Breast cancers
Pathology and predictive criteria
Molecular biology aspects

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2nd International Congres of Breast Disease Centers 9-10 /02/ 2012

Rationale

Breast cancer is a heterogeneous disease

Predictive markers are crucial for patients management

At present: only ER, PR and HER2 are applied to predict specific response to a therapy in breast cancer management

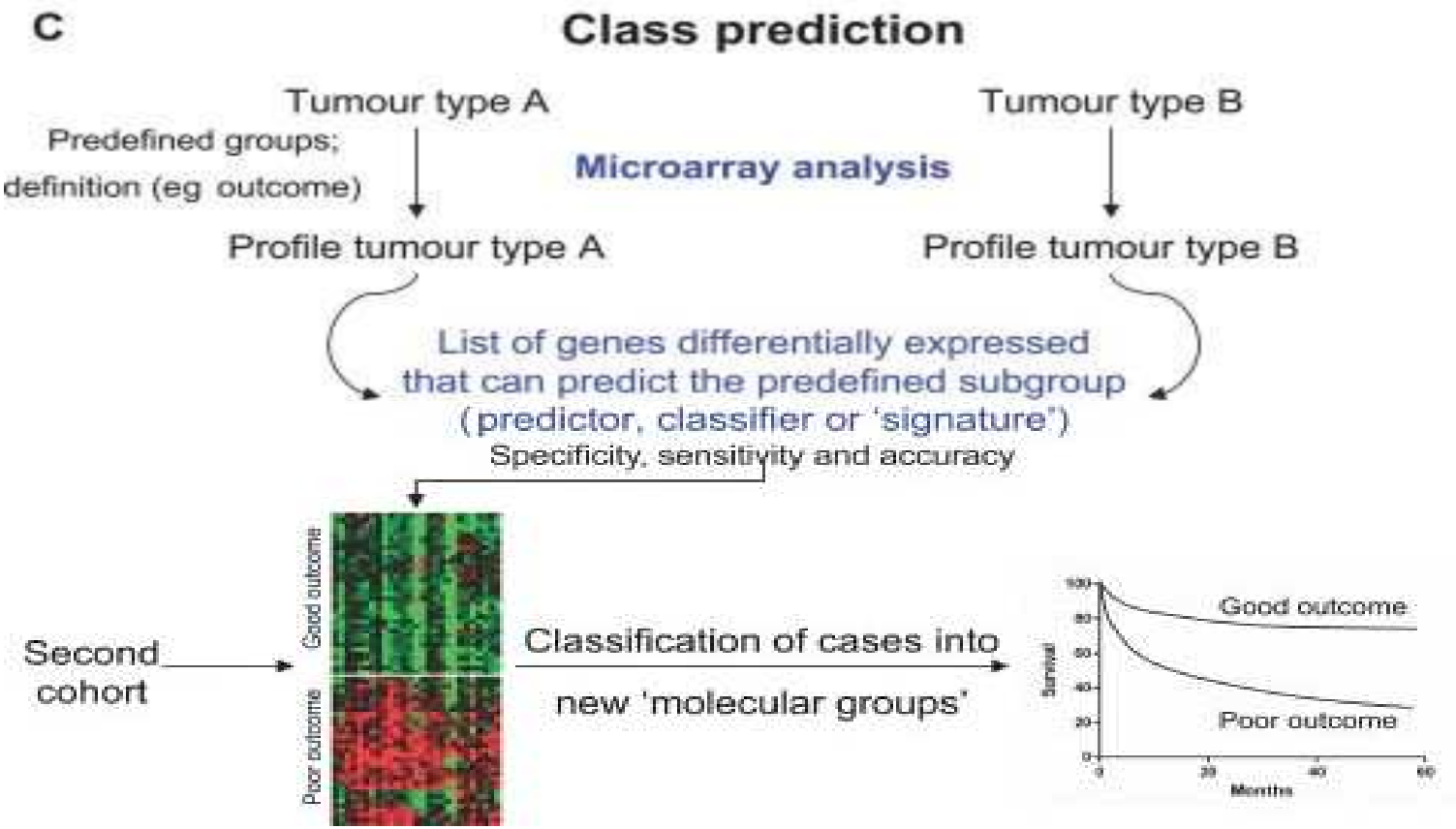
The present

1. Several treatment options
2. Several gene expression profiling studies
3. Availability of the Human Genome Project

Molecular complexity of breast carcinoma

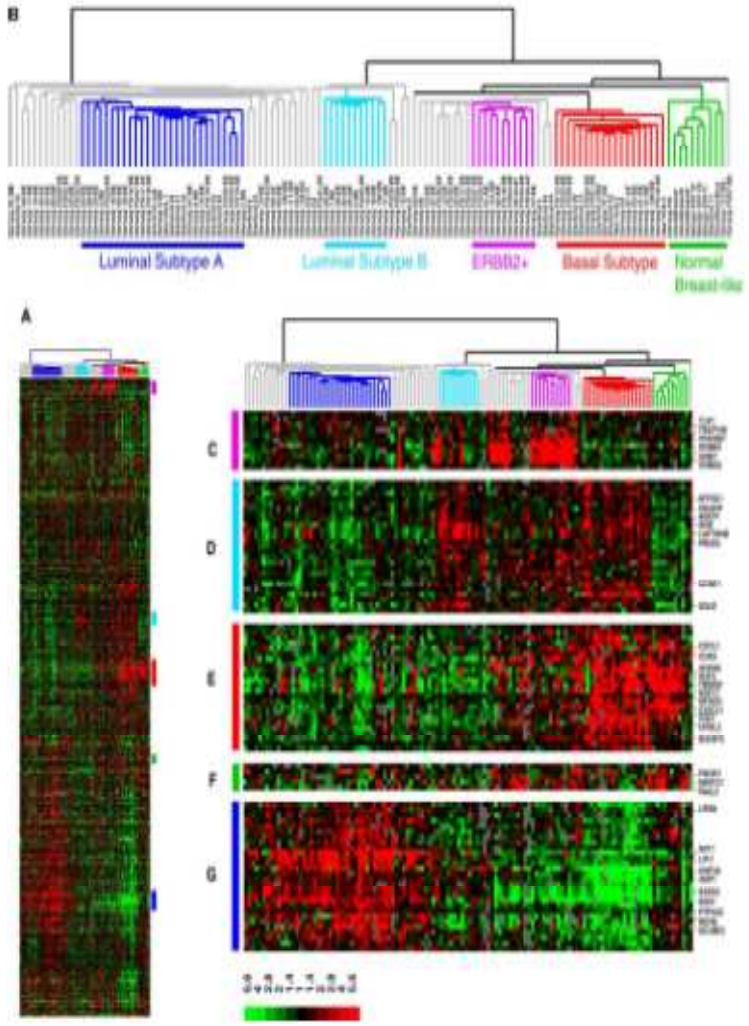
Potential new molecular targets for drug development

High throughput analysis



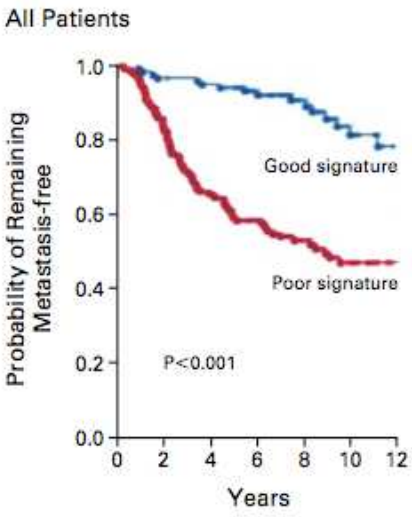
Weigelt & Reis-Filho , 2009

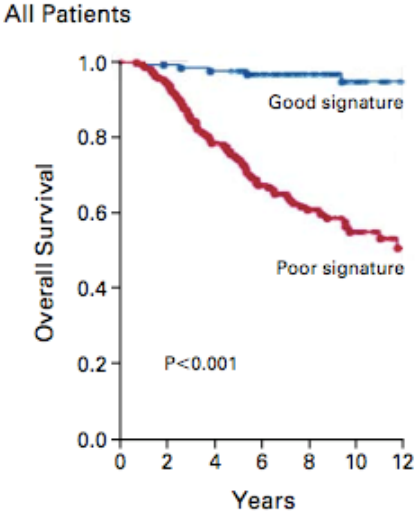
Breast cancer molecular classification (1)



(*Perou, 1999, 2000;Sorlié, 2001, 2003; van't Veer, 2003; van de Vijer, 2002*)

- 70 genes signature
- Five molecular subgroups
  - *Luminal A*
  - *Luminal B*
  - *Basal-like (TN/Claudin-Low)*
  - *HER2-like*
  - *Normal like*
- Prognosis and therapeutical consequences





Breast cancer molecular classification (2)

Molecular apocrine tumours (ER-, AR+, FOXA1+, HER2+/-

Open

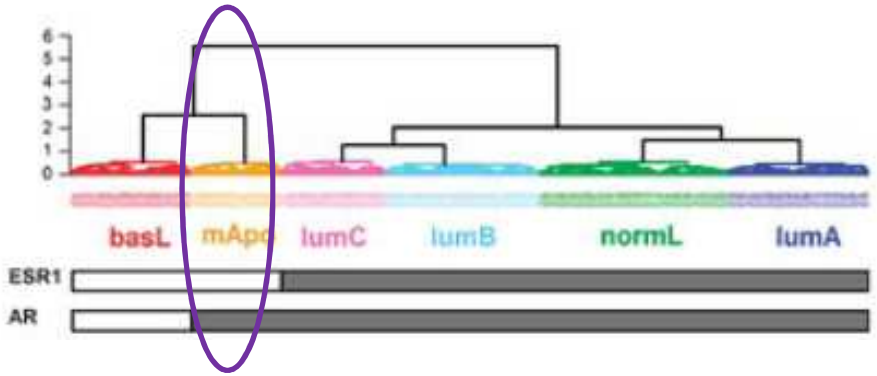
Oncogene (2011) 1–11

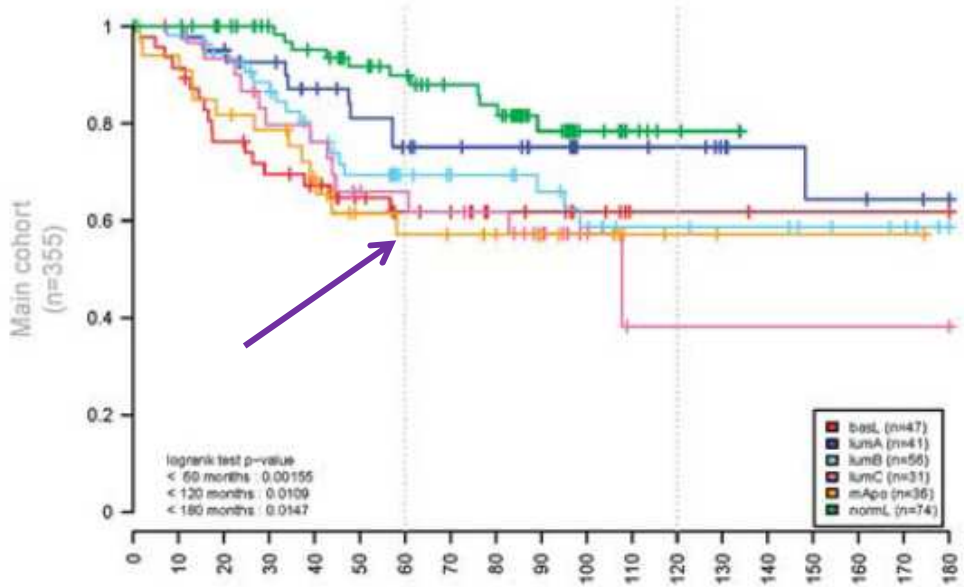
www.nature.com/onc

ONCOGENOMICS

A refined molecular taxonomy of breast cancer

M Guedj[1,15], L Marisa[1,15], A de Reynies[1,15], B Orsetti[2,3], R Schiappa[1], F Bibeau[4], G MacGrogan[5], F Lerebours[6], P Finetti[7], M Longy[5], P Bertheau[8], F Bertrand[6], F Bonnet[5], AL Martin[9], JP Feugeas[10,11,12], I Bièche[6], J Lehmann-Che[10,11,12], R Lidereau[6], H de Thé[10,11,12,15] and C Theillet[2,13,14,15]





Predictive markers

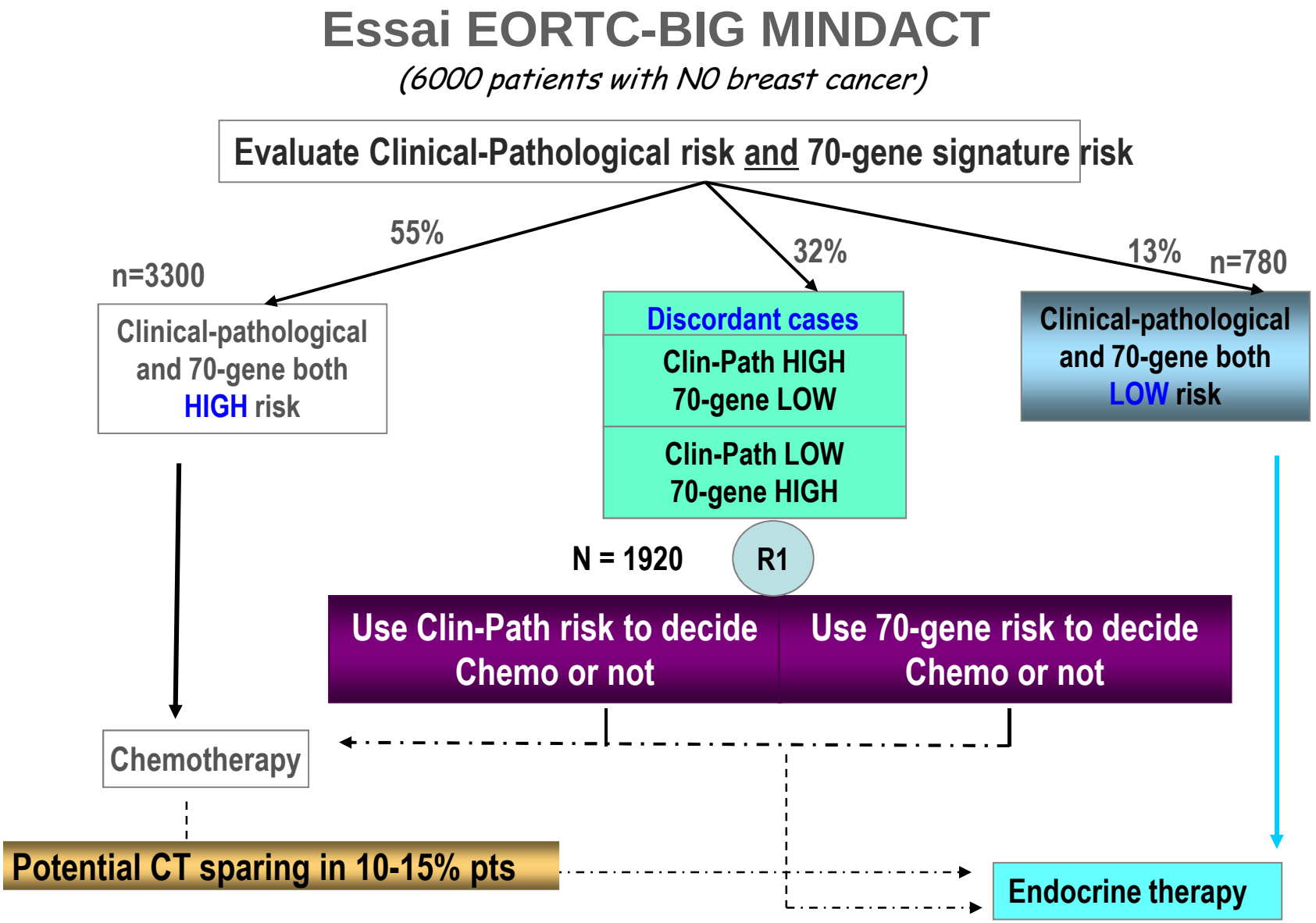
1. Definition: prediction generic or specific sensitivity to treatment; prediction resistance to treatment
2. Neoadjuvant setting: direct assessement of response to treatment
   - Monitoring tumour size during treatment
   - Surrogate marker for long term treatment : pCR

Predictive signatures

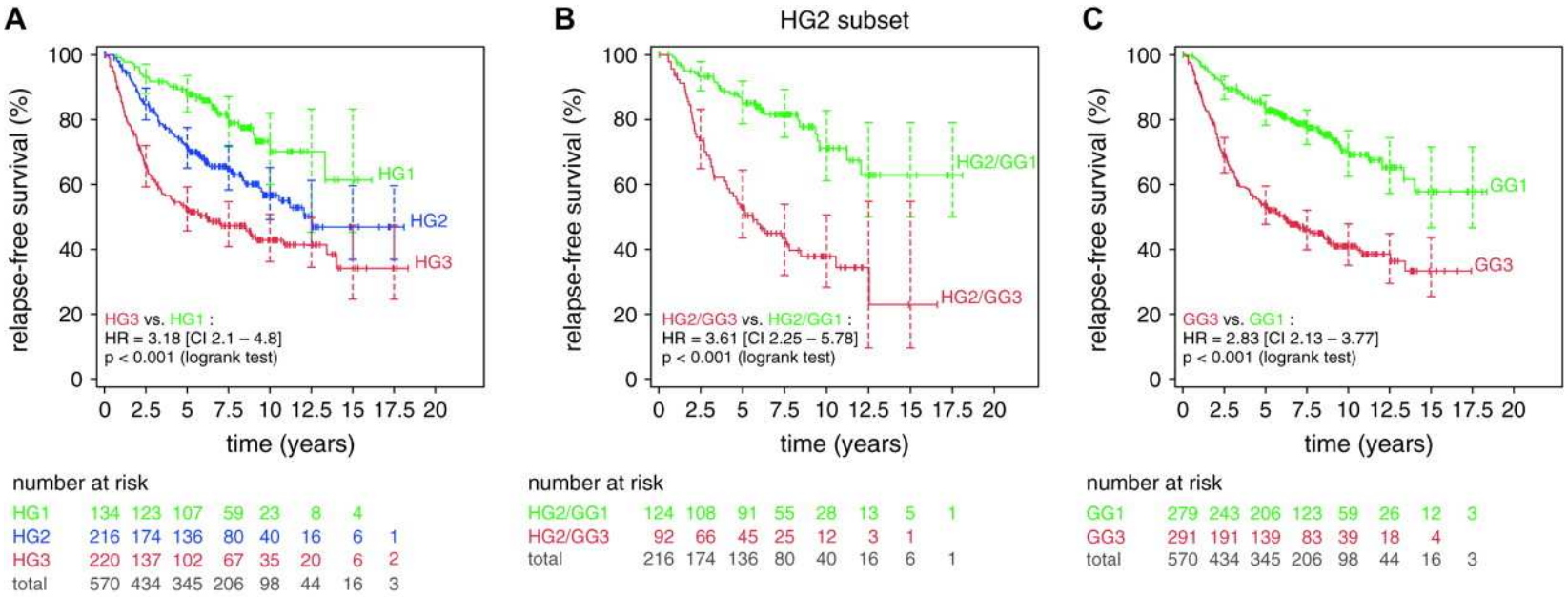
- **Some prognosis signatures → prediction of response to chemotherapy?**

  - ✓ **Recurrent score-RS (Oncotype DX™, Health care)**
  - ✓ **70 - gènes signature (MammaPrint™)**
  - ✓ **Genomic Grade index (GGI, MapQuant)**
  - ✓ **DLD30 (MD Anderson Cancer center)**
  - ✓ **……**

70- gènes signature (MammaPrint™)



Genomic grade index (GGI).

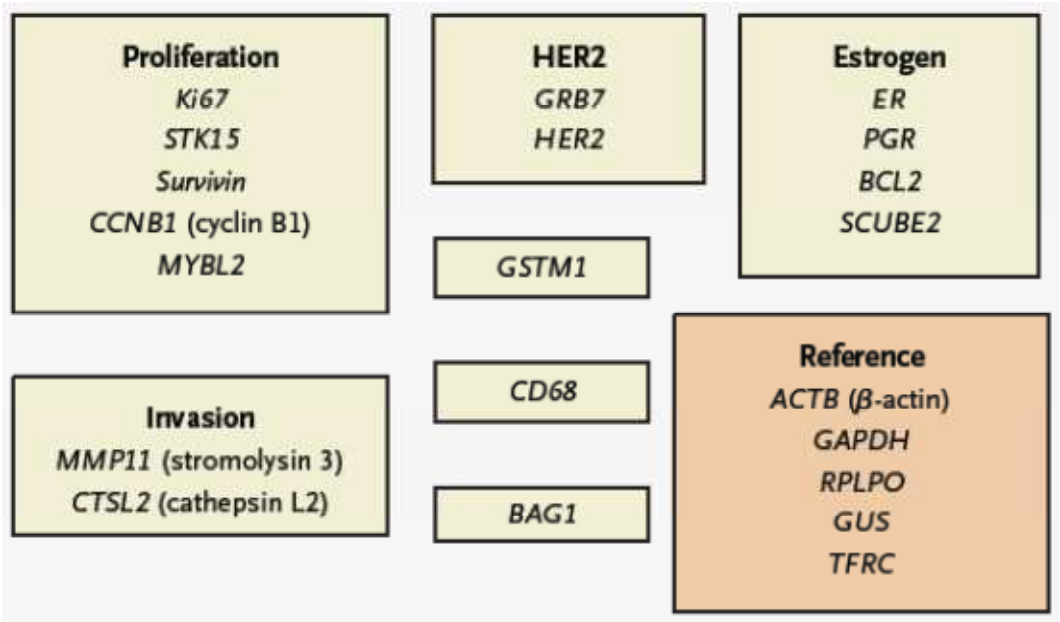


GGI ,

- **score based on 97 genes expression (proliferation and différentiation)**
- **Differential expression in grade 1 and 3 breast tumours**
- **Reclassification of intermediate grade tumours (grade 2)**

Sotiriou et al, JNCI, 2006

Panel of 21 (16+5) genes and the recurrence-score algorithm (Oncotype DX, Genomic Healt

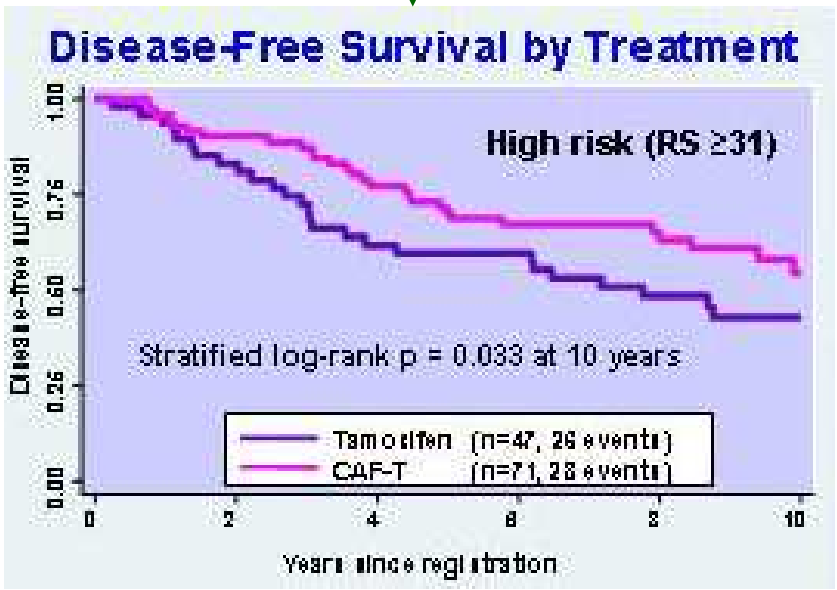


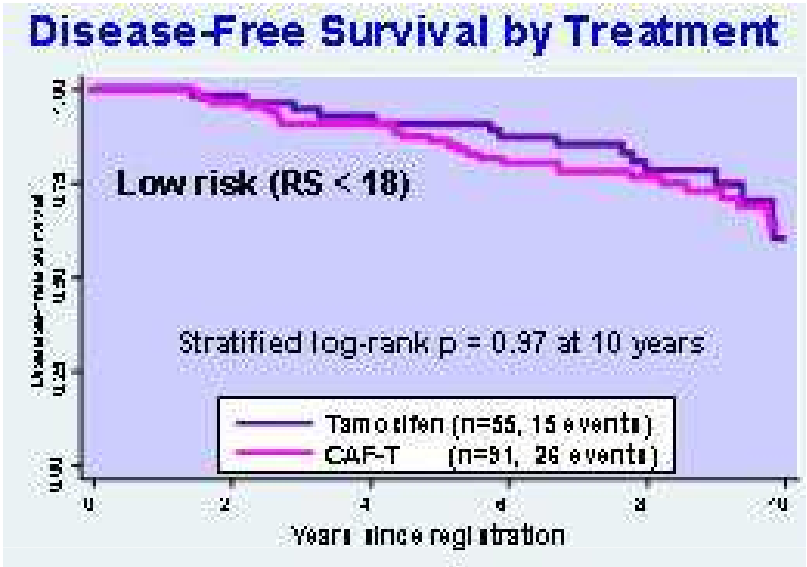
- **GRB7 group score** = 0.9 x GRB7 + 0.1 x HER2
- **ER group score** = (0.8 x ER + 1.2 x PGR + BCL2 + SCUBE2) ÷ 4
- **Proliferation group score** = (Survivin + KI67 + MYBL2 + CCNB1 + STK15) ÷ 5
- **Invasion group score** = CTSL2 ÷ 2
- **RSu** = + 0.47 x GRB7 group score – 0.34 x ER group score + 1.04 x proliferation group score + 0.10 x invasion group score + 0.05 x CD68 – 0.08 x GSTM1 – 0.07 x BAG1

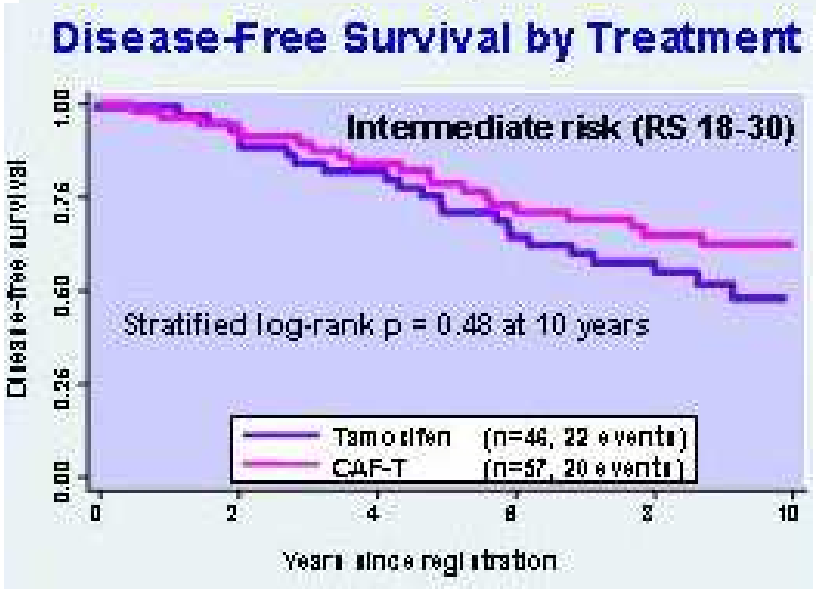
Paik S et al, 2008

Prediction

Benefit CAF for the group
of patients BK N+ with high RS







Albain et al 2010

Prospective validation

MINDACT

(Mammaprint)

- 6000 ptes
- N0 ER+, PR+, HER2-, Stages I & II
- Frozen samples
- DNA microarrays
- Randomisation : Patients with discordant risk (clin/ biol, 32%)
- MFI

TAILORx

(Oncotype DX)

- 10500 patientes
- N0 ER+, PR+, HER2-, Stages I & II
- Fixed samples
- RT-qPCR (16 targets genes)
- Randomisation : Patients with RS de 19 à 25 (44%)
- DFI

TP53 mutations and breast cancer response to high dose chemotherapy

OPEN ACCESS Freely available online 2007 PLoS MEDICINE

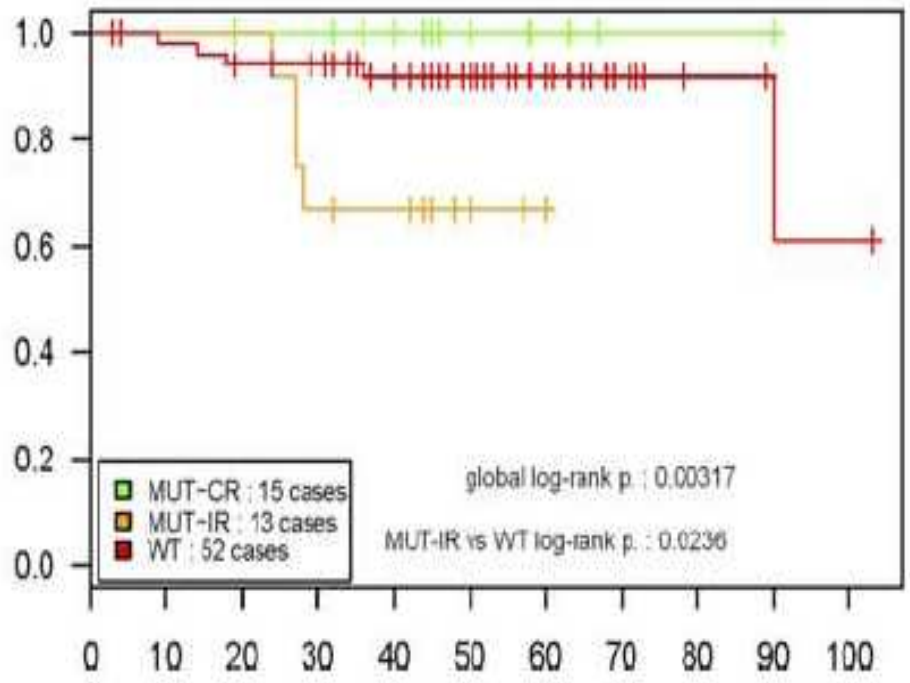
Exquisite Sensitivity of *TP53* Mutant and Basal Breast Cancers to a Dose-Dense Epirubicin–Cyclophosphamide Regimen

Philippe Bertheau[1,2☯], Elisabeth Turpin[3,4☯], David S. Rickman[5☯], Marc Espié[6], Aurélien de Reyniès[5], Jean-Paul Feugeas[3], Louis-François Plassa[3], Hany Soliman[3], Mariana Varna[1,2], Anne de Roquancourt[1], Jacqueline Lehmann-Che[3,4], Yves Beuzard[3], Michel Marty[6], Jean-Louis Misset[6], Anne Janin[1,2], Hugues de Thé[3,4*]

TP53	Mutated	Wild type
pCR	15	0
Non pCR	13	52

Fischer exact'test:<10^{-8}

OS



Pathological complete response only in mutated TP53 tumours

Conclusions

- Ten years of high throughput analysis in breast cancers ⟹ Molecular classification of breast carcinoma

- Today, in order to cover the main fields in breast cancer clinical research and daily practice, breast cancer centers should be associated with translational research platforms.

- Performances of these platforms can be optimized by their interaction with many centers at a national or international level.