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

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Disclosures

Advisory Committees	Exact Sciences Corporation, Genentech, a member of the Roche Group, Novartis, Olema Oncology
Consulting Agreements	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Stemline Therapeutics Inc
Contracted Research	MBrace Therapeutics, Puma Biotechnology Inc

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Section Head, Endocrine Therapy Research Program
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Miami, Florida

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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.

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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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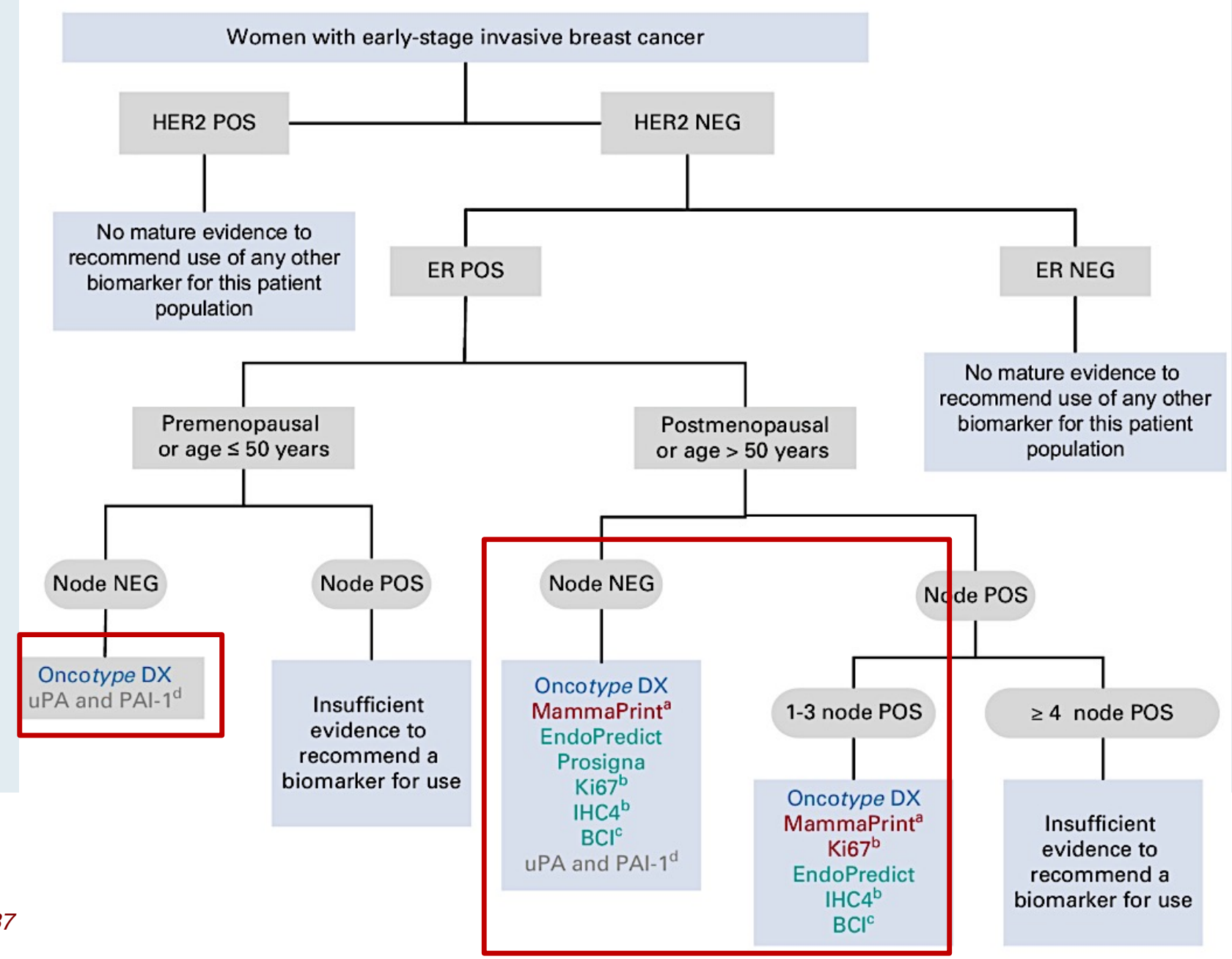
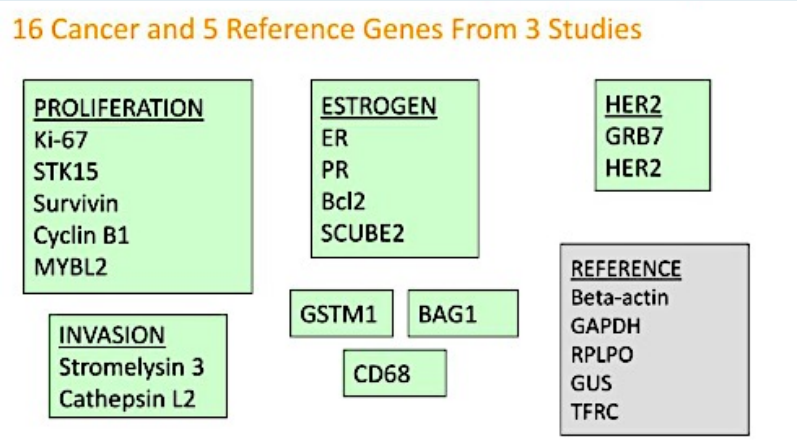
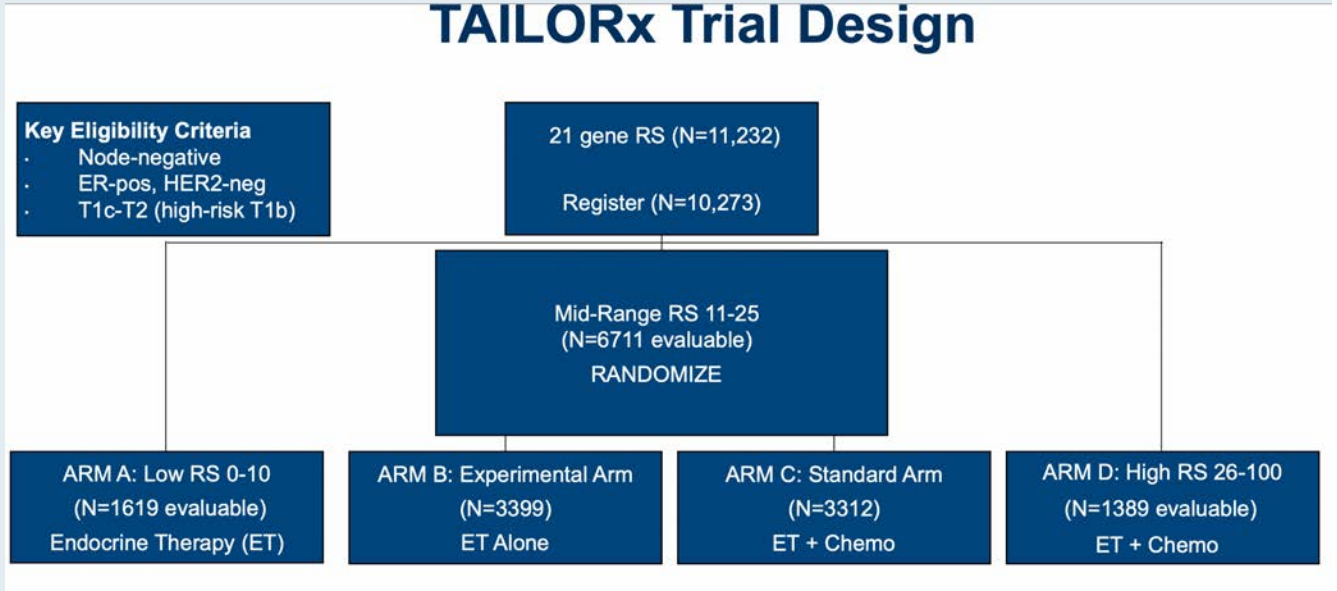


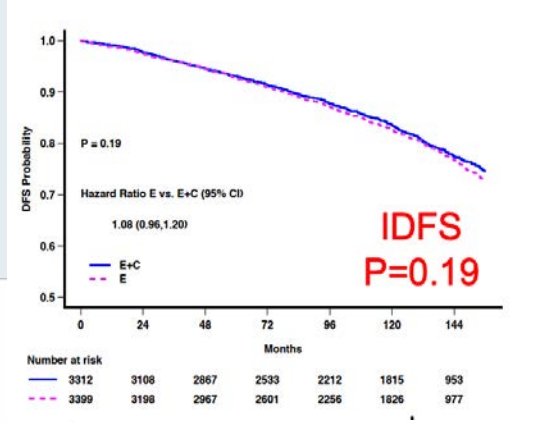
Andre F et al. J Clin Oncol. 2022;40:1816-1837

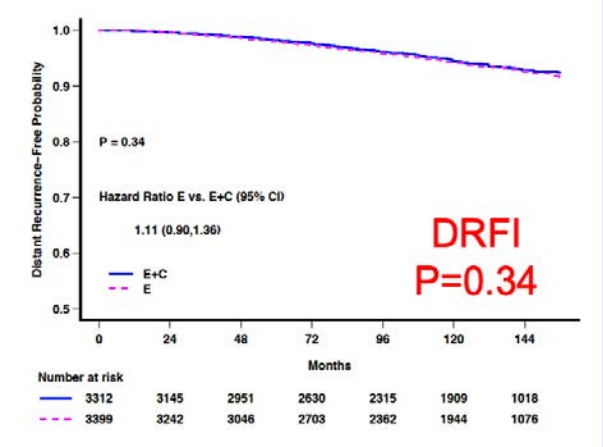
Onco*type*DX®: TAILORx Trial Key Results for Node-Negative Disease

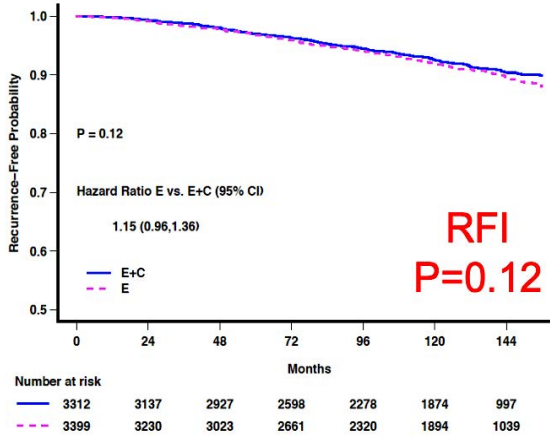


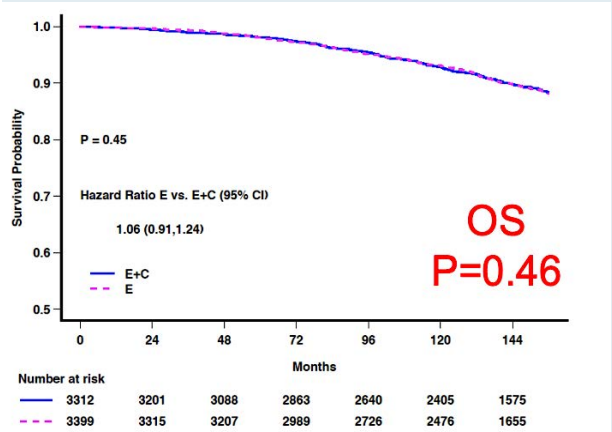
Intermediate risk (11-25):
No overall benefit to chemotherapy (2022 update)







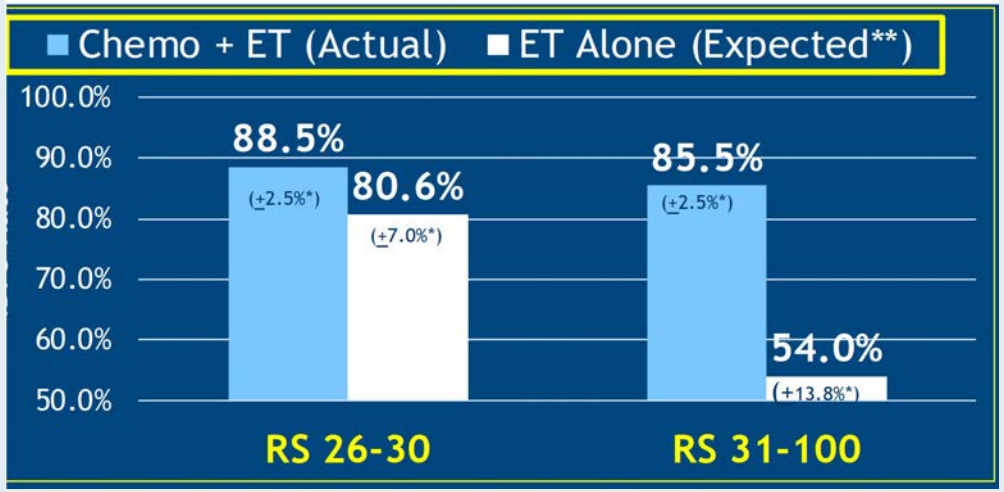


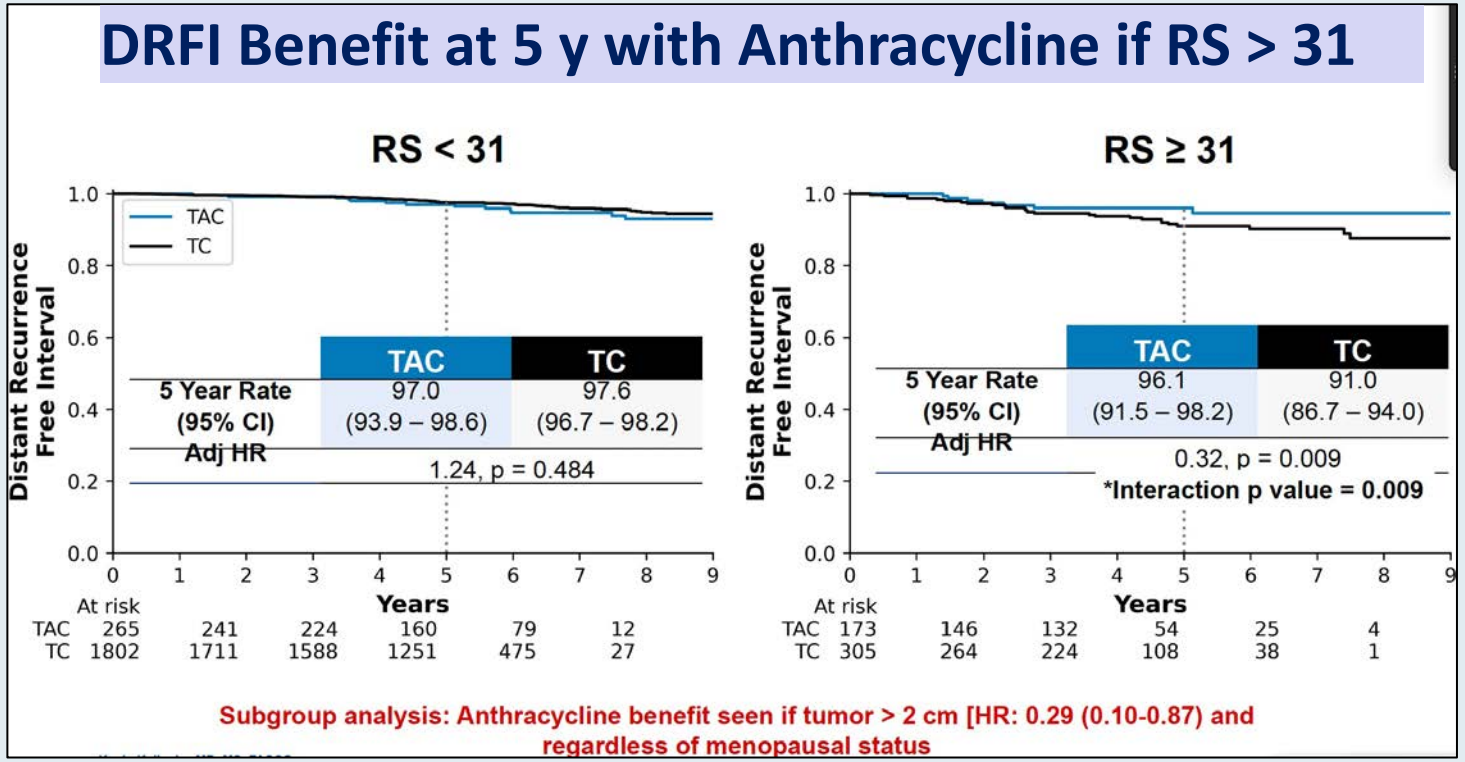


Sparano JA et al. SABCS 2022;Abstract GS1-05.

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

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





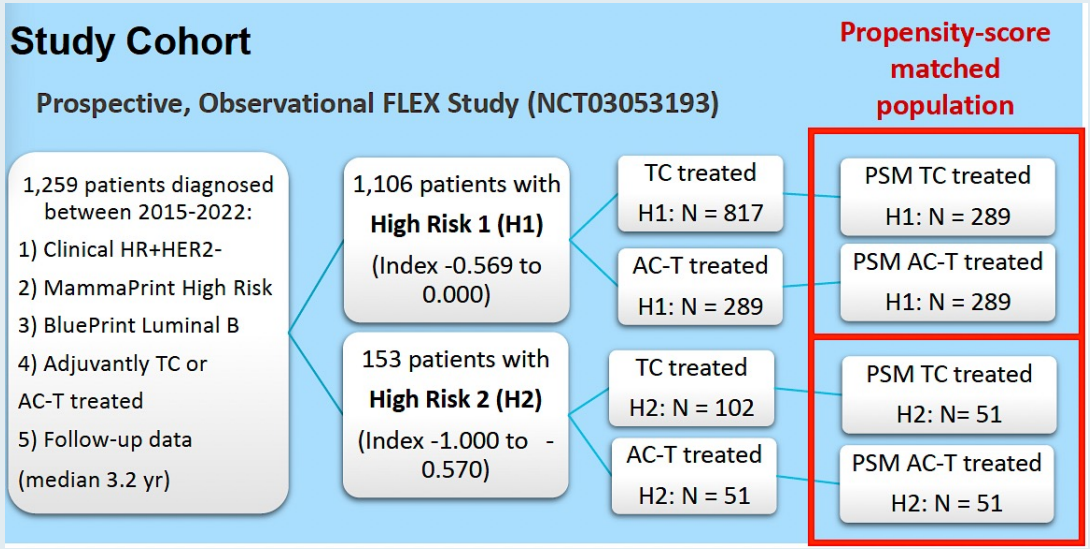
"No chemotherapy" rates estimated by combining

- 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

Sparano JA et al. *JAMA Oncol* 2020; Chen N et al. *Ann Oncol* 2025.

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

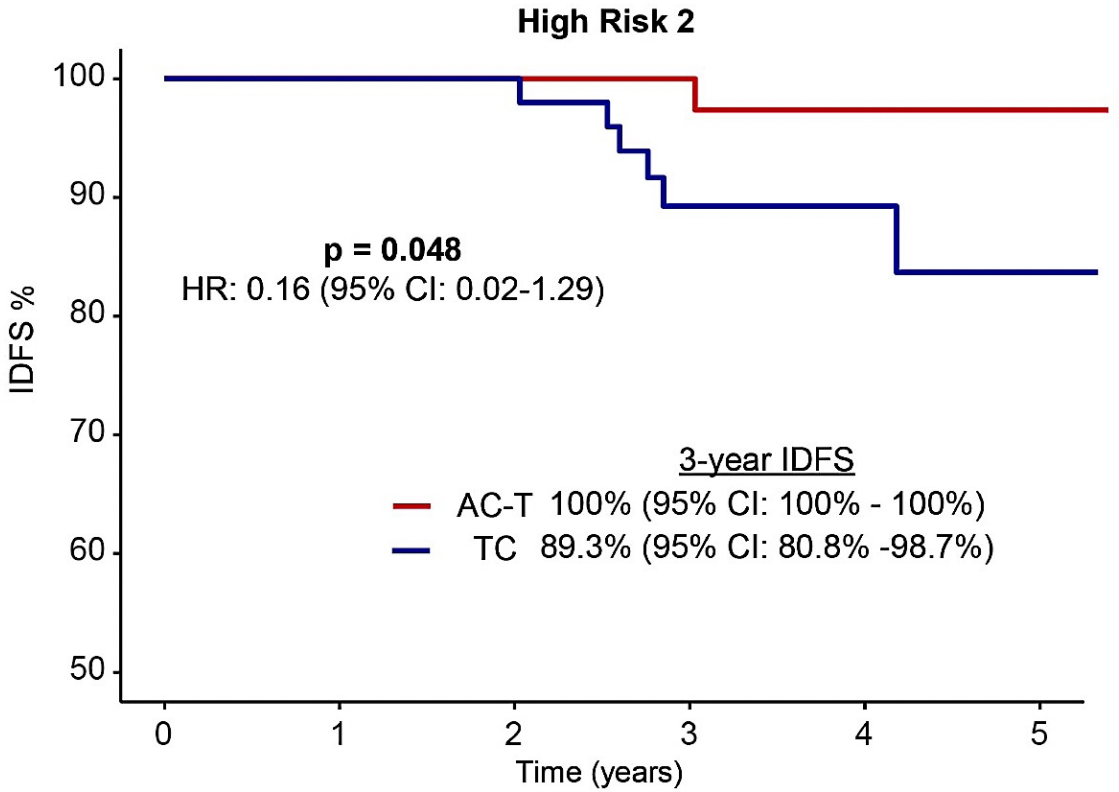


Conclusions

- 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



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

O'Shaughnessy J et al. SABCS 2025;Abstract PS2-07-03.

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Onco*type*DX: RxPONDER Trial Results Summary One to Three Positive Lymph Nodes

RxPONDER Trial Design

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

REGISTRATION

Recurrence Score 0-25 → RANDOMIZATION → Arm 1: Chemotherapy Followed by Endocrine Therapy

Recurrence Score > 25 → Off Study Chemotherapy Followed by Endocrine Therapy Recommended

RANDOMIZATION → Arm 2: Endocrine Therapy Alone

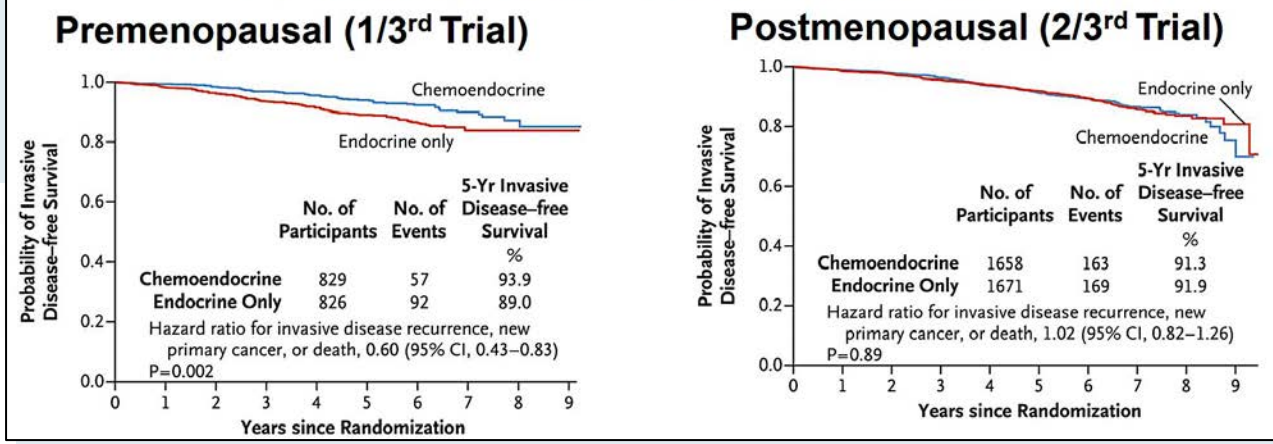
N = 5,000 pts

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



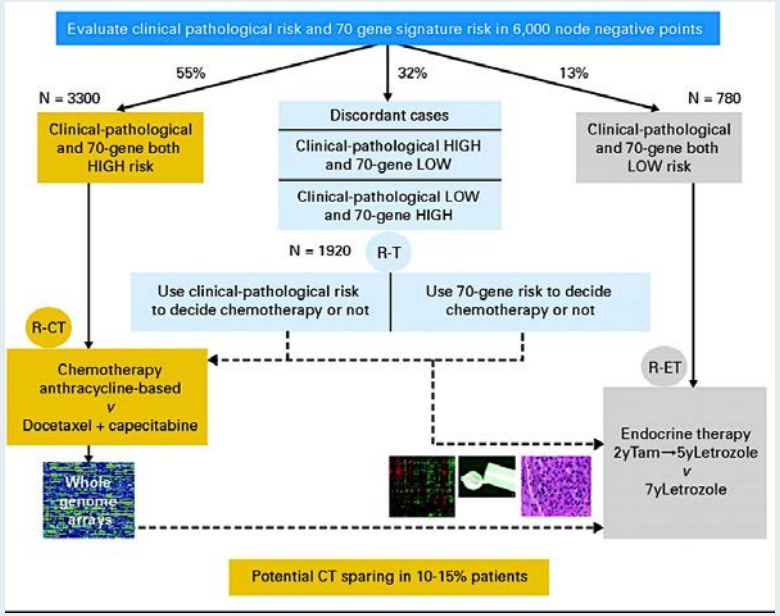
IDFS Benefit Modified by Score for Women Age ≤50

Women ≤50 yr			
≤10, endocrine only	145	91.0±2.6	0.31 (0.10–0.94)
≤10, chemoendocrine	135	97.9±1.5	
11–15, endocrine only	247	93.1±1.8	0.71 (0.33–1.51)
11–15, chemoendocrine	235	95.4±1.6	
16–20, endocrine only	227	85.1±2.6	0.58 (0.33–1.00)
16–20, chemoendocrine	224	92.2±2.0	
21–25, endocrine only	107	80.0±4.3	0.56 (0.27–1.17)
21–25, chemoendocrine	98	90.0±3.6	

Sparano JA et al. *JAMA Oncol* 2020; Chen N et al. *Ann Oncol* 2025.

MammaPrint: MindACT Trial Key Results

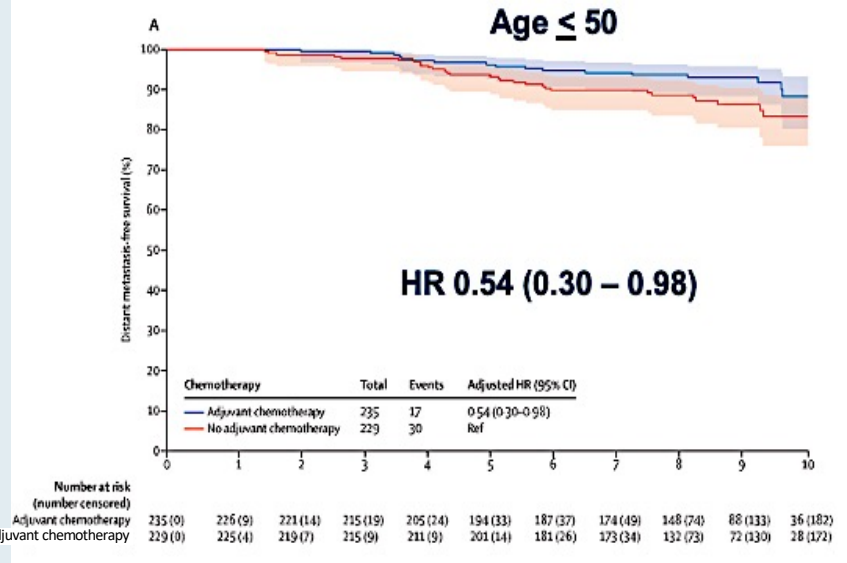
Clinical "high risk": <88% 10-yr BCSS
Modified Adjuvant! Online to determine
Model included: T size, Node (0-3), grade, ER status, age, comorbidity

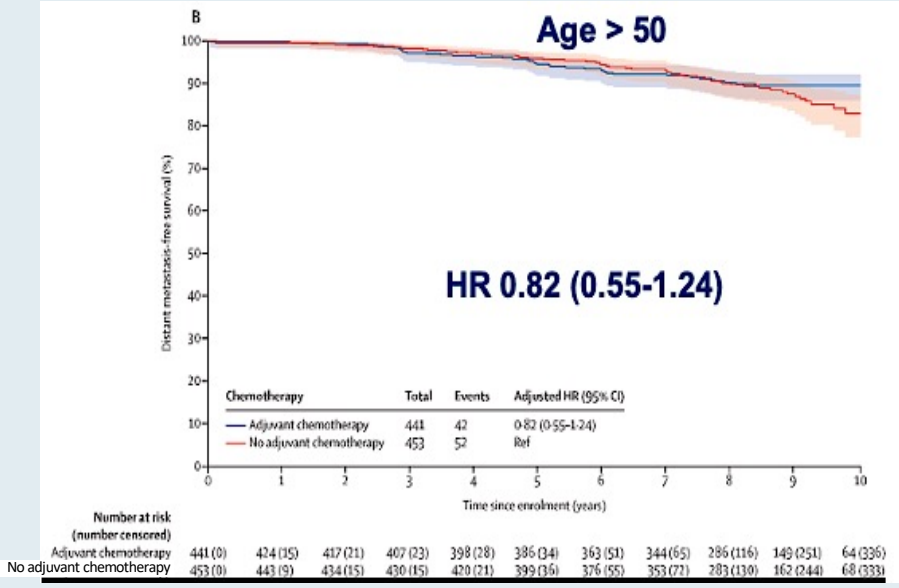


Met primary outcome: Lower bound of 95% CI >92% 5-y DMFS in the High Clinical/Low Genomic risk group

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%





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

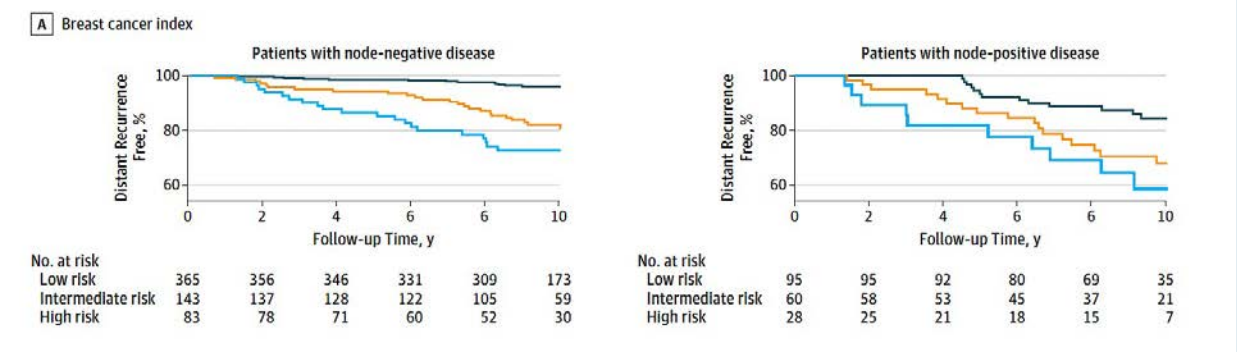
Breast Cancer Index (BCI)
- 7 genes – Proliferation and hormone receptor (HoxB13/IL17BR)

JAMA Oncology | Original Investigation

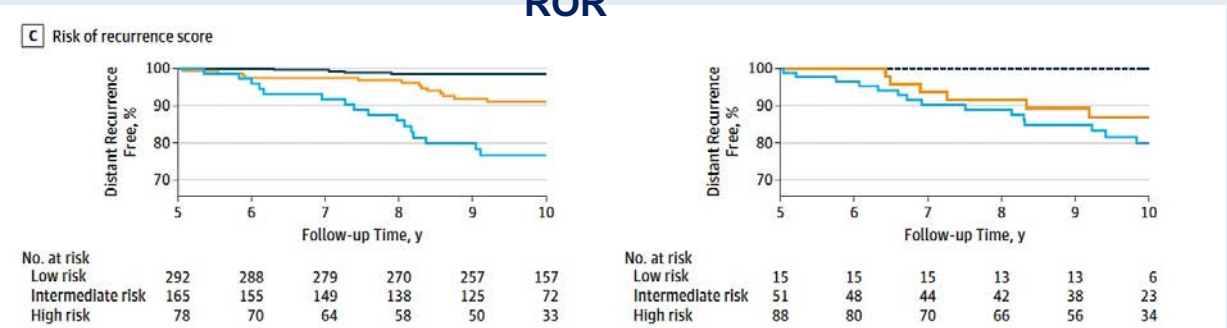
Comparison of the Performance of 6 Prognostic Signatures for Estrogen Receptor–Positive Breast Cancer
A Secondary Analysis of a Randomized Clinical Trial

- Largest retrospective prognostic validation in TransATAC Trial (included Onco*type* 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)

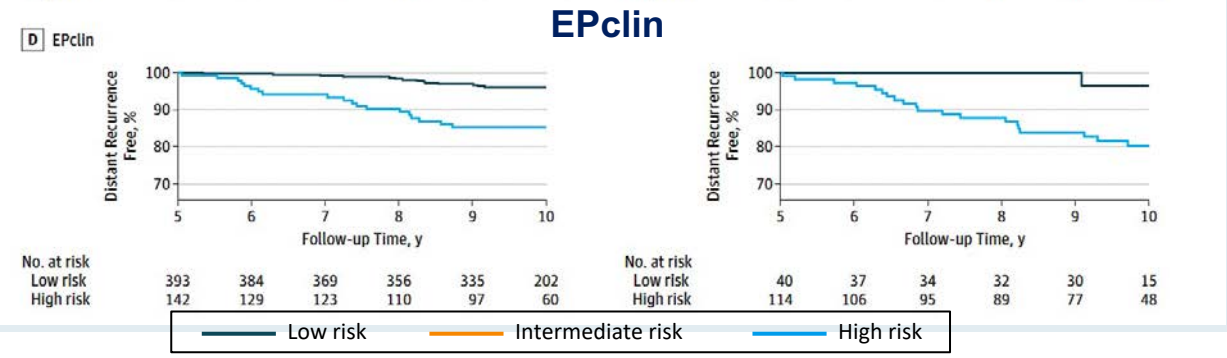
BCI



ROR



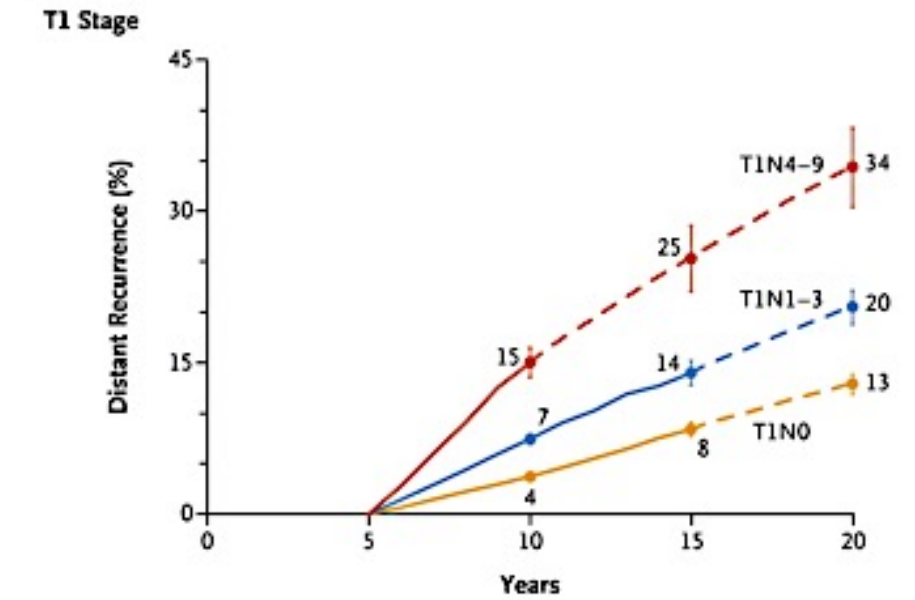
EPclin



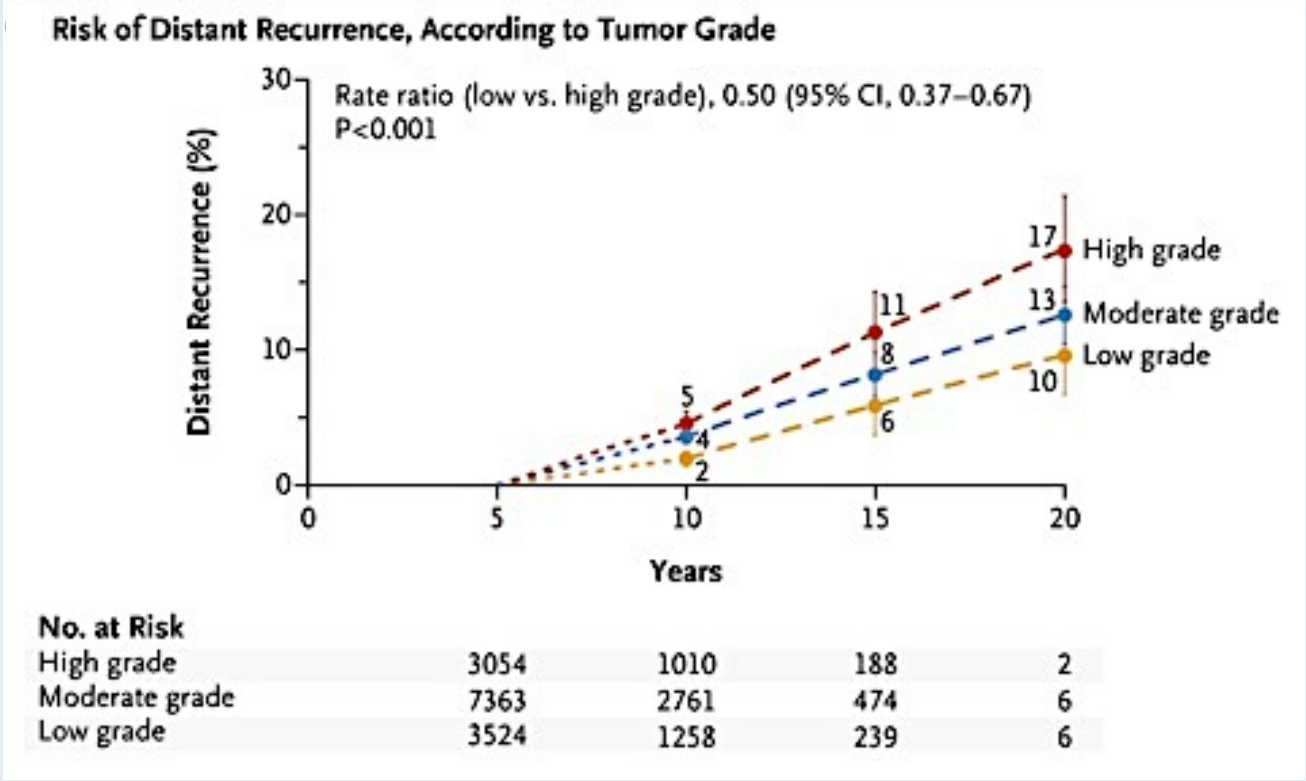
Sestak I et al. *JAMA Oncol* 2018;4(4):545-53.

Persistent Long-Term Risk of Distant Recurrence

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



No. at Risk				
T1N4–9	3,832	1193	214	32
T1N1–3	14,342	5138	817	154
T1N0	19,402	8020	2345	440

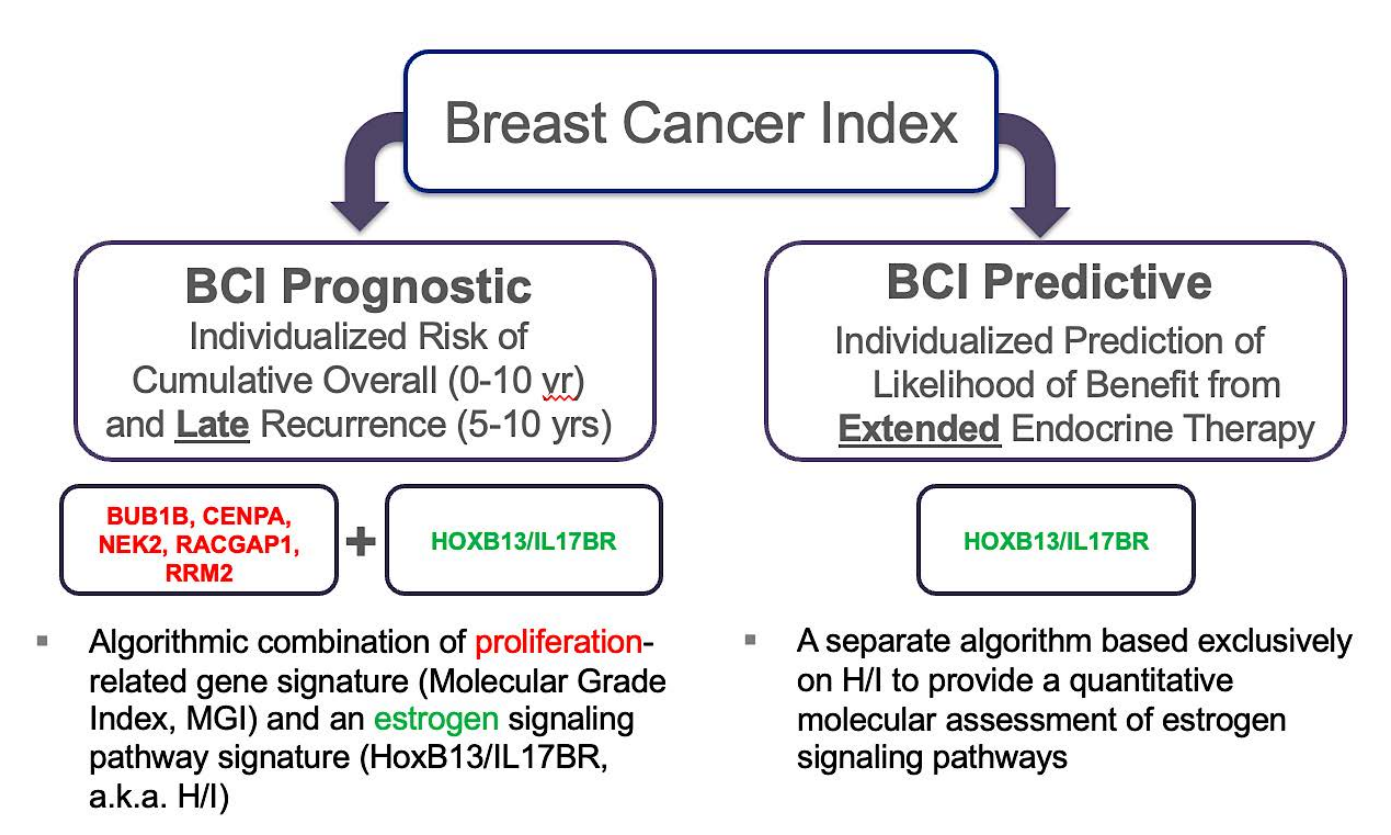


No. at Risk				
High grade	3054	1010	188	2
Moderate grade	7363	2761	474	6
Low grade	3524	1258	239	6

Pan H et al. *N Engl J Med* 2017;377(19):1836-46.

Breast Cancer Index (BCI)

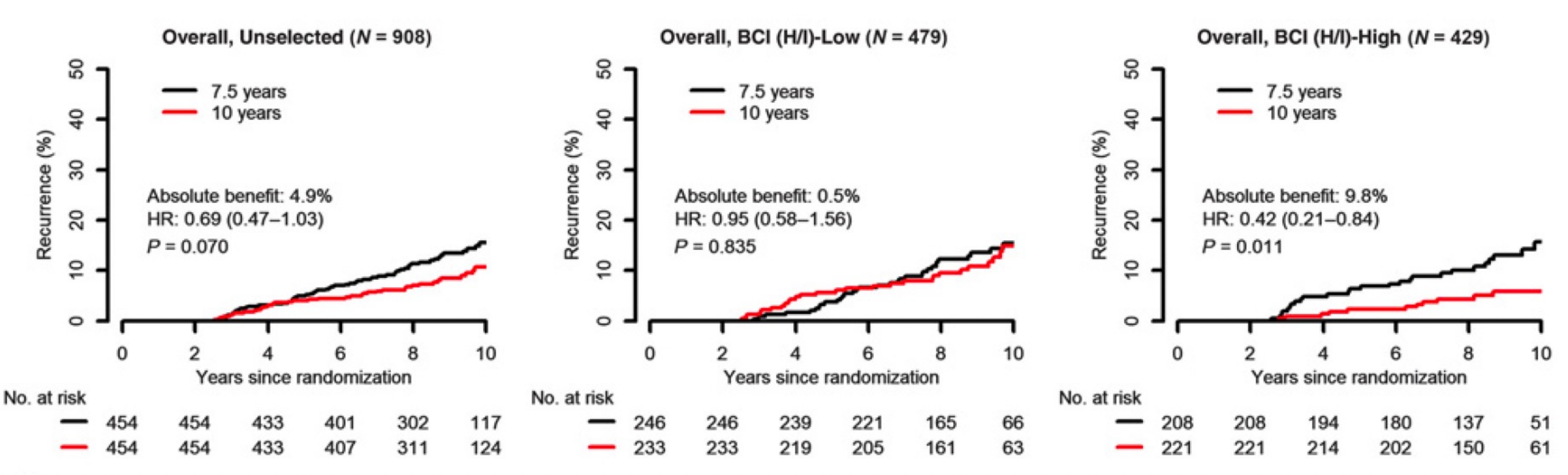
BCI Components



Distribution of BCI scores

Sgroi DC et al. *J Natl Cancer Inst* 2013;105(14):1036-42.

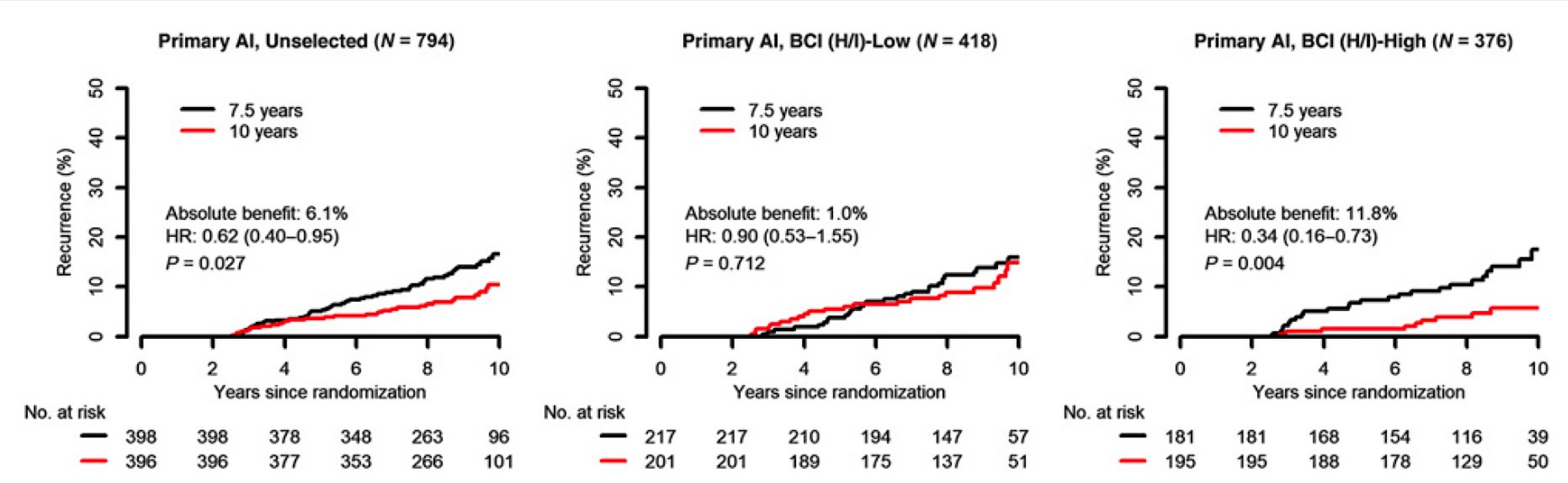
Predictive Performance by BCI H/I Groups Based on Recurrence-Free Interval in the Overall Cohort of the Phase III IDEAL Trial



Noordhoek I et al. *Clin Cancer Res* 2021;27(1):311-19.

RTP RESEARCH TO PRACTICE

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)



Noordhoek I et al. *Clin Cancer Res* 2021;27(1):311-19.

RTP RESEARCH TO PRACTICE

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

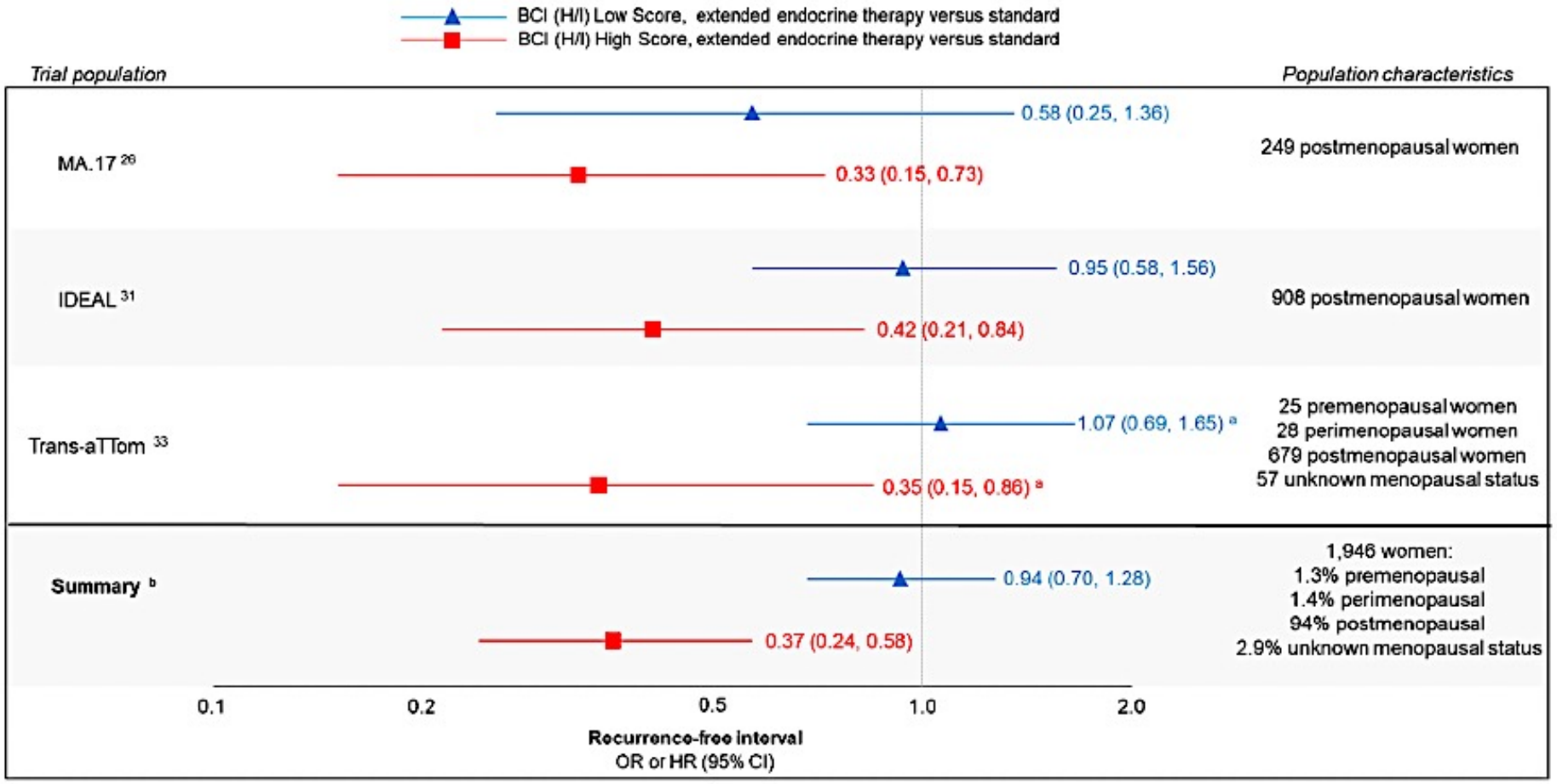
Groups	5-year letrozole		2.5-year letrozole		
	Number of Patients	10-year risk (95% CI)	Number of Patients	10-year risk (95% CI)	HR (95% CI)*
Overall (N=908)					
Unselected	454 (100%)	10.6% (7.1-14.0)	454 (100%)	15.5% (11.5-19.3)	0.69 (0.47-1.03)
BCI (H/I)-High	221 (49%)	5.9% (2.3-9.3)	208 (46%)	15.7% (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.

Noordhoek I et al. *Clin Cancer Res* 2021;27(1):311-19.

RTP RESEARCH TO PRACTICE

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.

Woolpert KM et al. Breast Cancer Res Treat 2024;203(3):407-417.

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 Onco*type* 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).

Andre F et al. J Clin Oncol. 2022;40:1816-1837

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	Onco*type* DX (*high/strong*)	Onco*type* DX (*high/strong*) MammaPrint[a] (*intermediate/strong*) EndoPredict (*intermediate/moderate*) Prosigna (*intermediate/moderate*) Ki67[b] (*intermediate/moderate*) IHC4[b] (*intermediate/moderate*) BCI[c] (*intermediate/moderate*)
1-3 positive nodes	Insufficient evidence to recommend a biomarker for use	Onco*type* DX (*high/strong*) MammaPrint[a] (*intermediate/strong*) EndoPredict (*intermediate/moderate*) Ki67[b] (*intermediate/strong*) IHC4[b] (*intermediate/moderate*) BCI[c] (*intermediate/moderate*)
≥ 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	

Andre F et al. J Clin Oncol. 2022;40:1816-1837

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

RTP RESEARCH TO PRACTICE

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	Onco*type* DX®, MammaPrint®, EndoPredict®, Breast Cancer Index®
Dr Chen	Onco*type* DX, Breast Cancer Index
Dr Jhaveri	Onco*type* DX
Dr Kalinsky	Onco*type* DX
Dr Mahtani	Onco*type* DX, MammaPrint, Breast Cancer Index
Dr Mouabbi	Onco*type* DX, MammaPrint, Breast Cancer Index
Dr Rugo	Onco*type* DX and MammaPrint
Dr Sharma	Onco*type* DX and MammaPrint

RTP RESEARCH TO PRACTICE

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

RTP RESEARCH TO PRACTICE

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 Onco*type* DX
Dr Jhaveri	Onco*type* DX
Dr Kalinsky	MammaPrint
Dr Mahtani	MammaPrint
Dr Mouabbi	MammaPrint
Dr Rugo	MammaPrint and Onco*type* DX*
Dr Sharma	Onco*type* DX 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 Onco*type* DX

RTP RESEARCH TO PRACTICE

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 Chen	Yes, for Stage II or low-risk Stage III disease in patients who are tolerating ET well and willing to do more
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 Mouabbi	Yes, for patients for whom we are considering extended ET
Dr Rugo	No*
Dr Sharma	Yes, for patients with high-risk, node-negative disease

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

RTP RESEARCH TO PRACTICE

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

RTP
RESEARCH
TO PRACTICE

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

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

RTP RESEARCH TO PRACTICE

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.

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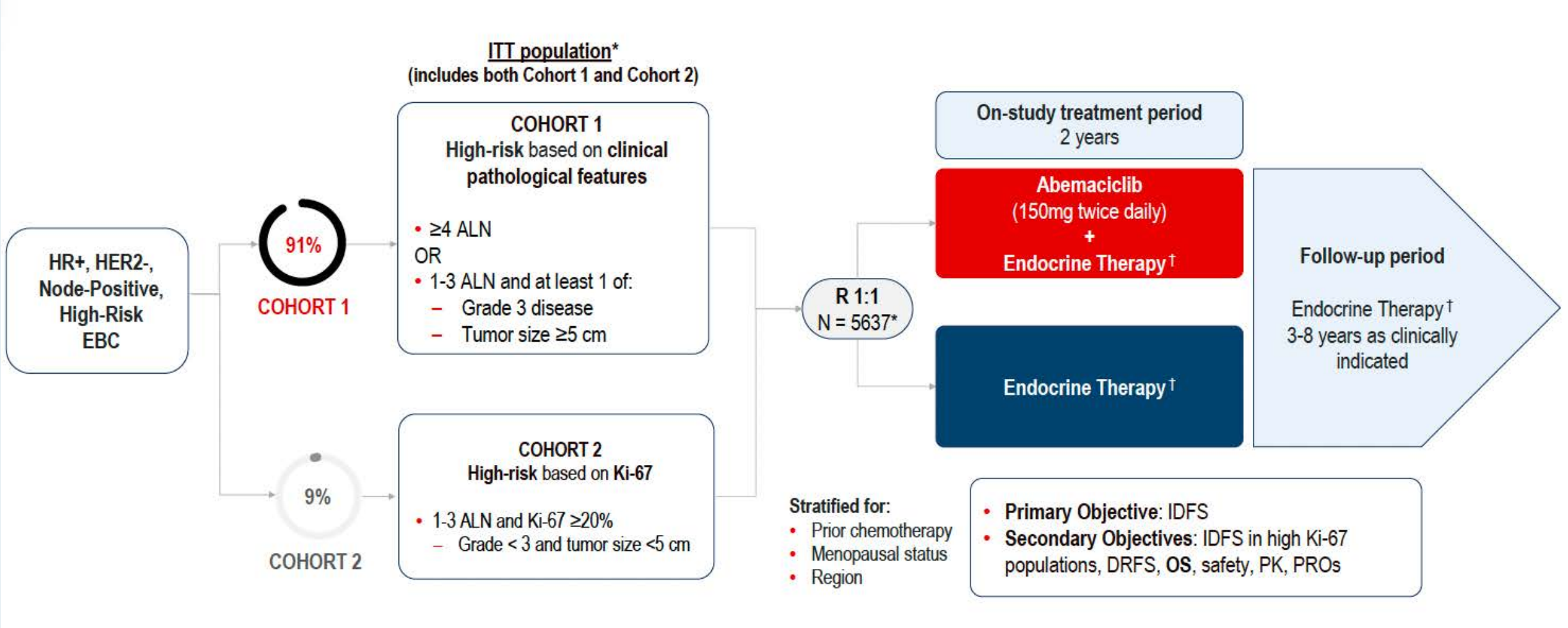
RESEARCH
TO PRACTICE

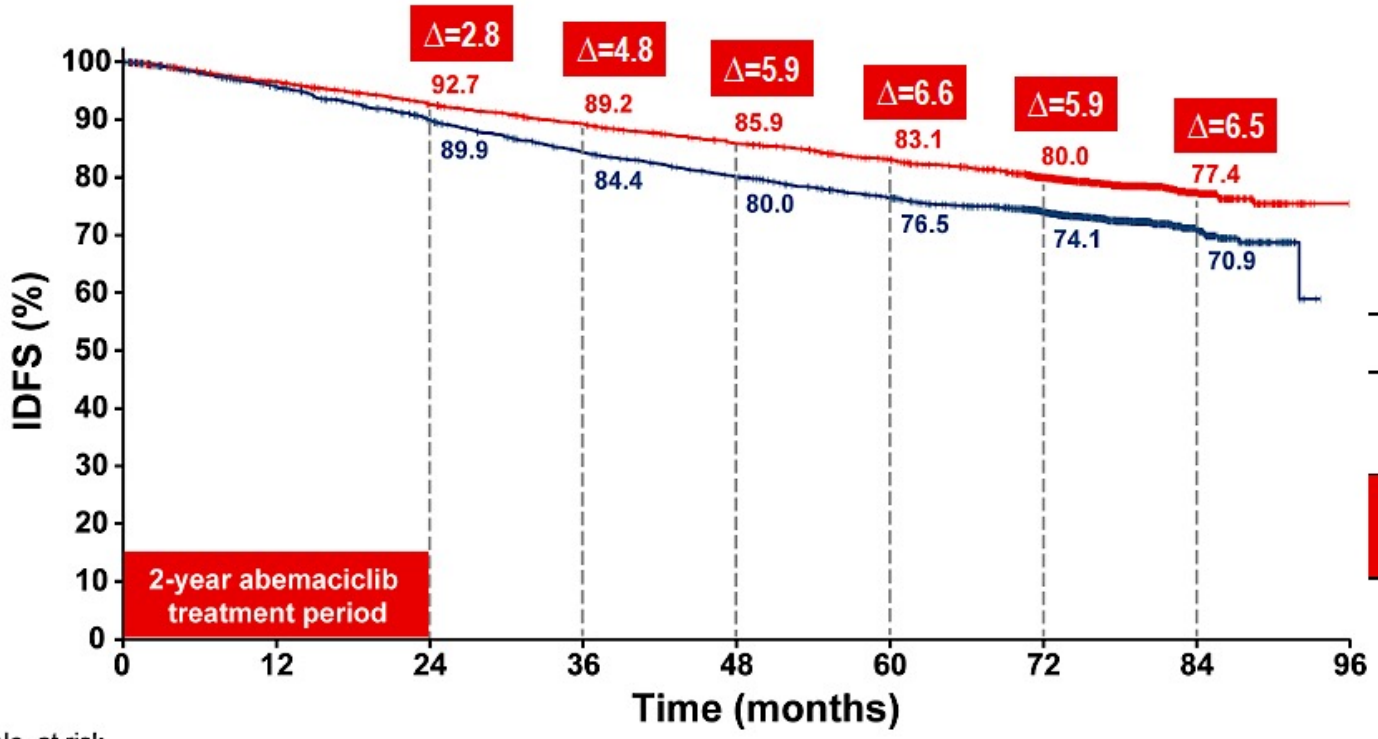
monarchE Study Design



Johnston S et al. ESMO 2025;Abstract LBA13. Johnston S et al. *Ann Oncol* 2026;37(2):155-65.

RTP RESEARCH TO PRACTICE

monarchE: Invasive Disease-Free Survival (IDFS) Outcomes



Number of IDFS events	
Abemaciclib + ET	ET
547	722

HR (95% CI): 0.734 (0.657, 0.820)
Nominal *P*<.0001

No. at risk

Abemaciclib + ET	2808	2549	2406	2285	2173	2056	1763	369	0
ET	2829	2573	2374	2193	2057	1923	1621	363	0

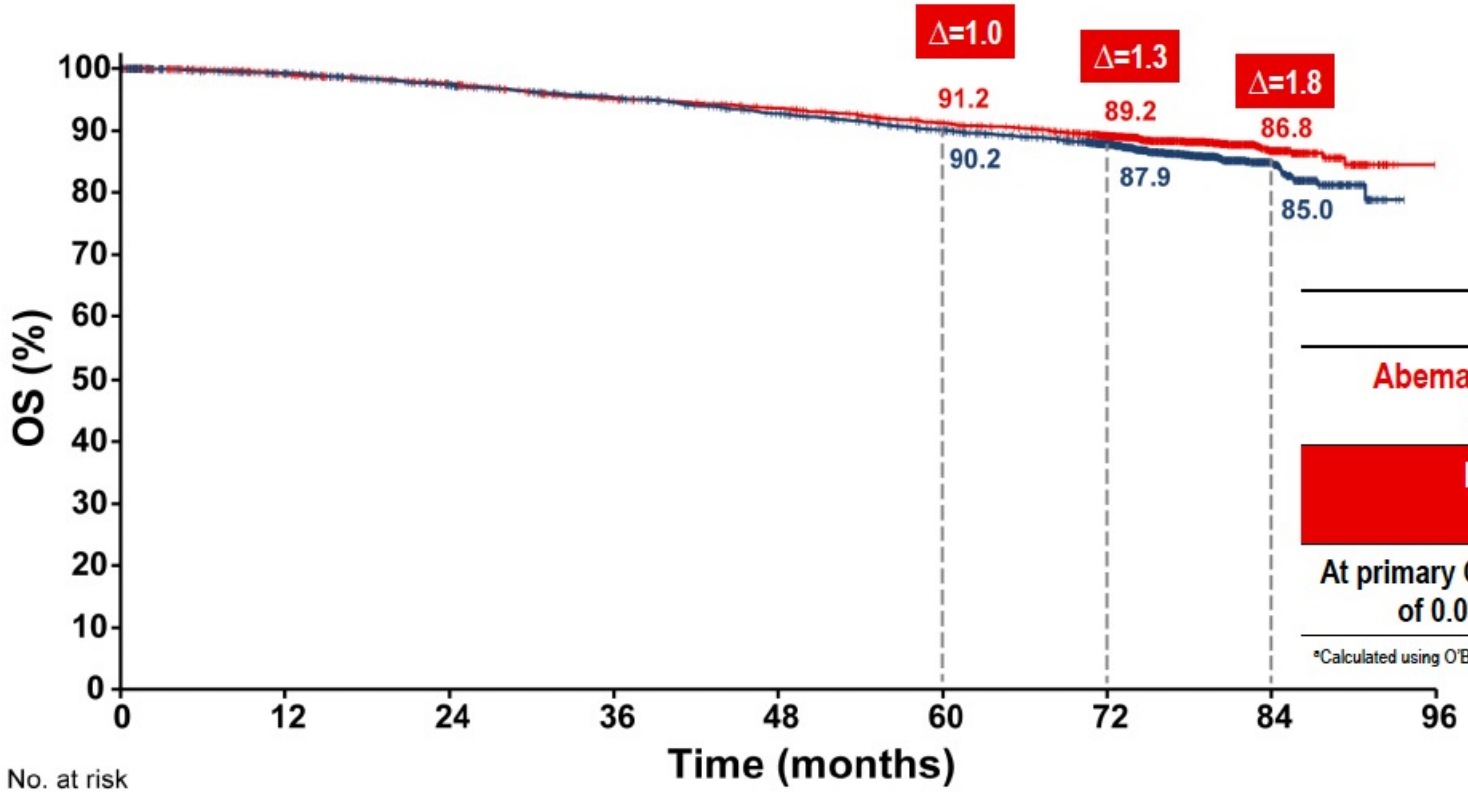
Abemaciclib + ET reduced the risk of IDFS events by 26.6% compared to ET alone

ET = endocrine therapy

Johnston S et al. ESMO 2025;Abstract LBA13. Johnston S et al. *Ann Oncol* 2026;37(2):155-65.

RTP RESEARCH TO PRACTICE

monarchE: Overall Survival (OS) Outcomes



Number of OS events	
Abemaciclib + ET	ET
301	360

HR (95% CI): 0.842 (0.722, 0.981)
P=0.0273

At primary OS testing, OS in ITT met the critical boundary of 0.0434 (2-sided)[a] for statistical significance

[a]Calculated using O'Brien-Fleming type stopping boundary based on the observed number of events

No. at risk

Abemaciclib + ET	2808	2614	2518	2407	2342	2236	1967	425	0
ET	2829	2664	2546	2443	2338	2215	1908	433	0

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

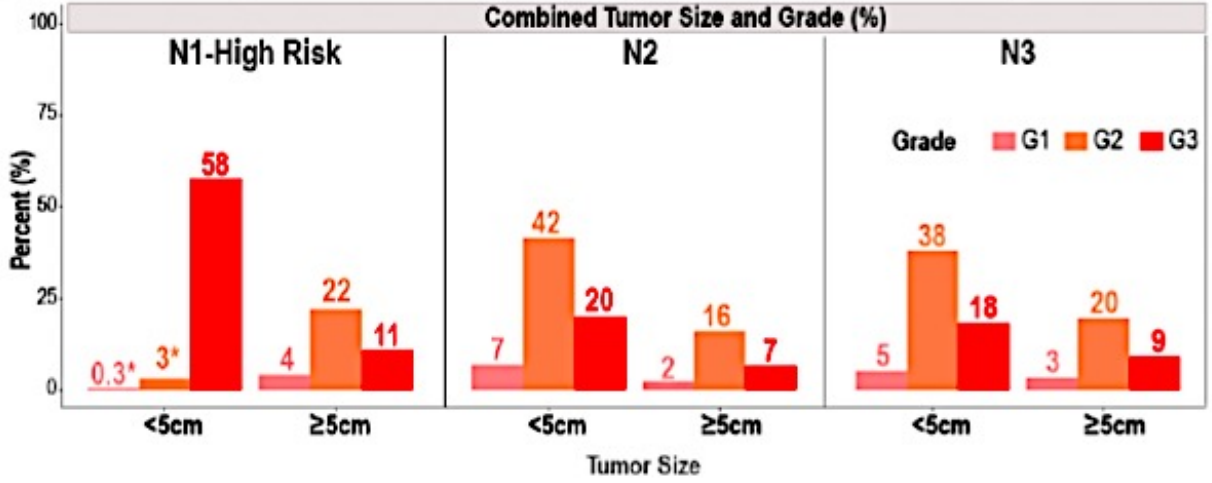
Johnston S et al. ESMO 2025;Abstract LBA13. Johnston S et al. *Ann Oncol* 2026;37(2):155-65.

RTP RESEARCH TO PRACTICE

monarchE: Subgroup Analysis by Nodal Status

Tumor Characteristics in Cohort 1

	N1-High Risk	N2	N3
Ki-67 (%)			
<20%	29	43	41
≥20%	49	33	36
Missing	23	24	24
Histology (%)			
Lobular	11	13	20
Ductal	72	68	62
Other	17	20	18

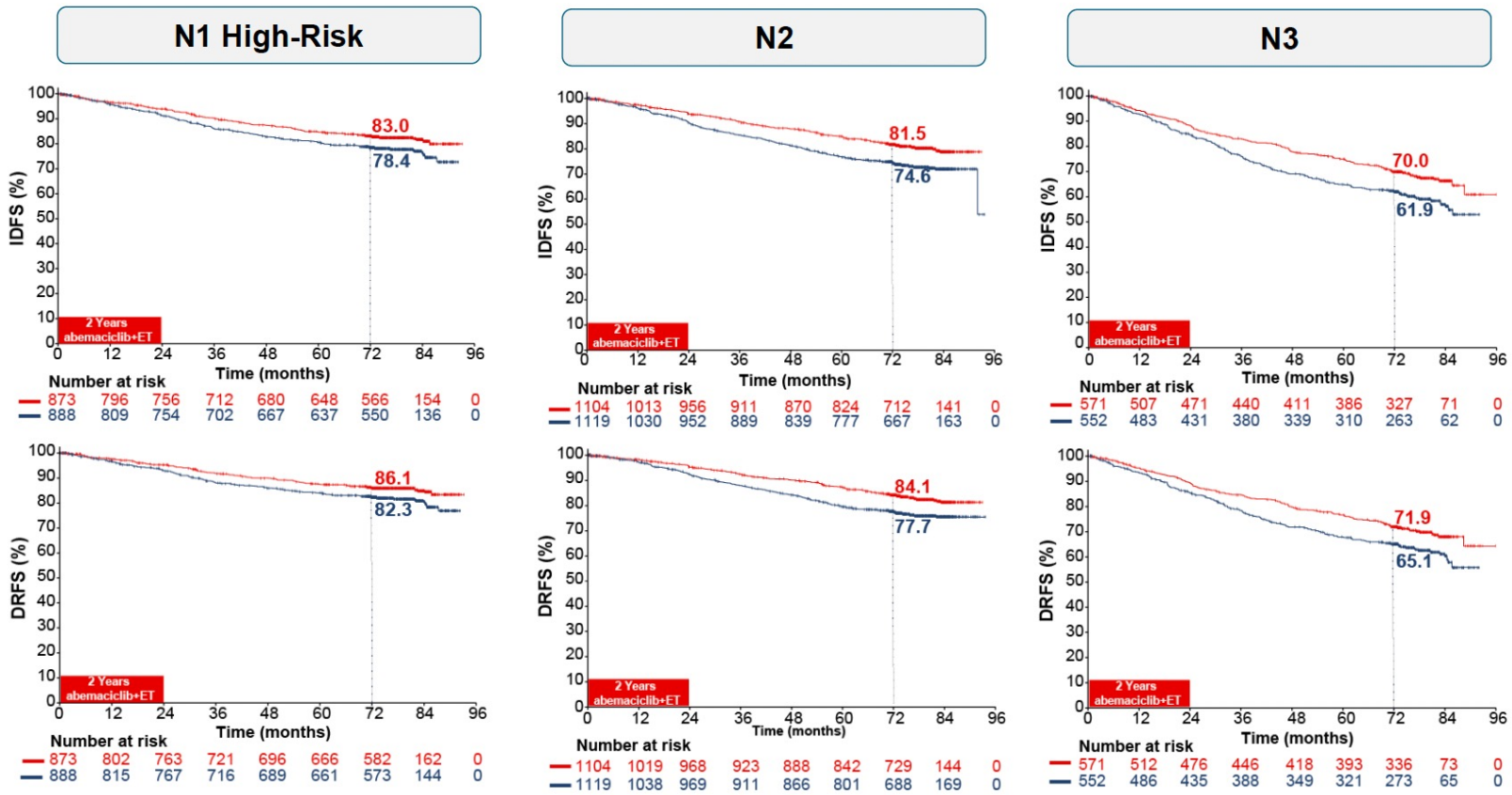


- monarchE eligible patients with N1 high risk disease presented more Grade 3 tumors and Ki-67 ≥20% compared to N2 and N3
- Distribution of ductal/lobular histology was similar in N1-high risk and N2 while N3 had more lobular tumors
- Over 40% of patients with N1-High risk disease received neoadjuvant 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

Cortés J et al. San Antonio Breast Cancer Symposium 2025;Abstract PS1-08-08.

RTP RESEARCH TO PRACTICE

monarchE: IDFS and DRFS by Nodal Status



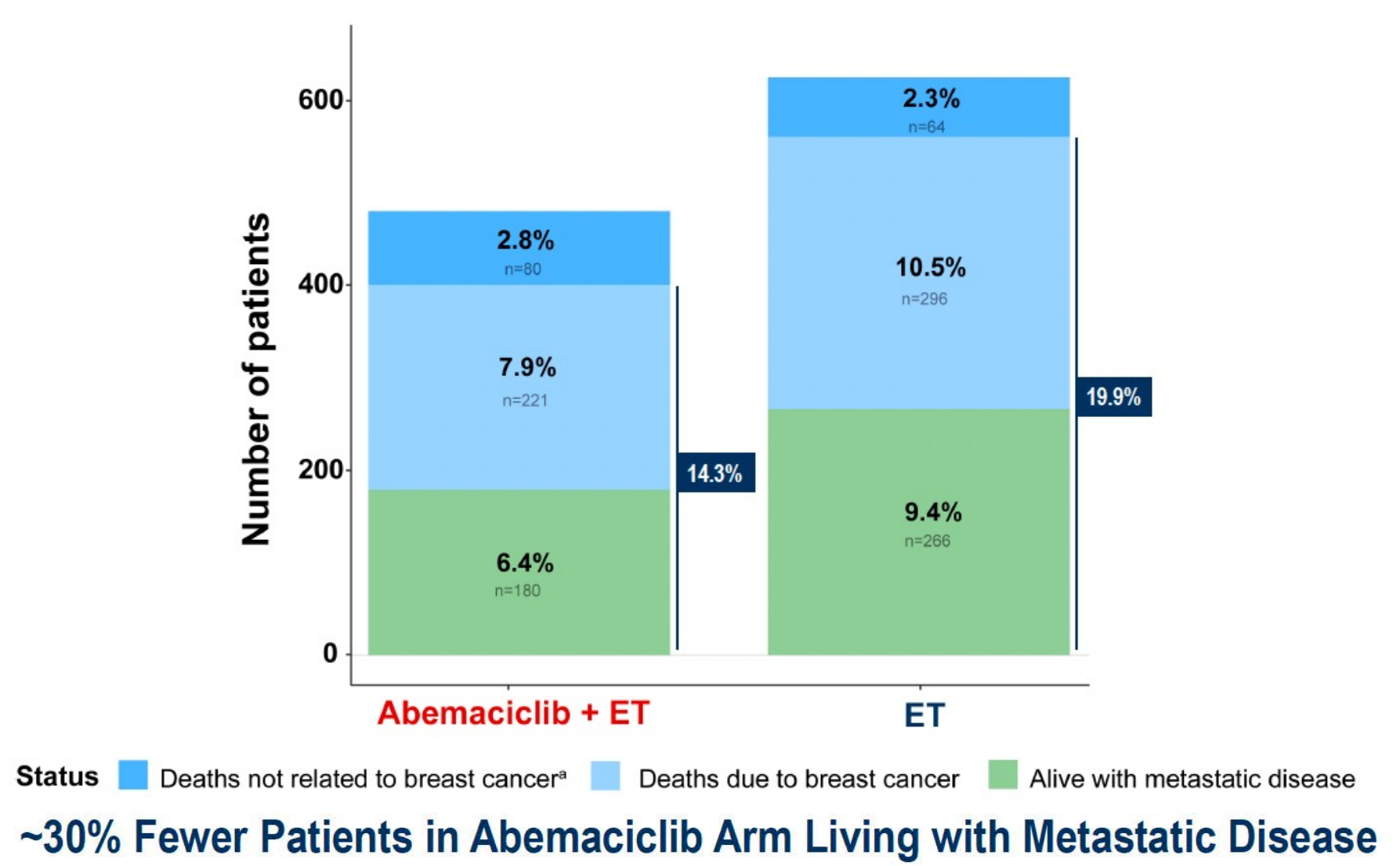
- In the ET alone arm, patients with N1-High risk and N2 disease had comparable risk of recurrence and death, while higher risk was observed in N3 subgroup
- Abemaciclib plus ET reduced the risk of IDFS events by 24.8% (N1), 31.5% (N2) and 27.4% (N3), compared to ET

DRFS = distant relapse-free survival

Cortés J et al. San Antonio Breast Cancer Symposium 2025;Abstract PS1-08-08.

RTP RESEARCH TO PRACTICE

monarchE: Survival Status



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

Johnston S et al. ESMO 2025;Abstract LBA13. Johnston S et al. *Ann Oncol* 2026;37(2):155-65.

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 ≥ 20%
      - Oncotype DX Breast Recurrence Score ≥ 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

R 1:1

RIB
400 mg/day
3 weeks on/1 week off for **3 y**
+
NSAI
Letrozole or anastrozole[b] for **≥5 y**
+ goserelin in men and premenopausal women

NSAI
Letrozole or anastrozole[b] for **≥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

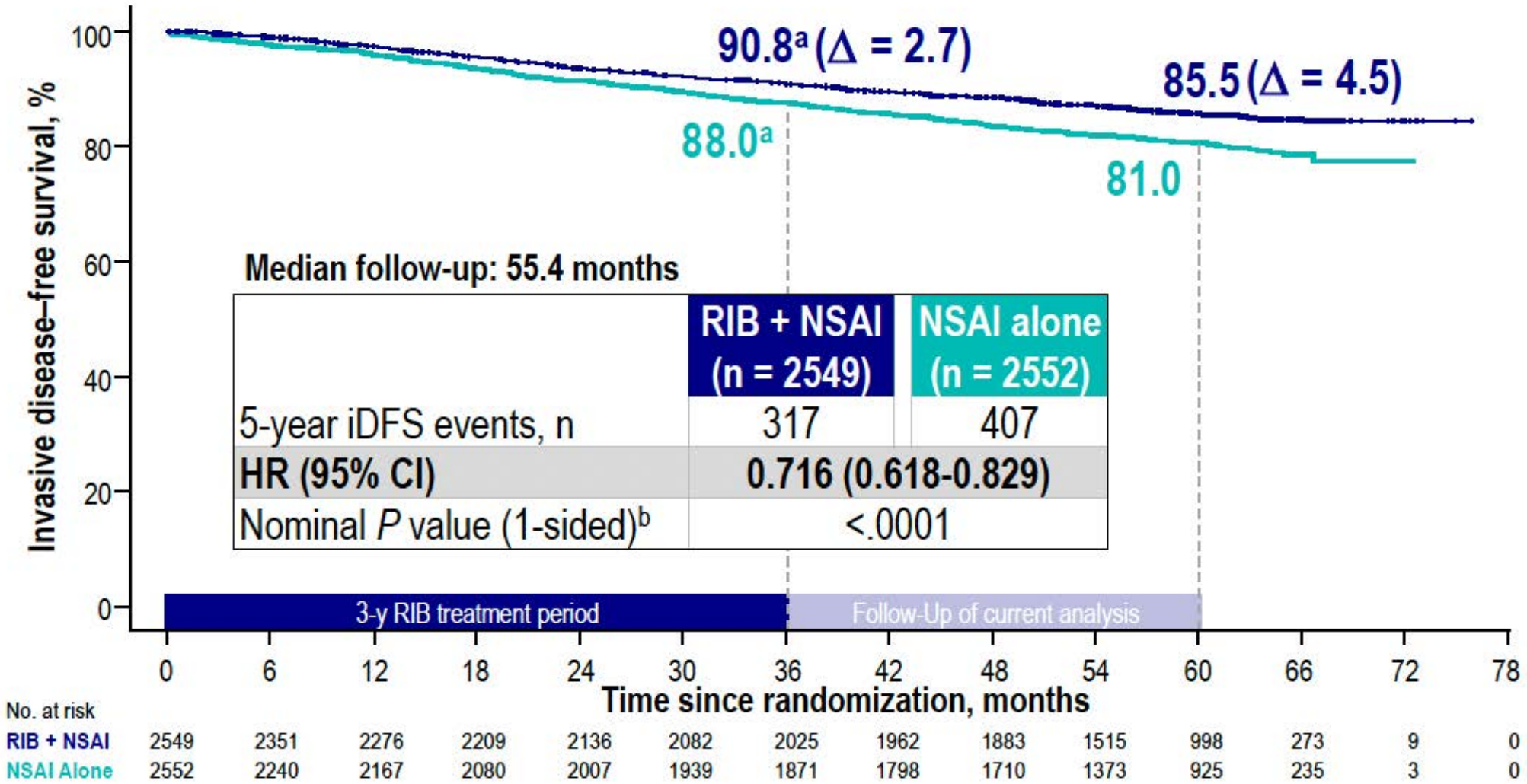
Efficacy outcomes for the 5-year analysis were estimated by the Kaplan-Meier method, and results are descriptive. The Cox proportional hazards model was used to estimate the HRs and 95% CIs.

RIB = ribociclib; NSAI = nonsteroidal aromatase inhibitor

Crown JP et al. ESMO 2025;Abstract LBA14.

RTP RESEARCH TO PRACTICE

NATALEE: IDFS Outcomes



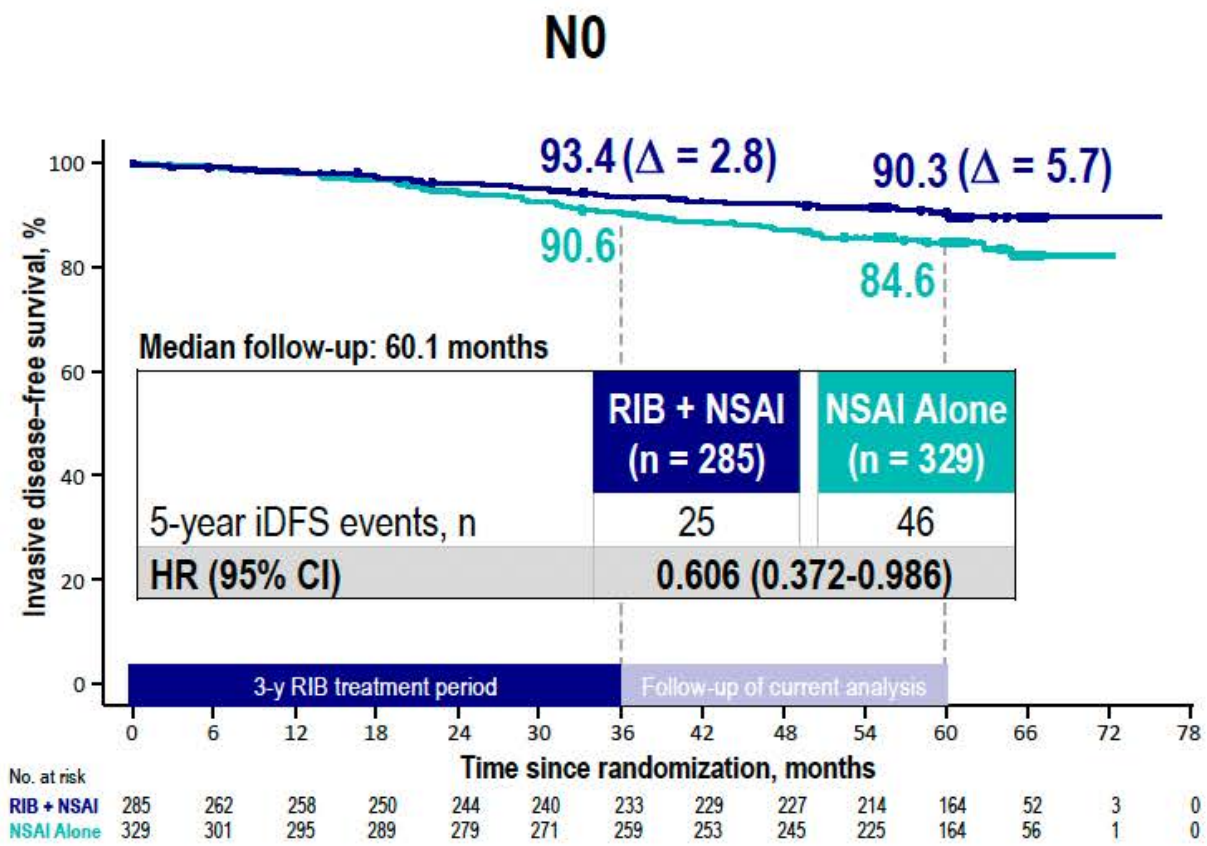
	RIB + NSAI (n = 2549)	NSAI alone (n = 2552)
5-year iDFS events, n	317	407
HR (95% CI)	**0.716 (0.618-0.829)**	
Nominal *P* value (1-sided)[b]	<.0001	

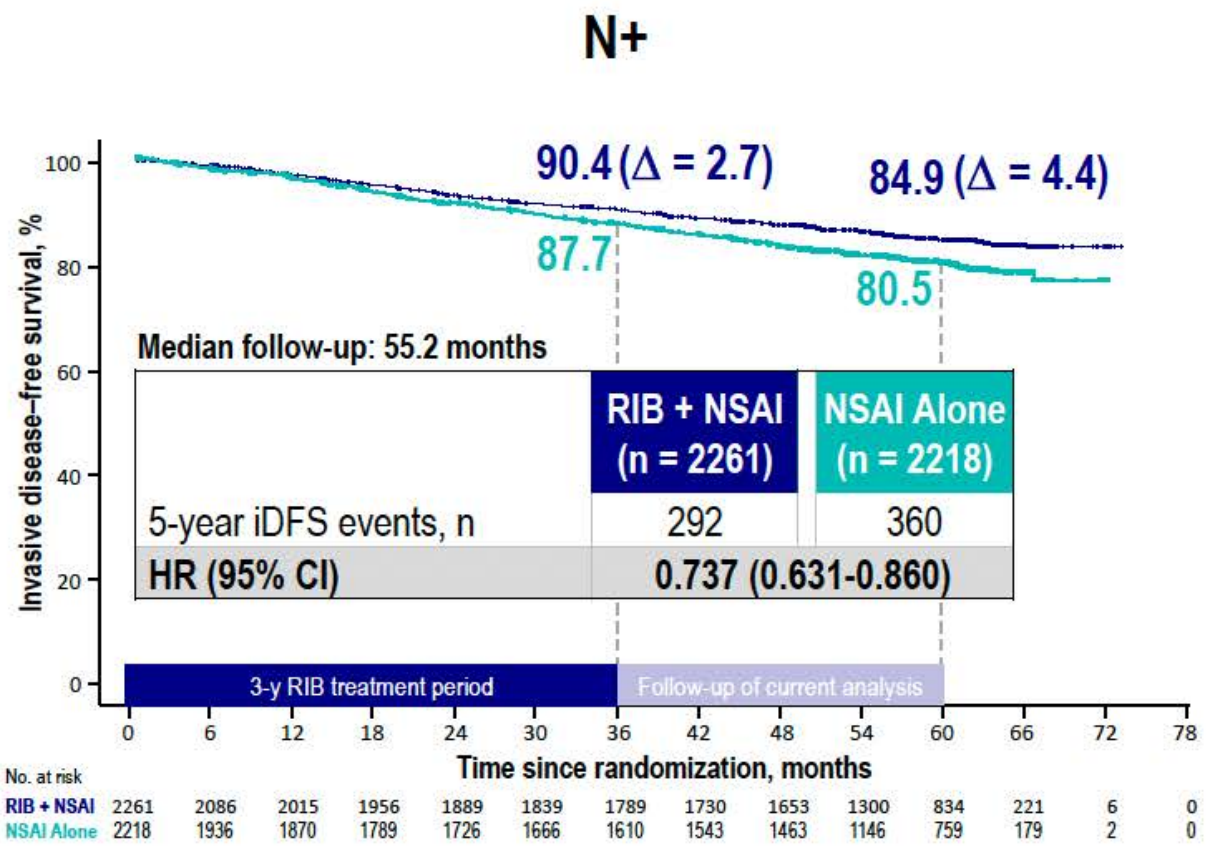
RIB = ribociclib; NSAI = nonsteroidal aromatase inhibitor

Crown JP et al. ESMO 2025;Abstract LBA14.

RTP RESEARCH TO PRACTICE

NATALEE: IDFS by Nodal Status

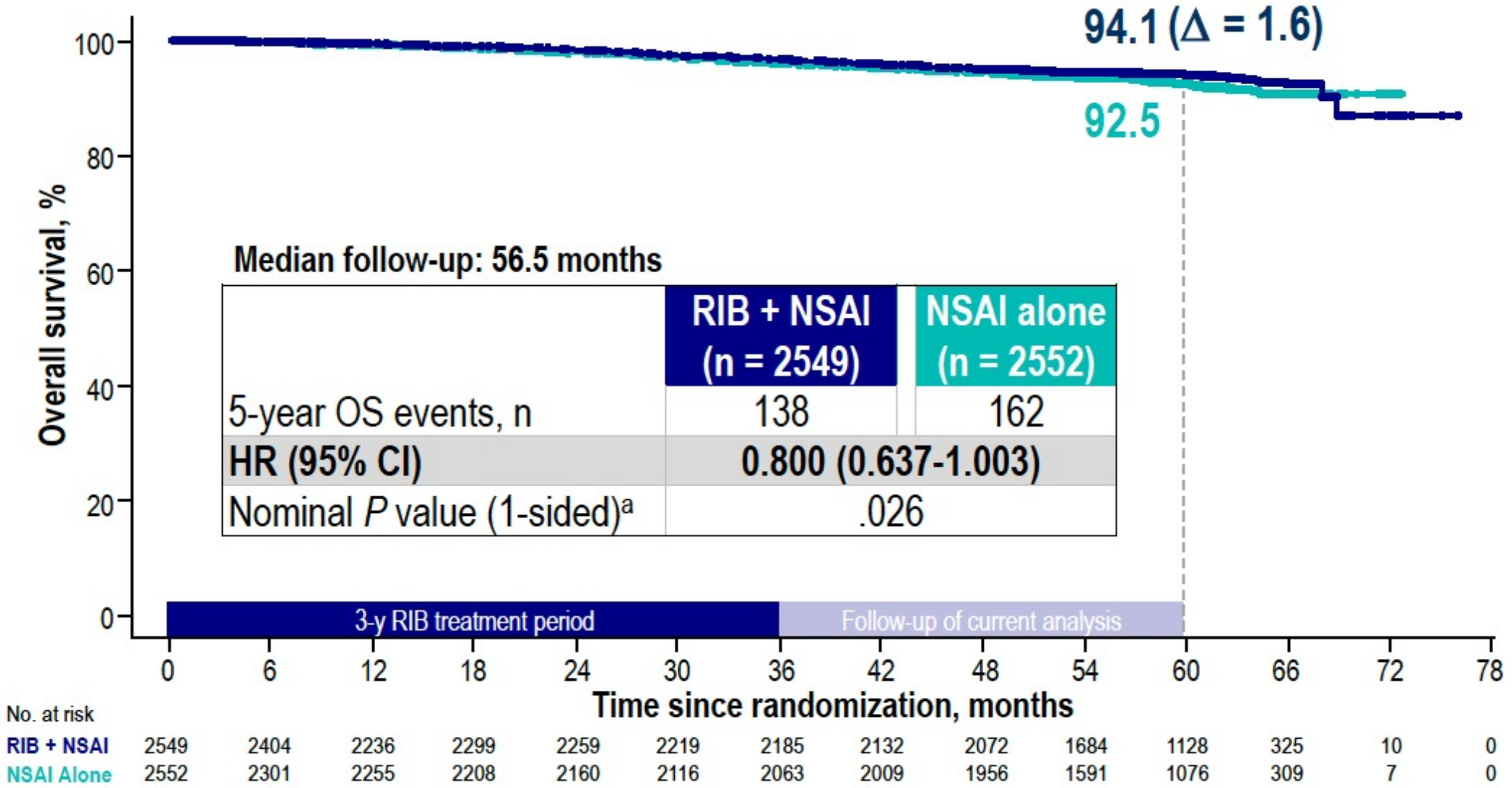




Crown JP et al. ESMO 2025;Abstract LBA14.

RTP RESEARCH TO PRACTICE

NATALEE: OS Outcomes

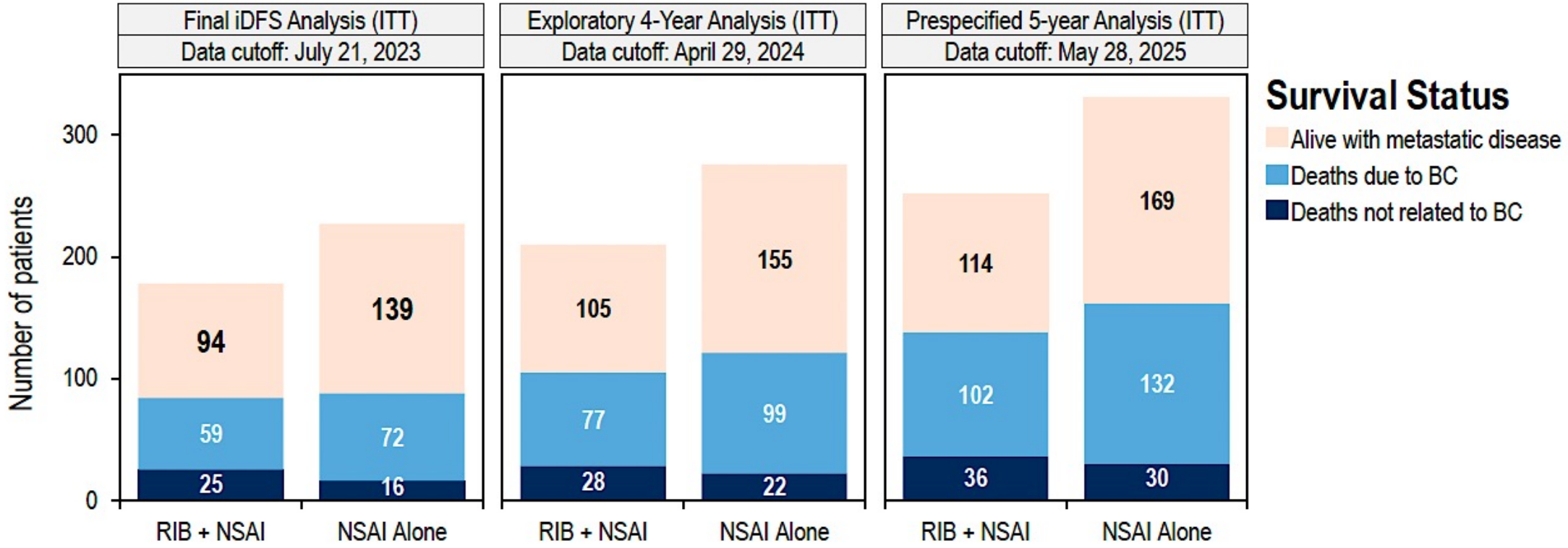


	RIB + NSAI (n = 2549)	NSAI alone (n = 2552)
5-year OS events, n	138	162
HR (95% CI)	**0.800 (0.637-1.003)**	
Nominal *P* value (1-sided)[a]	.026	

Crown JP et al. ESMO 2025;Abstract LBA14.

RTP RESEARCH TO PRACTICE

NATALEE: Survival Status over Time

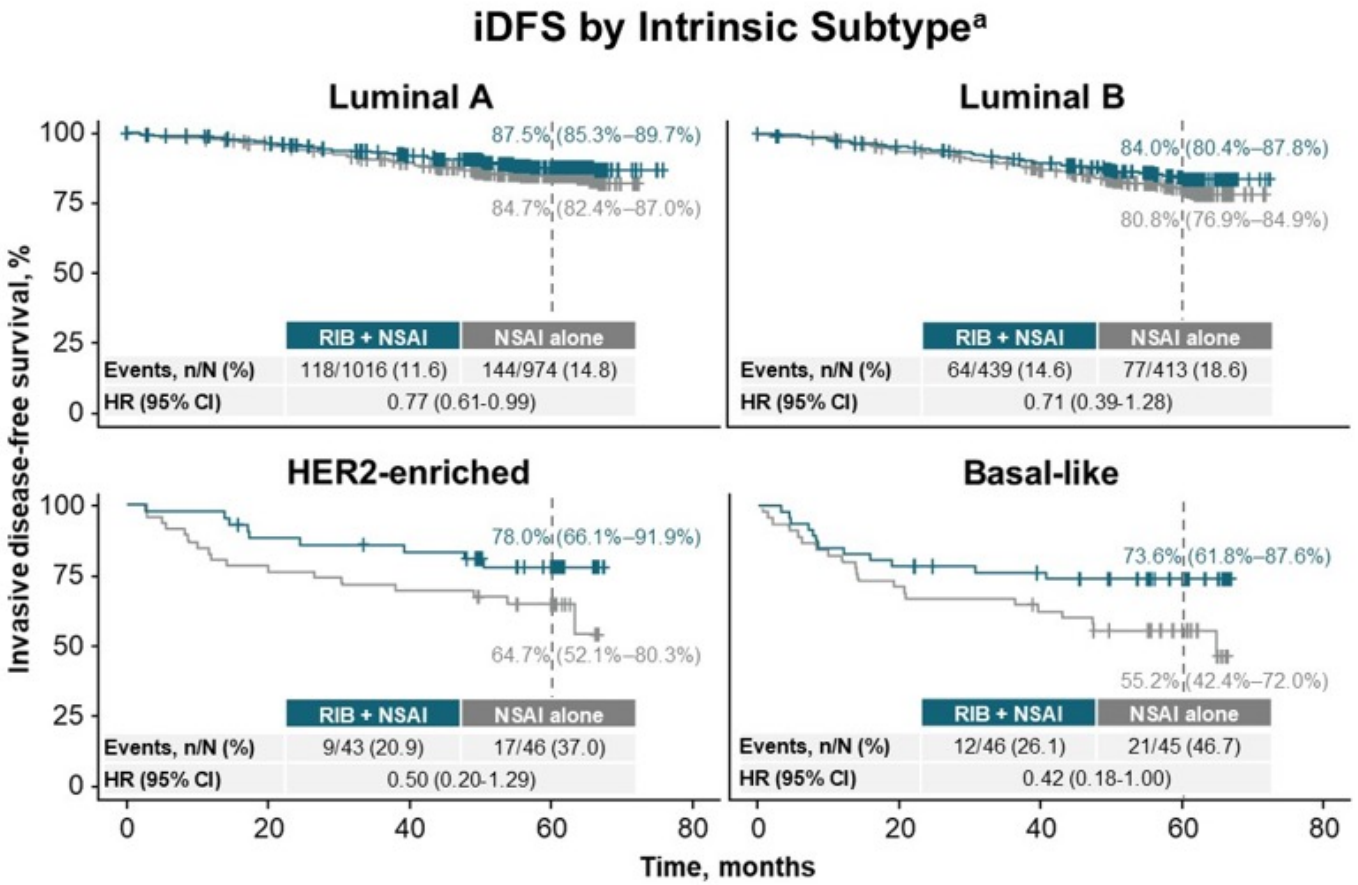


Approximate median follow-up (months)	36	44	57
OS HR (95% CI)	0.89 (0.66-1.20)	0.83 (0.64-1.07)	0.800 (0.637-1.003)

Crown JP et al. ESMO 2025;Abstract LBA14.

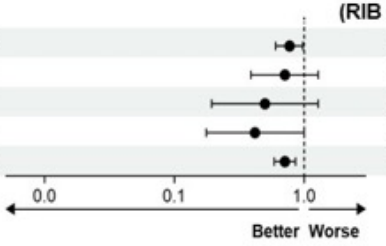
RTP RESEARCH TO PRACTICE

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



Ribociclib Treatment Benefit Across Intrinsic Subtypes[a,b]

Population	Events, n	Patients, n	*P*	HR for treatment benefit (RIB + NSAI vs NSAI alone)
Luminal A	262	1990	.038	0.77 (0.61-0.99)
Luminal B	141	852	.25	0.71 (0.39-1.28)
HER2-enriched	26	89	.15	0.50 (0.20-1.29)
Basal-like	33	91	.049	0.42 (0.18-1.00)
Biomarker	462	3022	.0004	0.72 (0.60-0.86)



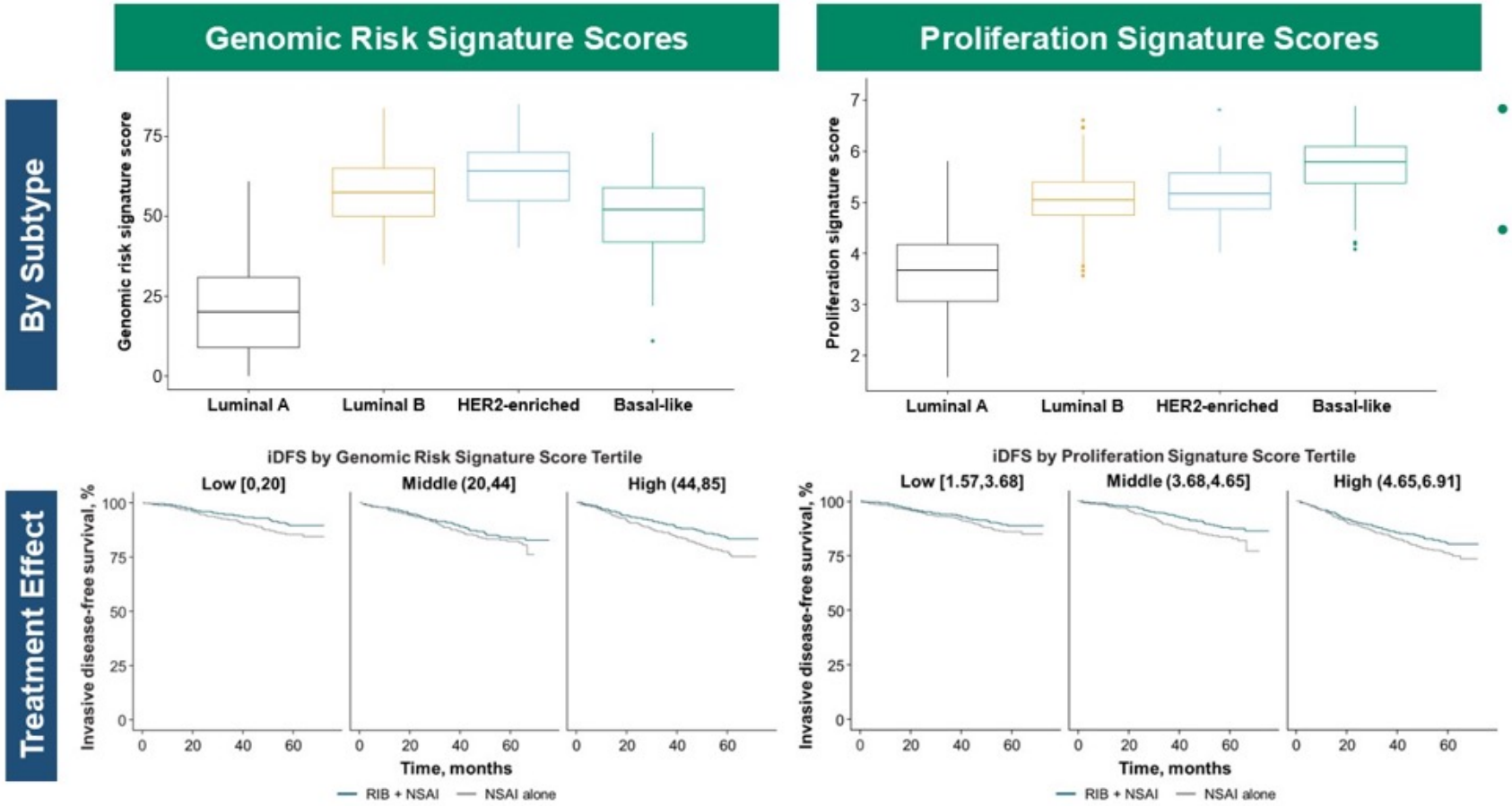
- Across treatment arms, PAM50 subtypes were strongly prognostic (hazard ratio vs luminal A: luminal B, 1.39; HER2-enriched, 2.62; basal-like, 3.92[c])
- No significant interaction between subtype and treatment was observed (*P*=.34[d])

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

Chia SKL et al. ASCO 2026;Abstract 501.

RTP RESEARCH TO PRACTICE

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



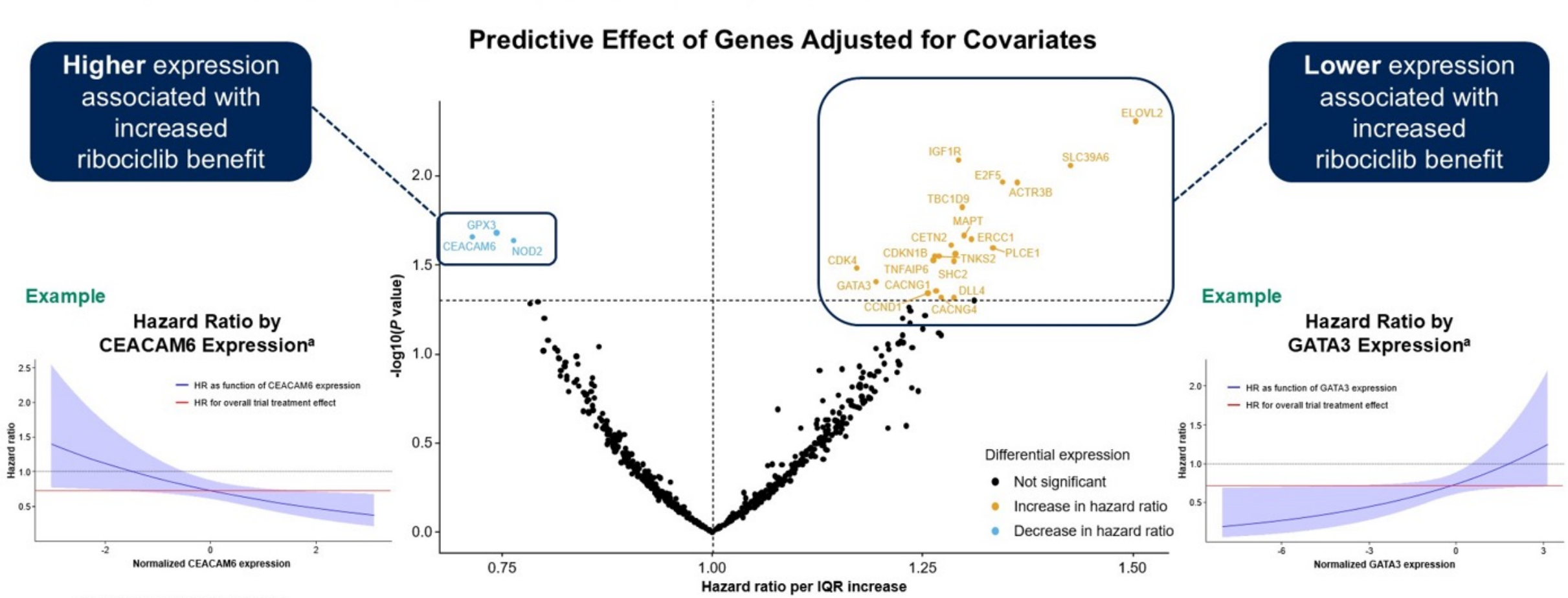
HER2, human epidermal growth factor receptor 2; PAM50, Prediction Analysis of Microarray 50.
[a] Nominal two-sided *P* value from likelihood ratio test without multiplicity correction.

- 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[a])
  - Of note, patients with N0 disease had significantly higher genomic risk scores and proliferation scores than those with N1-N3 disease

Chia SKL et al. ASCO 2026;Abstract 501.

RTP RESEARCH TO PRACTICE

NATALEE: Differential Gene Expression Affects Ribociclib Benefit



HR, hazard ratio; IQR, interquartile range.
[a] Estimated hazard ratio for ribociclib versus endocrine therapy alone (with 95% confidence band) as a continuous function of biomarker expression, derived from the Cox model interaction term. Values below the dotted line (hazard ratio = 1) indicate ribociclib benefit, while the red reference line (hazard ratio = 0.72) represents the overall trial treatment effect; the slope of the curve reflects how the magnitude of ribociclib benefit changes across the expression range of the biomarker.

Chia SKL et al. ASCO 2026;Abstract 501.

RTP RESEARCH TO PRACTICE

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

RTP RESEARCH TO PRACTICE

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 6: Clinician Survey Results

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

RTP RESEARCH TO PRACTICE

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.

RTP
RESEARCH
TO PRACTICE

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)

Rugo HS et al. *Ann Oncol* 2022;33(6):616-27.

RTP RESEARCH TO PRACTICE

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)

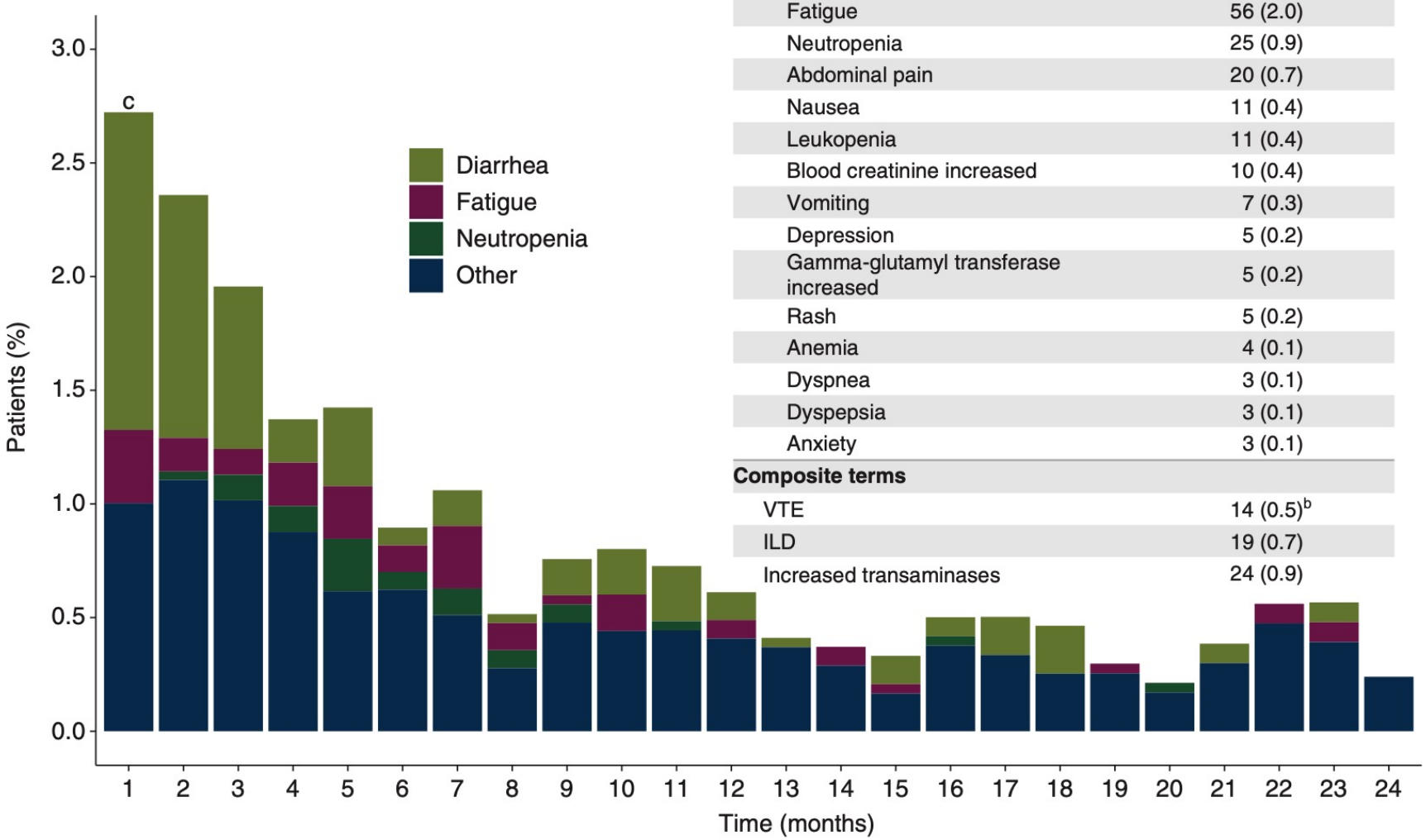
Consistent safety results from prior analyses, as all treated patients completed treatment ≥ 4 years ago
No relevant differences between treatment arms in causes of deaths due to AEs

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

Johnston S et al. ESMO 2025;Abstract LBA13. Johnston S et al. *Ann Oncol* 2026;37(2):155-65.

RTP RESEARCH TO PRACTICE

monarchE: AEs Leading to Discontinuation



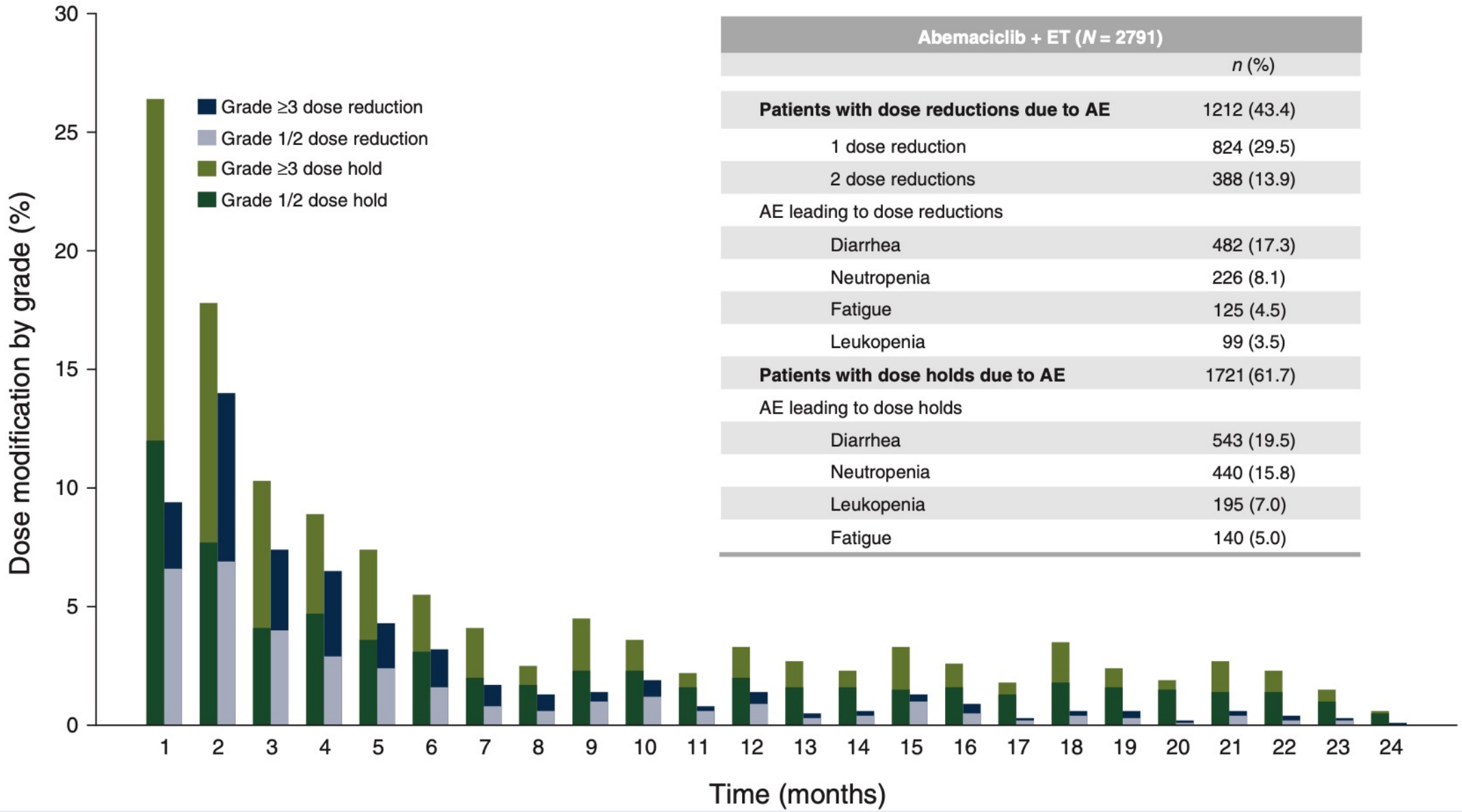
Abemaciclib + ET (*N* = 2791)	
AEs leading to discontinuation	***n* (%)**
Diarrhea	147 (5.3)
Fatigue	56 (2.0)
Neutropenia	25 (0.9)
Abdominal pain	20 (0.7)
Nausea	11 (0.4)
Leukopenia	11 (0.4)
Blood creatinine increased	10 (0.4)
Vomiting	7 (0.3)
Depression	5 (0.2)
Gamma-glutamyl transferase increased	5 (0.2)
Rash	5 (0.2)
Anemia	4 (0.1)
Dyspnea	3 (0.1)
Dyspepsia	3 (0.1)
Anxiety	3 (0.1)
Composite terms	
VTE	14 (0.5)[b]
ILD	19 (0.7)
Increased transaminases	24 (0.9)

Rugo HS et al. *Ann Oncol* 2022;33(6):616-27.

VTE = venous thromboembolism; ILD = interstitial lung disease

RTP RESEARCH TO PRACTICE

monarchE: AEs Leading to Dose Modifications

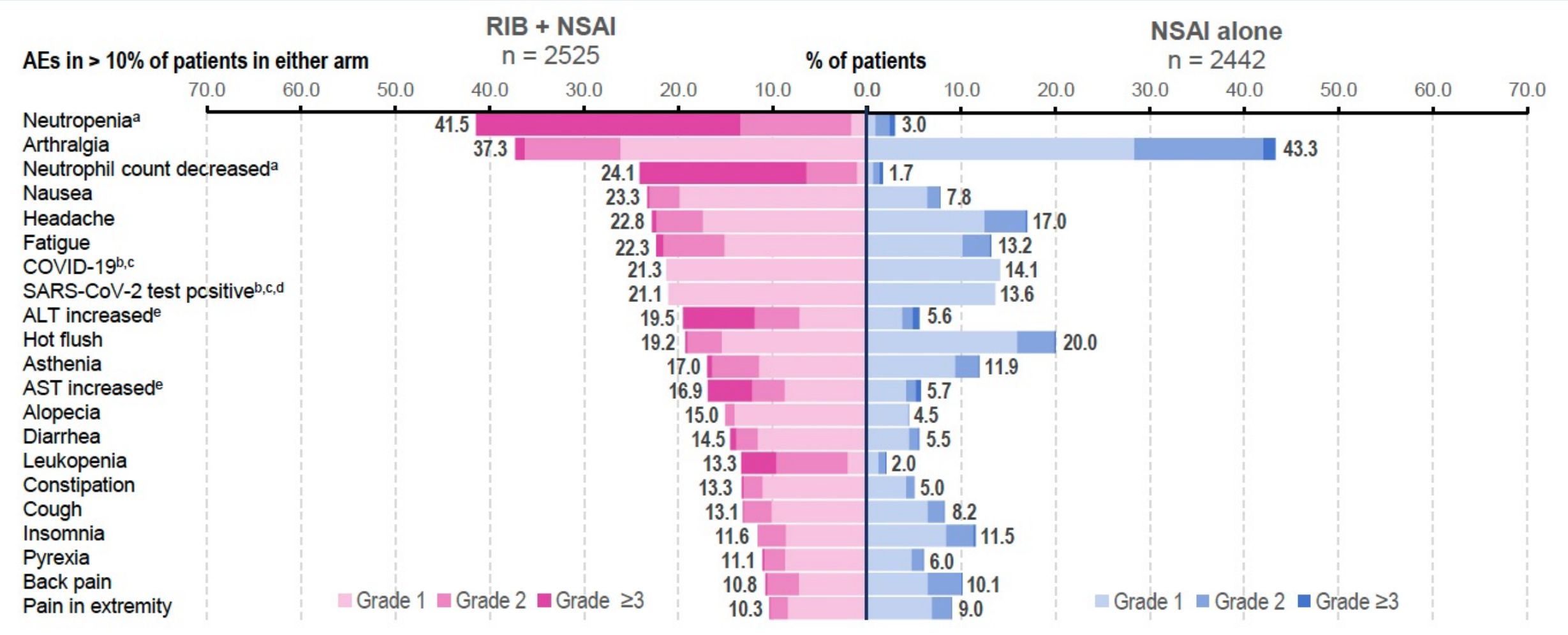


Abemaciclib + ET (*N* = 2791)	
	n (%)
Patients with dose reductions due to AE	1212 (43.4)
1 dose reduction	824 (29.5)
2 dose reductions	388 (13.9)
AE leading to dose reductions	
Diarrhea	482 (17.3)
Neutropenia	226 (8.1)
Fatigue	125 (4.5)
Leukopenia	99 (3.5)
Patients with dose holds due to AE	1721 (61.7)
AE leading to dose holds	
Diarrhea	543 (19.5)
Neutropenia	440 (15.8)
Leukopenia	195 (7.0)
Fatigue	140 (5.0)

Rugo HS et al. *Ann Oncol* 2022;33(6):616-27.

RTP RESEARCH TO PRACTICE

NATALEE: Overall Safety Profile



ALT = alanine aminostransferase; AST = aspartate aminotransferase

Barrios C et al. ESMO Breast 2024;Abstract 113MO.

RTP RESEARCH TO PRACTICE

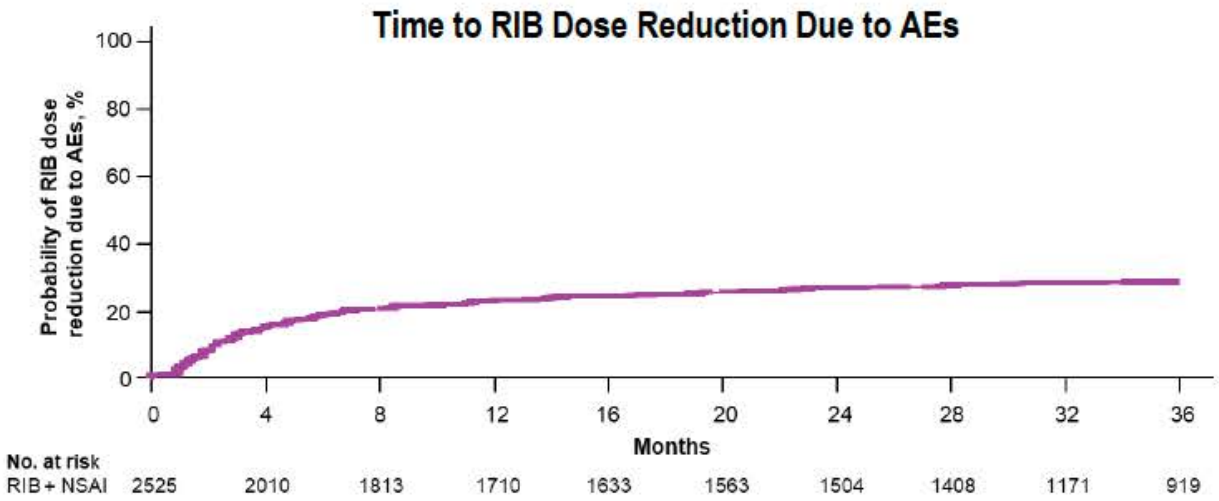
NATALEE: AEs of Special Interest (AESIs)

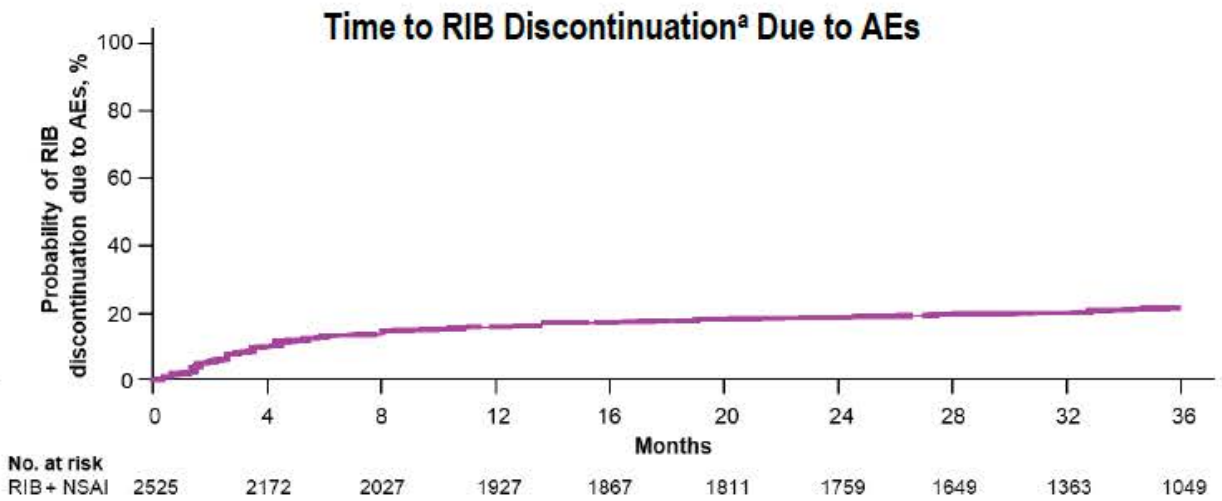
AESIs (grouped terms)	Neutropenia[a]		Liver-related AEs[c]		QT interval prolongation[d]	
	RIB + NSAI	NSAI alone	RIB + NSAI	NSAI alone	RIB + NSAI	NSAI alone
All grade	1579 (62.5)	113 (4.6)	667 (26.4)	273 (11.2)	134 (5.3)	34 (1.4)
Grade ≥3	1118 (44.3)	22 (0.9)	217 (8.6)	42 (1.7)	26 (1.0)	15 (0.6)
Time 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

Barrios C et al. ESMO Breast 2024;Abstract 113MO.

RTP RESEARCH TO PRACTICE

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)

RDI = relative dose intensity

Barrios C et al. ESMO Breast 2024;Abstract 113MO.

RTP RESEARCH TO PRACTICE

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[1,a]	**19%**
	Ribociclib	NATALEE[2,3]	**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.

PeerView

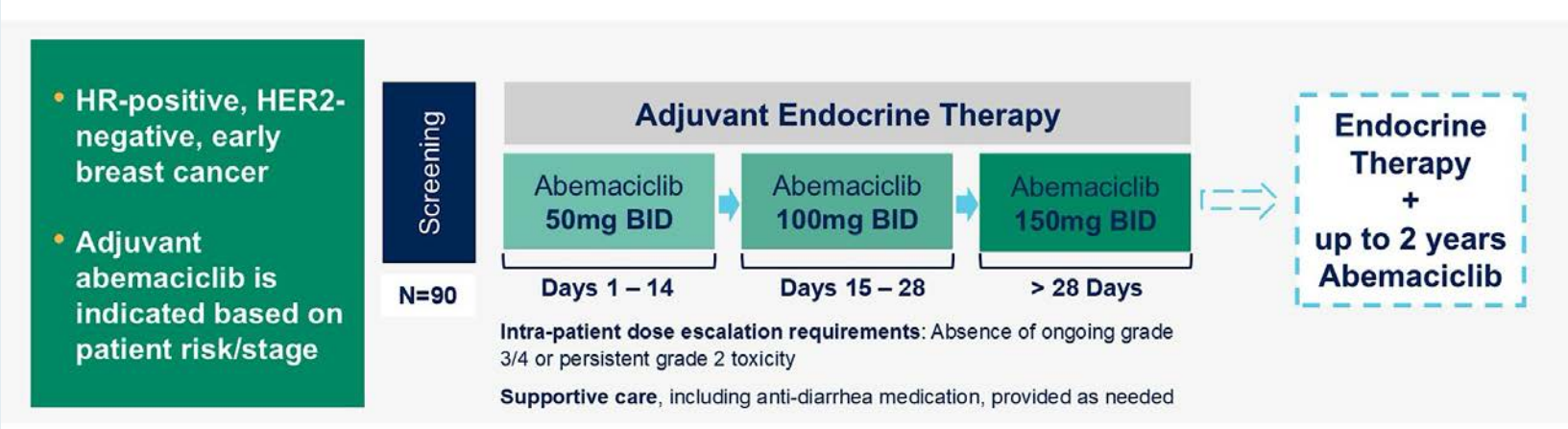
Content courtesy of Komal Jhaveri, MD, FACP, FASCO

EBC = early breast cancer

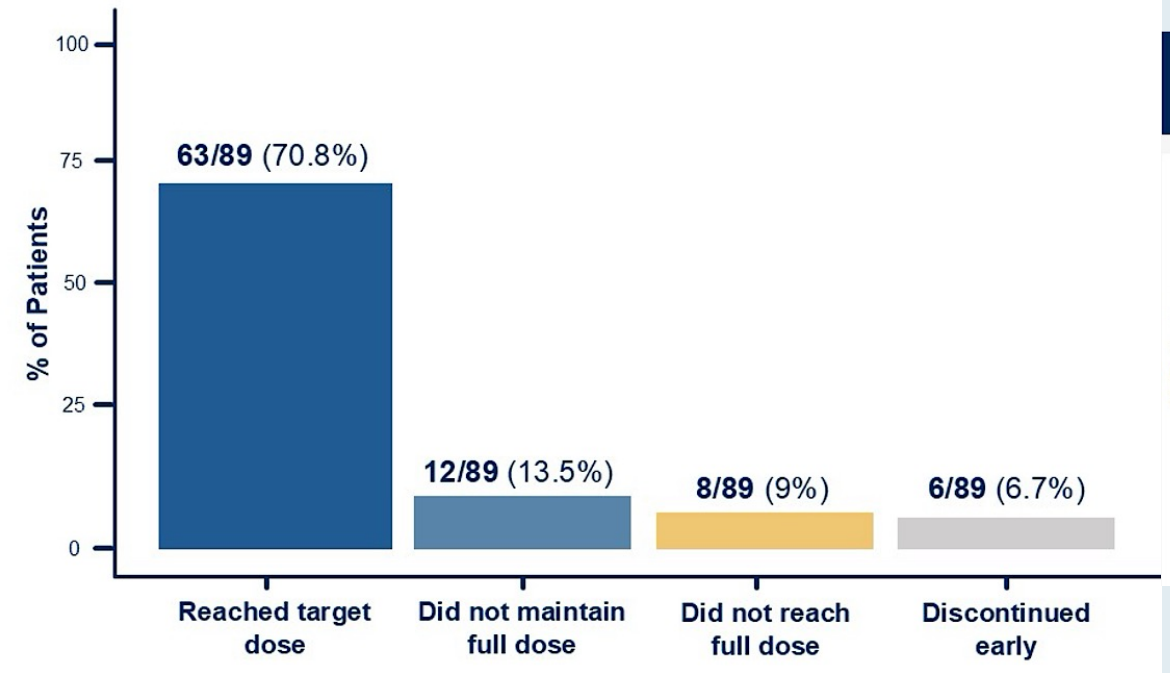
TRADE: Abemaciclib Dose Escalation

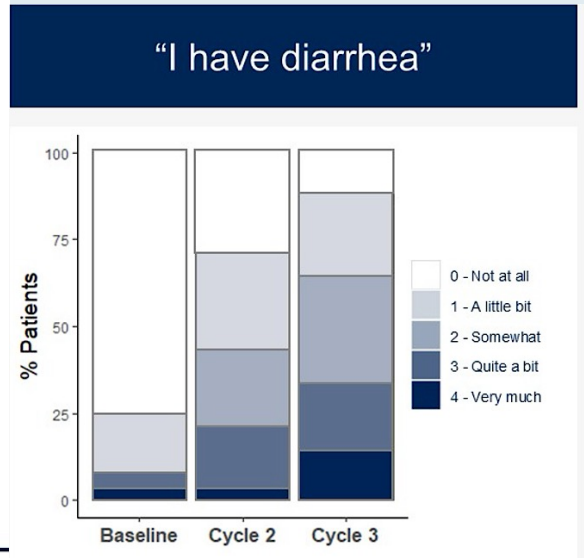
Patient disposition in monarchE

Outcome in monarchE	By 12 weeks	Overall at 2 years
Discontinued abemaciclib for any reason	10%	30.6%
• 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)





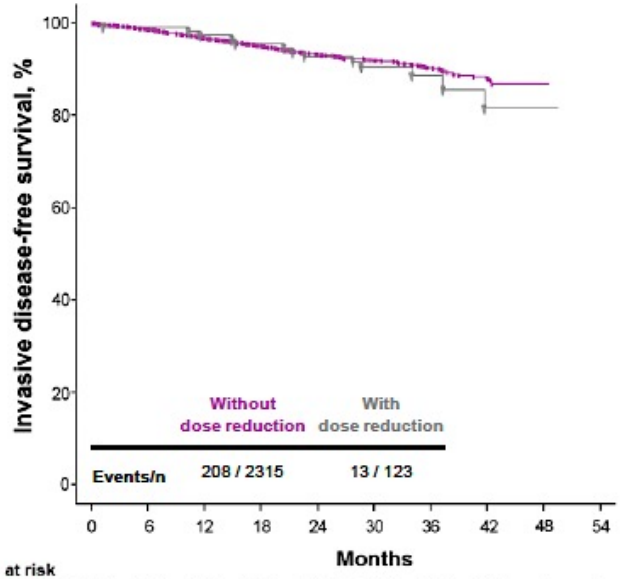
Courtesy of Komal Jhaveri, MD, FACP, FASCO

Mayer EL et al. *Ann Oncol* 2025

NATALEE: IDFS by Dose Reductions

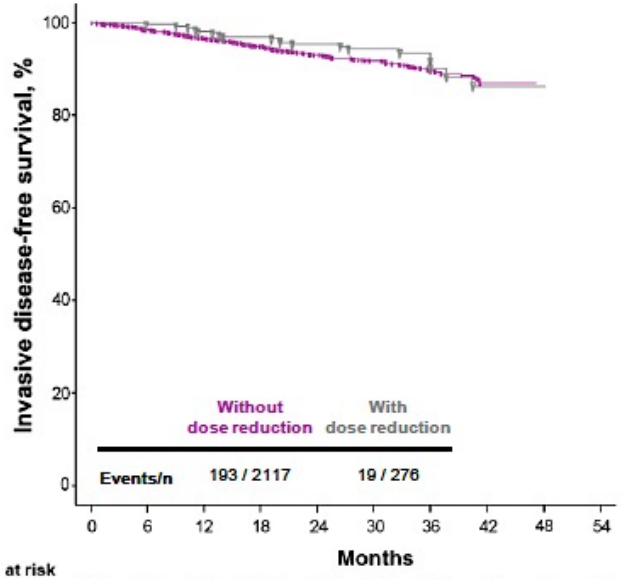
Landmark analysis revealed that RIB dose reduction due to AEs did not impact efficacy

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



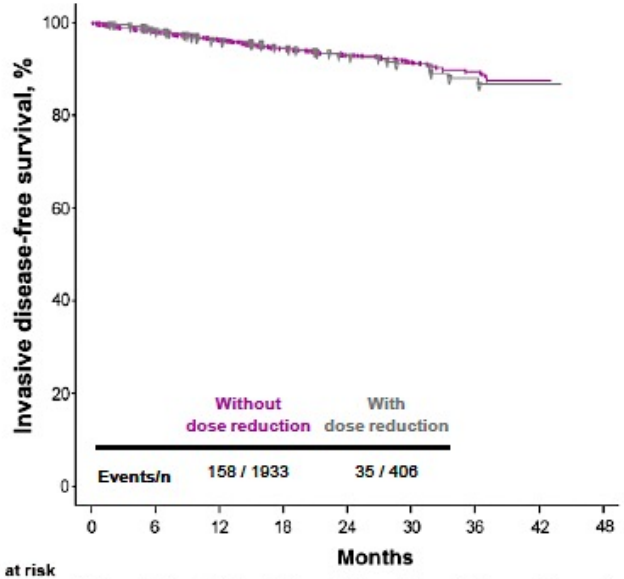
No. at risk										
Without dose reduction	2315	2219	2142	2076	1979	1603	1039	328	8	0
With dose reduction	123	115	110	105	100	80	46	21	1	0

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



No. at risk										
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)



No. at risk									
Without dose reduction	1933	1870	1820	1725	1394	914	288	14	0
With dose reduction	406	393	376	361	291	176	69	5	0

Barrios C et al. ESMO Breast 2024;Abstract 113MO.

RTP RESEARCH TO PRACTICE

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

RTP RESEARCH TO PRACTICE

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

RTP RESEARCH TO PRACTICE

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

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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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.

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SAN ANTONIO BREAST CANCER SYMPOSIUM®

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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

Presenting author: Aditya L. Bardia, MD
University of California, Los Angeles, Los Angeles, CA, USA

Abstract GS1-10

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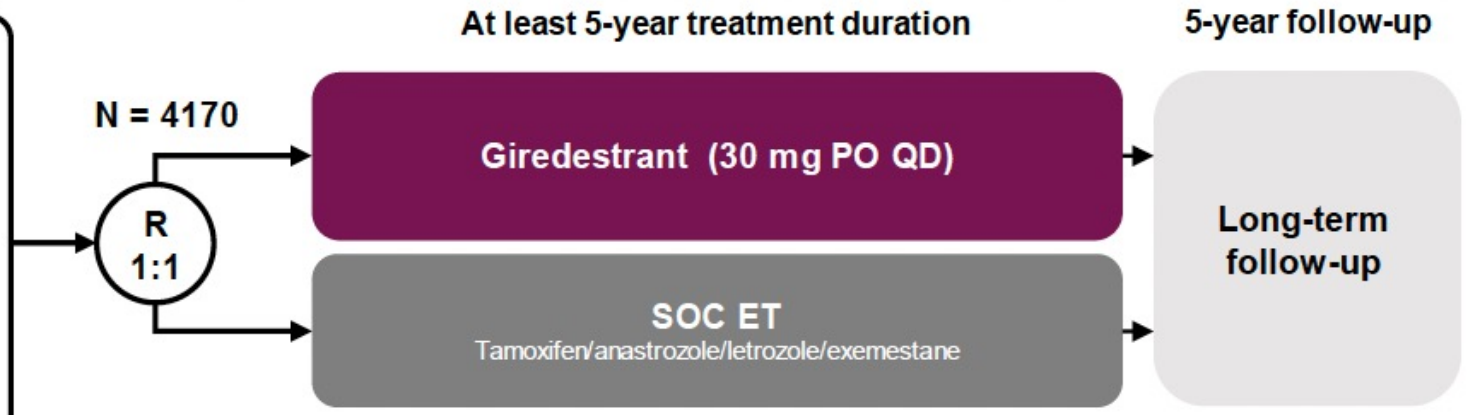
lidERA Breast Cancer Study Design

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

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

Bardia A et al. San Antonio Breast Cancer Symposium 2025;Abstract GS1-10.

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lidERA Breast Cancer: Patient Demographics

	Giredestrant n = 2084	SOC ET n = 2086
Median age, years (range)	54.0 (22–91)	54.0 (25–89)
Female sex, n (%)	2073 (99.5)	2075 (99.5)
Race, n (%)		
American Indian or Alaska Native	77 (3.7)	62 (3.0)
Asian	461 (22.1)	467 (22.4)
Black or African American	50 (2.4)	50 (2.4)
Other*	263 (12.6)	232 (11.1)
White	1233 (59.2)	1275 (61.1)
Region, n (%)		
Asia–Pacific	544 (26.1)	544 (26.1)
USA/Canada/Western Europe	860 (41.3)	905 (43.4)
Latin America/Africa/Eastern Europe	680 (32.6)	637 (30.5)
Menopausal status, n (%)†		
Pre-menopausal	849 (41.0)	838 (40.4)
Post-menopausal	1220 (59.0)	1236 (59.6)

	Giredestrant n = 2084	SOC ET n = 2086
ER status, n (%)‡		
Low-positive (1–10% of cells positive)	45 (2.2)	52 (2.5)
Positive (> 10% of cells positive)	2030 (97.8)	2031 (97.5)
AJCC stage at surgery, n (%)§		
I	254 (12.3)	283 (13.6)
II	1013 (49.0)	950 (45.7)
III	799 (38.7)	844 (40.6)
Nodal status, n (%) on surgical specimen‖		
pN0	449 (21.6)	441 (21.2)
pN1	968 (46.6)	953 (45.7)
pN2–3	662 (31.8)	691 (33.1)
Risk, n (%)		
High	1448 (69.5)	1447 (69.4)
Medium	636 (30.5)	639 (30.6)
Previous chemotherapy, n (%)		
No	396 (19.0)	450 (21.6)
Yes	1688 (81.0)	1636 (78.4)

Bardia A et al. San Antonio Breast Cancer Symposium 2025;Abstract GS1-10.

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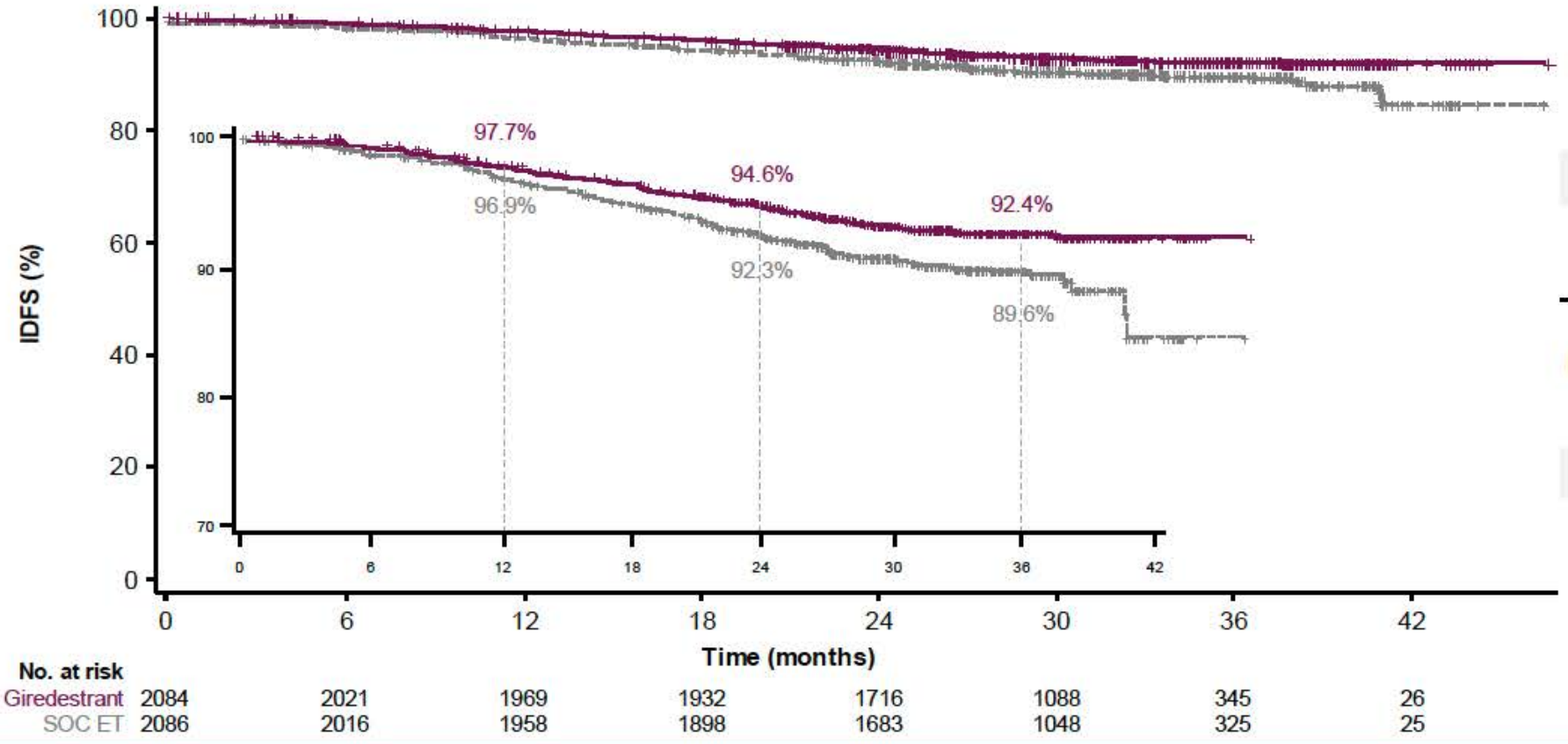
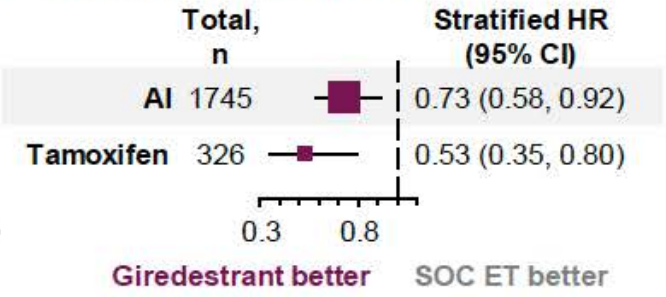
lidERA Breast Cancer: IDFS Outcomes



	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***	

Exploratory analysis: IDFS by SOC ET



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

Bardia A et al. San Antonio Breast Cancer Symposium 2025;Abstract GS1-10.

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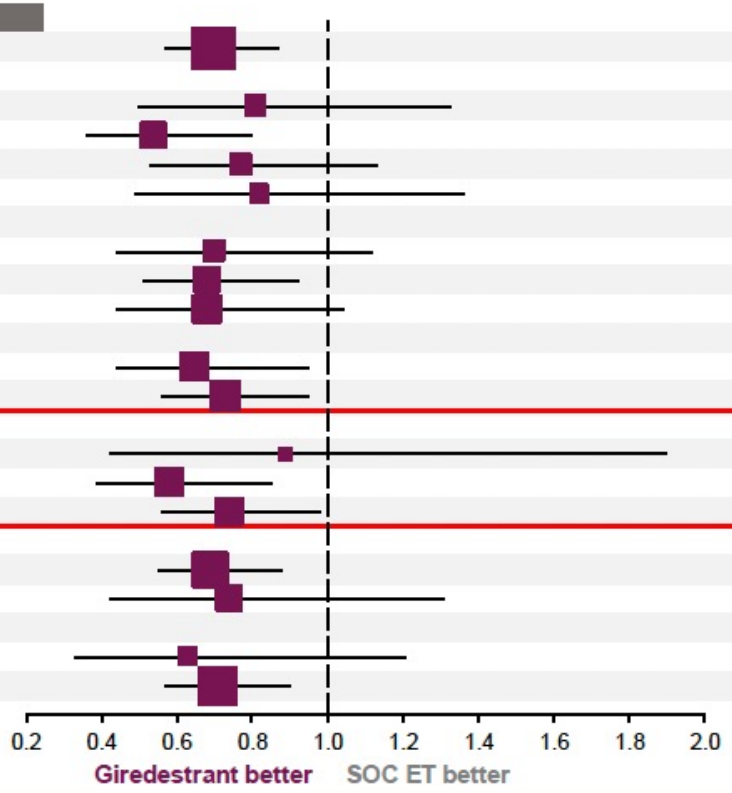
lidERA Breast Cancer: IDFS in Key Subgroups

	Total, n	Patients, n: Giredestrant	Patients, n: SOC ET	HR (95% CI)
All patients	4170	2084	2086	0.70 (0.57, 0.87)
Age group, years				
≤ 45	906	472	434	0.81 (0.50, 1.33)
> 45 to ≤ 55	1355	660	695	0.54 (0.36, 0.80)
> 55 to ≤ 65	1118	567	551	0.77 (0.53, 1.13)
> 65	791	385	406	0.82 (0.49, 1.36)
Region				
Asia–Pacific	1088	544	544	0.70 (0.44, 1.12)
Latin America/Africa/Eastern Europe	1317	680	637	0.68 (0.51, 0.92)
USA/Canada/Western Europe	1765	860	905	0.68 (0.44, 1.04)
Menopausal status				
Pre-menopausal	1680	841	839	0.65 (0.44, 0.95)
Post-menopausal	2490	1243	1247	0.73 (0.56, 0.95)
AJCC stage at surgery*				
I	537	254	283	0.89 (0.42, 1.90)
II	1963	1013	950	0.58 (0.39, 0.85)
III	1643	799	844	0.74 (0.56, 0.98)
Risk				
High	2895	1448	1447	0.69 (0.55, 0.88)
Medium	1275	636	639	0.74 (0.42, 1.31)
Previous chemotherapy				
No	787	392	395	0.63 (0.33, 1.21)
Yes	3383	1692	1691	0.71 (0.57, 0.90)



IDFS benefit was consistent across key prespecified subgroups

Bardia A et al. San Antonio Breast Cancer Symposium 2025;Abstract GS1-10.

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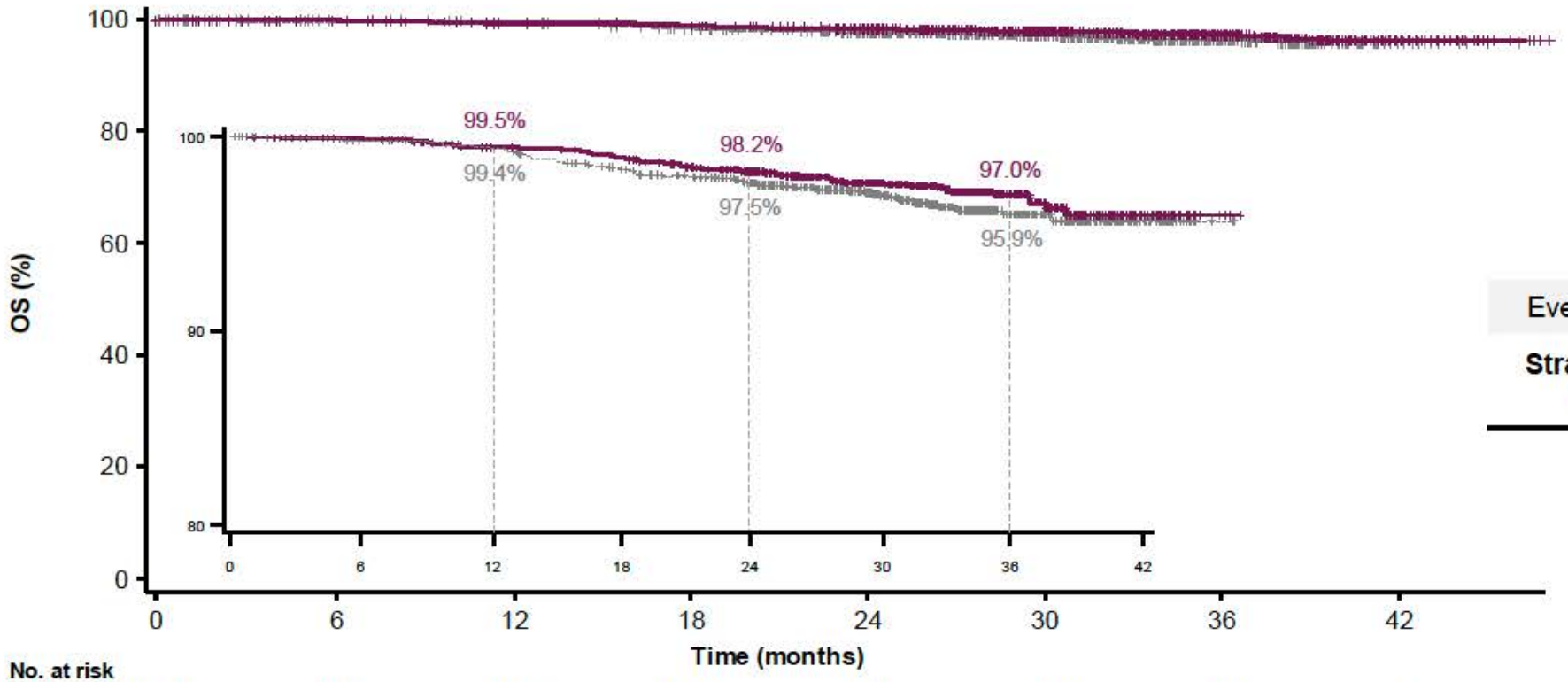
lidERA Breast Cancer: OS Outcomes



	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*	

No. at risk								
Giredestrant	2084	2043	2013	1997	1887	1300	530	52
SOC ET	2086	2040	2018	1971	1852	1270	504	49

Median follow-up: 32.3 months

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

Bardia A et al. San Antonio Breast Cancer Symposium 2025;Abstract GS1-10.

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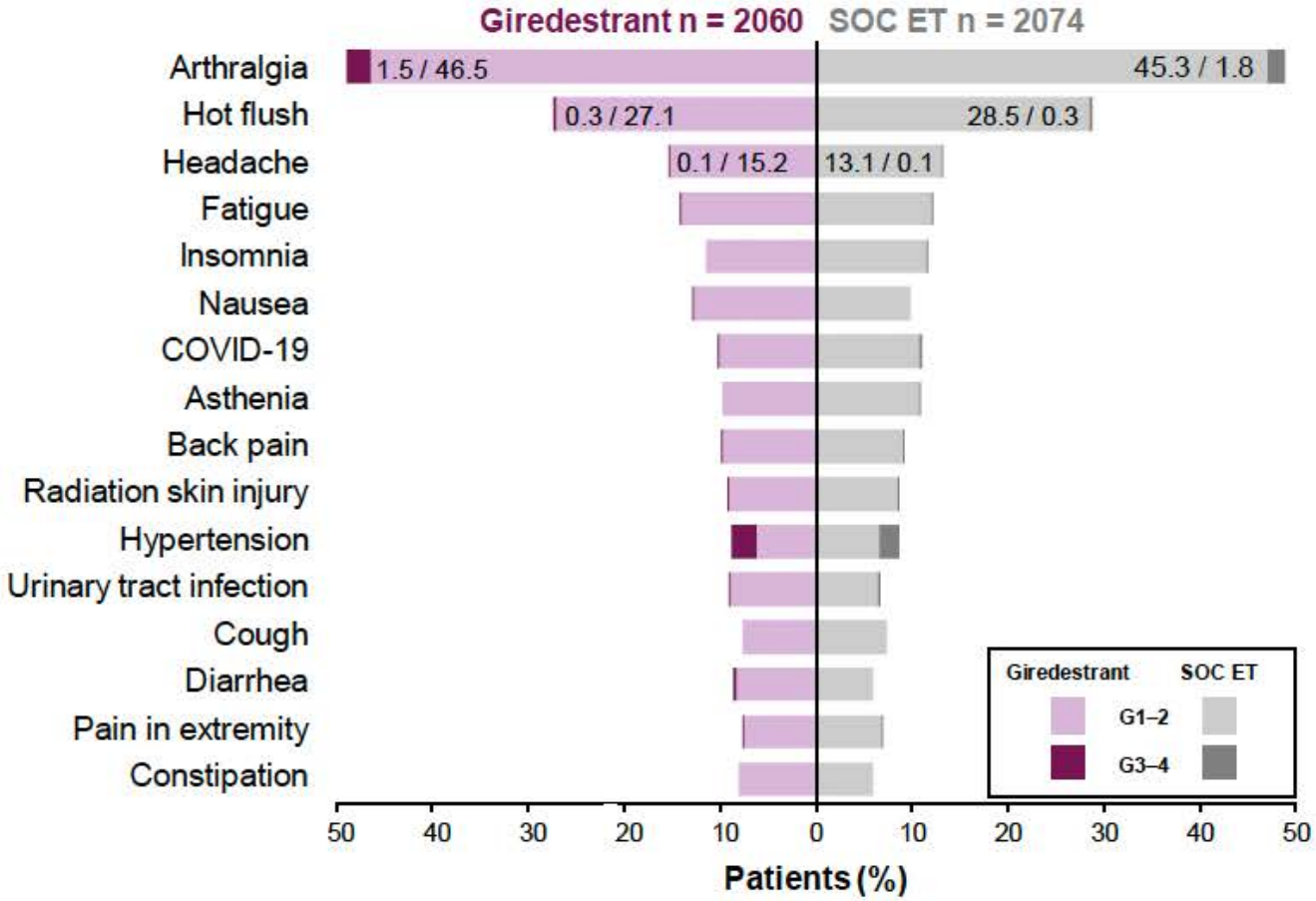
lidERA Breast Cancer: Safety Profile

Common TEAEs (≥ 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		
Patients, n (%) with selected AEs by medical concept*						
	G1	**G2**	**G3–4**	**G1**	**G2**	**G3–4**
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)

Bardia A et al. San Antonio Breast Cancer Symposium 2025;Abstract GS1-10.

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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

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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	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 Mouabbi	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

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

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Questions?

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