Endocrine Approaches for ER+ Early - Stage Breast Cancer

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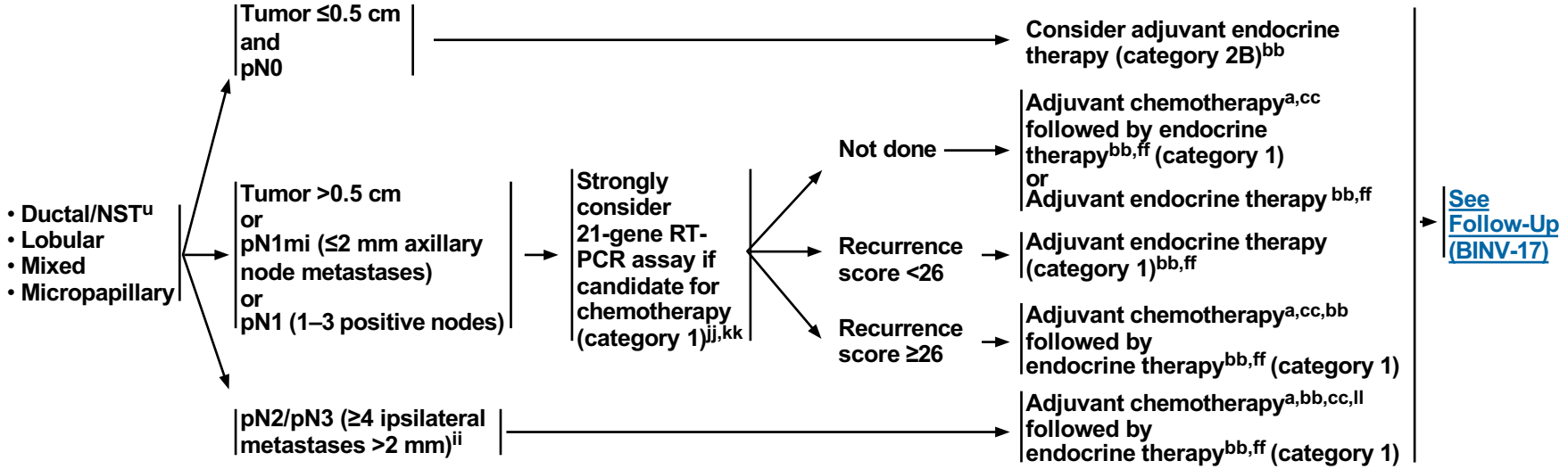
Primo 2023

Outline

- Big Picture
- Update on TAILORx and RxPonder
- SOFT/TEXT, ASTRRA
- MONARCHe
- OlympiA

SYSTEMIC ADJUVANT TREATMENT: HR-POSITIVE - HER2-NEGATIVE DISEASE[d,r,z] POSTMENOPAUSAL[aa] 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).

[r] See Special Considerations for Breast Cancer in Males (Sex Assigned at Birth) (BINV-J).

[u] According to WHO, carcinoma of NST encompasses multiple patterns including medullary pattern, cancers with neuroendocrine expression, and other rare patterns.

[z] Although patients with cancers with 1%–100% ER IHC staining are considered ER-positive and eligible for endocrine therapies, there are more limited data on the subgroup of cancers with ER-low–positive (1%–10%) results. The ER-low–positive group is heterogeneous with reported biologic behavior often similar to ER-negative cancers; thus individualized consideration of risks versus benefits of endocrine therapy and additional adjuvant therapies should be incorporated into decision-making. See Principles of Biomarker Testing (BINV-A).

[aa] See Definition of Menopause (BINV-O).

[bb] See Adjuvant Endocrine Therapy (BINV-K).

[cc] See Preoperative/Adjuvant Therapy Regimens (BINV-L).

[ff] Consider adjuvant bisphosphonate therapy for risk reduction of distant metastasis for 3–5 years in postmenopausal patients (natural or induced) with high-risk node-negative or node-positive tumors.

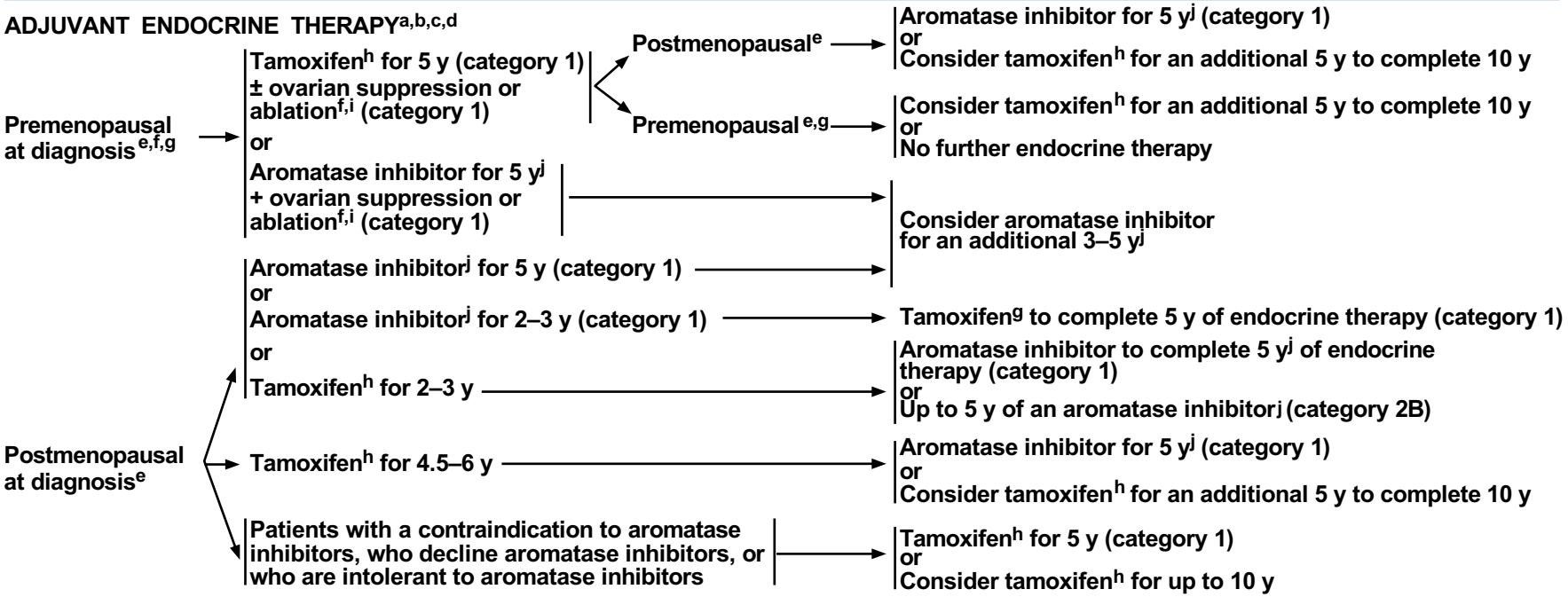
[ii] There are few data regarding the role of gene expression assays in those with ≥4 ipsilateral axillary lymph nodes. Decisions to administer adjuvant chemotherapy for this group should be based on clinical factors.

[jj] Other prognostic gene expression assays may be considered to help assess risk of recurrence but have not been validated to predict response to chemotherapy. See Gene Expression Assays for Consideration of Adjuvant Systemic Therapy (BINV-N).

[kk] Patients with T1b tumors with low-grade histology and no LVI should be treated with endocrine monotherapy as the TAILORx trial did not include patients with such tumors.

[ll] Addition of 1 year of adjuvant olaparib is an option for select patients with germline *BRCA1/2* mutation after completion of adjuvant chemotherapy. See BINV-L.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[a] If patient is not postmenopausal, sequential evaluation of hormonal status is recommended to consider an alternative endocrine agent.

[b] Baseline assessment of bone density recommended for patients receiving an aromatase inhibitor who are at risk of osteoporosis (eg, age >65, family history, chronic steroids).

[c] The use of a bisphosphonate (oral/IV) or denosumab is acceptable to maintain or to improve bone mineral density and reduce risk of fractures in postmenopausal (natural or induced) patients receiving adjuvant aromatase inhibitor therapy.

[d] In patients with HR-positive/HER2-negative, high-risk breast cancer (ie, those with ≥4 positive lymph nodes (confimed preoperatively and/or at surgery), or 1–3 positive lymph nodes with one or more of the following: grade 3 disease, tumor size ≥5 cm (on pre-operative imaging and/or at surgery), or a Ki-67 score of ≥20%) 2 years of adjuvant abemaciclib can be considered in combination with endocrine therapy. In patients eligible for both adjuvant olaparib and abemaciclib, the optimal sequence is not known.

[e] See Definition of Menopause (BINV-O).

[f] Evidence suggests that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal patients with HR-positive breast cancer is similar to that achieved with CMF alone.

[g] Safety data support administration of GnRH agonists before or with chemotherapy, especially if there is a goal to enhance fertility preservation. They can also be initiated after chemotherapy in patients who remain premenopausal.

[h] Some SSRIs like fluoxetine and paroxetine decrease the formation of endoxifen, 4-OH tamoxifen, and active metabolites of tamoxifen, and may impact its efficacy. Caution is advised about coadministration of these drugs with tamoxifen. However, SNRIs (citalopram and venlafaxine) appear to have minimal impact on tamoxifen metabolism. At this time, based on current data the panel recommends against *CYP2D6* gene testing for patients being considered for tamoxifen therapy.

[i] A balanced discussion of the risks and benefits associated with ovarian suppression therapy is critical, including the potential side effects of premature menopause. Aromatase inhibitor or tamoxifen for 5 y plus ovarian suppression should be considered, based on SOFT and TEXT clinical trial outcomes, for premenopausal patients at higher risk of recurrence (ie, young age, high-grade tumor, lymph node involvement).

[j] The three selective aromatase inhibitors (ie, anastrozole, letrozole, exemestane) have shown similar anti-tumor efficacy and toxicity profiles in randomized studies in the adjuvant and preoperative settings. The optimal duration of aromatase inhibitors in adjuvant therapy is uncertain. Patients with lymph node involvement may benefit from extended aromatase inhibitor duration (7.5–10 years total).

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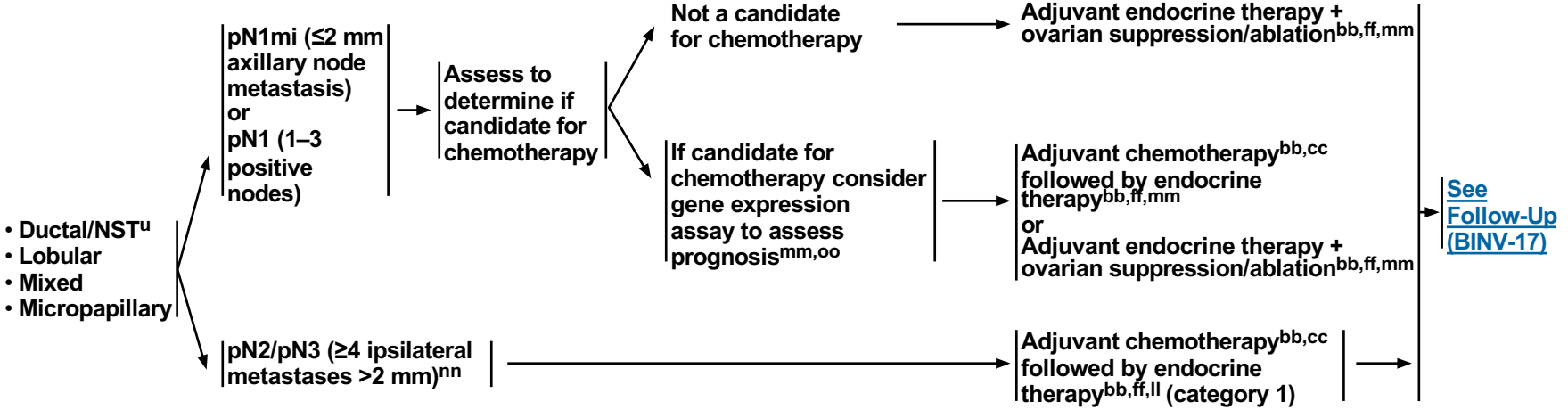

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[ff] Consider adjuvant bisphosphonate therapy for risk reduction of distant metastasis for 3–5 years in postmenopausal patients (natural or induced) with high-risk node-negative or node-positive tumors.
[ll] Addition of 1 year of adjuvant olaparib is an option for select patients with germline *BRCA1/2* mutation after completion of adjuvant chemotherapy. See BINV-L.
[mm] In premenopausal patients with RS <26, the addition of chemotherapy to endocrine therapy was associated with a lower rate of distant recurrence compared with endocrine monotherapy, but it is unclear if the benefit was due to the ovarian suppression effects promoted by chemotherapy.
[nn] There are few data regarding the role of gene expression assays in those with ≥4 ipsilateral axillary lymph nodes. Decisions to administer adjuvant chemotherapy for this group should be based on clinical factors.
[oo] See Gene Expression Assays for Consideration of Adjuvant Systemic Therapy (BINV-N).

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MOLECULAR ASSAYS FOR DECISION MAKING

TAILORx Methods: 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)

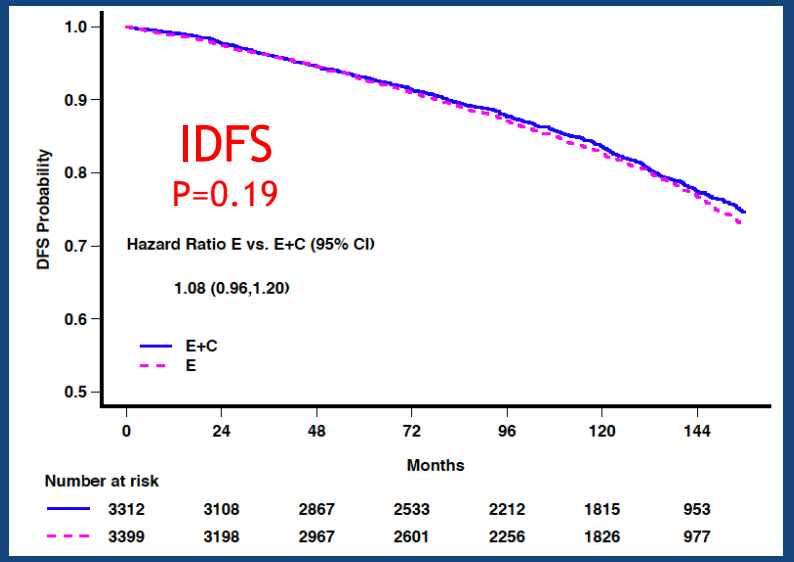
Mid-Range RS 11-25
(N=6711 evaluable)
RANDOMIZE
Stratification Factors: Menopausal Status, Planned Chemotherapy, Planned Radiation, and RS 11-15, 16-20, 21-25

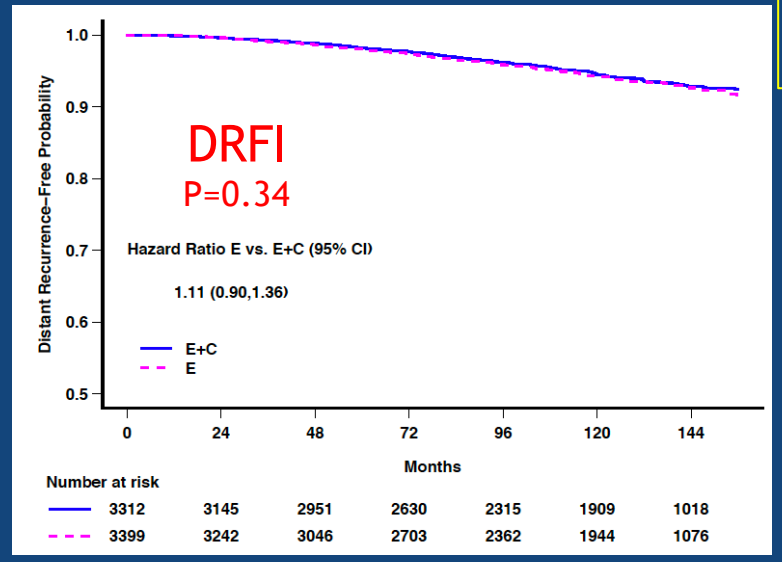
ARM D: High RS 26-100
(N=1389 evaluable)
ASSIGN
ET + Chemo

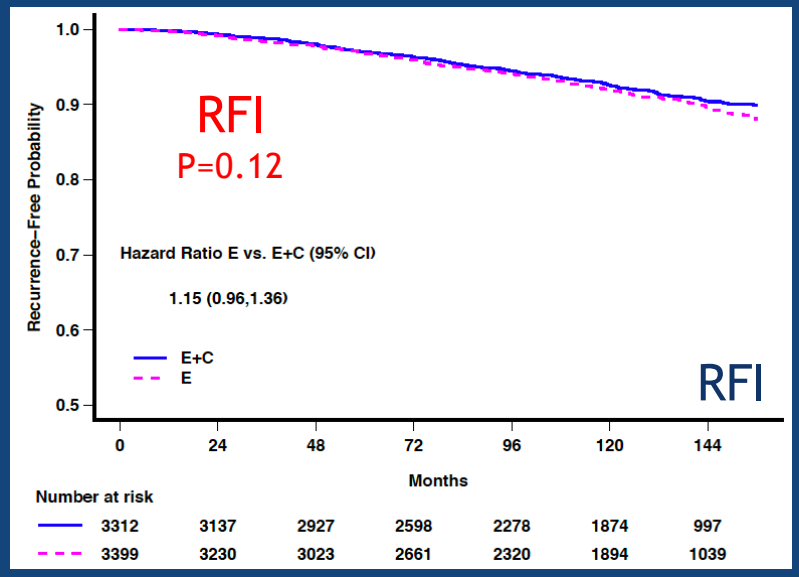
ARM B: Experimental Arm
(N=3399)
ET Alone

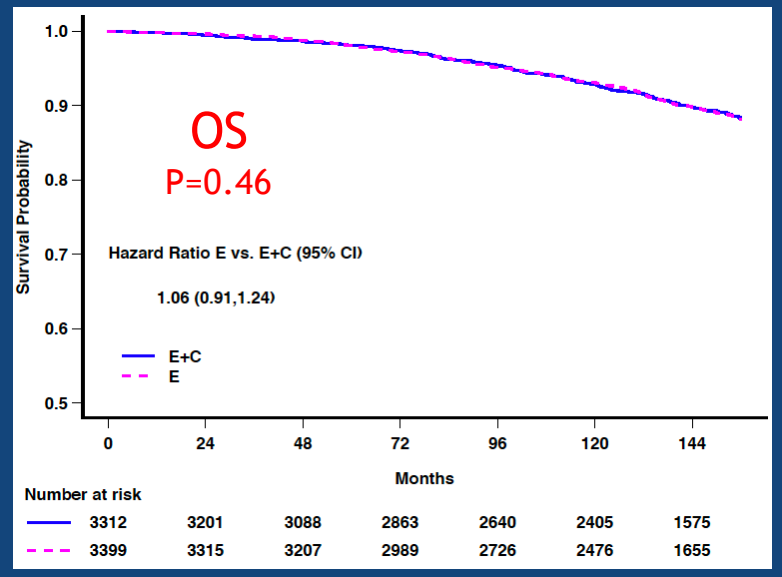
ARM C: Standard Arm
(N=3312)
ET + Chemo

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







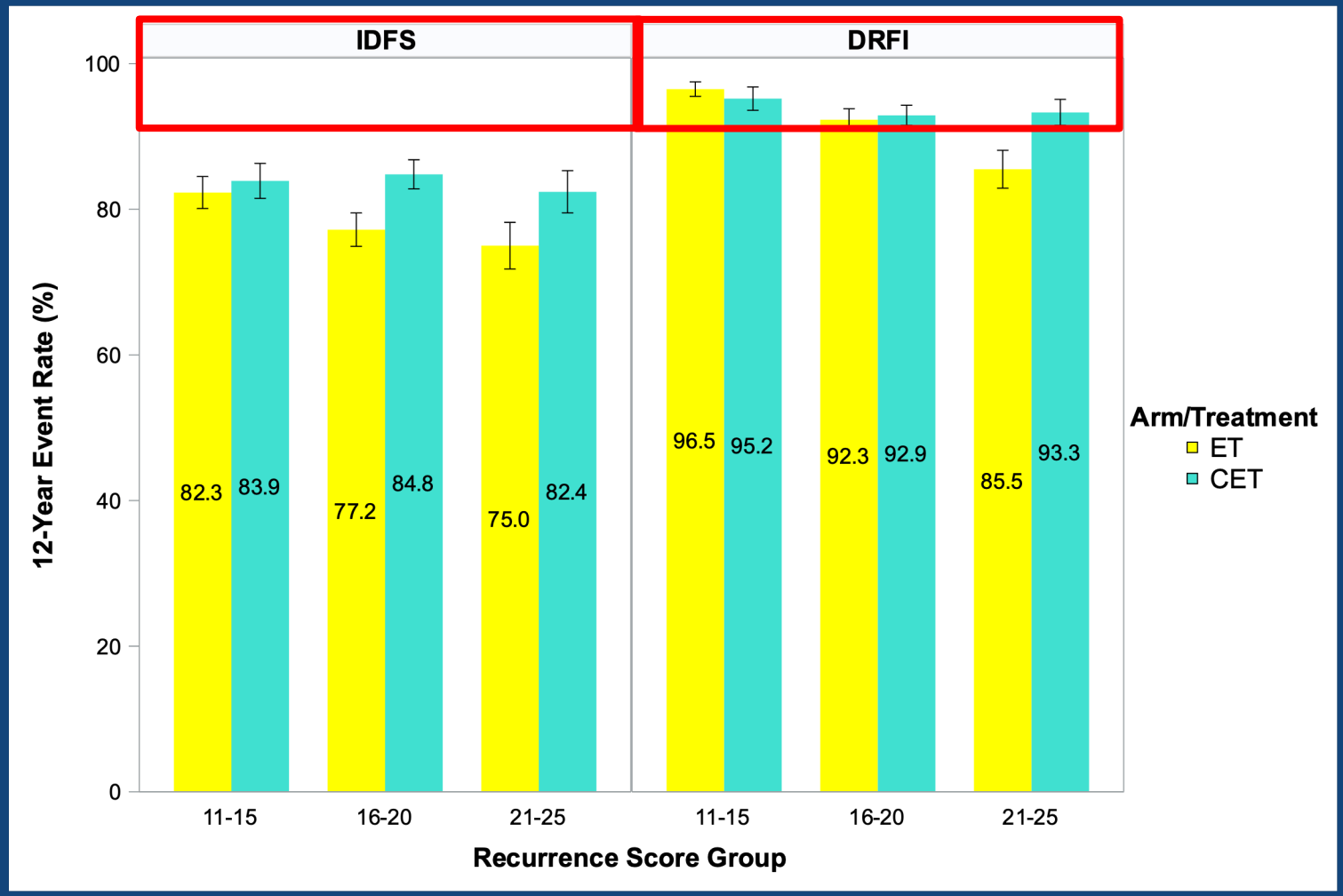


Primary trial conclusions unchanged:
ET non-inferior to CET (N=6711)

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

- No chemo benefit for RS 11-15
- Marginal benefit for RS 16-20
- Evident benefit for RS 21-25



RxPONDER (ER+ N1 RS 0-25): Efficacy IDFS by Menopausal Status[1]

RxPONDER Schema

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

Recurrence Score >25 → **Off study** Chemotherapy followed by ET recommended

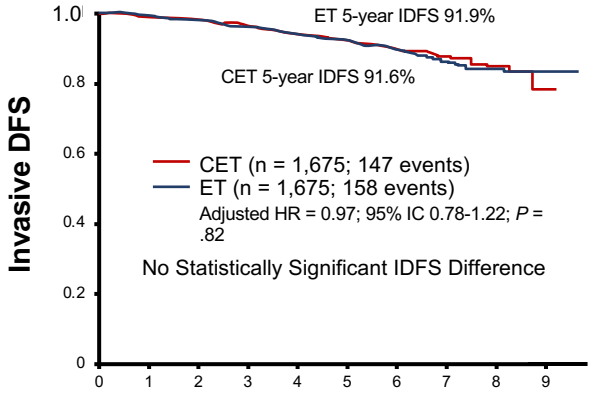
Recurrence Score 0-25 → R → N = 5,000

- **ARM 1** Chemotherapy followed by ET
- **ARM 2** ET alone

Stratified by
- Recurrence score: 0-13 vs 14-25
- Menopausal status: pre vs post
- Axillary surgery: ALND vs SLNB

IDFS Stratified by Menopausal Status

Postmenopausal

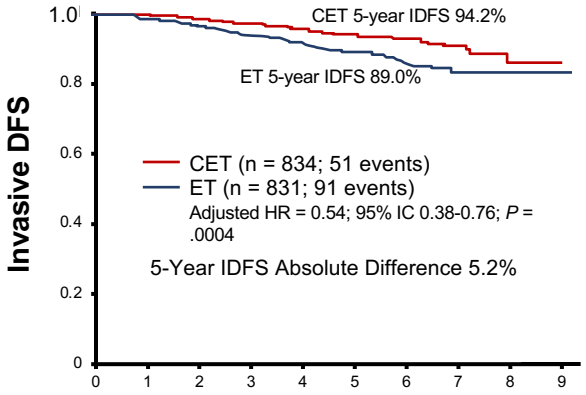


No. at Risk

CET	1,675	1,514	1,400	1,268	1,113	943	585	287	88	3
ET	1,675	1,567	1,462	1,308	1,167	975	601	298	104	9

No statistically significant difference

Premenopausal



No. at Risk

CET	834	763	704	625	535	454	272	116	34	1
ET	831	760	699	602	529	429	245	99	31	2

Significant absolute difference in distant recurrences 2.9% (3.1% CET vs 6% ET), though too few events to interpret statistically

RxPONDER Schema

Key Entry Criteria

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

REGISTRATION

Recurrence Score 0-25

Recurrence Score > 25

Off Study
Chemotherapy Followed by
Endocrine Therapy Recommended

RANDOMIZATION

N = 5,000 pts

Arm 1:
Chemotherapy Followed by
Endocrine Therapy

Arm 2:
Endocrine Therapy Alone

Stratification Factors
Recurrence Score: 0-13 vs.14-25
Menopausal Status: pre vs. post
Axillary Surgery: ALND vs. SLNB

Baseline Characteristics by Treatment Arm

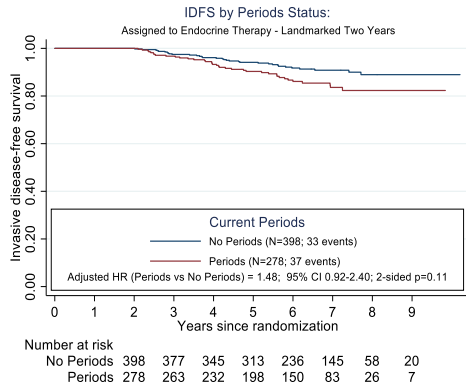
Baseline variable	Endocrine Therapy (n=2,506)	Chemotherapy (n=2,509)	Overall (n=5,015)
Menopausal status			
Premenopausal	33.2%	33.2%	33.2%
Postmenopausal	66.8%	66.8%	66.8%
Recurrence Score			
RS 0-13	42.7%	42.9%	42.8%
RS 14-25	57.3%	57.1%	57.2%
Nodal Dissection			
Full ALND	62.7%	62.5%	62.6%
Sentinel nodes only	37.4%	37.5%	37.4%
Positive Nodes			
1 node	65.9%	65.0%	65.5%
2 nodes	24.9%	25.7%	25.3%
3 nodes	9.2%	9.2%	9.2%
Grade			
Low	24.6%	24.7%	24.7%
Intermediate	64.1%	66.1%	65.1%
High	11.3%	9.2%	10.3%
Tumor size			
T1	58.5%	57.7%	58.1%
T2/T3	41.5%	42.3%	41.9%

Update on RxPONDER (SWOG1007): Who needs chemo?

- **Study design:** For patients with HR+/HER2- BC, 1-3 pos LN, Oncotype RS 0-25, is chemotherapy beneficial? Randomized pts to chemo + ET or ET alone
- **Results:** Chemotherapy benefit differed by menopausal status:
  - Postmenopausal: No benefit from chemotherapy in iDFS or DRFS
  - Premenopausal: All pts benefit from chemotherapy
- **Issue:**
  - For endocrine therapy, **75% received tamoxifen alone, only 17% had OFS**

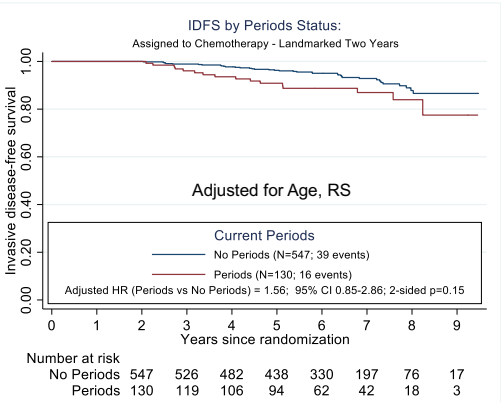
In a Landmarked Two-Year Analysis, No Longer Having Regular Periods Numerically Improved IDFS in Premenopausal Women

Endocrine Tx Alone (n=676)



No Regular Periods in 24 months = 58.9%

Chemo then Endocrine Tx (N=677)



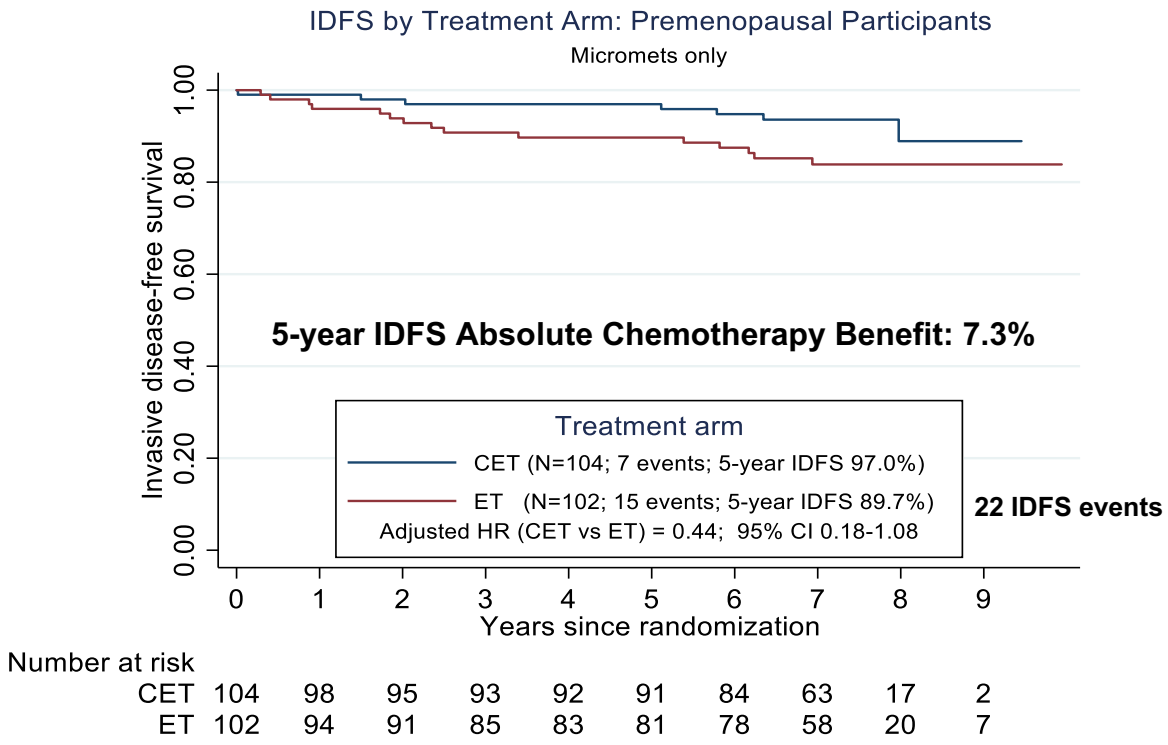
No Regular Periods in first 24 months = 80.8%

No Regular Menstrual Periods = At least two 6-month time periods in first 24 months

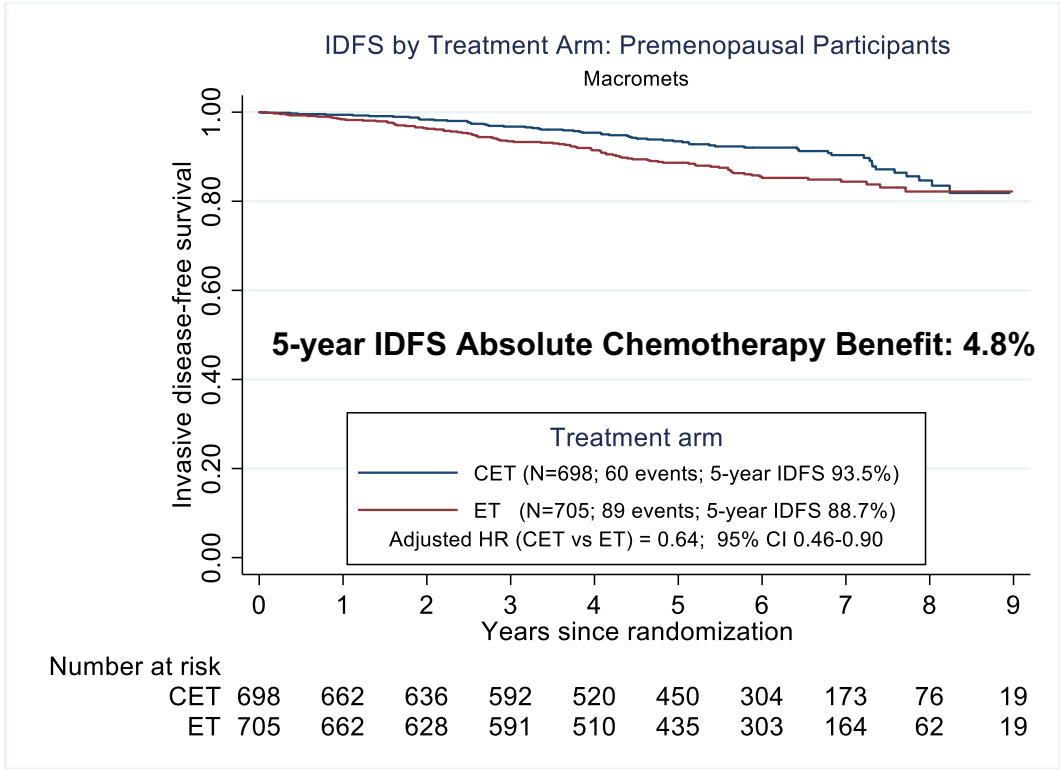
Kalinsky K et al *N Engl J Med*. 2021;
Cardoso et al, ASCO 2020,;
Piccart et al, Lancet Oncol 2021;
Kalinsky SABCS 2021

Premenopausal Women with p1Nmi and pN1 Benefit from Chemotherapy

pN1mi (N=206)



pN1 (N=1403)

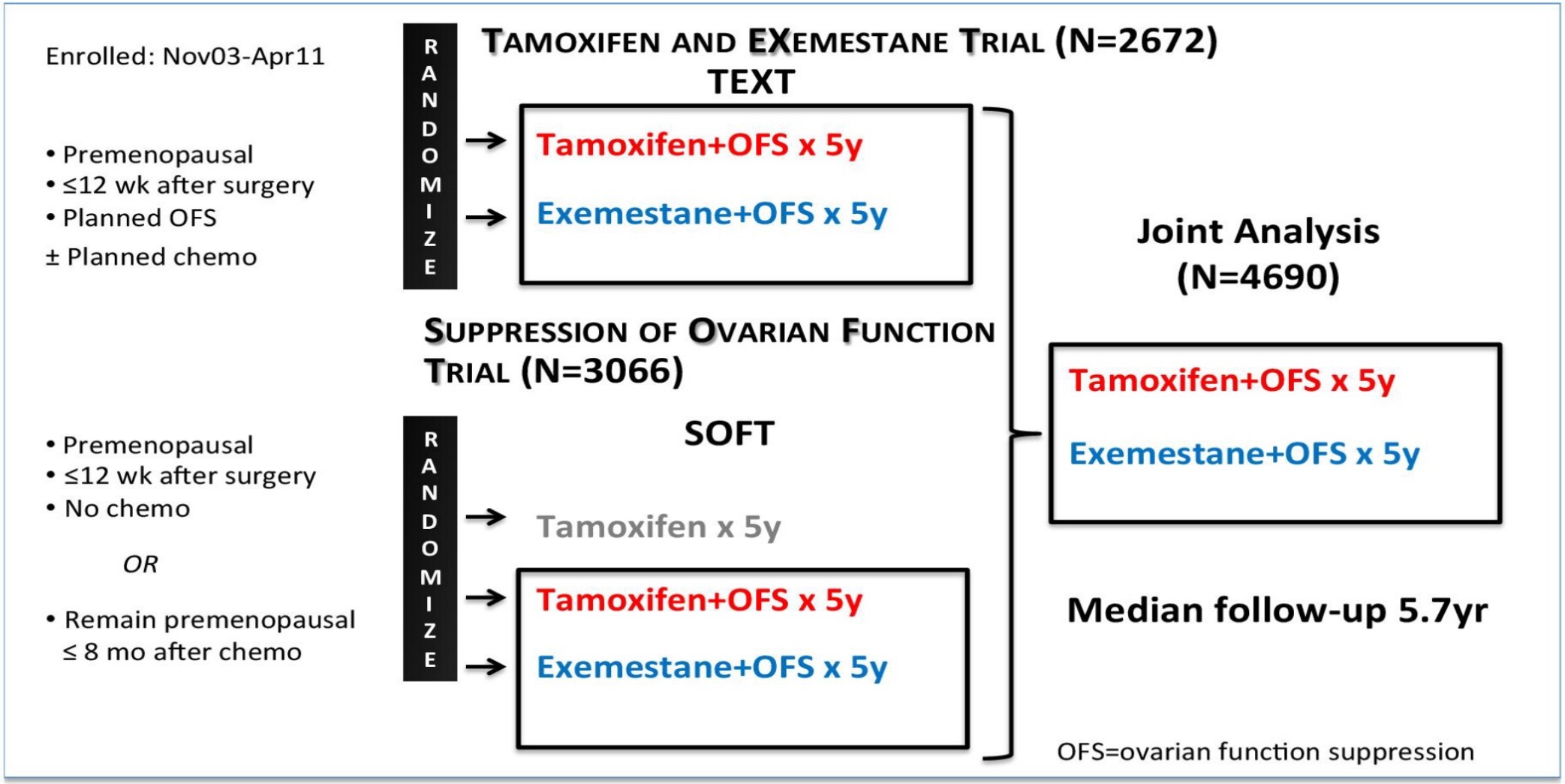


Prior to the amendment, 206/738 (27.9%) eligible premenopausal pts had micrometastases only and 45 pts (6%) unknown

Cox regression test for interaction of chemotherapy with micrometastases p= 0.40

Kalinsky K, et al. *N Engl J Med.* 2021;385:2336-47.

Text and Soft Joint Analysis

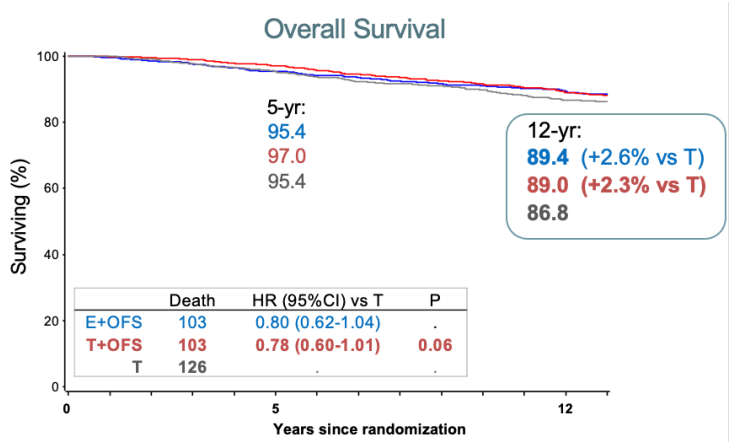


Update on SOFT and TEXT Trials: What is the role of OFS?

- **Study design:** Trials launched in 2003 to evaluate:
  - Is there a benefit of adding OFS to tamoxifen, in particular for pre-menopausal women (SOFT)
  - When OFS is given, is there a benefit of aromatase inhibitor vs. tamoxifen (SOFT and TEXT)
- **Previous results at 5 and 8 yrs median FU:**
  - Addition of OFS to tamoxifen reduces recurrence and death
  - Further reduction of distant recurrence, but not death, with exemestane + OFS vs. tamoxifen + OFS
  - Absolute benefit varies depending on underlying risk of recurrence; Tamoxifen alone sufficient for low risk
- **SABCS 2022: Planned update focusing on DR and OS**
  - Median FU of SOFT and TEXT was 12 and 13 years
  - 76% patients alive & in FU

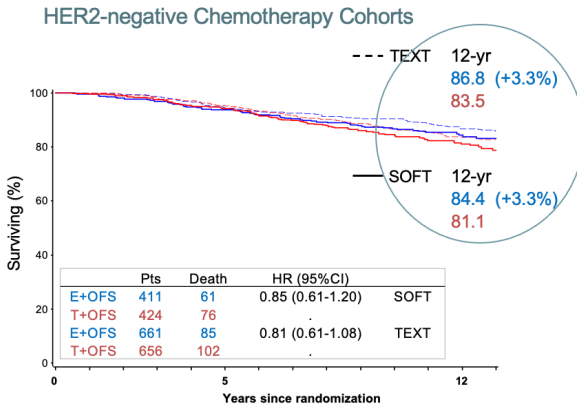
SOFT: Overall survival

- OFS adds to either tam (2.3%) or exe (2.6%)
- Benefit limited to high risk/prior chemo
- More substantial benefit (~10%) for those at higher clinical risk



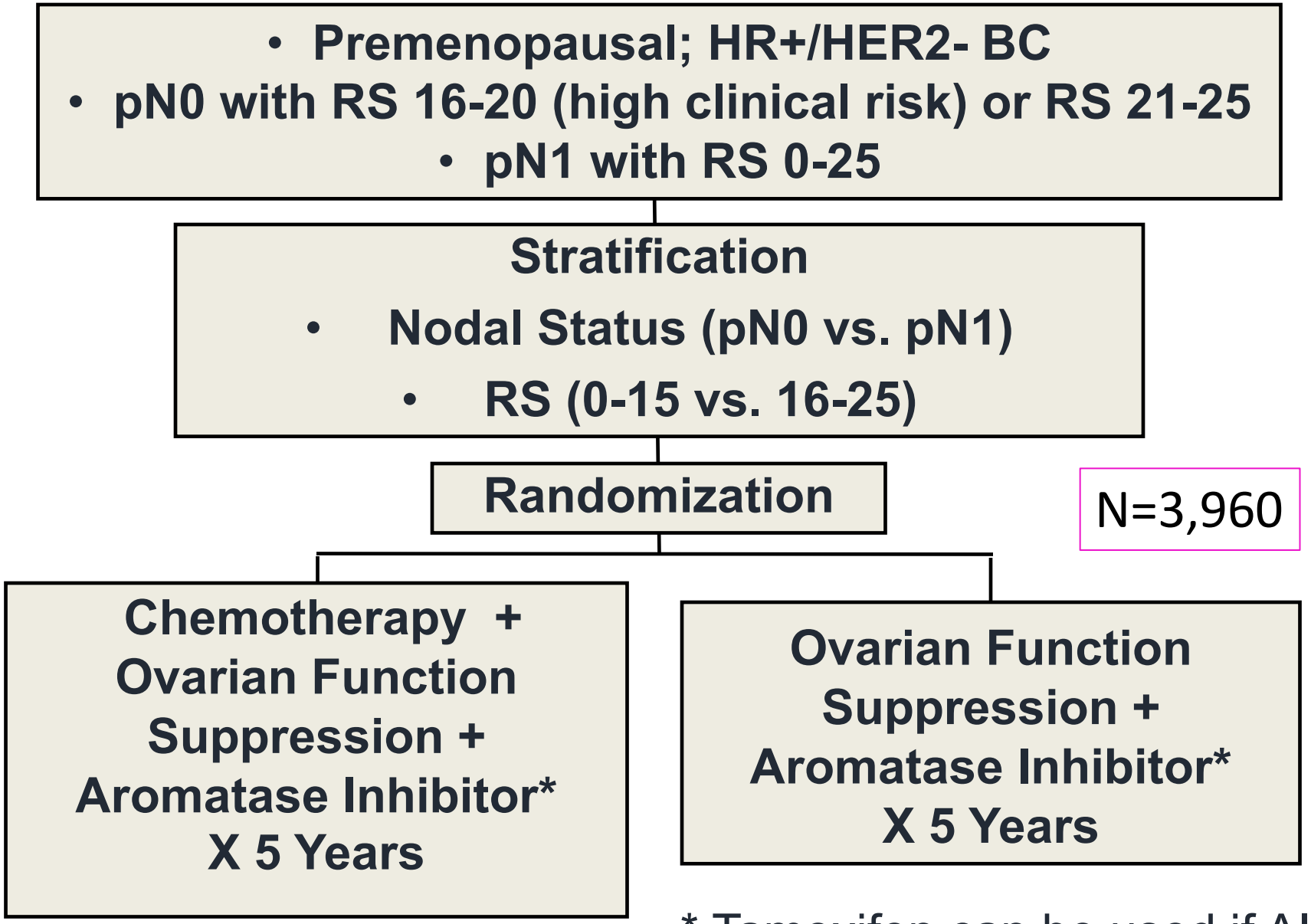
SOFT + TEXT: OS in chemo cohort

- E + OFS survival benefit (3.3%) over T+OFS



Regan et al SABCS 2021

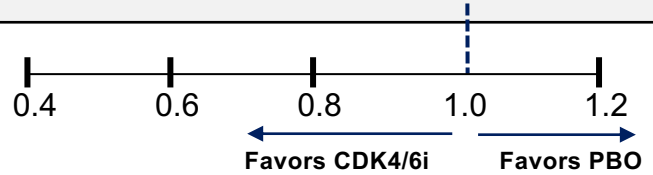
BR009: Schema



* Tamoxifen can be used if AI is not tolerated

Summary of CDK 4/6 inhibitors in the adjuvant setting

		2 year iDFS rate		3 year iDFS rate		iDFS Hazard ratio	Hazard ratio (95% CI)	*P* value	Significance reached vs placebo[a]
		Treatment arm	Placebo arm	Treatment arm	Placebo arm				
PAL	PALLAS[1]	93.9%	93.0%	89.3%	89.4%		0.96 (0.81-1.14)	0.65	✗
PAL	PENELOPE-B[2]	88.3%	84.0%	81.2%	77.7%		0.93 (0.74-1.17)	0.53	✗
ABE	MonarchE [3,b]	92.7%	90.0%	88.8%	83.4%		0.70 (0.59-0.82)	<0.0001	✓
RIBO	NATALEE	Not yet reported							



Comparisons between trials cannot be made in the absence of well-controlled, head-to-head studies.

1. Gnant M, et al. *J Clin Oncol*. 2022
2. Loibl S, et al. *J Clin Oncol*. 2021
3. Harbeck N, et al. *Ann Oncol*. 2021

monarchE Study Design (NCT03155997)

HR+, HER2-, node positive high-risk EBC

- Women or men
- Pre-/postmenopausal
- With or without prior neo- and/or adjuvant chemotherapy
- No metastatic disease
- Maximum of 16 months from surgery to randomization and 12 weeks of ET following the last non-ET

Cohort 1: High risk based on **clinical pathological features**

- ≥4 ALN OR
- 1-3 ALN and at least 1 of the below:
  - Grade 3 disease
  - Tumor size ≥5 cm

Cohort 2: High risk based on **Ki-67**

- 1-3 ALN and
- Ki-67 ≥20% and
- Grade 1-2 and tumor size <5 cm

Stratified for:

- Prior chemotherapy
- Menopausal status
- Region

R 1:1
N = 5637

On-study treatment period
2 years

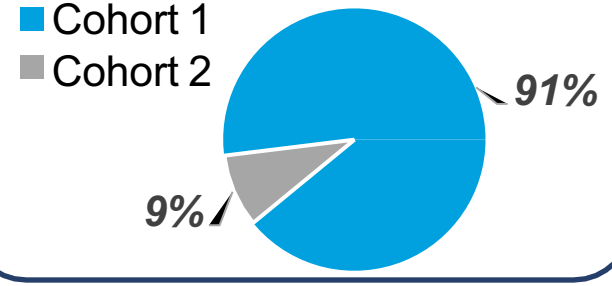
Abemaciclib
(150mg twice daily)
+
Endocrine Therapy: AI or tamoxifen

Endocrine Therapy: AI or tamoxifen

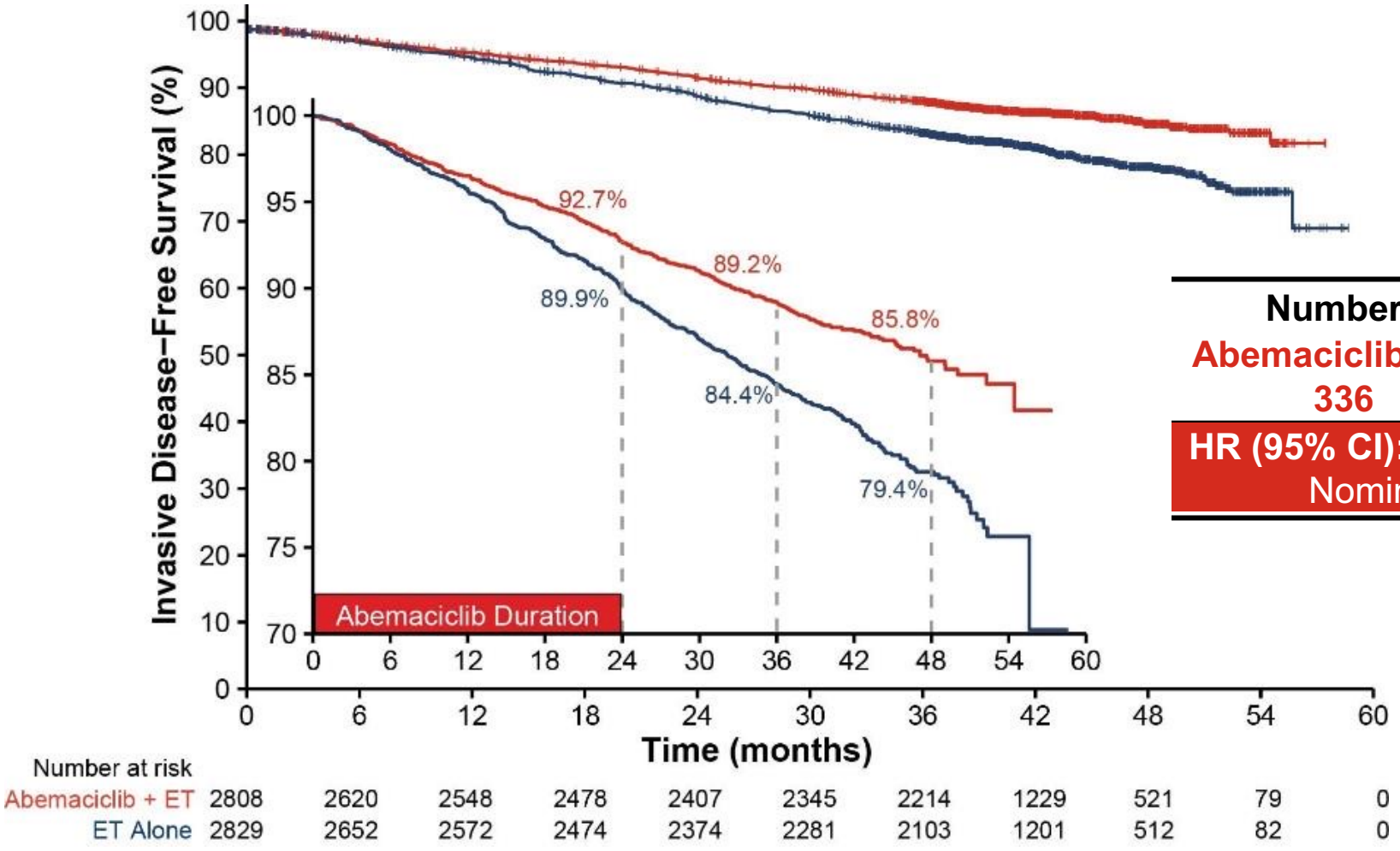
Follow-up period
Endocrine Therapy
3-8 years as clinically indicated

Primary Objective: IDFS
Secondary Objectives: IDFS in high Ki-67 populations, DRFS, OS, Safety, PK, PRO

ITT Population



IDFS Benefit in ITT Persists Beyond Completion of Abemaciclib



Number of IDFS events	
Abemaciclib + ET	ET Alone
336	499

HR (95% CI): 0.664 (0.578, 0.762)
Nominal p < 0.0001

33.6% reduction in the risk of developing an IDFS event with an increase in absolute benefit in IDFS 4-year rates (6.4%) compared to 2-and 3-year IDFS rates (2.8% and 4.8% respectively)

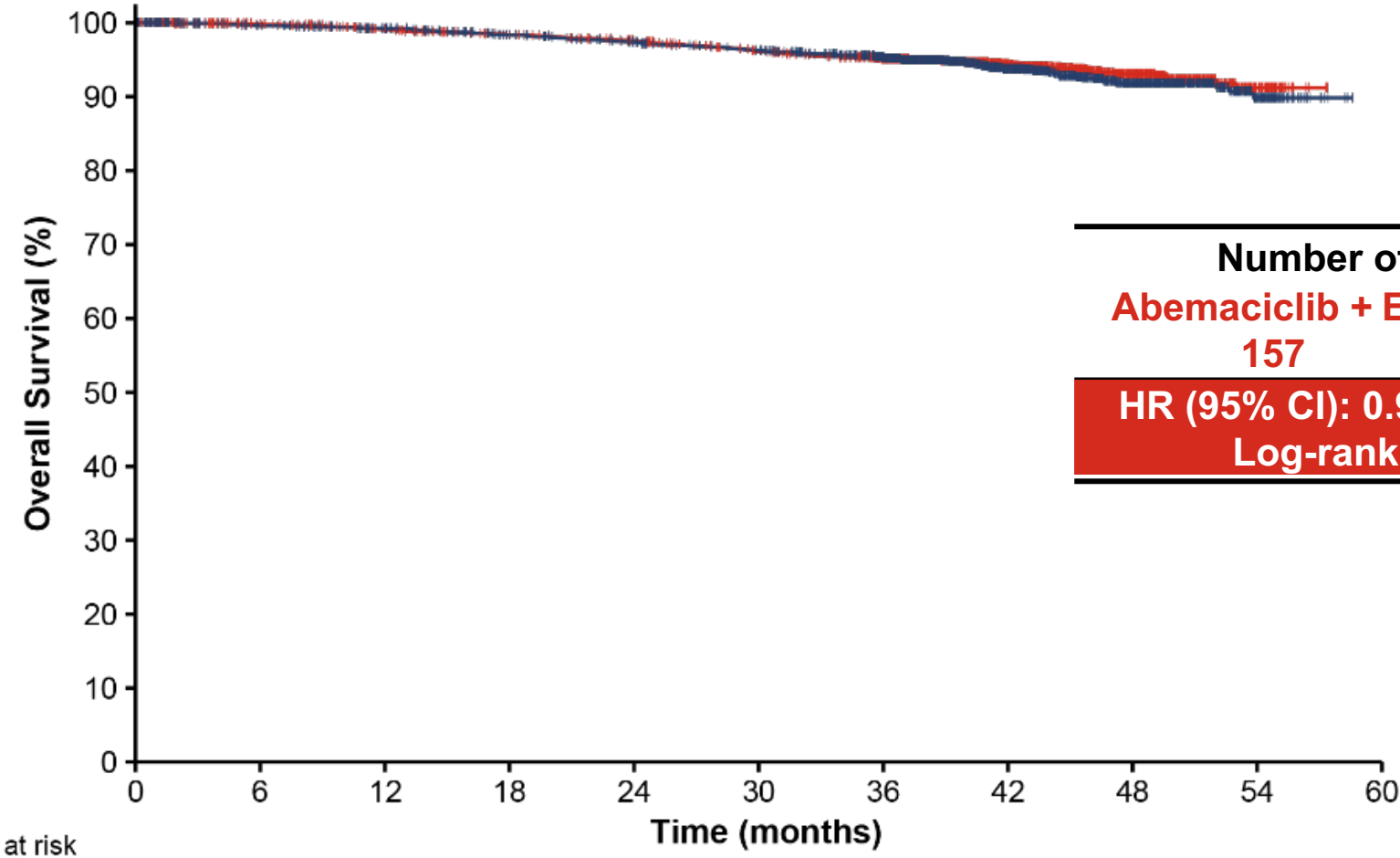
Abemaciclib Treatment Benefit Deepened Over Time

Analysis landmark	IDFS	DRFS
	Piecewise HR[a] (95% CI[b])	Piecewise HR[a] (95% CI[b])
Year 0-1	0.782 (0.583, 1.018)	0.725 (0.519, 0.983)
Year 1-2	0.674 (0.521, 0.858)	0.691 (0.521, 0.887)
Year 2-3	0.618 (0.477, 0.788)	0.651 (0.497, 0.851)
Year 3+	0.602 (0.428, 0.803)	0.581 (0.391, 0.818)

Study Treatment Period

[a]Piecewise hazard ratio as a post-hoc analysis was estimated using piecewise exponential model to assess the yearly treatment effect size;
[b]95% credible intervals were calculated by equal tails in the posterior samples of Bayesian exponential models

OS Data Remain Immature in ITT



Number of OS events

Abemaciclib + ET	ET Alone
157	173

HR (95% CI): 0.929 (0.748, 1.153)
Log-rank P = 0.5027

Fewer deaths (157 vs 173) were observed in the abemaciclib plus ET group versus the ET group

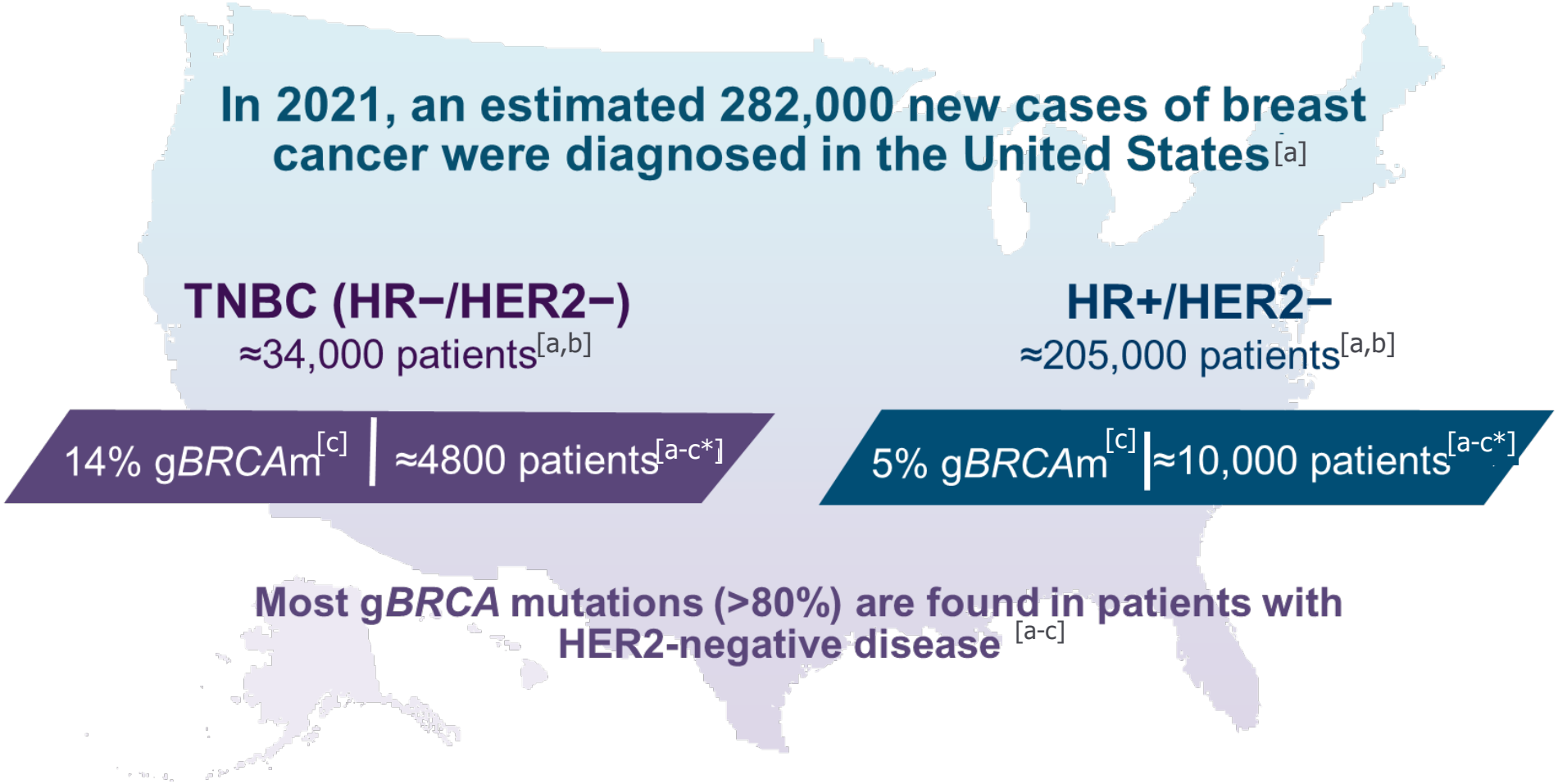
U.S. FDA Approval and ASCO/NCCN Adjuvant Chemotherapy and Targeted Therapy Guideline Rapid Recommendation Update

- 10/12/21: FDA approval
  - Abemaciclib + tamoxifen or an aromatase inhibitor for adjuvant treatment of HR+/HER2-, N+, early BC at high risk of recurrence and Ki-67 score ≥20% (by an FDA approved test)
  - The FDA also approved the Ki-67 IHC MIB-1 pharmDx (Dako Omnis; Agilent) assay as a companion diagnostic for selecting patients for abemaciclib

- ASCO/NCCN Guidelines
  - Strong recommendation for 2 years of abemaciclib (150 mg BID) + ET for HR+, HER2-, N+ early BC with a high risk of recurrence and a Ki-67 score of ≥ 20% as determined by an FDA-approved test
  - Strong recommendation for 2 years of abemaciclib + ET for ≥ 5 years for the broader population of patients with resected, HR+, HER2-, N+ early BC at high risk of recurrence, defined as:
    - ≥ 4+ ALNs OR 1-3+ ALNs PLUS grade 3 disease, tumor size ≥ 5 cm, or Ki-67 index ≥ 20%

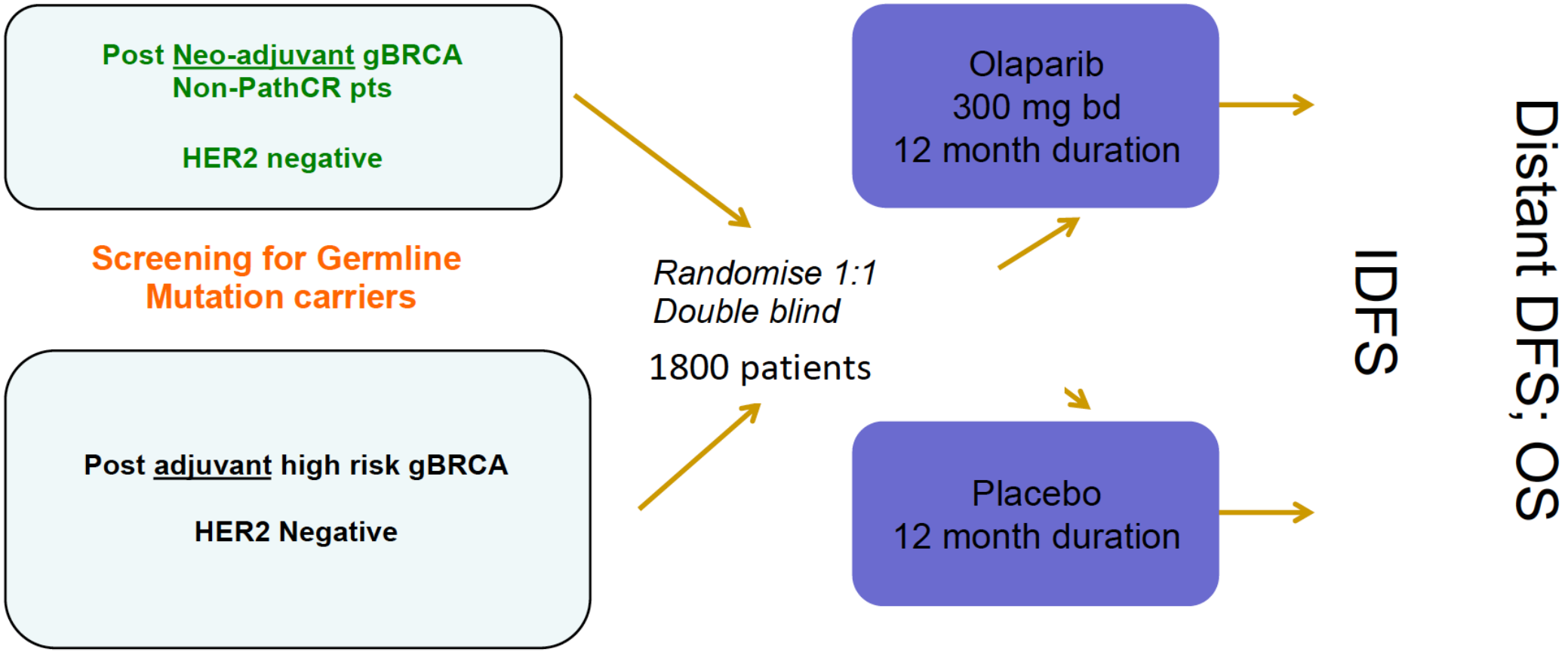
Giordano et al. *JCO*. 2022

gBRCA Mutations May Occur in Both HR-Positive/HER2−Negative and TNBC Subtypes



- Statistics shown on slide are from female breast cancer.
- *This number was derived from a study of biomarker prevalence in 488 patients with breast cancer between 2010 and 2012.
- HER2, human epidermal growth factor receptor 2; HR, hormone receptor; TNBC, triple negative breast cancer.
- a. National Cancer Institute (NCI). https://seer.cancer.gov/statfacts/html/breast-subtypes.html. Accessed May 6, 2021;
  b. Howlader N, et al. J Natl Cancer Inst. 2014;106; c. Tung N, et al. J Clin Oncol. 2016;34:1460-1468.

PARP Inhibitors: Role in the Adjuvant Setting?



- ClinicalTrials.gov. Accessed October 16, 2022. https://clinicaltrials.gov/ct2/show/NCT02000622.

OlympiA:
Patient Characteristics (cont)

	Olaparib (N = 921)	Placebo (N = 915)
Hormone receptor status*		
Hormone receptor ≥ 1% / HER2-†	168 (**18.2%**)	157 (**17.2%**)
Triple Negative Breast Cancer‡	751 (**81.5%**)	758 (**82.8%**)
Menopausal status (female only)		
Premenopausal	572/919 (62.2%)	553/911 (60.7%)
Postmenopausal	347/919 (37.8%)	358/911 (39.3%)
Prior chemotherapy		
Adjuvant (ACT)	461 (**50.1%**)	455 (**49.7%**)
Neoadjuvant (NACT)	460 (**49.9%**)	460 (**50.3%**)
Anthracycline and taxane regimen	871 (**94.6%**)	849 (**92.8%**)
Neo(adjuvant) platinum-based therapy	247 (**26.8%**)	239 (**26.1%**)
Concurrent endocrine therapy (HR–positive only)	146/168 (86.9%)	142/157 (90.4%)

- *Defined by local test results. †Following a protocol amended in 2015, the first patient with hormone receptor-positive disease was enrolled in December 2015. ‡2 patients are excluded from the summary of the triple negative breast cancer subset because they do not have confirmed HER2-negative status.
- Tutt A, et al. J Clin Oncol. 2021;39(suppl 15):abstr LBA1.

OlympiA:

Pathological Characteristics

CPS+EG score* (Neoadjuvant only)

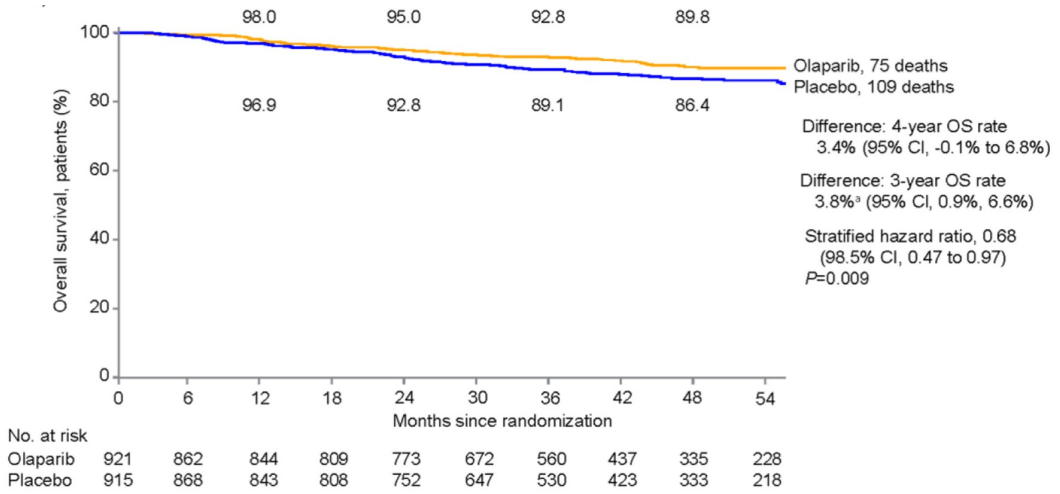
	Olaparib (n = 460)	Placebo (n = 460)
HR+/HER2-		
CPS+EG score ≤2†	13 (2.8%)	6 (1.3%)
CPS+EG score of 3 or 4	**88 (19.1%)**	**85 (18.5%)**
CPS+EG score of 5 or 6	3 (0.7%)	1 (0.2%)
Not recorded	0 (0.0%)	0 (0.0%)
Triple Negative Breast Cancer		
CPS+EG score ≤2	**151 (32.8%)**	**144 (31.3%)**
CPS+EG score of 3 or 4	**179 (38.8%)**	**197 (42.8%)**
CPS+EG score of 5 or 6	19 (4.1%)	14 (3.0%)
Not recorded	7 (1.5%)	13 (2.8%)

- *CPS + EG score is a staging system for disease-specific survival in patients with breast cancer treated with neoadjuvant chemotherapy incorporating pretreatment clinical stage, estrogen receptor status, nuclear grade and post-neoadjuvant chemotherapy pathological stage. †Reported as protocol deviations.
- a. Tutt A, et al. J Clin Oncol. 2021;39(suppl 15):abstr LBA1; b. Mittendorf EA, et al. J Clin Oncol 2011;29:1956-1962.

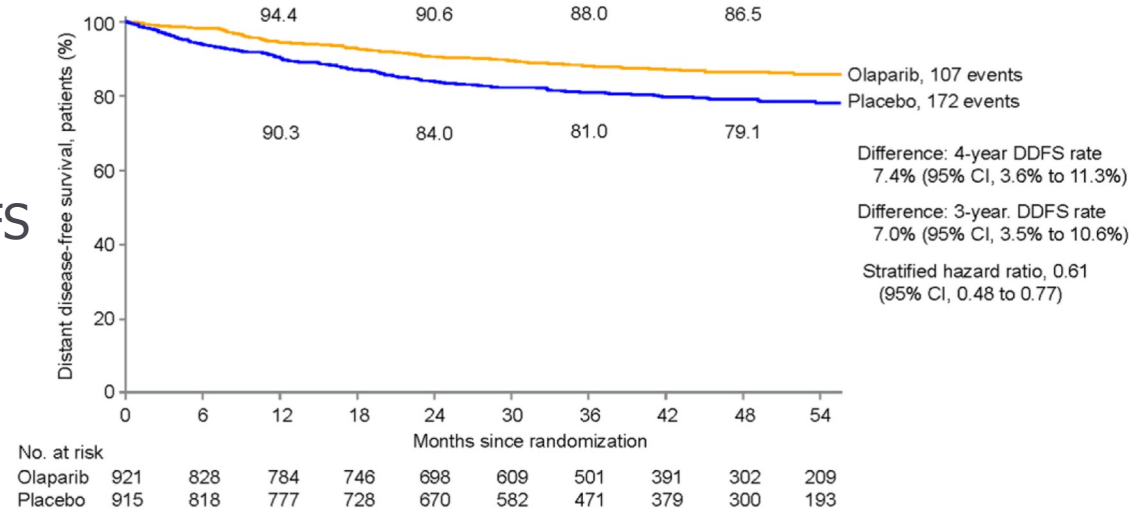
Overall Survival: 4 yr

OlympiA

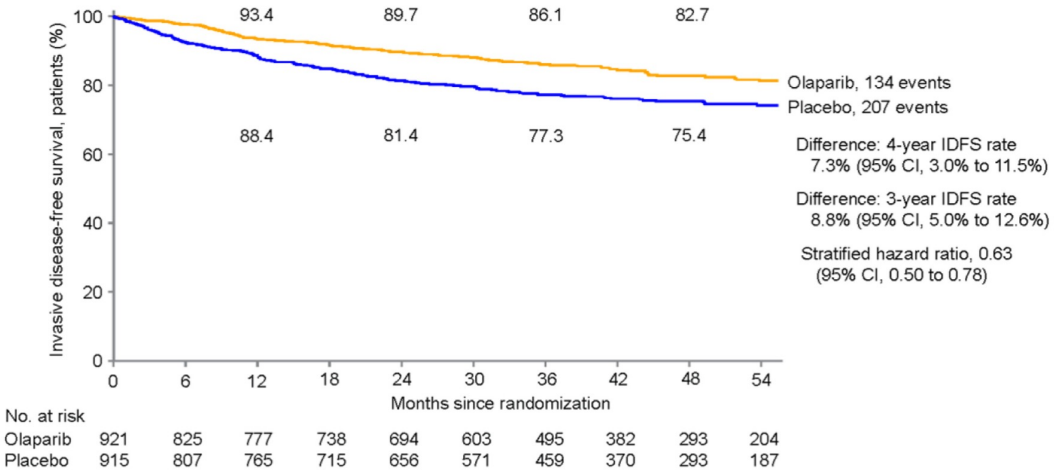
OS



DDFS



iDFS



- Geyer CE Jr, et al. Ann Oncol. 2022:S0923-7534(22)04165-5.

In High-Risk HR-Positive/HER2-Negative gBRCA Patients:

Olaparib or Abemaciclib?

Indication olaparib HR+HER2-

- Neoadjuvant: no pCR and CPS-EG ≥ 3*
- Adjuvant: ≥ 4 positive lymph nodes

Indication abemaciclib HR+HER2-

- FDA: N+ with high recurrence risk and Ki-67 ≥ 20%
- EMA: N+ with high recurrence risk
  - ≥ 4 positive lymph nodes
  - 1-3 pos lymph nodes and:
    T ≥ 5 cm or grade 3 or Ki-67 ≥ 20%

Agent	Investigational Arm	Placebo/Control Arm	HR (95% CI)[c]
3-years invasive disease-free survival			
Olaparib[a]	83.5%	77.2%	0.70 (0.38; 1.27)
Abemaciclib[b]	88.8%	83.4%	0.70 (0.59; 0.82)

- *CPS + EG Score: MD Anderson Cancer Center neoadjuvant therapy outcomes calculator. Mittendorf EA, et al. J Clin Oncol. 2011.
- a. Tutt ANJ, et al. N Engl J Med. 2021;384:2394-2405; b. Harbeck N, et al. Ann Oncol. 2021;32:1571-1581; c. Desai AP, et al. JCO Oncol Pract. 2022;18:e1247-e1254.

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]

Breast Cancer Index.

Recommendation 1.24. If a patient has node-negative or node-positive breast cancer with 1-3 positive nodes and has been treated with 5 years of primary endocrine therapy without evidence of recurrence, the clinician may offer the BCI test to guide decisions about extended endocrine therapy with either tamoxifen, an AI, or a sequence of tamoxifen followed by AI (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.25. If a patient has node-positive breast cancer with ≥ 4 positive nodes and has been treated with 5 years of primary endocrine therapy without evidence of recurrence, there is insufficient evidence to use the BCI test to guide decisions about extended endocrine therapy with either tamoxifen, an AI, or a sequence of tamoxifen followed by AI (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: strong).

- All patients with ≥4 nodes should receive extended ET (no evidence to use BCI or other tools)
- In patients with node negative of 1-3 LN+, can consider using BCI or other tests (e.g., CTS5 Dowset, JCO 2018; https://cts5-calculator.com) to help guide decisions about extended ET

Andrew et. al, JCO 2022

What Are the Current Guidelines? NCCN

Patient Population	Recommendation
HR+, T1–T2, pN0	BCI (H/I) Low (0-5) places the patient in the same low risk category for late recurrence as T1a,bN0M0 and no benefit in DFS or OS has been shown with EET in BCI (H/I) low patients
HR+, T1–T3, pN0 or pN1	BCI (H/I) High (5.1-10) confers higher risk for late recurrence and benefit from EET in MA.17, Trans-aTTom and IDEAL Trials

Take Home Messages: Early stage HR+ BC

- RxPonder
  - Inadequate endocrine therapy makes it difficult to evaluate results in premenopausal women; chemotherapy remains the standard of care; await next trial results
- SOFT and TEXT
  - In premenopausal women, OFS improves overall survival in patients with high risk early stage HR+ BC
  - With OFS, AI > tamoxifen in high risk disease
- Pts with high risk disease appear to benefit from extended ET
  - DATA trial results concordant with NSABP B-42
  - Role of BCI in decision making?
- Abemaciclib is a new SOC in patients with high risk early stage HR+ BC
- Olaparib should be considered for high risk ER+ patients with BRCA mutation

Case

- 42-year-old premenopausal woman presents with symptomatic mass in left breast
- Mammo shows 4-cm mass; core biopsy reveals grade 2 IDC, ER/PR –positive (>90%), HER2-; Ki-67 20%; enlarged axillary adenopathy
- LN biopsy + cancer
- PET CT staging negative
- Left mastectomy and axillary LN dissection

  –4.2 cm G2 IDC, 6/10 LN+, ER +, PR +, HER2-