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

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Harvard Medical School

Boston, Massachusetts

Disclosures

| | |
|------------------------------|---|
| Consulting Agreements | Aktis Oncology, AstraZeneca Pharmaceuticals LP, Genentech, a member of the Roche Group, Lilly, Novartis |
|------------------------------|---|

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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.
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- Piccart M et al. **70-gene signature** as an aid for treatment decisions in early breast cancer: **Updated results** of the phase 3 randomised **MINDACT trial** with an exploratory analysis by age. *Lancet Oncol* 2021;22(4):476-88.
- 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

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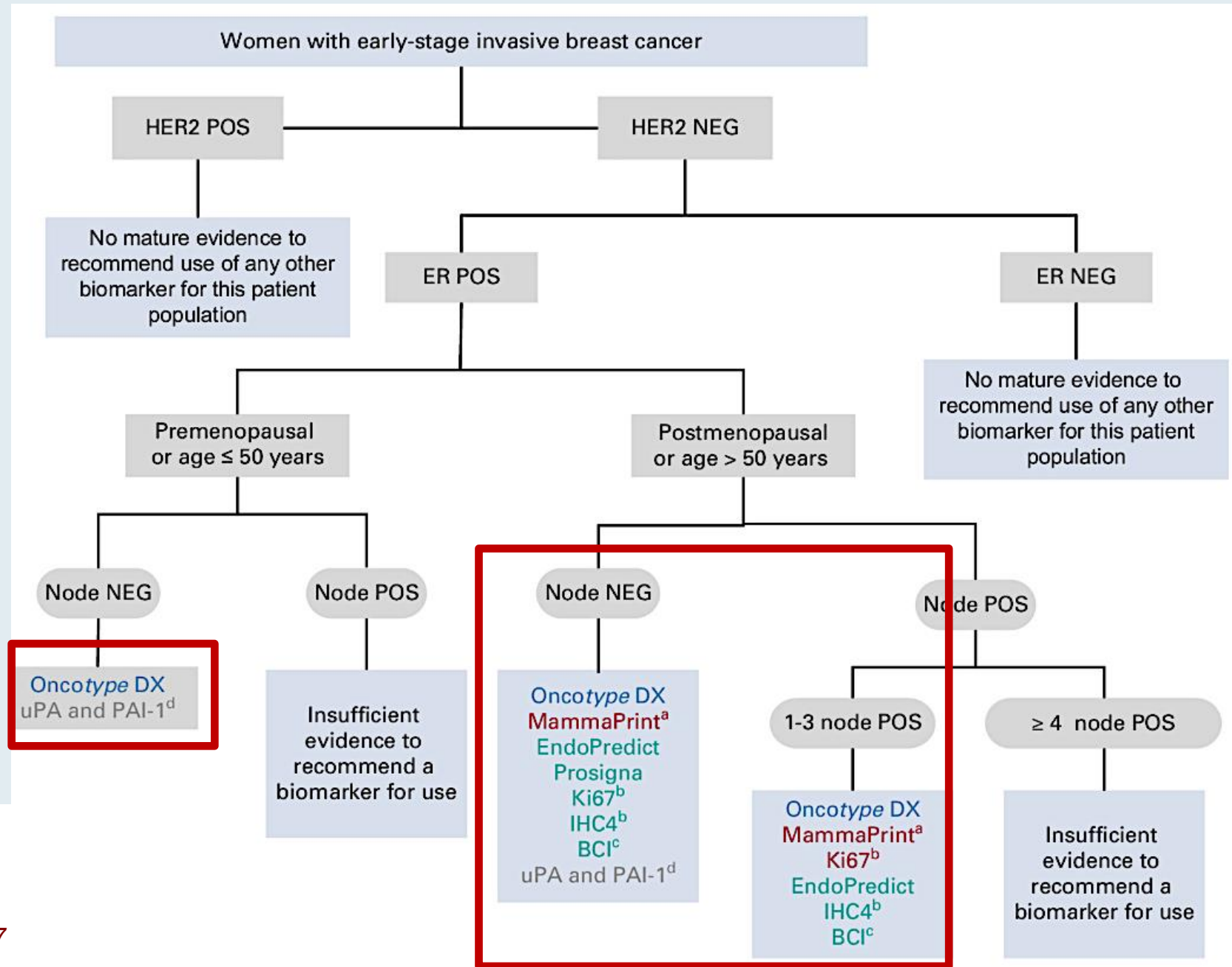
Module 7: Adjuvant Oral SERDs for HR-Positive, HER2-Negative Localized Breast Cancer

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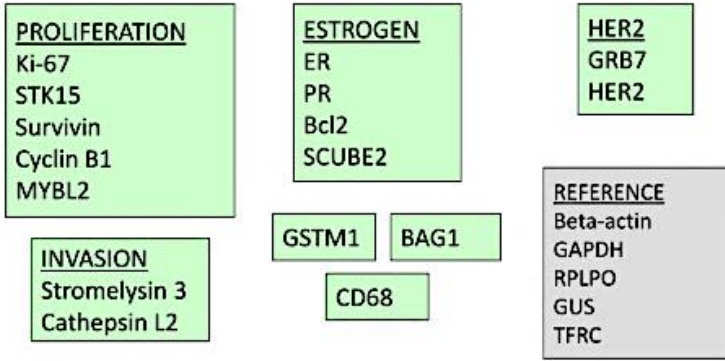
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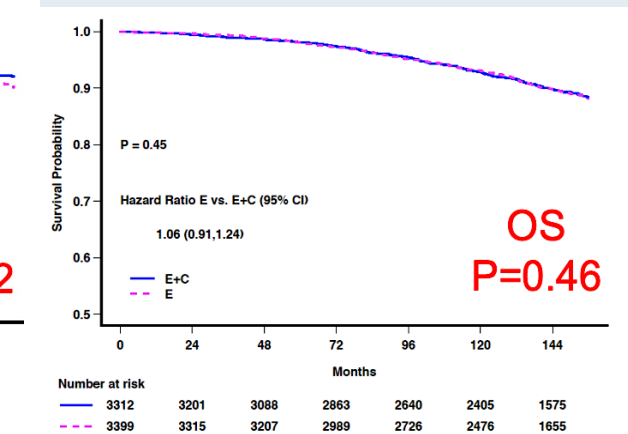
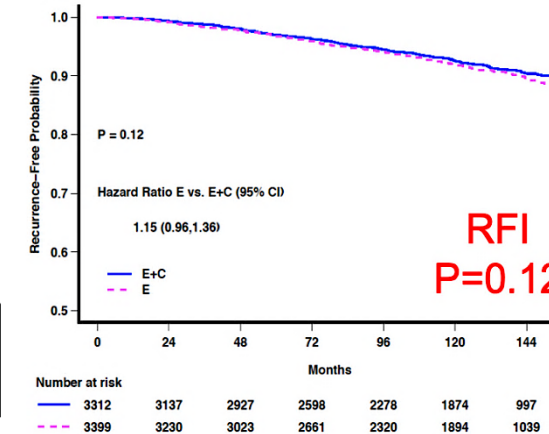
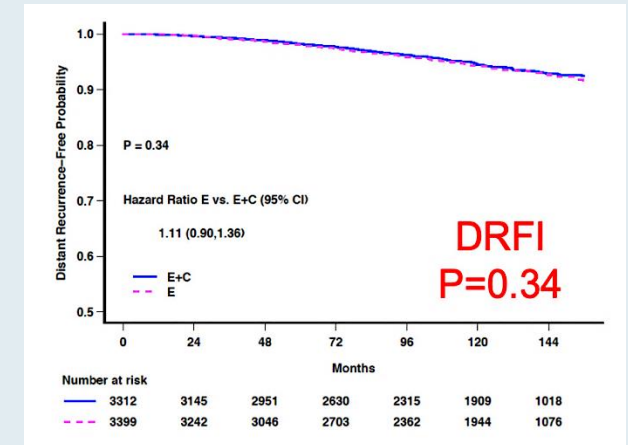
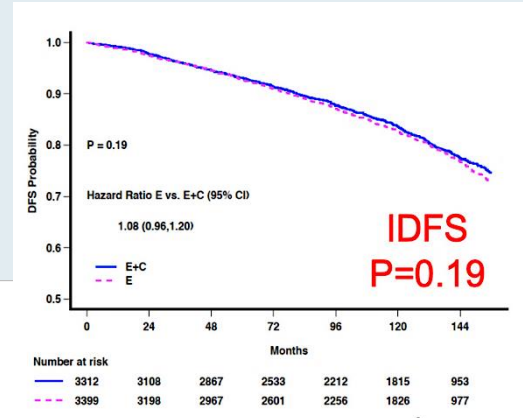
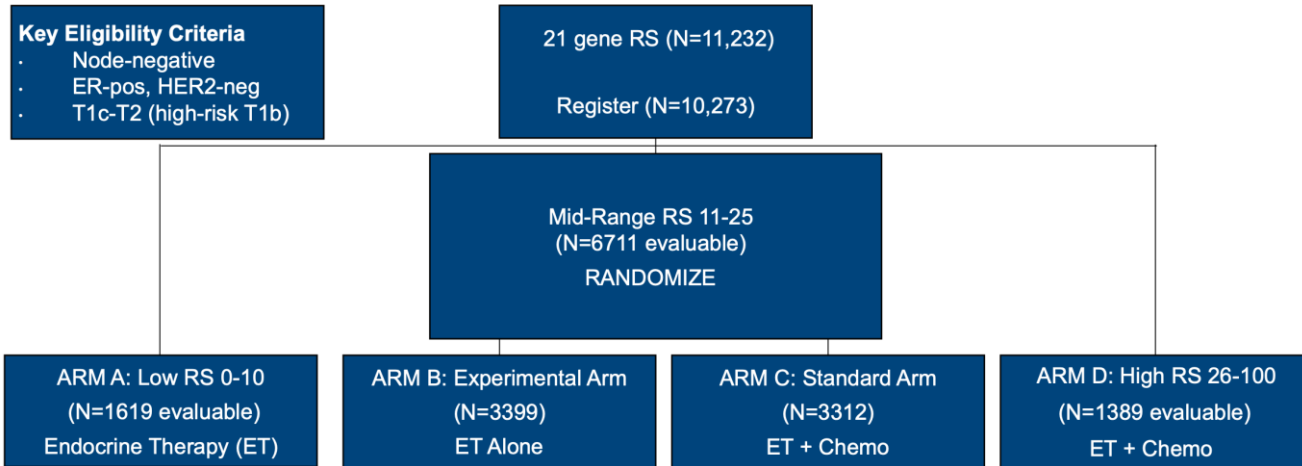
OncotypeDX®: TAILORx Trial Key Results for Node-Negative Disease

16 Cancer and 5 Reference Genes From 3 Studies



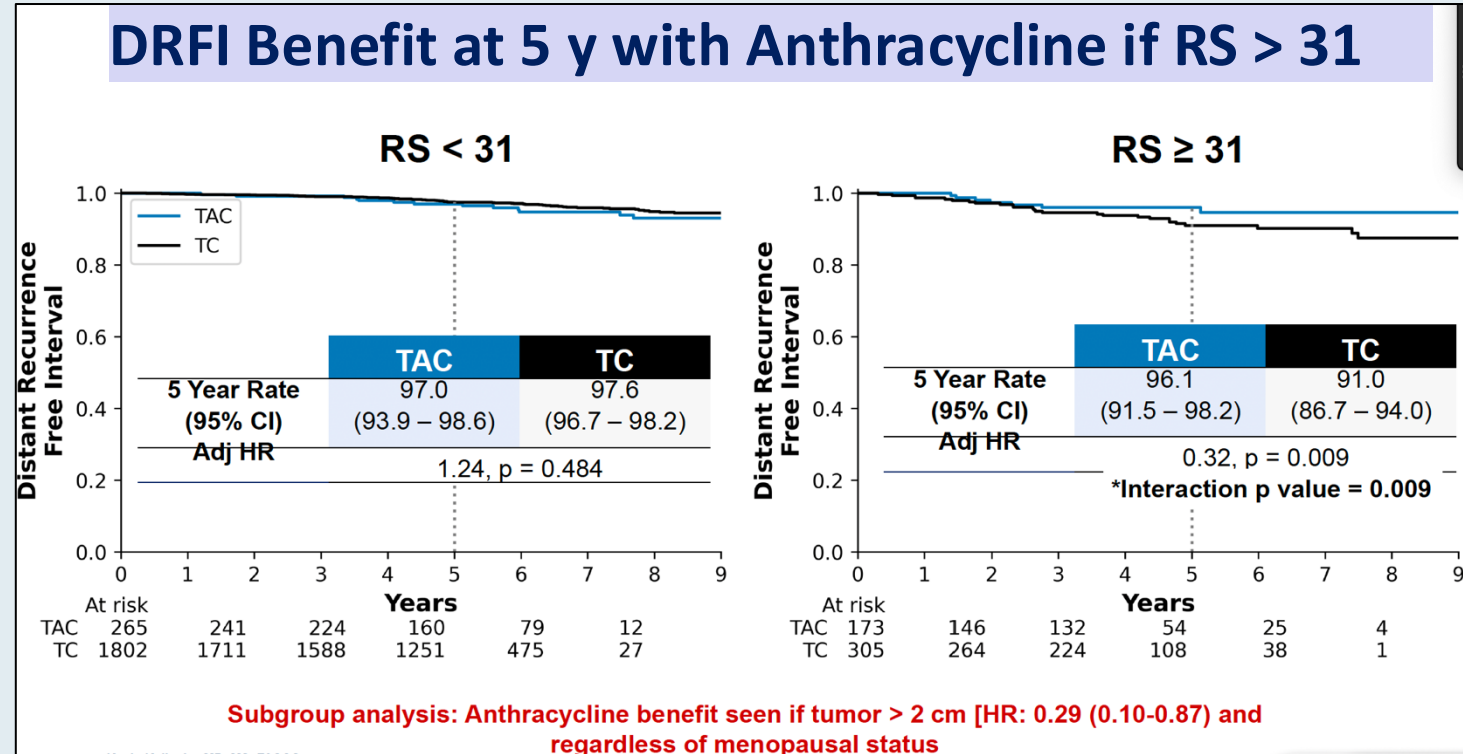
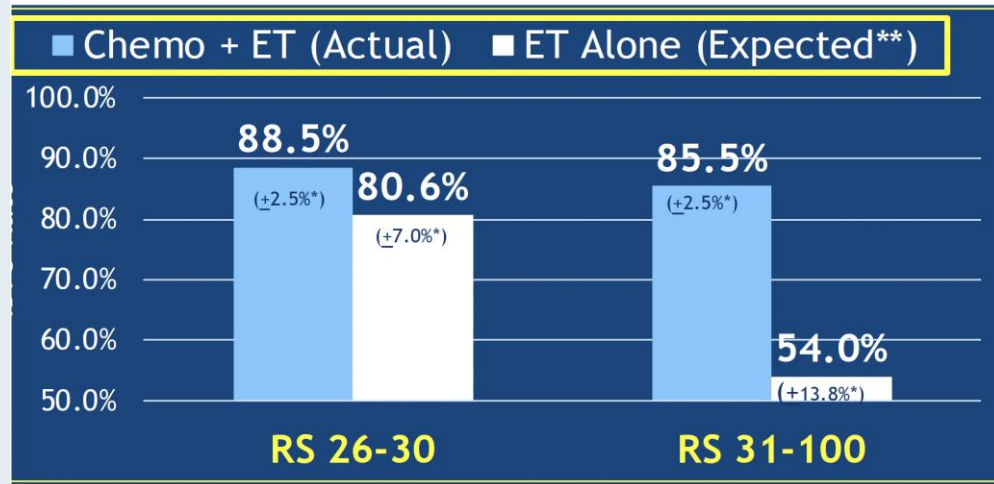
Intermediate risk (11-25):
No overall benefit to chemotherapy (2022 update)

TAILORx Trial Design



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

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



“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

Study Cohort

Prospective, Observational FLEX Study (NCT03053193)

1,259 patients diagnosed between 2015-2022:

- 1) Clinical HR+HER2-
- 2) MammaPrint High Risk
- 3) Blueprint Luminal B
- 4) Adjuvantly TC or AC-T treated
- 5) Follow-up data (median 3.2 yr)

1,106 patients with **High Risk 1 (H1)**
(Index -0.569 to 0.000)

153 patients with **High Risk 2 (H2)**
(Index -1.000 to -0.570)

TC treated
H1: N = 817

AC-T treated
H1: N = 289

TC treated
H2: N = 102

AC-T treated
H2: N = 51

Propensity-score matched population

PSM TC treated
H1: N = 289

PSM AC-T treated
H1: N = 289

PSM TC treated
H2: N = 51

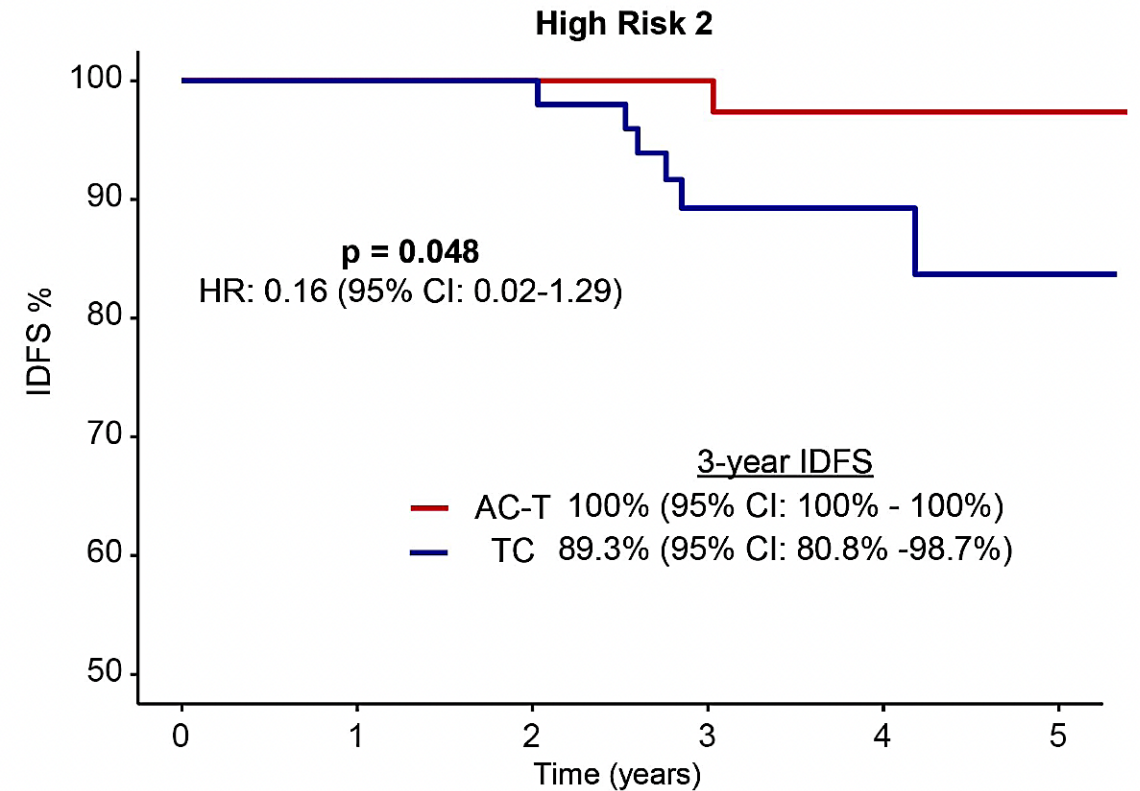
PSM AC-T treated
H2: N = 51

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



Numbers at Risk

| H2 | 0 | 1 | 2 | 3 | 4 | 5 |
|------|----|----|----|----|----|---|
| AC-T | 51 | 50 | 49 | 40 | 17 | 8 |
| TC | 51 | 51 | 50 | 30 | 16 | 9 |

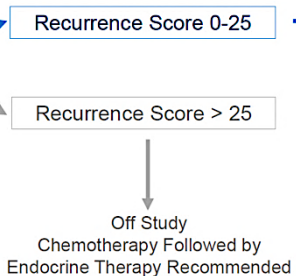
OncotypeDX: RxPONDER Trial Results Summary One to Three Positive Lymph Nodes

RxPONDER Trial Design

Key Entry Criteria

- Women age ≥ 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

RANDOMIZATION



N = 5,000 pts

Stratification Factors

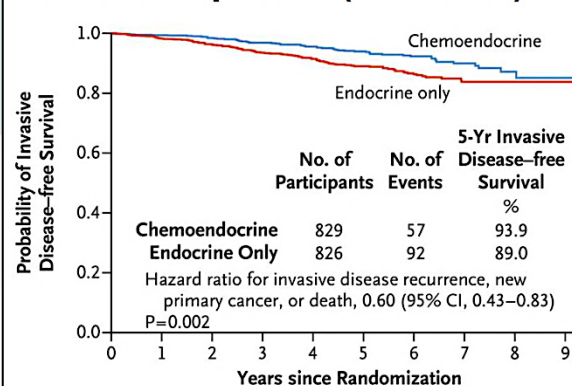
Recurrence Score: 0-13 vs. 14-25
Menopausal Status: pre vs. post
Axillary Surgery: ALND vs. SLNB

RxPONDER Population

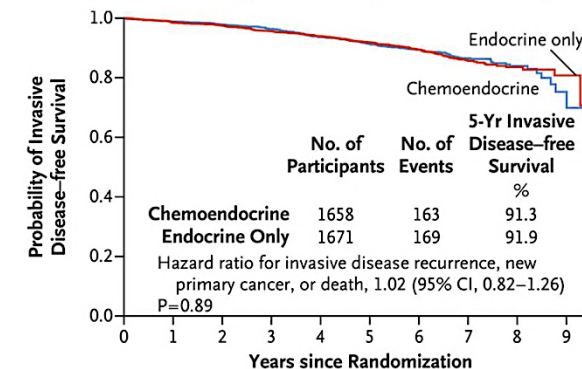
| | | | |
|-----------|-----|----------|-----|
| T1 | 58% | T3 | 5% |
| 1 LN+ | 66% | 3 LN+ | 9% |
| Grade 2 | 64% | Grade 3 | 10% |
| 40-49 yrs | 21% | < 40 yrs | 3% |

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

Premenopausal (1/3rd Trial)



Postmenopausal (2/3rd Trial)



IDFS Benefit Modified by Score for Women Age ≤ 50

Women ≤ 50 yr

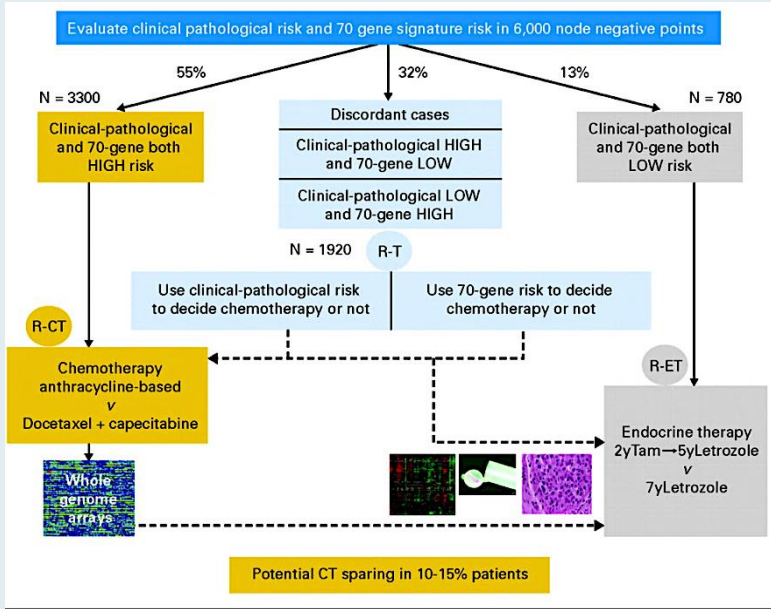
| Group | No. of Patients | 5-Yr Invasive Disease-free Survival (%) | Hazard Ratio (95% CI) |
|----------------------------|-----------------|---|-----------------------|
| ≤ 10 , endocrine only | 145 | 91.0 \pm 2.6 | 0.31 (0.10–0.94) |
| ≤ 10 , chemoendocrine | 135 | 97.9 \pm 1.5 | |
| 11–15, endocrine 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

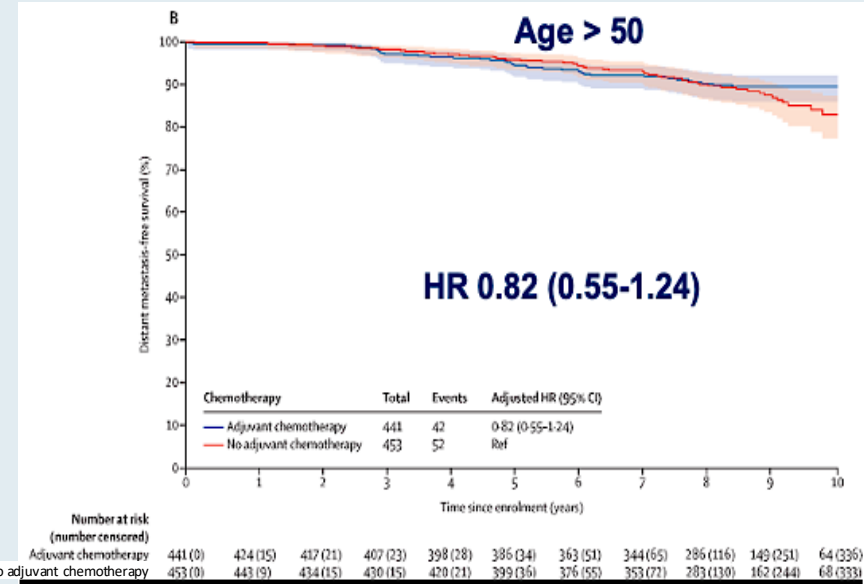
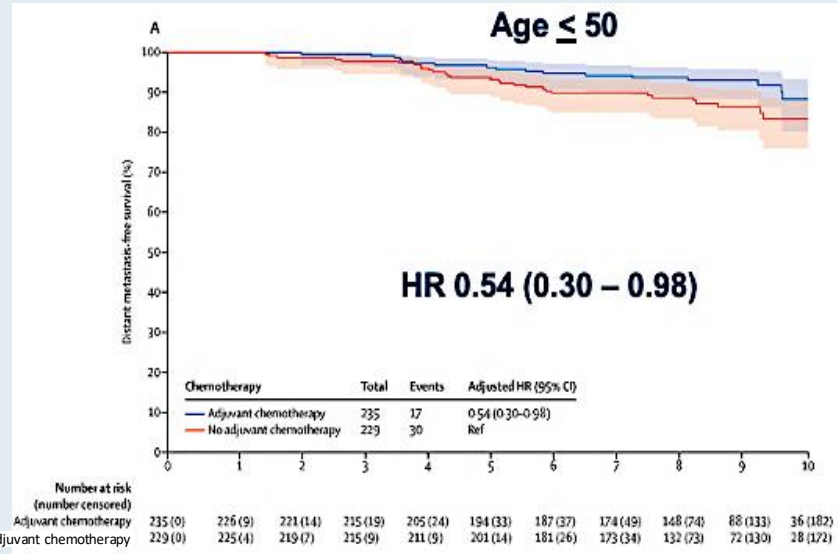
Clinical “high risk”: <88% 10-yr BCSS
 Modified Adjuvant! Online to determine
 Model included: T size, Node (0-3), grade, ER status, age, comorbidity

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% (92.5 – 96.2) | 95.9% (94-97.2) | 1.2% |
| 8-yr DMFS | 89.4% (86.8- 91,5) | 92% (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)

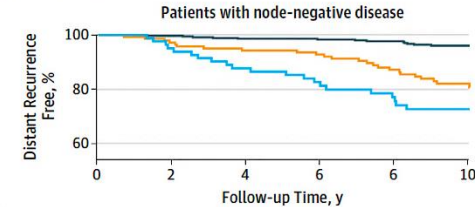
JAMA Oncology | Original Investigation

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

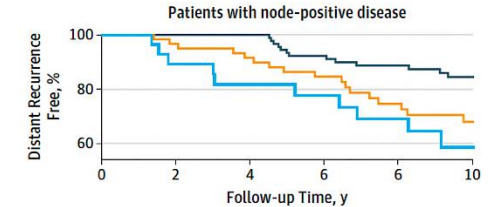
- Largest retrospective prognostic validation in TransATAC Trial (included Oncotype DX and BCI as well)
- N = 535 node-negative, 154 node-positive
- Examined risk years 0 to 10
- ROR, EPclin and BCI provided most prognostic information
- ROR HR 2.56 (1.96-3.35)
- EPclin HR 2.14 (1.71-2.68)
- BCI HR 2.46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

BCI

A Breast cancer index



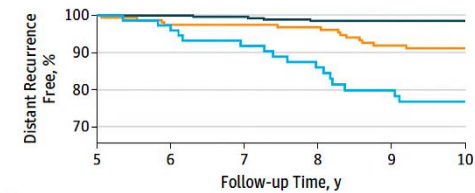
| No. at risk | 0 | 2 | 4 | 6 | 8 | 10 |
|-------------------|-----|-----|-----|-----|-----|-----|
| Low risk | 365 | 356 | 346 | 331 | 309 | 173 |
| Intermediate risk | 143 | 137 | 128 | 122 | 105 | 59 |
| High risk | 83 | 78 | 71 | 60 | 52 | 30 |



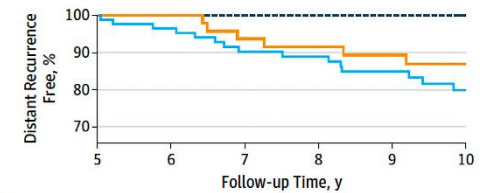
| No. at risk | 0 | 2 | 4 | 6 | 8 | 10 |
|-------------------|----|----|----|----|----|----|
| Low risk | 95 | 95 | 92 | 80 | 69 | 35 |
| Intermediate risk | 60 | 58 | 53 | 45 | 37 | 21 |
| High risk | 28 | 25 | 21 | 18 | 15 | 7 |

ROR

C Risk of recurrence score



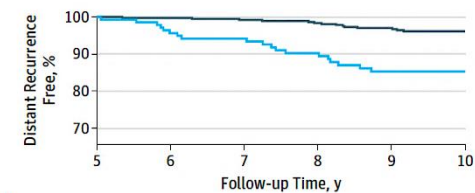
| No. at risk | 5 | 6 | 7 | 8 | 9 | 10 |
|-------------------|-----|-----|-----|-----|-----|-----|
| Low risk | 292 | 288 | 279 | 270 | 257 | 157 |
| Intermediate risk | 165 | 155 | 149 | 138 | 125 | 72 |
| High risk | 78 | 70 | 64 | 58 | 50 | 33 |



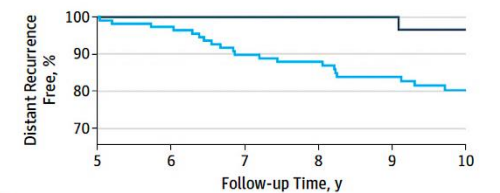
| No. at risk | 5 | 6 | 7 | 8 | 9 | 10 |
|-------------------|----|----|----|----|----|----|
| Low risk | 15 | 15 | 15 | 13 | 13 | 6 |
| Intermediate risk | 51 | 48 | 44 | 42 | 38 | 23 |
| High risk | 88 | 80 | 70 | 66 | 56 | 34 |

EPclin

D EPclin



| No. at risk | 5 | 6 | 7 | 8 | 9 | 10 |
|-------------------|-----|-----|-----|-----|-----|-----|
| Low risk | 393 | 384 | 369 | 356 | 335 | 202 |
| Intermediate risk | 142 | 129 | 123 | 110 | 97 | 60 |

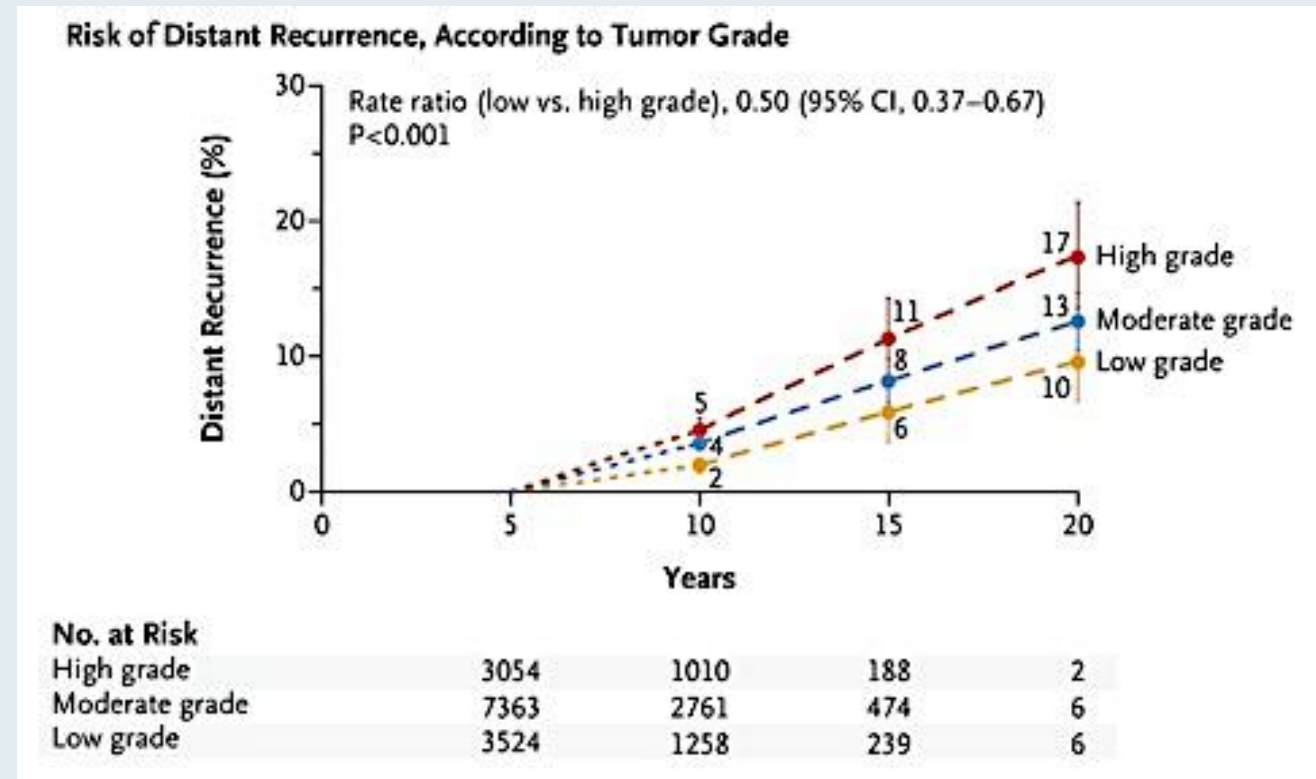
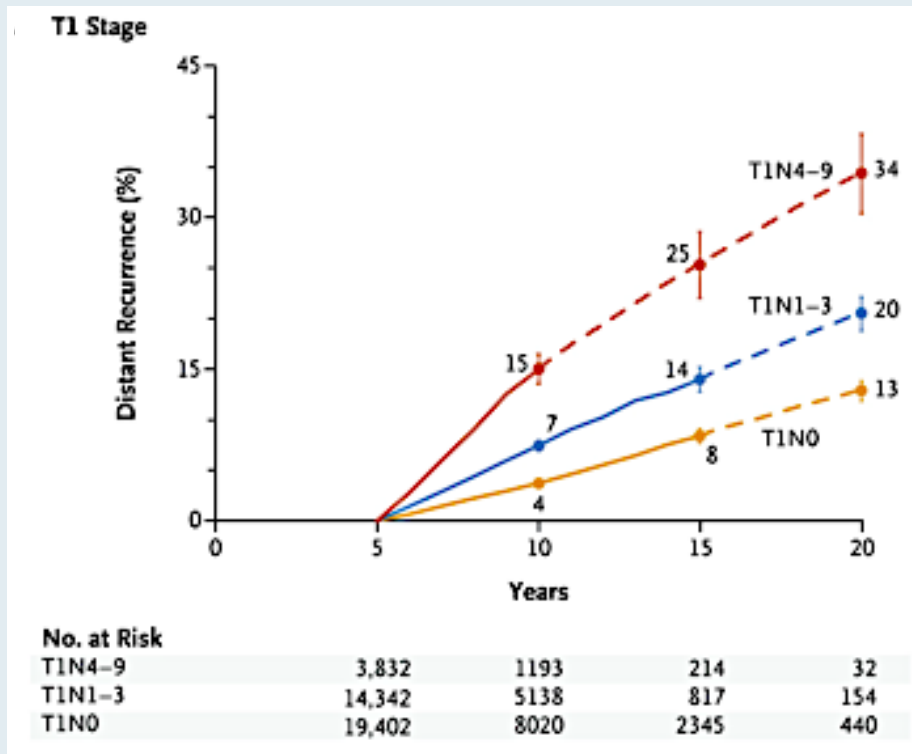


| No. at risk | 5 | 6 | 7 | 8 | 9 | 10 |
|-------------------|-----|-----|----|----|----|----|
| Low risk | 40 | 37 | 34 | 32 | 30 | 15 |
| Intermediate risk | 114 | 106 | 95 | 89 | 77 | 48 |

— Low risk — Intermediate risk — High risk

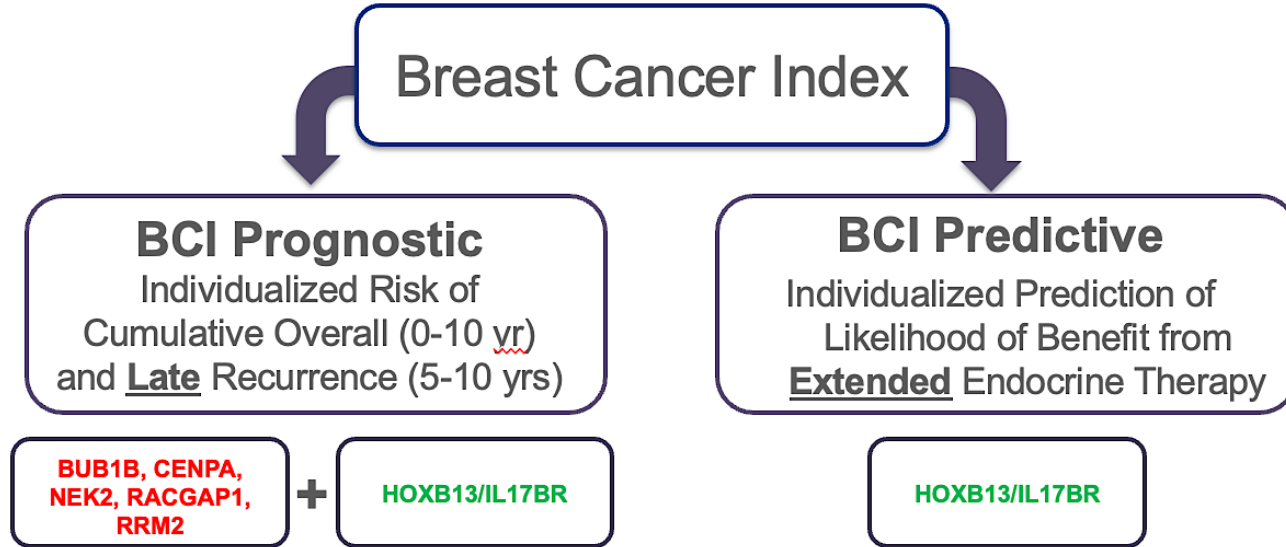
Persistent Long-Term Risk of Distant Recurrence

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



Breast Cancer Index

BCI components

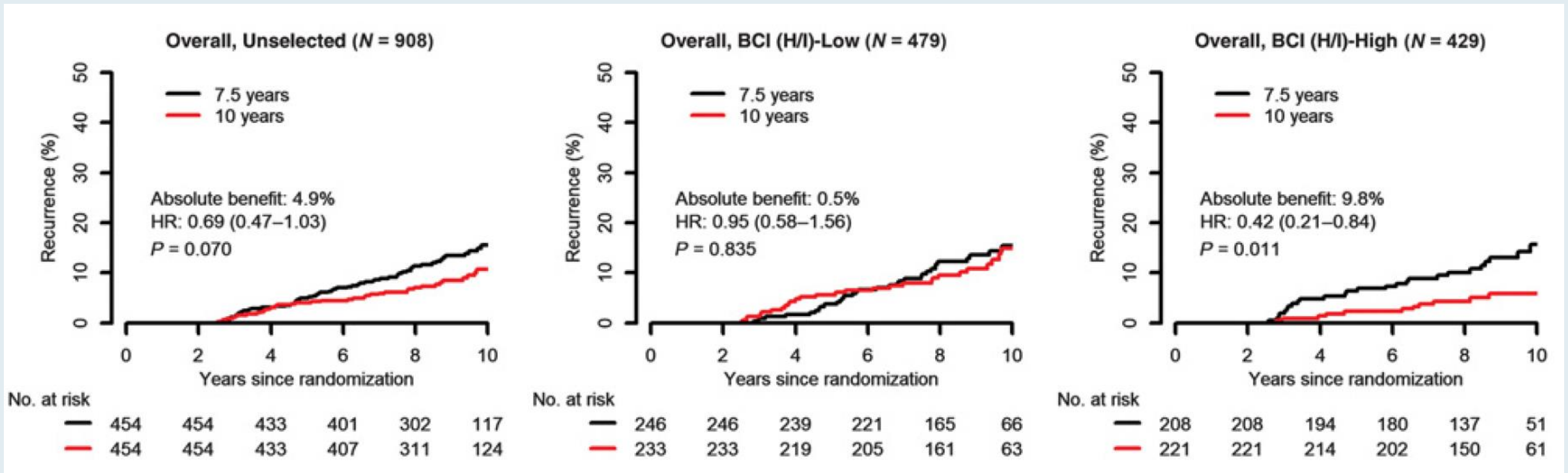


- Algorithmic combination of **proliferation**-related gene signature (Molecular Grade Index, MGI) and an **estrogen** signaling pathway signature (HoxB13/IL17BR, a.k.a. H/I)
- A separate algorithm based exclusively on H/I to provide a quantitative molecular assessment of estrogen signaling pathways

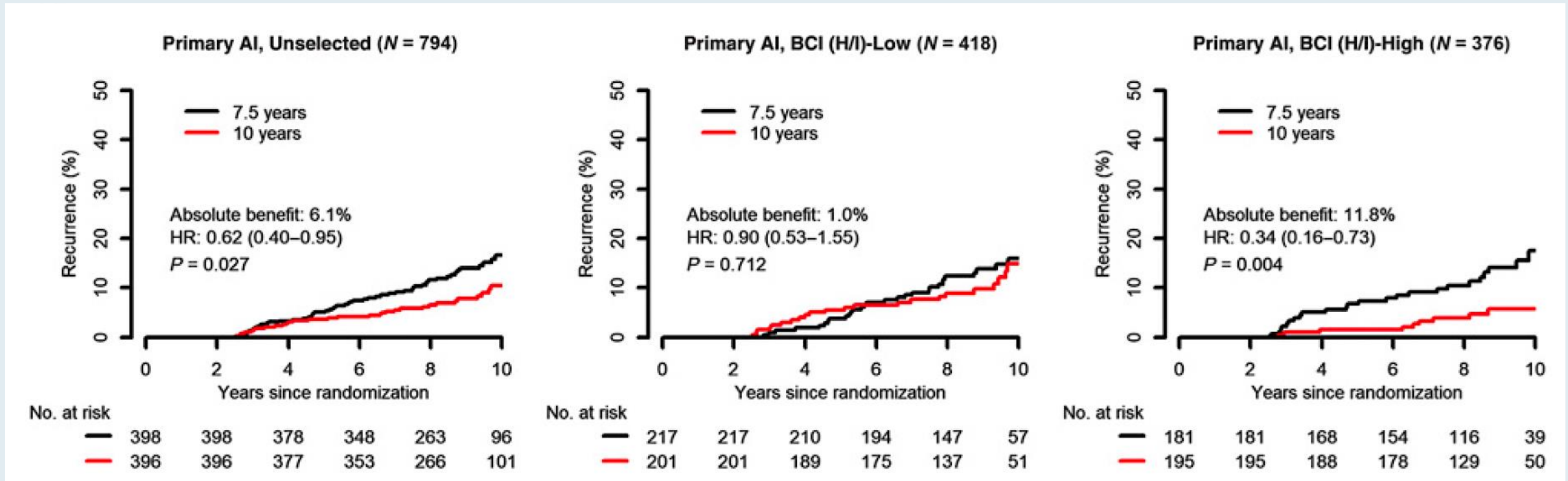
Distribution of BCI scores



Predictive Performance by Breast Cancer Index® (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)

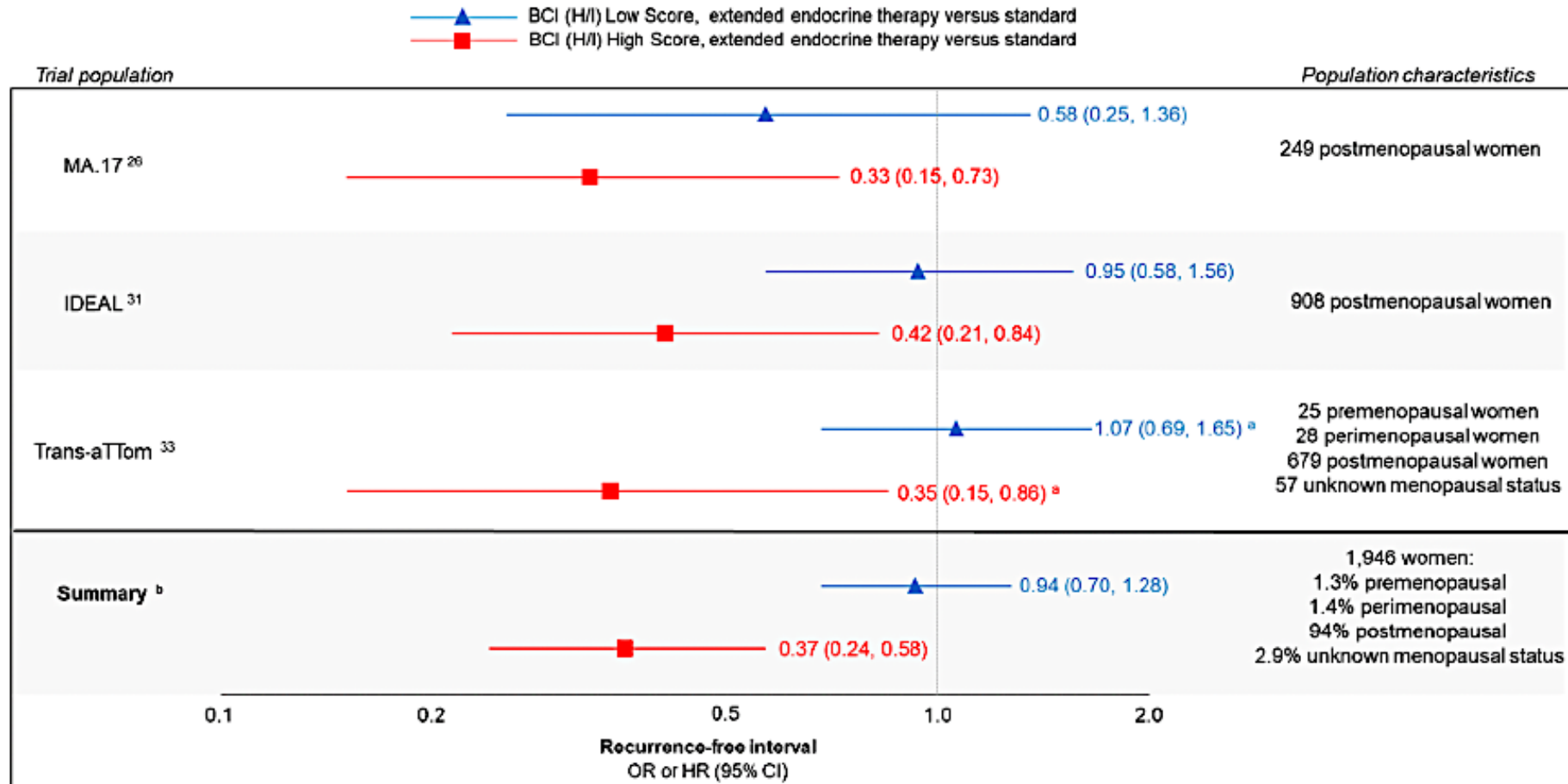


Risk of Recurrence at Year 10 Since Randomization for Patients Who Received 5 Years versus 2.5 Years of Additional Letrozole in the Overall Cohort and in the Primary AI Subset of the Phase III IDEAL Trial

| 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 ≥ 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 ≤ 50 Years (evidence quality/strength of recommendation) | Postmenopausal or Age > 50 Years (evidence quality/strength of recommendation) |
|--------------------|--|--|
| Node-negative | Oncotype DX (<i>high/strong</i>) | Oncotype DX (<i>high/strong</i>) MammaPrint ^a (<i>intermediate/strong</i>) EndoPredict (<i>intermediate/moderate</i>) Prosigna (<i>intermediate/moderate</i>) Ki67 ^b (<i>intermediate/moderate</i>) IHC4 ^b (<i>intermediate/moderate</i>) BCI ^c (<i>intermediate/moderate</i>) |
| 1-3 positive nodes | Insufficient evidence to recommend a biomarker for use | Oncotype DX (<i>high/strong</i>) MammaPrint ^a (<i>intermediate/strong</i>) EndoPredict (<i>intermediate/moderate</i>) Ki67 ^b (<i>intermediate/strong</i>) IHC4 ^b (<i>intermediate/moderate</i>) BCI ^c (<i>intermediate/moderate</i>) |
| ≥ 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[®], MammaPrint[®], EndoPredict[®], Breast Cancer Index[®]



Dr Jhaveri

Oncotype DX



Dr Kalinsky

Oncotype DX



Dr Mahtani

Oncotype DX, MammaPrint, Breast Cancer Index



Dr Mayer

Oncotype DX



Dr Rugo

Oncotype DX and MammaPrint



Dr Sharma









Oncotype DX and MammaPrint



Dr Shatsky









Oncotype DX, MammaPrint, Breast Cancer Index

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 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 Mayer | No | No | Yes, but offer OFS/OA as alternative |
|  | Dr Rugo | No | No* | No* |
|  | Dr Sharma | No | No | Yes, but offer OFS/OA as alternative |
|  | Dr Shatsky | No | No* | No* |

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 Jhaveri | Yes | Yes | Yes |
|  | Dr Kalinsky | Yes | Yes | Yes |
|  | Dr Mahtani | Yes | Yes | Yes |
|  | Dr Mayer | No | Yes, but offer OFS/OA as alternative | Yes |
|  | Dr Rugo | Yes | Yes | Yes |
|  | Dr Sharma | Yes | Yes | Yes |
|  | Dr Shatsky | 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 Jhaveri | | No | No | No |
|  Dr Kalinsky | | No | No | Yes |
|  Dr Mahtani | | No | No | Yes |
|  Dr Mayer | | No | No | No |
|  Dr Rugo | | No | No | No |
|  Dr Sharma | | No | No | No |
|  Dr Shatsky | | 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 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 Mayer

I have



Dr Rugo

I have



Dr Sharma









I have not and would not



Dr Shatsky









I have

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 Jhaveri | Oncotype DX |
|  | Dr Kalinsky | MammaPrint |
|  | Dr Mahtani | MammaPrint |
|  | Dr Mayer | Oncotype DX |
|  | Dr Rugo | MammaPrint and Oncotype DX* |
|  | Dr Sharma | Oncotype DX and MammaPrint |
|  | Dr Shatsky | MammaPrint and Oncotype DX* |









* 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?

| | |
|--|--|
|  Dr Brufsky | Yes, for node-positive disease when MammaPrint not available |
|  Dr Jhaveri | Yes, per patient preference and for N0 and N1, especially if patients are struggling with toxicities |
|  Dr Kalinsky | Yes, in situations where I'm on the fence about extending ET |
|  Dr Mahtani | Yes, for patients with N0 disease or up to 3 pos nodes |
|  Dr Mayer | No |
|  Dr Rugo | No* |
|  Dr Sharma | Yes, for patients with high-risk, node-negative disease |
|  Dr Shatsky | Yes, N0/N1 tumors with decent risk for late relapse |









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 Jhaveri | 5% to 10% | <5% |
|  | Dr Kalinsky | 10% | 10% |
|  | Dr Mahtani | 20% | 20% |
|  | Dr Mayer | NA | NA |
|  | Dr Rugo | NA | NA |
|  | Dr Sharma | 10% | 10% |
|  | Dr Shatsky | 25% | 5% |

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 Jhaveri | No |
|  Dr Kalinsky | No |
|  Dr Mahtani | No |
|  Dr Mayer | No |
|  Dr Rugo | No |
|  Dr Sharma | No |
|  Dr Shatsky | 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 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 Mayer | I have not and would not | NA |
|  | Dr Rugo | I have | Signatera |
|  | Dr Sharma | I have not and would not | NA |
|  | Dr Shatsky | I have | Signatera first, then Guardant Reveal™ if not enough tissue |

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

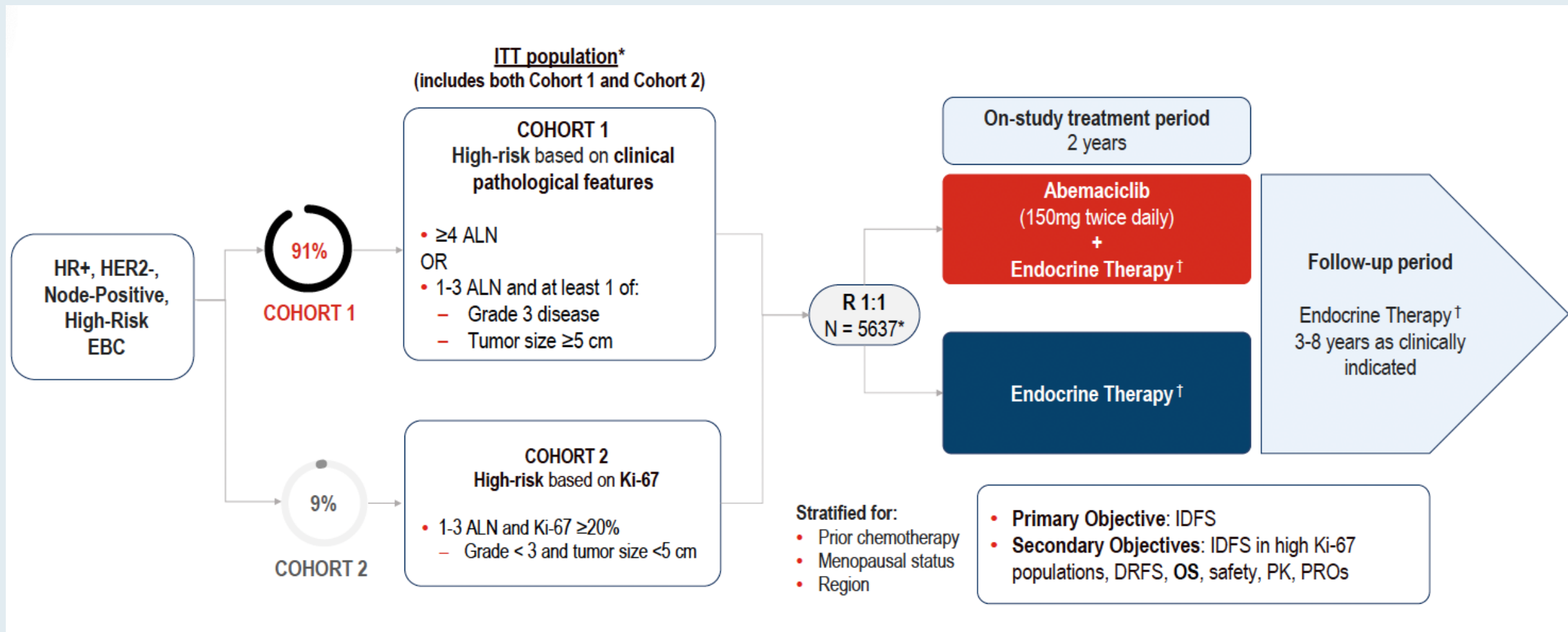
Module 6: Clinician Survey Results

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

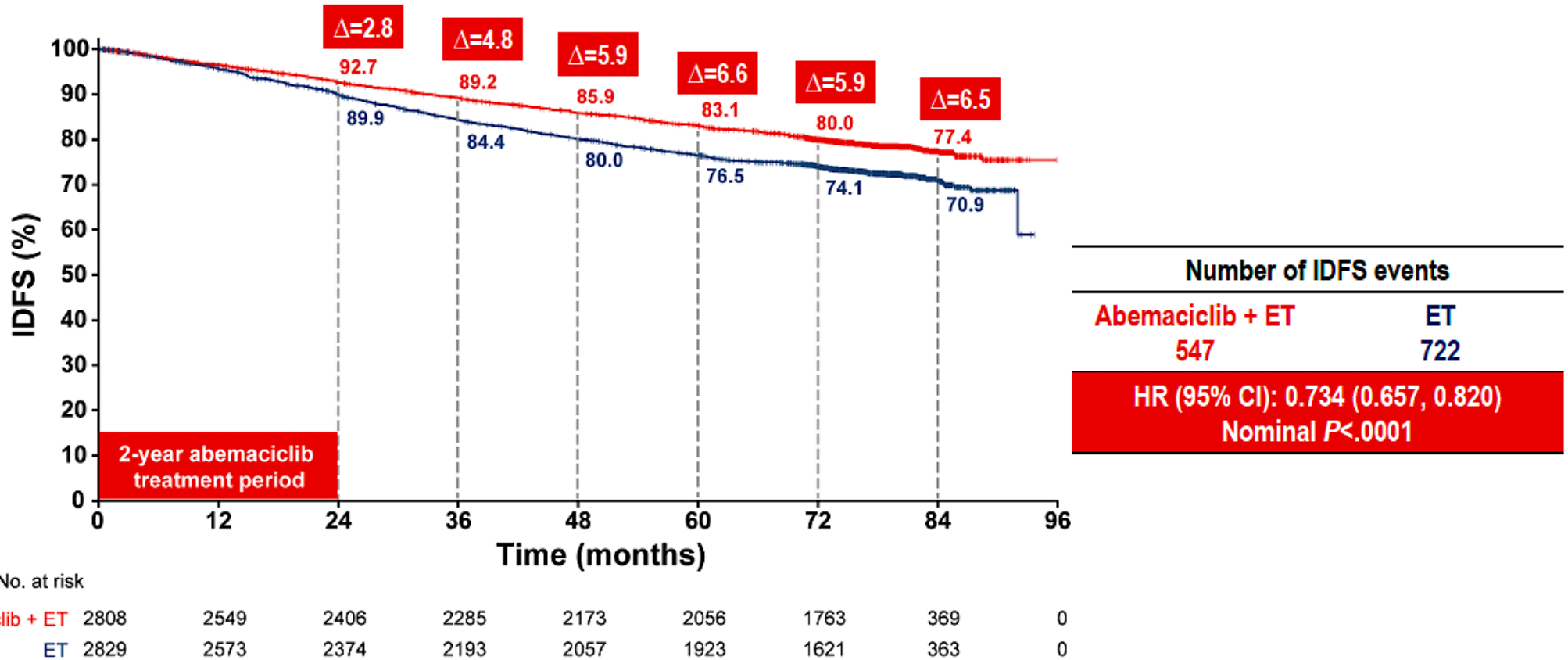
Key Datasets

- 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.

monarchE Study Design



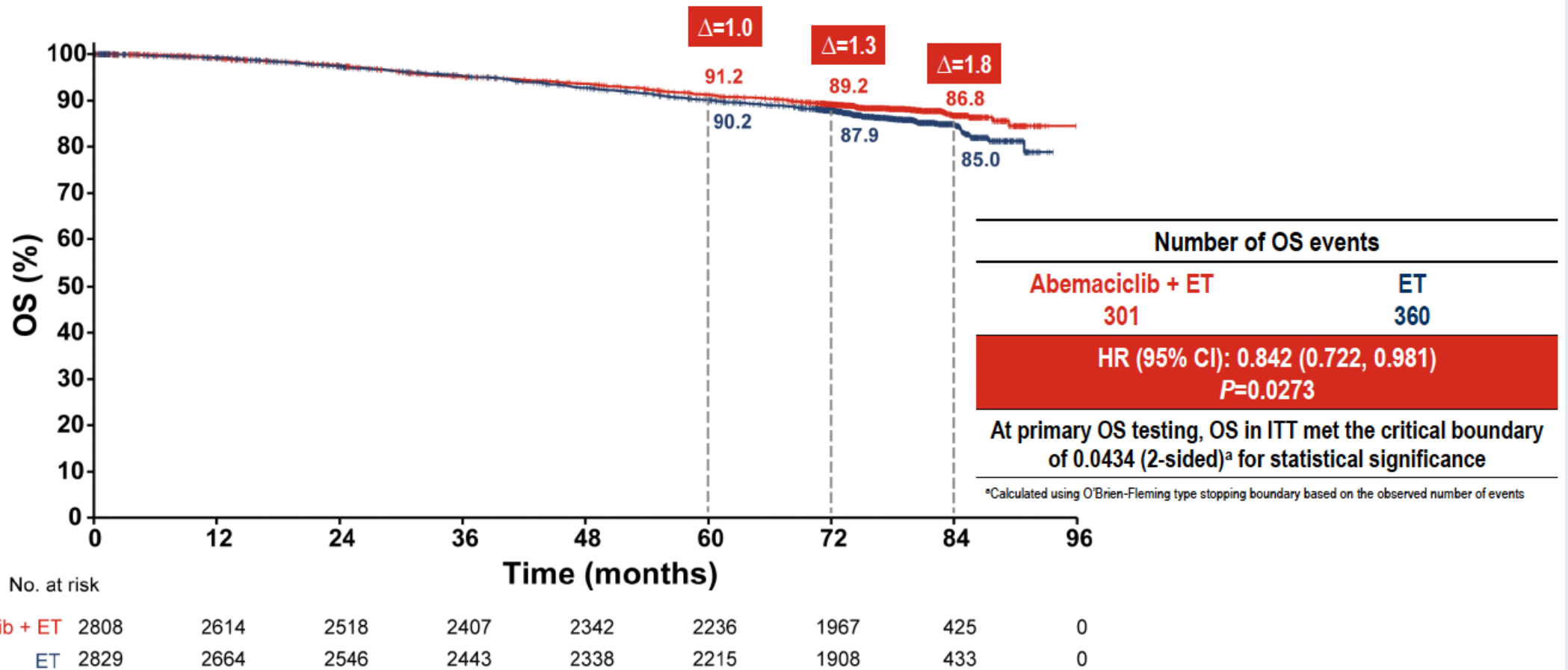
monarchE: Invasive Disease-Free Survival (IDFS) Outcomes



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

ET = endocrine therapy

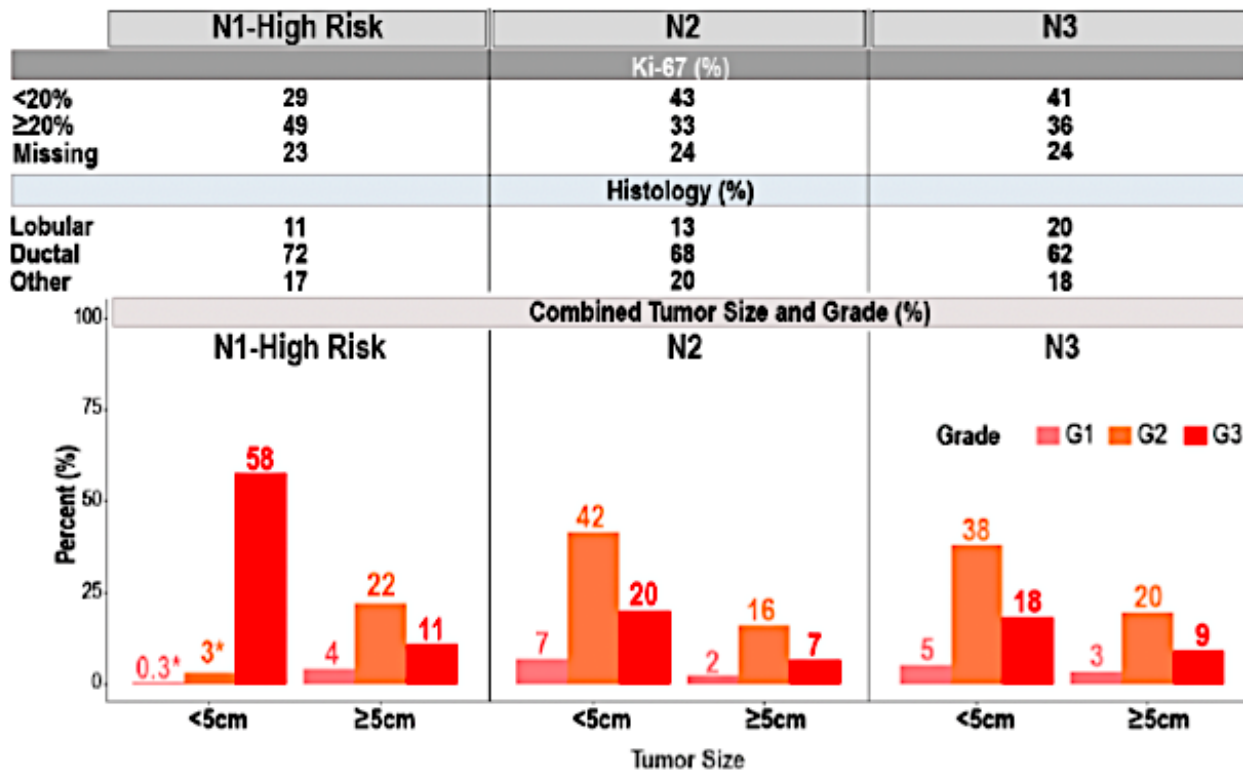
monarchE: Overall Survival (OS) Outcomes



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

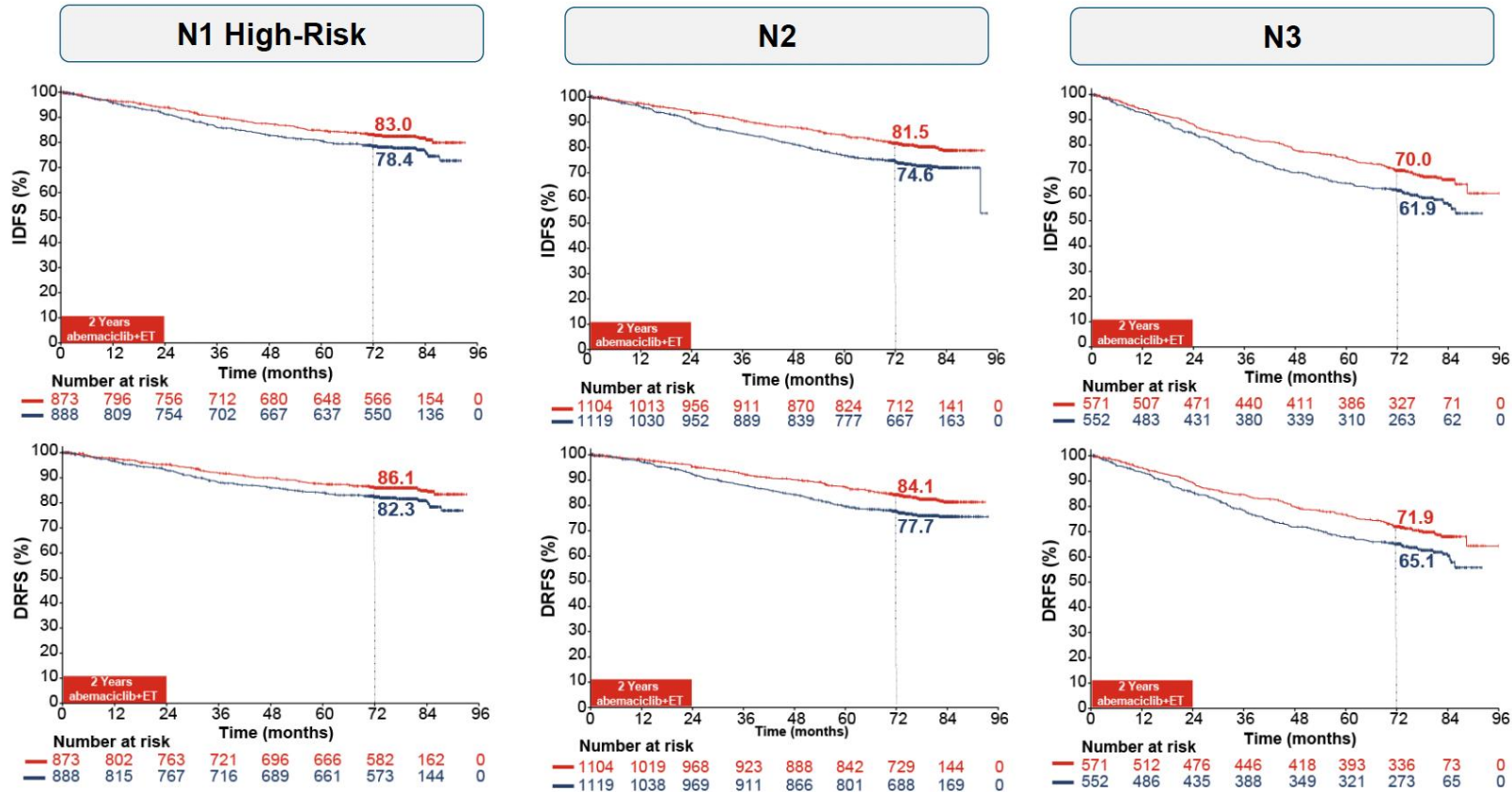
monarchE: Subgroup Analysis by Nodal Status

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

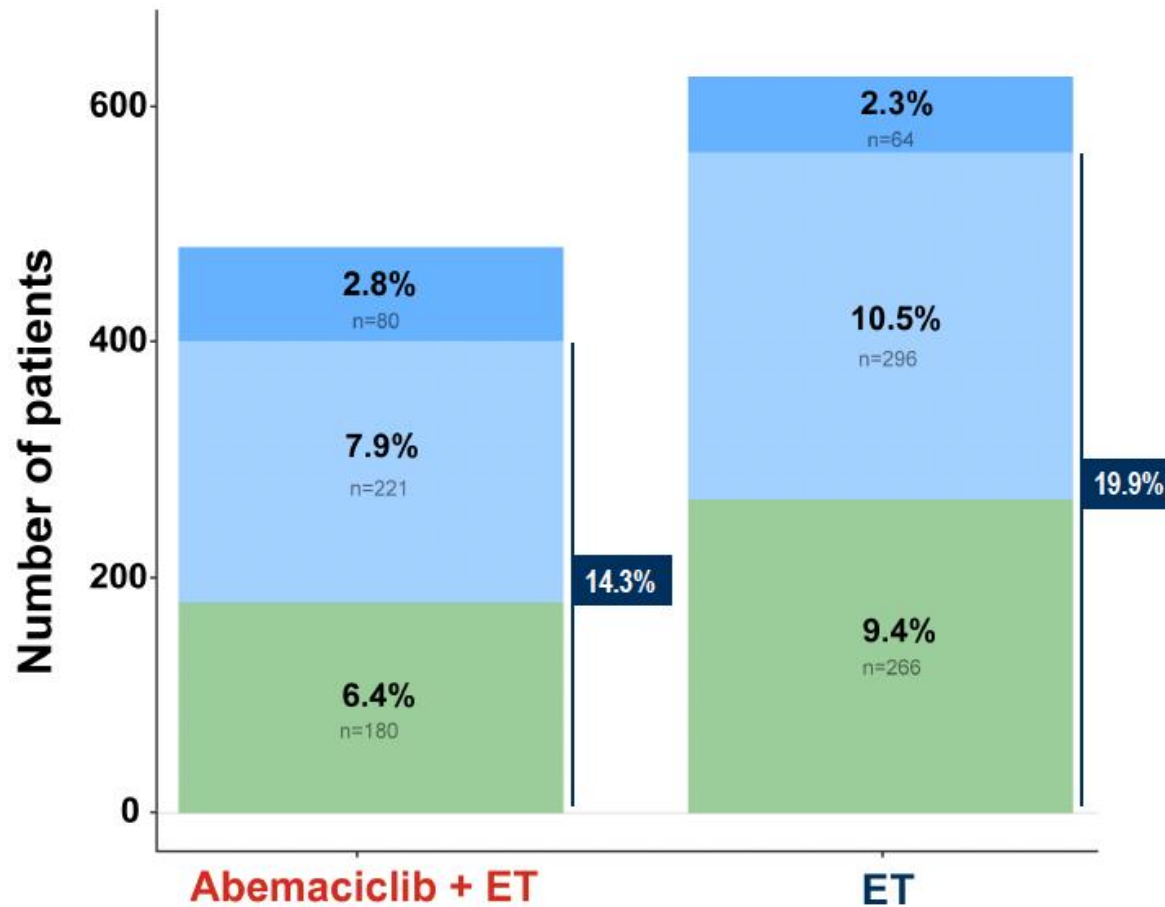
monarchE: IDFS and DRFS by Nodal Status



- 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



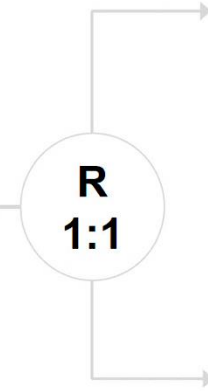
Status ■ Deaths not related to breast cancer^a ■ Deaths due to breast cancer ■ Alive with metastatic disease

~30% Fewer Patients in Abemaciclib Arm Living with Metastatic Disease

NATALEE Study Design

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

- Prior ET allowed up to 12 months
- **Anatomical stage IIA^a**
 - 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^a**
 - N0 or N1
- **Anatomical stage III**
 - N0, N1, N2, or N3



RIB
400 mg/day
3 weeks on/1 week off for 3 y
+
NSAI
Letrozole or anastrozole^b for \geq 5 y
+ goserelin in men and premenopausal women

NSAI
Letrozole or anastrozole^b 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

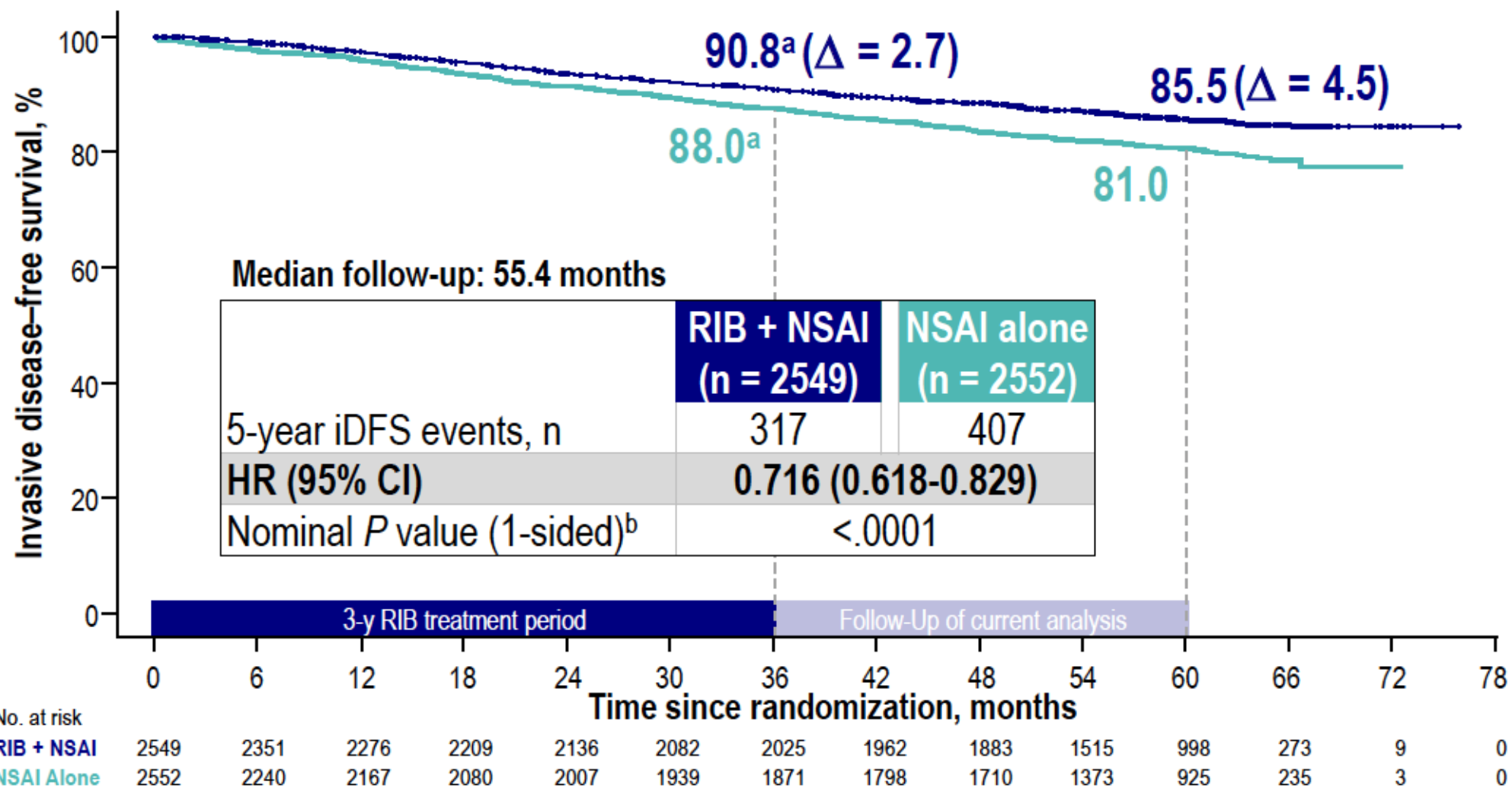
Exploratory End Points

- 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

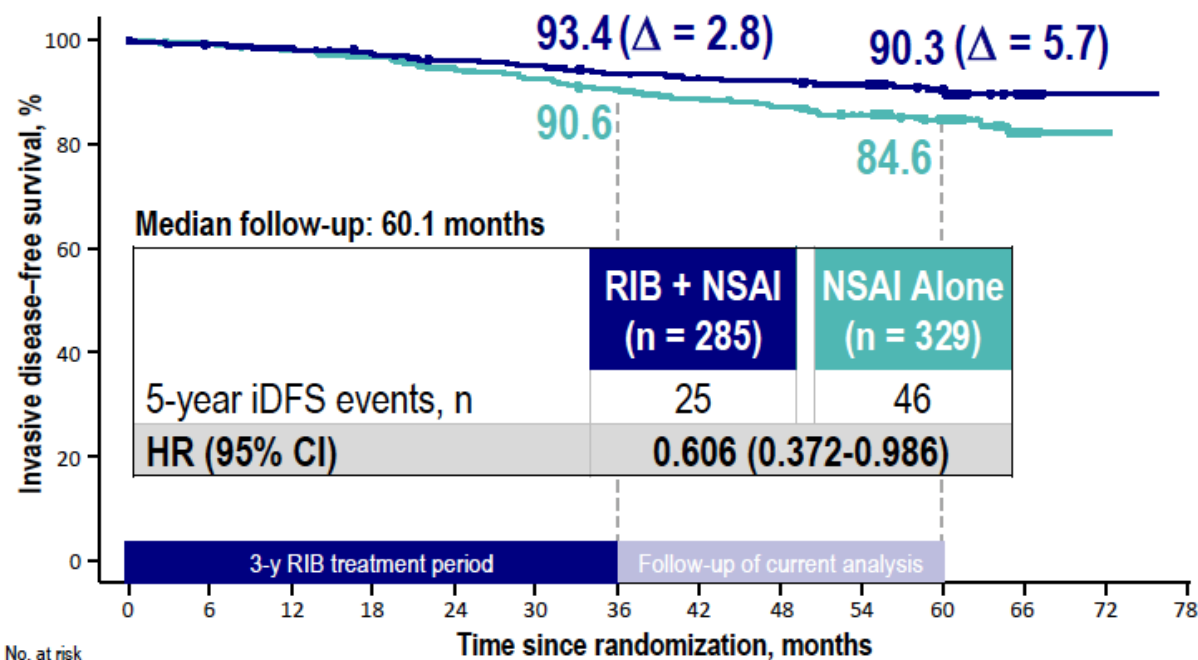
NATALEE: IDFS Outcomes



NSAI = nonsteroidal aromatase inhibitor

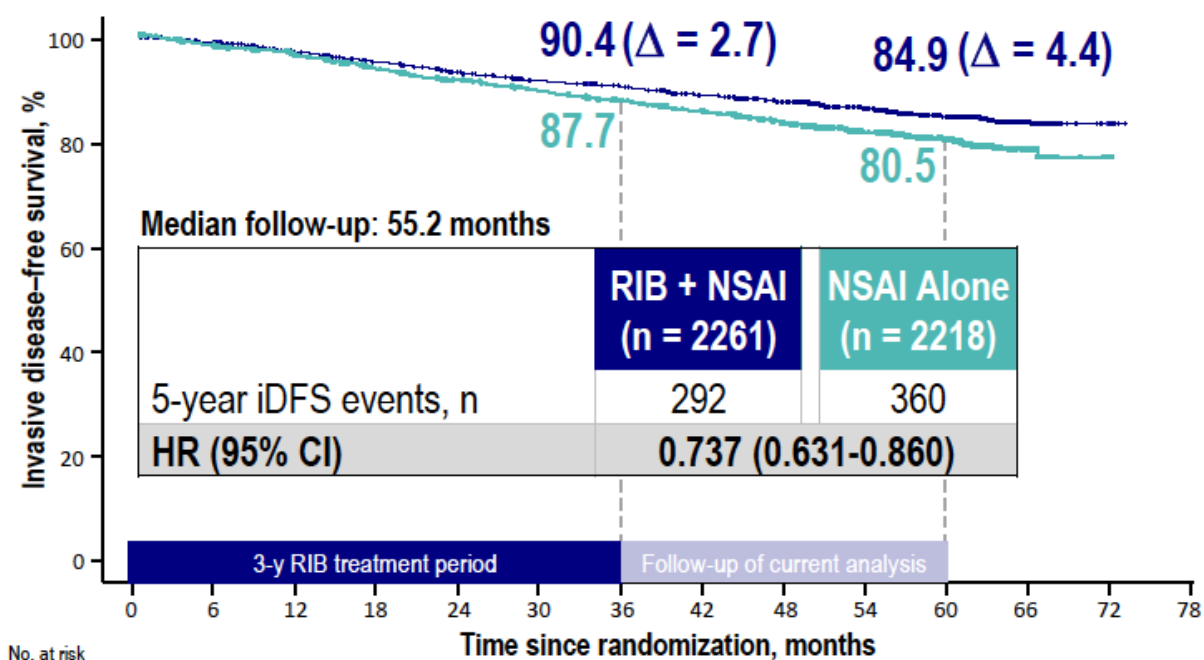
NATALEE: IDFS by Nodal Status

N0



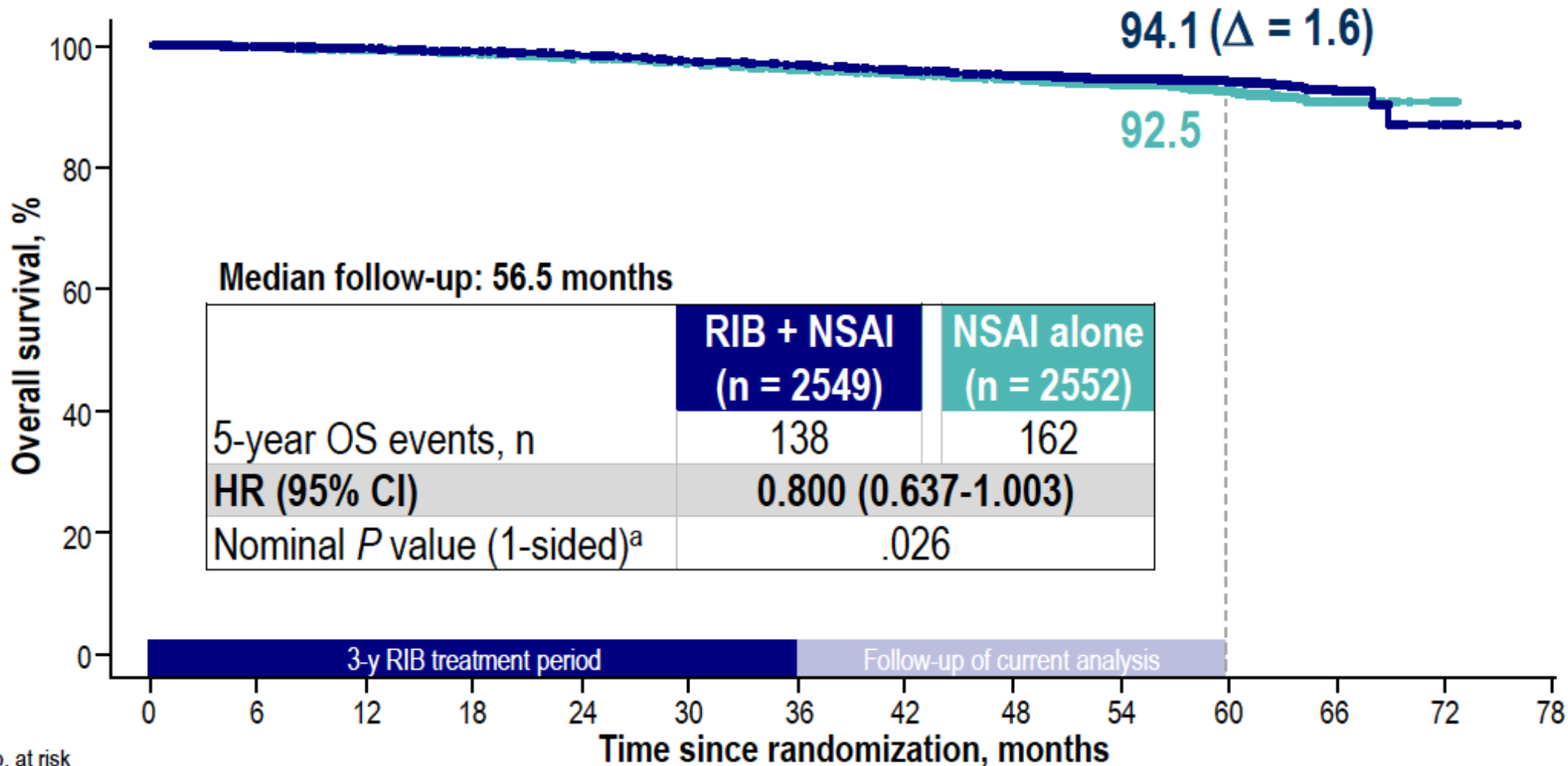
| No. at risk | 0 | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 | 54 | 60 | 66 | 72 | 78 |
|-------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|
| RIB + NSAI | 285 | 262 | 258 | 250 | 244 | 240 | 233 | 229 | 227 | 214 | 164 | 52 | 3 | 0 |
| NSAI Alone | 329 | 301 | 295 | 289 | 279 | 271 | 259 | 253 | 245 | 225 | 164 | 56 | 1 | 0 |

N+



| No. at risk | 0 | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 | 54 | 60 | 66 | 72 | 78 |
|-------------------|------|------|------|------|------|------|------|------|------|------|-----|-----|----|----|
| RIB + NSAI | 2261 | 2086 | 2015 | 1956 | 1889 | 1839 | 1789 | 1730 | 1653 | 1300 | 834 | 221 | 6 | 0 |
| NSAI Alone | 2218 | 1936 | 1870 | 1789 | 1726 | 1666 | 1610 | 1543 | 1463 | 1146 | 759 | 179 | 2 | 0 |

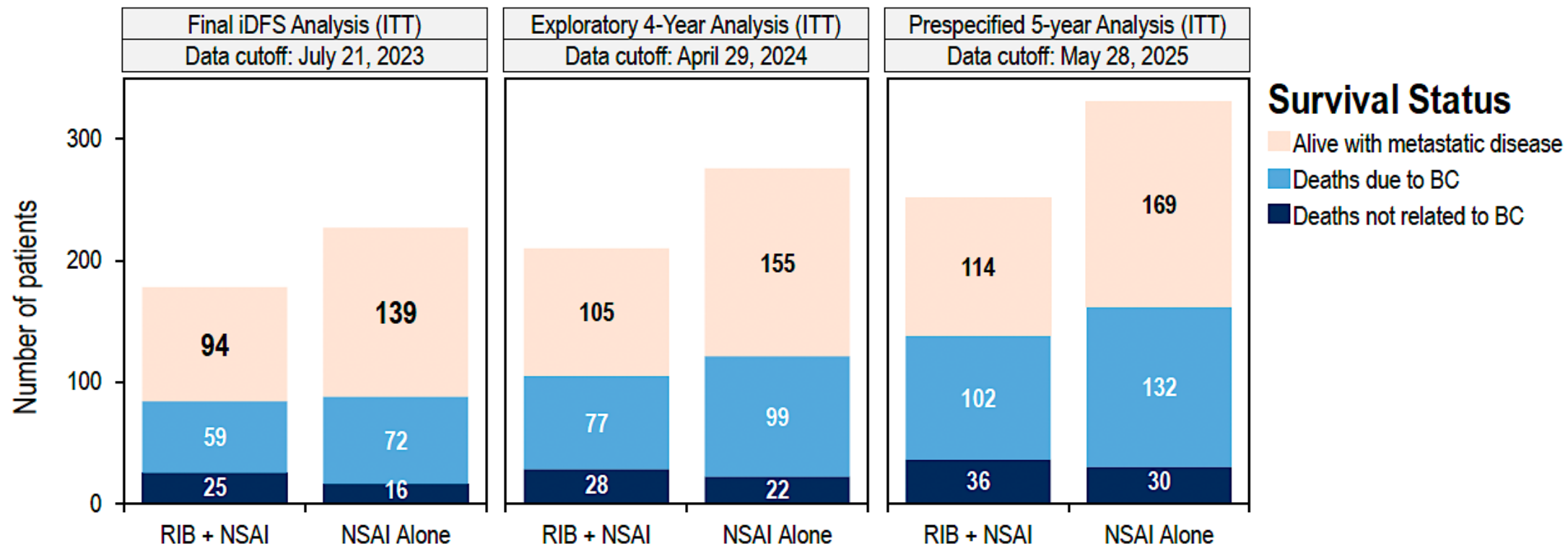
NATALEE: OS Outcomes



No. at risk

| | 0 | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 | 54 | 60 | 66 | 72 | 78 |
|--------------------|------|------|------|------|------|------|------|------|------|------|------|-----|----|----|
| RIB + NSAID | 2549 | 2404 | 2236 | 2299 | 2259 | 2219 | 2185 | 2132 | 2072 | 1684 | 1128 | 325 | 10 | 0 |
| NSAID Alone | 2552 | 2301 | 2255 | 2208 | 2160 | 2116 | 2063 | 2009 | 1956 | 1591 | 1076 | 309 | 7 | 0 |

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) |

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 breast cancer (BC) and the following nodal status?

| | | Node-negative | 2 positive nodes | 4 positive nodes |
|--|--|-----------------|------------------|------------------|
|  Dr Brufsky | | 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 Mayer | | Yes, ribociclib | Yes, either | Yes, abemaciclib |
|  Dr Rugo | | Yes, ribociclib | Yes, either | Yes, abemaciclib |
|  Dr Sharma | | Yes, ribociclib | Yes, either | Yes, either |
|  Dr Shatsky | | Yes, ribociclib | Yes, ribociclib | Yes, abemaciclib |

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 Jhaveri | | Yes, ribociclib | Yes, abemaciclib | Yes, abemaciclib |
|  Dr Kalinsky | | Yes, ribociclib | Yes, abemaciclib | Yes, abemaciclib |
|  Dr Mahtani | | No | Yes, ribociclib | Yes, either |
|  Dr Mayer | | Yes, ribociclib | Yes, either | Yes, abemaciclib |
|  Dr Rugo | | Yes, ribociclib | Yes, either | Yes, abemaciclib |
|  Dr Sharma | | No | Yes, either | Yes, either |
|  Dr Shatsky | | Yes, ribociclib | Yes, ribociclib | Yes, abemaciclib |

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

- 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, ^a 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) ^b | 242 (8.6) | 184 (6.6) | 52 (1.9) | 6 (0.2) |
| Infections ^c | 1429 (51.2) | 245 (8.8) | 1029 (36.9) | 155 (5.6) | 1102 (39.4) | 229 (8.2) | 790 (28.2) | 83 (3.0) ^d |
| 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 ^e | 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 ^f | 71 (2.5) | 2 (0.1) | 31 (1.1) | 38 (1.4) ^h | 17 (0.6) | 0 (0.0) | 9 (0.3) | 8 (0.3) |
| PE ^g | 28 (1.0) | N/A | N/A | 28 (1.0) ⁱ | 4 (0.1) | N/A | N/A | 4 (0.1) |
| ILD ^j | 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 ^k | 433 (15.5) | 241 (8.6) | 94 (3.4) | 98 (3.5) | 209 (7.5) | 143 (5.1) | 38 (1.4) | 28 (1.0) |

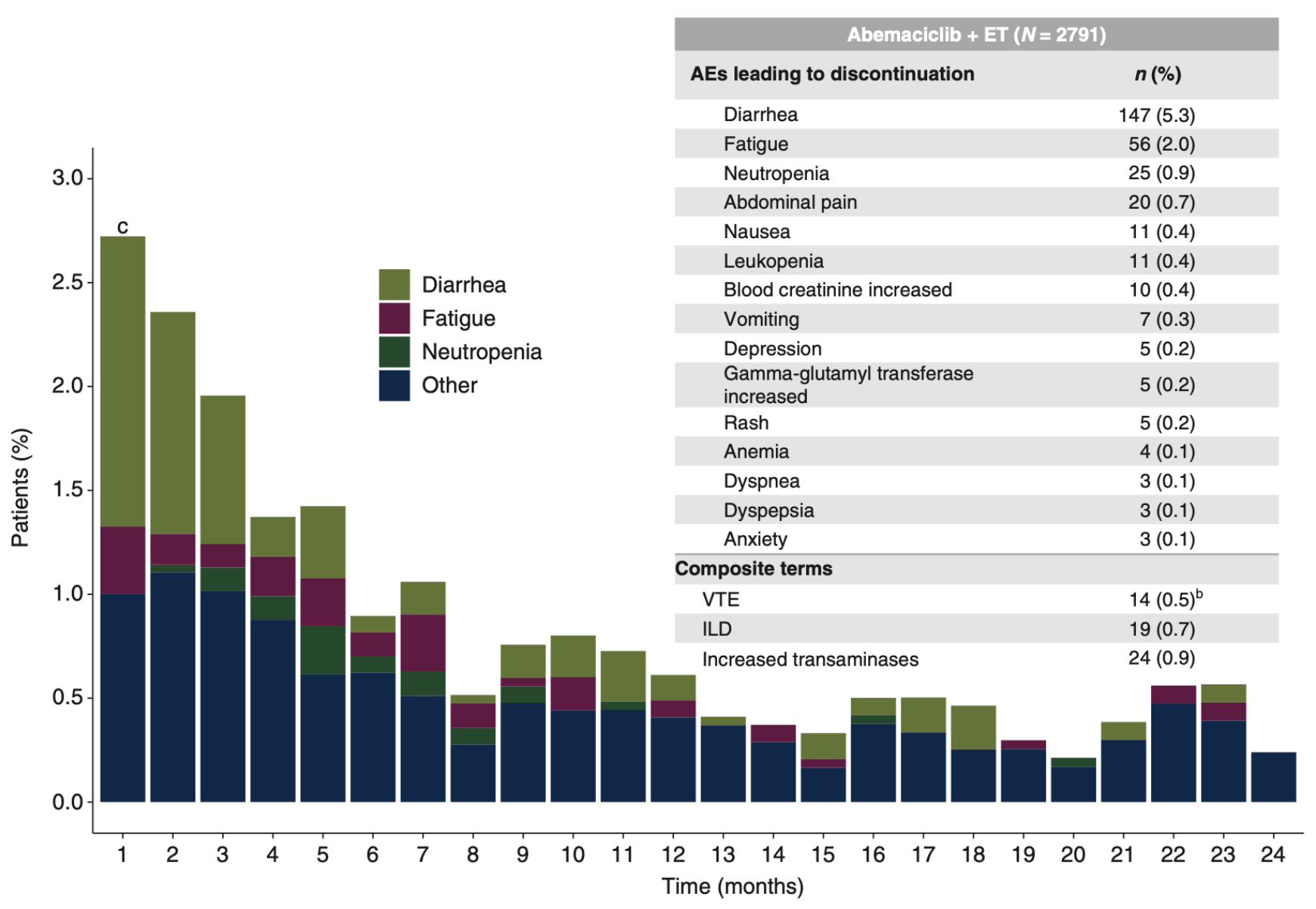
monarchE: Serious and Fatal Adverse Events (AEs) in Long-Term Follow-Up

| | Abemaciclib + ET N=2791, n (%) | | ET N=2800, n (%) | |
|---|-----------------------------------|-----------------------------------|-------------------------|-----------------------------------|
| | On Therapy ^a | Post-Discontinuation ^b | On Therapy ^a | Post-Discontinuation ^b |
| ≥1 SAE* LTFU, regardless of causality | NA | 197 (7.5) | NA | 213 (8.1) |
| Deaths due to AE by SOC and PT^c | 15 (0.5) | 44 (1.6) | 11 (0.4) | 30 (1.1) |
| 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) |

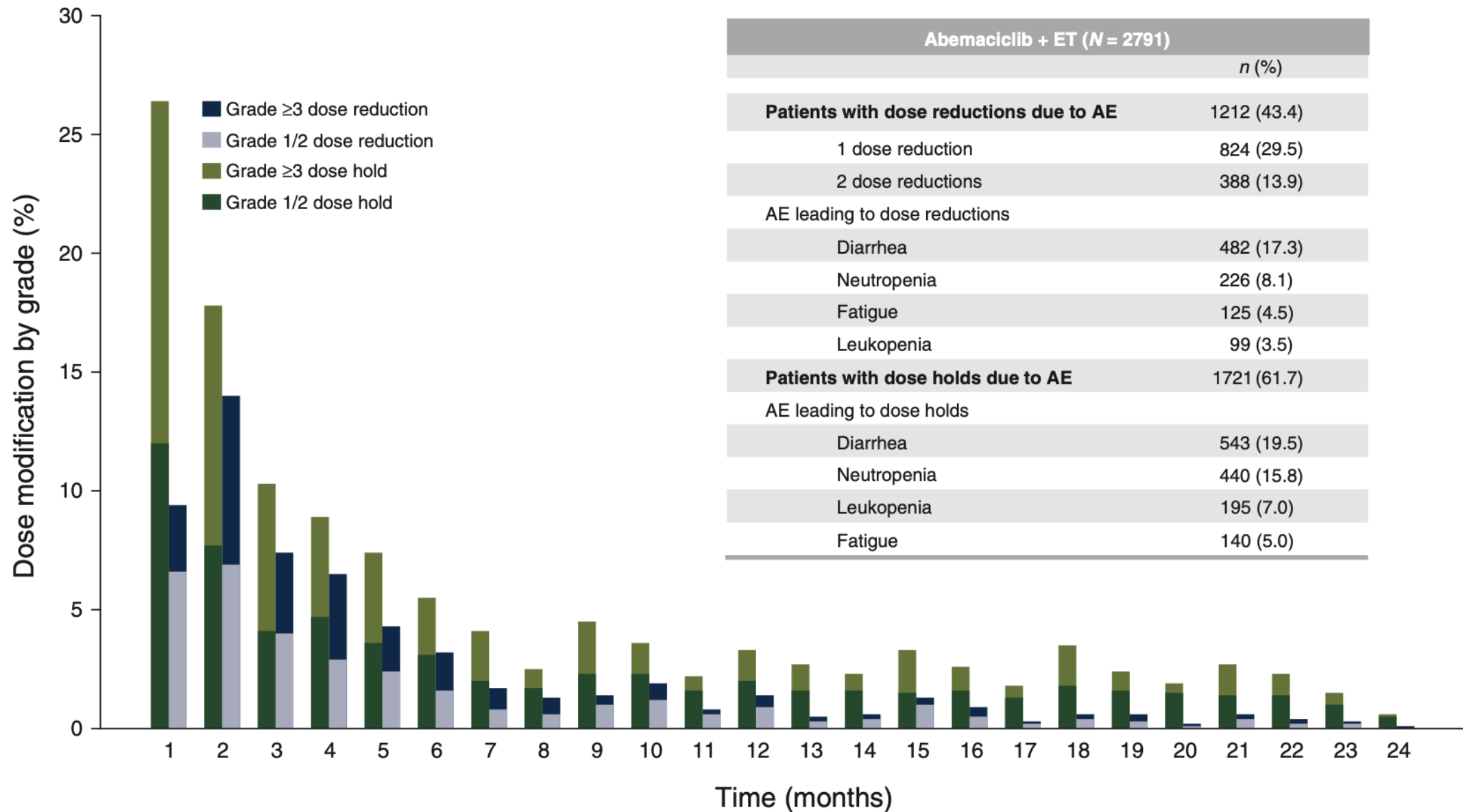
Consistent safety results from prior analyses, as all treated patients completed treatment ≥ 4 years ago
No relevant differences between treatment arms in causes of deaths due AEs

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

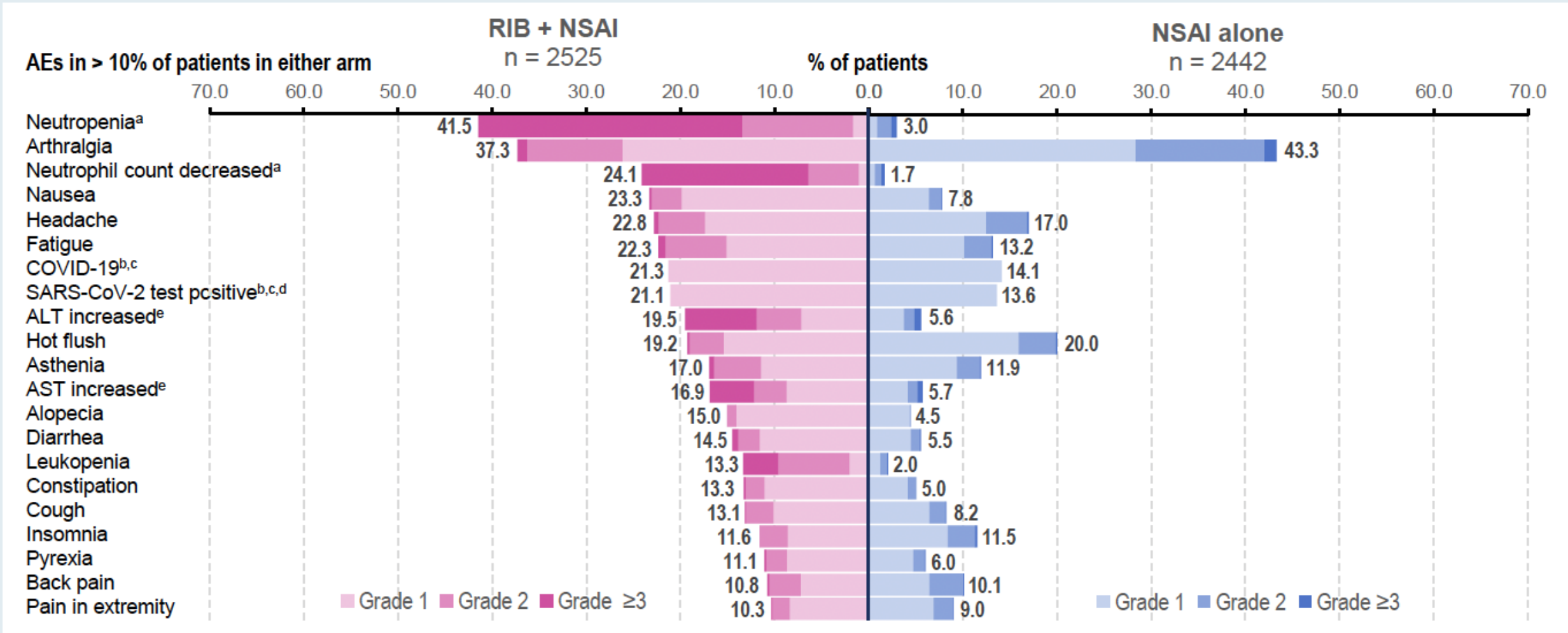
monarchE: AEs Leading to Discontinuation



monarchE: AEs Leading to Dose Modifications



NATALEE: Overall Safety Profile

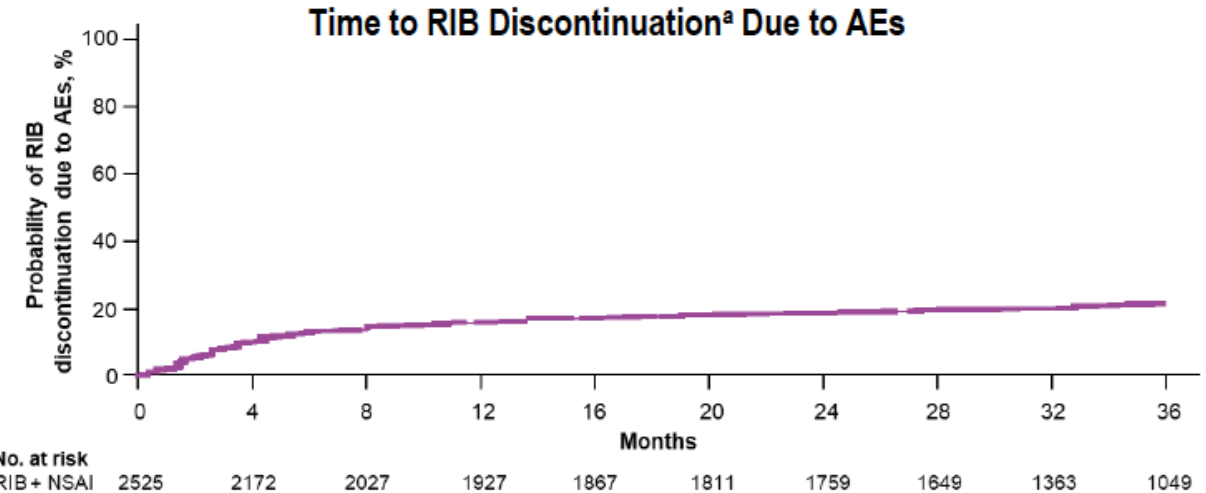
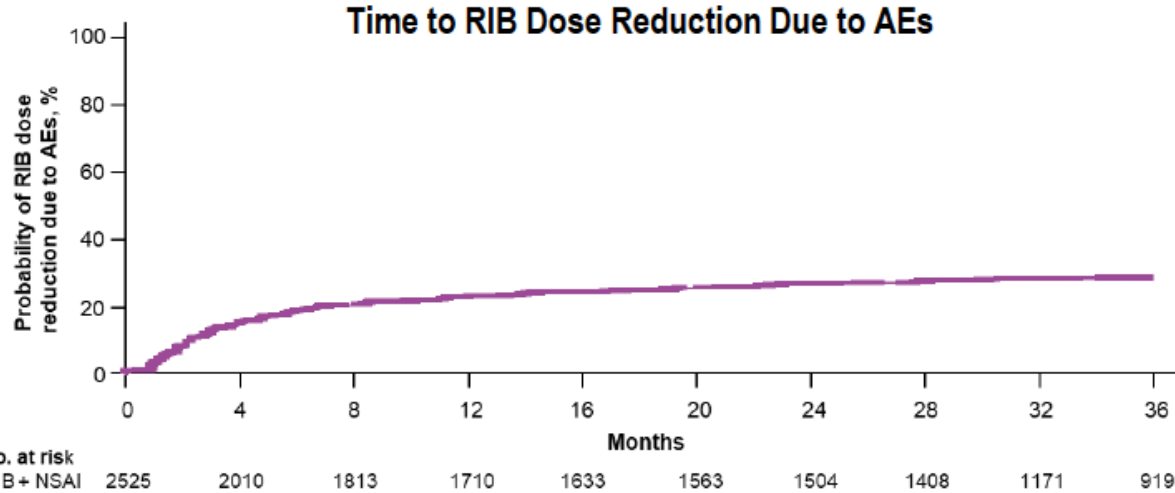


ALT = alanine aminotransferase; AST = aspartate aminotransferase

NATALEE: AEs of Special Interest (AESIs)

| AESIs (grouped terms) | Neutropenia ^a | | Liver-related AEs ^c | | QT interval prolongation ^d | |
|--|----------------------------|---------------|--------------------------------|----------------|---------------------------------------|---------------|
| | 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) ^b | 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



- 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%

- 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)

AEs and Dosing Must Be Considered: Distinct AE Profiles and Dosing Schedules of CDK4/6 Inhibitors in EBC

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

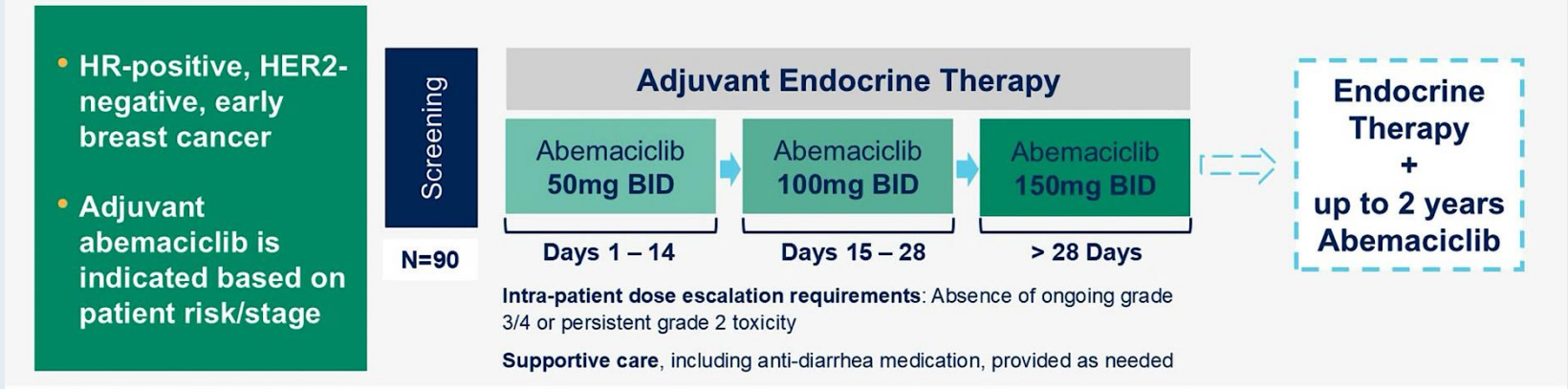
Dosing

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

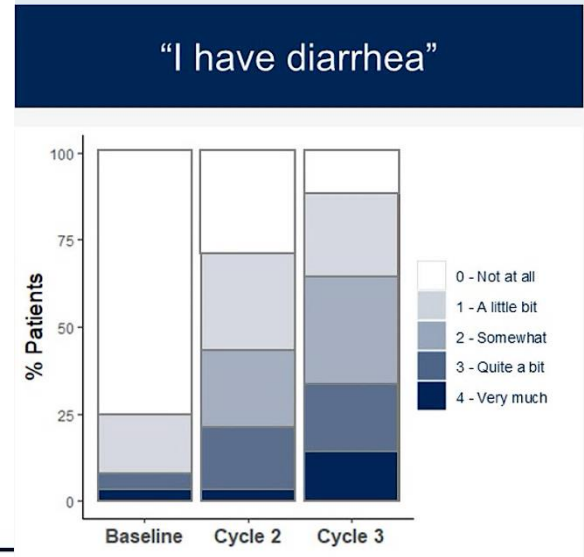
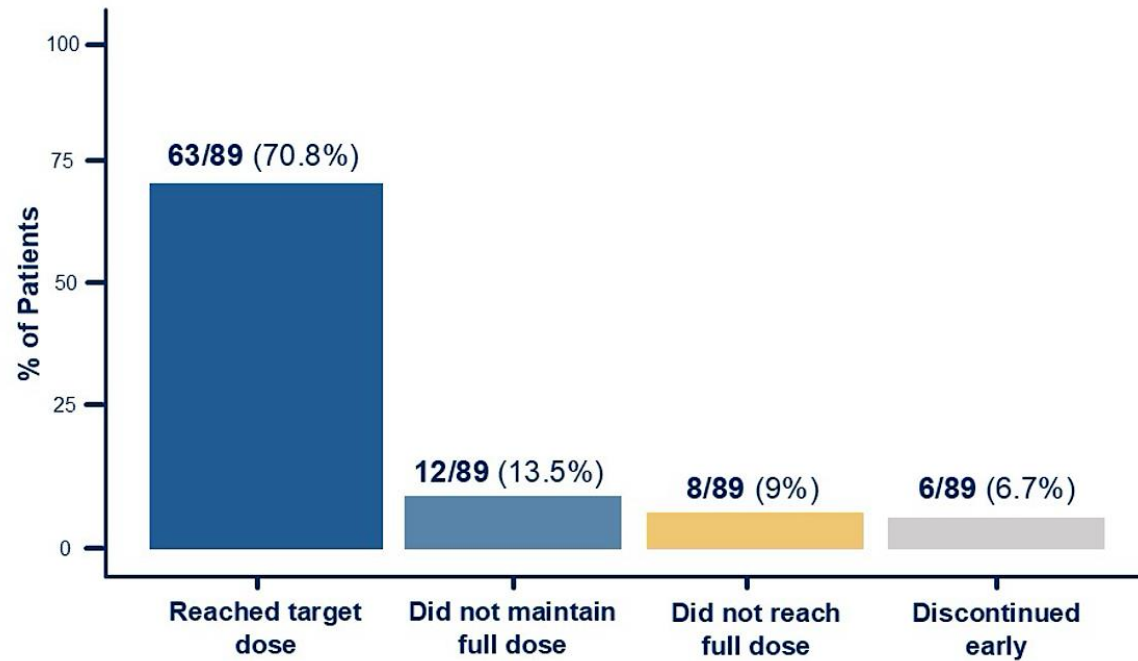
| Breast Cancer Status | CDK4/6i | Trial(s) | Discontinuation Rate Due to AE |
|----------------------|-------------|-------------------------|--------------------------------|
| HR+/HER2- EBC | Abemaciclib | monarchE ^{1,a} | 19% |
| | Ribociclib | NATALEE ^{2,3} | 19% |

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"> Discontinued for adverse events | 7% | 18.5% |
| Required abemaciclib dose reduction | 27% | 43.4% |



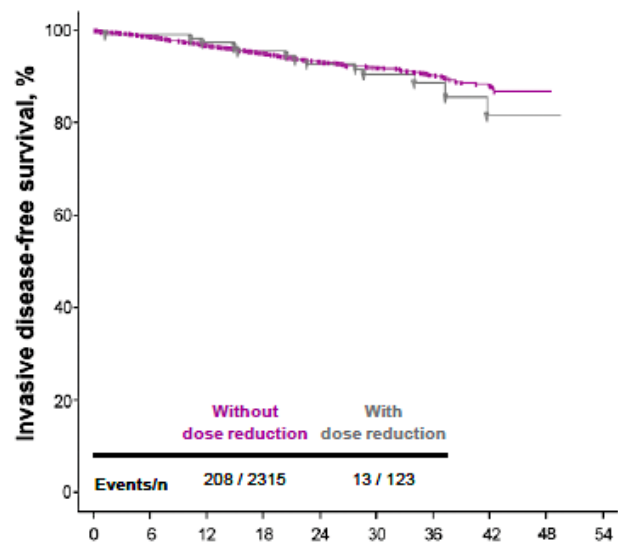
Primary endpoint: composite AE rate (discontinuation of adjuvant abemaciclib for any reason and/or need to dose reduce by 12 weeks of therapy)



NATALEE: IDFS by Dose Reductions

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

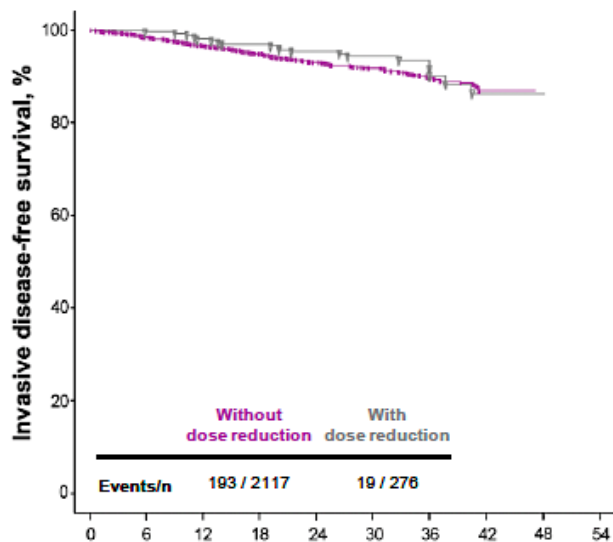
iDFS by Dose Reduction at 25th Percentile^a
(1.87 mo.)



Events/n 208 / 2315 13 / 123

| | Months | | | | | | | | | |
|------------------------|--------|------|------|------|------|------|------|-----|----|----|
| No. at risk | 0 | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 | 54 |
| Without dose reduction | 2315 | 2219 | 2142 | 2076 | 1979 | 1803 | 1039 | 328 | 8 | 0 |
| With dose reduction | 123 | 115 | 110 | 105 | 100 | 80 | 46 | 21 | 1 | 0 |

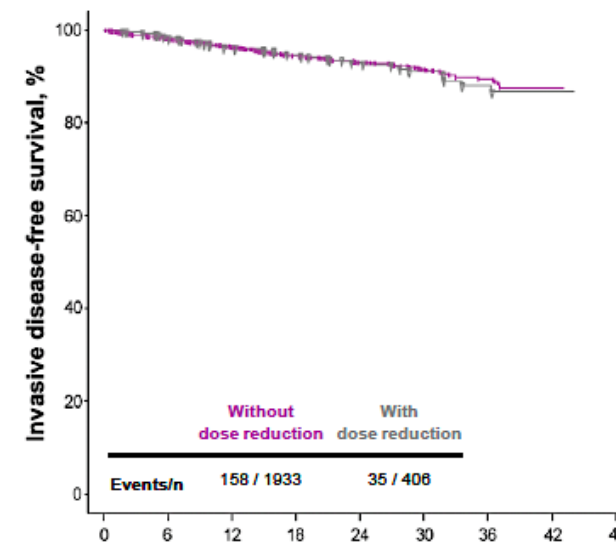
iDFS by Dose Reduction at 50th Percentile^a
(3.17 mo.)



Events/n 193 / 2117 19 / 276

| | Months | | | | | | | | | |
|------------------------|--------|------|------|------|------|------|-----|----|----|----|
| No. at risk | 0 | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 | 54 |
| Without dose reduction | 2117 | 2042 | 1981 | 1923 | 1835 | 1290 | 420 | 36 | 0 | 0 |
| With dose reduction | 276 | 266 | 256 | 245 | 232 | 157 | 55 | 5 | 1 | 0 |

iDFS by Dose Reduction at 75th Percentile^a
(7.28 mo.)



Events/n 158 / 1933 35 / 406

| | Months | | | | | | | | | |
|------------------------|--------|------|------|------|------|-----|-----|----|----|--|
| No. at risk | 0 | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 | |
| Without dose reduction | 1933 | 1870 | 1820 | 1725 | 1394 | 914 | 288 | 14 | 0 | |
| With dose reduction | 406 | 393 | 376 | 361 | 291 | 176 | 69 | 5 | 0 | |

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

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 Jhaveri

I have



Dr Kalinsky

I have



Dr Mahtani

I have



Dr Mayer

I have



Dr Rugo

I have



Dr Sharma









I have











Dr Shatsky

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 Jhaveri | | Ribociclib | Abemaciclib | Ribociclib |
|  Dr Kalinsky | | Ribociclib | Abemaciclib | No preference |
|  Dr Mahtani | | Ribociclib | Abemaciclib | No preference |
|  Dr Mayer | | Ribociclib | Abemaciclib | No preference |
|  Dr Rugo | | Ribociclib | Abemaciclib | No preference |
|  Dr Sharma | | Ribociclib | Abemaciclib | Ribociclib |
|  Dr Shatsky | | Ribociclib | Abemaciclib | No preference |

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 Jhaveri | | No preference | Abemaciclib |
|  Dr Kalinsky | | No preference | Abemaciclib |
|  Dr Mahtani | | No preference | Abemaciclib |
|  Dr Mayer | | No preference | Abemaciclib |
|  Dr Rugo | | No preference | Abemaciclib |
|  Dr Sharma | | No preference | No preference |
|  Dr Shatsky | | No preference | Abemaciclib |

COPD = chronic obstructive pulmonary disease

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

- 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

HENRY B. GONZALEZ CONVENTION CENTER • SAN ANTONIO, TX

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

Presenting author: Aditya L. Bardia, MD

University of California, Los Angeles, Los Angeles, CA, USA

Abstract GS1-10

IdERA Breast Cancer Study Design

Key eligibility criteria

- Participants with ER+, HER2-negative early breast cancer
- Stage I–III disease (anatomical)
 - pN0 and pT > 1 cm with Grade 3, or Ki67 ≥ 20%, or high score on genomic assay,* or pT4N0
 - Node-positive
- Pre- or post-menopausal†
- Breast cancer surgery within 12 months
- (Neo)adjuvant chemotherapy if indicated

Stratification factors

- Risk: Medium-‡ vs high-risk§ Stage I–III breast cancer
- Region: USA/Canada/Western Europe vs Asia–Pacific vs RoW
- Previous chemotherapy: No vs yes
- Menopausal status: Pre-menopausal vs post-menopausal

N = 4170

R
1:1

At least 5-year treatment duration

Giredestrant (30 mg PO QD)

SOC ET

Tamoxifen/anastrozole/letrozole/exemestane

5-year follow-up

Long-term
follow-up

Primary endpoint

- IDFS (excluding second primary non-breast cancer)

Key secondary endpoints

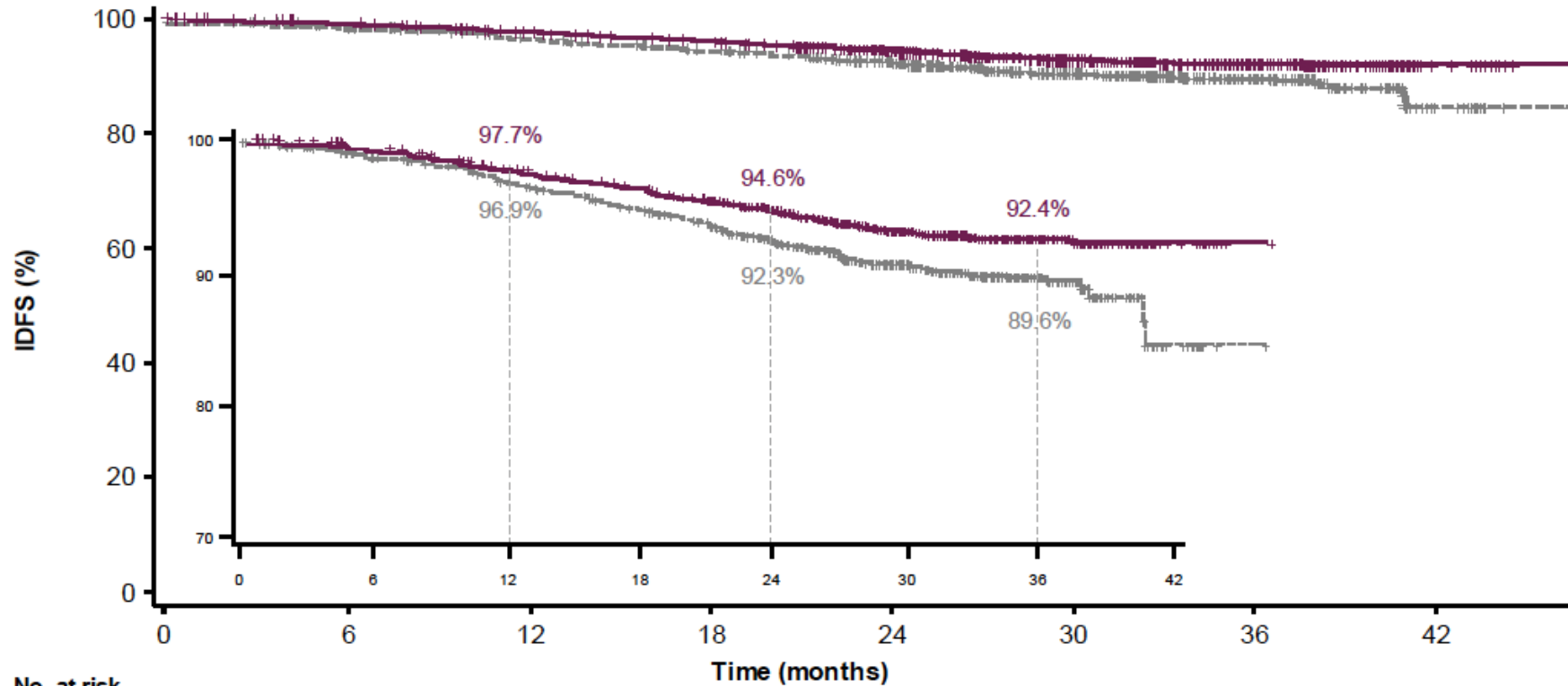
- DFS, DRFI, IDFS (including second primary non-breast invasive cancer with exception of non-melanoma skin cancers and *in situ* carcinomas of any site), LRRFI, OS, safety

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

IdERA Breast Cancer: Patient Demographics

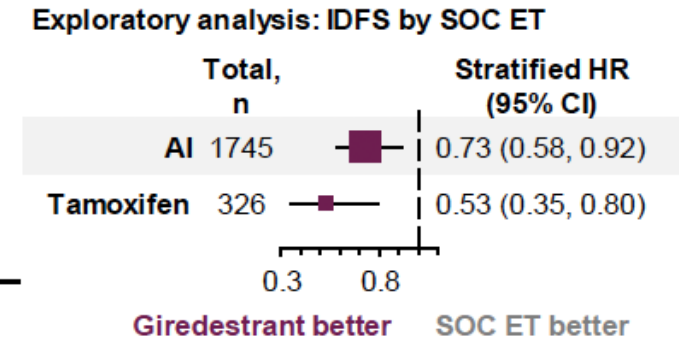
| | Giredestrant n = 2084 | SOC ET n = 2086 | | Giredestrant n = 2084 | SOC ET n = 2086 |
|---|--------------------------|--------------------|--|--------------------------|--------------------|
| Median age, years (range) | 54.0 (22–91) | 54.0 (25–89) | ER status, n (%)[‡] | | |
| Female sex, n (%) | 2073 (99.5) | 2075 (99.5) | Low-positive (1–10% of cells positive) | 45 (2.2) | 52 (2.5) |
| Race, n (%) | | | Positive (> 10% of cells positive) | 2030 (97.8) | 2031 (97.5) |
| American Indian or Alaska Native | 77 (3.7) | 62 (3.0) | AJCC stage at surgery, n (%)[§] | | |
| 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) | Nodal status, n (%) on surgical specimen | | |
| Region, n (%) | | | 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) | Risk, n (%) | | |
| Menopausal status, n (%)[†] | | | 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) | Previous chemotherapy, n (%) | | |
| | | | No | 396 (19.0) | 450 (21.6) |
| | | | Yes | 1688 (81.0) | 1636 (78.4) |

IdERA Breast Cancer: IDFS Outcomes



| No. at risk | 0 | 6 | 12 | 18 | 24 | 30 | 36 | 42 |
|--------------|------|------|------|------|------|------|-----|----|
| Giredestrant | 2084 | 2021 | 1969 | 1932 | 1716 | 1088 | 345 | 26 |
| SOC ET | 2086 | 2016 | 1958 | 1898 | 1683 | 1048 | 325 | 25 |

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

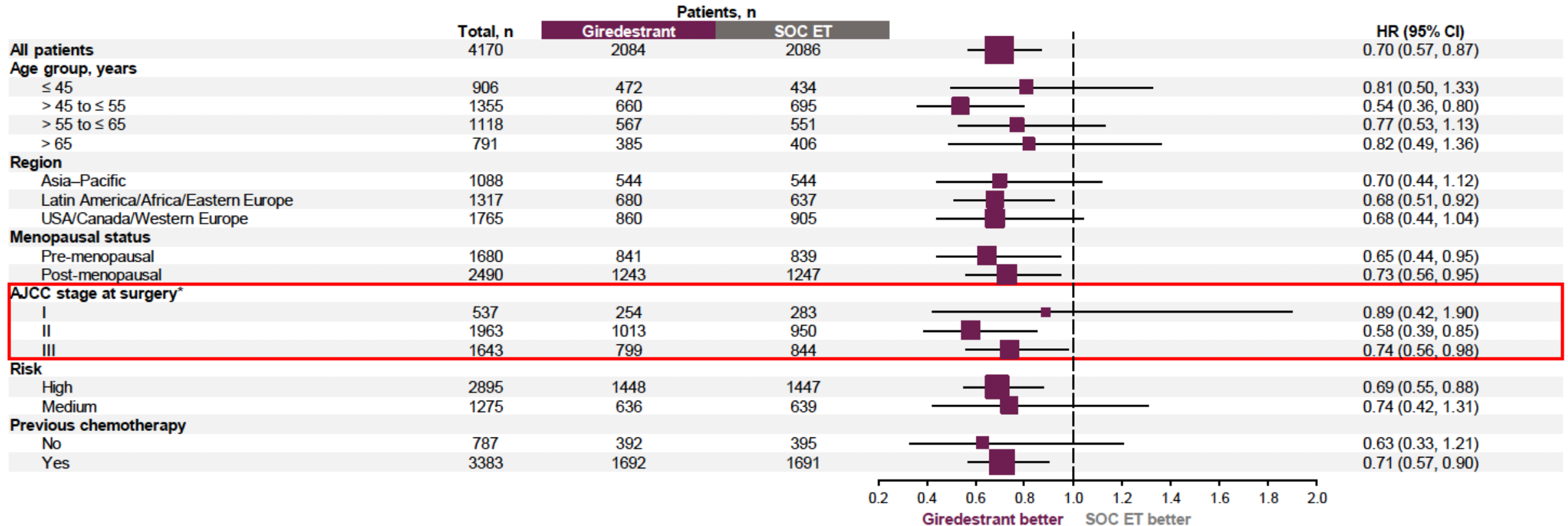


Median follow-up: 32.3 months

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

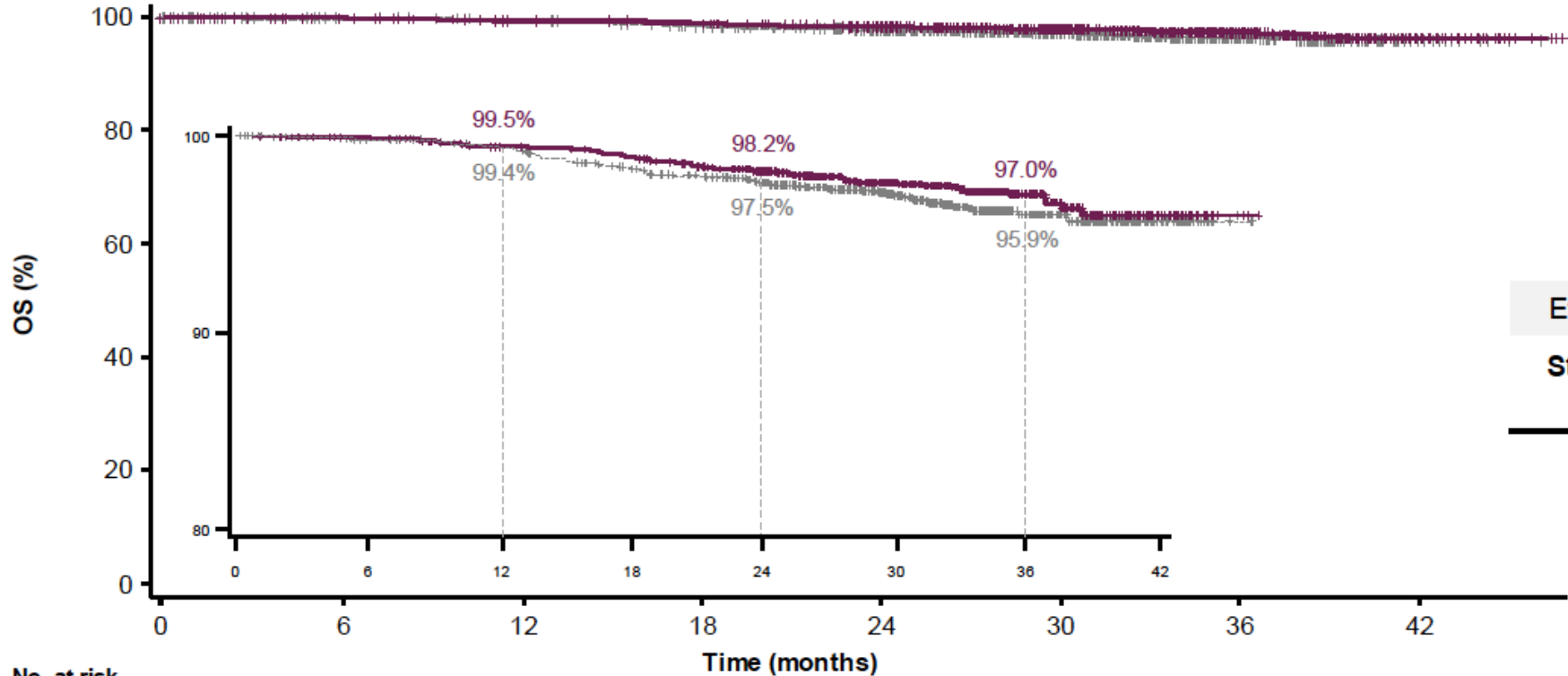


IdERA Breast Cancer: IDFS in Key Subgroups



IDFS benefit was consistent across key prespecified subgroups

lidERA Breast Cancer: OS Outcomes



| No. at risk | | 0 | 6 | 12 | 18 | 24 | 30 | 36 | 42 |
|--------------|------|------|------|------|------|------|-----|----|----|
| Giredestrant | 2084 | 2043 | 2013 | 1997 | 1887 | 1300 | 530 | 52 | |
| SOC ET | 2086 | 2040 | 2018 | 1971 | 1852 | 1270 | 504 | 49 | |

Giredestrant
n = 2084

SOC ET
n = 2086

Events, n (%) 57 (2.7) 71 (3.4)

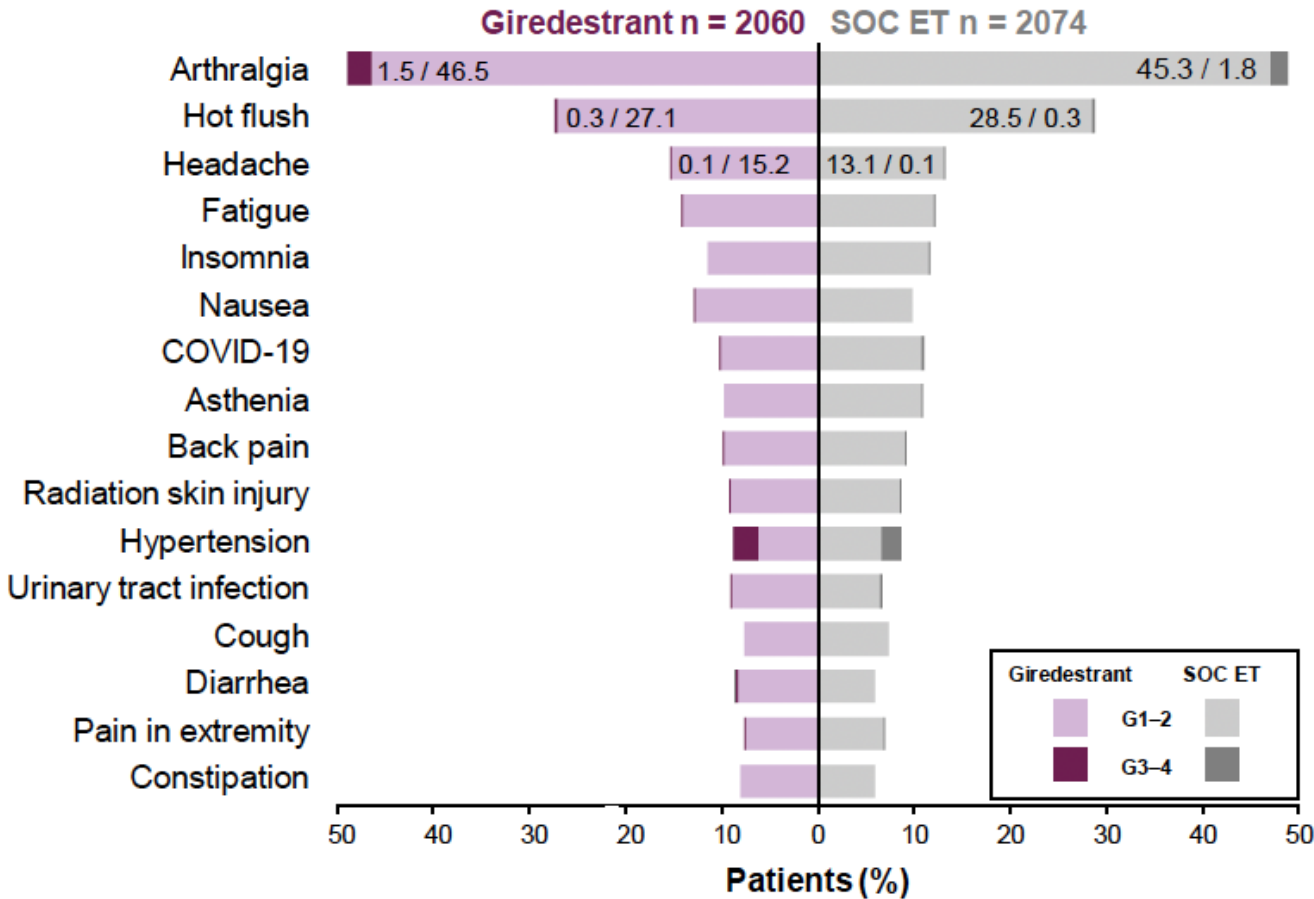
Stratified HR
(95% CI) **0.79**
(0.56, 1.12); p = 0.1863*

Median follow-up: 32.3 months

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 ($\geq 7.5\%$ of patients in either arm at any grade)



Selected AEs

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

Yes, for higher-risk Stage I, for Stage IIA not receiving or cannot tolerate CDK4/6i, and consider for Stage IIB/III after completion of CDK4/6i



Dr Rugo

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



Dr Sharma

Yes, for patients that match eligibility of the lidERA trial



Dr Shatsky

Yes, for all patients, if possible; in the post CDK4/6i space if not available to all patients

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 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



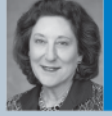
Dr Mahtani

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 Mayer

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 Rugo

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 Sharma

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 Shatsky

CDK4/6 inhibitor combined with giredestrant

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

Questions?