Competenze dell'infermiere e sicurezza nella pratica clinica oncologica: gestione della paziente con carcinoma mammario

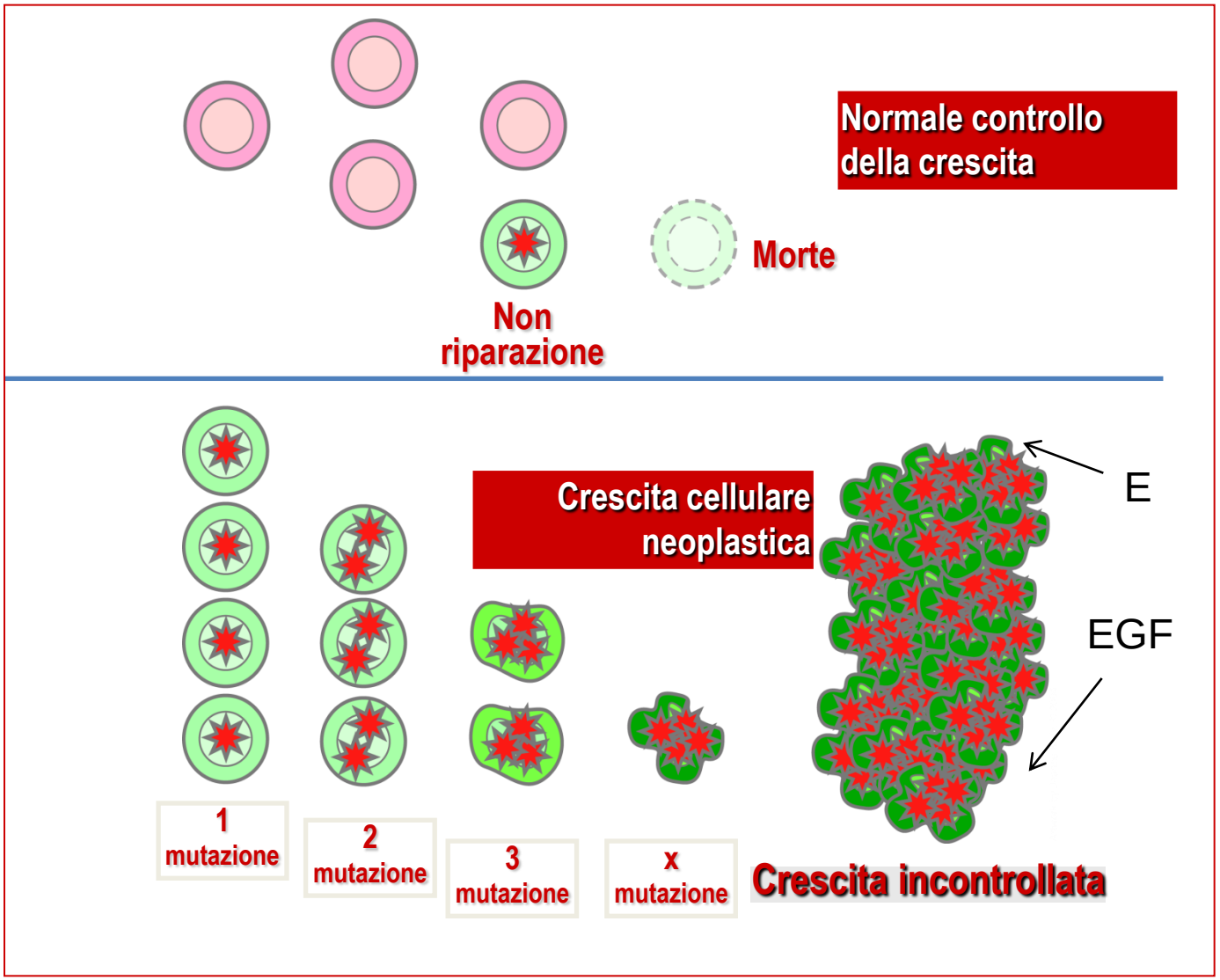
SESSIONE TEORICA

UTILIZZO DEI FARMACI BIOLOGICI NEL TRATTAMENTO DELLE PAZIENTI CON CARCINOMA MAMMARIO

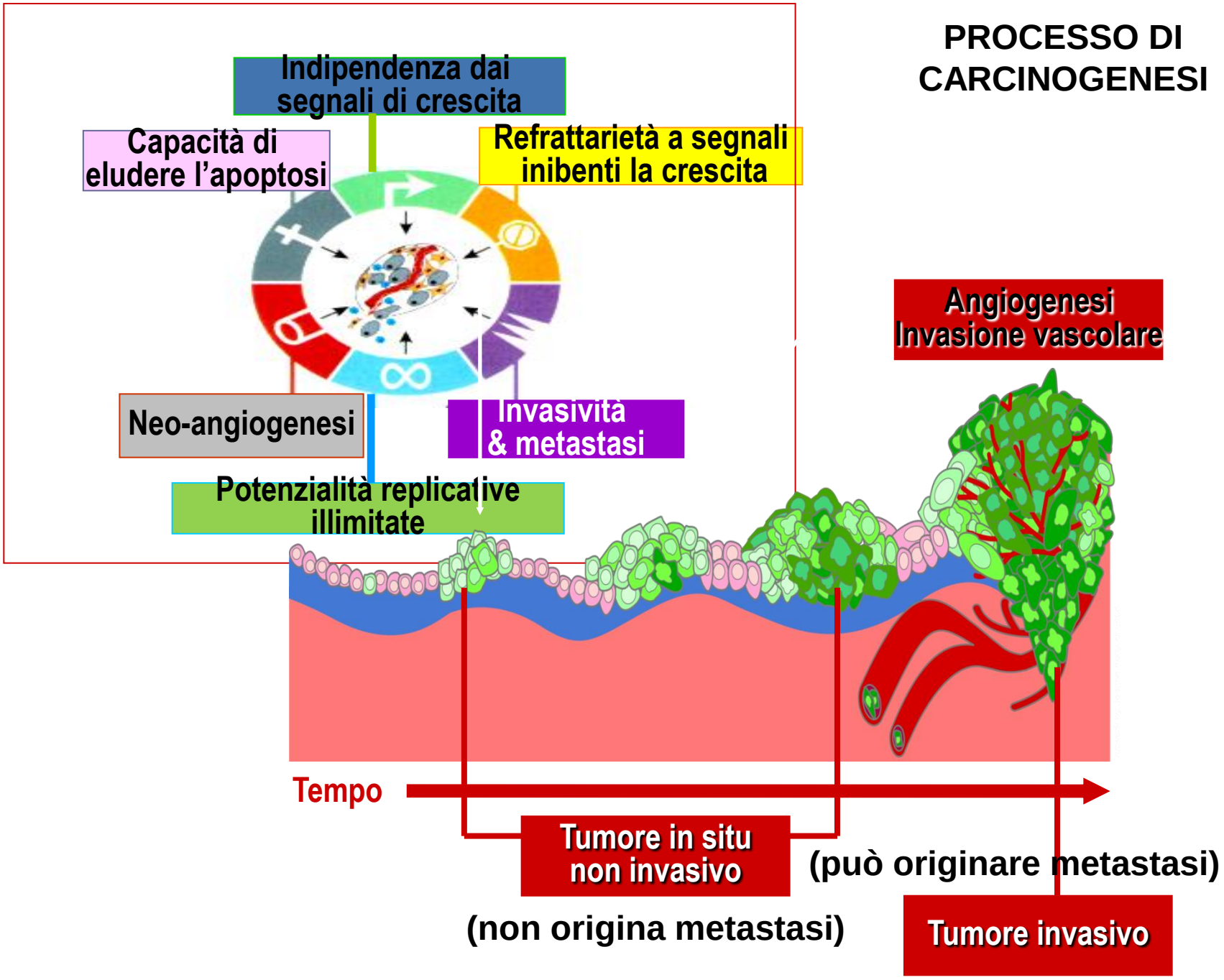
Dr. Monica Turazza

Ospedale "S. Cuore-Don Calabria" Negrar (Verona)

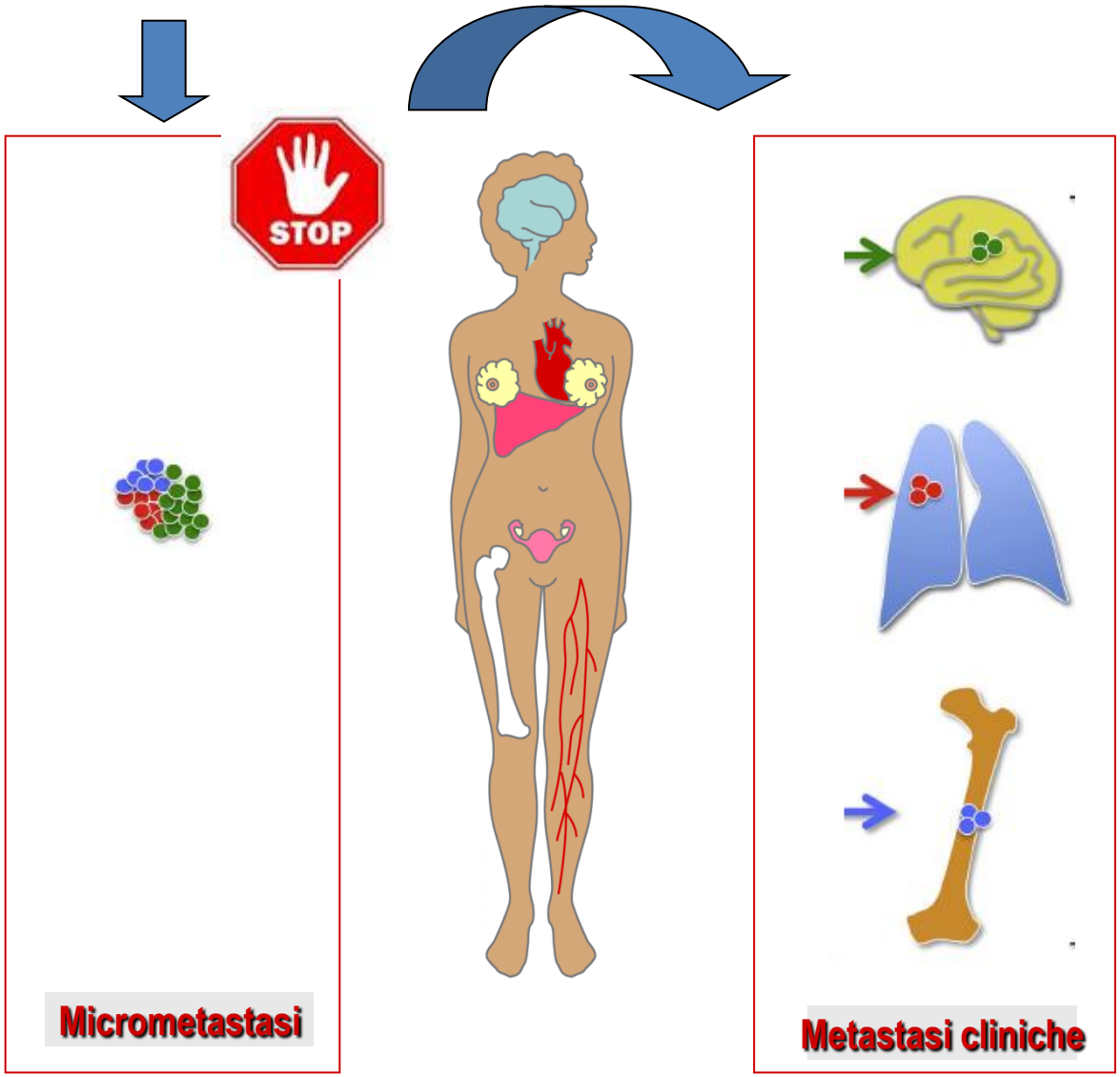
CRESCITA DELLA CELLULA TUMORALE: perdita di controllo



PROCESSO DI CARCINOGENESI



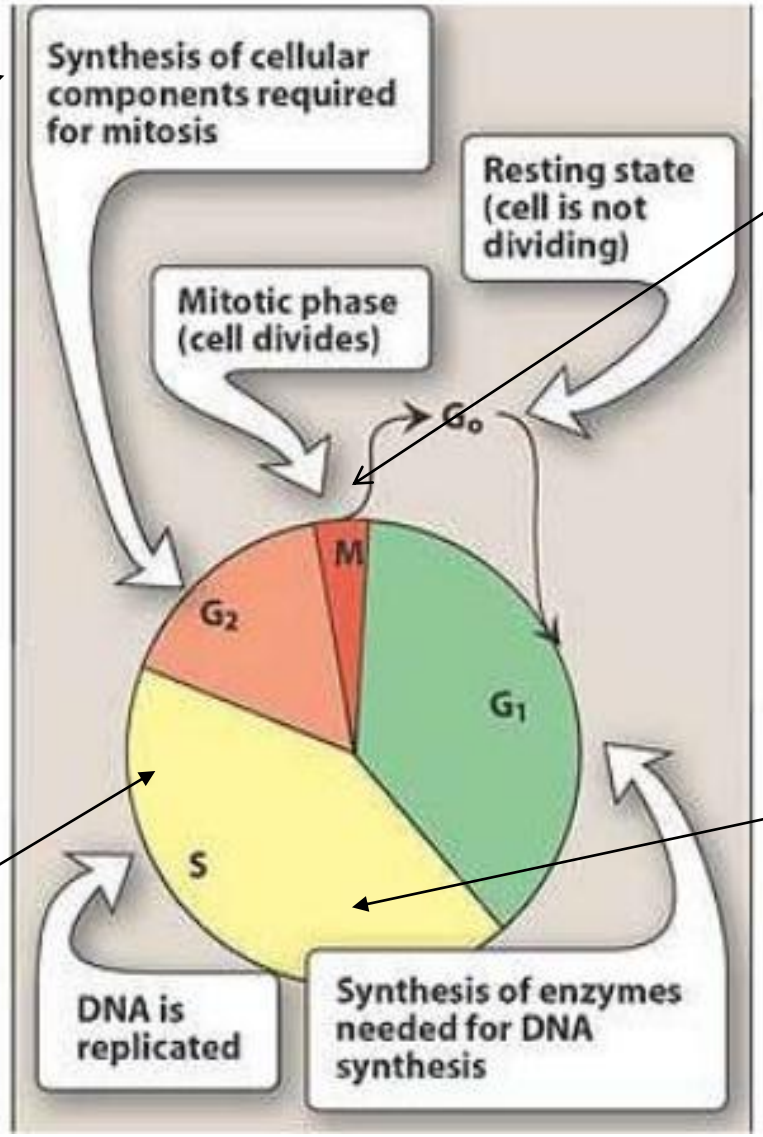
TERAPIA SISTEMICA



DEFINIZIONE DI TERAPIA SISTEMICA	STADIO DI MALATTIA	SCOPI-OBIETTIVI
ADIUVANTE	Localizzata “Early”	Prevenzione metastasi GUARIGIONE
PRIMARIA/ NEOADIUVANTE	Localmente avanzata (II,III)	Controllo locale Chirurgia radicale/conservativa Prevenzione metastasi GUARIGIONE
TERAPEUTICA	Metastatica (IV)	Qualità di Vita Regressione tumore Prolungamento sopravvivenza PALLIAZIONE

CHEMIOTERAPIA

Phases of cell cycle



Antibiotici citotossici e correlati (doxorubicina, epirubicina)

Antimitotici di origine naturale (alcaloidi della vinca- vinorelbina, taxani- paclitaxel e docetaxel)

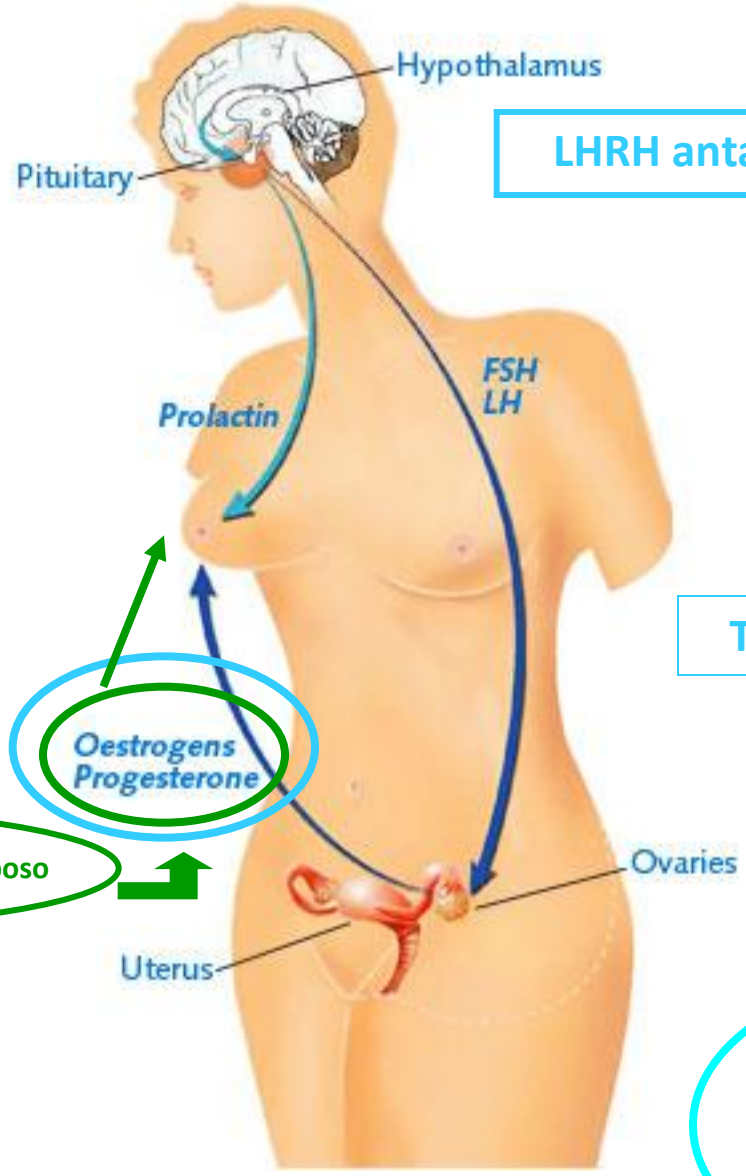
Antimetaboliti e inibitori della catena dei folati (methotrexate, fluorouracile)

Agenti alchilanti (ciclofosfamide, cisplatino derivati

ORMONOTERAPIA

POST-MENOPAUSA

Inibitori dell'aromatasi (letrozolo, anastrozolo, exemestane)



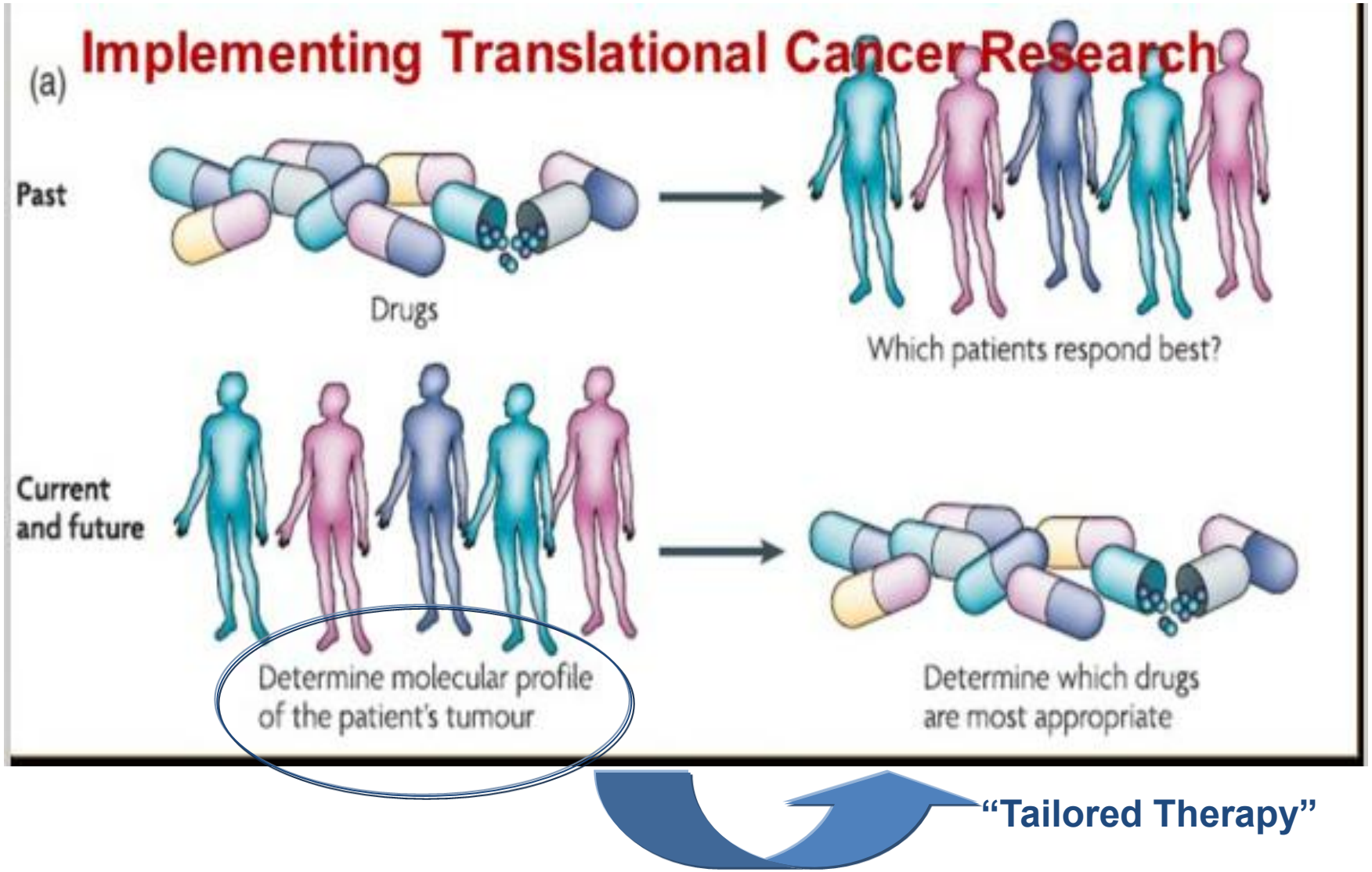
LHRH antagonisti

Tamoxifene

Fegato, ghiandole surrenaliche, tess. adiposo

PRE-MENOPAUSA

TERAPIA A BERSAGLIO MOLECOLARE


Implementing Translational Cancer Research
(a)
Past
Drugs
Which patients respond best?
Current and future
Determine molecular profile of the patient's tumour
Determine which drugs are most appropriate
"Tailored Therapy"

TERAPIE A BERSAGLIO MOLECOLARE

Farmaci diretti contro uno specifico bersaglio molecolare espresso selettivamente sulle cellule tumorali

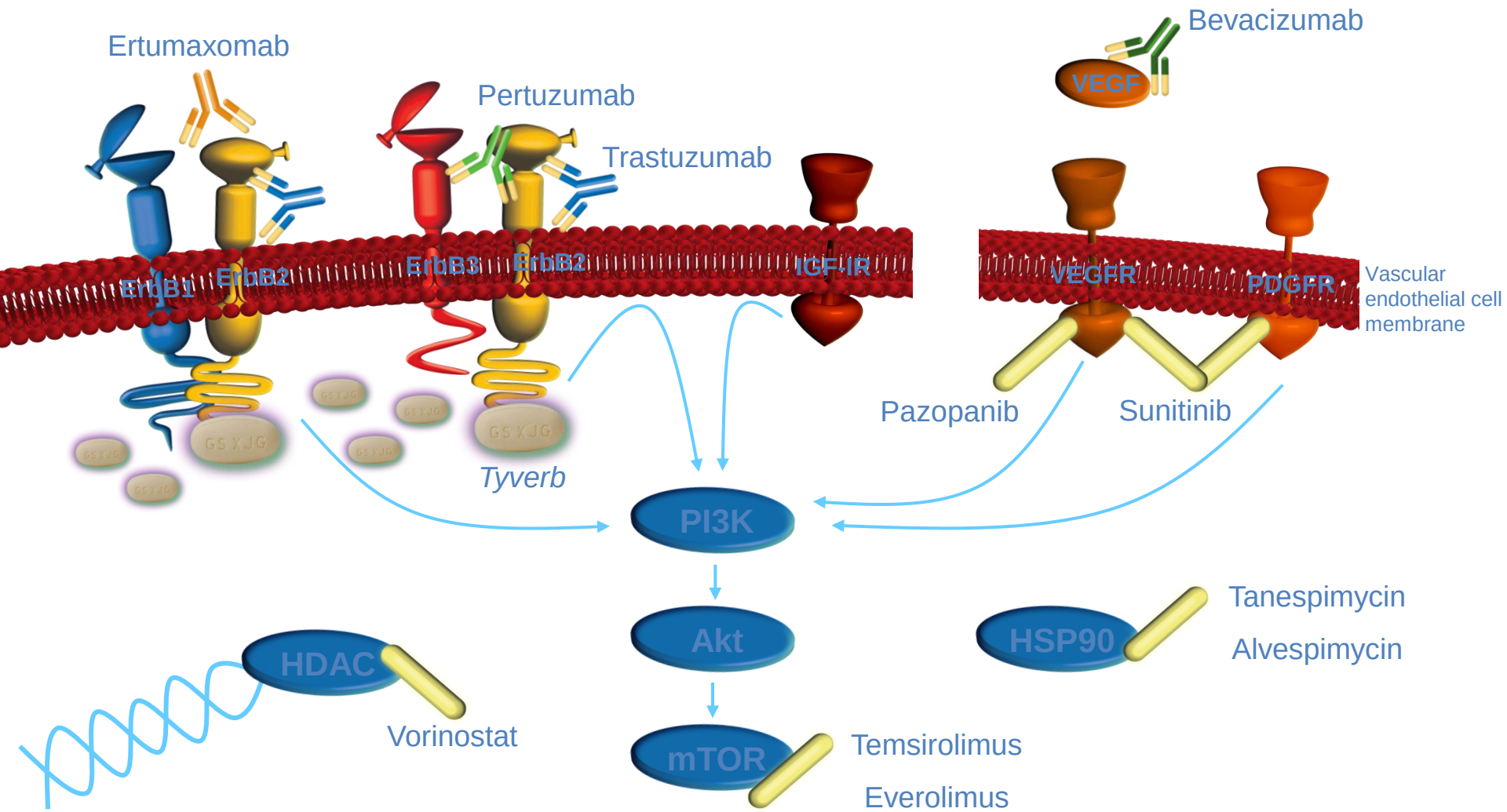
Azione selettiva e specifica verso le cellule tumorali

Tossicità minore e diversa rispetto la chemioterapia tradizionale

Possibile utilizzo in concomitanza di chemioterapia o ormonoterapia o radioterapia

Somministrazioni in alcuni casi per via orale/sc con miglior compliance e risparmio di risorse sanitarie

Targets and bullets in breast cancer

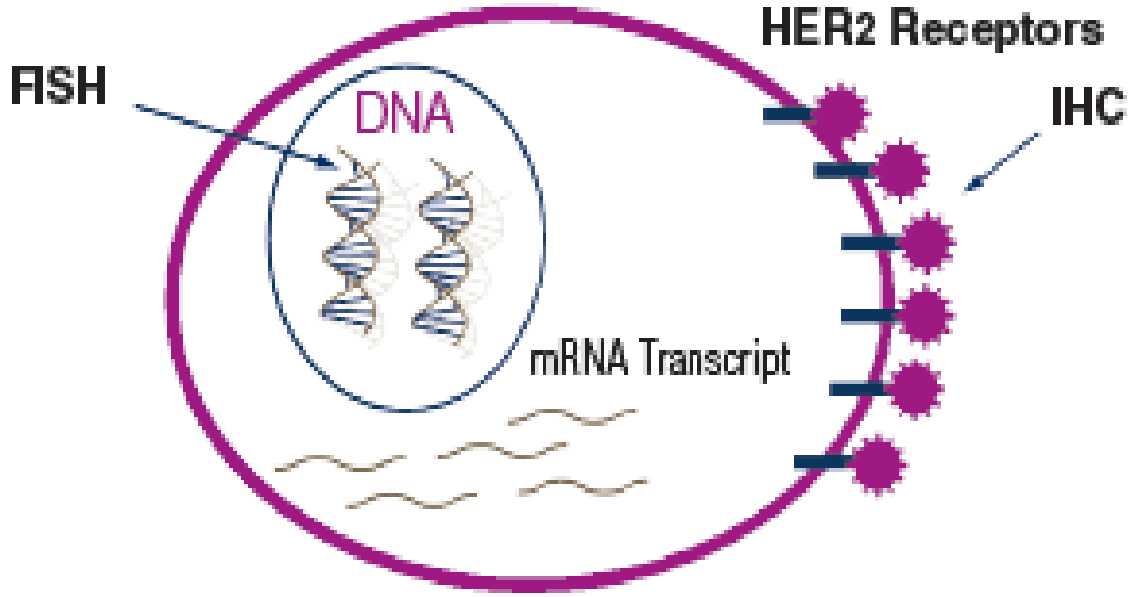


HDAC=histone deacetylase

Terapie a bersaglio molecolare nel carcinoma mammario

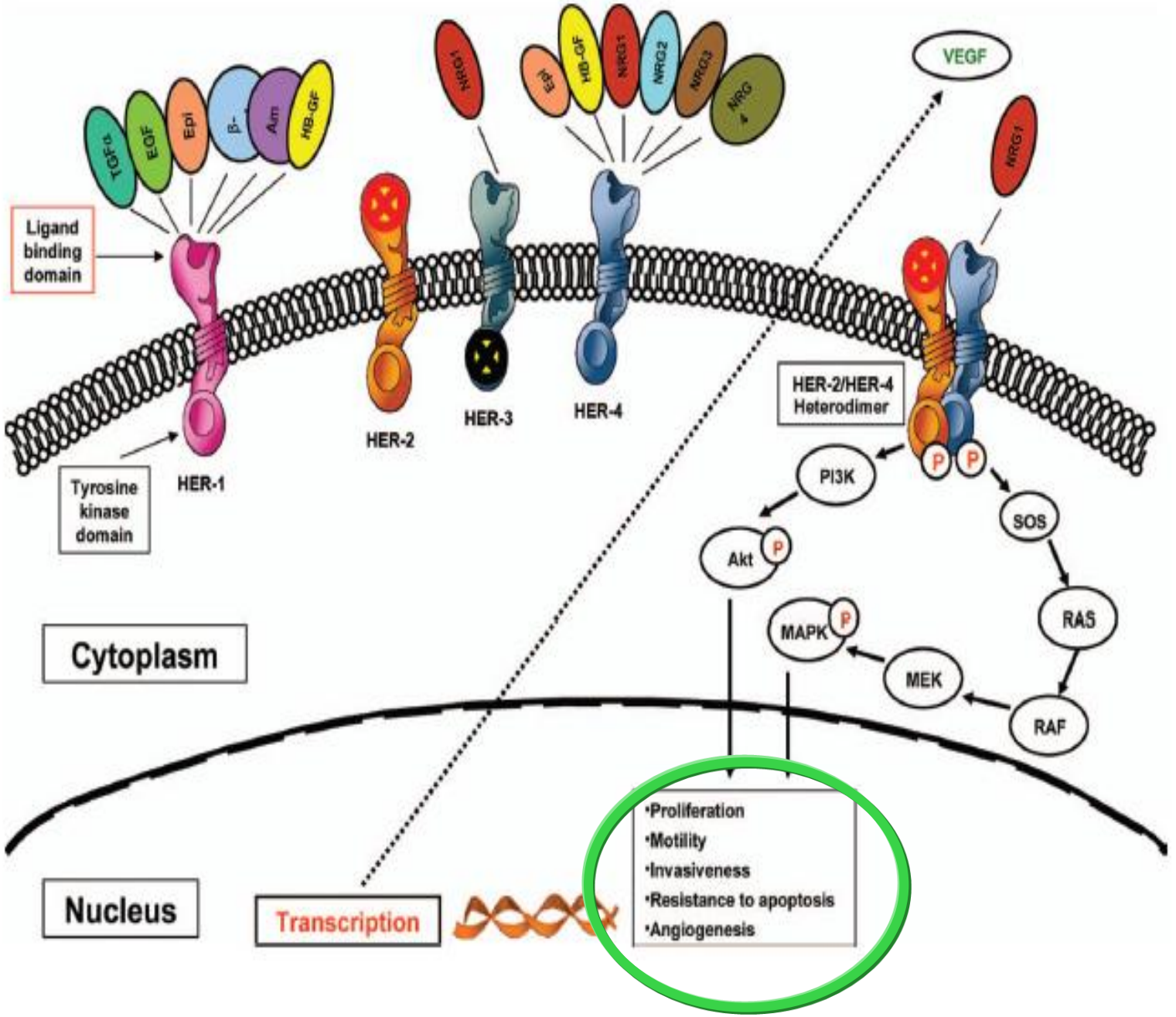
Trastuzumab	Anticorpo monoclonale umanizzato contro **Her2**
Pertuzumab	Anticorpo monoclonale umanizzato inibitore delle dimerizzazione di **Her2**
TDM1	Anticorpo farmaco coniugato (Trastuzumab-Emtansine) contro **Her2**
Lapatinib	Piccola molecola inibitore reversibile e selettivo della tirosin chinasi intracellulare di entrambi i recettori EGFR (ErbB1) e **HER2** l(ErbB2)
Everolimus	Molecola inibitore dell'**mTOR**C1
Denosumab	Anticorpo monoclonale umanizzato diretto contro **RANKL**
Bevacizumab	Anticorpo monoclonale umanizzato diretto contro il **VEGF**

ANTI-HER2 THERAPIES



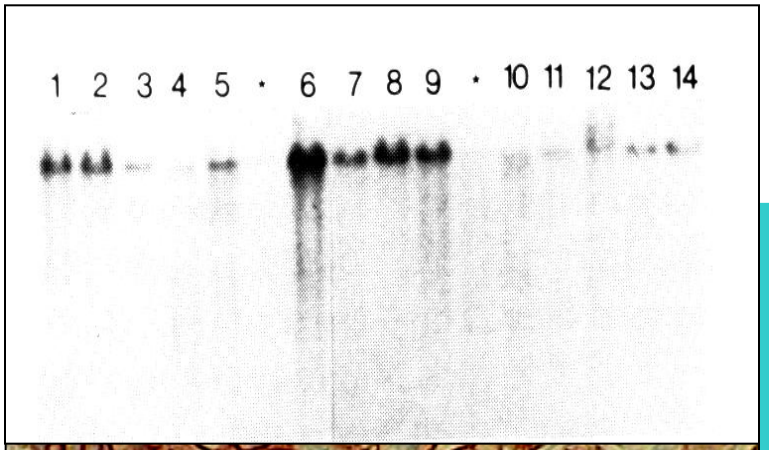
Breast Cancer Cell

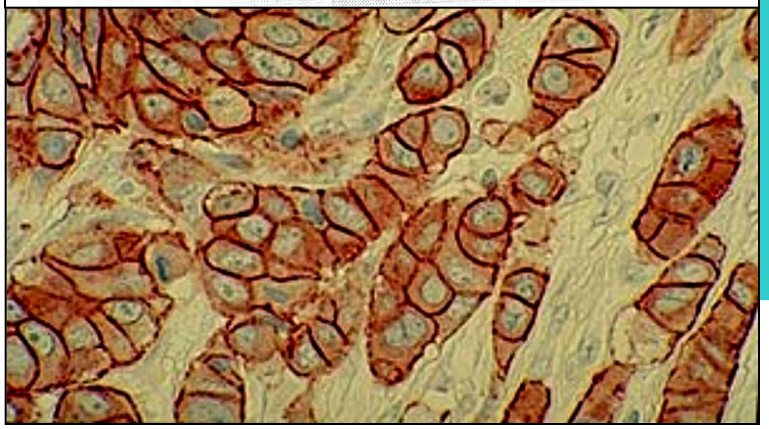
HER2 gene amplification is the underlying biological change that results in HER2 overexpression.


TGF-α
EGF
Epi
β-
Am
HB-GF
Ligand binding domain
Tyrosine kinase domain
HER-1
HER-2
HER-3
HER-4
NRG1
β3
HB-GF
NRG1
NRG2
NRG3
NRG 4
VEGF
NRG1
HER-2/HER-4 Heterodimer
P
P
PI3K
SOS
Akt
P
MAPK
P
RAS
MEK
RAF
Cytoplasm
Nucleus
Transcription
•Proliferation
•Motility
•Invasiveness
•Resistance to apoptosis
•Angiogenesis

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

HER2 gene amplification (Southern)





HER2 protein overexpression (IHC)

Median Survival

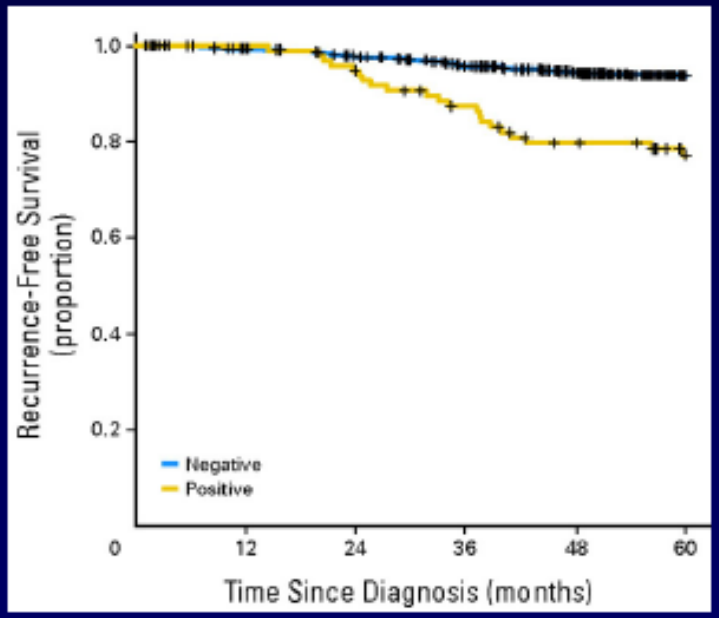
HER2 overexpression	3 yrs
HER2 normal	6-7 yrs

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

Outcomes for T1a/bN0 HER2+ Tumors

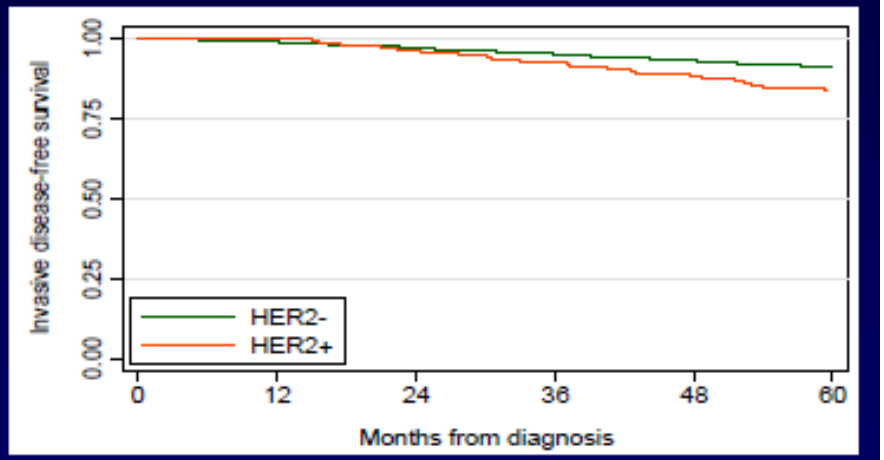
MD Anderson series

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



NCCN series

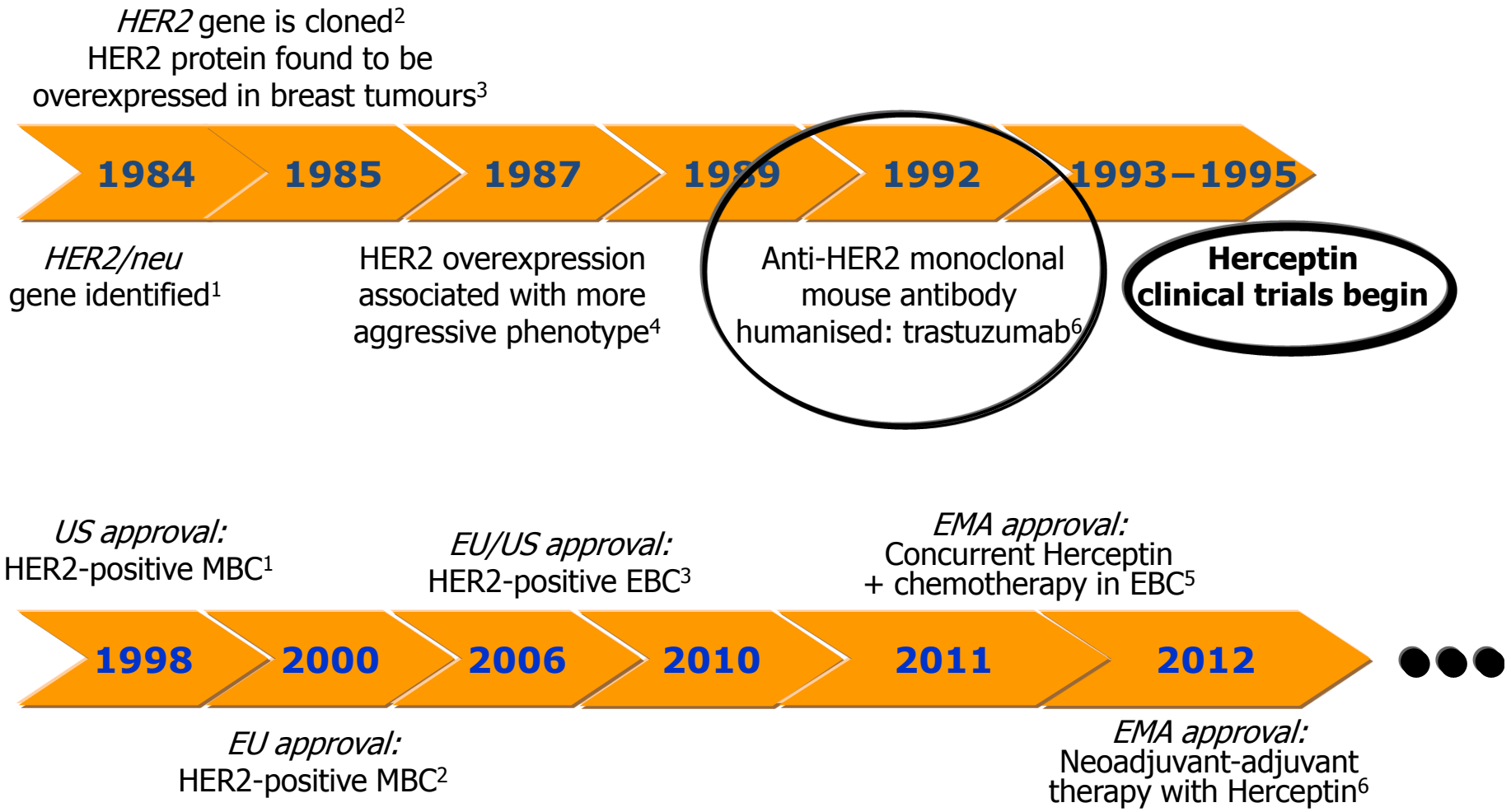
HER2 status	n	5 yr DFS
HER2+	255	83.3%
HER2-	3127	89.0%



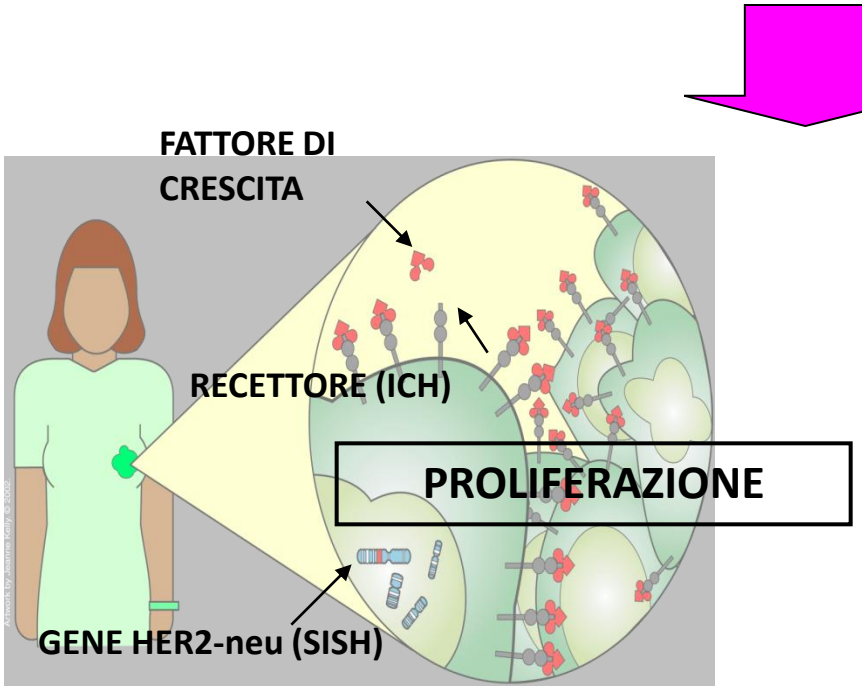
Gonzalez-Angulo AM, et al. *J Clin Oncol.* 2009;27(34):5700-5706. Vaz Duarte Luis IM, et al. *J Clin Oncol.* 2013;31(Suppl): Abstract 1006.

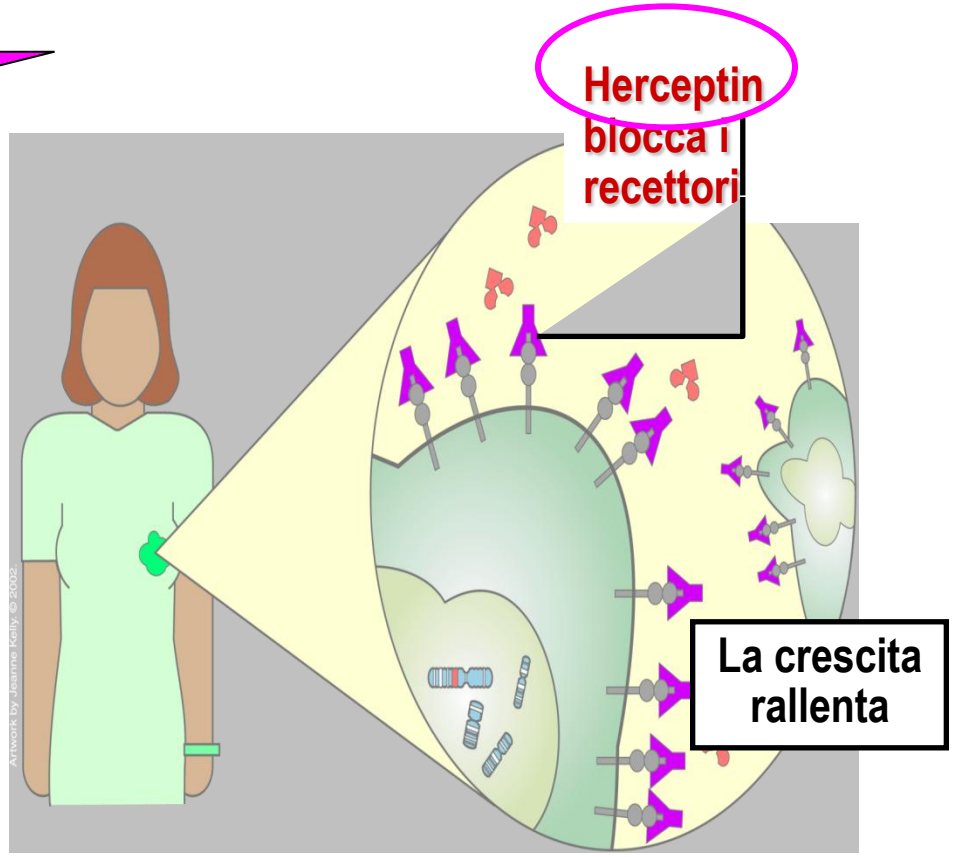
Tolaney SM, et al. *Cancer Res.* 2013;73(24 Suppl): Abstract S1-04.

From Bench to Bedside….



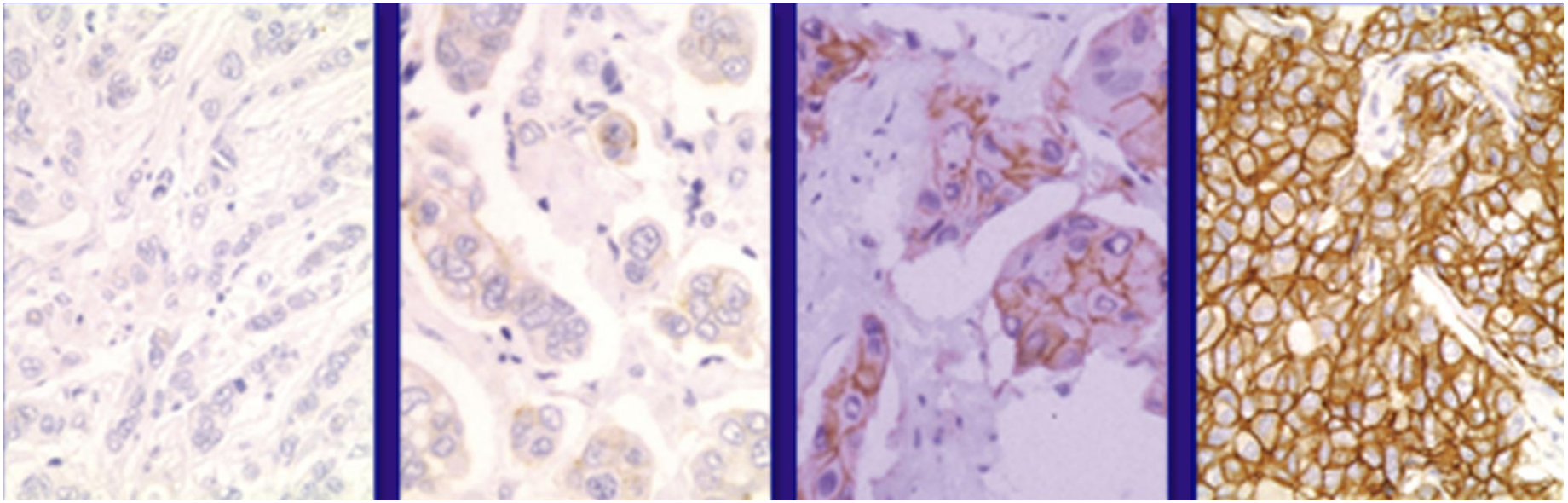
TERAPIA A BERSAGLIO MOLECOLARE ANTI-HER2





IHC Test Measures HER2 Protein Overexpression

Immunohistochemistry



IHC 0 **IHC 1+** **IHC 2+** **IHC 3+**

- IHC is scored on a 0-3+ scale based on staining intensity and completeness of membrane staining
- HercepTest® is an FDA-approved assay

HercepTest® PI. 3rd ed.

Published Ahead of Print on October 7, 2013 as 10.1200/JCO.2013.50.9984
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2013.50.9984

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update

Antonio C. Wolff, M. Elizabeth H. Hammond,* David G. Hicks,* Mitch Dowsett,* Lisa M. McShane,* Kimberly H. Allison, Donald C. Allred, John M.S. Bartlett, Michael Bilous, Patrick Fitzgibbons, Wedad Hanna, Robert B. Jenkins, Pamela B. Mangu, Soonmyung Paik, Edith A. Perez, Michael F. Press, Patricia A. Spears, Gail H. Vance, Giuseppe Viale, and Daniel F. Hayes**

Author affiliations appear at the end of this article.

ABSTRACT

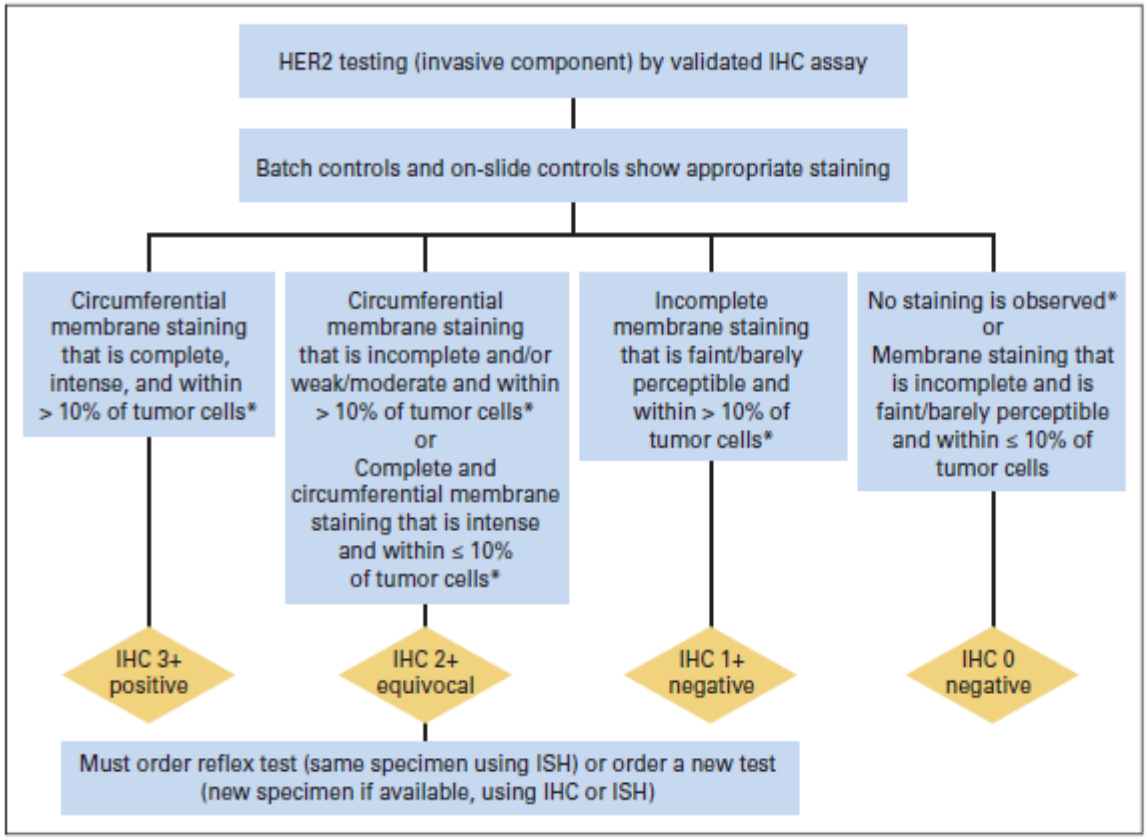
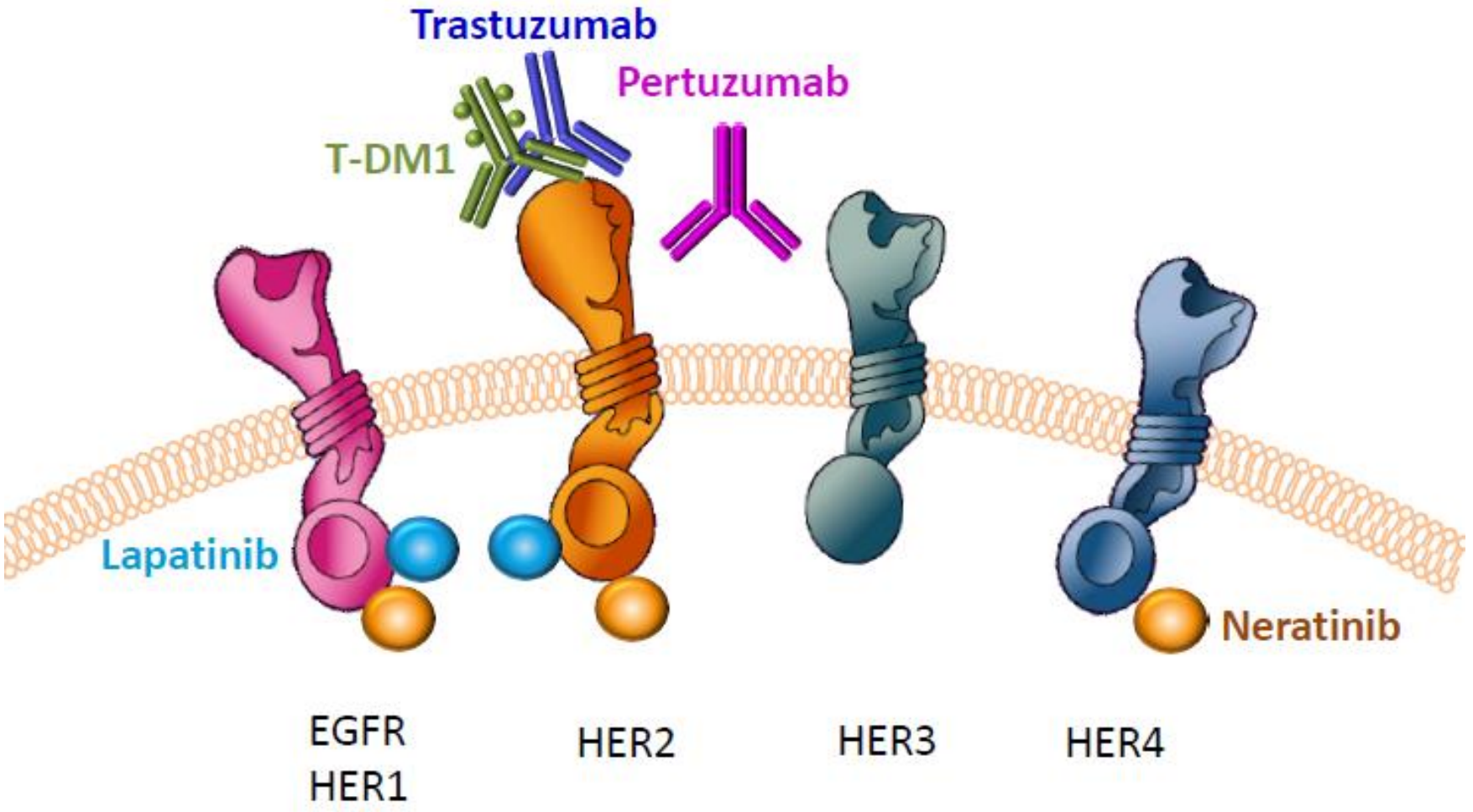
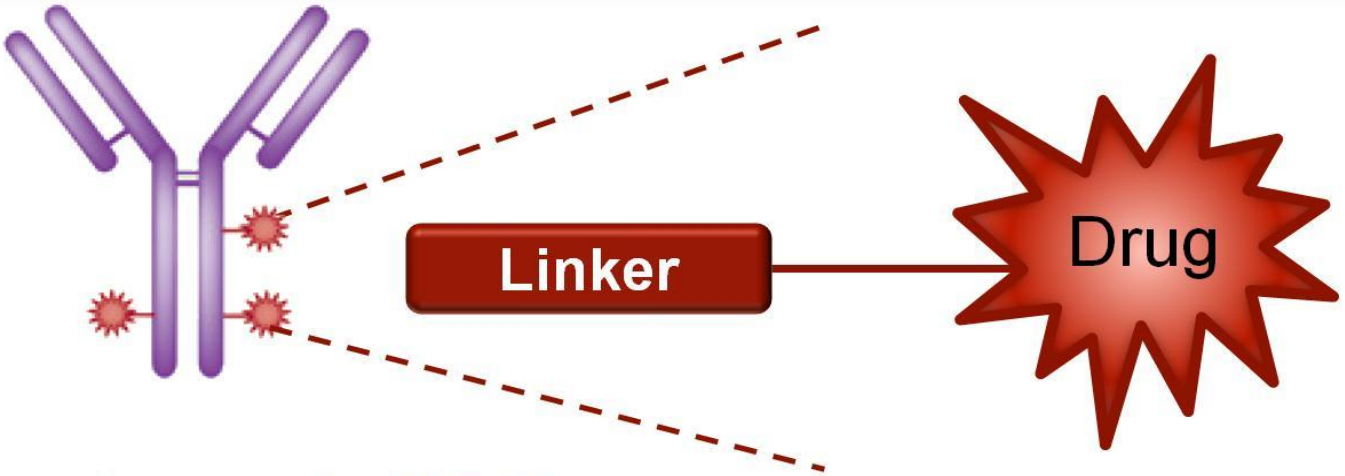


Fig 1. Algorithm for evaluation of human epidermal growth factor receptor 2 (HER2) protein expression by immunohistochemistry (IHC) assay of the invasive component of a breast cancer specimen. Although categories of HER2 status by IHC can be created that are not covered by these definitions, in practice they are rare and if encountered should be considered IHC 2+ equivocal. ISH, in situ hybridization. NOTE: the final reported results assume that there is no apparent histopathologic discordance observed by the pathologist. (*) Readily appreciated using a low-power objective and observed within a homogeneous and contiguous invasive cell population.

Anti-HER2 therapy and HER family



Antibody-Drug Conjugates
Basics

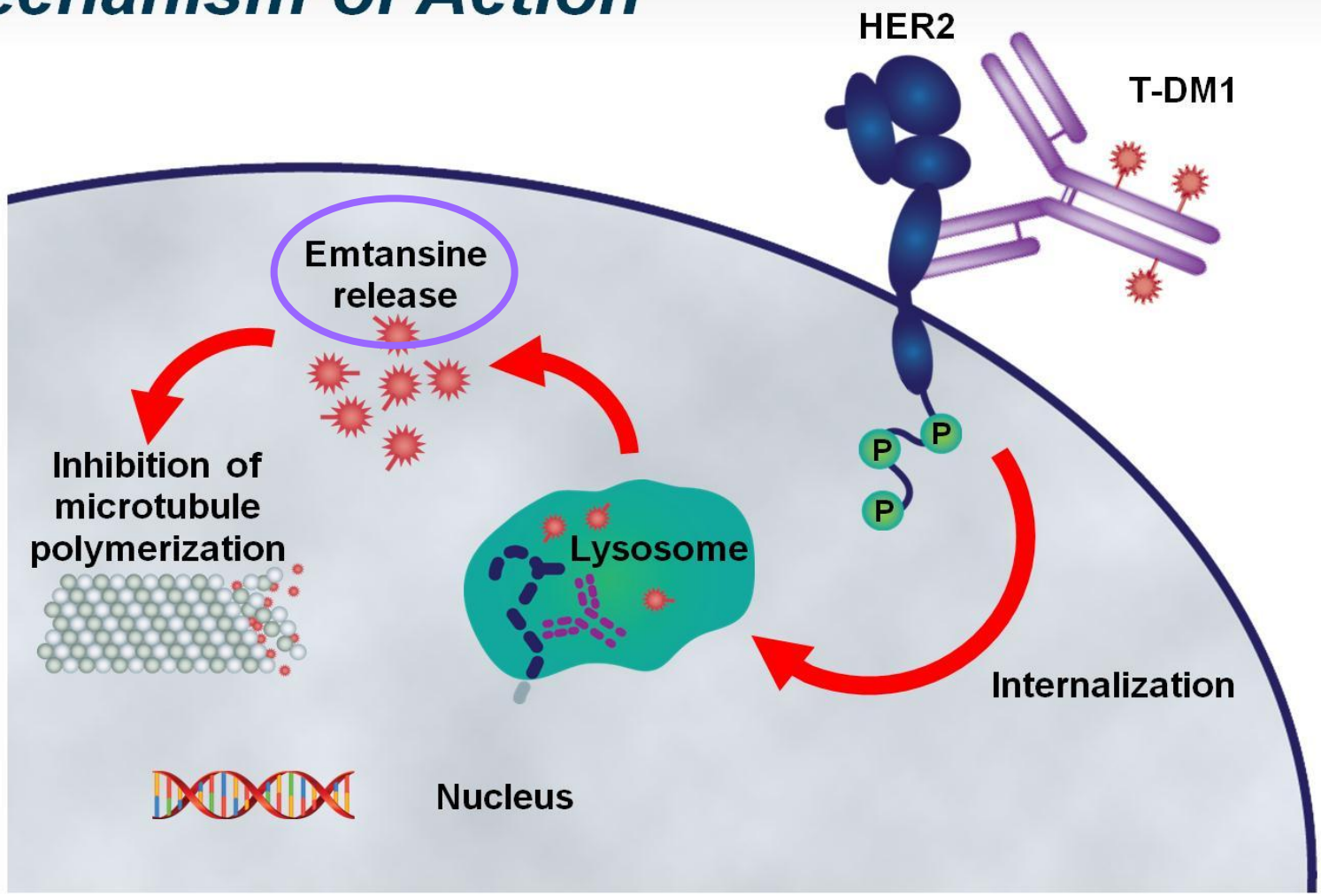


What makes an optimal ADC?

- Antibody
  - Target recognition unaltered compared with naked Ab
  - Abundant target expression and internalization
- Drug
  - Highly potent cytotoxic agent (≤ nM IC90 as a free drug)
  - Validated mechanism of action (microtubule inhibition, DNA damage)
- Linker
  - Stable in plasma to avoid premature release of the drug
  - Labile once internalized to release the drug in its active form

Teicher BA, et al.[8]

T-DM1
Mechanism of Action



LoRusso PM, et al.[9]

The New England
Journal of Medicine

VOLUME 344 MARCH 15, 2001 NUMBER 11

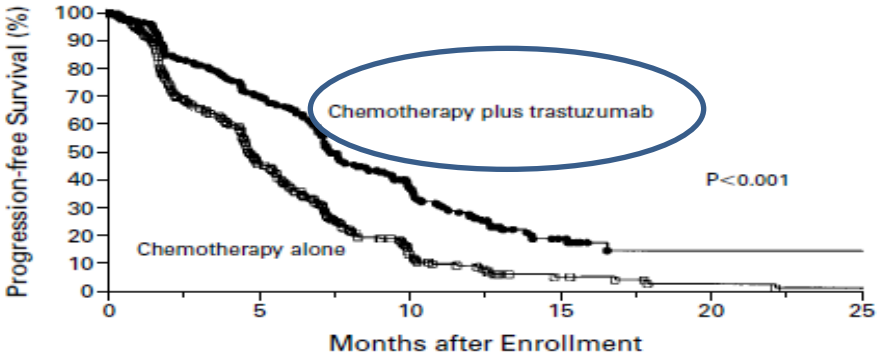
USE OF CHEMOTHERAPY PLUS A MONOCLONAL ANTIBODY AGAINST HER2 FOR METASTATIC BREAST CANCER THAT OVEREXPRESSES HER2

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.

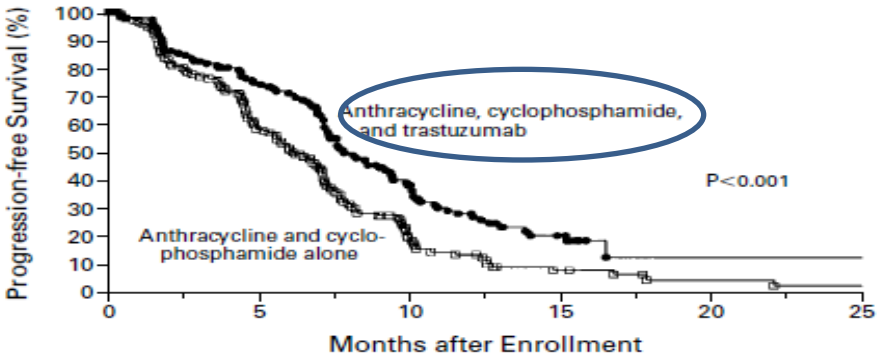
CHARACTERISTIC	AN ANTHRACYCLINE, CYCLOPHOSPHAMIDE, AND TRASTUZUMAB (N=143)*	AN ANTHRACYCLINE AND CYCLOPHOSPHAMIDE ALONE (N=138)†	PACLITAXEL AND TRASTUZUMAB (N=92)	PACLITAXEL ALONE (N=96)
Age — yr				
Mean ±SD	54±10.3	54±10.1	51±11.5	51±11.0
Range	27–76	25–75	25–77	26–73
Karnofsky score — no./no. analyzed (%)				
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



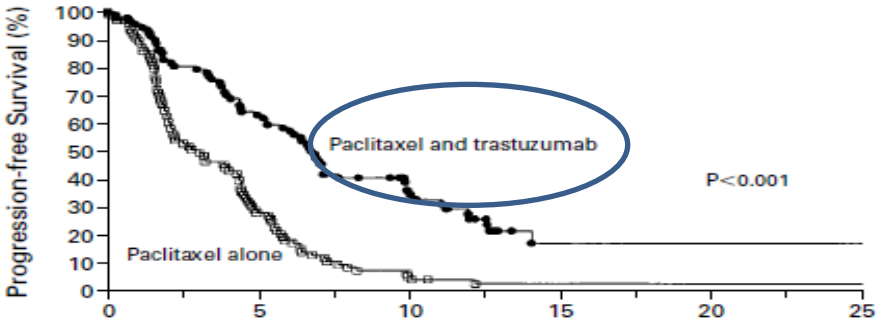
ab	235	152	63	15
one	234	103	25	6

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



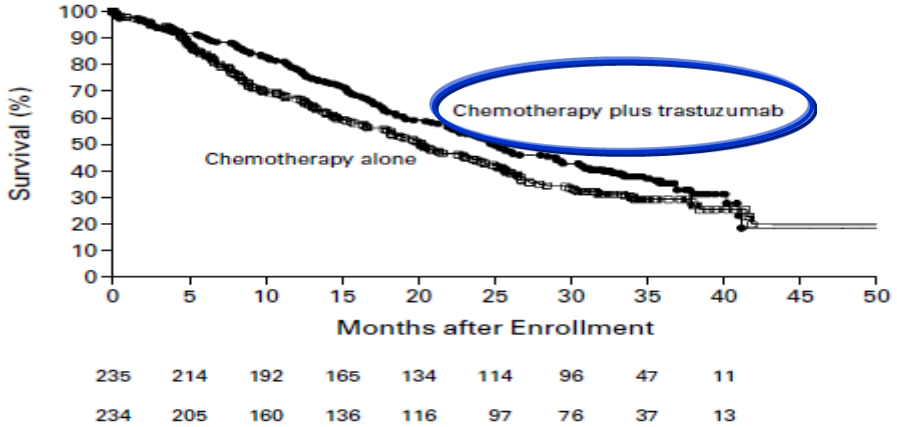
clophos-rastuzumab	143	98	40	12
d cyclo-lone	138	77	20	6

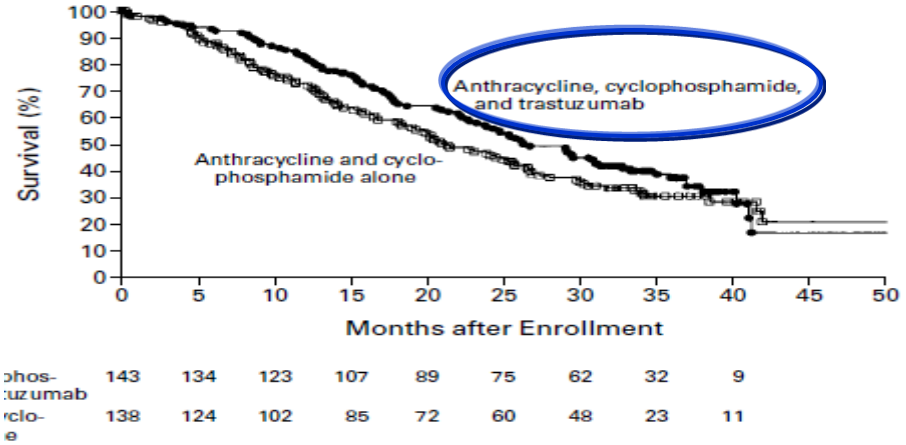
Median duration of response was 9.1 months for trastuzumab-group vs 6.1 months w/o trastuzumab

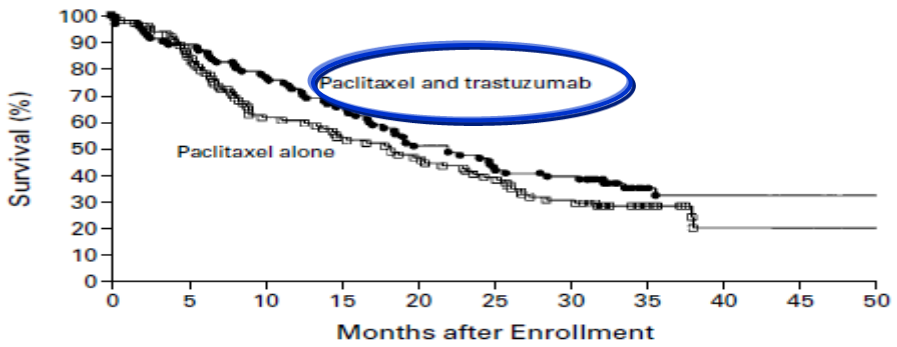


Overall survival

Reduced risk of death of 18-20%.







Capecitabine vs Capecitabine + Lapatinib

- Progressive, HER2+ MBC or LABC
- Previously treated with anthracycline, taxane and trastuzumab*
- No prior capecitabine

Lapatinib 1250 mg po qd continuously +
Capecitabine 2000 mg/m^2/d po days 1-14 q 3 wk

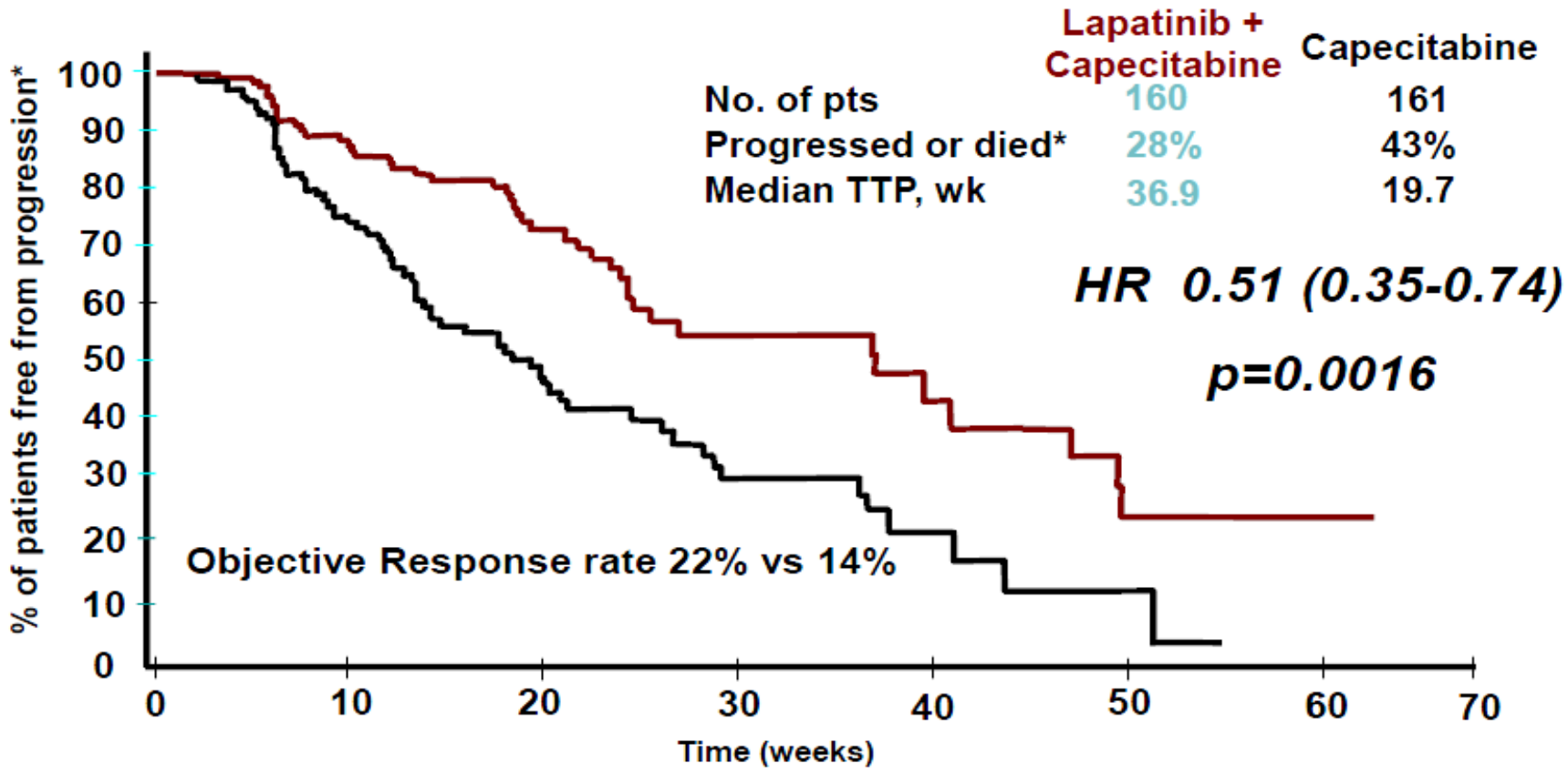
Capecitabine 2500 mg/m^2/d po days 1-14 q 3 wk

N=528

*Trastuzumab must have been administered for metastatic disease

Geyer et al, NEJM 2006

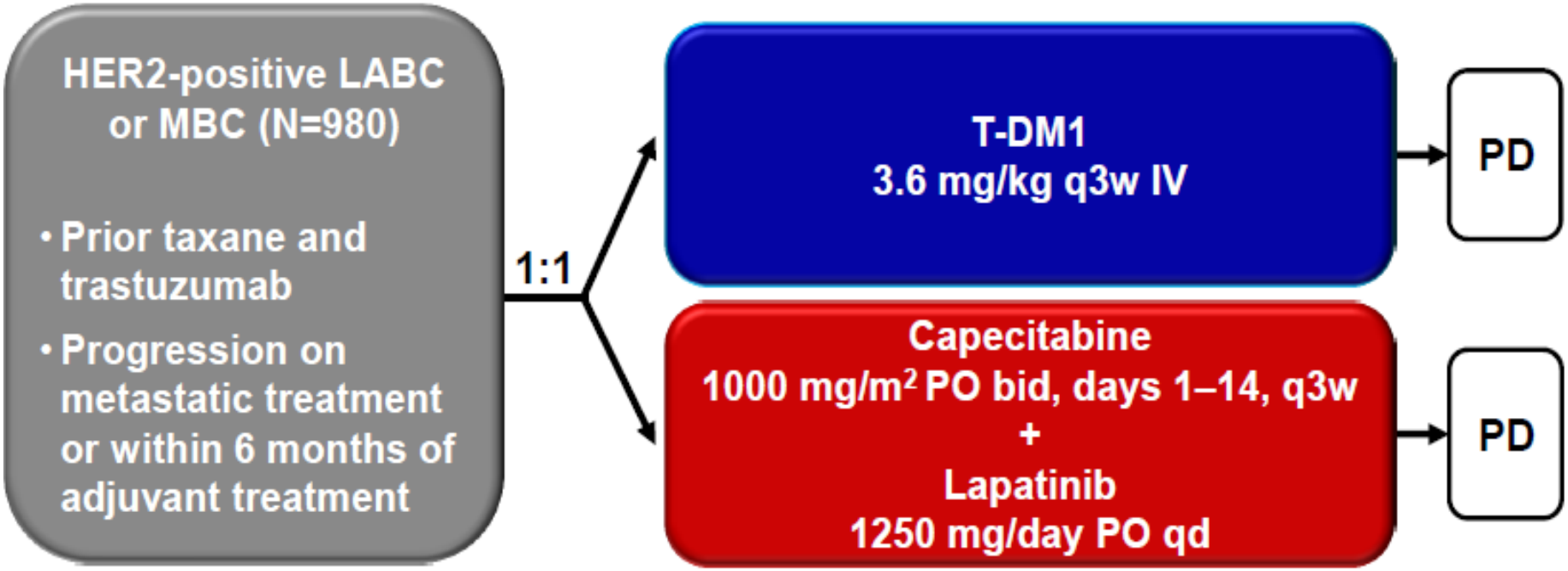
Capecitabine +/- Lapatinib: Time to Progression



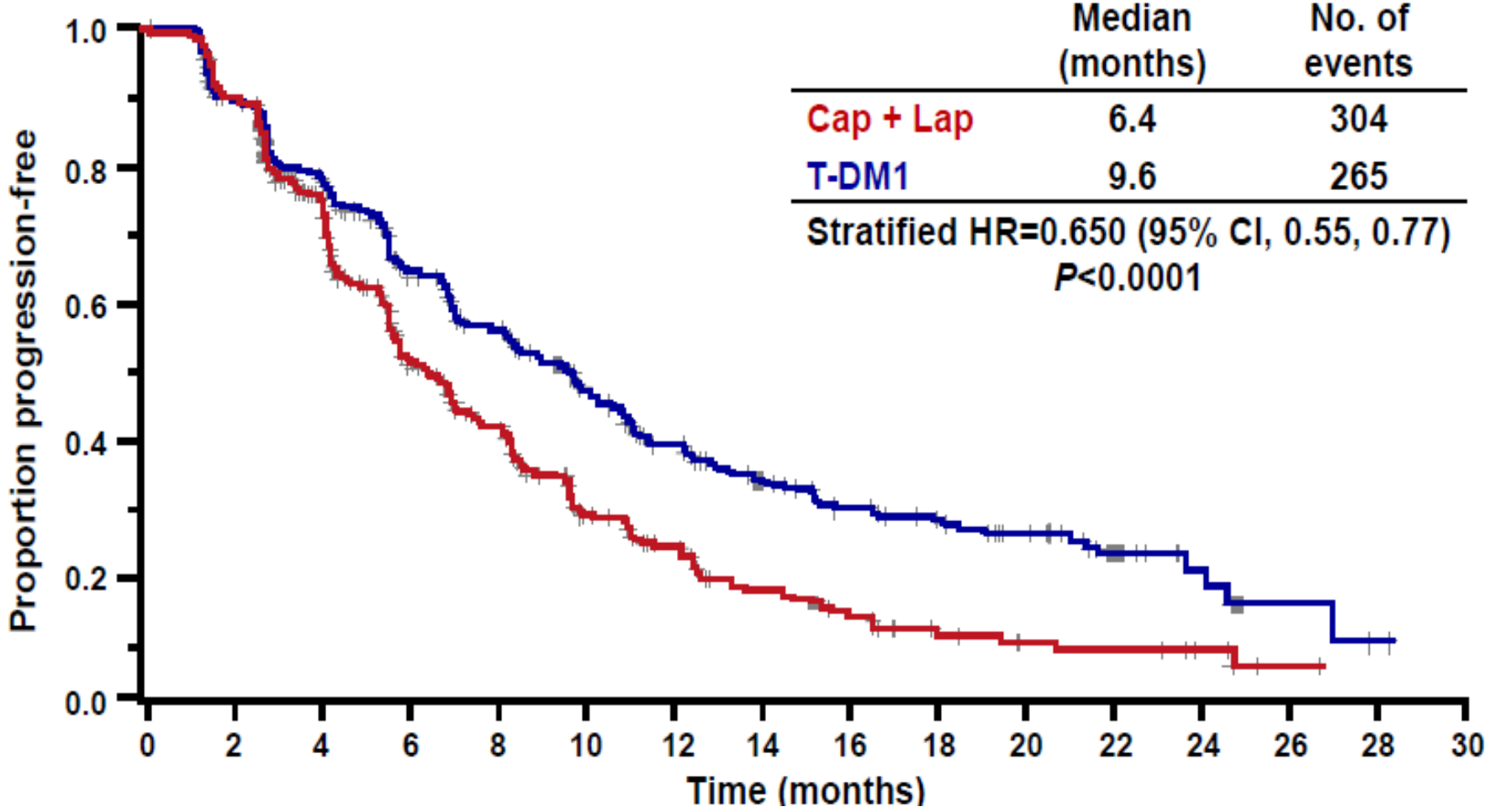
No Difference Seen In Overall Survival

Geyer et al, NEJM 2006

EMILIA Study Design



Progression-Free Survival by Independent Review

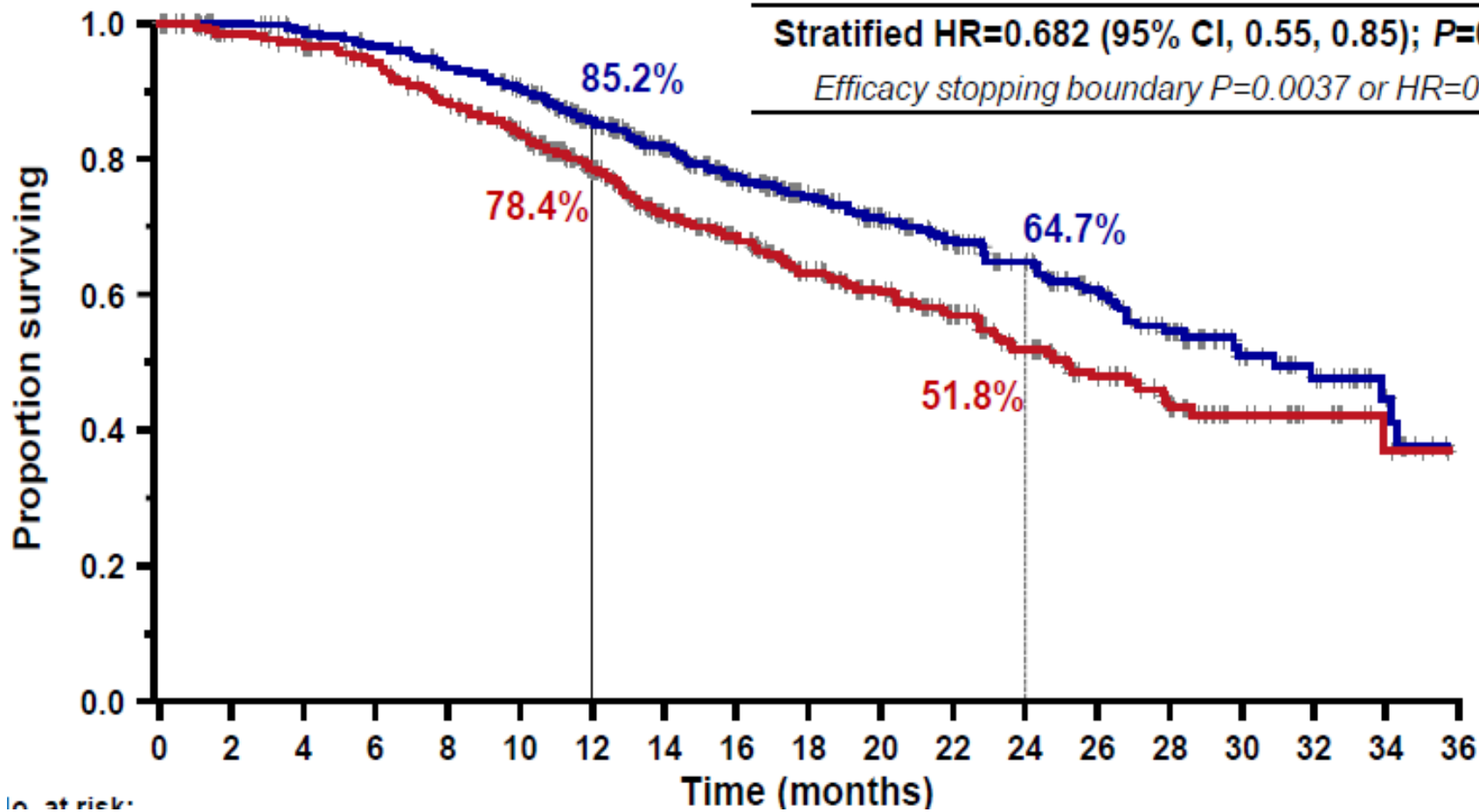


Overall Survival: Confirmatory Analysis

	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



Lancet Oncol. 2013 May;14(6):461-71. doi: 10.1016/S1470-2045(13)70130-X. Epub 2013 Apr 18.

Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study.

Swain SM[1], Kim SB, Cortés J, Ro J, Semiglazov V, Campone M, Ciruelos E, Ferrero JM, Schneeweiss A, Knott A, Clark E, Ross G, Benyunes MC, Baselga J.

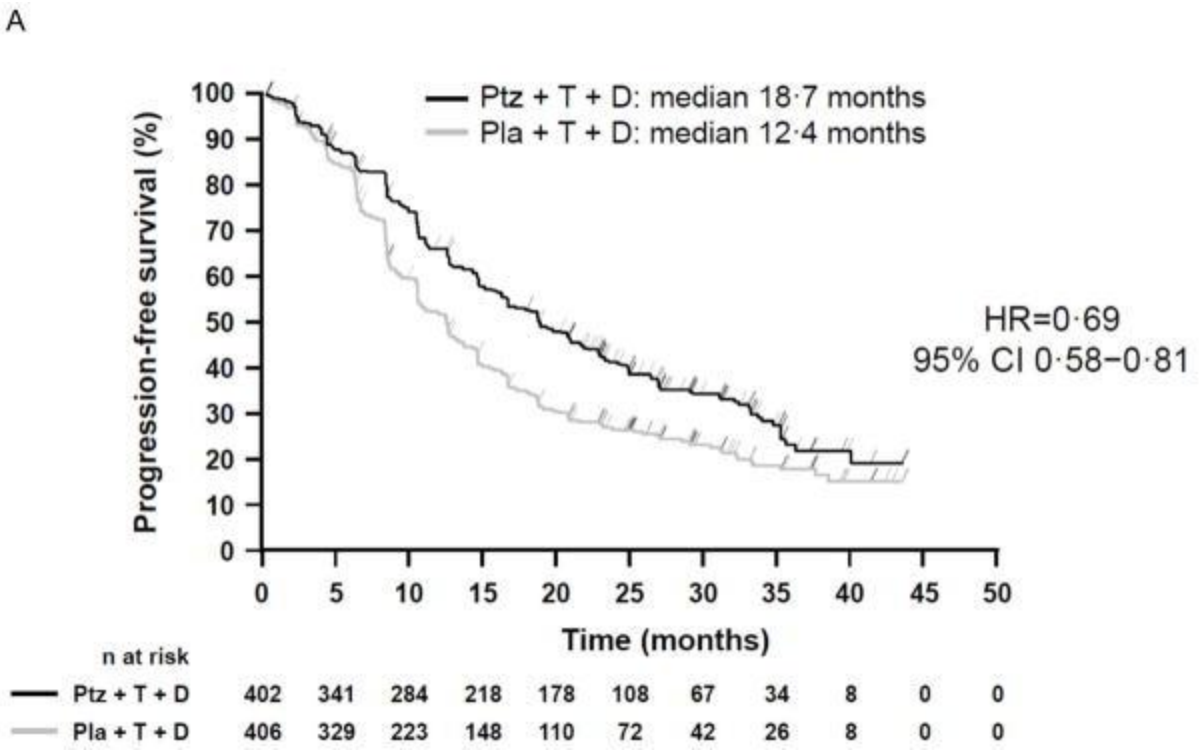
Author information

[1]Washington Cancer Institute, MedStar Washington Hospital Center, Washington, DC 20010, USA. Sandra.M.Swain@MedStar.net

Abstract

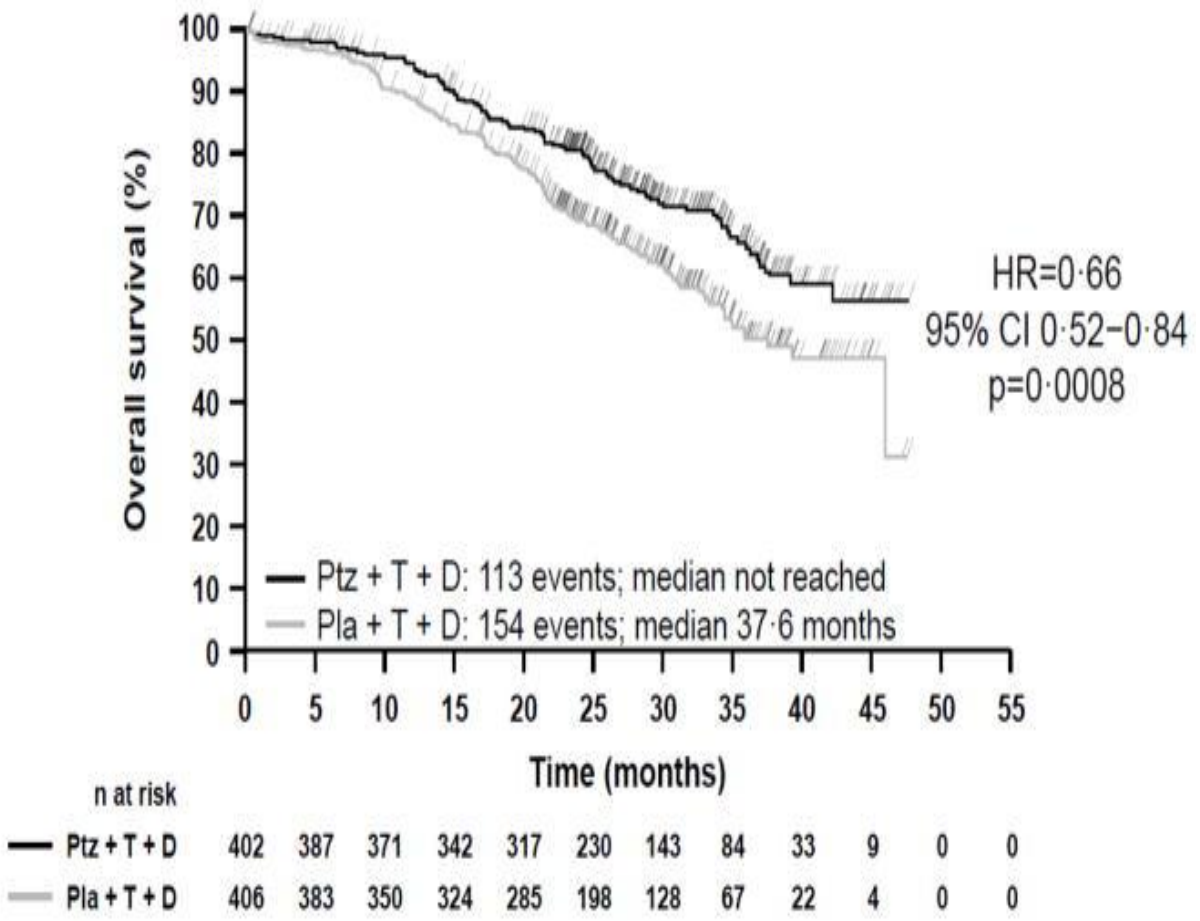
BACKGROUND: CLEOPATRA is a phase 3 study to compare the efficacy and safety of pertuzumab, trastuzumab, and docetaxel with placebo, trastuzumab, and docetaxel in patients with HER2-positive first-line metastatic breast cancer. The

Progression-free survival



Overall survival

A

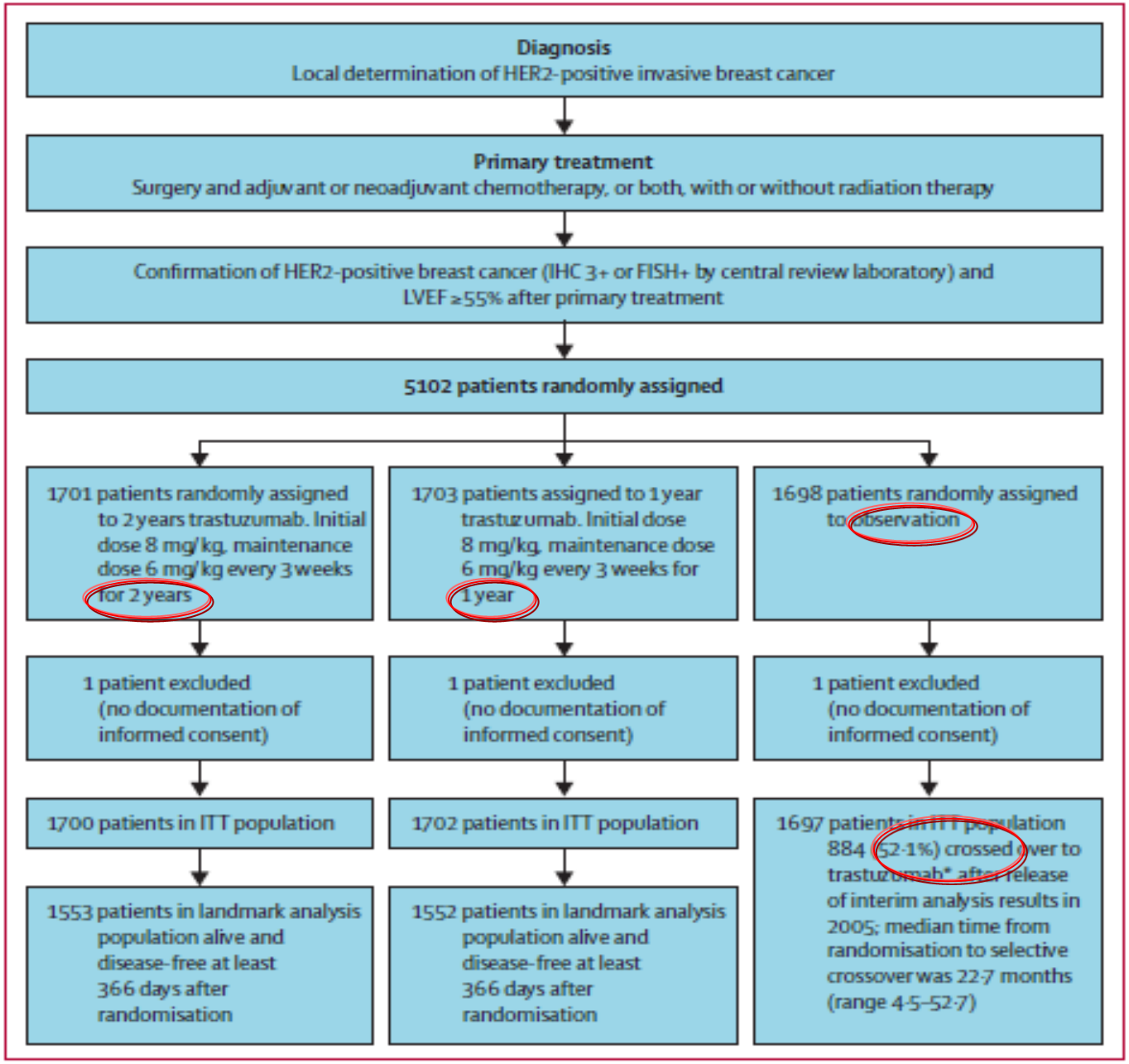


Up date from ESMO Congress 2014: median survival with adding pertuzumab vs only trastuzumab in 50.6 months vs 40.7 months.

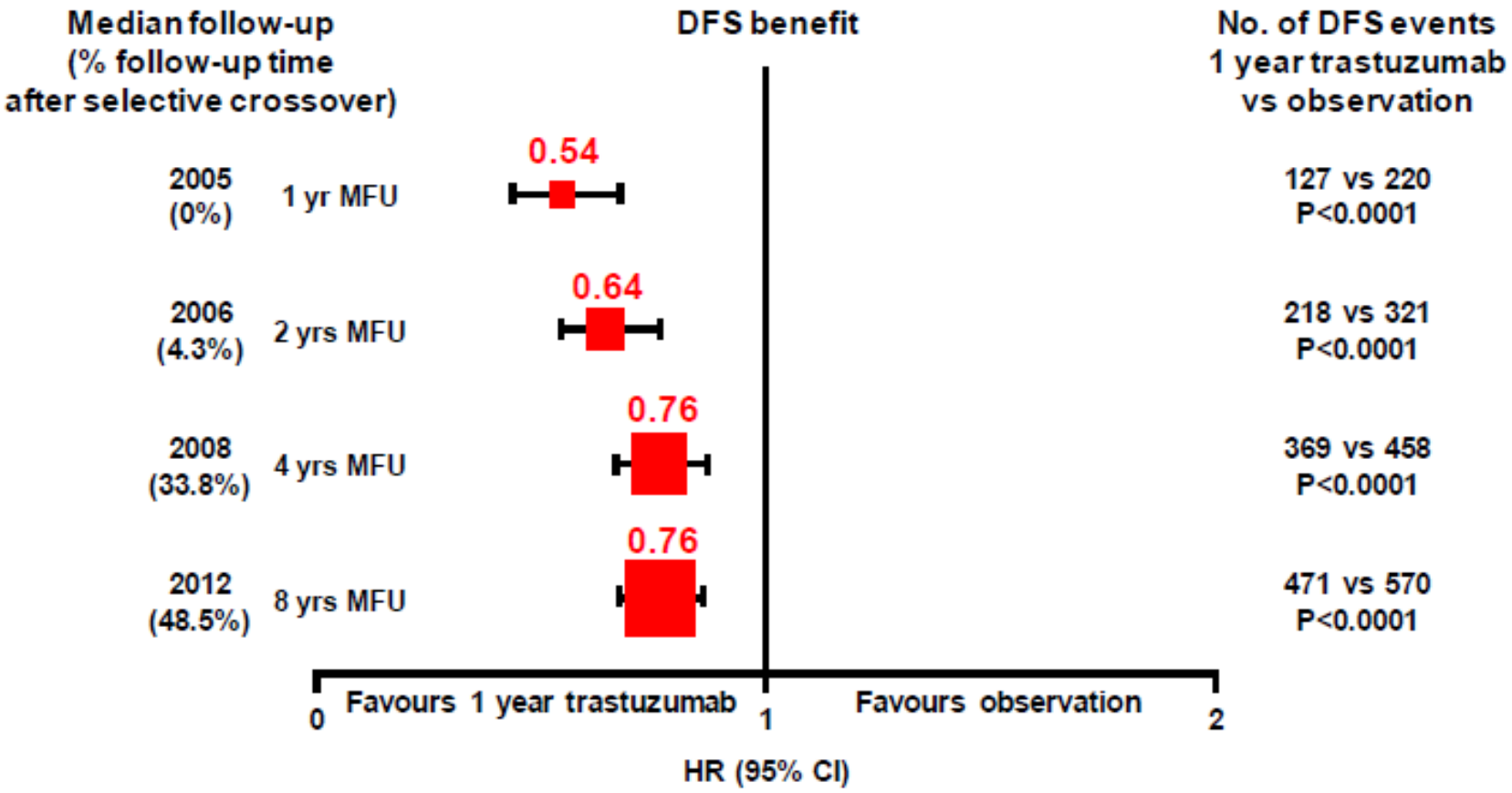
2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial

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

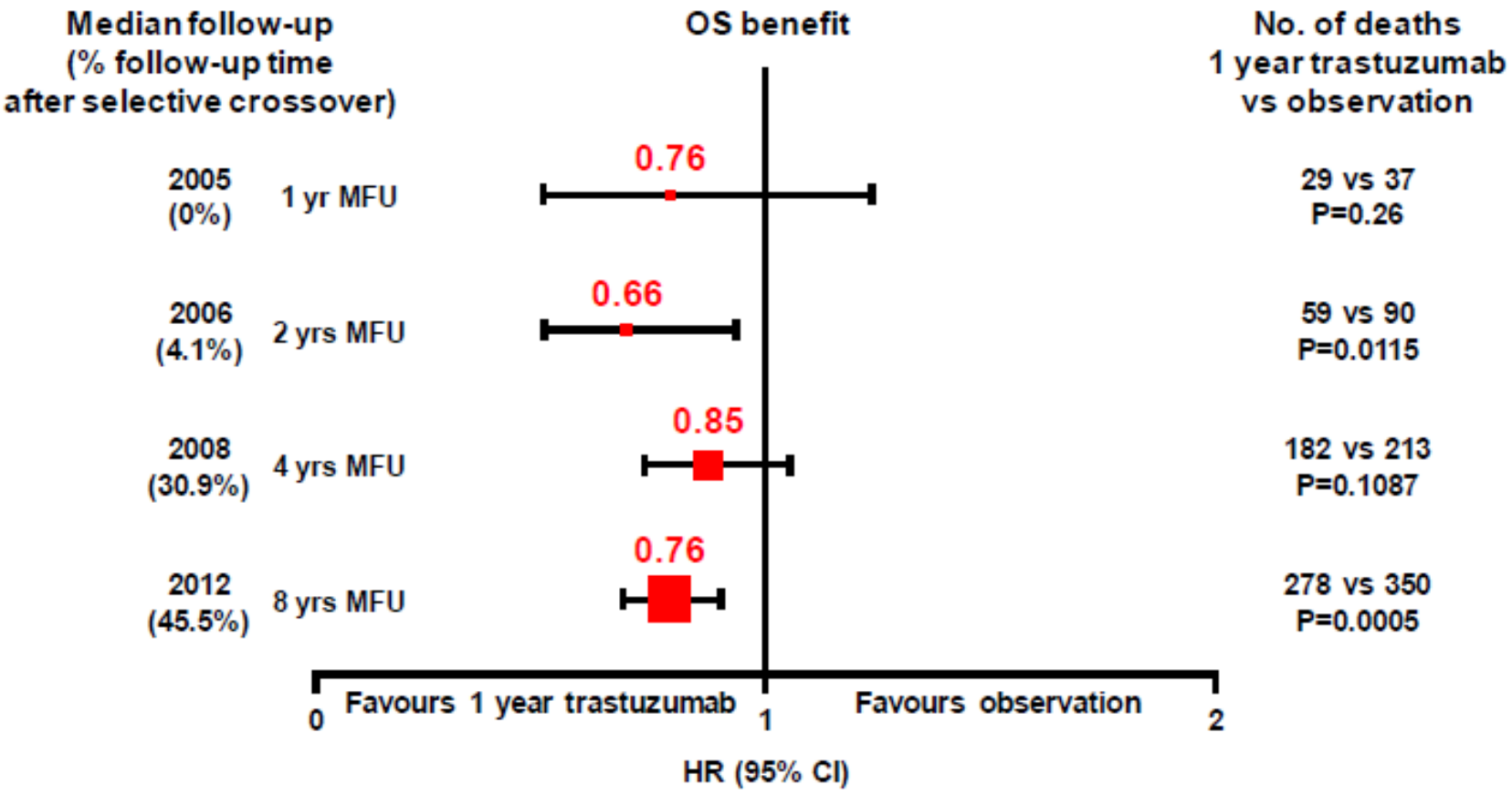

Diagnosis
Local determination of HER2-positive invasive breast cancer
Primary treatment
Surgery and adjuvant or neoadjuvant chemotherapy, or both, with or without radiation therapy
Confirmation of HER2-positive breast cancer (IHC 3+ or FISH+ by central review laboratory) and LVEF ≥55% after primary treatment
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

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

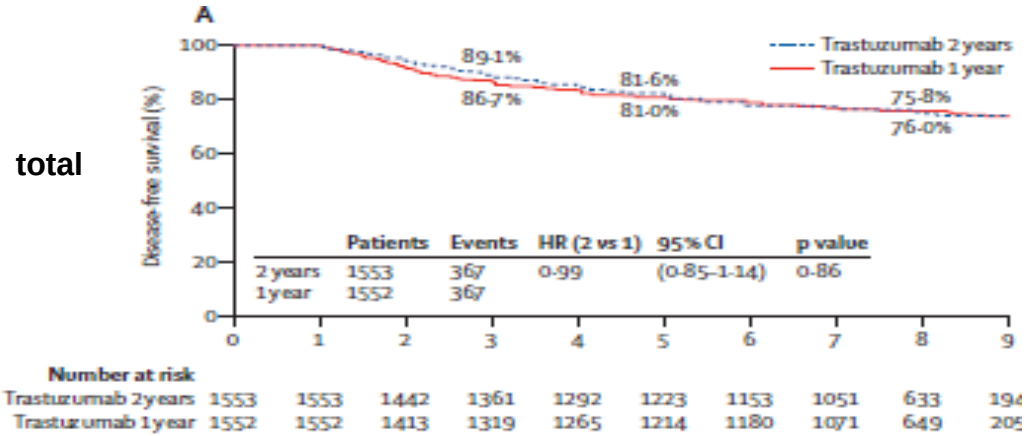


Extended from Gianni et al. Lancet Oncol. 2011.

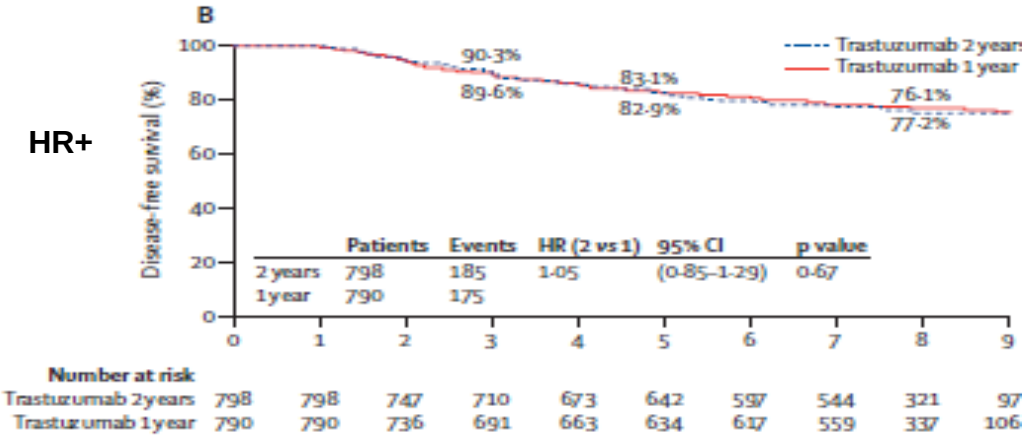
WHAT ABOUT THE DURATION OF TREATMENT?

HERA-results: 1yr vs 2yrs

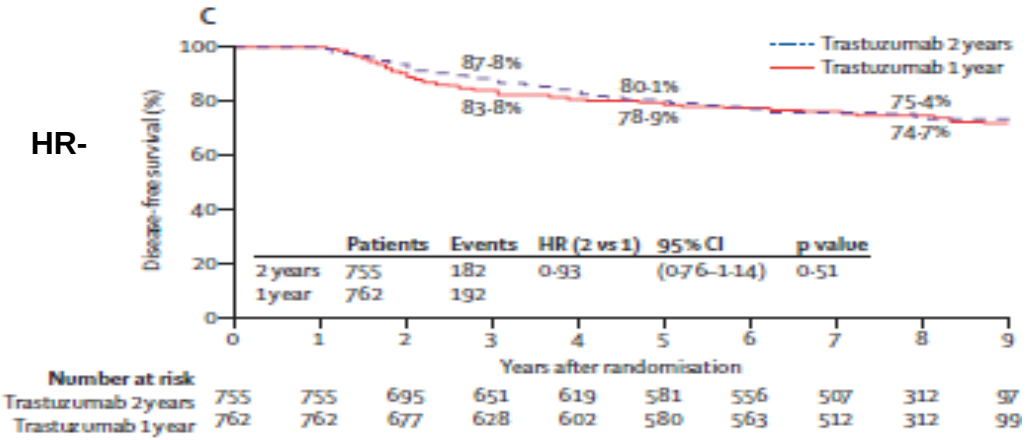
total



HR+



HR-



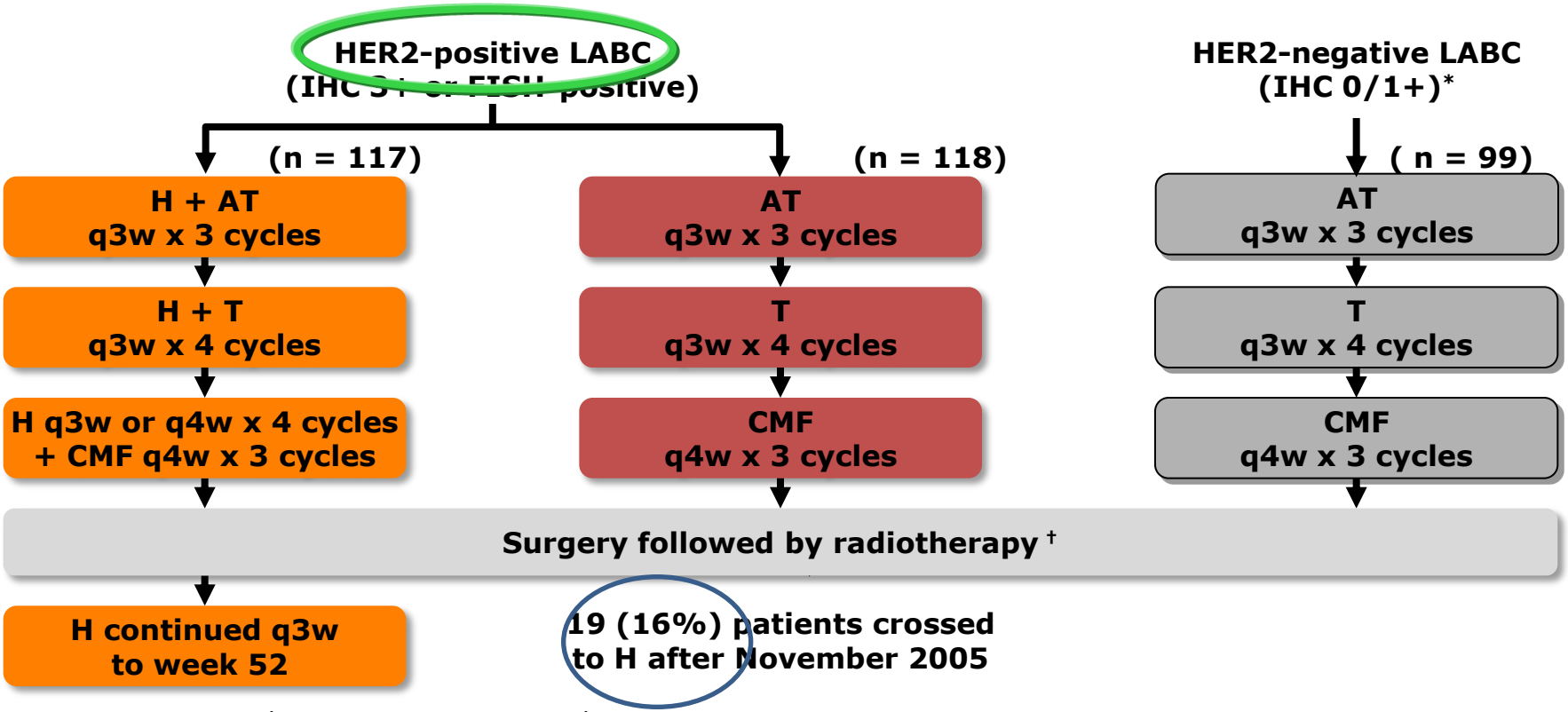
NOAH: Inclusion criteria

- 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

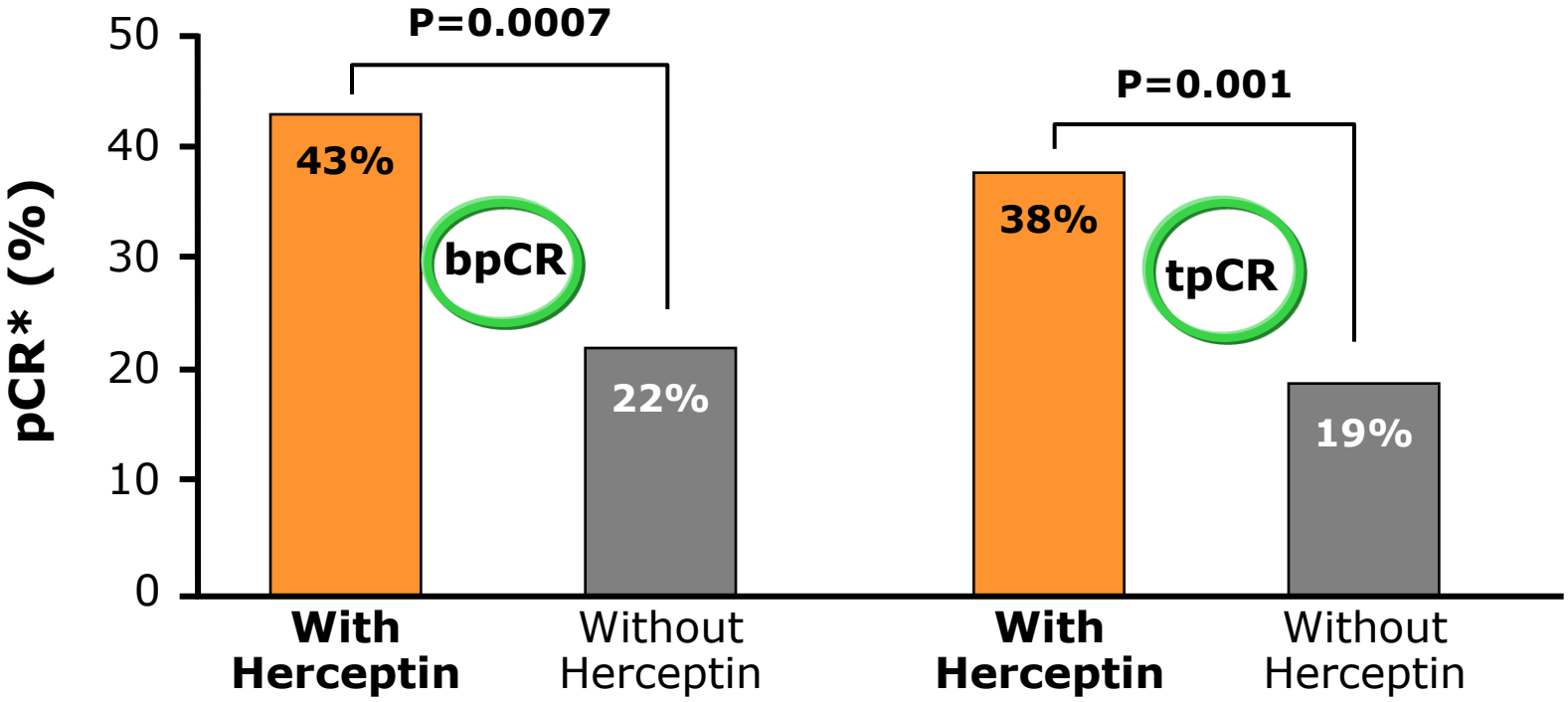


•H, trastuzumab (8 mg/kg loading dose then 6 mg/kg);
AT, doxorubicin (60 mg/m^2), paclitaxel (150 mg/m^2); T, paclitaxel (175 mg/m^2);
CMF, cyclophosphamide, methotrexate and fluorouracil 5-FU
* A separate treatment group of HER2-negative patients received chemotherapy only;
•† Hormone receptor-positive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

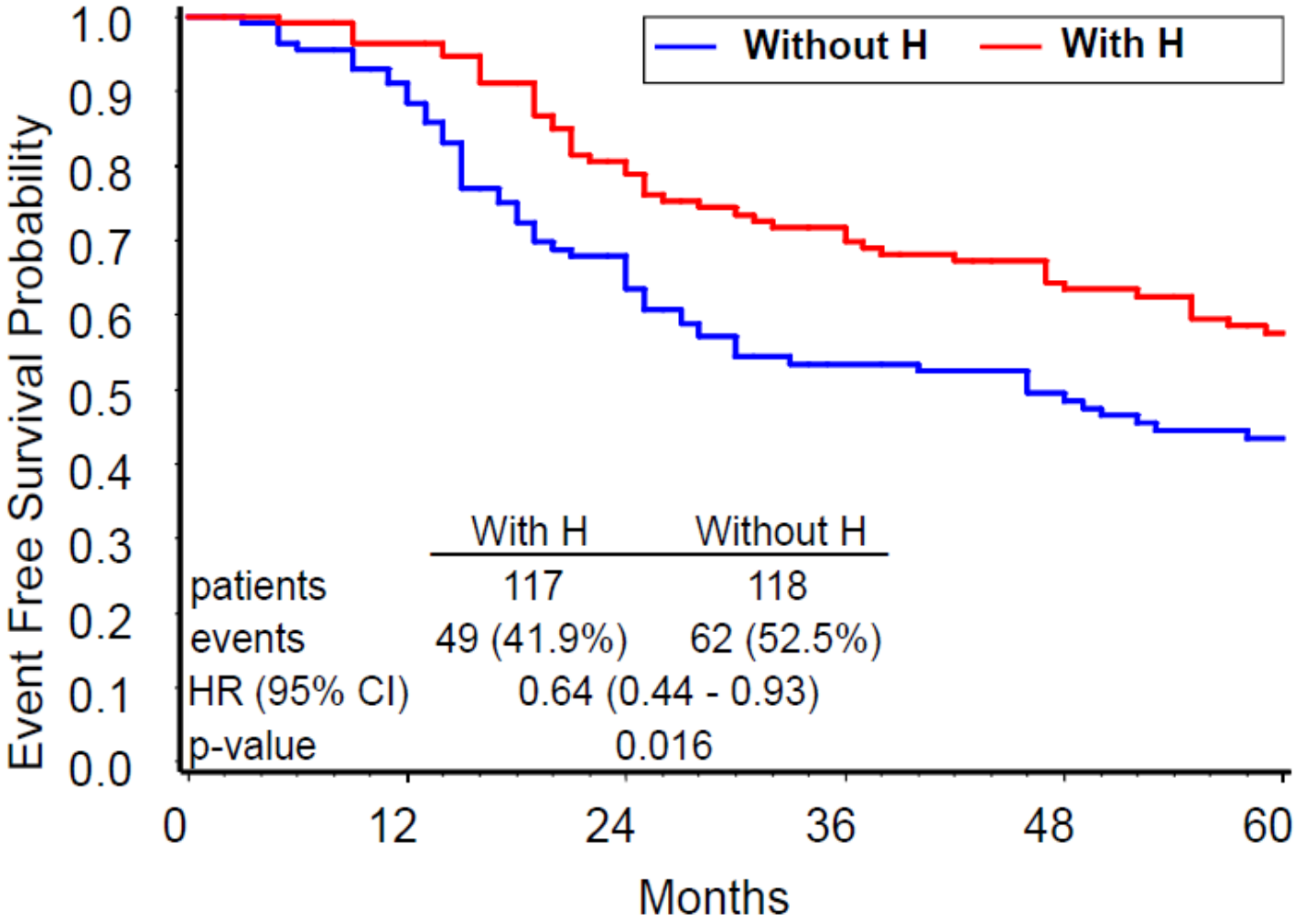


pCR, pathological complete response
bpCR, pathological complete response in breast tissue;
tpCR, total pathological complete response (in breast and axillary nodes)
*Absence of invasive tumour cells

Gianni L, *et al*. 2010

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

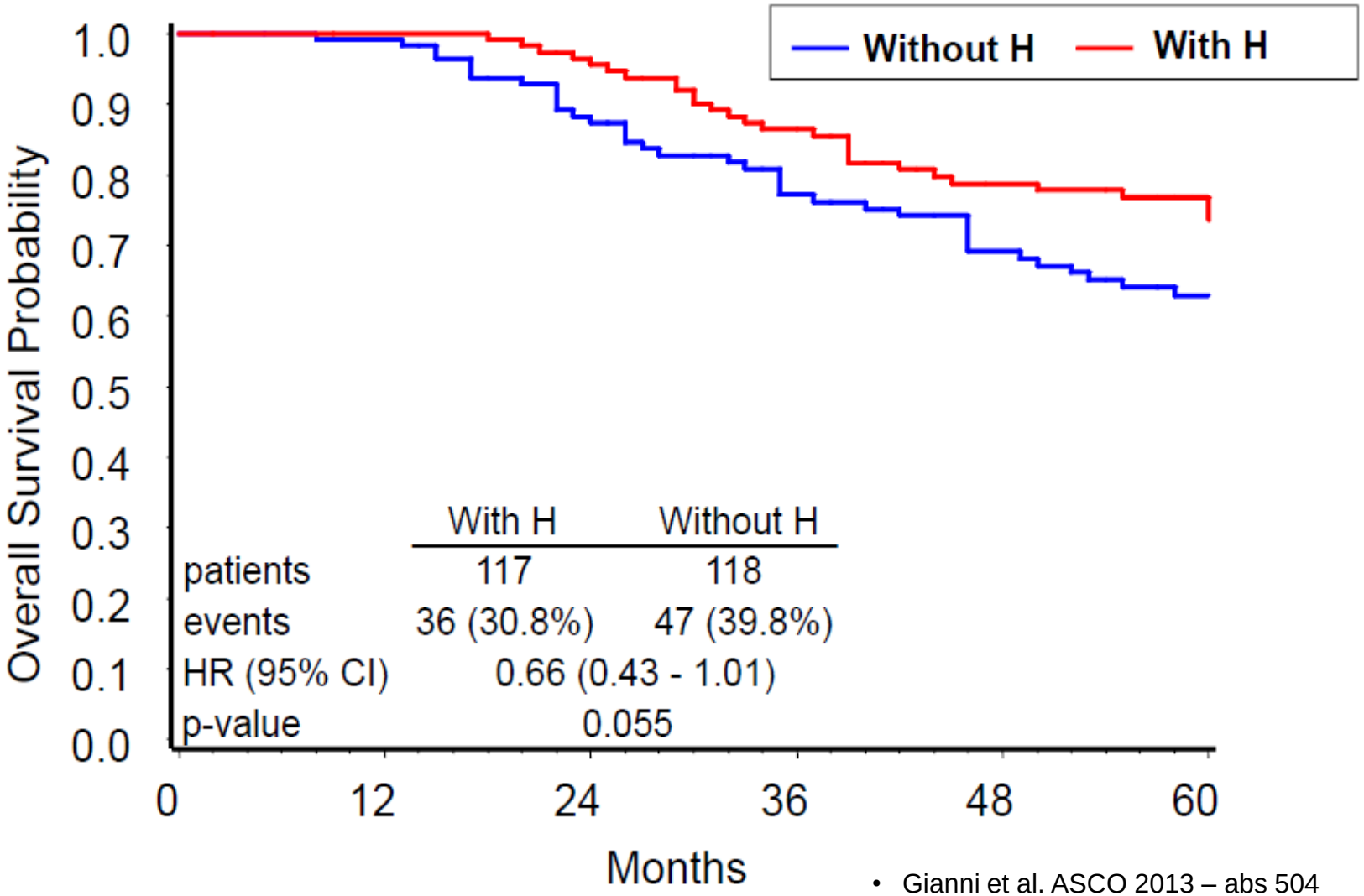
Significant EFS benefit with the addition of trastuzumab to chemotherapy in HER2-positive patients



- Gianni et al. ASCO 2013 – abs 504

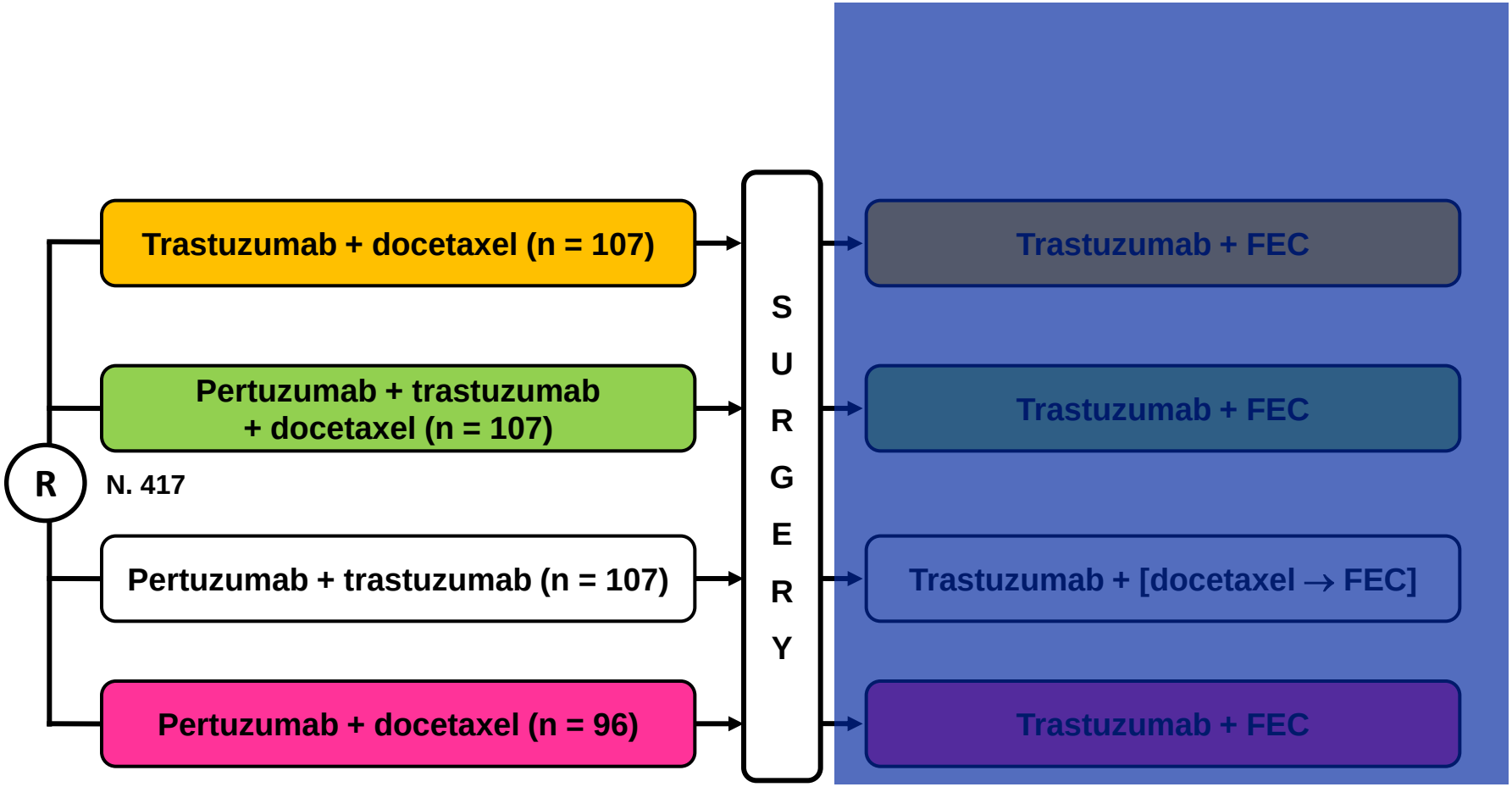
NOAH: Overall survival in the HER2-positive ITT population (follow-up data)

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



- Gianni et al. ASCO 2013 – abs 504

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

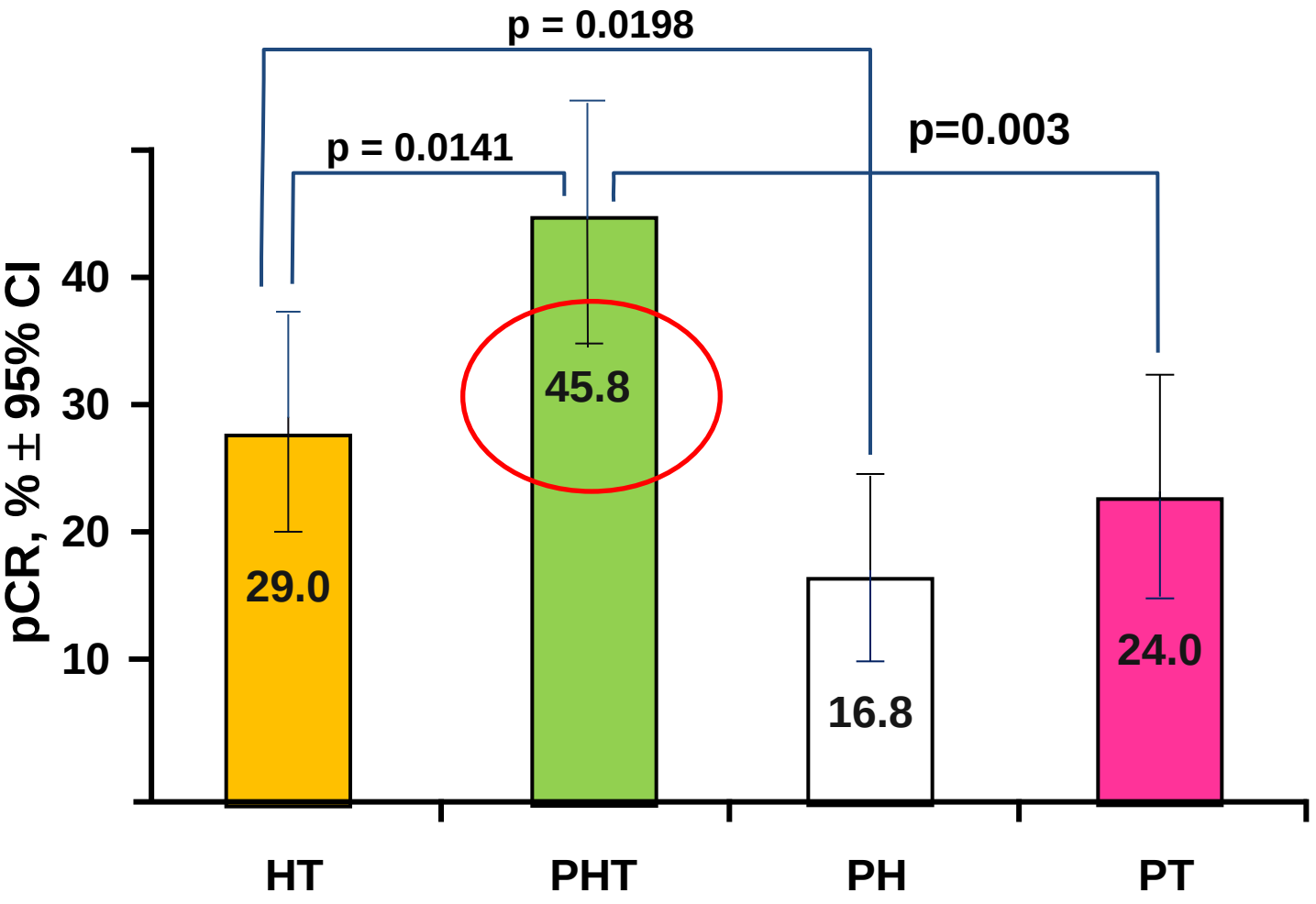


(NEOadjuvant Study of Pertuzumab and Herceptin in an Early Regimen Evaluation)

Gianni, Lancet Oncol 2012; 13

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

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



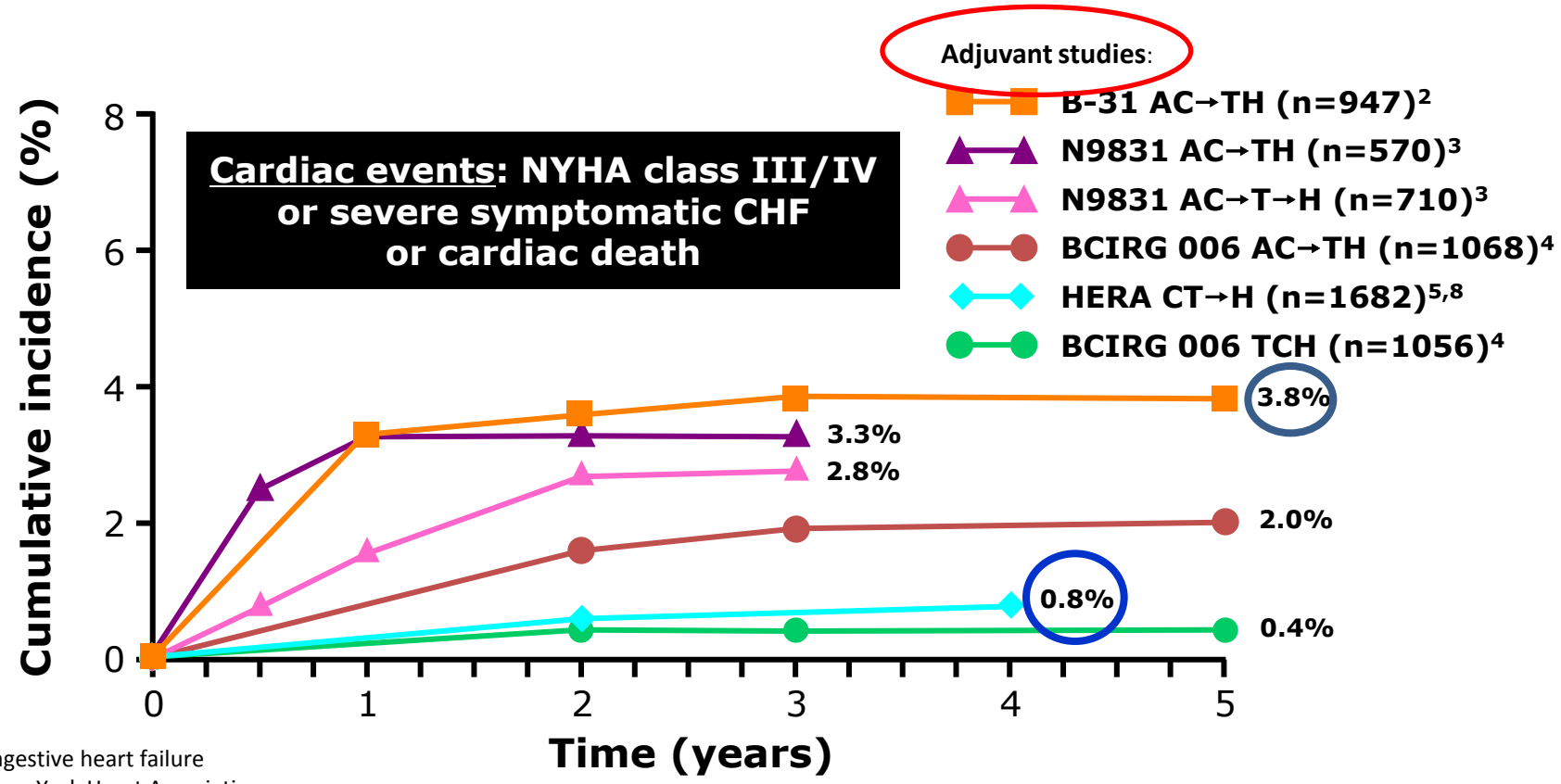
Gianni L, *et al. Lancet Oncol* 2012; **13:**25–32.

COMMON OR SEVERE TOXICITIES OF anti-HER2 BIOLOGIC AGENTS

Anti-HER2 Agent	Common or Serious Grade ¾ Adverse Events
Trastuzumab	**Cardiotoxicity** **Infusion reactions**
Lapatinib	**Diarrhea** **Rash**
Pertuzumab	**Neutropenia** **Febrile neutropenia** **Diarrhea** **Rash**
T-DM1	**Thrombocytopenia** **Liver Disfunction (elevate AST/ALT)**

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

Herceptin IV: Dosage and administration

Dosage

- Three-weekly schedule: loading dose of Herceptin 8 mg/kg followed by 6 mg/kg maintenance dose at 3-weekly intervals, beginning 3 weeks after the loading dose
- Weekly schedule: loading dose of Herceptin 4 mg/kg followed by 2 mg/kg maintenance dose every week, beginning 1 week after the loading dose
- EBC: Administration for 1 year or until disease recurrence, whichever occurs first
- MBC: Administration until disease progression

18 cycles

52 wks

Intravenous administration

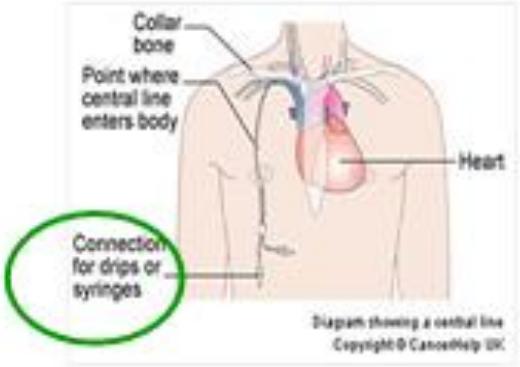
- First dose: administered over 90 minutes
- Observation time: 6 hours required after start of the first infusion to monitor for symptoms like fever and chills or other infusion-related symptoms
- Subsequent doses: administered over 30 minutes if well tolerated
- Observation time: 2 hours required after each administration

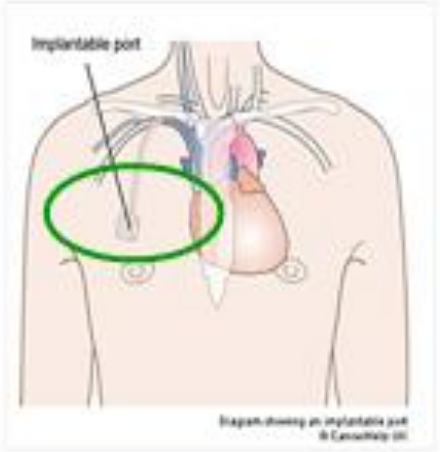
Herceptin® (trastuzumab). Summary of Product Characteristics

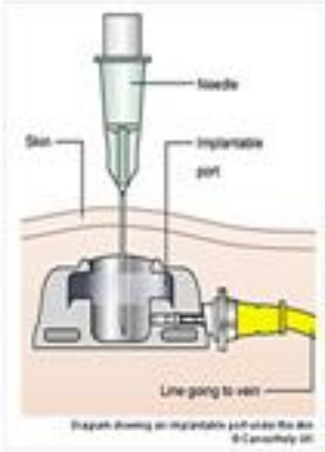
Cosa comporta per la paziente

- **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

Lancet Oncol 2012; 13: 869–78

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

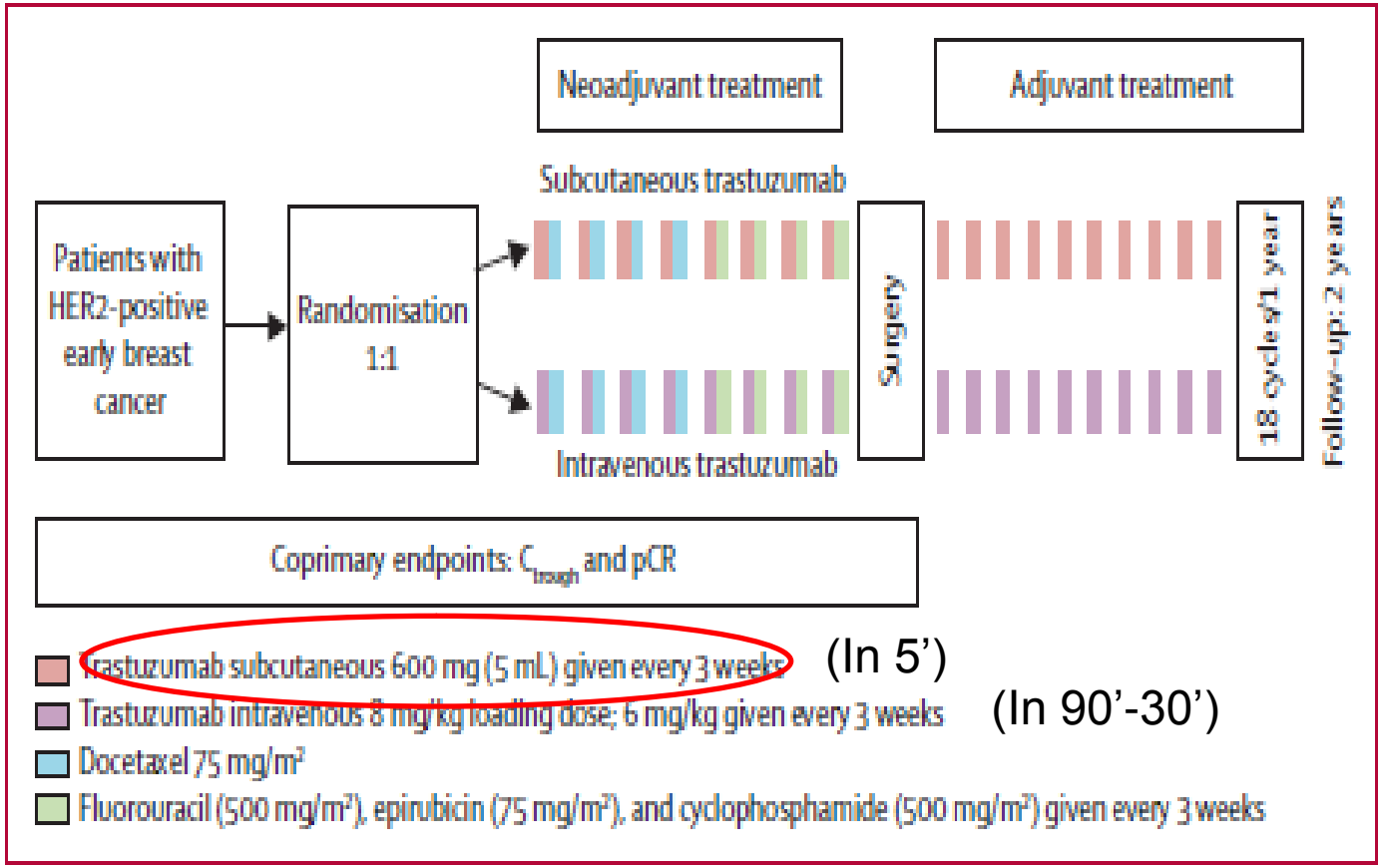


Figure 1: Study design

Hannah-results: efficacy

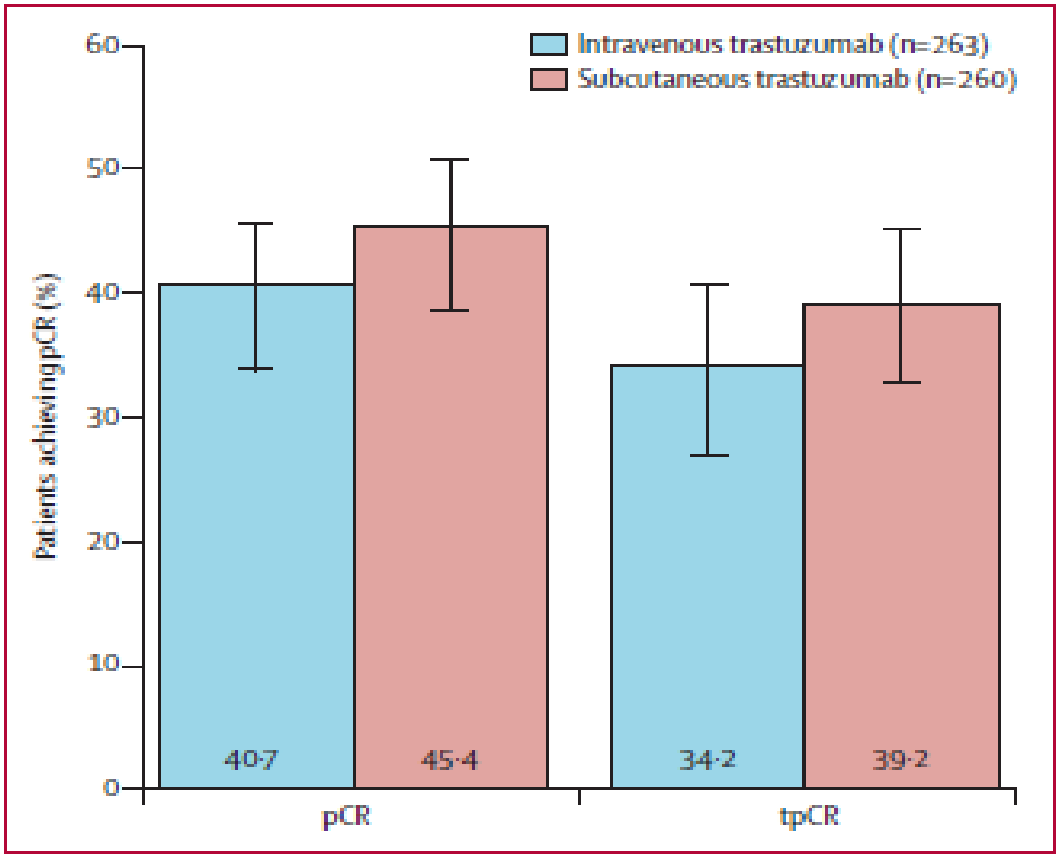


Figure 3: Proportion of patients who achieved a pathological complete response

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

Lancet Oncol 2013; 14: 962–70

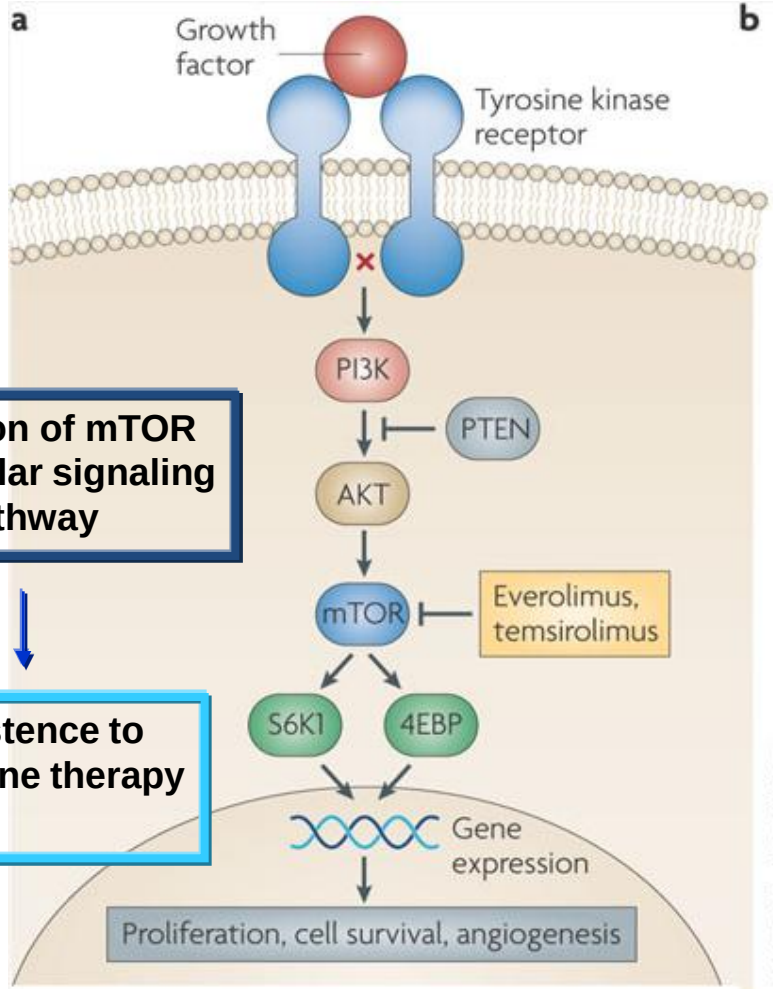
	n*
Subcutaneous preferred, n=216	
Time saving	195
Less pain/discomfort	88
Convenience to patient	35
Ease of administration	33
Problems with intravenous	25
Less stress/anxiety	15
Other	6
Intravenous preferred, n=16	
Fewer reactions (less pain, bruising, irritation, etc)	11
Other	5
Environment/staff	2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

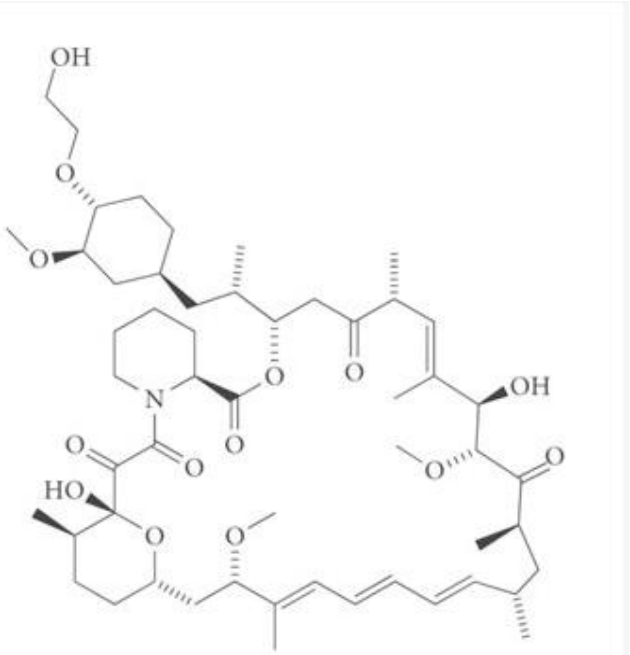
Interpretation Patient preference and safety results from PrefHer, combined with the known non-inferior efficacy and pharmacokinetic and safety profile data, suggest that a fixed dose of 600 mg trastuzumab administered subcutaneously every 3 weeks is a validated, well tolerated treatment option for HER2-positive breast cancer, and is the preferred treatment of patients.

Everolimus in postmenopausal Hormone-receptor-positive advanced breast cancer

Activation of mTOR intracellular signaling pathway

Resistence to endocrine therapy





Everolimus

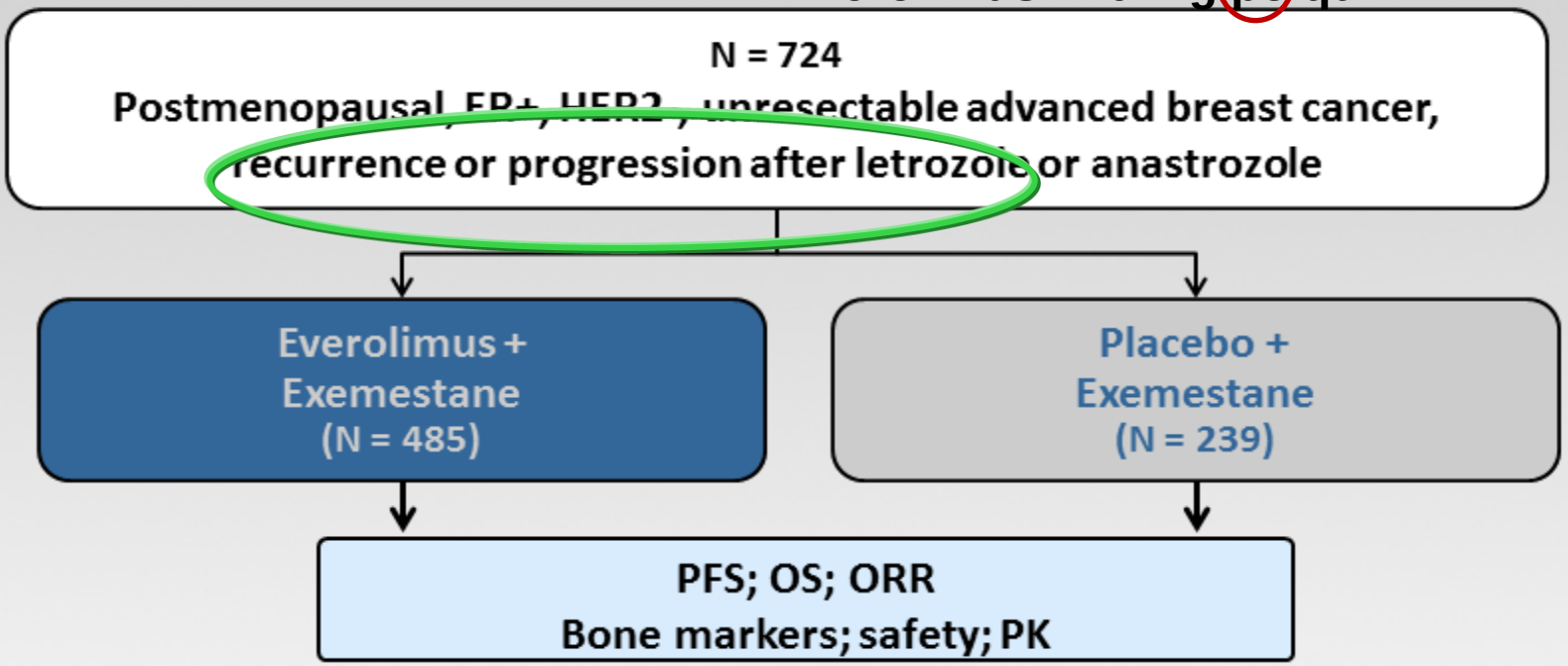
(1*R*,9*S*,12*S*,15*R*,16*E*,18*R*,19*R*,21*R*,23*S*,24*E*,26*E*,28*E*,30*S*, 32*S*,35*R*)-1,18- dihydroxy-12-{(1*R*)-2-[(1*S*,3*R*,4*R*)-4-(2-hydroxyethoxy)-3methoxycyclohexyl]-1 -methylethyl}-19,30-dimethoxy-15,17,21,23,29, 35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.$0^{4,9}$] hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone; $C_{53}H_{83}NO_{14}$; M_r = 958.2

Nature Reviews | Drug Discovery

Phase 3 BOLERO-2 Trial

Exemestane 25 mg po qd

Everolimus 10 mg po qd



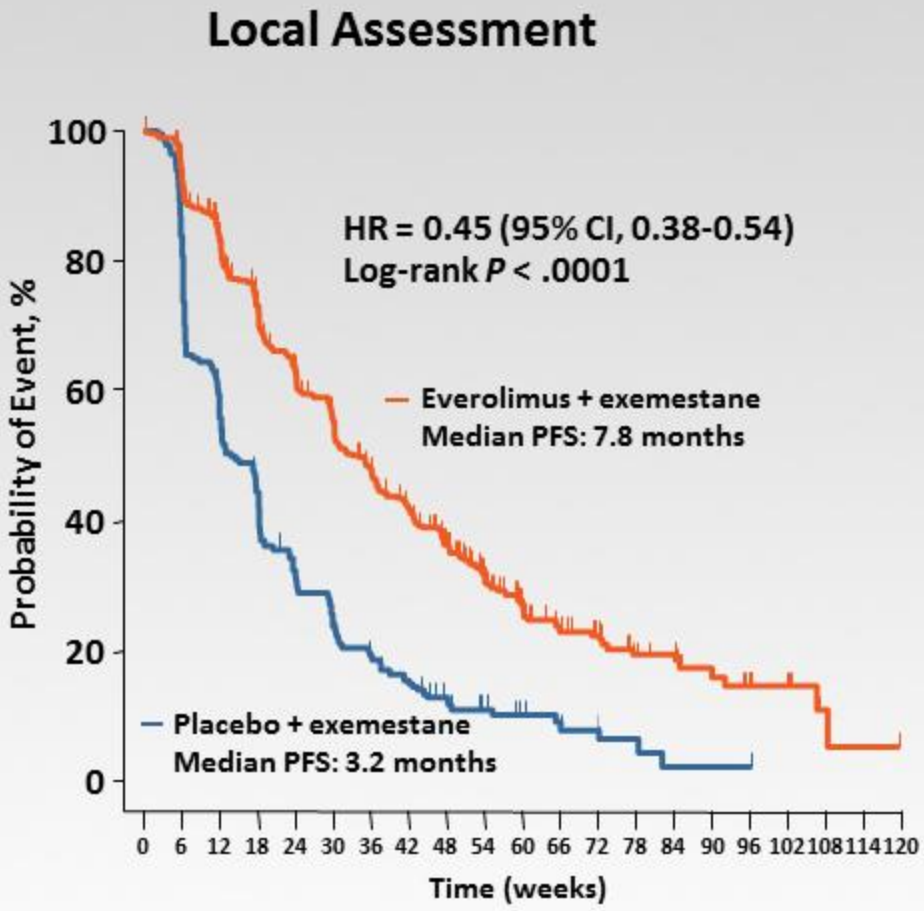
- **Stratification:**
  1. **Sensitivity to prior hormonal therapy**
  2. **Presence of visceral disease**
- **Treatment until disease progression or unacceptable toxicity**

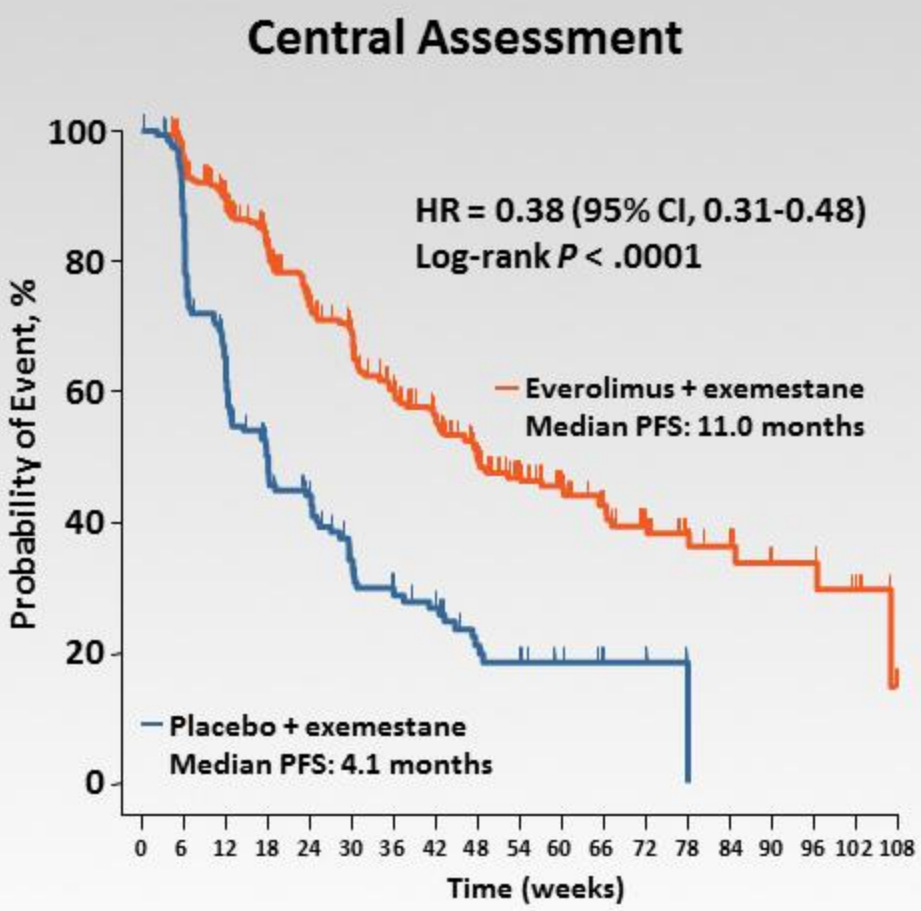
HER = human epidermal growth factor receptor; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics

Medscape EDUCATION

Baselga J, et al. *N Engl J Med*. 2012;366(6):520-529.

BOLERO-2: PFS in All Patients



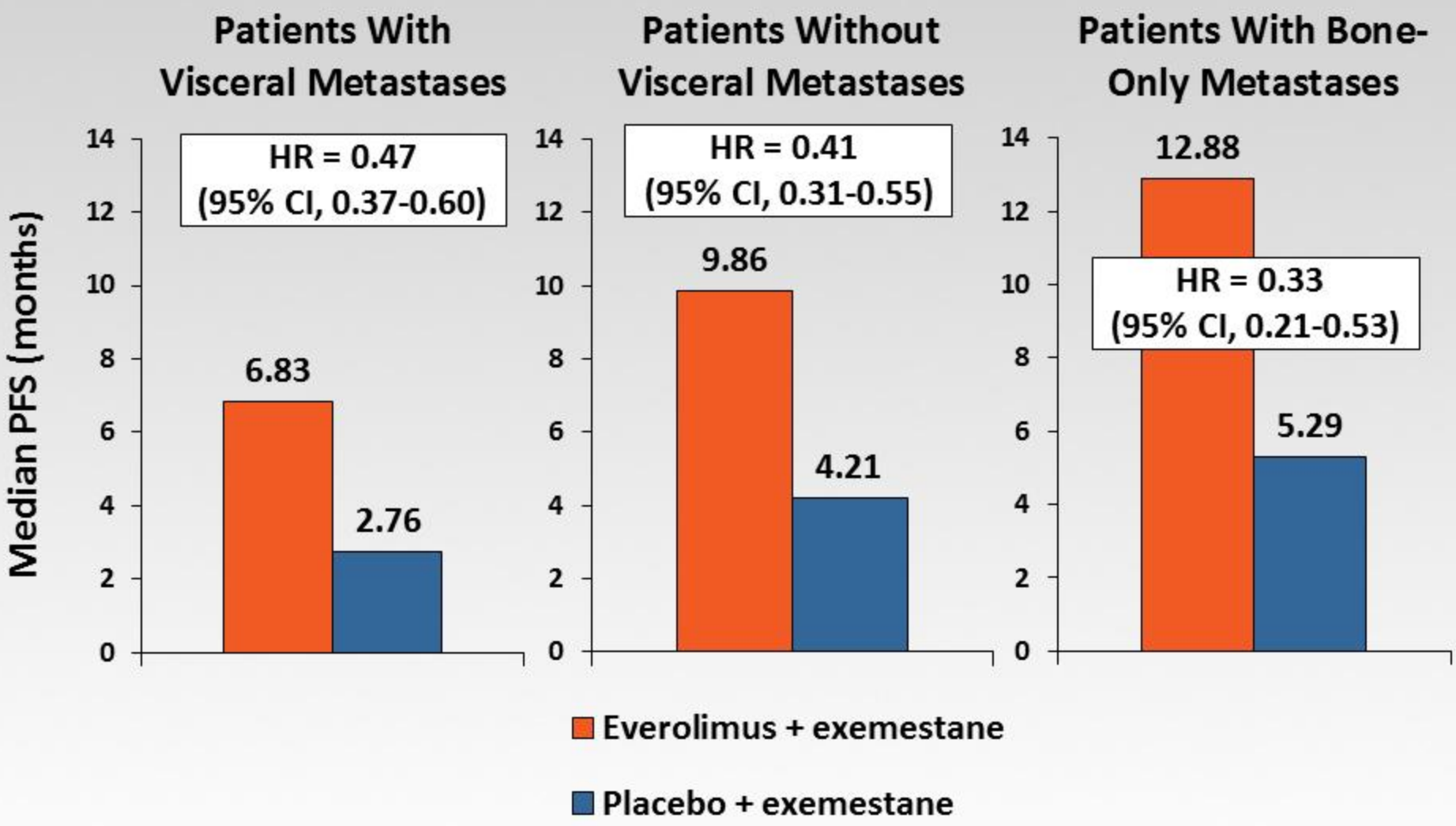


CI = confidence interval; HR = hazard ratio

Piccart M, et al. SABCS 2012. Abstract P6-04-02.

Medscape EDUCATION

BOLERO-2: PFS by Type of Metastases



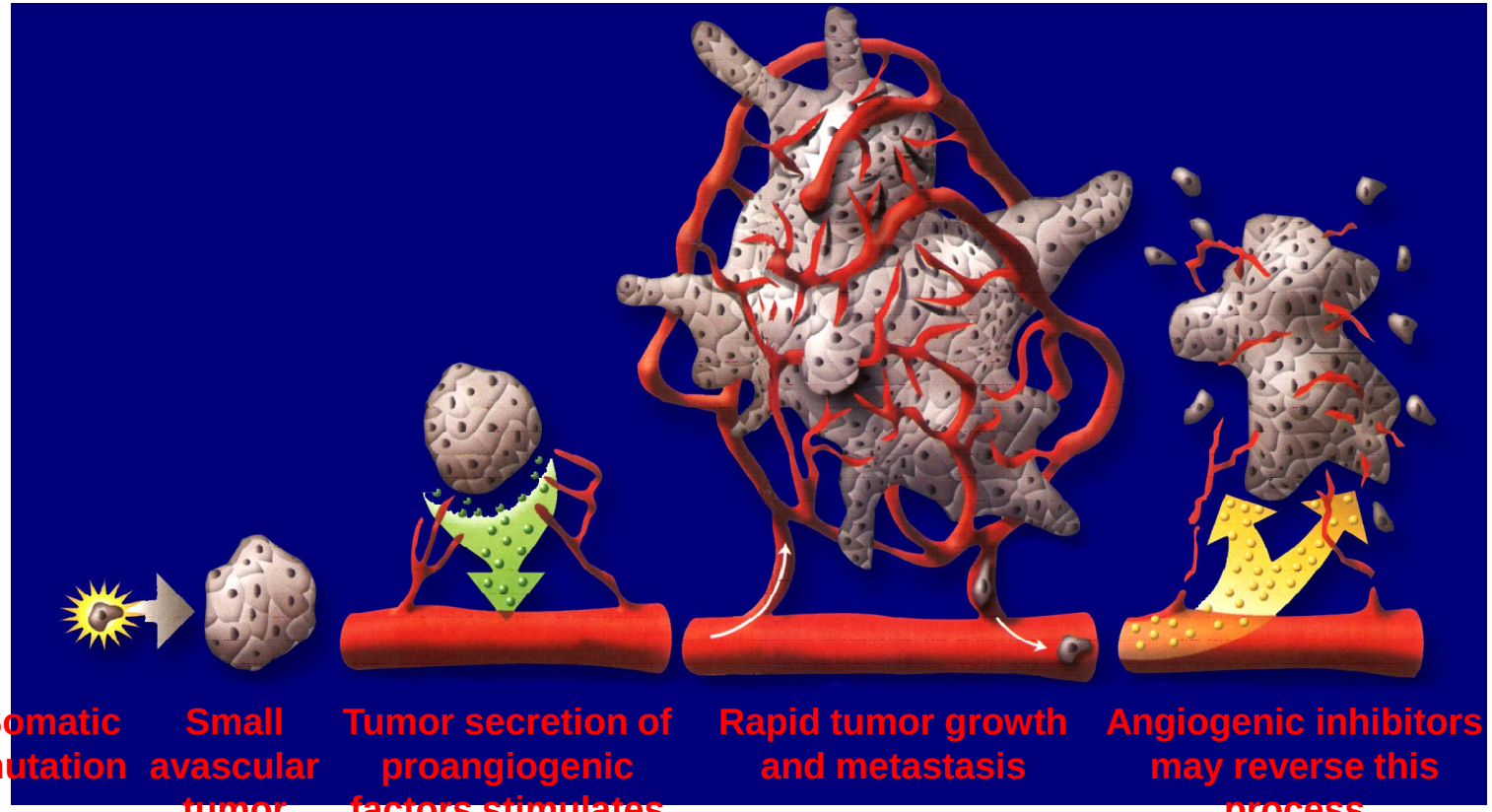
Campone M, et al. ESMO 2012. Abstract 324PD.

Medscape EDUCATION

Table 2. Adverse Events Irrespective of Relationship to Study Treatment (with at Least 10% Incidence in the Everolimus–Exemestane Group).

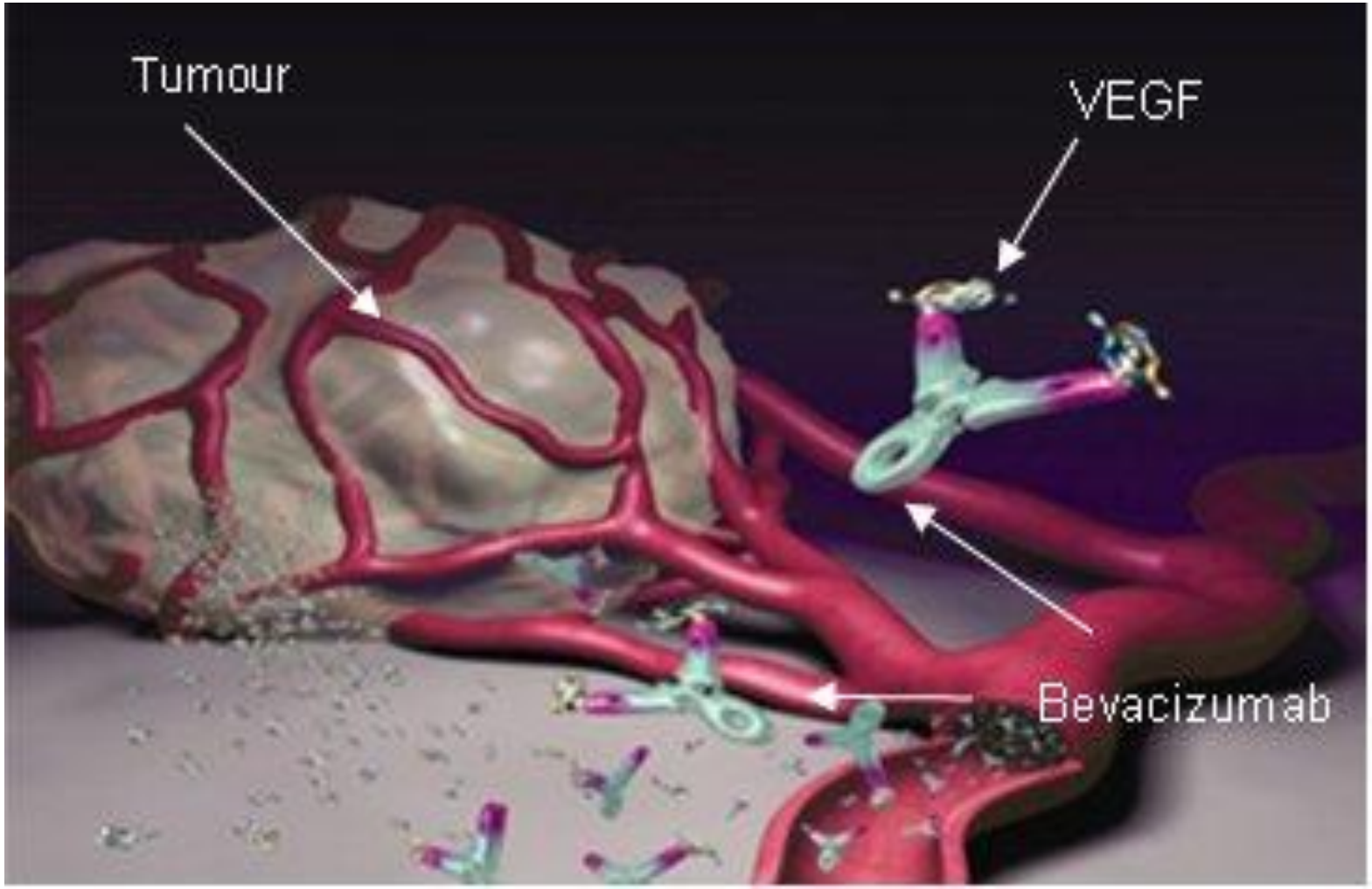
Adverse Event	Everolimus and Exemestane (N=482)			Placebo and Exemestane (N=238)		
	Any Event	Grade 3 Event	Grade 4 Event	Any Event	Grade 3 Event	Grade 4 Event
	percent					
Stomatitis	56	8	0	11	1	0
Rash	36	1	0	6	0	0
Fatigue	33	3	<1	26	1	0
Diarrhea	30	2	<1	16	1	0
Decreased appetite	29	1	0	10	0	0
Nausea	27	<1	<1	27	1	0
Cough	27	1	0	11	0	0
Dysgeusia	21	<1	0	5	0	0
Headache	19	<1	0	13	0	0
Decreased weight	19	1	0	5	0	0
Dyspnea	18	4	0	9	1	<1
Arthralgia	16	1	0	16	0	0
Anemia	16	5	1	4	<1	<1

Inhibiting Local Sprouting Tumor: Angiogenesis as an Anticancer Treatment



Folkman J. N Engl J Med. 1971;285:1182-1186.

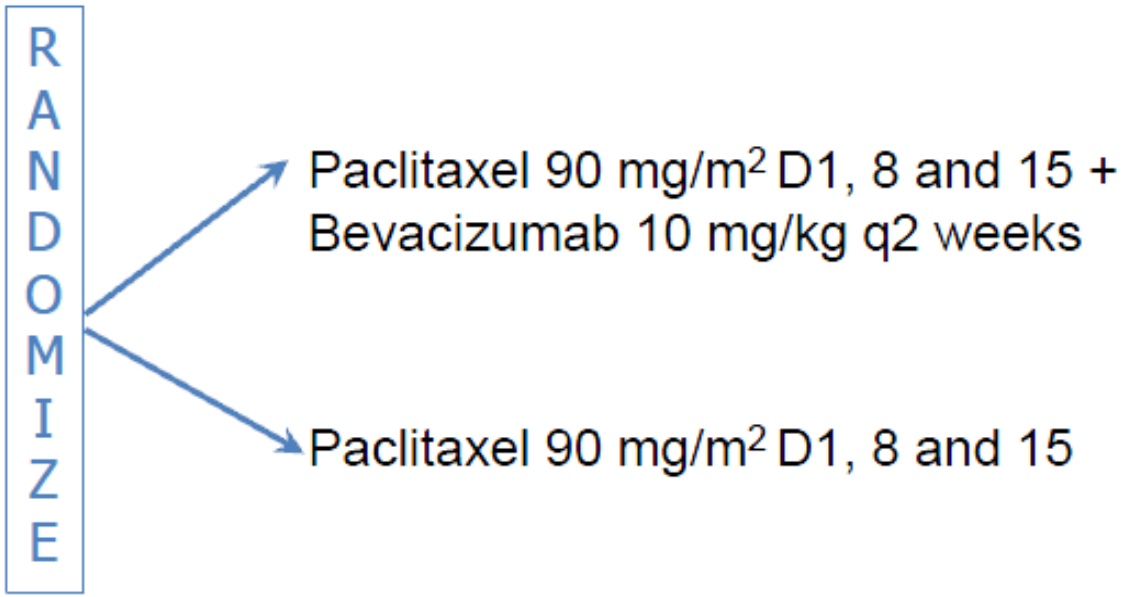
Bevacizumab



E2100: Study Design

Stratify:

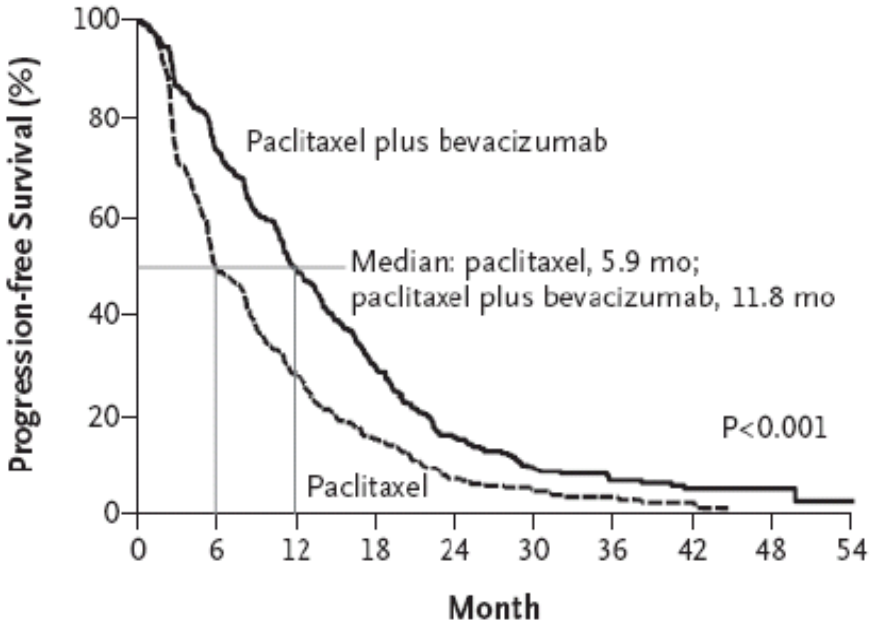
- DFI $\leq$ 24 mos. vs. > 24 mos.
- < 3 vs. $\geq$ 3 metastatic sites
- Adjuvant chemotherapy yes vs. no
- ER+ vs. ER- vs. ER unknown



Miller et al. NEJM 2007;357:2666-76

E2100: Progression-free Survival

A

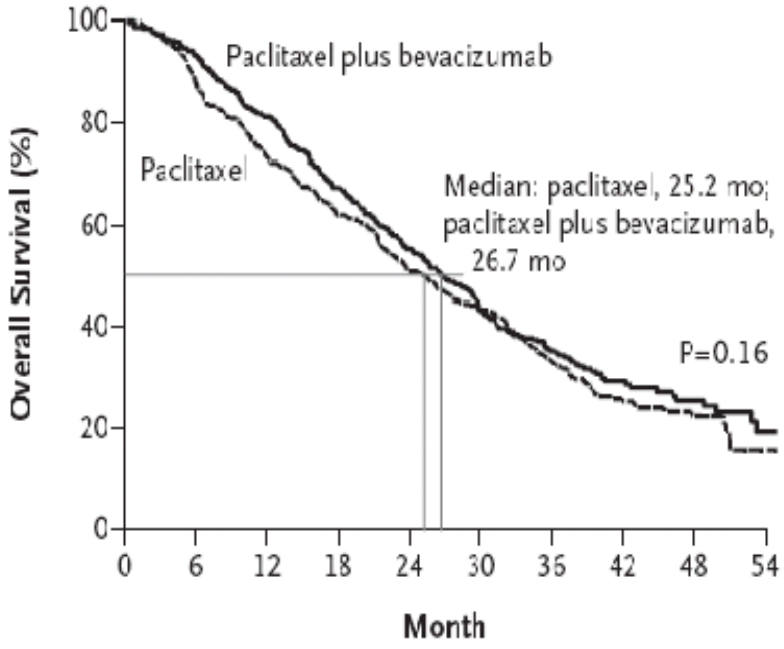


No. at Risk										
Paclitaxel plus bevacizumab	347	323	167	100	53	25	14	7	2	1
Paclitaxel	326	159	89	47	20	12	6	2	0	0

Miller et al. NEJM 2007;357:2666-76

E2100: Overall Survival

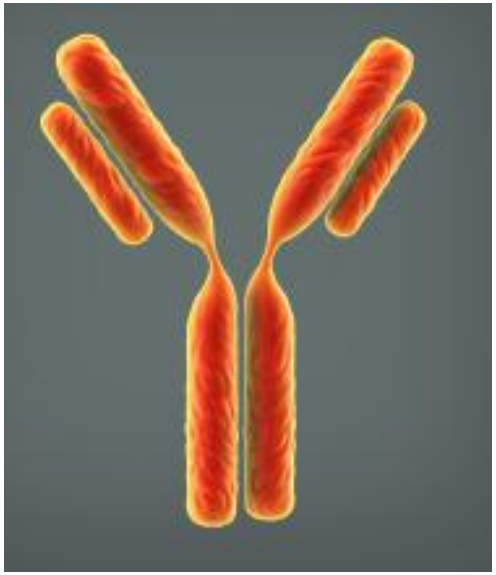
B



No. at Risk										
Paclitaxel plus bevacizumab	347	323	280	232	190	147	88	46	24	7
Paclitaxel	326	284	236	199	162	138	88	47	23	5

Miller et al. NEJM 2007;357:2666-76

Denosumab



- Denosumab is a fully human monoclonal antibody that binds human RANK Ligand with high affinity and specificity[1]
- By binding to RANK Ligand, denosumab prevents activation of its receptor on the surface of osteoclasts and their precursors
- In clinical trials, no neutralising antibodies were detected[2–4]

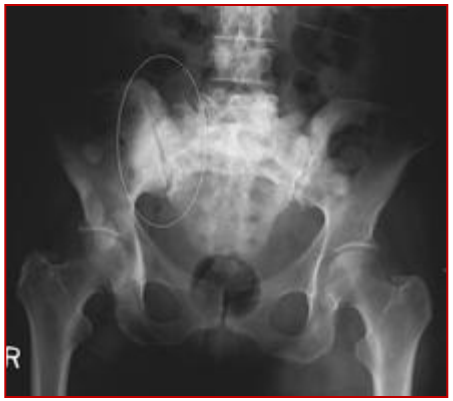
1. McClung MR et al. New Engl J Med 2006;354:821–31;
2. Stopeck AT et al. J Clin Oncol 2010;28:5132–9;
3. Fizazi K et al. Lancet 2011; Lancet 2011;377:813–22;
4. Henry DH et al. J Clin Oncol 2011;29:1125–32.

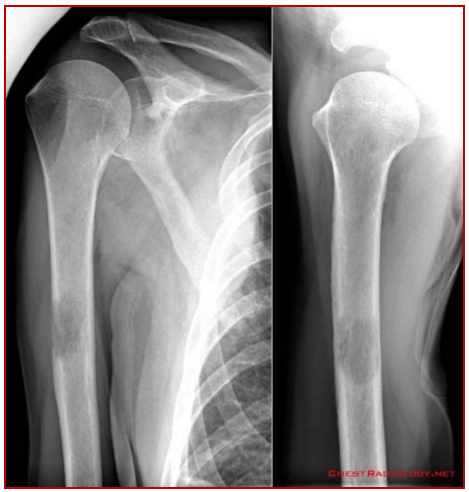
Bone metastases from Breast Cancer

- 70-80% of patients with MBC develop bone mets

- SREs occur in up 64% of MBC pts not with bisphoshonates

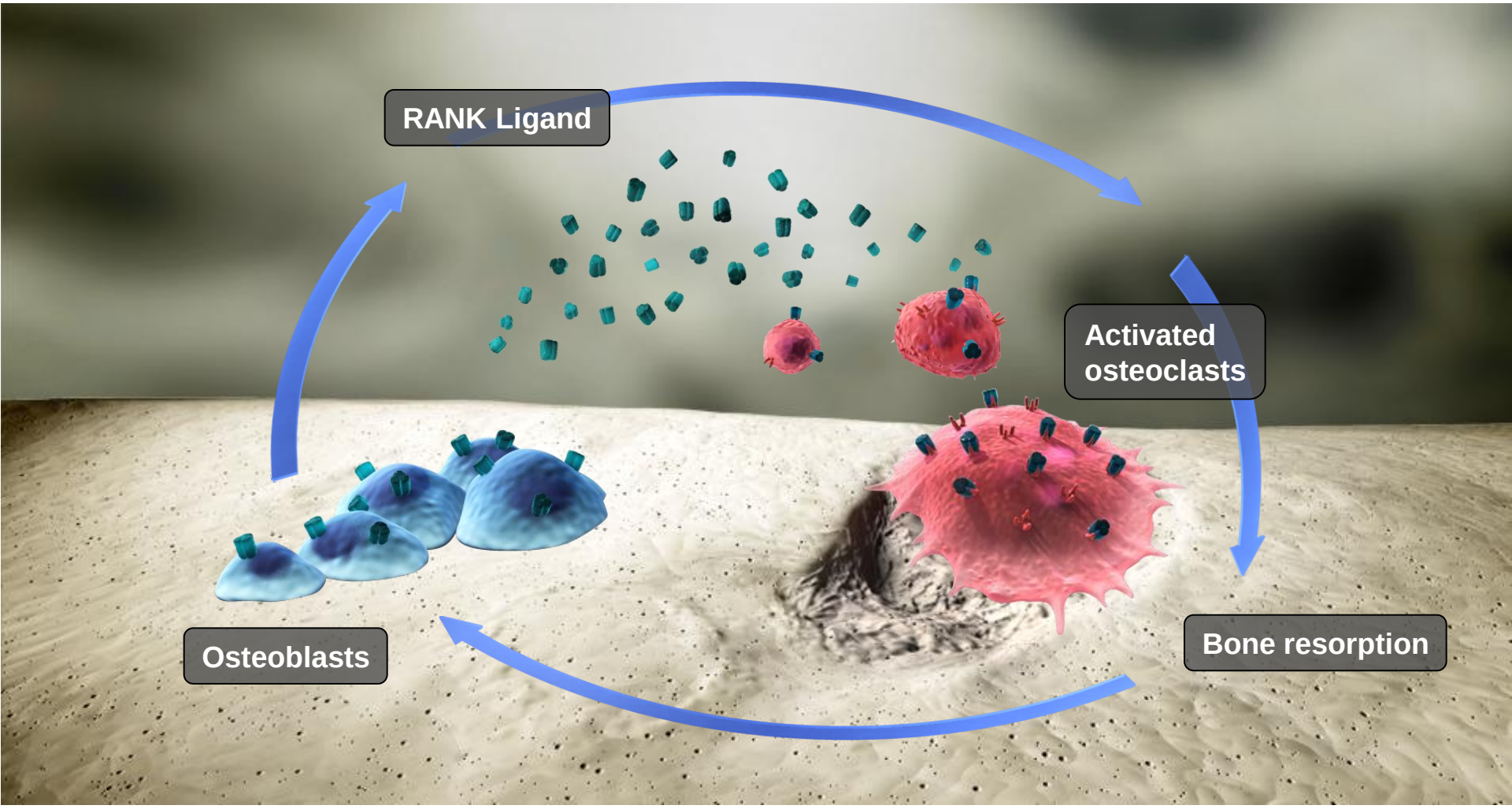
- ✓ Morbidity
- ✓ Reduced performance status
- ✓ Quality of life
- ✓ Reduced survival
- ✓ Hospital cost





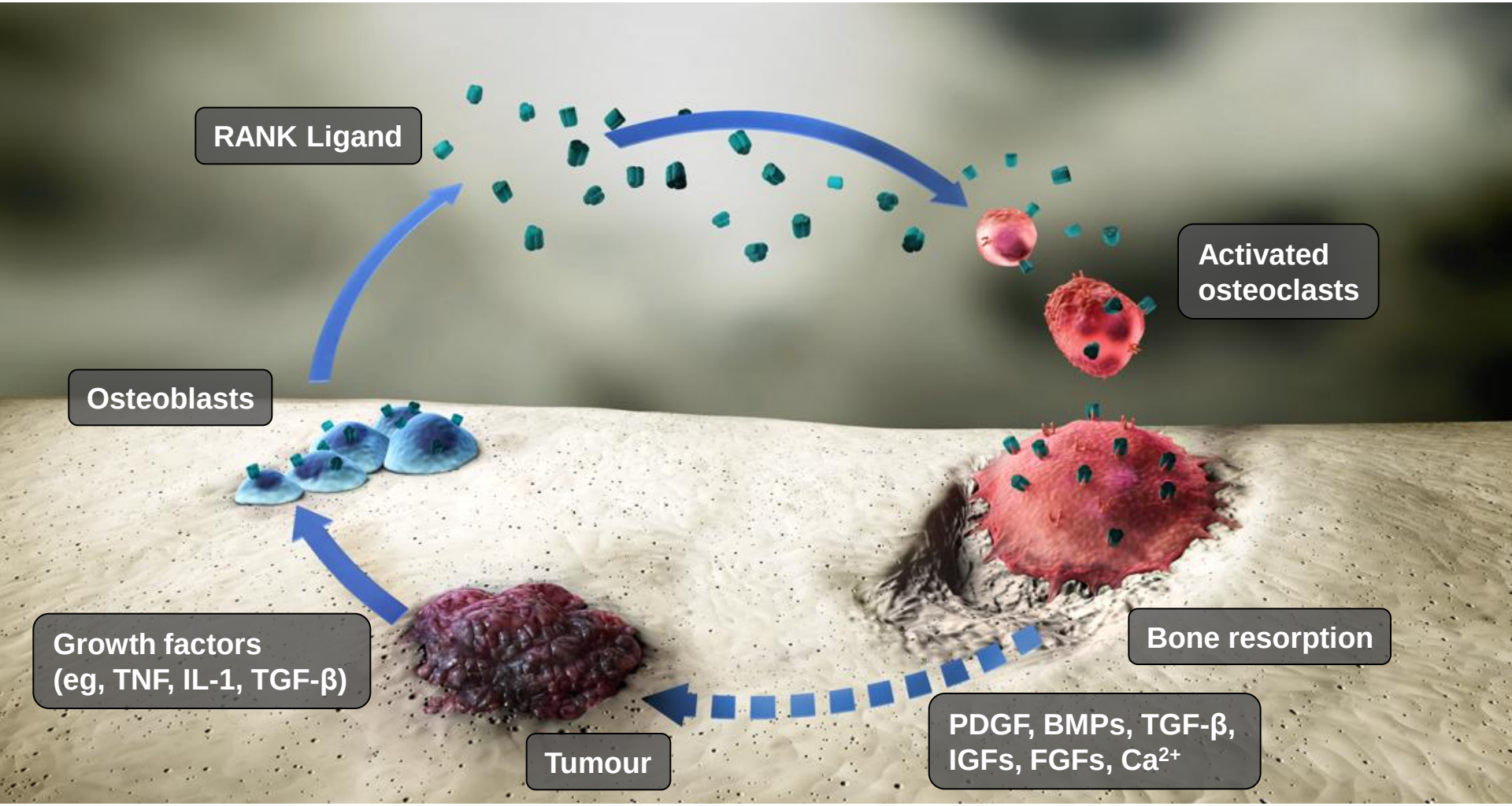
Lipton A. Cancer. 2003;97:848-853

Bone turnover



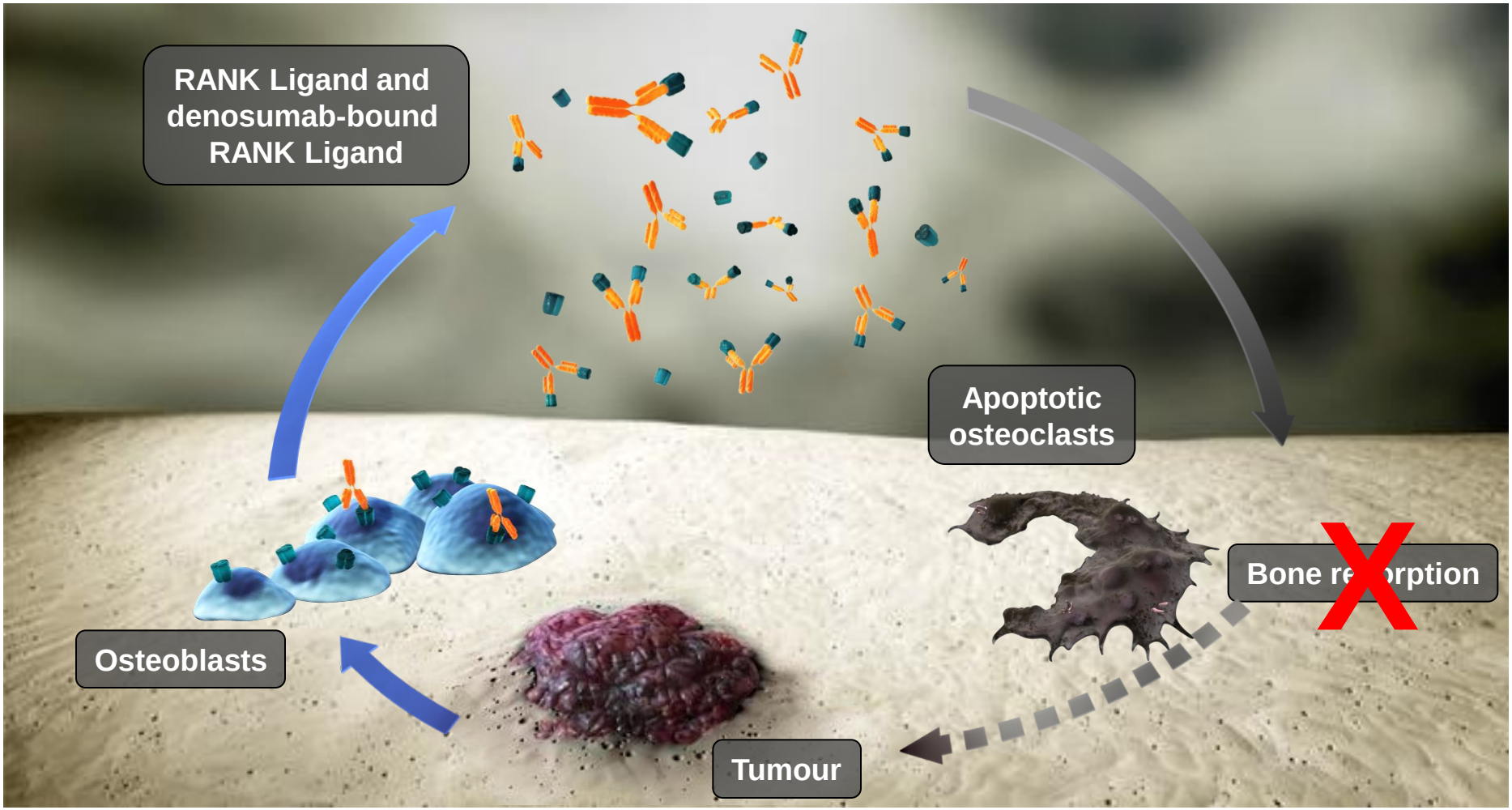
1. Adapted from: Boyle WJ, et al. Nature 2003;423:337–42;
2. Roodman GD. N Engl J Med 2004;350:1655–64.

The Vicious Cycle Of Bone Destruction



1. Adapted from: Boyle WJ, et al. Nature 2003;423:337–42;
2. Roodman GD. N Engl J Med 2004;350:1655–64.

Denosumab inhibits RANK Ligand to interrupt the vicious cycle of bone destruction



1. Adapted from: Boyle WJ, et al. Nature 2003;423:337–42;
2. McClung MR, et al. New Engl J Med 2006;354:821–31.

FDA-Approved Agents for Prevention of SREs in Metastatic Breast Cancer

AGENT	DRUG CLASS	DOSE AND SCHEDULE
Zoledronic Acid (IV)	Bisphosphonate	4 mg IV q3-4w
Pamidronate (IV)	Bisphosphonate	90 mg IV q3-4w
Denosumab **(SC)**	RANK-L targeted Mab	120 mg SQ q4w

Both ASCO and NCCN recommend all 3 agents[1,2]

- No agent is recommended over another
- Bone-modifying agent therapy is only recommended for patients with evidence of bone metastases

1.Van Poznak CH, et al. J Clin Oncol. 2011;29:1221-1227. 2. NCCN. Clinical practice guidelines in oncology: breast cancer. v.2.2013.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2013
Breast Cancer

- Patients should receive a dental exam and preventive dentistry before initiating bone-modifying agent therapy
- Frequent measurement of Ca, P, Mg
- Should be accompanied by calcium and Vit D supplementation.
- Duration of treatment: Biphosponate for up to 2 years. Denosumab unknown

FATTORI CHE INFLUENZANO LA PROGNOSI

- **Stadio di malattia**
- **Caratteristiche genetiche e biologiche**

(MALATTIA)

- **Adeguatezza del trattamento**

(CHI CURA)

schema
modalità di somministrazione
conservazione dei farmaci
valutazione tossicità

- **Condizioni cliniche, età, comorbidità**

(PAZIENTE)


Grazie