CORSO SUPERIORE SIFO IN FARMACIA CLINICA
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L'algoritmo terapeutico nel carcinoma della mammella Her2 positivo

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BREAST CANCER

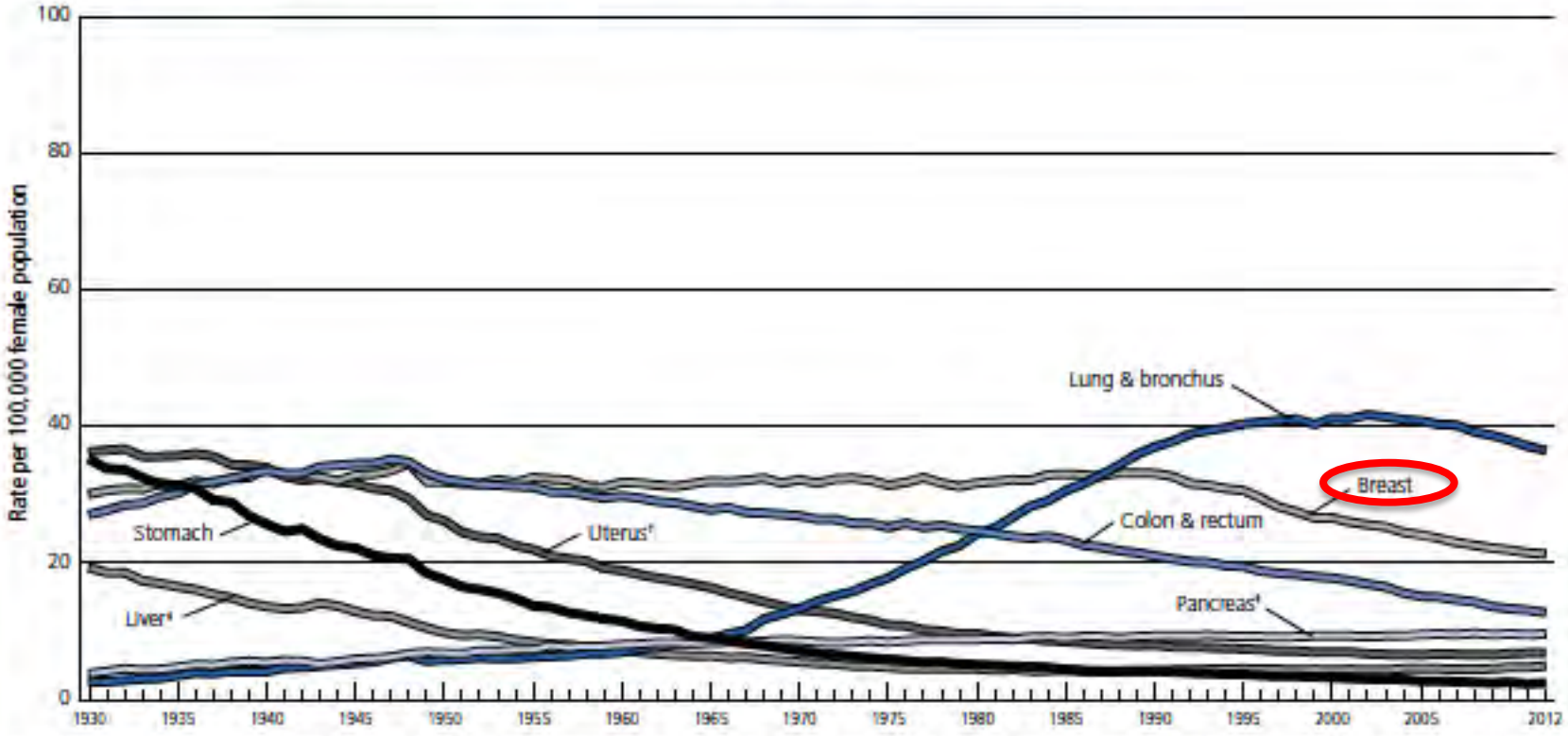
Worldwide incidence in females

*Incidence per 100,000 population.

Parkin DM, et al. *CA Cancer J Clin.* 1999;49:33-64.

Breast cancer : mortality and incidence (USA)

Figure 2. Trends in Age-adjusted Cancer Death Rates* by Site, Females, US, 1930-2012



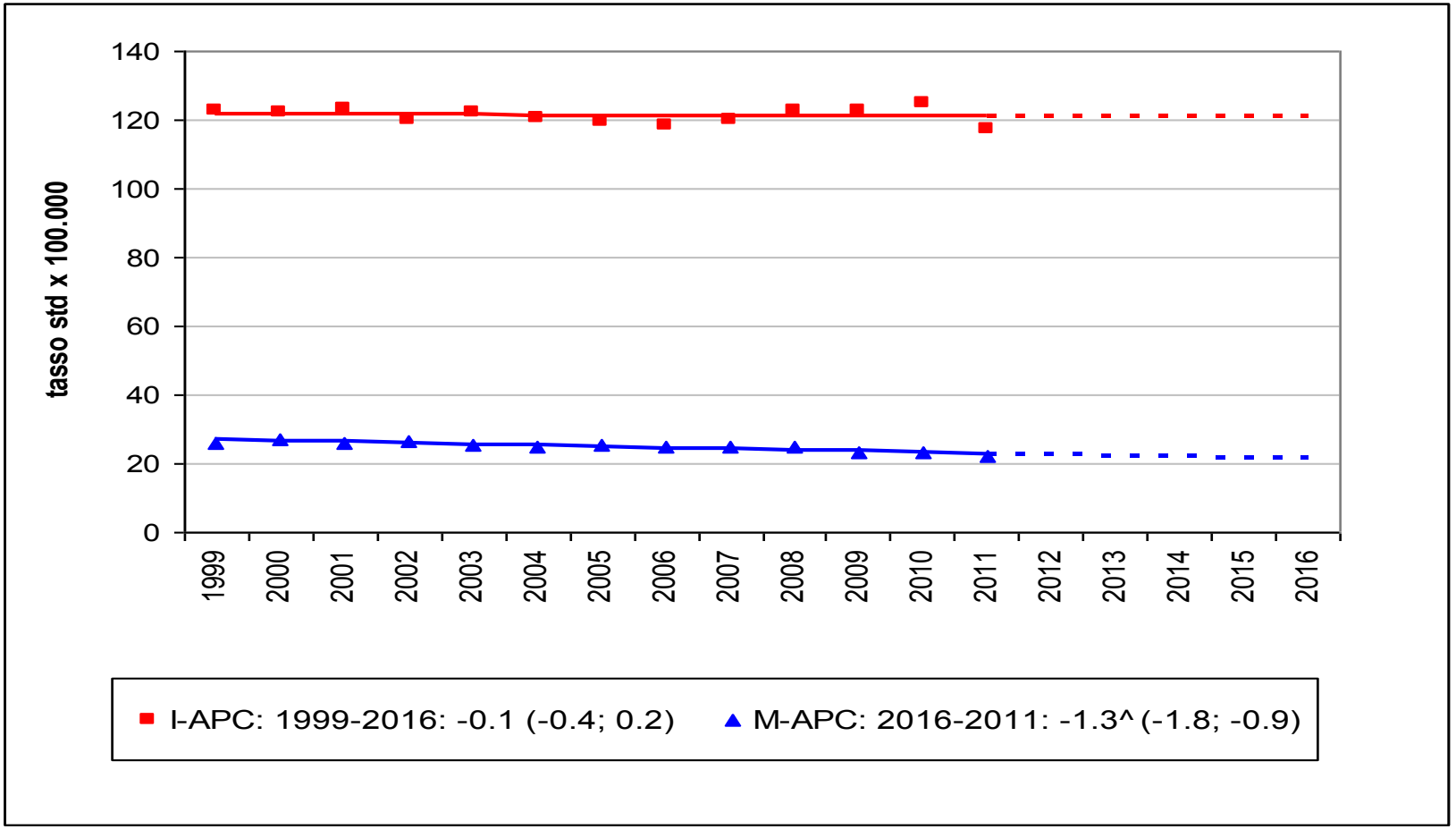
*Per 100,000, age adjusted to the 2000 US standard population. †Uterus refers to uterine cervix and uterine corpus combined. ‡Mortality rates for pancreatic and liver cancers are increasing.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancers of the liver, lung and bronchus, and colon and rectum are affected by these coding changes.

Source: US Mortality Volumes 1930 to 1959, US Mortality Data 1960 to 2012, National Center for Health Statistics, Centers for Disease Control and Prevention.

Carcinoma della mammella : incidenza e mortalità (Italia)

- ***Nel 2016 si stimano in Italia 50.000 nuove diagnosi (1% nei maschi)***
- ***Nel 2013 sono stati 11.939 i decessi (prima causa di morte per neoplasia nelle donne) secondo i dati ISTAT***

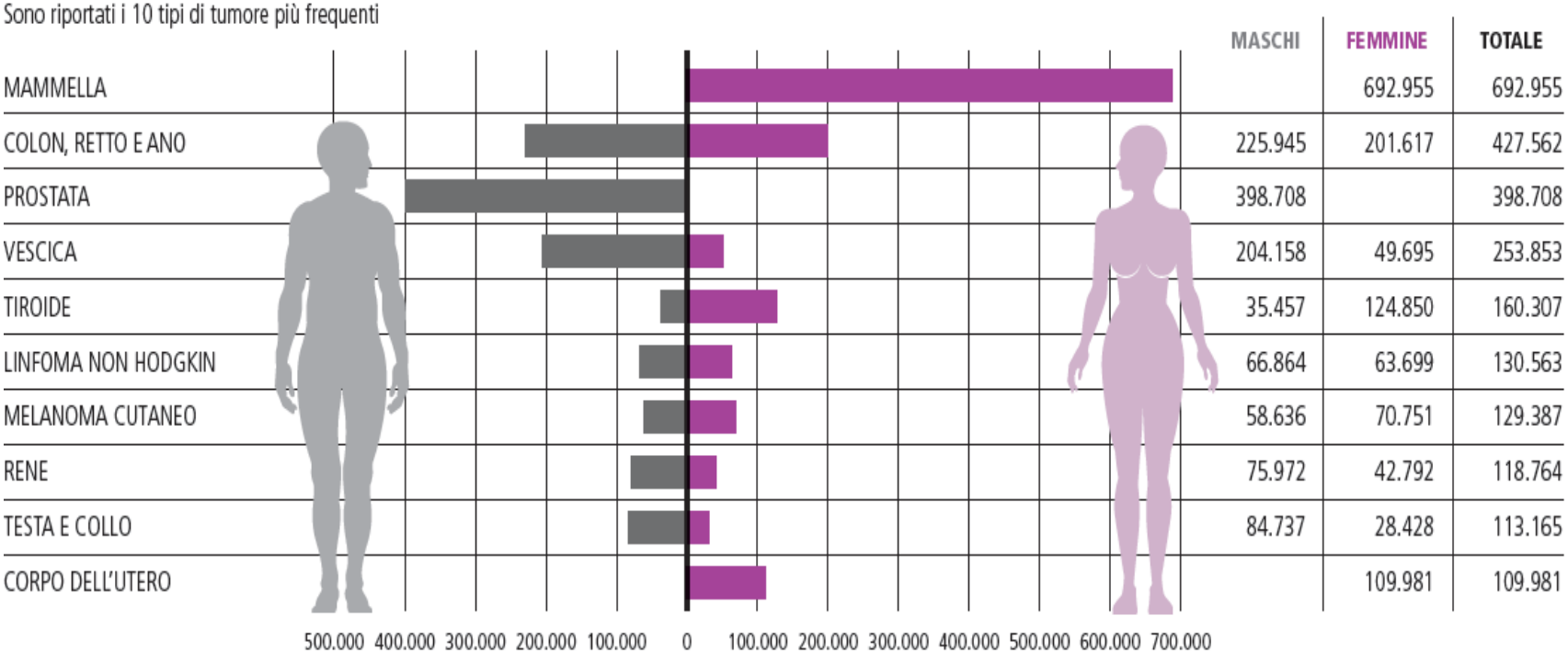


AIOM-AIRTUM I numeri del cancro 2016

Carcinoma della mammella : prevalenza (Italia)

NUMERO DI PERSONE VIVE DOPO UNA DIAGNOSI DI TUMORE, PER SESSO (ITALIA, 2015)

Sono riportati i 10 tipi di tumore più frequenti



	MASCHI	FEMMINE	TOTALE
MAMMELLA		692.955	692.955
COLON, RETTO E ANO	225.945	201.617	427.562
PROSTATA	398.708		398.708
VESCICA	204.158	49.695	253.853
TIROIDE	35.457	124.850	160.307
LINFOMA NON HODGKIN	66.864	63.699	130.563
MELANOMA CUTANEO	58.636	70.751	129.387
RENE	75.972	42.792	118.764
TESTA E COLLO	84.737	28.428	113.165
CORPO DELL'UTERO		109.981	109.981

AIOM-AIRTUM I numeri del cancro 2016

Carcinoma della mammella

Fattori di rischio

- ***Età***
- ***Familiarità ed ereditarietà***
- ***Fattori riproduttivi***
- ***Fattori ormonali***
- ***Fattori dietetici***
- ***Fattori antropometrici e metabolici***

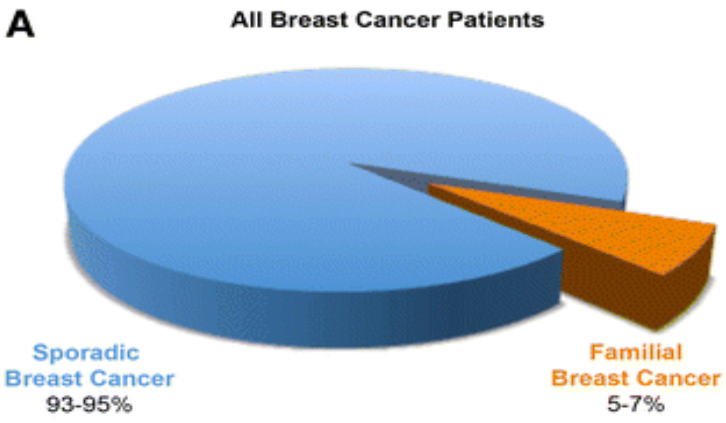
Probabilità di sviluppare un carcinoma mammario nelle diverse fascie d'età

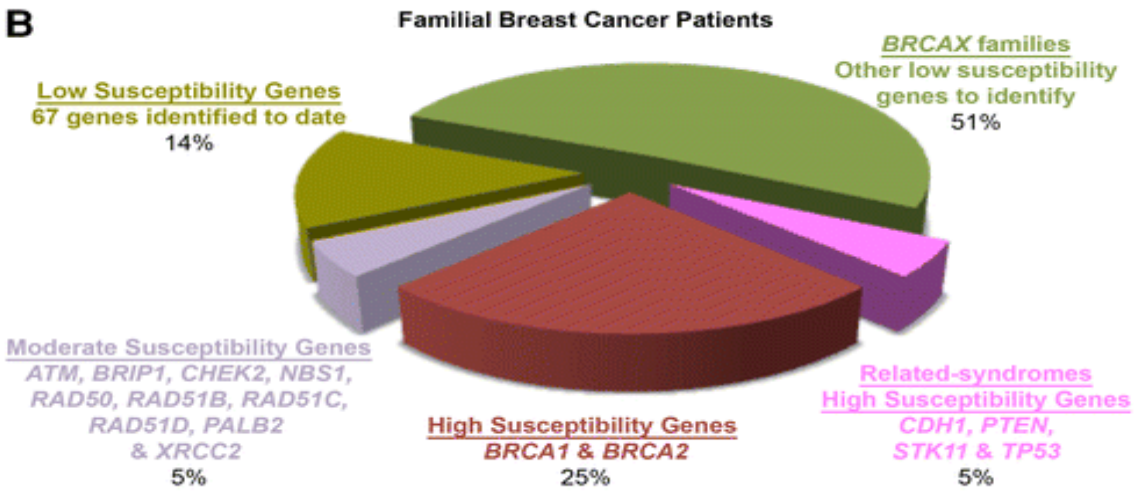
Età	%	Assoluto
30	0,44	1/227
40	1,47	1/68
50	2,38	1/42
60	3,56	1/28
70	3,82	1/26

www.cancer.gov/cancertopics/factsheet/Detection/probability-breast-cancer

Fattori genetici e familiari

- *Il 5-10% dei carcinomi mammari sono risultato di mutazioni genetiche trasmesse con meccanismo mendeliano di tipo dominante (mutazioni dei geni oncosoppressori BRCA 1 e BRCA 2)*
- *BRCA 1 e 2 codificano per proteine nucleari coinvolte nei meccanismi di riparo del danno sul DNA*
- *La mutazione dei due geni determina un incremento del rischio di cancro (85%) ad esordio in età più precoce*
- *Altre sindromi familiari associate a ca. mammella:*
  - *Li Fraumeni (mutazione a carico p53)*
  - *Codwen (mutazione a carico PTEN)*





Fattori Riproduttivi

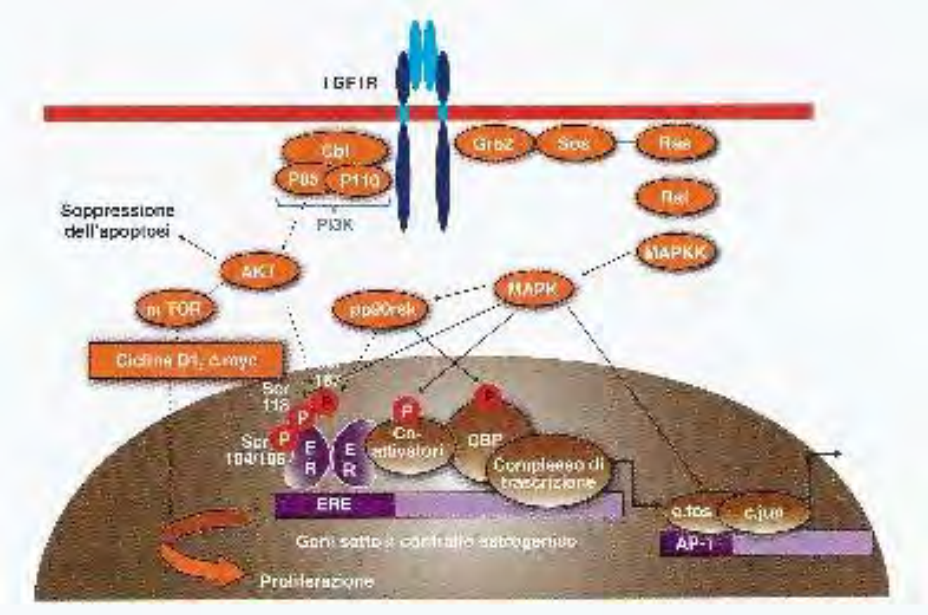
- ***Gravidanza***
  - ***Il potente stimolo differenziativo sull'epitelio ghiandolare riduce la suscettibilità***
  - ***Età della prima :correlazione inversa***
  - ***Numero delle gravidanze***
- ***Allattamento***

Fattori Endocrini

- ***Aumentata esposizione agli estrogeni***
  - ***Menarca precoce***
  - ***Menopausa tardiva***
  - ***Terapia ormonale sostitutiva (+ 1,5 rischio solo per somministrazioni oltre 8 anni)***
  - ***Contraccettivi orali (ruolo controverso per per le associazioni estro progestiniche a basso dosaggio)***

Fattori antropometrici e metabolici

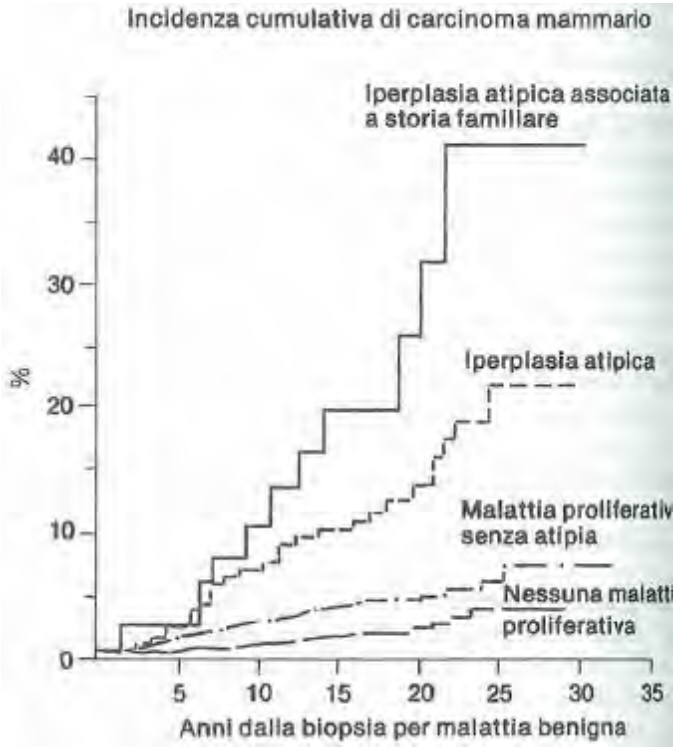
- **Obesità**
  - Eccesso di t. adiposo principale fonte di estrogeni in menopausa
- **Sindrome metabolica**
  - Obesità,diabete,iperlipemia, ipertensione
  - Incremento dei valori insulinemici e stimolazione del recettore per il fattore di crescita insulino simile 1 (IGF1R)

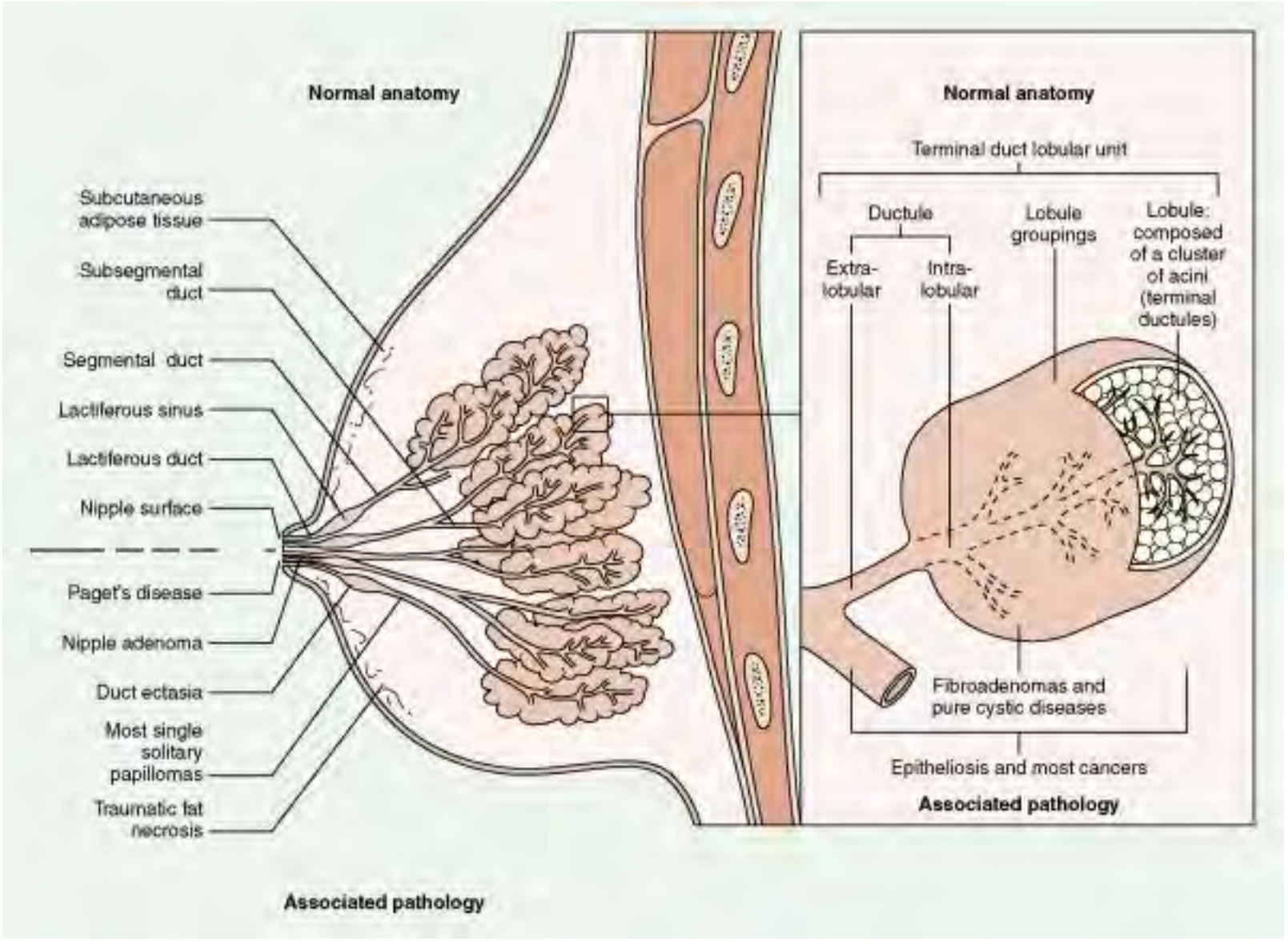


Pregresse patologie mammarie

- ***Un precedente ca.mammella condiziona un aumento di un ca controlaterale di + 1% annuo***

- ***Una precedente patologia benigna***

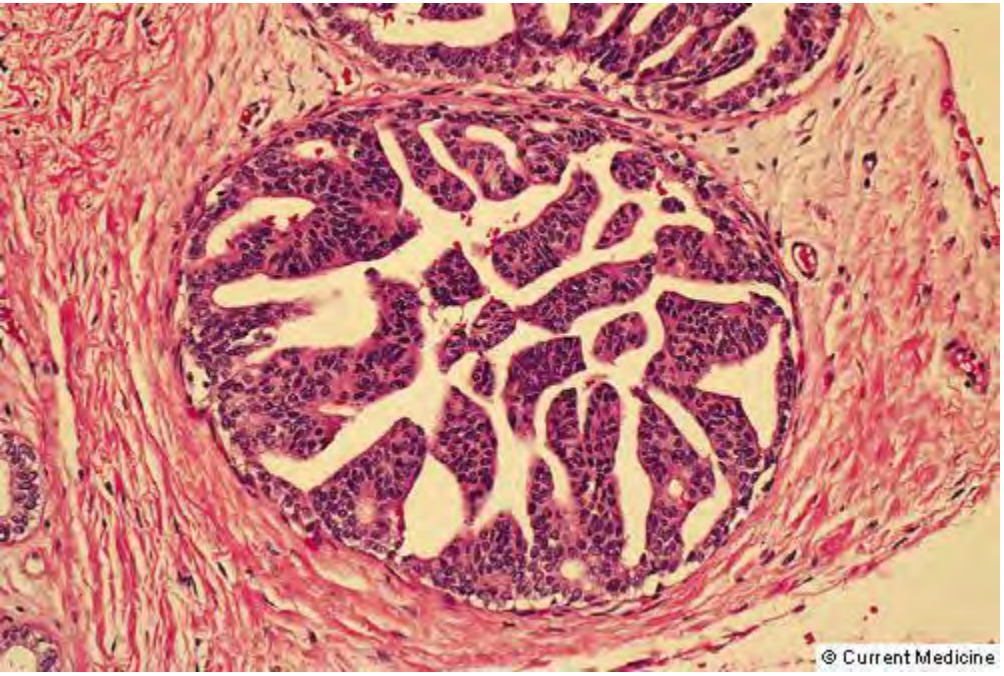



Normal anatomy
Subcutaneous adipose tissue
Subsegmental duct
Segmental duct
Lactiferous sinus
Lactiferous duct
Nipple surface
Paget's disease
Nipple adenoma
Duct ectasia
Most single solitary papillomas
Traumatic fat necrosis
Associated pathology
Normal anatomy
Terminal duct lobular unit
Ductule
Extra-lobular
Intra-lobular
Lobule groupings
Lobule: composed of a cluster of acini (terminal ductules)
Fibroadenomas and pure cystic diseases
Epitheliosis and most cancers
Associated pathology

BREAST CANCER
Pathology

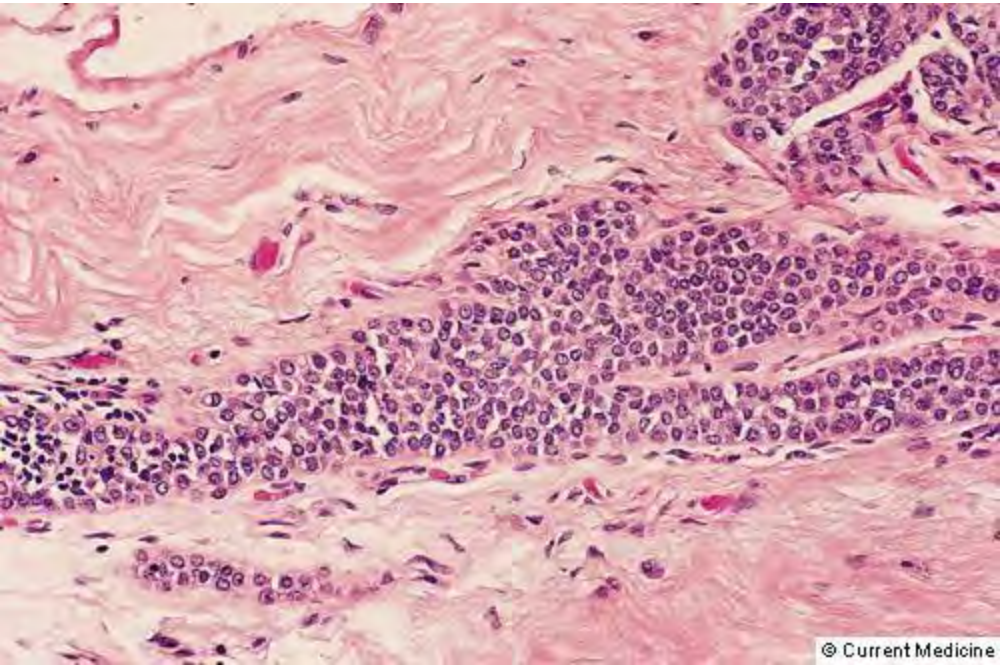
- ***Non-invasive carcinoma in situ***
  - ***Ductal carcinoma in situ (DCIS)***
  - ***Lobular carcinoma in situ (LCIS)***
- ***Invasive carcinoma***
  - ***Infiltrating ductal or lobular carcinoma***
  - ***Medullary, mucinous, and tubular carcinomas***
- ***Uncommon tumors***
  - ***Inflammatory carcinoma***
  - ***Paget's disease***

Carcinoma duttale in situ (DCIS)



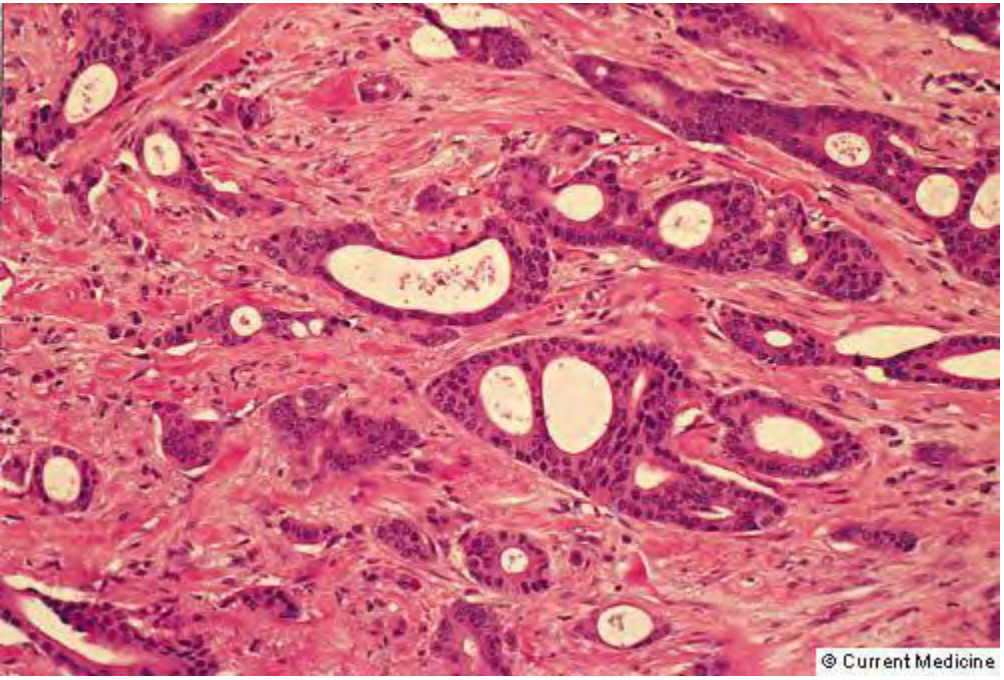
- *30-50% dei tumori diagnosticati in screening*
- *età mediana 45-65 aa.*
- *dopo exeresi di un DCIS rischio di neoplasia invasiva 11 volte maggiore*
- *bilaterale nel 10-15%*
- *la sopravvivenza supera il 95% indipendentemente dal tipo di trattamento locale utilizzato*

Carcinoma lobulare in situ (LCIS)



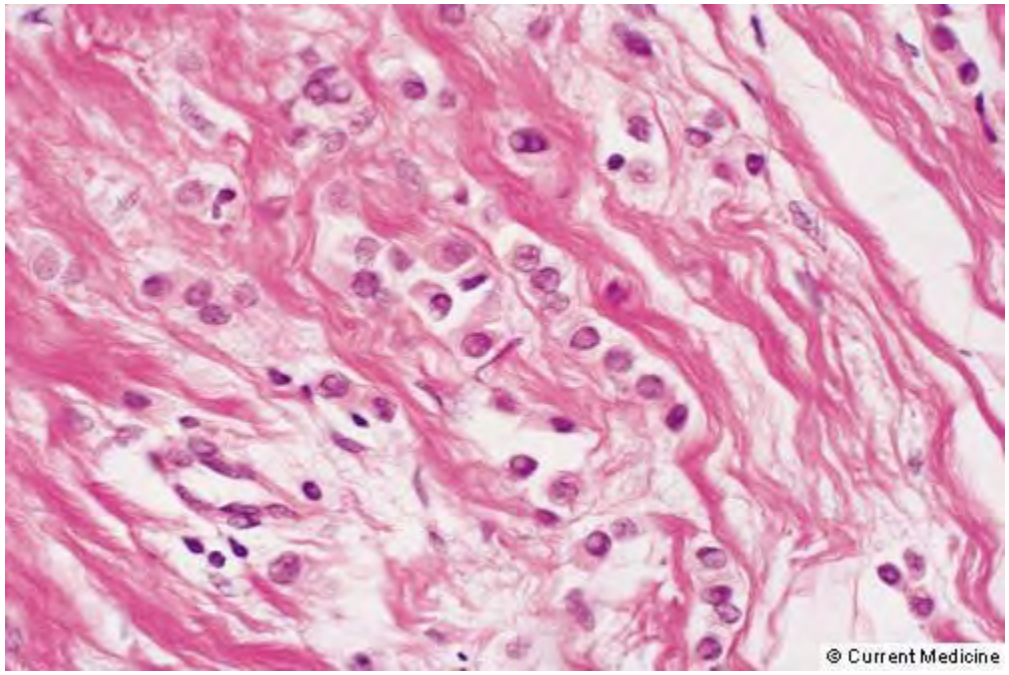
- *frequenza dal 1 al 6%*
- *multicentrico nel 70%*
- *bilaterale nel 30-40%*
- *età mediana di maggiore incidenza :44-46 anni*
- *rischio di sviluppo di npl infiltrante + 7 volte*
- *per la multicentricità e bilateralità può essere considerata la mastectomia profilattica bilaterale*

Carcinoma duttale infiltrante



- *65-80% dei t. della mammella*
- *3 gradi di differenziazione da G1 a G3 correlati con la prognosi*
- *Spesso associato a componente intraduttale che incrementa il rischio di recidiva locale*

Carcinoma lobulare infiltrante



- *10-14% dei t. mammella*
- *spesso multifocale*
- *bilaterale nel 6-28%*

Carcinomi rari

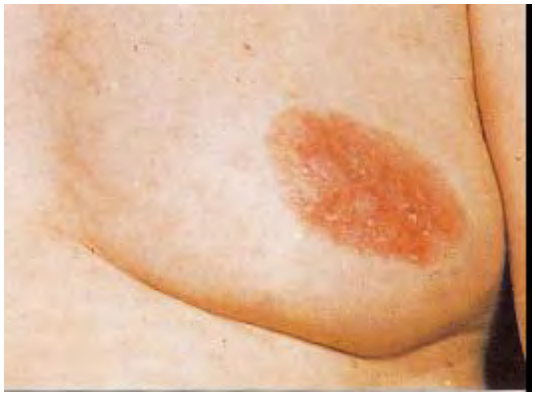
Tubulare : *2% di tutti i tumori. Insorge in donne >50 aa. Piccole dimensioni e buona prognosi*

Mucinoso*: 2% di tutti i tumori. Migliore prognosi rispetto al carcinoma duttale NAS*

Midollare*: 5-7% di tutti i tumori.Prevalente nelle più giovani (< 35 aa) con positività BRCA1-2.Spesso recettori ormonali neg. Migliore prognosi rispetto al carcinoma duttale NAS*

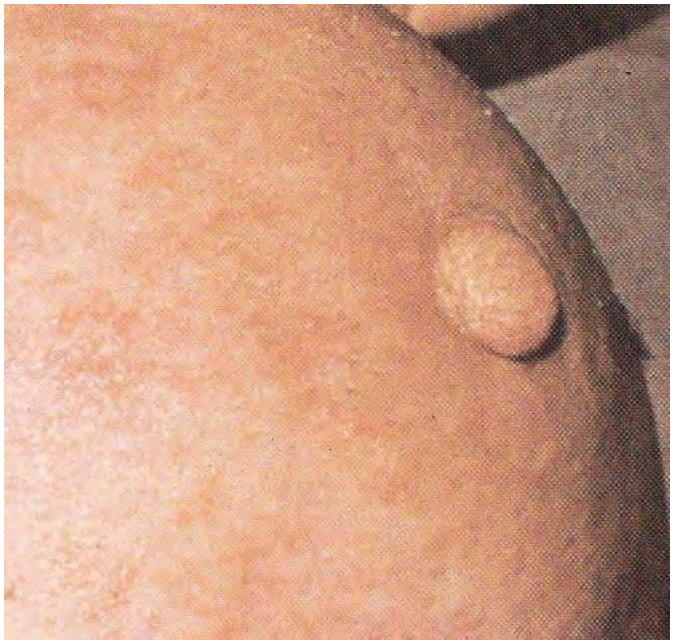
Papillare: *1-2% di tutti i tumori. Solido o cistico, a prognosi favorevole,frequente sanguinamento dal capezzolo*

Malattia di Paget



- *0,7- 4% dei t. della mammella*
- *Presenza di lesioni eczematodi di capezzolo ed areola spesso precedenti la tumefazione, rappresentata generalmente da un carcinoma duttale, infiltrante o in situ*

Carcinoma infiammatorio

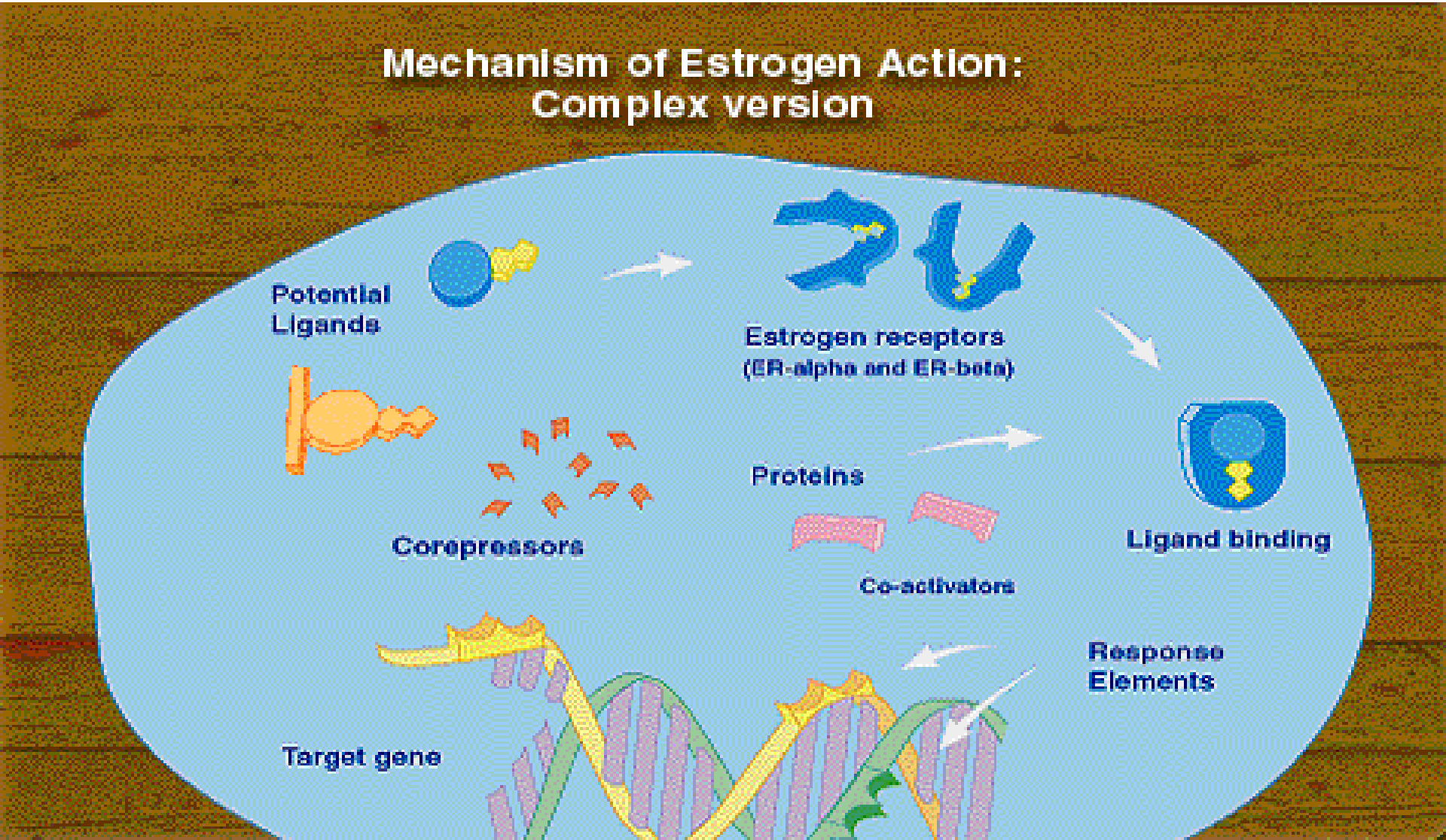


- *varietà aggressiva di carcinoma invasivo che infiltra i vasi linfatici della cute e conferisce alla pelle della mammella un aspetto detto a "buccia d'arancia" con una reazione infiammatoria della parte interessata che diventa rossa, tumefatta e dolente*

Fattori prognostici e predittivi nel carcinoma della mammella

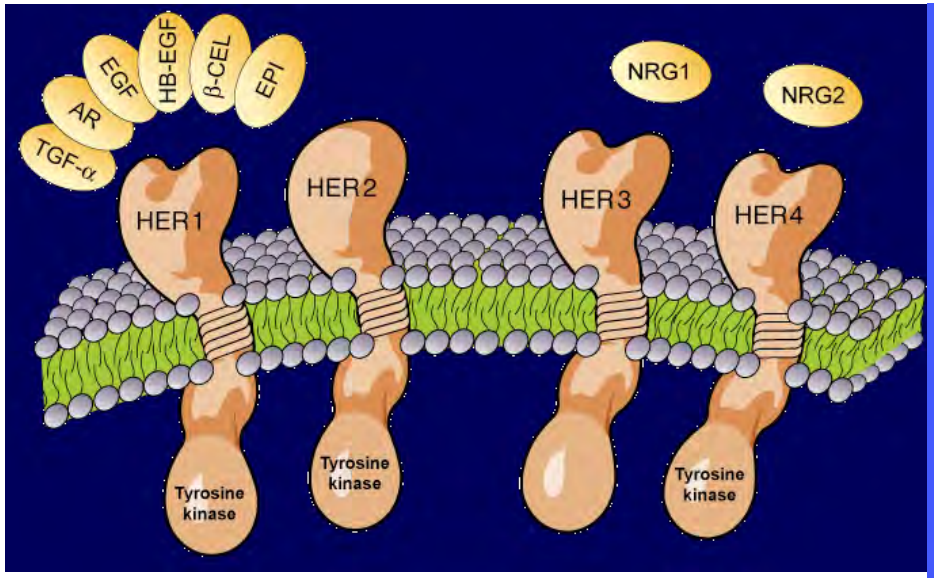
- Dimensioni del tumore
- Istotipo
- Grado istologico
- Stato dei linfonodi ascellari
- Stato dei recettori ormonali

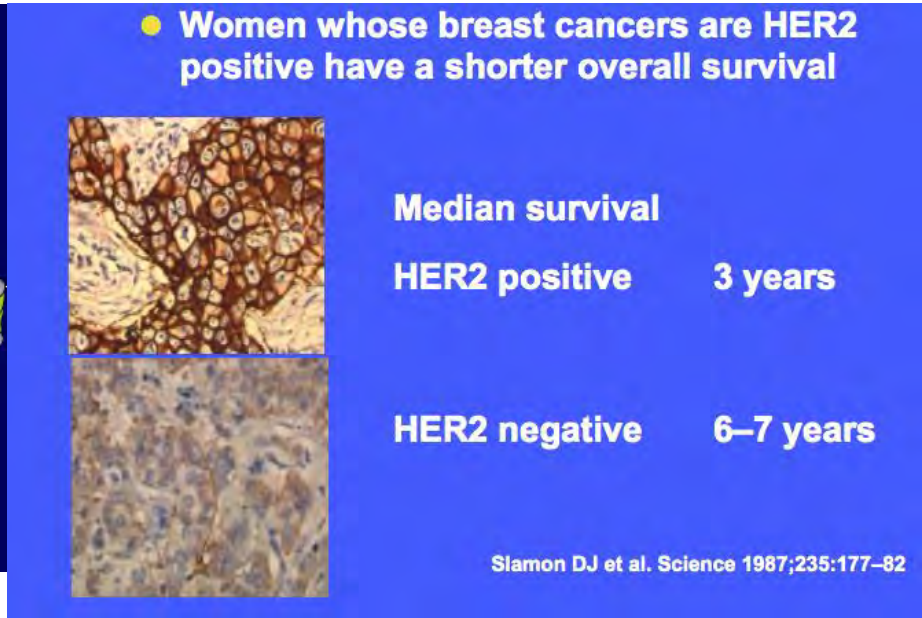
Fattori prognostici e predittivi nel carcinoma della mammella



Fattori prognostici e predittivi nel carcinoma della mammella

- Dimensioni del tumore
- Istotipo
- Grado istologico
- Stato dei linfonodi ascellari
- Stato dei recettori ormonali
- Stato di HER 2





Classificazione molecolare

- *È opinione comune che il decorso clinico diverso in pazienti con tumori istologicamente identici sia il risultato di differenze a livello molecolare*

- *Pertanto, è ragionevole ipotizzare che un accurato studio a livello molecolare possa fornire informazioni utili a caratterizzare in maniera più specifica la neoplasia,migliorando la capacità di prevederne il decorso e la risposta alla terapia*

Classificazione molecolare

- La introduzione della valutazione genomica del DNA e mRNA ha portato ad una nuova classificazione
- La tecnologie del micro-array consentono di determinare contemporaneamente l'espressione di un grande numero di geni e di combinare la quantificazione dell'espressione genica in modelli che possono far prevedere il decorso clinico della malattia in maniera più accurata di un qualsiasi gene considerato singolarmente.

Classificazione molecolare

- Facendo riferimento ad informazioni cliniche e patologiche predefinite, si individuano i profili ad esse correlati.
- Il primo studio che ha esaminato il profilo dell'espressione genica in un elevato numero di tumori della mammella, mediante microarrays, è stato pubblicato nel 2000 da Perou et al. che hanno analizzato 1.753 geni. Successivamente, l'elenco dei geni è stato modificato 534 geni, che costituiscono il c.d. intrisic subtype,la cui espressione è stata valutata in 115 casi di cancro della mammella

- il raggruppamento dei tumori consente di identificare 5 sottogruppi o classi molecolari
- Due di questi sottogruppi sono ER+ (luminale A e B) e tre ER- (basale,HER2 e normale).

HER2

I tumori HER2 hanno in genere un'amplificazione di HER2 ed un'elevata espressione dei geni dell'amplicon HER2, come GRB7.

Luminale B

Esprimono ER

- HER 2 negativi, bassa attività proliferativa ma con sensibilità ormonale incompleta
- Her 2 positivi , alta attività proliferativa , possono associatre t. endocrina e anti

Basale

I tumori basali (basal-like), non esprimono ER PgR ed HER2. Esprimono citocheratine proprie delle cellule basali e sono, caratterizzati dall'espressione di vari geni correlati alla proliferazione.(**TRIPLE NEGATIVE**) **(PROGNOSI PEGGIORE**)

Normale

normal-like,simili al tessuto normale o ai tumori benigni, non hanno una signature ben definita

Luminale A

Esprimono i recettori per gli estrogeni, sono HER 2 negativi e a bassa attività proliferativa e andamento indolente. Sensibili alla terapia ormonale. Hanno la migliore prognosi

Classificazione molecolare

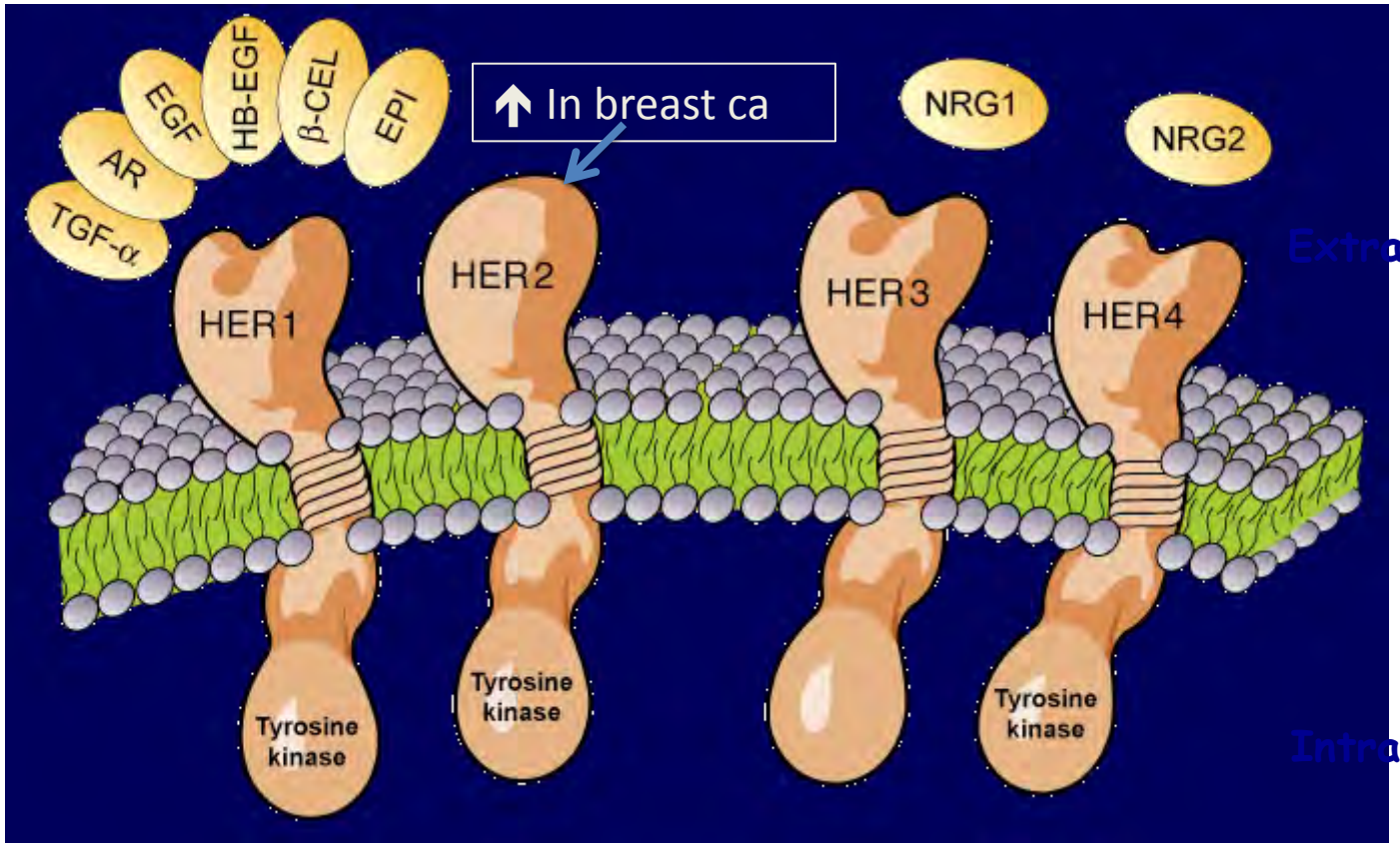
- *Fondamentalmente, i 5 sottogruppi molecolari di cancro della mammella differiscono tra di loro in termini di DFS e OS.*

- *I sottotipi basal-like e HER2 sono quelli più aggressivi ed hanno una più alta percentuale di mutazioni di TP53 ed una maggiore probabilità di essere G3 rispetto ai tumori luminali A.*

- *Vari metodi adoperati per identificare signatures con significato prognostico generale sono oggi disponibili . I più validati sono il 21-gene recurrence score(Oncotype DX) e il 70-gene prognostic predictor (MammaPrint). Essi sono in grado di prevedere la prognosi in maniera più accurata.*

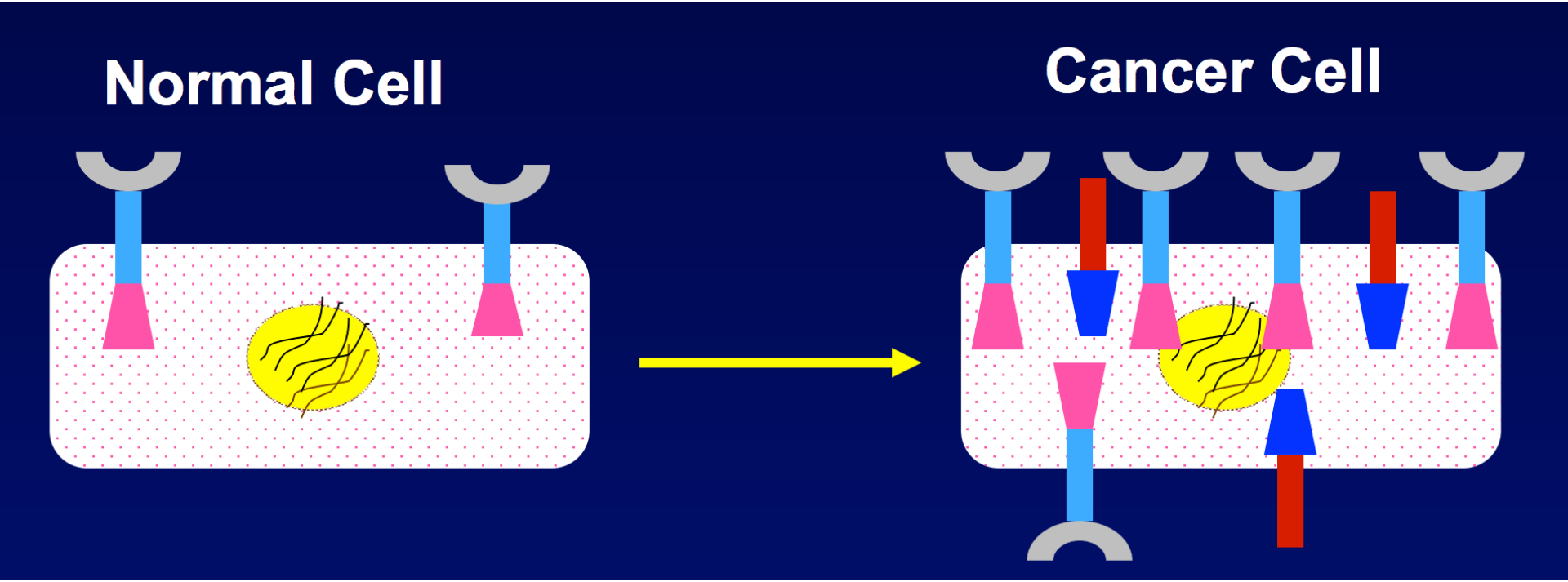
The HER Family

The epidermal growth factor family of receptors comprises 4 transmembrane proteins, each with different properties but all involved in the regulation of cell proliferation



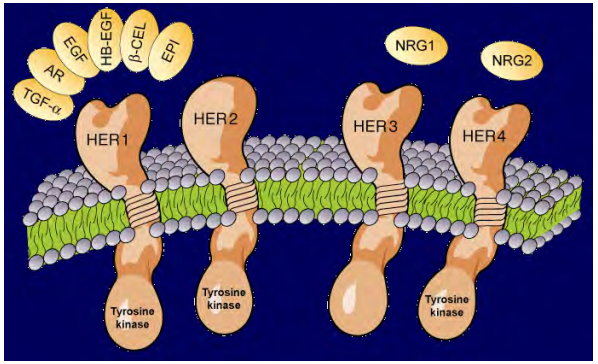
Courtesy of Kenneth Bloom.

EGF Receptors

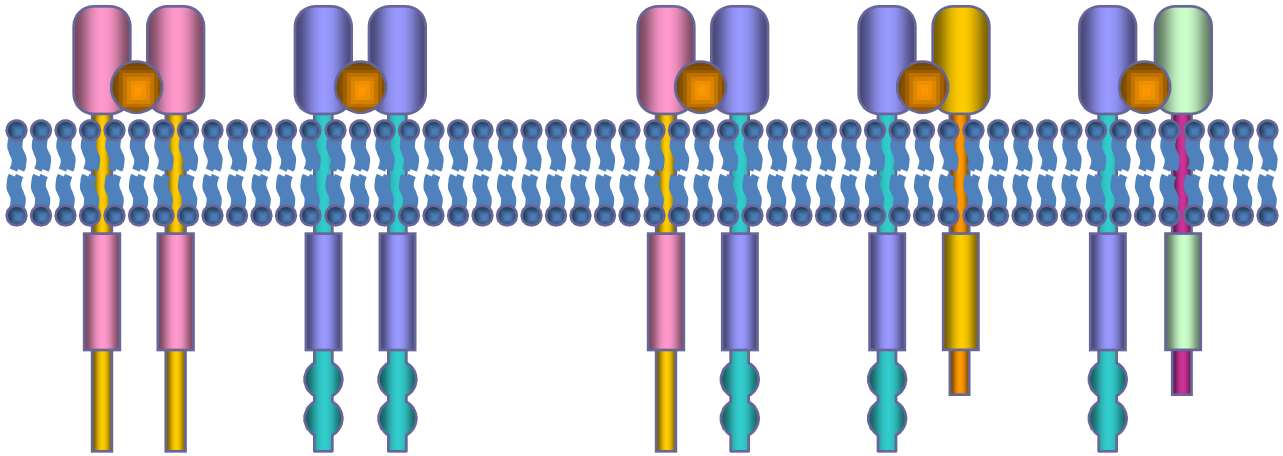


Role of HER2 in breast cancer

- HER2 gene amplification or receptor overexpression occurs in approximately 30% of metastatic breast cancers

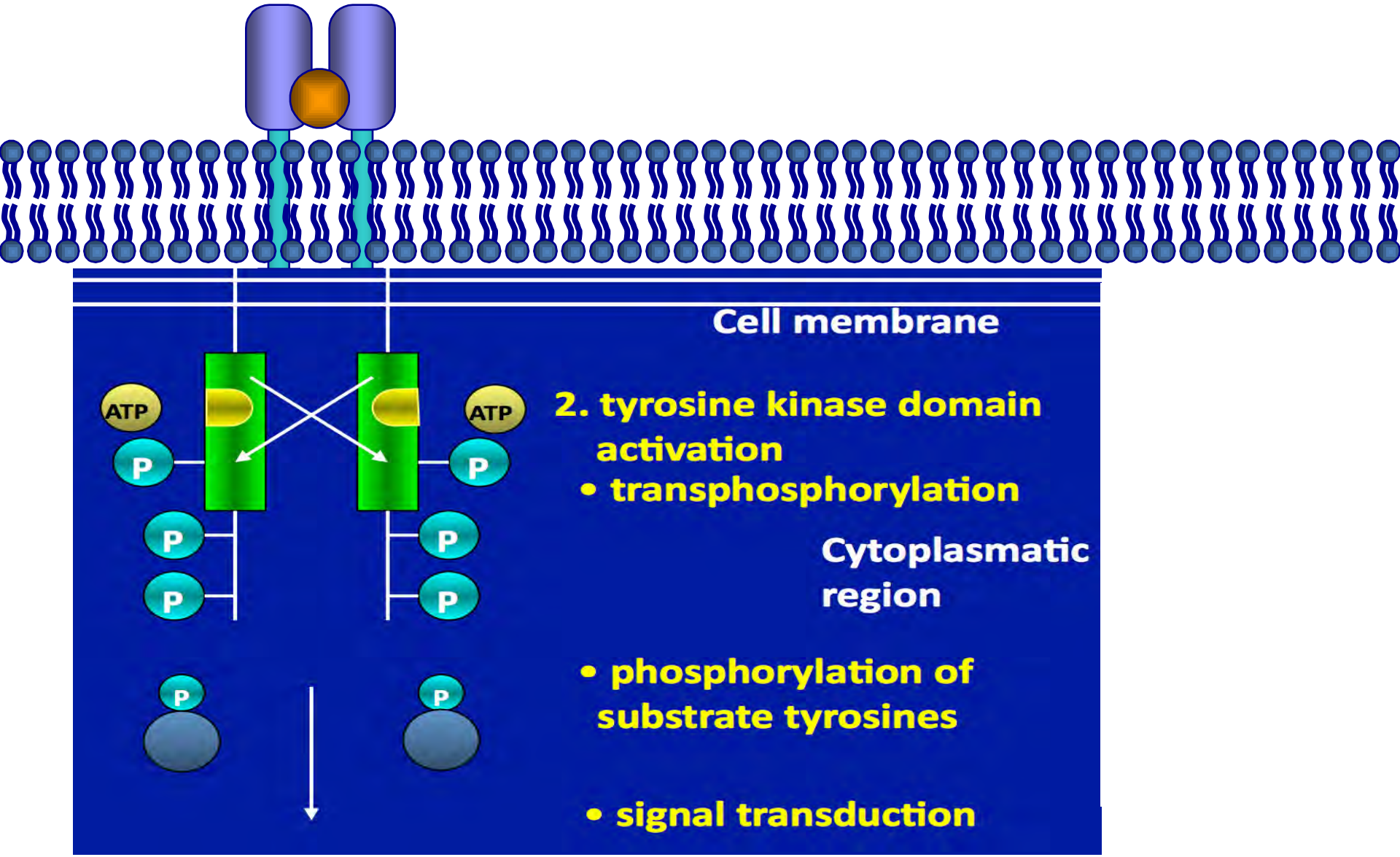


Homodimers and Heterodimers

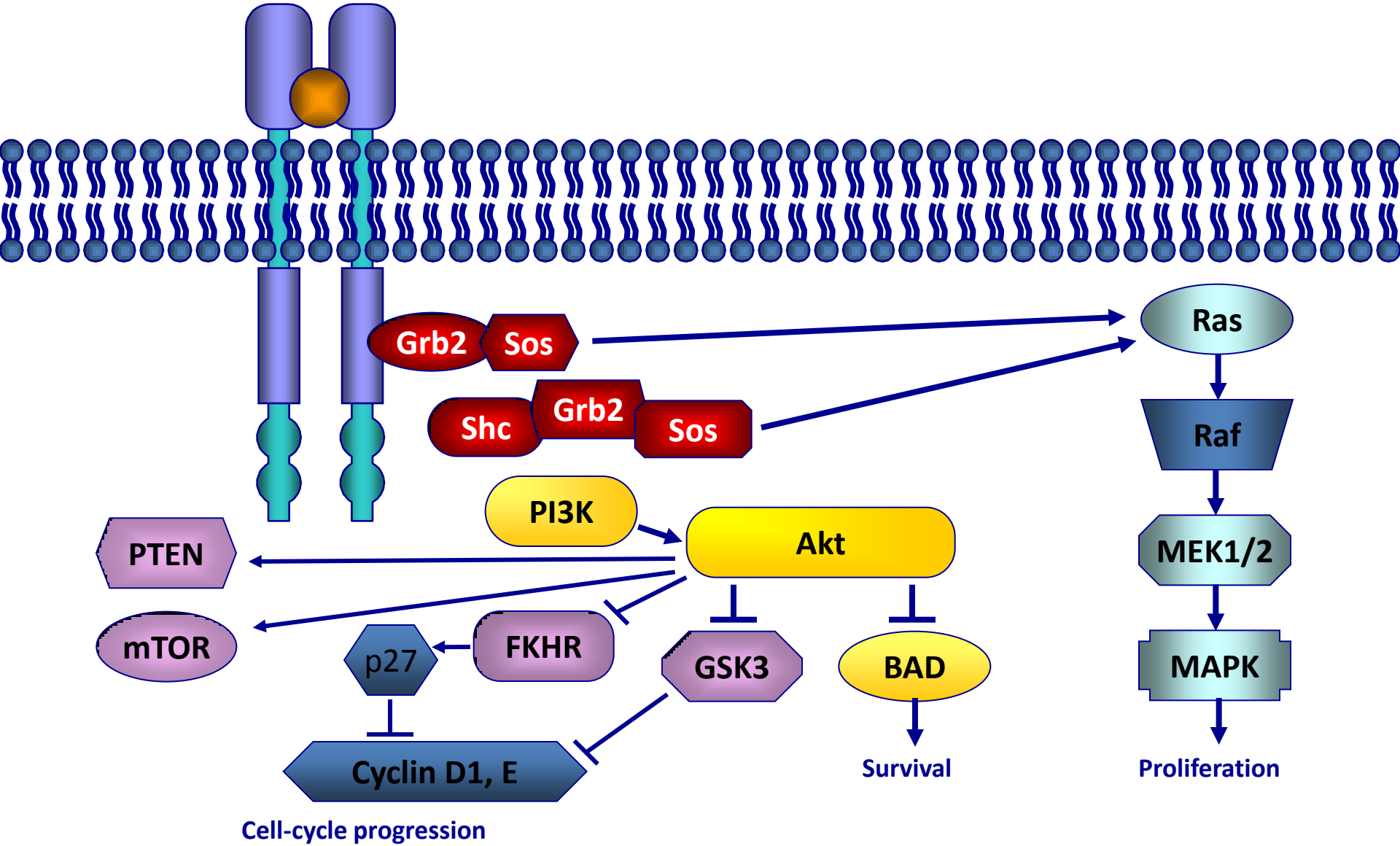


- **Ligand binding causes ErbB receptors to associate in pairs in a process called dimerization.**
- **Pairs can be formed between 2 identical receptors (homodimers) or between 2 different family members (heterodimers).**
- **ErbB-2 is the preferred dimerization partner with other ErbB receptors.**
- **Dimerization and autophosphorylation must occur for downstream signal transmission**

ErbB Signaling Pathway

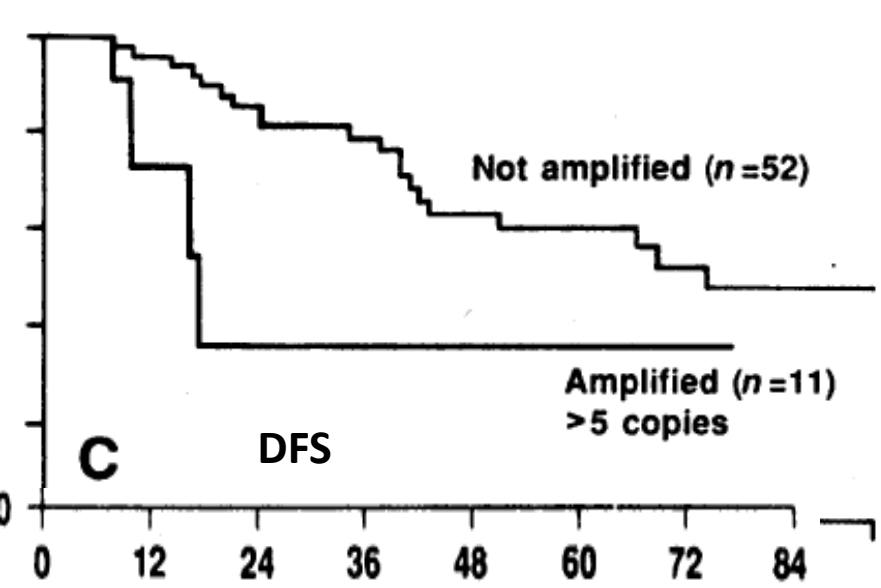


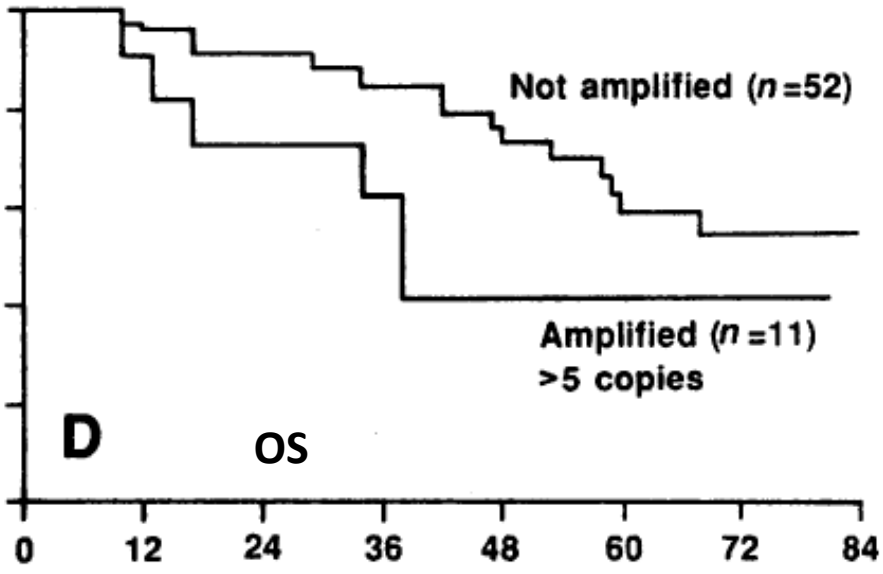
ErbB Signaling Pathway



Human Breast Cancer: Correlation of Relapse and Survival with Amplification of the HER-2/*neu* Oncogene

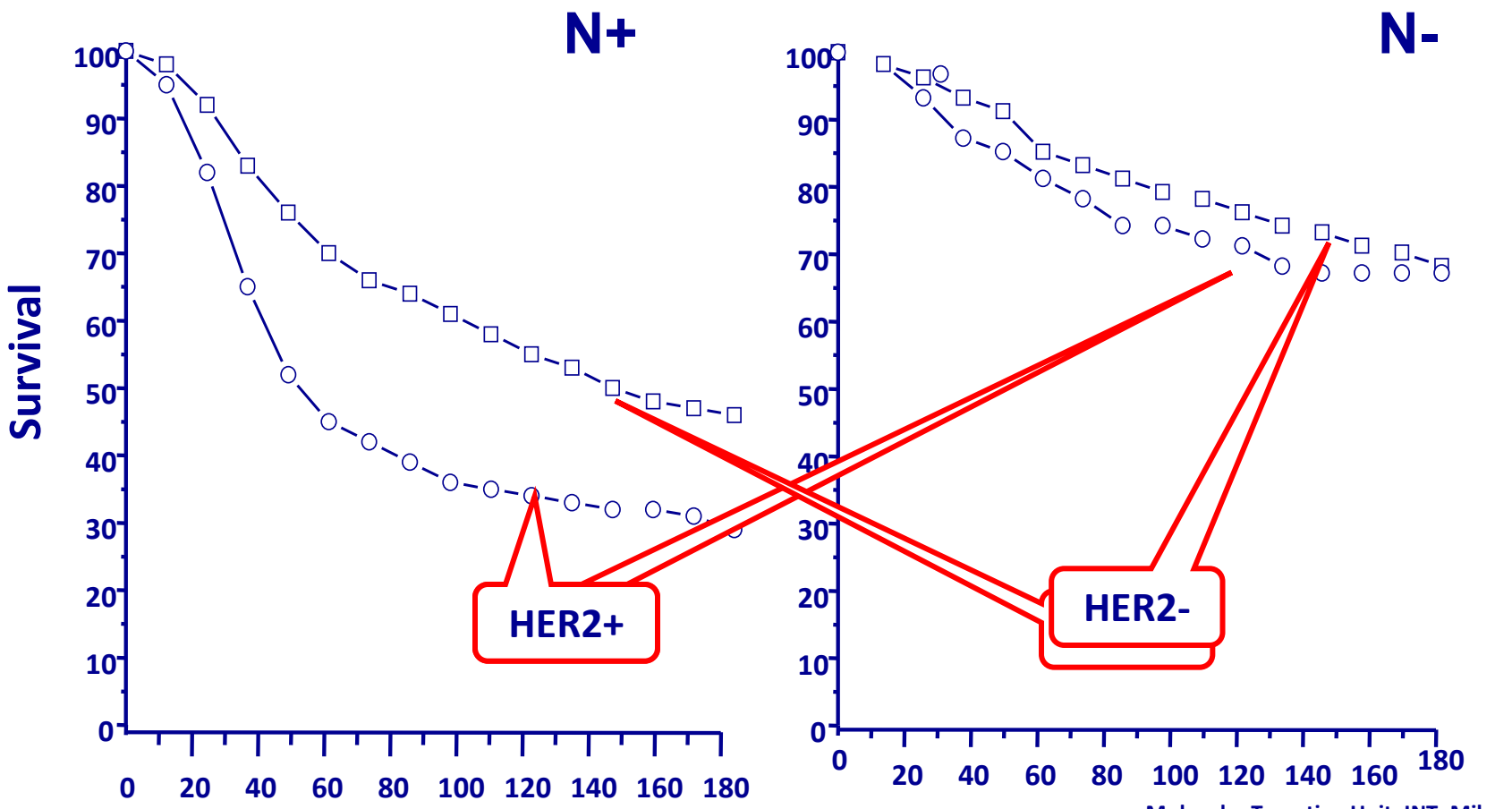
Dennis J. Slamon,* Gary M. Clark, Steven G. Wong, Wendy J. Levin, Axel Ullrich, William L. McGuire





Science 235: 177-82, 1987

Prognostic significance of HER2 according to nodal status in 2000 cases:



Molecular Targeting Unit, INT, Milan

Role of HER2 in breast cancer

- ***HER2 gene amplification or receptor overexpression occurs in approximately 30% of metastatic breast cancers***

- ***HER2-positive tumours are associated with poor prognosis and shortened disease-free/overall survival***

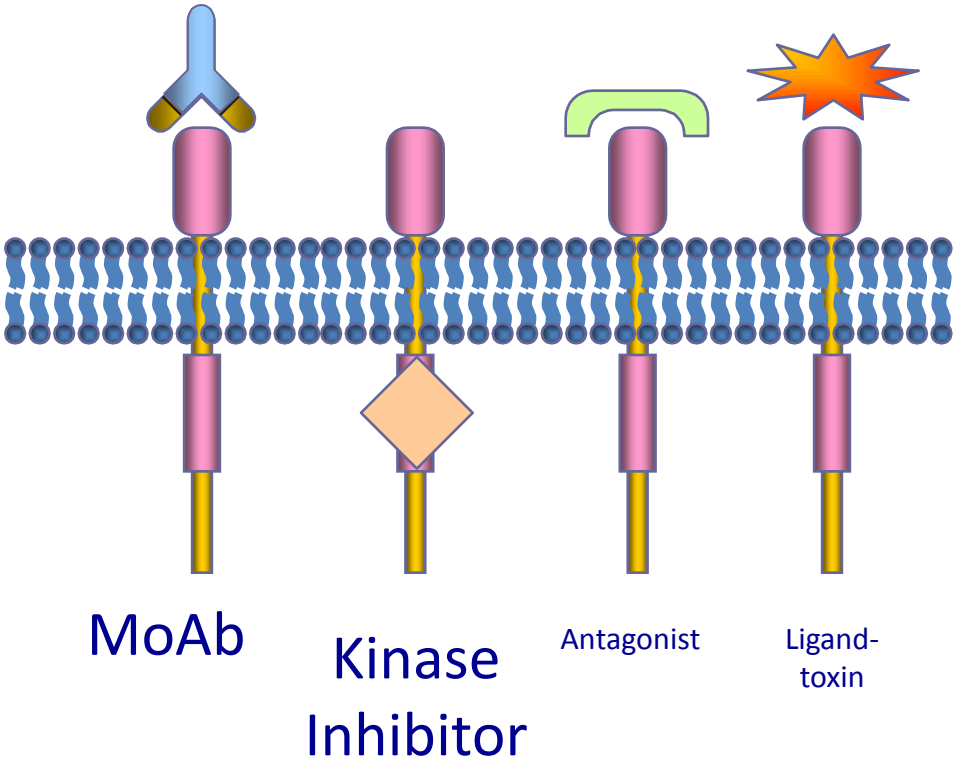
- ***HER2 receptor provides an extracellular target for novel and specific anticancer treatment (monoclonal antibodies- small molecules Tk-ib)***

The HER 2 Blockage

The old story

Strategies to Inhibit ErbB

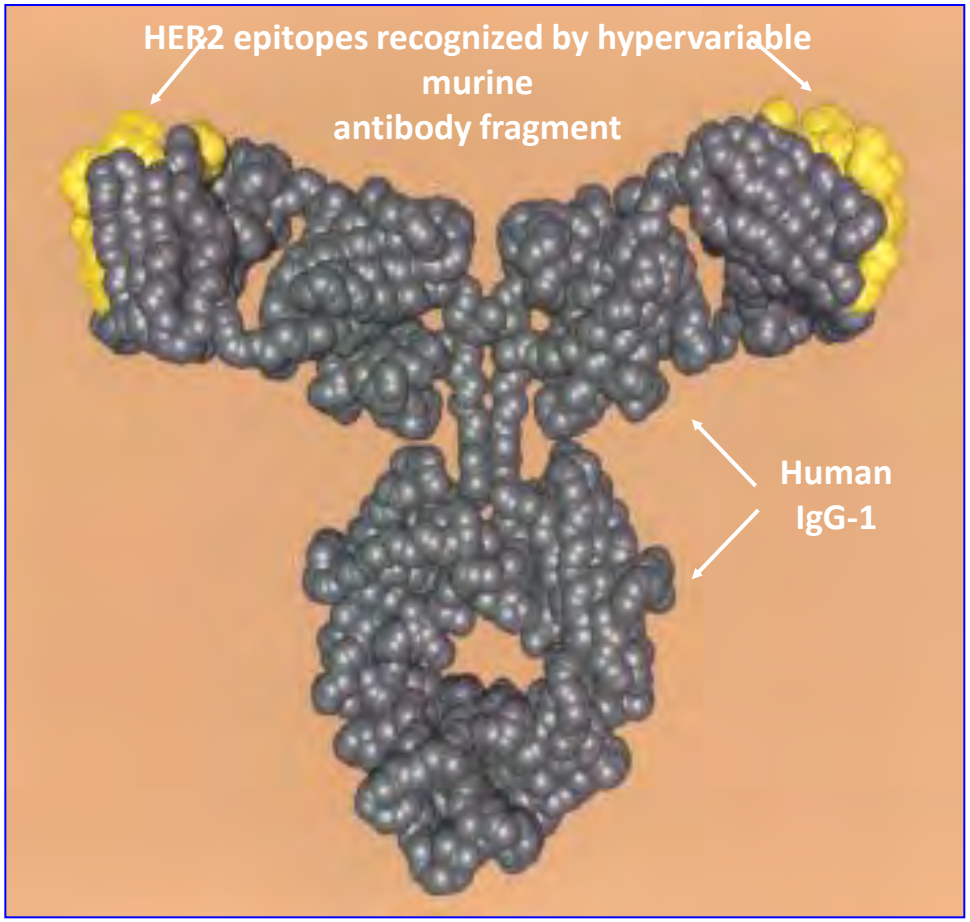
- ***MoAbs to block ligand binding or receptor dimerization***
- ***Small-molecule kinase inhibitors***
- *Competitive receptor antagonists*
- *Ligand-toxin or Ab-toxin conjugates*
- *Antisense oligonucleotides*
- *Vaccines*



MoAbs to block ligand binding or receptor dimerization

- ***Trastuzumab*** ***anti HER2***
- ***Cetuximab*** ***anti EGFR***
- ***Panitumab*** ***anti EGFR***

Trastuzumab: Humanized Anti-HER2 Antibody



- *Targets HER2 protein*
- *High affinity (K_d = 0.1 nM) and specificity*
- *95% human, 5% murine*
  - *Decreases potential for immunogenicity*
  - *Increases potential for recruiting immune effector mechanisms*

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.,

- Metastatic breast cancer
- HER 2 overexpression
- No prior CT
- Measurable disease
- KPS > 60%

Patients = 469

No Prior Anthra
- AC (138)
- AC + H (143)

Prior Anthra
- Paclitaxel (96)
- Paclitaxel + H (92)

The New England
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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.,

TABLE 3. RATES AND DURATIONS OF RESPONSES.*

VARIABLE	CHEMOTHERAPY PLUS TRASTUZUMAB (N=235)	CHEMOTHERAPY ALONE (N=234)	AN ANTHRACYCLINE, CYCLOPHOSPHAMIDE, AND TRASTUZUMAB (N=143)	AN ANTHRACYCLINE AND CYCLOPHOSPHAMIDE ALONE (N=138)	PACLITAXEL AND TRASTUZUMAB (N=92)	PACLITAXEL ALONE (N=96)
Complete response — no. (%)	18 (8)	8 (3)	11 (8)	6 (4)	7 (8)	2 (2)
Partial response — no. (%)	100 (43)	66 (28)	69 (48)	52 (38)	31 (34)	14 (15)
Complete and partial responses — no. (% [95% CI])	118 (50 [44–57])	74 (32 [26–38])	80 (56 [48–64])	58 (42 [34–50])	38 (41 [31–51])	16 (17 [9–24])
P value	<0.001		0.02		<0.001	
Median duration of response — mo	9.1	6.1	9.1	6.7	10.5	4.5
P value	<0.001		0.005		<0.01	

The New England
Journal of Medicine

VOLUME 344 MARCH 15, 2001 NUMBER 11

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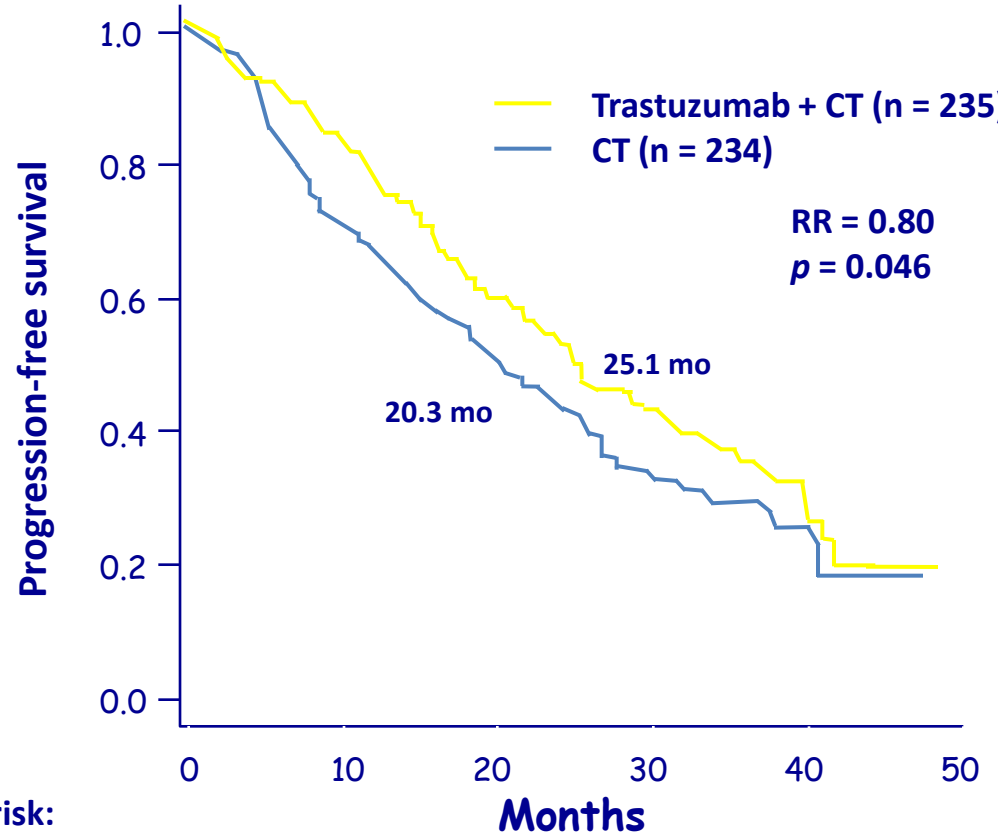
TABLE 2. RESULTS OF AN INTENTION-TO-TREAT ANALYSIS OF THE END POINTS.*

END POINT	CHEMOTHERAPY PLUS TRASTUZUMAB (N=235)	EITHER TYPE OF CHEMOTHERAPY ALONE (N=234)	AN ANTHRACYCLINE, CYCLOPHOSPHAMIDE, AND TRASTUZUMAB (N=143)	AN ANTHRACYCLINE AND CYCLOPHOSPHAMIDE ALONE (N=138)	PACLITAXEL AND TRASTUZUMAB (N=92)	PACLITAXEL ALONE (N=96)
Median time to disease progression — mo	7.4	4.6	7.8	6.1	6.9	3.0
P value	<0.001		<0.001		<0.001	
Relative risk of progression (95% CI)	0.51 (0.41–0.63)		0.62 (0.47–0.81)		0.38 (0.27–0.53)	
Median time to treatment failure — mo	6.9	4.5	7.2	5.6	5.8	2.9
P value	<0.001		<0.001		<0.001	
Relative risk of treatment failure (95% CI)	0.58 (0.47–0.70)		0.67 (0.52–0.86)		0.46 (0.33–0.63)	
Median survival — mo	25.1	20.3	26.8	21.4	22.1	18.4
P value	0.046		0.16		0.17	
Relative risk of death (95% CI)	0.80 (0.64–1.00)		0.82 (0.61–1.09)		0.80 (0.56–1.11)	

*Trastuzumab Combination Pivotal Trial: Overall Survival**



No. at risk:

H + CT	**235**	**192**	**134**	**96**	**11**
CT	**234**	**160**	**116**	**76**	**13**

Cumulative % of patients on CT alone crossing over to Trastuzumab at progression†

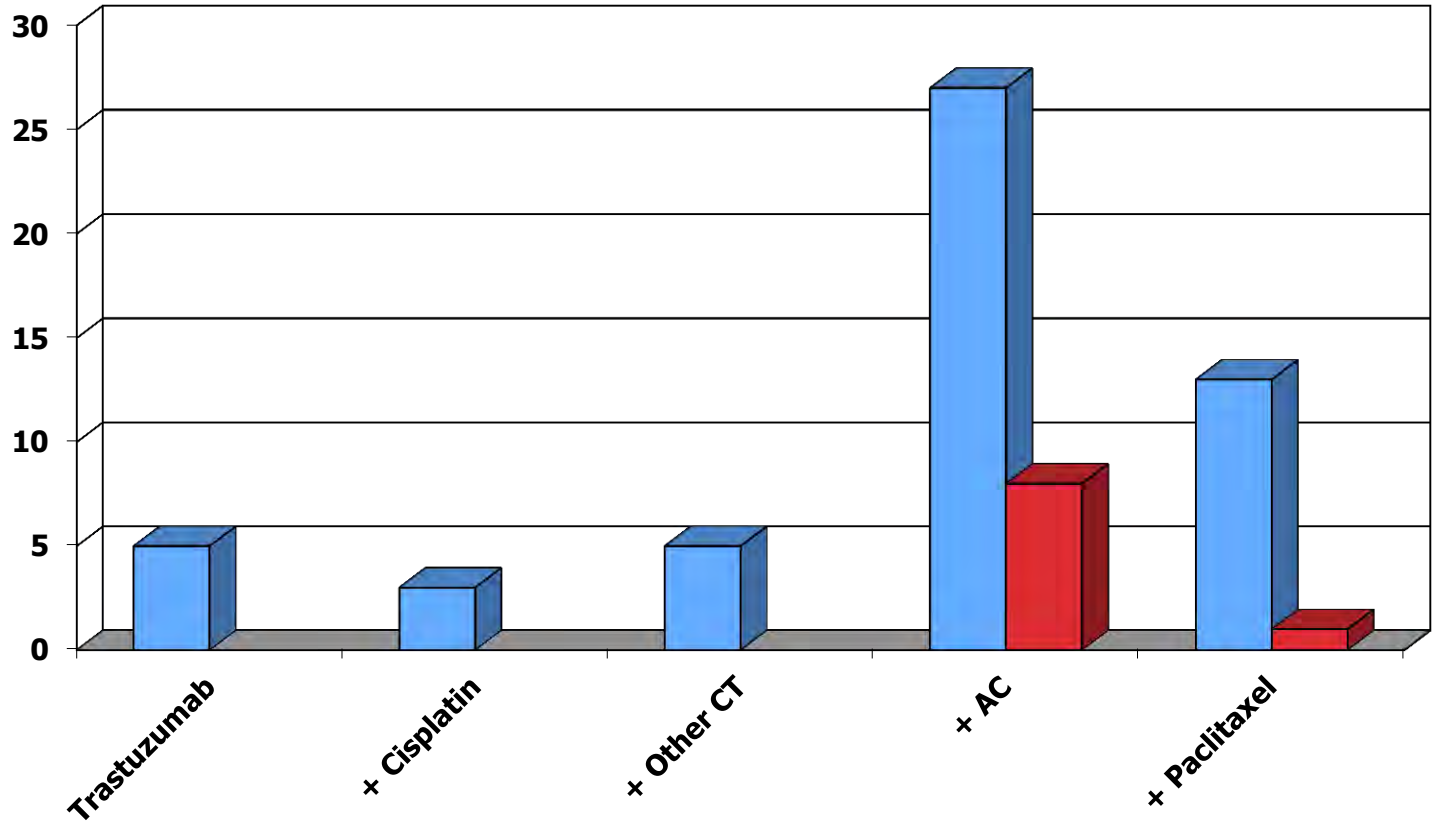
Month	%
5	24
15	62
25	65
40	72

* Median follow-up: 35 mo (range: 30–51).

† These patients are still reported in the CT arm despite crossover to Herceptin.

Slamon et al. *N Engl J Med*. 2001;344:783.

. . . but has been associated with cardiac dysfunction



Modified from Seidman A et al
J Clin Oncol 20(5):1215-1221, 2001

Herceptin-associated cardiotoxicity: why?

- ***Preclinical animal studies do not support inherent cardiotoxic potential of Herceptin***

- ***Herceptin may be interfering with***
  - ***growth and repair after anthracycline-induced damage***
  - ***myocyte survival pathways (role of HER2 on cardiogenesis and myocardial protection)***
  - ***pharmacokinetics of anthracyclines***

VOLUME 23 · NUMBER 19 · JULY 1 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Phase II Trial of the Efficacy and Safety of Trastuzumab Combined With Docetaxel in Patients With Human Epidermal Growth Factor Receptor 2–Positive Metastatic Breast Cancer Administered As First-Line Treatment: The M77001 Study Group

Michel Marty, Francesco Cognetti, Dominique Maraninchi, Ray Snyder, Louis Mauriac,

Table 2. Summary of Efficacy Between the Two Treatment Arms

Outcome	Trastuzumab + Docetaxel (n = 92)	Docetaxel Alone (n = 94)	*P*
ORR, %	61	34	.0002
CR, %	7	2	
PR, %	54	32	
SD, %	27	44	
DR, median, months	11.7	5.7	.009
TTP, median, months	11.7	6.1	.0001
OS, median, months*	31.2	22.7	.0325

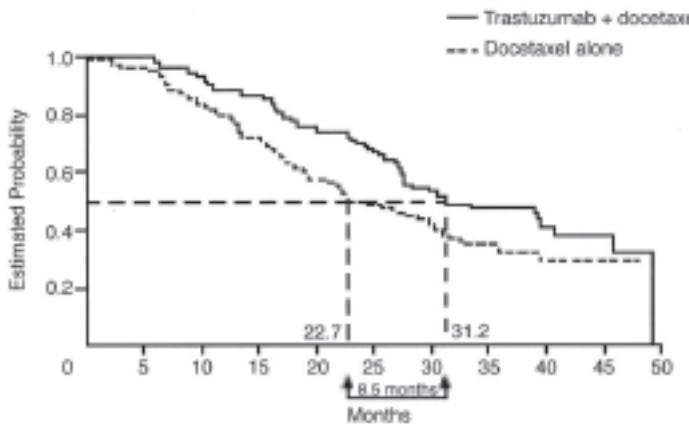


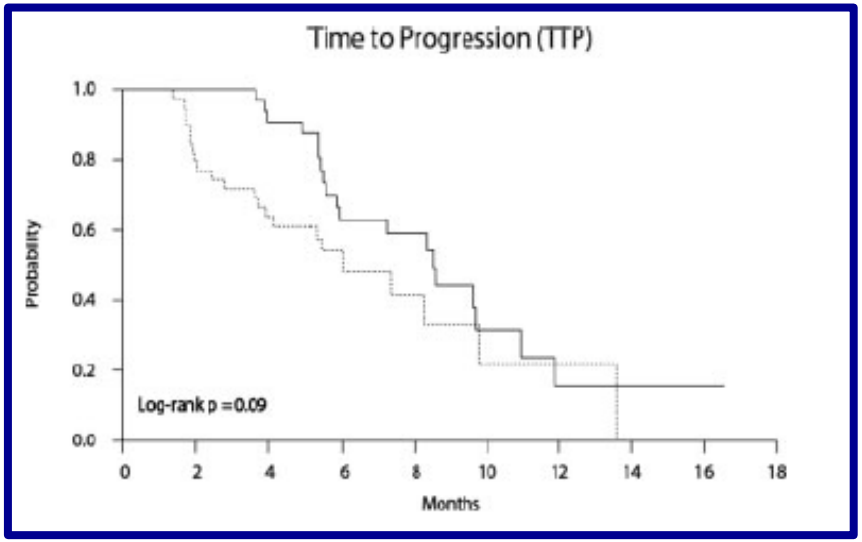
Table 5. Changes in LVEF From Baseline: Worst Value Up to Cycle 6 and Overall (% of patients)

LVEF Worst Value	Up to Cycle 6		Overall*	
	Trastuzumab + Docetaxel (n = 83)	Docetaxel Alone (n = 71)	Trastuzumab + Docetaxel (n = 86)	Docetaxel Alone (n = 76)
Increase or no change	41	41	20	33
Absolute decrease < 15%	48	54	63	60
Absolute decrease ≥ 15%	11	6	17	8
Absolute value < 40%	1	0	1	0

Trastuzumab Plus Vinorelbine or Taxane Chemotherapy for HER2-overexpressing Metastatic Breast Cancer: The Trastuzumab and Vinorelbine or Taxane Study

Overall Response

	Treatment arm			
	A (N = 41) Trast+Vin		B (N = 40) Trast+Tax	
Response	No.	%	No.	%
Best response (strict criteria)				
Complete response	5	12	2	5
Partial response	16	39	14	35
Stable disease	7	17	7	18
Progressive disease	0	0	10	25
Unevaluable*	13	31	7	18
Best response (strict criteria plus unconfirmed responses)				
Complete response	7	17	3	8
Partial response	20	49	20	50
Stable disease	5	12	3	8
Progressive disease	0	0	9	23
Unevaluable	9	22	5	13



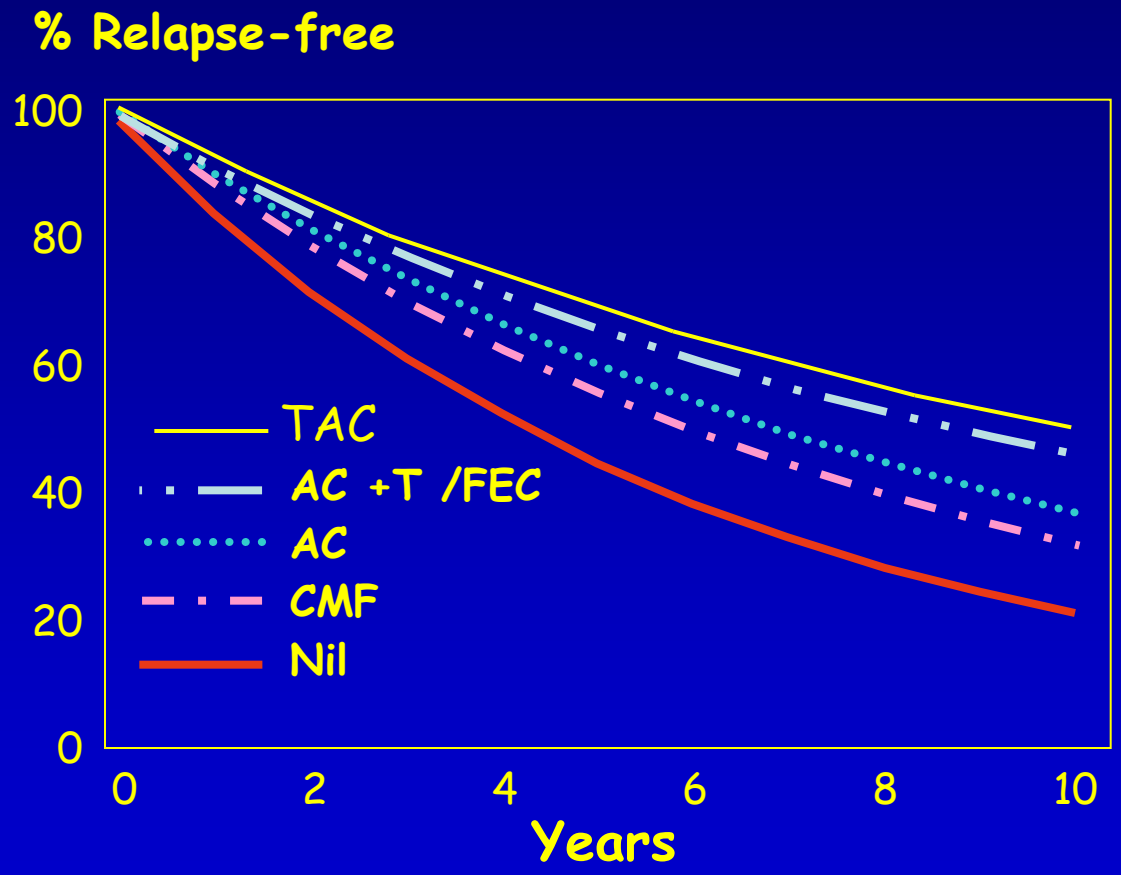
Burstein H. Cancer 2007;110:965–72

Conclusions

- ***Trastuzumab added to chemotherapy significantly increases responses and survival indexes respect chemotherapy alone in Her 2 positive metastatic breast cancer patients***

- ***All international guidelines claim chemotherapy with trastuzumab as standard of care in Her 2 positive metastatic breast cancer patients***

Evolvement of Adjuvant Chemotherapy

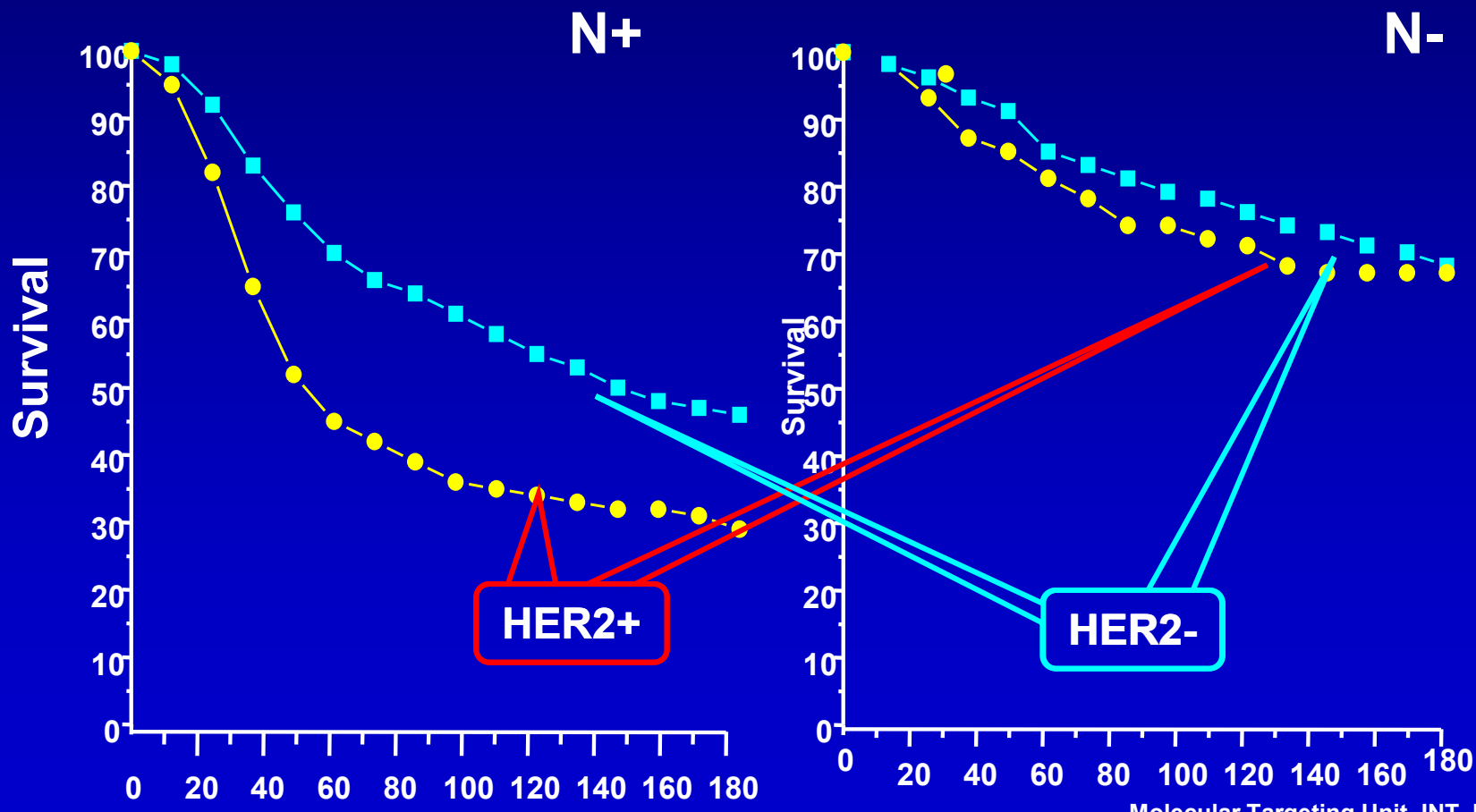


Relapse risk/year

TAC[3] = 6,5% (-32%)
AC +T[2] = 8,3% (-17%)
AC[1] = 10% (-11%)
CMF[1] = 11,4% (-14%)
Nil[1] = 15,0 %

*[1] Early Breast Cancer Trialists' Collaboration Group 2000
*[2] Henderson, JCO 2003
[3] Nabholtz, ASCO 2002

Prognostic significance of HER2 according to nodal status in 2000 cases:



JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Trastuzumab Plus Adjuvant Chemotherapy for Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: Planned Joint Analysis of Overall Survival From NSABP B-31 and NCCTG N9831

Edith A. Perez, Edward H. Romond, Vera J. Suman, Jong-Hyeon Jeong, George Sledge, Charles E. Geyer Jr,

J Clin Oncol 32. © 2014

NSABP B-31

Control: AC + T

Arm 1

Arm 2

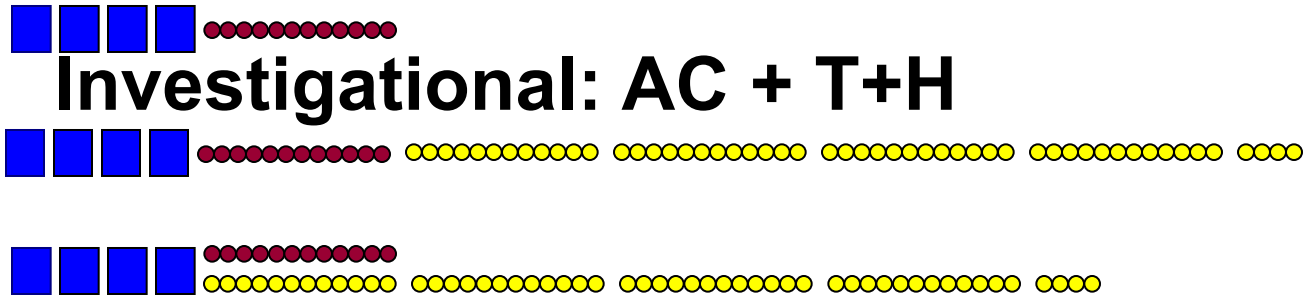
NCCTG N9831

Arm A

Arm B

Arm C

Investigational: AC + T+H



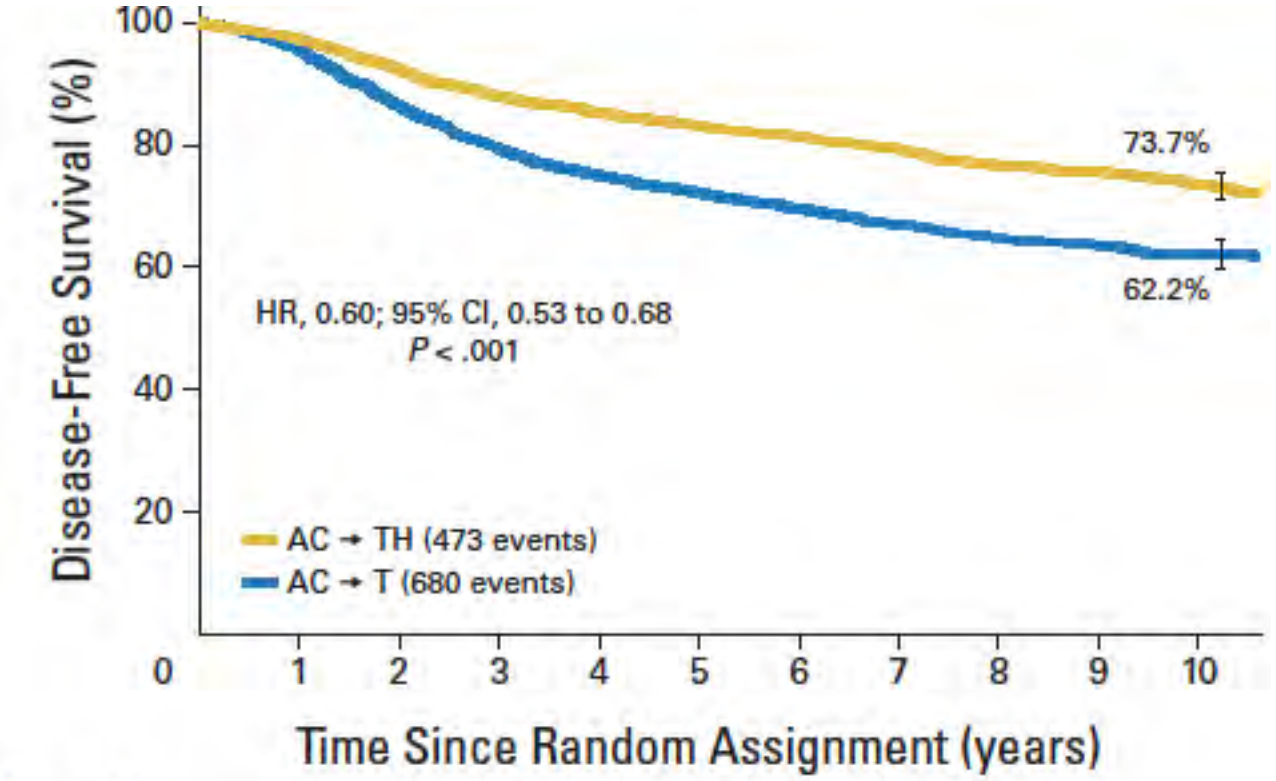
= doxorubicin/cyclophosphamide (AC) 60/600 mg/m^2 q 3 wk x 4

= paclitaxel (T) 175 mg/m^2 q 3 wk x 4

= paclitaxel (T) 80 mg/m^2/wk x 12

= trastuzumab (H) 4mg/kg LD + 2 mg/kg/wk x 51

Disease-Free Survival

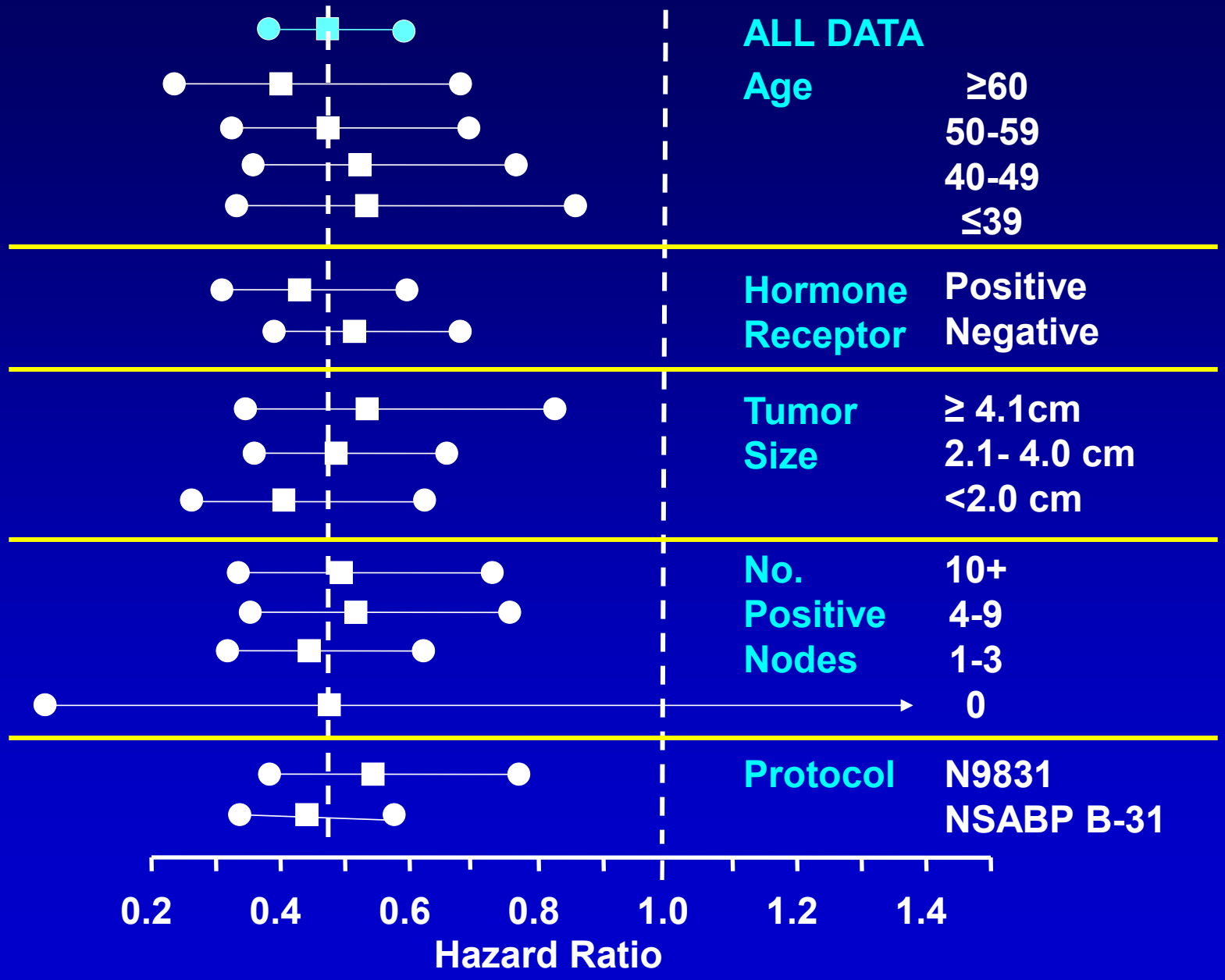


No. at risk

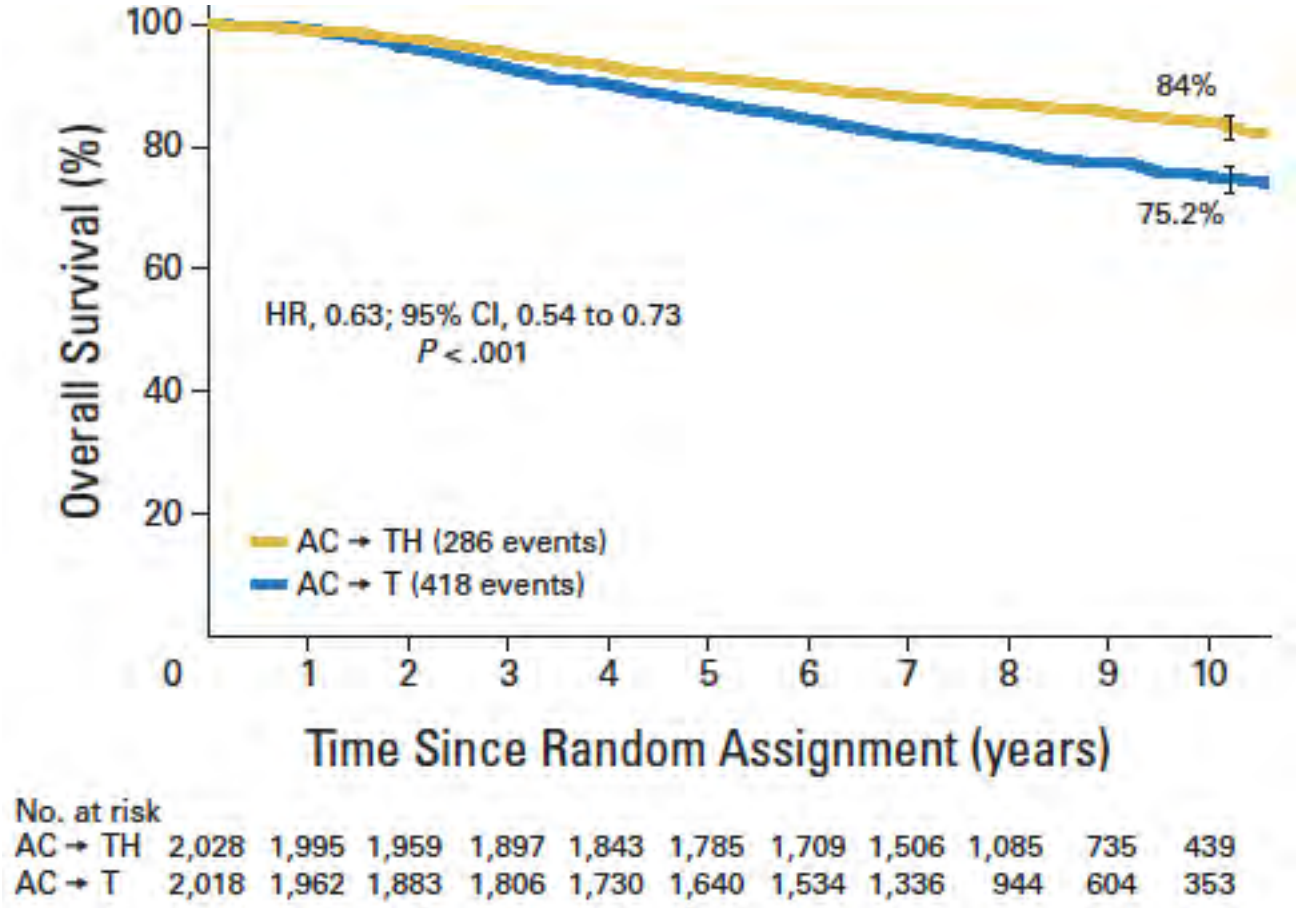
AC → TH	2,028	1,959	1,848	1,747	1,675	1,611	1,514	1,293	910	619	350
AC → T	2,018	1,887	1,689	1,529	1,423	1,329	1,232	1,027	705	449	255

Perez H et Al. J Clin Oncol 32. 2014

Forest Plot For Disease-Free Survival



Overall Survival



No. at risk

AC → TH	2,028	1,995	1,959	1,897	1,843	1,785	1,709	1,506	1,085	735	439
AC → T	2,018	1,962	1,883	1,806	1,730	1,640	1,534	1,336	944	604	353

Perez H et Al. J Clin Oncol 32. 2014

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Trastuzumab Plus Adjuvant Chemotherapy for Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: Planned Joint Analysis of Overall Survival From NSABP B-31 and NCCTG N9831

Edith A. Perez, Edward H. Romond, Vera J. Suman, Jong-Hyeon Jeong, George Sledge, Charles E. Geyer Jr,

- ***The addition of trastuzumab to paclitaxel after doxorubicin and cyclophosphamide in early-stage HER2-positive breast cancer results in a substantial and durable improvement in survival as a result of a sustained marked reduction in cancer recurrence***

- ***1 year of trastuzumab initiated concurrently with a taxane is considered the standard of care.***

Perez H et Al. J Clin Oncol 32. 2014

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 20, 2005 VOL. 353 NO. 16

Trastuzumab after Adjuvant Chemotherapy in HER2-Positive Breast Cancer

Martine J. Piccart-Gebhart, M.D., Ph.D., Marion Procter, M.Sci., Brian Leyland-Jones, M.D., Ph.D., Aron Goldhirsch, M.D.,

HERA TRIAL

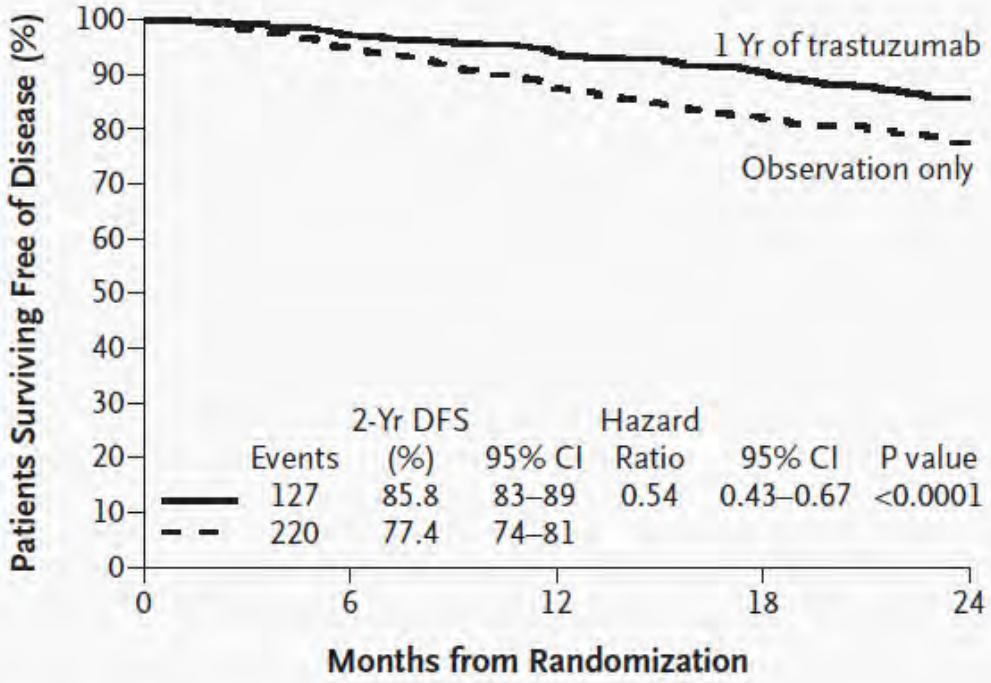
6675 pts

Herc x 1anno

Herc x 2 anni

Controllo

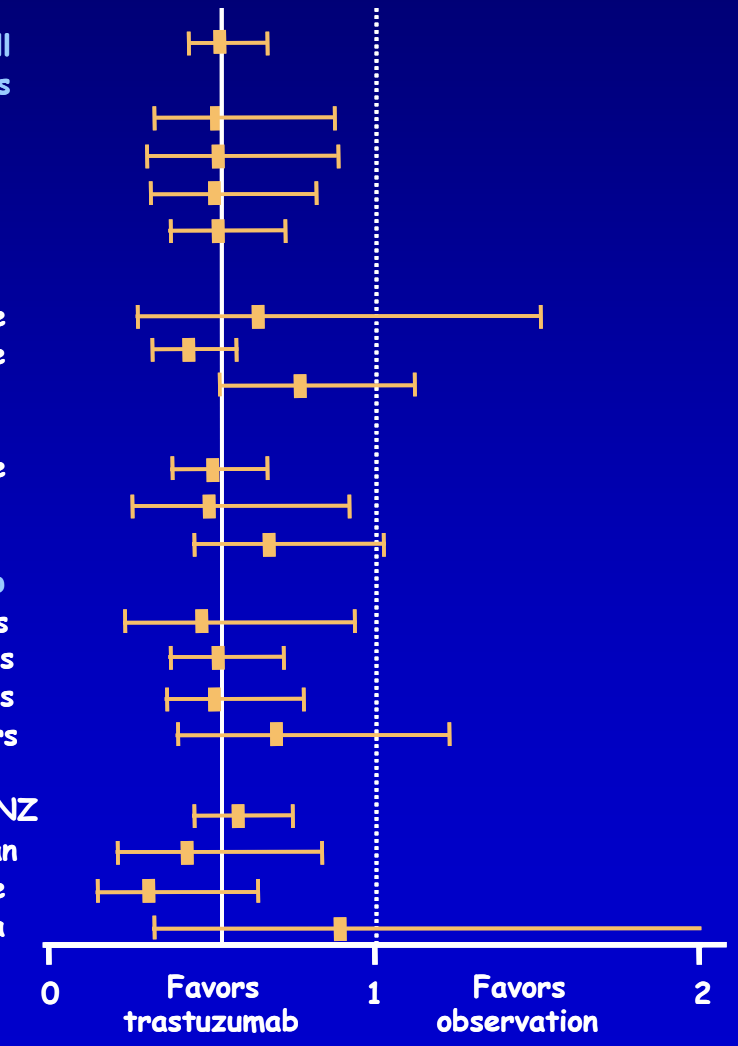
A



No. at Risk

1 Yr of trastuzumab	1694	1172	885	532	268
Observation only	1693	1108	767	445	224

DFS BENEFIT IN SUBGROUPS
HR: 1 year trastuzumab vs observation



	n	Hazard ratio
All	3387	0.54
Nodal status		
Any, neo-adjuvant chemotherapy	358	0.53
0 pos, no neo-adjuvant chemotherapy	1100	0.52
1-3 pos, no neo-adjuvant chemotherapy	972	0.51
≥4 pos, no neo-adjuvant chemotherapy	953	0.53
Adjuvant chemotherapy regimen		
No anthracycline or taxane	203	0.64
Anthracycline, no taxane	2307	0.43
Anthracycline + taxane	872	0.77
Receptor status/endocrine therapy		
Negative	1674	0.51
Pos + no endocrine therapy	467	0.49
Pos + endocrine therapy	1234	0.68
Age group		
<35 yrs	251	0.47
35-49 yrs	1490	0.52
50-59 yrs	1091	0.53
≥60 yrs	549	0.70
Region		
Europe, Nordic, Canada, SA, Aus, NZ	2430	0.58
Asia Pacific, Japan	405	0.42
Eastern Europe	364	0.31
Central + South America	188	0.90

SAFETY ANALYSIS POPULATION
Cardiotoxicity

	Observation N=1736	1 year trastuzumab N=1677
Decrease by > 10 EF points and LVEF < 50%	2.2 %	7.1 %
Same LVEF criteria and symptomatic CHF NYHA class III/IV, confirmed by cardiologist	0 % (95% CI: 0.00-0.21)	0.5% (95% CI: 0.25-1.02)
Cardiac death	0.1%	0%

Conclusions

- ***One year of treatment with trastuzumab after adjuvant chemotherapy significantly improves disease-free survival among women with HER2-positive breast cancer***

- ***Addition of Trastuzumab to chemotherapy is the new standard in the breast cancer adjuvant setting***

Primary Systemic Therapy (PST): rationale

- ***Established therapeutic strategy for stage II/III and inflammatory breast cancer***
- ***Significant downstaging of primary tumour and axillary node involvement***
  - ***reduced need for radical surgery***
- ***Efficacy similar to adjuvant therapy (NSABP-B18)***
  - ***no risk of postponing surgery***
- ***Pathological response is a tool for rapid definition of actual merits of new therapies and approaches***

Does pCR translate into long-term clinical benefits?

Pathological complete response (pCR) independently predicts for survival outcomes

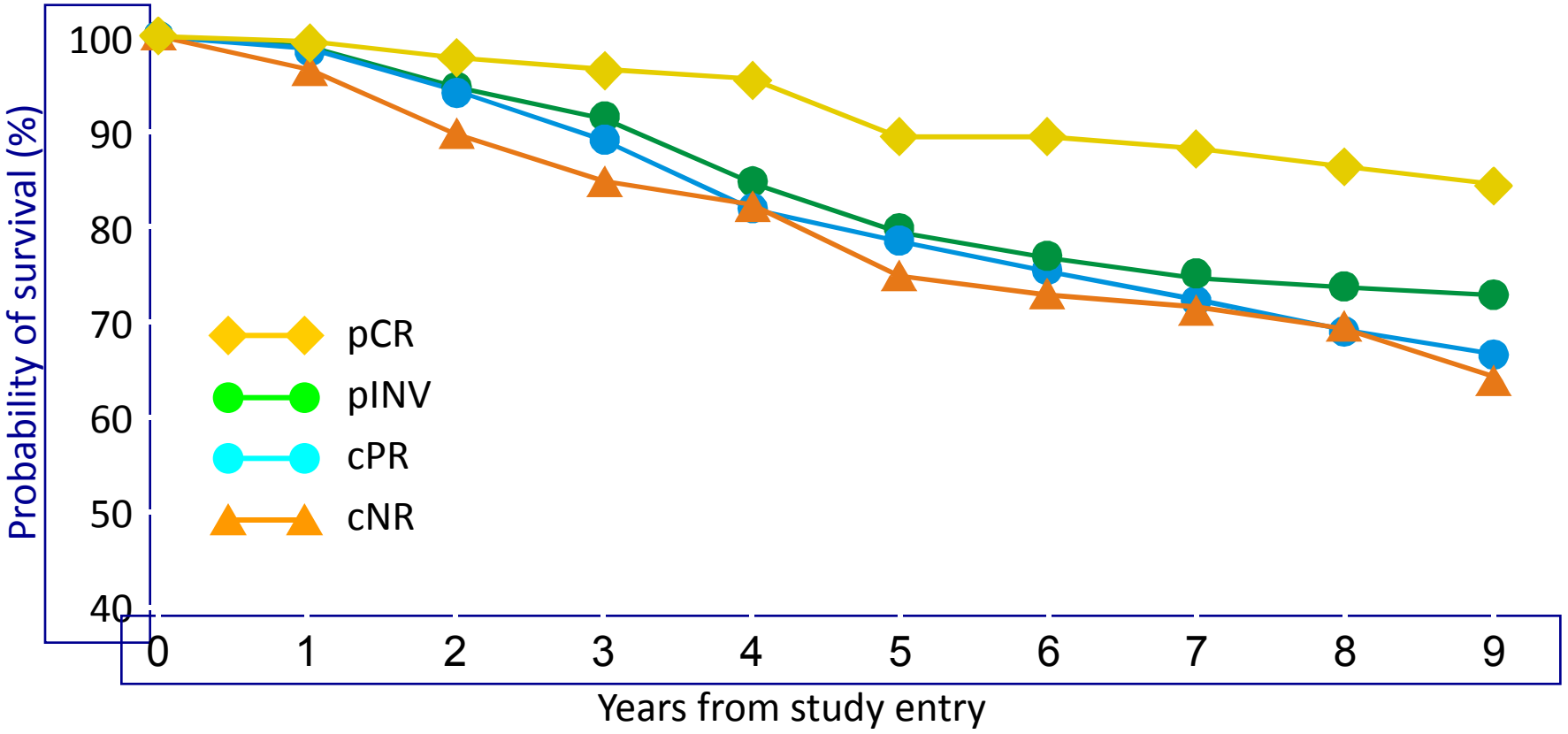
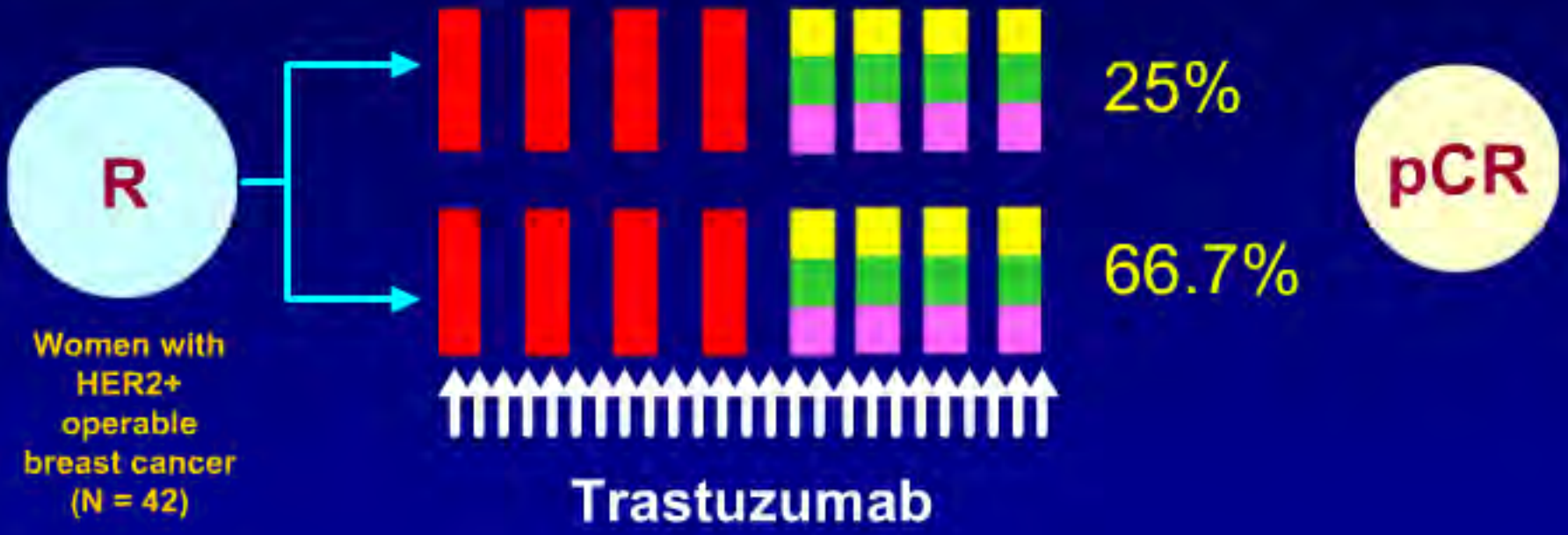


Figure adapted from Wolmark N, et al. J Natl Cancer Inst Monogr 2001;30:96–102

Trastuzumab "ups" 3: dramatically increases pathological complete response when used in the neo adjuvant setting with Paclitaxel➔FEC



Paclitaxel 225 mg/mq, 24 hours infusion q 3wks

Fluorouracil, 500 mg/m^2 IV Days 1 and 4
Epirubicin, 75 mg/m^2 IV Day 1
Cyclophosphamide, 500 mg/m^2, IV Day 1 q3 wks

Buzdar AU et al J Clin Oncol 2005

Herceptin® PST compares favourably with anthracycline plus taxane-based PST

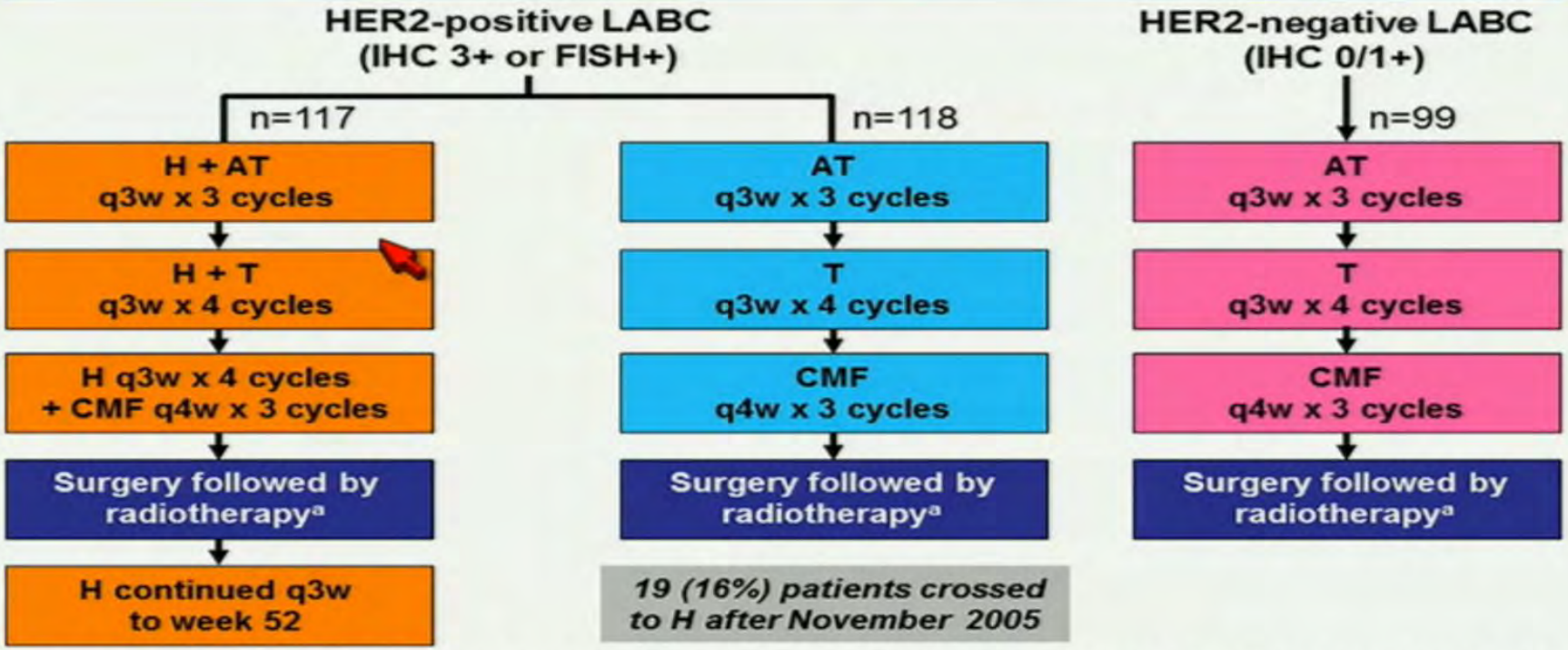
Study	Author	n	Regimen	CR (%)	pCR (%)
NSABP B-27	Bear 2003	752	AC x 4 → Doc x 4	64	26
GeparDuo	Minckwitz 2003	197	AT x 4 → Doc x 4	57	22
Aberdeen	Smith 2002	55	CVAPd x 4 → Doc x 4	94	34
AGO	Untch 2002	242	(E x 3 → Pac x 3) q2w	NA	18
ECTO	Gianni 2002	270	APac x 4 → CMF x 4	52	22
MD Anderson*	Buzdar 2004	23	Herceptin + (P → FEC)	NA	65

**HER2-positive patients*

Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort

Luca Gianni, Wolfgang Eiermann, Vladimir Semiglazov, Alexey Manikhas, Ana Lluch, Sergey Tjulandin, Milvia Zambetti, Federico Vazquez,

Study design

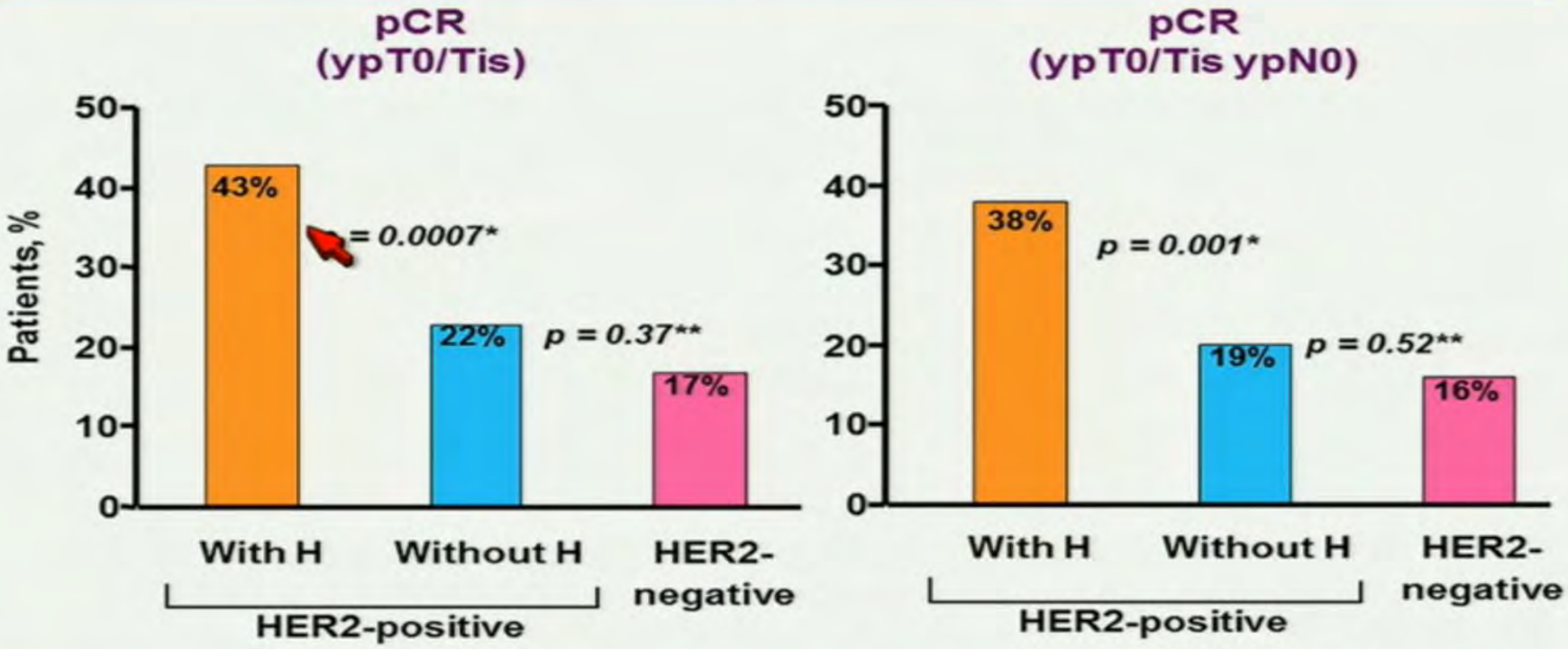


AT, doxorubicin (60 mg/m^2), paclitaxel (150 mg/m^2); H, trastuzumab (8 mg/kg loading dose then 6 mg/kg); T, paclitaxel (175 mg/m^2); [a]Hormone receptor-positive patients will receive adjuvant tamoxifen

lancet Vol 375 January 30, 2010

Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort

pCR in Intent-to-treat population

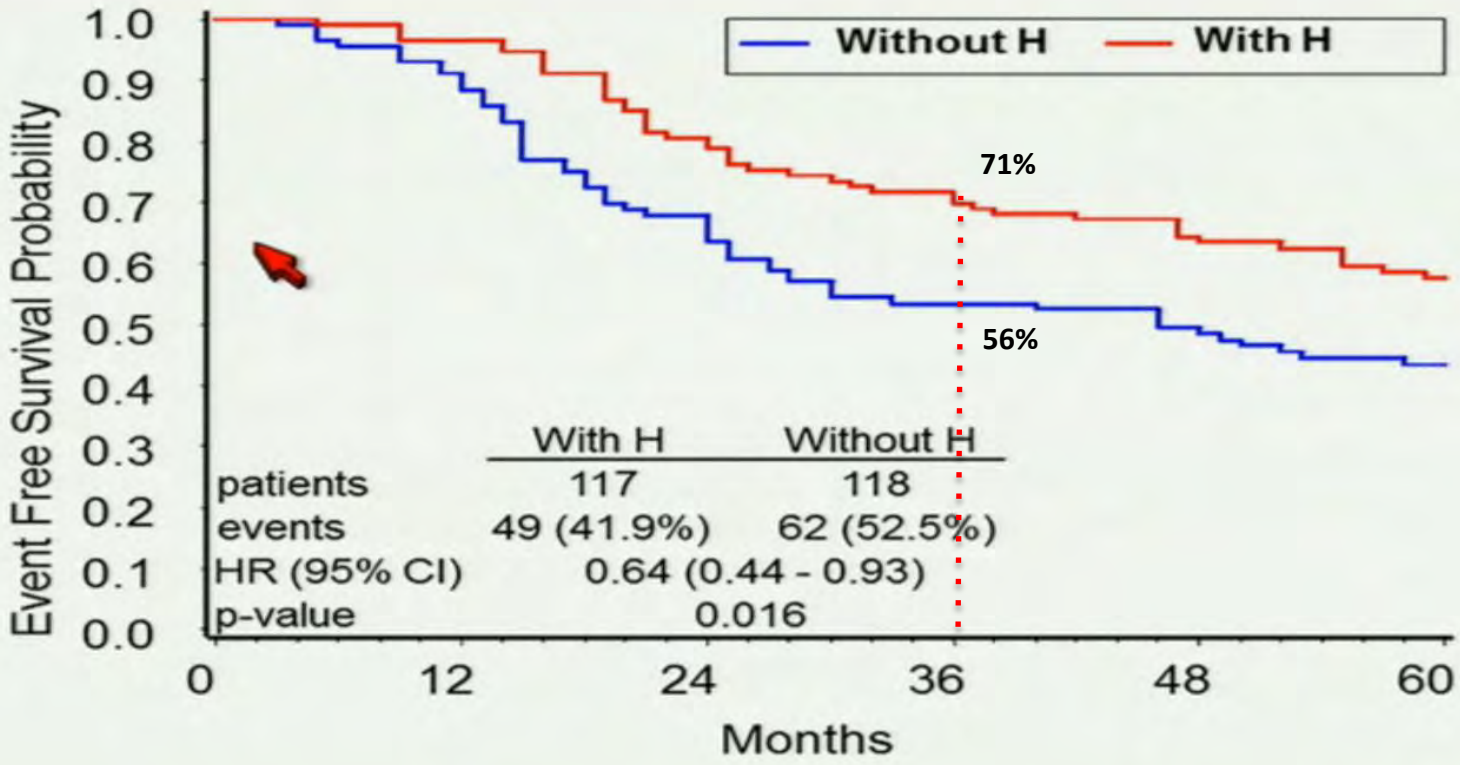


*p-value for HER2-pos with H vs w/o H; **p-value for HER2-pos vs HER2-neg

L. Gianni et al, Lancet 2010

Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort

EFS in HER2-positive ITT population

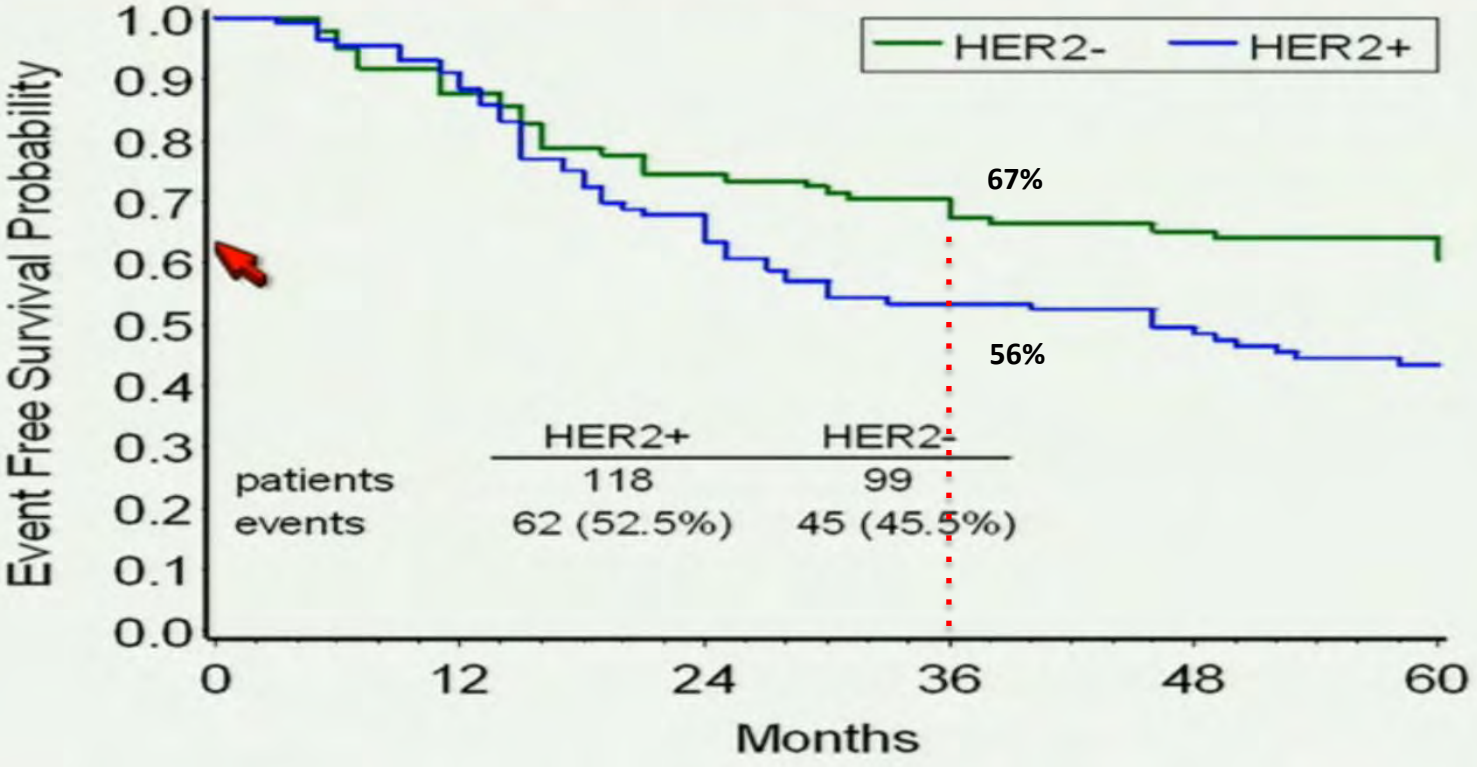


Gianni L. Lancet Vol 375 January 30, 2010

Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort

Luca Gianni, Wolfgang Eiermann, Vladimir Semiglazov, Alexey Manikhas, Ana Lluch, Sergey Tjulandin, Milvia Zambetti, Federico Vazquez,

EFS in HER2-positive (without trastuzumab) and HER2-negative ITT population



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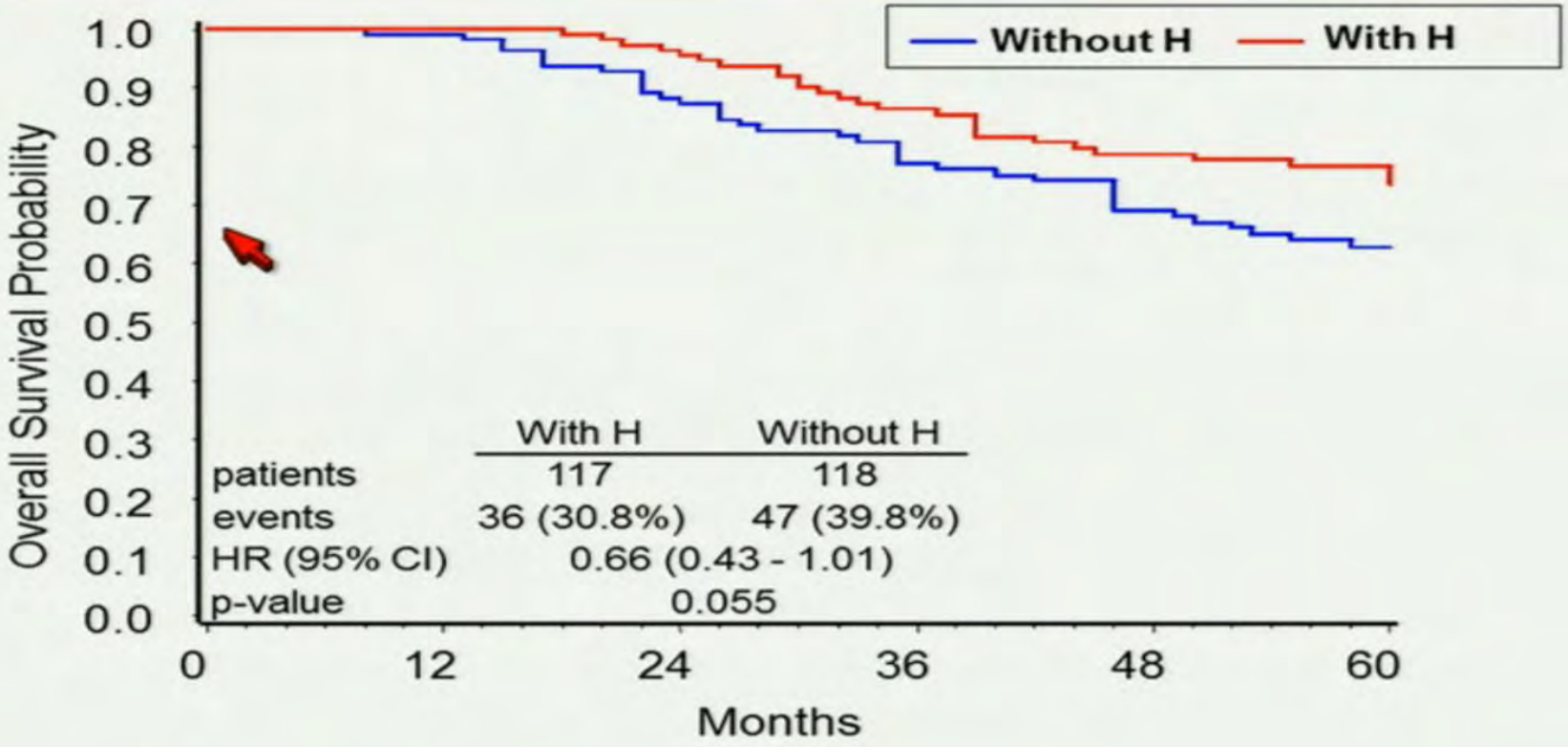
OS in HER2-positive ITT population



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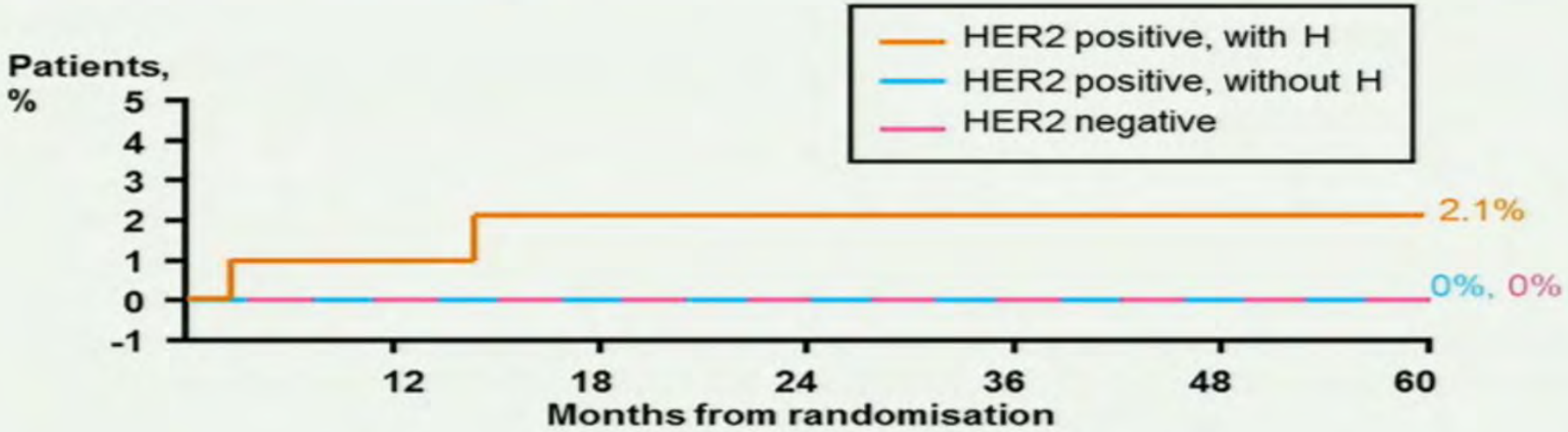
Luca Gianni, Wolfgang Eiermann, Vladimir Semiglazov, Alexey Manikhas, Ana Lluch, Sergey Tjulandin, Milvia Zambetti, Federico Vazquez,

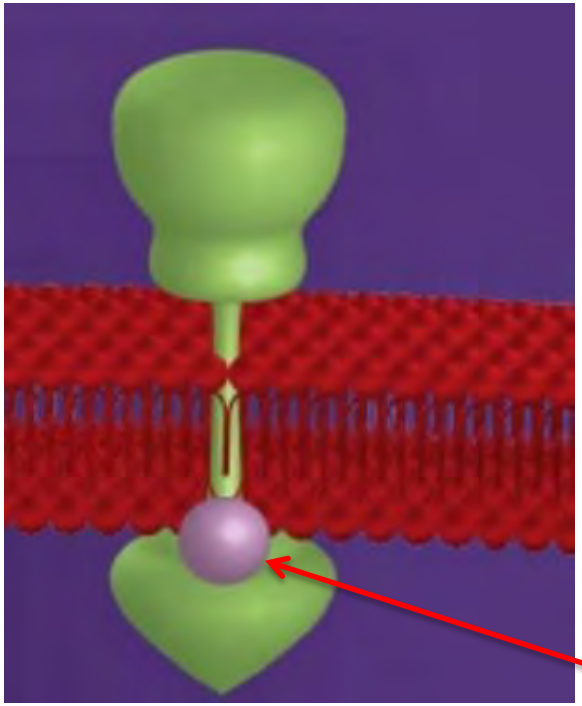
Cumulative incidence of CHF

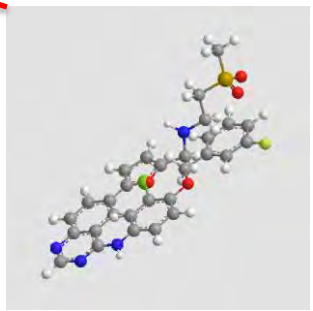


CHF was classified as New York Heart Association grade III

Gianni L. Lancet Vol 375 January 30, 2010

Lapatinib





Small molecule (Tyverb®)

- *Directed toward kinase domain (intracellular target)*
- *Can directly and efficientily inhibit phosphorylation and activation of downstream signalling pathways*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lapatinib plus Capecitabine for HER2-Positive Advanced Breast Cancer

Charles E. Geyer, M.D., John Forster, M.Sc., Deborah Lindquist, M.D.,

- 324 breast cancer pts.
- HER 2 overexpression
- Locally advanced or metastatic
- Failed after TX Anthra Trastuzumab
- Measurable disease
- PS = 0-1
- FE normal range

Capecitabine + Lapatinib

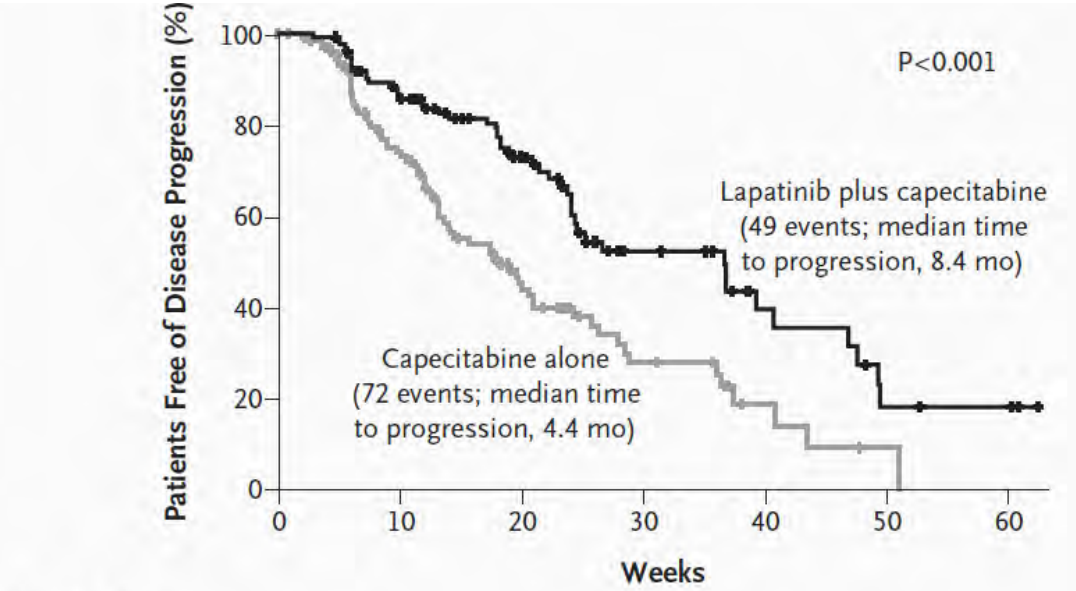
Capecitabine

N Engl J Med 2006;355:2733-43.

Lapatinib plus Capecitabine for HER2-Positive Advanced Breast Cancer

Charles E. Geyer, M.D., John Forster, M.Sc., Deborah Lindquist, M.D.,

Overall Response Rate	
Capecitabine + Lapatinib	22%
Capecitabine	14%



N Engl J Med 2006;355:2733-43.

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Lapatinib or Trastuzumab Plus Taxane Therapy for Human Epidermal Growth Factor Receptor 2–Positive Advanced Breast Cancer: Final Results of NCIC CTG MA.31

Karen A. Gelmon, Frances M. Boyle, Bella Kaufman, David G. Huntsman, Alexey Manikhas, Angelo Di Leo,

- **652 Metastatic breast cancer pts.**
- **HER 2 overexpression**
- **No prior therapy**
- **Measurable disease**
- **PS = 0-2**
- **LVEF > 50%**

Taxane + Lapatinib

Taxane + Trastuzumab

J Clin Oncol 33, 2015

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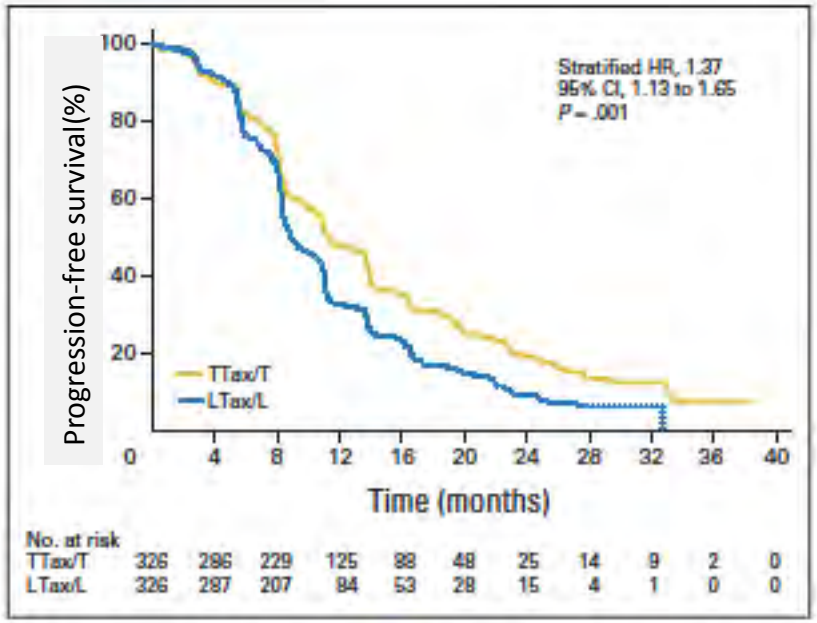
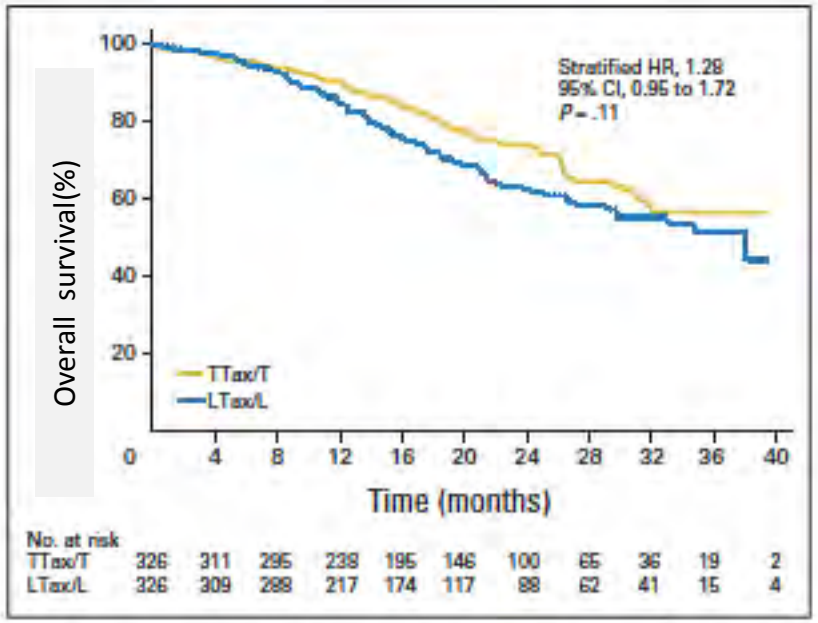




J Clin Oncol 33, 2015

Studies with anti HER 2 molecules plus hormonal therapy in the first line metastatic breast cancer

- ***Hormonal therapy and trastuzumab represent one of the oldest and one of the newest treatment modalities for BC, respectively.***
- ***Recent data have suggested that HER2 overexpression is associated with resistance to hormonal therapy and there is considerable preclinical evidence to support the existence of interaction or cross talk between HER2 and estrogen-receptor signalling pathways in BC***
- ***a range of clinical trials showed the addition of trastuzumab to hormonal therapy provide BC patients with benefits in clinical practice.***
- ***For patients with bone-only spreading disease and indolent disease progression, the combination of anti-HER2 and endocrine therapy as first-line treatment represents a valid therapeutic option.***

Studies with anti HER 2 molecules plus hormonal therapy in the first line metastatic breast cancer

Author	*N.* of patients	Treatment	PFS (months)	OS (months)	Response Rate (%)
Kaufman et al. 2009 (TANDEM study)	207	Anastrozole 1 mg po daily + T iv (4 mg/kg loading dose, then 2 mg/kg weekly)	4.8	28.5	21
		Anastrozole 1 mg po daily	2.4 ($p = 0.002$)	23.9 ($p = 0.325$)	7 ($p = 0.018$)
Huober et al. 2012 (ELECTRA)	92	Letrozole 2.5 mg po daily + T iv (4 mg/kg loading dose, then 2 mg/kg weekly)	14.1	NR	27
		Letrozole 2.5 mg po daily	3.3 ($p = 0.23$)	NR	13 ($p = 0.002$)
Johnston et al. 2009 (EGF30008)	263	Letrozole 2.5 mg po + Lapatinib 1500 mg po daily	8.2	33.3	28
		Letrozole 2.5 mg po + placebo po daily	3.0 ($p = 0.019$)	32.3 ($p = 0.113$)	15 ($p = 0.021$)

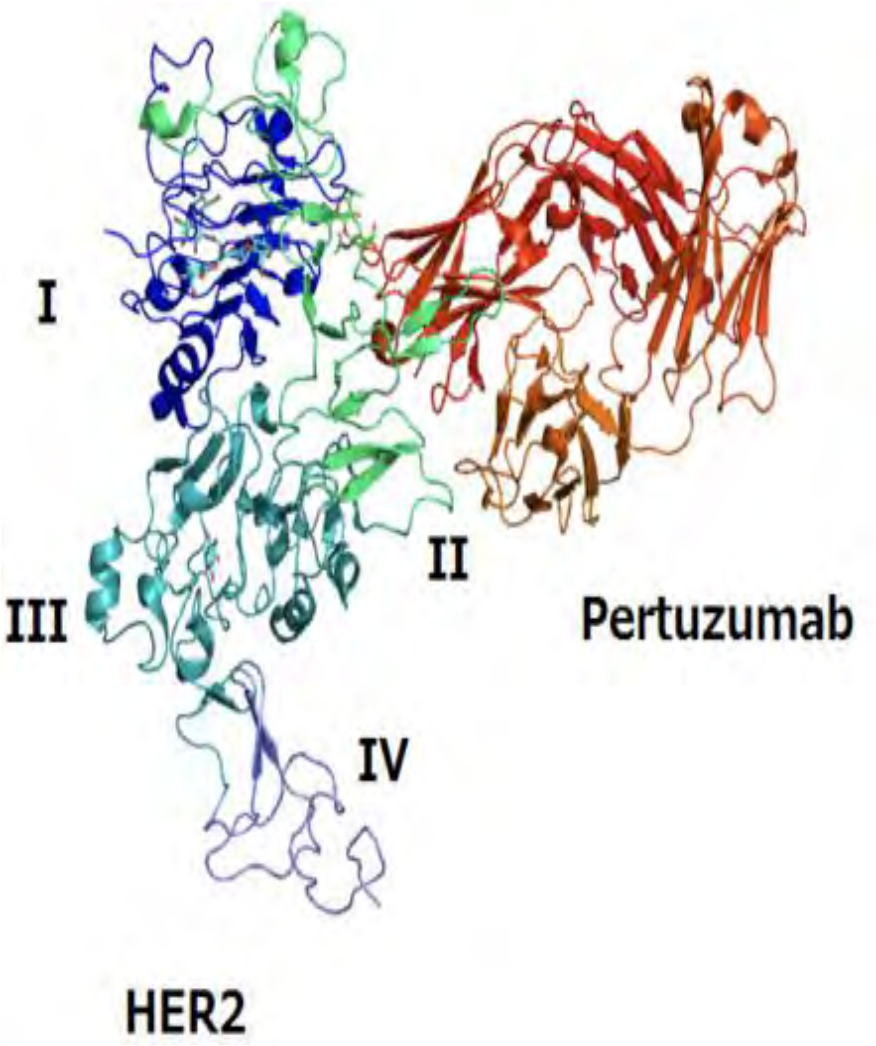
PFS progresson free survival, *OS* overall survival, *T* trastuzumab

The HER 2 Blockage :the old story Conclusions

- *Trastuzumab plus chemotherapy (Taxanes , Vinorelbine, Anthracyclines, Carboplatin) is the recommended first-line combination for Her2 metastastic breast cancer patients*
- *Trastuzumab plus endocrine therapy represents a valid therapeutic option as first-line treatment for Her2 and Er positive patients with indolent disease progression*
- *Chemotherapy plus Trastuzumab (prolonged for one year) is the recommendend combination in the adjuvant setting*
- *Chemotherapy with trastuzumab (prolonged for one year postoperatively) is the recommended combination in the neoadjuvant setting*
- *Lapatinib plus Capecitabine is the recommended second line combination*

The HER 2 Blockage
The new story

Pertuzumab

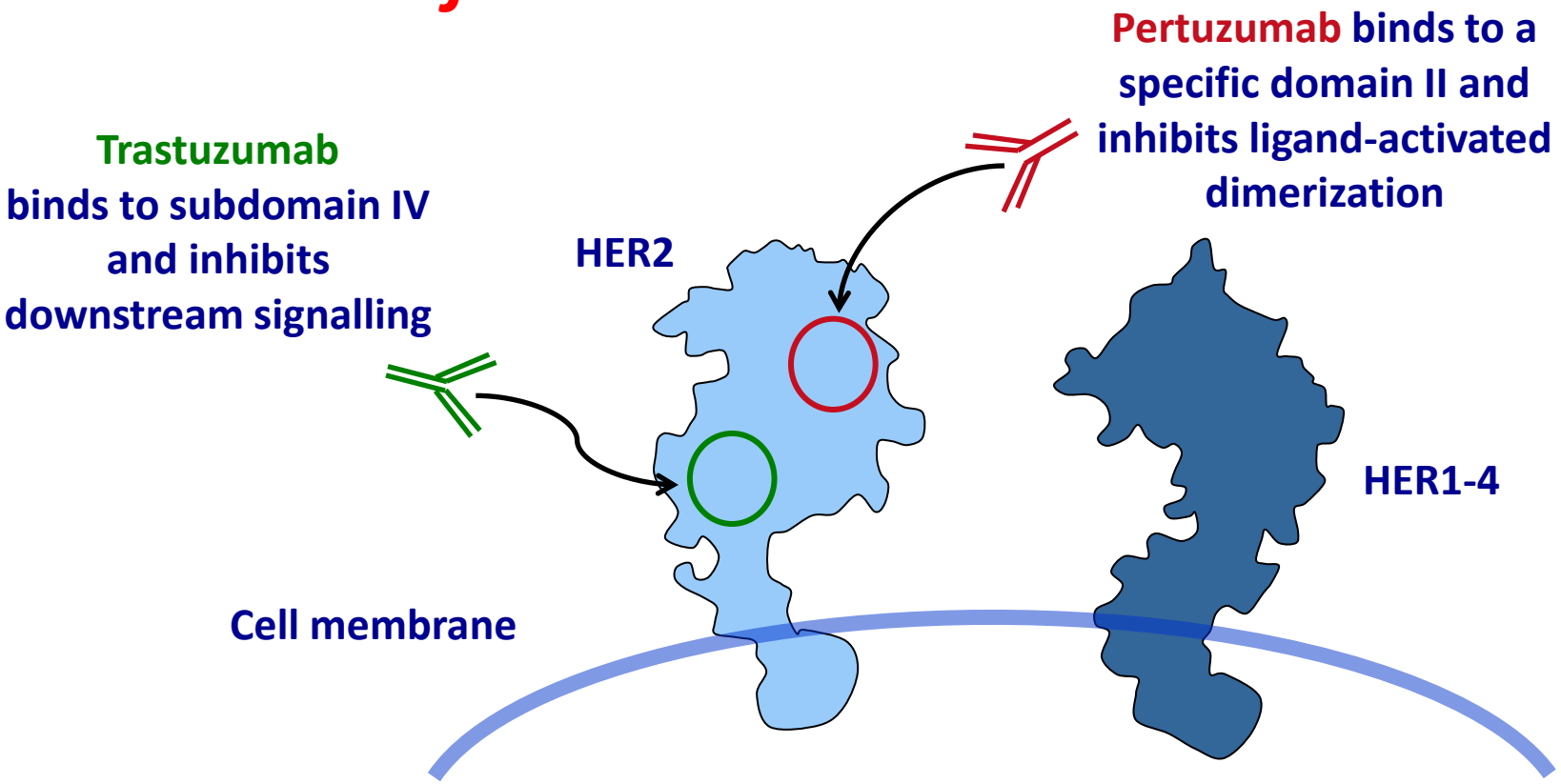


- **A humanized recombinant monoclonal antibody directed against the extracellular dimerization domain of the HER-2 tyrosine kinase receptor**
- **Brand name: Perjeta**
- **FDA and EMA approved for the first line treatment of Her2 positive breast cancer patients**

Pertuzumab

- ***Pertuzumab binds to ErbB2 near the center of domain II, sterically blocking a binding pocket necessary for receptor dimerization and signaling***
- ***Pertuzumab binding mediates the same antibody-dependent cytotoxic effects as trastuzumab binding***
- ***Trastuzumab and pertuzumab bind to different epitopes in the the extracellular domain of ErbB2***

Pertuzumab and Trastuzumab: Mechanisms of Action

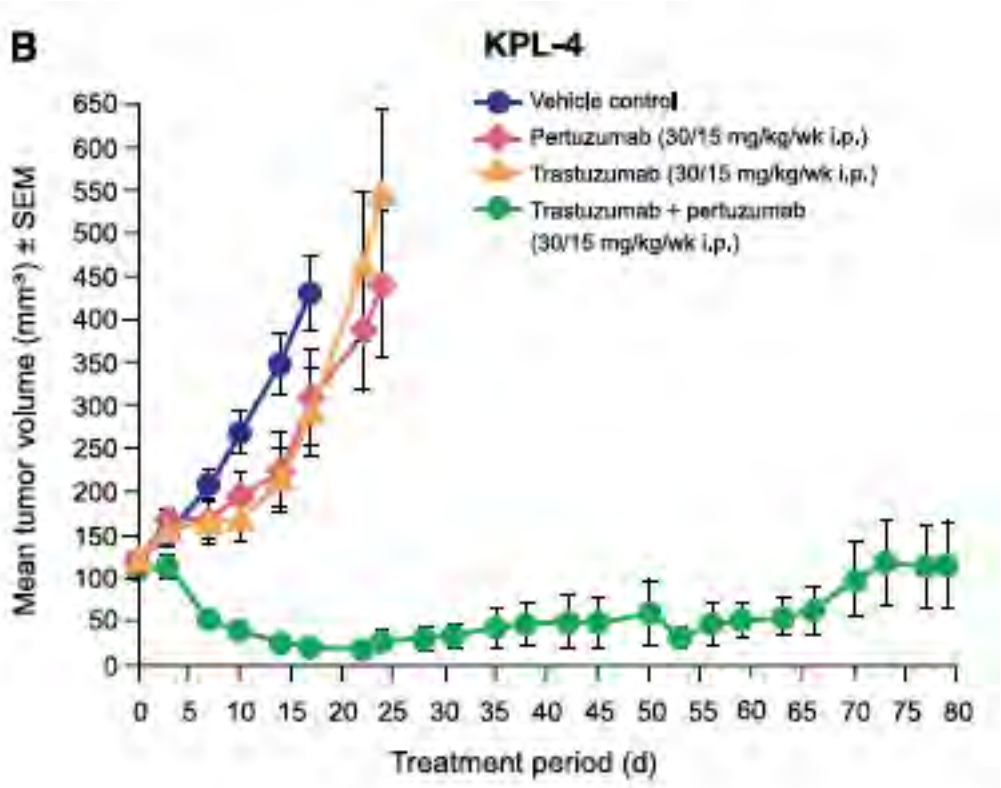


The combined regimen of pertuzumab and trastuzumab offers the potential for a more comprehensive HER blockade

Franklin MC, et al. *Cancer Cell*. 2004;5(4):317-328.

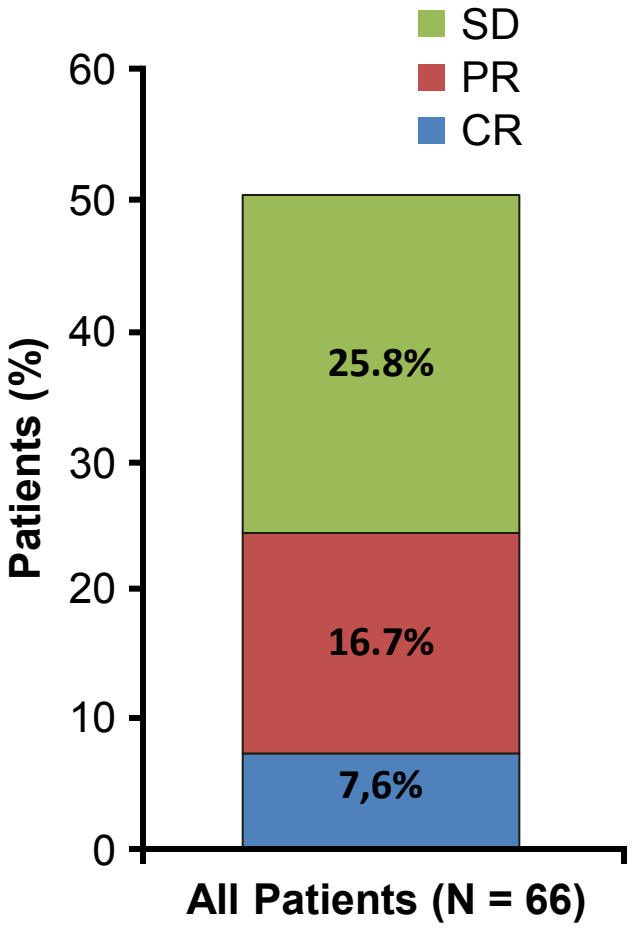
Trastuzumab + Pertuzumab: preclinical data

- *Preclinical data show that the combination of trastuzumab and pertuzumab has a strongly enhanced antitumor effect and induces tumor regression in Her2 positive breast cancer xenograft models,something that cannot be achieved by either monotherapy.*
- *The enhanced efficacy of the combination was also observed after tumor progression during trastuzumab monotherapy*



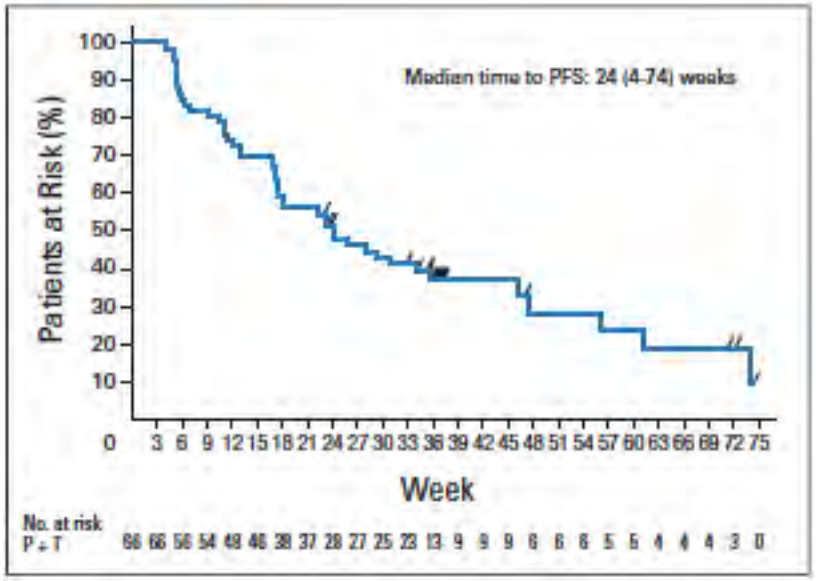
Scheuer W. Cancer Res 2009;69(24):9330–6]

Phase II Trial of Pertuzumab and Trastuzumab in Patients With Human Epidermal Growth Factor Receptor 2–Positive Metastatic Breast Cancer That Progressed During Prior Trastuzumab Therapy



Responses were durable:

- **Median duration of response: 5.8 mos**



- **Cardiac dysfunction was minimal, and no patients withdrew as a result of cardiac-related adverse events**

Baselga J, et al. J Clin Oncol. 2010;28:1138-1144.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pertuzumab, Trastuzumab, and Docetaxel in HER2-Positive Metastatic Breast Cancer

Sandra M. Swain, M.D., José Baselga, M.D., Sung-Bae Kim, M.D., Jungsil Ro, M.D.,

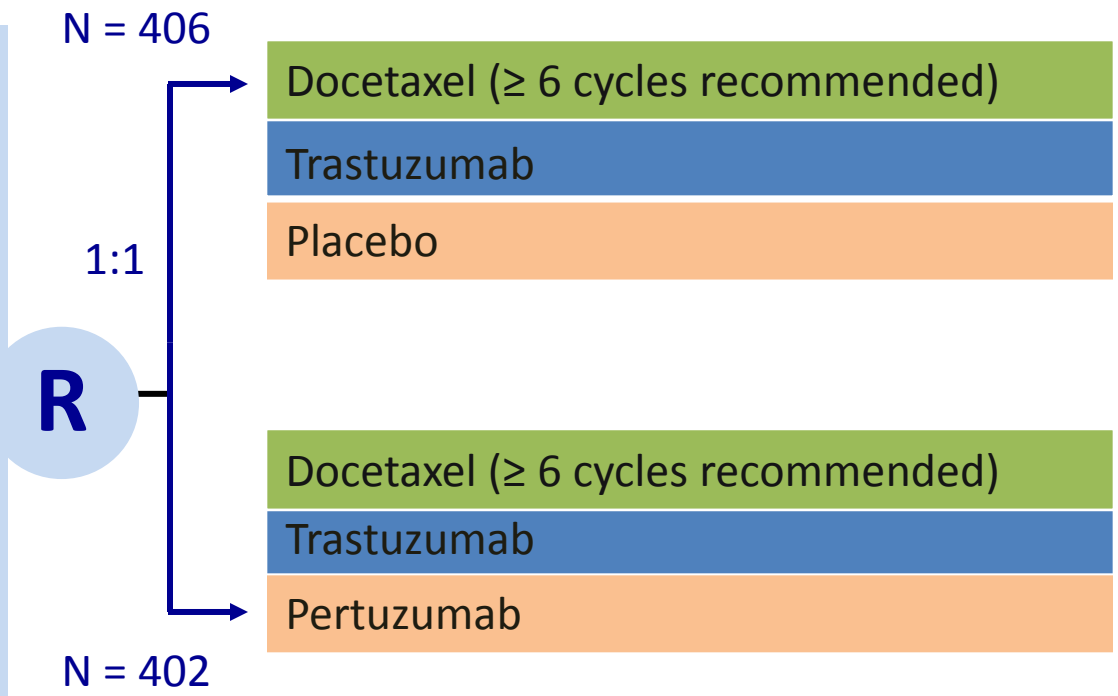
CLEOPATRA Study Design

Centrally confirmed HER2-positive locally recurrent, unresectable or MBC

≤ 1 hormonal regimen for MBC

Prior (neo)adjuvant systemic Rx, including trastuzumab and/or taxane allowed if followed by DFS ≥ 12 mos

Baseline LVEF ≥ 50%; no CHF or LVEF < 50% during or after previous trastuzumab



Primary endpoint: Independently assessed PFS

N Engl J Med 2015;372:724-34.

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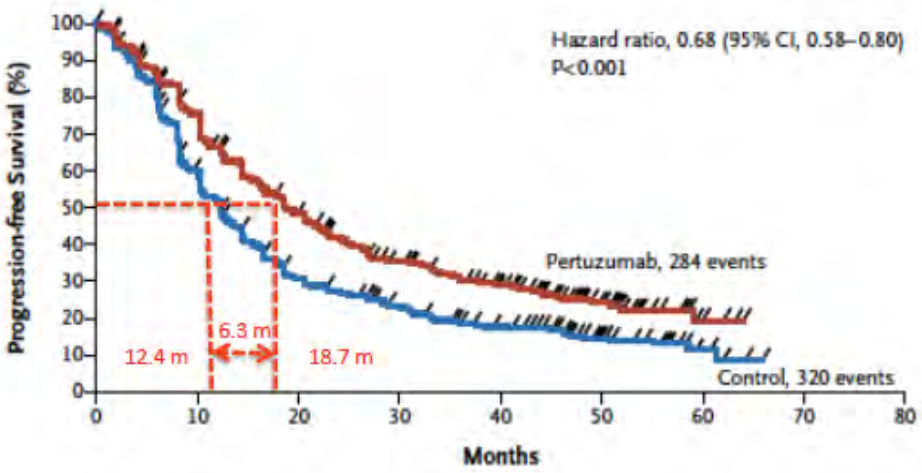

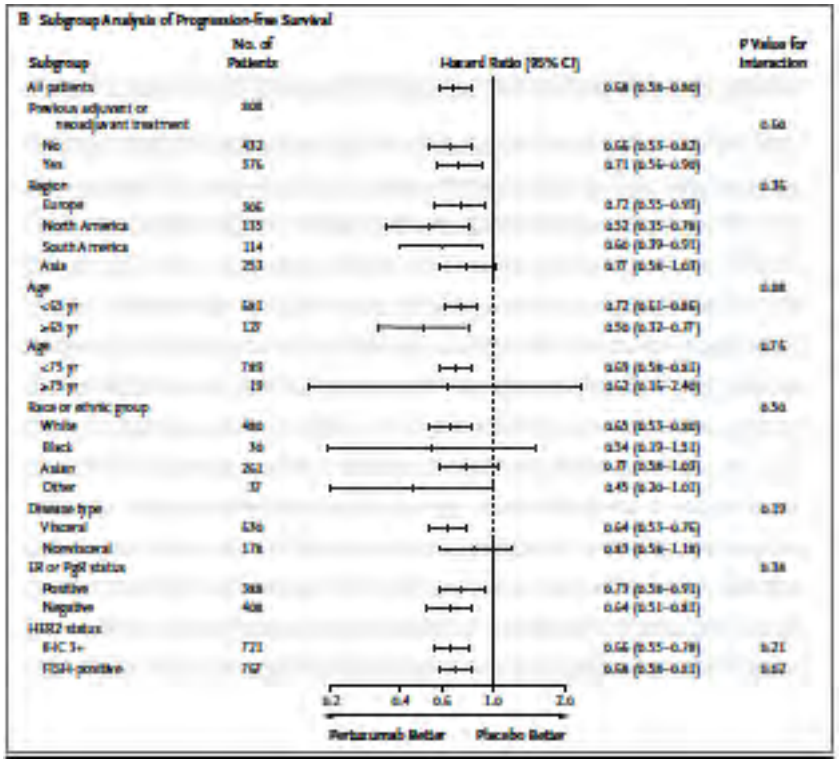

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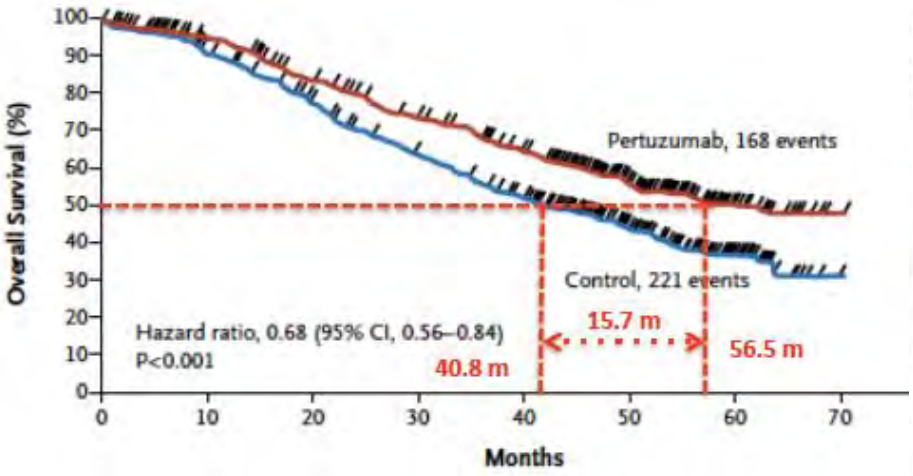
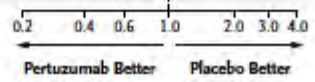


B Subgroup Analysis of Overall Survival

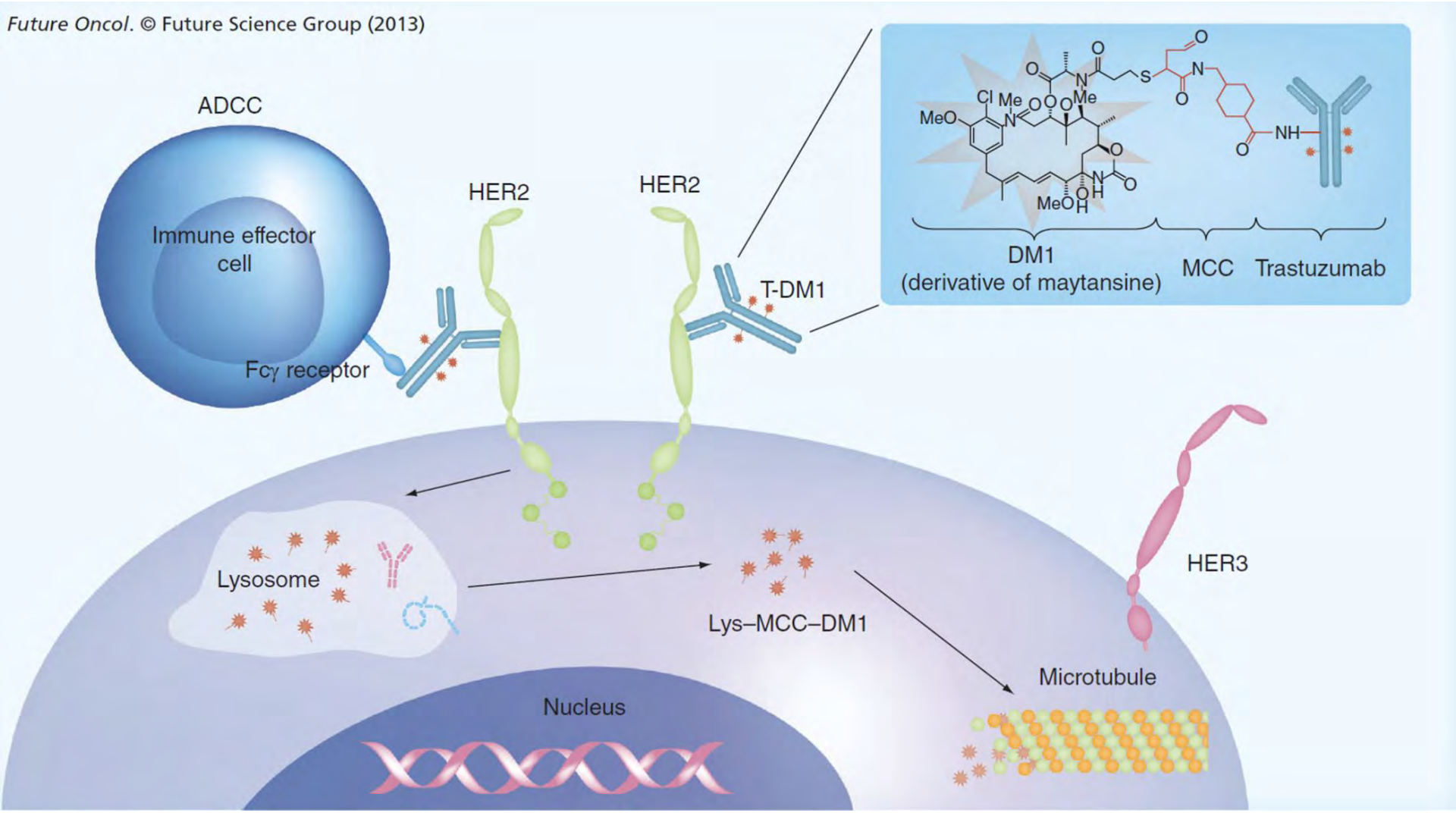
Subgroup	No. of Patients	Hazard Ratio (95% CI)	P Value for Interaction
All patients	808	0.67 (0.55–0.82)	
Previous adjuvant or neoadjuvant treatment			0.63
No	432	0.64 (0.48–0.85)	
Yes	376	0.70 (0.53–0.93)	
Region			0.36
Europe	306	0.65 (0.47–0.91)	
North America	135	0.63 (0.37–1.07)	
South America	114	0.50 (0.30–0.85)	
Asia	253	0.82 (0.57–1.16)	
Age			0.27
<65 yr	681	0.70 (0.56–0.87)	
≥65 yr	127	0.53 (0.31–0.90)	
Age			0.84
<75 yr	789	0.68 (0.55–0.83)	
≥75 yr	19	0.85 (0.26–2.73)	
Race or ethnic group			0.40
White	480	0.63 (0.49–0.82)	
Black	30	0.41 (0.11–1.45)	
Asian	261	0.82 (0.58–1.17)	
Other	37	0.37 (0.13–1.06)	
Disease type			0.03
Visceral	630	0.59 (0.48–0.74)	
Nonvisceral	178	1.11 (0.66–1.85)	
ER or PgR status			0.47
Positive	388	0.71 (0.53–0.96)	
Negative	408	0.61 (0.47–0.81)	
HER2 status			
IHC 3+	721	0.66 (0.53–0.81)	0.52
FISH-positive	767	0.69 (0.56–0.85)	0.14



N Engl J Med 2015;372:724-34.

Second-line and Further Therapy
TDM-1

Trastuzumab/Emtansine (TDM1): Novel Antibody–Drug Conjugate



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 8, 2012 VOL. 367 NO. 19

Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer

Sunil Verma, M.D., David Miles, M.D., Luca Gianni, M.D., Ian E. Krop, M.D., Ph.D., Manfred Welslau, M.D.,

EMILIA TRIAL

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

Patients with HER2-positive locally advanced or MBC* (N = 991)

T-DM1 3.6 mg/kg by IV every 3 wks
(n = 495)

→ *PD*

Capecitabine 1000 mg/m^2 orally twice daily on Days 1-14, every 3 wks +
Lapatinib 1250 mg/day orally continuously
(n = 496)

*All pts received previous taxane and trastuzumab

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

NEJM 2012;367:1783-91.

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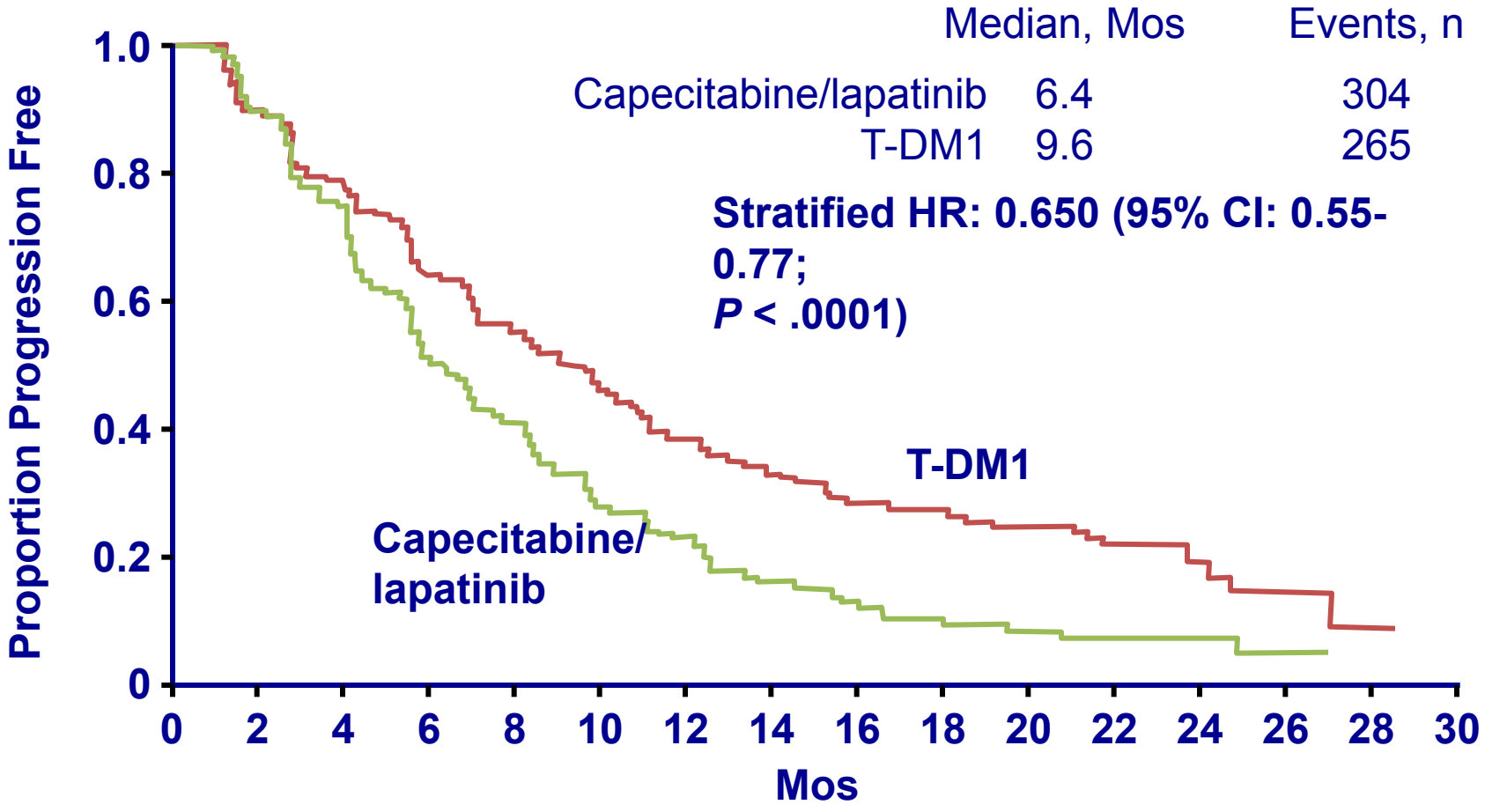

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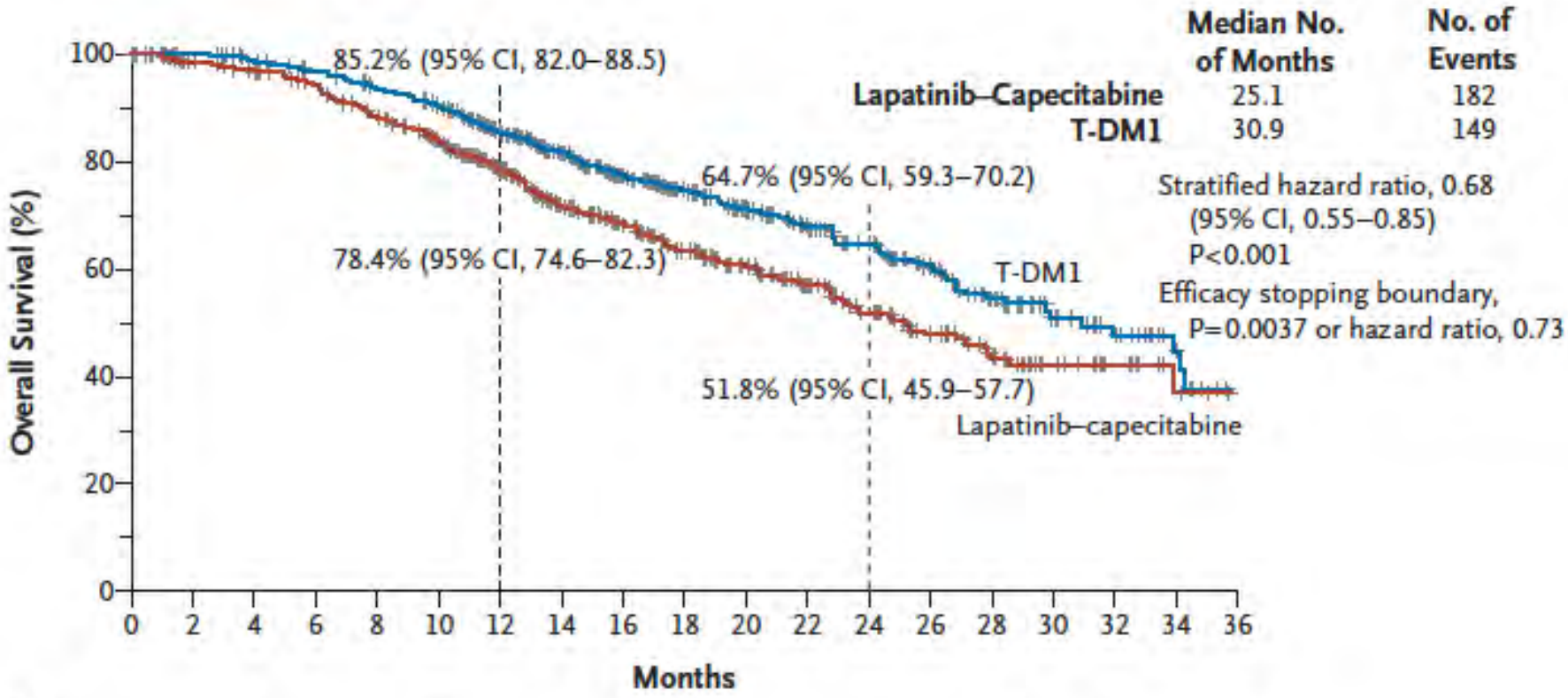

No. at Risk

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

NEJM 2012;367:1783-91.

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EMILIA TRIAL

Table 2. Objec

Variable
Complete or p
No. of pat
Percent (9
Complete resp
Partial respon
Duration of cc respon
Median
95% CI

Table 3. Adverse Events in the Safety Population.*

Adverse Event	Lapatinib plus Capecitabine (N=488)		T-DM1 (N=490)	
	Events of Any Grade	Events of Grade 3 or Above	Events of Any Grade	Events of Grade 3 or Above
	number of patients (percent)			
Any event	477 (97.7)	278 (57.0)	470 (95.9)	200 (40.8)
Specific events†				
Diarrhea	389 (79.7)	101 (20.7)	114 (23.3)	8 (1.6)
Palmar–plantar erythrodysesthesia	283 (58.0)	80 (16.4)	6 (1.2)	0
Vomiting	143 (29.3)	22 (4.5)	93 (19.0)	4 (0.8)
Neutropenia	42 (8.6)	21 (4.3)	29 (5.9)	10 (2.0)
Hypokalemia	42 (8.6)	20 (4.1)	42 (8.6)	11 (2.2)
Fatigue	136 (27.9)	17 (3.5)	172 (35.1)	12 (2.4)
Nausea	218 (44.7)	12 (2.5)	192 (39.2)	4 (0.8)
Mucosal inflammation	93 (19.1)	11 (2.3)	33 (6.7)	1 (0.2)
Anemia	39 (8.0)	8 (1.6)	51 (10.4)	13 (2.7)
Elevated ALT	43 (8.8)	7 (1.4)	83 (16.9)	14 (2.9)
Elevated AST	46 (9.4)	4 (0.8)	110 (22.4)	21 (4.3)
Thrombocytopenia	12 (2.5)	1 (0.2)	137 (28.0)	63 (12.9)

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- ***T-DM1 showed improved efficacy vs capecitabine plus lapatinib***
  - ***Significant PFS improvement (HR: 0.650; P < .0001)***
  - ***OS benefit (HR: 0.68; P =<0.001)***
- ***Favorable safety profile***
- ***T-DM1 is an important new therapeutic option for patients with HER2+ MBC that has been previously treated with trastuzumab.***

NEJM 2012;367:1783-91.

Is there a role for TDM1 as first line chemotherapy in HER 2 MBC?

Phase III, Randomized Study of Trastuzumab Emtansine ± Pertuzumab vs Trastuzumab + Taxane for First-line Treatment of HER2-positive MBC: Primary Results from the MARIANNE Study

Paul Anthony Ellis

MARIANNE Study Design

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

N = 1095

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

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

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

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

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

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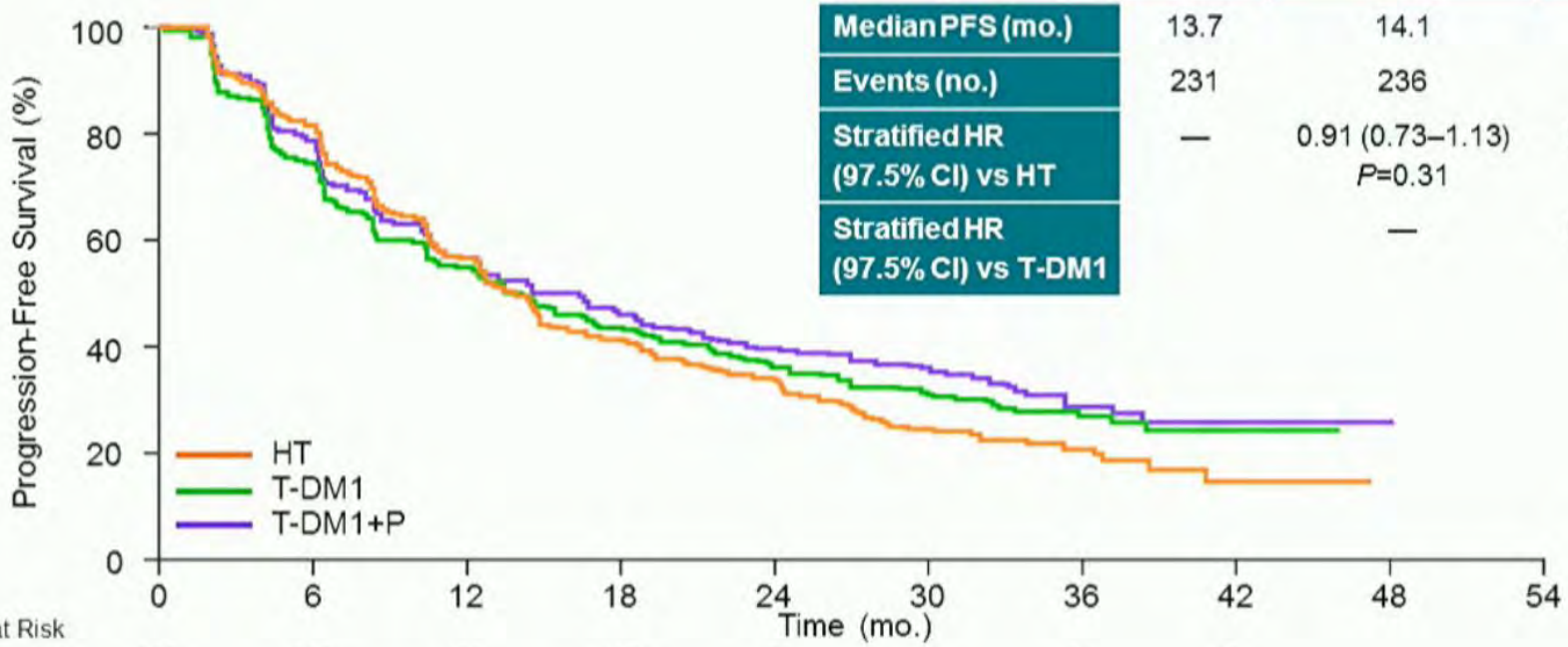
Progression-Free Survival by IRF

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



No. at Risk								
HT	365	265	163	107	75	50	21	5
T-DM1	367	257	176	133	104	67	28	3
T-DM1+P	363	261	177	135	109	75	25	5	1

PRESENTED AT: ASCO Annual '15 Meeting

Phase III, Randomized Study of Trastuzumab Emtansine ± Pertuzumab vs Trastuzumab + Taxane for First-line Treatment of HER2-positive MBC: Primary Results from the MARIANNE Study

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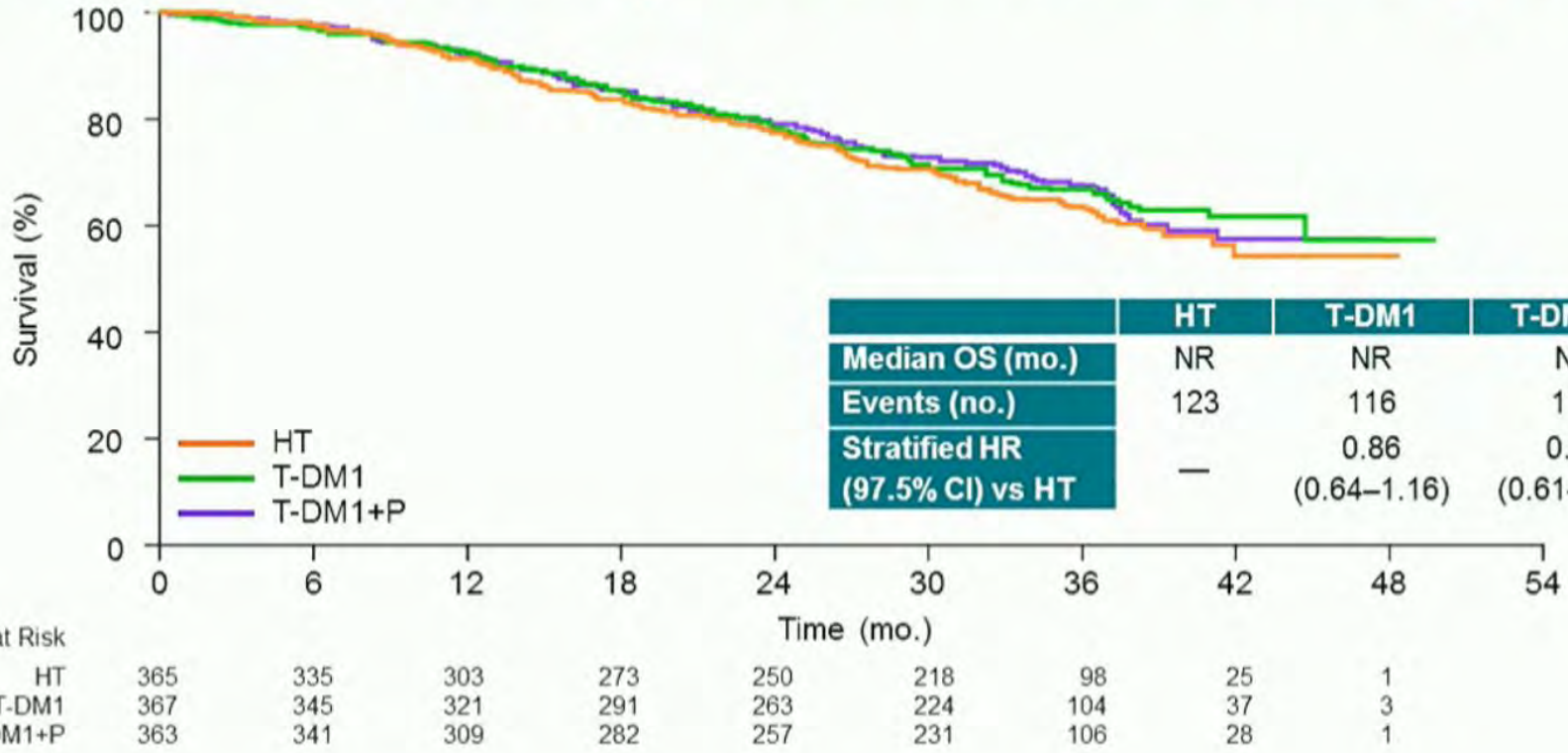
Overall Survival (First Interim Analysis)



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

No. at Risk

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

NR, not reached.

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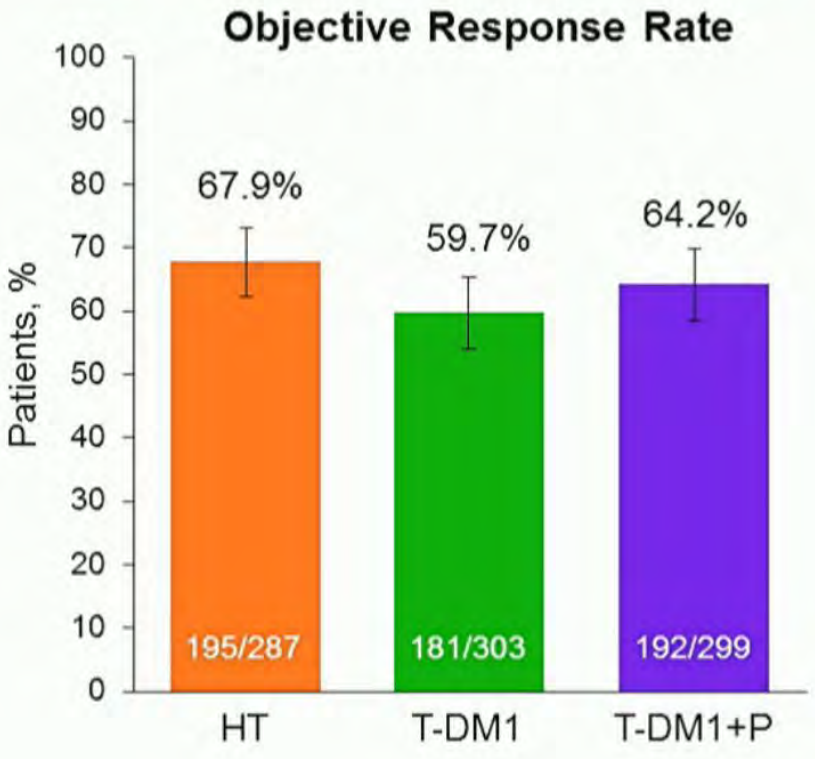
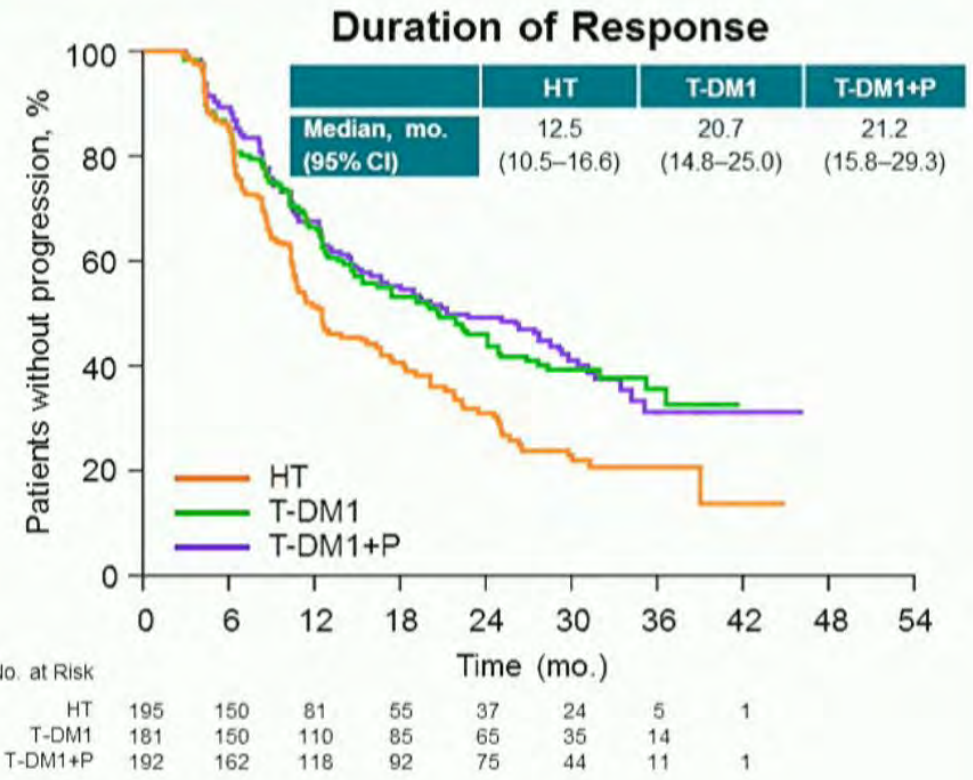
Objective Response and Duration of Response by IRF





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Phase III, Randomized Study of Trastuzumab Emtansine ± Pertuzumab vs Trastuzumab + Taxane for First-line Treatment of HER2-positive MBC: Primary Results from the MARIANNE Study

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Overview of Adverse Events

	HT (n = 353)	T-DM1 (n = 361)	T-DM1+P (n = 366)
Any AE, %	98.6	98.9	98.6
Grade ≥3 AE, %	54.1	45.4	46.2
AE leading to death, %	1.7	1.1	1.9
AE leading to discontinuation of any treatment component, %	29.7	18.3	19.1
LVEF <50% and ≥15% point decrease from baseline, %	4.5	0.8	2.5

The HER 2 Blockage :the old story Conclusions

- *Trastuzumab plus chemotherapy (Taxanes , Vinorelbine, Anthracyclines, Carboplatin) is the recommended first-line combination for Her2 metastastic breast cancer patients*
- *Trastuzumab plus endocrine therapy represents a valid therapeutic option as first-line treatment for Her2 and Er positive patients with indolent disease progression*
- *Chemotherapy plus Trastuzumab (prolonged for one year) is the recommendend combination in the adjuvant setting*
- *Chemotherapy with trastuzumab (prolonged for one year postoperatively) is the recommended combination in the neoadjuvant setting*
- *Lapatinib plus Capecitabine is the recommended second line combination*

The HER 2 Blockage :the new story Conclusions

- *Trastuzumab plus Pertuzumab plus chemotherapy (Taxanes) is the recommended first-line combination for Her2 metastastic breast cancer patients*
- *Trastuzumab plus endocrine therapy represents a valid therapeutic option as first-line treatment for Her2 and Er positive patients with indolent disease progression*
- *Chemotherapy plus Trastuzumab (prolonged for one year) is the recommendend combination in the adjuvant setting*
- *Chemotherapy with pertuzumab plus trastuzumab (prolonged for one year postoperatively) is the recommended combination in the neoadjuvant setting*
- *TDM 1 is the second line recommended chemotherapy*
- *Lapatinib plus Capecitabine is the recommended third line combination*

L'algoritmo terapeutico nel carcinoma della mammella Her2 positivo nel 2016

HER 2 pos MBC Pts

1st Line	Trastuzumab + Pertuzumab + CT
2nd Line	TD1
3rd Line	Lapatinib + Capecitabine

HER 2 – Er pos MBC Pts

1st Line	Trastuzumab + Aromatase Inhibitor

HER 2 pos adjuvant

CT + Trastuzumab Prolonged for 1 year

HER 2 pos neo- adjuvant

Trastuzumab + Pertuzumab + CT

Milestones of HER2/anti-HER2 therapies in BC