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

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Disclosures

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

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Drug Discovery, Delivery and Experimental Therapeutics Program
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PROJECT CHAIR
Neil Love, MD
Research To Practice
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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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- 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.

RTP RESEARCH TO PRACTICE

Key Datasets

- 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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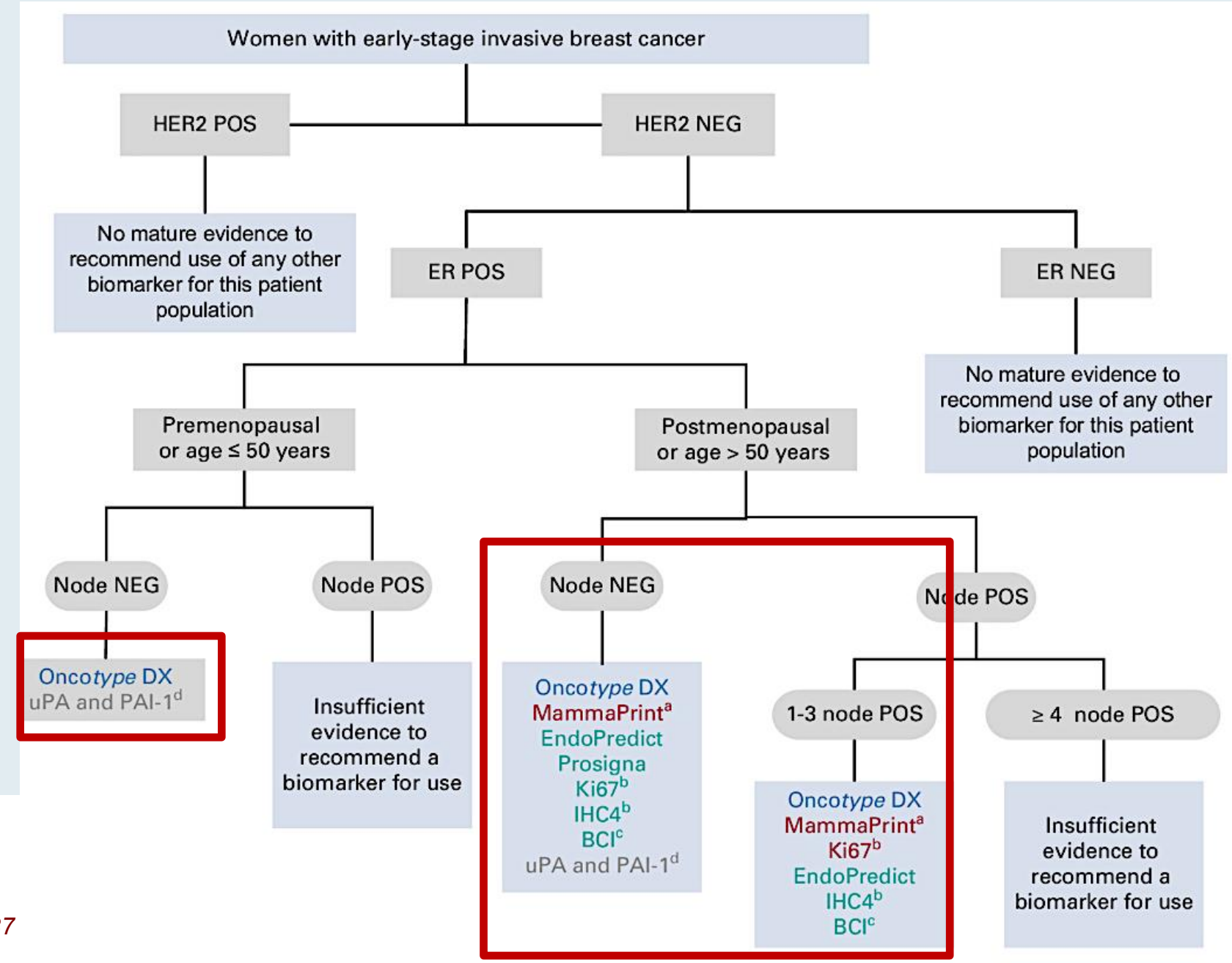
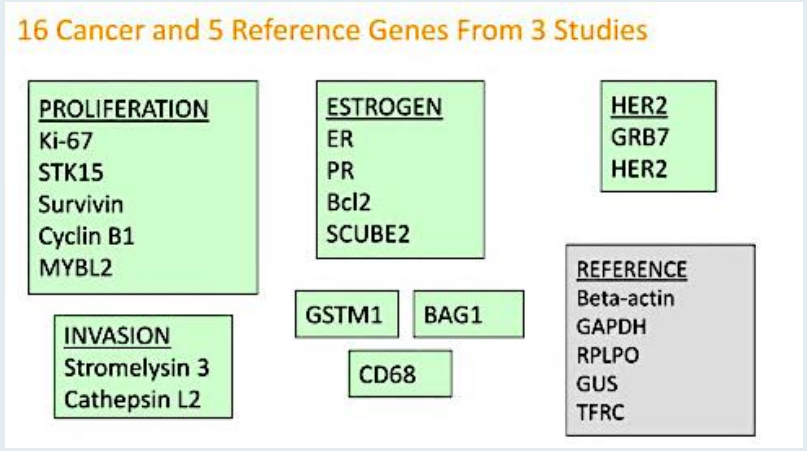
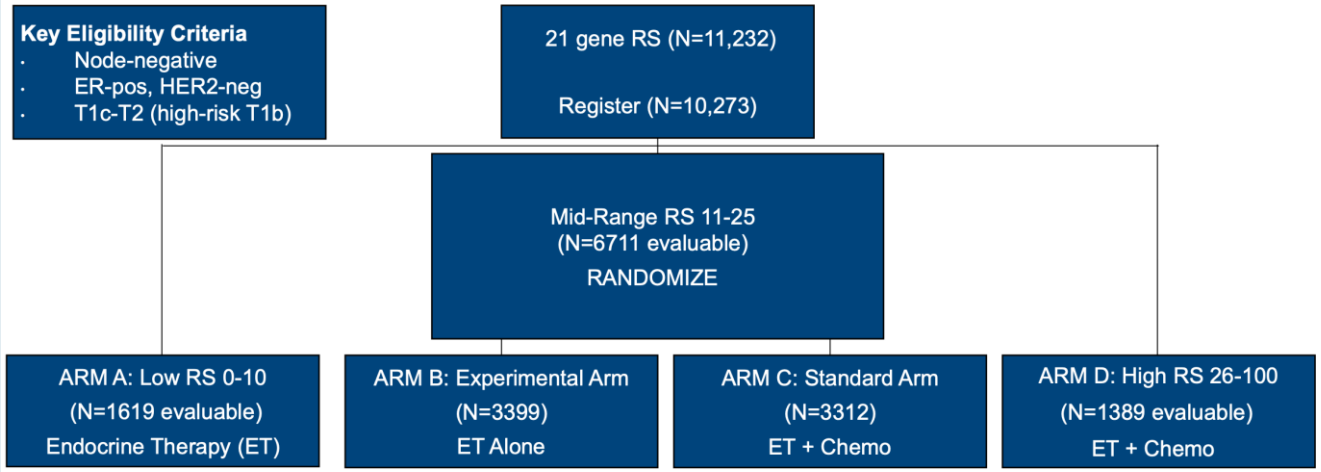


Andre F et al. J Clin Oncol. 2022;40:1816-1837

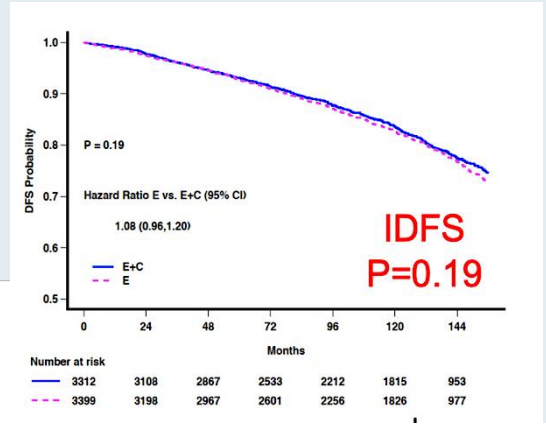
Oncotype DX®: TAILORx Key Results (Node-negative)

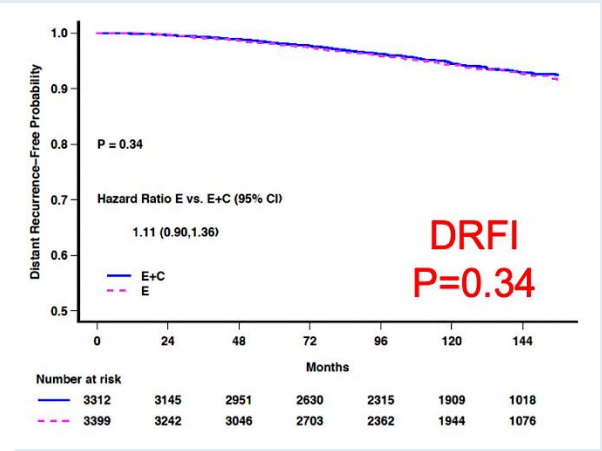


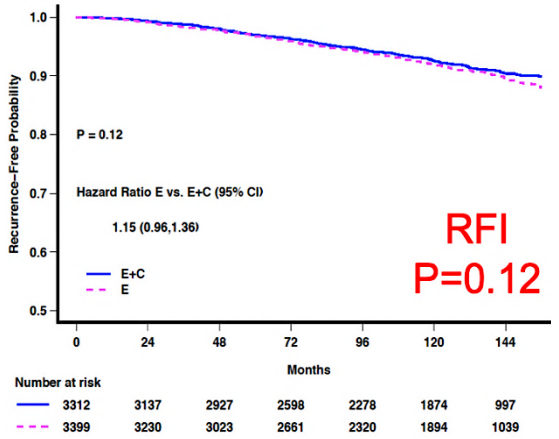
TAILORx Trial Design

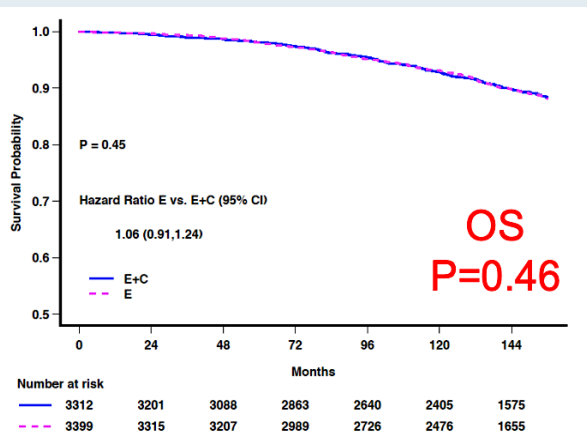


Intermediate risk (11-25): No overall benefit to chemotherapy (2022 update)





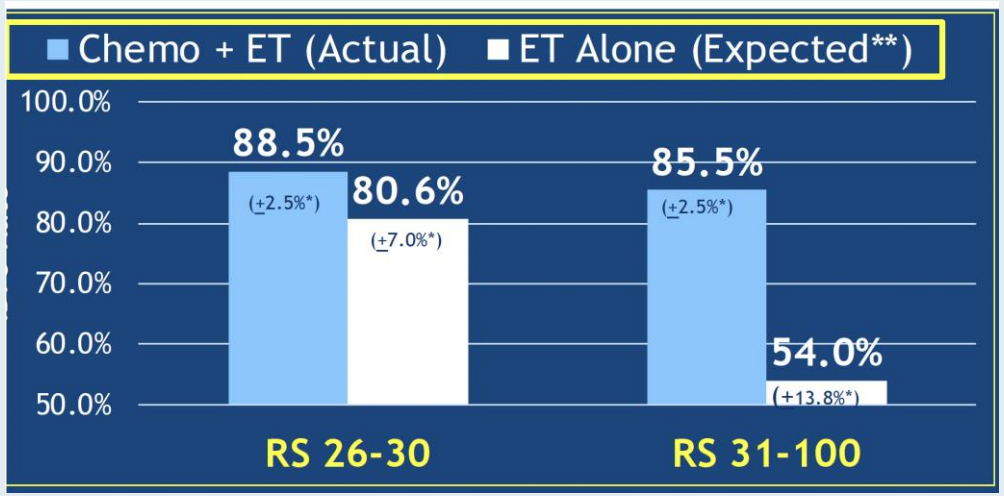




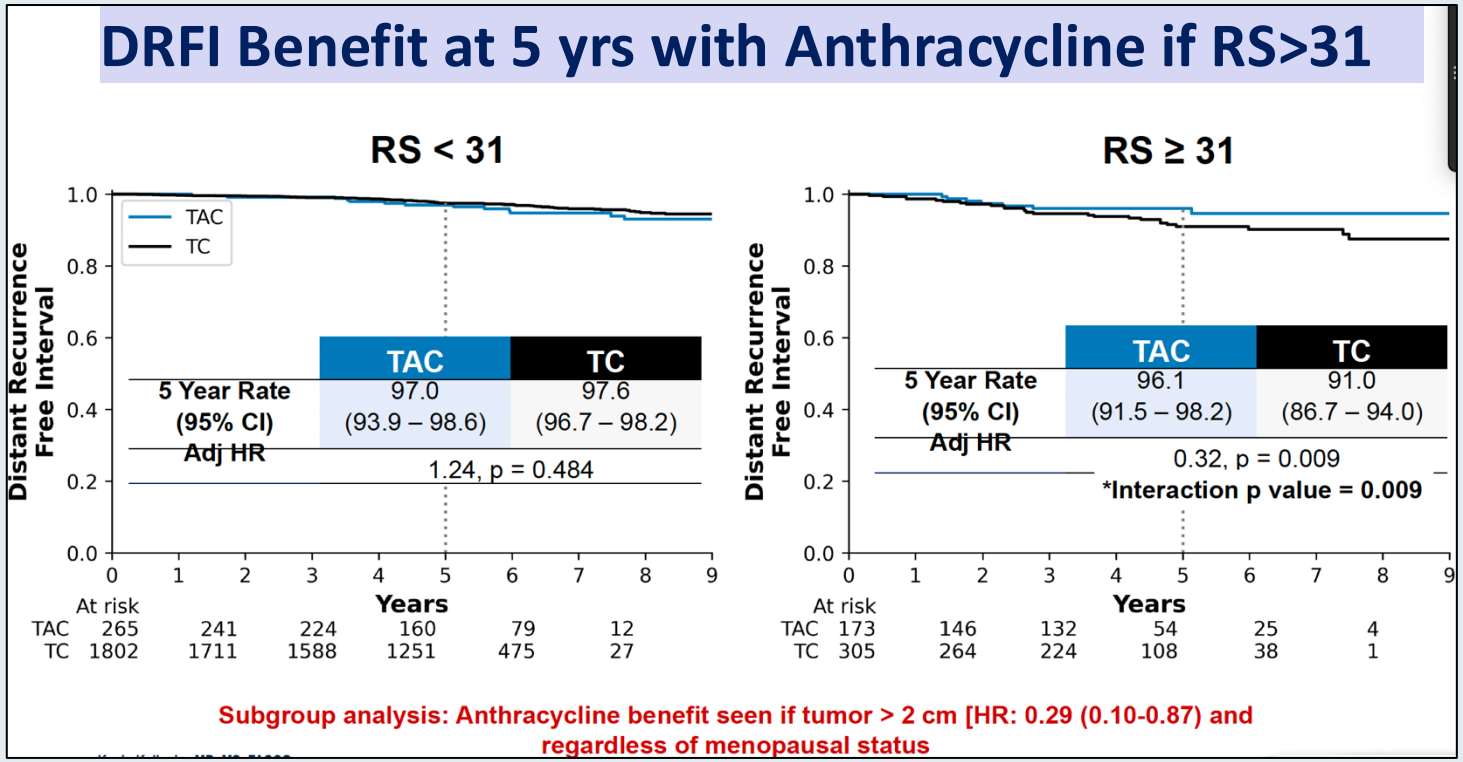
Sparano JA et al. SABCS 2022; Abstract GS1-05.

Chemotherapy and Anthracycline Benefits for Patients with High RS (>25) Tumors

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



DRFI Benefit at 5 yrs with Anthracycline if RS>31



Subgroup analysis: Anthracycline benefit seen if tumor > 2 cm [HR: 0.29 (0.10-0.87) and regardless of menopausal status

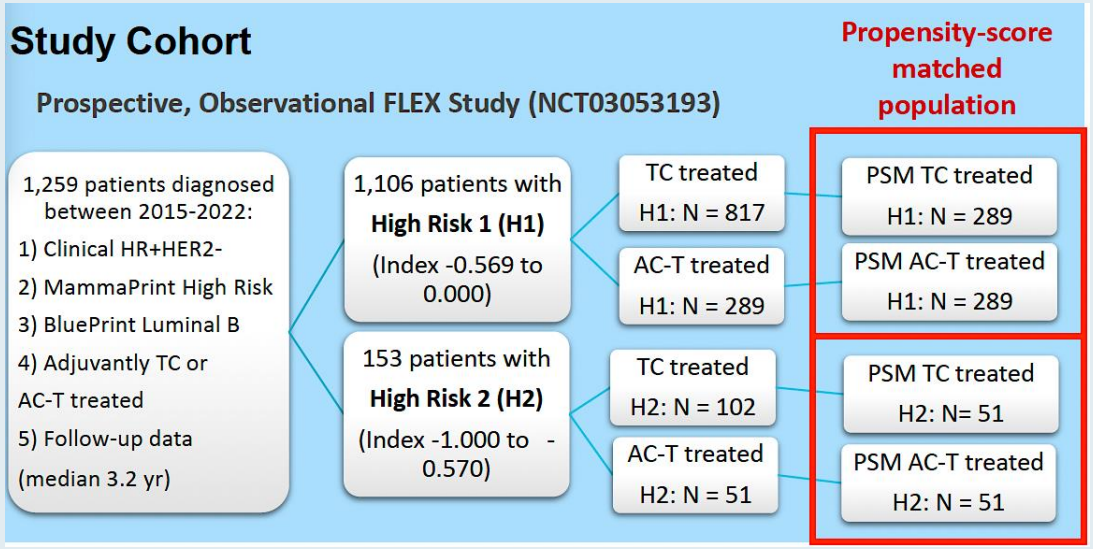
"No chemotherapy" rates estimated by combining

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

N=2549 TAILORx patients. 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

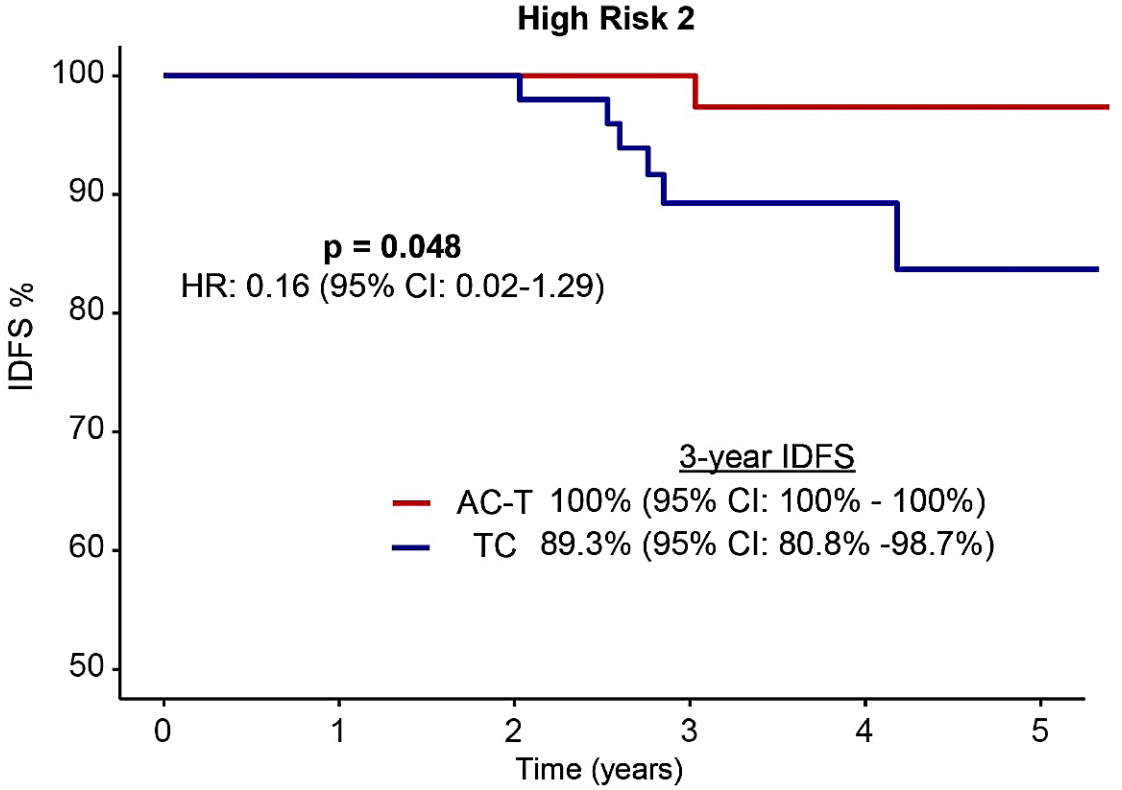


Conclusions

- 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.

OncotypeDX: RxPONDER Results Summary (1-3 LN+)

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

Recurrence Score > 25

Off Study
Chemotherapy Followed by Endocrine Therapy Recommended

RANDOMIZATION

N = 5,000 pts

Arm 1:
Chemotherapy Followed by Endocrine Therapy

Arm 2:
Endocrine Therapy Alone

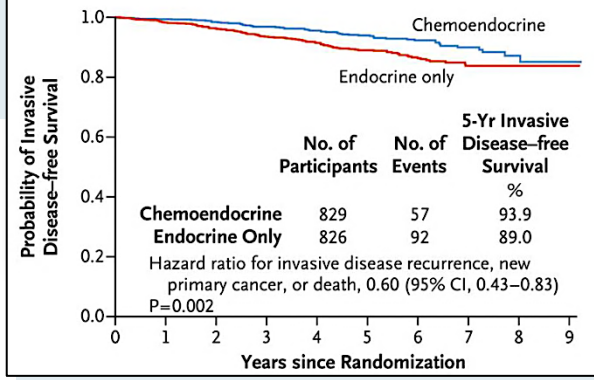
Stratification Factors
Recurrence Score: 0-13 vs.14-25
Menopausal Status: pre vs. post
Axillary Surgery: ALND vs. SLNB

RxPONDER Population

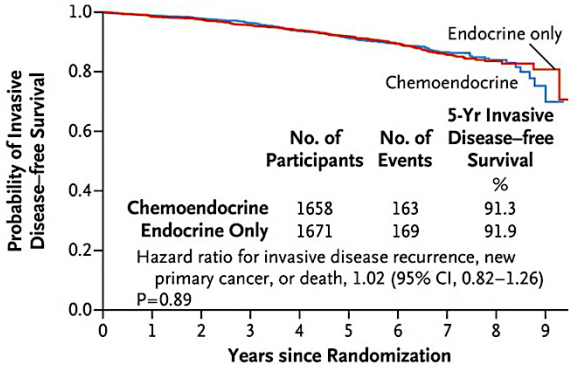
T1	58%	T3	5%
1 LN+	66%	3 LN+	9%
Grade 2	64%	Grade 3	10%
40-49 yrs	21%	< 40 yrs	3%

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

Premenopausal (1/3rd Trial)



Postmenopausal (2/3rd Trial)



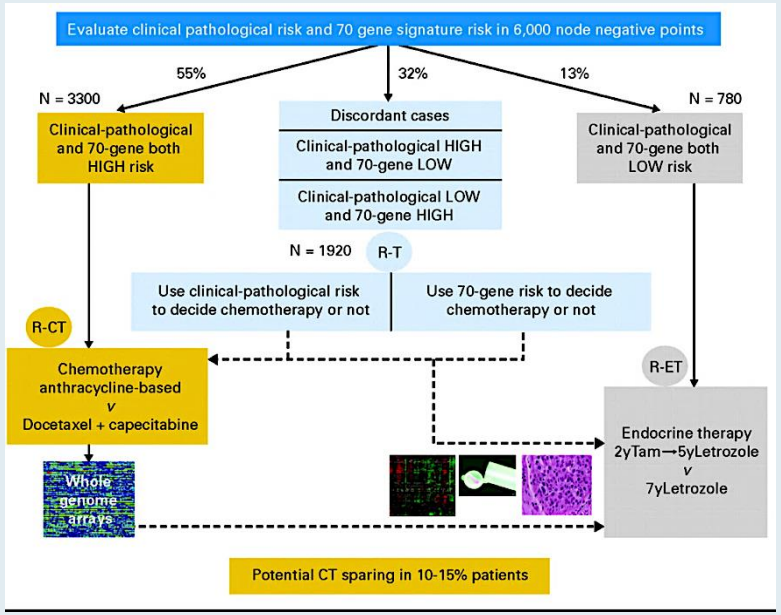
iDFS Benefit Modified by Score in Women ≤ Age 50

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	

Kalinsky K et al. N Engl J Med 2021;385(25):2336-47.

MammaPrint: MindACT Key Results

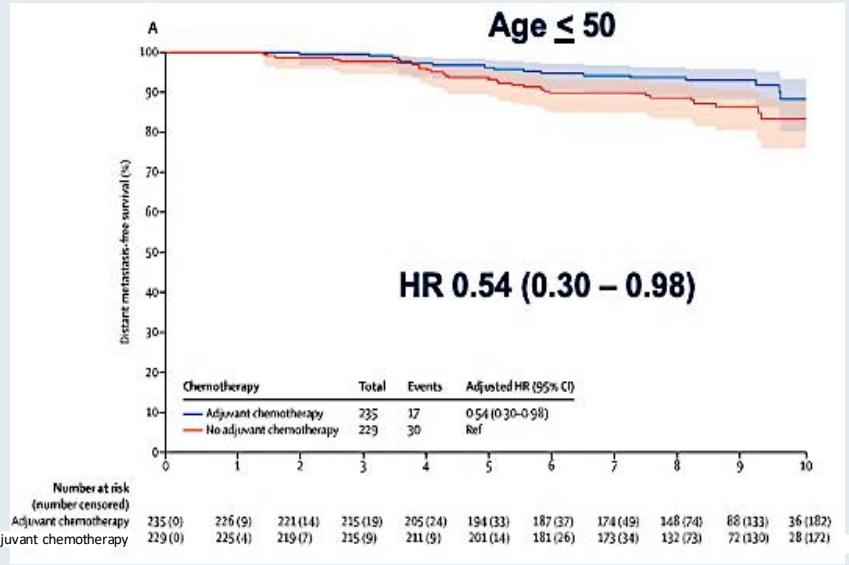
Clinical "high risk": <88% 10-yr BCSS
Modified Adjuvant Online to determine
Model included: T size, Node (0-3), grade, ER status, age, comorbidity

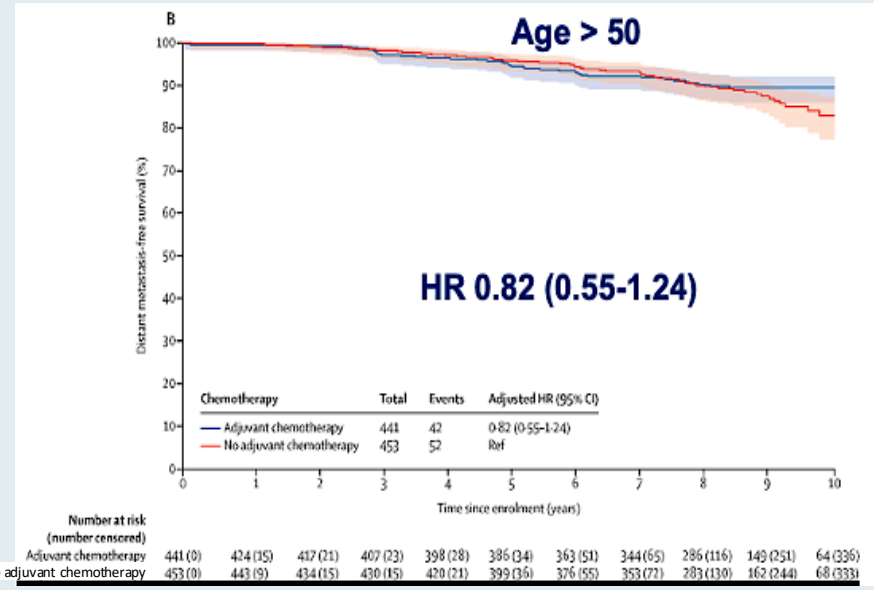


Met primary outcome: Lower bound of 95% CI >92% 5-y DMFS in the High Clinical/Low Genomic risk group

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%





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

PROSIGNA® ROR, ENDOPREDICT EPclin and Breast Cancer Index (BCI)

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

EPclin (EndoPredict®)
- 12-genes – Proliferation and hormone receptor

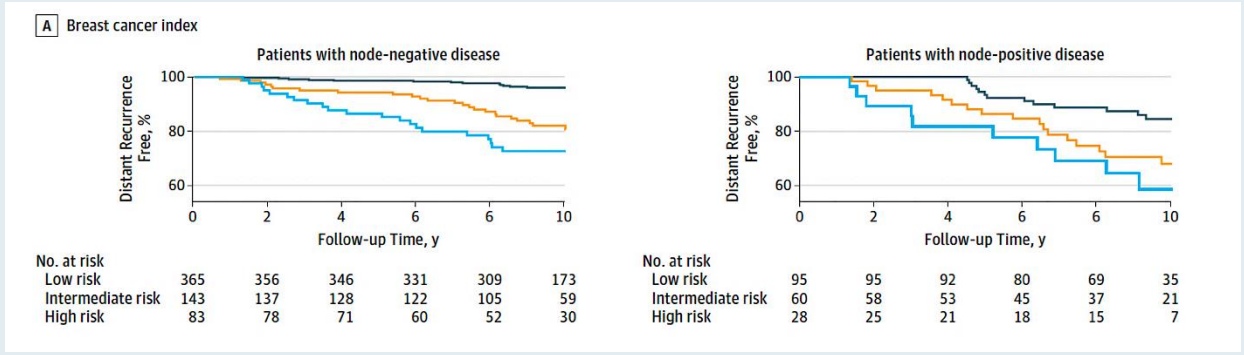
Breast Cancer Index® (BCI)
- 7-genes – Proliferation and hormone receptor (HoxB13/IL17BR)

JAMA Oncology | Original Investigation

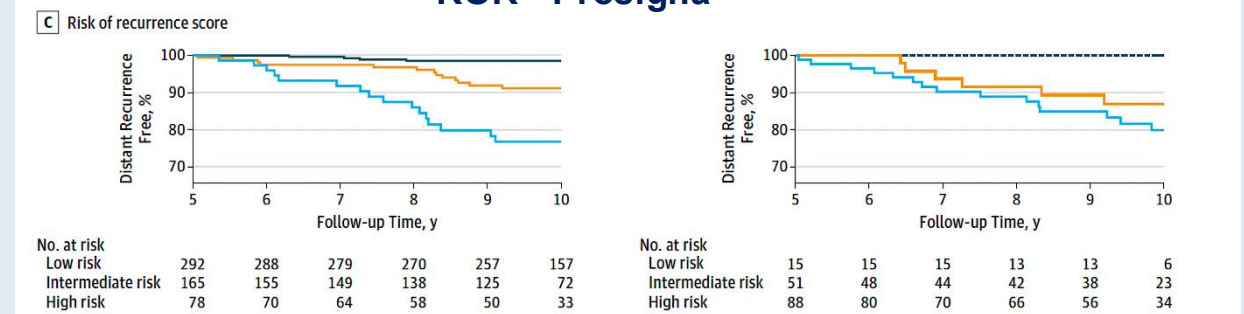
Comparison of the Performance of 6 Prognostic Signatures for Estrogen Receptor–Positive Breast Cancer
A Secondary Analysis of a Randomized Clinical Trial

- Largest retrospective prognostic validation in TRANS-ATAC Trial (included Onco*type* DX and BCI as well)
- N=535 node-negative, 154 node-positive
- Examined risk years 0-10
- 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

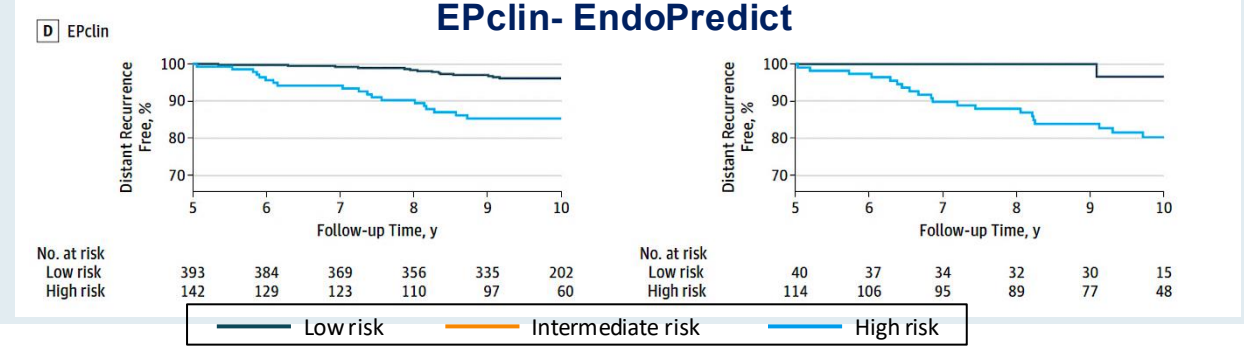
BCI



ROR - Prosigna



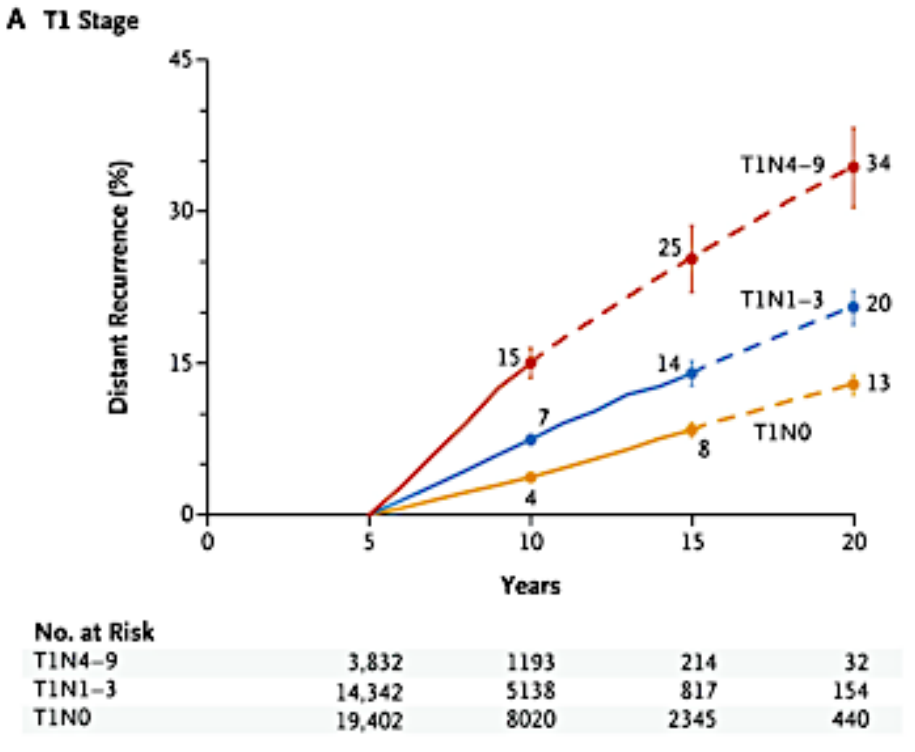
EPclin- EndoPredict



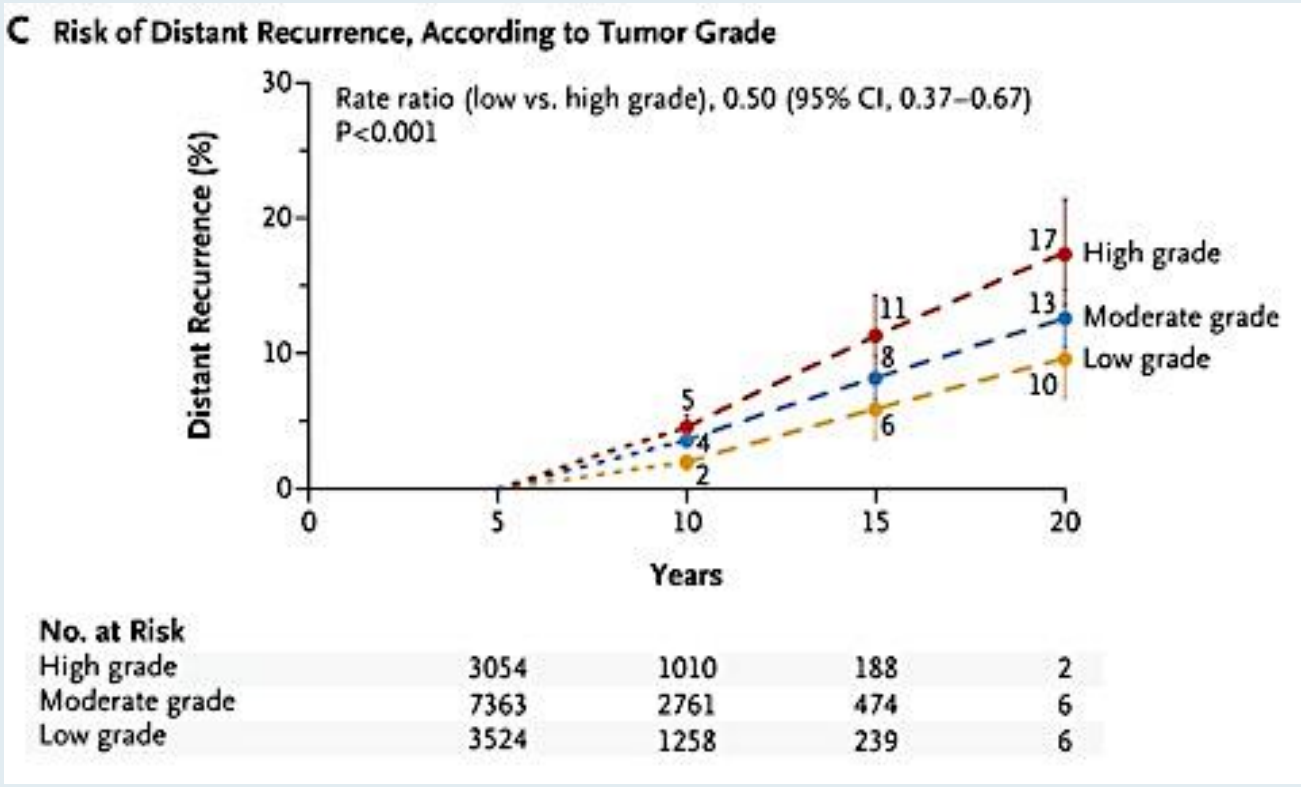
Sestak I et al. JAMA Oncol. 2018;4(4):545-53.

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

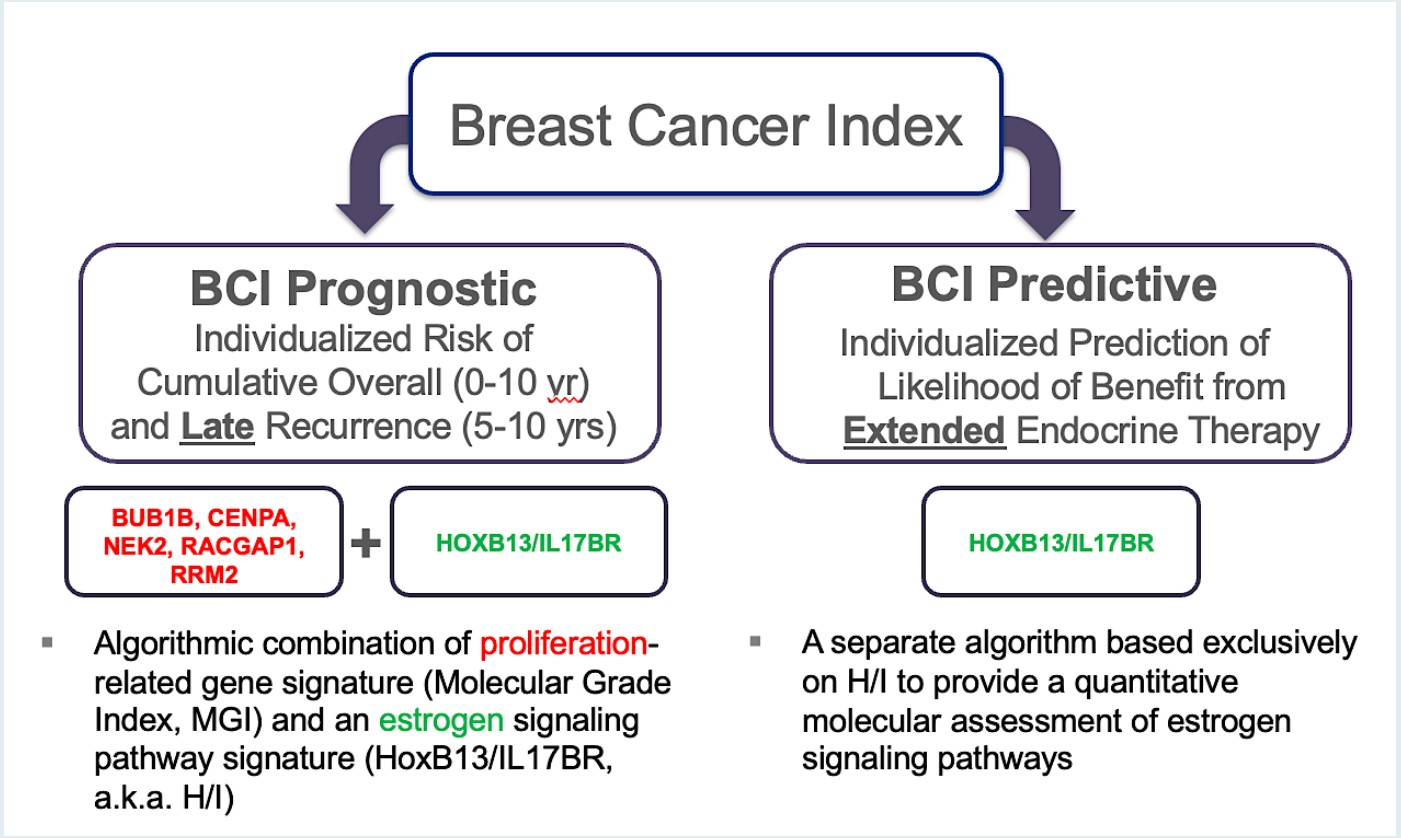


No. at Risk				
High grade	3054	1010	188	2
Moderate grade	7363	2761	474	6
Low grade	3524	1258	239	6

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

Breast Cancer Index

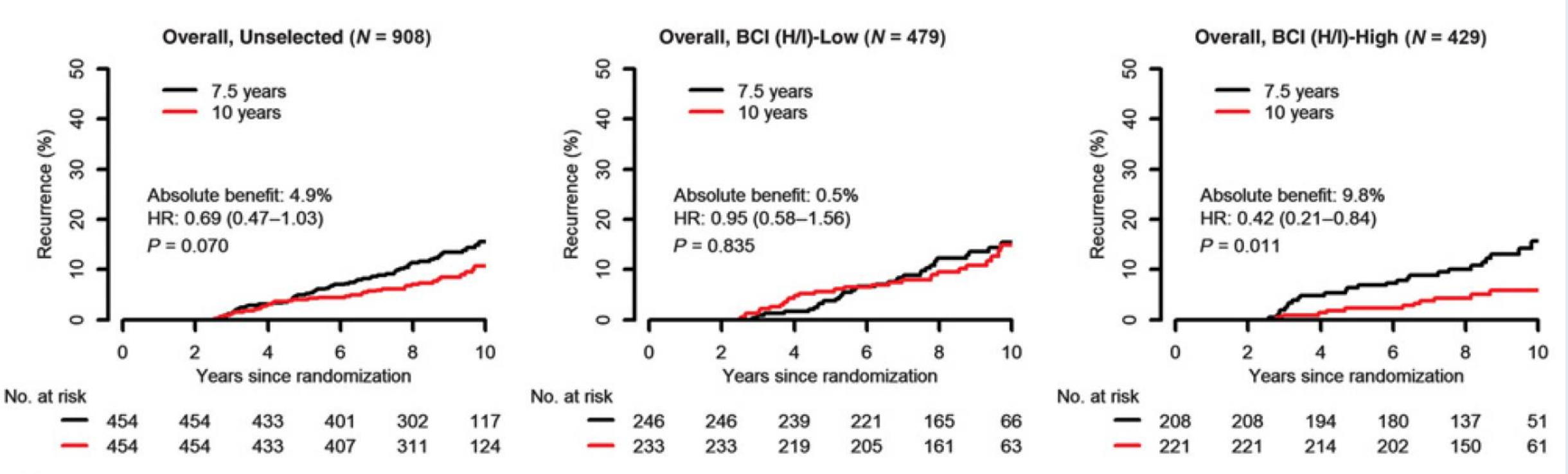
BCI Components



Distribution of BCI scores

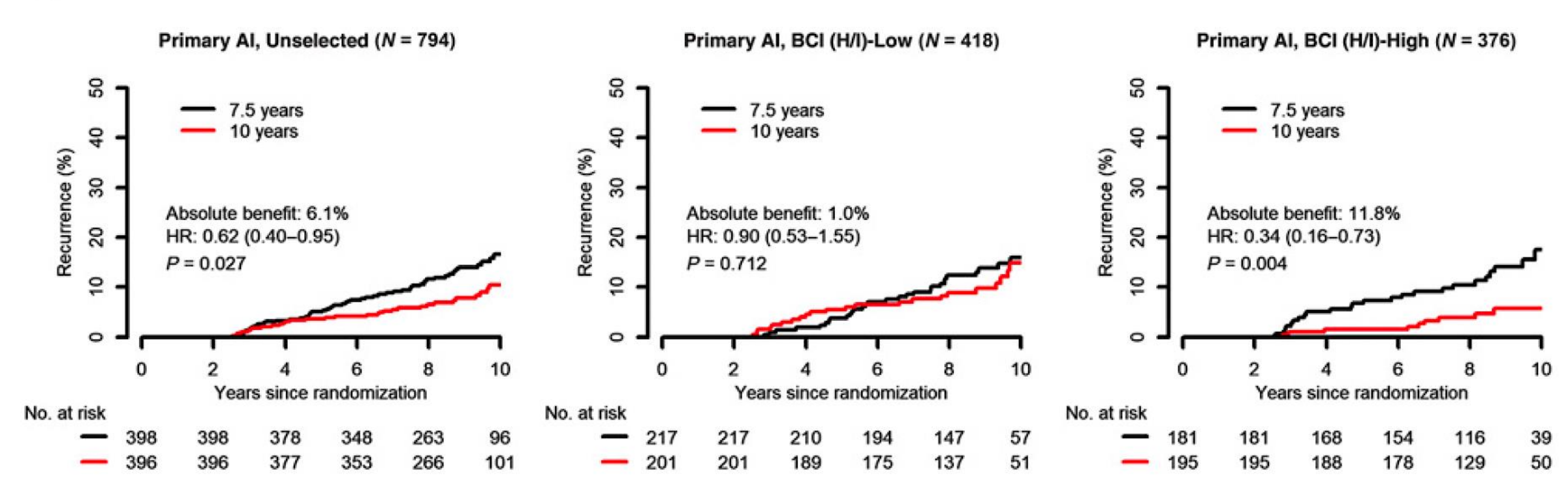
Sgroi DC et al. J Natl Cancer Inst 2013;105(14):1036-42.

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



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

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.

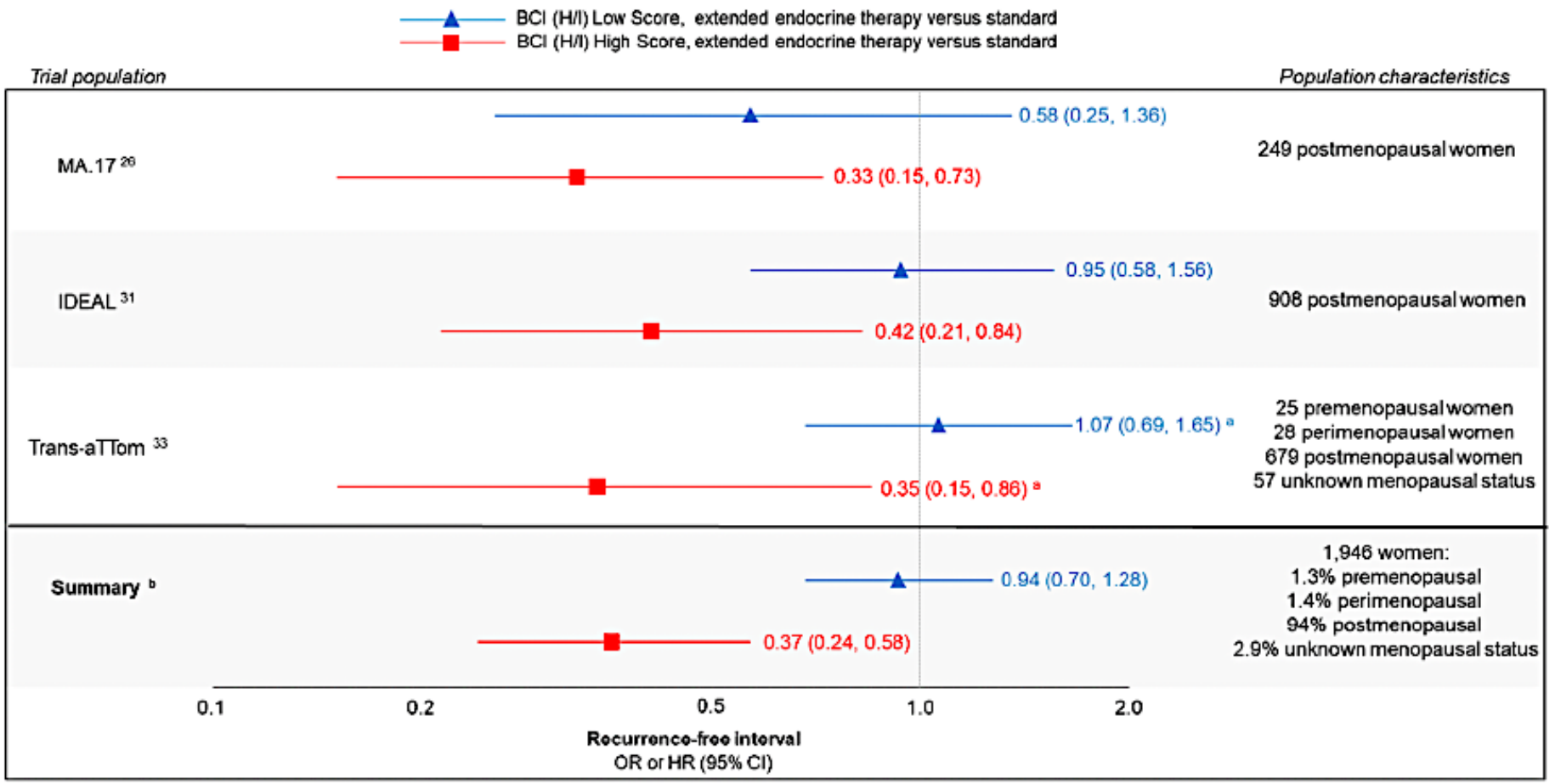
Risk of Recurrence at Year 10 Since Randomization for Patients Who Received 5 Years versus 2.5 Years of Additional Letrozole in the Overall Cohort and in the Primary AI Subset of the Phase III IDEAL Trial

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.

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

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 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).

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	Oncotype DX (*high/strong*)	Oncotype 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	Oncotype 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	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

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 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

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 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

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 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

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 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

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 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

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Module 6: Clinician Survey Results

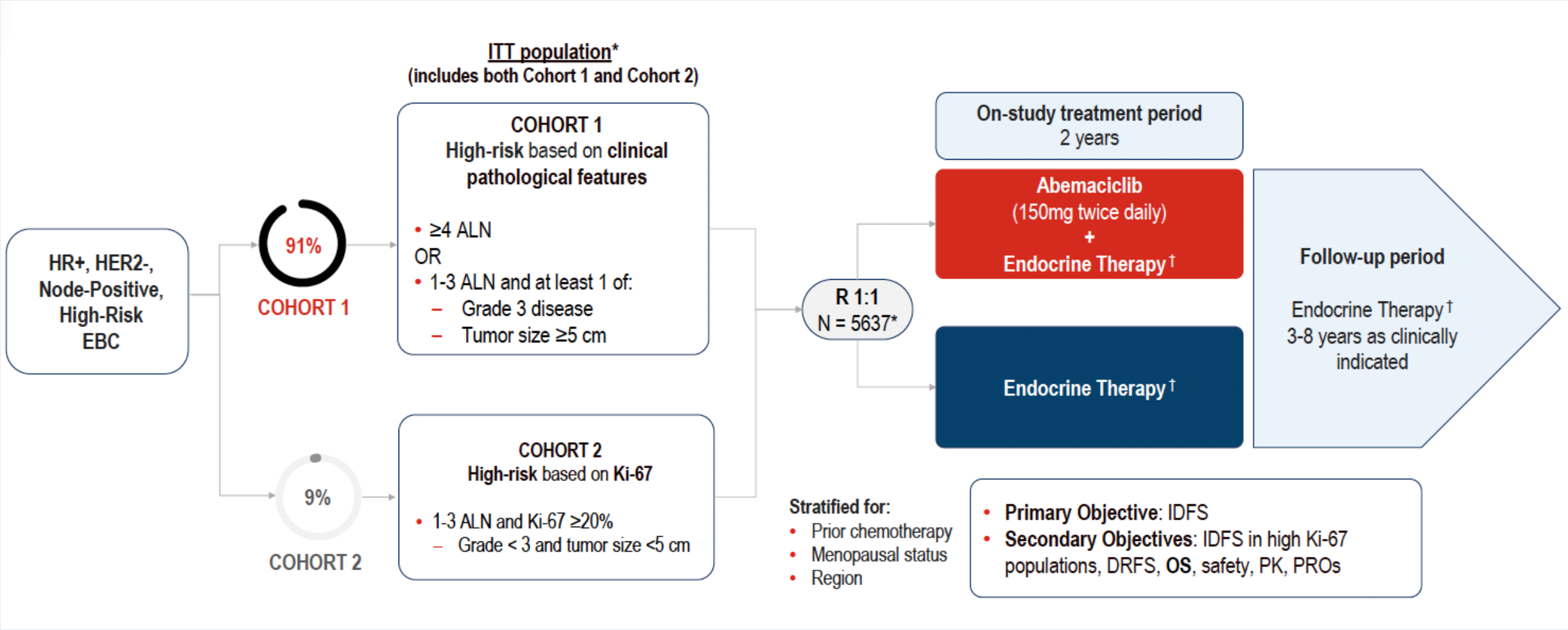
Module 7: Adjuvant Oral SERDs for HR-Positive, HER2-Negative Localized Breast Cancer

RTP
RESEARCH TO PRACTICE

Key Datasets

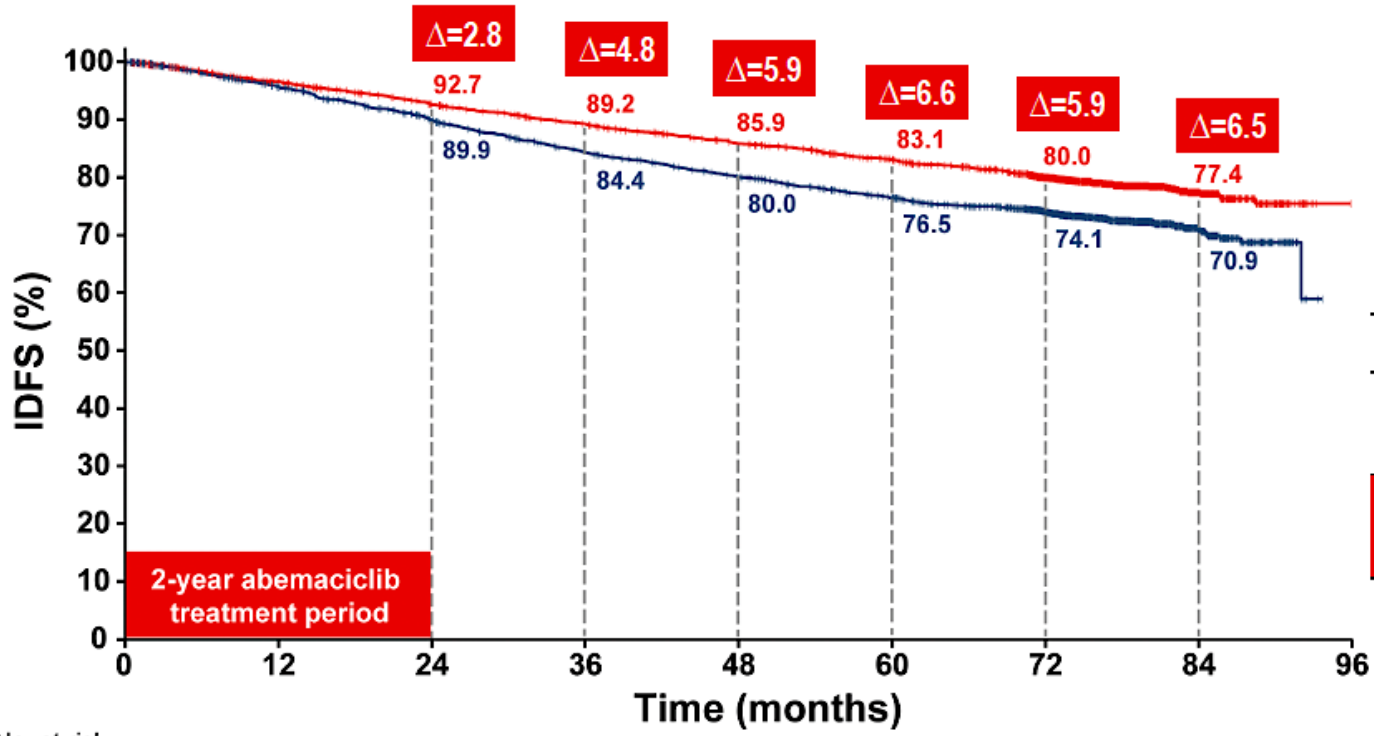
- Johnston S et al. **monarchE**: **Primary overall survival** (OS) results of adjuvant abemaciclib + endocrine therapy (ET) for HR+, HER2-, high-risk early breast cancer (EBC). ESMO 2025;Abstract LBA13.
- Johnston S et al. **Overall survival** with **abemaciclib** in early breast cancer. *Ann Oncol* 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



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

monarchE: Invasive Disease-Free Survival (IDFS) Outcomes



Number of IDFS events	
Abemaciclib + ET	ET
547	722

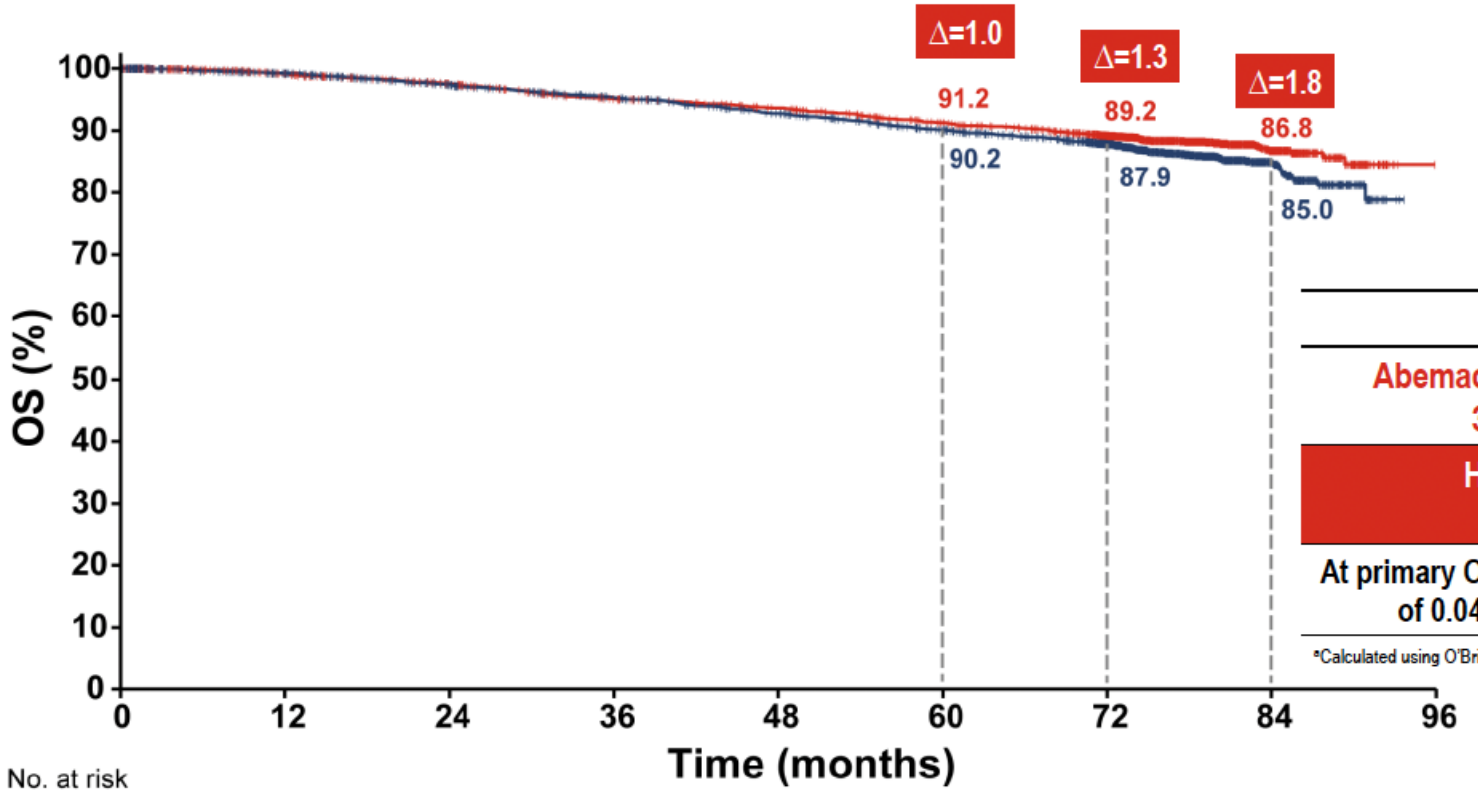
HR (95% CI): 0.734 (0.657, 0.820)
Nominal *P*<.0001

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.

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

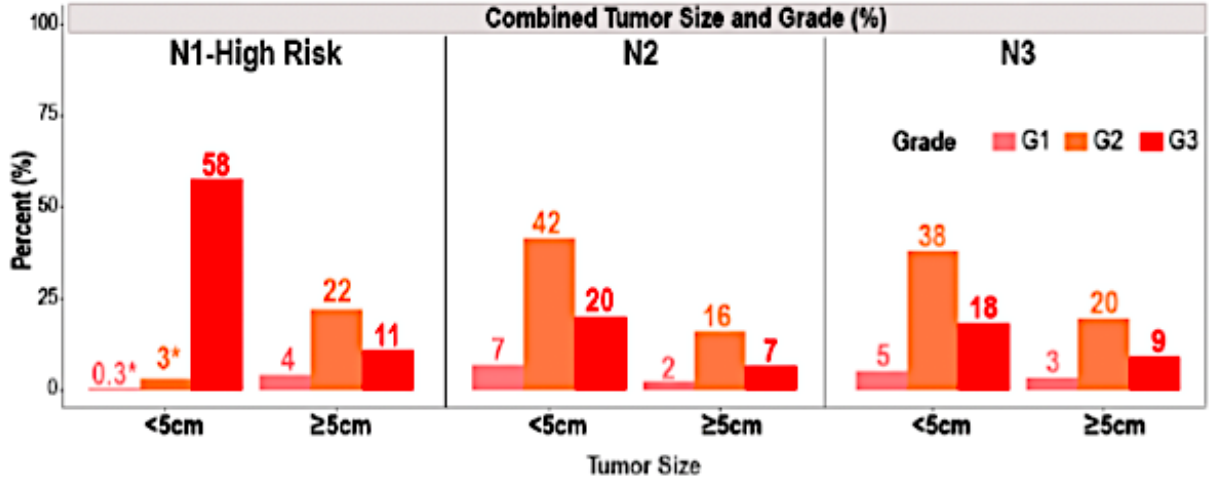
At a median follow-up of 6.3 years, abemaciclib + ET reduced the risk of death by 15.8% compared to ET alone

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

monarchE: Subgroup Analysis by Nodal Status

Tumor Characteristics in Cohort 1

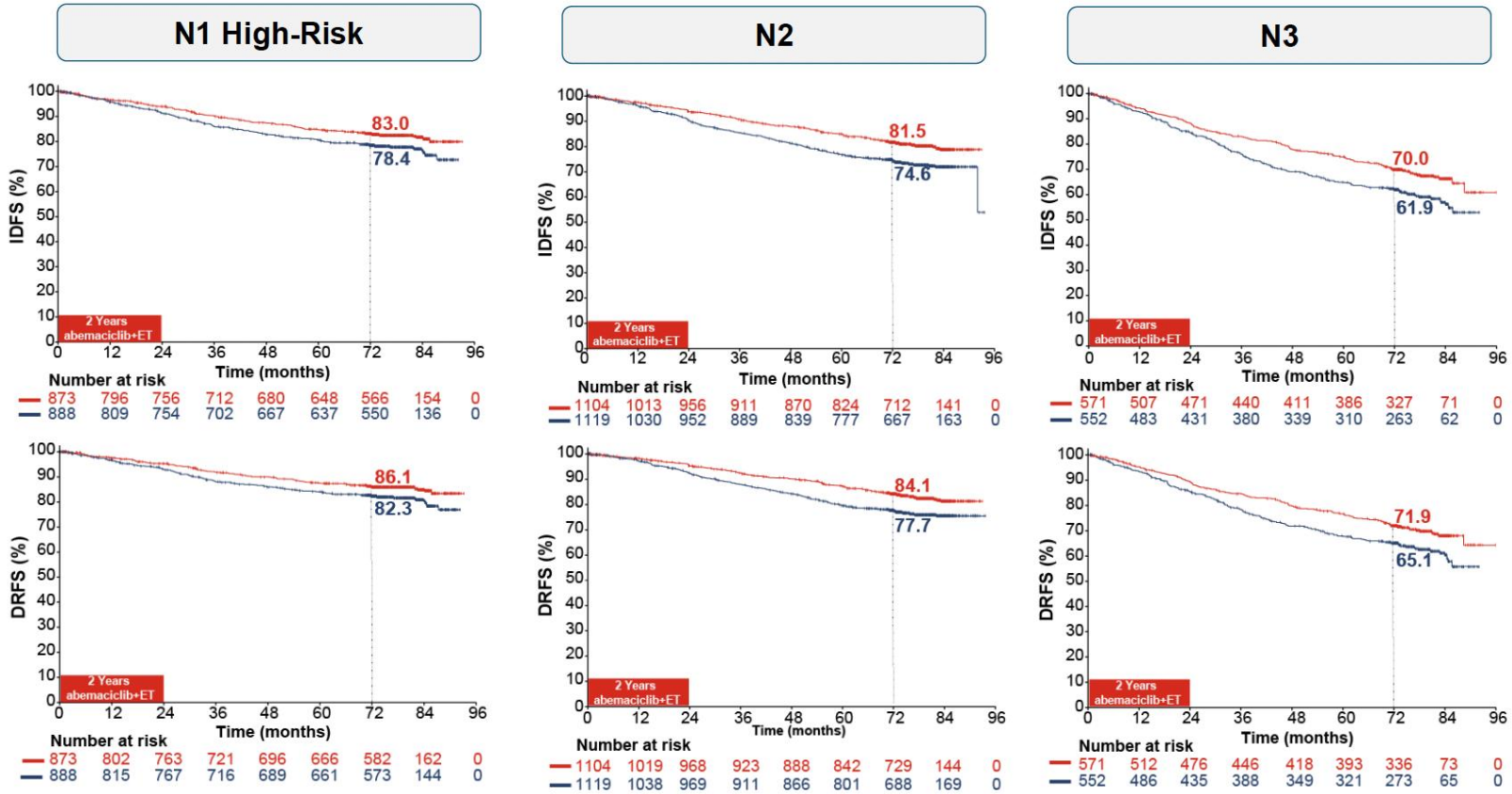
	N1-High Risk	N2	N3
Ki-67 (%)			
<20%	29	43	41
≥20%	49	33	36
Missing	23	24	24
Histology (%)			
Lobular	11	13	20
Ductal	72	68	62
Other	17	20	18



- 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.

monarchE: IDFS and DRFS by Nodal Status

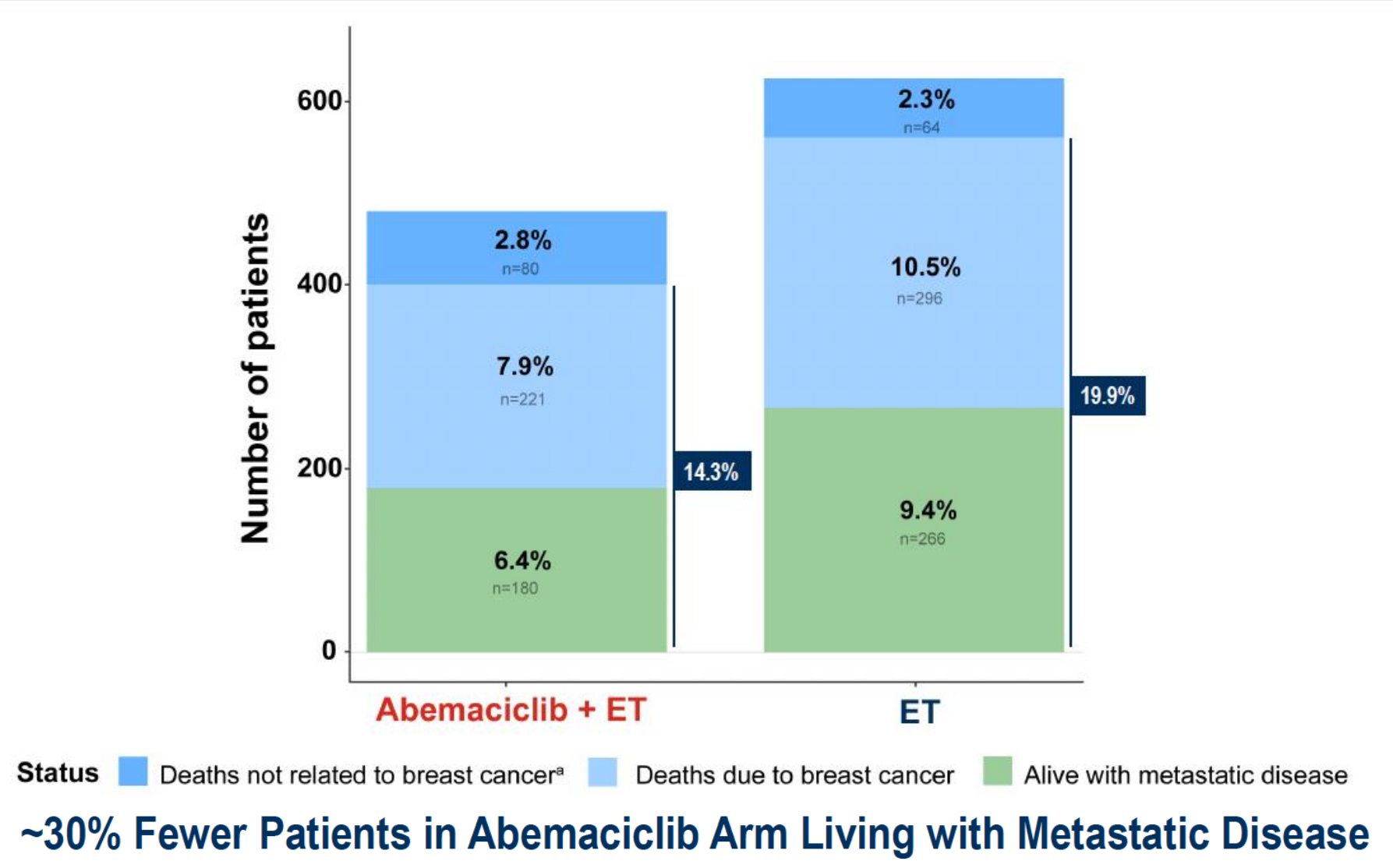


- In the ET alone arm, patients with N1-High risk and N2 disease had comparable risk of recurrence and death, while higher risk was observed in N3 subgroup
- Abemaciclib plus ET reduced the risk of IDFS events by 24.8% (N1), 31.5% (N2) and 27.4% (N3), compared to ET

DRFS = distant relapse-free survival

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

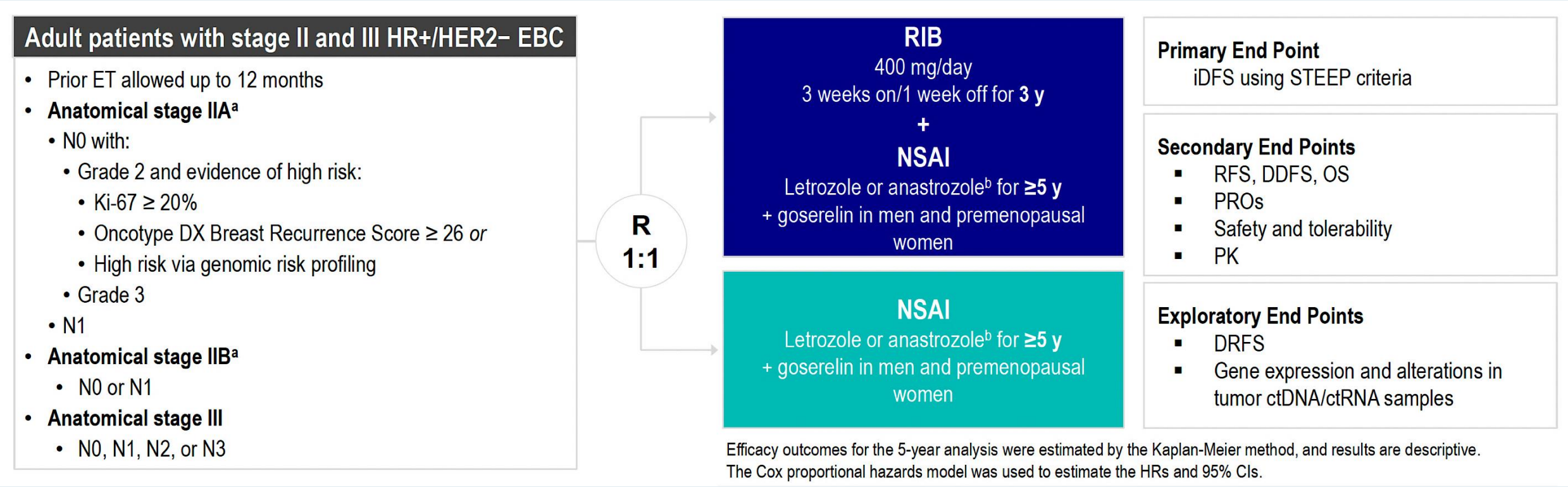
monarchE: Survival Status



~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.

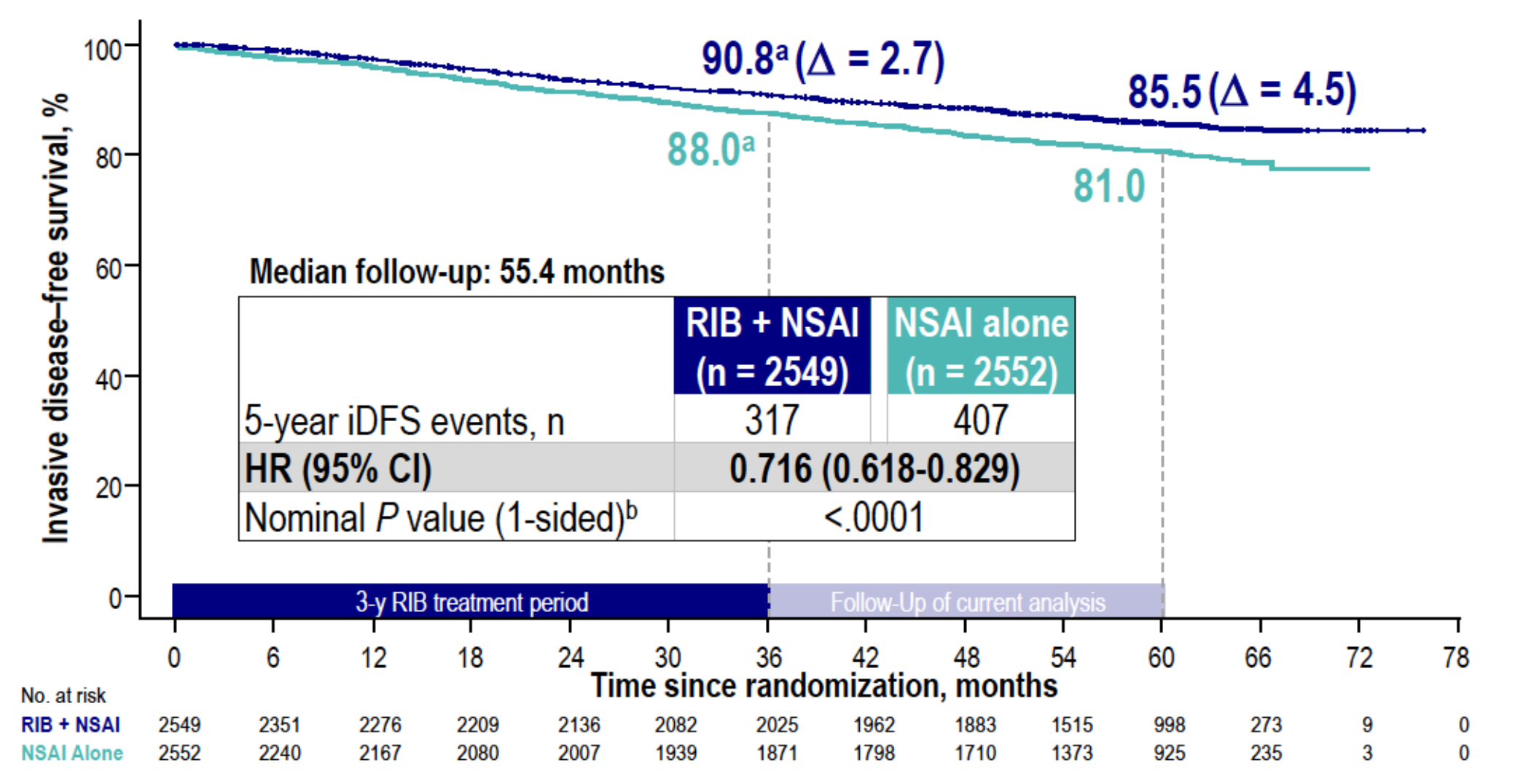
NATALEE Study Design



RIB = ribociclib; NSAI = nonsteroidal aromatase inhibitor

Crown JP et al. ESMO 2025;Abstract LBA14.

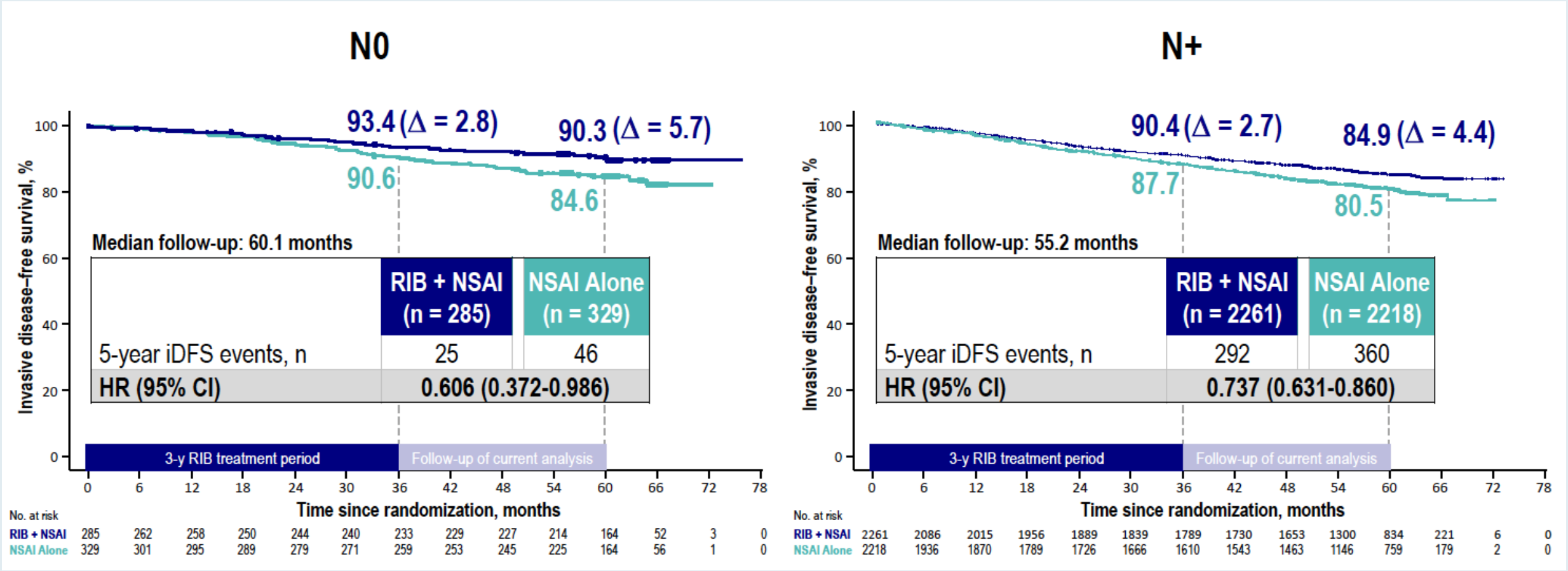
NATALEE: IDFS Outcomes



NSAI = nonsteroidal aromatase inhibitor

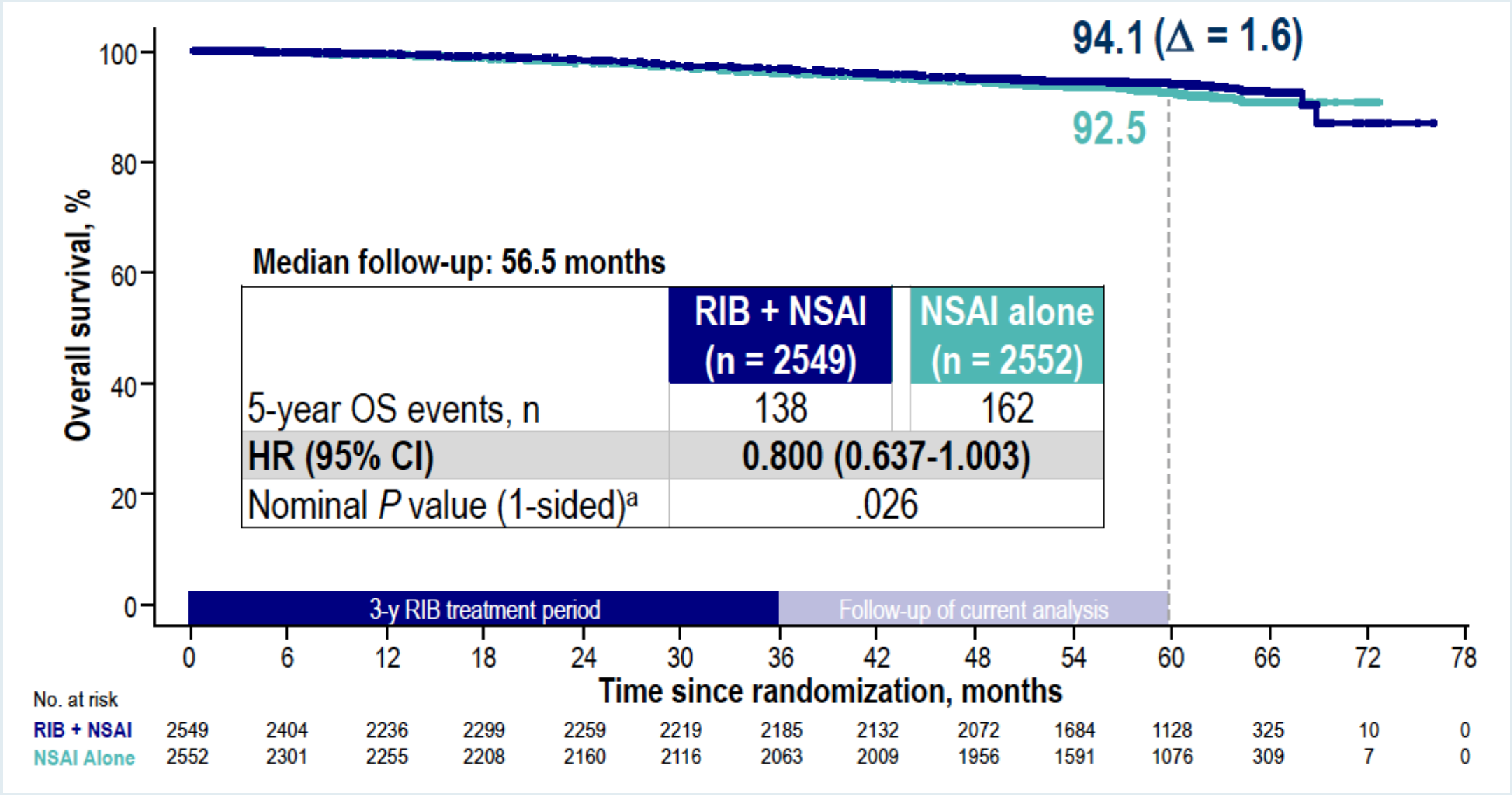
Crown JP et al. ESMO 2025;Abstract LBA14.

NATALEE: IDFS by Nodal Status



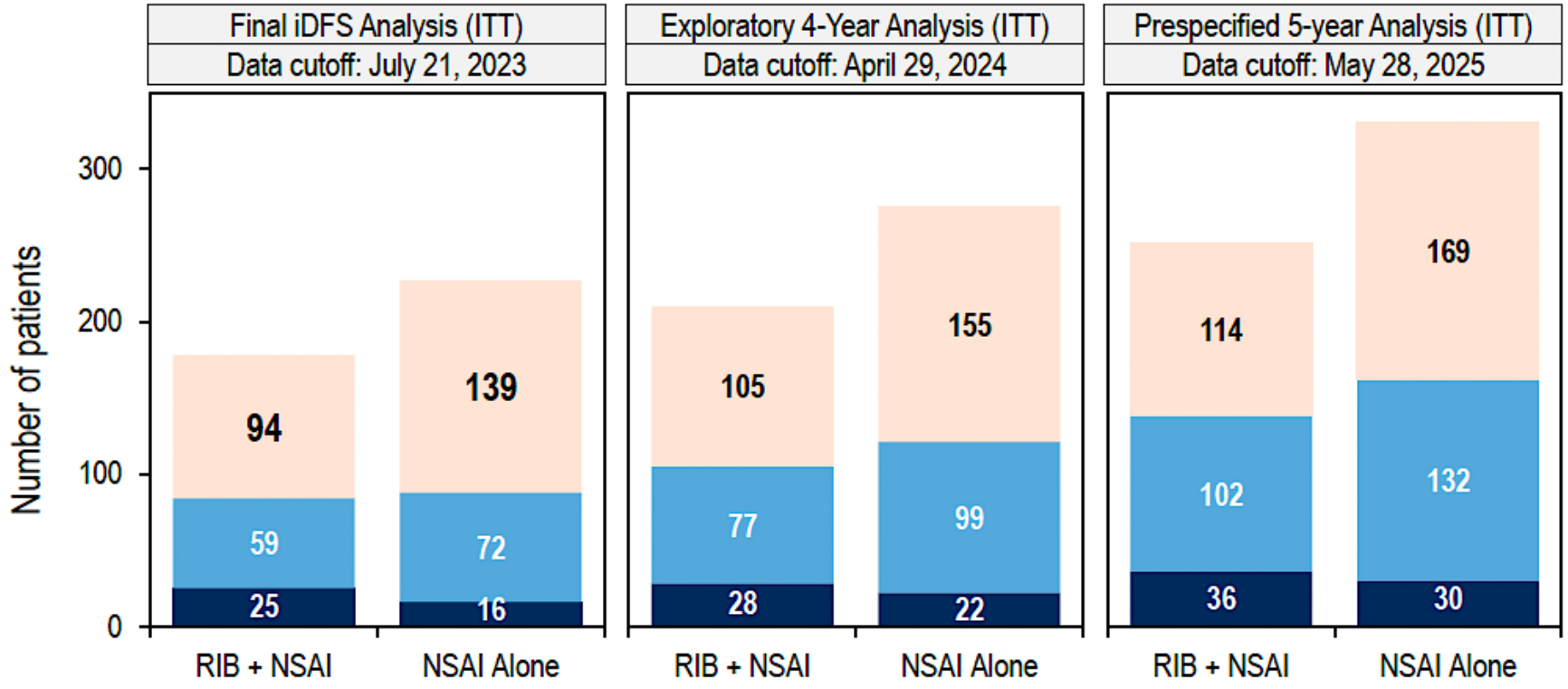
Crown JP et al. ESMO 2025;Abstract LBA14.

NATALEE: OS Outcomes



Crown JP et al. ESMO 2025;Abstract LBA14.

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.

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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 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

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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.

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

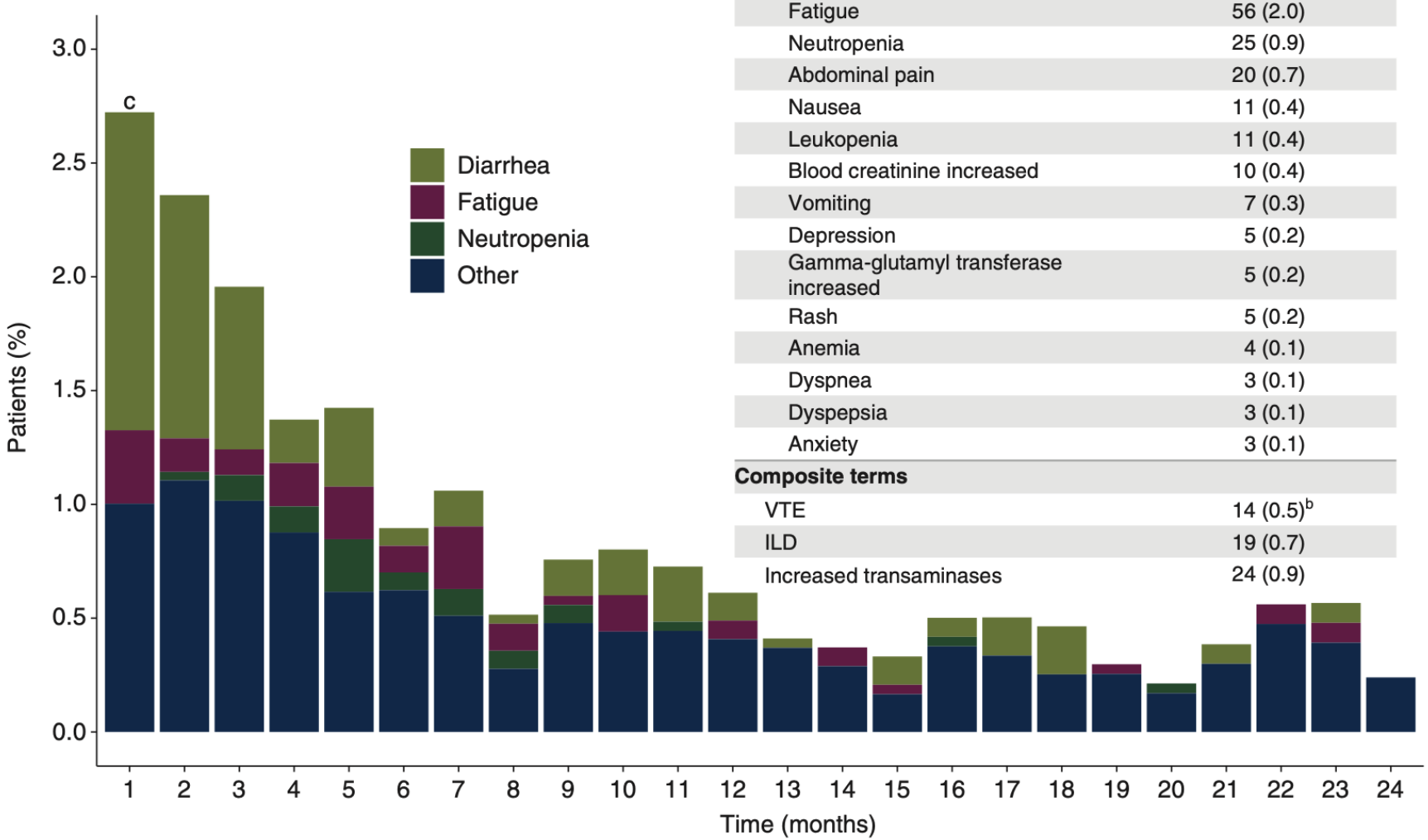
	Abemaciclib + ET N=2791, n (%)		ET N=2800, n (%)	
	On Therapy[a]	Post-Discontinuation[b]	On Therapy[a]	Post-Discontinuation[b]
≥1 SAE* LTFU, regardless of causality	**NA**	**197 (7.5)**	**NA**	**213 (8.1)**
Deaths due to AE by SOC and PT[c]	**15 (0.5)**	**44 (1.6)**	**11 (0.4)**	**30 (1.1)**
Infections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

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

monarchE: AEs Leading to Discontinuation

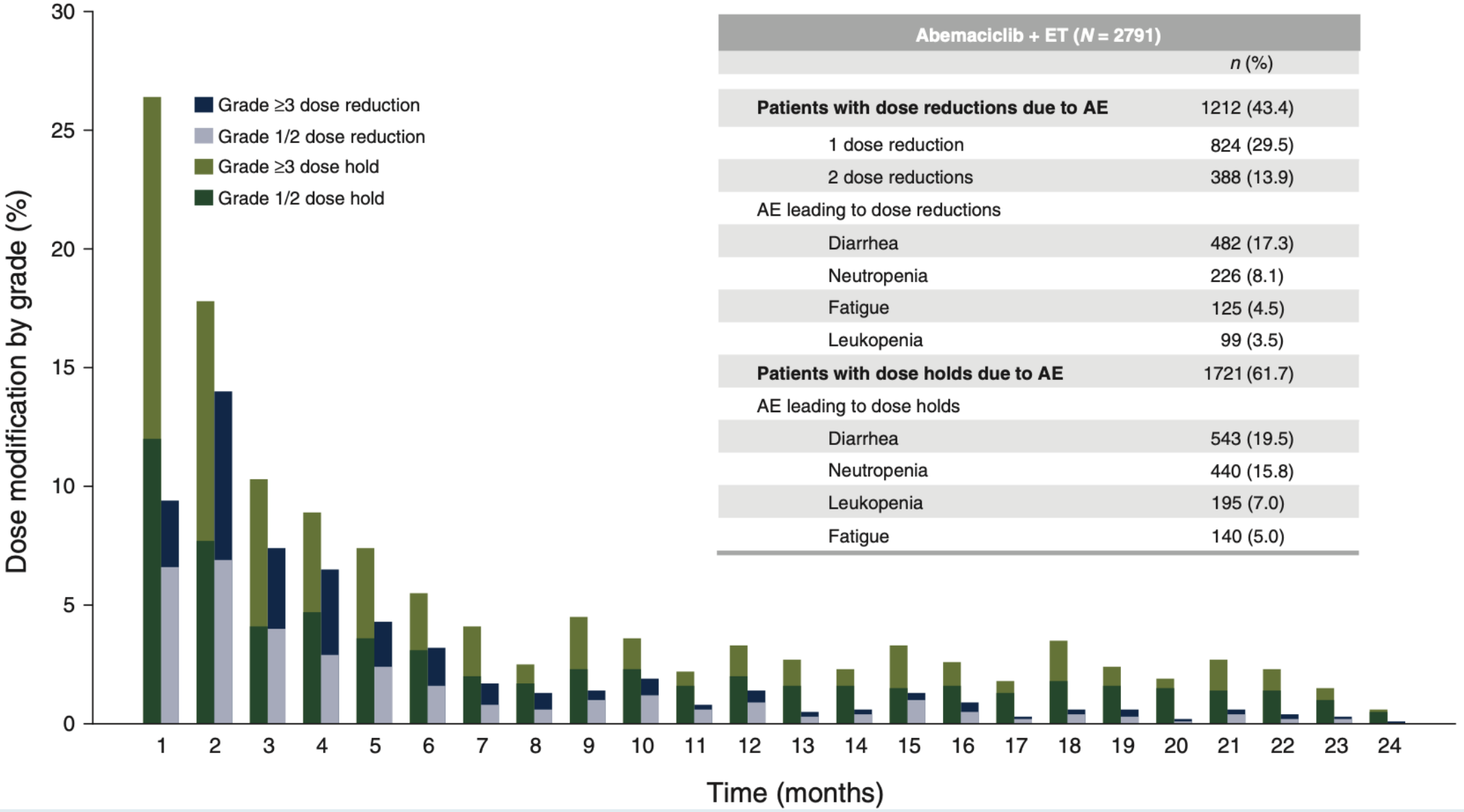


Abemaciclib + ET (*N* = 2791)	
AEs leading to discontinuation	***n* (%)**
Diarrhea	147 (5.3)
Fatigue	56 (2.0)
Neutropenia	25 (0.9)
Abdominal pain	20 (0.7)
Nausea	11 (0.4)
Leukopenia	11 (0.4)
Blood creatinine increased	10 (0.4)
Vomiting	7 (0.3)
Depression	5 (0.2)
Gamma-glutamyl transferase increased	5 (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

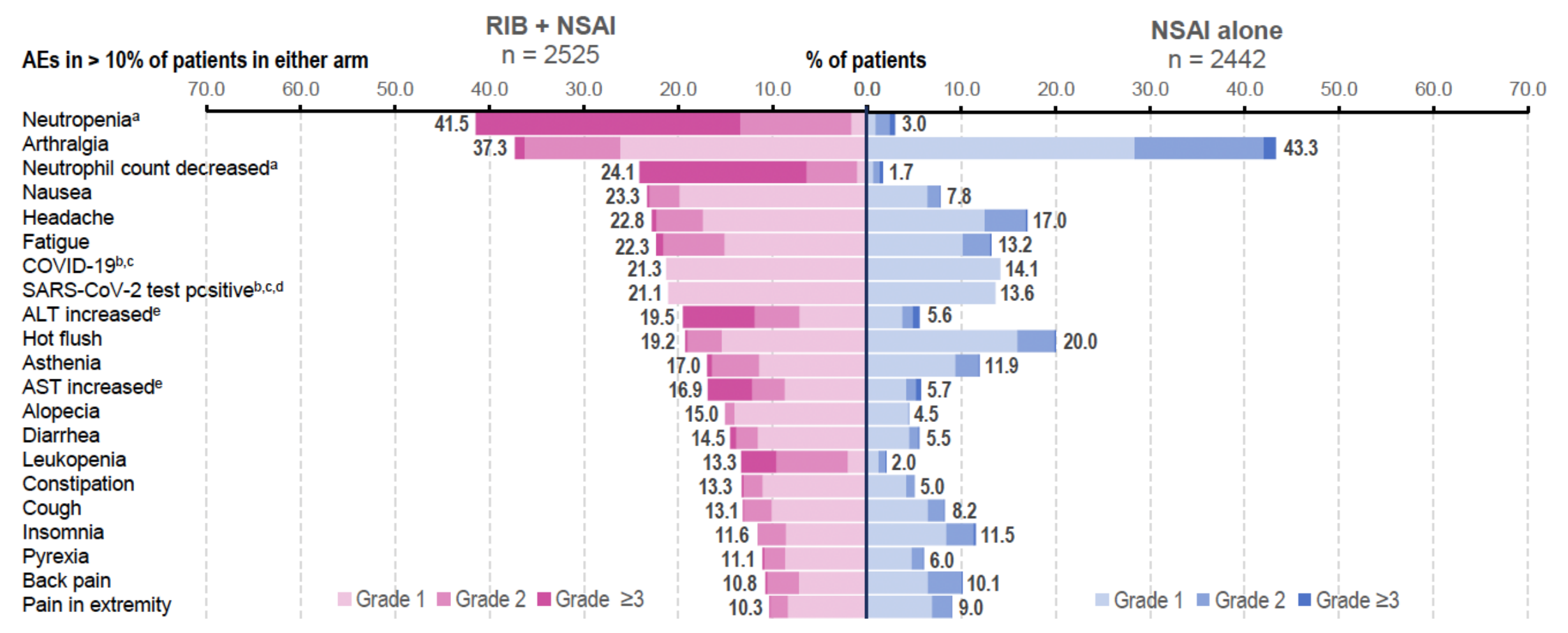
monarchE: AEs Leading to Dose Modifications



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.

NATALEE: Overall Safety Profile



ALT = alanine aminostransferase; AST = aspartate aminotransferase

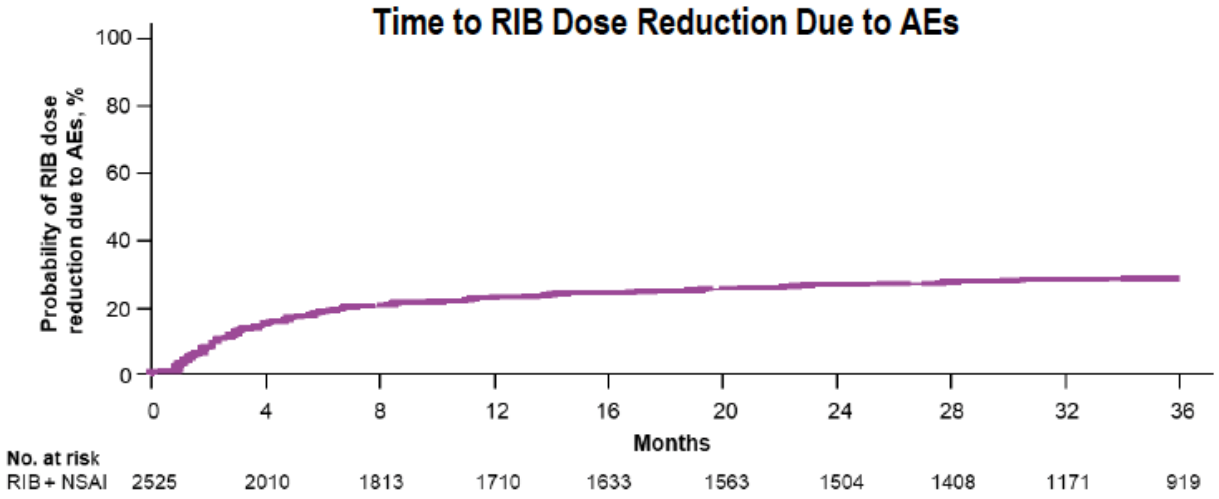
Barrios C et al. ESMO Breast 2024;Abstract 113MO.

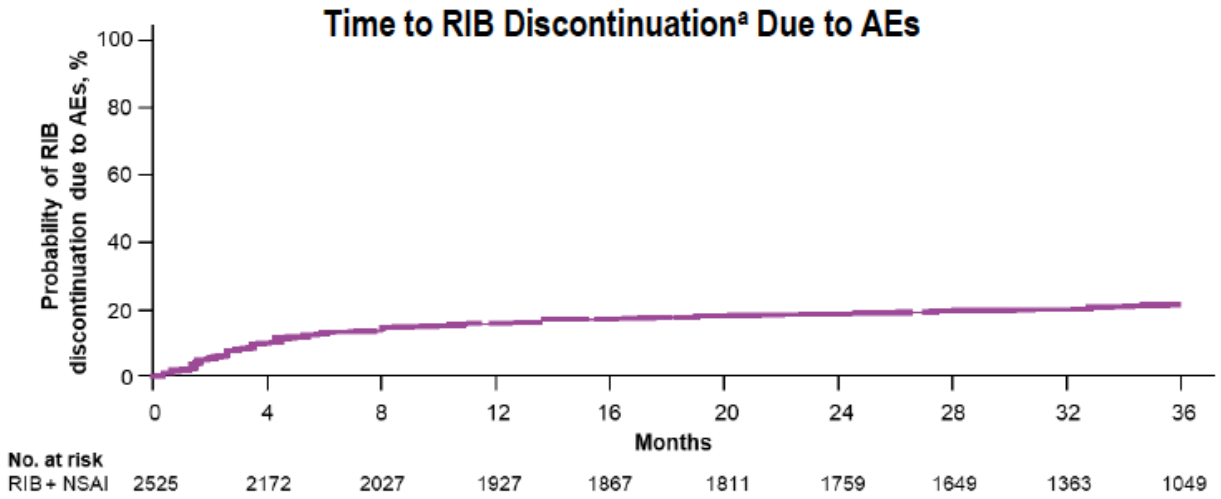
NATALEE: AEs of Special Interest (AESIs)

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.

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)

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

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%**

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.

Courtesy of Komal Jhaveri, MD

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%

- HR-positive, HER2-negative, early breast cancer
- Adjuvant abemaciclib is indicated based on patient risk/stage

Screening

N=90

Adjuvant Endocrine Therapy

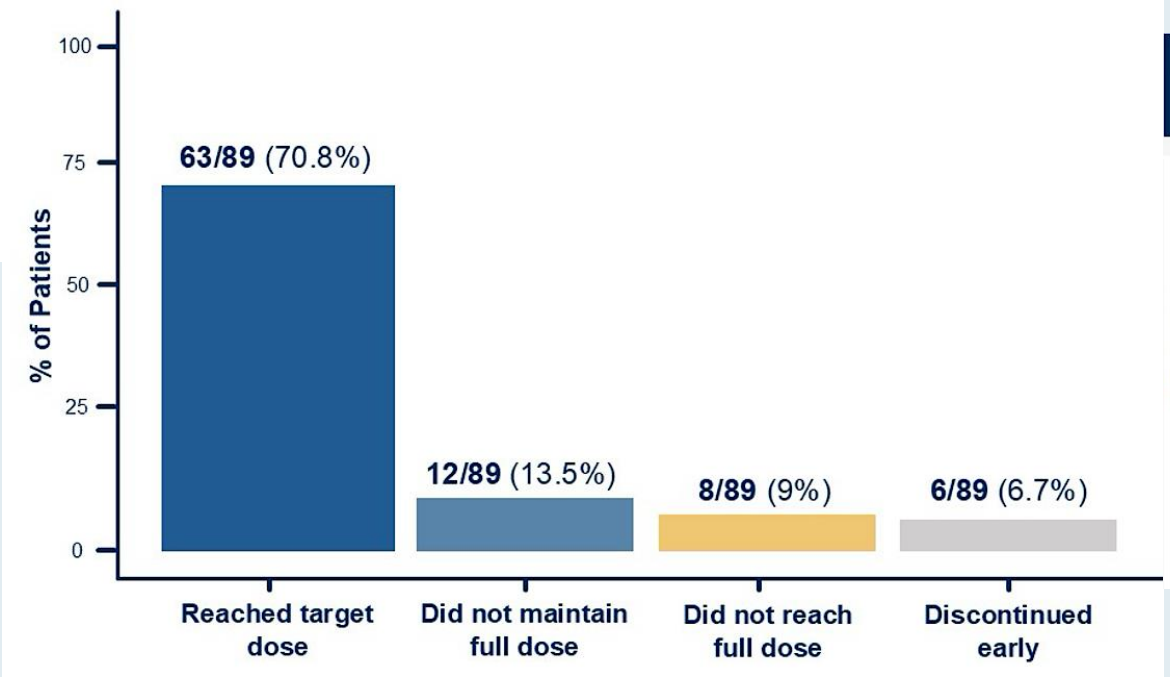
Abemaciclib **50mg BID** (Days 1 – 14) → Abemaciclib **100mg BID** (Days 15 – 28) → Abemaciclib **150mg BID** (> 28 Days)

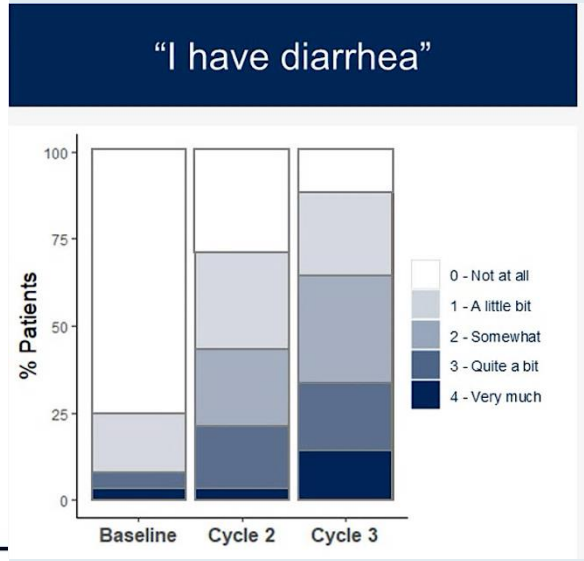
⇒ **Endocrine Therapy + up to 2 years Abemaciclib**

Intra-patient dose escalation requirements: Absence of ongoing grade 3/4 or persistent grade 2 toxicity

Supportive care, including anti-diarrhea medication, provided as needed

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





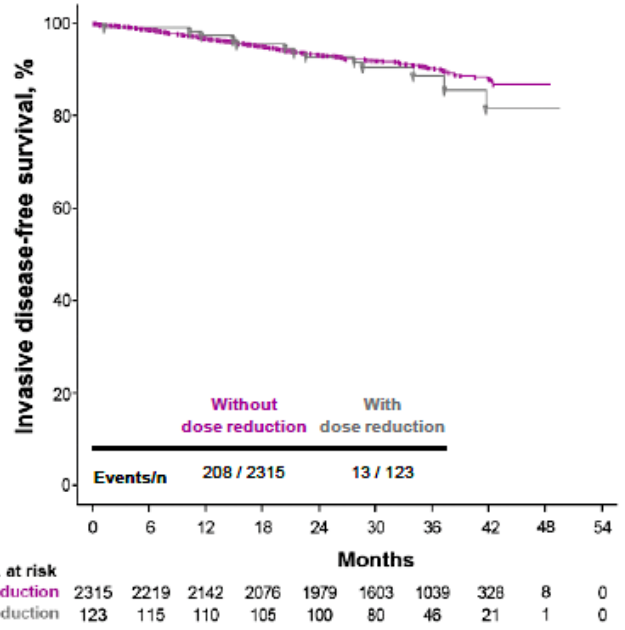
Courtesy of Komal Jhaveri, MD

Mayer EL et al. Ann Oncol. 2025

NATALEE: IDFS by Dose Reductions

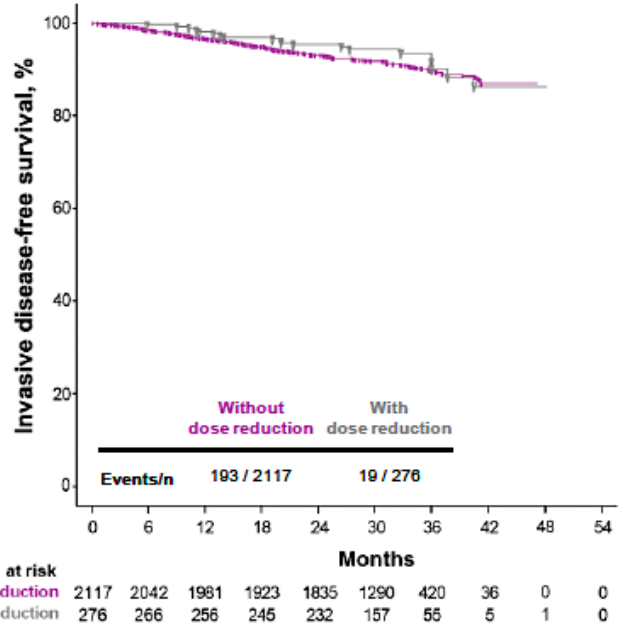
Landmark analysis revealed that RIB dose reduction due to AEs did not impact efficacy

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



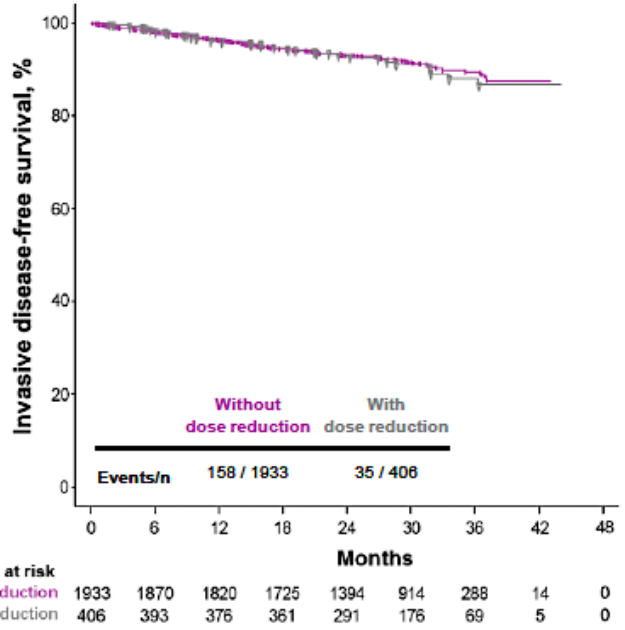
No. at risk										
Without dose reduction	2315	2219	2142	2076	1979	1603	1039	328	8	0
With dose reduction	123	115	110	105	100	80	46	21	1	0

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.

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

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

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 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

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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

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.

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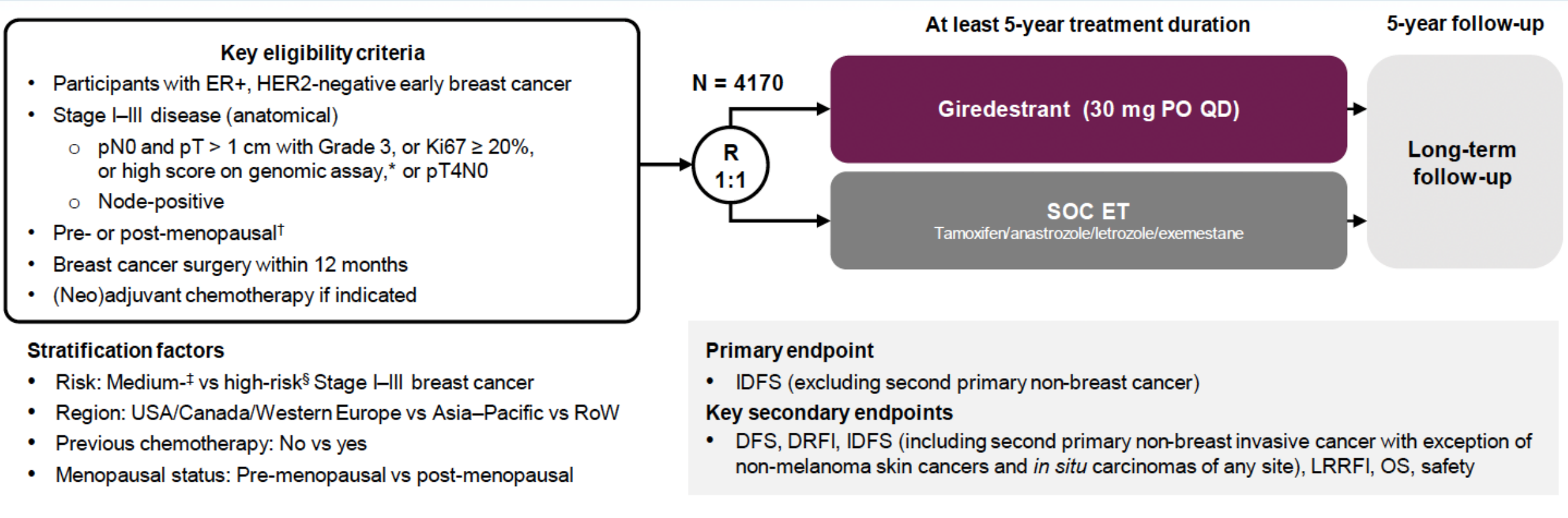
Giredestrant vs standard-of-care endocrine therapy as adjuvant treatment for patients with estrogen receptor-positive, HER2-negative early breast cancer: Results from the global Phase III lidERA Breast Cancer trial

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

Abstract GS1-10

lidERA Breast Cancer Study Design



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

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

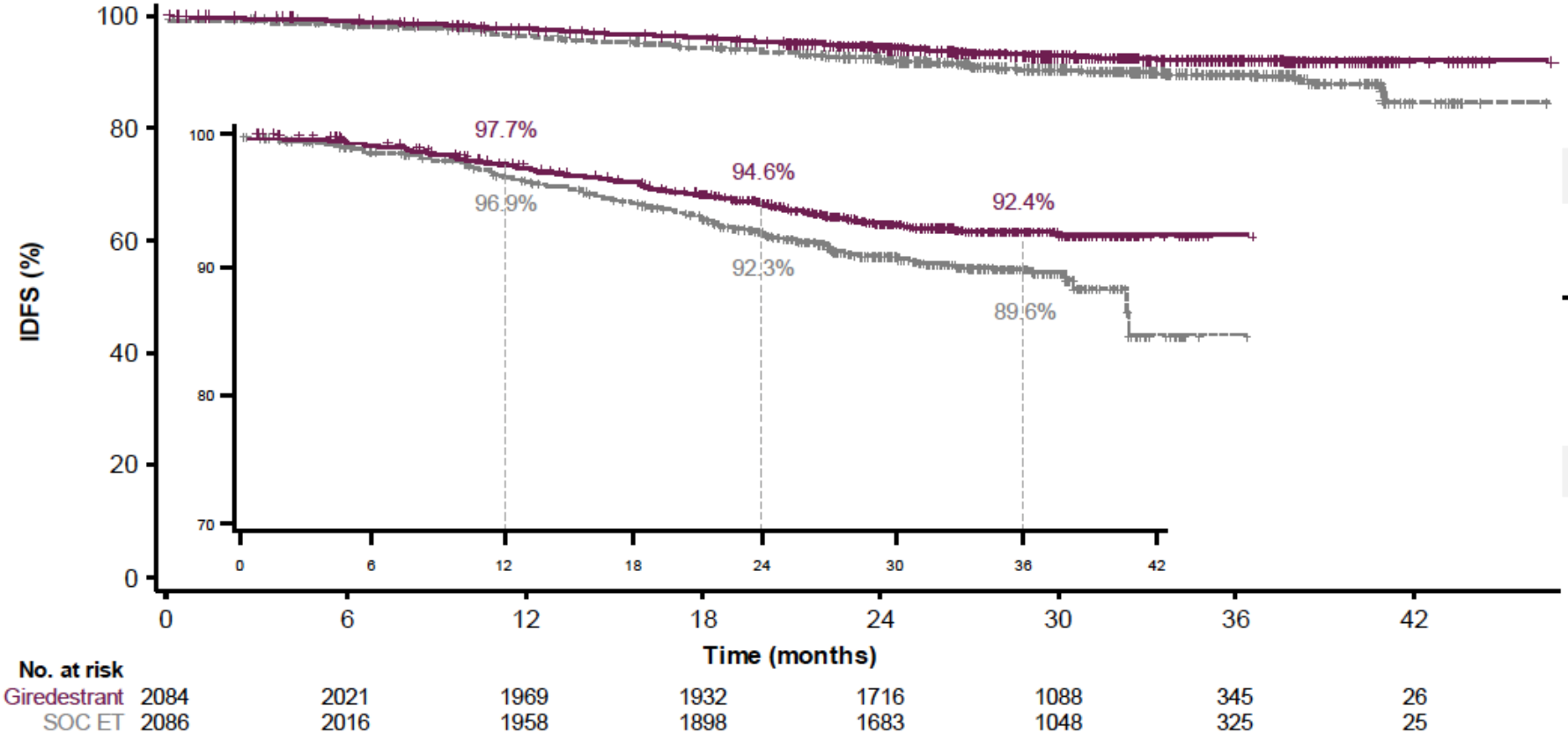
lidERA Breast Cancer: Patient Demographics

	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.

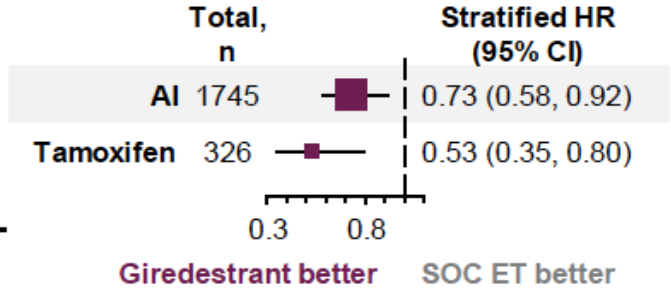
lidERA Breast Cancer: IDFS Outcomes



No. at risk								
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***	

Exploratory analysis: IDFS by SOC ET



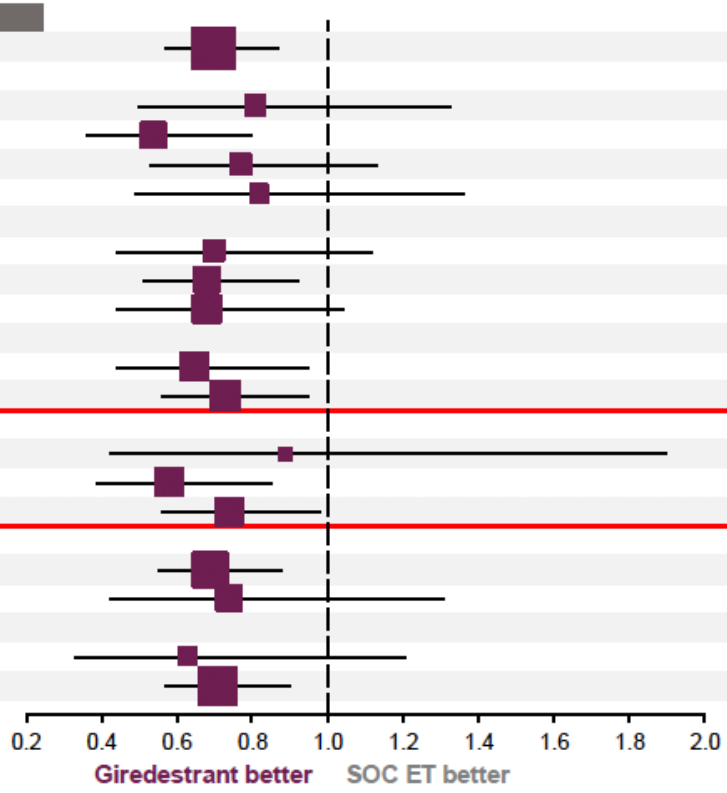
Median follow-up: 32.3 months

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.

lidERA Breast Cancer: IDFS in Key Subgroups

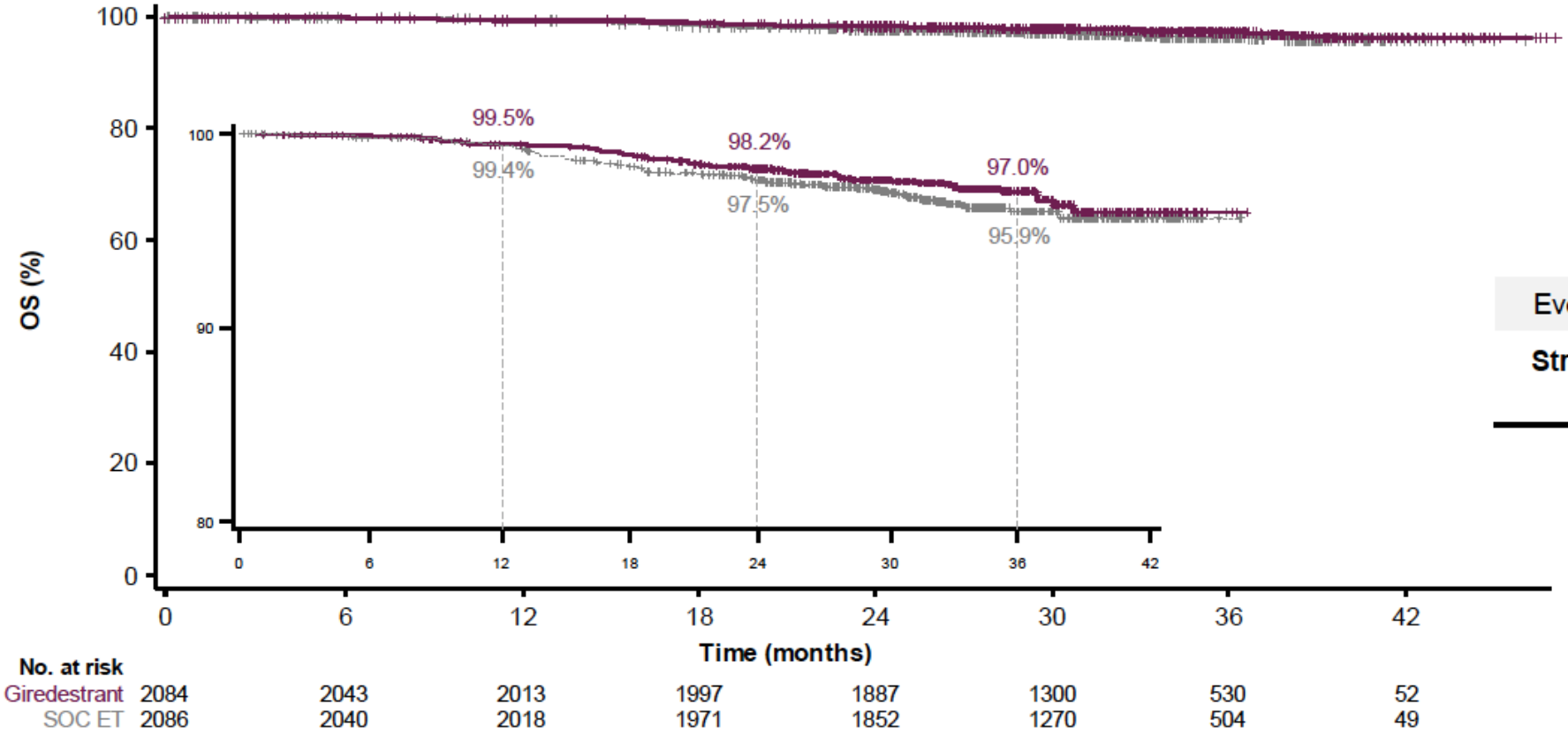
	Total, n	Patients, n: Giredestrant	Patients, n: SOC ET	HR (95% CI)
All patients	4170	2084	2086	0.70 (0.57, 0.87)
Age group, years				
≤ 45	906	472	434	0.81 (0.50, 1.33)
> 45 to ≤ 55	1355	660	695	0.54 (0.36, 0.80)
> 55 to ≤ 65	1118	567	551	0.77 (0.53, 1.13)
> 65	791	385	406	0.82 (0.49, 1.36)
Region				
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.

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

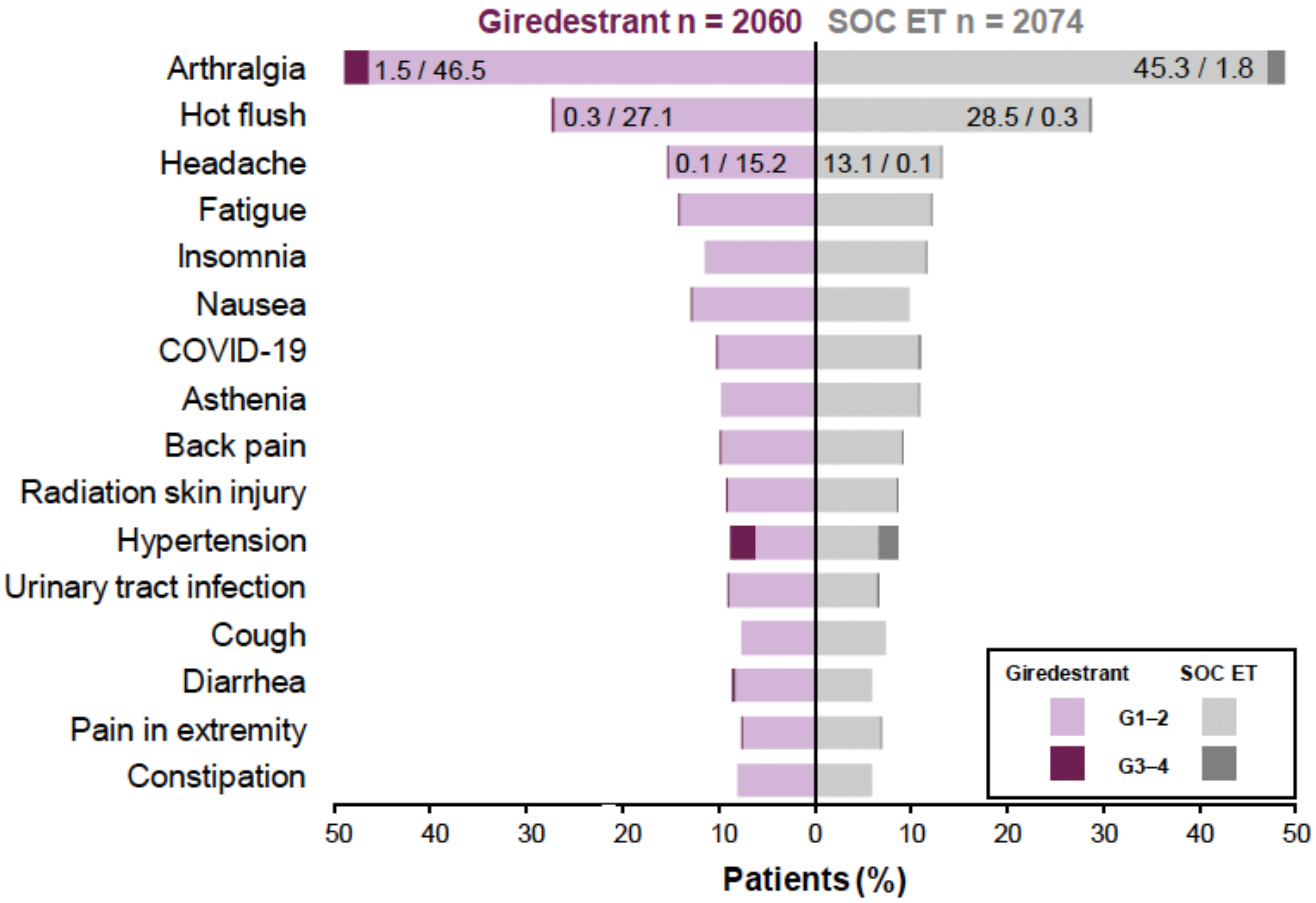
Median follow-up: 32.3 months

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.

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.

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

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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 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

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Questions?

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