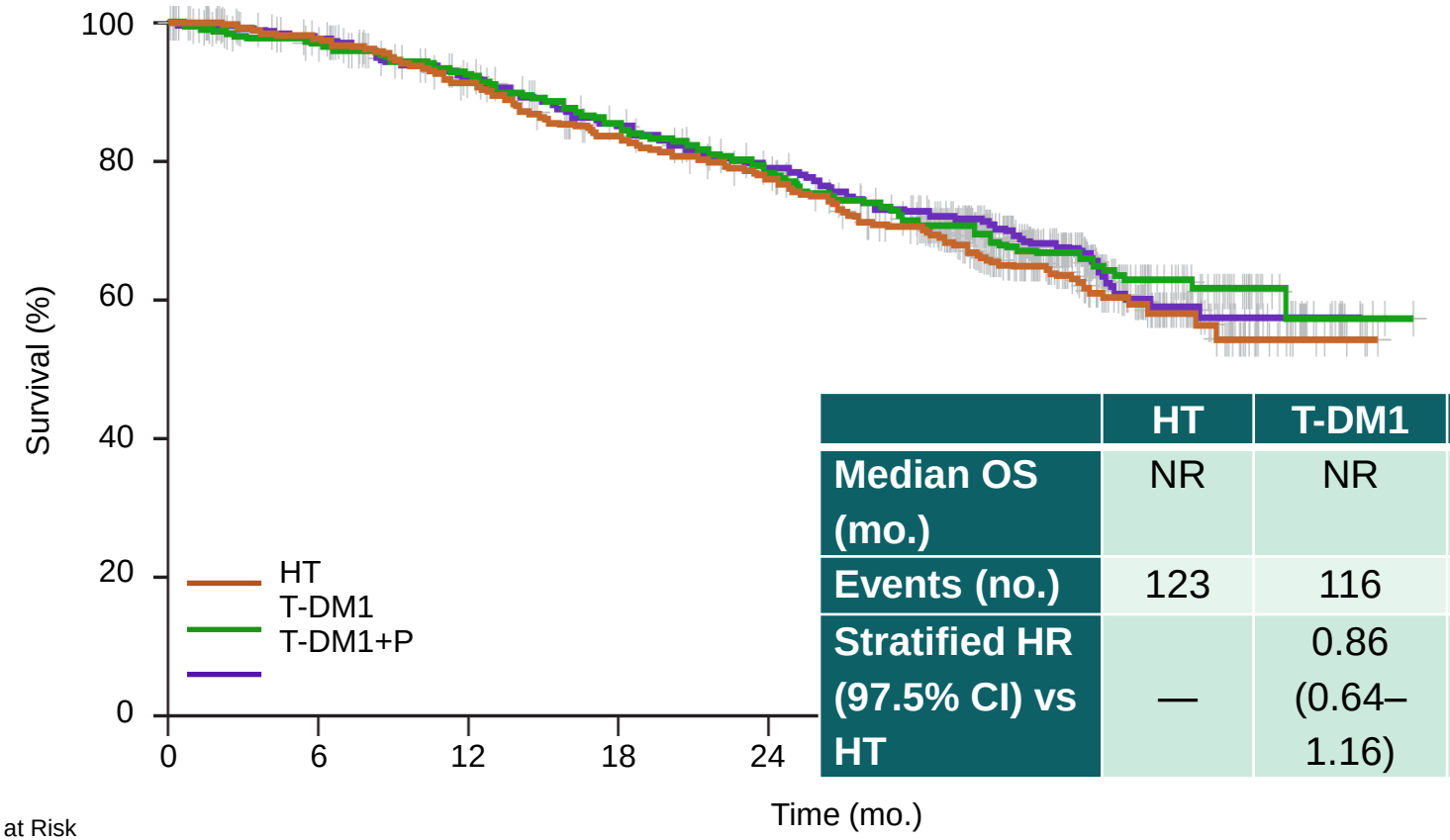


No. at Risk

HT	365	265	163	107	75	50	21	5	
T-DM1	367	257	176	133	104	67	28	3	
T-DM1+P	363	261	177	135	109	75	25	5	1

Ellis P, et al. ASCO 2015

Overall Survival (First Interim Analysis)



	HT	T-DM1	T-DM1+P
Median OS (mo.)	NR	NR	NR
Events (no.)	123	116	115
Stratified HR (97.5% CI) vs HT	—	0.86 (0.64–1.16)	0.82 (0.61–1.11)

No. at Risk

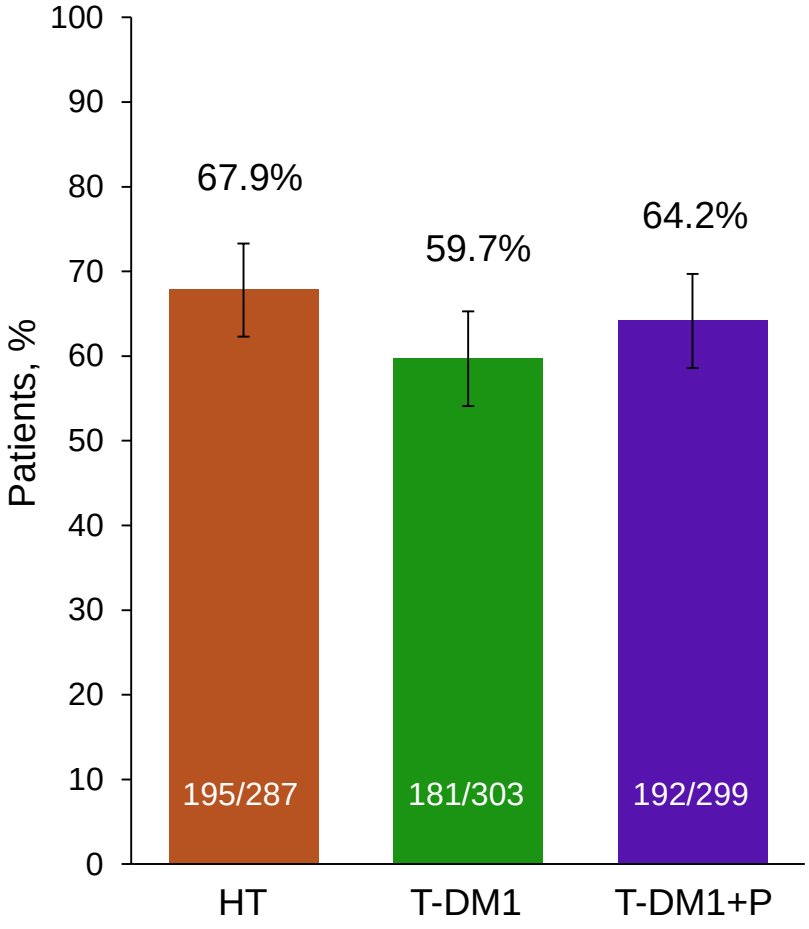
HT	365	335	303	273	250	218	98	25	1
T-DM1	367	345	321	291	263	224	104	37	3
T-DM1+P	363	341	309	282	257	231	106	28	1

NR, not reached.

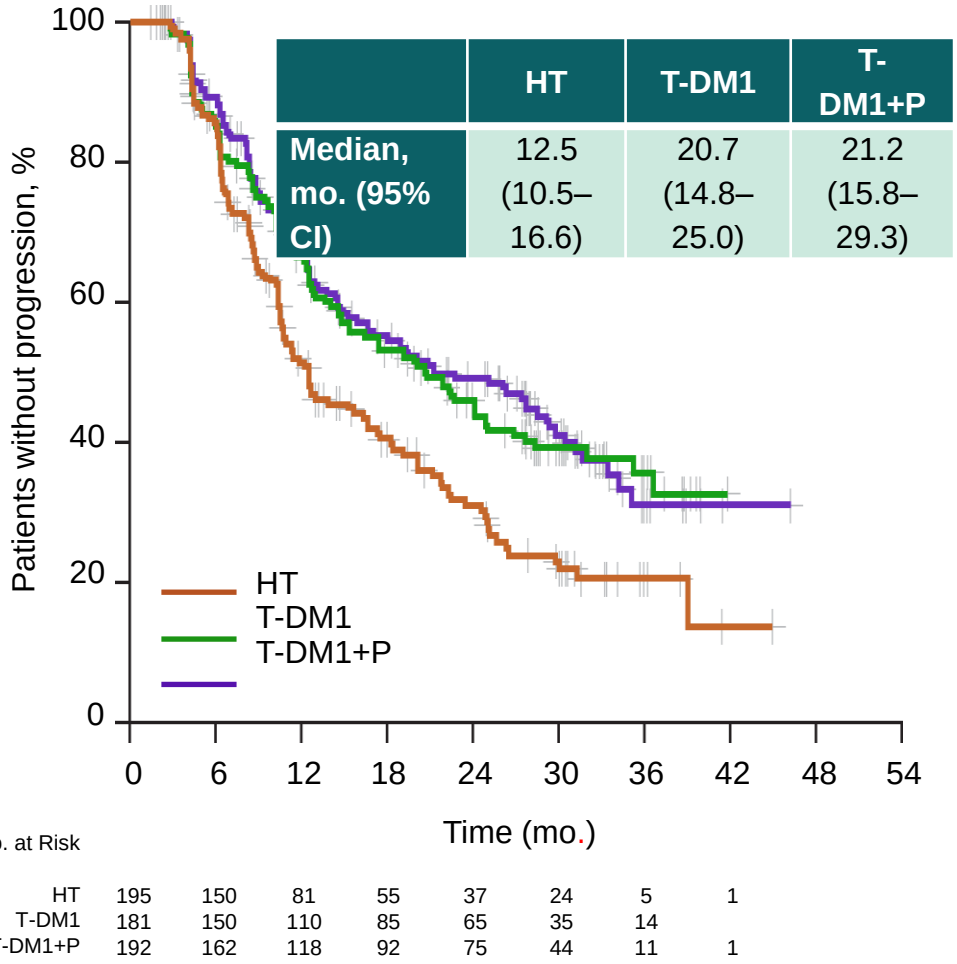
Ellis P, et al. ASCO 2015

Objective Response and Duration of Response by IRF

Objective Response Rate



Duration of Response



	HT	T-DM1	T-DM1+P
Median, mo. (95% CI)	12.5 (10.5–16.6)	20.7 (14.8–25.0)	21.2 (15.8–29.3)

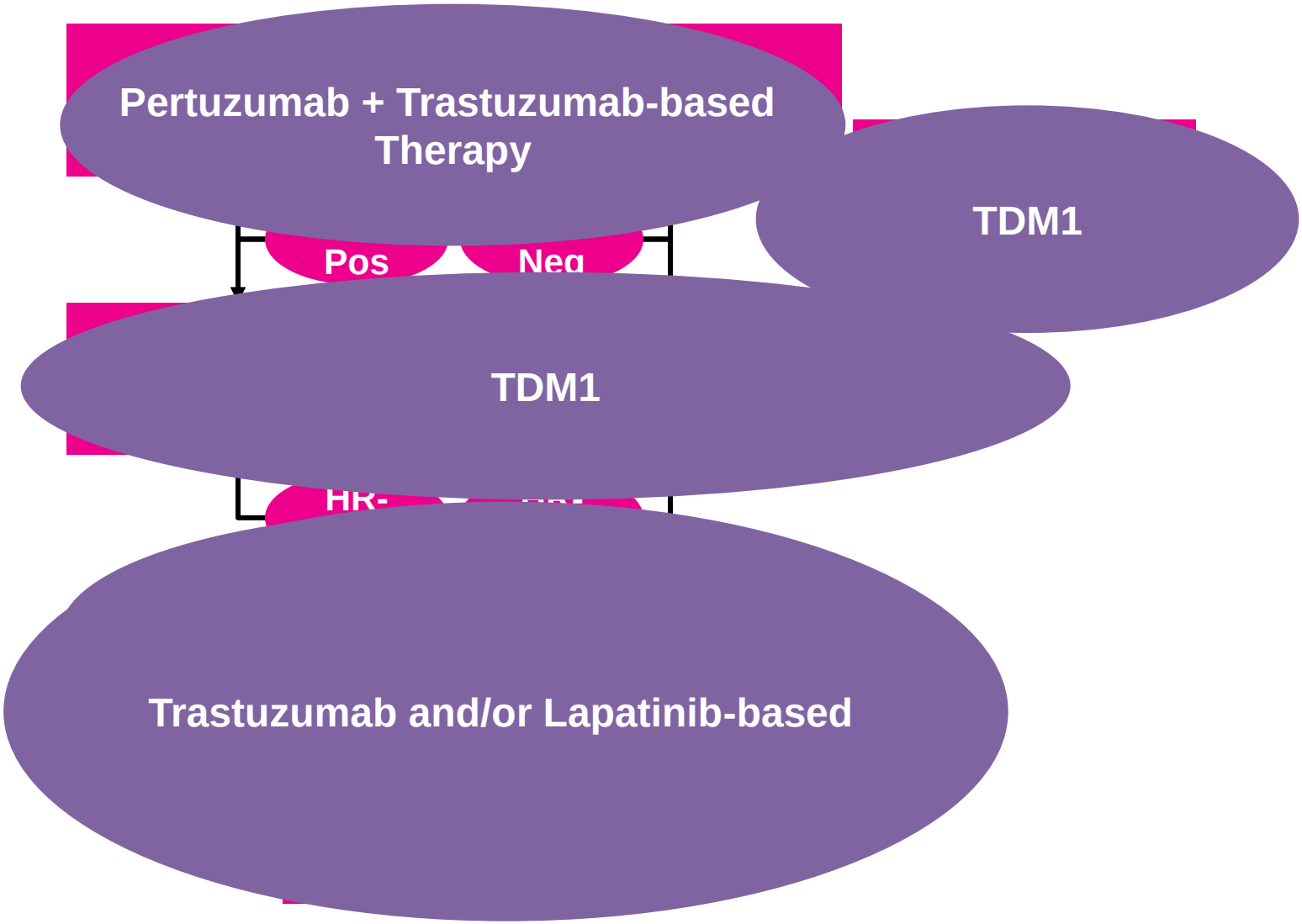
No. at Risk

HT	195	150	81	55	37	24	5	1
T-DM1	181	150	110	85	65	35	14	
T-DM1+P	192	162	118	92	75	44	11	1

Error bars depict 95% confidence intervals.

Ellis P, et al. ASCO 2015

Conclusion


Pertuzumab + Trastuzumab-based Therapy
TDM1
Pos
Neg
TDM1
Trastuzumab and/or Lapatinib-based

Prespectives on Current Strategies in the Management of Her2+Breast Cancer – Early Breast Cancer

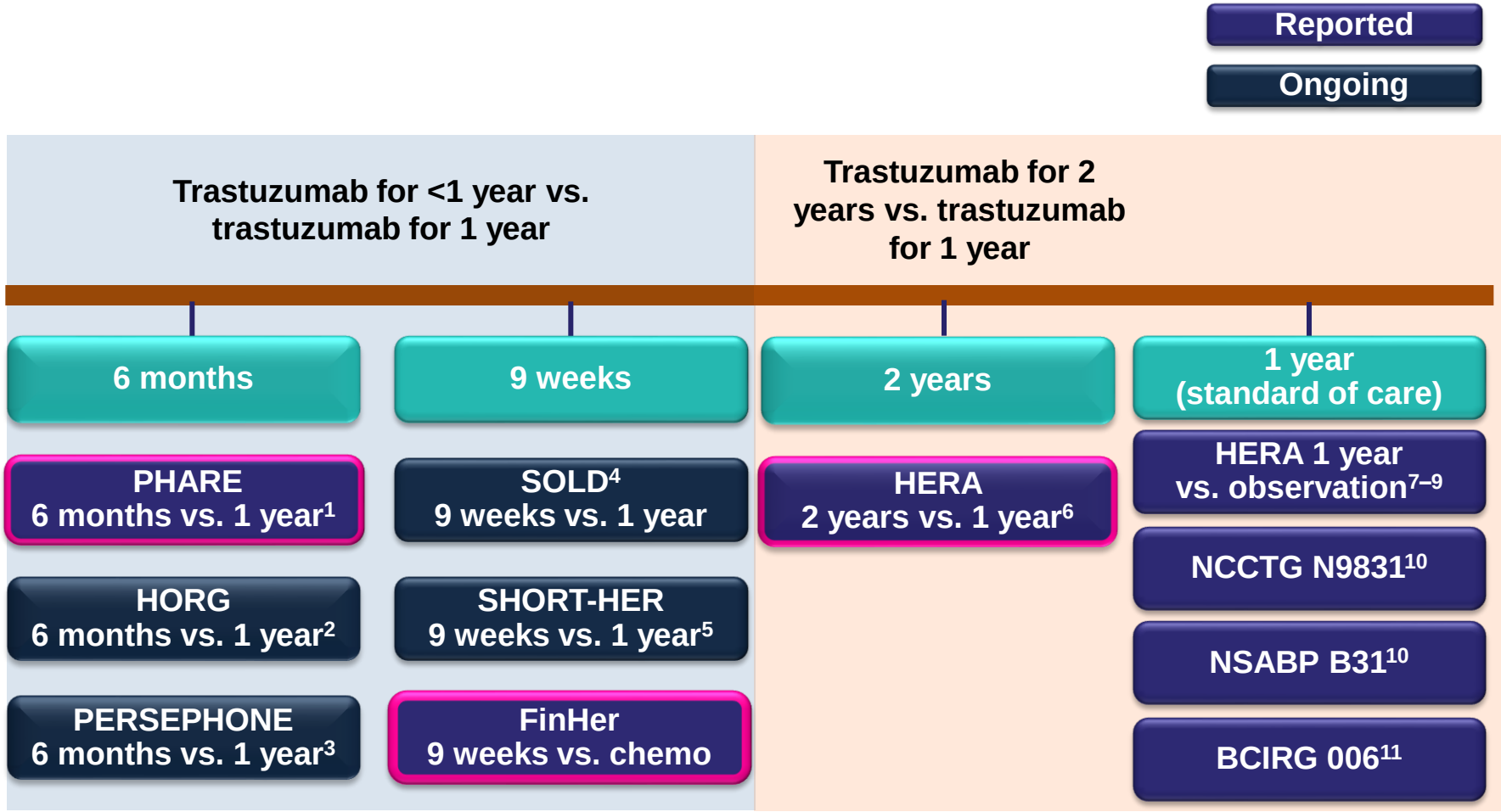
DFS and OS benefits demonstrated during long-term follow-up in the four pivotal clinical trials of trastuzumab for 1 year

			DFS		OS	
Study	**Follow-up (years)**	**N**	**HR**	**p value**	**HR**	**p value**
HERA[1–4] CT+/–RT→H vs. CT+/–RT	1	3387	0.54	< 0.0001	0.76	0.26
	2	3401	0.64	< 0.0001	0.66	0.0115
	4	3401	0.76	< 0.0001	0.85	0.1087
	8	3401	0.76	< 0.0001	0.76	0.0005
NCCTG N9831/ NSABP B-31[5–7] AC→TH→H vs. AC→T	2	3351	0.48	< 0.0001	–	–
	4	4045	0.52	< 0.001	0.61	< 0.001
	8.4	4046	0.60	< 0.0001	0.63	< 0.0001
BCIRG 006[8]						
AC→TH→H vs. AC→T	5.5	3222	0.64	< 0.001	0.63	< 0.001
TCH vs. AC→T			0.75	0.04	0.77	0.04

CT, chemotherapy; DFS, disease-free survival; H, trastuzumab; HR, hazard ratio; OS, overall survival; RT, radiotherapy; T, taxane.

1. Piccart-Gebhart MJ, *et al*; *N Engl J Med* 2005; **353:**1659-1672;
2. Smith I, *et al*. *Lancet* 2007; **369:**29-36;
3. Gianni L, *et al*; *Lancet Oncol* 2011; **12:**236-244;
4. Goldhirsch A, *et al*. *Lancet* 2013 [Epub ahead of print];
5. Romond EH, *et al*. *N Engl J Med* 2005; **353:**1673-1684;
6. Perez EA, *et al*. *J Clin Oncol* 2011; **29:**3366-3373;
7. Romond EH, *et al*. SABCS 2012 (abstract S5-5; oral presentation);
8. Slamon D, *et al*. *N Engl J Med* 2011; **365:**1273-1283.

Several ongoing trials are investigating the optimal duration of trastuzumab in EBC



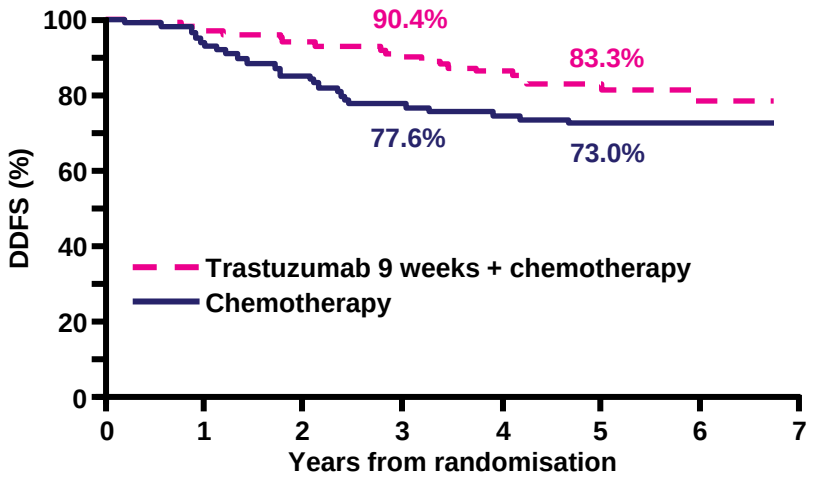
Trastuzumab for 1 year remains the standard of care in EBC, as recommended by international guidelines[12–14]

1. Pivot X, *et al*. *Lancet Oncol* 2013; **14:**741–748; 2. http://clinicaltrials.gov/ct2/show/NCT00615602; 3. Earl HM, *et al*. ASCO 2013 (Abstract TPS667); 4. http://clinicaltrials.gov/ct2/show/NCT00593697; 5. http://clinicaltrials.gov/ct2/show/NCT00629278; 6. Goldhirsch A, *et al*. *Lancet* 2013 [Epub ahead of print]; 7. Piccart-Gebhart MJ, *et al*. *N Engl J Med* 2005; **353:**1659–1672; 8. Smith I, *et al*. *Lancet* 2007; **369:**29–36; 9. Gianni L, *et al*. *Lancet Oncol* 2011; **12:**236–244; 10. Perez EA, *et al*. *J Clin Oncol* 2011; **29:**3366–3373; 11. Slamon D, *et al. N Engl J Med* 2011; **365:**1273–1283;

12. NCCN Clinical Practice Guidelines in Oncology; Breast Cancer V1.2013; 13. Senkus E, *et al*. *Ann Oncol* 2013 [Epub ahead of print]; 14. Goldhirsch A, *et al*. *Ann Oncol* 2013 [Epub ahead of print].

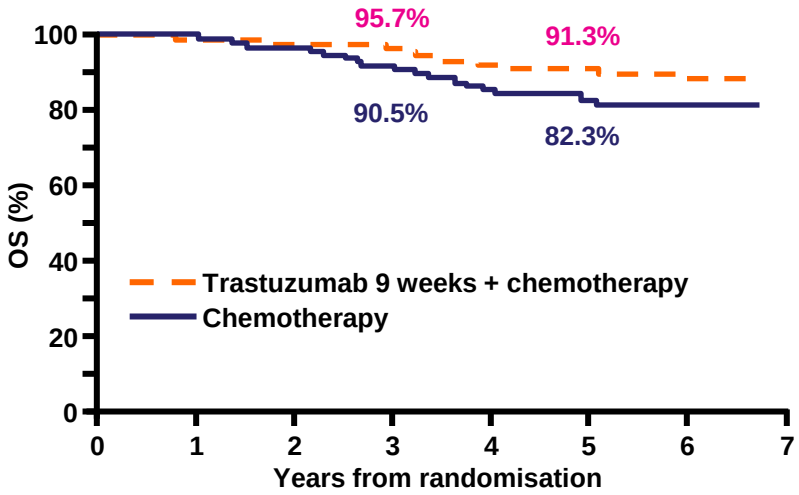
FinHer: No statistically significant improvement in DDFS or OS with 9 weeks of trastuzumab vs. chemotherapy alone

DDFS



	Patients	Events	HR (9 weeks vs. none)	95% CI	p value
9 weeks	115	22	0.65	(0.38, 1.12)	0.12
Chemo	116	31			

OS



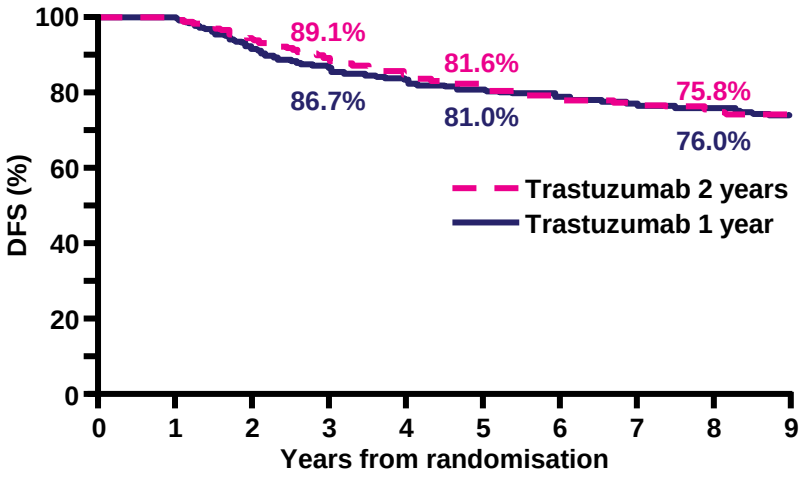
	Patients	Events	HR (9 weeks vs. none)	95% CI	p value
9 weeks	115	12	0.55	(0.27, 1.11)	0.094
Chemo	116	21			

CI, confidence interval; DDFs, distant disease-free survival.

Joensuu H, *et al*. *J Clin Oncol* 2009

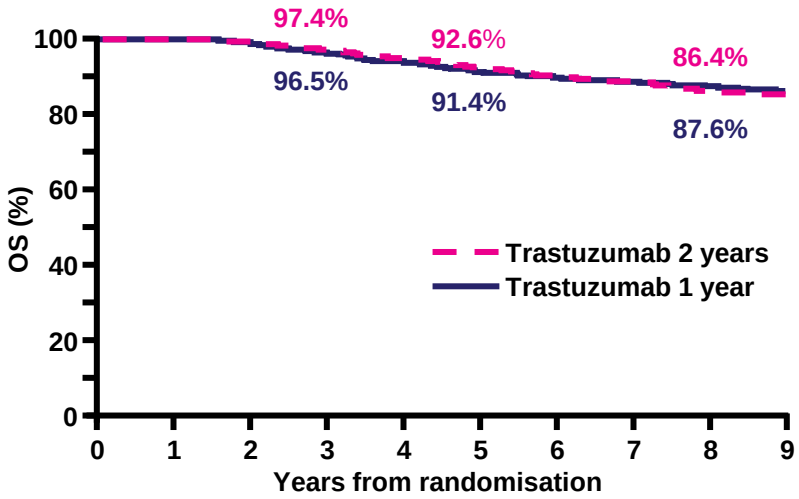
HERA: Trastuzumab for 2 years was as efficacious as the standard 1 year of treatment, with no additional benefit

DFS[1]



	Patients	Events	HR (2 vs. 1 year)	95% CI	p value
2 years	1553	367	0.99	(0.84, 1.14)	0.86
1 year	1552	367			

OS[2]

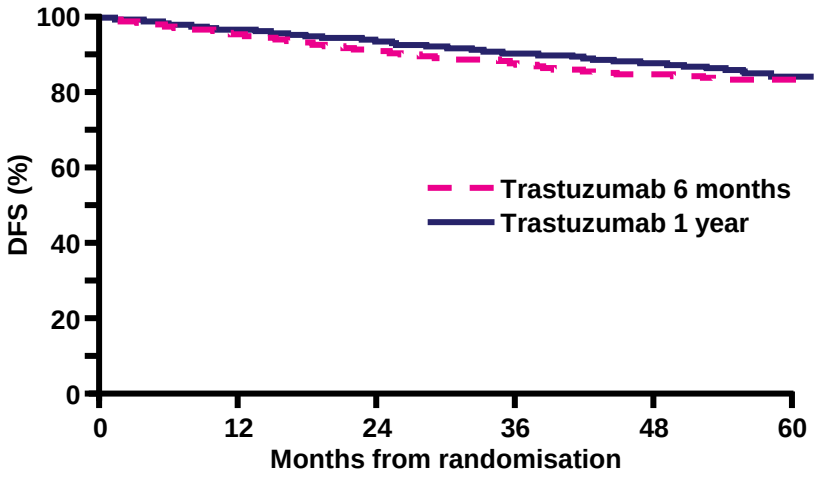


	Patients	Events	HR (2 vs. 1 year)	95% CI	p value
2 years	1553	196	1.05	(0.86, 1.28)	0.63
1 year	1552	186			

1. Goldhirsch A, *et al*. *Lancet* 2013 [Epub ahead of print];
2. Goldhirsch A, *et al*. SABCS 2012 (Abstract S5-2; oral presentation).

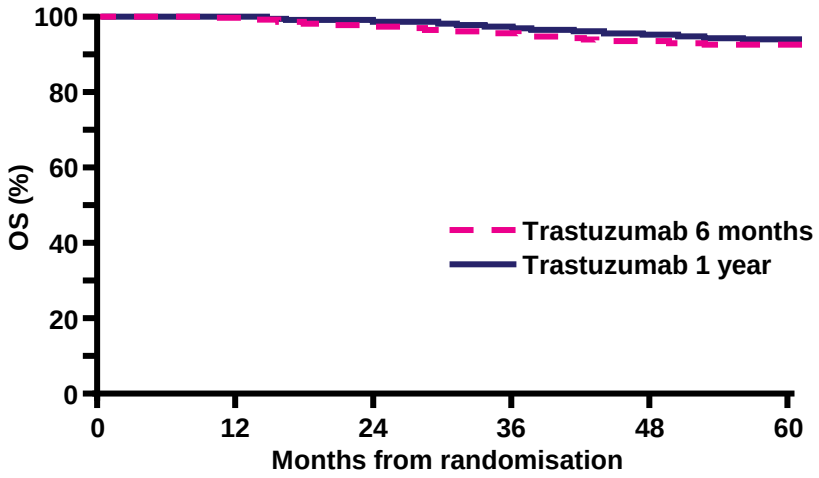
PHARE: Non-inferiority of 6 months vs. 1 year of trastuzumab was not demonstrated

DFS



	Patients	Events	HR (6 months vs. 1 year)	95% CI	p value
6 months	1690	93	1.46	(1.06, 2.01)	0.03
1 year	1690	66			

OS



	Patients	Events	HR (6 months vs. 1 year)	95% CI	p value
6 months	1690	219	1.28*	(1.05, 1.56)	0.29
1 year	1690	175			

HR (95% CI): 1.46 (1.06, 2.01)
(above the prespecified non-inferiority CI of 1.15)

Pivot X, *et al*. *Lancet Oncol* 2013

Neoadjuvant Studies I

	NOAH	GeparQuinto		NeoAltto			CHER-LOB			NSABP B-41		
Scheme	**Ch + T**	**Ch + T**	**Ch + L**	**Ch + T**	**Ch + L**	**Ch + TL**	**Ch + T**	**Ch + L**	**Ch + TL**	**Ch + T**	**Ch + L**	**Ch + TL**
Primary endpoint	**EFS**	**pCR breast & axilla***		**pCR breast**			**pCR breast & axilla**			**pCR breast**		
n	115	307	308	154	149	152	36	39	46	177	171	171
pCR (%) breast	43	50	35	29	25	**51**	NR	NR	**NR**	52	53	**62**
pCR (%) breast & axila	38	31	22	28	20	**47**	26	29	**43**	49	47	**60**

*pCR excludes ducatl in situ carcinoma

Ch, chemotherapy; EFS, event free-survival; L, lapatinib; n, sample; pCR, pathological complete response; T, trastuzumab

Neoadjuvant Studies II

	Neosphere				Tryphaena	TBCRC-006
Scheme	**Ch + T**	**Ch + P**	**Ch + TP**	**TP**	**Ch + TP**	**TL**
Primary endpoint	**pCR breast**				**Cardiotoxicity**	**pCR breast**
n	107	94	107	108	225	66
pCR (%) breast	29	24	**46**	17	**62**	**28**
pCR (%) breast & axila	21	18	**39**	11	**48**	NR

Ch, chemotherapy; L, lapatinib; n, sample; P, pertuzumab; pCR, pathological complete response; T, trastuzumab

NeoSphere: study design and pCR results

Patients with operable or locally advanced/ inflammatory HER2-positive BC

Chemo-naive & primary tumors >2 cm (N=417)

TD (n=107)
trastuzumab (8→6 mg/kg)
docetaxel (75→100 mg/m^2)

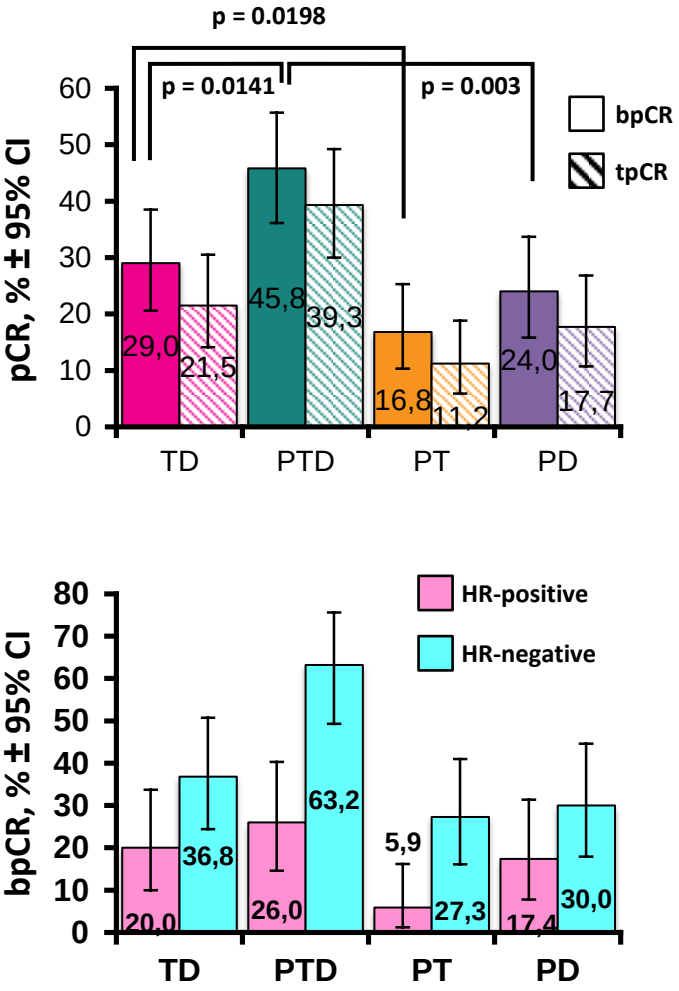
PTD (n=107)
pertuzumab (840→420 mg)
trastuzumab (8→6 mg/kg)
docetaxel (75→100 mg/m^2)

PT (n=107)
pertuzumab (840→420 mg)
trastuzumab (8→6 mg/kg)

PD (n=96)
pertuzumab (840→420 mg)
docetaxel (75→100 mg/m^2)

Study dosing: q3w x 4

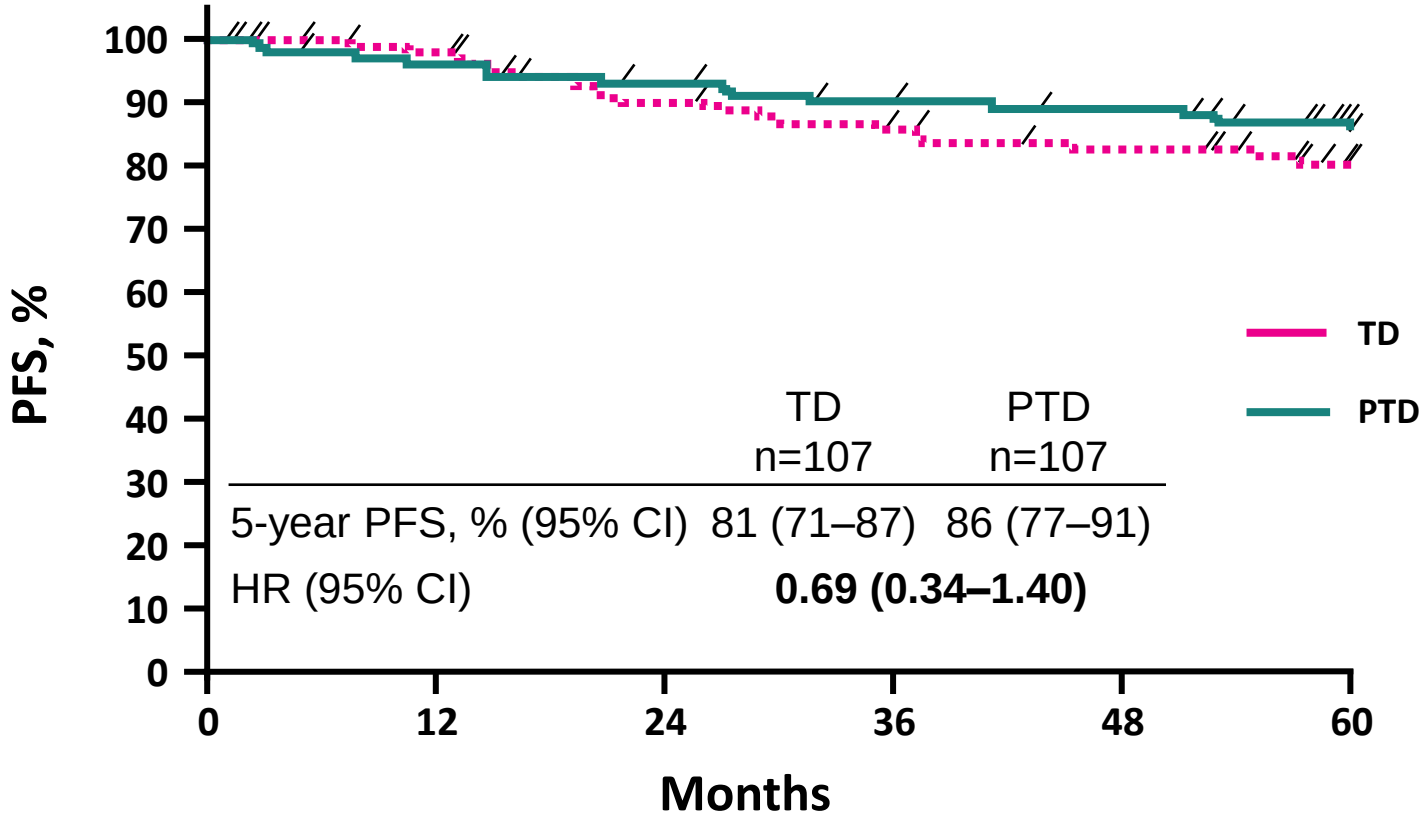
SURGERY



HR, hormone receptor;
HR-positive = estrogen and/or progesterone receptor-positive;
HR-negative = estrogen and progesterone receptor-negative

Gianni L, et al. Lancet Oncol 2012;

PFS for TD vs PTD, ITT population



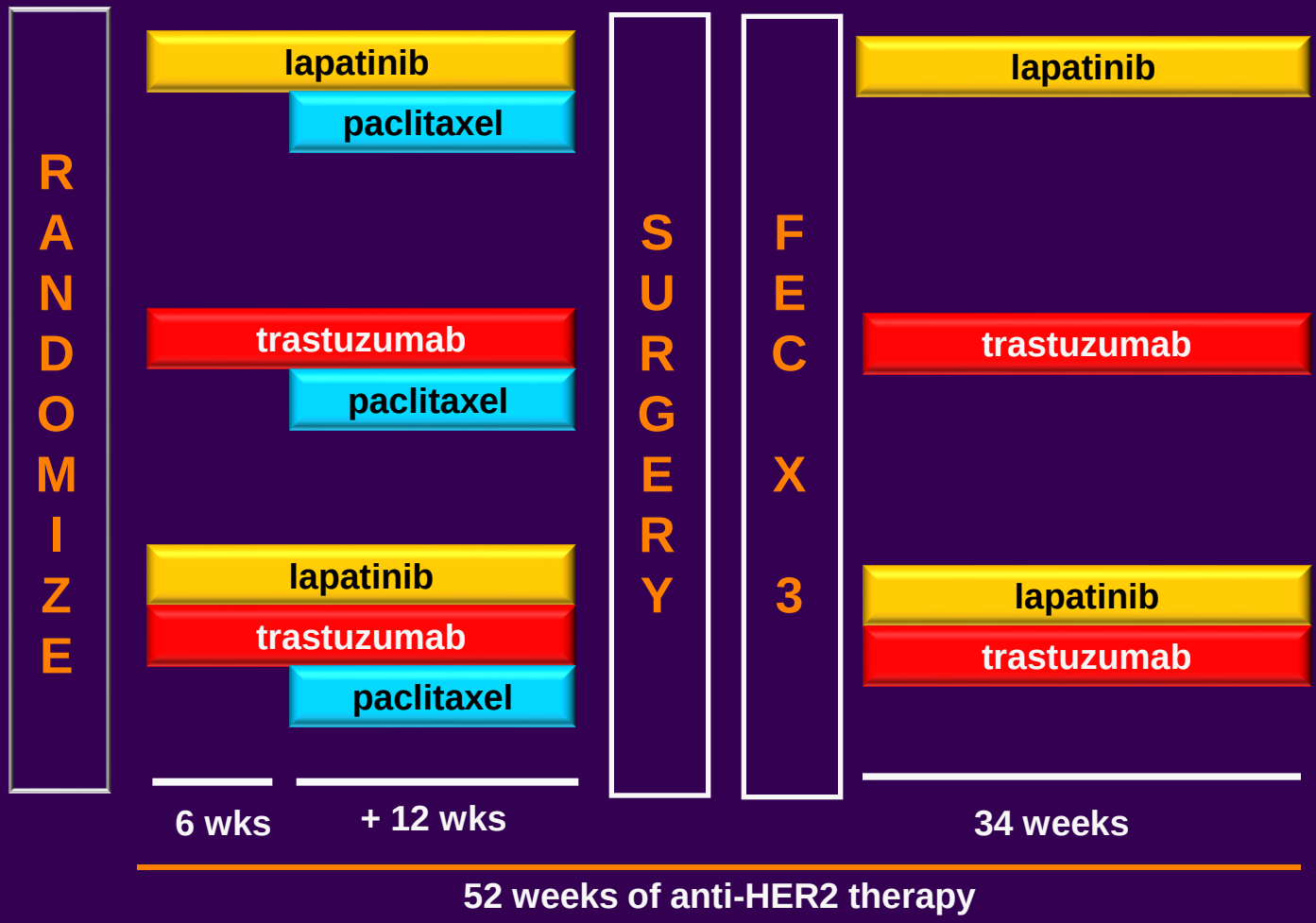
n at risk						
TD	107	101	89	83	78	58
PTD	107	99	94	88	86	63

Kaplan–Meier curves are truncated at 60 months (the end of scheduled follow-up). However, summary statistics shown here take into account all follow-up
Three late events occurred with PTD: two cases of PD at 63 and 71 months, and one death due to an unrelated cerebrovascular accident without PD at 76 months

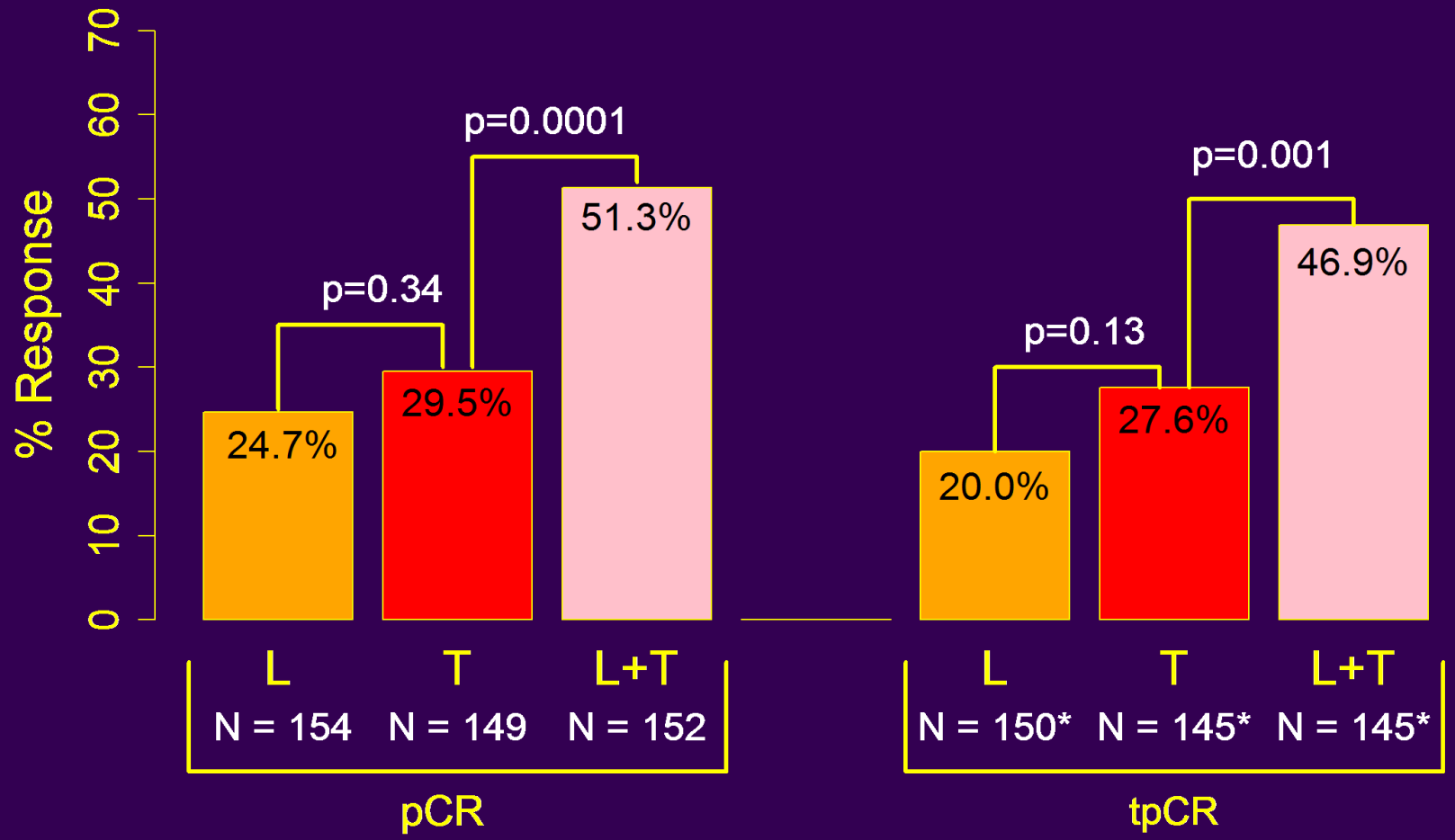
NeoALLTO: Study Design

Invasive operable HER2+ BC
T > 2 cm
(inflammatory BC excluded)
LVEF ≥ 50%
N=450

Stratification:
- T ≤ 5 cm vs. T > 5 cm
- ER or PgR + vs. ER & PgR –
- N 0-1 vs. N ≥ 2
- Conservative surgery or not



Efficacy – pCR and tpCR



Pathological Complete Response

Locoregional (total) pCR

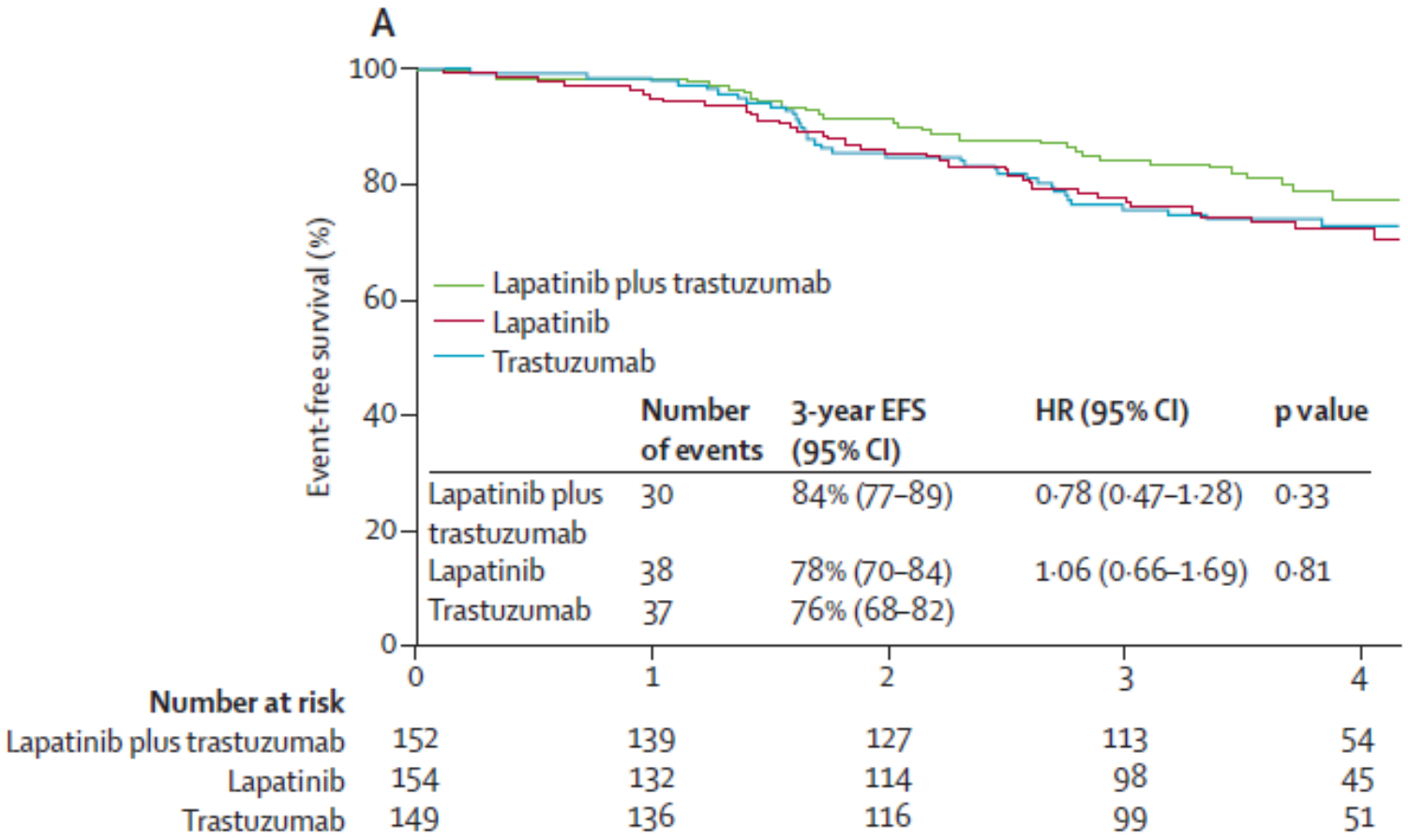
* Excludes 15 patients with non-evaluable nodal status

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

pCR pathologic complete response

NeoALTTO: DFS

ITT

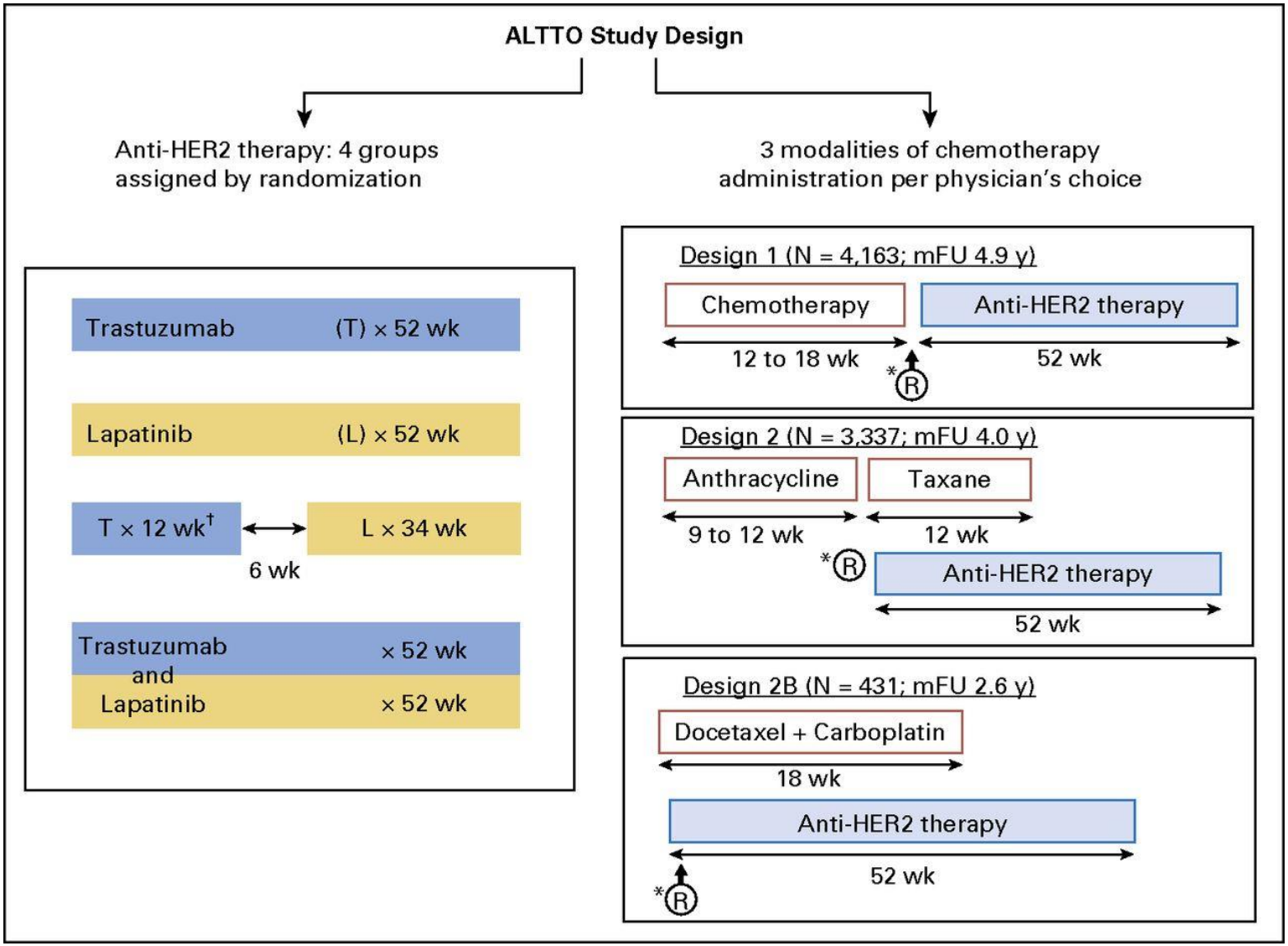


	Number of events	3-year EFS (95% CI)	HR (95% CI)	p value
Lapatinib plus trastuzumab	30	84% (77–89)	0·78 (0·47–1·28)	0·33
Lapatinib	38	78% (70–84)	1·06 (0·66–1·69)	0·81
Trastuzumab	37	76% (68–82)		

Number at risk					
Lapatinib plus trastuzumab	152	139	127	113	54
Lapatinib	154	132	114	98	45
Trastuzumab	149	136	116	99	51

De Azambuja E, et al. Lancet Oncol 2014

ALTTO Study Design



Piccart M, et al. J Clin Oncol 2015

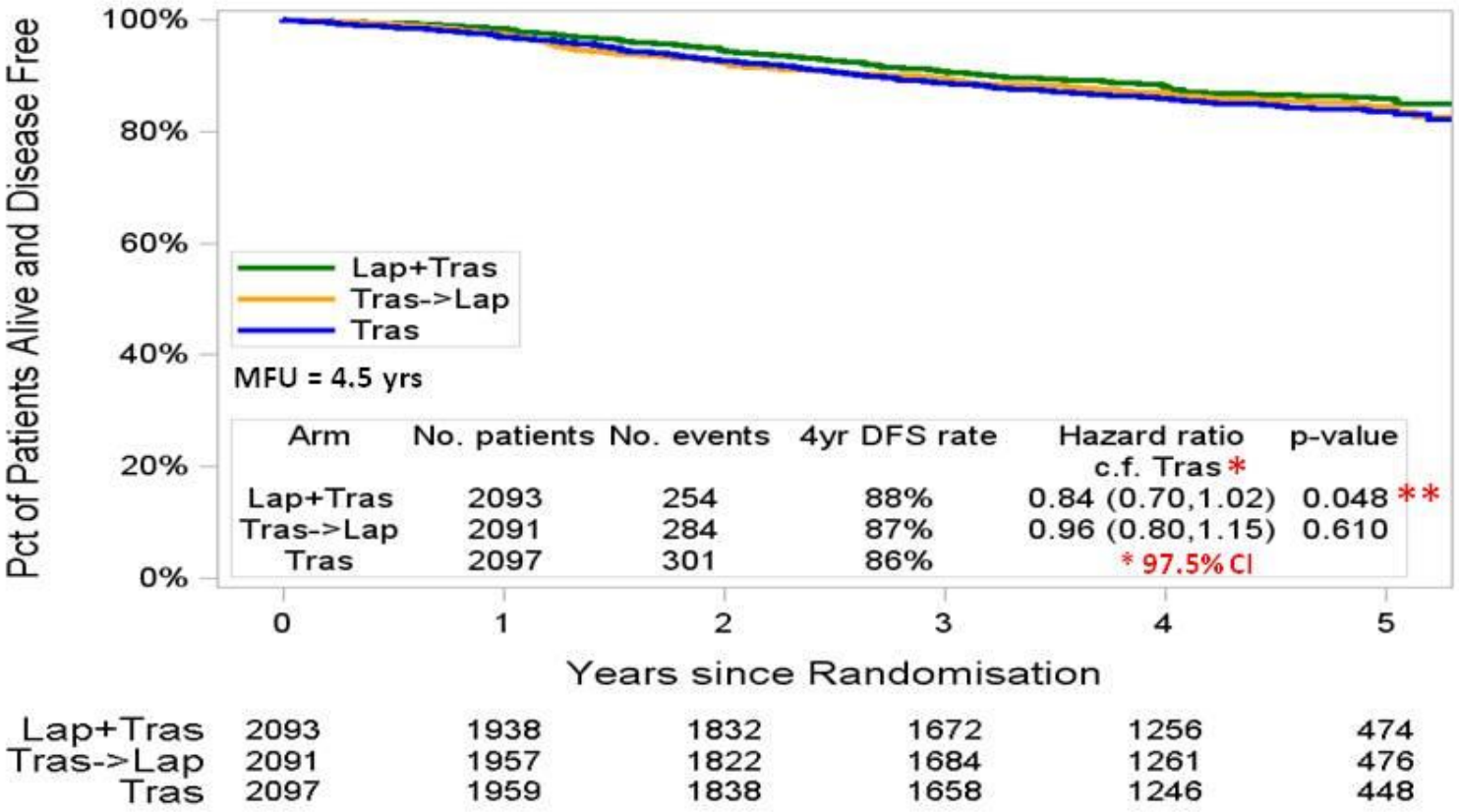
CURRENT ANALYSIS PLAN

Statistical procedures for the two remaining pairwise comparisons are:

Comparison	Assumptions
L + T vs. T	Test superiority in ITT population at alpha = **0.025**
T→ L vs. T	Test non-inferiority in per protocol population (PPP) at alpha = **0.025**

Piccart M, et al. J Clin Oncol 2015

DFS ANALYSIS



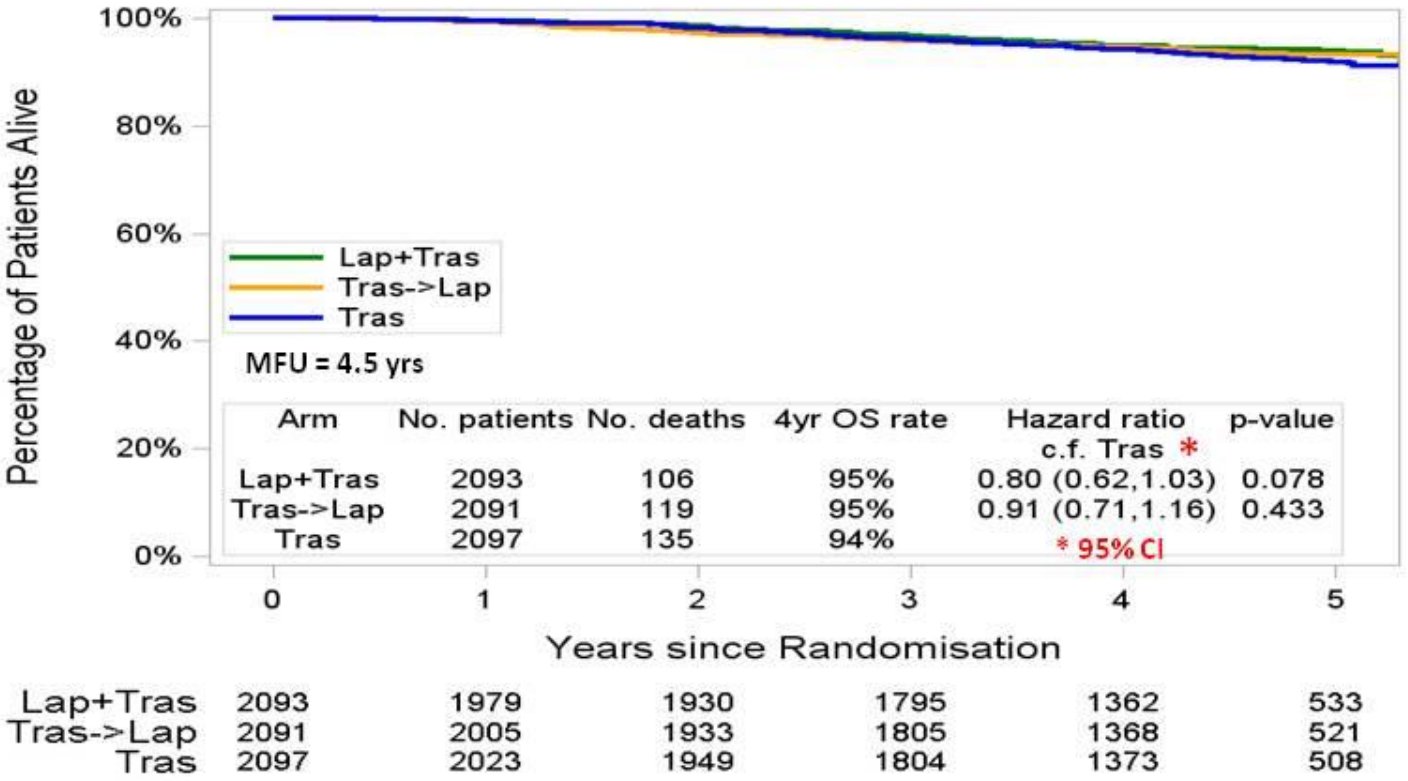
Arm	No. patients	No. events	4yr DFS rate	Hazard ratio c.f. Tras *	p-value
Lap+Tras	2093	254	88%	0.84 (0.70,1.02)	0.048 **
Tras->Lap	2091	284	87%	0.96 (0.80,1.15)	0.610
Tras	2097	301	86%	* 97.5% CI	

Lap+Tras	2093	1938	1832	1672	1256	474
Tras->Lap	2091	1957	1822	1684	1261	476
Tras	2097	1959	1838	1658	1246	448

** p-value ≤ 0.025 required for statistical significance

Piccart M, et al. J Clin Oncol 2015

OS ANALYSIS



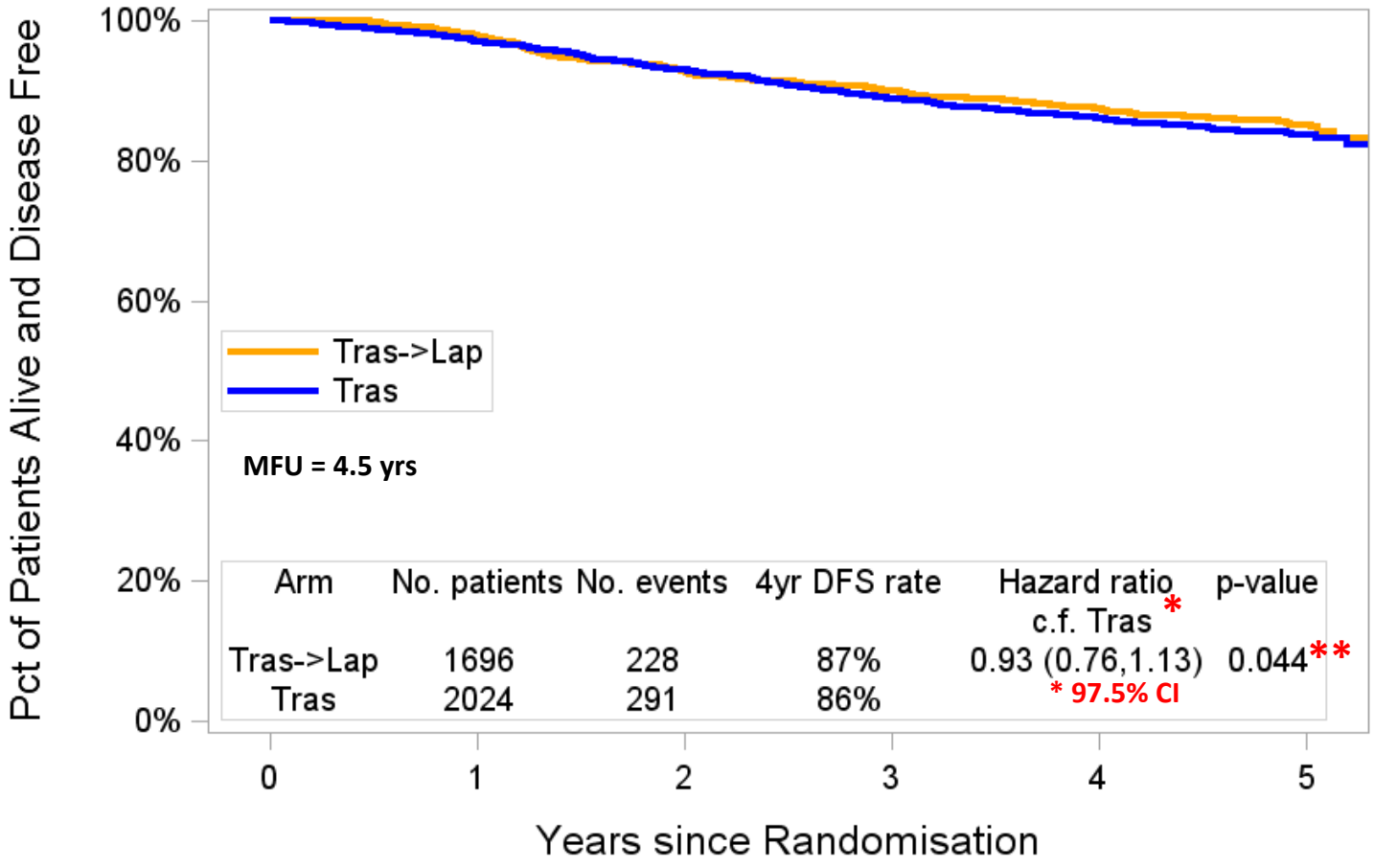
Arm	No. patients	No. deaths	4yr OS rate	Hazard ratio c.f. Tras *	p-value
Lap+Tras	2093	106	95%	0.80 (0.62,1.03)	0.078
Tras->Lap	2091	119	95%	0.91 (0.71,1.16)	0.433
Tras	2097	135	94%		

* 95% CI

Piccart M, et al. J Clin Oncol 2015

DFS NON-INFERIORITY ANALYSIS

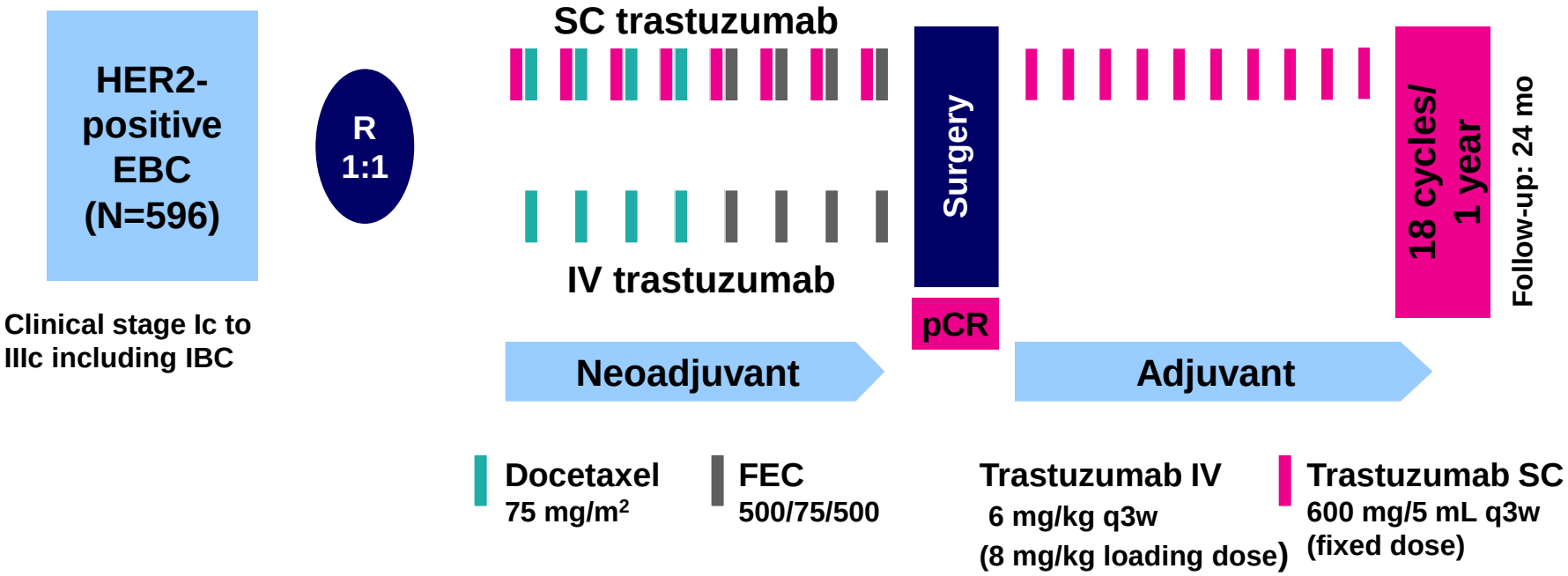
Note: Null hypothesis hazard ratio is 1.11



Tras->Lap	1696	1650	1541	1429	1087	422
Tras	2024	1931	1814	1636	1230	442

**p-value ≤ 0.025 required for statistical significance

HannaH Phase III Study



Objective:

Show non-inferiority of SC vs. IV based on co-primary endpoints

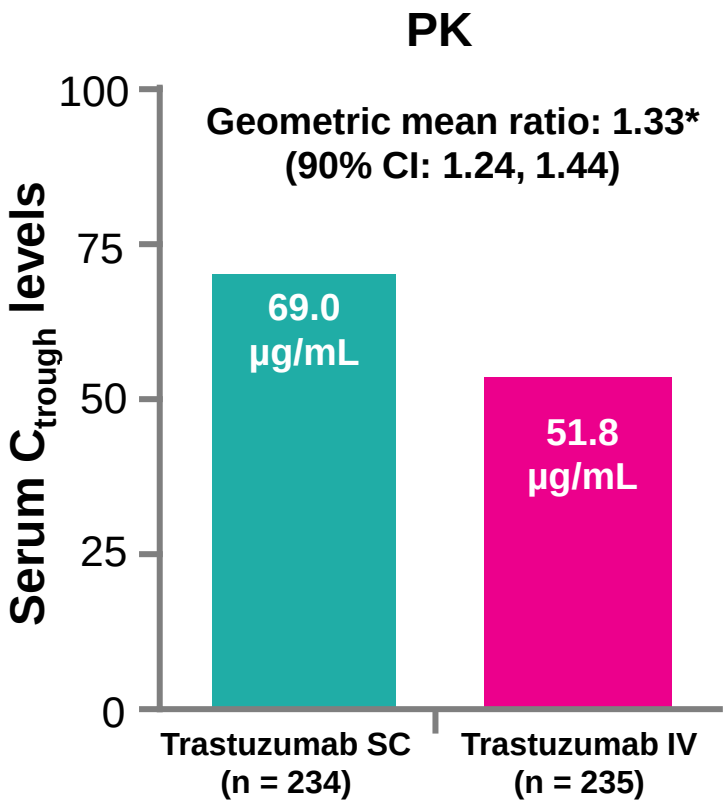
- **PK: observed trastuzumab C_{trough} pre-dose Cycle 8 (pre-surgery)**
- **Efficacy: pathological complete response (pCR) in the breast**

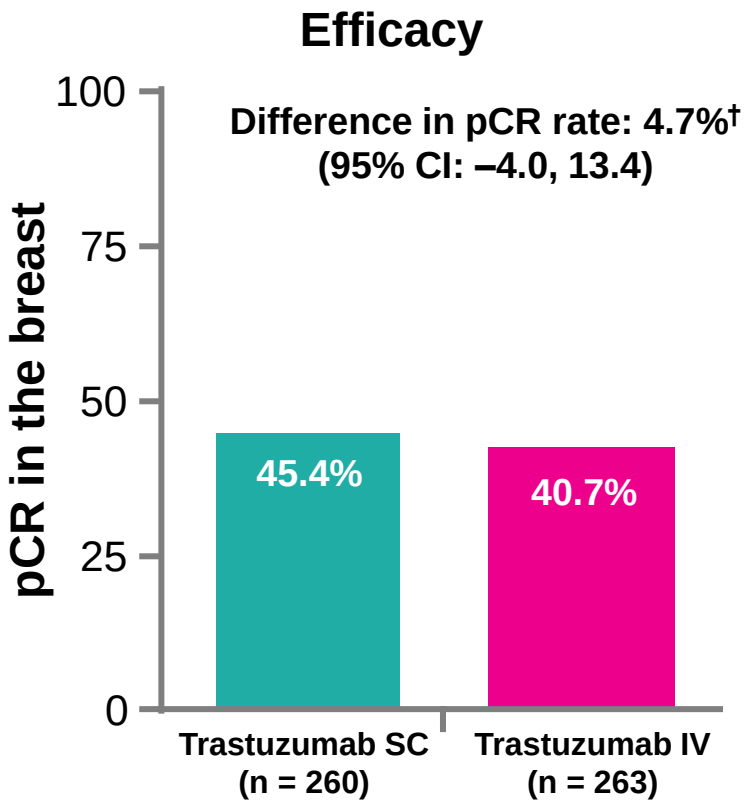
IBC, inflammatory breast cancer. FEC, 5-fluorouracil, epirubicin and cyclophosphamide

Jackisch C, et al. EBCC 2012

HannaH: Both co-primary endpoints met

Trastuzumab SC demonstrated a comparable efficacy and PK profile to the IV formulation





* Non-inferiority margin for the ratio between groups of 0.80
† Non-inferiority margin for the difference between groups of –12.5%
CI, confidence interval

Ismael G, et al. Lancet Oncol 2012

CONCLUSIONS

1. 1-year Trastuzumab is the standard of care in patients treated
    a. In adjuvant
    b. In neoadjuvant
2. Pertuzumab in combination with Trastuzumab is a new approved approach in the neoadjuvant setting
3. SC Trastuzumab might be a more convenient strategy to administer trastuzumab