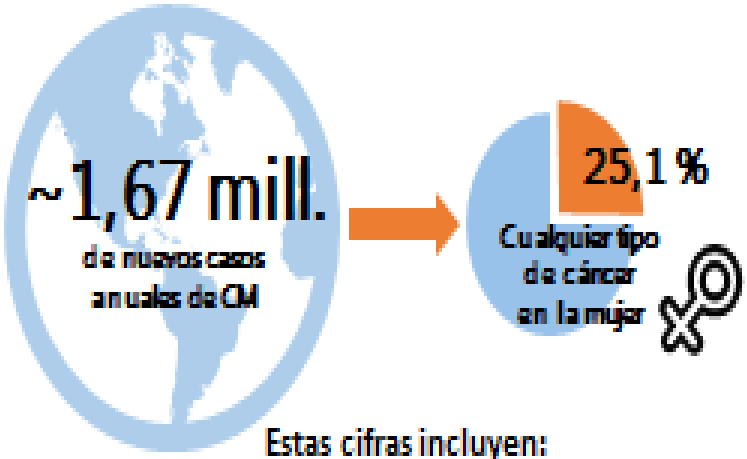
MEJORAS EN EL TRATAMIENTO SISTÉMICO DEL CÁNCER DE MAMA. PLATAFORMAS GENÓMICAS

Juan Lao
Hospital Universitario Miguel Servet

Datos estadísticos sobre el cáncer de mama

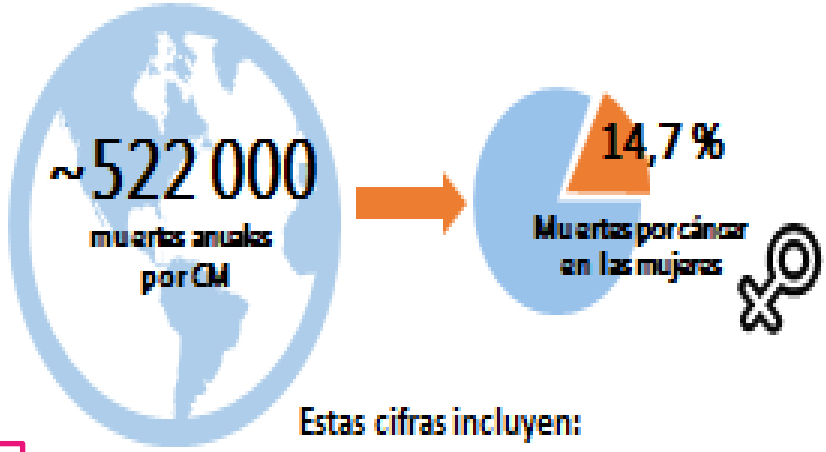
El CM es el cáncer más frecuente en mujeres en todo el mundo[1,2]



Estas cifras incluyen:

- 458.718 mujeres en Europa (28,6 %)[2]
- 232.714 mujeres en EE.UU. (29,9 %)[2]

El CM es la principal causa de muerte por cáncer en las mujeres en el mundo[1,2]



Estas cifras incluyen:

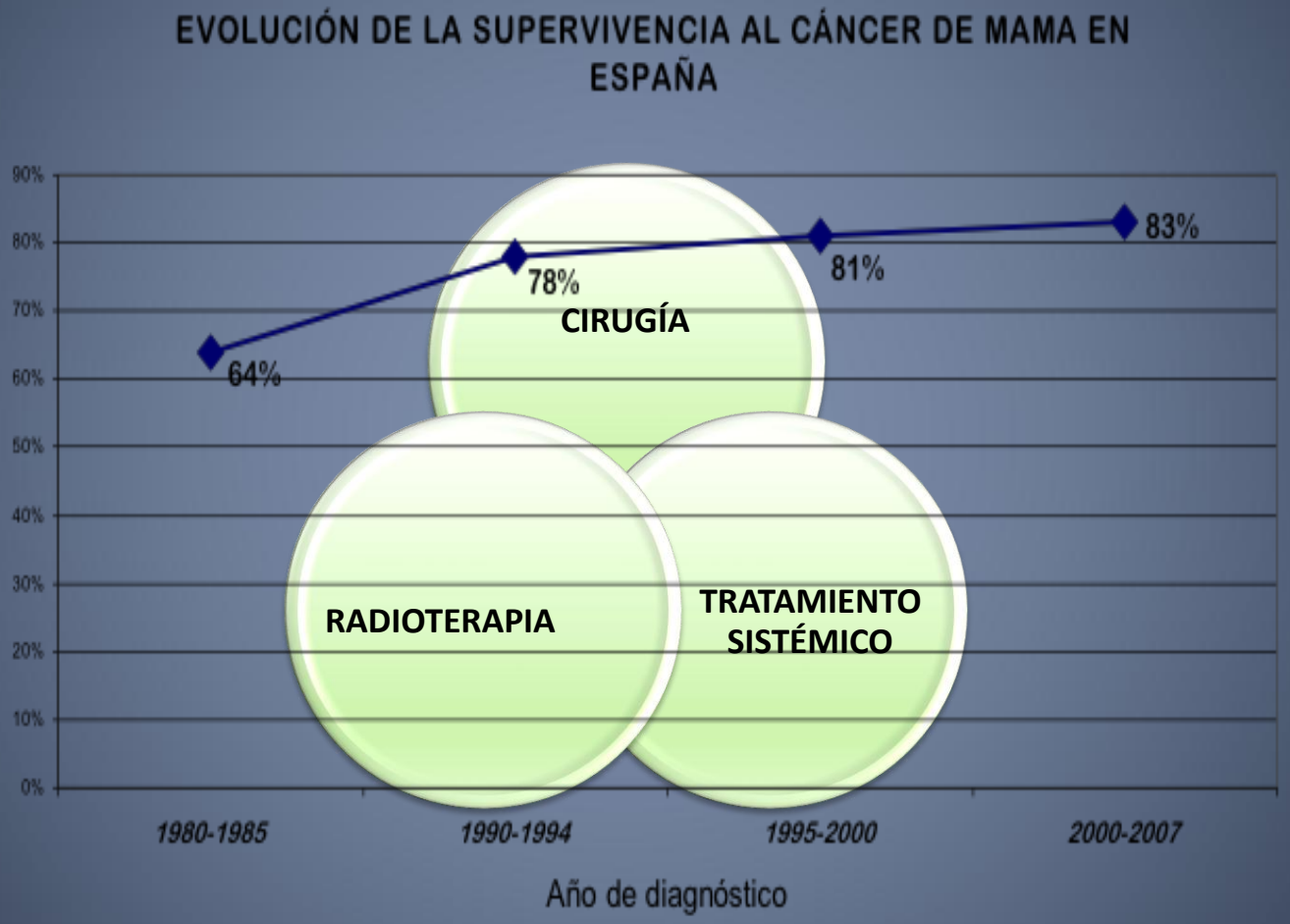
- 131.347 muertes en Europa (16,9 %)[2]
- 43.909 muertes en EE.UU. (15,0 %)[2]

1. Ferlay J, et al. Int J Cancer 2015; 136:E359–e386;
2. GLOBOCAN database, http://globocan.iarc.fr/Default.aspx (consultado en septiembre de 2016).

Cáncer de mama en España 2017

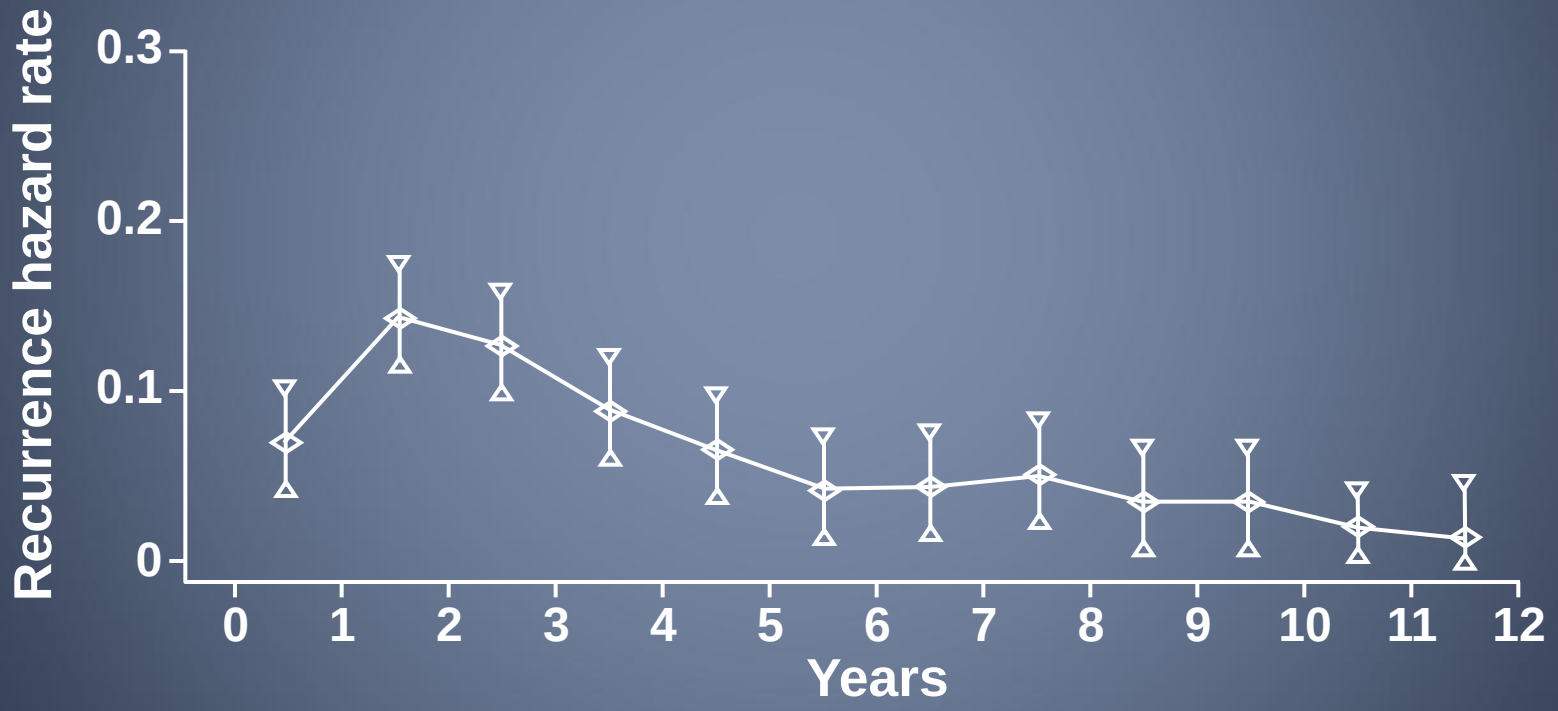
- **27.747 casos nuevos anuales**
  - **71% > 50 años; 48% > 60 años**
- **61 % estadios localizados.**
- **6.212 fallecimientos**
- **Supervivencia a 5 años cercana al 90 % en estadios precoces (<25 % si enfermedad avanzada).**
- **104.210 mujeres vivas con cáncer de mama a cinco años**

SEOM 2017



Fuente: EUROCARE-5, Lancet Oncol 2014;15:23-34

Riesgo de recaida a lo largo del tiempo



Saphner; JCO 1996

Riesgo de recurrencia: RE +

Table 1: Risk of Distant Recurrence 10 to 20 Years After Diagnosis and Discontinuation of Endocrine Therapy at 5 Years

Tumor Subgroup	10 Years	15 Years	20 Years
T1N0	4%	9%	14%
T1N1 (1–3 nodes)	8%	15%	23%
T1N2 (4–9 nodes)	16%	30%	41%
T2N0	8%	14%	21%
T2N1 (1–3 nodes)	12%	20%	29%
T2N2 (4–9 nodes)	20%	35%	47%

Pan *et al.*, J Clin Oncol 34, 2016 (suppl; abstr 505)

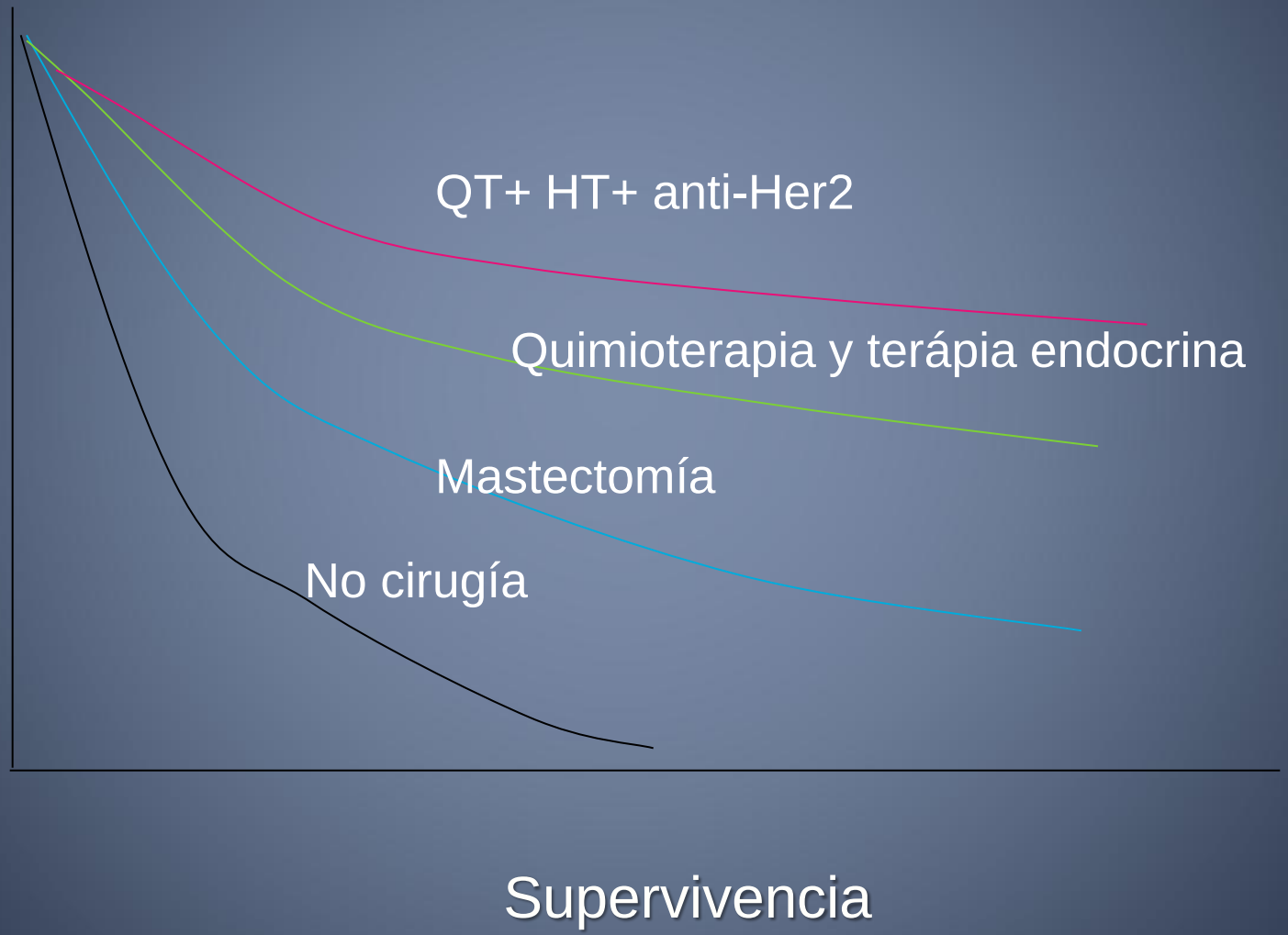
TRATAMIENTO SISTÉMICO ADYUVANTE

DEFINICION DE ADYUVANCIA

- La terapia sistémica adyuvante se define como:

  - la administración de quimioterapia citotóxica, terapias dirigidas (como el tratamiento hormonal o las terapias anti-Her2) o inmunoterapia tras la cirugía con la intención de destruir o inhibir el crecimiento de las micrometástasis.

Incremento de la supervivencia en estadios precoces con los tratamientos adyuvantes



Factores pronósticos y predictivos

- Status axilar
- Tamaño
- Subtipo histológico
- Grado histológico
- RE/RP
- Her-2
- Proliferación: ki-67/índice mitótico
- Fenotipo/perfil molecular
- Otros: edad, ínvasión linfovascular, p53, raza.

Determinando la necesidad de QT adyuvante en cáncer de mama

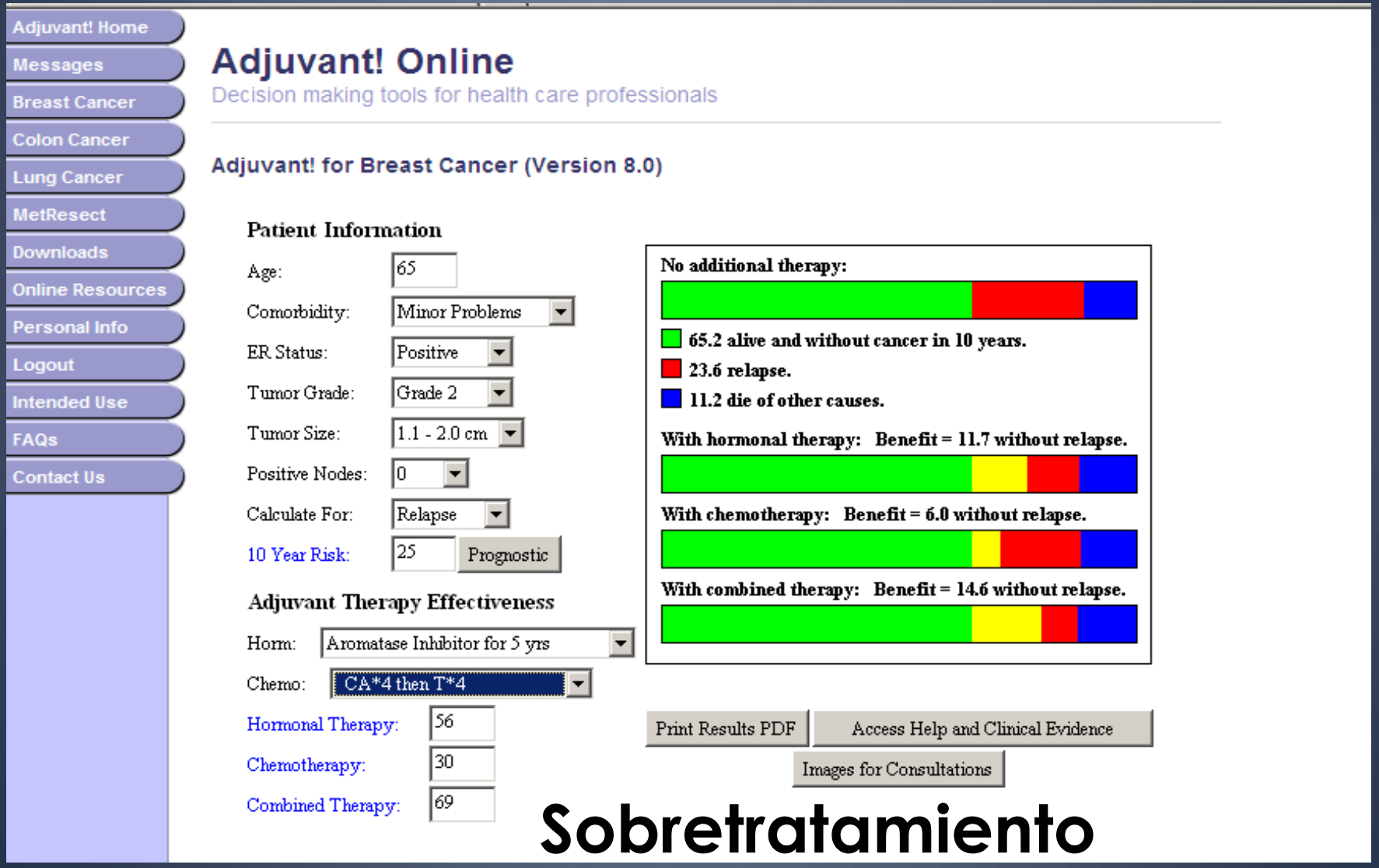
FACTORES CLÍNICOS
-Edad.
-Comorbilidad.
-Decisión de la paciente.

FACTORES TUMORALES
-Tamaño tumoral.
-Número de adenopatías.
-Grado tumoral.
-Situación receptores hormonales (RE, RP) y Her2.

ADYUVANT! ONLINE

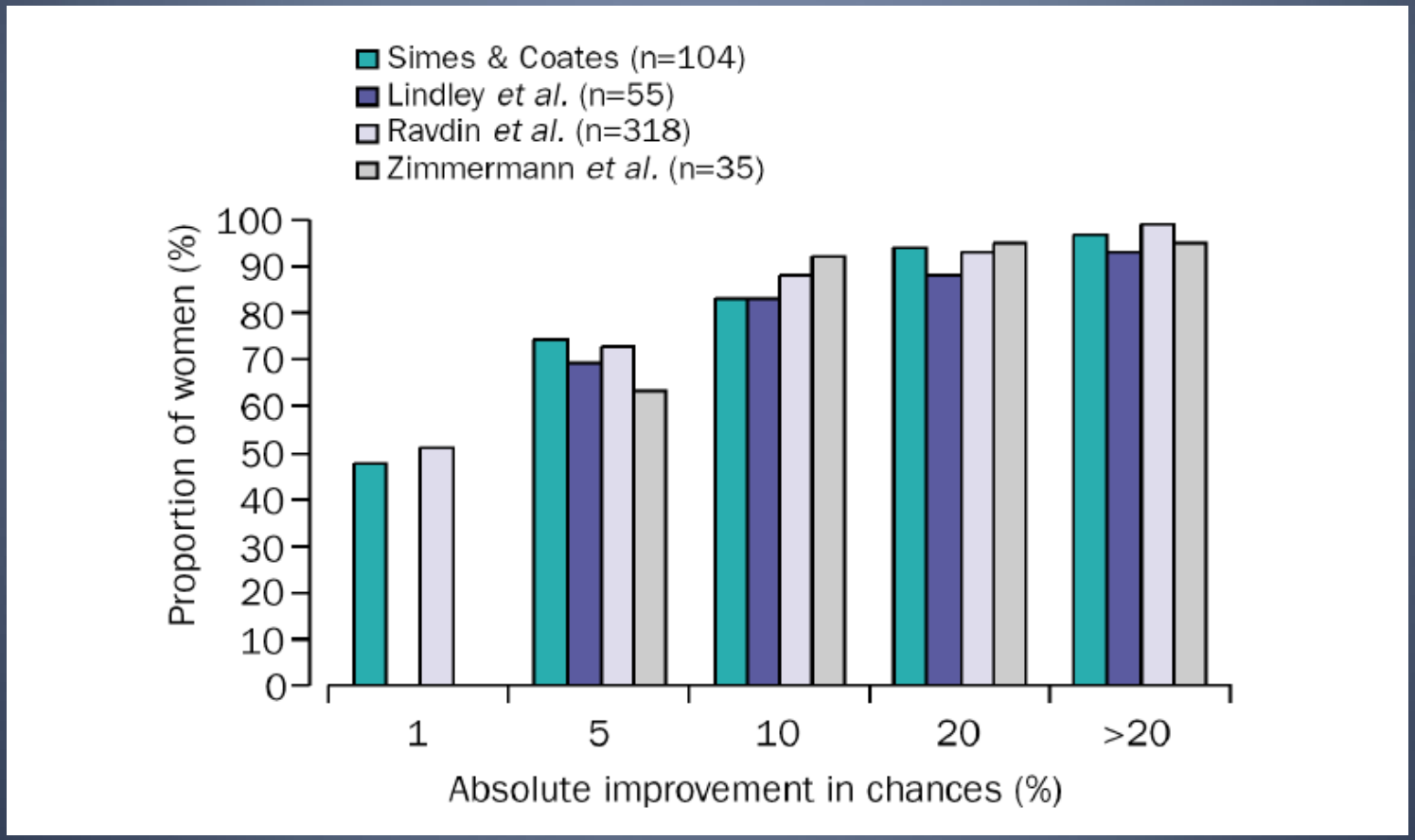
Con estos parámetros, se estima que el 60% de las pacientes con Ca mama en estadios iniciales reciben tto QT adyuvante. Solo el 2-15% obtendrán beneficio. [Lancet 2005]

¿QUÉ BENEFICIO APORTA LA ADYUVANCIA?



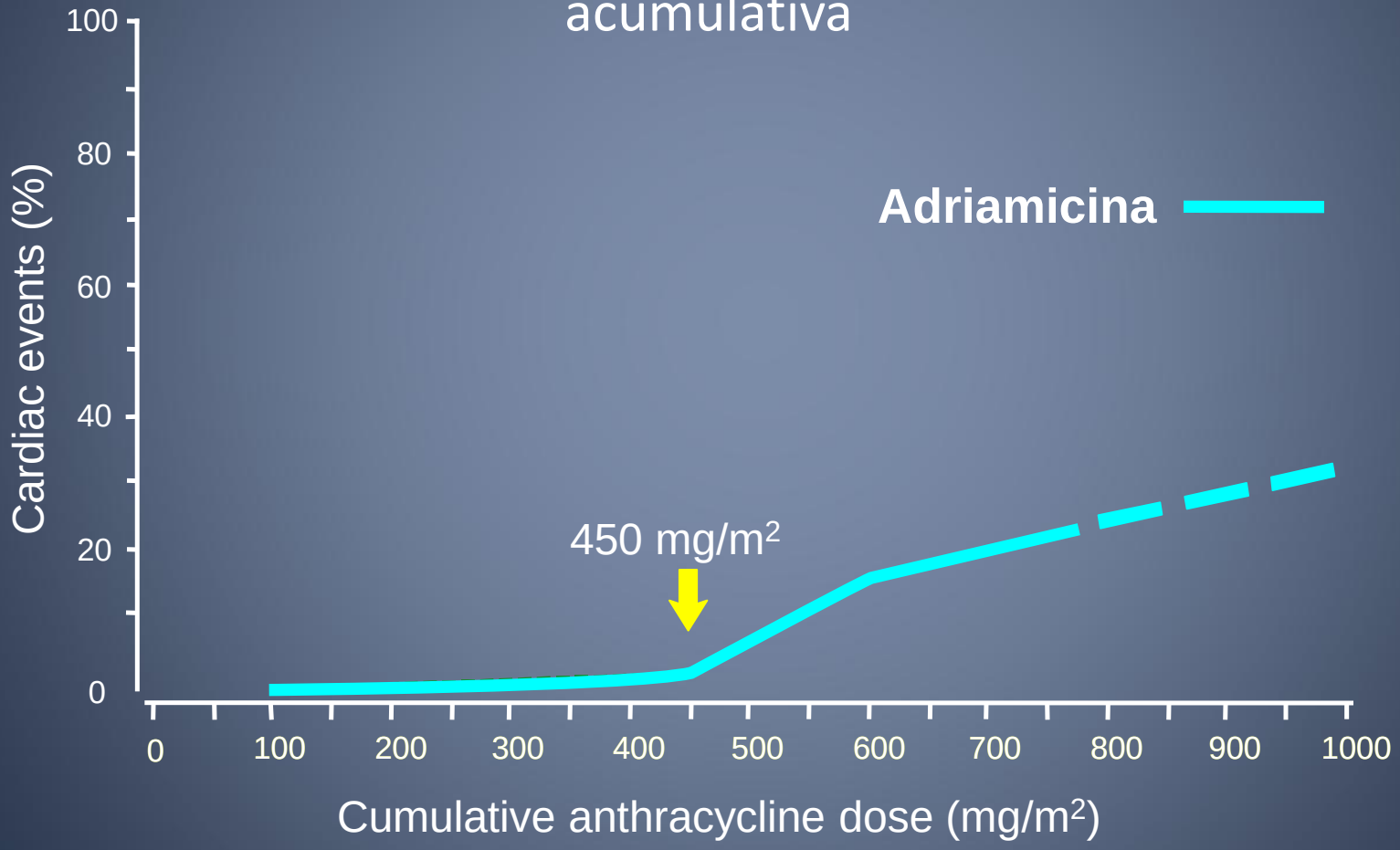
Sobretratamiento

Un 50% de las mujeres consideran que la quimioterapia merece la pena por un 1% de beneficio en supervivencia



SIN EMBARGO: TOXICIDAD

Riesgo de desarrollo de I. Cardiaca en función de la dosis acumulativa



S. XXI. Una nueva visión

Perou et al. Nature 2000

Sorlie et al. PNAS 2001

Microarrays

Pronóstico de los subtipos

van't Veer et al. Nature 2002

Microarrays

Primer test genético

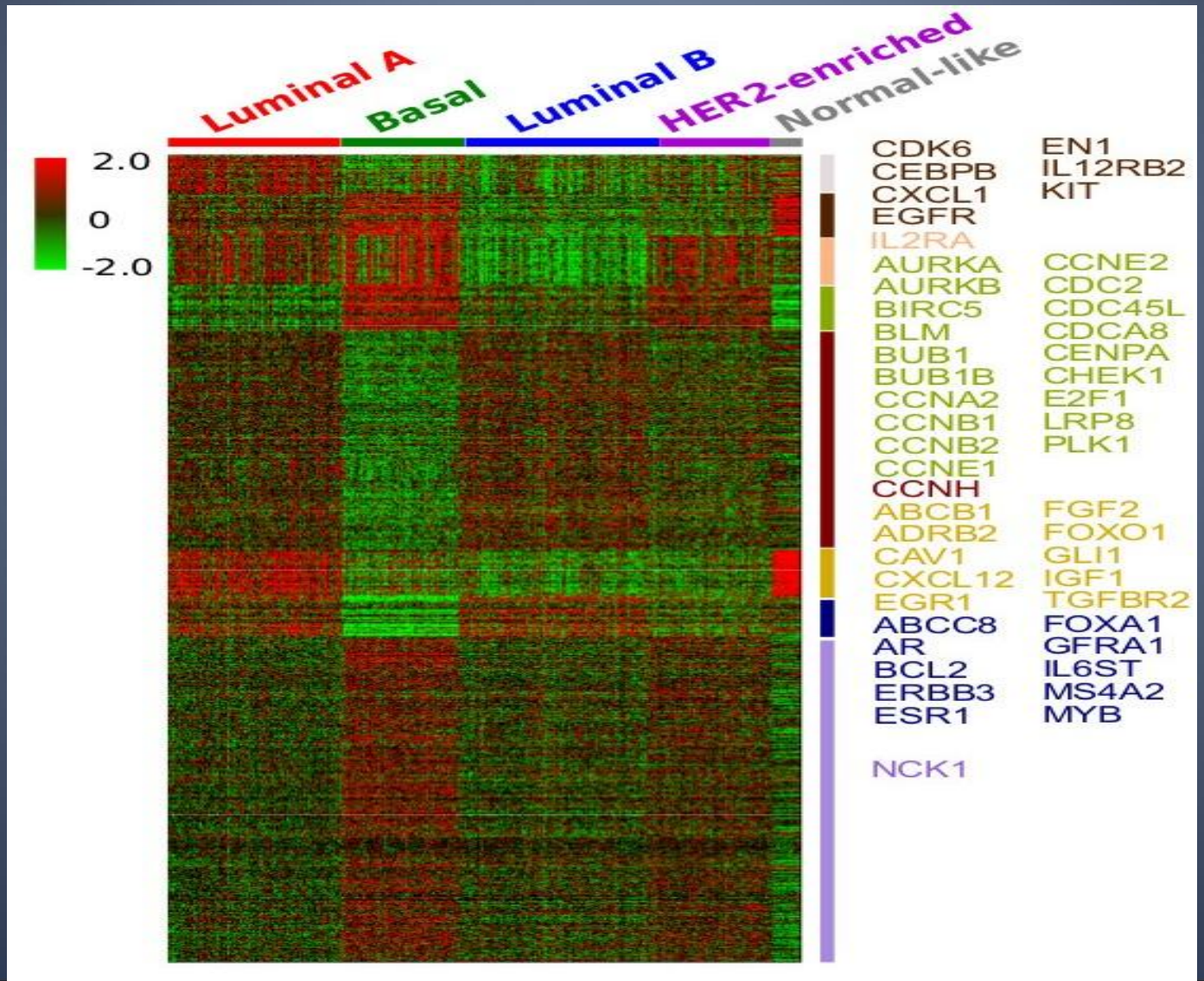
Paik et al. NEJM 2004

Aplicabilidad de RT-qPCR on FFPE

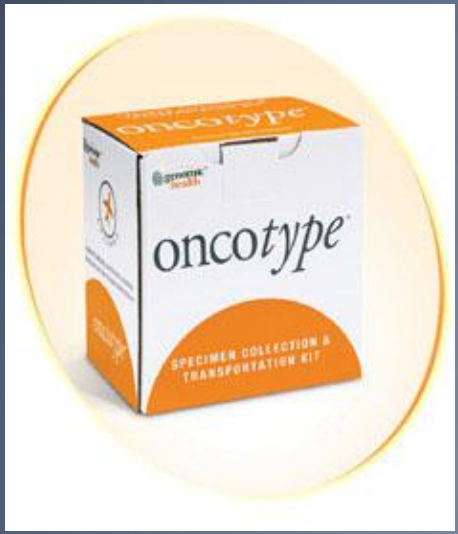
Oncotype Dx

El cáncer de mama deja de ser una única enfermedad
El conocimiento de la biología del tumor > factores clásicos

S. XXI. Una nueva visión:clasificaciòn molecular



PLATAFORMAS GENÓMICAS



prosigna® Breast cancer prognostic gene signature assay

	Oncotype Dx[1,2]	Endopredict[3]	PAM50[4]	Mammaprint[5]
Genes	16+5 genes	8 genes	50 genes	70 genes
Tecnología	qPCR		nCounter	Microarray
	N0/N1			N0
Validaciones Clínicas Retrospectivas	NSABP-B14/20	ABCSG-6/8	TransATAC, ABCSG-8	
Validaciones Clínicas Prospectivas	TAILORX			MINDACT

1. Paik et al. NEJM 2004, 2. Paik et al. JCO 2006, 3. Parker et al. JCO 2009, 4. Dowsett et al. JCO 2013, 5. van't Veer et al. Nature 2002.

OncotypeDX

Genomic Health
-California (USA)

Genomic Health
LIFE. CHANGING.

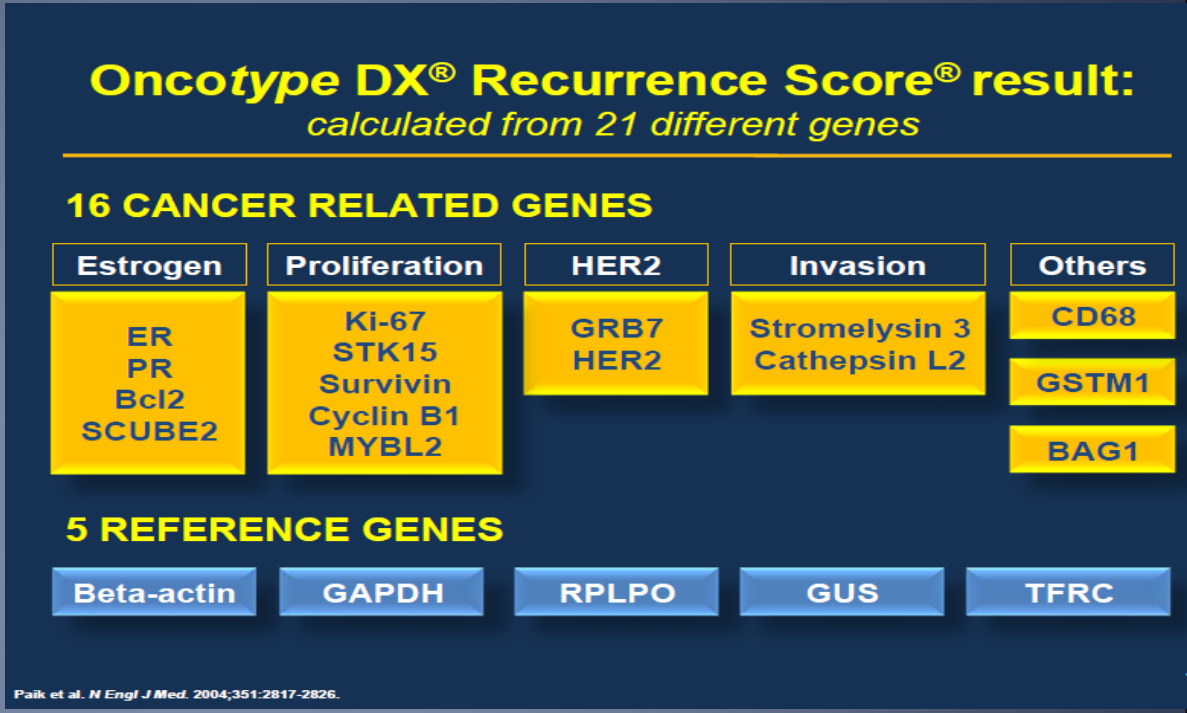
Oncotype: Desarrollo

Selección de 250 genes candidatos (literatura, bases de datos genómicas, etc)

PCR

447 pacientes del brazo de TAM en B20

16+5



RSU = +0.47 x GRB7 score -0.34 x ER score +1.04 xProliferation score +0.1 x Invasion score +0.05 x CD68 score -0.08 x GSTM1 score -0.07BAG1 score.

Recurrence Score = 20x(RSU-6.7)

Oncotype: N-

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

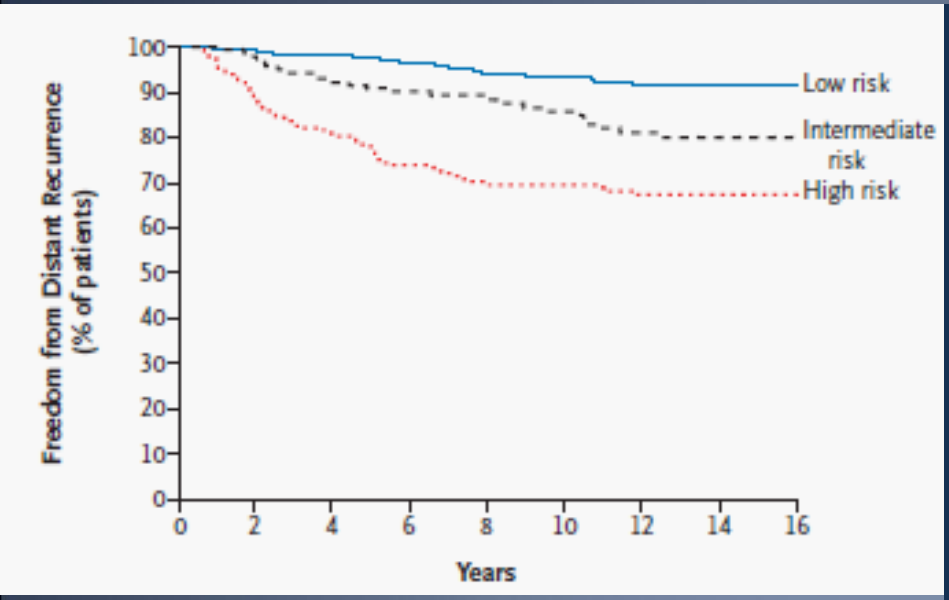
A Multigene Assay to Predict Recurrence of Tamoxifen-Treated, Node-Negative Breast Cancer

Soonmyung Paik, M.D., Steven Shak, M.D., Gong Tang, Ph.D., Chungyeul Kim, M.D., Joffre Baker, Ph.D., Maureen Cronin, Ph.D., Frederick L. Baehner, M.D., Michael G. Walker, Ph.D., Drew Watson, Ph.D., Taesung Park, Ph.D., William Hiller, H.T., Edwin R. Fisher, M.D., D. Lawrence Wickerham, M.D., John Bryant, Ph.D., and Norman Wolmark, M.D.

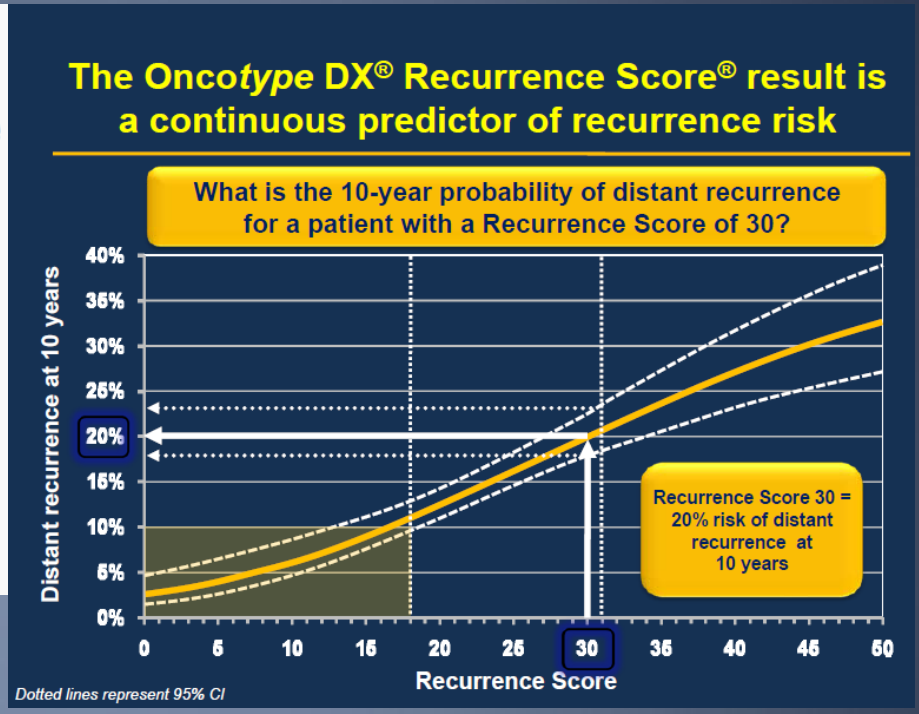
675 bloques tumorales de pacientes del brazo TAM en estudio B14
Objetivo primario: Recaída a distancia.

NEJM 2004

Oncotype: ganglios negativos



High vs Low p <0.001



Risk	%	RS	Rate of 10y DR	95% CI
Low	51	<18	6.8	4-9.6
Intermediate	22	18-31	14.3	8.3-20.3
High	27	>31	30.5	23.6-37.4

Oncotype: ganglios negativos

VOLUME 24 · NUMBER 23 · AUGUST 10 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Gene Expression and Benefit of Chemotherapy in Women With Node-Negative, Estrogen Receptor–Positive Breast Cancer

Soonmyung Paik, Gong Tang, Steven Shak, Chungyeul Kim, Joffre Baker, Wanseop Kim, Maureen Cronin, Frederick L. Baehner, Drew Watson, John Bryant, Joseph P. Costantino, Charles E. Geyer Jr, D. Lawrence Wickerham, and Norman Wolmark

651 bloques tumorales de pacientes del brazo TAM (227) y CMF-T (424) en estudio B20
Objetivo primario: Recaída a distancia.

JCO 2006

Oncotype: N-

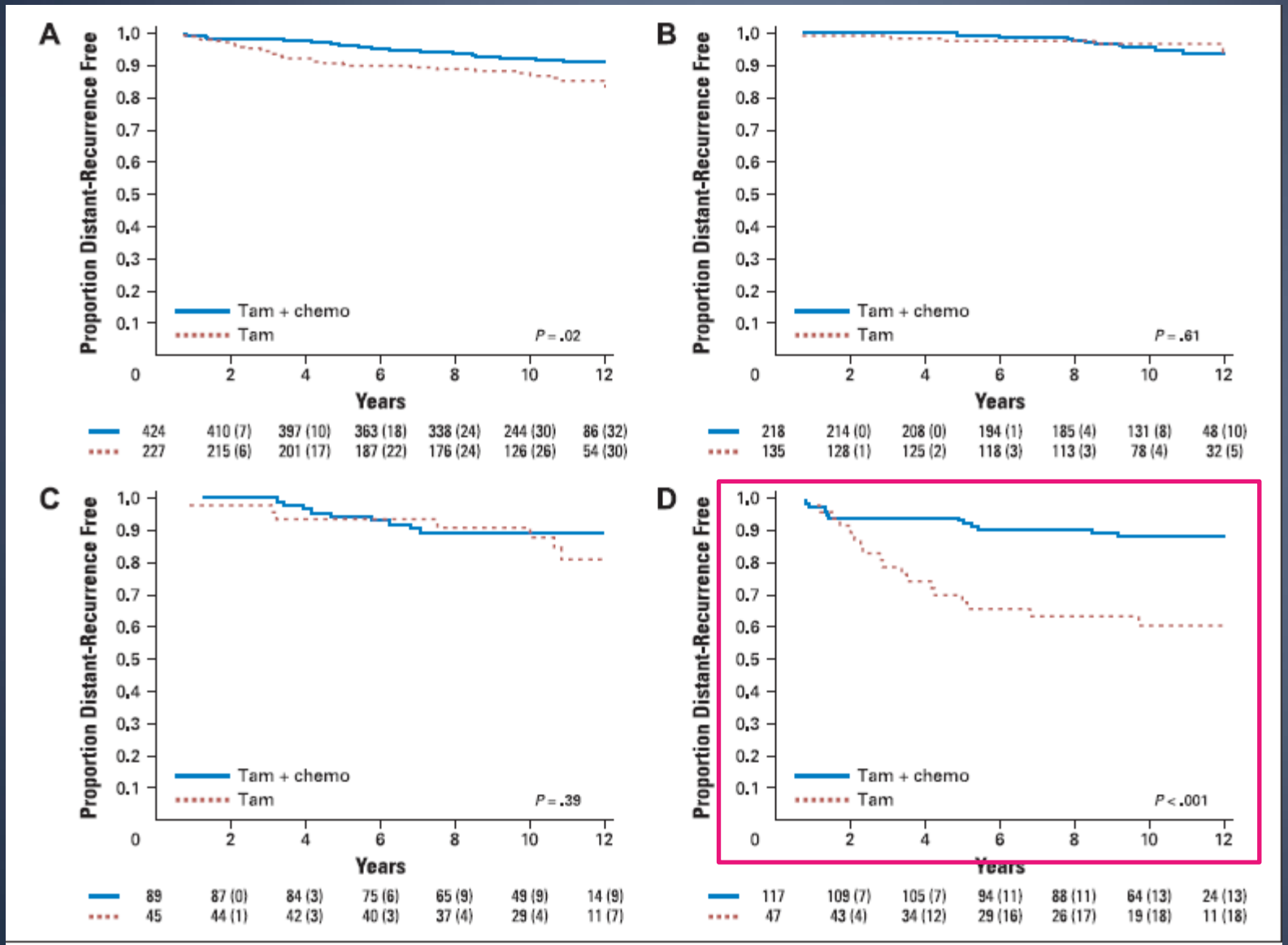


Fig 2. Kaplan-Meier plots for distant recurrence comparing treatment with tamoxifen (Tam) alone versus treatment with tamoxifen plus chemotherapy (Tam + chemo). (A) All patients; (B) low risk (recurrence score [RS] < 18); (C) intermediate risk (RS 18-30); (D) high risk (RS ≥ 31). The number of patients at risk and the number of distant recurrences (in parentheses) are provided below each part of the figure.

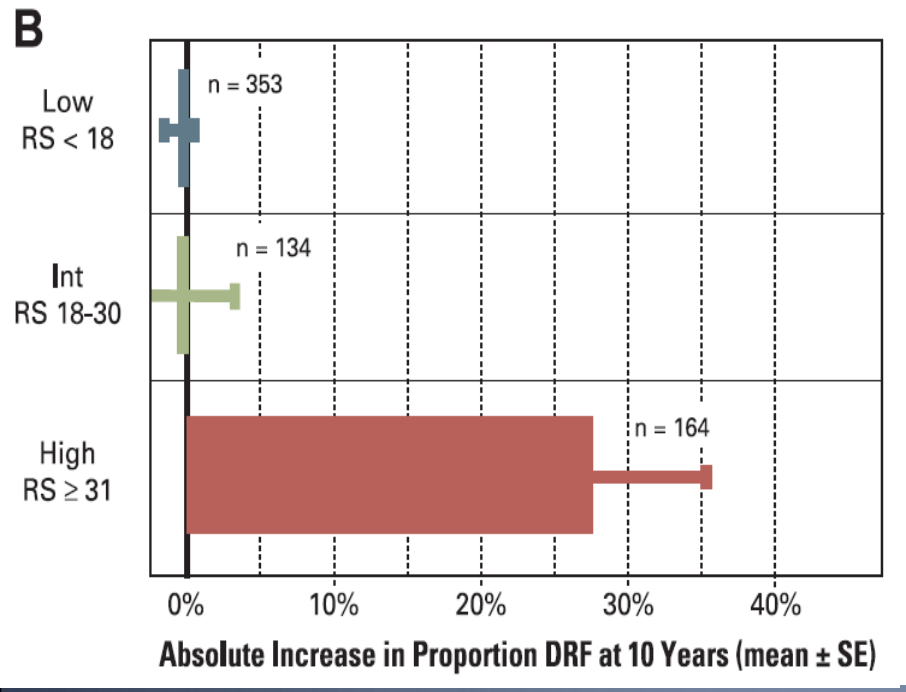
A=Todas

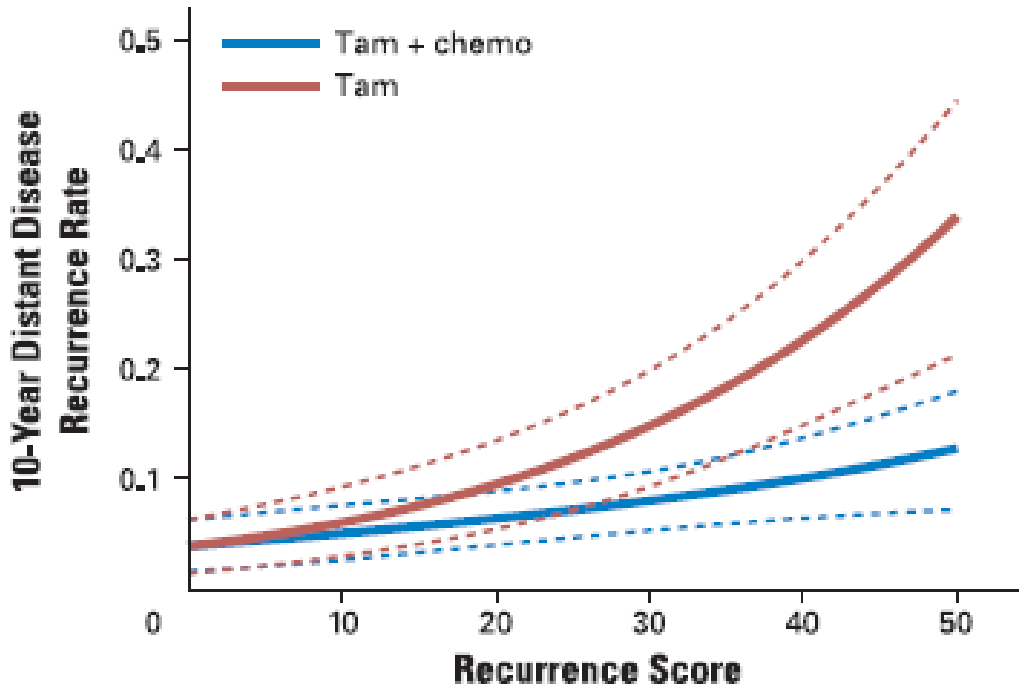
B=Low

C=Med

D=High

Oncotype: N-





Risk	%	RS	Rate of 10y DRF (TAM)	Rate of 10y DRF (CMFT)
Low	54.2	<18	96.8	95.6
Intermediate	20.6	18-31	90.9	89.1
High	25.2	>31	60.5	88.1

Recurrence Score® result can add prognostic discrimination not always provided by traditional prognostic factors

- Age
  - 44% of patients < 40 years old had low Recurrence Score results (ie, there is a large fraction of younger patients for whom chemotherapy benefit may be minimal)
- Tumor size
  - 46% of patients with large tumors (> 4 cm) had low Recurrence Score results
  - Some patients with small tumors (< 1 cm) had intermediate or high Recurrence Score results
- Tumor grade
  - Assessment by local pathologists revealed that, even for poorly differentiated tumors, 36% of patients had low Recurrence Score result
  - Approximately 20% of poorly differentiated tumors still had a low Recurrence Score result

Paik S, et al. *J Clin Oncol.* 2006;24:3726-3734.

Oncotype: N+

VOLUME 28 · NUMBER 11 · APRIL 10 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Prediction of Risk of Distant Recurrence Using the 21-Gene Recurrence Score in Node-Negative and Node-Positive Postmenopausal Patients With Breast Cancer Treated With Anastrozole or Tamoxifen: A TransATAC Study

Mitch Dowsett, Jack Cuzick, Christopher Wale, John Forbes, Elizabeth A. Mallon, Janine Salter, Emma Quinn, Anita Dunbier, Michael Baum, Aman Buzdar, Anthony Howell, Roberto Bugarini, Frederick L. Baehner, and Steven Shak

Pacientes del ensayo **ATAC** (n: 9366) Tamoxifeno vs Anastrozol vs Combinación.

-Resultados a 5 años (Howell, Lancet 2005): PFS HR 0.87 para Anastrozol.

-Resultados a 10 años (Cuzick, Lancet 2010): PFS HR 0.86 para Anastrozol.

1372 bloques tumorales: 67% T1 y 71% N0.
Objetivo primario: Recurrencia a distancia, OS.

JCO 2010

Oncotype: N+

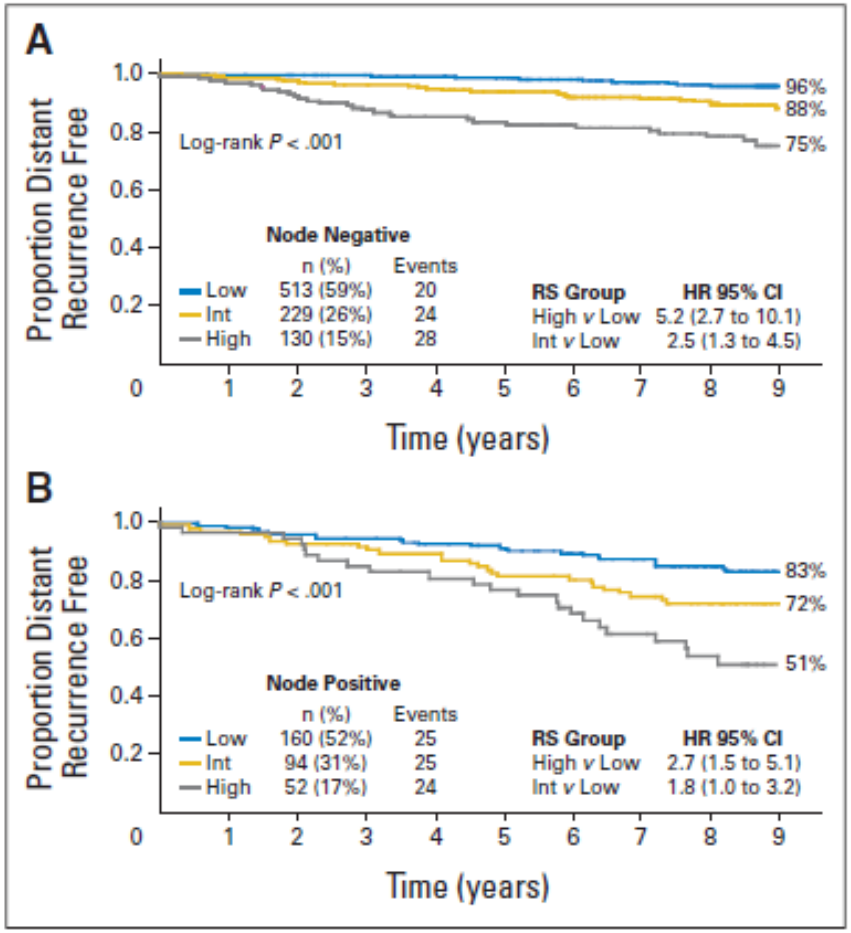


Fig 1. (A) Kaplan-Meier plots of distant recurrence by recurrence score group in node negative patients, both treatment arms (N = 872). Hazard ratios (HR) for RS group adjusted for tumor size, grade, age, and treatment. (B) Kaplan-Meier plots of distant recurrence by recurrence score group in node positive patients, both treatment arms (N = 306). HRs for RS group adjusted for tumor size, grade, age, treatment, and number of positive nodes.

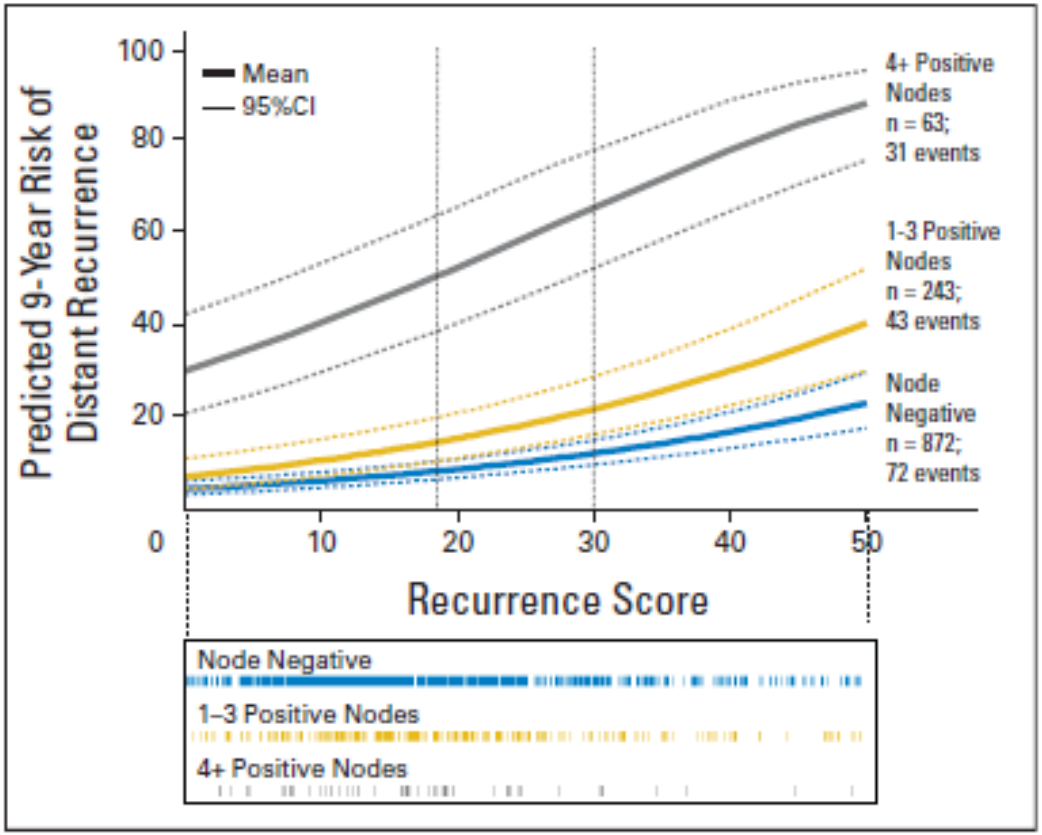
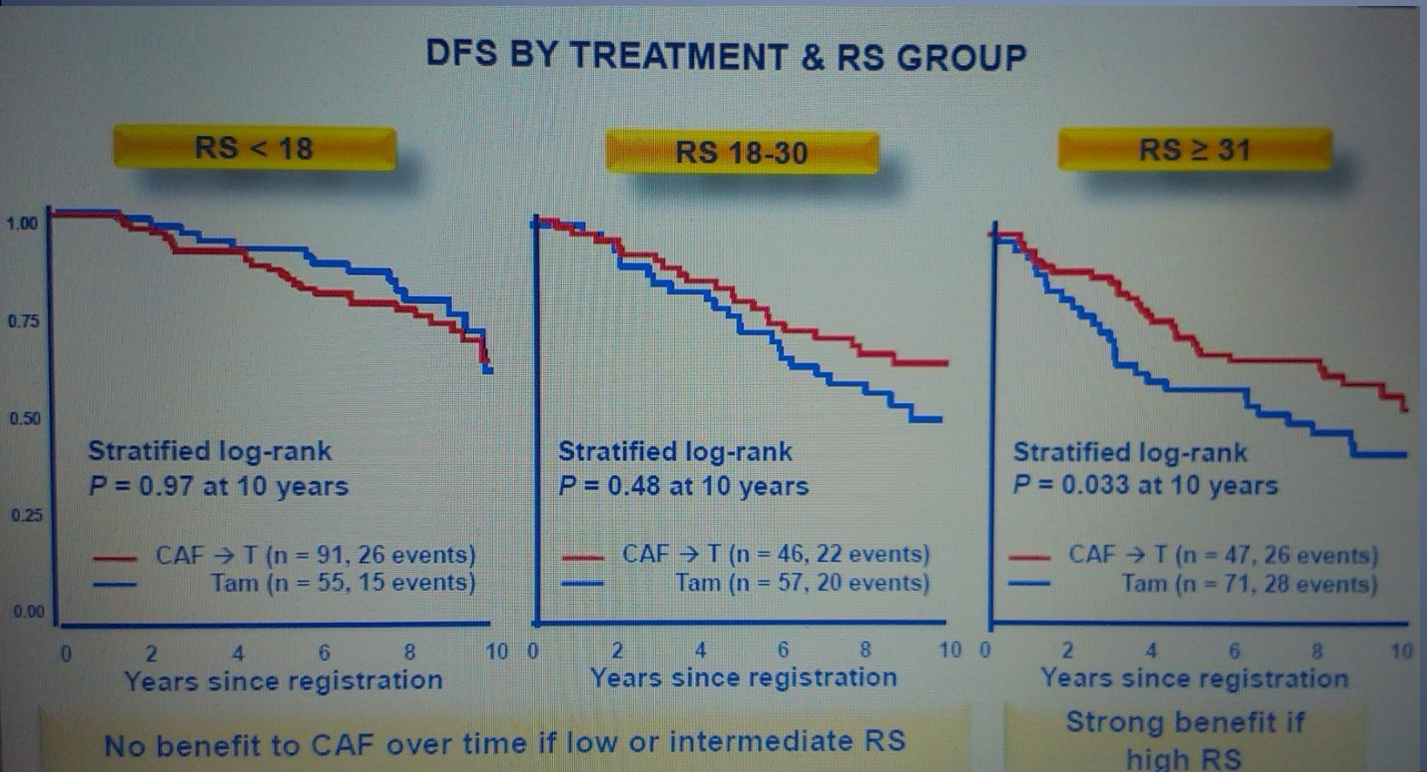


Fig 2. Predicted risk of distant recurrence and 95% CI as a continuous function of the recurrence score (RS), by number of positive nodes. Vertical lines delineate the borders between the prespecified RS groups. Rug plot shows the similarity of the distributions of RS in patients with 0, 1 to 3, and 4+ positive nodes.

Oncotype N+

Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal womenwith node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. Albain et al.

Estudio SWOG-8814 (fase 3): CAF-T vs TAM solo en N+.
367 muestras tumorales (CAF-T 219, TAM 148).
Objetivo primario: PFS según tratamiento y RS.



Score	PFS
Low	HR 1.02 p 0.97
Med	?
High	HR 0.59 p 0.03

Lancet 2009

Genomic Health | oncotype DX
Breast Recurrence Score

Genomic Health, Inc.
301 Penobscot Drive, Redwood City, CA 94063 USA
Estados Unidos/Canadá: +1.866.ONCOTYPE
Internacional: www.oncotypedx.com/contact
www.oncotypedx.com
Número CLIA 05D1018272

1

Informe de cáncer de mama: ganglios positivos

Pronóstico y beneficio de la quimioterapia (1–3 N+)

2

Paciente/Identificador: PATIENT, SAMPLE
Sexo: Female
Fecha de nacimiento: 01-Jan-1950
Nº historia clínica/paciente nº: 556677771
Fecha de obtención de la muestra: Unable to Obtain
Tipo/identificador de la muestra: Breast/C83L0ZF1N
Número de estudio: ReportStudy597

Petición: OR123456789-01
Fecha de recepción de la muestra: 05-Aug-2015
Fecha del informe: 05-Aug-2015
Cliente: Community Medical Center
Médico solicitante: Dr. Ordering
Destinatario adicional: Dr. Additional
Patólogo: Dr. Pathologist

3

Resultado Recurrence Score®

13

El test **Oncotype DX® Breast Recurrence Score** utiliza la RT-PCR para determinar la expresión de un conjunto de 21 genes en tejidos tumorales. El resultado Recurrence Score se calcula a partir de los resultados de expresión génica y varía entre 0 y 100.

Los hallazgos son aplicables a las mujeres que padecen cáncer de mama con receptores estrogénicos positivos (RE+) con 1 a 3 ganglios positivos y que serán tratadas durante 5 años con tamoxifeno (tam). Se desconoce si los hallazgos son aplicables a otras pacientes que no cumplan estos criterios.

Experiencia clínica: Los resultados presentados a continuación proceden de un estudio clínico de validación que incluyó a 367 pacientes del estudio SWOG 8814. En el estudio se incluyó a pacientes posmenopáusicas con cáncer de mama RE+ y N+, que fueron distribuidas aleatoriamente para recibir tamoxifeno solo o quimioterapia CAF seguida de tamoxifeno (CAF-T). El criterio de valoración de este estudio fue la supervivencia libre de enfermedad (tiempo transcurrido hasta la recidiva local o a distancia, hasta la aparición de un nuevo cáncer de mama primario o hasta el fallecimiento de la paciente por cualquier causa); se presenta el riesgo a los 5 años.[1]

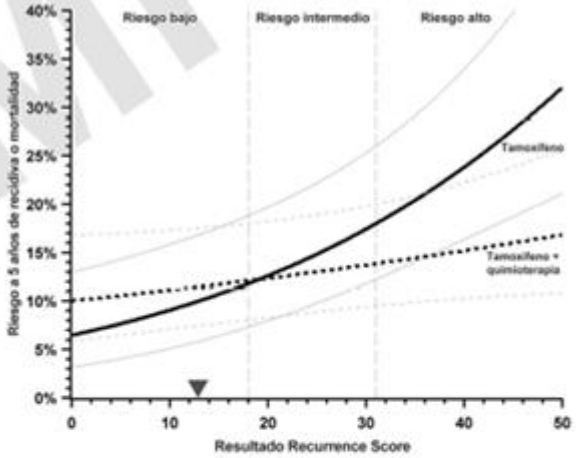
4

Pronóstico y beneficio de la quimioterapia: riesgo de recidiva o mortalidad a 5 años tras 5 años de tamoxifeno, en base al resultado Recurrence Score

1–3 ganglios positivos
Riesgo a 5 años de recidiva o mortalidad

Tamoxifeno solo
10% ——
(IC del 95%: 6%-17%)

Tamoxifeno + quimioterapia
11% - - - - - -
(IC del 95%: 7%-18%)



[1] Albain et al. Lancet Oncol. 2010.

Director del laboratorio: S. Shak, MD; J. Anderson, MD; F. Baehner, MD & P. Joseph, MD

Genomic Health, Inc. desarrolló y determinó las características de rendimiento de este test. No se requiere la aprobación o el permiso de la FDA. El laboratorio sigue la normativa CLIA y está cualificado para llevar a cabo test de alta complejidad. Test para uso clínico. No debe ser considerado como en desarrollo o para investigación.

GHI504 Rev.02B

Estudios farmacoeconómicos

Citation	Publication year	Country	Nodal status	Patients outcomes	Cost-effectiveness
Hornberger et al.	2005	USA	N0	Estimated Improved Outcomes	Cost-saving
Lyman et al.	2007	USA	N0	Estimated Improved Outcomes	Cost-saving
Cosler et al.	2009	USA	N0	Estimated Improved Outcomes	Cost-saving
Bacchi et al	2010	Brasil	N0	Estimated Improved Outcomes	Cost-saving
Klang et al.	2010	Israel	N0	Estimated Improved Outcomes	Cost-effective
O'Leary et al.	2010	Australia	N0	Estimated Improved Outcomes	Cost-effective
Tsoi et al.	2010	Canada	N0	Estimated Improved Outcomes	Cost-effective
De Lima Lopez et al.	2011	Singapore	N0	Estimated Improved Outcomes	Cost-saving
Hornberger et al.	2011	USA	N0	Estimated Improved Outcomes	Cost-saving
Lacey et al.	2011	Ireland	N0	Estimated Improved Outcomes	Cost-effective
Madaras et al.	2011	Hungary	N0	Estimated Improved Outcomes	Cost-effective
Hannouf et al.	2012	Canada	N0	Estimated Improved Outcomes	Cost-effective
Reed et al.	2012	USA	N0	Estimated Improved Outcomes	Cost-effective
Valtaire et al.	2012	France	N0	Estimated Improved Outcomes	Cost-saving
Yang et al.	2012	USA	N0	Estimated Improved Outcomes	Cost-effective
Davidson et al.	2013	Canada	N0	Estimated Improved Outcomes	Cost-effective
Paulden et al.	2013	Canada	N0	Estimated Improved Outcomes	Cost-effective
Yamauchi et al.	2014	Japan	N0	Estimated Improved Outcomes	Cost-effective
Bargallo et al.	2015	Mexico	N0	Estimated Improved Outcomes	Cost-effective
Jahn et al.	2015	Austria	N0	Estimated Improved Outcomes	Cost-effective
Katz et al.	2015	France	N0	Estimated Improved Outcomes	Cost-saving
Smyth et al	2015	Ireland	N0	Estimated Improved Outcomes	Cost-saving

Estudios farmacoeconómicos

Citation	Publication year	Country	Nodal Status	Patients outcomes	Cost-effectiveness
Kondo et al.	2010	Japan	N0 & N+	Estimated Improved Outcomes	Cost-effective
Vanderlaan et al.	2011	USA	N+	Estimated Improved Outcomes	Cost-saving
Blohmer et al.	2012	Germany	N0 & N+	Estimated Improved Outcomes	Cost-saving
Hall et al.	2012	UK	N+	Estimated Improved Outcomes	Cost-effective
Lamond et al.	2012	Canada	N0 & N+	Estimated Improved Outcomes	Cost-effective
Hannouf et al.	2013	Canada	N+	Estimated Improved Outcomes	Cost-effective
Holt et al.	2013	UK	N0 & pmic	Estimated Improved Outcomes	Cost-effective
Nerich et al.	2014	France	N0 & N+ (1 node)	Estimated Improved Outcomes	Cost-effective
Fischer et al	2015	Germany	N+	Estimated Improved Outcomes	Cost-effective
Kip M et al	2015	Netherlands	N0 & pmic	Estimated Improved Outcomes	Cost-effective

Testing in Ireland in the 18 months since reimbursement is estimated to have resulted in net savings of over €790K

Economic impact of Onco*type* DX® testing on the Irish healthcare system (Oct '11 to Feb '13)

CT

Onco*type* DX®

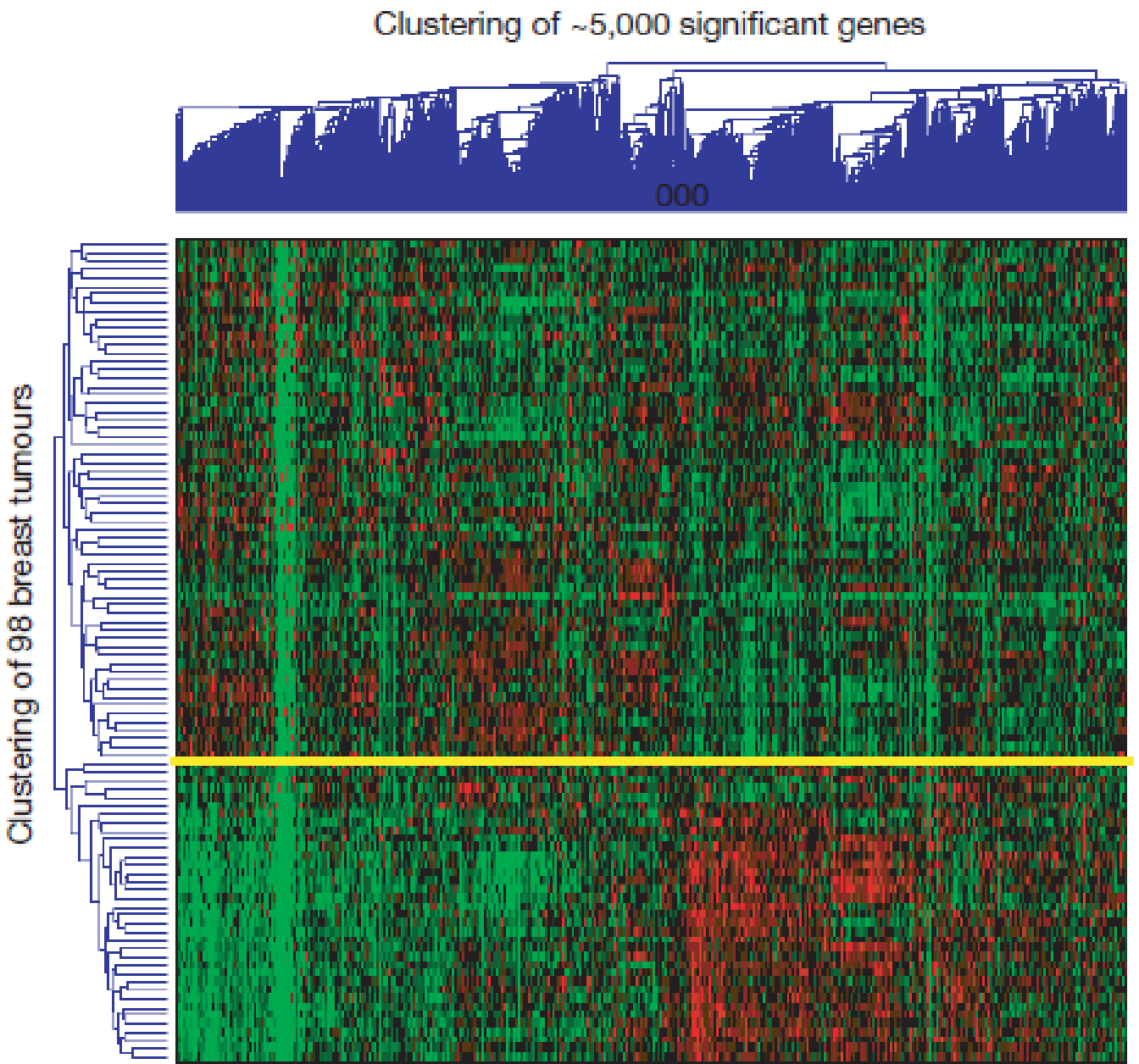
Consistent with previously reported studies, this real world evidence demonstrates that Onco*type* DX® testing results in a significant net reduction in CT use and can result in overall savings to the healthcare payer

Smyth et al, 2015

MammaPrint

Agendia
-Amsterdam

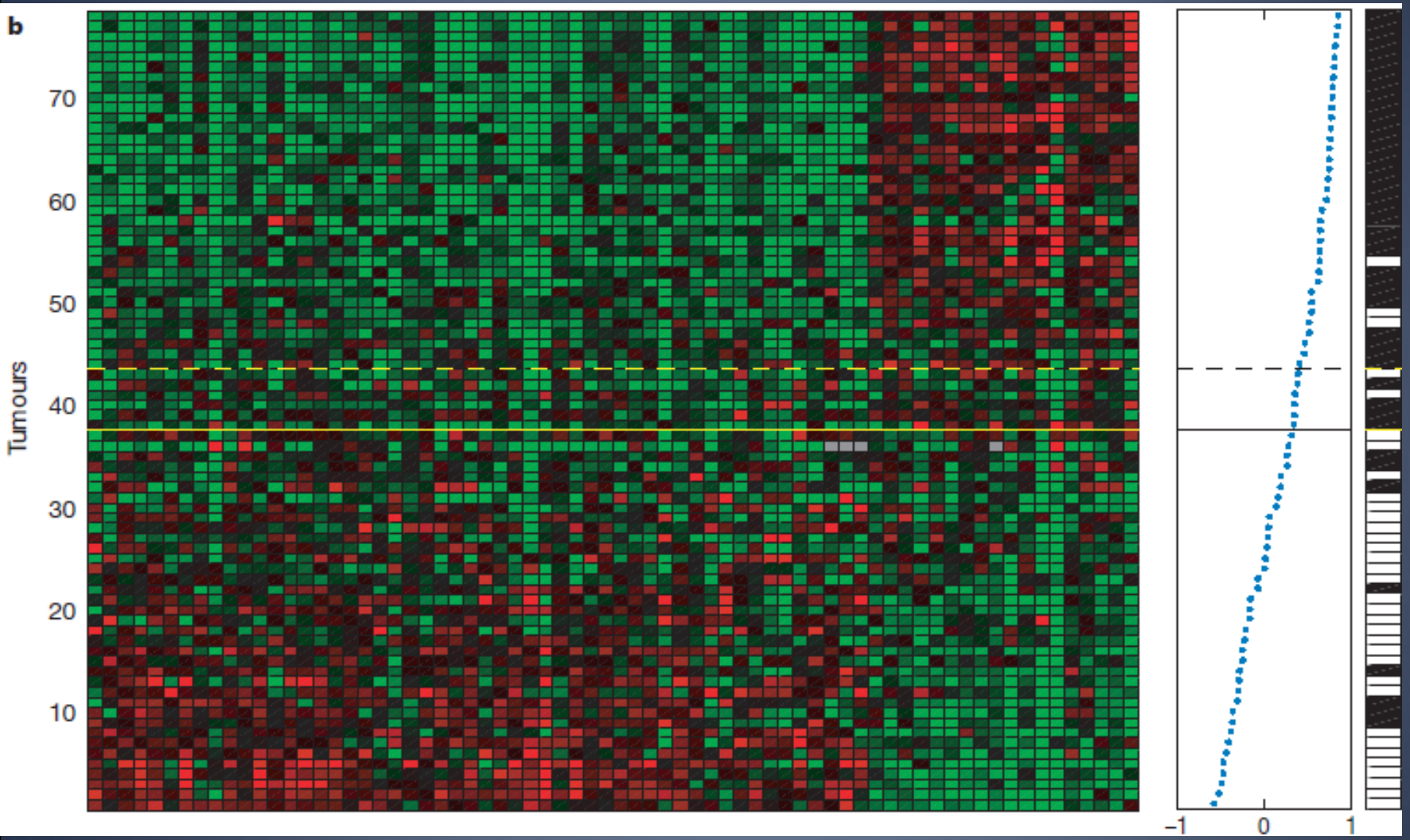
Mammaprint: Desarrollo



98 muestras.

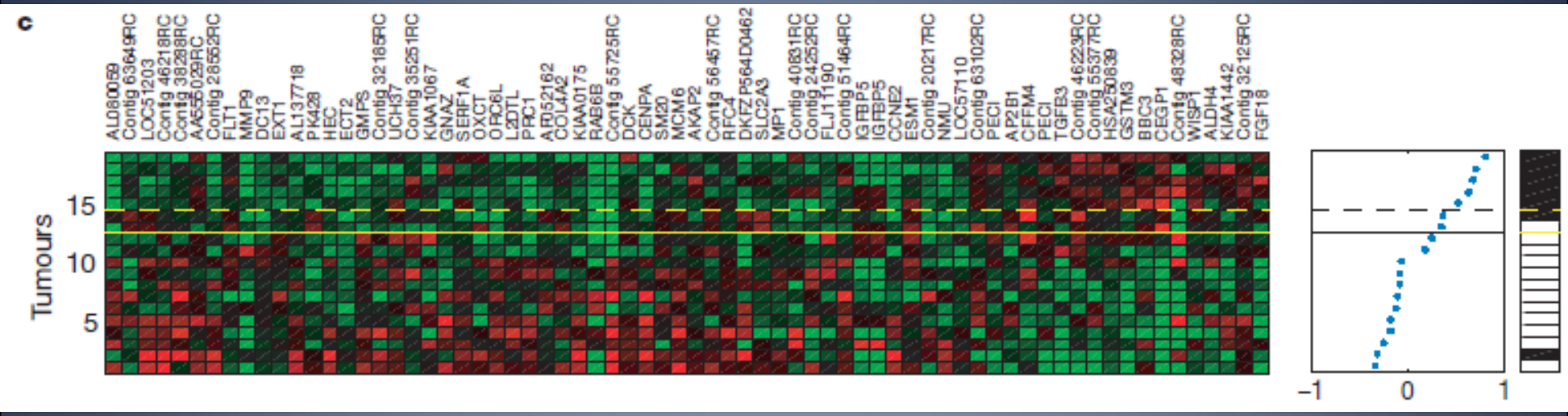
4968 genes.

Mammaprint: Desarrollo



78 pacientes N-
231 genes

Mammaprint: Desarrollo



VALIDACIÓN INICIAL

19 pacientes N-.

70 genes.

Grupos de buen y mal pronóstico según desarrollo de metástasis. (p 0.0018)

Mammaprint: Validación

The New England Journal of Medicine

VOLUME 347 DECEMBER 19, 2002 NUMBER 25

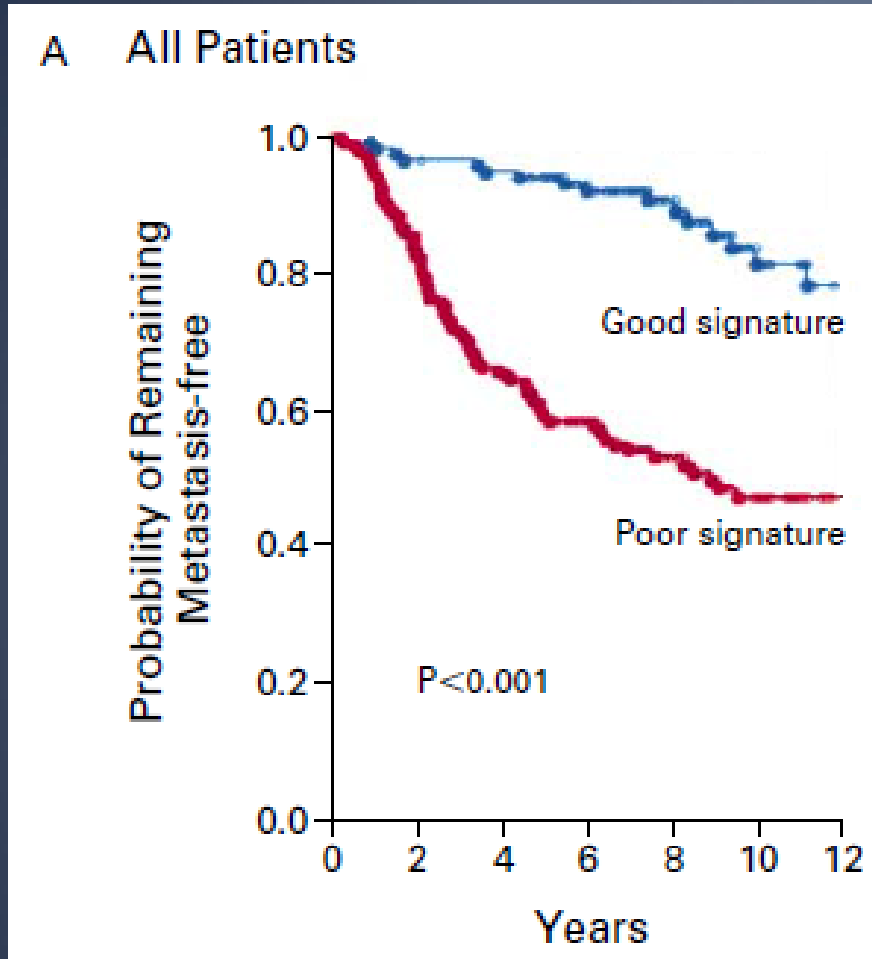
A GENE-EXPRESSION SIGNATURE AS A PREDICTOR OF SURVIVAL IN BREAST CANCER

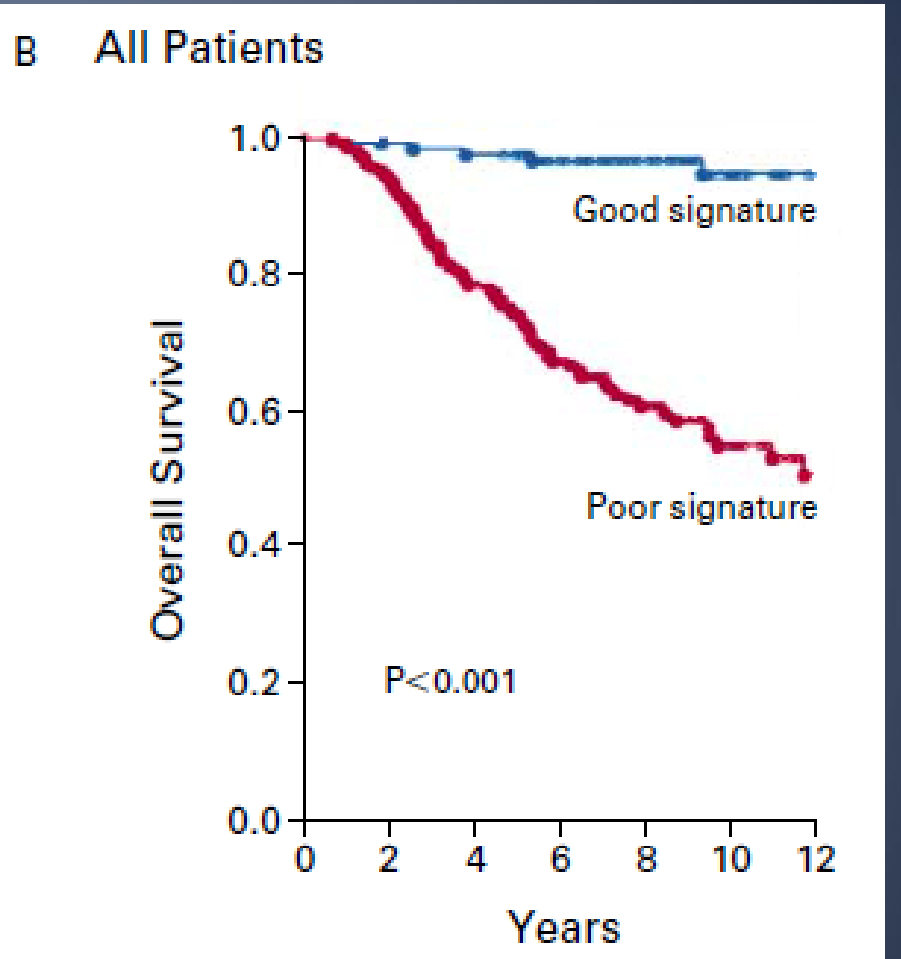
Marc J. van de Vijver, M.D., Ph.D., Yudong D. He, Ph.D., Laura J. van 't Veer, Ph.D., Hongyue Dai, Ph.D., Augustinus A.M. Hart, M.Sc., Dorien W. Voskuil, Ph.D., George J. Schreiber, M.Sc., Johannes L. Peterse, M.D., Chris Roberts, Ph.D., Matthew J. Marton, Ph.D., Mark Parrish, Douwe Atsma, Anke Witteveen, Annuska Glas, Ph.D., Leonie Delahaye, Tony van der Velde, Harry Bartelink, M.D., Ph.D., Sjoerd Rodenhuis, M.D., Ph.D., Emiel T. Rutgers, M.D., Ph.D., Stephen H. Friend, M.D., Ph.D., and René Bernards, Ph.D.

295 pacientes Ca mama banco tejidos. Edad < 53 años.
151 N- y 144 N+ (61 de las pacientes N- pertenecían al estudio previo).
Objetivo primario: Recaída a distancia.

NEJM 2002

MammaPrint: Validación





Grupo	N (N-)	DRF 10y	OS 10y
Buen pronóstico	115 (60)	94.7%	94.5%
Mal pronóstico	180 (91)	60.5%	54.6%

MammaPrint: TRANSBIG

302 muestras tumorales (T1-2 N-RE+)

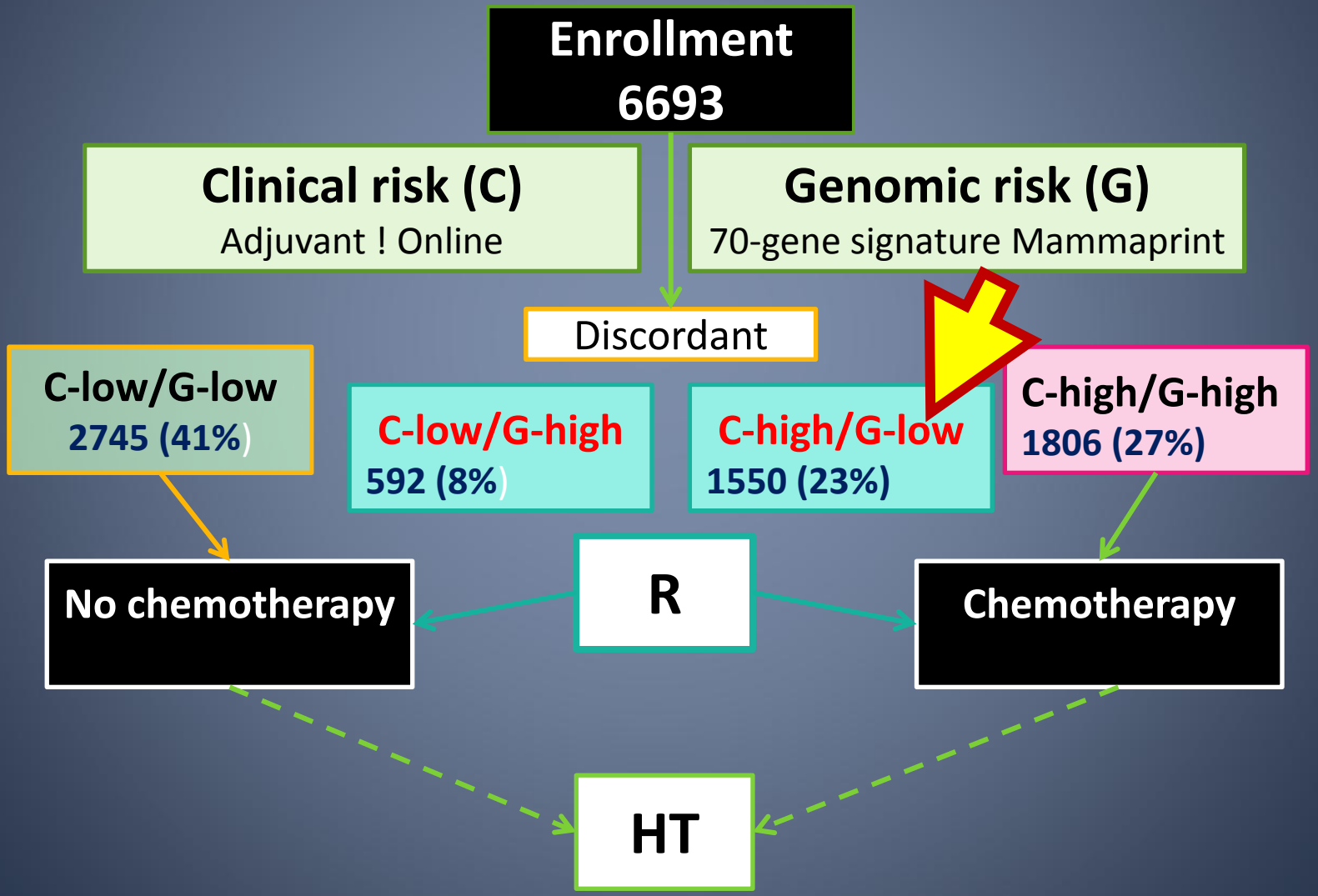
Clinical Low Risk (n 80)		Clinical High Risk (n 222)	
MP Low	MP High	MP Low	MP High
52 (65%)	28 (35%)	59 (26.5%)	163 (73.5%)

Un 35 % de las consideradas de bajo riesgo clínico fueron reclasificadas por MP como alto riesgo y un 26,5 % de las de alto riesgo clínico fueron bajo riesgo por mammaprint.

	MP High vs MP Low	P
TTR (A)	2.32 (1.35-4)	0.002
PFS (B)	1.5 (1.04-2.16)	0.032
OS (C)	2.79 (1.6-4.87)	0.001

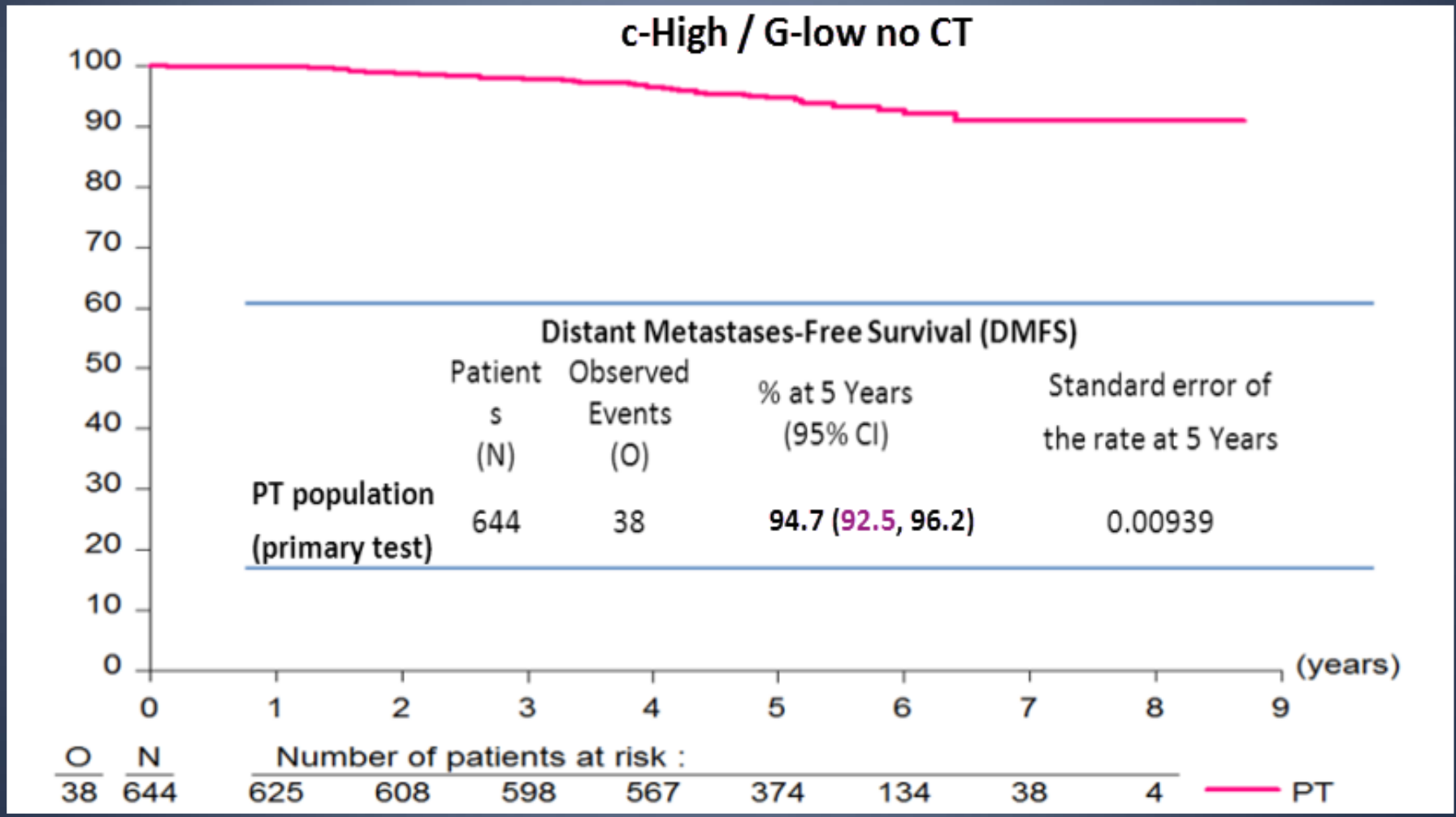
J Natl Cancer Inst 2006

MINDACT T1-3 N0-1



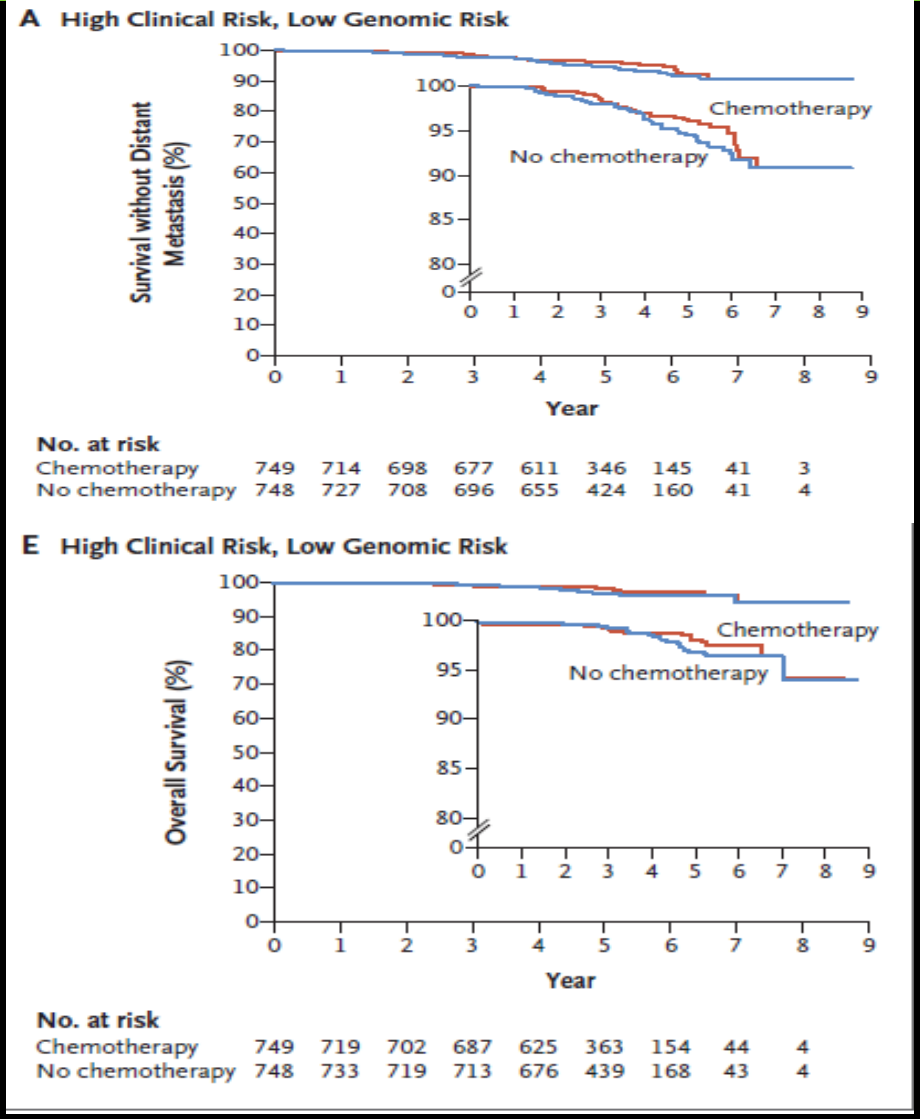
Cardoso F et al. NEJM 2016

Distant Metastasis Free Survival



Cardoso F et al. NEJM 2016

C-high / G-low	DMFS
Chemo	**95.9%** (CI, 94.0% to 97.32)
No-chemo	**94.8%** (CI, **92.3%** to 95.9%)



C-high: 3556

C-high / G-low: 1550

C-high / G-high: 1806

Chemo reduction: 46.2%

DFMS: Distant Metastases Free Survival

Cardoso F et al. NEJM 2016

Potential Cost Savings in Chemotherapy & Treatment/Prevention of Associated Adverse Events

Chemotherapy Treatment Components	Average Cost
Cost of Chemotherapy Drugs	1,002€
Cost of Administration & Monitoring	1,646€
Cost of Treatment of Adverse Events	756€
Cost of Preventing Adverse Events	3,561€
Total Cost	**6,965€**

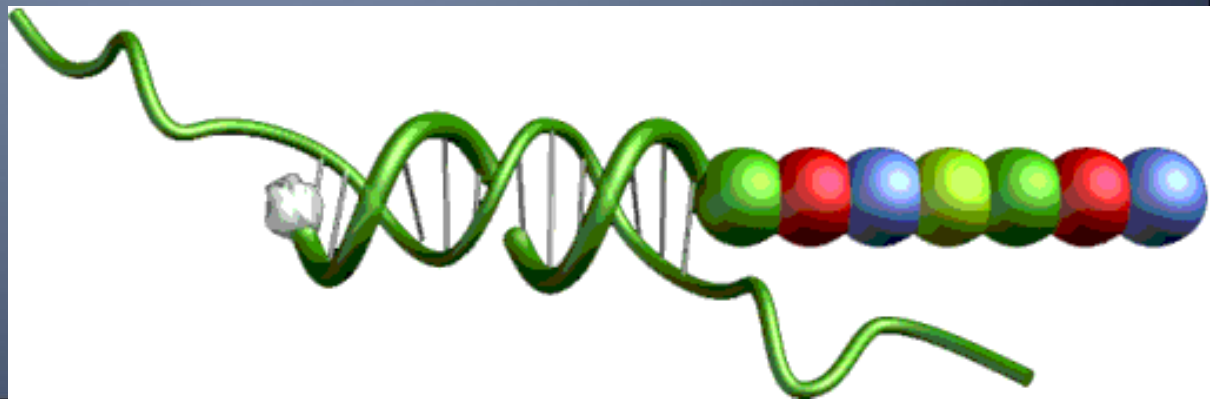
Lacey et al. (2011)."Cost utility of the 21-gene breast cancer assay in the Irish healthcare setting", 2010.

Treatment Recommended by St. Gallen	Clinical Decision-Making Protocols	MMP LOW RISK	MMP HIGH RISK	Total (N)	LOW RISK No Chemotherapy (%)	COST of Chemotherapy ALL PATIENTS	SAVINGS OF EXCLUDING Chemotherapy (LOW RISK)	COST OF SCREENING MMP	NET SAVINGS TOTAL
ET, consider CT	ER+, HER2- *(Gr II or LN 1-3 or 2-5cm)*	186	137	323	58%	2,249,695 €	1,295,490 €	864,025 €	431,465 €

The Potential Net Cost Saving of 431,465€ accounts for 20% of Chemotherapy Total Cost

PAM50

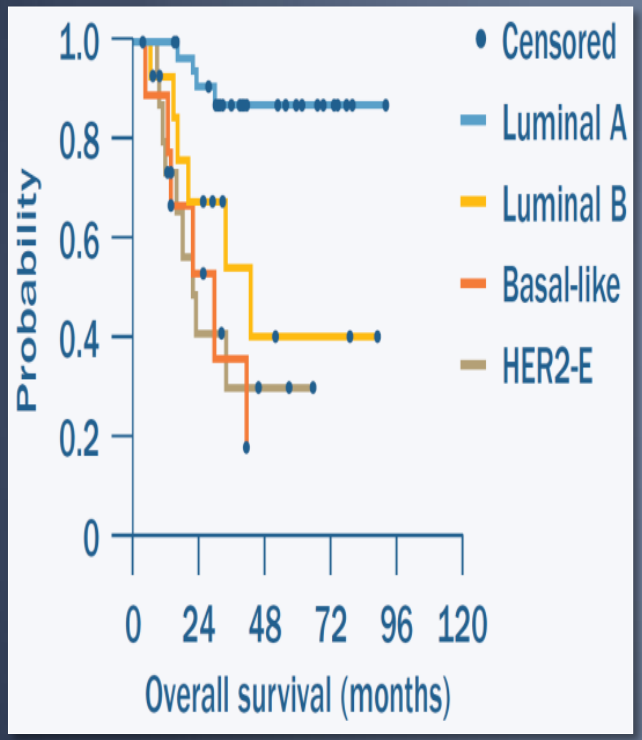
NanoString
-Seattle (USA)



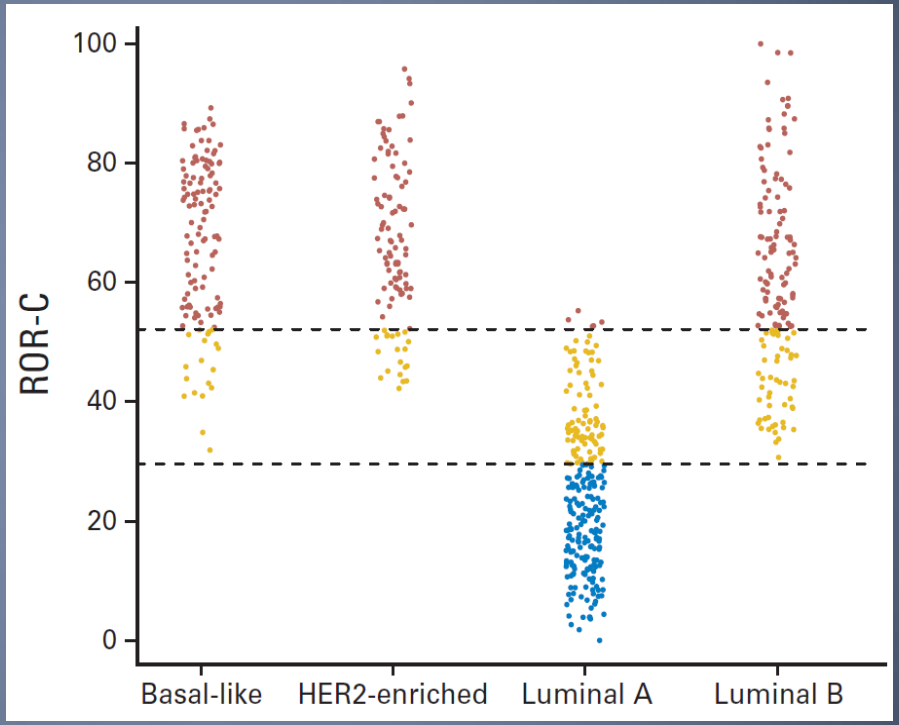
PAM50

- Formalin-fixed, paraffin- embedded tissue and RT-PCR or nanotechnology-based nCounter digital gene expression platform
- mRNA expression of 50 genes + 5 housekeeping control genes
- Categorization of tumors into the four intrinsic subtypes with prediction of outcome (lum A, lum B, HER2-enriched, and basal-like) with high classification agreement with microarray "intrinsic" subtyping
- ROR (Prosigna) for risk staratification

Plataformas Genómicas e información biológica



ROR-C (tumor size and subtype model) scores categorize intrinsic subtypes



Parker JS, et al. J Clin Oncol. 2009;27(8):1160-1167.

PAM50

VOLUME 27 · NUMBER 8 · MARCH 10 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Supervised Risk Predictor of Breast Cancer Based on Intrinsic Subtypes

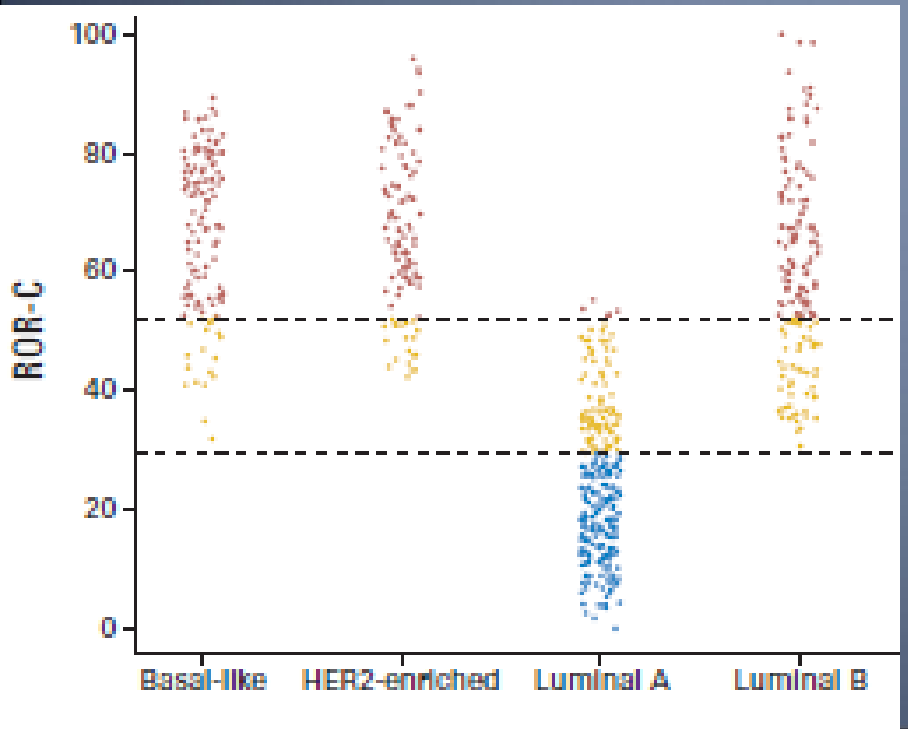
Joel S. Parker, Michael Mullins, Maggie C.U. Cheang, Samuel Leung, David Voduc, Tammi Vickery, Sherri Davies, Christiane Fauron, Xiaping He, Zhiyuan Hu, John F. Quackenbush, Inge J. Stijleman, Juan Palazzo, J.S. Marron, Andrew B. Nobel, Elaine Mardis, Torsten O. Nielsen, Matthew J. Ellis, Charles M. Perou, and Philip S. Bernard

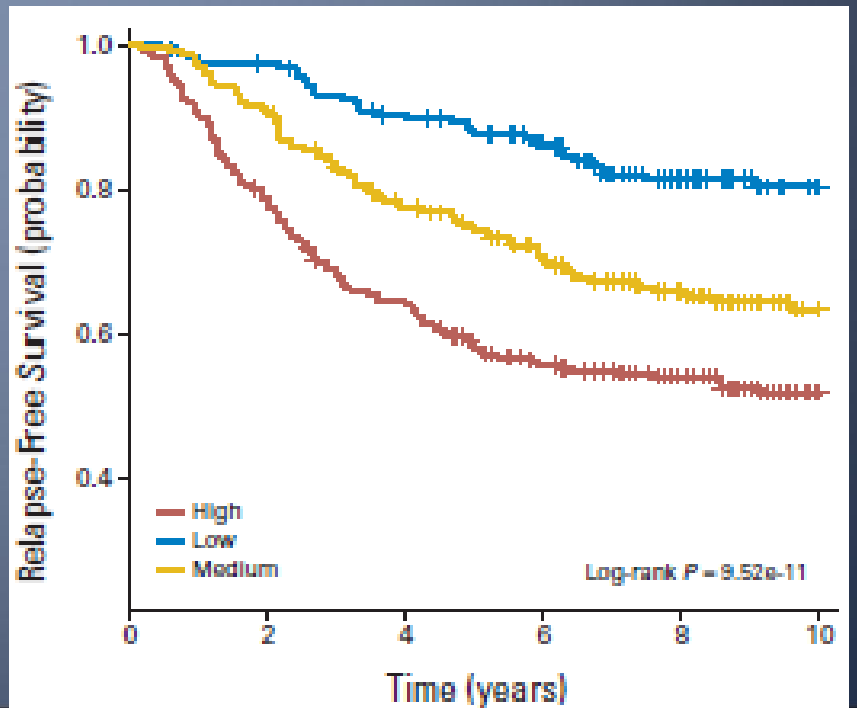
894 muestras de banco de tejidos
(761 sin QT y 133 con QT)
Tumores T1-2, N+/-, Her2+/-, RH+/-.

PAM50: ROR SCORE

ROR = 54.7 x LumB x LumA x Her2 x Basal-like x Proliferación x Tamaño tumoral

-Low, Intermediate, High según el riesgo de recaída a distancia.
-Puntos de corte en pacientes del estudio transATAC.
-Menos pacientes en grupo intermedio que Oncotype.





Prosigna (PAM 50)

- **Decisiones en quimioterapia**

  Ganglios Negativos: Identifica un grupo (50%) de bajo riesgo de recurrencia a 10 años (<4%)

  Ganglos Positivos: Identifica un grupo (50%) de bajo riesgo de recurrencia (<5%)

  Recurrencia Tardia: Predice recurrencia entre lo 5-10 años en RH +

ENDOPREDICT

EndoPredict

- It uses FFPE tissue and RT-PCR
- It measures expression of 8 genes plus 4 control:
  - 3 proliferation-associated genes (BIRC5, UBE2C, DHCR7),
  - 5 HR-associated genes (RBBP8, IL6ST, AZGP1, MGP, STC2), plus
  - 3 normalisation genes (CALM2, OAZ1 and RPL37A) and 1 DNA reference gene (HBB)
- The EP score is calculated to give a scale from 0 to 15. EP scores of <5 are designated as 'low risk' and EP scores of 5 or more as 'high risk'

EndoPredict

- The EPclin score is calculated by adding clinical data about tumour size and nodal status to the EP score
- EPclin score predicts the likelihood of 10-year distant metastasis in women with ER+ HER2- BC
- Is used to identify tumour types that will not benefit from chemotherapy
- One EndoPredict test costs £1000 if performed in a local laboratory or £1500 if it is sent to the distributor's laboratory compared to >$3,000 for Oncotype DX

VOLUME 34 · NUMBER 10 · APRIL 1, 2016

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline

Lyndsay N. Harris, Nofisat Ismaila, Lisa M. McShane, Fabrice Andre, Deborah E. Collyar, Ana M. Gonzalez-Angulo, Elizabeth H. Hammond, Nicole M. Kuderer, Minetta C. Liu, Robert G. Mennel, Catherine Van Poznak, Robert C. Bast, and Daniel F. Hayes

Patient Characteristics	Evidence Characteristics	OncotypeDX	Prosigna (PAM50 ROR)	EndoPredict	Mammaprint
ER/PgR-positive, Her2-negative, Node-negative	Type:	Evidence	Evidence	Evidence	Evidence
	Evidence Quality:	High	High	Intermediate	Intermediate
	Strength of Recommendation:	Strong	Strong	Moderate	Moderate
ER/PgR-positive, Her2-negative, Node-positive	Type:	Evidence	Evidence	Evidence	Evidence
	Evidence Quality:	Intermediate	Intermediate	Insufficient	Intermediate
	Strength of Recommendation:	Moderate	Moderate	Moderate	Moderate
Her2-positive or Triple Negative	Type:	Consensus	Consensus	Consensus	Consensus
	Evidence Quality:	Insufficient	Insufficient	Insufficient	Low/ Insufficient
	Strength of Recommendation:	Strong	Strong	Strong	Moderate/ Strong

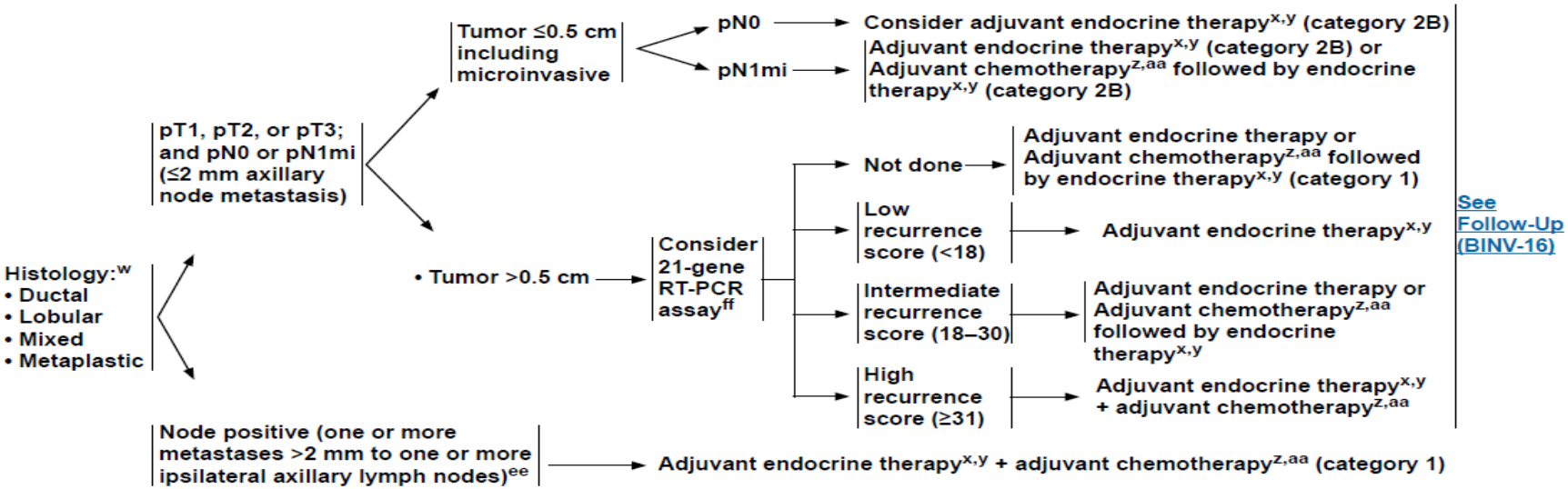
¿QUÉ RECOMIENDAN LAS GUÍAS?

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2017
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR-POSITIVE - HER2-NEGATIVE DISEASE[b]



[b] See Principles of HER2 Testing (BINV-A).

[w] Mixed lobular and ductal carcinoma, should be graded based on the ductal component and treated based on this grading. For metaplastic carcinoma, the prognostic value of the histologic grading is uncertain. However, when a specific histologic subtype of metaplastic carcinoma is present and accounts for more than 10% of the tumor, the subtype is an independent prognostic variable.

[x] Consider adjuvant bisphosphonate therapy in postmenopausal (natural or induced) patients receiving adjuvant endocrine therapy.

[y] Evidence supports that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal women with hormone receptor-positive breast cancer is similar to that achieved with CMF alone. See Adjuvant Endocrine Therapy (BINV-J).

[z] Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. Available data suggest that sequential or concurrent endocrine therapy with radiation therapy is acceptable. See Adjuvant Endocrine Therapy (BINV-J) and Preoperative/Adjuvant Therapy Regimens (BINV-K).

[aa] There are limited data to make chemotherapy recommendations for those >70 y of age. See NCCN Clinical Practice Guidelines for Older Adult Oncology.

[ee] The 21-gene RT-PCR assay recurrence score can be considered in select patients with 1–3 involved ipsilateral axillary lymph nodes to guide the addition of combination chemotherapy to standard hormone therapy. A retrospective analysis of a prospective randomized trial suggests that the test is predictive in this group similar to its performance in node-negative disease.

[ff] Other prognostic multigene assays may be considered to help assess risk of recurrence but have not been validated to predict response to chemotherapy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

¿QUÉ RECOMIENDAN LAS GUÍAS?

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2017
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR-POSITIVE - HER2-NEGATIVE DISEASE[b]

- Tumor ≤0.5 cm including microinvasive
  - pN0 → Consider adjuvant endocrine therapy[x,y] (category 2B)
  - pN1mi → Adjuvant endocrine therapy[x,y] (category 2B) or Adjuvant chemotherapy[z,aa] followed by endocrine therapy[x,y] (category 2B)
- pT1, pT2, or pT3; and pN0 or pN1mi (≤2 mm axillary node metastasis)
- Histology:[w]
  - Ductal
  - Lobular
  - Mixed
  - Metaplastic
- • Tumor >0.5 cm → Consider 21-gene RT-PCR assay[ff]
  - Not done → Adjuvant endocrine therapy or Adjuvant chemotherapy[z,aa] followed by endocrine therapy[x,y] (category 1)
  - Low recurrence score (<18) → Adjuvant endocrine therapy[x,y]
  - Intermediate recurrence score (18–30) → Adjuvant endocrine therapy or Adjuvant chemotherapy[z,aa] followed by endocrine therapy[x,y]
  - High recurrence score (≥31) → Adjuvant endocrine therapy[x,y] + adjuvant chemotherapy[z,aa]
- Node positive (one or more

See Follow-Up (BINV-16)

this group similar to its performance in node-negative disease.

[ff]Other prognostic multigene assays may be considered to help assess risk of recurrence but have not been validated to predict response to chemotherapy.

ablation in premenopausal women with hormone receptor-positive breast cancer is similar to that achieved with CMF alone. See Adjuvant Endocrine Therapy (BINV-J).

[ff]Other prognostic multigene assays may be considered to help assess risk of recurrence but have not been validated to predict response to chemotherapy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Annals of Oncology 26 (Supplement 5): v8–v30, 2015
doi:10.1093/annonc/mdv298

Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

E. Senkus[1], S. Kyriakides[2], S. Ohno[3], F. Penault-Llorca[4,5], P. Poortmans[6], E. Rutgers[7], S. Zackrisson[8] & F. Cardoso[9], on behalf of the ESMO Guidelines Committee*

[1]Department of Oncology and Radiotherapy, Medical University of Gdańsk, Gdańsk, Poland; [2]Europa Donna Cyprus, Nicosia, Cyprus; [3]Breast Oncology Center, Cancer Institute Hospital, Tokyo, Japan; [4]Department of Pathology, Centre Jean Perrin, Clermont-Ferrand; [5]EA 4677 Université d'Auvergne, Clermont-Ferrand, France; [6]Radboud University Medical Center, Nijmegen, The Netherlands; [7]Department of Surgery, Netherlands Cancer Institute, Amsterdam, The Netherlands; [8]Department of Diagnostic Radiology, Lund University, Malmö, Sweden; [9]Breast Unit, Champalimaud Clinical Center, Lisbon, Portugal

Table 6. Summary of biomarkers used in treatment decision making

Biomarker	Prognostic	Predictive	Technical validation	Clinical validation	Test and scoring recommendations	Patient selection
ER	++	+++	Yes LOE IB	Yes	IHC	Hormonal treatment
PgR	+++	+	Yes LOE IB	No	IHC	If negative, chemotherapy in some cases
HER2	++	+++	Yes LOE IB	Yes	IHC ≥ 10% cells with complete membrane staining ISH: number of HER2 gene copies ≥6 or the ratio HER2/ chromosome 17 ≥2	Anti-HER2 treatment
Ki67	++	+	No	No	IHC no final consensus on cut-off but values below 10% are considered low and above 30% are high	Chemotherapy if elevated
Intrinsic subtypes	++	++	Yes	Yes	Gene expression profile (not for IHC surrogates)	Different responses to neoadjuvant chemotherapy according to the subtype
First generation signatures (MammaPrint, Oncotype Dx)	+++	++	Yes	Validated retrospectively in prospective clinical trials, prospective clinical validation ongoing	Gene expression profile, RT-PCR	Chemotherapy if high risk or high score
Second generation signatures (Prosigna®, Endopredict®)	++	++	Yes	Validated retrospectively in prospective clinical trials	N-Counter TM technology, RT-PCR	Prognosis, chemotherapy if high risk or high score

ER, oestrogen receptor; IHC, immunohistochemistry; RT-PCR, reverse transcription polymerase chain reaction; LOE, level of evidence; PgR, progesterone receptor; ISH, *in situ* hybridisation; HER2, human epidermal growth factor 2 receptor.

PERSPECTIVAS DE FUTURO CON LAS PLATAFORMAS GENÓMICAS

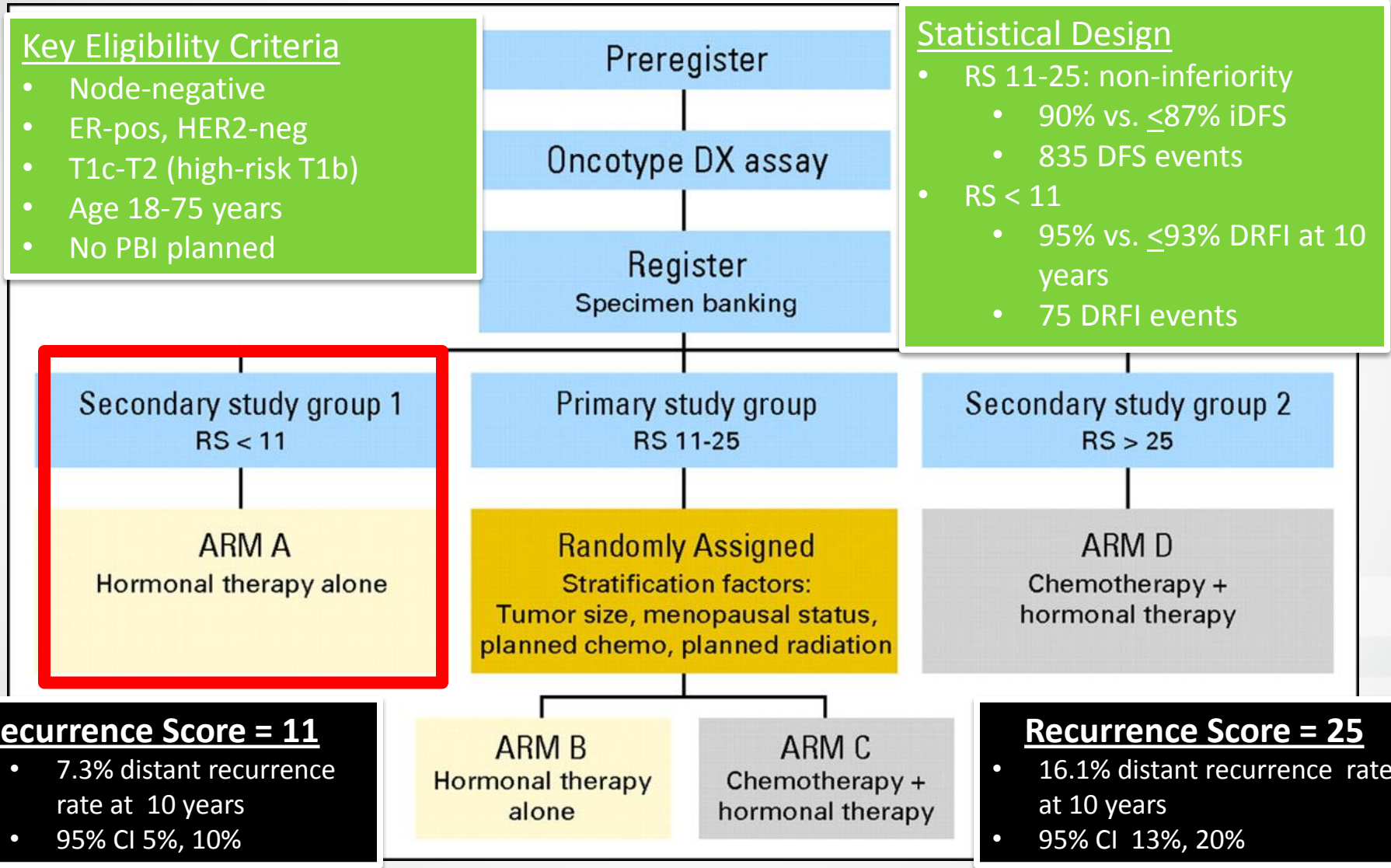
DEBEN LAS PACIENTES DE RIESGO INTERMEDIO RECIBIR QUIMIOTERAPIA?

Methods: TAILORx Design & Rationale for RS Cutpoints

Enrollment period: April 7 , 2006 to October 6 , 2010 (N=10,273 eligible)

Key Eligibility Criteria

- Node-negative
- ER-pos, HER2-neg
- T1c-T2 (high-risk T1b)
- Age 18-75 years
- No PBI planned



Statistical Design

- RS 11-25: non-inferiority
  - 90% vs. ≤87% iDFS
  - 835 DFS events
- RS < 11
  - 95% vs. ≤93% DRFI at 10 years
  - 75 DRFI events

Recurrence Score = 11

- 7.3% distant recurrence rate at 10 years
- 95% CI 5%, 10%

Recurrence Score = 25

- 16.1% distant recurrence rate at 10 years
- 95% CI 13%, 20%

Sparano J A , and Paik S JCO 2008;26:721-728

DEBEN UTILIZARSE LAS PLATAFORMAS GENÓMICAS EN PACIENTES CON AFECTACIÓN GANGLIONAR?

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

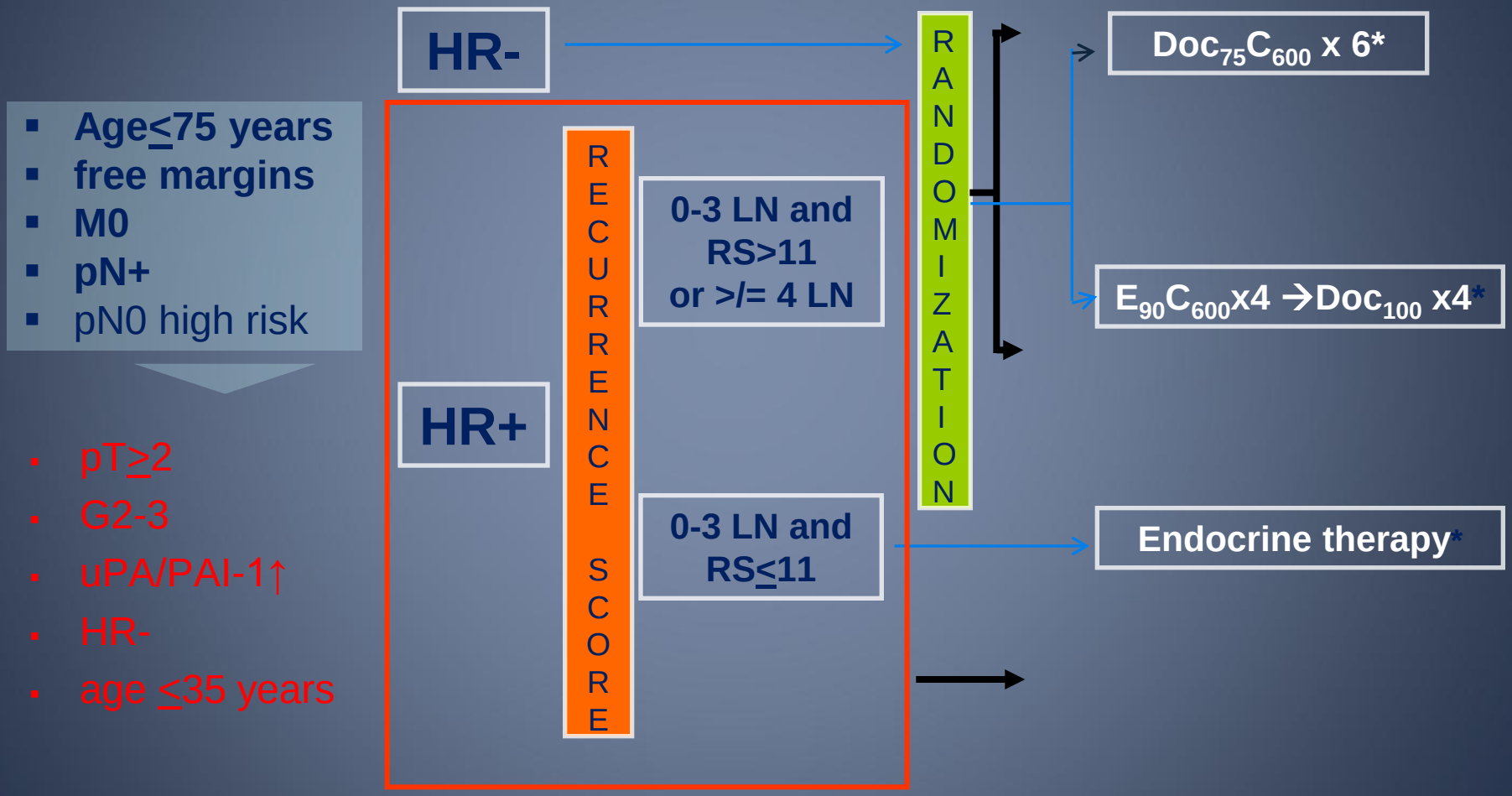
West German Study Group Phase III PlanB Trial: First Prospective Outcome Data for the 21-Gene Recurrence Score Assay and Concordance of Prognostic Markers by Central and Local Pathology Assessment

Oleg Gluz, Ulrike A. Nitz, Matthias Christgen, Ronald E. Kates, Steven Shak, Michael Clemens, Stefan Kraemer, Bahriye Aktas, Sherko Kuemmel, Toralf Reimer, Manfred Kusche, Volker Heyl, Fatemeh Lorenz-Salehi, Marianne Just, Daniel Hofmann, Tom Degenhardt, Cornelia Liedtke, Christer Svedman, Rachel Wuerstlein, Hans H. Kreipe, and Nadia Harbeck

PlanB: Design

HER2-negative primary breast cancer

WSG
WOMEN'S HEALTHCARE STUDY GROUP

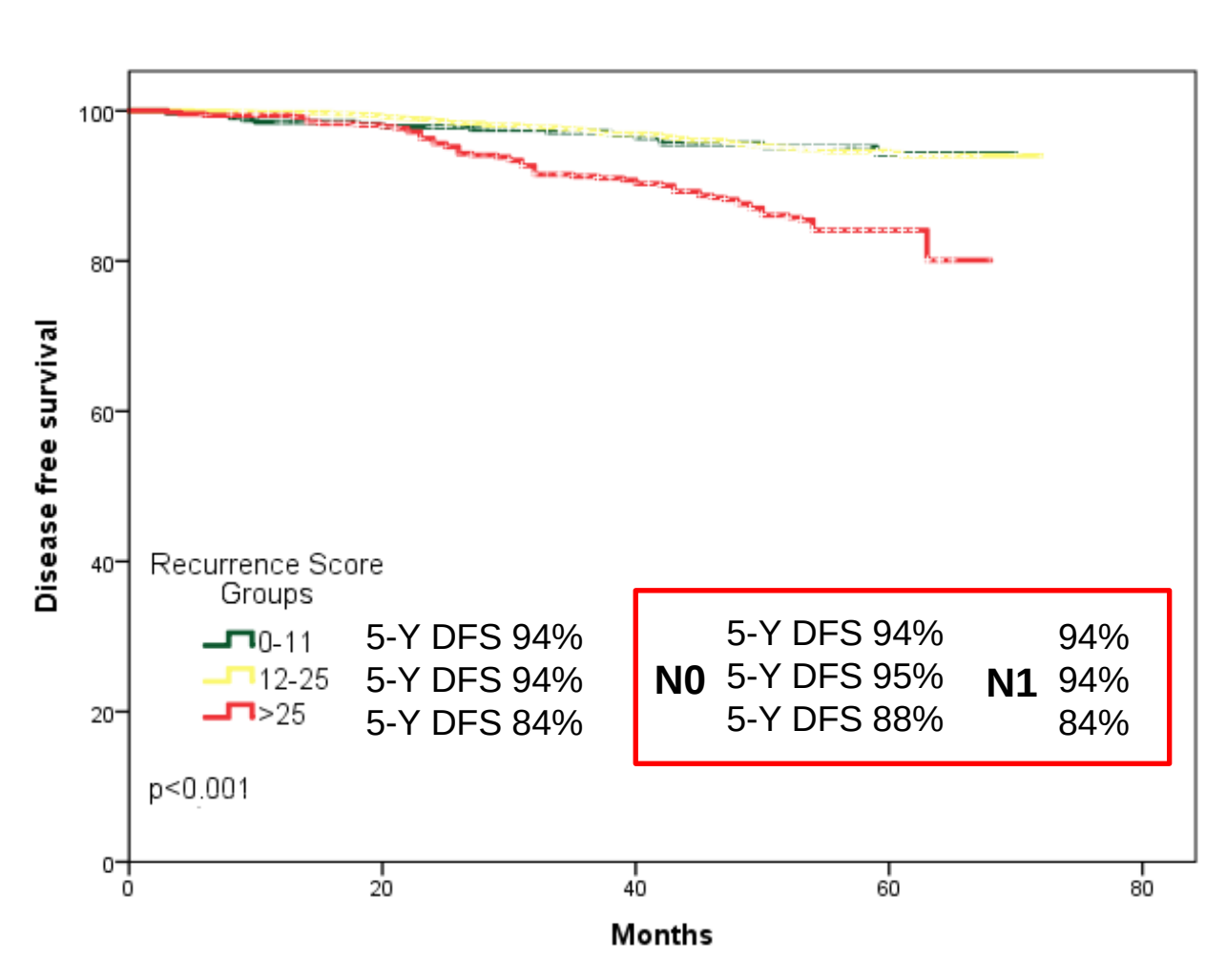


- endocrine therapy and RT according to national guidelines
- E: Epirubcin; Doc: Docetaxel; C: Cyclophosphamid

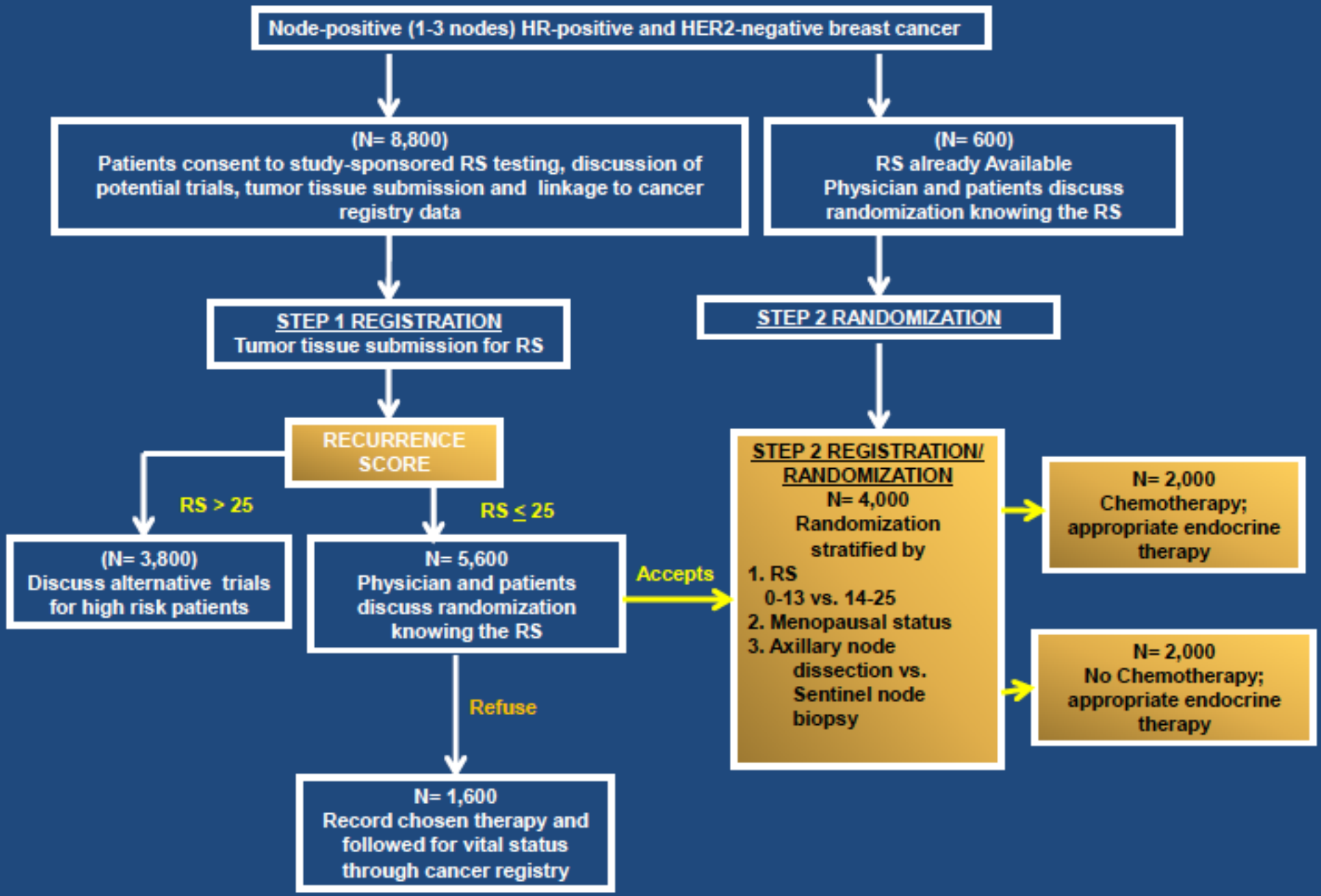
PlanB: Five-year disease-free survival in per-protocol population (n=2160)

(no chemotherapy in pN0-1 RS 0-11)

WSG
WOMEN'S HEALTHCARE STUDY GROUP



RxPONDER)S1007): Schema and Patient Flow



PERMITEN LAS PLATAFORMAS DETECTAR LAS RECAIDAS TARDÍAS?

PODEMOS SELECCIONAR QUE PACIENTES SE VAN A BENEFICIAR DE TRATAMIENTOS MÁS PROLONGADOS?

PAM 50

Imaging, Diagnosis, Prognosis

Clinical Cancer Research

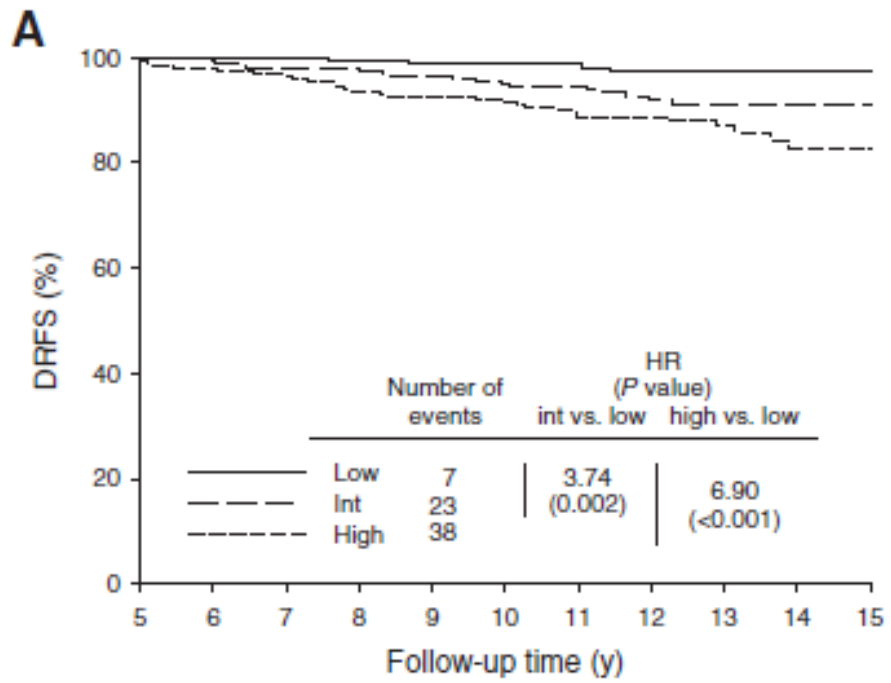
The PAM50 Risk-of-Recurrence Score Predicts Risk for Late Distant Recurrence after Endocrine Therapy in Postmenopausal Women with Endocrine-Responsive Early Breast Cancer

Martin Filipits[1], Torsten O. Nielsen[16], Margaretha Rudas[2], Richard Greil[6], Herbert Stöger[8], Raimund Jakesz[3], Zsuzsanna Bago-Horvath[2], Otto Dietze[7], Peter Regitnig[9], Christine Gruber-Rossipal[10], Elisabeth Müller-Holzner[12], Christian F. Singer[4], Brigitte Mlineritsch[6], Peter Dubsky[3], Thomas Bauernhofer[8], Michael Hubalek[12], Michael Knauer[11], Harald Trapl[13], Christian Fesl[5], Carl Schaper[14], Sean Ferree[15], Shuzhen Liu[16], J. Wayne Cowens[15], and Michael Gnant[3], for the Austrian Breast and Colorectal Cancer Study Group

ROR	Recaída 15y
Low	2.4%
Med	9.1%
High	17.5%

1246 muestras tumorales de pacientes del ABCSG-8 trial (N+/-).

TAM5y vs TAM2y + ANAS3y.



CAMBIO EN LA ESTADIFICACIÓN DEL CÁNCER DE MAMA

8ª edición del Manual de Estadiaje del American Joint Committe on Cancer

Estadio IB

- **T1, Gr 1, PR-,** N0, M0, RE+, HER2-
- **T1, Gr 3, PR+,** N0, M0, RE+, HER2-
- **T2, Gr 1-2, PR+,** N0, M0, RE+, HER2-

Estadio IIA

- **T1, Gr 3, PR-,** N0, M0, RE+, HER2-
- **T2, Gr 1, PR-,** N0, M0, RE+, HER2-
- **T2, Gr 3, PR+,** N0, M0, RE+, HER2-

Estadio IIB

- **T2, Gr 2, PR-,** N0, M0, RE+, HER2-

Estadio IIIA

- **T2, Gr 3, PR-,** N0, M0, RE+, HER2-

Estadio según la 8ª edición. Estadio pronóstico usando T, N, M, grado, RE, RP y HER2

Con un RS<11, todas estas pacientes son clasificadas como Estadio IA

Qué hacemos en nuestra comunidad?

Valoración multidisciplinar en comité de tumores de mama

Criterios para solicitud Oncotype en Aragón

SOLICITUD de ONCOTYPE para DECISIÓN TERAPÉUTICA en CÁNCER INFILTRANTE de MAMA

PACIENTE	Apellidos, Nombre: Edad: años NHC:
MÉDICO	*Dr.* Nº Colegiado: *Hospital: H.U. Miguel Servet* *e-mail: Tfno:976765500 ext 3825*

CRITERIOS CLÍNICOS (deben cumplirse todos)

- ☐ *Mujer < 70 años*
- ☐ *Cirugía completa en los dos meses previos*
- ☐ *Her2 negativo*
- ☐ *RE positivos (Allred > 4)*
- ☐ *N0 o N1(mic)*
- ☐ *Paciente susceptible de quimioterapia adyuvante*

GRUPOS PRONÓSTICOS (alguno de ellos):

- ☐ *Postmenopáusicas: T1b–T1c--T2*

o

- ☐ *Premenopáusicas: T1b*

con alguno de los siguientes signos →

- ☐ Invasión angiovascular
- ☐ Grado 3 (nuclear o histológico)
- ☐ Ki67 > 14%

- ☐ Premenopáusicas: T1c---T2

OBSERVACIONES

Nombre, fecha y firma del solicitante:	*Nombre, fecha y firma del anatomopatólogo:*

Ejemplo informe oncotype

Genomic Health® | oncotype DX® Breast Cancer Assay

Genomic Health, Inc.
301 Penobscot Drive, Redwood City, CA 94063 USA
USA/Canada: +1.866.ONCOTYPE
International: www.oncotypedx.com/contact
www.oncotypedx.com
CLIA Number 05D1018272

Breast Cancer Report - Node Negative
Prognosis

Patient/ID: 524014
Gender: Female
Date of Birth: 21-Jul-1948
Medical Record/Patient #: 524014
Date of Collection: 14-Jan-2016
Specimen Type/ID: Breast/16B0000677 A 10

Report Number: OR000745217-01
Specimen Received: 17-Feb-2016
Date Reported: 23-Feb-2016
Client: Palex Medical S.A.
Ordering Physician: Dr. Laura Garcia Claveria
Additional Recipient: Ms. Jaume Clariana

Recurrence Score® Result

11

***Oncotype DX*® Breast Cancer Assay** uses RT-PCR to determine the expression of a panel of 21 genes in tumor tissue. The Recurrence Score result is calculated from the gene expression results and ranges from 0-100.

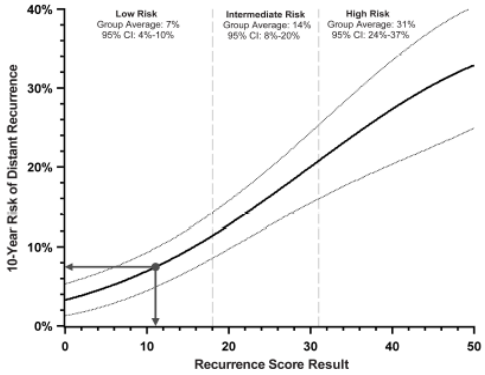
The findings are applicable to women who have stage I or II node negative (N–), estrogen receptor positive (ER+) breast cancer, and will be treated with 5 years of tamoxifen (tam). It is unknown whether the findings apply to other patients outside these criteria.

Clinical Experience: The following results are from a clinical validation study that included 668 patients from the NSABP B-14 study. The study included female patients with stage I or II, N–, ER+ breast cancer treated with 5 years of tam.[1]

Prognosis: 10-Year Risk of Distant Recurrence after 5 Years of Tam, Based on the Recurrence Score Result (from NSABP B-14)

10-Year Risk of Distant Recurrence

Tam Alone
7%
(95% CI: 5%-10%)



[1] Paik et al. N Engl J Med. 2004.

Laboratory Director(s): Patrick Joseph, MD

This test was developed and its performance characteristics determined by Genomic Health, Inc. The laboratory is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing. This test is used for clinical purposes. It should not be regarded as investigational or for research. These results are adjunctive to the ordering physician's workup.

GHI004 Rev027

Genomic Health® | oncotype DX® Breast Cancer Assay

Genomic Health, Inc.
301 Penobscot Drive, Redwood City, CA 94063 USA
USA/Canada: +1.866.ONCOTYPE
International: www.oncotypedx.com/contact
www.oncotypedx.com
CLIA Number 05D1018272

Breast Cancer Report - Node Negative
Prediction of Chemotherapy Benefit

Patient/ID: 524014
Gender: Female
Date of Birth: 21-Jul-1948

Report Number: OR000745217-01
Specimen Received: 17-Feb-2016
Date Reported: 23-Feb-2016

Recurrence Score® Result

11

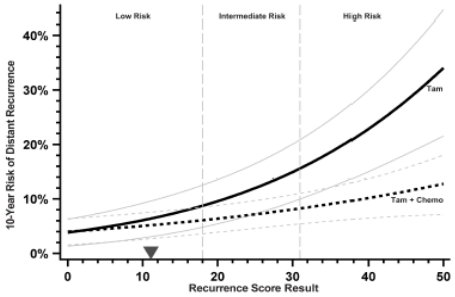
The findings are applicable to women who have stage I or II node negative (N–), estrogen receptor positive (ER+) breast cancer and will be treated with 5 years of tamoxifen (tam). It is unknown whether the findings apply to other patients outside these criteria.

Clinical Experience: The following results are from a clinical validation study that included 651 patients from the NSABP B-20 study. The study included female patients with stage I or II, N–, ER+ breast cancer. Patients were randomized to either tam alone or tam plus CMF or MF chemotherapy. For patients in the pre-specified group with Recurrence Score results ≥ 31, the group average 10-year risks (95% CI) of distant recurrence were 40% (25%, 54%) for tam alone and 12% (6%, 18%) for tam + CMF/MF.[1]

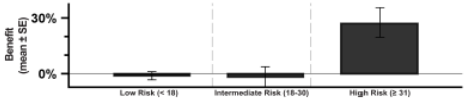
Prediction of Chemotherapy Benefit after 5 Years of Tam, Based on the Recurrence Score Result (from NSABP B-20)

Tam Alone ——

Tam + Chemo - - - - - -



Absolute Benefit of Chemotherapy at 10 Years by Recurrence Score Risk Group



[1] Paik et al. J Clin Oncol. 2006.

Laboratory Director(s): Patrick Joseph, MD

This test was developed and its performance characteristics determined by Genomic Health, Inc. The laboratory is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing. This test is used for clinical purposes. It should not be regarded as investigational or for research. These results are adjunctive to the ordering physician's workup.

GHI004 Rev027

NUESTRA EXPERIENCIA (JUNIO 2015-MARZO 2017)

- 512 pacientes intervenidas de carcinoma de mama (HUMS + HNSG)
- Se realizó Oncotype dx en 92 pacientes (17.9 %)

CARACTERÍSTICAS DE LAS PACIENTES	
EDAD	56 años
ESTADO HORMONAL	40.2 % premenopausicas
SUBTIPO TUMORAL	77.1 % carcinoma ductal infiltrante
TUMOR	77.1 % < 2 cm
AFECTACIÓN GANGLIONAR	83.6 % N0, 16.4 % N1mic
KI-67	52.2 % > 30 %

NUESTRA EXPERIENCIA (JUNIO 2015-MARZO 2017)

CLASIFICACIÓN DE RIESGO ONCOTYPE	NÚMERO DE PACIENTES	PORCENTAJE
BAJO (<18)	**47**	**51.1%**
INTERMEDIO (18-31)	**35**	**38 %**
ALTO (>31)	**10**	**10.9 %**

NUESTRA EXPERIENCIA (JUNIO 2015-MARZO 2017)

TRATAMIENTO	ESTIMACIÓN PREVIA A ONCOTYPE	TRAS ONCOTYPE
HORMONOTERAPIA	**36 (39.1 %)**	**55 (59.8 %)**
QUIMIOTERAPIA SEGUIDO DE HORMONOTERAPIA	**56 (60.9 %)**	**37 (40.2 %)**

En un total de 50 pacientes (54.35 %) existió cambio en el plan de tratamiento tras la realización de Oncotype
En 35 pacientes (38 %) se cambió de quimioterapia a hormonoterapia
En 15 pacientes (16.3 %) recibieron QT cuando inicialmente se había planteado tratamiento con Hormonoterapia

GRACIAS