CASES FROM THE COMMUNITY
Investigators Discuss the Optimal Role of Endocrine-Based and Other Strategies in the Management of HR-Positive Breast Cancer

Part 3 of a 3-Part CME Satellite Symposium Series

Thursday, December 11, 2025

7:00 PM – 9:00 PM CT

Faculty

Angela DeMichele, MD, MSCE
Komal Jhaveri, MD, FACP, FASCO
Erica Mayer, MD, MPH, FASCO
Hope S Rugo, MD
Seth Wander, MD, PhD

Moderator

Neil Love, MD

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Faculty

Angela DeMichele, MD, MSCE
Mariann T and Robert J MacDonald Professor
in Breast Cancer
Director, Clinical/Translational Research, Solid Tumor
Oncology, Hematology/Oncology Division
Co-Leader, Breast Cancer Program
Abramson Cancer Center
Co-Director, 2-PREVENT Breast Cancer Translational Center
of Excellence
Senior Scholar, Center for Clinical Epidemiology and
Biostatistics
Perelman School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Komal Jhaveri, MD, FACP, FASCO
Patricia and James Cayne Chair for Junior Faculty
Associate Attending Physician
Breast Medicine Service and Early Drug Development Service
Section Head, Endocrine Therapy Research Program
Clinical Director, Early Drug Development Service
Department of Medicine
Memorial Sloan Kettering Cancer Center
Associate Professor of Medicine
Weill Cornell College of Medicine
New York, New York

Erica Mayer, MD, MPH, FASCO
Director of Breast Cancer Clinical Research
Breast Oncology Center
Dana-Farber Cancer Institute
Associate Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Hope S Rugo, MD
Director, Women's Cancers Program
Division Chief, Breast Medical Oncology
Professor, Department of Medical Oncology
and Therapeutics Research
City of Hope Comprehensive Cancer Center
Duarte, California
Professor Emeritus, UCSF

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Faculty (Continued)

Seth Wander, MD, PhD
Director of Precision Medicine
Termeer Center for Targeted Therapies
Director of Translational Research
Breast Oncology Program
Massachusetts General Hospital
Assistant Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Moderator

Neil Love, MD
Research To Practice
Miami, Florida

Dr DeMichele — Disclosures
Faculty

Consulting Agreements	Pfizer Inc
Contracted Research	Genentech, a member of the Roche Group, NeoGenomics, Novartis, Pfizer Inc

Dr Jhaveri — Disclosures
Faculty

Consultant/Advisory Board Roles	Arvinas, AstraZeneca Pharmaceuticals LP, Bicycle Therapeutics, Blueprint Medicines, Daiichi Sankyo Inc, Eisai Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Halda Therapeutics, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Menarini Group, Merck, Novartis, Olema Oncology, Pfizer Inc, RayzeBio Inc, Scorpion Therapeutics, Stemline Therapeutics Inc, Zymeworks Inc
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Dr Mayer — Disclosures
Faculty

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

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Dr Rugo — Disclosures
Faculty

Advisory Committees and Consulting Agreements	BioNTech SE, Bristol Myers Squibb, Helsinn Therapeutics (US) Inc, Napo Pharmaceuticals
Contracted Research (Funding to City of Hope)	Bicycle Therapeutics, Genentech, a member of the Roche Group, Stemline Therapeutics Inc
Contracted Research (Funding to Prior Institution, UCSF)	Ambrx Inc, AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Lilly, Merck, Novartis, Pfizer Inc, Stemline Therapeutics Inc

Dr Wander — Disclosures
Faculty

Consulting Agreements	Arvinas, AstraZeneca Pharmaceuticals LP, Biovica International AB, Foundation Medicine, Genentech, a member of the Roche Group, Gilead Sciences Inc, Hologic Inc, Lilly, Menarini Group, Novartis, Pfizer Inc, Puma Biotechnology Inc, Regor Therapeutics, Stemline Therapeutics Inc, Veracyte Inc
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Dr Love — Disclosures

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Cases from the Community: Investigators Discuss Available Research Guiding the Management of Relapsed/Refractory Multiple Myeloma — What Happened at ASH 2025?

A CME/MOC-Accredited Live Webinar

Monday, December 15, 2025

5:00 PM – 6:00 PM ET

Faculty

Sagar Lonial, MD, FACP, FASCO

María-Victoria Mateos, MD, PhD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Practical Perspectives on the Current and Future Management of Immune Thrombocytopenia — What Happened at ASH 2025?

A CME/MOC-Accredited Live Webinar

Tuesday, December 16, 2025

5:00 PM – 6:30 PM ET

Faculty

Hanny Al-Samkari, MD
Cindy Neunert, MD, MSCS
Francesco Zaja, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Practical Perspectives on the Current Role of Bispecific Antibodies in the Management of Lymphoma — What Happened at ASH 2025?

A CME/MOC-Accredited Live Webinar

Wednesday, December 17, 2025
5:00 PM – 6:00 PM ET

Faculty

Michael Dickinson, MD
Laurie H Sehn, MD, MPH

Moderator

Neil Love, MD

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Expert Second Opinion: Investigators Discuss the Optimal Management of Gastrointestinal Cancers

A CME Symposium Series Held Adjunct to the
2026 ASCO® Gastrointestinal Cancers Symposium

HER2-Positive Gastrointestinal Cancers

Thursday, January 8, 2026

7:15 PM – 8:45 PM PT
(10:15 PM – 11:45 PM ET)

Advanced Gastroesophageal Cancers

Friday, January 9, 2026

6:00 PM – 8:00 PM PT
(9:00 PM – 11:00 PM ET)

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RESEARCH TO PRACTICE

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

A CME/MOC-Accredited Interactive Grand Rounds Series

Through April 2026

Faculty

Adam M Brufsky, MD, PhD
Kevin Kalinsky, MD, MS, FASCO
Reshma L Mahtani, DO
Komal Jhaveri, MD, FACP, FASCO
Erica Mayer, MD, MPH, FASCO
Hope S Rugo, MD

Additional faculty to be announced.

Host a 1-hour session at your institution:
Email Meetings@ResearchToPractice.com
or call (800) 233-6153

CLL and DLBCL series also available.

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Save The Date

Fifth Annual
National General Medical Oncology Summit

A Multitumor CME/MOC-, NCPD- and ACPE-Accredited Educational Conference Developed in Partnership with Florida Cancer Specialists & Research Institute

Friday to Sunday, April 24 to 26, 2026

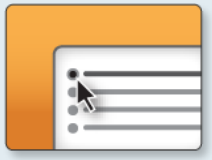
The Ritz-Carlton Orlando, Grande Lakes | Orlando, Florida

Moderated by Neil Love, MD

Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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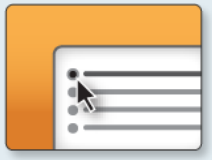
Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get CME Credit: A credit link will be provided in the chat room at the conclusion of the program.

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Seth Wander, MD, PhD

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Neil Love, MD

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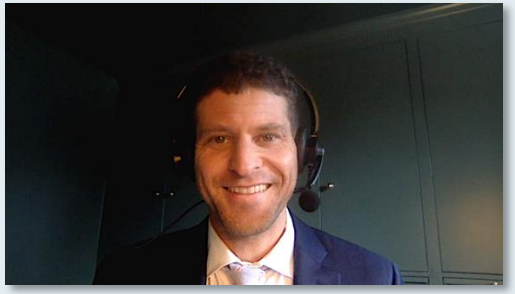
Contributing General Medical Oncologists

Laila Agrawal, MD
Norton Cancer Institute
Louisville, Kentucky



Eric Fox, DO
Bryn Mawr Medical Specialists Association
Bryn Mawr, Pennsylvania

Alan B Astrow, MD
Weill Cornell Medicine
Brooklyn, New York

Sunil Gandhi, MD
Florida Cancer Specialists & Research Institute
Lecanto, Florida

Gigi Chen, MD
John Muir Health
Cancer Medical Group
Walnut Creek, California

Zanetta S Lamar, MD
Florida Oncology and Hematology
Naples, Florida

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Contributing General Medical Oncologists

Laurie Matt-Amaral, MD, MPH
Northeast Ohio Medical University
College of Medicine
Akron, Ohio

Swati Vishwanathan, MD
WVU Medicine
Bridgeport, West Virginia

Eleonora Teplinsky, MD
Valley-Mount Sinai
Comprehensive Cancer Care
Paramus, New Jersey

Richard Zelkowitz, MD
Hartford HealthCare Cancer Institute
Bridgeport, Connecticut

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Agenda

Module 1: Current Role of Genomic Assays in Treatment Decision-Making for Localized Hormone Receptor (HR)-Positive Breast Cancer — Dr DeMichele

Module 2: Role of CDK4/6 Inhibitors and Other Novel Strategies in Therapy for HR-Positive, HER2-Negative Localized Breast Cancer — Dr Jhaveri

Module 3: Evolving Up-Front Treatment Paradigm for HR-Positive, HER2-Negative Metastatic Breast Cancer (mBC) — Dr Rugo

Module 4: Clinical Utility of Agents Targeting the PI3K/AKT/mTOR Pathway for Patients with Progressive HR-Positive mBC — Dr Mayer

Module 5: Current and Future Role of Oral Selective Estrogen Receptor Degraders for Progressive HR-Positive mBC — Dr Wander

Sir Richard Peto FRS

National Cancer Institute Consensus Conference on Early Breast Cancer

September 9, 1985

Agenda

Module 1: Current Role of Genomic Assays in Treatment Decision-Making for Localized Hormone Receptor (HR)-Positive Breast Cancer — Dr DeMichele

Module 2: Role of CDK4/6 Inhibitors and Other Novel Strategies in Therapy for HR-Positive, HER2-Negative Localized Breast Cancer — Dr Jhaveri

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Module 5: Current and Future Role of Oral Selective Estrogen Receptor Degraders for Progressive HR-Positive mBC — Dr Wander

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Penn Medicine

Current Role of Genomic Assays in Treatment Decision-Making for Localized HR-Positive Breast Cancer

Angela DeMichele, MD, MSCE, FASCO
Mariann T. and Robert J. MacDonald Professor in Breast Cancer
Director, Clinical/Translational Research, Solid Tumor Oncology, Hematology/Oncology Division
Co-Leader, Breast Cancer Program, Abramson Cancer Center
Co-Director, 2-PREVENT Breast Cancer Translational Center of Excellence
Senior Scholar, Center for Clinical Epidemiology and Biostatistics
Perelman School of Medicine, University of Pennsylvania

RTP Session – SABCS 2025

Outline

- Similarities/Differences between assays
- Key studies informing use of 21-gene Recurrence Score® (Onco*type* DX®)
- Key studies on use of 70-gene assay (MammaPrint®)
- Complements to these assays
  - RSClin®
  - BluePrint®
- Key studies on use of Breast Cancer Index®

Genomic Predictors of Outcome in ER+ Early Breast Cancer

Genomic Assay	Genes/Platform	Main Output	Early risk validation?	Late risk validation?
Onco*type* DX	21 genes, RT-PCR, central lab	RS 0-100 (risk, chemo benefit)	Yes	Limited (up to 9 years)
MammaPrint	70 gene signature, array/NGS	Low vs. High genomic risk	Yes	Limited
Prosigna® (PAM50 ROR)	50 genes, NanoString	PAM50 intrinsic subtype + ROR score	Yes	Yes, 10-y distant recurrence risk
EndoPredict® (EPclin)	RT-PCR EP + size/nodes	EP clin low/intermediate/high	Yes	Yes, very low late risk groups
Breast Cancer Index (BCI)	H/I + molecular grade, RT-PCR	Continuous risk + H/I high/low	No	Yes, late recurrence risk/extended ET

Correlation between assays, but drivers are different

TABLE 2. Variance of RS, ROR, BCI, and EP Scores as Accounted for by RS's Four Modules

	RS		ROR		EP		BCI	
RS Module	Sum of Squares	Variance Explained (%)	Sum of Squares	Variance Explained (%)	Sum of Squares	Variance Explained (%)	Sum of squares	Variance Explained (%)
Proliferation (unthresholded)	17,628	19.4	241,358	72.5	1,878	50.0	1,186	54.3
Estrogen	53,656	59.1	1,799	0.5	759	20.2	59	2.7
Invasion	1,215	1.3	1,610	0.5	24	0.7	5	0.3
HER2 (unthresholded)	1,948	2.2	4,371	1.3	23	0.6	51	2.4
Residuals	16,349	18.0	83,882	25.2	1,067	28.4	880	40.3

- Correlation *r* 0.67-0.74
- Onco*type* DX determined more strongly by **estrogen module** and weakly by proliferation
- Others determined more strongly by **proliferation features**

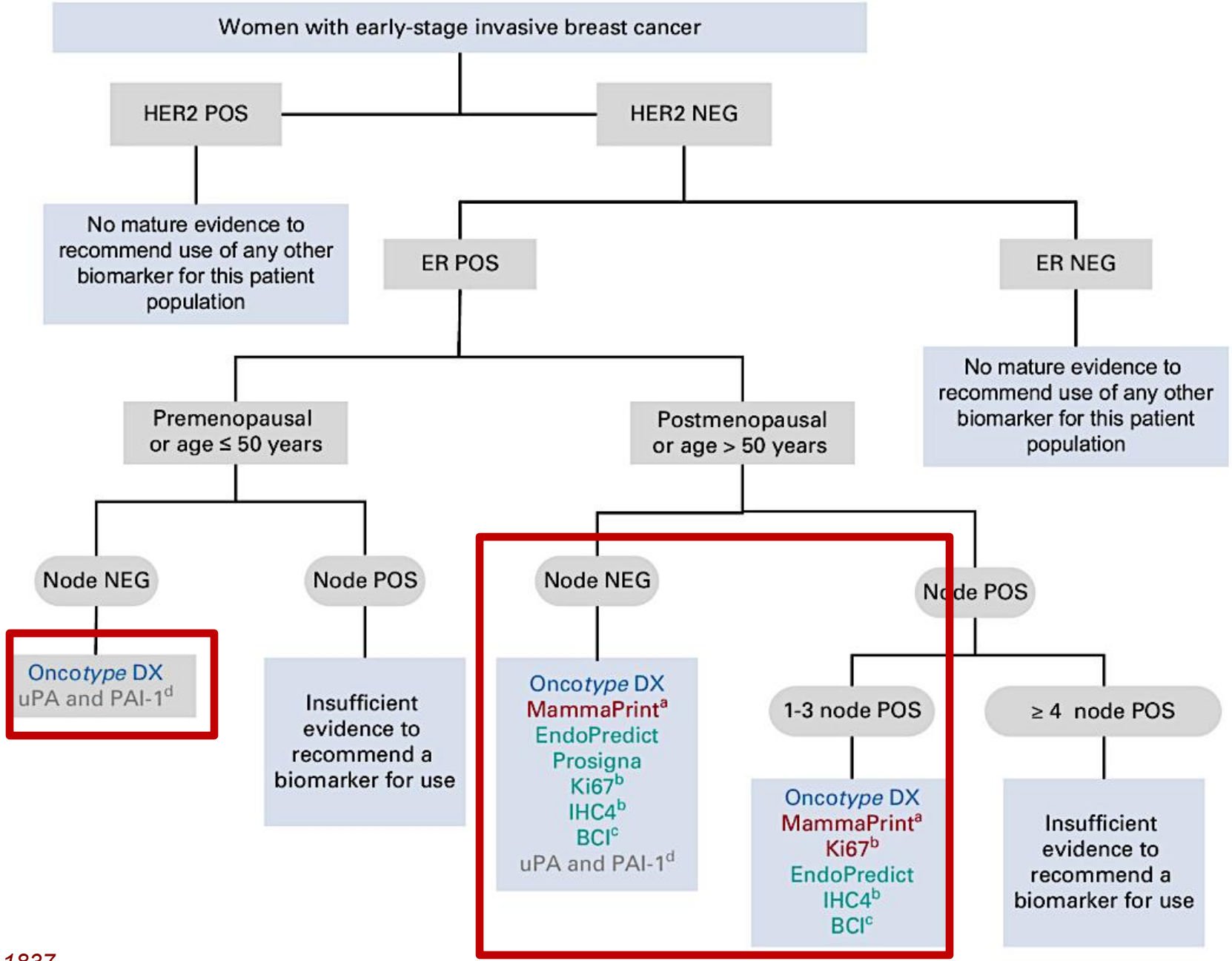
Buus, JCO, 2021

Penn Medicine

Predictors of early risk (0-5 years):

Onco*type* **DX, MammaPrint, Prosigna, EndoPredict, Breast Cancer Index**

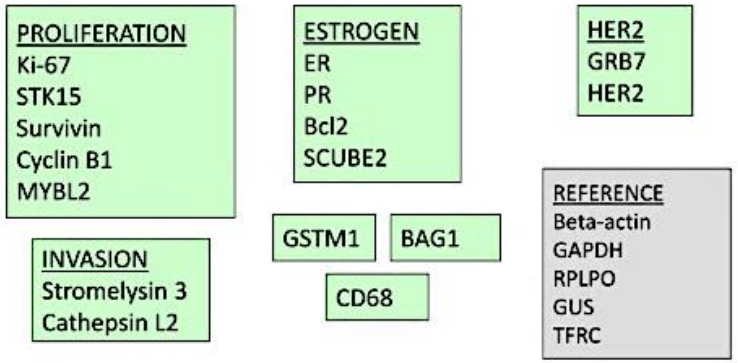
ASCO Guideline 2022



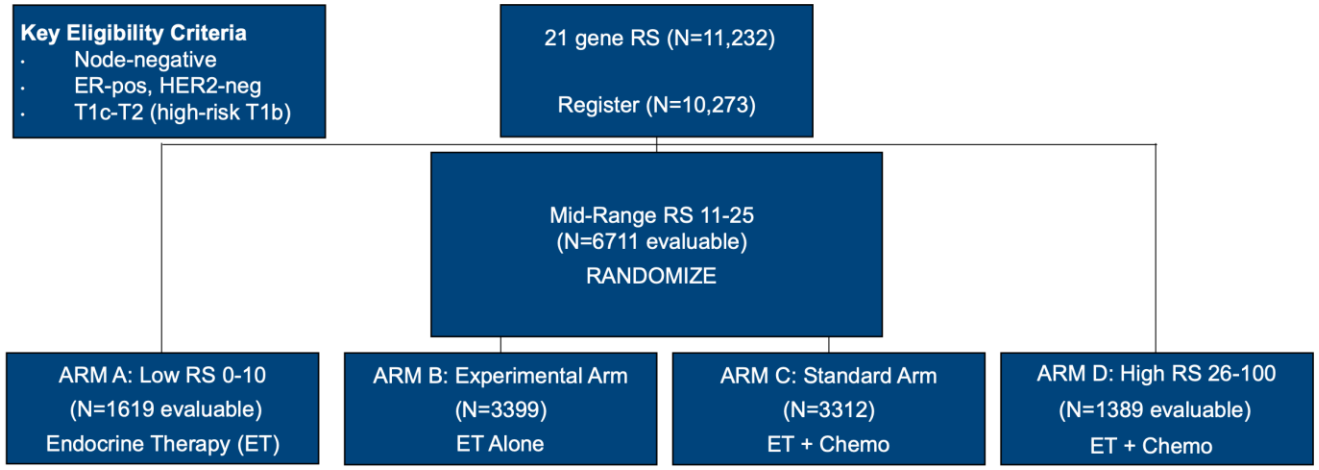
Andre F, et al. J Clin Oncol. 2022;40:1816-1837

Oncotype DX: TAILORx Key Results (Node-negative)

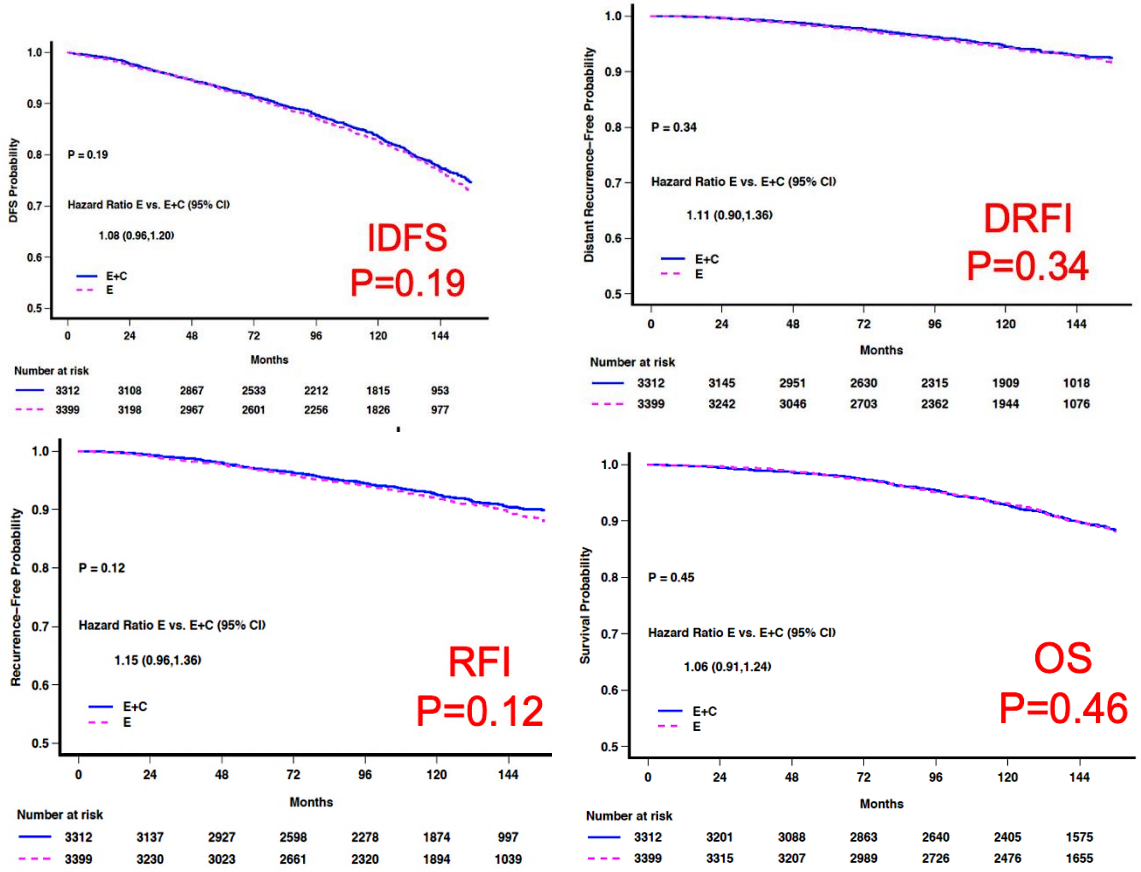
16 Cancer and 5 Reference Genes From 3 Studies



TAILORx Trial Design



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



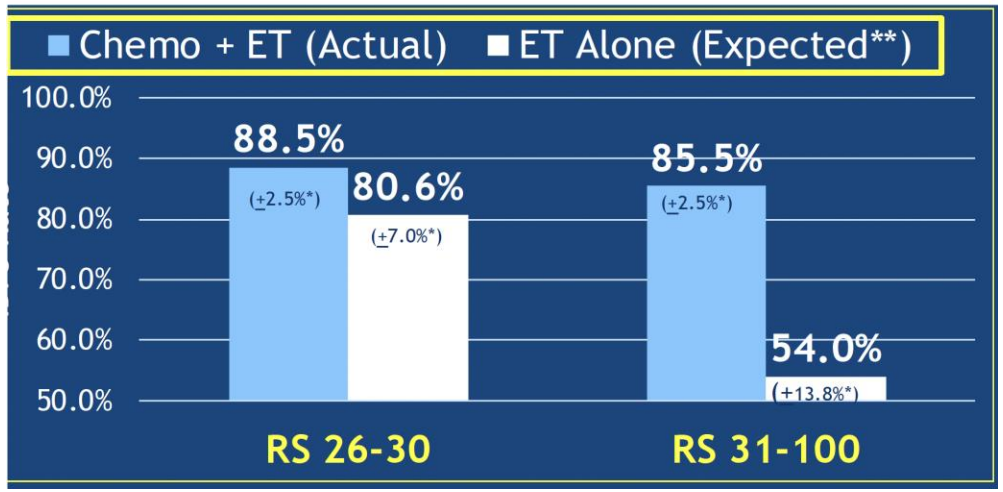
Sparano, SABCS, 2022

Figures courtesy K. Kalinsky

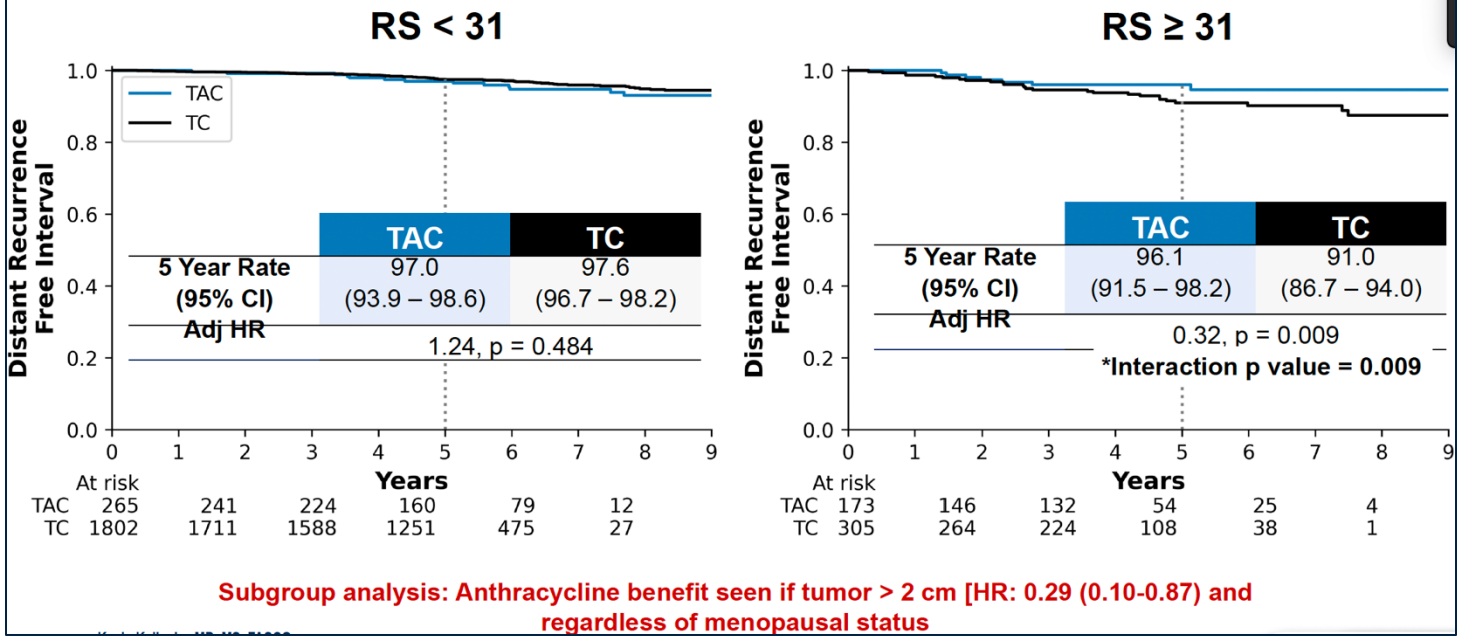
Penn Medicine

Chemotherapy & anthracycline benefits in 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, JAMA Oncology, 2020; Chen, Annals Oncology, 2025

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OncotypeDX: RxPONDER Key Results (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

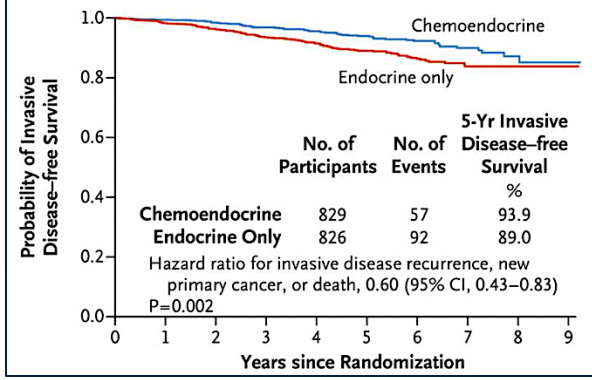
Stratification Factors
Recurrence Score: 0-13 vs.14-25
Menopausal Status: pre vs. post
Axillary Surgery: ALND vs. SLNB

RxPONDER Population

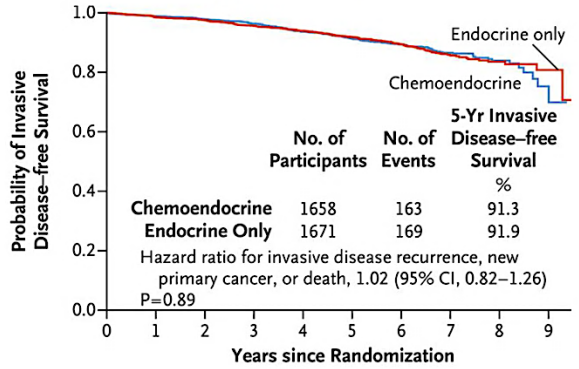
T1	58%	T3	5%
1 LN+	66%	3 LN+	9%
Grade 2	64%	Grade 3	10%
40-49 yrs	21%	< 40 yrs	3%

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, NEJM, 2021

Penn Medicine

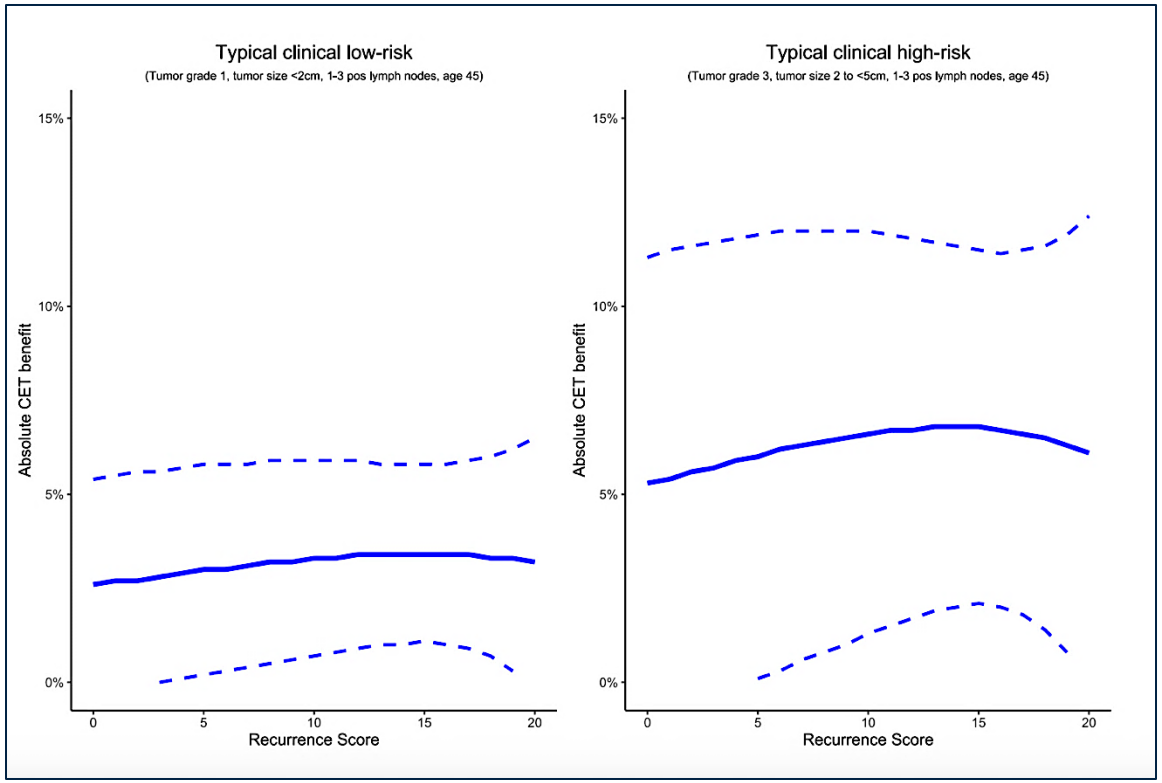
RSClin Refines LN- and LN+ Risk, Adjusting for Clinical and Pathologic Factors (age, grade, tumor size, and, for post-meno NP, # nodes)

Node Negative

Women ≤ 50 yrs & RS 16-25 by RS and Clinical Risk

	Estimated Absolute Chemo Benefit Not Stratified by Clinical Risk	Clinical Risk	No.	Estimated Absolute Chemo Benefit Stratified by Clinical Risk
RS 16-20 (N=886)	Δ +0.6% (±SE 2.1%)	Low	671 (76%)	Δ -0.5% (±SE 2.2%)
		High	215 (24%)	Δ +3.1% (±SE 5.4%)
RS 21-25 (N=476)	Δ +7.8% (+SE 3.4%)	Low	319 (67%)	Δ +5.9% (±SE 3.4%)
		High	157 (33%)	Δ +11.7% (±SE 7.2%)

Node Positive



Sparano, JCO, 2021; Pusztai, JCO, 2024

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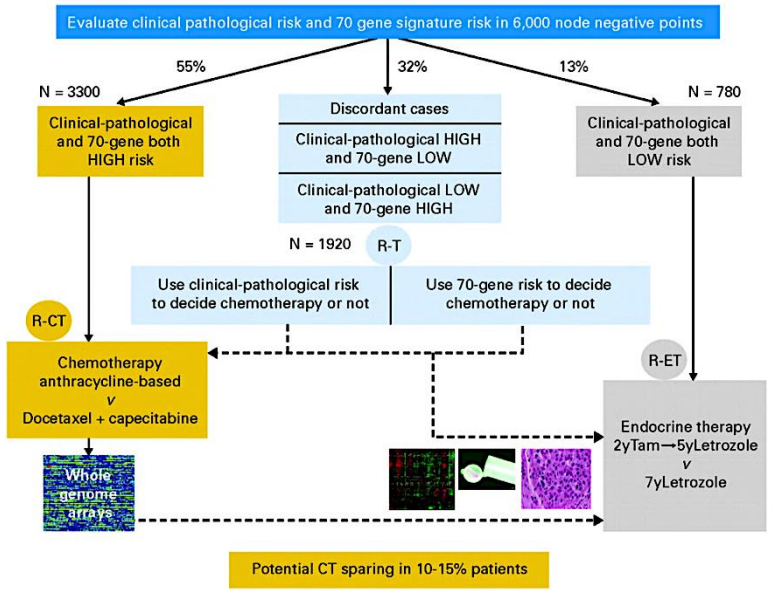
MammaPrint: MindACT Key Results

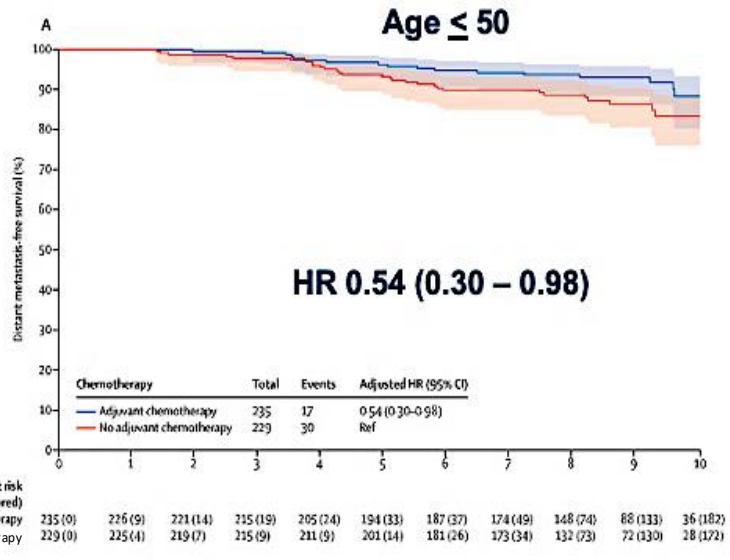
Clinical "high risk": <88% 10-yr BCSS
Modified Adjuvant Online to determine
Model included: T size, Node (0-3), grade, ER status, age, comorbidity

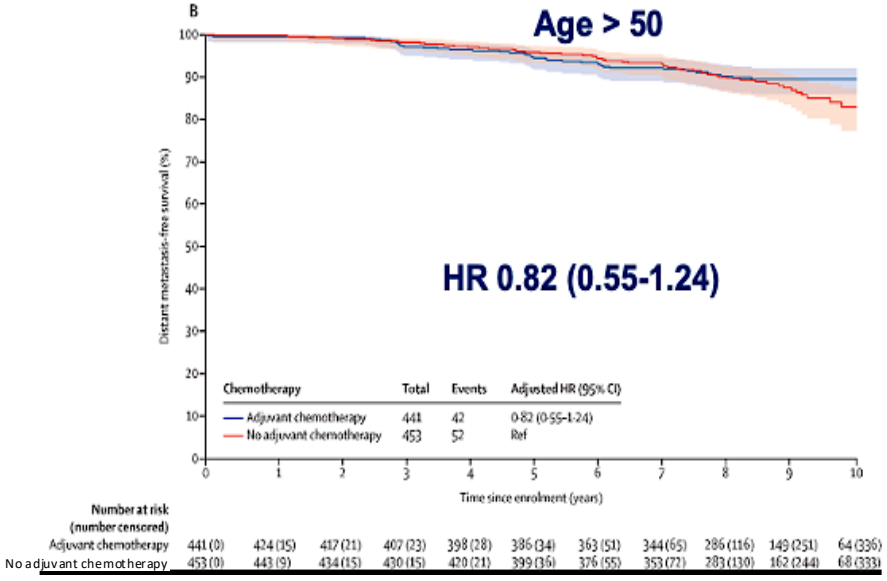


Met primary outcome: Lower bound of 95% CI >92% 5-y DMFS in the High Clinical/Low Genomic risk group

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, NEJM, 2016; Piccart, Lancet Oncology, 2021

Penn Medicine

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

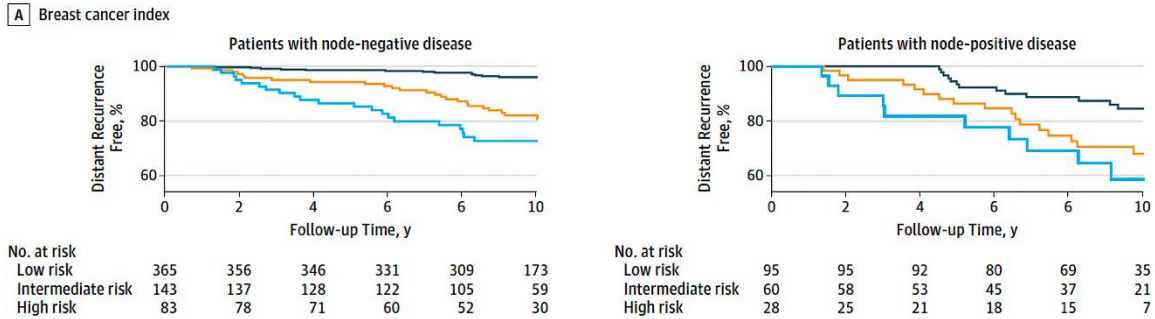
Breast Cancer Index (BCI)
- 7-genes – Proliferation and hormone receptor (HoxB13/IL17BR)

JAMA Oncology | Original Investigation

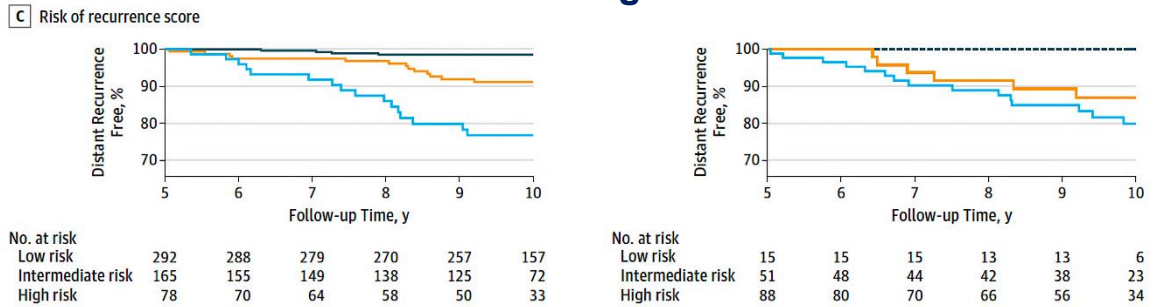
Comparison of the Performance of 6 Prognostic Signatures for Estrogen Receptor–Positive Breast Cancer
A Secondary Analysis of a Randomized Clinical Trial

- 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

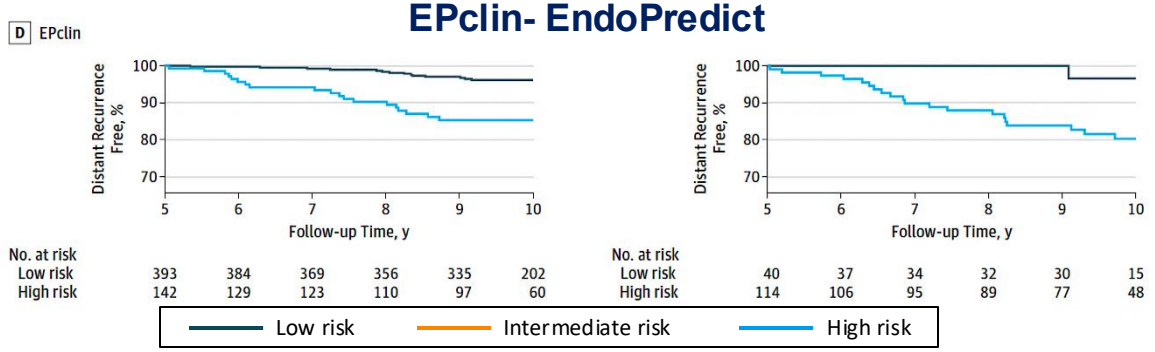
BCI



ROR - Prosigna



EPclin- EndoPredict



Sestak, JAMA Oncol. 2018;4(4):545-553. Published online February 15, 2018.

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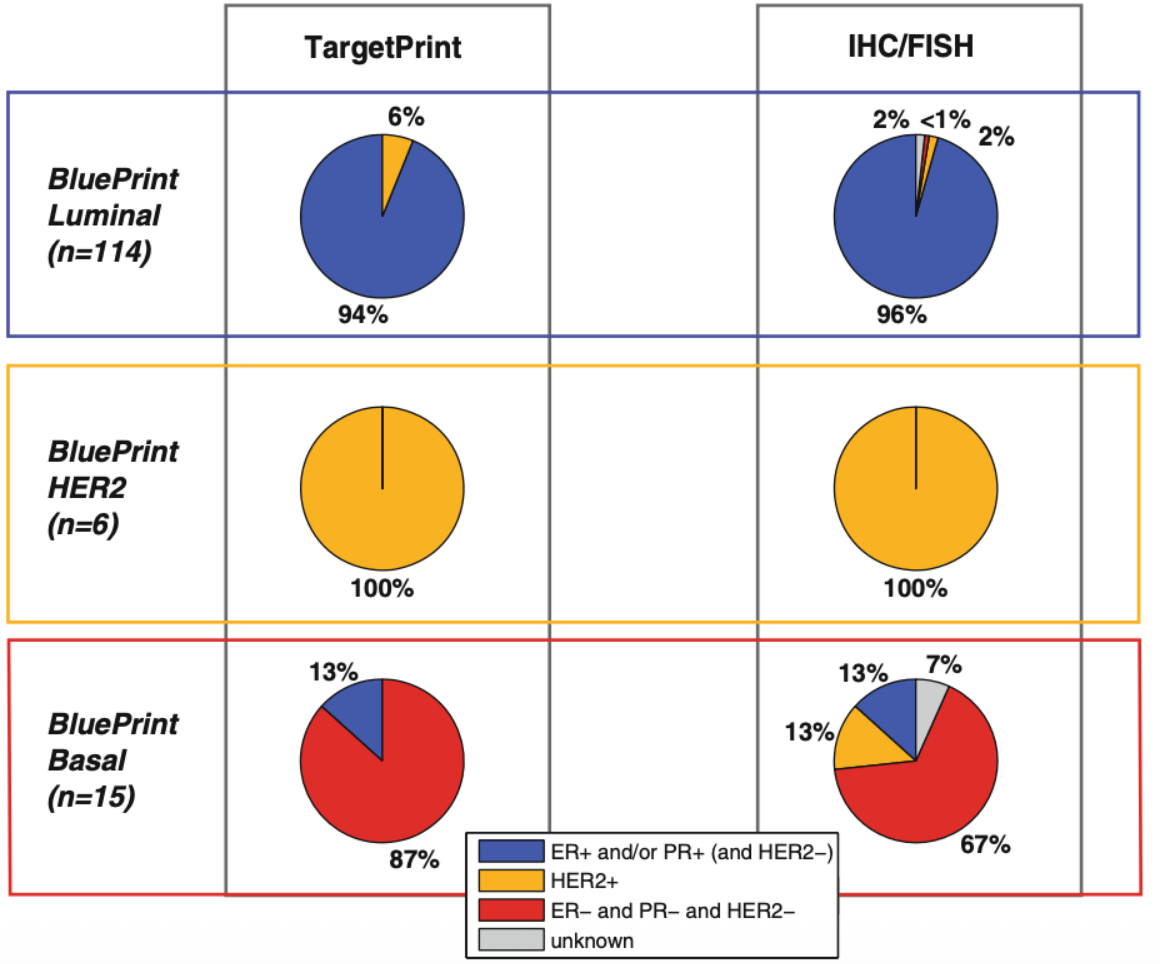
BluePrint

BluePrint

- 80-gene RNA-based molecular subtyping assay
- Classifies: Luminal-type, HER2-type, Basal-type
- “Functional subtype” – not identical to intrinsic subtype but can differentiate for therapeutic decisions

BluePrint validation against IHC/FISH
Concordance > 99%



Nguyen B, et al. Ann Surg Oncol. 2012;19:3257-3263

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ASCO Guideline: Oncotype DX 21-gene RS

Oncotype DX (21-gene recurrence score, 21-gene RS).

Recommendation 1.1. If a patient has node-negative breast cancer, the clinician may use the Oncotype DX test to guide decisions for adjuvant endocrine and chemotherapy (Type: evidence-based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.2. In the group of patients in Recommendation 1.1 with Oncotype DX recurrence score ≥ 26, the clinician should offer chemoendocrine therapy (Type: evidence-based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.3. In the group of patients in Recommendation 1.1 who are 50 years of age or younger with Oncotype DX recurrence score 16 to 25, the clinician may offer chemoendocrine therapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.4. If a patient is postmenopausal and has node-positive breast cancer with 1-3 positive nodes, the clinician may use the Oncotype DX test to guide decisions for adjuvant endocrine and chemotherapy (Type: evidence-based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.5. In the group of patients in Recommendation 1.4, the clinician should offer chemoendocrine therapy for those whose Oncotype DX recurrence score is ≥ 26 (Type: evidence-based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.6. If a patient is premenopausal and has node-positive breast cancer with 1-3 positive nodes, the Oncotype DX test should not be offered to guide decisions for adjuvant systemic chemotherapy (Type: evidence-based; Evidence quality: high; Strength of recommendation: moderate).

Recommendation 1.7. If a patient has node-positive breast cancer with ≥ 4 positive nodes, the evidence on the clinical utility of routine Oncotype DX test to guide decisions for adjuvant endocrine and chemotherapy is insufficient to recommend its use (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).
Qualifying statement: The genomic assay is prognostic and may be used for shared patient-physician treatment decision making.

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

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ASCO Guideline: MammaPrint, Prosigna, EndoPredict

MammaPrint (70-gene signature).

Recommendation 1.8. If a patient is older than 50 and has high clinical risk breast cancer that is node-negative or node-positive with 1-3 positive nodes, the clinician may use the MammaPrint test to guide decisions for adjuvant endocrine and chemotherapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: strong).

Prosigna (PAM50).

Recommendation 1.15. If a patient is postmenopausal and has breast cancer that is node-negative, the clinician may use the Prosigna test to guide decisions for adjuvant systemic chemotherapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

EndoPredict (12-gene risk score).

Recommendation 1.12. If a patient is postmenopausal and has breast cancer that is node-negative or node-positive with 1-3 positive nodes, the clinician may use the EndoPredict test to guide decisions for adjuvant endocrine and chemotherapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.13. If a patient is premenopausal and has breast cancer that is node-negative or node-positive with 1-3 positive nodes, the clinician should not use the EndoPredict test to guide decisions for adjuvant endocrine and chemotherapy (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

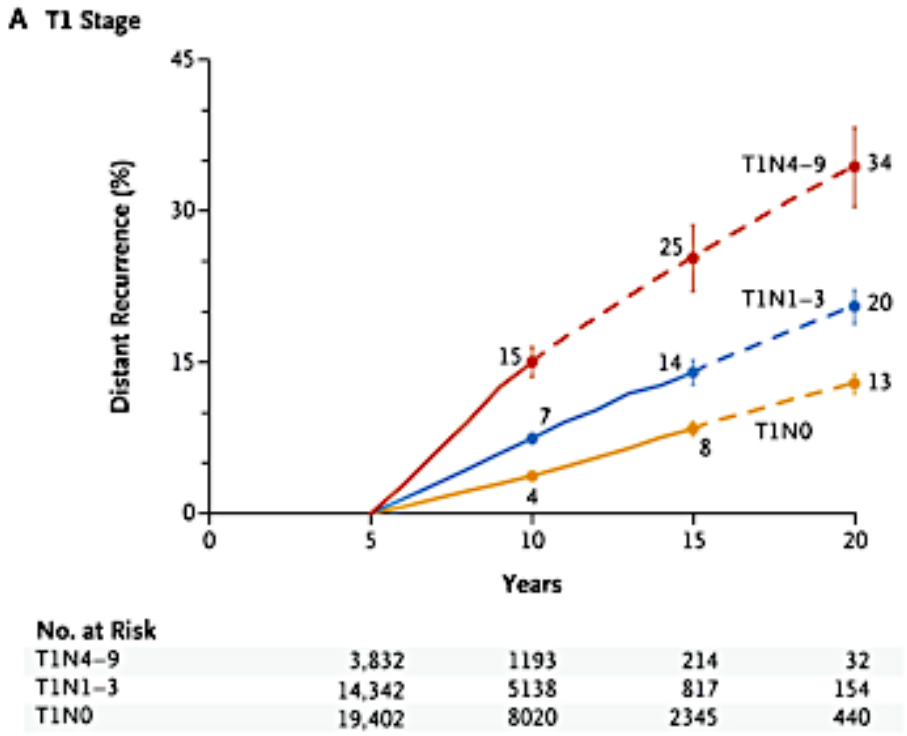
Recommendation 1.14. If a patient has breast cancer with $\geq$ 4 positive nodes, evidence on the clinical utility of routine use of the EndoPredict test to guide decisions for adjuvant endocrine and chemotherapy is insufficient (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

Late recurrence risk
(At or beyond 5 years)

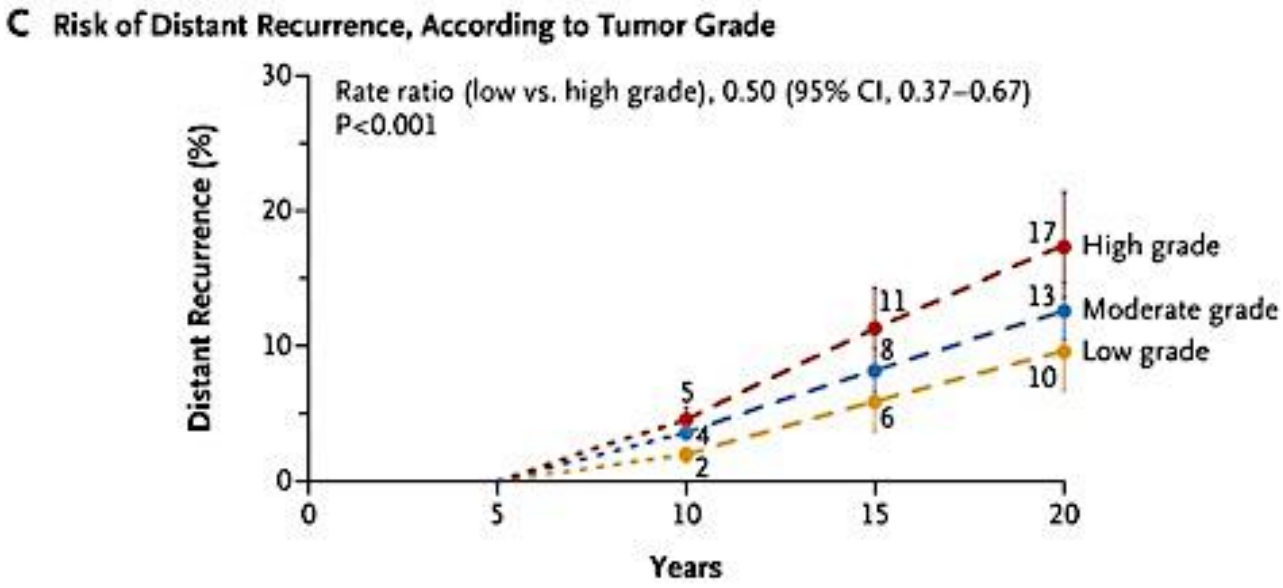
Breast Cancer Index (BCI)

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 et al. N Engl J Med. 2017 Nov 9;377(19):1836-1846

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Extension of Adjuvant Endocrine Therapy: 5 vs 10 Years

	Trial	Duration of Therapy (y)		N	Median Follow-up (y)	Disease-free Survival[1]	Absolute Benefit	Hazard Ratio or Rate Ratio (95% CI)
TAM ➔ AI	MA.17	TAM x 5y	→ Placebo x 5y → AI x 5y	2587 2583	2.5	89.8% 94.4%	4.6%	HR 0.58 (0.45-0.76) P<0.001
TAM ➔ AI	NSABP B-33	TAM x 5y	→ Placebo x 5y → AI x 5y	779 783	2.5	89% 91%	2%	RR: 0.68 P=0.07
TAM ➔ AI	ABCSG 6A	TAM x 5y	→ Placebo x 3y → AI x 3y	469 387	5.2	88.2% 92.9%	4.7%	HR 0.62 (0.40-0.96) P=0.031
TAM ➔ TAM	aTTom	TAM x 5y	→ No treatment → TAM x 5y	3485 3468	10	68% 72%	4%	RR 0.85 (0.76-0.95) P=0.003
TAM ➔ TAM	ATLAS	TAM x 5y	→ No treatment → TAM x 5y	3418 3428	7.6	74.9% 78.6%	3.7%	RR 0.84 (0.76-0.94) p=0.002
AI ➔ AI	MA.17R	TAM x 0-5y → AI x 5y	→ Placebo → AI x 5y	959 959	6.3	91% 95%	4%	HR 0.66 (0.48-0.91) P=0.01
AI ➔ AI	NSABP B-42	AI x 5y	→ Placebo x 5y → AI x 5y	1983 1983	6.9	81.3% 84.7%	3.4%	HR 0.85 (0.73-0.99) P=0.048*
AI ➔ AI	AERAS (N-SAS BC 05)*	AI x 5y	→ No treatment → AI x 5y	843 840	4.9	84.4% 91.9%	7.5%	HR 0.548 P=0.0004

1. Based on disease-free survival or cumulative risk of recurrence rates as reported in the primary publications (note that the definitions of disease-free were not identical across trials)

1. Goss PE et al, J Natl Cancer Inst 2005;97:1262–71. 2. Mamounas EP et al., J Clin Oncol 2008;26:1965-1971. 3. Jakesz et al., J Natl Cancer Inst. 2007 Dec 19;99(24):1845-53. 4. Davies C et al., Lancet. 2013 ;381(9869):805-16. 5. Gray et al., J Clin Oncol 31, 2013 (suppl; abstr 5). 6. Goss PE et al., N Engl J Med. 2016 Jun 5 (Online) 7. Mamounas et al Lancet 2018 November 30 (online)

Genomic Predictors of Outcome in ER+ Early Breast Cancer

Genomic Assay	Genes/Platform	Main Output	Early risk validation?	Late risk validation?
Onco*type* DX	21 genes, RT-PCR, central lab	RS 0-100 (risk, chemo benefit)	Yes	Limited (up to 9 years)
MammaPrint	70 gene signature, array/NGS	Low vs. High genomic risk	Yes	Limited
Prosigna (PAM50 ROR)	50 genes, NanoString	PAM50 intrinsic subtype + ROR score	Yes	Limited
EndoPredict (EPclin)	RT-PCR EP + size/nodes	EP clin low/intermediate/ high	Yes	Limited
Breast Cancer Index (BCI)	H/I + molecular grade, RT-PCR	Continuous risk + H/I high/low	No	Yes, late recurrence risk/extended ET

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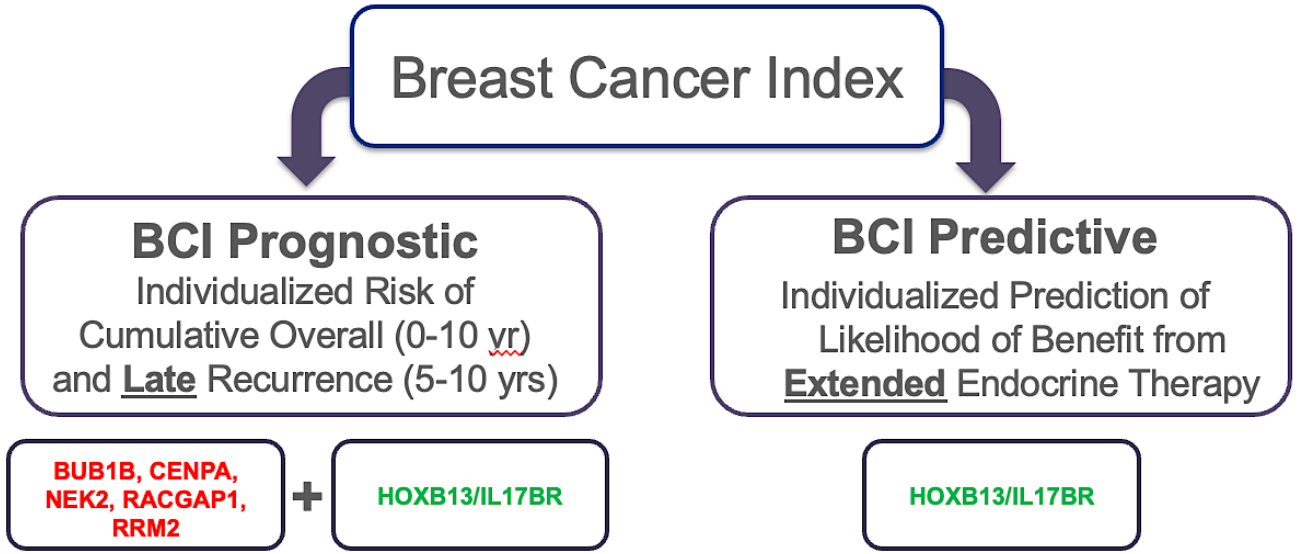
Breast Cancer Index

BCI Components



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

Distribution of BCI scores

Sgroi, JNCI, 2013

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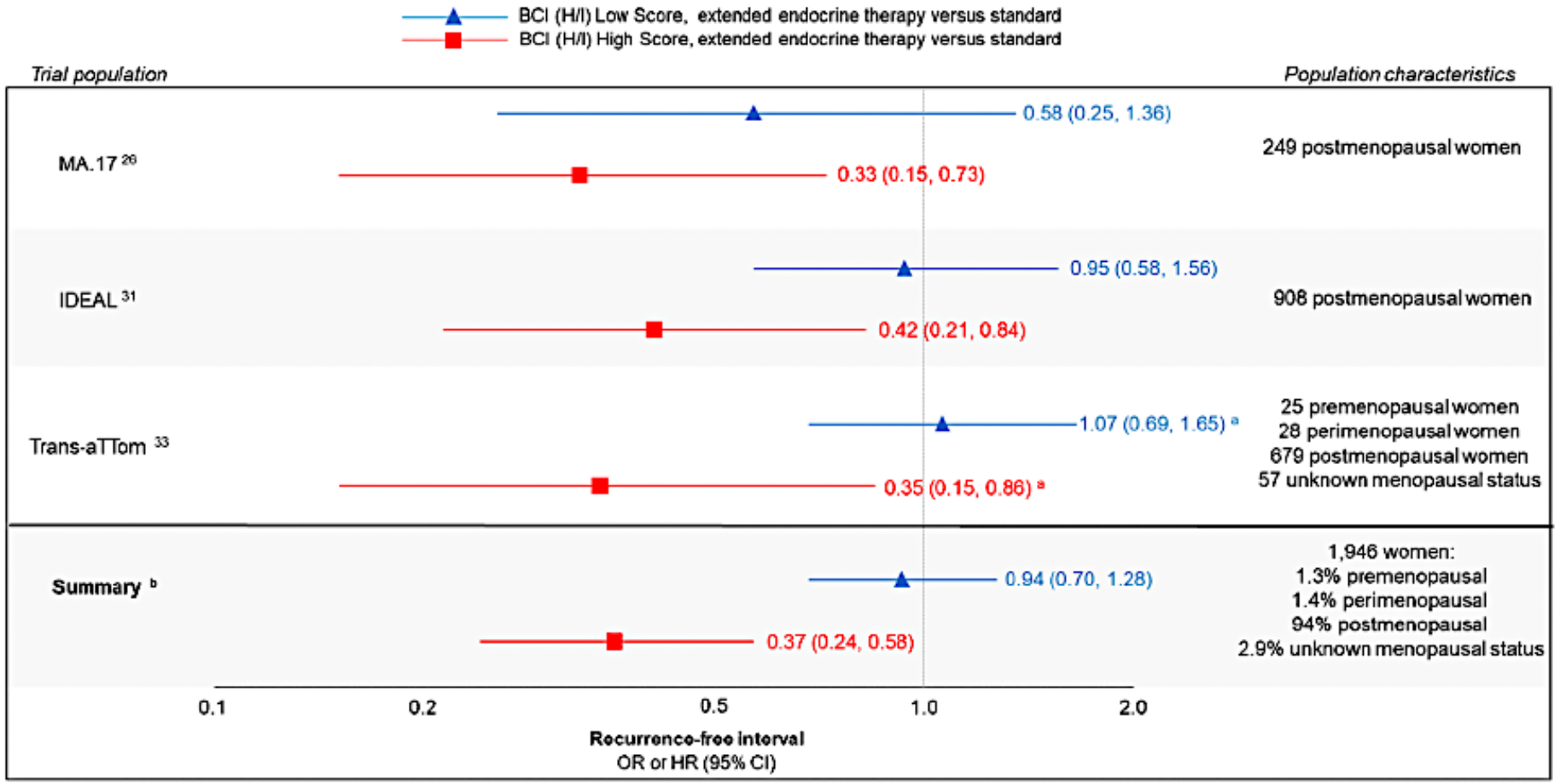
BCI validation in extended adjuvant therapy trials



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, BCRT, 2024

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ASCO Guideline: Extended Adjuvant Therapy

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

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

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

Breast Cancer Index.

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

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

Clinical treatment score post-5 years.

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

Summary: ASCO Guideline 2022

ER+ and HER2–	Premenopausal or Age ≤ 50 Years (evidence quality/strength of recommendation)	Postmenopausal or Age > 50 Years (evidence quality/strength of recommendation)
Node-negative	Oncotype DX (*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

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Case Presentation: 47-year-old premenopausal woman with an ER-positive, HER2-negative, node-negative IDC after partial mastectomy/RT entered on prospective, observational FLEX study: MammaPrint® low-risk

Dr Laurie Matt-Amaral (Akron, Ohio)

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

How often do you encounter patients who discontinue adjuvant endocrine therapy due to tolerability issues?

Which genomic assay do you prefer to guide adjuvant therapy decision-making for your patients with HR-positive, HER2-negative localized breast cancer?

When, if ever, do you order a genomic assay in the neoadjuvant setting?

RTP
RESEARCH TO PRACTICE

Improved 3-year IDFS with anthracycline-based therapy for patients with 70-gene signature High 2, Luminal B, HR+HER2- early-stage breast cancer

Joyce O'Shaughnessy[1], Adam Brufsky[2], Cathy Lynne Graham[3], Cynthia R. C. Osborne[4], Rakhshanda Layeequr Rahman[5], Ahmed Elkhanany[6], Eric Allen Brown[7], Linsey P. Gold[7], Nathalie M. Johnson[8], Danilo Giffoni[9], J. Jaime Alberty-Oller[10], Reshma L. Mahtani[11], Harshini Ramaswamy[12], Nicole Stivers[12], Andrea R. Menicucci[12], William Audeh[12], FLEX Investigators' Group

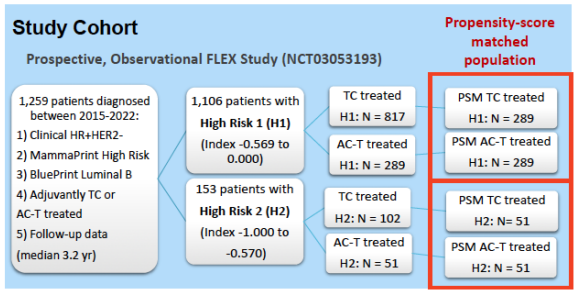
[1]Baylor University Medical Center, Texas Oncology, Sarah Cannon Research Institute, Dallas, TX; [2]University of Pittsburgh, Pittsburgh, PA; [3]Piedmont Cartersville Breast, Carterville, GA; [4]Texas Oncology, Dallas, TX; [5]Texas Tech University Health Sciences Center School of Medicine, Lubbock, TX; [6]Baylor College of Medicine, Houston, Texas; [7]Comprehensive Breast Care, Troy, MI; [8]Legacy Health System, Portland, OR; [9]London Regional Cancer Program, London, Ontario, CA; [10]Kings County Hospital Center, Brooklyn, NY; [11]Miami Cancer Institute, Baptist Health South Florida, Miami, FL;[12]Medical Affairs, Agendia, Inc., Irvine, CA

San Antonio Breast Cancer Symposium®
Presentation ID: PS2-07-03, Date: Dec 10, 2025

Introduction

- ABC trials[1] found no significant differences in outcomes among patients with clinically high-risk HR+, HER2- breast cancer when comparing adjuvant therapy with taxane+cyclophosphamide (TC) vs. an anthracycline- and taxane-based regimen (TaxAC)
- The MammaPrint®, 70-gene assay, identifies patients who derive (neo)adjuvant chemotherapy benefit[2] and the BluePrint, 80-gene assay, further classifies genomic molecular cancer subtype
- Here we provide an updated analysis[3] within a propensity score matched population (PSM) examining the utility of MammaPrint in identifying patients with BluePrint Luminal B, HR+HER2- breast cancer likely to benefit from anthracycline+taxane (AC-T) vs. TC

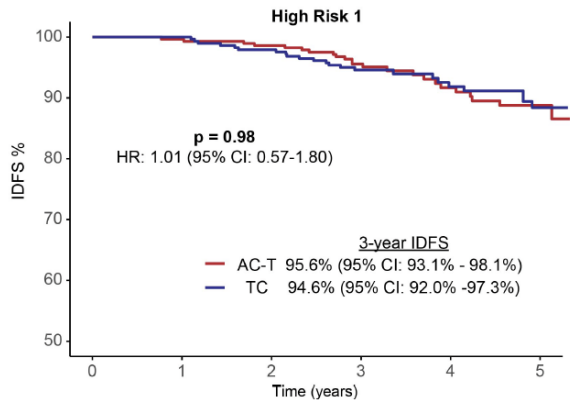
Methods



Statistics

- PSM was performed to balance differences in age, tumor size and nodal status between the TC and AC-T -treated pts for the H1 and H2 groups, separately.
- 3-yr invasive disease-free survival (IDFS)[4], was compared within H1 and H2 groups using Kaplan-Meier analysis and log-rank tests, stratified by TC vs. AC-T
- Cox proportional hazards models were used to evaluate the effect of CT regimen and clinical features on survival within each group

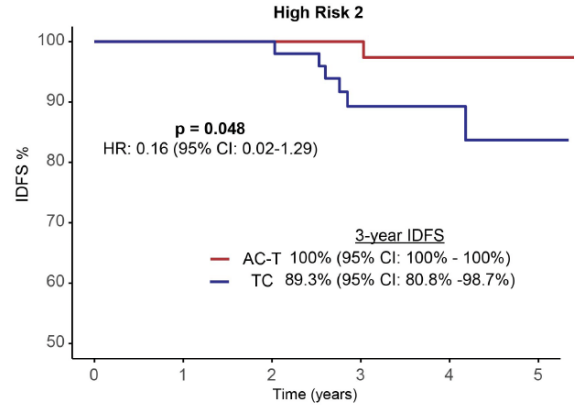
Figure 1. IDFS in patients with High Risk 1 cancer: AC-T vs. TC



Numbers at Risk

H1	0	1	2	3	4	5
AC–T	289	286	277	210	129	59
TC	289	288	276	207	132	70

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

Tables 1-2. Clinical Characteristics of FLEX patients with HR+HER2- disease PSM between AC-T or TC treatment in High Risk 1 (left) and High Risk 2 (right)

High Risk 1	AC-T (N=289)	TC (N=289)	Overall (N=578)	P-value
Age (Years)				
Mean (SD)	54 (± 11)	54 (± 11)	54 (± 11)	0.955
Menopausal Status				
Pre-/Peri-	94 (32.5%)	97 (33.6%)	191 (33.0%)	0.97
Post-	170 (58.8%)	163 (56.4%)	333 (57.6%)	
Unknown	25 (8.7%)	29 (10.0%)	54 (9.3%)	
Race/Ethnicity				
AAPI	10 (3.5%)	15 (5.2%)	25 (4.3%)	0.965
AIAN	1 (0.3%)	0 (0%)	1 (0.2%)	
Black	35 (12.1%)	29 (10.0%)	64 (11.1%)	
Latin American/Hispanic	21 (7.3%)	13 (4.5%)	34 (5.9%)	
Multiple	1 (0.3%)	1 (0.3%)	2 (0.3%)	
White	203 (70.2%)	210 (72.7%)	413 (71.5%)	
Unknown	18 (6.2%)	21 (7.3%)	39 (6.7%)	
Tumor Size				
T1	146 (50.5%)	144 (49.8%)	290 (50.2%)	0.99
T2	125 (43.3%)	131 (45.3%)	256 (44.3%)	
T3	15 (5.2%)	10 (3.5%)	25 (4.3%)	
T4	1 (0.3%)	1 (0.3%)	2 (0.3%)	
Unknown	2 (0.7%)	3 (1.0%)	5 (0.9%)	
Lymph Node Status				
LN-	159 (55.0%)	182 (63.0%)	341 (59.0%)	0.371
LN+	128 (44.3%)	106 (36.7%)	234 (40.5%)	
Unknown	2 (0.7%)	1 (0.3%)	3 (0.5%)	
Grade				
G1	46 (15.9%)	42 (14.5%)	88 (15.2%)	0.995
G2	182 (63.0%)	190 (65.7%)	372 (64.4%)	
G3	58 (20.1%)	55 (19.0%)	113 (19.6%)	
Unknown	3 (1.0%)	2 (0.7%)	5 (0.9%)	

High Risk 2	AC-T (N=51)	TC (N=51)	Overall (N=102)	P-value
Age (Years)				
Mean (SD)	50 (± 11)	52 (± 11)	51 (± 11)	0.681
Menopausal Status				
Pre-/Peri-	23 (45.1%)	24 (47.1%)	47 (46.1%)	0.998
Post-	24 (47.1%)	22 (43.1%)	46 (45.1%)	
Unknown	4 (7.8%)	5 (9.8%)	9 (8.8%)	
Race				
AAPI	5 (9.8%)	2 (3.9%)	7 (6.9%)	
AIAN	0 (0%)	0 (0%)	0 (0%)	
Black	12 (23.5%)	6 (11.8%)	18 (17.6%)	
Latin American/Hispanic	2 (3.9%)	2 (3.9%)	4 (3.9%)	
Multiple	0 (0%)	0 (0%)	0 (0%)	
White	28 (54.9%)	39 (76.5%)	67 (65.7%)	0.645
Unknown	4 (7.8%)	2 (3.9%)	6 (5.9%)	
Tumor Stage				
T1	22 (43.1%)	31 (60.8%)	53 (52.0%)	0.456
T2	25 (49.0%)	19 (37.3%)	44 (43.1%)	
T3	3 (5.9%)	0 (0%)	3 (2.9%)	
T4	0 (0%)	0 (0%)	0 (0%)	
Unknown	1 (2.0%)	1 (2.0%)	2 (2.0%)	
Lymph Node Status				
LN-	27 (52.9%)	33 (64.7%)	60 (58.8%)	0.8
LN+	22 (43.1%)	16 (31.4%)	38 (37.3%)	
Unknown	2 (3.9%)	2 (3.9%)	4 (3.9%)	
Grade				
G1	1 (2.0%)	6 (11.8%)	7 (6.9%)	0.352
G2	16 (31.4%)	19 (37.3%)	35 (34.3%)	
G3	34 (66.7%)	25 (49.0%)	59 (57.8%)	
Unknown	0 (0%)	1 (2.0%)	1 (1.0%)	

Data presented as n (%) unless indicated otherwise; Unknown values excluded; P values of less than 0.05 were considered significant; Abbreviations: N, sample size; SD, standard deviation; AAPI, Asian American and Pacific Islander; AIAN, American Indian or Alaska Native

Tables 3-4. Univariate and Multivariate Cox Proportional Hazards

Association of Clinical Variables on IDFS among High Risk 1			
Variable		**HR (univariable)**	**HR (multivariable)**
Age	Mean (SD)	1.02 (0.99-1.05, p=0.146)	1.02 (0.99-1.05, p=0.221)
Tumor Stage	T1	ref	ref
	T2/3	4.43 (1.98-9.95, p<0.001)*	4.05 (1.74-9.43, p=0.001)*
Lymph Node Status	LN-	ref	ref
	LN+	1.42 (0.80-2.54, p=0.232)	1.16 (0.63-2.14, p=0.632)
Grade	Non G3	ref	ref
	G3	1.09 (0.54-2.21, p=0.800)	1.12 (0.55-2.26, p=0.758)
Chemo Regimen	TC	ref	ref
	AC-T	1.01 (0.57-1.80, p=0.980)	0.99 (0.52-1.67, p=0.812)

Association of Clinical Variables on IDFS among High Risk 2			
H2 IDFS		**HR (univariable)**	**HR (multivariable)**
Age	Mean (SD)	1.03 (0.96-1.11, p=0.383)	1.02 (0.94-1.10, p=0.676)
Tumor Stage	T1	ref	ref
	T2/3	0.92 (0.21-4.12, p=0.916)	1.20 (0.22-6.54, p=0.836)
Lymph Node Status	LN-	ref	ref
	LN+	1.30 (0.29-5.81, p=0.734)	1.39 (0.22-8.84, p=0.730)
Grade	Non G3	ref	ref
	G3	0.26 (0.05-1.34, p=0.107)	0.30 (0.05-1.65, p=0.165)
Chemo Regimen	TC	Ref	ref
	AC-T	0.16 (0.02-1.29, p=0.048)*	0.18 (0.02-1.57, p=0.120)

Data presented as Hazard Ratio (95% CI, p-value). P values of 0.05 or less were considered significant.

Results

- Among all patients, 1,106 had H1 and 153 had H2 HR+HER2- breast cancer
- PSM resulted in no significant differences in clinical/pathologic features between the two chemotherapy groups within each H1 and H2 cohort (Tables 1-2)
- For patients with H1 BC, no significant difference in 3-yr IDFS was observed between AC-T (95.6%) and TC (94.6%) treatment (p = 0.98) (Figure 1)
  - The non-significant absolute difference in IDFS for patients with H1 tumors at 4- and 5-years remained <1%
- In contrast, H2 patients treated with TC had a significantly worse 3-yr IDFS of 89.3% compared with 100% for AC-T-treated patients, with an absolute benefit of 10.7% (p = 0.048) (Figure 2)
  - At 4- and 5-years the absolute differences in IDFS for patients with H2 cancers were 8.1% and 13.7%, respectively, in favor of AC-T treatment
- Multivariate Cox regression analysis within the H1 group showed no association with improved IDFS with AC-T, while the use of AC-T in patients with H2 showed a trend towards improved IDFS compared to TC, but did not reach significance likely due to sample size (Tables 3-4)

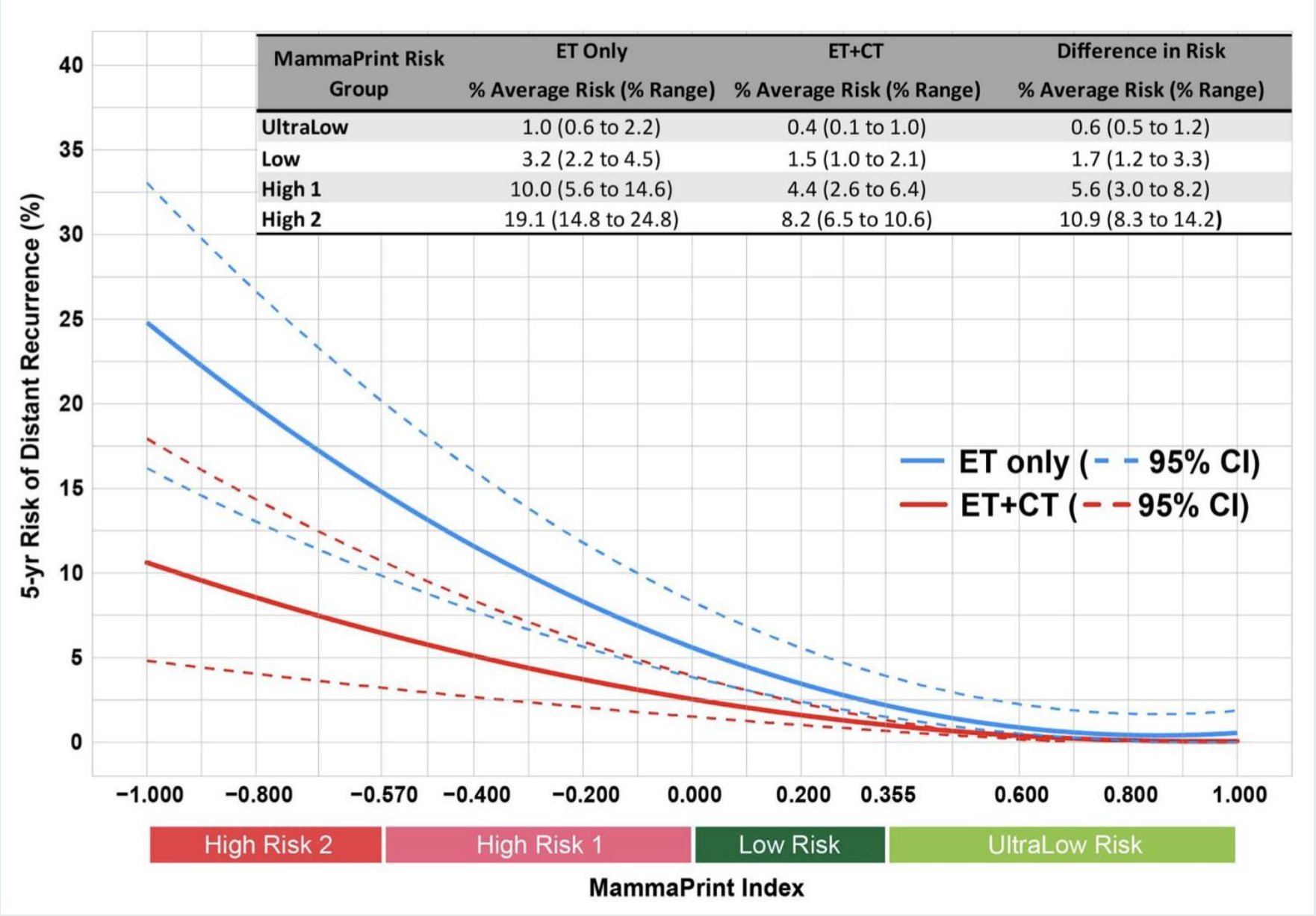
Conclusions

- 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

References: [1]Geyer et al., J Clin Oncol 2024 . [2]Brufsky, et al., JNCI Cancer Spectrum, 2025. [3]O'Shaughnessy, et al; J Clin Oncol 42, 2024 (suppl 16; abstr 511). [4]Tolaney, et al., J Clin Oncol 2021

FLEX Registry: Prediction of Chemotherapy Benefit by MammaPrint Risk Group

MammaPrint Risk Group	ET Only % Average Risk (% Range)	ET+CT % Average Risk (% Range)	Difference in Risk % Average Risk (% Range)
UltraLow	1.0 (0.6 to 2.2)	0.4 (0.1 to 1.0)	0.6 (0.5 to 1.2)
Low	3.2 (2.2 to 4.5)	1.5 (1.0 to 2.1)	1.7 (1.2 to 3.3)
High 1	10.0 (5.6 to 14.6)	4.4 (2.6 to 6.4)	5.6 (3.0 to 8.2)
High 2	19.1 (14.8 to 24.8)	8.2 (6.5 to 10.6)	10.9 (8.3 to 14.2)



Brufsky AM et al. *JNCI Cancer Spectr* 2025;9(5):pkaf079.

Dr Swati Vishwanathan
(Bridgeport, West Virginia)

Case Presentation: 44-year-old premenopausal woman after MRM for T2N0, ER-positive, HER2-negative IDC, Oncotype DX® Recurrence Score (RS®) of 19

Dr Alan Astrow
(Brooklyn, New York)

Case Presentation: 64-year-old woman with locally advanced (19 cm), ER-positive, HER2-low (IHC 1+) Stage IIIB mucinous carcinoma BC: Oncotype DX RS of 18

RTP
RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

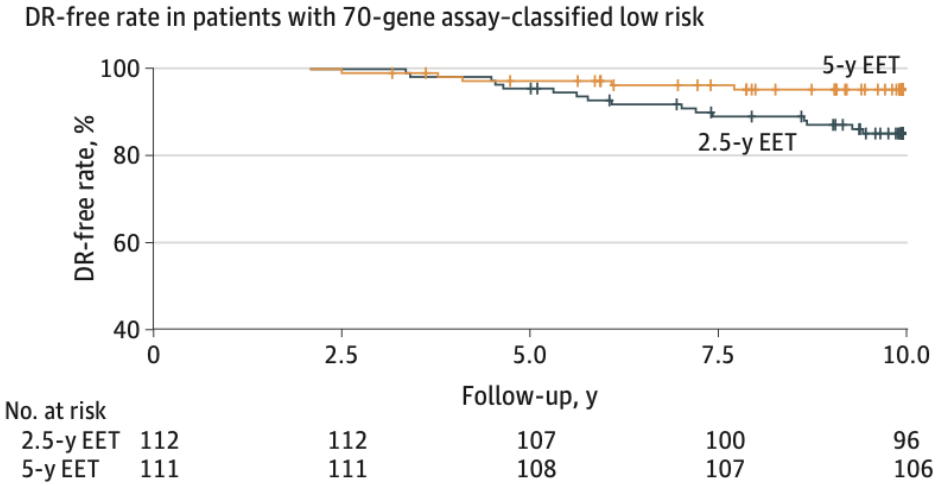
How do you choose between chemotherapy or ovarian suppression for premenopausal patients with an intermediate risk of recurrence?

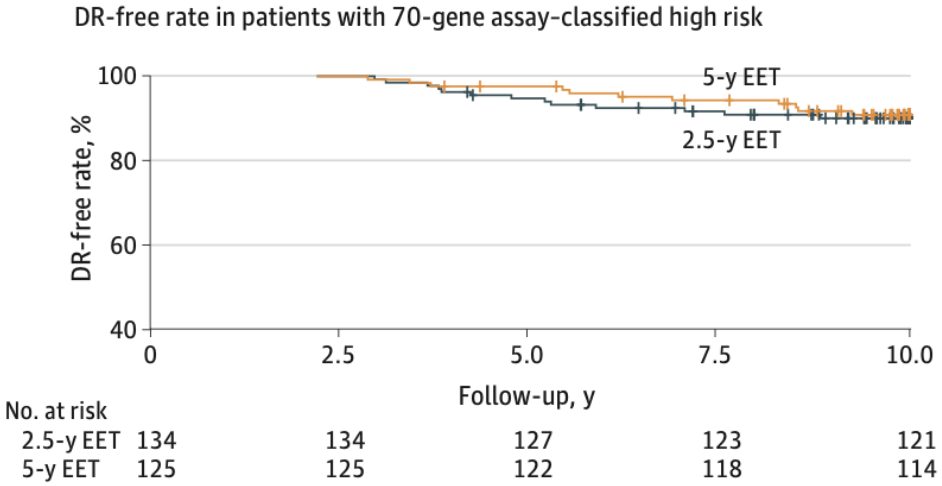
In which situations do you order a genomic assay to determine whether to continue adjuvant endocrine treatment beyond 5 years? Which genomic assay do you prefer in this situation?

How meaningful do you find a genomic assay result indicating a low risk of recurrence if a patient has locally advanced disease?

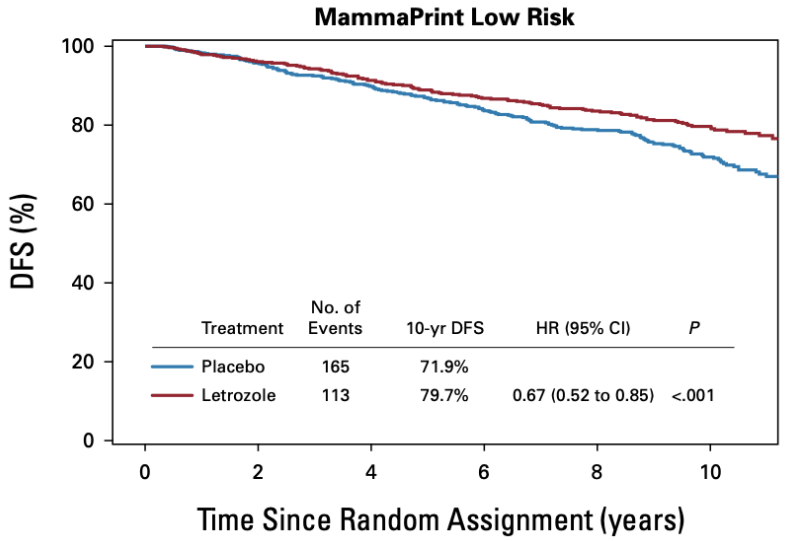
Extended Endocrine Therapy Benefit by MammaPrint Risk Group

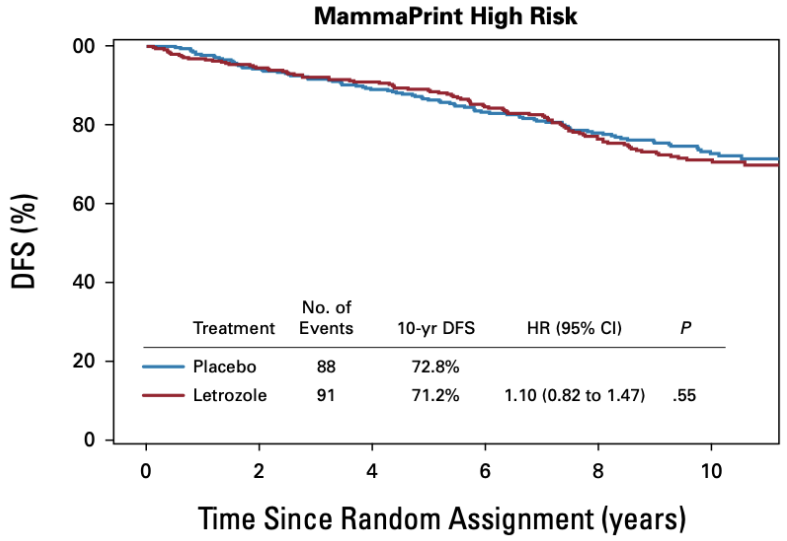
IDEAL Trial





NSABP-B-42 Trial





van 't Veer LJ et al. *JAMA Netw Open* 2024;7(11):e2447530; Rastogi P et al. *J Clin Oncol* 2024;42(30):3561-9.

Agenda

Module 1: Current Role of Genomic Assays in Treatment Decision-Making for Localized Hormone Receptor (HR)-Positive Breast Cancer — Dr DeMichele

Module 2: Role of CDK4/6 Inhibitors and Other Novel Strategies in Therapy for HR-Positive, HER2-Negative Localized Breast Cancer — Dr Jhaveri

Module 3: Evolving Up-Front Treatment Paradigm for HR-Positive, HER2-Negative Metastatic Breast Cancer (mBC) — Dr Rugo

Module 4: Clinical Utility of Agents Targeting the PI3K/AKT/mTOR Pathway for Patients with Progressive HR-Positive mBC — Dr Mayer

Module 5: Current and Future Role of Oral Selective Estrogen Receptor Degraders for Progressive HR-Positive mBC — Dr Wander

RTP RESEARCH TO PRACTICE

Role of CDK4/6 Inhibitors in HR-Positive, HER2-Negative Localized BC

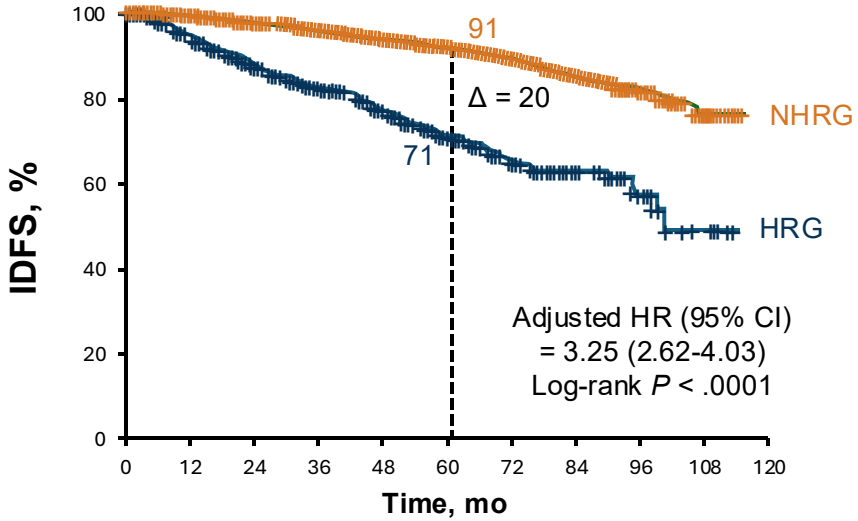
Komal Jhaveri, MD, FACP, FASCO
Patricia and James Cayne Chair for Junior Faculty
Associate Attending, Breast Medicine and Early Drug Development Service
Section Head, Endocrine Therapy Research Program
Memorial Sloan Kettering Cancer Center

Associate Professor
Weill Cornell Medical College
New York, New York

Risk of Recurrence Risk is High in Patients with Node-Positive HR+, HER2- EBC

- Disease recurrence occurs within 5 years on standard ET in 30% of patients with node-positive, HR+, HER2- EBC
- Real-word evidence from the Flatiron Health database reflected this pattern in patients with clinical and pathologic features resembling those studied in cohort 1 of the monarchE study
- Intensifying treatment may be beneficial

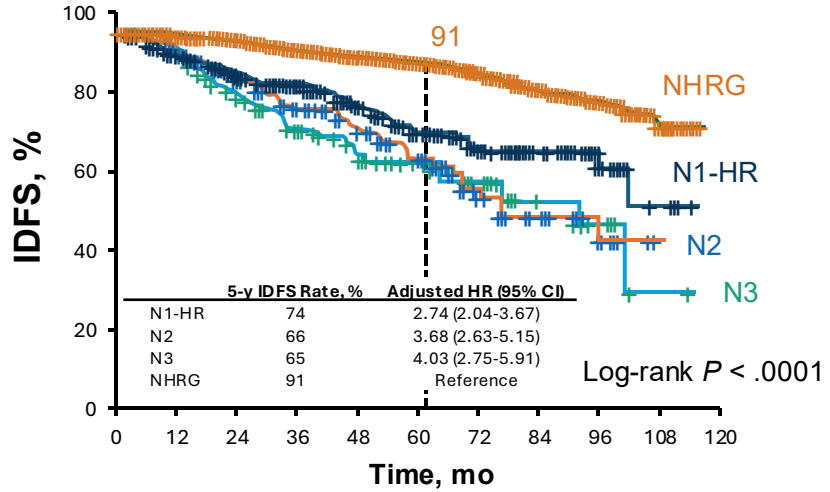
IDFS in High-Risk Group vs Non-High-Risk Group



No. at Risk											
NHRG	3,999	3,491	2,835	2,217	1,706	1,159	727	438	209	51	0
HRG	546	468	367	287	218	156	95	51	24	5	0

Risk of recurrence is more than 3-fold in patients similar to those of cohort 1 in monarchE

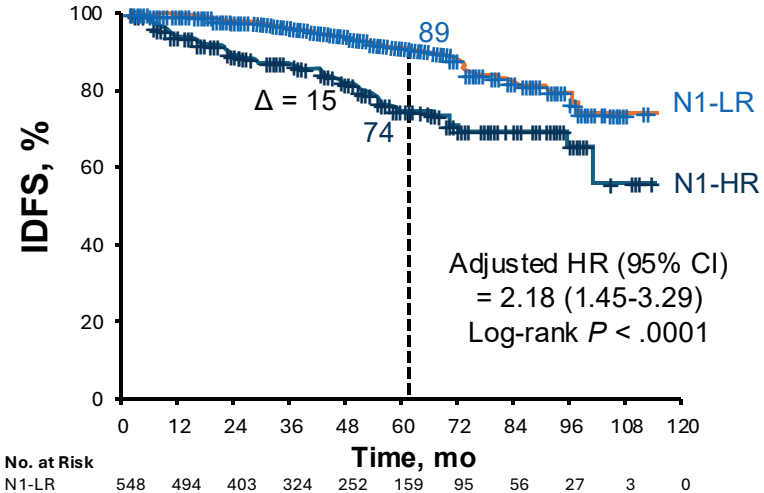
IDFS in High-Risk Group by Nodal Status vs Non-High-Risk Group



No. at Risk											
NHRG	3,999	3,491	2,835	2,217	1,706	1,159	727	438	209	51	0
N1-HR	286	242	190	150	118	81	51	27	13	4	0
N2	161	135	106	81	60	46	25	14	6	0	
N3	99	91	71	56	40	29	19	10	5	1	0

Risk of recurrence is at least 2.7-fold in patients across nodal subgroups

IDFS in N1-HR vs N1-LR Subgroups



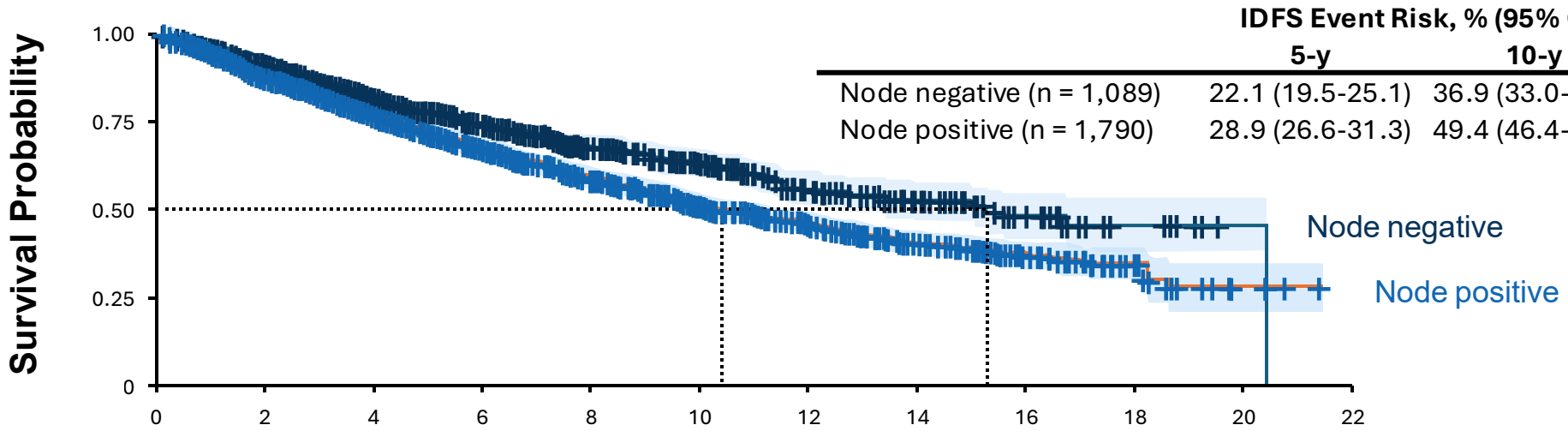
No. at Risk											
N1-LR	548	494	403	324	252	159	95	56	27	3	0
N1-HR	286	242	190	150	118	81	51	27	13	4	0

In patients with high-risk N1 disease
- Increased by 2.2 fold
- Differs by 15% at 5 years

Tolaney SM, et al. NCODA. 2025.

Risk of Recurrence is High in Node-Negative HR+, HER2- EBC

- Using ConcertAI Patient360 database, restrospective analysis was performed inpatients with stage II/III HR+, HER2- EBC ≥18 years who underwent surgery and received adjuvant ET
- For patients with EBC cohort (N = 3,133), approximately one-third (n = 1,089) had node-negative disease and high risk of recurrence (5-year risk: 22.1 %)



No. at Risk (No. Censored)												
Node negative	1,089 (0)	909 (82)	570 (343)	398 (467)	265 (571)	181 (639)	99 (705)	52 (747)	27 (769)	10 (785)	1 (794)	0 (794)
Node positive	1,790 (0)	1,423 (144)	995 (413)	715 (586)	504 (711)	321 (836)	208 (923)	123 (987)	66 (1,036)	23 (1,076)	5 (1,090)	0 (1,095)

O'Shaughnessy J et al. *Breast* 2025;81:104437.

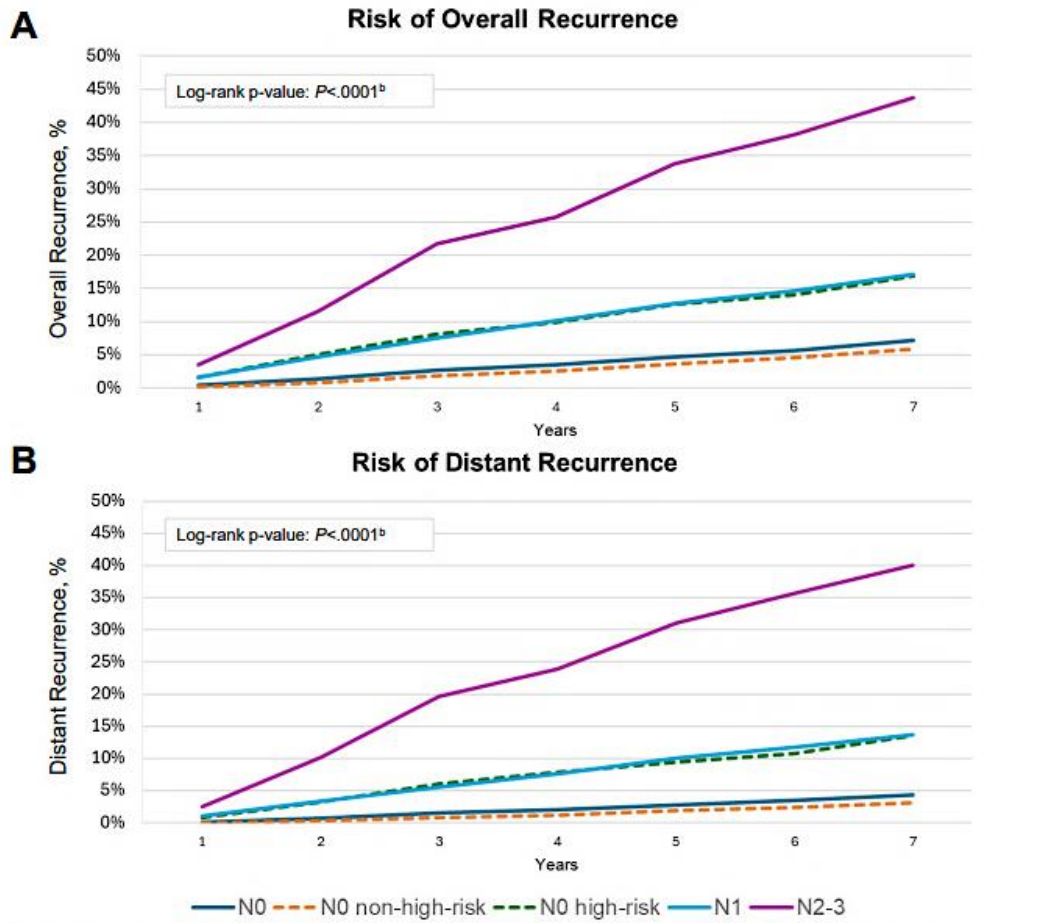
Risk of Recurrence in Node-Negative and Node-Positive HR+ BC

- Of 15,017 patients diagnosed with EBC in the Flatiron database, 7564 met inclusion criteria (**Figure 1**):
  - **N0 disease**: 5557 (73.5%)
    - **N0 high-risk**: 679/5557 (12.2%)
    - **N0 non–high-risk**: 4878/5557 (87.8%)
  - **N1 disease**: 1560 (20.6%)
  - **N2-3 disease**: 447 (5.9%)
- Median follow-up was **79.1 mo** (quartile [Q]1-Q3 45.7-113.6 mo)

All cause mortality risk by nodal status

Incidence (95% CI), %	N0	N0 Non-high-risk	No High risk	N1	N2-3
3-year	2.5 (2.1-3.0)	2.4 (1.9-2.9)	3.7 (2.4-5.6)	3.8 (2.9-5.0)	11.3 (8.5-15.0)
5-year	5.8 (5.0-6.6)	5.4 (4.7-6.3)	8.1 (5.9-11.1)	9.1 (7.6-11.0)	21.5 (17.4-26.4)
7-year	11.2 (10.0-12.5)	10.4 (9.2-11.7)	16.8 (13.0-21.4)	15.9 (13.5-18.6)	34.9 (29.5-41.0)

Overall (A) and Distant (B) Recurrence Risk

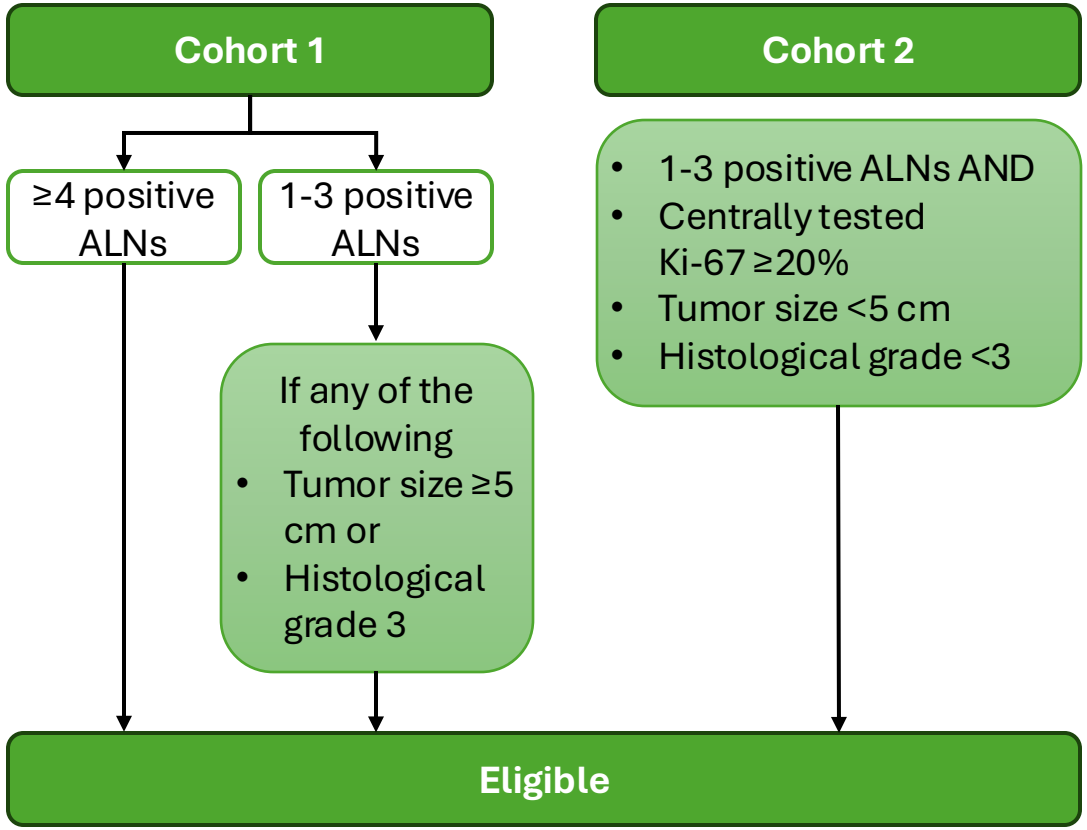


[a] Kaplan-Meier analysis started at initial diagnosis date. Patients without an event were censored on their last confirmed structured activity date.
[b] Overall and distant ROR log-rank differences were evaluated between N0, N1, and N2-3 groups

Jhaveri K et al. Ann Oncol. 2024

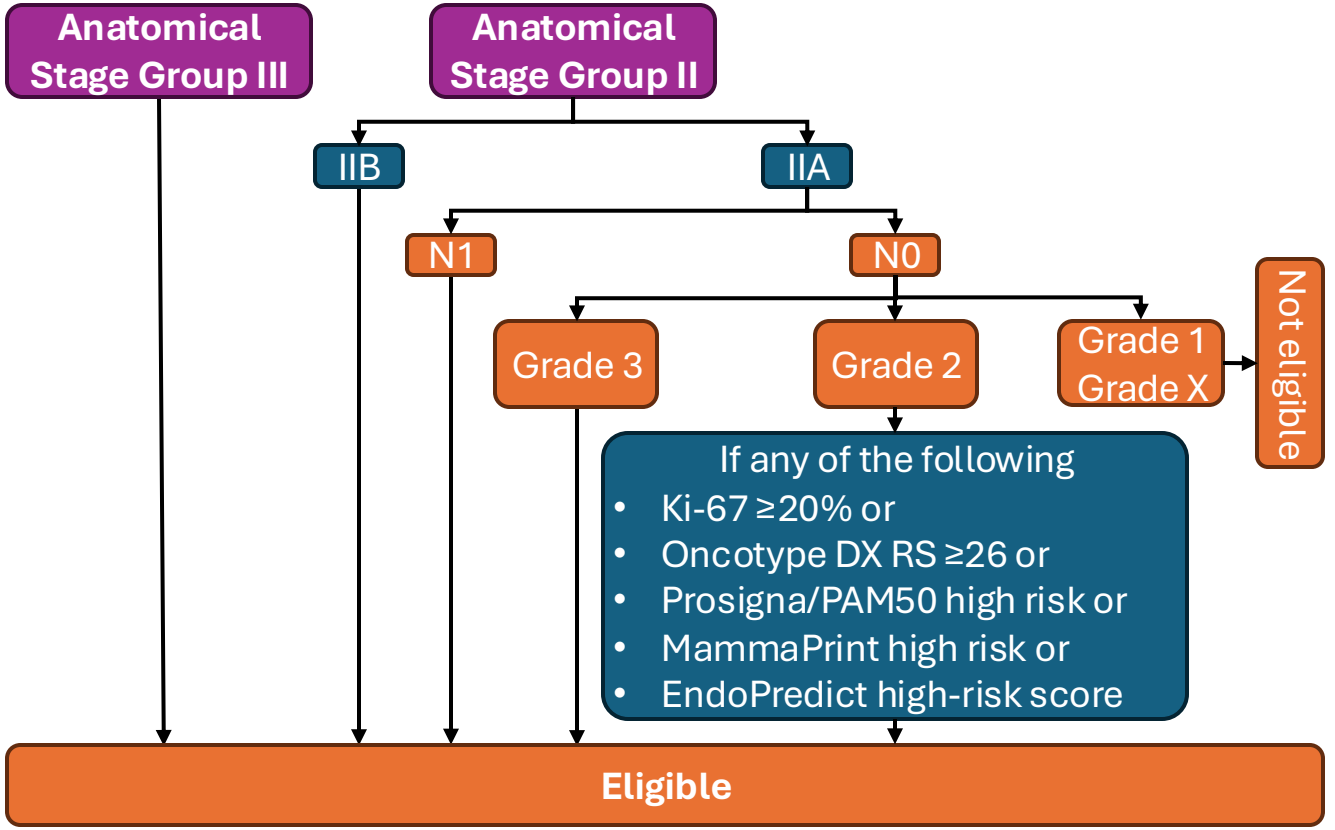
Who are Candidates for Adjuvant CDK4/6i Therapy: Different Eligibility Criteria and Indications Based on monarchE and NATALEE

monarchE Eligibility Criteria



Abemaciclib with ET (tamoxifen or an AI) indicated for adjuvant treatment of patients with HR+/HER2-, node-positive, EBC at high risk of recurrence

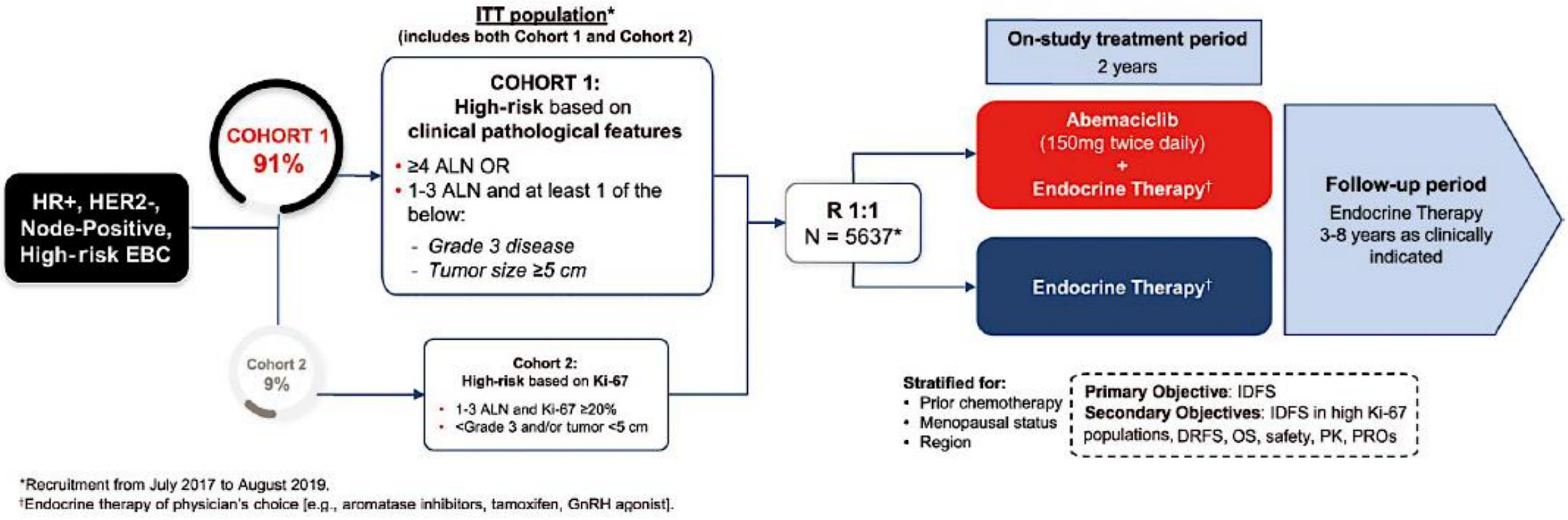
NATALEE Eligibility Criteria



Ribociclib with an AI indicated for adjuvant treatment of patients with HR+/HER2-, stage II and III EBC at high risk of recurrence, including those with node-negative disease

Slamon D et al. ASCO 2023. Abstract LBA500; Slamon D et al Ther Adv Med Oncol 2023

monarchE: Study Design



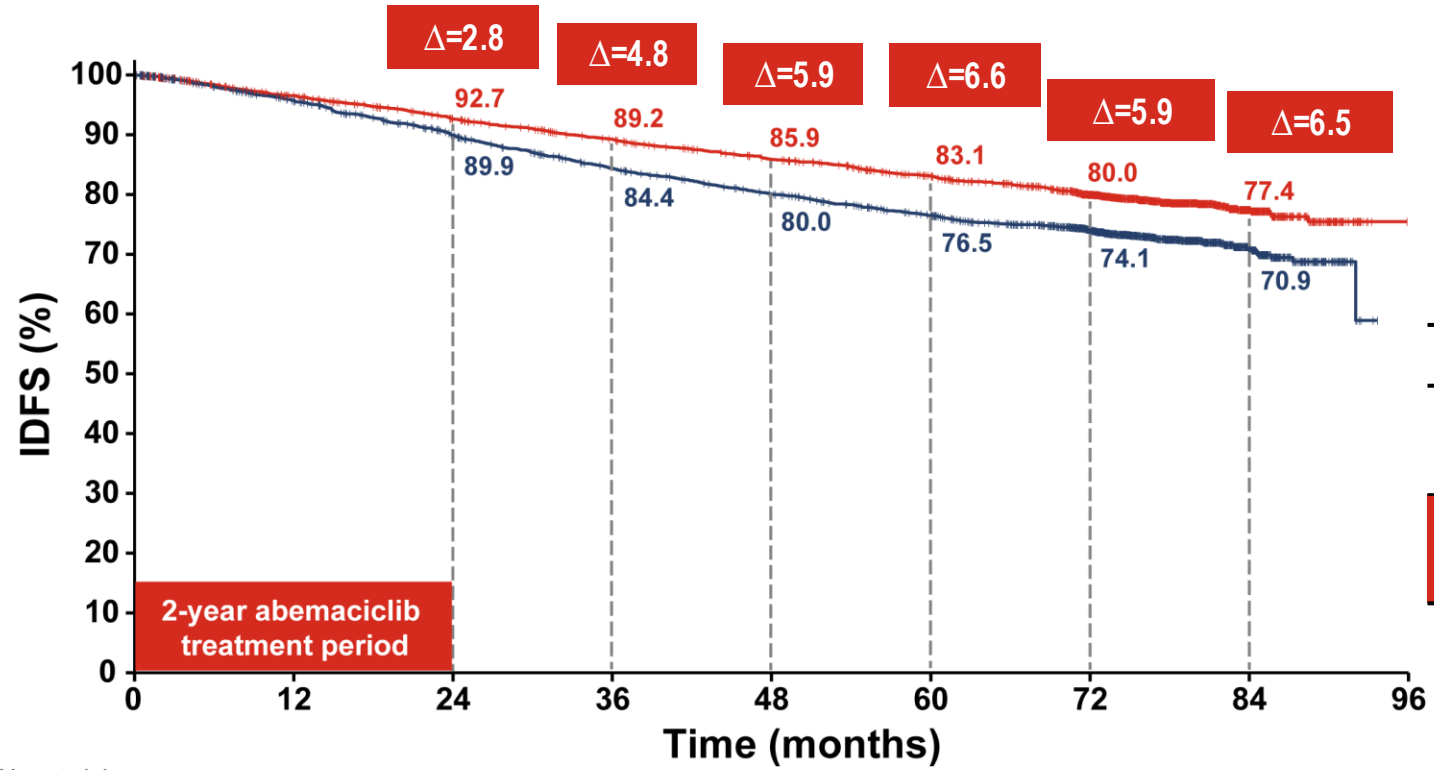
*Recruitment from July 2017 to August 2019.
†Endocrine therapy of physician's choice [e.g., aromatase inhibitors, tamoxifen, GnRH agonist].

- Median Age: 51 (15% age 65+)
- 40% N1; 60% N2
- 95% prior (neo)adjuvant chemo

- **Here, we report 5-year efficacy results from a prespecified monarchE analysis**
  - **Data cutoff July 3rd, 2023**
- **Extent of follow-up at OS IA3 allows for robust estimation of IDFS and DRFS at the critical 5-year landmark**
- **Median follow-up time is 4.5 years (54 months)**
- **All patients are off abemaciclib**
  - **More than 80% of patients have been followed for at least 2 years since completing abemaciclib**

Harbeck et al. ESMO 2023; Johnston S et al. J Clin Oncol. 2020; 38, 3987

Sustained IDFS Benefit in ITT: Evolution of Yearly Rates



No. at risk

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

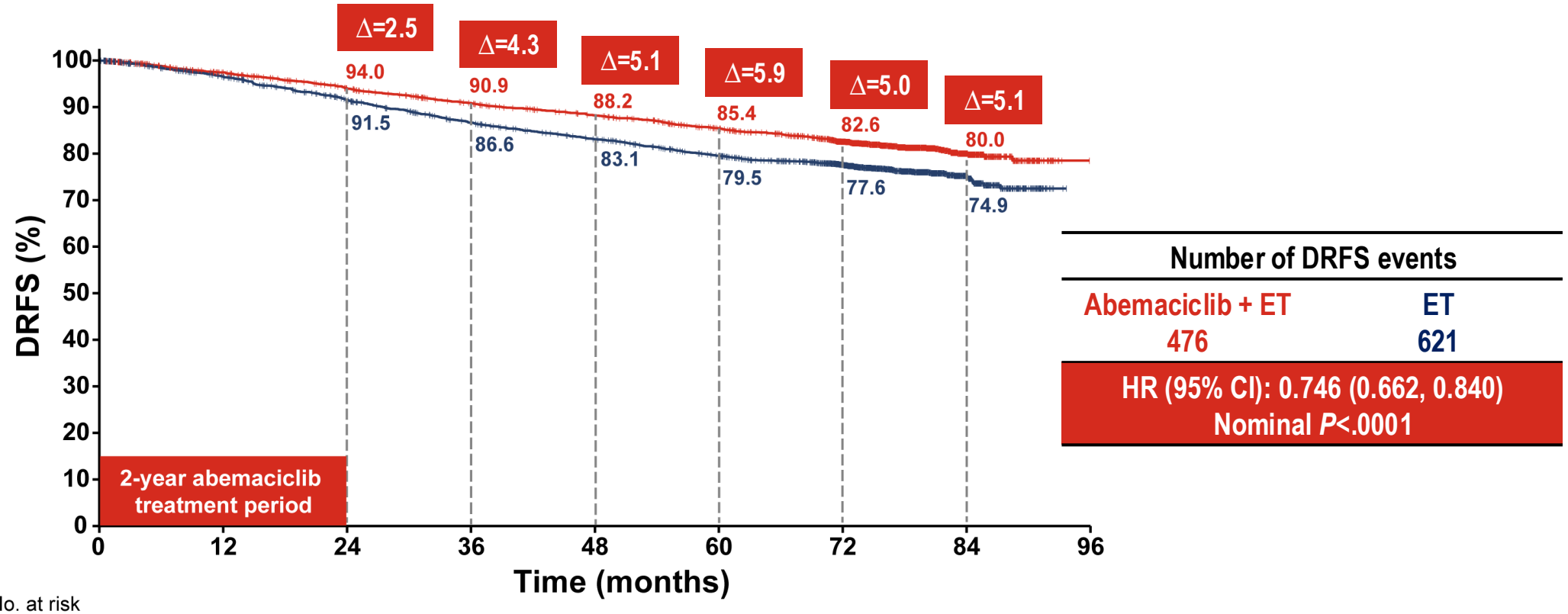
Number of IDFS events	
Abemaciclib + ET	ET
547	722

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

Johnston S et al. Ann Oncol. 2025

Sustained DRFS Benefit in ITT: Evolution of Yearly Rates



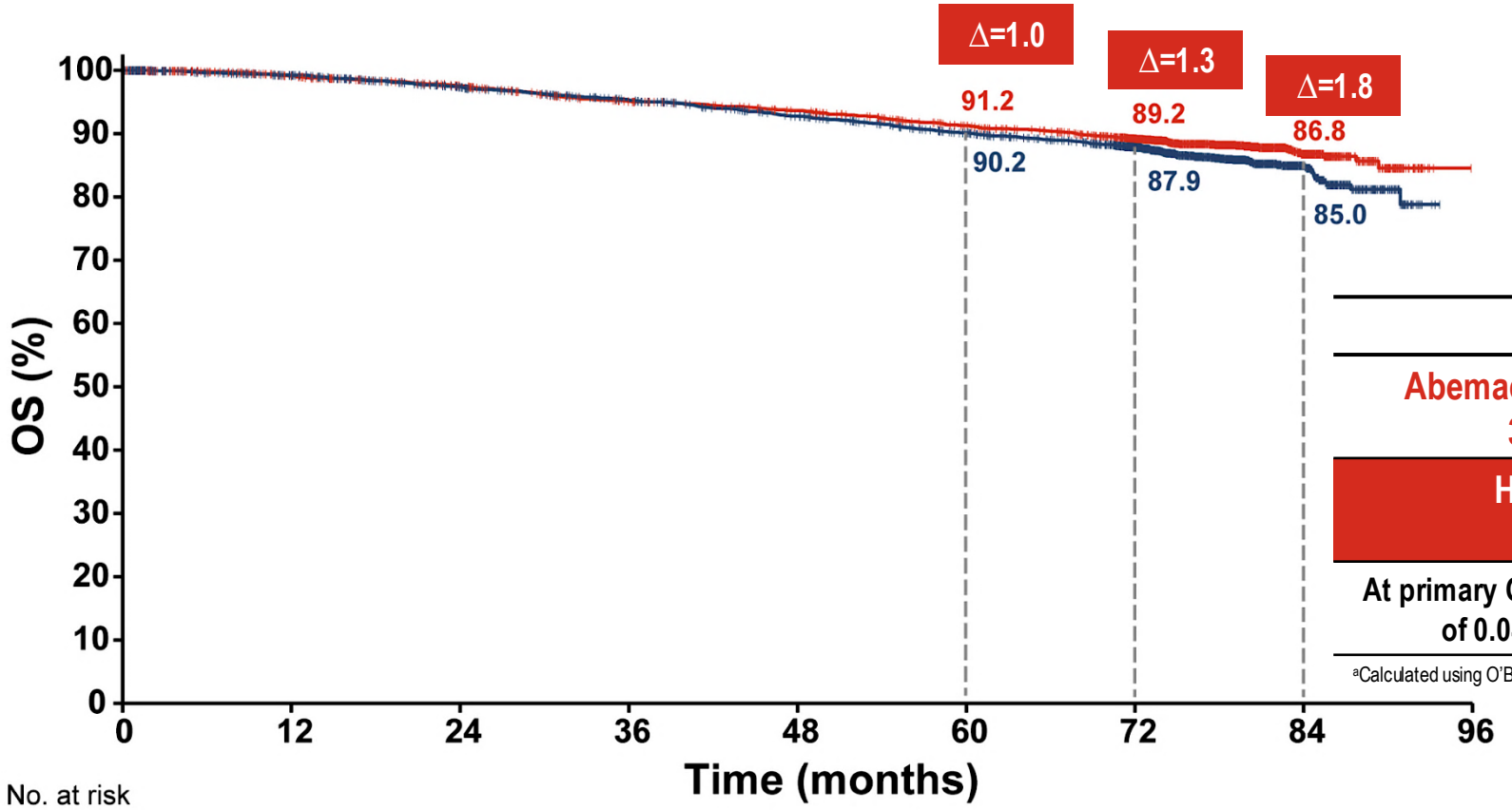
Abemaciclib + ET reduced the risk of DRFS events by 25.4% compared to ET alone
Additionally, consistent DRFS benefit observed across prespecified subgroups

[a]Data in supplement

Stephen Johnston, MD, PhD

Johnston S et al. Ann Oncol. 2025

Key Secondary Endpoint: Overall Survival in ITT



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

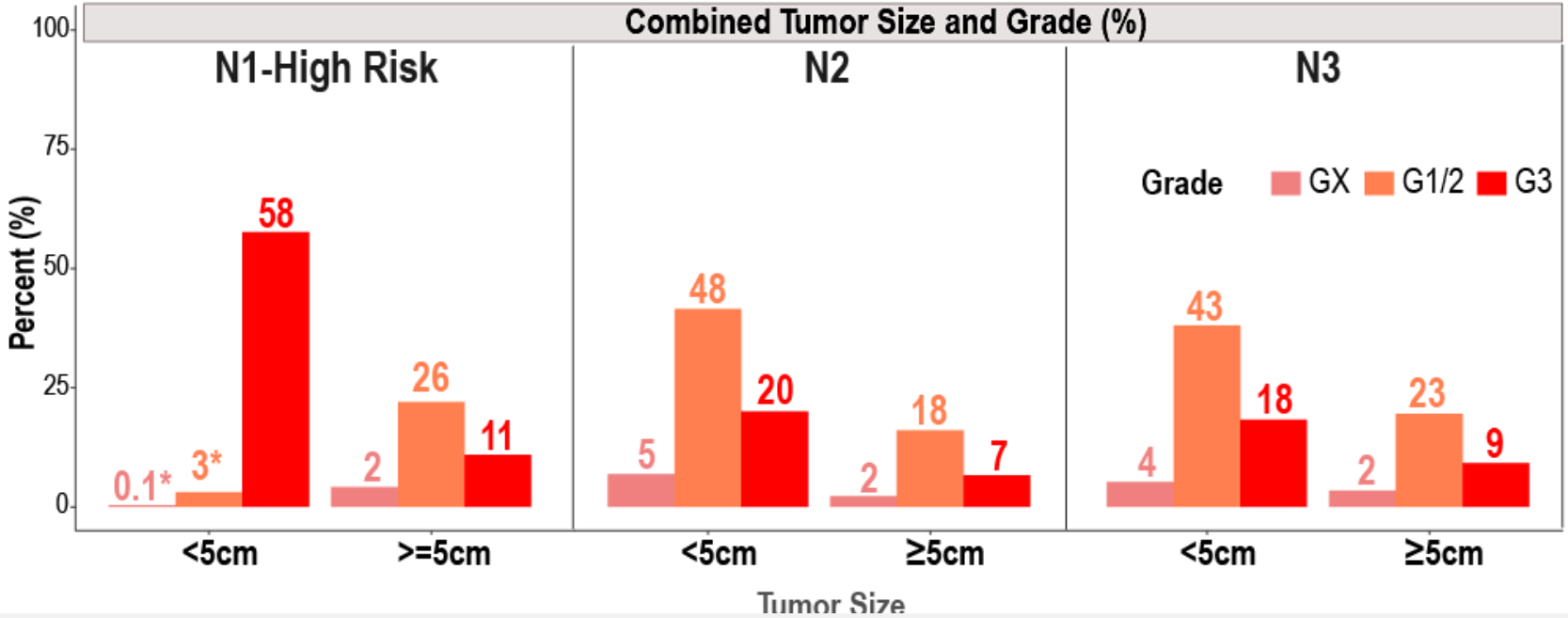
[a]Calculated using O'Brien-Fleming type stopping boundary based on the observed number of events

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. Ann Oncol. 2025

monarchE: Subgroup Analysis of Adjuvant Abemaciclib + Endocrine Therapy For HR+, HER2-, High-Risk Early Breast Cancer By Nodal Status

	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



-Over 40% with N1-High risk disease received Neoadjuvant chemotherapy compared to <30% with N3 disease

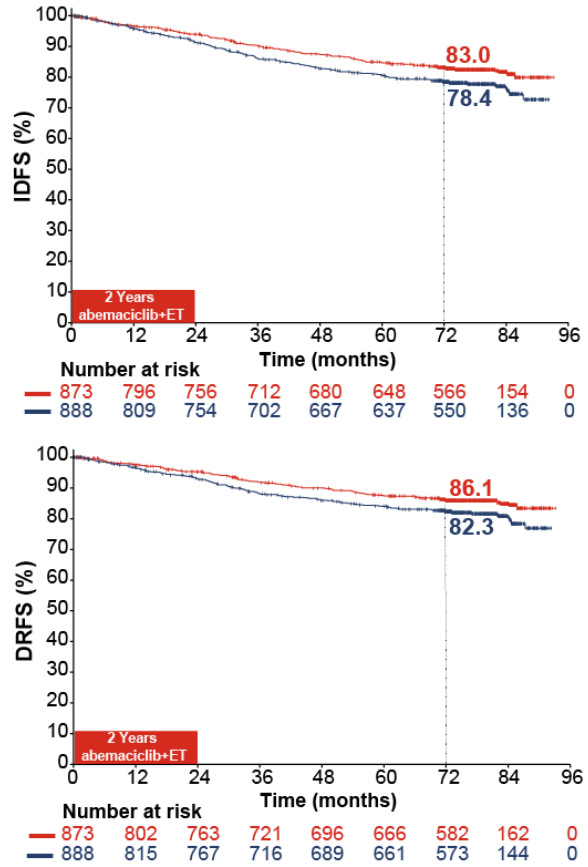
-Conversely, adjuvant chemotherapy and radiation therapy was higher in N2 and N3 disease

Patients with N1 high risk disease presented more G3 tumors and Ki-67 ≥20% compared to N2 and N3

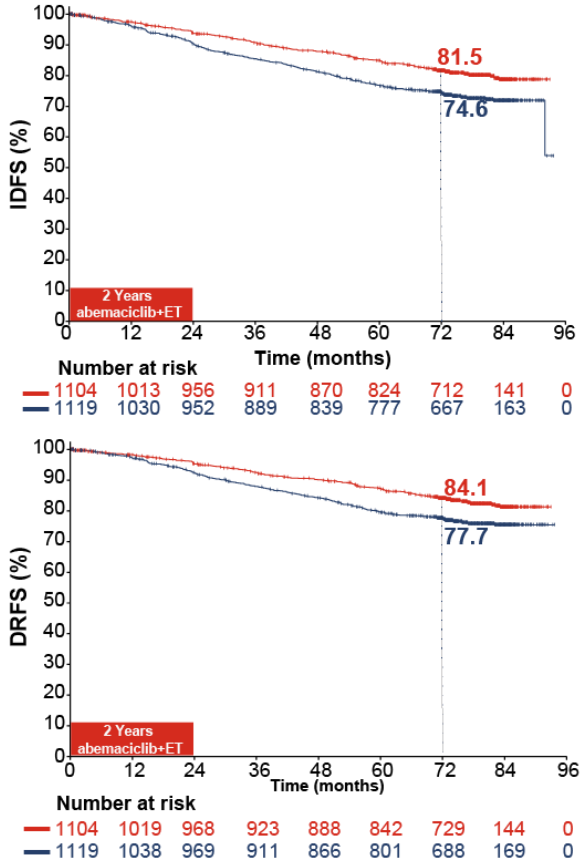
Cortes et al.; SABCS 2025

monarchE subgroup analysis: Consistent and sustained IDFS and DRFS benefit across all ALN subgroups

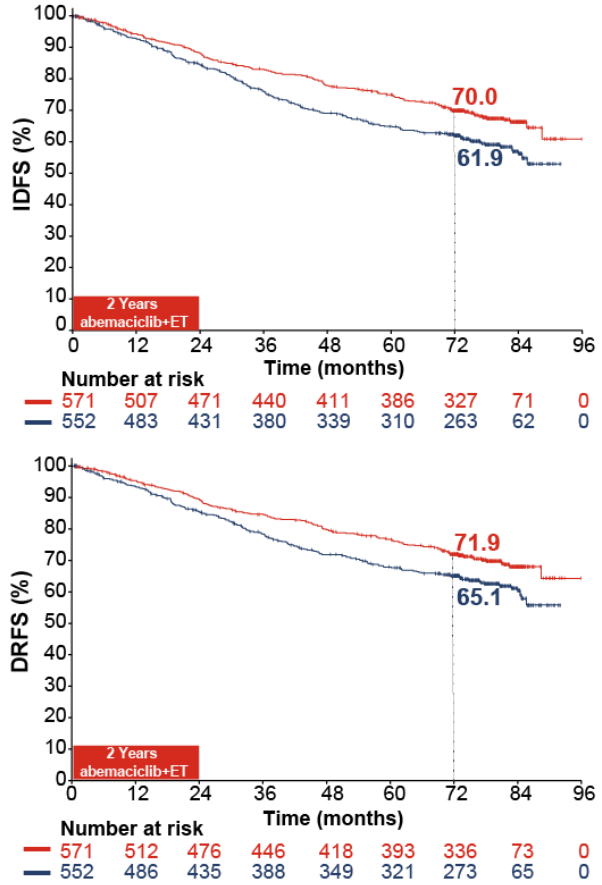
N1 High-Risk



N2



N3



In the ET alone arm, N1 and N2 disease had comparable recurrence risk, with higher risk 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.

Cortes et al.; SABCS 2025

Study Design: NATALEE

An open-label, multicenter, randomized, phase 3 trial[1,2]

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[c]

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

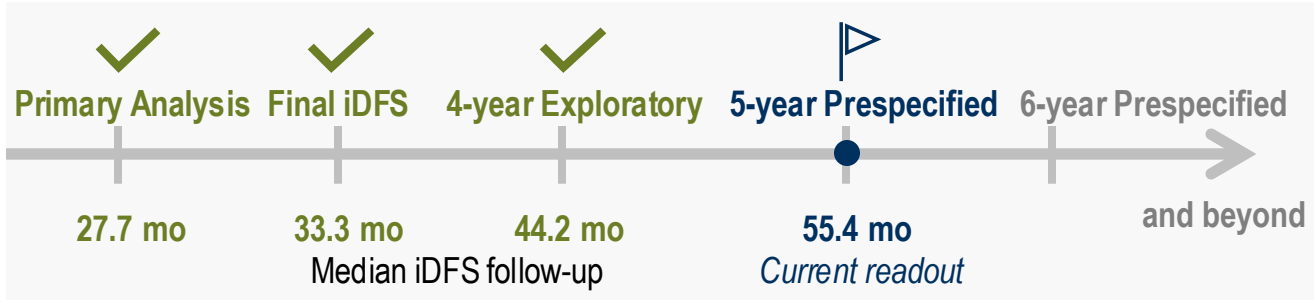
NSAI
Letrozole or anastrozole[b] for **≥ 5 y**
+ goserelin in men and premenopausal women

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.



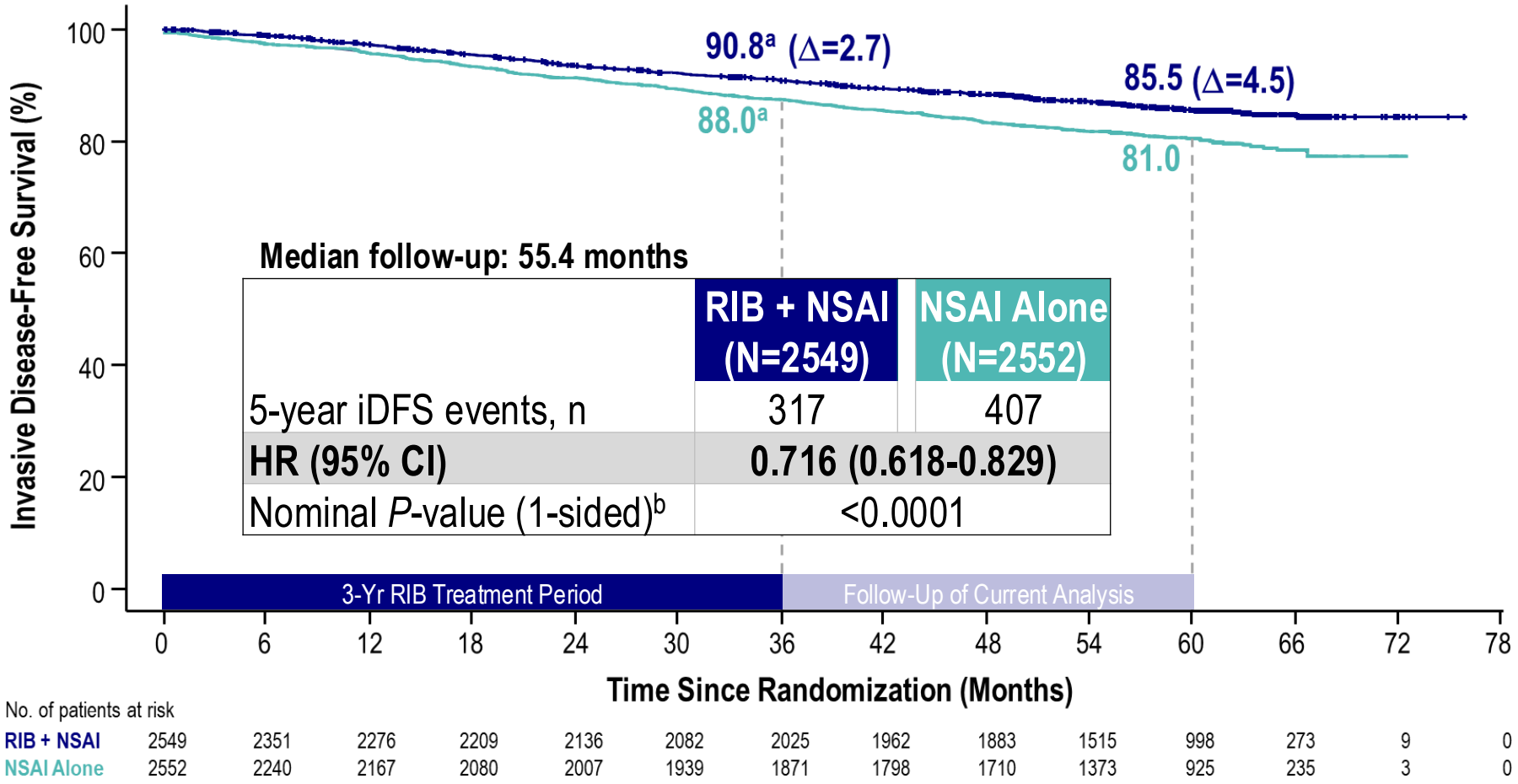
Key patient characteristics:

- Median age 52; ~44% premenopausal
- Stage IIA: 20%; IIB: 20%; III: 60%
- N0: 28%; N1: 41%; N2/N3: 19%
- Prior chemo: 88%

Crown J et al. ESMO Open; 2025

iDFS in the ITT Population

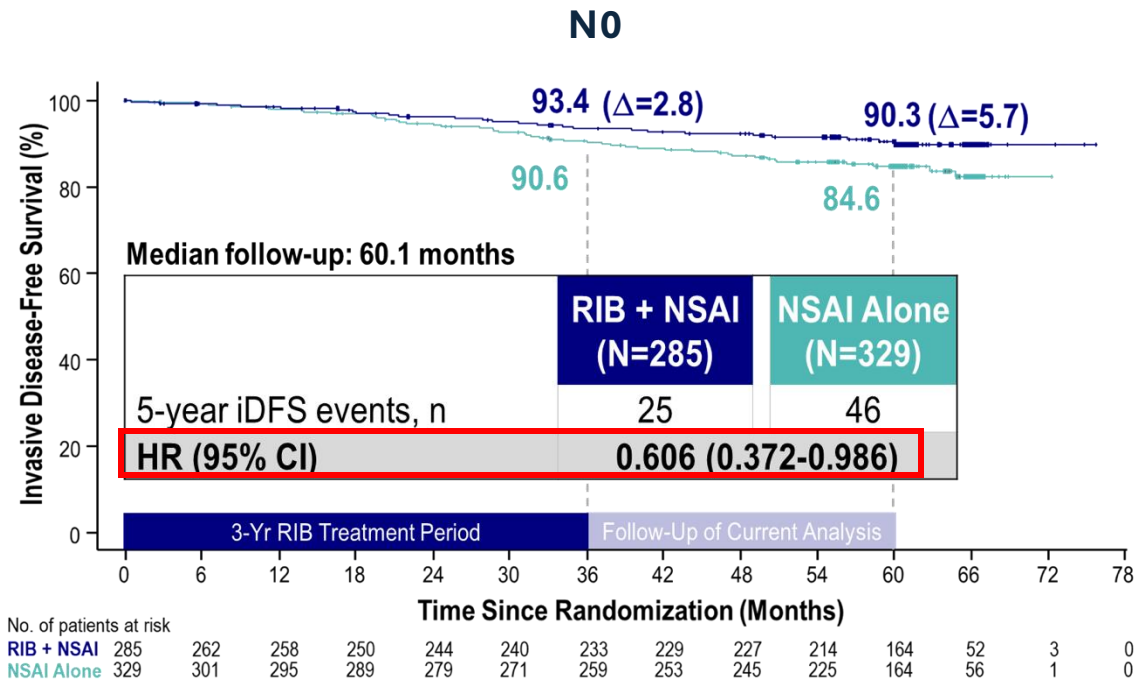
With 55.4 months of follow-up, RIB continues to demonstrate a durable iDFS benefit

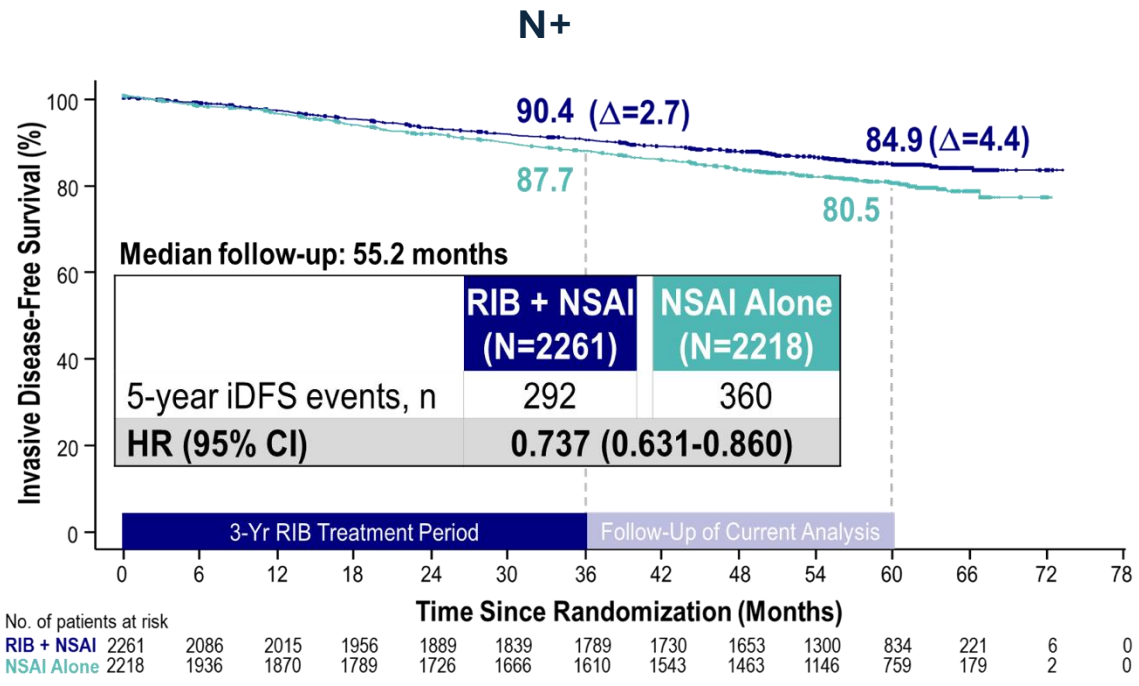


[a]The difference between percentages does not equal 2.7 due to rounding.
[b]Comparison of survival between treatment arms was generated by stratified log-rank test (1-sided P-value, informational and not pre-planned).
CI, confidence interval; HR, hazard ratio; IDFS, invasive disease-free survival; ITT, intention to treat; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

Crown J et al. ESMO Open; 2025

iDFS by Nodal Status in NATALEE





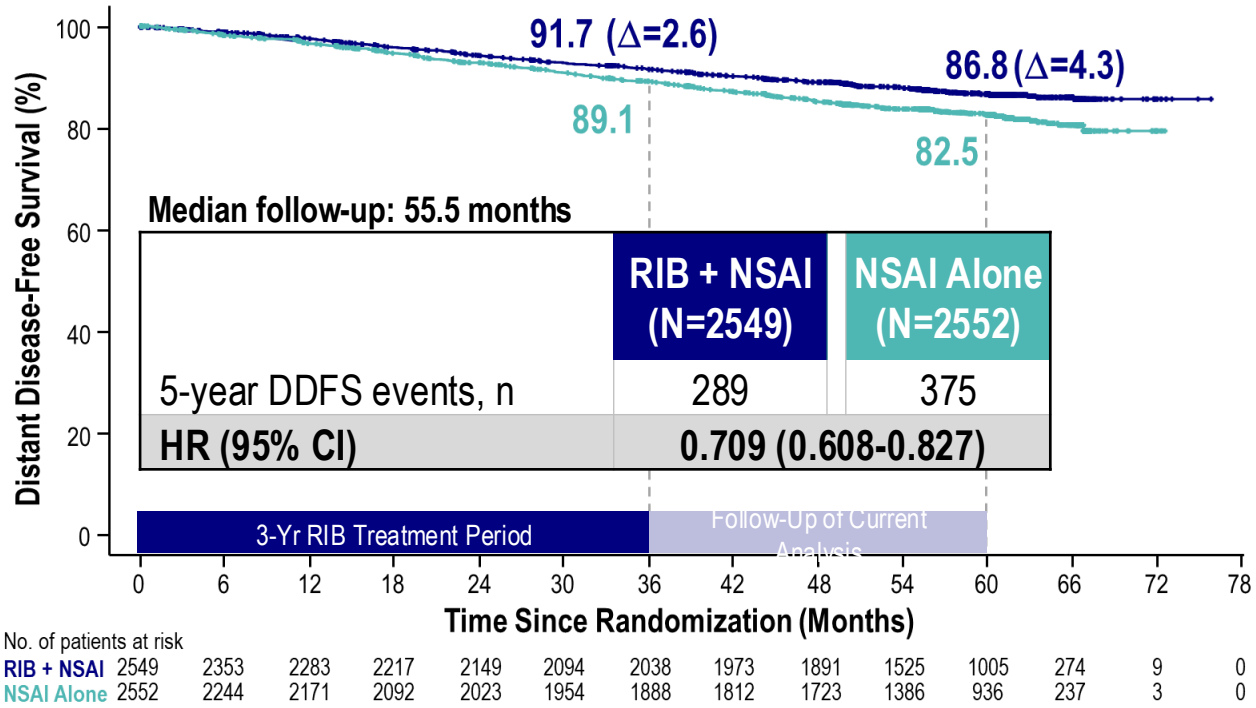
HR, hazard ratios; iDFS, invasive disease-free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

Crown J et al. ESMO Open 2025. Oral LBA14.

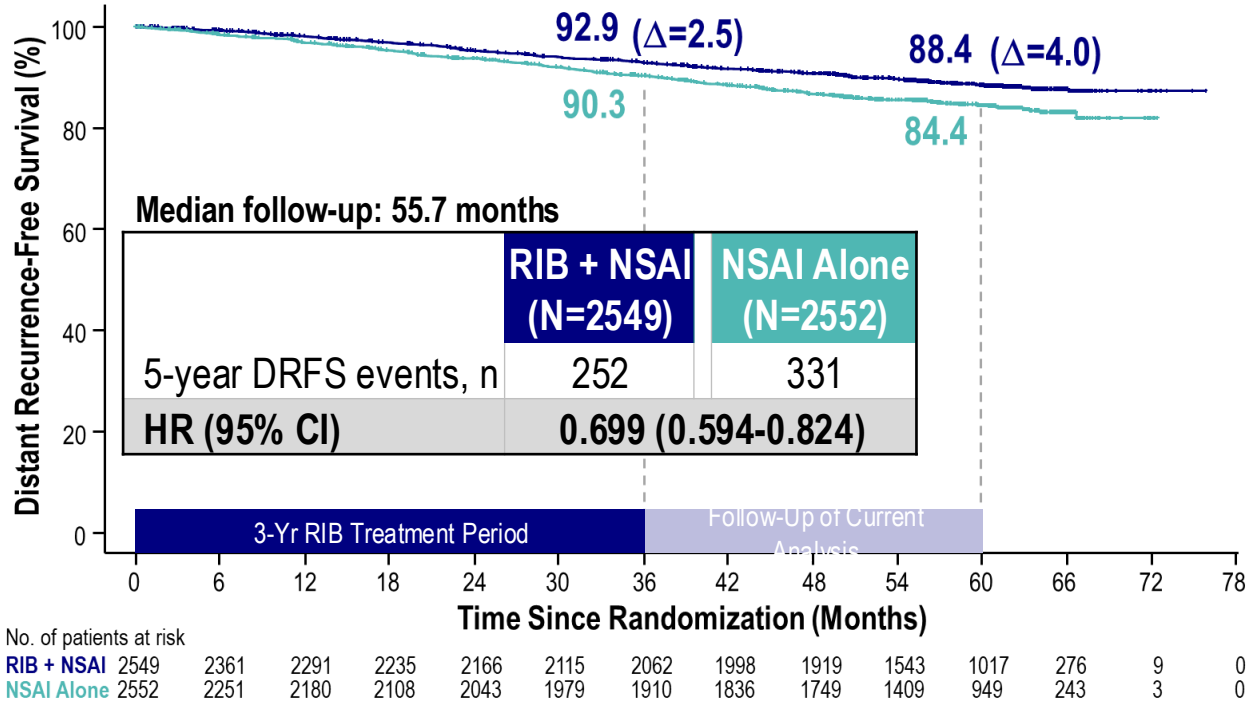
NATALEE: Secondary and Exploratory Endpoints

RIB + NSAI demonstrated continued benefit in DDFS and DRFS

DDFS



DRFS



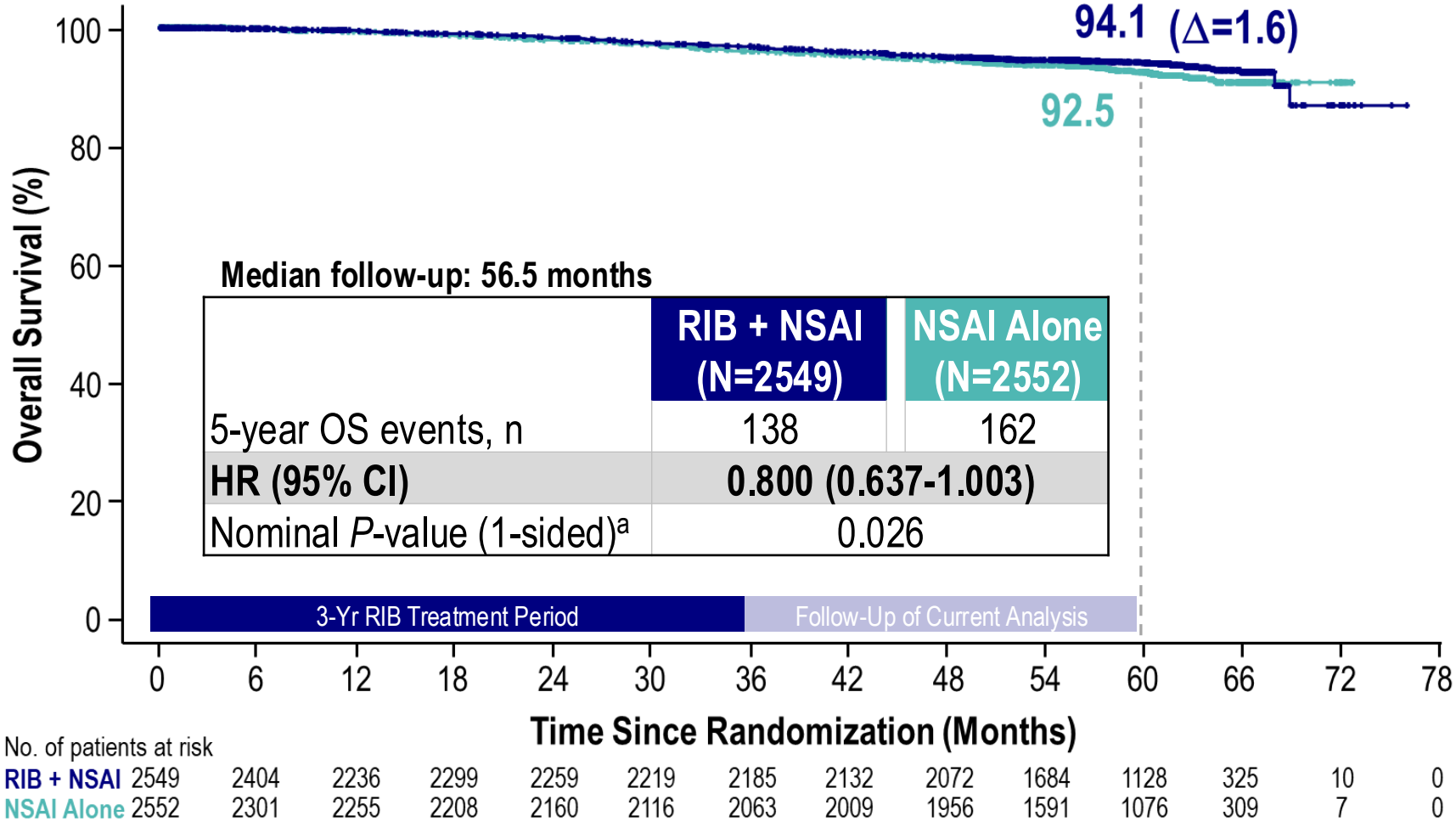
CI, confidence interval; DDFS, distant disease-free survival; DRFS, distant recurrence-free survival; HR, hazard ratio; ITT, intention to treat; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

John Crown, M.D.

Crown J et al. ESMO Open 2025. Oral LBA14.

OS in the ITT Population

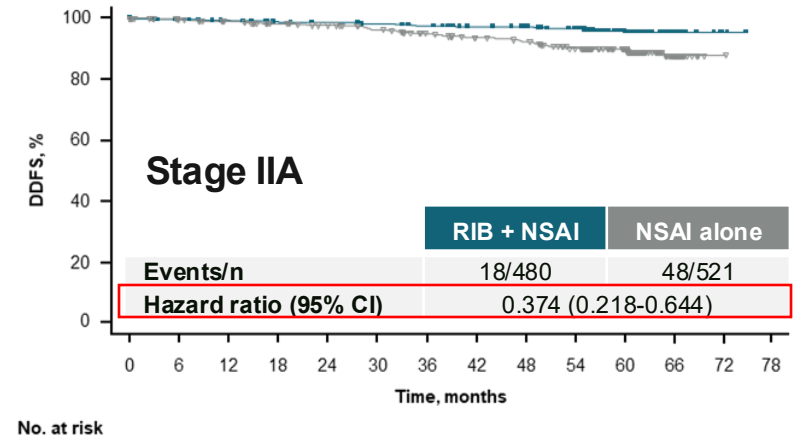
As OS data matures, a positive trend favoring RIB + NSAI treatment continues to emerge

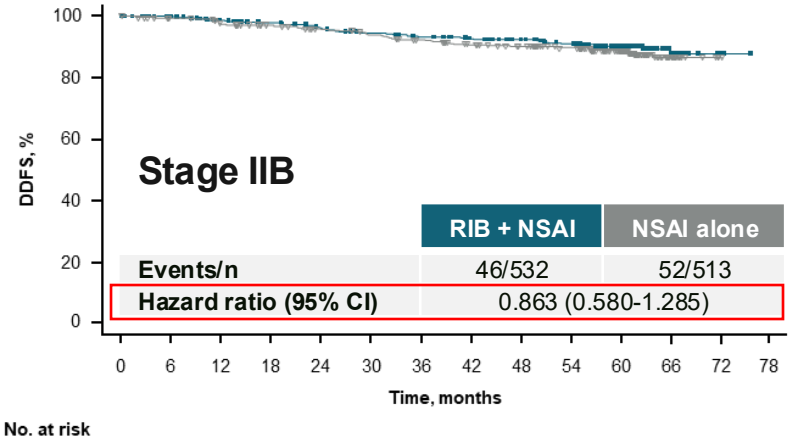


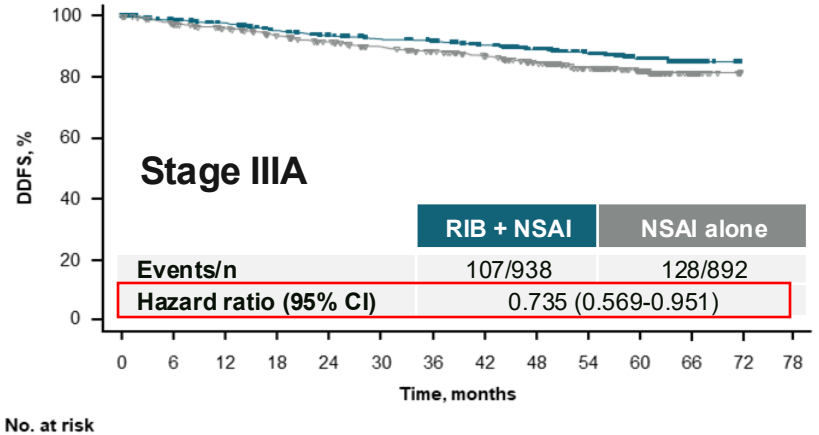
[a]Comparison of survival between treatment arms was generated by stratified log-rank test (1-sided P-value, informational and not pre-planned).
CI, confidence interval; HR, hazard ratio; ITT, intention to treat; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; RIB, ribociclib.

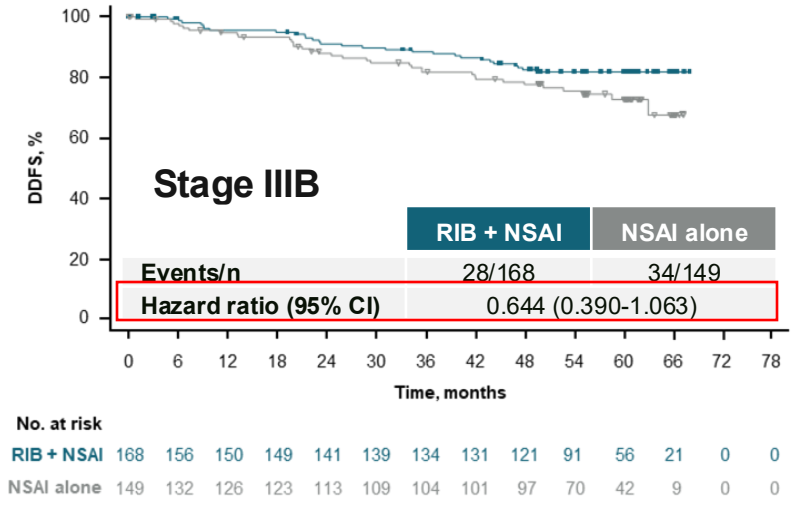
Crown J et al. ESMO Open 2025. Oral LBA14.

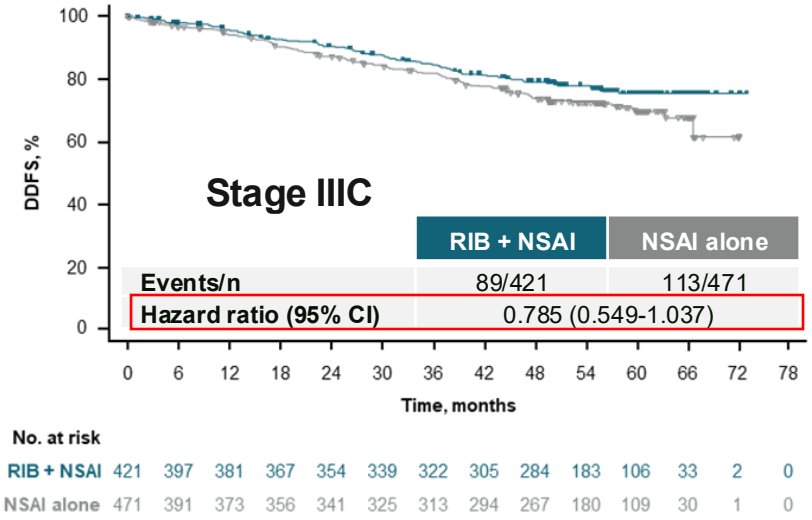
RIB + NSAI Continued to Improve DDFS Over NSAI Alone Across Anatomical Stages









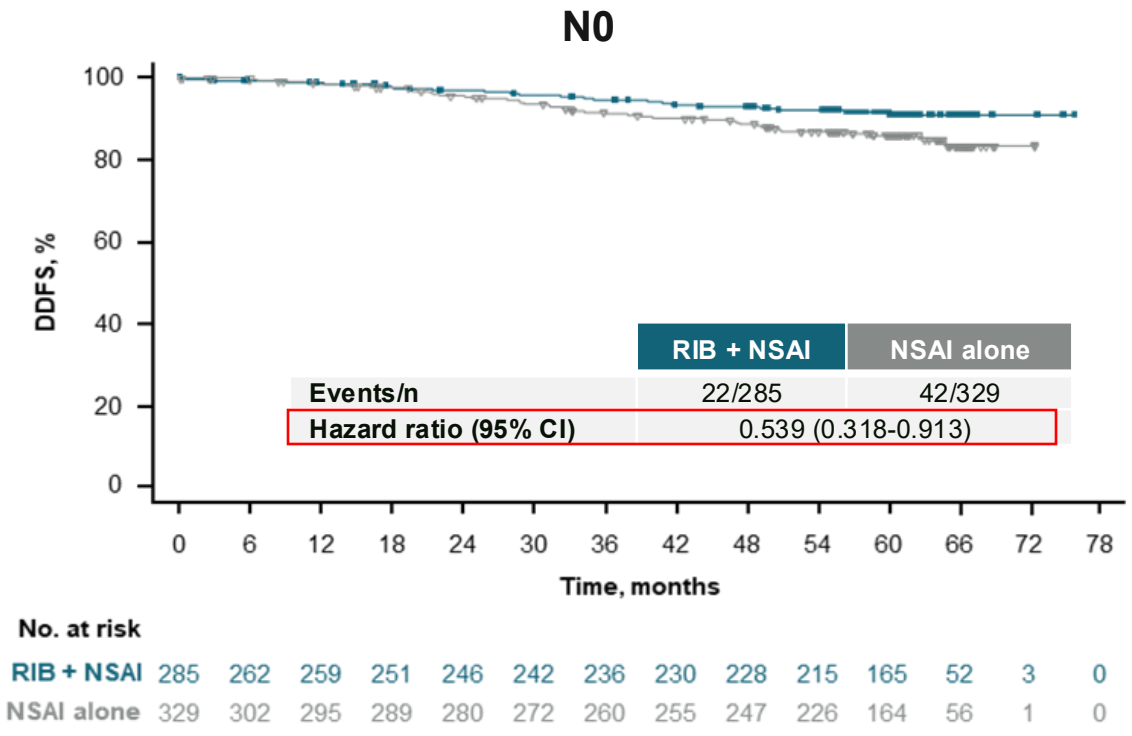


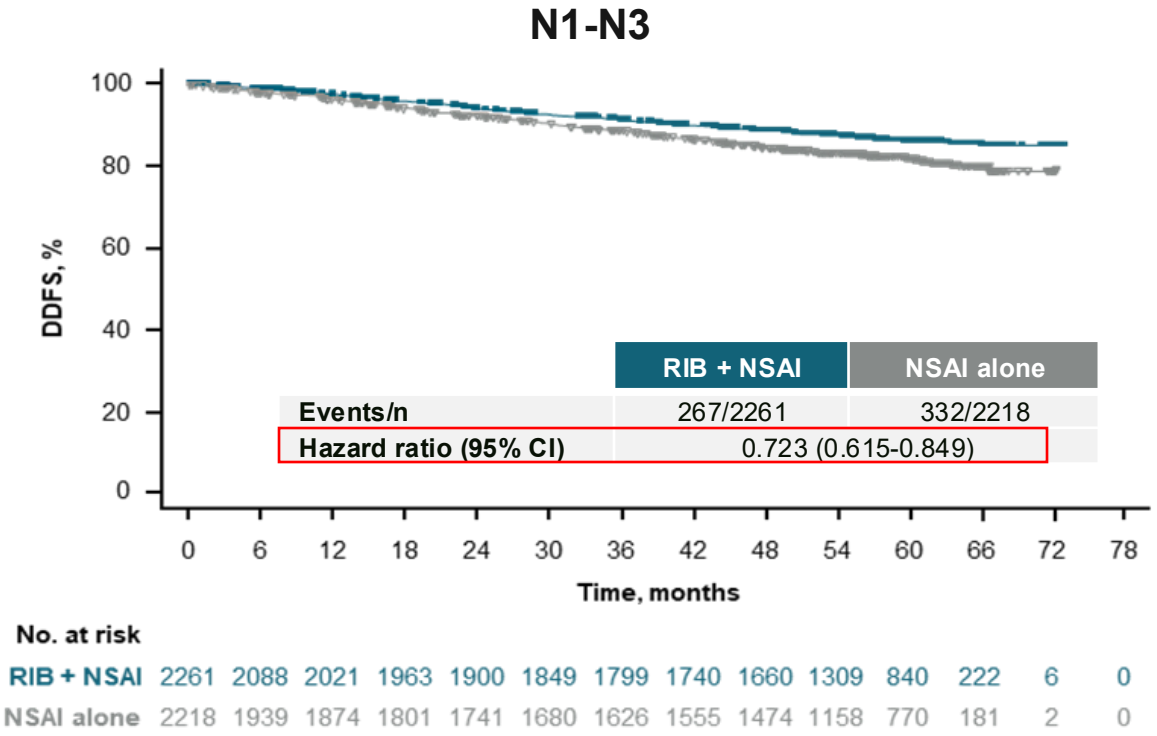
Absolute DDFS Benefit Across Stages

Stage	3-y DDFS rate, %		3-y abs. benefit	5-y DDFS rate, %		5-y abs. benefit
	RIB + NSAI	NSAI alone		RIB + NSAI	NSAI alone	
IIA	97.5	95.0	**Δ2.5**	95.9	89.7	**Δ6.2**
IIB	93.2	92.4	**Δ0.8**	90.2	89.0	**Δ1.2**
IIIA	91.6	88.5	**Δ3.1**	85.9	82.0	**Δ3.9**
IIIB	88.5	81.7	**Δ6.8**	81.7	72.8	**Δ8.9**
IIIC	84.6	81.8	**Δ2.8**	75.5	69.5	**Δ6.0**

Hurvitz SABCS 2025. Poster [PS3-09-08]

DDFS Benefit was Consistent Regardless of Nodal Status and Increased From 3 to 5 y



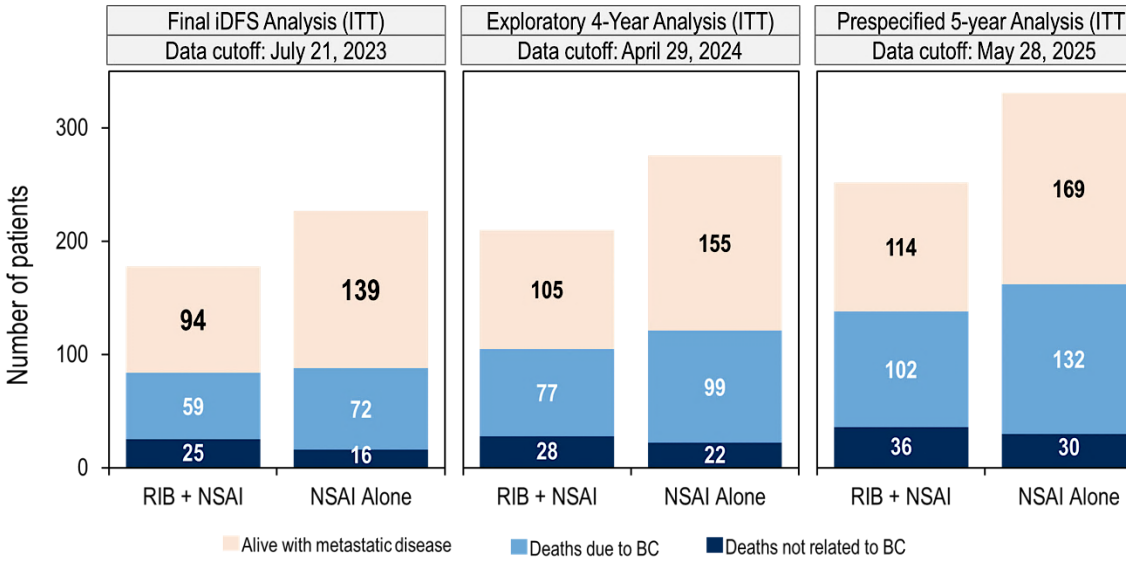


Subgroup	3-y DDFS rate, %		3-y abs. benefit	5-y DDFS rate, %		5-y abs. benefit
	RIB + NSAI	NSAI alone		RIB + NSAI	NSAI alone	
Nodal status						
N0	94.6	91.5	**Δ3.1**	91.6	85.8	**Δ5.8**
N1-N3	91.3	88.8	**Δ2.5**	86.1	82.0	**Δ4.1**

Hurvitz SABCS 2025 LBA Poster [PS3-09-08]

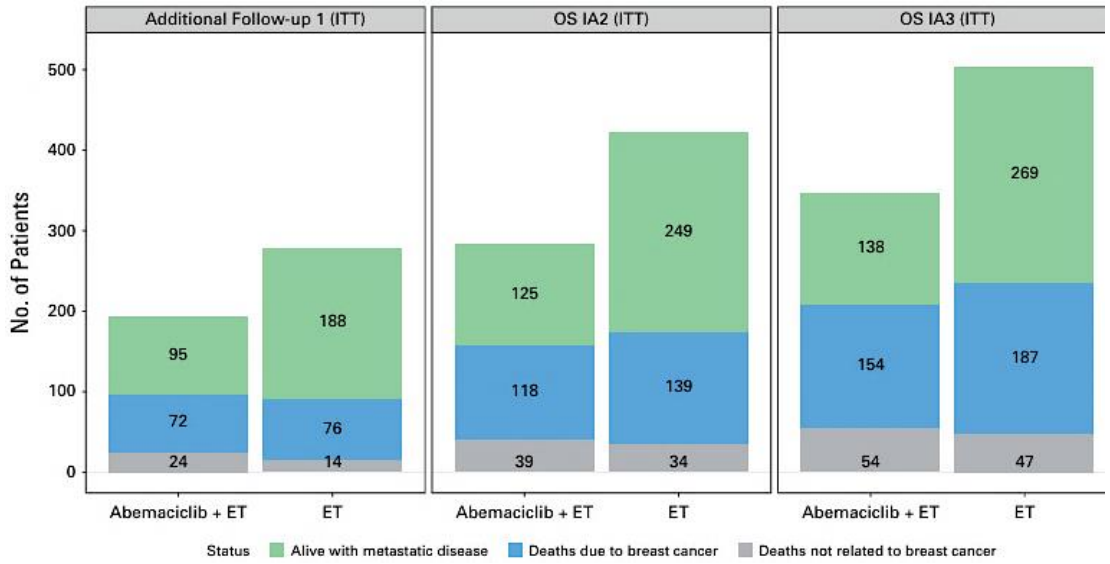
Living With Metastatic Disease

Living with metastatic disease in NATALEE[1]



~median follow up, mo	44	57
No. of events	226	300
OS HR (95% CI)	0.827 (0.636-1.074)	0.800 (0.637-1.003)

Living with metastatic disease in monarchE[2]



~median follow up, mo	44	55
No. of events	330	442
OS HR (95% CI)	0.929 (0.748-1.153)	0.903 (0.749-1.088)

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

ABEMA, abemaciclib; ET, endocrine therapy; HR, hazard ratio; ITT, intention to treat; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; RIB, ribociclib

.

1. Crown J et al. ESMO Open 2025. Oral LBA14. 2. Rastogi P et al J Clin Oncol 42, 987-993(2024).

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.

monarchE: Age considerations

	Abemaciclib + ET		
	Overall	**<65**	**≥65***
Abemaciclib dose adjustments due to AEs, %	n=2791	n=2361	n=430
Interruptions	62	60	68
Reductions	44	42	55
Discontinuations	18	15	38
Discontinuations without prior dose reductions	10	8	19

*Patients ≥75 years had higher rates of abemaciclib dose adjustments and discontinuations due to AEs

Hamilton E, et al. ASCO 2023

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

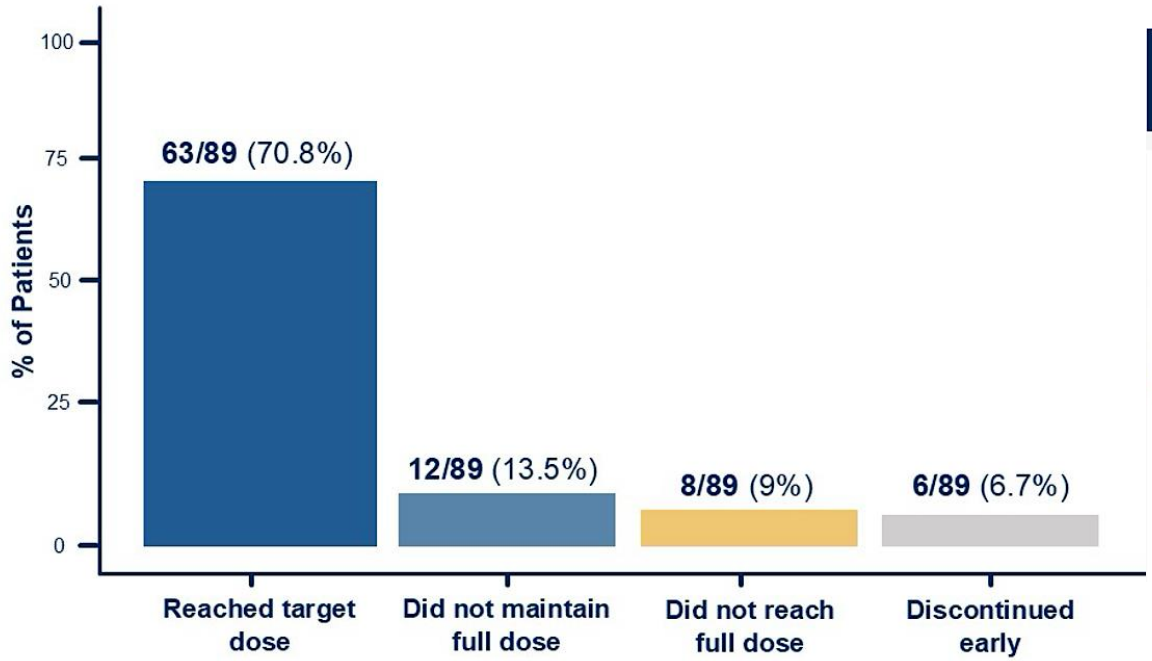
Abemaciclib 50mg BID	Abemaciclib 100mg BID	Abemaciclib 150mg BID
Days 1 – 14	Days 15 – 28	> 28 Days

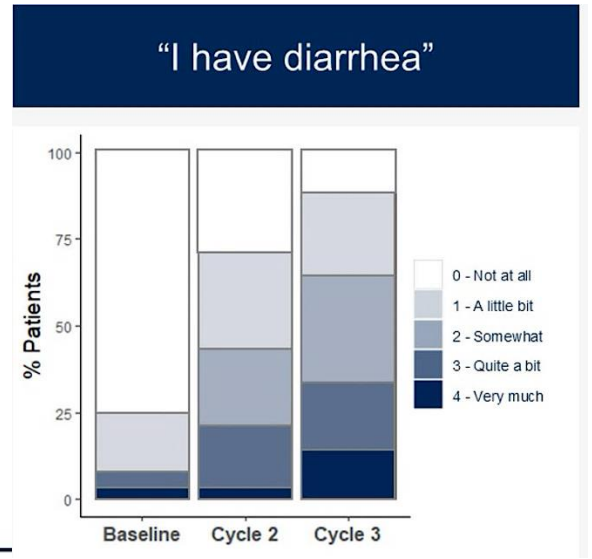
Endocrine Therapy + up to 2 years Abemaciclib

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)

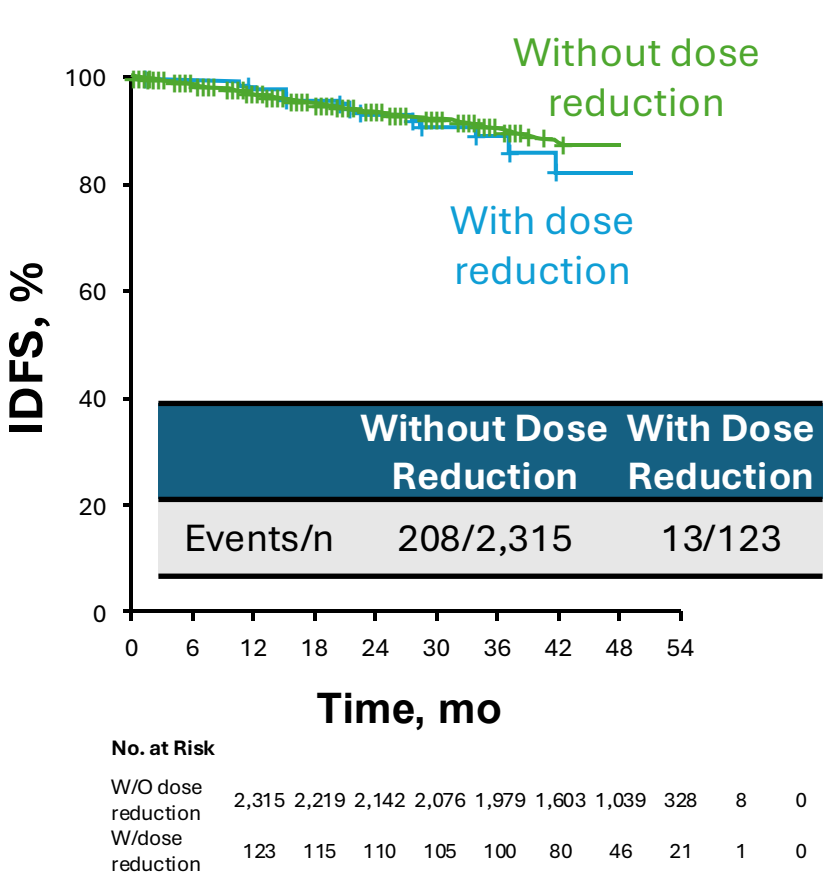




Mayer EL et al. Ann Oncol. 2025

NATALEE Study: IDFS Maintained with AE-related Dose Reductions

25th Percentile(1.87 mo)[a]

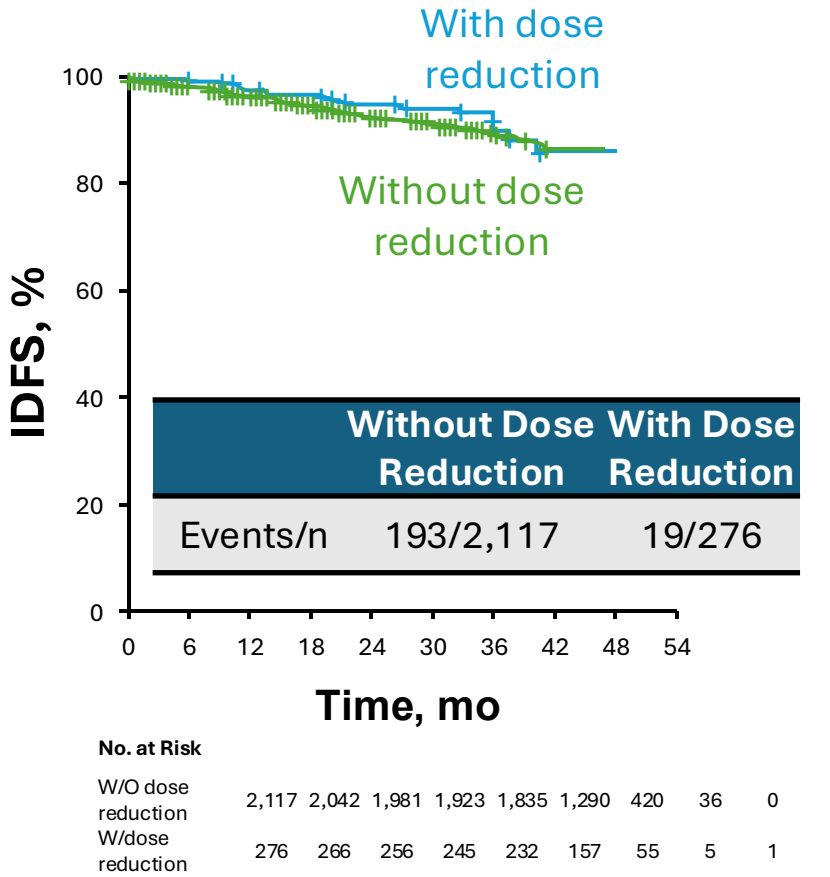


	Without Dose Reduction	With Dose Reduction
Events/n	208/2,315	13/123

No. at Risk

W/O dose reduction	2,315	2,219	2,142	2,076	1,979	1,603	1,039	328	8	0
W/dose reduction	123	115	110	105	100	80	46	21	1	0

50th Percentile (3.17 mo)[a]

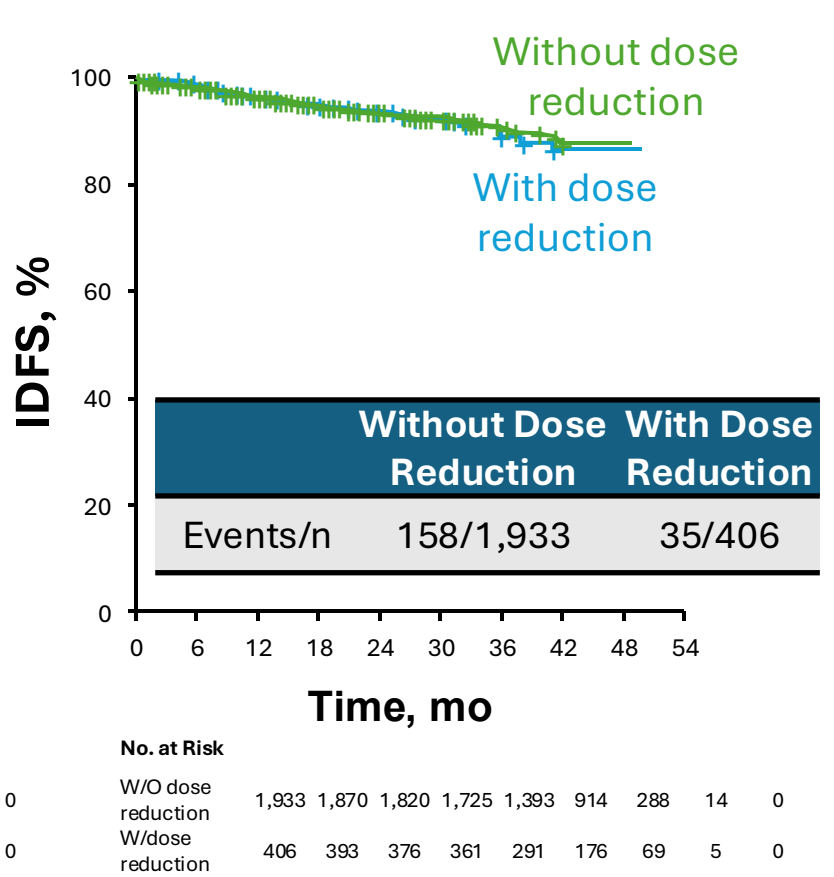


	Without Dose Reduction	With Dose Reduction
Events/n	193/2,117	19/276

No. at Risk

W/O dose reduction	2,117	2,042	1,981	1,923	1,835	1,290	420	36	0	0
W/dose reduction	276	266	256	245	232	157	55	5	1	0

75th Percentile (7.28 mo)[a]



	Without Dose Reduction	With Dose Reduction
Events/n	158/1,933	35/406

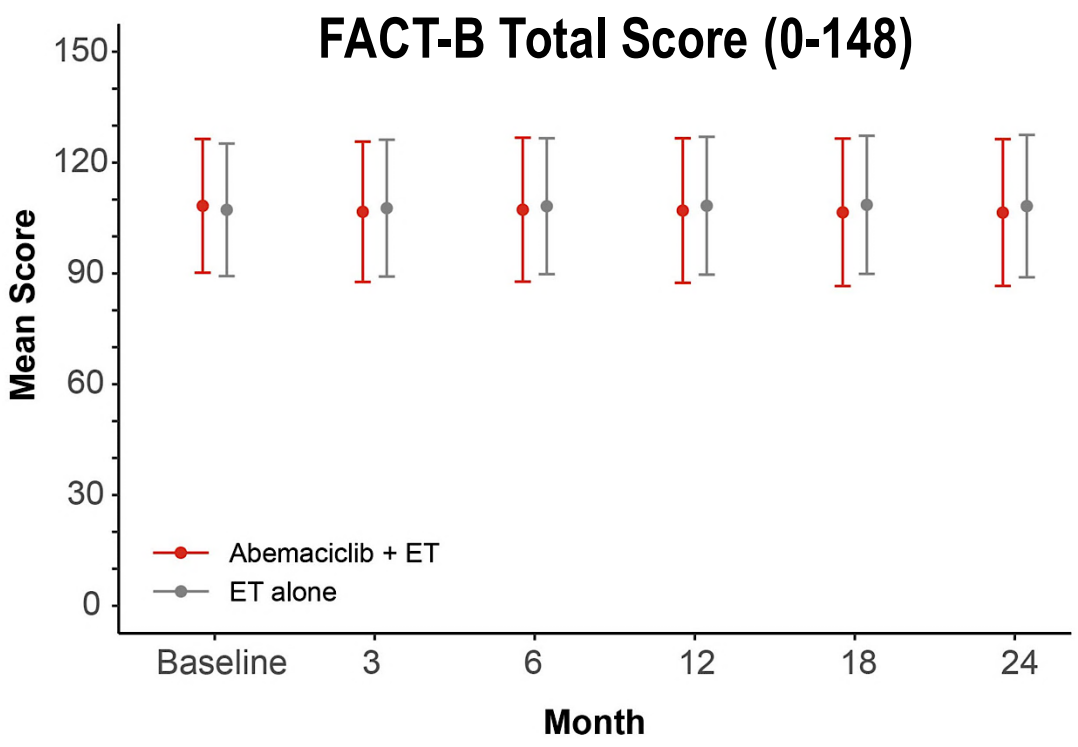
No. at Risk

W/O dose reduction	1,933	1,870	1,820	1,725	1,393	914	288	14	0	
W/dose reduction	406	393	376	361	291	176	69	5	0	

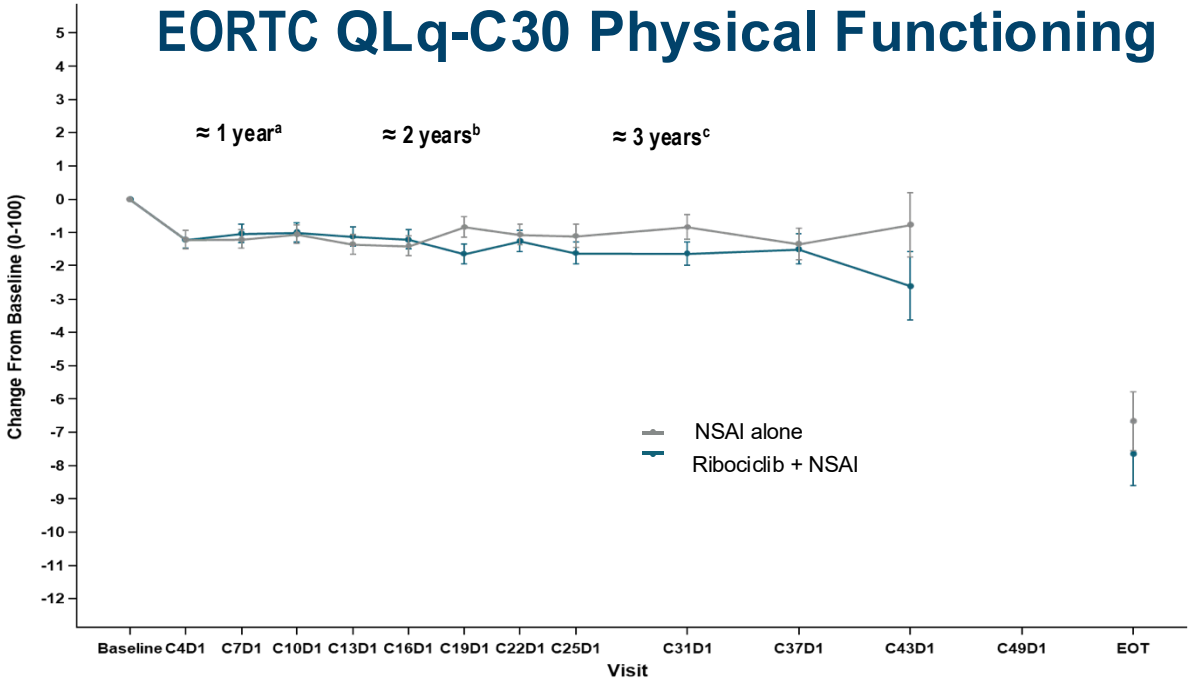
Barrios C et al. ESMO Breast. 2024. Abstract 1130MO

QOL maintained over time with Adjuvant CDK4/6 Inhibitors

MONARCH-E



NATALEE



Tolaney S et al. Eur J Cancer. 2024;199:113555 ; Fasching P, et al. Virtual Plenary 2023

Summary: Benefit of Adjuvant CDK4/6i

	NATALEE Ribociclib	MonarchE Abemaciclib
Median Follow up	4.6 years	6.3 years
5-year iDFS	**HR 0.72 (0.62-0.83)** 85.5% vs. 81.0% **Relative Δ ~28%** **Absolute Δ 4.5%**	
7-year iDFS		**HR 0.73 (0.66-0.82)** 77.4% vs. 70.9% **Relative Δ~ 27%** **Absolute Δ 6.5%** **(OS: Relative Δ~ 15.8%)**

Safety: manageable; QOL maintained

Crown et al ESMO 2025; Johnston et al ESMO 2025; Adapted from DeMichele SKCC 2025

Case Presentation: 55-year-old woman with ER-positive, HER2-negative Stage IIB, T2N1 IDC after neoadjuvant dose-dense AC-T, lumpectomy and adjuvant radiation therapy

Dr Eleonora Teplinsky (Paramus, New Jersey)

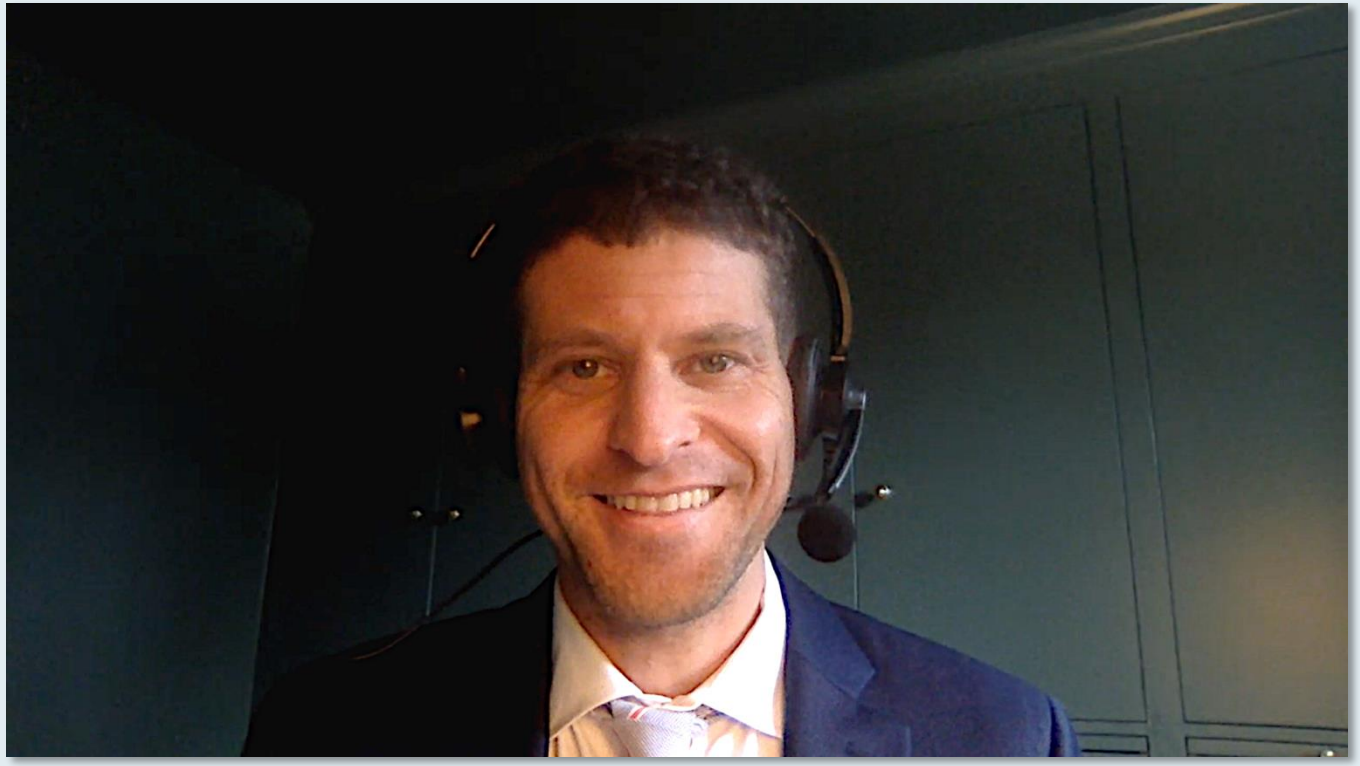
RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

How are you selecting between adjuvant abemaciclib and ribociclib for patients who are eligible for both?

What dose and schedule of abemaciclib do you typically start with in the adjuvant setting? Is it preferable to start at 150 mg BID and dose-reduce as needed or employ a dose-escalation strategy as in the recently presented TRADE study?

Case Presentation: 67-year-old woman with ER-positive, HER2-negative BC with surgically removed solitary lung metastasis after 4 years of adjuvant letrozole



Dr Eric Fox (Bryn Mawr, Pennsylvania)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

What would you recommend for a patient who develops oligometastatic disease, which is completely resected, while receiving an adjuvant aromatase inhibitor?

Is there a role for ctDNA testing in informing treatment decision-making for patients like this?

Agenda

Module 1: Current Role of Genomic Assays in Treatment Decision-Making for Localized Hormone Receptor (HR)-Positive Breast Cancer — Dr DeMichele

Module 2: Role of CDK4/6 Inhibitors and Other Novel Strategies in Therapy for HR-Positive, HER2-Negative Localized Breast Cancer — Dr Jhaveri

Module 3: Evolving Up-Front Treatment Paradigm for HR-Positive, HER2-Negative Metastatic Breast Cancer (mBC) — Dr Rugo

Module 4: Clinical Utility of Agents Targeting the PI3K/AKT/mTOR Pathway for Patients with Progressive HR-Positive mBC — Dr Mayer

Module 5: Current and Future Role of Oral Selective Estrogen Receptor Degraders for Progressive HR-Positive mBC — Dr Wander

RTP RESEARCH TO PRACTICE

Evolving Up-Front Treatment Paradigm for HR+, HER2- mBC

Hope S. Rugo, MD
Director, Women's Cancers Program
Division Chief, Breast Medical Oncology
Professor, Department of Medical Oncology & Therapeutics Research
City of Hope Comprehensive Cancer Center
Professor Emeritus, UCSF

Optimal First-Line Therapy for HR+/HER2- mBC

- Chemotherapy versus AI/CDK4/6 inhibitor in patients with high risk features
  - What is the evidence?
- Biomarkers to drive treatment approach
  - Targeting PI3K
  - Targeting emerging ESR1 mutations

The Phase II RIGHT Choice Trial: ET/Ribociclib vs Combination Chemotherapy for Premenopausal Woman with mBC and Visceral Crisis or Symptomatic Disease

- Pre-/perimenopausal women
- HR+/HER2–ABC (>10% ER+)
- No prior systemic therapy for ABC
- Measurable disease per RECIST 1.1
- Aggressive disease
  - Symptomatic visceral metastases
  - Rapid disease progression or impending visceral compromise
  - Markedly symptomatic non-visceral disease
- ECOG PS ≤ 2
- Total bilirubin ≤ 1.5 ULN
- N = 222

R 1:1

Ribociclib
(600 mg once daily, 3 weeks on/1 week off)
+ Letrozole or anastrozole
+ goserelin

Investigator's choice of combination CT
Docetaxel + capecitabine
Paclitaxel + gemcitabine
Capecitabine + vinorelbine

Tumor imaging evaluation
Q6W for 1st 12 weeks, Q8W for next 32 weeks, then Q12W

Stratified by (1) the presence or absence of liver metastases and by (2) DFI < or ≥ 2 years

Primary endpoint
- PFS (locally assessed per RECIST 1.1)

Secondary endpoint
- TTF
- 3-month TFR
- ORR
- CBR
- TTR
- OS
- Safety
- QOL

Exploratory endpoints
- Biomarker analyses
- Healthcare resource utilization

Demographics

Median age: 44

De novo MBC: 65%

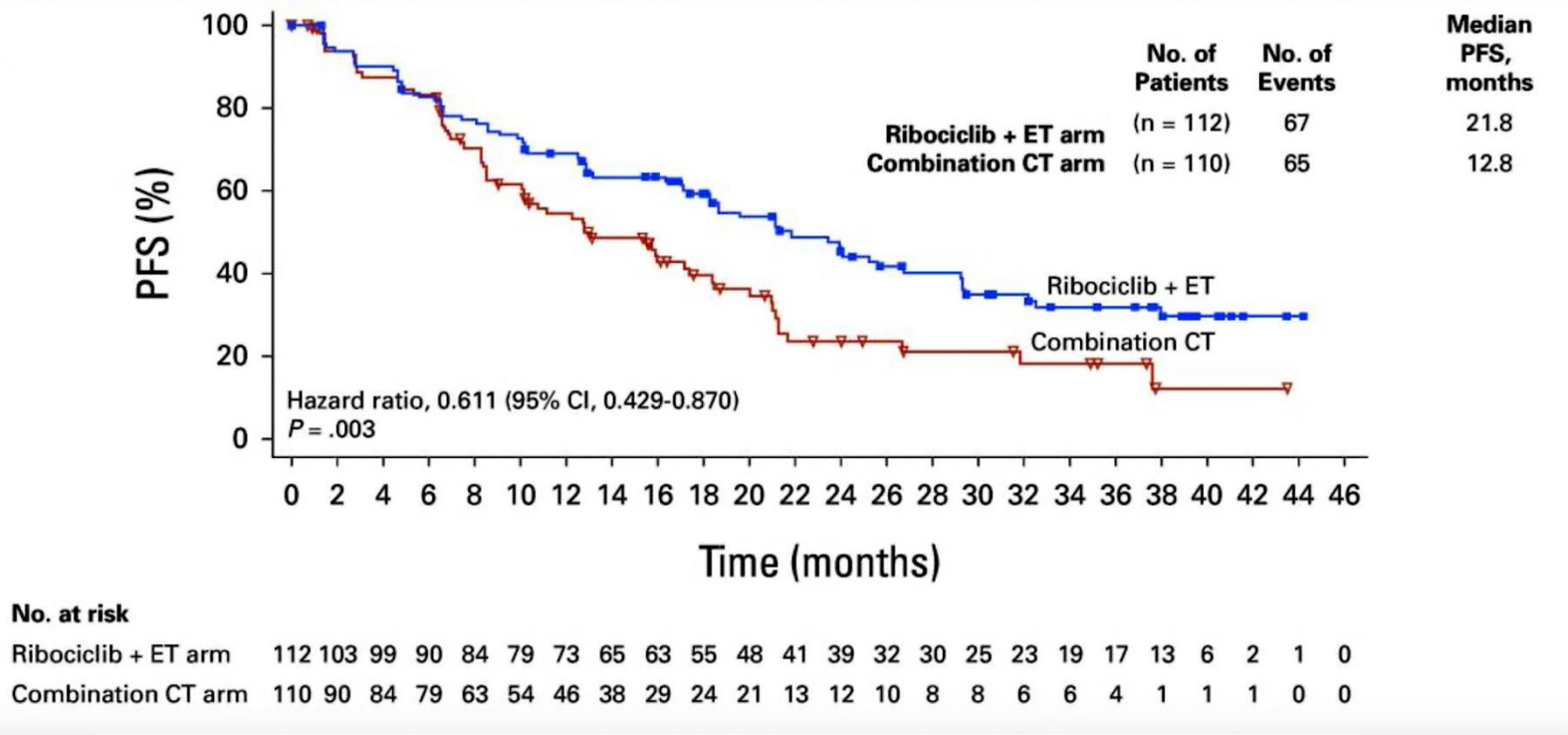
Visceral mets: 78%

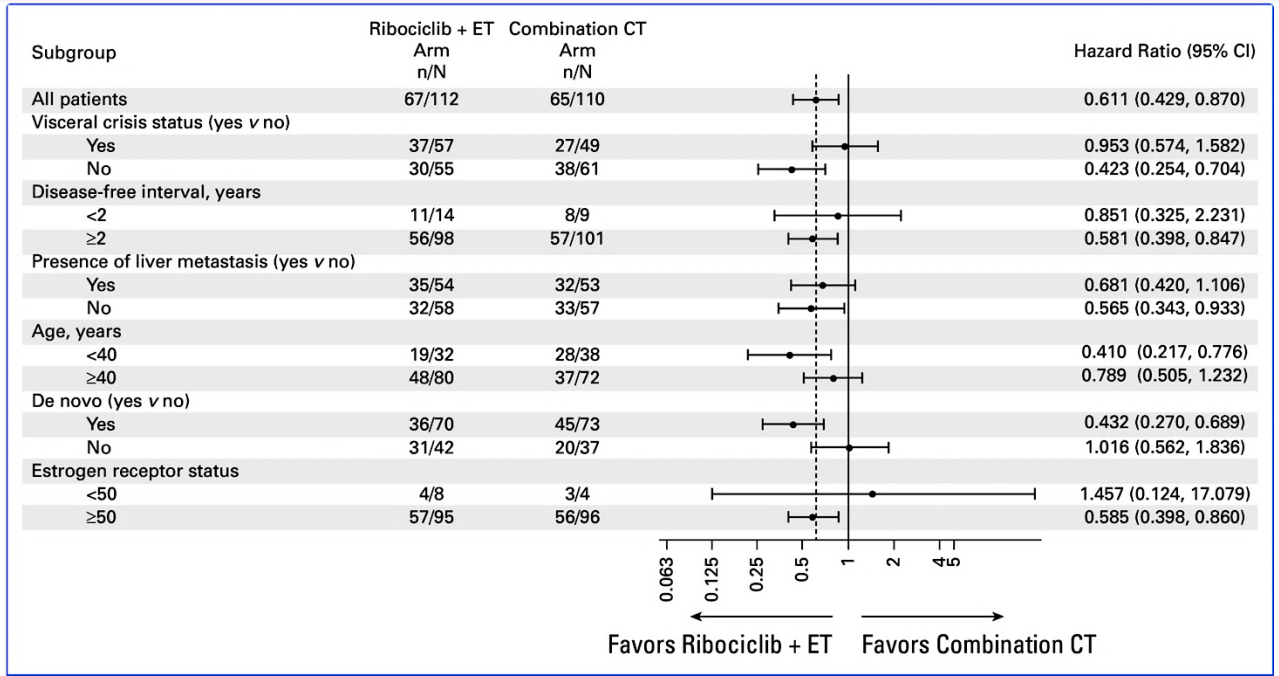
'Visceral' crisis (inv assessed): 52%

Symptomatic visceral mets: ~67%

.
ABC, advanced breast cancer; CBR, clinical benefit rate; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; QoL, quality of life; TFR, treatment-free remission; TTF, time to treatment failure; TTR, time to recurrence.

Lu et al, JCO 2024





- Time to response:
  - 4.9 (ET/R) vs 3.2 (CT) mo
  - HR 0.76 [95% CI, 0.55 to 1.06]
- ORR
  - 66.1 vs 61.8%
    - CR: 6.3 vs 2.7%
- Safety
  - More neutropenia with ET/R
  - More nausea, vomiting, anemia, diarrhea, alopecia, fatigue and PPE with CT
- OS
  - Early

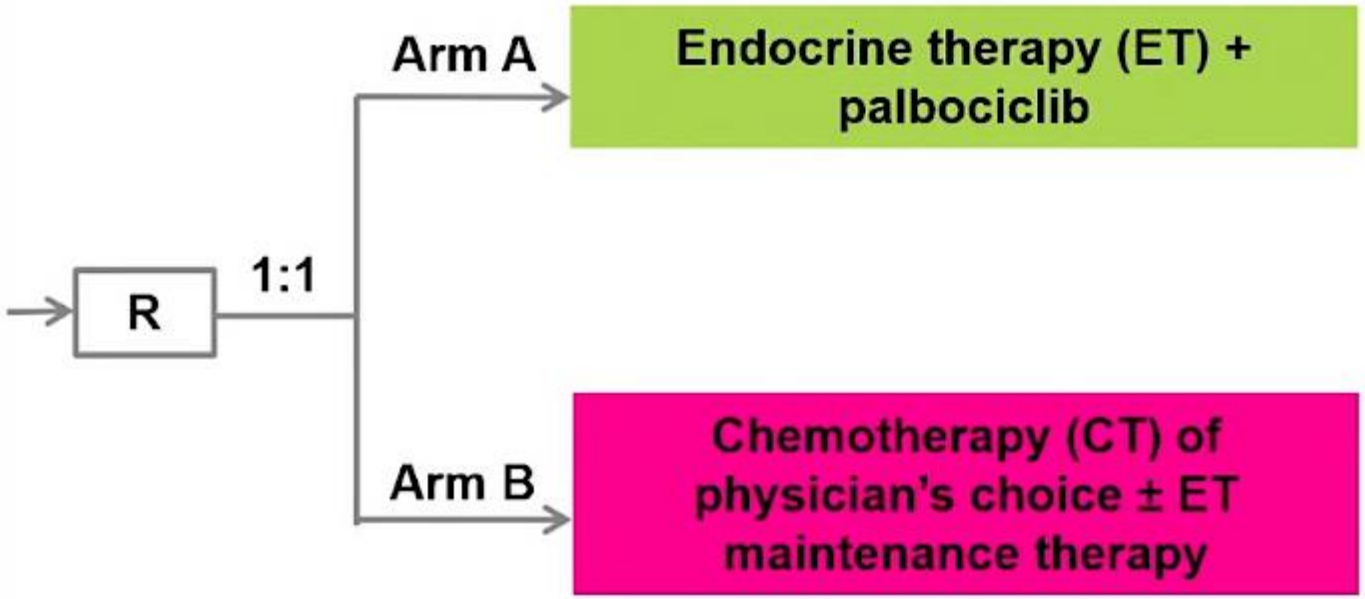
Lu et al, JCO 2024

PADMA Study Design

Patient Population
N=150

- HR-positive/HER2-negative
- Female or male
- Indication for mono-chemotherapy
- No prior treatment for metastatic/relapsed disease
- No asymptomatic bone-only, oligo-metastatic disease
- No uncontrolled/untreated CNS metastases
- Live-expectancy >6 months

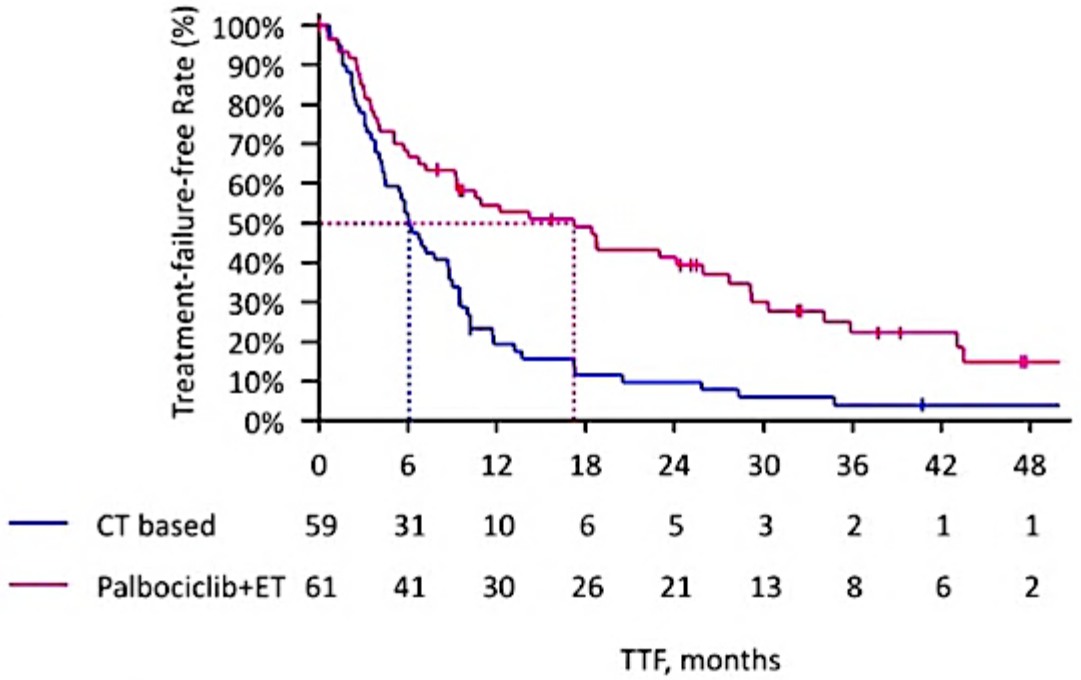
Stratification:
- Endocrine resistant vs endocrine sensitive
- Symptomatic vs asymptomatic metastatic disease



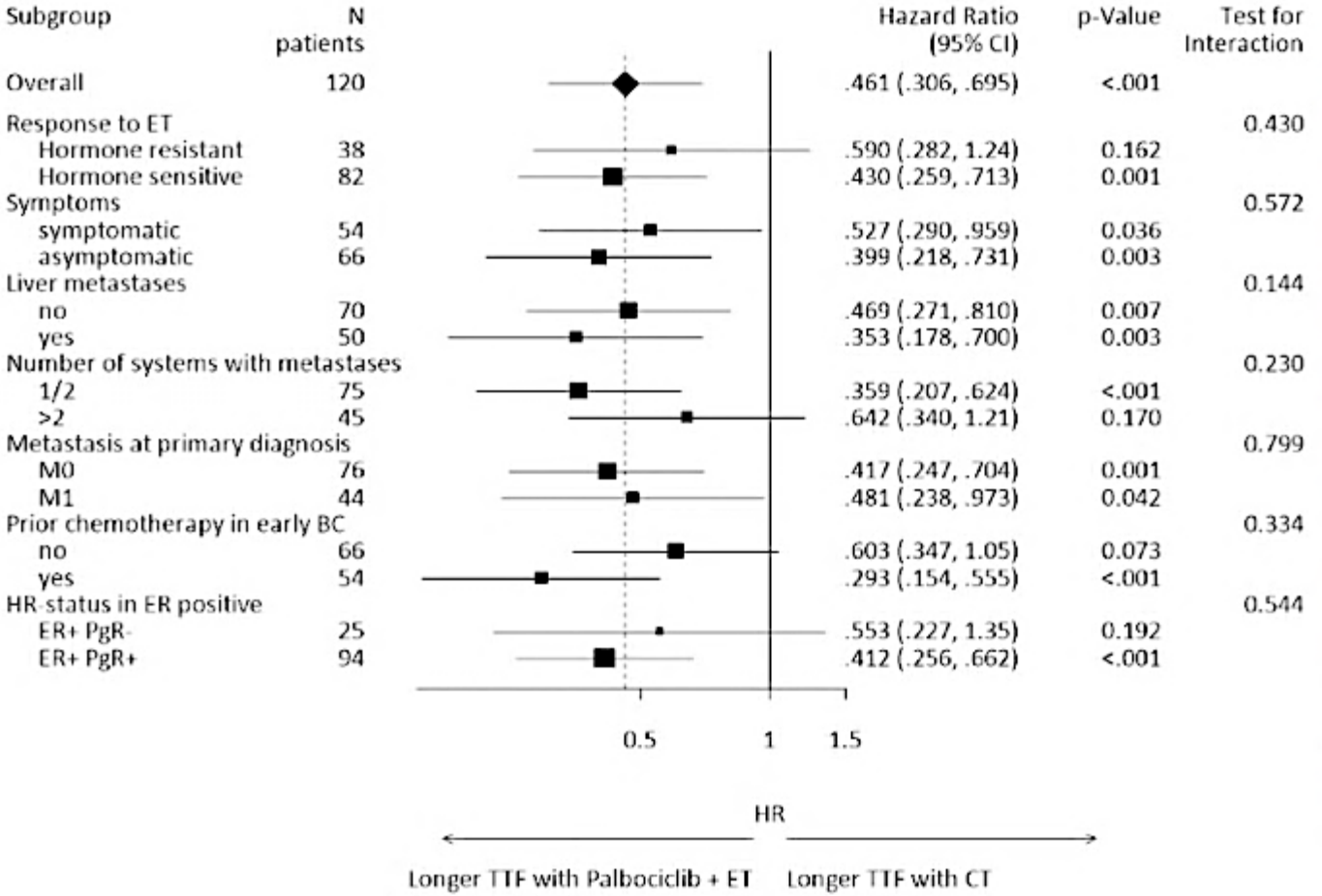
ET with palbociclib: AI or fulvestrant ± GnRHa
ET maintenance: tamoxifen, AI or fulvestrant ± GnRHa
CT: paclitaxel, capecitabine, epirubicin, or vinorelbine

Loibl S et al. SABCS 2024;Abstract LB1-03.

Primary Endpoint



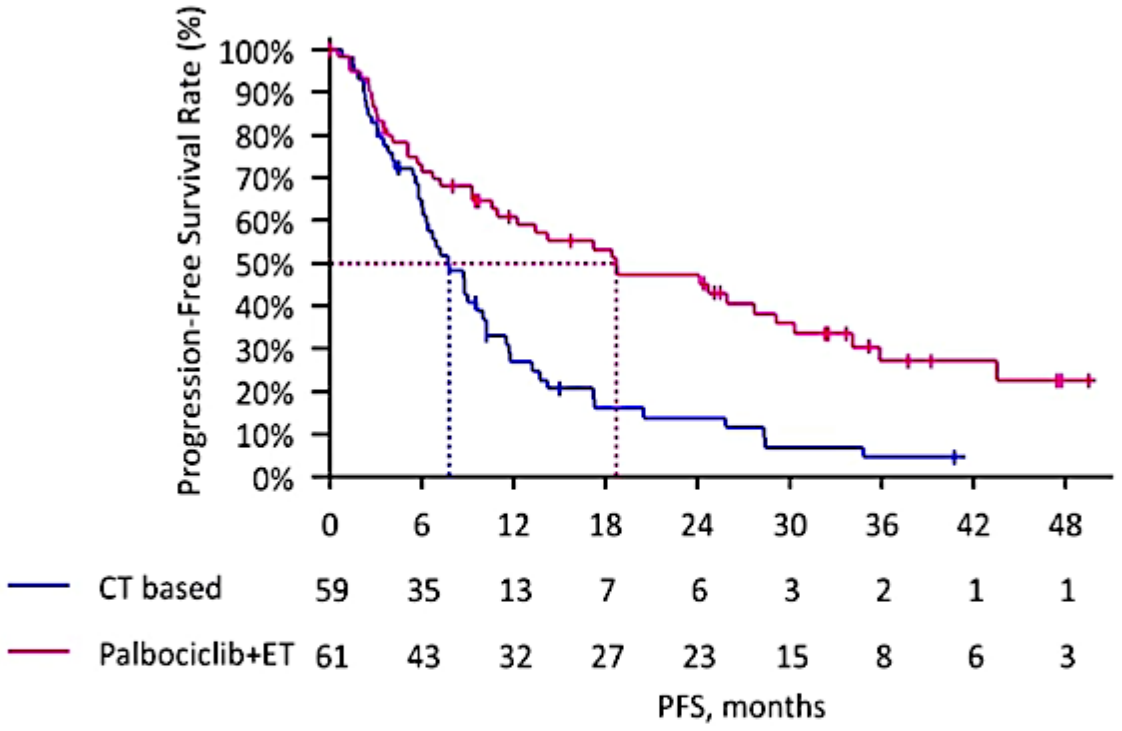
	Palbociclib + ET	CT
TTF events, N (%)	45 (73.8)	55 (93.2)
Median TTF months	17.2	6.1
HR 0.46: 95% CI (0.31-0.69), p<0.001 (log-rank)		



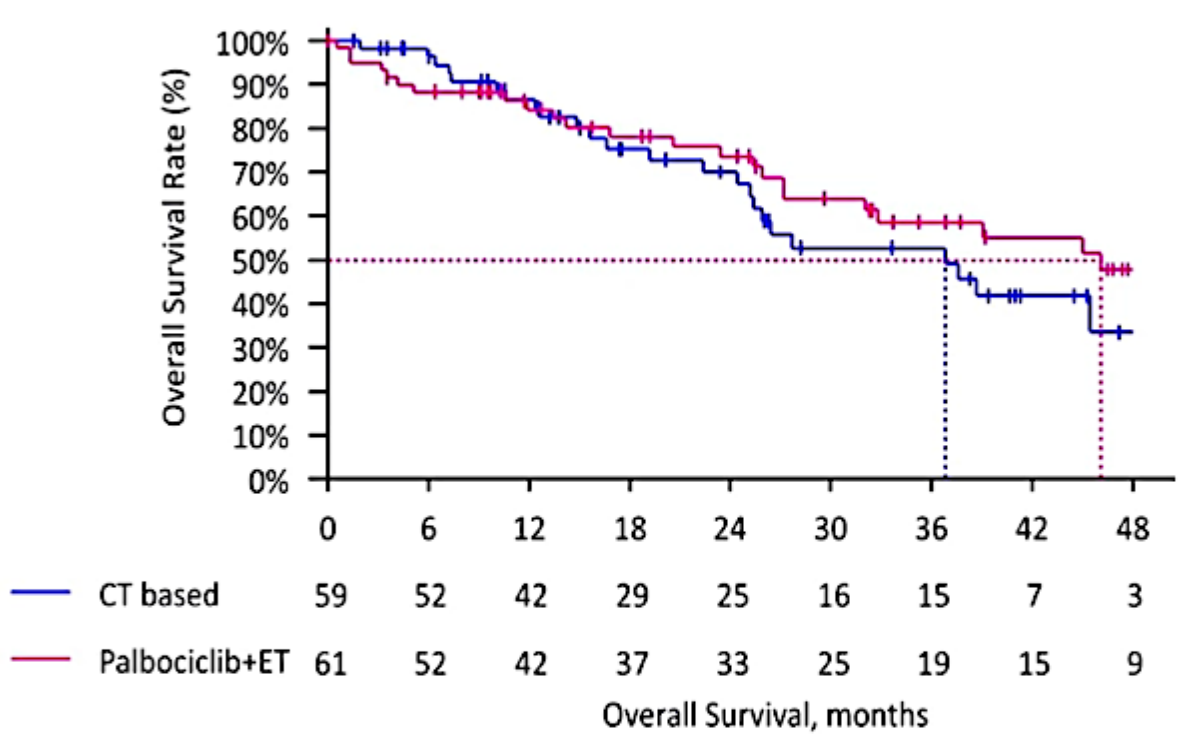
Median follow-up of 36.8 (range 0-74.4) months

Loibl S et al. SABCS 2024;Abstract LB1-03.

Secondary Endpoints



	Palbociclib + ET	CT
PFS events, N (%)	40 (65.6)	50 (84.7)
Median PFS months	18.7	7.8
HR 0.45 95% CI (0.29-0.70), p<0.001 (log-rank)		



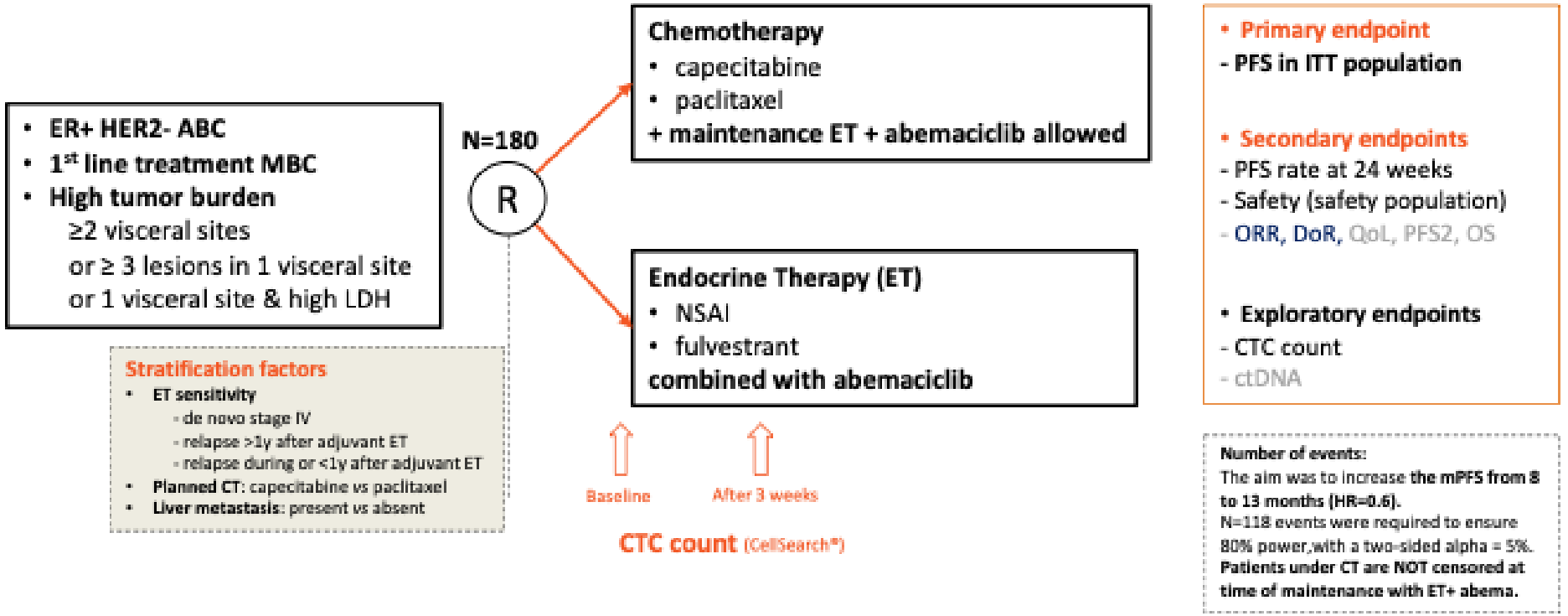
	Palbociclib + ET	CT
OS events, N (%)	25 (41.0)	24 (40.7)
Median OS months	46.1	36.8
Proportional hazard cannot be assumed		

PADMA

GBG GERMAN BREAST GROUP

Loibl S et al. SABCS 2024;Abstract LB1-03.

AMBRE Trial: Chemotherapy vs ET/CDK4/6i



- Median age 59 – 65
- de novo to ET ~27%
- ≥2 visceral sites: 44%; ≥3 lesions/one organ: 63%, high LDH 12-13%
- Liver mets ~77%

- **Chemotherapy**
  - Capecitabine: 66.3%; Paclitaxel: 33.7%
- ET choice: 72.4% AI and 26.6% fulvestrant
- ET maintenance: 21.8% (6.9% ET monotherapy)

Dieras et al, SABCS 2025;Abstract RF7-06.

Results

Other endpoints

- No difference in ORR (p=0.393)

Medi

ema (HR 0.46,

r from standard CT

100%
75%
50%
25%
0%
0

Num

Standard CT 89
ET + Abemaciclib 91
63
43
23
15

56% (ET) had

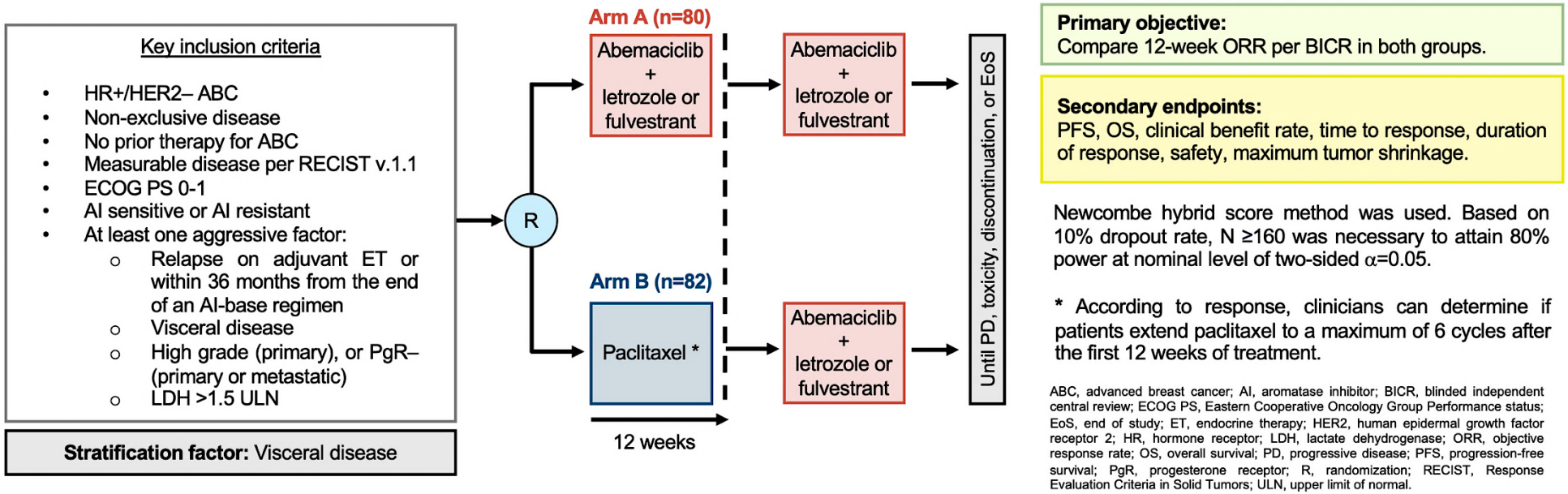
had <5 CTC/7.5mL;

CT; more diarrhea,
neutropenia with ET/Abema,

- This trial demonstrates the superior efficacy and tolerability of ET plus abemaciclib as 1L therapy for HR+/HER2− metastatic breast cancer compared with single agent chemotherapy
- Along with the Right Choice and PADMA, this further confirms the importance of the ET + CDK4/6i combination therapy in this setting, even compared with more tolerable single agent chemotherapy in patients with higher risk, poor prognosis disease who are considered chemotherapy candidates

Dieras et al, SABCS 2025;Abstract RF7-06.

ABIGAIL: Phase II Study of Abemaciclib/ET +/- Paclitaxel Induction for Patients with MBC and Aggressive Disease Criteria



Demographics

- 61 vs 70% recurrent disease; 36 vs 28% de novo
- Median age 57-60

Primary Endpoint

- **12 week ORR 58.8 vs 40.2% (OR 2.11; 95% CI 1.13-3.96, p=0.0193)**
- SD, PD or discontinuation: 41.2 vs 59.8%
- 8 vs 5 not evaluable

Toxicity as expected

de la Haba-Rodríguez et al, ESMO 2024

CDK4/6 inhibitors – Phase III Registration Studies Efficacy Results

Agent	Trial	Line	PFS HR	*p*	CBR (%)	ORR (%) *[eval.]*	*OS HR*	*p*
Palbociclib	PLM-2	**SEN**	0.58	*< .0001*	85%	55% (Δ 10%)	**0.956**	***0.33***
	PLM-3	**RES**	0.46	*< .0001*	67%	25% (Δ 14%)	**0.81**	***0.022***
Ribociclib	MNL-2	**SEN**	0.57	*< .0001*	80%	53% (Δ 15%)	**0.76**	***0.004***
	MNL-3	**SEN/RES**	0.59	*< .0001*	70%	41% (Δ 12%)	**0.724**	***0.0045***
	MNL-7	**SEN/RES**	0.55	*< .0001*	79%	51% (Δ 15%)	**0.712**	***0.00973***
Abemaciclib	MRC-3	**SEN**	0.54	*< .0001*	78%	59% (Δ 15%)	**0.854**	***0.0664***
	MRC-2	**RES**	0.54	*< .0001*	NK	48% (Δ 27%)	**0.757**	***0.0137***

SEN, Sensitive to endocrine therapy by ABC-3; RES: Resistant criteria to prior endocrine therapy by ABC-3; CBR, clinical benefit rate; CDK, cyclin-dependent kinase; HR, hazard ratio; NK, not known; ORR, overall response rare; PFS, progression-free survival.

1. Palbociclib EU SmPC, 2019; 2. Ribociclib EU SmPC, 2019; 3. Abemaciclib EU SmPC 2019; Geotz SABCS 2023

P-VERIFY: Overall Survival[1]

Subanalysis of Patients Who Started Index Treatment in 2017 or Later

This subanalysis included 5735 patients treated with palbociclib plus AI, 1279 treated with ribociclib plus AI, and 1036 treated abemaciclib plus AI

Groups	After sIPTW Adjusted HR	95% CI	*P-value*
Ribociclib vs Palbociclib	**1.00**	0.89-1.13	0.9728
Abemaciclib vs Palbociclib	**0.96**	0.84-1.09	0.5326
Abemaciclib vs Ribociclib	**0.96**	0.81-1.13	0.6077

OS was a secondary endpoint in all 3 pivotal first-line CDK4/6 inhibitor RCTs: **Palbociclib + LET did not show a statistically significant OS difference in PALOMA-2[2]**. Abemaciclib + NSAI did not show a statistically significant OS difference in MONARCH-3[3]. Ribociclib + LET demonstrated a statistically significant OS difference in MONALEESA-2[4]

Observational retrospective analyses cannot establish causality between treatments and outcomes, and these analyses are not intended to demonstrate efficacy in particular subgroup. Small patient numbers is a limitation of this analysis. These results are not intended to be compared with clinical trials and should be interpreted with caution in the context of the totality of evidence.

AI=aromatase inhibitor; CDK4/6=cyclin-dependent kinase 4/6; CI=confidence interval; HZ=hazard ratio; LET=letrozole; NSAI=nonsteroidal aromatase inhibitor; RCT=randomized clinical trials; sIPTW=stabilized inverse probability treatment weighting.

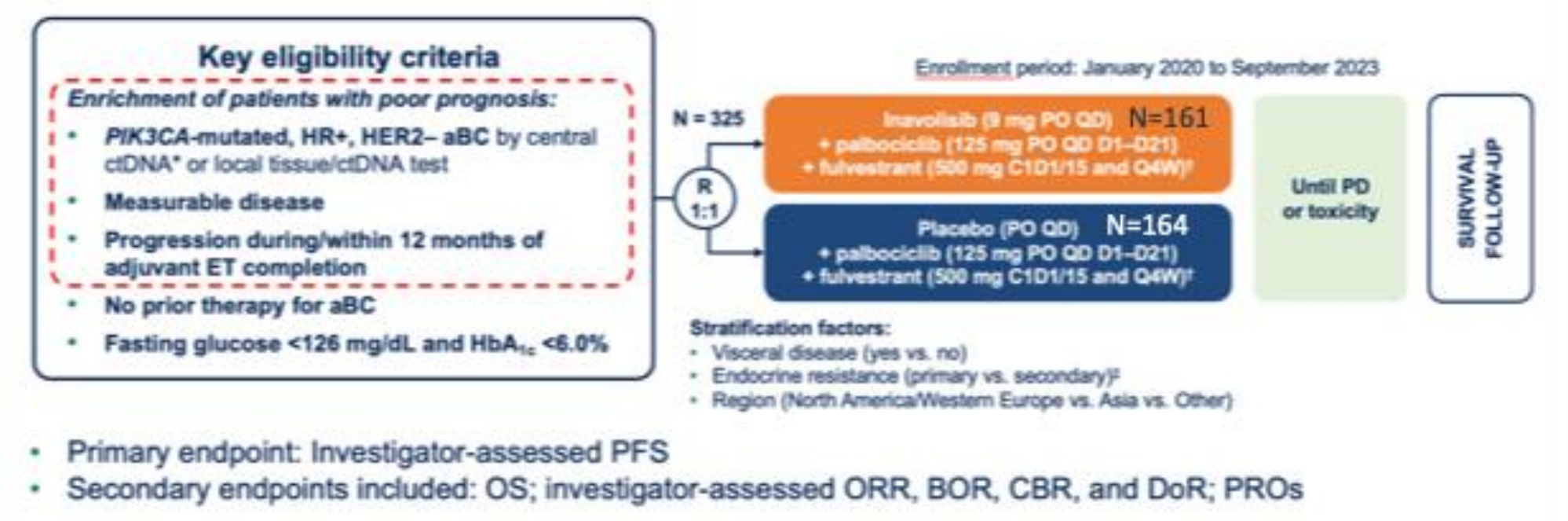
1. Rugo HS, et al. ESMO Open 2025 2. Slamon DJ, et al. J Clin Oncol. 2024 Mar 20;42(9):994-1000. 3. Goetz MP, et al. Ann Oncol 2024 Aug;35(8):718-727. 4. Hortobagyi GN, et al. N Engl J Med 2022 Mar 10;386(10):942-950.

Decisions about First-Line Therapy in Endocrine Sensitive Disease: Selecting the Right CDK4/6i

- Differences in patient populations impact results from phase III trials
- Treatment should be individualized for each patient's unique situation
  - Underlying patient characteristics
    - Cardiac issues
    - Liver enzyme abnormalities
    - GI conditions
  - Disease burden
  - Genomic mutations
  - Duration of disease control on prior therapy

INAVO120 (Phase 3): First-Line Inavolisib/Palbociclib/Fulvestrant for Patients with PIK3CA-Mutated Early Relapsing HR+, HER2– MBC

Median FU 34.2 mo

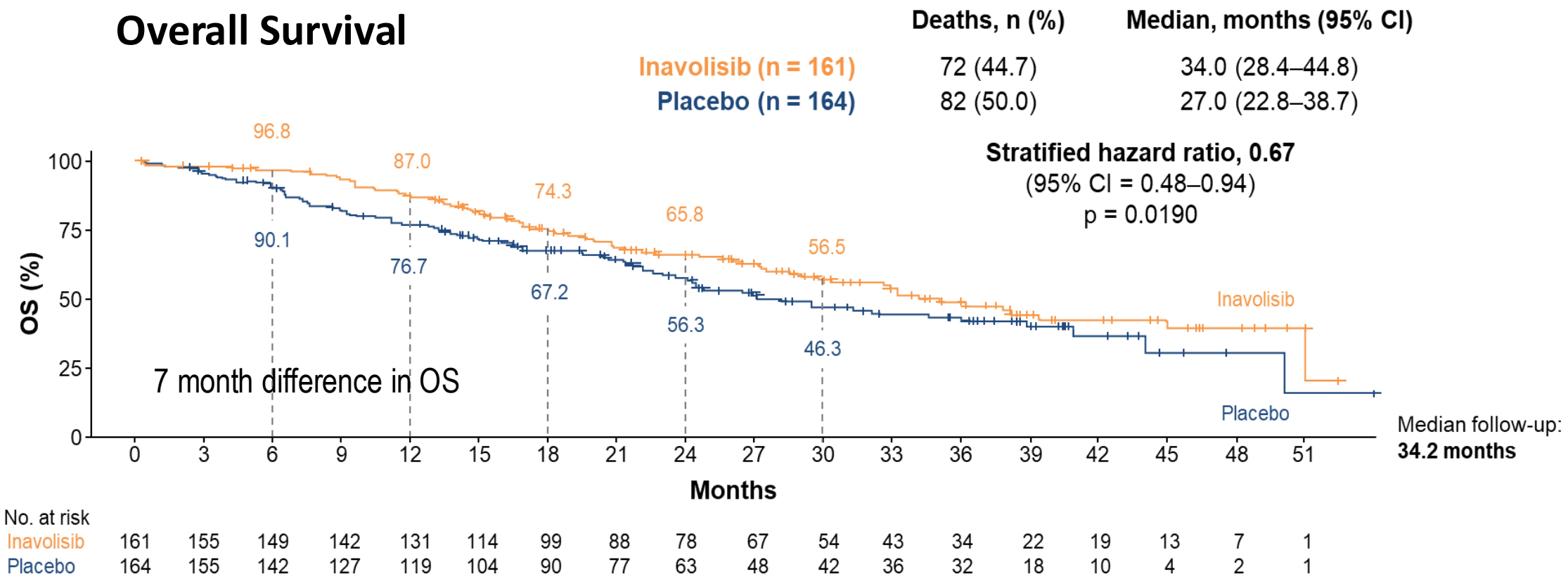


Demographics

- 34% primary, ~ 66% secondary endocrine resistance
- 48% premenopausal
- 80% visceral mets, 50% liver
- **48% adjuvant tamoxifen (38% Asian)**
- Most had central ctDNA testing
- **Post progression therapy**
  - 15.4% in the control arm received PI3Ki

Turner et al NEJM 2024; Jhaveri et al, NEJM 2025

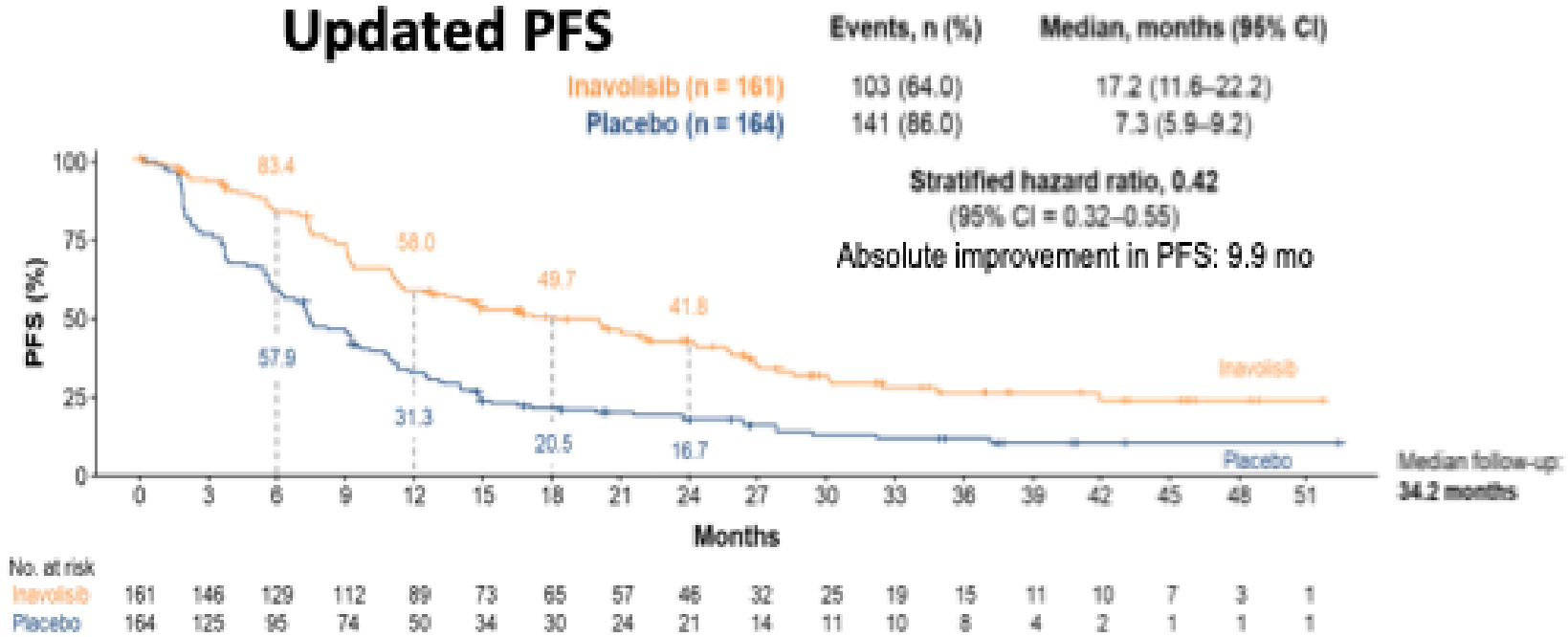
INAVO120 Updated Results



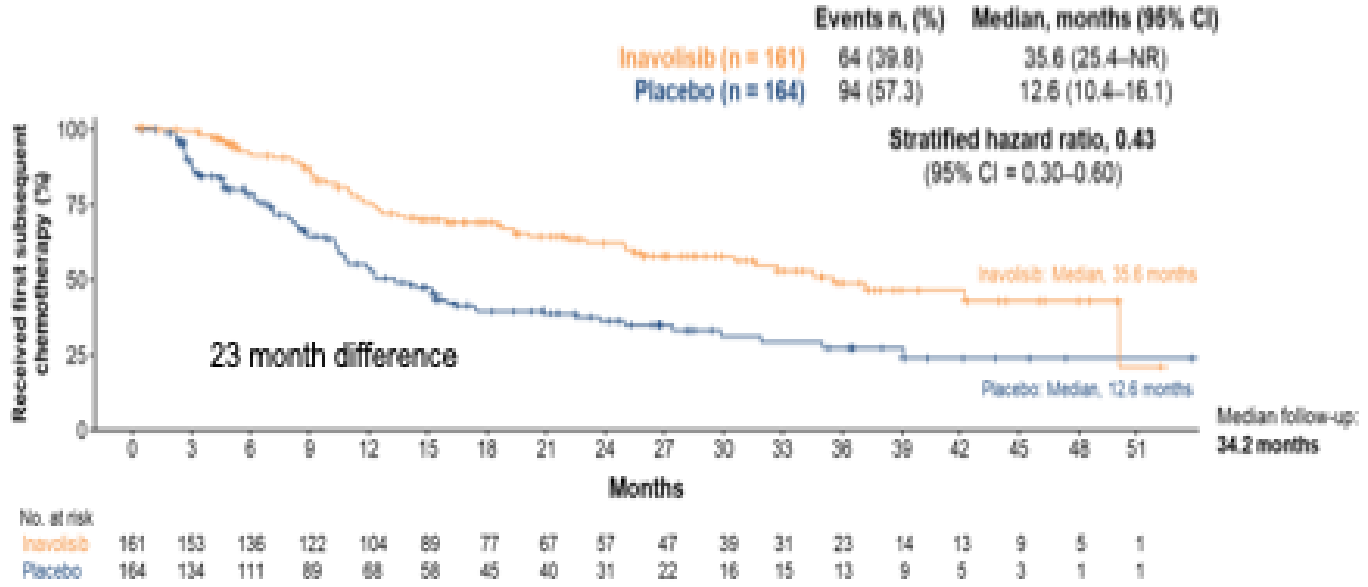
Turner et al, ASCO 2025; Jhaveri et al, NEJM 2025

INAVO120
Updated Results

Updated PFS

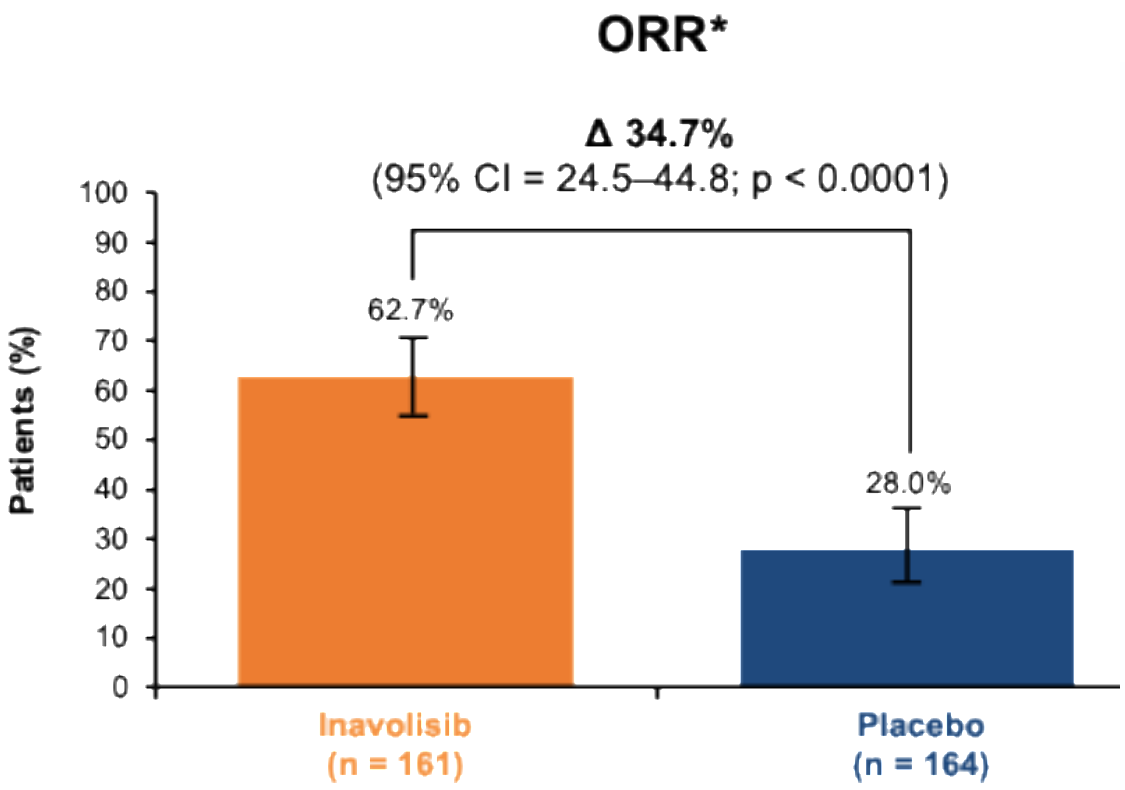


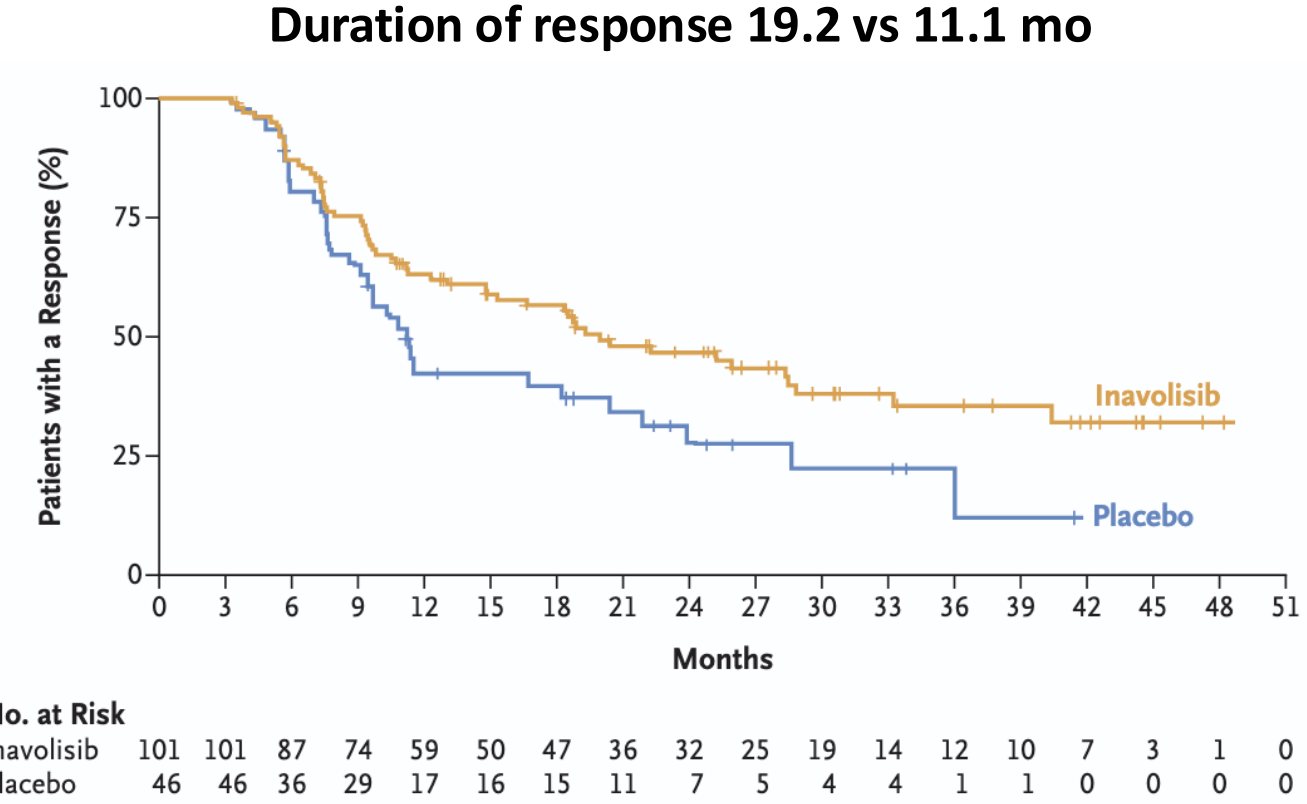
Time to first subsequent chemotherapy



Turner et al, ASCO 2025; Jhaveri et al, NEJM 2025

INAVO120 Updated Results





Turner et al, ASCO 2025; Jhaveri et al, NEJM 2025

INAVO120 Updated Results

Safety

	Inavolisib (n = 161)		Placebo (n = 163)	
Patients, n (%)	**Any grade**	**Grade 3 or 4**	**Any grade**	**Grade 3 or 4**
Neutropenia	147 (91.3)	133 (82.6)	148 (90.8)	131 (80.4)
Thrombocytopenia	80 (49.7)	22 (13.7)	75 (46.0)	8 (4.9)
Stomatitis or mucosal inflammation	89 (55.3)	9 (5.6)	47 (28.8)	0
Anemia	64 (39.8)	11 (6.8)	62 (38.0)	3 (1.8)
Hyperglycemia	102 (63.4)	11 (6.8)	22 (13.5)	0
Diarrhea†	84 (52.2)	6 (3.7)	26 (16.0)	0
Nausea	47 (29.2)	0	32 (19.6)	0
Rash	43 (26.7)	0	32 (19.6)	1 (0.6)
Ocular toxicities‡	47 (29.2)	1 (0.6)	26 (16.0)	0
Aspartate transaminase/ alanine transaminase increase	34 (21.1)	7 (4.3)	37 (22.7)	4 (2.5)
Vomiting	26 (16.1)	2 (1.2)	10 (6.1)	2 (1.2)
Lymphopenia	6 (3.7)	1 (0.6)	15 (9.2)	3 (1.8)
Pneumonitis§	5 (3.1)	1 (0.6)	2 (1.2)	0

Discontinuation of inavolisib due to AE: 6.8%

Turner et al, ASCO 2025; Jhaveri et al, NEJM 2025

SERENA-6 Study Design and Disposition Over Time

Phase III, randomized, double-blind, placebo-controlled study (NCT04964934)

- Female/male patients with ER+/HER2– ABC*
- All patients that have received AI + CDK4/6i (palbociclib, ribociclib, or abemaciclib) as initial endocrine-based therapy for ABC for at least 6 months
- *ESR1*m detected in ctDNA with no evidence of disease progression

R 1:1
N=315

Camizestrant (75 mg qd) + continuing CDK4/6i + placebo for AI

Stratification factors
- Visceral vs non-visceral
- *ESR1*m detection at first test vs at a subsequent test
- Time from initiation of AI + CDK4/6i to randomization: <18 vs ≥18 months
- Palbociclib vs ribociclib vs abemaciclib

Continuing AI (anastrozole/ letrozole) + CDK4/6i + placebo for camizestrant

Primary endpoint

PFS by investigator assessment (RECIST v1.1)

Secondary endpoints
- PFS2**
- OS**
- Safety
- Patient-reported outcomes

Treatment continued until disease progression, unacceptable toxicity, patient withdrawal or death

Screened, N=3325

Patients on first-line AI + CDK4/6i for ≥6 months

***ESR1*m testing** (every 2–3 months)

***ESR1*m surveillance, n=3256**

Patients with *ESR1*m detected, n=548

Positive on first test: 51%*
Positive after 2-5 tests: 38%*
Positive after >5 tests 11%*

Randomized, n=315

Patients tested for *ESR1*m in ctDNA with Guardant360 CDx every 2–3 months at time of routine staging scans

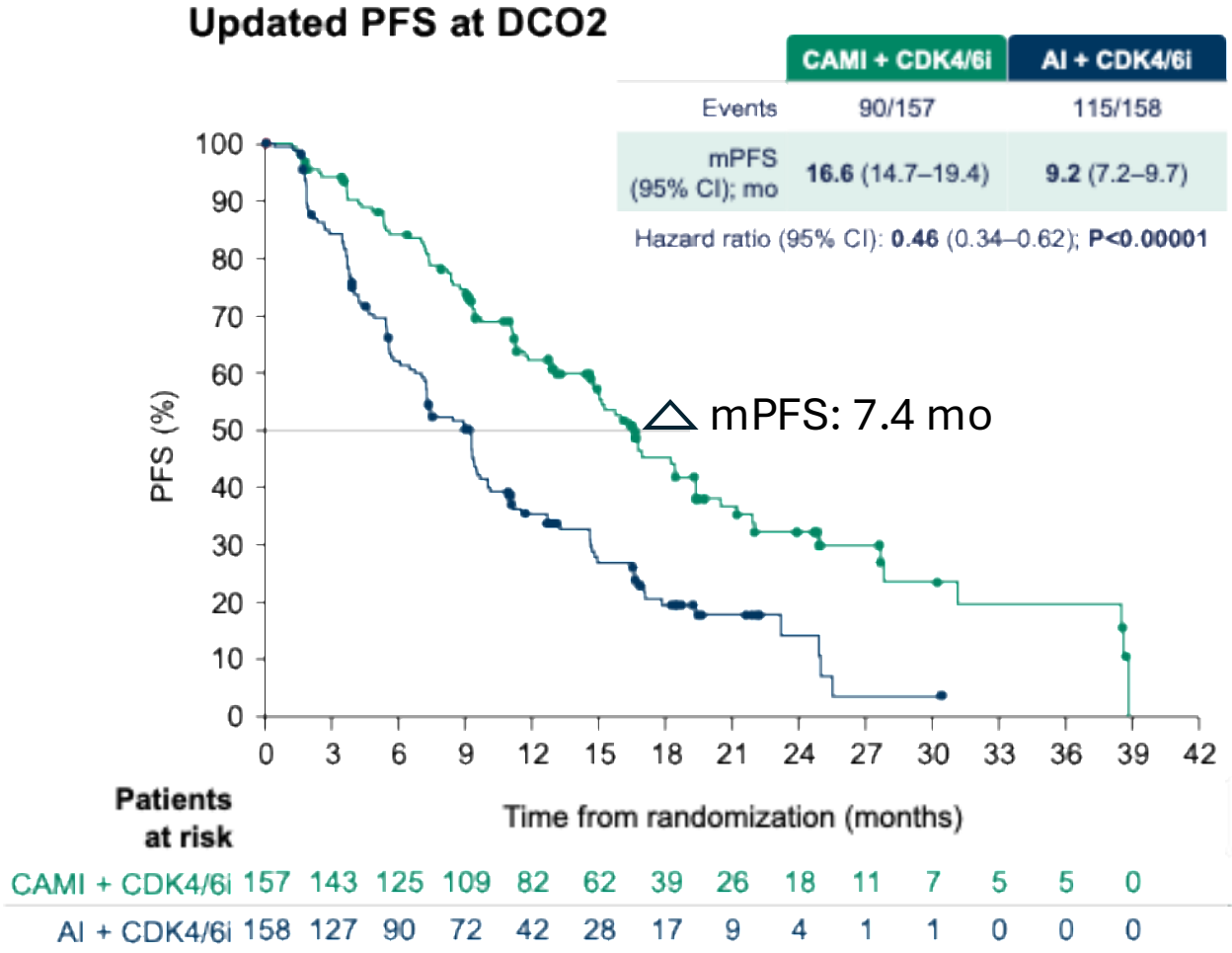
Patients ongoing in surveillance when screening closed, n=1949

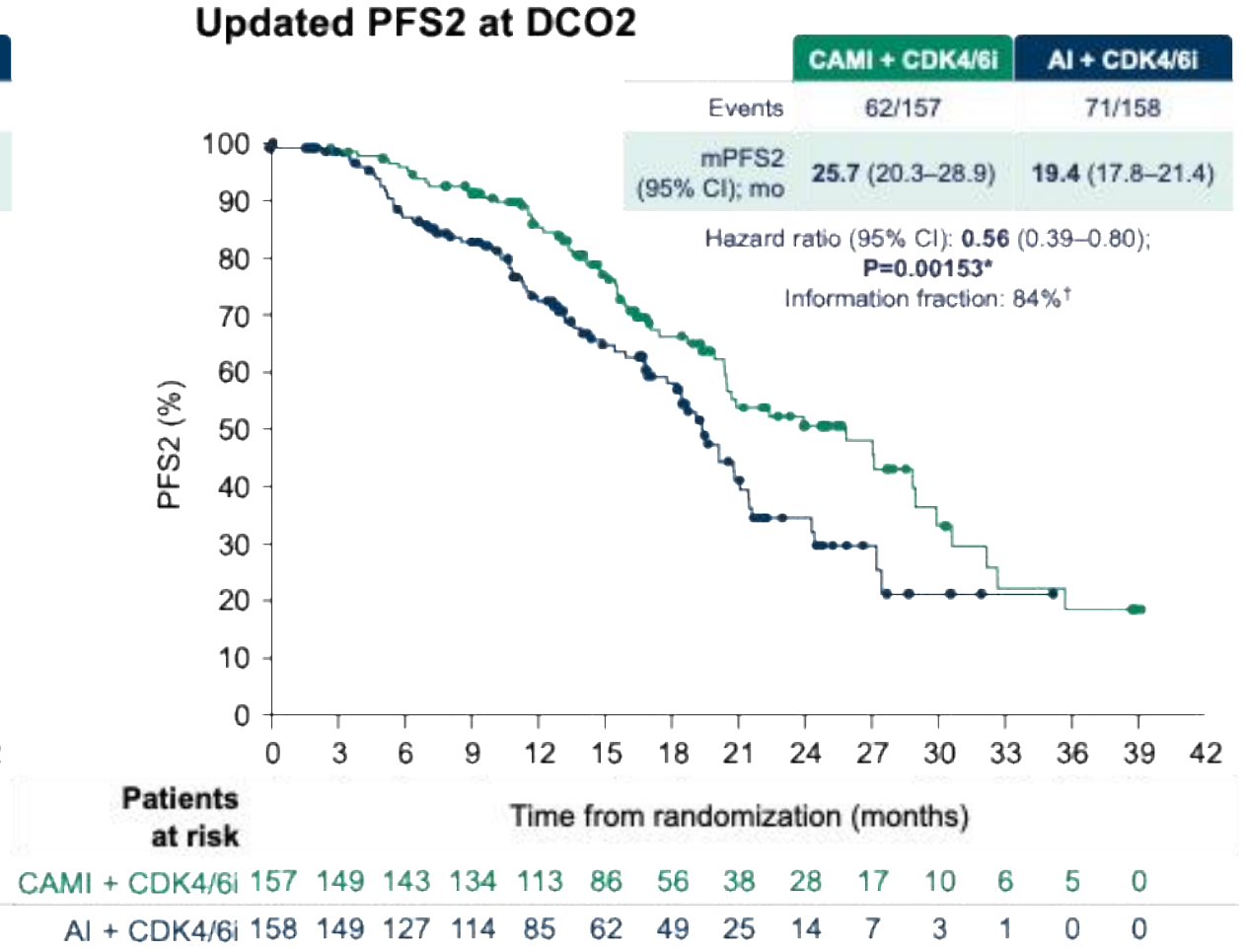
Discontinued (n=233) due to:
- Screen failure (n=200)
  - Concurrent disease progression (n=53)
  - Patient not meeting other eligibility criteria (n=48)
  - Reason not provided (n=99)
- Withdrew consent, lost to follow-up or unknown (n=33)

- ctDNA C1D1 and C3D1
- Median time to positive test when first test was positive: ~18 mo
- Median time to randomization: 23 mo
- 75-76% palbociclib

An estimate of the proportion of patients with emerging *ESR1*m during the study period is 42%, calculated from the 548 patients with a positive test/(the number of patients tested for *ESR1*m [n=3256] minus the number of patients that were **still ongoing in surveillance when screening closed [n=1949]).**

Turner N, ASCO 2025; Bidard FC, NEJM 2025

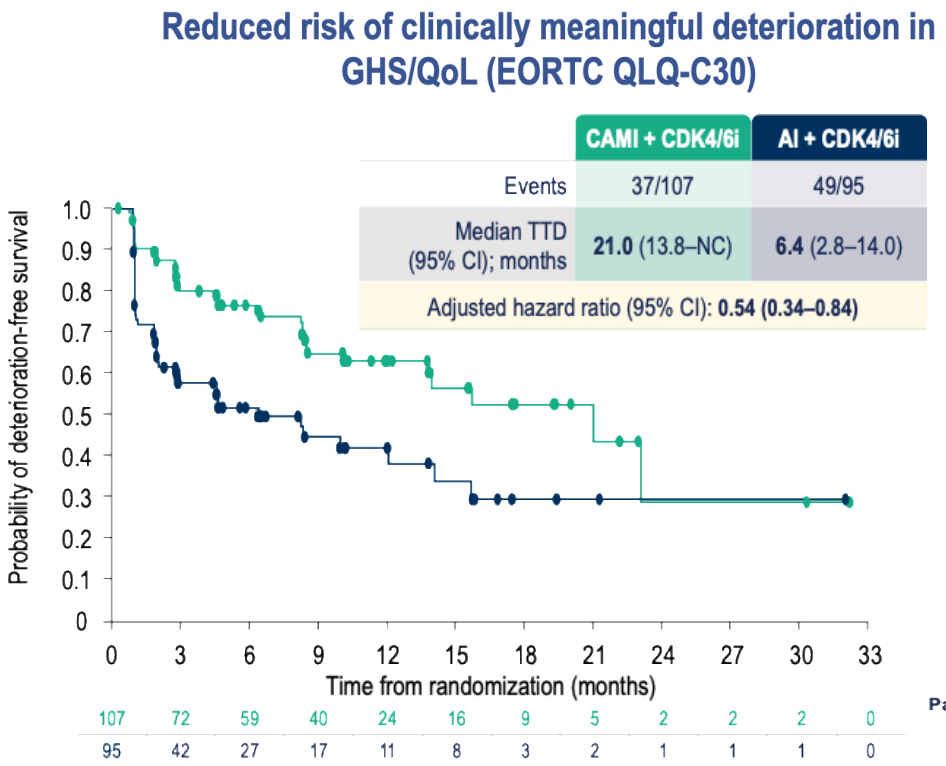


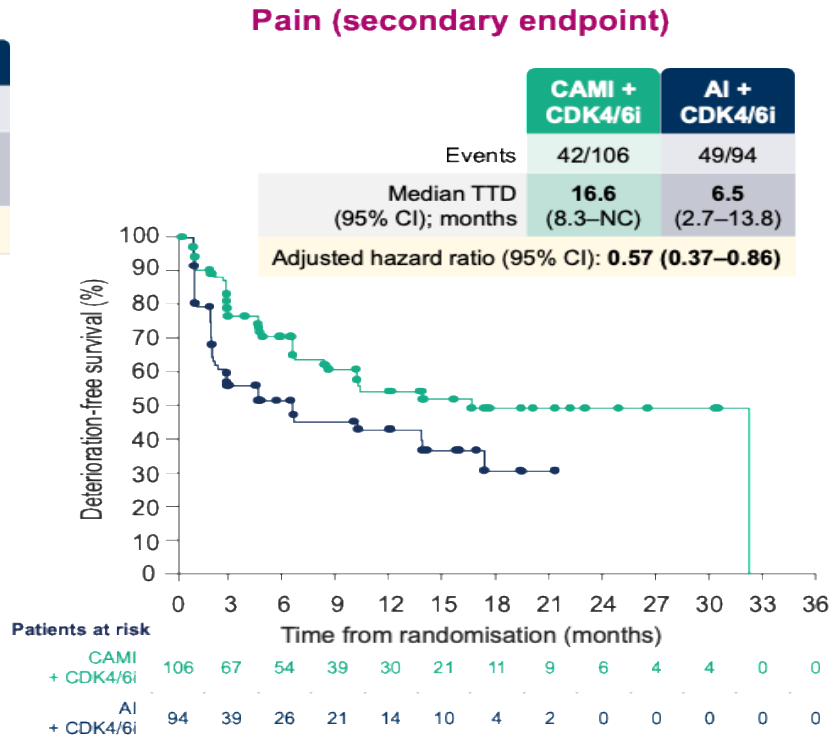


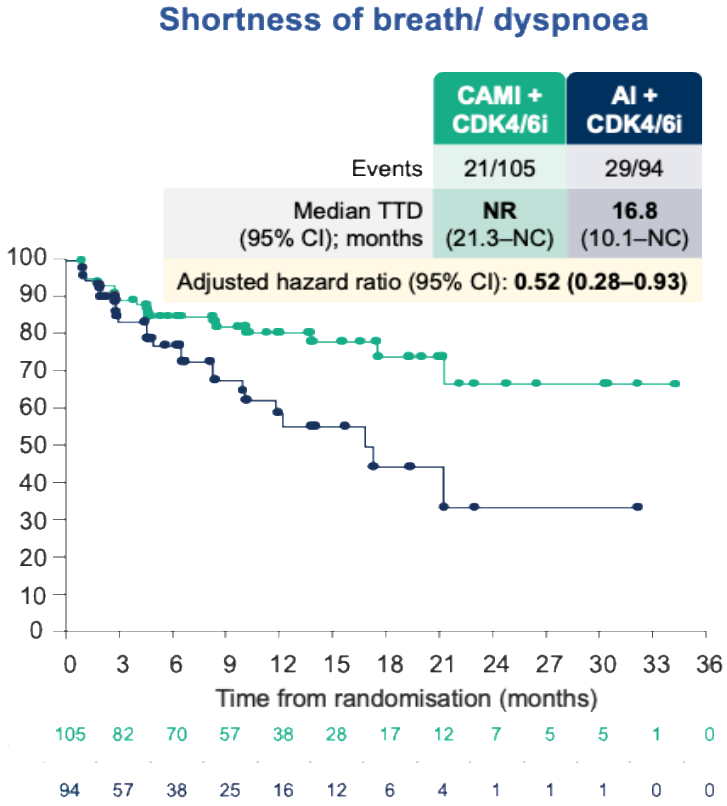
- Time to 1st subsequent therapy
  - HR: 0.47 (0.35–0.62)
- Time to next subsequent therapy
  - HR: 0.57 (0.40–0.81)

Bidard et al, SABCS 2025; Abstract RF7-03.

Reduced Risk of Clinically Meaningful Deterioration in GHS/QoL (EORTC QLQ-C30)



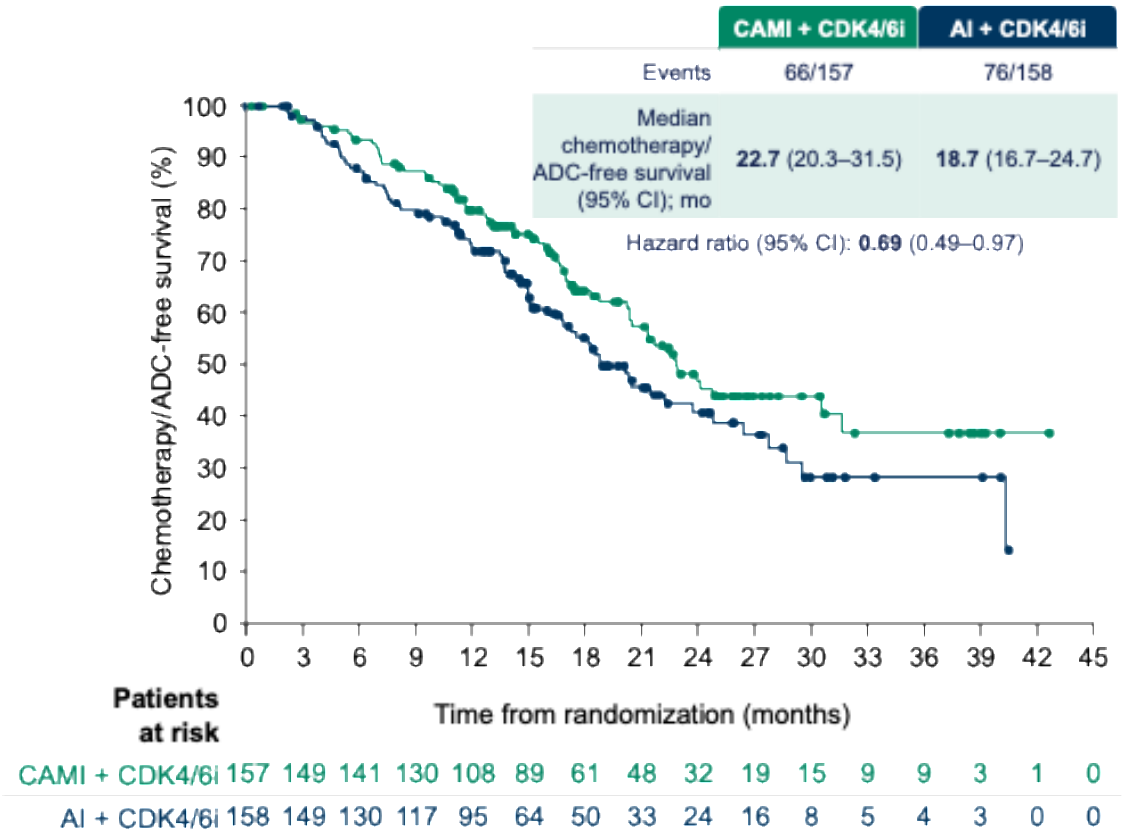




Mayer et al, ESMO 2025

Additional Endpoints

Chemo/ADC free Survival



- Switch resulted in marked decrease in ESR1 ctDNA
  - In the AI + CDK4/6i arm, ESR1m allele frequency increased >500% from baseline in 24.4% vs 0.8% of patients in the camizestrant + CDK4/6i arm
  - Median change from baseline at C3D1
    - Minus 100% for switch
    - +66.7% for no switch
  - OS immature (22%)

Is switching based on emerging ESR1 mutations ready for prime-time?

Bidard et al, SABCS 2025; Abstract RF7-03.

Pending Phase III Clinical Trials in the First-Line Setting: Oral SERDs and Targeted Agents

Trial completed accrual

Oral SERD Trials	Giredestrant	Camizestrant	Elacestrant
1L: Combination with CDK4/6i	**persevERA** NCT04546009 N=992 Giredestrant/palbociclib vs letrozole/palbociclib	**SERENA-4** NCT04711252 N=1370 Camizestrant/palbociclib vs anastrozole/palbociclib	
1L: Primary ET resistance	**pionERA** NCT06065748 N=1050 Giredestrant/CDK4/6i vs Fulvestrant/CDK4/6i		**ELEVATE** NCT05563220 N=30 Elacestrant + abemaciclib (Phase II)

- **Targeting CDK4 (atirmociclib)**
  - FourLight-3 (NCT06760637)
- **Targeting PIK3CA with triplet therapy**
  - Endocrine sensitive disease: INAVO123 (NCT06790693); PIKALO-2 (tersolisib, NCT07174336)
  - Endocrine resistant disease: CAPItello-292 (NCT04862663); VIKTORIA-2 (gedatolisib, NCT06757634); PIKALO-2 (tersolisib; NCT07174336)

Conclusions

- Multiple studies have now showed that ET + CDK4/6 inhibition results in improved PFS compared to mono or combination chemotherapy
  - Includes patients with a higher visceral disease burden and symptomatic disease
- Primary ET resistance with a PI3K mutation
  - Improved PFS and OS adding inavolisib to fulvestrant/palbociclib
  - Low use of sequential PI3K inhibitors in the control arm, but no reasonable endocrine partner post fulvestrant
- Switching based on emerging ESR1 mutation without radiographic disease progression
  - No access to oral SERDS on PD for the majority of patients (approved late in study)
  - Improved PFS, PFS2 and time to chemotherapy
  - Delayed time to deterioration in GHS/QOL primarily due to pain and fatigue domains
  - Potential option for patients with endocrine sensitive disease and increasing symptoms in particular
    - Median time to first test with mutation 18 months, time to randomization 23 months
- Impact of adjuvant CDK4/6i (and oral SERD) therapy unknown

Case Presentation: 80-year-old woman with type 2 diabetes, well-controlled hypertension and recurrent ER+HER2-negative mBC after 4 years of adjuvant letrozole

Dr Sunil Gandhi (Lecanto, Florida)

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

Which CDK4/6 inhibitor do you prefer in the up-front setting for elderly patients with HR-positive, HER2-negative mBC? Is palbociclib still a reasonable option for these patients?

Agenda

Module 1: Current Role of Genomic Assays in Treatment Decision-Making for Localized Hormone Receptor (HR)-Positive Breast Cancer — Dr DeMichele

Module 2: Role of CDK4/6 Inhibitors and Other Novel Strategies in Therapy for HR-Positive, HER2-Negative Localized Breast Cancer — Dr Jhaveri

Module 3: Evolving Up-Front Treatment Paradigm for HR-Positive, HER2-Negative Metastatic Breast Cancer (mBC) — Dr Rugo

Module 4: Clinical Utility of Agents Targeting the PI3K/AKT/mTOR Pathway for Patients with Progressive HR-Positive mBC — Dr Mayer

Module 5: Current and Future Role of Oral Selective Estrogen Receptor Degraders for Progressive HR-Positive mBC — Dr Wander

RTP RESEARCH TO PRACTICE

2025

Clinical Utility of Agents Targeting the PI3K/AKT/mTOR Pathway for Patients with Progressive HR-Positive mBC

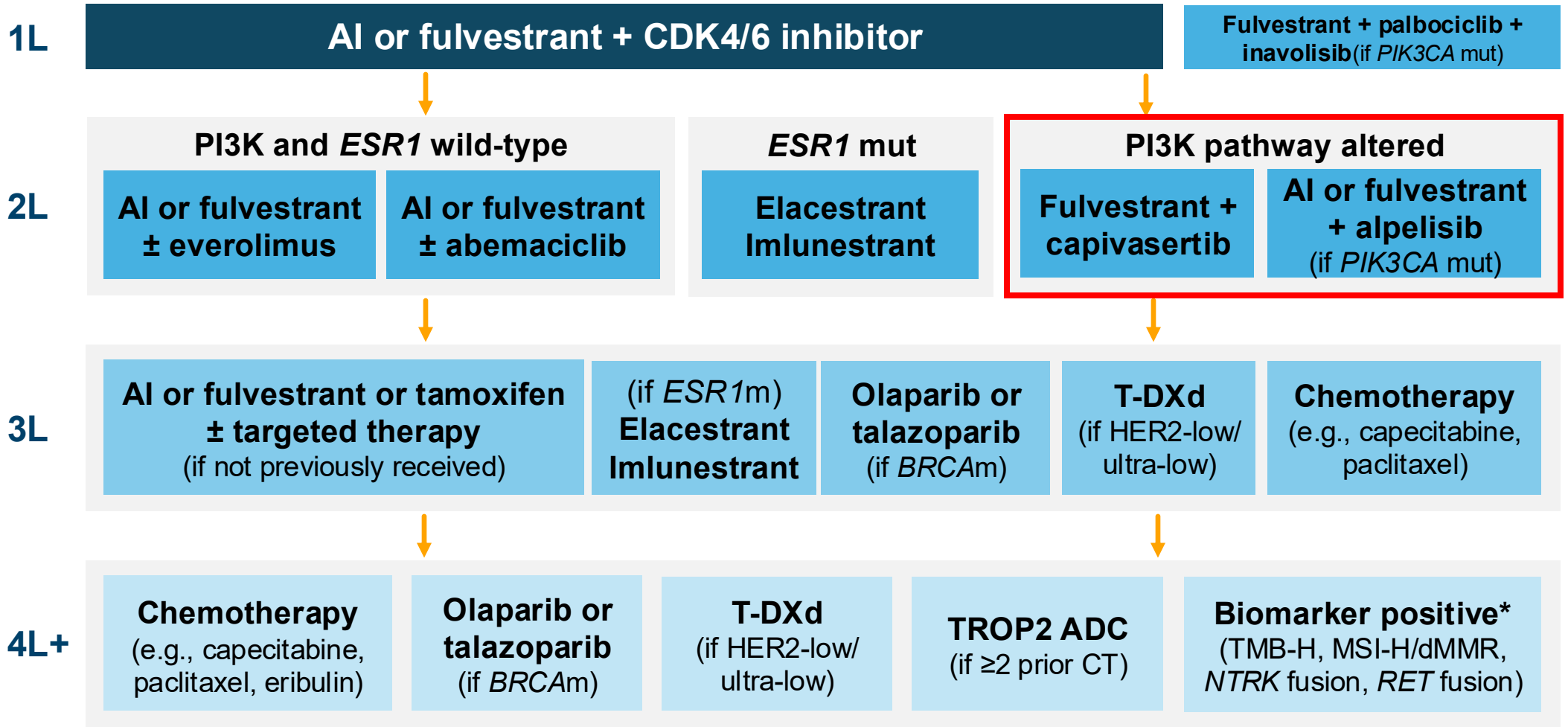
Erica L. Mayer MD, MPH

Director of Breast Clinical Trials, Dana-Farber Cancer Institute
Boston, MA

Dana-Farber Cancer Institute

HARVARD MEDICAL SCHOOL

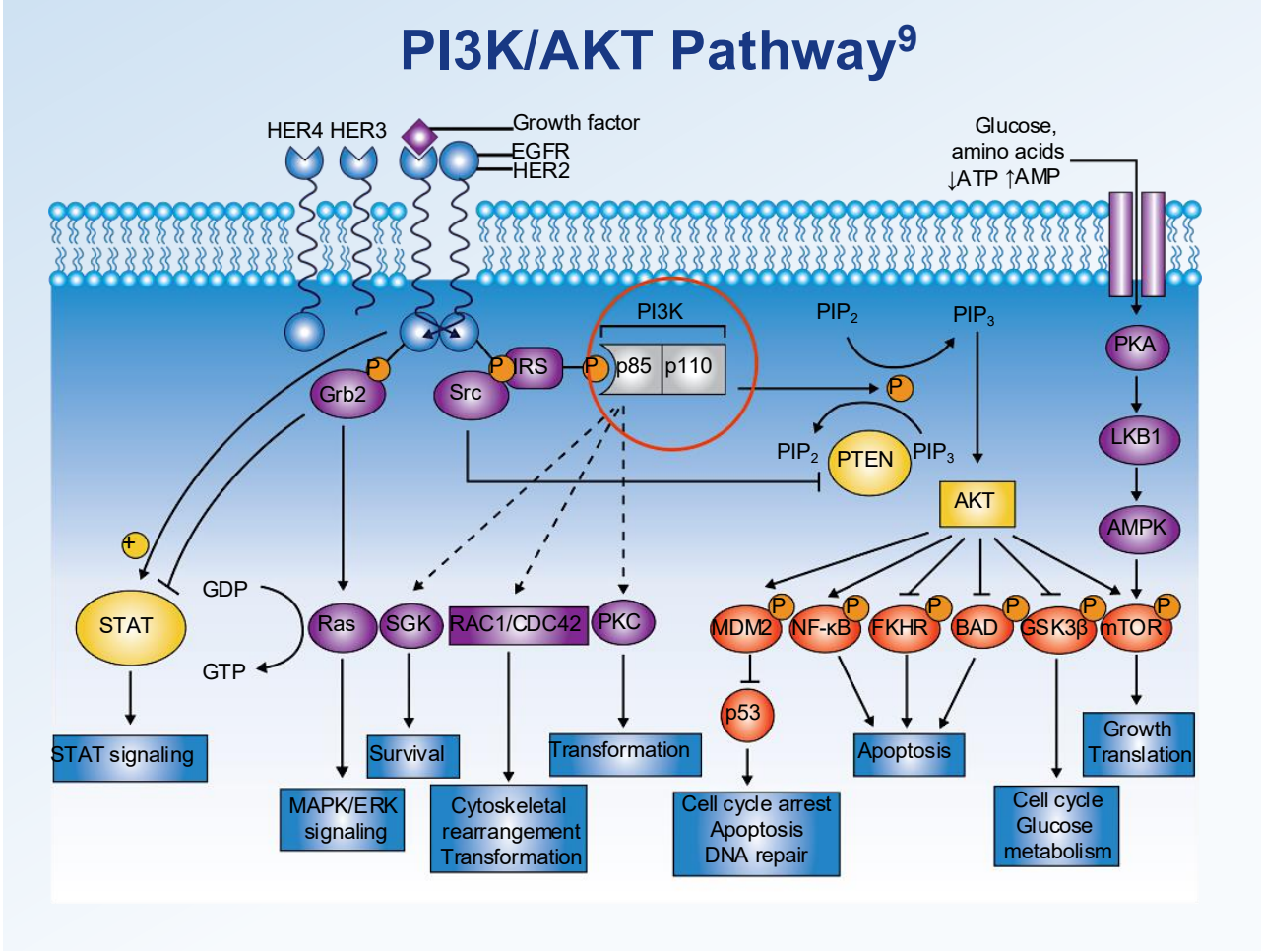
Treatment Algorithm for HR+/HER2- MBC



Slide adapted from Ana Garrido-Castro. *TMB-H: Pembrolizumab; MSI-H: Pembrolizumab, Dostarlimab; NTRK fusion: Larotrectinib, Entrectinib; RET fusion: Selpercatinib

Why is Inhibition of the mTOR/PI3K/AKT Pathway Important?

- PI3K/AKT/mTOR pathway is frequently altered in HR+ BC and has been implicated in resistance to endocrine therapies[1,2]
- ≈40% of HR+ BC harbor a PIK3CA mutation, leading to hyperactivation of the PI3K pathway[3-5]
- PI3K signaling promotes estrogen-independent growth of ER+ BC cells, and this growth is inhibited by the addition of PI3K inhibitors to antiestrogens[6-8]

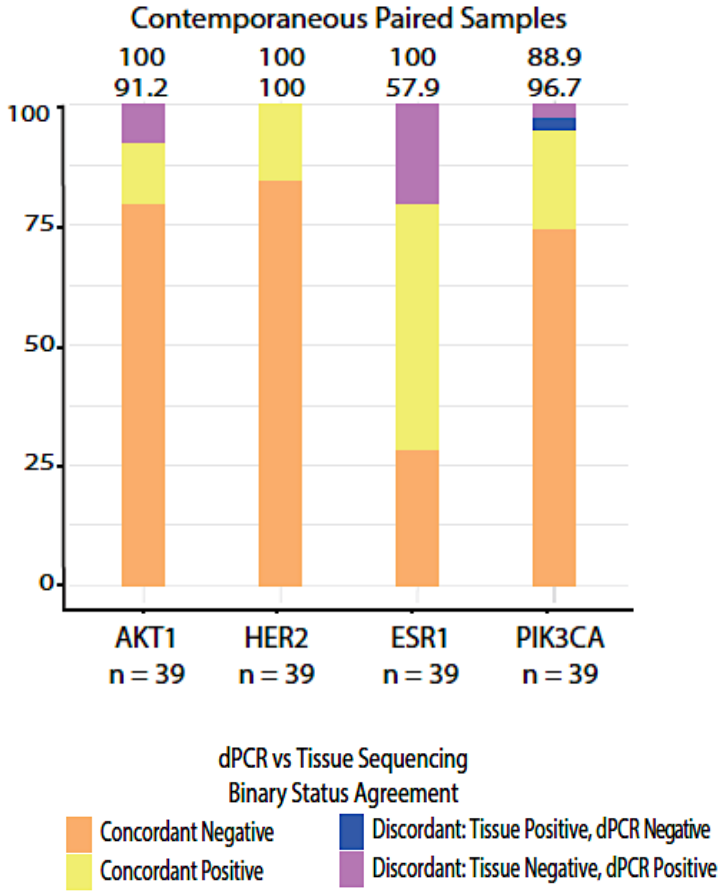


1. Miller TW et al. *J Clin Oncol*. 2011;29:4452-4461. 2. Bosch A et al. *Sci Transl Med*. 2015;7283ra51. 3. Mayer IA et al. *Clin Cancer Res*. 2017;23:26-34. 4. Loi S et al. *Proc Natl Acad Sci*. 2010;107:10208-10213. 5. Stemke-Hale K et al. *Cancer Res*. 2008;68:6084-6091. 6. Miller TW et al. *JCI*. 2010;120:2406-2413. 7. Crowder RJ et al. *Cancer Res*. 2009;69:3955-3962. 8. Miller TW et al. *Cancer Discovery*. 2011;1:338-351. 9. Hennessy BT et al. *Nat Rev Drug Discov*. 2005;4:988-1004.

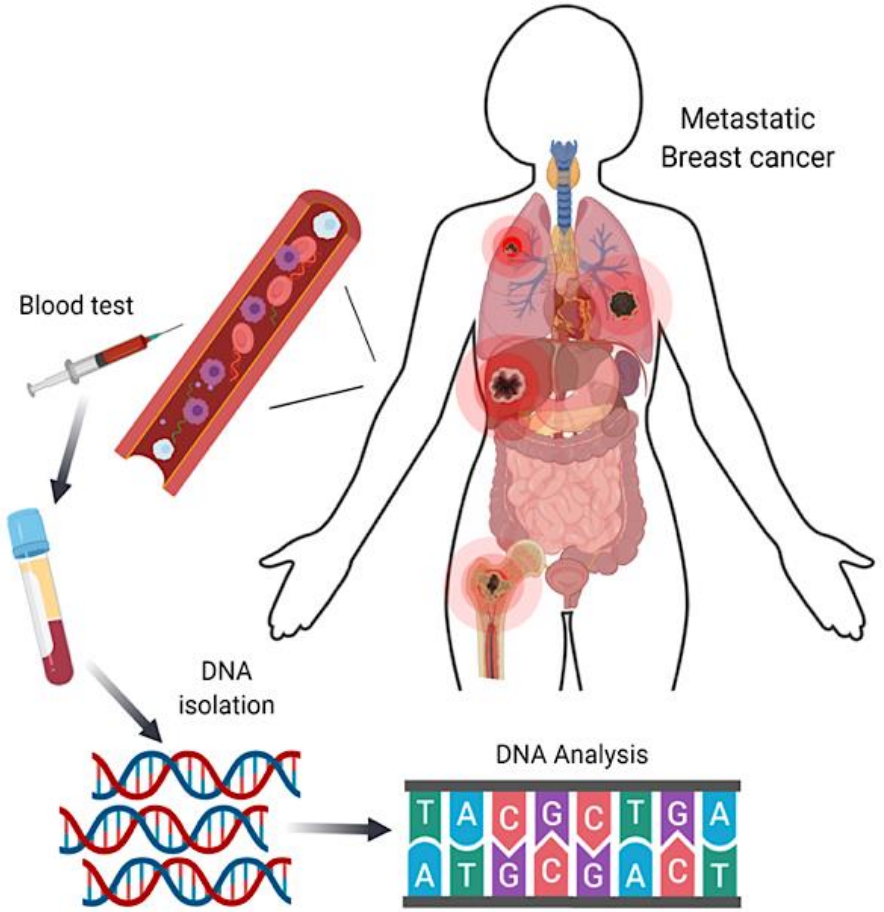
What is Best Method to Test for PI3K Pathway Mutations?

- PIK3CA mutations can be identified in tissue, MBC or primary, or ctDNA

- ctDNA testing identifies more *ESR1* mutations than contemporaneous biopsy



Different metastases may develop different resistance mutations



Turner NC et al. *Lancet Oncol.* 2020;21(10):1296-1308.

Capivasertib + Fulvestrant in AI-Resistant HR+/HER2- BC *CAPItello-291 Phase 3*

Study Design

Patients with HR+/HER2– ABC

- Men and pre-/post-menopausal women
- Recurrence while on or <12 months from end of adjuvant AI, or progression while on prior AI for ABC
- ≤2 lines of prior endocrine therapy for ABC
- ≤1 line of chemotherapy for ABC
- Prior CDK4/6 inhibitors allowed (at least 51% required)
- No prior SERD, mTOR inhibitor, PI3K inhibitor, or AKT inhibitor
- HbA1c <8.0% (63.9 mmol/mol) and diabetes not requiring insulin allowed
- FFPE tumor sample from the primary/recurrent cancer available for retrospective central molecular testing

R1:1 (N=708)

Stratification factors:
- Liver metastases (yes/no)
- Prior CDK4/6 inhibitor (yes/no)
- Region*

Capivasertib	400 mg twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks
Placebo	Twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks

Dual primary endpoints

PFS by investigator assessment
- Overall
- AKT pathway-altered tumors (≥1 qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration)

Key secondary endpoints

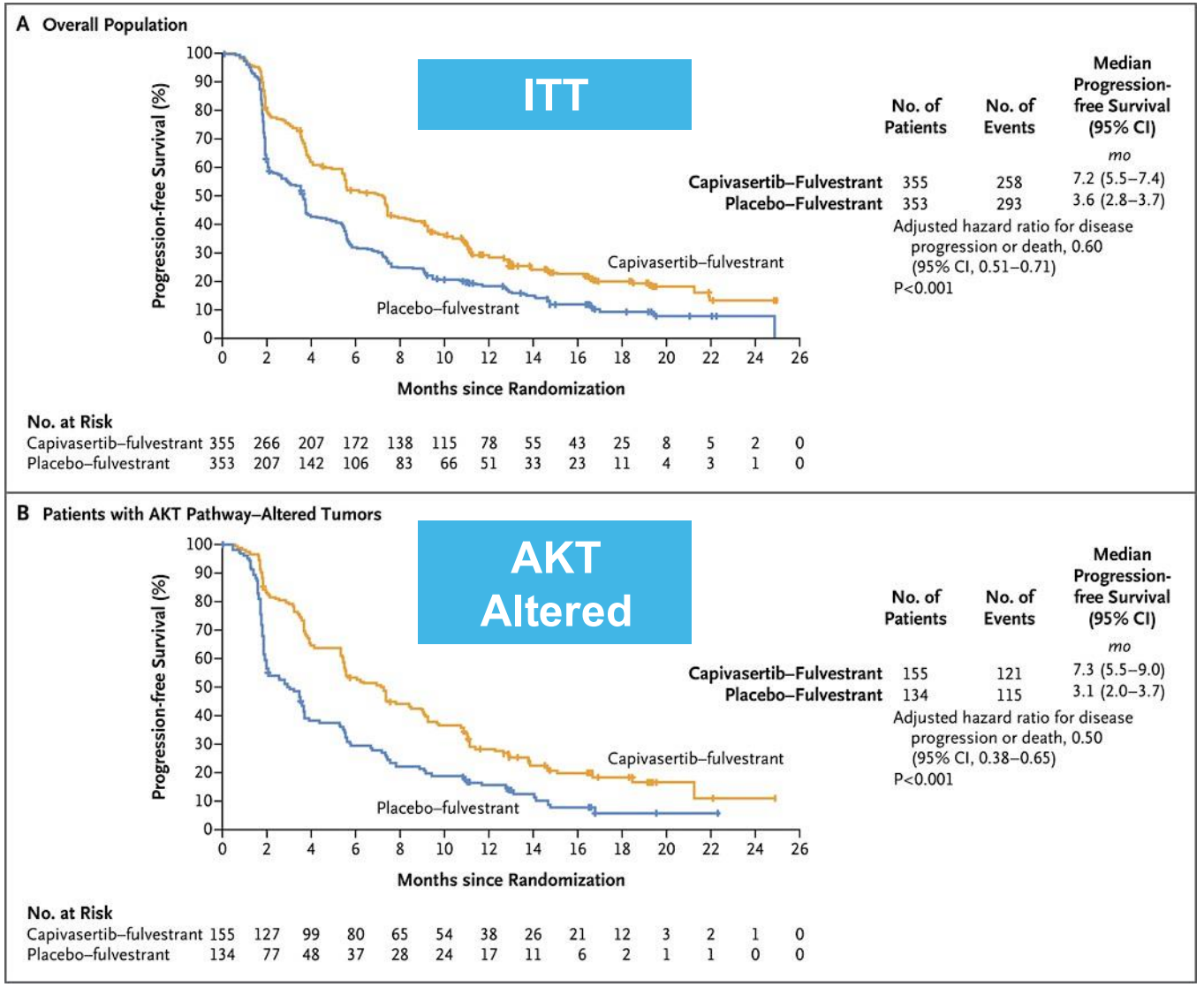
Overall survival
- Overall
- AKT pathway-altered tumors

Objective response rate
- Overall
- AKT pathway-altered tumors

Turner NC, et al. SABCS 2022. Oral Presentation GS3-04. Turner NC, et al. N Engl J Med. 2023;388(22):2058-2070.

CAPItello-291: Investigator-Assessed PFS in Overall Population and AKT-Pathway Altered

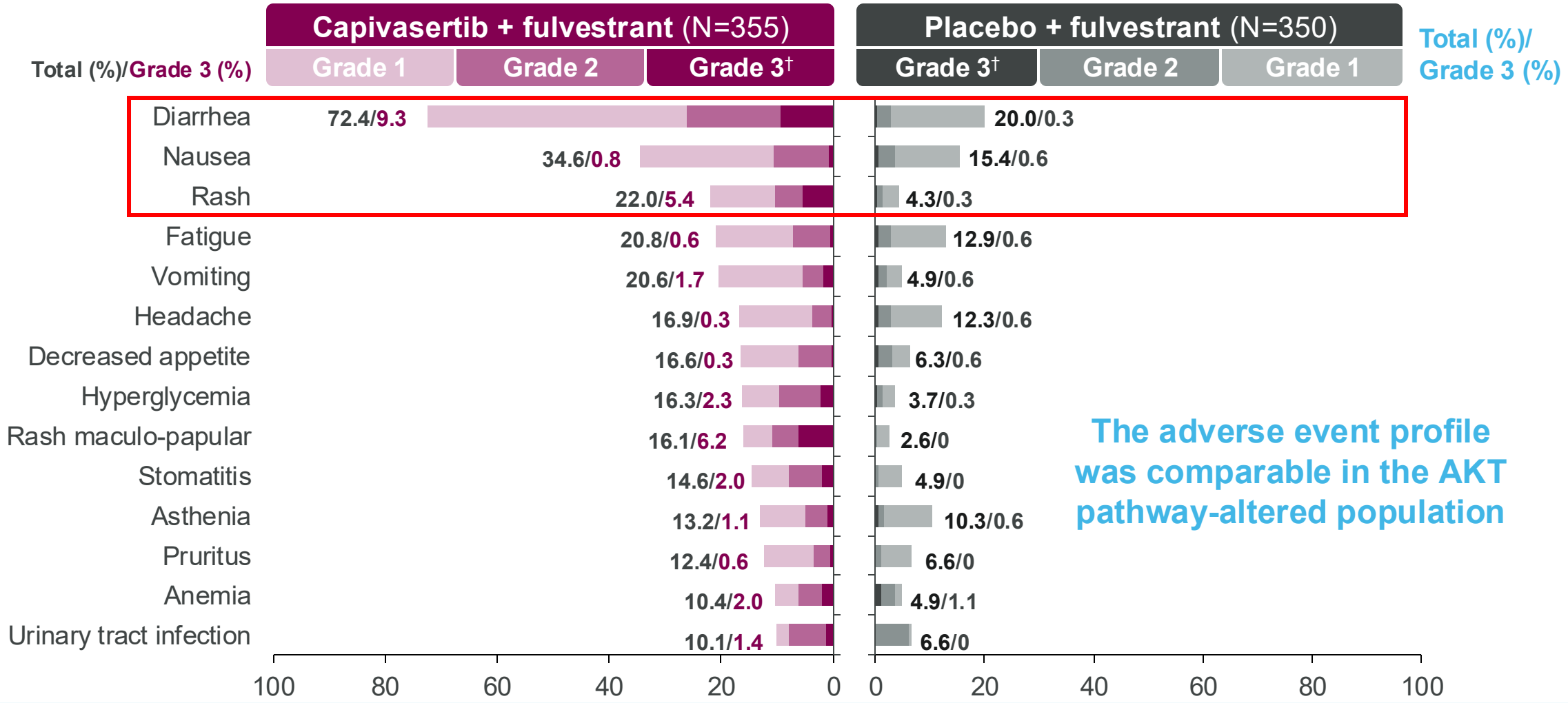
- Study met dual primary endpoints, showing significantly prolonged PFS with capivasertib + FULV vs placebo + FULV in overall and AKT pathway–altered populations (41% AKT altered)
- 69% prior CDK4/6i
- Exploratory analysis observed improved PFS in nonaltered subpopulation (HR: 0.70; 95% CI: 0.56-0.88)
  - 16% unknown mutation status



Dana-Farber Cancer Institute

Turner NC, et al. N Engl J Med. 2023;388(22):2058-2070.

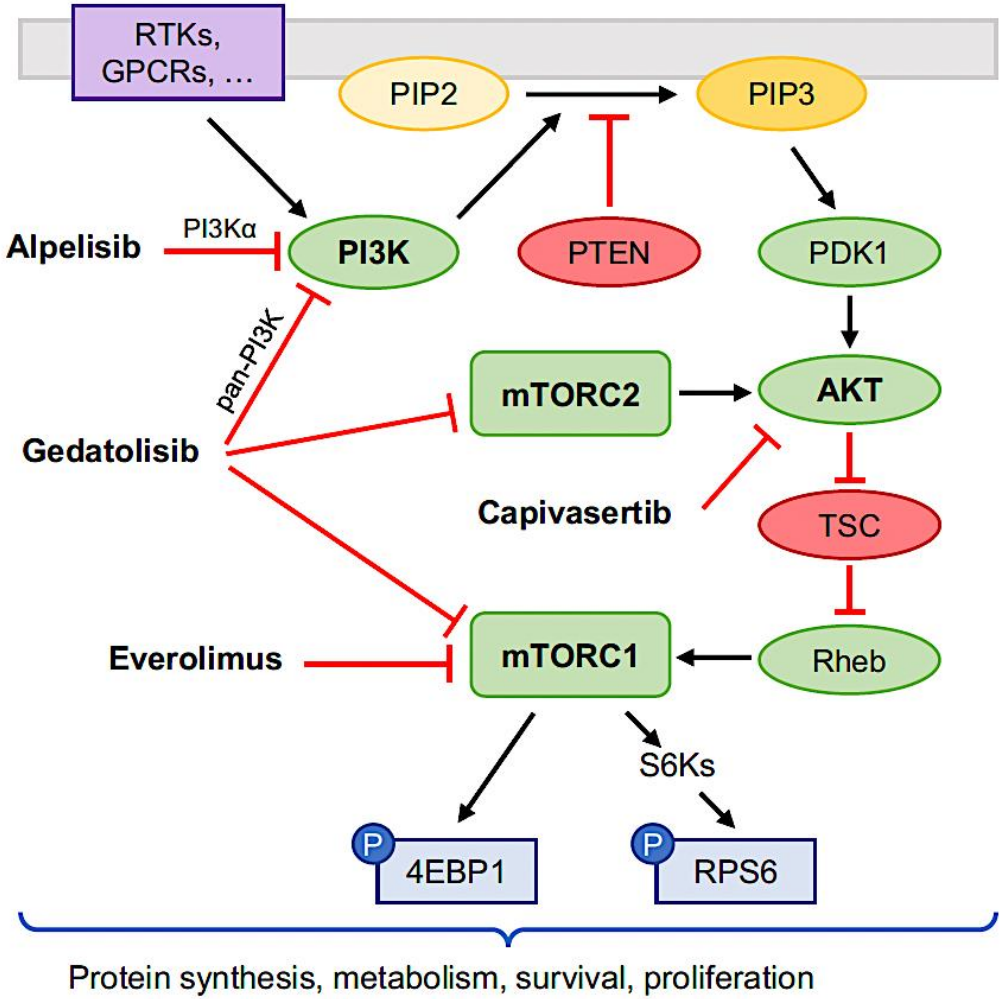
Adverse Events (>10% of patients) – Overall Population



The adverse event profile was comparable in the AKT pathway-altered population

•Adverse events of any grade related to rash (group term including rash, rash macular, maculo-papular rash, rash papular and rash pruritic) were reported in 38.0% of the patients in the capivasertib + fulvestrant arm (grade ≥3 in 12.1%) and in 7.1% of those in the placebo + fulvestrant group (grade ≥3 in 0.3%). †All events shown were Grade 3 except one case of Grade 4 hyperglycemia in the capivasertib + fulvestrant arm. *This presentation is the intellectual property of the author/presenter. Contact them at nick.turner@icr.ac.uk for permission to reprint and/or distribute.

Inhibiting the PI3K/AKT/mTOR Pathway



Drug	PAM specificity	Cell-free Assay Ki (nM)					
		PI3Kα	PI3Kβ	PI3Kγ	PI3Kδ	mTOR	AKT1/2/3
Gedatolisib	pan-PI3K, mTORC1/2	0.4	6	8	6	1	-
Alpelisib	PI3Kα	5	>1000	250	290	-	-
Capivasertib	AKT	-	-	-	-	-	3/8/8
Everolimus	mTORC1	-	-	-	-	1.6-2.4	-

Rosetti S et al, NPJ Breast Cancer 2024.

VIKTORIA-1 Study Design

Gedatolisib: PI3K/AKT/mTOR (PAM) inhibitor

HR+/HER2-
Advanced Breast Cancer

Eligibility Criteria

- Pre- & postmenopausal women & men
- Progression on/after CDK4/6i + NSAI
- ≤2 lines of prior ET for ABC
- Measurable disease, RECIST v1.1
- Screening result for *PIK3CA* status
- No T2DM with HbA1c >6.4% or T1DM
- No prior mTORi, PI3Ki, or AKTi
- No prior chemotherapy for ABC

Stratification Factors

- Lung/liver metastases (yes/no)
- Time to progression on immediate prior therapy (≤ or >6 months)
- Region (US/Canada or ROW)

STUDY 1
PIK3CA-WT

R 1:1:1
(N=392)

Assign

STUDY 2
PIK3CA-MT

R 3:1:3

Arm A†

Gedatolisib	180 mg IV once weekly, 3 weeks on, 1 week off
Palbociclib	125 mg daily, 21 days on, 7 days off
Fulvestrant	500 mg; cycle 1, days 1 & 15, then every 4 weeks

Arm B†

Gedatolisib	180 mg IV once weekly, 3 weeks on, 1 week off
Fulvestrant	500 mg; cycle 1, days 1 & 15, then every 4 weeks

Arm C

Fulvestrant	500 mg; cycle 1, days 1 & 15, then every 4 weeks

Optional cross-over to Arm A or B at progression

- Gedatolisib† + Palbociclib + Fulvestrant
- Gedatolisib† + Fulvestrant
- Alpelisib + Fulvestrant

Primary Endpoints

PFS (BICR)
Arm A vs. Arm C
Arm B vs. Arm C

Secondary Endpoints

OS
Response
Safety
QoL

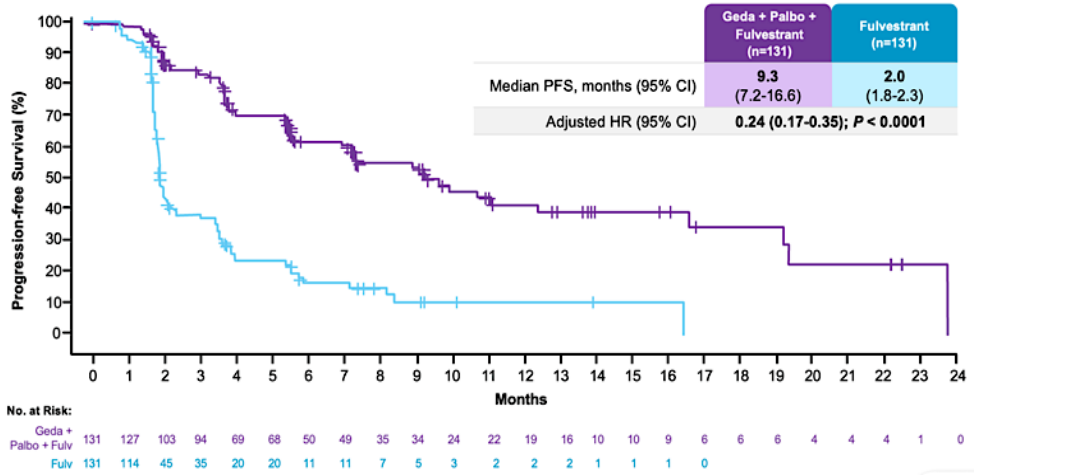
†Prophylactic use of a steroid-containing "swish and spit" regimen was protocol-mandated; oral non-sedating antihistamine therapy was recommended

Dana-Farber Cancer Institute

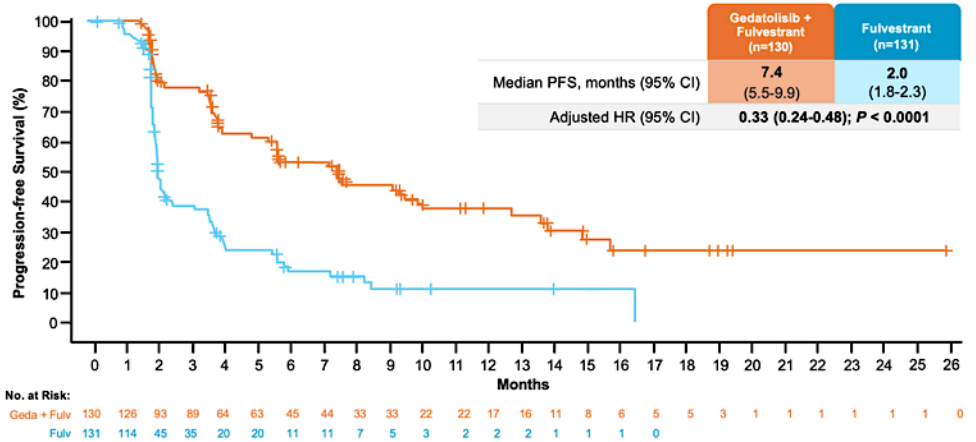
Hurvitz SA et al, ESMO 2025.
Erica L. Mayer MD, MPH | 2025

VIKTORIA-1 Results

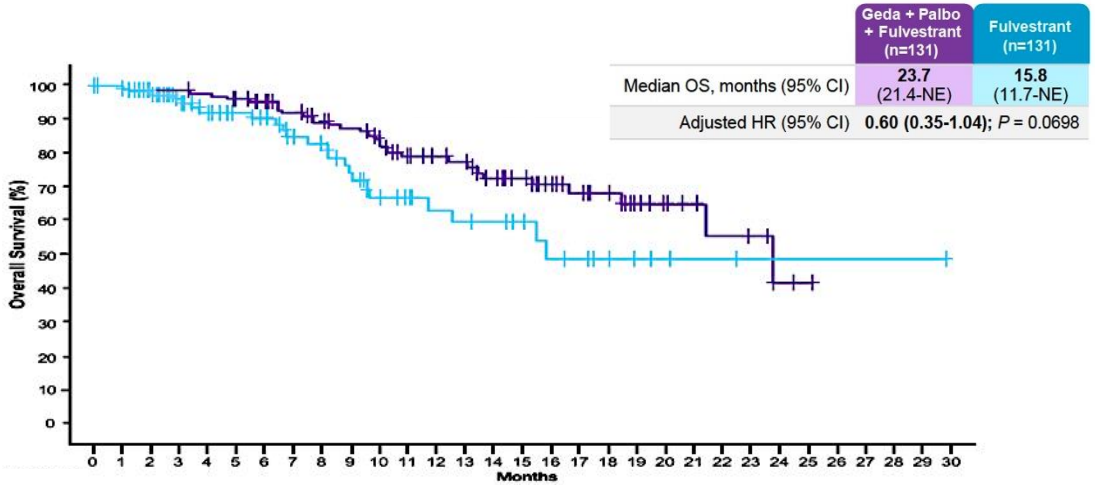
PFS Gedatolisib Triplet vs. Fulvestrant



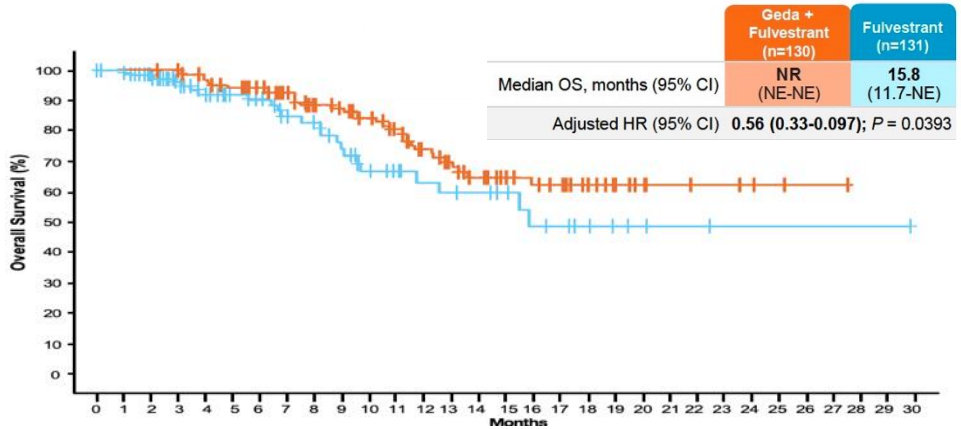
PFS Gedatolisib Doublet vs. Fulvestrant



Interim OS Censored at Cross-Over Gedatolisib Triplet vs. Fulvestrant



Interim OS Censored at Cross-Over Gedatolisib Doublet vs. Fulvestrant



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Hurvitz SA et al, ESMO 2025.

VIKTORIA-1 PFS in Key Subgroups

Subgroup	Gedatolisib + Palbociclib + Fulvestrant n/N	Gedatolisib + Palbociclib + Fulvestrant mPFS, mo.	Gedatolisib + Fulvestrant n/N	Gedatolisib + Fulvestrant mPFS, mo.
Age				
<65 years	39/93	9.3	52/96	5.6
≥65 years	20/38	9.7	17/34	7.7
Menopause status				
Pre/perimenopause	9/28	11.1	19/37	5.6
Postmenopause	50/101	8.9	50/93	7.6
Geographic area				
US/Canada	6/21	19.3	9/21	14.9
Europe	29/57	9.3	31/55	7.6
Latin America	16/35	5.6	20/36	5.6
Asia Pacific	8/18	16.6	9/18	7.3
Presence of visceral metastasis				
Yes	44/102	10.7	57/102	7.3
No	15/29	8.9	12/28	9.3
Liver metastasis				
Yes	37/74	9.2	46/82	7.3
No	22/57	9.9	23/48	10.0
Lines of prior tx for ABC				
<2	52/115	9.7	62/114	7.3
≥2	7/16	5.4	7/16	10.0
TTP on immediate prior tx				
≤6 months	13/26	7.4	14/26	5.6
>6 months	46/105	9.9	55/104	7.6
Prior CDK4/6i for ABC				
Ribociclib	29/59	8.9	31/62	5.6
Palbociclib	21/56	16.6	26/47	7.7
Abemaciclib	13/23	5.4	15/26	5.6

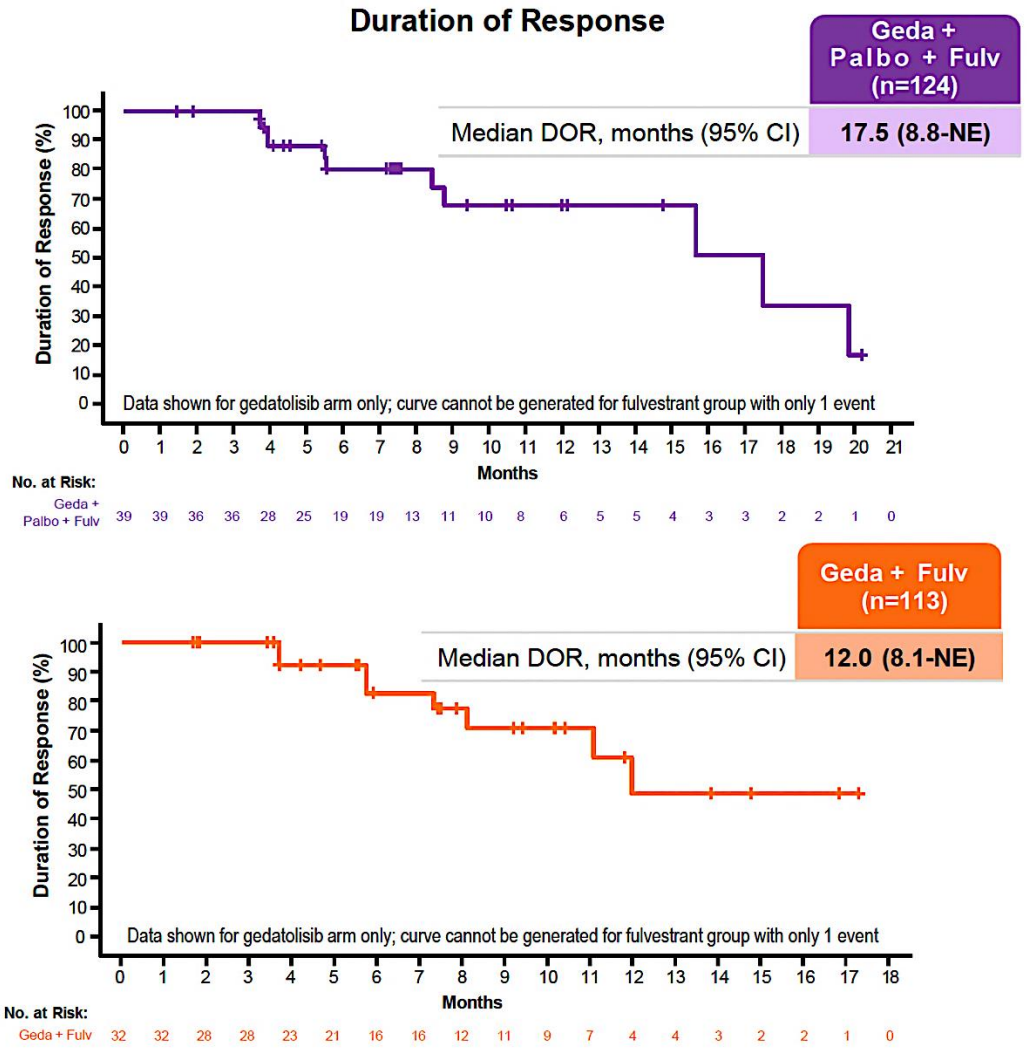
Hurvitz SA et al, ESMO 2025.

VIKTORIA-1 Tumor Response (BICR Assessment)

Patients with Evaluable Disease

Endpoint, n (%)	Geda + Palbo + Fulvestrant (n=124)	Gedatolisib + Fulvestrant (n=113)	Fulvestrant (n=105)
Best Overall Response			
Complete response	1 (0.8)	0	0
Partial response	38 (30.6)	32 (28.3)	1 (1.0)
Stable disease	67 (54.0)	55 (48.7)	40 (38.1)
Progressive disease	17 (13.7)	26 (23.0)	62 (59.0)
Not evaluable	1 (0.8)	0	2 (1.9)
Objective Response Rate*	39 (31.5)	32 (28.3)	1 (1.0)
Clinical Benefit Rate†	62 (50.0)	55 (48.7)	12 (11.4)
Disease Control Rate‡	106 (85.5)	87 (77.0)	41 (39.0)
Median DOR, months [95% CI]	17.5 [8.8-NE]	12.0 [8.1-NE]	NR [NE]

*Defined as CR+PR
†Defined as CR+PR+SD >24 weeks as assessed by BICR
‡Defined as CR+PR+SD
Abbreviations: BICR, blinded independent central review; CI, confidence interval; CR, complete response; DOR, duration of response; Fulv, fulvestrant; Geda, gedatolisib; NE, not estimable; no., number; NR, not reached; Palbo, palbociclib; PR, partial response; SD, stable disease.



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Safety and Tolerability

Treatment-Related Adverse Events (Safety Population)*

SAE and discontinuation, n (%)	Gedatolisib + palbociclib + fulvestrant (n=130)			Gedatolisib + fulvestrant (n=130)			Fulvestrant (n=123)		
Pts with ≥1 SAE	14 (10.8)			12 (9.2)			1 (0.8)		
Study treatment D/C due to TRAE	3 (2.3)			4 (3.1)			0		
Deaths due to TRAE†	2 (1.5)			0			0		
Adverse events, n (%)	**Gedatolisib + palbociclib + fulvestrant (n=130)**			**Gedatolisib + fulvestrant (n=130)**			**Fulvestrant (n=123)**		
	Any Grade	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Stomatitis‡	**90 (69.2)**	**25 (19.2)**	**0**	**74 (56.9)**	**16 (12.3)**	**0**	**0**	**0**	**0**
Neutropenia‡	85 (65.4)	68 (52.3)	13 (10.0)	2 (1.5)	0	1 (0.8)	1 (0.8)	1 (0.8)	0
Nausea	57 (43.8)	5 (3.8)	0	56 (43.1)	1 (0.8)	0	4 (3.3)	0	0
Rash‡	**36 (27.7)**	**6 (4.6)**	**0**	**42 (32.3)**	**7 (5.4)**	**0**	**0**	**0**	**0**
Vomiting	36 (27.7)	2 (1.5)	0	30 (23.1)	0	0	1 (0.8)	0	0
Fatigue	29 (22.3)	2 (1.5)	0	27 (20.8)	1 (0.8)	0	5 (4.1)	0	0
Diarrhea§	**22 (16.9)**	**2 (1.5)**	**0**	**16 (12.3)**	**1 (0.8)**	**0**	**0**	**0**	**0**
Hyperglycemia‡,§	**12 (9.2)**	**3 (2.3)**	**0**	**15 (11.5)**	**3 (2.3)**	**0**	**0**	**0**	**0**

Abbreviations: D/C, discontinued; Pts, patients; SAE, serious adverse event; TRAE, treatment-related adverse event (per investigator)
*Shown are adverse events of any grade that occurred in at least 20% of the patients in any trial group unless otherwise noted
†Grade 5 events include one considered related to palbociclib (pneumonia) and one due to hepatic failure in a patient with multiple liver metastasis considered related to all three drugs (and likely associated with disease)
‡For stomatitis, neutropenia, rash, and hyperglycemia, combined preferred terms shown; if a patient experienced multiple terms, it was counted once for the highest grade.
§ Additional events of clinical importance

Key Toxicities Across Available PI3K Pathway Inhibitors

	SOLAR-1		INAVO120		Capitello291		VIKTORIA-1	
	Alpelisib		Inavolisib		Capivasertib		Gedatolisib	
	All Grade	Grade 3+	All Grade	Grade 3+	All Grade	Grade 3+	All Grade	Grade 3+
Hyperglycemia	63.7%	36.6%	58.6%	5.6%	16.3%	2.3%	9.2%	2.3%
Diarrhea	57.7%	6.7%	48.1%	3.7%	72.4%	9.3%	16.9%	1.5%
Mucositis	24.6%	2.5%	51.2%	5.6%	14.6%	2.0%	69.2%	19.2%
Rash	35.6%	9.9%	25.3%	0.0%	38.0%	12.1%	27.7%	4.6%
	Inclusion A1c <6.4%		Inclusion A1c <6%		Inclusion A1c <8%		Inclusion A1c <6.4%	

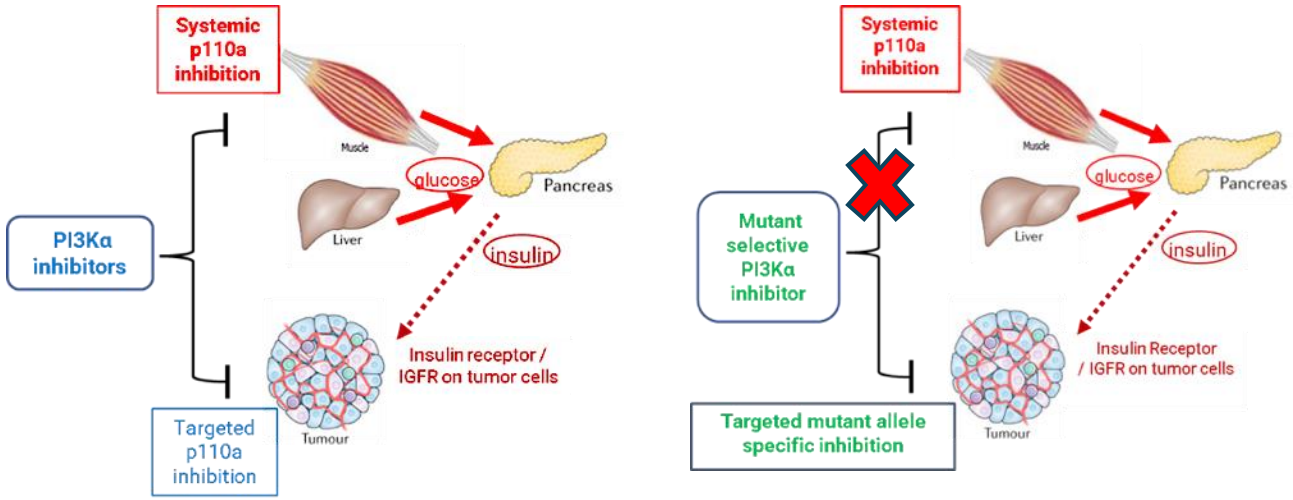
How can we Harness the Power of PIK3CA Inhibition with Improved Tolerability? Mutant Selective PIK3CA Inhibitors

WT PI3Kα inhibition leads to dose-limiting toxicities, which may limit efficacy

- Hyperglycemia (65% all gr)
- Diarrhea (60% all gr)
- Rash (36% all gr)

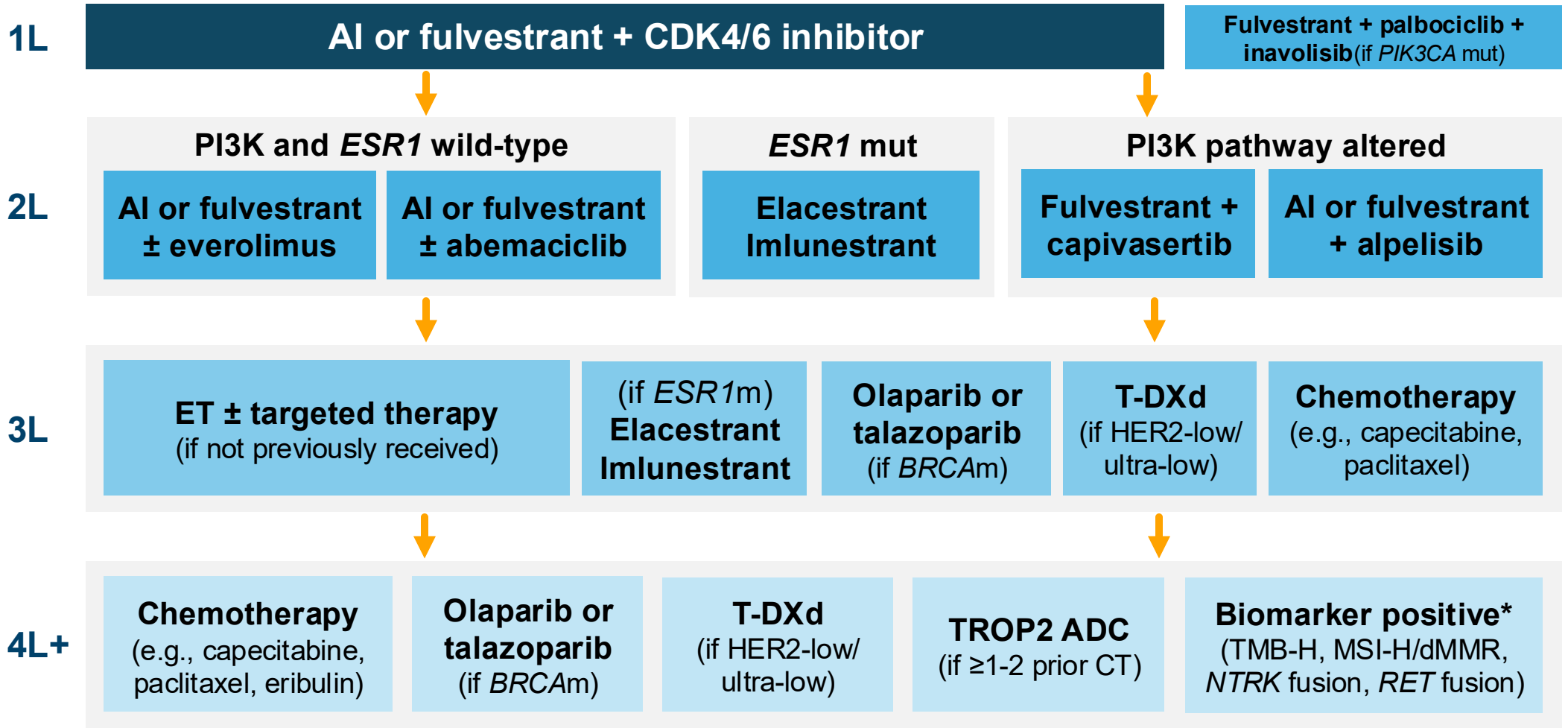
Selective targeting of oncogenic PI3K activation without inhibiting normal PI3K function in host tissues may improve therapeutic index

AGENT
RLY-2608: Zovegalisib
STX-478/LY4064809: Tersolisib

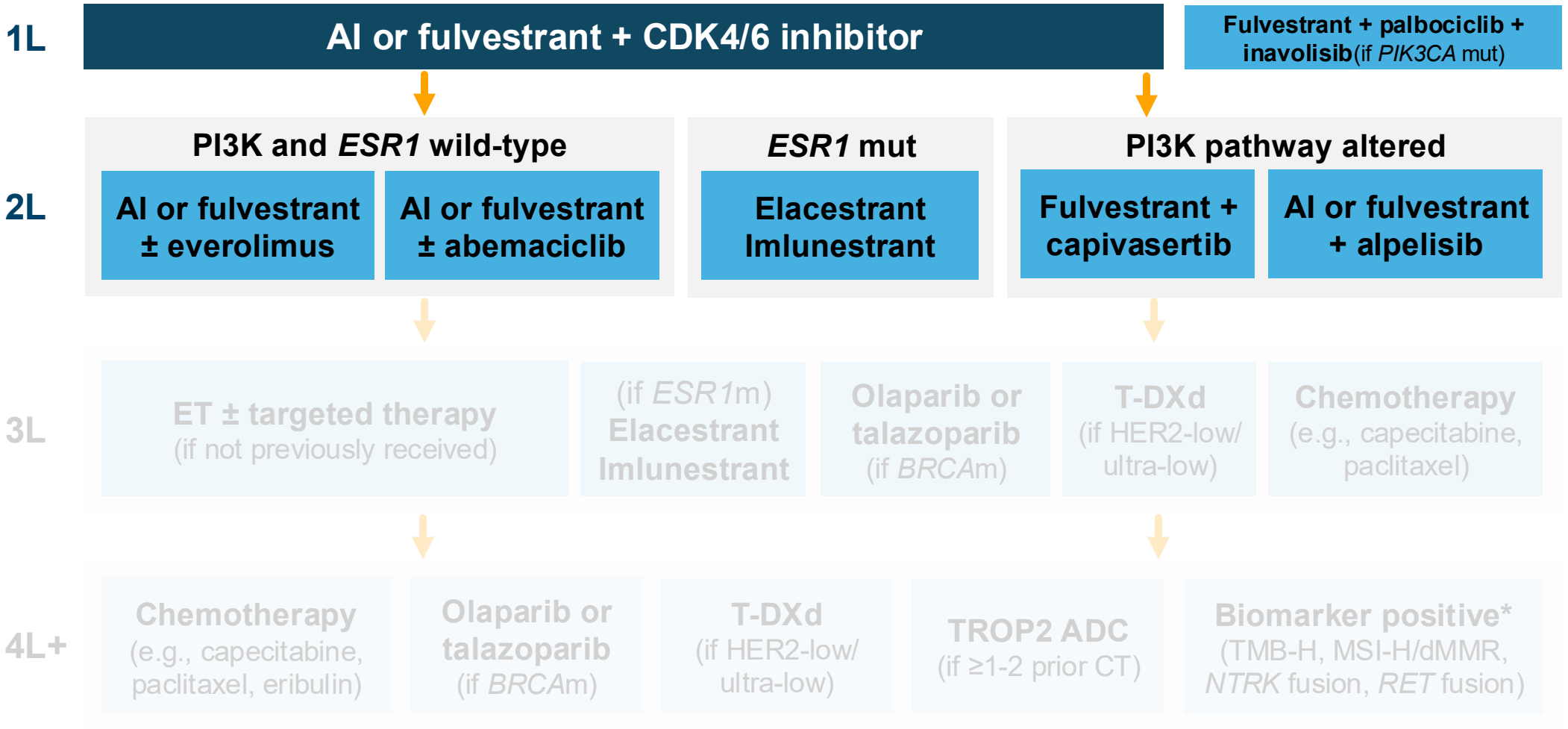


Dent R. Presented at: ESMO Breast Cancer 2021; May 5-8, 2021; Virtual; Kalinsky K, et al. Clin Cancer Res. 2009;15:5049-5059.

Treatment Algorithm for HR+/HER2- MBC



Treatment Algorithm for HR+/HER2- MBC



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Slide adapted from Ana Garrido-Castro.

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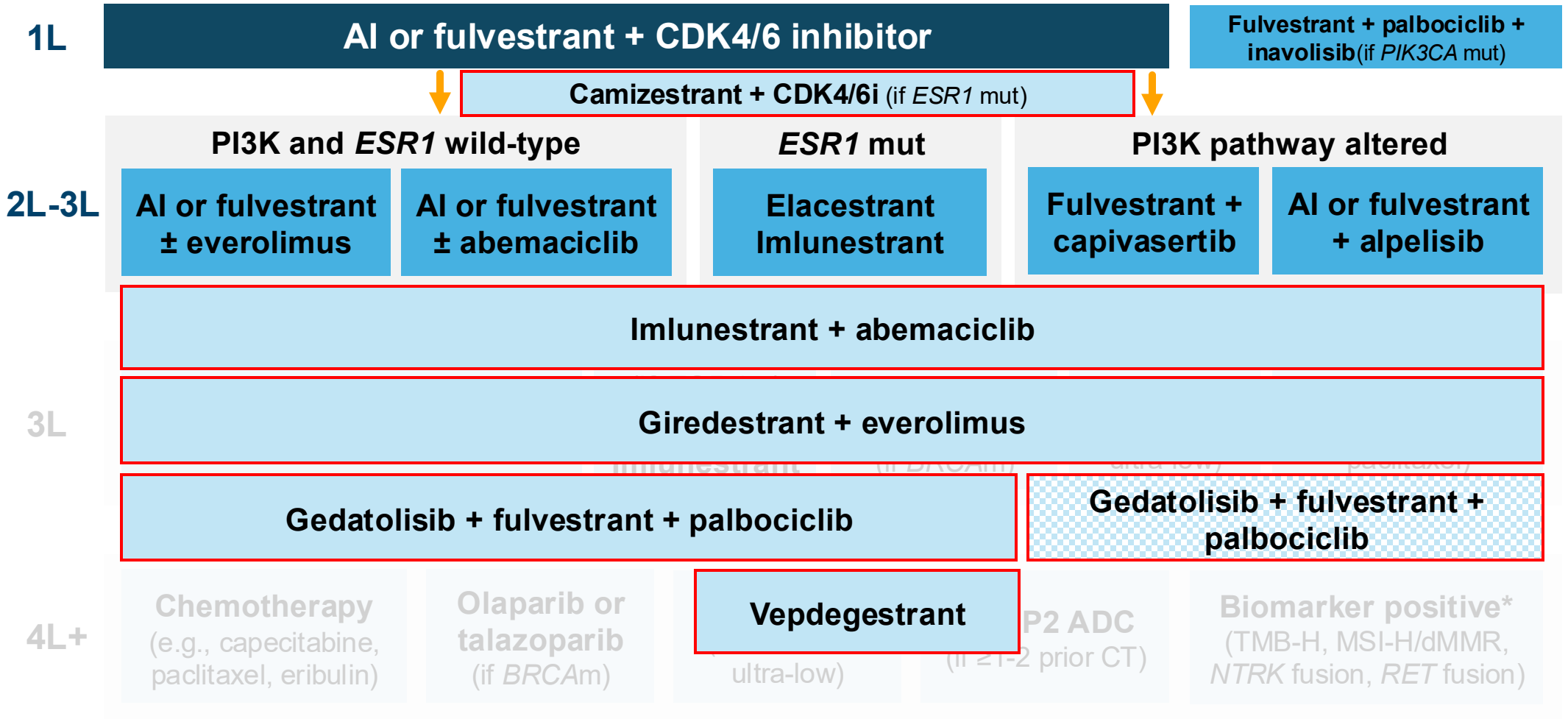
Treatment Algorithm for HR+/HER2- MBC



Slide adapted from Ana Garrido-Castro.

CASES FROM THE COMMUNITY
Investigators Discuss the Optimal Role of Endocrine-Based and Other Strategies in the Management of HR-Positive Breast Cancer

Part 3 of a 3-Part CME Satellite Symposium Series

Thursday, December 11, 2025

7:00 PM – 9:00 PM CT

Faculty

Angela DeMichele, MD, MSCE
Komal Jhaveri, MD, FACP, FASCO
Erica Mayer, MD, MPH, FASCO
Hope S Rugo, MD
Seth Wander, MD, PhD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

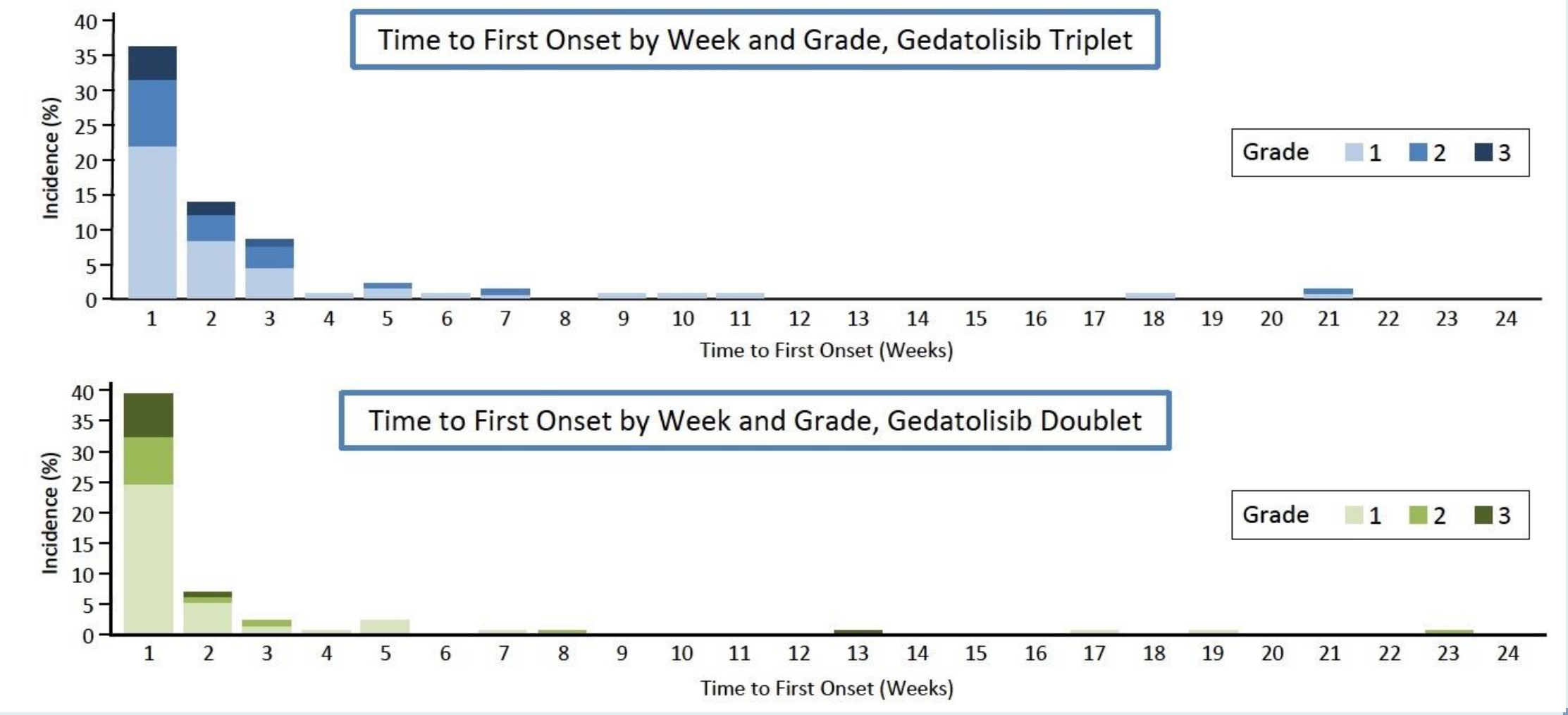
SAN ANTONIO BREAST CANCER SYMPOSIUM®
UT Health San Antonio Mays Cancer Center
AACR American Association for Cancer Research
Abstract RF7-04
DECEMBER 9–12, 2025
HENRY B. GONZALEZ CONVENTION CENTER • SAN ANTONIO, TX

Gedatolisib, a multitarget PI3K/AKT/mTOR inhibitor, plus fulvestrant with or without palbociclib for second-line treatment of patients with HR+/HER2-/*PIK3CA*-WT advanced breast cancer: updated results from the randomized, phase 3 VIKTORIA-1 trial

Barbara Pistilli, Rachel M. Layman, Giuseppe Curigliano, Fabrice André, Massimo Cristofanilli, Miguel Martin, Robert Wesolowski, Sung-Bae Kim, Gun Min Kim, Martin E. Richardet, Jorge Carlos Nadal, Alistair Ring, Jorge Luis Martínez Rodríguez, Hyo S. Han, Antonio Giordano, Keren Moss, Sarah C. Mutka, Brian Sullivan, Samuel Suzuki, Igor Gorbatchevsky, Sara A. Hurvitz

Barbara Pistilli, MD
Gustave Roussy, Villejuif, France
December 11, 2025

Phase III VIKTORIA-1: Time to First Onset of Stomatitis



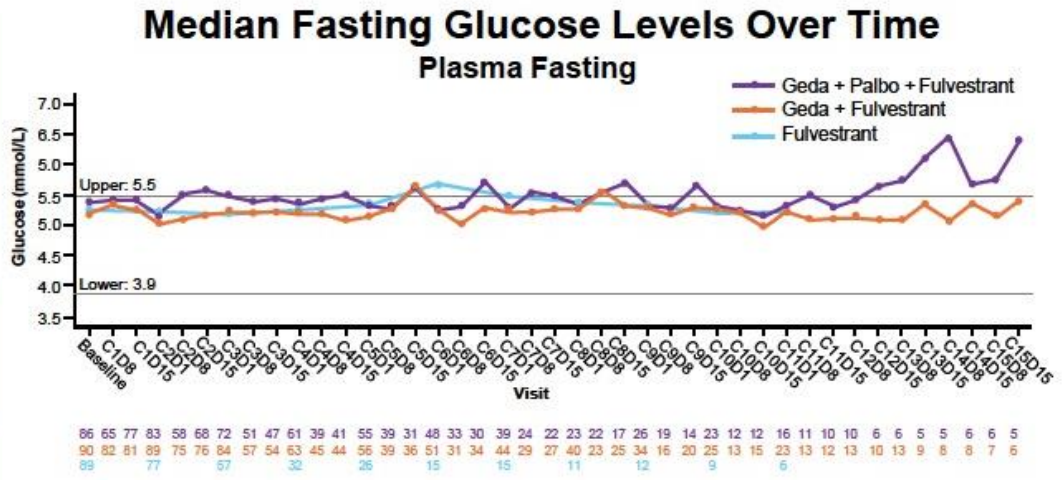
Pistilli B et al. SABCS 2025;Abstract RF7-04.

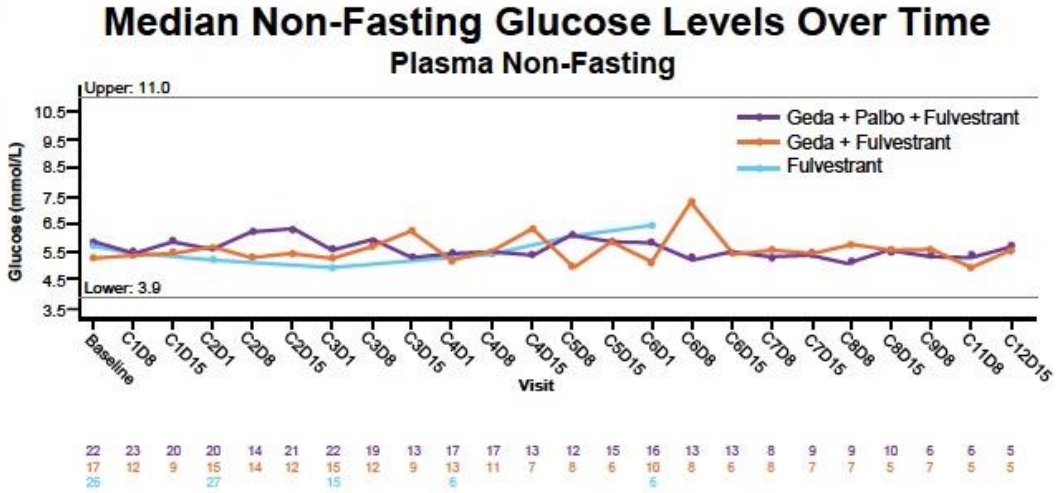
Phase III VIKTORIA-1: Median Glucose Levels

Hyperglycemia, n (%)	Geda + Palbo + Fulvestrant (n=130)	Gedatolisib + Fulvestrant (n=130)	Fulvestrant (n=123)
All grades	12 (9.2)	15 (11.5)	0
HbA1c (%), median (range)	n=91	n=89	n=72
Baseline (B)	5.4 (4.1-6.4)	5.4 (4.0-6.3)	5.3 (4.0-6.3)
End of treatment (EOT)	5.9 (4.3-8.8)	5.9 (4.5-14.1)	5.5 (4.6-6.8)
Change, B to EOT	0.5 (-1.6 - 2.9)	0.6 (-0.7 - 8.2)	0.2 (-0.6 - 1.3)

Gedatolisib did not produce clinically relevant hyperglycemia and had no dose reductions or withdrawals due to hyperglycemia

Abbreviations: B, baseline; C, cycle; EOT, end of treatment; Geda, gedatolisib; HbA1c, hemoglobin A1c; Palbo, palbociclib





Pistilli B et al. SABCS 2025;Abstract RF7-04.

Phase III VIKTORIA-1: Authors' Conclusions

- VIKTORIA-1 is the first study to demonstrate a statistically significant and clinically meaningful improvement in PFS with PAM inhibition in patients with *PIK3CA*-WT disease, all of whom received prior CDK4/6i
- Significant efficacy was observed irrespective of the duration of prior treatment.
- Measures to mitigate stomatitis were effective; most patients experienced resolution to a lower grade of stomatitis in about 2 weeks
- Notably, hyperglycemia was low in both gedatolisib arms, and HbA1c levels were stable over time
- Both gedatolisib regimens delayed time to definitive deterioration of well-being (EQ-5D-5L) vs fulvestrant

Gedatolisib plus fulvestrant, with or without palbociclib, represents a potential new standard of care for patients with HR+, HER2-negative, *PIK3CA*-WT ABC whose disease progressed on or after treatment with a CDK4/6 inhibitor

Pistilli B et al. SABCS 2025;Abstract RF7-04.

Dr Laila Agrawal
(Louisville, Kentucky)

Case Presentation: 68-year-old woman with ER-positive, HER2-low (IHC 1+), PIK3CA-mutant mBC with disease progression after 2 years of adjuvant letrozole

Dr Richard Zelkowitz
(Bridgeport, Connecticut)

Tolerability of inavolisib, fulvestrant and palbociclib

RTP
RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

For which patients with PIK3CA-mutant, HR-positive, HER2-negative mBC are you prioritizing inavolisib/ palbociclib/fulvestrant in the first-line setting?

What has been your experience with inavolisib/palbociclib/ fulvestrant in terms of tolerability? Does the addition of inavolisib result in significant toxicity beyond that seen with a CDK4/6 inhibitor and endocrine therapy alone?

QUESTIONS FOR THE FACULTY

How do you manage the hyperglycemia associated with agents targeting the PI3K/AKT/mTOR pathway? Do you preemptively recommend metformin for patients receiving any of these agents?

How often do you monitor fasting blood glucose and HbA1c levels in patients receiving agents targeting the PI3K/AKT/mTOR pathway? Do you recommend that your patients use home glucose monitors?

Case Presentation: 63-year-old woman with ER-positive, HER2-low PIK3CA-mutant mBC and disease progression on first-line palbociclib/ fulvestrant

Dr Eleonora Teplinsky (Paramus, New Jersey)

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

How do you select between capivasertib/fulvestrant and alpelisib/fulvestrant for patients who are eligible for both?

If gedatolisib/fulvestrant with or without palbociclib were available, how do you envision it fitting in?

Are there any additional recommendations that you would have made in the case of Dr Teplinsky's patient with capivasertib-related hyperglycemia despite dose reductions/interruptions?

Agenda

Module 1: Current Role of Genomic Assays in Treatment Decision-Making for Localized Hormone Receptor (HR)-Positive Breast Cancer — Dr DeMichele

Module 2: Role of CDK4/6 Inhibitors and Other Novel Strategies in Therapy for HR-Positive, HER2-Negative Localized Breast Cancer — Dr Jhaveri

Module 3: Evolving Up-Front Treatment Paradigm for HR-Positive, HER2-Negative Metastatic Breast Cancer (mBC) — Dr Rugo

Module 4: Clinical Utility of Agents Targeting the PI3K/AKT/mTOR Pathway for Patients with Progressive HR-Positive mBC — Dr Mayer

Module 5: Current and Future Role of Oral Selective Estrogen Receptor Degraders for Progressive HR-Positive mBC — Dr Wander

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SAN ANTONIO BREAST CANCER SYMPOSIUM®
UT Health San Antonio Mays Cancer Center
AACR American Association for Cancer Research
DECEMBER 9–12, 2025
HENRY B. GONZALEZ CONVENTION CENTER • SAN ANTONIO, TX

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

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

Aditya L. Bardia,* Peter Schmid,* Miguel Martín, Sara A. Hurvitz, Kyung Hae Jung, Mothaffar F. Rimawi, Shigehira Saji, Gustavo Werutsky, Nadia Harbeck, Sherene Loi, Akiko Ogiya, Manuel Ruiz-Borrego, Ahmet Alacacıoğlu, Jiong Wu, Chenglin Ye, Mario Liste-Hermoso, Nimali P. Withana, Tanja Badovinac Crnjevic, Mona D. Shah, Pablo Pérez-Moreno, Charles E. Geyer, Jr.*

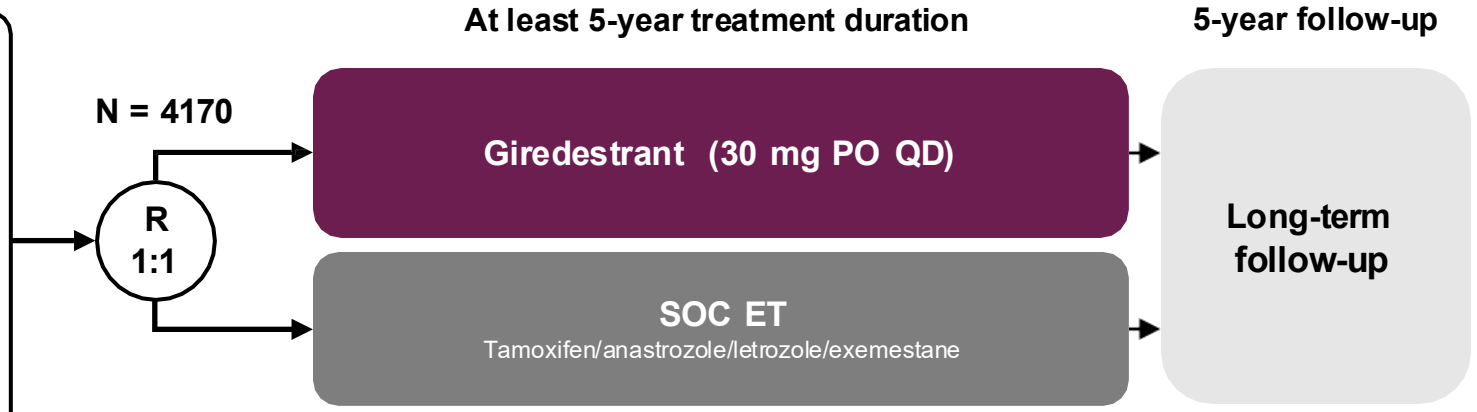
* Equal contributions

lidERA Breast Cancer study design

A global, randomized, open-label, multicenter Phase III trial

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

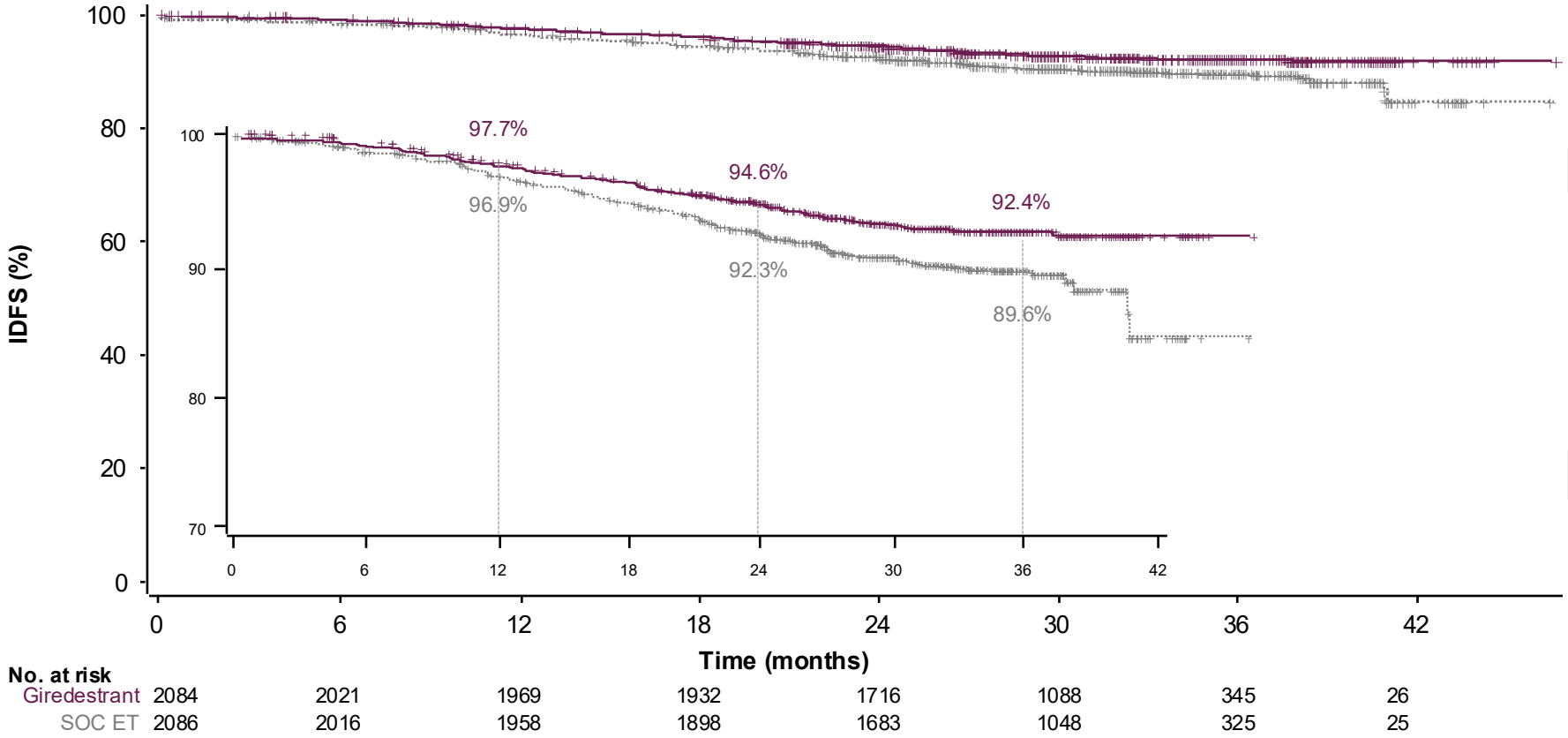
- DFS, DRFI, IDFS (including second primary non-breast invasive cancer with exception of non-melanoma skin cancers and *in situ* carcinomas of any site), LRRFI, OS, safety

Giredestrant is currently also being investigated in combination with abemaciclib in the adjuvant setting (lidERA Breast Cancer substudy 1)

Enrollment: August 2021 to September 2023. Up to 12 weeks of ET ± CDK4/6i were allowed. ER+ was defined as ≥ 1% positive cells by immunohistochemistry. * OncotypeDx ≥ 26 or high-risk Mammaprint.
† Pre-menopausal patients on aromatase inhibitors or giredestrant had to receive ovarian function suppression with an approved luteinizing hormone-releasing hormone agonist. ‡ Medium risk: pN0 and primary tumor > 1 cm with high-risk biologic features (Grade 3, or Ki67 ≥ 20%, or high score on genomic assay [if available]) and pN1 with low-risk biologic features (Grade 1/2 and Ki67 < 20% and tumor ≤ 5 cm and low score on genomic assay [if available]). § High risk: pT4, or pN2, or pN3 and pN1 with high-risk biologic features (Grade 3, or Ki67 ≥ 20%, or tumor > 5 cm, or high score on genomic assay [if available]).
CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DFS, disease-free survival; DRFI, distant recurrence-free interval; ER+, estrogen receptor-positive; ET, endocrine therapy; IDFS, invasive disease-free survival; LRRFI, locoregional recurrence-free interval; OS, overall survival; PO, orally; QD, once daily; R, randomization; RoW, rest of the world; SOC, standard-of-care.
ClinicalTrials.gov number, NCT04961996. Adapted from Geyer CE, *et al*. ASCO 2023 (TPS616), with permission.

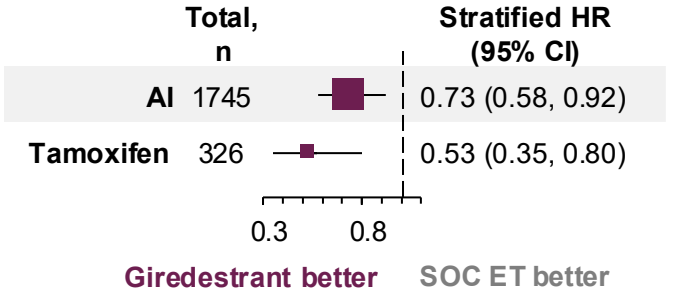
Presented by: Aditya L. Bardia, MD.

Primary endpoint: IDFS



	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

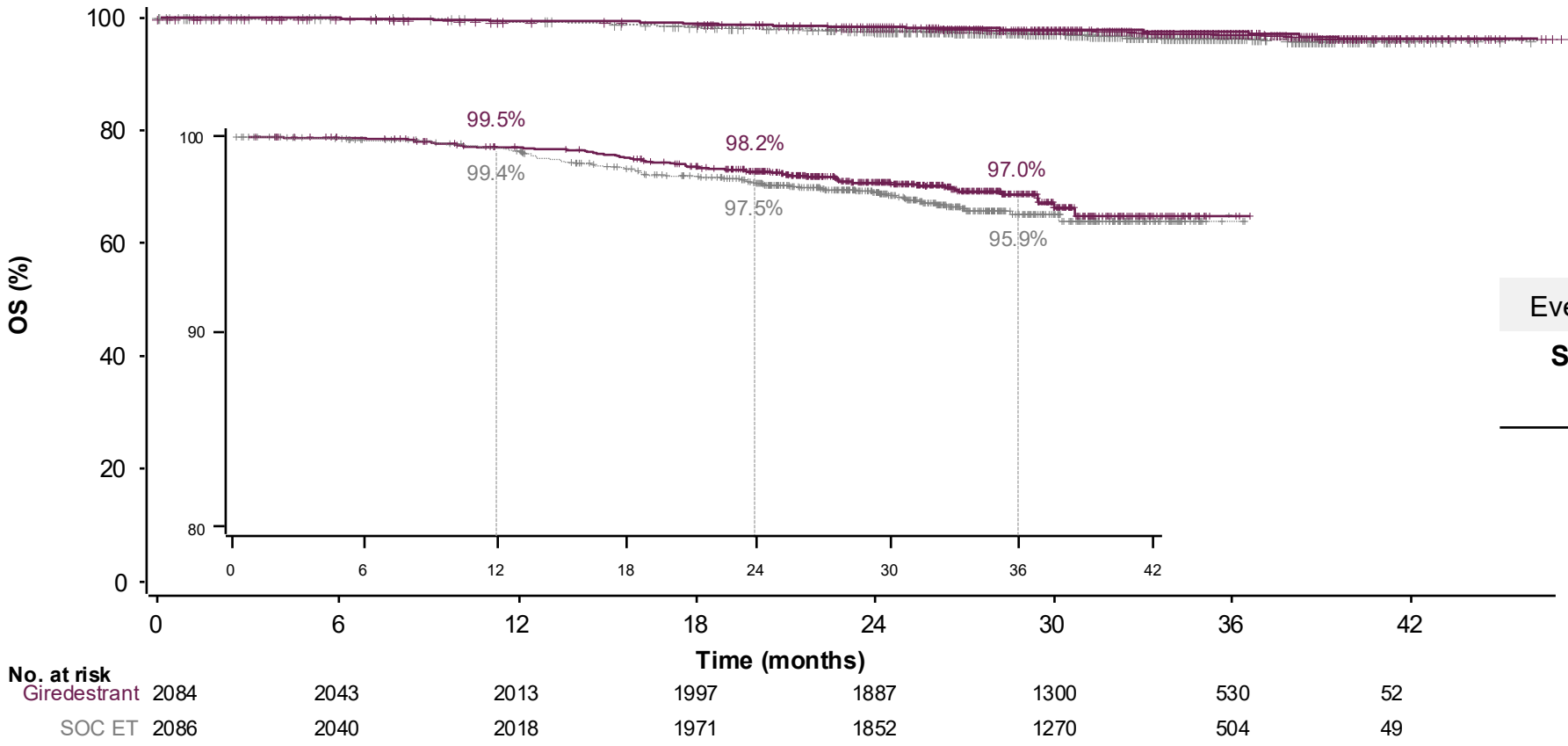


Median follow-up: 32.3 months

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

Data cutoff: August 8, 2025. Median follow-up, 32.4 months in the giredestrant arm and 32.3 months in the SOC ET arm; maximum follow-up, 46.6 months and 46.3 months, respectively. * Log-rank (2-sided). p-value boundary for IDFS interim analysis was 0.0217 (2-sided). AI, aromatase inhibitor; CI, confidence interval; ET, endocrine therapy; HR, hazard ratio; IDFS, invasive disease-free survival; SOC, standard-of-care.

Interim overall survival



	Giredestrant n = 2084	SOC ET n = 2086
Events, n (%)	57 (2.7)	71 (3.4)
Stratified HR (95% CI)	**0.79** (0.56, 1.12); p = 0.1863*	

Median follow-up: 32.3 months

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

Data cutoff: August 8, 2025. Median follow-up, 32.4 months in the giredestrant arm and 32.3 months in the SOC ET arm; maximum follow-up, 46.6 months and 46.3 months, respectively. At the data cutoff, the 1st OS IA was conducted (maturity 31.2% with respect to the final OS analysis). * Log-rank (2-sided). p-value boundary for the 1st OS IA was 0.0001 (2-sided). Includes one death from a patient who was randomized but never dosed. Excludes one death from a patient with missing date of death. CI, confidence interval; ET, endocrine therapy; HR, hazard ratio; IA, interim analysis; OS, overall survival; SOC, standard-of-care.

Presented by: Aditya L. Bardia, MD.

Conclusions

- Since approval of AIs in the 2000s, lidERA Breast Cancer is the first trial to demonstrate benefit with a novel ET in early breast cancer (eBC).
- With a median follow-up of 32.3 months, the lidERA trial demonstrated a statistically significant and clinically meaningful improvement with upfront giredestrant over standard-of-care ET in ER+, HER2-negative, Stage I-III eBC
  - IDFS hazard ratio: 0.70 (95% CI: 0.57, 0.87; p = 0.0014).
  - 3-year IDFS rates: 92.4% vs 89.6%.
- Overall Survival trended in favor of the giredestrant arm.
- DRFI was improved vs standard-of-care ET, with a 31% reduction in risk of developing distant metastatic disease.
- The safety profile was favorable and consistent with the known profile.
  - The discontinuation rate was lower with giredestrant compared with standard-of-care ET.

Overall, the results support giredestrant as a potential new standard for patients with HR+/HER2- early breast cancer

AI, aromatase inhibitor; CI, confidence interval; DRFI, distant recurrence-free interval; ER+, estrogen receptor-positive; ET, endocrine therapy; HR+, hormone receptor-positive; IDFS, invasive disease-free survival; OS, overall survival.

Mass General Brigham
Cancer Institute

Current and Future Role of Oral SERDs for Progressive HR+ Metastatic Breast Cancer

December 11th, 2025
Research To Practice
Endocrine-Based Therapy in the Management of Breast Cancer
San Antonio Breast Cancer Symposium

Seth A. Wander, MD, PhD
Director of Precision Medicine, Termeer Center for Targeted Therapies
Director of Translational Research, Breast Oncology Program
Mass General Brigham Cancer Institute
Assistant Professor of Medicine, Harvard Medical School
swander@mgh.harvard.edu

Oral SERDs for Progressive HR+ mBC

- **Detecting and targeting ESR1: approaches and pharmacology**
- **EMERALD: elacestrant monotherapy (and real-world data)**
- **EMBER3: imlunestrant +/- abemaciclib**
- **evERA: giredestrant + everolimus**
- **Summary, Future Directions, Key Questions**

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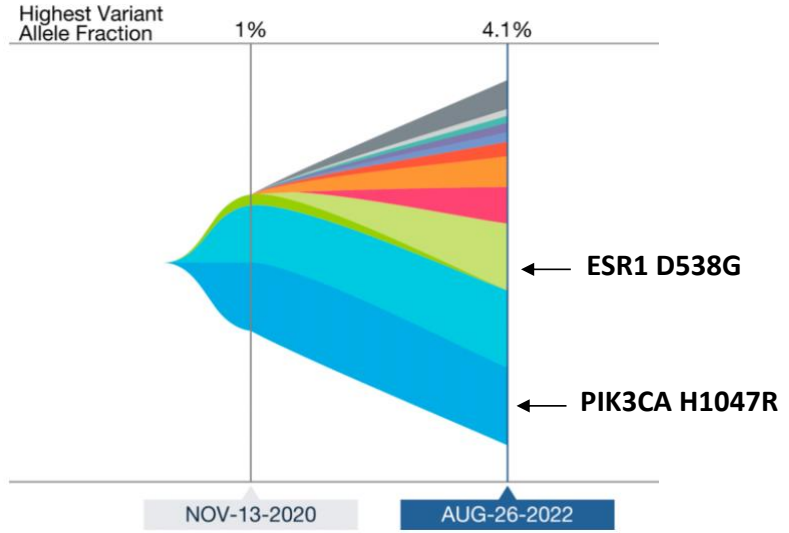
ESR1 Mutations Arise Under Selective Pressure

PIK3CA mutations are early events, present at baseline (~40%) = **Truncal**

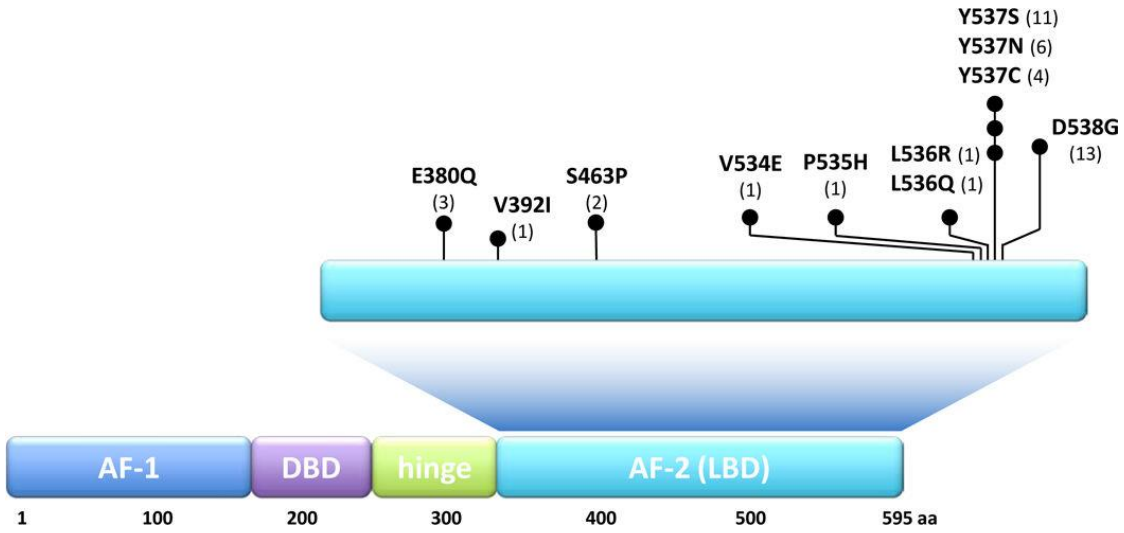
ESR1 mutations are rare in primary/untreated HR+ breast cancer (<5%)
Arise after exposure to aromatase inhibitors = **Acquired**
25-40% frequency in 2nd-3rd line metastatic setting

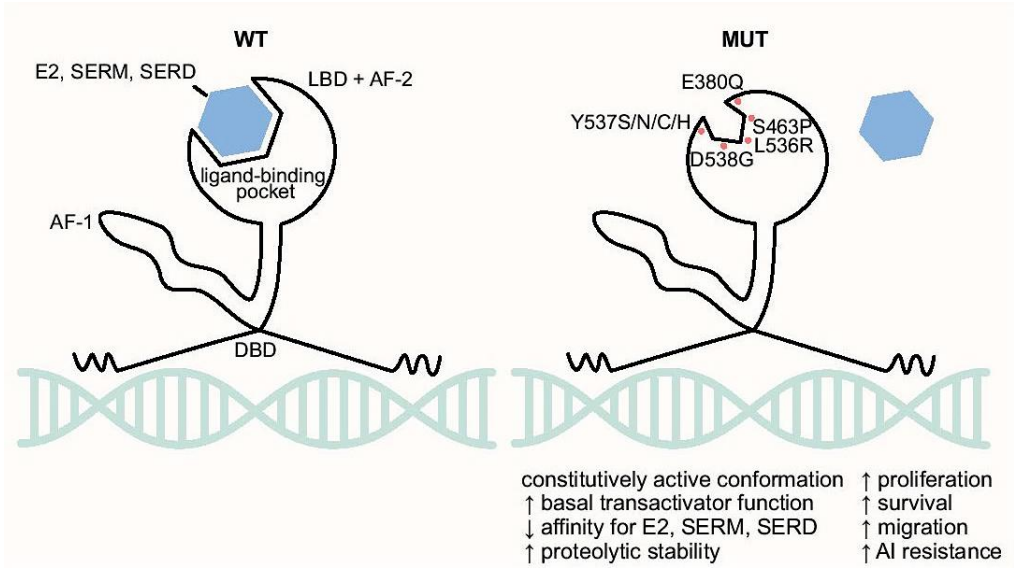
ESR1 mutations are enriched in the ligand-binding domain
Constitutive signaling in the absence of ligand



Diagnosis

Resistance to Antiestrogens





Jeselsohn R et al Nat Rev Clin Onc 2015
Brett JO et al Breast Cancer Res 2021

Biopsy Approach and Sequencing Methodology

Tissue Biopsy

Invasive, biopsy

Provides ER/PR/HER2/PDL1, etc

Limited insights into heterogeneity

May utilize archival specimens

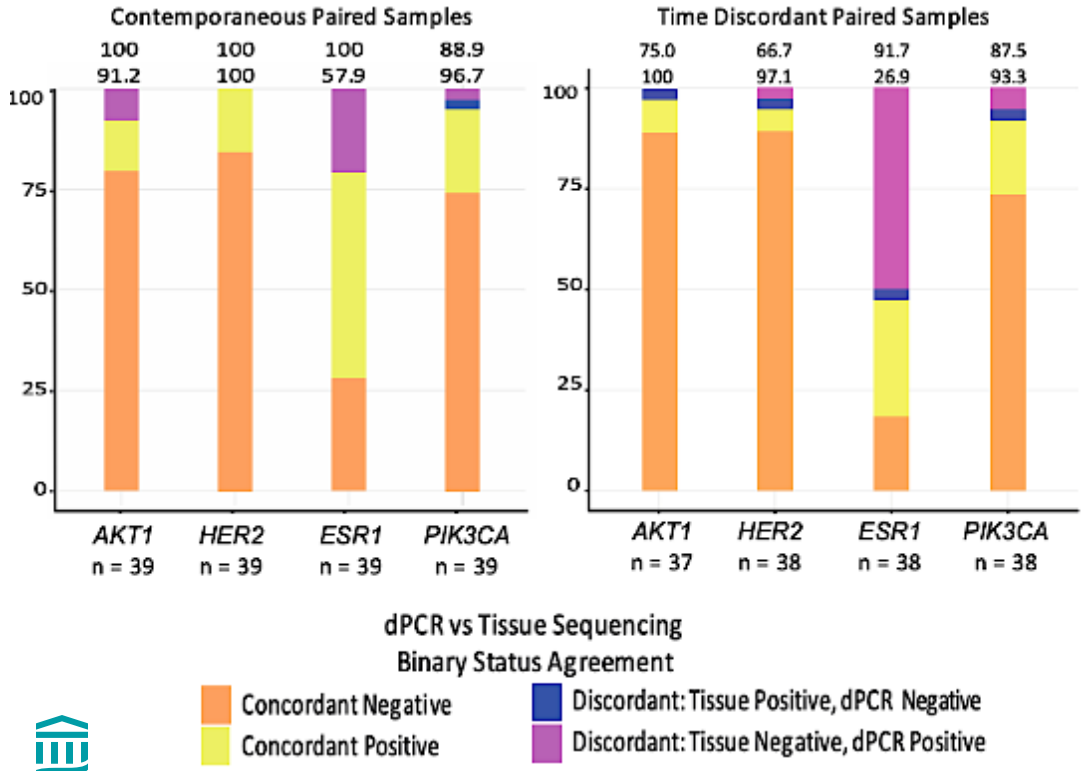
Liquid Biopsy

Non-invasive blood test

Unable to assess receptor status

Reflects tumor heterogeneity

Updated sequencing in real-time



Generally high concordance rates, 80-90%+, between simultaneous solid and liquid biopsies for key genes (PIK3CA, PTEN, AKT – slightly less for ESR1)

Turner N et al Lancet Onc 2020; Urso L et al Front Onc 2021; Vasan N et al ASCO 2024

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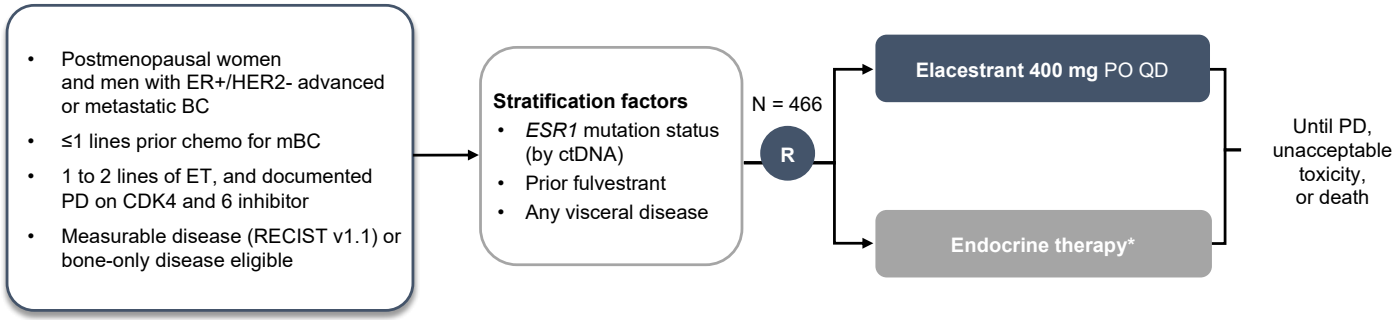
EMERALD: Elacestrant Phase III, Efficacy

Patient Characteristics: Elacestrant vs. Control

- Prior Chemotherapy: 20% vs 24%
- ESR1m: 48% vs 47%
- Two prior lines of ET: 46% vs 41%

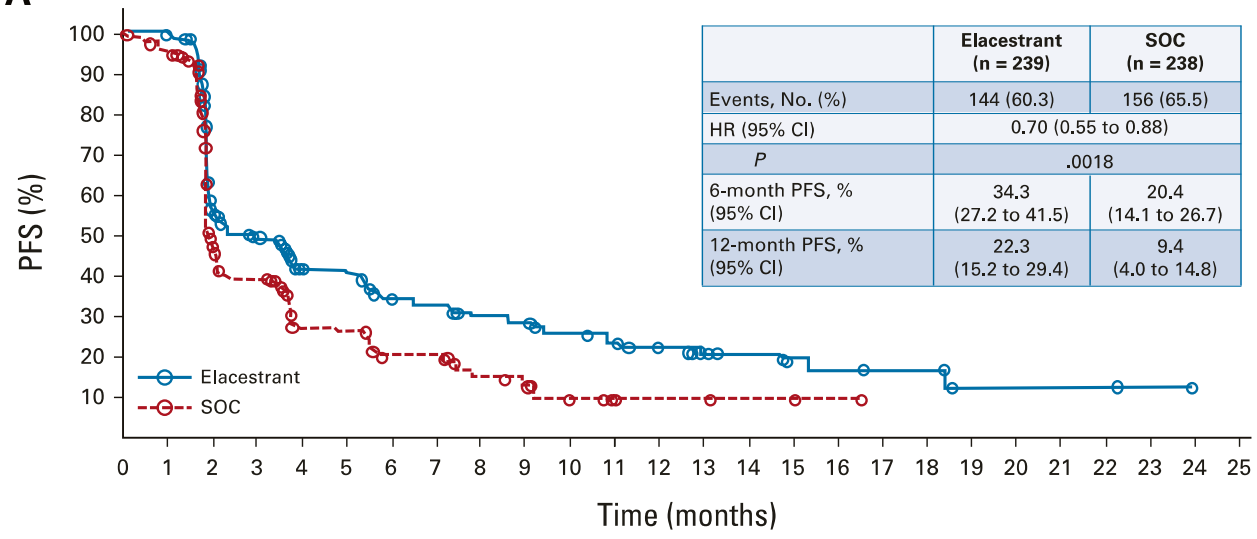


Median PFS Improvements:

ITT: 1.94 > 2.79m; HR (95%CI) 0.68 (0.52-0.90), p=0.0049

ESR1m: 1.87 > 3.78m; HR (95%CI) 0.50 (0.34-0.74), p=0.0005

A

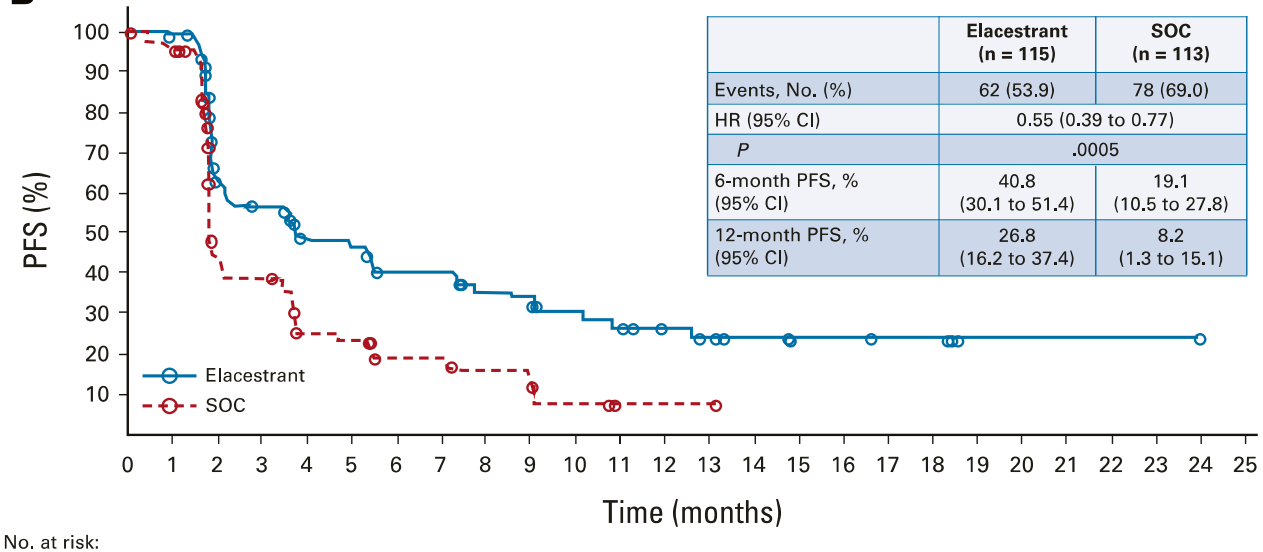


	Elacestrant (n = 239)	SOC (n = 238)
Events, No. (%)	144 (60.3)	156 (65.5)
HR (95% CI)	0.70 (0.55 to 0.88)	
P	.0018	
6-month PFS, % (95% CI)	34.3 (27.2 to 41.5)	20.4 (14.1 to 26.7)
12-month PFS, % (95% CI)	22.3 (15.2 to 29.4)	9.4 (4.0 to 14.8)

No. at risk:

Elacestrant	239	223	106	89	60	57	42	40	34	33	27	24	19	13	11	8	7	6	6	2	2	2	2	1	0
SOC	238	206	84	68	39	38	25	25	16	15	7	4	3	3	2	2	1	0							

B



	Elacestrant (n = 115)	SOC (n = 113)
Events, No. (%)	62 (53.9)	78 (69.0)
HR (95% CI)	0.55 (0.39 to 0.77)	
P	.0005	
6-month PFS, % (95% CI)	40.8 (30.1 to 51.4)	19.1 (10.5 to 27.8)
12-month PFS, % (95% CI)	26.8 (16.2 to 37.4)	8.2 (1.3 to 15.1)

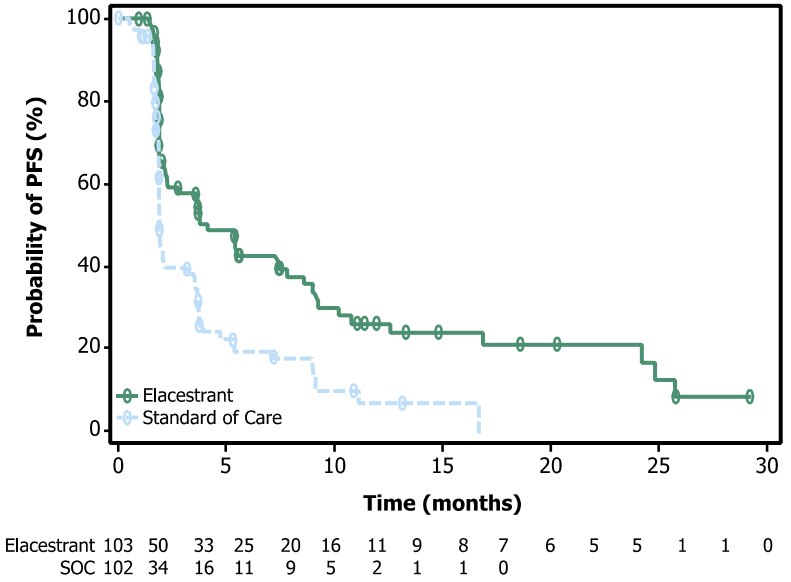
No. at risk:

Elacestrant	115	105	54	46	35	33	26	26	21	20	16	14	11	9	7	5	5	4	4	1	1	1	1	1	0
SOC	113	99	39	34	19	18	12	12	9	9	4	1	1	1	0										

Bidard FC et al JCO 2022

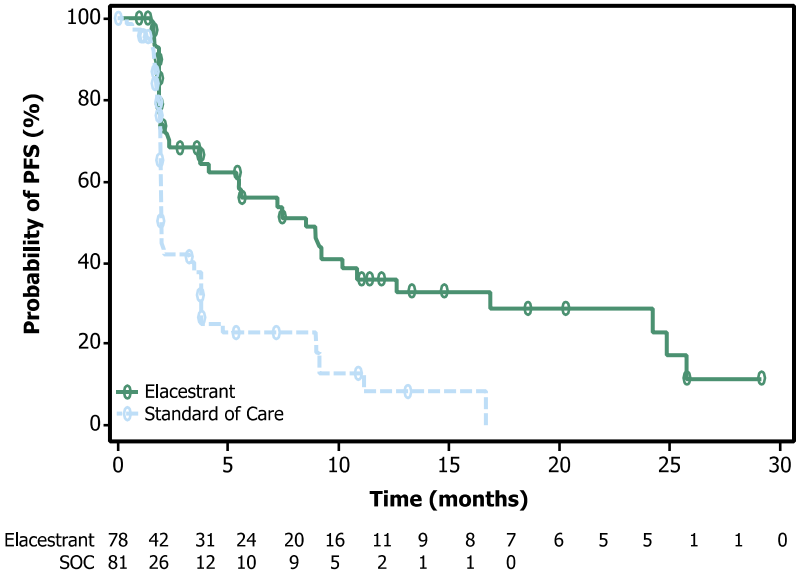
EMERALD: Efficacy Subgroups

At least 6 mo CDK4/6i



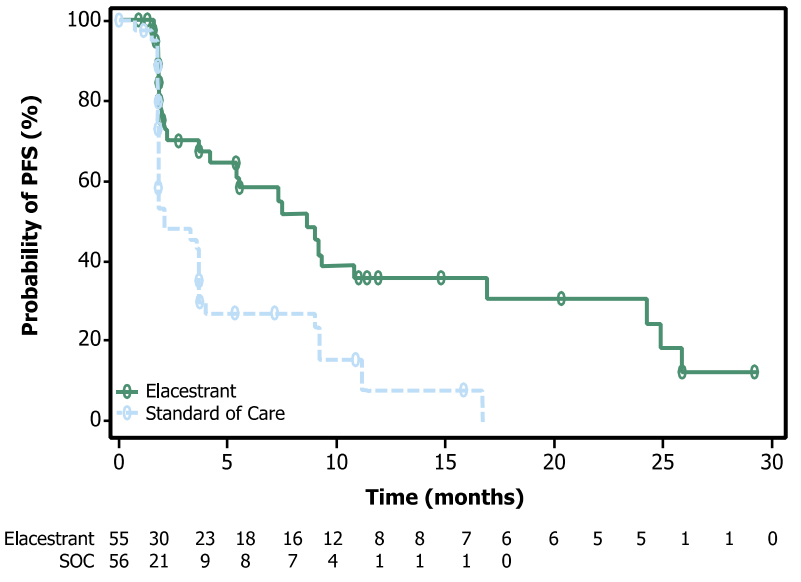
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)
PFS rate at 12 months, % (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)	

At least 12 mo CDK4/6i



	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (4.14 - 10.84)	**1.91** (1.87 - 3.68)
PFS rate at 12 months, % (95% CI)	35.81 (21.84 - 49.78)	8.39 (0.00 - 17.66)
Hazard ratio (95% CI)	**0.410** (0.262 - 0.634)	

At least 18 mo CDK4/6i



	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (5.45 - 16.89)	**2.10** (1.87 - 3.75)
PFS rate at 12 months, % (95% CI)	35.79 (19.54 - 52.05)	7.73 (0.00 - 20.20)
Hazard ratio (95% CI)	**0.466** (0.270 - 0.791)	

Bardia et al CCR 2024

EMERALD: Elacestrant Toxicity

AEs[c] Occurring in ≥ 10% of Patients in Any Arm	Elacestrant		Total		Fulvestrant		AI	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Nausea	83 (35.0)[d]	6 (2.5)	43 (18.8)	2 (0.9)	26 (16.1)	0	17 (25.0)	2 (2.9)
Fatigue	45 (19.0)	2 (0.8)	43 (18.8)	2 (0.9)	35 (21.7)	1 (0.6)	8 (11.8)	1 (1.5)
Vomiting	45 (19.0)[e]	2 (0.8)	19 (8.3)	0	12 (7.5)	0	7 (10.3)	0
Decreased appetite	35 (14.8)	2 (0.8)	21 (9.2)	1 (0.4)	12 (7.5)	0	9 (13.2)	1 (1.5)
Arthralgia	34 (14.3)	2 (0.8)	37 (16.2)	0	28 (17.4)	0	9 (13.2)	0
Diarrhea	33 (13.9)	0	23 (10.0)	2 (0.9)	14 (8.7)	1 (0.6)	9 (13.2)	1 (1.5)
Back pain	33 (13.9)	6 (2.5)	22 (9.6)	1 (0.4)	16 (9.9)	1 (0.6)	6 (8.8)	0
AST increased	31 (13.1)	4 (1.7)	28 (12.2)	2 (0.9)	20 (12.4)	2 (1.2)	8 (11.8)	0
Headache	29 (12.2)	4 (1.7)	26 (11.4)	0	18 (11.2)	0	8 (11.8)	0
Constipation	29 (12.2)	0	15 (6.6)	0	10 (6.2)	0	5 (7.4)	0
Hot flush	27 (11.4)	0	19 (8.3)	0	15 (9.3)	0	4 (5.9)	0
Dyspepsia	24 (10.1)	0	6 (2.6)	0	4 (2.5)	0	2 (2.9)	0
ALT increased	22 (9.3)	5 (2.1)	23 (10.0)	1 (0.4)	17 (10.6)	0	6 (8.8)	1 (1.5)

- Grade 3-4 AEs: 7.2% elacestrant vs. 3.1% SOC
- Discontinuation due to AEs: 3.4% elacestrant vs. 0.9% SOC

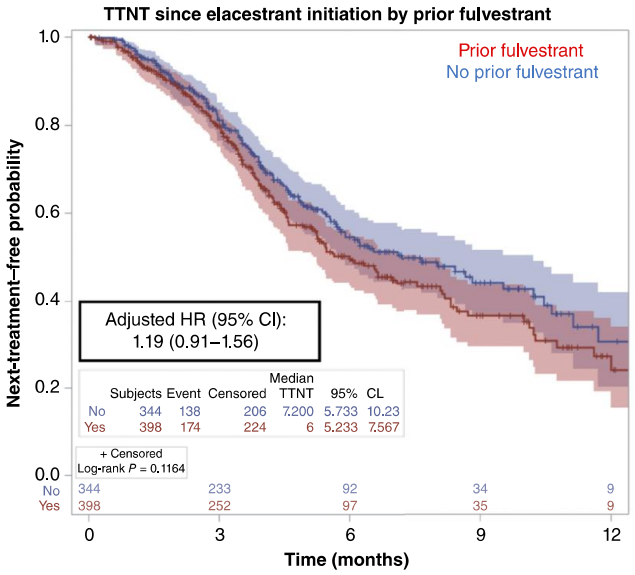
Bidard FC et al JCO 2022

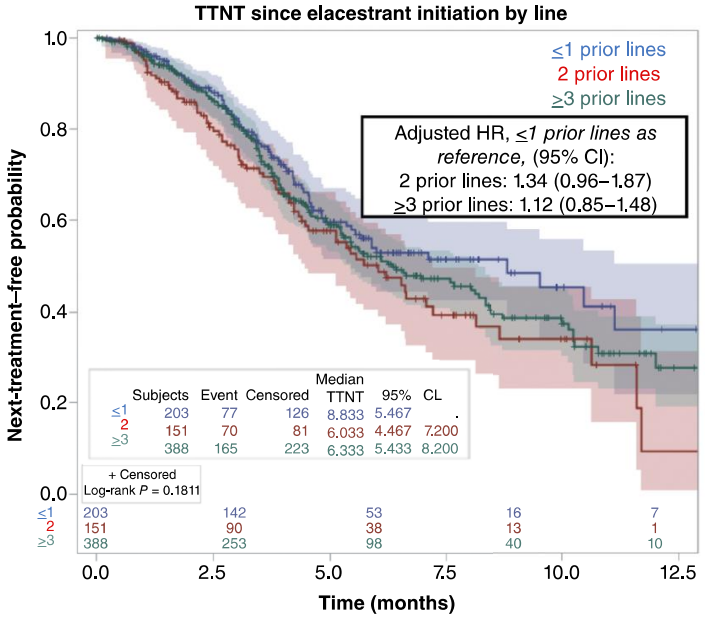
EMERALD: Elacestrant Real-World Data

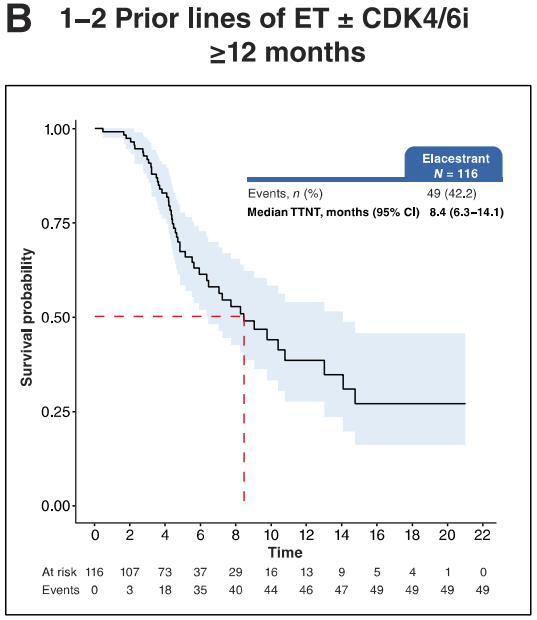
Retrospective claims-based clinico-genomic database analyses

Lloyd et al
GuardantINFORM
n=742
52% prior fulvestrant
38% prior chemotherapy
75% visceral disease

Rugo et al
Komodo/FMI
n=306
72% prior fulvestrant
50% prior chemotherapy
87% visceral disease
94% 1L CDKi >12m





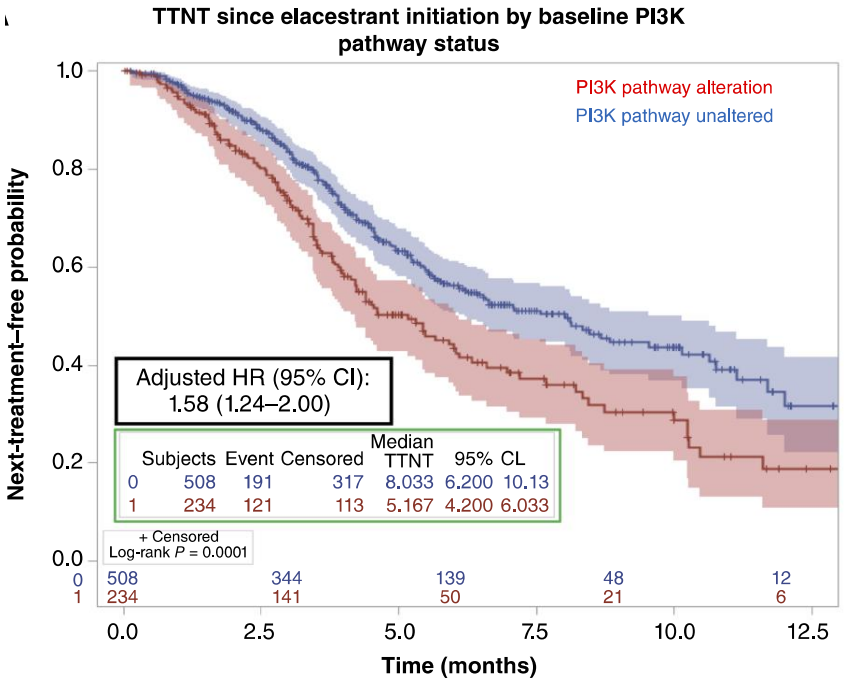


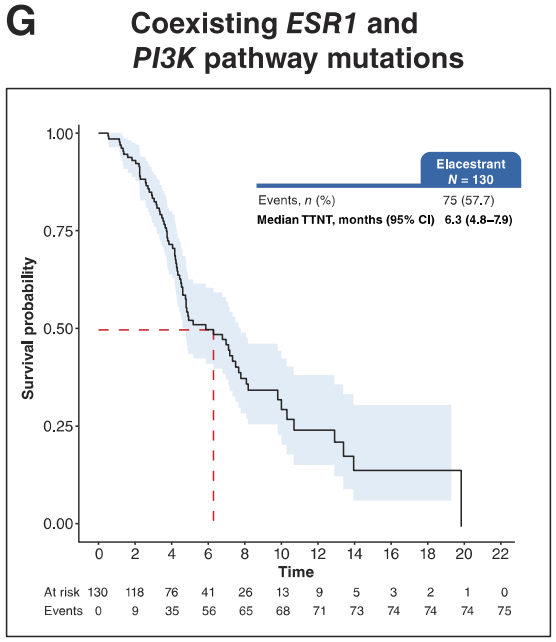
Median TTNT 6-9 months

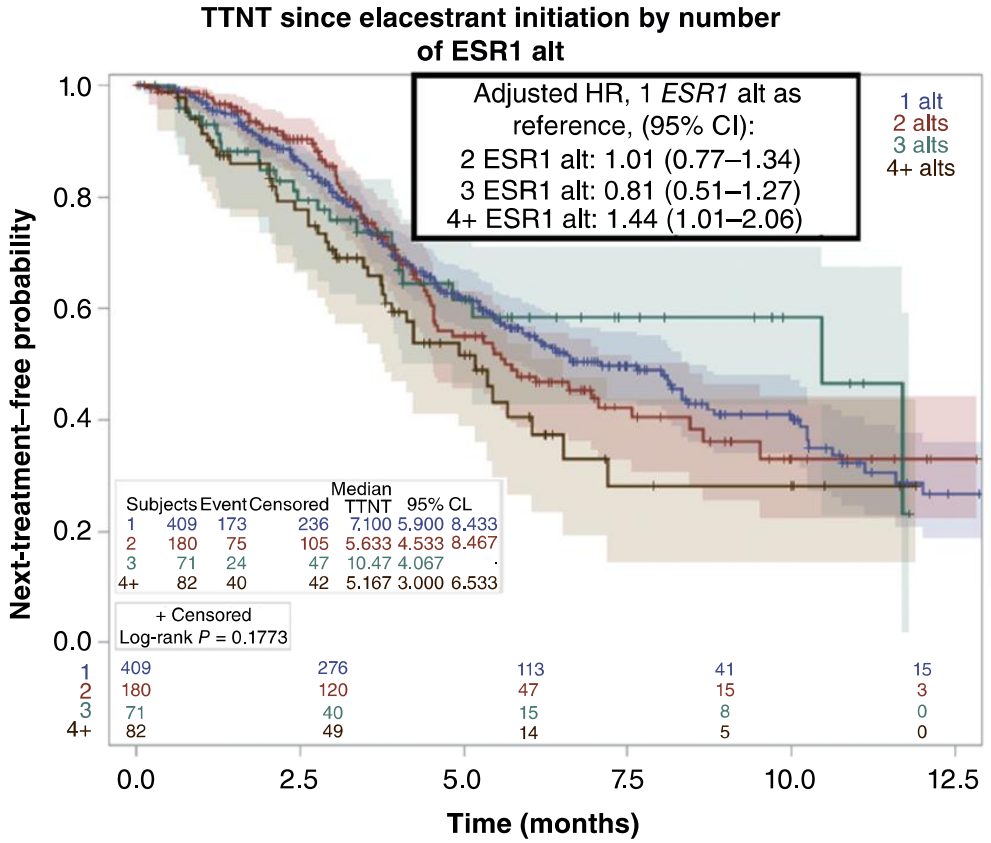
- Trend toward longer TTNT
  - with less prior therapy (eg @2L)
  - without prior fulvestrant
- No impact with visceral metastatic disease

EMERALD: Elacestrant Real-World Data

- Concurrent ESR1/PIK3CA altercations with reduced TTNT
- Equally efficacious with ESR1 Y537S vs other alterations
- Trend toward inferior outcomes with higher degree of polyclonality (4+ alterations)







Lloyd MR et al CCR 2025; Rugo H et al CCR 2025

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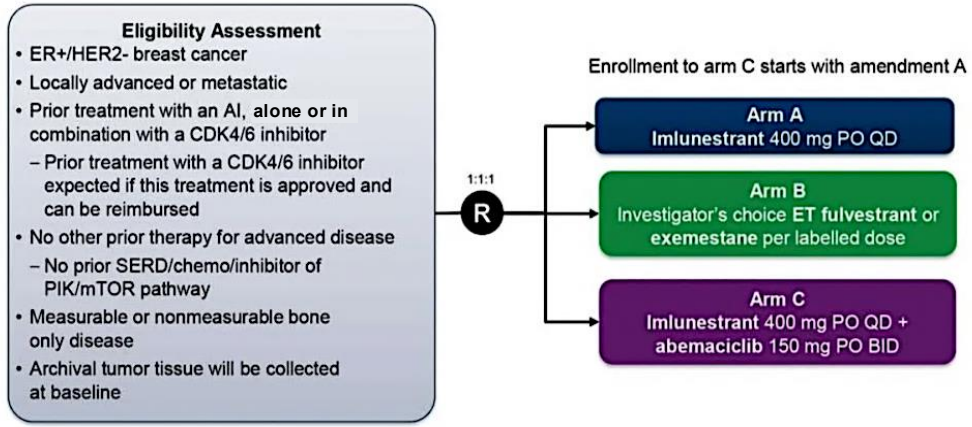
EMBER3: Imlunestrant Phase III

Patient Characteristics: Imlunestrant vs. Control

- No prior chemotherapy, 1 prior line of ET
- ~40% of patients were CDK4/6i-naive
- ESR1m: 41.7% vs 35.8

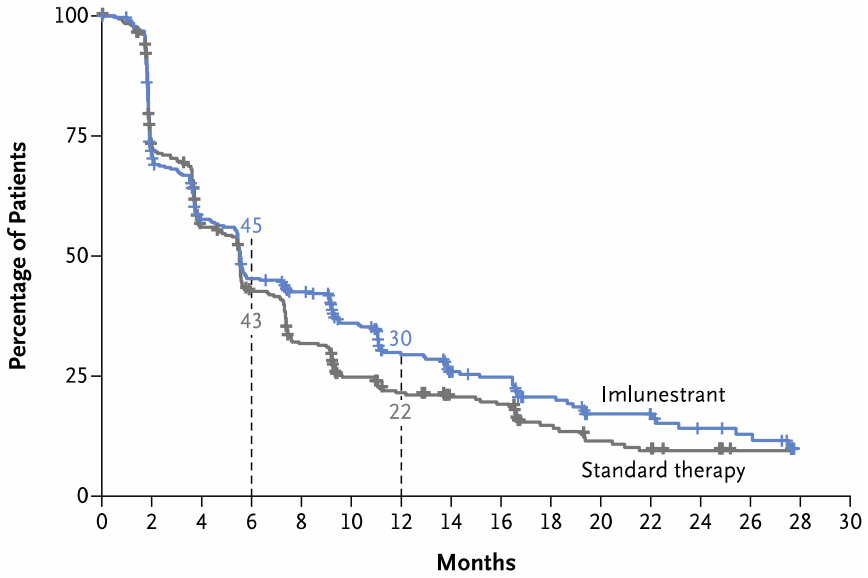


Median PFS Improvements:

ITT: 5.5 > 5.6m; HR (95%CI) 0.87 (0.72-1.04), p=0.12

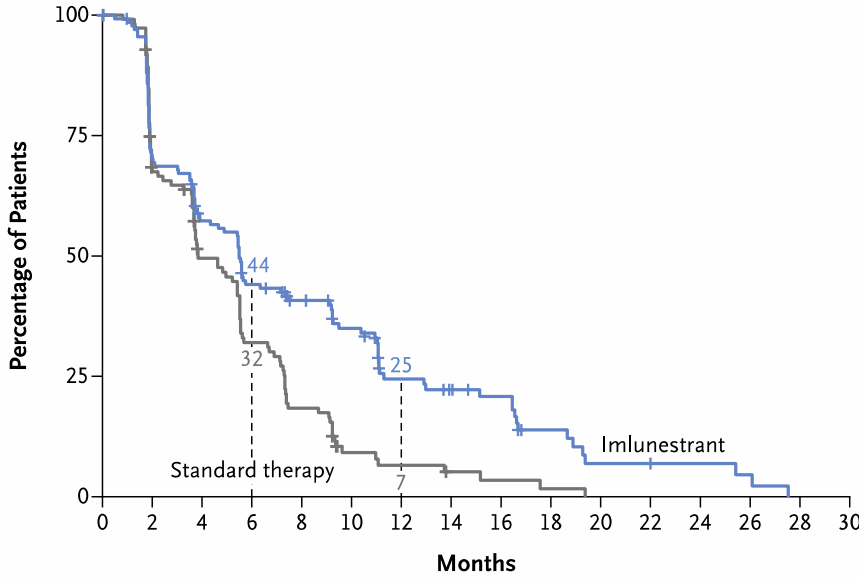
ESR1m: 3.8 > 5.5m; Restricted mean survival diff (95%CI) 2.6m (1.2-3.9), p<0.001

B Progression-free Survival among All Patients, Imlunestrant vs. Standard Therapy



No. at Risk																
Imlunestrant	331	225	173	135	118	89	62	47	43	30	20	19	13	10	0	0
Standard therapy	330	221	165	122	89	63	51	41	38	23	17	14	10	2	0	0

A Progression-free Survival among Patients with *ESR1* Mutations, Imlunestrant vs. Standard

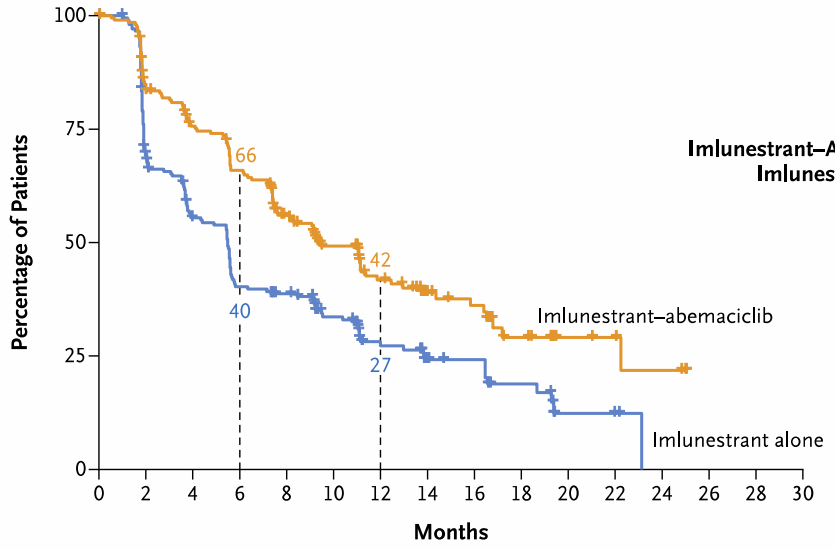


No. at Risk																
Imlunestrant	138	95	74	56	45	35	22	18	15	8	4	4	3	2	0	0
Standard therapy	118	74	51	33	19	7	5	3	2	1	0	0	0	0	0	0

Jhaveri KL et al NEJM 2024

EMBER3: Imlunestrant + Abemaciclib Efficacy

A Progression-free Survival among All Patients, Imlunestrant–Abemaciclib vs. Imlunestrant Alone

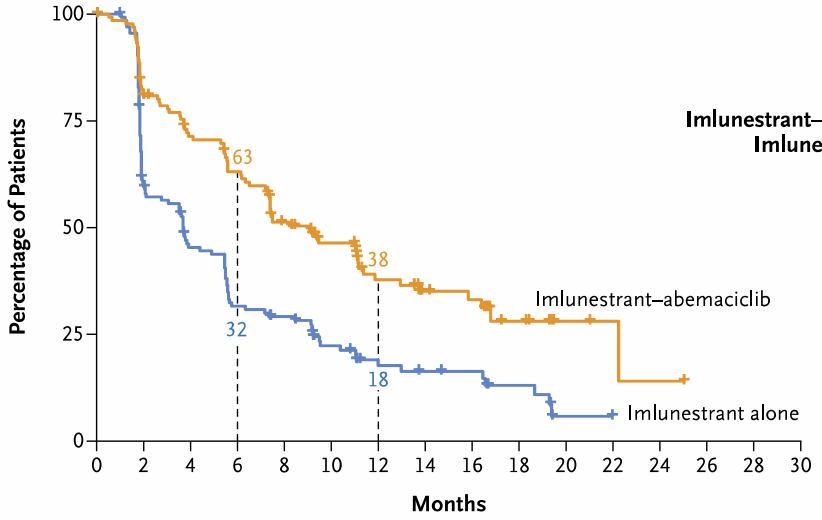


No. at Risk																
Imlunestrant–abemaciclib	213	165	141	122	96	72	48	29	25	13	6	5	3	0	0	0
Imlunestrant alone	213	140	106	77	67	48	29	20	18	10	3	2	0	0	0	0

	No. of Patients	No. of Events	Median Progression-free Survival (95% CI)
			mo
Imlunestrant–Abemaciclib	213	114	9.4 (7.5–11.9)
Imlunestrant Alone	213	149	5.5 (3.8–5.6)

Hazard ratio for disease progression or death, 0.57 (95% CI, 0.44–0.73)
P<0.001

B Progression-free Survival among Patients with Previous CDK4/6 Inhibitor Treatment, Imlunestrant–Abemaciclib vs. Imlunestrant Alone



No. at Risk																
Imlunestrant–abemaciclib	139	105	87	76	58	43	29	19	17	8	3	2	1	0	0	0
Imlunestrant alone	140	79	56	39	32	21	13	11	10	6	1	0	0	0	0	0

	No. of Patients	No. of Events	Median Progression-free Survival (95% CI)
			mo
Imlunestrant–Abemaciclib	139	79	9.1 (7.2–11.2)
Imlunestrant Alone	140	109	3.7 (2.1–5.5)

Hazard ratio for disease progression or death, 0.51 (95% CI, 0.38–0.68)

Jhaveri KL et al NEJM 2024

EMBER3: Imlunestrant +/- Abemaciclib Toxicity

Table 2. Adverse Events According to Grade (Safety Population).*

Event	Imlunestrant (N=327)		Standard Therapy (N=324)		Imlunestrant–Abemaciclib (N=208)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)					
Any adverse event	270 (82.6)	56 (17.1)	273 (84.3)	67 (20.7)	204 (98.1)	101 (48.6)
Fatigue†	74 (22.6)	1 (0.3)	43 (13.3)	2 (0.6)	80 (38.5)	10 (4.8)
Diarrhea	70 (21.4)	1 (0.3)	38 (11.7)	0	179 (86.1)	17 (8.2)
Nausea	56 (17.1)	1 (0.3)	42 (13.0)	0	101 (48.6)	4 (1.9)
Arthralgia	46 (14.1)	2 (0.6)	46 (14.2)	1 (0.3)	19 (9.1)	1 (0.5)
Aspartate aminotransferase increase	41 (12.5)	3 (0.9)	41 (12.7)	3 (0.9)	34 (16.3)	5 (2.4)
Back pain	35 (10.7)	2 (0.6)	23 (7.1)	1 (0.3)	10 (4.8)	1 (0.5)
Alanine aminotransferase increase	34 (10.4)	1 (0.3)	33 (10.2)	2 (0.6)	28 (13.5)	10 (4.8)
Anemia†	33 (10.1)	7 (2.1)	41 (12.7)	9 (2.8)	91 (43.8)	16 (7.7)
Abdominal pain†	29 (8.9)	1 (0.3)	18 (5.6)	2 (0.6)	41 (19.7)	4 (1.9)
Vomiting	29 (8.9)	2 (0.6)	16 (4.9)	1 (0.3)	65 (31.2)	1 (0.5)
Decreased appetite	26 (8.0)	1 (0.3)	12 (3.7)	1 (0.3)	41 (19.7)	2 (1.0)
Thrombocytopenia†	18 (5.5)	3 (0.9)	16 (4.9)	4 (1.2)	38 (18.3)	3 (1.4)
Neutropenia†	17 (5.2)	7 (2.1)	15 (4.6)	6 (1.9)	100 (48.1)	41 (19.7)
Leukopenia†	17 (5.2)	2 (0.6)	15 (4.6)	0	54 (26.0)	9 (4.3)
Rash†	9 (2.8)	0	12 (3.7)	0	21 (10.1)	3 (1.4)
Hypercreatinemia†	9 (2.8)	1 (0.3)	7 (2.2)	0	45 (21.6)	2 (1.0)

Grade 3-4 AEs

Imlunestrant 17.1%

SOC ET 20.7%

Imlu + Abema 48.6%

AE – Discontinuation Rate

Imlunestrant 4%

SOC ET 1%

Imlu + Abema 6%

Jhaveri KL et al NEJM 2024

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evERA: Phase III Giredestrant + Everolimus

A global, randomised, open-label, Phase III trial

Key eligibility criteria*

- ER+, HER2 aBC (1 L of therapy)
- [illegible] aBC setting
- PD or relapse during/post-CDK4/6i + ET
- No prior chemotherapy in the aBC setting
- Measurable disease per RECIST v1.1 or evaluable bone metastases

Enrolment period: August 2022 to October 2024

N = 373*

R 1:1

Giredestrant (30 mg) + everolimus (10 mg)†

SOC ET‡ + everolimus (10 mg)†
‡Exemestane/fulvestrant/tamoxifen

Until PD or unacceptable toxicity

©Dexamethasone mouthwash prophylaxis and treatment was strongly recommended per SWISH trial protocol[1]

* Trial was enriched to 55% of patients with *ESR1*m at baseline (centrally tested via circulating tumour DNA)

Stratification factors

- Prior treatment with fulvestrant (yes vs no)
- *ESR1*m (yes vs no/indeterminate)
- Site of disease (visceral [lung and/or liver involvement] vs non-visceral)

Co-primary endpoints (RECIST v1.1)

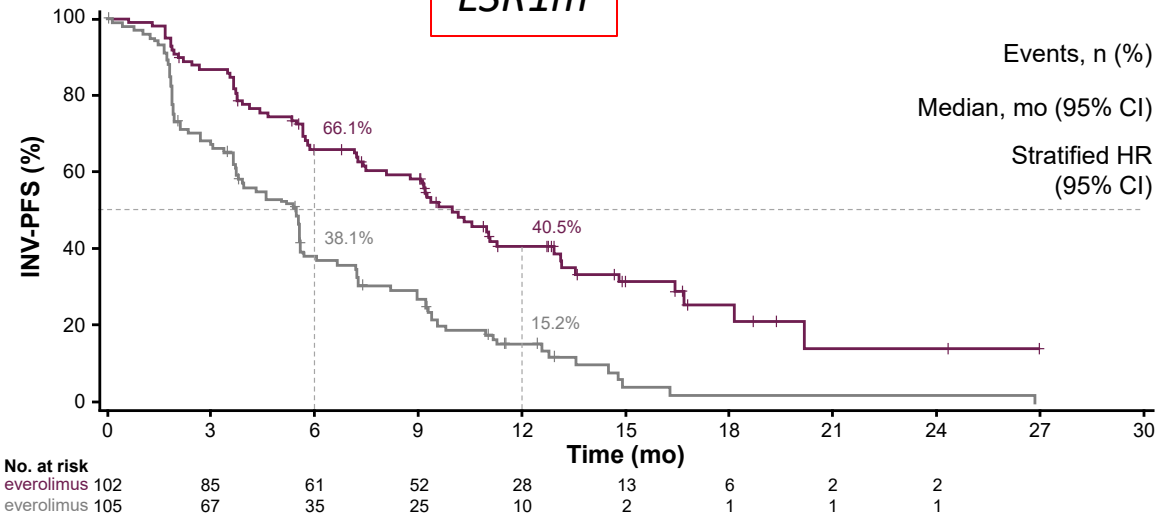
- INV-PFS in patients whose tumours had *ESR1*m
- INV-PFS in the ITT population

Key secondary endpoints

- OS
- INV-assessed ORR, DoR

evERA: Phase III Giredestrant + Everolimus, Efficacy

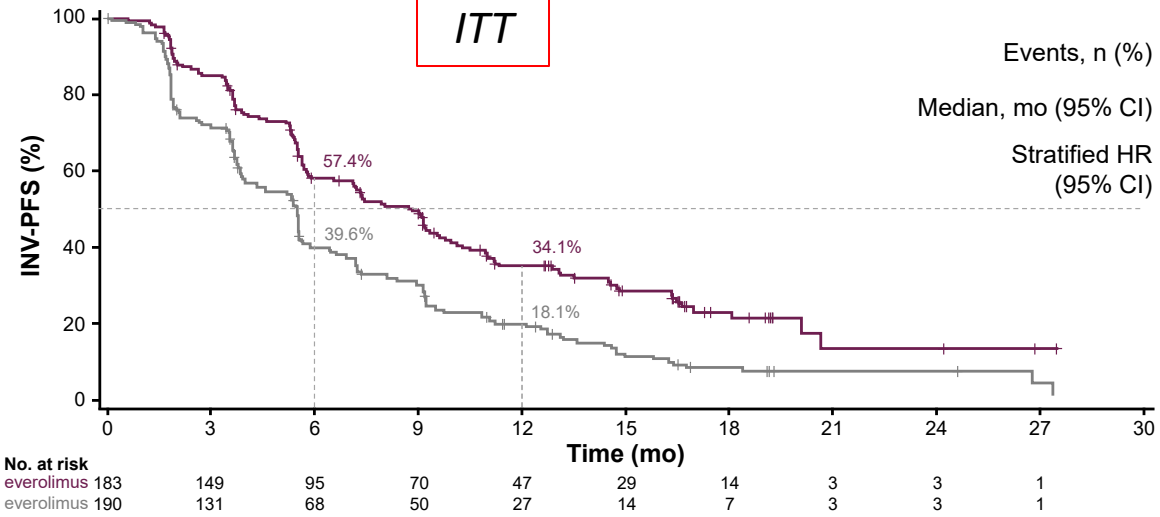
ESR1m



	Giredestrant + everolimus n = 102	SOC ET + everolimus n = 105
Events, n (%)	63 (61.8)	89 (84.8)
Median, mo (95% CI)	**9.99** (8.08, 12.94)	**5.45** (3.75, 5.62)
Stratified HR (95% CI)	**0.38** (0.27, 0.54); p < 0.0001	

55.5% ESR1m Overall

ITT

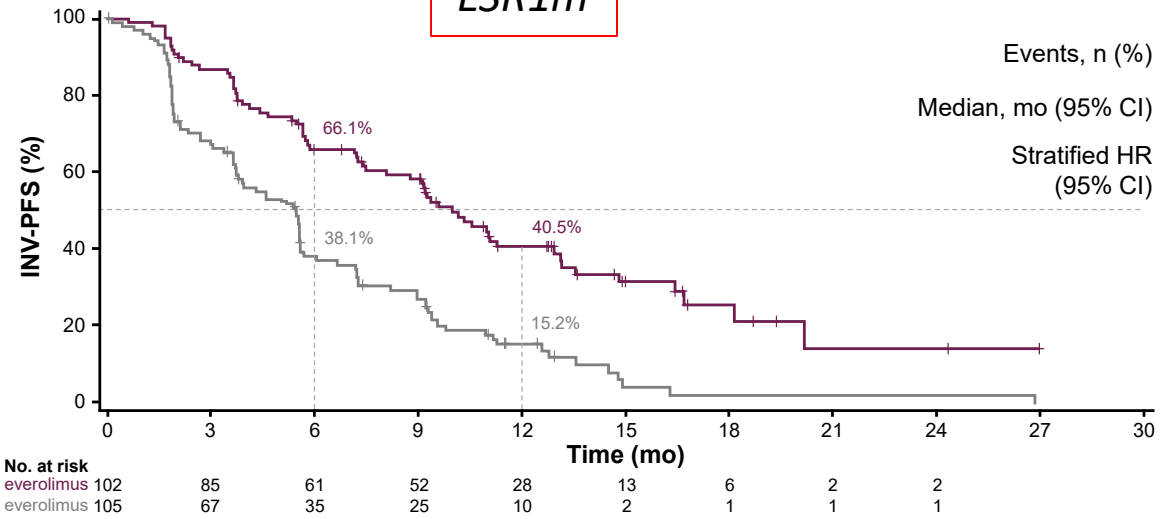


	Giredestrant + everolimus n = 183	SOC ET + everolimus n = 190
Events, n (%)	126 (68.9)	163 (85.8)
Median, mo (95% CI)	8.77 (6.60, 9.59)	5.49 (4.01, 5.59)
Stratified HR (95% CI)	**0.56** (0.44, 0.71); p < 0.0001	

Mayer E et al ESMO 2025;Abstract LBA16

evERA: Phase III Giredestrant + Everolimus, Efficacy

ESR1m



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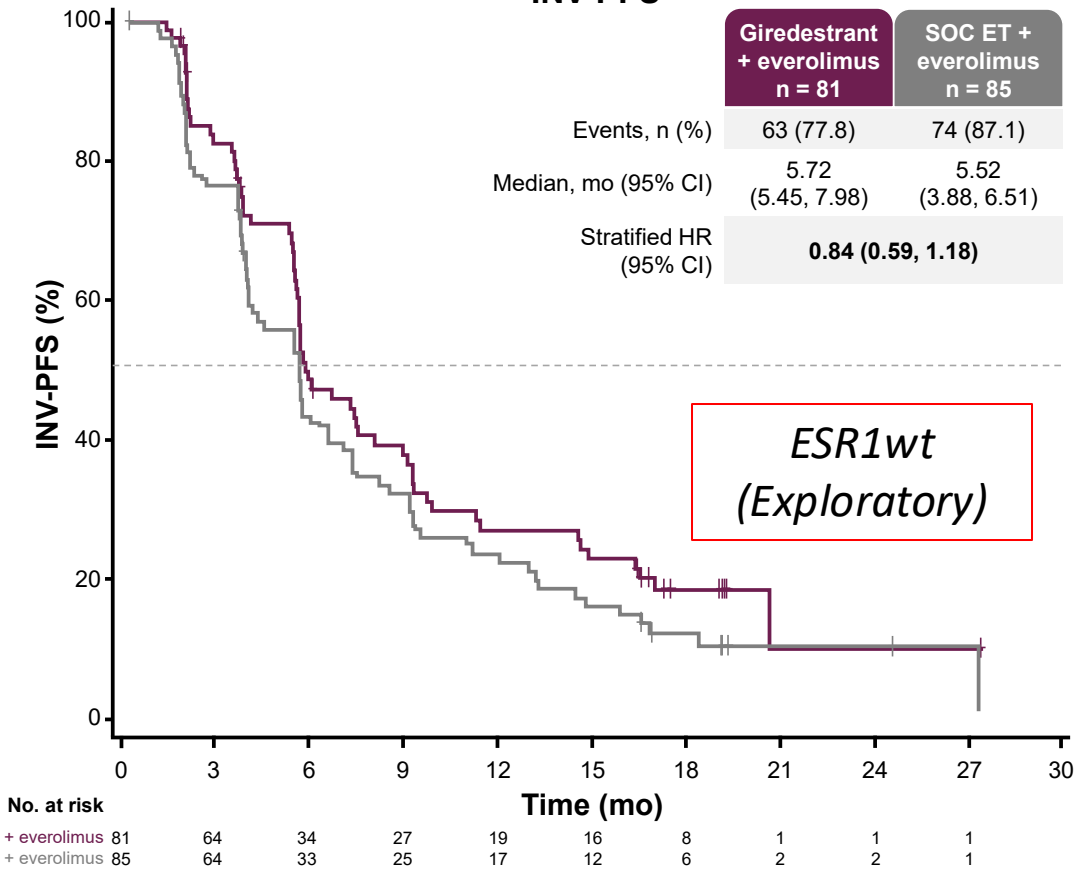
Stratified HR (95% CI)	**0.38** (0.27, 0.54); p < 0.0001	

55.5% ESR1m Overall

INV-PFS

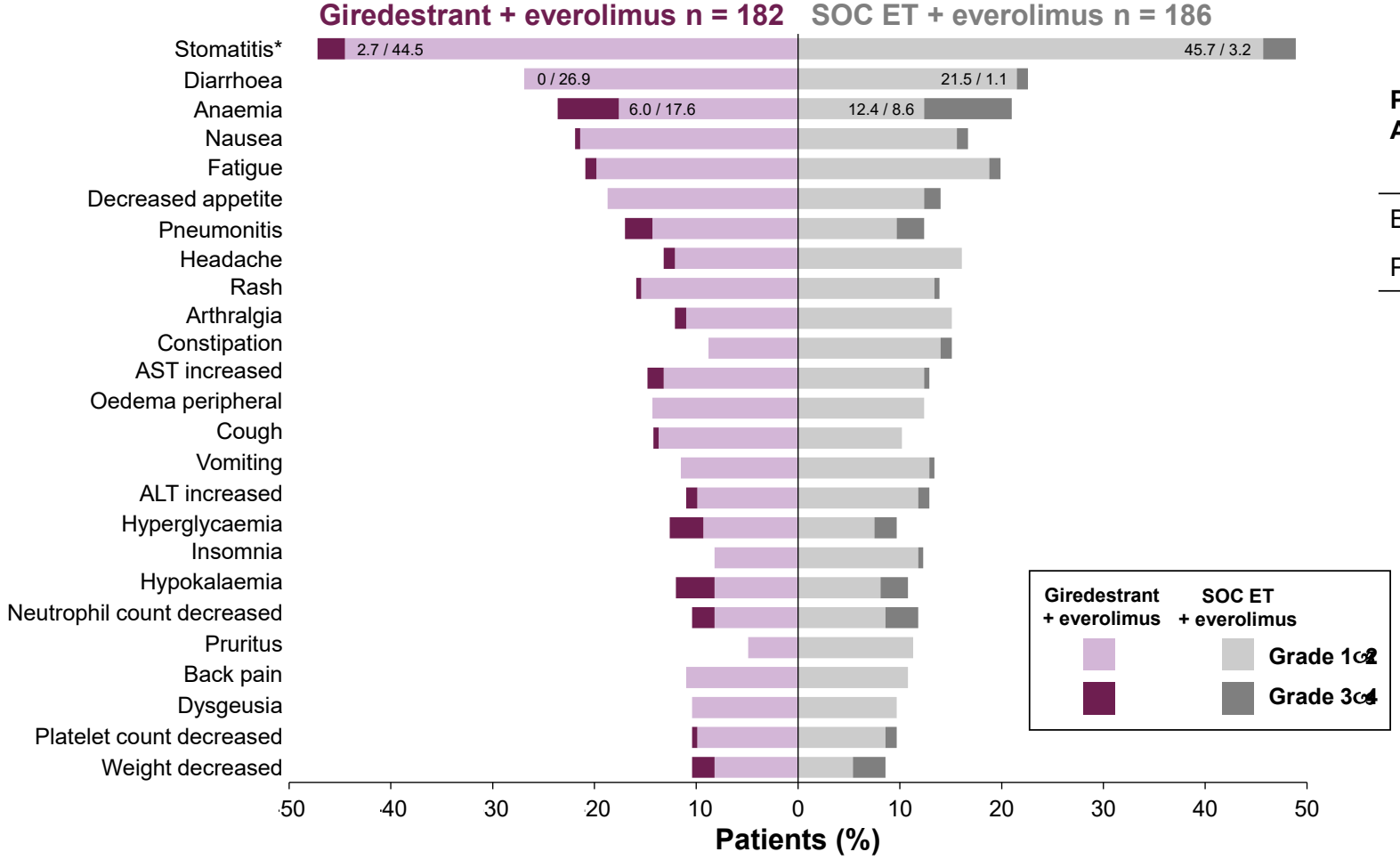


	Giredestrant + everolimus n = 81	SOC ET + everolimus n = 85
Events, n (%)	63 (77.8)	74 (87.1)
Median, mo (95% CI)	5.72 (5.45, 7.98)	5.52 (3.88, 6.51)
Stratified HR (95% CI)	**0.84 (0.59, 1.18)**	

ESR1wt (Exploratory)

evERA: Phase III Giredestrant + Everolimus, Toxicity

Common TE



Selected AEs

Patients with AE, n	Giredestrant + everolimus n = 182		SOC ET + everolimus n = 186	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Bradycardia†	7 (3.8)	0	1 (0.5)	0
Photopsia	0	0	0	0

Grade 3-4 AEs

Giredestrant Combo 51.1%

SOC ET Combo 37.1%

AE – Discontinuation Rate

Giredestrant 8.2%; SOC ET 6.5%

Evero (w/G) 17%; Evero (w/SOC) 11.8%

Oral SERDs for Progressive HR+ mBC

- **Detecting and targeting ESR1: approaches and pharmacology**
- **EMERALD: elacestrant monotherapy (and real-world data)**
- **EMBER3: imlunestrant +/- abemaciclib**
- **evERA: giredestrant + everolimus**
- **Summary, Future Directions, Key Questions**

Current and Evolving Therapeutic Landscape: ER+ MBC

1st Line::
AI/OS + CDK4/6i
(Ribociclib)

Fulvestrant + Palbo
+ Inavolisib
(PIK3CAm,
ET refractory)

NGS
Biopsy/ctDNA @
baseline
ctDNA @
progression

2nd Line::
Fulvestrant +/- Abemaciclib

Fulvestrant + Alpelisib
(*PIK3CAm*)

Fulvestrant + Capivasertib
(*PIK3CAm, AKTm, PTENm*)

Elacestrant or Imlunestrant
(*ESR1m*)

Olaparib
(*BRCAm*)

NGS
ctDNA at
progression

3rd Line (and beyond)::
Antiestrogen + Everolimus

Trastuzumab Deruxtecan (ADC, HER2-low)

Chemotherapy (many choices)

Sacituzumab Govitecan (ADC)

Datopotamab Deruxtecan (ADC)

**Ongoing clinical trials exploring:
New antiestrogens (KAT6i) and doublets/triplets
New CDK4/2 inhibitors
New targeted agents (PI3K, RAS pathway)
New ADCs

Current and Evolving Therapeutic Landscape: ER+ MBC

(+) Phase III Data (not yet approved)
Camizestrant Switch via ESR1 ctDNA?

1st Line::
AI/OS + CDK4/6i
(Ribociclib)

Fulvestrant + Palbo
+ Inavolisib
(PIK3CAm,
ET refractory)

NGS
Biopsy/ctDNA @
baseline
ctDNA @
progression

2nd Line::
Fulvestrant +/- Abemaciclib

Fulvestrant + Alpelisib
(*PIK3CAm*)

Fulvestrant + Capivasertib
(*PIK3CAm, AKTm, PTENm*)

Elacestrant or Imlunestrant
(*ESR1m*)

Olaparib
(*BRCAm*)

(+) Phase III Data (not yet approved)
<u>Single Agent</u>: Vepdegestrant?

<u>Doublet/Triplet</u>:
Imlunestrant + Abemaciclib?
Giredestrant + Everolimus?
Gedatolisib + Fulvestrant +/- Palbociclib?

NGS
ctDNA at
progression

3rd Line (and beyond)::
Antiestrogen + Everolimus

Trastuzumab Deruxtecan (ADC, HER2-low)

Chemotherapy (many choices)

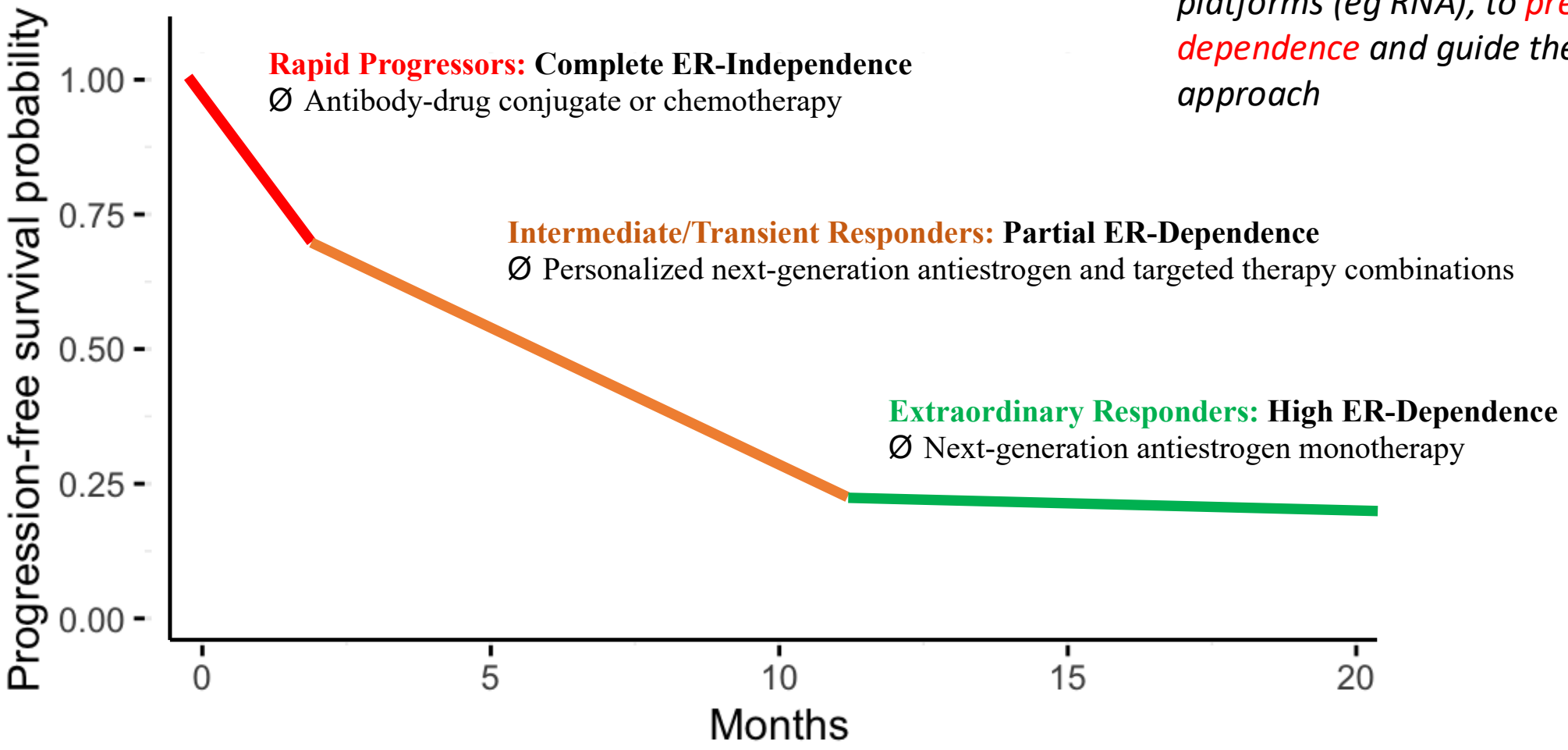
Sacituzumab Govitecan (ADC)

Datopotamab Deruxtecan (ADC)

**Ongoing clinical trials exploring:
New antiestrogens (KAT6i) and doublets/triplets
New CDK4/2 inhibitors
New targeted agents (PI3K, RAS pathway)
New ADCs

Defining Relevant Patient Populations for Precision Therapeutics

Utilize multi-gene signatures, and new platforms (eg RNA), to predict ER-dependence and guide therapeutic approach



Rapid Progressors: Complete ER-Independence
Ø Antibody-drug conjugate or chemotherapy

Intermediate/Transient Responders: Partial ER-Dependence
Ø Personalized next-generation antiestrogen and targeted therapy combinations

Extraordinary Responders: High ER-Dependence
Ø Next-generation antiestrogen monotherapy

Wander SA ASCO 2025 and Teysir J et al ASCO Ed Book 2025

Summary, Key Questions, and Future Directions

- ESR1 mutations emerge under selective pressure during estrogen deprivation; rare in primary tumors and untreated metastatic disease

- EMERALD: elacestrant monotherapy has activity in ESR1m disease; improved outcomes in patients with longer duration on 1st line ET/CDK4/6i
- Real world data suggests median TTNT 6-9 months on elacestrant; inferior outcomes with concurrent ESR1/PIK3CAm; equivalent activity in ESR1 Y537S

- EMBER3: imlunestrant monotherapy with activity in ESR1m; doublet therapy with abemaciclib provokes benefit ~9-10 months (regardless of prior CDK4/6i progression)

- evERA: giredestrant and everolimus doublet demonstrated significant benefit compared to standard ET and everolimus (also 9-10 months)

- Oral SERDs are well tolerated, without increased safety signals in combination regimens

Summary, Key Questions, and Future Directions

- Is there a role for oral SERD monotherapy in HR+/HER2- metastatic breast cancer? In which patients?
- How will earlier deployment of next-generation antiestrogens impact the resistance landscape?

- Which doublet and triplet regimens will provoke the most benefit?
  - When should they be deployed (1st line, 2nd line, later)?

- How should we approach patients without actionable genomic changes in the 2nd line?
  - ESR1wt, no PI3K pathway changes > gedatolisib combination?
  - Will a next-generation antiestrogen have a role in this population?

- Dynamic changes in ctDNA level and targetable alterations (eg. ESR1) are likely to become part of routine clinical decision-making.
  - How will we select optimal drug combinations and monitor response via liquid biopsy?

- Ongoing efforts (multigene and transcriptional signatures) will refine our ability to predict ER-dependence, and promote better personalization for patients in the 2nd-3rd line metastatic setting

CASES FROM THE COMMUNITY
Investigators Discuss the Optimal Role of Endocrine-Based and Other Strategies in the Management of HR-Positive Breast Cancer

Part 3 of a 3-Part CME Satellite Symposium Series

Thursday, December 11, 2025

7:00 PM – 9:00 PM CT

Faculty

Angela DeMichele, MD, MSCE
Komal Jhaveri, MD, FACP, FASCO
Erica Mayer, MD, MPH, FASCO
Hope S Rugo, MD
Seth Wander, MD, PhD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

SAN ANTONIO BREAST CANCER SYMPOSIUM®
UT Health San Antonio Mays Cancer Center
AACR American Association for Cancer Research
Abstract RF7-01
DECEMBER 9–12, 2025
HENRY B. GONZALEZ CONVENTION CENTER • SAN ANTONIO, TX

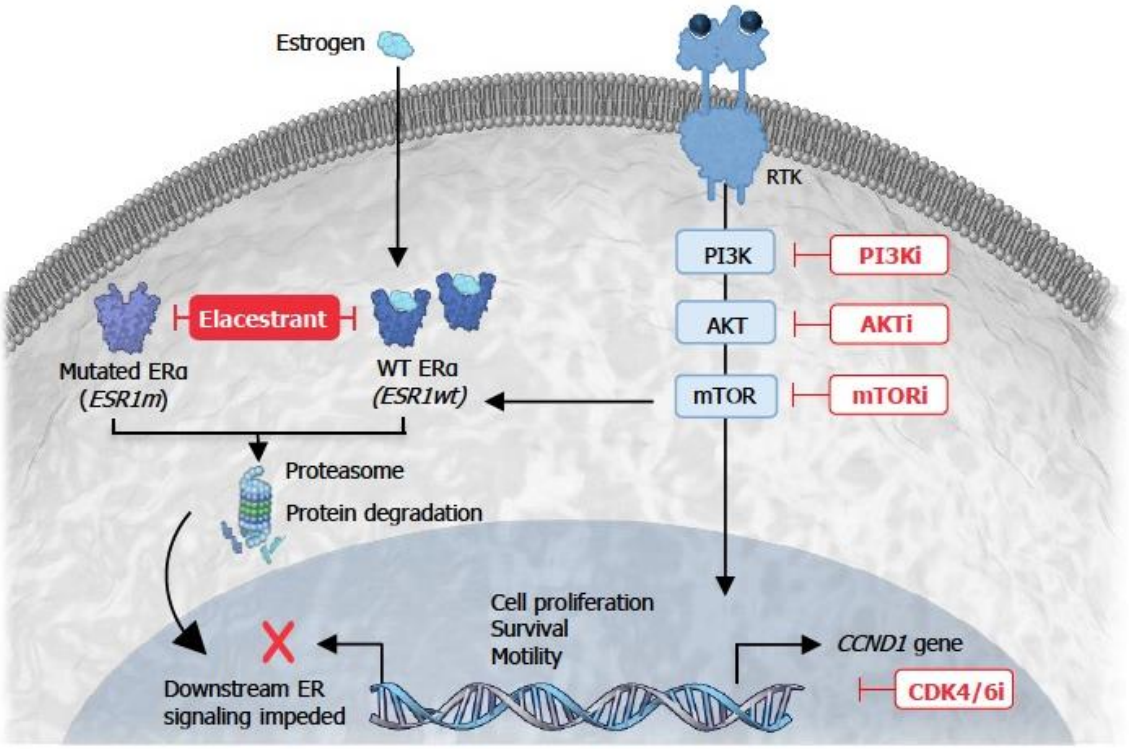
Elacestrant in combination with everolimus or abemaciclib in patients with ER+/HER2- locally advanced or metastatic breast cancer: phase 2 results from ELEVATE, an open-label umbrella trial

Hope S. Rugo,[1] Sara M. Tolaney,[2] Nancy Chan,[3] Giuliano Borges,[4] Rinat Yerushalmi,[5] Marina N. Sharifi,[6] Wassim McHayleh,[7] Thaddeus Beck,[8] Neelima Vidula,[9] Erika Hamilton,[10] Kristine J. Rinn,[11] Joyce O'Shaughnessy,[12] Giuseppe Curigliano,[13] Javier Cortés,[14] Paula Muñoz Romero,[15] Giulia Tonini,[15] Alessandro Paoli,[15] Li Cheng,[16] Jennifer A. Crozier,[16] Tomer Wasserman,[16] Virginia Kaklamani[17]

1. City of Hope Cancer Center, Duarte, CA, USA; 2. Dana-Farber Cancer Institute, Boston, MA, USA; 3. NYU Langone Health, New York, NY, USA; 4. Catarina Pesquisa Clínica, Santa Catarina, Brazil; 5. Rabin Medical Center, Petah Tikva, Israel; 6. University of Wisconsin, Madison, WI, USA; 7. AdventHealth Cancer Institute, Orlando, FL, USA; 8. Highlands Oncology, Springdale, AR, USA; 9. Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; 10. Sarah Cannon Research Institute, Nashville, TN, USA; 11. Cancer Care Northwest, Spokane, WA, USA; 12. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, TX, USA; 13. Istituto Europeo di Oncologia, IRCCS, and University of Milano, Milano, Italy; 14. International Breast Cancer Center (IBCC), Quironsalud Group, Barcelona, Spain; 15. Menarini Group, Florence, Italy; 16. Menarini Group, New York, NY, USA; 17. University of Texas Health Sciences Center San Antonio, San Antonio, TX, USA

Biological Rationale for Elacestrant

- Disease progression in patients with ER+/HER2- mBC on 1L ET + CDK4/6i is associated with mechanisms of resistance that impact the efficacy of subsequent therapy.[1,2]
- Elacestrant is the only single-agent oral SERD that significantly improved PFS vs SOC ET in all patients with mBC (HR 0.70; 95% CI 0.55-0.88) in the Ph 3 EMERALD trial.[3]
- Elacestrant was approved by regulatory authorities based on improved PFS vs SOC ET in patients with *ESR1*m mBC (HR 0.55; 95% CI 0.39-0.77).[3]
- The registrational Ph3 ADELA trial with elacestrant in combination with everolimus is being conducted in patients with *ESR1*m mBC.[4]
- Here we report outcomes of elacestrant in combination with everolimus or abemaciclib from the Ph 2 ELEVATE trial.[5]

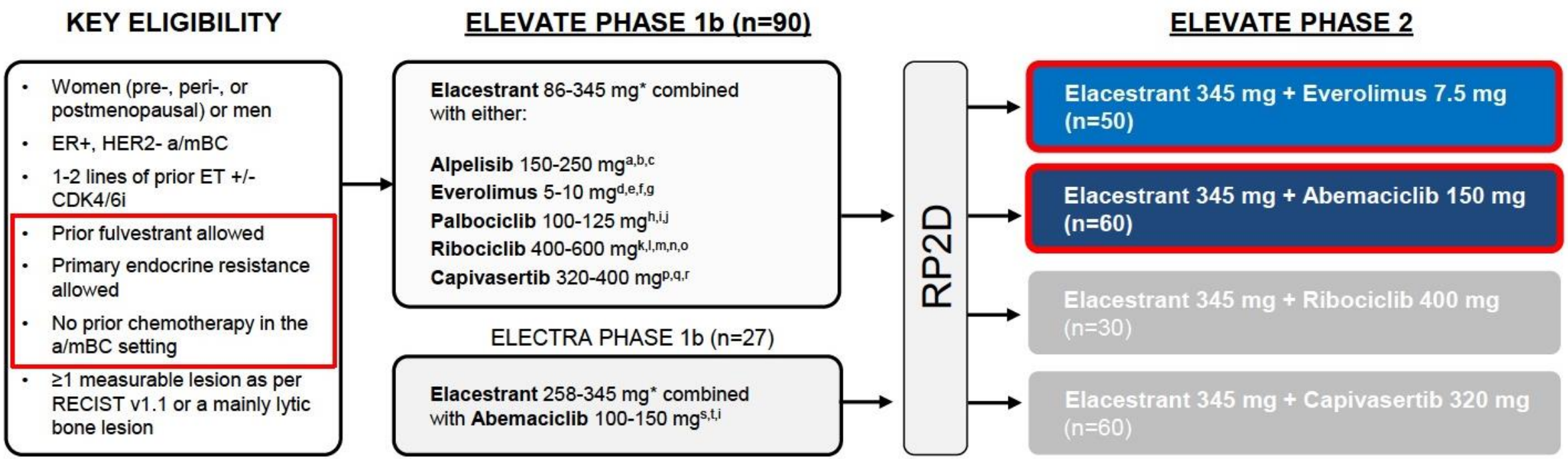


References: Adapted from Brufsky A, et al. *The Oncologist.* 2018;23:528–539. 2. Vasan N, et al. *Ann Oncol.* 2019;30(suppl_10):x3-x11.

1L, first-line; AKT, protein kinase B; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER, estrogen receptor; *ESR1m*, estrogen receptor 1 mutation; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; i=inhibitor; mTOR, mechanistic target of rapamycin; mBC, metastatic breast cancer; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase; Ph, phase; SERD, selective estrogen receptor antagonist and degrader; SOC, standard-of-care; wt, wild-type.

References: 1. Osborne CK, et al. Annu Rev Med. 2011;62:233-247; 2. Hanker AB, et al. Cancer Cell 37:496-513, 2020; 3. Bidard FC, et al. Lancet Oncol. 2022;23(11):1367-1377; 4. Elacestrant + Everolimus in Patients ER+/HER2-, ESR1mut, Advanced Breast Cancer Progressing to ET and CDK4/6i. (ADELA). https://clinicaltrials.gov/study/NCT06382948; 5. Open-Label Umbrella Study To Evaluate Safety And Efficacy Of Elacestrant In Various Combination In Participants With Metastatic Breast Cancer (ELEVATE). https://clinicaltrials.gov/study/NCT05563220.

Phase II ELEVATE Study Design



Elacestrant 86 mg is equivalent to 100 mg elacestrant hydrochloride; elacestrant 172 mg is equivalent to 200 mg elacestrant hydrochloride; elacestrant 258 mg is equivalent to 300 mg elacestrant hydrochloride; elacestrant 345 mg is equivalent to 400 mg elacestrant hydrochloride. [a]Elacestrant 258 mg + alpelisib 250 mg (cohort 1); [b]Elacestrant 258 mg* + alpelisib 200 mg (cohort -1); [c]Elacestrant 258 mg* + alpelisib 150 mg (cohort -2); [d]Elacestrant 258 mg* + everolimus 5 mg (cohort 1); [e]Elacestrant 345 mg* + everolimus 5 mg (cohort 2); [f]Elacestrant 345 mg* + everolimus 10 mg (cohort 3); [g]Elacestrant 345 mg* + everolimus 7.5 mg (cohort 4); [h]Elacestrant 258 mg* + palbociclib 100 mg (cohort 1); [i]Elacestrant 345 mg* + palbociclib 100 mg (cohort 2); [j]Elacestrant 345 mg* + palbociclib 125 mg (cohort 3); [k]Elacestrant 86 mg* + ribociclib 400 mg (cohort 1); [l]Elacestrant 172 mg* + ribociclib 400 mg (cohort 2); [m]Elacestrant 258 mg* + ribociclib 400 mg (cohort 3); [n]Elacestrant 172 mg* + ribociclib 600 mg (cohort 4); [o]Elacestrant 345 mg* + ribociclib 400 mg (cohort 5); [p]Elacestrant 258 mg* + capivasertib 320 mg (cohort 1); [q]Elacestrant 345 mg* + capivasertib 320 mg (cohort 2); [r]Elacestrant 345 mg* + capivasertib 400 mg (cohort 3); [s]Elacestrant 258 mg* + abemaciclib 100 mg (cohort 1); [t]Elacestrant 345 mg* + abemaciclib 100 mg (cohort 2); [i]Elacestrant 345 mg* + abemaciclib 150 mg (cohort 3). a/mBC, advanced or metastatic breast cancer; CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DoR, duration of response; ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; n, number; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; v, version.

References: 1. Open-Label Umbrella Trial to Evaluate Safety and Efficacy of Elacestrant in Various Combination in Patients With Metastatic Breast Cancer (ELEVATE). ClinicalTrials.gov. May 20, 2024. Accessed August 26, 2024. https://clinicaltrials.gov/trial/NCT05563220. 2. A Phase 1b/2, Open-Label Umbrella trial to Evaluate Safety and Efficacy of Elacestrant in Various Combinations in Patients with Metastatic Breast Cancer (ELEVATE). STML-ELA-0222. Updated December 22, 2023.

Rugo HS et al. SABCS 2025;Abstract RF7-01.

Phase II ELEVATE: Authors' Conclusions

- Elacestrant in combination with everolimus or abemaciclib showed clinically meaningful PFS in patients with ER+/HER2- mBC.
  - **mPFS elacestrant + everolimus: 8.3 months**
  - **mPFS elacestrant + abemaciclib: 14.3 months**
- Both combinations continue to demonstrate a known safety profile that is consistent with everolimus or abemaciclib plus standard ET.
  - No bradycardia or photopsia were reported, and no new safety signals were observed
  - Low rates of drug withdrawal or dose reduction.
- **Elacestrant has the potential to become an ET backbone for combination strategies with abemaciclib or everolimus, supporting an all-oral approach.**

ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; PFS, progression-free survival

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Rugo HS et al. SABCS 2025;Abstract RF7-01.

Dr Zanetta Lamar
(Naples, Florida)

Future use of oral SERDs in the adjuvant setting: similarities and differences between oral SERDs

Dr Laila Agrawal
(Louisville, Kentucky)

Patients with disease recurrence after prior adjuvant CDK4/6 inhibitor

Dr Gigi Chen
(Walnut Creek, California)

Metastatic disease with both PI3K/AKT/PTEN alteration and an ESR1 mutation

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QUESTIONS FOR THE FACULTY

Do you anticipate that oral SERDs will become standard adjuvant therapy in the near future?

How do you choose between elacestrant and imlunestrant for patients with progressive ESR1-mutated, HR-positive, HER2-negative mBC? How do they differ in terms of their side-effect profiles?

In which situations, if any, would you combine an oral SERD with a CDK4/6 inhibitor? What about an oral SERD with everolimus?

QUESTIONS FOR THE FACULTY

How do you approach subsequent treatment for patients who receive an adjuvant CDK4/6 inhibitor and develop metastatic recurrence? Do you assess for biomarkers and tailor treatment based on the results? If a patient in this situation were found to have an ESR1 mutation, what would you most likely recommend?

How do you choose between an oral SERD and capivasertib/ fulvestrant for patients who are eligible for both strategies? How would a history of preexisting diabetes affect your decision?

Case Presentation: 103-year-old woman with locally advanced ER-positive, HER2-negative BC, with disease progression on letrozole, now with ESR1 mutation

Dr Alan Astrow (Brooklyn, New York)

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QUESTIONS FOR THE FACULTY

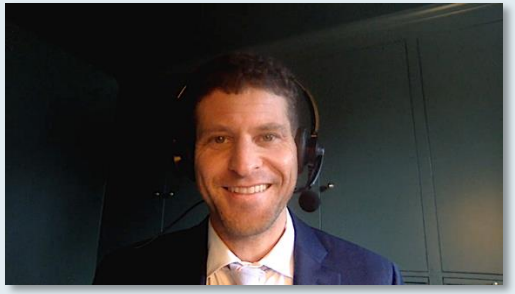
Would you ever recommend an oral SERD for a patient with ESR1-mutated, HR-positive mBC who hasn't previously been exposed to a CDK4/6 inhibitor, particularly for an older patient like this?

Do you base your decision to use oral SERDs largely on patient age/fitness? Are oral SERDs a reasonable treatment choice for younger patients? What about patients with visceral disease?

Would you consider chemotherapy or an antibody-drug conjugate for this patient if she were to experience disease progression?

Contributing General Medical Oncologists

Laila Agrawal, MD
Norton Cancer Institute
Louisville, Kentucky



Eric Fox, DO
Bryn Mawr Medical Specialists Association
Bryn Mawr, Pennsylvania

Alan B Astrow, MD
Weill Cornell Medicine
Brooklyn, New York

Sunil Gandhi, MD
Florida Cancer Specialists & Research Institute
Lecanto, Florida

Gigi Chen, MD
John Muir Health
Cancer Medical Group
Walnut Creek, California

Zanetta S Lamar, MD
Florida Oncology and Hematology
Naples, Florida

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Contributing General Medical Oncologists

Laurie Matt-Amaral, MD, MPH
Northeast Ohio Medical University
College of Medicine
Akron, Ohio

Swati Vishwanathan, MD
WVU Medicine
Bridgeport, West Virginia

Eleonora Teplinsky, MD
Valley-Mount Sinai
Comprehensive Cancer Care
Paramus, New Jersey

Richard Zelkowitz, MD
Hartford HealthCare Cancer Institute
Bridgeport, Connecticut

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Cases from the Community: Investigators Discuss Available Research Guiding the Management of Relapsed/Refractory Multiple Myeloma — What Happened at ASH 2025?

A CME/MOC-Accredited Live Webinar

Monday, December 15, 2025

5:00 PM – 6:00 PM ET

Faculty

Sagar Lonial, MD, FACP, FASCO

María-Victoria Mateos, MD, PhD

Moderator

Neil Love, MD

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