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# Optimizing Therapy for Patients with Hormone Receptor-Positive Localized Breast Cancer

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# Disclosures

|                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
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| <b>Nonrelevant Financial Relationships</b>           | Breast Cancer Research Foundation, Fred's Team, Manhasset Women's Coalition Against Breast Cancer, National Cancer Institute (BRIMM/UG3 CA239861 Award)                                                                                                                                                                                                                                                                                                                                                                                                                      |

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# Key Datasets

- Andre F et al. **Biomarkers for adjuvant endocrine and chemotherapy** in early-stage breast cancer: ASCO Guideline update. *J Clin Oncol* 2022;40:1816-37.
- Sparano JA et al. Trial Assigning Individualized Options for treatment (**TAILORx**): **An update** including 12-year event rates. San Antonio Breast Cancer Symposium 2022;Abstract GS1-05.
- Sparano JA et al. **Clinical** outcomes in early breast cancer with a **high 21-gene Recurrence Score** of 26 to 100 assigned to **adjuvant chemotherapy plus endocrine therapy**: A **secondary analysis of the TAILORx** randomized clinical trial. *JAMA Oncol* 2020;6(3):367-74.
- Chen N et al. **Impact of anthracyclines** in **genomic high-risk, node-negative, HR-positive/HER2-negative** breast cancer. *Ann Oncol* 2025;36(11):1356-65.
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- Sestak I et al. **Comparison** of the performance of 6 **prognostic signatures** for estrogen receptor-positive breast cancer: A **secondary analysis of a randomized clinical trial**. *JAMA Oncol* 2018;4(4):545-53.
- Noordhoek I et al. **Breast Cancer Index** predicts **extended endocrine benefit** to individualize selection of patients with HR+ early-stage breast cancer for **10 years of endocrine therapy**. *Clin Cancer Res* 2021;27(1):311-19.

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- Woolpert KM et al. **Biomarkers predictive** of a response to **extended endocrine therapy** in breast cancer: A systematic review and meta-analysis. *Breast Cancer Res Treat* 2024;203(3):407-17.
- Johnston S et al. **monarchE: Primary overall survival** (OS) results of adjuvant abemaciclib + endocrine therapy (ET) for HR+, HER2-, high-risk early breast cancer (EBC). ESMO 2025;Abstract LBA13.
- Johnston S et al. **Overall survival** with **abemaciclib** in early breast cancer. *Ann Oncol* 2026;37(2):155-65.
- Cortés J et al. **monarchE: Subgroup analysis** of adjuvant abemaciclib + endocrine therapy for HR+, HER2-, high-risk early breast cancer by nodal status. San Antonio Breast Cancer Symposium 2025;Abstract PS1-08-08.
- Crown JP et al. **Adjuvant ribociclib** (RIB) **plus nonsteroidal aromatase inhibitor** (NSAI) in patients (pts) with HR+/HER2– early breast cancer (EBC): **NATALEE 5-year outcomes**. ESMO 2025;Abstract LBA14.
- Rugo HS et al. **Adjuvant abemaciclib** combined **with endocrine therapy** for high-risk early breast cancer: **Safety and patient-reported outcomes** from the **monarchE** study. *Ann Oncol* 2022;33(6):616-27.
- Barrios C et al. **NATALEE update: Safety and treatment (tx) duration** of **ribociclib** (RIB) + **nonsteroidal aromatase inhibitor** (NSAI) in patients (pts) with HR+/HER2– early breast cancer (EBC). ESMO Breast 2024;Abstract 113MO.
- Mayer EL et al. **TRADE: A phase II** trial to assess the **tolerability of abemaciclib dose escalation** in early-stage HR-positive/HER2-negative breast cancer. *Ann Oncol* 2025;31(1):117-24.
- Bardia A et al. **Giredestrant** vs standard-of-care endocrine therapy as **adjuvant treatment** for patients with estrogen receptor-positive, HER2-negative early breast cancer: **Results from the global phase III lidERA Breast Cancer trial**. San Antonio Breast Cancer Symposium 2025;Abstract GS1-10.

# **Management of Hormone Receptor (HR)-Positive Localized Breast Cancer**

**Module 1: Risk Assessment and Genomic Assays for HR-Positive, HER2-Negative Localized Breast Cancer**

**Module 2: Clinician Survey Results**

**Module 3: Adjuvant CDK4/6 Inhibitors for High-Risk, HR-Positive, HER2-Negative Localized Breast Cancer**

**Module 4: Clinician Survey Results**

**Module 5: Tolerability and Other Practical Considerations with Adjuvant CDK4/6 Inhibitor Therapy**

**Module 6: Clinician Survey Results**

**Module 7: Adjuvant Oral SERDs for HR-Positive, HER2-Negative Localized Breast Cancer**

# Management of Hormone Receptor (HR)-Positive Localized Breast Cancer

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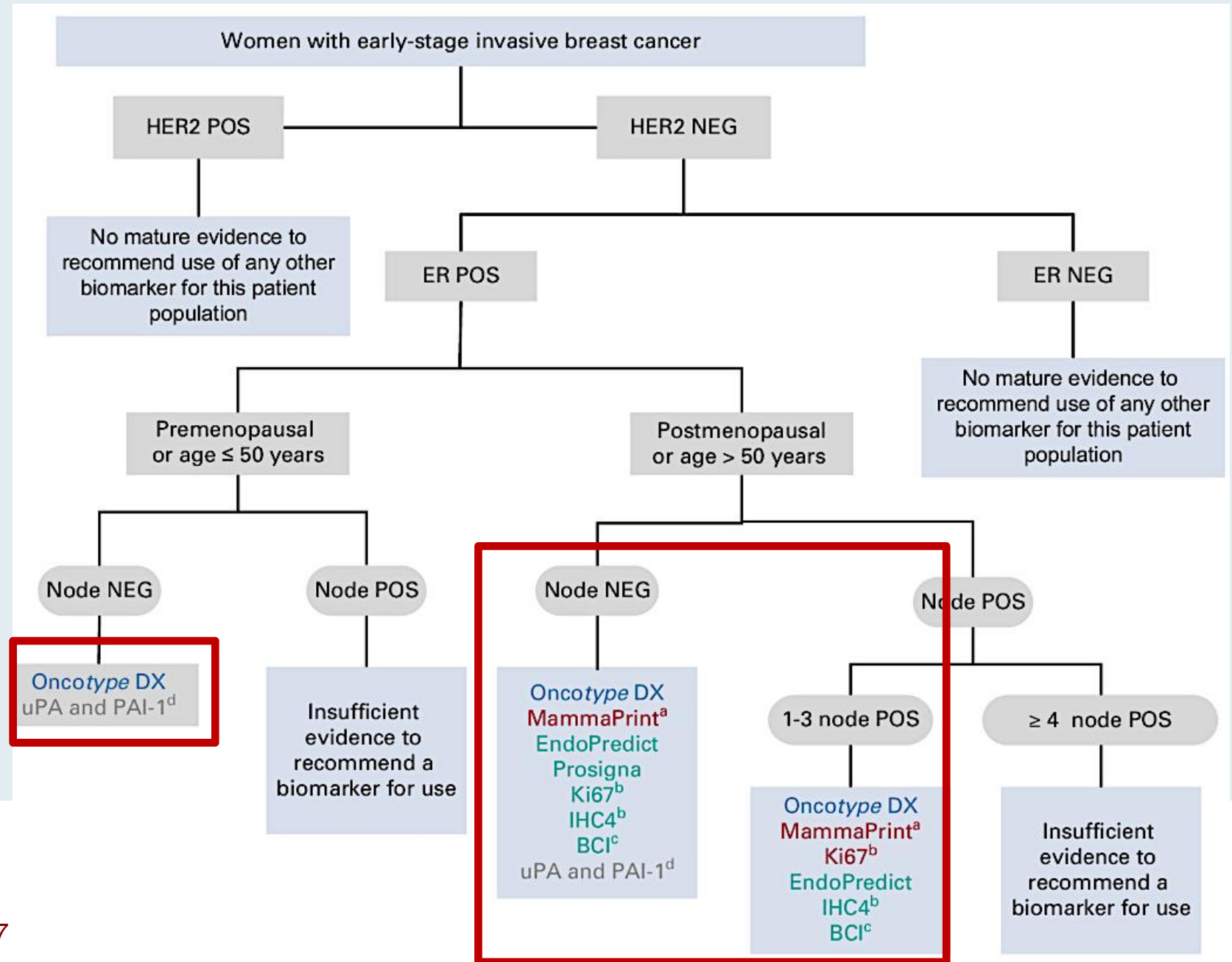
### Module 7: Adjuvant Oral SERDs for HR-Positive, HER2-Negative Localized Breast Cancer

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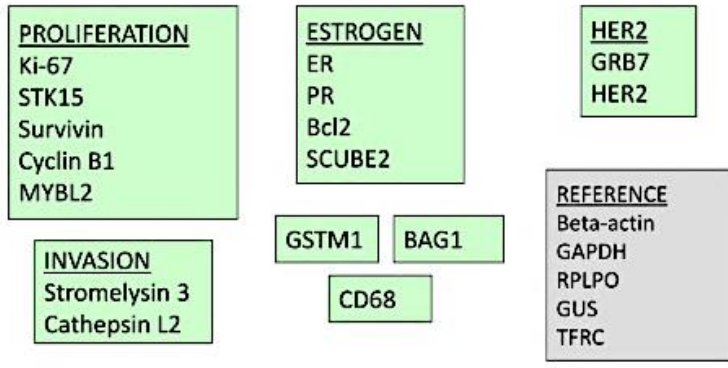
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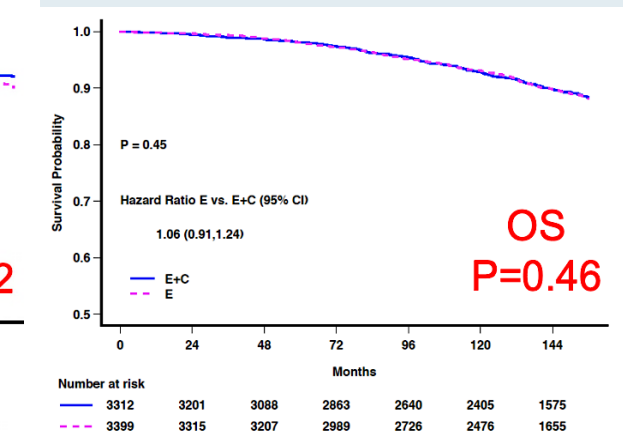
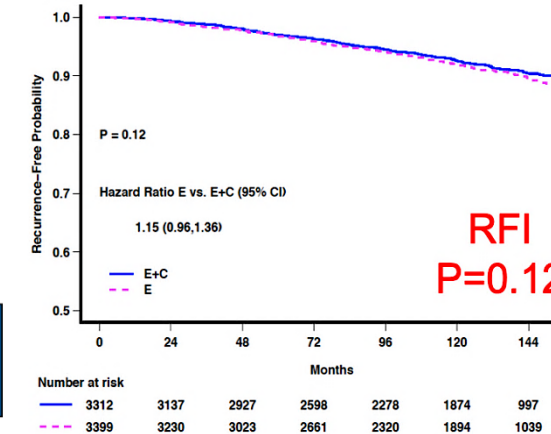
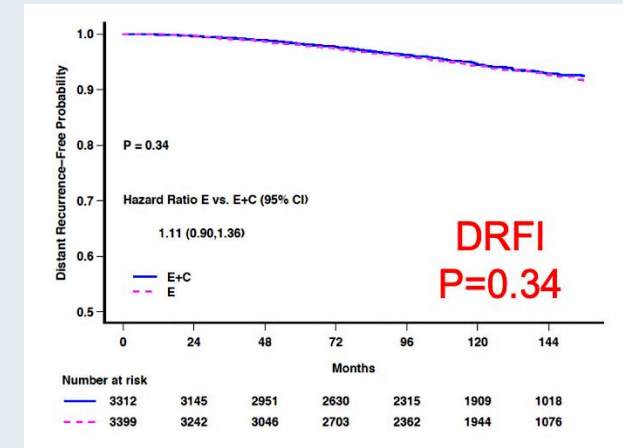
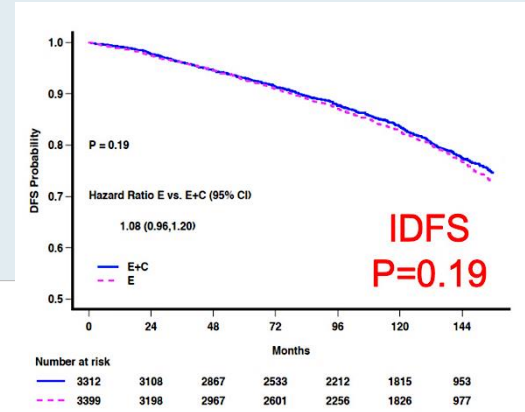
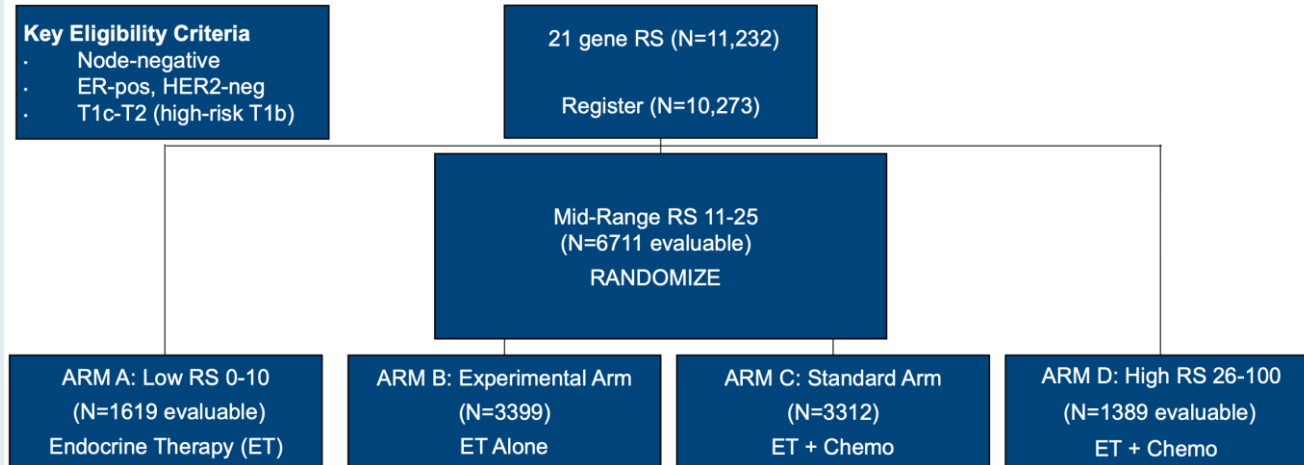
# OncotypeDX®: TAILORx Trial Key Results for Node-Negative Disease

16 Cancer and 5 Reference Genes From 3 Studies



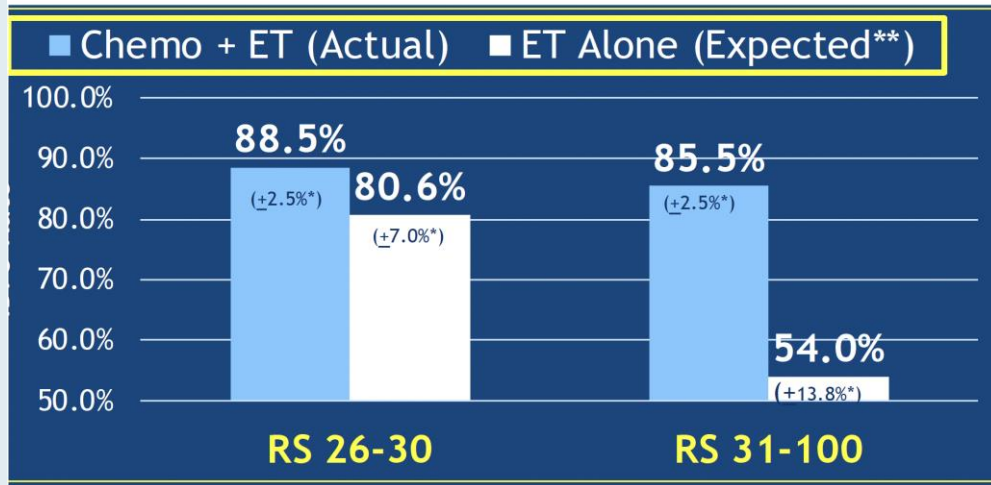
**Intermediate risk (11-25):  
No overall benefit to chemotherapy (2022 update)**

## TAILORx Trial Design

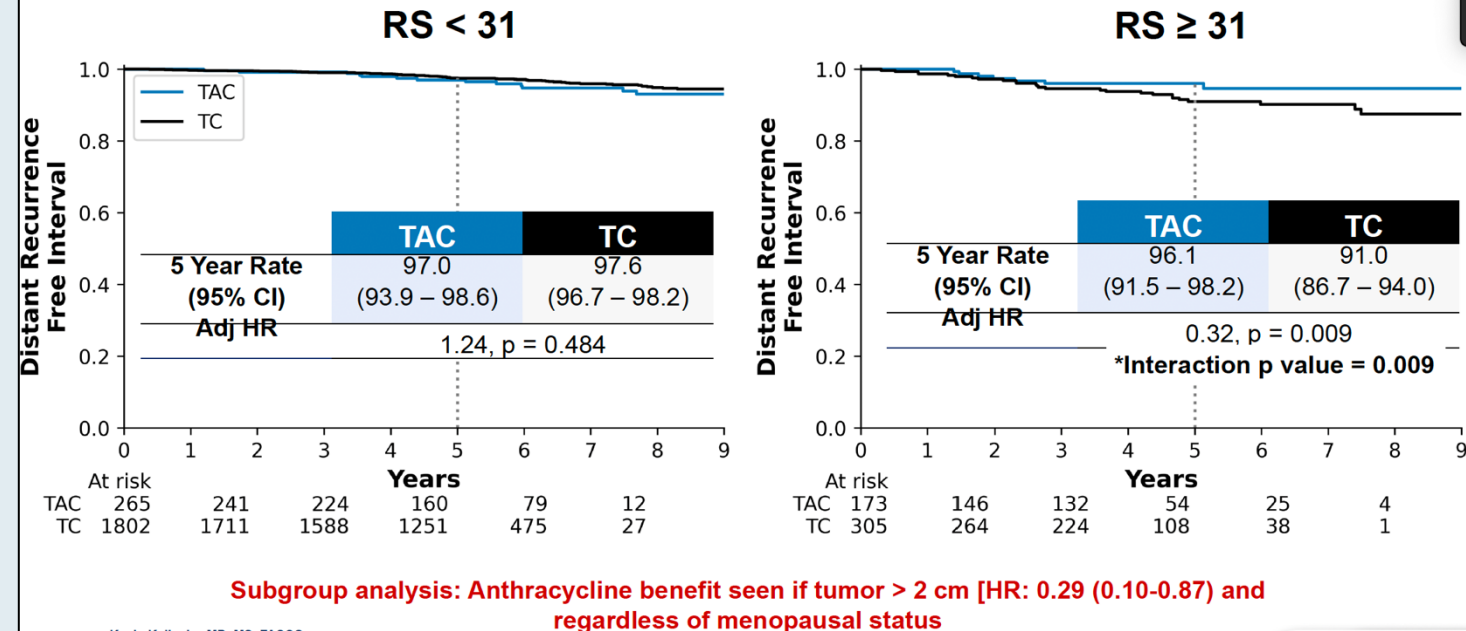


# Chemotherapy and Anthracycline Benefits for Patients with High Recurrence Scores® (>25)

High Risk (RS > 25): Expected benefit with chemotherapy



## DRFI Benefit at 5 y with Anthracycline if RS > 31

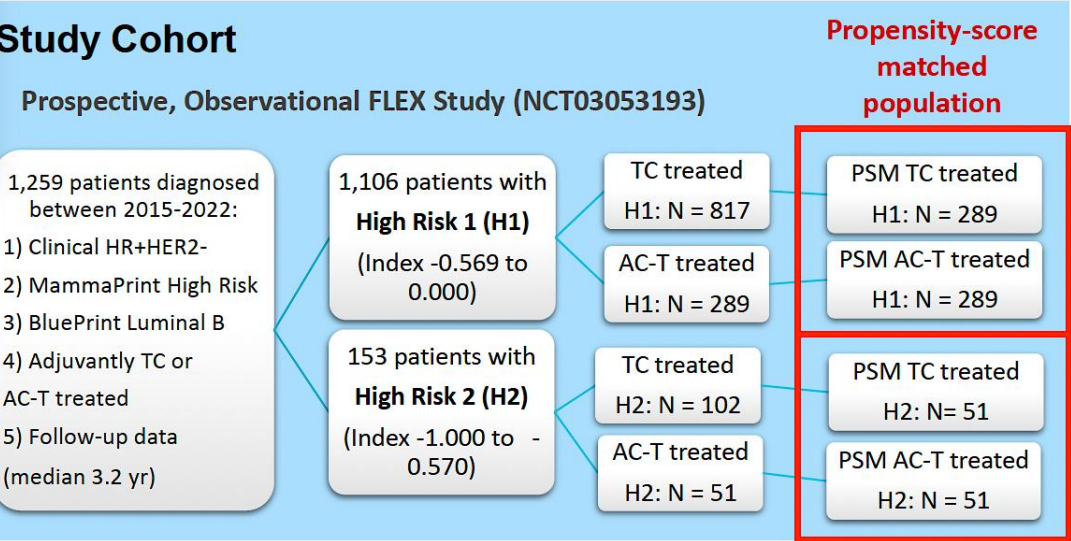


“No chemotherapy” rates estimated by combining

- patient-specific distant recurrence risk information with
- patient-specific chemotherapy benefit information
- from the ERBB2-negative cohort of NSABP B20

TAILORx N = 2,549. T-AC vs TC  
 5-y DRFI 96.1 vs 91%, HR 0.31, p = 0.006  
 5-y DRFS 95.4% vs 89.8%, aHR 0.49, p = 0.032  
 OS NS

# Propensity-Score Matched Analysis of Real-World FLEX Data: IDFS with Anthracycline-Based Therapy for Patients with MammaPrint® High 2, Luminal B, HR-Positive, HER2-Negative Localized Breast Cancer

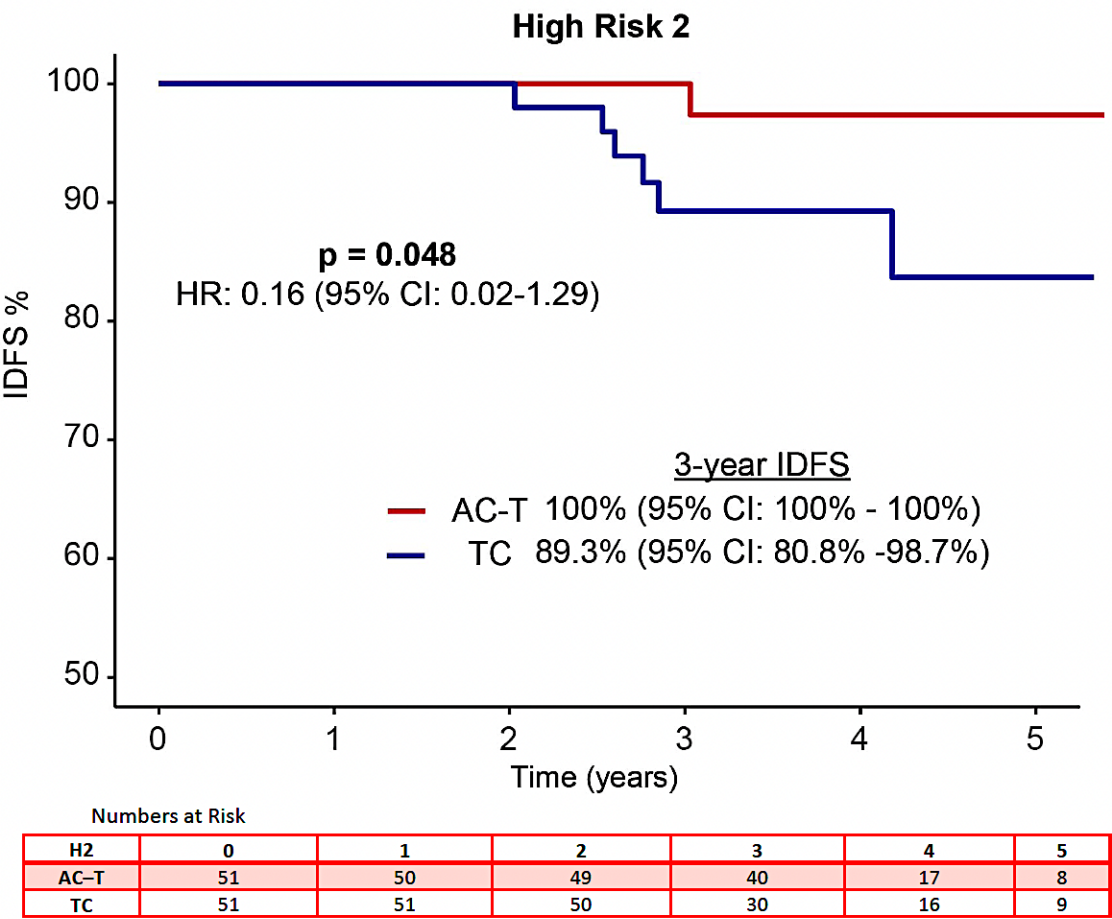


## Conclusions

- In this PSM analysis of a non-randomized, prospective, real-world FLEX Study data with 3.2 years median follow-up, patients with H2, HR+HER2-cancer had significantly improved IDFS with AC-T compared to TC
- Although adjusted analyses were limited by few events, the direction and magnitude of benefit remained consistent
- In contrast, patients with H1 cancer did not benefit more from AC-T vs. TC
- These findings further support the utility of MammaPrint in informing chemotherapy selection in patients with HR+HER2- breast cancer

IDFS = invasive disease-free survival

Figure 2. IDFS in patients with High Risk 2 cancer: AC-T vs TC



# OncotypeDX: RxPONDER Trial Results Summary One to Three Positive Lymph Nodes

## RxPONDER Trial Design

### Key Entry Criteria

- Women age  $\geq 18$  yrs
- ER and/or PR  $\geq 1\%$ , 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

R  
E  
G  
I  
S  
T  
R  
A  
T  
I  
O  
N

Recurrence Score 0-25

Recurrence Score > 25

Off Study  
Chemotherapy Followed by  
Endocrine Therapy Recommended

R  
A  
N  
D  
O  
M  
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Z  
A  
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N = 5,000 pts

Arm 1:  
Chemotherapy Followed by  
Endocrine Therapy

Arm 2:  
Endocrine Therapy Alone

### Stratification Factors

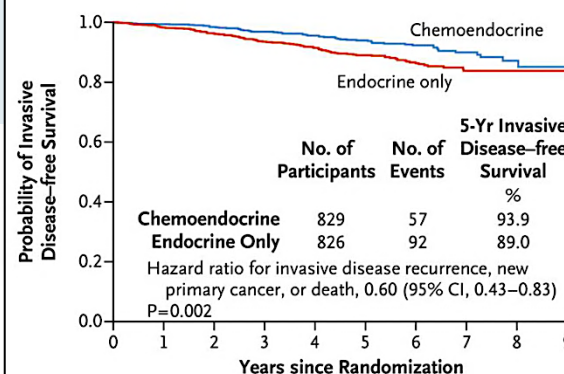
Recurrence Score: 0-13 vs. 14-25  
Menopausal Status: pre vs. post  
Axillary Surgery: ALND vs. SLNB

### RxPONDER Population

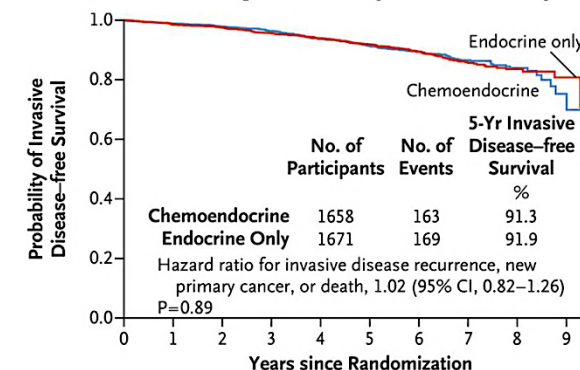
|           |     |          |     |
|-----------|-----|----------|-----|
| T1        | 58% | T3       | 5%  |
| 1 LN+     | 66% | 3 LN+    | 9%  |
| Grade 2   | 64% | Grade 3  | 10% |
| 40-49 yrs | 21% | < 40 yrs | 3%  |

## RxPONDER: Chemo Benefit Different by Menopausal Status if RS 0-25

### Premenopausal (1/3<sup>rd</sup> Trial)



### Postmenopausal (2/3<sup>rd</sup> Trial)



## IDFS Benefit Modified by Score for Women Age $\leq 50$

### Women $\leq 50$ yr

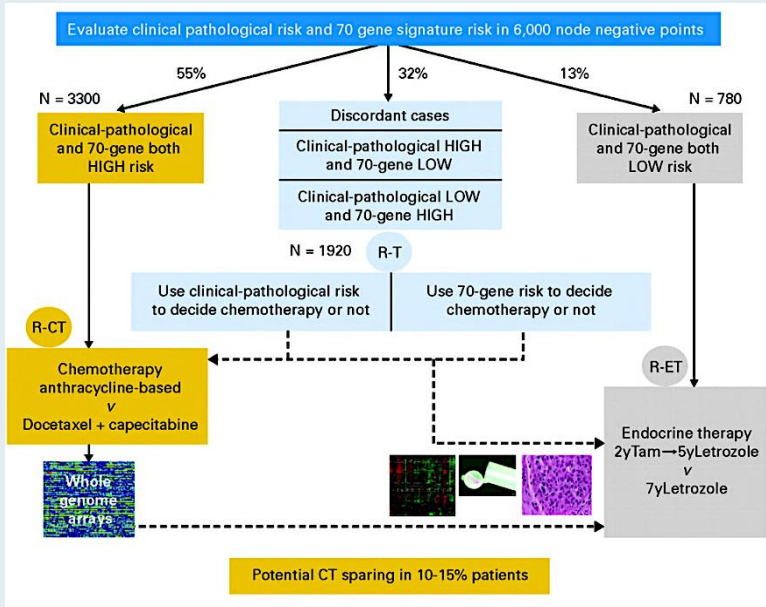
|                            |     |                |                  |
|----------------------------|-----|----------------|------------------|
| $\leq 10$ , endocrine only | 145 | 91.0 $\pm$ 2.6 | 0.31 (0.10–0.94) |
| $\leq 10$ , chemoendocrine | 135 | 97.9 $\pm$ 1.5 |                  |
| 11–15, endocrine only      | 247 | 93.1 $\pm$ 1.8 | 0.71 (0.33–1.51) |
| 11–15, chemoendocrine      | 235 | 95.4 $\pm$ 1.6 |                  |
| 16–20, endocrine only      | 227 | 85.1 $\pm$ 2.6 | 0.58 (0.33–1.00) |
| 16–20, chemoendocrine      | 224 | 92.2 $\pm$ 2.0 |                  |
| 21–25, endocrine only      | 107 | 80.0 $\pm$ 4.3 | 0.56 (0.27–1.17) |
| 21–25, chemoendocrine      | 98  | 90.0 $\pm$ 3.6 |                  |

# MammaPrint: MindACT Trial Key Results

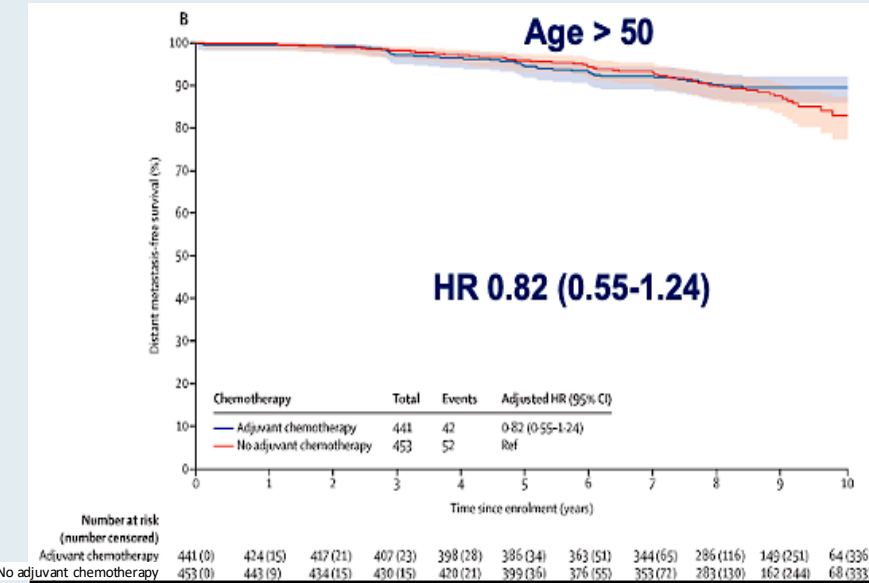
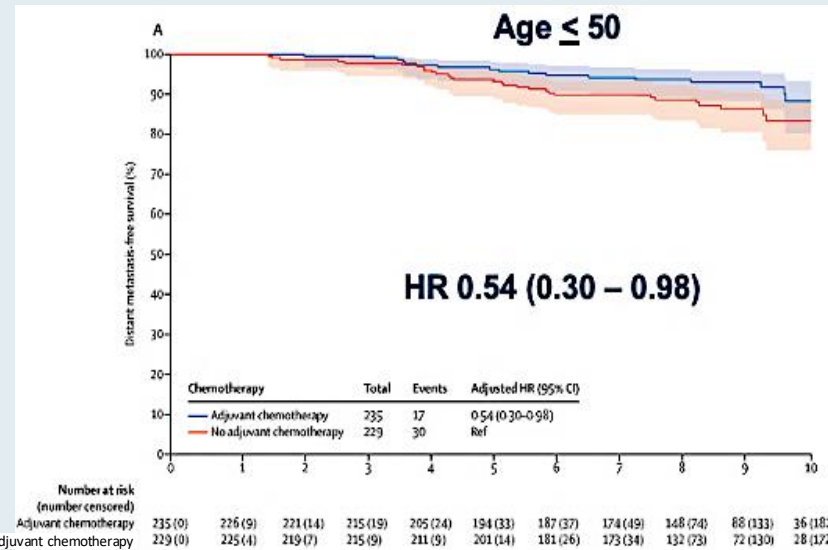
Clinical “high risk”: <88% 10-yr BCSS  
Modified Adjuvant! Online to determine  
Model included: T size, Node (0-3), grade, ER status, age, comorbidity

Chemo benefit increases over time overall. Lost in those age >50, maintained in those age <50

|           | ET                     | CET                | Absolute diff |
|-----------|------------------------|--------------------|---------------|
| 5-y DMFS  | 94.7%<br>(92.5 – 96.2) | 95.9%<br>(94-97.2) | 1.2%          |
| 8-yr DMFS | 89.4%<br>(86.8- 91,5)  | 92%<br>(896-93.8)  | 2.6%          |



Met primary outcome: Lower bound of 95% CI >92% 5-y DMFS in the High Clinical/Low Genomic risk group



BCSS = breast cancer-specific survival; DMFS = distant metastasis-free survival

Cardoso F et al. *N Engl J Med* 2016; Piccart M et al. *Lancet Oncol* 2021.

# Prosigna® ROR, EndoPredict® EPclin and Breast Cancer Index®

## ROR (risk of recurrence, Prosigna)

- 50-gene RNA-based molecular subtyping assay
- ROR available in US; PAM50 not available

## EPclin (EndoPredict)

- 12 genes – Proliferation and hormone receptor

## Breast Cancer Index (BCI)

- 7 genes – Proliferation and hormone receptor (HoxB13/IL17BR)

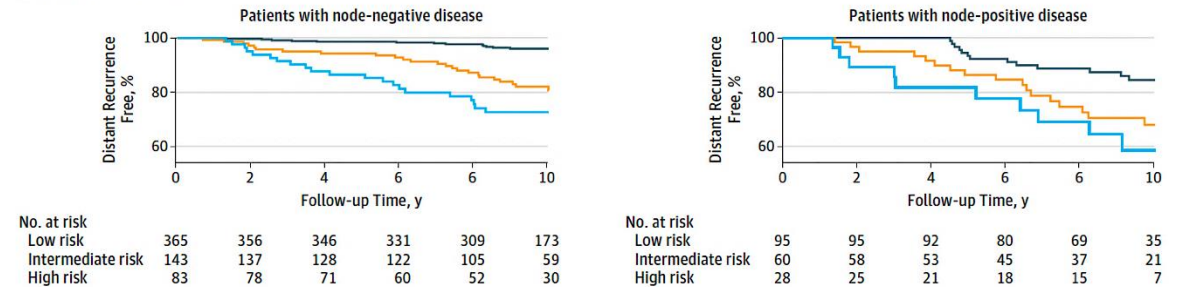
JAMA Oncology | Original Investigation

## Comparison of the Performance of 6 Prognostic Signatures for Estrogen Receptor-Positive Breast Cancer A Secondary Analysis of a Randomized Clinical Trial

- Largest retrospective prognostic validation in TransATAC Trial (included Oncotype DX and BCI as well)
- N = 535 node-negative, 154 node-positive
- Examined risk years 0 to 10
- ROR, EPclin and BCI provided most prognostic information
- ROR HR 2.56 (1.96-3.35)
- EPclin HR 2.14 (1.71-2.68)
- BCI HR 2.46 (1.88-3.23)

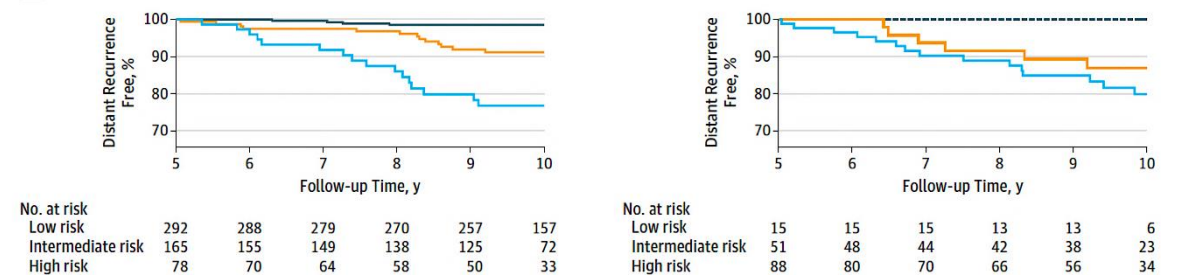
## BCI

A Breast cancer index



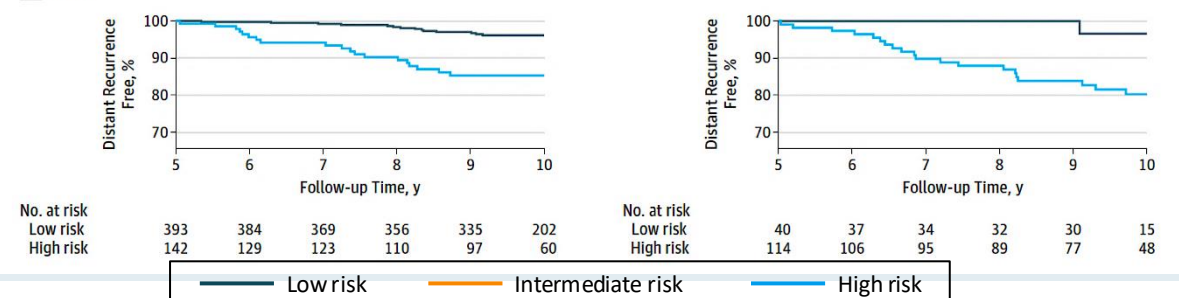
## ROR

C Risk of recurrence score



## EPclin

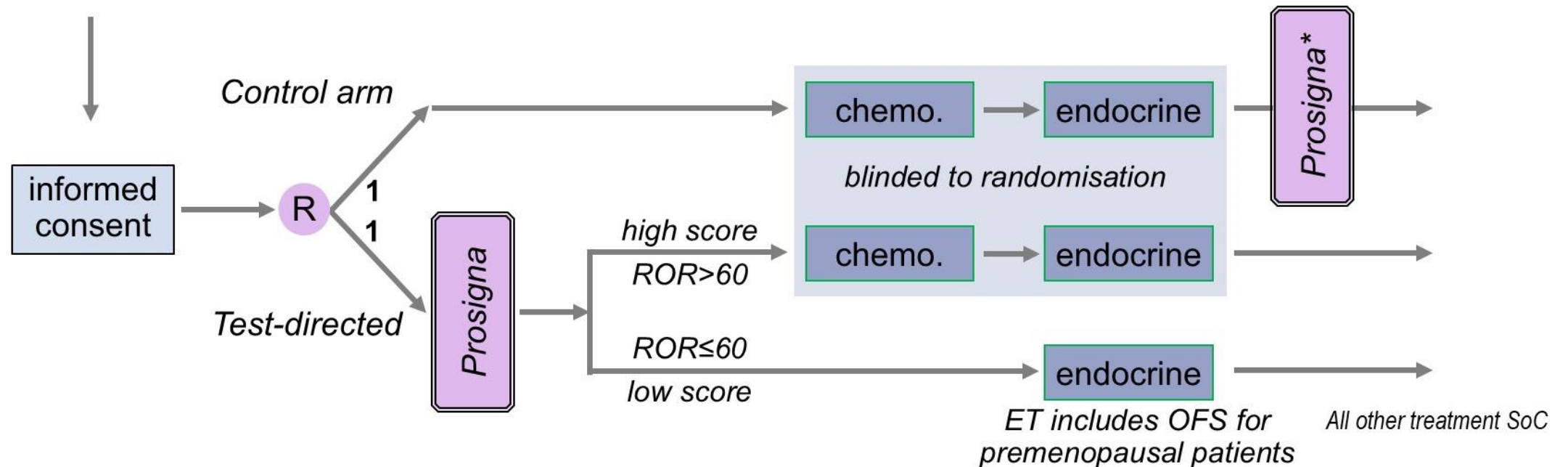
D EPclin



# Phase III OPTIMA Study Design

## Main eligibility criteria

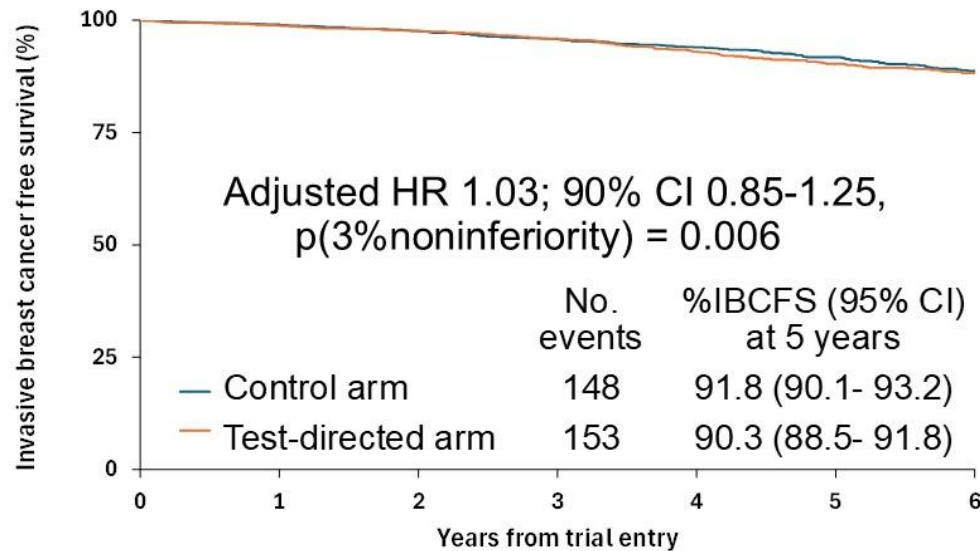
- Women & men age  $\geq 40$  with excised breast cancer
- ER-pos (IHC $>10\%$ ) & HER2-neg
- Nodes:  $\triangleright 0-9N+$ ,  
 $\triangleright$  minimum T-size requirement if N0/ N1mi
- Neoadjuvant chemotherapy prohibited



\*Control arm Prosigna testing used for analysis only. U.K. control arm testing performed following recruitment completion

# Phase III OPTIMA: Invasive Breast Cancer-Free Survival (IBCFS)

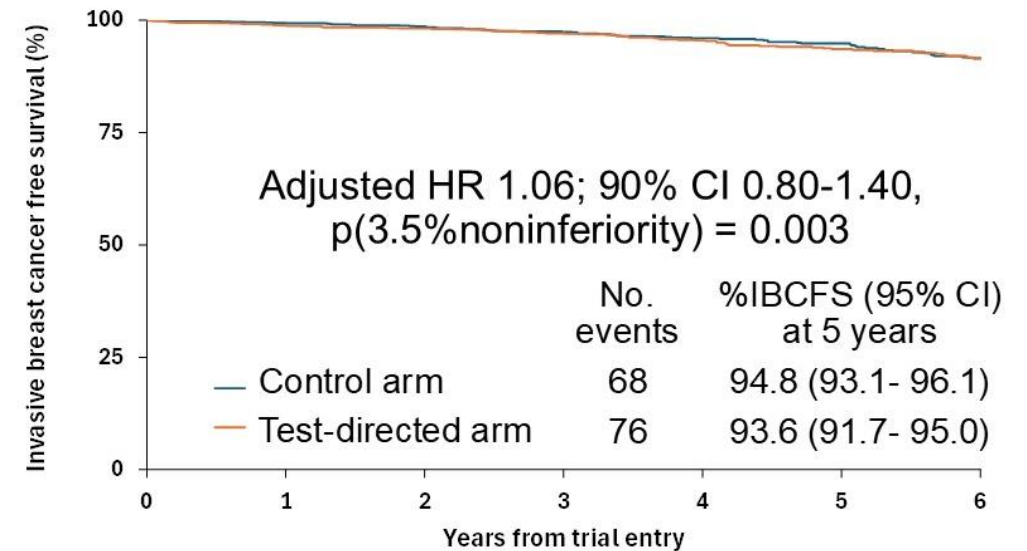
Complete Per Protocol population



|                 |      |      |      |      |     |     |     |
|-----------------|------|------|------|------|-----|-----|-----|
| Number at risk: |      |      |      |      |     |     |     |
| Control         | 2059 | 1818 | 1563 | 1283 | 999 | 741 | 485 |
| Test-directed   | 2094 | 1857 | 1591 | 1303 | 989 | 724 | 481 |

Demonstrated non-inferiority limit = 2%  
 No certainty of chemotherapy benefit  
 1.5% observed 5-year difference –favors chemotherapy

ROR  $\leq 60$  subpopulation



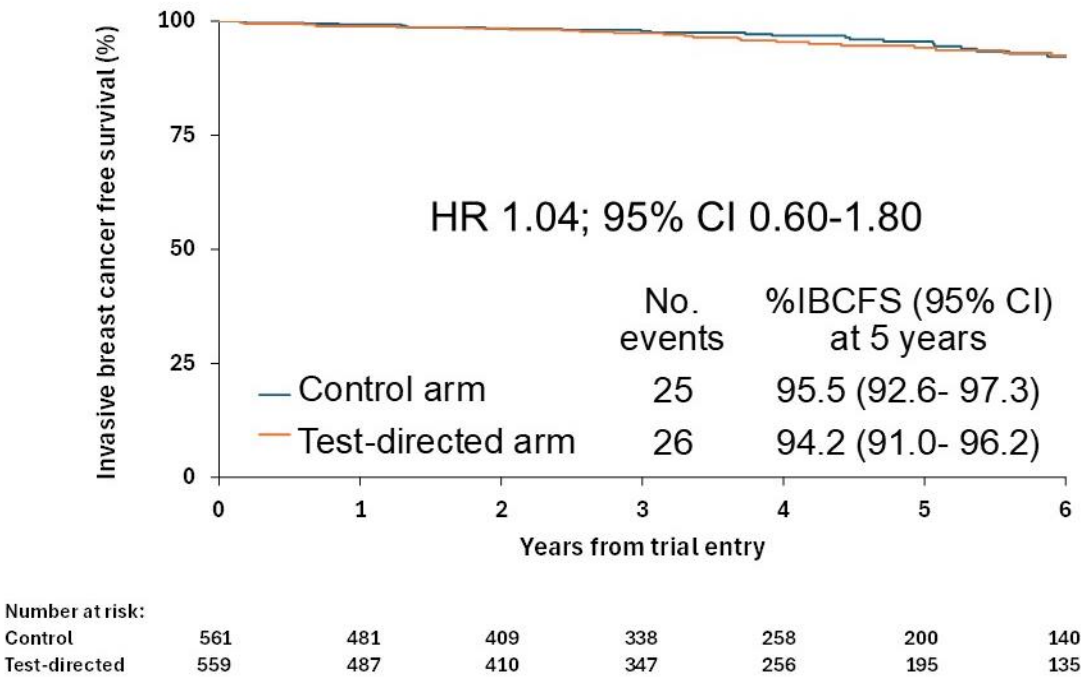
|                 |      |      |      |     |     |     |     |
|-----------------|------|------|------|-----|-----|-----|-----|
| Number at risk: |      |      |      |     |     |     |     |
| Control         | 1358 | 1207 | 1043 | 862 | 672 | 504 | 337 |
| Test-directed   | 1421 | 1257 | 1086 | 905 | 694 | 503 | 342 |

Demonstrated non-inferiority limit = 2%  
 No certainty of chemotherapy benefit  
 1.2% observed 5-year difference –favors chemotherapy

ROR = risk of recurrence

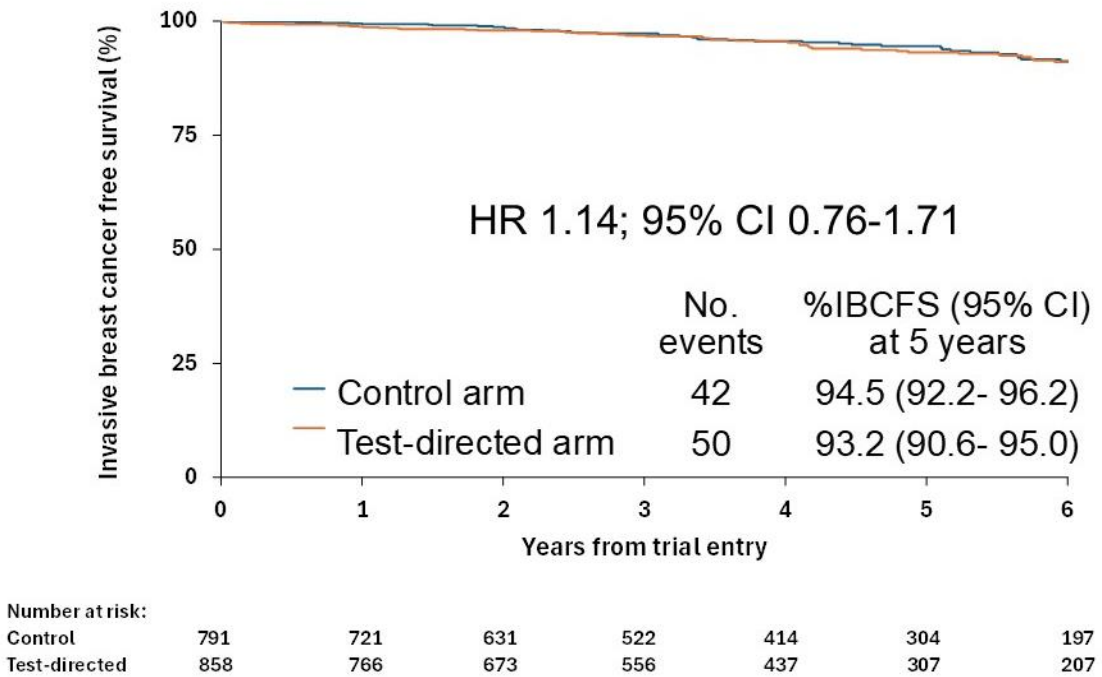
# Phase III OPTIMA: IBCFS and Menopausal Status (Low ROR Score)

Premenopausal



1.3% observed 5-year difference -favors chemotherapy

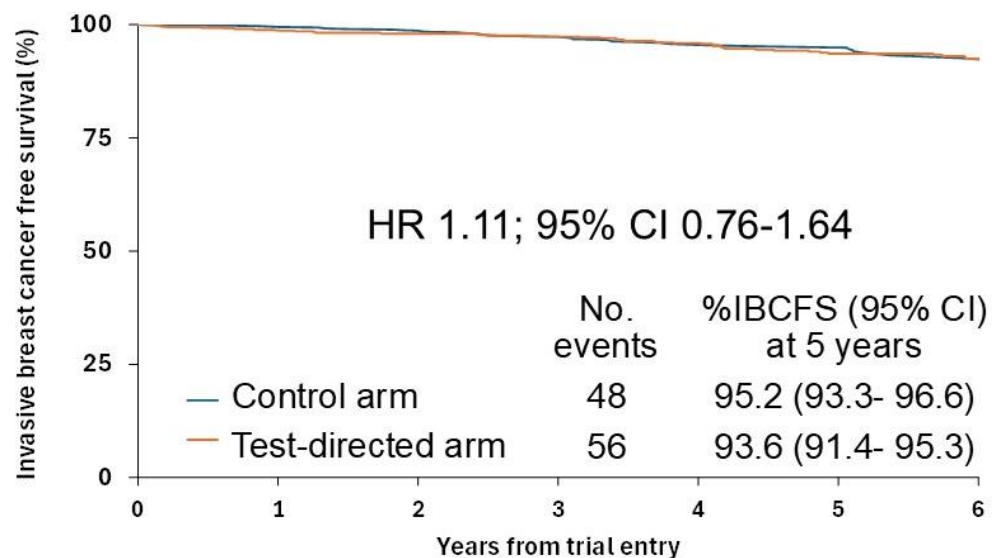
Postmenopausal



1.3% observed 5-year difference -favors chemotherapy

# Phase III OPTIMA: IBCFS and Nodal Status (Low ROR Score)

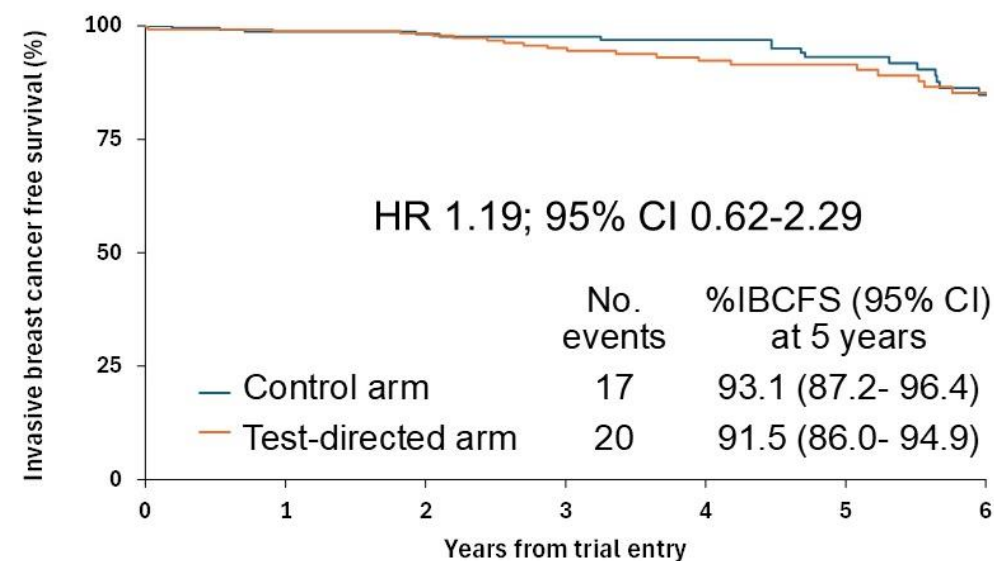
## 1-3 involved nodes



|                 |      |     |     |     |     |     |     |
|-----------------|------|-----|-----|-----|-----|-----|-----|
| Number at risk: |      |     |     |     |     |     |     |
| Control         | 1015 | 914 | 798 | 651 | 499 | 382 | 264 |
| Test-directed   | 1063 | 953 | 829 | 700 | 539 | 389 | 270 |

1.6% observed 5-year difference -favors chemotherapy

## 4-9 involved nodes

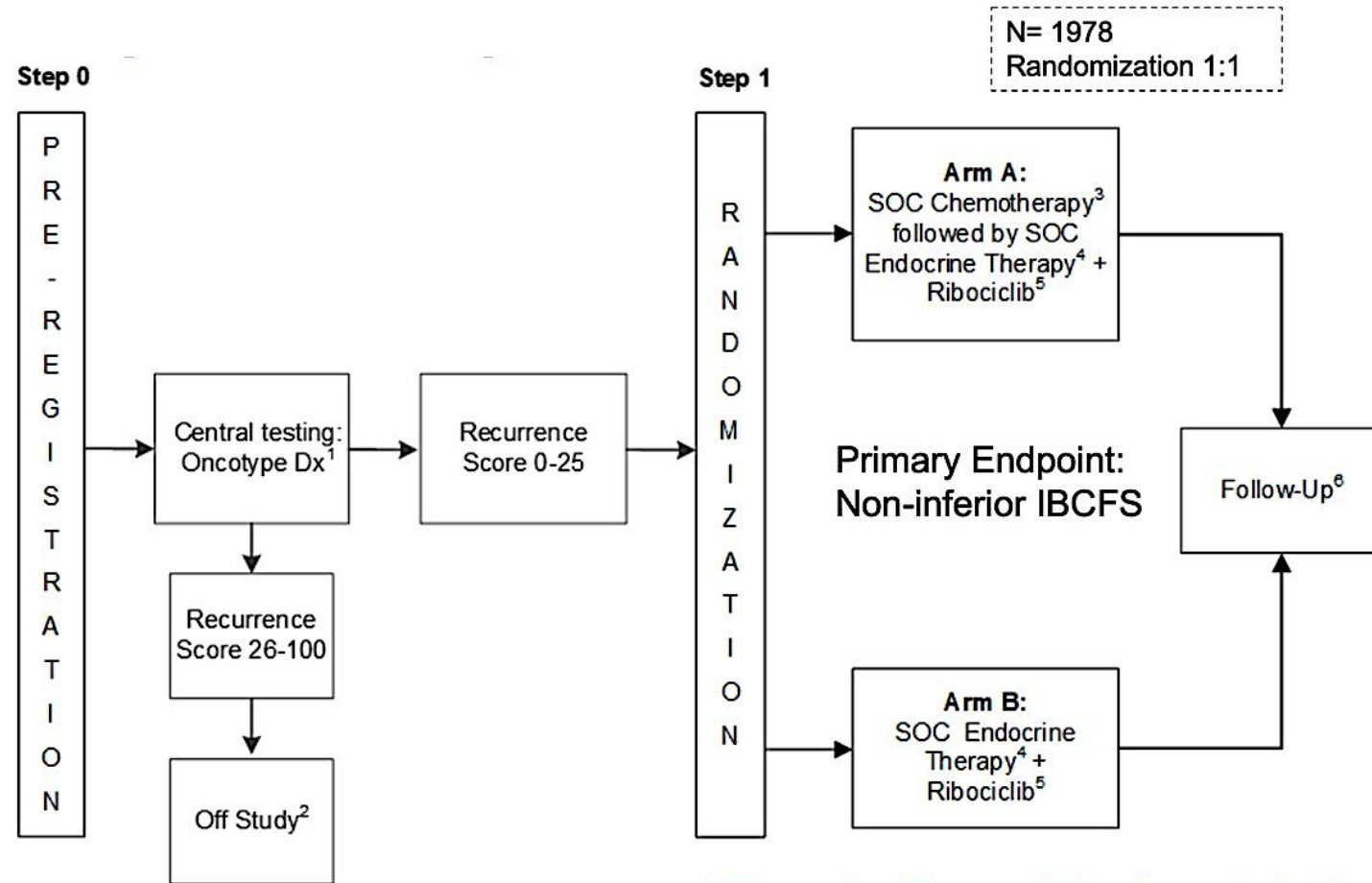


|                 |     |     |     |     |     |    |    |
|-----------------|-----|-----|-----|-----|-----|----|----|
| Number at risk: |     |     |     |     |     |    |    |
| Control         | 243 | 214 | 181 | 155 | 125 | 84 | 48 |
| Test-directed   | 269 | 232 | 197 | 158 | 118 | 86 | 49 |

1.6% observed 5-year difference -favors chemotherapy

# Phase III RxFINE-Low (EA1242) Study Design

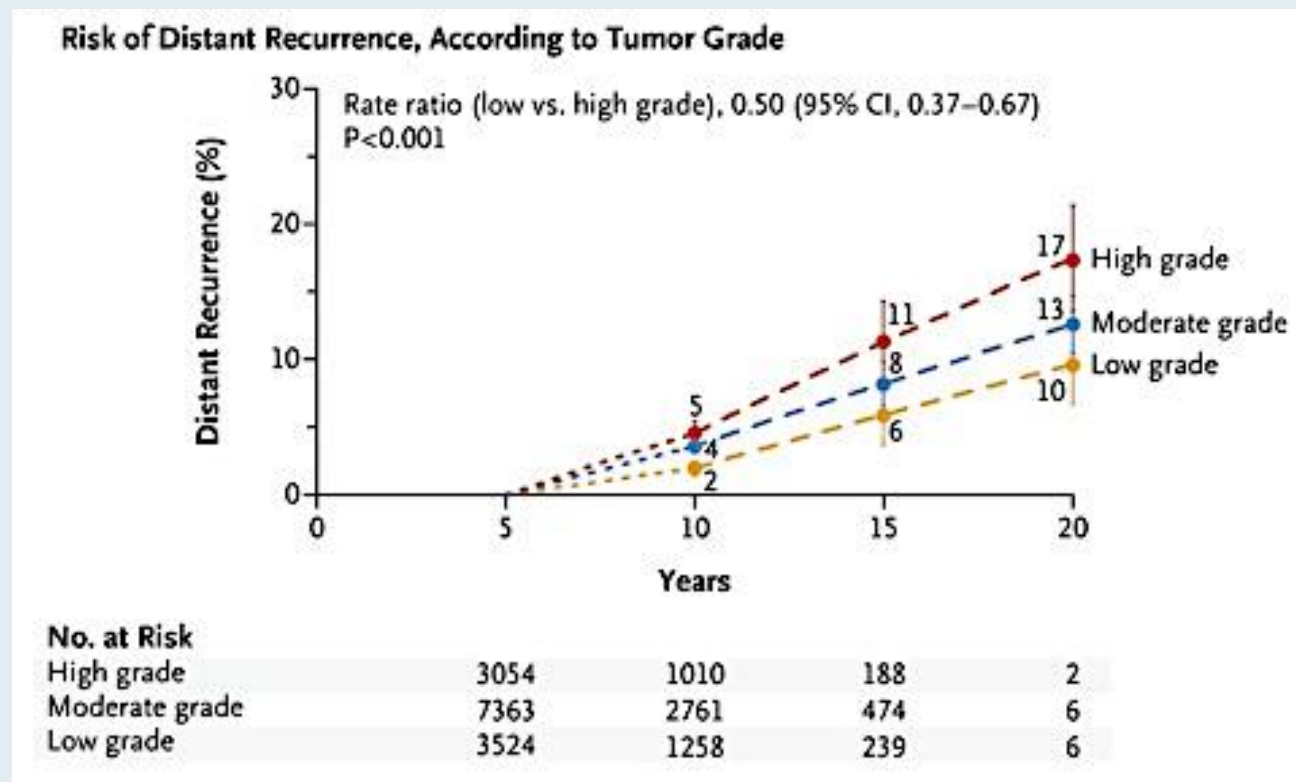
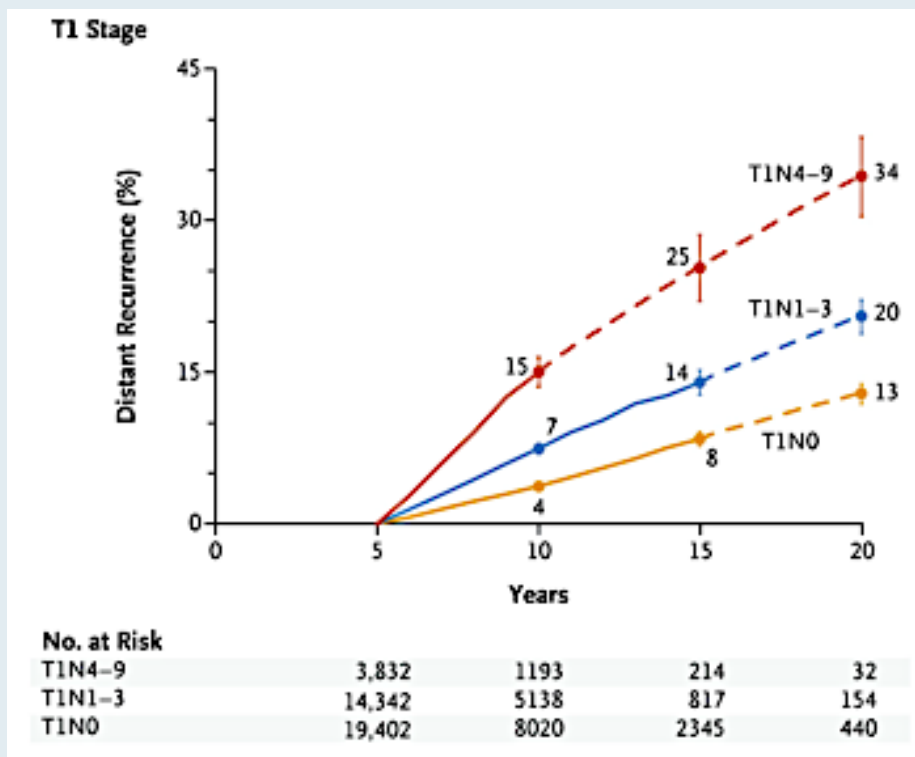
- Postmenopausal
- Stage: pT0-T3 with 3 positive ipsilateral lymph nodes (micro-or macrometastatic disease) and no planned axillary lymph node dissection (ALND) after definitive surgery in the breast and axilla with curative intent
- pT0-T3 with N2 or N3
- pT3 with N0-N3
- Must have undergone axillary staging with sentinel lymph node biopsy (SLNB), targeted axillary dissection (TAD), or ALND



*\*See protocol for complete schema footnotes*

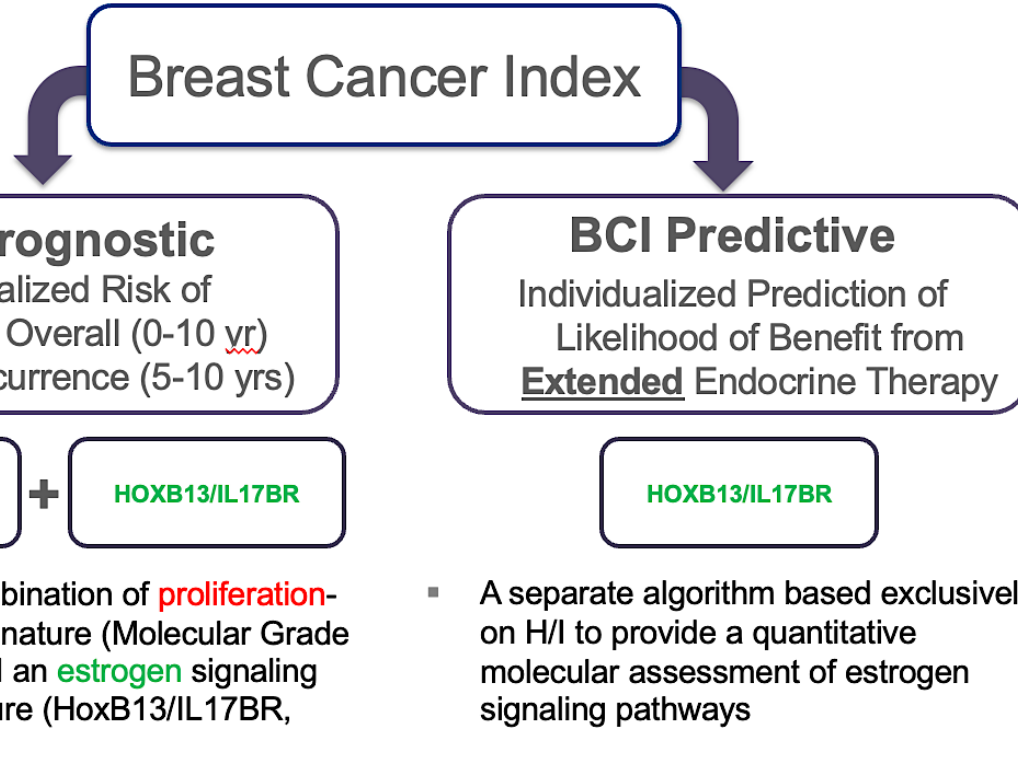
# Persistent Long-Term Risk of Distant Recurrence

Risk of late distant recurrence after 5 years of adjuvant endocrine therapy persists across all clinical stages.



# Breast Cancer Index (BCI)

## BCI Components



## Distribution of BCI scores

Low Risk (<4.8%) / Low Likelihood of Benefit

~45%

High Risk (>4.8%) / High Likelihood of Benefit

~30%

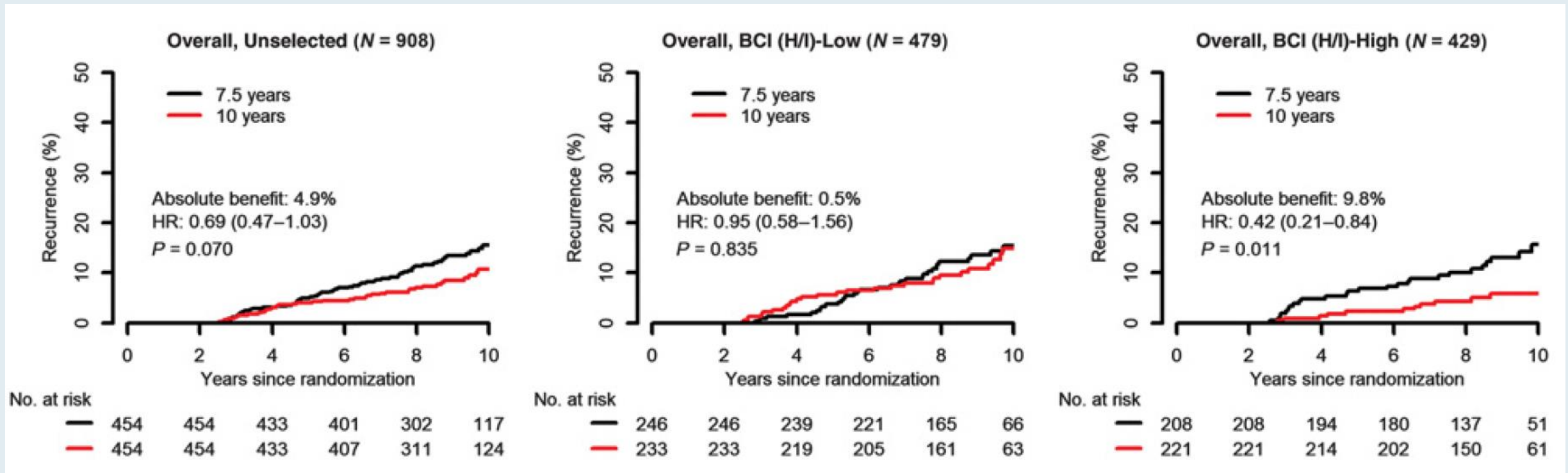
High Risk (>4.8%) / Low Likelihood of Benefit

~15%

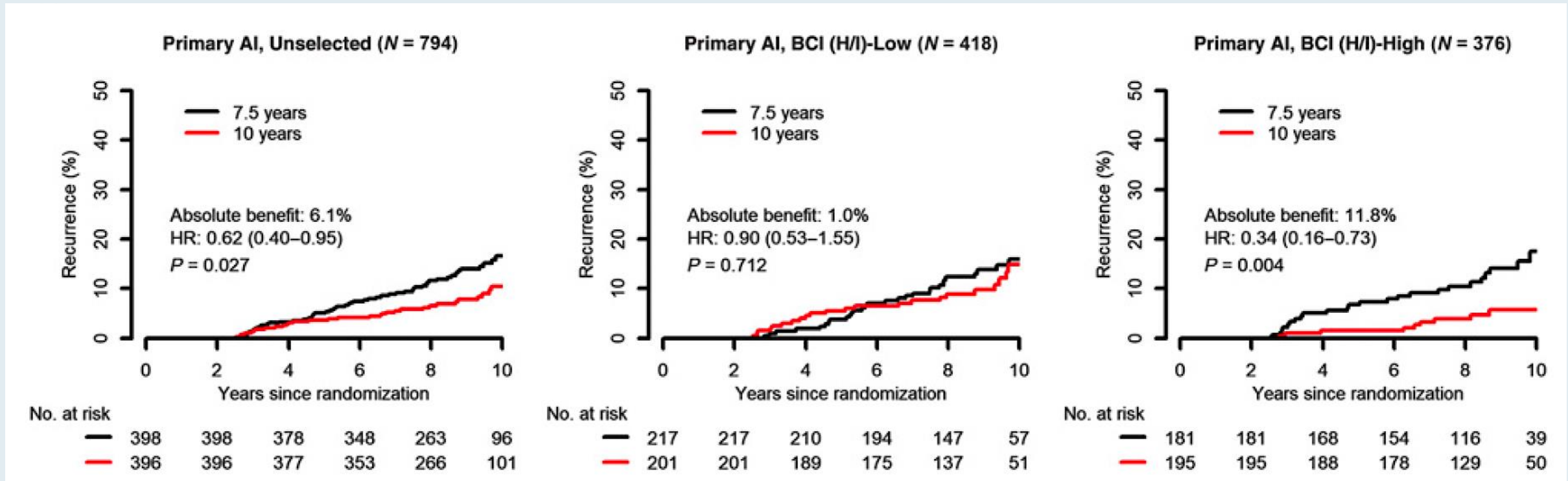
Low Risk (<4.8%) / High Likelihood of Benefit

~10%

# Predictive Performance by BCI H/I Groups Based on Recurrence-Free Interval in the Overall Cohort of the Phase III IDEAL Trial



# Predictive Performance by BCI H/I Groups Based on Recurrence-Free Interval in the Subset of Patients in the Phase III IDEAL Trial Who Received a Primary Aromatase Inhibitor (AI)

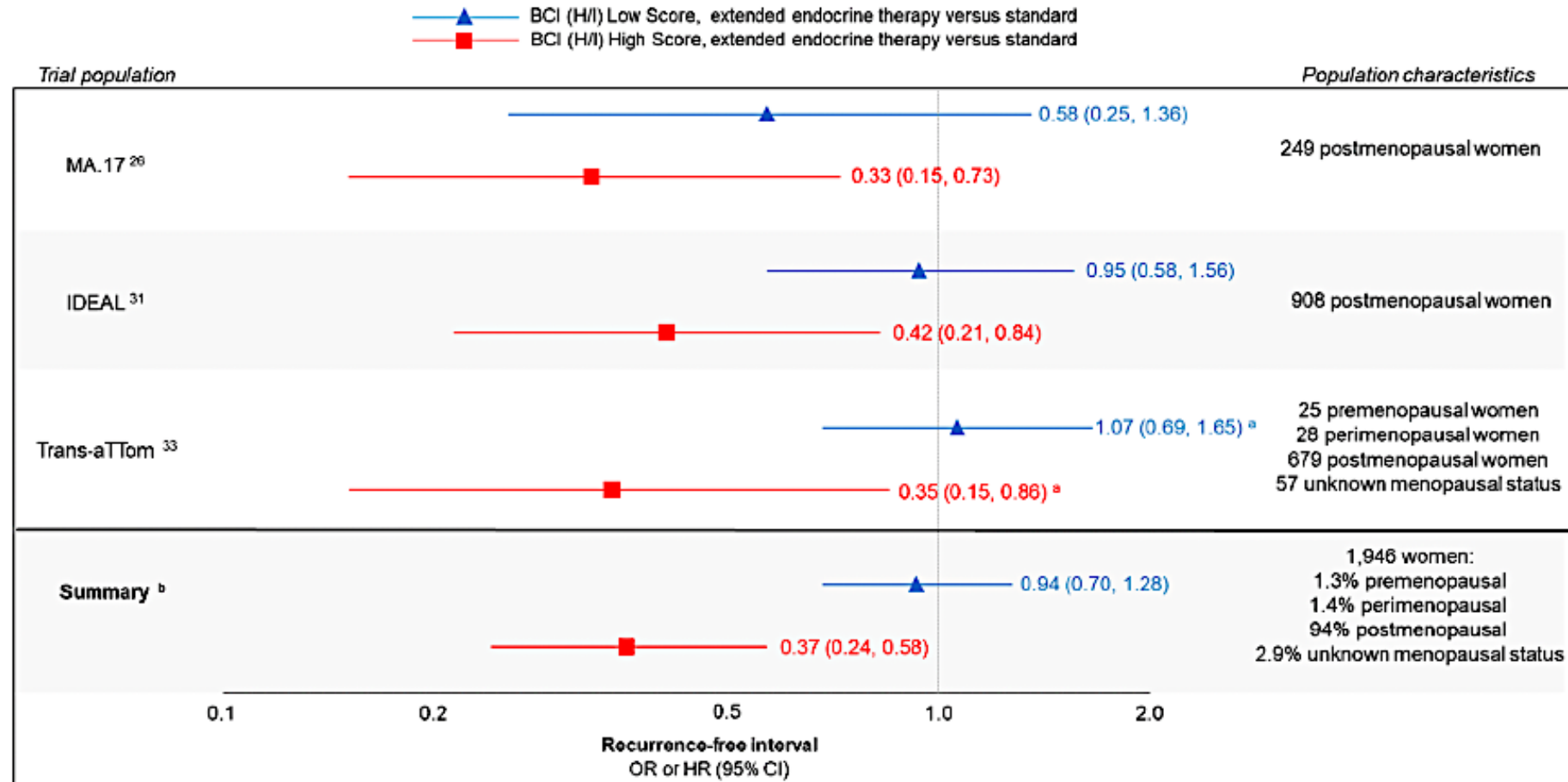


# Risk of Recurrence at Year 10 Since Randomization for Patients Who Received 5 Years versus 2.5 Years of Additional Letrozole in the Overall Cohort and in the Primary AI Subset of the Phase III IDEAL Trial

| Groups             | 5-year letrozole   |                       | 2.5-year letrozole |                       | HR (95% CI)*     |
|--------------------|--------------------|-----------------------|--------------------|-----------------------|------------------|
|                    | Number of Patients | 10-year risk (95% CI) | Number of Patients | 10-year risk (95% CI) |                  |
| Overall (N=908)    |                    |                       |                    |                       |                  |
| Unselected         | 454 (100%)         | 10.6% (7.1-14.0)      | 454 (100%)         | 15.5% (11.5-19.3)     | 0.69 (0.47-1.03) |
| BCI (H/I)-High     | 221 (49%)          | 5.9% (2.3-9.3)        | 208 (46%)          | 15.7% (9.5-21.5)      | 0.42 (0.21-0.84) |
| BCI (H/I)-Low      | 233 (51%)          | 14.9% (9.1-20.3)      | 246 (54%)          | 15.4% (10.1-20.4)     | 0.95 (0.58-1.56) |
| Primary AI (N=794) |                    |                       |                    |                       |                  |
| Unselected         | 396 (100%)         | 10.5% (6.6-14.2)      | 398 (100%)         | 16.6% (12.1-20.8)     | 0.62 (0.40-0.95) |
| BCI (H/I)-High     | 195 (49%)          | 5.7% (1.9-9.4)        | 181 (45%)          | 17.5% (10.1-24.4)     | 0.34 (0.16-0.73) |
| BCI (H/I)-Low      | 201 (51%)          | 14.9% (8.2-21.1)      | 217 (55%)          | 15.9% (10.2-21.3)     | 0.90 (0.53-1.55) |

\*HR was calculated to compare 5-year letrozole vs. 2.5-year letrozole. HR=hazard ratio. CI=confidence interval.

# BCI Validation in Extended-Adjuvant Therapy Trials



a. Estimates reported are from most recent update on results from this population.

b. Summary statistic calculated using a random effects model incorporating each study's OR or HR and its associated 95% confidence interval.

# ASCO Guideline: Extended Adjuvant Therapy

## Extended Endocrine Therapy for ER-Positive HER2-Negative Breast Cancer

### *Oncotype DX, EndoPredict, Prosigna, Ki67, or IHC4.*

**Recommendation 1.23.** If a patient has node-negative breast cancer and has had 5 years of endocrine therapy without evidence of recurrence, there is insufficient evidence to use Oncotype DX, EndoPredict, Prosigna, Ki67, or IHC4 scores to guide decisions about extended endocrine therapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

### *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  $\geq 4$  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).

### *Clinical treatment score post-5 years.*

**Recommendation 1.26.** If a patient is postmenopausal and had invasive breast cancer and is recurrence-free after 5 years of adjuvant endocrine therapy, the clinical treatment score post-5 years (CTS5) web tool may be used to calculate the estimated risk of late recurrence (recurrence between years 5-10), which could assist in decisions about extended endocrine therapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

## Summary: ASCO Guideline 2022

| ER+ and HER2–           | Premenopausal or Age $\leq$ 50 Years<br>(evidence quality/strength of recommendation)  | Postmenopausal or Age $>$ 50 Years<br>(evidence quality/strength of recommendation)                                                                                                                                                                                                                                                                        |
|-------------------------|----------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Node-negative           | Oncotype DX ( <i>high/strong</i> )                                                     | Oncotype DX ( <i>high/strong</i> )<br>MammaPrint <sup>a</sup> ( <i>intermediate/strong</i> )<br>EndoPredict ( <i>intermediate/moderate</i> )<br>Prosigna ( <i>intermediate/moderate</i> )<br>Ki67 <sup>b</sup> ( <i>intermediate/moderate</i> )<br>IHC4 <sup>b</sup> ( <i>intermediate/moderate</i> )<br>BCI <sup>c</sup> ( <i>intermediate/moderate</i> ) |
| 1-3 positive nodes      | Insufficient evidence to recommend a biomarker for use                                 | Oncotype DX ( <i>high/strong</i> )<br>MammaPrint <sup>a</sup> ( <i>intermediate/strong</i> )<br>EndoPredict ( <i>intermediate/moderate</i> )<br>Ki67 <sup>b</sup> ( <i>intermediate/strong</i> )<br>IHC4 <sup>b</sup> ( <i>intermediate/moderate</i> )<br>BCI <sup>c</sup> ( <i>intermediate/moderate</i> )                                                |
| $\geq$ 4 positive nodes | Insufficient evidence to recommend a biomarker for use                                 |                                                                                                                                                                                                                                                                                                                                                            |
| HER2+ (ER+ or ER–)      | No mature evidence to recommend use of any other biomarker for this patient population |                                                                                                                                                                                                                                                                                                                                                            |
| ER–/HER2–               | No mature evidence to recommend use of any other biomarker for this patient population |                                                                                                                                                                                                                                                                                                                                                            |

# Management of Hormone Receptor (HR)-Positive Localized Breast Cancer

**Module 1:** Risk Assessment and Genomic Assays for HR-Positive, HER2-Negative Localized Breast Cancer

**Module 2: Clinician Survey Results**

**Module 3:** Adjuvant CDK4/6 Inhibitors for High-Risk, HR-Positive, HER2-Negative Localized Breast Cancer

**Module 4:** Clinician Survey Results

**Module 5:** Tolerability and Other Practical Considerations with Adjuvant CDK4/6 Inhibitor Therapy

**Module 6:** Clinician Survey Results

**Module 7:** Adjuvant Oral SERDs for HR-Positive, HER2-Negative Localized Breast Cancer

Outside of a clinical trial, which genomic assay(s) do you routinely order to assist with decision-making regarding adjuvant systemic therapy for your patients with HR-positive, HER2-negative localized breast cancer (BC)?



Dr Brufsky

*Oncotype DX*<sup>®</sup>, MammaPrint<sup>®</sup>, EndoPredict<sup>®</sup>, Breast Cancer Index<sup>®</sup>



Dr Chen

*Oncotype DX*, Breast Cancer Index



Dr Jhaveri

*Oncotype DX*



Dr Kalinsky

*Oncotype DX*



Dr Mahtani

*Oncotype DX*, MammaPrint, Breast Cancer Index



Dr Mouabbi

*Oncotype DX*, MammaPrint, Breast Cancer Index



Dr Rugo

*Oncotype DX* and MammaPrint



Dr Sharma

*Oncotype DX* and MammaPrint

Would you recommend adjuvant chemotherapy for a 40-year-old premenopausal patient with node-negative, HR-positive, HER2-negative localized BC and the 21-gene Recurrence Score® (RS) listed below?

|                                                                                     |             | RS = 8 | RS = 17                              | RS = 20                              |
|-------------------------------------------------------------------------------------|-------------|--------|--------------------------------------|--------------------------------------|
|    | Dr Brufsky  | No     | No                                   | Yes, but offer OFS/OA as alternative |
|    | Dr Chen     | No     | No                                   | Yes, but offer OFS/OA as alternative |
|    | Dr Jhaveri  | No     | Yes, but offer OFS/OA as alternative | Yes, but offer OFS/OA as alternative |
|    | Dr Kalinsky | No     | No                                   | Yes                                  |
|    | Dr Mahtani  | No     | Yes, but offer OFS/OA as alternative | Yes, but offer OFS/OA as alternative |
|  | Dr Mouabbi  | No     | No                                   | No                                   |
|  | Dr Rugo     | No     | No*                                  | No*                                  |
|  | Dr Sharma   | No     | No                                   | Yes, but offer OFS/OA as alternative |

OFS/OA = ovarian function suppression/ovarian ablation; \* Would offer OFS/OA

Would you recommend adjuvant chemotherapy for a 40-year-old premenopausal patient with HR-positive, HER2-negative localized BC with 3 positive nodes and the 21-gene RS listed below?

|                                                                                     |             | RS = 8                               | RS = 17                              | RS = 20                              |
|-------------------------------------------------------------------------------------|-------------|--------------------------------------|--------------------------------------|--------------------------------------|
|    | Dr Brufsky  | Yes, but offer OFS/OA as alternative | Yes, but offer OFS/OA as alternative | Yes, but offer OFS/OA as alternative |
|    | Dr Chen     | Yes, but offer OFS/OA as alternative | Yes                                  | Yes                                  |
|    | Dr Jhaveri  | Yes                                  | Yes                                  | Yes                                  |
|    | Dr Kalinsky | Yes                                  | Yes                                  | Yes                                  |
|    | Dr Mahtani  | Yes                                  | Yes                                  | Yes                                  |
|  | Dr Mouabbi  | Yes, but offer OFS/OA as alternative | Yes, but offer OFS/OA as alternative | Yes, but offer OFS/OA as alternative |
|  | Dr Rugo     | Yes                                  | Yes                                  | Yes                                  |
|  | Dr Sharma   | Yes                                  | Yes                                  | Yes                                  |

OFS/OA = ovarian function suppression/ovarian ablation

Would you recommend adjuvant chemotherapy for a 65-year-old postmenopausal patient with HR-positive, HER2-negative localized BC with 3 positive nodes and the 21-gene RS listed below?

|                                                                                     |             | RS = 8 | RS = 17 | RS = 20 |
|-------------------------------------------------------------------------------------|-------------|--------|---------|---------|
|    | Dr Brufsky  | No     | No      | No      |
|    | Dr Chen     | No     | No      | No      |
|    | Dr Jhaveri  | No     | No      | No      |
|    | Dr Kalinsky | No     | No      | Yes     |
|    | Dr Mahtani  | No     | No      | Yes     |
|  | Dr Mouabbi  | No     | No      | No      |
|  | Dr Rugo     | No     | No      | No      |
|  | Dr Sharma   | No     | No      | No      |

Have you ordered or would you order a genomic assay to assist with treatment decision-making in the localized setting for any patients with HR-positive, HER2-negative localized BC and 4 or more positive nodes?



**Dr Brufsky**

**I have**



**Dr Chen**

**I have**



**Dr Jhaveri**

**I have not but would for the right patient**



**Dr Kalinsky**

**I have not but would for the right patient**



**Dr Mahtani**

**I have not and would not**



**Dr Mouabbi**

**I have not and would not**



**Dr Rugo**

**I have**



**Dr Sharma**

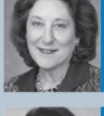
**I have not and would not**

Outside of a clinical trial, which genomic assay(s) do you routinely order to assist with decision-making in the neoadjuvant setting for your patients with HR-positive, HER2-negative localized BC?

|                                                                                     |             |                                     |
|-------------------------------------------------------------------------------------|-------------|-------------------------------------|
|    | Dr Brufsky  | MammaPrint                          |
|    | Dr Chen     | MammaPrint and <i>Oncotype DX</i>   |
|    | Dr Jhaveri  | <i>Oncotype DX</i>                  |
|    | Dr Kalinsky | MammaPrint                          |
|    | Dr Mahtani  | MammaPrint                          |
|    | Dr Mouabbi  | MammaPrint                          |
|  | Dr Rugo     | MammaPrint and <i>Oncotype DX</i> * |
|  | Dr Sharma   | <i>Oncotype DX</i> and MammaPrint   |

\* All my patients with HR+ disease screen for I-SPY with rare exceptions and we order Mammaprint and BluePrint. I will occasionally order *Oncotype DX*

Outside of a clinical trial, do you routinely employ Breast Cancer Index (BCI) to determine whether to continue adjuvant endocrine therapy beyond 5 years for patients with HR-positive, HER2-negative localized BC? If so, in which clinical situations?

|                                                                                     |                    |                                                                                                                      |
|-------------------------------------------------------------------------------------|--------------------|----------------------------------------------------------------------------------------------------------------------|
|    | <b>Dr Brufsky</b>  | <b>Yes, for node-positive disease when MammaPrint not available</b>                                                  |
|    | <b>Dr Chen</b>     | <b>Yes, for Stage II or low-risk Stage III disease in patients who are tolerating ET well and willing to do more</b> |
|    | <b>Dr Jhaveri</b>  | <b>Yes, per patient preference and for N0 and N1, especially if patients are struggling with toxicities</b>          |
|    | <b>Dr Kalinsky</b> | <b>Yes, in situations where I'm on the fence about extending ET</b>                                                  |
|    | <b>Dr Mahtani</b>  | <b>Yes, for patients with N0 disease or up to 3 pos nodes</b>                                                        |
|   | <b>Dr Mouabbi</b>  | <b>Yes, for patients for whom we are considering extended ET</b>                                                     |
|  | <b>Dr Rugo</b>     | <b>No*</b>                                                                                                           |
|  | <b>Dr Sharma</b>   | <b>Yes, for patients with high-risk, node-negative disease</b>                                                       |

ET = endocrine therapy; \* No due to reimbursement issues, but I would for patients with poor tolerance to ET and high-risk disease

Approximately what proportion of the time would you estimate that having the results from BCI cause you to change your recommendation regarding extended-adjuvant endocrine therapy (ET)?

|                                                                                     |             | Recommending ET to not recommending | Not recommending ET to recommending |
|-------------------------------------------------------------------------------------|-------------|-------------------------------------|-------------------------------------|
|    | Dr Brufsky  | 25%                                 | 25%                                 |
|    | Dr Chen     | 15%                                 | 5%                                  |
|    | Dr Jhaveri  | 5% to 10%                           | <5%                                 |
|    | Dr Kalinsky | 10%                                 | 10%                                 |
|    | Dr Mahtani  | 20%                                 | 20%                                 |
|  | Dr Mouabbi  | 80%                                 | 20%                                 |
|  | Dr Rugo     | NA                                  | NA                                  |
|  | Dr Sharma   | 10%                                 | 10%                                 |

NA = not applicable

Outside of a clinical trial, do you routinely employ any genomic assays other than Breast Cancer Index to determine whether to continue adjuvant endocrine therapy beyond 5 years for patients with HR-positive, HER2-negative localized BC?

|                                                                                     |             |                 |
|-------------------------------------------------------------------------------------|-------------|-----------------|
|    | Dr Brufsky  | Yes, MammaPrint |
|    | Dr Chen     | No              |
|    | Dr Jhaveri  | No              |
|    | Dr Kalinsky | No              |
|    | Dr Mahtani  | No              |
|    | Dr Mouabbi  | Yes, MammaPrint |
|  | Dr Rugo     | No              |
|  | Dr Sharma   | No              |

Have you ordered or would you order a circulating tumor DNA (ctDNA)-based molecular residual disease (MRD) assay to assist with clinical decision-making for a patient with localized BC? If you were to order a ctDNA-based MRD assay for a patient with localized BC, which specific assay(s) would you use?

|                                                                                     |             | Order a ctDNA-based MRD assay?             | Assay      |
|-------------------------------------------------------------------------------------|-------------|--------------------------------------------|------------|
|    | Dr Brufsky  | I have                                     | Signatera™ |
|    | Dr Chen     | I have                                     | Signatera  |
|    | Dr Jhaveri  | I have not and would not                   | NA         |
|    | Dr Kalinsky | I have not but would for the right patient | Signatera  |
|    | Dr Mahtani  | I have not and would not                   | NA         |
|  | Dr Mouabbi  | I have                                     | Signatera  |
|  | Dr Rugo     | I have                                     | Signatera  |
|  | Dr Sharma   | I have not and would not                   | NA         |

NA = not applicable

# **Management of Hormone Receptor (HR)-Positive Localized Breast Cancer**

**Module 1: Risk Assessment and Genomic Assays for HR-Positive, HER2-Negative Localized Breast Cancer**

**Module 2: Clinician Survey Results**

**Module 3: Adjuvant CDK4/6 Inhibitors for High-Risk, HR-Positive, HER2-Negative Localized Breast Cancer**

**Module 4: Clinician Survey Results**

**Module 5: Tolerability and Other Practical Considerations with Adjuvant CDK4/6 Inhibitor Therapy**

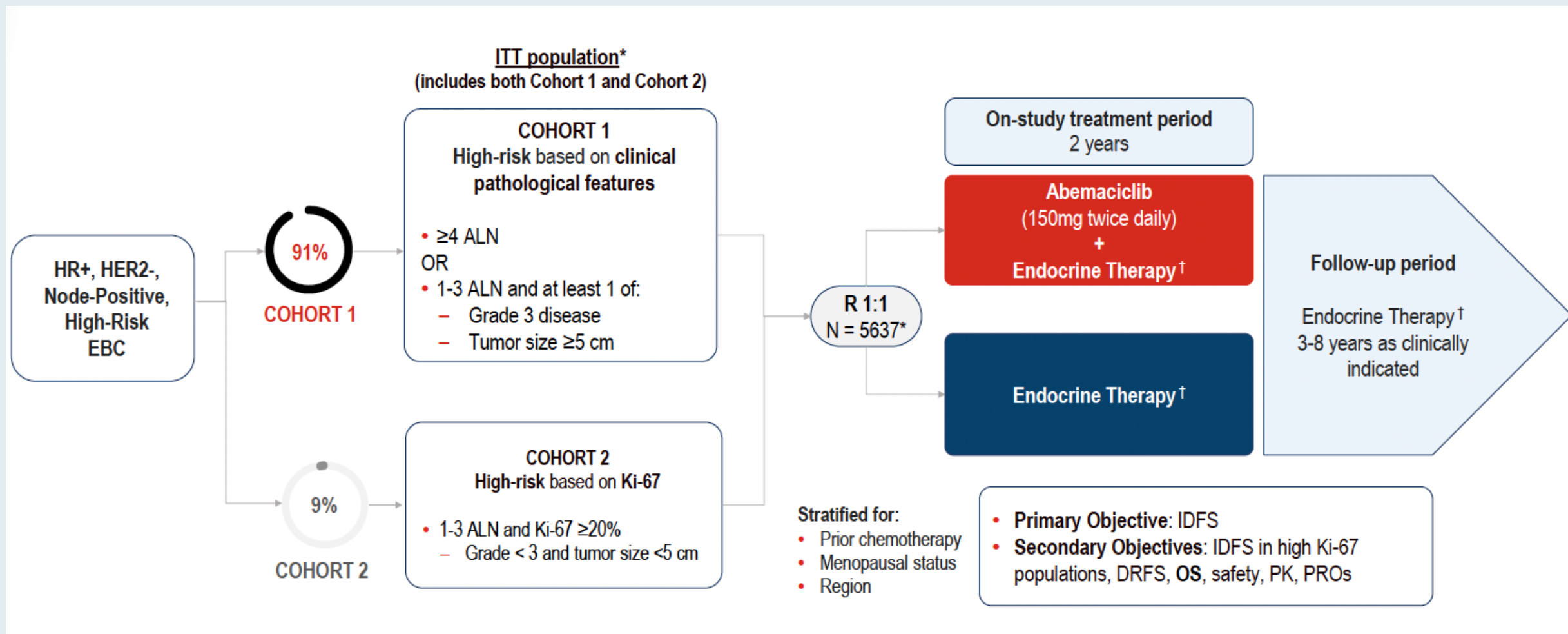
**Module 6: Clinician Survey Results**

**Module 7: Adjuvant Oral SERDs for HR-Positive, HER2-Negative Localized Breast Cancer**

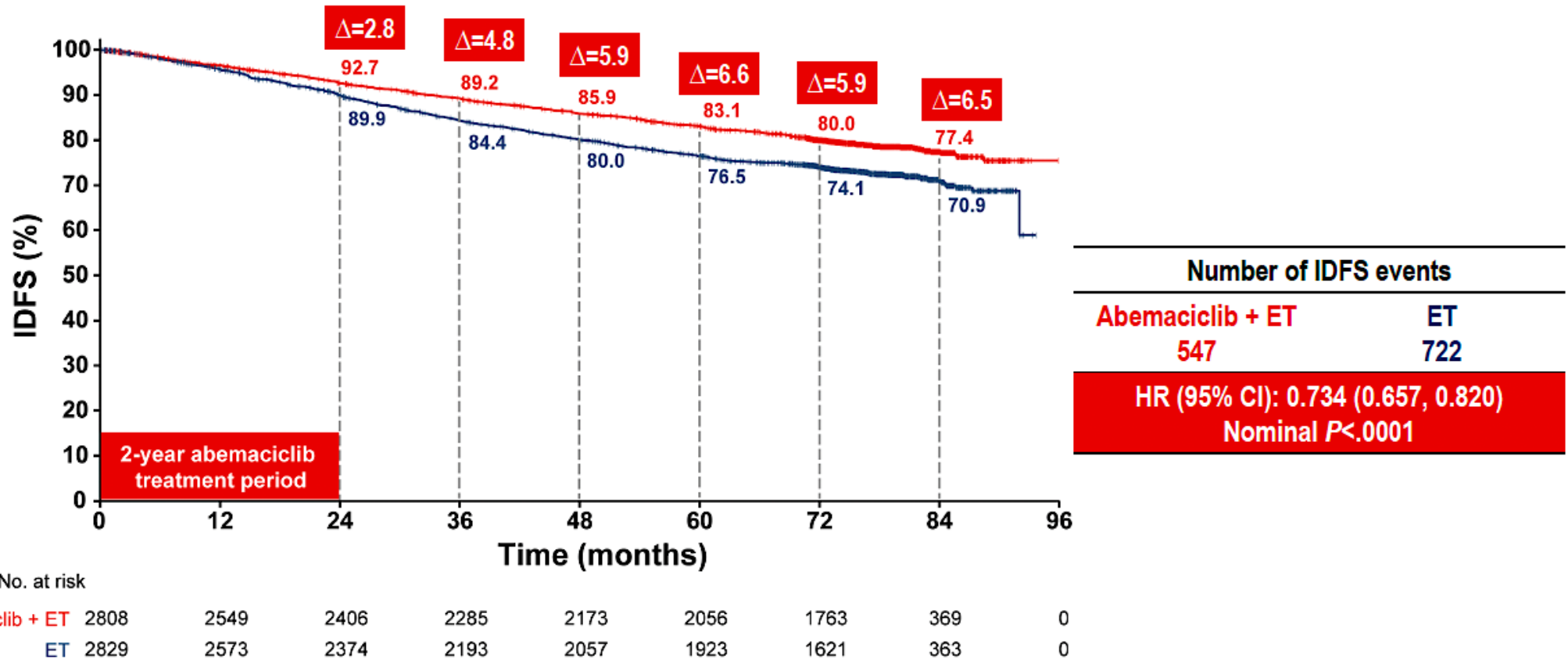
# Key Datasets

- Johnston S et al. **monarchE: Primary overall survival** (OS) results of adjuvant abemaciclib + endocrine therapy (ET) for HR+, HER2-, high-risk early breast cancer (EBC). ESMO 2025;Abstract LBA13.
- Johnston S et al. **Overall survival** with **abemaciclib** in early breast cancer. *Ann Oncol* 2026;37(2):155-65.
- Cortés J et al. **monarchE: Subgroup analysis** of adjuvant abemaciclib + endocrine therapy for HR+, HER2-, high-risk early breast cancer by nodal status. San Antonio Breast Cancer Symposium 2025;Abstract PS1-08-08.
- Crown JP et al. **Adjuvant ribociclib (RIB) plus nonsteroidal aromatase inhibitor (NSAI)** in patients (pts) with HR+/HER2- early breast cancer (EBC): **NATALEE 5-year outcomes**. ESMO 2025;Abstract LBA14.
- Chia SKL et al. Prognostic and predictive impact of baseline gene expression (exp) in the **NATALEE trial** of adjuvant (adj) ribociclib (RIB) + nonsteroidal aromatase inhibitor (NSAI) in HR+/HER2- early breast cancer (EBC). ASCO 2026;Abstract 501.

# monarchE Study Design



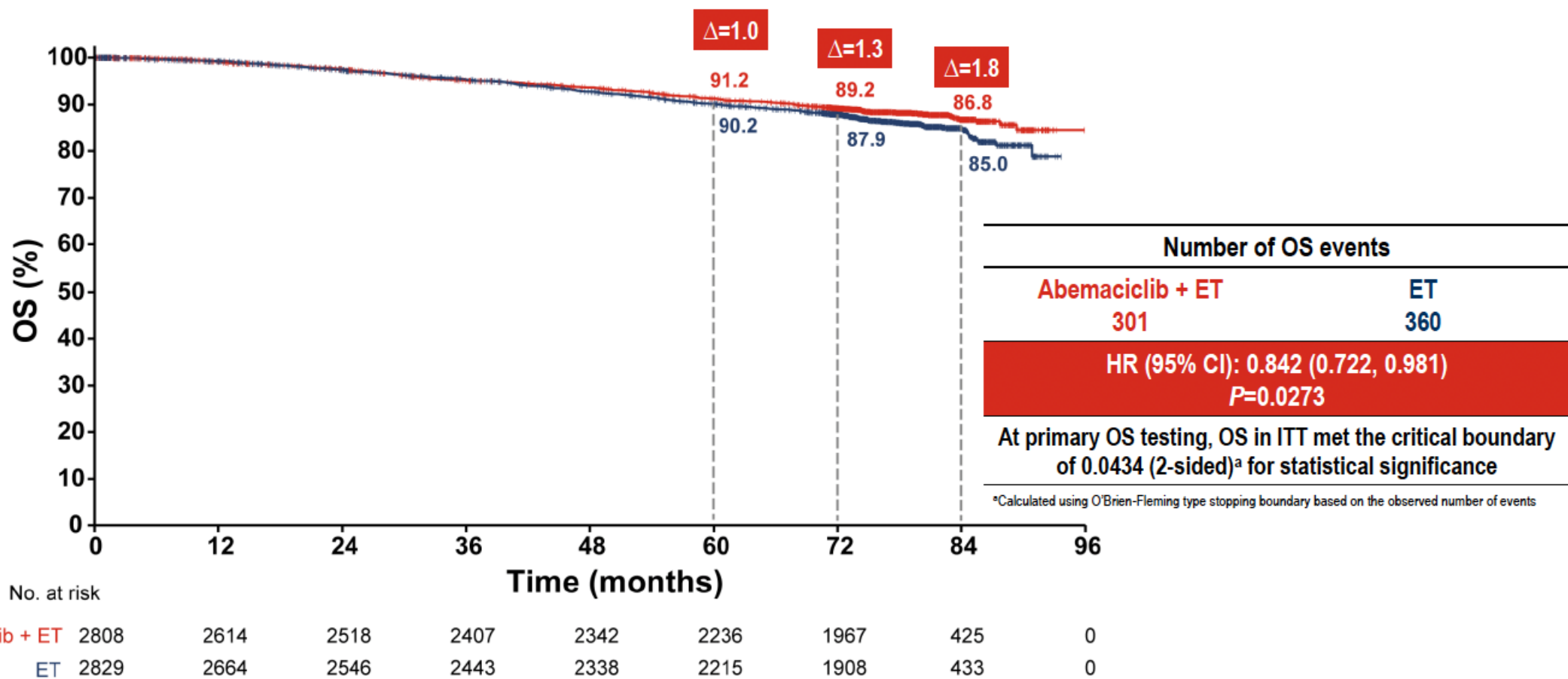
# monarchE: Invasive Disease-Free Survival (IDFS) Outcomes



**Abemaciclib + ET reduced the risk of IDFS events by 26.6% compared to ET alone**

ET = endocrine therapy

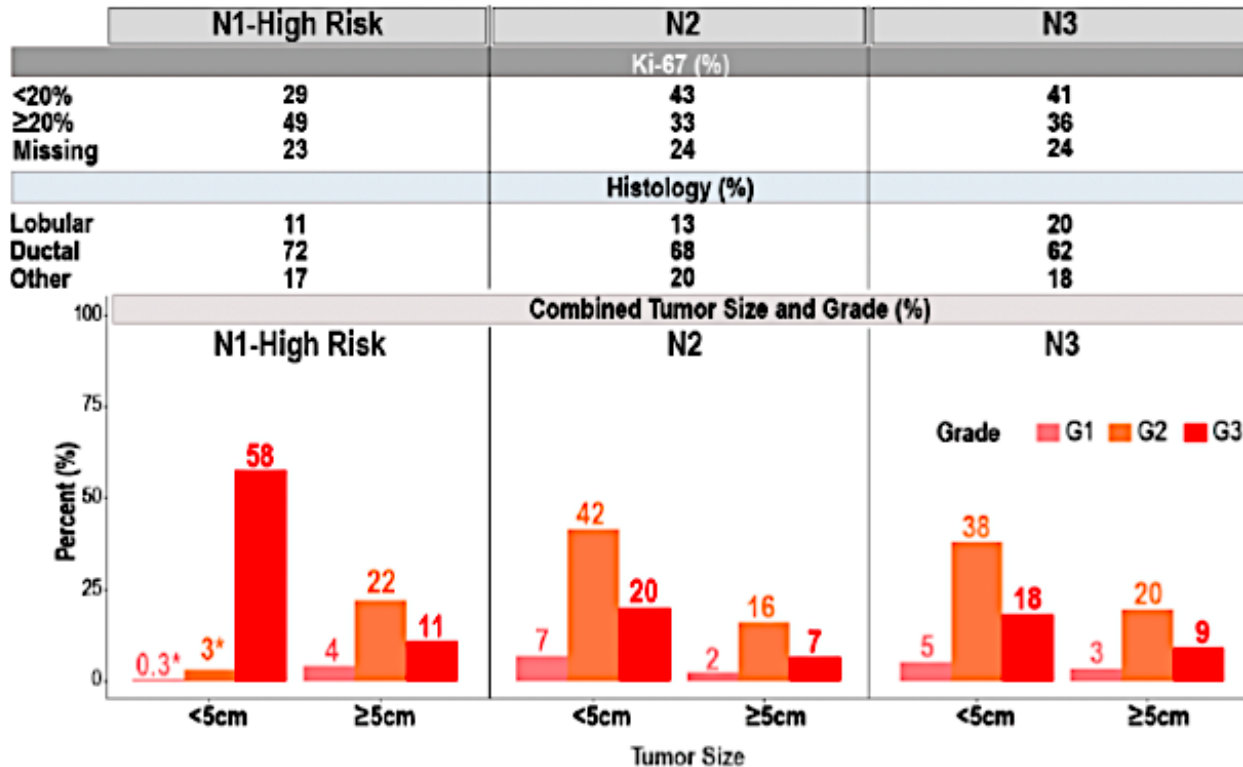
# monarchE: Overall Survival (OS) Outcomes



At a median follow-up of 6.3 years, abemaciclib + ET reduced the risk of death by 15.8% compared to ET alone

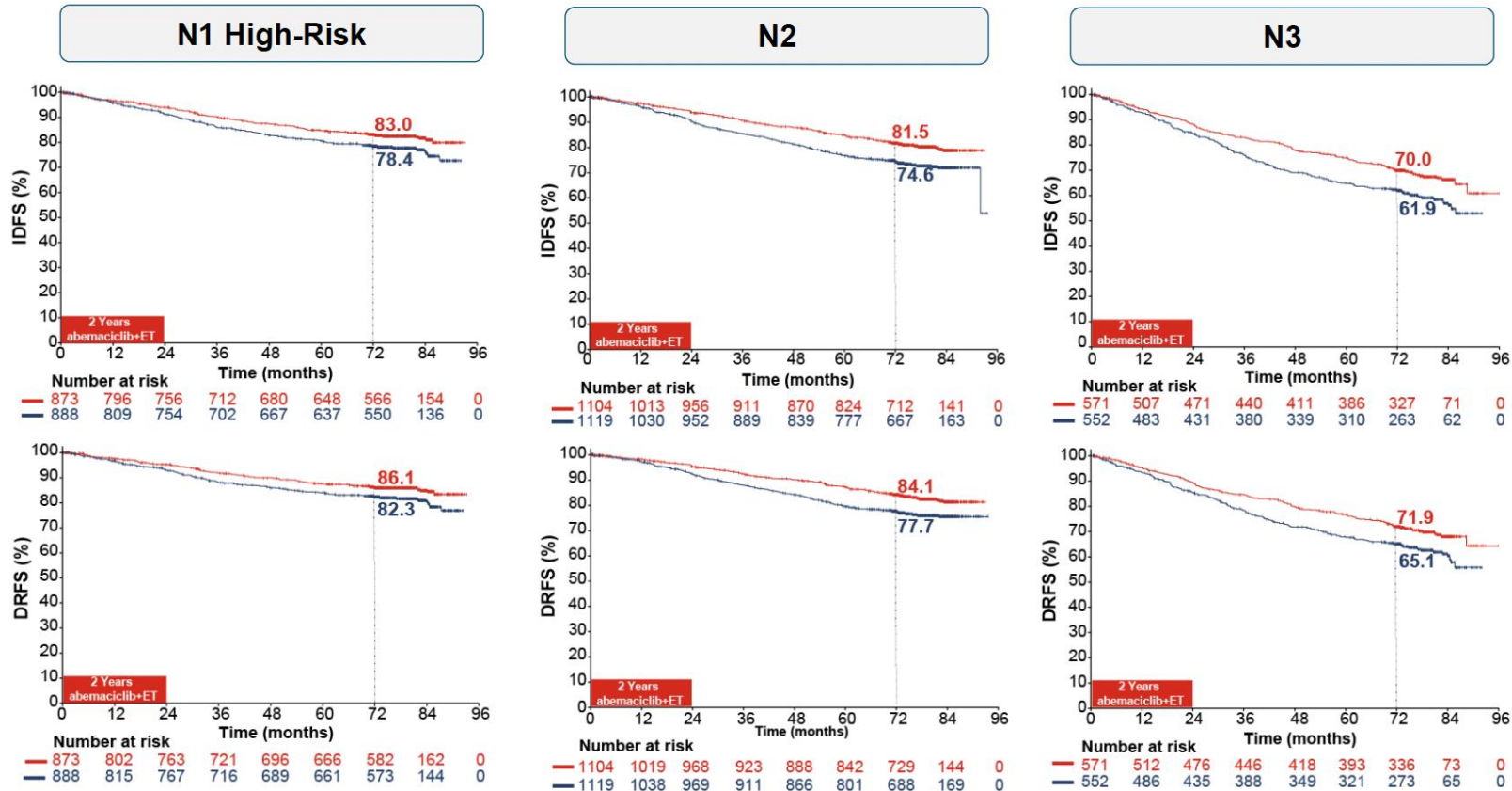
# monarchE: Subgroup Analysis by Nodal Status

## Tumor Characteristics in Cohort 1



- monarchE eligible patients with N1 high risk disease presented more Grade 3 tumors and Ki-67 ≥20% compared to N2 and N3
- Distribution of ductal/lobular histology was similar in N1-high risk and N2 while N3 had more lobular tumors
- Over 40% of patients with N1-High risk disease received neoadjuvant chemotherapy compared to less than 30% of those with N3 disease
- Conversely, the use of adjuvant chemotherapy and radiation therapy was higher among patients with N2 and N3 disease

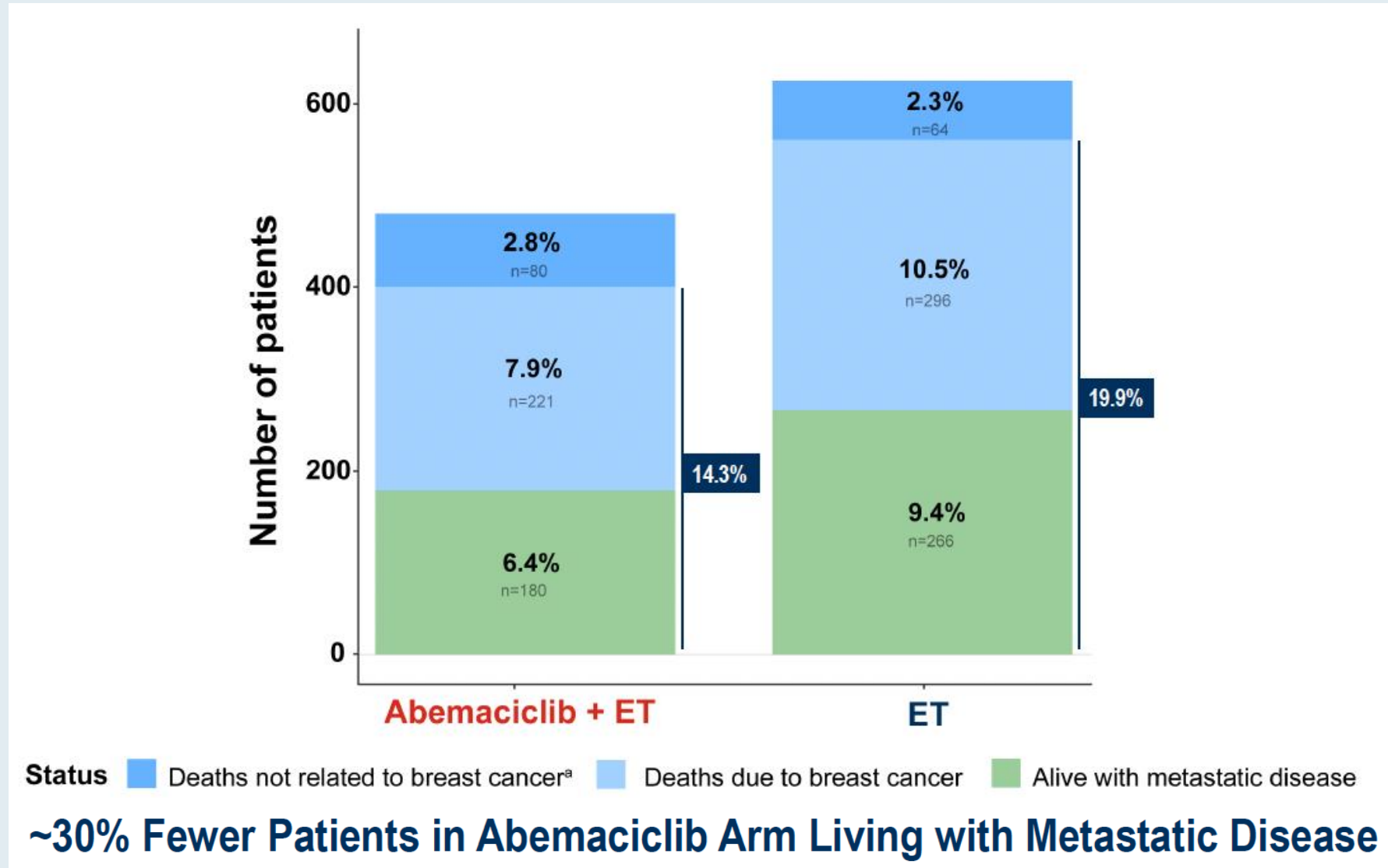
# monarchE: IDFS and DRFS by Nodal Status



- In the ET alone arm, patients with N1-High risk and N2 disease had comparable risk of recurrence and death, while higher risk was observed in N3 subgroup
- Abemaciclib plus ET reduced the risk of IDFS events by 24.8% (N1), 31.5% (N2) and 27.4% (N3), compared to ET

DRFS = distant relapse-free survival

# monarchE: Survival Status



# NATALEE Study Design

## Adult patients with stage II and III HR+/HER2- EBC

- Prior ET allowed up to 12 months
- **Anatomical stage IIA<sup>a</sup>**
  - N0 with:
    - Grade 2 and evidence of high risk:
      - Ki-67  $\geq$  20%
      - Oncotype DX Breast Recurrence Score  $\geq$  26 or
      - High risk via genomic risk profiling
    - Grade 3
  - N1
- **Anatomical stage IIB<sup>a</sup>**
  - N0 or N1
- **Anatomical stage III**
  - N0, N1, N2, or N3

**R**  
**1:1**

### RIB

400 mg/day  
3 weeks on/1 week off for 3 y

+

### NSAI

Letrozole or anastrozole<sup>b</sup> for  $\geq$ 5 y  
+ goserelin in men and premenopausal women

### NSAI

Letrozole or anastrozole<sup>b</sup> for  $\geq$ 5 y  
+ goserelin in men and premenopausal women

### Primary End Point

iDFS using STEEP criteria

### Secondary End Points

- RFS, DDFS, OS
- PROs
- Safety and tolerability
- PK

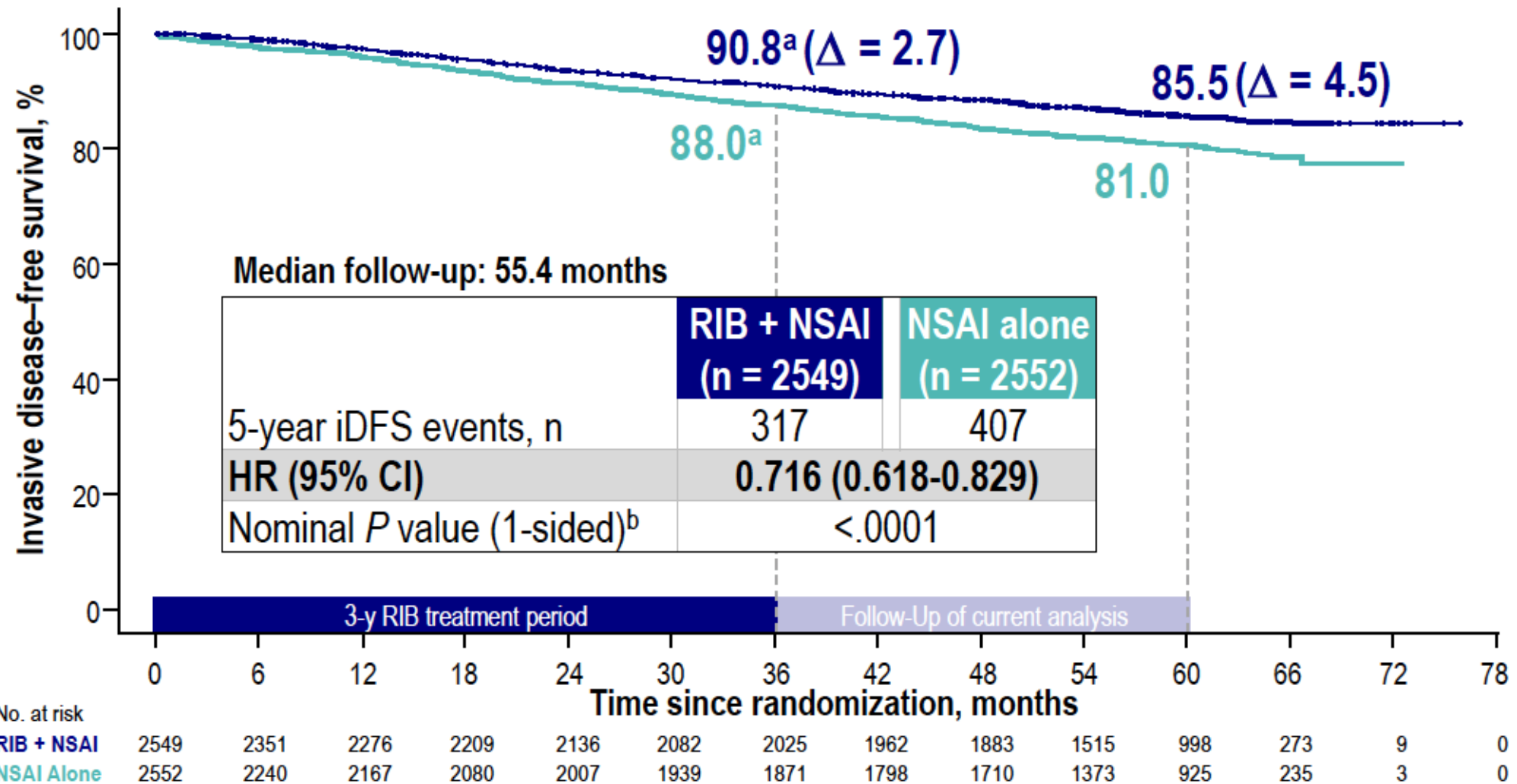
### Exploratory End Points

- DRFS
- Gene expression and alterations in tumor ctDNA/ctRNA samples

Efficacy outcomes for the 5-year analysis were estimated by the Kaplan-Meier method, and results are descriptive. The Cox proportional hazards model was used to estimate the HRs and 95% CIs.

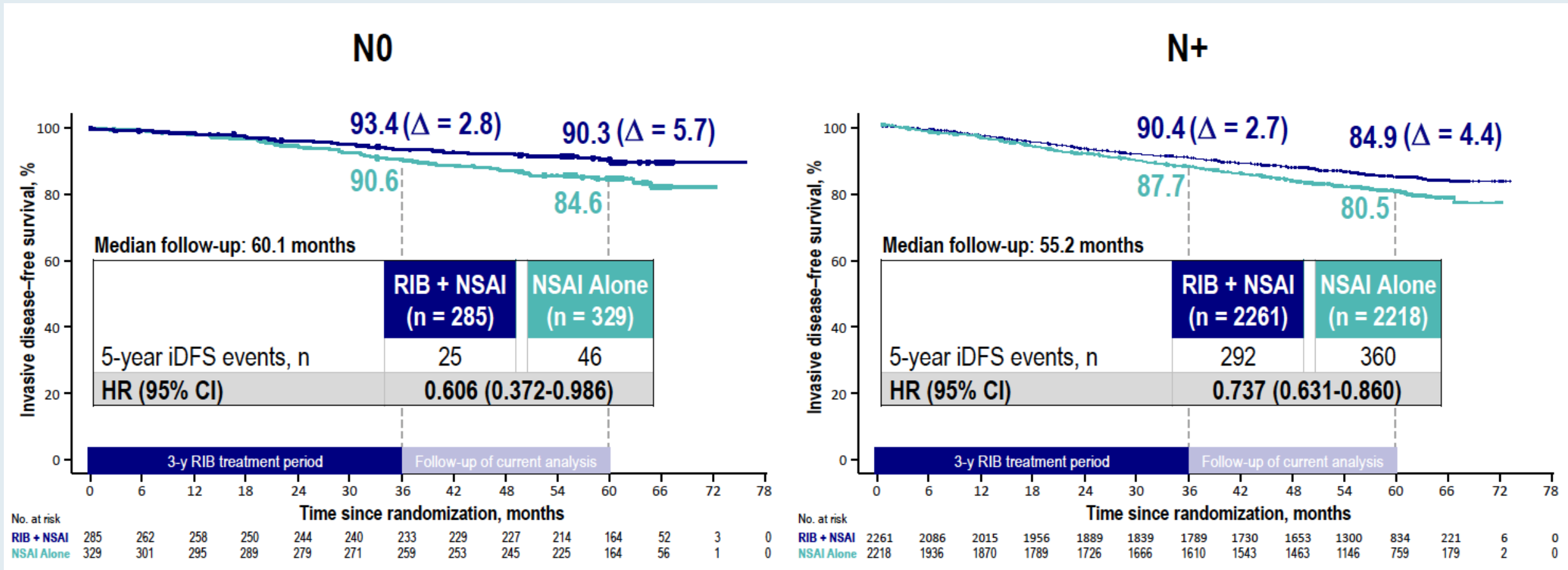
RIB = ribociclib; NSAI = nonsteroidal aromatase inhibitor

# NATALEE: IDFS Outcomes

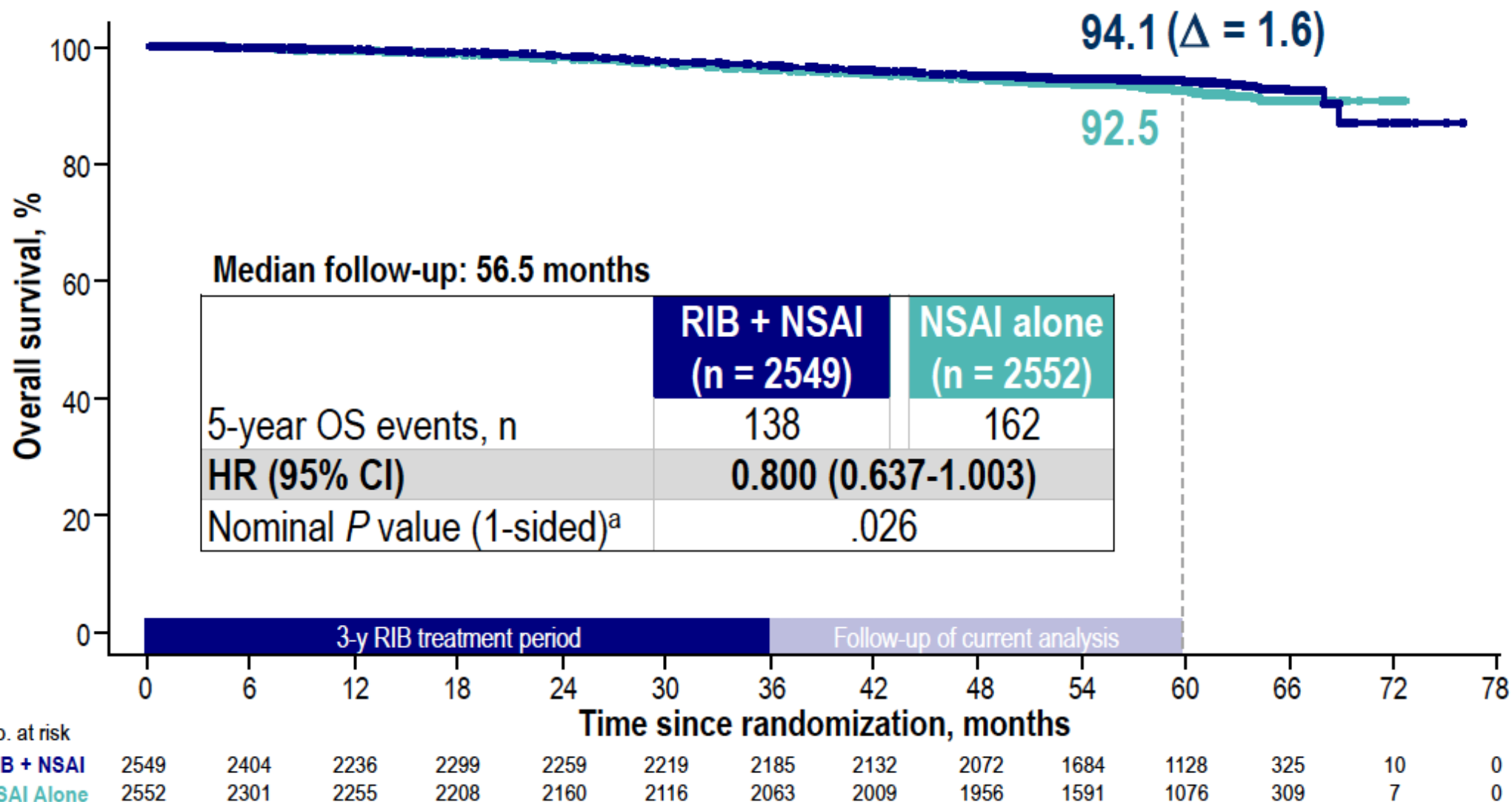


RIB = ribociclib; NSAI = nonsteroidal aromatase inhibitor

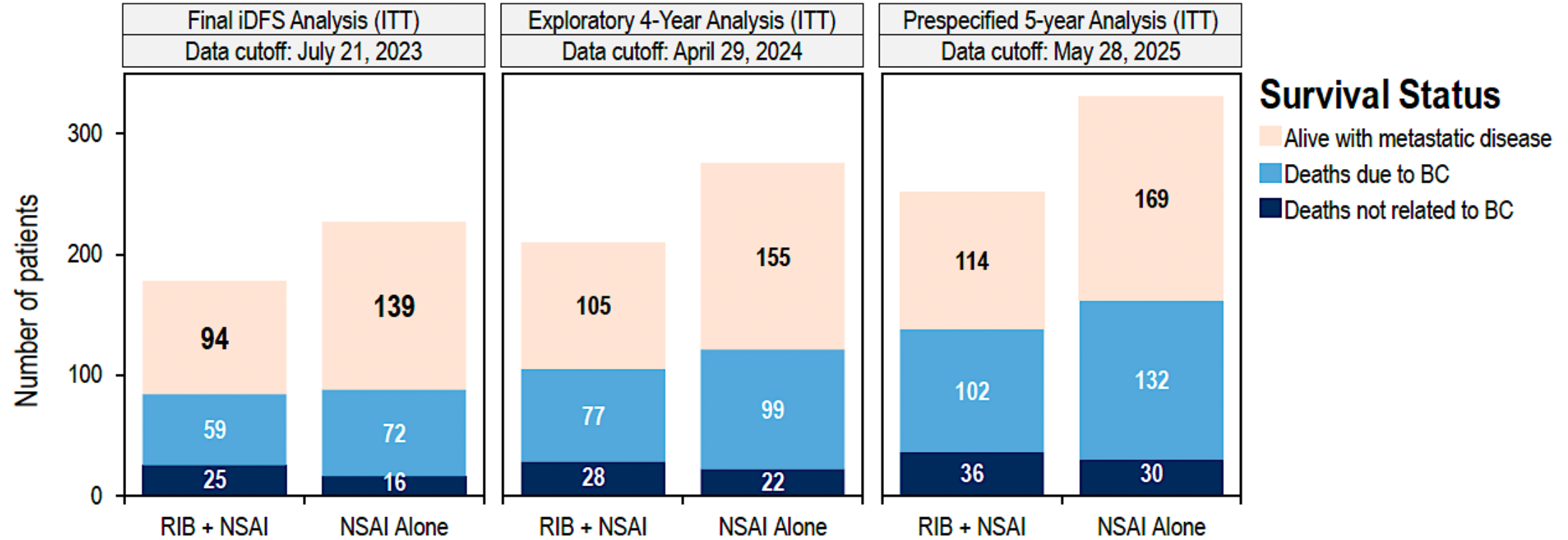
# NATALEE: IDFS by Nodal Status



# NATALEE: OS Outcomes

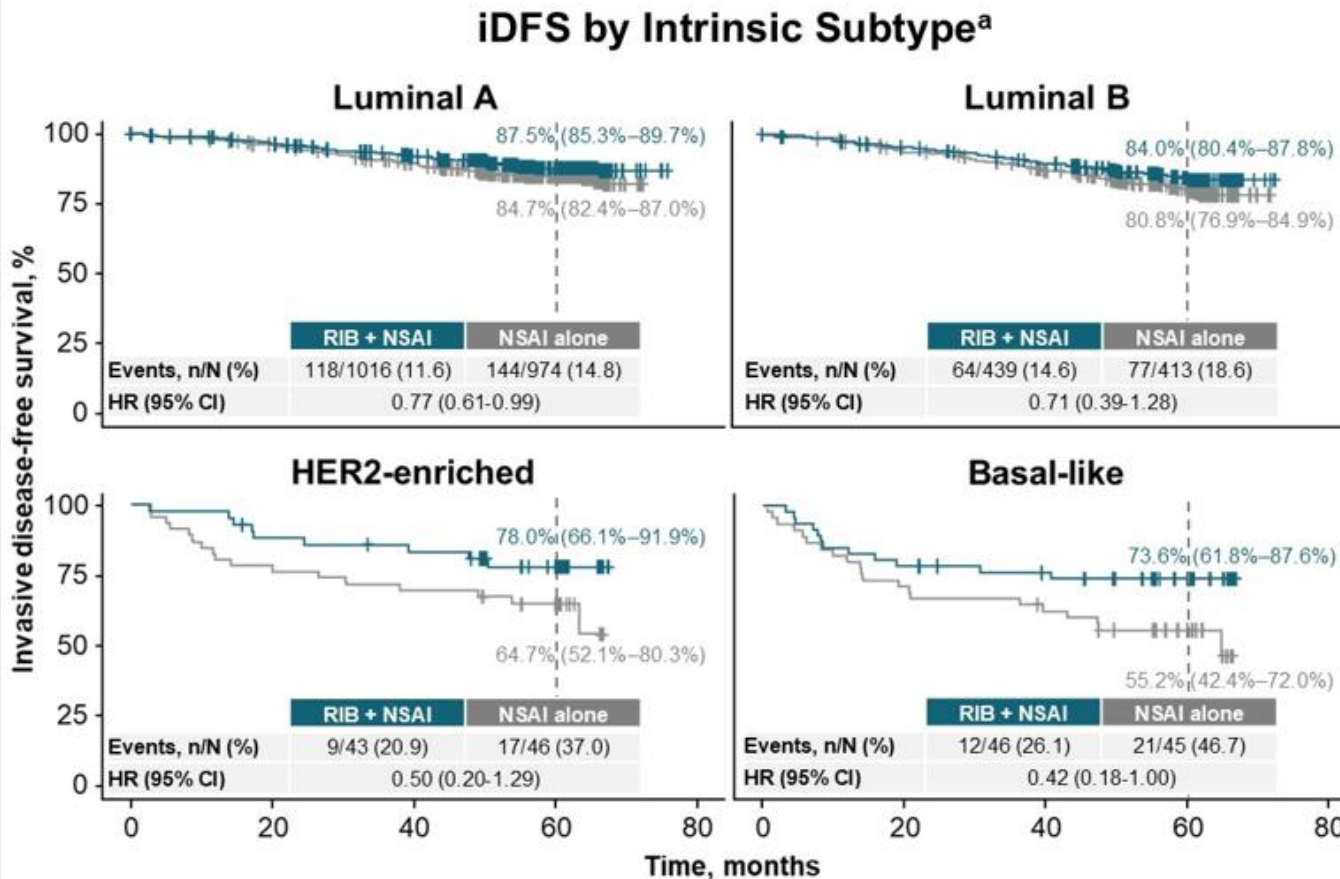


# NATALEE: Survival Status over Time

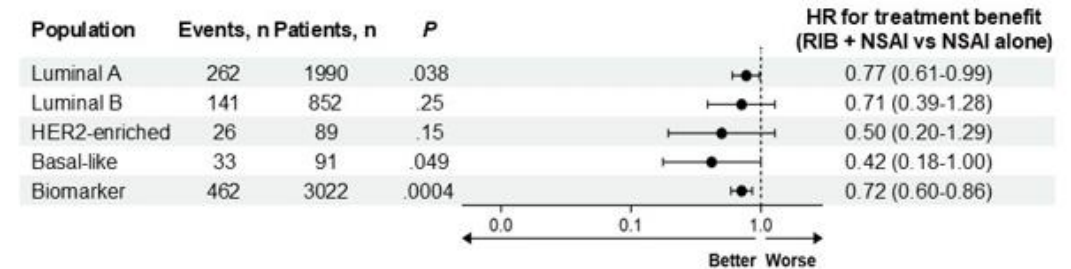


|                                       |                  |                  |                     |
|---------------------------------------|------------------|------------------|---------------------|
| Approximate median follow-up (months) | 36               | 44               | 57                  |
| OS HR (95% CI)                        | 0.89 (0.66-1.20) | 0.83 (0.64-1.07) | 0.800 (0.637-1.003) |

# NATALEE: Ribociclib Treatment Benefit Is Observed Across PAM50-Based Intrinsic Subtypes



## Ribociclib Treatment Benefit Across Intrinsic Subtypes<sup>a,b</sup>



- Across treatment arms, PAM50 subtypes were strongly prognostic (hazard ratio vs luminal A: luminal B, 1.39; HER2-enriched, 2.62; basal-like, 3.92<sup>c</sup>)
- No significant interaction between subtype and treatment was observed ( $P=.34^d$ )

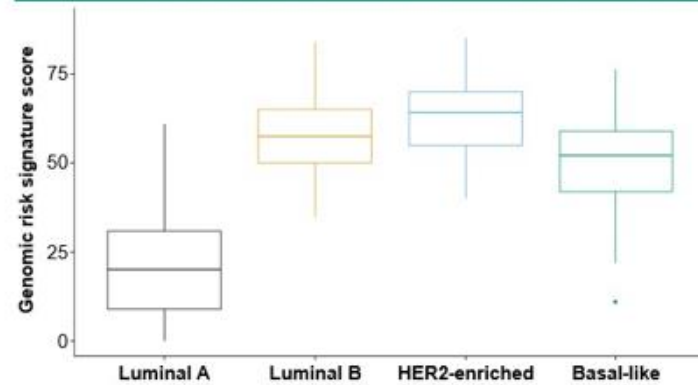
HER2, human epidermal growth factor receptor 2; HR, hazard ratio; iDFS, invasive disease-free survival; NSAI, nonsteroidal aromatase inhibitor; PAM50, Prediction Analysis of Microarray 50; RIB, ribociclib.

<sup>a</sup> HRs were estimated using Cox proportional hazards models stratified by the four main strata and including a term for biomarker-by-treatment interaction. <sup>b</sup> The p-values for treatment effects within individual biomarker subgroups are model-based nominal two-sided Wald p-values without multiplicity correction. <sup>c</sup> HRs were obtained from Cox proportional hazards models stratified by the four main strata and adjusted for treatment group. <sup>d</sup> Nominal two-sided p-value from likelihood ratio test without multiplicity correction.

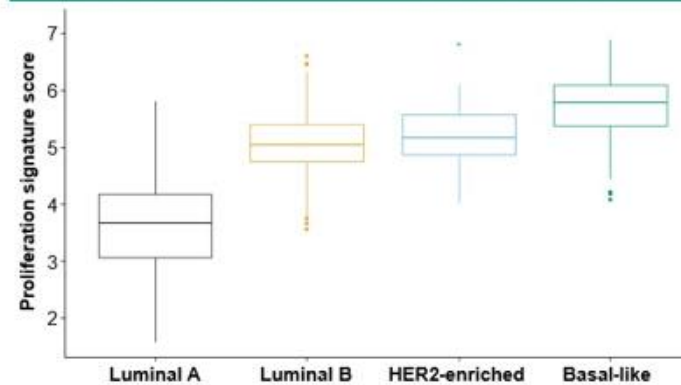
# NATALEE: Higher Genomic Risk Signature and Proliferation Signature Scores Are Associated with Increased Ribociclib Benefit

By Subtype

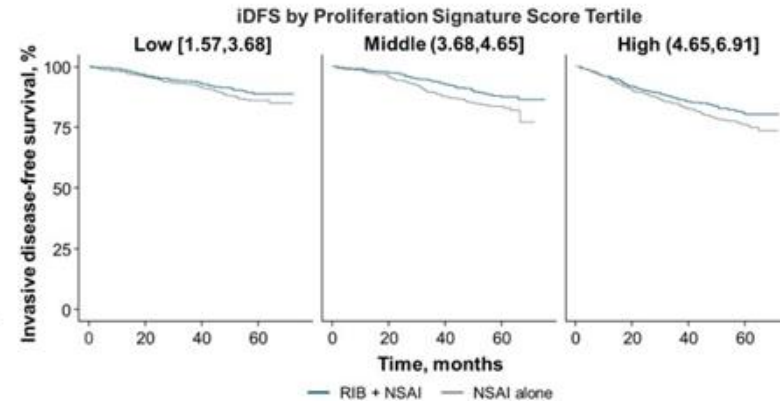
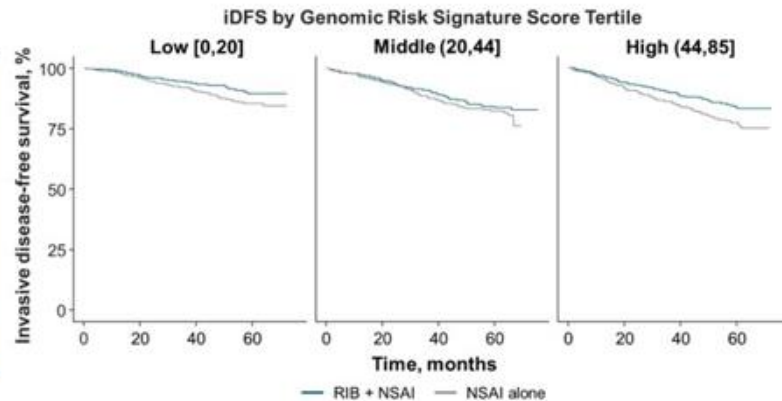
Genomic Risk Signature Scores



Proliferation Signature Scores



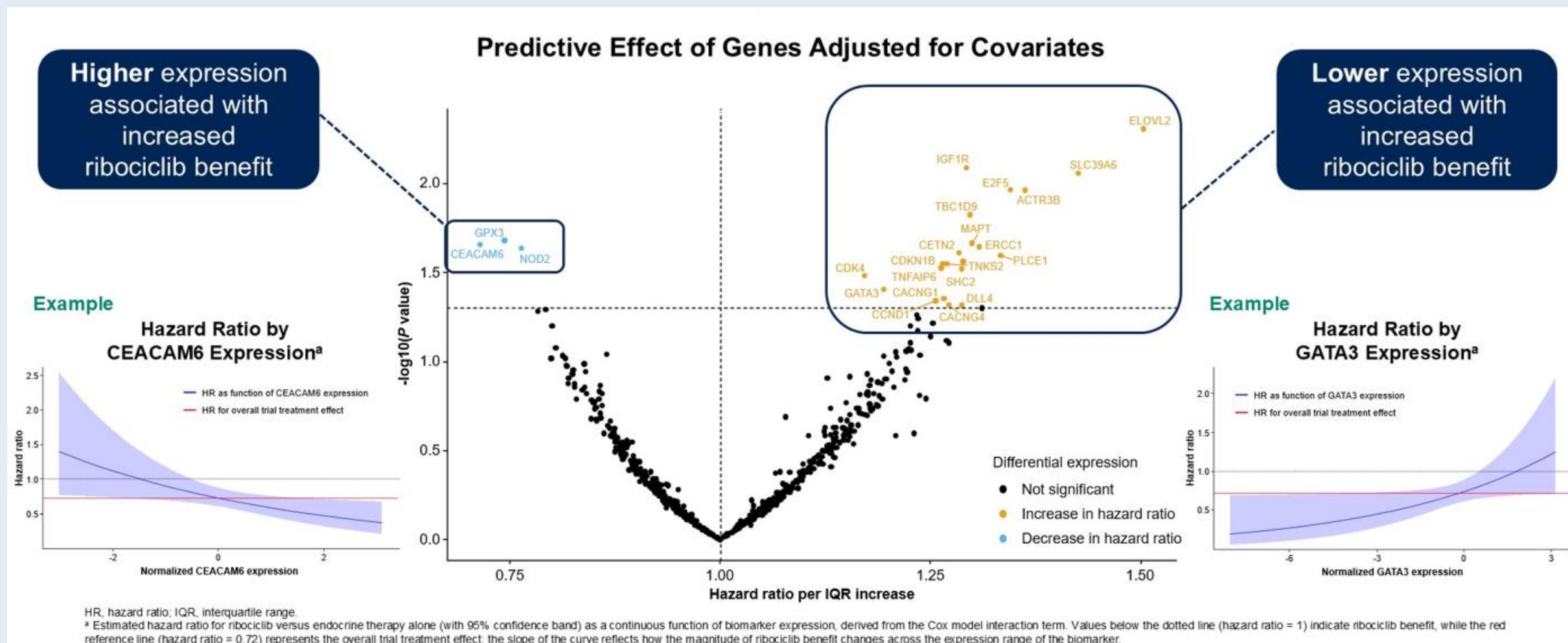
Treatment Effect



- Gene signatures were associated with PAM50 subtypes
- Higher genomic risk signature or proliferation signature scores showed a trend for increased ribociclib benefit, with no significant treatment interaction ( $P=.42$  and  $P=.84$ , respectively<sup>a</sup>)
- Of note, patients with N0 disease had significantly higher genomic risk scores and proliferation scores than those with N1-N3 disease

HER2, human epidermal growth factor receptor 2; PAM50, Prediction Analysis of Microarray 50.  
<sup>a</sup> Nominal two-sided  $P$  value from likelihood ratio test without multiplicity correction.

# NATALEE: Differential Gene Expression Affects Ribociclib Benefit



# **Management of Hormone Receptor (HR)-Positive Localized Breast Cancer**

**Module 1: Risk Assessment and Genomic Assays for HR-Positive, HER2-Negative Localized Breast Cancer**

**Module 2: Clinician Survey Results**

**Module 3: Adjuvant CDK4/6 Inhibitors for High-Risk, HR-Positive, HER2-Negative Localized Breast Cancer**

**Module 4: Clinician Survey Results**

**Module 5: Tolerability and Other Practical Considerations with Adjuvant CDK4/6 Inhibitor Therapy**

**Module 6: Clinician Survey Results**

**Module 7: Adjuvant Oral SERDs for HR-Positive, HER2-Negative Localized Breast Cancer**

Regulatory and reimbursement issues aside, would you generally recommend an adjuvant CDK4/6 inhibitor in addition to adjuvant endocrine therapy to a patient with 5.5-cm, Grade 2, HR-positive, HER2-negative localized BC and the following nodal status?

|                                                                                     |             | Node-negative   | 2 positive nodes | 4 positive nodes |
|-------------------------------------------------------------------------------------|-------------|-----------------|------------------|------------------|
|    | Dr Brufsky  | Yes, ribociclib | Yes, abemaciclib | Yes, abemaciclib |
|    | Dr Chen     | Yes, ribociclib | Yes, abemaciclib | Yes, abemaciclib |
|    | Dr Jhaveri  | Yes, ribociclib | Yes, abemaciclib | Yes, abemaciclib |
|    | Dr Kalinsky | Yes, ribociclib | Yes, abemaciclib | Yes, abemaciclib |
|    | Dr Mahtani  | Yes, ribociclib | Yes, either      | Yes, either      |
|  | Dr Mouabbi  | Yes, ribociclib | Yes, either      | Yes, either      |
|  | Dr Rugo     | Yes, ribociclib | Yes, either      | Yes, abemaciclib |
|  | Dr Sharma   | Yes, ribociclib | Yes, either      | Yes, either      |

Regulatory and reimbursement issues aside, would you generally recommend an adjuvant CDK4/6 inhibitor in addition to adjuvant endocrine therapy to a patient with 2.5-cm Grade 2, HR-positive, HER2-negative localized BC and the following nodal status?

|                                                                                     |             | Node-negative   | 2 positive nodes | 4 positive nodes |
|-------------------------------------------------------------------------------------|-------------|-----------------|------------------|------------------|
|    | Dr Brufsky  | No              | No               | Yes, abemaciclib |
|    | Dr Chen     | No              | Yes, abemaciclib | Yes, abemaciclib |
|    | Dr Jhaveri  | Yes, ribociclib | Yes, abemaciclib | Yes, abemaciclib |
|    | Dr Kalinsky | Yes, ribociclib | Yes, abemaciclib | Yes, abemaciclib |
|    | Dr Mahtani  | No              | Yes, ribociclib  | Yes, either      |
|  | Dr Mouabbi  | No              | Yes, either      | Yes, either      |
|  | Dr Rugo     | Yes, ribociclib | Yes, either      | Yes, abemaciclib |
|  | Dr Sharma   | No              | Yes, either      | Yes, either      |

# **Management of Hormone Receptor (HR)-Positive Localized Breast Cancer**

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**Module 7: Adjuvant Oral SERDs for HR-Positive, HER2-Negative Localized Breast Cancer**

# Key Datasets

- Rugo HS et al. **Adjuvant abemaciclib** combined **with endocrine therapy** for high-risk early breast cancer: **Safety and patient-reported outcomes** from the **monarchE** study. *Ann Oncol* 2022;33(6):616-27.
- Barrios C et al. **NATALEE update: Safety and treatment (tx) duration** of **ribociclib (RIB) + nonsteroidal aromatase inhibitor (NSAI)** in patients (pts) with HR+/HER2– early breast cancer (EBC). ESMO Breast 2024;Abstract 113MO.
- Mayer EL et al. **TRADE: A phase II** trial to assess the **tolerability of abemaciclib dose escalation** in early-stage HR-positive/HER2-negative breast cancer. *Ann Oncol* 2025;31(1):117-24.

# monarchE: Overall Safety Profile

**Table 1. Clinically relevant adverse events observed in the abemaciclib + ET arm regardless of causality**

|                                           | Abemaciclib + ET (N = 2791) |             |             |                        | ET alone (N = 2800) |            |             |                       |
|-------------------------------------------|-----------------------------|-------------|-------------|------------------------|---------------------|------------|-------------|-----------------------|
|                                           | Any grade                   | G1          | G2          | G ≥ 3                  | Any grade           | G1         | G2          | G ≥ 3                 |
| ≥10% in the abemaciclib + ET arm          |                             |             |             |                        |                     |            |             |                       |
| Patients with ≥1 AE, <sup>a</sup> n (%)   | 2745 (98.4)                 | 165 (5.9)   | 1192 (42.7) | 1388 (49.7)            | 2486 (88.8)         | 634 (22.6) | 1396 (49.9) | 456 (16.3)            |
| Diarrhea                                  | 2331 (83.5)                 | 1255 (45.0) | 857 (30.7)  | 219 (7.8) <sup>b</sup> | 242 (8.6)           | 184 (6.6)  | 52 (1.9)    | 6 (0.2)               |
| Infections <sup>c</sup>                   | 1429 (51.2)                 | 245 (8.8)   | 1029 (36.9) | 155 (5.6)              | 1102 (39.4)         | 229 (8.2)  | 790 (28.2)  | 83 (3.0) <sup>d</sup> |
| Neutropenia                               | 1278 (45.8)                 | 178 (6.4)   | 554 (19.8)  | 546 (19.6)             | 157 (5.6)           | 66 (2.4)   | 68 (2.4)    | 23 (0.8)              |
| Fatigue                                   | 1133 (40.6)                 | 632 (22.6)  | 421 (15.1)  | 80 (2.9)               | 499 (17.8)          | 378 (13.5) | 117 (4.2)   | 4 (0.1)               |
| Nausea                                    | 824 (29.5)                  | 623 (22.3)  | 187 (6.7)   | 14 (0.5)               | 252 (9.0)           | 198 (7.1)  | 52 (1.9)    | 2 (0.1)               |
| Anemia                                    | 681 (24.4)                  | 383 (13.7)  | 241 (8.6)   | 57 (2.0)               | 104 (3.7)           | 75 (2.7)   | 19 (0.7)    | 10 (0.4)              |
| Headache                                  | 546 (19.6)                  | 415 (14.9)  | 123 (4.4)   | 8 (0.3)                | 421 (15.0)          | 321 (11.5) | 95 (3.4)    | 5 (0.2)               |
| Vomiting                                  | 491 (17.6)                  | 375 (13.4)  | 101 (3.6)   | 15 (0.5)               | 130 (4.6)           | 98 (3.5)   | 29 (1.0)    | 3 (0.1)               |
| Stomatitis <sup>e</sup>                   | 385 (13.8)                  | 309 (11.1)  | 72 (2.6)    | 4 (0.1)                | 151 (5.4)           | 133 (4.8)  | 18 (0.6)    | 0 (0.0)               |
| Thrombocytopenia                          | 373 (13.4)                  | 276 (9.9)   | 61 (2.2)    | 36 (1.3)               | 52 (1.9)            | 40 (1.4)   | 8 (0.3)     | 4 (0.1)               |
| Decreased appetite                        | 329 (11.8)                  | 243 (8.7)   | 70 (2.5)    | 16 (0.6)               | 68 (2.4)            | 53 (1.9)   | 13 (0.5)    | 2 (0.1)               |
| Alopecia                                  | 313 (11.2)                  | 283 (10.1)  | 30 (1.1)    | N/A                    | 75 (2.7)            | 68 (2.4)   | 7 (0.3)     | 0 (0.0)               |
| Alanine aminotransferase increase (ALT)   | 343 (12.3)                  | 184 (6.6)   | 82 (2.9)    | 77 (2.8)               | 157 (5.6)           | 113 (4.0)  | 25 (0.9)    | 19 (0.7)              |
| Aspartate aminotransferase increase (AST) | 330 (11.8)                  | 220 (7.9)   | 58 (2.1)    | 52 (1.9)               | 137 (4.9)           | 103 (3.7)  | 19 (0.7)    | 15 (0.5)              |
| Rash                                      | 312 (11.2)                  | 239 (8.6)   | 61 (2.2)    | 11 (0.4)               | 127 (4.5)           | 104 (3.7)  | 23 (0.8)    | 0 (0.0)               |
| Other AEs of interest—composite terms     |                             |             |             |                        |                     |            |             |                       |
| VTE <sup>f</sup>                          | 71 (2.5)                    | 2 (0.1)     | 31 (1.1)    | 38 (1.4) <sup>h</sup>  | 17 (0.6)            | 0 (0.0)    | 9 (0.3)     | 8 (0.3)               |
| PE <sup>g</sup>                           | 28 (1.0)                    | N/A         | N/A         | 28 (1.0) <sup>i</sup>  | 4 (0.1)             | N/A        | N/A         | 4 (0.1)               |
| ILD <sup>j</sup>                          | 89 (3.2)                    | 44 (1.6)    | 34 (1.2)    | 11 (0.4)               | 37 (1.3)            | 26 (0.9)   | 10 (0.4)    | 1 (0.0)               |
| Pneumonitis                               | 49 (1.8)                    | 21 (0.8)    | 21 (0.8)    | 7 (0.3)                | 10 (0.4)            | 7 (0.3)    | 3 (0.1)     | 0 (0.0)               |
| Radiation pneumonitis                     | 25 (0.9)                    | 13 (0.5)    | 10 (0.4)    | 2 (0.1)                | 15 (0.5)            | 9 (0.3)    | 5 (0.2)     | 1 (0.0)               |
| Increased transaminases <sup>k</sup>      | 433 (15.5)                  | 241 (8.6)   | 94 (3.4)    | 98 (3.5)               | 209 (7.5)           | 143 (5.1)  | 38 (1.4)    | 28 (1.0)              |

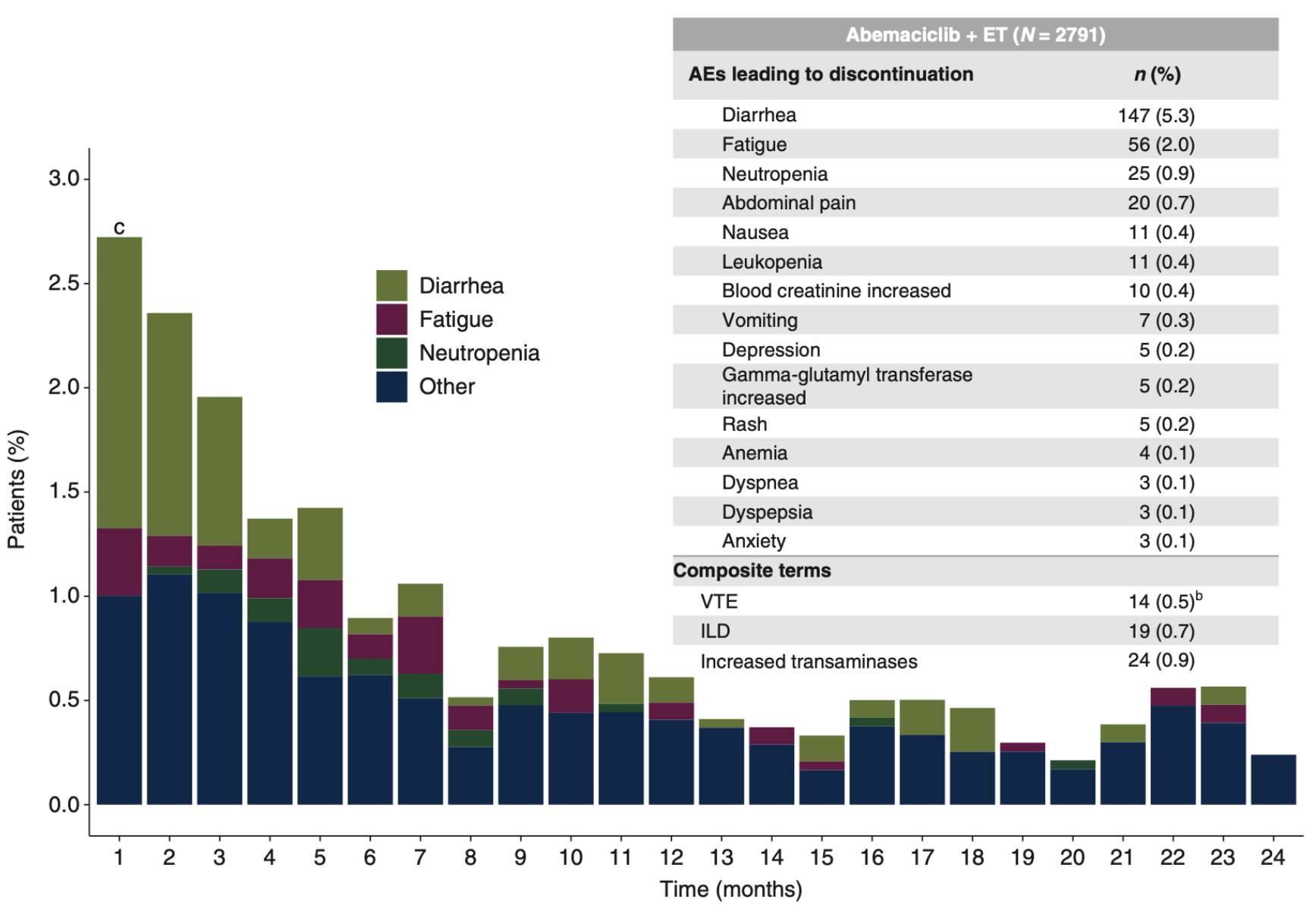
# monarchE: Serious and Fatal Adverse Events (AEs) in Long-Term Follow-Up

|                                                   | Abemaciclib + ET        |                                   | ET                      |                                   |
|---------------------------------------------------|-------------------------|-----------------------------------|-------------------------|-----------------------------------|
|                                                   | N=2791, n (%)           |                                   | N=2800, n (%)           |                                   |
|                                                   | On Therapy <sup>a</sup> | Post-Discontinuation <sup>b</sup> | On Therapy <sup>a</sup> | Post-Discontinuation <sup>b</sup> |
| <b>≥1 SAE* LTFU, regardless of causality</b>      | <b>NA</b>               | <b>197 (7.5)</b>                  | <b>NA</b>               | <b>213 (8.1)</b>                  |
| <b>Deaths due to AE by SOC and PT<sup>c</sup></b> | <b>15 (0.5)</b>         | <b>44 (1.6)</b>                   | <b>11 (0.4)</b>         | <b>30 (1.1)</b>                   |
| Infections and infestations                       | 3 (0.1)                 | 13 (0.5)                          | 5 (0.2)                 | 5 (0.2)                           |
| COVID-19                                          | 3 (0.1)                 | 6 (0.2)                           | 1 (<0.1)                | 2 (0.1)                           |
| Second primary neoplasm                           | 0 (0)                   | 13 (0.5)                          | 1 (<0.1)                | 7 (0.3)                           |
| Cardiac disorders                                 | 5 (0.2)                 | 6 (0.2)                           | 0 (0)                   | 9 (0.3)                           |

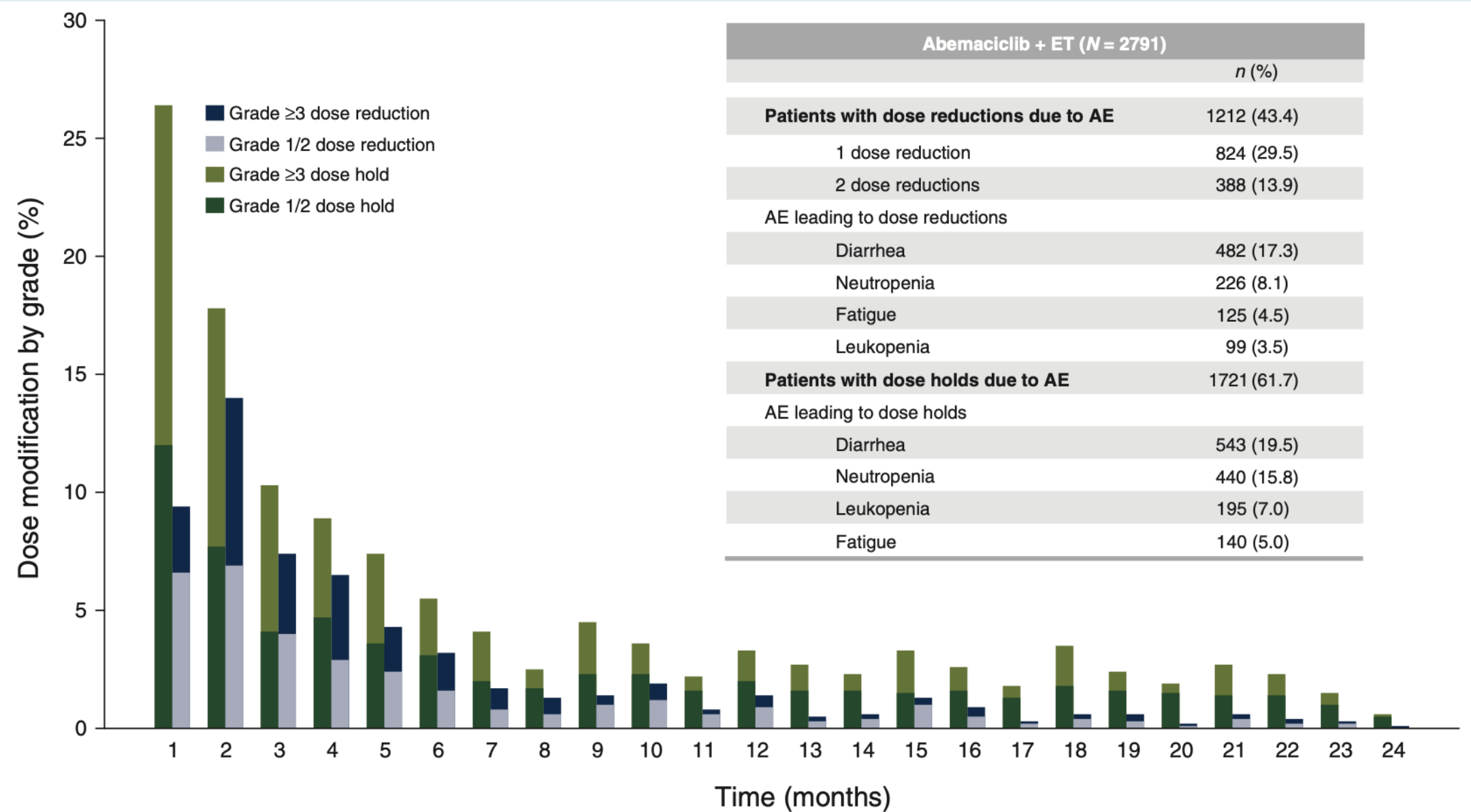
**Consistent safety results from prior analyses, as all treated patients completed treatment ≥ 4 years ago**  
**No relevant differences between treatment arms in causes of deaths due to AEs**

SAE = serious adverse event; LTFU = long-term follow-up; SOC = standard of care

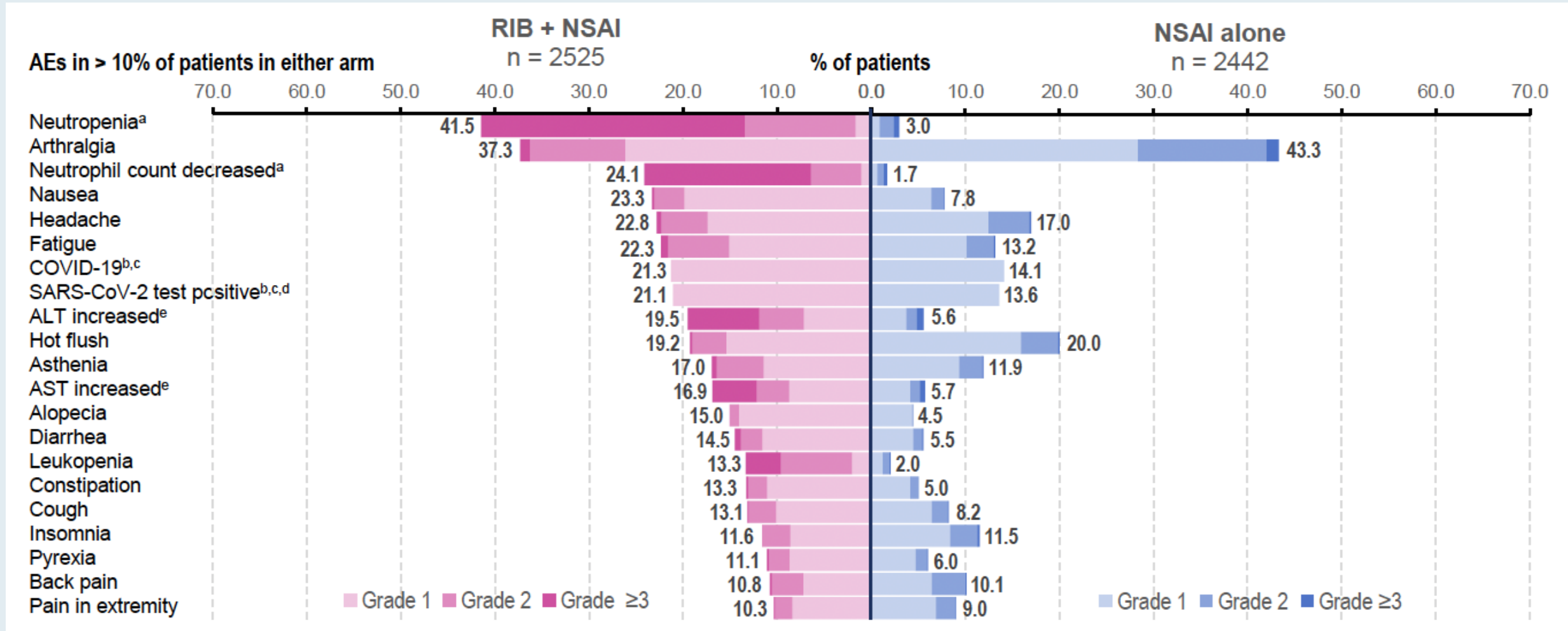
# monarchE: AEs Leading to Discontinuation



# monarchE: AEs Leading to Dose Modifications



# NATALEE: Overall Safety Profile



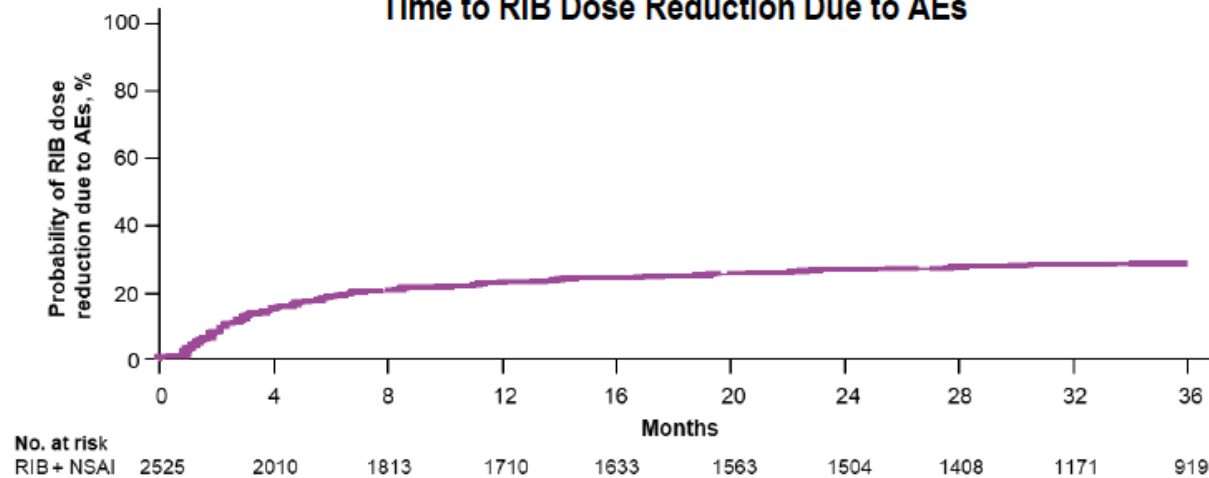
ALT = alanine aminotransferase; AST = aspartate aminotransferase

## NATALEE: AEs of Special Interest (AESIs)

| AESIs (grouped terms)                                                                | Neutropenia <sup>a</sup>   |               | Liver-related AEs <sup>c</sup> |                | QT interval prolongation <sup>d</sup> |               |
|--------------------------------------------------------------------------------------|----------------------------|---------------|--------------------------------|----------------|---------------------------------------|---------------|
|                                                                                      | RIB + NSAI                 | NSAI alone    | RIB + NSAI                     | NSAI alone     | RIB + NSAI                            | NSAI alone    |
| All grade                                                                            | 1579 (62.5)                | 113 (4.6)     | 667 (26.4)                     | 273 (11.2)     | 134 (5.3)                             | 34 (1.4)      |
| Grade ≥3                                                                             | 1118 (44.3)                | 22 (0.9)      | 217 (8.6)                      | 42 (1.7)       | 26 (1.0)                              | 15 (0.6)      |
| Time to first grade ≥2 based on laboratory values, median mo. (range)                | 1.0 (0.9-1.0) <sup>b</sup> | NE            | 2.8 (0.5-36.7)                 | 9.1 (0.5-33.3) | 0.5 (0.5-1.5)                         | 1.4 (0.9-2.8) |
| Time to resolution of grade ≥2 to ≤1 based on laboratory values, median mo. (95% CI) | 1.0 (NE)                   | 1.0 (1.0-1.0) | 0.9 (0.7-1.0)                  | 1.4 (1.0-2.5)  | 0.2 (0.0-0.5)                         | 1.1 (0.5-NE)  |
| Dose reductions, RIB, %                                                              | 14.2                       | 0             | 2.6                            | 0              | 0.1                                   | 0             |
| Discontinuations, any component, %                                                   | 1.1                        | 0             | 8.9                            | 0.1            | 0.4                                   | 0             |

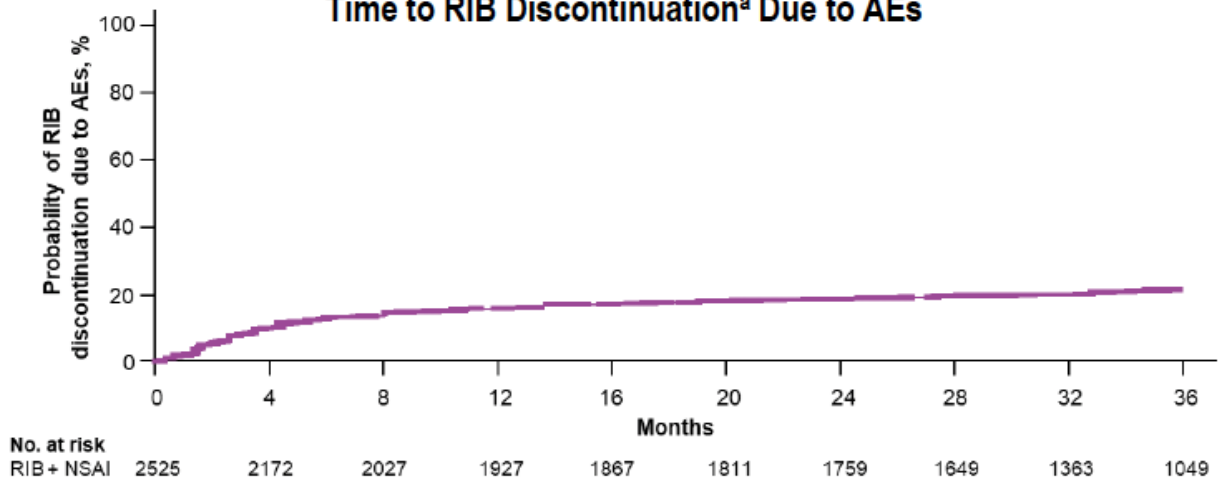
# NATALEE: AE-Related Dose Reduction and Discontinuation

Time to RIB Dose Reduction Due to AEs



- AE-related RIB dose reductions occurred in 22.8% of patients
  - Most commonly due to neutropenia (8.5%) and neutrophil count decreased (5.6%)
- Median time to AE-related RIB dose reduction: 3.15 months (range, 0.26-34.17 months)
- Median RDI during RIB treatment: 94%

Time to RIB Discontinuation<sup>a</sup> Due to AEs



- Most common AEs leading to discontinuation: ALT increased (7.1%) and AST increased (2.8%)
- Of 19.7% who discontinued due to AEs, 14.0% discontinued without prior dose reduction and 5.7% had their dose reduced before discontinuing
- Median time to AE-related RIB discontinuation: 4.17 months (range, 0.10-35.75 months)

RDI = relative dose intensity

# AEs and Dosing Must Be Considered: Distinct AE Profiles and Dosing Schedules of CDK4/6 Inhibitors for Localized Breast Cancer

**Abemaciclib**

**Adverse Events**

- Neutropenia (41%-46%)
- Diarrhea (81%-86%)
- Increased ALT (13%-16%)
- Increased AST (12%-15%)
- Thromboembolic events (5%)

**Schedule**

Continuous daily dosing

**Dosing**

Starting dose in EBC: 150 mg BID  
1st dose reduction: 100 mg BID  
2nd dose reduction: 50 mg BID

**Ribociclib**

**Adverse Events**

- Neutropenia (69%-78%)
- Diarrhea (29%-35%)
- Increased ALT (15%-46%)
- Increased AST (13%-44%)
- QTc prolongation (6%)

**Schedule**

3 wk on/1 wk off

**Dosing**

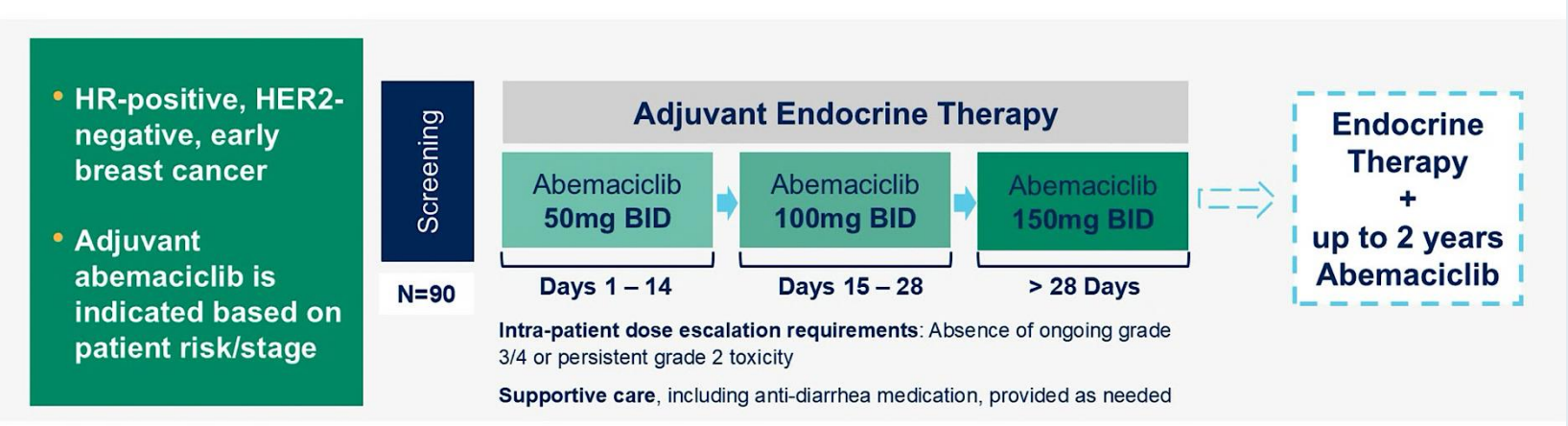
Starting dose in EBC: 400 mg/day  
1 (and only) dose reduction option  
available in EBC: 200 mg/day

| Breast Cancer Status | CDK4/6i     | Trial(s)                | Discontinuation Rate Due to AE |
|----------------------|-------------|-------------------------|--------------------------------|
| HR+/HER2– EBC        | Abemaciclib | monarchE <sup>1,a</sup> | 19%                            |
|                      | Ribociclib  | NATALEE <sup>2,3</sup>  | 19%                            |

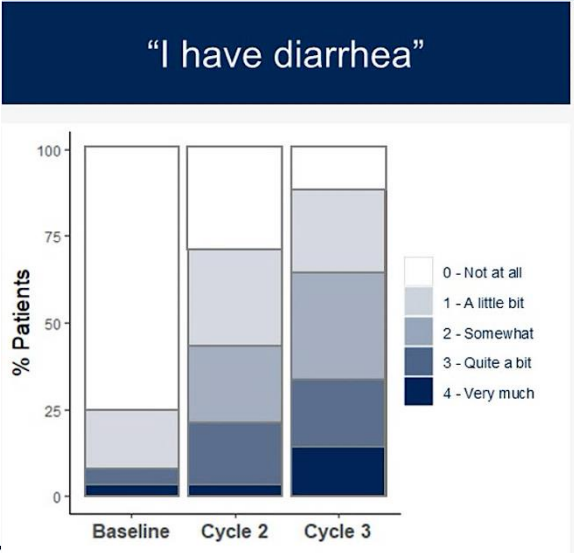
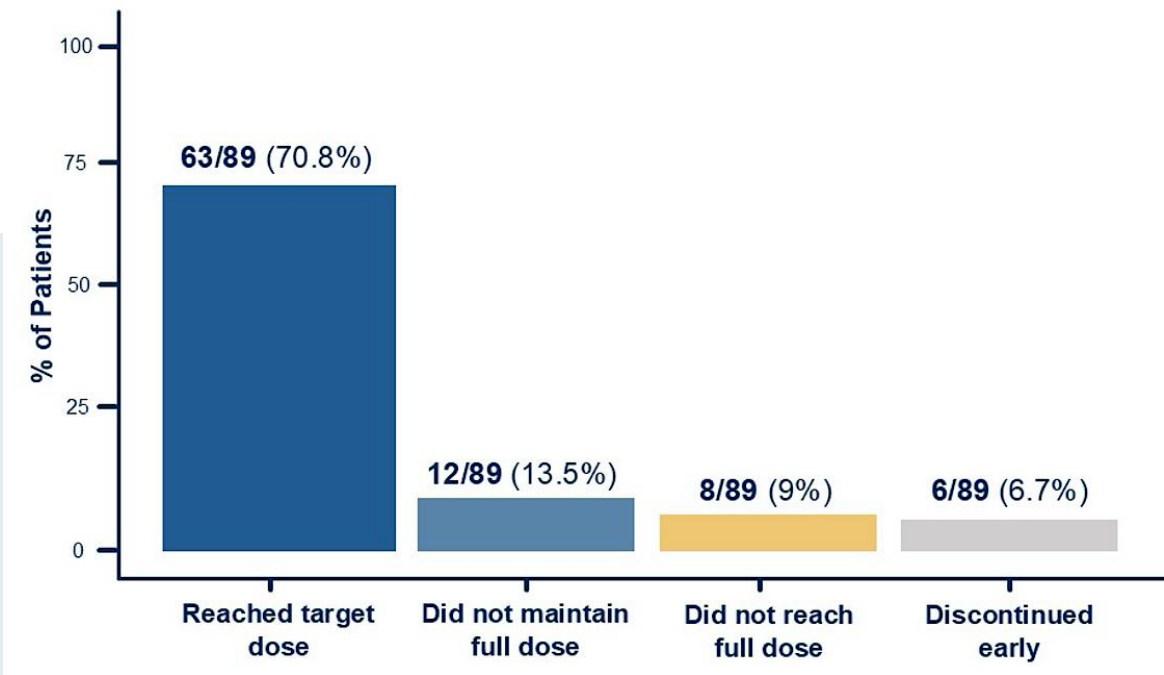
1. Rugo HS, et al. *Ann Oncol.* 2022;33(6):616-627. 2. Slamon D, et al. *N Engl J Med.* 2024 Mar 21;390(12):1080-1091. 3. Hortobagyi GN, et al. SABCS 2023. Abstract GS03-03.

# TRADE: Abemaciclib Dose Escalation

| Patient disposition in monarchE                                                 |             |                    |
|---------------------------------------------------------------------------------|-------------|--------------------|
| Outcome in monarchE                                                             | By 12 weeks | Overall at 2 years |
| Discontinued abemaciclib for any reason                                         | 10%         | 30.6%              |
| <ul style="list-style-type: none"><li>Discontinued for adverse events</li></ul> | 7%          | 18.5%              |
| Required abemaciclib dose reduction                                             | 27%         | 43.4%              |



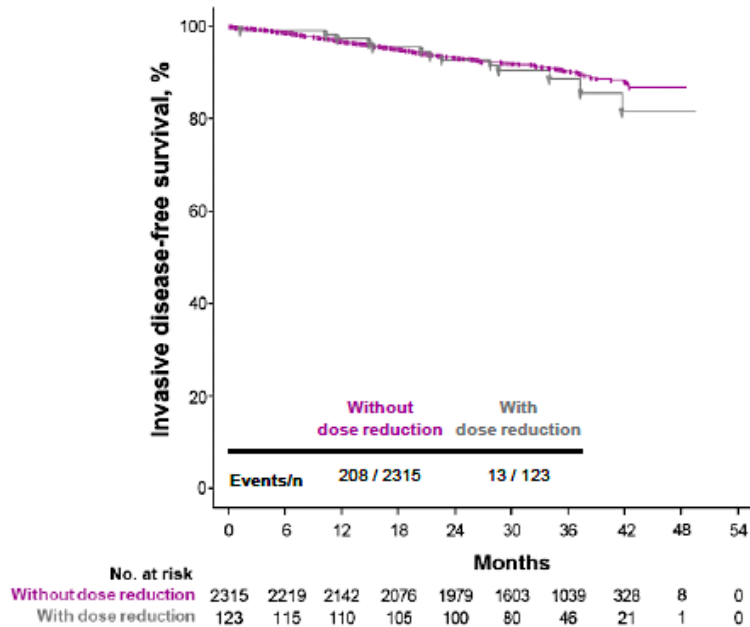
**Primary endpoint:** composite AE rate (discontinuation of adjuvant abemaciclib for any reason and/or need to dose reduce by 12 weeks of therapy)



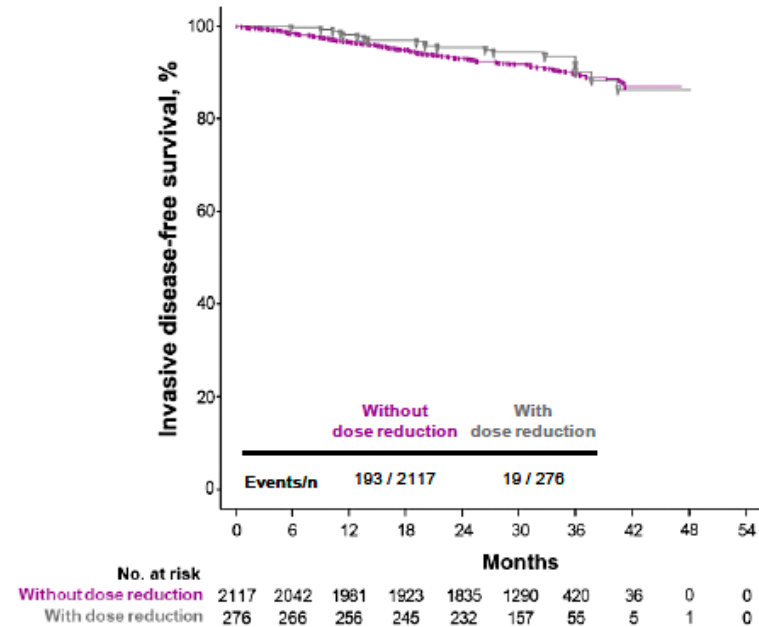
# NATALEE: IDFS by Dose Reductions

Landmark analysis revealed that RIB dose reduction due to AEs did not impact efficacy

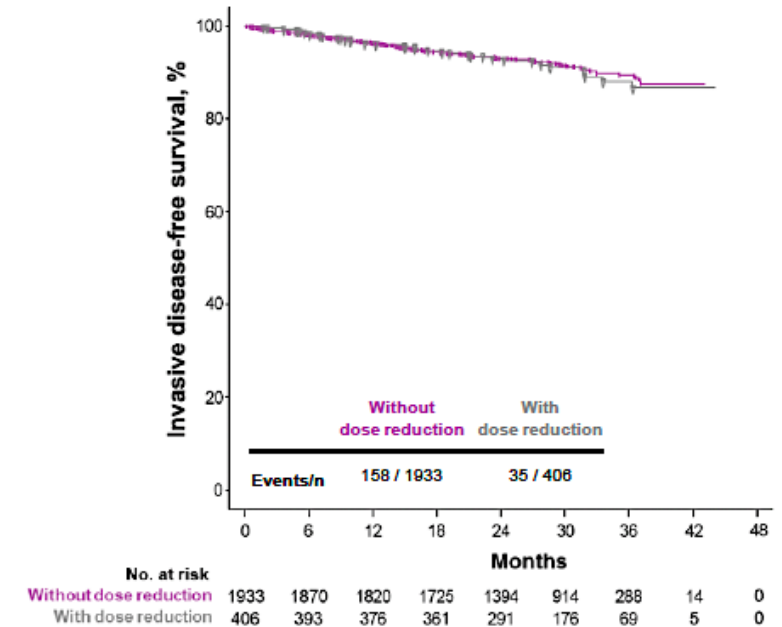
iDFS by Dose Reduction at 25th Percentile<sup>a</sup>  
(1.87 mo.)



iDFS by Dose Reduction at 50th Percentile<sup>a</sup>  
(3.17 mo.)



iDFS by Dose Reduction at 75th Percentile<sup>a</sup>  
(7.28 mo.)



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Have you employed or would you employ an initial dose-escalation strategy rather than initiating therapy at the recommended starting dose for any of your patients with HR-positive localized BC receiving an adjuvant CDK4/6 inhibitor?



**Dr Brufsky**

**I have not but would for the right patient**



**Dr Chen**

**I have**



**Dr Jhaveri**

**I have**



**Dr Kalinsky**

**I have**



**Dr Mahtani**

**I have**



**Dr Mouabbi**

**I have**



**Dr Rugo**

**I have**



**Dr Sharma**

**I have**

Assuming eligibility to receive abemaciclib or ribociclib, which CDK4/6 inhibitor would you prefer in the adjuvant setting for a patient with HR-positive localized BC and a history of ...?

|                                                                                     |             | Colitis    | Chronic liver disease | Chronic renal disease |
|-------------------------------------------------------------------------------------|-------------|------------|-----------------------|-----------------------|
|    | Dr Brufsky  | Ribociclib | Abemaciclib           | Ribociclib            |
|    | Dr Chen     | Ribociclib | Abemaciclib           | Ribociclib            |
|    | Dr Jhaveri  | Ribociclib | Abemaciclib           | Ribociclib            |
|    | Dr Kalinsky | Ribociclib | Abemaciclib           | No preference         |
|    | Dr Mahtani  | Ribociclib | Abemaciclib           | No preference         |
|  | Dr Mouabbi  | Ribociclib | Abemaciclib           | Ribociclib            |
|  | Dr Rugo     | Ribociclib | Abemaciclib           | No preference         |
|  | Dr Sharma   | Ribociclib | Abemaciclib           | Ribociclib            |

Assuming eligibility to receive abemaciclib or ribociclib, which CDK4/6 inhibitor would you prefer in the adjuvant setting for a patient with HR-positive localized BC and a history of ...?

|                                                                                     |             | COPD          | NYHA Class I congestive heart failure |
|-------------------------------------------------------------------------------------|-------------|---------------|---------------------------------------|
|    | Dr Brufsky  | No preference | Abemaciclib                           |
|    | Dr Chen     | No preference | No preference                         |
|    | Dr Jhaveri  | No preference | Abemaciclib                           |
|    | Dr Kalinsky | No preference | Abemaciclib                           |
|    | Dr Mahtani  | No preference | Abemaciclib                           |
|  | Dr Mouabbi  | Ribociclib    | Abemaciclib                           |
|  | Dr Rugo     | No preference | Abemaciclib                           |
|  | Dr Sharma   | No preference | No preference                         |

COPD = chronic obstructive pulmonary disease

# **Management of Hormone Receptor (HR)-Positive Localized Breast Cancer**

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**Module 7: Adjuvant Oral SERDs for HR-Positive, HER2-Negative Localized Breast Cancer**

# Key Datasets

- Bardia A et al. **Giredestrant** vs standard-of-care endocrine therapy as **adjuvant treatment** for patients with estrogen receptor-positive, HER2-negative early breast cancer: **Results from the global phase III lidERA Breast Cancer trial**. San Antonio Breast Cancer Symposium 2025;Abstract GS1-10.



**DECEMBER 9–12, 2025**

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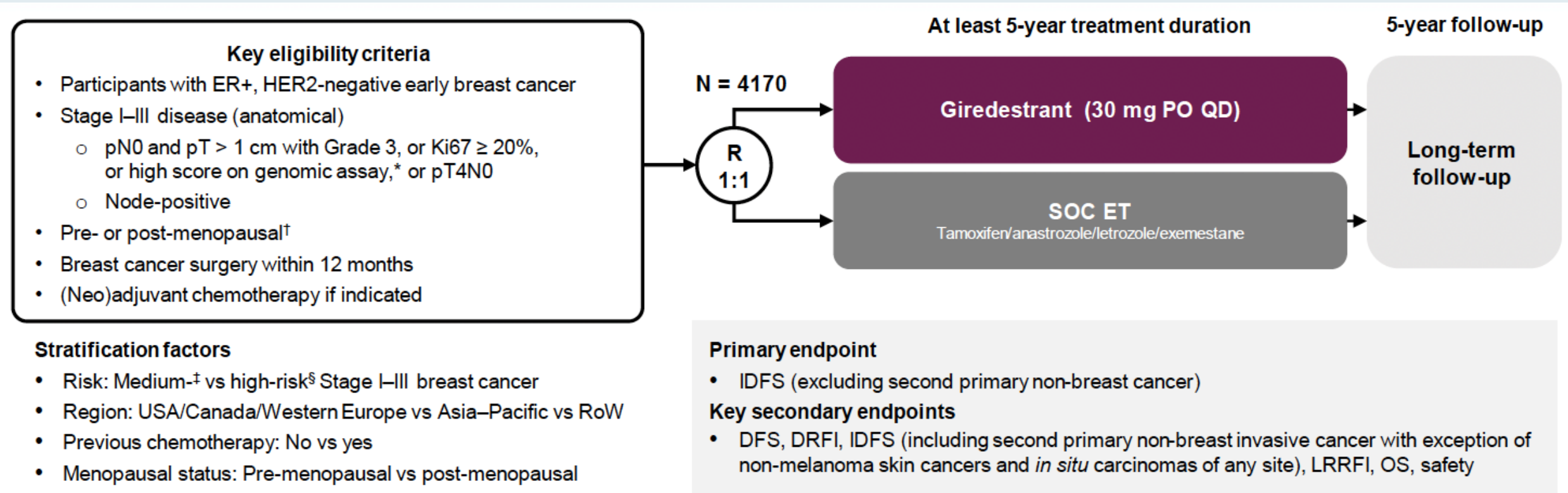
# **Giredestrant vs standard-of-care endocrine therapy as adjuvant treatment for patients with estrogen receptor-positive, HER2-negative early breast cancer: Results from the global Phase III lidERA Breast Cancer trial**

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Abstract GS1-10

# IdERA Breast Cancer Study Design

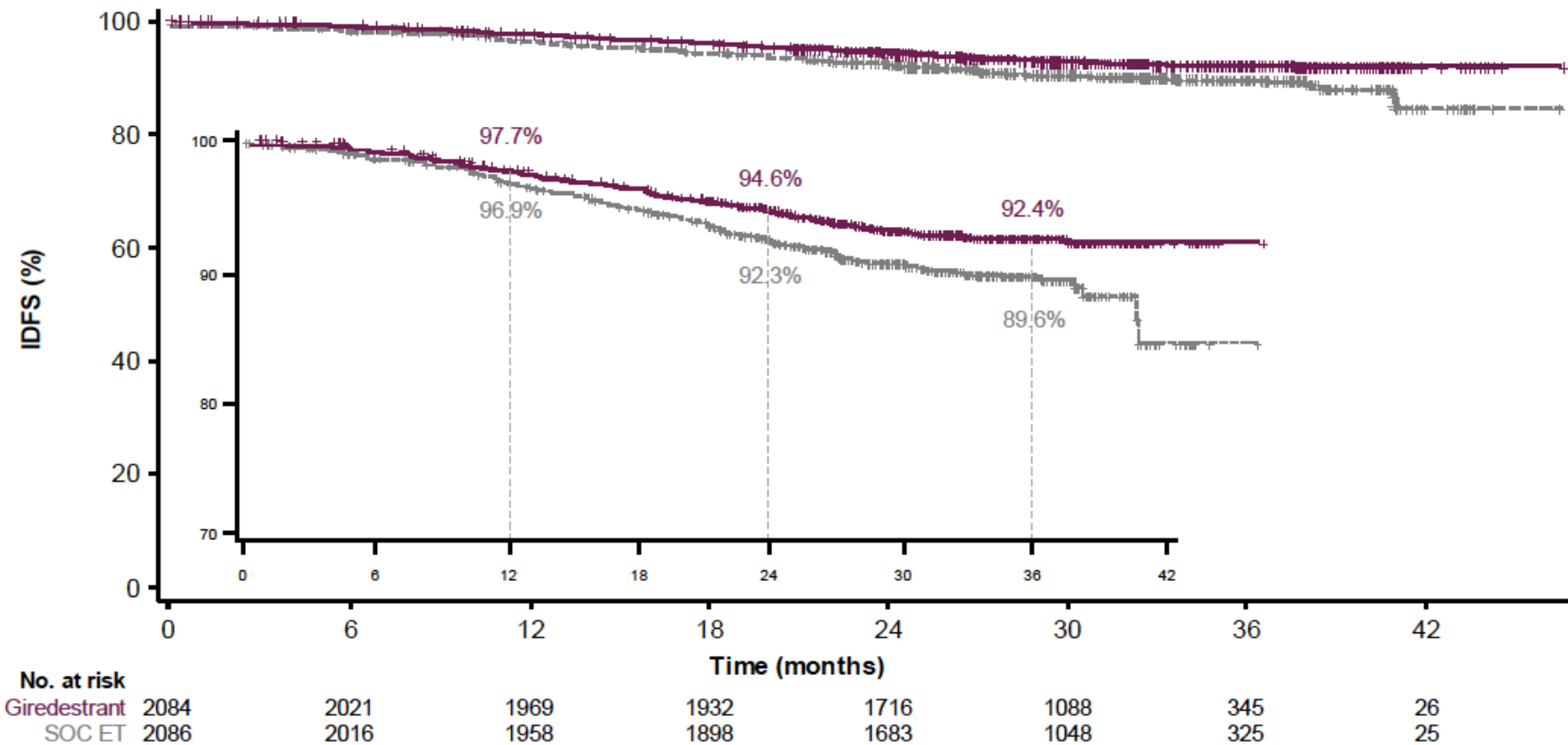


DRFI = distant recurrence-free interval; LRRFI = locoregional recurrence-free interval

# IdERA Breast Cancer: Patient Demographics

|                                             | Giredestrant<br>n = 2084 | SOC ET<br>n = 2086 |                                                              | Giredestrant<br>n = 2084 | SOC ET<br>n = 2086 |
|---------------------------------------------|--------------------------|--------------------|--------------------------------------------------------------|--------------------------|--------------------|
| <b>Median age, years (range)</b>            | 54.0 (22–91)             | 54.0 (25–89)       | <b>ER status, n (%)<sup>†</sup></b>                          |                          |                    |
| <b>Female sex, n (%)</b>                    | 2073 (99.5)              | 2075 (99.5)        | Low-positive (1–10% of cells positive)                       | 45 (2.2)                 | 52 (2.5)           |
| <b>Race, n (%)</b>                          |                          |                    | Positive (> 10% of cells positive)                           | 2030 (97.8)              | 2031 (97.5)        |
| American Indian or Alaska Native            | 77 (3.7)                 | 62 (3.0)           | <b>AJCC stage at surgery, n (%)<sup>§</sup></b>              |                          |                    |
| Asian                                       | 461 (22.1)               | 467 (22.4)         | I                                                            | 254 (12.3)               | 283 (13.6)         |
| Black or African American                   | 50 (2.4)                 | 50 (2.4)           | II                                                           | 1013 (49.0)              | 950 (45.7)         |
| Other*                                      | 263 (12.6)               | 232 (11.1)         | III                                                          | 799 (38.7)               | 844 (40.6)         |
| White                                       | 1233 (59.2)              | 1275 (61.1)        | <b>Nodal status, n (%) on surgical specimen<sup>  </sup></b> |                          |                    |
| <b>Region, n (%)</b>                        |                          |                    | pN0                                                          | 449 (21.6)               | 441 (21.2)         |
| Asia–Pacific                                | 544 (26.1)               | 544 (26.1)         | pN1                                                          | 968 (46.6)               | 953 (45.7)         |
| USA/Canada/Western Europe                   | 860 (41.3)               | 905 (43.4)         | pN2–3                                                        | 662 (31.8)               | 691 (33.1)         |
| Latin America/Africa/Eastern Europe         | 680 (32.6)               | 637 (30.5)         | <b>Risk, n (%)</b>                                           |                          |                    |
| <b>Menopausal status, n (%)<sup>†</sup></b> |                          |                    | High                                                         | 1448 (69.5)              | 1447 (69.4)        |
| Pre-menopausal                              | 849 (41.0)               | 838 (40.4)         | Medium                                                       | 636 (30.5)               | 639 (30.6)         |
| Post-menopausal                             | 1220 (59.0)              | 1236 (59.6)        | <b>Previous chemotherapy, n (%)</b>                          |                          |                    |
|                                             |                          |                    | No                                                           | 396 (19.0)               | 450 (21.6)         |
|                                             |                          |                    | Yes                                                          | 1688 (81.0)              | 1636 (78.4)        |

# IdERA Breast Cancer: IDFS Outcomes



|                                  | Giredestrant<br>n = 2084                 | SOC ET<br>n = 2086 |
|----------------------------------|------------------------------------------|--------------------|
| Events, n (%)                    | 140 (6.7)                                | 196 (9.4)          |
| <b>Stratified HR</b><br>(95% CI) | <b>0.70</b><br>(0.57, 0.87); p = 0.0014* |                    |

Exploratory analysis: IDFS by SOC ET

|           | Total,<br>n | Stratified HR<br>(95% CI) |
|-----------|-------------|---------------------------|
| AI        | 1745        | 0.73 (0.58, 0.92)         |
| Tamoxifen | 326         | 0.53 (0.35, 0.80)         |

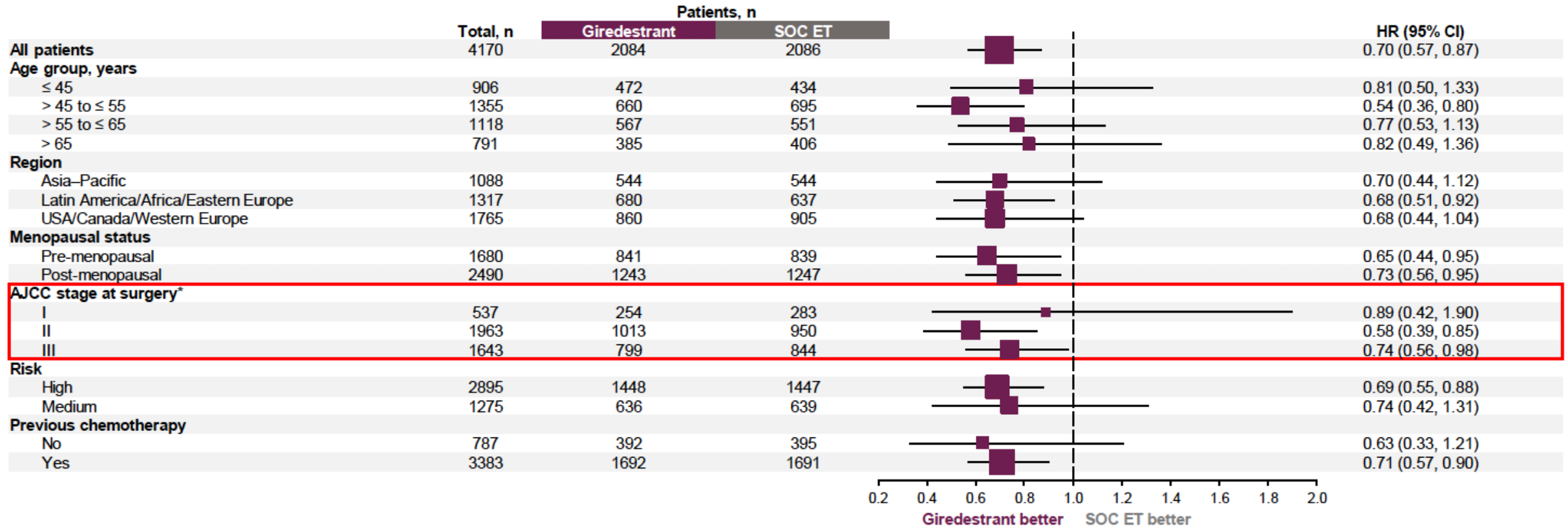
0.3 0.8

Giredestrant better SOC ET better

Median follow-up: 32.3 months

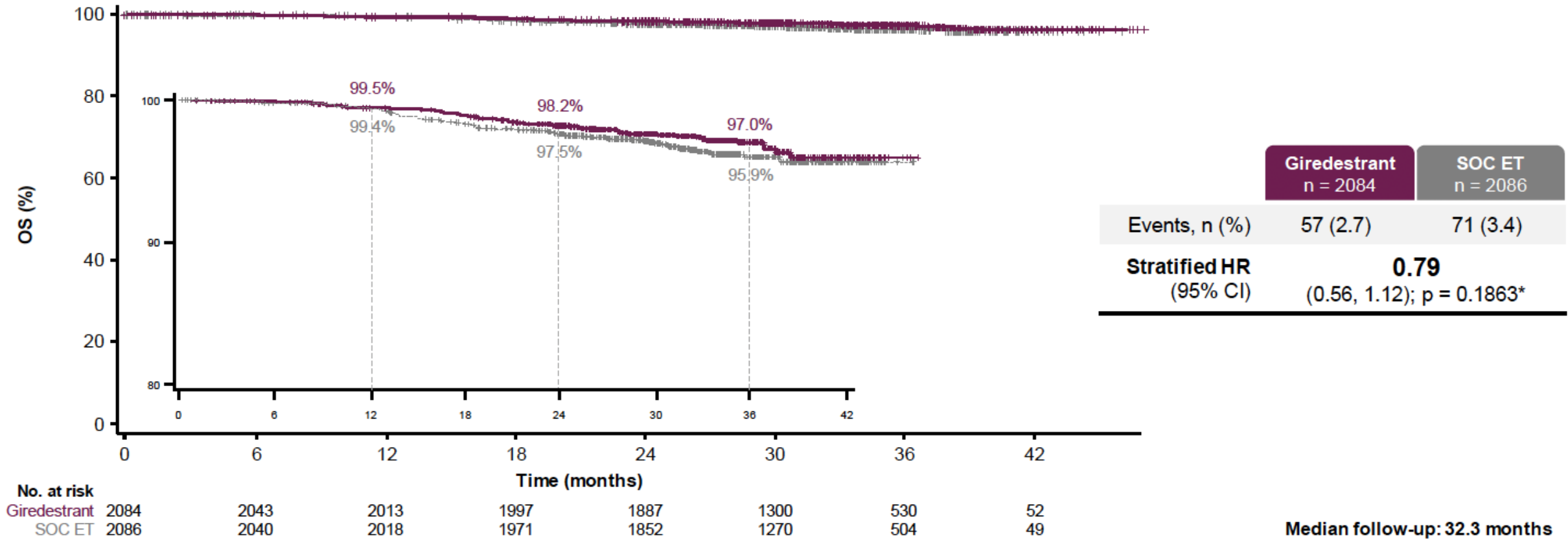
**Statistically significant and clinically meaningful improvement in IDFS:  
Giredestrant reduced the risk of invasive disease recurrence or death by 30% compared with SOC ET**

# IdERA Breast Cancer: IDFS in Key Subgroups



**IDFS benefit was consistent across key prespecified subgroups**

# lidERA Breast Cancer: OS Outcomes

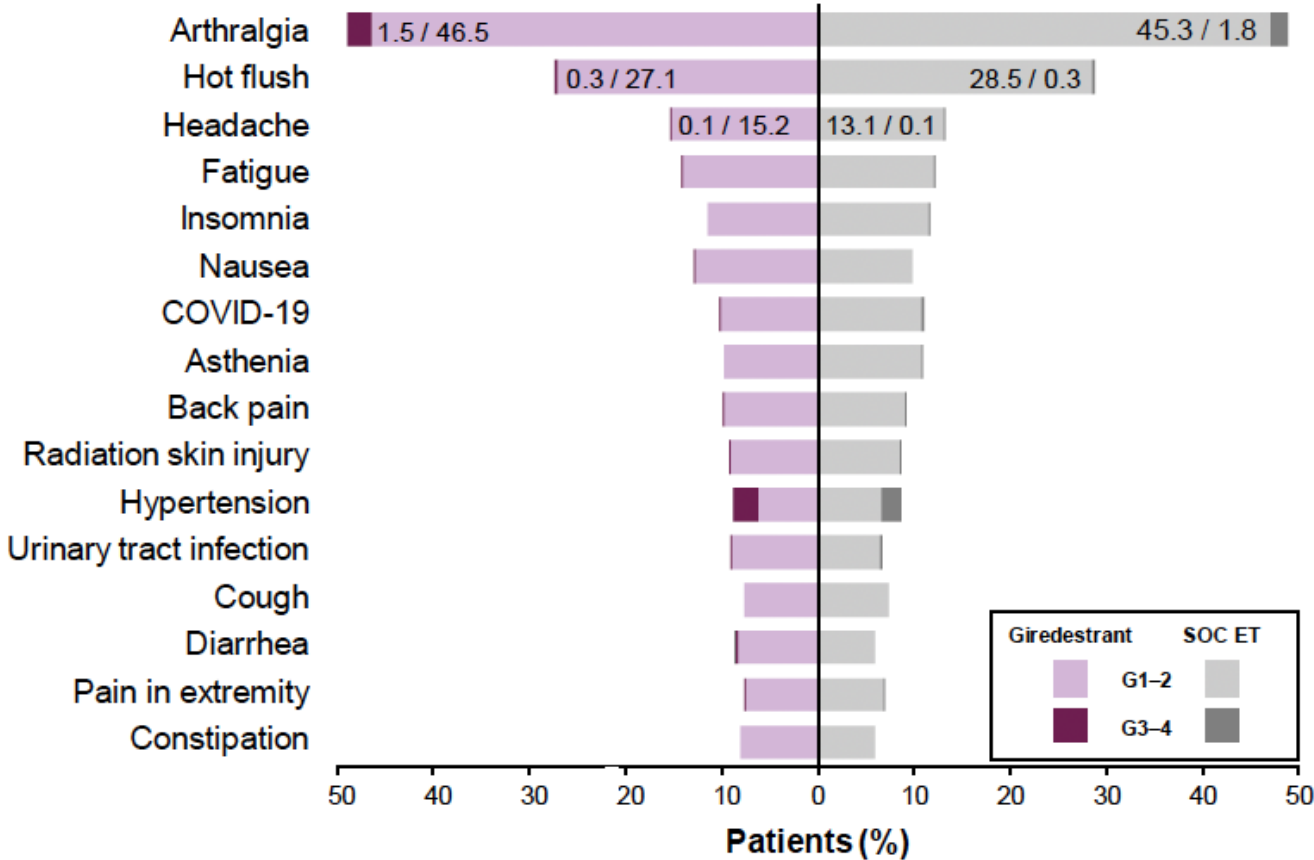


**While OS data were immature, a clear positive trend was observed. OS testing will continue at future analyses**

# lidERA Breast Cancer: Safety Profile

## Common TEAEs (≥ 7.5% of patients in either arm at any grade)

Giredestrant n = 2060 SOC ET n = 2074



## Selected AEs

|                                                                   | Giredestrant<br>n = 2060 | SOC ET<br>n = 2074 |
|-------------------------------------------------------------------|--------------------------|--------------------|
| <b>Patients, n (%) with treatment discontinuations due to AEs</b> |                          |                    |
| Musculoskeletal disorders                                         | 38 (1.8)                 | 92 (4.4)           |
| • Arthralgias (PT)                                                | 32 (1.6)                 | 76 (3.7)           |
| Vasomotor disorders                                               | 2 (< 0.1)                | 18 (0.9)           |
| • Hot flush (PT)                                                  | 1 (< 0.1)                | 16 (0.8)           |

|                                                       | Giredestrant<br>n = 2060 |             |                   | SOC ET<br>n = 2074 |                  |            |
|-------------------------------------------------------|--------------------------|-------------|-------------------|--------------------|------------------|------------|
| Patients, n (%) with selected AEs by medical concept* |                          |             |                   |                    |                  |            |
|                                                       | G1                       | G2          | G3–4              | G1                 | G2               | G3–4       |
| Bradycardia†                                          | 217<br>(10.5)            | 15<br>(0.7) | 0                 | 64<br>(3.1)        | 2<br>( $< 0.1$ ) | 0          |
| Venous thromboembolic events                          | 4<br>(0.2)               | 12<br>(0.6) | 2<br>( $< 0.1$ )‡ | 3<br>(0.1)         | 7<br>(0.3)       | 7<br>(0.3) |

Based on recently presented findings from the Phase III lidERA trial, would you like to have access to adjuvant giredestrant today for your patients with HR-positive, HER2-negative localized BC?



**Dr Brufsky**

**Yes, for patients with higher-risk disease**



**Dr Chen**

**Yes, most beneficial for patients who are not tolerating an AI well**



**Dr Jhaveri**

**Yes, for those who can't tolerate a CDK4/6i and those who are reluctant to take a CDK4/6i due to toxicity**



**Dr Kalinsky**

**Yes, for patients with higher-risk disease after CDK4/6i or if cannot tolerate standard ET**



**Dr Mahtani**

**Yes, for patients with high-risk disease**



**Dr Mouabbi**

**Yes, for patients who are receiving AI monotherapy**



**Dr Rugo**

**Yes, for high-risk disease as defined in the trial**



**Dr Sharma**

**Yes, for patients that match eligibility of the lidERA trial**

ET = endocrine therapy; CDK4/6i = CDK4/6 inhibitor

If giredestrant were available, regulatory and reimbursement issues aside, what would you generally recommend for patients who met the criteria for both an adjuvant CDK4/6 inhibitor and adjuvant giredestrant?



**Dr Brufsky**

CDK4/6i with standard adjuvant ET for the initial 2 to 3 years of tx, then switch to giredestrant after discontinuation of the CDK4/6i



**Dr Chen**

**CDK4/6 inhibitor combined with giredestrant**



**Dr Jhaveri**

CDK4/6i with standard adjuvant ET for the initial 2 to 3 years of tx, then switch to giredestrant after discontinuation of the CDK4/6i



**Dr Kalinsky**

CDK4/6i with standard adjuvant ET for the initial 2 to 3 years of tx, then switch to giredestrant after discontinuation of the CDK4/6i



**Dr Mahtani**

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**Dr Sharma**

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# Questions?