Tailoring Treatment in HR Positive, Her2 Negative Early Breast Cancer

Shiva Moghadam
Radiation Oncologist
Motamed Cancer Institute

An overview of Two Landmark Trials:

- TAILORx
- RxPONDER

TAILORx trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer

J.A. Sparano, R.J. Gray, D.F. Makower, K.I. Pritchard, K.S. Albain, D.F. Hayes, C.E. Geyer, Jr., E.C. Dees, M.P. Goetz, J.A. Olson, Jr., T. Lively, S.S. Badve, T.J. Saphner, L.I. Wagner, T.J. Whelan, M.J. Ellis, S. Paik, W.C. Wood, P.M. Ravdin, M.M. Keane, H.L. Gomez Moreno, P.S. Reddy, T.F. Goggins, I.A. Mayer, A.M. Brufsky, D.L. Toppmeyer, V.G. Kaklamani, J.L. Berenberg, J. Abrams, and G.W. Sledge, Jr.

Introduction

- Breast cancer is the most common cancer in women in the United States and worldwide.
- Hormone-receptor–positive, axillary node–negative disease accounts for approximately half of all cases of breast cancer in the United States.
- Adjuvant chemotherapy reduces the risk of recurrence, with effects that are proportionally greater in younger women but that are little affected by nodal status, grade, or the use of adjuvant endocrine therapy.

These findings led a National Institutes of Health consensus panel to recommend adjuvant chemotherapy for most patients, a practice that has contributed to declining breast cancer mortality. However, the majority of patients may receive chemotherapy unnecessarily.

*The 21-gene recurrence-score assay (Oncotype DX, Genomic Health) is one of several commercially available gene-expression assays that provide prognostic information in hormone-receptor–positive breast cancer.

*The recurrence score based on the 21-gene assay ranges from 0 to 100 and is predictive of chemotherapy benefit when it is high, whether a high score is defined as 31 or higher or 26 or higher; when the recurrence score is low (0 to 10), it is prognostic for a very low rate of distant recurrence (2%) at 10 years that is not likely to be affected by adjuvant chemotherapy.

Although expert panels recommend the use of the 21-gene assay, uncertainty remains as to whether chemotherapy is beneficial for the majority of patients, who have a mid-range recurrence score.

The Trial Assigning Individualized Options for Treatment (TAILORx) was designed to address these gaps in our knowledge by determining whether chemotherapy is beneficial for women with a mid-range recurrence score of 11 to 25.

TAILORx: Design

- Female 18-75
- ER and / or PR +ve
- HER2-ve
- 1.1 – 5.0 cm and any grade
- 0.6-1.0 cm and grade 2/3
- Node-negative

ONCOTYPE DX

- Unblinded, RS result known to participants

TAILORx: Design

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- Node-negative

ONCOTYPE DX

RS >25 → CT+ET

RS 0-10 → ET

TAILORx: Design

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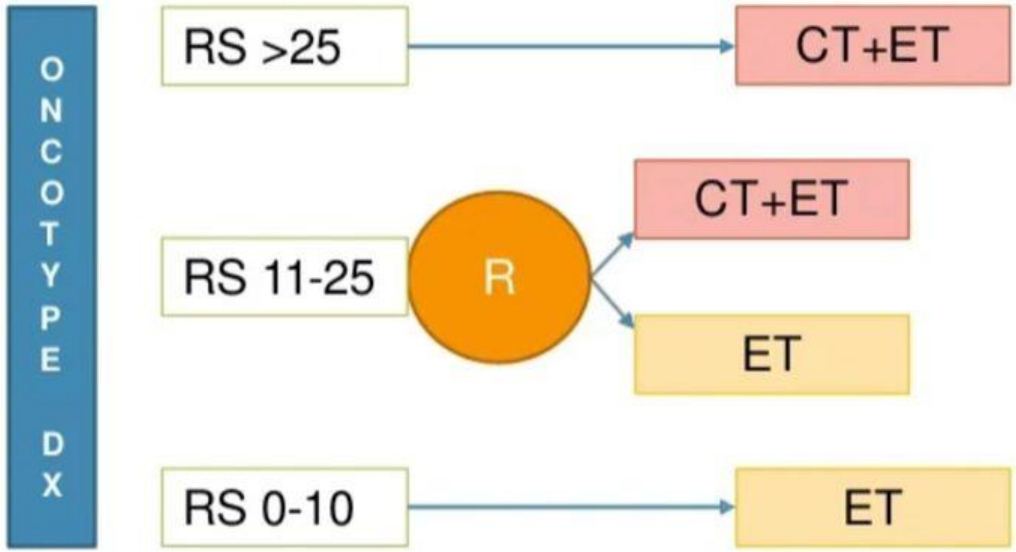


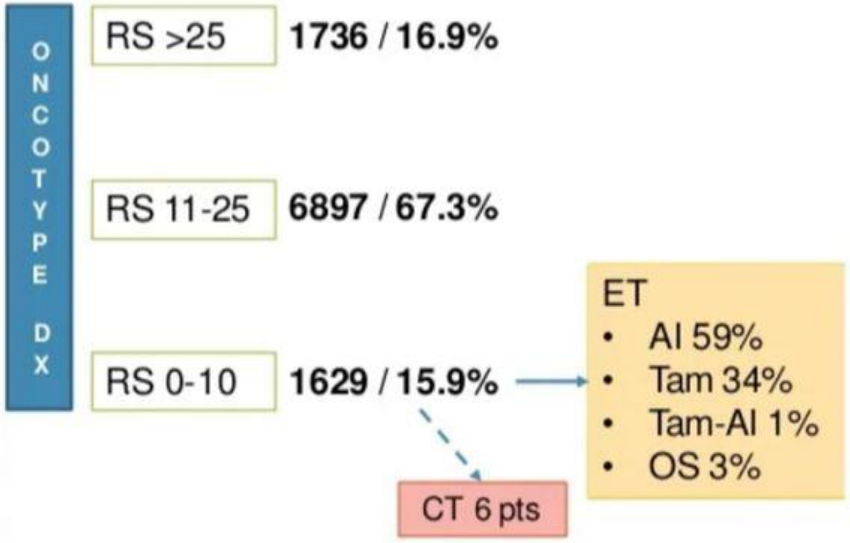
- primary endpoint – IDFS
- sample size based on non-inferiority of ET versus CT+ET in the 11-25 RS population

Table 1. Characteristics of the Patients in the Intention-to-Treat Population at Baseline.*

Characteristic	Recurrence Score of ≤10	Recurrence Score of 11–25		Recurrence Score of ≥26
	Endocrine Therapy (N=1619)	Endocrine Therapy (N=3399)	Chemoendocrine Therapy (N=3312)	Chemoendocrine Therapy (N=1389)
Median age (range) — yr	58 (25–75)	55 (23–75)	55 (25–75)	56 (23–75)
Age ≤50 yr — no. (%)	429 (26)	1139 (34)	1077 (33)	409 (29)
Menopausal status — no. (%)†				
Premenopausal	478 (30)	1212 (36)	1203 (36)	407 (29)
Postmenopausal	1141 (70)	2187 (64)	2109 (64)	982 (71)
Tumor size in the largest dimension — cm‡				
Median (IQR)	1.5 (1.2–2.0)	1.5 (1.2–2.0)	1.5 (1.2–2.0)	1.7 (1.3–2.3)
Mean	1.74±0.76	1.71±0.81	1.71±0.77	1.88±0.99
Histologic grade of tumor — no./total no. (%)				
Low	530/1572 (34)	959/3282 (29)	934/3216 (29)	89/1363 (7)
Intermediate	931/1572 (59)	1884/3282 (57)	1837/3216 (57)	590/1363 (43)
High	111/1572 (7)	439/3282 (13)	445/3216 (14)	681/1363 (50)
Estrogen-receptor expression — no. (%)				
Negative	5 (<1)	6 (<1)	3 (<1)	40 (3)
Positive	1614 (>99)	3393 (>99)	3309 (>99)	1349 (97)
Progesterone-receptor expression — no./total no. (%)				
Negative	28/1583 (2)	267/3339 (8)	251/3240 (8)	405/1353 (30)
Positive	1555/1583 (98)	3072/3339 (92)	2989/3240 (92)	948/1353 (70)
Clinical risk — no./total no. (%)§				
Low	1227/1572 (78)	2440/3282 (74)	2359/3214 (73)	589/1359 (43)
High	345/1572 (22)	842/3282 (26)	855/3214 (27)	770/1359 (57)
Primary surgery — no. (%)				
Mastectomy	516 (32)	935 (28)	917 (28)	368 (26)
Breast conservation	1103 (68)	2464 (72)	2395 (72)	1021 (74)
Adjuvant chemotherapy — no. (%)				
Yes	8 (0.5)	185 (5.4)	2704 (81.6)	1300 (93.6)
No	1611 (99.5)	3214 (94.6)	608 (18.4)	89 (6.4)

TAILORx: Demographics

- from April 2006 – Oct 2010 10 273 eligible pts recruited at 1,000 sites (USA, Australia, Canada, Ireland, New Zealand, Peru)



Sparano et al. N Engl J Med 2015;373:2005-2014

Table 2. Estimated Survival Rates According to Recurrence Score and Assigned Treatment in the Intention-to-Treat Population.*

End Point and Treatment Group	Rate at 5 Yr	Rate at 9 Yr
	percent	
Invasive disease–free survival†		
Score of ≤10, endocrine therapy	94.0±0.6	84.0±1.3
Score of 11–25, endocrine therapy	92.8±0.5	83.3±0.9
Score of 11–25, chemoendocrine therapy	93.1±0.5	84.3±0.8
Score of ≥26, chemoendocrine therapy	87.6±1.0	75.7±2.2
Freedom from recurrence of breast cancer at a distant site		
Score of ≤10, endocrine therapy	99.3±0.2	96.8±0.7
Score of 11–25, endocrine therapy	98.0±0.3	94.5±0.5
Score of 11–25, chemoendocrine therapy	98.2±0.2	95.0±0.5
Score of ≥26, chemoendocrine therapy	93.0±0.8	86.8±1.7

End Point and Treatment Group	Rate at 5 Yr	Rate at 9 Yr
	percent	
Freedom from recurrence of breast cancer at a distant or local–regional site		
Score of ≤10, endocrine therapy	98.8±0.3	95.0±0.8
Score of 11–25, endocrine therapy	96.9±0.3	92.2±0.6
Score of 11–25, chemoendocrine therapy	97.0±0.3	92.9±0.6
Score of ≥26, chemoendocrine therapy	91.0±0.8	84.8±1.7
Overall survival		
Score of ≤10, endocrine therapy	98.0±0.4	93.7±0.8
Score of 11–25, endocrine therapy	98.0±0.2	93.9±0.5
Score of 11–25, chemoendocrine therapy	98.1±0.2	93.8±0.5
Score of ≥26, chemoendocrine therapy	95.9±0.6	89.3±1.4

Table 3. Estimated Survival Rates According to Recurrence Score and Assigned Treatment among Women 50 Years of Age or Younger in the Intention-to-Treat Population.*

End Point and Treatment Group	Rate at 5 Yr	Rate at 9 Yr
	percent	
Invasive disease–free survival†		
Score of ≤10, endocrine therapy	95.1±1.1	87.4±2.0
Score of 11–15, endocrine therapy	95.1±1.1	85.7±2.2
Score of 11–15, chemoendocrine therapy	94.3±1.3	89.2±1.9
Score of 16–20, endocrine therapy	92.0±1.3	80.6±2.5
Score of 16–20, chemoendocrine therapy	94.7±1.1	89.6±1.7
Score of 21–25, endocrine therapy	86.3±2.3	79.2±3.3
Score of 21–25, chemoendocrine therapy	92.1±1.8	85.5±3.0
Score of ≥26, chemoendocrine therapy	86.4±1.9	80.3±2.9
Freedom from recurrence of breast cancer at a distant site		
Score of ≤10, endocrine therapy	99.7±0.3	98.5±0.8
Score of 11–15, endocrine therapy	98.8±0.6	97.2±1.0
Score of 11–15, chemoendocrine therapy	98.5±0.7	98.0±0.8
Score of 16–20, endocrine therapy	98.1±0.7	93.6±1.4
Score of 16–20, chemoendocrine therapy	98.9±0.5	95.2±1.3
Score of 21–25, endocrine therapy	93.2±1.7	86.9±2.9
Score of 21–25, chemoendocrine therapy	96.4±1.2	93.4±2.3
Score of ≥26, chemoendocrine therapy	91.1±1.6	88.7±2.1

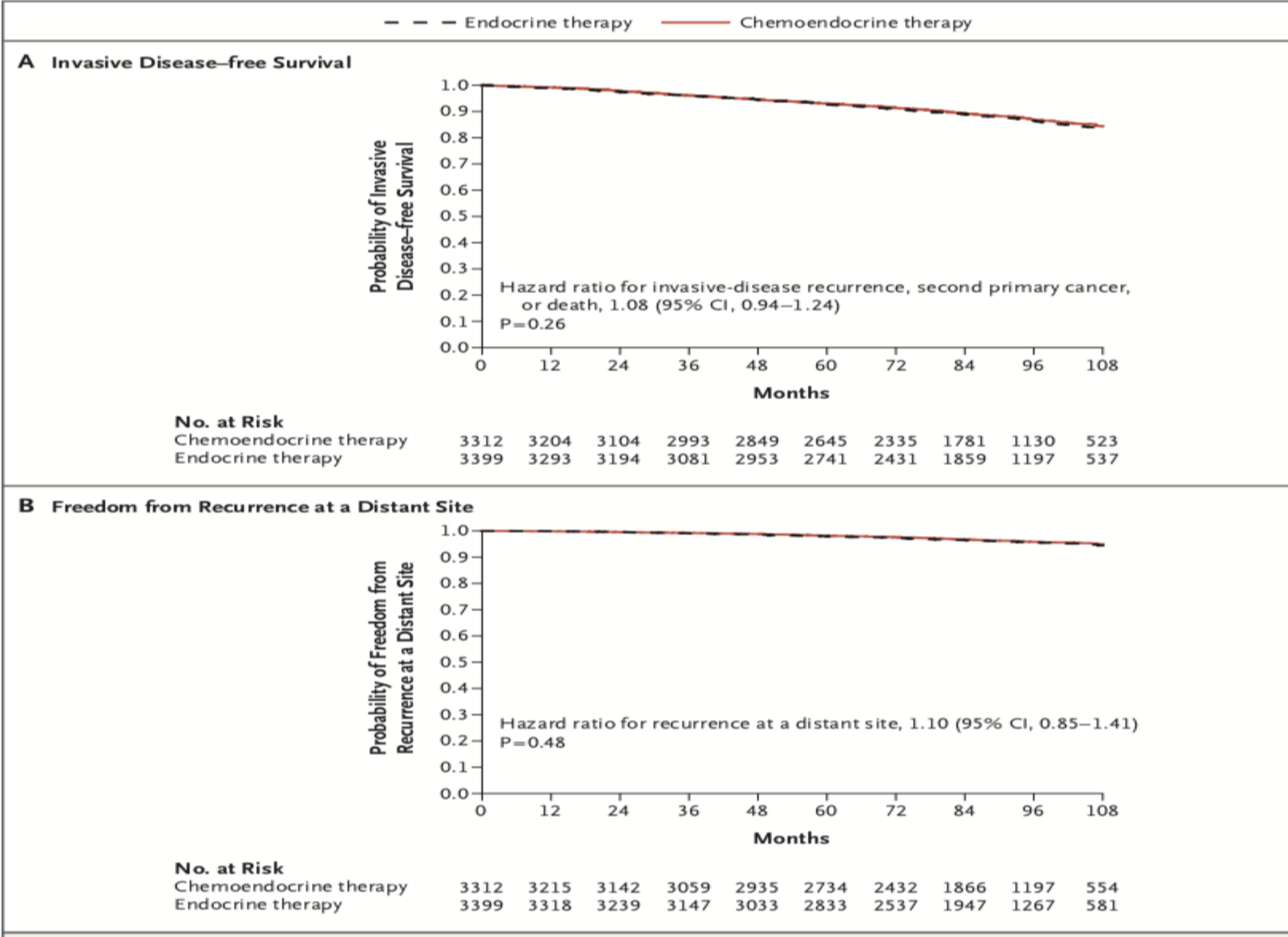


Figure 2. Clinical Outcomes among Patients with a Recurrence Score of 11 to 25.

SO

What Does TAILORx tell us?

In this trial, among 6711 women with hormone-receptor–positive, HER2-negative, axillary node–negative breast cancer and a midrange recurrence score of 11 to 25 on the 21-gene assay, endocrine therapy was not inferior to chemoendocrine therapy, which provides evidence that adjuvant chemotherapy was not beneficial in these patients.

- *The 9-year rate of distant recurrence in women with a recurrence score of 11 to 25 in our trial was approximately 5%, irrespective of chemotherapy use,*
- *Updated results for patients with a low recurrence score of 10 or less, who were previously reported as having a 1% distant recurrence rate at 5 years in our trial,now indicate a 9-year rate of distant recurrence of approximately 3%.*

Although the rate of nonadherence to the assigned treatment was 12% overall, the sample size was adjusted to compensate for this, and the as-treated analysis produced results similar to those of the intention-to-treat analysis.

- A total of 40% of women who were 50 years of age or younger had a recurrence score of 15 or lower, which was associated with a low rate of recurrence with endocrine therapy alone.

- Exploratory analyses indicated that chemotherapy was associated with some benefit for women 50 years of age or younger who had a recurrence score of 16 to 25 (a range of scores that was found in 46% of women in this age group).

A greater treatment effect from adjuvant chemotherapy has been noted in younger women, which may be at least partly explained by an antiestrogenic effect associated with premature menopause induced by chemotherapy

The results of this trial suggest that the 21-gene assay may identify up to 85% of women with early breast cancer who can be spared adjuvant chemotherapy

Especially

- those who are older than 50 years of age and have a recurrence score of 25 or lower

- as well as women 50 years of age or younger with a recur- rence score of 15 or lower

RxPONDER trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

21-Gene Assay to Inform Chemotherapy Benefit in Node-Positive Breast Cancer

K. Kalinsky, W.E. Barlow, J.R. Gralow, F. Meric-Bernstam, K.S. Albain, D.F. Hayes, N.U. Lin, E.A. Perez, L.J. Goldstein, S.K.L. Chia, S. Dhesy-Thind, P. Rastogi, E. Alba, S. Delaloge, M. Martin, C.M. Kelly, M. Ruiz-Borrego, M. Gil-Gil, C.H. Arce-Salinas, E.G.C. Brain, E.-S. Lee, J.-Y. Pierga, B. Bermejo, M. Ramos-Vazquez, K.-H. Jung, J.-M. Ferrero, A.F. Schott, S. Shak, P. Sharma, D.L. Lew, J. Miao, D. Tripathy, L. Pusztai, and G.N. Hortobagyi

ABSTRACT

BACKGROUND

RxPONDER: Adjuvant ET ± Chemotherapy in HR+/HER2- EBC With 1-3 Positive Lymph Nodes and RS ≤ 25

- Randomized phase III trial

Stratified by RS score (0-13 vs 14-25), menopausal status (pre vs post), axillary surgery (ALND vs SLNB)

Adults with HR+/HER2- EBC and 1-3 positive LN without distant mets*; able to receive adjuvant taxane and/or anthracycline-based CT†; axillary staging by SLNB or ALND; RS 0-25‡ (N = 5015)

Chemotherapy followed by ET (n = 2509)

ET alone (n = 2506)

Baseline characteristics generally well balanced between treatment arms

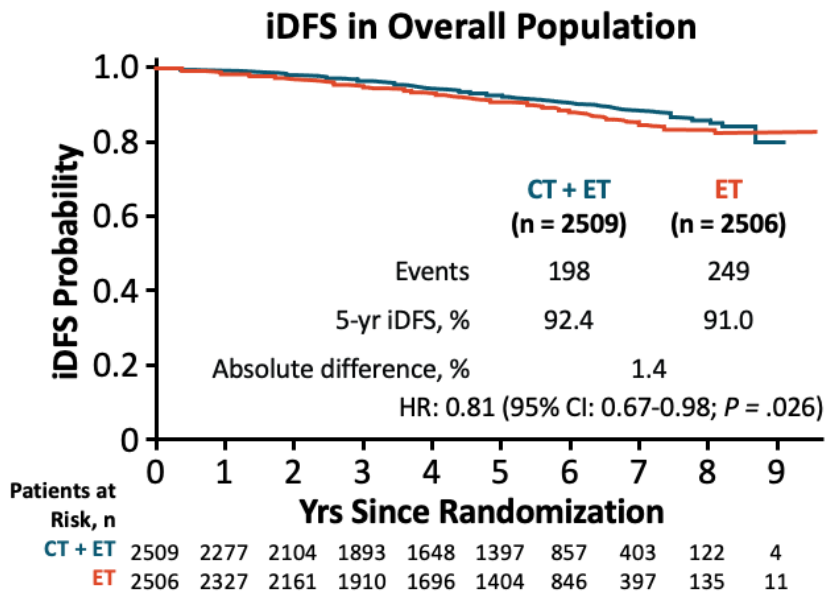
*Protocol amended to exclude patients with pN1mic as only nodal disease after 2493 patients randomized. †Approved CT regimens: TC, FAC (or FEC), AC/T (or EC/T), FAC/T (or FEC/T); AC alone or CMF not allowed. ‡Patients with RS > 25 recommended to be treated with CT followed ET off study.

- Primary endpoint: iDFS
- Key secondary endpoints: OS, distant DFS, local DFI, toxicity, QoL

- Objective to demonstrate chemotherapy benefit (if any) greater at higher vs lower RS
  - No planned non-inferiority analysis

RxPONDER: iDFS (Primary Endpoint)

- In this population with RS 0-25, RS did not predict relative CT benefit for iDFS
  - HR: 1.02 (95% CI: 0.98-1.06; *P* = .30)
- CT use and RS independently prognostic for iDFS
  - iDFS events **less likely** among patients who received CT
    - HR: 0.81 (95% CI: 0.67-0.96; *P* = .026)



RxPONDER: Prespecified Analysis by Menopausal Status

- Menopausal status influences chemotherapy benefit for iDFS

Baseline Characteristics by Menopausal Status

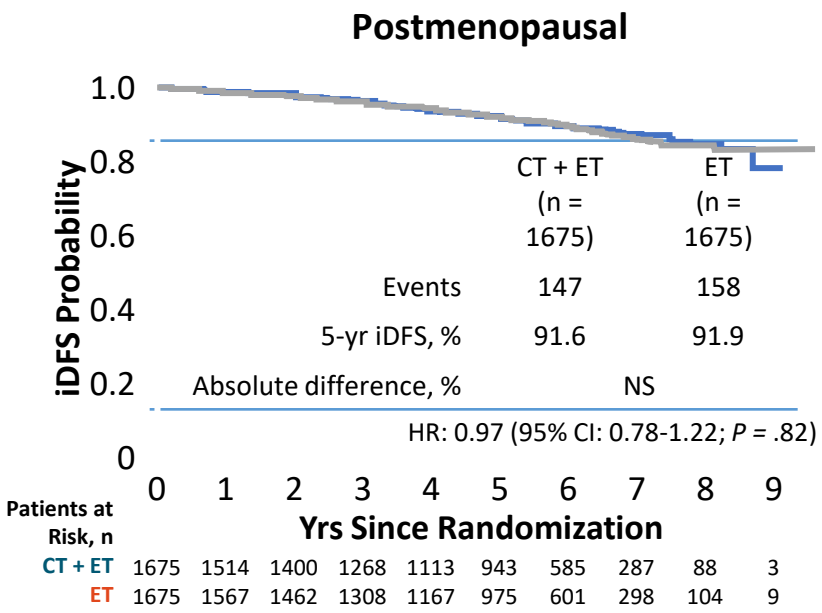
Characteristic, %	Postmenopausal (n = 3350)	Premenopausal (n = 1665)
Age group		
▪ **< 40 yrs**	0.2	8.5
▪ **40-49 yrs**	1.9	60.8
▪ **50-59 yrs**	34.9	30.5
▪ **60-69 yrs**	45.7	0.2
▪ **70+ yrs**	17.3	0
Recurrence score		
▪ **RS 0-13**	44.8	38.7
▪ **RS 14-25**	55.2	61.3
Nodal dissection		
▪ **Full ALND**	60.7	66.4
▪ **Sentinel LN only**	39.3	33.6

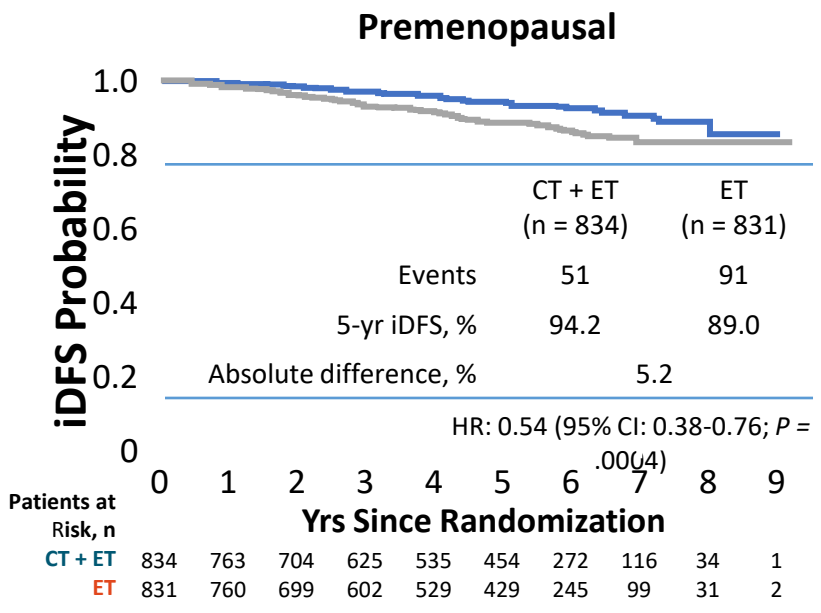
Characteristic, %	Postmenopausal (n = 3350)	Premenopausal (n = 1665)
Positive nodes		
▪ **1**	65.6	65.3
▪ **2**	25.1	25.7
▪ **3**	9.3	9.0
Grade		
▪ **Low**	26.0	22.0
▪ **Intermediate**	63.5	68.3
▪ **High**	10.6	9.7
Tumor size		
▪ **T1**	59.1	56.2
▪ **T2/T3**	41.9	43.9

✓ Among postmenopausal women, iDFS at 5 years was 91.9% in the endocrine-only group and 91.3% in the chemoendocrine group, with no chemotherapy benefit (hazard ratio for invasive disease recurrence, new primary cancer [breast cancer or another type], or death, 1.02; 95% confidence interval [CI], 0.82 to 1.26; P = 0.89).

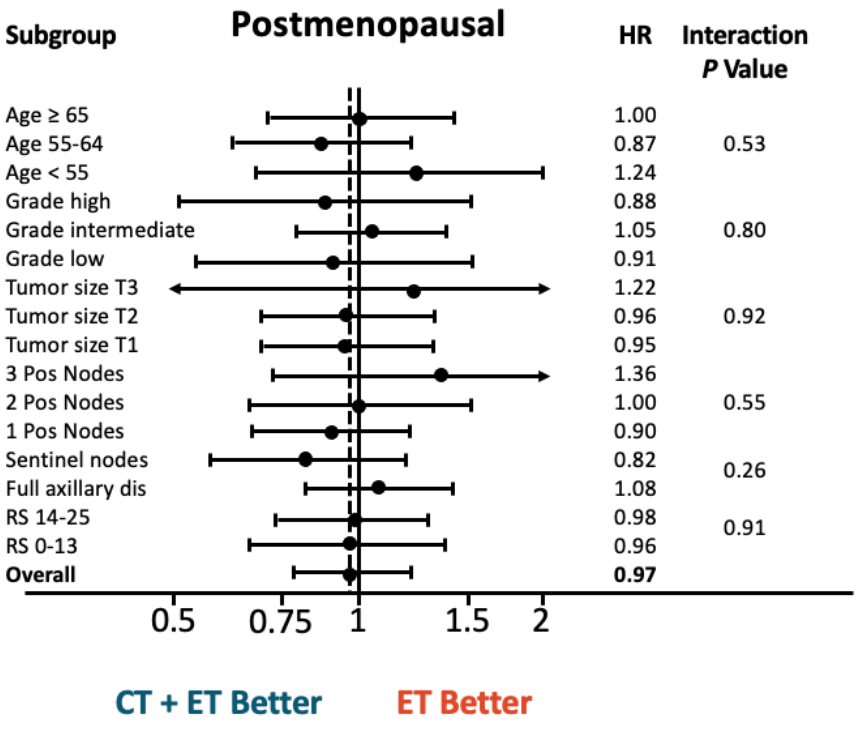
✓ Among premenopausal women, iDFS at 5 years was 89.0% with endocrine-only therapy and 93.9% with chemoendocrine therapy (hazard ratio, 0.60; 95% CI, 0.43 to 0.83; P = 0.002), with a similar increase in distant relapse–free survival (hazard ratio, 0.58; 95% CI, 0.39 to 0.87; P = 0.009). The relative chemotherapy benefit did not increase as the recurrence score increased.

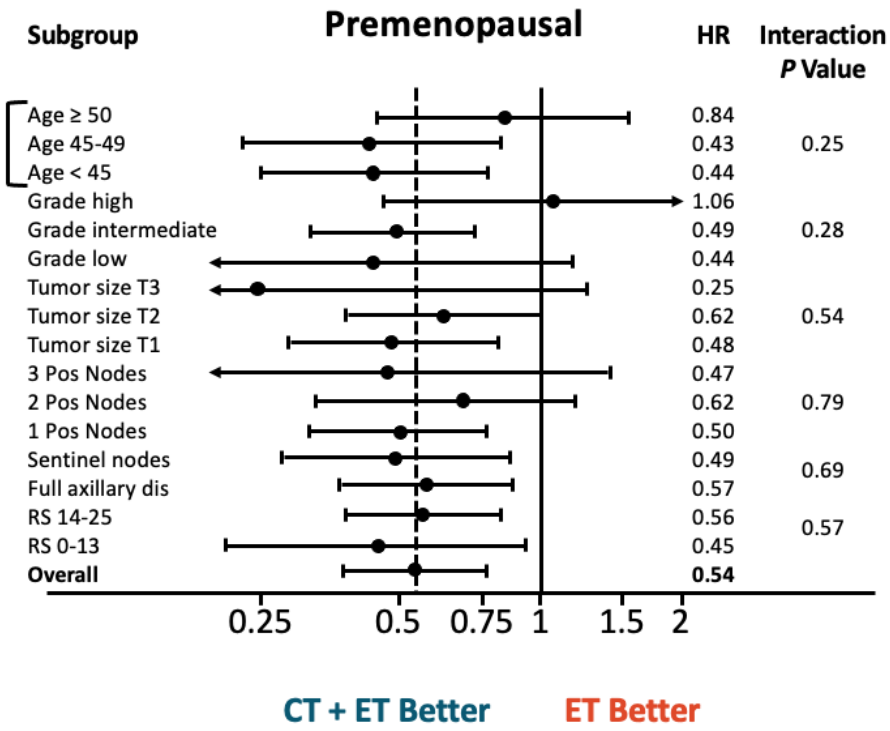
IDFS by Menopausal Status





RxPONDER: iDFS by Menopausal Status Across Subgroups





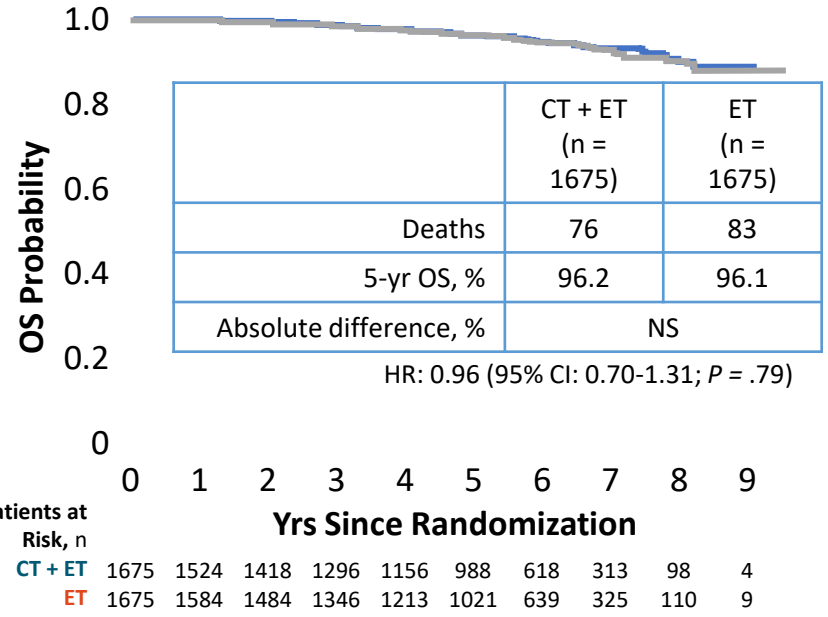
iDFS by RS and Menopausal Status

Postmenopausal	CT + ET	ET
RS 0-13	**n = 765**	**n = 736**
▪ Events, n	56	58
▪ 5-yr iDFS, %	93.4	92.9
▪ Absolute diff, %	NS	
▪ HR (95% CI)	0.96 (0.66-1.38); *P* = .81	
RS 14-25	**n = 910**	**n = 939**
▪ Events, n	91	100
▪ 5-yr iDFS, %	90.1	91.2
▪ Absolute diff, %	NS	
▪ HR (95% CI)	0.98 (0.74-1.30; *P* = .89)	

Premenopausal	CT + ET	ET
RS 0-13	**n = 311**	**n = 334**
▪ Events, n	10	25
▪ 5-yr iDFS, %	96.5	92.6
▪ Absolute diff, %	3.9	
▪ HR (95% CI)	0.46 (0.22-0.97); *P* = .04	
RS 14-25	**n = 523**	**n = 497**
▪ Events, n	41	66
▪ 5-yr iDFS, %	92.8	86.6
▪ Absolute diff, %	6.2	
▪ HR (95% CI)	0.57 (0.39-0.84); *P* = .005	

OS by Menopausal Status

Postmenopausal

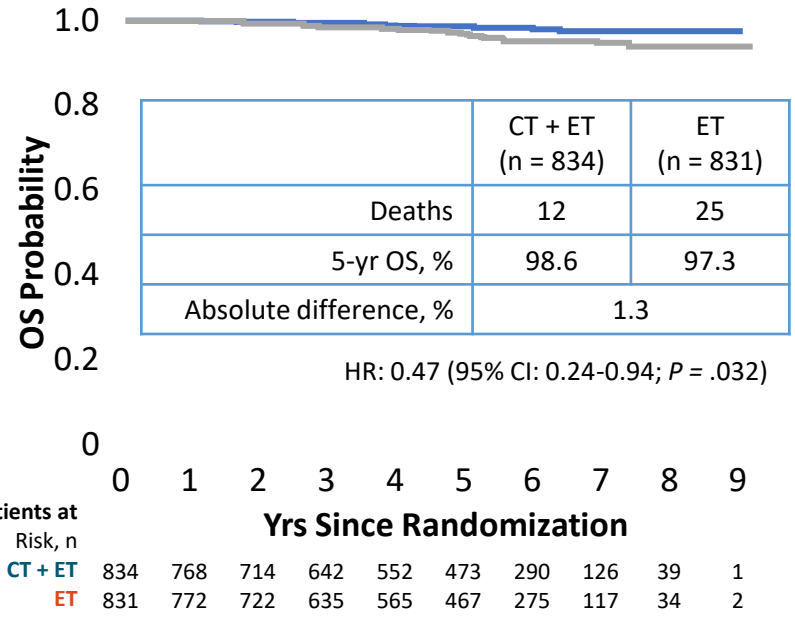


	CT + ET (n = 1675)	ET (n = 1675)
Deaths	76	83
5-yr OS, %	96.2	96.1
Absolute difference, %	NS	

HR: 0.96 (95% CI: 0.70-1.31; *P* = .79)

Patients at Risk, n										
CT + ET	1675	1524	1418	1296	1156	988	618	313	98	4
ET	1675	1584	1484	1346	1213	1021	639	325	110	9

Premenopausal



	CT + ET (n = 834)	ET (n = 831)
Deaths	12	25
5-yr OS, %	98.6	97.3
Absolute difference, %	1.3	

HR: 0.47 (95% CI: 0.24-0.94; *P* = .032)

Patients at Risk, n										
CT + ET	834	768	714	642	552	473	290	126	39	1
ET	831	772	722	635	565	467	275	117	34	2

The premenopausal result

The analysis showed a convincing demonstration of chemotherapy superiority for both Invasive Disease Free Survival and Overall Survival.

This is likely due to an imbalance in treatment caused by chemotherapy-induced menopause?

- GnRHa use was reported for 16% of patients in the ET arm and 3% in the chemotherapy + ET arm
- %31of patients were age >61% ,50were age ;50-40chemotherapy-induced menopause is common with older pre-menopausal patients

- The chemotherapy - menopause issue also affects both TAILORx & MINDACT

The postmenopausal result

No benefit from chemotherapy was demonstrated for patients with RS 25≥

- Numerically fewer distant recurrence events for chemotherapy + ET group but far from achieving statistical significance in a superiority analysis
- There was no evidence for any subgroup effect
  - In particular, results for the 1N+ and combined 3-2N+ group were the same
    - the confidence interval for the 3-2N+ group is very broad as they make up only 34% of the postmenopausal population

RxPONDER results summary

- Interim analysis at median 5.1 years follow-up presented at SABCS 2020

- **Analysis showed menopausal status influenced chemotherapy benefit**
  - Premenopausal :statistically significant IDFS and OS benefit for chemotherapy
  - Postmenopausal :no evidence of chemotherapy benefit

- **No evidence for increasing chemotherapy benefit according to RS ;i.e .the primary objective was <u>not met</u>**

Conclusions

- ✗ **"Premenopausal women with positive nodes and RS 25-olikely benefit significantly from chemotherapy"**

- ✗ **"Postmenopausal women with 3-1positive nodes and RS 25-ocan likely safely forego adjuvant chemotherapy without compromising IDFS"**

Treatment De-Escalation Strategies in HR+/HER2- EBC

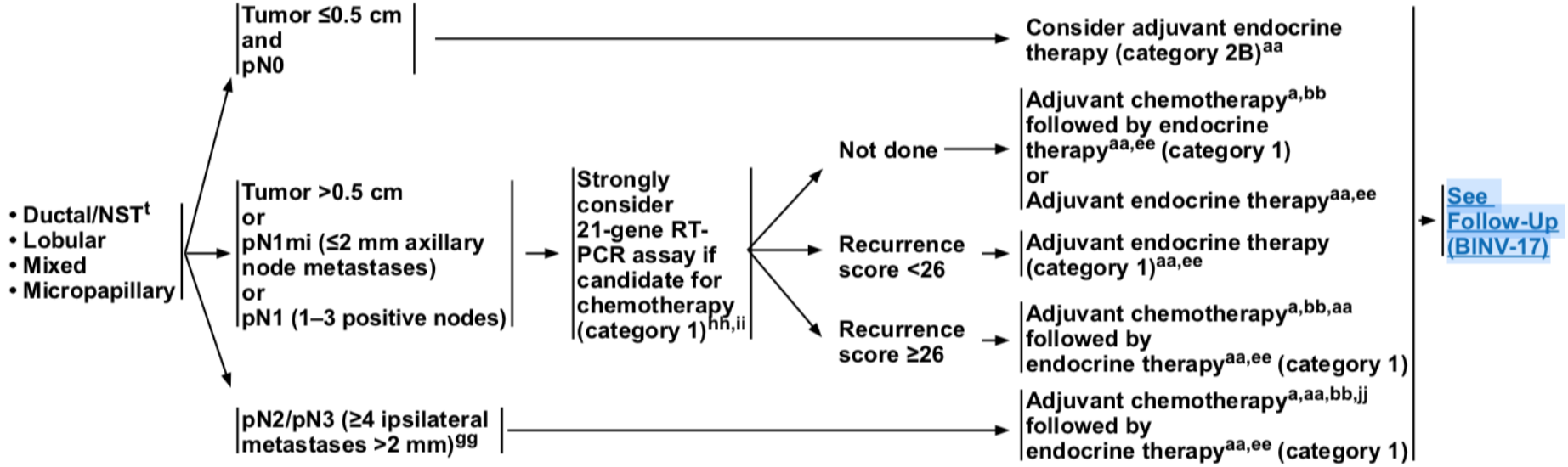
- **TAILORx:** Suggest that the 21-gene assay may identify up to 85% of women with early breast cancer who can be spared adjuvant chemotherapy

✓ *those who are older than 50 years of age and have a RS of 25 or lower*

✓ *as well as women 50 years of age or younger with a RS of 15 or lower*

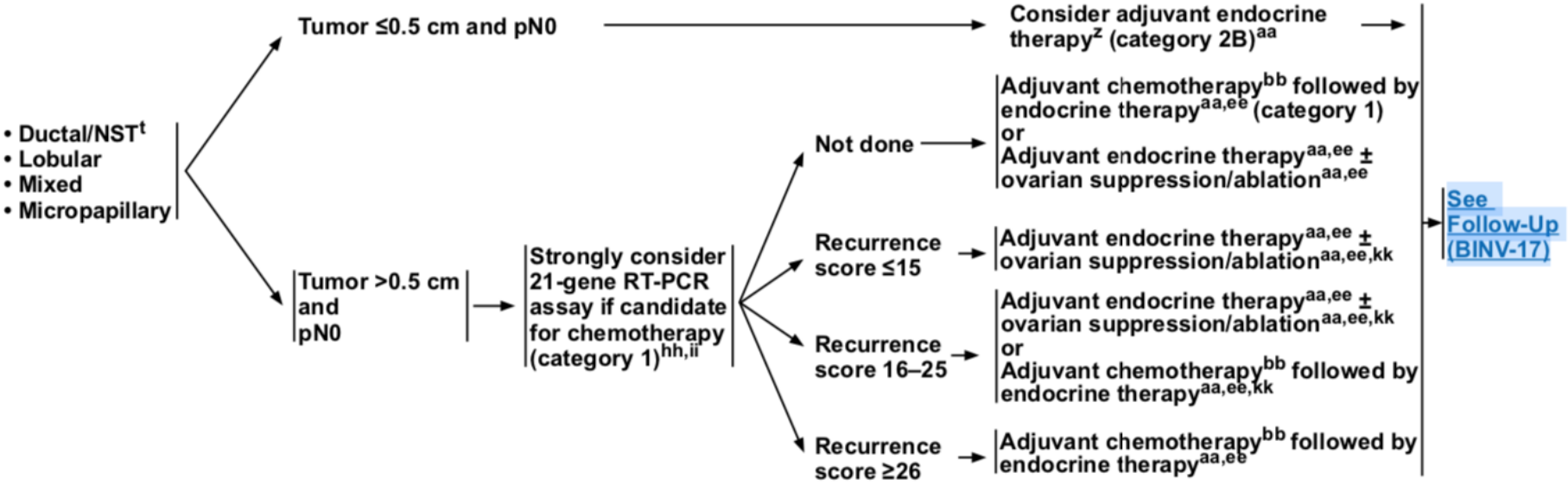
- **RxPONDER:** In an interim analysis of adj CT for HR+/HER2- EBC with 1-3 positive nodes and RS ≤ 25, postmenopausal women did not benefit, whereas premenopausal women did
  - Premenopausal patients experienced a 46% decrease in iDFS events and a 53% decrease in deaths, leading to a 5-yr OS absolute improvement of 1.3%

SYSTEMIC ADJUVANT TREATMENT: HR-POSITIVE - HER2-NEGATIVE DISEASE[d,q,y] POSTMENOPAUSAL[z] PATIENTS with pT1–3 AND pN0 or pN+ TUMORS



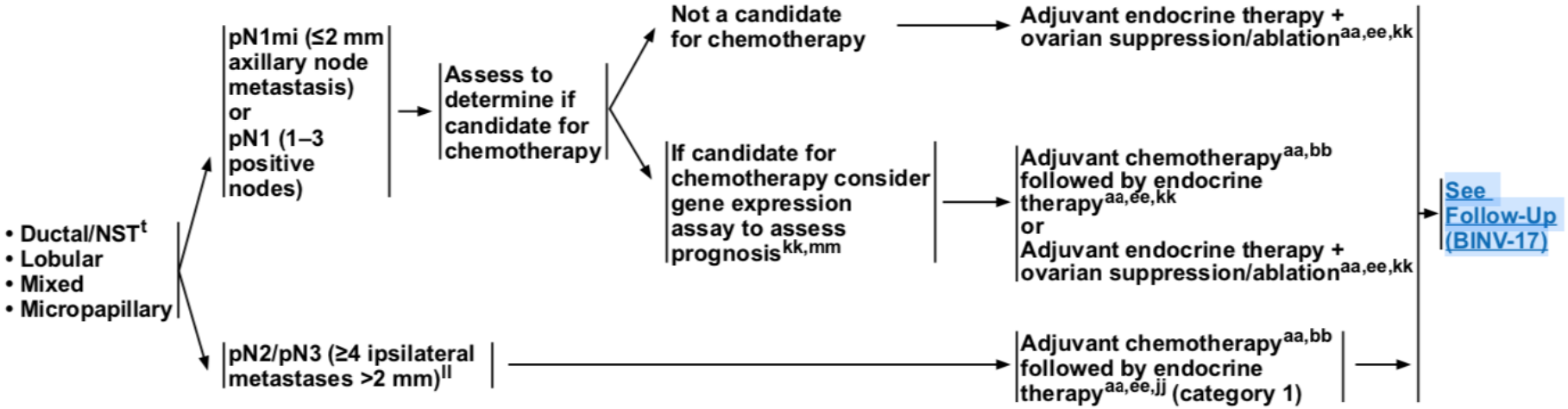
[a] For tools to aid optimal assessment and management of older adults, see NCCN Guidelines for Older Adult Oncology.
[d] See Principles of Biomarker Testing (BINV-A).

SYSTEMIC ADJUVANT TREATMENT: HR-POSITIVE - HER2-NEGATIVE DISEASE[d,q,y]
PREMENOPAUSAL[z] PATIENTS with pT1–3 AND pN0 TUMORS



[d] See Principles of Biomarker Testing (BINV-A).
[q] See Special Considerations for Breast Cancer in Males (Sex Assigned at Birth) (BINV-J).

SYSTEMIC ADJUVANT TREATMENT: HR-POSITIVE - HER2-NEGATIVE DISEASE[d,q,y] PREMENOPAUSAL[z] PATIENTS with pT1–3 AND pN+ TUMORS



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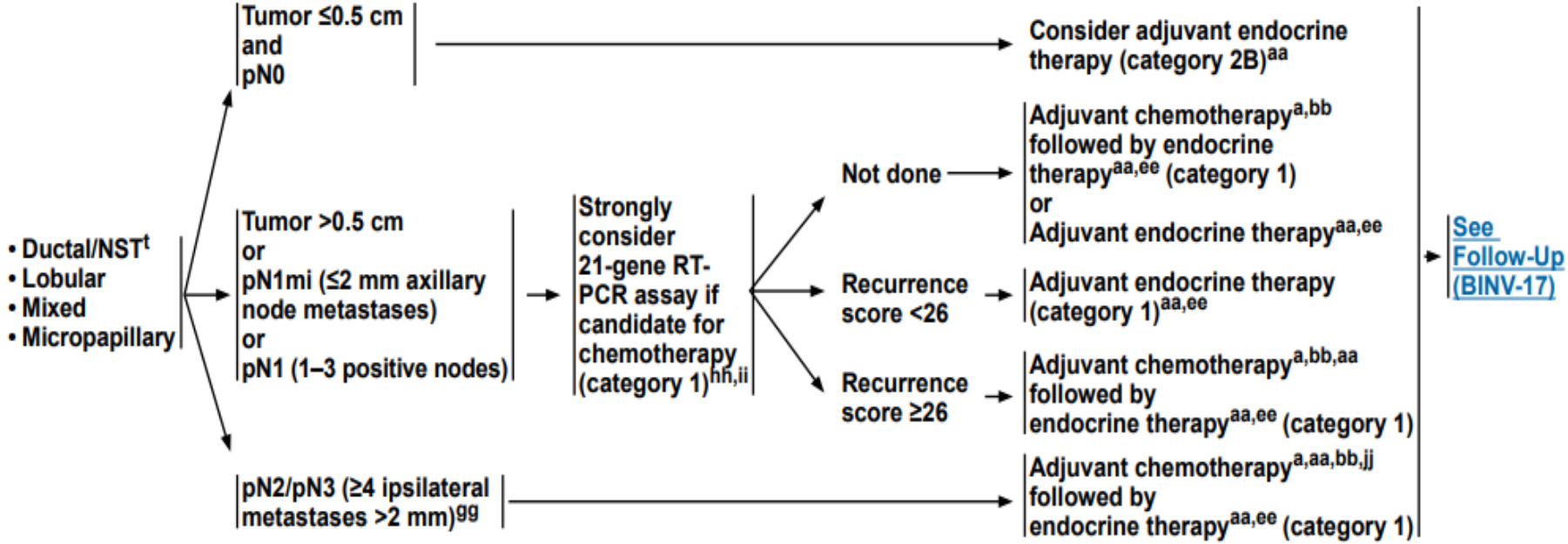
NCCN Guidelines Version 4.2022
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC ADJUVANT TREATMENT: HR-POSITIVE - HER2-NEGATIVE DISEASE[d,q,y] POSTMENOPAUSAL[z] PATIENTS with pT1–3 AND pN0 or pN+ TUMORS



[a] For tools to aid optimal assessment and management of older adults, see NCCN Guidelines for Older Adult Oncology.


THANK YOU