Current Role of Genomic Assays for Hormone Receptor (HR)-Positive Localized Breast Cancer

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Outline

- Phase III RxPONDER trial evaluating the role of chemotherapy for patients with ER-positive, HER2-negative localized breast cancer with 1 to 3 positive lymph nodes and a 21-gene Recurrence Score (RS) of ≤25

- Updated findings, including 12-year event rates, from the Phase III TAILORx study

- 21-gene RS and neoadjuvant chemotherapy decision making

- Insight regarding poor correlation between the RS and chemotherapy response in premenopausal patients

ASCO special articles

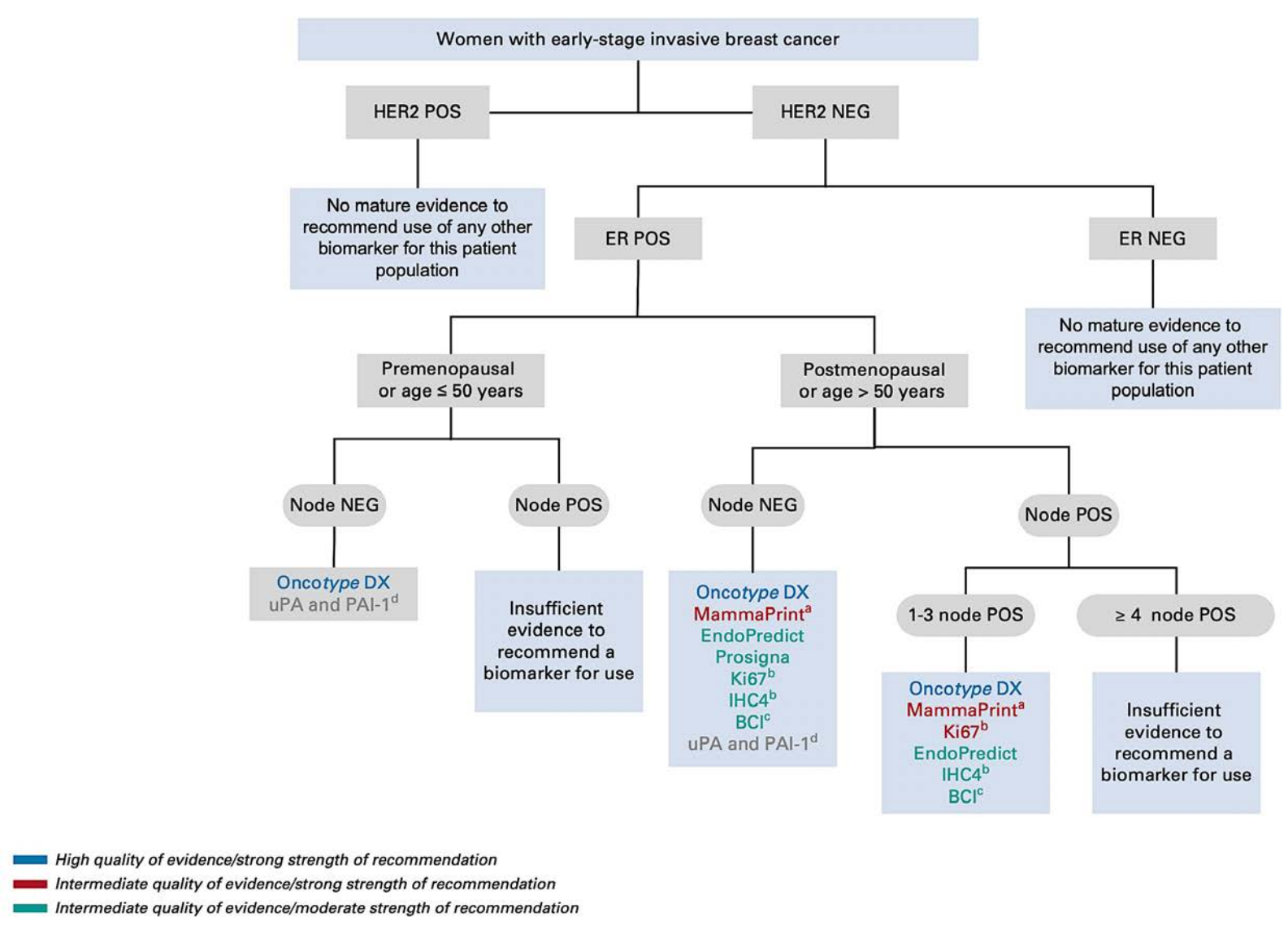
Biomarkers for Adjuvant Endocrine and Chemotherapy in Early-Stage Breast Cancer: ASCO Guideline Update

Fabrice Andre, MD[1]; Nofisat Ismaila, MD, MSc[2]; Kimberly H. Allison, PhD[3]; William E. Barlow, PhD[4]; Deborah E. Collyar, BSc[5]; Senthil Damodaran, MD, PhD[6]; N. Lynn Henry, MD, PhD[7]; Komal Jhaveri, MD[8,9]; Kevin Kalinsky, MD, MS[10]; Nicole M. Kuderer, MD[11]; Anya Litvak, MD[12]; Erica L. Mayer, MD, MPH[13]; Lajos Pusztai, MD[14]; Rachel Raab, MD[15]; Antonio C. Wolff, MD[16]; and Vered Stearns, MD[16]

J Clin Oncol 2022;40(16):1816-37.

RTP RESEARCH TO PRACTICE

Biomarkers for Adjuvant Endocrine and Chemotherapy in Localized Breast Cancer: ASCO Guideline Update



Andre F et al. *J Clin Oncol* 2022;40(16):1816-37.

RTP RESEARCH TO PRACTICE

San Antonio Breast Cancer Symposium®, December 7-10, 2021

RxPONDER: A Clinical Trial Rx for Positive Node, Endocrine Responsive Breast Cancer

Updated results from a phase 3 randomized clinical trial in participants (pts) with 1-3 positive lymph nodes, hormone receptor-positive (HR+) and HER2-negative breast cancer with recurrence score of 25 or less: SWOG S1007

Kevin Kalinsky, William E Barlow, Julie R Gralow, Funda Meric-Bernstam, Kathy S Albain, Daniel F Hayes, Nancy U Lin, Edith A Perez, Lori J Goldstein, Stephen K Chia, Sukhbinder Dhesy-Thind, Priya Rastogi, Emilio Alba, Suzette Delaloge, Miguel Martin, Catherine M Kelly, Manuel Ruiz-Borrego, Miguel Gil Gil, Claudia Arce-Salinas, Etienne G.C. Brain, Eun Sook Lee, Jean-Yves Pierga, Begoña Bermejo, Manuel Ramos-Vazquez, Kyung Hae Jung, Jean-Marc Ferrero, Anne F. Schott, Steven Shak, Priyanka Sharma, Danika L. Lew, Jieling Miao, Debasish Tripathy, Lajos Pusztai, Gabriel N. Hortobagyi

On Behalf of the RxPonder Investigators

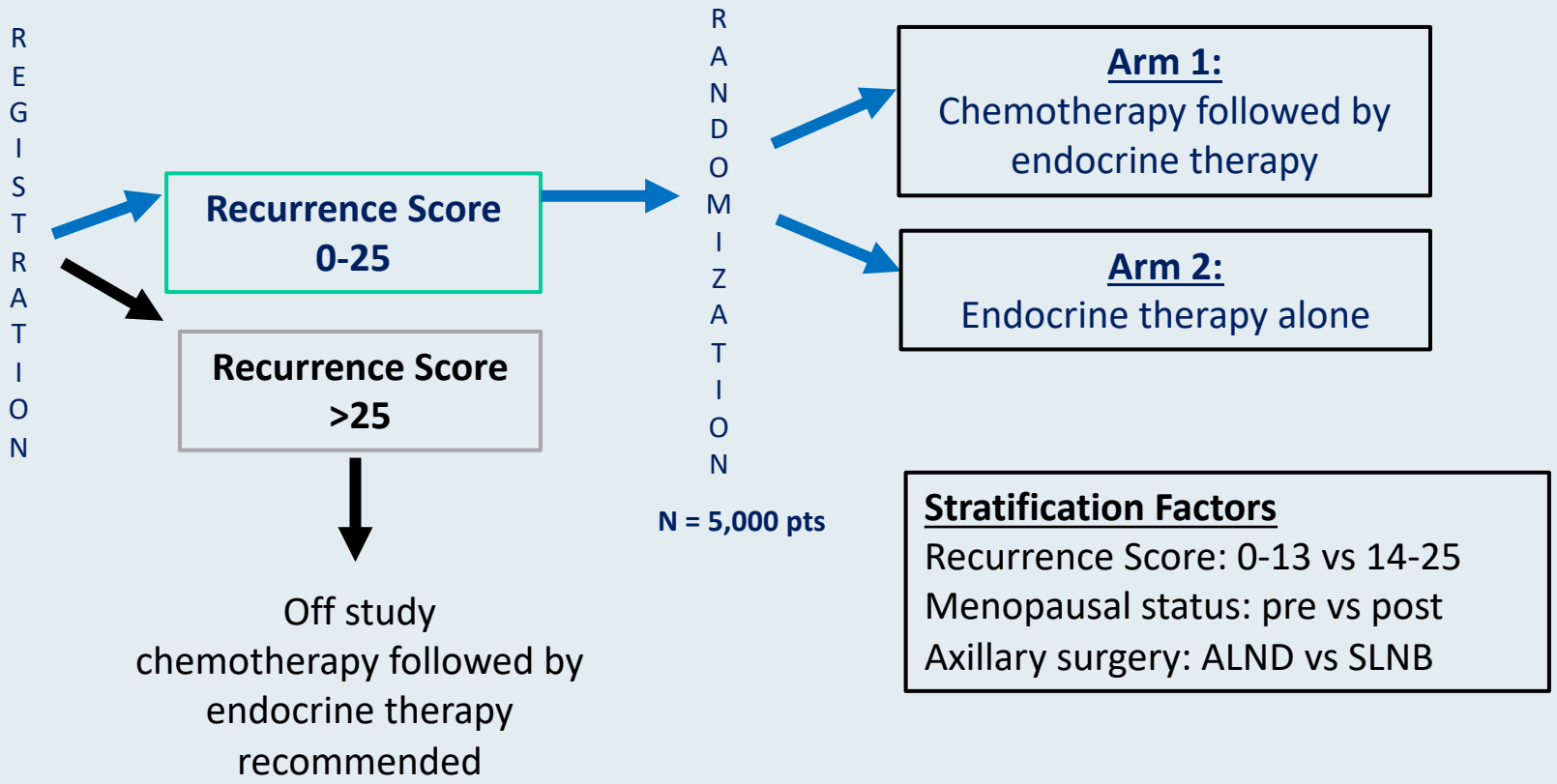
SABCS 2021;Abstract GS2-07.

RTP RESEARCH TO PRACTICE

RxPONDER Trial Schema

Key Entry Criteria

- Women age ≥18
- ER and/or PR ≥1%, HER2-negative breast cancer with 1*-3 positive LN without distant metastasis
- Able to receive adjuvant taxane and/or anthracycline-based chemotherapy†
- Axillary staging by SLNB or ALND



* After randomization of 2,493 pts, the protocol was amended to exclude enrollment of pts with pN1mic as only nodal disease.

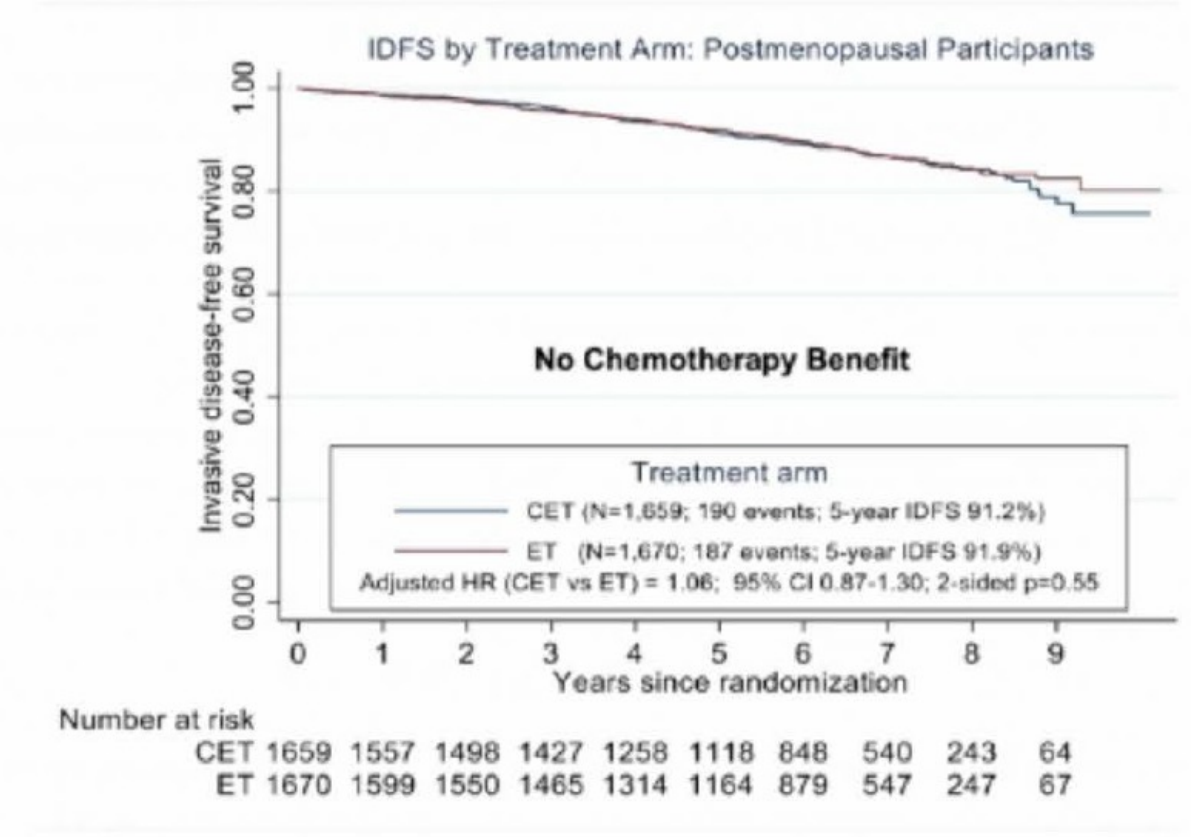
† Approved chemotherapy regimens included TC, FAC (or FEC), AC/T (or EC/T), FAC/T (or FEC/T). AC alone or CMF not allowed.

LN = lymph node; SLNB = sentinel lymph node biopsy; ALND = axillary lymph node dissection; pts = patients

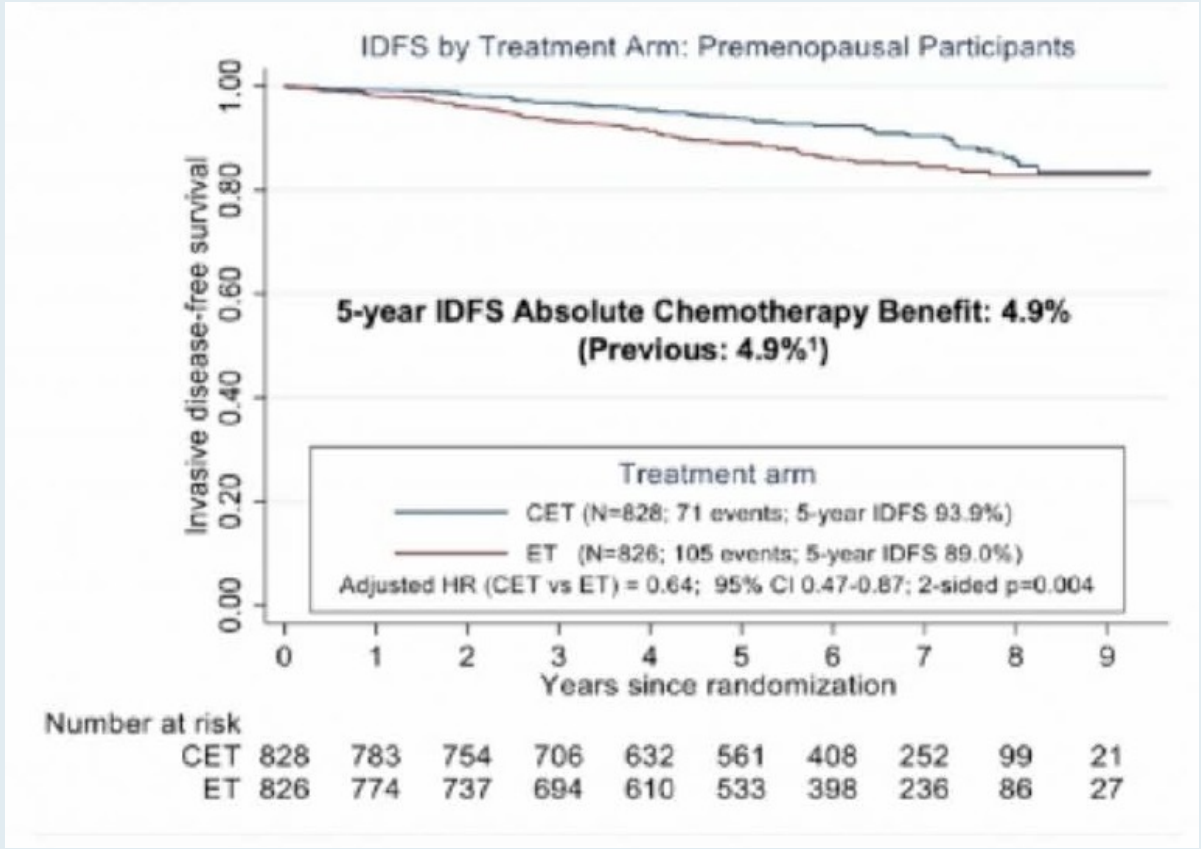
Kalinsky K et al. SABCS 2020;Abstract GS3-00.

RxPONDER Updated Analysis: IDFS Stratified by Menopausal Status

Postmenopausal



Premenopausal



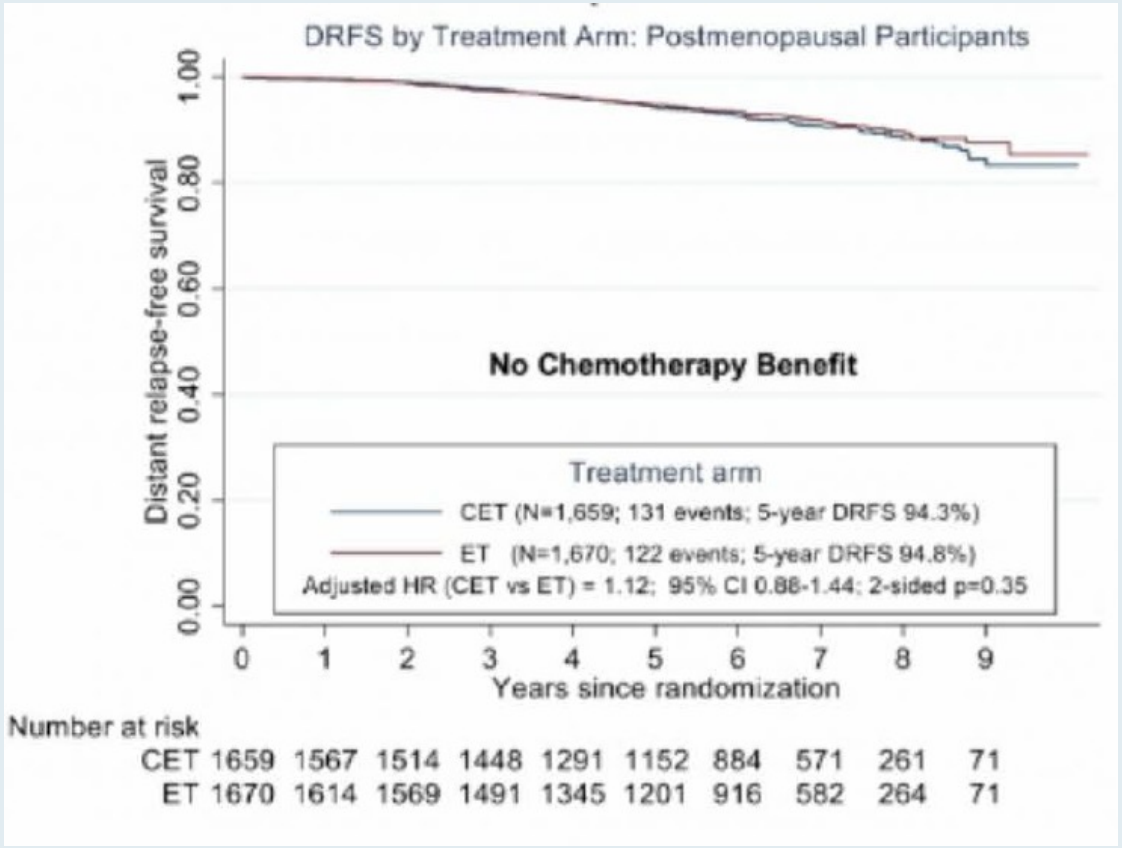
IDFS = invasive disease-free survival

Kalinsky K et al. SABCS 2021;Abstract GS2-07.

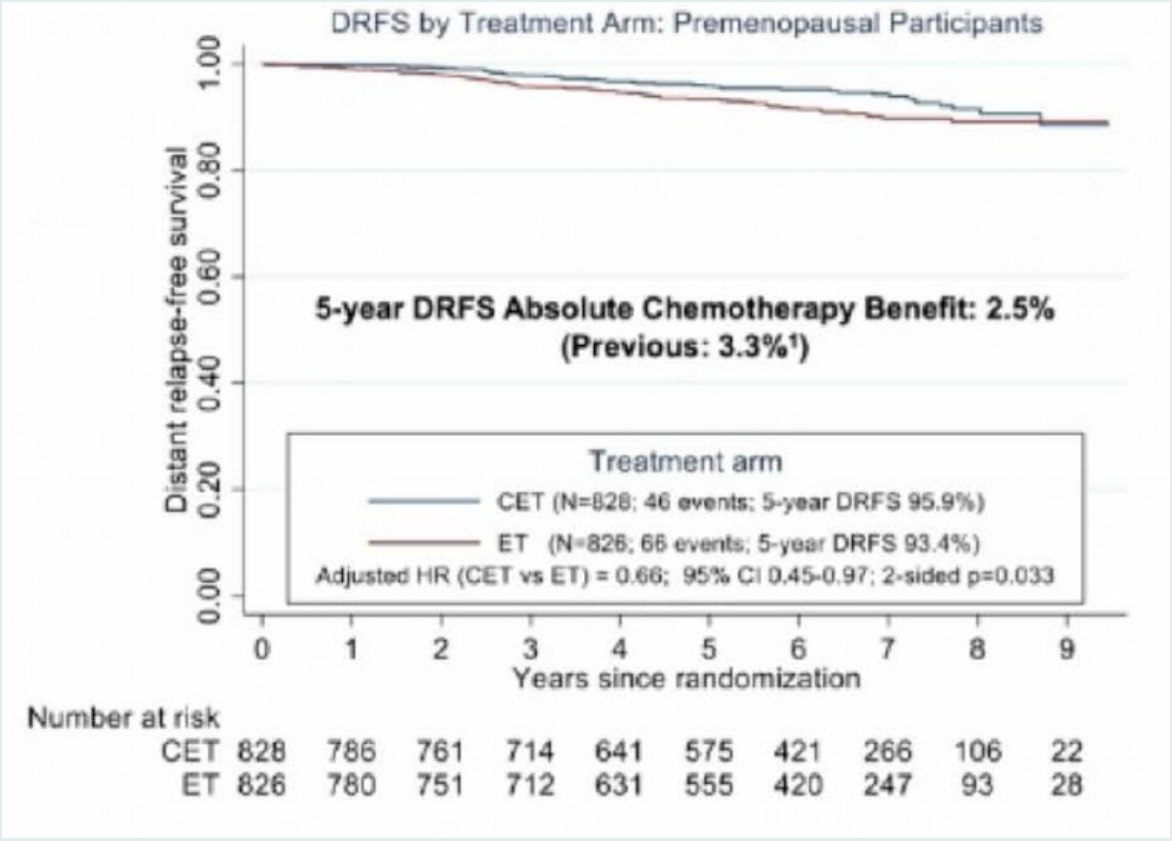
RTP RESEARCH TO PRACTICE

RxPONDER Updated Analysis: DRFS Stratified by Menopausal Status

Postmenopausal



Premenopausal



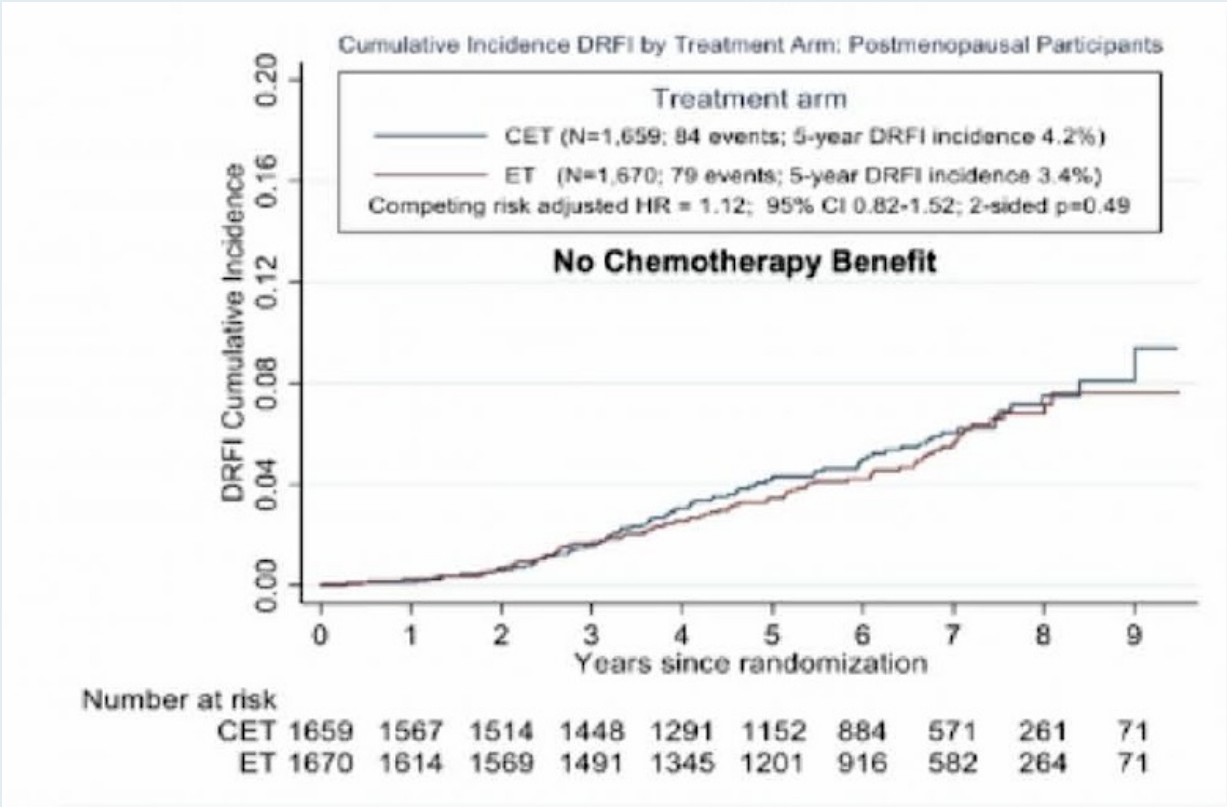
DRFS = distant recurrence-free survival

Kalinsky K et al. SABCS 2021;Abstract GS2-07.

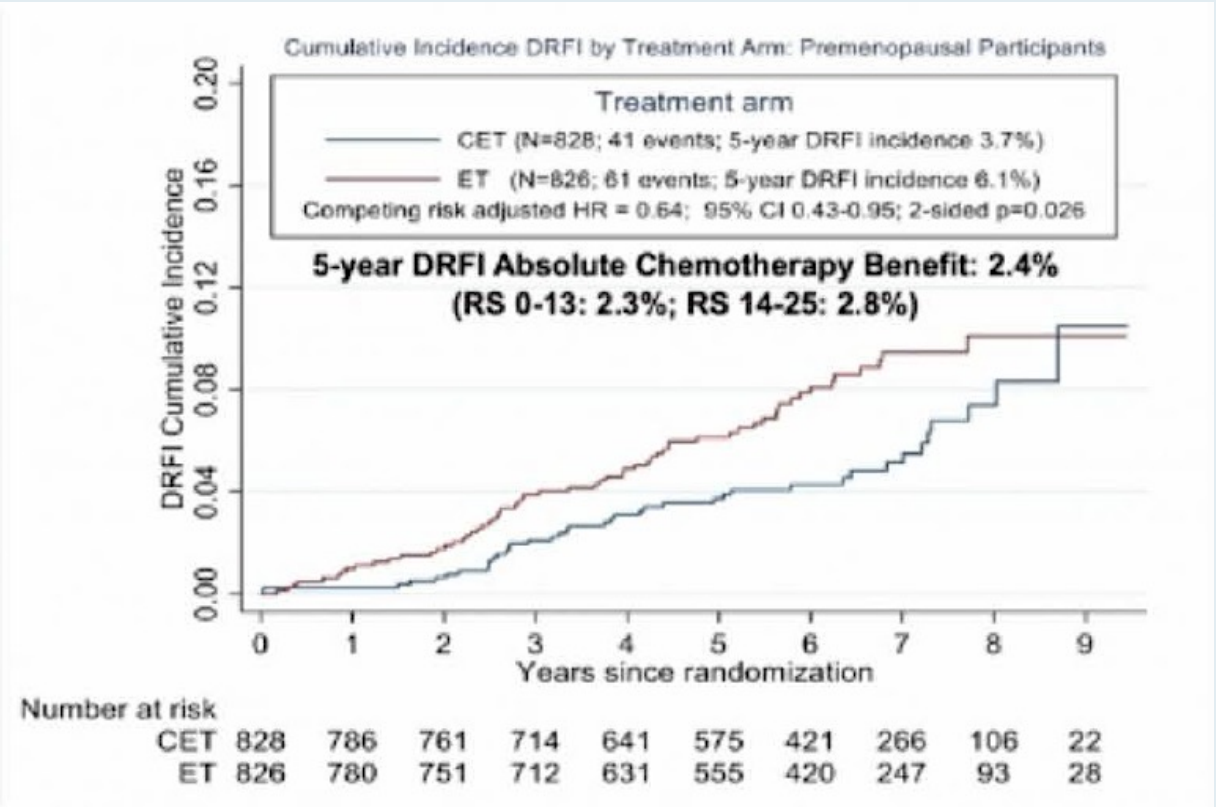
RTP RESEARCH TO PRACTICE

RxPONDER New Analysis: DRFI Stratified by Menopausal Status

Postmenopausal



Premenopausal



Time from randomization assignment to date of first invasive recurrence (distant) or death from breast cancer

In multivariate analysis, higher RS (continuous) and larger tumor size remained independently prognostic in both treatment arms

DRFI = distant recurrence-free interval

Kalinsky K et al. SABCS 2021;Abstract GS2-07.

RTP RESEARCH TO PRACTICE

Trial Assigning IndividuaLized Options for TReatment (TAILORx): An Update Including 12-Year Event Rates

Joseph A. Sparano, Robert J. Gray, Della F. Makower, Kathy S. Albain, Daniel F. Hayes, Charles E. Geyer, Elizabeth Claire Dees, Matthew P. Goetz, John A. Olson, Jr., Tracy G. Lively, Sunil Badve, Thomas J. Saphner, Timothy J. Whelan, Virginia Kaklamani, & George W. Sledge, Jr.

on behalf of the TAILORx Investigators

Funding: U.S. NIH/NCI U10CA180820, U10CA180794, UG1CA189859, UG1CA190140, UG1CA233160, UG1CA23337, UG1CA189869; U.S. Postal Service Breast Cancer Stamp Fund; Canadian Cancer Society Research Institute grants 015469, 021039; Breast Cancer Research Foundation, Komen Foundation.

TAILORx Study Design: 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=1619 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

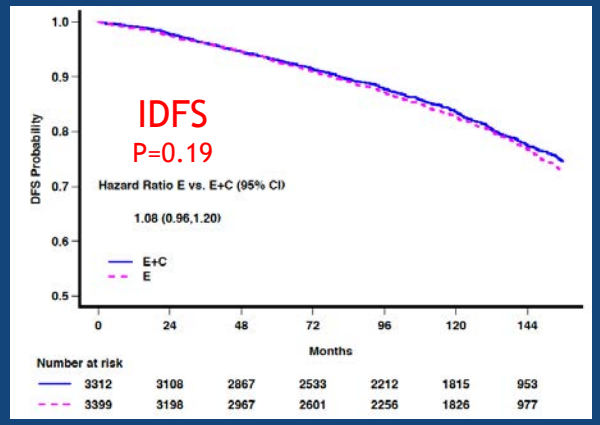
ARM D: High RS 26-100
(N=1389 evaluable)
ASSIGN
ET + Chemo

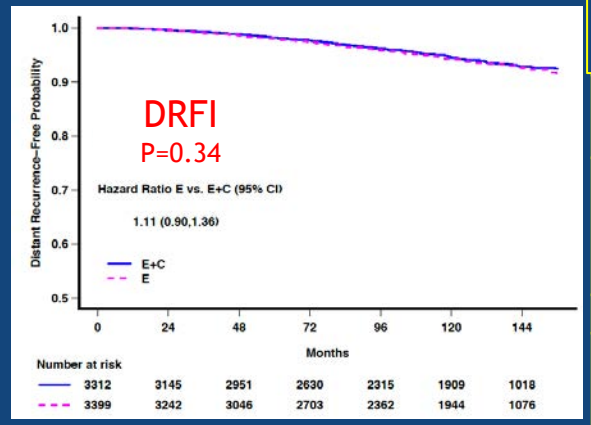
ARM B: Experimental Arm
(N=3399)
ET Alone

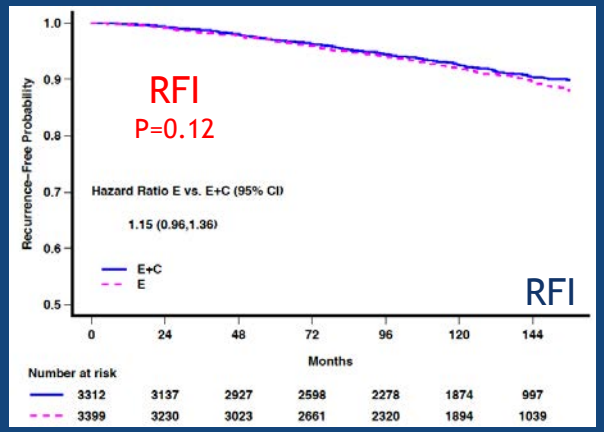
ARM C: Standard Arm
(N=3312)
ET + Chemo

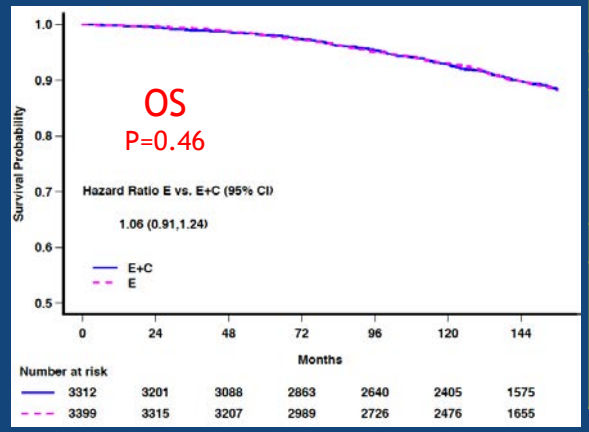
Sparano et al. NEJM 2018
(PMID: 31157962)

TAILORx: Updated Analysis - Kaplan-Meier Curves in RS 11-25 Arms (ITT population)





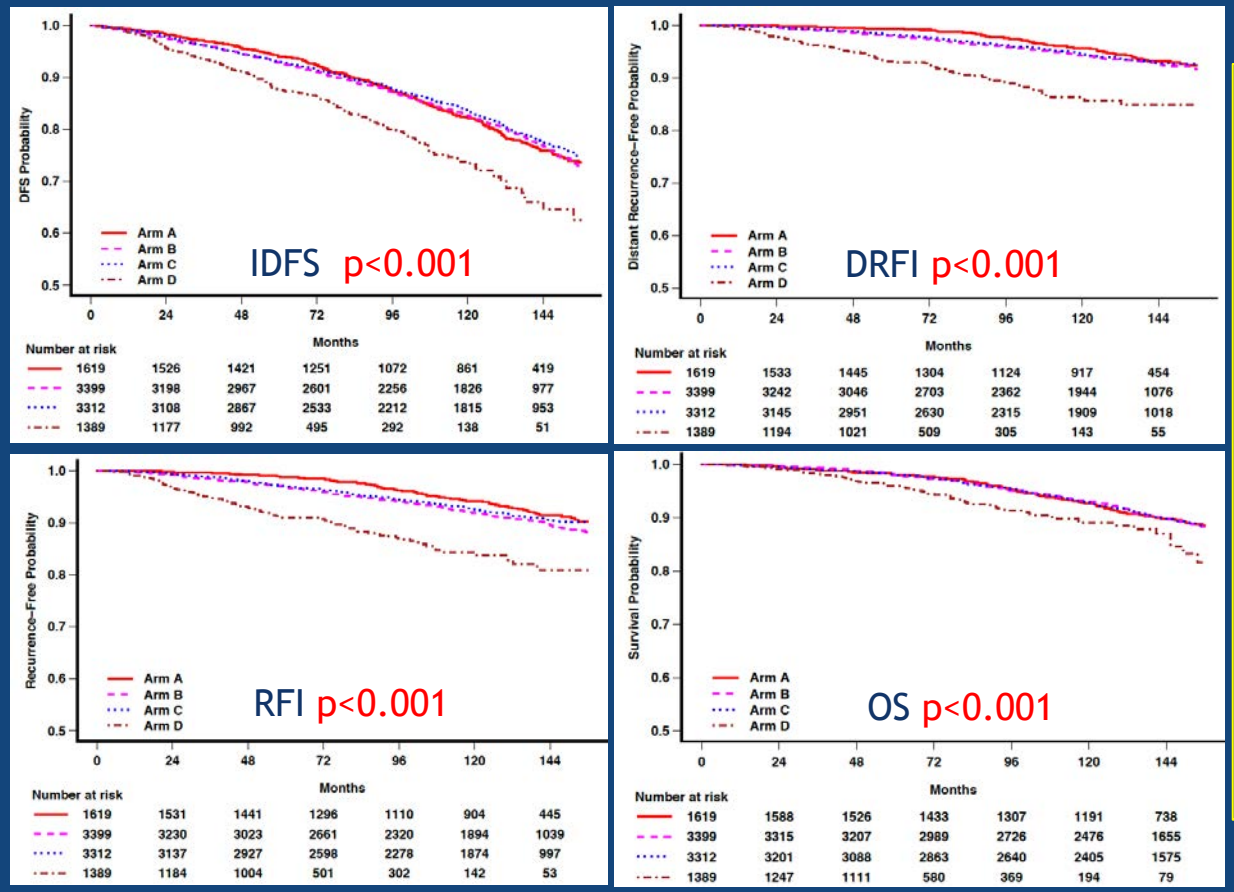




Primary trial conclusions unchanged:
ET non-inferior to CET (N=6711)

Event	Hazard Ratio: Arm B vs. C (95% CI)
IDFS	Primary analysis: 1.08 (0.94, 1.24, p=0.26)
	Updated analysis: 1.08 (0.96, 1.20)
DRFI	Primary analysis: 1.10 (0.85,1.41, p=0.48)
	Updated analysis: 1.11 (0.90, 1.36)
RFI	Primary analysis: 1.11 (0.90, 1.37, p=0.33)
	Updated analysis: 1.15 (0.96, 1.36)
OS	Primary analysis: 0.99 (0.79, 1.22, p=0.89)
	Updated analysis: 1.06 (0.91, 1.24)

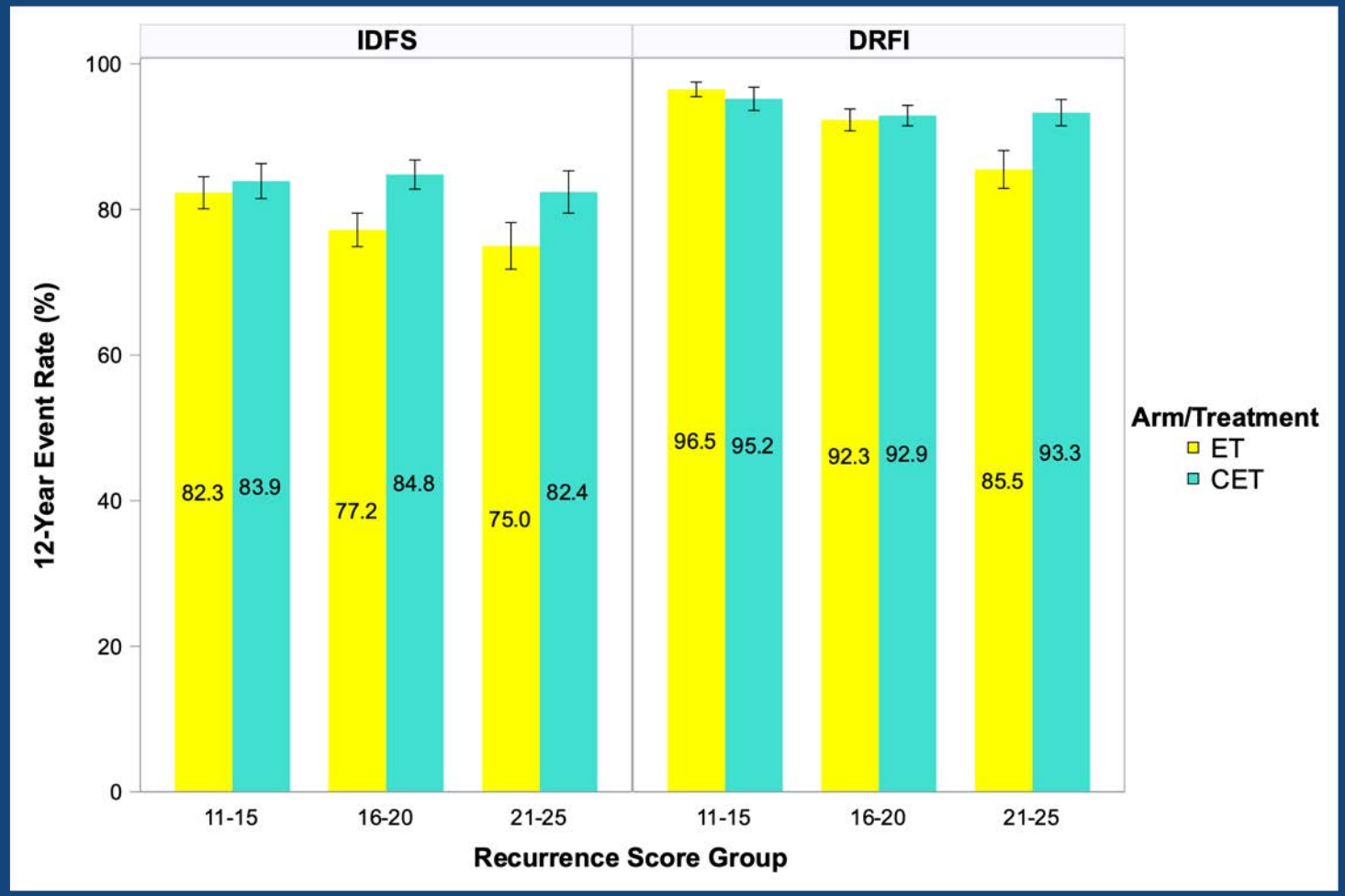
TAILORx: Updated Analysis- Kaplan-Meier Curves in All Arms (ITT population)



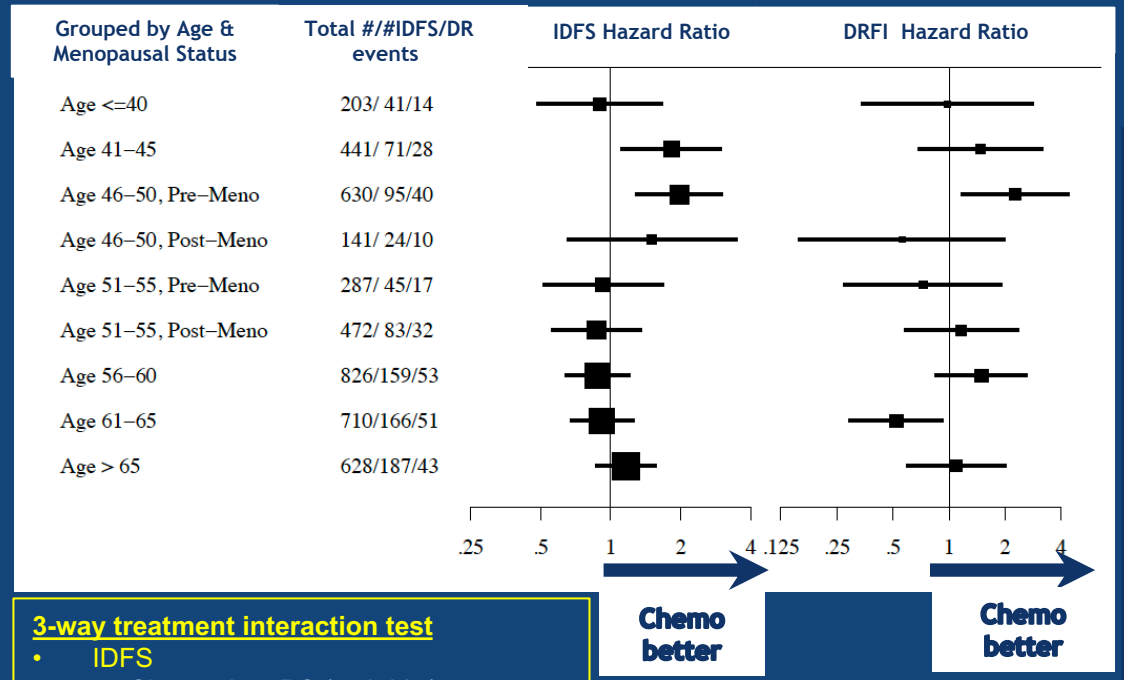
12-Year Event Rates (N=9719)

- **RS prognostic for all endpoints**
- **RS 0-10 (Arm A) – ET Alone**
  - DFRI rate: 93.2% (SE 0.8)
  - RFI rate: 91.4% (SE 0.9)
- **RS 11-25 (Arms B & C) – ET vs. CET**
  - < 1 % difference for all endpoints
    - IDFS: 76.8 vs. 77.4%
    - DRFI: 92.6 vs. 92.8%
    - RFI: 89.6 vs. 90.4%
    - OS: 89.8 vs. 89.8%
- **RS 26-100 (Arm D) – CET**
  - DFRI rate: 84.8% (SE 1.8)
  - RFI rate: 80.9 (SE 2.2)

TAILORx: Updated Analysis – Event Rates in RS 11-25 Arms and ≤ 50 Years (ITT Population)



TAILORx: Updated Analysis - Effect of Age, RS, and Clinical Risk on Chemotherapy Benefit (ITT Population)



3-way treatment interaction test

- IDFS
  - Chemo-Age-RS (p=0.007)
  - Chemo-Menopause-RS (p=0.06)
- DRFI
  - Chemo-Age-RS (p=0.43)
  - Chemo-Menopause-RS (p=0.26)

12-Year DRFI Rates in Age ≤ 50 Years & RS 16-25

	Estimated Absolute Chemo Benefit Not Stratified by Clinical Risk	Clinical Risk	No.	Estimated Absolute Chemo Benefit Stratified by Clinical Risk
RS 16-20 (N=886)	Δ +0.4% (±SE 2.1%)	Low	671 (76%)	Δ -0.5% (±SE 2.2%)
		High	215 (24%)	Δ +3.1% (±SE 5.4%)
RS 21-25 (N=476)	Δ +7.8% (+SE 3.4%)	Low	319 (67%)	Δ +5.9% (±SE 3.4%)
		High	157 (33%)	Δ +11.7% (±SE 7.2%)

Conclusion

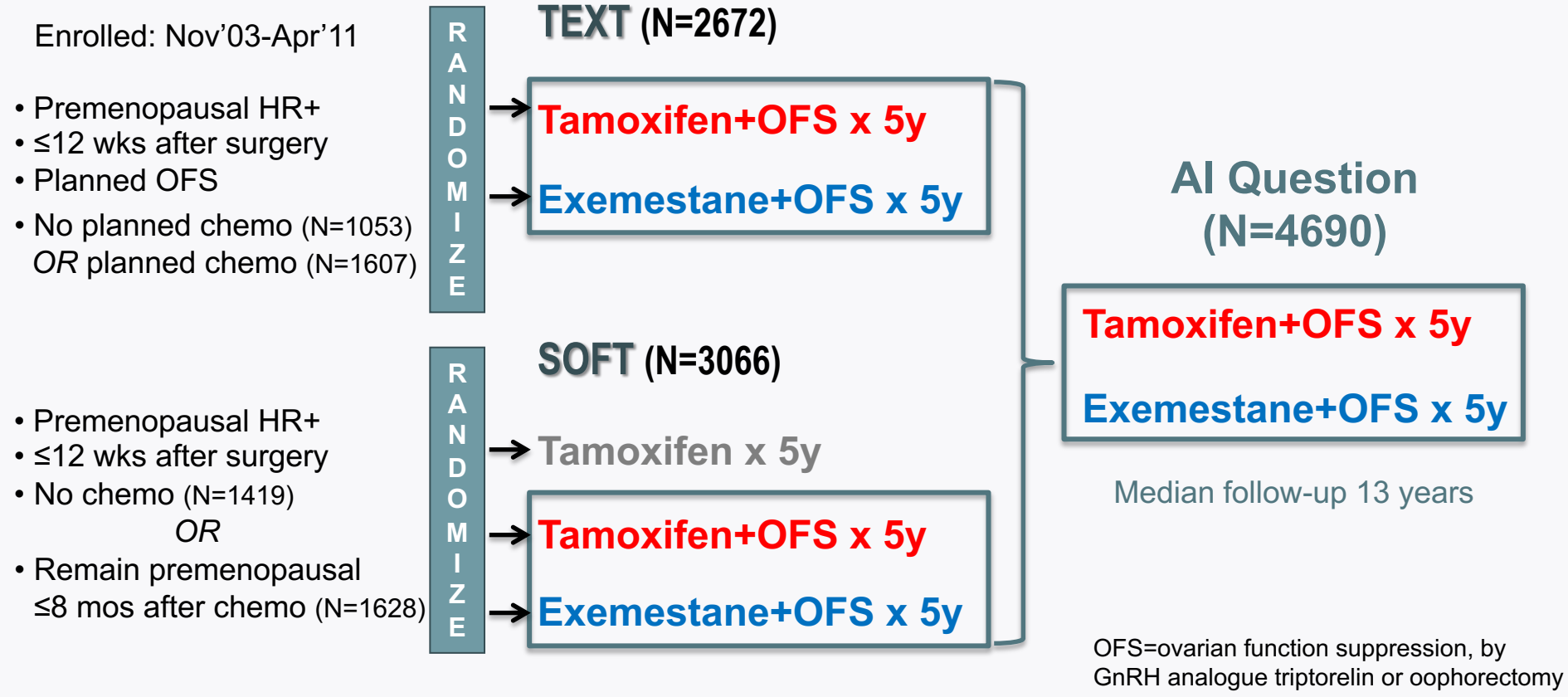
- Adjuvant chemotherapy provides no benefit in postmenopausal ER+/HER2- node negative patients (RS 11-25) and postmenopausal ER+/HER2-, 1-3 + LN (RS 0-25).

- Why did chemotherapy provide benefit in TailoRx and RxPonder premenopausal patients?
  - Endocrine Hypothesis:
    - Endocrine only arm: Inadequate endocrine therapy delivered (mostly tamoxifen and without OFS)
    - Chemotherapy treatment resulted in ovarian suppression not measured adequately
  - Cytotoxic hypothesis: chemotherapy eliminates micro-metastatic disease, independent of endocrine effects[1]

1.Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. Lancet 365:1687-1717, 2005

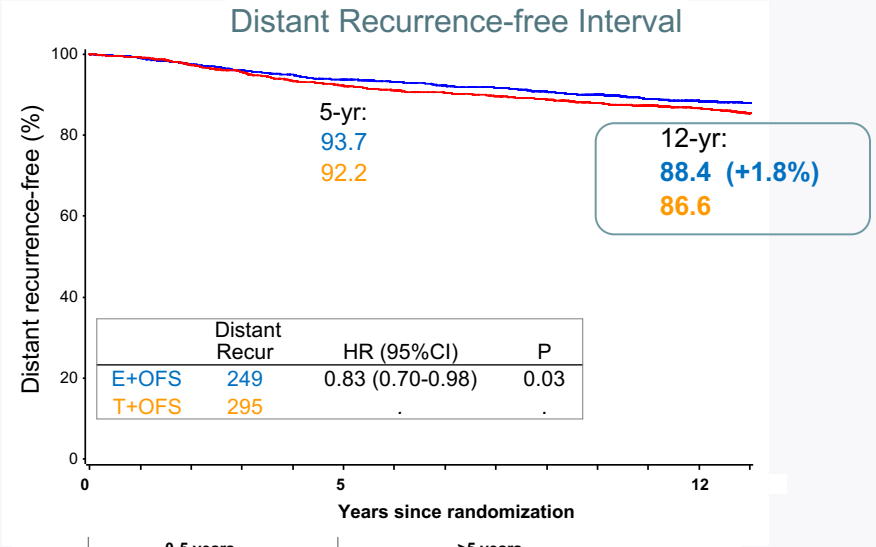
SOFT and TEXT

TEXT and SOFT Designs

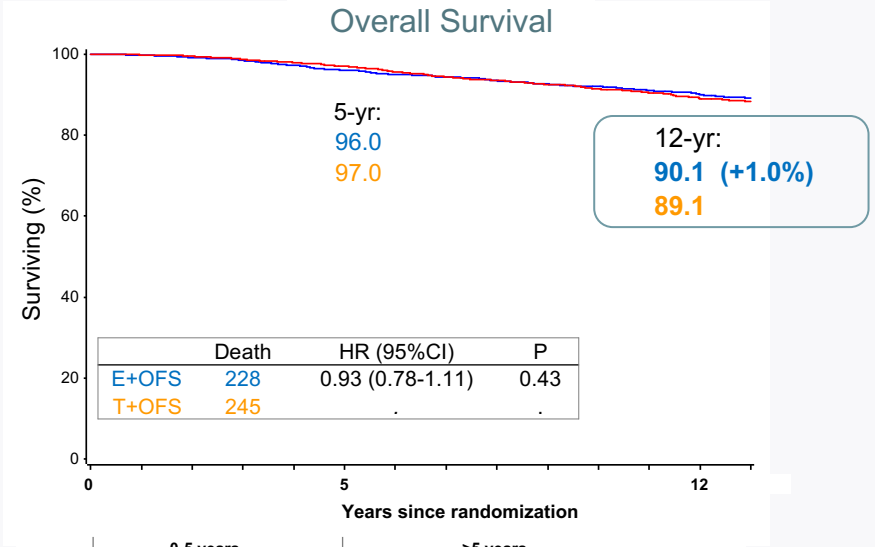


Pagani et al. NEJM 2014; Francis et al. NEJM 2014, Regan SABCS 2021

AI Question: SOFT+TEXT Overall Populations
13 years median follow-up



	0-5 years		>5 years	
	Recur	HR (95% CI)	Recur	HR (95% CI)
E+OFS:	139	0.78 (0.63-0.98)	110	0.90 (0.70-1.17)
T+OFS:	175	.	120	.
.	.	.	.	.
At risk:	4690 pts	21535 pyfu	3947 pts	26891 pyfu



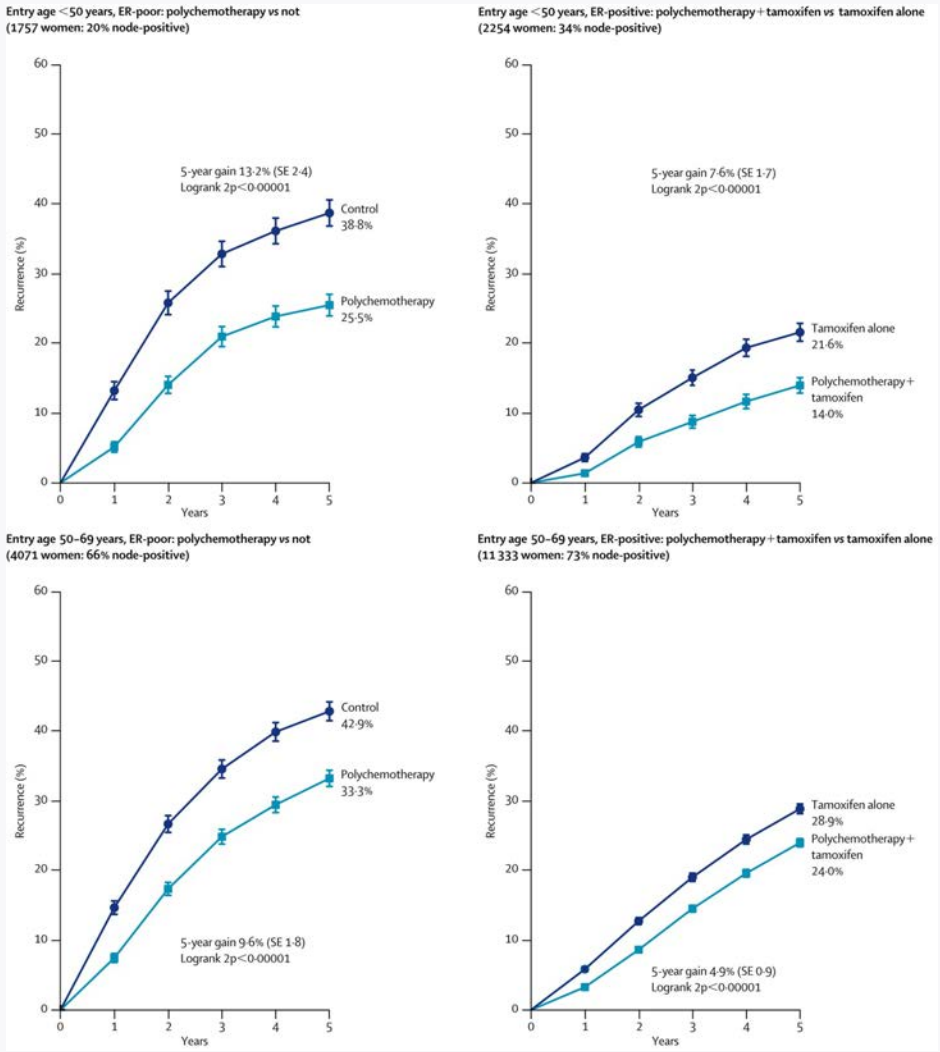
	0-5 years		>5 years	
	Deaths	HR (95% CI)	Deaths	HR (95% CI)
E+OFS:	91	1.34 (0.98-1.84)	137	0.77 (0.62-0.97)
T+OFS:	68	.	177	.
.	.	.	.	.
At risk:	4690 pts	22467 pyfu	4283 pts	30294 pyfu

E+OFS vs T+OFS: absolute reduction in distant recurrence, 1.8% at 12 years
absolute reduction in death, 1.0% at 12 years

pyfu=person-years follow-up

Regan SABCS 2021 and J Clin Oncol (in press)

Polychemotherapy versus not, by entry age <50 or 50-69 years and ER status (Oxford Overview)

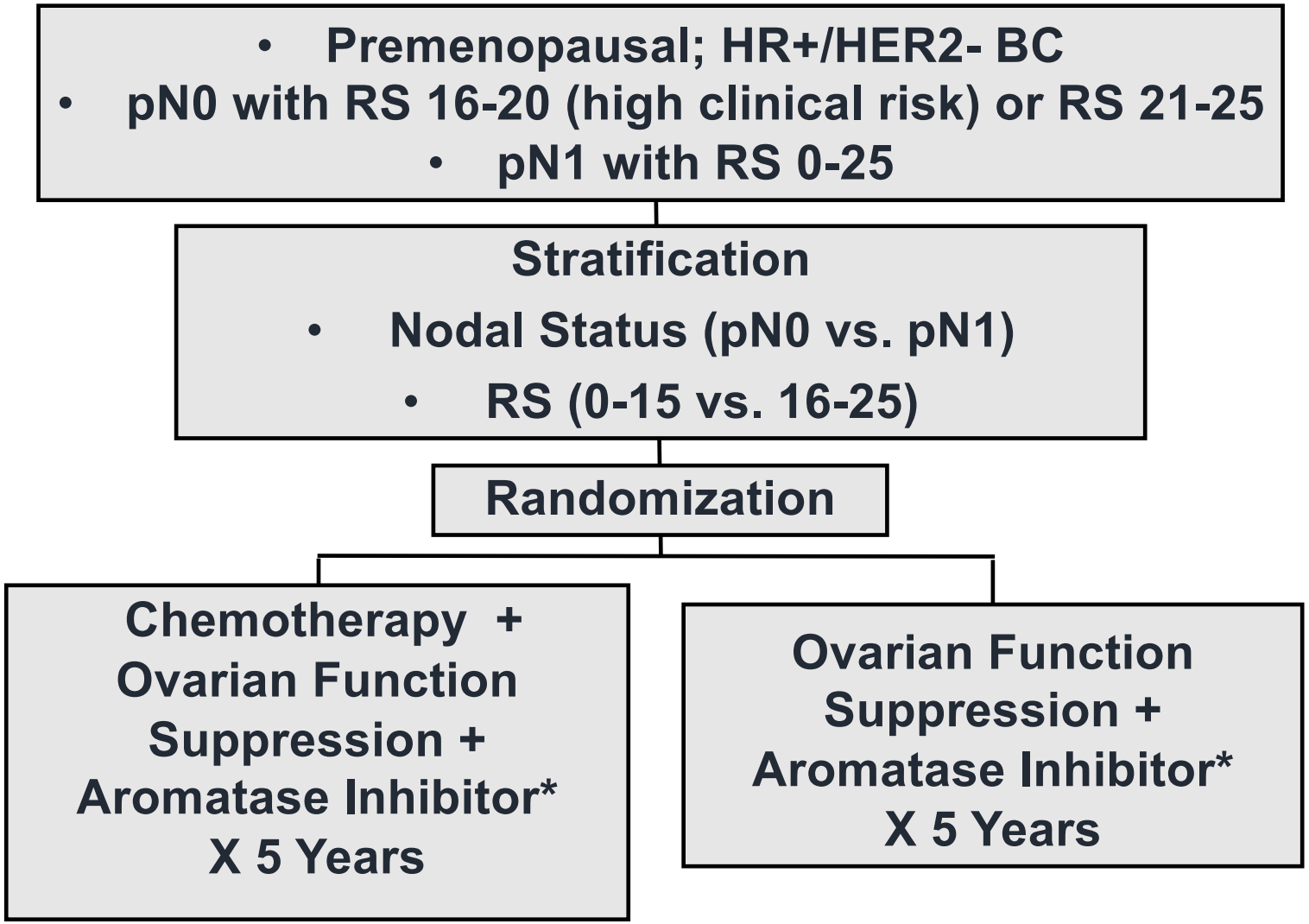


Age < 50: Enriched with tumors that harbor deficiencies in DNA repair?

Proportional risk reductions are a bit smaller, but clearly still evident

Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Lancet 2005

BR009: Schema (slide courtesy of Terry Mamounas)



* Tamoxifen can be used if AI is not tolerated

Outline

- Phase III RxPONDER trial evaluating the role of chemotherapy for patients with ER-positive, HER2-negative localized breast cancer with 1 to 3 positive lymph nodes and a 21-gene Recurrence Score (RS) of ≤25

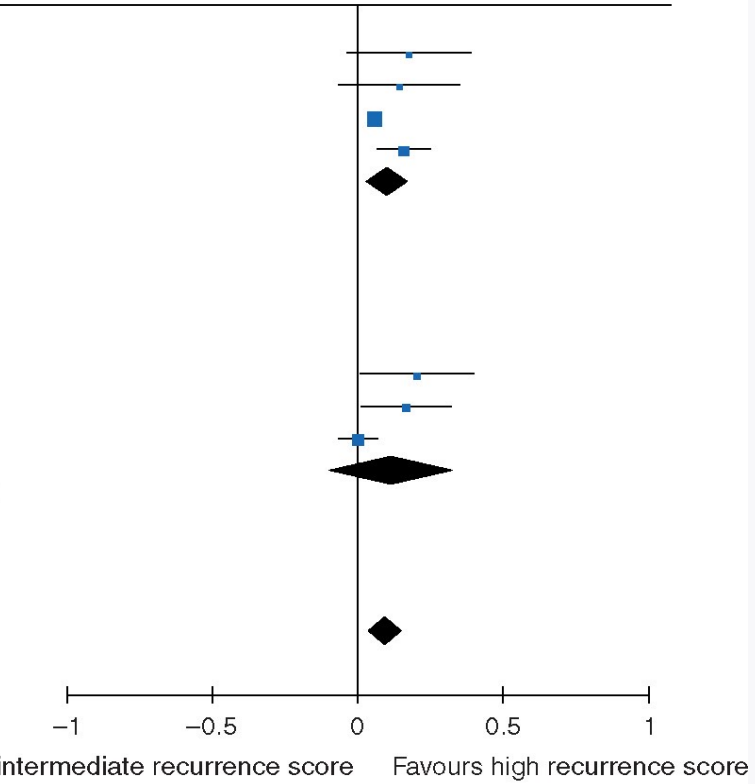
- Updated findings, including 12-year event rates, from the Phase III TAILORx study

- 21-gene RS and neoadjuvant chemotherapy decision making

- Insight regarding poor correlation between the RS and chemotherapy response in premenopausal patients

Meta-analysis: pCR rates in Breast Cancer Patients Receiving Neoadjuvant Chemotherapy stratified based on 21-gene expression assay at diagnosis. Is pCR the best endpoint to determine chemotherapy benefit?

Reference	pCR: High recurrence score	pCR: Low–intermediate recurrence score	Weight(%)	Risk difference
High recurrence score >25				
Zelnak *et al.*[25]	3 of 17	0 of 11	5.9	0.18 (–0.04, 0.39)
Bear *et al.*[29]	2 of 14	0 of 14	6.2	0.14 (–0.07, 0.35)
Kantor *et al.*[26]	47 of 605	15 of 772	30.9	0.06 (0.03, 0.08)
Thekkekara *et al.*[23]	11 of 70	0 of 40	17.8	0.16 (0.07, 0.25)
Subtotal	63 of 706	15 of 837	60.9	0.11 (0.03, 0.18)
Heterogeneity: $\tau^2 = 0.00$ $\chi^2 = 5.75$, 3 d.f., $P = 0.12$; $I^2 = 48\%$				
Test for overall effect: $Z = 2.91$, $P = 0.004$				
High recurrence score >30				
Pivot *et al.*[27]	7 of 24	5 of 57	6.9	0.20 (0.01,0.40)
Yardley *et al.*[24]	4 of 24	0 of 36	9.7	0.17 (0.01, 0.32)
Soran *et al.*[28]	0 of 23	0 of 37	22.5	0.00 (–0.07, 0.07)
Subtotal	11 of 71	5 of 130	39.1	0.11 (–0.10, 0.33)
Heterogeneity: $\tau^2 = 0.03$ $\chi^2 = 14.66$, 2 d.f., $P = 0.001$; $I^2 = 86\%$				
Test for overall effect: $Z = 1.06$, $P = 0.29$				
Total	74 of 777	20 of 967	100.0	0.10 (0.04, 0.15)
Heterogeneity: $\tau^2 = 0.00$ $\chi^2 = 14.00$, 6 d.f., $P = 0.03$; $I^2 = 57\%$				
Test for overall effect: $Z = 3.24$, $P = 0.001$				
Test for subgroup differences: $\chi^2 = 0.01$, 1 d.f., $P = 0.94$; $I^2 = 0\%$				

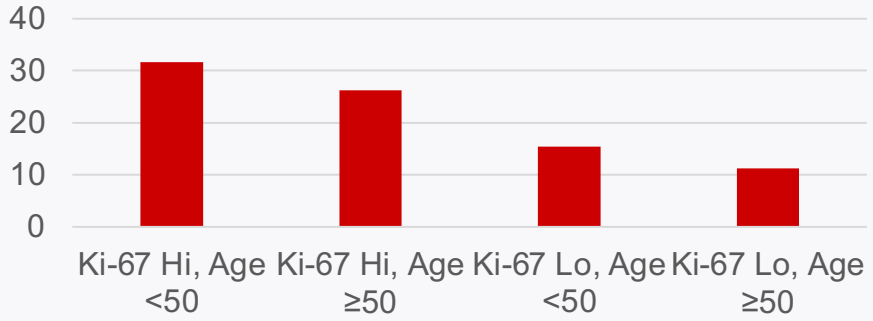


Boland et al. British Journal of Surgery, 2021

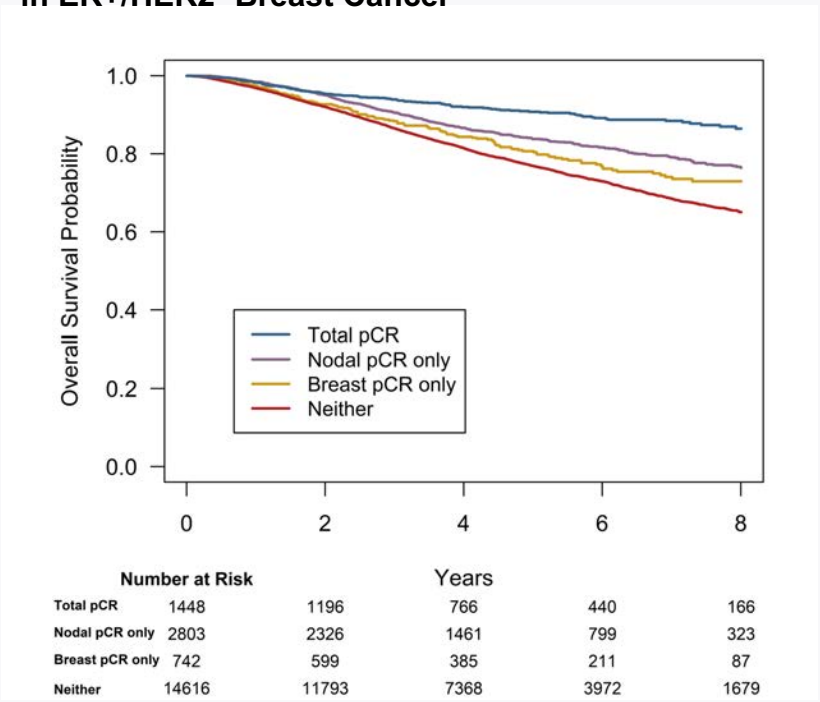
ER+/HER2- Breast Cancer Treated with Neoadjvuant Chemotherapy: Total pCR vs nodal pCR

NCDB: 2010-2018, 20,084 cN+ ER+/HER2- BC pts treated with NAC.

- 7.4% had total pCR
- **14.3% had nodal-only pCR**



Nodal pCR is highly prognostic for survival in ER+/HER2- Breast Cancer



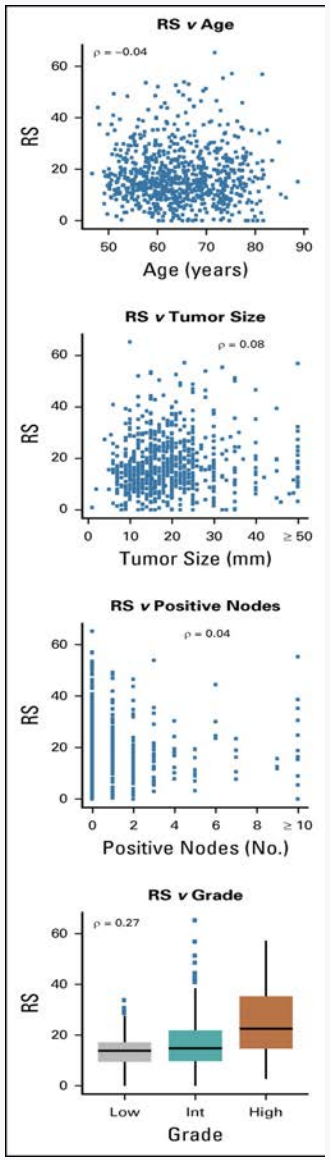
NCDB: Nodal pCR more likely in a) premenopausal pts and b) high Ki-67.

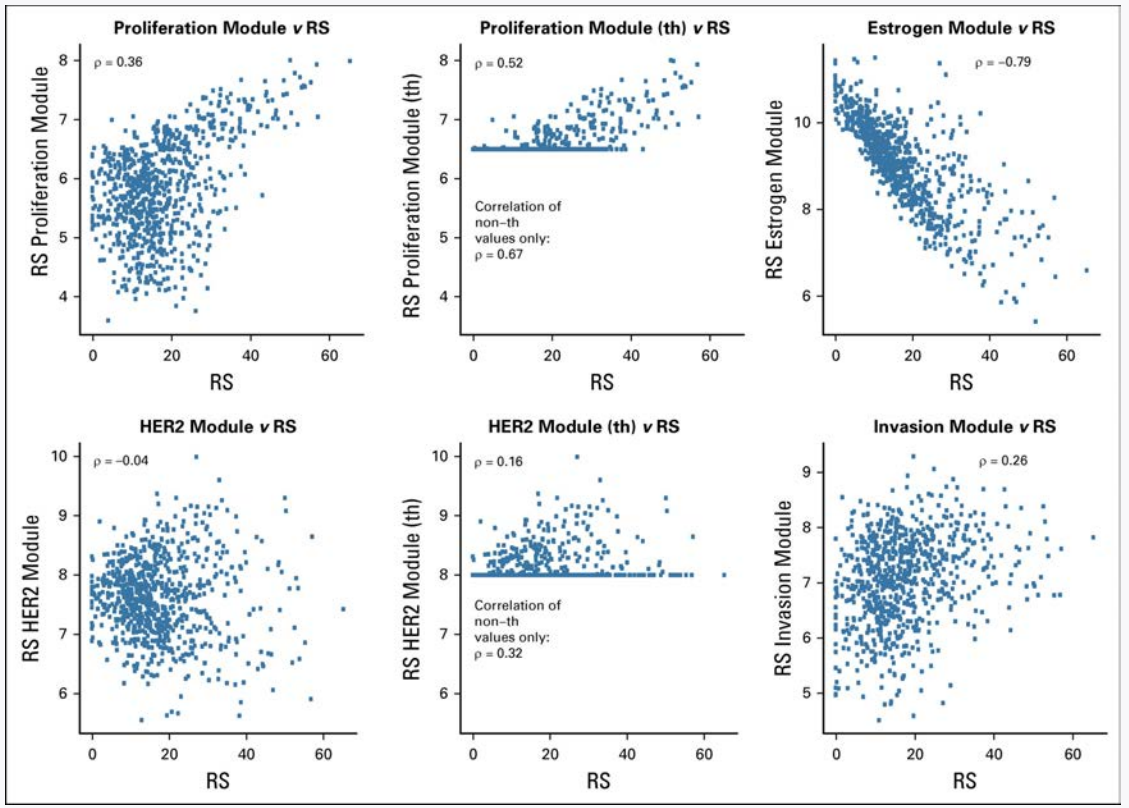
RxPONDER inclusion criteria (cT1-3, N1, Grade I or II, ER+/PR+/Her2-)

- Nodal pCR varied by age: 17.5% in age < 50 vs 13.6% in age ≥ 50, p<0.001
- Nodal pCR also varied by Ki-67: 16.8% in Ki-67 ≥ 20% vs 7.9% in Ki-67 < 20%, p<0.001

Moldovenau et al. SABCS 2022

Molecular Drivers of Oncotype DX, A TransATAC Study: The RS is mainly driven by the Estrogen Module





The estrogen module explained more than half of RS's variance (59.1%), while the proliferation module accounted for approximately a fifth of RS's information (19.4%)

Buus et al. J Clin Oncol 2021

Conclusion

- TAILORx and RxPONDER have provided prospective evidence for lack of adjuvant chemotherapy benefit in postmenopausal patients with RS <25
- In contrast, the RS may not be predictive of chemotherapy benefit in age <50 patients
  - NRG BR009 will provide the definitive answer to this question
- The RS is poorly correlated with the proliferation module but highly correlated with ER
- Additional clinical and pathological biomarkers may provide additional insight into those patients that derive benefit from chemotherapy.

1.Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. Lancet 365:1687-1717, 2005

Appendix – all integrated 12/7/22

Editorial Review

- Major findings from the Phase III RxPONDER trial evaluating the role of chemotherapy for patients with ER-positive, HER2-negative localized breast cancer with 1 to 3 positive lymph nodes and a 21-gene Recurrence Score (RS) of ≤25
  - Slides 3-7 (Outdated – SABCS 2020)
  - Appendix (Note to Dr Goetz: Consider replacing with slides 26-30)
  - Response: This is just fine; Action: RxPONDER 2020 data replaced with appendix data
- Updated findings, including 12-year event rates, from the Phase III TAILORx study
  - Slides 8-13
- Other recent studies informing the use of the 21-gene RS to guide neoadjuvant and adjuvant treatment decision-making
  - Slides 18, 20, 22-23
- Available data sets with and current clinical utility of other genomic assays for ER-positive localized breast cancer
  - Not addressed
  - Appendix (Note to Dr Goetz: Consider adding slides 31-32)
  - Response: This is just fine; Action: ASCO Biomarkers Guidelines moved up from appendix

- **Please be advised that Dr Goetz included slides on SOFT and TEXT (slides 15-18) which is assigned to Dr Kaklamani
  - Response: I believe we should keep these for the following reason. See slide 14. A major question clinicians are asking is why is there chemotherapy benefit in premenopausal but not postmenopausal patients for the same RS. I indicated two hypotheses based on 1) SOFT/TEXT---better endocrine therapy will negate the need for chemotherapy (slide 15/16) and the Oxford overview (slide 17), demonstrating greater benefit of adjuvant chemotherapy especially in young women, regardless of endocrine treatment. I then move to slide 18, to show that this question will be definitively answered by the NRG study

RTP RESEARCH TO PRACTICE