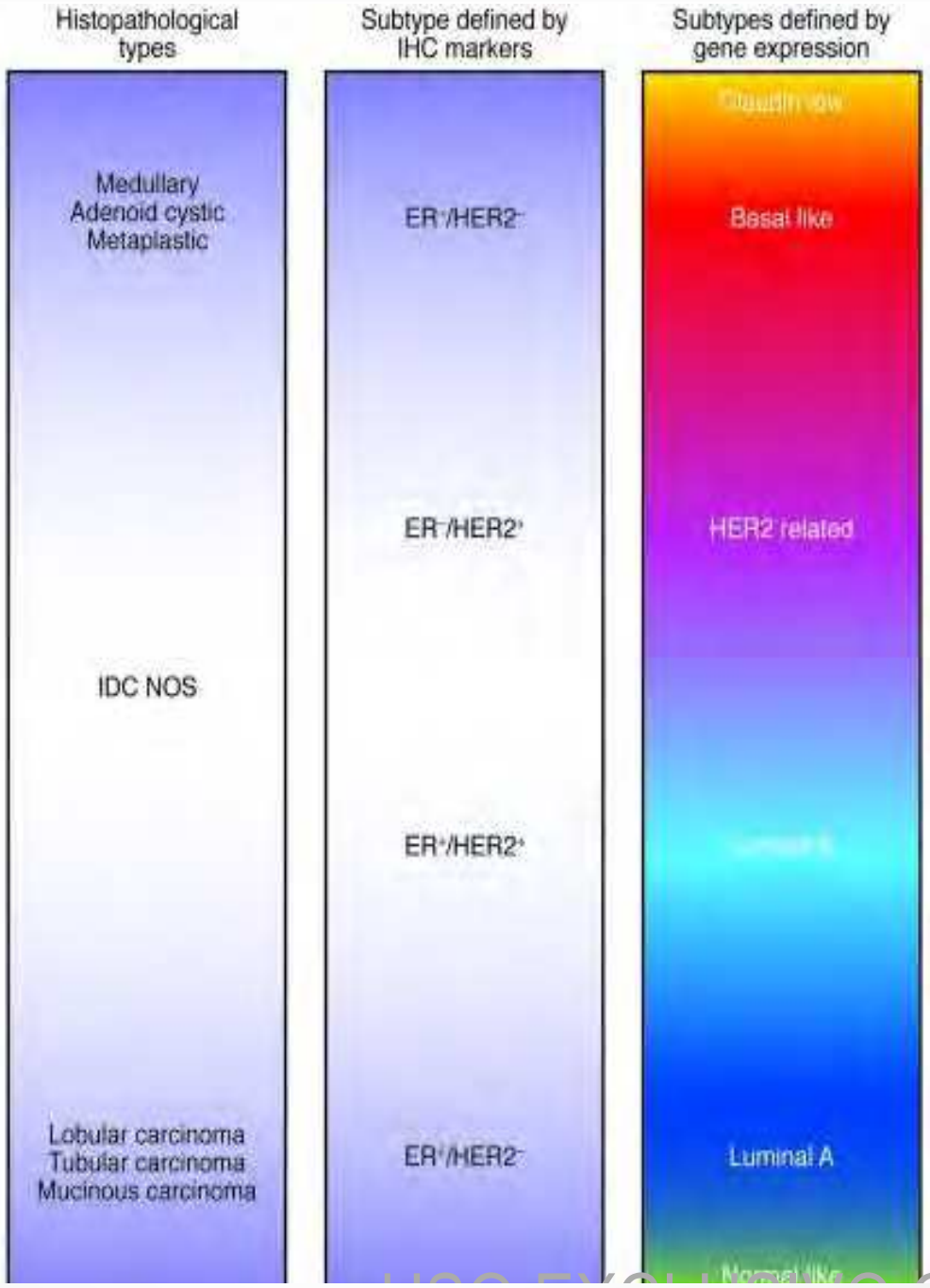
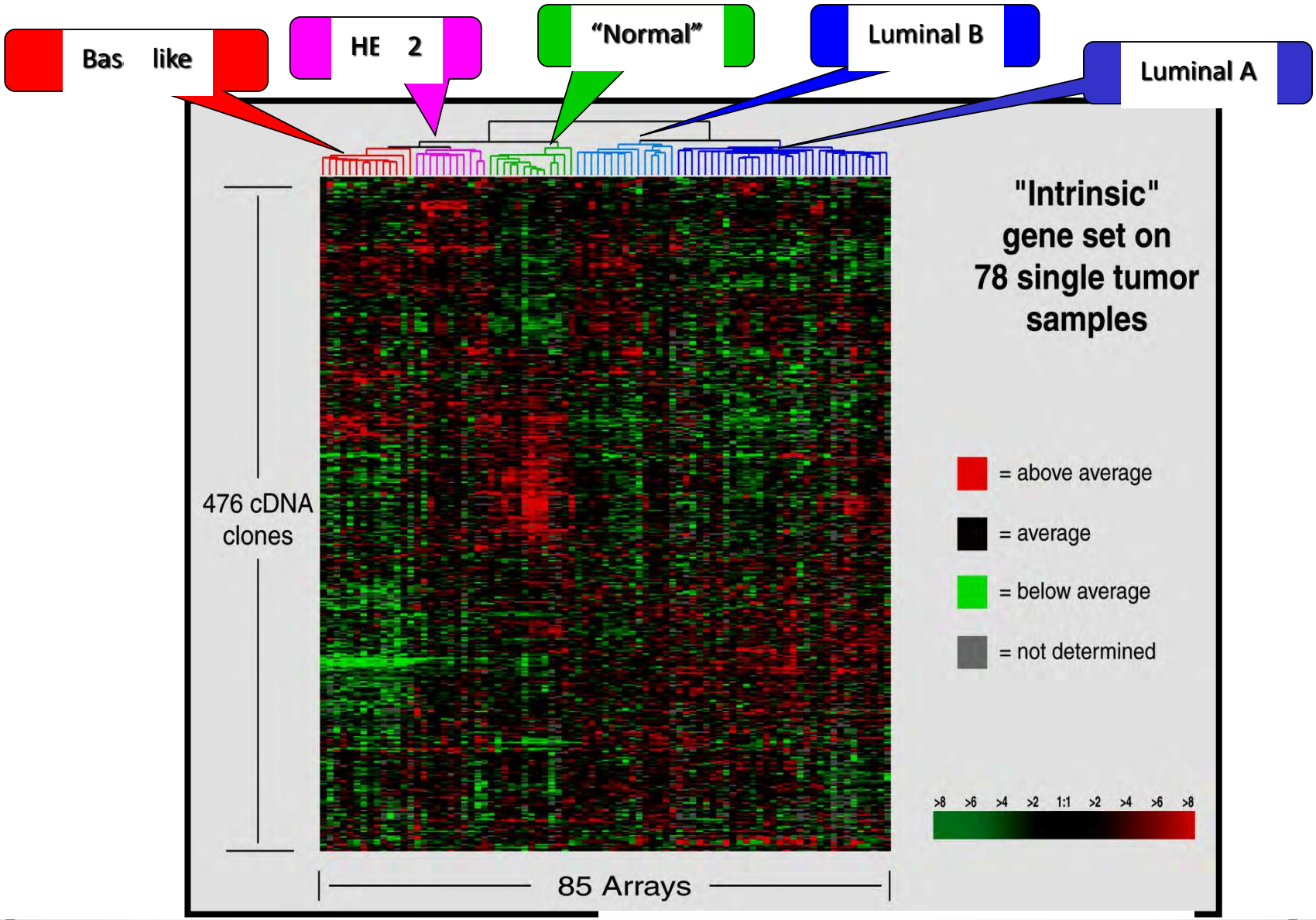
SUBTIPOS MOLECULARES EN CÁNCER DE MAMA: Comportamiento Clínico y Tratamiento dirigido

Silvia Antolín Novoa
Complejo Hospitalario Universitario A Coruña
XVII Reunión anual de la Red de programas de cribado de cáncer
Santiago 11/6/2014


Histopathological types
Subtype defined by IHC markers
Subtypes defined by gene expression
Medullary
Adenoid cystic
Metaplastic
IDC NOS
Lobular carcinoma
Tubular carcinoma
Mucinous carcinoma
ER+/HER2-
ER-/HER2+
ER+/HER2+
ER+/HER2-
Basal like
HER2 related
Luminal A

Molecular Portrait of Breast Cancers

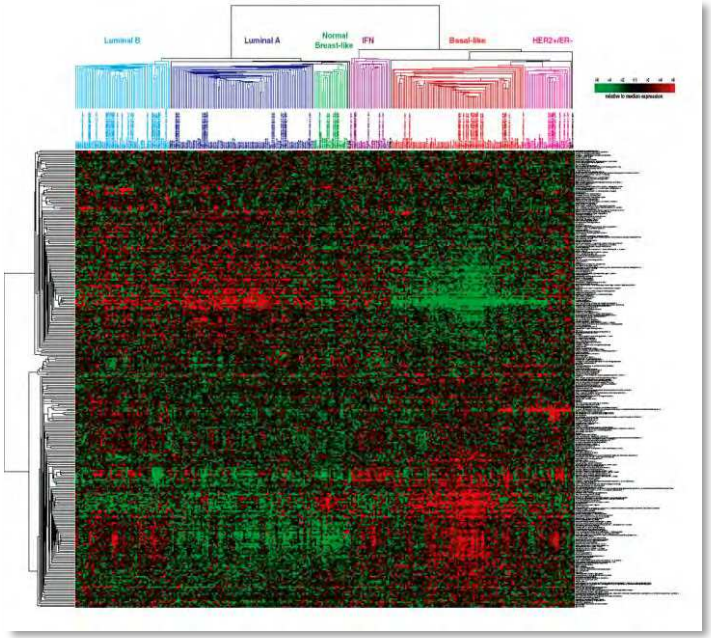


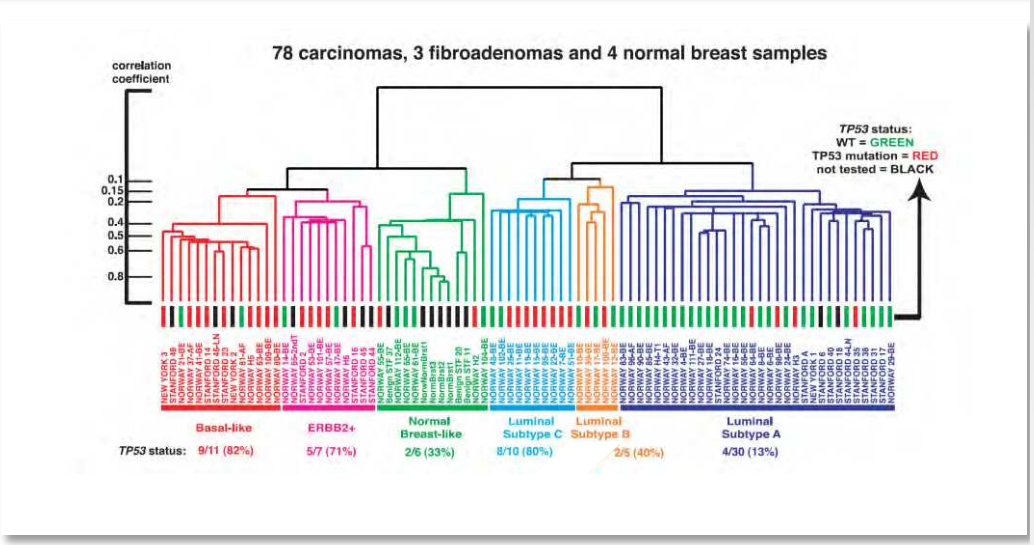
Perou CM, Sorlie T et al . Nature 2000

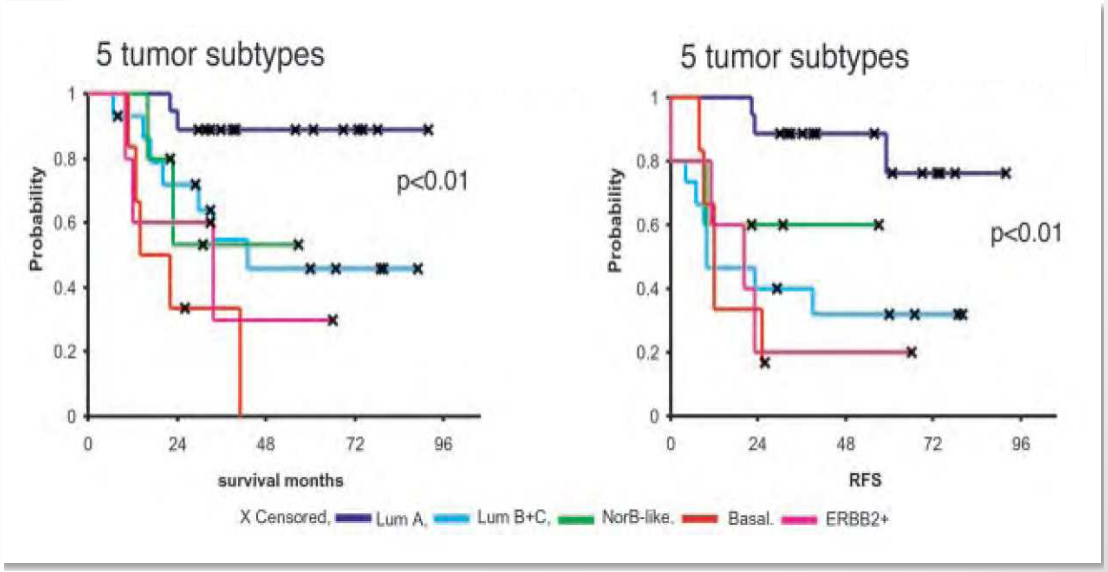
letters to nature

Molecular portraits of human breast tumours

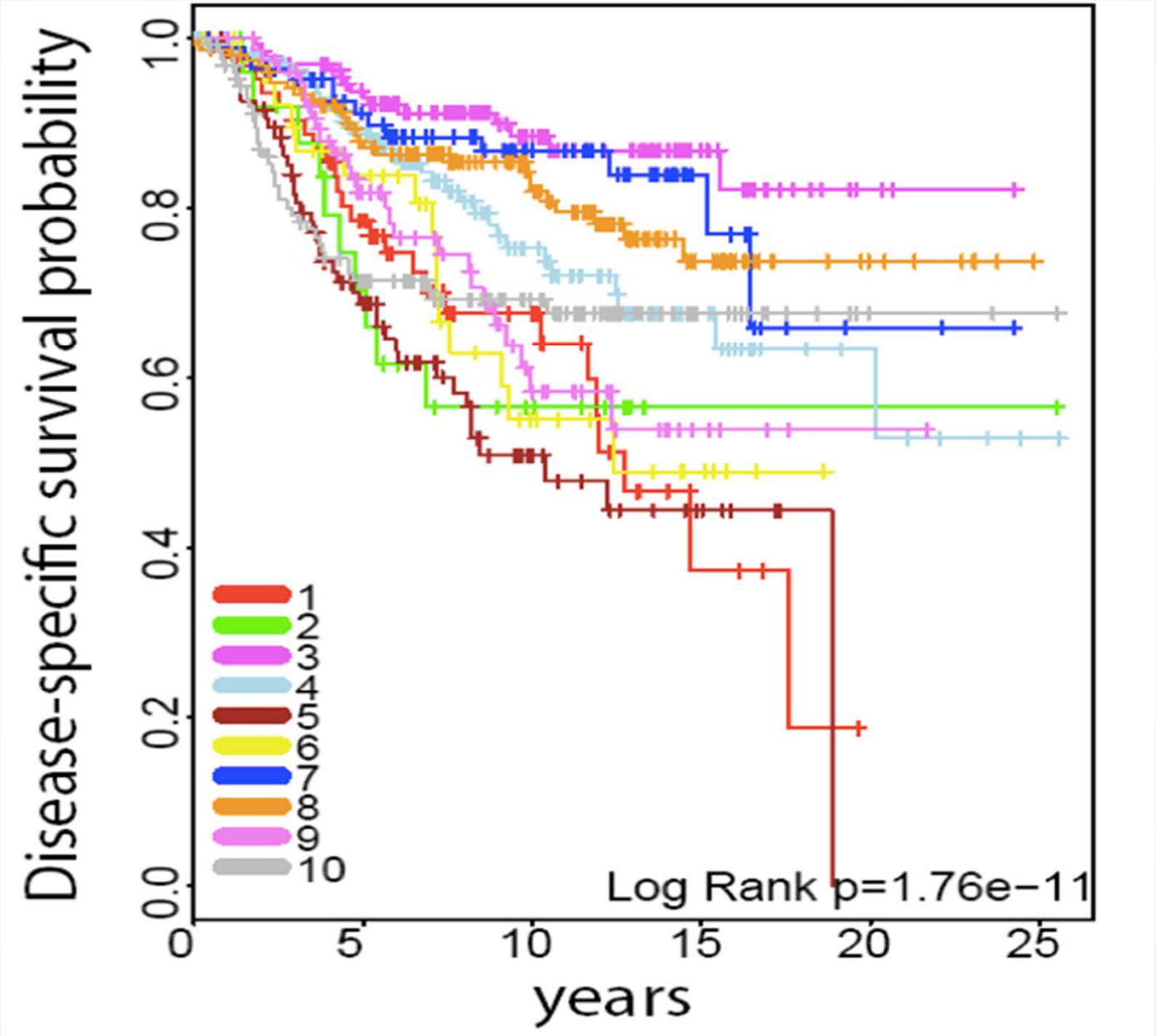
Charles M. Perou*†, Therese Sørlie†‡, Michael B. Eisen*, Matt van de Rijn§, Stefanie S. Jeffrey‖, Christian A. Rees*, Jonathan R. Pollack¶, Douglas T. Ross¶, Hilde Johnsen‡, Lars A. Akslen#, Øystein Fluge☆, Alexander Pergamenschikov*, Cheryl Williams*, Shirley X. Zhu§, Per E. Lønning**, Anne-Lise Børresen-Dale‡, Patrick O. Brown¶†† & David Botstein*



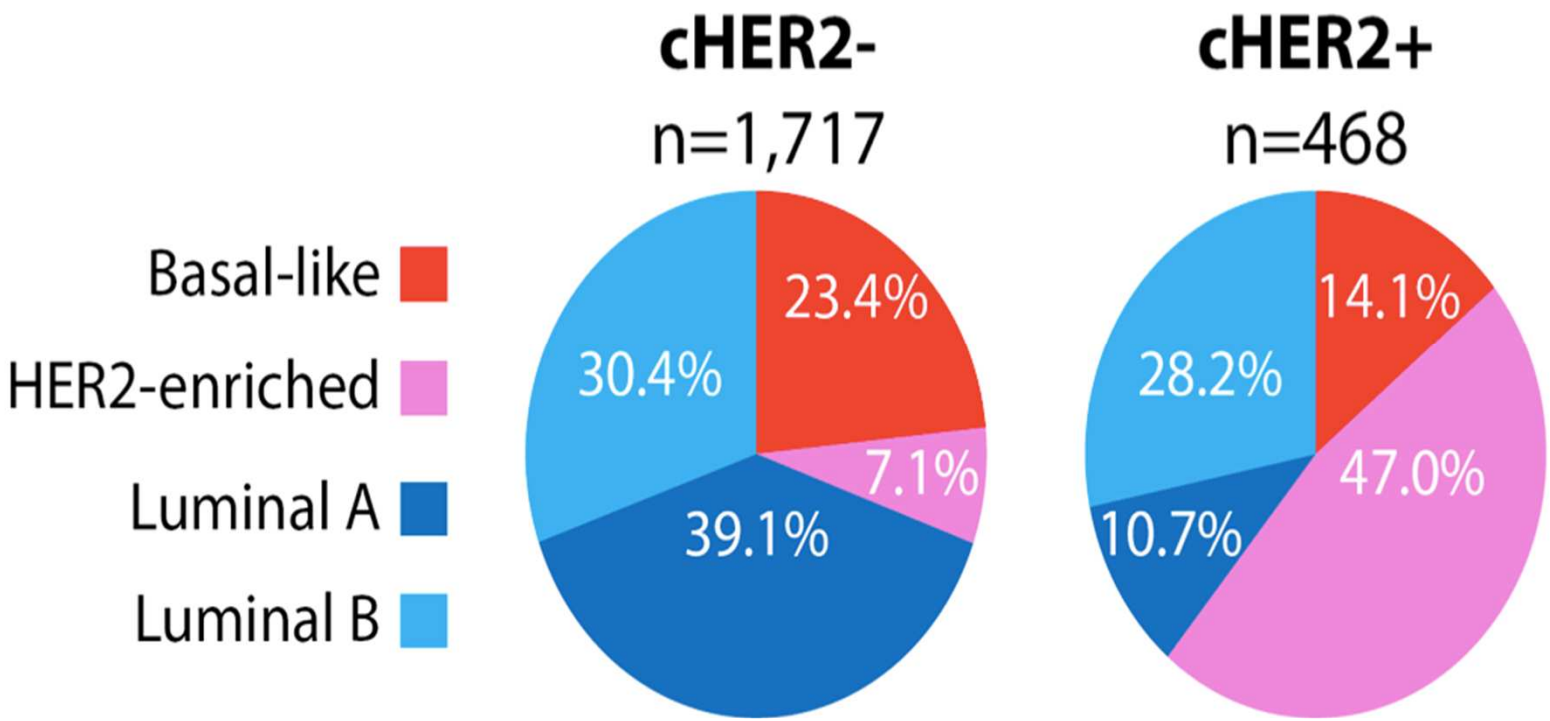




Sorlie, T et al. PNAS, 2001
Perou, CM et al. Nature, 2000
Perreard, L et al. Breast Cancer Res, 2006



Curtis et al, nature 2012

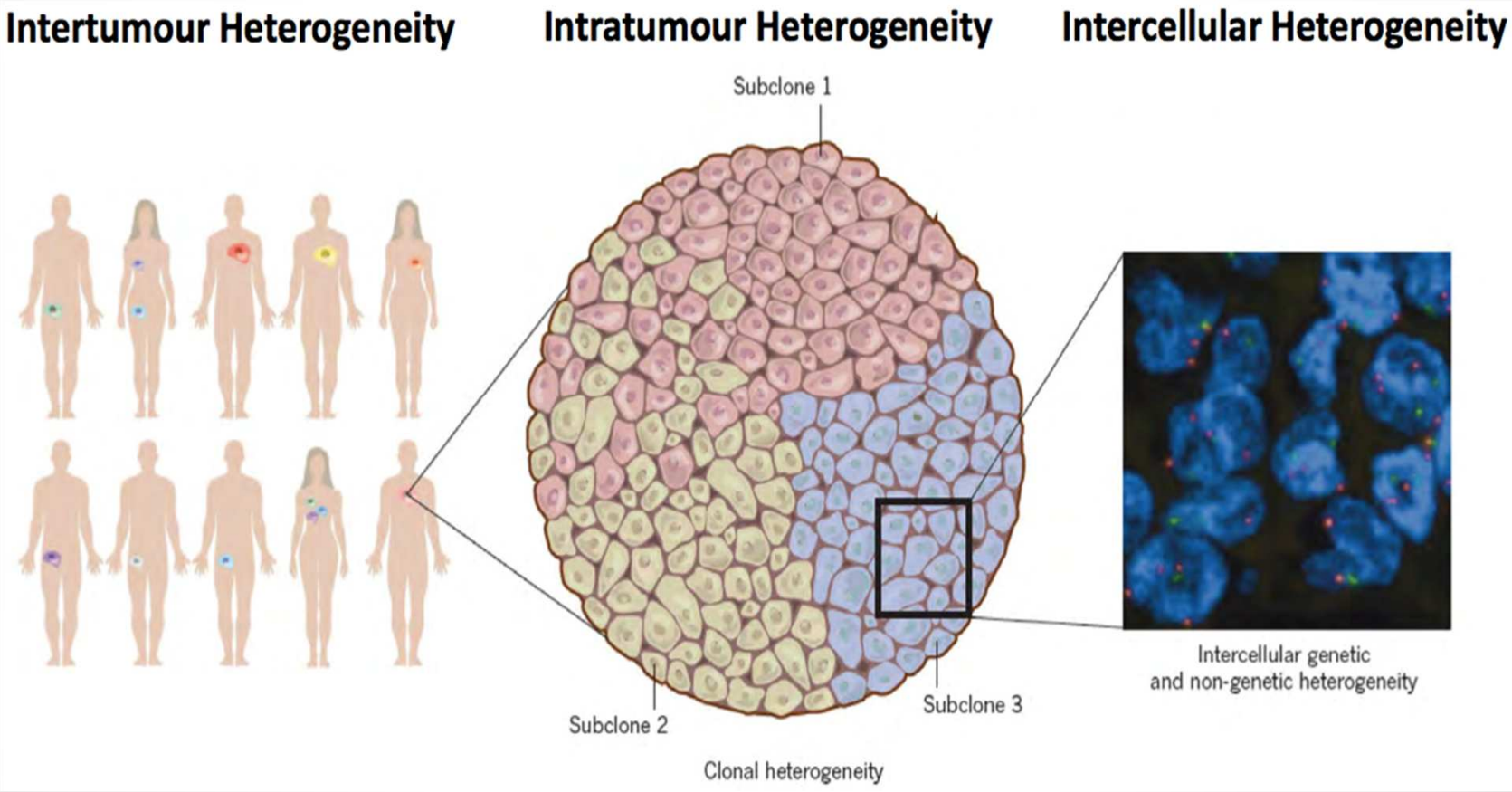


- HER2-positivity enriches 6.62-fold for the **HER2E subtype** and diminishes 3.65-fold and 1.66-fold for the **Luminal A** and **Basal-like** subtypes, respectively.

- The proportion of **Luminal B** tumors based on cHER2 status was not significantly different.

Nature 2012

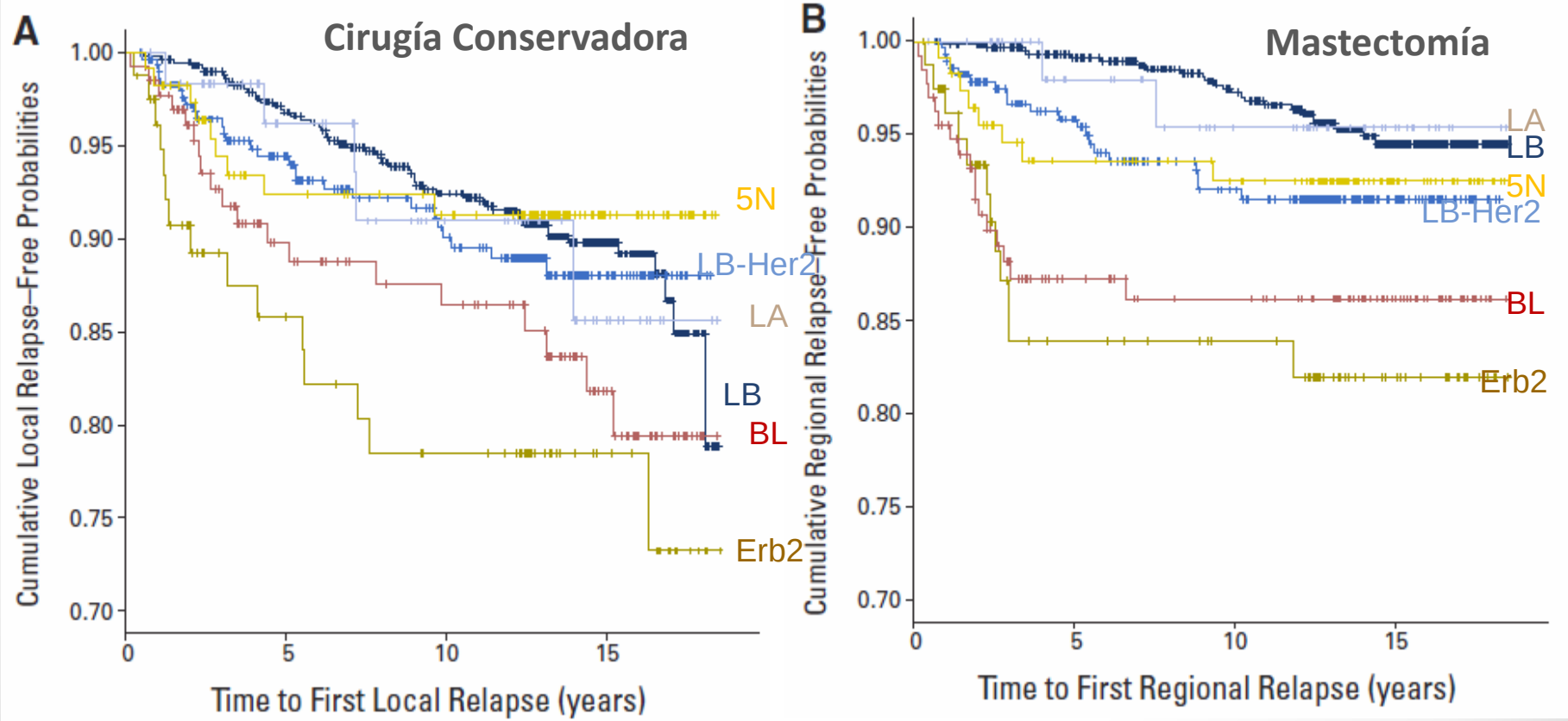
IMPLICATIONS FOR THERAPY AND OUTCOME



VOLUME 28 · NUMBER 10 · APRIL 1 2010
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Breast Cancer Subtypes and the Risk of Local and Regional Relapse

K. David Voduc, Maggie C.U. Cheang, Scott Tyldesley, Karen Gelmon, Torsten O. Nielsen, and Hagen Kennecke



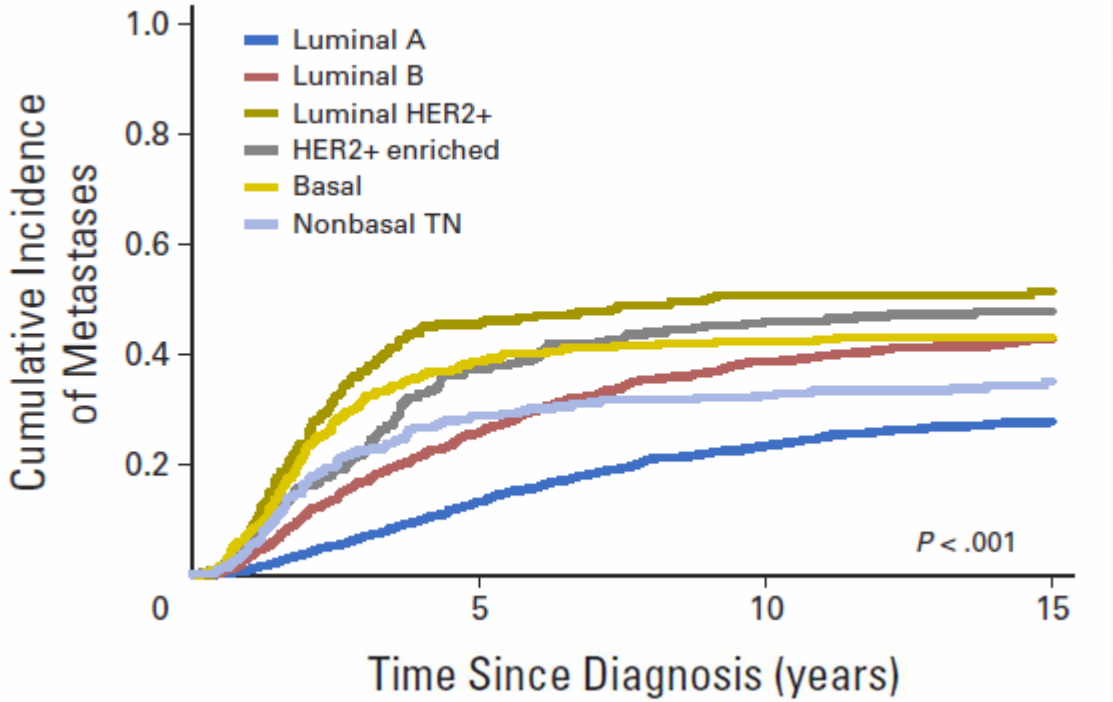
- ✓ **2985 pacientes**
- ✓ **Seguimiento: 12 años**
- ✓ **325 R Locales y 227 R Ganglionares loco-regionales**

VOLUME 28 · NUMBER 20 · JULY 10 2010
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

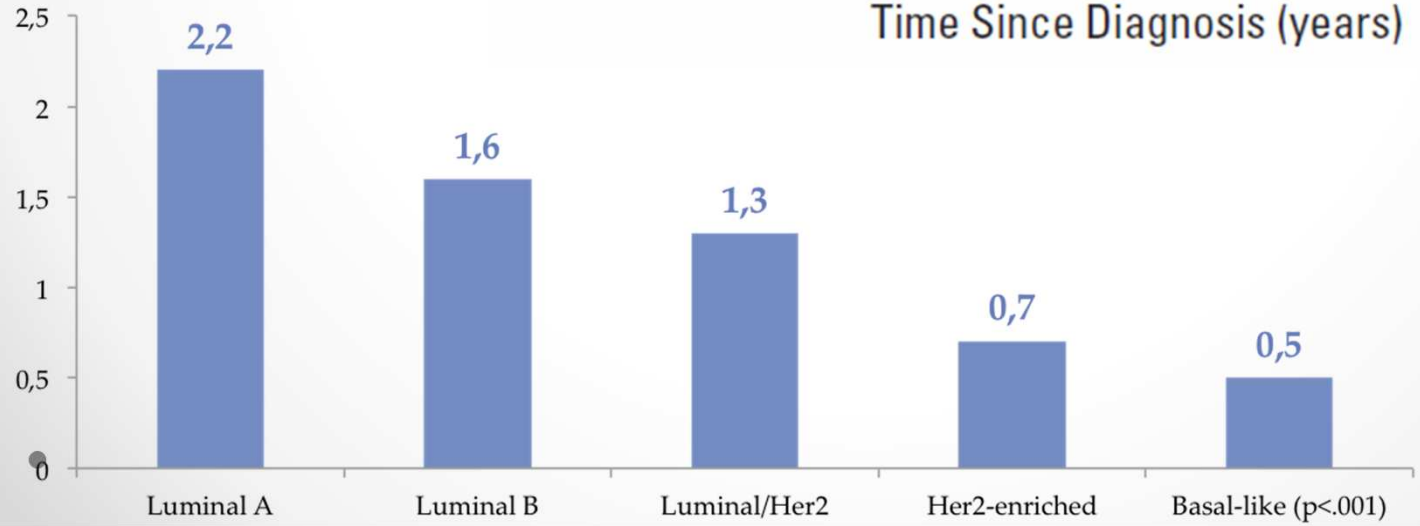
Metastatic Behavior of Breast Cancer Subtypes

Hagen Kennecke, Rinat Yerushalmi, Ryan Woods, Maggie Chon U. Cheang, David Voduc, Caroline H. Speers,

Media de seguimiento es de **14.8** años (n=3726).



Median OS



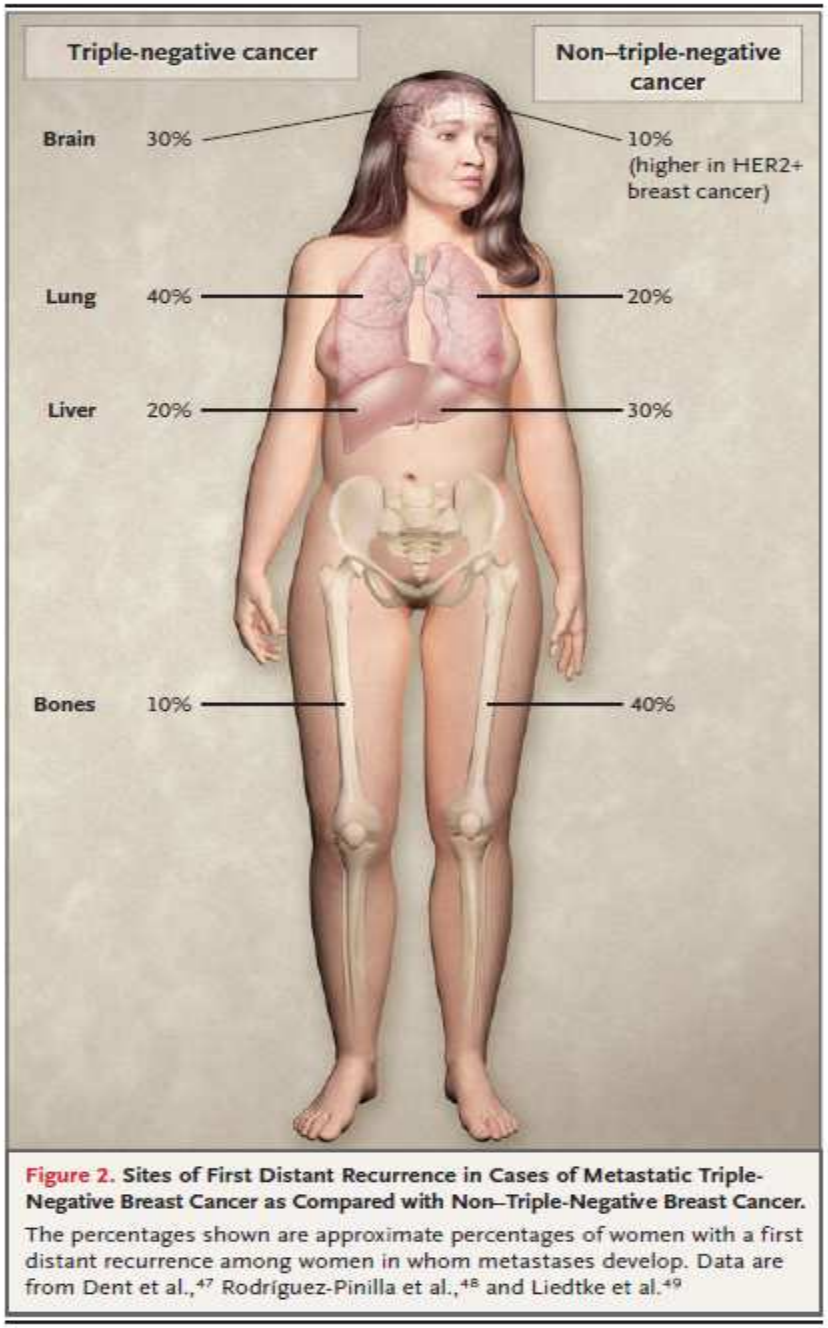
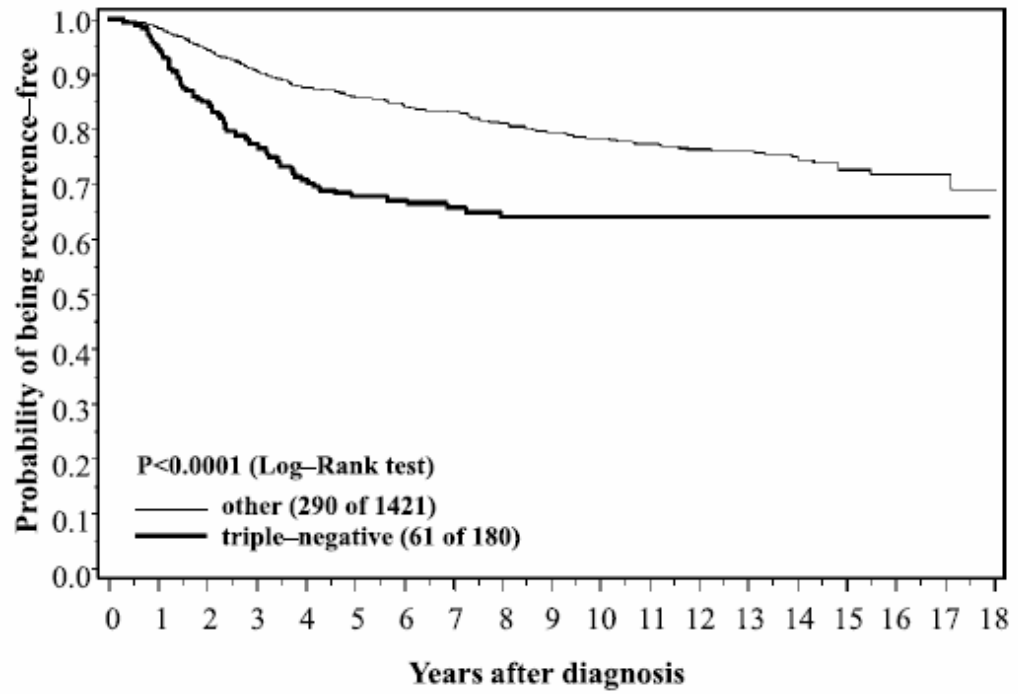
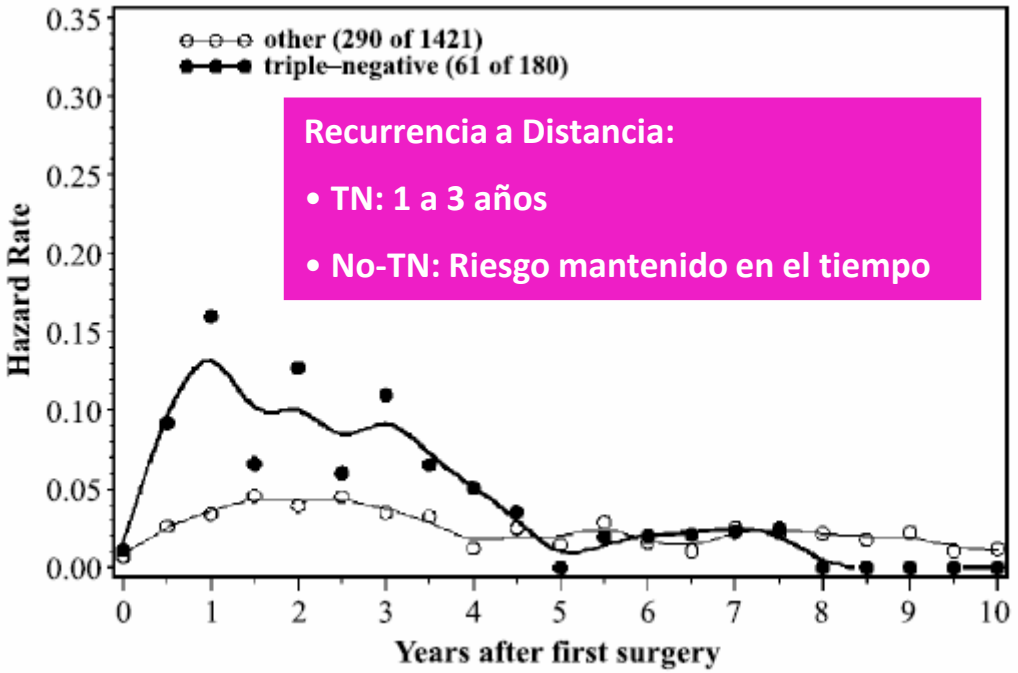


Figure 2. Sites of First Distant Recurrence in Cases of Metastatic Triple-Negative Breast Cancer as Compared with Non–Triple-Negative Breast Cancer.

The percentages shown are approximate percentages of women with a first distant recurrence among women in whom metastases develop. Data are from Dent et al.,[47] Rodríguez-Pinilla et al.,[48] and Liedtke et al.[49]





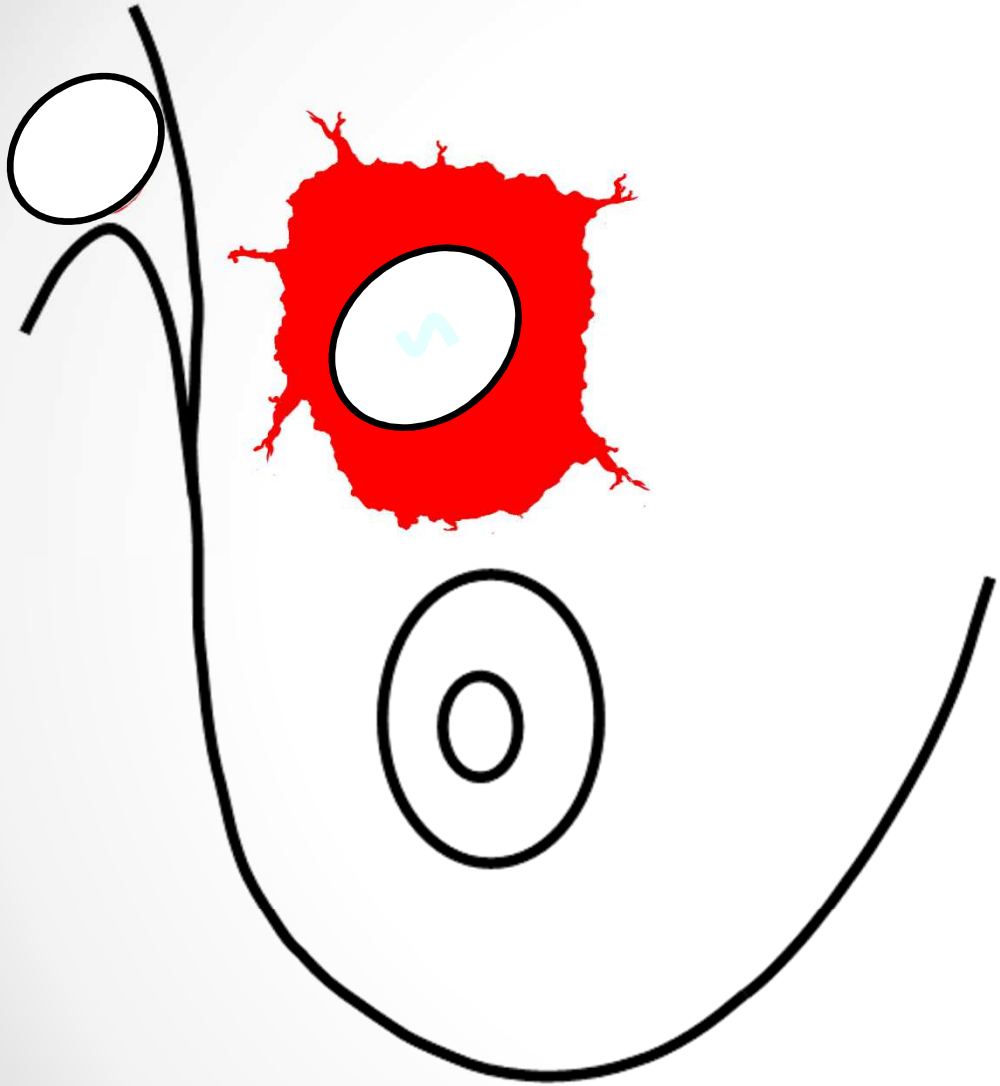
Recurrencia a Distancia:

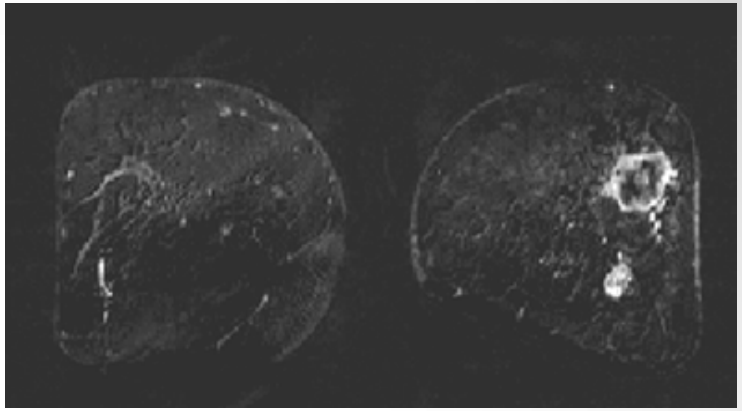
- **TN: 1 a 3 años**
- **No-TN: Riesgo mantenido en el tiempo**

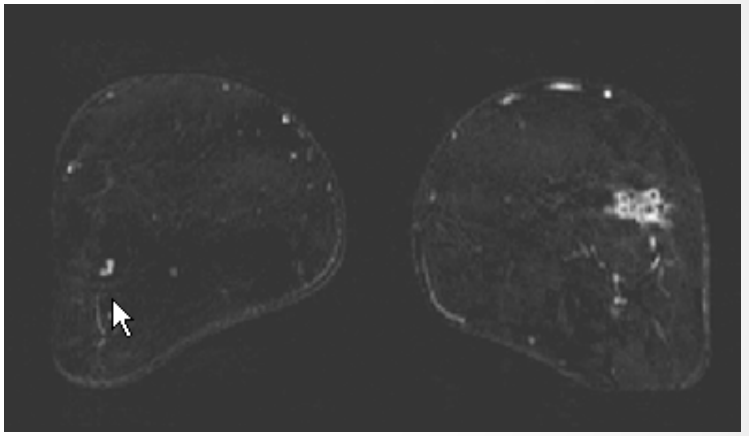
Dent et al. CCR 2007

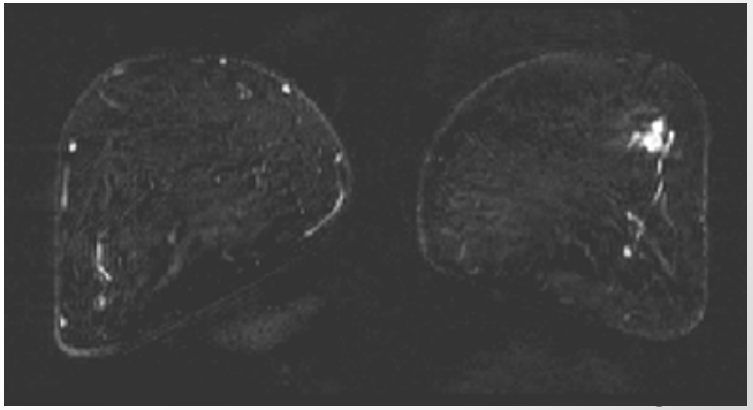
Foulkes et al. NEJM 2010

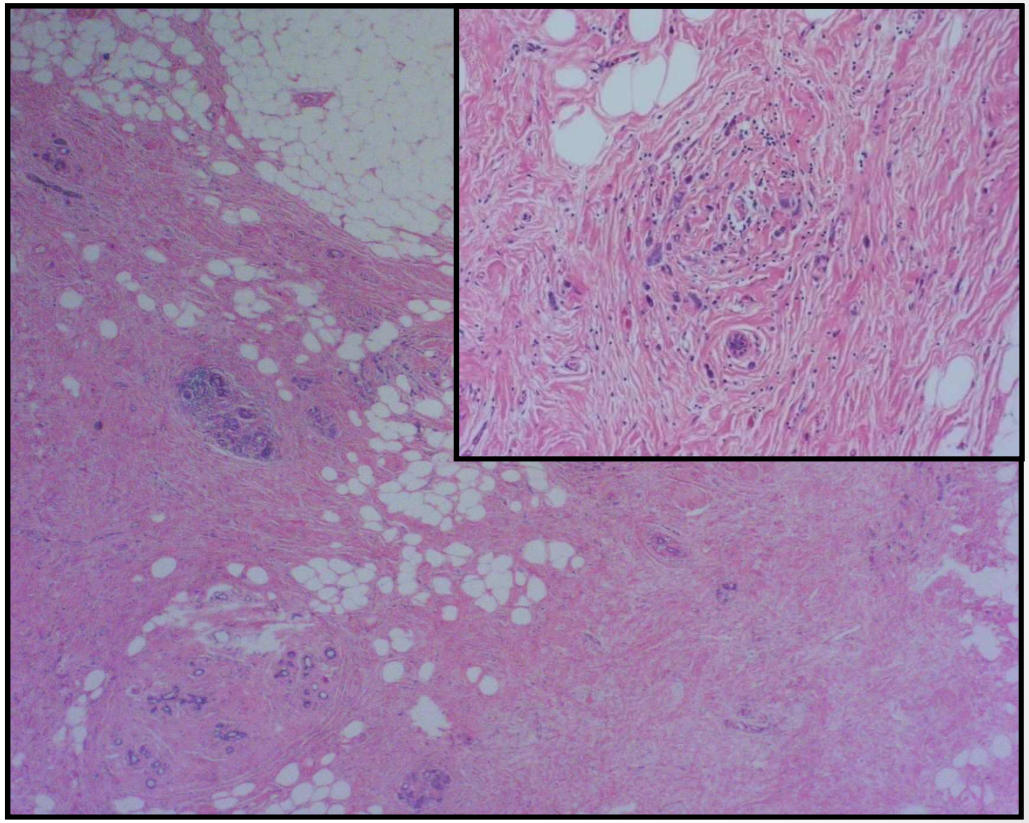
TRATAMIENTO DIRIGIDO

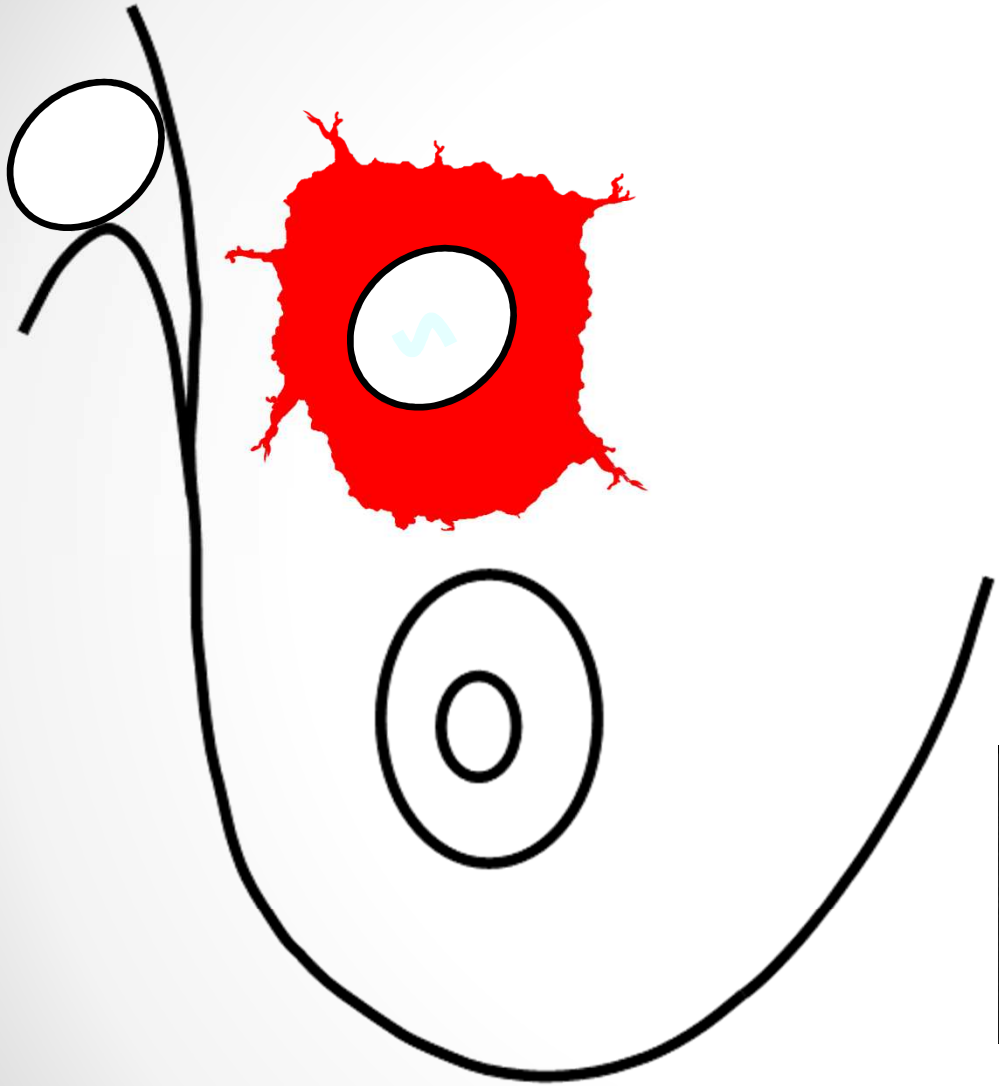


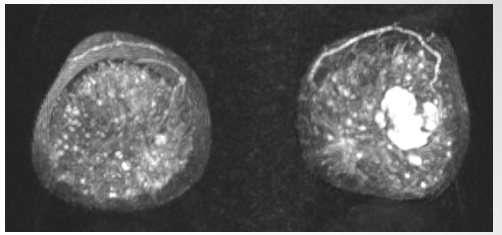


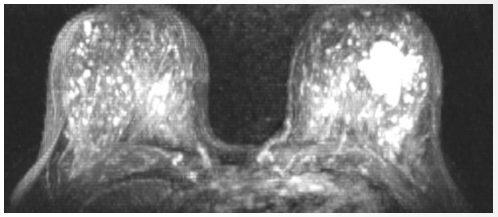


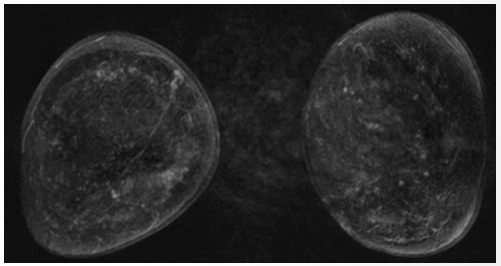


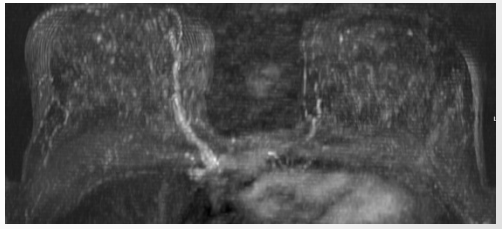


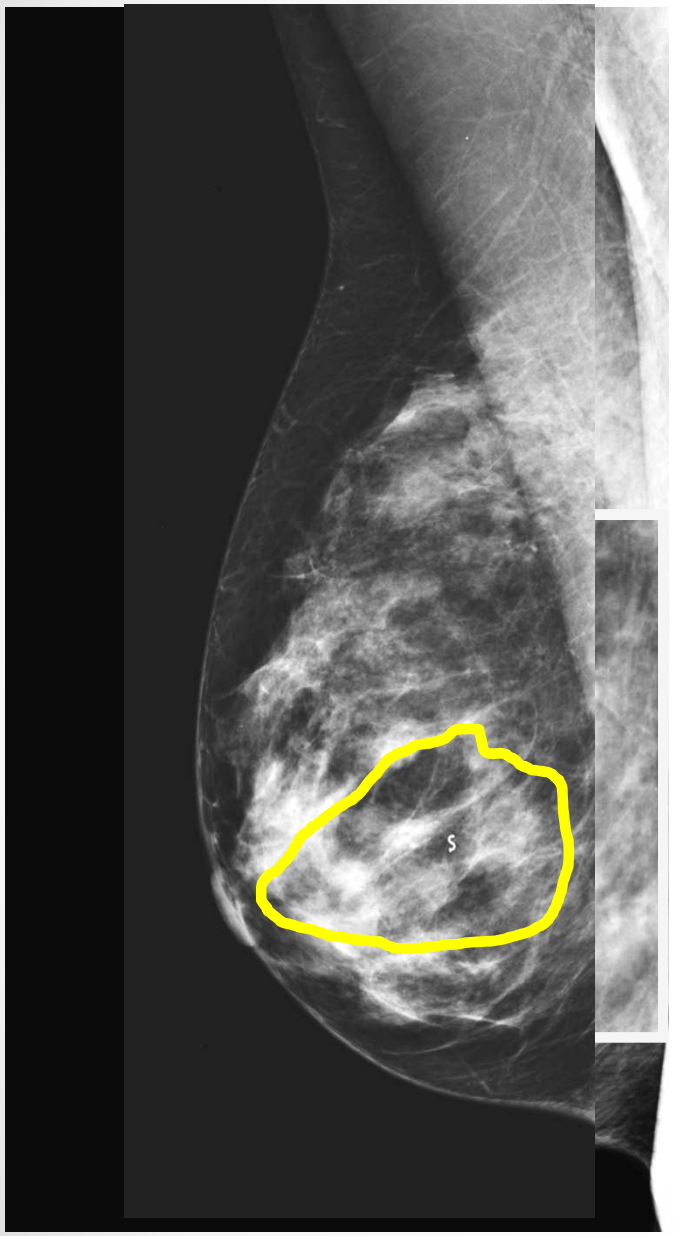








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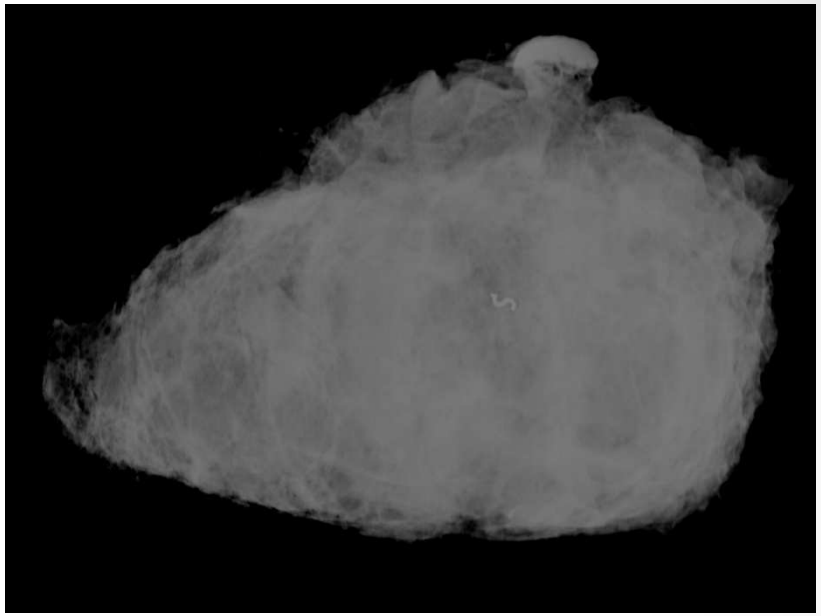
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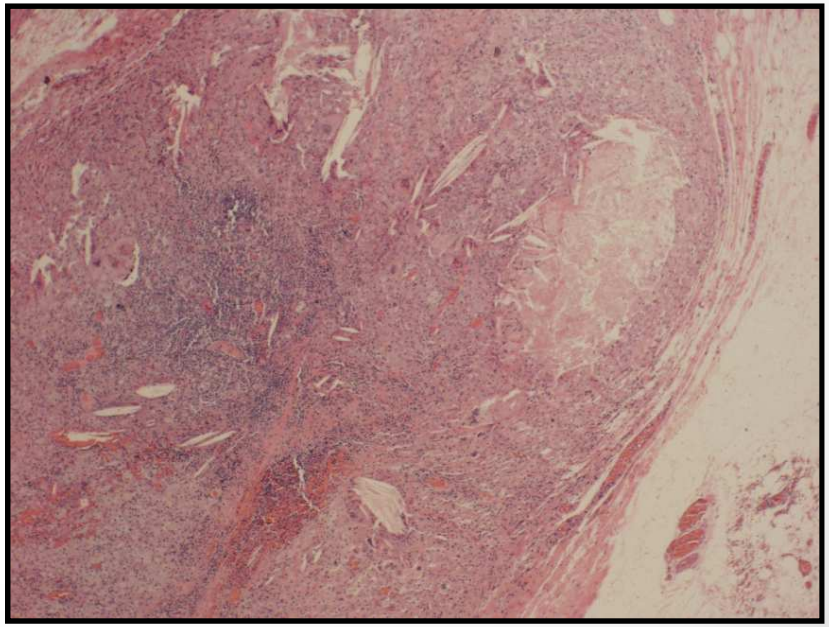
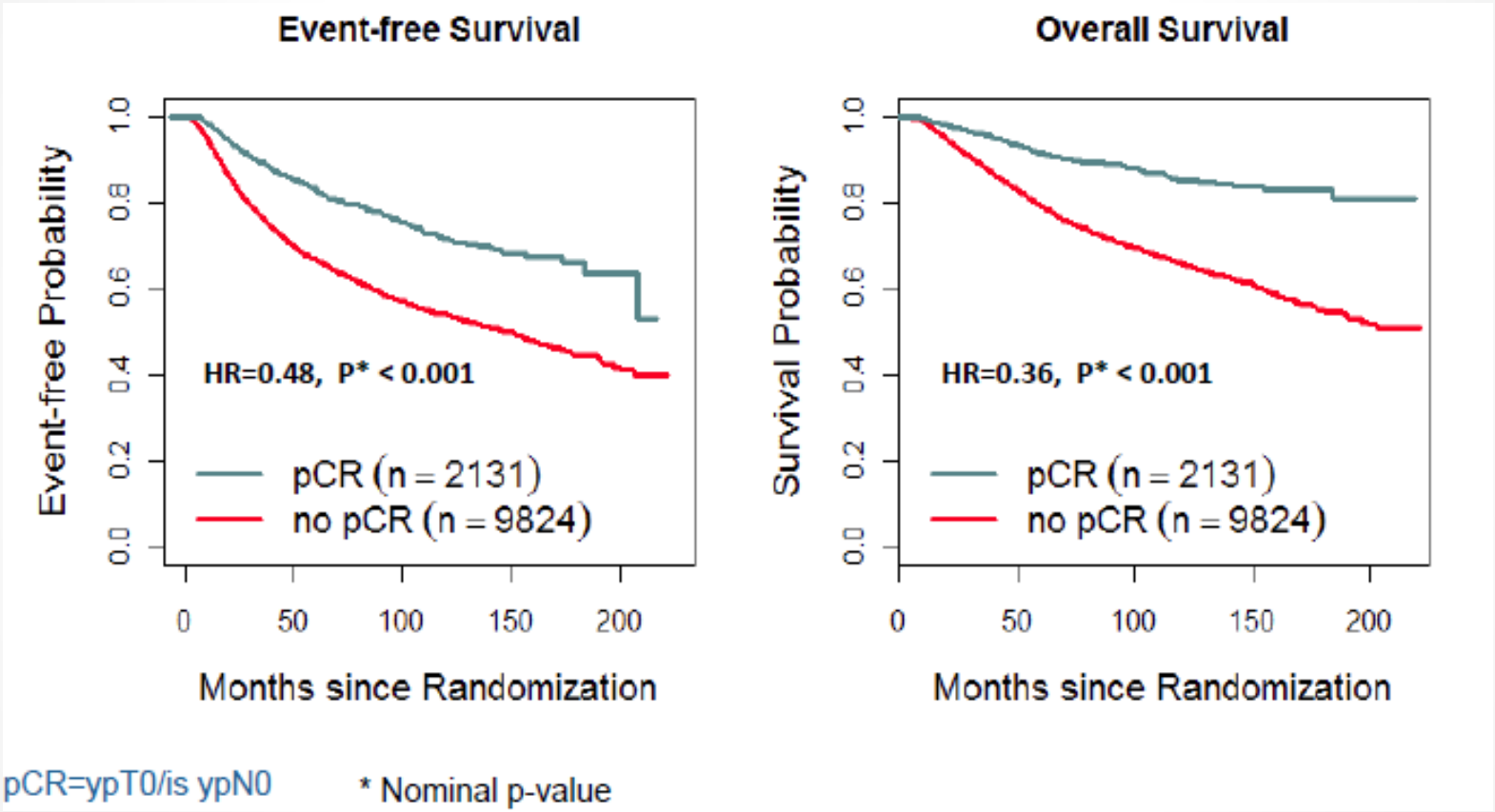




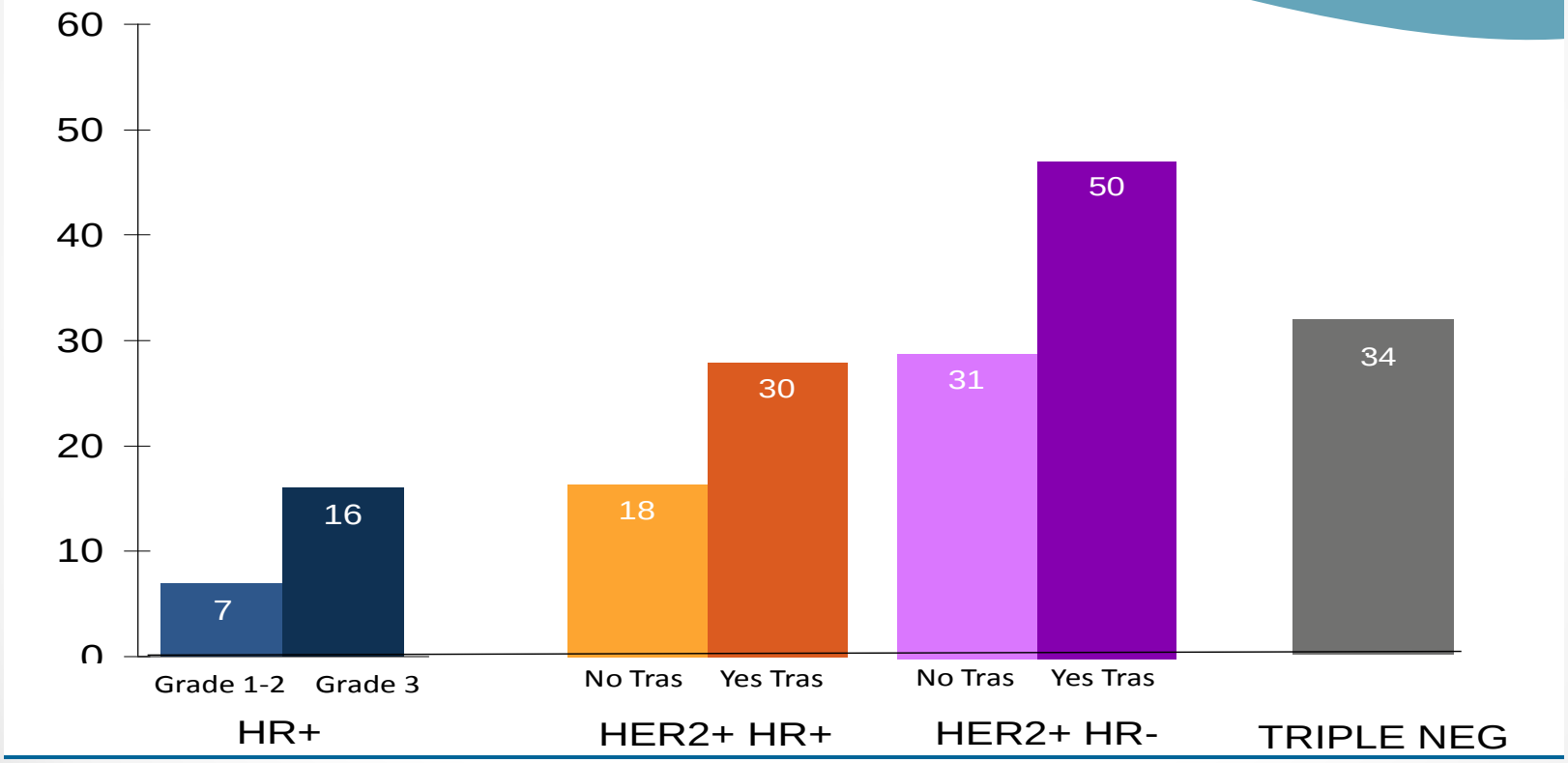
pCR=ypT0/is ypN0

* Nominal p-value

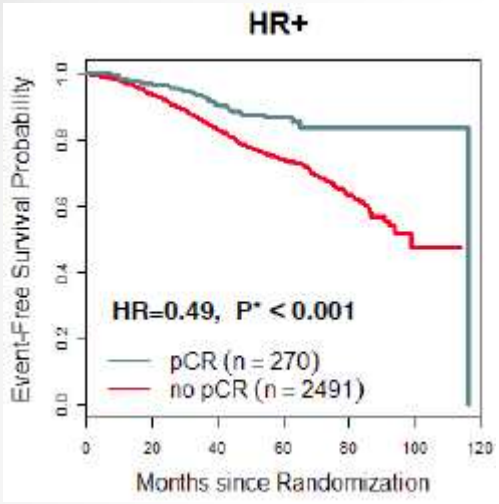
www.thelancet.com Published online February 14, 2014 http://dx.doi.org/10.1016/S0140-6736(13)62422-8

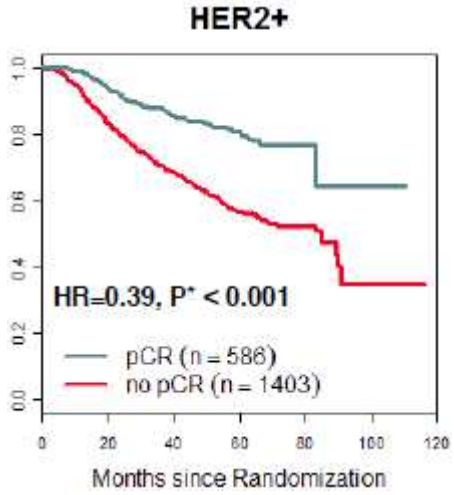
pCR Rates by Tumor Subtypes

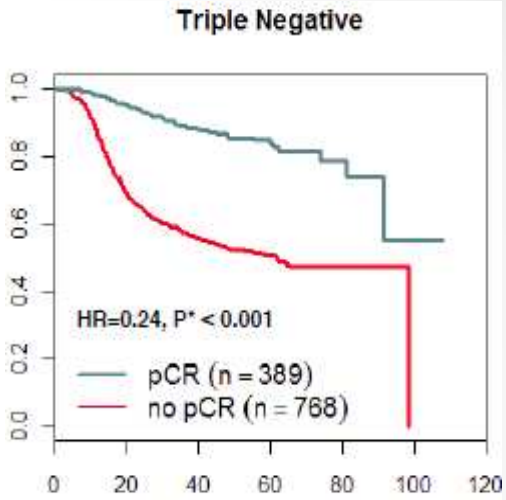
CTNeoBC

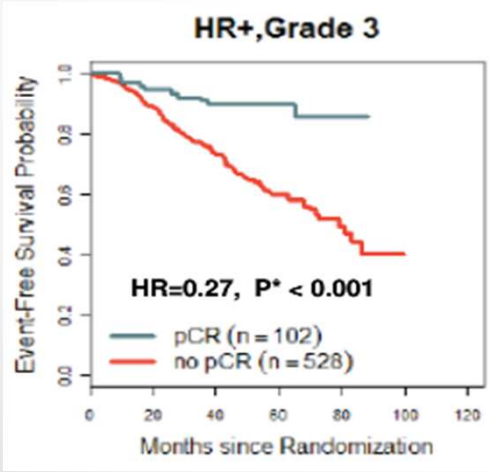


www.thelancet.com Published online February 14, 2014 http://dx.doi.org/10.1016/S0140-6736(13)62422-8









www.thelancet.com Published online February 14, 2014 http://dx.doi.org/10.1016/S0140-6736(13)62422-8

¿SE CONOCEN OTROS FACTORES PREDICTORES DE RESPUESTA PATOLÓGICA COMPLETA?

Factors Predictive of Higher pCR Rate

Factor	Higher pCR rate
Tumor size	Smaller size
Tumor grade	Higher grade
Histological type	Ductal > lobular
ER/PR	Negative
HER-2	Positive
Proliferative markers	Higher

¿CON QUÉ TRATAR?

Treatment by Molecular Class

Class	Treatment	Additional Therapies
ER and/or PR-expressors	Aromatase inhibitors SERMs	± chemotherapy
HER2-amplified	Trastuzumab, lapatinib ,Pertuzumab	± chemotherapy, hormone therapy
Triple-negative (ER, PR, HER2)	Chemotherapy (Platinum salts [?]) ¿Inhibidores de la PARP?	± bevacizumab

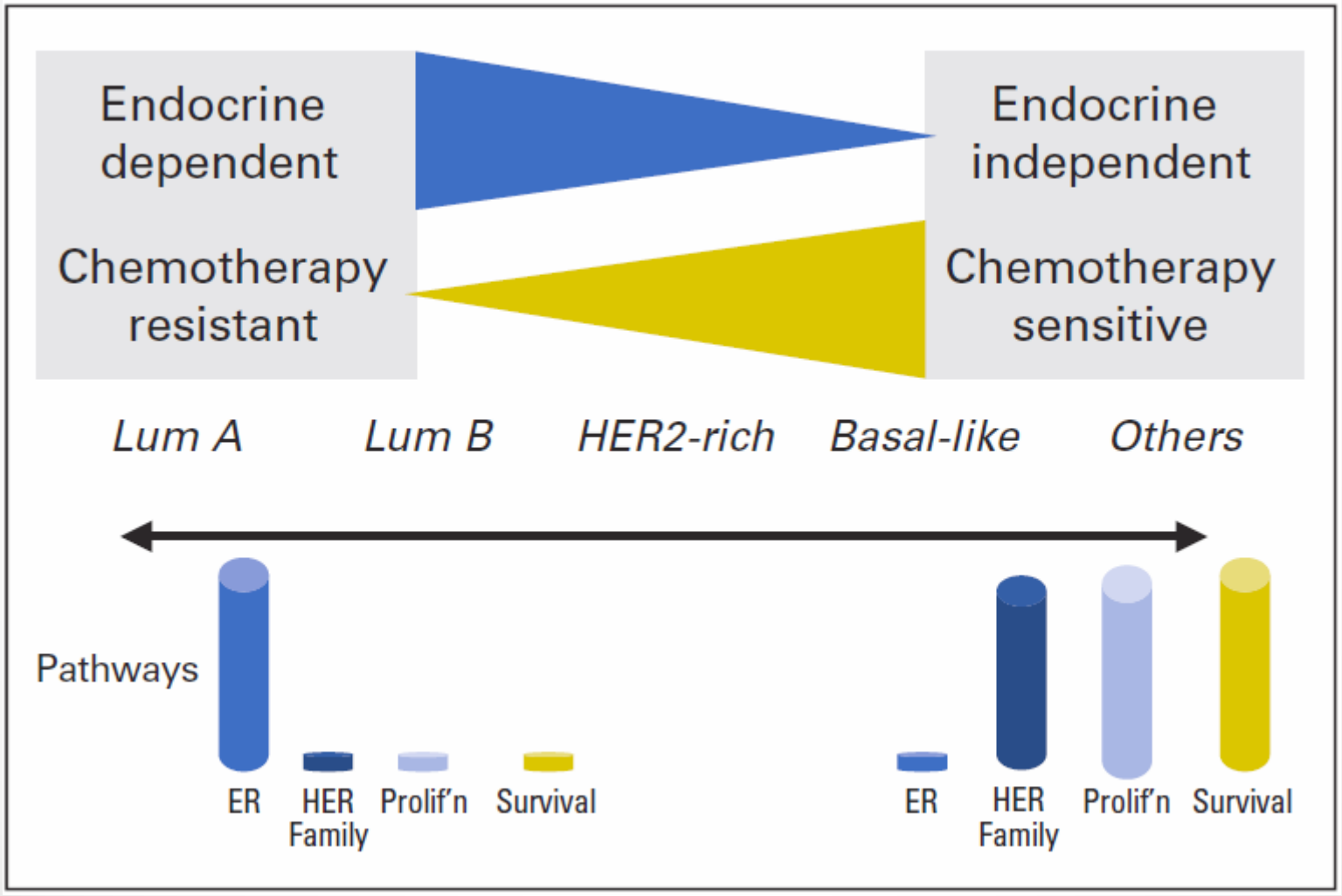
CÁNCER DE MAMA LUMINAL

VOLUME 30 · NUMBER 12 · APRIL 20 2012

JOURNAL OF CLINICAL ONCOLOGY

COMMENTS AND CONTROVERSIES

Daniel F. Hayes, *Breast Oncology Program, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI*



BJC

British Journal of Cancer (2013) 108, 285–291 | doi: 10.1038/bjc.2012.557

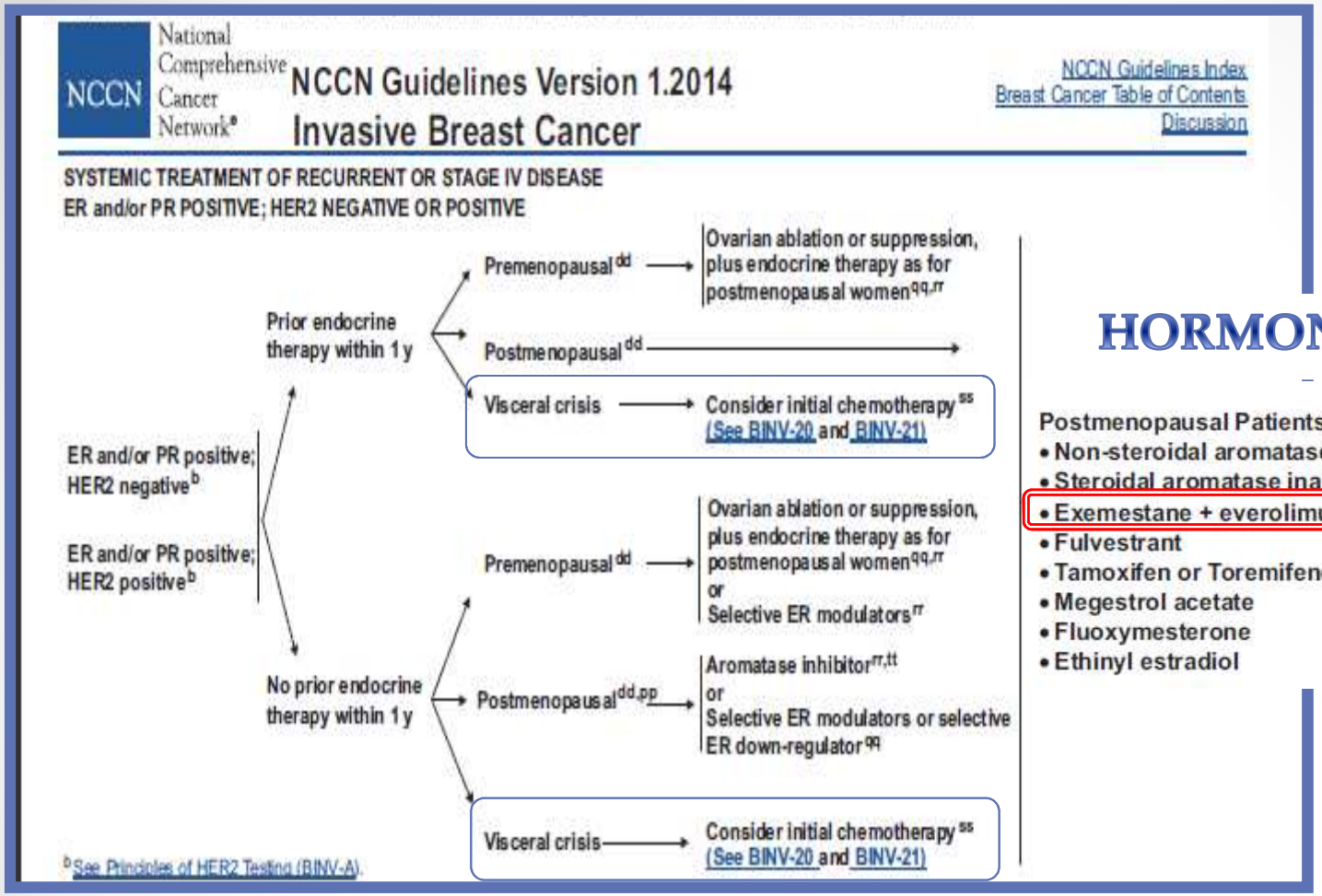
Clinical benefit from neoadjuvant chemotherapy in oestrogen receptor-positive invasive ductal and lobular carcinomas

Table 2. Surgical and pathological outcomes

	ILC ($n = 177$)		IDC ($n = 1718$)		
	No. of patients	%	No. of patients	%	χ^2 *P*-value
Final surgical outcome					
Conservative	33	19	576	34	<0.001
Mastectomy	139	79	1078	63	
No surgery	5	3	64	4	
Pathological response					
No pCR	165	93	1404	82	<0.001
pCR	6	3	246	14	

Abbreviations: IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; pCR = pathological complete response.

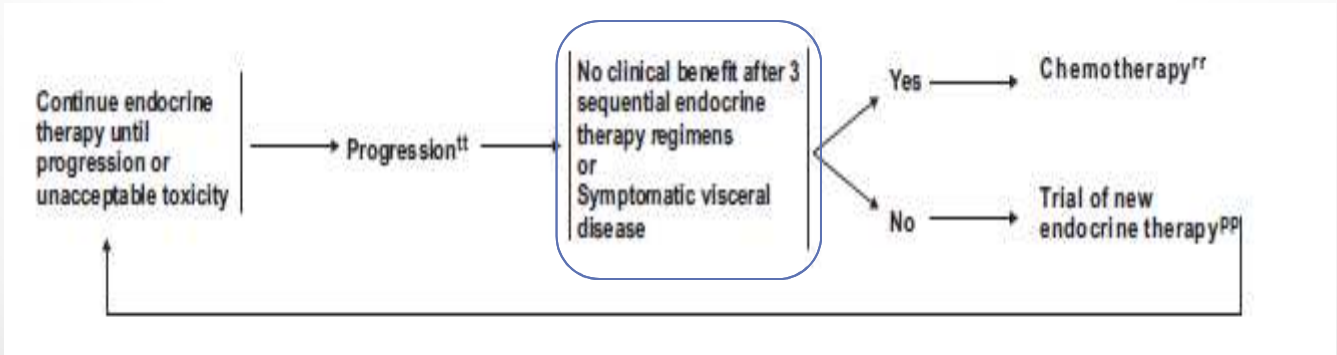
LUMINAL



HORMONAL THERAPY

Postmenopausal Patients

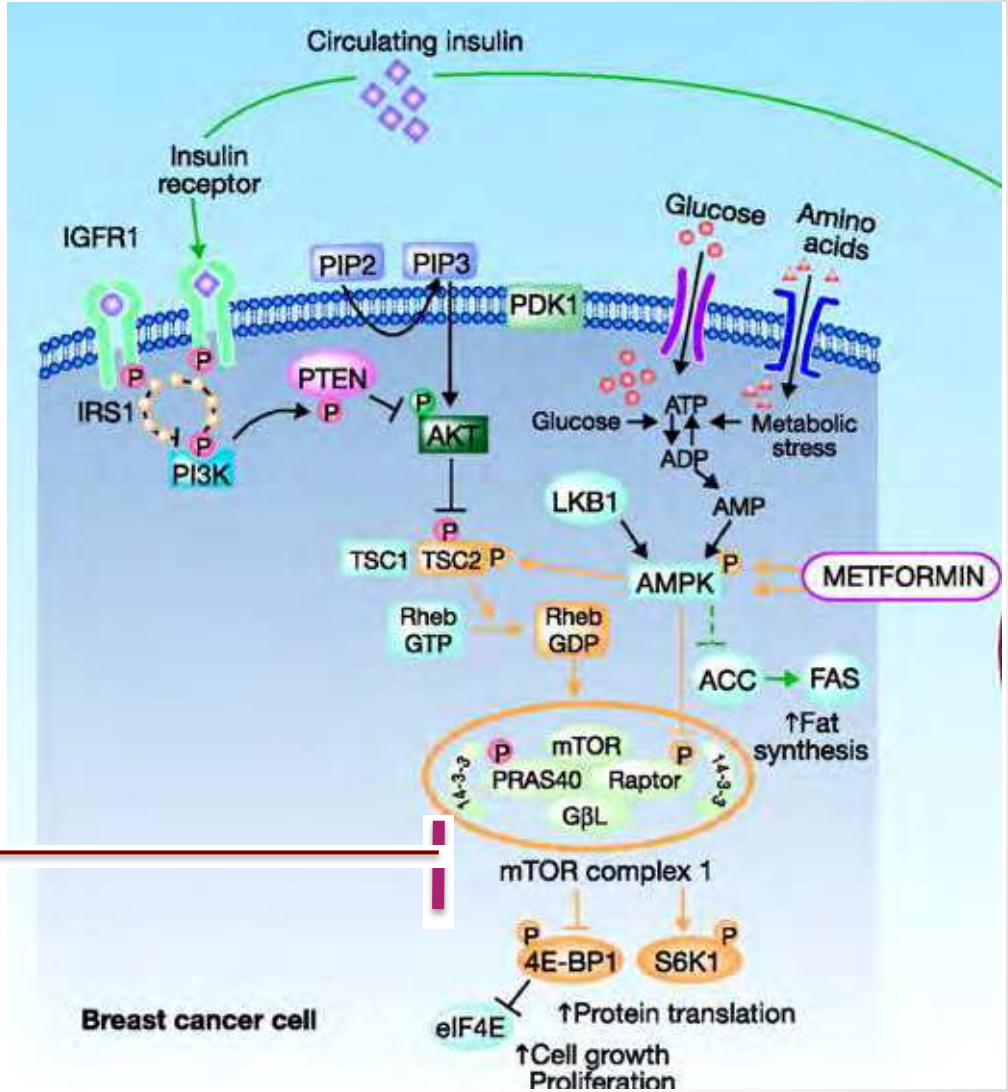
- Non-steroidal aromatase inhibitor (anastrozole, letrozole)
- Steroidal aromatase inactivator (exemestane)
- Exemestane + everolimus[1]
- Fulvestrant
- Tamoxifen or Toremifene
- Megestrol acetate
- Fluoxymesterone
- Ethinyl estradiol



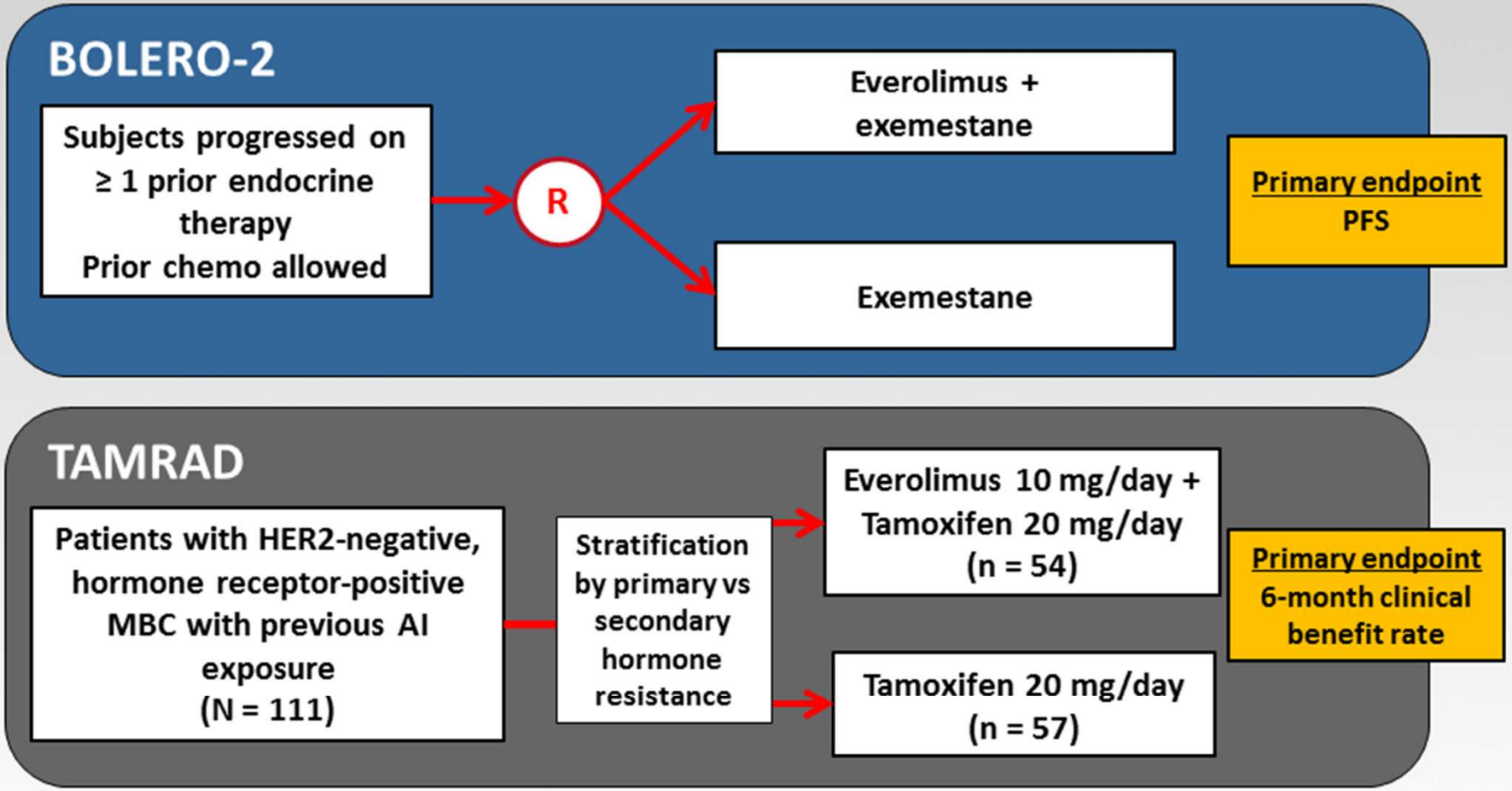
CASO 1

- Mujer de 69 años: CDI de mama Derecha en 2012
- RE y RP positivos, Her 2 Negativo
- Ki-67: 5%. Luminal A
- Estudio de extensión: Enf pulmonar y adenopática
- Asintomática. ECOG 0
- Letrozol
- Respuesta hasta el 2014 → Progresión Pulmonar

Everolimus

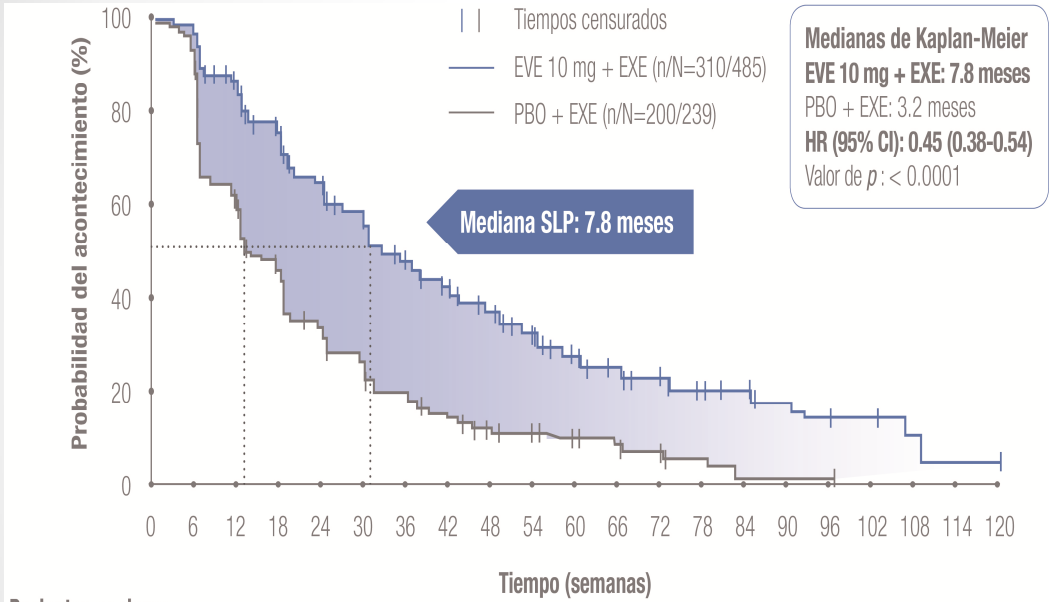

Circulating insulin
Insulin receptor
IGFR1
PIP2
PIP3
PDK1
Glucose
Amino acids
IRS1
PI3K
PTEN
AKT
Glucose
ATP
ADP
Metabolic stress
LKB1
AMP
TSC1
TSC2
AMPK
METFORMIN
Rheb GTP
Rheb GDP
ACC
FAS
↑Fat synthesis
mTOR
PRAS40
Raptor
GβL
14-3-3
mTOR complex 1
4E-BP1
S6K1
eIF4E
↑Protein translation
↑Cell growth
Proliferation
Breast cancer cell

Options after Progression on Endocrine Therapy



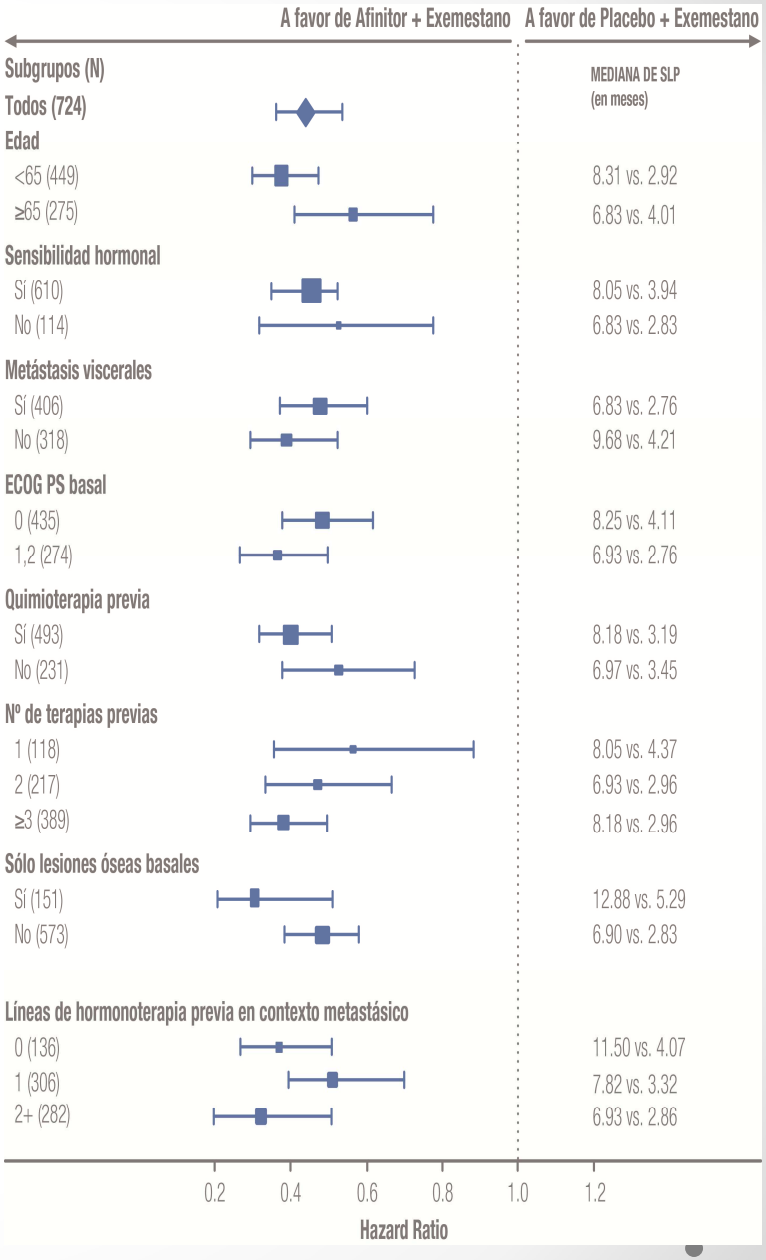
PFS = progression-free survival

Baselga J, et al. *N Engl J Med.* 2012;366(6):520-529.
Bachelot T, et al. *J Clin Oncol.* 2012;30(22):2718-2724.



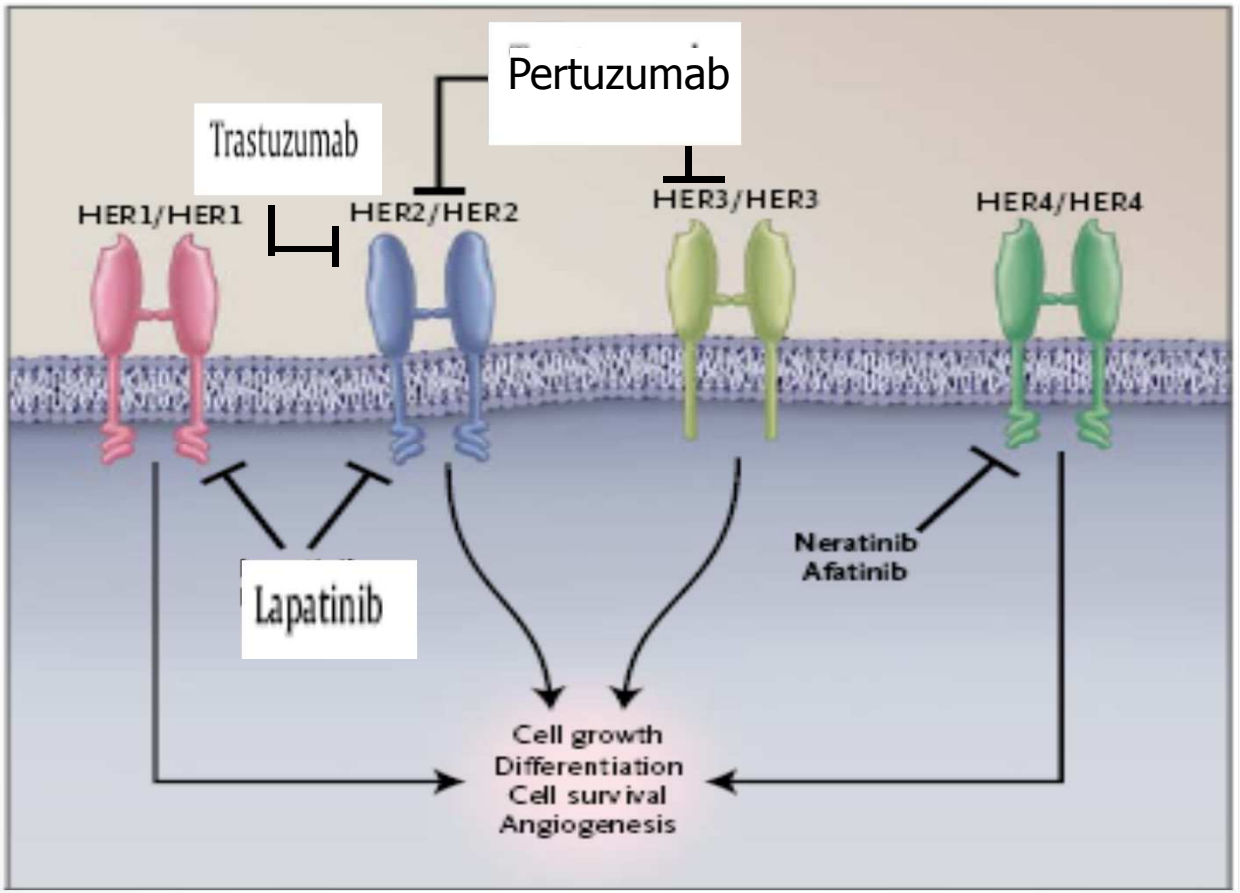
Pacientes en riesgo

EVE 10 mg + EXE	485	436	366	304	257	221	185	158	124	91	66	50	35	24	22	13	10	8	2	1	0
PBO + EXE	239	190	132	96	67	50	39	30	21	15	10	8	5	3	1	1	1	0	0	0	0



Adaptado de Piccart M, et al, ASCO 2012, abstract 559 (poster)
Baselga et al N Engl J Med 366,520-9 2012

CÁNCER DE MAMA HER2 POSITIVO

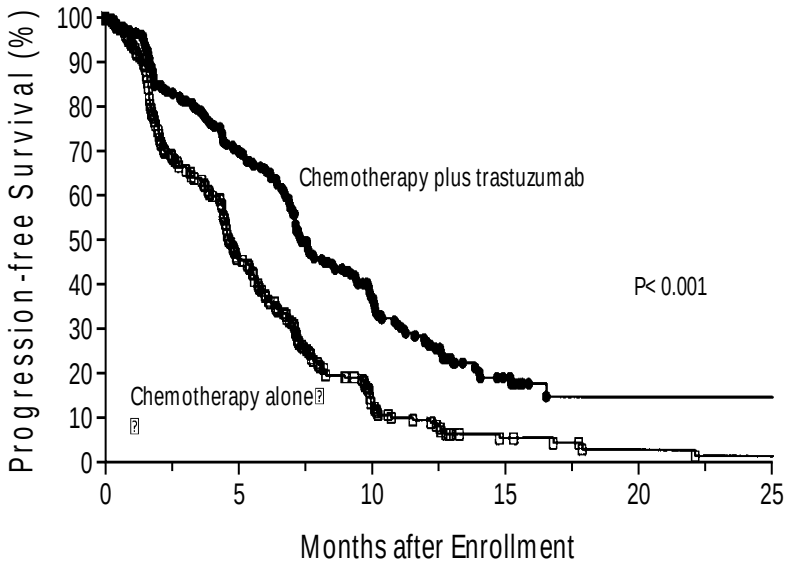


The New England
Journal of Medicine

VOLUME 344 MARCH 15, 2001 NUMBER 11

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

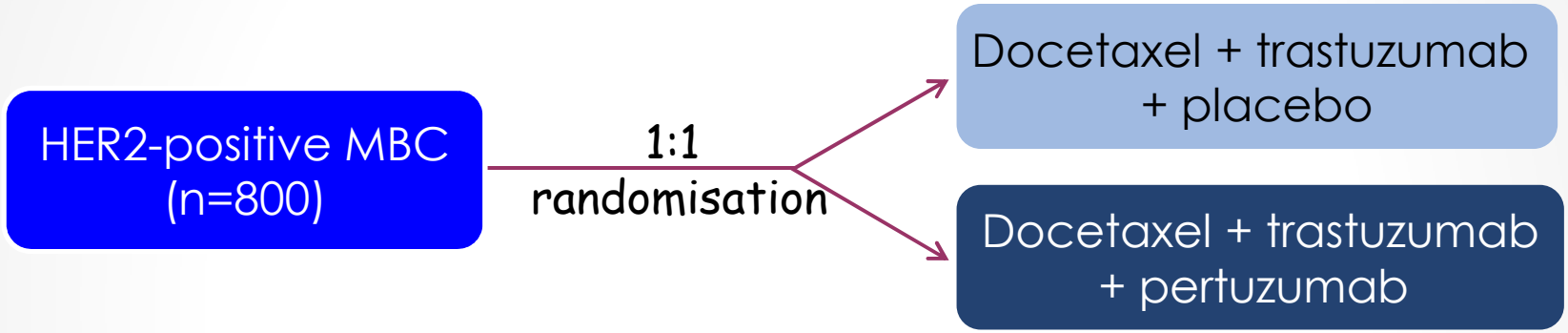
A



NO. AT RISK

Chemotherapy plus trastuzumab	235	152	63	15
Chemotherapy alone	234	103	25	6

CLEOPATRA: A phase III trial of Trastuzumab plus Docetaxel with or without Pertuzumab in first-line her2-positive mbc



An international Phase III, randomised, double-blind, placebo-controlled study (approx. 250 sites worldwide)

- Primary endpoint:
  - PFS by independent review
- Enrolment stratified by:
  - Prior treatment for breast cancer
  - Geographic region of enrolment

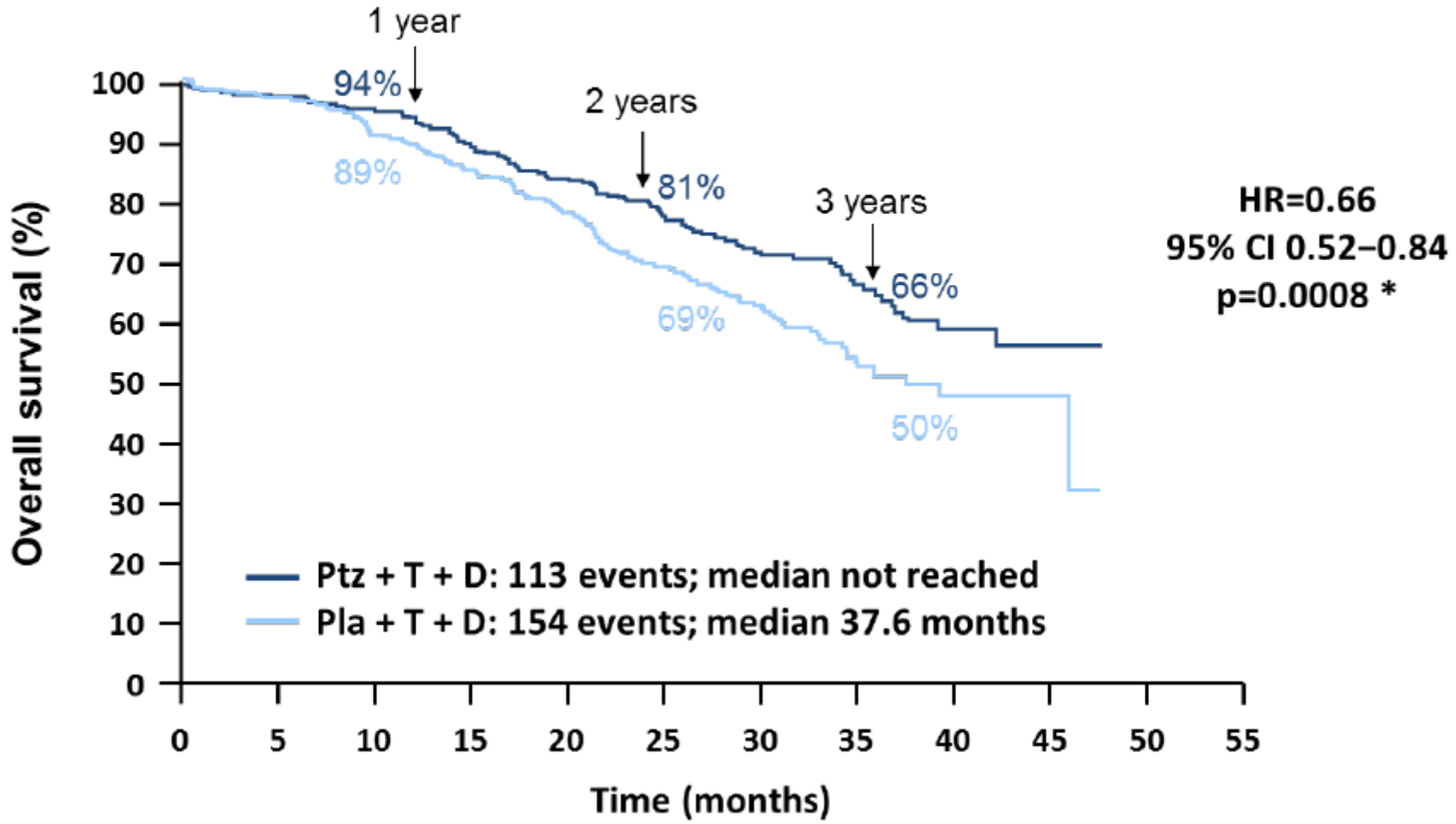

The NEW ENGLAND JOURNAL of MEDICINE

JANUARY 12, 2012

Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer

MBC = metastatic breast cancer; PFS = progression-free survival

Figure 5: Kaplan-Meier Curve of Overall Survival for CLEOPATRA

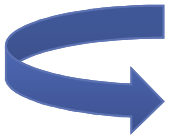


* Boundary for statistical significance: p≤0.0138

Swain SM et al, Lancet Oncology 2013

CASO 2

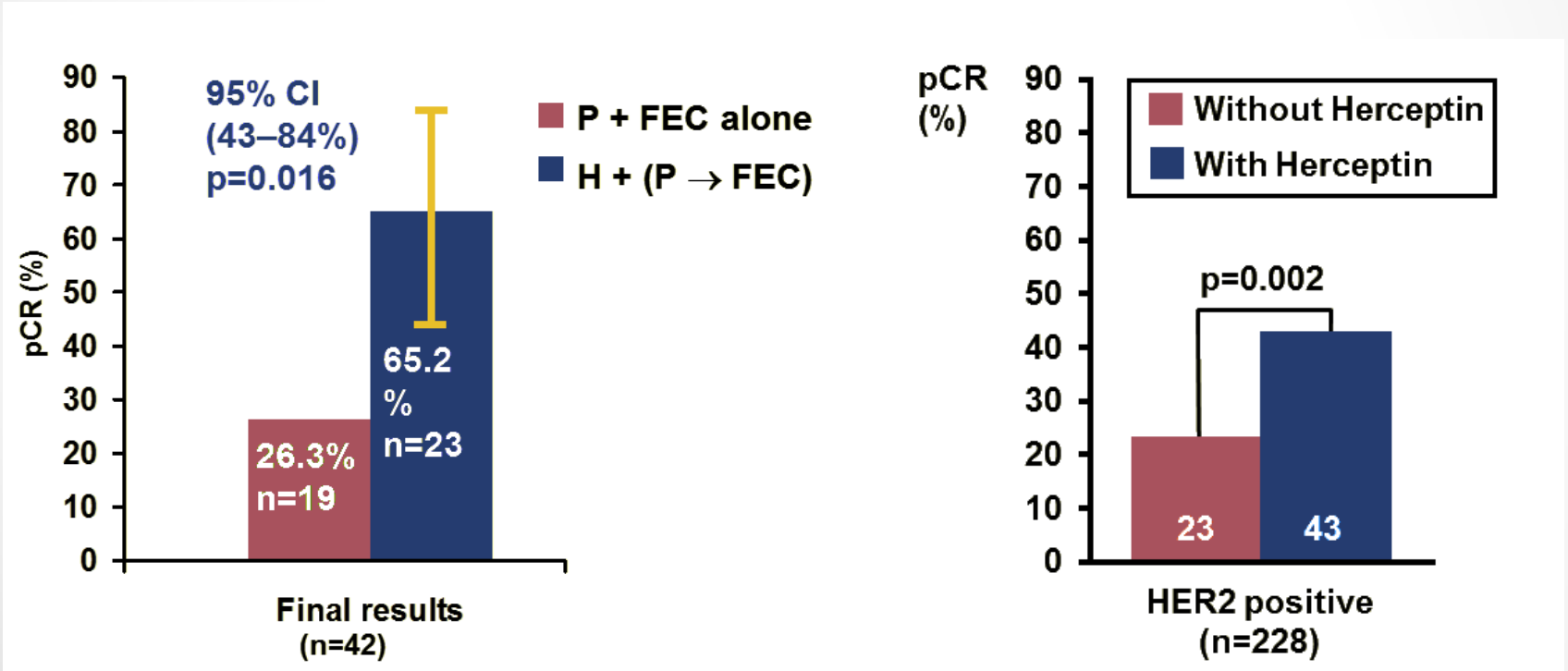
- Mujer de 50 años
- Carcinoma Ductal Infiltrante mama HER2 +++
- RH: Negativos
- Estadio IV: Enf hepática y ósea al diagnóstico
- ECOG 1



Docetaxel + Trastuzumab + Pertuzumab

Neoadjuvant Herceptin significantly improves pCR rates

MDACC



NOAH

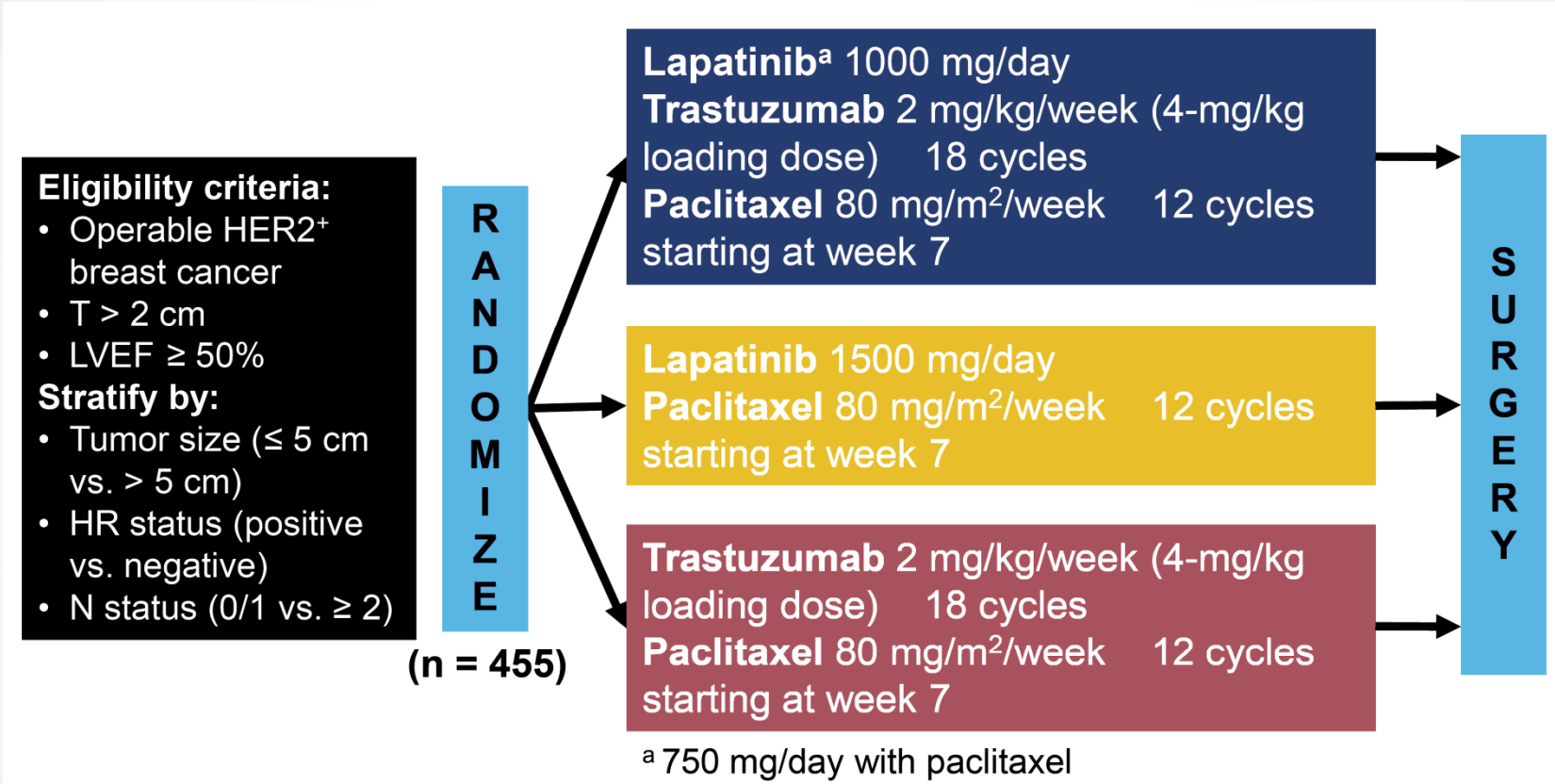
Buzdar et al. *JCO* 2005

Gianni et al. Lancet 2010

Trastuzumab

Lapatinib

NeoALTTO Study



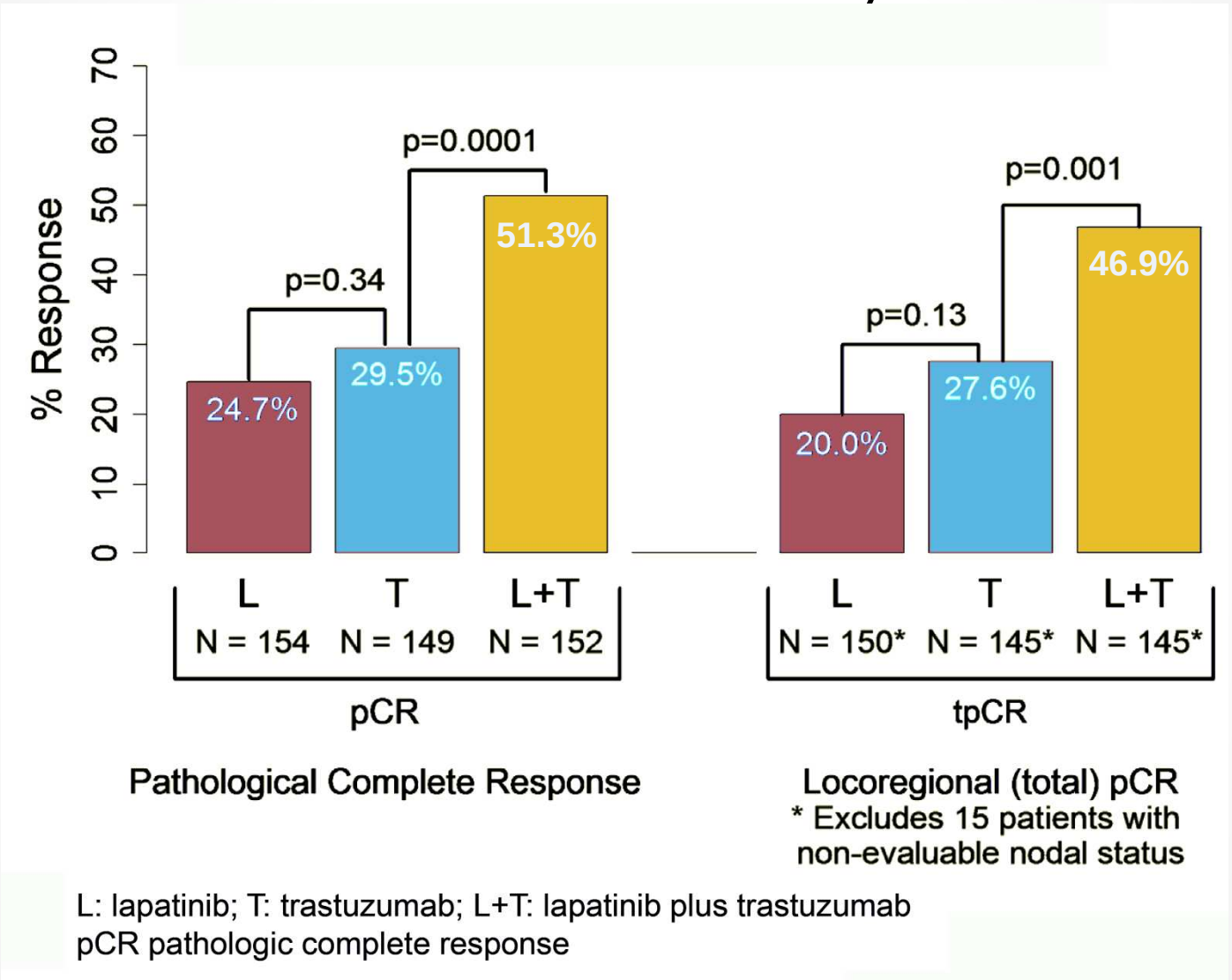
Primary endpoint: pCR rate
Secondary endpoints including: total pCR, OR at week 6, safety

Baselga et al. Lancet 2012

Trastuzumab

Lapatinib

NeoALTTO Study



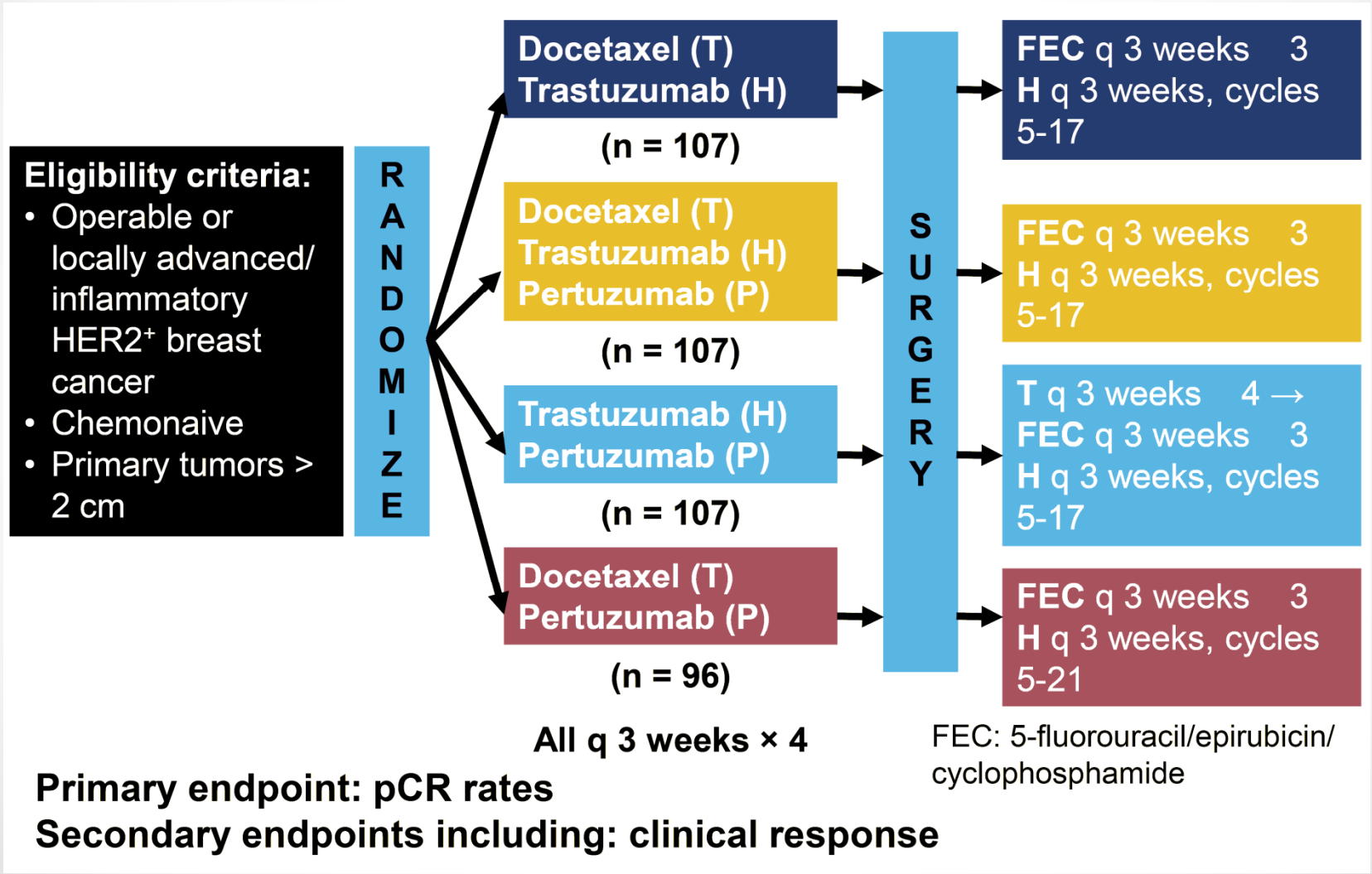
L: lapatinib; T: trastuzumab; L+T: lapatinib plus trastuzumab
pCR pathologic complete response

Baselga et al. Lancet 2012

Trastuzumab

Pertuzumab

NeoSphere Study



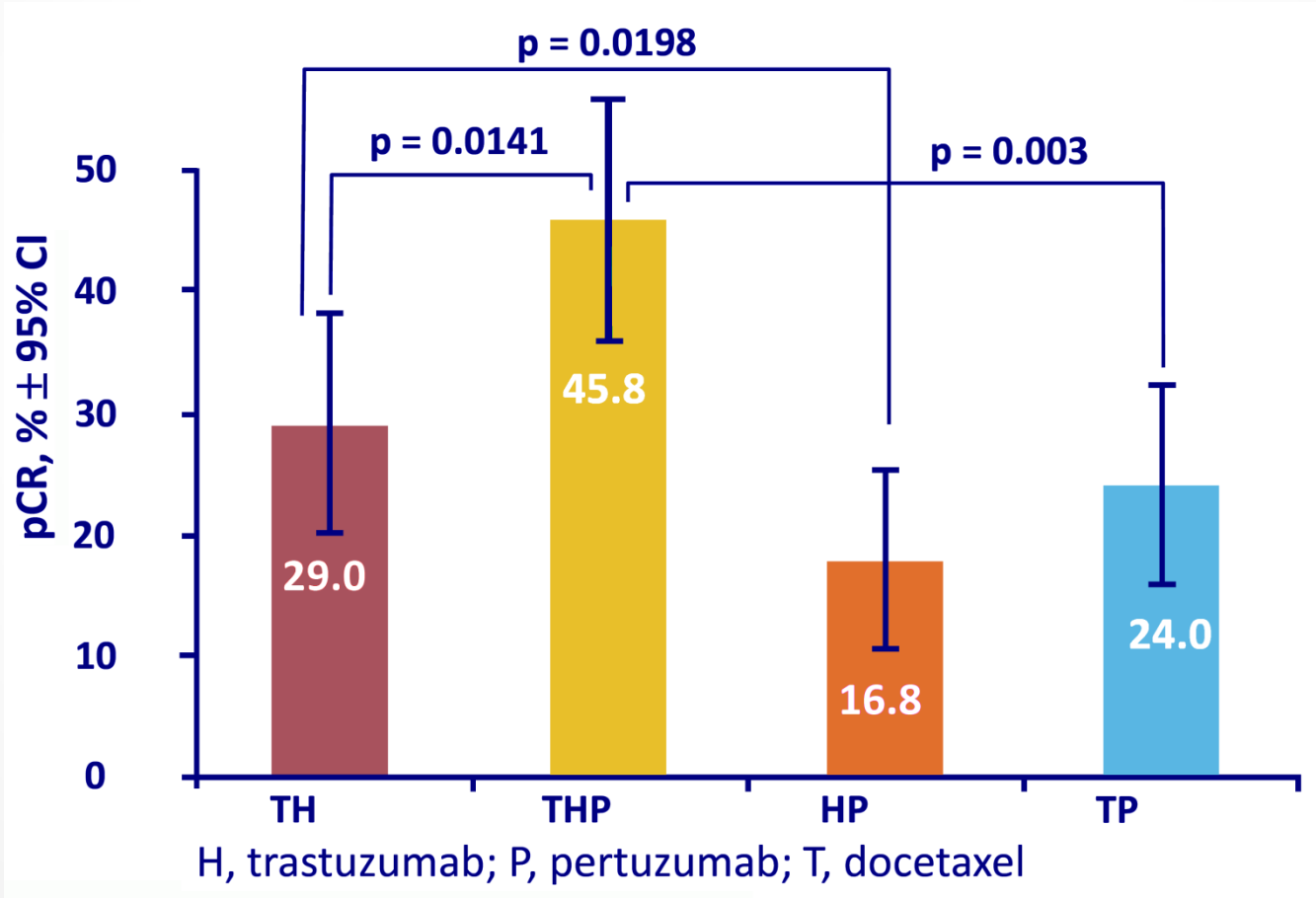
Gianni et al. Lancet Oncology 2012

Trastuzumab

Pertuzumab

NeoSphere Study

pCR (no invasive residual in breast)



Gianni et al. Lancet Oncology 2012

REVIEW

Therapeutic implications of estrogen receptor signaling in HER2-positive breast cancers

Rita Nahta · Ruth M. O'Regan

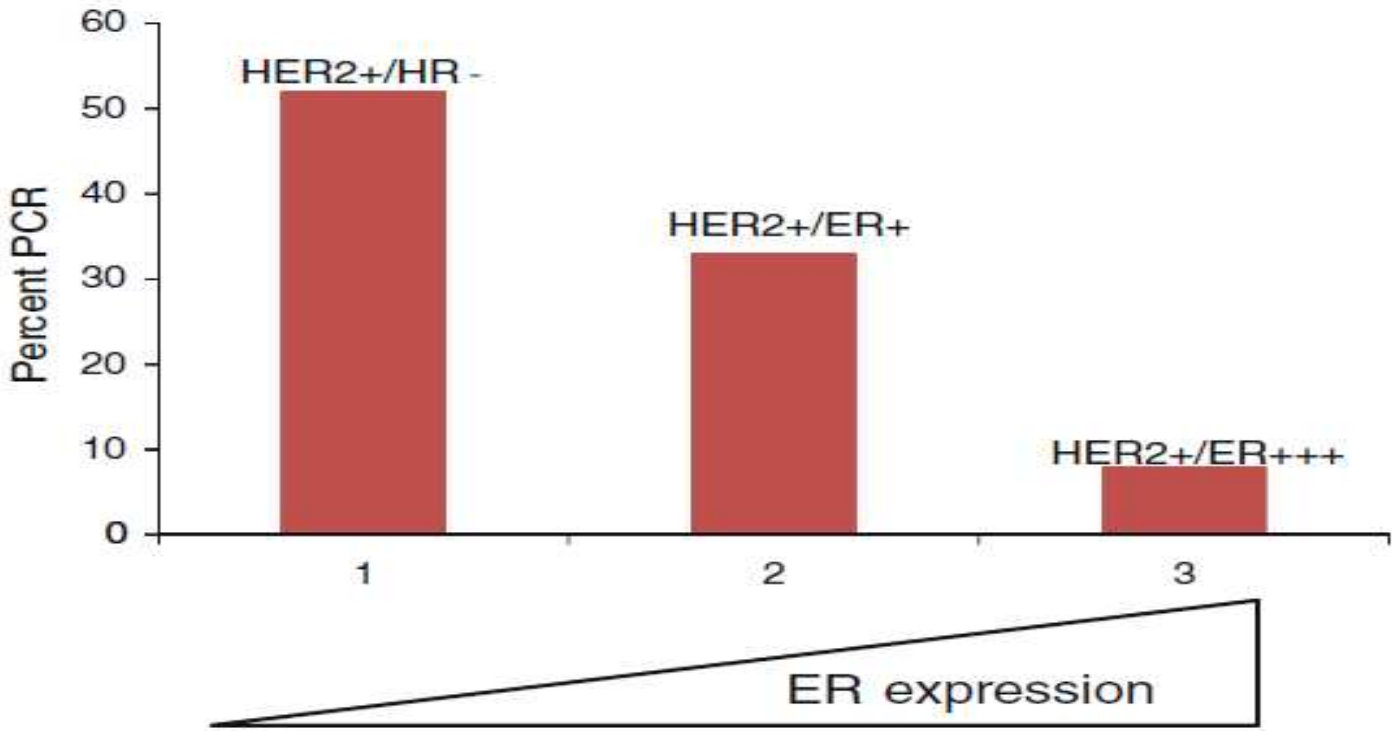
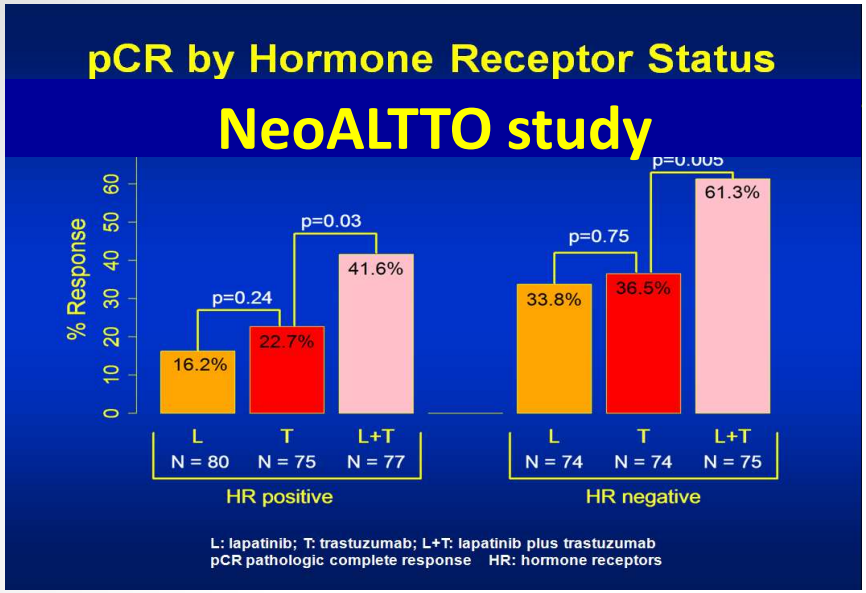


Fig. 2 Pathologic complete response (PCR) rates for patients with HER2-positive breast cancers based on ER expression treated pre-operatively with trastuzumab-based chemotherapy. PCR rates are lower in HER2-positive cancers that express high levels of ER, compared to those with minimal or no expression of ER [10

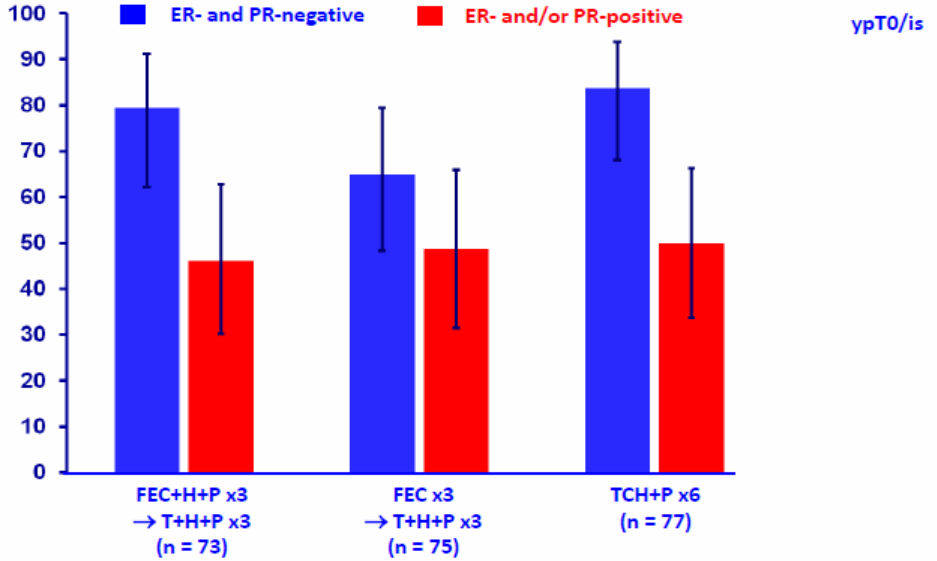
Breast Cancer Res Treat (2012) 135:39–48

RPc SEGÚN EXPRESIÓN DE RECEPTORES HORMONALES

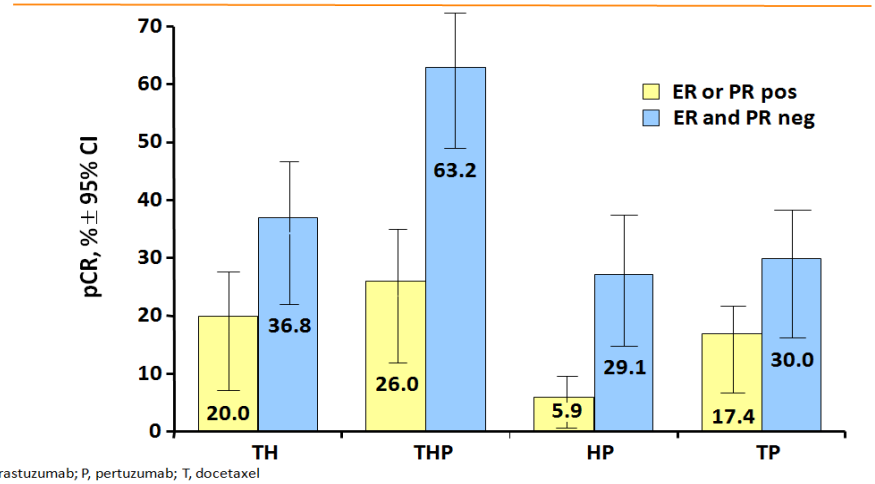


San Antonio Breast Cancer Symposium – Cancer Therapy and Research Center at UT Health Science Center – December 8-12, 2010

Phase II Study TRYPHAENA

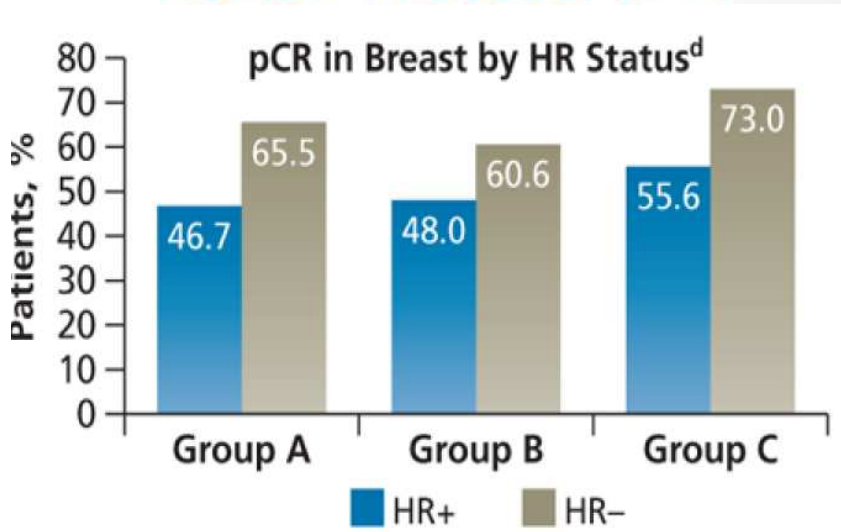


NeoSphere: pCR and hormone receptors status



H, trastuzumab; P, pertuzumab; T, docetaxel

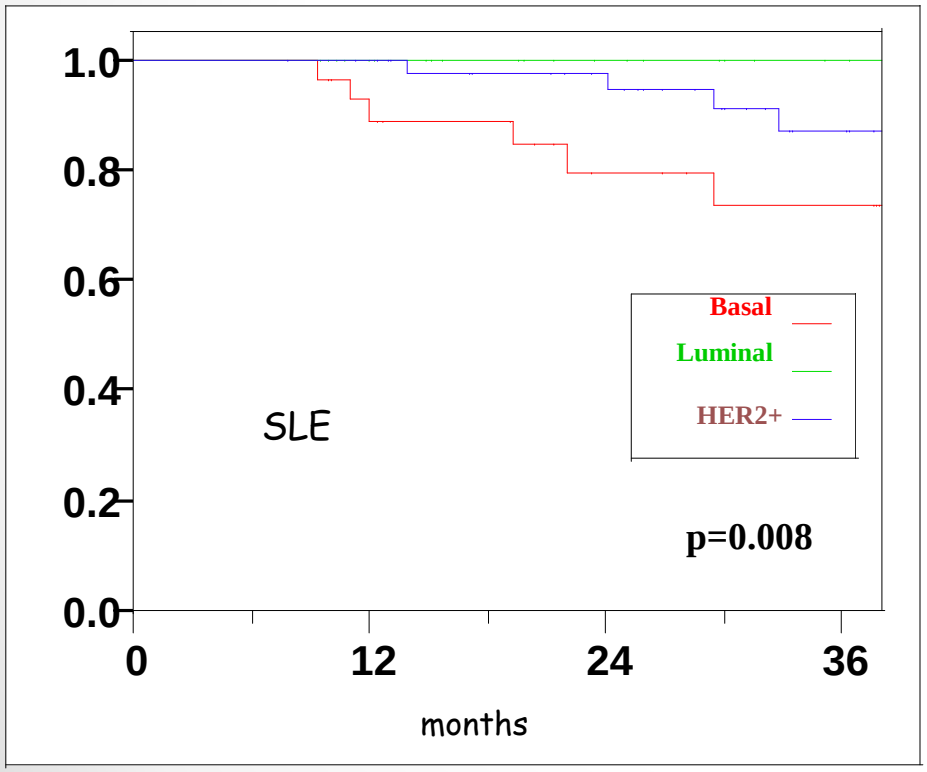
NSABP Protocol B-41

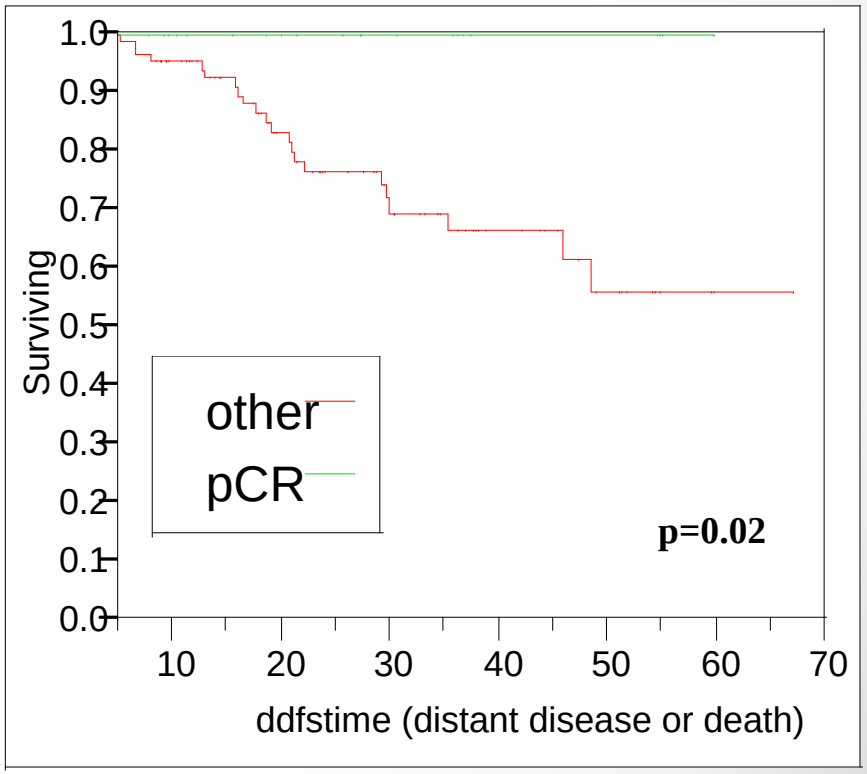


CÁNCER DE MAMA TRIPLE NEGATIVO

La paradoja del CMTN en neoadyuvancia

- Gran respuesta a QT neoadyuvante
- Cuando no hacen RPC: Recaída precoz – gran agresividad





Carey, Clin Cancer Res 2007

Table 1. Molecular subtypes of triple-negative breast cancer [Lehmann *et al*. 2011].

TNBC subtypes	Molecular characteristics	Potential therapies
Basal-like 1	Cell cycle function Proliferation DNA damage response	Chemotherapy PARP inhibitor
Basal-like 2	Cell cycle function Proliferation Growth factor signaling	Chemotherapy PARP inhibitor
Mesenchymal	EMT Cell motility Differentiation Proliferation	Src inhibitor PI3K pathway inhibitor Wnt pathway inhibitor
Mesenchymal stem-like	EMT Cell motility Differentiation Growth factor signaling Angiogenesis	Src inhibitor PI3K pathway inhibitor Wnt pathway inhibitor
Luminal androgen receptor	AR signaling Luminal cytokeratine	AR antagonist Hsp90 inhibitor PI3K pathway inhibitor
Immunomodulatory	Immune cell processes	Immune targeted agents

AR, androgen receptor; EMT, epithelial mesenchymal transition; PARP, poly ADP ribose polymerase; TNBC, triple-negative breast cancer.

CASO 3

- Mujer de 40 años con un Tumor Triple Negativo
- Antraciclinas y Taxanos en Adyuvancia hace 2 años
- Presenta actualmente: Tos seca, múltiples metástasis pulmonares y hepáticas
- Pruebas de función hepática alteradas
- ECOG 2

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2014
Invasive Breast Cancer

NCCN Guidelines Index
Breast Cancer Table of Contents
Discussion

CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER[1]

Preferred single agents:

Anthracyclines
- Doxorubicin
- Pegylated liposomal doxorubicin

Taxanes
- Paclitaxel

Anti-metabolites
- Capecitabine
- Gemcitabine

Other microtubule inhibitors
- Vinorelbine
- Eribulin

Other single agents:
- Cyclophosphamide
- Carboplatin
- Docetaxel
- Albumin-bound paclitaxel
- Cisplatin
- Epirubicin
- Ixabepilone

Chemotherapy combinations:
- CAF/FAC (cyclophosphamide/doxorubicin/fluorouracil)
- FEC (fluorouracil/epirubicin/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)
- Gemcitabine/carboplatin
- Paclitaxel/bevacizumab[2]

Therapy Questions HER-2 Negative or Triple-Negative BC

- **Which is the most appropriate neoadjuvant chemotherapy regimen in HER-2 negative or triple-negative breast cancer**
  - **Addition of Gemcitabine, Capecitabine to anthracycline/taxane**
  - **Optimal sequence of the anthracycline and the taxane regimen**
  - **What is the role of platinum in TNBC?**
  - **Do we need anthracyclines in TNBC?**
- **Bevacizumab in HER-2 negative breast cancer**
- **PARP inhibitors in TNBC**

CONCLUSIONES

1).- El Cáncer de mama no es una enfermedad única

2).- 5 Subtipos biológicos:

- Luminal A
- Luminal B
- Luminal B HER2
- HER2
- Triple Negativo

3).- Más agresivos: Triple Negativo y HER 2

- Más capacidad para metastatizar
- Supervivencias más cortas

CONCLUSIONES

4).- Luminales:

Terapia Hormonal +/- Everolimus

5).- subtipo HER2:

- Quimioterapia + Bloqueo vía her (Herceptin, Lapatinib…)
- Quimioterapia + Doble bloqueo (Herceptin +Pertuzumab)

6).- Triple Negativo:

- Quimioterapia: con Platinos?
  +/- Bevacizumab?
  +/- Inhibidores de PARP?

GRACIAS