The TAILORx Trial: A review of the data and implications for practice

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Trial Assigning IndividuaLized Options for TReatment (TAILORx):

Phase III trial of chemoendocrine therapy versus endocrine therapy alone in hormone receptor-positive, HER2-negative, node-negative breast cancer and an intermediate prognosis 21-gene recurrence score

Joseph A. Sparano, Robert J. Gray, William C. Wood, Della F. Makower, Tracy G. Lively, Thomas J. Saphner, Maccon M. Keane, Henry L. Gomez, Pavan Reddy, Timothy F. Goggins, Ingrid A. Mayer, Deborah Toppmeyer, Adam Brufsky, Matthew P. Goetz, Daniel F. Hayes, Elizabeth Claire Dees, Kathleen I. Pritchard, Charles E. Geyer, John A. Olson, & George W. Sledge

on behalf of the TAILORx Investigators

Canadian Cancer Trials Group

Alliance for Clinical Trials in Oncology

Federally Funded Research

ECOG-ACRIN cancer research group

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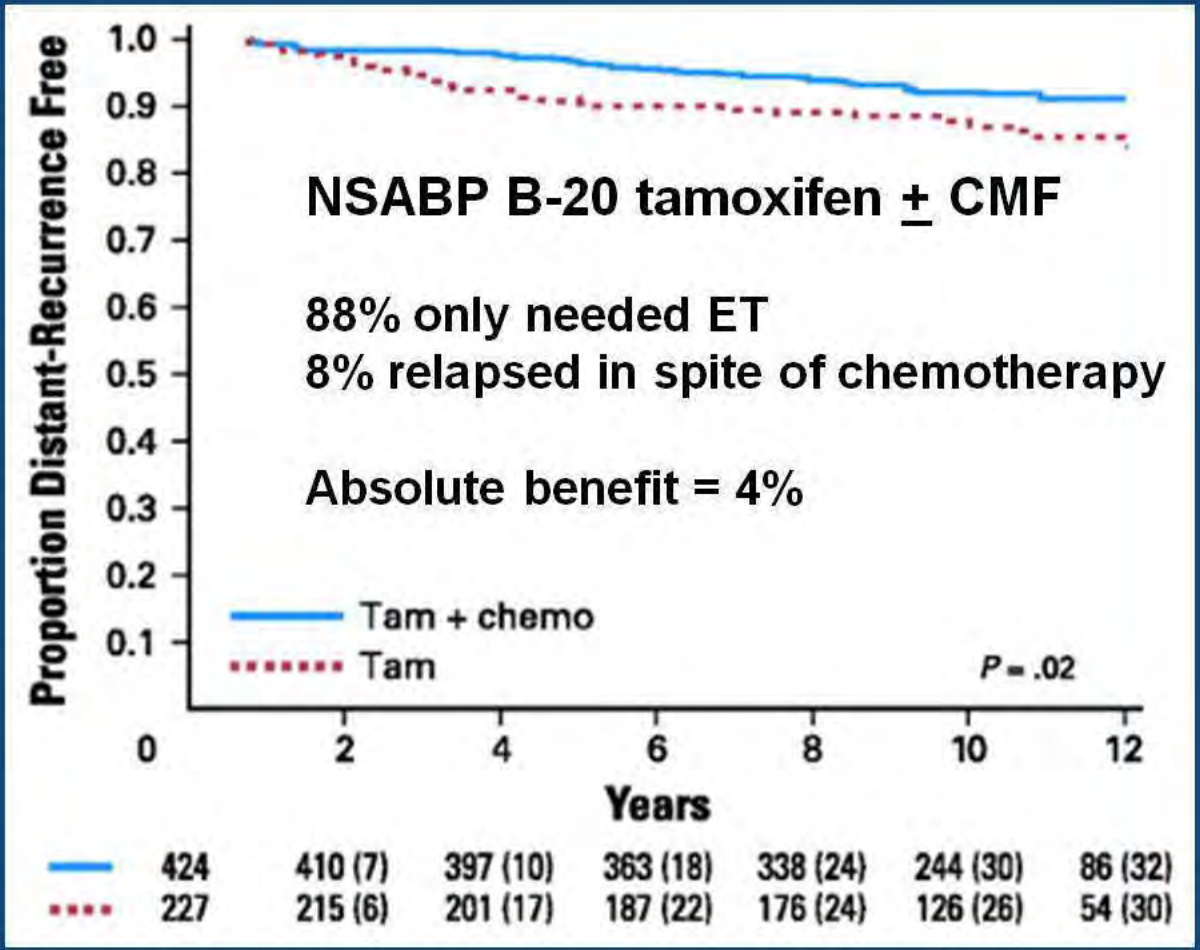
The Problem of Overtreatment



Paik et al. J Clin Oncol 2006

Early 2000s:

Most ER+ node-negative breast cancer patients received chemo

Most did not benefit

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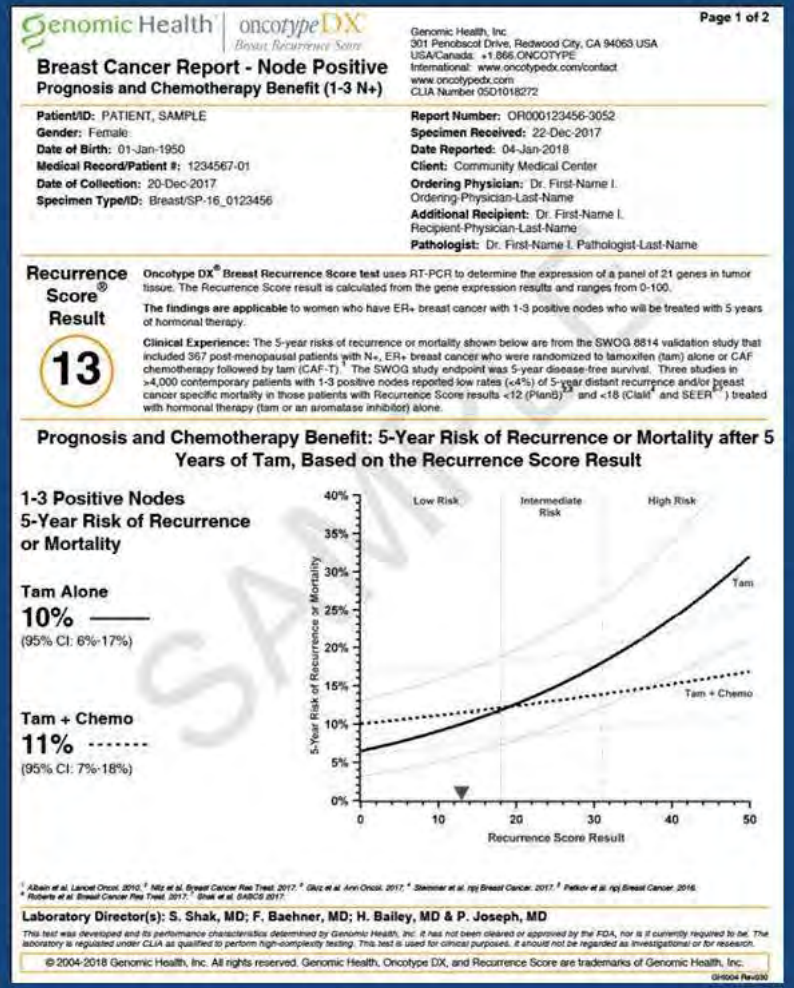
Presented By Lisa Carey at 2018 ASCO Annual Meeting

Oncotype Dx® Recurrence Score

- Available beginning 2006
- Wide adoption in U.S.
- Impact primarily in ↓ chemotherapy use
- Cost ~ $4500 per assay
- Recommended by ASCO, NCCN, Cancer Care Ontario (based on "prospective / retrospective" data)

Prospective trials: TailoRx, RxPonder (node +)



Genomic Health | oncotypeDX Breast Recurrence Score

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www.oncotypedx.com
CLIA Number 05D1018272

Breast Cancer Report - Node Positive
Prognosis and Chemotherapy Benefit (1-3 N+)

Patient/ID: PATIENT, SAMPLE
Gender: Female
Date of Birth: 01-Jan-1950
Medical Record/Patient #: 1234567-01
Date of Collection: 20-Dec-2017
Specimen Type/ID: Breast/SP-16_0123456

Report Number: OR000123456-3052
Specimen Received: 22-Dec-2017
Date Reported: 04-Jan-2018
Client: Community Medical Center
Ordering Physician: Dr. First-Name I. Ordering-Physician-Last-Name
Additional Recipient: Dr. First-Name I. Recipient-Physician-Last-Name
Pathologist: Dr. First-Name I. Pathologist-Last-Name

Recurrence Score® Result
13

Oncotype DX® Breast Recurrence Score test uses RT-PCR to determine the expression of a panel of 21 genes in tumor tissue. The Recurrence Score result is calculated from the gene expression results and ranges from 0-100.

The findings are applicable to women who have ER+ breast cancer with 1-3 positive nodes who will be treated with 5 years of hormonal therapy.

Clinical Experience: The 5-year risks of recurrence or mortality shown below are from the SWOG 8814 validation study that included 367 post-menopausal patients with N+, ER+ breast cancer who were randomized to tamoxifen (tam) alone or CAF chemotherapy followed by tam (CAF-T).[1] The SWOG study endpoint was 5-year disease-free survival. Three studies in >4,000 contemporary patients with 1-3 positive nodes reported low rates (<4%) of 5-year distant recurrence and/or breast cancer specific mortality in those patients with Recurrence Score results <12 (PlanB)[2,3] and <18 (Clalit[4] and SEER[5]) treated with hormonal therapy (tam or an aromatase inhibitor) alone.

Prognosis and Chemotherapy Benefit: 5-Year Risk of Recurrence or Mortality after 5 Years of Tam, Based on the Recurrence Score Result

1-3 Positive Nodes
5-Year Risk of Recurrence or Mortality

Tam Alone
10% ——
(95% CI: 6%-17%)

Tam + Chemo
11% - - - - - -
(95% CI: 7%-18%)

[1] Albain et al. Lancet Oncol. 2010; [2] Mitz et al. Breast Cancer Res Treat. 2017; [3] Gluz et al. Ann Oncol. 2017; [4] Steinmetz et al. npj Breast Cancer. 2017; [5] Petkov et al. npj Breast Cancer. 2016; [6] Roberts et al. Breast Cancer Res Treat. 2017; [7] Shak et al. SABCS 2017.

Laboratory Director(s): S. Shak, MD; F. Baehner, MD; H. Bailey, MD & P. Joseph, MD

This test was developed and its performance characteristics determined by Genomic Health, Inc. It has not been cleared or approved by the FDA, nor is it currently required to be. The laboratory is regulated under CLIA as qualified to perform high-complexity testing. This test is used for clinical purposes. It should not be regarded as investigational or for research.

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GH004 Rev030

Kurian et al, JNCI 2017; Henry et al, JCO 2016

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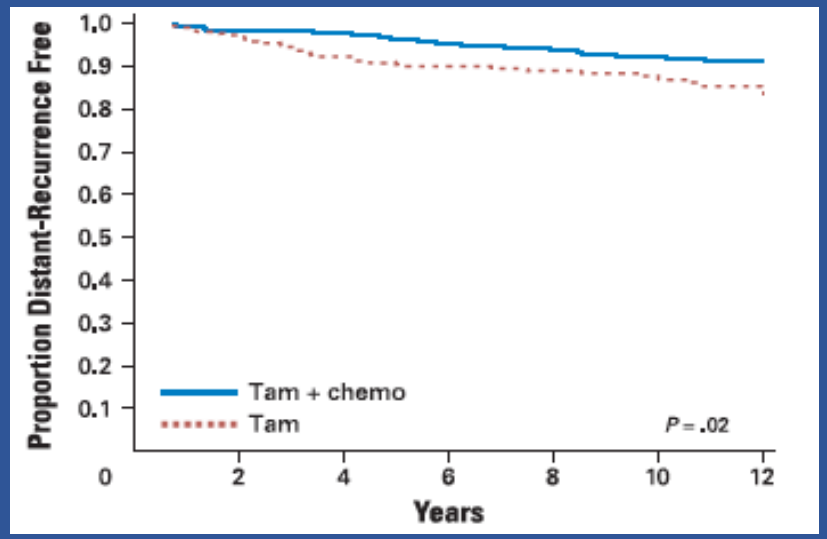
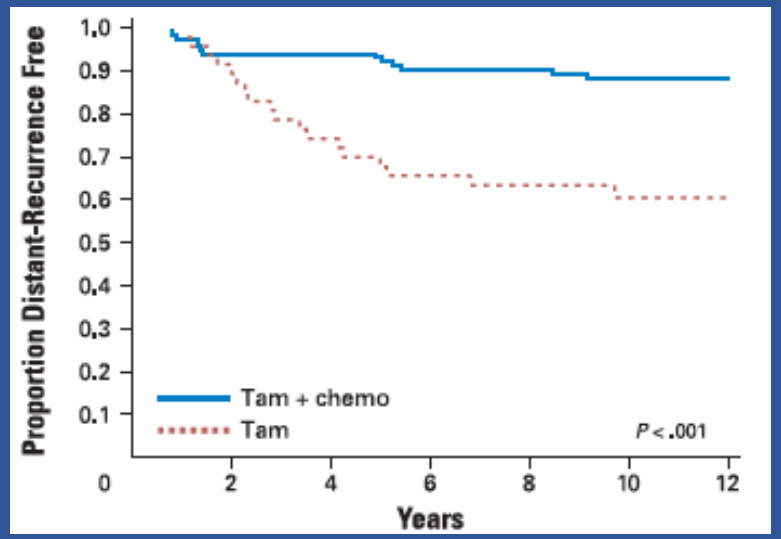
Retrospective data on the benefits of chemotherapy based upon OncotypeDx RS: Unclear in the Intermediate Group

NSABP- B20 Trial: TAM +/- (±C)MF (N=668)



ALL PATIENTS

10 yr DRFS
88% vs. 92%, p=0.02



HIGH RS (>/= 31)

10 year DRFS
61% vs. 88%, p=0.001

Rationale for TAILORx

- Target Population: HR+, HER2-neg, node-neg BCA
  - 50% of all breast cancers in U.S.
  - Adjuvant chemo recommended, but benefit small
  - Most are overtreated
- Assay Selected: 21-Gene Assay (Recurrence Score)
- Two prospective validation studies in ER+, node-neg BCA
  - Prognostic (B14 study - tamoxifen): low recurrence with ET if RS low
  - Predictive (B20 study – tam +/- CMF): large chemo benefit if RS high
- Uncertain chemo benefit for mid-range RS

Paik et al. N Eng J Med 2004;351:2817-26; Paik et al. J Clin Oncol 2006;24:3726-34; Sparano J, Paik S. J Clin Oncol 2008; 26: 721-728

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TAILORx Methods: Treatment Assignment & Randomization

Accrued between April 2006 – October 2010

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

↓

Register (N=10,273)

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

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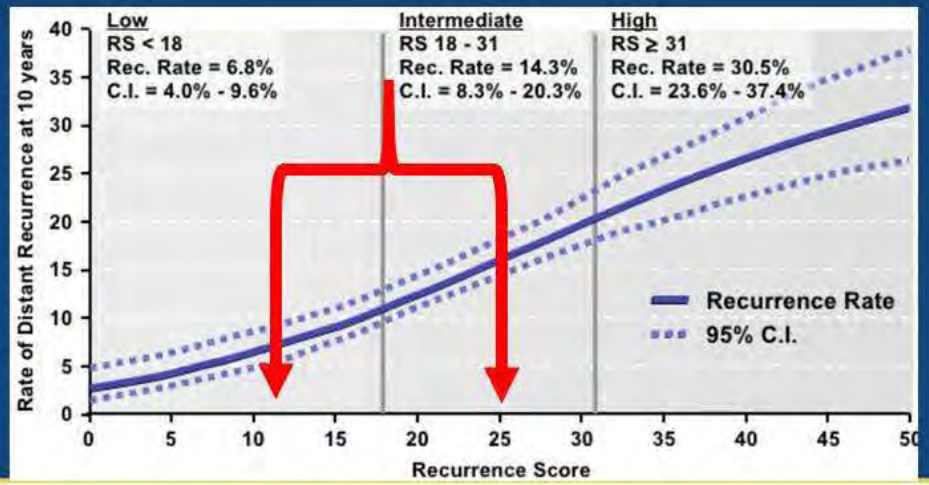
TAILORx Randomized Trial

Mid-Range RS 11-25
(N=6711 evaluable)
RANDOMIZE

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

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

TailoRx randomized population



Non-inferiority, 5-yr IDFS threshold HR 1.32

Sparano J et al, ASCO 2018

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TAILORx Methods: Key Eligibility Criteria

Met NCCN Guidelines for Recommending or Considering Adjuvant Chemotherapy

- Women with invasive breast cancer
- Age 18-75 years
- Node-negative
- ER and/or PR-positive in local lab (before ASCO-CAP guidelines)
- HER2-negative in local lab
- Tumor size - 1.1–5.0 cm (or 0.6-1.0 cm and int-high grade)
- Willing to have chemotherapy treatment assigned or randomized based on RS assay results

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TAILORx Methods: Endpoints

- Primary endpoints:
  - RS 11-25: IDFS
  - RS 0-10: DRFI

	Distant Recurrence	Local-Regional Recurrence	Contralateral Breast Cancer	Other Second Primary Cancer	Death
Invasive disease-free survival (IDFS)	X	X	X	X	X
Distant recurrence-free interval (DRFI)	X				
Relapse-free interval (RFI)	X	X			
Overall survival (OS)					X

Hudis et al. J Clin Oncol 2007; 25(15):2127-32

TAILORx Methods: Statistical Analysis Plan for RS 11-25

- Non-inferiority design for randomized arms
- Intention-to-treat for primary analysis, as-treated analysis also planned
- Hazard ratio margin 1.322 for IDFS (5 year IDFS rate 90% vs. 87%)
  - Null hypothesis of no difference, type I error rate 10% (1-sided), type II 5%
  - *P* values shown are stratified log-rank test, and hazard ratios shown are from stratified proportional hazards models
  - Sample size adjusted for non-adherence rate (12%) - Lachin-Foulkes correction
  - Full information - 835 IDFS events
- Exploratory interaction tests for subgroups that may derive chemo benefit (ITT)

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TAILORx Results - ITT Population: Demographics & Treatment in RS 11-25 Arms (N=6,711)

- **Patient characteristics**
  - Median age 55 years, and 33% were 50 or younger
  - 63% had tumor size 1-2 cm and 57% had intermediate grade histology (57%)
  - Clinical risk criteria: 74% low risk, 26% high risk
- **Systemic Treatment**
  - Endocrine therapy
    - Comparable adherence and duration in both arms
    - Postmenopausal – included AI in 90%
    - Premenopausal – included OS in 15%
  - Chemotherapy
    - Most common regimens were TC (56%) and anthracycline-containing (36%)

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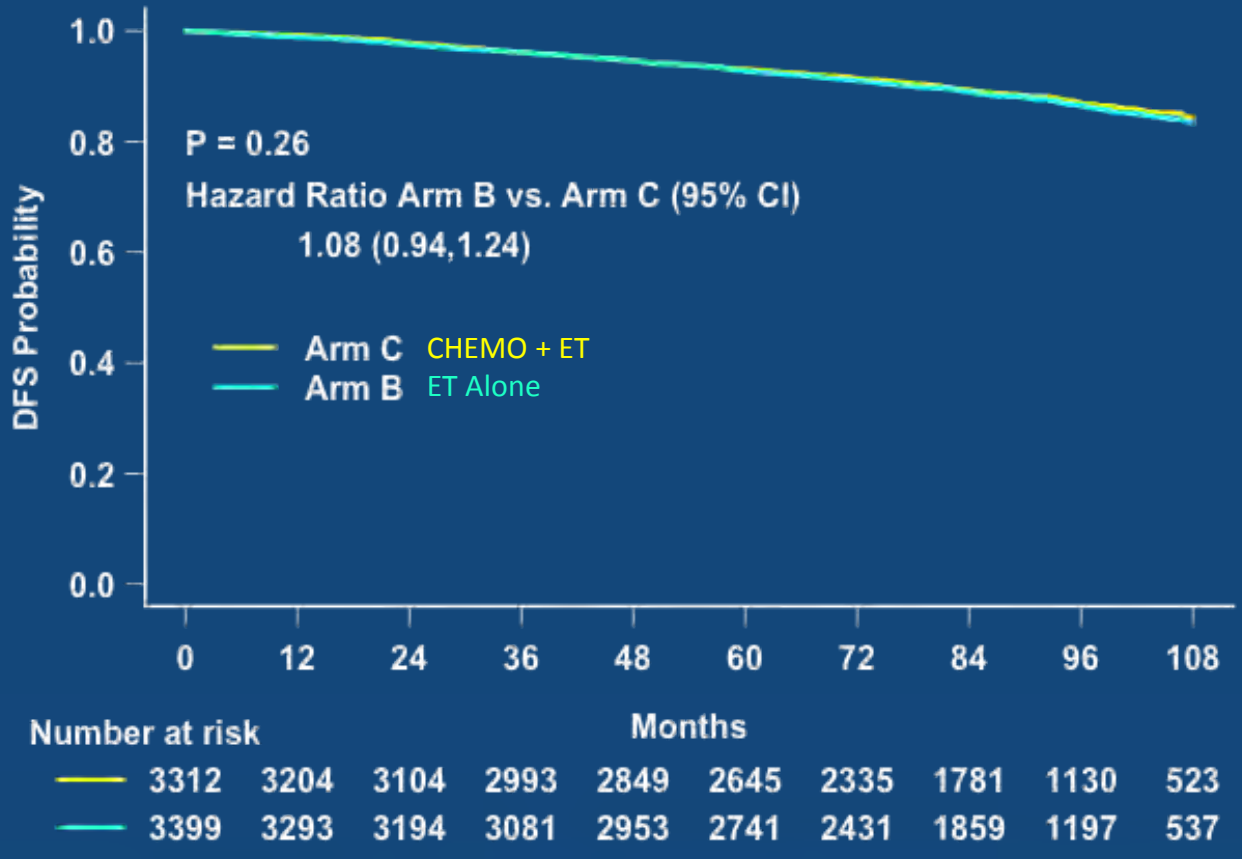
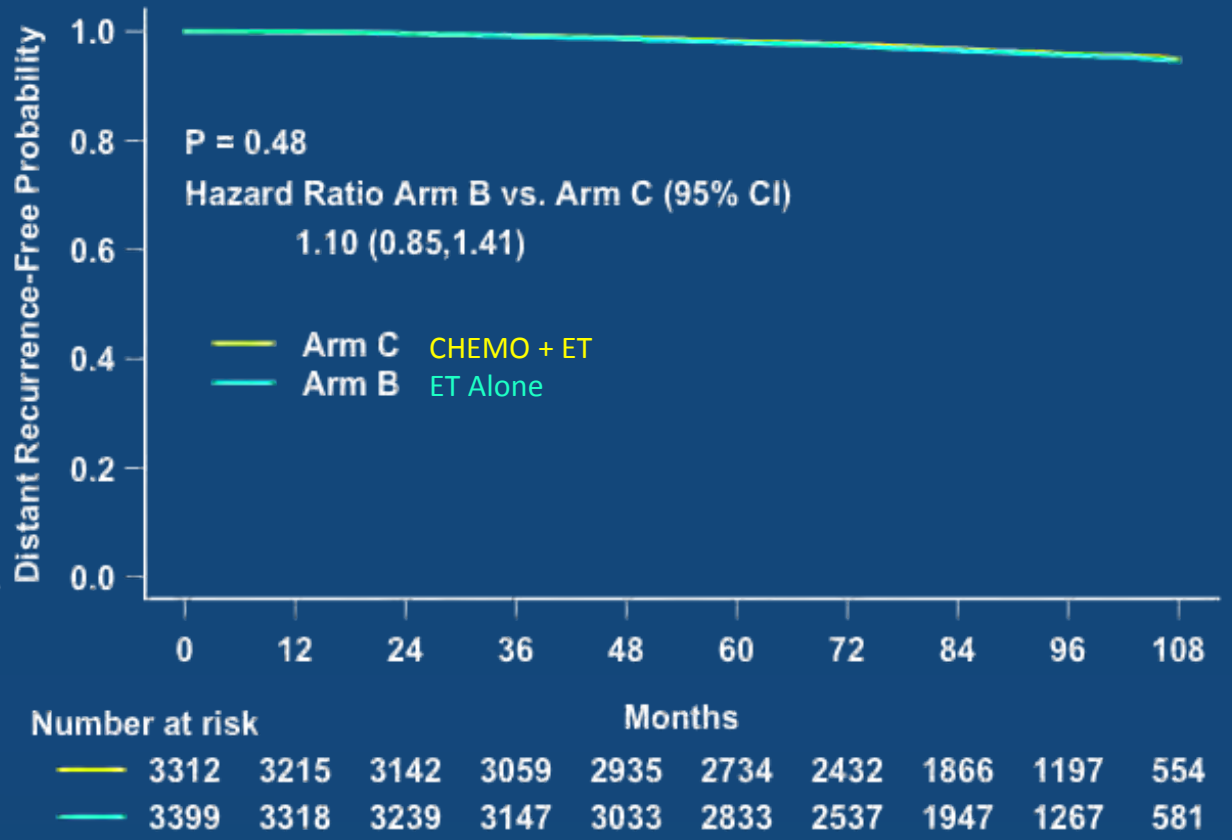
TAILORx Results - ITT Population: RS 11-25 (Arms B & C)

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

Primary Endpoint
Invasive Disease-Free Survival



Secondary Endpoint
Distant Relapse-Free Interval



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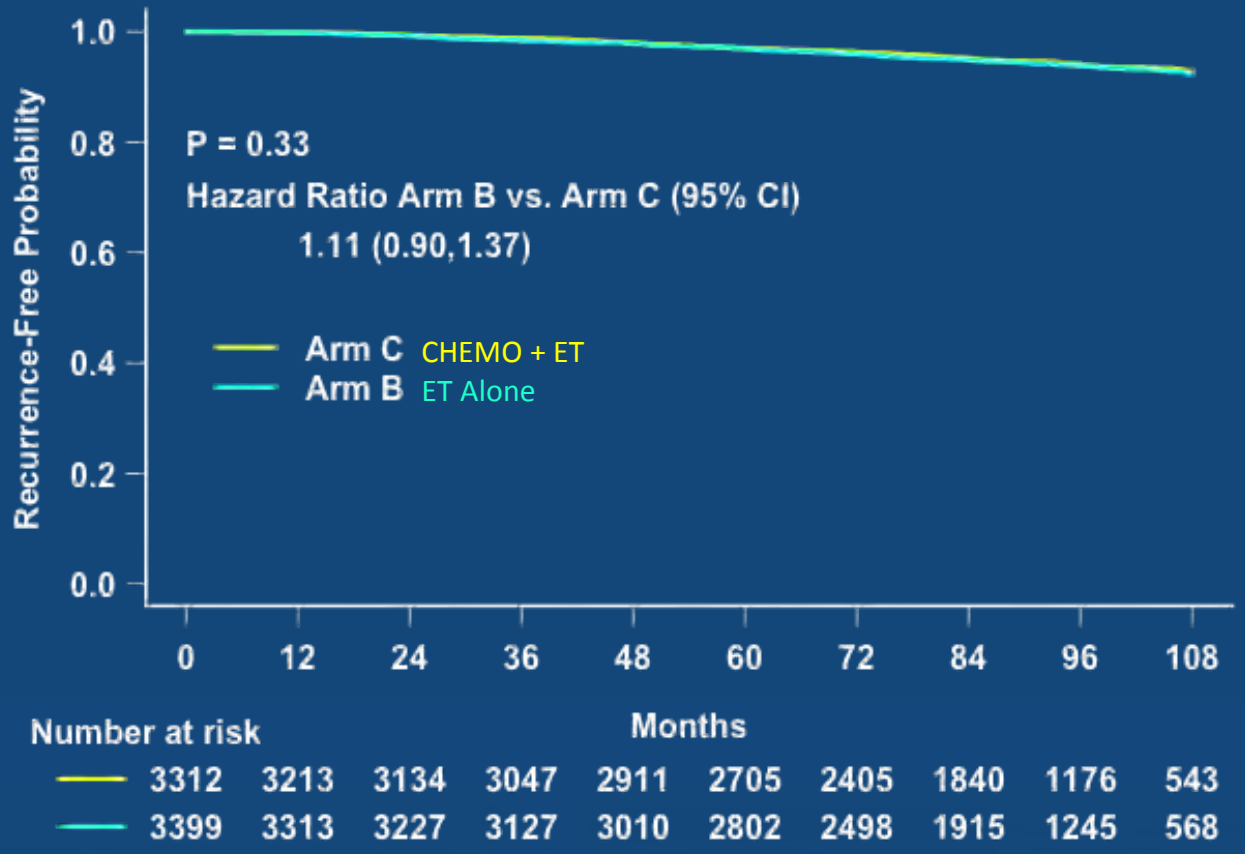
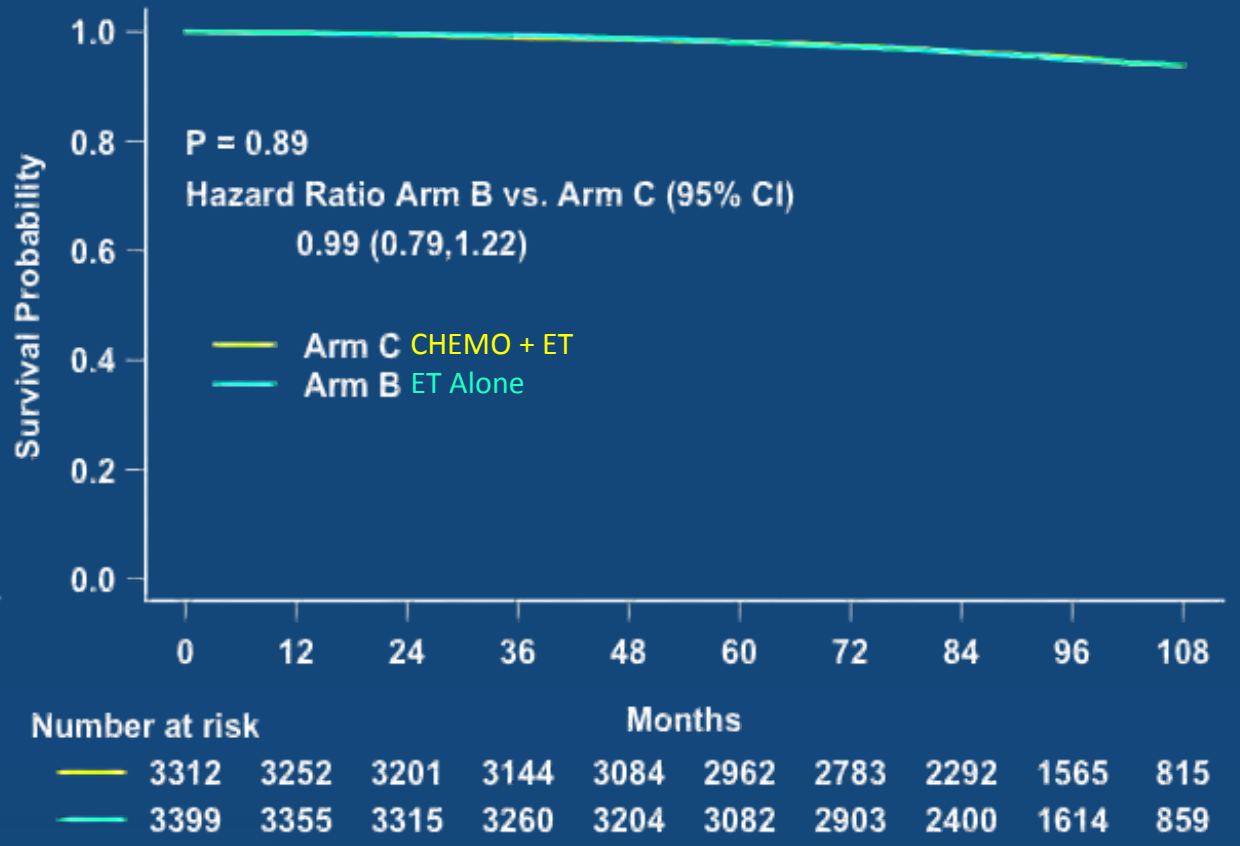
TAILORx Results – ITT Population: RS 11-25 (Arms B & C)

Other Secondary Endpoints

Relapse-Free Interval



Overall Survival



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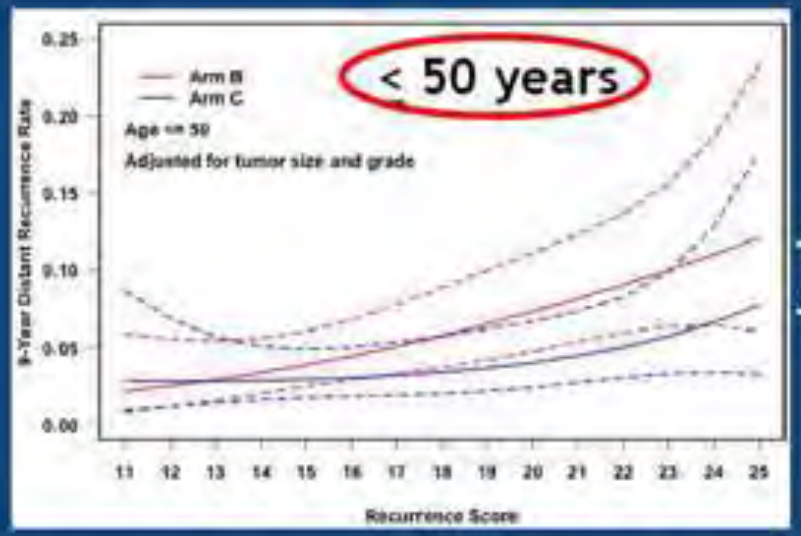
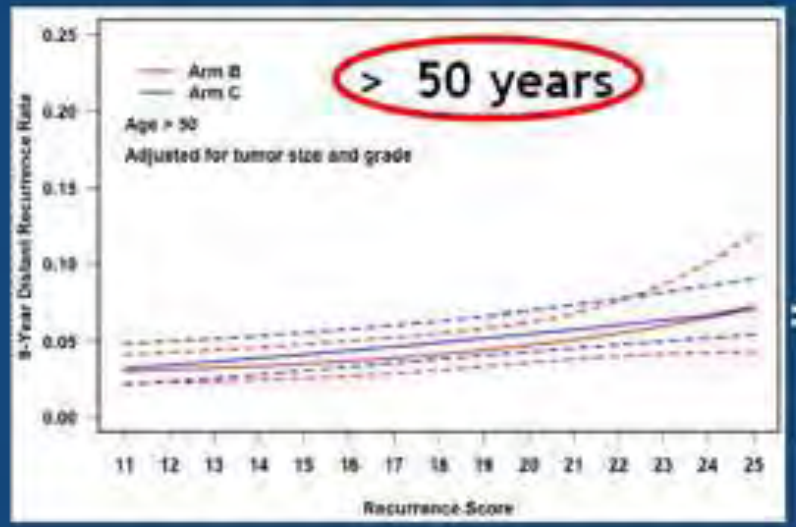
Interesting Exploratory Analyses Randomized Arms

Interaction with age



iDFS Δ with chemo ~ 6%



iDFS Δ with chemo ~ ≤1%

DFS Hazard Ratios for Subsets
Arm B vs. Arm C

Group	Ratio	95% Conf Int
Premeno	1.36	(1.06, 1.75)
Postmeno	0.99	(0.84, 1.17)

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TAILORx Results: Summary

- Primary conclusions
  - RS 11-25: ET was non-inferior to chemotherapy + ET (primary endpoint - ITT)
  - RS 0-10: Distant recurrence rates very low (2-3%) with ET alone at 9 years
  - RS 26-100: Significantly higher event rates, driven by more recurrences despite adjuvant chemo plus ET
- Other observations
  - Age – RS – Chemo treatment interaction:
    - Some chemo benefit in women 50 or younger with a RS 15-25
    - Greatest impact on distant recurrence with RS 21-25

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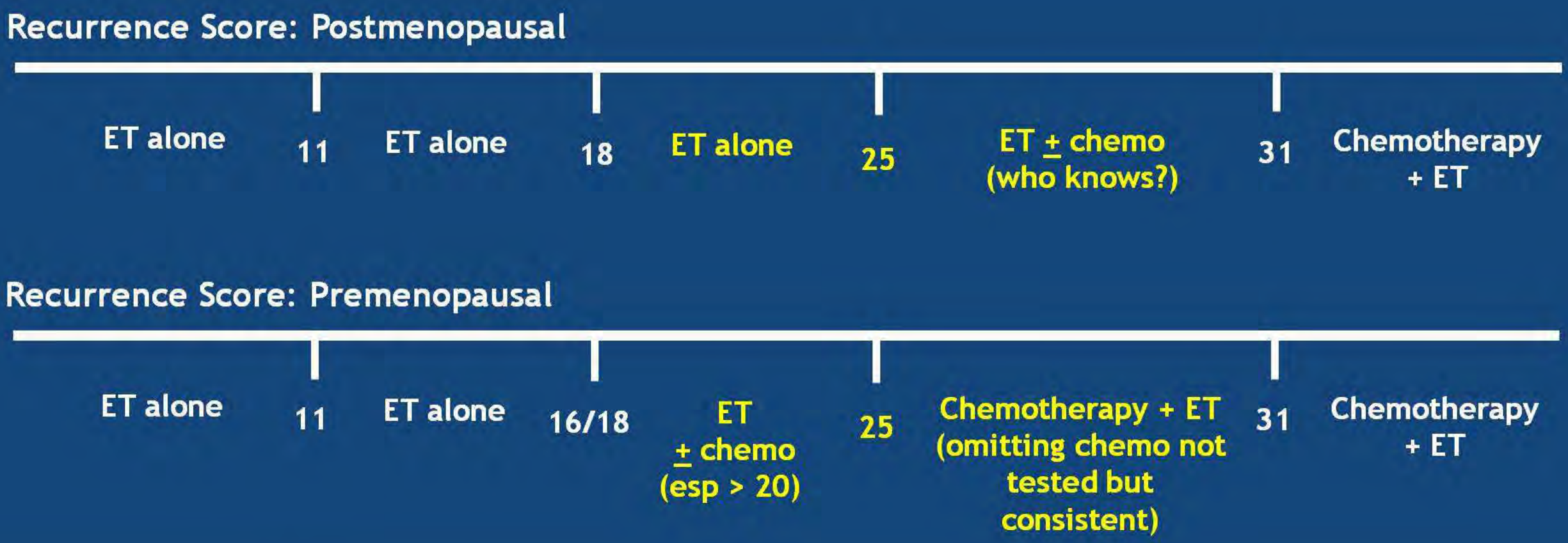
How Does This Affect Practice Tomorrow? (for node-negative patients appropriate for chemo)



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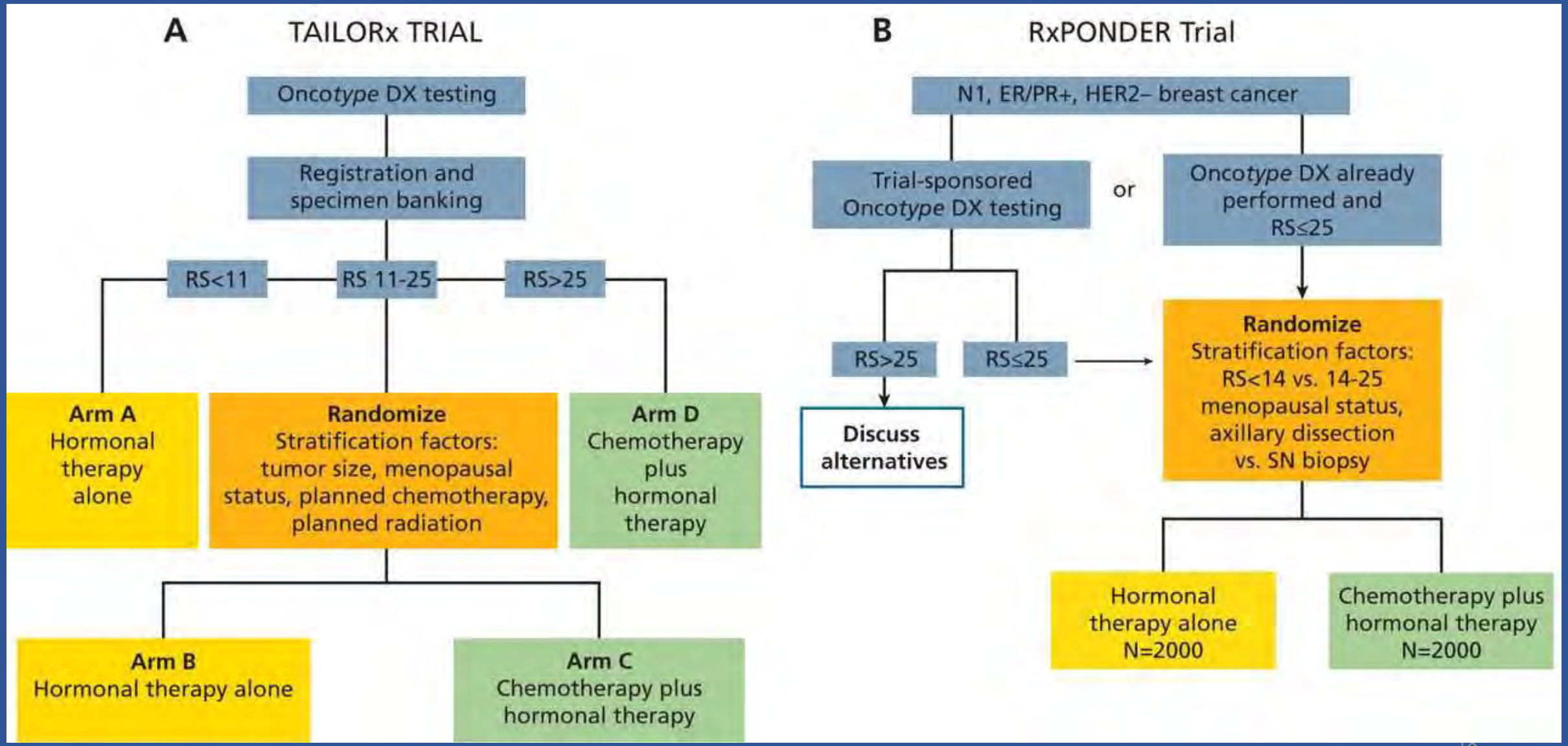
RxPONDER Trial will address patients with positive lymph nodes



Thank you!