Peut on prédire l'avenir avec les « outils de biologie moléculaire » pour poser les bonnes indications des traitements systémiques ?

Pr.Mario Campone
Institut de Cancérologie de l'ouest
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INTRODUCTION

le cancer du sein est une maladie hétérogène

Principe du traitement adjuvant : Eradication des micro-métastases circulantes

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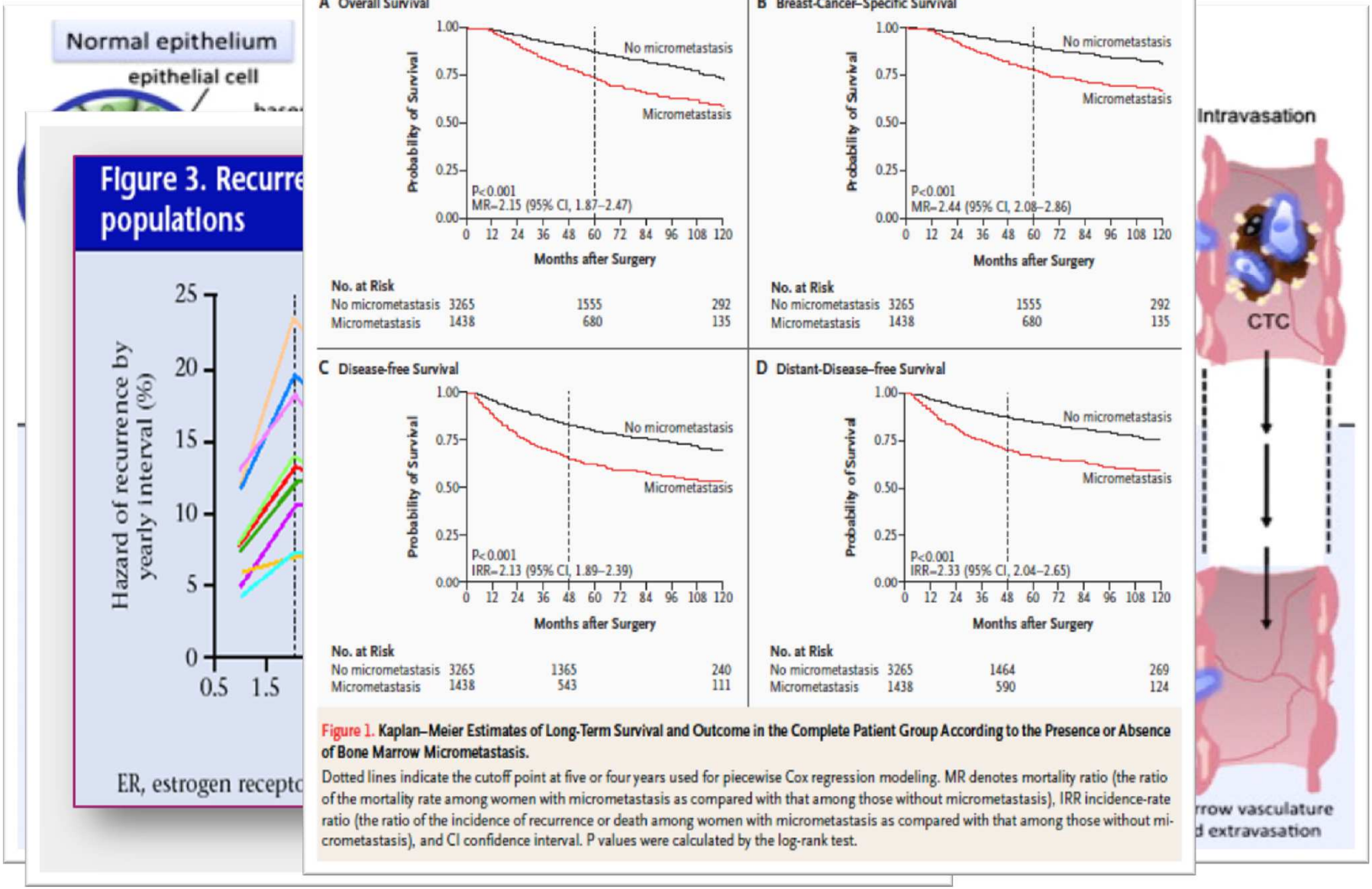

Figure 1. Kaplan–Meier Estimates of Long-Term Survival and Outcome in the Complete Patient Group According to the Presence or Absence of Bone Marrow Micrometastasis.

Dotted lines indicate the cutoff point at five or four years used for piecewise Cox regression modeling. MR denotes mortality ratio (the ratio of the mortality rate among women with micrometastasis as compared with that among those without micrometastasis), IRR incidence-rate ratio (the ratio of the incidence of recurrence or death among women with micrometastasis as compared with that among those without micrometastasis), and CI confidence interval. P values were calculated by the log-rank test.

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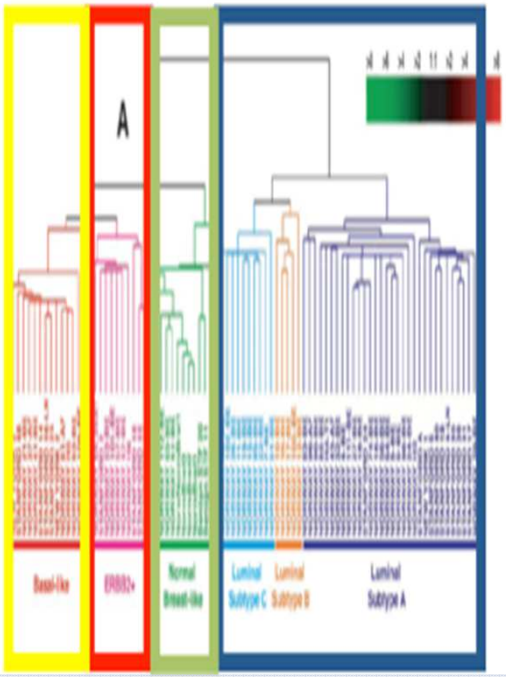
Phénotypique

- pTN
- Grade : I, II, II
- Expression RH + (70%)
- Expression HER2 (15%)
- Pas d'expression de RH et HER2 (15 à 20%)
- UPA/PA1

Moléculaire

Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications

Therese Sørlie[a,b,c], Charles M. Perou[a,d], Robert Tibshirani[e], Turid Aas[f], Stephanie Geisler[f], Hilde Johnsen[b], Trevor Hastie[e], Michael B. Eisen[h], Matt van de Rijn[i], Stefanie S. Jeffrey[k], Thor Thorsen[a], Hanne Quist[f], John C. Matese[c], Patrick O. Brown[m], David Botstein[i], Per Eystein Lønning[f], and Anne-Lise Børresen-Dale[a,n]



Fonctionnelle

A pathway-based classification of human breast cancer

Michael L. Gatza[a], Joseph E. Lucas[a,b], William T. Barry[a,c], Jong Wook Kim[a,d], Quanli Wang[a,b], Matthew D. Crawford[a], Michael B. Datto[e], Michael Kelley[f], Bernard Mathey-Prevot[a,g], Anil Potti[a,f], and Joseph R. Nevins[a,d,1]

[a]Duke Institute for Genome Sciences and Policy, [b]Department of Statistical Science, [c]Department of Biostatistics and Bioinformatics, [d]Department of Molecular Genetics and Microbiology, [e]Department of Pathology, [f]Department of Medicine, and [g]Department of Pediatrics, Duke University Medical Center, Durham, NC 27710

Edited by Joan S. Brugge, Harvard Medical School, Boston, MA, and approved March 2, 2010 (received for review November 5, 2009)

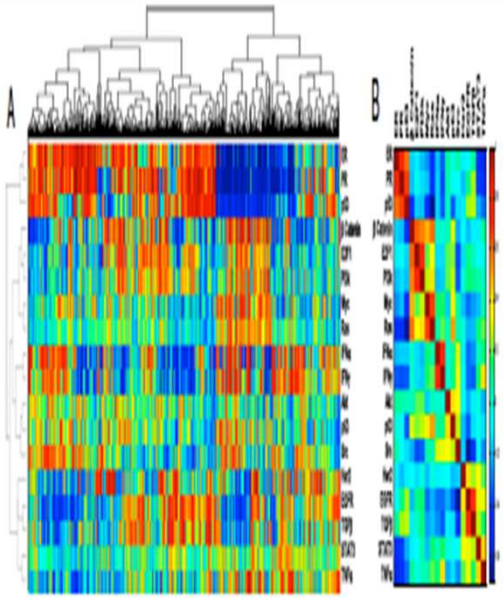


Fig. 2. Patterns of pathway activity that characterize breast cancer. (A) Heat map depicting the two-way hierarchical clustering of the predicted probability of 1,143 breast tumor samples and 18 pathways. Low (blue) and high (red) pathway activity and predicted probabilities are shown. (B) Heat map depicting the correlation coefficient of pathway coregulation (red indicates a positive correlation; blue, a negative correlation).

PHÉNOTYPE : PR NEGATIF

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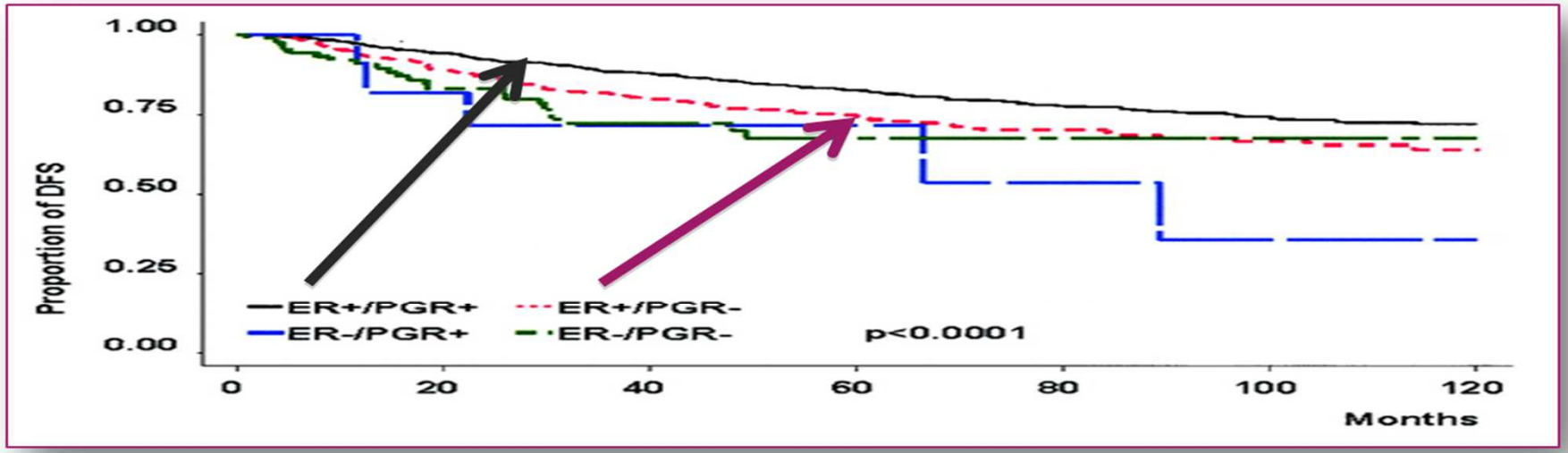
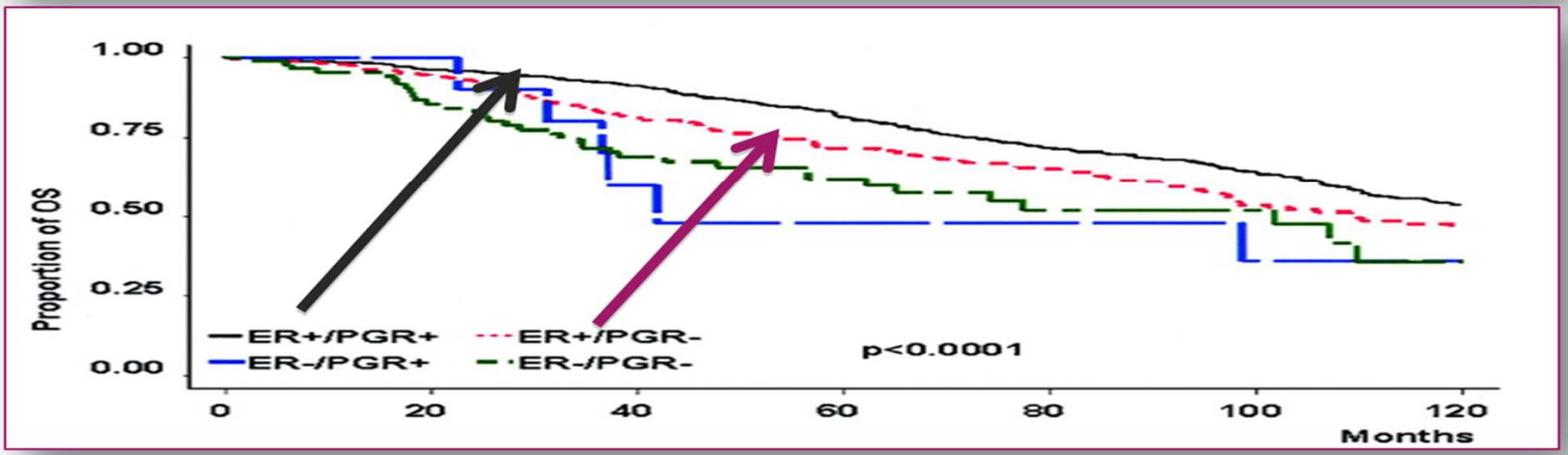
Progesterone Receptor Status Significantly Improves Outcome Prediction Over Estrogen Receptor Status Alone for Adjuvant Endocrine Therapy in Two Large Breast Cancer Databases

By Valerie-Jeanne Bardou, Grazia Arpino, Richard M. Elledge, C. Kent Osborne, and Gary M. Clark





Bardou, V.-J. et al. J Clin Oncol; 21:1973-1979 2003

JOURNAL OF CLINICAL ONCOLOGY

It Is Not Time to Stop Progesterone Receptor Testing in Breast Cancer

R. Colomer, M. Beltran, and J. Dorcas
Institut Catala d'Oncologia, Girona, Spain

H. Cortes-Funes, J. Hornedo, V. Valentin, C. Vargas, C. Mendiola, and E. Ciruelos
Hospital Universitario 12 de Octubre, Madrid, Spain.

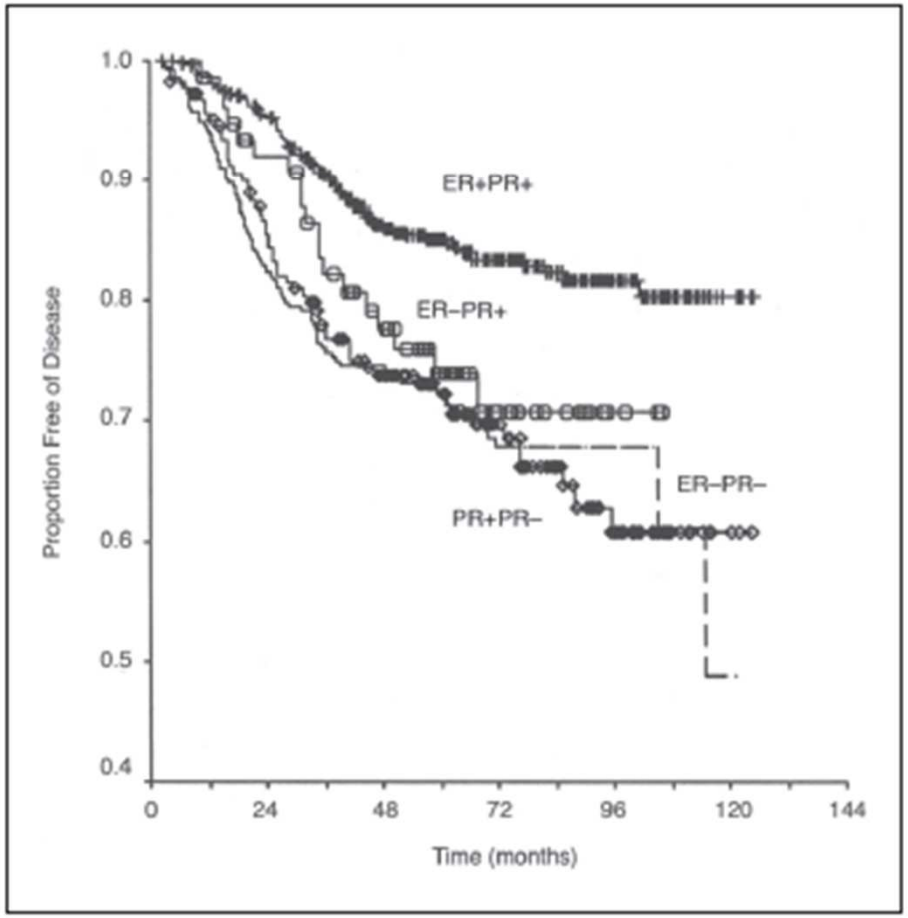


Fig 1. Disease-free survival curves by hormone receptor subgroups (N = 1,039). ER, estrogen receptor; PR, progesterone receptor.

Prompted by their observations, we have analyzed the combined ER and PR values in a series of 1,228 consecutive patients from the Hospital 12 de Octubre in Madrid, Spain, treated during the period from 1992 to 1998. In this series, follow-up is available, which allows a true predictive evaluation of the hormone receptor status. Stage distribution was the following: stage I, 268 (21.9%); stage II, 693 (56.5%); stage III, 145 (11.8%); and stage IV, 120 (9.8%). Hormone receptors were determined using monoclonal antibody-based commercial immunoassay (Abbott Laboratories, Abbott Park, IL). Both receptors were known in 1,153 cases. Median follow-up in the series was 5.8 years. In the nonmetastatic patients, the proportion of cases treated with adjuvant tamoxifen was 69%, and this was more frequent in ER+ and/or PR+ than in ER− and PR− cases (84% ER+/PR+, 75% ER−/PR+, 83% ER+/PR−, and 31% ER−/PR−). During the follow-up, 306 patients have died, and 255 nonmetastatic patients have relapsed. Our hormone receptor subgroup results contrast markedly with those reported by Olivotto et al; in our series, we have found that the number of ER−/PR+ patients is not insignificant (7%, 82 cases). The number of patients ER+/PR+ was 534 (46%); ER+/PR− was 215 (19%); and ER−/PR− was 322 (28%).

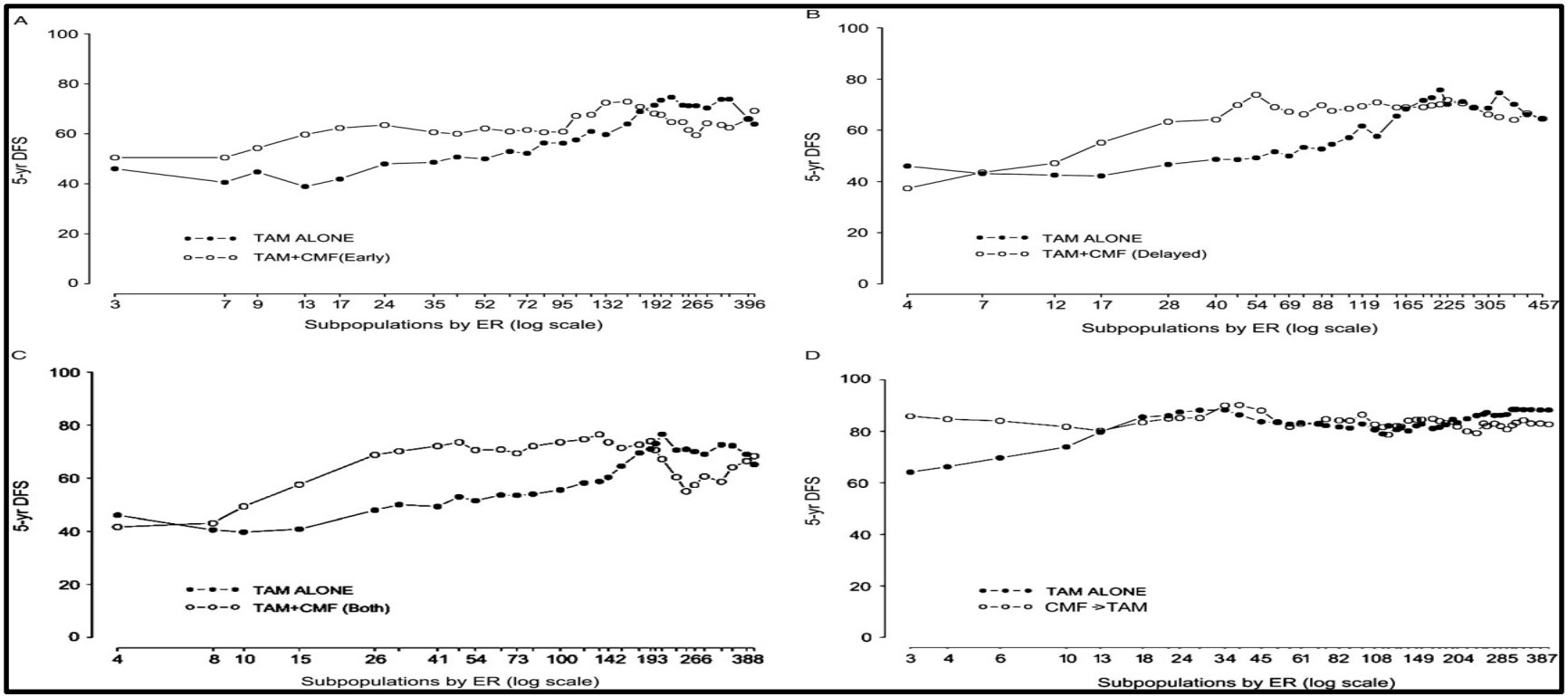
FONCTIONNEL: INTENSITÉ D'EXPRESSION

Original article

Annals of Oncology 16: 716–725, 2005
doi:10.1093/annonc/mdi163
Published online 7 April 2005

Timing of CMF chemotherapy in combination with tamoxifen in postmenopausal women with breast cancer: role of endocrine responsiveness of the tumor

M. Colleoni[1]*, S. Li[2], R. D. Gelber[2], A. S. Coates[3], M. Castiglione-Gertsch[4], K. N. Price[2], J. Lindtner[5], C.-M. Rudenstam[6], D. Crivellari[7], J. Collins[8], O. Pagani[9], E. Simoncini[10], B. Thürlimann[11], E. Murray[12], J. Forbes[13], D. Eržen[5], S. Holmberg[14], A. Veronesi[7] & A. Goldhirsch[1,9]
On behalf of the International Breast Cancer Study Group (IBCSG)†



Colleoni, M. et al. Ann Oncol 2005 16:716-725; doi:10.1093/annonc/mdi163

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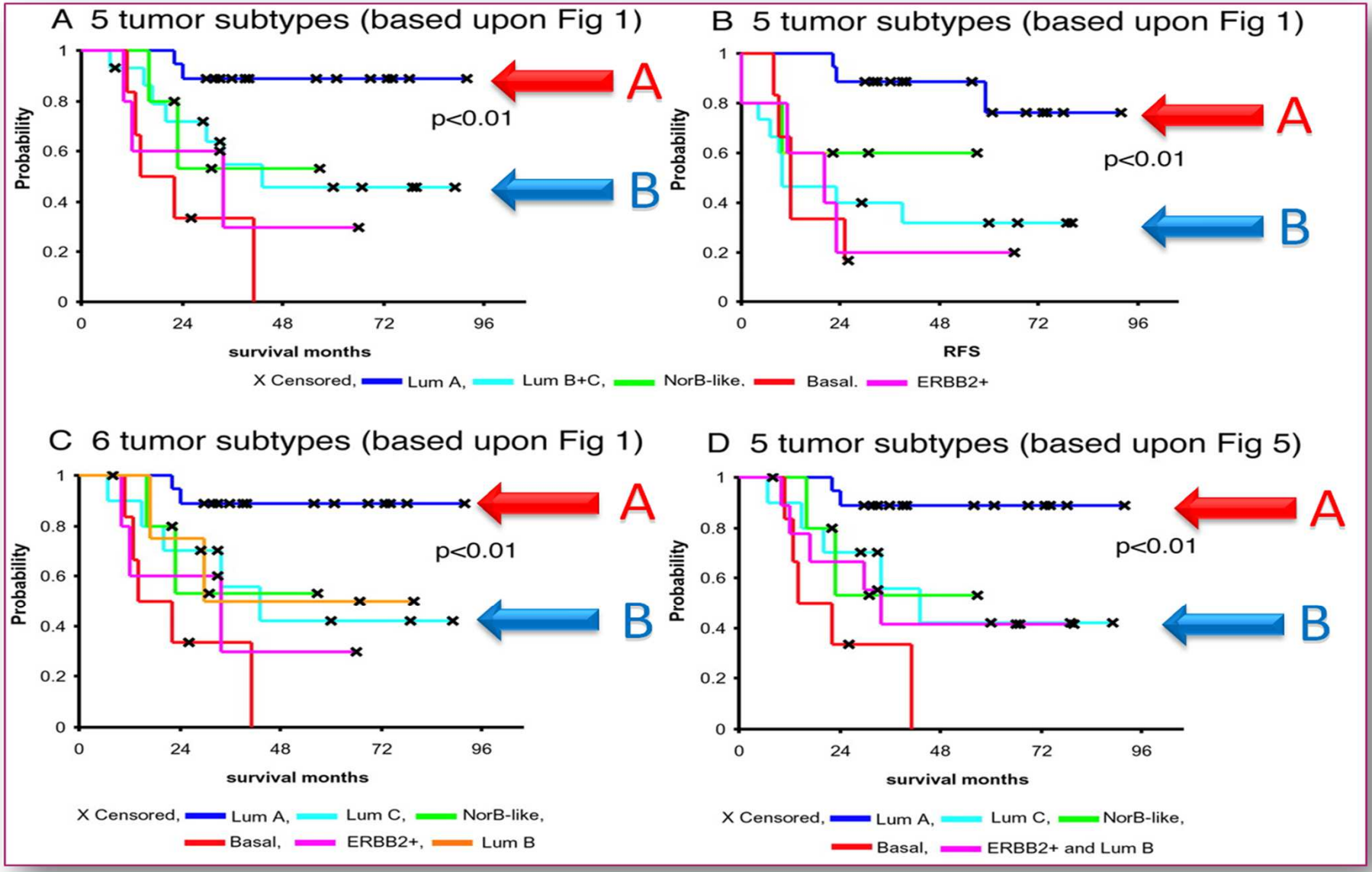
MOLÉCULAIRE



Les Chemins de la prise de décision

L'oncologue

Pronostique

Prédictif

La patiente

Leading Edge
Review

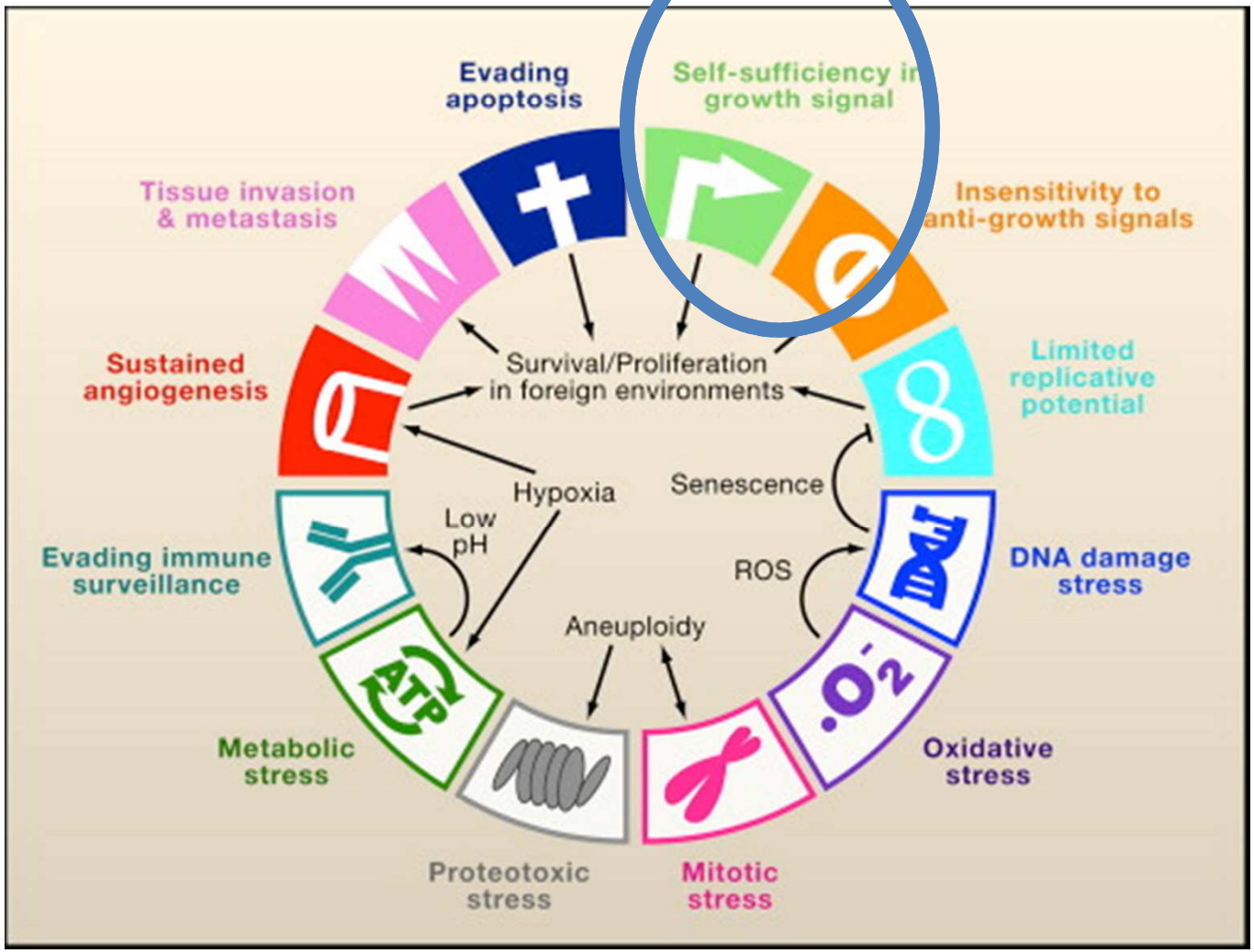
Cell

Institut de Cancérologie de l'Ouest

Principles of Cancer Therapy: Oncogene and Non-oncogene Addiction

Ji Luo,[1] Nicole L. Solimini,[1] and Stephen J. Elledge[1,*]
[1]Howard Hughes Medical Institute, Department of Genetics, Harvard Medical School, Department of Medicine, Division of Genetics, Brigham and Women's Hospital, Boston, MA 02115, USA
*Correspondence: selledge@genetics.med.harvard.edu
DOI 10.1016/j.cell.2009.02.024

Tumeur



Leading Edge
Review

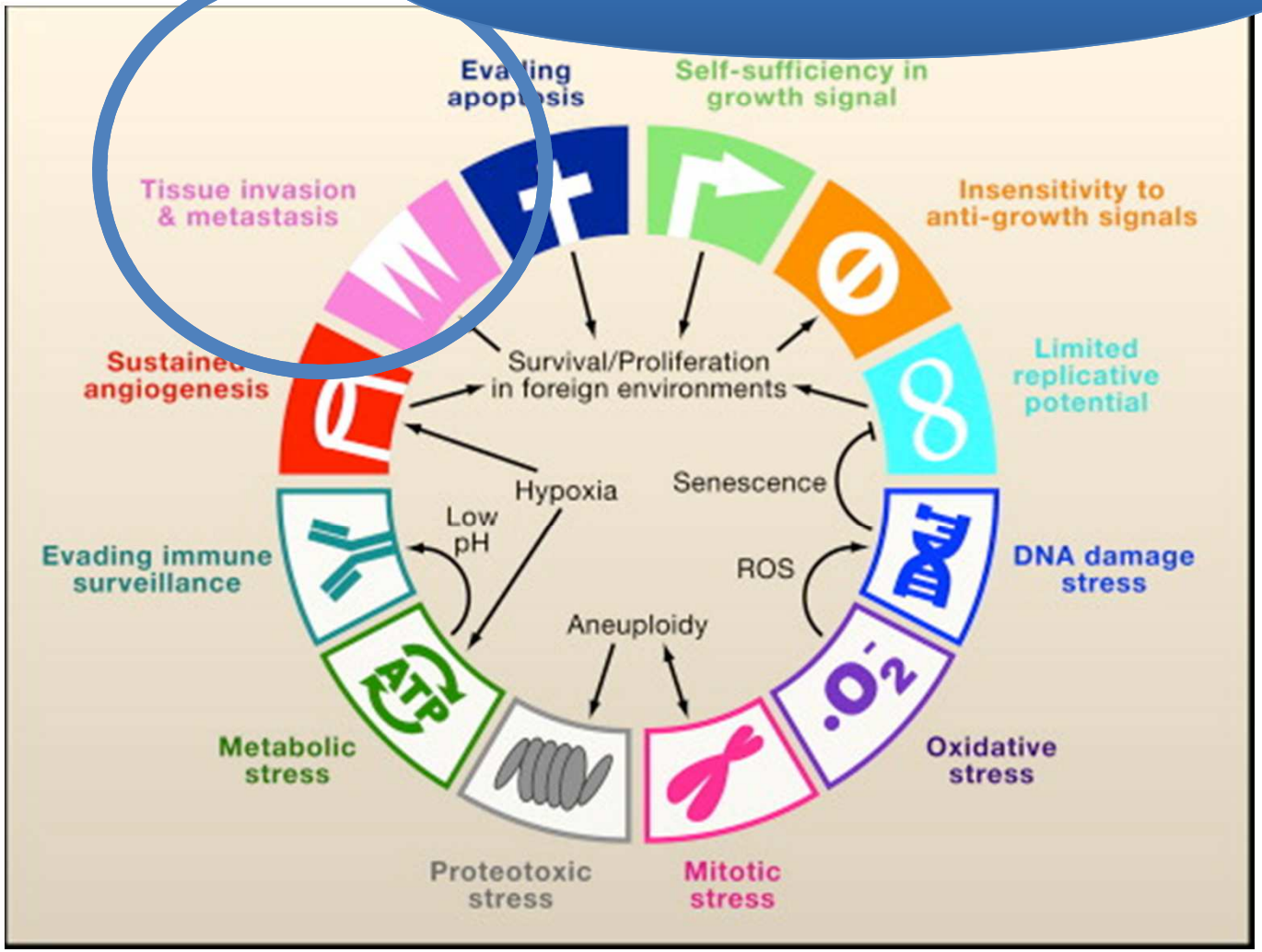
Cell

Institut de Cancérologie de l'Ouest

Principles of Cancer Therapy: Oncogene and Non-oncogene Addiction

Ji Luo,[1] Nicole L. Solimini,[1] and Stephen J. Elledge[1,*]
[1]Howard Hughes Medical Institute, Department of Genetics, Harvard Medical School, Department of Medicine, [illegible]
Brigham and Women's Hospital, Boston, MA 02115, USA
*Correspondence: selledge@genetics.med.harvard.edu
DOI 10.1016/j.cell.2009.02.024

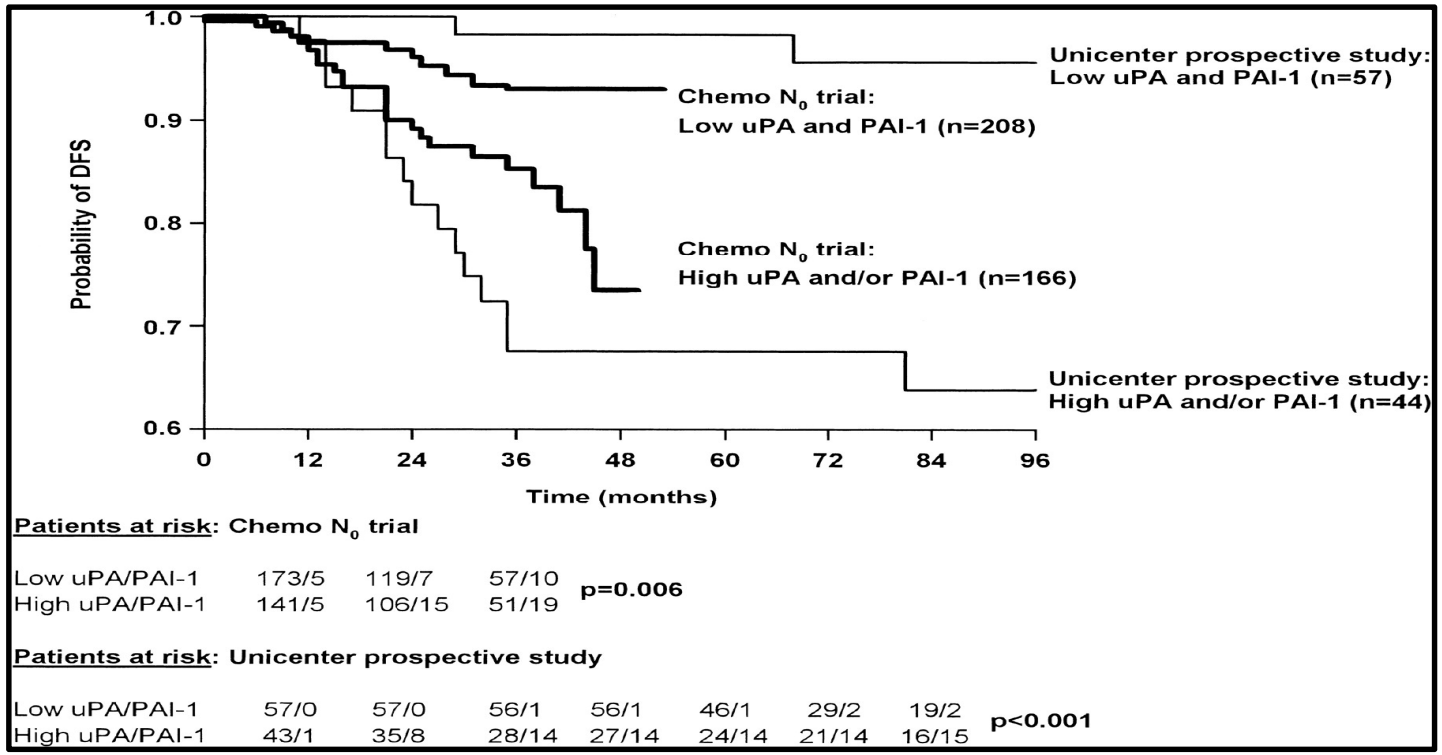
Environnement



Randomized Adjuvant Chemotherapy Trial in High-Risk, Lymph Node-Negative Breast Cancer Patients Identified by Urokinase-Type Plasminogen Activator and Plasminogen Activator Inhibitor Type 1

Fritz Jänicke, Anita Prechtl, Christoph Thomssen, Nadia Harbeck, Christoph Meisner, Michael Untch, C. G. J. Fred Sweep, Hans-Konrad Selbmann, Henner Graeff, Manfred Schmitt

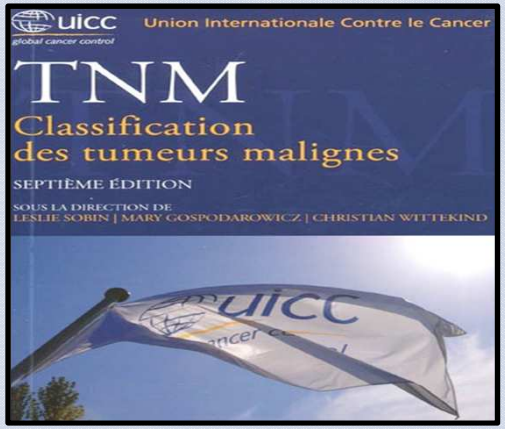
For the German Chemo N_0 Study Group



Janicke, F. et al. J. Natl. Cancer Inst. 2001 93:913-920; doi:10.1093/jnci/93.12.913

Pronostique

Clinique



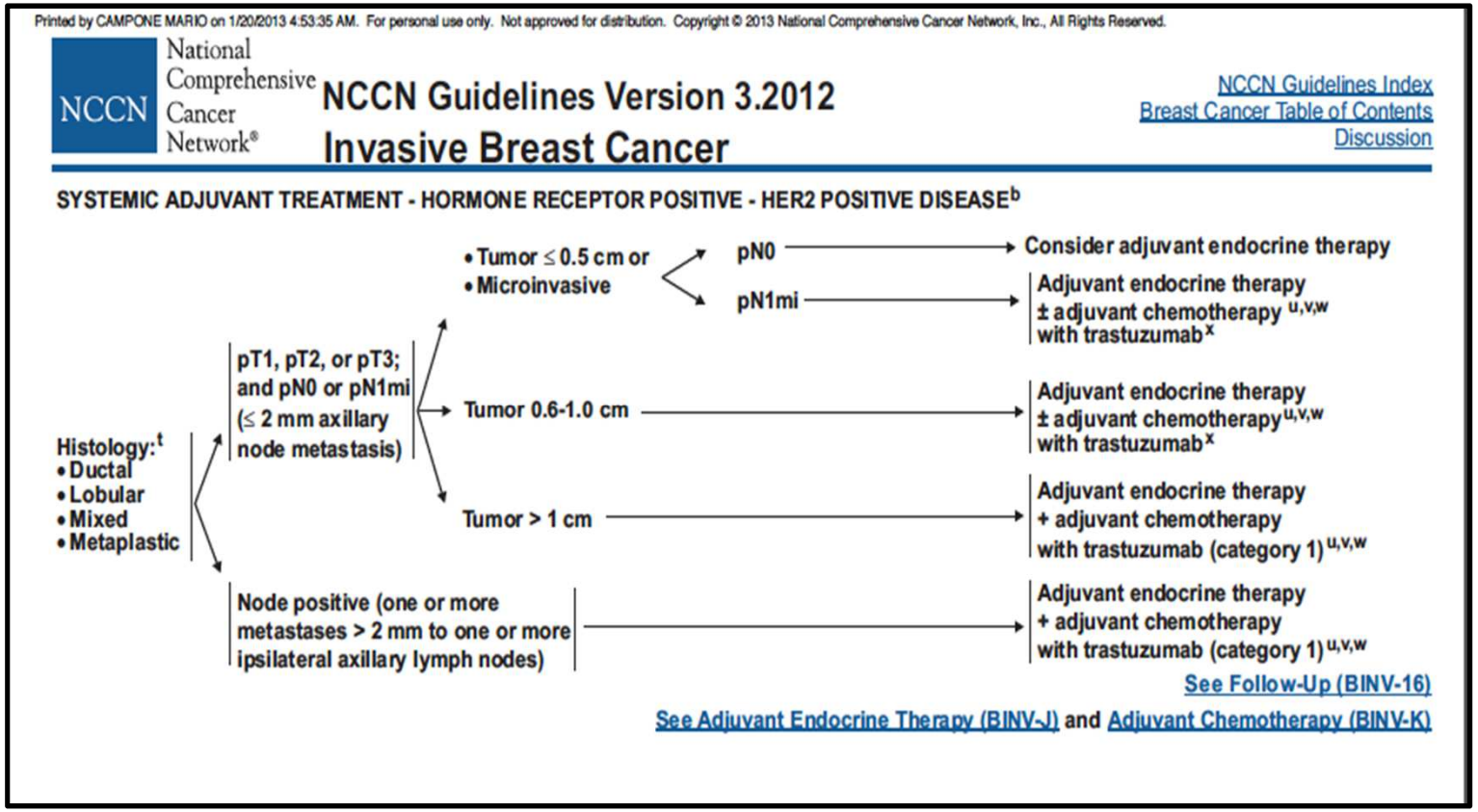
Histologique

- <u>pN</u>
  - pN- vs pN+
- pT
  - 10mm vs >20mm
- Grade histologique
  - SBR I vs SBR II-III
- RH
  - RH+ vs RH-

Biochimique

- UPA/PA1

ASCO



Recommandations INCA

L'association de chimiothérapie et trastuzumab dans les tumeurs infracentrimétriques pT1ab, N0 n'est pas contre indiquée mais à, elle seule, la surexpression de HER2 ne peut la justifier. Son indication doit tenir compte des autres facteurs pronostiques utilisés pour prescrire une chimiothérapie.

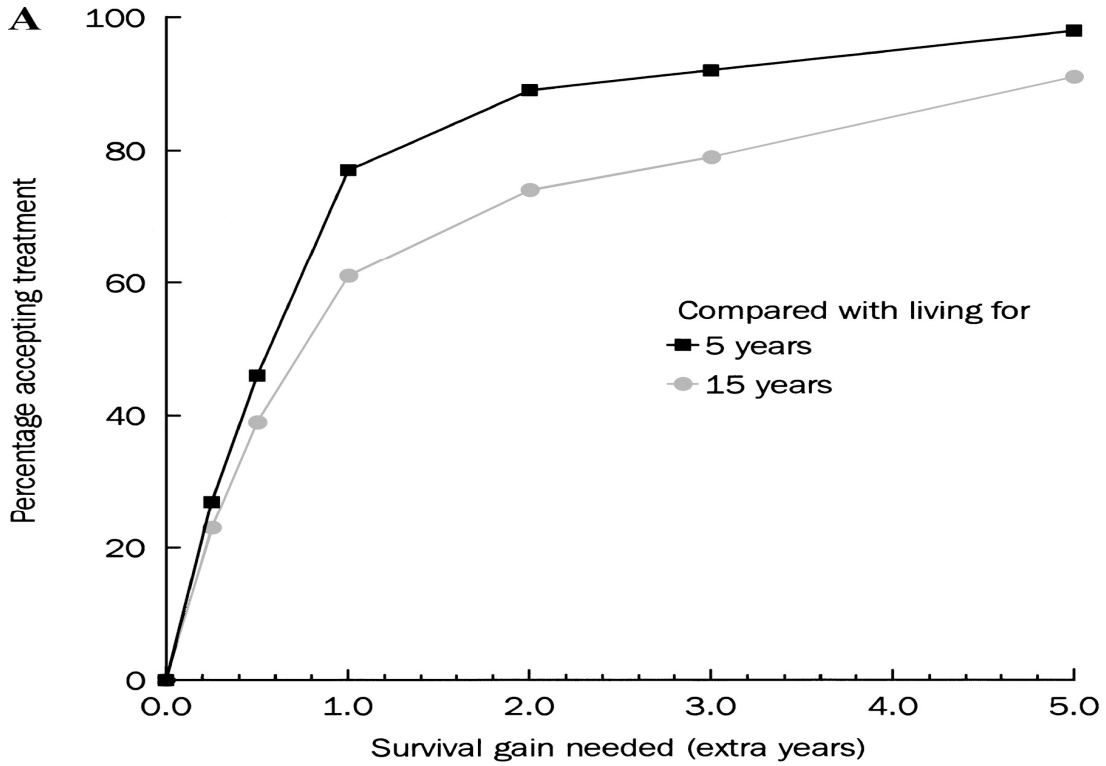
Prédictif

Une variable prédictive de la réponse au traitement est un cas particulier de variable pronostique. C'est une variable d'interaction qui modifie l'effet d'un traitement ou d'une exposition sur un événement futur. En épidémiologie, on préférera le terme de « modificateur d'effet ».

Prédictif

CT	anti-HER2+	Anti-Estrogènes
• ?	• HER2+	• RH+

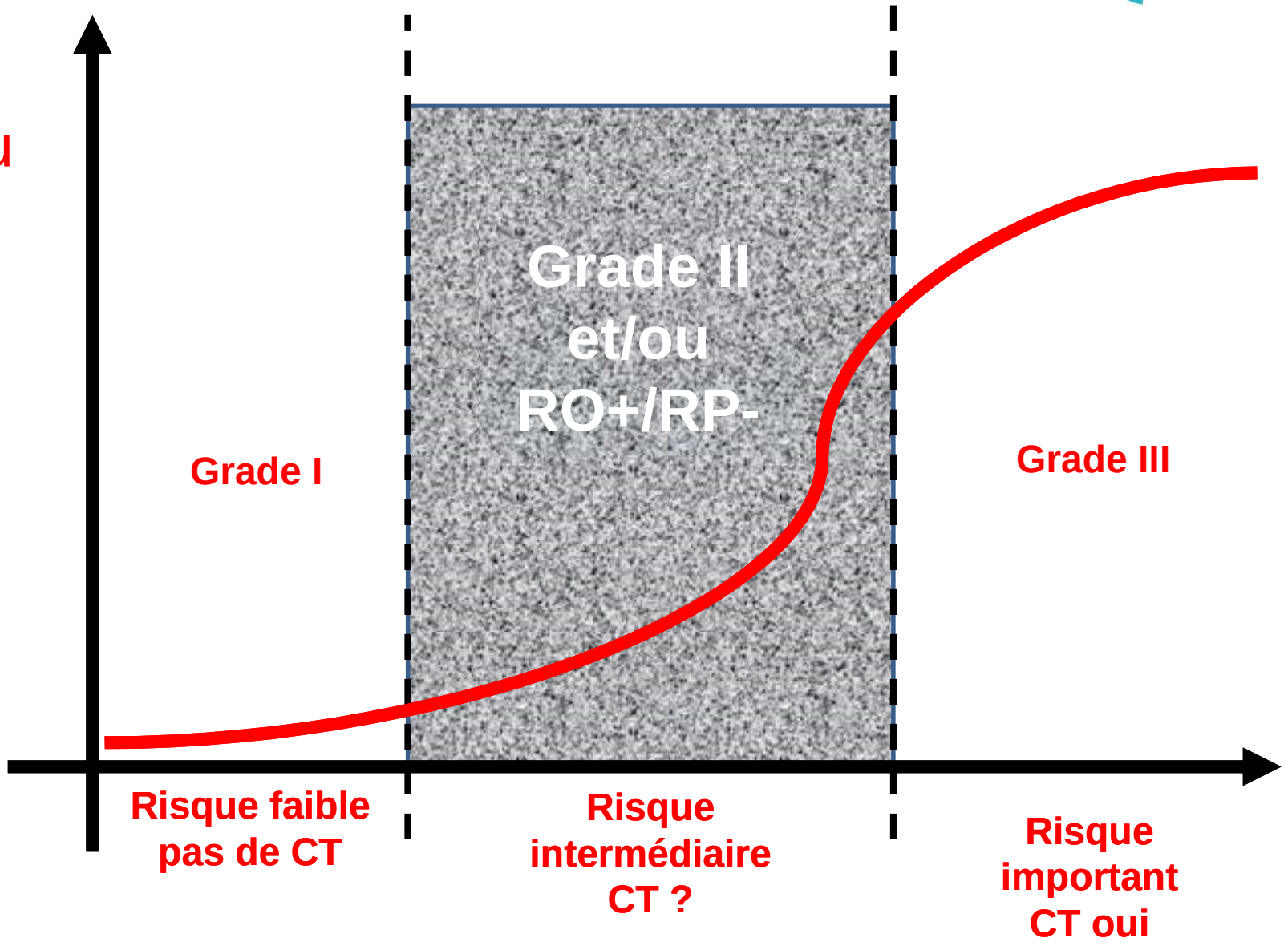
A) Proportion of patients who would consider the extra years in survival plotted sufficient to accept adjuvant chemotherapy compared with 1) 5 years or 2) 15 years of survival without such treatment.



La patiente

Simes R J , Coates A S J Natl Cancer Inst Monogr 2001;2001:146-152

pN0 ou
pN+
(1-3)
RH+



Le Guide de la bonne Indication adjuvante

Référentiel :

- **NIH**
- **Saint Paul de Vence**
- **Saint Gallen**
- **Adjuvant Online**
- **NPI**
- **Signatures**

Comment avancer ?

HORMONOSENSIBILITE

Luminal----------Triple négatif

Les OUTILS

Signature Génomique
ONCOTYPE DX
Grade Génomique
Adjuvant ONLINE
NPI

HORMONOSENSIBILITE

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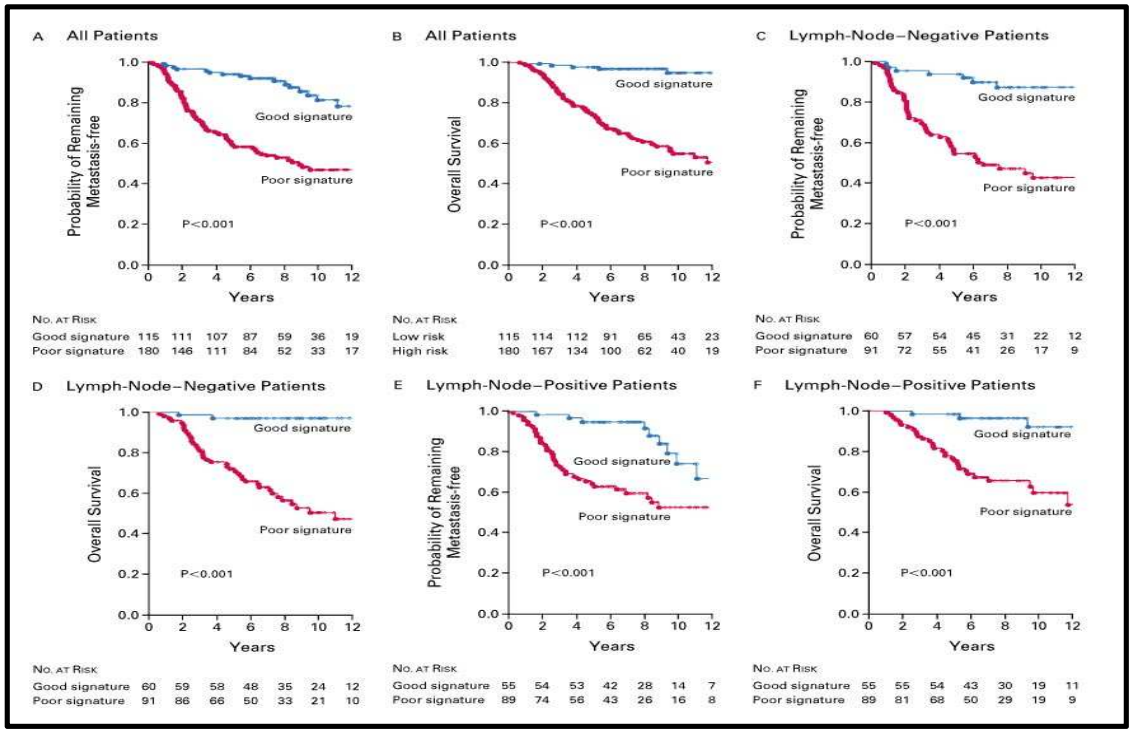
Signature Génomique

HORMONOSENSIBILITE

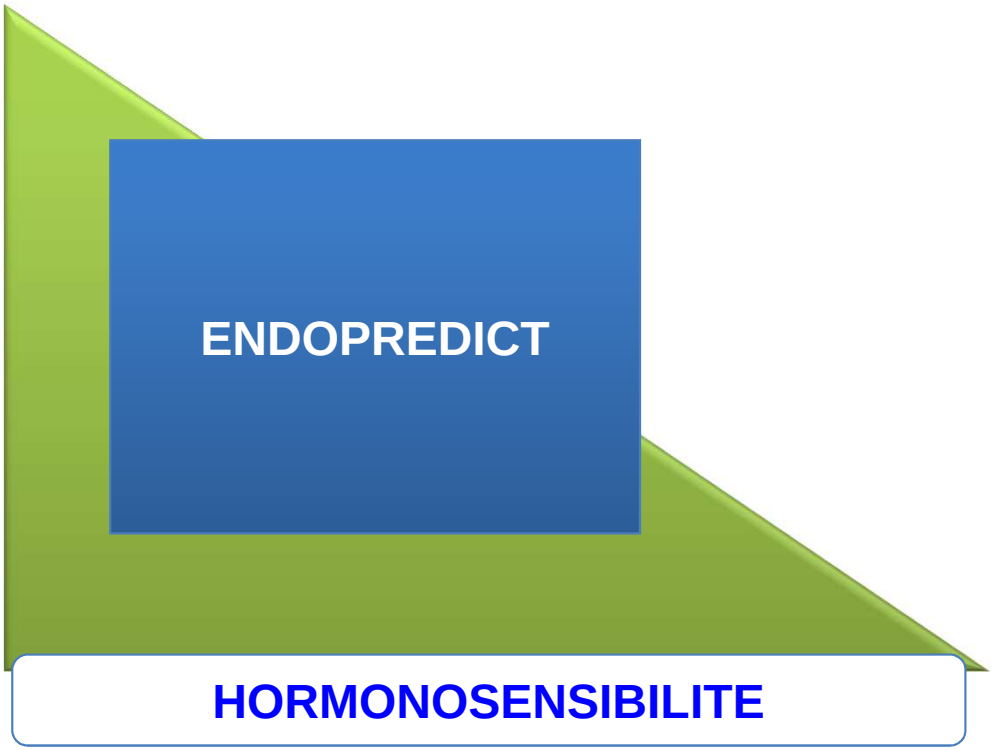
Signature Amsterdam

- 295 patientes :
  - 151 N- :
    - 10 TT adjuvant
  - 144 N+:
    - 120 TTT adjuvant
- Follow-up de 7,8 ans
- 78 gènes :
  - Invasion
  - Angiogenèse
  - Transduction du signal



van de Vijver, M. J. et al. N Engl J Med 2002;347:1999-2009

ENDOPREDICT
UN TEST PRONOSTIQUE POUR LES RH+ IDENTIFIANT LES RISQUES DE RECHUTE PRÉCOCES ET TARDIFS.



ENDOPREDICT

Imaging, Diagnosis, Prognosis

Clinical Cancer Research

A New Molecular Predictor of Distant Recurrence in ER-Positive, HER2-Negative Breast Cancer Adds Independent Information to Conventional Clinical Risk Factors

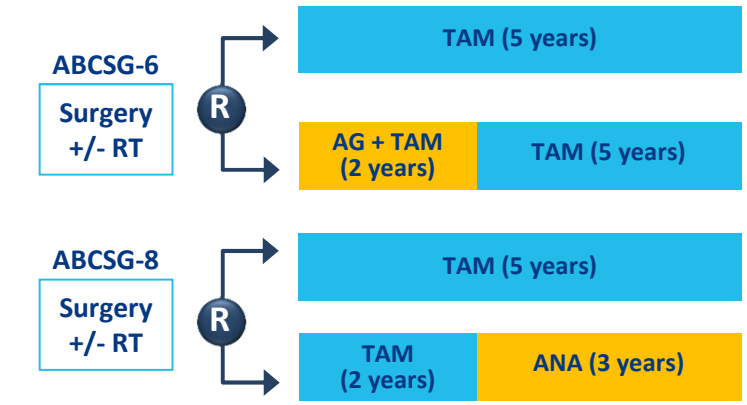
Martin Filipits[1], Margaretha Rudas[2], Raimund Jakesz[3], Peter Dubsky[3], Florian Fitzal[3], Christian F. Singer[4], Otto Dietze[7], Richard Greil[8], Andrea Jelen[5], Paul Sevelda[6], Christa Freibauer[9], Volkmar Müller[10], Fritz Jänicke[10], Marcus Schmidt[11], Heinz Kölbl[11], Achim Rody[12], Manfred Kaufmann[12], Werner Schroth[13], Hiltrud Brauch[13], Matthias Schwab[13], Peter Fritz[13,14], Karsten E. Weber[16], Inke S. Feder[15], Guido Hennig[15], Ralf Kronenwett[16], Mathias Gehrmann[15], and Michael Gnant[3], for the EP Investigators

- Sélection de 8 gènes et construction d'un algorithme ***BIRC5***, ***UBE2C***, ***DHCR7***, ***RBBP8***, ***IL6ST***, ***AZGP1***, ***MGP***, ***STC2*** and 3 normalization genes ***CALM2***, ***OAZ1***, and ***RPL37A.***

$$^{S}clin = 0.35 \cdot T + 0.64 \cdot N + 0.28 \cdot S\ (D)$$

- **Where *t* codes the tumor size (1: ≤ 1 cm, 2: >1 to ≤ 2cm, 3: > 2 to < 5 cm, and 4: > 5 cm) and n the nodal status**
- **1: negative, 2: 1-3 positive nodes, 3: 4-10 positive nodes, and 4: > 10 positive nodes**

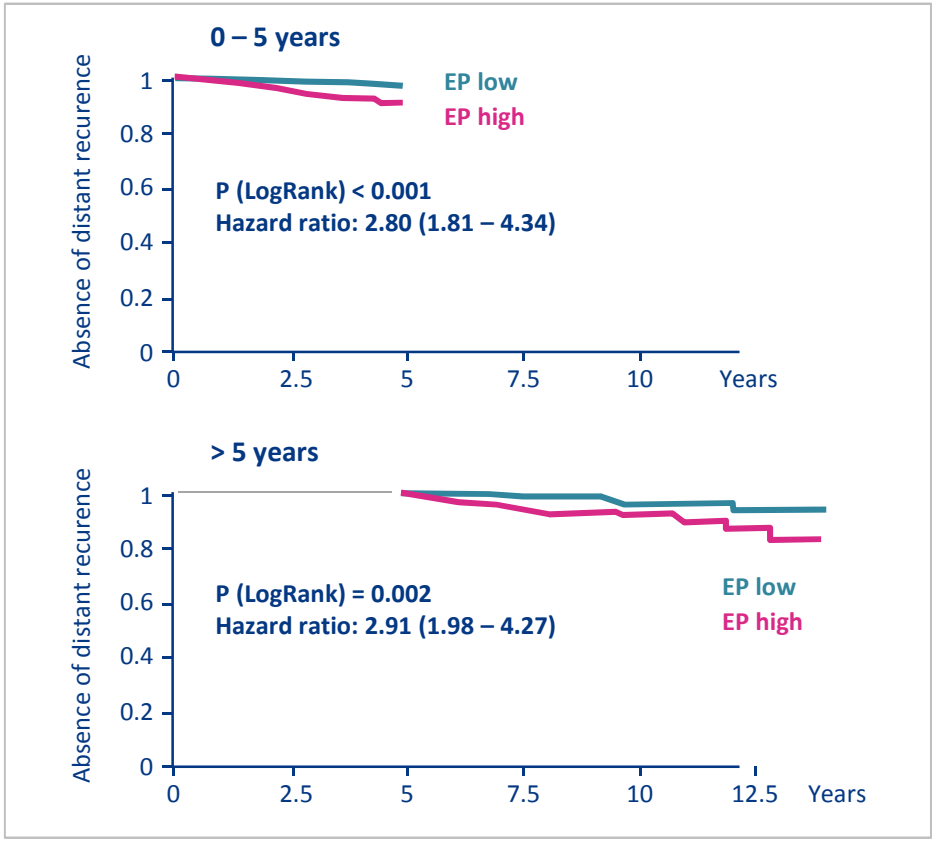
Design de l'étude : résultats



Jakesz R et al. Lancet 2005
Jonat W et al., Lancet Oncol, 2006
Dubsky P et al., JCO 2012

Sequence analysis

- **1,702 ER+ / HER2- postmenopausal breast cancer patients**
- **Median age 63.8 years**
- **Two-thirds T<2cm and N0**
- **4% G3, 22% Ki67 > 14%**
- **No adjuvant chemotherapy**
- **998 patients at risk after 5 years (median FU: 7.12 years)**



- **Le group endopredict de bas risque (49%) a un avantage en survie avant et après 5 ans**
- **96,3% sont sans métastases entre 5 et 10 ans**

Endopredict : paramètre pronostic indépendant
ni le grade, ni le Ki67 ne sont prédicteurs de métastases tardives

P. Dubsky *et al.*, SABCS 2012, S4-3

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Grade Génomique

HORMONOSENSIBILITE

INDEX GENOMIQUE

Gene Expression Profiling in Breast Cancer: Understanding the Molecular Basis of Histologic Grade To Improve Prognosis

Christos Sotiriou, Pratyaksha Wirapati, Sherene Loi, Adrian Harris, Steve Fox, Johanna Smeds, Hans Nordgren, Pierre Farmer, Viviane Praz, Benjamin Haibe-Kains, Christine Desmedt, Denis Larsimont, Fatima Cardoso, Hans Peterse, Dimitry Nuyten, Marc Buyse, Marc J. Van de Vijver, Jonas Bergh, Martine Piccart, Mauro Delorenzi

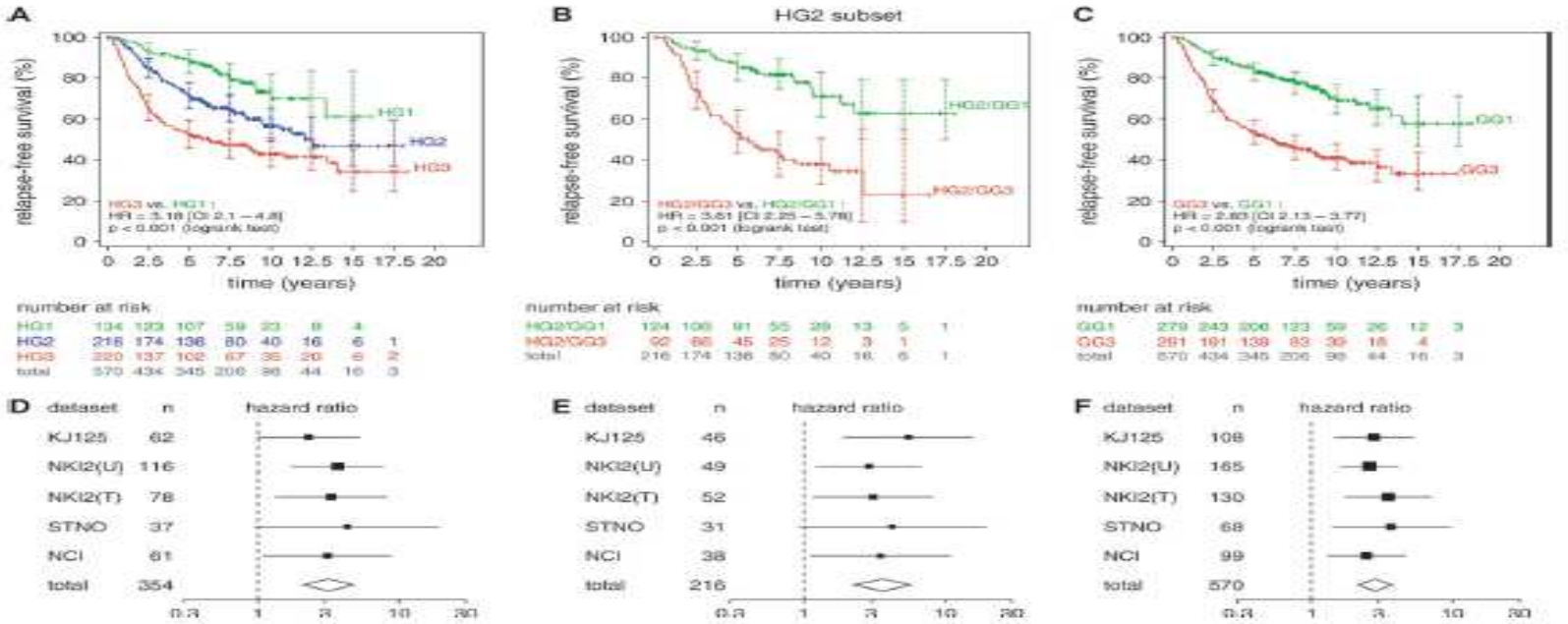
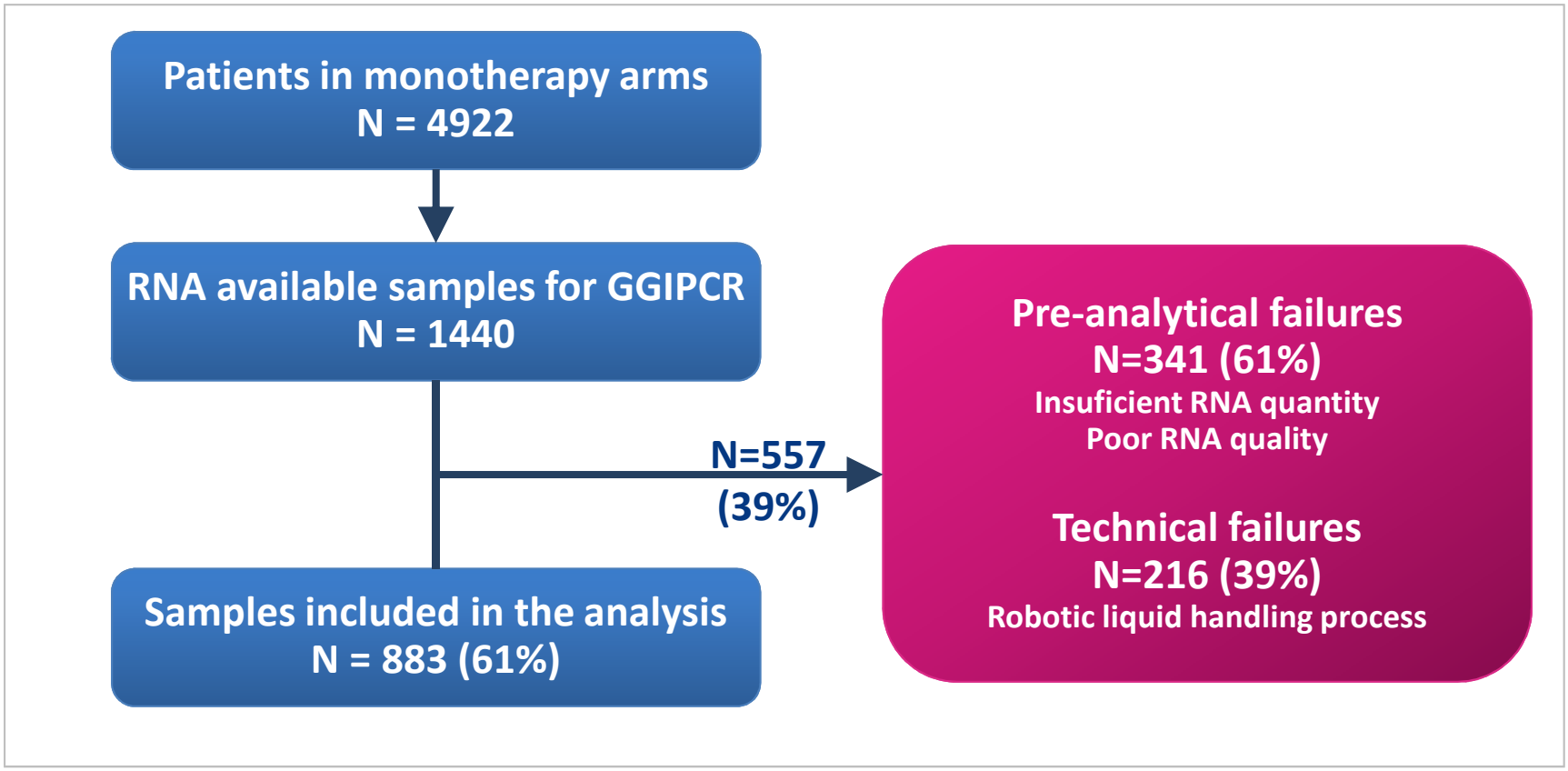
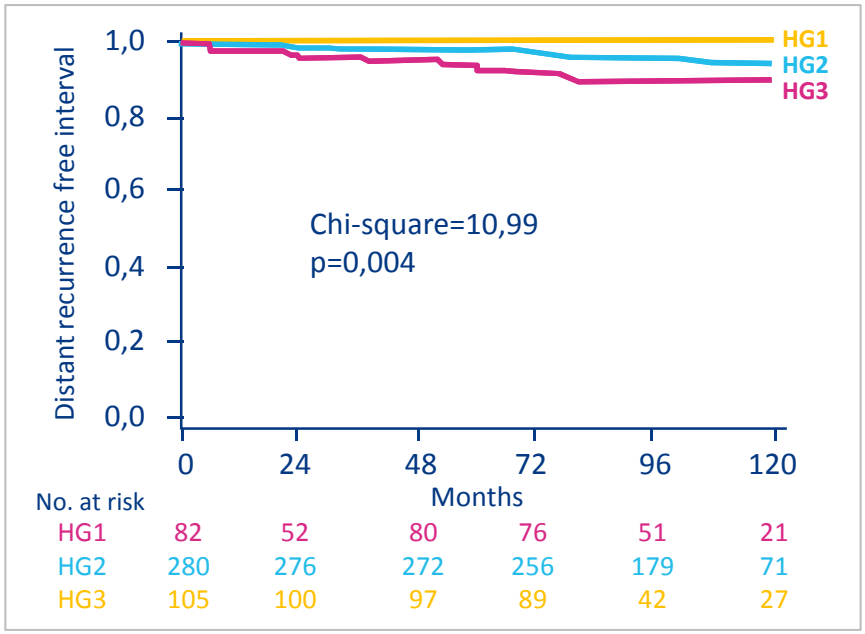


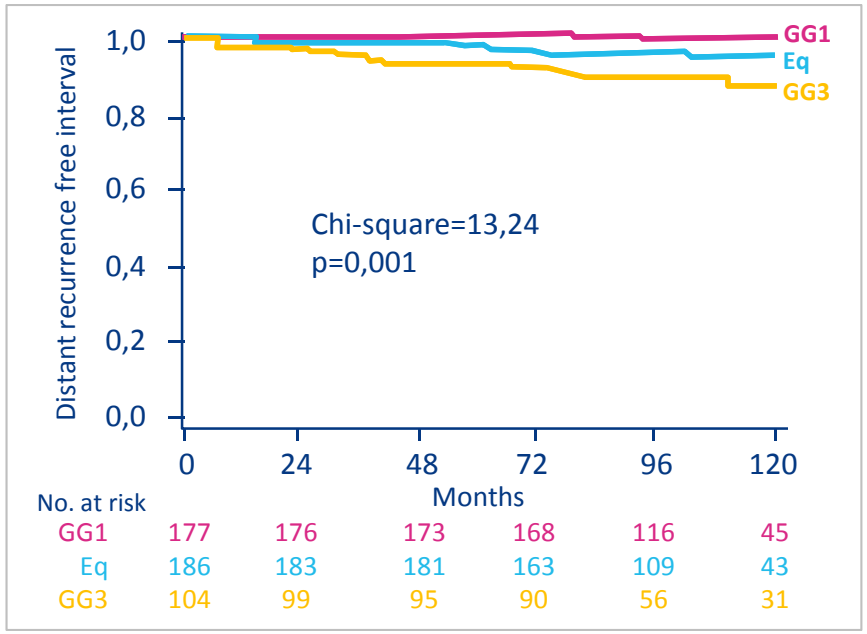
Fig. 2. Relapse-free survival analysis for all validation datasets. Only 570 patients with complete histologic grade (HG) and relapse-free survival information were included. Kaplan–Meier analyses were conducted with pooled data. Number of patients at risk and 95% confidence intervals (CIs) for the relapse-free survival estimates (shown as **error bars**) are indicated at 2.5-year intervals. Difference in relapse-free survival between two groups is summarized by the hazard ratio (HR) for recurrence with its 95% CI. NKI2(U) = untreated subset of dataset NKI2; NKI2(T) = treated subset of dataset NKI2. **A**) Analysis of the whole dataset by HG1 (**green**), HG2 (**blue**), or HG3 (**red**). **B**) Analysis of patients with HG2 tumors by gene expression grade (GG). The 217 patients with HG2 tumors were separated into low- and high-risk subsets by GG as GG1 (**green**) and GG3 (**red**), respectively. **C**) Analysis of the whole dataset of 572 patients by GG. GG1 = **green**; GG3 = **red**. All statistical tests were two-sided. To show consistency among different datasets, forest plots of the hazard ratios and confidence intervals for individual datasets are shown below the corresponding Kaplan–Meier plots (panels **D**, **E**, and **F**, corresponding to panels **A**, **B**, and **C**, respectively). All statistical tests were two-sided.

Design de l'étude



Grade génomique grade SBR : même combat !!!





Grade SBR

	10 year DRFI (%)	95% CI
HG1 (18%)	100	(100-100)
HG2 (60%)	94	(91-97)
HG3 (22%)	90	(84-96)

Grade génomique

	10 year DRFI (%)	95% CI
GG1 (38%)	99	(97-100)
Eq (40%)	94	(90-98)
GG3 (22%)	87	(80-94)

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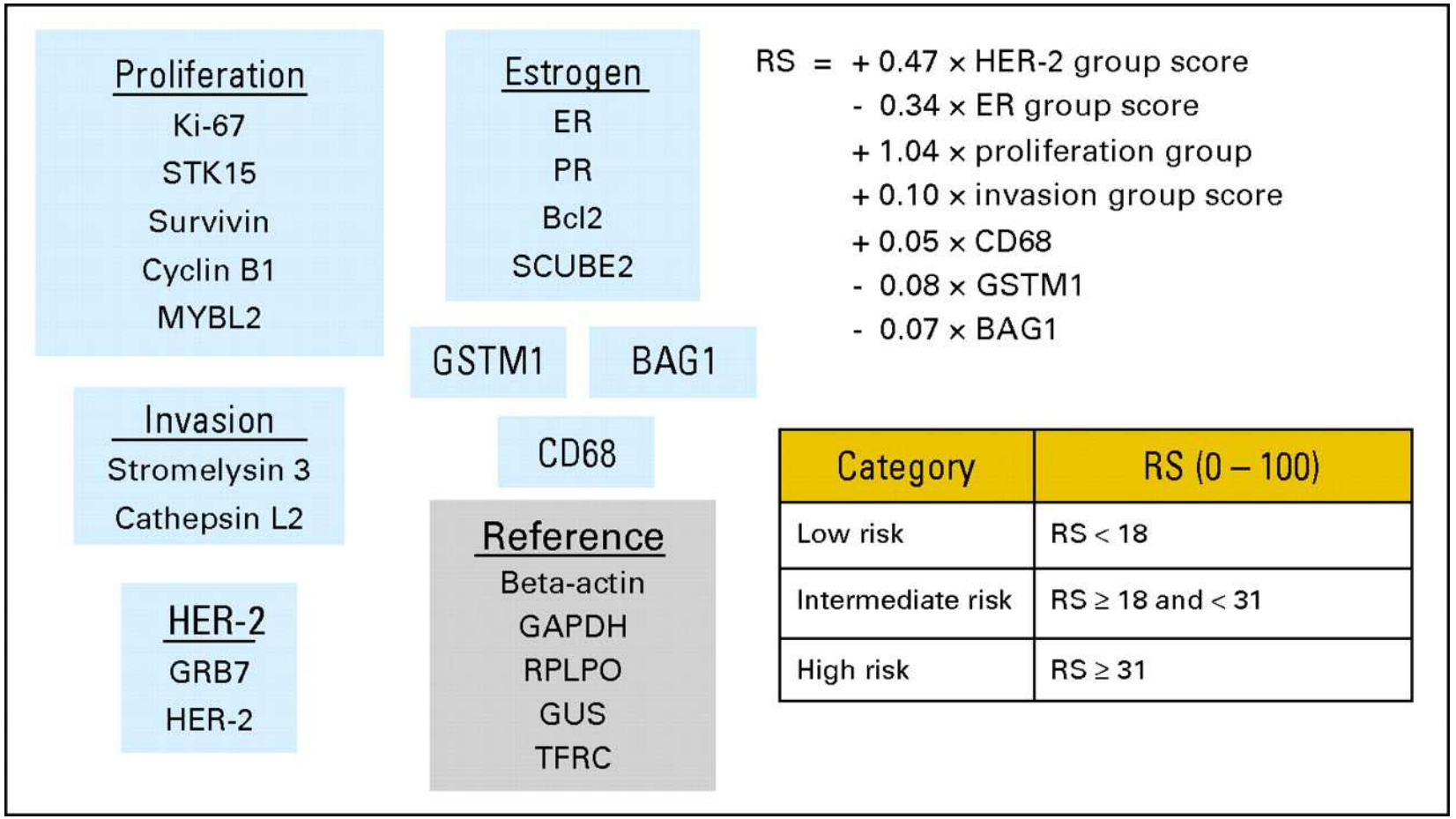
ONCOTYPE DX

HORMONOSENSIBILITE

Oncotype Dx (Genomic Health, Redwood City, CA) recurrence score (RS): genes and algorithm.



Category	RS (0 – 100)
Low risk	RS < 18
Intermediate risk	RS ≥ 18 and < 31
High risk	RS ≥ 31

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

JOURNAL OF CLINICAL ONCOLOGY

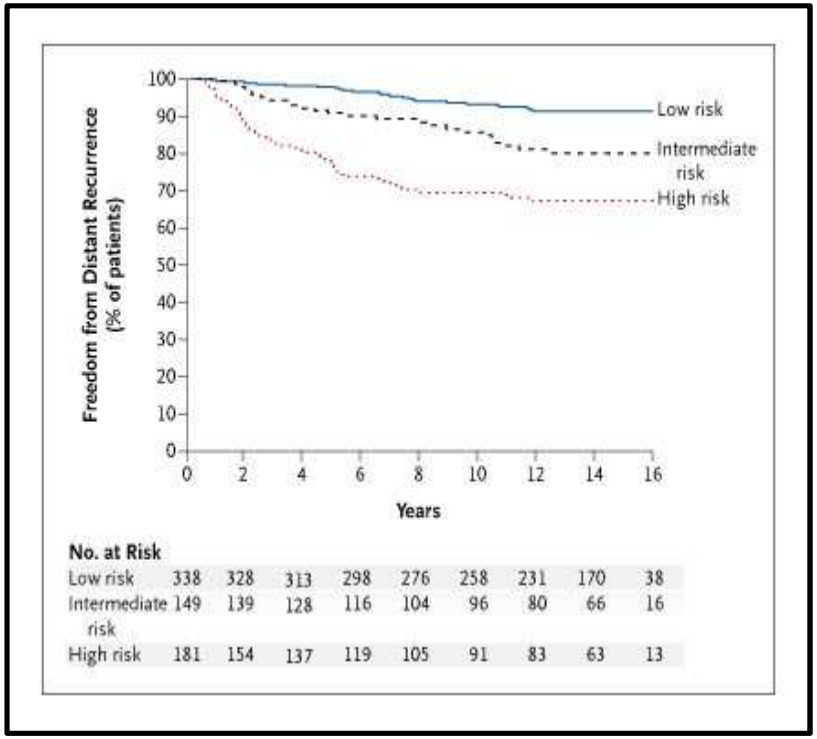


Table 1. Kaplan–Meier Estimates of the Rate of Distant Recurrence at 10 Years, According to Recurrence-Score Risk Categories.*

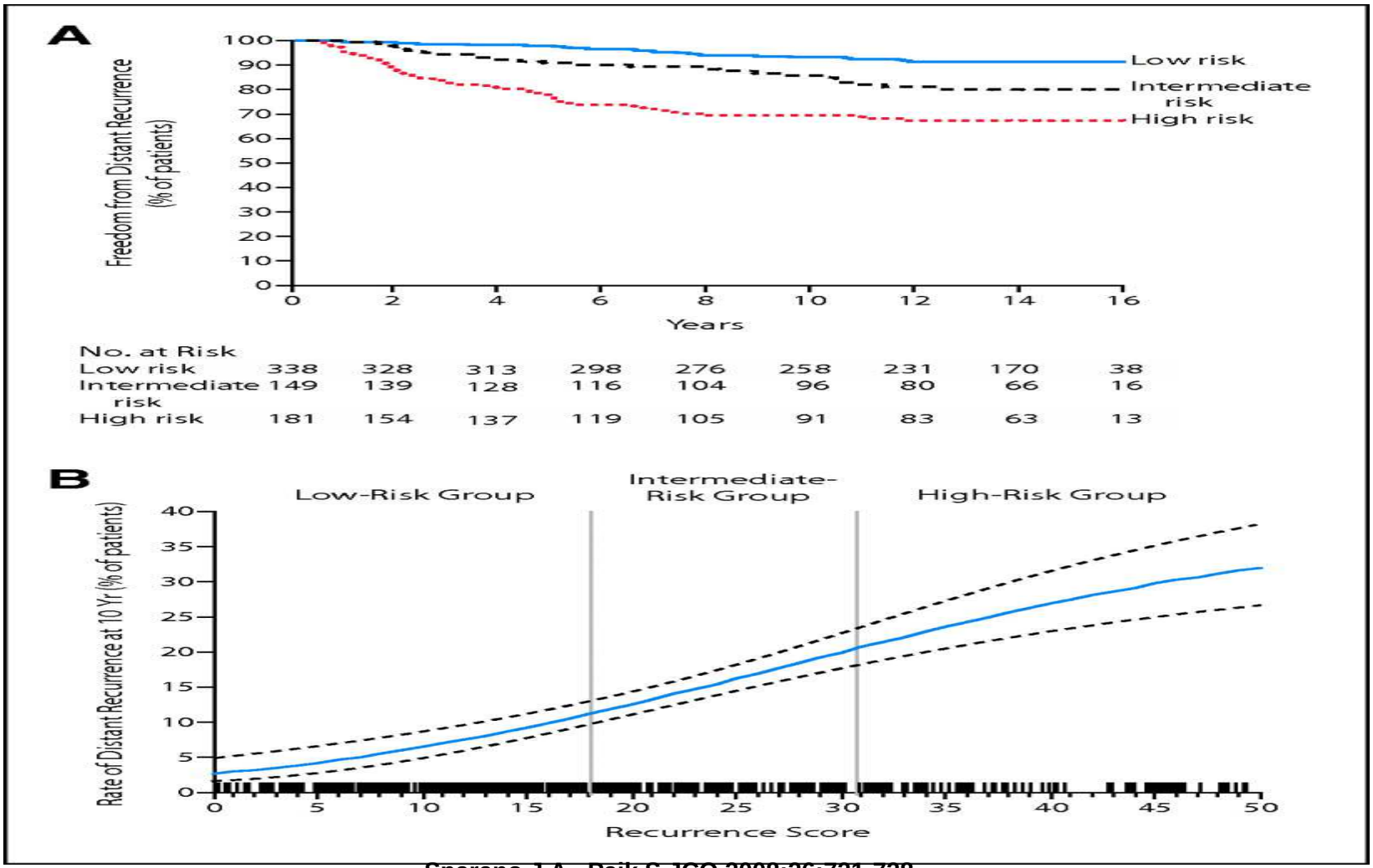
Risk Category	Percentage of Patients	Rate of Distant Recurrence at 10 Yr (95% CI)†
		percent
Low	51	6.8 (4.0–9.6)
Intermediate	22	14.3 (8.3–20.3)
High	27	30.5 (23.6–37.4)‡

* A low risk was defined as a recurrence score of less than 18, an intermediate risk as a score of 18 or higher but less than 31, and a high risk as a score of 31 or higher.
† CI denotes confidence interval.
‡ P<0.001 for the comparison with the low-risk category.

Kaplan-Meier Estimates of the Rate of Distant Recurrence at 10 Years, According to Recurrence-Score Risk Categories.

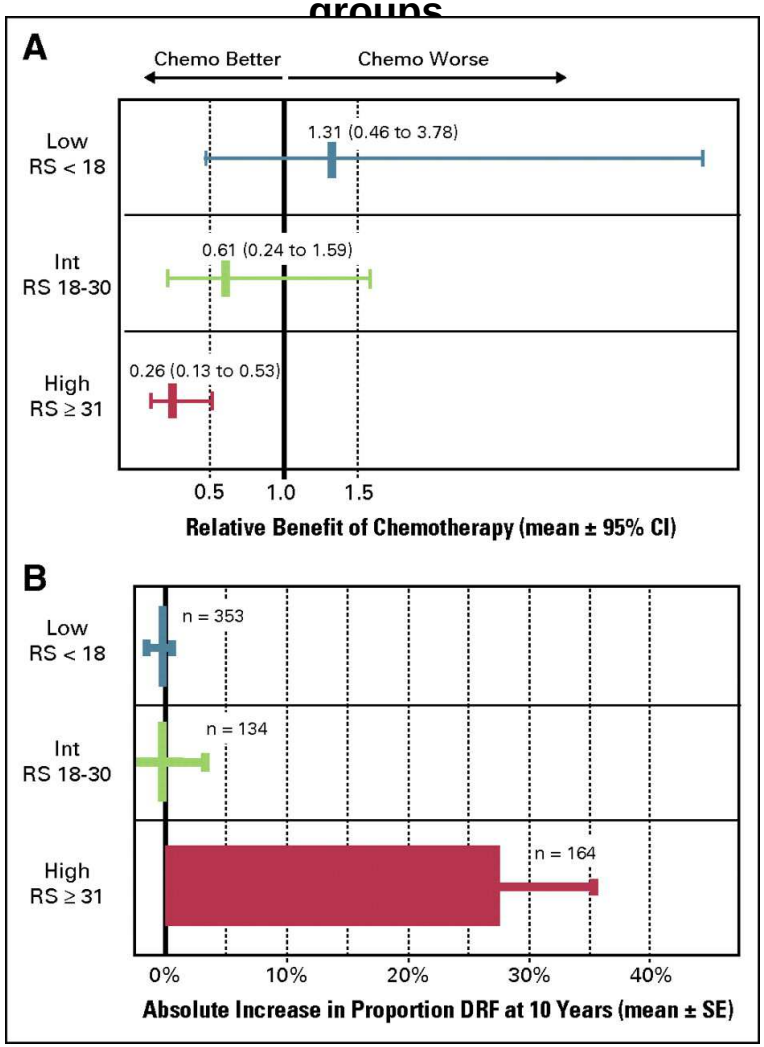
Paik, S. et al. N Engl J Med 2004;351:2817-2826

Oncotype Dx (Genomic Health, Redwood City, CA) recurrence score predicts distant recurrence when analyzed as either a (A) categoric or (B) continuous variable.



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

(A) Relative and (B) absolute risk of chemotherapy (Chemo) benefit as a function of recurrence score (RS) risk category in low, intermediate (Int), and high recurrence score groups



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

JOURNAL OF CLINICAL ONCOLOGY

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Association between the 21-gene recurrence score (RS) and benefit from adjuvant paclitaxel (Pac) in node-positive (N+), ER-positive breast cancer patients (pts): Results from NSABP B-28

Abs S1-10. Mamounas EP *et al.*

ONCOTYPE DX

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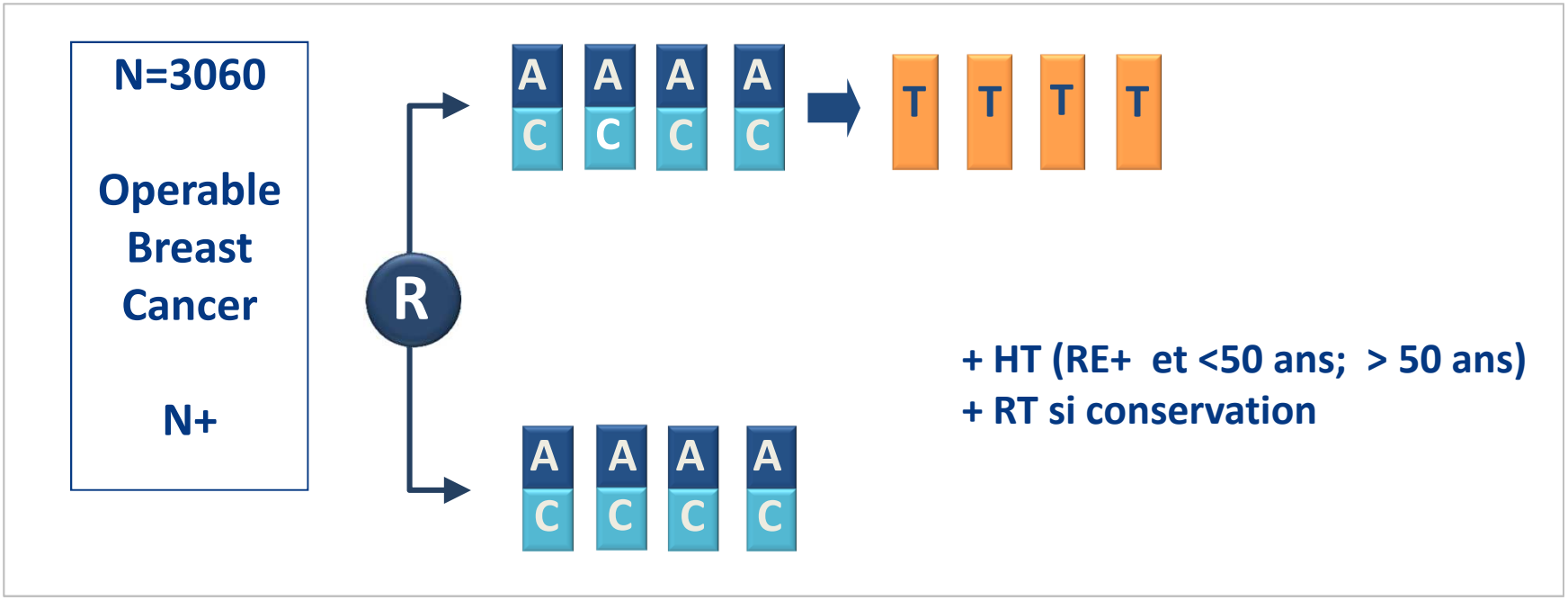
NSABP-B28

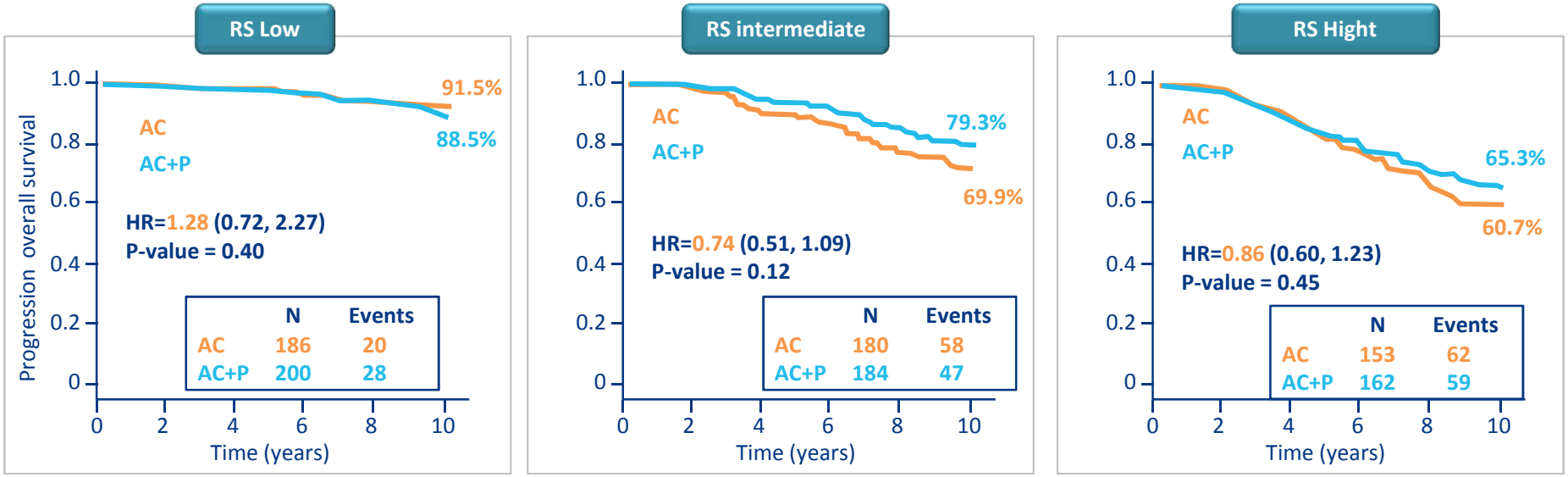


Réduction du risque d'événement DFS de 17% (HR=0.83, p=0.006)
Amélioration de la survie globale non significative (HR=0.93, p=0.46)

J Clin Oncol, 2005, Mamounas

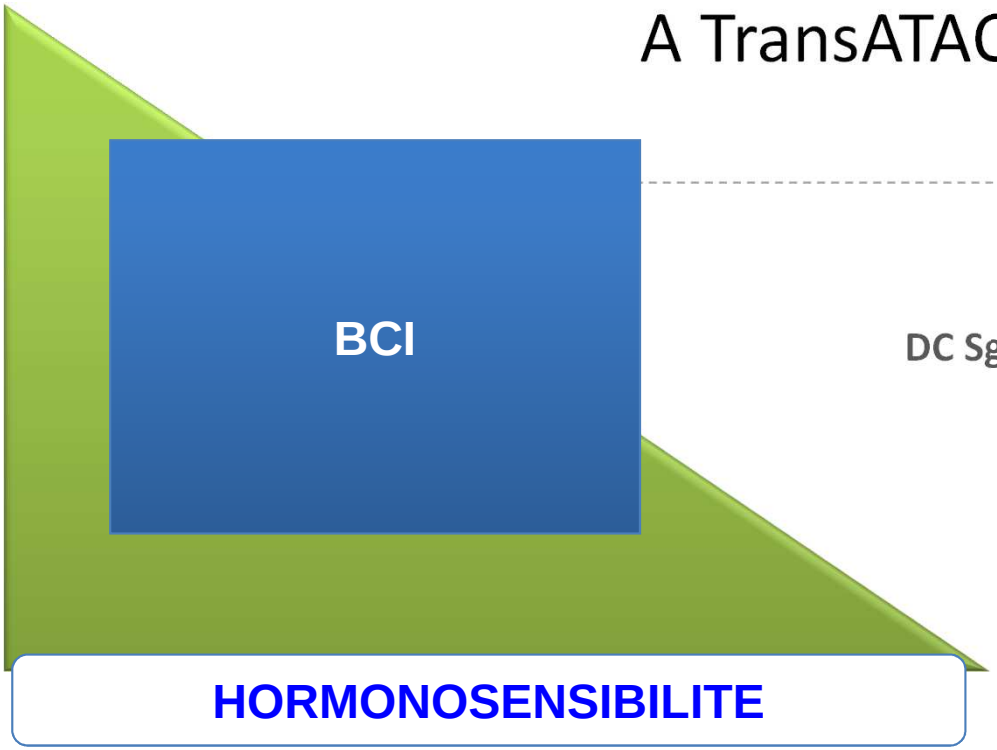
Oncotype DX et bénéfice du paclitaxel dans les cancers du sein N+, RE+ de l'étude NSABP-B28

Survie globale selon le score Oncotype DX



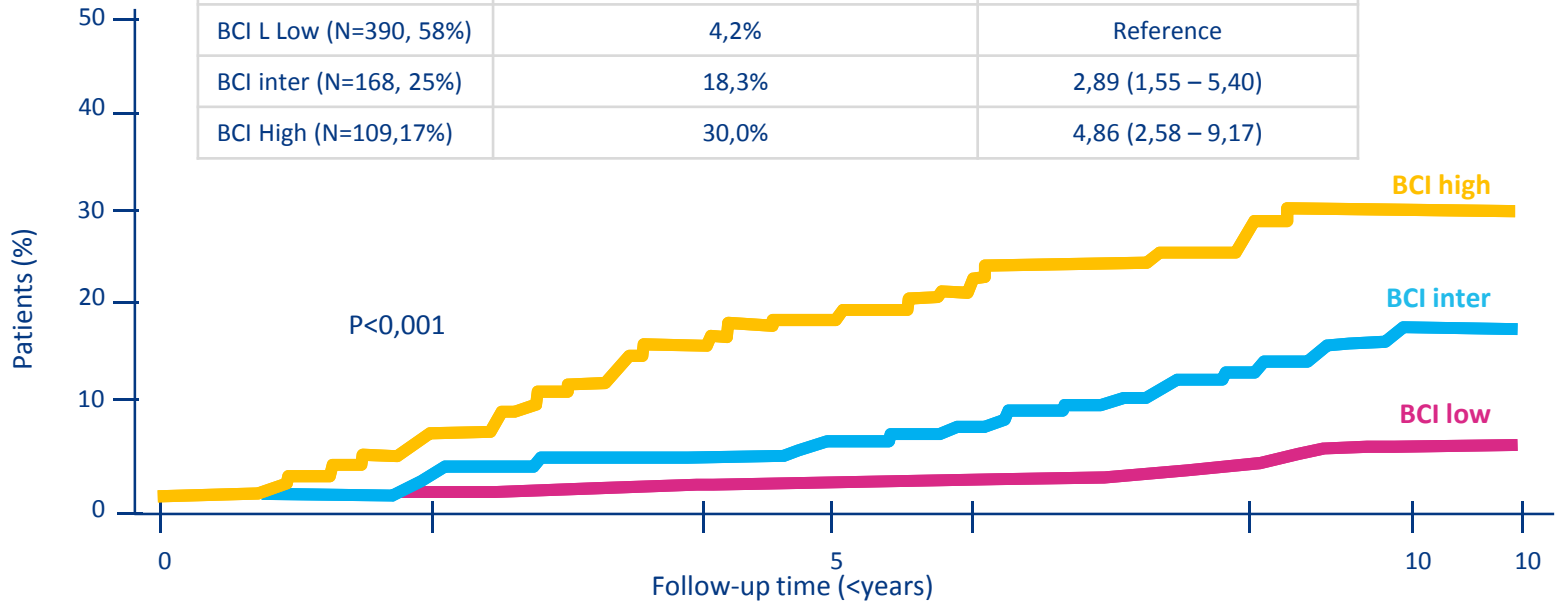
Test for common treatment benefit of adding paclitaxel to AC: P-value=0.30

Comparative performance of breast cancer Index (BCI) vs. Oncotype Dx and IHC4 in the prediction of late recurrence in hormonal receptor-positive lymph node-negative breast cancer patients: A TransATAC Study



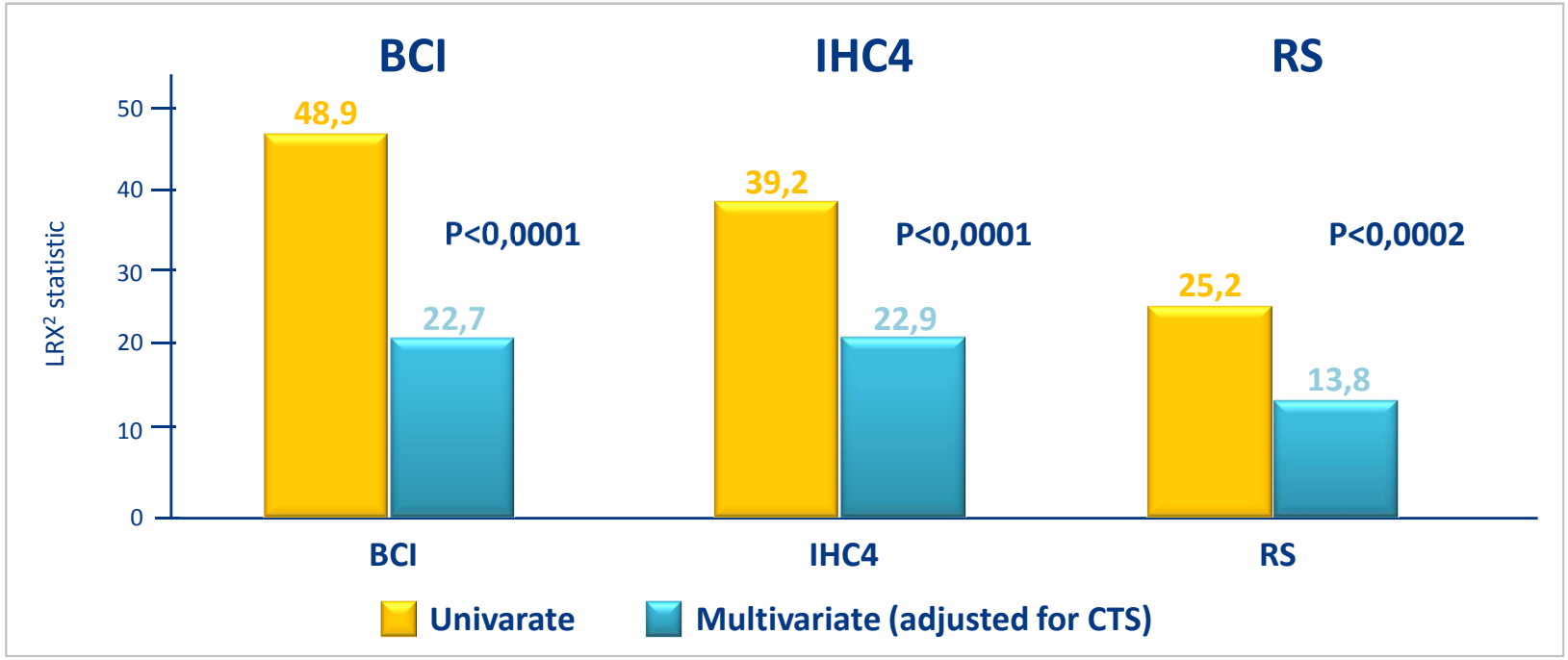
DC Sgroi et *al.*, SABCS 2012, S1-9

All study patients	10-yr rate of distant recurrence	HR(95% CI)(adjused for CTS)
BCI L Low (N=390, 58%)	4,2%	Reference
BCI inter (N=168, 25%)	18,3%	2,89 (1,55 – 5,40)
BCI High (N=109,17%)	30,0%	4,86 (2,58 – 9,17)



- **BCI subdivise la population des cancers du sein N0, RE+, traités par HT en 3 sous-groupe de pronostic distinct**

DC. Sgroi *et al.*, SABCS 2012, S 1-9



- **BCI a une valeur pronostique additionnelle comparable à IHC4,**
- **BCI et IHC4 semblent faire mieux que Oncotype DX**

- **Comme les autres prédicteurs IHC4 et Oncotype DX, BCI prédit la récidive à distance dans les cancers du sein localisés, N0, RE+ recevant une HT**

- **Seul le BCI prédit la récidive à distance tardive dans les cancers du sein localisés, N0, RE+ recevant une HT**

DC. Sgroi *et al.*, SABCS 2012, S 1-9

Les algorythmes

Adjuvant online NPI

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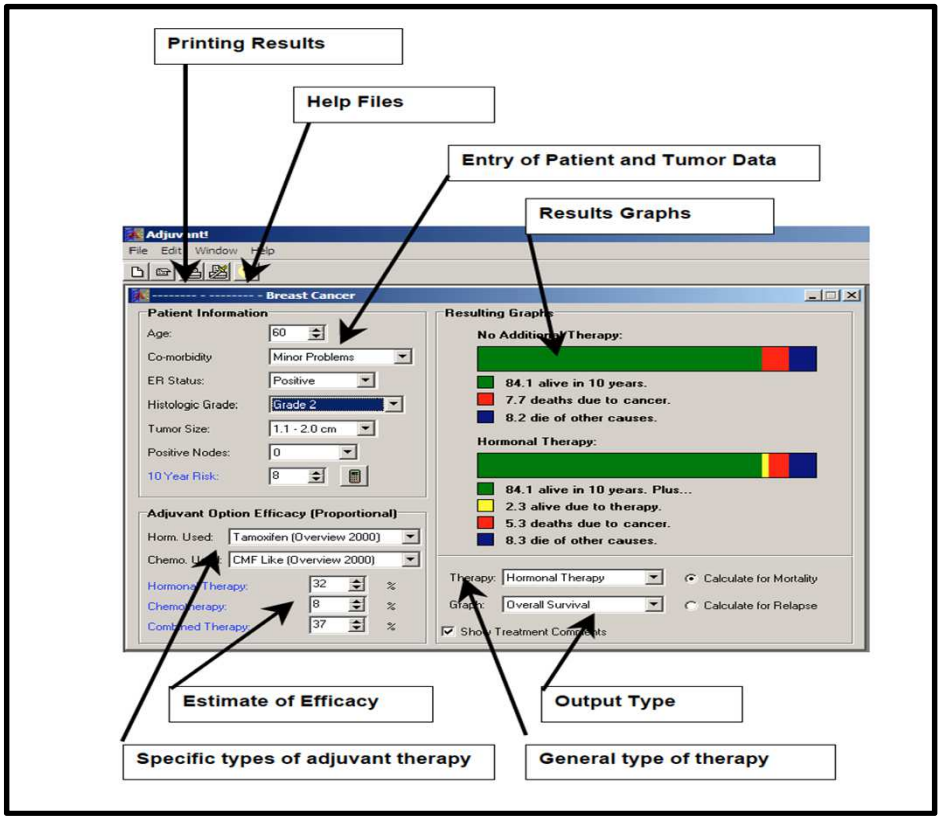
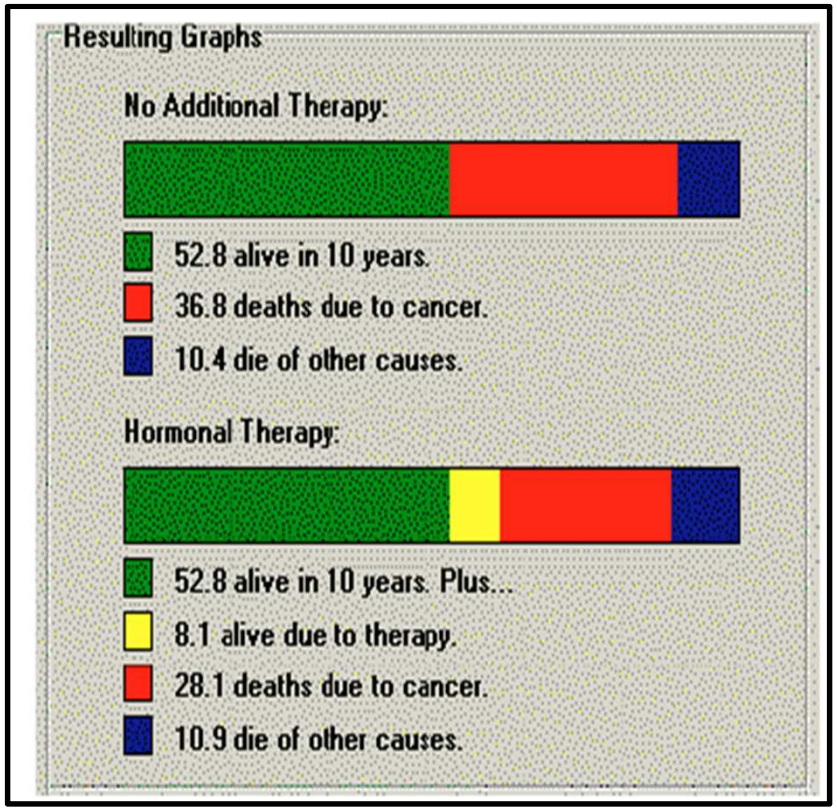
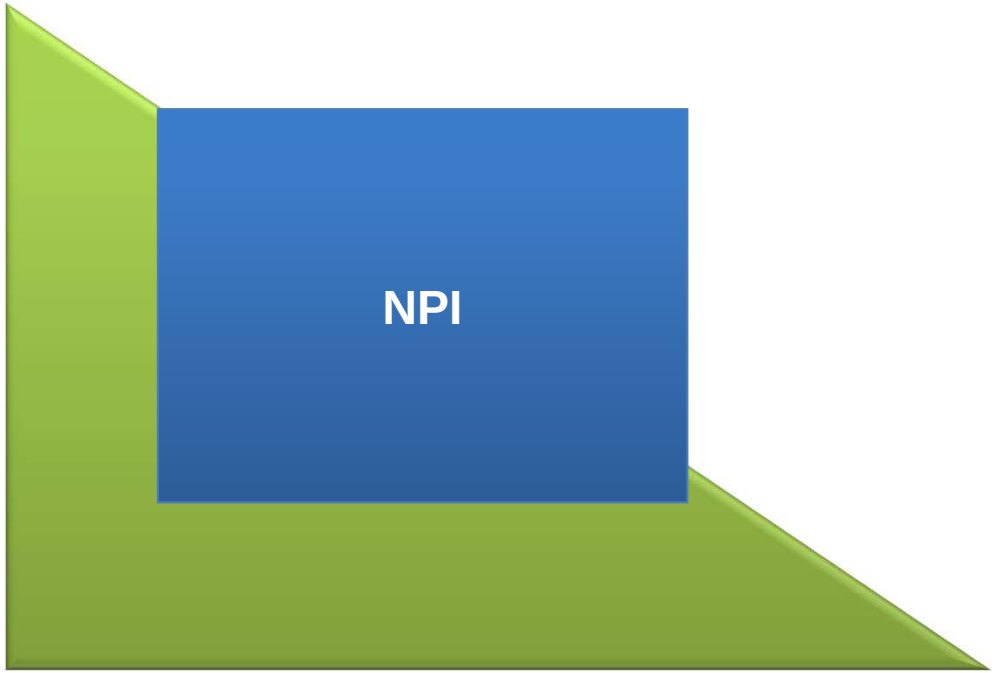
Adjuvant ONLINE

HORMONOSENSIBILITE


Printing Results
Help Files
Entry of Patient and Tumor Data
Results Graphs
Adjuvant!
File Edit Window Help
Breast Cancer
Patient Information
Age: 60
Co-morbidity: Minor Problems
ER Status: Positive
Histologic Grade: Grade 2
Tumor Size: 1.1 - 2.0 cm
Positive Nodes: 0
10 Year Risk: 8
Adjuvant Option Efficacy (Proportional)
Horm. Used: Tamoxifen (Overview 2000)
Chemo. Used: CMF Like (Overview 2000)
Hormonal Therapy: 32 %
Chemotherapy: 8 %
Combined Therapy: 37 %
Resulting Graphs
No Additional Therapy:
84.1 alive in 10 years.
7.7 deaths due to cancer.
8.2 die of other causes.
Hormonal Therapy:
84.1 alive in 10 years. Plus...
2.3 alive due to therapy.
5.3 deaths due to cancer.
8.3 die of other causes.
Therapy: Hormonal Therapy
Graph: Overall Survival
Calculate for Mortality
Calculate for Relapse
Show Treatment Comments
Estimate of Efficacy
Output Type
Specific types of adjuvant therapy
General type of therapy


Resulting Graphs
No Additional Therapy:
52.8 alive in 10 years.
36.8 deaths due to cancer.
10.4 die of other causes.
Hormonal Therapy:
52.8 alive in 10 years. Plus...
8.1 alive due to therapy.
28.1 deaths due to cancer.
10.9 die of other causes.



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The Nottingham Prognostic Index

The Nottingham Prognostic Index was calculated using the following formula: tumor size in cm x 0.2 + lymph-node stage (1, 2 or 3) + histologic grade (1, 2 or 3). When only node negative patients are analysed the lymph-node stage is 1 for all cases. The Nottingham "excellent prognosis" group was defined according to Galea et al. as those patients with an index value = 2.4 (ref).

Nottingham Prognostic Index	Score
Excellent prognosis group	<=2.4
Good prognosis group	<=3.4
Moderate prognosis group	>3.4 and <=5.4
Poor prognosis group	>5.4

Galea MH, Blamey RW, Elston CE, Ellis IO. The Nottingham Prognostic Index in primary breast cancer. Breast Cancer Research & Treatment 1992;22(3):207-19.

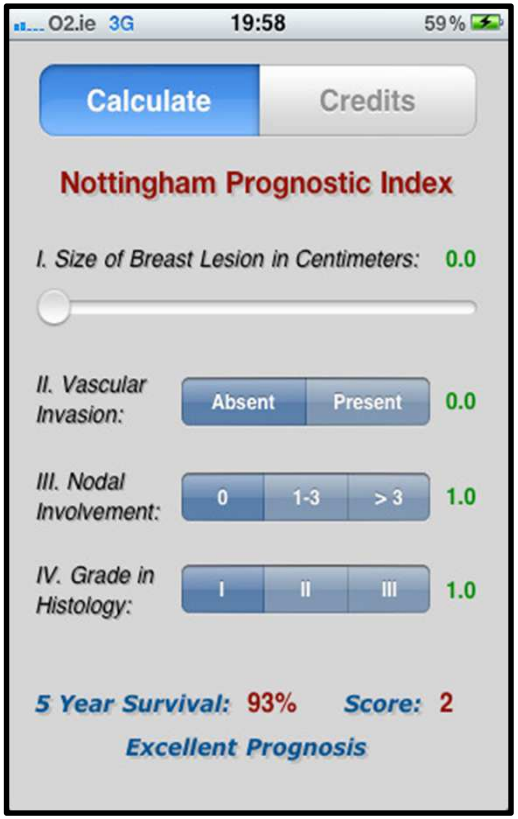
NPI calculator

Tumor size in cm

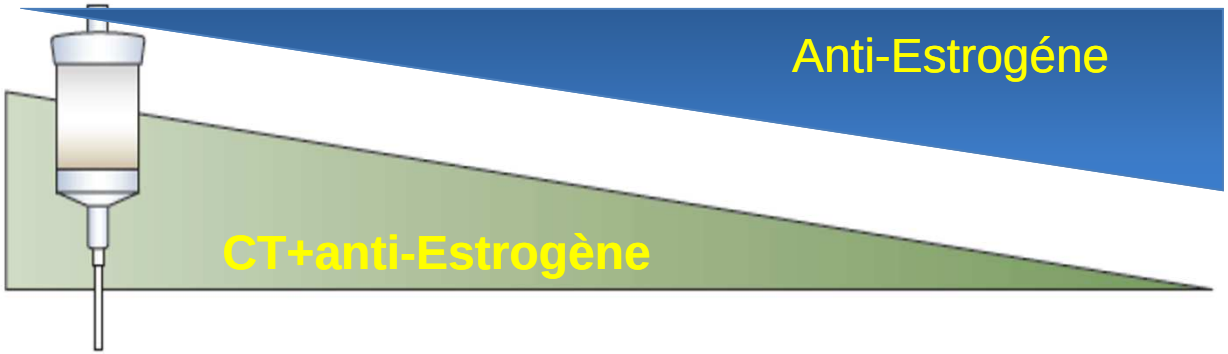
Histologic grade 1

Number of positive axillary lymph nodes 0

Calculate



CONCLUSION



In favor of adjuvant chemotherapy

- ER negative
- Ductal histology
- Grade 3
- High proliferation
- High uPA and PAI1

Against adjuvant chemotherapy

- ER positive
- Lobular histology
- Grade 1
- Low proliferation
- Low uPA and PAI1
- Luminal A

Bedard and Cardoso, Nat Rev Clin Oncol 2011

Institut de Cancérologie de l'Ouest

SYNTHÈSE des recommandations

CANCER DU SEIN INFILTRANT NON METASTATIQUE

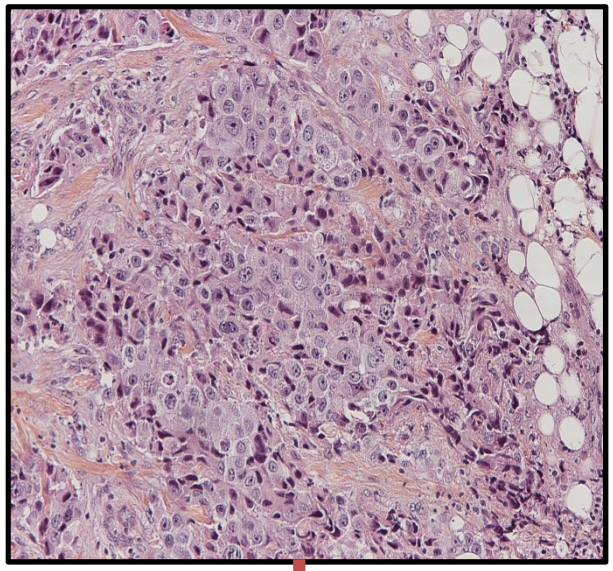
INSTITUT NATIONAL DU CANCER

www.e-cancer.fr

Recommandations

Compte tenu des limites de ces outils, leur utilisation doit être prudente. Il n'est pas recommandé de décider d'un traitement adjuvant à partir de ces seuls outils.

Un Cancer est constitué par : Stroma et cellules néoplasique



Ces signatures explorent essentiellement le compartiment tumorale

Ne tient pas compte des régulation épigénètique

ADN

ARN

Protéines
Corrélation parfaite ?