MASTECTOMÍA PROFILÁCTICA Y TERAPÉUTICA EN PACIENTES BRCA+

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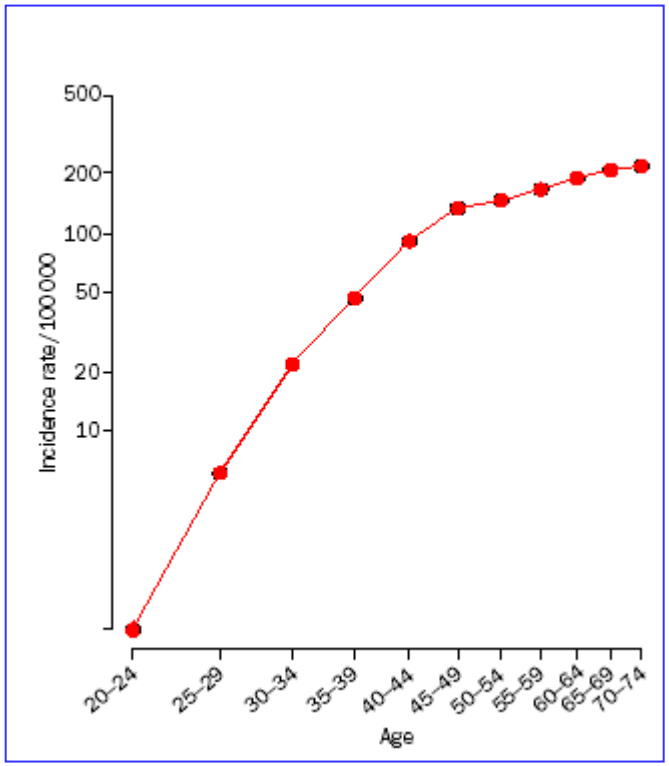
Table 1. Risk Factors for Breast Cancer.*

Risk Factor	Relative Risk
BRCA1 or *BRCA2* mutation	10.0–32.0
Family history of cancer (no known mutation)†	
1 first-degree relative	1.5–2.0
2 first-degree relatives	3.0
3 or more first-degree relatives	4.0
1 second-degree relative	1.2–1.5
Therapeutic radiation to chest at <30 yr of age‡	7.0–17.0
Hormonal factors	
Late (age >30 yr) parity or nulliparity	1.2–1.7
Early (age <12 yr) menarche or late menopause (age >55 yr)	1.2–1.3
Combined hormone-replacement therapy (e.g., for 10 or more yr)	1.5
Postmenopausal obesity	1.2–1.9
Alcohol consumption (2 drinks/day vs. none)	1.2
Smoking before first live birth	1.2
Sedentary lifestyle	1.1–1.8
White race	1.1–1.5
Breast density (very dense vs. mainly fatty)	5.0
Atypical ductal or lobular hyperplasia or lobular carcinoma in situ on previous breast biopsy	4.0



Ellen Warner, M.D. N ENGL J MED 365;11

Riesgos y opciones

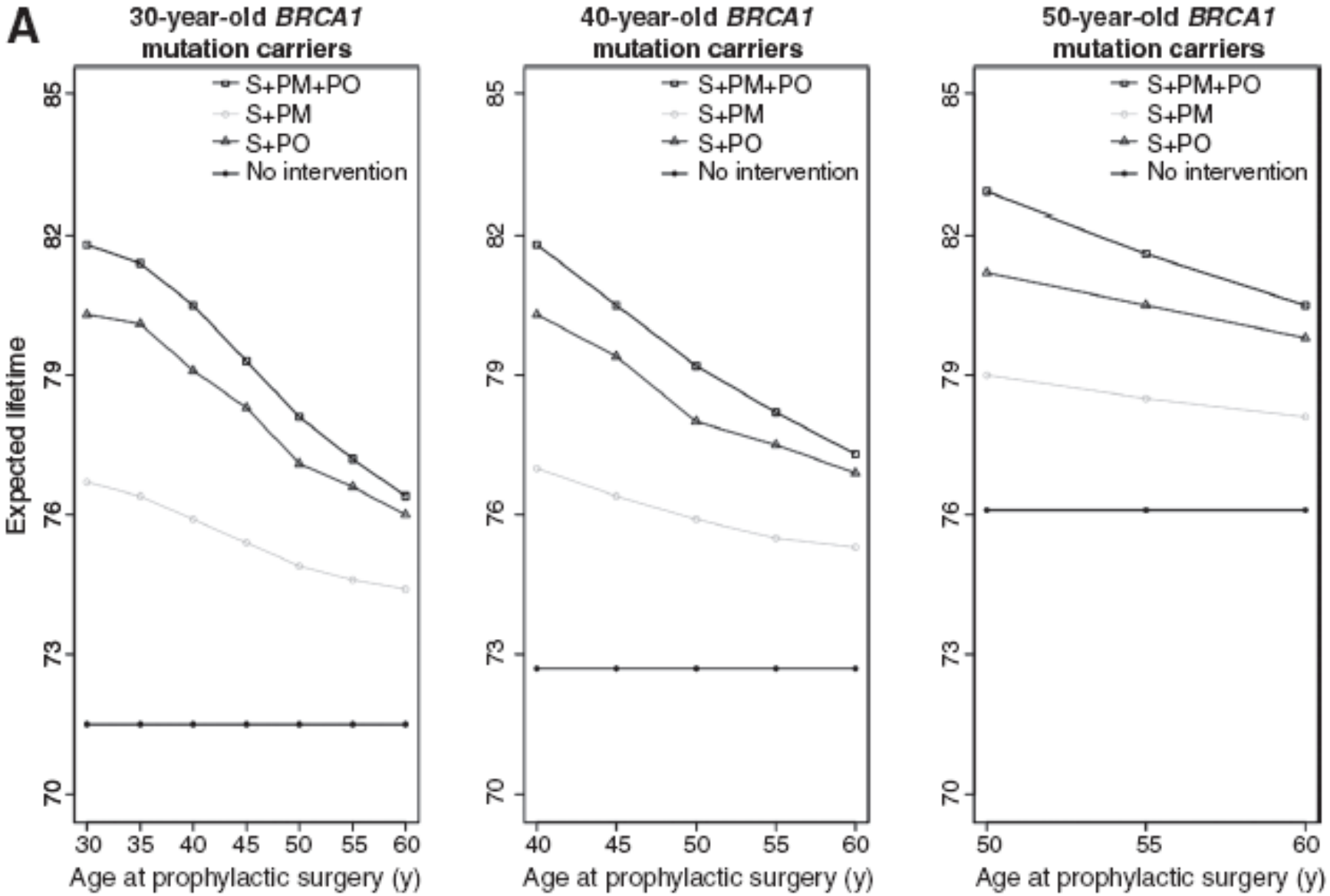
- BRCA 1 y 2:
  - 40-66% de probabilidad de cáncer de mama
  - 13-46% de probabilidad de cáncer de ovario
- Opciones:
  - Mastectomía profiláctica: ↓Riesgo de CM en un 90-95%
  - Ooforectomía profiláctica: ↓Riesgo de CO en un 80-90%
    ↓Riesgo CM en un 50-70% (PREM)

    Dudas en BRCA1

    Exceso de mortalidad por Parkinson y Demencia.
  - Cribado específico
  - SERMs
- Impacto real desconocido.
- ¿Hay un exceso de indicaciones basadas en la cirugía oncoplástica?

	Life expectancy,[a] y					
	BRCA1 mutation carrier Age at carrier status determination, y			*BRCA2* mutation carrier Age at carrier status determination, y		
Strategy	30	40	50	30	40	50
No S and no PM and no PO	41.5	32.7	26.1	48.6	39.4	30.7
Gain in life expectancy, y						
S[b]	2.6	2.2	1.4	1.6	1.4	1.0
PM	5.2	4.3	2.8	3.1	2.7	2.0
PO	7.4	6.1	3.3	3.0	2.4	1.3
PM and PO	10.3	9.1	6.8	4.4	3.9	3.4
S and PO	8.8	7.6	5.1	3.7	3.1	2.4
Gain in life expectancy when prophylactic surgery is delayed by 5 y						
Delayed PM	4.6	3.0	1.7	2.9	2.3	1.3
Delayed PO	7.0	5.0	2.7	2.9	2.2	0.9
Delayed PM and PO	9.6	7.0	4.8	4.1	3.4	2.3
S and delayed PM	4.9	3.7	2.4	3.0	2.5	1.7
S and delayed PO	8.6	6.7	4.4	3.6	3.0	2.0
S and delayed (PM and PO)	9.9	7.8	5.5	4.2	3.6	2.7
Gain in life expectancy when prophylactic surgery is delayed by 10 y						
Delayed PM	3.7	1.8	1.0	2.5	1.7	0.8
Delayed PO	5.5	2.8	2.1	2.3	1.2	0.5
Delayed PM and PO	8.2	5.0	3.2	3.7	3.0	1.4
S and delayed PM	4.4	3.2	2.0	2.8	2.2	1.5
S and delayed PO	7.6	5.3	3.7	3.3	2.7	1.6
S and delayed PM and PO	9.0	6.5	4.4	4.0	3.6	2.0

Sigal et al, Cancer Epidemiol Biomark Prev 2012



Sigal et al, Cancer Epidemiol Biomark Prev 2012

Satisfacción e impacto sociopsicológico

- 54 pts. Mastectomía bilateral + RI
- Posición: 77%
- Simetría: 89%
- Tasa de complicación: 18%
- Reintervención: 11%
- Satisfacción: 3 cuestionarios: Alta
- Repetir misma cirugía: 100%

- *Isern AE et al, J Plast Reconstr Aesthet Surg. 2008*

- 23 estudios. 4000 pts
- most of the women deemed high risk by family history (but not necessarily BRCA 1 or 2 mutation carriers) who underwent these procedures would not have died from breast cancer, even without prophylactic surgery. Therefore, women need to understand that this procedure should be considered only among those at very high risk of the disease. For women who had already been diagnosed with a primary tumor, the data were particularly lacking for indications for contralateral prophylactic mastectomy. While it appeared that contralateral mastectomy may reduce the incidence of cancer in the contralateral breast, there was insufficient evidence about whether, and for whom, CPM actually improved survival.

Lostumbo LT et al, Cochrane Database Syst Rev 2004

- Physical morbidity is not uncommon following PM, and many women underwent unanticipated re-operations (usually due to problems with reconstruction): 30-49%.
- Regarding psychosocial outcomes, women generally reported satisfaction with their decisions to have PM but reported satisfaction less consistently for cosmetic outcomes, with diminished satisfaction often due to surgical complications. Therefore, physical morbidity and post-operative surgical complications were areas that should be considered when deciding about PM
- Of the psychosocial outcomes measured, body image and feelings of femininity were the most adversely affected.

Lostumbo LT et al, Cochrane Database Syst Rev 2004

- 620 pts 1960-93 con MPC
- >10 años de seguimiento: Satisfechas: 83%
- Menor satisfacción con mastectomía subcutánea
- Satisfacción negativa en:
  - Sentimiento de femineidad: 33%
  - Apariencia corporal: 26%
  - Relaciones sexuales: 23%

Frost M et al, J Clin Oncol 2005

Nuevas tendencias en el tratamiento del cáncer de mama c-erb-B2+

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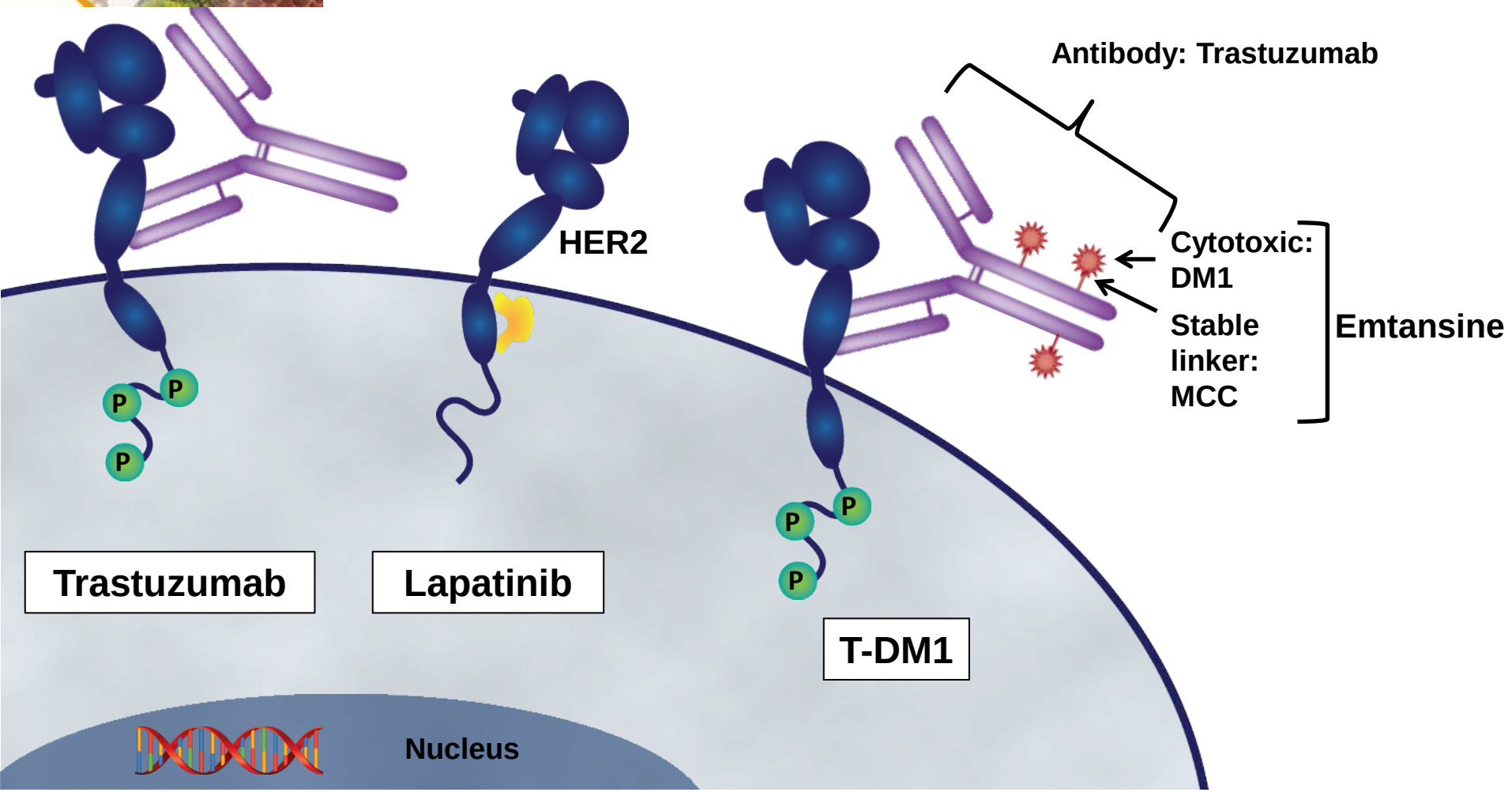
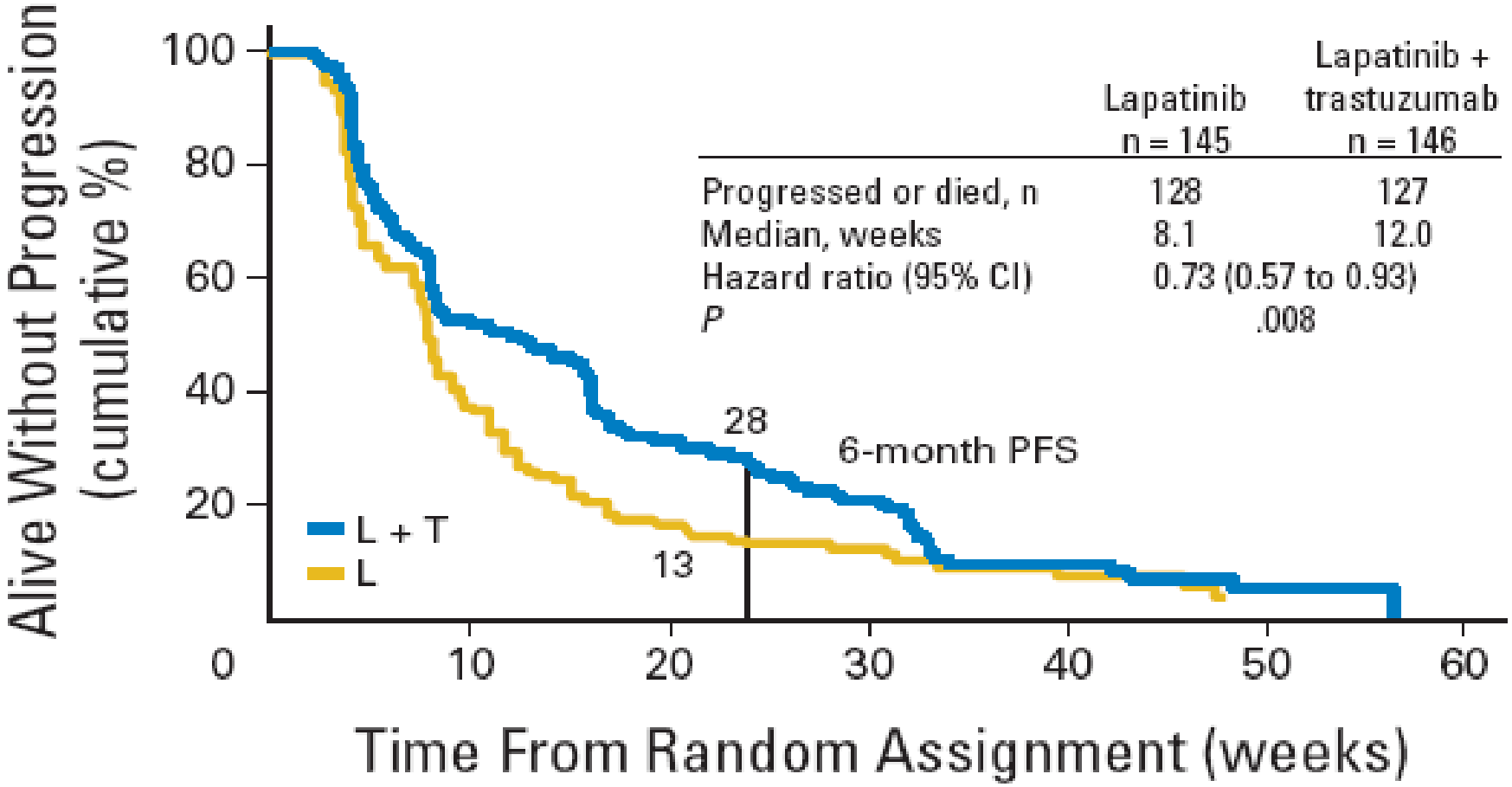
- Paradigma de la terapia dirigida en cáncer de mama. Vía HER2: Valor pronóstico y predictivo
- Impacto en supervivencia en enfermedad avanzada y en la enfermedad inicial

Targeted Therapies for HER2+ Breast Cancer: Trastuzumab, Lapatinib, and T-DM1



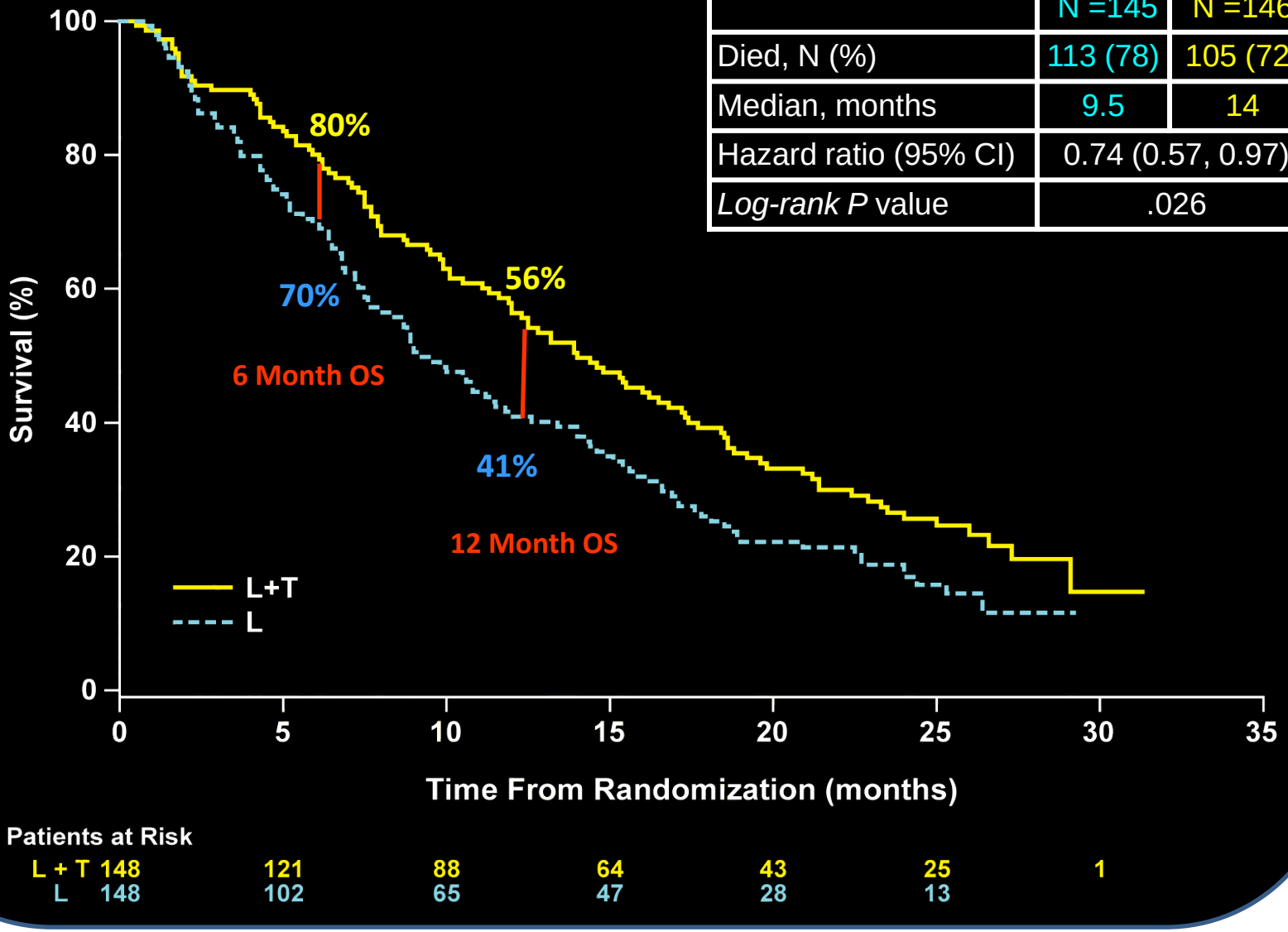
Spector NL, Blackwell KL. *J Clin Oncol* 2009; Nelson MH, et al. *Ann Pharmacother* 2006; Lewis Phillips GD, et al. *Cancer Res* 2008.



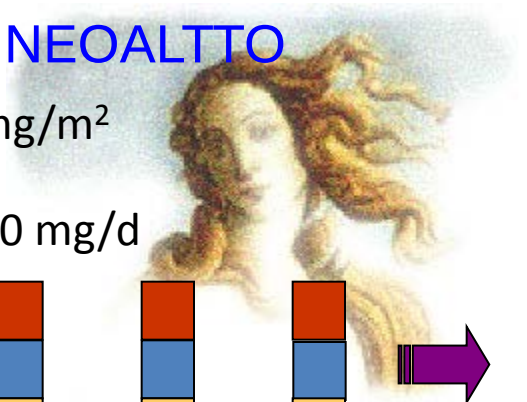
El doble bloqueo de Her-2 incrementa SLP y SG en cáncer de mama metastásico Her2+. *Blackwell KL et al; JCO 2010*

Updated Overall Survival in ITT

	L N =145	L+T N =146
Died, N (%)	113 (78)	105 (72)
Median, months	9.5	14
Hazard ratio (95% CI)	0.74 (0.57, 0.97)	
Log-rank P value	.026	



ESTUDIO NEOALTTO



Paclitaxel 80 mg/m^2

Lapatinib: 1500 mg/d

CIR

Lapatinib: 1000 mg/d → 750 mg/d

6 sem

12 sem

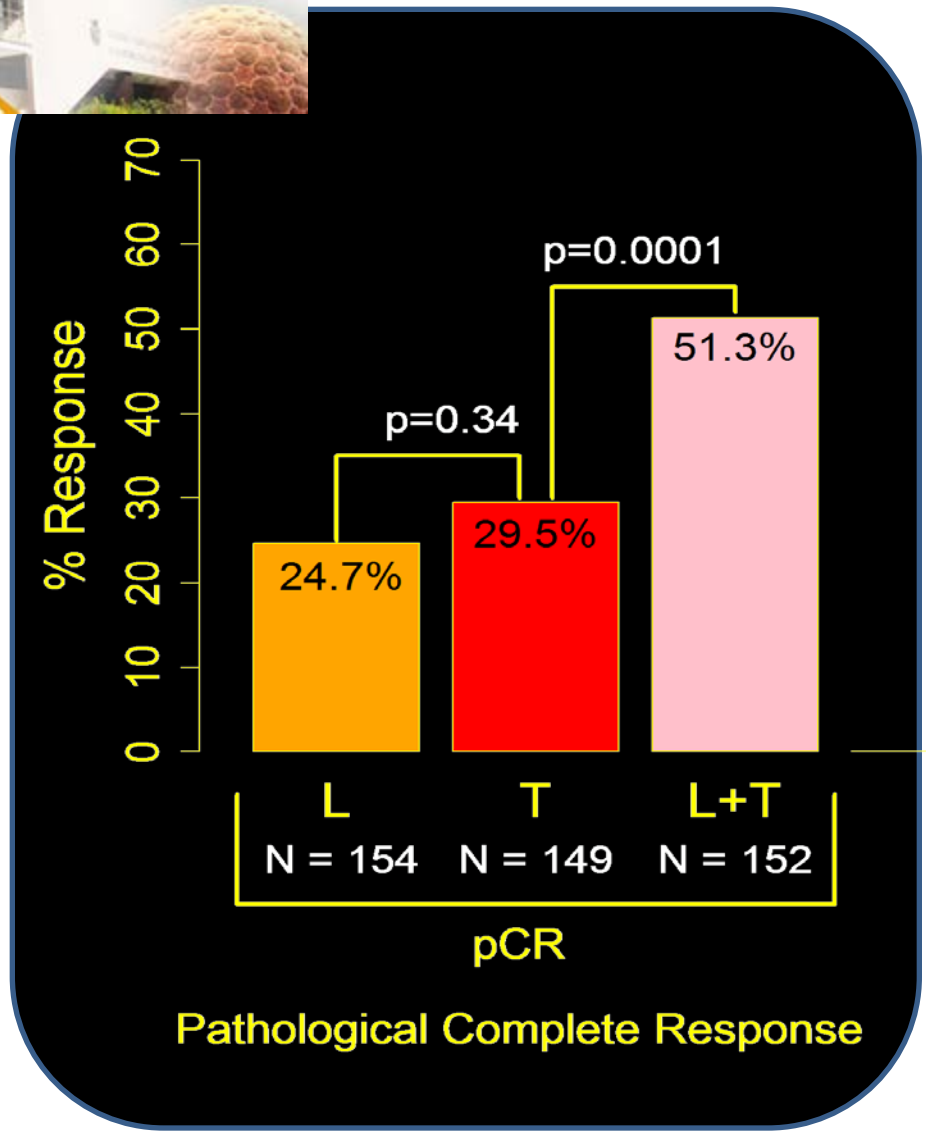
FEC cada 3 sem

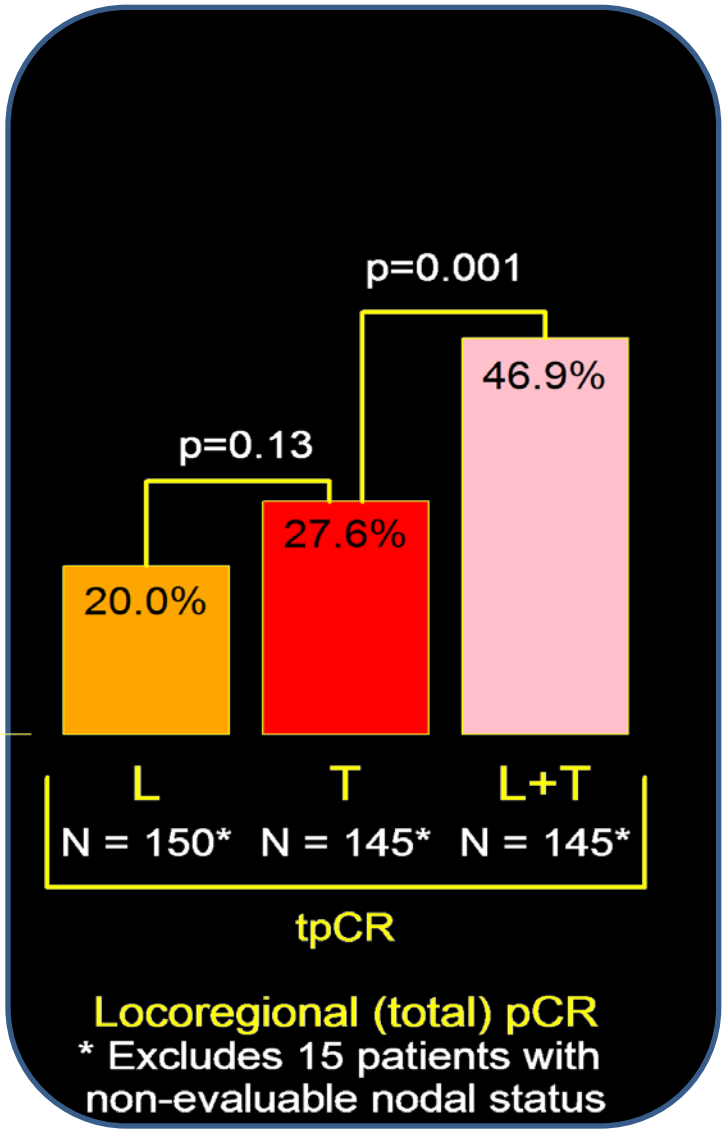
34 sem

34 sem

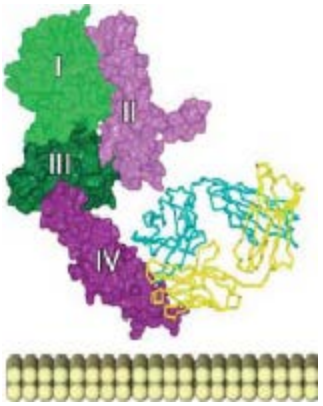
34 sem

Eficacia: pCR and tpCR

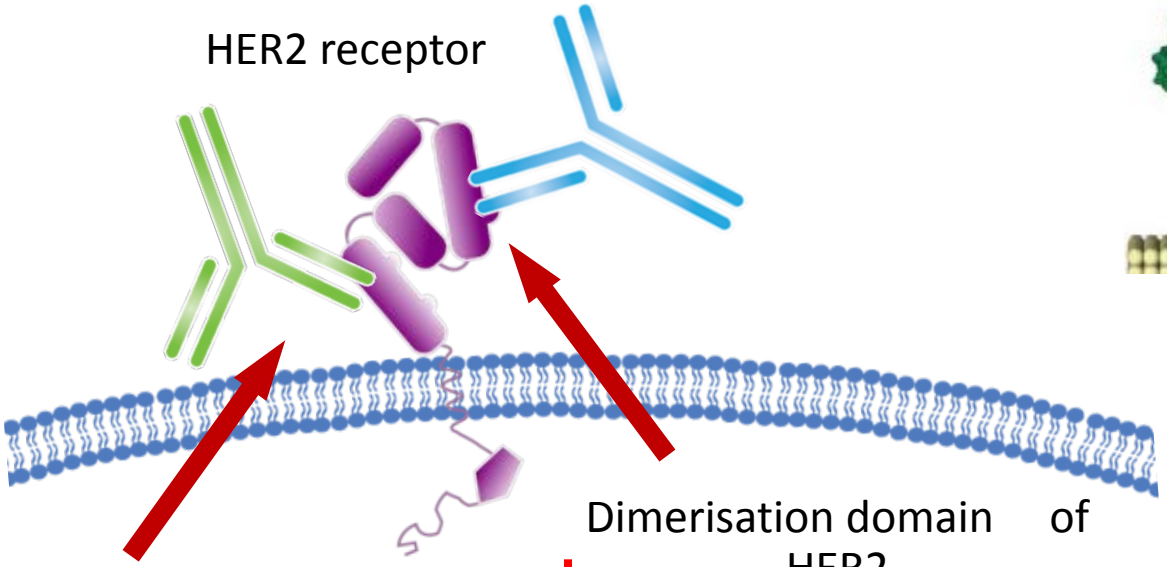


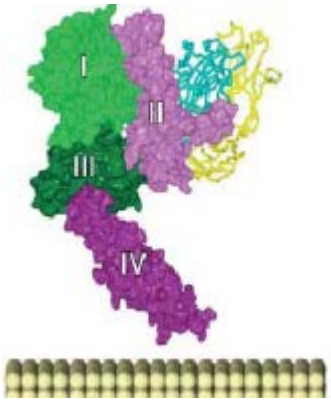


Pertuzumab se une al subdominio responsable de la formación de dímeros



Trastuzumab





Pertuzumab

- Herceptin continually suppresses HER2 activity
- Flags cells for destruction by the immune system
- Does not inhibit HER2 dimerisation

- Pertuzumab inhibits HER2 forming dimer pairs
- Suppresses multiple HER signalling pathways
- Flags cells for destruction by the immune system

Papel de Trastuzumab+ Pertuzumab en la 1ª línea: El estudio CLEOPATRA

HER2-positivo CMM (n=800[a])

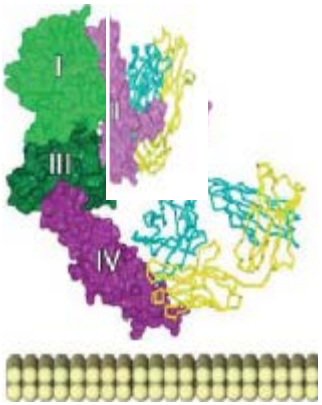
1:1

Docetaxel + Trastuzumab + Placebo

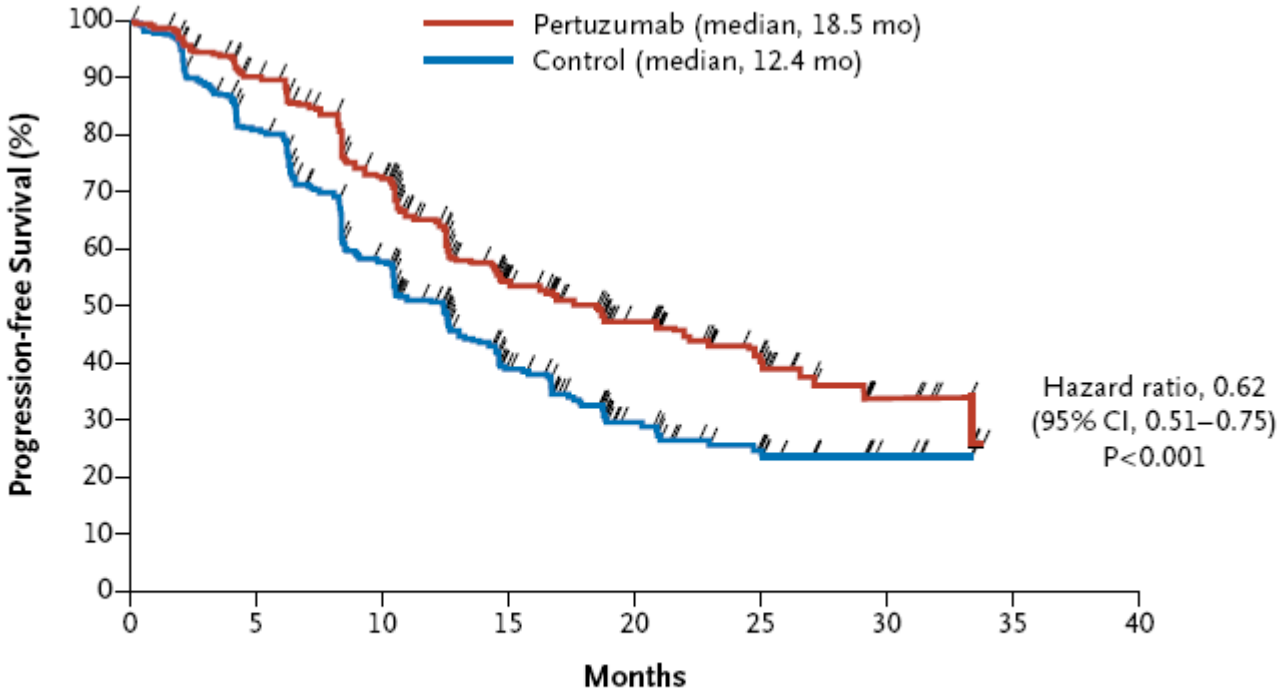
Docetaxel + Trastuzumab + Pertuzumab

Ensayo clínico Internacional fase III, doble ciego, controlado con placebo

- Objetivos
  - SLP y SG
  - QoL
  - Análisis de Biomarcadores



Baselga J et al, N Eng J Med 2012

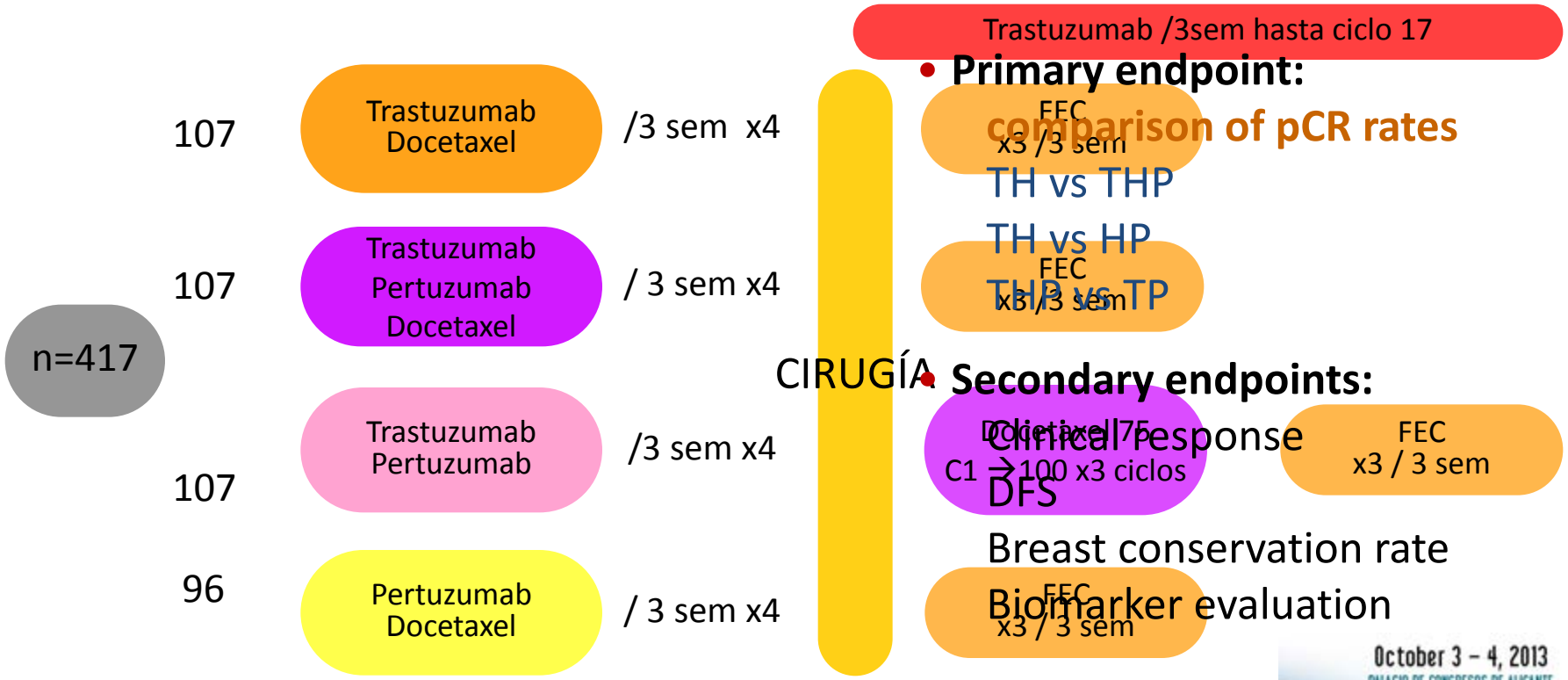


No. at Risk

Pertuzumab	402	345	267	139	83	32	10	0	0
Control	406	311	209	93	42	17	7	0	0

- Her2 +
- >2 cm
- Operable y Loc. Avanz.

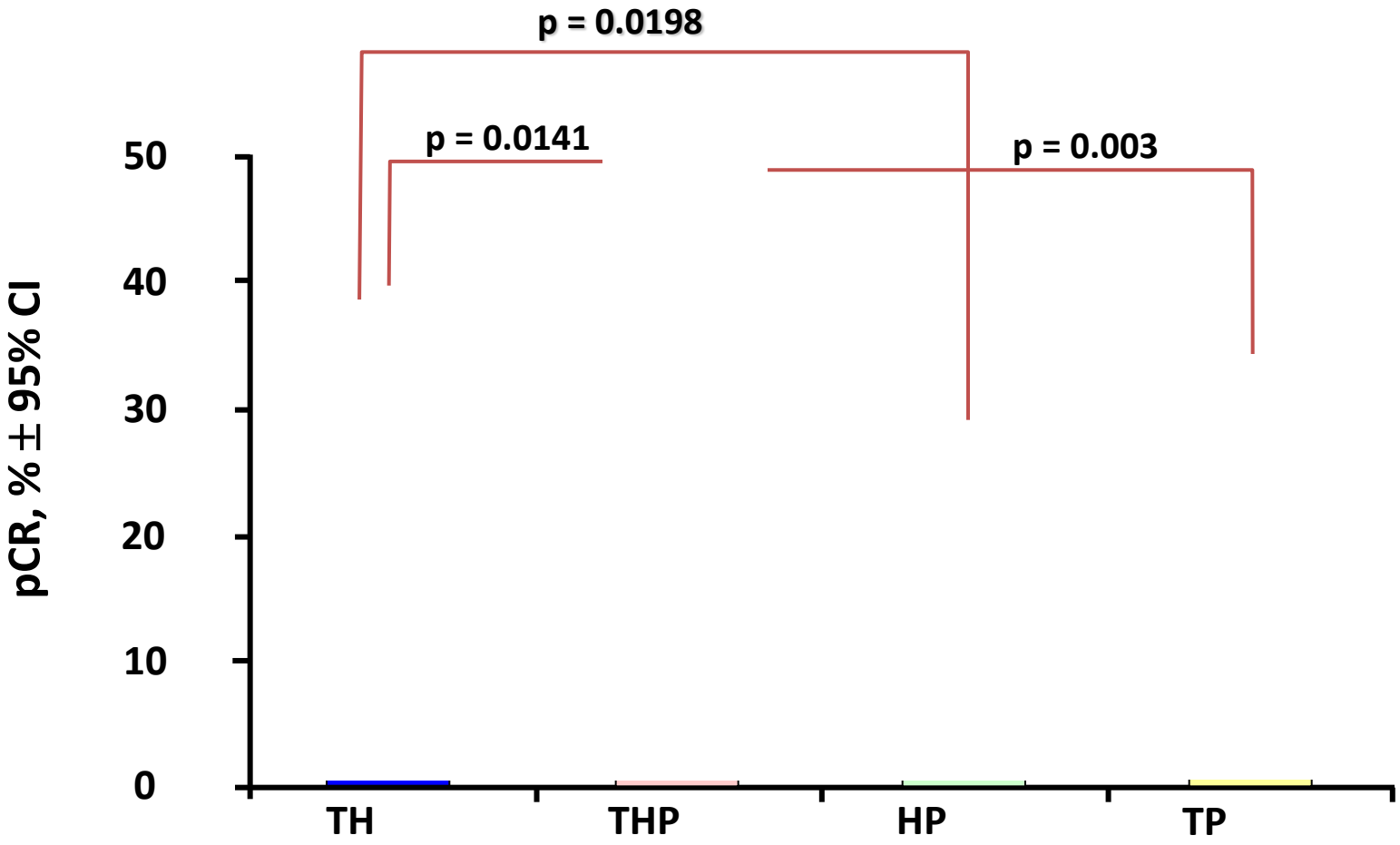
Diseño del Neosphere



- **Primary endpoint:**
  - **comparison of pCR rates**
    - TH vs THP
    - TH vs HP
    - THP vs TP
- **Secondary endpoints:**
  - Clinical response
  - DFS
  - Breast conservation rate
  - Biomarker evaluation

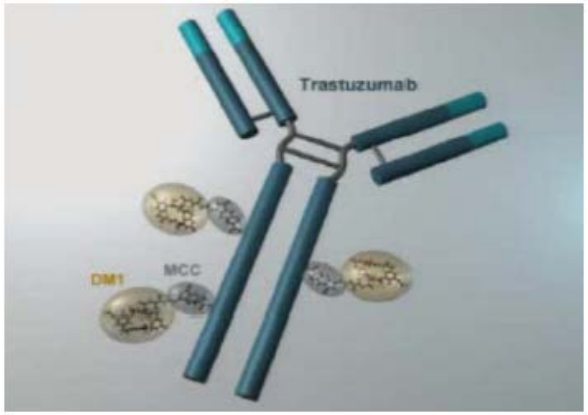
FEC = 5-fluorouracilo, epirrubicina, ciclofosfamida;

NeoSphere. Eficacia. Objetivo 1º: pCR



H, trastuzumab; P, pertuzumab; T, docetaxel

T-DM1: Conjugado Anticuerpo-Quimioterapia



Diana de expresión selectiva: HER2

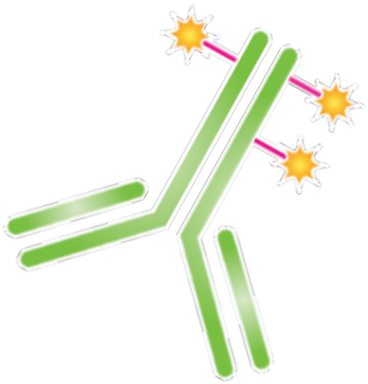
Anticuerpo monoclonal: Trastuzumab

Agente citotóxico: DM1

Quimioterapia, derivada de la maytansina

Linker

MCC: Muy estable
Ruptura intracelular

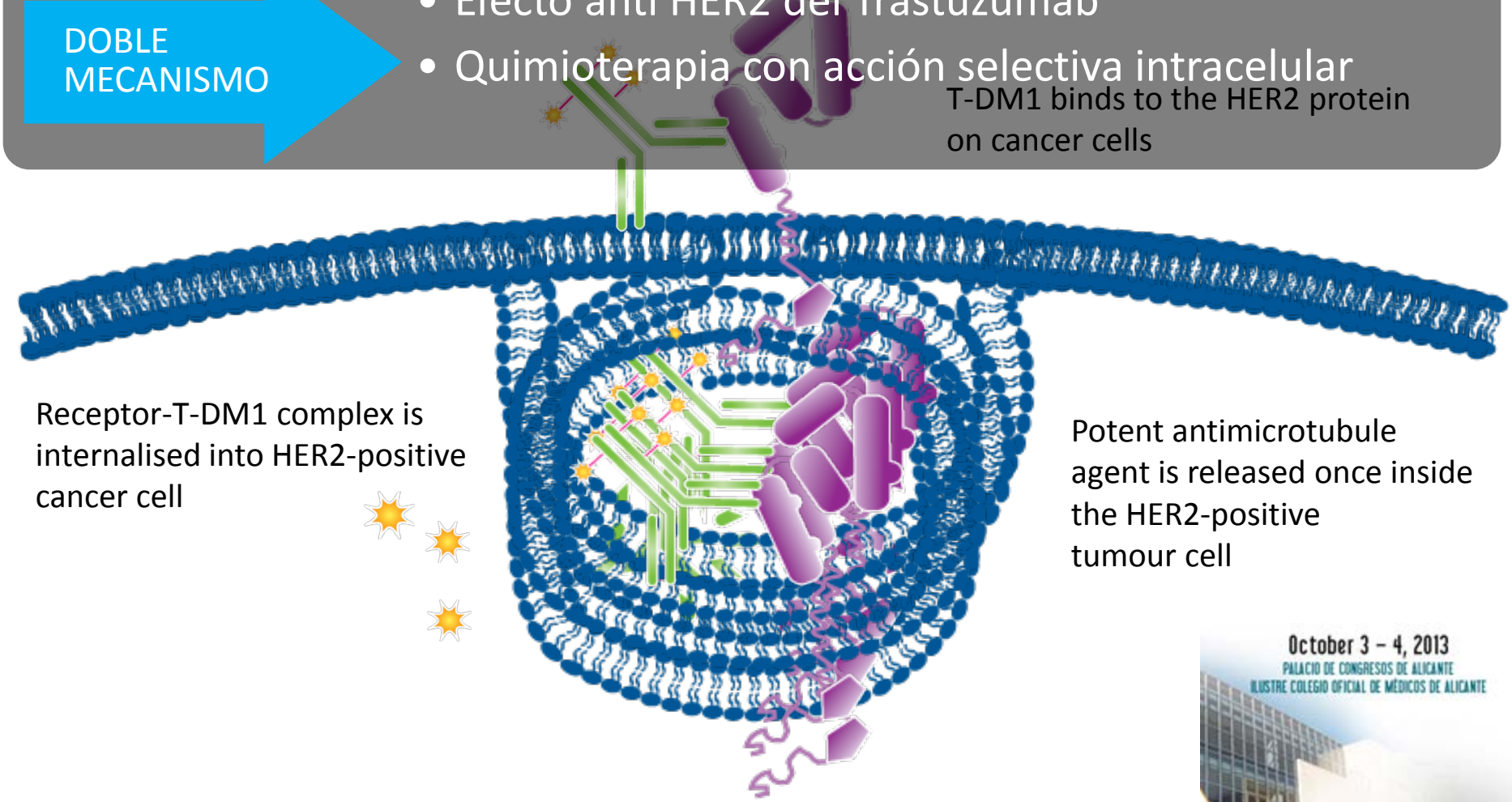


T-DM1

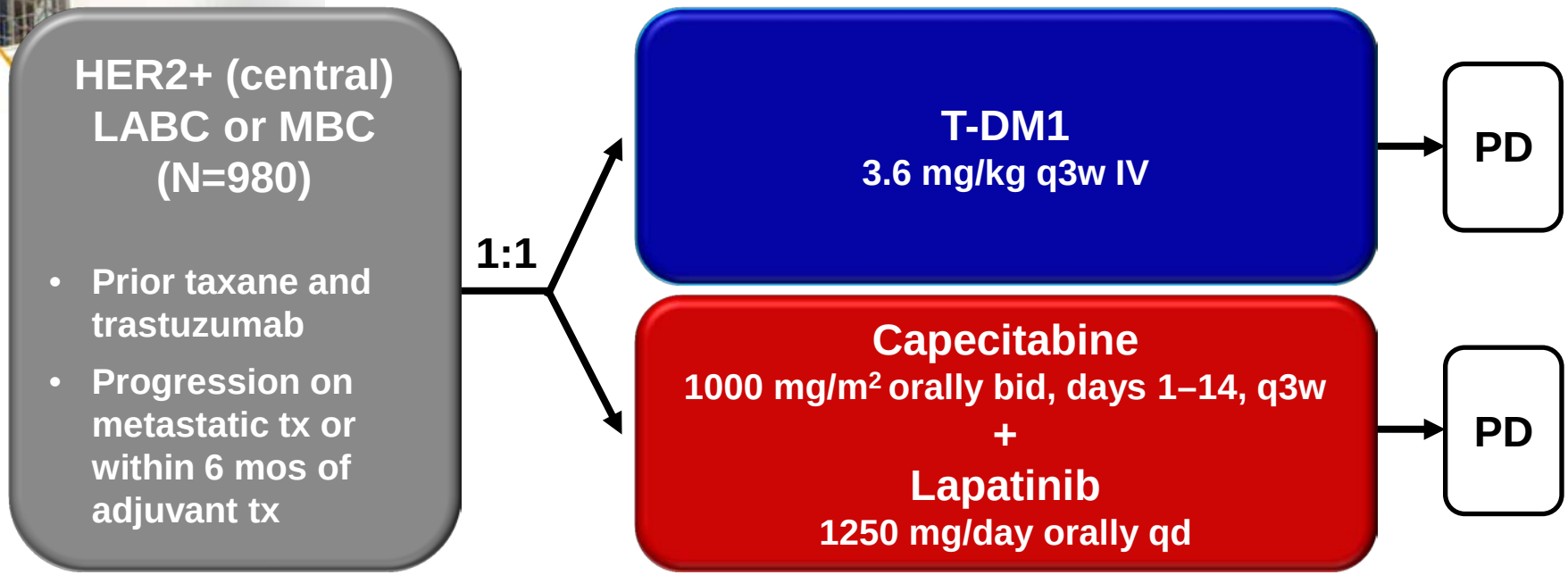
T-DM1 deposita selectivamente una altísima carga citotóxica en la célula HER2+

DOBLE MECANISMO

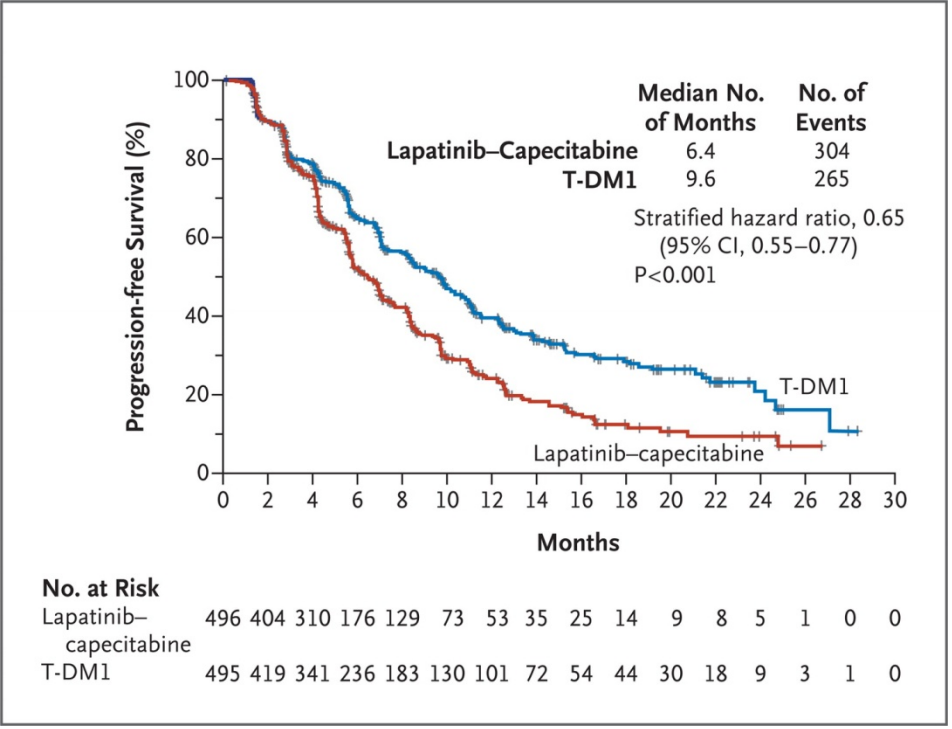
- Efecto anti HER2 del Trastuzumab
- Quimioterapia con acción selectiva intracelular



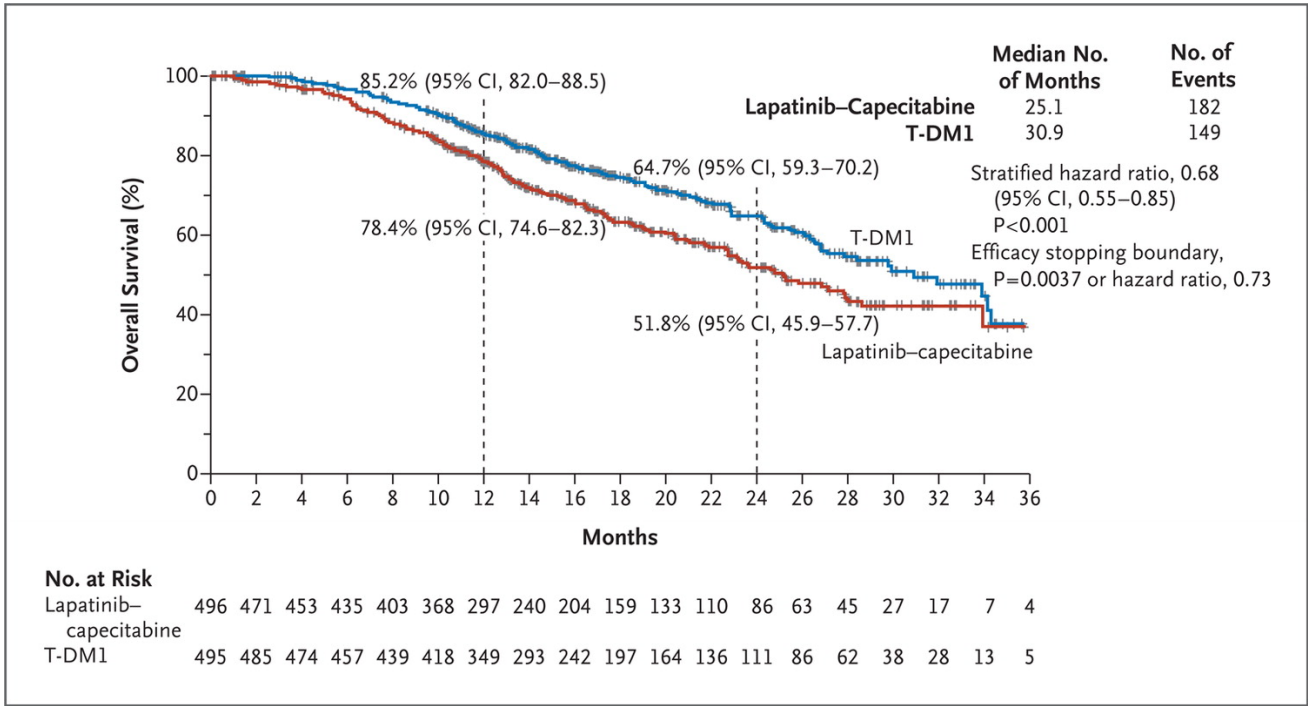
EMILIA Study Design



- **Stratification factors:** World region, number of prior chemo regimens for MBC or unresectable LABC, presence of visceral disease
- **Primary end points:** PFS by independent review, OS, and safety
- **Key secondary end points:** PFS by investigator, ORR, duration of response, time to symptom progression



Verma S et al, N Eng J Med 2012



RESONANCIA MAMARIA Y RESPUESTA PATOLÓGICA COMPLETA.

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Indicaciones para RMN

Lesion characterization

Neoadjuvant chemotherapy

Infiltrating lobular carcinoma

Infiltrating ductal carcinoma

Axillary adenopathy, primary unknown

Postoperative tissue reconstruction

Silicone and non-silicone breast augmentation

Invasion deep to the fascia

Contralateral breast examination in patients with breast malignancy

Postlumpectomy for residual disease

Surveillance of high-risk patients

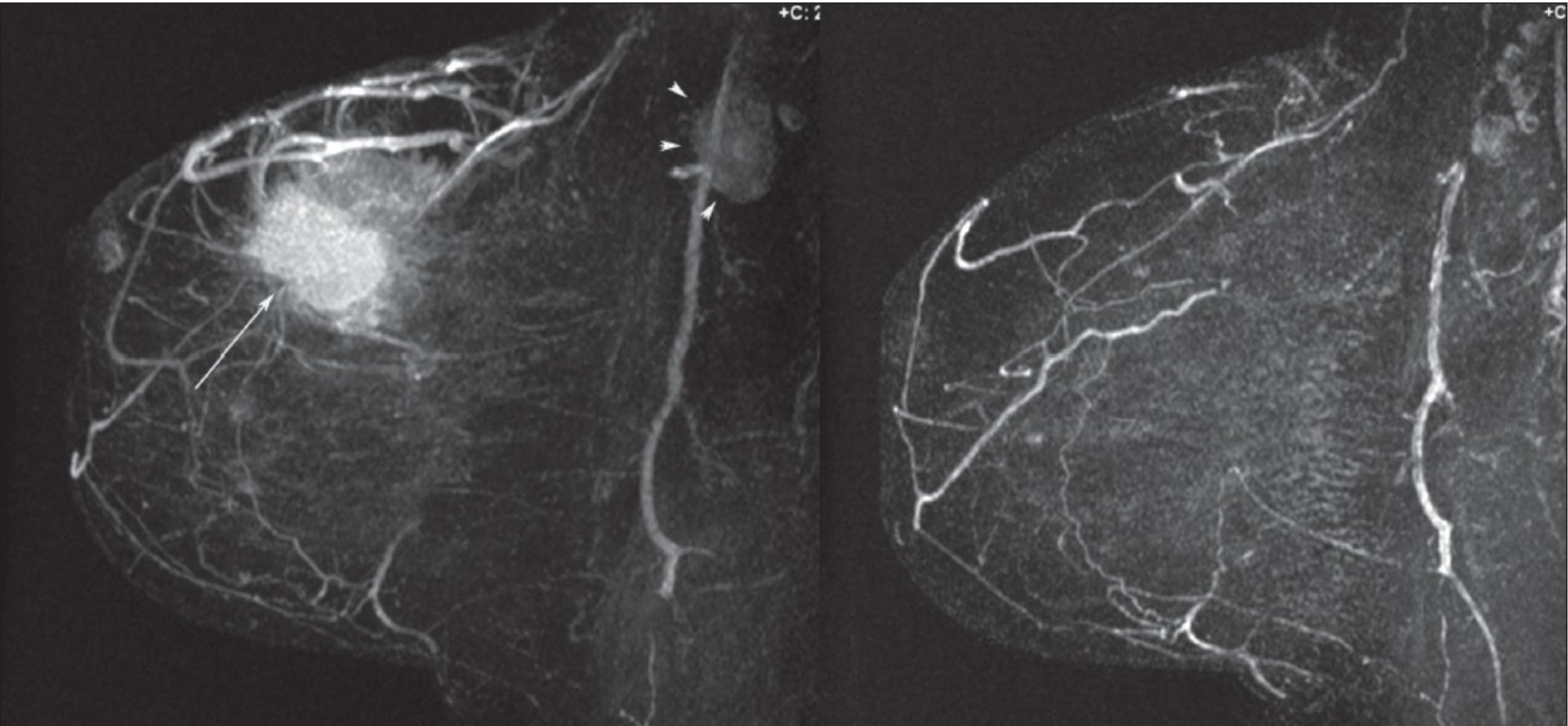
Recurrence of breast cancer

American College of Radiology Practice Guidelines for the Performance of Magnetic Resonance Imaging of the Breast

Cancer

- 746 pts
- rCR: 182/746 (24%)
- pCR: 179/746 (24%)
- Overall accuracy: 74%
- VPN HER2+: 62%
- VPN TN: 60%

De los Santos J et al, Cancer 2013


+C: 2
+C

Insights Imaging (2013) 4:163–175
DOI 10.1007/s13244-013-0219-y

ORIGINAL ARTICLE

The role of magnetic resonance imaging in assessing residual disease and pathologic complete response in breast cancer patients receiving neoadjuvant chemotherapy: a systematic review

M. B. I. Lobbes · R. Prevos · M. Smidt · V. C. G. Tjan-Heijnen · M. van Goethem · R. Schipper · R. G. Beets-Tan · J. E. Wildberger

3119 estudios------→35 (2539 pts). 27 prospectivos

	SENSIBILIDAD	ESPECIFICIDAD	VPP	VPN	
	25-100%	50-97%	47-73%	71-100%	

- Buena correlación
- Variable según fenotipo tumoral
- Variable según agente antineoplásico empleado
- Muy superior al examen físico, a la mamografría y a la ecografia
- Riesgo de infra y sobreestimación

Reflexiones

- Predecir la pCR…
  - …¿sirve para algo?
- Predicción positiva: pCR SÍ
  - ¿Vamos a obviar la cirugía?
- Predicción negativa: pCR NO
  - A fecha de hoy no cambia la decisión de tto

Conclusión

- La RMN sirve para lo que sirve

Resistencia a la terapia hormonal

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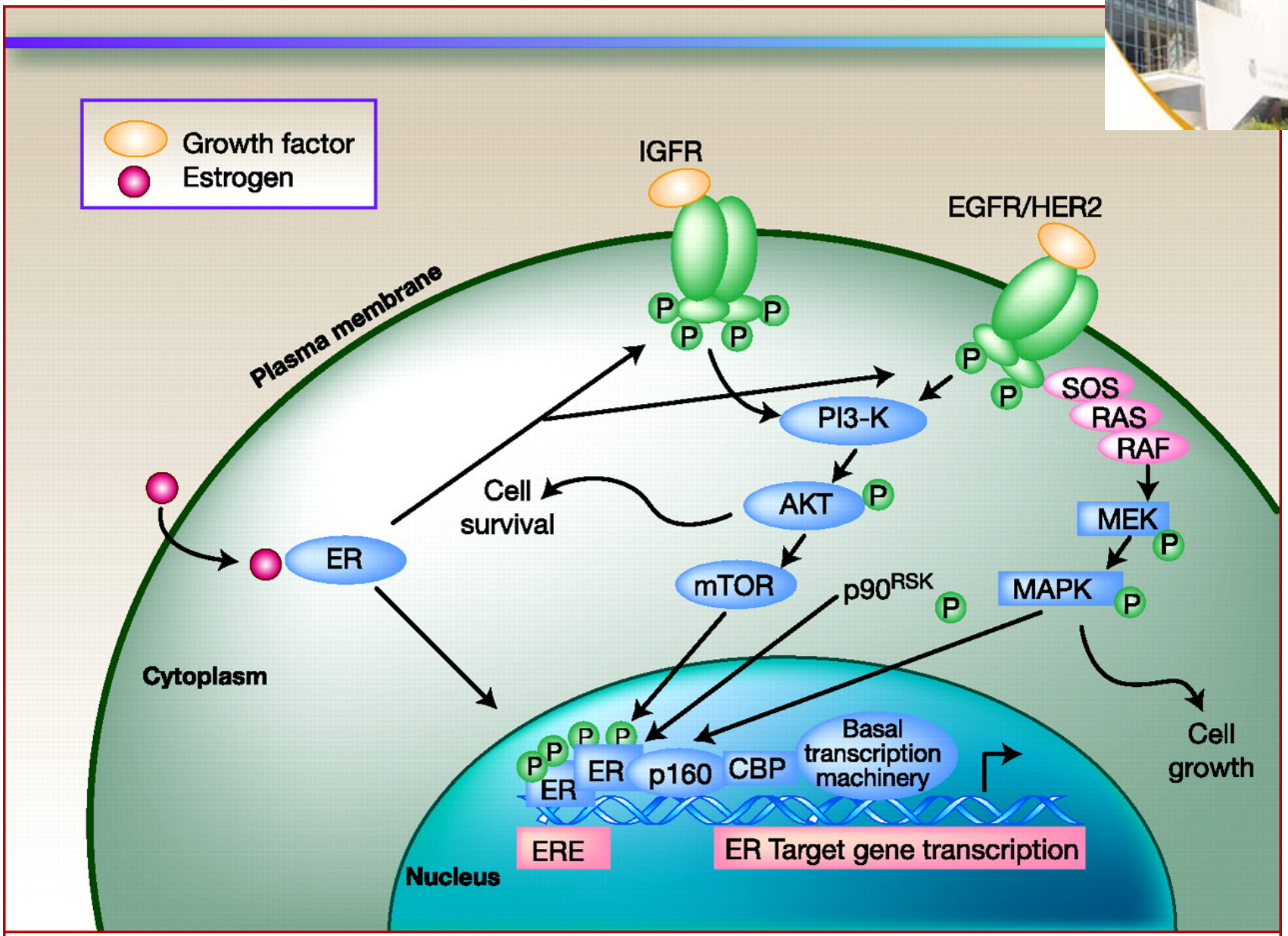
a

AI
F
E
T
HB-EGF
MMPs
ER
G-Protein
GFRs:
EGFR
HER2
IGFR
P
b
Cytokines
Hypoxia
Os/ROS
Stress
c
Jagged
Delta
NICD
Notch
PI3K
Ras
AKT
MAPK
p38
JNK
ER
CoA
Src
Migration
Invasion
Phosphorylation
(ER,TFs, CoAs)
e
Altered expression
miRNAs
d
High levels CoA
or
Low levels CoR
e
miRNAs
ER
CoA
Transcription
AP-1/SP-1
CoR
No
Transcription
Nucleus
Endocrine resistance


Growth factor
Estrogen
IGFR
EGFR/HER2
Plasma membrane
P
PI3-K
SOS
RAS
RAF
Cell survival
AKT
MEK
ER
mTOR
p90RSK
MAPK
Cytoplasm
Cell growth
Basal transcription machinery
ER
p160
CBP
ERE
ER Target gene transcription
Nucleus

TAMRAD

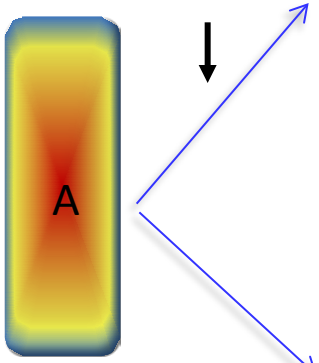
Bachelot T, et al. SABCS 2010. Abstract S1-6.

- Estudio fase II Aleatorizado
  - Objetivo primario: CBR a 6 m (RC + RP + EE)

Estratos: Resistencia hormonal 1ª vs 2ª

- RRHH+
- HER2-
- M1
- IA Previos

- (N = 111)

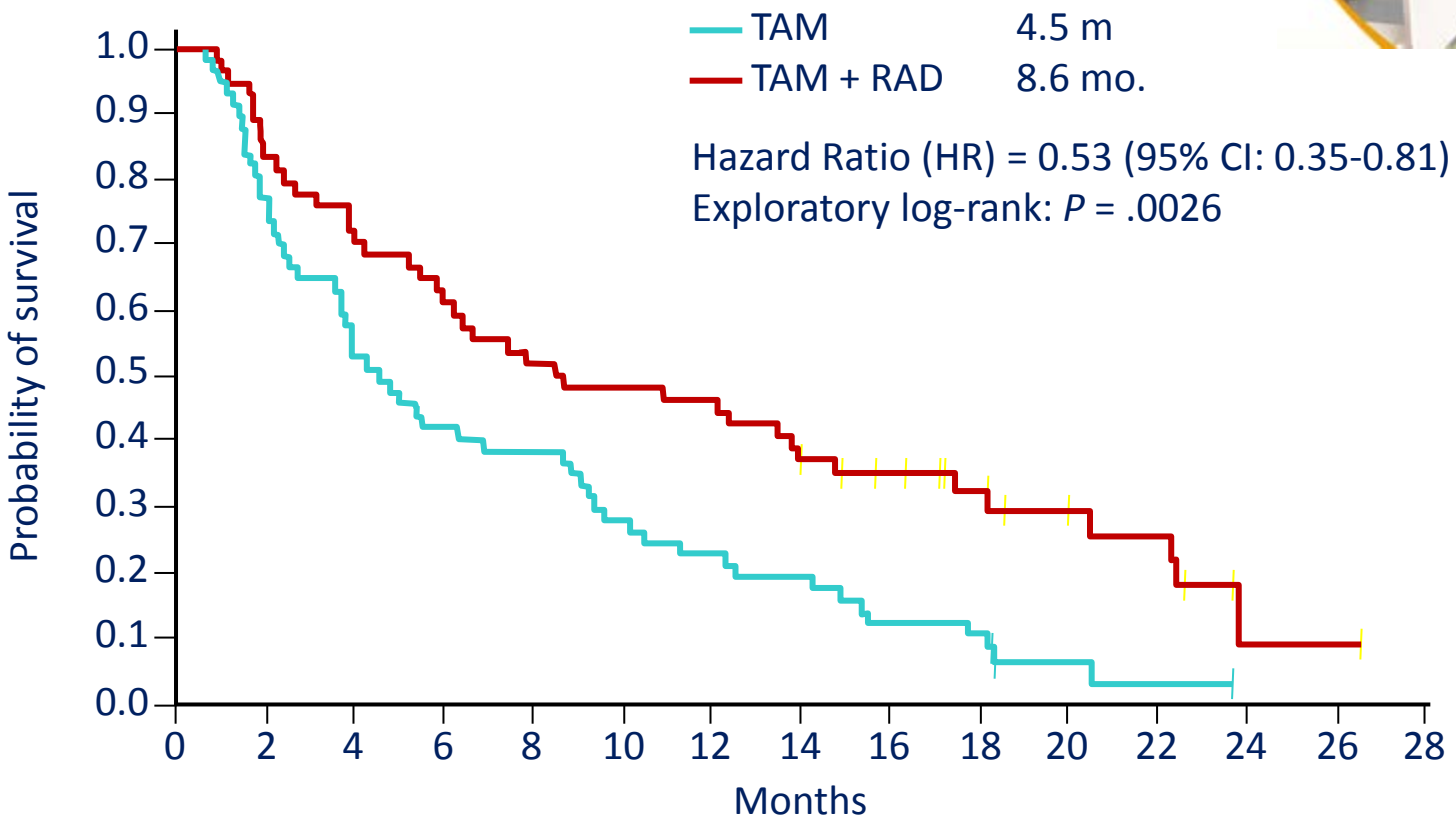


Everolimus 10 mg/ día + Tamoxifeno 20 mg/día
(n = 54)

Tamoxifeno 20 mg/día
(n = 57)

*Primary resistance: relapse during adjuvant AI therapy or progression during first 6 mos of initiating AI for metastatic disease. Secondary resistance: late relapse (at or after 6 mos) or previous response to AI therapy for metastatic breast cancer and subsequent progression.

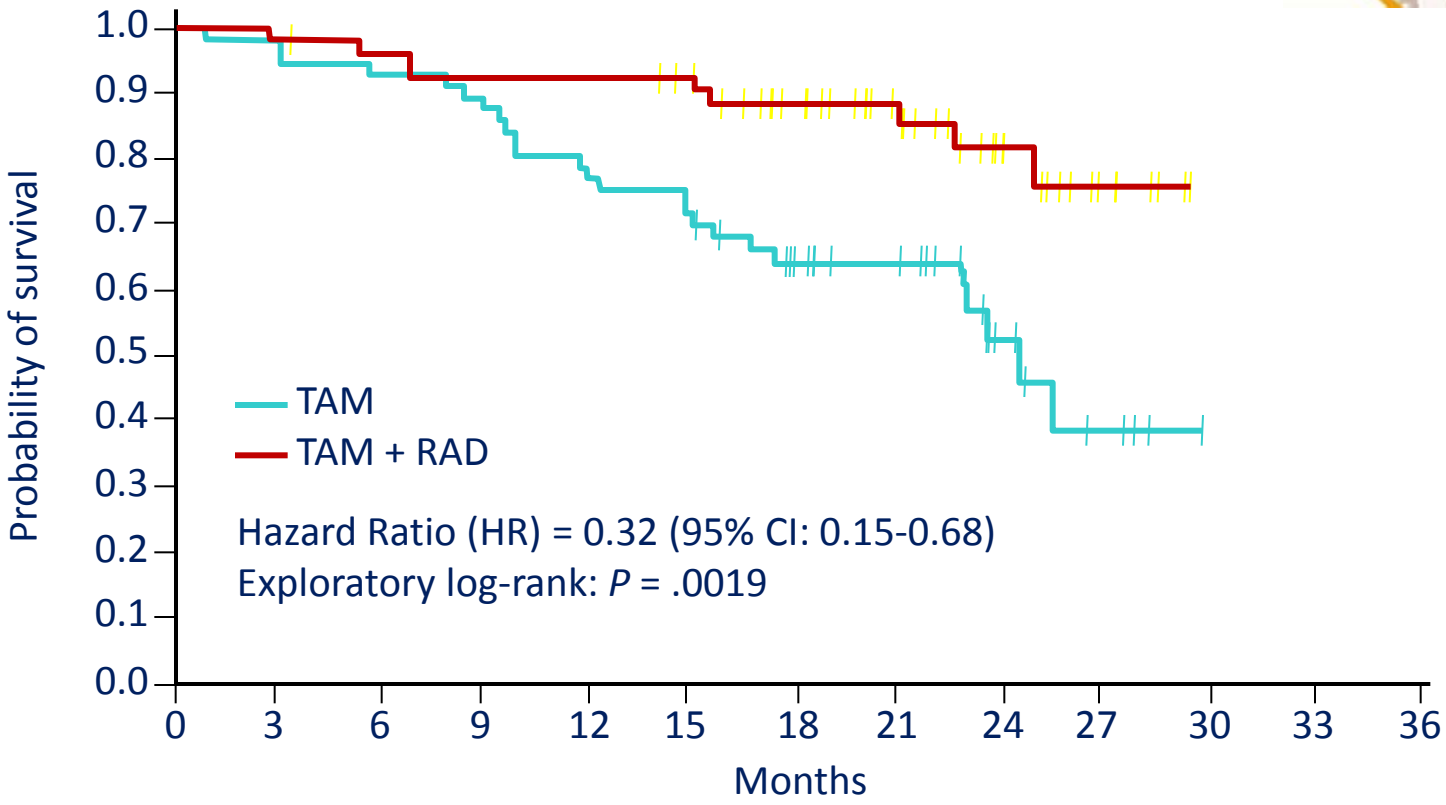
TAMRAD: SLP



Patients at risk:														
TAM + RAD: n =	54	45	39	34	28	26	25	19	16	12	9	7	1	1	0
TAM: n =	57	44	30	24	22	16	13	11	7	6	2	1	0	0	0

Bachelot T, et al. SABCS 2010. Abstract S1-6.

TAMRAD: SG



Patients at risk:											
TAM + RAD: n =	54	53	51	49	49	45	38	26	14	6	0
TAM: n =	57	55	53	50	44	38	30	22	9	4	0

Bachelot T, et al. SABCS 2010. Abstract S1-6.

BOLERO-2 (Ph III): Everolimus in Advanced BC

N = 724

- Postmenopausal ER+
- Unresectable locally advanced or metastatic BC
- Recurrence or progression after letrozole or anastrozole

R
2:1

- EVE 10 mg daily + EXE 25 mg daily (n = 485)
- Placebo + EXE 25 mg daily (n = 239)

Stratification: Sensitivity to prior hormone therapy and presence of visceral metastases

Endpoints

- **Primary:** PFS (local assessment)
- **Secondary:** OS, ORR, QOL, safety, bone markers, PK

BC = breast cancer; ER+ = estrogen receptor-positive; EVE = everolimus; EXE = exemestane; ORR, overall response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; QOL = quality of life.

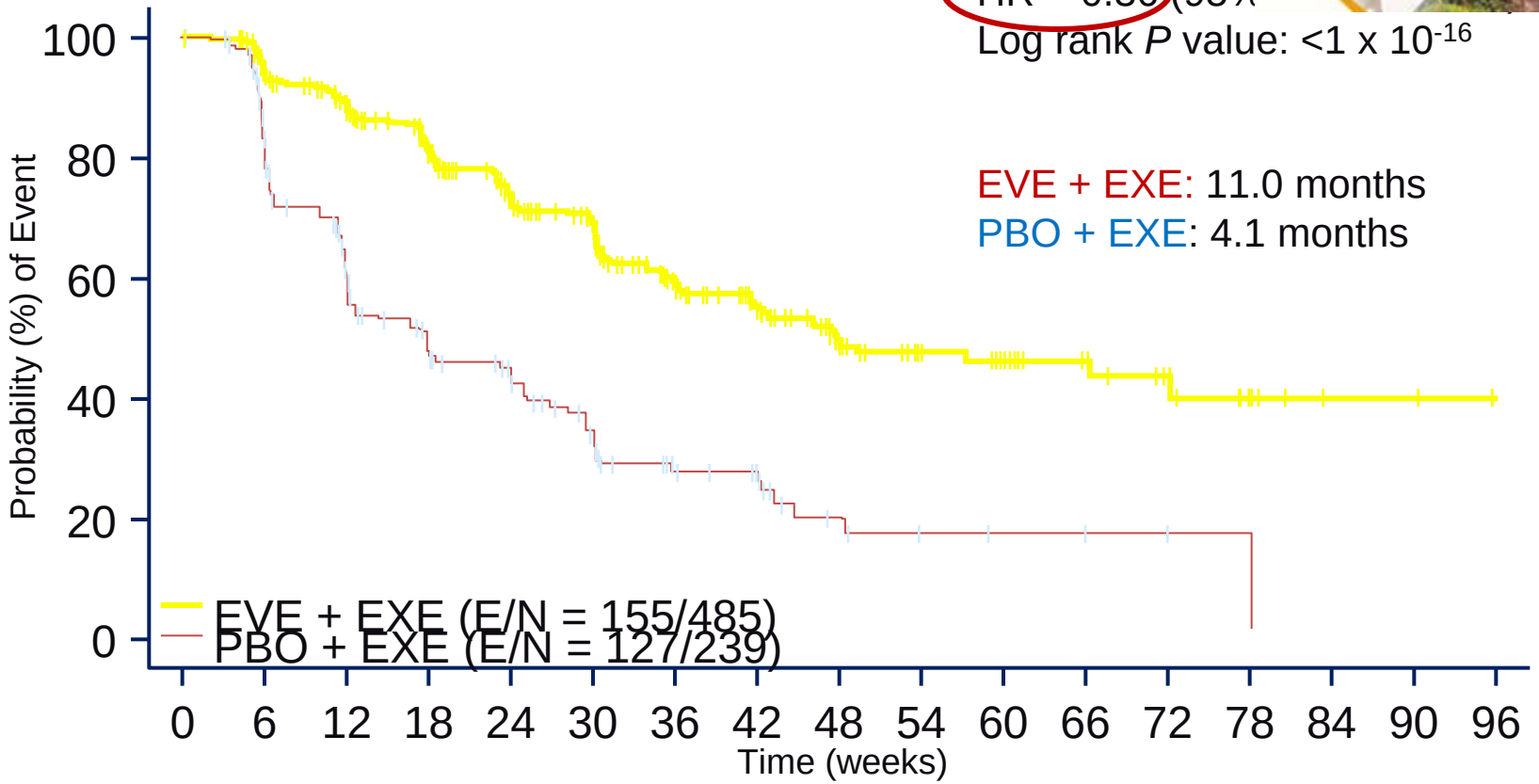
BOLERO-2 (12 mo f/up): PFS Central

HR = 0.36 (95%

Log rank *P* value: <1 x 10^{-16}

EVE + EXE: 11.0 months

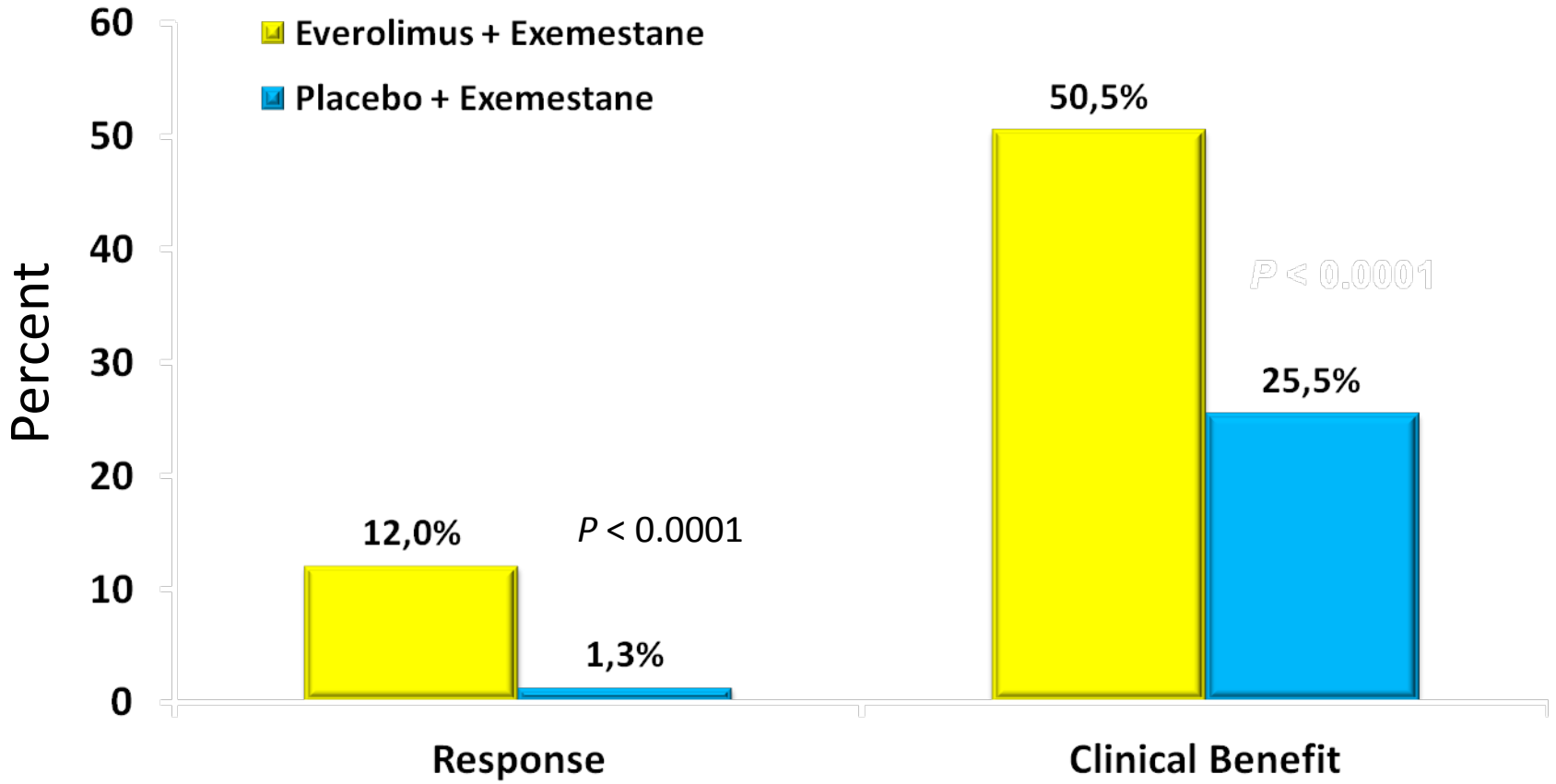
PBO + EXE: 4.1 months



Number of patients still at risk

Everolimus	485	422	351	284	224	176	119	86	57	38	32	22	12	7	2	2	0
Placebo	239	179	112	74	56	36	23	18	8	5	4	4	3	1	0	0	0

BOLERO-2 (12 mo f/up): Response & Clinical Benefit



Hortobagyi G. et al, SABCS 2011 (Abstract #S3-7)

En conclusión

- Por primera vez en 15 años, disponemos de una alternativa más para el tratamiento de los tumores luminales
- El impacto de everolimus supone una reducción del riesgo de progresar de un 64%, equiparable al impacto de trastuzumab en cáncer de mama HERR2+ o al de Imatinib en el tratamiento del GIST