

Case # 3:
**The Use of Gene Expression
Profiles in Node-Negative Endocrine-
Responsive Early Breast Cancer**

Christos Markopoulos, MD
Athens University Medical School
Athens, Greece

Case History



- A 59-year-old postmenopausal woman is diagnosed with left breast cancer following an abnormal routine screening mammogram.
- Breast conserving surgery and sentinel node mapping are performed.

- Pathology:**
- Tumor size = 0.8 cm with clear surgical margins
 - Infiltrating ductal carcinoma, **Grade 3**
 - No vascular or lymphatic channel invasion
 - ER 60% and PR 45% cells positive
 - HER2 negative
 - SLN negative

ECOG Performance Status: 0

Clinical Course: Radiation therapy to the left breast is planned.

Part I:

- How would you estimate this patient's risk of recurrence?

1.

Clinical and histologic parameters

2.

3.

Genetic profiling

4.

5.

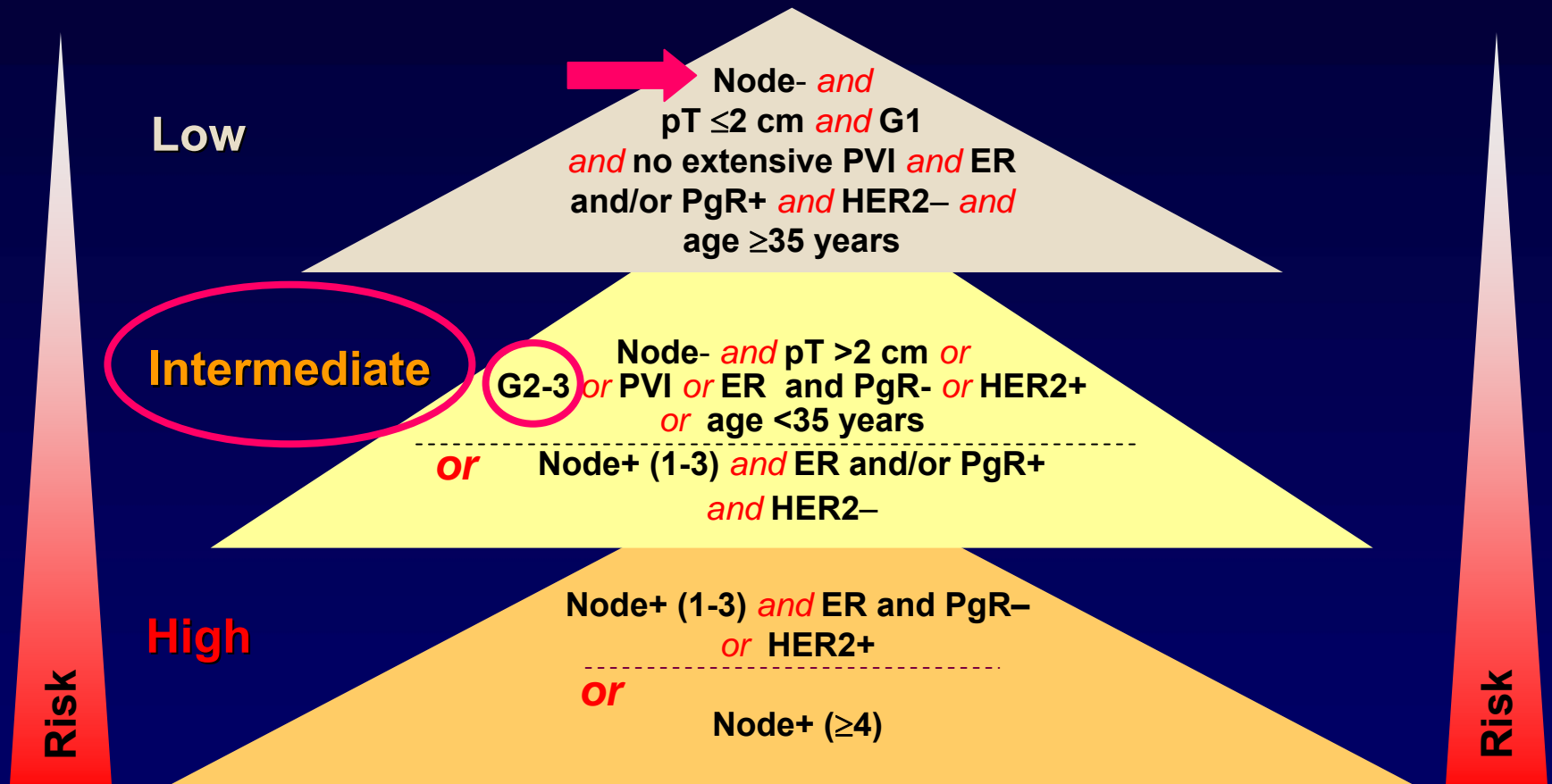
Combination of both

	Criteria	Parameters	Estimation
St Gallen Criteria	<ul style="list-style-type: none"> • Clinical <i>and</i> histologic 	Age, pT, LN, Grade, PVI, ER, PgR, HER2	<ul style="list-style-type: none"> • Risk of Recurrence
Adjuvant! Online	<ul style="list-style-type: none"> • Clinical <i>and</i> histologic • Mathematical algorithm 	Age, pT, LN, Grade, ER	<ul style="list-style-type: none"> • Risk of BCRD* at 10-years • Efficacy of therapy (<i>based on the PRR+ analysis - Oxford overview</i>)
Mammaprint	<ul style="list-style-type: none"> • Genomic • Fresh <i>or</i> frozen tissue 	70-gene assay	<ul style="list-style-type: none"> • Prognosis (<i><61yrs, Stage I-II, T<5cm, LN-, ER+/-</i>)
Oncotype DX®	<ul style="list-style-type: none"> • Genomic • Paraffin sections 	Expression of 16 Ca-related and 5 Reference genes	<ul style="list-style-type: none"> • Risk of recurrence (<i>ER+</i>) • ChemoT benefit

*BCRD= breast cancer-related death

+PRR= proportional risk reduction

Risk of Recurrence in Early Breast Cancer: St Gallen 2007—Revised Definitions of Risk



pT = pathologic tumor size; G = grade (histologic and/or nuclear) ; PVI = peritumoral vascular invasion.

Adapted with permission from Piccart-Gebhart MJ. Plenary presentation. SABCS; 2005; San Antonio, Texas.
 Goldhirsch A, et al. *Ann Oncol.* 2007;18(7):1133-1144.

Adjuvant! Online

Risk of Relapse at 10 Years

Shared Decision Making

Name: _____ (Breast Cancer)

Age: 59 General Health: Excellent

Estrogen Receptor Status: Positive Histologic Grade: 3

Tumor Size: 0.1 - 1.0 cm Nodes Involved: 0

Decision: No Additional Therapy

20%



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

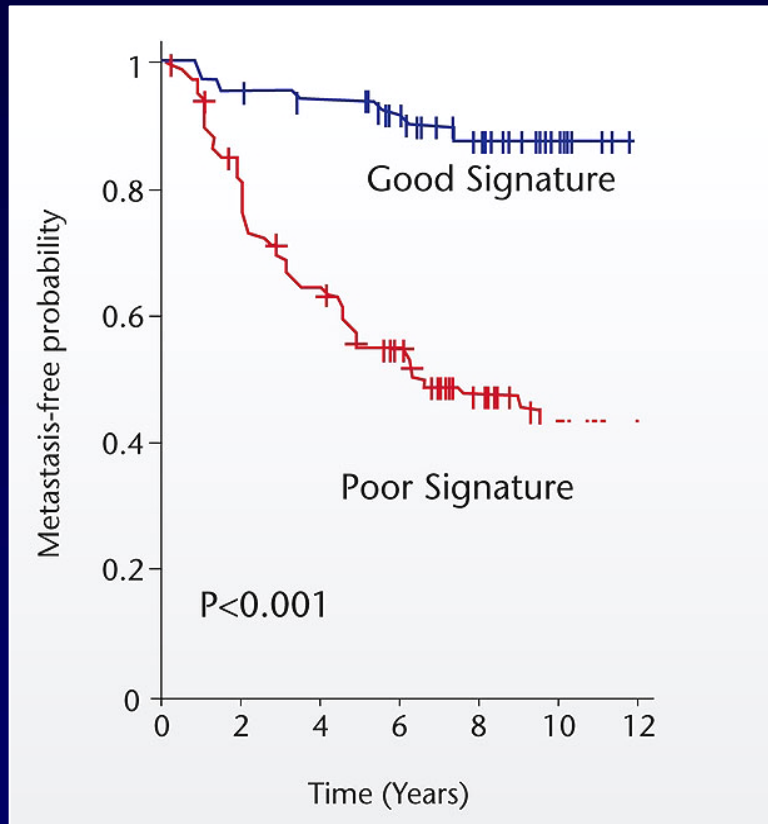
 20 out of 100 women relapse.

 5 out of 100 women die of other causes.

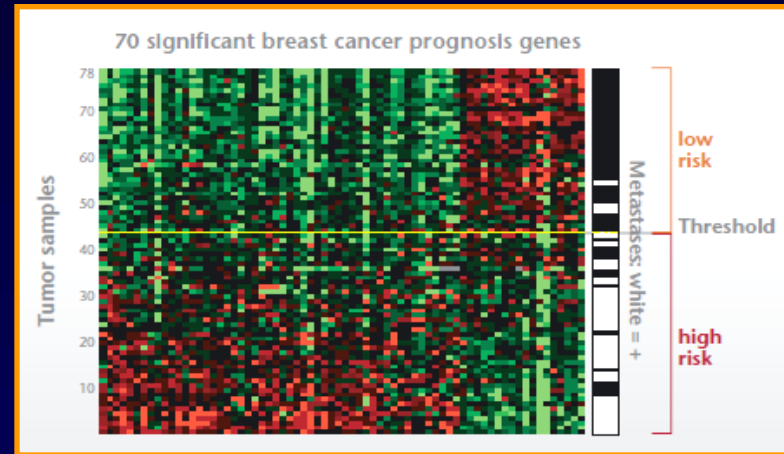
MammaPrint

Reports Whether a Patient with Breast Cancer Is at a High or Low Risk for Distant Metastasis

Age<61, T<5cm, LN-, Stage I&II, ER+/-



van de Vijver MJ et al. *N Engl J Med.* 2002;347(25):1999-2009.



- **Low risk:** 95% chance of being metastasis-free within 5 years
90% within 10 years
- **High risk:** 78% chance of being metastasis-free within 5 years
71% within 10 years¹

1. Buyse M, et al. *J Natl Cancer Inst.* 2006;98(17):1183-1192.

Oncotype DX Recurrence Score

- The Oncotype DX Recurrence Score[®] (RS) assay predicts **likelihood of recurrence (prognostic)** and magnitude of adjuvant **treatment benefit for chemotherapy (predictive)**. **Consistent results** across multiple independent studies.
 - LN-negative, ER-positive breast cancer treated with tamoxifen
 - Groups: low RS (<18), intermediate RS (18-30), high RS (≥ 31)
 - Patients with low RS (<18): no benefit from chemotherapy

Oncotype DX 21-Gene RS Assay

16 Cancer and 5 Reference Genes From 3 Studies

PROLIFERATION

Ki-67
STK15
Survivin
Cyclin B1
MYBL2

ESTROGEN

ER
PR
Bcl2
SCUBE2

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

GSTM1

BAG1

INVASION

Stromelysin 3
Cathepsin L2

CD68

REFERENCE

Beta-actin
GAPDH
RPLPO
GUS
TFRC

HER2

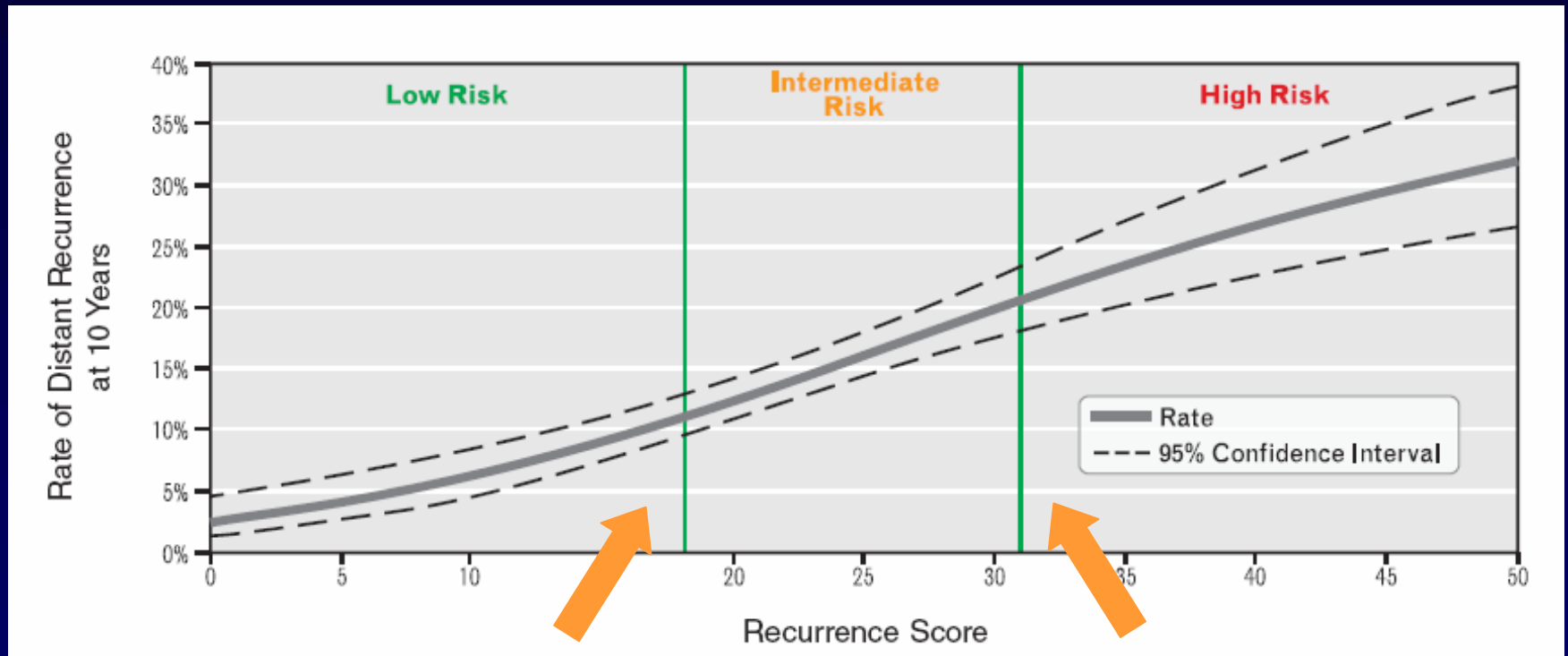
GRB7
HER2

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

*Paik s, et al. *N Engl J Med.* 2004;351(27):2817-2826.

Oncotype DX Is a Standardized and Quantitative Assay

Recurrence Score in N-, ER+



Lower RSs

- Lower likelihood of recurrence
- Minimal, if any, chemotherapy benefit

Higher RSs

- Greater likelihood of recurrence
- Clear chemotherapy benefit

NCCN Practice Guidelines in Oncology (v1.2008)

**Systemic Adjuvant Treatment
Hormone Receptor Positive, HER2- Disease**

pT1, pT2,
or pN0 or
pN1mi

**Consider
21-gene
RT-PCR
assay**

Not done → Adjuvant
endocrine
therapy ±
adjuvant
chemotherapy
(category 1)

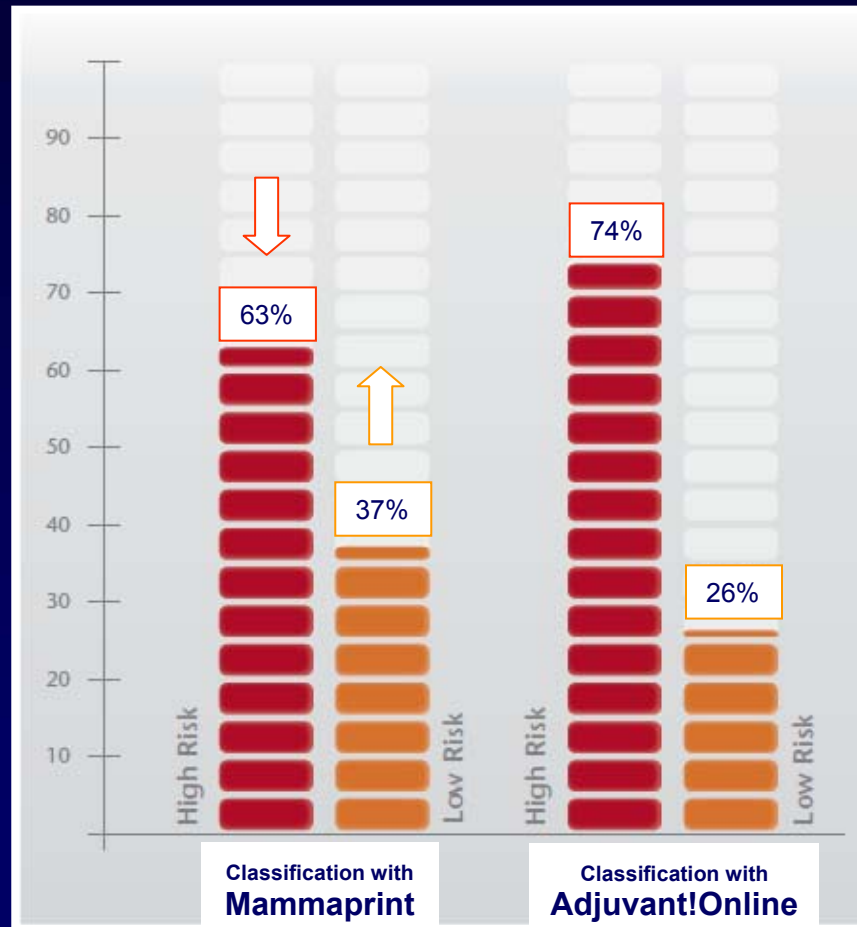
Low RS → Adjuvant
endocrine
therapy (category 2B)

Int RS → Adjuvant
endocrine
therapy ± adjuvant
chemotherapy
(category 2B)

High RS → Adjuvant
endocrine
therapy +
adjuvant
chemotherapy
(category 2B)

- Tumor 0.6 cm – 1.0 cm
moderately/poorly
differentiated
or unfavorable features
- Tumors > 1cm

Mammaprint / Adjuvant! Online TRANSBIG Study



Oncotype DX / Adjuvant! Online

* 465 patients with HR+ disease and 0-3 LN+ treated by AC or AT and Tam

Odds Ratio for Recurrence by Oncotype DX Recurrence Score in Adjuvant! Online Risk Groups

	Adjuvant! Low (n = 202)	Adjuvant! Interm (n = 138)	Adjuvant! High (n = 125)
RS Ratio: Inter / Low	2.55 (1.11-5.85)* P = .03	9.37 (3.01-29.92) P < .001	0.89 (0.3-2.63) P = .83
RS Ratio: High / Low	4.00 (1.73-9.25) P = .001	5.78 (1.7-19.6) P = .004	2.62 (1.05-6.51) P = .04

*(95% confidence intervals)

Median follow-up: 76 months

- For each risk category by Adjuvant! Online, RS provided additional prognostic information and *vice versa*
- Best scenario: Low RS and low risk with Adjuvant! Online
- If either of the two shows poor risk: Increased risk of relapse

Part II:

- **What would be your choice of adjuvant therapy using St Gallen Criteria and Adjuvant! Online estimation?**

1. Endocrine therapy alone

2. Chemotherapy followed by endocrine therapy



3. I could not decide and will order gene profiling test

4.

- I would strongly suggest participation in trials exploring gene profiling

5.

- I could use Mammaprint (*fresh or frozen tissue*) or Oncotype DX (*paraffin sections*)

Treatment Choice of Adjuvant Therapy Using St Gallen Criteria

Treatment allocation by therapeutic target and risk categories.

		HER2 Negative Highly Responsive	
		Pre	Post
R I S K G O R Y	Node negative and at least one of the following features		
	pT >2 cm, Grade 2-3	E	E
	vascular invasion, HER2+,	C → E	C → E
	ER and PgR absent, age <35 years		
	Intermediate		

Patient Information

Age:

Comorbidity:

ER Status:

Tumor Grade:

Tumor Size:

Positive Nodes:

Calculate For:

10 Year Risk:

Adjuvant Therapy Effectiveness

Horm:

Chemo:

Tumor Size:

Positive Nodes:

Calculate For:

10 Year Risk:

Adjuvant Therapy Effectiveness

Horm:

Chemo:

No additional therapy:



74.7 alive and without cancer in 10 years.

20.6 relapse.

4.7 die of other causes.

With hormonal therapy: Benefit = **7.5** without relapse.



With chemotherapy: Benefit = 4.5 without relapse.



With combined therapy: Benefit = 10.3 without relapse.



With hormonal therapy: Benefit = **10.7** without relapse.



With chemotherapy: Benefit = 4.5 without relapse.



With combined therapy: Benefit = **13.0** without relapse.



Tam

+

CMF

AI

+

CMF

Patient Information

Age:

Comorbidity:

ER Status:

Tumor Grade:

Tumor Size:

Positive Nodes:

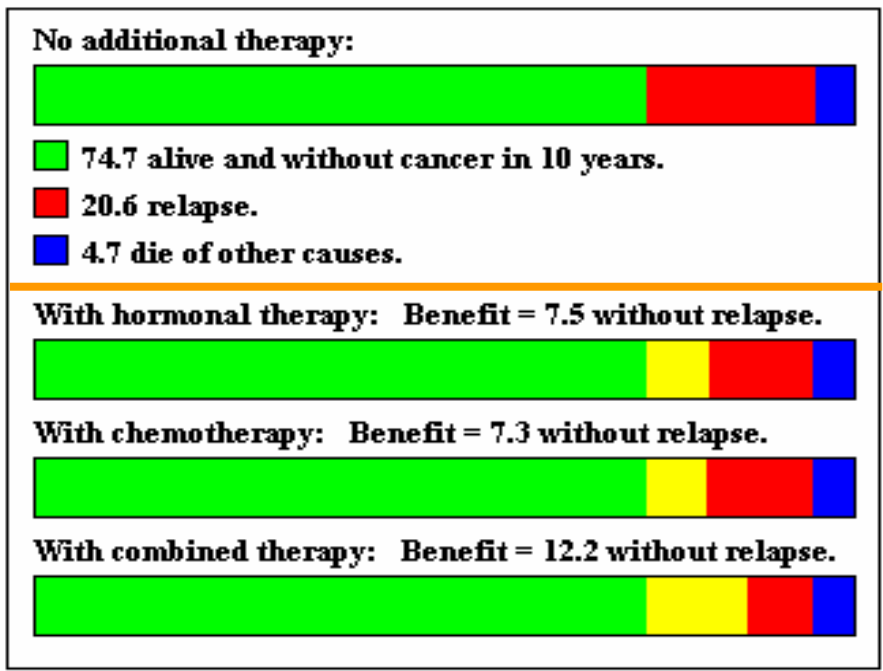
Calculate For:

10 Year Risk:

Adjuvant Therapy Effectiveness

Horm:

Chemo:



Tumor Size:

Positive Nodes:

Calculate For:

10 Year Risk:

Adjuvant Therapy Effectiveness

Horm:

Chemo:



Tam

+

AC

AI

+

AC

Part II:

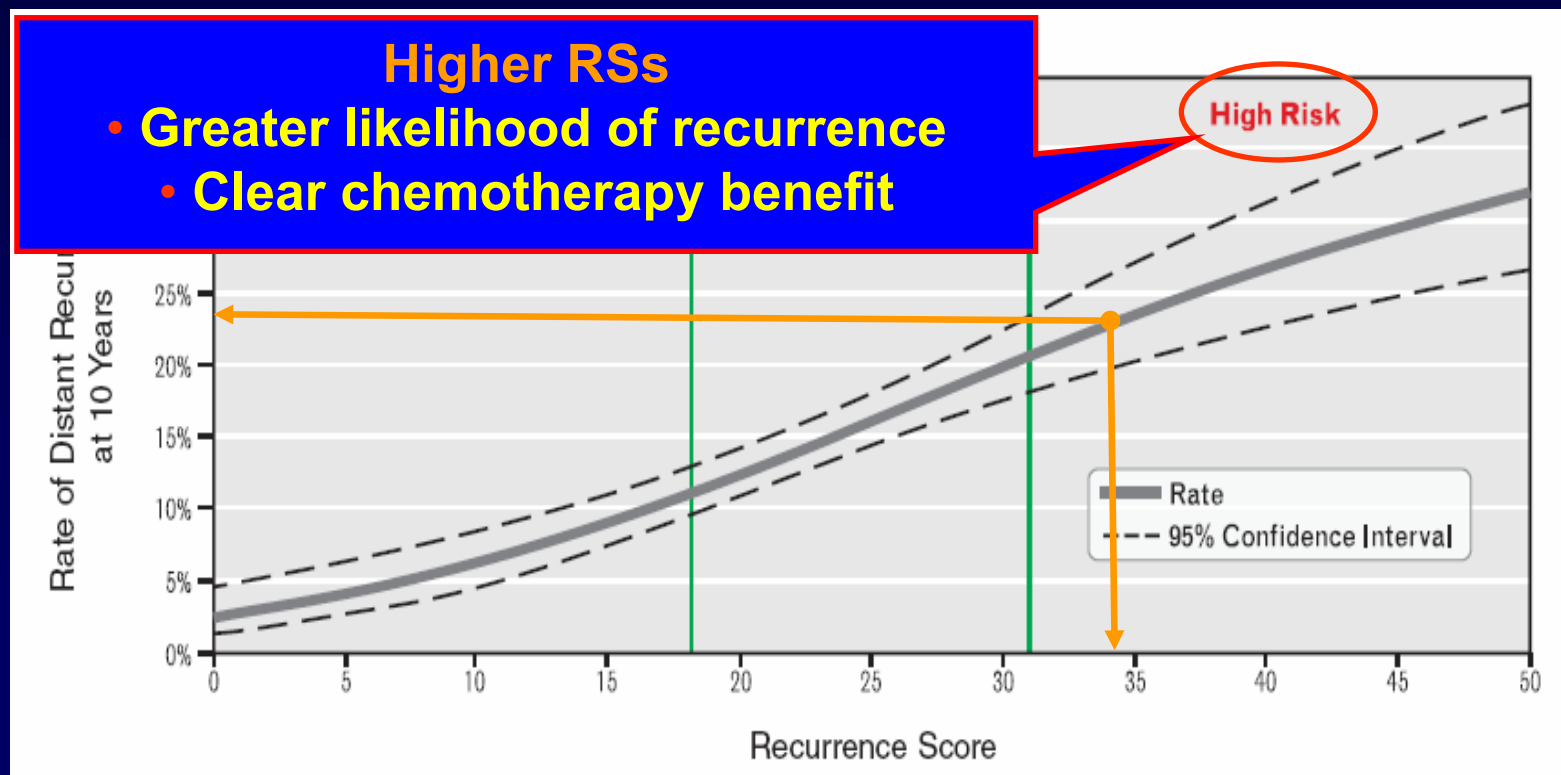
- What would be your choice of adjuvant therapy using St Gallen Criteria and Adjuvant! Online estimation?

1. Endocrine therapy alone
2. Chemotherapy followed by endocrine therapy
3. I could not decide and will order gene profiling test

- 4.
5.
 - Most benefit with adjuvant endocrine therapy
 - Little benefit by adding chemotherapy

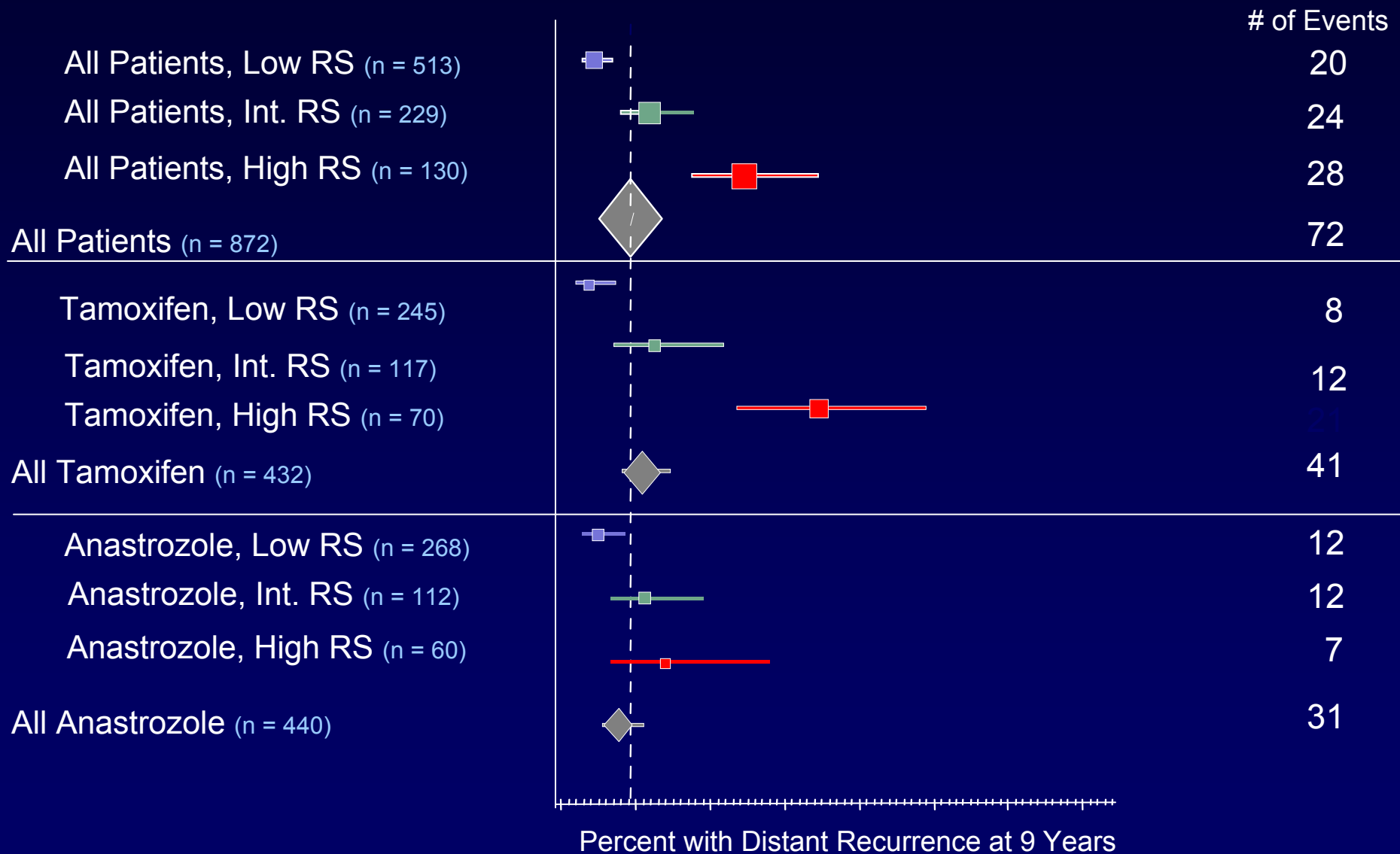
Oncotype DX Recurrence Score Is **34**

Average rate of distant recurrence at 10 years
is **23%** (95% CI: 19%-27%)

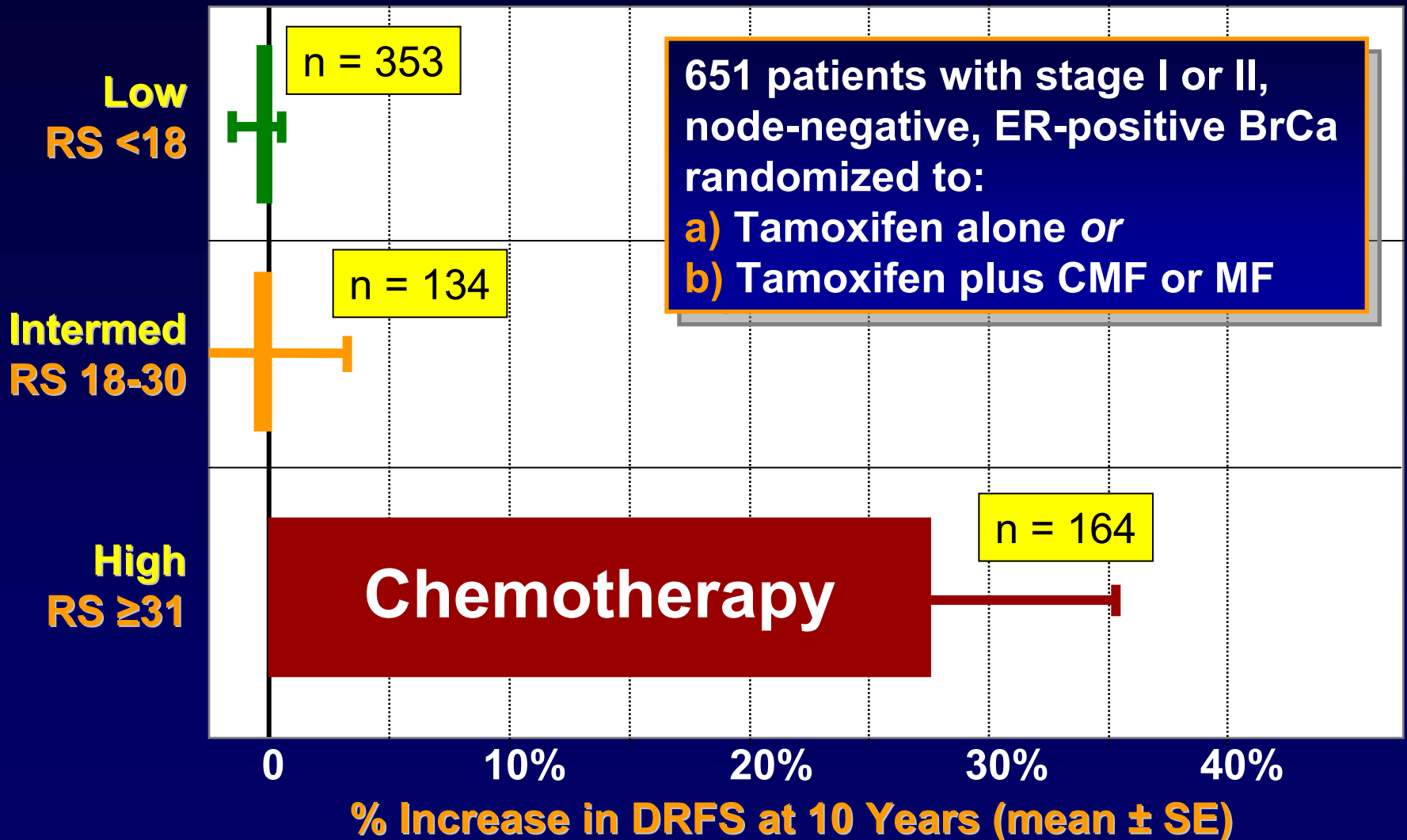


Recurrence Score in node-negative, ER+ patients

TransATAC: Percent with Distant Recurrence at 9 Years Node Negative



NASBP B-20 Results: Absolute % Increase in DRFS at 10 Years



Part II & III:

- What would be your choice of adjuvant therapy using St Gallen Criteria and Adjuvant! Online estimation?

- Most benefit with adjuvant endocrine therapy
 - Little benefit by adding chemotherapy

- The patient has a recurrence score of 34. What would be your treatment decision now?

Chemotherapy followed by endocrine therapy