The Role of the Onco*type* DX® Assay in the Treatment Selection for ER-positive, HER2-negative and Node-positive Breast Cancer

Does Every ER-positive, Node-positive Patient Need Adjuvant Chemotherapy?

The Onco*type* DX® Assay and Node-positive Breast Cancer

- Case Study: Is Chemotherapy Always Necessary in Node-positive Disease
- Node-positive Breast Cancer: Historical View vs Current View
- The Prognostic and Predictive Value of the Onco*type* DX Assay in Node-positive Disease
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- Case Study Follow-up: Is Chemotherapy Always Necessary in Node-positive Disease?

Case Study: Can This Patient be Spared From Adjuvant Chemotherapy?

Patient CB (64 years old)

Medical history

- Infiltrating adenocarcinoma in right breast
  - Metastases found in 1 node
- Type 2 diabetes
  - Mild peripheral neuropathy
  - Mild peripheral vascular disease
  - No renal impairment
- Chronic atrial fibrillation
  - Takes digoxin and warfarin daily

Physical exam

- Irregular heart rate in the low 80s
- No evidence of congestive heart failure
- Healing from lumpectomy and axillary wounds (sentinel node sampling)
- All other tests within normal limits

Characteristic	Description
Tumor size	2.2 cm
Tumor grade	2
Lymph nodes	1 of 15 nodes positive
ER/PR status	ER+/PR+
HER2 status	Negative

- **How can the Onco*type* DX® Recurrence Score® result be used to inform the adjuvant treatment decision?**

When Can Onco*type* DX® Testing be Considered in Node-positive Early Stage Breast Cancer?

- Patients with micrometastases
- Patients with 1-3 positive nodes including:
  - Patients with or without comorbidities who are at risk of chemotherapy toxicity or want to avoid chemotherapy
  - Patients considering chemotherapy who want a reliable estimate of risk to help their decision

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Nodal Status Spans a Continuum from Node-negative to Node-positive Disease

Historical view: risk of recurrence can be discretely described based on nodal status

No positive nodes → low risk	Positive nodes → high risk

Emerging view: risk of recurrence is a continuous variable

low	moderate	high

Because nodal status reflects a continuous biology of breast cancer

Node negative	Node positive		
	Micrometastases	1-3 nodes	≥ 4 nodes

Validity of the Oncotype DX® Assay Has Been Demonstrated in Multiple Studies and Guidelines Along a Continuum of Nodal Status

Information supporting the Oncotype DX assay along a continuum of nodal status

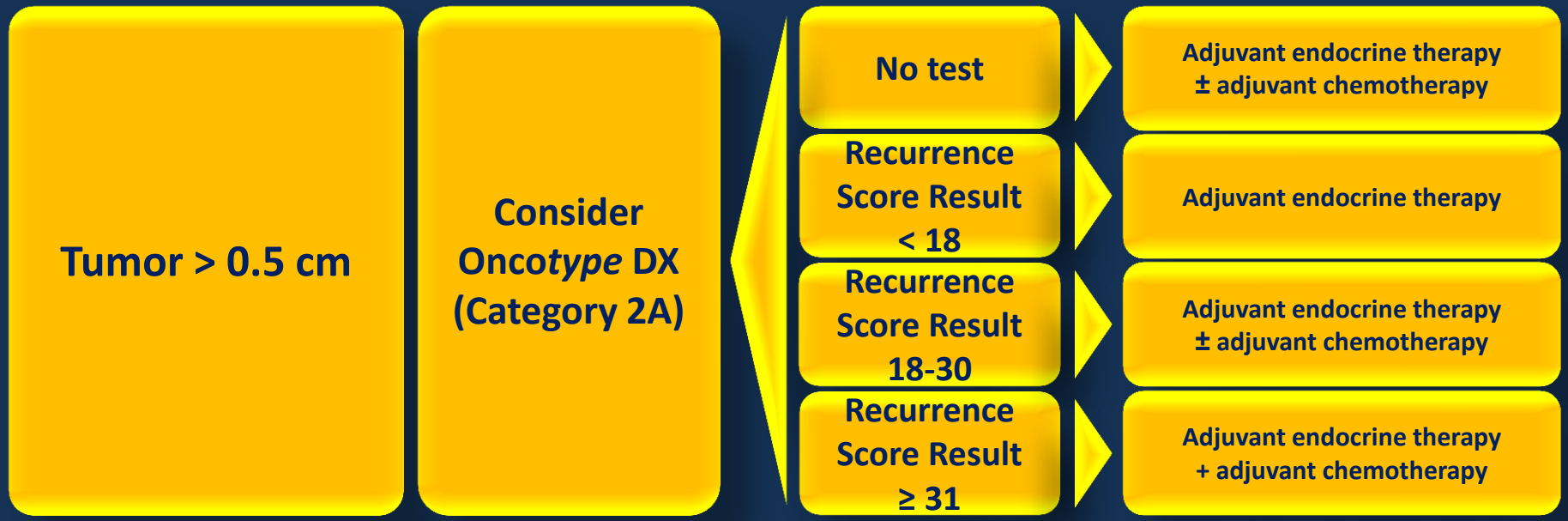
Node negative	Node positive		
NØ	**Micrometastases**	**1-3 Nodes**	**≥ 4 Nodes**
• NSABP B-14 and B-20 studies[1,2] • NCCN® and ASCO® Guidelines[3,4]	• NCCN Guidelines[3]	• SWOG 8814[5] • TransATAC[6] • E2197[7] • NSABP B-28[8]	• SWOG 8814[5] • TransATAC[6] • NSABP B-28[8]

1. Paik S, et al. *N Engl J Med*. 2004;351:2817.
2. Paik S, et al. *J Clin Oncol*. 2006;24:726.
3. NCCN Practice Guidelines in Oncology – v.3.2013.
4. Harris L, et al. *J Clin Oncol*. 2007;25:5287.
5. Albain KS, et al. *Lancet Oncol*. 2010;11(1):55-65.
6. Dowsett M, et al. *J Clin Oncol*. 2010; 28(11):1829-1834.
7. Goldstein LJ, et al. *J Clin Oncol*. 2008;26:4063-4071.
8. Mamounas E et al. *ASCO Breast Cancer Symposium* 2012. Abstract 1.

NCCN Guidelines® Include Oncotype DX® Testing in the Treatment-Decision Pathway for Node-negative and Micrometastatic Disease

HR(+), HER2(-) disease

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



Adapted from NCCN Practice Guidelines in Oncology – v.3.2013.

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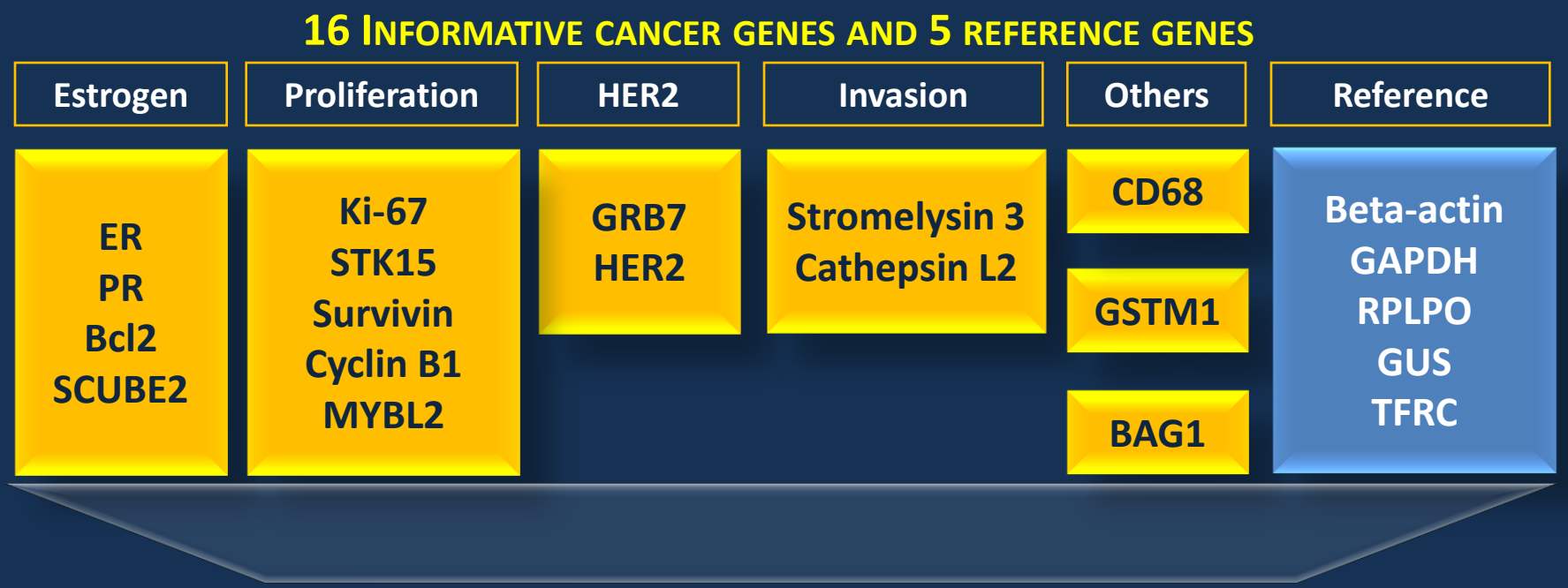
- Case Study Resolution: Is Chemotherapy Always Necessary in Node-positive Disease?

The Oncotype DX® Assay Uses a Genomic Approach to Predict Recurrence Risk and Response to Adjuvant Therapy



Risk category	The Recurrence Score® value (0-100)
Low	< 18
Intermediate	18-30
High	≥ 31

Paik S, et al. *N Engl J Med*. 2004;351:2817.

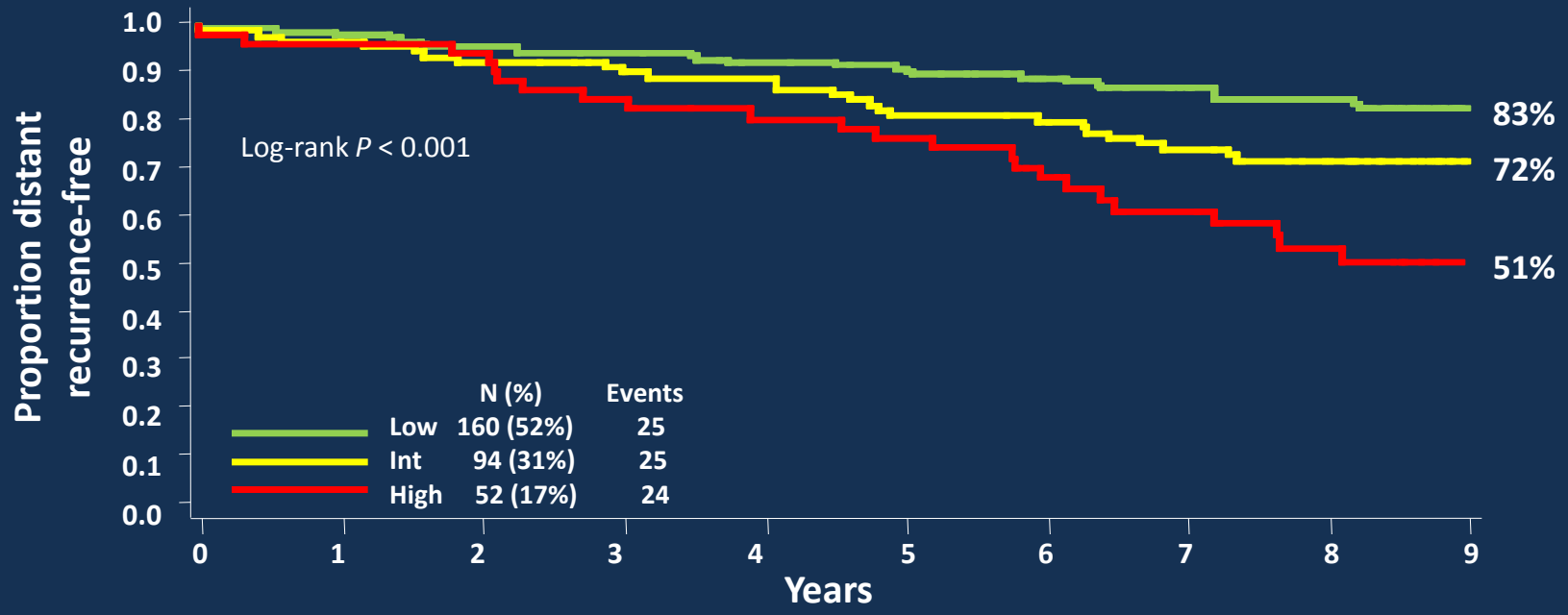
Clinical Validation of the Oncotype DX® Assay in Node-positive Patients

Study	Design	Total N	Nodal status	Prognostic	Predictive
TransATAC[1]	Prospective; tam vs AI	1231	Neg/Pos	Yes	N/A
ECOG 2197[2]	Prospective; hormonal + AC vs AT	465	Neg/Pos	Yes	N/A
NSABP B-28[3]	Prospective; tam + AC vs AC-P	1065	Pos	Yes	N/A
SWOG 8814[4]	Prospective; tam ± chemo	367	Pos	Yes	Yes Recurrence Score® result predicts chemotherapy benefit

1. Dowsett M, et al. *J Clin Oncol.* 2010;28:1829-1834.
2. Goldstein LJ, et al. *J Clin Oncol*. 2008;26:4063-4071.
3. Mamounas EP, et al. Presented at *ASCO Breast* 2012. Abstract 1.
4. Albain KS, et al. *Lancet Oncol*. 2010;11:55-65.

TransATAC Study: Recurrence Score® Value is Prognostic in Node-positive Patients

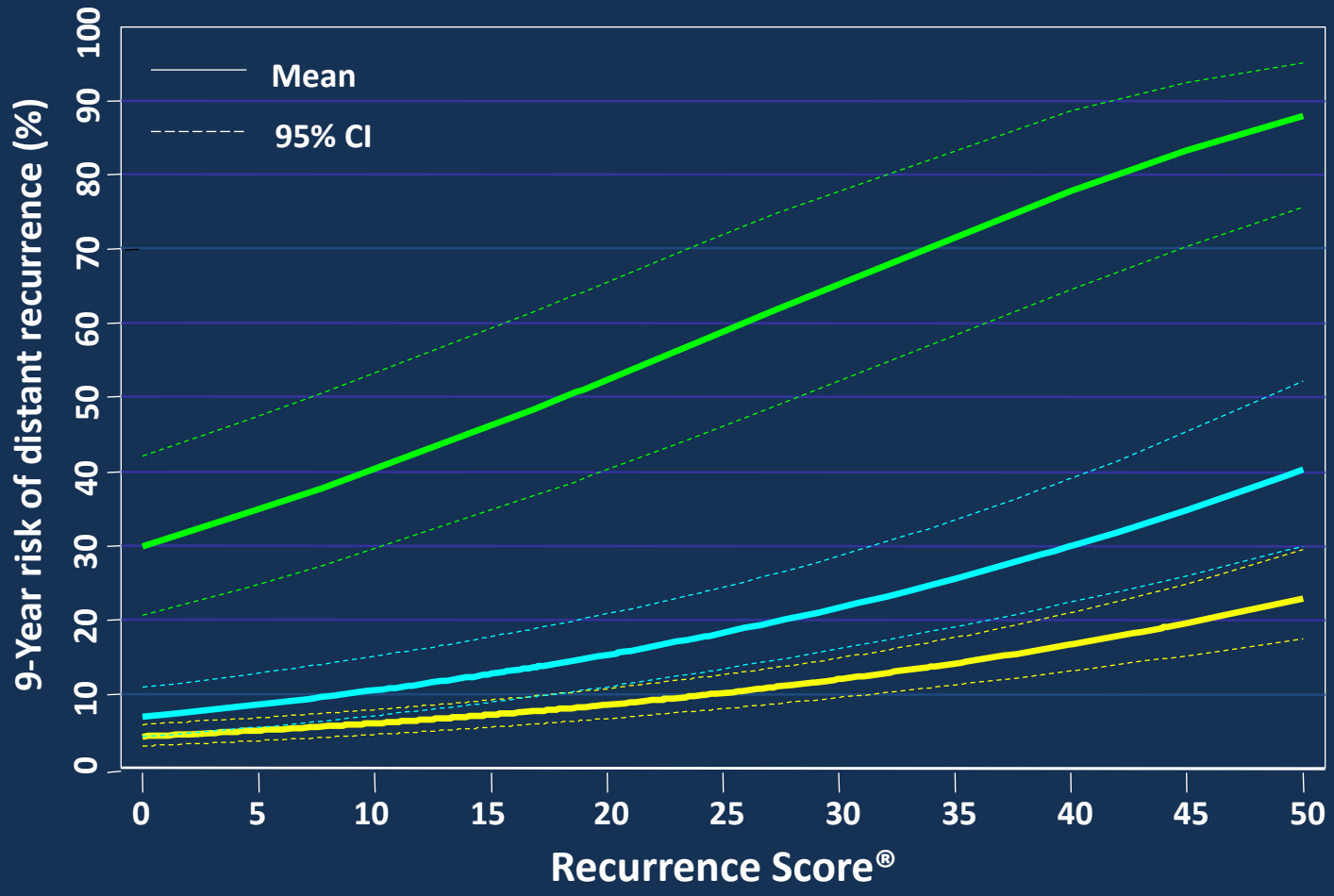
Node+ (n = 306; both treatment arms)



The Recurrence Score group	Hazard ratio (95% CI)
High vs Low	2.7 (1.5-5.1)
Int vs Low	1.8 (1.0-3.2)

Dowsett M, et al. *J Clin Oncol*. 2010; 28(11):1829-1834.

Rate of Distant Recurrence Increases with the Number of Positive Nodes for all Recurrence Score® Values

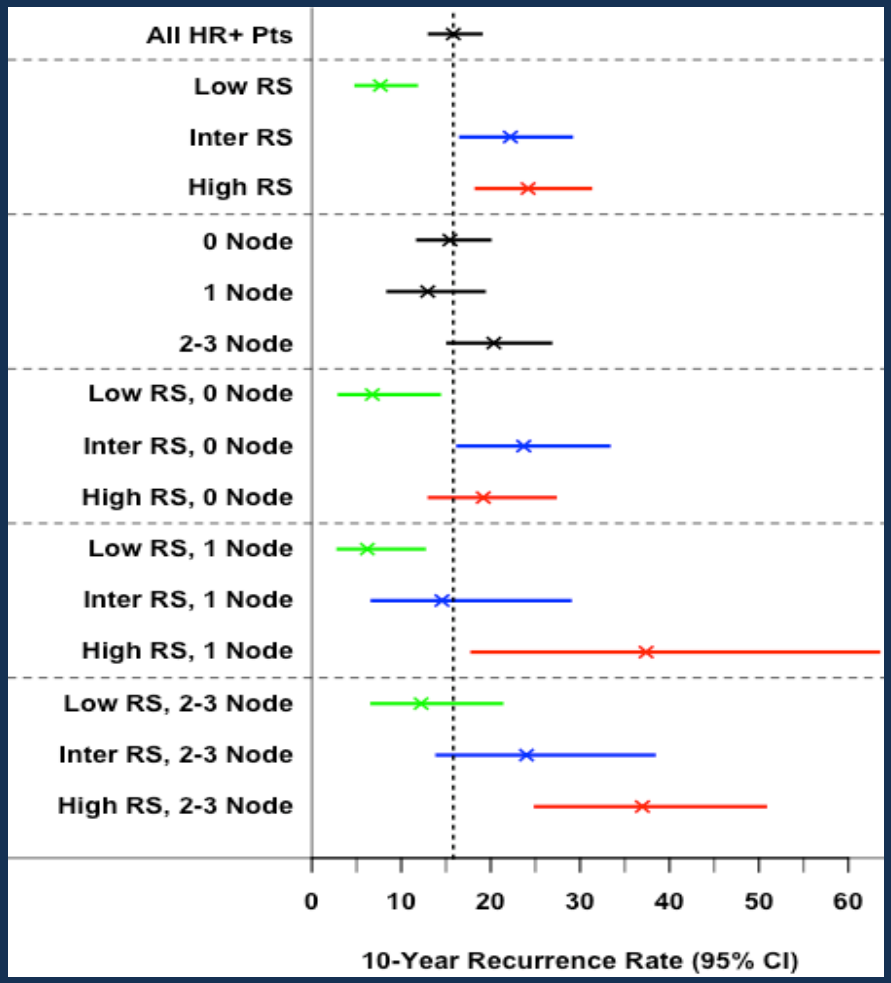


Not all node-positive patients have the same risk of recurrence

Dowsett M, et al. *J Clin Oncol*. 2010; 28(11):1829-1834.

ECOG 2197: The Recurrence Score® Result Predicts Risk of Recurrence Irrespective of Nodal Status

10-Year Recurrence Rates



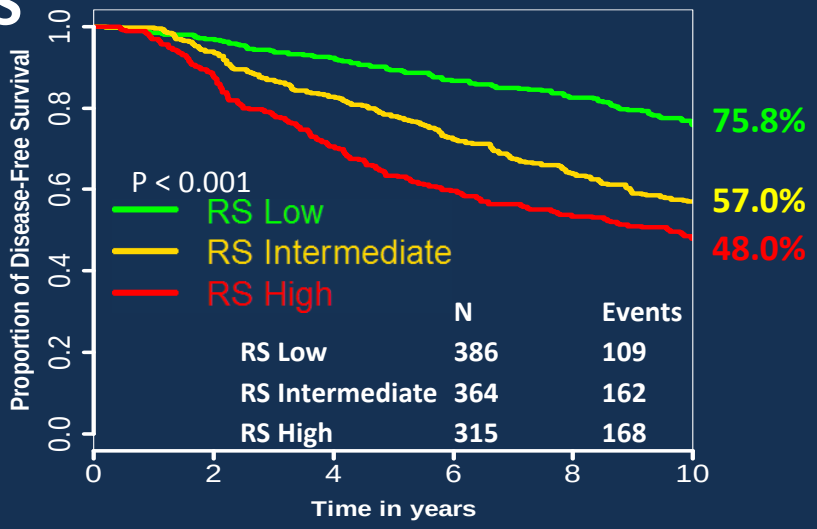
There is little difference in recurrence rates for 1 and 0 positive nodes

The Recurrence Score result was a highly significant predictor of recurrence in chemo-treated patients regardless of nodal status N- (p=0.003) or N+ (p=0.0007).

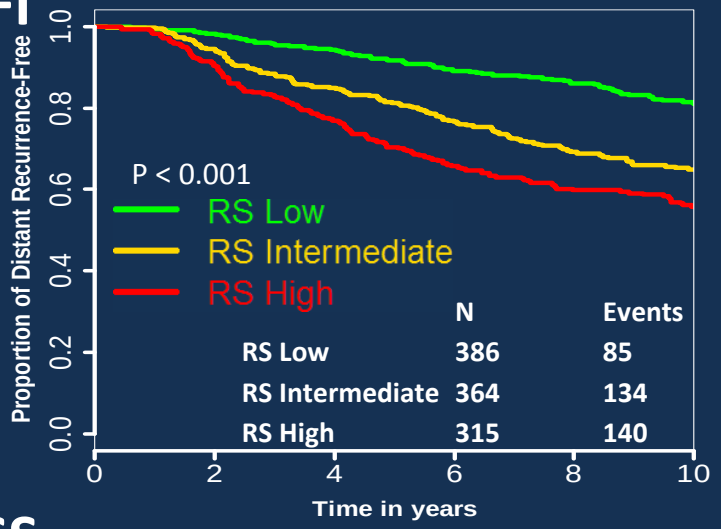
Sparano JA et al. *J Clin Oncol* 2012; 30 (suppl; abstr 1021).

NSABP B-28: The Recurrence Score® Result is Prognostic in Chemo-treated Node-positive Patients by all Endpoints

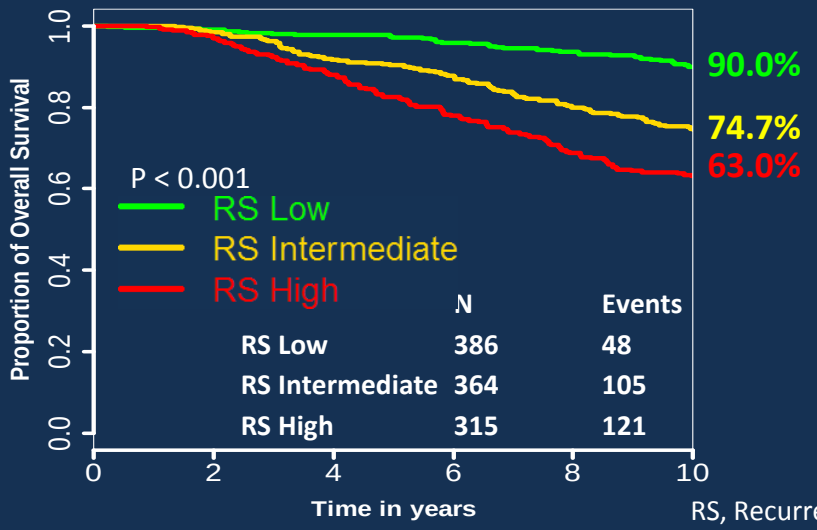
DFS



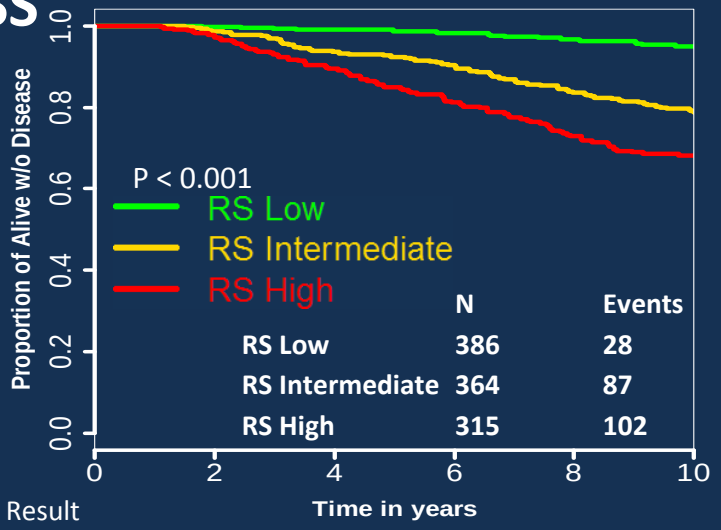
DRFI



OS



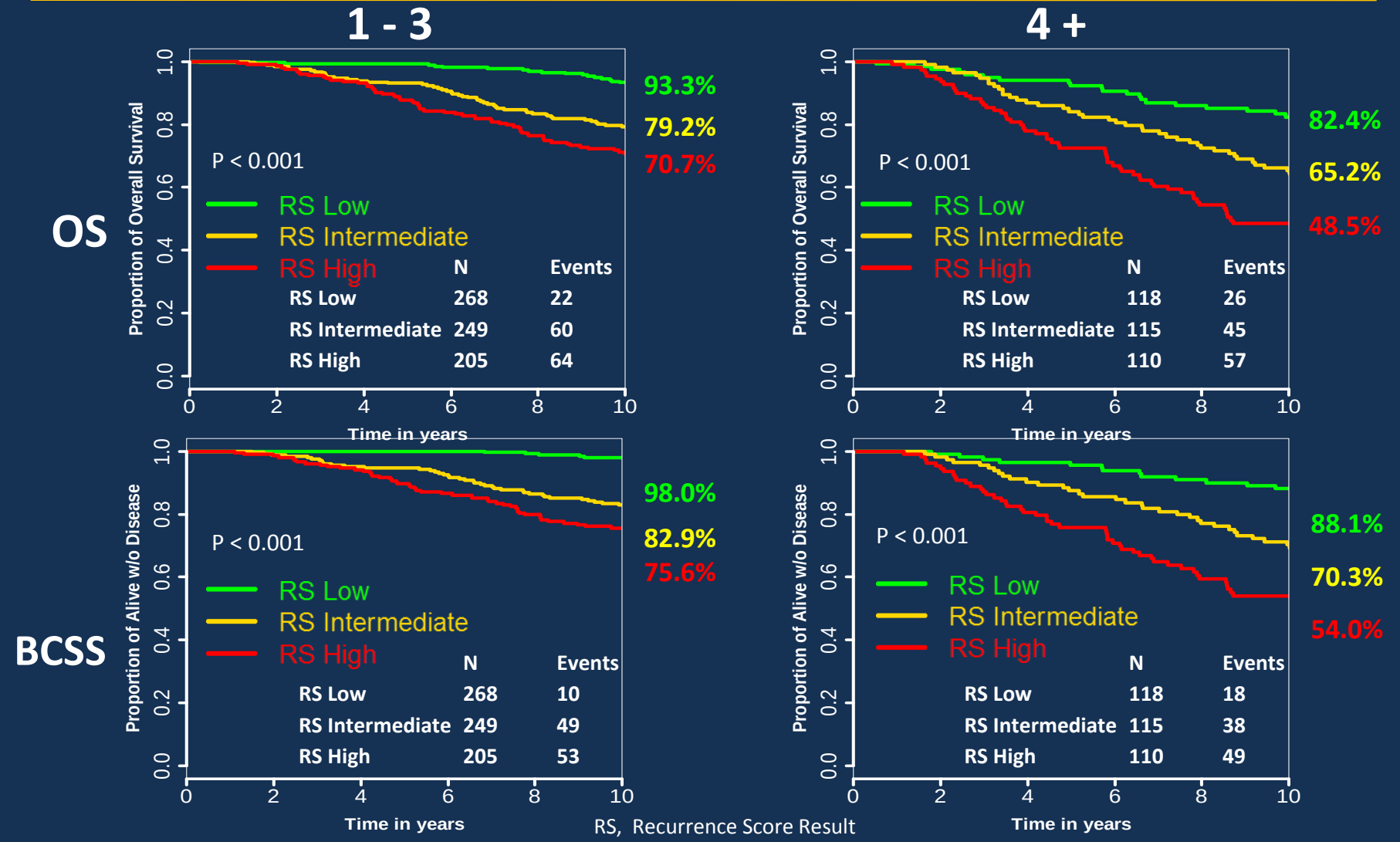
BCSS



RS, Recurrence Score Result

Mamounas et al. ASCO Breast Cancer Symposium 2012.

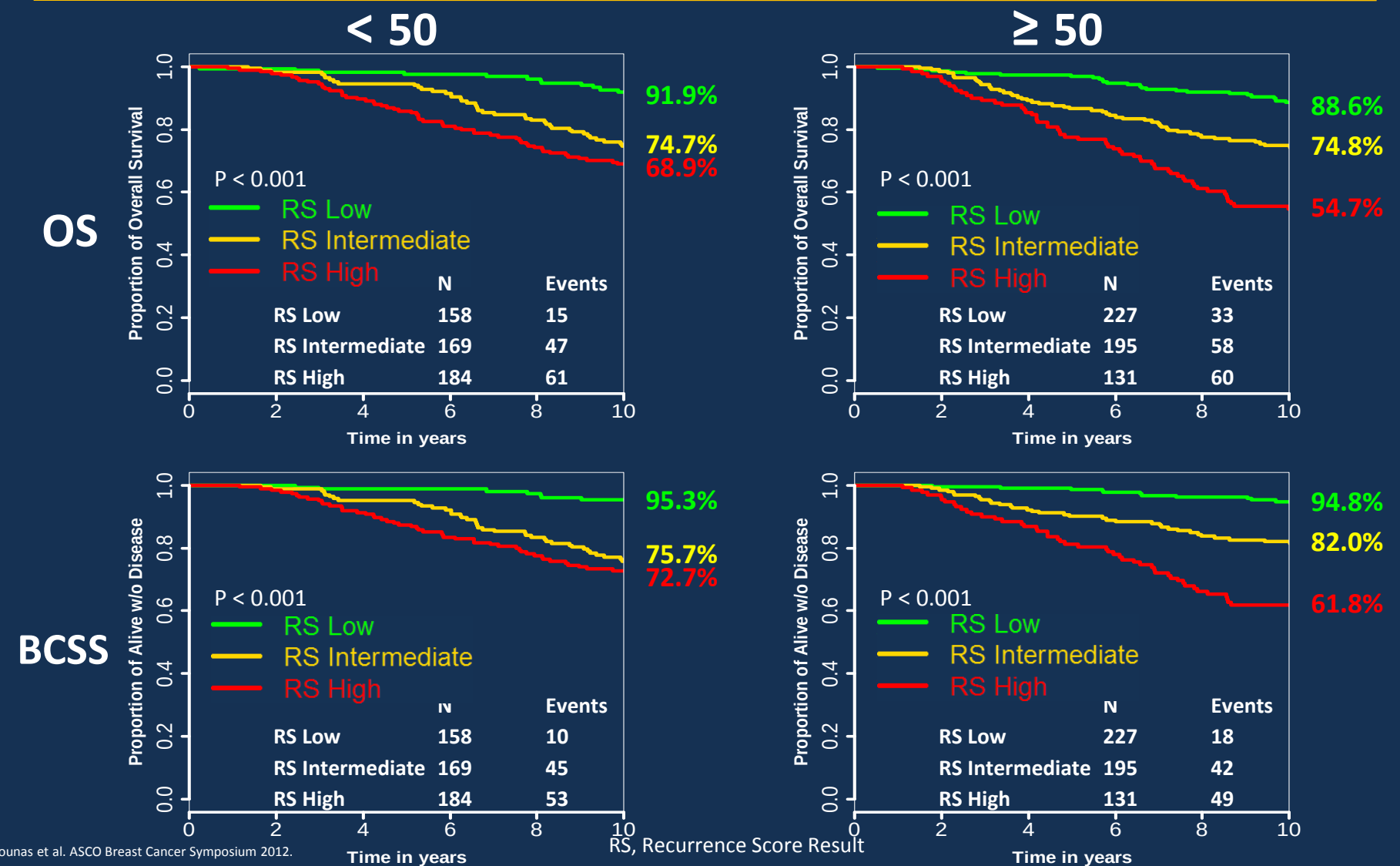
NSABP B-28: The Recurrence Score® Result is Prognostic in Chemo-treated 1-3 or 4+ Node-positive Patients



RS, Recurrence Score Result

Mamounas et al. ASCO Breast Cancer Symposium 2012.

NSABP B-28: The Recurrence Score® Result is Prognostic in Chemo-treated Node-positive Patients Regardless of Age <50 or ≥ 50

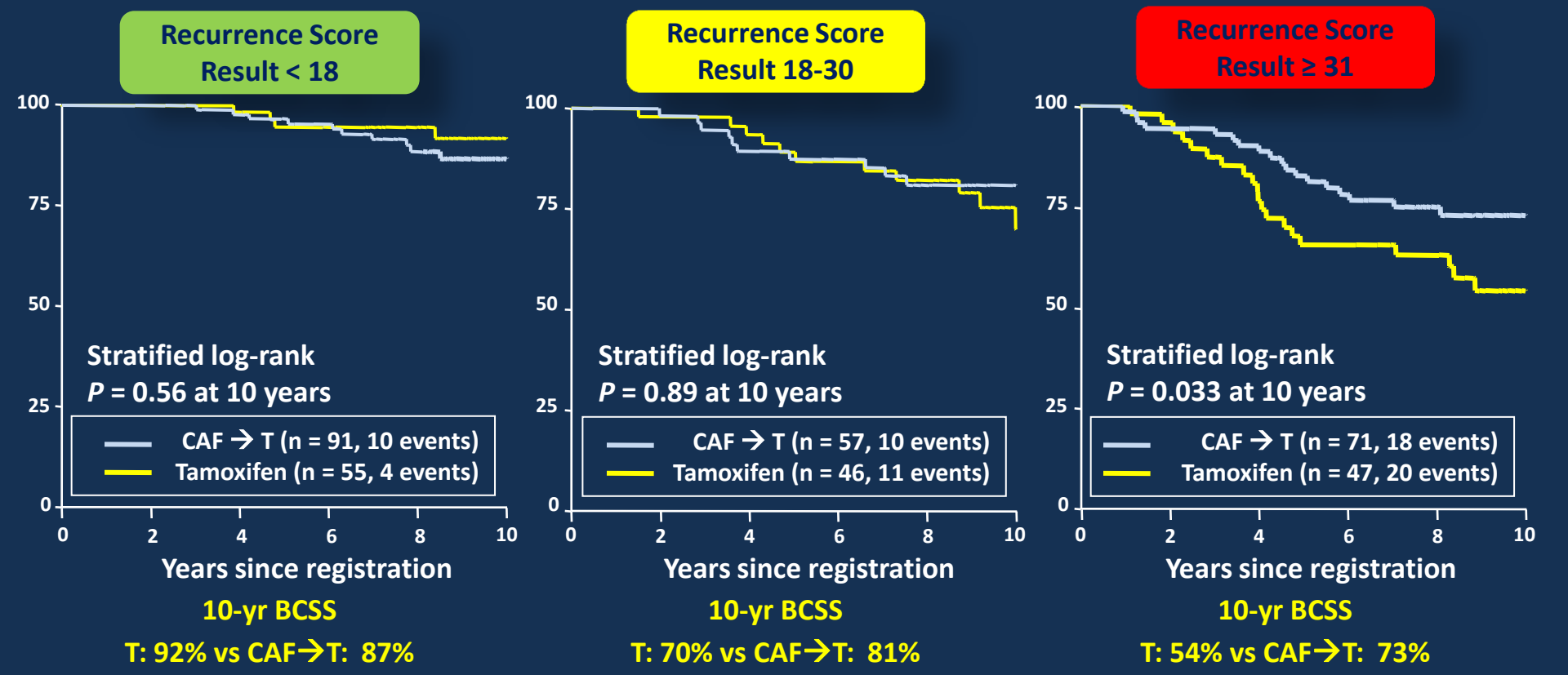


RS, Recurrence Score Result

Mamounas et al. ASCO Breast Cancer Symposium 2012.

SWOG 8814: Breast Cancer-Specific Survival of Node-positive Patients by Treatment and the Recurrence Score® Group

BREAST CANCER-SPECIFIC SURVIVAL BY TREATMENT



- No benefit to CAF over time for low Recurrence Score results

Interaction *P* = 0.021

- Strong benefit to CAF over time for high Recurrence Score results

Albain KS, et al. *Lancet Oncol*. 2010;11(1):55-65.

RS, Recurrence Score® result

The Oncotype DX® Report Provides Valuable Information Along a Continuum of ER+ Breast Cancer

genomic health | oncotype DX Breast Cancer Assay

Page 3 of 4

Genomic Health, Inc.
301 Penobscot Drive
Redwood City, CA 94063 USA
Toll Free Tel 866-ONCOTYPE (866-662-6897)
Worldwide Tel +1 650-569-2080
www.oncotypeDX.com

PATIENT REPORT

Patient/ID: Doe, Jane
Sex: Female
DOB: 01/01/1950

Requisition: R00003G
Order Received: 10/15/2008
Date Reported: 10/23/2008

RESULTS

Breast Cancer Recurrence Score = 6

The findings summarized in the Clinical Experience sections of this report are applicable to the patient populations defined in each section. It is unknown whether the findings apply to patients outside these criteria.

CLINICAL EXPERIENCE: PROGNOSIS AND CHEMOTHERAPY BENEFIT FOR NODE POSITIVE, HR-POSITIVE PATIENTS

The following results are from a clinical study involving 367 patients from the SWOG 8814 Study. This study included post-menopausal female patients with Node Positive, Hormone Receptor (HR)-Positive breast cancer. Patients were randomized to either tamoxifen alone or CAF chemotherapy followed by tamoxifen (CAF-T). The endpoint for this study was disease-free survival (time to local or distant recurrence, new primary breast cancer, or death from any cause) and outcomes after 5 years of follow-up were presented. Note that this differs from the endpoint and follow-up time used in the two NSABP studies of Node Negative, ER-Positive patients. For patients in the pre-specified group with Recurrence Scores ≥ 31 and 1–3 positive nodes, the group average 5-year rates (95% CI) of recurrence or death were 31% (17%, 52%) for Tam alone and 28% (15%, 46%) for CAF-T. For patients in the pre-specified group with Recurrence Scores ≥ 31 and ≥ 4 positive nodes, the group average 5-year rates (95% CI) of recurrence or death were 52% (33%, 74%) for Tam alone and 32% (20%, 50%) for CAF-T. *San Antonio Breast Cancer Symposium 2007* Abstract #10.

Recurrence Score vs Recurrence or Death in Node Positive, HR-Positive Breast Cancer
Prognosis and Chemotherapy Benefit (Difference Between Rates)

Laboratory Director: Patrick Joseph, MD

CLIA Number 05D1018272

This test was developed and its performance characteristics determined by Genomic Health, Inc. The laboratory is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing. This test is used for clinical purposes. It should not be regarded as investigational or for research. These results are adjunctive to the ordering physician's workup.

Online Ordering and Reports Available — Please contact Customer Service at customerservice@genomichealth.com

GHI004 Rev017

- The Oncotype DX report provides valuable information on:
  - Prognosis
  - Predicted chemotherapy benefit
  - Quantitative data on ER/PR/HER2
- Node-positive report contains an additional page with prognosis and predicted chemo benefit information specific to node-positive patients

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The Oncotype DX® Assay Changes Treatment Decisions in Multiple Studies Worldwide

Study	Country	Type	Patients (N)	Nodal status	Change (%)
Gligorov[1]	France	Prospective	96	N0/N1mi	36
Holt[2]	England	Prospective	142	N0/N1mi	26.8
Blohmer[3]	Germany	Prospective	366	N0/N1	33.1
Bargallo[4]	Mexico	Prospective	96	N0/N1	32
De Boer[5]	Australia	Prospective	151	N0/N1	23.8
Oratz[6]	US	Retrospective	160	N1	51

1. Gligorov et al. *ASCO* 2012. Abstract 568.
2. Holt et al. *SABCS 2011*. Poster P5-14-26.
3. Blohmer et al. *J Med Econ*. 2012.
4. Bargallo et al. *ESMO* 2012.
5. de Boer et al. *SABCS 2011*. Poster P4-09-18
6. Oratz et al. *J Oncol Pract*. 2011.

Use of the Onco*type* DX® Assay in the Node-positive Setting Changes Treatment Decisions

Study	Country	N	Nodal status	Total Change, %
Blohmer[3]	Germany	122	N1	27%
Bargallo[4]	Mexico	34	N1	38%
De Boer[5]	Australia	50	N1	26%
Oratz[6]	US	138	N1	**51%**

1. Gligorov et al. *ASCO* 2012. Abstract 568.
2. Holt et al. *SABCS 2011*. Poster P5-14-26.
3. Blohmer et al. *J Med Econ.* 2012.
4. Bargallo et al. *ESMO* 2012.
5. de Boer et al. *SABCS 2011*. Poster P4-09-18
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Patient CB (64 years old)

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Physical exam

- Irregular heart rate in the low 80s
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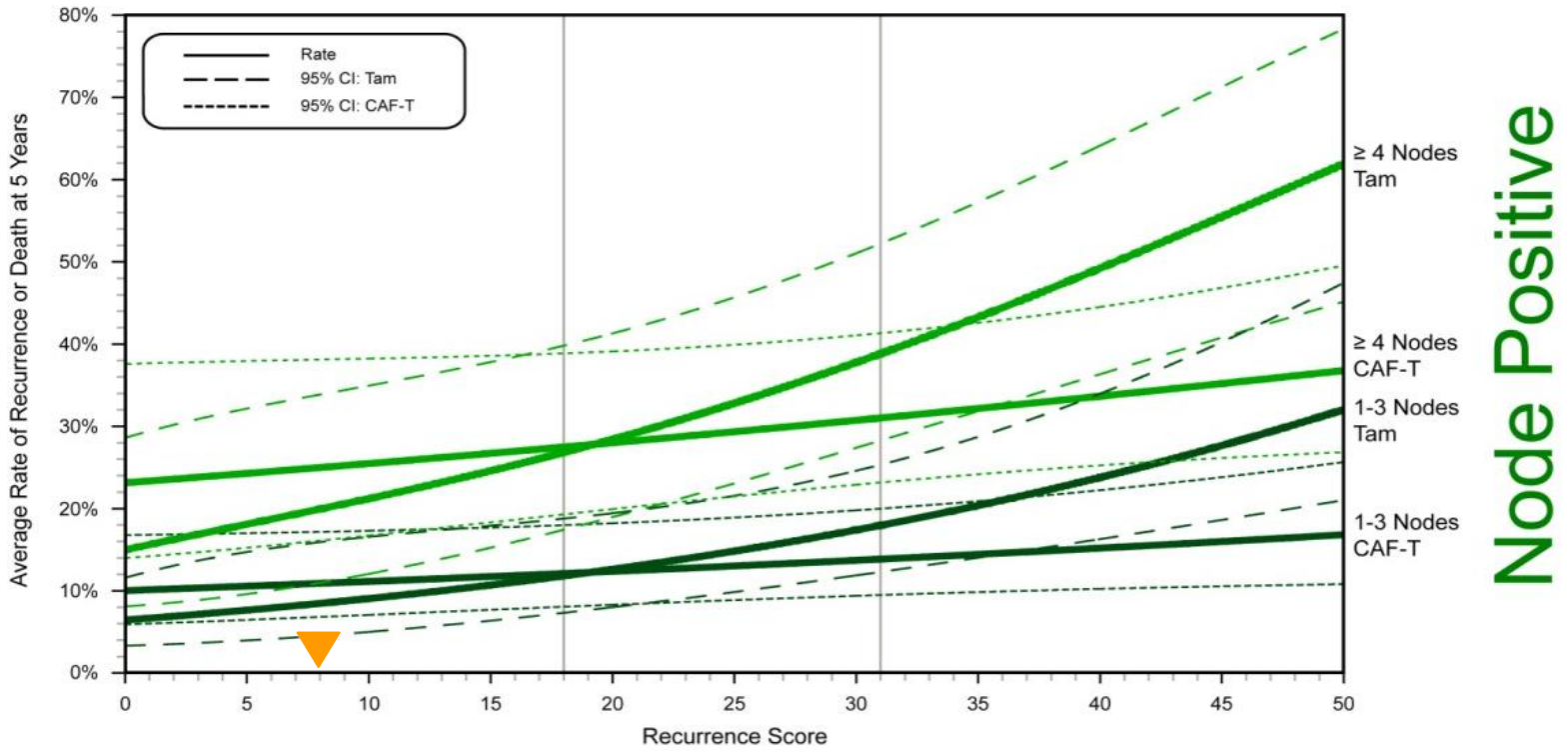
Characteristic	Description
Tumor size	2.2 cm
Tumor grade	2
Lymph nodes	1 of 15 nodes positive
ER/PR status	ER+/PR+
HER2 status	Negative
Oncotype DX® Recurrence Score®	8

- **How can the Onco*type* DX Recurrence Score result be used to inform the adjuvant treatment decision?**

Case Study: Prognosis and Predicted Chemotherapy Benefit

Recurrence Score® vs Recurrence or Death in NODE-POSITIVE, HR+ Breast Cancer
Prognosis and Chemotherapy Benefit (Difference Between Rates)



For node-positive patients, this page of the Onco*type* DX® report should be used to discuss risk of recurrence and predicted chemotherapy benefit.

Case Study: The Recurrence Score® Result Provides Individualized Treatment Information

- CB considers the treatment options.
- You explain that her diabetes and heart problems could make chemotherapy a difficult course for her.
- Based on her Recurrence Score result, you and CB realize that she has a low risk of recurrence, despite nodal involvement.
- You both agree that CB should have hormonal therapy without chemotherapy.

The Oncotype DX® Breast Cancer Assay Adds Value to Treatment Decision-Making Across the Continuum of Nodal Status

- The Oncotype DX Recurrence Score® result allows for an individualized assessment of risk and likely response to adjuvant treatment, which can spare those who may not benefit from chemotherapy across the continuum of nodal status.
- NCCN Guidelines® include Oncotype DX testing in the adjuvant treatment decision pathway for patients with node-negative or micrometastatic disease.
- The risk of distant recurrence increases with increasing number of positive nodes.
- A low Recurrence Score result suggests a low risk of distant recurrence for patients with 1-3 positive nodes.