Robert H. Lurie Comprehensive Cancer Center of Northwestern University

NCCN National Comprehensive Cancer Network®

Assessment of Risk Recurrence: Adjuvant Online, OncotypeDx & Mammaprint

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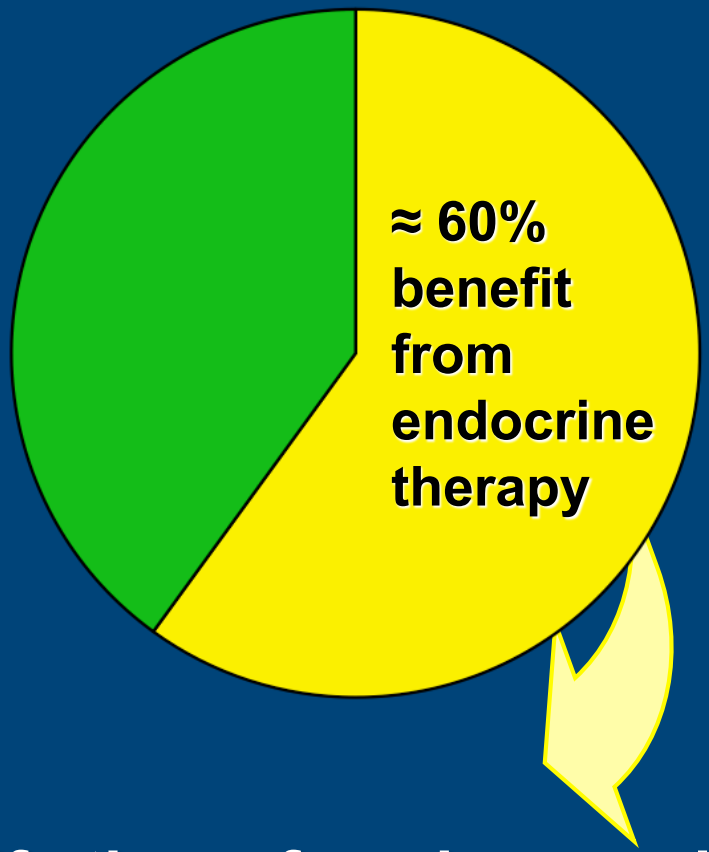
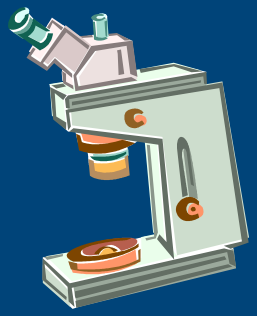
ER a/o PgR Positive Breast Cancer Selection of Adjuvant Therapy



Can we identify those for whom endocrine therapy is all that is needed to confer an excellent outcome?

Traditional Pathology
There is room for improvement!



LOW Risk

INTERMEDIATE Risk

HIGH Risk

In reality!

In reality!

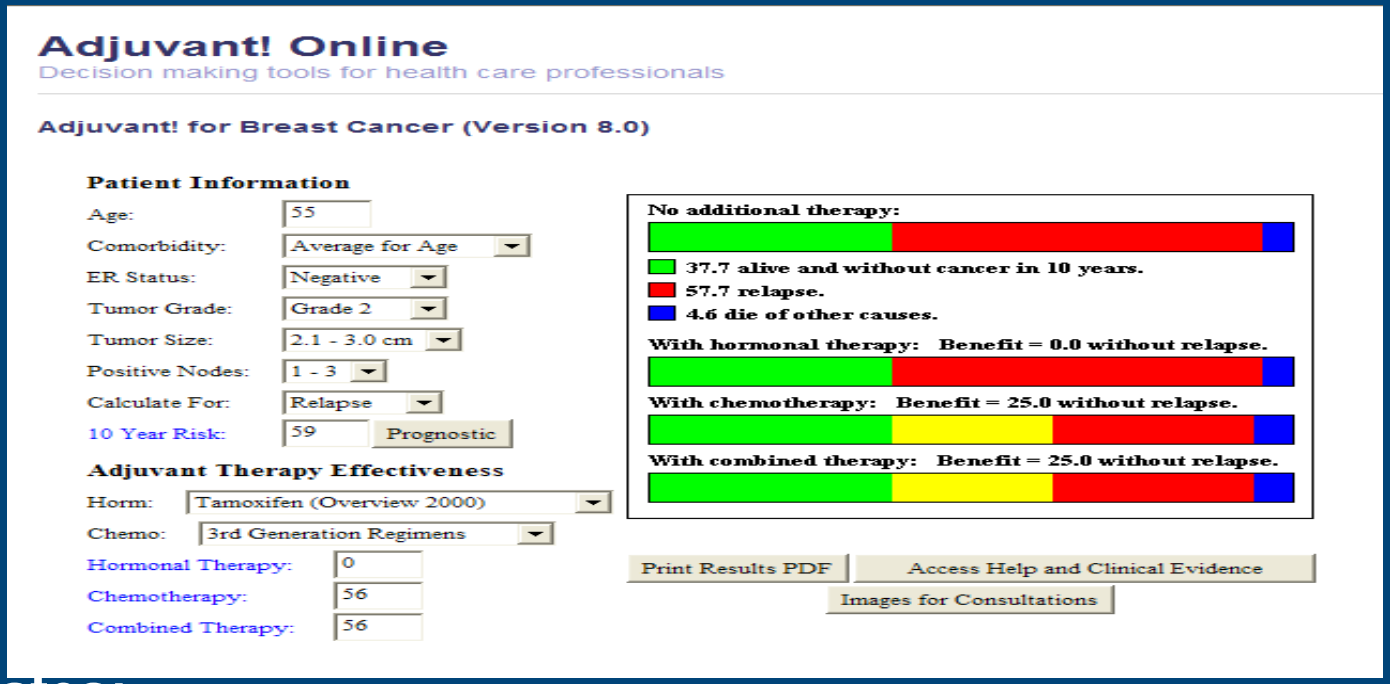
“Classical” Prognostic/Predictive Factors

Factor	Prognostic?	Predictive?
TNM Stage	Yes	No
N of ALNs	Yes	No
Size of primary	Yes	No
Tumor grade	Yes	Yes
ER/PgR	Yes	Yes
Mitotic rate	Yes	?
HER2	?	Yes
Patient Age	Yes	Yes

Genomic Profiling in Breast Cancer Treatment

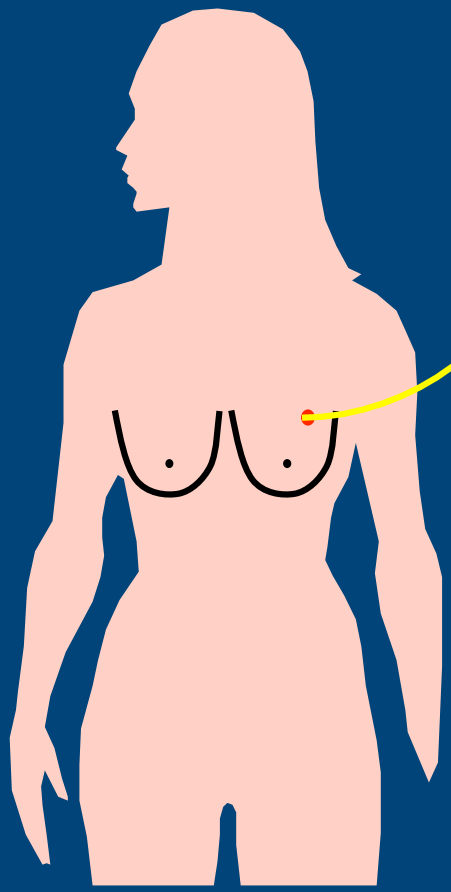
- Do genomic profiles assist in assigning baseline prognosis independent of classic prognostic factors?
- Do genomic profiles provide predictive information independent of classic predictive factors?

Adjuvant! Online
www.adjuvantonline.com



- Estimates:
  - Risk of cancer-related mortality or relapse without therapy
  - Risk reduction with therapy
  - Risk of side effects from therapy
- Limitations
  - Prognostic factors not all inclusive
    - HER2 status not included
    - Small tumors not well characterized

Available at: http://www.adjuvantonline.com



46-year-old,
premenopausal
T = 1.4cm (ductal)
One micrometastasis

ER ++, PgR ++, HER2 –
Ki67 < 5%
Grade I

- Endocrine responsiveness: "HIGH"
- Need to "optimize" endocrine therapy: TEXT trial discussed
- Added benefit from chemotherapy: "MODEST"

CONSULT ADJUVANT ON LINE!

Shared Decision Making

Name: _____ (Breast Cancer)

Age: 46 General Health: Good

Estrogen Receptor Status: Positive Histologic Grade: 1

Tumor Size: 1.1 - 2.0 cm Nodes Involved: 0

Chemotherapy Regimen: Anthracycline (Overview 2000)

Decision: No Additional Therapy

80 out of 100 women are alive and without cancer in 10 years.

18 out of 100 women relapse.

2 out of 100 women die of other causes.

Decision: Hormonal Therapy

7 out of 100 women are alive and without cancer because of therapy.

Decision: Chemotherapy

8 out of 100 women are alive and without cancer because of therapy.

Decision: Combined Therapy

12 out of 100 women are alive and without cancer because of therapy.

Oncotype Dx

- RT-PCR Multiplex Assay using formalin-fixed paraffin embedded tissue sections
- Commercially available Centralized Testing
- 21 Gene Recurrence Score for Node Negative ER+ (IHC) Patients
- Initial study using NSABP tissues showed strong positive and negative predictive value for disease recurrence in patients treated with tamoxifen alone and with CMF chemotherapy
- Recent ASCO 2005 presentation showed strong stand alone prognostic value in untreated patients
- Of the 21 genes, the ER and Ki-67 have the most predictive power (Bcl2 augments ER)
- Recent evidence is emerging that ER mRNA measurement may outperform IHC in correctly predicting response to tamoxifen and AI's.

21 Gene Recurrence Score (RS) Assay

16 Cancer and 5 Reference Genes From 3 Studies

PROLIFERATION
Ki-67
STK15
Survivin
Cyclin B1
MYBL2

ESTROGEN
ER
PR
Bcl2
SCUBE2

GSTM1

BAG1

CD68

INVASION
Stromolysin 3
Cathepsin L2

HER2
GRB7
HER2

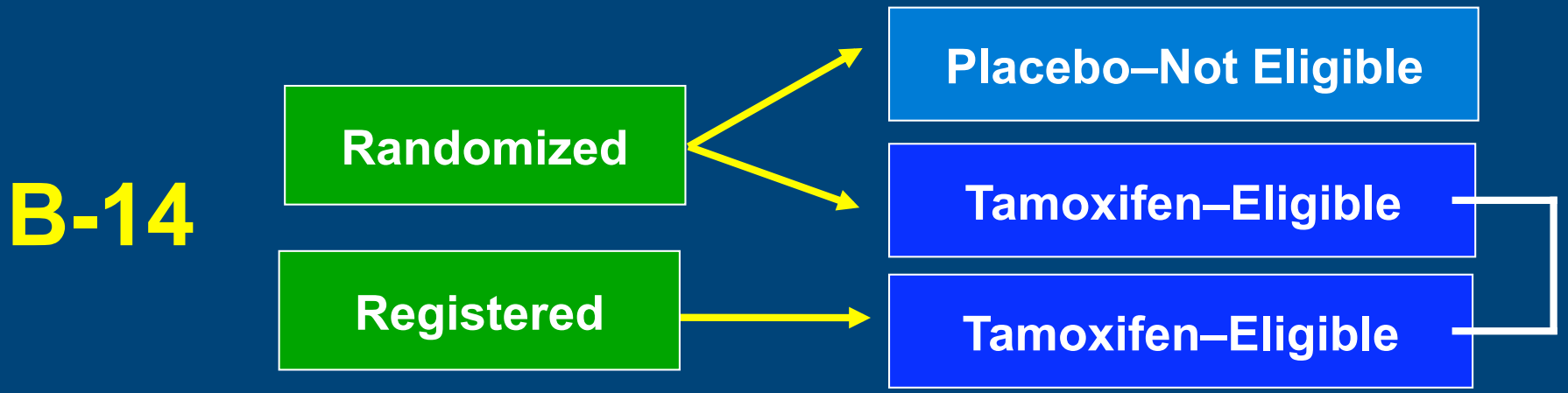
REFERENCE
Beta-actin
GAPDH
RPLPO
GUS
TFRC

RS = + 0.47 x HER2 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

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

21 Gene Recurrence Score (RS) Assay-NSABP B-14 Prospective Clinical Validation Study

- **Objective**
  - Validate Recurrence Score as predictor of distant recurrence in N-, ER+, tamoxifen-treated patients



  - Pre-specified 21 gene assay, algorithm, endpoints, analysis plan
  - Blinded laboratory analysis of three 10 μ sections

Paik et al, NEJM 2004

B-14 Results
DRFS—Low, Intermediate and High RS Groups

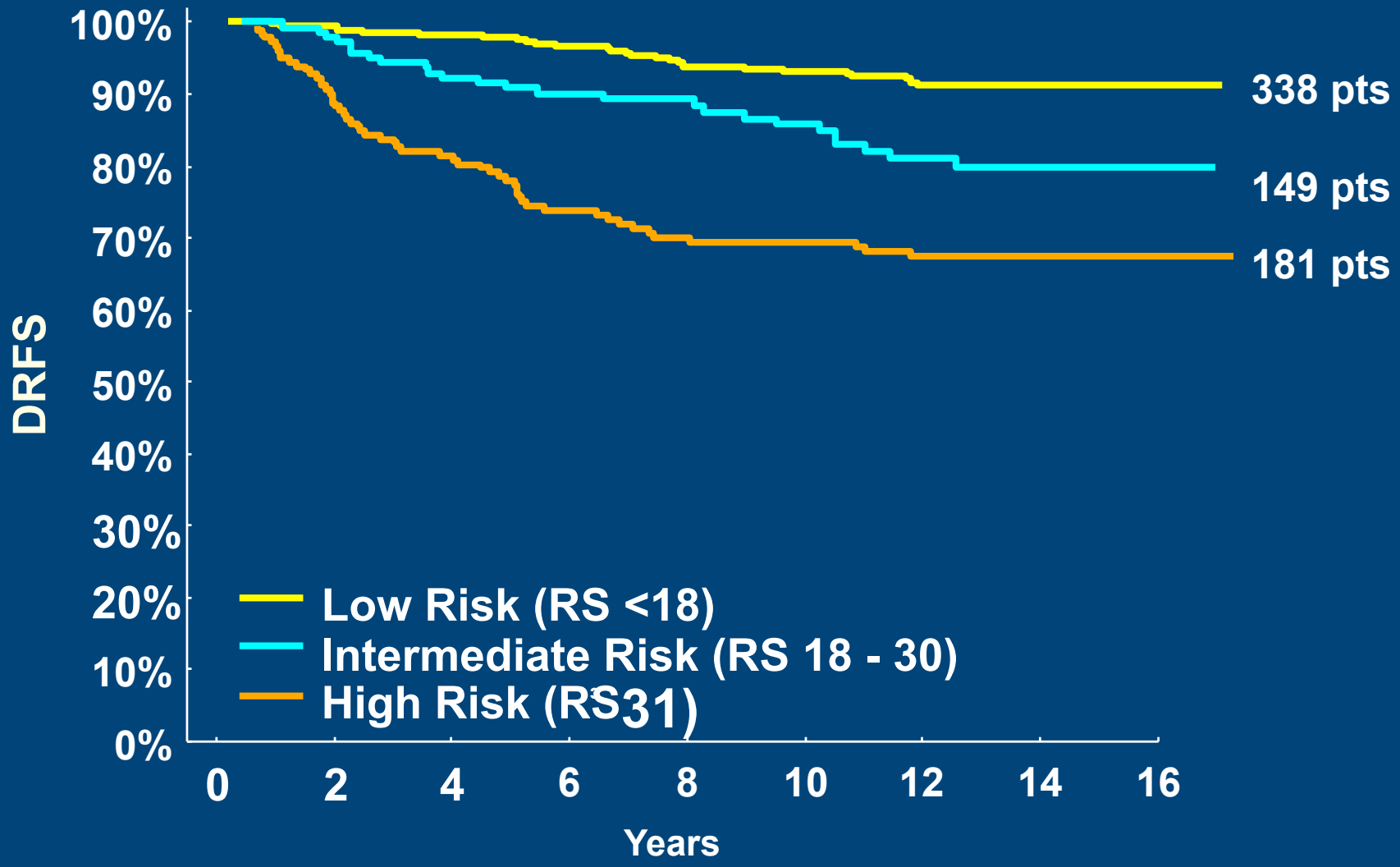
Risk Group	% of Patients	10-yr Rate	95% CI Recurrer
Low (RS<18)	51%	6.8%	4.0%, 9.6%
Intermediate (RS 18-30)	22%	14.3%	8.3%, 20.3%
High (RS≥31)	27%	30.5%	23.6%, 37.4%

Test for the 10-year DRFS comparison between the Low and High risk groups: p<0.00001

Paik et al, NEJM 2004

B-14 Results

DRFS—Low, Intermediate and High RS Groups



Paik et al, NEJM 2004

Tamoxifen Benefit and 21 Gene Recurrence Score (RS) Assay

NSABP B-14 Tam Benefit Study in N-, ER+ Pts

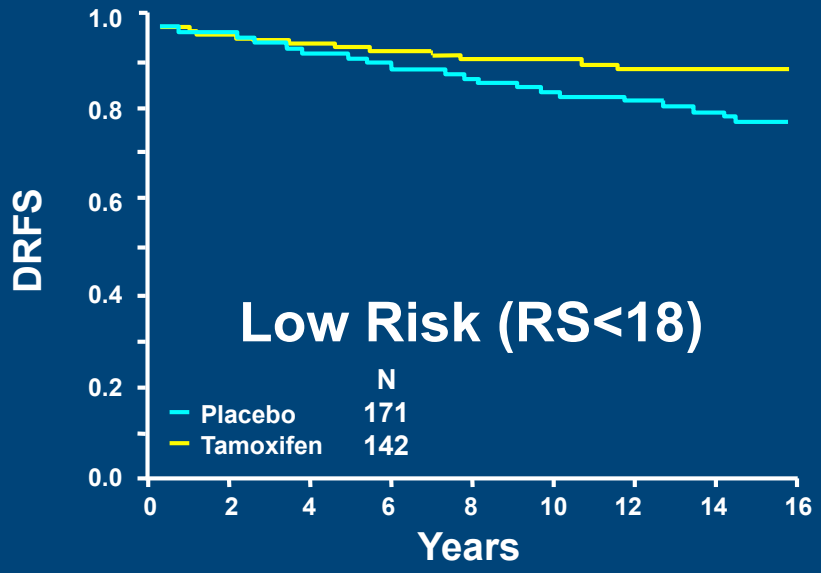
Design

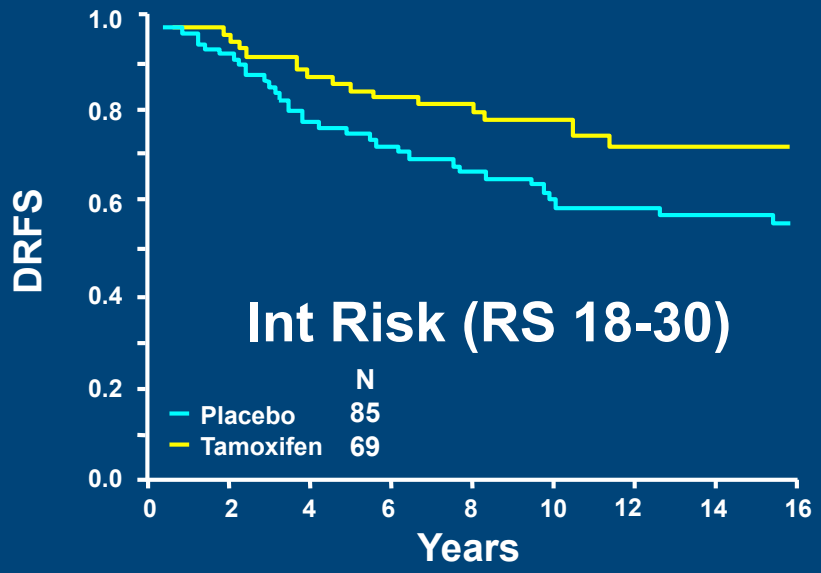
Objective

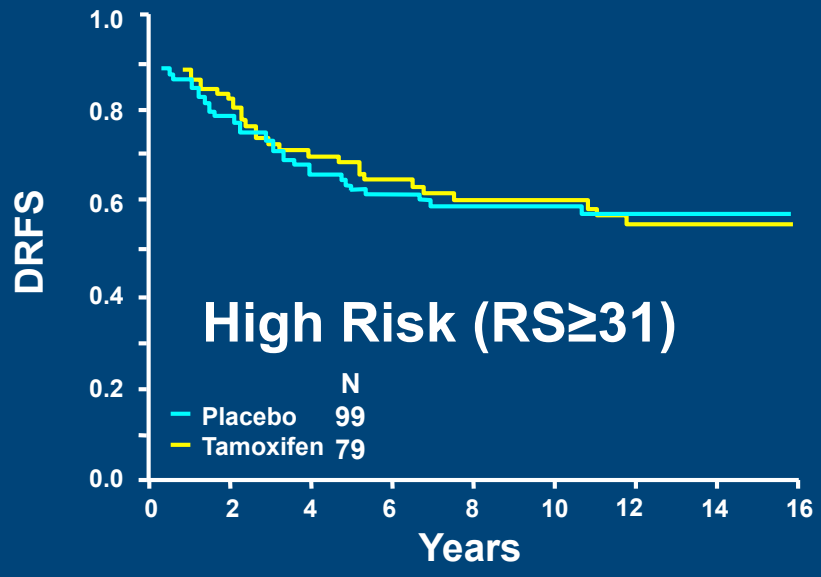
Determine whether the 21 gene RS assay captures:

1) prognosis
2) response to tamoxifen
3) both

B-14 Benefit of Tam
By Recurrence Score Risk Category







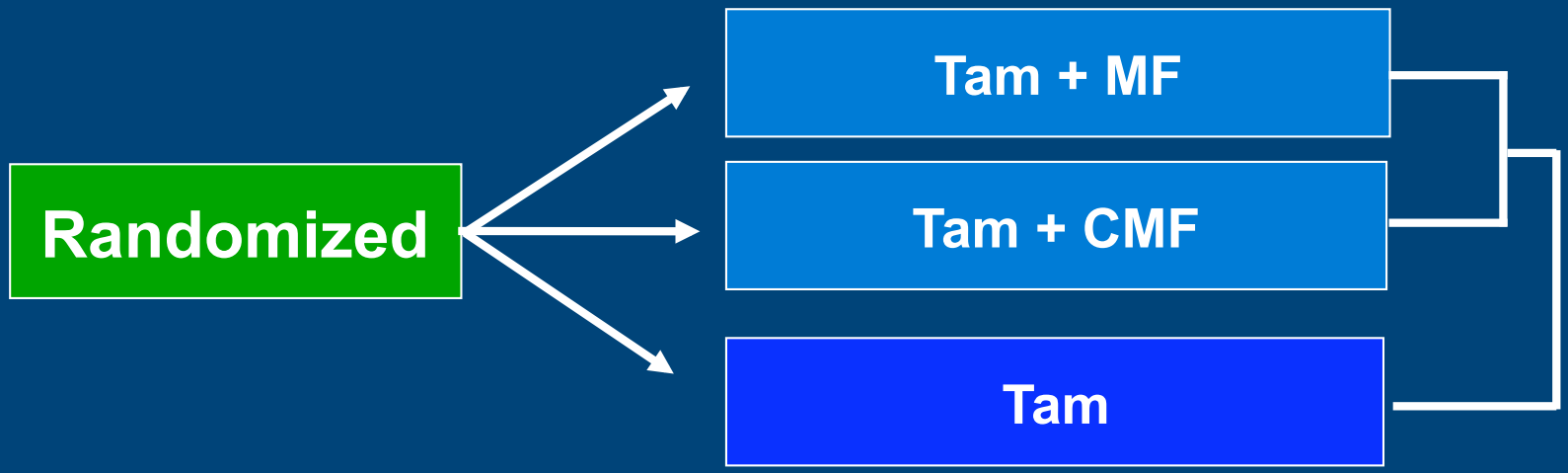
Interaction p=0.06

Paik et al SABCS 2005

Chemotherapy Benefit and 21 Gene Recurrence Score (RS) Assay

NSABP B-20 Chemo Benefit Study in N-, ER+ Pts

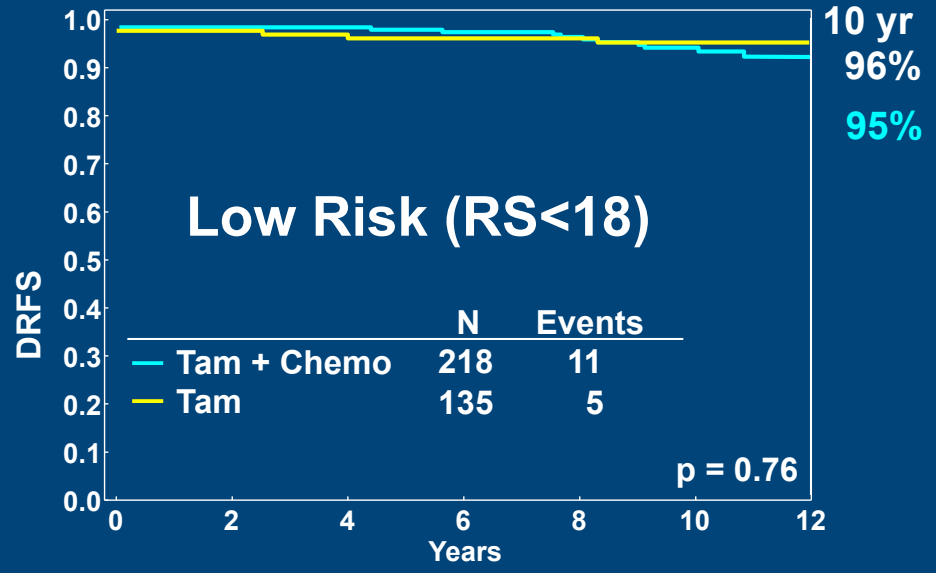
Design

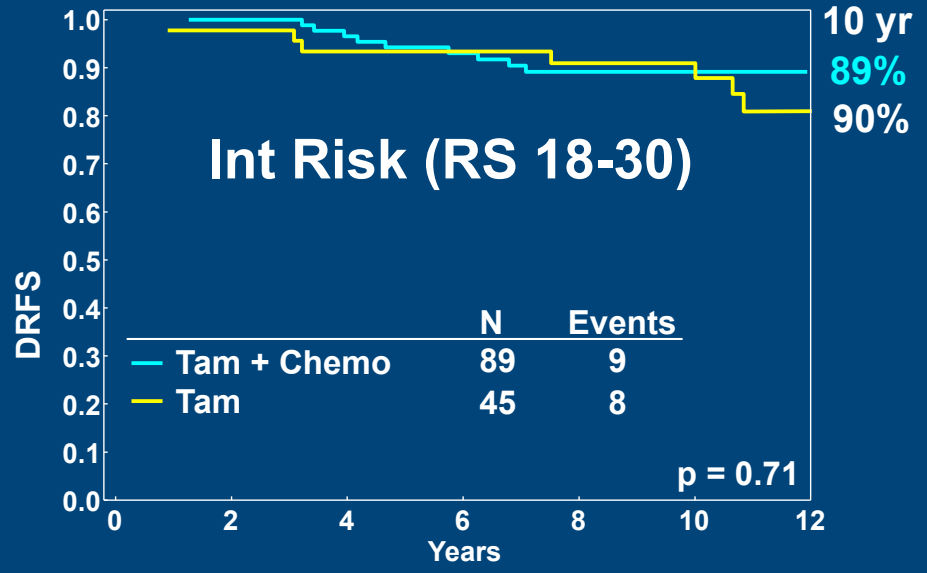


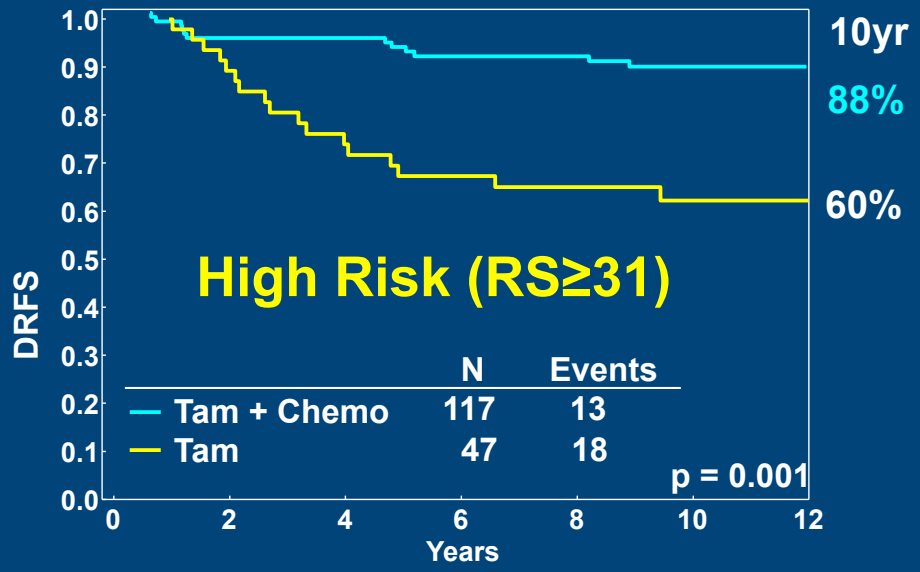
Objective

Determine the magnitude of the chemotherapy benefit as a function of 21 gene Recurrence Score assay

Benefit of Chemotherapy Based on RS







Paik et al SABCS 2005

Important Caveat

- Likely that many patients in B-14 & B-20 had microscopic nodal involvement as more intense scrutiny of nodes was not routinely done!!

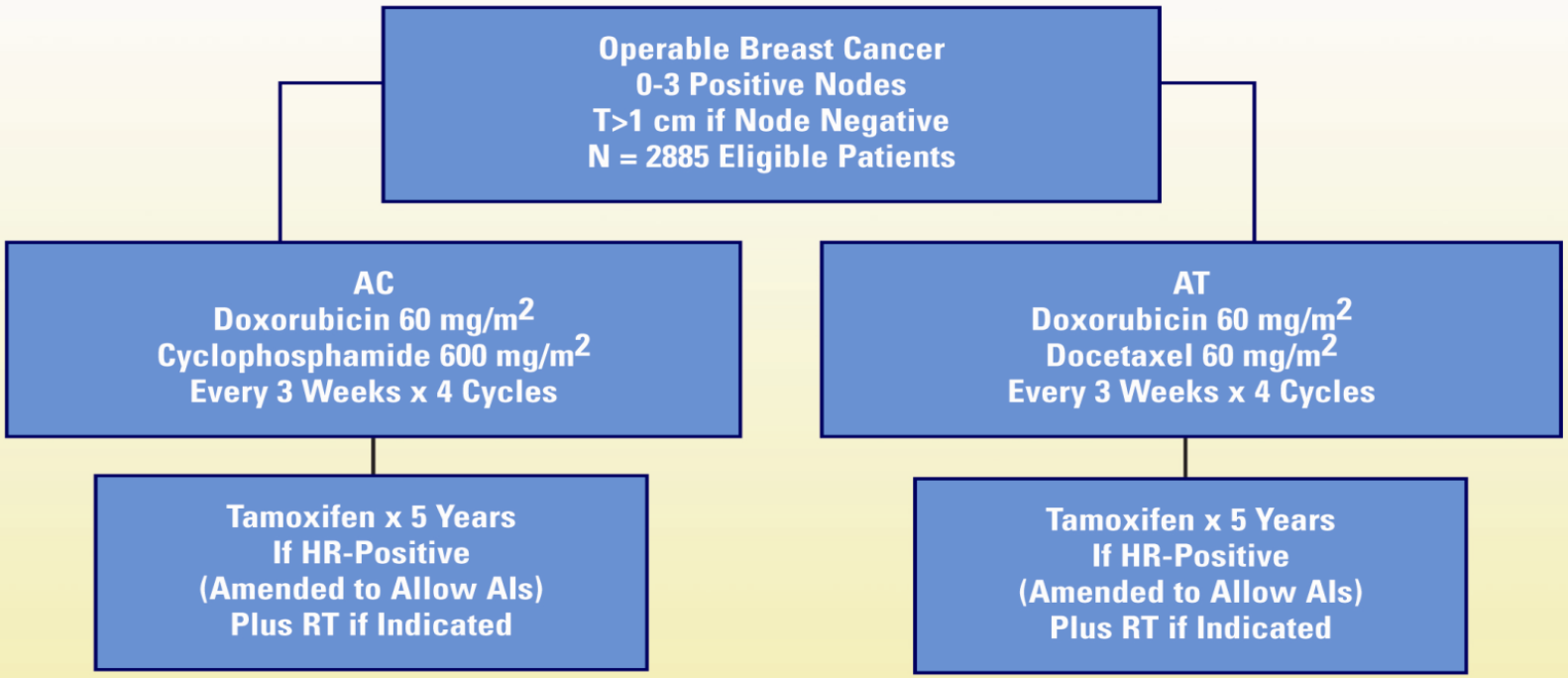
ASCO Guidelines

"The Oncotype DX tumor marker test is recommended for patients with node-negative breast cancer that is ER-positive and/or PR-positive, which is the case for 50 percent of breast cancer patients. The test measures multiple genes at once to estimate the risk of breast cancer recurrence. Patients with a low recurrence score may be able to receive only hormone therapy and avoid chemotherapy. Sparing patients from unnecessary treatment may not only improve their quality of life, but it also will reduce overall health care costs".

JCO 11.20.07

Original E2197: Study Design and Results

Figure 1: E2197 Study Design and Results



RESULTS:

- No difference between arms
- Median follow-up 76 months
- 96.8% reported follow-up until death or for at least 5 years

ASCO -Goldstein, Abstract #526

Objectives in E-2197 Genomic Analysis

General:

- Improve ability to identify individuals who benefit from chemotherapy, or specific chemotherapy regimens that vary in duration or drugs used

Specific:

1. **To evaluate the prognostic utility of 21 Gene Assay RS in pts with HR-Pos disease treated with adjuvant chemotherapy**
2. To perform an exploratory analysis for individual genes associated with prognosis in patients with HR-Pos and HR-Neg disease treated with adjuvant chemotherapy (analysis ongoing)
3. To perform an exploratory analysis to identify individual genes associated with differential sensitivity to AC versus AT (analysis ongoing)

ASCO - Goldstein, Abstract #526

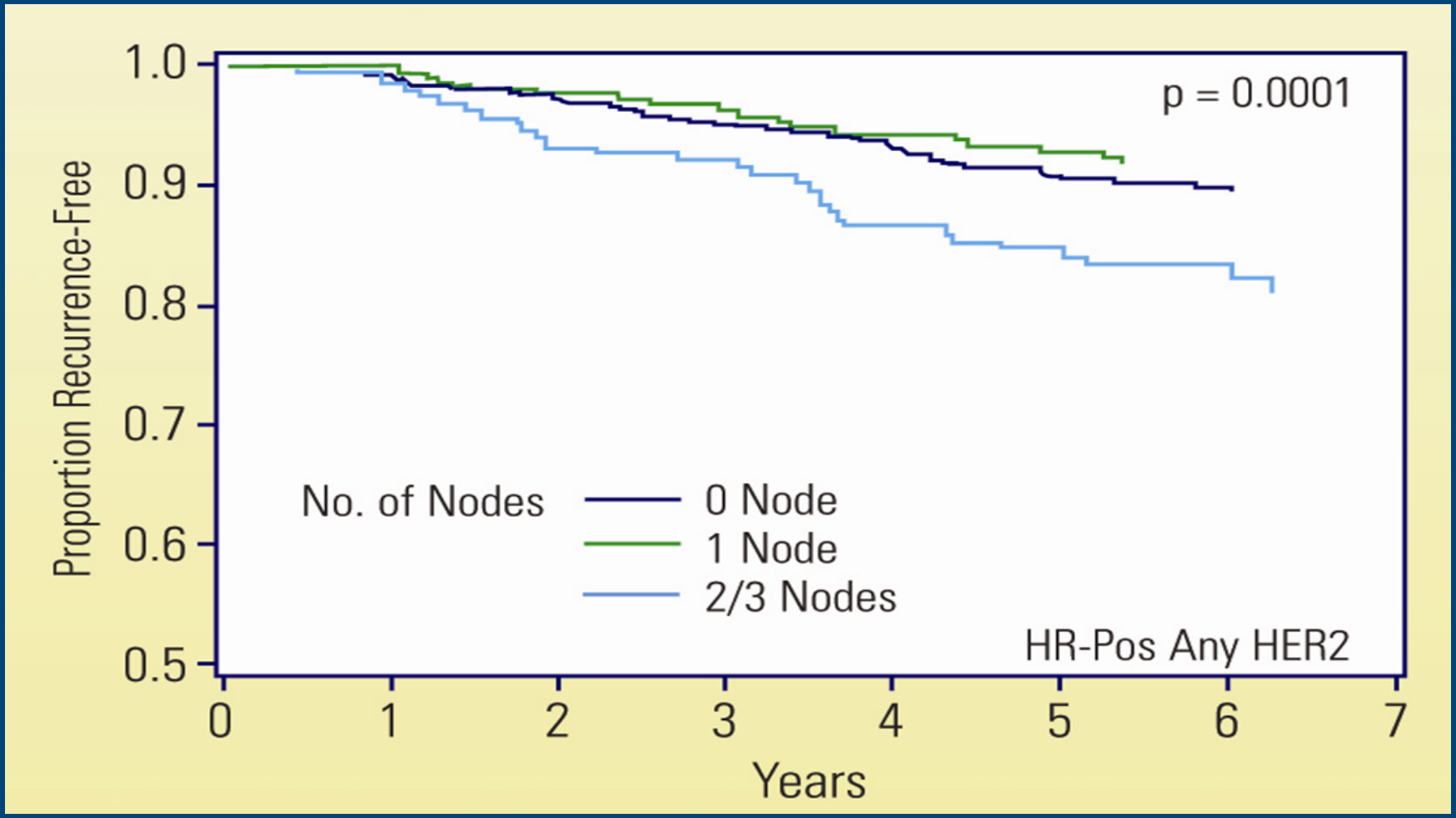
Results: Distribution of RS by HR Status

Group	RS	HR-Pos*	HR-Neg*
Low	< 18	198 (46%)	1 (0%)
Intermediate	18 - 30	142 (30%)	2 (1%)
High	≥ 31	125 (24%)	308 (99%)

- RS Distribution for HR-Pos Disease Similar to Prior Studies Including Only Node-Negative Disease

Outcomes by Nodal Status

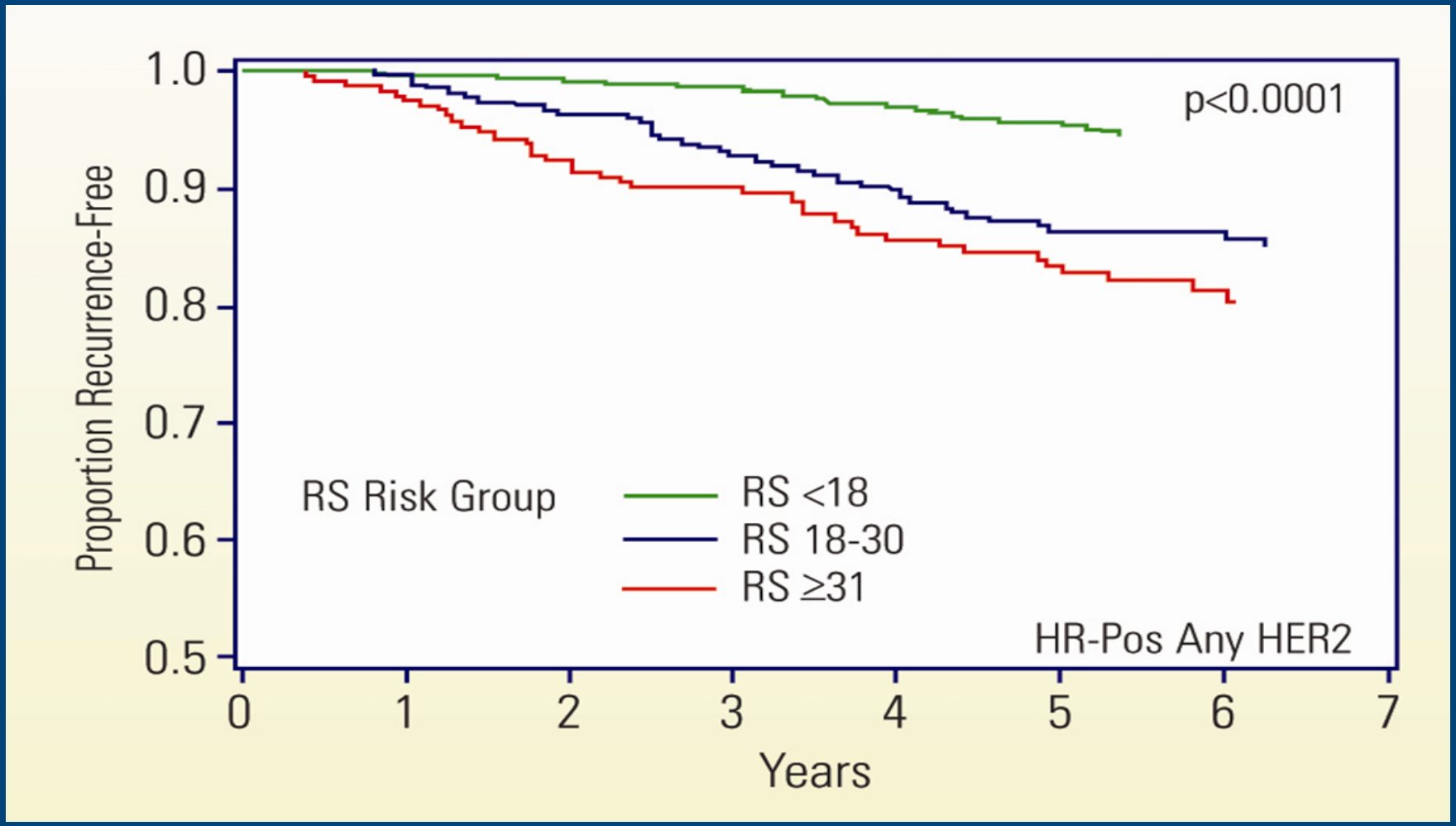
All of these patients received chemotherapy (either AC or AT)



ASCO - Abstract #526

Outcomes by Recurrence Score

All of these patients received chemotherapy (either AC or AT)



ASCO - Abstract #526

5-Year Event Rates by Nodal Status & RS

Recurrence Rates Are Very Low (≤ 5%) if the RS < 18 Irrespective of Axillary Lymph Node Status

RS	Nodes	RFI (%)	DFS (%)	OS (%)
Low <18	Neg	96	93	95
	Pos	95	91	97
Int 18-30	Neg	86	87	97
	Pos	87	77	86
High ≥ 31	Neg	87	80	92
	Pos	75	61	72

ASCO - Abstract #526

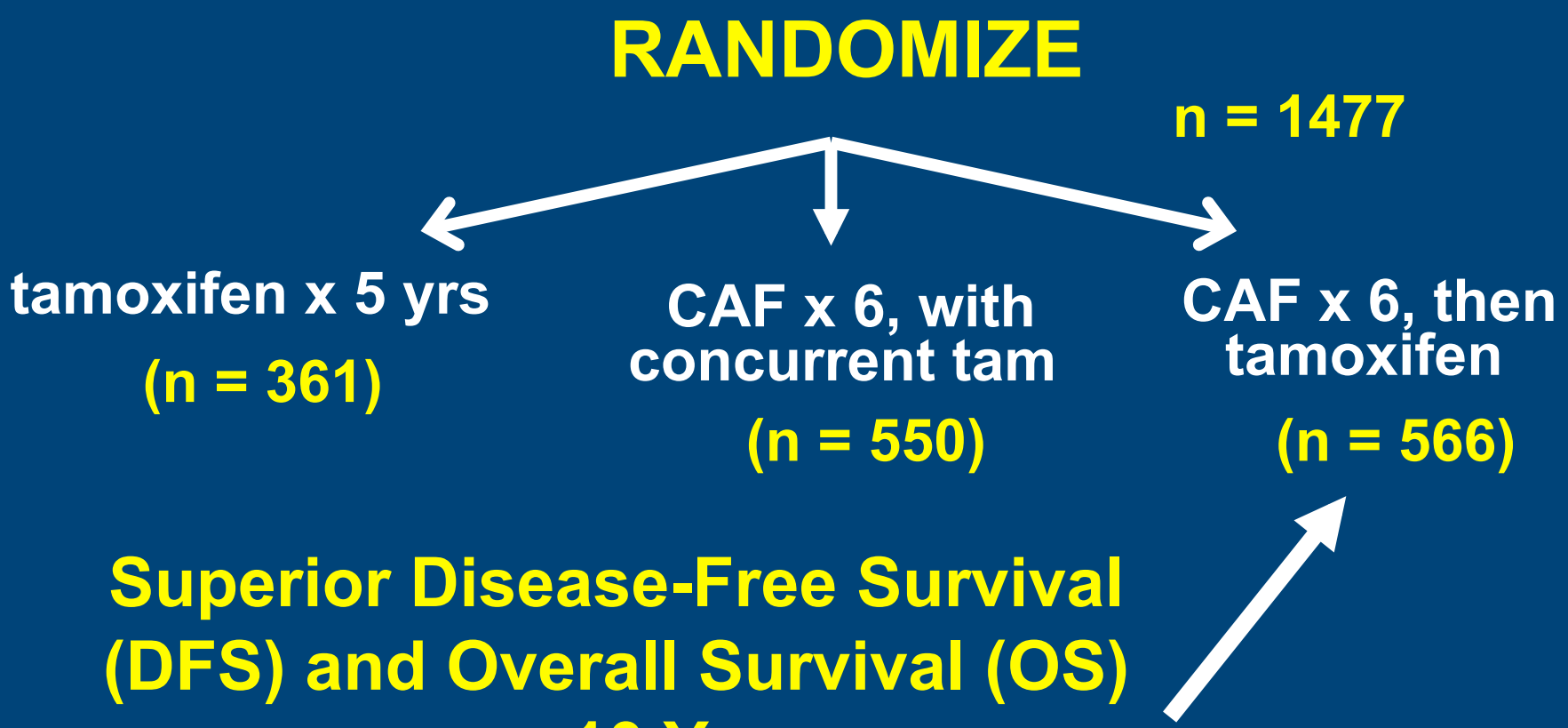
San Antonio Breast Cancer Symposium
December, 2007

LOYOLA MEDICINE
We also treat the human spirit.®

Prognostic and Predictive Value of the 21-Gene Recurrence Score Assay in Postmenopausal, Node-Positive (N+), ER-Positive (ER+) Breast Cancer SWOG 8814, TBCI 0100

K. Albain, for The Breast Cancer Intergroup of North America

Phase III SWOG 8814 (TBCI 0100)
Postmenopausal, N+, ER+



Superior Disease-Free Survival (DFS) and Overall Survival (OS) over 10 Years

Albain, et al. Breast Cancer Res Treat 2005

SWOG 8814/TBCI 0100
Sample Size for This Analysis

Patients with samples - 666

(45% of parent trial)

↓

RT-PCR obtained - 601 (90%)

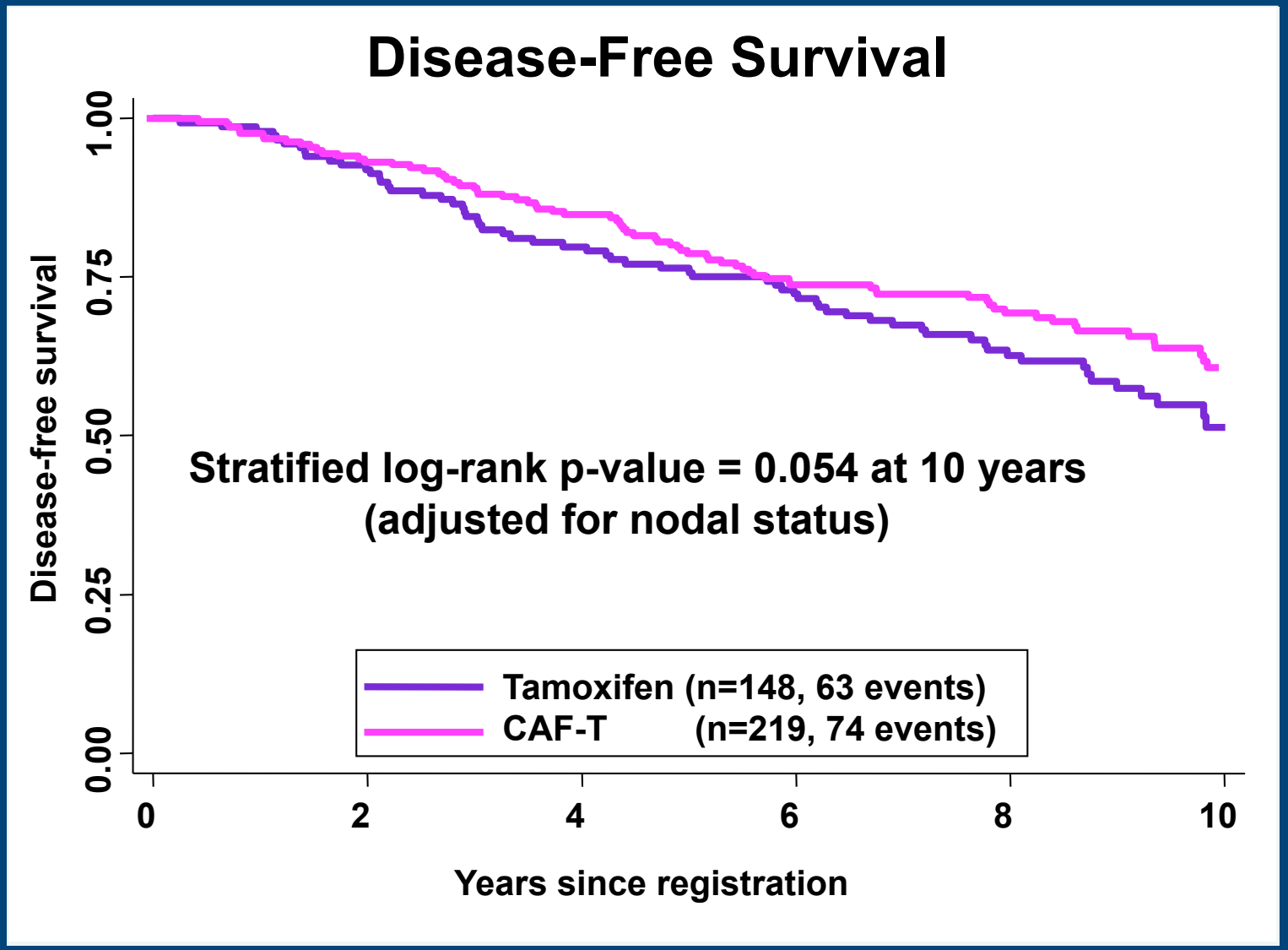
Tamoxifen alone	148
CAFT (concurrent)	234
CAF-T (sequential)	219

↓

Final sample for primary analysis

148 + 219 = 367 (40% of parent trial)

Outcomes in RS Subset Mirror Those Reported in Main Trial: Superiority of CAF-T



Comparative Distribution of RS
SWOG 8814: Less Low RS, More High RS

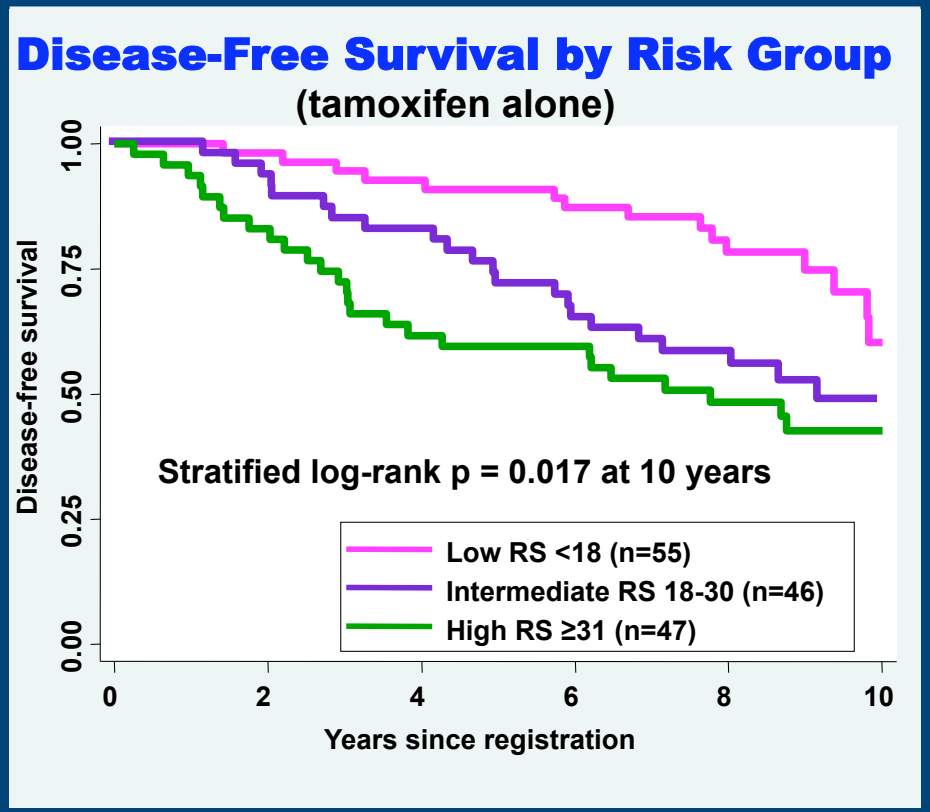
Study	Low Risk (RS < 18)	Int. Risk (RS 18-30)	High Risk (RS ≥ 31)
NSABP B14*	51%	22%	27%
NSABP B20*	54%	21%	25%
Kaiser controls*	56%	19%	25%
ECOG 2197**	49%	31%	20%
SWOG 8814***	40%	28%	32%

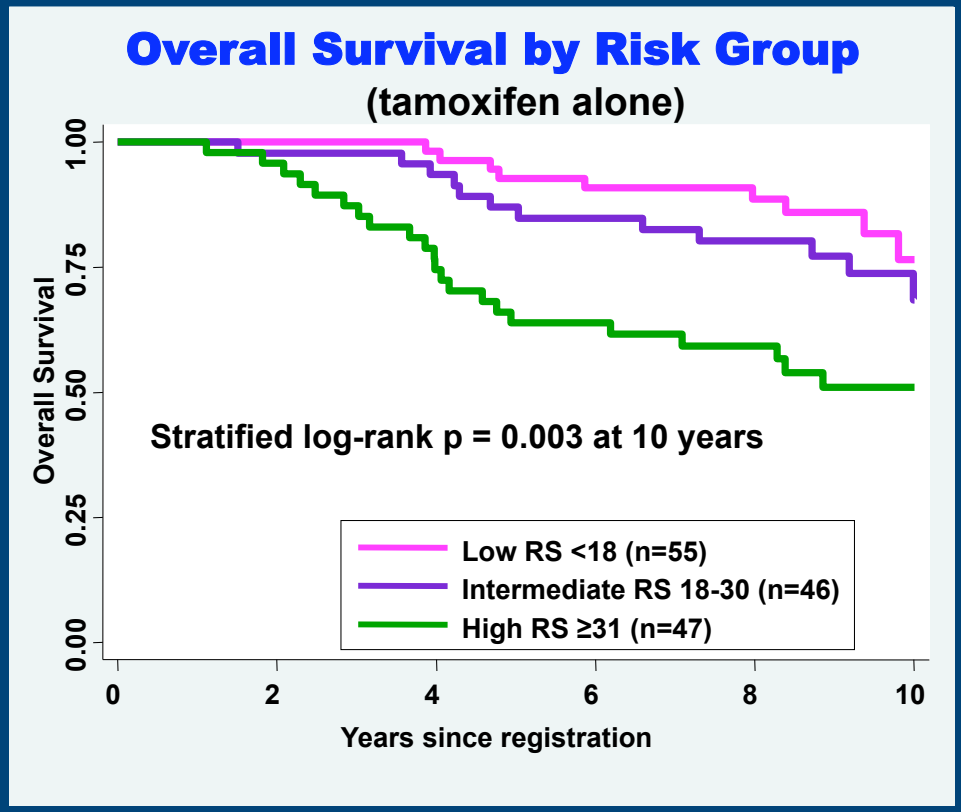
*node(-): Paik, et al. NEJM 2004 & JCO 2006; Habel, et al. Breast Ca Res Treat 2006

**node- or 1-3+: Goldstein, et al. Proc ASCO 2007

***node+, postmenopausal: this analysis - no difference by age

SWOG 8814/TBCI 0100
21-Gene Recurrence Score is Prognostic for DFS and OS in Tamoxifen Arm



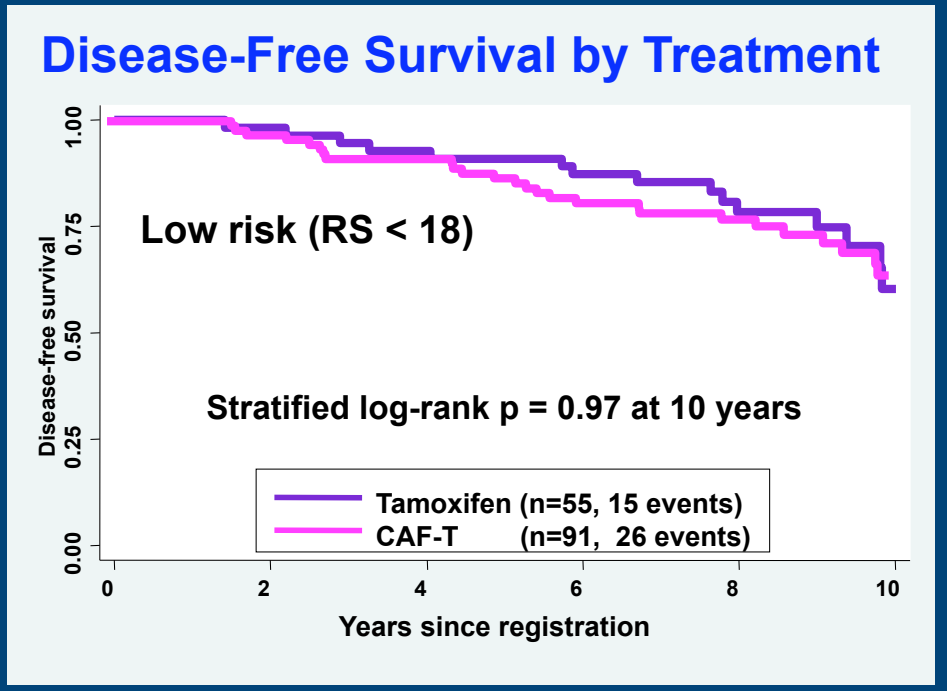


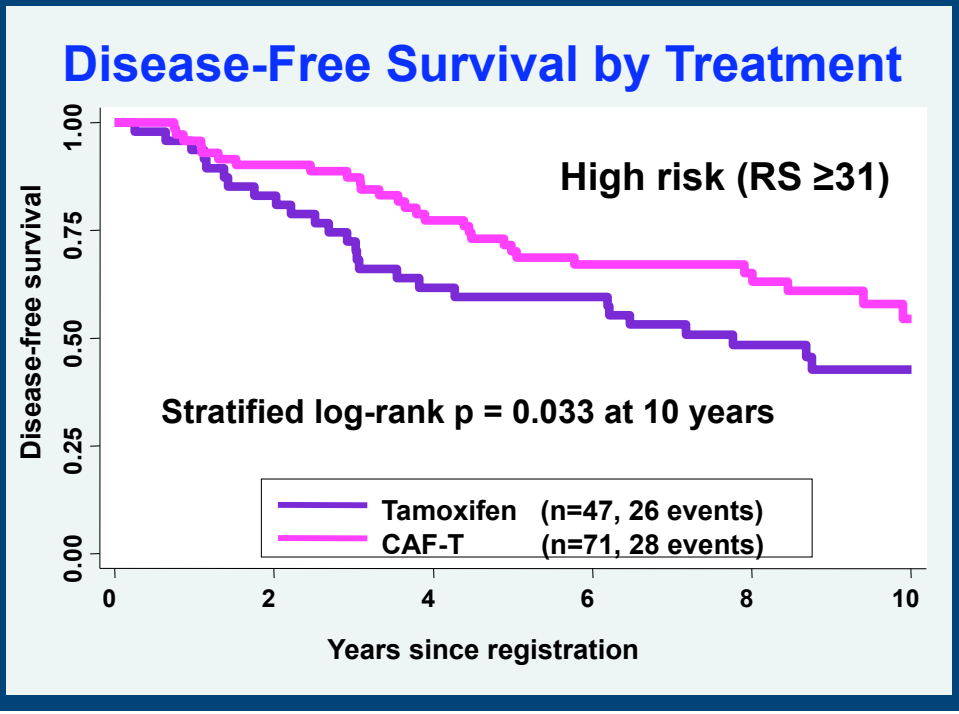
10-yr: 60%, 49%, 43%

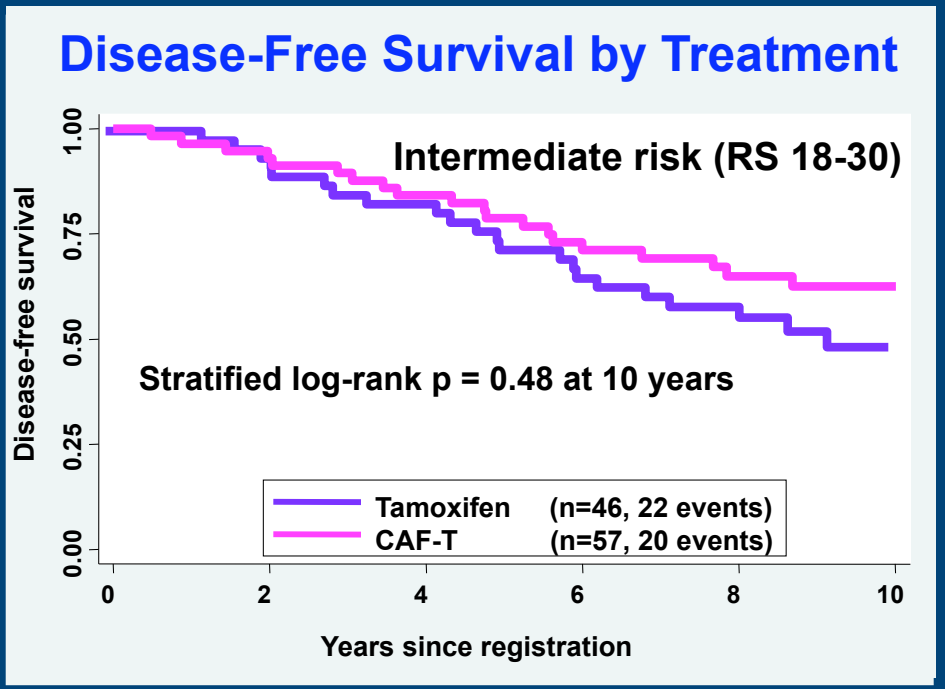
10-yr: 77%, 68%, 51%

No benefit to CAF over time if low RS

Strong benefit if high RS





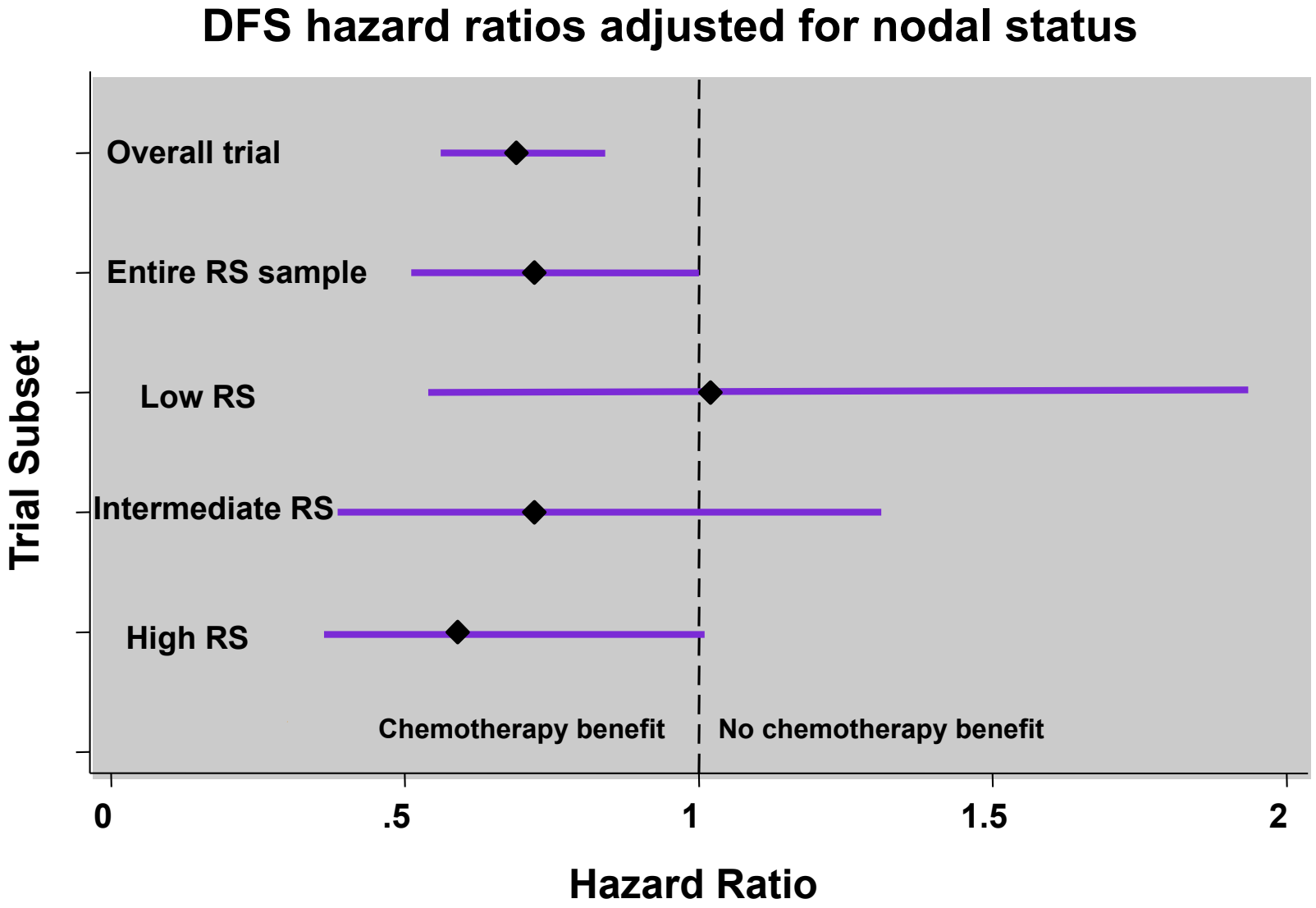


SWOG 8814/TBCI 0100
Ten-Year DFS Point Estimates (95% CI)

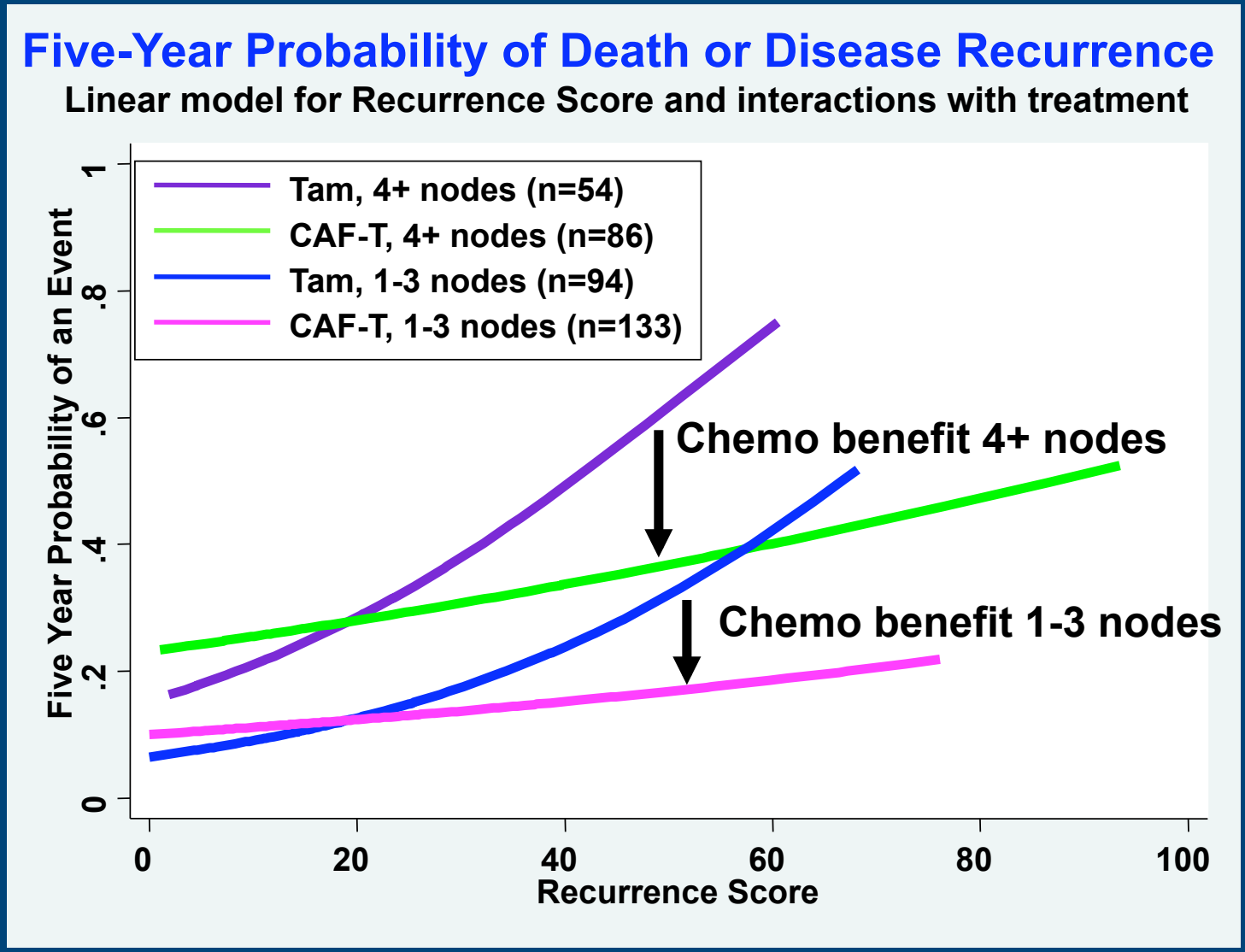
Recurrence Score Risk Category	Tamoxifen Alone	CAF followed by tamoxifen
Low (< 18)*	60% (40%, 76%)	64% (50%, 75%)
Intermediate (18-30)	49% (32%, 63%)	63% (48%, 74%)
High (≥ 31)	43% (28%, 57%)	55% (40%, 67%)

*40% event rate over 10 years and resistance to CAF

Comparison of CAF-T to Tamoxifen Alone



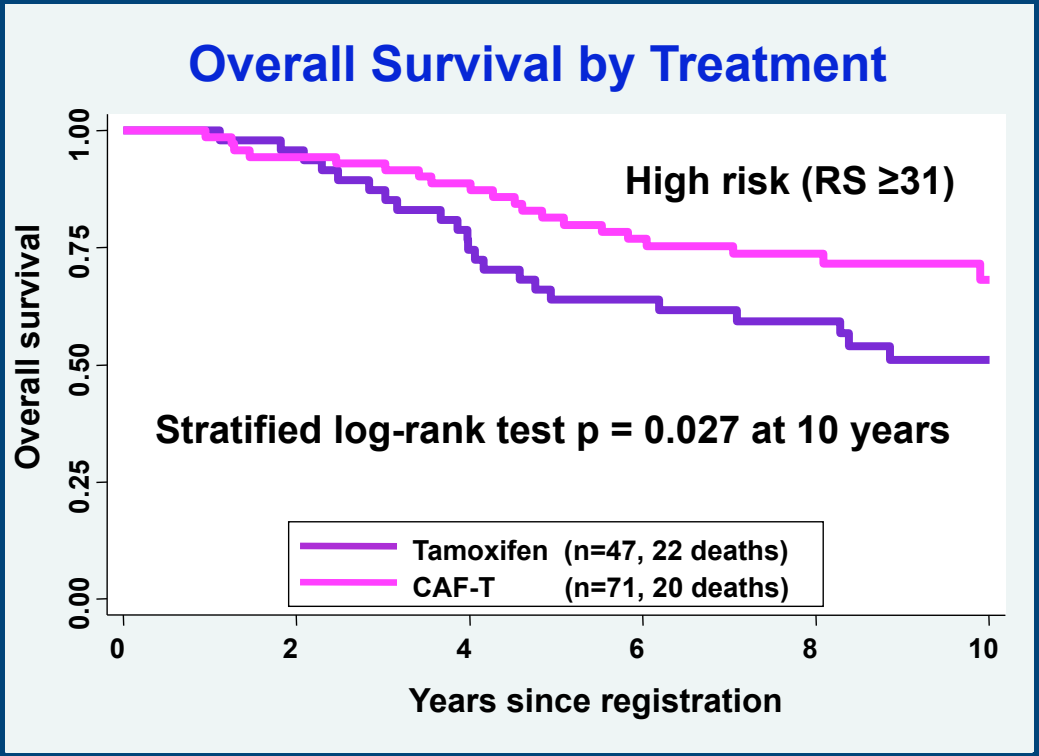
CAF Benefit Greatest in Higher RS for Both Nodal Subsets, with No Benefit in Lower RS



The RS is Also Predictive for Overall Survival in SWOG 8814/TBCI 0100

- No benefit to CAF in low RS in first 5 years (HR 1.05) or over entire time period (HR 1.18)

- Strong impact of CAF in high RS first 5 years
  HR 0.43 (0.21, 0.90)
  and over entire period
  HR 0.56 (0.31, 1.01)
  10-year estimates:
  Tam 51% (35%, 65%)
  CAF-T 68% (51%, 79%)



70 Gene Assay

- 70 gene assay predicts for distant recurrence in patients with node-negative breast cancer
- Requires frozen tissue
- Has not been validated as a predictor for outcome from hormonal therapy or chemotherapy
- MINDACT Trial (Microarray In Node negative Disease may Avoid ChemoTherapy) trial is ongoing

ASCO 2007 Update of Recommendations for the Use of Tumor Markers in Breast Cancer

CONCLUSIONS

Evidence of clinical utility

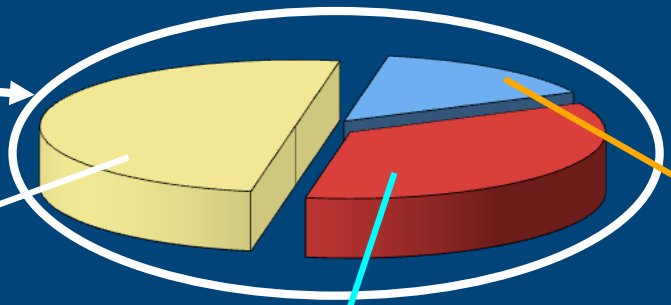
- CA 15-3, CA 27-29, CEA — for monitoring response in MBC
- ER, PgR, HER_2 — for tailoring therapy
- UPA, PA-1 — for avoiding adjuvant chemo if low and ER high
- 21 Gene Assay — for avoiding adjuvant chemo if RS low

Insufficient evidence of clinical utility

- DNA PLOIDY (Flow cytometry)
- Ki67
- p53
- Cathepsin P
- Cyclin E
- Topoisomerase II
- Proteomics
- 70 Gene Assay
- Bone marrow micrometastases
- Circulating tumor cells

TAILORx (n=10,500 women) and MINDACT (n=6,000 women) Bringing Molecular Prognostic Signatures to Daily Clinical Practice

Node-negative B.C. population



- High risk 21-gene R.S.
  OR
- High risk 70-gene signature
  +
- High risk adjuvant on line

CHEMOTHERAPY

- Medium risk 21-gene R.S.
  OR
- Discordant risk group (mostly low risk 70-gene signature but high risk adjuvant on line)

- RANDOMIZE CHEMO YES or NO (TailorX)
- RANDOMIZE FOR the decision-making tool (Mindact)

- Low risk 21-gene R.S.
  OR
- Low risk 70-gene signature
  +

Low risk adjuvant on line

ENDOCRINE THERAPY