Carcinoma mammario:
quando la donna è giovane

IL TRATTAMENTO ADIUVANTE E NEOADIUVANTE NEL CARCINOMA MAMMARIO HER2-POSITIVO

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24 giugno 2015

Treatment recommendations for HER2-positive breast cancer

	Neoadjuvant–adjuvant therapy for HER2-positive early breast cancer		
	Neoadjuvant	**Adjuvant**	**Duration**
ESMO 2013	• Herceptin should be added to neoadjuvant chemotherapy in patients with HER2-positive tumours	• Tumours ≥1 • Use of Herceptin should be discussed with patients with small node-negative breast cancers • pN positive	**1 year of Herceptin**
NCCN 2015	• Patients who are HER2-positive and receiving pre-operative chemotherapy should also receive Herceptin	• patients with tumours 0.6–1.0 • Tumours ≤ 0.5 or microinvasive and pN0 or pN1mic • Tumours > 1.0 • All pN positive (metastases > 2mm)	**1 year of Herceptin**
St. Gallen 2015	• Herceptin should be incorporated into neoadjuvant therapy in patients with HER2-positive disease	• Tumours ≥1 • Node-negative tumours 0.5–1.0 (TH w/o Anthra-regimen) • Excludes: Node-negative tumours 0.1–0.5 cm (pT1a)	**1 year of Herceptin**

RESEARCH ARTICLE

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Observational study on adjuvant trastuzumab in HER2-positive early breast cancer patients

G Mustacchi*[1], F Puglisi[2], AM Molino[3], D Crivellari[4], C Ghiotto[5], A Ferro[6], A Brunello[7], S Saracchini[8], M Turazza[9], E Cretella[10], A Iop[11], M Malagoli[12] & M Stefani[13]

13 Oncology Centres in the NorthEast of Italy for a total of 1245 patients investigated

To investigate the use of adjuvant trastuzumab in HER2+ breast cancer in a REAL-LIFE setting OUT OF CLINICAL TRIAL

FutureOncology 2015

Table 1. Baseline characteristics of patients.

Characteristic	AT yes (n = 949)	AT no (n = 296)	p-value
Age <76 years and stage I, II and III	–	–	–
Mean age years (range)	53.7 (23.9–75.8)	57.7 (30–75.9)	NS
Mean follow-up, months (95% CI)	37.4 (36.6–38.7)	62.1 (58.5–65.2)	0.00002
Stage (%):			
– Stage I	353 (37.2)	155 (52.4)	0.05
– Stage II	373 (39.3)	90 (30.4) *	0.05
– Stage III	223 (23.5)	51 (17.2)	NS
Adjuvant/neoadjuvant chemo regimens (%):			
– None	9 (0.9)	125 (42.2)	0.00001
– CMF-like	16 (1.7)	17 (5.7)	NS
– Anthra combo	316 (33.3)	87 (29.4)	NS
– Anthra mono	5 (0.5)	2 (0.7)	NS
– Taxane	70 (7.4)	1 (0.3)	NS
– Anthra/taxane	518 (54.6)	55 (18.6)	0.000001
– Platins/vinorelbine	5 (0.5)	1 (0.3)	NS
– Unknown	10 (1)	8 (1.7)	NS

AT: Adjuvant trastuzumab; CMF: Cyclophosphamide methotrexate fluorouracil. NS: Not significant.

* (148/296 diagnosed before adjuvant trastuzumab aproval in Italy)

“Trattamento adiuvante delle neoplasie mammarie pT1a-b pN0 HER2-positive: lo studio PROMHER”

303 pazienti investigate provenienti da 28 centri italiani pT≤10mm e pNs- HER2+

Identificare quante sono state trattate con terapia adiuvante sistemica contenente trastuzumab e quali caratteristiche clinico-patologiche ne hanno influenzato la scelta

Oncologia Medica
Ospedale “Sacro Cuore Don Calabria”
Negrar - Verona

RISULTATI

34 (11%) NESSUNA TERAPIA SISTEMICA

65 (23%) TERAPIA SISTEMICA ADIUVANTE SENZA TRASTUZUMAB

204 (66%) TERAPIA SISTEMICA ADIUVANTE CON TRASTUZUMAB
(CT 36%, OT 6%, CT+OT 57%)

pT,età,Ki67, recettori ormonali

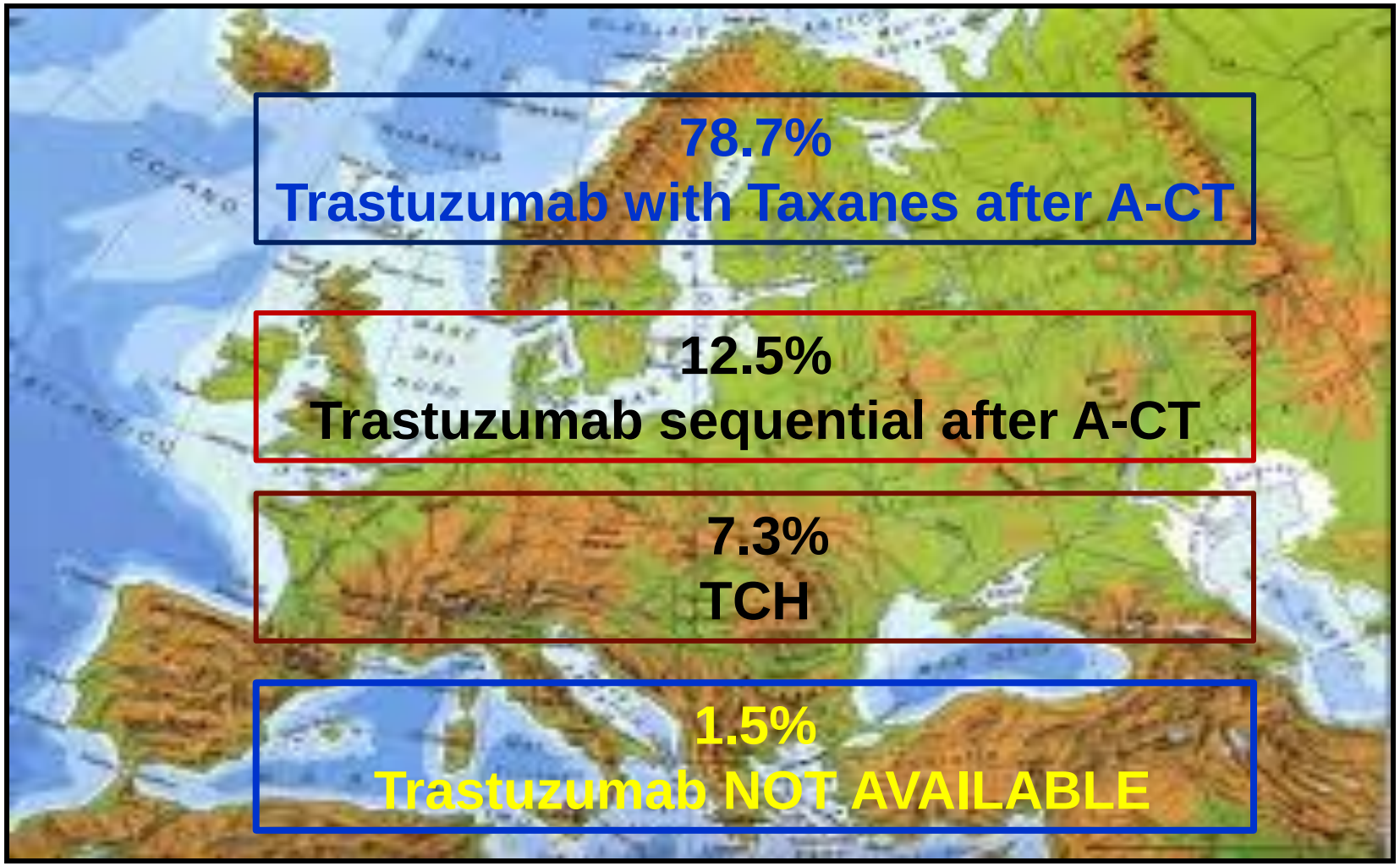
Follow up mediano: 38.6 mesi
Local e Distant Disease Free Survival

No TSA (34)	TSA senza T (65)	TSA con T (204)
5 (15%)	2 (3%)	3 (1%)

Tasso di sopravvivenza libera da malattia stimata a 5 anni:

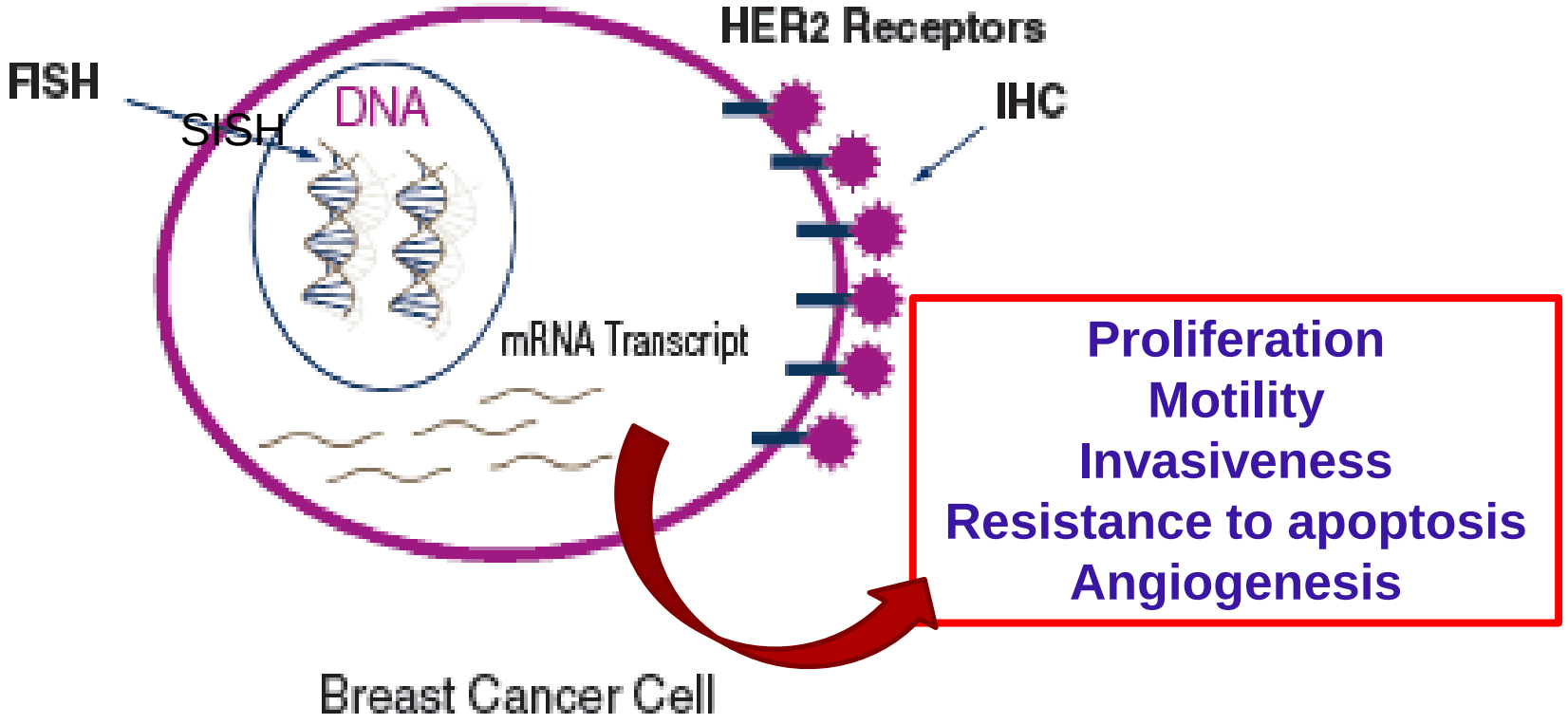
No TSA	69,6	
TSA senza T	94,3%	
TSA con T	95%	p<0,001

A VIEW OF COMMON PRACTICE IN EUROPE….



D.Zavadas et al Ann Oncol, 2014, 25(8)-1558

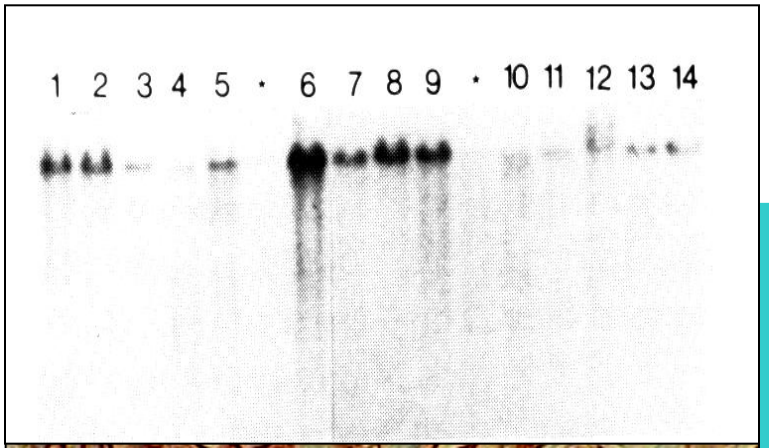
Her2 positivity: 18-20% of breast cancers

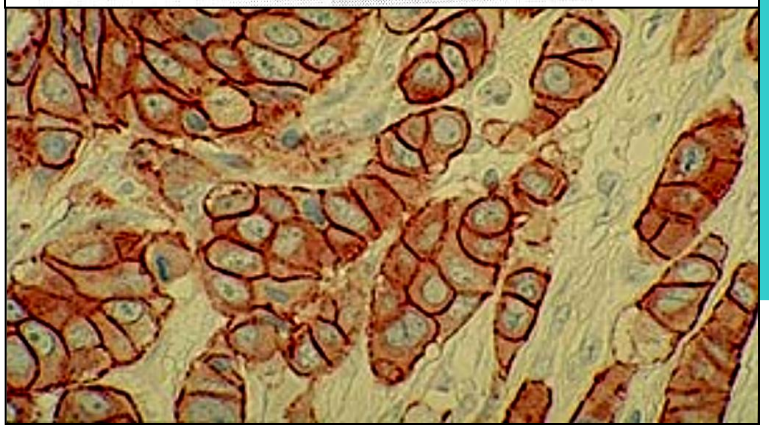


HER2 gene amplification is the underlying biological change that results in HER2 overexpression.

HER2/Neu (ErbB2) oncogene is associated with poor prognosis in breast cancer

HER2 gene amplification (Southern)





HER2 protein overexpression (IHC)

Median Survival

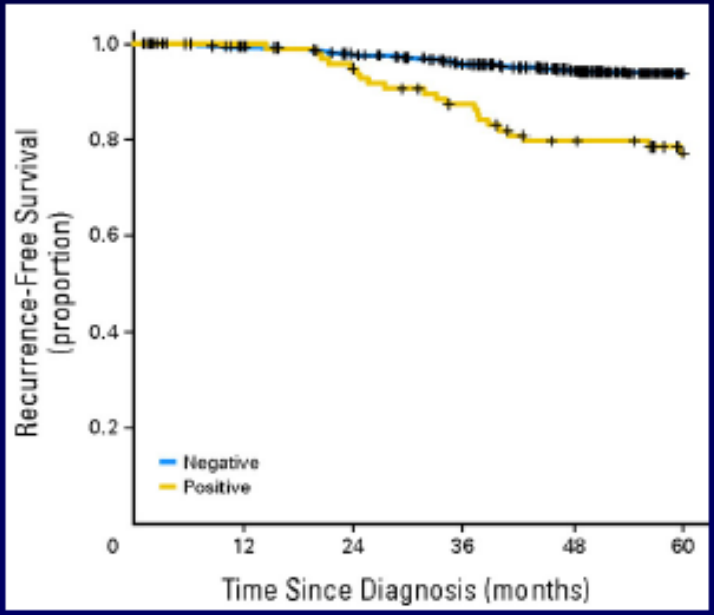
HER2 overexpression	3 yrs
HER2 normal	6-7 yrs

Slamon *et al. Science* 237:177, 1987

Outcomes for T1a/bN0 HER2+ Tumors

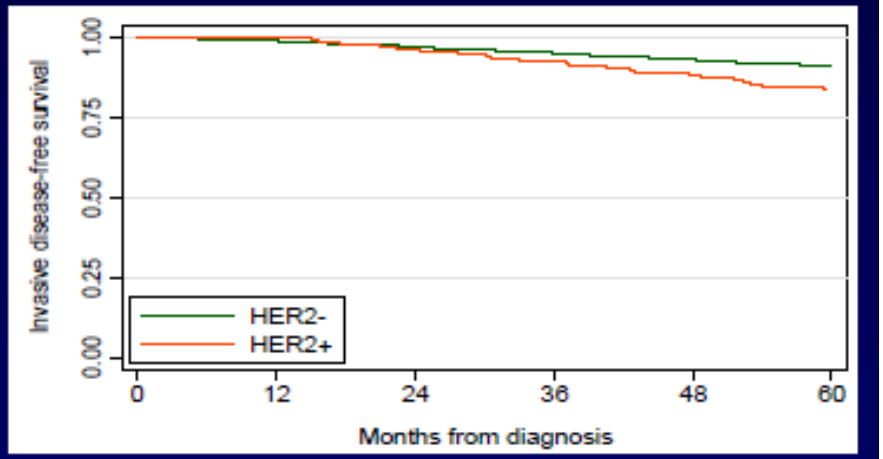
MD Anderson series

HER2 status	n	5 yr RFS
HER2+	98	77.1%
HER2-	867	93.7%



NCCN series

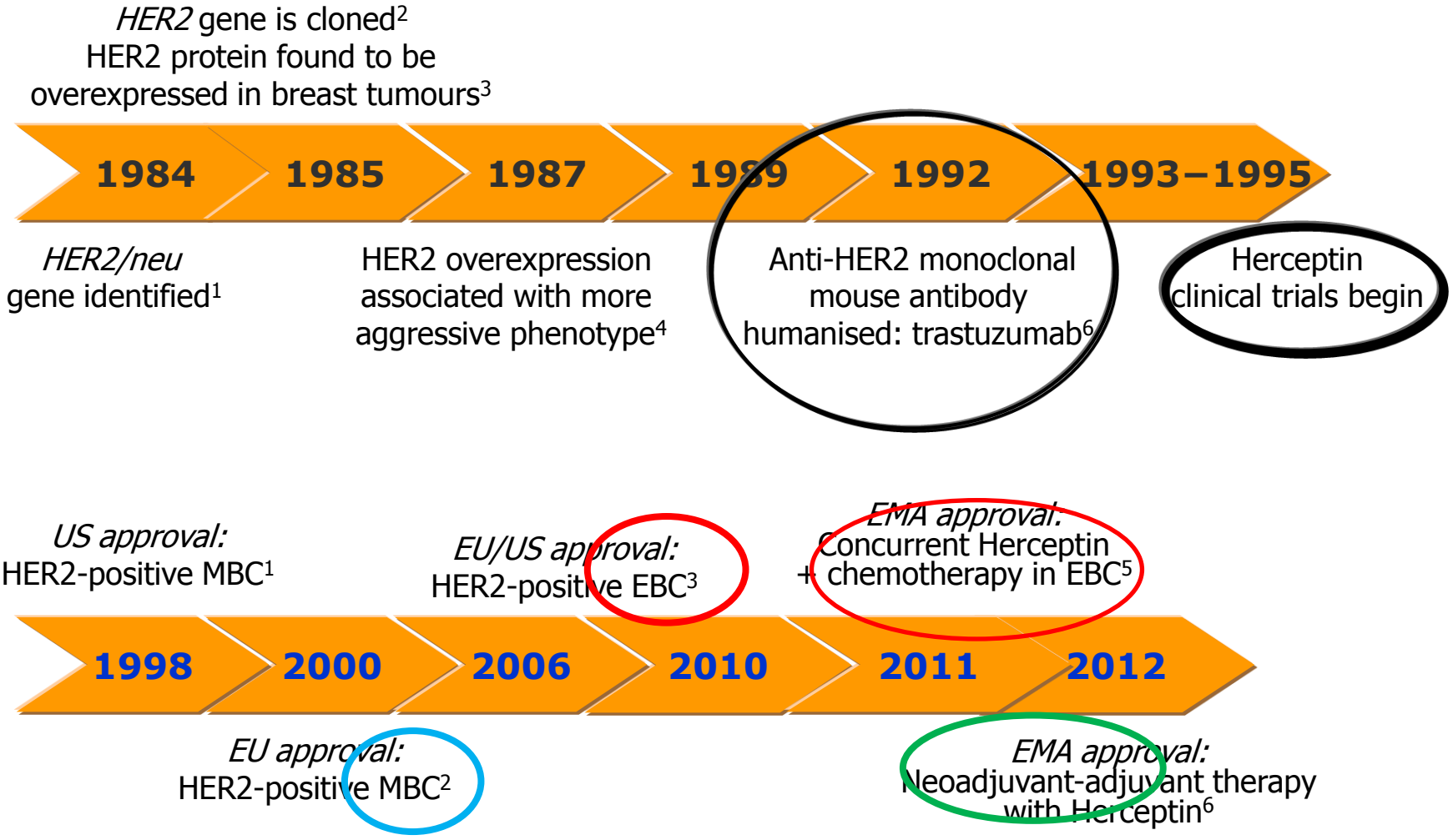
HER2 status	n	5 yr DFS
HER2+	255	83.3%
HER2-	3127	89.0%



Gonzalez-Angulo AM, et al. *J Clin Oncol.* 2009;27(34):5700-5706. Vaz Duarte Luis IM, et al. *J Clin Oncol.* 2013;31(Suppl): Abstract 1006.

Tolaney SM, et al. *Cancer Res.* 2013;73(24 Suppl): Abstract S1-04.

From Bench to Bedside….



The New England
Journal of Medicine

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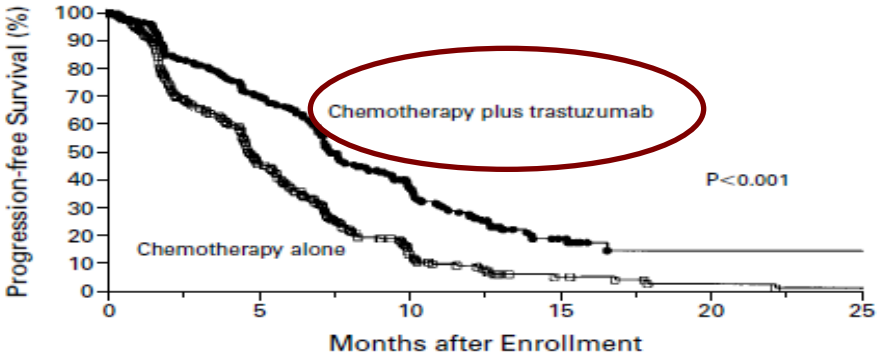
USE OF CHEMOTHERAPY PLUS A MONOCLONAL ANTIBODY AGAINST HER2 FOR METASTATIC BREAST CANCER THAT OVEREXPRESSES HER2

DENNIS J. SLAMON, M.D., PH.D., BRIAN LEYLAND-JONES, M.D., STEVEN SHAK, M.D., HANK FUCHS, M.D., VIRGINIA PATON, PHARM.D., ALEX BAJAMONDE, PH.D., THOMAS FLEMING, PH.D., WOLFGANG EIERMANN, M.D., JANET WOLTER, M.D., MARK PEGRAM, M.D., JOSE BASELGA, M.D., AND LARRY NORTON, M.D.*

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.

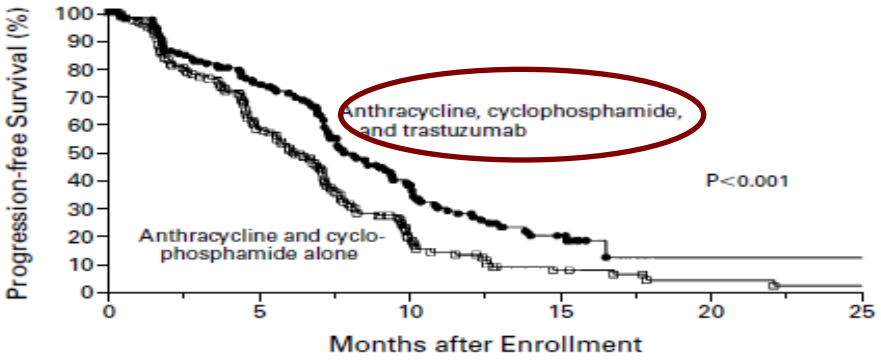
CHARACTERISTIC	AN ANTHRACYCLINE, CYCLOPHOSPHAMIDE, AND TRASTUZUMAB (N=143)*	AN ANTHRACYCLINE AND CYCLOPHOSPHAMIDE ALONE (N=138)†	PACLITAXEL AND TRASTUZUMAB (N=92)	PACLITAXEL ALONE (N=96)
Age — yr				
Mean ±SD	54±10.3	54±10.1	51±11.5	51±11.0
Range	27–76	25–75	25–77	26–73
Karnofsky score — no./no. analyzed (%)				
90–100	91/138 (66)	89/135 (66)	68/90 (76)	61/94 (65)
60–80	47/138 (34)	46/135 (34)	22/90 (24)	33/94 (35)
Median no. of positive lymph nodes at diagnosis	1.0	0.5	5.0	6.0
Prior therapy — no./no. analyzed (%)				
Adjuvant chemotherapy	81/142 (57)	50/136 (37)	88/91 (97)	95/95 (100)
Hormonal therapy (as adjuvant, for metastasis, or both)	88/142 (62)	76/134 (57)	49/89 (55)	53/95 (56)
Radiotherapy (as adjuvant, for metastasis, or both)	69/143 (48)	76/136 (56)	60/89 (67)	72/95 (76)
Median disease-free interval — mo	24.5	22.8	22.4	18.9
Degree of overexpression of HER2 — no./no. analyzed (%)‡				
2+	35/143 (24)	42/138 (30)	24/92 (26)	19/96 (20)
3+	108/143 (76)	96/138 (70)	68/92 (74)	77/96 (80)
No. of metastatic sites at enrollment — no./no. analyzed (%)				
≤1	48/143 (34)	49/136 (36)	31/91 (34)	27/95 (28)
2	38/143 (27)	48/136 (35)	32/91 (35)	35/95 (37)
≥3	57/143 (40)	39/136 (29)	28/91 (31)	33/95 (35)

Progression-free survival



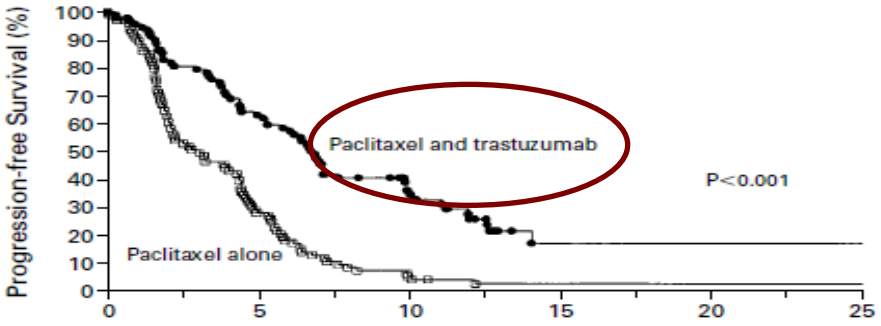
ab	235	152	63	15
one	234	103	25	6

Rate of overal response was 50% for trastuzumab-group vs 32% w/o trastuzumab (p < 0.001)



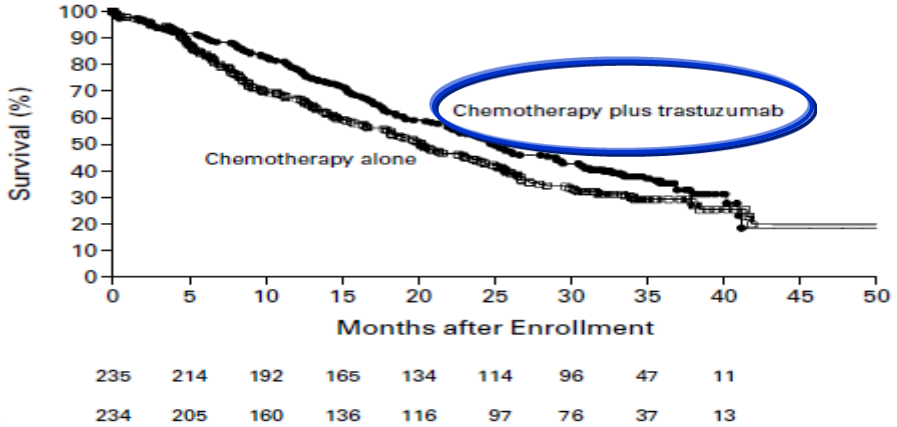
clophos-rastuzumab	143	98	40	12
d cyclo-lone	138	77	20	6

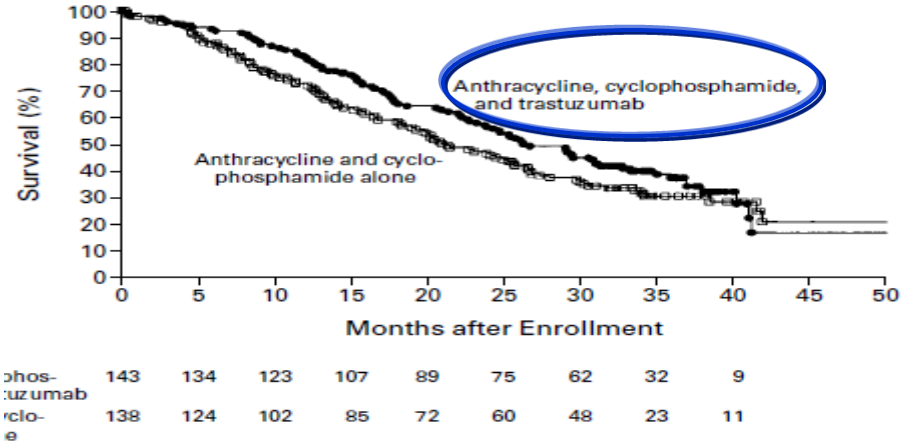
Median duration of response was 9.1 months for trastuzumab-group vs 6.1 months w/o trastuzumab

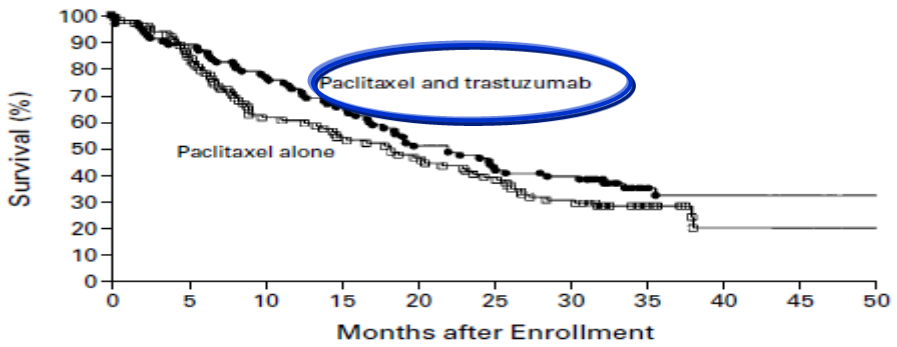


Overall survival

Reduced risk of death of 18-20%.



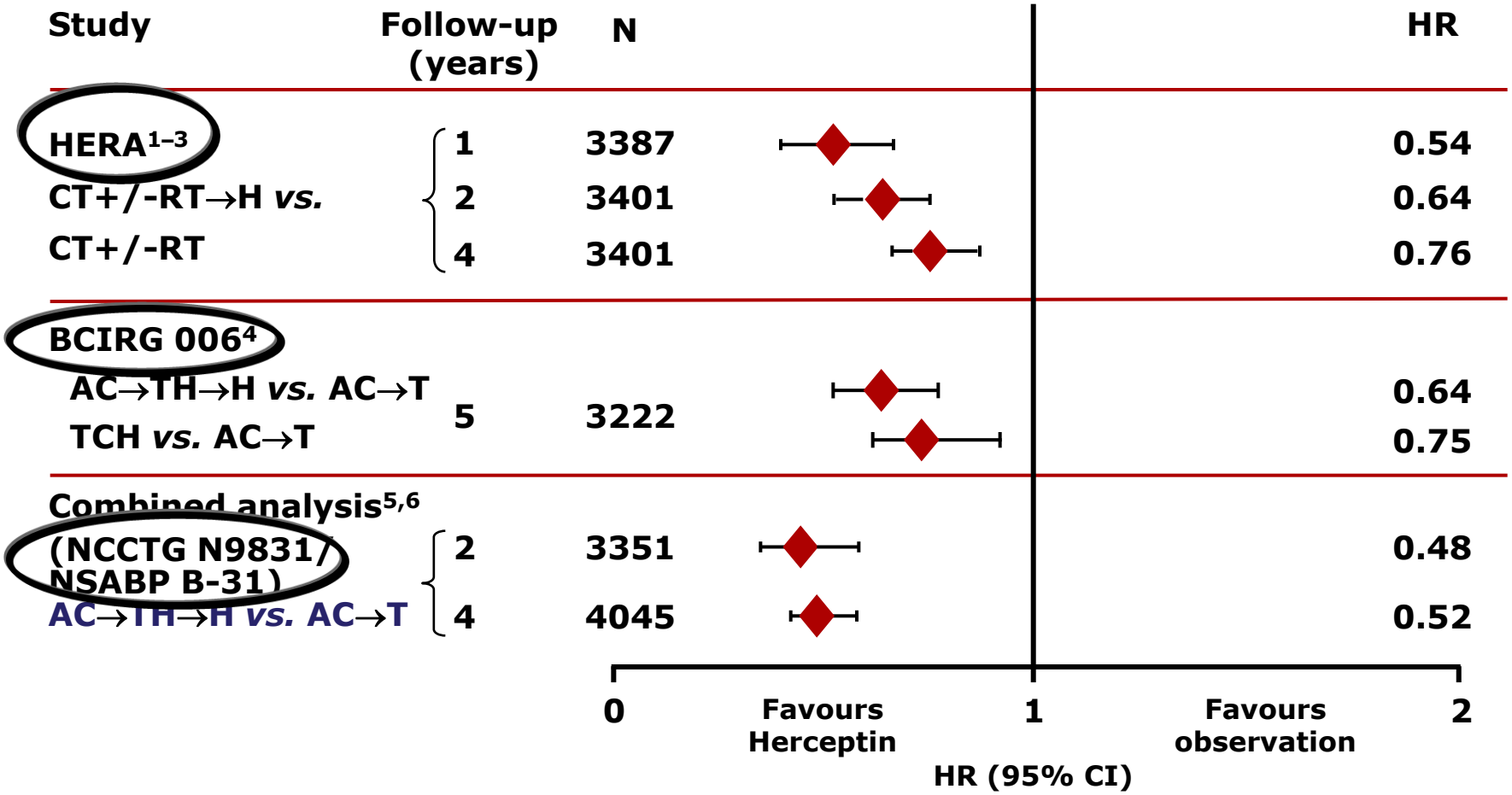




CARDIAC EVENTS IDENTIFIED IN METASTATIC BREAST CANCER trials

	H + P	P	H + AC	AC	H + D	D	ANA+H	ANA
Symptomatic heart failure	8.8	4.2	28	9.6	1.1	0	1	0
NYHA III-IV (New York Heart Association)	4	1	19	3	NR	NR	0	0

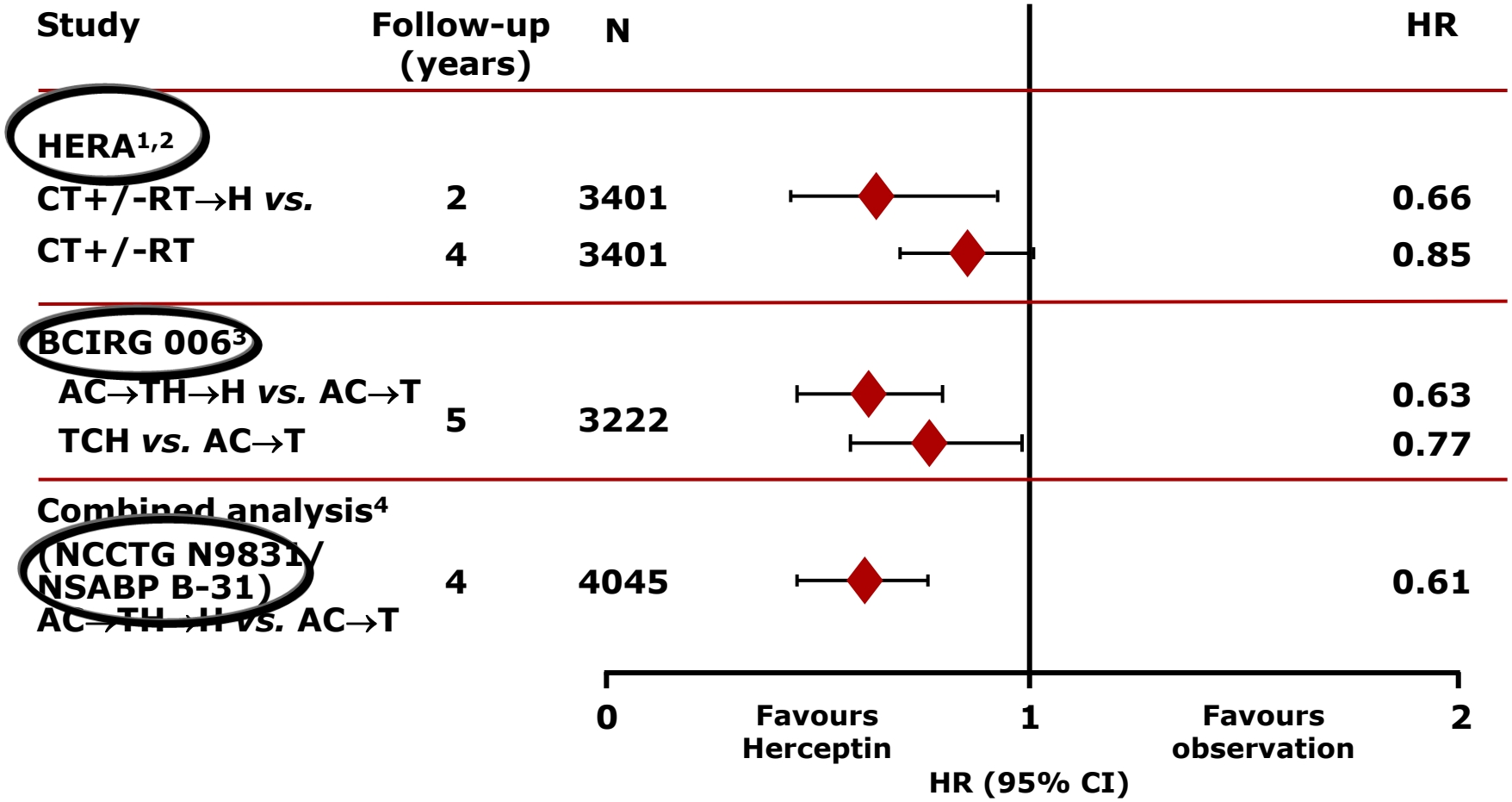
Consistent disease-free survival benefit with adjuvant Herceptin for 1 year



1. Piccart-Gebhart MJ, *et al.* 2005; 2. Smith I, *et al*. 2007; 3. Gianni L, *et al*. 2011
4. Slamon D, *et al*. 2011; 5. Romond EH, *et al*. 2005; 6. Perez EA, *et al*. 2011

HR, hazard ratio

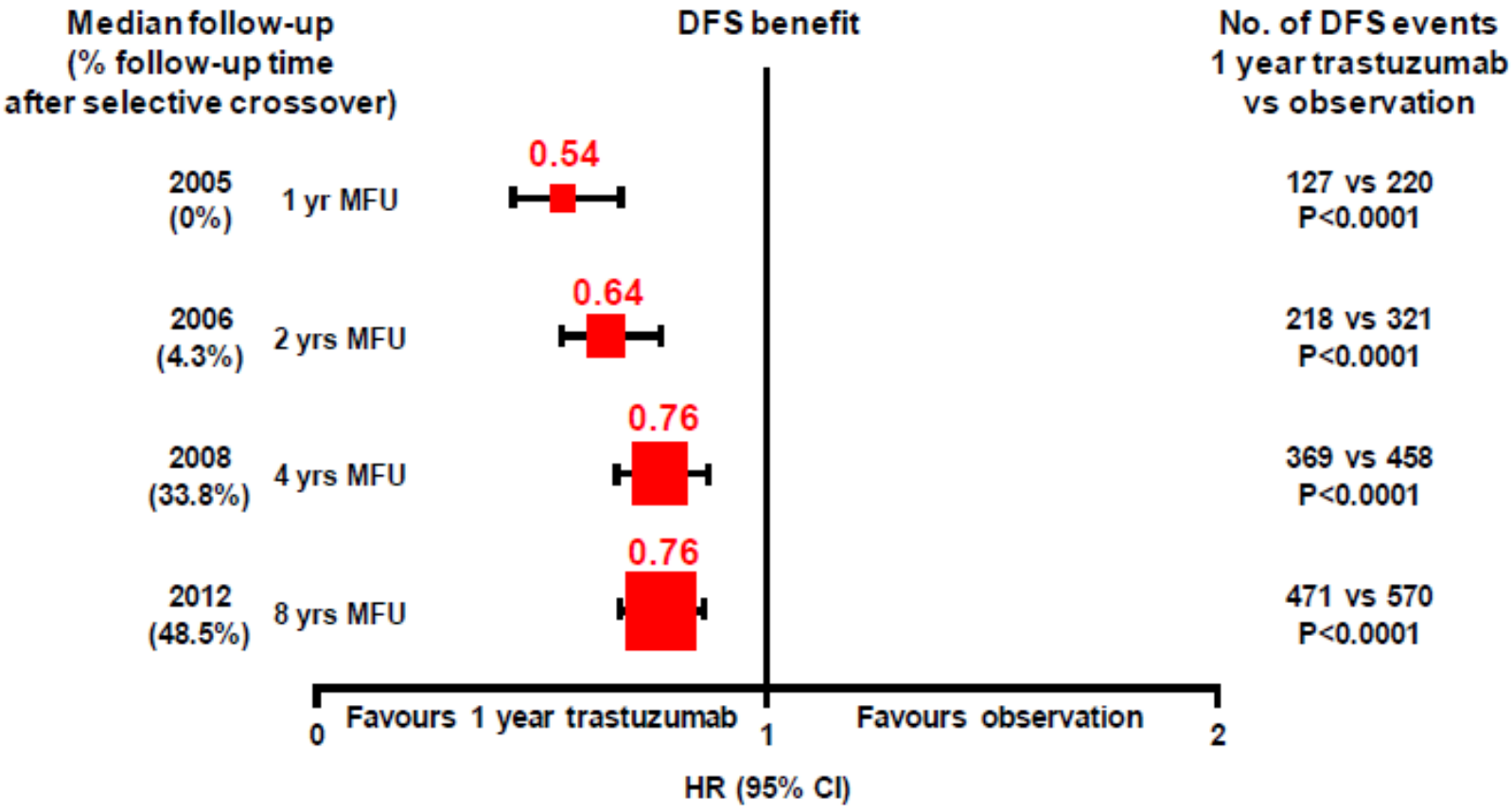
Consistent overall survival benefit with adjuvant Herceptin for 1 year



HR, hazard ratio

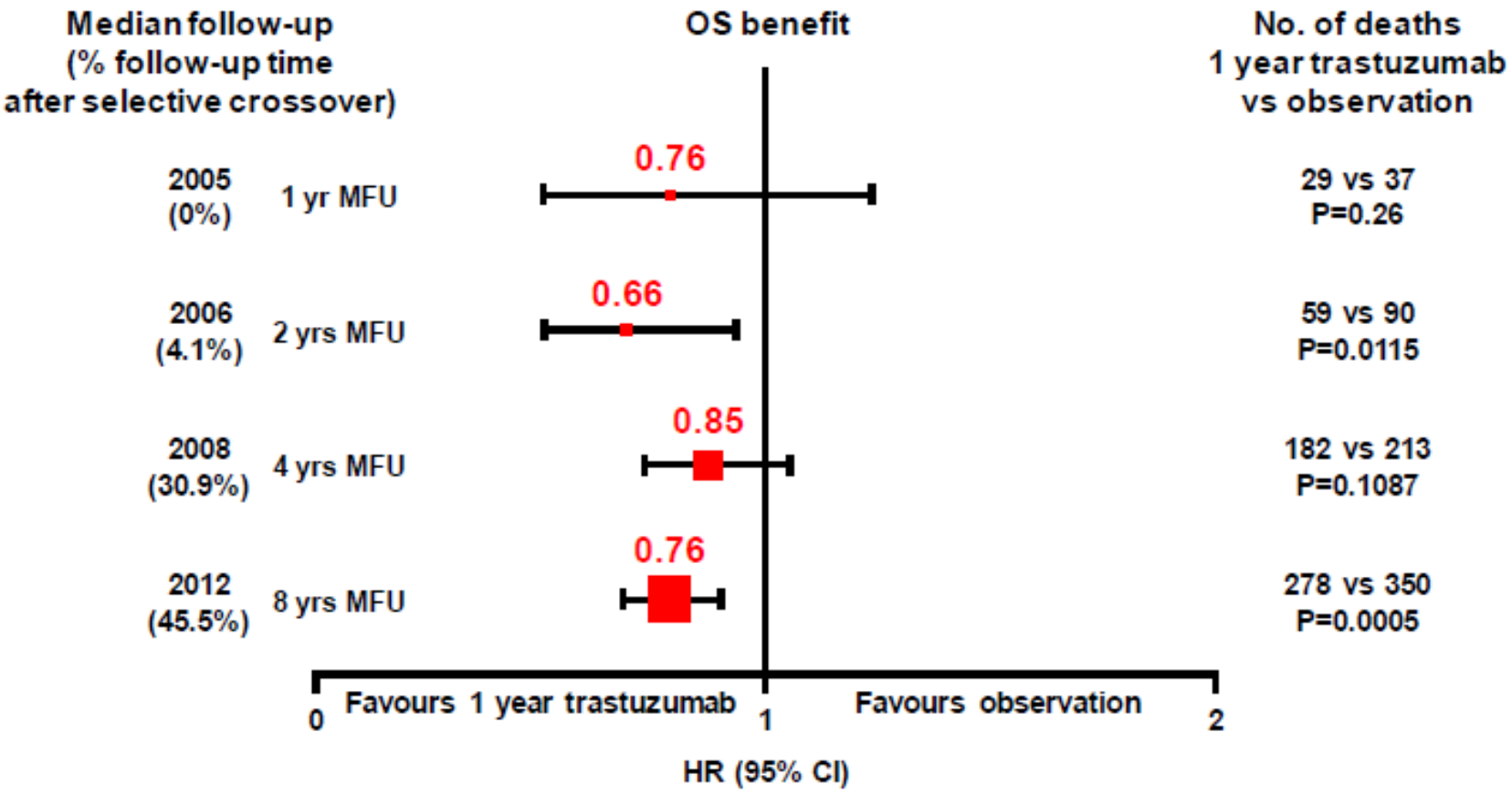
1. Smith I, *et al*. 2007; 2. Gianni L, *et al*. 2011
3. Slamon D, *et al.* 2011; 4. Perez EA, *et al.* 2011

SUMMARY OF DFS ITT ANALYSES FOR 1 YEAR TRASTUZUMAB VS. OBSERVATION ACROSS ANALYSIS TIME POINTS



Extended from Gianni et al. Lancet Oncol. 2011.

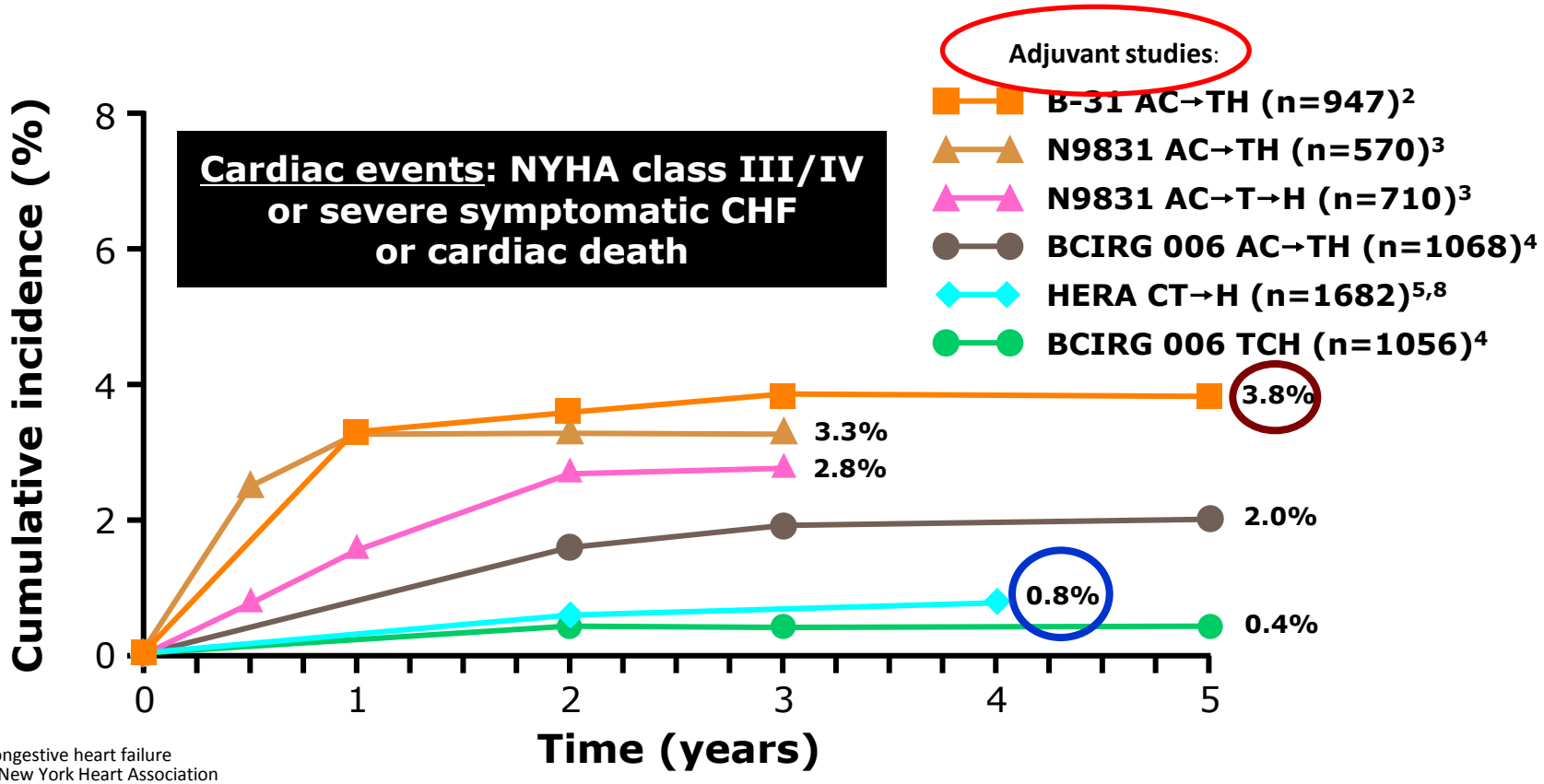
SUMMARY OF OS ITT ANALYSES FOR 1 YEAR TRASTUZUMAB VS. OBSERVATION ACROSS ANALYSIS TIME POINTS



Extended from Gianni et al. Lancet Oncol. 2011.

Herceptin has a consistent safety profile based on experience in ~1,000,000 patients[1]

- Herceptin is well tolerated with a consistent safety and tolerability profile[2–7]
- Low cumulative incidence of cardiac events after long-term follow-up[2–7]



- CHF, congestive heart failure
  NYHA, New York Heart Association

1. PSUR 03/2011; 2. Rastogi P, *et al.* 2007; 3. Perez EA, *et al.* 2008; 4. Slamon D, *et al.* 2011
5. Procter M, *et al.* 2010; 6. Gianni L, *et al.* 2011; 7. Perez EA, *et al.* 2011; 8. Suter T, *et al.* 2007

CARDIAC EVENTS IN «EARLY BREAST CANCER TRIALS»

EBC trials (1-yr trastuzumab)	Therapy	Number of patients	% Asymptomatic LVEF decline	% Severe CHF	Cardiac death
HERA	H (1 year)	1678	3	0.6	0
NSABP B-31	AC--PH	947	NR	3.8 cumulative 5yr incidence	0
NCCTG N9831	AP--PH	570	NR	3.3 cumulative 3yr incidence	0
BCIRG 006	AC--DH	1068	18	1.9	0
BCIRG 006	DCarboH	1056	8.6	0.4	0

Slamon 2006; Rastogy 2007; Smith 2007; Perez 2008

	Recovery (% of patients)	Median Time (days)
Cardiac death	-	-
Severe CHF	80	124
Symptomatic CHF	67	151
Confirmed significant LVEF drop	69	192

CARDIAC ADVERSE EVENTS IN HERA trial

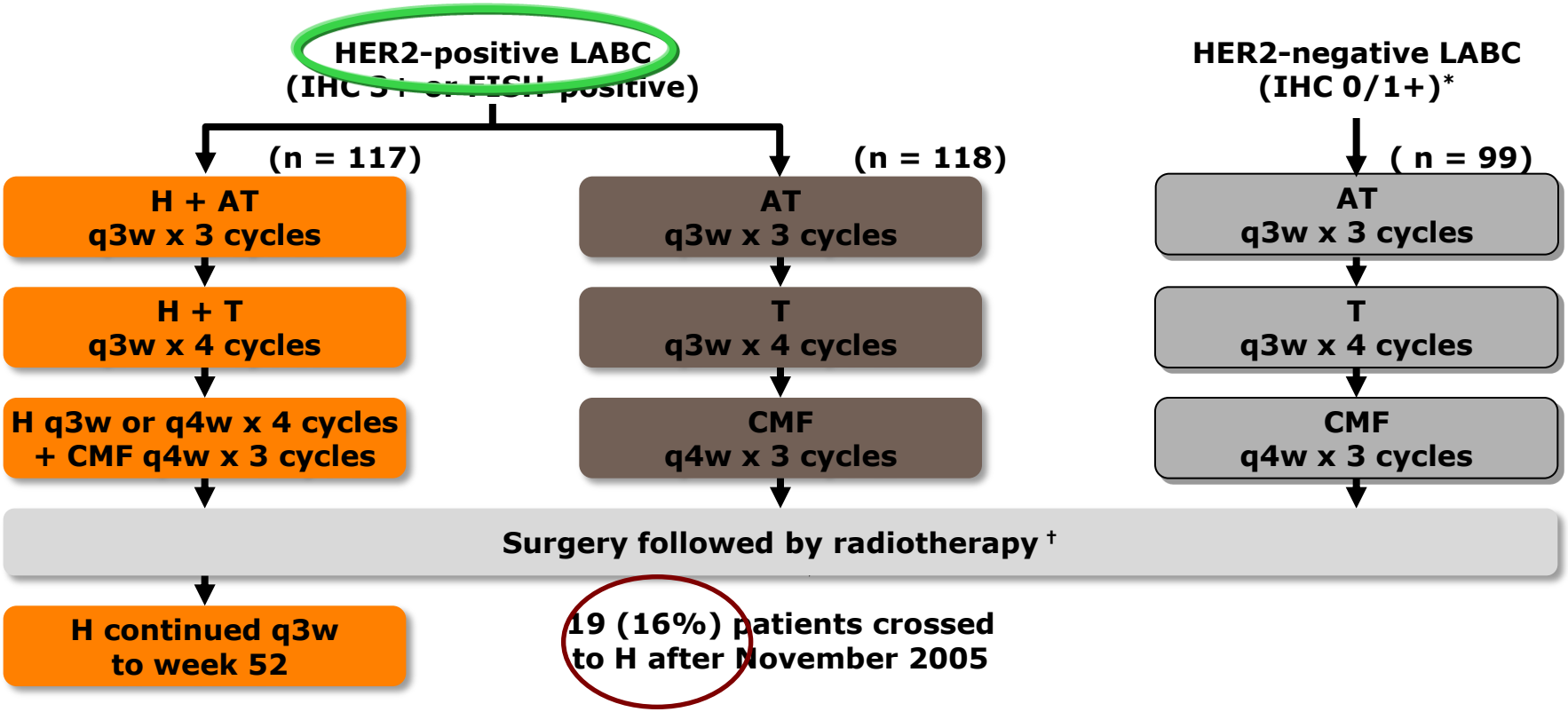
NOAH: Inclusion criteria

- Histologically proven locally advanced breast cancer (T3N1/T4) or any T plus N2/N3, or any T plus involvement of ipsilateral supraclavicular nodes
- HER2-positive disease was defined as IHC 3+ overexpression or HER2 amplification by FISH according to a central laboratory
  - For the observational arm, HER2-negative disease was defined as IHC 0 or 1+ on the basis of local laboratory testing
- Mandatory hormone receptor assessment
- LVEF ≥55%

Gianni L, Eiermann W, Semiglazov V, *et al. Lancet* 2010; 375:377–384.

NOAH (MO16432): Study design

An international, open-label, Phase III study of neoadjuvant–adjuvant trastuzumab in patients with locally advanced or inflammatory HER2-positive breast cancer

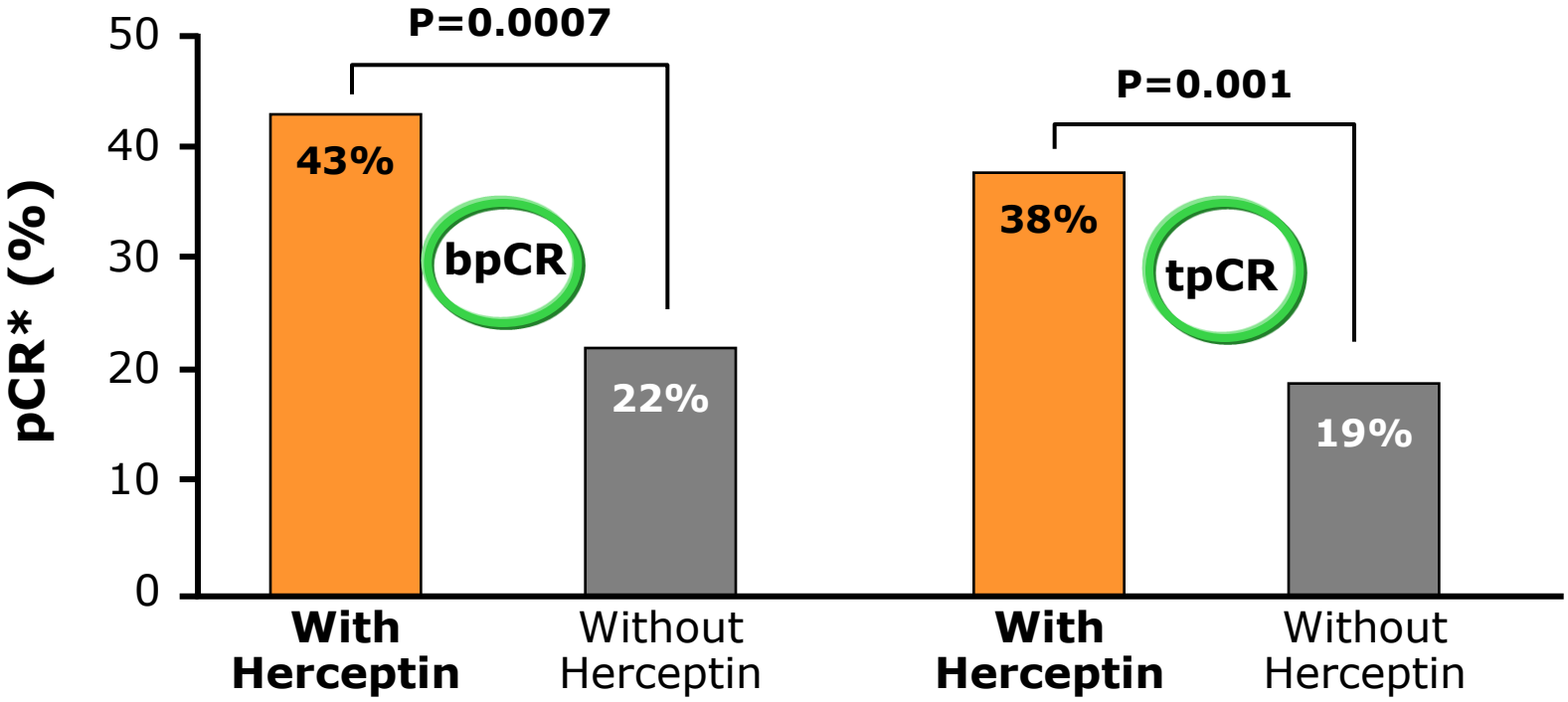


•H, trastuzumab (8 mg/kg loading dose then 6 mg/kg);
AT, doxorubicin (60 mg/m^2), paclitaxel (150 mg/m^2); T, paclitaxel (175 mg/m^2);
CMF, cyclophosphamide, methotrexate and fluorouracil 5-FU
* A separate treatment group of HER2-negative patients received chemotherapy only;
•† Hormone receptor-positive patients received adjuvant tamoxifen.

- Gianni et al. ASCO 2013 – abs 504
- Gianni L, Eiermann W, Semiglazov V, *et al. Lancet* 2010; 375:377–384.

NOAH neoadjuvant–adjuvant study: Significant improvement in pCR rates with Herceptin

Significant improvement in pCR with addition of Herceptin to chemotherapy in HER2-positive treatment groups

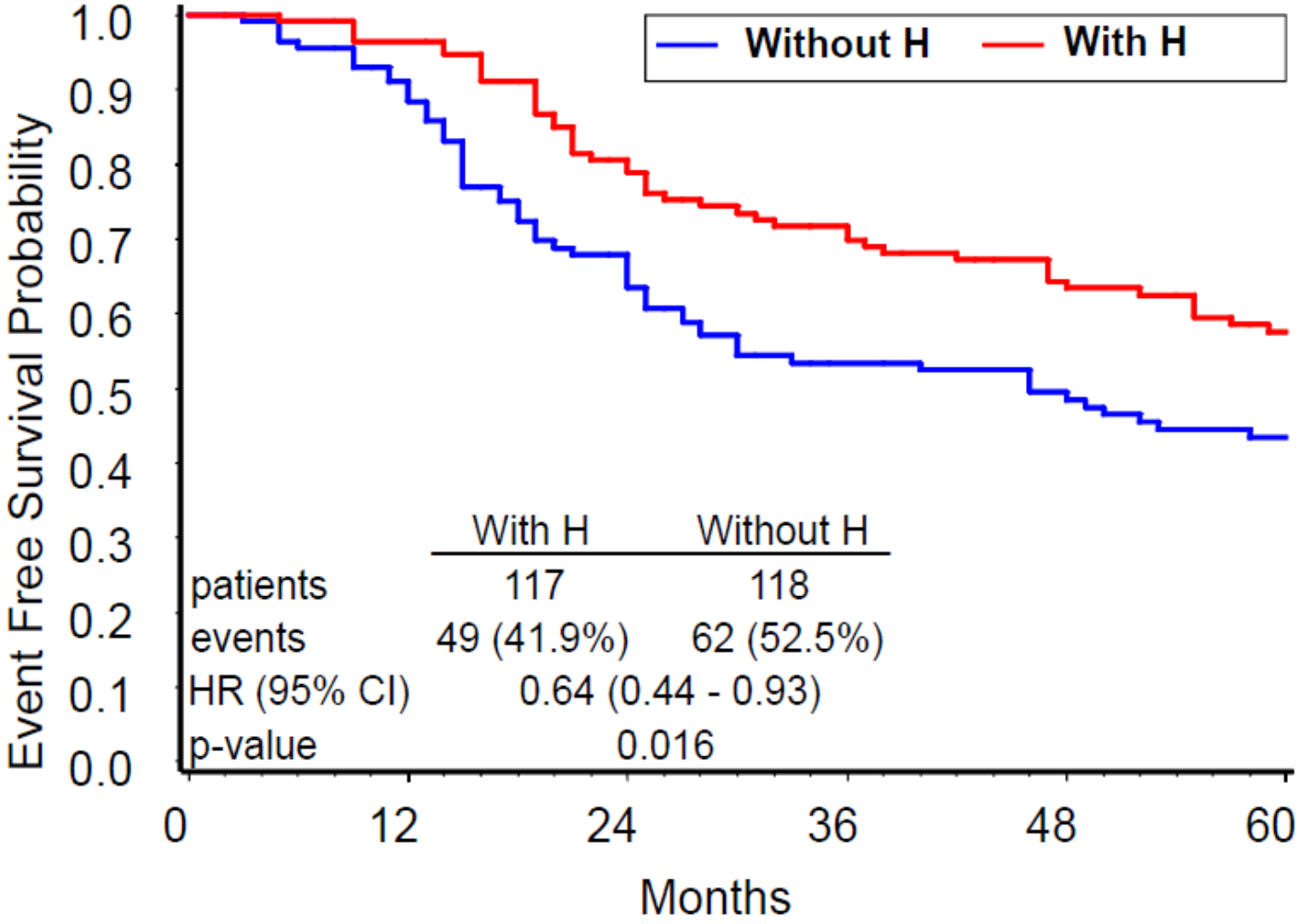


pCR, pathological complete response
bpCR, pathological complete response in breast tissue;
tpCR, total pathological complete response (in breast and axillary nodes)
*Absence of invasive tumour cells

Gianni L, *et al*. 2010

NOAH: EFS (primary endpoint) in HER2-positive ITT population (follow-up data)

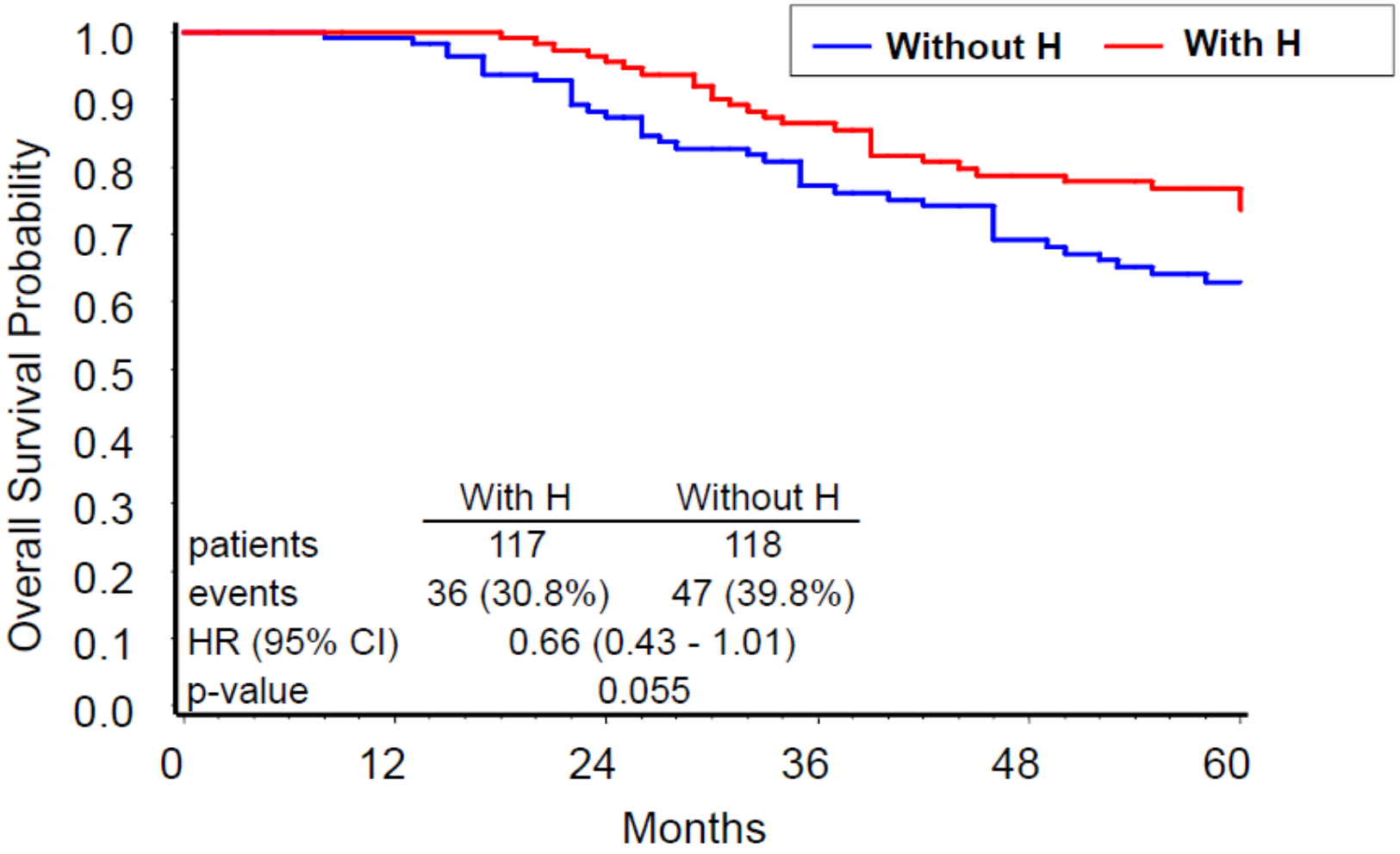
Significant EFS benefit with the addition of trastuzumab to chemotherapy in HER2-positive patients



- Gianni et al. ASCO 2013 – abs 504

NOAH: Overall survival in the HER2-positive ITT population (follow-up data)

Trend towards overall survival benefit with the addition of trastuzumab to chemotherapy in HER2-positive patients

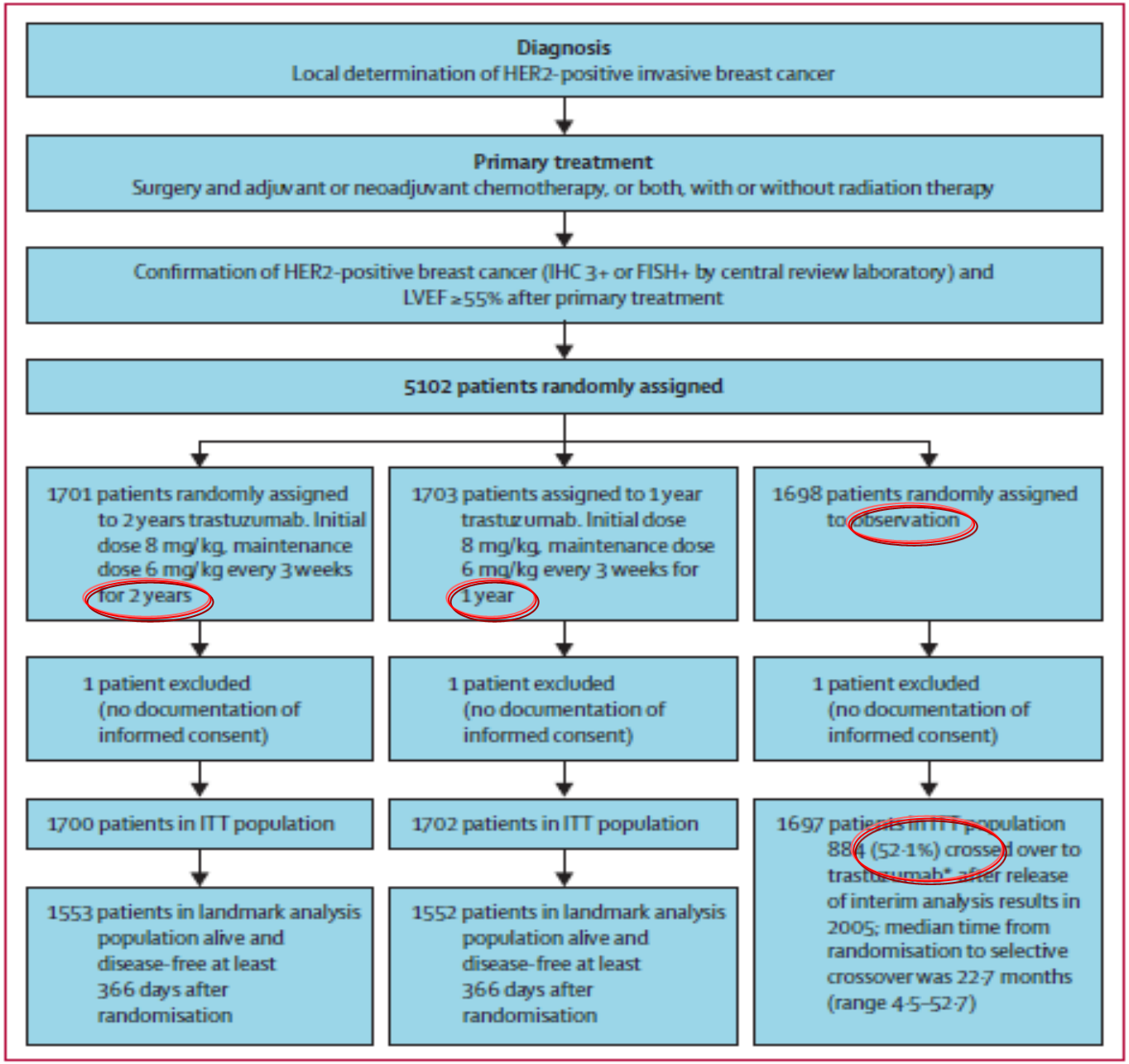


- Gianni et al. ASCO 2013 – abs 504

2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial

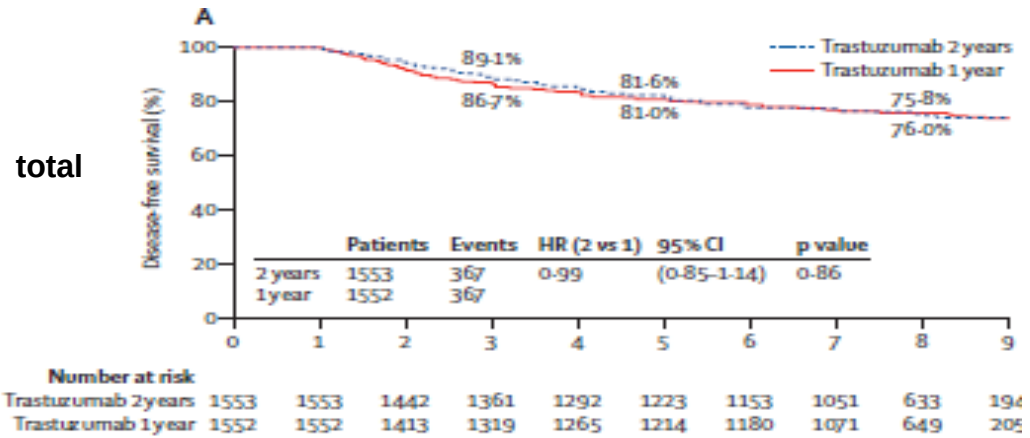
Aron Goldhirsch, Richard D Gelber, Martine J Piccart-Gebhart, Evandro de Azambuja, Marion Procter, Thomas M Suter, Christian Jackisch, David Cameron, Harald A Weber, Dominik Heinzmann, Lissandra Dal Lago, Eleanor McFadden, Mitch Dowsett, Michael Untch, Luca Gianni, Richard Bell, Claus-Henning Köhne, Anita Vindevoghel, Michael Andersson, A Murray Brunt, Douglas Otero-Reyes, Santai Song, Ian Smith, Brian Leyland-Jones*, Jose Baselga*, for the Herceptin Adjuvant (HERA) Trial Study Team

Lancet 2013; 382: 1021–28

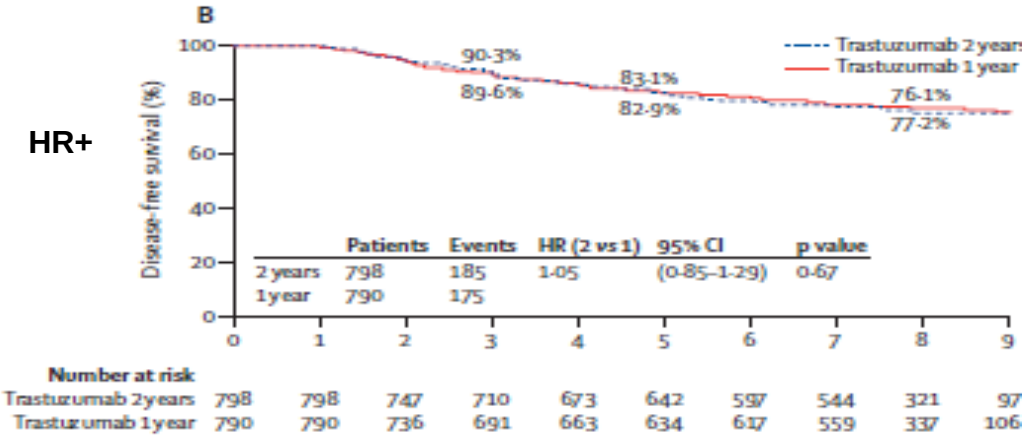

Diagnosis
Local determination of HER2-positive invasive breast cancer
Primary treatment
Surgery and adjuvant or neoadjuvant chemotherapy, or both, with or without radiation therapy
Confirmation of HER2-positive breast cancer (IHC 3+ or FISH+ by central review laboratory) and LVEF ≥55% after primary treatment
5102 patients randomly assigned
1701 patients randomly assigned to 2 years trastuzumab. Initial dose 8 mg/kg, maintenance dose 6 mg/kg every 3 weeks for 2 years
1703 patients assigned to 1 year trastuzumab. Initial dose 8 mg/kg, maintenance dose 6 mg/kg every 3 weeks for 1 year
1698 patients randomly assigned to observation
1 patient excluded (no documentation of informed consent)
1 patient excluded (no documentation of informed consent)
1 patient excluded (no documentation of informed consent)
1700 patients in ITT population
1702 patients in ITT population
1697 patients in ITT population
884 (52·1%) crossed over to trastuzumab* after release of interim analysis results in 2005; median time from randomisation to selective crossover was 22·7 months (range 4·5–52·7)
1553 patients in landmark analysis population alive and disease-free at least 366 days after randomisation
1552 patients in landmark analysis population alive and disease-free at least 366 days after randomisation

HERA-results: 1yr vs 2yrs

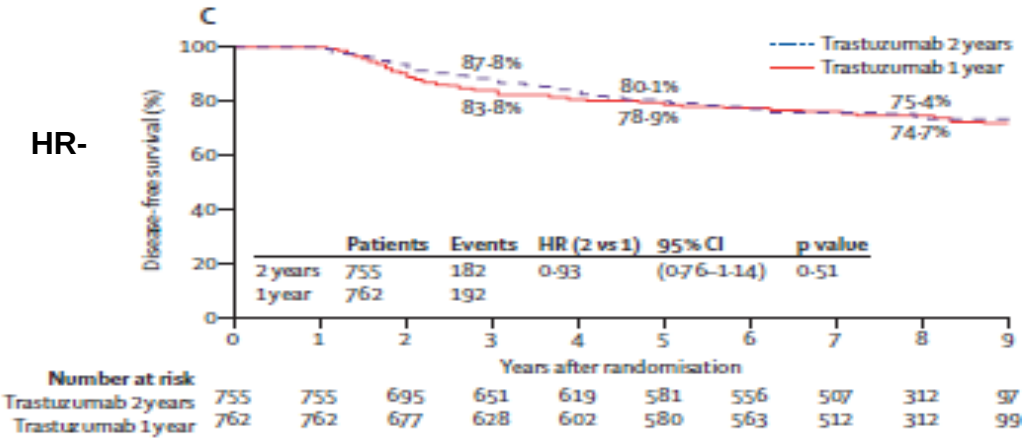
total



HR+



HR-



FinHER study

- Adjuvant setting

- Docetaxel/vinorelbina + trastuzumab for 9 weeks -->FEC

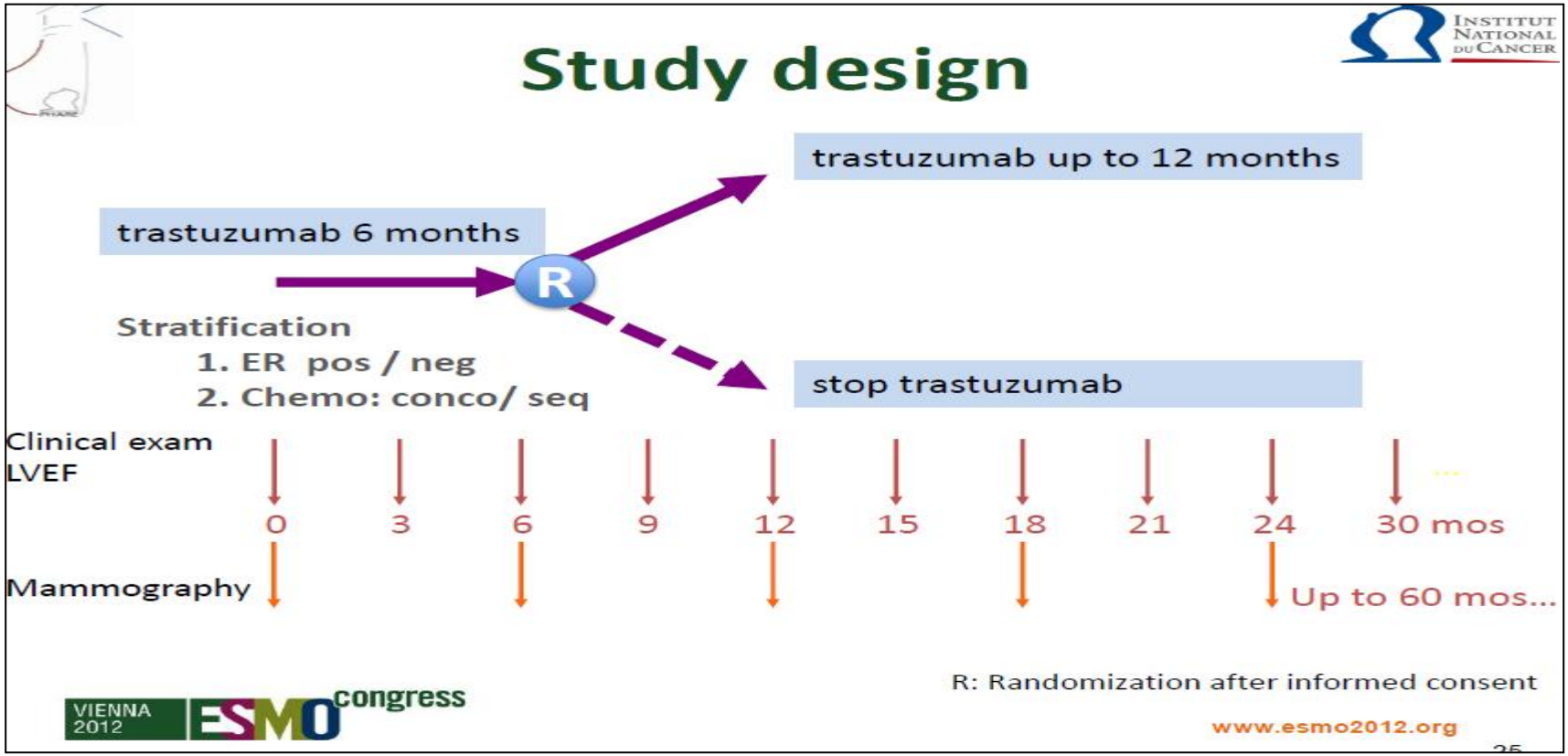
Table 4. FinHer: Adjuvant chemotherapy plus short trastuzumab; updated (5-year) results in HER-2+ patients

	Chemo	Chemo + trastuzumab	HR (95% CI)	*p*-value
Distant disease-free survival, %	73.0	83.3	0.65 (0.38, 1.12)	0.12
Overall survival, %	82.3	91.3	0.55 (0.27, 1.11)	0.094

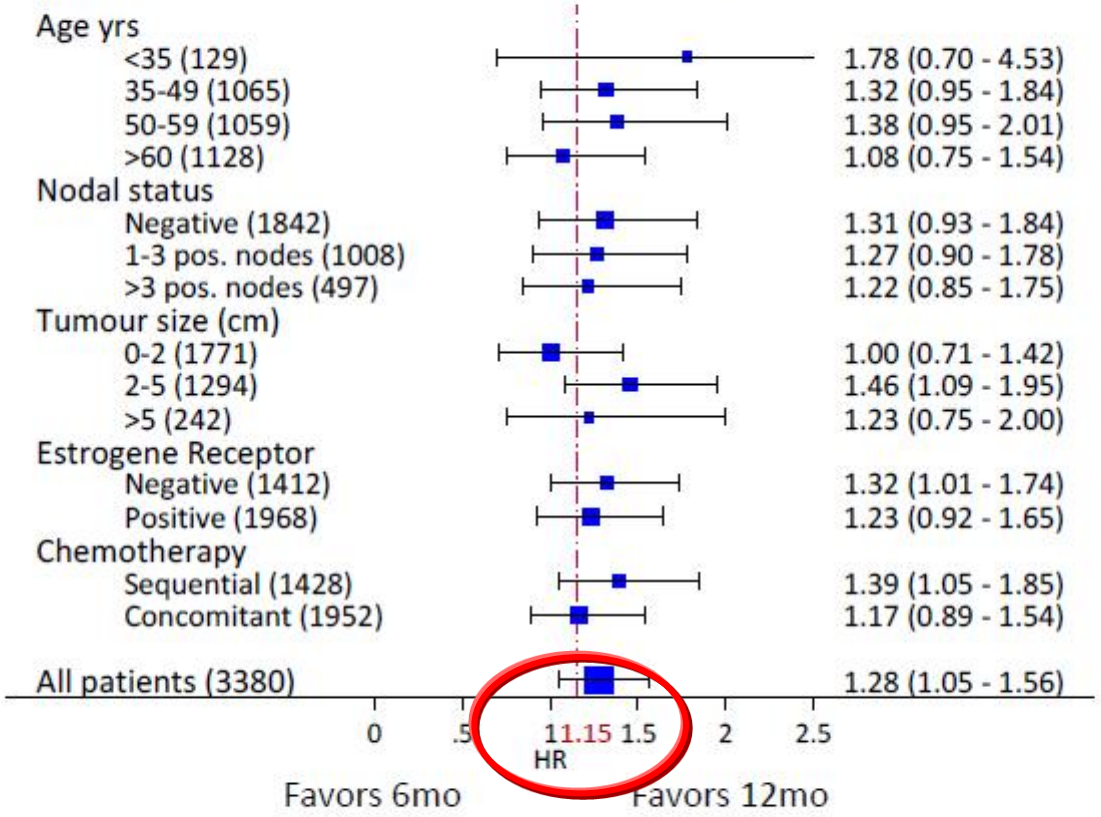
Based on Joensuu H, Bono P, Kataja V et al. Fluorouracil, epirubicin, and cyclophosphamide with either docetaxel or vinorelbine, with or without trastuzumab, as adjuvant treatment of breast cancer: Final results of the FinHer Trial. J Clin Oncol 2009;27:5685–5692.

(only 200 patients treated: underpowered trial)

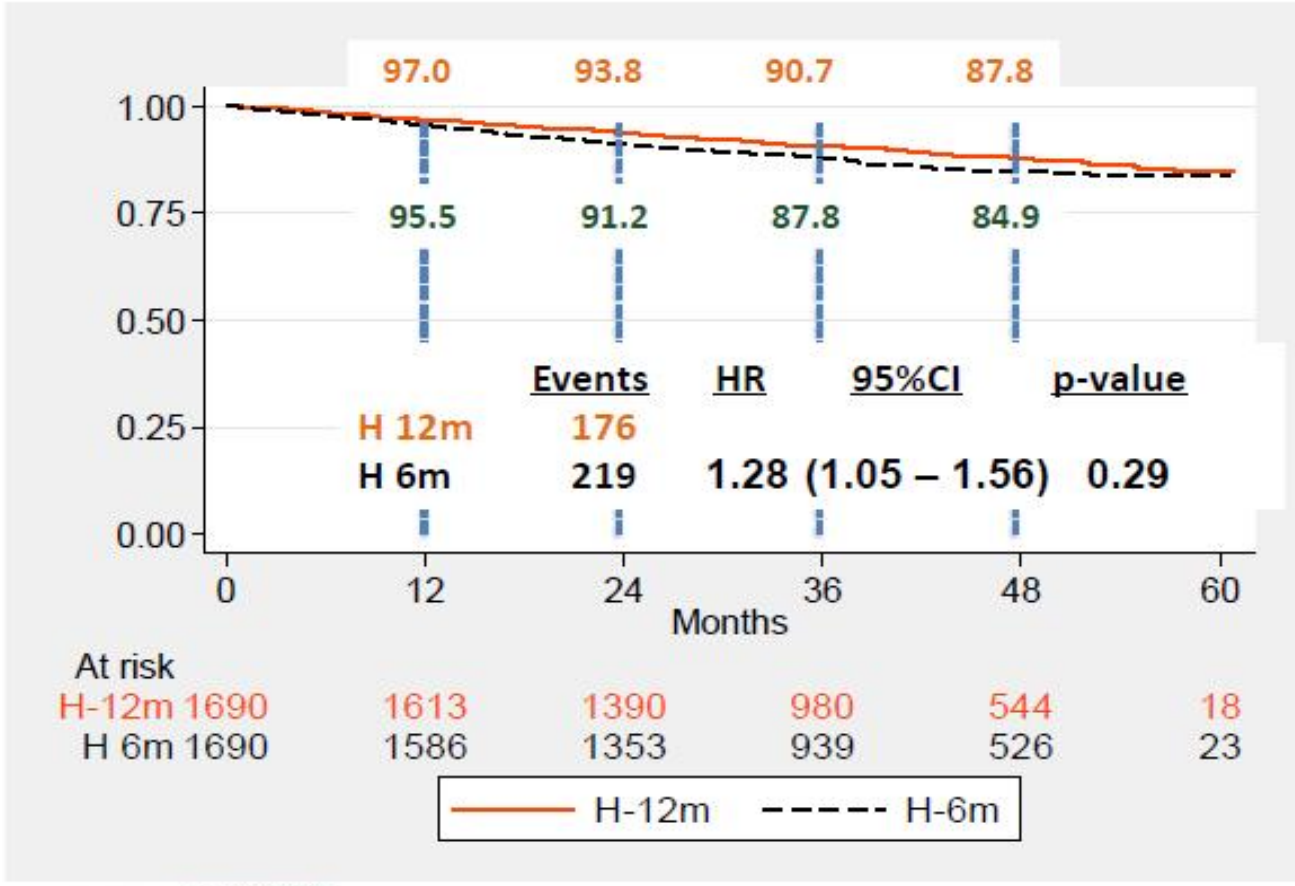

Protocol of
Herceptin*
Adjuvant with
Reduced
Exposure
PHARE
INSTITUT NATIONAL DU CANCER
PHARE* Trial results comparing 6 to 12 months of trastuzumab in adjuvant early breast cancer
Xavier Pivot, Gilles Romieu, Hervé Bonnefoi, Jean-Yves Pierga, Pierre Kerbrat, Thomas Bachelot, Alain Lortholary, Marc Espié, 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.
VIENNA 2012 ESMO congress
*lighthouse in French
www.esmo2012.org


Study design
INSTITUT NATIONAL DU CANCER
trastuzumab up to 12 months
trastuzumab 6 months
R
Stratification
1. ER pos / neg
2. Chemo: conco/ seq
stop trastuzumab
Clinical exam
LVEF
0 3 6 9 12 15 18 21 24 30 mos
Mammography
Up to 60 mos...
R: Randomization after informed consent
VIENNA 2012 ESMO congress
www.esmo2012.org

DFS Forest plot

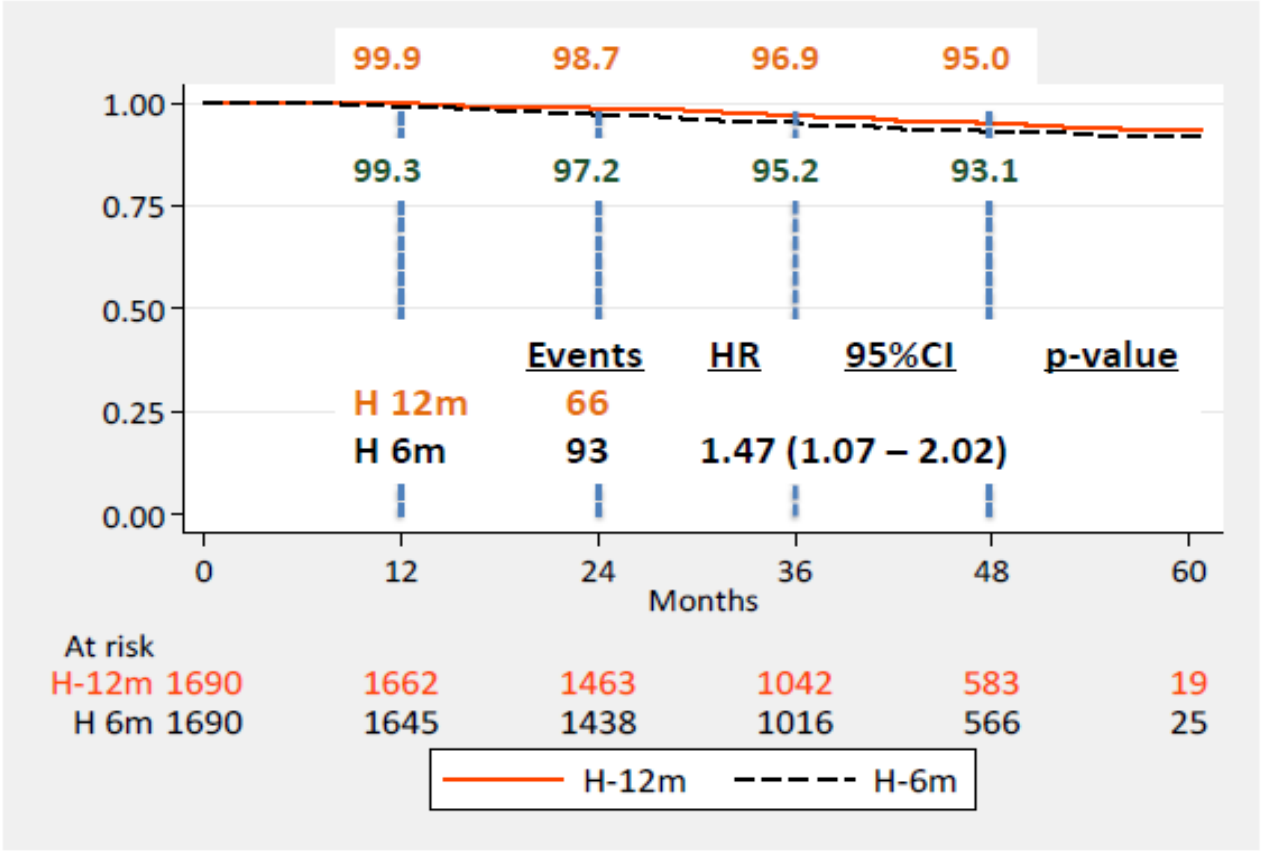


Disease Free Survival



Overall Survival

42.5mos. median FU



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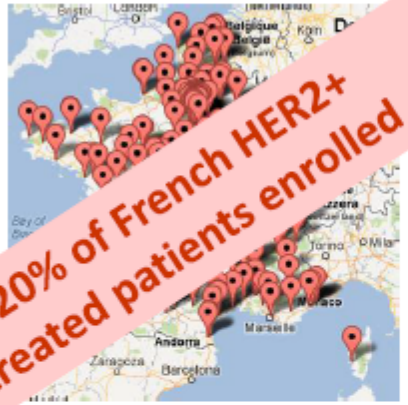
www.esmo2012.org

* Cox model stratified by ER status and concomitant chemotherapy

Study information

Activated: 30/05/2006



Randomization
3384 patients

4 patients excluded from analysis
1 Informed consent not signed
1 Randomized twice
2 HER2 negative after FISH testing

Trastuzumab 12 months
1690 patients

Trastuzumab 6 months
1690 patients

- May 28th 2010 – IDMC meeting

"After careful thought and lengthy debate we recommend that entry to the trial be suspended. We do not recommend, at this time, a crossover to a longer duration of intervention for the 6 month group but would reserve the option of such a recommendation for the future, dependent on how the data develop"

VIENNA 2012 ESMO congress

Closed: 09/07/2010
Database locked: 31/07/2012

www.esmo2012.org

original article

Annals of Oncology 00: 1–8, 2015
doi:10.1093/annonc/mdv213

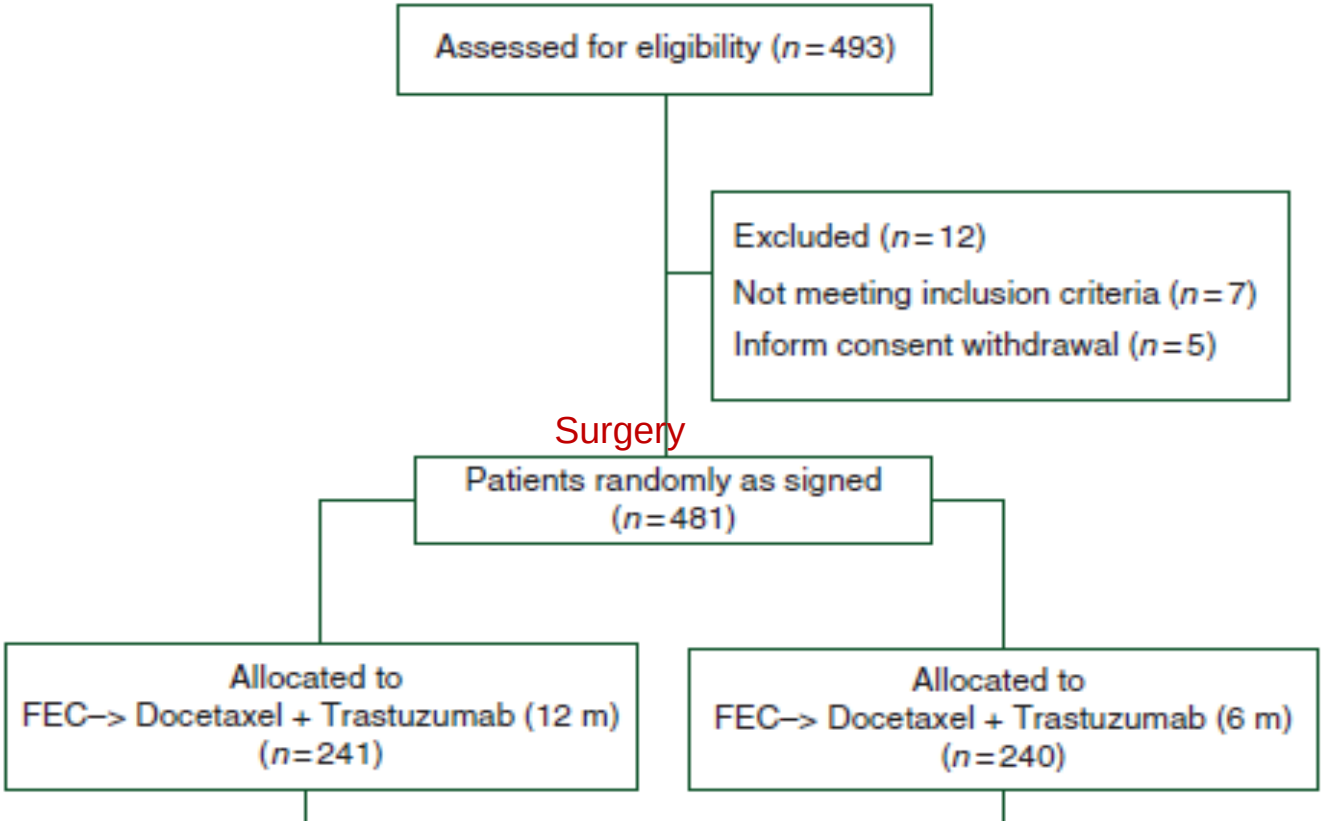
Six versus 12 months of adjuvant trastuzumab in combination with dose-dense chemotherapy for women with HER2-positive breast cancer: a multicenter randomized study by the Hellenic Oncology Research Group (HORG)

D. Mavroudis[1*], E. Saloustros[2], N. Malamos[3], S. Kakolyris[4], I. Boukovinas[5], P. Papakotoulas[6], N. Kentepozidis[7], N. Ziras[8] & V. Georgoulias[9], on behalf of the Breast Cancer Investigators of the Hellenic Oncology Research Group (HORG), Athens, Greece

[1]*Department of Medical Oncology, University General Hospital of Heraklion, Heraklion;* [2]*Oncology Unit, General Hospital of Heraklion "Venizelio";* [3]*Department of Medical Oncology, Elena Venizelou Hospital, Athens;* [4]*Department of Medical Oncology, University General Hospital of Alexandroupolis, Alexandroupolis;* [5]*Department of Medical Oncology, Bioklinic of Thessaloniki, Thessaloniki;* [6]*Department of Medical Oncology, Theageneio Hospital, Thessaloniki;* [7]*Department of Medical Oncology, 251 Airforce General Hospital, Athens;* [8]*Department of Medical Oncology, Metaxa Hospital, Athens;* [9]*Department of Medical Oncology, University of Crete, School of Medicine, Heraklion, Greece*

Received 19 January 2015; revised 13 April 2015; accepted 23 April 2015

STUDY DESIGN



TREATMENT SCHEDULE

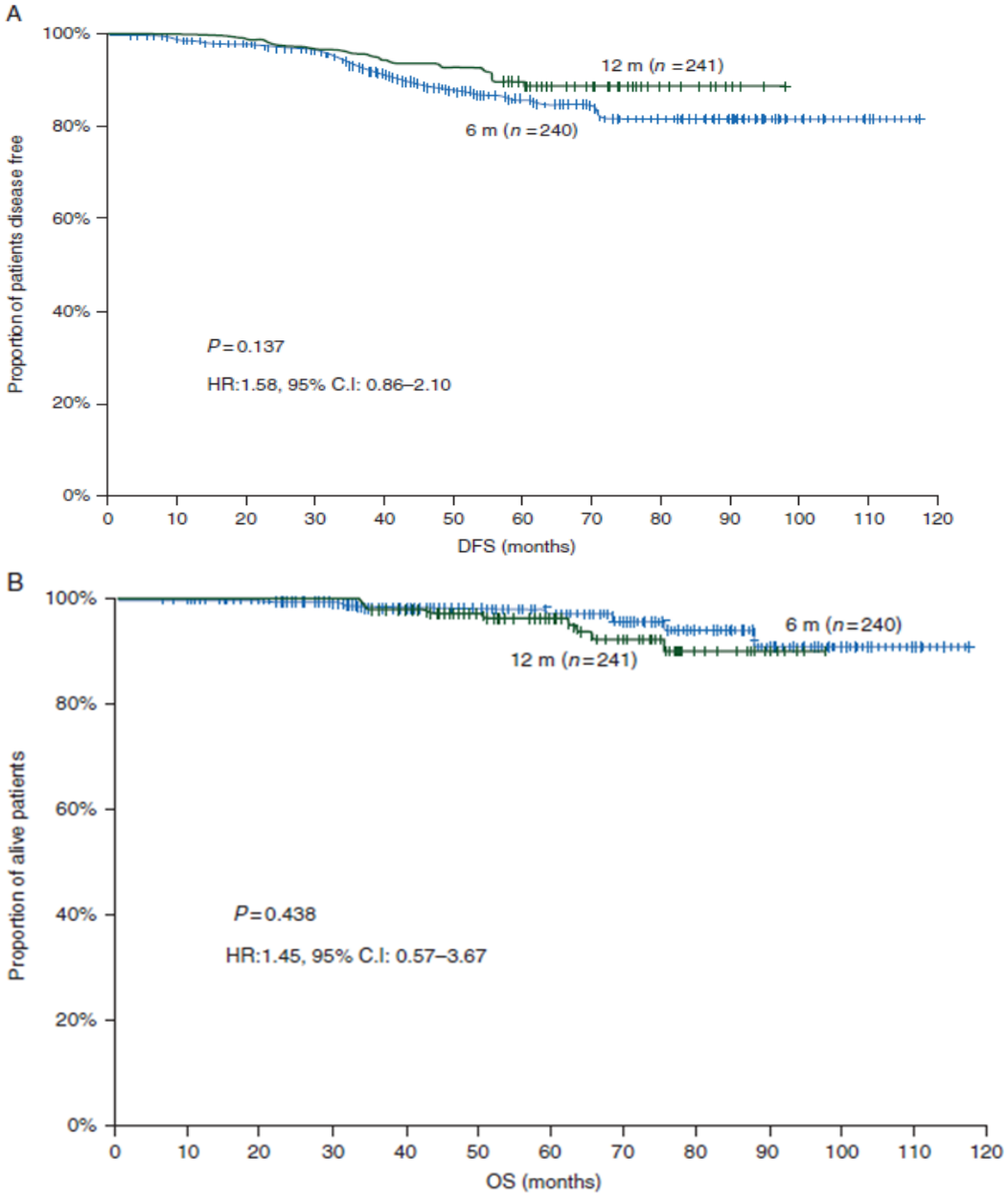
Epirubicine 75mg/mq/iv/q 2wk; Cyclophoshamide 700mg/mq/iv/q 2wks; 5-fluorouracil 700 mg/mq/iv/q 2wks

Docetaxel 75 mg/mq/iv/q 2wks;Trastuzumab 8mg/kg→6mg/Kg/iv/ q2wks, maintenance 6mg/Kg/iv/q3wk

Filgrastim 5ug/Kg days 3-10

Radiation and hormonal therapy following standard care.

RESULTS


A
100%
80%
60%
40%
20%
0%
Proportion of patients disease free
12 m (n =241)
6 m (n =240)
P=0.137
HR:1.58, 95% C.I: 0.86–2.10
0
10
20
30
40
50
60
70
80
90
100
110
120
DFS (months)
B
100%
80%
60%
40%
20%
0%
Proportion of alive patients
6 m (n=240)
12 m (n=241)
P=0.438
HR:1.45, 95% C.I: 0.57–3.67
0
10
20
30
40
50
60
70
80
90
100
110
120
OS (months)

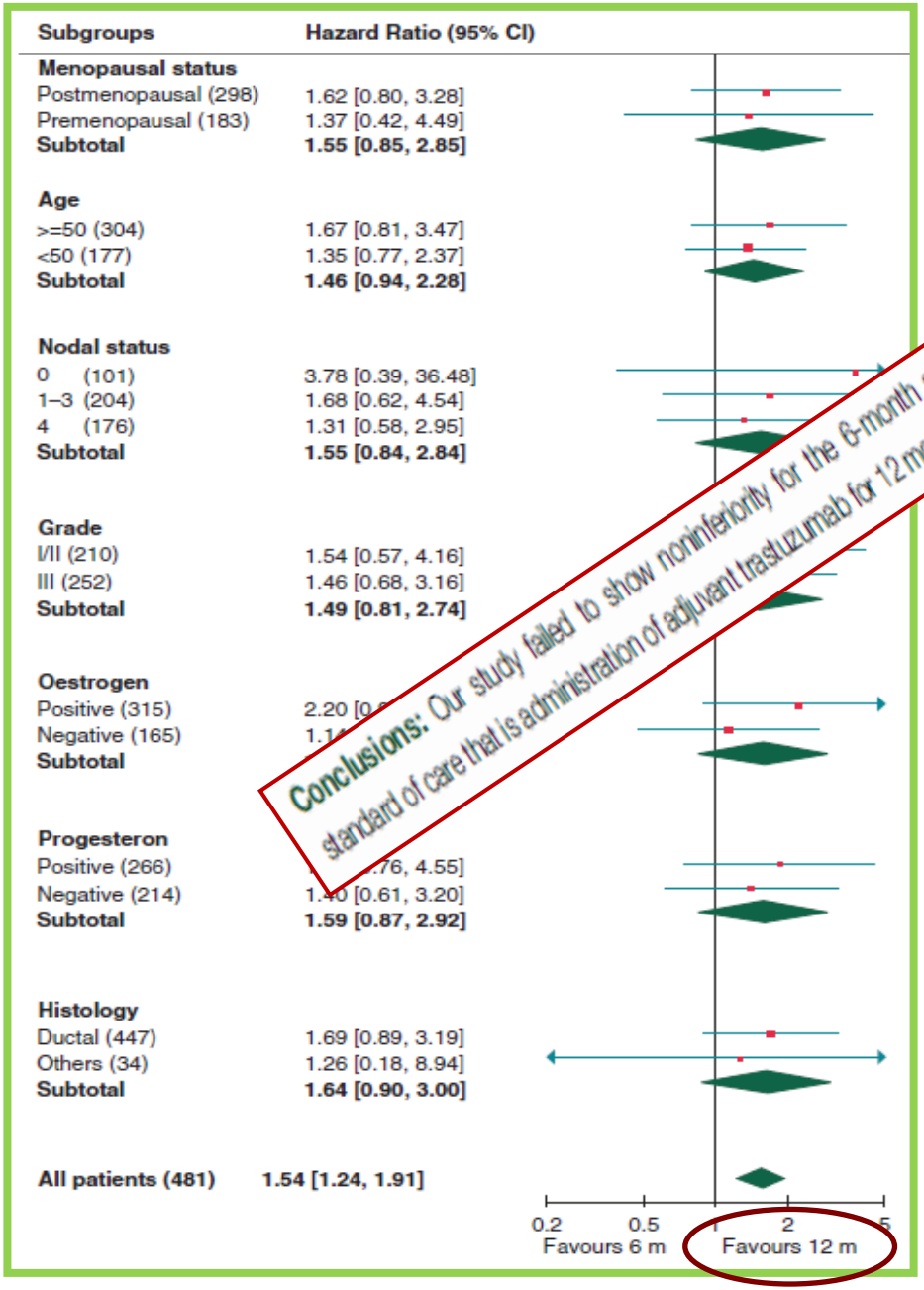


Table 2. Grade II–IV adverse events

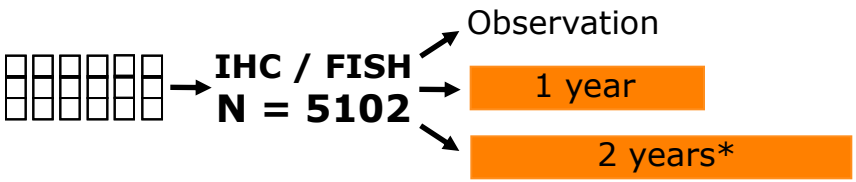
	Treatment groups			
	Trastuzumab 6 months (*N* = 241)		Trastuzumab 6 months (*N* = 240)	
	Grade II–IV		Grade II–IV	
	n	%	*n*	%
	44	18.2	47	19.5
Neutropenia	1	0.4	1	0.4
Thrombocytopenia	2	0.8	3	1.2
Vomiting	13	5.4	14	5.8
Diarrhea	5	2.0	8	3.2
Neurosensory	3	1.2	1	0.4
Allergy	3	1.2	5	2.0
Skin/nail toxicity	5	2.1	–	–
Hand/foot	7	2.8	3	1.2
Cardiotoxicity	–	–	2	0.8

Conclusions: Our study failed to show noninferiority for the 6-month arm. The results further support the current standard of care that is administration of adjuvant trastuzumab for 12 months.

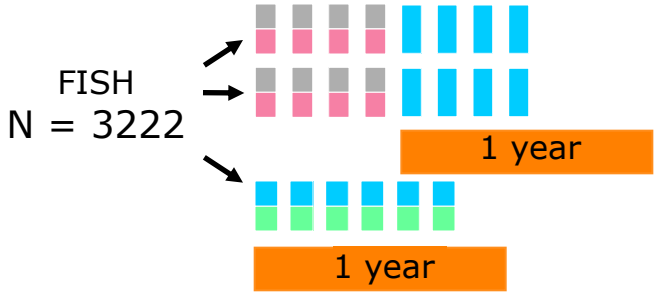
Figure 3. Univariate forest plot including patient, disease, and treatment characteristics related to disease-free survival.

Four pivotal trials have established adjuvant Herceptin for 1 year as the standard of care in HER2-positive EBC

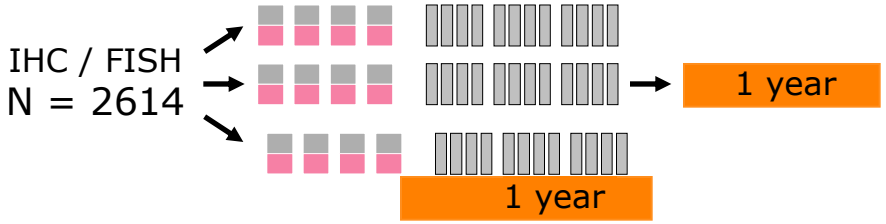
HERA (ex-USA)–Gianni L, *et al*. 2011



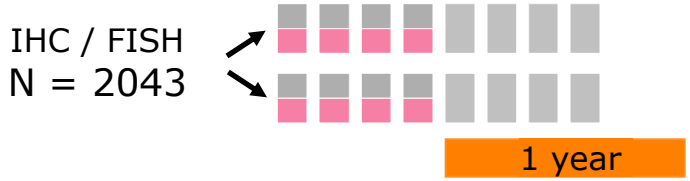
BCIRG 006 (global)–Slamon D, *et al.* 2011



NCCTG N9831 (USA)-Perez EA, *et al.* 2011



NSABP B-31 (USA)-Perez EA, *et al.* 2011



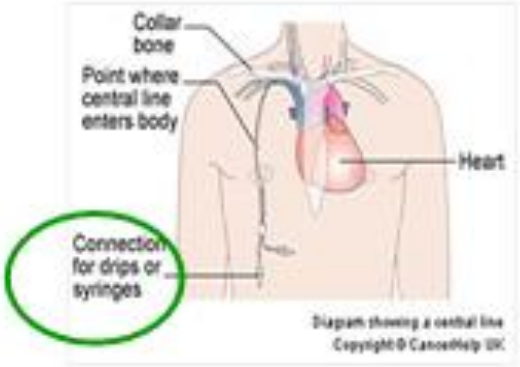
Chemotherapy +/- RT | Doxorubicin + cyclophosphamide | Docetaxel | Docetaxel + carboplatin | **Herceptin** | Paclitaxel

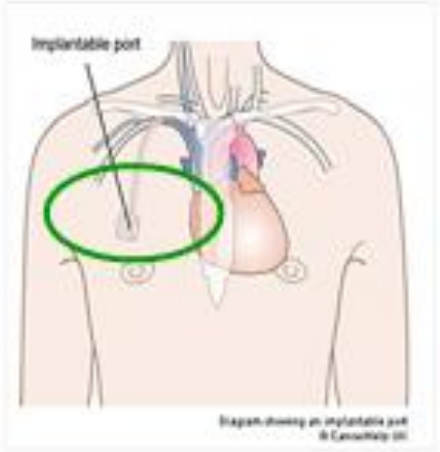
EBC, early breast cancer; IHC, immunohistochemistry; FISH, fluorescence *in situ* hybridisation
*HERA 2-year data are pending

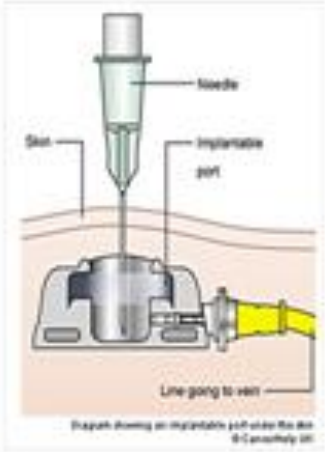
Cosa comporta per la paziente

- **Prelievi più volte/mese**
- **Accessi ambulatoriali più volte/mese**
- **Permanenza in ambulatorio da 30 minuti ad alcune ore**
- **Posizionamento di accessi venosi centrali**

(chemioterapie per via ev)







Subcutaneous versus intravenous administration of (neo)adjuvant trastuzumab in patients with HER2-positive, clinical stage I–III breast cancer (HannaH study): a phase 3, open-label, multicentre, randomised trial

Gustavo Ismael, Roberto Hegg, Susanne Muehlbauer, Dominik Heinzmann, Bert Lum, Sung-Bae Kim, Tadeusz Pienkowski, Mikhail Lichinitser, Vladimir Semiglazov, Bohuslav Melichar, Christian Jackisch

Panel: Research in context

Systematic review

The standard route of administration of trastuzumab is by intravenous injection. When recombinant human hyaluronidase (rHuPH-20) became available, development of a subcutaneous formulation of trastuzumab was possible allowing for administration of larger volumes. At the time of study design, results from a phase 1 study were available, which showed that subcutaneous trastuzumab could be given in about 5 min, and could lead to similar systemic exposure and was well tolerated.[9] On the basis of pharmacokinetic data from this study, the fixed dose of 600 mg subcutaneous trastuzumab was developed.

HannaH-study

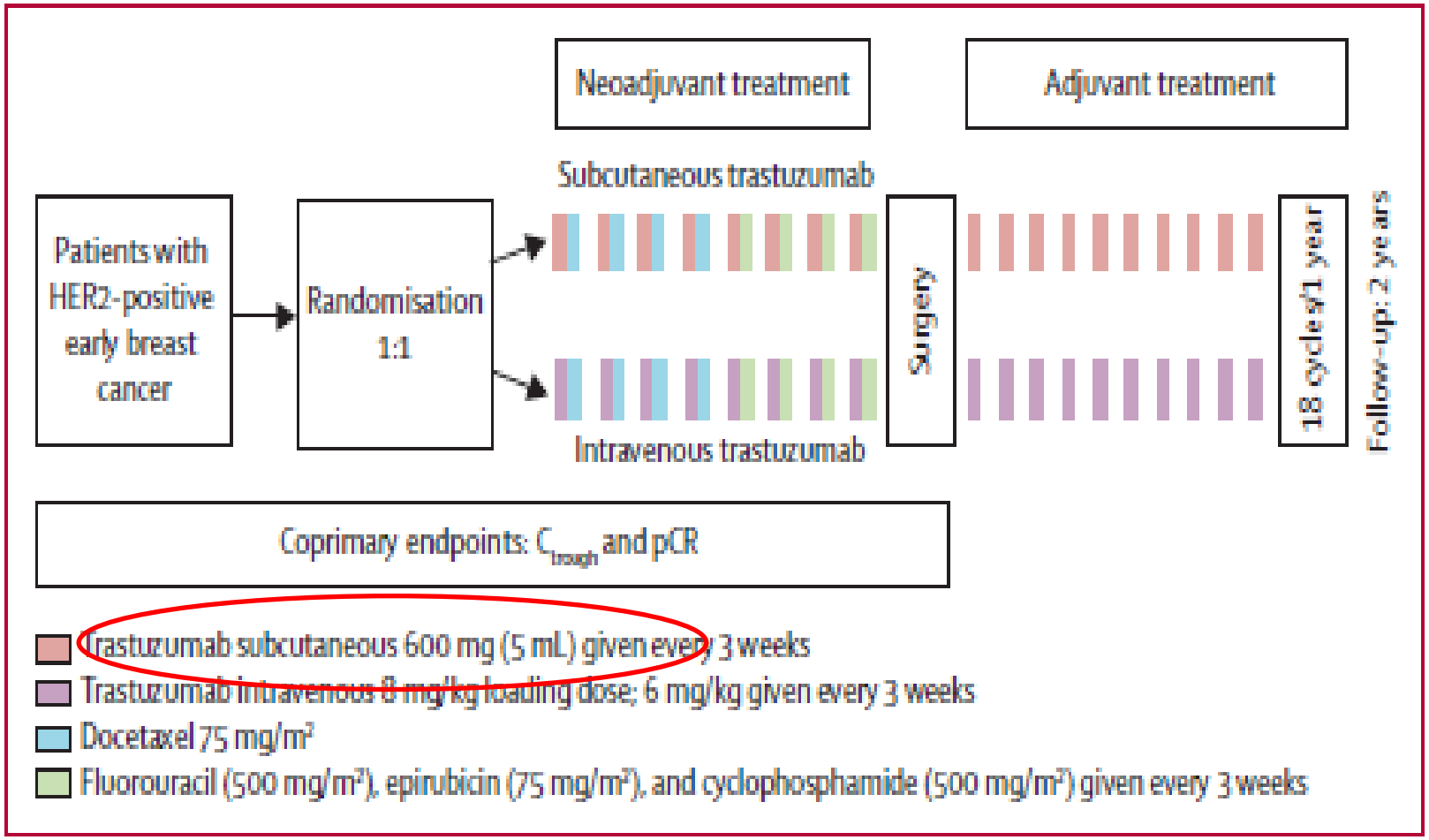


Figure 1: Study design

Hannah-results: efficacy

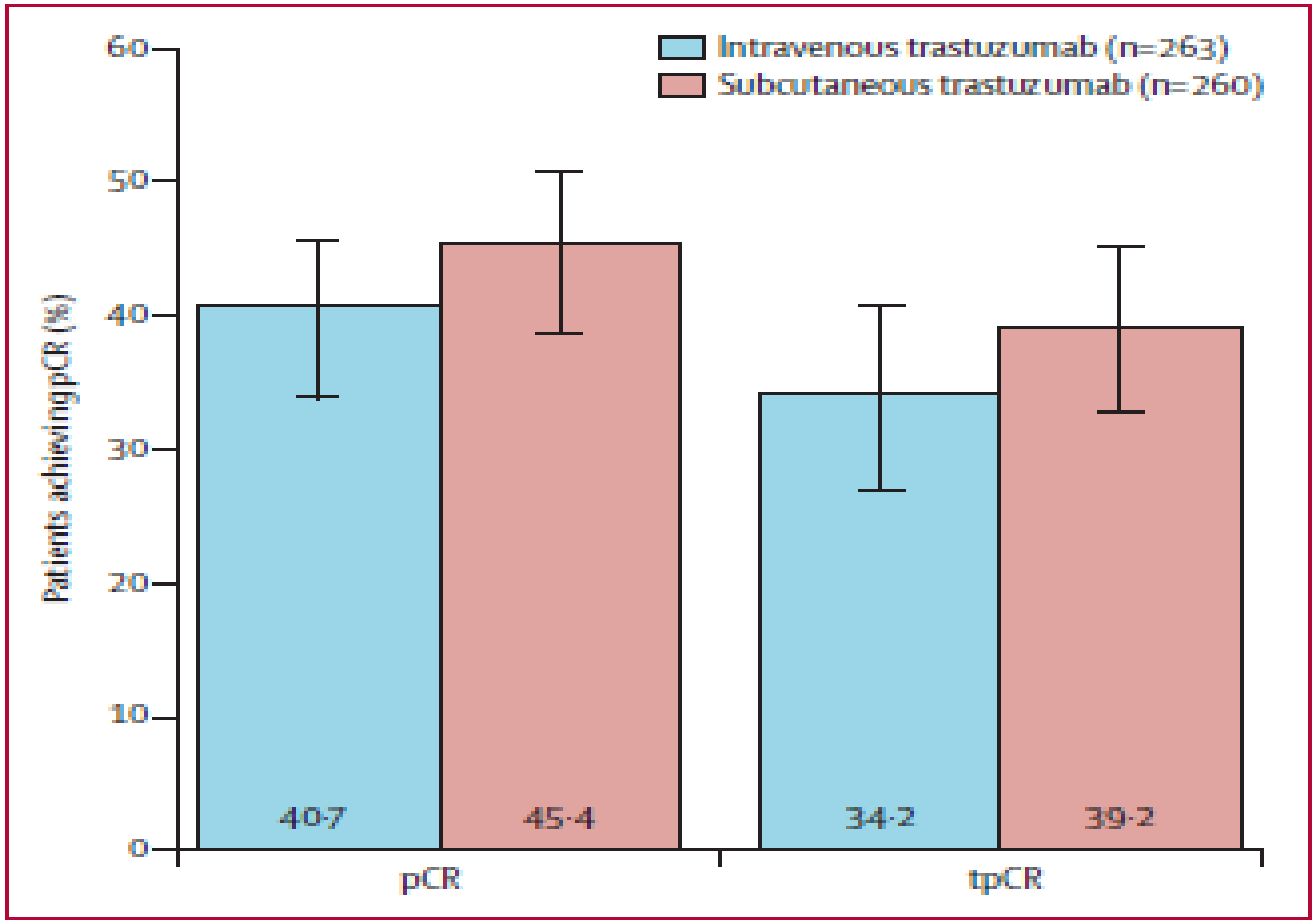


Figure 3: Proportion of patients who achieved a pathological complete response

Preference for subcutaneous or intravenous administration of trastuzumab in patients with HER2-positive early breast cancer (PrefHer): an open-label randomised study

Xavier Pivot, Joseph Gligorov, Volkmar Müller, Peter Barrett-Lee, Sunil Verma, Ann Knoop, Giuseppe Curigliano, Vladimir Semiglazov, Guillermo López-Vivanco, Valerie Jenkins, Nana Scotto, Stuart Osborne, Lesley Fallowfield, for the PrefHer Study Group

Lancet Oncol 2013; 14: 962–70

Summary

Background Subcutaneous trastuzumab has shown non-inferior efficacy and a similar pharmacokinetic and safety

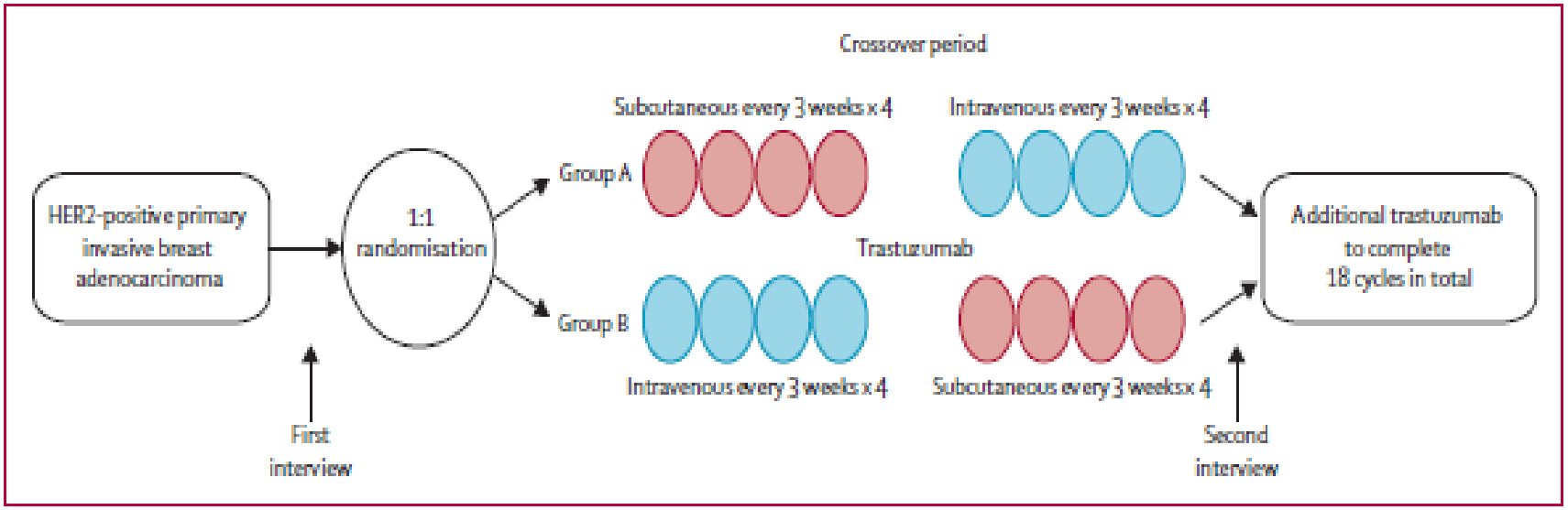


Figure 1: Study design

Panel: Research in context

Systematic review

Trastuzumab is currently administered intravenously according to bodyweight. Addition of recombinant human hyaluronidase (rHuPH20) allowed development of a fixed-dose subcutaneous formulation. The phase 3 HannaH study showed non-inferior efficacy and a similar pharmacokinetic and safety profile between the subcutaneous and intravenous formulations of trastuzumab.[12] A subcutaneous single-use injection device is under development and shows bioequivalence to subcutaneous administration via hand-held syringe.[13] Patient preference for subcutaneous or intravenous administration of trastuzumab has not been taken into account to date.

Interpretation

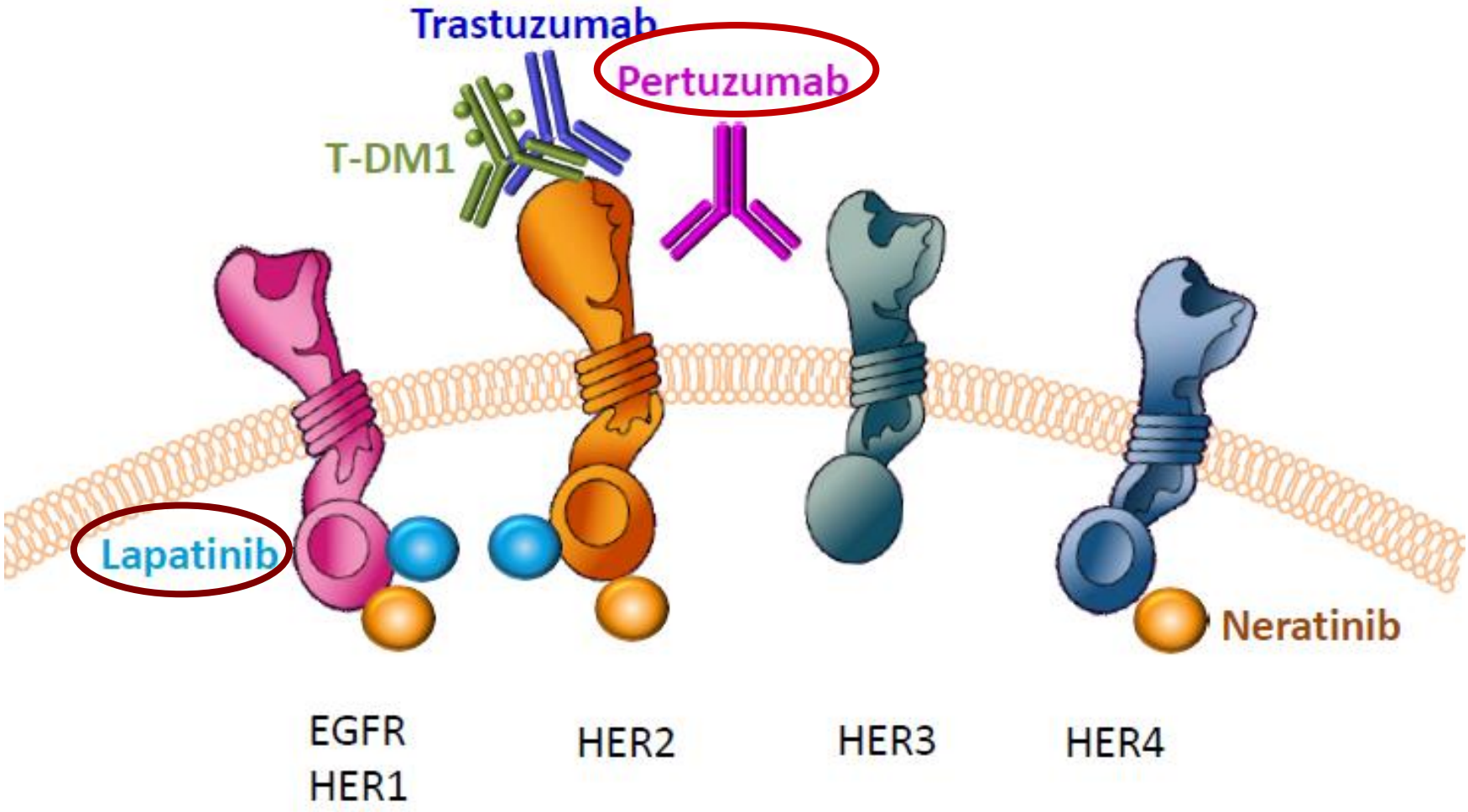
Patient preference and safety results from PrefHer, combined with efficacy, pharmacokinetic, and safety results from HannaH, suggest that a fixed dose of 600 mg subcutaneous trastuzumab every 3 weeks is a validated, well tolerated treatment option for HER2-positive breast cancer and is preferred by patients.

	n*
Subcutaneous preferred, n=216	
Time saving	195
Less pain/discomfort	88
Convenience to patient	35
Ease of administration	33
Problems with intravenous	25
Less stress/anxiety	15
Other	6
Intravenous preferred, n=16	
Fewer reactions (less pain, bruising, irritation, etc)	11
Other	5
Environment/staff	2
Perceived efficacy	1
Ecological considerations	1

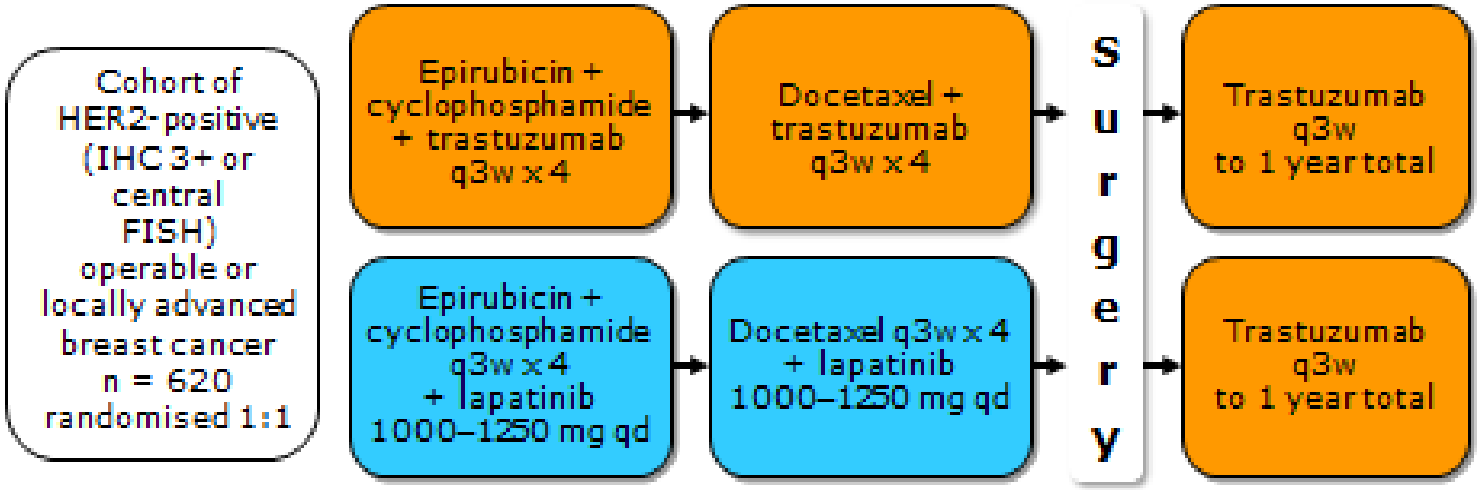
Responses to the question "What are the two main reasons for your preference?" were recorded verbatim by the interviewer. Four experienced researchers independently scrutinised the dataset and provided over-arching themes or core categories for coding. When broad consensus about these had been reached each researcher independently coded every patient's response; the researchers then reconciled codings with each other and determined if any thematic categories could reasonably be collapsed together or if a new category was required. * Some patients gave more than one reason for preference.

Table 2: Primary reasons for patients' preferences (evaluable intention-to-treat population)

Anti-HER2 therapy and HER family



GeparQuinto: Phase III comparison of trastuzumab vs lapatinib with chemotherapy as neoadjuvant therapy



Graphical elaboration from text data

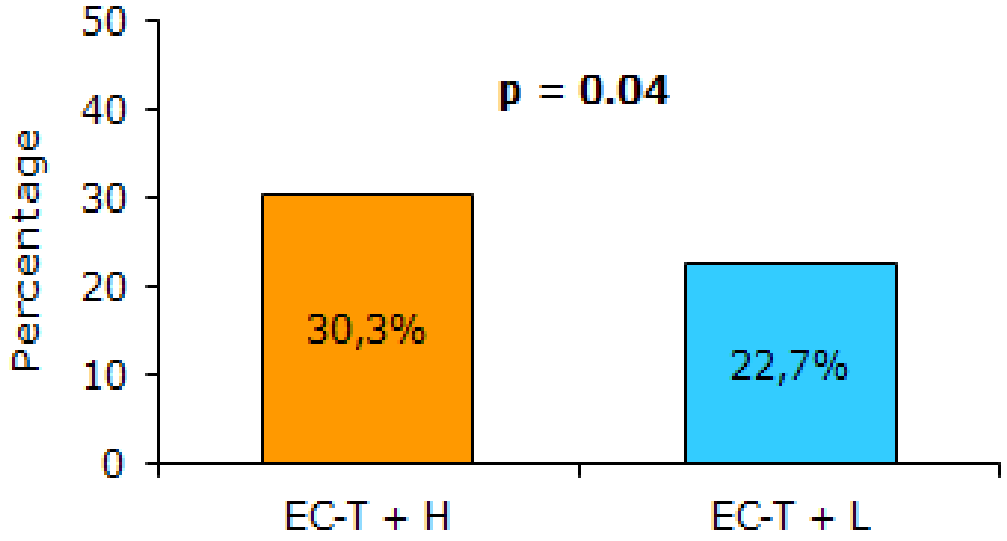
Primary endpoint: pCR defined as no microscopic evidence of residual tumour (invasive or non-invasive) in any resected specimens of the breast and axillary lymph nodes

Epirubicin 100 mg/m^2 + cyclophosphamide 600 mg/m^2 q3w x 4;
docetaxel 100 mg/m^2 q3w x 4;
trastuzumab 8 mg/kg loading dose followed by 6 mg/kg q3w for 12 months;

Untch M, Lancet Oncol. 2012;13:135-44.

GeparQuinto: pCR for trastuzumab vs lapatinib

Trastuzumab-treated patients had a significantly higher pCR rate than those treated with lapatinib



pCR definition: No residual disease in breast and nodes

Graphical elaboration from text data

EC, epirubicin + cyclophosphamide; T, docetaxel; H, trastuzumab
L, lapatinib

Untch M, Lancet Oncol. 2012;13:135-44.,

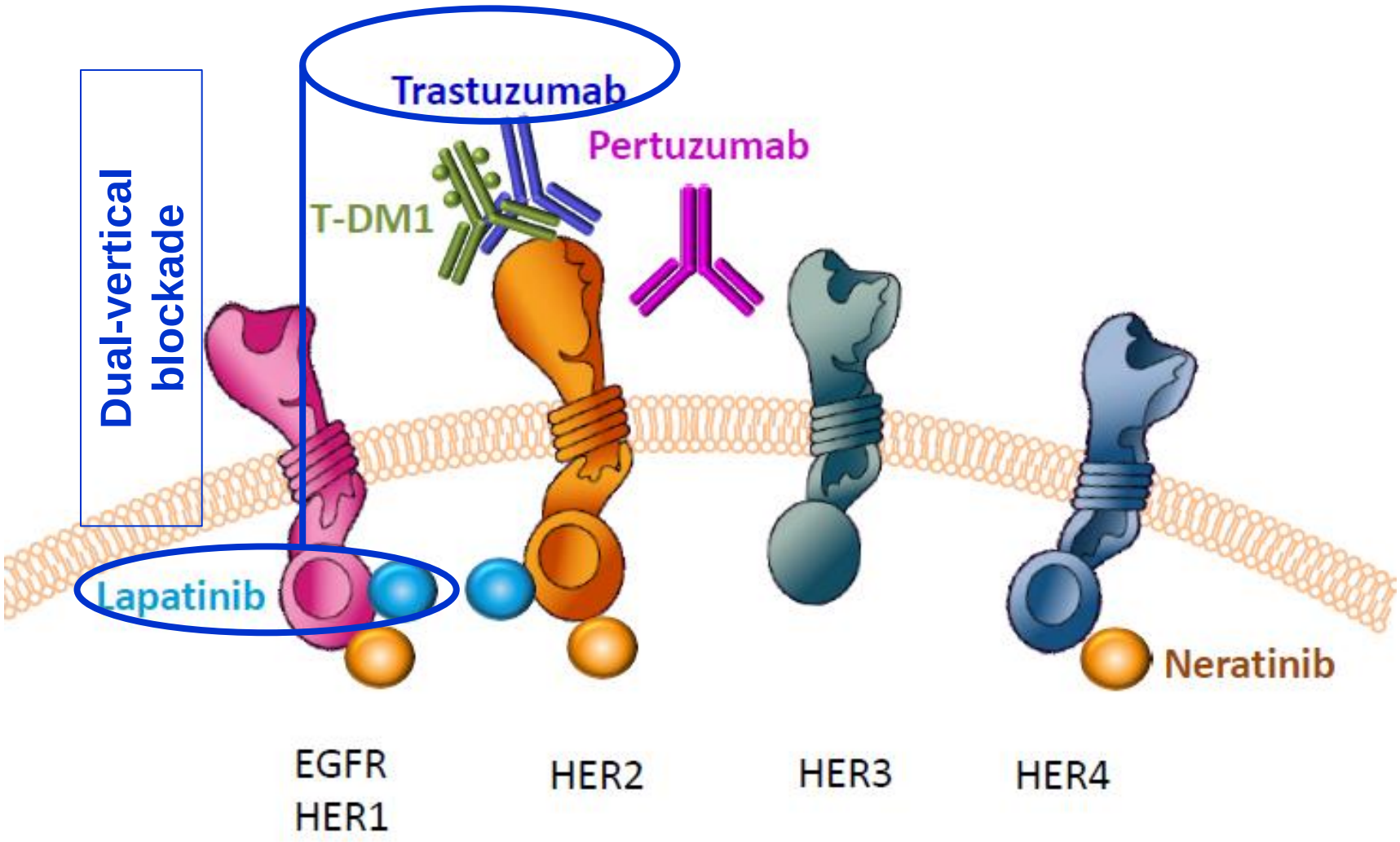
GeparQuinto

The overall benefit-risk was substantially better for trastuzumab compared with lapatinib

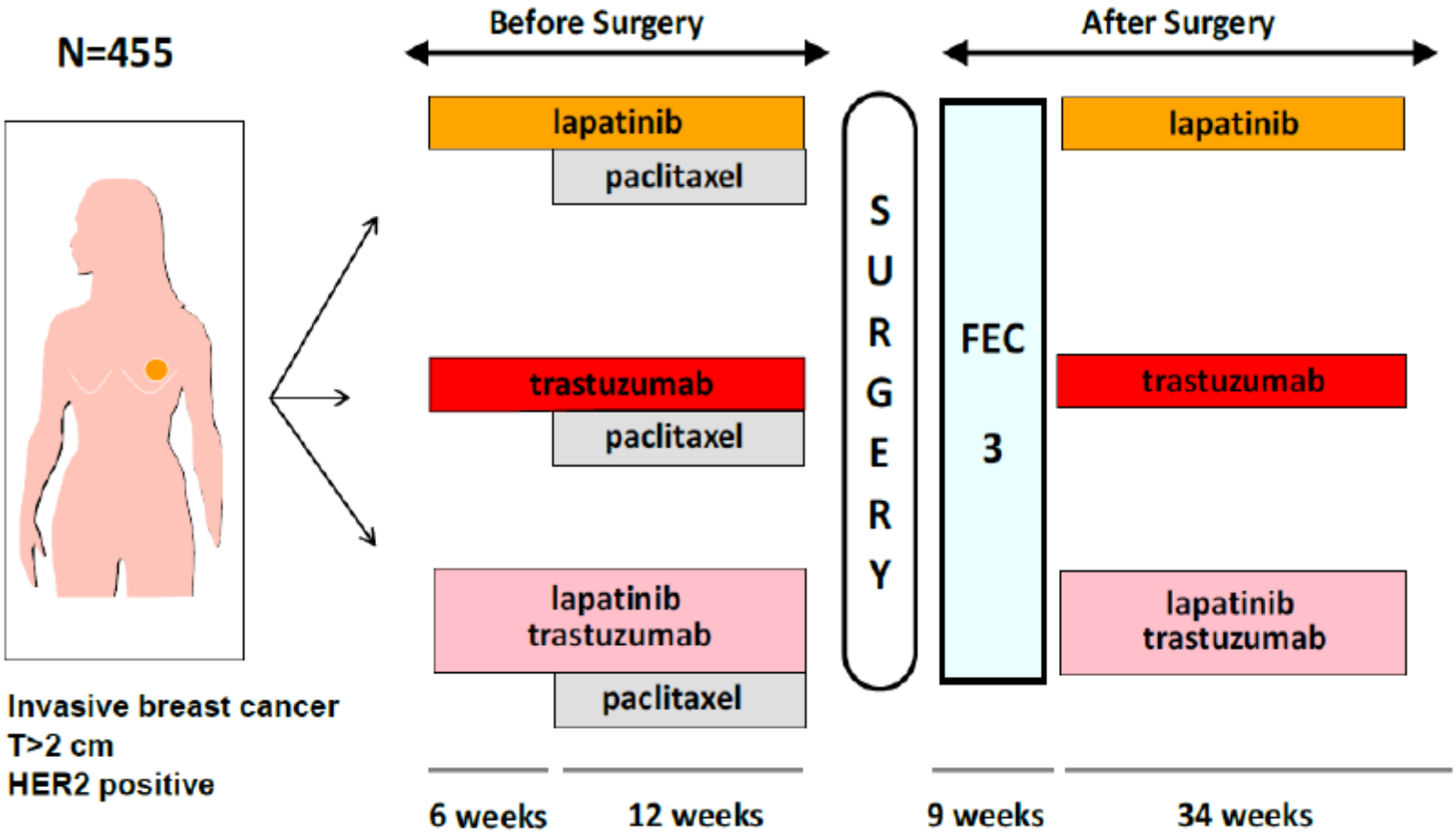
- 33.1% (n=102) of patients receiving lapatinib did not complete treatment as planned
  - Compared with only 14% (n=43) of trastuzumab-treated patients
- 39.3% (n=120) of patients receiving lapatinib had their dose reduced to manage adverse events
  - Most common Grade 3/4 adverse event was diarrhoea
    - 11.7% in the lapatinib arm
    - 2.6% in the trastuzumab arm

Untch M, Loibl S, Bischoff J *et al. Lancet Oncol* 2012; 11: 70397-7

Anti-HER2 therapy and HER family

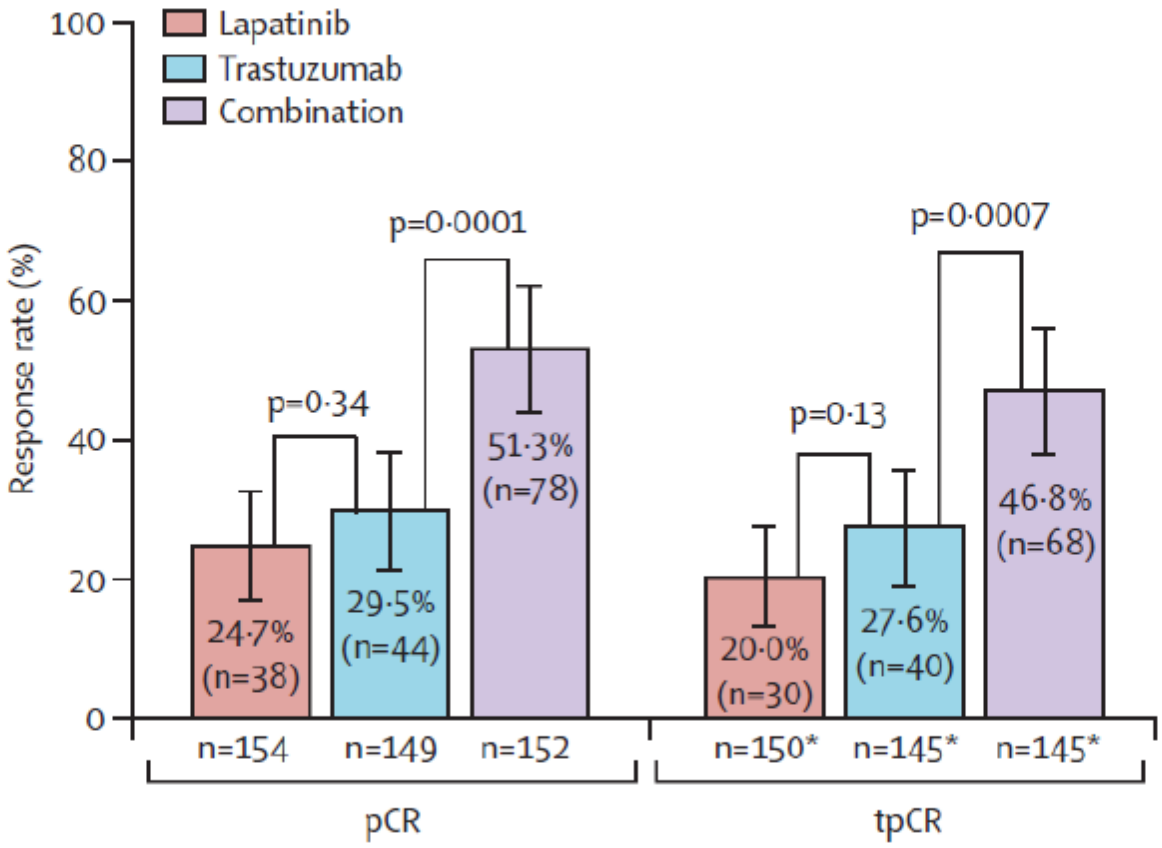


NeoALTTO; Study design



Baselga J et al.; *Lancet* 379: 633, 2012

Efficacy; **pCR** (no invasive cancer in the breast), **tpCR** (no invasive cancer in the breast and no Ax) rates

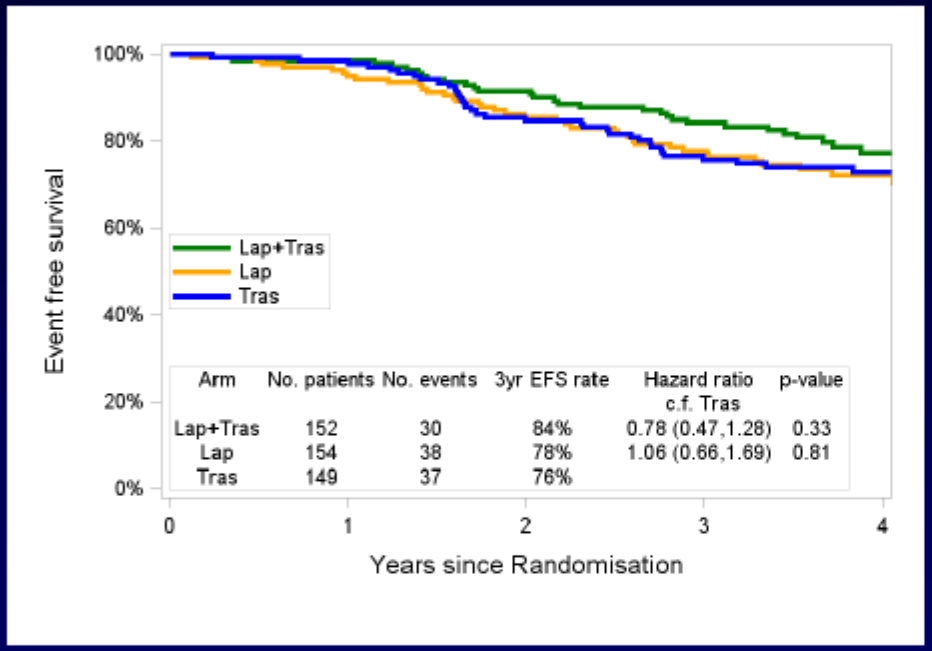


Dual inhibition of HER2 might be a valid approach to treatment of HER2-positive breast cancer in the neoadjuvant setting.

Baselga J et al.; *Lancet* 379: 633, 2012

Event-Free Survival Analysis

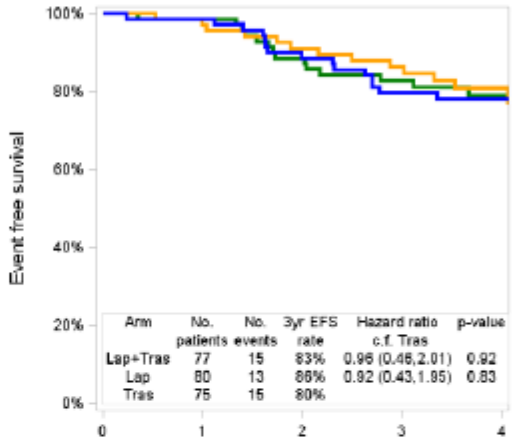
All patients



Arm	No. patients	No. events	3yr EFS rate	Hazard ratio c.f. Tras	p-value
Lap+Tras	152	30	84%	0.78 (0.47,1.28)	0.33
Lap	154	38	78%	1.06 (0.66,1.69)	0.81
Tras	149	37	76%		

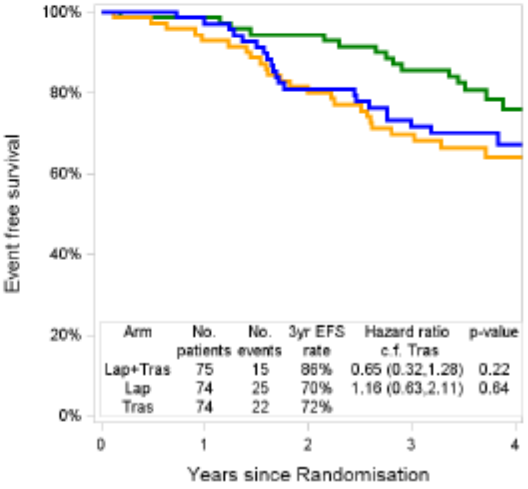
Tests for interaction according to HR status
Lap + Tras vs Tras *P* = .48
Lap vs Tras *P* = .56

HR positive



Arm	No. patients	No. events	3yr EFS rate	Hazard ratio c.f. Tras	p-value
Lap+Tras	77	15	83%	0.96 (0.46,2.01)	0.92
Lap	80	13	86%	0.92 (0.43,1.95)	0.83
Tras	75	15	80%		

HR negative

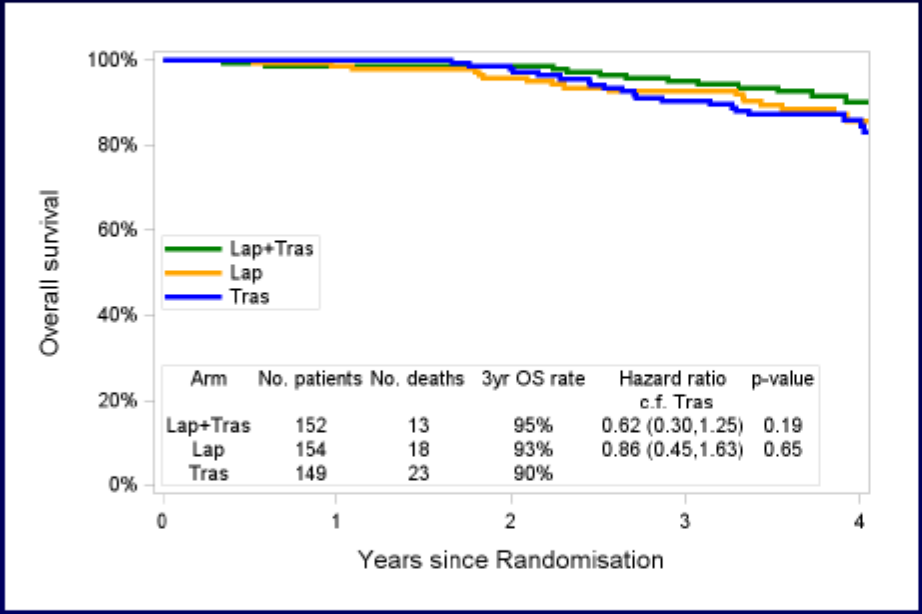


Arm	No. patients	No. events	3yr EFS rate	Hazard ratio c.f. Tras	p-value
Lap+Tras	75	15	86%	0.65 (0.32,1.28)	0.22
Lap	74	25	70%	1.16 (0.63,2.11)	0.64
Tras	74	22	72%		

Piccart M, et al. *Cancer Res*. 2013;73(24 Suppl): Abstract S1-01.

Overall Survival Analysis

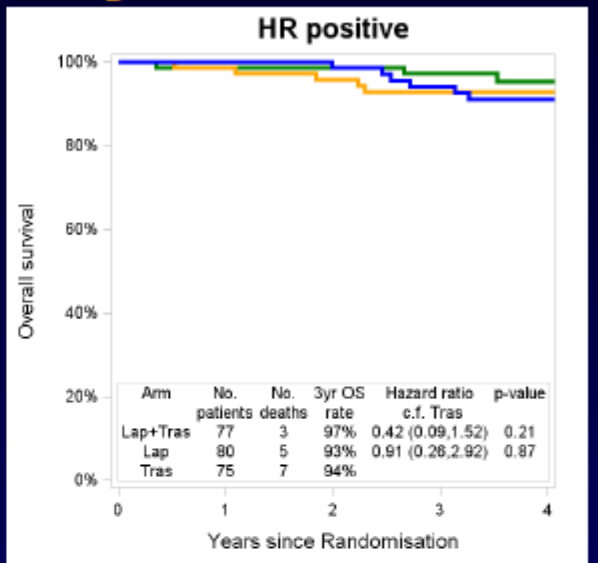
All patients



Arm	No. patients	No. deaths	3yr OS rate	Hazard ratio c.f. Tras	p-value
Lap+Tras	152	13	95%	0.62 (0.30,1.25)	0.19
Lap	154	18	93%	0.86 (0.45,1.63)	0.65
Tras	149	23	90%		

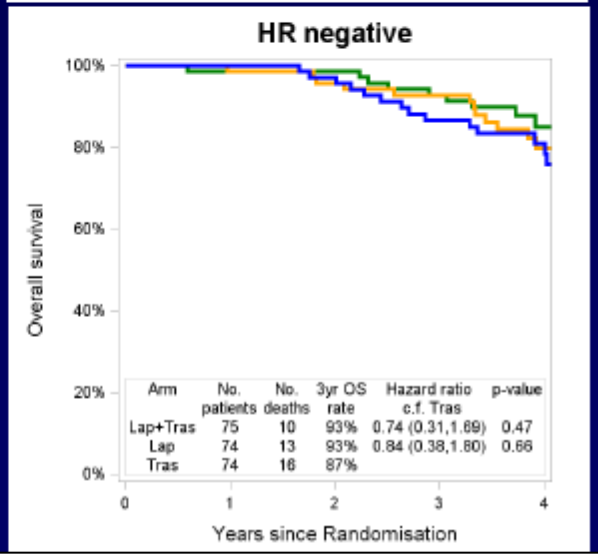
Tests for interaction according to HR status
Lap + Tras vs Tras *P* = .54
Lap vs Tras *P* = .90

HR positive



Arm	No. patients	No. deaths	3yr OS rate	Hazard ratio c.f. Tras	p-value
Lap+Tras	77	3	97%	0.42 (0.09,1.52)	0.21
Lap	80	5	93%	0.91 (0.26,2.92)	0.87
Tras	75	7	94%		

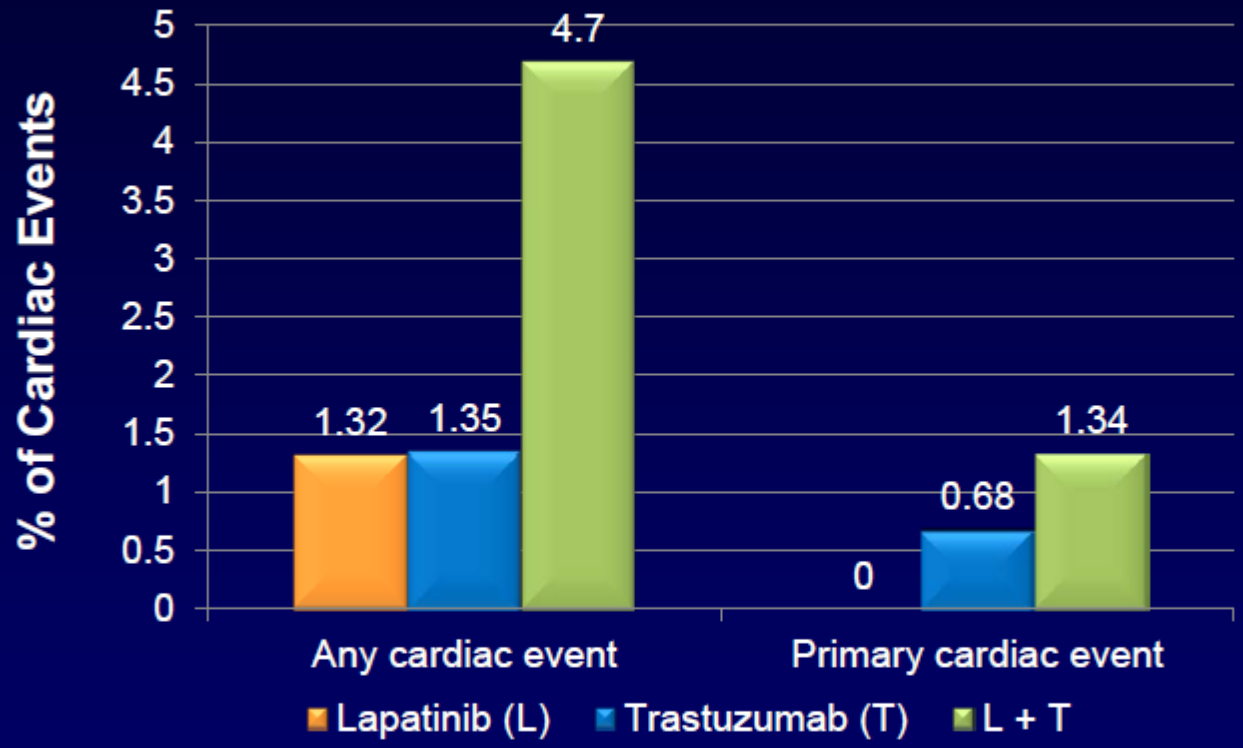
HR negative



Arm	No. patients	No. deaths	3yr OS rate	Hazard ratio c.f. Tras	p-value
Lap+Tras	75	10	93%	0.74 (0.31,1.69)	0.47
Lap	74	13	93%	0.84 (0.38,1.80)	0.66
Tras	74	18	87%		

Piccart M, et al. *Cancer Res*. 2013;73(24 Suppl): Abstract S1-01.

Cardiac Safety

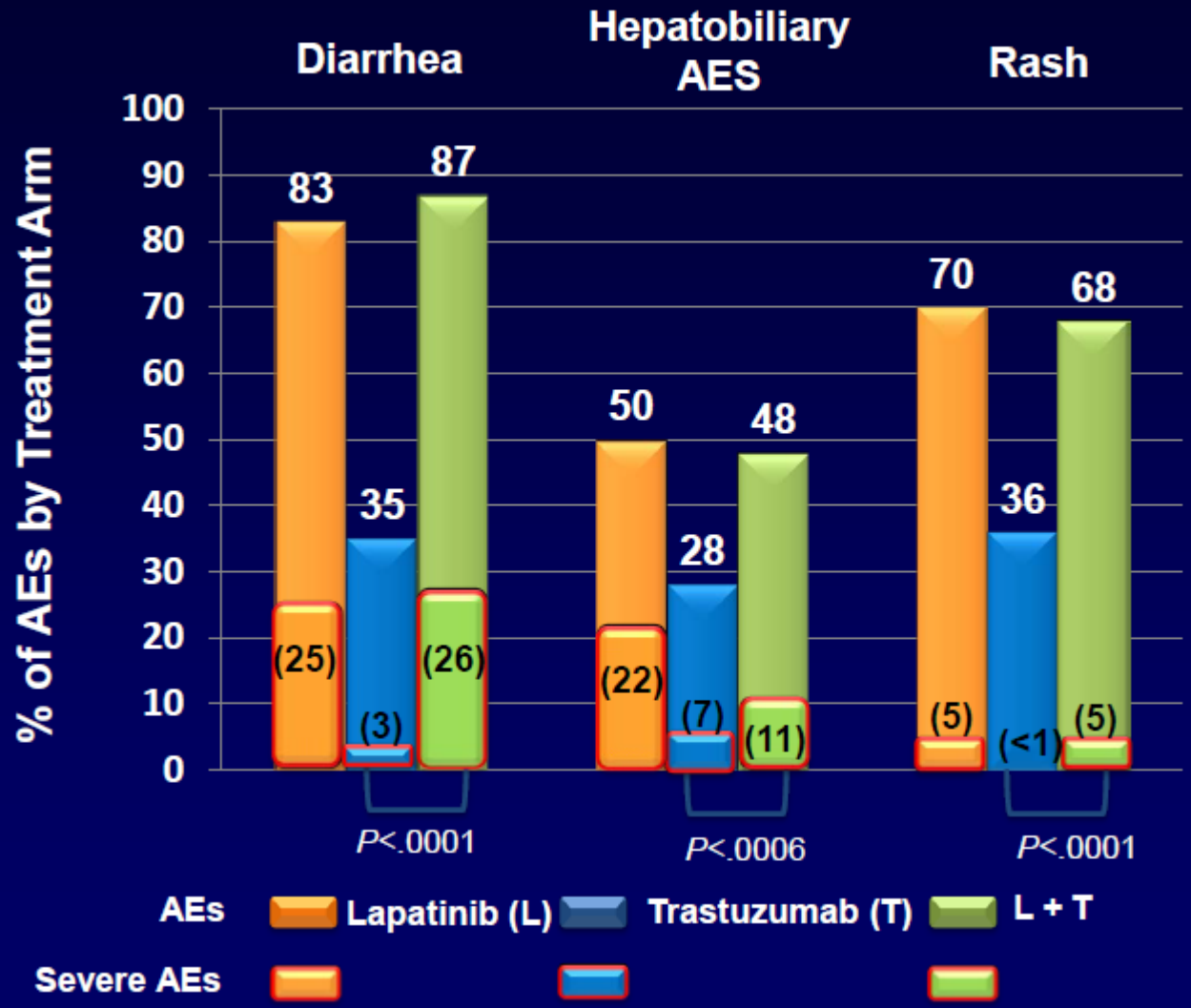


Note: No major cardiac dysfunction was observed in the neoadjuvant phase. One patient in each group presented a LVEF <50% and a decrease of >10% from baseline (Baselga, et al)

Baselga J, et al. *Lancet.* 2012;379(9816):633-640.

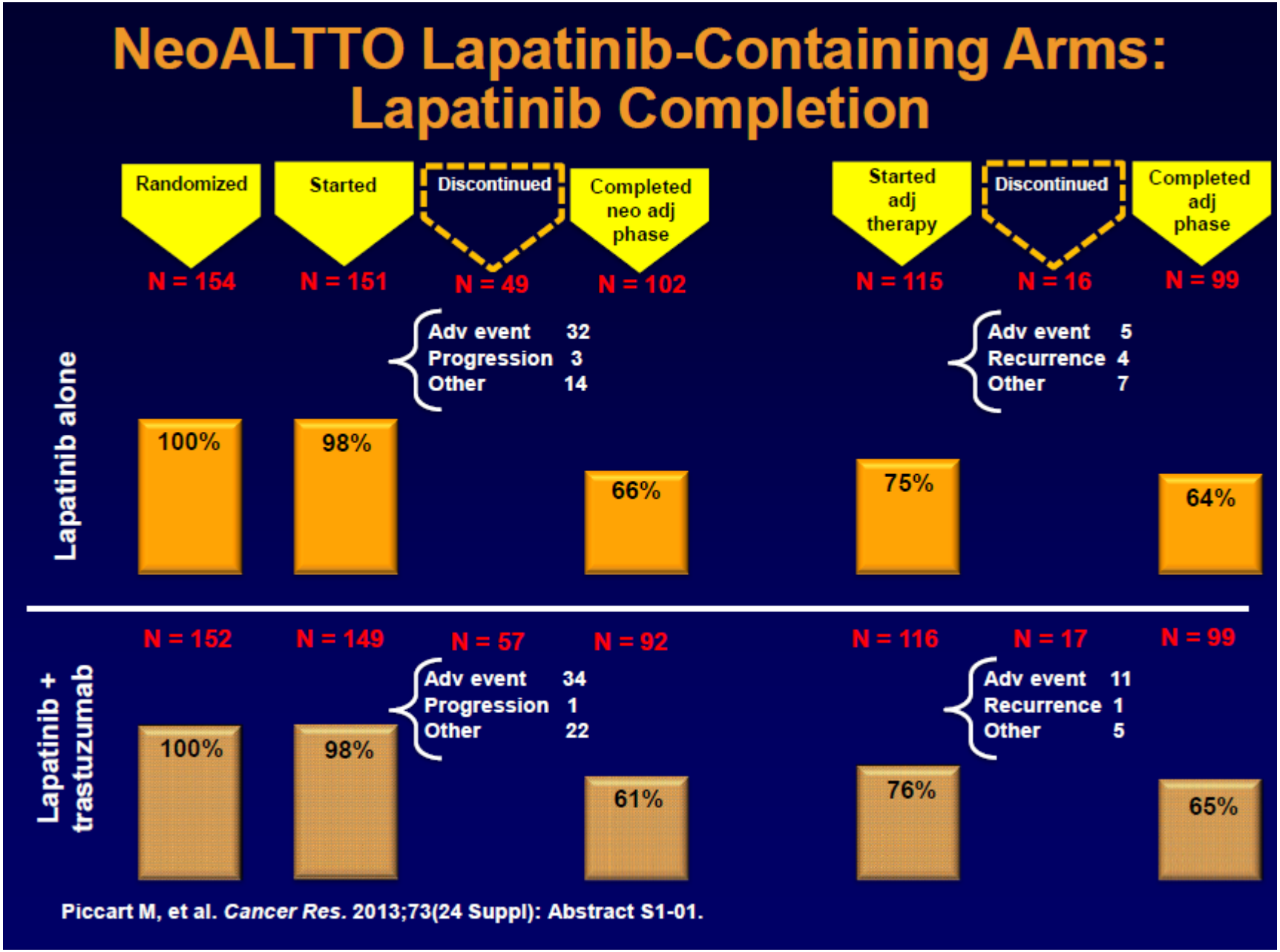
Piccart M, et al. *Cancer Res.* 2013;73(24 Suppl): Abstract S1-01.

Main Differences in AEs by Treatment Arm



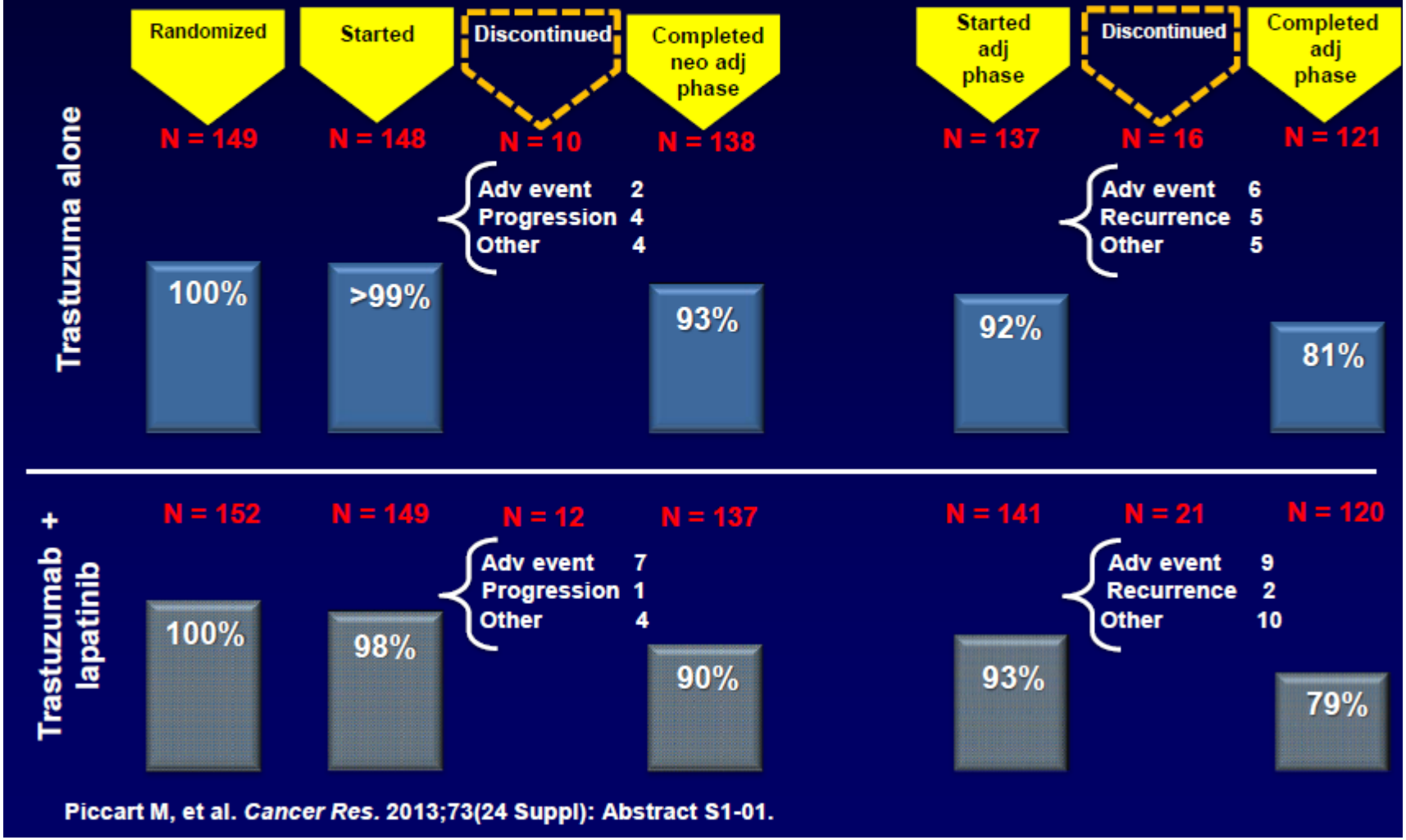
Piccart M, et al. *Cancer Res.* 2013;73(24 Suppl): Abstract S1-01.

NeoALTTO Lapatinib-Containing Arms: Lapatinib Completion



Piccart M, et al. *Cancer Res.* 2013;73(24 Suppl): Abstract S1-01.

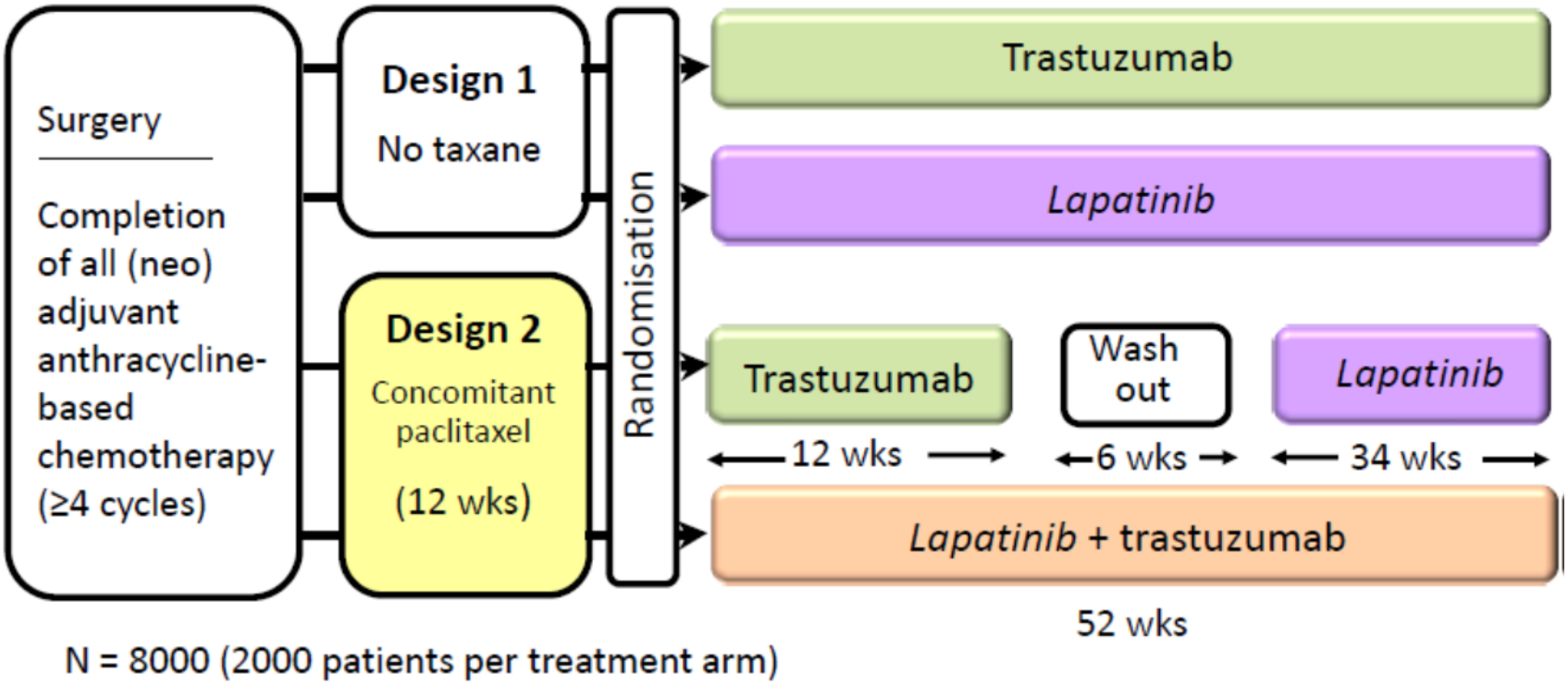
NeoALTTO Trastuzumab Containing Arms: Trastuzumab Completion



Piccart M, et al. *Cancer Res*. 2013;73(24 Suppl): Abstract S1-01.

USE OF ANTI-HER 2 «VERTICAL BLOCKAGE» in adjuvant setting (ALTTO study)

(**A**djuvant **L**apatinib and/or **T**rastuzumab **T**reatment **O**ptimisation)



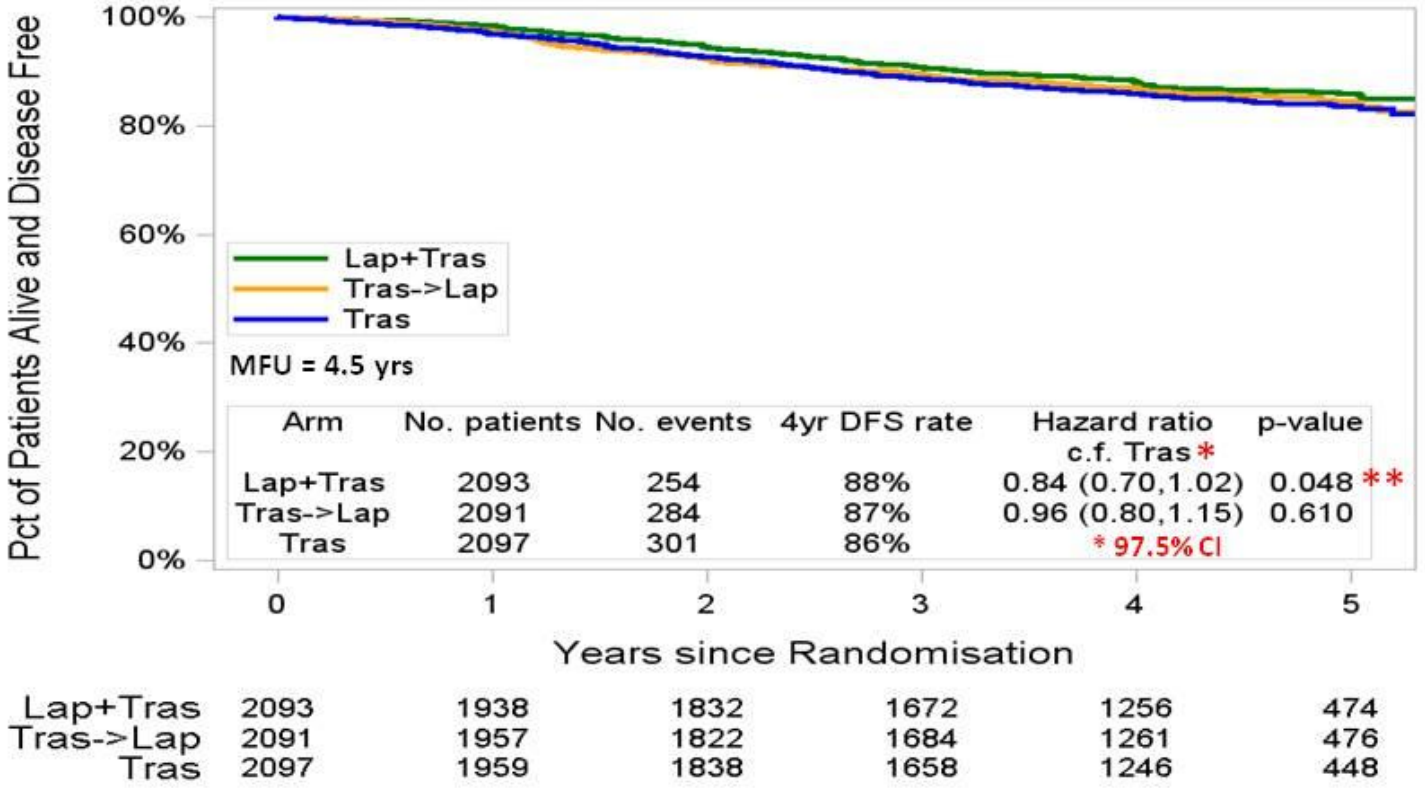
N = 8000 (2000 patients per treatment arm)

Design 1: after completation of CT
Design 2: a) concomitant “Paclitaxel” or “Docetaxel”;
b) concomitant “Docetaxel”+ “Carboplatin”

ALTTO (EGF106708) study design outline

EFFICACY RESULTS
(on 6281 randomized patients - excluded patients in «L» alone arm

DISEASE-FREE SURVIVAL (DFS) ANALYSIS



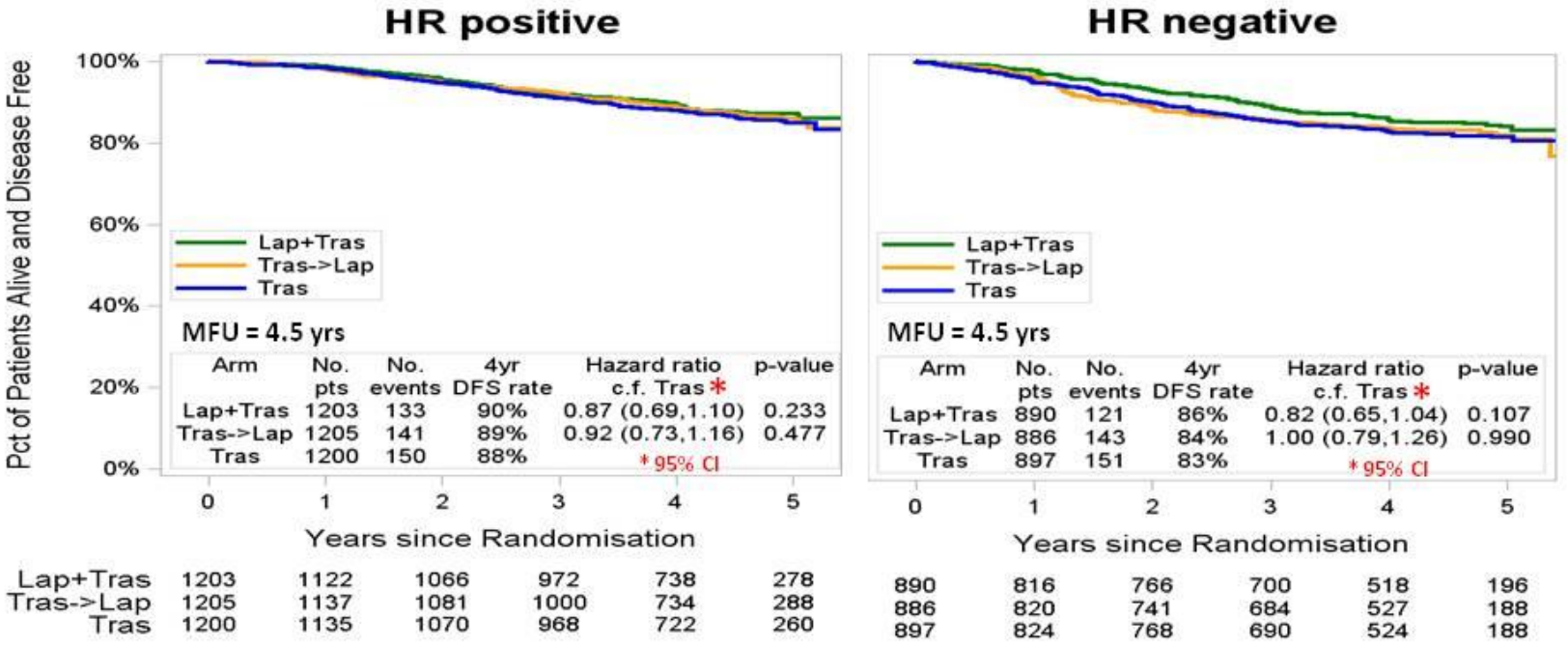
Arm	No. patients	No. events	4yr DFS rate	Hazard ratio c.f. Tras*	p-value
Lap+Tras	2093	254	88%	0.84 (0.70,1.02)	0.048**
Tras->Lap	2091	284	87%	0.96 (0.80,1.15)	0.610
Tras	2097	301	86%		

* 97.5% CI

** p-value ≤ 0.025 required for statistical significance

Presented By Martine Piccart-Gebhart at 2014 ASCO Annual Meeting

DFS BY HORMONE RECEPTOR STATUS

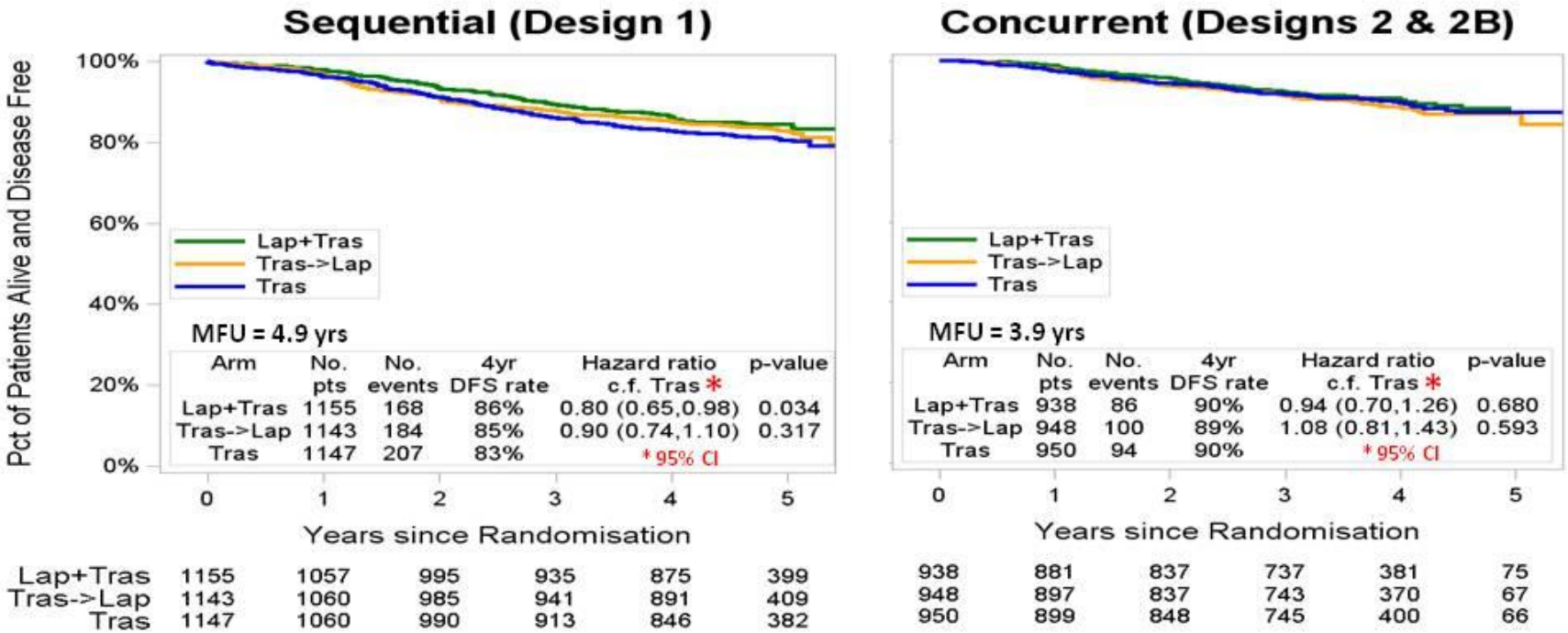


Interaction tests p = 0.70 L + T

p = 0.60 T → L

Presented By Martine Piccart-Gebhart at 2014 ASCO Annual Meeting

DFS BY CHEMOTHERAPY TIMING

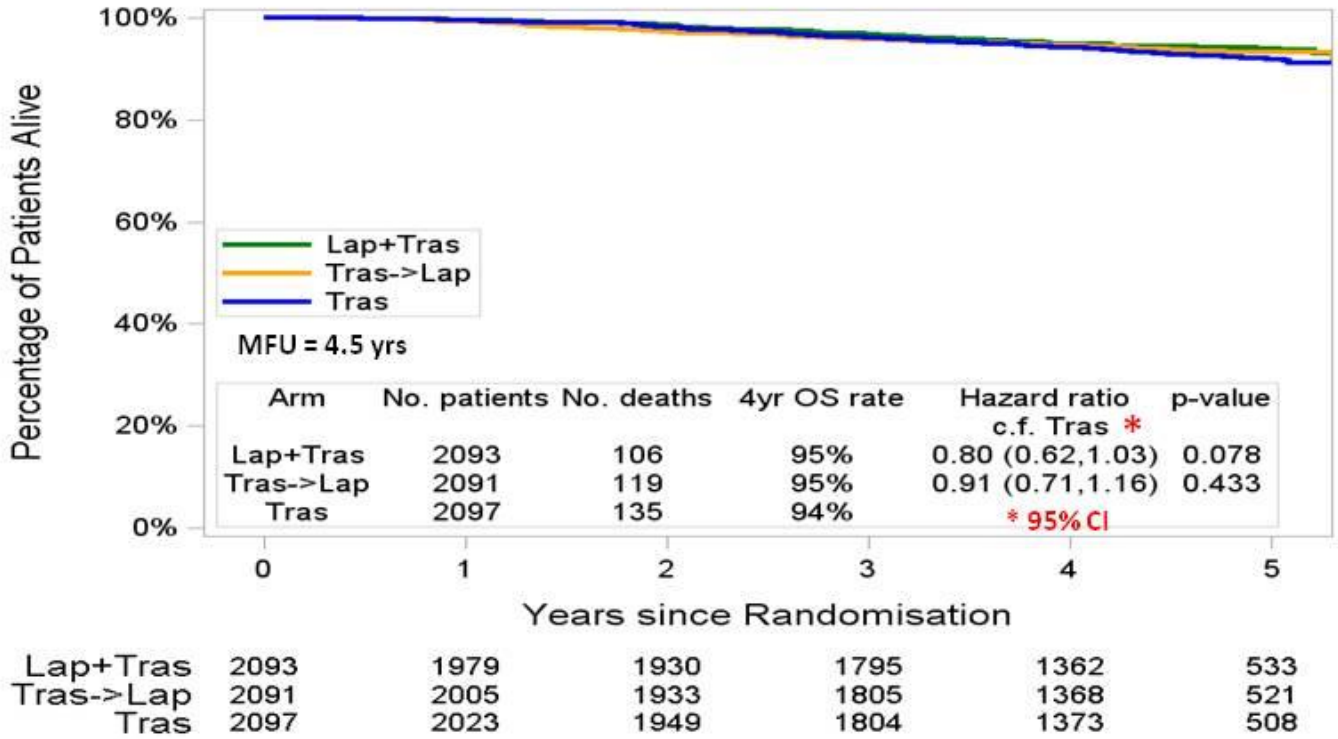


Interaction tests p = 0.41 L + T

p = 0.31 T → L

Presented By Martine Piccart-Gebhart at 2014 ASCO Annual Meeting

OVERALL SURVIVAL (OS) ANALYSIS



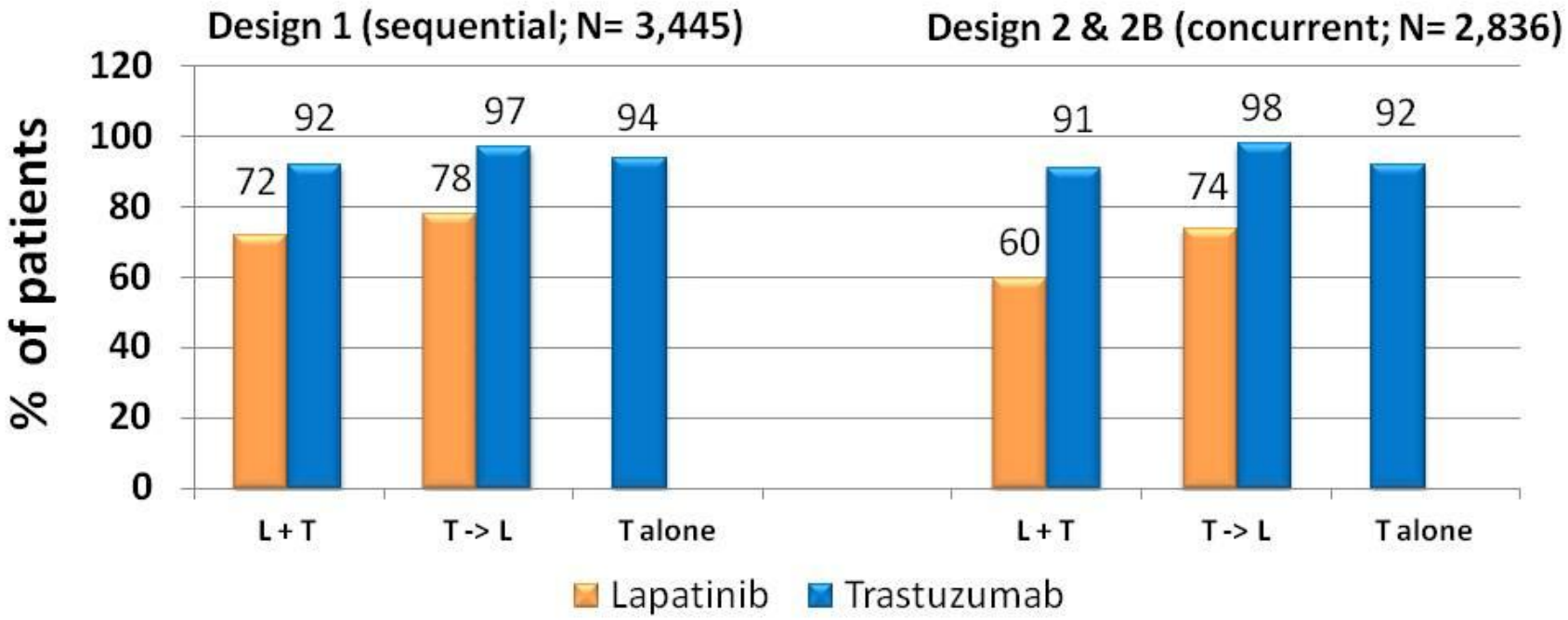
Arm	No. patients	No. deaths	4yr OS rate	Hazard ratio c.f. Tras *	p-value
Lap+Tras	2093	106	95%	0.80 (0.62,1.03)	0.078
Tras->Lap	2091	119	95%	0.91 (0.71,1.16)	0.433
Tras	2097	135	94%		

* 95% CI

Lap+Tras	2093	1979	1930	1795	1362	533
Tras->Lap	2091	2005	1933	1805	1368	521
Tras	2097	2023	1949	1804	1373	508

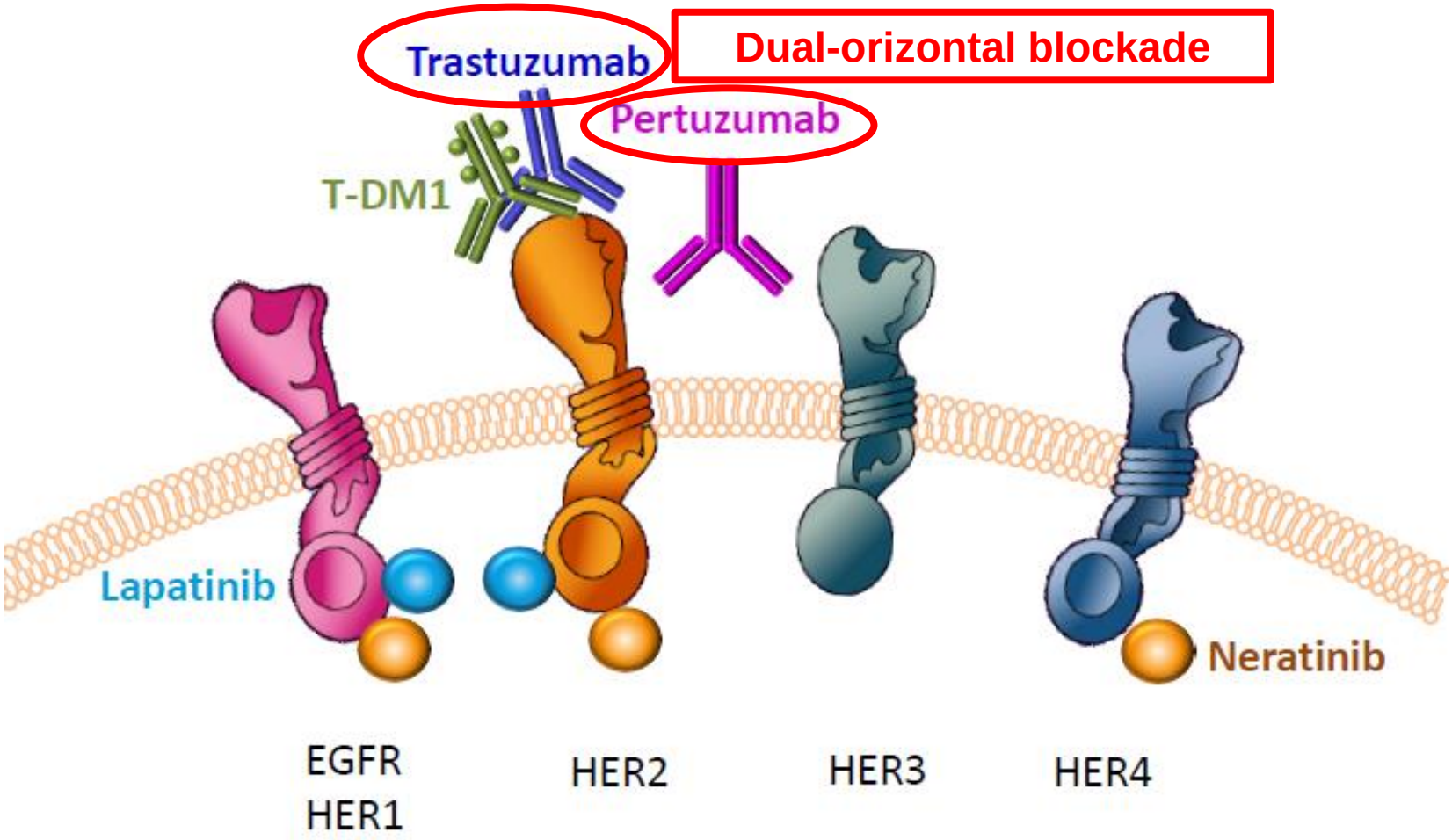
Presented By Martine Piccart-Gebhart at 2014 ASCO Annual Meeting

PROPORTION OF PATIENTS RECEIVING ≥ 85% OF THE PLANNED DOSE OF ANTI-HER2 DRUGS

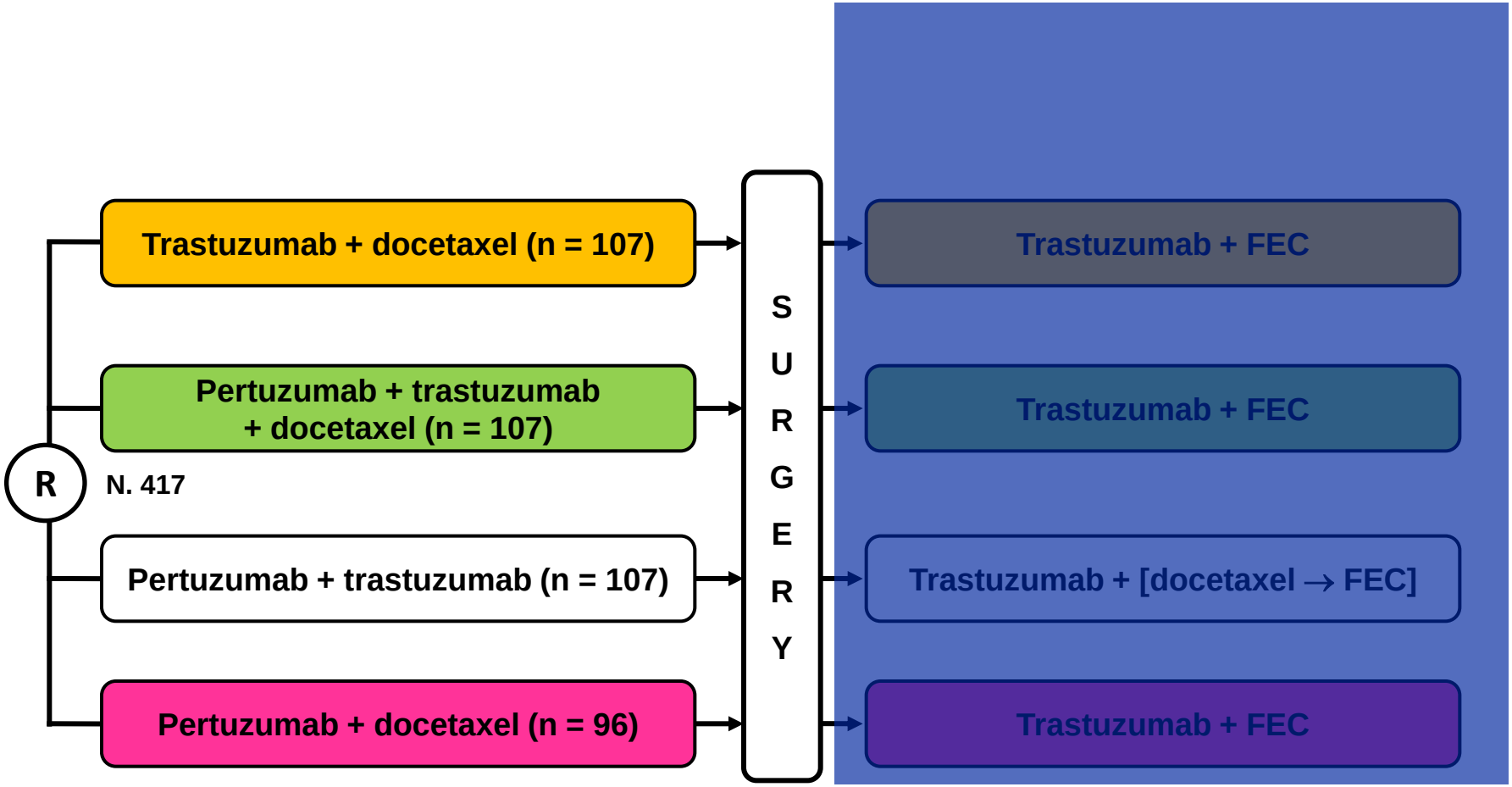


Presented By Martine Piccart-Gebhart at 2014 ASCO Annual Meeting

Anti-HER2 therapy and HER family



NeoSphere: Randomised, open-label study of pertuzumab and/or trastuzumab with a taxane in the neoadjuvant setting



(NEOadjuvant Study of Pertuzumab and Herceptin in an Early Regimen Evaluation)

Gianni, Lancet Oncol 2012; 13

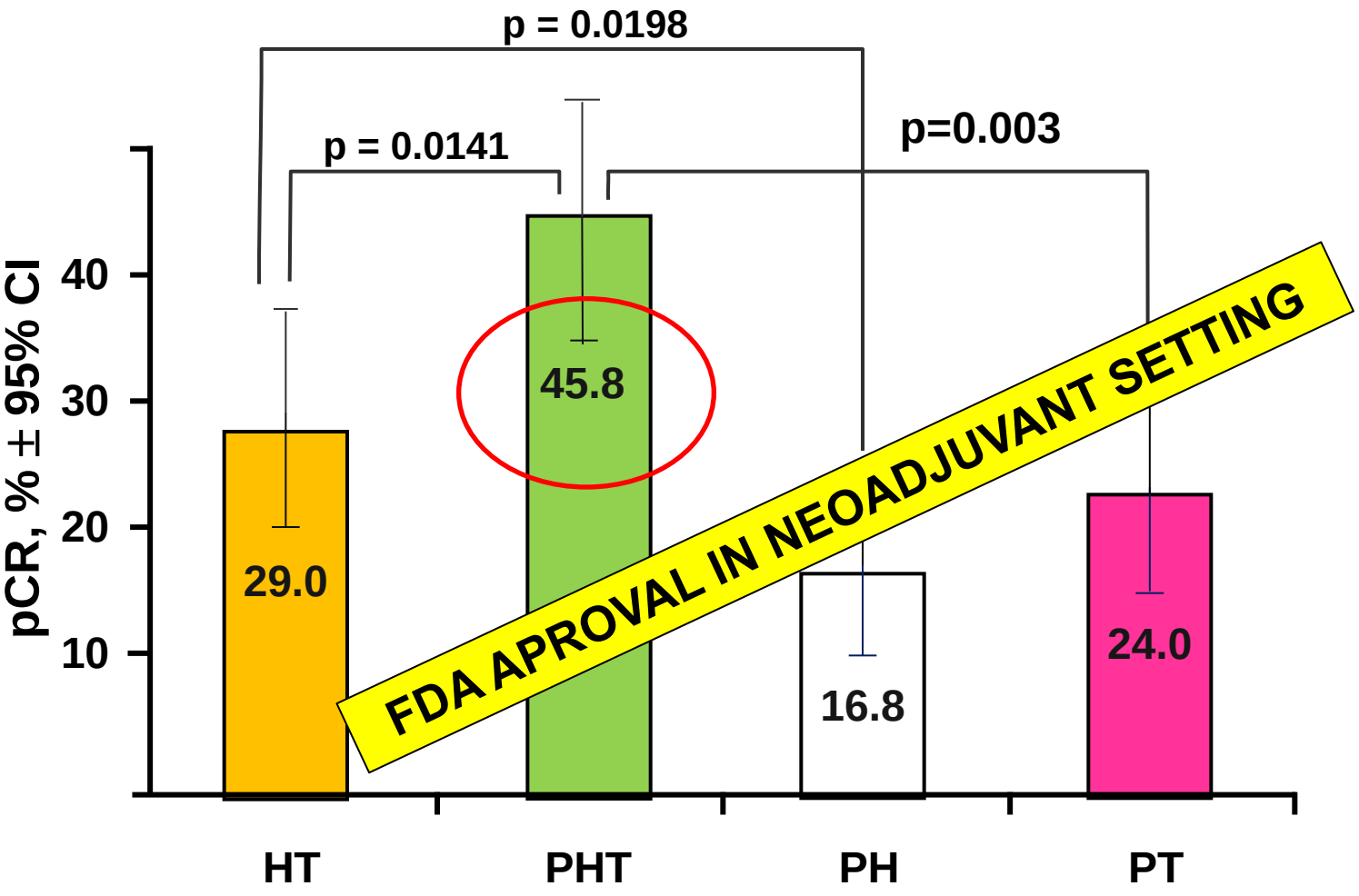
NeoSphere: Summary

- Patient population
  - Women aged ≥18 years with locally advanced, inflammatory or early HER2-positive breast cancer (N = 417)
- Study design
  - Phase II study of neoadjuvant trastuzumab and pertuzumab in the treatment of patients with HER2-positive breast cancer
- Primary endpoint
  - pCR rate at time of surgery
- Key secondary endpoints
  - Clinical response rate, time to response
  - Rate of breast-conserving surgery
  - Safety

Gianni L, *et al. Lancet Oncol* 2012; **13**:25–32

NeoSphere: Pertuzumab and trastuzumab plus docetaxel significantly increased the pCR rate vs other arms

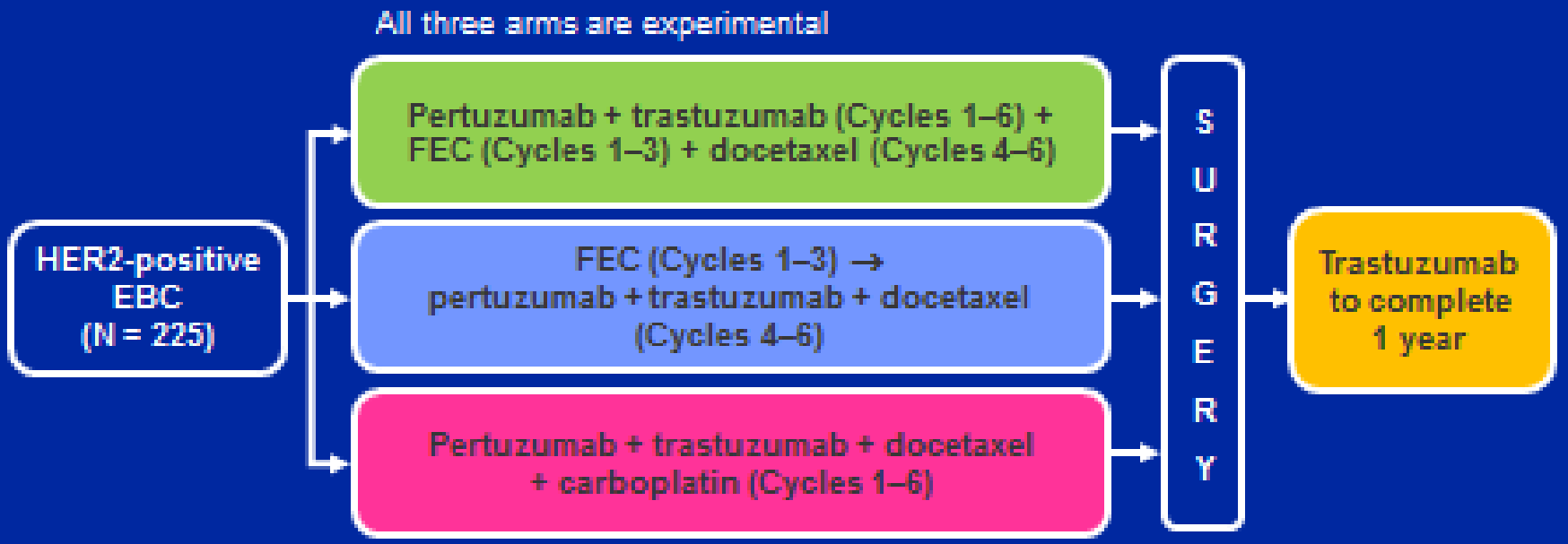
H, trastuzumab; P, pertuzumab; pCR, pathological complete response; T, docetaxel



Gianni L, *et al. Lancet Oncol* 2012; **13:**25–32.

TRYPHAENA: A Phase II study of pertuzumab and trastuzumab in the neoadjuvant setting

(TolleRabilitY of Pertuzumab, Herceptin, and AnthracyclinEs in Neo-Adjuvant breast cancer)



FEC, 5-fluorouracil, epirubicin, cyclophosphamide

Schneeweiss A, et al. SABCS 2011 (Abstract S5-6; oral presentation) available at http://sabcs11.mzinga.com/sabcs.htm - Last access October 2013; www.clinicaltrials.gov/ct2/show/NCT00976989

Schneeweiss A, et al. Ann Oncol. 2013;24:2278-84.

TRYPHAENA: Summary

- Results from TRYPHAENA indicate a low incidence of symptomatic and asymptomatic LVSD across all arms
  - Concurrent administration of pertuzumab plus trastuzumab with epirubicin resulted in similar cardiac tolerability compared with sequential administration or the anthracycline-free regimen
- Neutropenia, febrile neutropenia, leukopenia and diarrhoea were the most frequently reported adverse events (grade ≥3) across all arms
- Regardless of chemotherapy chosen, the combination of pertuzumab with trastuzumab in the neoadjuvant setting resulted in high pCR rates (57–66%)

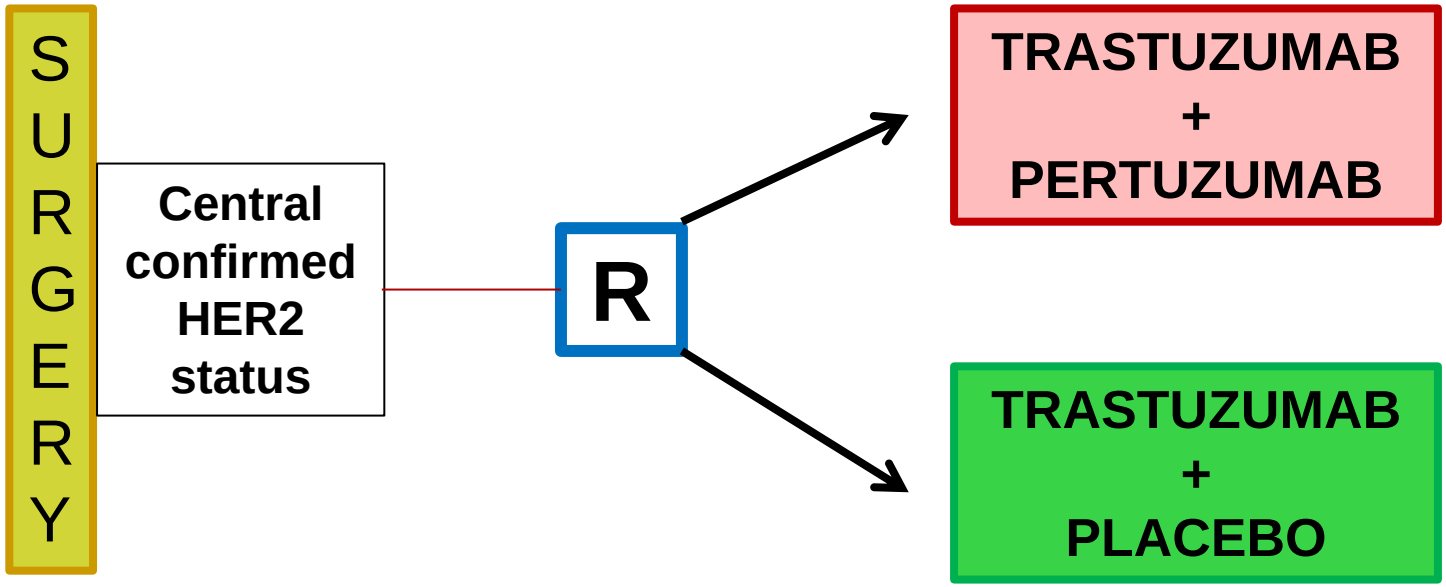
TRYPHAENA supports the ongoing APHINITY study, a Phase III trial to evaluate pertuzumab and trastuzumab plus standard chemotherapy in the adjuvant setting

LVSD, left ventricular systolic dysfunction; pCR, pathological complete response

Schneeweiss A, et al. Ann Oncol. 2013;24:2278-84;

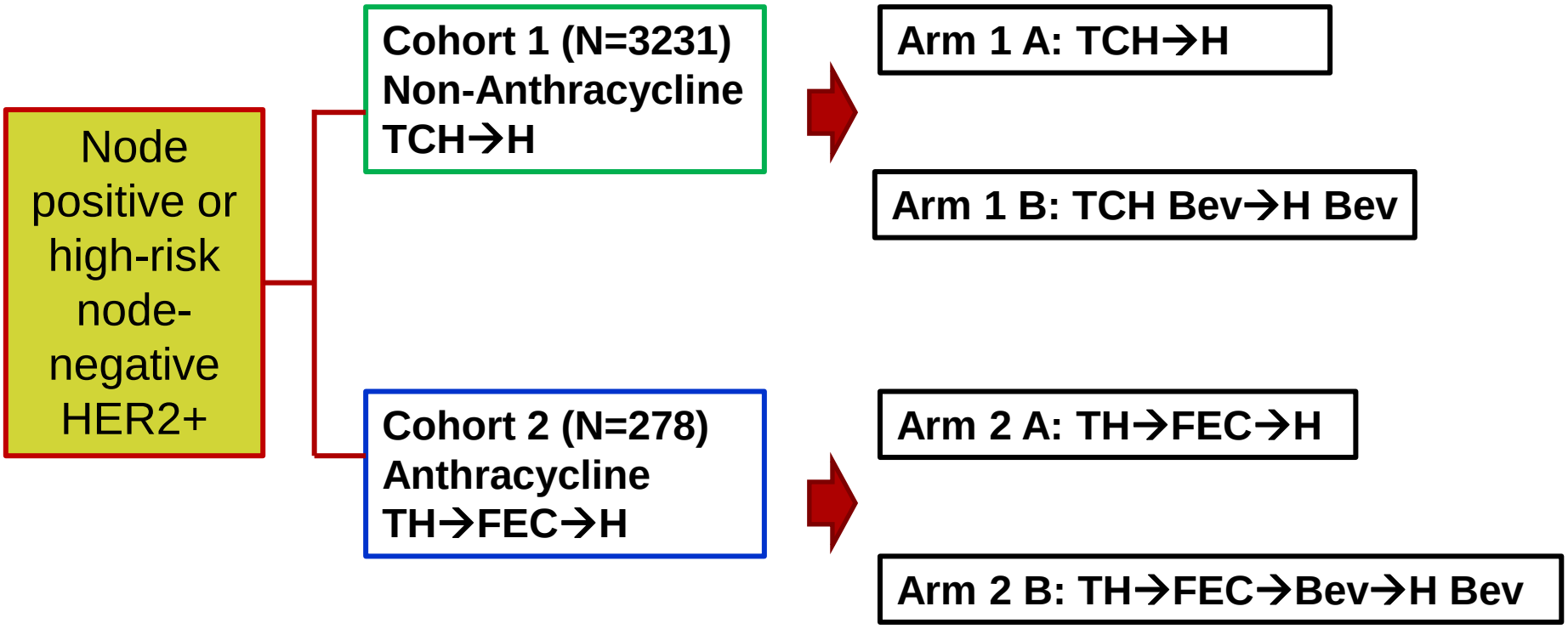
DUAL ORIZONTAL BLOCKADE BETTER IN ADIUVANT SETTING?

…..WAITING FOR «APHINITY TRIAL results»



ESCALATION ATTEMPTS WITH ANTI-HER2 THERAPIES…

RANDOMIZED PHASE III TRIAL OF ADJUVANT BEVACIZUMAB IN HER2-POSITIVE BREAST CANCER: BETH STUDY



Slamon D et al, SABCS 2013

RANDOMIZED PHASE III TRIAL OF ADJUVANT BEVACIZUMAB IN HER2-POSITIVE BREAST CANCER: BETH

Median Follow up 38 months

	IDFS	OS
Without Bevacizumab	92%	96%
With Bevacizumab	92%	97%

Slamon D et al, SABCS 2013

CAN AGGRESSIVE CHEMOTHERAPY BE SPARED IN SELECTED PATIENTS?

SMALL HER2+ BREAST CANCER: THE DANA FARBER PROSPECTIVE PHASE II STUDY

N=406

Median age 55
T1a 20%
T1b 35%
T1c 42%
T2 9%
N0 98.5%
HR+ 67%

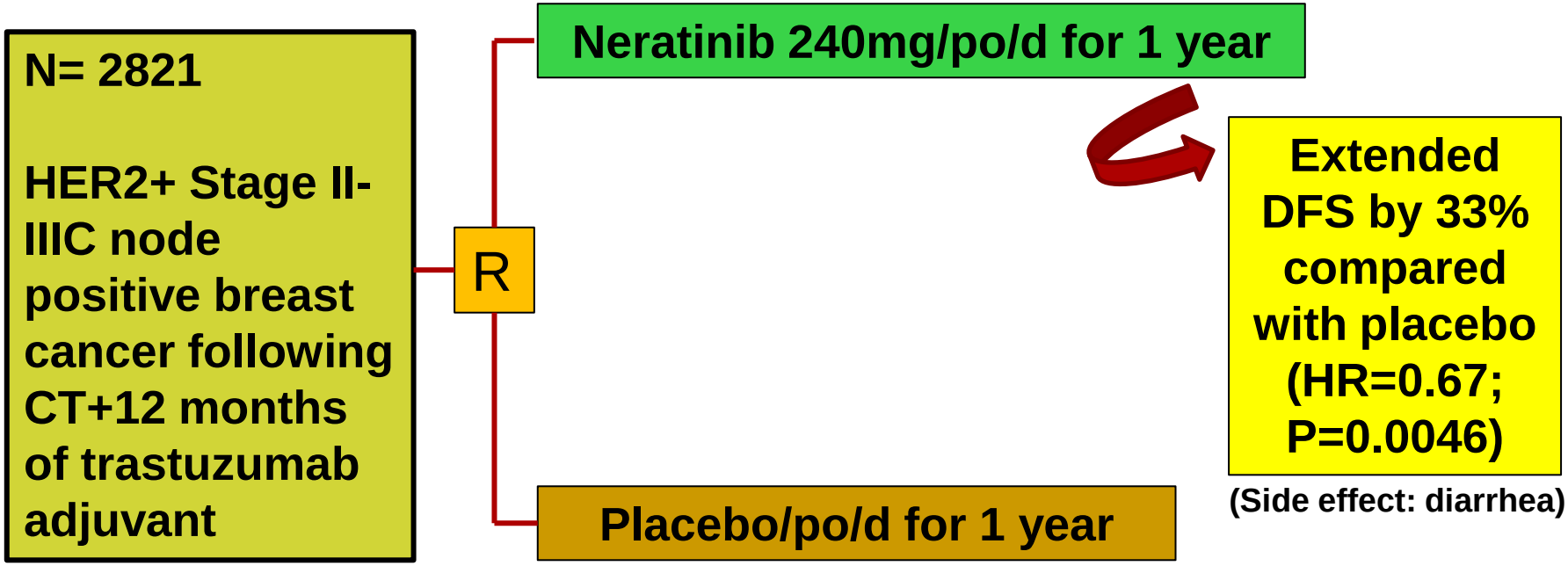
Paclitaxel weekly x12
Trastuzumab weekly x52

3y DFS= 98.7%
(95% CI: 97.6-99.8%)

Tolaney SM et al, NEJM 2015

EXTENDED ADJUVANT NERATINIB EXTENET PHASE III TRIAL

(Oral Tyrosine Kinase irreversible inhibitor of HER1, HER2, HER4)



At 2 years of Follow up:
absolute benefit for all patients 2.3
absolute benefit for HR positive 4.2

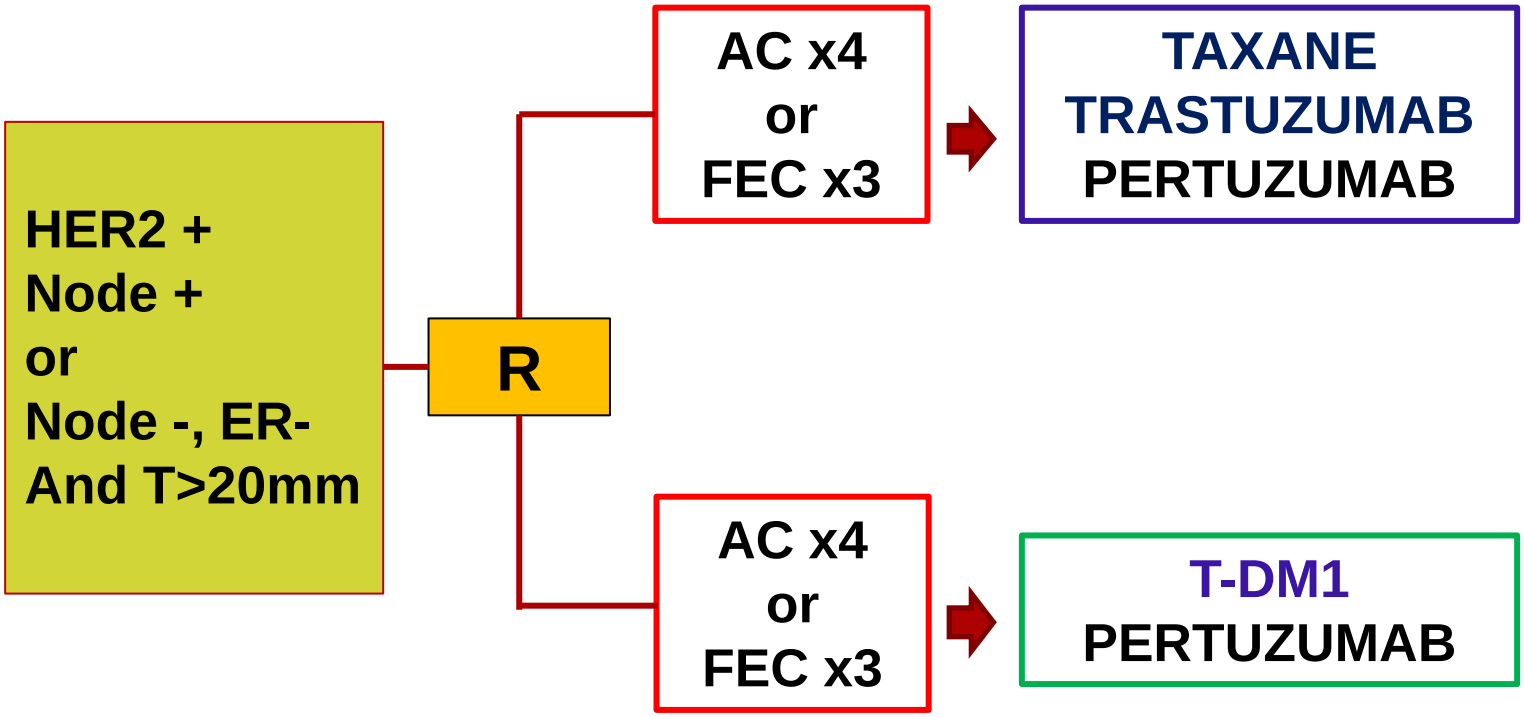
ASCO, 2015

(On going) KATHERINE: POST NEOADJUVANT T-DM1 IN PATIENTS WITH RESIDUAL TUMOR FOLLOWING NEOADJUVANT CT + TRASTUZUMAB

Primary endpoint: IDFS

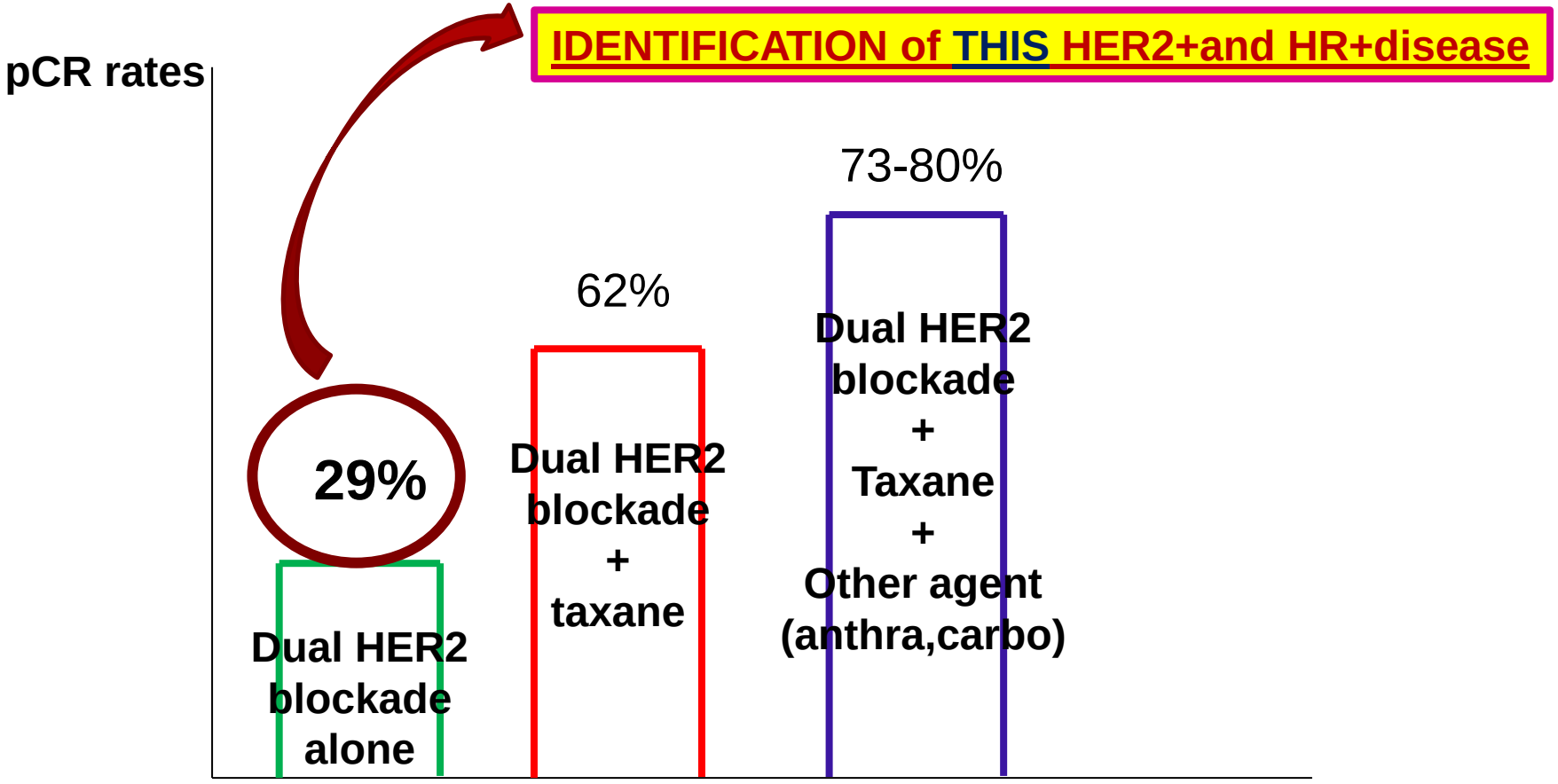
(about 900/1400 patients recruited as today – march 2015, by M. Piccart)

(On going)THE KAITLIN ADJUVANT TRIAL: T-DM1 INSTEAD OF TAXANE



(1300/2500 patients recruited as today - march 2015, by M. Piccart

(future) IS CHEMOTHERAPY ALWAYS MANDATORY IN HER2 + DISEASE?



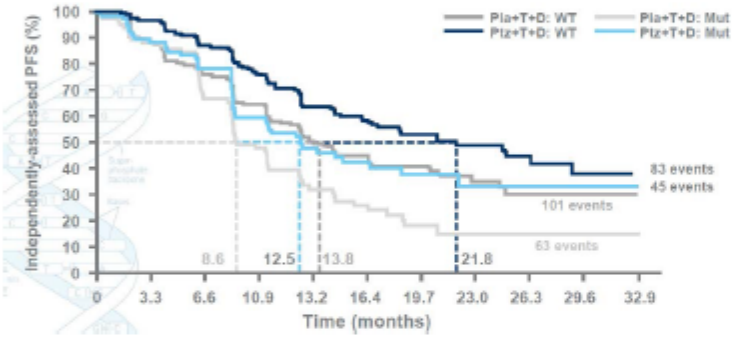
Based on Neosphere,NeoAltto,Tryphaena

IS PIK3CA MUTATION AS MEDIATOR OF (DUAL) HER2 BLOCKADE RESISTANCE?

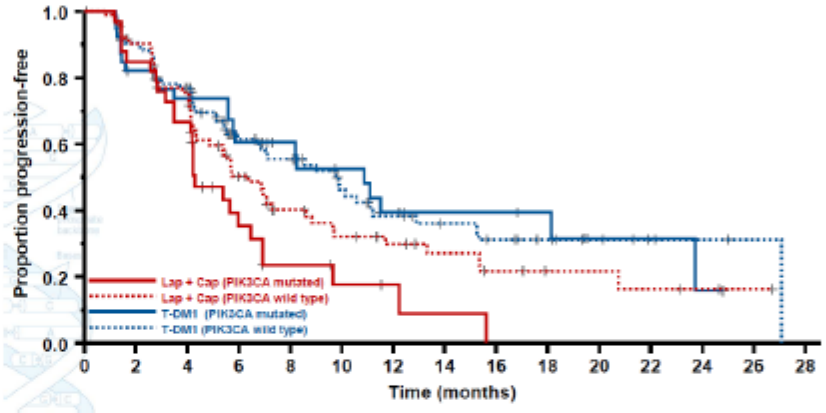
Pertuzumab and T-DM1 Biomarker Program

PIK3CA mutations (32% incidence):
A strong candidate prognostic marker but weak predictive marker!

CLEOPATRA



EMILIA



	Single blockade median PFS	Dual blockade median PFS	HR	Lapatinib + CAP median PFS	T-DM1	HR
PIK3CA stats mutant	8.6 months	12.5 months	0.64	4.3 months	10.9 months	0.45
Wild type	13.8 months	21.8 months	0.67	6.4 months	9.8 months	0.74

Dual blockade works in both cohorts… but larger magnitude of benefit in wild type cohort

T-DM1 works in both cohorts… but larger magnitude of benefit in mutated cohort

Baselga J, et al. *J Clin Oncol*. 2014;32(33):3753-3761. Baselga J, et al. 2013;73: Abstract: LB-63.

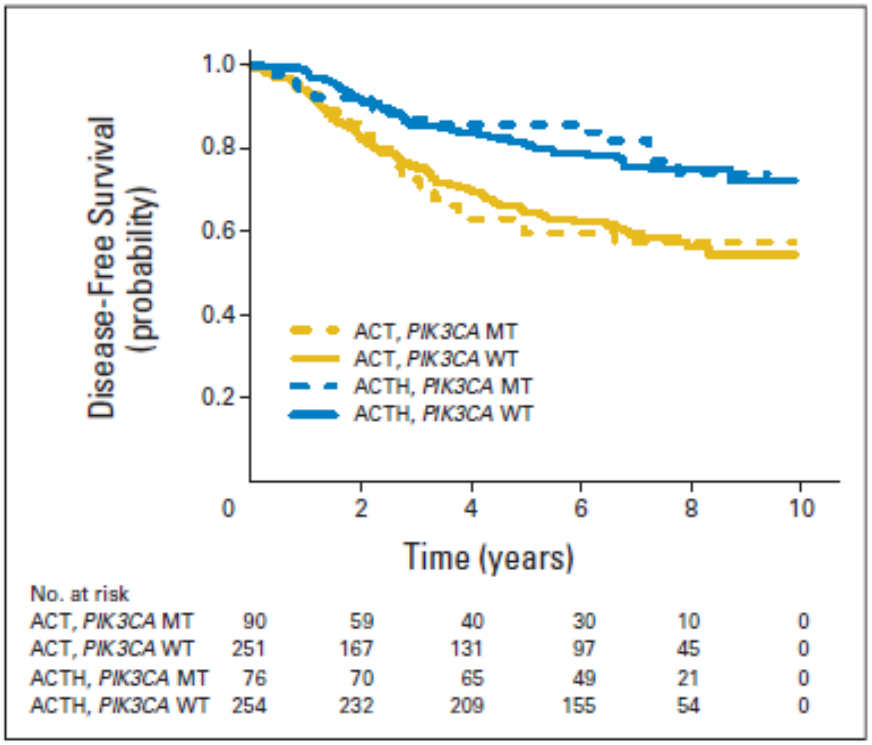
VOLUME 33 · NUMBER 12 · APRIL 20 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Intrinsic Subtypes, *PIK3CA* Mutation, and the Degree of Benefit From Adjuvant Trastuzumab in the NSABP B-31 Trial

Katherine L. Pogue-Geile, Nan Song, Jong-Hyeon Jeong, Patrick G. Gavin, Seong-Rim Kim, Nicole L. Blackmon, Melanie Finnigan, Priya Rastogi, Louis Fehrenbacher, Eleftherios P. Mamounas, Sandra M. Swain, D. Lawrence Wickerham, Charles E. Geyer Jr, Joseph P. Costantino, Norman Wolmark, and Soonmyung Paik



No. at risk

ACT, *PIK3CA* MT	90	59	40	30	10	0
ACT, *PIK3CA* WT	251	167	131	97	45	0
ACTH, *PIK3CA* MT	76	70	65	49	21	0
ACTH, *PIK3CA* WT	254	232	209	155	54	0

1578 patients → 671 randomly selected for PIK3CA hotspots mutation → 24.7% mutated

Failure of PIK3CA mutation to define subset of patient with differential benefit for trastuzumab in adjuvant setting. Hypothesis: different behaviour of predictive marker in the different settings (adjuvant, neoadjuvant, metastatic due to tumor burden)

355 patients recruited in «neoALTTO trial»

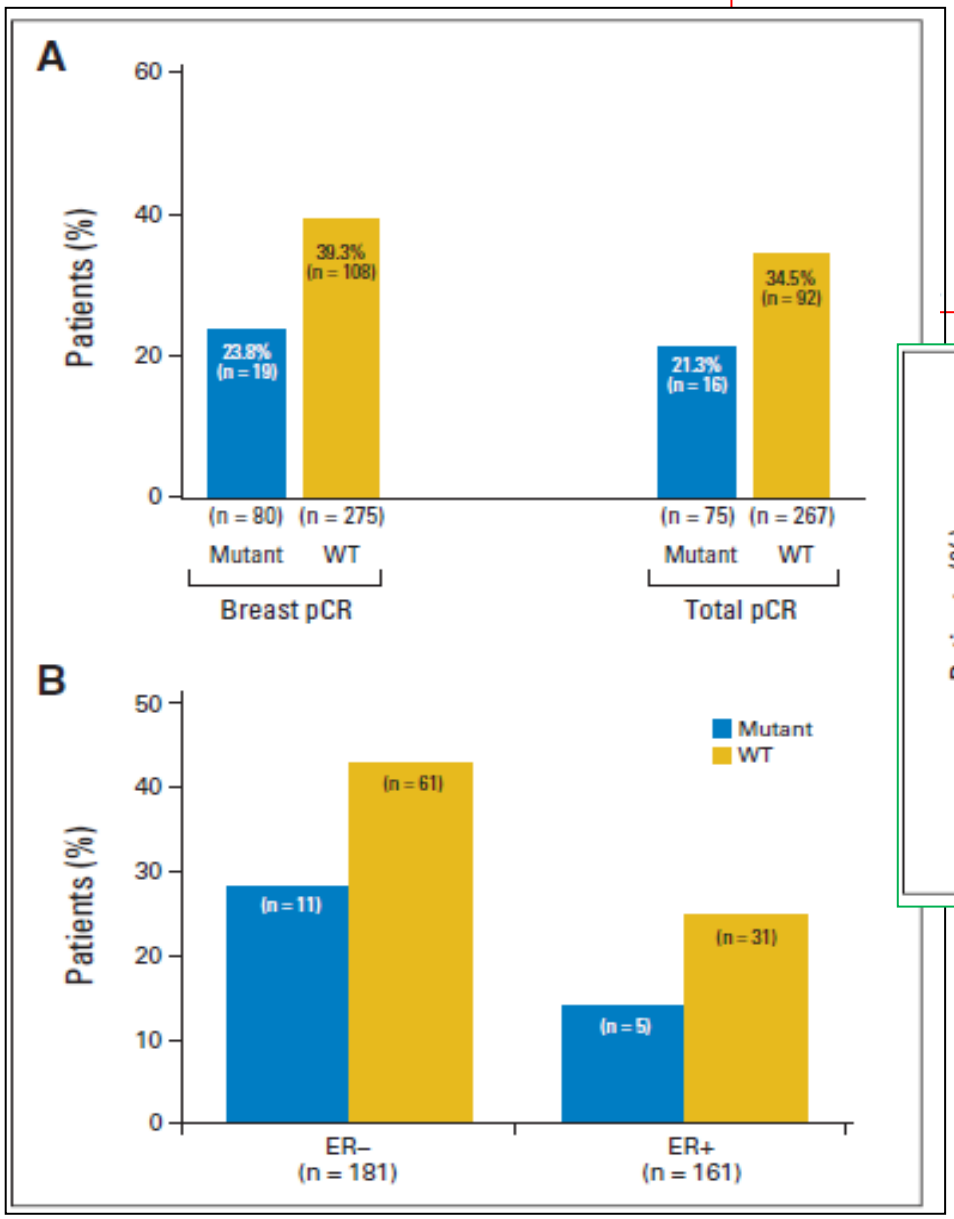
VOLUME 33 · NUMBER 12 · APRIL 20 2015

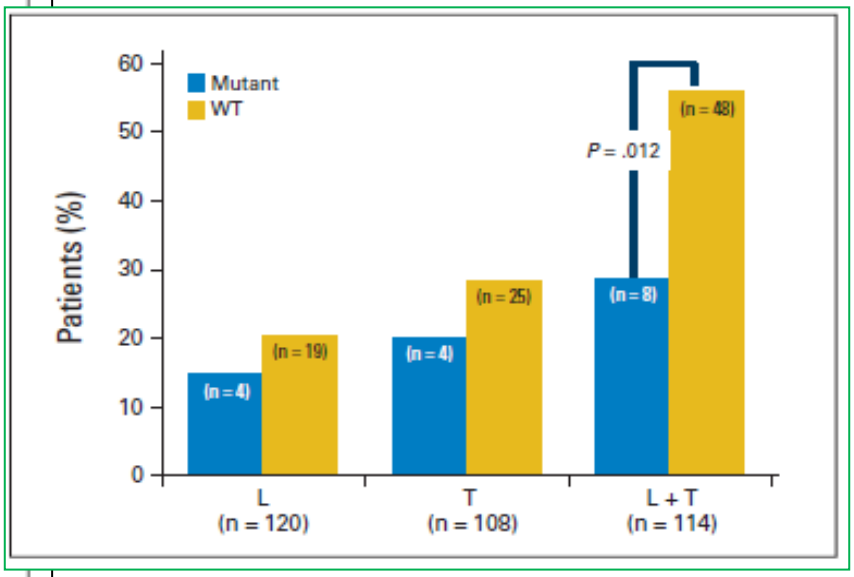
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

PIK3CA Mutations Are Associated With Decreased Benefit to Neoadjuvant Human Epidermal Growth Factor Receptor 2–Targeted Therapies in Breast Cancer

Ian J. Majewski, Paolo Nuciforo, Lorenza Mittempergher, Astrid J. Bosma, Holger Eidtmann, Eileen Holmes, Christos Sotiriou, Debora Fumagalli, Jose Jimenez, Claudia Aura, Ludmila Prudkin, Maria Carmen Diaz-Delgado, Lorena de la Pena, Sherene Loi, Catherine Ellis, Nikolaus Schulz, Evandro de Azambuja, Nadia Harbeck, Martine Piccart-Gebhart, René Bernards, and José Baselga





In this study, we find that mutations in *PIK3CA* downstream of HER2 correlate with a lower response to HER2-targeted neoadjuvant therapy in breast cancer as measured by pCR. There is no significant difference for *PIK3CA* mutation status in survival follow-up (EFS and OS).

A PIK3CA inhibitor might have an impossible task in the presence of chemotherapy

ON GOING DESIGN NEOADJUVANT TRIAL

ENDOCRINE THERAPY + **DUAL HER2 BLOCKADE** +/- **PIK3CA INHIBITORS**

VOLUME 33 · NUMBER 12 · APRIL 20 2015

JOURNAL OF CLINICAL ONCOLOGY

EDITORIAL

PIK3CA Genotype and Treatment Decisions in Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer

David W. Cescon, *Princess Margaret Cancer Centre, University Health Network, University of Toronto, and Campbell Family Institute for Breast Cancer Research, Toronto, Ontario, Canada*
Philippe L. Bedard, *Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, Ontario,*

we will learn whether knowledge of *PIK3CA* mutations can improve the precision with which we apply HER2-targeted therapies; for the present, we will continue to rely on the first (and still only) actionable genomic alteration in breast cancer: amplification of *HER2*.

WORK IN PROGRESS


grazie dell' attenzione