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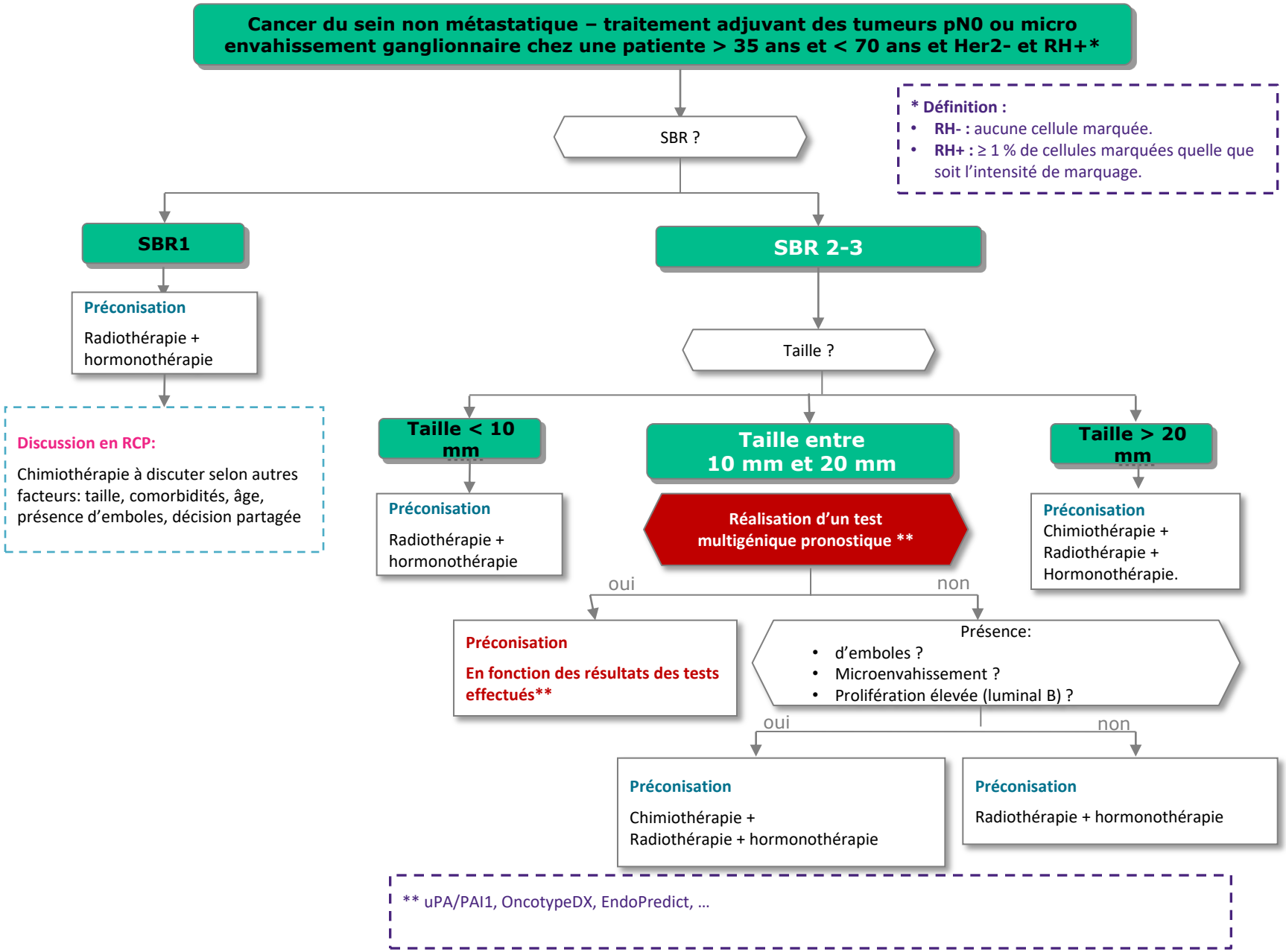
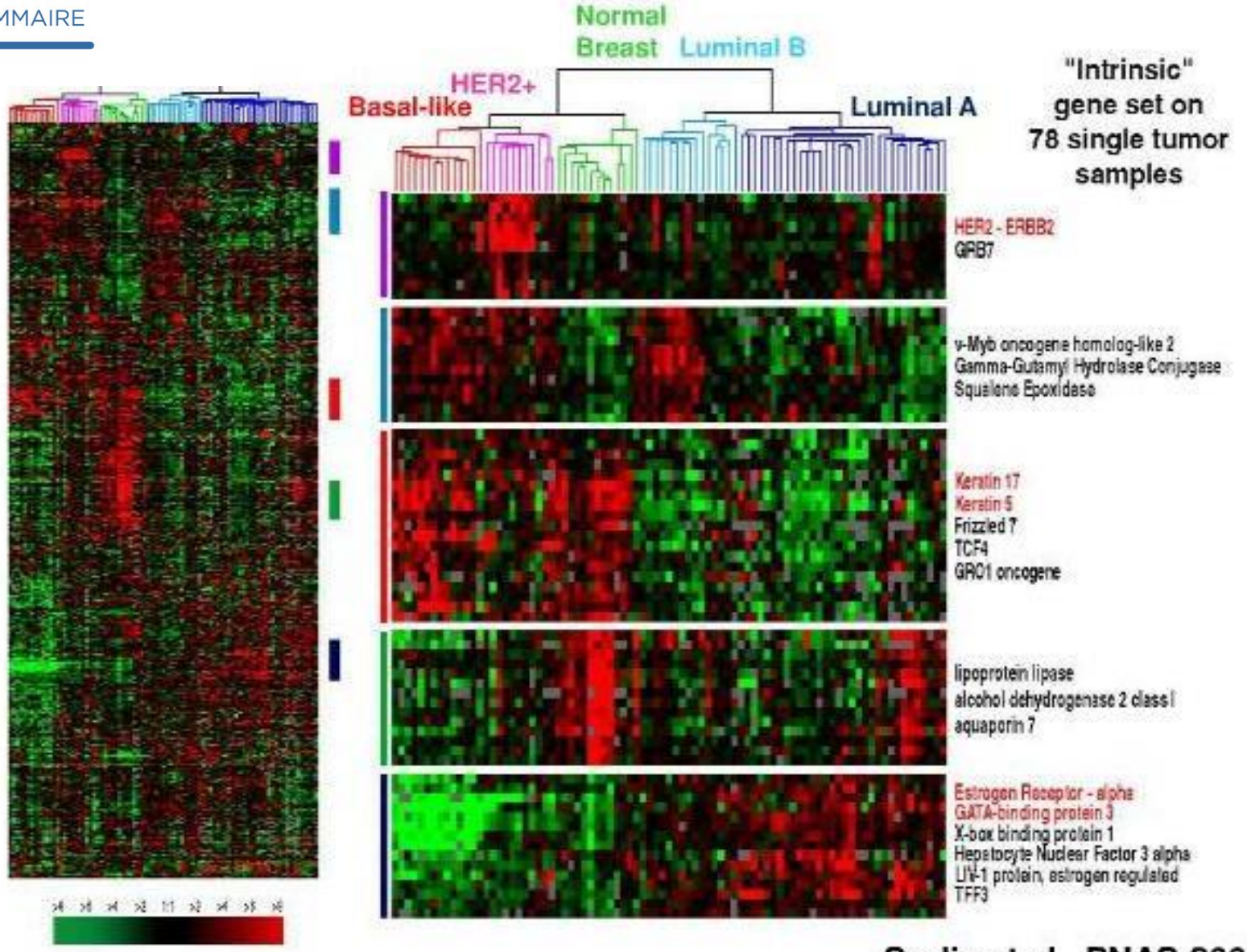
# Quand utiliser les signatures moléculaires pronostiques ?

Olivier Trédan
Centre Léon Bérard






Sorlie et al., PNAS 2001

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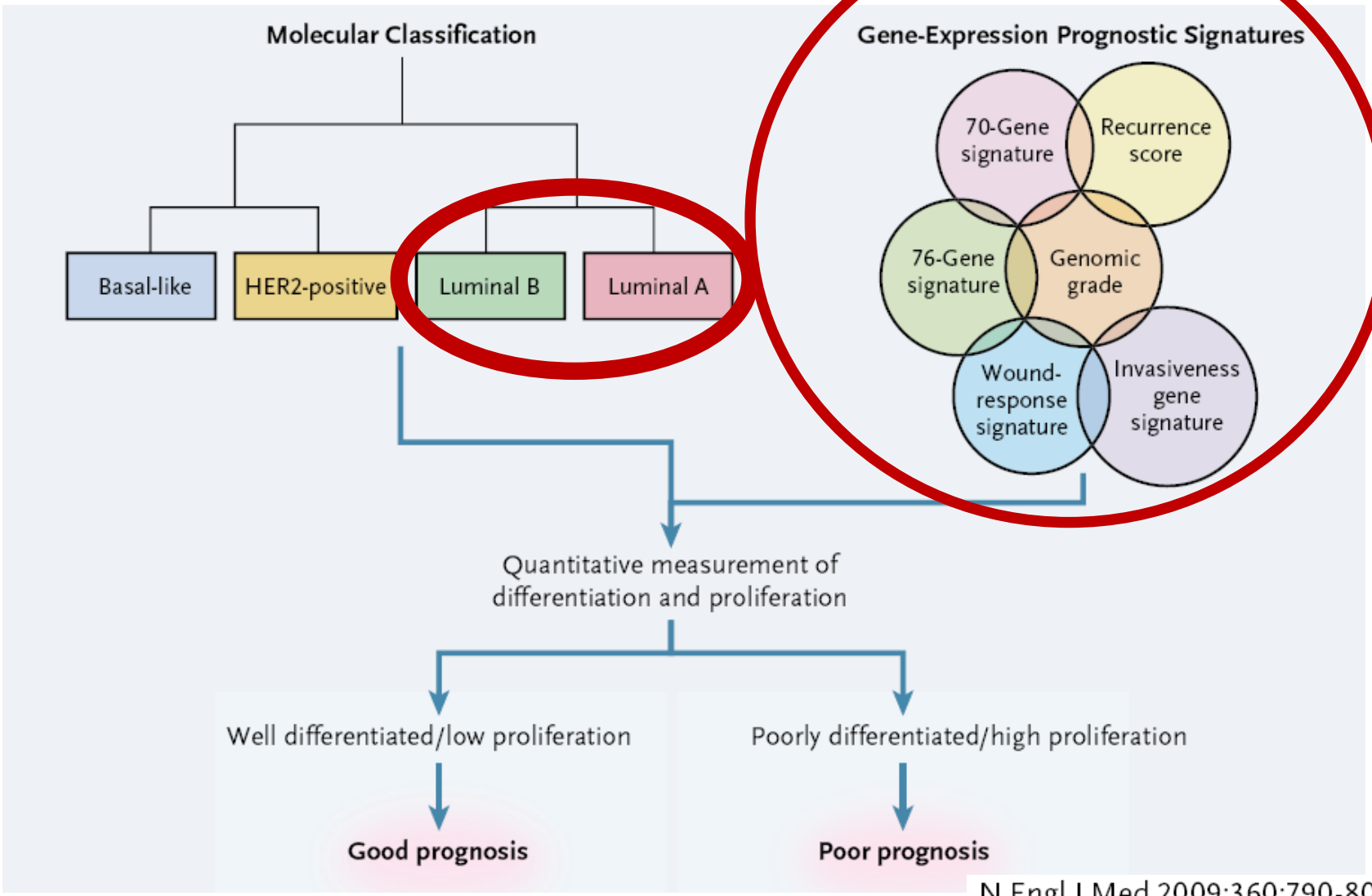


N Engl J Med 2009;360:790-800.



Christos Sotiriou & Lajos Pusztai

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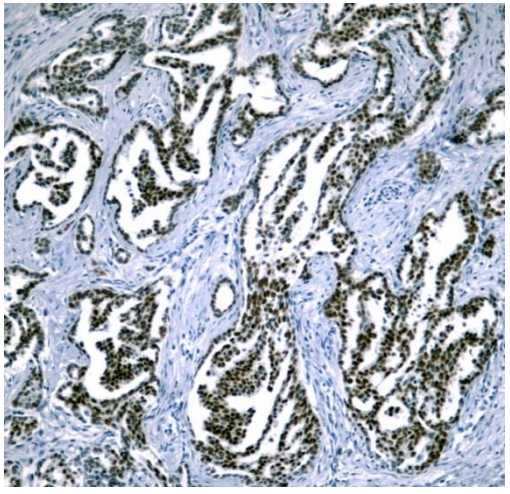
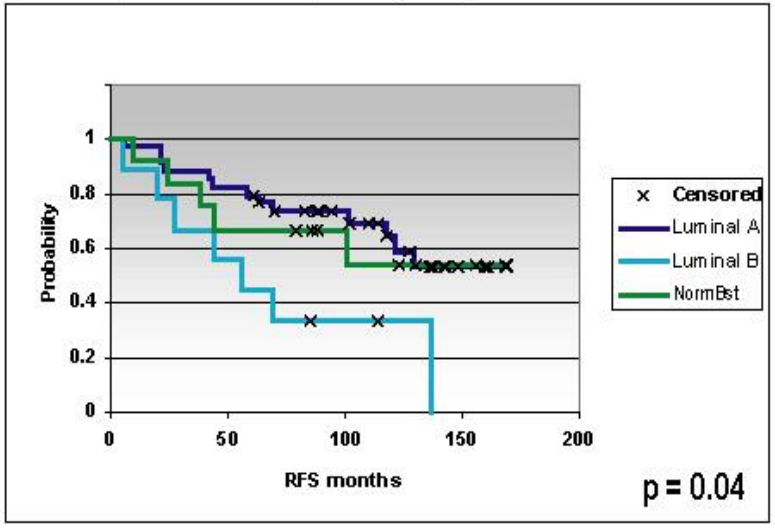


## Luminal A

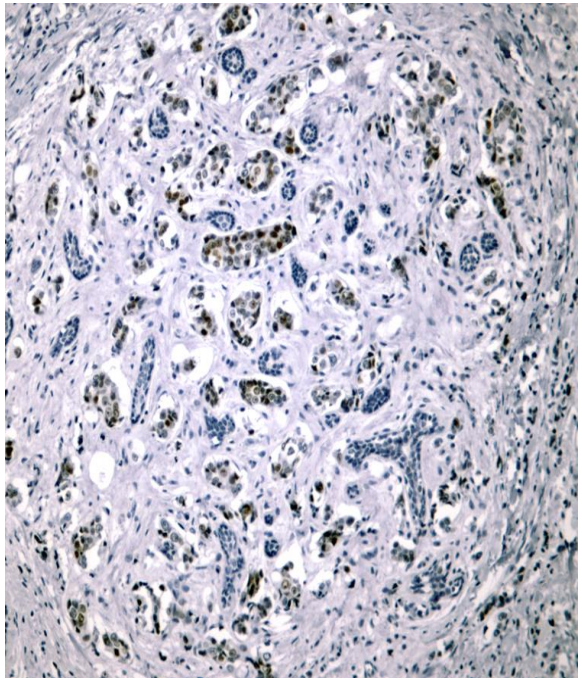
- RE+
- Et tous
  - RP +
  - HER2 -
  - Ki67 bas
  - bas risque molec

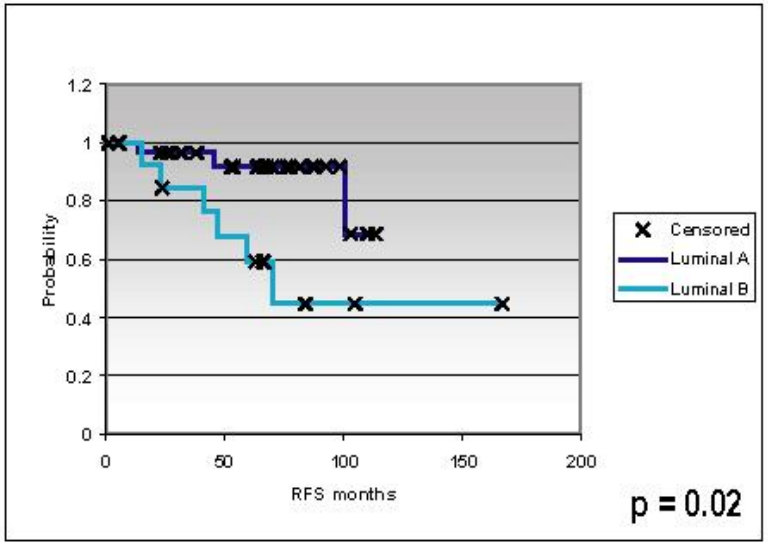
60 Sample ER+ Tamoxifen-Treated Test Set
Ma et al., Cancer Cell 5, 1-10 (2004).




## Luminal B

- RE+
- Et au moins
  - RP faible
  - Ki67 élevé
  - Haut risque molec






45 Tamoxifen Treated Test Set #2
Chang et al., PNAS 102, 3738-43 (2005) + UNC

## Luminal B HER2 +

- RE+, HER2 3+
- Quelque soit RP
- Quelque soit Ki67

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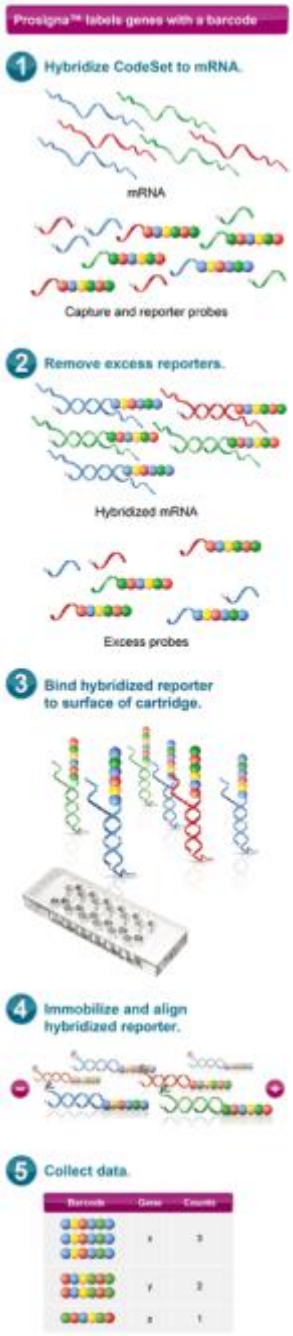
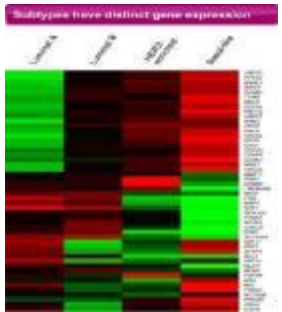
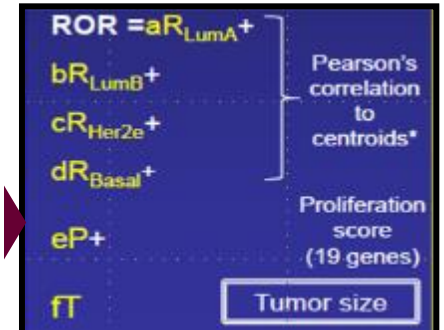
# Prosigna (PAM50)

(NanoString Technology, USA )




**RECONNAISSANCE DES SOUS-TYPES « MOLECULAIRES » (LumA, LumB, HER2-enrichi, Basal)**

## tissu fixé, inclus en paraffine

**puce ADN avec le signal numérique (1 gène = 1 code bar)**

## 50 GENES SELECTIONNES

## TEST « LOCAL »

**(l'analyse se fait dans les laboratoires avec équipements spécifique )**

**SIGNATURE**

## RECHUTE TARDIVE (à 10 ans)

## BAS RISQUE (ROR)

**+ HORMONOTHERAPIE / - CHIMIOTHERAPIE**

## RISQUE INTERMEDIAIRE (ROR)

## HAUT RISQUE (ROR)

**+ HORMONOTHERAPIE / + CHIMIOTHERAPIE**

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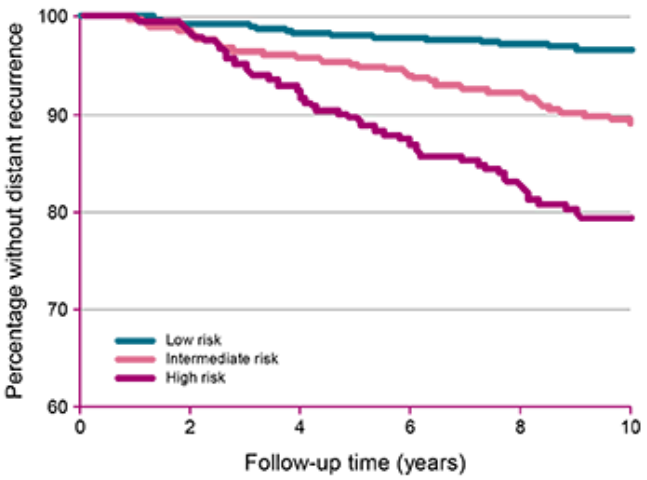
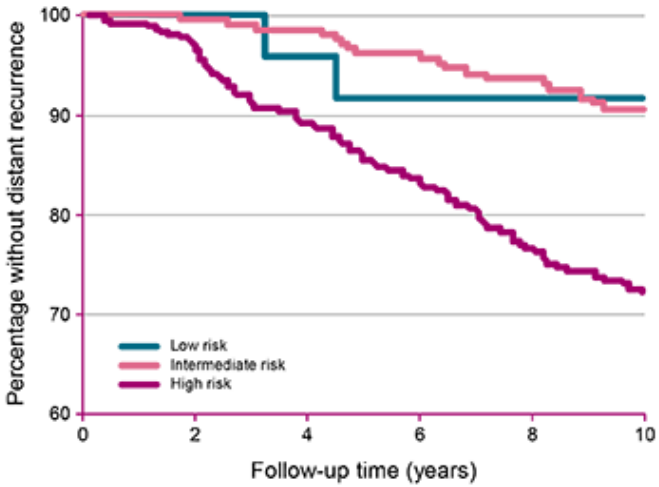
# Prosigna (PAM50)
## (NanoString Technology, USA )




DRFS in node-negative patients[1]




DRFS in patients with 1 to 3 positive nodes[1]

**RISQUE BAS : >95% DE SURVIE SANS RECHUTE (Dg + 10 ans)**
**RISQUE HAUT : <80% DE SURVIE SANS RECHUTE (Dg + 10 ans)**

**N0**

TransATAC + ABCSG-8 : **2400 pts**
RH+ / HER2- T1-2 N0/N+ postménop 5 ans d'anti-œstrogènes adj
tous les groupes de risque
tous les sous-types moléculaires

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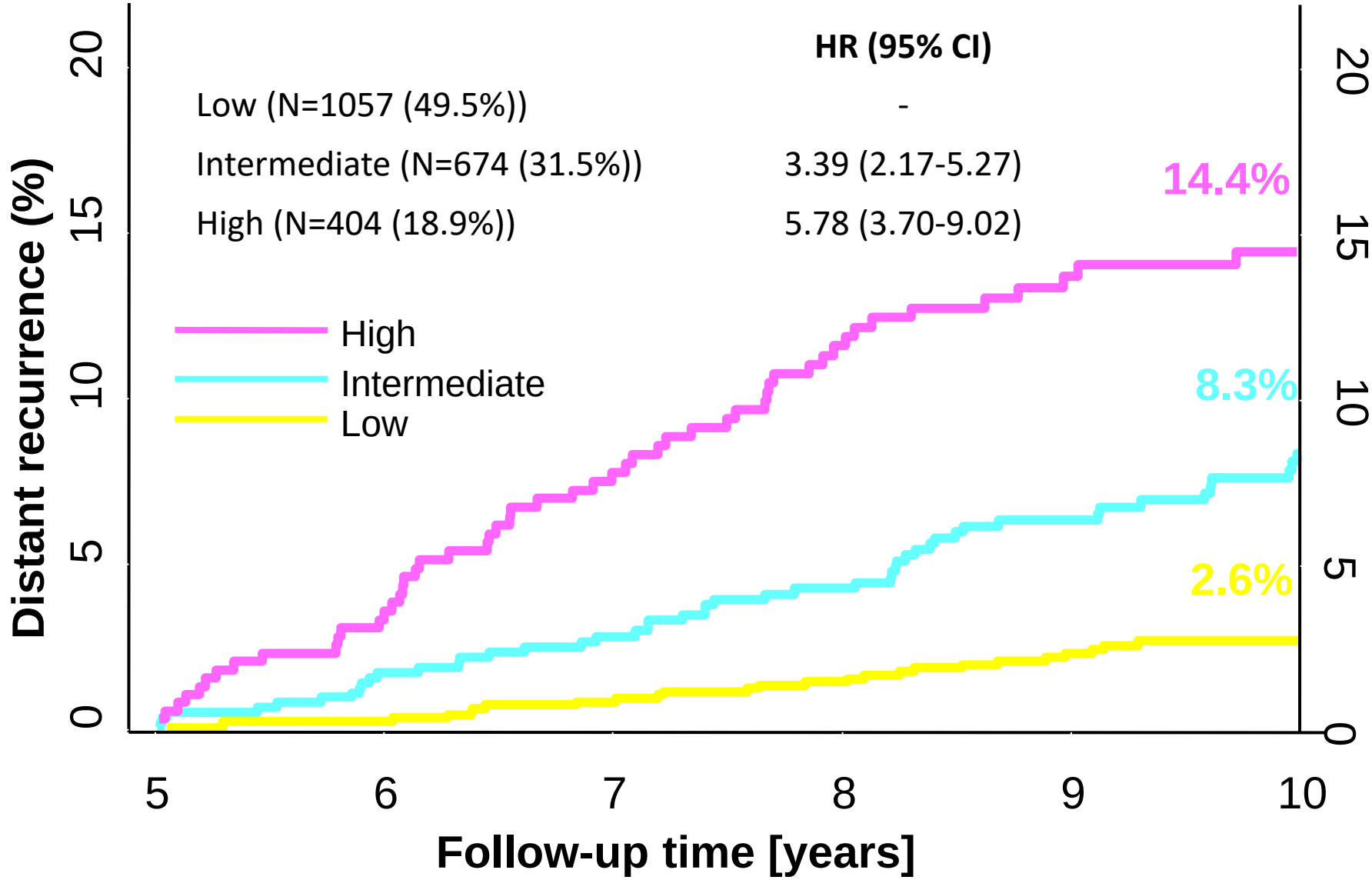
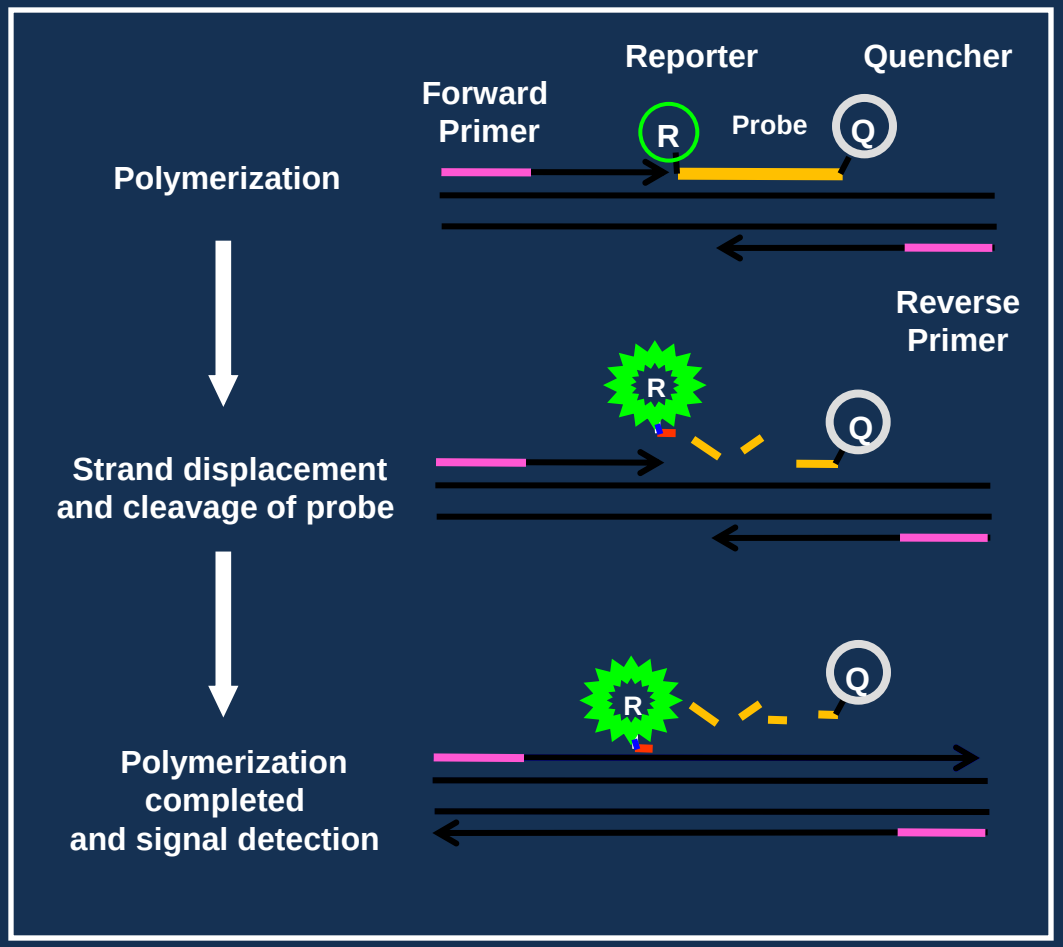
# Prosigna (PAM50)
## pour les rechutes tardives



# Oncotype DX® Uses RT-PCR Technology and is Analytically Validated




- RT-PCR works well with RNA from formalin-fixed paraffin-embedded tissue
- RT-PCR provides >65,000-fold range of measurement
- RT-PCR reactions can be repeated with high quantitative precision
- Standardized RT-PCR optimized for use of small RNA fragments and various sources of pre-analytical variability

# Oncotype DX® Recurrence Score

## 16 CANCER RELATED GENES

| Estrogen | Proliferation | HER2 | Invasion | Others |
|---|---|---|---|---|
| ER<br>PR<br>Bcl2<br>SCUBE2 | Ki-67<br>STK15<br>Survivin<br>Cyclin B1<br>MYBL2 | GRB7<br>HER2 | Stromelysin 3<br>Cathepsin L2 | CD68<br>GSTM1<br>BAG1 |

## 5 REFERENCE GENES

| Beta-actin | GAPDH | RPLPO | GUS | TFRC |
|---|---|---|---|---|



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

# Oncotype DX® Recurrence Score Calculation and Risk Categories

**Recurrence Score =**

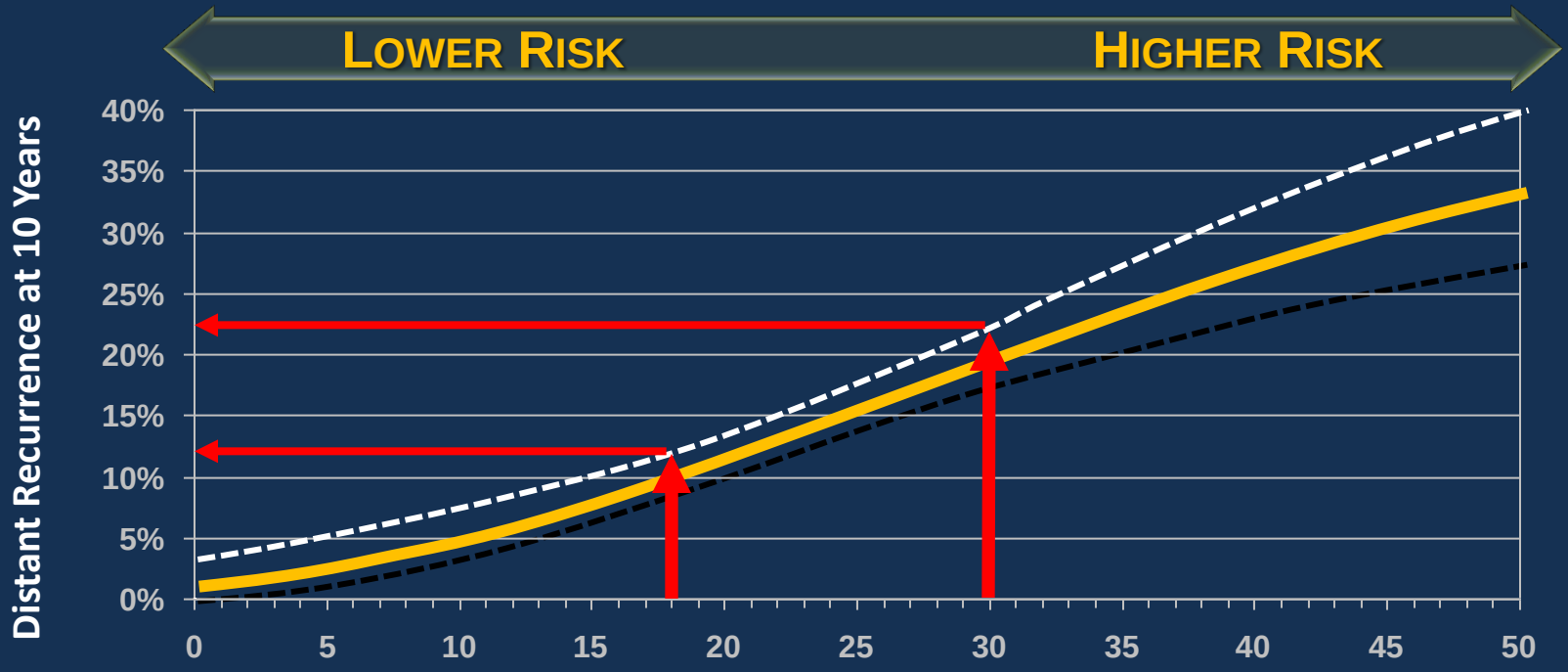
**+ 0.47 x HER2 Group Score**
**- 0.34 x Estrogen Group Score**
**+ 1.04 x Proliferation Group Score**
**+ 0.10 x Invasion Group Score**
**+ 0.05 x CD68**
**- 0.08 x GSTM1**
**- 0.07 x BAG1**

| ***Risk Group*** | ***Recurrence Score*** |
|---|---|
| **Low risk** | **<18** |
| **Intermediate risk** | **18 - 30** |
| **High risk** | **≥31** |



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

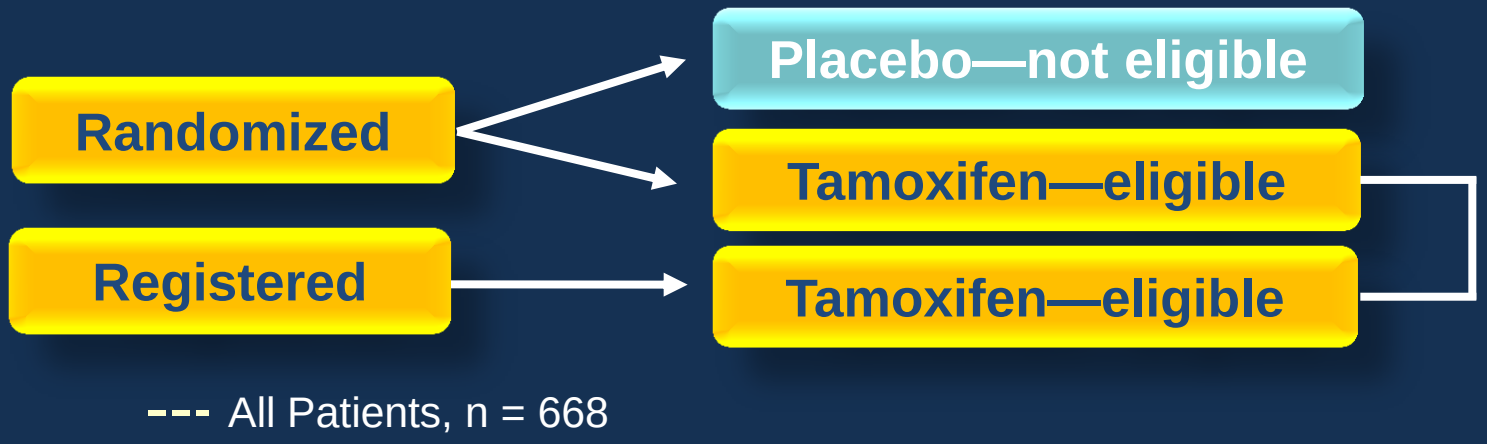
# Oncotype DX® Recurrence Score Calculation and Risk Categories




| | |
|---|---|
| **Low risk** | Recurrence Score **<18** |
| **Intermediate risk** | **18 - 30** |
| **High risk** | **≥31** |

# Oncotype DX® Clinical Validation: NSABP B-14

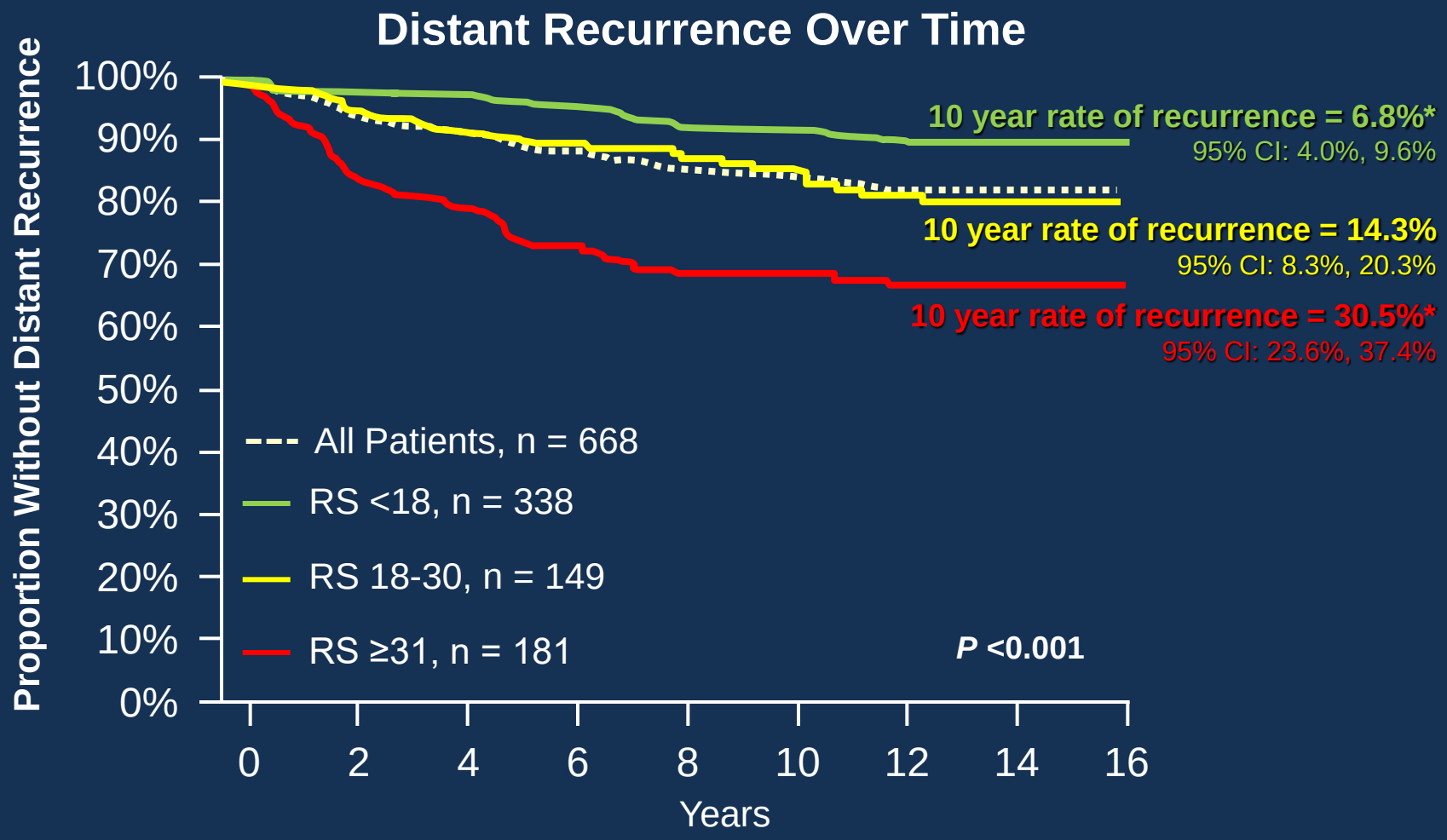
- Objective: Prospectively validate Recurrence Score as predictor of distant recurrence in N–, ER+ patients






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

# Oncotype DX® Clinical Validation:
## NSABP B-14 – Distant Recurrence

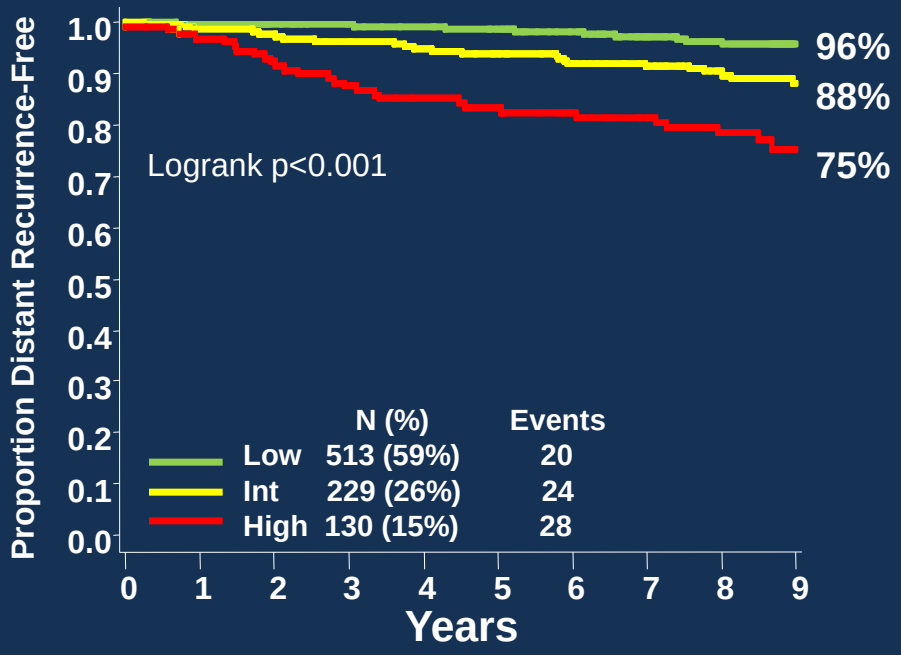



*10-year Distant Recurrence comparison between low-and high-risk groups: *P* <0.001

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

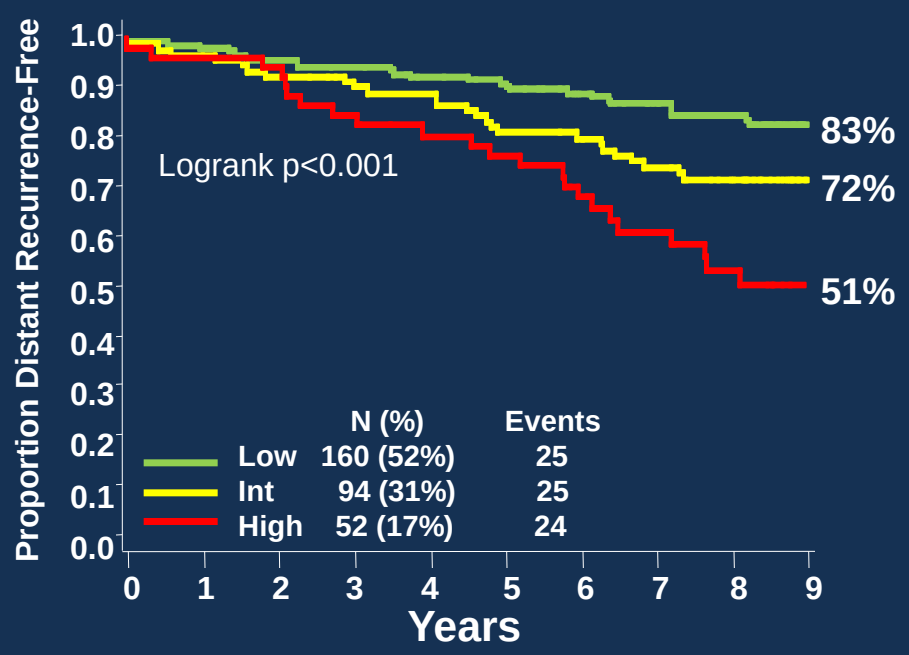
# Oncotype DX® Clinical Validation: TransATAC

## Node Negative (n=872) (both treatment arms)




| RS Group | HR* (95% CI) |
|---|---|
| High vs Low | 5.2 (2.7 – 10.1) |
| Int vs Low | 2.5 (1.3 – 4.5) |

## Node Positive (n=306) (both treatment arms)




| RS Group | HR* (95% CI) |
|---|---|
| High vs Low | 2.7 (1.5 – 5.1) |
| Int vs Low | 1.8 (1.0 – 3.2) |

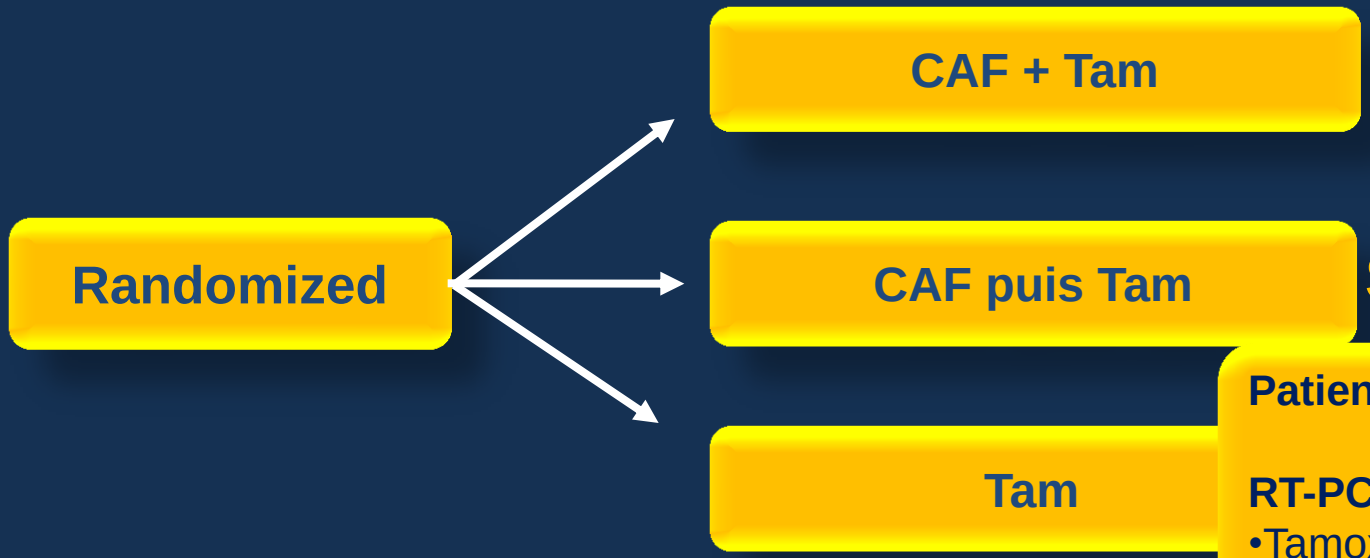
***Hazard Ratio for RS Group adjusted for tumor size, grade, age and treatment**



Dowsett M, et al. SABCS 2008; abstract 53.

# Oncotype DX® Clinical Validation:
## SWOG 8814 sub-analysis

- Objective: To determine the relationship between RS and chemotherapy benefit in **N+,** ER+ patients




**SUB ANALYSIS**

**Patients with samples (n=666)**

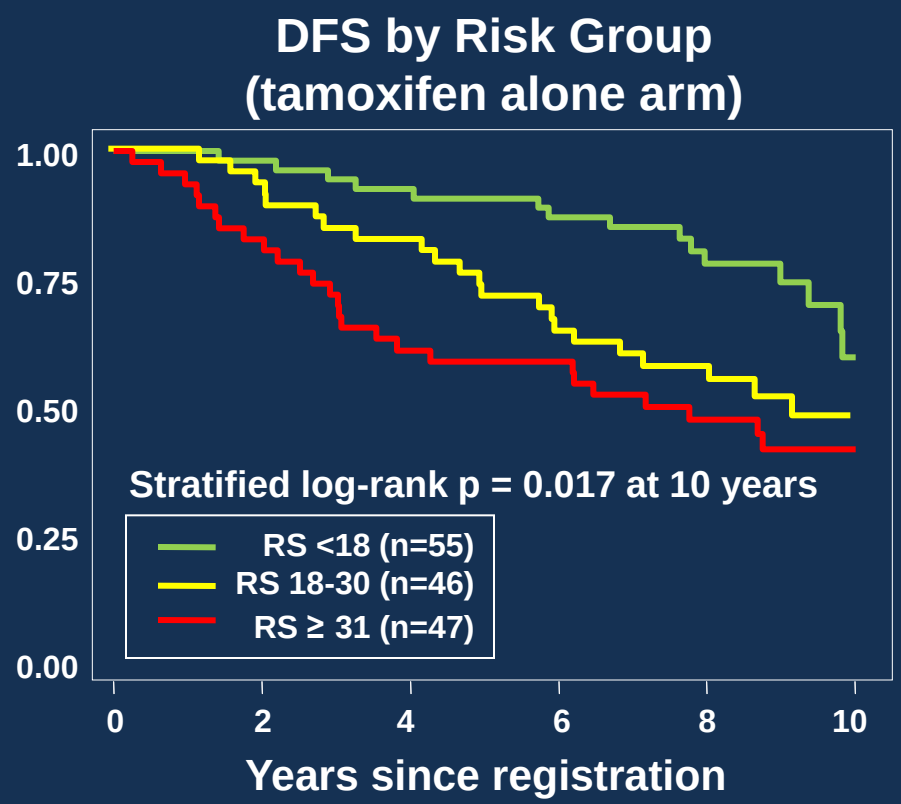
**RT-PCR obtained (n=601)**
- Tamoxifen alone (n=148)
- CAF + T (n=243)
- CAF → T (n=219)

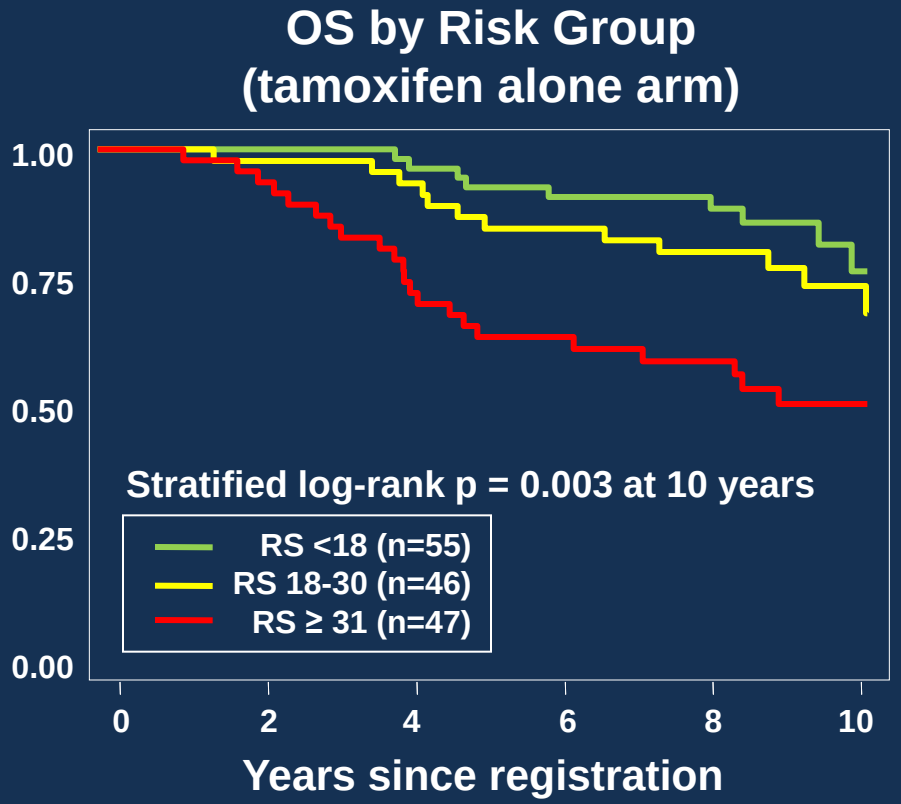
**Sample for primary analysis**
- 148 + 219 = 367

(40% of parent trial)

Albain, SABCS 2007, Abstract #10

# Oncotype DX® Clinical Validation:
## SWOG 8814 sub-analysis for N+ pts on Tam




**10-year DFS: 60%, 49%, 43%**

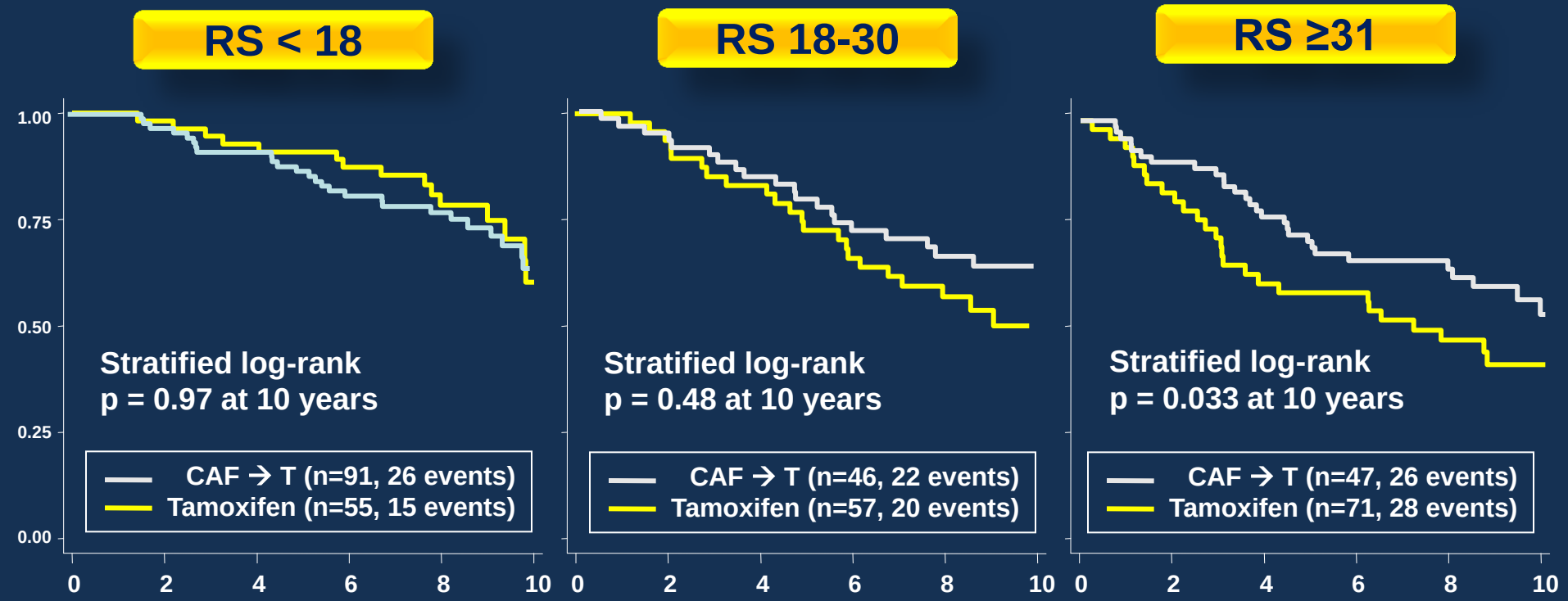
**10-year OS: 77%, 68%, 51%**



Albain, SABCS 2007, Abstract #10

# High Recurrence Score Predictive of Chemotherapy Benefit in Node-Positive Patients

## DFS BY TREATMENT & RS GROUP




No benefit to CAF over time if low RS

Strong benefit if high RS

Albain, SABCS 2007, Abstract #10

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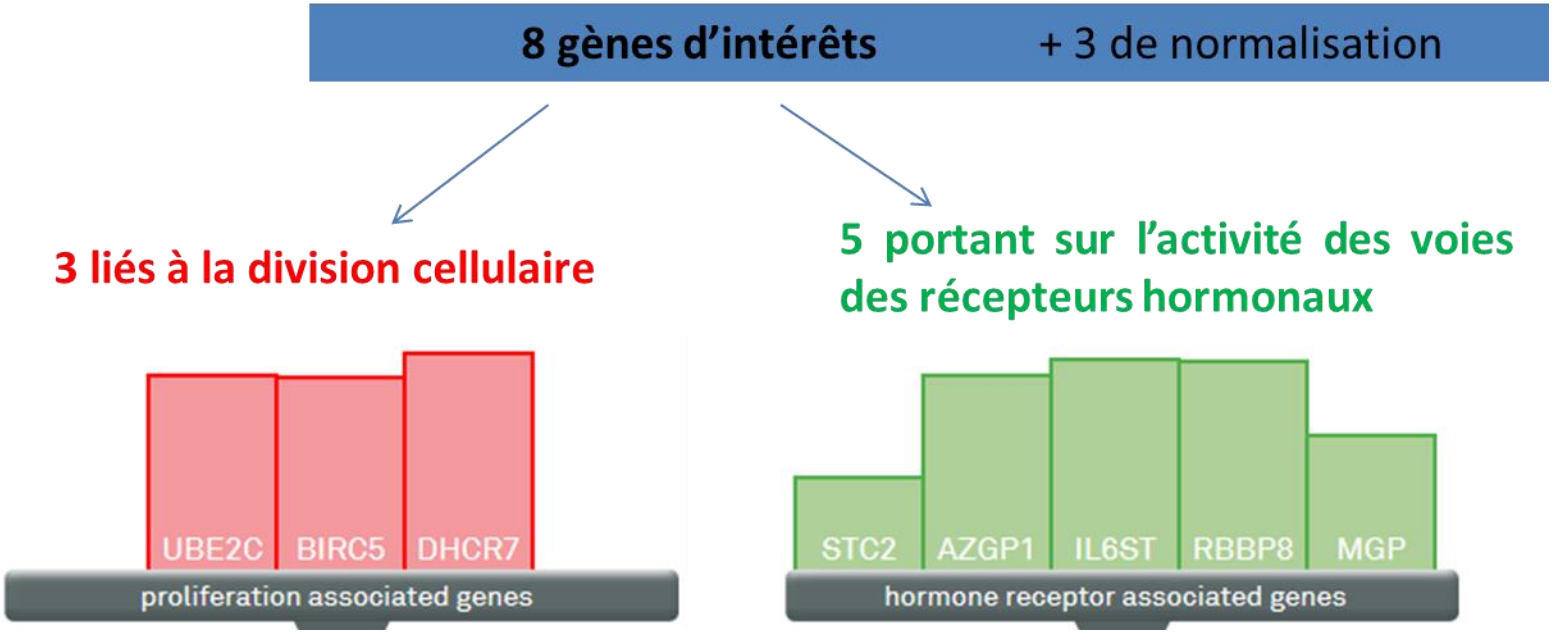
# Test EndoPredict

- **Il s'agit d'un test d'expression génique par RT-PCR à partir d'un échantillon tumoral fixé dans de la paraffine**
- 12 gènes spécifiques sont testés



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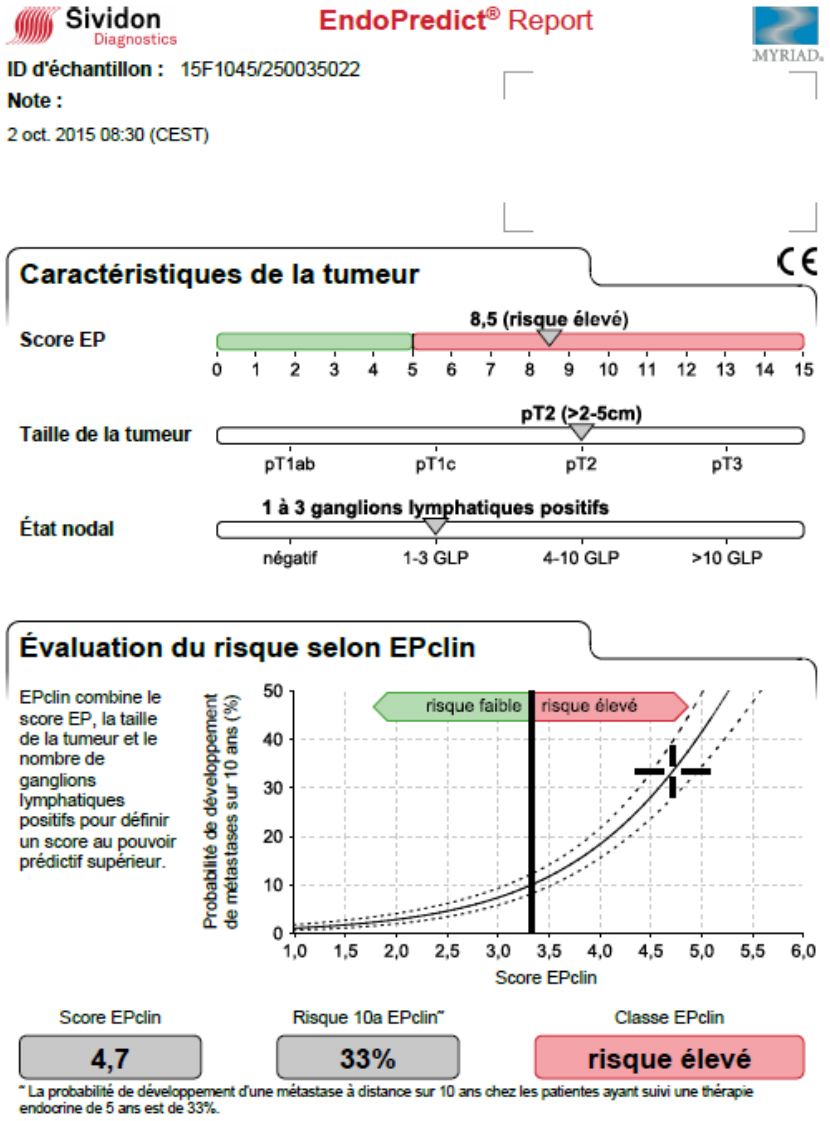
# Test EndoPredict

- Classification du **risque selon le EP score**
  - Bas
  - Elevé
- Classification du **risque selon le EPclin score**
  (EP score + T + N)
  - Bas
  - Elevé
- Détermination de la **probabilité d'une rechute à distance à 10 ans** selon le EPclin score
  - 0-100 %



# Rapport type EndoPredict®

Sividon Diagnostics

## EndoPredict® Report

MYRIAD

**ID d'échantillon :**

**Note :**

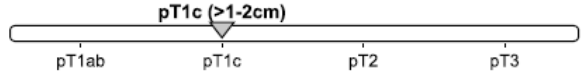
9 juin 2016 14:32 (CEST)

### Caractéristiques de la tumeur

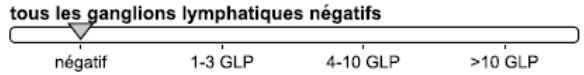
CE

**Score EP**


**Taille de la tumeur**

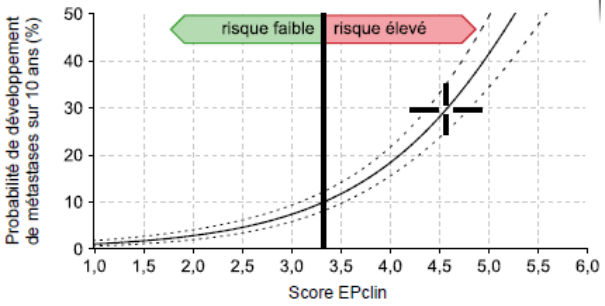



**État nodal**




### Évaluation du risque selon EPclin

EPclin combine le score EP, la taille de la tumeur et le nombre de ganglions lymphatiques positifs pour définir un score au pouvoir prédictif supérieur.




| Score EPclin | Risque 10a EPclin˜ | Classe EPclin |
|---|---|---|
| 4,6 | 30% | risque élevé |

˜ La probabilité de développement d'une métastase à distance sur 10 ans chez les patientes ayant suivi une thérapie endocrine de 5 ans est de 30%.

**Validation par le pathologiste**

Les contrôles indiqués ont été effectués et le résultat du test est valide.

**Signature autorisée**

Basé sur : Filipits et al. (2011): A new molecular predictor of distant recurrence in ER-positive, HER2-negative breast cancer adds independent information to conventional clinical risk factors. Clinical Cancer Research 17: 6012-6020.


Sividon Diagnostics

EndoPredict® Report

MYRIAD

**ID d'échantillon :**

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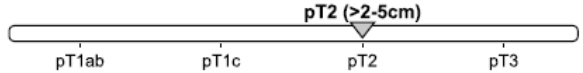
9 juin 2016 14:32 (CEST)


### Caractéristiques de la tumeur

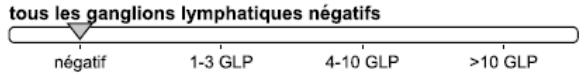
CE

**Score EP**


**Taille de la tumeur**




**État nodal**

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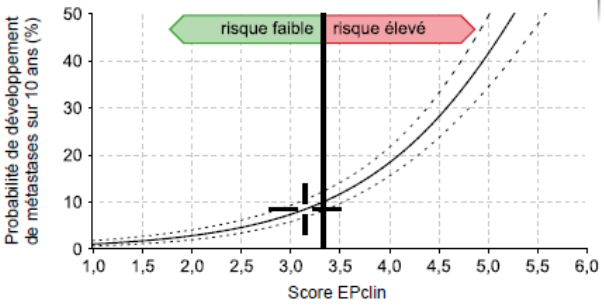


| Score EPclin | Risque 10a EPclin˜ | Classe EPclin |
|---|---|---|
| 3,1 | 8% | risque faible |

˜ La probabilité de développement d'une métastase à distance sur 10 ans chez les patientes ayant suivi une thérapie endocrine de 5 ans est de 8%.


**Validation par le pathologiste**

Les contrôles indiqués ont été effectués et le résultat du test est valide.

**Signature autorisée**

Basé sur : Filipits et al. (2011): A new molecular predictor of distant recurrence in ER-positive, HER2-negative breast cancer adds independent information to conventional clinical risk factors. Clinical Cancer Research 17: 6012-6020.

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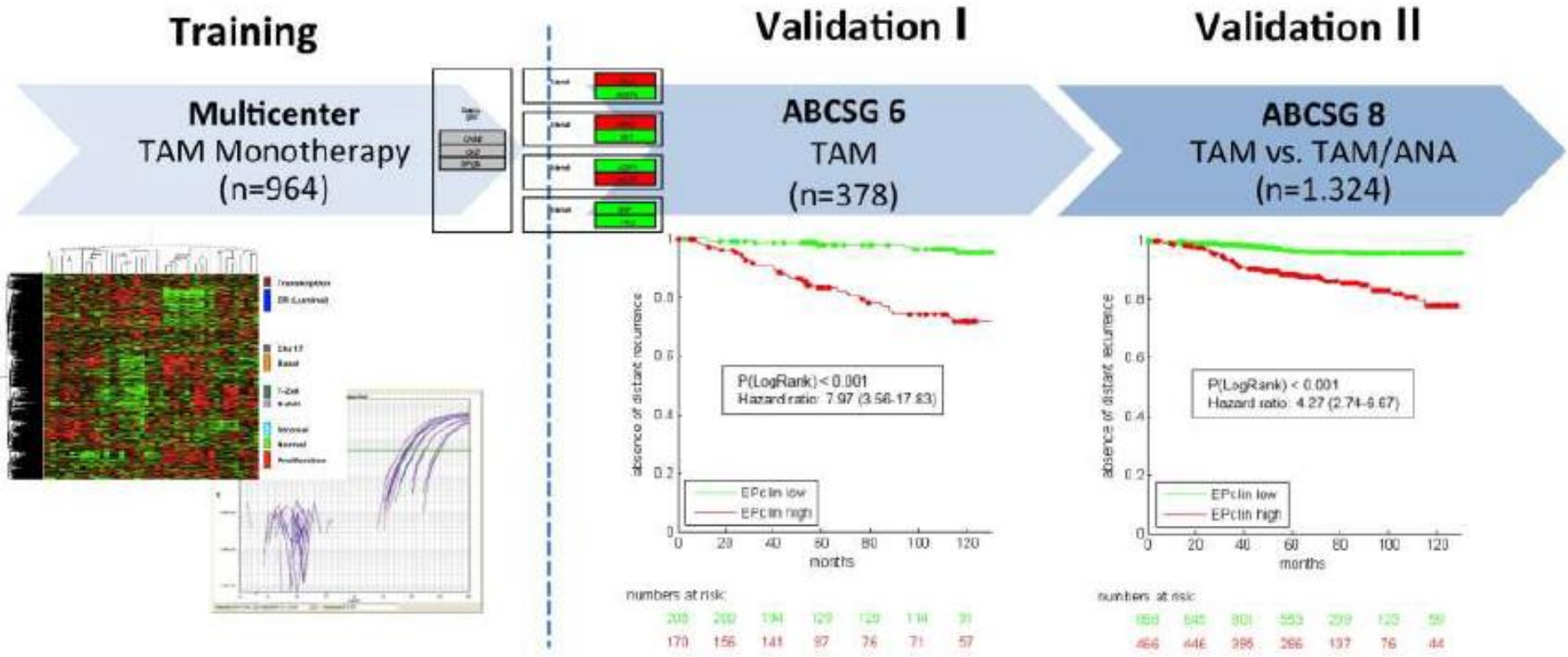
# Test EndoPredict




- **Validated in two independent prospective-retrospective studies**
- **Evidence level: Ib (according to Simon et al., J Natl Cancer Inst, 2009)**

Filipits et al., Clin Cancer Res. 2011
Dubsky et al., Ann Oncol. 2012

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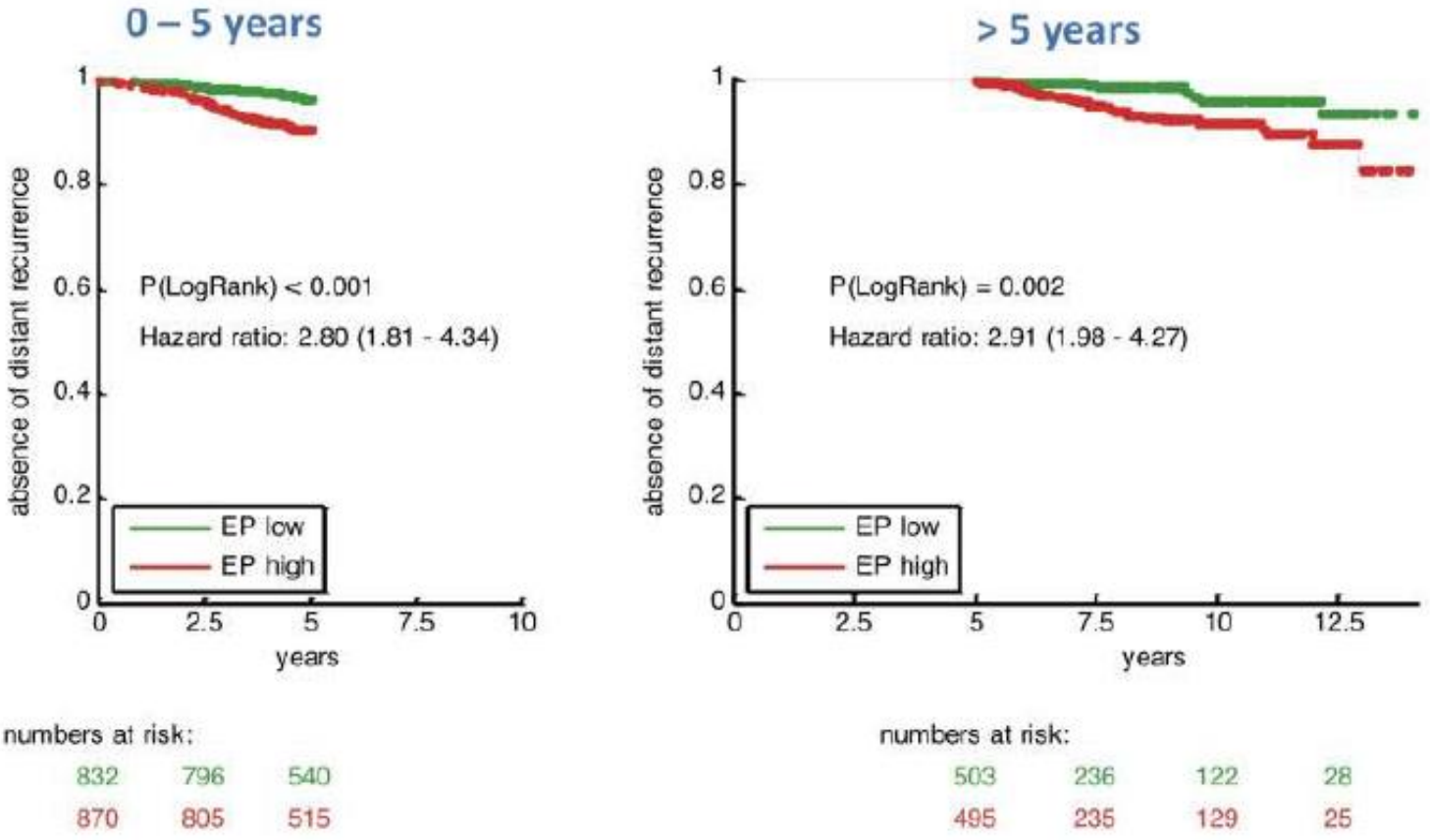
# Test EndoPredict

## Results




- The EndoPredict low-risk group (49%) had a significantly improved clinical outcome before and after 5 years of follow-up. 96.3% were free of distant metastases between 5 and 10 years in the EP low risk group.

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# Test EndoPredict

**Clinical validation of the EndoPredict test in node-positive chemotherapy-treated ER+/HER2- breast cancer patients: results from the GEICAM/9906 trial**

*Breast Cancer Research* 2014, **16**:R38 doi:10.1186/bcr3642

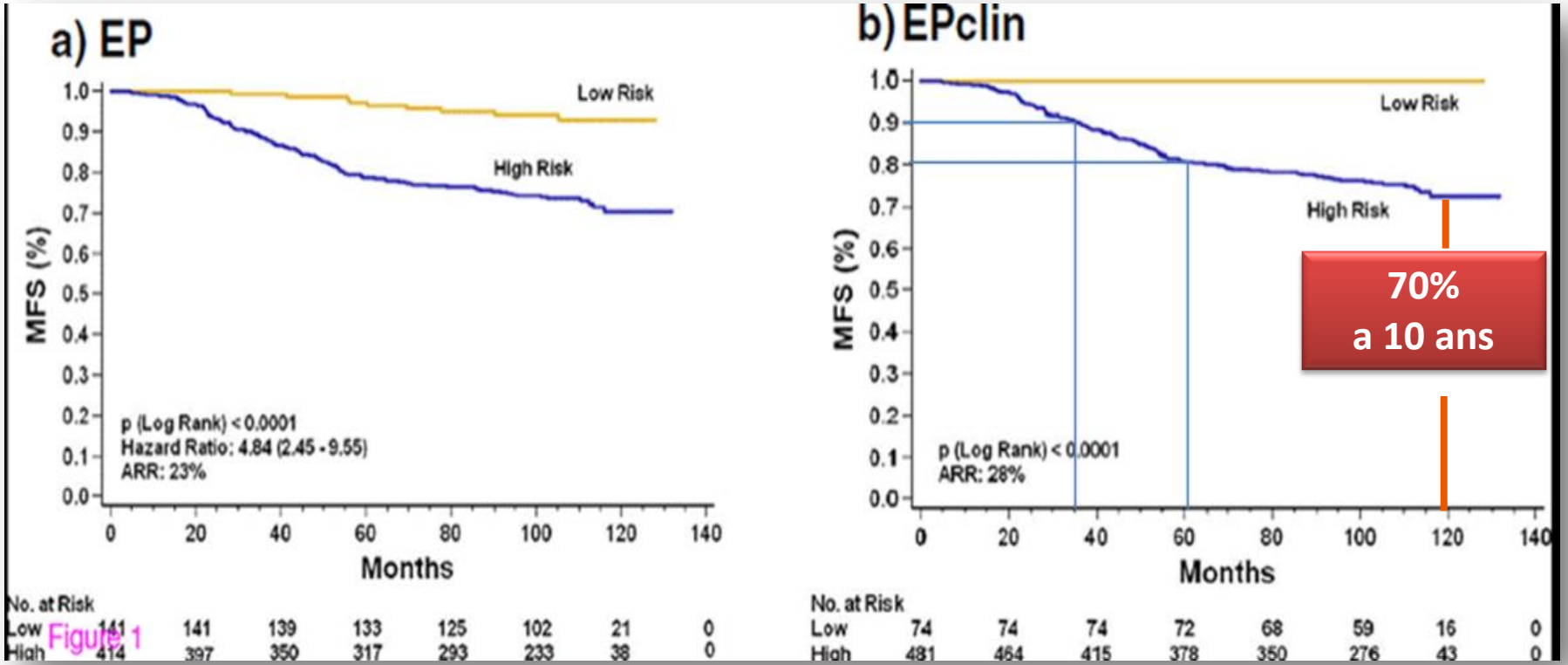


Figure 1

**EP low vs high risk**

**EPclin low vs high risk**

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*JAMA Oncol*. doi:10.1001/jamaoncol.2017.5524
Published online February 15, 2018.

JAMA Oncology | Original Investigation

# Comparison of the Performance of 6 Prognostic Signatures for Estrogen Receptor–Positive Breast Cancer
## A Secondary Analysis of a Randomized Clinical Trial

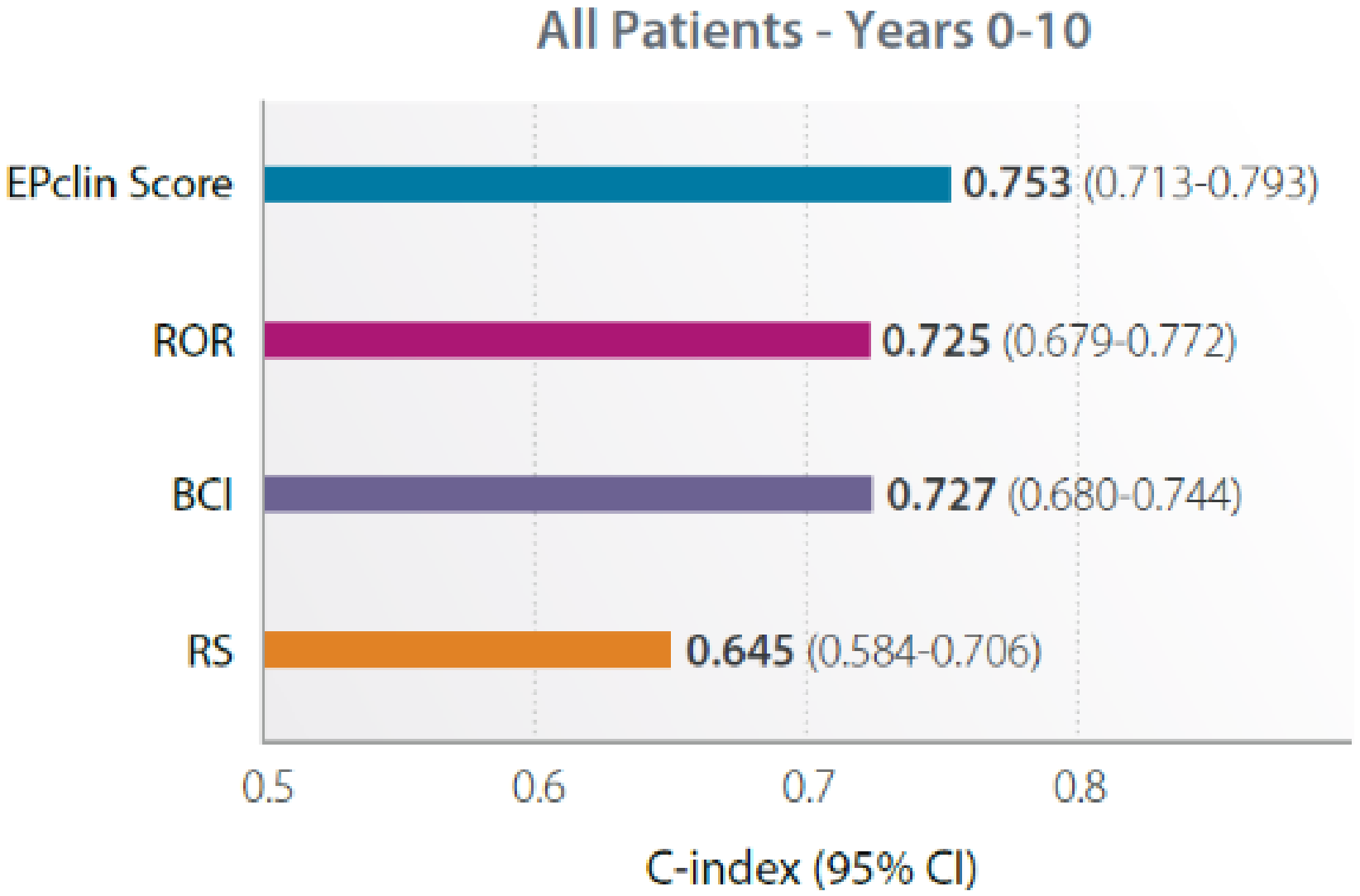
Ivana Sestak, PhD; Richard Buus, PhD; Jack Cuzick, PhD; Peter Dubsky, MD; Ralf Kronenwett, MD; Carsten Denkert, MD; Sean Ferree, PhD; Dennis Sgroi, MD; Catherine Schnabel, PhD; Frederick L. Baehner, MD; Elizabeth Mallon, PhD; Mitch Dowsett, PhD

- Patient group:
  - primary breast cancer; ER+, HER2-; node negative and positive; postmenopausal
- Treatment:
  - 5 years endocrine therapy only (tamoxifen or anastrozole monotherapy)
- Number of patients: 774
    - N0: 591 (76%)
    - N+ 1-3: 183 (24%)
- Primary endpoint: Time to distant recurrence
- Median follow-up: 10 years

## eTable 1. Baseline Characteristics According to Nodal Status

| | Node-negative (N=591) | Node-positive (N=183) |
|---|---|---|
| **Mean age, years (SD)** | 63.4 (7.9) | 66.4 (8.3) |
| **Mean BMI, kg/m$^2$ (SD)** | 27.3 (4.9) | 26.7 (4.7) |
| **Grade** | | |
| 1 | 23.2% | 21.9% |
| 2 | 59.7% | 58.5% |
| 3 | 17.1% | 19.7% |
| **Mean tumour size, mm (SD)** | 17.6 (8.5) | 24.2 (12.2) |
| **Distant recurrence** | | |
| **0-10 years** | 58 (9.8%) | 40 (21.9%) |
| **5-10 years** | 34/535 (6.4%) | 21/154 (13.6%) |

SD=Standard Deviation, kg-kilogram, m=metre, mm=millimetre


All Patients - Years 0-10
EPclin Score
0.753 (0.713-0.793)
ROR
0.725 (0.679-0.772)
BCI
0.727 (0.680-0.744)
RS
0.645 (0.584-0.706)
0.5
0.6
0.7
0.8
C-index (95% CI)

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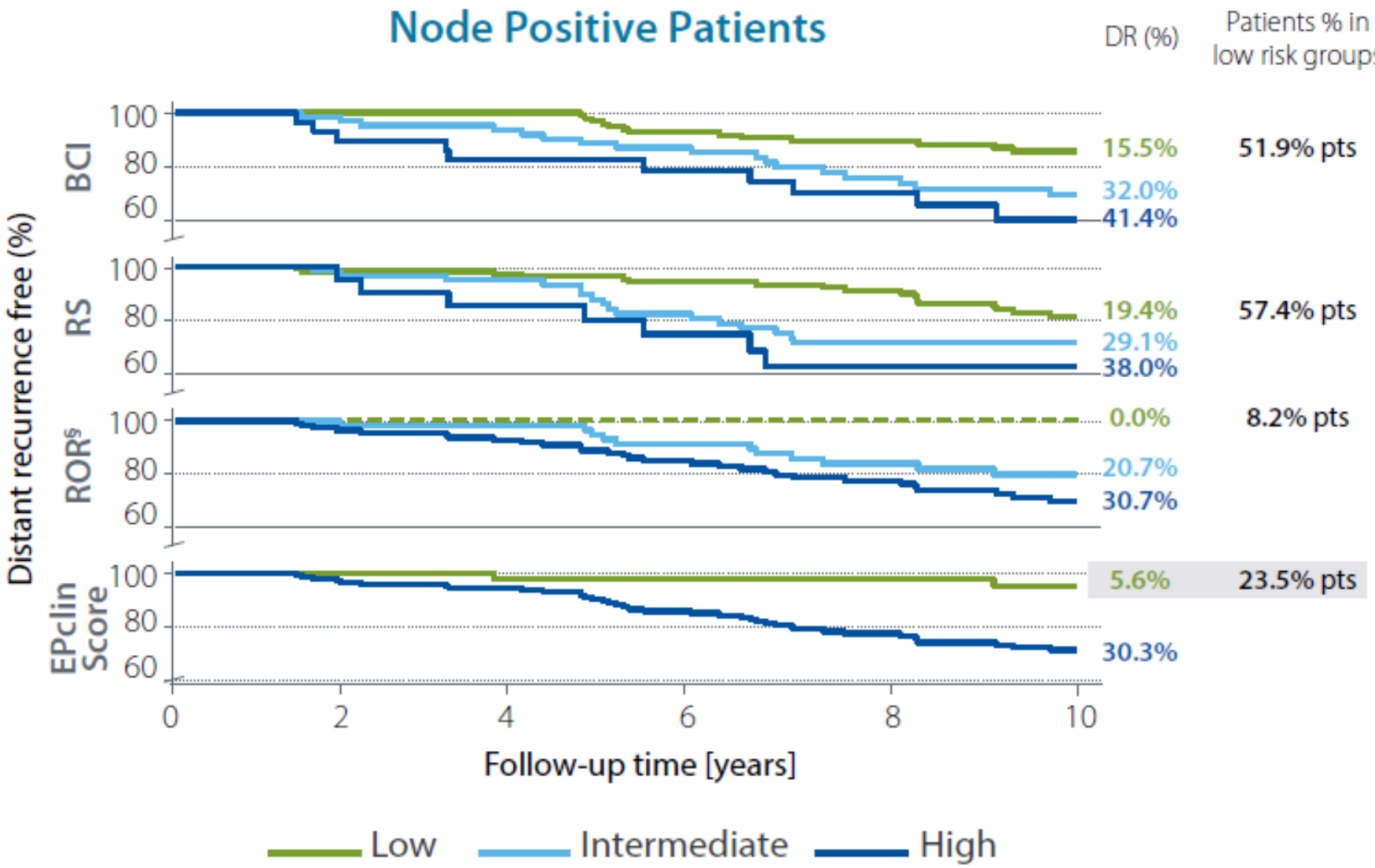
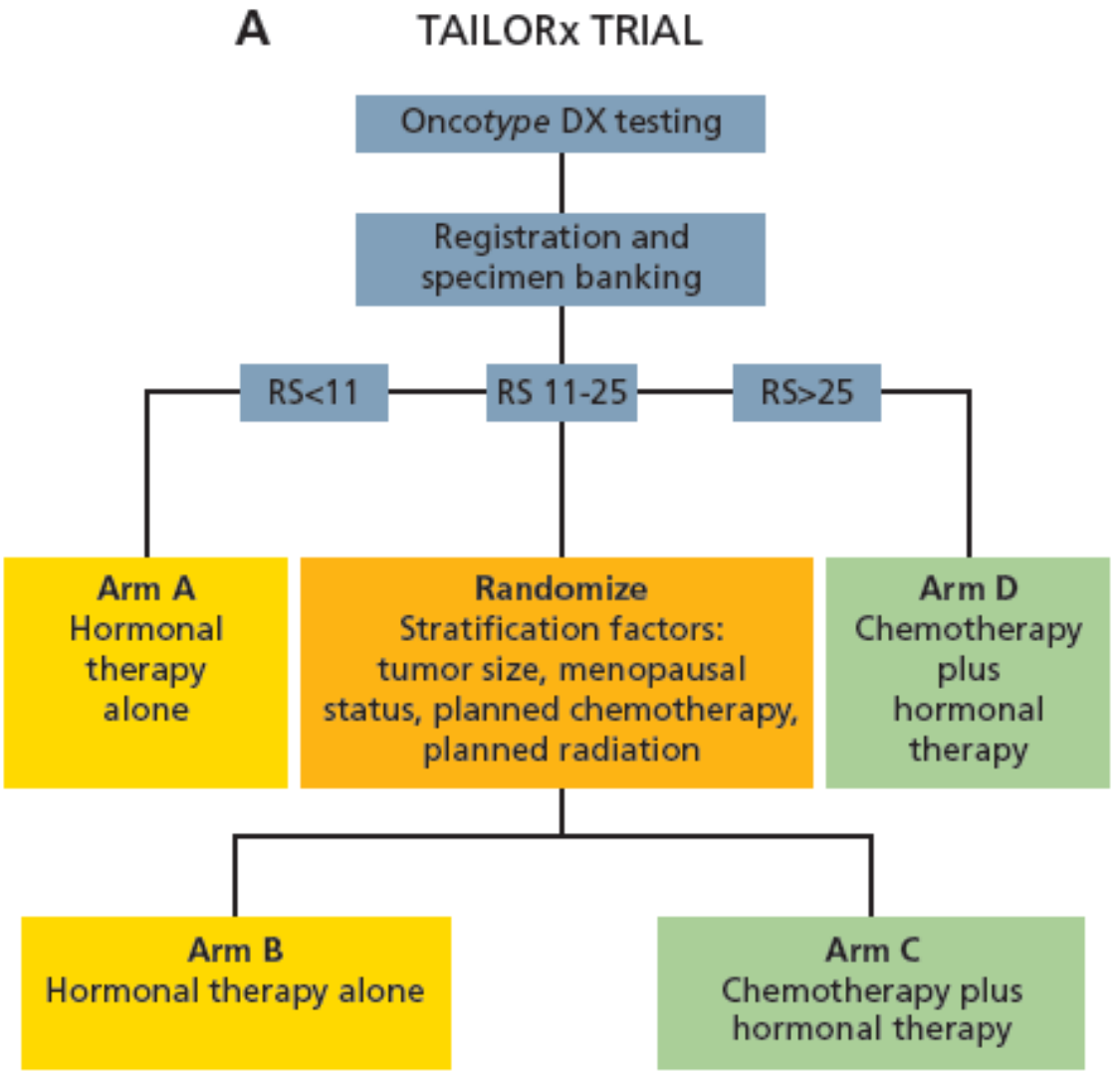


# Essai prospectif TAILORx

- N-
- RH+
- HER2-
- Pre et Post Menop.



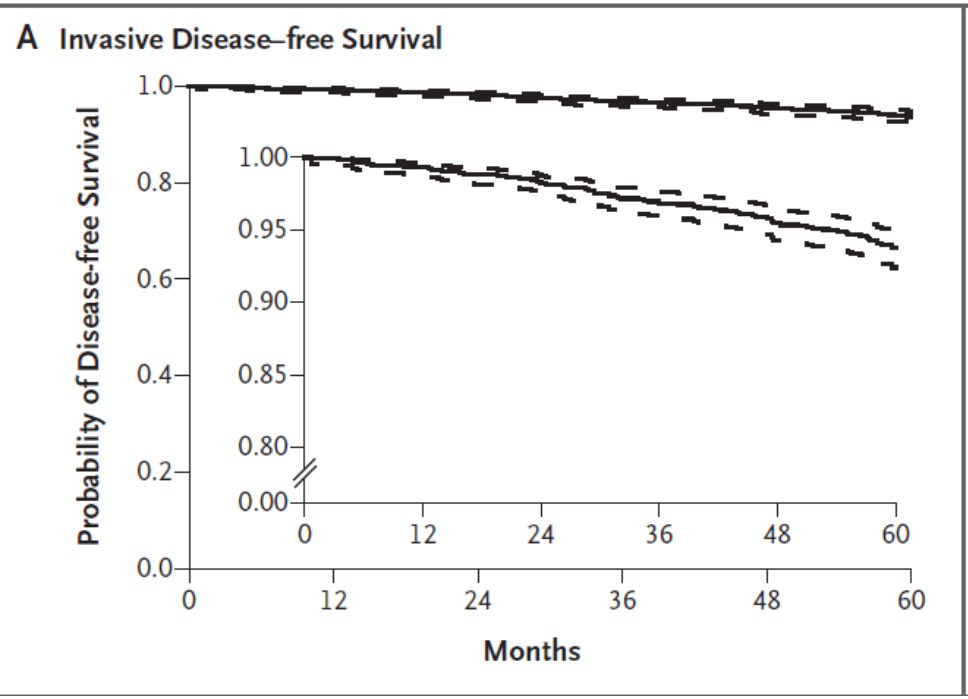
# TAILORx: résultats de la cohorte bas risque
## (ce n'est pas l'obj principal)

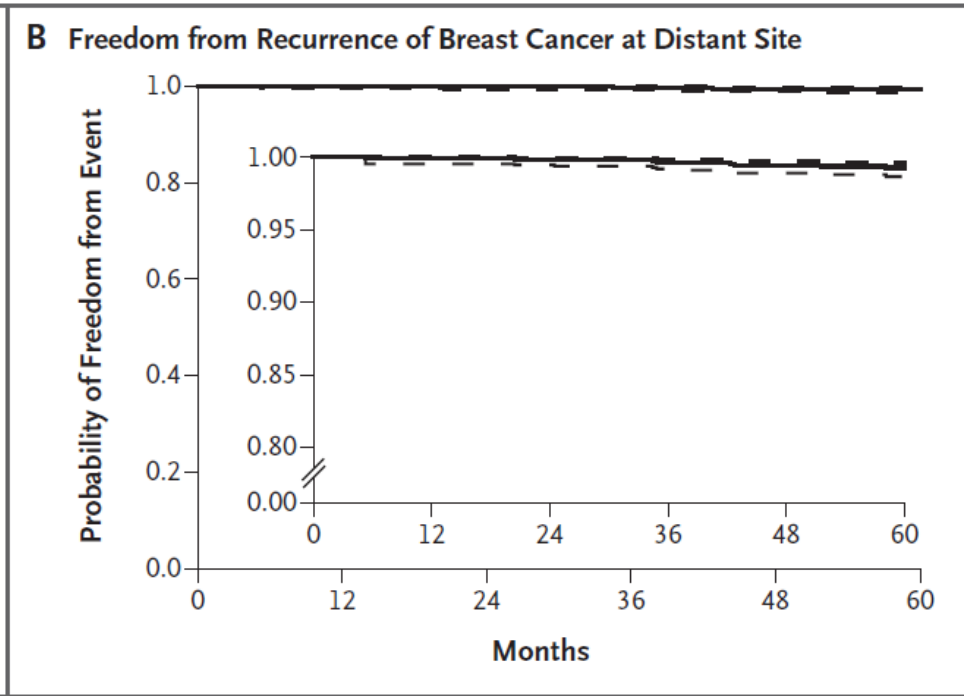
Table 1. Characteristics of the Patients at Baseline, According to Recurrence-Score Cohort.*

| Characteristic | Recurrence Score, 0–10 (N = 1626) | Recurrence Score, 11–25 (N = 6897) | P Value |
|---|---|---|---|
| Tumor size in the greatest dimension | | | |
| Median (interquartile range) — cm | 1.5 (1.2–2.0) | 1.5 (1.2–2.0) | 0.31 |
| Mean — cm | 1.74±0.77 | 1.71±0.79 | 0.23 |
| Distribution — no./total no. (%) | | | 0.42 |
| <1.0 cm | 128/1626 (8) | 568/6883 (8) | |
| 1.0–1.9 cm | 993/1626 (61) | 4270/6883 (62) | |
| 2.0–2.9 cm | 366/1626 (23) | 1543/6883 (22) | |
| 3.0–3.9 cm | 104/1626 (6) | 358/6883 (5) | |
| ≥4.0 cm | 35/1626 (2) | 144/6883 (2) | |
| Histologic grade of tumor — no./total no. (%) | | | <0.001 |
| Low | 530/1578 (34) | 1941/6665 (29) | |
| Intermediate | 937/1578 (59) | 3812/6665 (57) | |
| High | 111/1578 (7) | 912/6665 (14) | |

Sparano NEJM 2015

# TAILORx: résultats de la cohorte bas risque RS < 11




**IDFS @ 5 ans : 93.8%**

**MFS @ 5 ans : 99.3%**

Sparano NEJM 2015

EORTC - 10041

The future of cancer therapy

BIG - 3-04

Breast International Group

# MINDACT

## « Microarray for node negative disease may avoid chemotherapy »

## Primary analysis of the EORTC 10041/ BIG 3-04 MINDACT study: A prospective, randomized study evaluating the clinical utility of the 70-gene signature (MammaPrint®) combined with common clinical-pathological criteria for selection of patients for adjuvant chemotherapy in breast cancer with 0 to 3 positive nodes

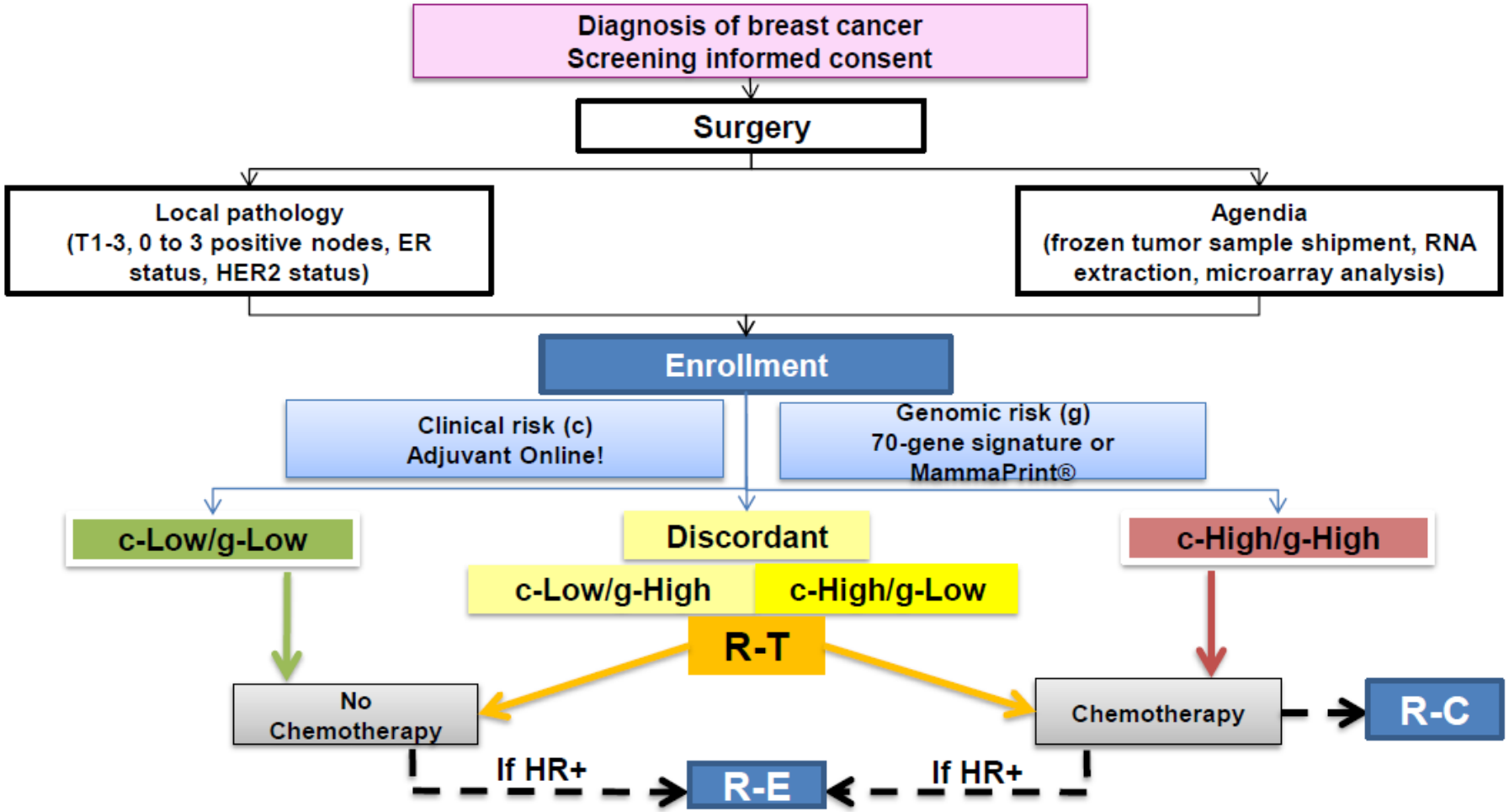
*Martine Piccart, Emiel Rutgers, Laura van' t Veer, Leen Slaets, Suzette Delaloge, Giuseppe Viale, Jean Yves Pierga, Peter Vuylsteke, Etienne Brain, Suzan Vrijaldenhoven, Peter Neijenhuis, Bruno Coudert, Tineke Smilde, Miguel Gil, Alastair Thompson, Isabel T. Rubio, Rodolfo Passalaqua, Erika Matos, Urlike Nitz, Mauro Delorenzi, Geraldine Thomas, Theodora Goulioti, Carolyn Straehle, Konstantinos Tryfonidis, Jan Bogaerts & Fatima Cardoso*

***On behalf of the European Commission supported TRANSBIG consortium and MINDACT investigators***

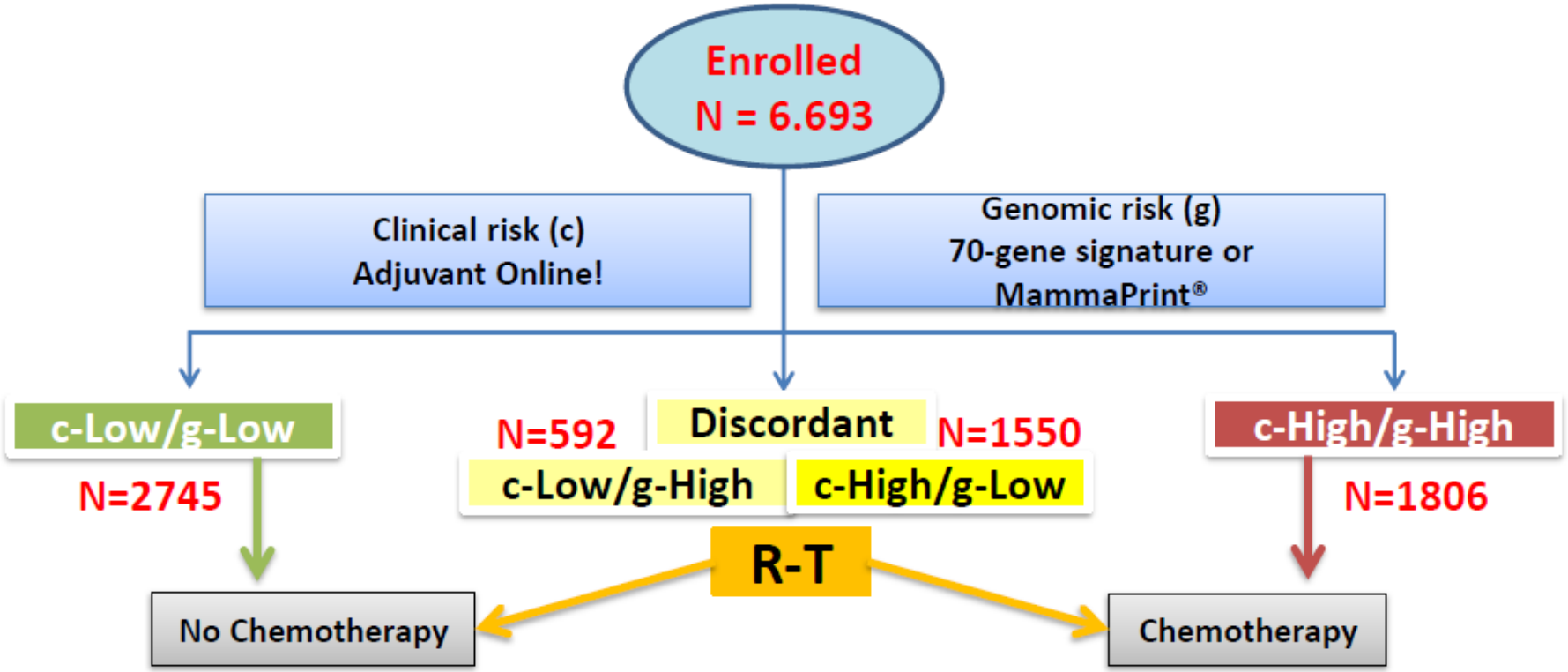
TRANSBIG

***Presented at AACR, April 18, 2016***

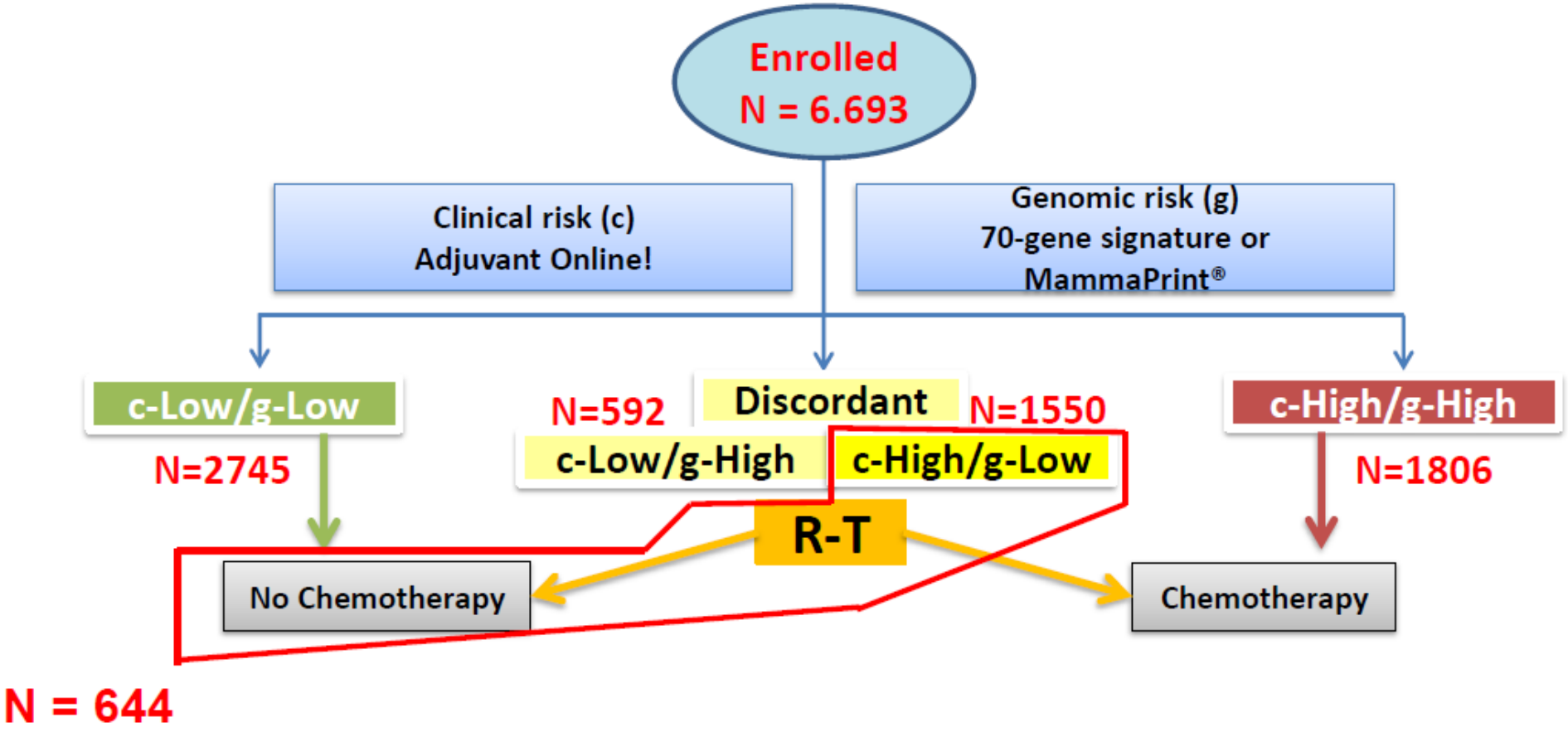
# The MINDACT study design



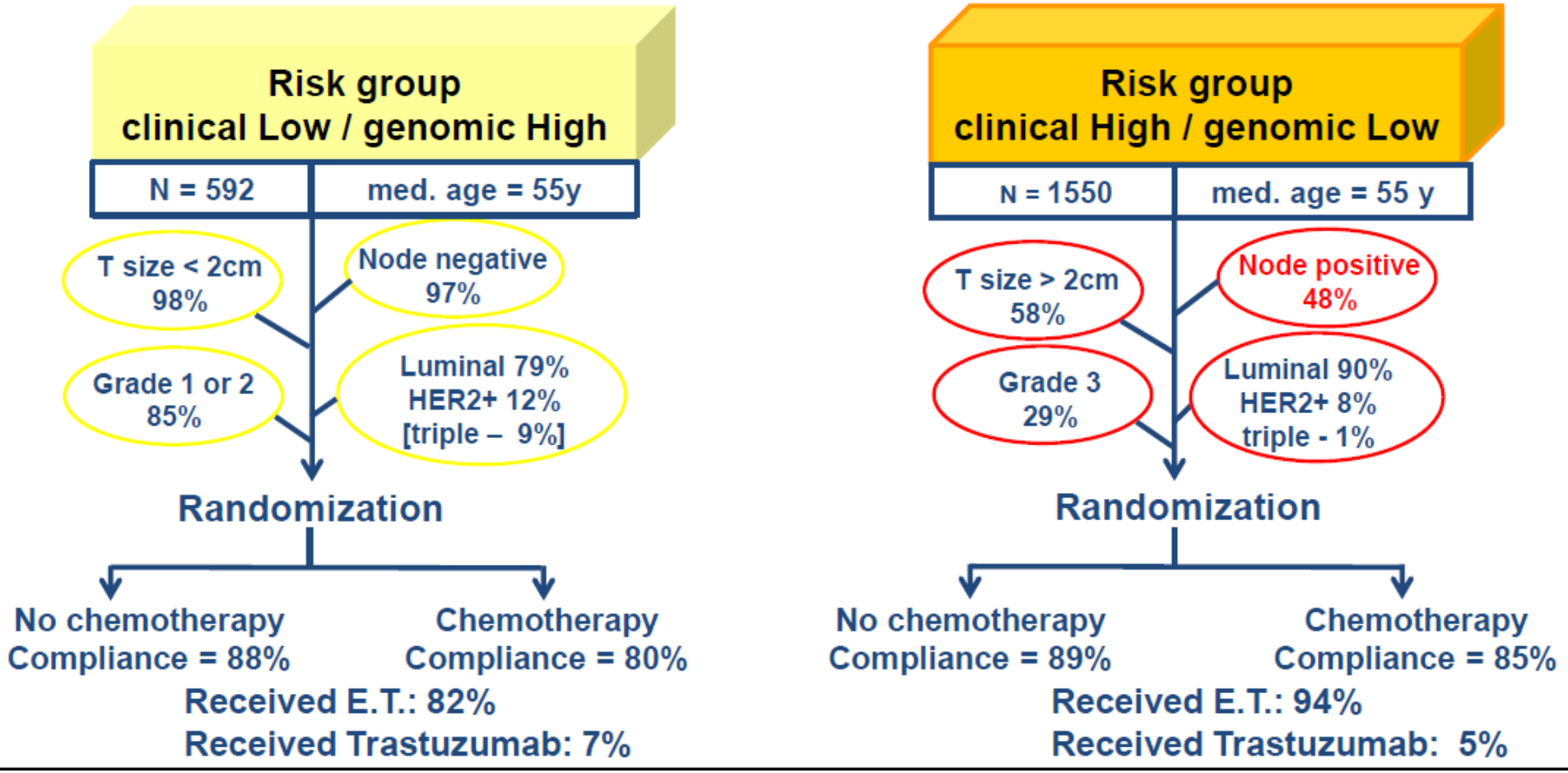
# The MINDACT study: Patient enrollment



# The primary analysis population



# MINDACT: patient demographics and compliance with assigned therapy



# B) DISCORDANT RISK GROUPS: PRIMARY TEST

**The primary analysis population**

**Discordant risks**

**c-Low /g-High**

**c-High/g-Low**

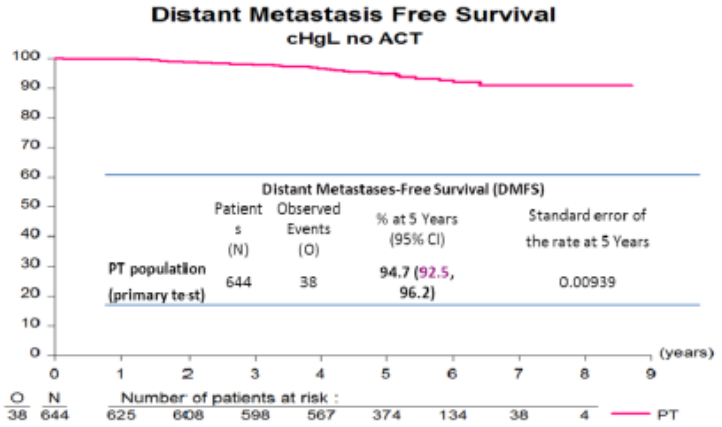
**RANDOMIZATION**

**No chemotherapy N = 748**

**CT**

**No change in risk post enrollement and no CT received N = 644**

**The primary statistical test (DMFS at 5Y)**

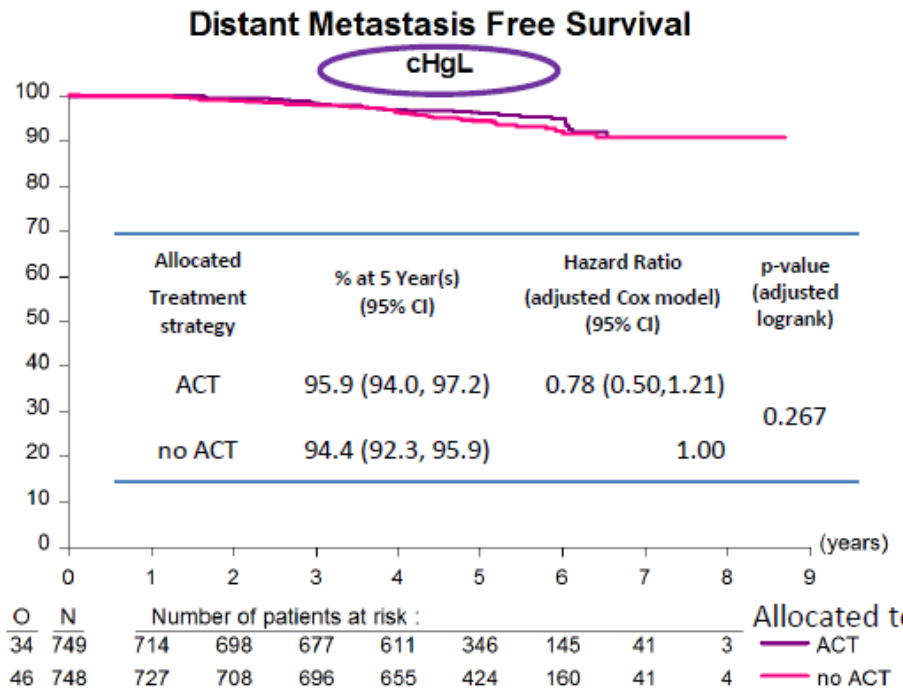


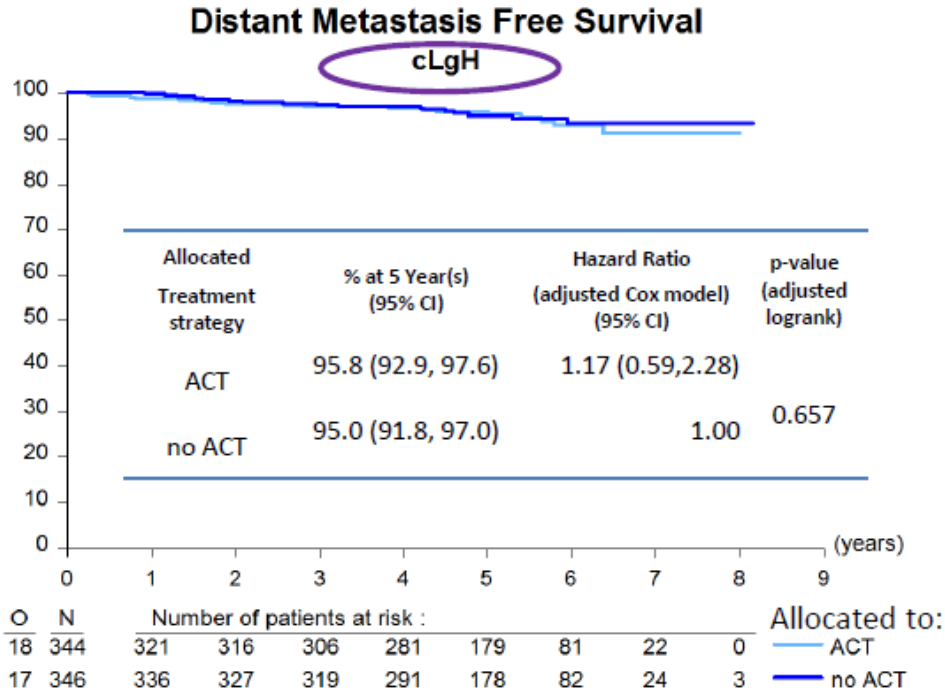

**Null Ho set à 92%**

**Observed 5Y DMFS = 94.7%**

**95% CI ≈ 92.5 – 96.2% excludes 92% !!!**

# Efficacy: ACT vs no ACT in discordant risk groups
## Intent-to-treat analysis



# Aucun bénéfice du test pour les c-Low !

| c-Low/g-High CT vs no CT per protocol population | | | | | | |
|---|---|---|---|---|---|---|
| | **Treatment received** | **Pts** | **Observed Events** | **% at 5 Year(s)** (95% CI) | **Hazard Ratio** (adjusted Cox model) (95% CI) | **p-value** (adjusted logrank) |
| **DMFS** | CT | 224 | 11 | **96.1** (92.4, 98.1) | **0.90** (0.40,2.01) | 0.798 |
| | no CT | 254 | 14 | **93.9** (89.6, 96.5) | 1.00 | |
| **DFS** | CT | 224 | 17 | **92.7** (87.9, 95.7) | **0.74** (0.40,1.39) | 0.355 |
| | no CT | 254 | 25 | **90.5** (85.7, 93.8) | 1.00 | |
| **OS** | CT | 224 | 5 | **98.1** (94.9, 99.3) | **0.72** (0.23,2.24) | 0.572 |
| | no CT | 254 | 8 | **97.0** (93.8, 98.6) | 1.00 | |

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# Intérêt discutable du test pour les c-High…

| c-High/g-Low CT vs no CT per protocol population | | | | | | |
|---|---|---|---|---|---|---|
| | **Treatment received** | **Patients** | **Observed Events** | **% at 5 Year(s)** (95% CI) | **Hazard Ratio** (adjusted Cox model) (95% CI) | **p-value** (adjusted logrank) |
| **DMFS** | CT | 592 | 22 | **96.7** (94.7, 98.0) | **0.65** (0.38,1.10) | 0.106 |
| | no CT | 636 | 37 | **94.8** (92.6, 96.3) | 1.00 | |
| **DFS** | CT | **592** | **39** | **93.3 (90.7, 95.2)** | **0.64 (0.43,0.95)** | **0.026** |
| | no CT | **636** | **66** | **90.3 (87.6, 92.4)** | **1.00** | |
| **OS** | CT | 592 | 10 | **98.8** (97.4, 99.5) | **0.63** (0.29,1.37) | 0.245 |
| | no CT | 636 | 18 | **97.3** (95.6, 98.4) | 1.00 | |

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# Cas clinique 1

- Patiente de 55 ans sans ATCD non ménopausée
- Dépistage: mammo normale , écho : sur rayon 2h à 4 cm du mamelon, masse hypoéchogène atténuante ACR4c de 9 mm du sein gauche , aires ganglionnaires sans gg suspect
- Biopsie sous écho: lobulaire infiltrant SBR2, ER+,PR+, HER2 neg.
- Palpation mammaire et des aires ganglionnaires normale
- IRM mammaire: lésion unique gauche ACR6 de 10 mm sans gg suspect
- Tumorectomie après repérage écho et ganglion sentinelle:
- Carcinome infiltrant de type lobulaire pléomorphe mesurant 7x6 mm de grade 2 (ER+,PR+,HER2-),pas de CIS, pas d'embole vasculaire
- Marges chirugicales: résection in sano avec marge minimale de 2 mm en externe
- Ganglion sentinelle: 1 ganglion siège d'une micrométastase de 0,5mm sans rupture capsulaire et 2 ganglions lymphatiques histologiquement normaux

**Que faites-vous si la signature multigénique est en faveur d'un risque de rechute faible ? chimio ou pas ?**

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# Cas clinique 2

- Patiente de 60 ans ménopausée sans ATCD
- Dépistage retrouvant sur la mammographie une opacité correspondant en écho à une image ACR5 de 10 mm QSI sein droit , aires ganglionnaires axillaires normales en écho
- Palpation retrouvant un nodule de 10 mm du QSI du sein droit sans adénopathie axillaire palpable
- La biopsie retrouve un carcinome infiltrant SBR1 ER+PR+HER2-
- Tumorectomie avec ganglion sentinelle: carcinome infiltrant SBR1 ER+++100%, PR++80%,HER2-,pas d'embole, exérèse in sano avec marges à 3mm en interne.
- 2 ganglions sentinelles dont 1 sur les 2 présente une macrométastase de 3mm sans effraction capsulaire

**Que faites-vous si la signature multigénique est en faveur d'un risque de rechute faible ? chimio ou pas ?**