TRANSBIG multi-centre independent validation of the Rotterdam 76-gene prognostic signature for patients with node-negative breast cancer.

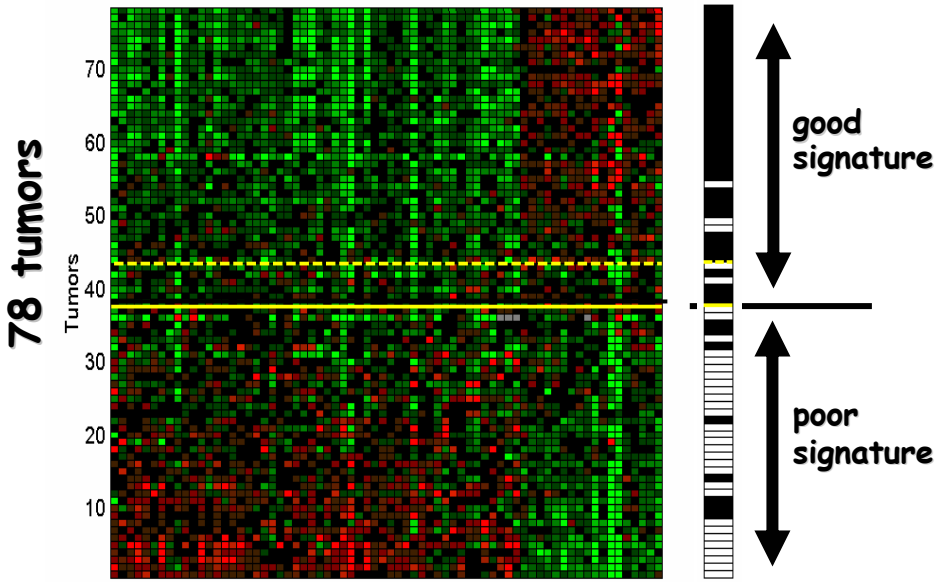
Christine Desmedt, Fanny Piette, Fatima Cardoso, Yixin Wang, Sherene Loi, Françoise Lallemand, Jan Klijn, Benjamin Haibe-Kains, Giuseppe Viale, Mauro Delorenzi, Yi Zhang, Mahasti Saghatchian d'Assignies, Jonas Bergh, Rosette Lidereau, Paul Ellis, Adrian Harris, John Foekens,Marc Buyse, Martine J. Piccart, Christos Sotiriou

on behalf of the TRANSBIG Consortium

Partially funded by the European Commission's Framework VI Programme

Amsterdam 70-gene signature

70-gene signature



Van't Veer et al., Nature, 2002

The « 70 gene prognosis signature »:

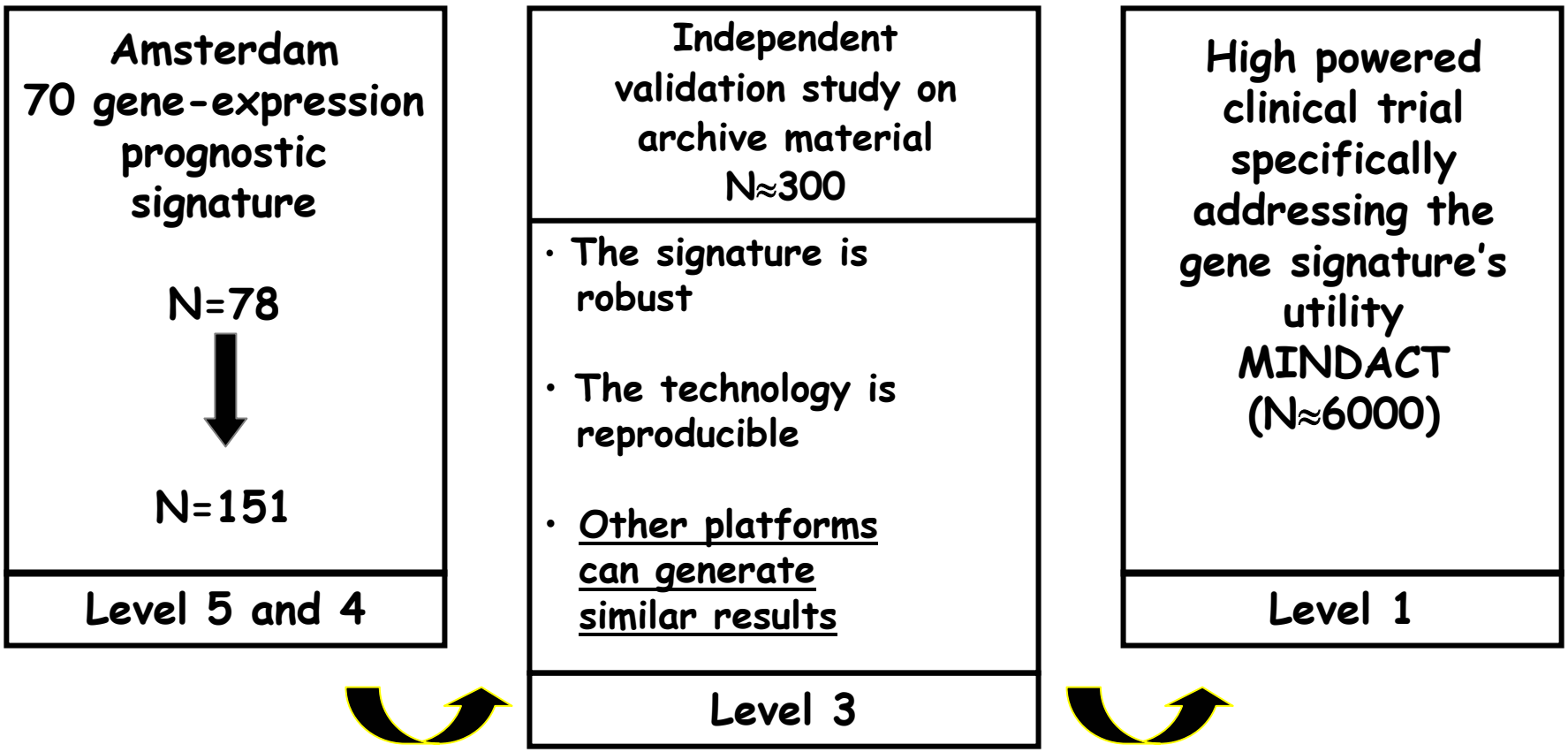
- is a powerful prognostic tool
- outperforms clinical /pathological criteria (St Gallen, NIH)
- could reduce « overtreatment »

Validation series

n=151 node – patients (+ 144 node + patients)

Van de Vijver, NEJM, 2002

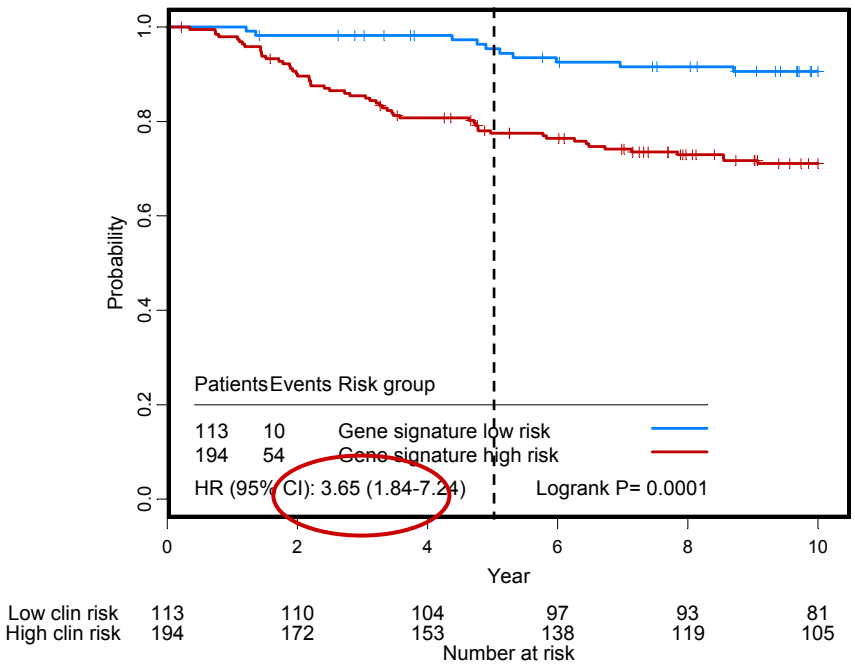
Background TRANSBIG



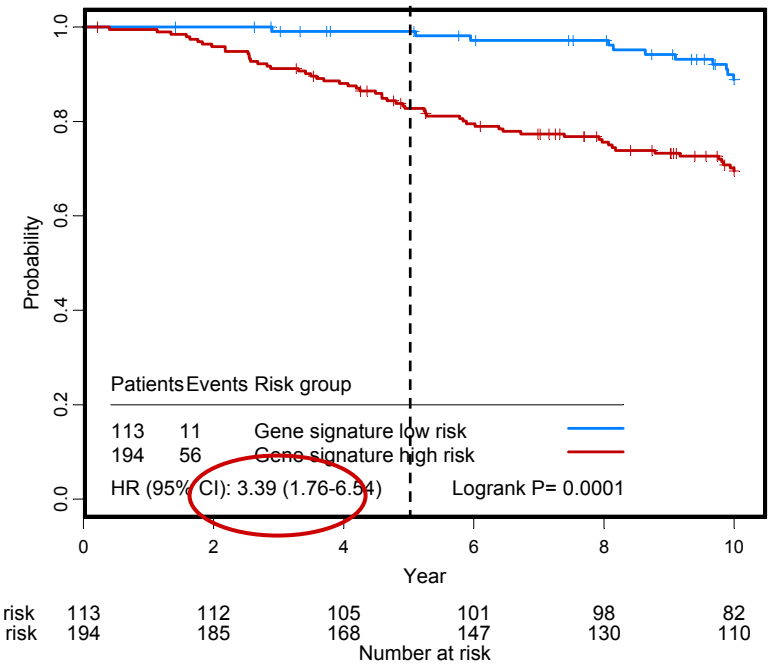
E.U. GRANT, 6th Framework Programme

TRANSBIG Validation of the Amsterdam signature

Time to distant metastases



Overall Survival



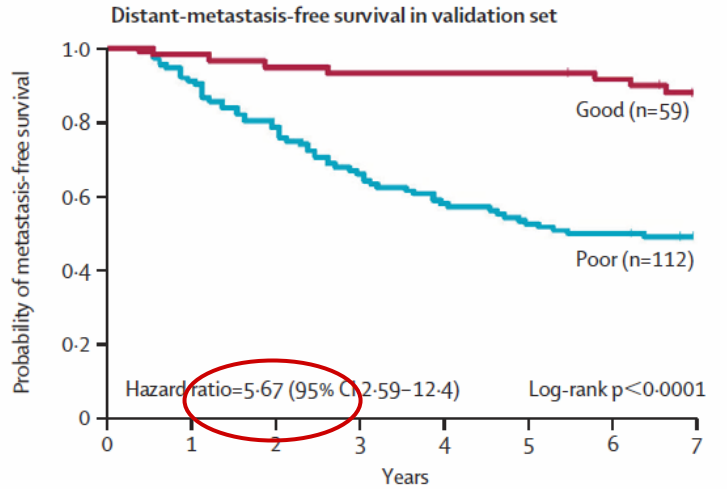
JNCI under revision

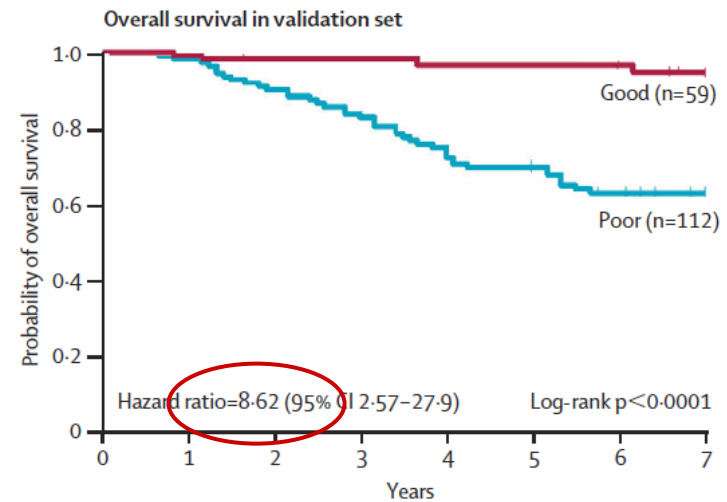
Gene-expression profiles to predict distant metastasis of lymph-node-negative primary breast cancer

Yixin Wang, Jan G M Klijn, Yi Zhang, Anieta M Sieuwerts, Maxime P Look, Fei Yang, Dmitri Talantov, Mieke Timmermans, Marion E Meijer-van Gelder, Jack Yu, Tim Jatkoe, Els M J J Berns, David Atkins, John A Foekens

Lancet 2005

Training set= 115 N- pts
(80 ER+/35 ER-)
Test set= 171 N- pts
(129 ER+/42 ER-)
1 center
No systemic therapy
Median FU:101 months
Clinical endpoint:TDM
Affymetrix Platform

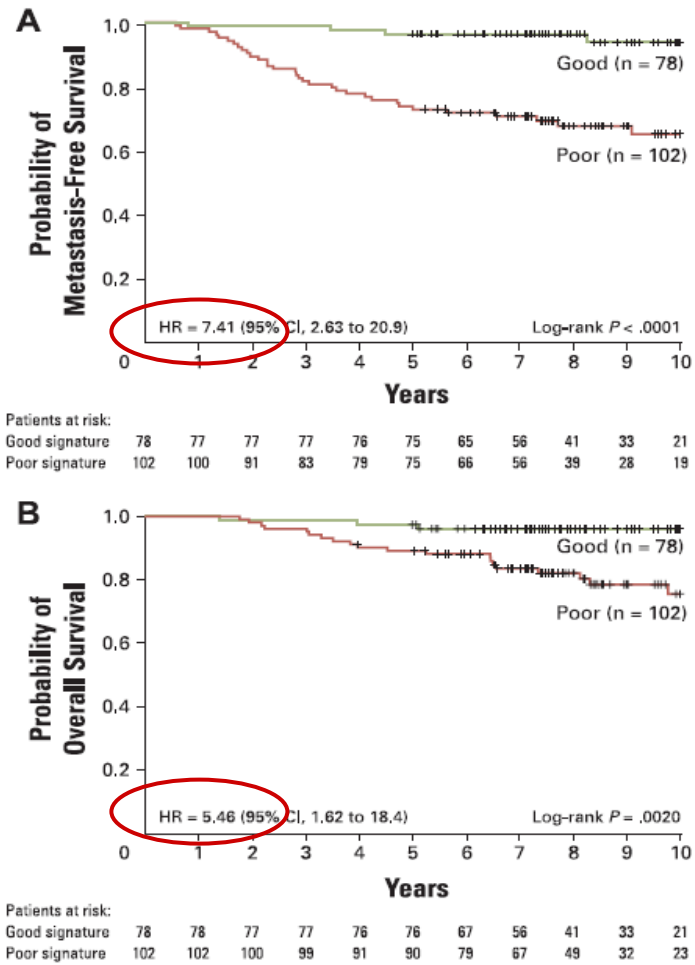




JOURNAL OF CLINICAL ONCOLOGY

Multicenter Validation of a Gene Expression–Based Prognostic Signature in Lymph Node–Negative Primary Breast Cancer

John A. Foekens, David Atkins, Yi Zhang, Fred C.G.J. Sweep, Nadia Harbeck, Angelo Paradiso, Tanja Cufer, Anieta M. Sieuwerts, Dmitri Talantov, Paul N. Span, Vivianne C.G. Tjan-Heijnen, Alfredo F. Zito, Katja Specht, Heinz Hoefler, Rastko Golouh, Francesco Schittulli, Manfred Schmitt, Louk V.A.M. Beex, Jan G.M. Klijn, and Yixin Wang



180 N- pts
4 centers
No systemic therapy
Median FU:100 months
Clinical endpoint:TDM

Study Objective

Test the 76-gene signature
using the SAME validation TRANSBIG series

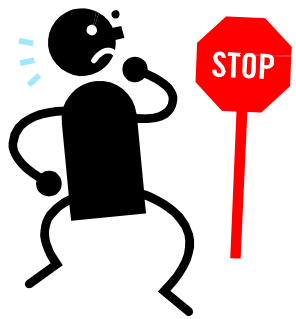
Similar performance?

⇩

MINDACT

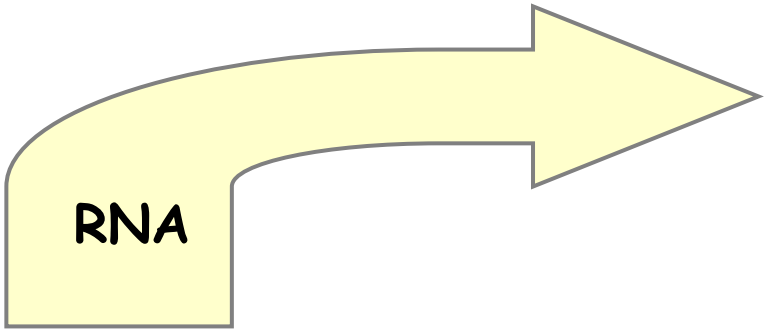
Strikingly different performance?

⇩



⇨

- Delay MINDACT
- Further work needed...



Brussels

Jules Bordet Institute

Gene expression profiling

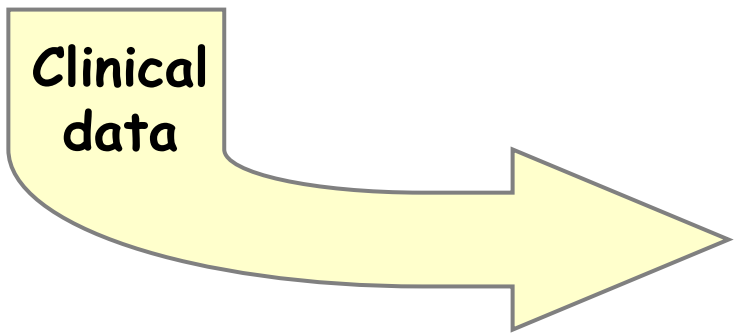
Raw data

5 TRANSBIG Institutions

- UK (Guy's, Oxford) : 1984 => 1996
- France (IGR, CRH) : 1978 => 1998
- Sweden (Karolinska) : 1980 => 1990

Veridex

Low vs High risk signature classification

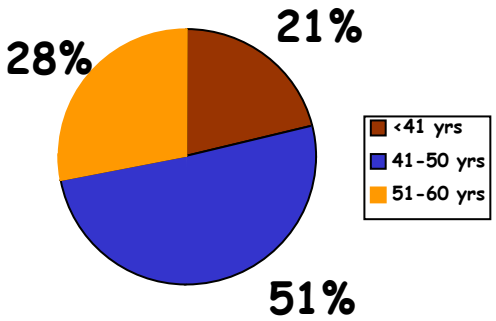


IDDI

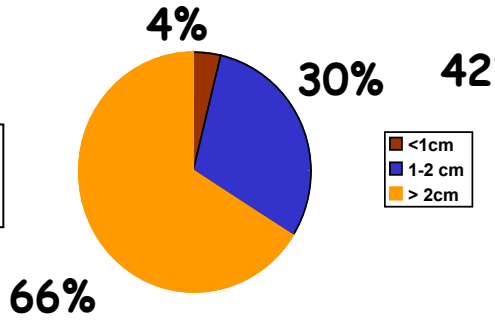
Comparison of clinical vs gene signature of prognostic risk

Patients Characteristics in the 2 validation series

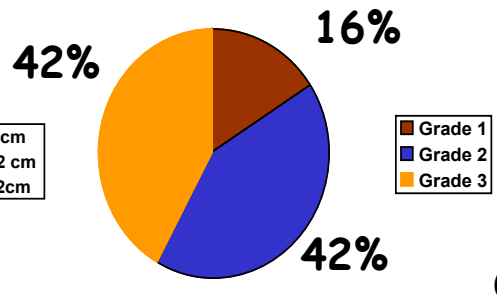
Age



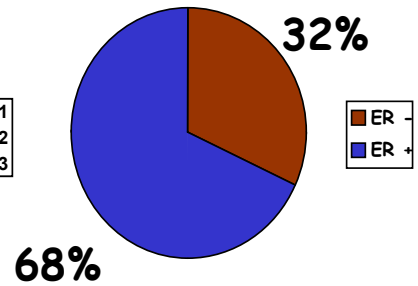
Tumor Size



Tumor Grade



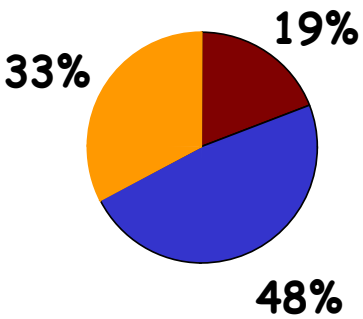
ER status



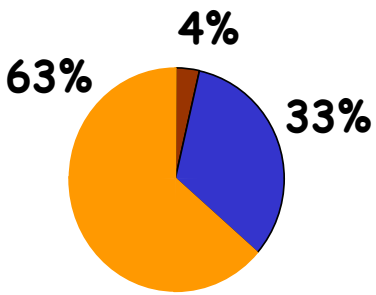
Median FU= 14.0 yrs

Rotterdam N=198

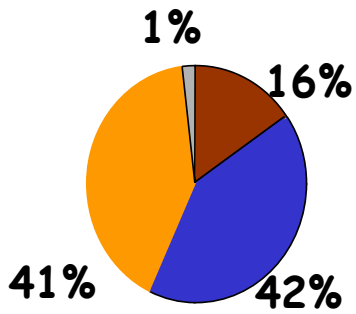
Age



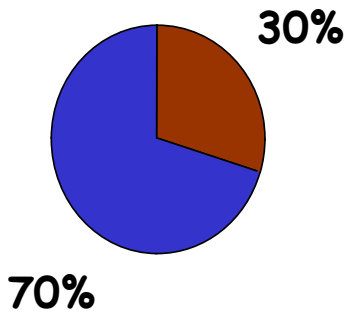
Tumor Size



Tumor Grade



ER status



Median FU= 13.6 yrs

Amsterdam N=302

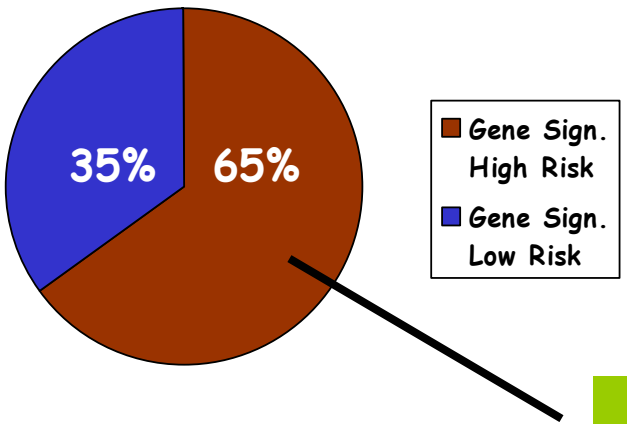
Results

Patient's data

Clinical Risk defined by the Adjuvant! Software
(www.adjuvantonline.com)

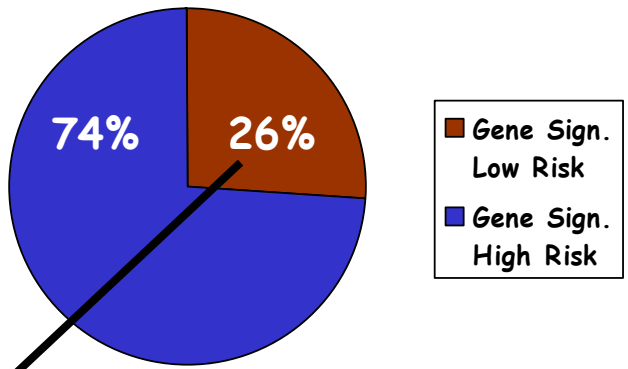
LOW Clinical Risk

N=46



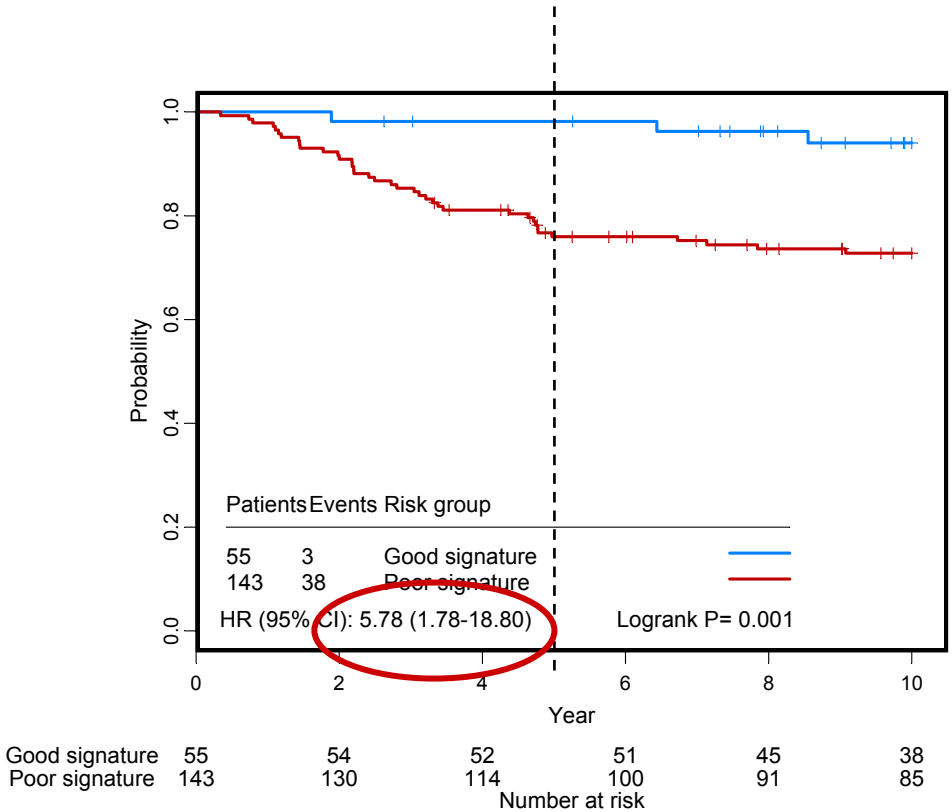
HIGH Clinical Risk

N=152



Discordant cases

Time to Distant Metastases



5-year survival:

low risk group: 0.98 (0.88-1.00)

high risk group: 0.76 (0.68-0.82)

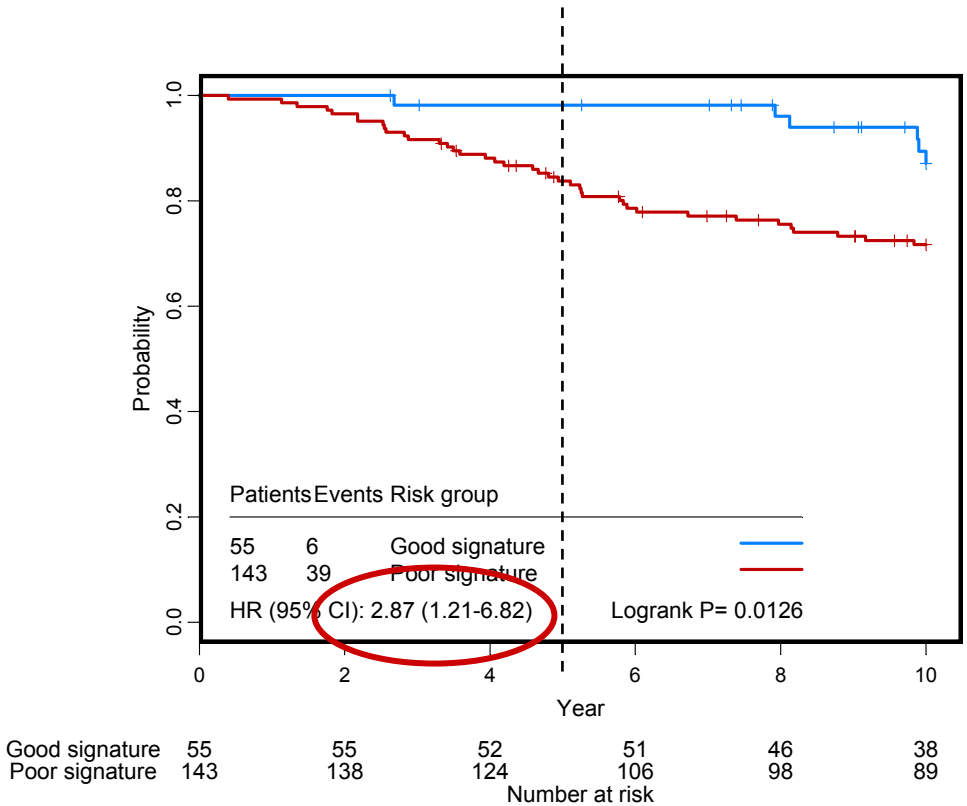
10 year survival:

low risk group: 0.94 (0.83-0.98)

high risk group: 0.73 (0.65-0.79)

HR and logrank p-value were obtained after stratification for the centre

Overall Survival



5-year survival:

low risk group: 0.98 (0.88-1.00)

high risk group: 0.84 (0.77-0.89)

10 year survival:

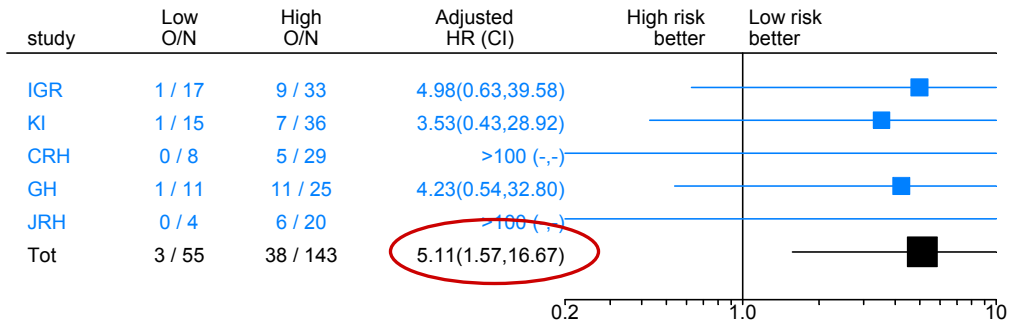
low risk group: 0.87 (0.73-0.94)

high risk group: 0.72 (0.63-0.78)

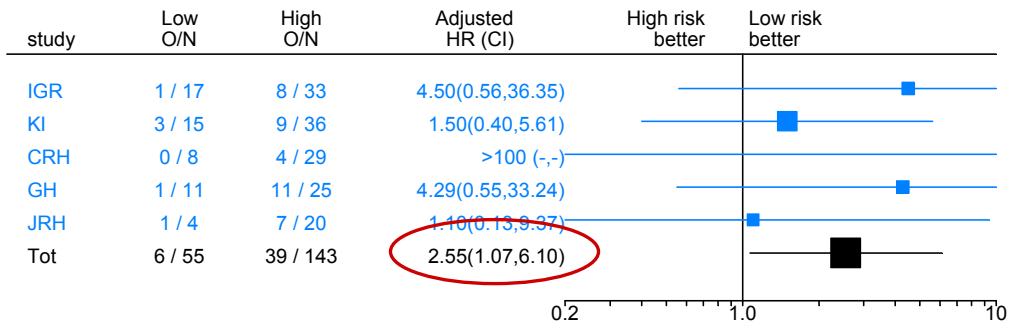
HR and logrank p-value were obtained after stratification for the centre

76-gene signature adjusted for Clinical Risk (Adjuvant!)

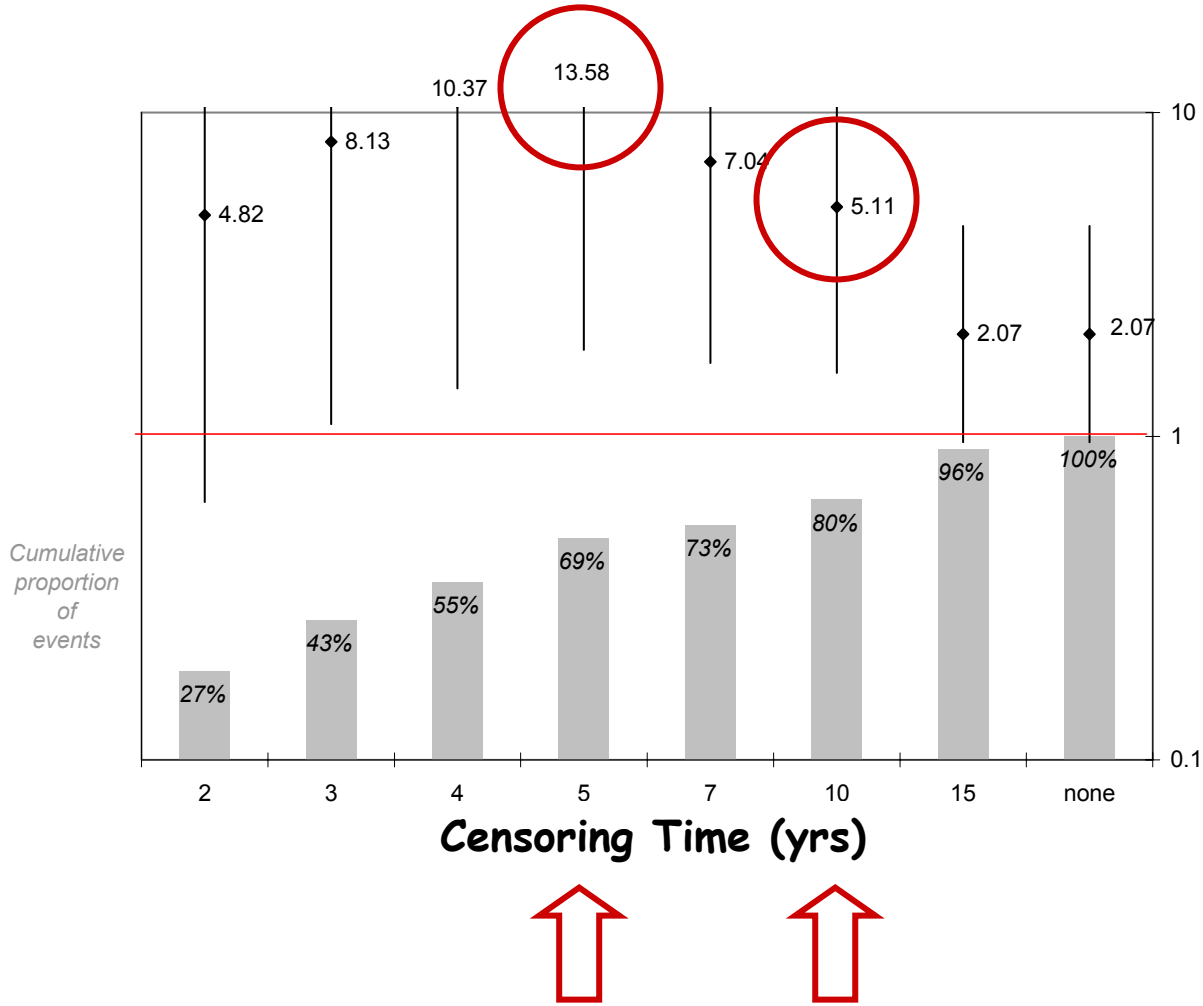
Time to Distant Metastases



Overall Survival



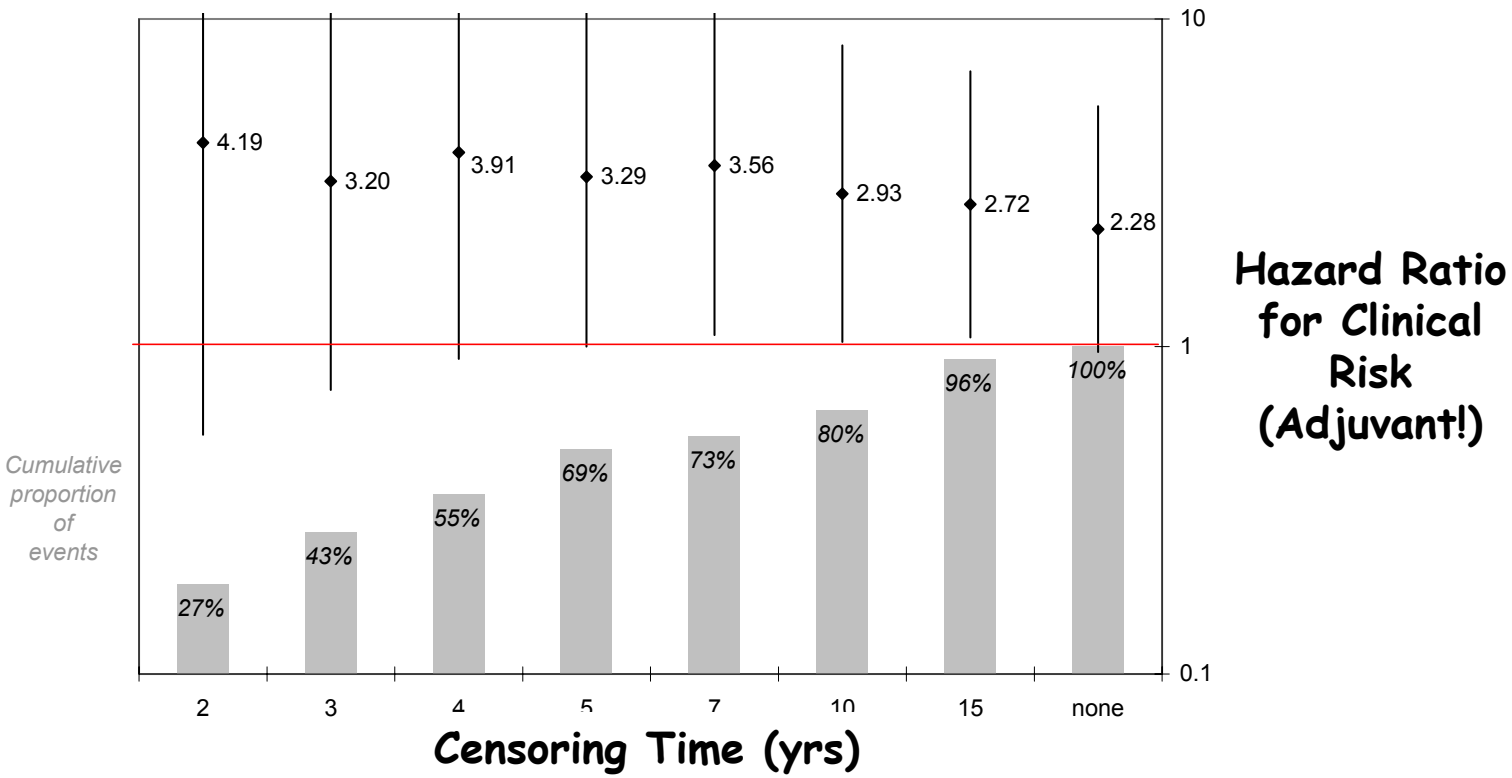
Time-dependency of the signature



Hazard Ratio for Gene Sign. Adjusted for Clinical Risk (Adjuvant!)

Similar phenomenon was seen with the Amsterdam signature!

Clinical Risk (Adjuvant!) over time



Conclusions

1. We have independently validated the Rotterdam 76-gene signature using the TRANSBIG validation series.

2. The performances of the Rotterdam and Amsterdam signatures are similar.

3. We observed a strong time dependency of both signatures, which was not seen for the clinical risk.

Conclusions

4. This independent multi-center study adds to the growing evidence that gene expression signatures are of clinical relevance, especially to identify patients at high risk of early distant metastases.

5. This two-year intensive "validation" work reinforces the belief that the time is right to launch a prospective trial (MINDACT) that will validate the added value of these signatures for adjuvant treatment tailoring.

Acknowledgements

Fanny Piette
Marc Buyse

Martine Piccart – Project leader
Christos Sotiriou - Lab coordinator
Fatima Cardoso - TransBig coordinator
Sherene Loi
Giuseppe Viale
Mauro Delorenzi
Mahasti Saghatchian d'Assignies
Jonas Bergh
Rosette Lidereau
Paul Ellis
Adrian Harris

John Foekens
Jan Klijn

Yixin Wang
Yi Zhang

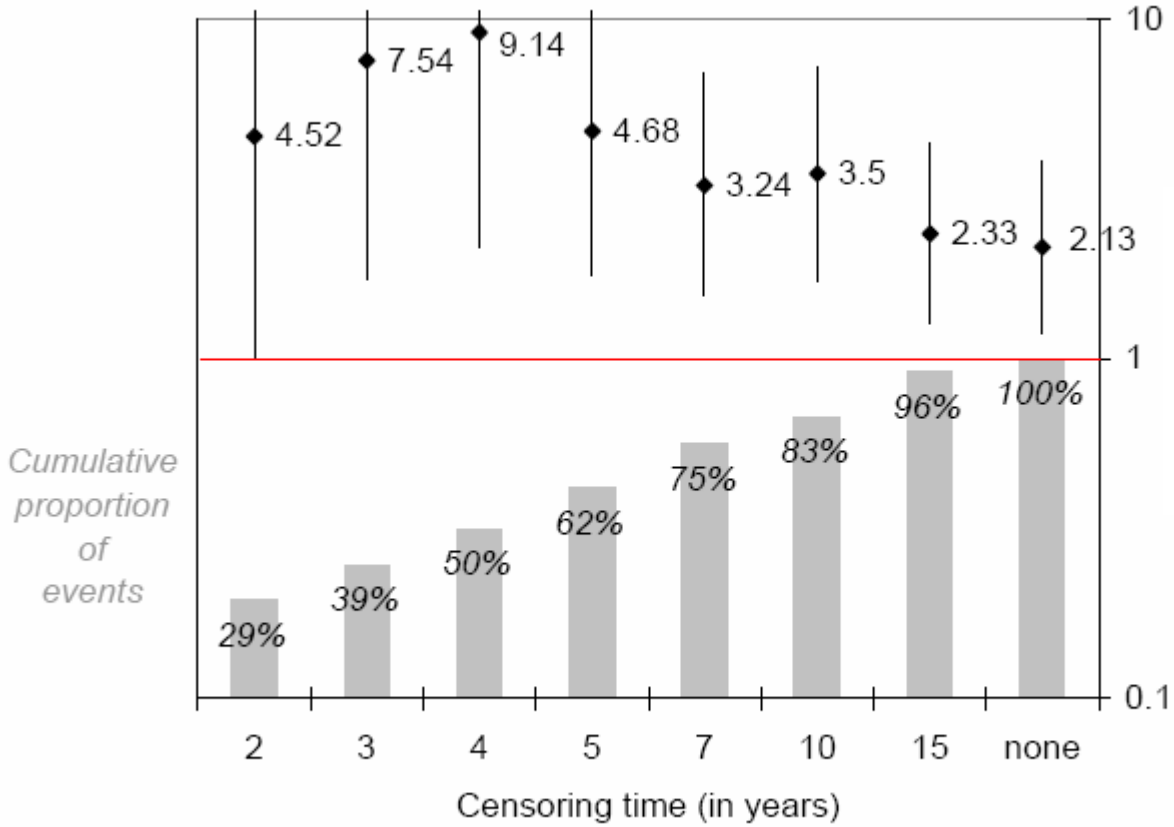
F. Lallemand
B. Haibe-Kains

On behalf on the TransBig Consortium

Partially funded by the European Commission's Framework VI Programme

Backup

Time-dependency of the signature AMSTERDAM SIGNATURE

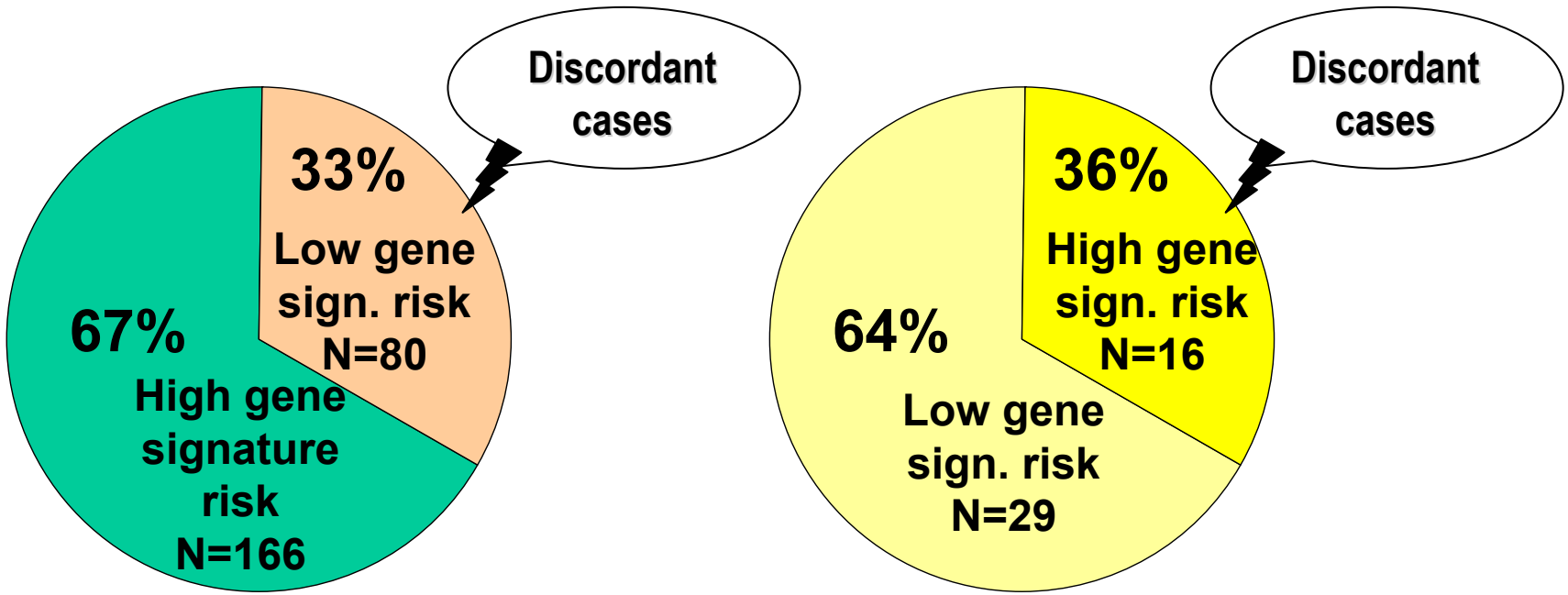


Hazard Ratio for Gene Sign. Adjusted for Clinical Risk (Adjuvant!)

CONCORDANCE BETWEEN CLINICAL AND GENE SIGNATURE RISK CLASSIFICATIONS

Amsterdam Signature

Threshold for low clinical risk defined as predicted 10-year O.S. > 90%



High clinical risk N=246

Low clinical risk N=45

Discordant cases with other clinical risk classifications	
St-Gallen = 35% NPI = 36%	St-Gallen = 43% NPI = 54%