XXIX Curso Avanzado de Oncología Médica

14 al 17 de JUNIO de 2017

San Lorenzo de El Escorial (Madrid)

CAOM 2017

Con el Aval Científico de: SEOM Sociedad Española de Oncología Médica

Organizado por: Grupo Oncosur

Situación Actual del Tratamiento Adyuvante en Cáncer de Mama

Luis Manso MD, PhD

Unidad Cáncer de Mama y T. Ginecológicos
Hosp. Univ. 12 de Octubre
Madrid

AGENDA

- Introducción, Fx Pronósticos y Predictivos.
- Heterogeneidad del cáncer de mama.
- Quimioterapia.
- Hormonoterapia.
- ¿Se puede evitar la quimioterapia en algunas pacientes?
- Terapia anti-HER2.
- Hábitos de vida.

AGENDA

Escalating and De-Escalating Treatment in Early Breast Cancer across Subtypes and Treatment Modalities

INTRODUCCIÓN

- El objetivo del tratamiento adyuvante es eliminar la enfermedad micro-metastásica.

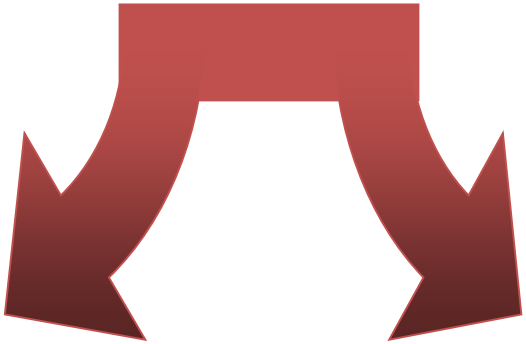
Para empezar…

- No dispones de métodos para detectar si existe enfermedad micro-metastásica.
- No podemos medir a corto plazo la eficacia del tratamiento.
- Gran parte de tu actividad se concentrará en un ejercicio de estimación de riesgos y probabilidad de mejora.
- Cada vez más tu paciente querrá participar en la gestión del riesgo.

Surg Gynecol Obstet. 1955 Jan;100(1):102-8.
The cytologic demonstration and significance of tumor cells in the mesenteric venous blood in patients with colorectal carcinoma.
FISHER ER, TURNBULL RB Jr.

INTRODUCCIÓN

Decisiones terapeúticas en el tratamiento adyuvante del cáncer de mama precoz:



En quién puede evitarse el tratamiento?

Qué tratamiento es el mejor?

Factores pronósticos

TNM, GRADO, RE, HER2, HISTOLOGIA COMORBILIDADES, EDAD

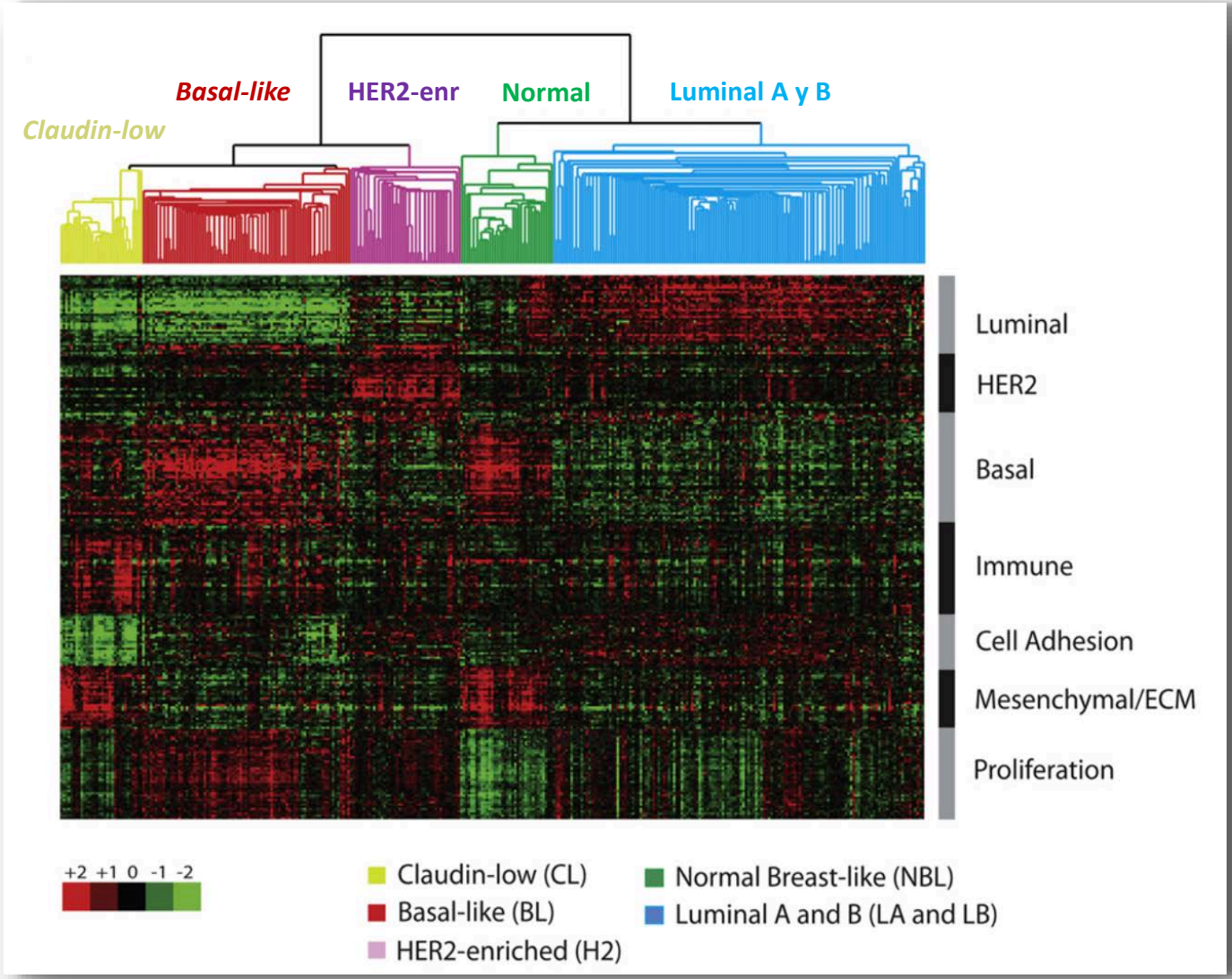
Factores predictivos

TNM, GRADO, **RE, HER2,** HISTOLOGIA COMORBILIDADES, EDAD

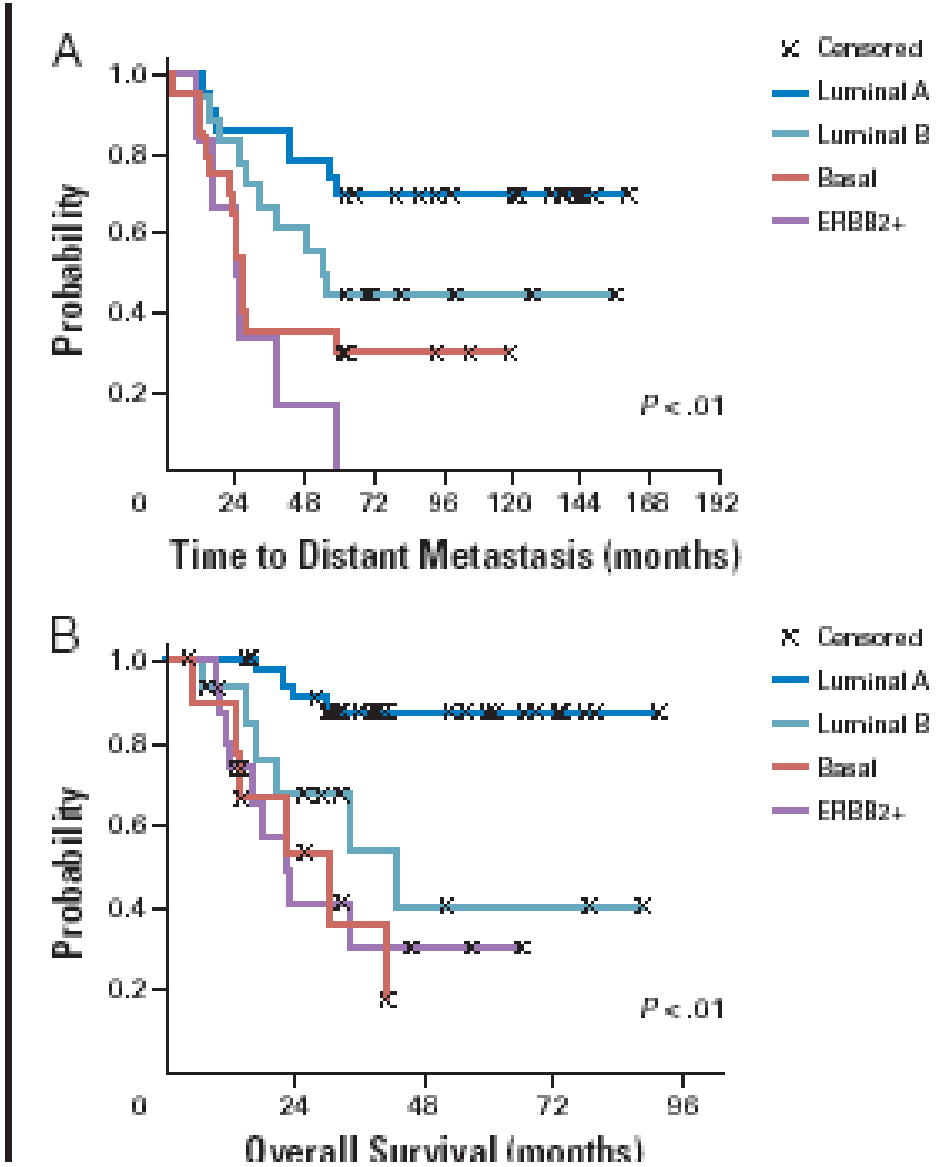
DÓNDE ESTAMOS

Perou C. Nature 2000.

Prat A. Mol Oncol 2011.



SUBTIPOS INTRÍNSECOS



DÓNDE ESTAMOS

Category	IHQ	Therapy
Luminal A	RE and RP +ve HER2 –ve Ki-67 < 20 %	Hormonal therapy and CT if: RS high, Grade 3 or ≥ 4 +ve nodes
Luminal B (HER2 –ve)	RE+ve and HER2-ve and: RP –ve and/or Ki-67 ≥ 20%	Hormonal therapy Chemotherapy for most
Luminal B (HER2 +ve)	RE+ve and any RP HER2 +ve Ki-67 any	Hormonal therapy Anti-HER2 therapy Chemotherapy
HER2 "enriched"	RE and RP -ve HER2 +ve	Anti-HER2 therapy Chemotherapy
Triple negative	RE and RP -ve HER2 -ve	Chemotherapy

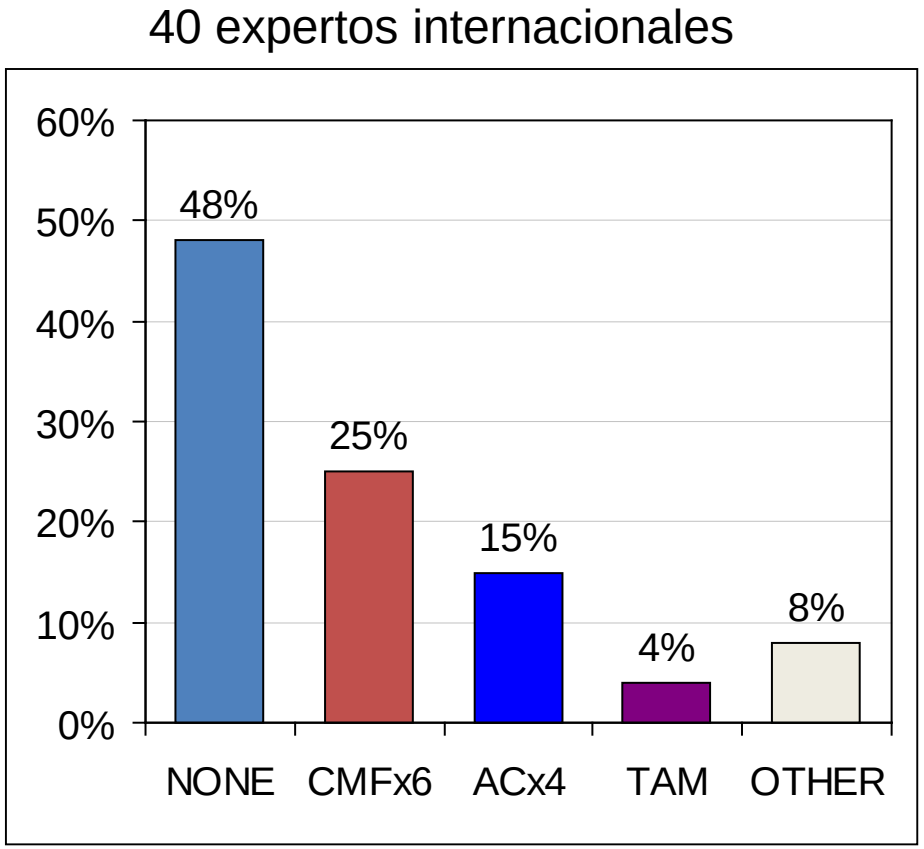
Discordancia en el tratamiento adyuvante

61 años
Postmenopaúsica

Ca ductal infiltrante grado 2

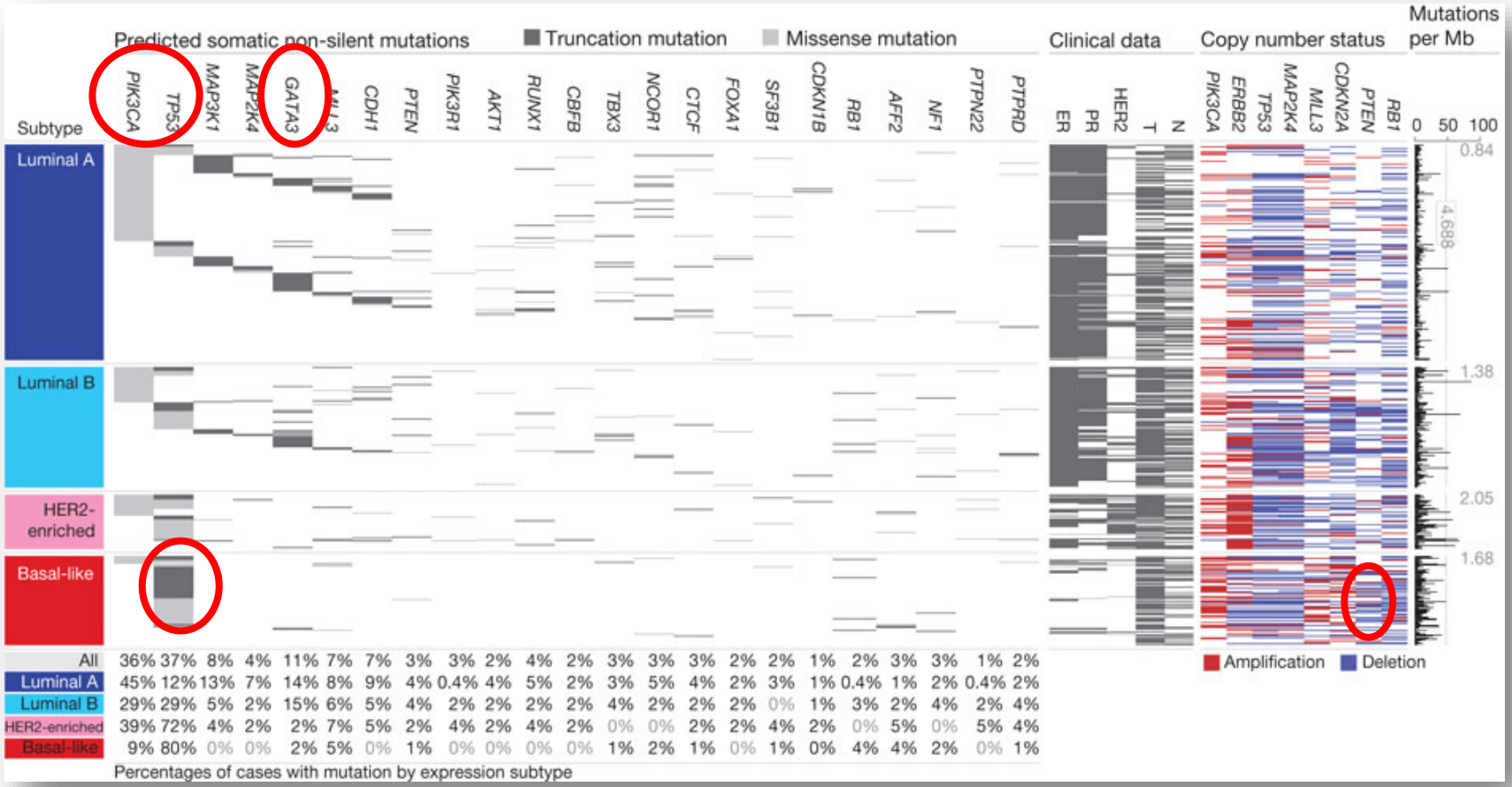
pT1b (0,9cm) N0 M0

RE – RP – HER2 -



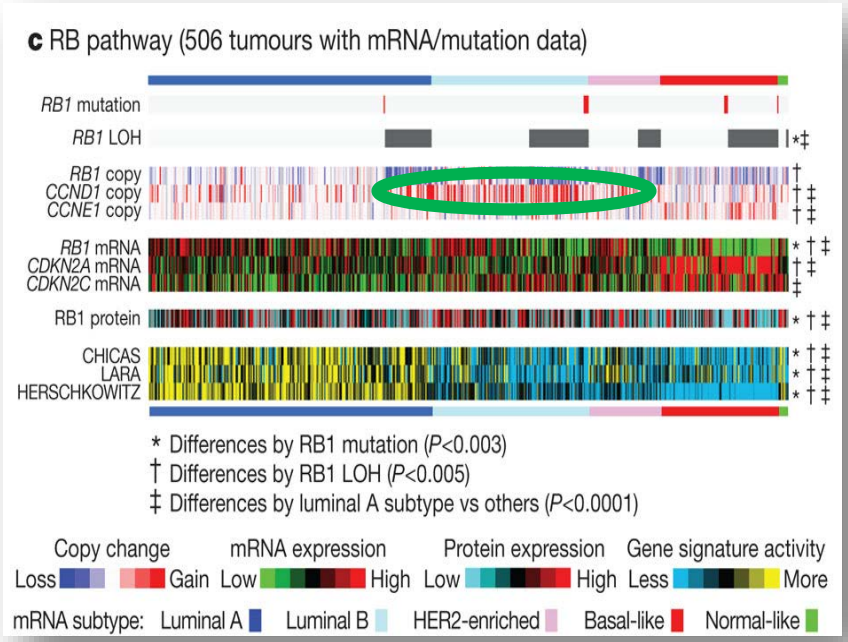
Courtesy: Martine Piccart

THE CANCER GENOME ATLAS

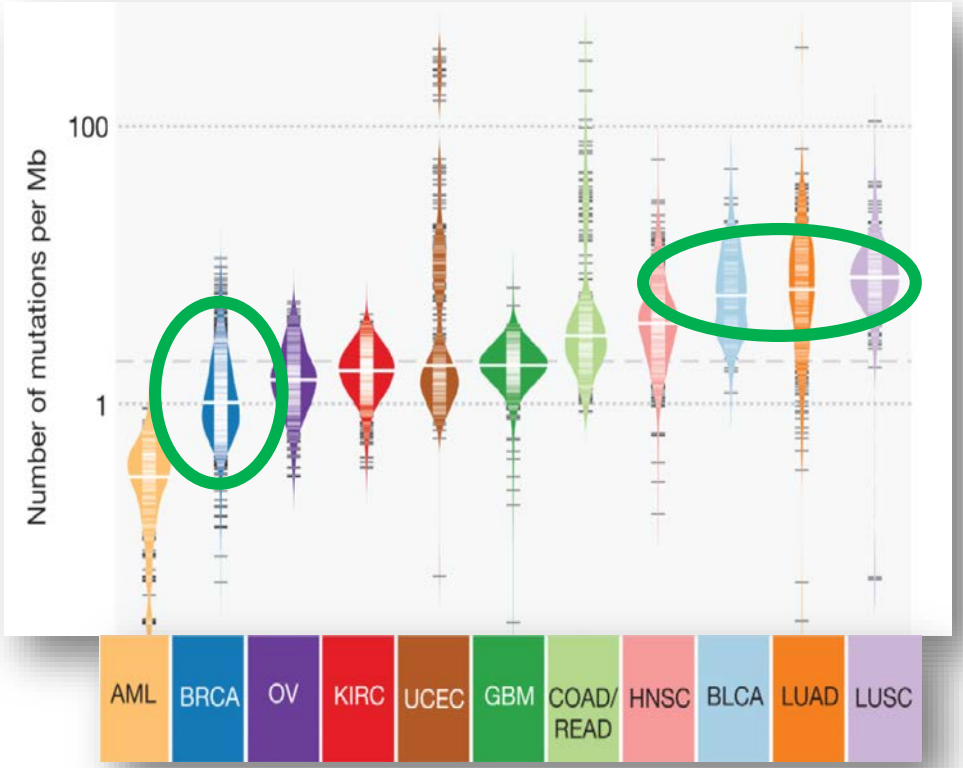


Koboldt DC. Nature 2012.

THE CANCER GENOME ATLAS



Koboldt DC. Nature 2012.



Kandoth C. Nature 2013.

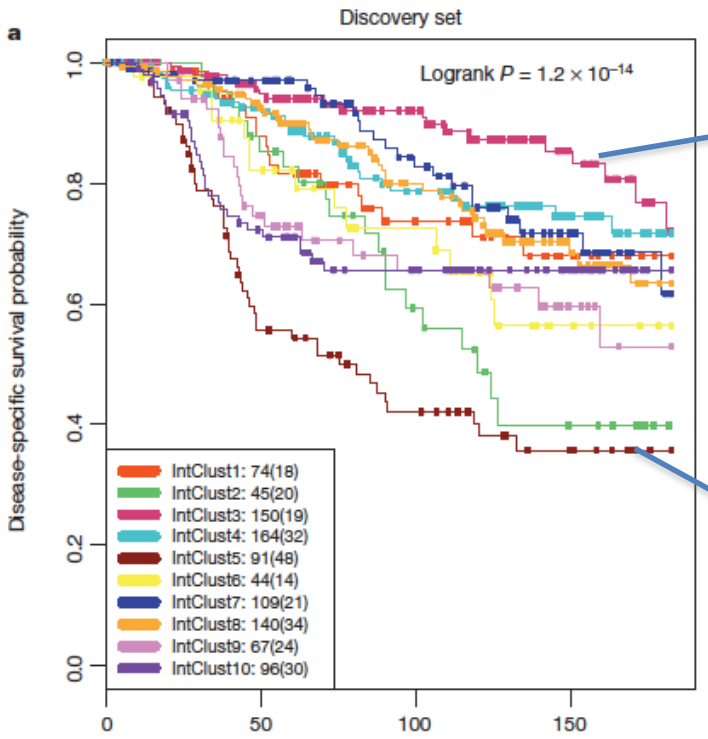
Molecular Heterogeneity of Luminal Breast Cancers

BREAST CANCER

Divide and conquer?

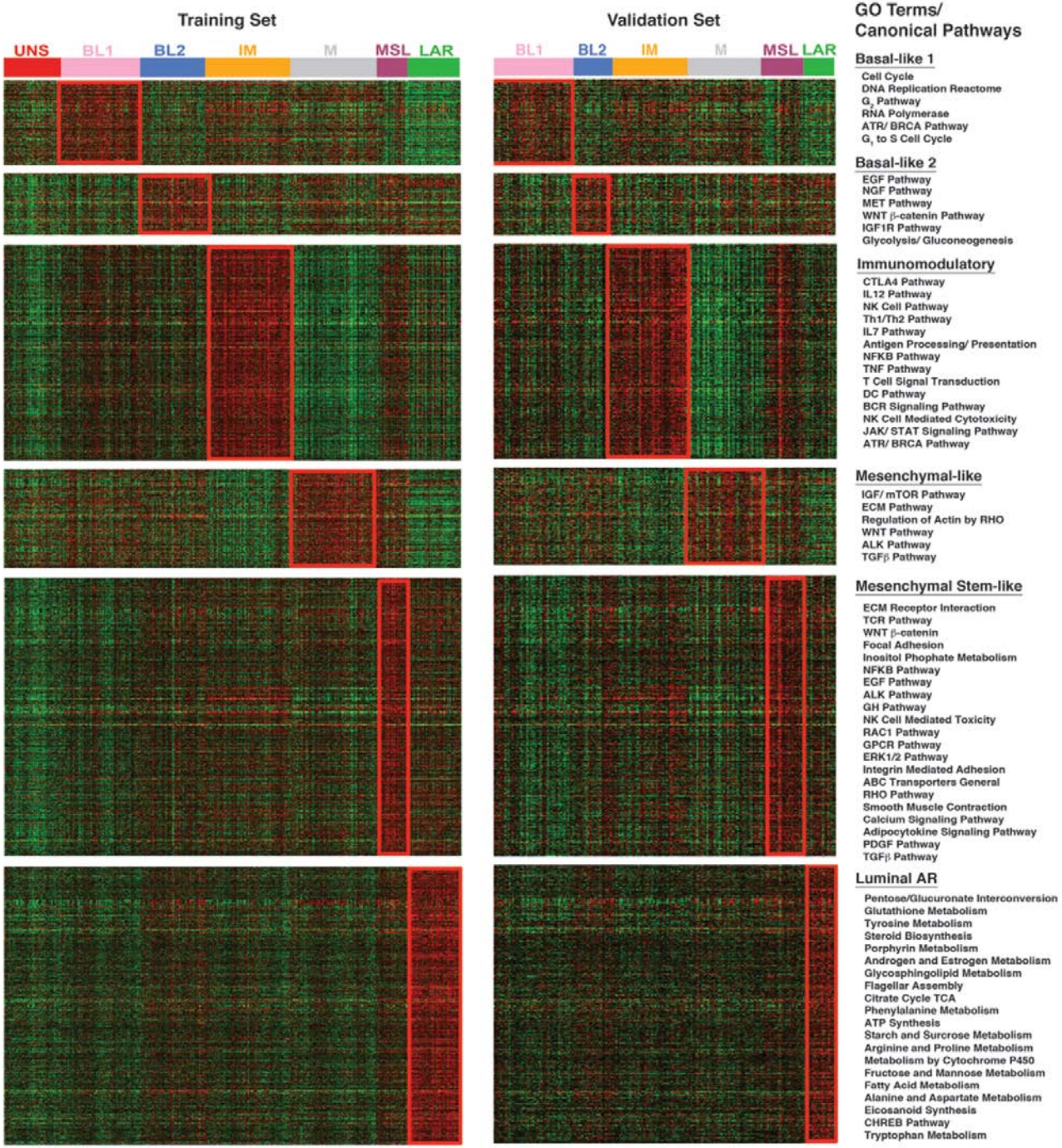
RESEARCH HIGHLIGHTS

Nature Reviews Cancer | AOP, published online 11 May 2012; doi:10.1038/nrc3279



-ER-positive of different histological subtypes that have few CNAs. These tumours most often have changes in *TRG and TRA (*T cell receptor (TCR) genes) *and are associated with increased immune infiltration and a good prognosis .*

The subgroups identified include oestrogen receptor (ER)-positive luminal tumours with a *cis acting 11q13–14 alteration that have a particularly poor prognosis, possibly owing to the expression of a number of genes in this region that are associated with cell cycle regulation.*

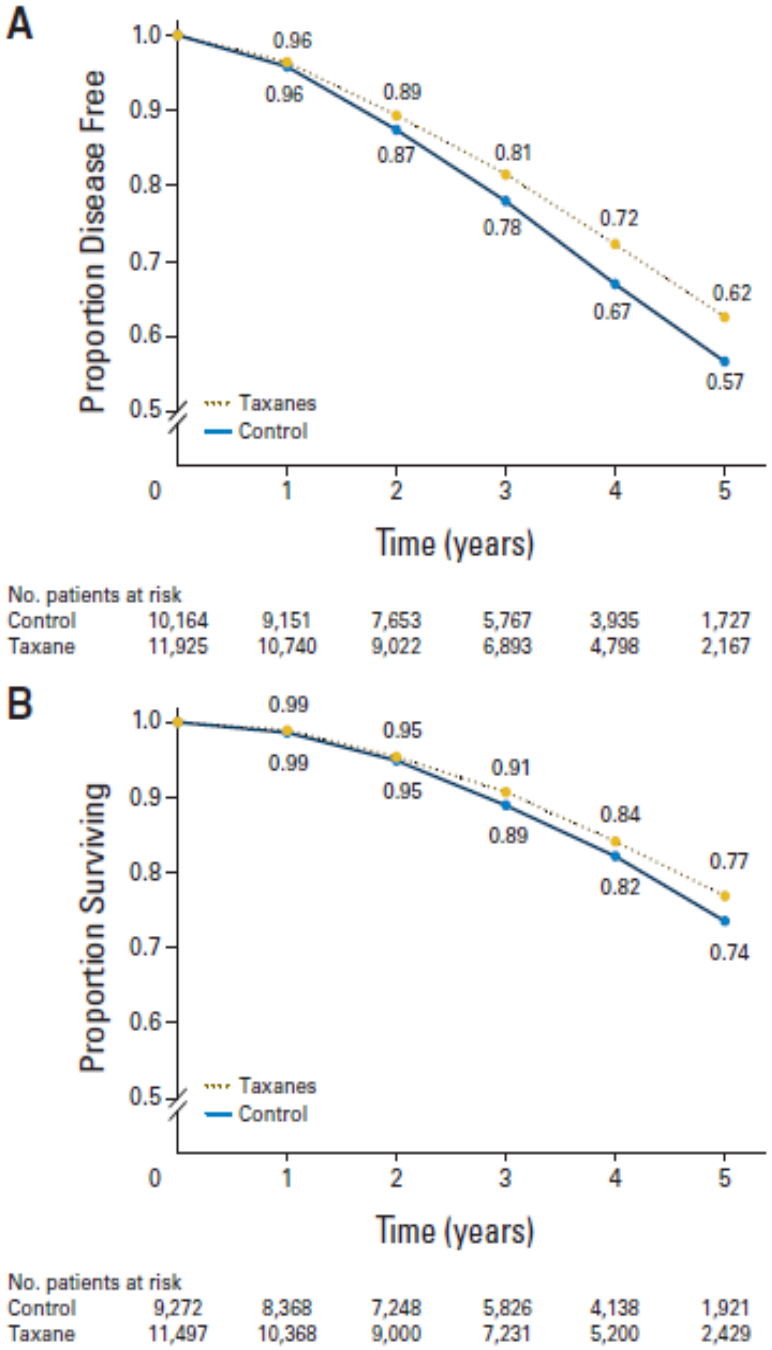


Lehman et al., JCI 2011

Quimioterapia

CONCEPTOS BÁSICOS

- Indicada en (casi) todas las pacientes con tumores triple negativo o HER2 positivo, y en la mayoría de pacientes luminal B (Ki-67 elevado y/o RP negativo y/o grado 3).
- Se recomienda usar el mejor esquema de quimioterapia disponible.



Disminución del riesgo de recurrencia con HR entre 0.63 y 0.97, con p significativa en 7/13 estudios. P < 0.00001 en el análisis global

No diferencias entre paclitaxel y docetaxel, y entre esquemas secuenciales o concomitantes

No diferencias en el análisis por subgrupos:
-Expresión de RE -Afectación nodal -Edad -Estado menopáusico

Disminución del riesgo de muerte con HR entre 0.76 y 0.91, P < 0.0001

En administración concomitante no existe significancia estadística en SG. Gran heterogeneidad de los estudios.

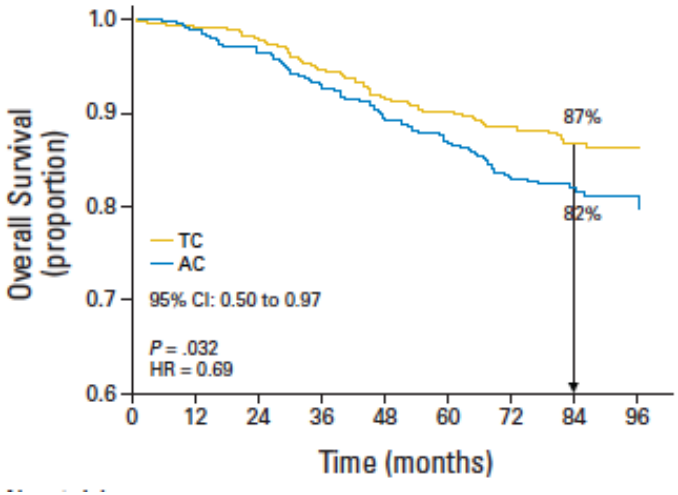
Laurentiis M et al. J Clin Oncol 2008 26: 44-53

VOLUME 27 · NUMBER 8 · MARCH 10 2009

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Docetaxel With Cyclophosphamide Is Associated With an Overall Survival Benefit Compared With Doxorubicin and Cyclophosphamide: 7-Year Follow-Up of US Oncology Research Trial 9735

Stephen Jones, Frankie Ann Holmes, Joyce O'Shaughnessy, Joanne L. Blum, Svetislava J. Vukelja, Kristi J. McIntyre, John E. Pippen, James H. Bordelon, Robert L. Kirby, John Sandbach, William J. Hyman, Donald A. Richards, Robert G. Mennel, Kristi A. Boehm, Wally G. Meyer, Lina Asmar, Daniel Mackey, Stefan Riedel, Hyman Muss, and Michael A. Savin



- Cardiac mortality increases with anthracycline regimens (RR, 1.56; SE, 0.24; 2P = .02).
- Increased risk for myelodysplastic syndromes and treatment-related leukemia.
- Median follow-up time of 7 years, overall survival (OS) was superior for TC relative to AC (hazard ratio [HR], 0.69; 95% CI, 0.50 to 0.97; P = .032).

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Anthracyclines in Early Breast Cancer: The ABC Trials—USOR 06-090, NSABP B-46-I/USOR 07132, and NSABP B-49 (NRG Oncology)

Joanne L. Blum, Patrick J. Flynn, Greg Yothers, Lina Asmar, Charles E. Geyer Jr, Samuel A. Jacobs, Nicholas J. Robert, Judith O. Hopkins, Joyce A. O'Shaughnessy, Chau T. Dang, Henry Leonidas Gómez, Louis Fehrenbacher, Svetislava J. Vukelja, Alan P. Lyss, Devchand Paul, Adam M. Brufsky, Jong-Hyeon Jeong, Linda H. Colangelo, Sandra M. Swain, Eleftherios P. Mamounas, Stephen E. Jones, and Norman Wolmark

- TC as an effective nonanthracycline regimen appropriate for comparison with TaxAC regimens.

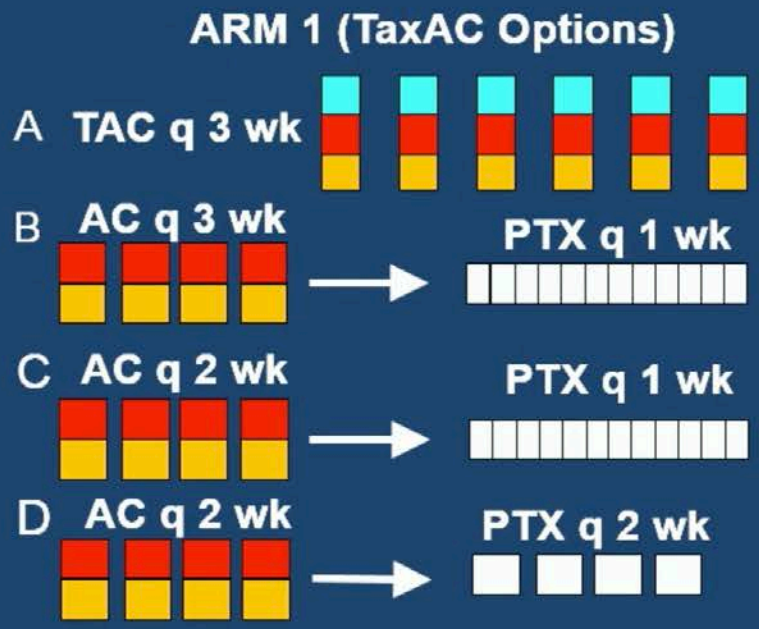
- The primary aim of the ABC trials was to determine if TC6 was noninferior to the TaxAC regimens.

ABC Trials Schema

Node+ or High Risk Node-Negative

Stratification Variables

Number of + Nodes (0, 1-3, 4-9, 10+); Hormone Receptor (ER or PgR+, Both Negative)

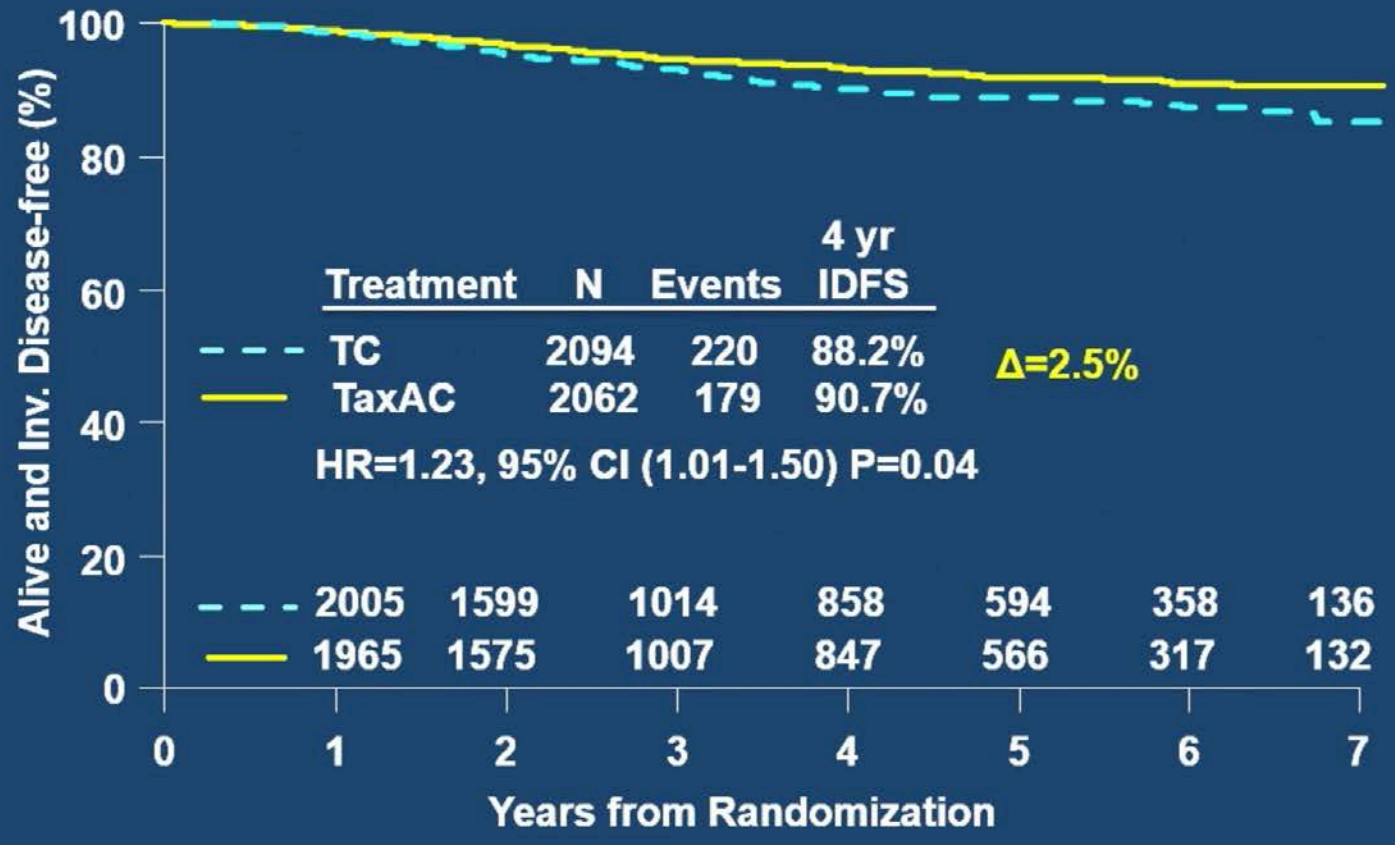


Arm 1 Options Per Study

- **USOR 06-090 - 1A only**
- **NSABP B-46I/USOR 07132 - 1A only**
- **NSABP B-49 - investigator choice 1A-1D**

Endocrine therapy for ER+ or PgR+ patients for minimum of 5 years

ABC Trials: Invasive Disease Free Survival



Presented by: Joanne L. Blum, MD, PhD.

Prospective WSG Phase III PlanB trial: Final analysis on adjuvant 4xEC→4xDoc vs. 6xDocetaxel/Cyclophosphamide in high clinical and intermediate/high genomic risk HER2-negative early breast cancer

WSG

WOMEN'S HEALTHCARE STUDY GROUP

Nadia Harbeck, Oleg Gluz, Michael Clemens, Wolfram Malter, Toralf Reimer, Benno Nuding, Bahriye Aktas, Andrea Stefek, Anke Pollmanns, Fatemeh Lorenz-Salehi, Christoph Uleer, Petra Krabisch, Sherko Kuemmel, Cornelia Liedtke, Steven Shak, Rachel Wuerstlein, Matthias Christgen, Ronald E. Kates, Hans H. Kreipe, and Ulrike Nitz, on behalf of the WSG PlanB investigators

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

Presented by: Nadia Harbeck, MD

Background

- Role of anthracycline (A) - containing regimens in early breast cancer (BC) still under discussion.
- EBCTCG meta-analysis[1] demonstrated:
  - BC mortality reduced by adding taxanes to A (RR 0.86; SE 0.04)
  - BC mortality reduced by one-third with modern A-T regimens
  - Increased cardiac mortality with A-use (RR 1.56; SE 0.24)
- USOR trial demonstrated superior OS for 4x TC vs. 4x AC[2].
- Joint analysis of ABC trials[3] demonstrated improved iDFS for A-T regimens vs. 6xTC after median 3.3y follow-up.
  - Small absolute benefits; benefit increased with higher clinical risk
- So far, no predictive factor validated for clinical use.

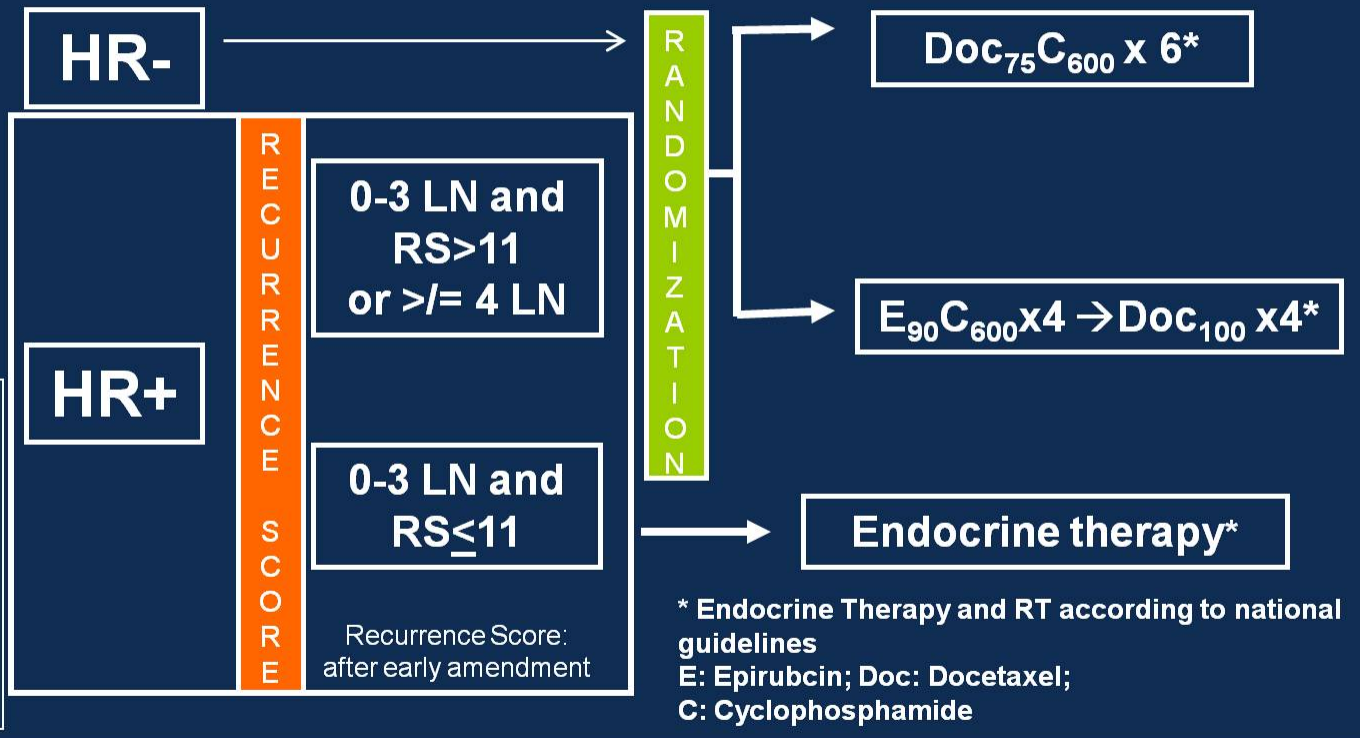
[1]EBCTCG, Lancet 2012; [2]Jones et al, JCO 2009; [3]Blum et al, JCO 2017

PlanB: Design
HER2-negative early breast cancer

WSG
WOMEN'S HEALTHCARE STUDY GROUP

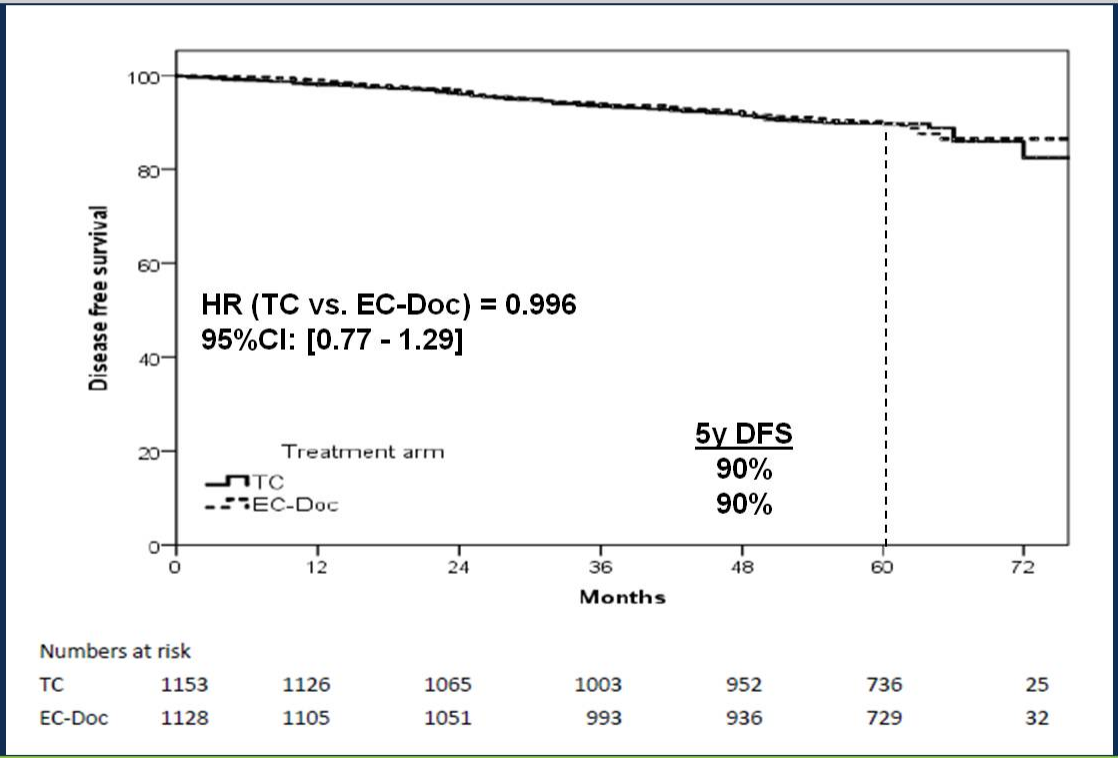
- **Age≤75 years**
- **cM0**
- free margins
- **pN+**
- **pN0 high risk**

- pT≥2
- G2-3
- uPA/PAI-1↑
- HR-
- age ≤35 years



*** Endocrine Therapy and RT according to national guidelines**
E: Epirubcin; Doc: Docetaxel;
C: Cyclophosphamide

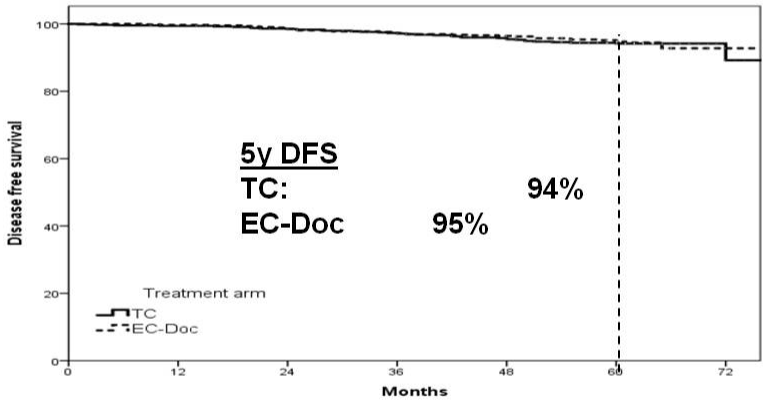
PlanB: Disease-free survival (DFS) by chemotherapy arm (ITT population)



PlanB: Disease-free survival (DFS) according to Recurrence Score (HR+)*

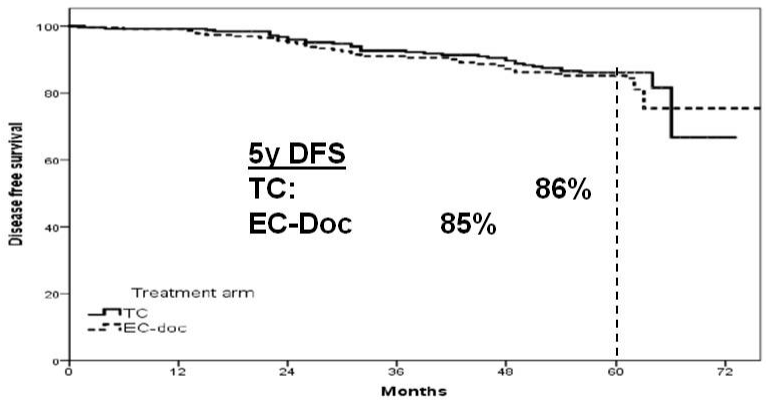
WSG
WOMEN'S HEALTHCARE STUDY GROUP

RS≤25



Numbers at risk							
TC	657	649	615	588	559	431	19
EC-Doc	649	638	616	591	561	448	21

RS>25



Numbers at risk							
TC	254	251	237	220	210	169	1
EC-Doc	231	227	212	195	183	149	5

*ITT patients with RS measured; after early amendment

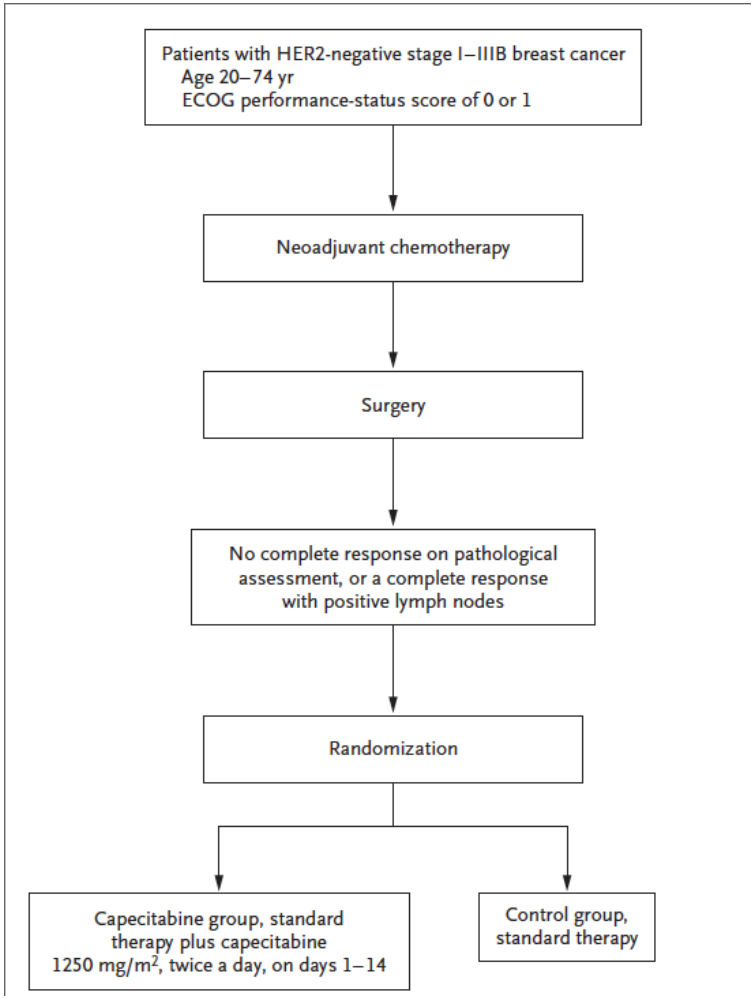
The NEW ENGLAND JOURNAL of MEDICINE

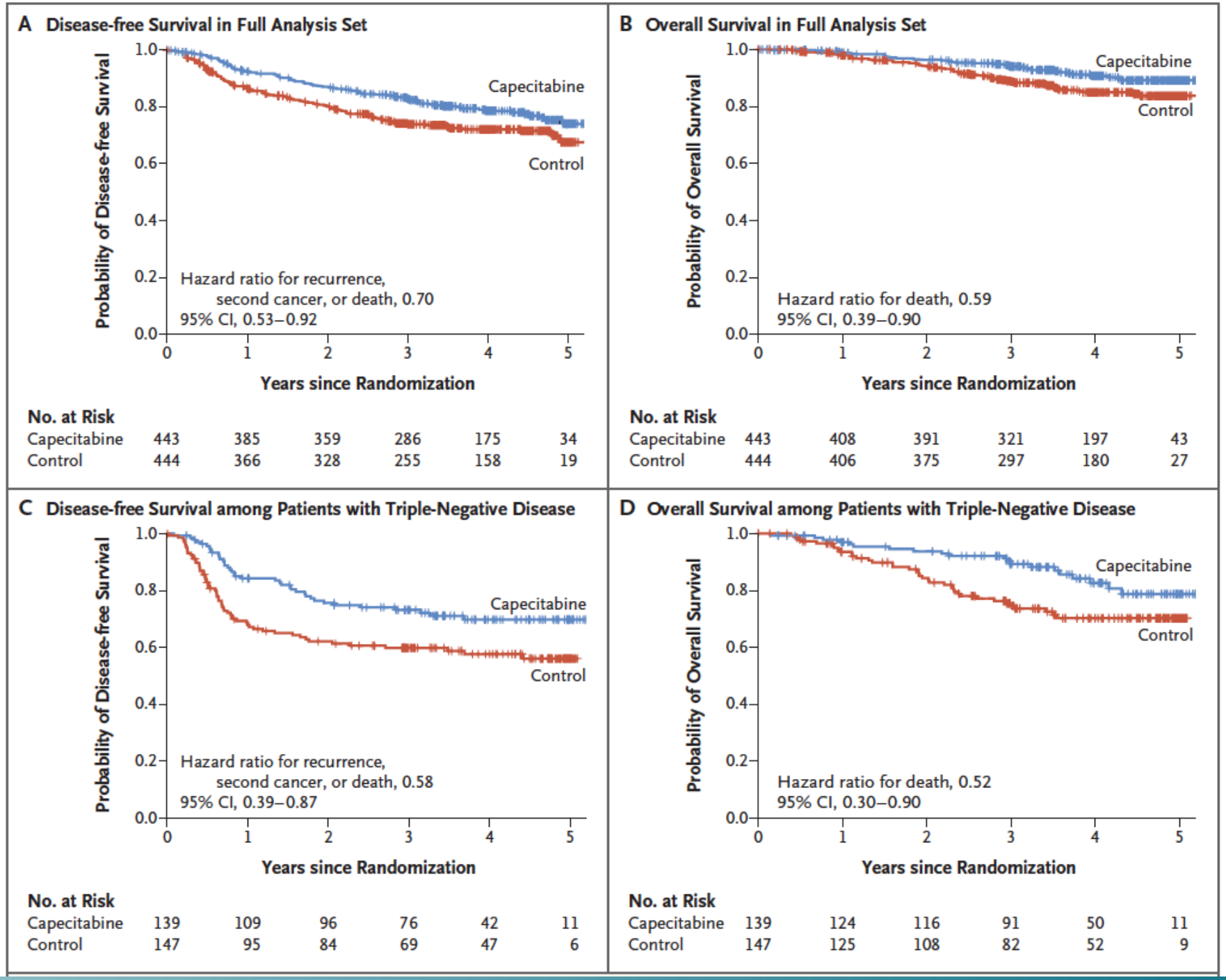
ORIGINAL ARTICLE

Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy

N. Masuda, S.-J. Lee, S. Ohtani, Y.-H. Im, E.-S. Lee, I. Yokota, K. Kuroi, S.-A. Im, B.-W. Park, S.-B. Kim, Y. Yanagita, S. Ohno, S. Takao, K. Aogi, H. Iwata, J. Jeong, A. Kim, K.-H. Park, H. Sasano, Y. Ohashi, and M. Toi

NEJM.ORG JUNE 1, 2017




A Disease-free Survival in Full Analysis Set
Probability of Disease-free Survival
1.0
0.8
0.6
0.4
0.2
0.0
Capecitabine
Control
Hazard ratio for recurrence, second cancer, or death, 0.70
95% CI, 0.53–0.92
0
1
2
3
4
5
Years since Randomization
No. at Risk
Capecitabine 443 385 359 286 175 34
Control 444 366 328 255 158 19
B Overall Survival in Full Analysis Set
Probability of Overall Survival
Capecitabine
Control
Hazard ratio for death, 0.59
95% CI, 0.39–0.90
Years since Randomization
No. at Risk
Capecitabine 443 408 391 321 197 43
Control 444 406 375 297 180 27
C Disease-free Survival among Patients with Triple-Negative Disease
Probability of Disease-free Survival
Capecitabine
Control
Hazard ratio for recurrence, second cancer, or death, 0.58
95% CI, 0.39–0.87
Years since Randomization
No. at Risk
Capecitabine 139 109 96 76 42 11
Control 147 95 84 69 47 6
D Overall Survival among Patients with Triple-Negative Disease
Probability of Overall Survival
Capecitabine
Control
Hazard ratio for death, 0.52
95% CI, 0.30–0.90
Years since Randomization
No. at Risk
Capecitabine 139 124 116 91 50 11
Control 147 125 108 82 52 9

Hormonoterapia

TRATAMIENTO HORMONAL

- **Bloqueo del receptor: SERM**
  - TAMOXIFENO
- **Degradación del receptor:**
  - FULVESTRANT
- **Reducción de síntesis:**
  - Inhibidores de aromatasa (postmenopausica)
    - Esteroideos: EXEMESTANO
    - No esteroideos: ANASTROZOL, LETROZOL
  - Ablación de función ovárica (premenopaúsicas)
    - OOFORECTOMÍA, RADIOTERAPIA
    - ANÁLOGOS LHRH (goserelina, triptorelina)

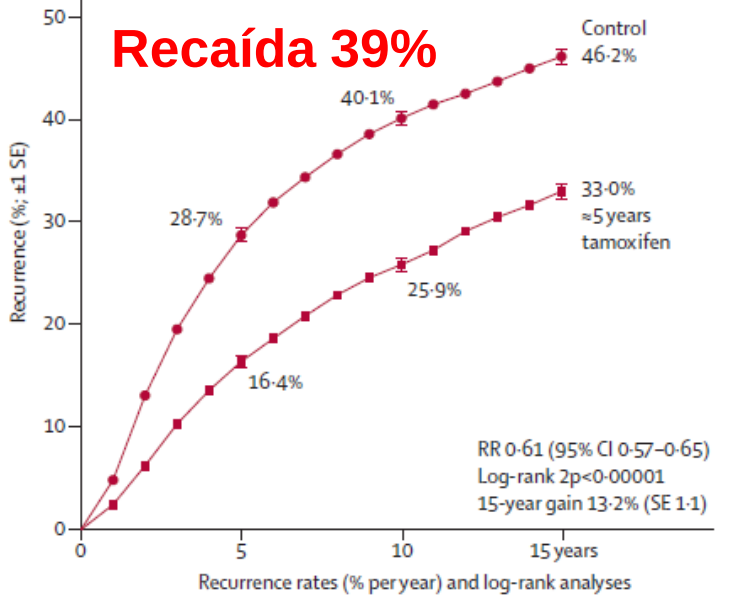
Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

www.thelancet.com Vol 378 August 27, 2011

Recurrence

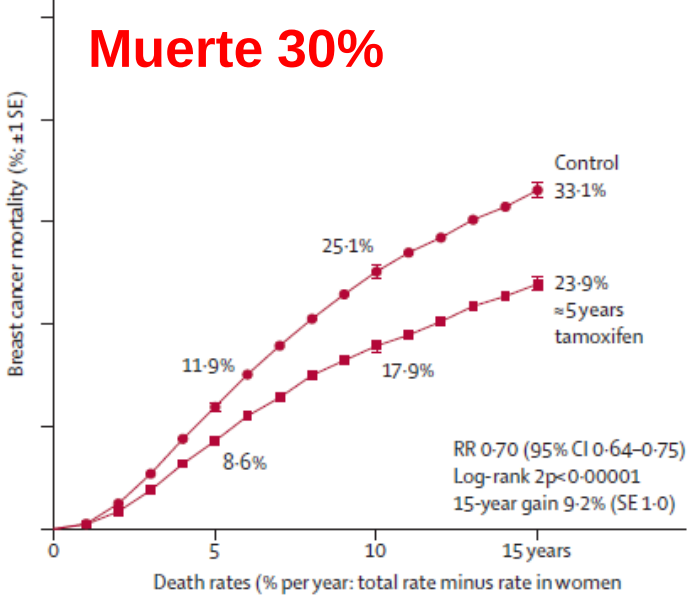
10 645 women (100% ER positive, 44% node positive, 51% chemotherapy)



	Years 0–4	Years 5–9	Years 10–14	Year 15+
Tamoxifen	3·74 (891/23 819)	2·62 (454/17 315)	2·06 (220/10 657)	1·75 (88/5034)
Control	6·71 (1466/21 862)	3·46 (499/14 420)	2·11 (182/8620)	1·76 (71/4045)
Rate ratio	0·53 (SE 0·03)	0·68 (SE 0·06)	0·97 (SE 0·10)	0·88 (SE 0·16)
(O–E)/V	−343·3/535·1	−82·5/217·5	−3·3/93·3	−4·4/35·5

Breast cancer mortality

10 645 women



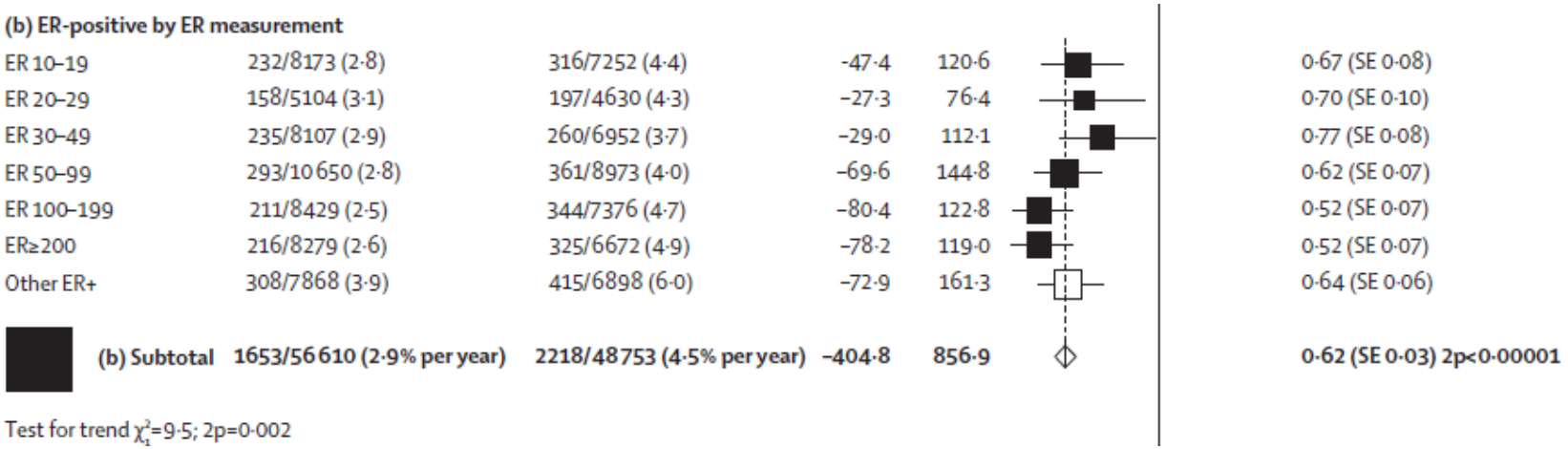
Years 0–4	Years 5–9	Years 10–14	Year 15+
1·79 (SE 0·08)	2·25 (SE 0·11)	1·54 (SE 0·11)	1·48 (SE 0·16)
2·46 (SE 0·10)	3·23 (SE 0·13)	2·28 (SE 0·14)	1·89 (SE 0·19)
0·71 (SE 0·05)	0·66 (SE 0·05)	0·68 (SE 0·08)	0·88 (SE 0·14)
−84·4/244·8	−95·8/233·2	−38·6/99·4	−5·7/42·6

Tamoxifeno 20 mg/día 5 años tras tratamiento con QT reduce RIESGO RECURRENCIA 39% a 15 años y RIESGO DE MUERTE por CM 30% a los 15 años

Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

www.thelancet.com **Vol 378 August 27, 2011**



(b) ER-positive by ER measurement						
ER 10–19	232/8173 (2·8)	316/7252 (4·4)	-47·4	120·6		0·67 (SE 0·08)
ER 20–29	158/5104 (3·1)	197/4630 (4·3)	-27·3	76·4		0·70 (SE 0·10)
ER 30–49	235/8107 (2·9)	260/6952 (3·7)	-29·0	112·1		0·77 (SE 0·08)
ER 50–99	293/10650 (2·8)	361/8973 (4·0)	-69·6	144·8		0·62 (SE 0·07)
ER 100–199	211/8429 (2·5)	344/7376 (4·7)	-80·4	122·8		0·52 (SE 0·07)
ER≥200	216/8279 (2·6)	325/6672 (4·9)	-78·2	119·0		0·52 (SE 0·07)
Other ER+	308/7868 (3·9)	415/6898 (6·0)	-72·9	161·3		0·64 (SE 0·06)
(b) Subtotal	**1653/56610 (2·9% per year)**	**2218/48753 (4·5% per year)**	**-404·8**	**856·9**		**0·62 (SE 0·03) 2p<0·00001**

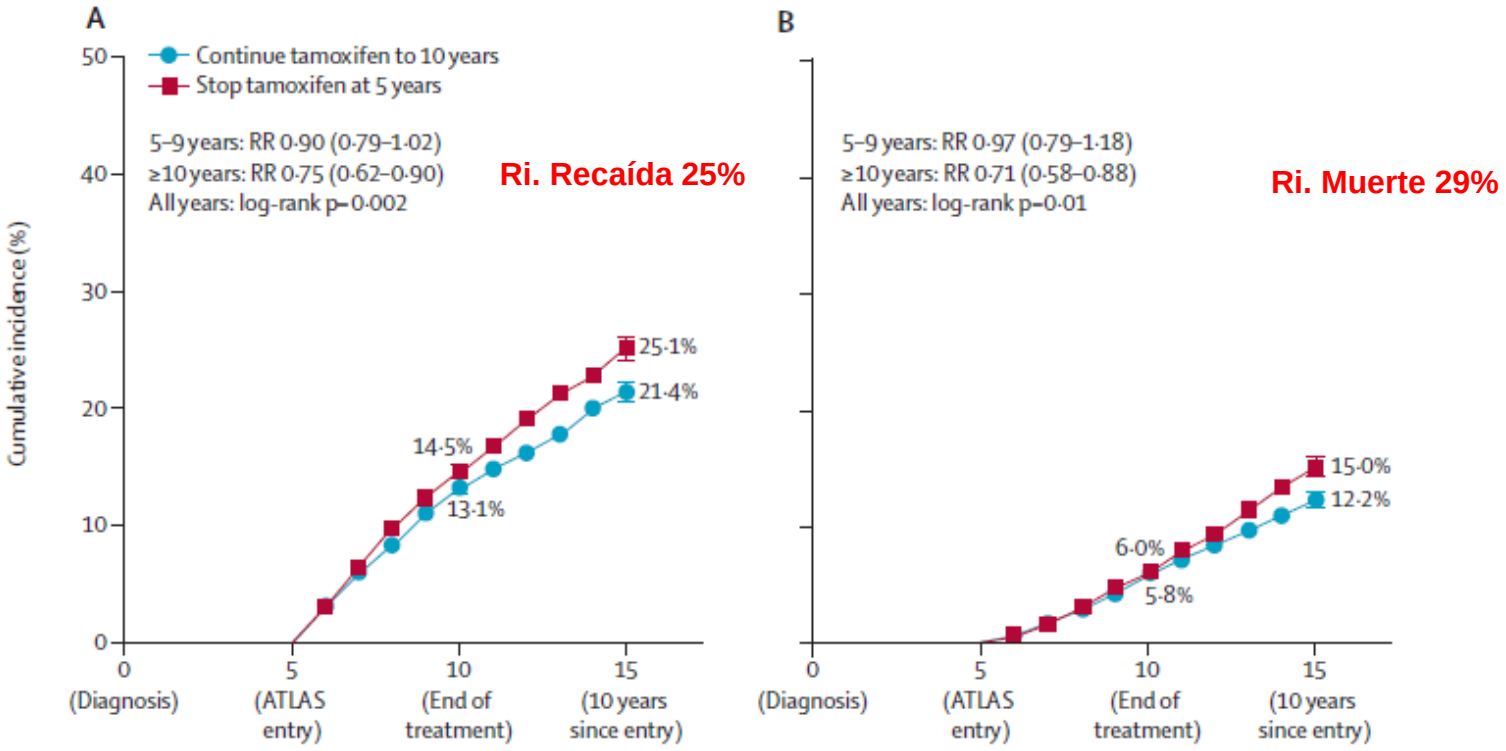
Test for trend χ^2_1=9·5; 2p=0·002

Even in marginally ER-positive disease (10–19 fmol/mg cytosol protein) the recurrence reduction was substantial (RR 0·67 [SE 0·08])

Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial

www.thelancet.com Vol 381 March 9, 2013

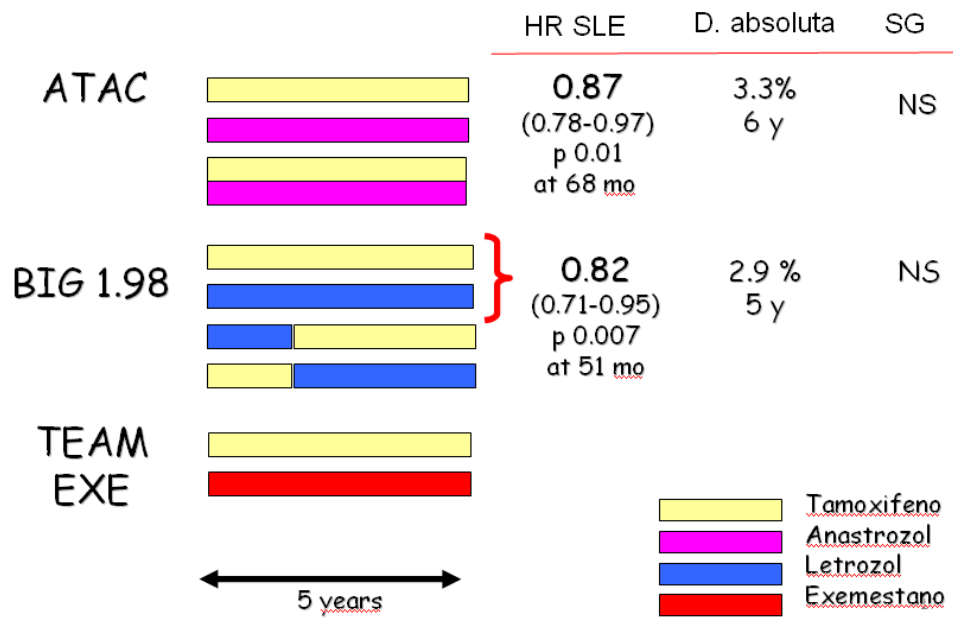
Christina Davies, Honqchao Pan, Jon Godwin, Richard Gray, Rodriqo Arriaqada, Vinod Raina, Mirta Abraham, Victor Huqo Medeiros Alencar, Atef Badran,



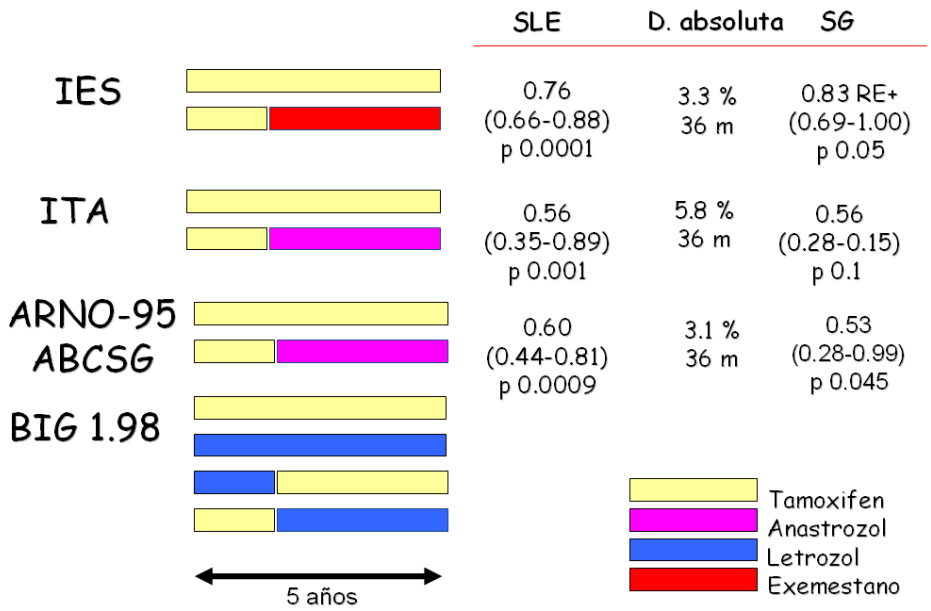
	5–9 years	10–14 years	≥15 years	5–9 years	10–14 years	≥15 years
Continue tamoxifen to 10 years	2·83% (428/15115)	1·96% (165/8439)	2·54% (24/945)	1·17% (SE 0·09)	1·38% (SE 0·12)	1·64% (SE 0·39)
Stop tamoxifen at 5 years	3·16% (471/14889)	2·66% (214/8038)	3·03% (26/859)	1·21% (SE 0·09)	2·01% (SE 0·15)	2·29% (SE 0·47)
Rate ratio, from (O–E)/V	0·90 (SE 0·06)	0·74 (SE 0·09)	0·85 (SE 0·26)	0·97 (SE 0·10)	0·70 (SE 0·10)	0·79 (SE 0·27)
Log-rank O–E and variance V	−24·8/224·7	−29·1/94·7	−2·1/12·5	−3·2/94·0	−27·2/77·5	−2·5/10·6

12894 pts include / Analysis of 6846 ER+ (53%)

Adyuvancia en Postmenopausia: IA de inicio



Adyuvancia en Postmenopausia: IA secuencial



VOLUME 28 · NUMBER 3 · JANUARY 20 2010
JOURNAL OF CLINICAL ONCOLOGY

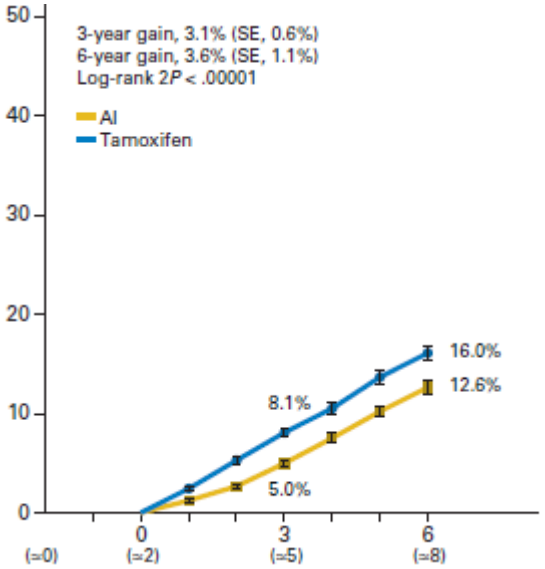
Meta-Analysis of Breast Cancer Outcomes in Adjuvant Trials of Aromatase Inhibitors Versus Tamoxifen

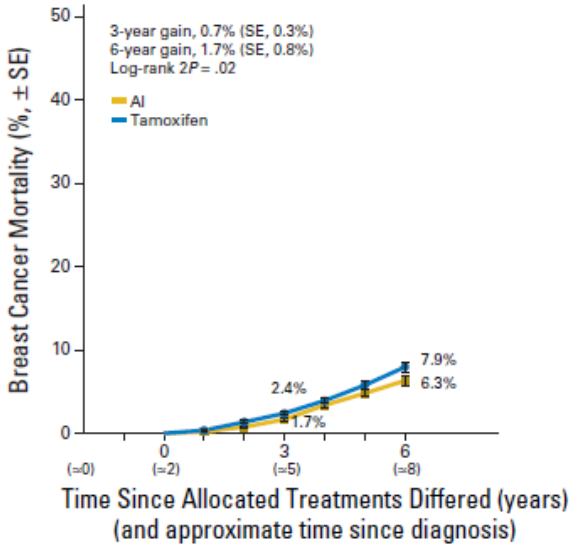
Mitch Dowsett, Jack Cuzick, Jim Ingle, Alan Coates, John Forbes, Judith Bliss, Marc Buyse, Michael Baum, Aman Buzdar, Marco Colleoni, Charles Coombes, Claire Snowdon, Michael Gnant, Raimund Jakesz, Manfred Kaufmann, Francesco Boccardo, Jon Godwin, Christina Davies, and Richard Peto

Cohorte1: 5 años de IA versus 5 años de tamoxifeno

Cohorte 2: 2-3 años de tamoxifeno seguido de 2-3 años de IA versus 5 años de tamoxifeno

Con la estrategia *switch* tras 2-3 años existe una marcada reducción del riesgo de recaída (del 40%) en los 3 años siguientes de seguimiento y mejoría discreta de la supervivencia global del 0.7%, estadísticamente significativa, que no se evidencia en el grupo de terapia *up front.*





VOLUME 32 · NUMBER 21 · JULY 20 2014
JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

Adjuvant Endocrine Therapy for Women With Hormone Receptor–Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Focused Update

Adyuvancia en Postmenopausia

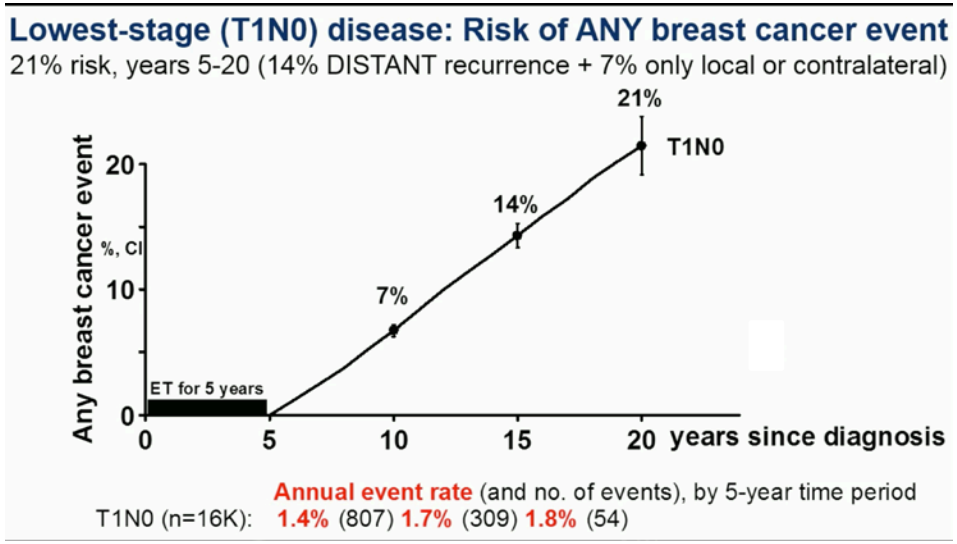
Tamoxifeno 10 años		ATLAS aTTom
IA 5 años		ATAC BIG 1.98 TEAM
TAM 5 años	IA 5 años	MA.17
TAM 2-3años	IA completar 5 años	IES ITA ARNO-95 ABSCG BIG 1.98
IA 2-3 años	TAM completar 5 años	BIG 1.98

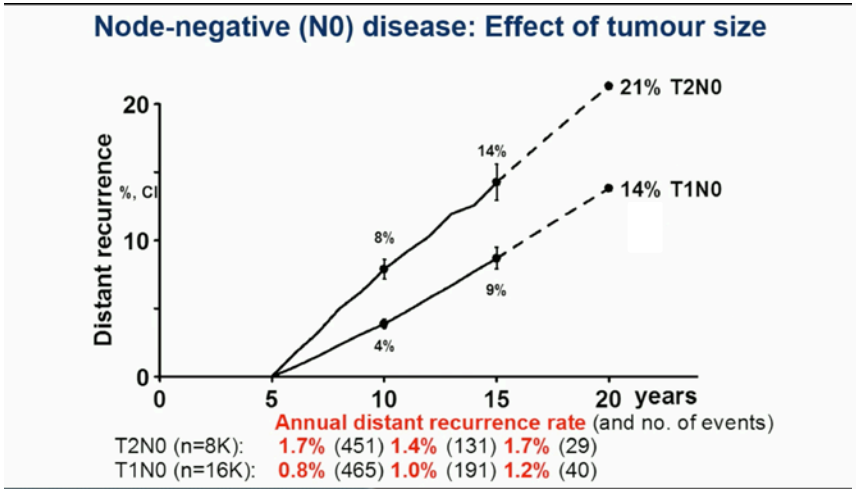
Type: Evidence-Based, Evidence Quality: High, Strength of Recommendation:Strong

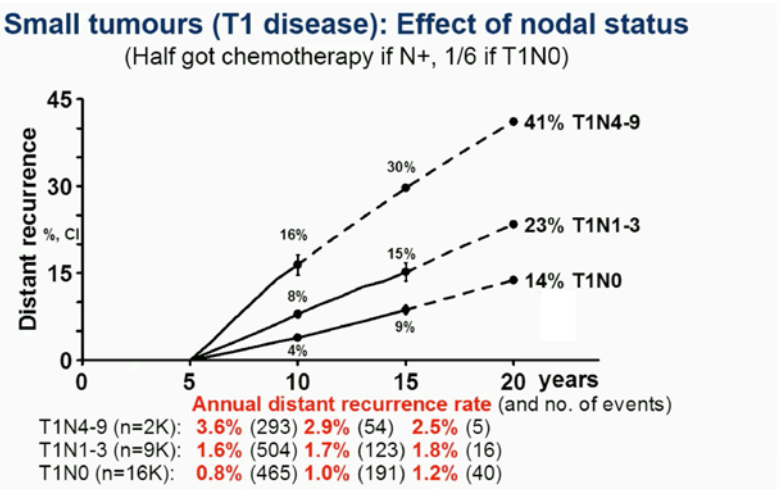
Type: Informal consensus, Evidence Quality: Low, Strength of Recommendation: Weak;

Risk of Recurrence beyond 5 y

Early Breast Cancer Trialist ´s Collaborative Group







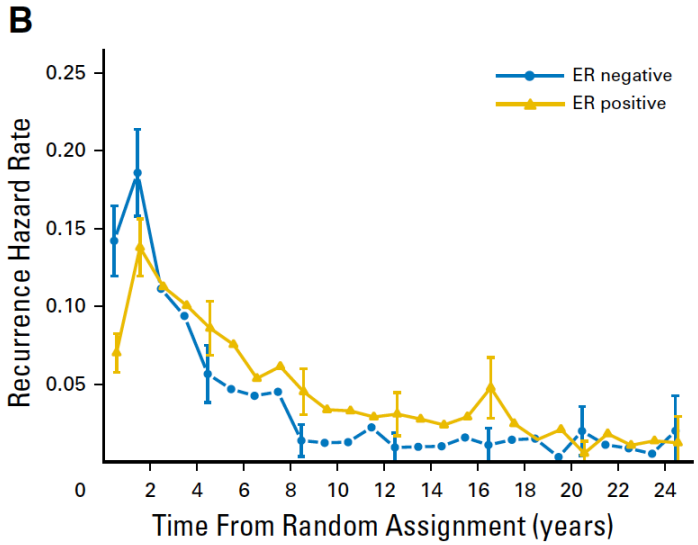
Presented By Hongchao Pan at 2016 ASCO Annual Meeting

Risk of Recurrence beyond 5 y

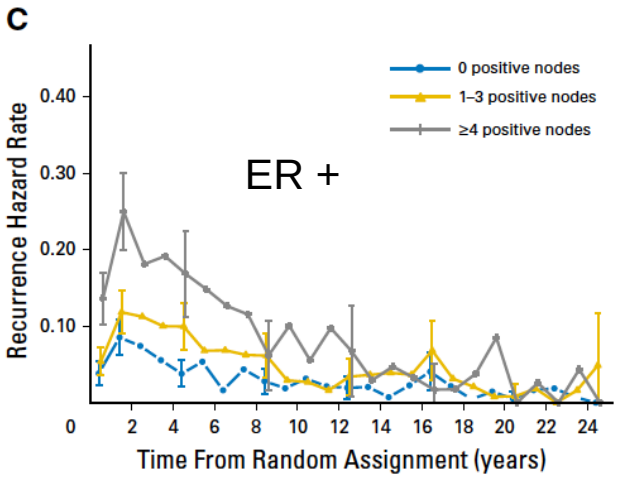
IBCSG I-V

Marco Colleoni JCO March 2016

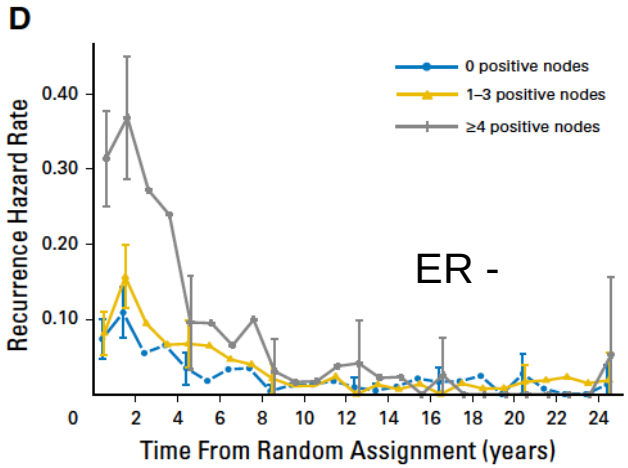
4,105 patients, median follow-up of 24 years



8	657	517	438	373	314	
8	1,159	828	635	501	363	



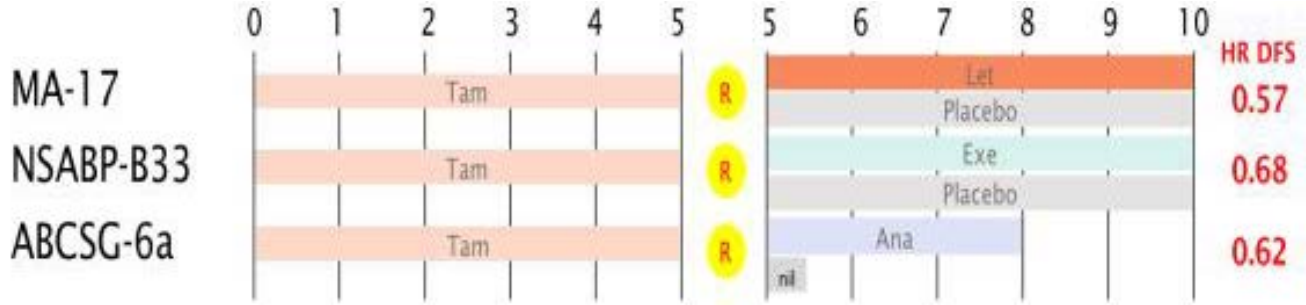
No. at risk							
0 positive nodes	640	488	402	316	256	199	124
1–3 positive nodes	671	445	306	242	185	121	48
≥4 positive nodes	497	226	120	77	60	43	20



No. at risk							
0 positive nodes	409	295	254	221	186	153	92
1–3 positive nodes	399	263	196	167	146	126	62
≥4 positive nodes	340	99	67	50	41	35	21

WATH WE KNEW BEFORE TODAY?

- **Hormone receptor positive breast cancer shows significant long-term risk of relapse:**
  - **>50% of disease relapses occur after the five years of follow-up.**
  - **Extending adjuvant therapy is appealing.**



- **Prolonging tamoxifen treatment (after Tam) is beneficial.**
- **Adding AI after 5 years of Tam is beneficial.**

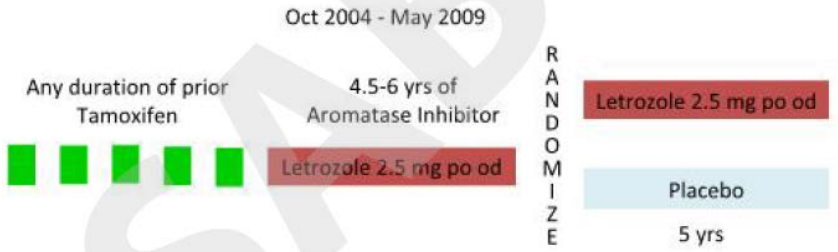
Shall we extend adjuvant duration after AI in the fist 5 years??

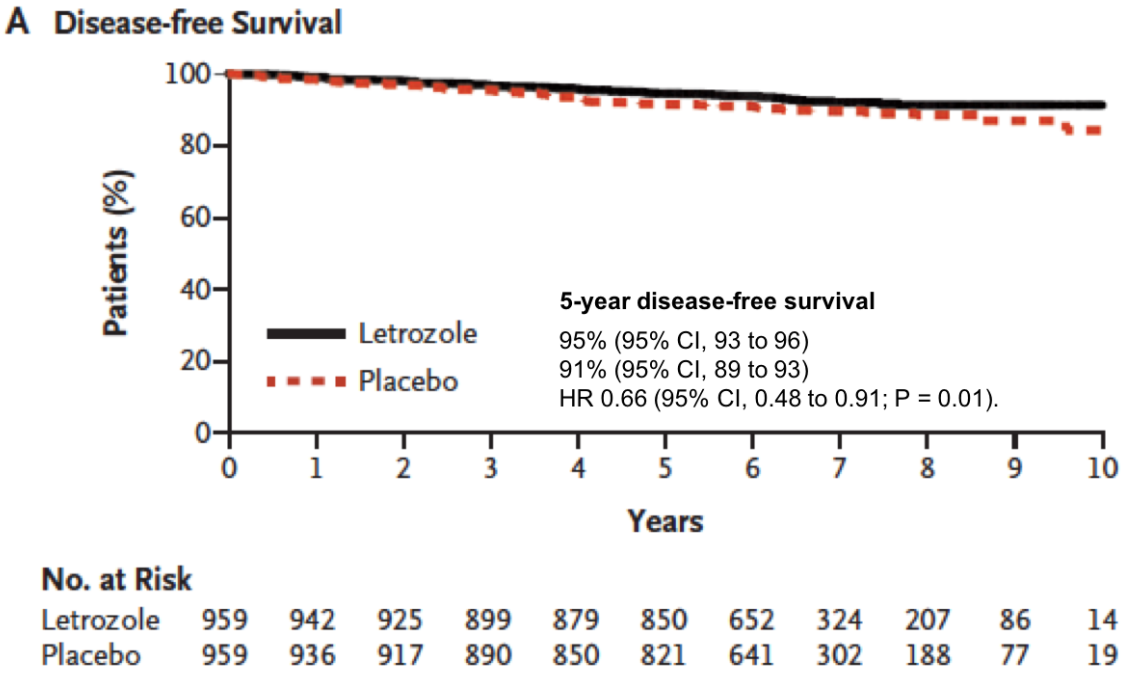
The NEW ENGLAND JOURNAL of MEDICINE

Extending Aromatase-Inhibitor Adjuvant Therapy to 10 Years

June 5, 2016, at NEJM.org.

P.E. Goss, J.N. Ingle, K.I. Pritchard, N.J. Robert, H. Muss, J. Gralow, K. Gelmon, T. Whelan, K. Strasser-Weippl, S. Rubin, K. Sturtz, A.C. Wolff, E. Winer, C. Hudis, A. Stopeck, J.T. Beck, J.S. Kaur, K. Whelan, D. Tu, and W.R. Parulekar





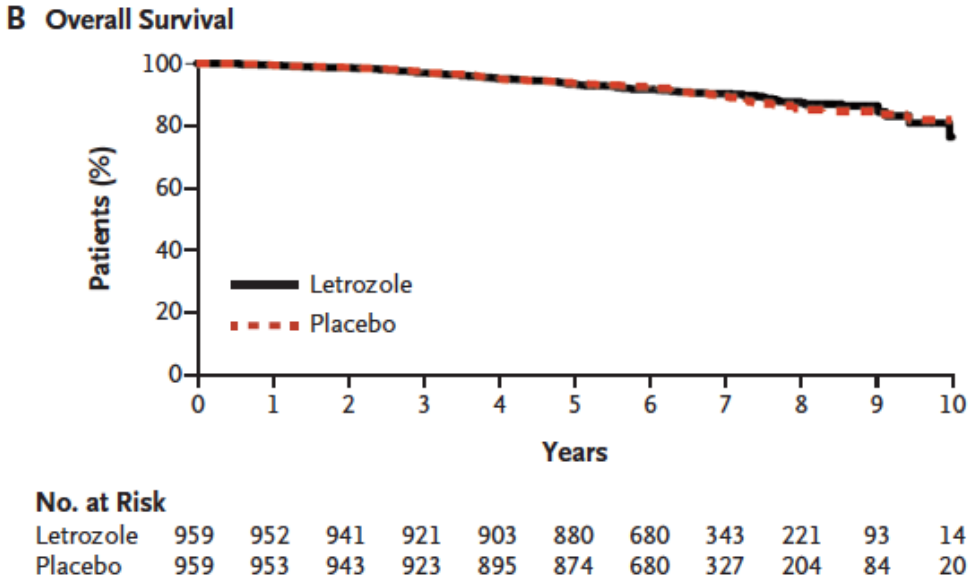
The NEW ENGLAND JOURNAL of MEDICINE

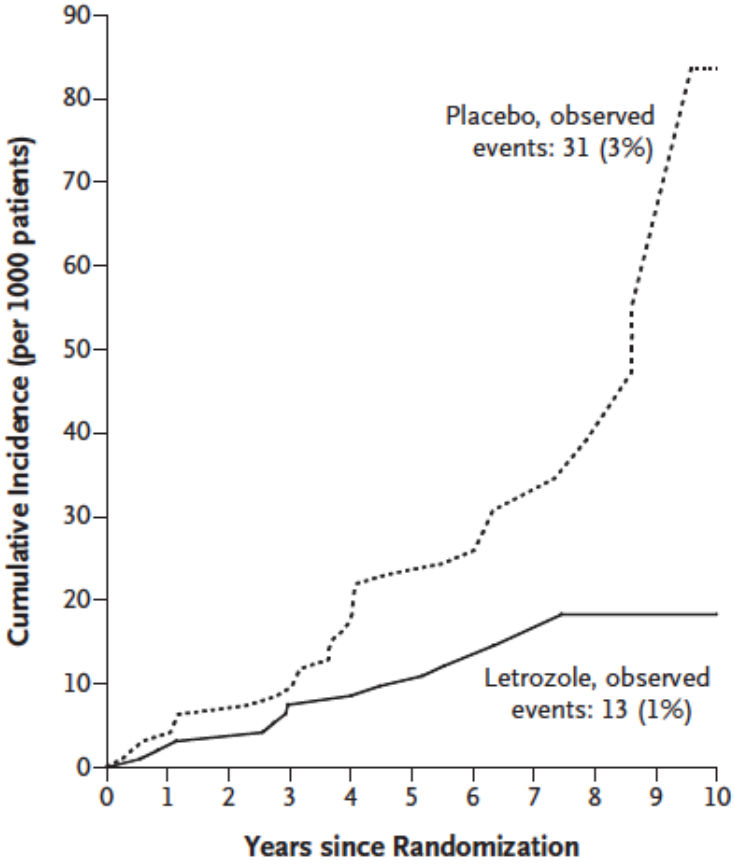
Extending Aromatase-Inhibitor Adjuvant Therapy to 10 Years

June 5, 2016, at NEJM.org.

P.E. Goss, J.N. Ingle, K.I. Pritchard, N.J. Robert, H. Muss, J. Gralow, K. Gelmon, T. Whelan, K. Strasser-Weippl, S. Rubin, K. Sturtz, A.C. Wolff, E. Winer, C. Hudis, A. Stopeck, J.T. Beck, J.S. Kaur, K. Whelan, D. Tu, and W.R. Parulekar

Cumulative Incidence of Contralateral Breast Cancer.





The downside of extending Endocrine therapy: Side Effects

Table 3. Adverse Events.*

Event	Letrozole (N=959)	Placebo (N=954)	P Value
	number (percent)		
Bone fracture‡	133 (14)	88 (9)	0.001
New-onset osteoporosis	109 (11)	54 (6)	<0.001

- Bone pain 18% vs 14% (MA17R)

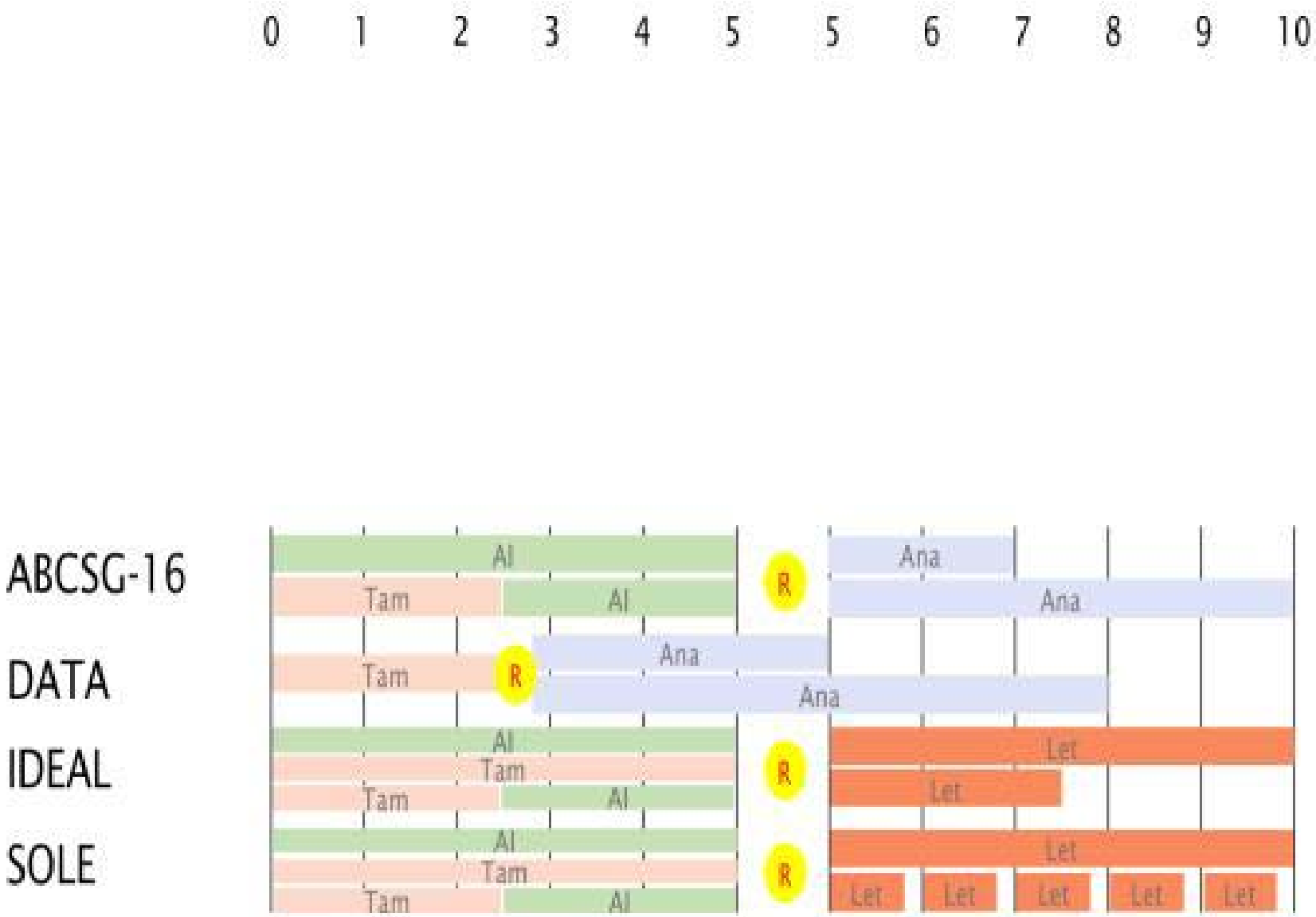
NSABP B-42 and NCIC MA.17R Comparison of HRs for Various Endpoints

Trial	Effect	Endpoint			
		DFS	BCFI	DR	OS
B-42 (n=3,923 631 events)	HR	0.85*	0.71	0.72	1.15
	P-value	0.048	0.003	0.03	0.22
MA.17R[1] (n=1,918 165 events)	HR	0.80***	0.66**	NR	0.97
	P-value	0.06	0.01	NR	0.83

* DFS (Recurrence + CBC + Non-breast CA + Deaths as first Events)
** Selected as DFS in MA.17R (Recurrence + CBC)
*** DFS (Recurrence + CBC + Deaths as first events)

[1]Goss P. et al: NEJM 2016

Trial Designs Extended Adjuvant Therapy



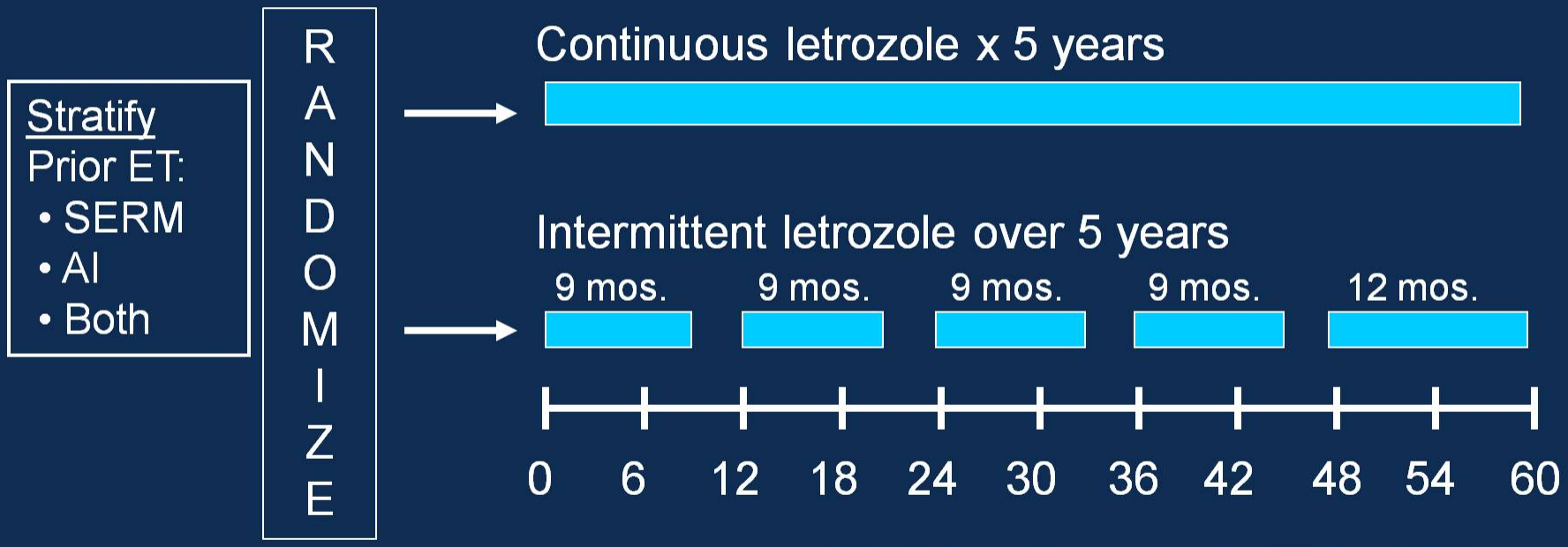
Attempt of a Summary

- "... careful assessment of potential risks and benefits is required before recommending extended therapy ..." (E. Mamounas)
- "... results do not support extended adjuvant AI use after 5 years of sequential endocrine therapy for all ..." (V. Tjan-Heijnen) "... suggests benefit for a selected group of patients ..."
- "... No significant differences in disease-related outcomes ..." (E. Blok) "... significant difference in prevention of 2nd primary breast cancer ..."

SOLE: Study of Letrozole Extension

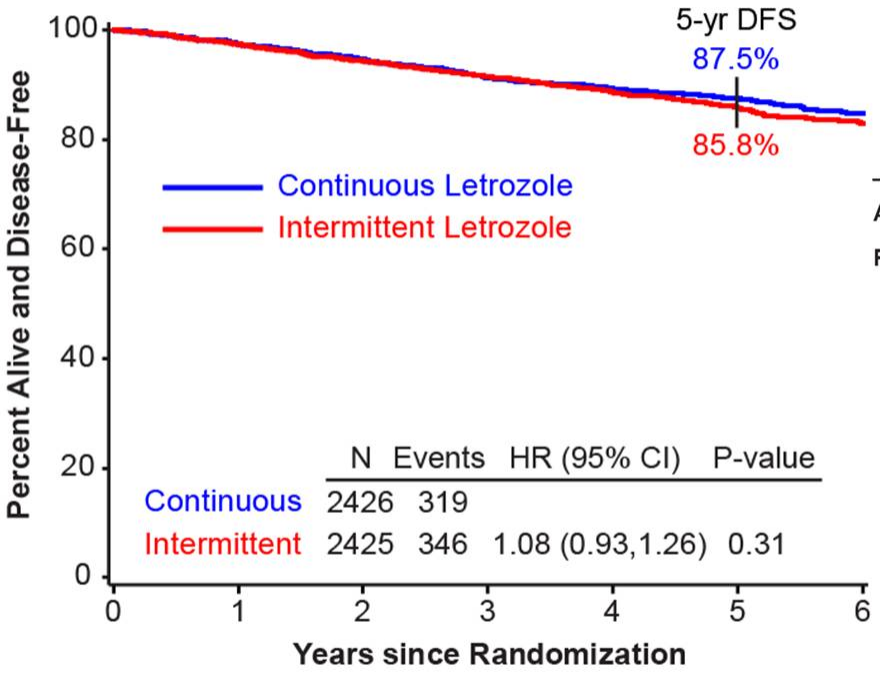
After 4 to 6 years of Prior Adjuvant Endocrine Therapy

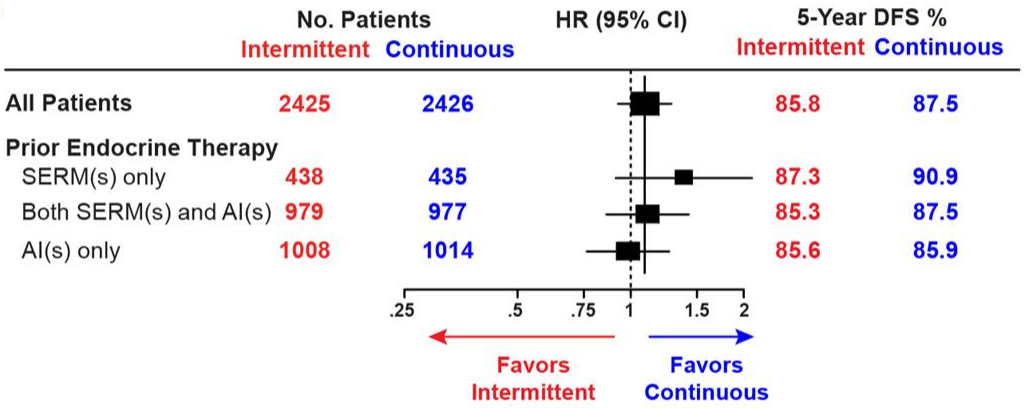
Postmenopausal, HR-positive, Node-positive



4884 Patients Randomized in ITT, Nov 2007 - July 2012

Primary Endpoint: Disease-Free Survival

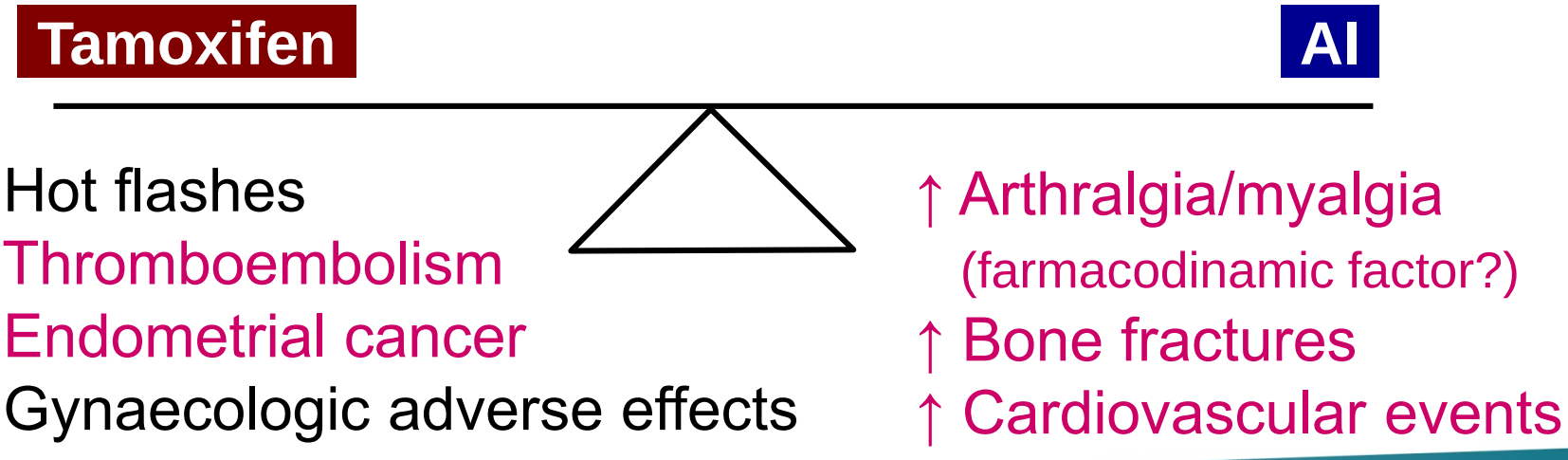




60 mos. median follow-up

- Patients at moderate or high risk of recurrence after 5 years of adjuvant therapy involving a switch from tamoxifen to an AI should be recommended to continue AI to a cumulative total of 5 years AI.

- In daily practice after 5 years of initial AI it is not necessary to provide further endocrine therapy, depends upon tolerance and absolute risk



ADYUVANCIA HORMONAL EN PREmenopausicas

- Tamoxifeno 20 mg/día durante 5-10 años es el estándar en pacientes premenopaúsicas RE+.

- En pacientes jóvenes (<35 años) y/o no quedan amenorreicas tras la quimioterapia se debe plantear tratamiento con exemestano + análogo. (SOFT, TEXT)

Paciente de 59 años postmenopáusica
Carcinoma ductal infiltrante grado 2
T1c (17 mm)
N0
RE 90%; RP 90%; HER2 negativo
Ki-67 4%

¿Se puede evitar la quimioterapia en pacientes hormono-dependientes?

¿De qué TEST Riesgo Recaída disponemos?

- Genomic Grade
- Mamaprint (70-gene)
- Oncotype DX (21-gene)
- PAM50 (50-gene)
- Rotterdam (76-gene)
- ….
- 115 firmas genéticas publicadas (“Meta-analysis”. Fan….and C. Perou. BMC medical genetics 2011)

¿De qué TEST Riesgo Recaída disponemos?

The three most commonly used molecular prognostic profiles are:

- a 70-gene assay (MammaPrint)
- a 21-gene assay (Oncotype DX).
- a 50-gene assay (PAM 50)

"Prognostic" and *"predictive"* tools

Richard Buus[2],

Prognostic signatures

Signature	Information included
Clinical Treatment Score **(CTS)**	Nodal status, grade, tumour size, age, treatment
Immunohistochemical markers **(IHC4)**	ER, PgR, Ki67, HER2
Oncotype Recurrence Score **(RS)**	21 genes (oestrogen, proliferation, invasion, HER2 genes)
Breast Cancer Index **(BCI)**	H/I and 5 proliferation genes (Molecular Grade Index)
Prosigna **(ROR)**	46 genes, proliferation score, tumour size (EU cut-offs from transATAC for N- and N+)
EndoPredict **(EPclin)**	12 genes (proliferation, differentiation, oestrogen); nodal status and tumour size

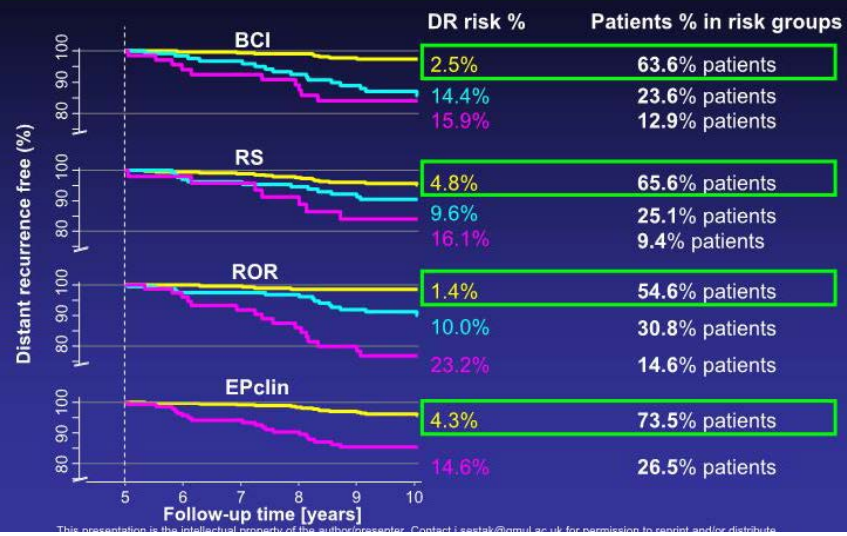
- Important questions:
  1. Comparative accuracy for prognosis → Value of chemotherapy?
  2. Prediction of late recurrence → Value of extended endocrine therapy?

Conclusions

- Unique cohort with well annotated samples, mature clinical outcome, and prognostic information for six signatures

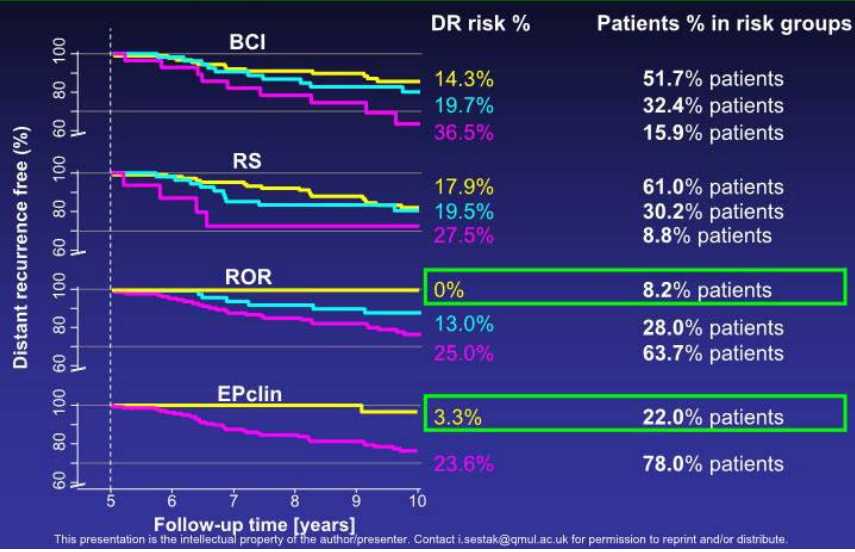
- Prediction of recurrence in years 0-10:
  - *Node-negative:*
    - All signatures good predictors and identify patients with a low DR risk
      → value of chemotherapy limited
  - *Node-positive:*
    - ROR/EPclin identify patients with low DR risk
      → value of chemotherapy limited

DR free (%) in years 5-10 – node-negative



San Antonio Breast Cancer Symposium – December 6-10, 2016

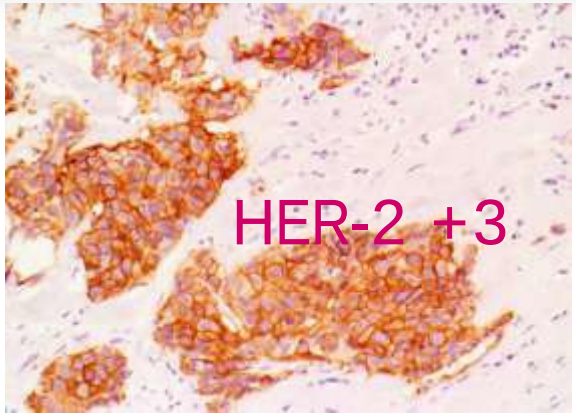
DR free (%) in years 5-10 – node-positive

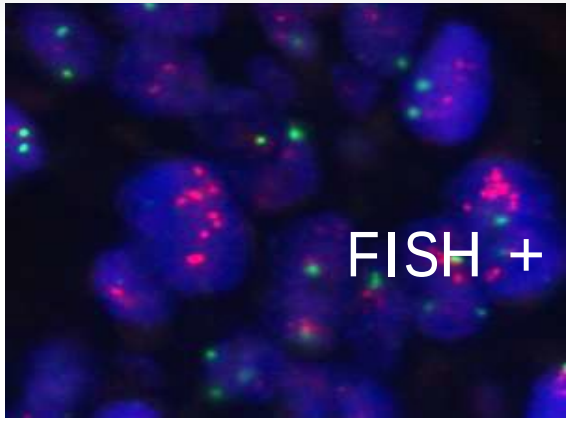


This presentation is the intellectual property of the author/presenter. Contact i.sestak@qmul.ac.uk for permission to reprint and/or distribute.

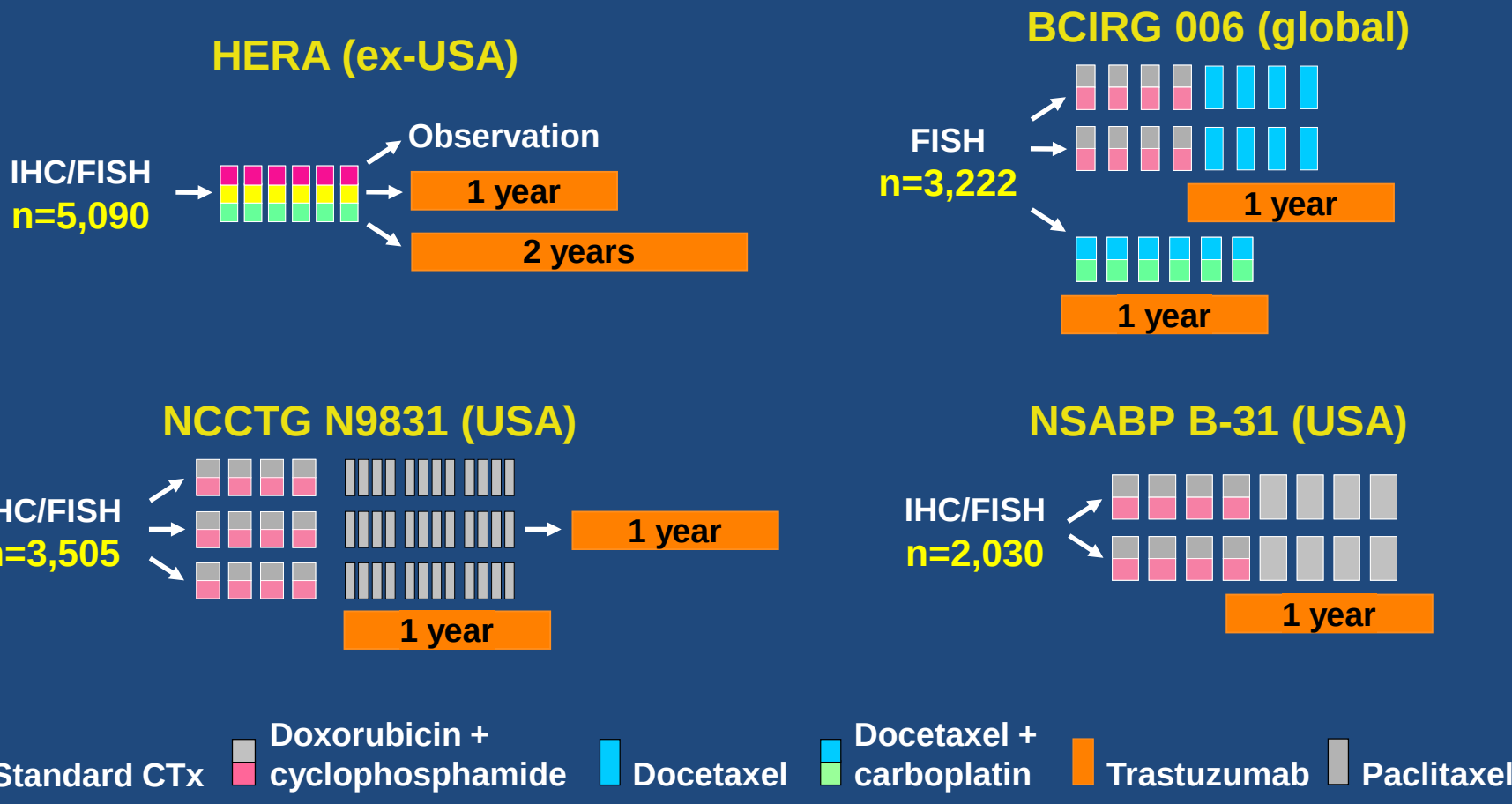
- Prediction of recurrence in years 5-10:
  - *Node-negative:*
    - BCI, ROR and EPclin good predictors for late DR (above and beyond CTS)
    - All signatures identify patients with low risk of late DR
      → extended endocrine therapy not justified
  - *Node-positive:*
    - ROR/EPclin identify patients at low risk of late DR
      → extended endocrine therapy not justified

Tratamiento de pacientes HER-2





Adjuvant trastuzumab has an extensive evidence base with >13,000 patients treated in four major trials



Piccart-Gebhart, et al. NEJM 2005
Romond, et al. NEJM 2005; Slamon, et al. SABCS 2006

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer

Edward H. Romond, M.D., Edith A. Perez, M.D., John Bryant, Ph.D.,

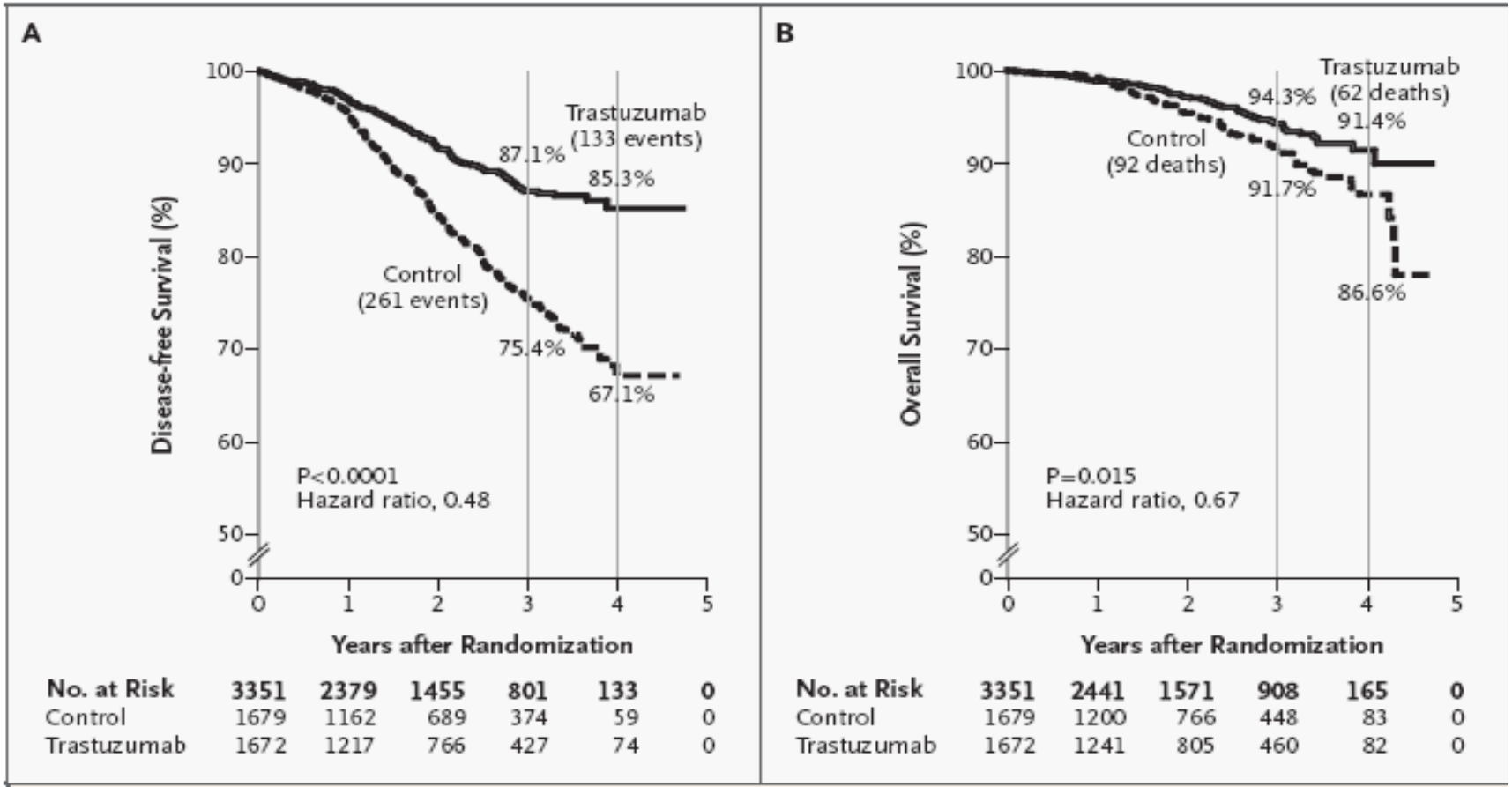
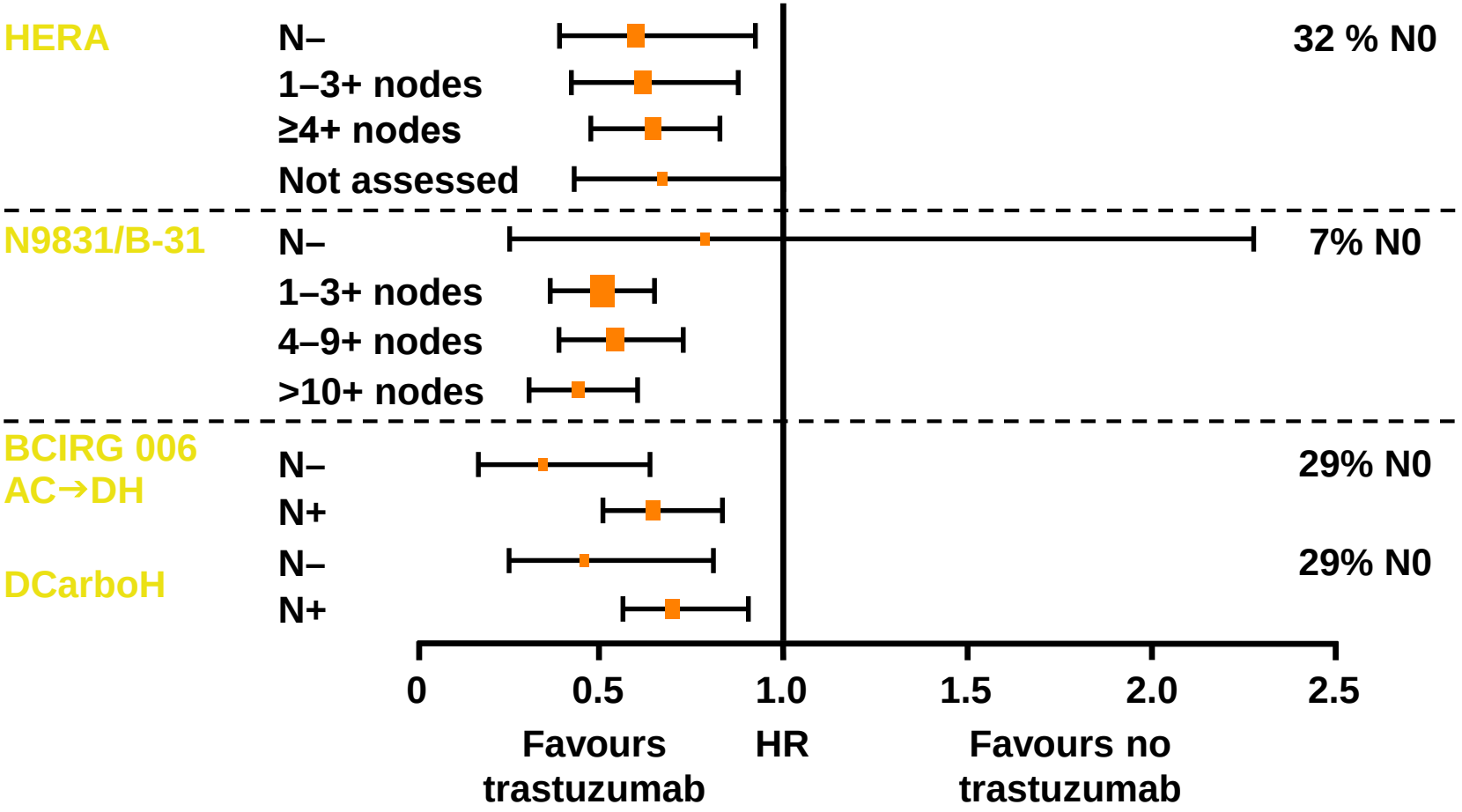


Figure 2. Kaplan–Meier Estimates of Disease-free Survival (Panel A) and Overall Survival (Panel B).
The hazard ratios are for the comparison of the trastuzumab group with the control group.

. N Engl J Med. 2005;353: 1659-1672.

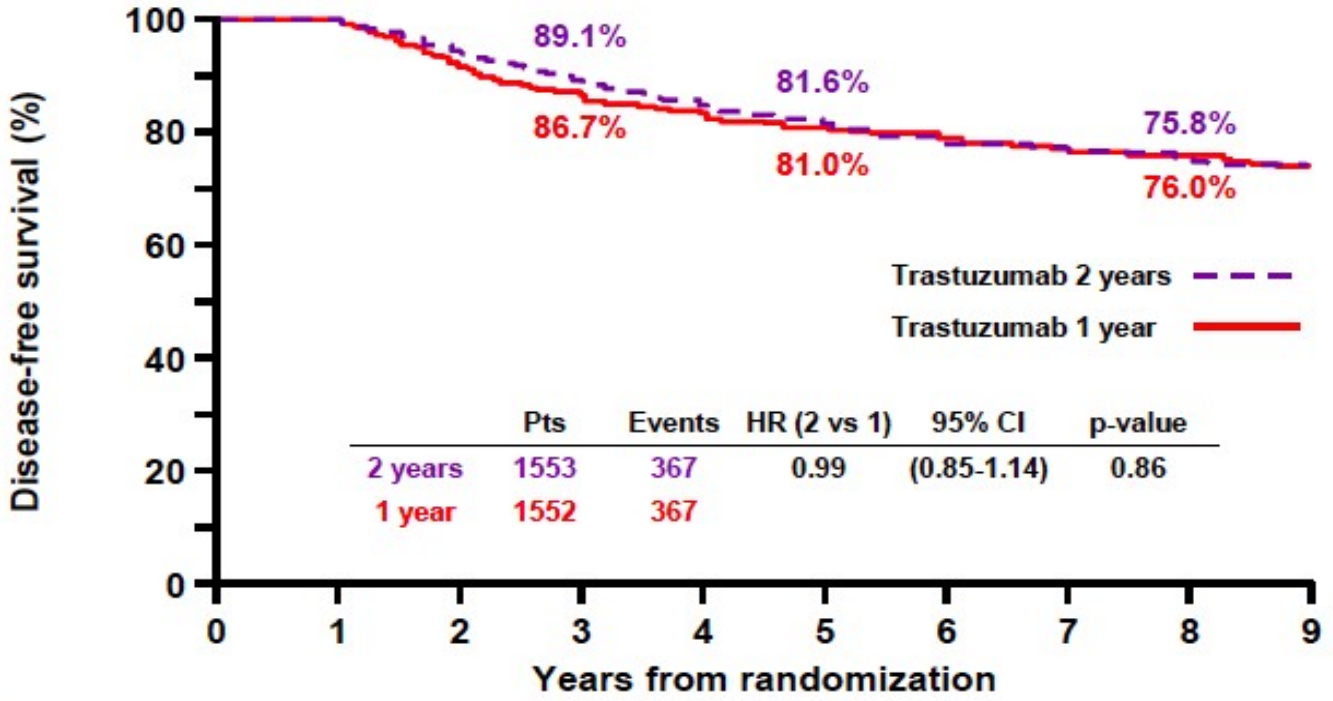
Trastuzumab provides DFS benefit irrespective of node involvement



Slamon, et al. SABCS 2006
Perez, et al. ASCO 2007; Smith, et al. Lancet 2007

N = node

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



No. at risk

Trastuzumab 2 years	1553	1553	1442	1361	1292	1223	1153	1051	633	194
Trastuzumab 1 year	1552	1552	1413	1319	1265	1214	1180	1071	649	205

M. Piccart et al. SABCS 2012

The NEW ENGLAND JOURNAL of MEDICINE JANUARY 8, 2015

Adjuvant Paclitaxel and Trastuzumab for Node-Negative, HER2-Positive Breast Cancer

Sara M. Tolaney, M.D., M.P.H., William T. Barry, Ph.D., Chau T. Dang, M.D.,

- **Uncontrolled, single-group, multicenter, investigator-initiated study of adjuvant paclitaxel and trastuzumab in 406 patients with tumors measuring up to 3 cm in greatest dimension.**

- **Patients received weekly treatment with paclitaxel and trastuzumab for 12 weeks, followed by 9 months of trastuzumab monotherapy.**

- **The primary end point was survival free from invasive disease**

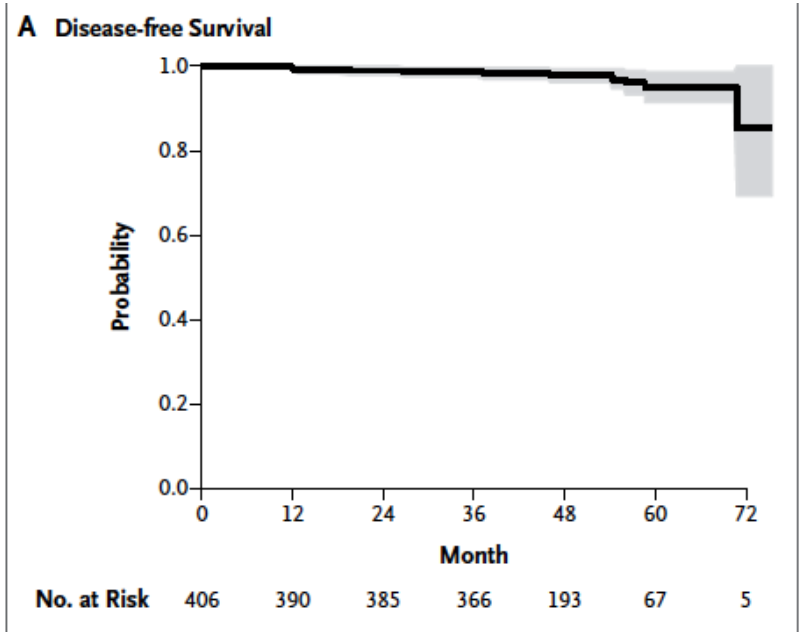
Adjuvant Paclitaxel and Trastuzumab for Node-Negative, HER2-Positive Breast Cancer

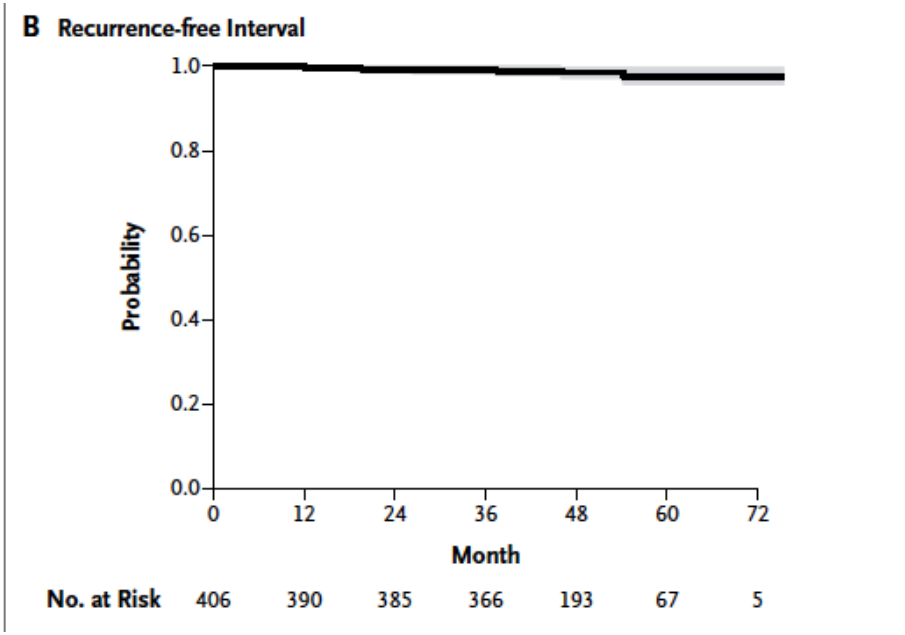
JANUARY 8, 2015

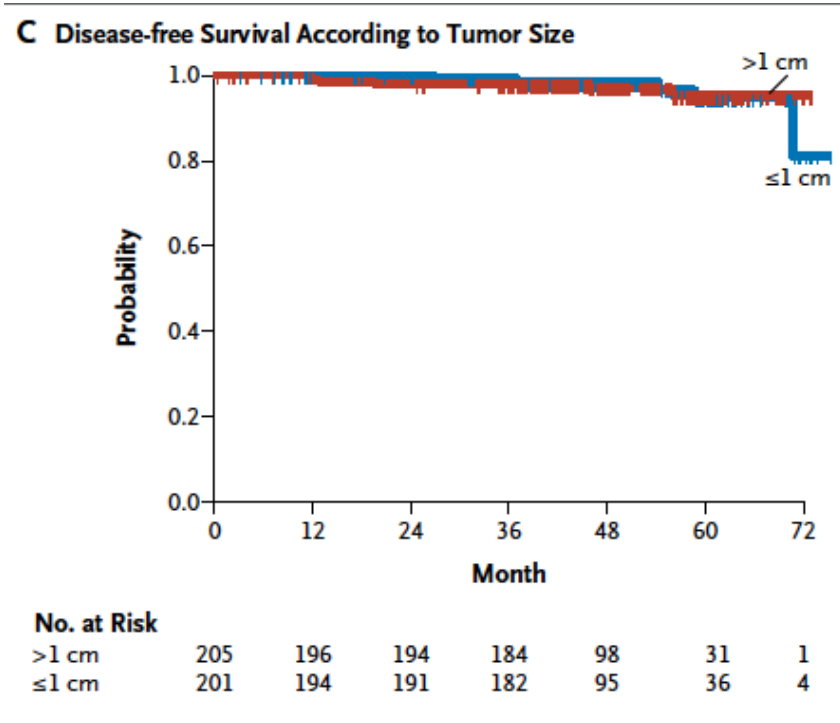
Sara M. Tolaney, M.D., M.P.H., William T. Barry, Ph.D., Chau T. Dang, M.D.,

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Patients (N=406)
	no. (%)
Age group	
<50 yr	132 (32.5)
50–59 yr	137 (33.7)
60–69 yr	96 (23.6)
≥70 yr	41 (10.1)
Sex	
Female	405 (99.8)
Male	1 (0.2)
Race†	
White	351 (86.5)
Black	28 (6.9)
Asian	11 (2.7)
Other	16 (3.9)
Primary tumor	
Size	
T1mic: ≤0.1 cm	9 (2.2)
T1a: >0.1 to ≤0.5 cm	68 (16.7)
T1b: >0.5 to ≤1.0 cm	124 (30.5)
T1c: >1.0 to ≤2.0 cm	169 (41.6)
T2: >2.0 to ≤3.0 cm	36 (8.9)
Nodal status	
N0	400 (98.5)
N1mic	6 (1.5)
Histologic grade	
I: well-differentiated	44 (10.8)
II: moderately differentiated	131 (32.3)
III: poorly differentiated	228 (56.2)
Unknown	3 (0.7)
HER2-positive status	406 (100)
Estrogen-receptor status	
Positive	260 (64.0)
Negative	141 (34.7)
Borderline	5 (1.2)
Progesterone-receptor status	
Positive	201 (49.9)
Negative	196 (48.3)
Borderline	8 (2.0)
Unknown	1 (0.2)
Hormone-receptor status	
Positive	272 (67.0)
Negative	134 (33.0)


A Disease-free Survival
Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
48
60
72
Month
No. at Risk 406 390 385 366 193 67 5


B Recurrence-free Interval
Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
48
60
72
Month
No. at Risk 406 390 385 366 193 67 5


C Disease-free Survival According to Tumor Size
>1 cm
≤1 cm
Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
48
60
72
Month
No. at Risk
>1 cm 205 196 194 184 98 31 1
≤1 cm 201 194 191 182 95 36 4

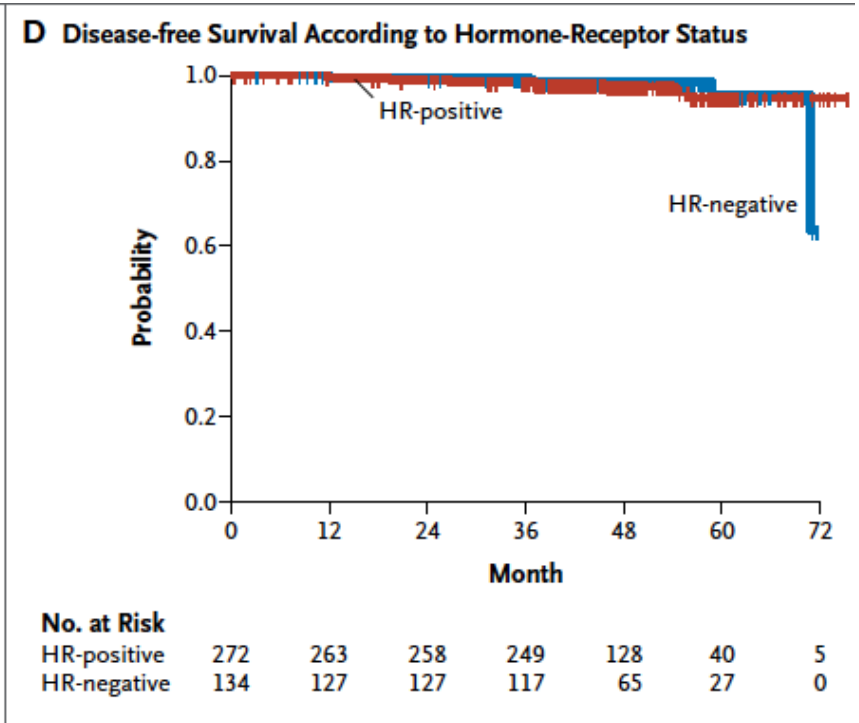

D Disease-free Survival According to Hormone-Receptor Status
HR-positive
HR-negative
Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
48
60
72
Month
No. at Risk
HR-positive 272 263 258 249 128 40 5
HR-negative 134 127 127 117 65 27 0

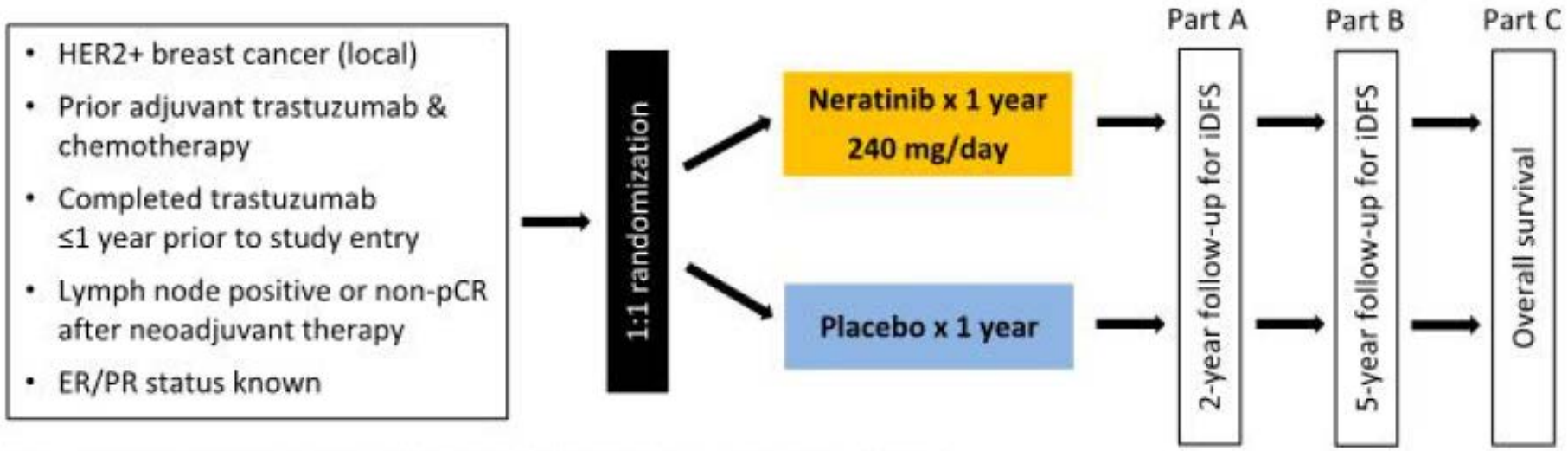
Table 3. Most Common Adverse Events Occurring during Protocol Therapy.

Event	Maximum Grade			Total
	Grade 2	Grade 3	Grade 4	
	number of patients (percent)			
Fatigue	81 (20.0)	9 (2.2)	0	90 (22.2)
Diarrhea	47 (11.6)	6 (1.5)	0	53 (13.1)
Neuropathy	39 (9.6)	14 (3.4)	0	53 (13.1)
Neutropenia	26 (6.4)	15 (3.7)	2 (0.5)	43 (10.6)
Hyperglycemia	35 (8.6)	7 (1.7)	0	42 (10.3)
Leukopenia	28 (6.9)	10 (2.5)	0	38 (9.4)
Allergic reaction	28 (6.9)	6 (1.5)	1 (0.2)	35 (8.6)
Elevated alanine amino-transferase level	23 (5.7)	7 (1.7)	0	30 (7.4)
Anemia	28 (6.9)	1 (0.2)	0	29 (7.1)

Seven-year (yr) follow-up of adjuvant paclitaxel (T) and trastuzumab (H) (APT trial) for node-negative, HER2-positive breast cancer (BC)

- Updated analysis with 7-yr DFS.
- The 7-yr DFS was 93.3% (95% CI 90.4-96.2).
- 7-yr DFS for HR+ pts was 94.6% (95% CI 91.8-97.5).
- 7-yr HR- pts was 90.7% (95% CI 84.6-97.2).

ExteNET: final study design

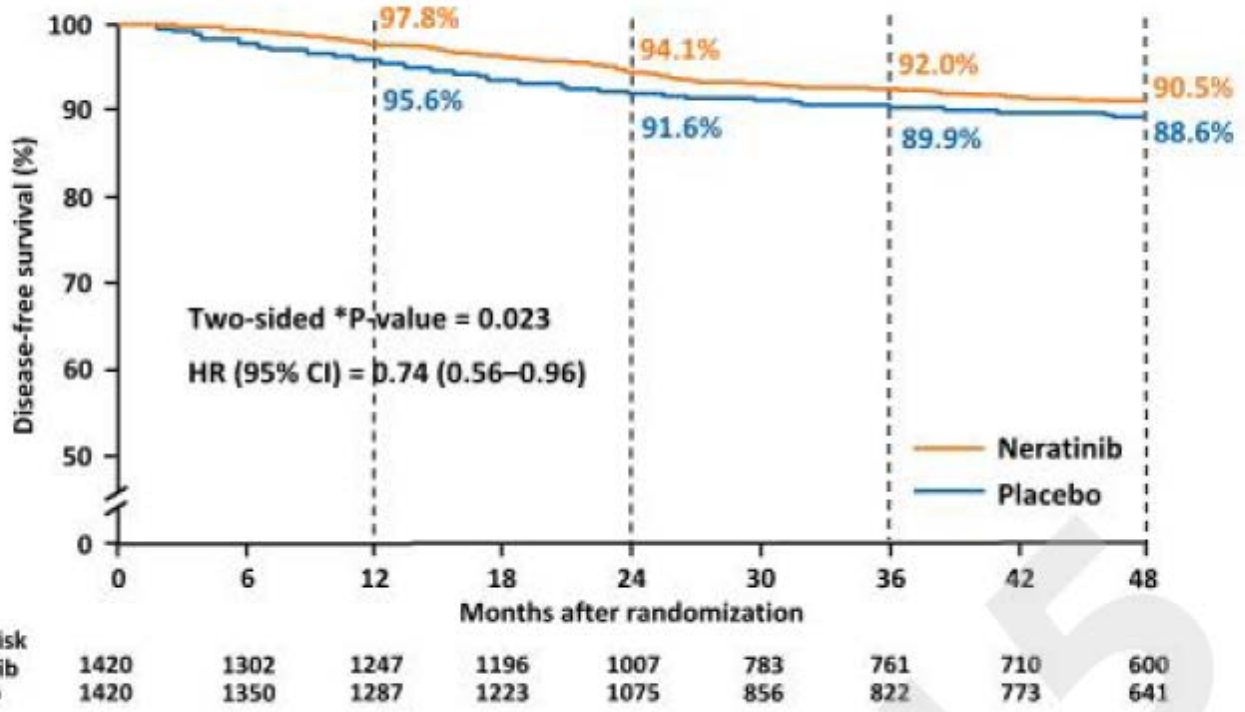


Primary analysis: invasive DFS (iDFS) in ITT population (n=2840)

- iDFS at 2 years: HR=0.67 (0.50–0.91); p=0.009
  - Hormone receptor-positive (n=1631; 57.4%); HR=0.51; p=0.001
  - Centrally-confirmed HER2-positive 60% (n=1463; 51%); HR=0.51; p=0.002

Chan A et al. Lancet Oncol 2015 in press

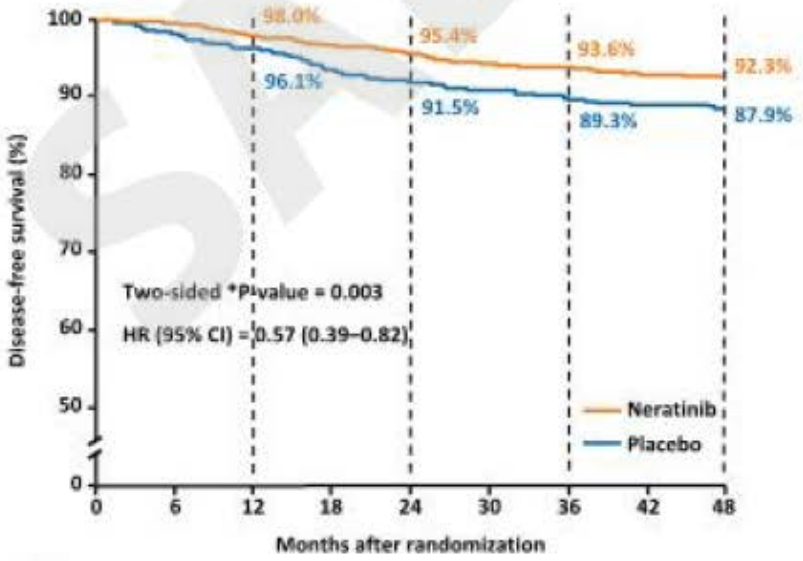
3-year iDFS analysis (ITT: n=2840)



* p value descriptive

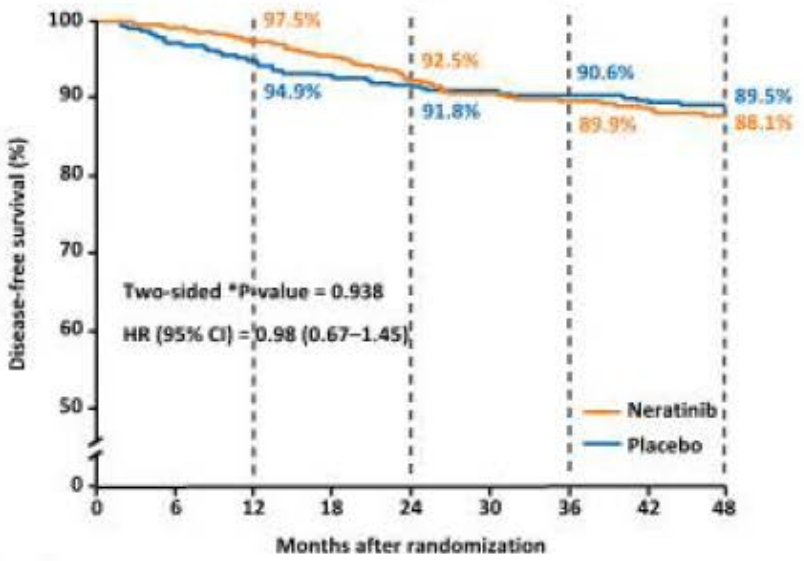
3-year iDFS analysis:
Hormone receptor status

Hormone receptor-positive



No. at risk									
Neratinib	816	746	710	682	581	454	445	418	353
Placebo	815	777	745	709	617	494	472	445	367

Hormone receptor-negative



No. at risk									
Neratinib	604	556	537	514	426	329	316	292	247
Placebo	605	573	542	514	458	362	350	328	274

* p value descriptive

The **APHINITY** Study

Adjuvant Pertuzumab and Herceptin in Initial Therapy

BIG 4-11 / BO25126 / TOC4939g

A randomized comparison of chemotherapy plus trastuzumab plus placebo versus chemotherapy plus trastuzumab plus pertuzumab as adjuvant therapy in patients with HER2-positive early breast cancer

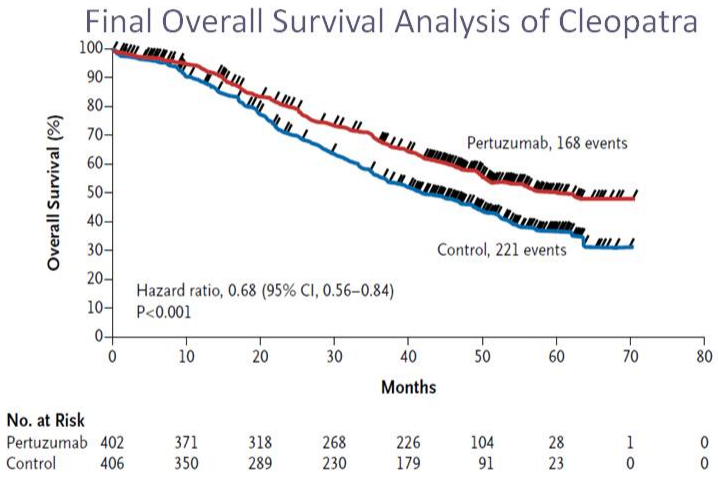
G. von Minckwitz, M. Procter, E. de Azambuja, D. Zardavas, M. Benyunes, G. Viale, T. Suter, A. Arahmani, N. Rouchet, E. Clark, A. Knott, I. Lang, C. Levy, D. Yardley, J. Bines, R. Gelber, M. Piccart, J. Baselga
for the APHINITY Steering Committee and Investigators

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

BIG
Breast International Group

APHINITY: Rationale

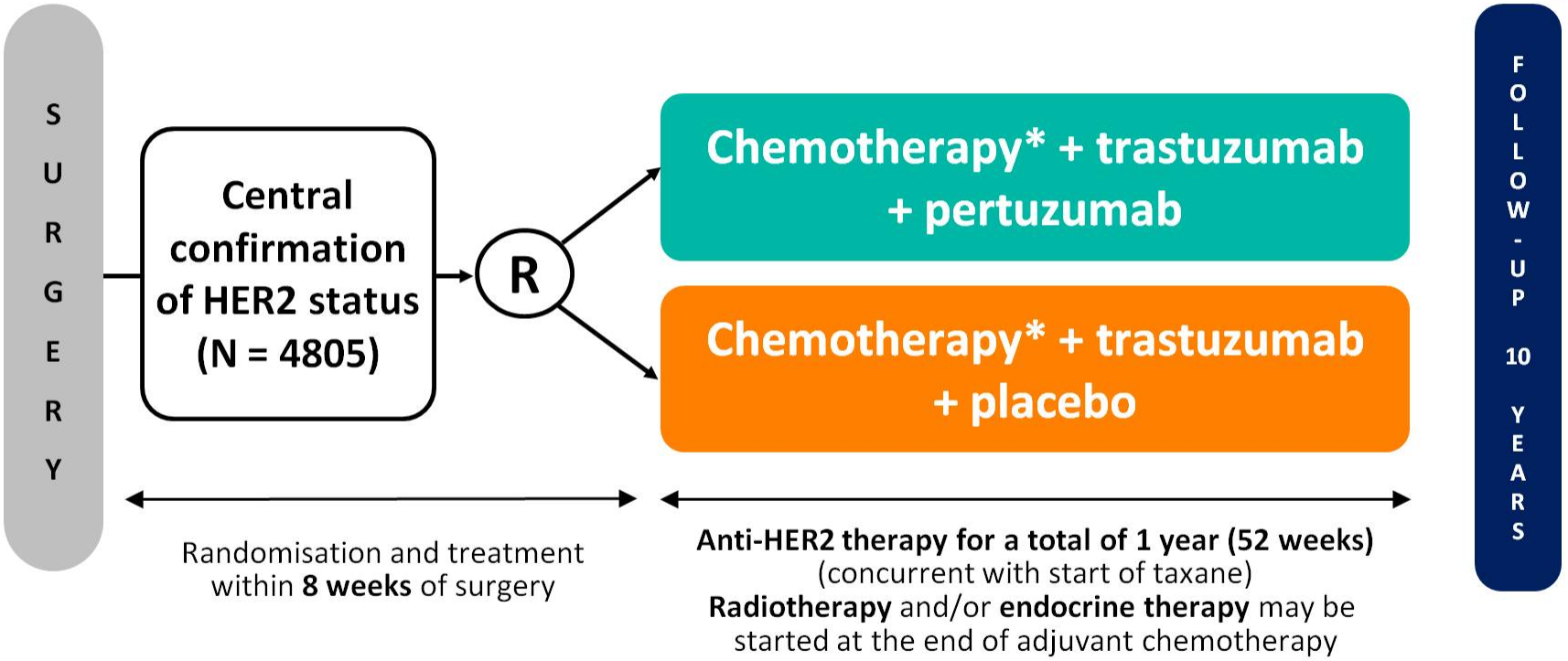
- Pertuzumab has complementary mechanisms of action with trastuzumab.[1-3]
  - Trastuzumab binds close to the transmembrane domain, inhibiting HER2 dimerization
  - Pertuzumab binds to the dimerization domain, inhibiting HER2 hetero-dimerization with other HER family receptors [4-7]
- In patients with HER2-positive metastatic breast cancer pertuzumab added to trastuzumab and docetaxel significantly improved both progression-free and overall survival.[8,9]
- In the neoadjuvant setting, the addition of pertuzumab to trastuzumab plus docetaxel significantly improved pathological complete response rate.[10,11]
- Recurrences of HER2-positive early breast cancer still occur for a significant proportion of patients in the long-term.[12]



[1]Baselga J, Nat Rev Cancer 2009; [2]Scheuer W, Cancer Res 2009; [3]Hubbard SR Cancer Cell 2005; [4]Molina MA et al. Cancer Res 2001; [5]Junttila TT et al. Cancer Cell 2009; [6]Franklin MC et al. Cancer Cell 2004; [7]Agus DB et al. Cancer Cell 2002
[8]Baselga J, NEJM 2012; [9]Swain SM, NEJM 2015; [10]Swain SM, Oncologist 2013; [11]Gianni L, Lancet Oncol 2012; [12]Cameron D, Lancet 2017

BIG Breast International Group

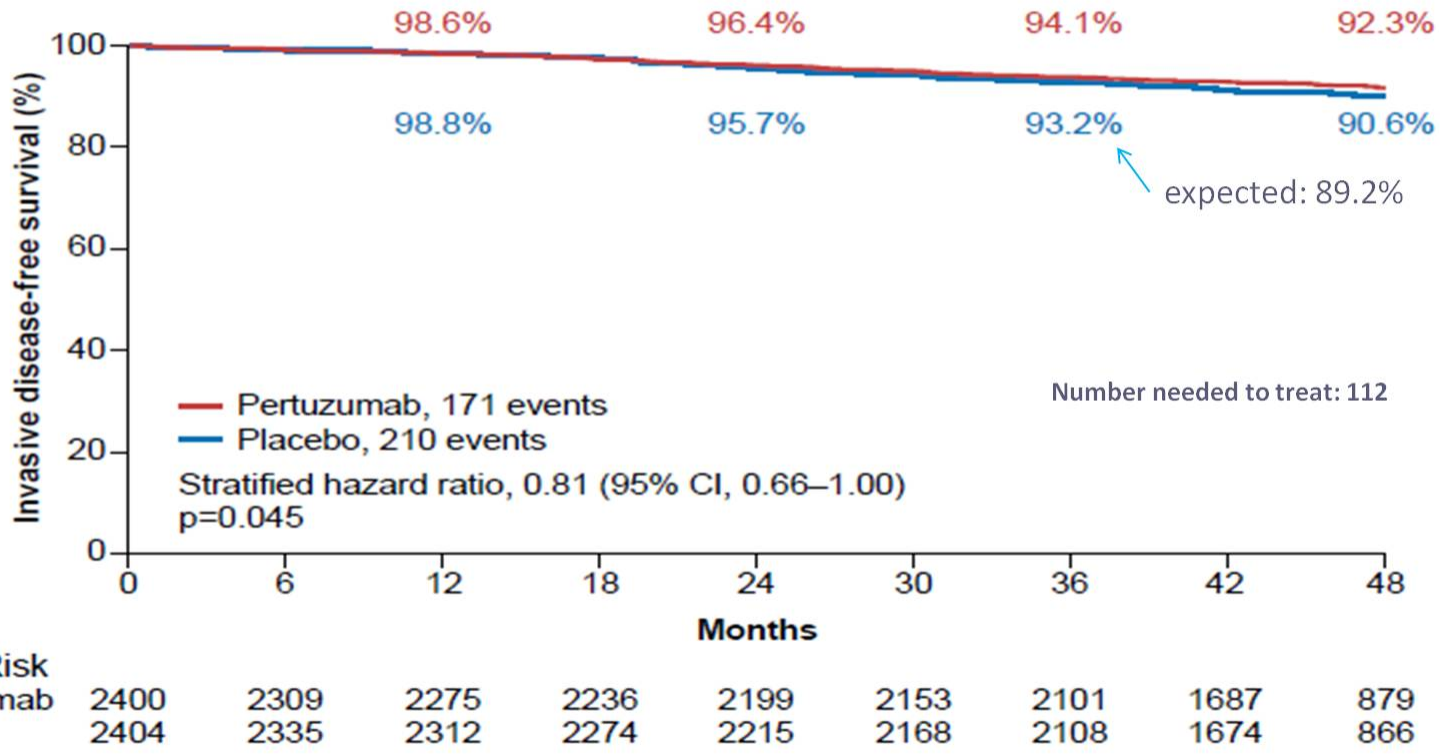
APHINITY: Trial Design



*A number of standard anthracycline-taxane-sequences or a non-anthracycline (TCH) regimen were allowed

BIG Breast International Group

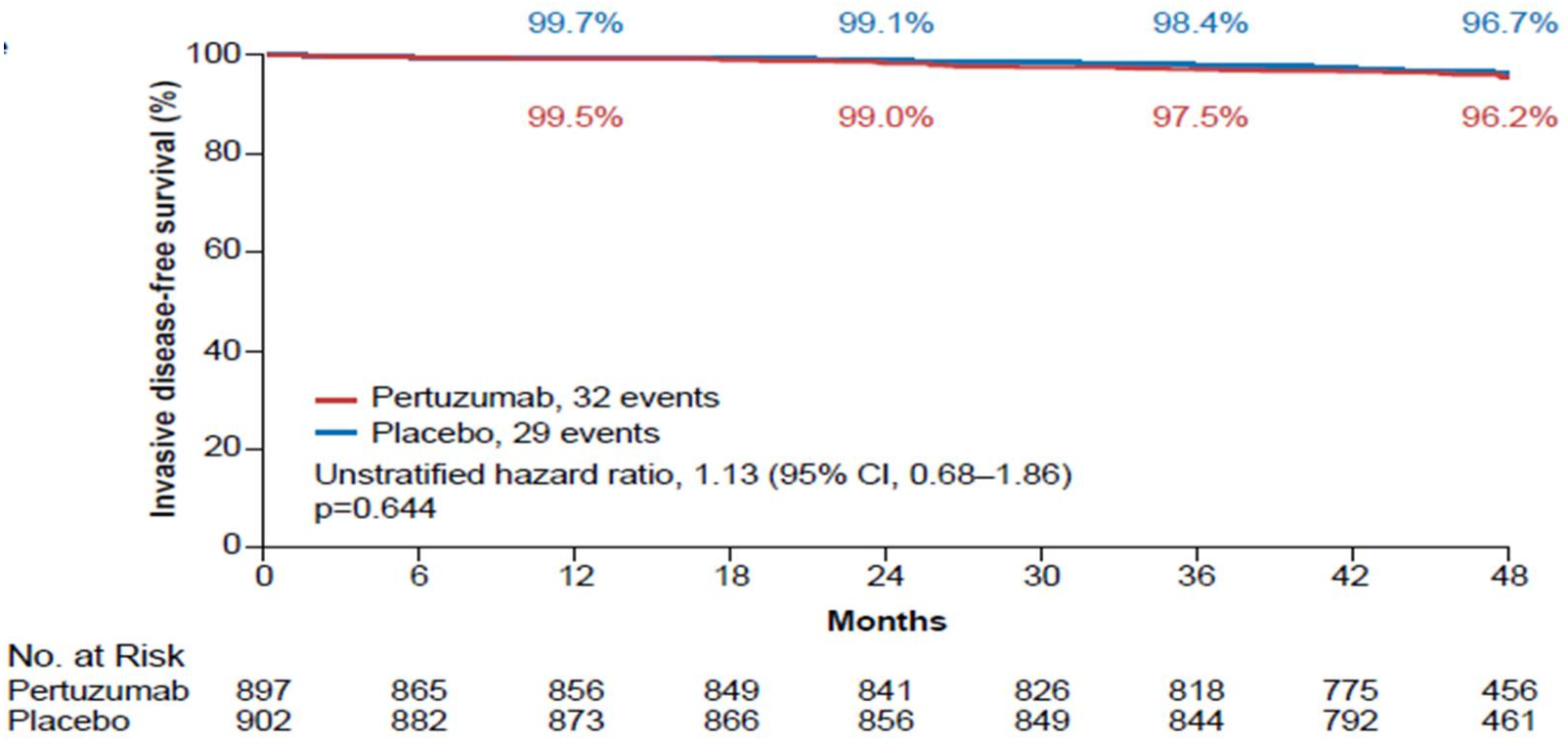
APHINITY: Intent-to-Treat Primary Endpoint Analysis Invasive Disease-free Survival



BIG
Breast International Group

Presented By Gunter Von Minckwitz at 2017 ASCO Annual Meeting

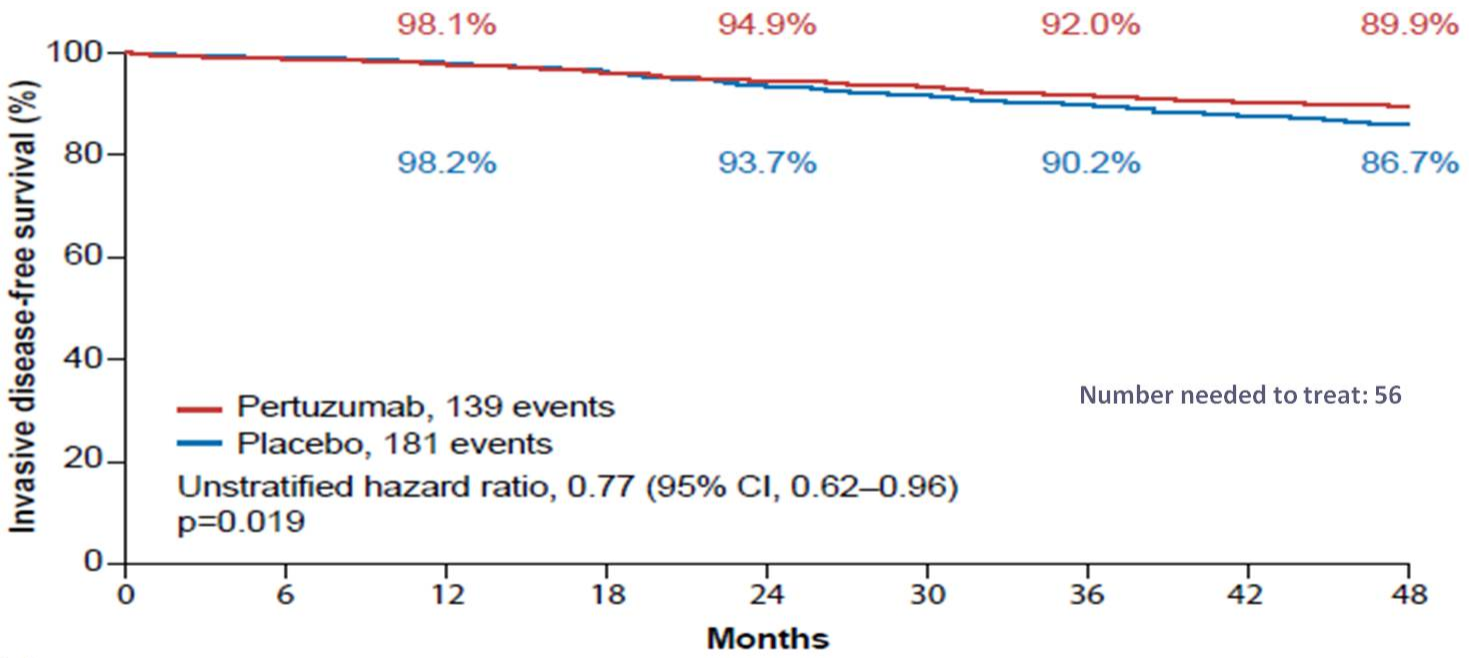
APHINITY: Node-negative Subgroup



BIG
Breast International Group

Presented By Gunter Von Minckwitz at 2017 ASCO Annual Meeting

APHINITY: Node-positive Subgroup

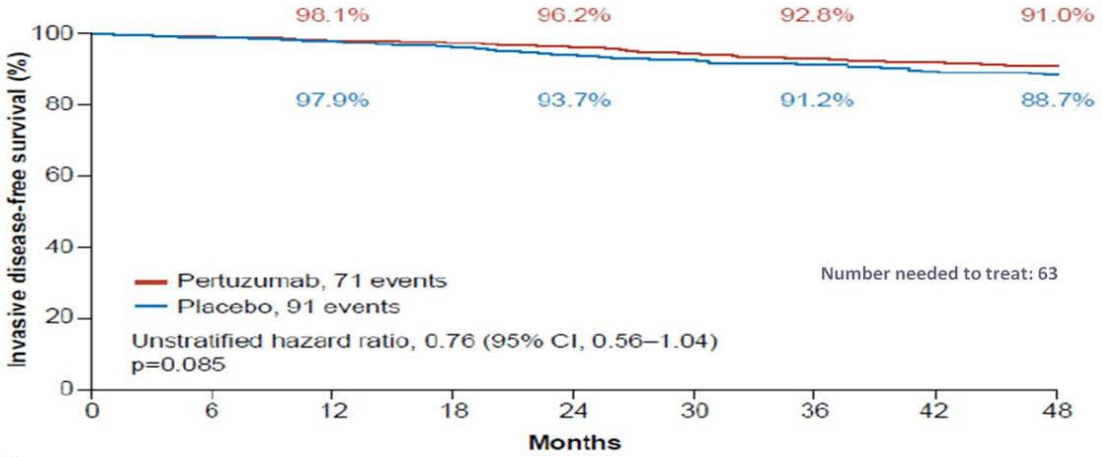


No. at Risk									
Pertuzumab	1503	1444	1419	1387	1358	1327	1283	912	423
Placebo	1502	1453	1439	1408	1359	1319	1264	882	405

BIG
Breast International Group

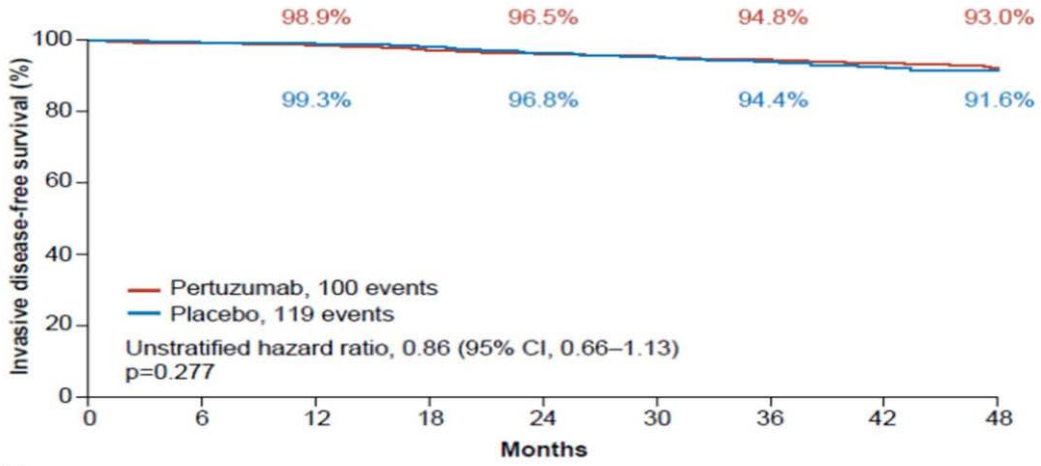
Presented By Gunter Von Minckwitz at 2017 ASCO Annual Meeting

APHINITY: Hormone Receptor-negative Subgroup



No. at Risk									
Pertuzumab	864	836	821	813	797	774	755	600	314
Placebo	858	827	811	793	771	758	730	569	302

APHINITY: Hormone Receptor-positive Subgroup



No. at Risk									
Pertuzumab	1536	1473	1454	1423	1402	1379	1346	1087	565
Placebo	1546	1508	1501	1481	1444	1410	1378	1105	564

NNT= 1/RRA (RRA: reducción del riesgo absoluto)

- **Población global:** 1/0.9 = 112 pacientes.
- **Población N+:** 1/1.8= 56 pacientes.
- **Población HR-:** 1/1.6= 63 pacientes.

- Coste?
- Toxicidad?

EDITORIAL

Kathy D. Miller, M.D.

- The toxic effects (and cost) are too great for too many to benefit too few.
- A dichotomous approach based on biologic risk stratification is needed.
- Trials that involve patients at truly high risk continuing to explore new therapies.
- Patients at low risk should do less.
- Neoadjuvant therapy may be a better guide.

June 5, 2017, at NEJM.org.

Impacto de la vida saludable tras el diagnóstico de cáncer de mama

- **Bajar el IMC**

- **Limitar consumo de alcohol**

- **Incrementar el ejercicio físico**

Muchas gracias

- Luis Manso Sánchez
  - lmanso.hdoc@salud.madrid.org
  - luigimanso@gmail.com

- Servicio Oncología Médica. Hospital Universitario 12 de Octubre, Avd. Córdoba sn 28041 Madrid.