

Multigene Testing in NCCN Breast Cancer Treatment Guidelines, v1.2011

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Selection of Adjuvant Systemic Therapy in NCCN Breast Cancer Guidelines

- Biological stratification
 - Identifies biologically important subtypes or categories of breast cancer
- Histological/Anatomical stratification
 - Dominant factor for determining prognosis
- Multi-gene array stratification
 - Used in predicting benefit to chemotherapy

Prognostic/Predictive Uses in NCCN Breast Treatment Guideline

	Prognostic	Predictive
Biological features	Yes	Yes
Anatomic features	Yes	No
Multi-gene assays	No	Yes

Version 1.2011



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HISTOLOGY

HORMONE RECEPTOR STATUS

HER2 STATUS

Ductal
Lobular
Mixed
Metaplastic

ER-positive
and/or
PR positive

HER2 positive

HER2 negative

ER-negative
and
PR-negative

HER2 positive

HER2 negative

Tubular
Colloid

ER-positive
and/or
PR positive

ER-negative
and
PR-negative



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SYSTEMIC ADJUVANT TREATMENT HORMONE RECEPTOR POSITIVE - HER2 NEGATIVE DISEASE

Histology:
• Ductal
• Lobular
• Mixed
• Metaplastic

pT1, pT2, or pT3; and pN0 or pN1mi (≤ 2 mm axillary node metastasis)

• Tumor ≤ 0.5 cm or
• Microinvasive

pN0

Consider adjuvant endocrine therapy

pN1mi

Adjuvant endocrine therapy (category 2B)

Tumor > 0.5 cm

Consider 21-gene RT-PCR assay (category 2B)

Not done

Adjuvant endocrine therapy ± adjuvant chemotherapy (category 1)

Low

recurrence score (< 18)

Adjuvant endocrine therapy (category 2B)

Intermediate recurrence score (18-30)

Adjuvant endocrine therapy ± adjuvant chemotherapy (category 2B)

High

recurrence score (≥ 31)

Adjuvant endocrine therapy + adjuvant chemotherapy (category 2B)

Node positive (one or more metastases > 2 mm to one or more ipsilateral axillary lymph nodes)

Adjuvant endocrine therapy + adjuvant chemotherapy (category 1)

Gene Profiling Technology:

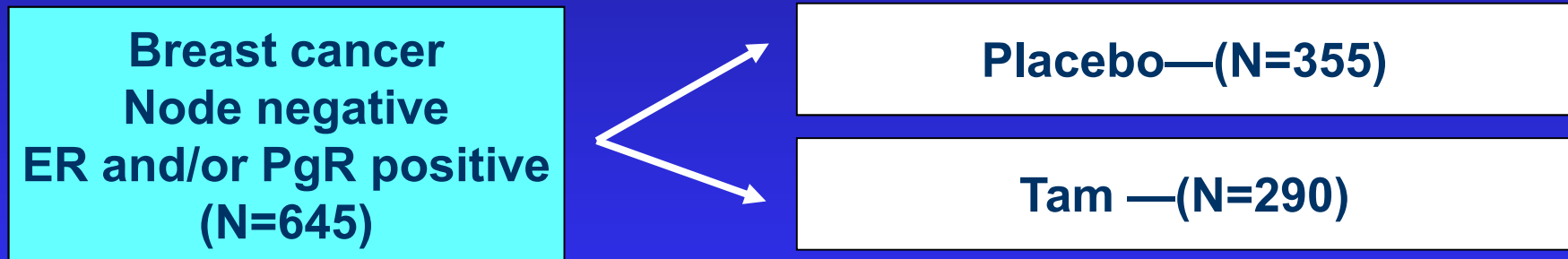


Oncotype DX™ Technology: Algorithm and Recurrence Score (RS)

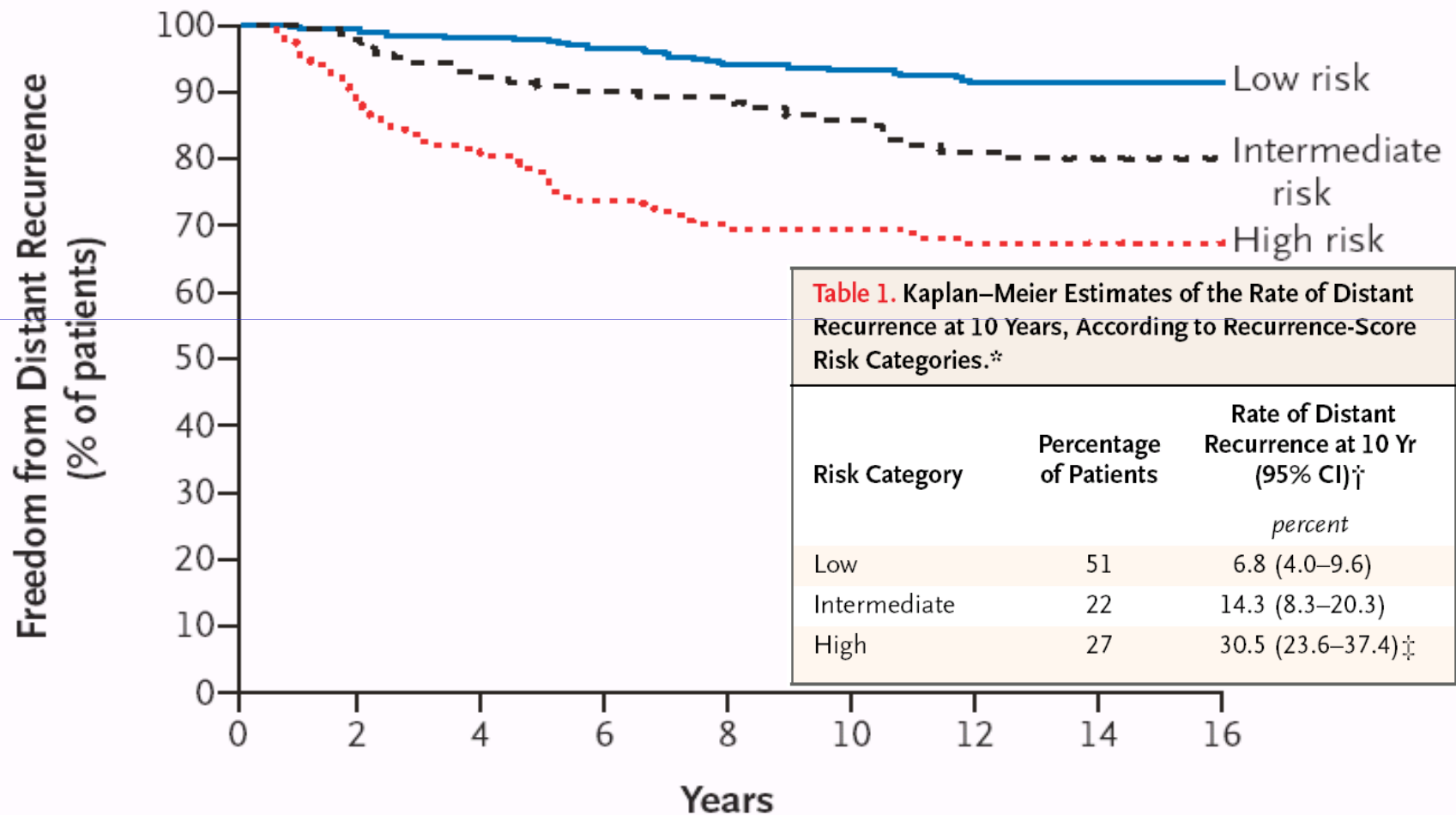
$$\begin{aligned} \text{RS} = & +0.47 \times \text{HER2 Group Score} \\ & -0.34 \times \text{ER Group Score} \\ & +1.04 \times \text{Proliferation Score} \\ & +0.10 \times \text{Invasion Group Score} \\ & +0.05 \times \text{CD68} \\ & -0.08 \times \text{GSTM1} \\ & -0.07 \times \text{BAG1} \end{aligned}$$

Recurrence Category	RS (0-100)
Low risk	<18
Intermediate risk	18-30
High risk	≥31

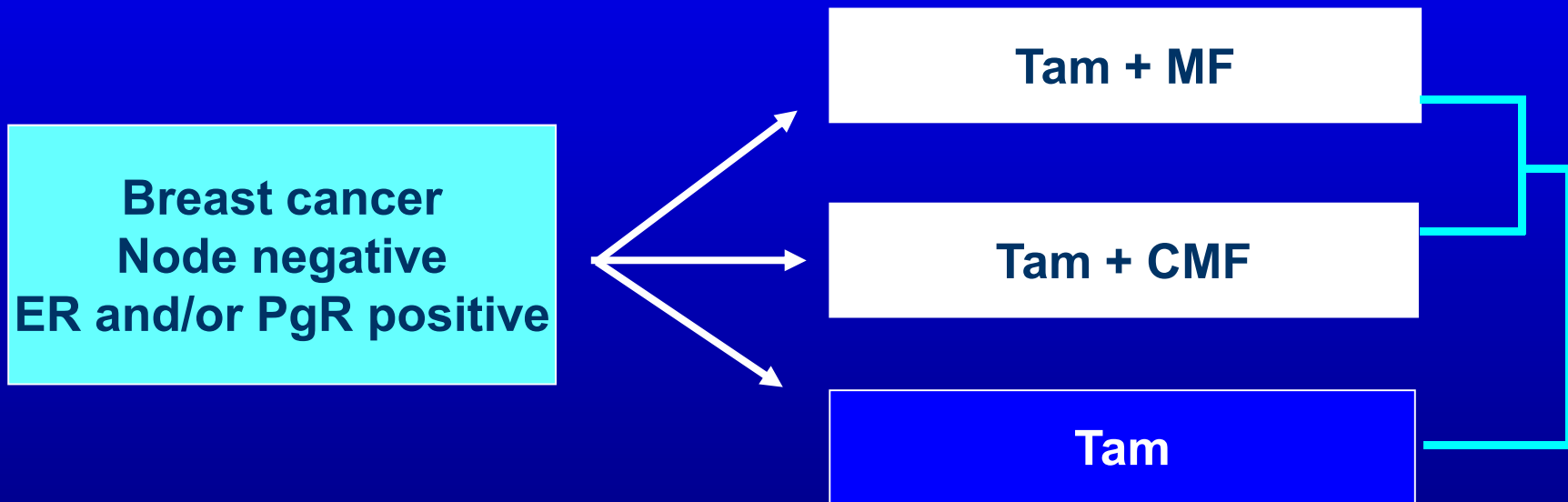
RS as a predictive factor for benefit from tamoxifen: NSABP B-14



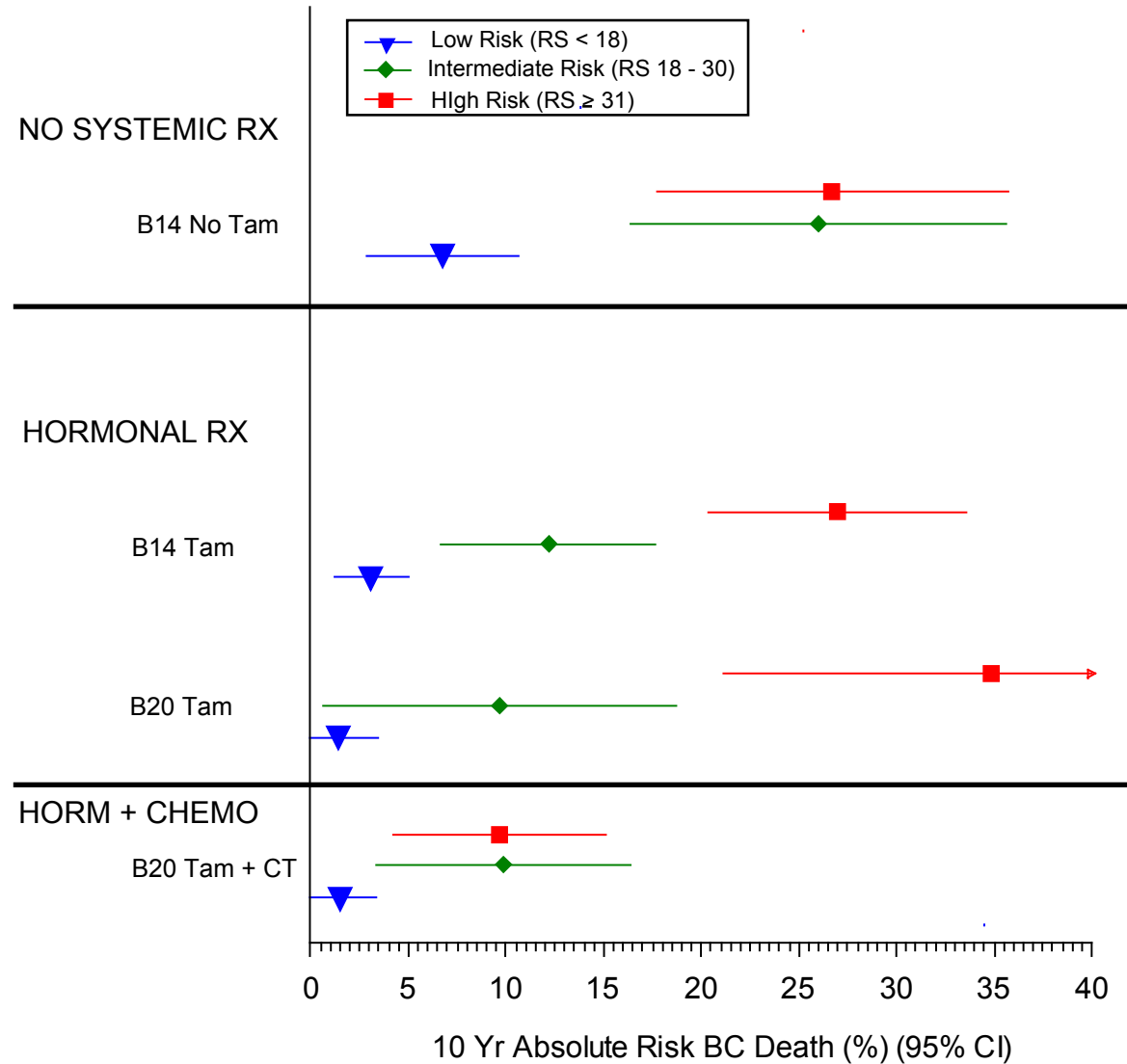
21 Gene RT-PCR Assay Validation Study B-14



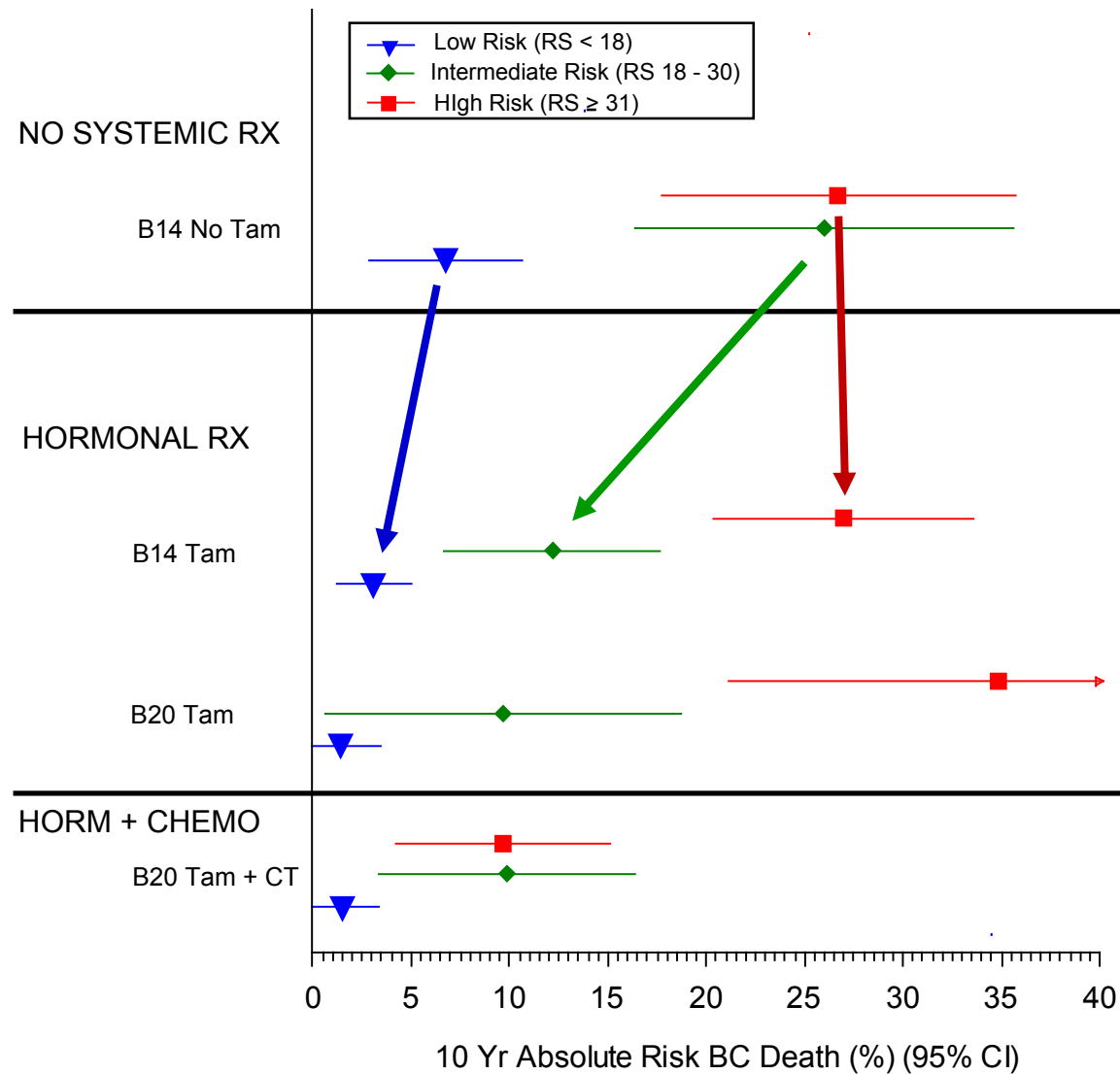
RS as a predictive factor for benefit from adjuvant chemotherapy: NSABP B-20



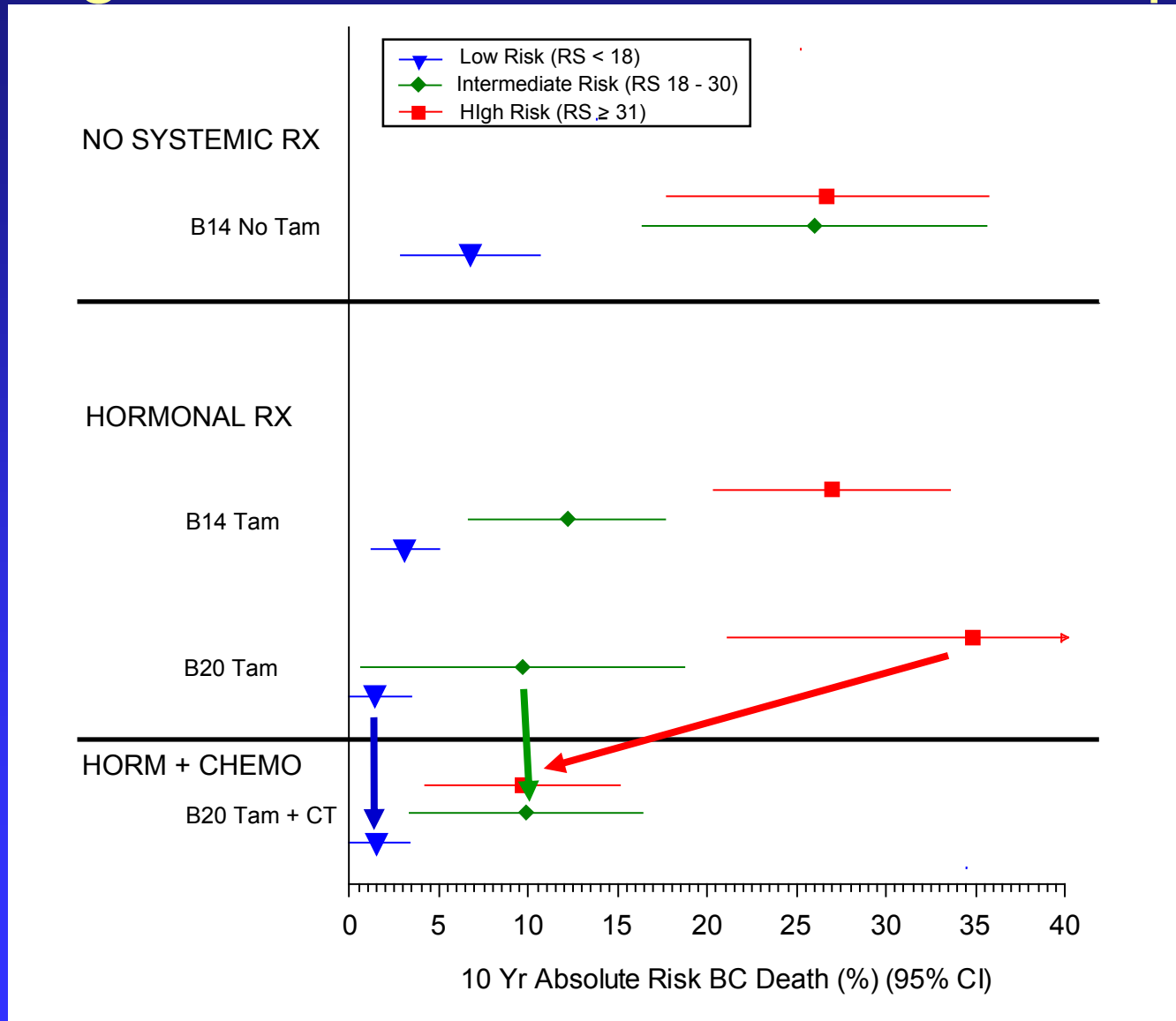
RS and Breast Cancer Death in NSABP B-14 and B-20



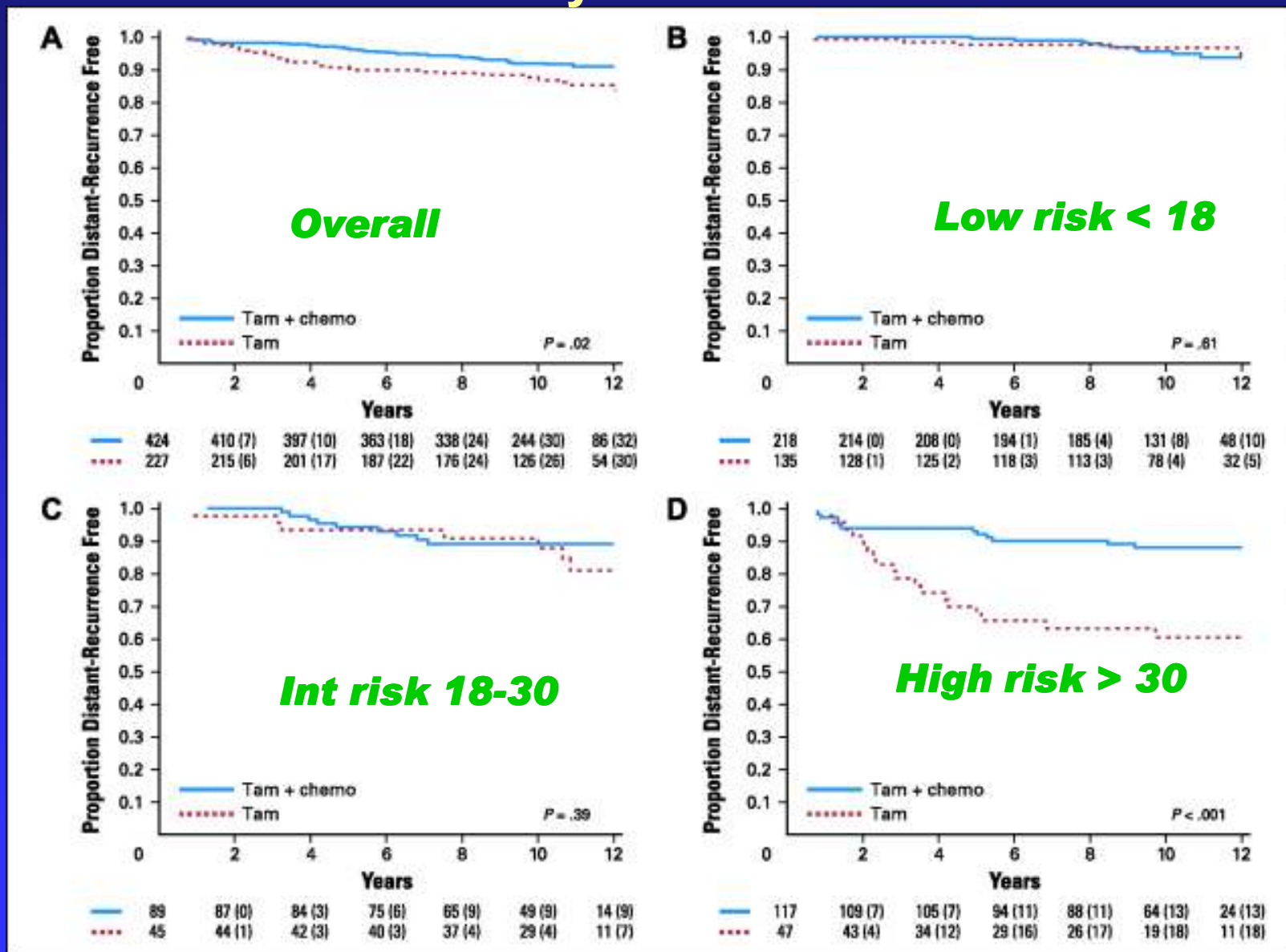
Largest Tamoxifen Benefit Observed in Low and Intermediate Recurrence Score Groups



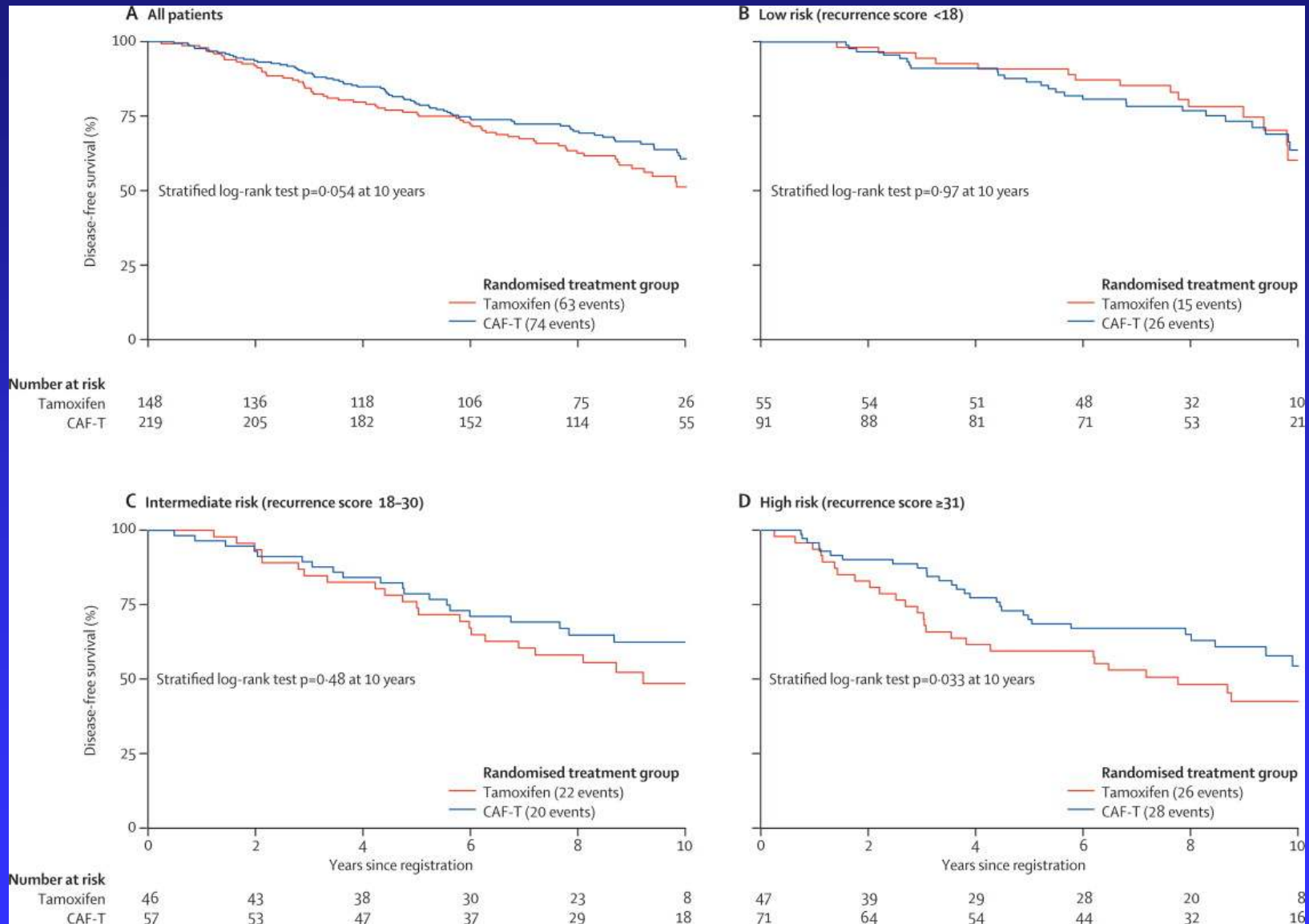
Largest Chemotherapy Benefit Observed in High Risk Recurrence Score Group



NSABP B-20 Outcome by Recurrence Score

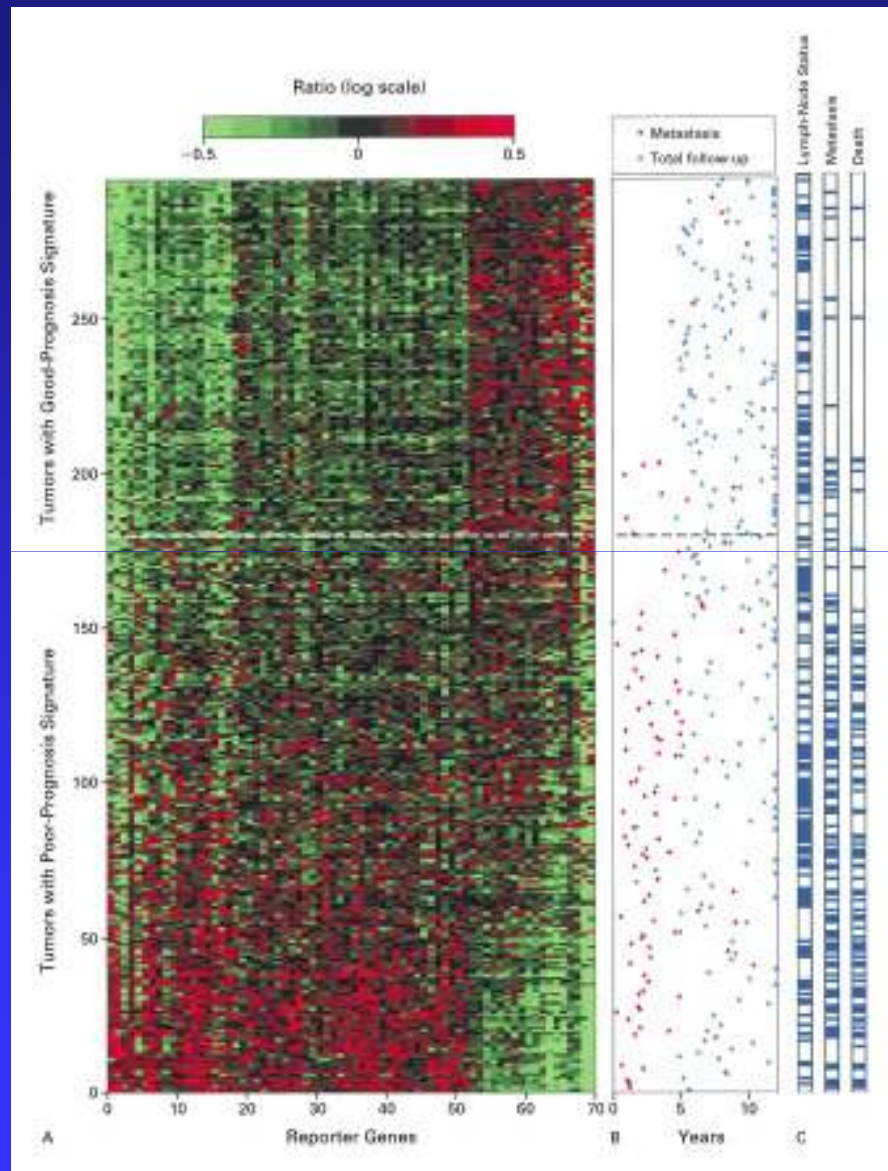


SWOG 8814: ER+ LN+, TAM ± CAF chemotherapy



Albain KS, et al. Lancet Oncology 2010;11:55

Pattern of Expression of Genes Used to Determine the Prognosis and Clinical Characteristics of 295 Patients with Breast Cancer

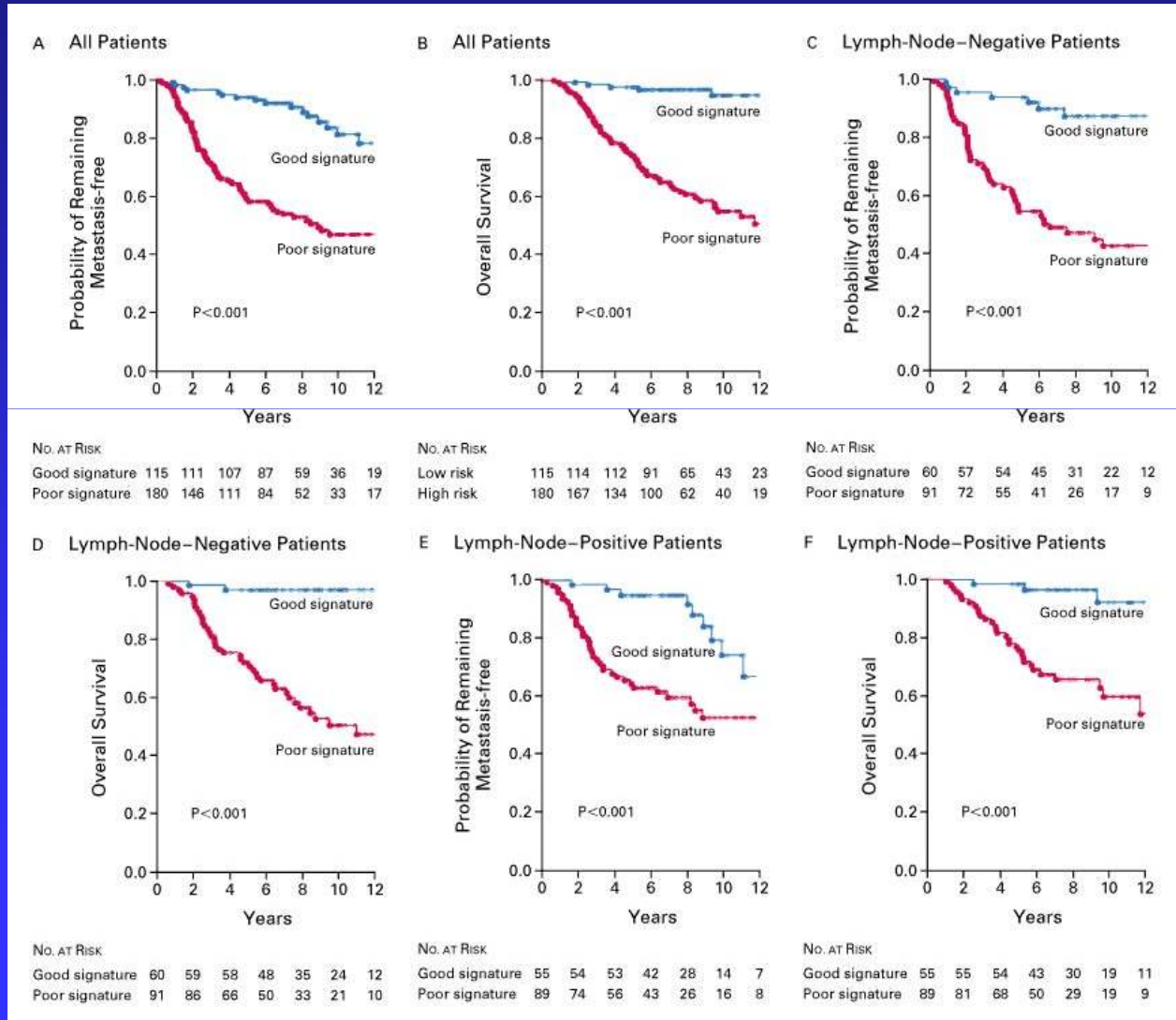


van de Vijver, M. et al. N Engl J Med 2002;347:1999-2009

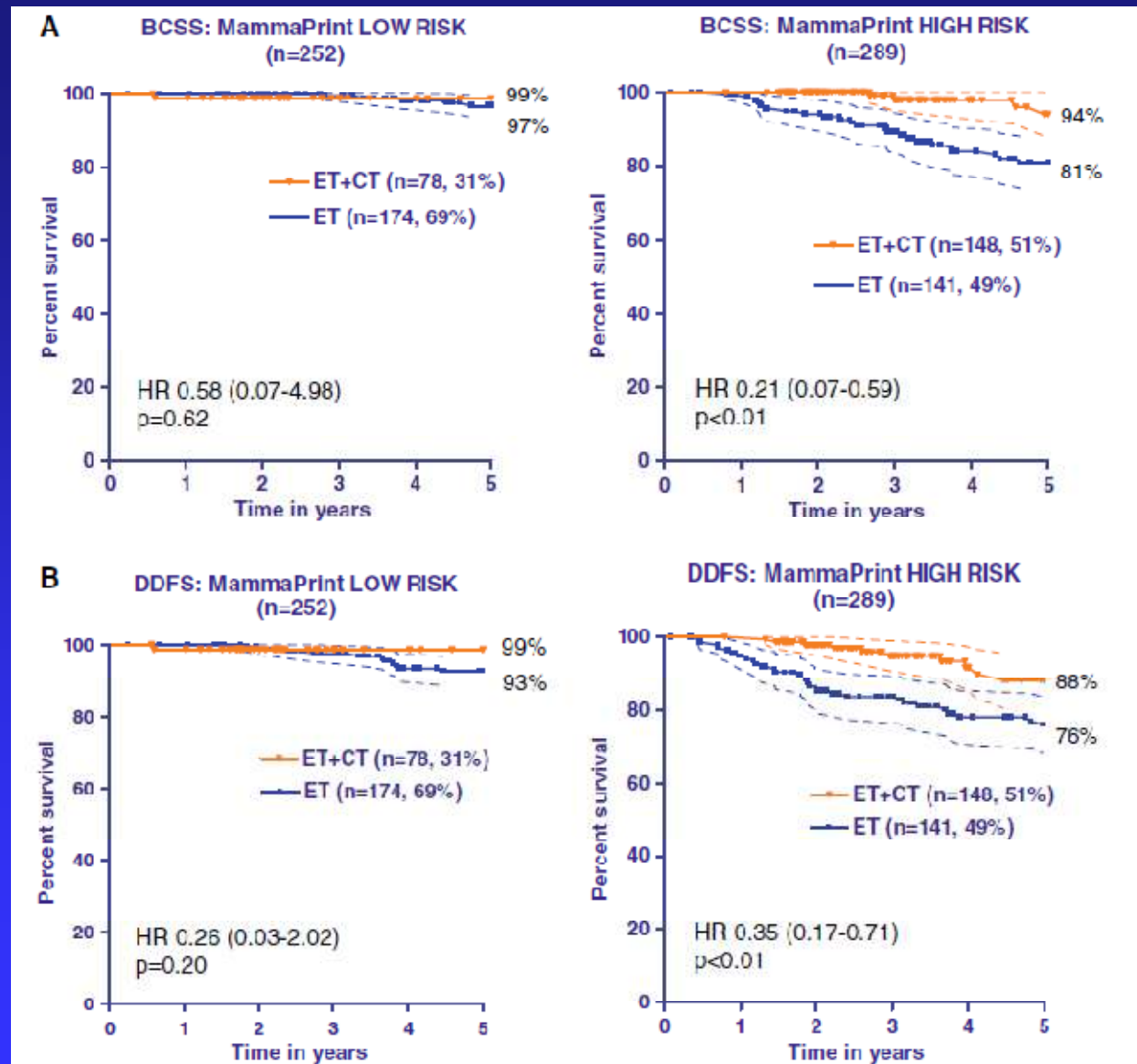


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Overall Survival among All Patients (Panels A, and B, Respectively), Patients with Lymph-Node-Negative Disease (Panels C and D, Respectively), and Patients with Lymph-Node-Positive Disease (Panels E and F, Respectively)



70-Gene (MammaPrint) Predictive Data



MammoPrint Predictive Value for Adjuvant Chemotherapy

- Pooled data from 1637 subjects
 - 7 trials
 - Non-phase III trials
 - Subjects retrospectively identified
 - Only 541 subjects with T1-3 disease, 0-3 + ALNs included
 - Multiple chemotherapies, non-random assignment
 - Median follow-up included subjects 7.1 yrs
 - Outcome censored at 5-years

Table 1. Commercially Available Genomic Assays for the Prediction of Clinical Outcome in Patients with Breast Cancer.*

Variable	MammaPrint	Oncotype DX	Theros	MapQuant Dx
Provider	Agendia	Genomic Health	Biotheranostics	Ipsogen
Type of assay	70-Gene assay	21-Gene recurrence score	2-Gene ratio of HOXB13 to IL17R (H/I) and molecular-grade index	Genomic grade
Type of tissue sample	Fresh or frozen	Formalin-fixed, paraffin-embedded	Formalin-fixed, paraffin-embedded	Fresh or frozen
Technique	DNA microarrays	Q-RT-PCR	Q-RT-PCR	DNA microarrays
Centrally certified laboratory†	Yes	Yes	Yes	Yes
Indication	To aid in prognostic prediction in patients <61 yr of age with stage I or II, node-negative disease with a tumor size of ≤5 cm	To predict the risk of recurrence in patients with ER-positive, node-negative disease treated with tamoxifen; to identify patients with a low risk of recurrence who may not need adjuvant chemotherapy	To stratify ER-positive patients into groups with a predicted low risk or high risk of recurrence and a predicted good or poor response to endocrine therapy	To restratify grade 2 tumors into low-risk grade 1 or high-risk grade 3 tumors, specifically for invasive, primary, ER-positive grade 2 tumors
Level of evidence (I–V)‡	III	II	III	III
FDA clearance	Yes	No	No	No
Availability	Europe and United States	Europe and United States	United States	Europe

* ER denotes estrogen receptor, FDA Food and Drug Administration, and Q-RT-PCR quantitative reverse-transcriptase–polymerase chain reaction.

† Laboratories were certified according to the criteria of the Clinical Laboratory Improvement Amendments or by the International Organization for Standardization.

‡ Levels of evidence are measured on a scale ranging from I (strongest) to V (weakest).⁵⁴

Summary

- This review discusses the results of DNA microarray signatures in breast cancer.
- These signatures have been useful in the classification of breast cancers, and they have an association with clinical outcomes.
- Surprisingly, there is little overlap in the types of genes among several useful microarray signatures.
- **The true value of these signatures will become apparent only when prospective trials, now in progress, have been completed.**



ASCO Tumor Marker Guideline 2007

Multiparameter Gene Expression Analysis for Breast Cancer

- *Oncotype DX*[™] can be used to determine prognosis in newly diagnosed patients with node-negative, estrogen-receptor positive breast cancer who will receive tamoxifen.
 - To predict risk of recurrence in patients considering tamoxifen
 - To predicted therapeutic benefit from adjuvant tamoxifen and may not require adjuvant chemotherapy
 - To predict therapeutic benefit from adjuvant chemotherapy (specifically CMF)
- The precise clinical utility and appropriate application for other multigene assays were insufficiently defined to recommend their use.

St Gallen 2009

“In an important change from the previous St Gallen conference and after a long debate, the Panel supported the use of a validated multigene-profiling assay, if readily available, as an adjunct to high-quality phenotyping of breast cancer in cases in which the indication for adjuvant chemotherapy remained uncertain.”



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