Use of Genomic Classifiers to Inform Therapeutic Decision-Making for Patients with ER-Positive Localized Breast Cancer

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Disclosures

Advisory Committee	AstraZeneca Pharmaceuticals LP, Cardinal Health, CStone Pharmaceuticals, Daiichi Sankyo Inc, Genentech, Novartis, Pfizer Inc, Roche Laboratories Inc
Contracted Research	Deciphera Pharmaceuticals Inc, Prescient Therapeutics, Radius Health Inc
Data and Safety Monitoring Board	Celgene Corporation, Roche Laboratories Inc

Case Presentation: Dr Goetz

41 y/o female presented with a palpable left breast mass. Biopsy demonstrated invasive ductal carcinoma, grade 2. No lymphovascular invasion. Estrogen 100%, PR 100%, HER2 negative at 0.

Patient underwent lumpectomy and sentinel lymph node biopsy. Final pathology revealed a 1.4-cm invasive ductal carcinoma and sentinel lymph nodes were negative.
21 gene Recurrence Score® was 9.

Case Presentation: Professor Johnston

38 year old pre-menopausal woman:
HR Manager, married with 5 year old daughter, no FH

March 2019:
Symptomatic Left Breast Mass
2 cm M5 with micro-calcifications, U5
Axilla negative on USS
Core biopsy ER++ HER2 2+ IDC
BRCA 1/2 negative

April 2019:
Left Mastectomy and Sentinel Node Biopsy:
1.8 cm grade II invasive ductal cancer
0/3 negative nodes, no LVI
ER 8, PR 5, HER2 D-DISH negative

Prognostic Scores:
Nottingham Prognostic Index (NPI) = 2.36 (0.2x1.8 + 0 + 2) = 93% 5yr OS
Onco*type* DX® Recurrence Score 21

Case Presentation: Dr Burstein

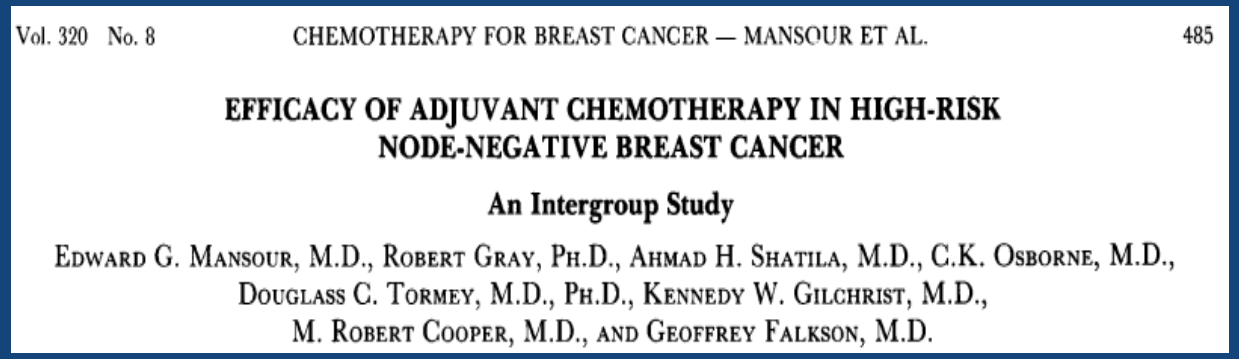
A healthy 57 year old woman was found on screening mammography to have an abnormality in the left breast. She underwent core biopsy which revealed invasive ductal carcinoma, grade 3 of 3. The tumor was ER positive 90%, PR positive 50%, and HER2 negative (0) by IHC. She subsequently underwent lumpectomy and sentinel lymph node biopsy. The invasive cancer measured 1.3 cm in size, grade 3, LVI negative. There was a 3 mm focus of invasive cancer in one of 3 sentinel lymph nodes.

In addition to adjuvant endocrine therapy, would you:

- Give adjuvant chemotherapy for high grade, node positive breast cancer?
- Not give adjuvant chemotherapy because too low a stage?
- Order a 21 gene recurrence score to decide on whether to give chemotherapy?

Role of Adjuvant Chemotherapy in Early Breast Cancer: Landscape in 2000

- U.S. N.I.H consensus panel in 2000 concluded "…*adjuvant ..chemotherapy … should be recommended to the majority of women with localized breast cancer regardless of lymph node, menopausal, or … receptor status.*"



Vol. 320 No. 8 CHEMOTHERAPY FOR BREAST CANCER — MANSOUR ET AL. 485

EFFICACY OF ADJUVANT CHEMOTHERAPY IN HIGH-RISK NODE-NEGATIVE BREAST CANCER

An Intergroup Study

EDWARD G. MANSOUR, M.D., ROBERT GRAY, PH.D., AHMAD H. SHATILA, M.D., C.K. OSBORNE, M.D., DOUGLASS C. TORMEY, M.D., PH.D., KENNEDY W. GILCHRIST, M.D., M. ROBERT COOPER, M.D., AND GEOFFREY FALKSON, M.D.

Mansour et al. N Eng J Med 1989; 320:485-490

SPECIAL ARTICLE

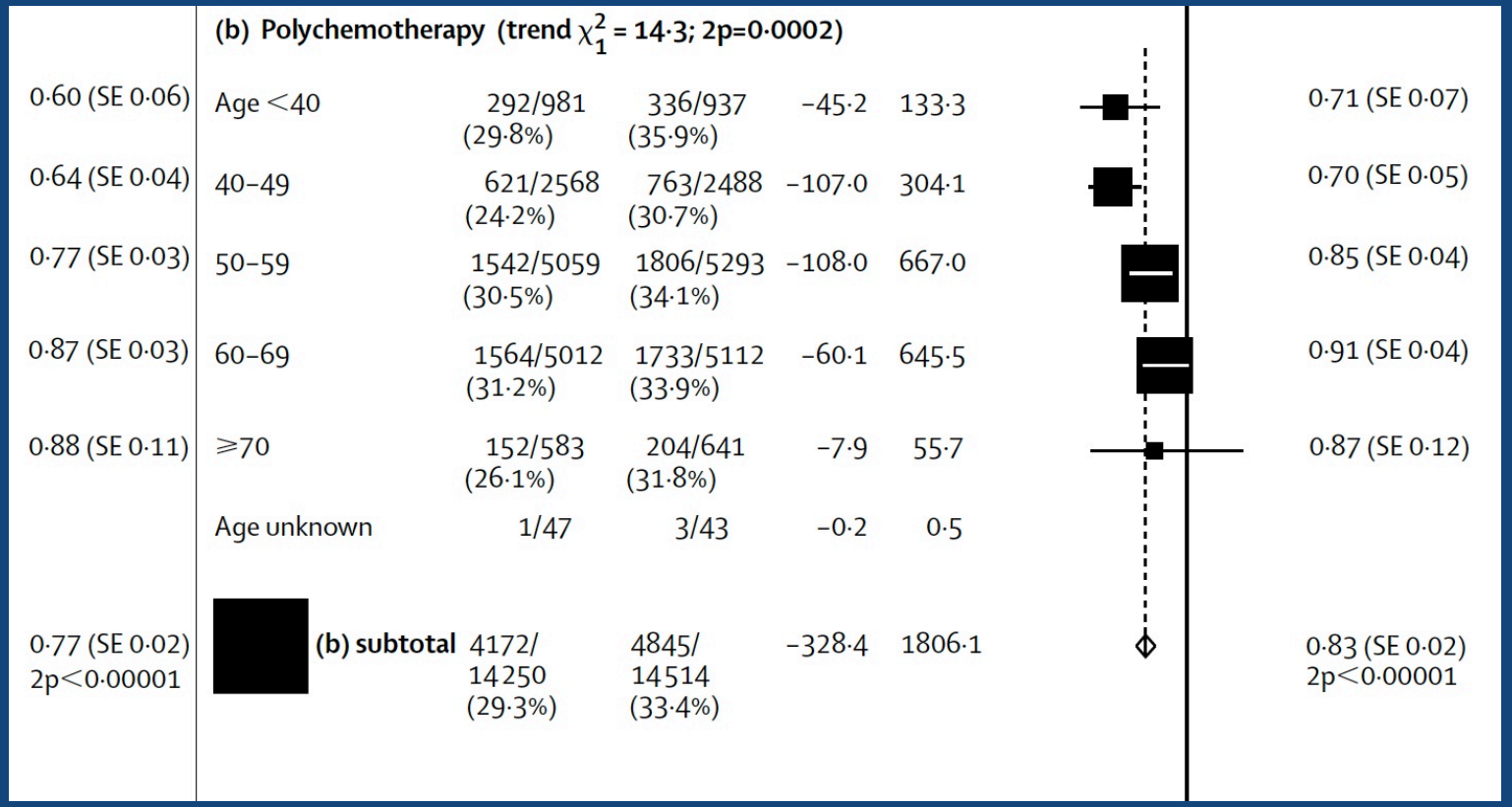
National Institutes of Health Consensus Development Conference Statement: Adjuvant Therapy for Breast Cancer, November 1–3, 2000

*National Institutes of Health Consensus Development Panel**

JNCI 2001; 93: 979-989

Early Breast Cancer Trialists Collaborative Group: Greater treatment effect of adjuvant chemotherapy with younger age

- "…polychemotherapy (eg, with FAC or FEC) reduces the annual breast cancer death rate ….
- … by about **38%** (SE 5) for women younger than 50 years of age and …
- … by about **20%** (SE 4) for those of age 50-69 years …
- …largely irrespective of the use of tamoxifen and of … (ER) status, nodal status, or other tumour characteristics."



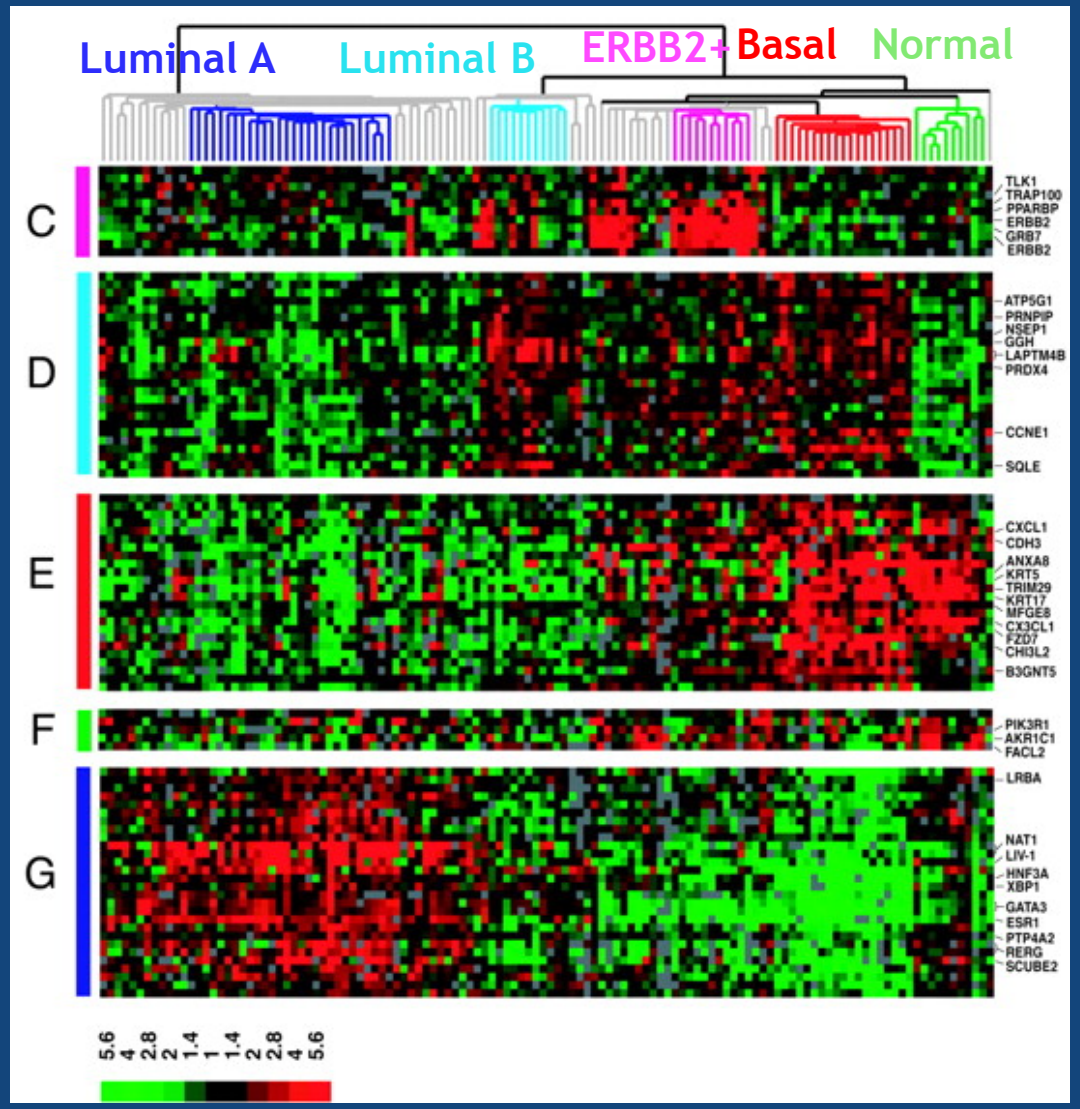
Breast cancer mortality at 15 years

EBCTCG. Lancet. 2005;365:1687-717

Gene Expression Assays in Breast Cancer

- Unsupervised analysis
  - Breast cancer is heterogeneous
  - Distinct subtypes
  - Prognosis varies by subtype (PAM50)

- Supervised analysis
  - Several other prognostic assays (21-gene, 70-gene, others)
  - Lack of concordance in prognostic classification

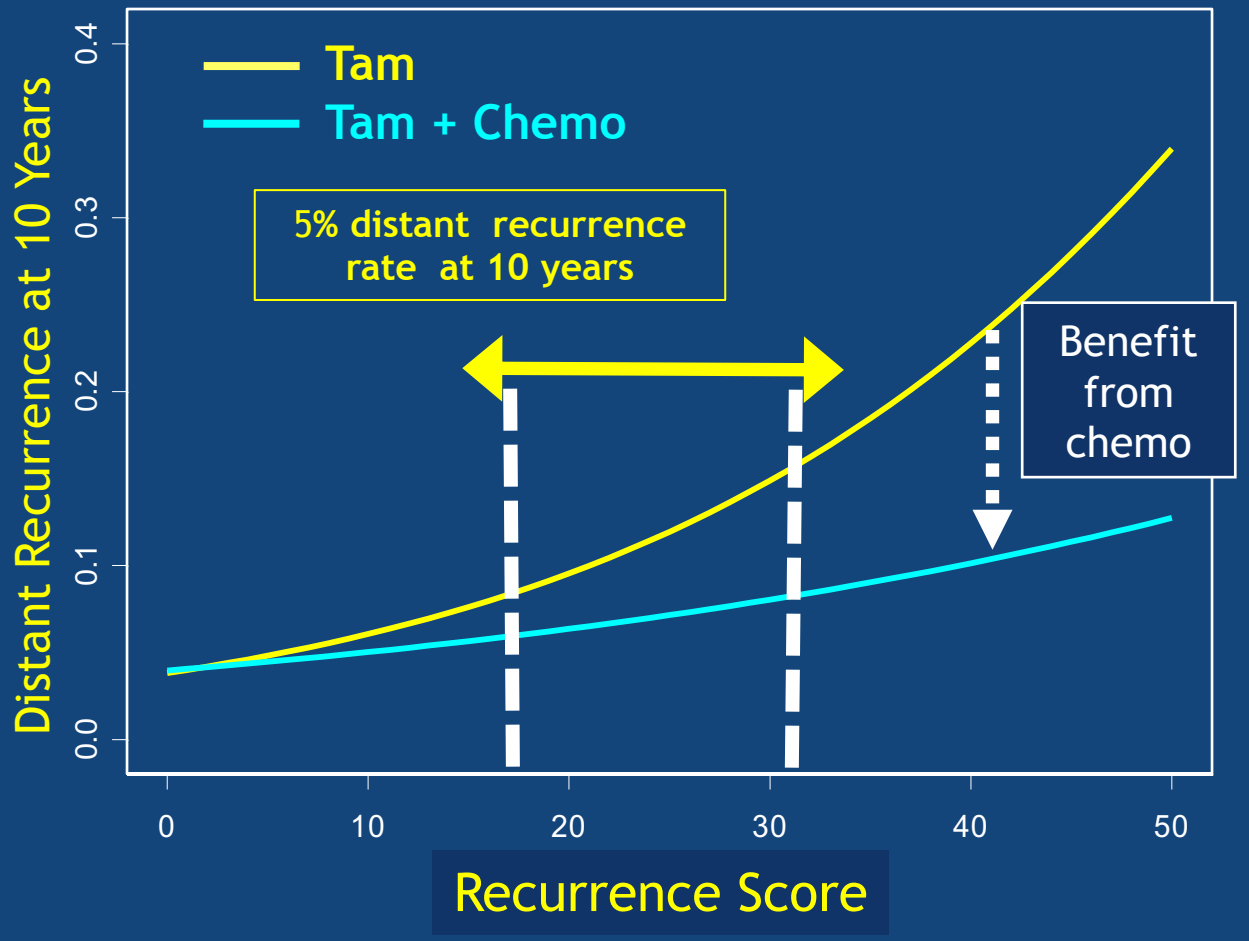


Sorlie et al PNAS 2003; 100(14): 8418-8423
Bartlett JM et al. J Natl Cancer Inst. 2016;108(9)

TAILORx: Rationale for Adjusting RS Ranges

- **TAILORx population excluded HER2+**
  - 21-gene assay includes HER2 module (*HER2*, *GRB7*) - higher recurrence
  - Most HER2+ tumors have high RS
  - Different RS distribution
- **RS assay used selectively in practice - therapeutic equipoise**
  - Typically int. grade tumors, 1-2 cm in size
  - More tumors in mid-range group
- **RS range adjusted for mid-range (B20)**
  - Preserve prediction in high risk group
  - Minimize potential for undertreatment

B20: Relationship Between Continuous RS and Distant Recurrence by Treatment



Sparano J, Paik S. J Clin Oncol 2008; 26: 721-728

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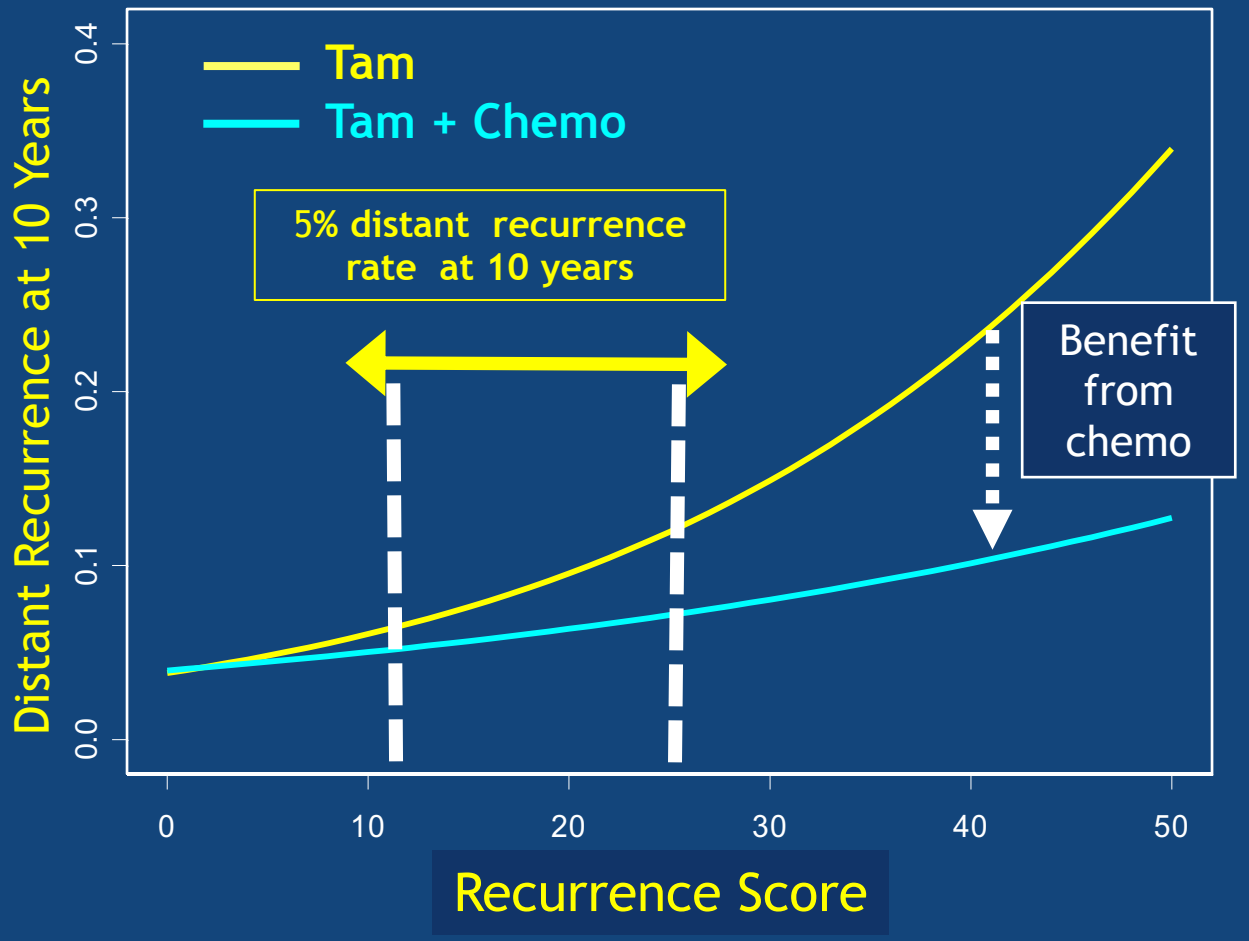


Sparano J, Paik S. J Clin Oncol 2008; 26: 721-728

TAILORx: Treatment Assignment & Randomization

Accrued Between April 2006 - October 2010

Key Eligibility Criteria
- Node-negative
- ER-pos, HER2-neg
- T1c-T2 (high-risk T1b)

Preregister - Oncotype DX RS (N=11,232)

Register (N=10,273)

Statistical Design
- Non-inferiority - IDFS
- HR 1.332 (90 vs. 87% 5-yr DFS)
- Type I 10%, type II 5%
- Full info– 835 IDFS events

ARM A: Low RS 0-10
(N=1629 evaluable)
ASSIGN
Endocrine Therapy (ET)

Mid-Range RS 11-25
(N=6711 evaluable)
RANDOMIZE
Stratification Factors: Menopausal Status, Planned Chemotherapy, Planned Radiation, and RS 11-15, 16-20, 21-25

ARM D: High RS 26-100
(N=1389 evaluable)
ASSIGN
ET + Chemo

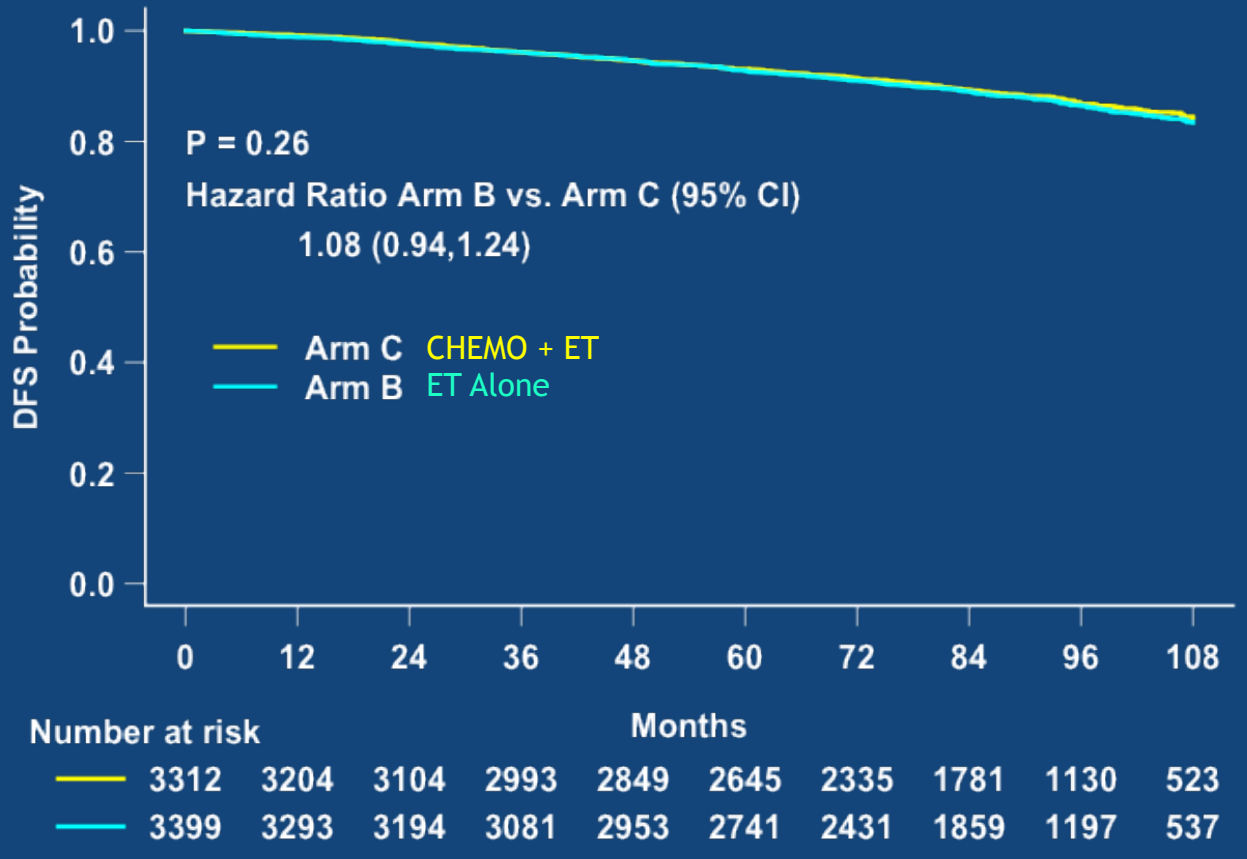
ARM B: Experimental Arm
(N=3399)
ET Alone

ARM C: Standard Arm
(N=3312)
ET + Chemo

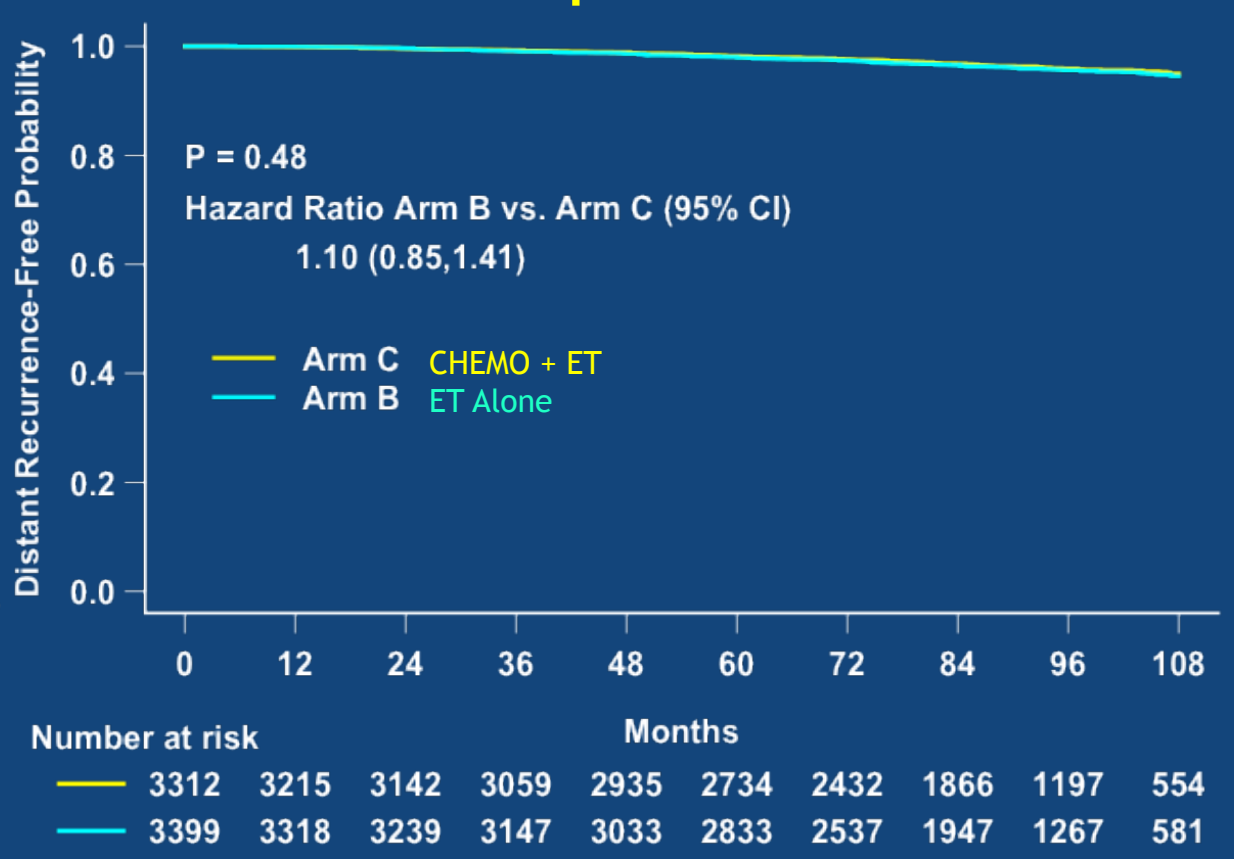
TAILORx Results - ITT Population: RS 11-25 (Arms B & C)

836 IDFS events (after median of 7.5 years), including 338 (40.3%) with recurrence as first event, of which 199 (23.8%) were distant

Primary Endpoint
Invasive Disease-Free Survival



Secondary Endpoint
Distant Relapse-Free Interval

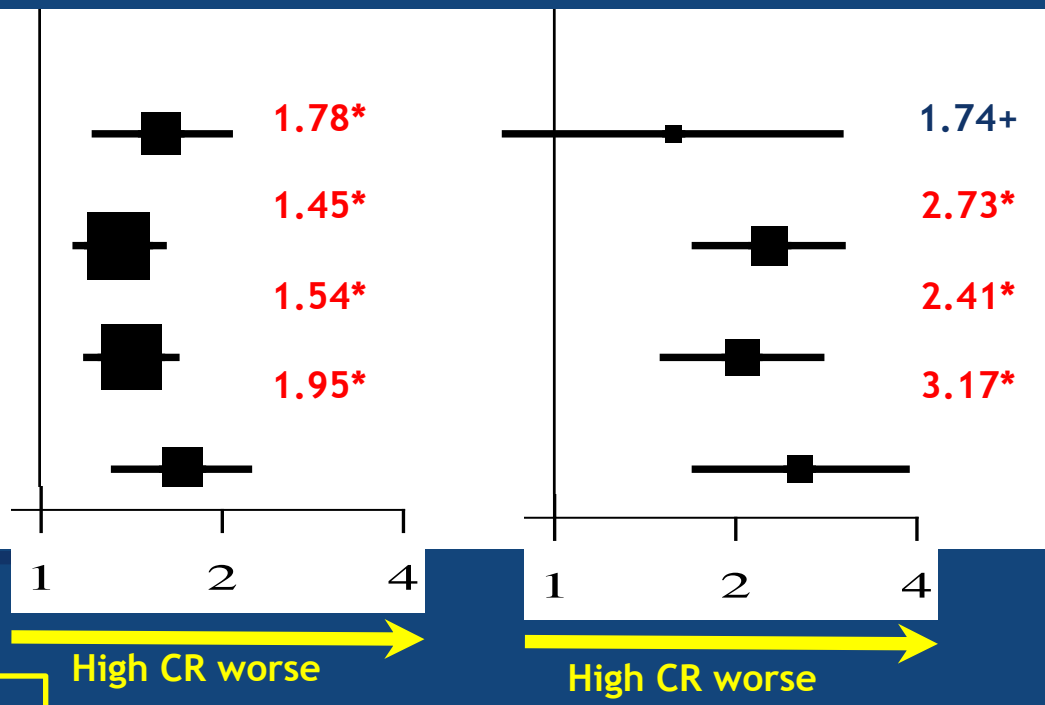


Sparano et al. N Engl J Med 2018; 379(2):111-121

TAILORx: Impact of Clinical Risk (CR) on Prognosis by RS Group

(N=9427) 30% clinical high risk & 70% clinical low risk

Grouped by RS	Total #/#IDFS/DR events	IDFS Hazard Ratio	DRFI Hazard Ratio
All Patients (n=9427)			
RS <= 10: Endocrine Therapy	1572/176/ 30	1.78*	1.74+
RS 11–25: Endocrine Therapy	3282/422/127	1.45*	2.73*
RS 11–25: Chemoendocrine Therapy	3214/389/113	1.54*	2.41*
RS > 25: Chemoendocrine Therapy	1359/184/ 96	1.95*	3.17*



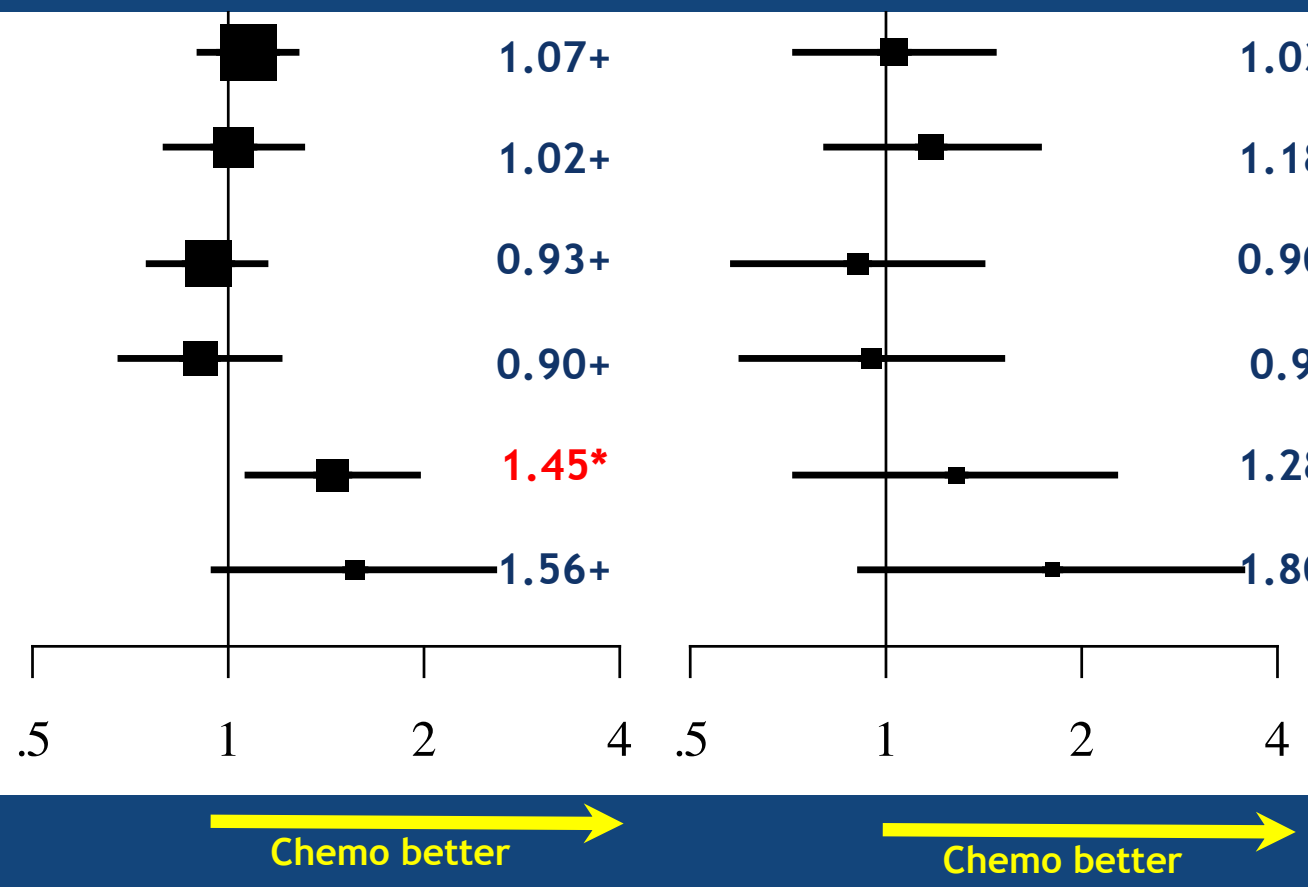
Multivariate model for distant recurrence in RS 11-25 group:
(N=6496 cases and 240 distant recurrences):
- Clinical risk: HR for high vs. low risk 2.42, p<0.001
- Continuous RS: HR 1.08, p<0.001 (HR for a 1 point higher RS)

Hazard ratio > 1 - high clinical risk worse
+95% CI overlap 1
*95% CI don't overlap 1

Sparano et al. N Engl J Med 2019;380(25):2395-2405.

TAILORx: Impact of Clinical Risk (CR) on Prediction of Chemotherapy Benefit by Age in RS 11-25 Group (ET vs. Chemo +ET)

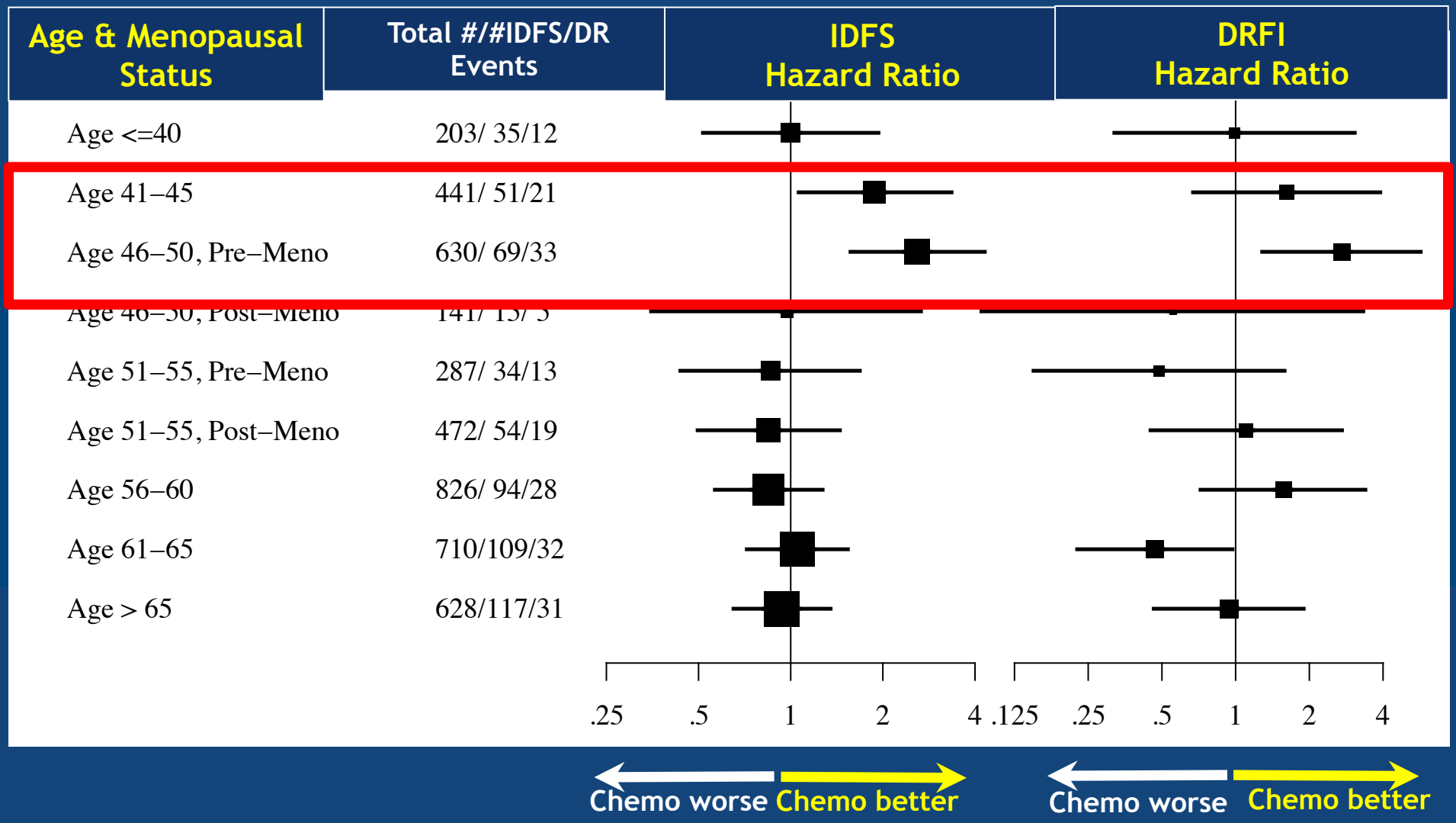
Grouped by Clinical Risk and Age	Total #/#IDFS/DR events	IDFS Hazard Ratio	DRFI Hazard Ratio
All Patients, Low Clinical Risk	4799/541/129	1.07+	1.03+
All Patients, High Clinical Risk	1697/270/111	1.02+	1.18+
Age > 50, Low Clinical Risk	3173/361/ 80	0.93+	0.90+
Age > 50, High Clinical Risk	1180/204/ 73	0.90+	0.95
Age <= 50, Low Clinical Risk	1626/180/ 49	1.45*	1.28+
Age <= 50, High Clinical Risk	517/ 66/ 38	1.56+	1.80+



Hazard ratio > 1 - chemo better
+95% CI overlap with 1
*95% CI don't overlap 1

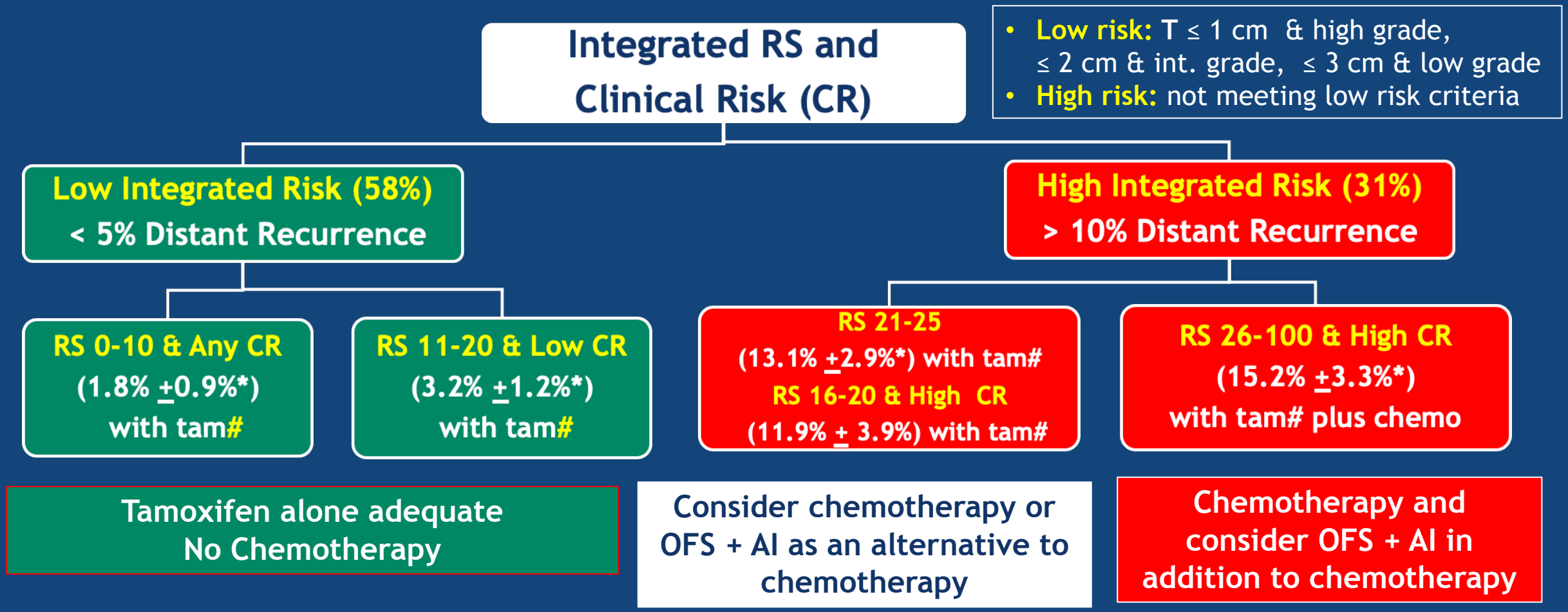
Sparano et al. N Engl J Med 2019;380(25):2395-2405.

TAILORx: Exploratory Analysis - Impact of Age and Menopausal Status on Chemotherapy Benefit for RS 16-25



Sparano et al. N Engl J Med 2019;380(25):2395-2405.

Integrated Risk: Potential Clinical Utility of Integrated RS and Clinical Risk for Guiding Treatment in Women ≤ 50 Years

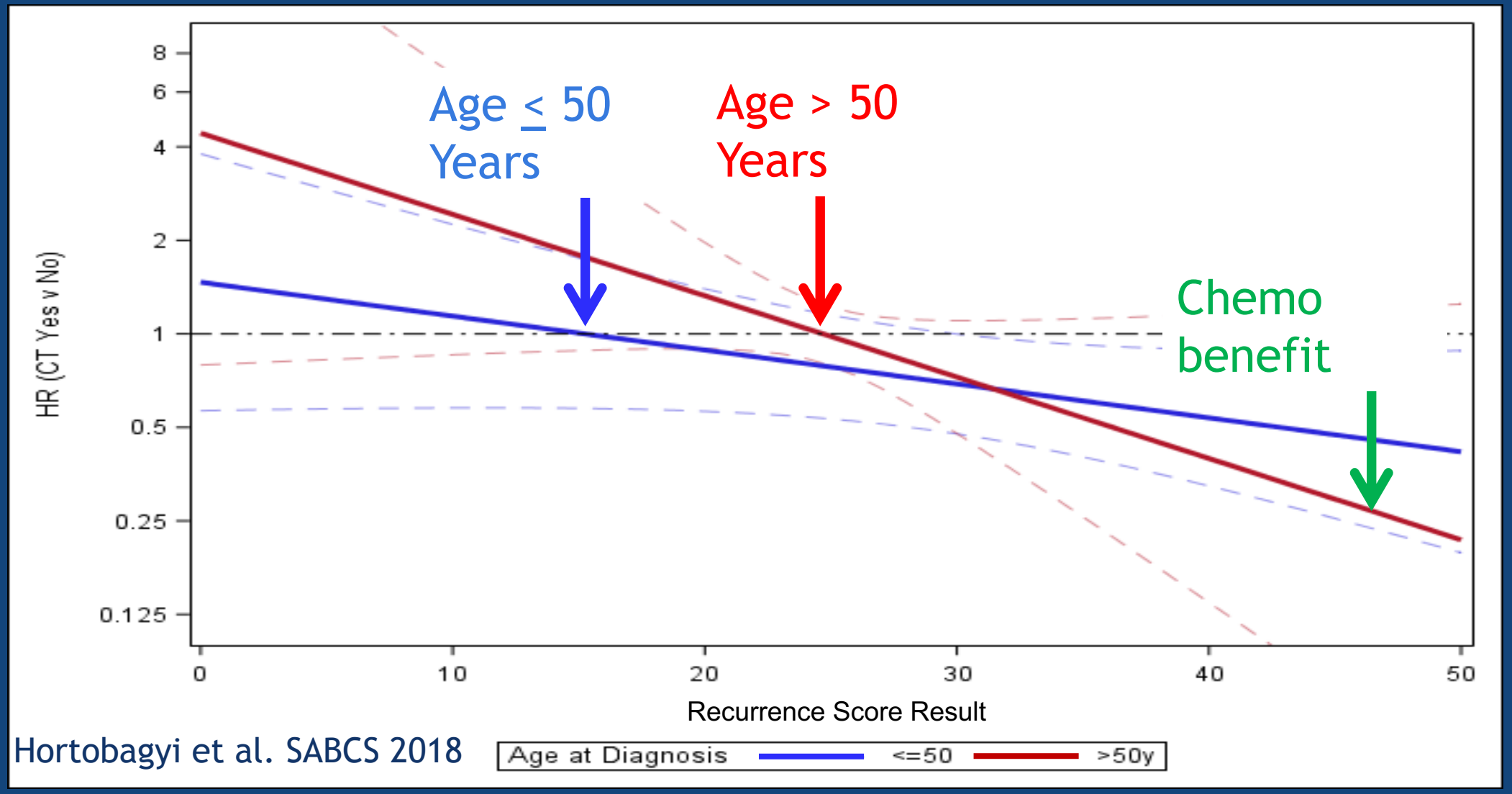


*Kaplan Meier estimates of 9-year distant recurrence rates

tamoxifen in 78% (including 35% who crossed over to an AI), or OFS +/- AI in 13%; 9% AI other

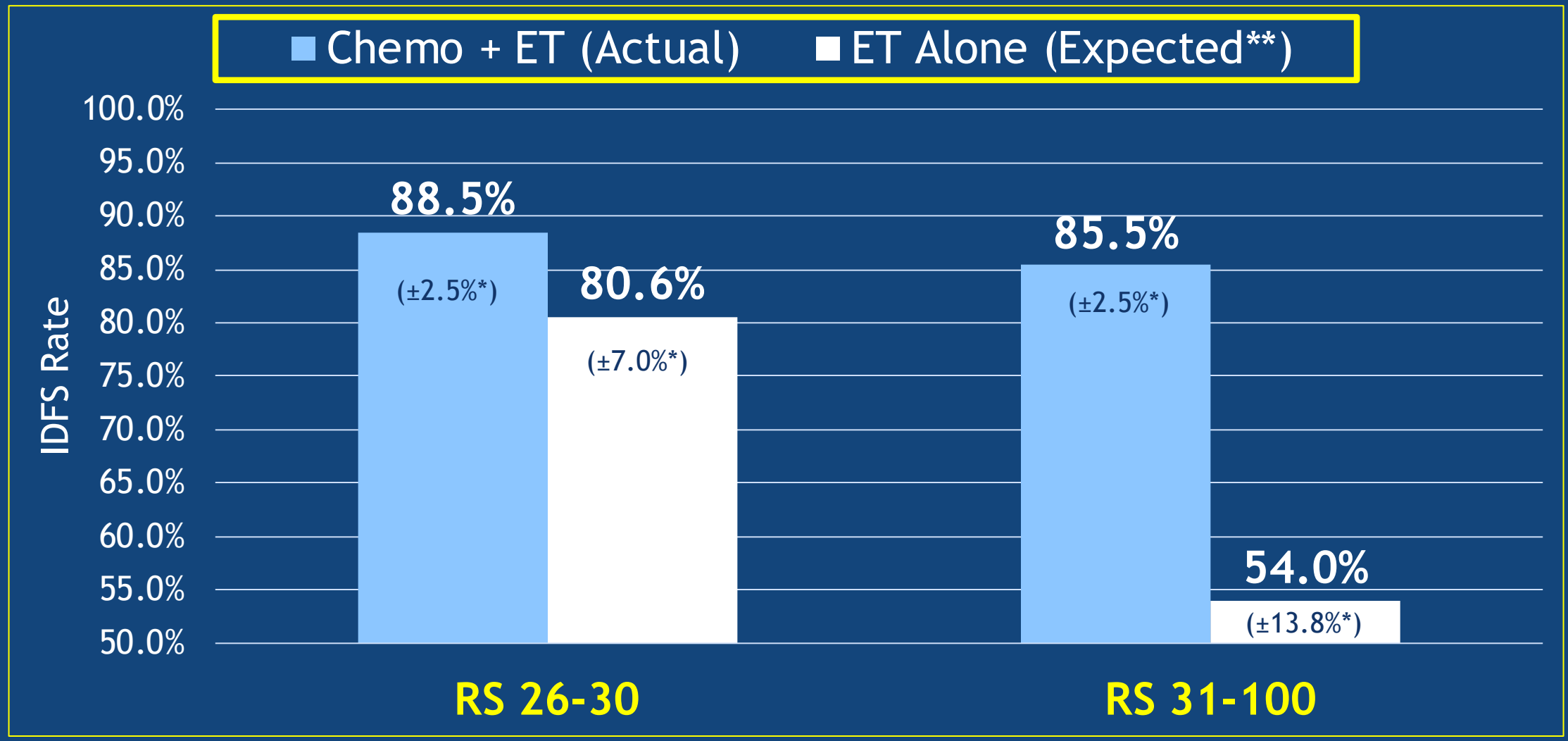
Prediction: Hazard Ratio for Chemotherapy Benefit as a Function of Continuous RS and Age (SEER)

Cox proportional hazards regression with propensity weighting (N=70,087)



Hortobagyi et al. SABCS 2018

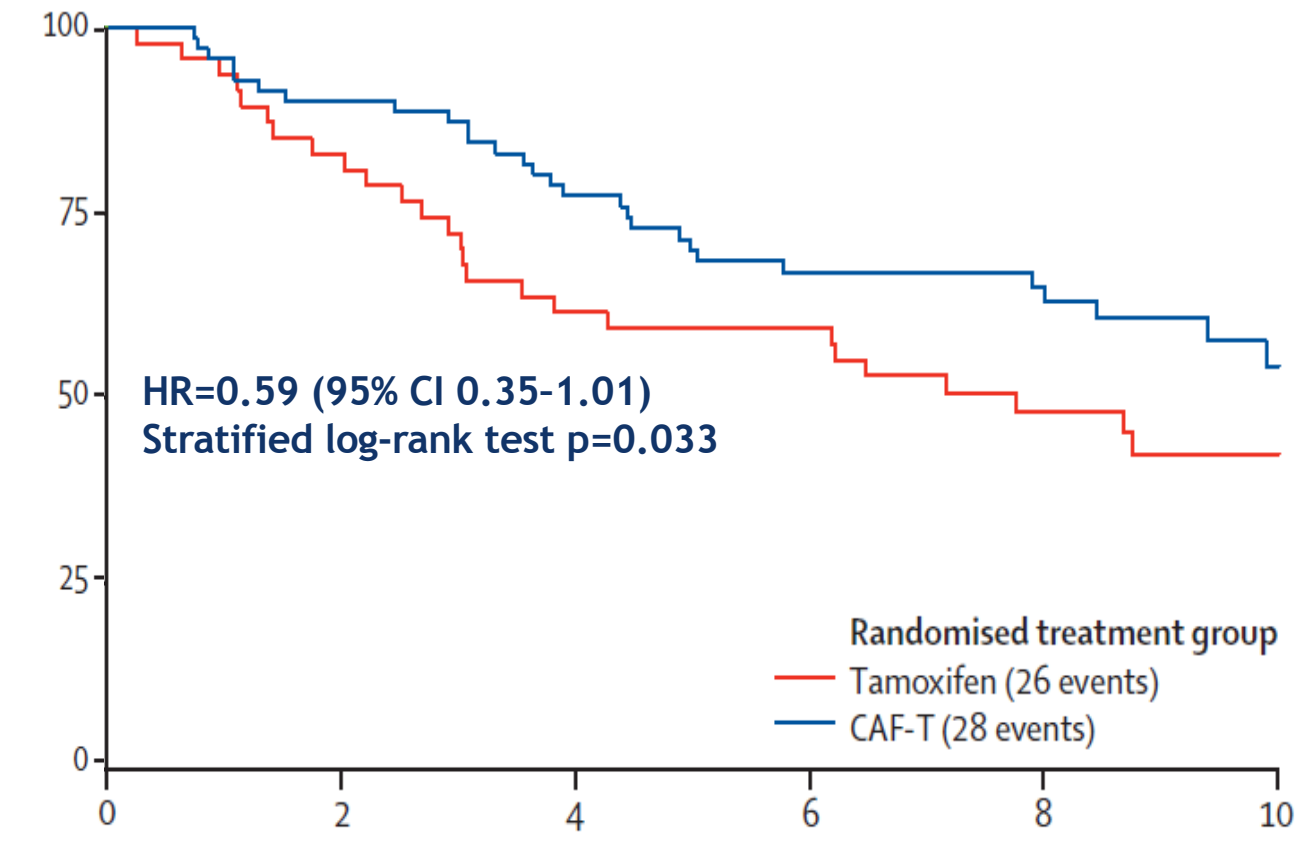
DRFI in RS 26-100 in TAILORx: Comparison of Actual Outcomes for Patients Treated with Chemo plus ET (N=1300) vs. Expected with ET Alone Stratified by RS (9-Yr Estimates)



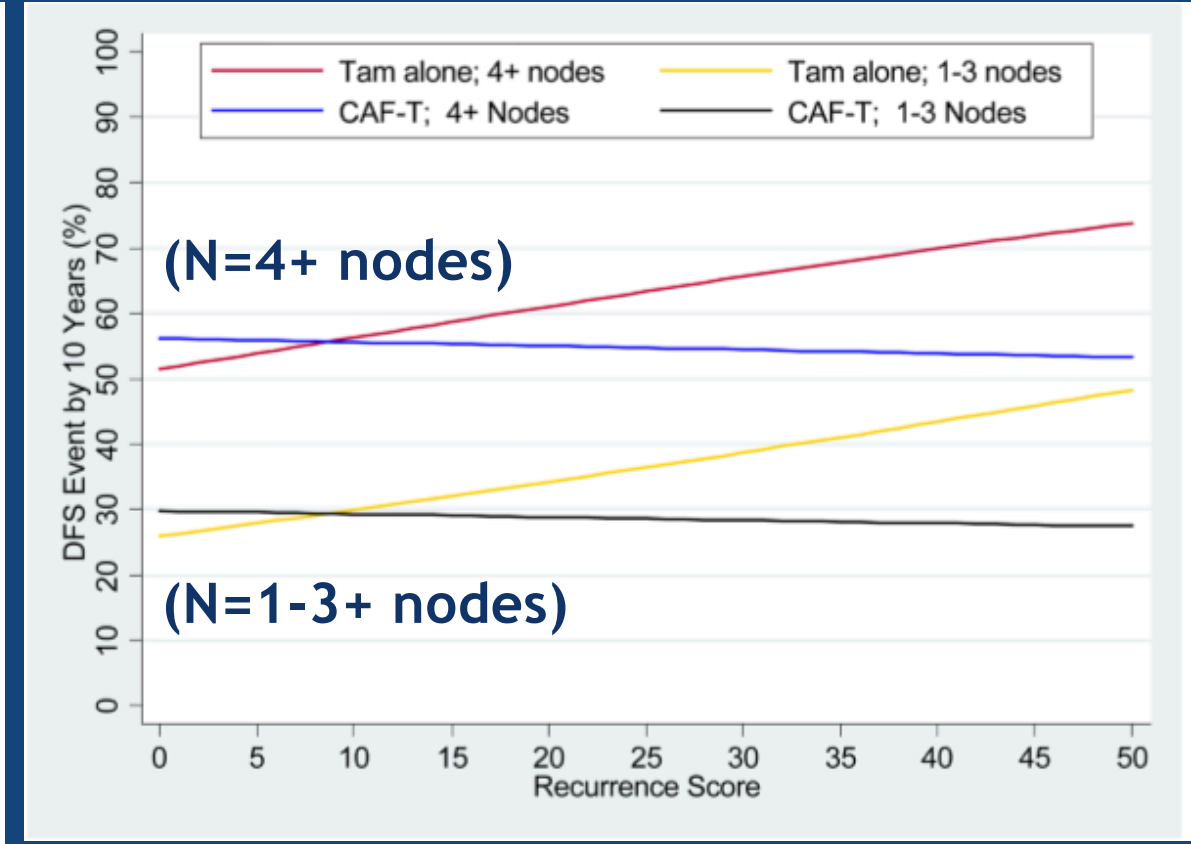
Sparano et al. ESMO 2019 & JAMA Oncol 2019. doi: 10.1001/jamaoncol.2019.4794

Prognosis and Prediction in Node-Positive Breast Cancer (S8814)
(N=367 postmenopausal ER+, node-pos - tam x 5 years +/- CAF)

10-year DFS: RS ≥31



10-year DFS: Impact of Nodal Status and RS

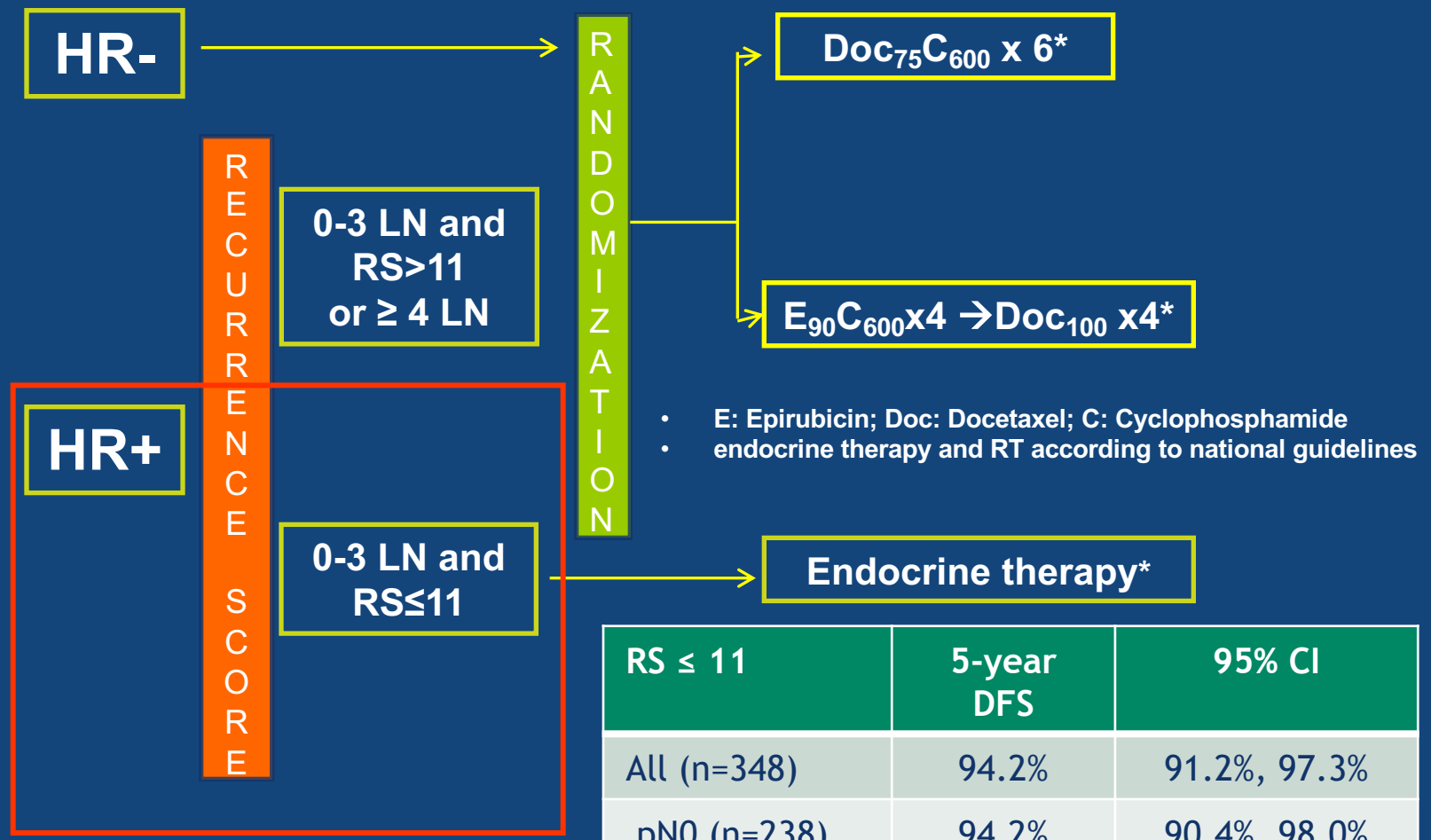


Albain et al. Lancet Oncol 2010; 11(1): 55-65

Prognosis in Node-Positive Breast Cancer

- **Age≤75 years**
- **free margins**
- **M0**
- **pN+**
- pN0 high risk

- pT≥2
- G2-3
- uPA/PAI-1↑
- HR-
- age ≤35 years



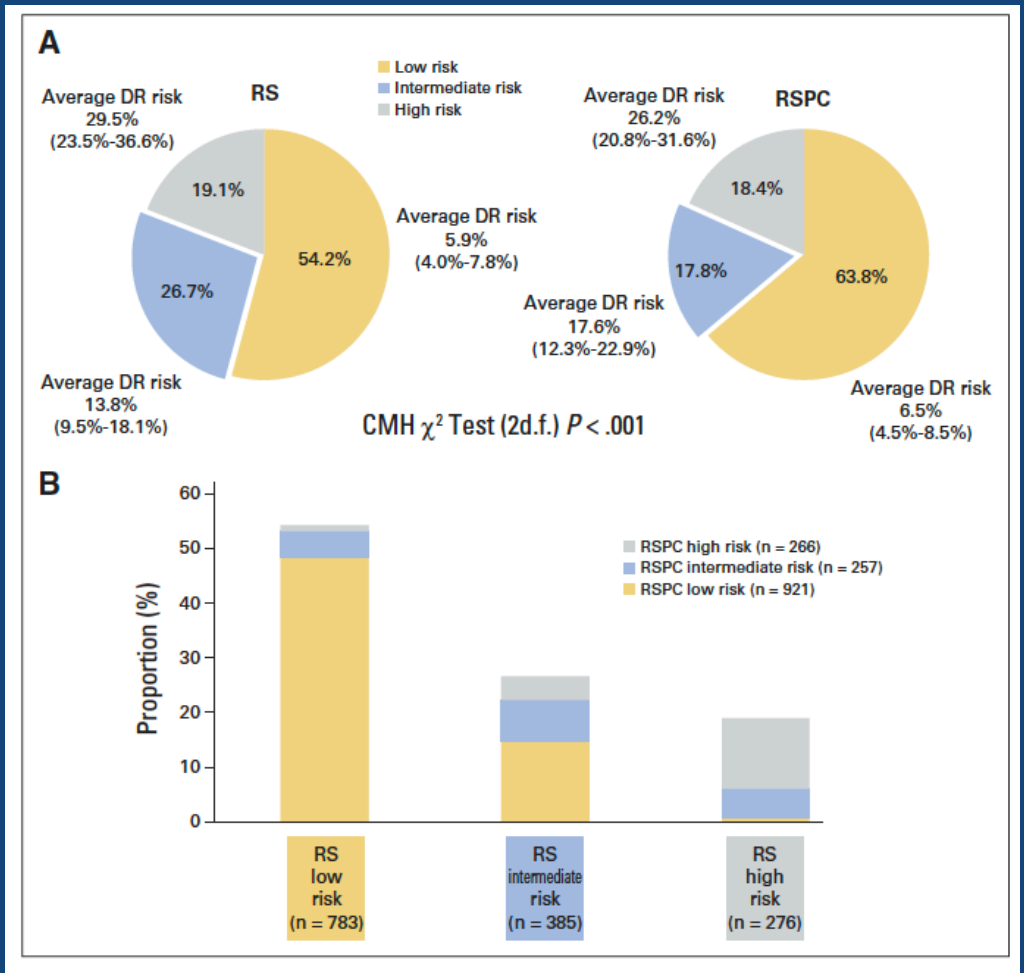
- E: Epirubicin; Doc: Docetaxel; C: Cyclophosphamide
- endocrine therapy and RT according to national guidelines

RS ≤ 11	5-year DFS	95% CI
All (n=348)	94.2%	91.2%, 97.3%
pN0 (n=238)	94.2%	90.4%, 98.0%
pN1 (n=110)	94.4%	89.5%, 99.3%

Nitz et al Breast Cancer Res Treat (2017) 165:573–583

RSPC Model: RS Alone and Integrated With Pathologic and Clinical Factors

Tumor size = 2.5 cm (high clinical risk except *low grade*)



Age (years)	45	55	65
Endocrine Rx	Tamoxifen	AI	AI
RS 23	**15%**	**12%**	**12%**
Low grade	*13%*	*10%*	*9%*
Int. grade	17%	13%	12%
High grade	32%	24%	22%
RS 16	**10%**	**8%**	**8%**
Low grade	*10%*	*7%*	*7%*
Int. grade	13%	10%	9%
High grade	24%	18%	17%

Clinical risk definitions (MINDACT criteria calibrated to Adjuvant! V8):
Low risk: T ≤ 1 cm & high grade, ≤ 2 cm & int. grade, ≤ 3 cm & low grade
High risk: not meeting low risk criteria

Tang et al. JCO 2011; 29: 4365-4572

Genomic Classifiers in Early Breast Cancer: **Conclusions**

- Gene-expression assays provide ***prognostic*** information (Level 1AB - 2C)
  - ER+, HER2-negative breast cancer
  - Node-negative and low-volume node-positive disease (1-3+ axillary nodes)
- 21-gene assay (RS) provides ***predictive*** information (Level 1A & B)
  - Chemotherapy benefit (level 1B) in node-neg (B20) and node-pos (S8814) BCA for high RS
  - Lack of chemotherapy benefit (level 1A) in node-neg BCA with RS 0-25 (TAILORx)
  - "Preferred" assay in NCCN guidelines (V2.2018, 10/5/18), ASCO guidelines updated
  - Integrating clinicopathologic factors adds prognostic but not predictive information
    - Identifies women ≤ 50 yrs at high risk (≥10%) with tamoxifen alone who may benefit from OFS + AI, possibly as an alternative to chemotherapy (RS 21-25, or RS 16-20 & high CR)
  - Awaiting results of RxPONDER trial for RS 0-25 in 1-3 positive nodes for chemo benefit
- 70-gene assay provides *prognostic* information (Level 1A & B)
  - May be used in clinical high risk (1-3+ nodes) to spare chemotherapy
- Assays not interchangeable – lack of concordance in risk classification

Krop et al. J Clin Oncol 2017; Andre et al. J Clin Oncol 2019; NCCN V2.2018 10/5/18