HUMANITAS
CENTRO CATANESE DI ONCOLOGIA

SOCIETA' ITALIANA DI FARMACIA OSPEDALIERA
E DEI SERVIZI FARMACEUTICI DELLE AZIENDE SANITARIE

fondata nel 1952

Corso residenziale interattivo a cura
della sezione regionale SIFO Sicilia

"SOSTENIBILITÀ E INNOVAZIONE DEL SISTEMA DELLE CURE ONCOLOGICHE IN SICILIA:
ASPETTI SCIENTIFICI, REGOLATORI E CLINICI"

Anticorpi monoclonali: la scelta, la sicurezza, la vigilanza

Il clinico tra presente e futuro

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Resp. Unità Funzionale
Dir. Ricerca Clinica

Catania, 21 nov 2014

Biologia molecolare
Consente lo studio

La differente espressione di geni coinvolti in neoplasie *(Genomica)*

E le proteine da essi prodotte *(Proteomica)*

Al fine di determinare un dettagliato profilo molecolare neoplastico su cui agire

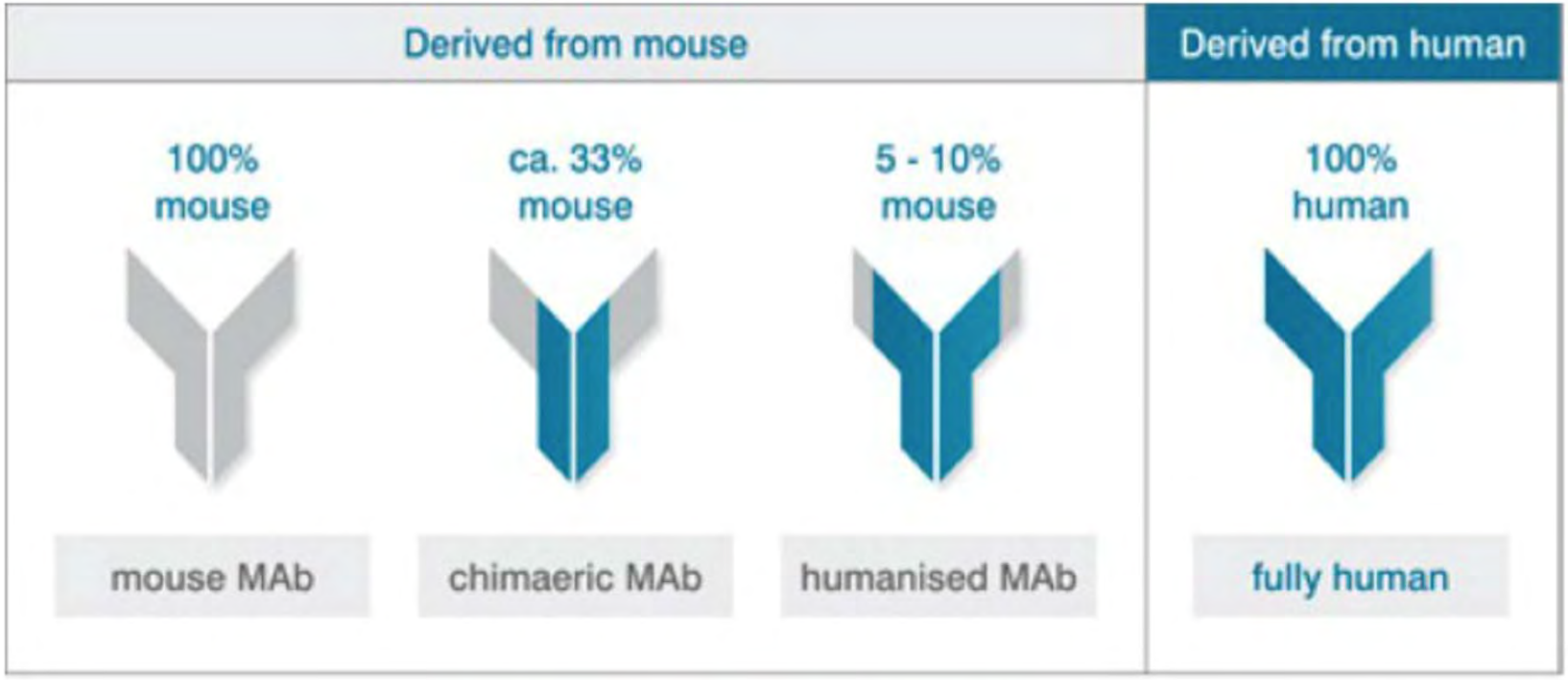
Le “Bombe Intelligenti”

Encarta Enciclopedia, DOE/Science Source/Photo Researchers, Inc.

Le “Bombe Intelligenti”

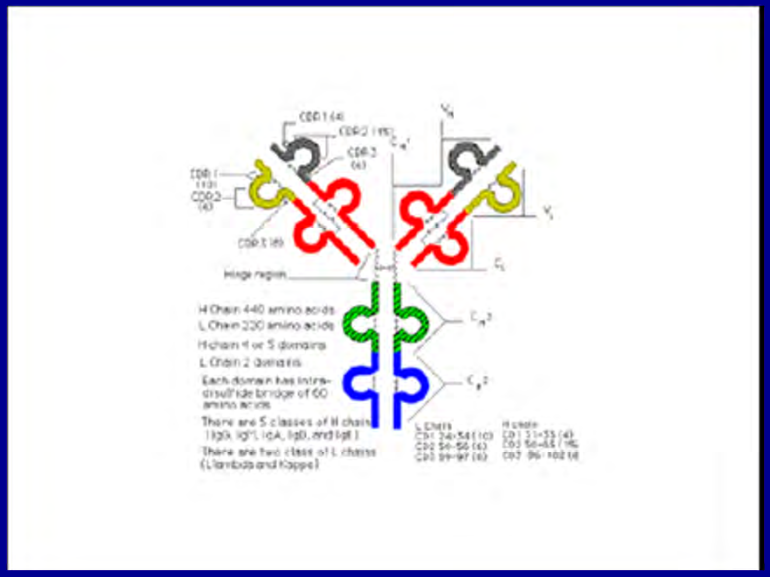
Anticorpi Monoclonali

Types of monoclonal antibodies



Advantages of fully human antibodies:

- Minimized immunogenicity
- Multiple treatments possible
- Improved serum half-life

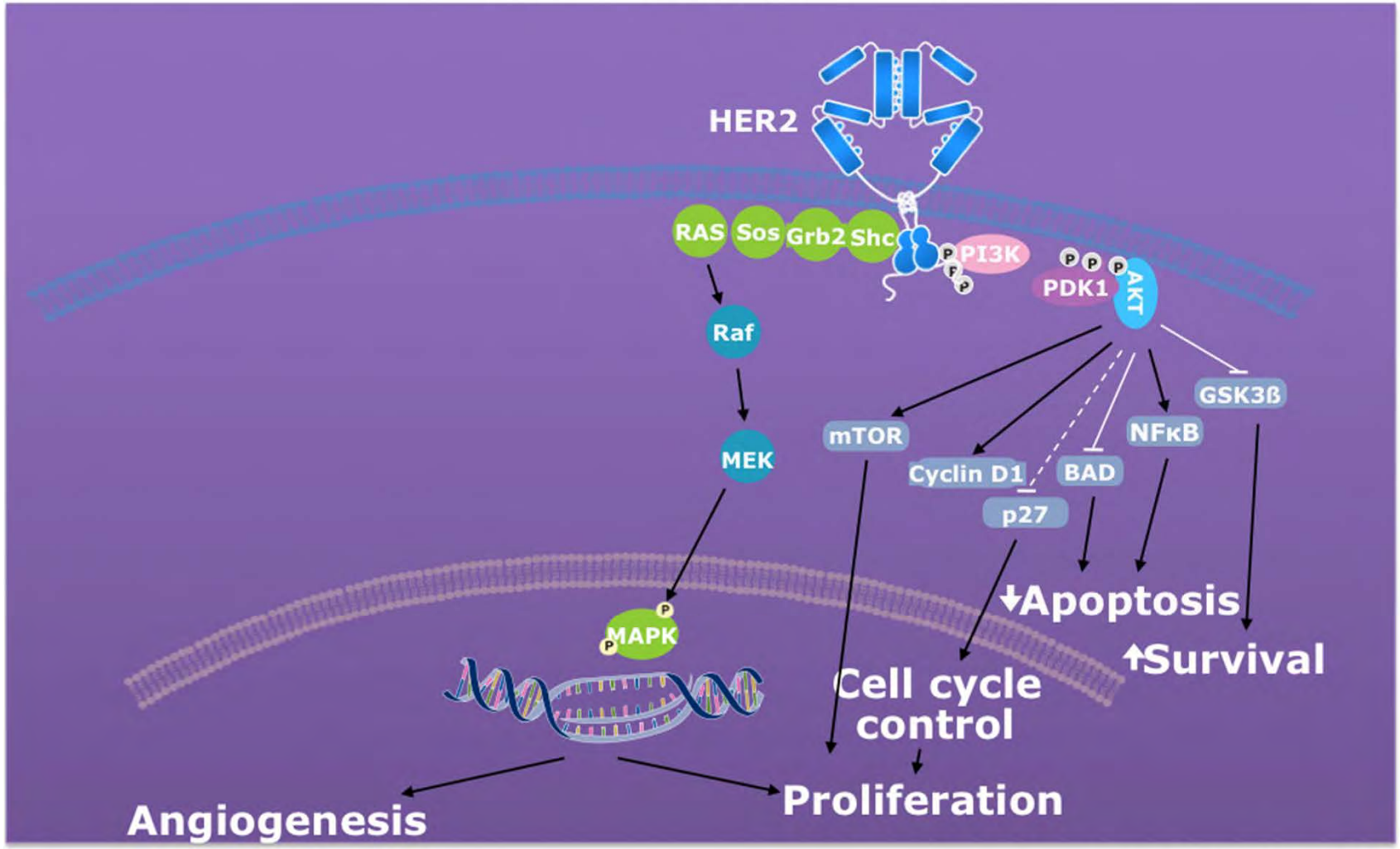


Il primo anticorpo monoclonale ad essere utilizzato negli ospedali è stato il rituximab, nato dodici anni fa, e' capace di reagire contro il CD20 un antigene presente sulla superficie delle cellule in oltre il 95% dei linfomi del tipo non-Hodgkin.

Table 1. FDA Approved Monoclonal Antibodies Used to Treat Cancer.			
Drug	**Trade Name**	**Target**	**Cancer Type**
Trastuzumab	Herceptin	HER2	Breast, gastric
Pertuzumab	Parjeta	HER2	Breast
Cetuximab	Erbitux	HER1	Squamous cell carcinoma
Panitumumab	Vectibix	HER1	Colon
Bevacizumab	Avastin	VEGF	Glioblastoma, NSCLC, colorectal, kidney
Rituximab	Rituxan	CD20	B-cell non-Hodgkin lymphoma, chronic lymphocytic leukemia
Alemtuzumab	Campath	CD52	B-cell chronic lymphocytic leukemia
Ofatumumab	Arzerra	CD20	Chronic lymphocytic leukemia
Ipilimumab	Yervoy	CTLA-4	Melanoma

Abbreviations: HER, human epidermal growth factor receptor; VEGF, vascular endothelial growth factor; CD, cluster of differentiation; CTLA, cytotoxic T-lymphocyte antigen.

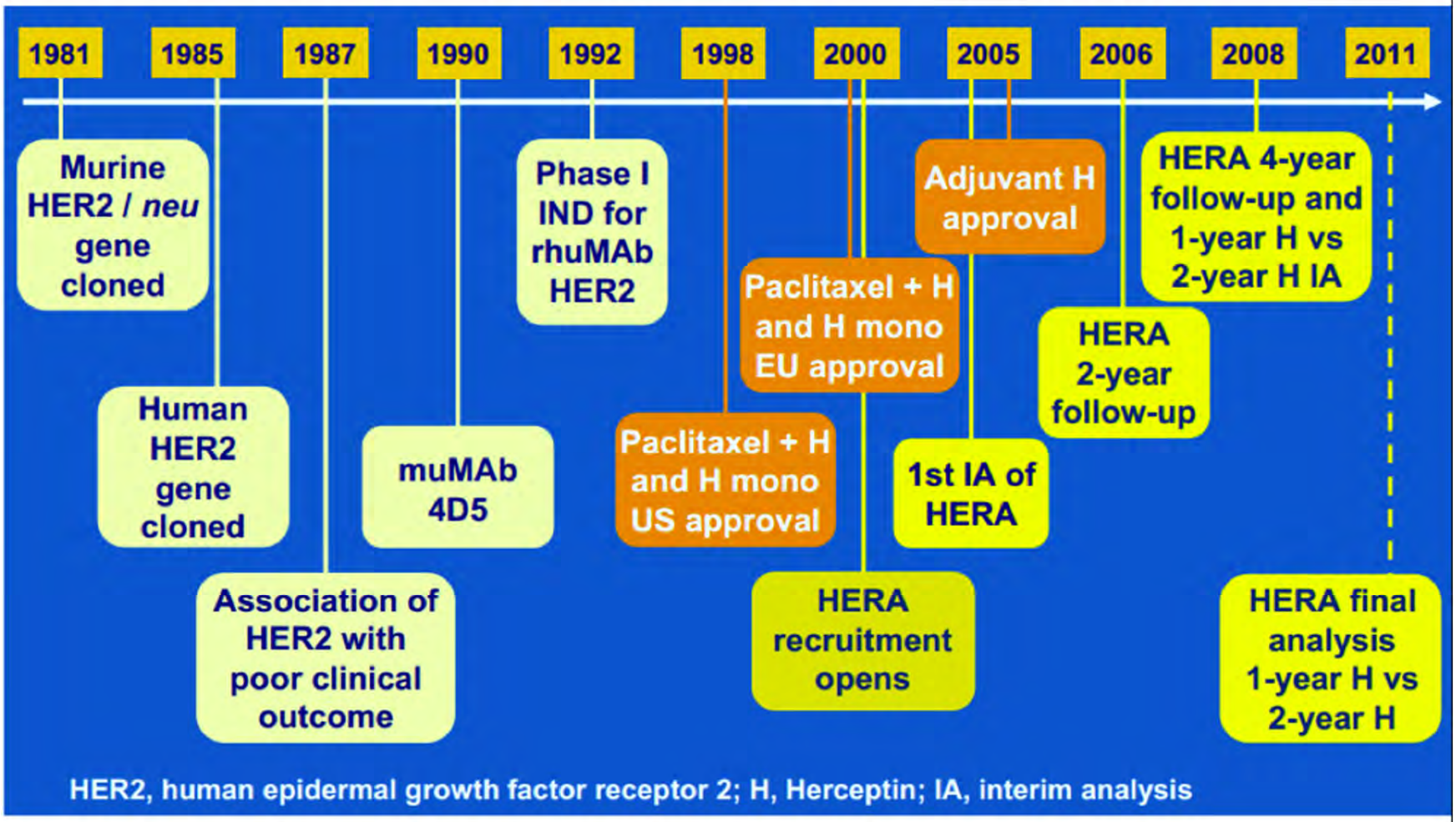
HER2 signalling



Graphical elaboration from text data

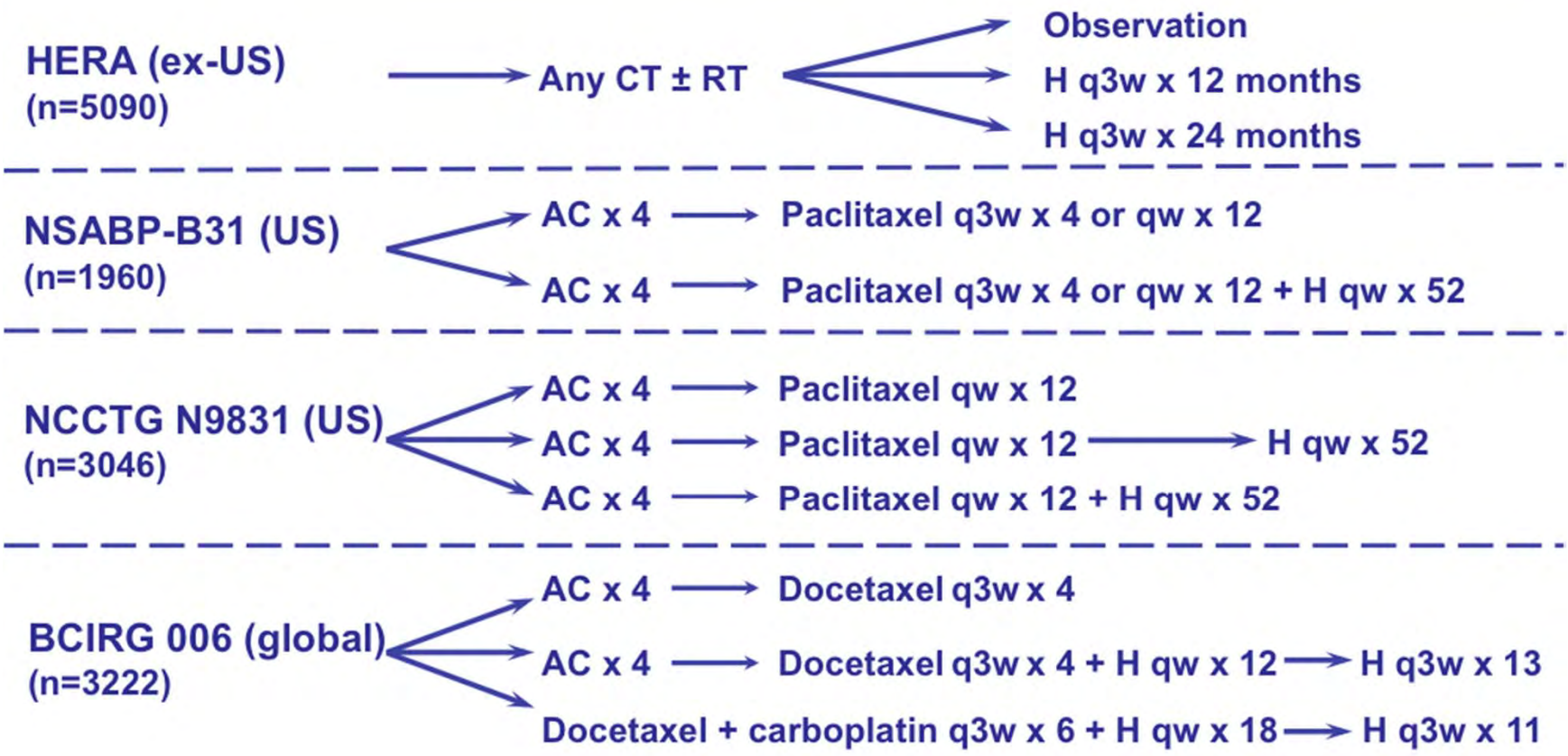
Olayioye et al. EMBO J 2000;19:3159–3167;
Rowinsky et al. Annu Rev Med 2004;55:433–457

The slow history of trastuzumab[1]



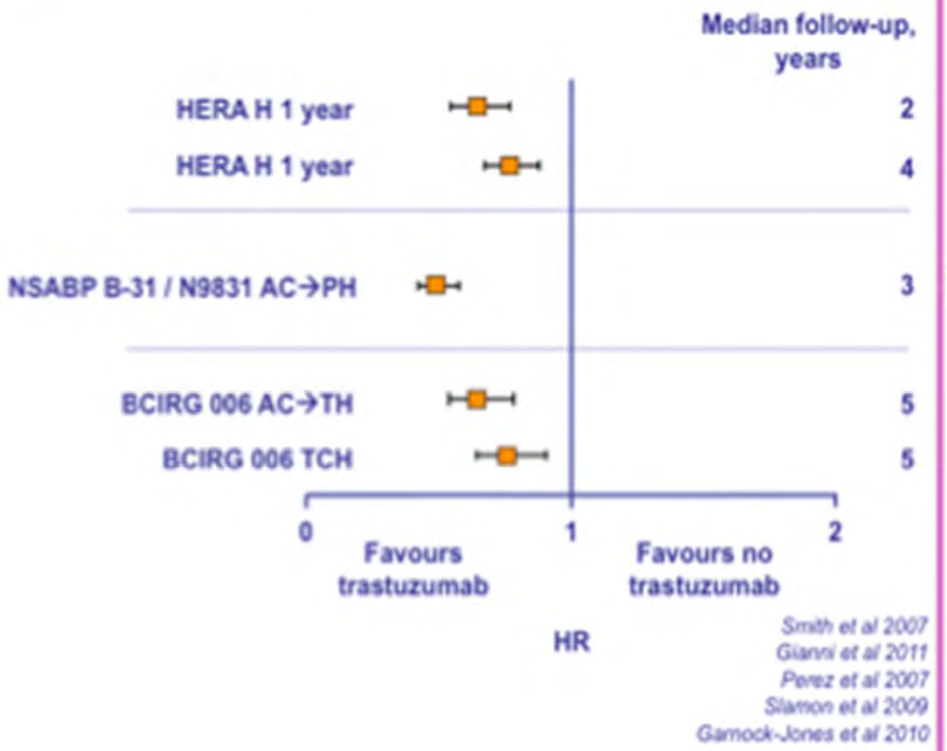
Baselga J. Pros and Cons of Neoadjuvant Trials to Support Drug Approval http://www.fda.gov/downloads/Drugs/NewsEvents/UCM344989.pdf last accessed on August 2013

Trastuzumab adjuvant programme: >14,000 patients

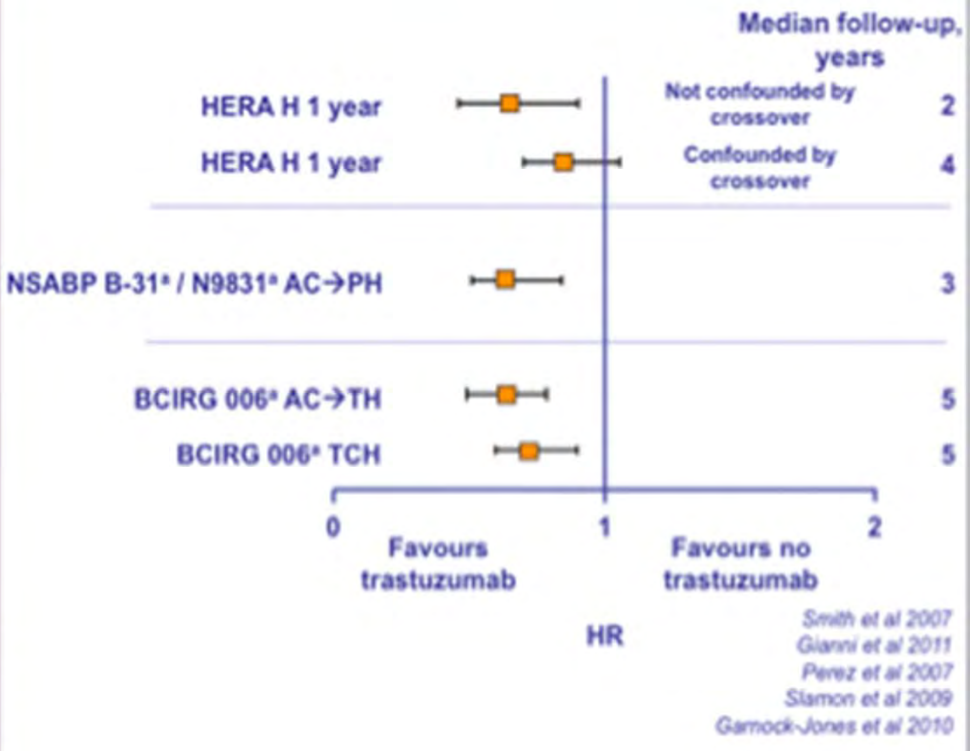


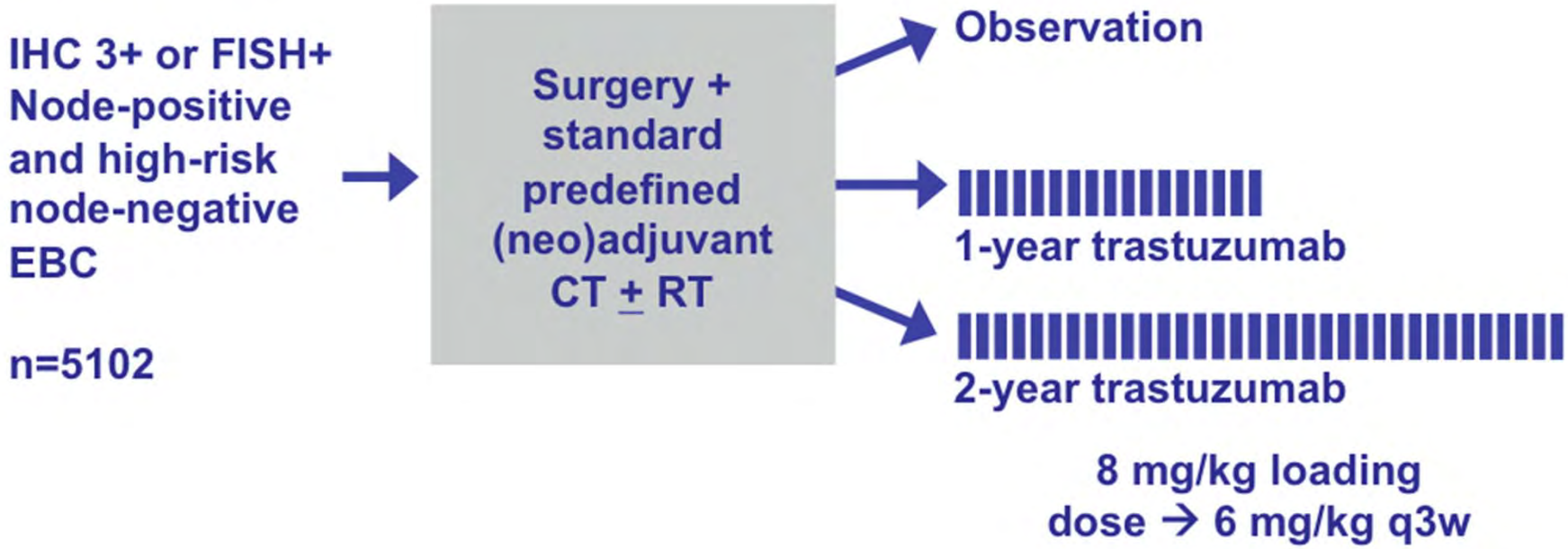
CT, chemotherapy (as approved by the HERA protocol)
RT, radiotherapy; H, Trastuzumab; AC, doxorubicin + cyclophosphamide

Adjuvant trastuzumab in EBC: reported overall survival



Adjuvant trastuzumab in EBC: reported DFS





- Trastuzumab q3w after standard adjuvant therapy
- 1 vs. 2 years of treatment
- Crossover permitted after 1st interim efficacy analysis

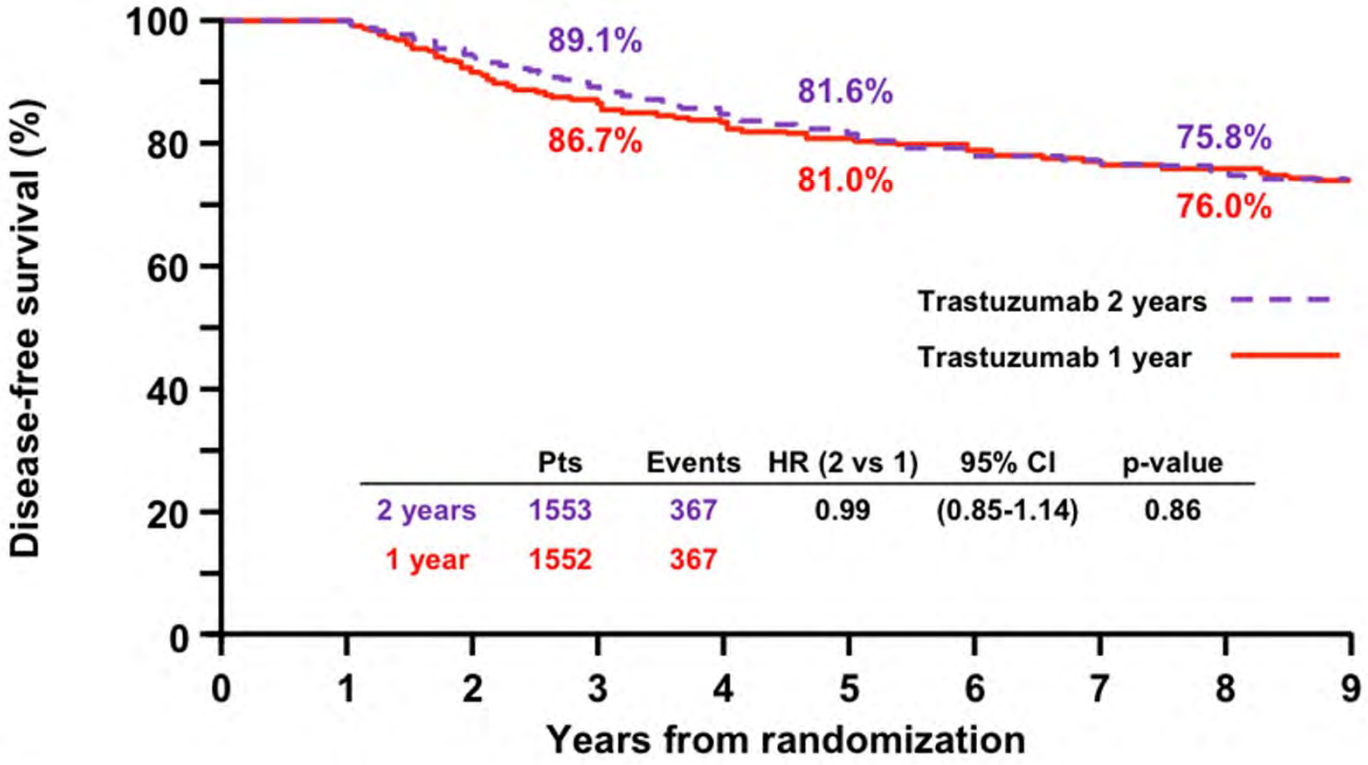
EBC, early breast cancer; CT, chemotherapy;
RT, radiotherapy; q3w, every 3 weeks

Piccart-Gebhart et al 2005

HERA TRIAL: 2 years versus 1 year of trastuzumab after adjuvant chemotherapy in women with HER2-positive early breast cancer at 8 years of median follow up

ESMO Congress, Vienna – 1 October 2012

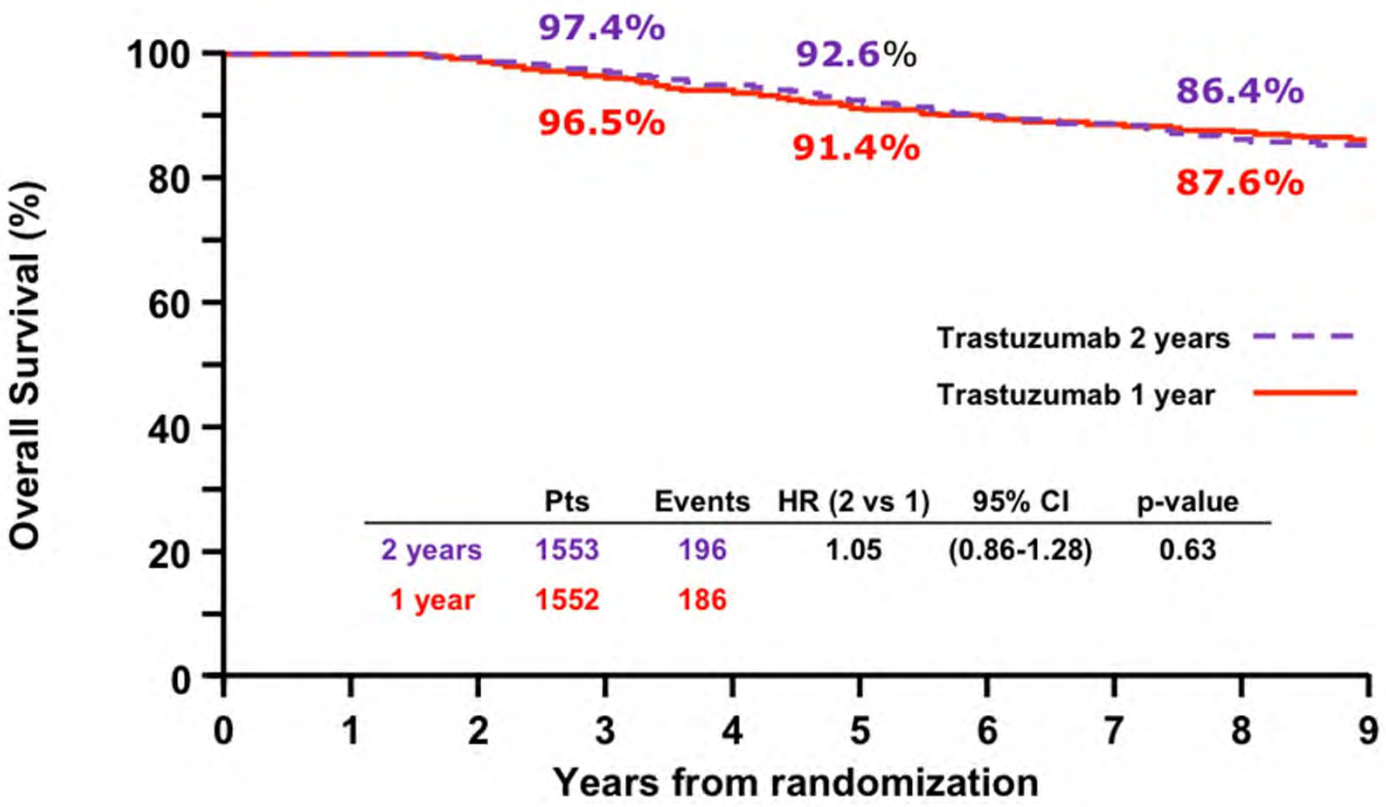
DFS FOR 2 YEARS VS. 1 YEAR TRASTUZUMAB AT 8 YRS MFU



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

de Azambuja E. Oral presentation SABCS 2012 - Available free online at http://sabcs12.m2usa.com/sabcsdsv.html Last access September 2013 Cancer Research 2012 72:24 SUPPL. 3
Goldhirsch A. Lancet. 2013;382:1021-8

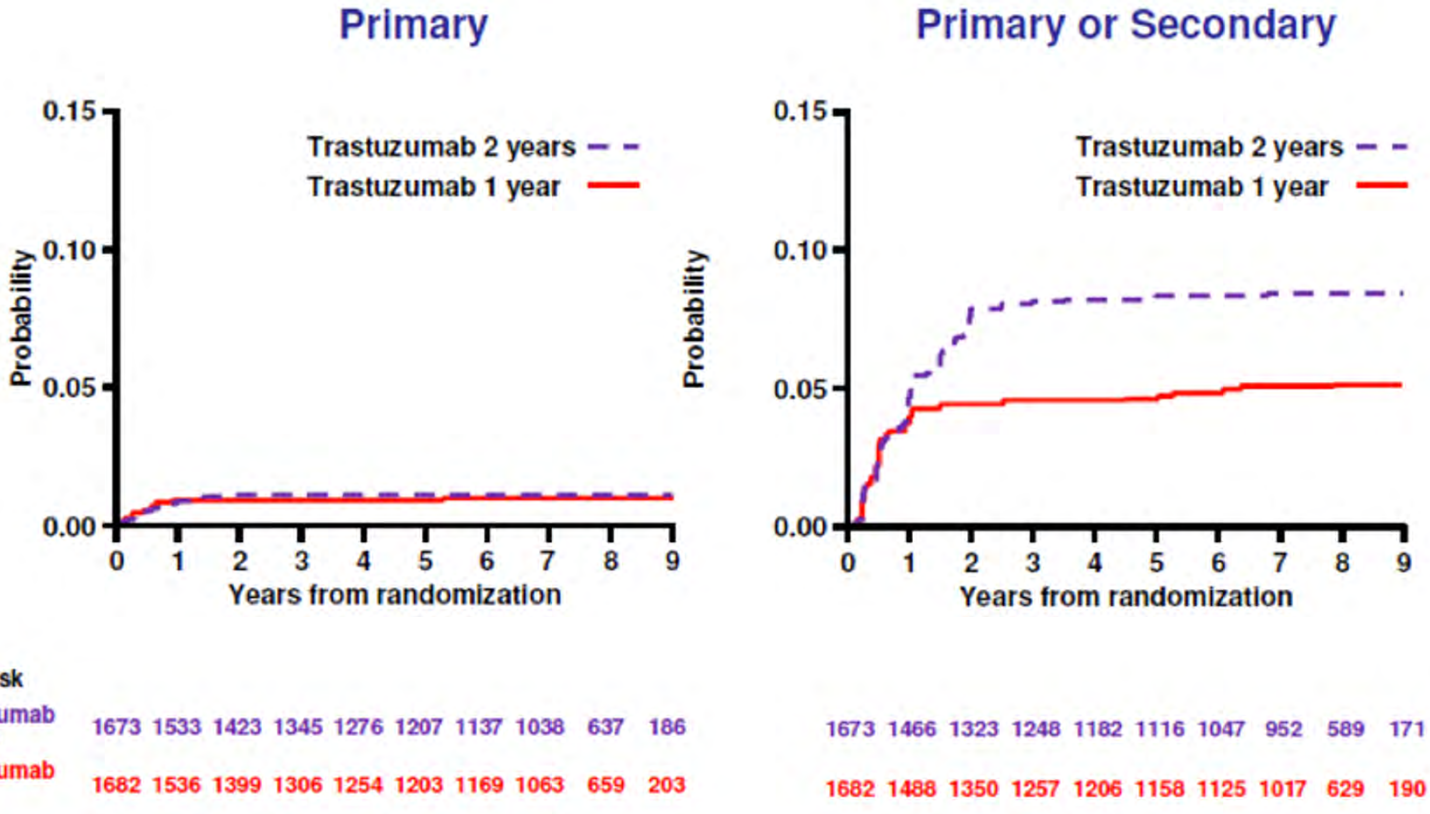
OS FOR 2 YEARS VS. 1 YEAR TRASTUZUMAB AT 8 YRS MFU



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

de Azambuja E. Oral presentation SABCS 2012 - Available free online at http://sabcs12.m2usa.com/sabcsdsv.html Last access September 2013 Cancer Research 2012 72:24 SUPPL. 3

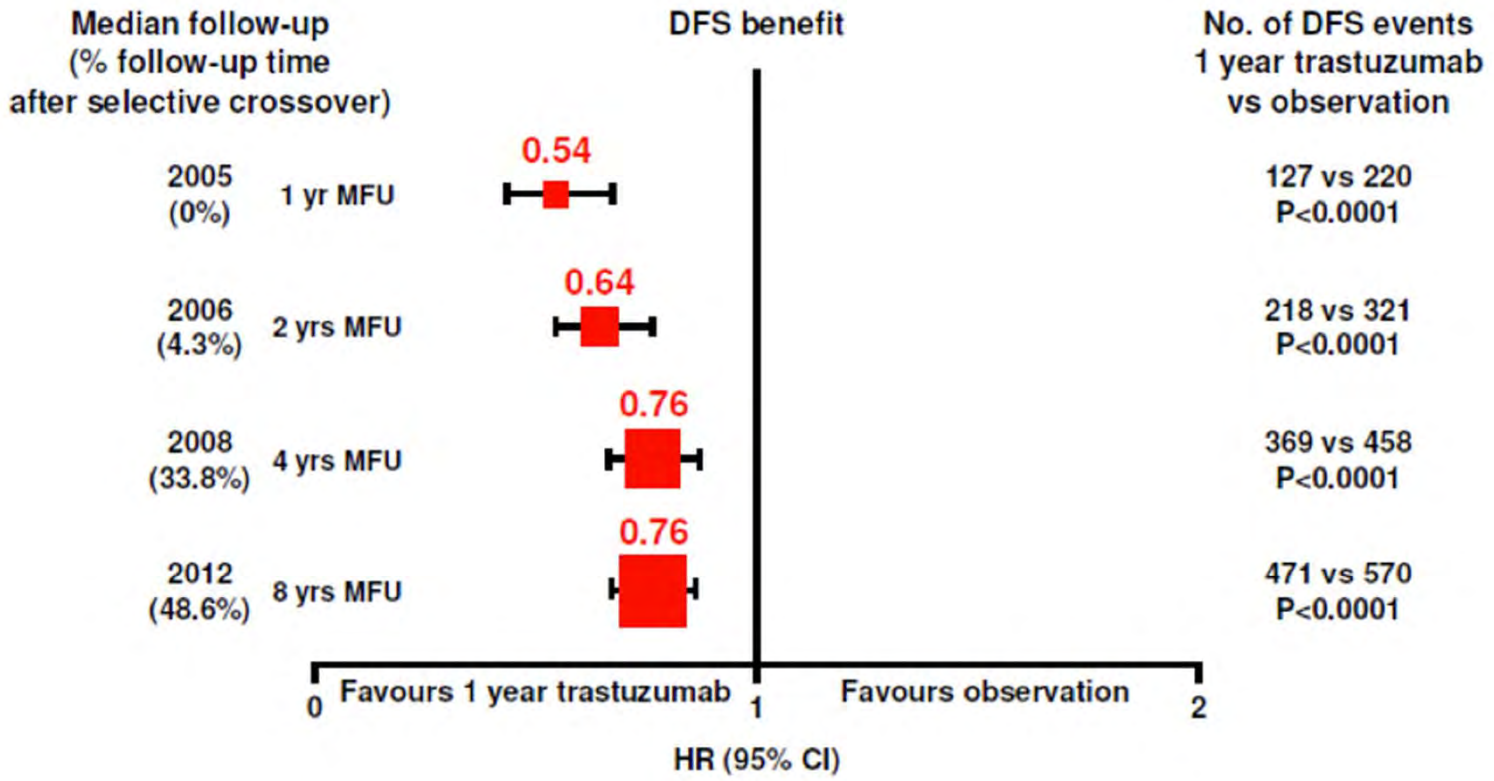
CUMULATIVE INCIDENCE OF CARDIAC ENDPOINTS*



* Competing risk analysis with disease-free survival events considered as competing risks
The majority of cardiac events are reversible (Procter et al. JCO 2010)

de Azambuja E. Oral presentation SABCS 2012 - Available free online at http://sabcs12.m2usa.com/sabcsdsv.html Last access September 2013 Cancer Research 2012 72:24 SUPPL. 3
Goldhirsch A. Lancet. 2013;382:1021-8

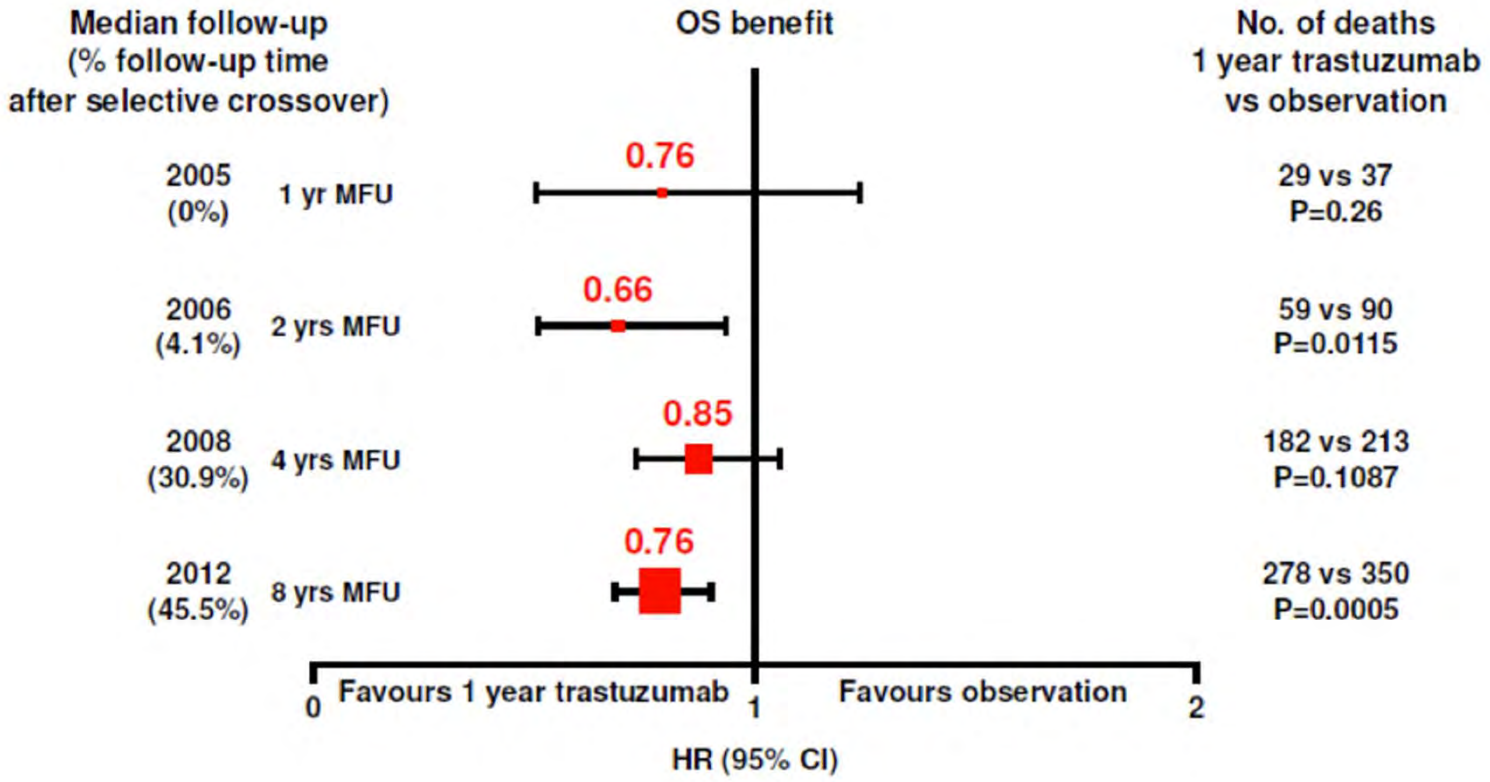
SUMMARY OF DFS ITT ANALYSES FOR 1 YEAR TRASTUZUMAB VS. OBSERVATION ACROSS ANALYSIS TIME POINTS



Extended from Gianni et al. Lancet Oncol. 2011.

de Azambuja E. Oral presentation SABCS 2012 - Available free online at http://sabcs12.m2usa.com/sabcsdsv.html Last access September 2013 Cancer Research 2012 72:24 SUPPL. 3
Goldhirsch A. Lancet. 2013;382:1021-8

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



Extended from Gianni et al. Lancet Oncol. 2011.

de Azambuja E. Oral presentation SABCS 2012 - Available free online at http://sabcs12.m2usa.com/sabcsdsv.html Last access September 2013 Cancer Research 2012 72:24 SUPPL. 3
Goldhirsch A. Lancet. 2013;382:1021-8

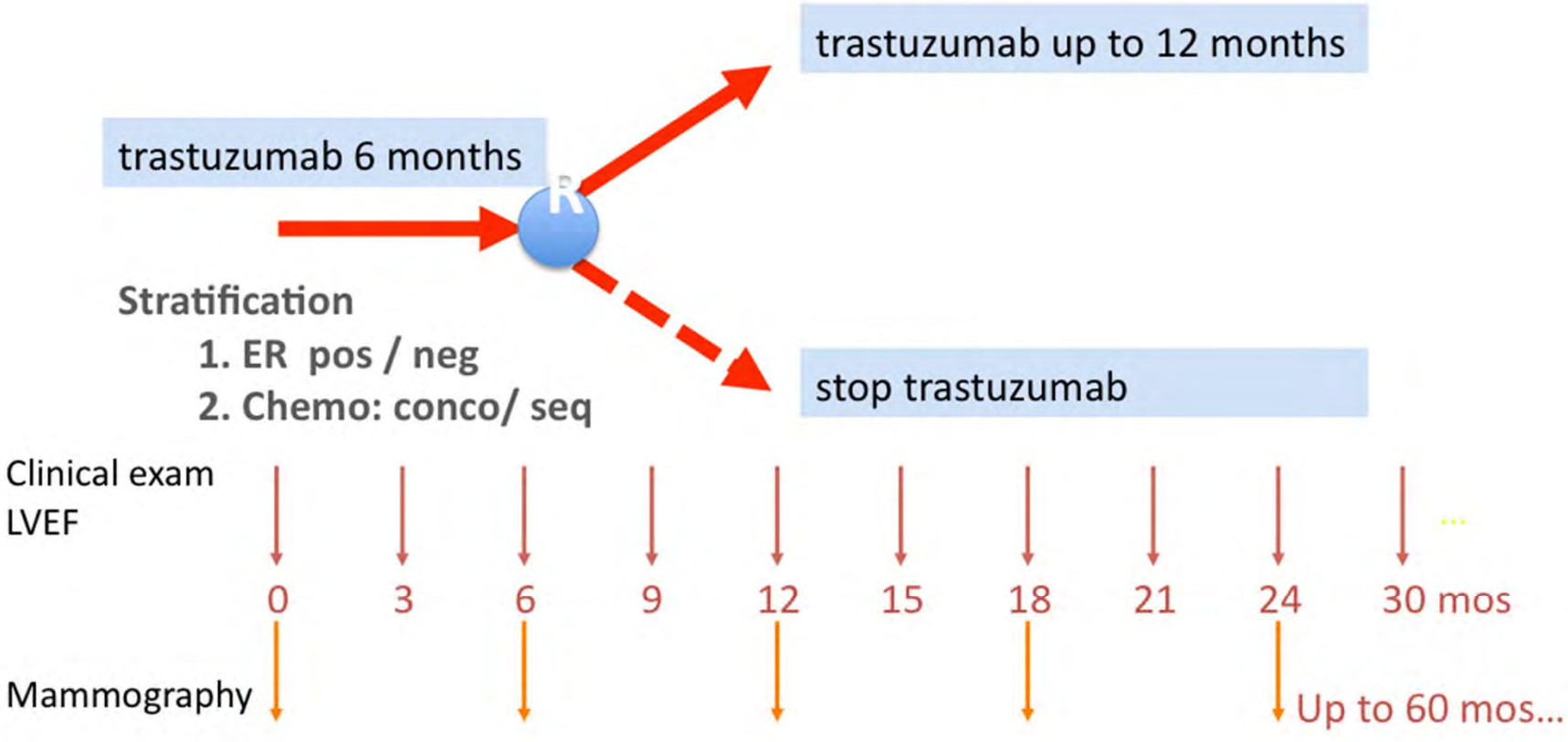
SUMMARY: ANALYSIS OF DFS AND OS FOR 1 YEAR TRASTUZUMAB VS. OBSERVATION AT 8 YRS MFU

- HERA results at 8 yrs MFU show sustained and statistically significant DFS and OS benefit for 1 year trastuzumab versus observation in ITT analyses despite selective crossover.

- 1 year of trastuzumab remains the standard of care as part of an adjuvant therapy for patients with HER2-positive early breast cancer.

de Azambuja E. Oral presentation SABCS 2012 - Available free online at http://sabcs12.m2usa.com/sabcsdsv.html Last access September 2013 Cancer Research 2012 72:24 SUPPL. 3
Goldhirsch A. Lancet. 2013;382:1021-8

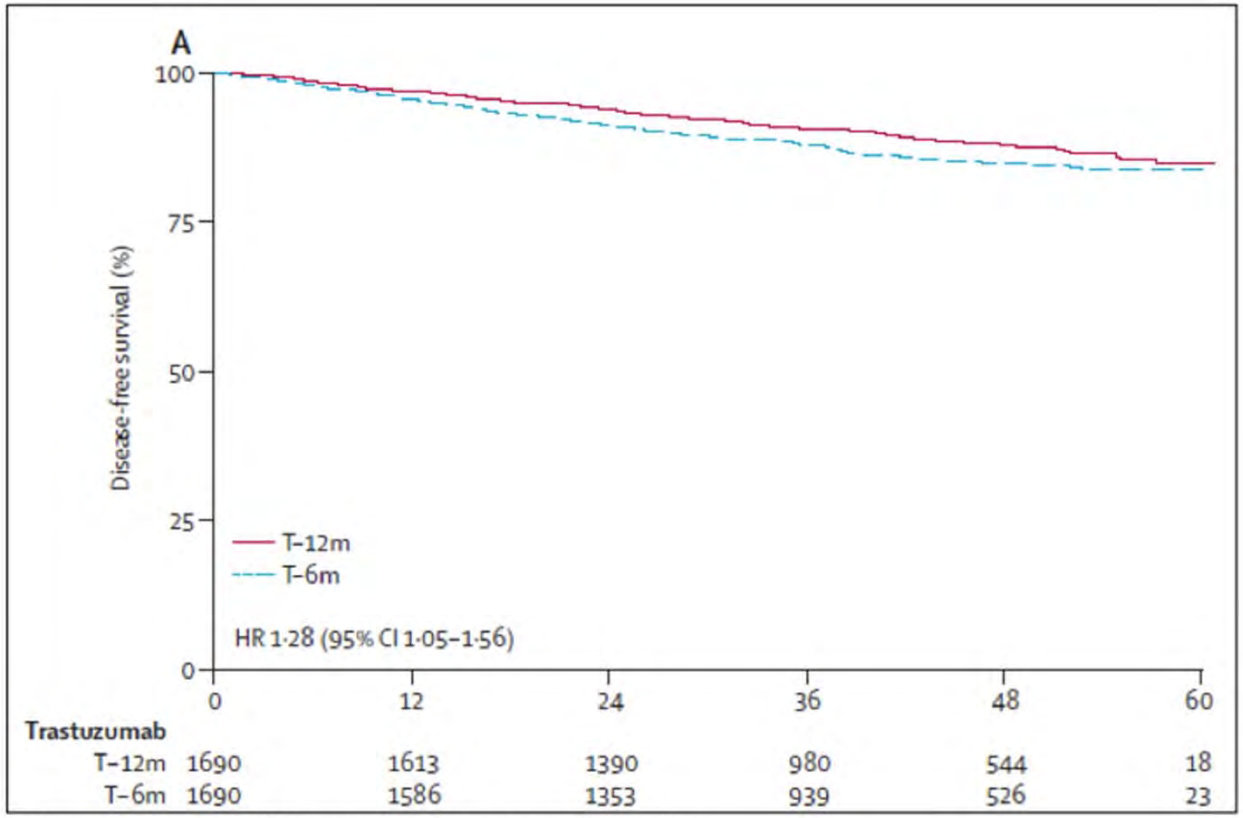
PHARE: Study design



R: Randomization after informed consent

1. Pivot X., Oral presentation – SABCS 2012
Available free online at http://sabcs12.m2usa.com/sabcsdsv.html Last access September 2013
2. Pivot X. Lancet Oncol 2013; 14:741-48

Disease Free Survival



Disease-free survival (A) according to trastuzumab duration

1. Pivot X., Oral presentation – SABCS 2012
Available free online at http://sabcs12.m2usa.com/sabcsdsv.html Last access September 2013
2. Pivot X. Lancet Oncol 2013; 14:741-48

International Consensus Panel: 2011 St. Gallen

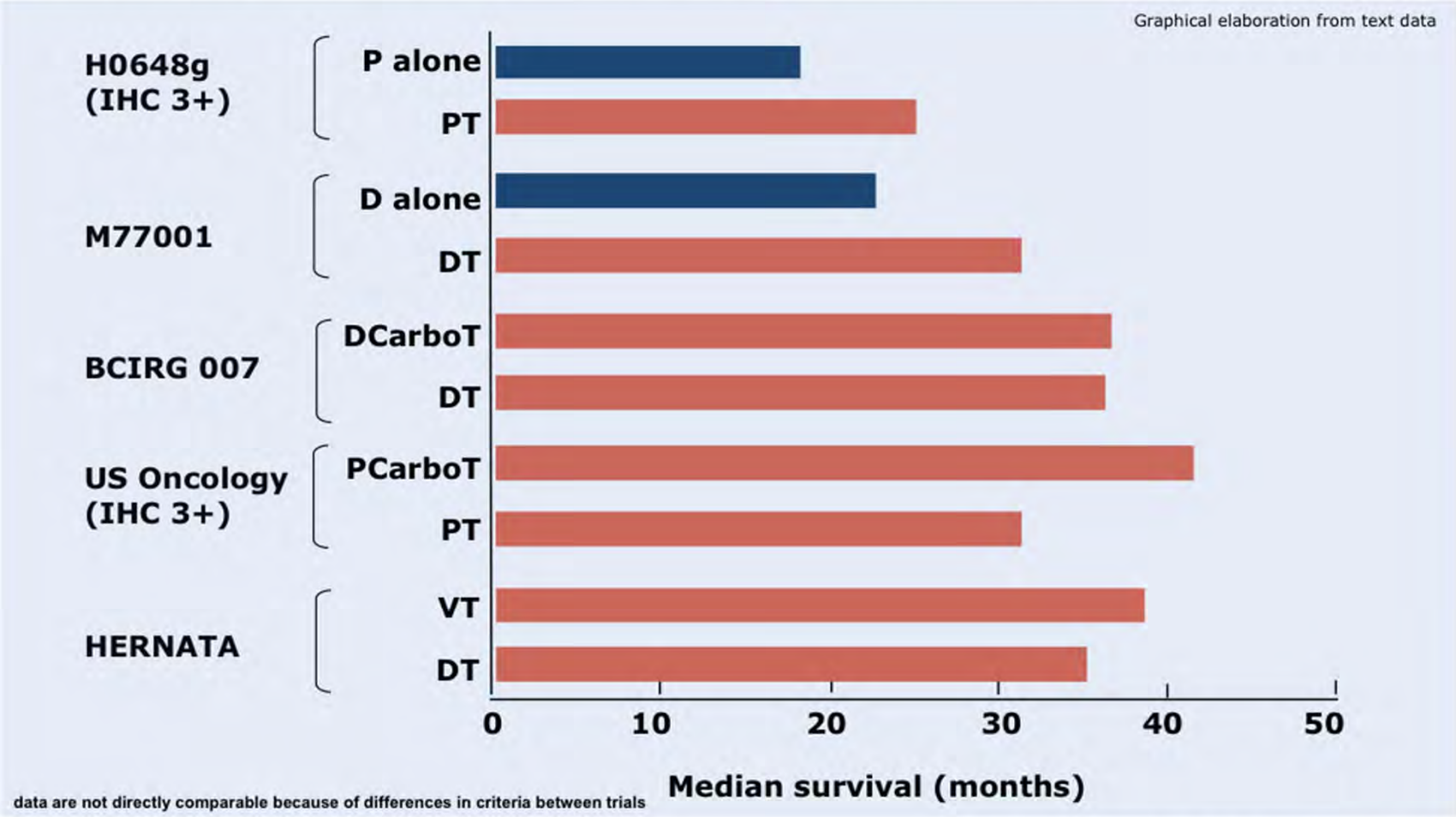
Panelists' Answers

- Is trastuzumab for 1 year, with concurrent chemotherapy (usually a taxane) or following chemotherapy (HERA-like), a standard adjuvant treatment for:

(i) HER2-positive phenotype?

a) Yes: 100%, *b) No: 0%*

Trastuzumab results in 1°- line MBC



IHC, immunohistochemistry; P, paclitaxel
T, Trastuzumab; D, docetaxel,; Carbo, carboplatin

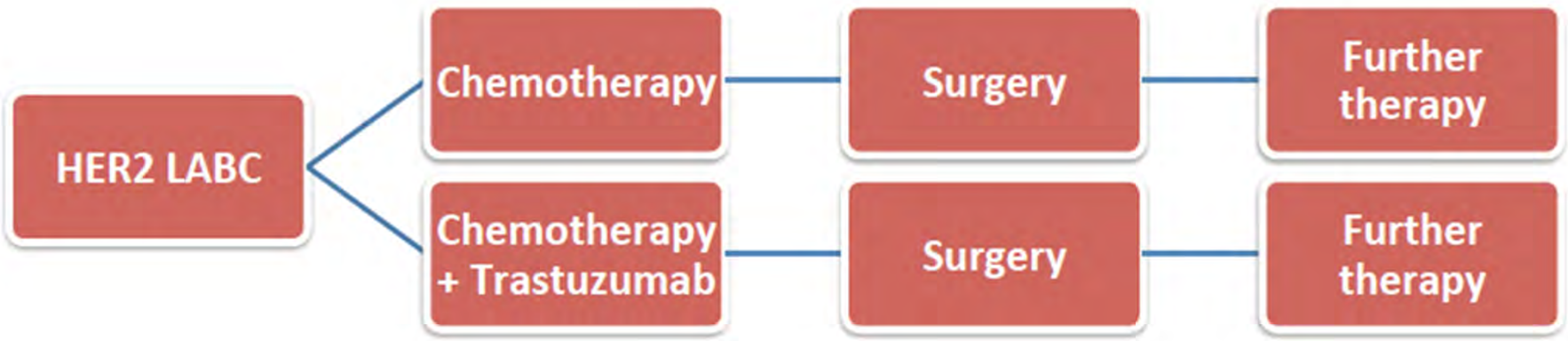
Smith et al Anti-Cancer Drugs 2001 12:SUPPL. 4 (S3-S10);
Marty et al J Clin Oncol 2005; 23:4265-4274;
Valero et al J Clin Oncol. 2011;29:149-56;
Robert et al J Clin Oncol. 2006;24:2786-92;
Andersson M. et al J Clin Oncol. 2011;29:264-71

pCR Rates

- Anthracyclines 4% to 20%
- Taxanes -30%
- Trastuzumab -40%
- Endocrine 0% to 5%

Gonzalez-Angulo AM, et al. *Adv Exp Med Biol.* 2007;608;1-22.

Trastuzumab Based Neoadjuvant Therapy



Trastuzumab Based Neoadjuvant Trials

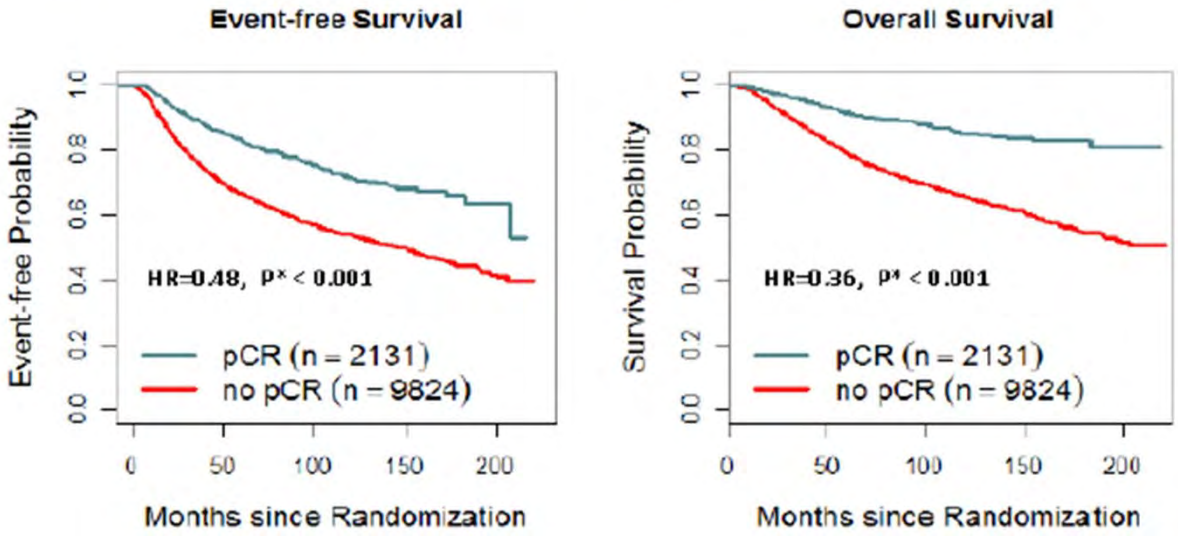
Study	N	Chemo Backbone	pCR Chemo	pCR Chemo + T	Notes
MDACC	42	P-FEC	(26%)	(65%)	<2% T4
NOAH	235	APx3-Px4-CMFx3	22% (19%)	43% (38%)	43% T4
GeparQuattro	445	EC-D(X)	16%	32%	19% T4

Buzdar et al, JCO 2005
Gianni et al, Lancet 2010
Untch et al, Lancet 2010

San Antonio Breast Cancer Symposium – December 4 - 8, 2012

CTNeoBC

Association of pCR on EFS and OS



pCR=ypT0/is ypN0 * Nominal p-value

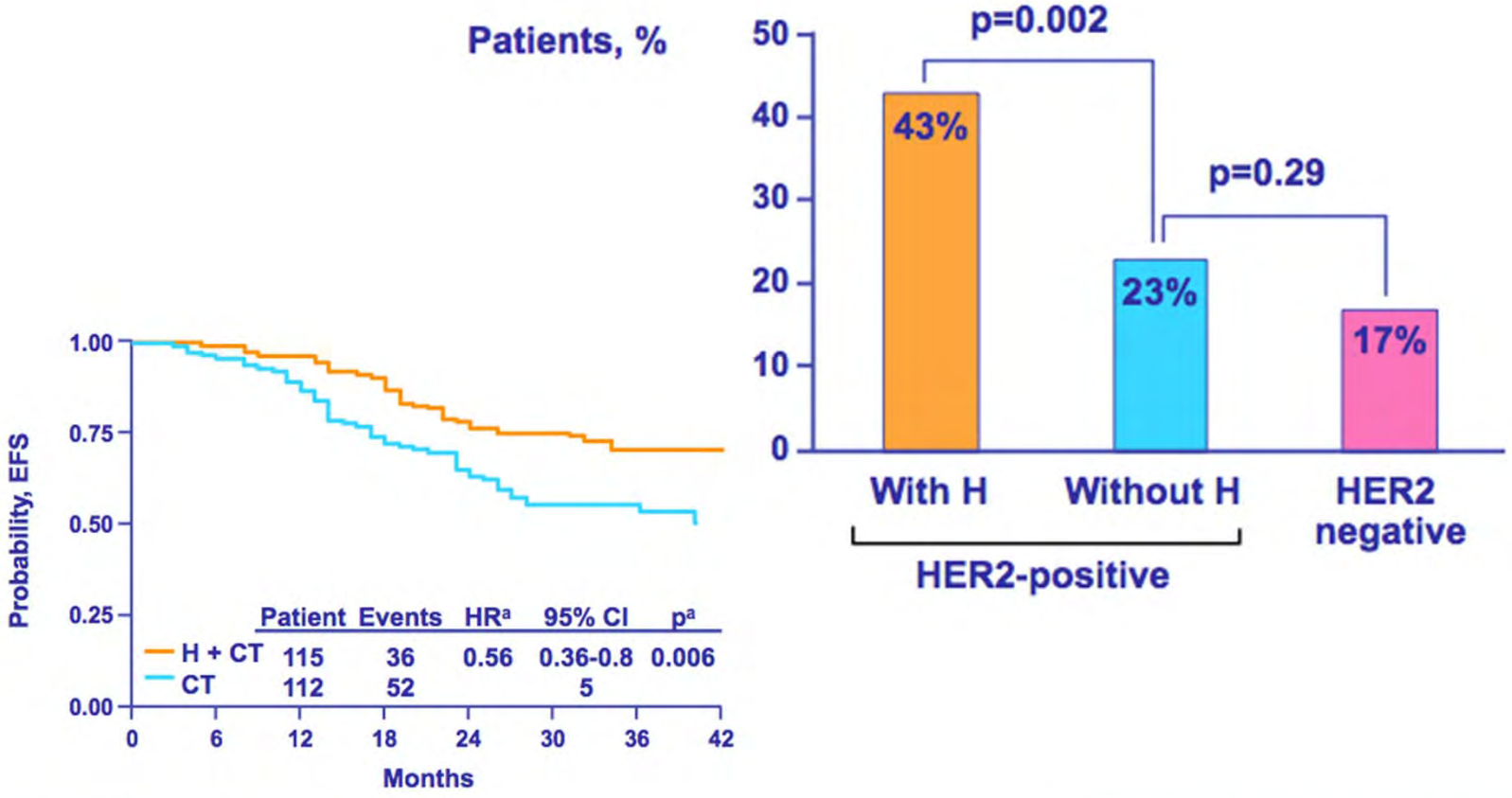
pCR association with long term outcomes (EFS and OS):

- **Individual patients who attain a pCR have a more favorable long-term outcome.**

Cortazar P et al; SABCS 2012; S1-11

Neoadjuvant Herceptin significantly improves pCR rates in the NOAH trial

pCR of primary tumour: intent-to-treat population

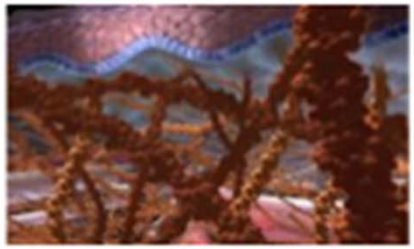


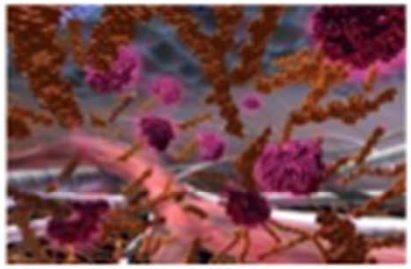
Median follow-up is 3 years
aUnadjusted for stratification variables: adjusted HR=0.55, p=0.0062
HR, hazard ratio; CI, confidence interval; CT, chemotherapy

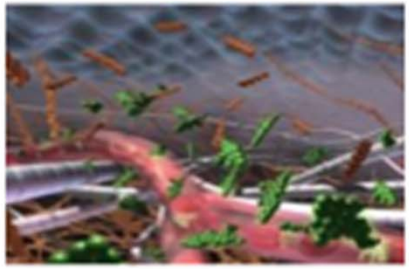
Baselga et al 2007; Gianni et al 2007

Development of a subcutaneous formulation of trastuzumab

Subcutaneous administration of trastuzumab has been made possible by the use of recombinant human hyaluronidase as an excipient

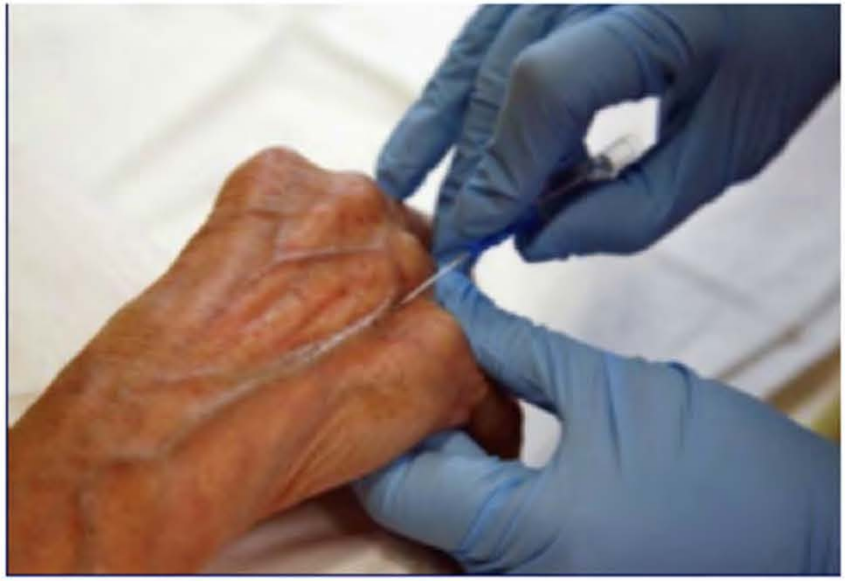




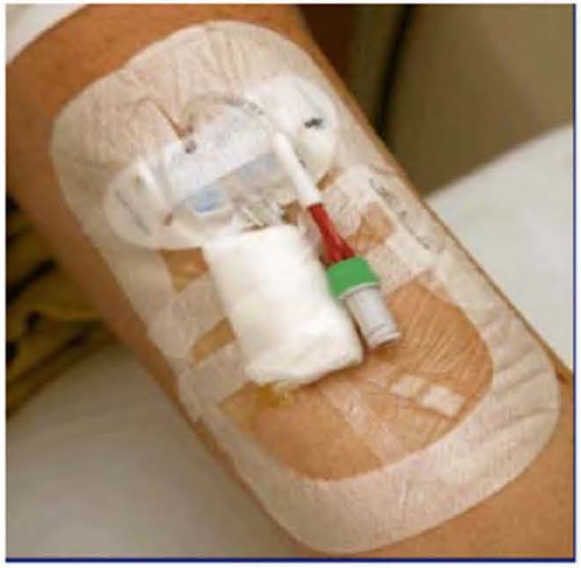


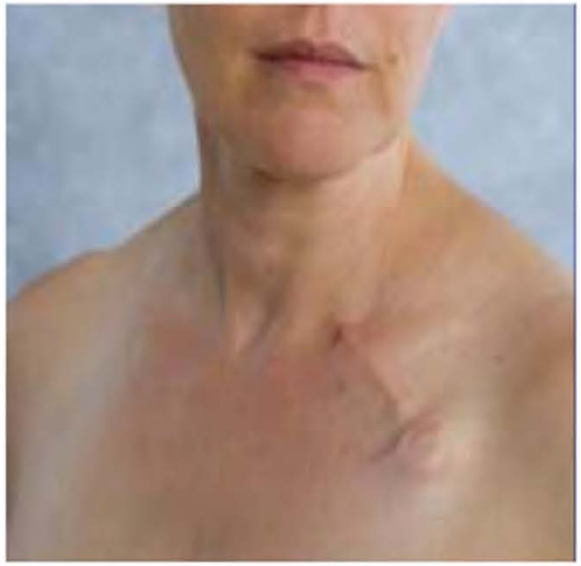
- Subcutaneous administration of large volumes is restricted by the structure and physiology of the subcutaneous layer
  - Contains a matrix of hyaluronan fibres and collagen fibres, which limits subcutaneous administration to <1 mL
- Hyaluronan is broken down by the naturally occurring enzyme, hyaluronidase, on a daily basis
- Recombinant human hyaluronidase (rHuPH20) causes temporary and local degradation of hyaluronan
  - Results in a temporary increase in the local subcutaneous dispersion area, enabling large volumes of fluids to be administered
- After subcutaneous administration, skin returns to normal

Haller MF. *Pharm Tech* 2007; 10:861-864



- Spiacevole (ripetute)
- Danno vene periferiche
- Spesso necessita Porth



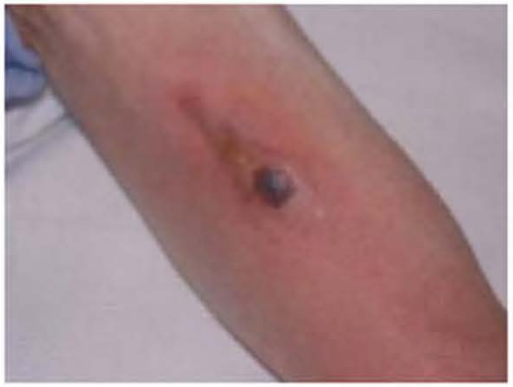


Lavaggi ripetuti

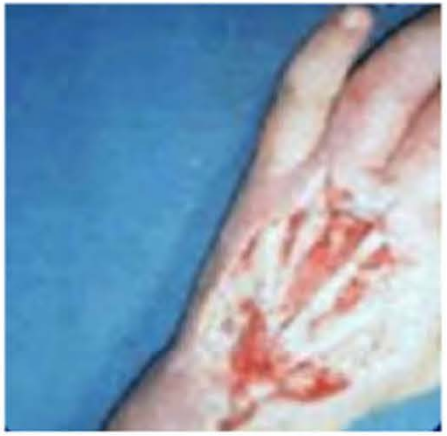
Limitazione attività

From Pivot X, Fallowfield L *et al*. St. Gallen 2013 Poster 207, modified

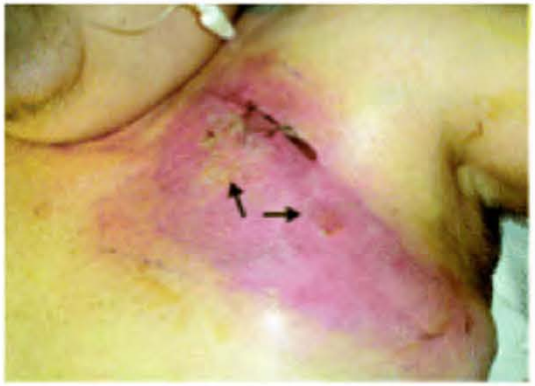
EV: Stravaso e Necrosi



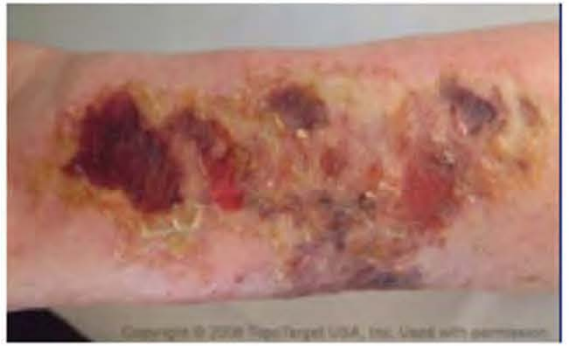
PICC Line
(paclitaxel)



Incannulazioni
ripetute



Port
(Trabectidina)



Stravaso di Antracicline

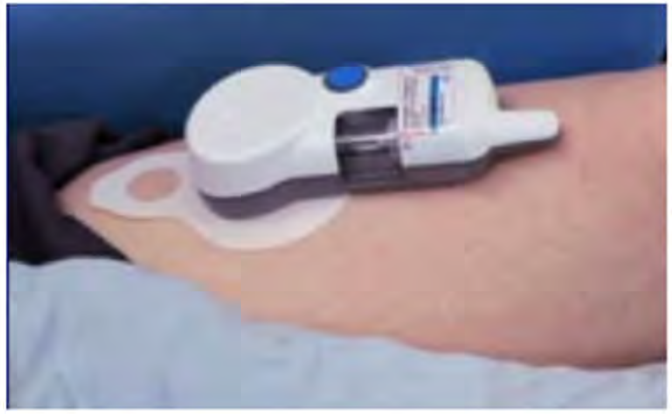
From Pivot X, Fallowfield L *et al*. St. Gallen 2013 Poster 207, modified

Potenziali vantaggi di Trastuzumab SC

Siringa tradizionale

Single injectable device

- Dose fissa
- Non necessario accesso venoso permanente
- Tempo di somministrazione più breve
- Meno invasivo per la vita quotidiana
- Potenzialmente domiciliare
- Autosomministrabile (Pazienti selezionati)



From Pivot X, Fallowfield L *et al*. St. Gallen 2013 Poster 207, modified

Trial BP22023:
Phase I dose finding/dose confirmation of trastuzumab SC

- Open-label, 2-part, phase I/Ib dose-finding and dose confirmation study
- 2 centers in New Zealand and 1 in Australia
- Patient population
  - 24 healthy male volunteers and 42 female patients with HER2-positive breast cancer

Primary objective

- To select the dose of trastuzumab SC that results in comparable exposure to trastuzumab IV at 6 mg/kg in healthy male volunteers and in patients with HER2-positive EBC
  - Evaluated by analyzing the area under the serum concentration–time curve (AUC)

Secondary objective

- To assess the safety and tolerability of IV and SC trastuzumab in healthy male volunteers and patients with HER2-positive EBC

Wynne C, *et al*. J Clin Pharmacol. 2013;53:192-201

HannaH (BO22227)
Phase III study

Randomised, open-label, Phase III,
Neoadj Doce x 3 → FEC x 3
Plus Trastuzumab IV or SC

non-inferiority study
to compare:
PK, efficacy and safety
of trastuzumab SC and IV in HER2-positive EBC

HannaH: First co-primary endpoint met (pharmacokinetics)

	trastuzumab IV n=235	trastuzumab SC n=234
Primary endpoint: Observed C_{trough} pre-dose Cycle 8		
Geometric mean (µg/mL)	**51.8**	**69.0**
Geometric mean ratio (GMR) SC *vs.* IV (90% CI)	**1.33 (1.24; 1.44)**	

	Intravenous trastuzumab (n=235)	Subcutaneous trastuzumab (n=234)
Primary pharmacokenetic endpoint		
C_{trough} predose cycle 8		
Mean (µg/mL; SD)	57·8 (30·3)	78·7 (43·9)
Geometric mean (µg/mL; percentage coefficient of variation)*	51·8 (52·5%)	69·0 (55·8%)
Secondary pharmacokinetic endpoints		
Patients >20 µg/mL at predose cycle 8	232 (98·7%)	227 (97·0%)
Mean (SD) C_{max} at cycle 7 (µg/mL)†	221 (118·0)	149 (64·8)
Mean (SD) T_{max} at cycle 7 (days)‡	0·05 (0·04)	4·12 (2·91)
Mean (SD) $AUC_{0\text{-}21\ days}$ (µg/mL×day)	2056 (598)	2268 (875)
Geometric mean $AUC_{0\text{-}21\ days}$ (µg/mL×day; percentage coefficient of variation)§	1978 (29·1%)	2108 (38·5%)

$AUC_{0\text{-}21\ days}$=area under the serum concentration–time curve from 0–21 days; C_{max}=maximum serum concentration. T_{max}=time to C_{max}. *Geometric mean ratio 1·33 (90% CI 1·24–1·44). †Geometric mean ratio 0·67 (90% CI 0·63–0·71). ‡n=233 in subcutaneous trastuzumab group. §Geometric mean ratio 1·07 (90% CI 1·01–1·12).

Table 2: Trastuzumab pharmacokinetic parameters before surgery in the per-protocol pharmacokinetic population

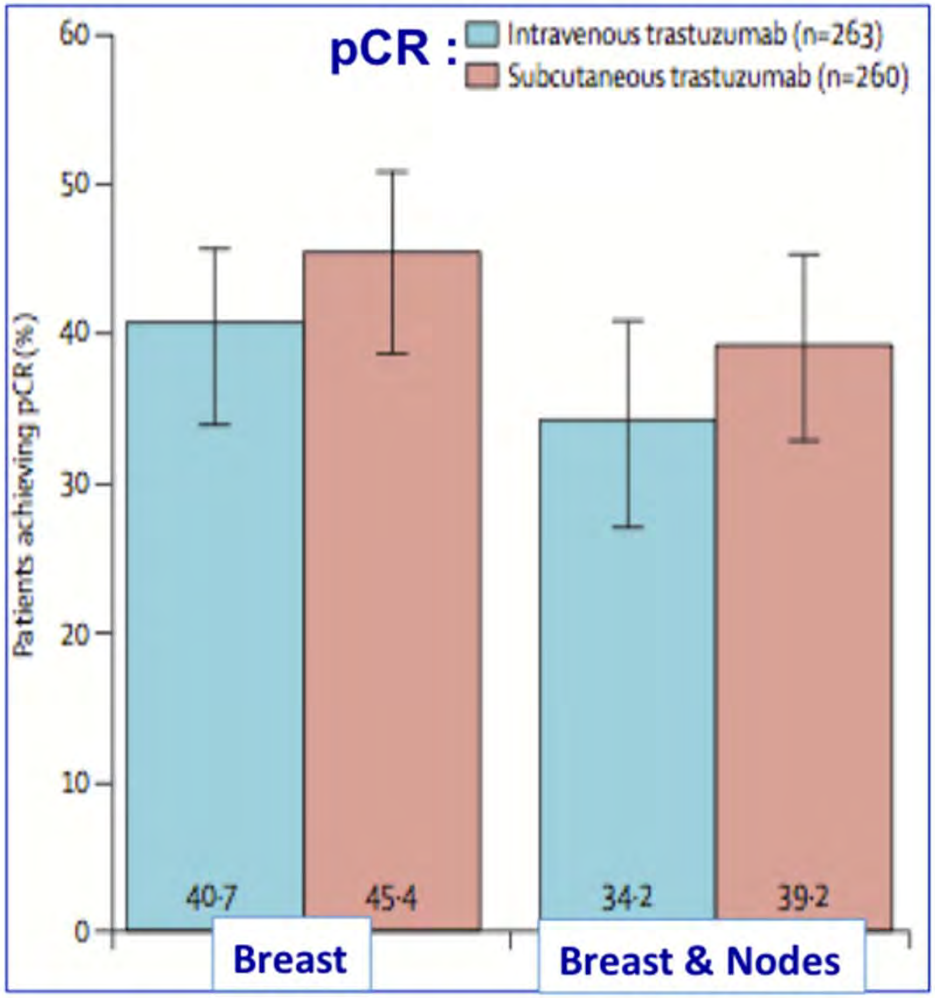
Pharmacokinetic per protocol population

Non-inferiority of SC *vs.* IV demonstrated:

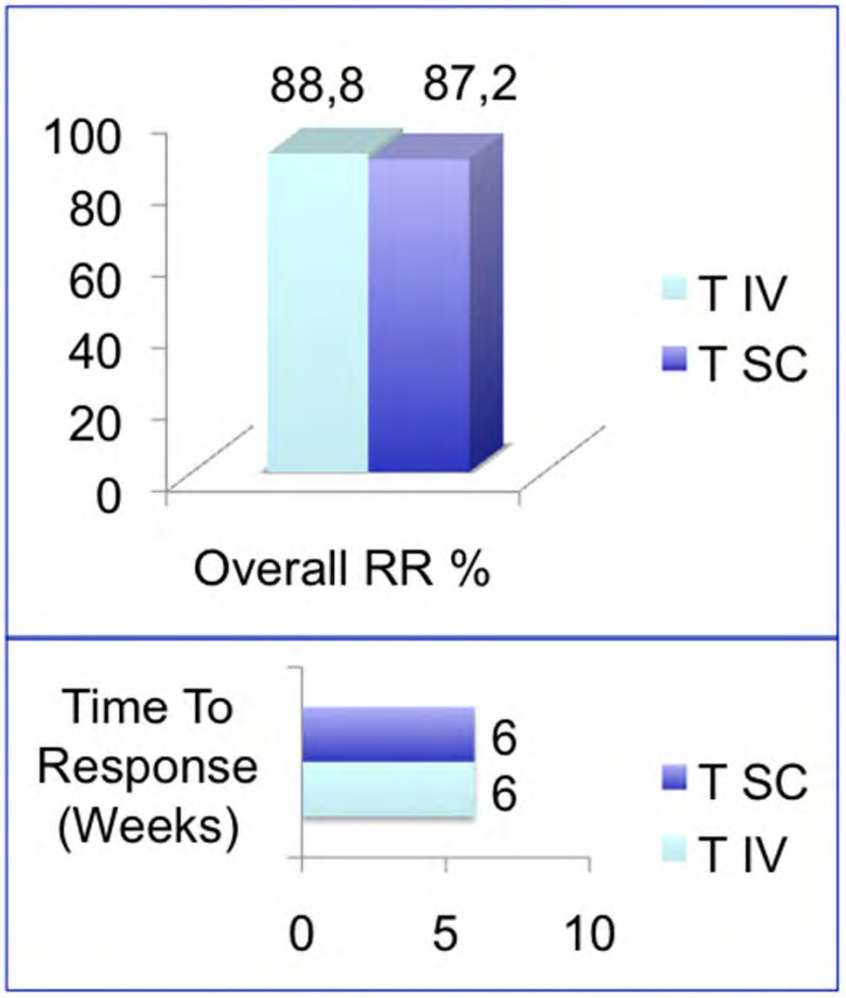
lower bound of 90% CI greater than pre-specified non-inferiority margin for geometric mean ratio SC *vs.* IV of 0.8

Ismael G, *et al*. Lancet Oncol. 2012;13:869-78

HannaH:Response Rate



Ismael G, Lancet Oncol 2012; 13:869–878



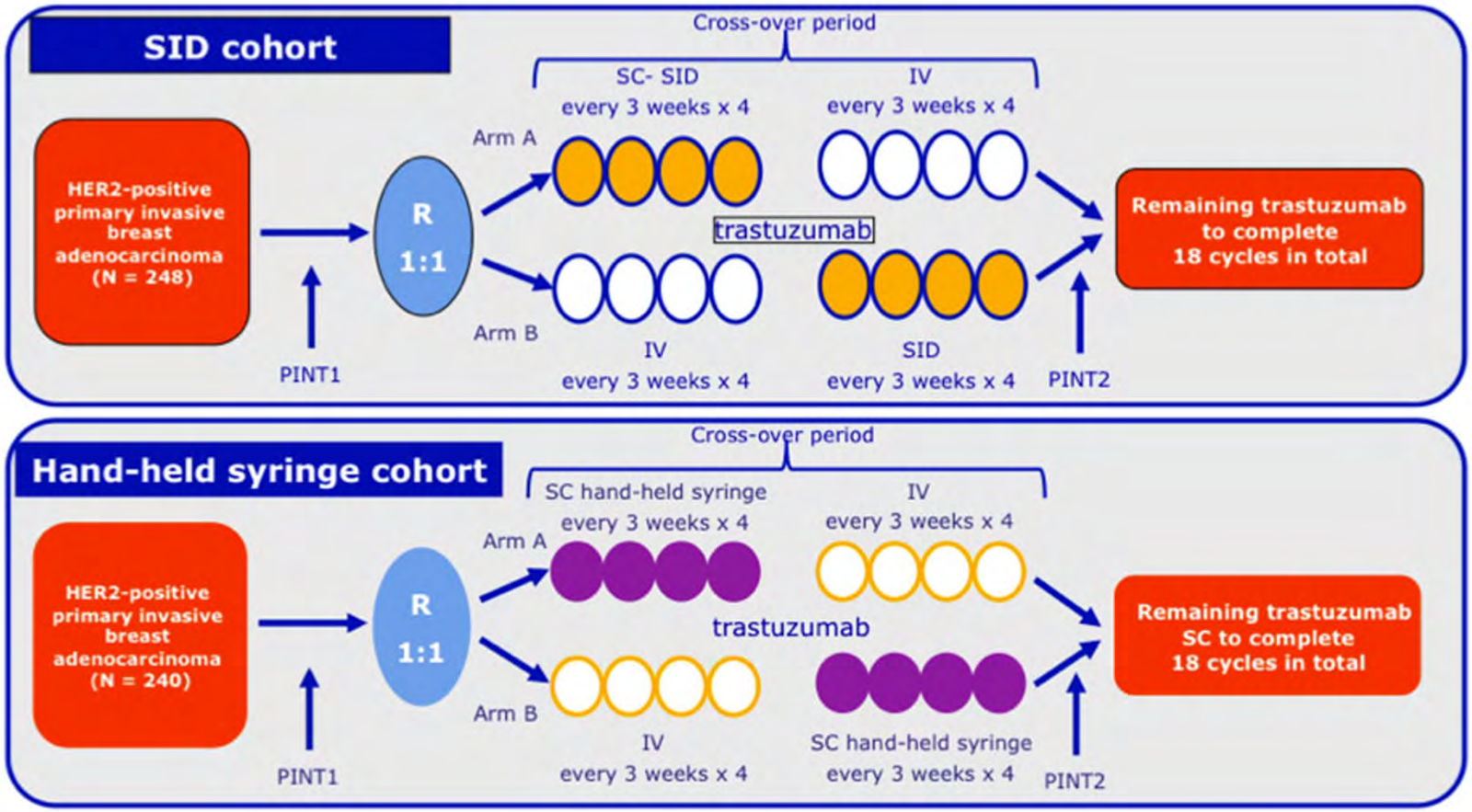
Jackisch C, EBCC Abst 1BA - Eur J of Cancer 2012, 48 : SUPPL. 1 (S37)

PrefHer (MO22982) study

A global, randomised, two-cohort cross-over preference study

Neoadjuvant Chemo + IV Trastuzumab → Surgery
RANDOM to
Trastuzumab
SC vs Iv or Viceversa

PrefHer: Study Design



Stratification factor: *de novo* vs. non-*de novo* trastuzumab (to balance the sequence groups for the proportion of patients with prior trastuzumab IV treatment).
IV, intravenous; PINT, Patient Interview; R, randomised; SC, subcutaneous; SID, single-use injection device

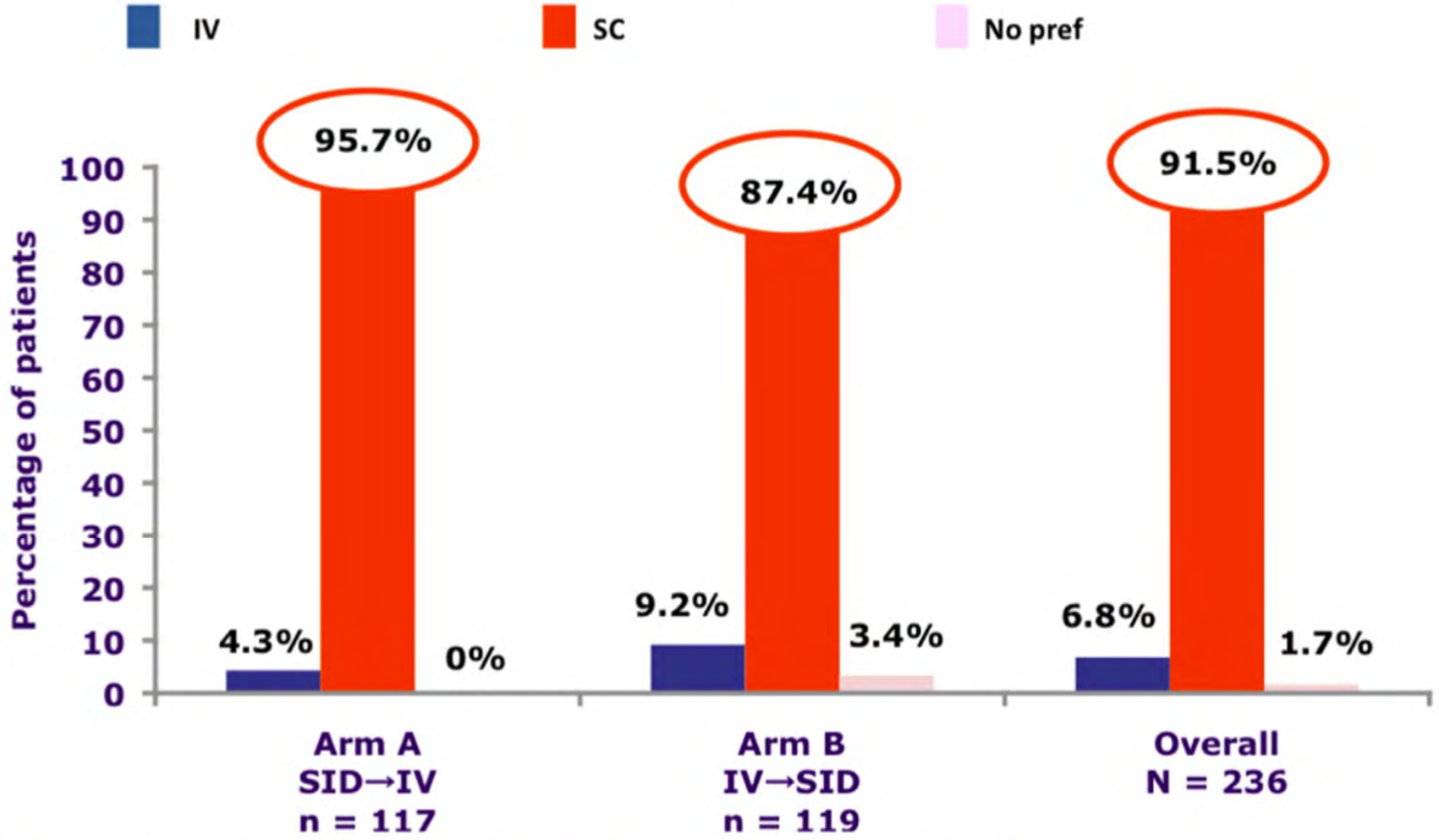
Pivot X, Fallowfield L *et al*. St. Gallen 2013 Poster 207; *Lancet Oncol* 2013; 14: 962–70; Modified

PrefHer: Endpoints

- **Primary**
  - Overall preference for the SC or IV route of trastuzumab administration
    - Assessed by a single direct question:
      "All things considered, which method of administration did you prefer?"
- **Secondary**
  - Safety and tolerability
  - Event-free survival
  - Immunogenicity (anti-trastuzumab and rHuPH20 antibodies in the blood) (Cohort 1 only)
  - Healthcare professional (HCP) satisfaction/perceived time savings with trastuzumab SC
- **Exploratory**
  - Factors that influence patients' preferences for SC or IV administration
  - Patient satisfaction with SID self-administration (Cohort 1 only)
- **TaM sub-study**
  - To assess medical care utilisation, including collection of time of administration and resource use data, at selected sites in both cohorts

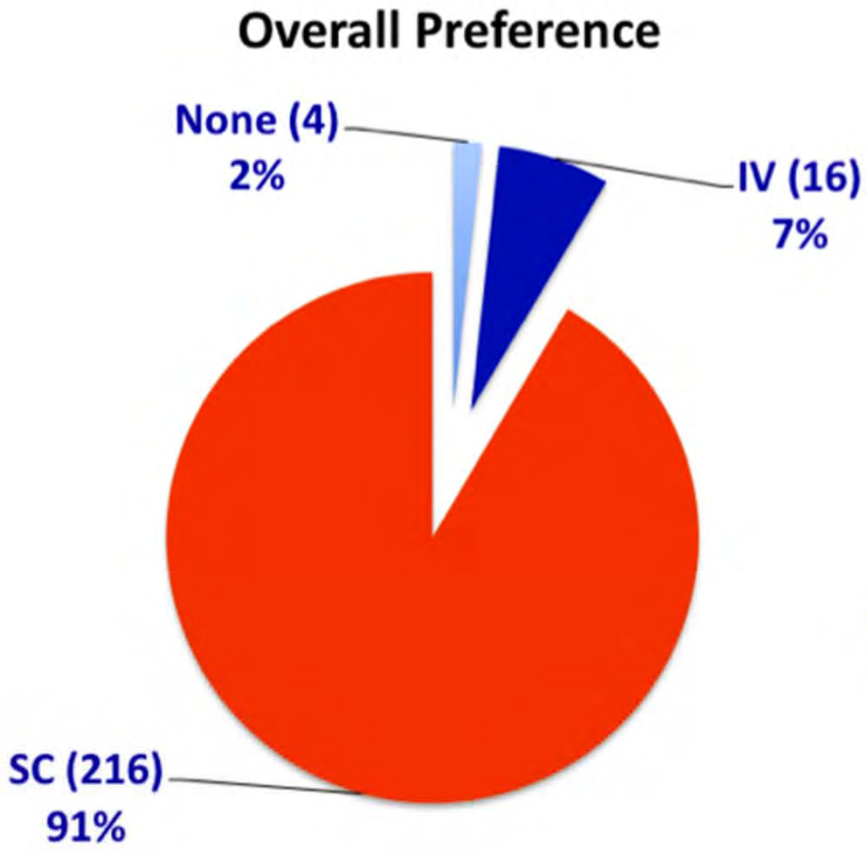
Pivot X, Fallowfield L *et al*. St. Gallen 2013 Poster 207; *Lancet Oncol* 2013; 14: 962–70; Modified

PrefHer: Preferred trastuzumab SC over IV, irrespective of study arm *(evaluable ITT population)*



Pivot X, Fallowfield L *et al*. St. Gallen 2013 Poster 207; *Lancet Oncol* 2013; 14: 962–70; Modified

"All things considered, wich method of administration did you prefer?"



Overall preference for SC
p< 0.0001 vs
Null hypothesis

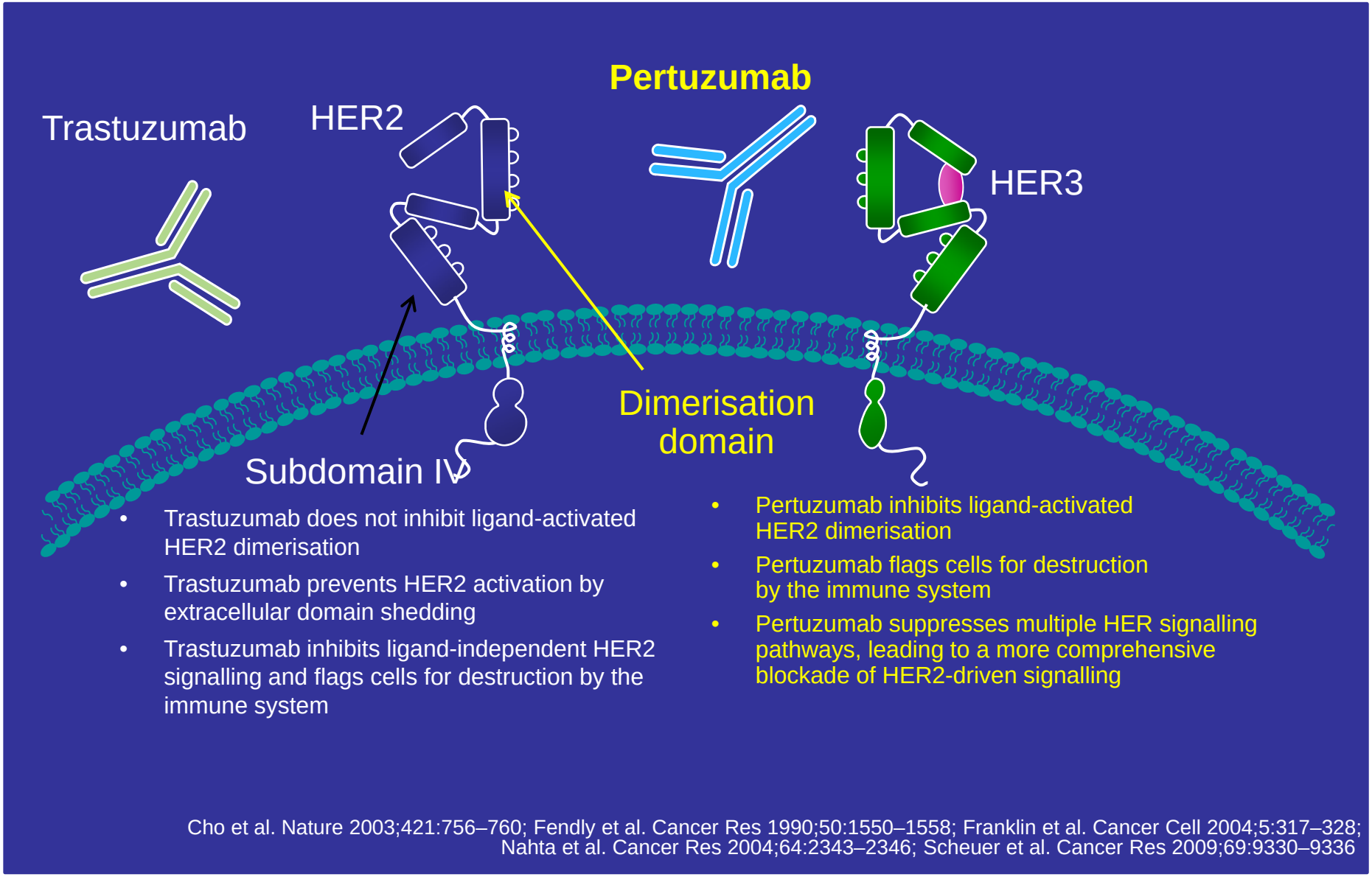
65% preference for SC against
two-sided
alternative hypothesis

Pivot X, Fallowfield L *et al*. St. Gallen 2013 Poster 207; *Lancet Oncol* 2013; 14: 962–70; Modified

Pertuzumab

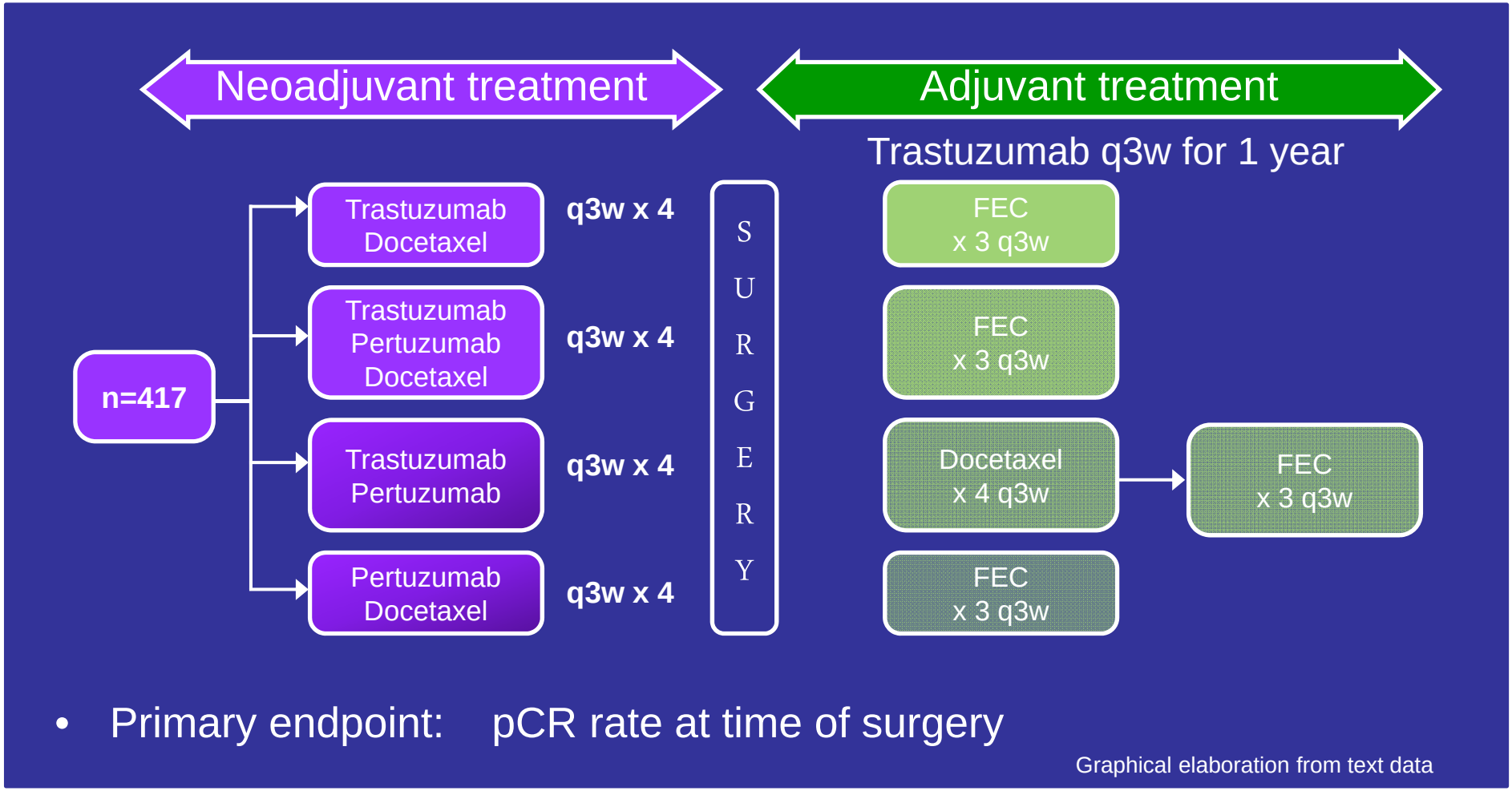
First HER2 Dimerization Inhibitor, synergistic and complementary activity with trastuzumab

Pertuzumab: Mechanism of Action



Cho et al. Nature 2003;421:756–760; Fendly et al. Cancer Res 1990;50:1550–1558; Franklin et al. Cancer Cell 2004;5:317–328; Nahta et al. Cancer Res 2004;64:2343–2346; Scheuer et al. Cancer Res 2009;69:9330–9336

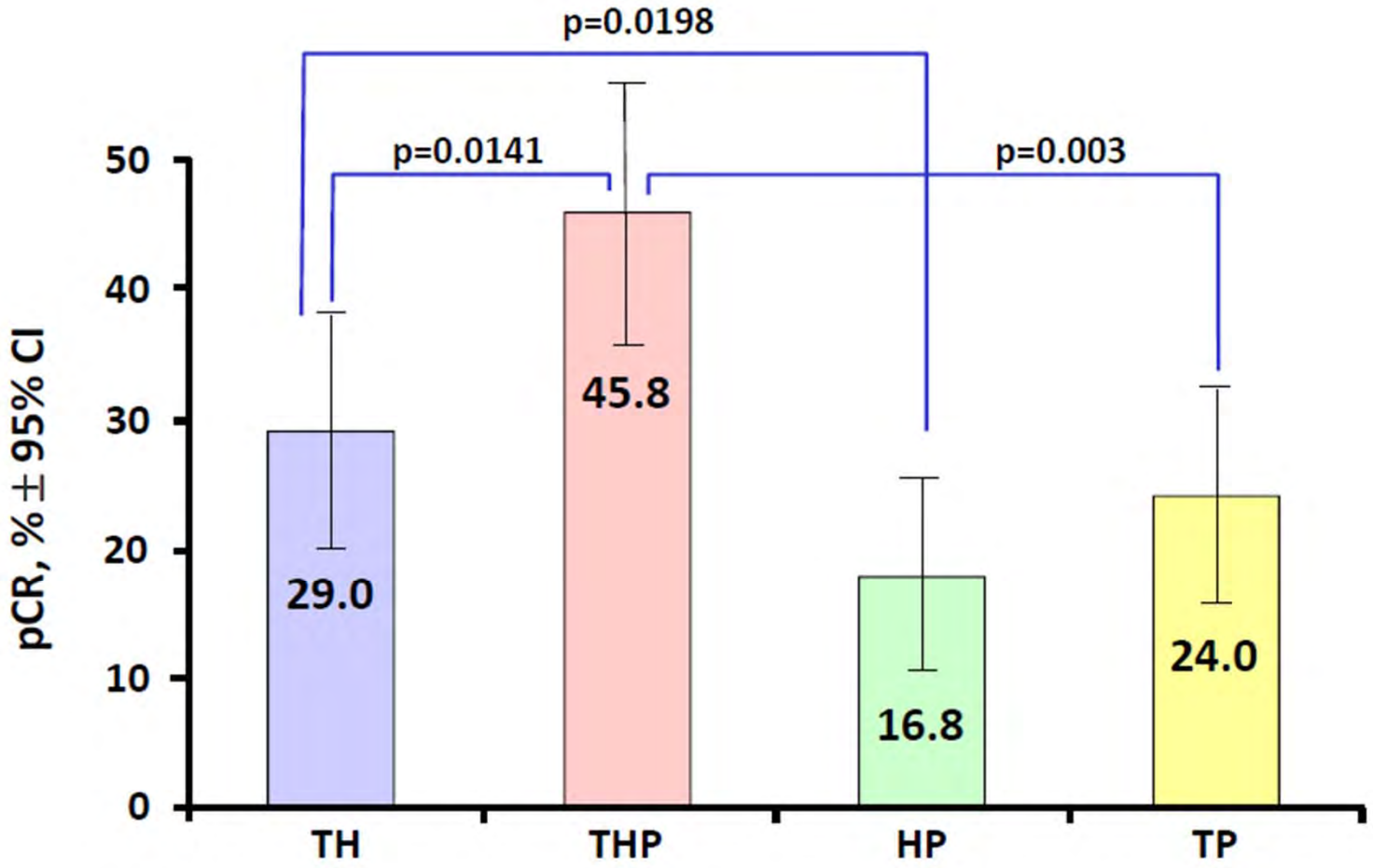
NEOSPHERE: neoadjuvant trastuzumab and pertuzumab in HER2-positive EBC



EBC = early-stage breast cancer; FEC = 5-fluorouracil, epirubicin, cyclophosphamide; pCR = pathological complete response; q3w = every 3 weeks

Gianni et al. Lancet Oncol. 2012;13:25-32

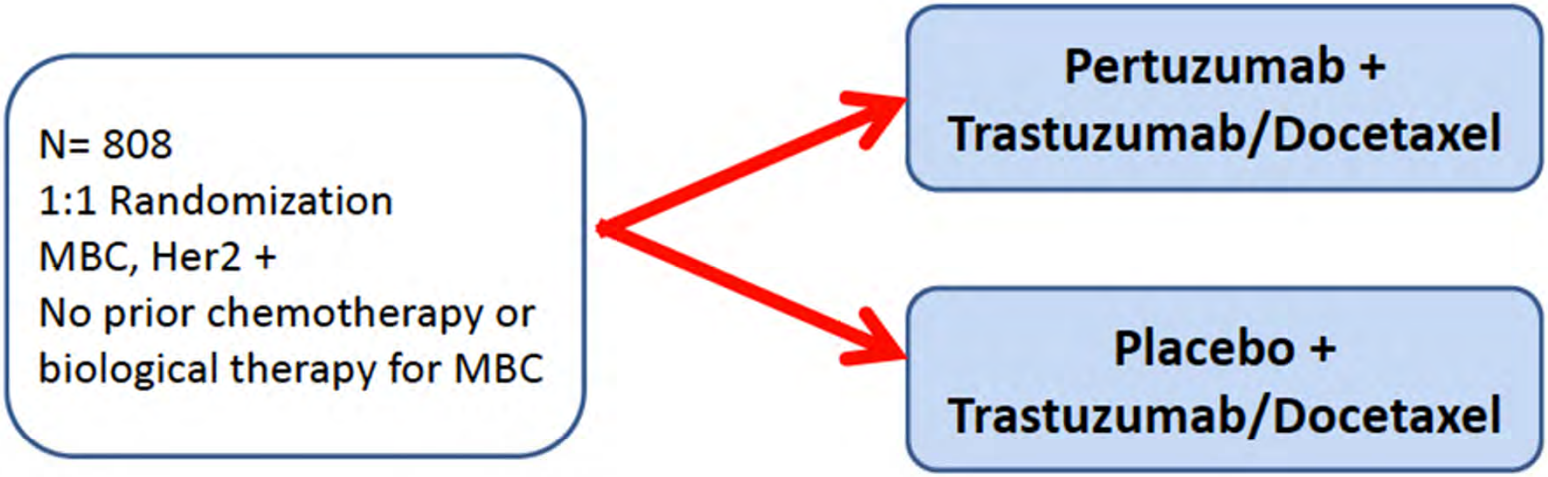
NEOSPHERE: pCR rates, ITT population



H, trastuzumab; P, pertuzumab; T, docetaxel
p values from Cochran-Mantel-Haenszel test and adjusted for multiplicity

1. Gianni et al. Oral presentation SABCS 2011
Cancer Res December 15, 2011; 71(24 Supplement): S5-1
2. Gianni et al. Lancet Oncol. 2012;13:25-32

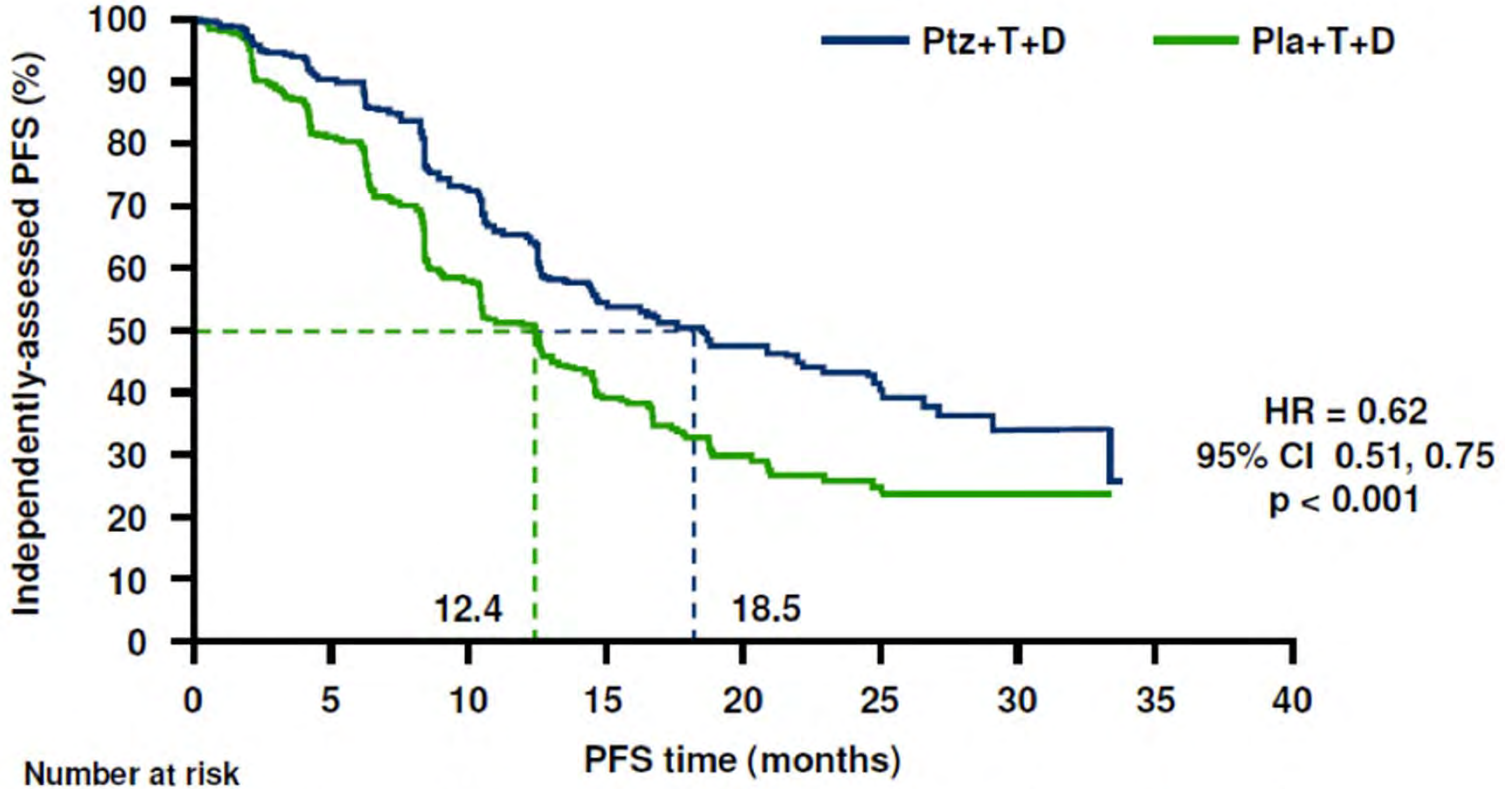
Cleopatra: Phase III Trial of Pertuzumab In Combination of Trastuzumab/Docetaxel



Trastuzumab (8 mg /kg LD then 6 mg/ kg Q3W and Docetaxel 75 mg/m2 Q3W
Pertuzumab 840 mg LD then 420 mg Q3W

Baselga; N Engl J Med 2012;366:109-119.

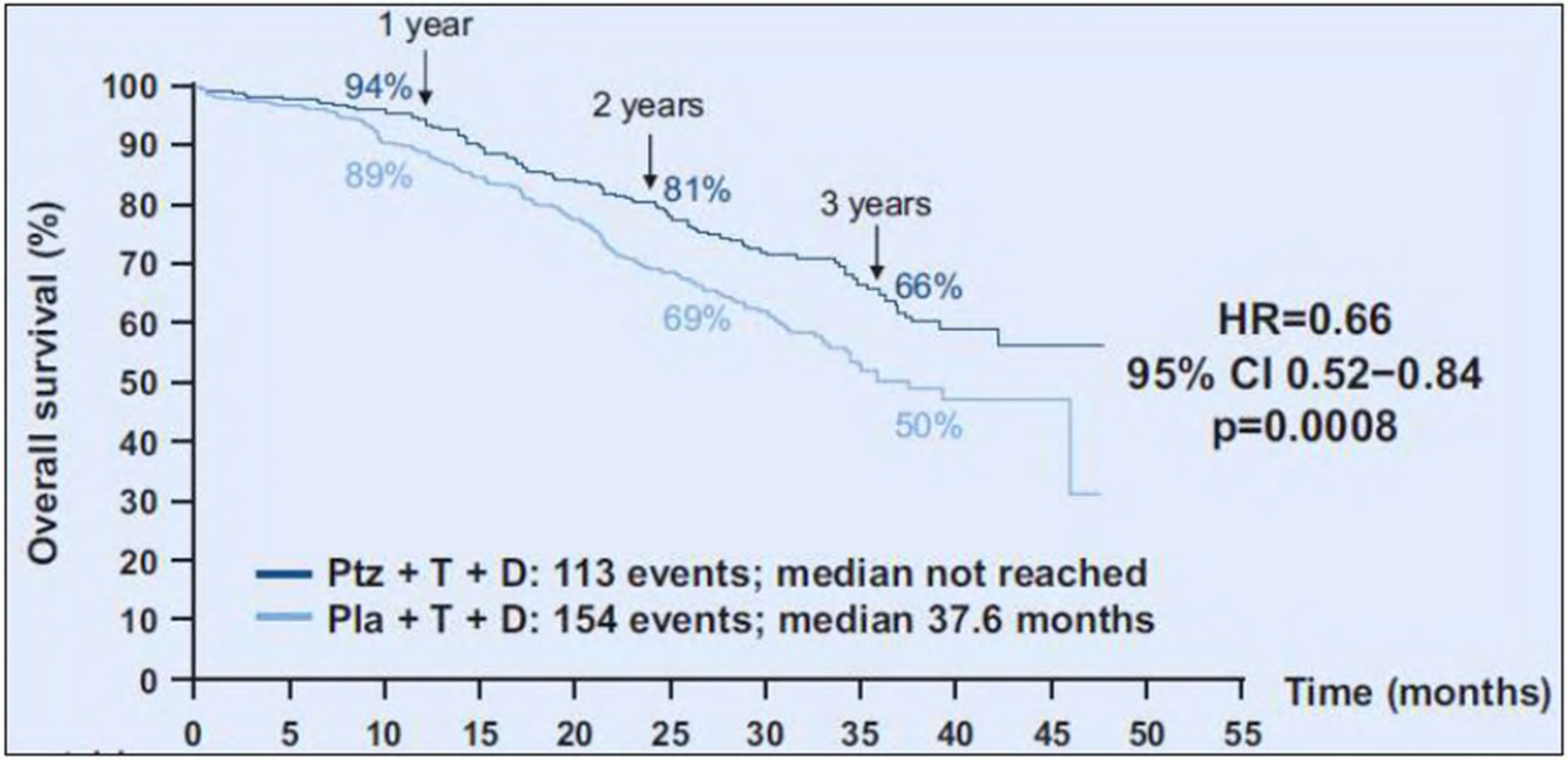
CLEOPATRA: PFS, independently assessed (n = 433 PFS events)



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

Baselga Oral presentation – SABCS 2012
Available free online at http://sabcs12.m2usa.com/sabcsdsv.html Last access September 2013
Baselga et al. N Engl J Med. 2012 ;366:109-19

OS in Phase III Trial of Pertuzumab In Combination of Trastuzumab/Docetaxel

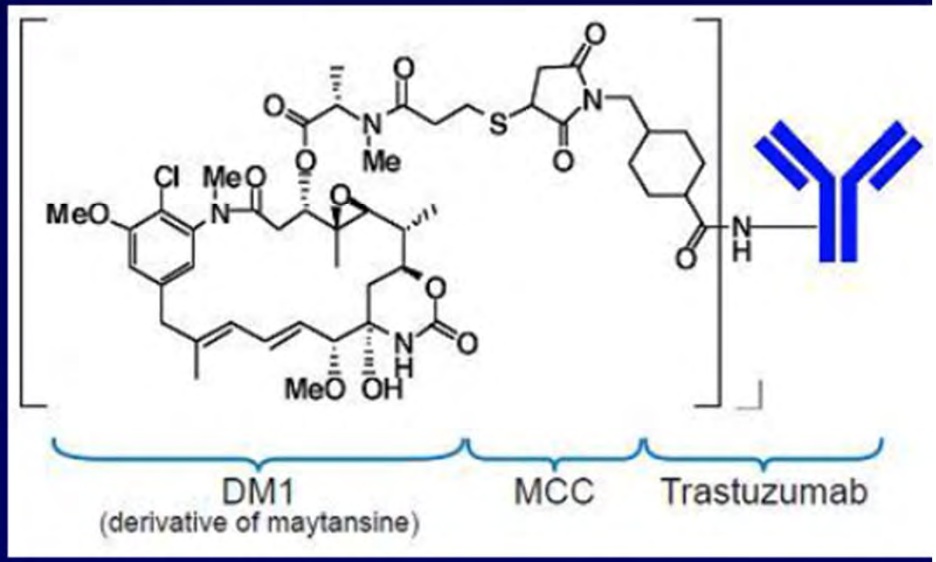


At 30 months median follow-up

SABCS 2012 P5-18-26. N Engl J Med 2012;366:109-119.

T-DM1 Introduction

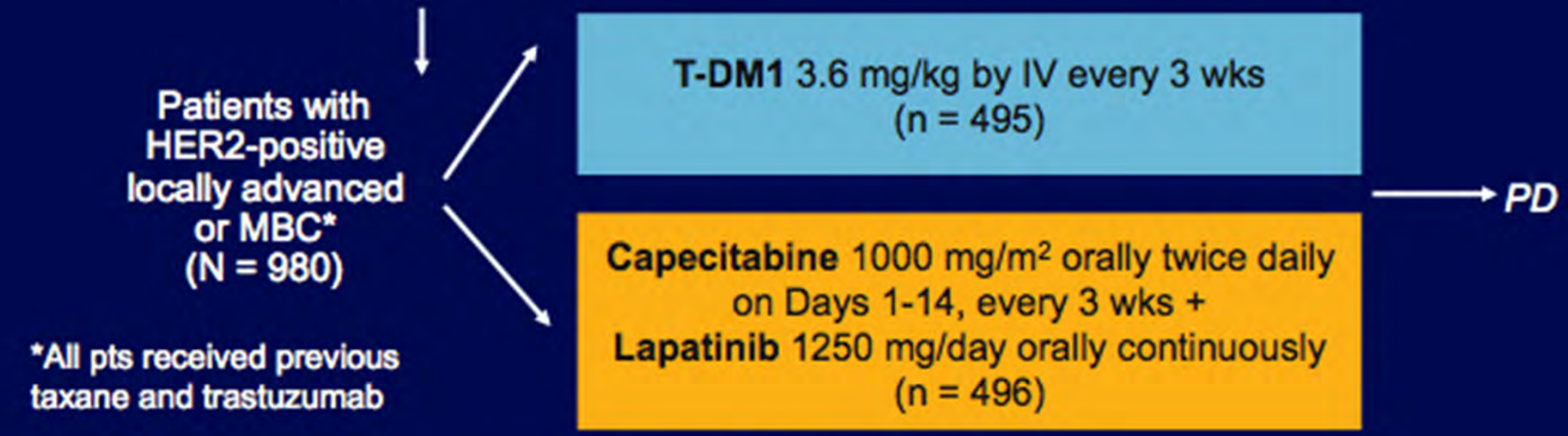
- Trastuzumab-DM1 (T-DM1): anti-HER2 antibody drug–conjugate
  - Combines the HER2-targeting properties of trastuzumab with targeted delivery of a highly potent anti-microtubule derivative, DM1
  - After binding to HER2, T-DM1 undergoes receptor-mediated internalization, resulting in intracellular release of DM1
  - Will it allow omission of separate systemic cytotoxic?



Adapted from Perez et al, ESMO 2010

EMILIA Phase III Study: T-DM1 vs Lapatinib/Capecitabine in HER2+ MBC

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

Blackwell KL, et al. ASCO 2012. Abstract LBA1.