Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

Hormone Receptor-Positive Breast Cancer

A Multitumor CME/MOC-Accredited Live Webinar Series

Thursday, January 11, 2024
5:00 PM – 6:00 PM ET

Faculty

Stephanie L Graff, MD, FACP
Erica Mayer, MD, MPH, FASCO

Moderator

Neil Love, MD

RTP Year in Review 2024

Faculty

Stephanie L Graff, MD, FACP
Associate Professor of Medicine
Warren Alpert Medical School of Brown University
Director of Breast Oncology, Lifespan Cancer Institute
Co-Lead, Breast Cancer Translational Disease Research Group
Legorreta Cancer Center at Brown University
Medical Advisor, Dr Susan Love Foundation for Breast Cancer Research
Providence, Rhode Island

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

MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Lilly, and Stemline Therapeutics Inc.

Dr Love — Disclosures

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Dr Graff — Disclosures

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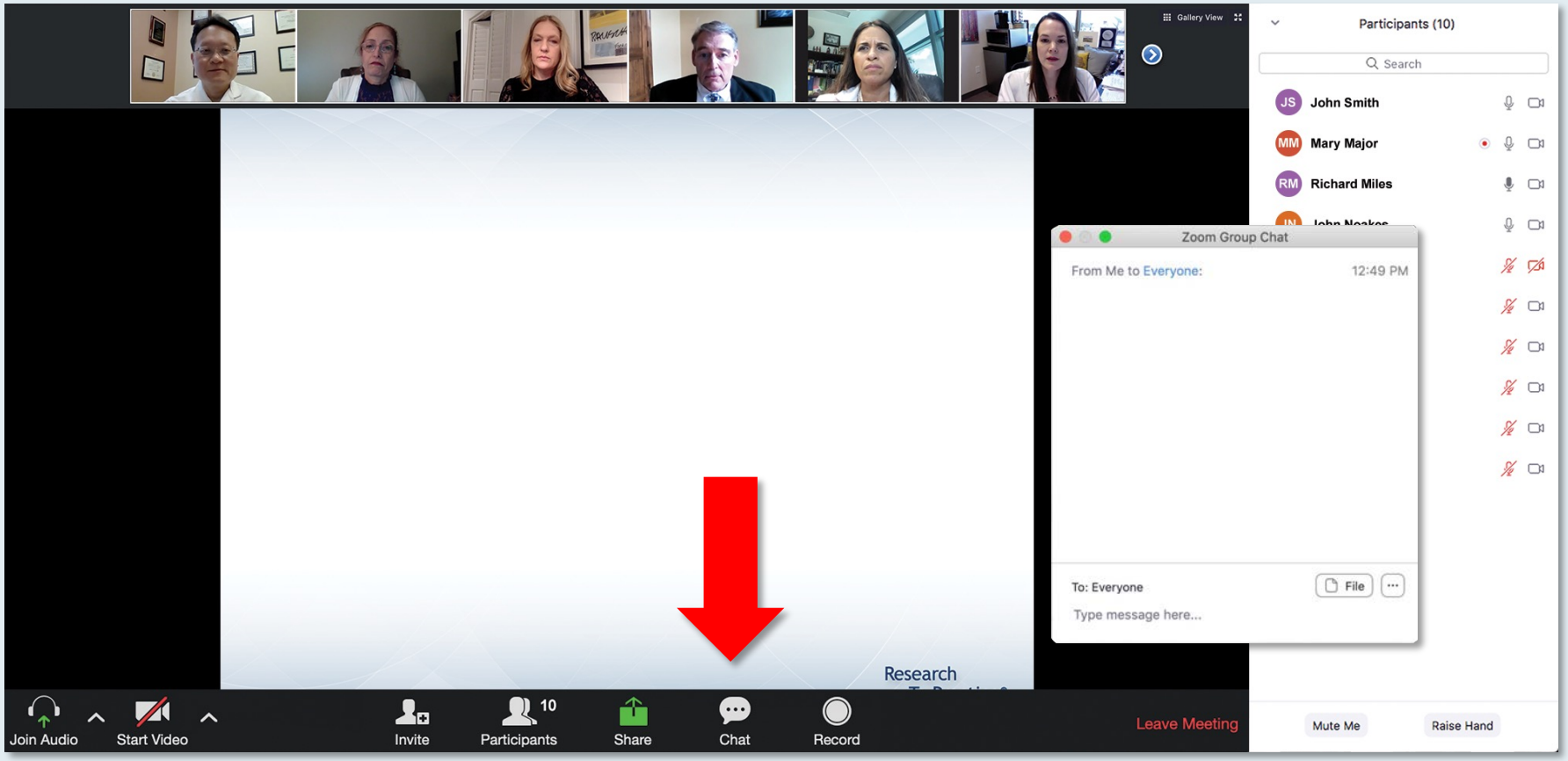
Research Funding (All Funds to Institution)	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Novartis
Nonrelevant Financial Relationship	HCA Healthcare (stock ownership)

Dr Mayer — Disclosures

Consulting Agreements	AstraZeneca Pharmaceuticals LP, Lilly, Novartis

We Encourage Clinicians in Practice to Submit Questions



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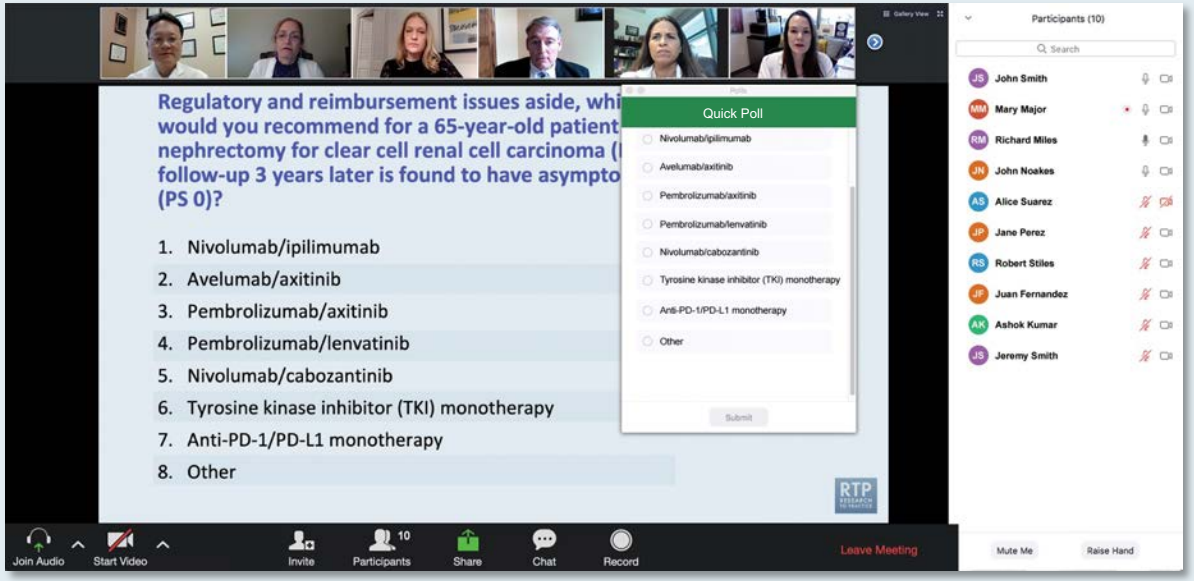

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ONCOLOGY TODAY

WITH DR NEIL LOVE

Implications of Recent Data Sets for the Current and Future Management of Breast Cancer

ADITYA BARDIA, MD, MPH
MASSACHUSETTS GENERAL HOSPITAL

SARA M TOLANEY, MD, MPH
DANA-FARBER CANCER INSTITUTE

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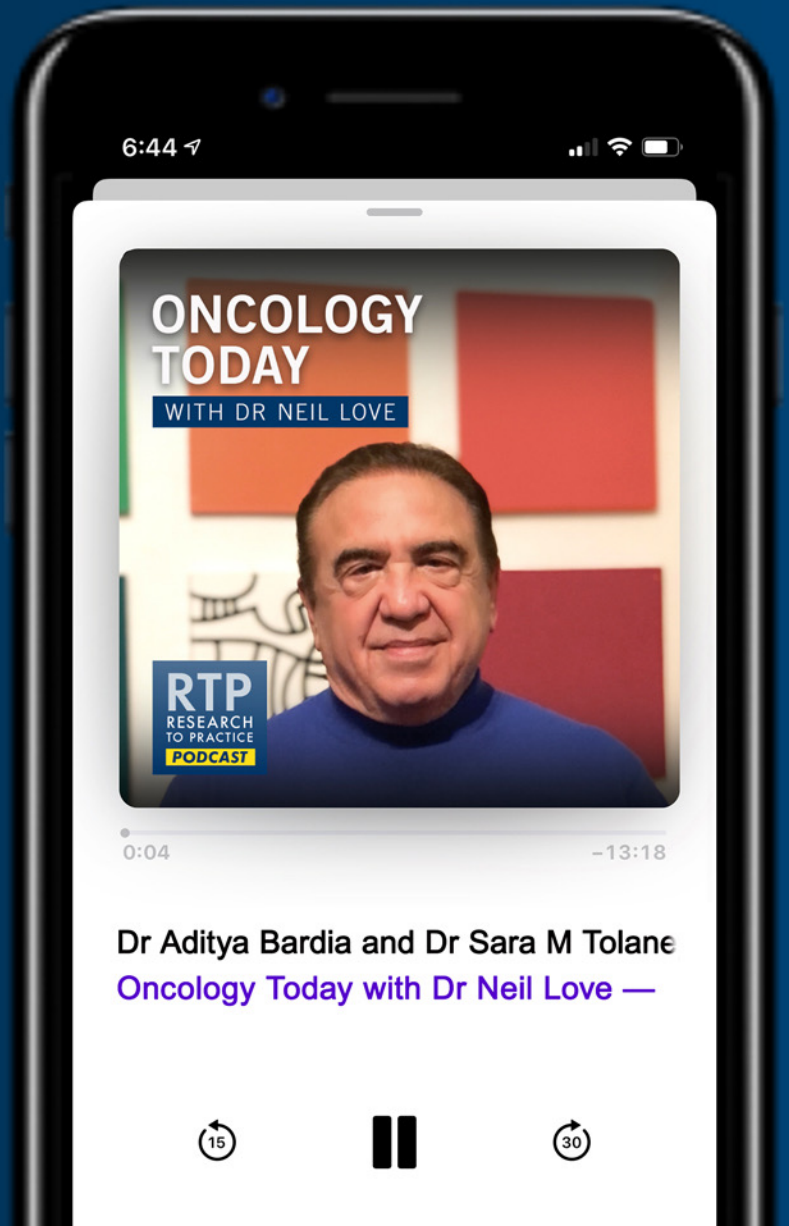

Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Management of Gastroesophageal Cancers

Part 1 of a 2-Part CME Symposium Series Held in Conjunction with the 2024 ASCO Gastrointestinal Cancers Symposium

Thursday, January 18, 2024

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

Faculty

David H Ilson, MD, PhD

Professor Markus Moehler, MD

Rutika Mehta, MD, MPH

Manish A Shah, MD

Moderator

Harry H Yoon, MD, MHS

RTP RESEARCH TO PRACTICE

Consensus or Controversy? Clinical Investigators Provide Perspectives on Biomarker Assessment and Related Treatment Decision-Making for Patients with Colorectal Cancer

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Tanios Bekaii-Saab, MD

John Strickler, MD

Cathy Eng, MD

Moderator

Christopher Lieu, MD

RTP RESEARCH TO PRACTICE

Consensus or Controversy? Investigator Perspectives on the Current and Future Role of Immune Checkpoint Inhibitors in the Management of Hepatobiliary Cancers

Saturday, January 20, 2024
8:30 AM – 9:30 AM ET

Faculty

Ahmed Omar Kaseb, MD, CMQ
Arndt Vogel, MD, PhD

Moderator

Neil Love, MD

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Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Management of Prostate Cancer

Part 1 of a 2-Part CME Symposium Series Held in Conjunction with the 2024 ASCO Genitourinary Cancers Symposium

Thursday, January 25, 2024

6:15 PM – 8:15 PM PT (9:15 PM – 11:15 PM ET)

Faculty

Rahul Aggarwal, MD

Emmanuel S Antonarakis, MD

Elisabeth I Heath, MD

A Oliver Sartor, MD

Moderator

Alan H Bryce, MD

RTP RESEARCH TO PRACTICE

Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Management of Urothelial Bladder Cancer

Part 2 of a 2-Part CME Symposium Series Held in Conjunction with the 2024 ASCO Genitourinary Cancers Symposium

Friday, January 26, 2024

7:00 PM – 9:00 PM PT (10:00 PM – 12:00 AM ET)

Faculty

Matthew Milowsky, MD

Peter H O'Donnell, MD

Jonathan E Rosenberg, MD

Arlene Siefker-Radtke, MD

Moderator

Evan Y Yu, MD

RTP RESEARCH TO PRACTICE

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HER2-Positive and Triple-Negative Breast Cancer

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JW Marriott Miami Turnberry

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Agenda

INTRODUCTION: Endocrinology and Pharmacology of Hormonal Therapy for Breast Cancer

MODULE 1: Current and Emerging Strategies for Localized Hormonal Receptor (HR)-Positive Breast Cancer — Dr Graff

MODULE 2: Advances in the Care of Patients with HR-Positive Metastatic Breast Cancer — Dr Mayer

Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

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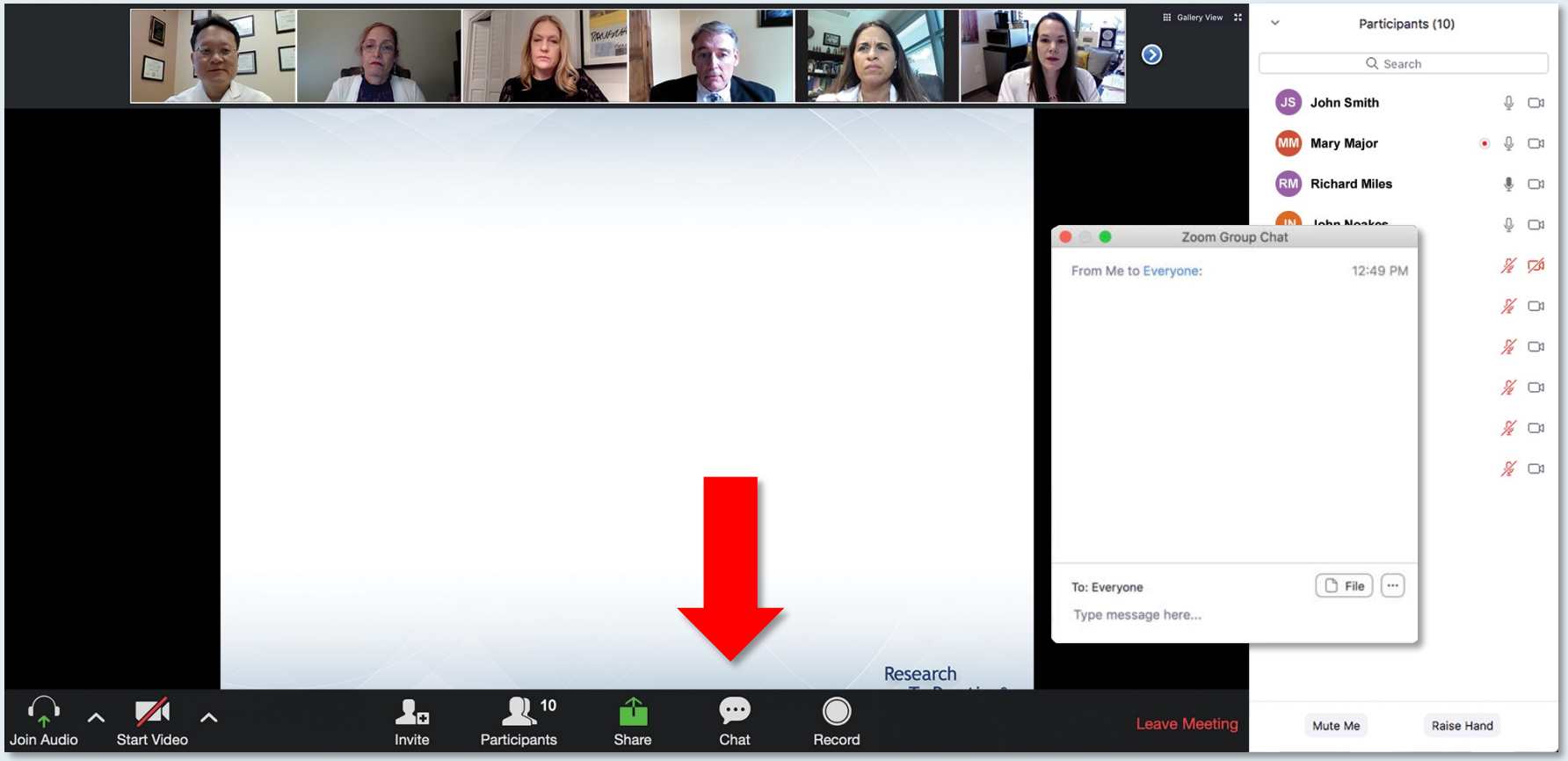

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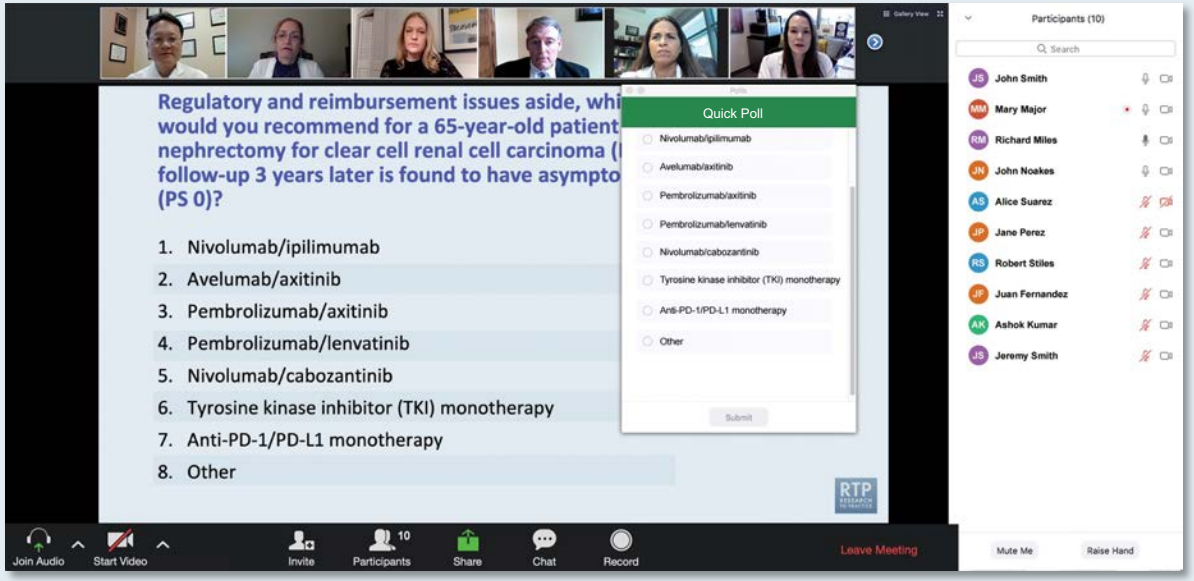

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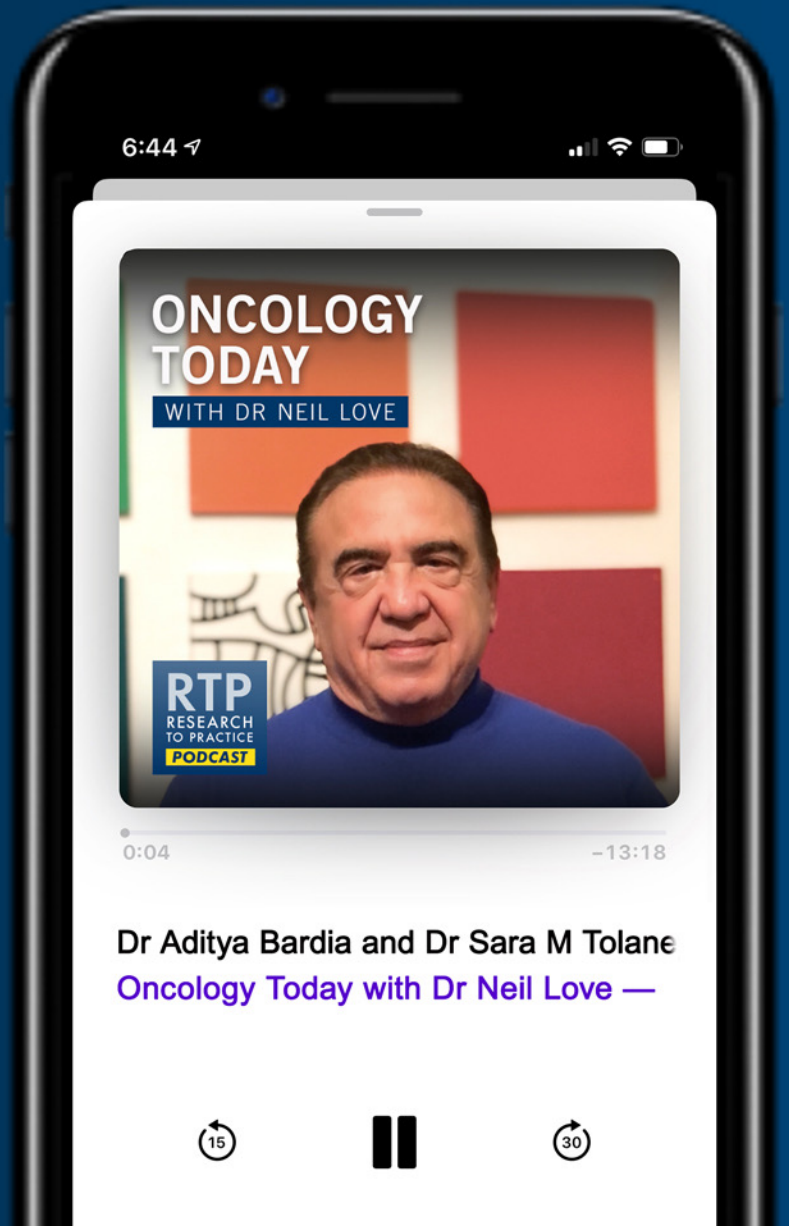

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Third Annual **National General Medical Oncology Summit**

Friday, March 22, 2024

6:00 PM – 6:30 PM

Welcome Reception

6:30 PM – 8:30 PM

Keynote Session: ER-Positive Metastatic Breast Cancer

Erika Hamilton, MD
Kevin Kalinsky, MD, MS
Joyce O'Shaughnessy, MD
Hope S Rugo, MD

Third Annual **National General Medical Oncology Summit**

Saturday, March 23, 2024

7:30 AM – 9:10 AM

Hodgkin and Non-Hodgkin Lymphoma

Ann S LaCasce, MD, MMSc
Matthew Lunning, DO
Kami Maddocks, MD
Andrew D Zelenetz, MD, PhD

9:30 AM – 10:20 AM

Gynecologic Cancers

Bradley J Monk, MD
David M O'Malley, MD

10:20 AM – 11:10 AM

Localized Breast Cancer; SABCS 2023 Review

Virginia Kaklamani, MD, DSc
Kevin Kalinsky, MD, MS
Joyce O'Shaughnessy, MD

11:10 AM – 12:00 PM

Metastatic Breast Cancer, Triple-Negative Breast Cancer, HER2-Positive Breast Cancer; SABCS 2023 Review

Erika Hamilton, MD
Virginia Kaklamani, MD, DSc
Hope S Rugo, MD

Third Annual **National General Medical Oncology Summit**

Saturday, March 23, 2024

12:30 PM – 1:20 PM

Prostate Cancer

Emanuel S Antonarakis, MD
Rana R McKay, MD

1:20 PM – 2:10 PM

Urothelial Bladder Cancer

Matthew D Galsky, MD
Jonathan E Rosenberg, MD

2:10 PM – 3:00 PM

Renal Cell Carcinoma

Eric Jonasch, MD
Brian Rini, MD

3:20 PM – 4:10 PM

Targeted Therapy for Non-Small Cell Lung Cancer

Ibiayi Dagogo-Jack, MD
Helena Yu, MD

4:10 PM – 5:00 PM

Nontargeted Treatments for Lung Cancer

Edward B Garon, MD, MS
Corey J Langer, MD

Third Annual **National General Medical Oncology Summit**

Sunday, March 24, 2024

7:30 AM – 8:20 AM

Multiple Myeloma

Natalie S Callander, MD
Paul G Richardson, MD

8:20 AM – 9:10 AM

Gastroesophageal Cancers

Yelena Y Janjigian, MD
Samuel J Klempner, MD

9:30 AM – 10:20 AM

Hepatobiliary Cancers

Ghassan Abou-Alfa, MD, MBA
Richard S Finn, MD

10:20 AM – 11:10 AM

Colorectal Cancer

Kristen K Ciombor, MD, MSCI
John Strickler, MD

11:10 AM – 12:00 PM

Topic and faculty to be announced

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Dr Graff — Disclosures

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Current and Emerging Strategies for Early-Stage HR-Positive Breast Cancer

Stephanie L. Graff, MD FACP
Legoretta Cancer Center at Brown University
Lifespan Cancer Institute
Providence, Rhode Island

Key Data Sets

Stephanie L Graff, MD, FACP

- Taylor C et al. Using Onco*type* DX breast Recurrence Score® assay to define the **role of neoadjuvant endocrine therapy** in **early-stage** hormone receptor-positive breast cancer. *Breast Cancer Res Treat* 2023;199(1):91-8.
- Trapani D et al. Identifying **patterns** and **barriers** in **Onco*type* DX** Recurrence Score testing in **older patients with early-stage**, estrogen receptor-positive breast cancer: Implications for guidance and reimbursement. *JCO Oncol Pract* 2023;19(8):560-70.
- Loi S et al. A randomized, double-blind trial of **nivolumab (NIVO)** vs placebo (PBO) with **neoadjuvant chemotherapy** (NACT) followed by **adjuvant endocrine therapy (ET) ± NIVO** in patients (pts) with **high-risk**, ER+ HER2− **primary breast cancer** (BC). ESMO 2023;Abstract LBA20.
- Cardoso F et al. **KEYNOTE-756**: **Phase III** study of **neoadjuvant pembrolizumab** (pembro) or placebo (pbo) + **chemotherapy** (chemo), followed by **adjuvant pembro** or pbo + **endocrine therapy** (ET) for **early-stage high-risk** ER+/HER2– breast cancer. ESMO 2023;Abstract LBA21.

Key Data Sets

Stephanie L Graff, MD, FACP (continued)

- Hortobagyi G et al. **Ribociclib (RIB) + nonsteroidal aromatase inhibitor** (NSAI) as **adjuvant** treatment in patients with HR+/HER2− **early breast cancer**: **Final invasive disease–free survival** (iDFS) analysis from the **NATALEE** trial. San Antonio Breast Cancer Symposium 2023;Abstract GS03-03.
- Johnston SRD et al. **Abemaciclib** plus **endocrine therapy** for hormone receptor-positive, HER2-negative, node-positive, **high-risk early breast cancer (monarchE):** Results from a preplanned interim analysis of a randomised, open-label, phase 3 trial. *Lancet Oncol* 2023;24(1):77-90.
- Harbeck N et al. **Adjuvant abemaciclib** plus **endocrine therapy** for HR+, HER2-, **high-risk early breast cancer**: Results from a preplanned **monarchE overall survival interim analysis**, including 5-year efficacy outcomes. ESMO 2023;Abstract LBA17.
- Pagani O et al. **Adjuvant exemestane** with **ovarian suppression** in **premenopausal** breast cancer: Long-term follow-up of the **combined TEXT and SOFT** trials. *J Clin Oncol* 2023;41(7):1376-82.

Key Data Sets

Stephanie L Graff, MD, FACP (continued)

- Gray RG et al. Effects of **ovarian ablation or suppression** on breast cancer **recurrence and survival**: Patient-level **meta-analysis** of 14,993 pre-menopausal women in 25 randomized trials. ASCO 2023;Abstract 503.
- Partridge AH et al. Interrupting endocrine therapy to attempt pregnancy after breast cancer. *N Engl J Med* 2023;388(18):1645-56.
- Robertson J et al. **SERENA-3**: A randomized pre-surgical window of opportunity study assessing dose and duration of **camizestrant** treatment in **post-menopausal** women with ER-positive, HER2-negative **primary breast cancer**. San Antonio Breast Cancer Symposium 2023;Abstract RF01-01.

Key Data Sets

Erica Mayer, MD, MPH, FASCO

- Jhaveri K et al. Phase III study of **inavolisib** or placebo in combination **with palbociclib** and **fulvestrant** in patients with **PIK3CA-mutant**, hormone receptor-positive, HER2-negative **locally advanced** or **metastatic** breast cancer**: INAVO120** primary analysis. San Antonio Breast Cancer Symposium 2023;Abstract GS03-13.
- Goetz M et al. **MONARCH 3: Final overall survival** results of **abemaciclib** plus a nonsteroidal aromatase inhibitor **as first-line therapy** for HR+, HER2- **advanced breast cancer**. San Antonio Breast Cancer Symposium 2023;Abstract GS01-12.
- Turner NC et al. **Capivasertib** in hormone receptor-positive **advanced breast cancer**. *N Engl J Med* 2023;388(22):2058-70.
- Howell S et al. **Capivasertib** and **fulvestrant** for patients with **aromatase inhibitor-resistant** HR positive/HER2-negative **advanced breast cancer**: Exploratory analysis of PFS by AKT pathway gene from the Phase 3 **CAPItello-291** trial. San Antonio Breast Cancer Symposium 2023;Abstract PS17-03.
- Lu J et al. **Elacestrant** vs standard-of-care in ER+/HER2- advanced or metastatic breast cancer **(mBC)** with **ESR1 mutation**: Key biomarkers and clinical subgroup analyses from the phase 3 **EMERALD** trial. San Antonio Breast Cancer Symposium 2023;Abstract PS17-02.

Key Data Sets

Erica Mayer, MD, MPH, FASCO (continued)

- Burstein HJ et al. **Testing** for **ESR1** mutations to guide therapy for hormone receptor-positive, human epidermal growth factor receptor 2-negative **metastatic breast cancer: ASCO guideline** Rapid Recommendation Update. *J Clin Oncol* 2023;41(18):3423-5.
- Oliveira M et al. Clinical activity of **camizestrant**, a next-generation SERD, versus **fulvestrant** in patients with a **detectable ESR1 mutation**: Exploratory analysis of the **SERENA-2** phase 2 trial. ASCO 2023;Abstract 1066.
- Jhaveri K et al. **Imlunestrant monotherapy** and in combination with **abemaciclib**, with or without an aromatase inhibitor, in estrogen receptor-positive (ER+), HER2-negative (HER2-) **advanced breast cancer** (aBC): Updated results from the **EMBER** study. San Antonio Breast Cancer Symposium 2023;Abstract PS15-09.
- Tolaney SM et al. **Final overall survival** (OS) analysis from the phase 3 **TROPiCS-02** study of **sacituzumab govitecan** (SG) in patients (pts) with hormone receptor–positive/HER2-negative (HR+/HER2–) metastatic breast cancer **(mBC).** ASCO 2023;Abstract 1003.

Key Data Sets

Erica Mayer, MD, MPH, FASCO (continued)

- Bardia A et al. Randomized phase 3 study of **datopotamab deruxtecan vs chemotherapy** for patients with **previously-treated inoperable or metastatic** hormone receptor-positive, HER2-negative breast cancer: Results from **TROPION-Breast01**. San Antonio Breast Cancer Symposium 2023;Abstract GS02-01.
- Modi S et al. **Trastuzumab deruxtecan (T-DXd)** versus treatment of physician's choice (TPC) in patients (pts) with **HER2-low** unresectable and/or metastatic breast cancer (mBC): **Updated survival** results of the randomized, phase III **DESTINY-Breast04 study.** ESMO 2023;Abstract 376O.
- Modi S et al**. Trastuzumab deruxtecan (T-DXd)** vs treatment of physician's choice (TPC) in patients (pts) with **HER2-low**, hormone receptor-positive (HR+) unresectable and/or metastatic breast cancer (mBC): **Exploratory biomarker analysis** of **DESTINY-Breast04**. ASCO 2023;Abstract 1020.
- Hamilton EP et al. A phase 2 study of **HER3-DXd** in patients (pts) with metastatic breast cancer (MBC). ASCO 2023;Abstract 1004.
- Krop IE et al. **Patritumab deruxtecan (HER3-DXd),** a human epidermal growth factor receptor 3-directed antibody-drug conjugate, in patients with previously treated human epidermal growth factor receptor 3-expressing metastatic breast cancer: A multicenter, Phase I/II trial. *J Clin Oncol* 2023;41(36):5550-60.

Agenda

INTRODUCTION: Endocrinology and Pharmacology of Hormonal Therapy for Breast Cancer

MODULE 1: Current and Emerging Strategies for Localized Hormonal Receptor (HR)-Positive Breast Cancer — Dr Graff

MODULE 2: Advances in the Care of Patients with HR-Positive Metastatic Breast Cancer — Dr Mayer

Agenda

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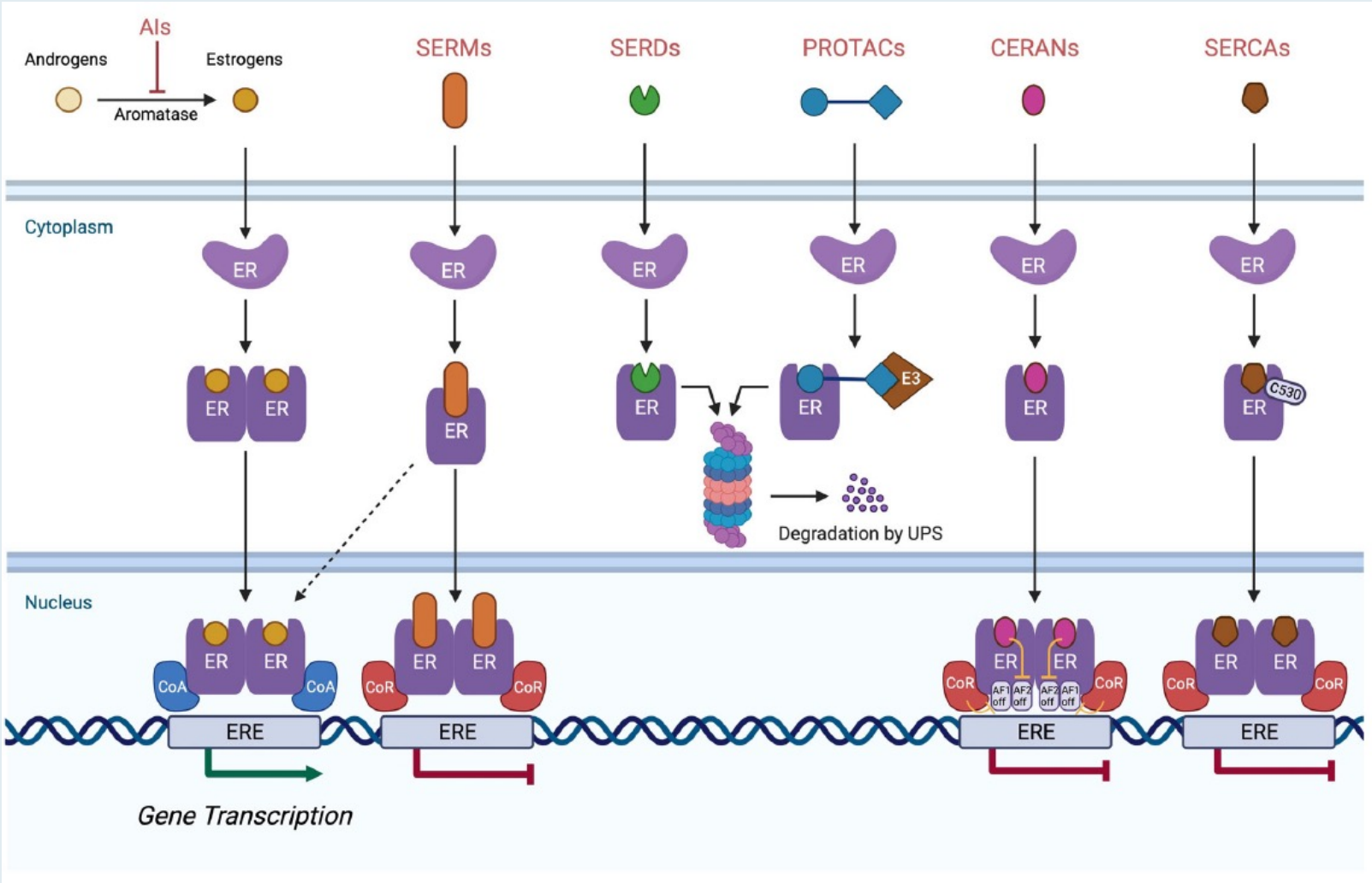
2023: What a year!

- Mirroring the rest of oncology, breast cancer remains an incredibly fast paced field with multiple new agents and evolving data
- New drug approvals and new results continue to modify treatment paradigms
- Toxicity and tolerability are key and may be differentiators
- New findings hopefully result in better and longer outcomes for our patients

Courtesy of Erica Mayer, MD, MPH, FASCO

Mechanisms of Action of Antiestrogen Therapies



AI = aromatase inhibitor; SERM = selective estrogen receptor modulator; SERD = selective estrogen receptor downregulator; PROTAC = proteolysis-targeting chimera; CERAN = complete estrogen receptor antagonist; SERCA = selective estrogen receptor covalent antagonist; ERE = estrogen-responsive element

Patel R et al. *NPJ Breast Cancer* 2023 April 5;9(1):20.

For patients who experience disease progression on a CDK4/6 inhibitor with endocrine therapy for ER-positive metastatic breast cancer, testing is indicated for alterations in which of the following?

1. PIK3CA
2. ESR1
3. AKT/PTEN
4. All of the above
5. PIK3CA and ESR1 only
6. PIK3CA and AKT/PTEN only
7. ESR1 and AKT/PTEN only
8. I’m not sure

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of ER-Positive Metastatic Breast Cancer

Part 1 of a 3-Part CME Satellite Symposium Series in Partnership with the 2023 San Antonio Breast Cancer Symposium®

Tuesday, December 5, 2023

7:15 PM – 9:15 PM CT (8:15 PM – 10:15 PM ET)

Faculty

Francois-Clement Bidard, MD, PhD
Erika Hamilton, MD
Komal Jhaveri, MD, FACP
Virginia Kaklamani, MD, DSc
Hope S Rugo, MD

Moderator

Neil Love, MD

RTP Year in Review 2024

RTP Year in Review 2024

INAVO120: Phase III study of inavolisib (GDC-0077) or placebo in combination with palbociclib and fulvestrant in PIK3CA-mutant, HR+/HER2- MBC: Study Design

Key eligibility criteria

Enrichment of patients with poor prognosis:

- ***PIK3CA*-mutated, HR+, HER2- ABC** by central ctDNA* or local tissue/ctDNA test
- **Measurable disease**
- **Progression during/within 12 months of adjuvant ET completion**

- **No prior therapy for ABC**
- **Fasting glucose <126 mg/dL and HbA_{1C} <6.0%**

Enrolment period: December 2019-September 2023

N=325

R 1:1

Inavolisib (9 mg QD PO) + palbociclib (125 mg PO QD D1-D21) + fulvestrant (500 mg C1D1/15 and Q4W)**

Placebo (PO QD) + palbociclib (125 mg PO QD D1-D21) + fulvestrant (500 mg C1D1/15 and Q4W)**

Until PD or toxicity

SURVIVAL FOLLOW-UP

Stratification factors:

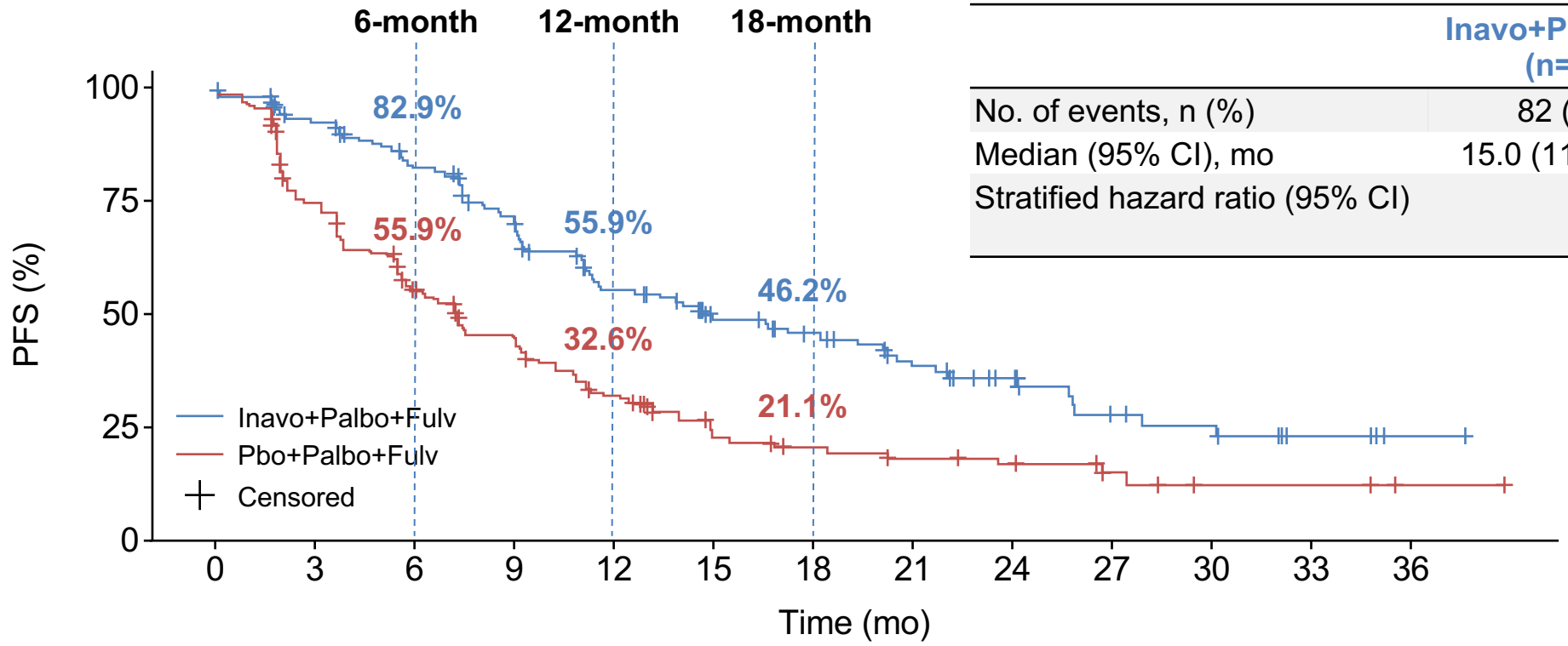
- Visceral Disease (Yes vs. No)
- Endocrine Resistance (Primary vs. Secondary)†
- Region (North America/Western Europe; Asia; Other)

Endpoints

- Primary: PFS by Investigator
- Secondary: OS‡, ORR, BOR, CBR, DOR, PROs

* Central testing for *PIK3CA* mutations was done on ctDNA using FoundationOne®Liquid (Foundation Medicine). In China, the central ctDNA test was the PredicineCARE NGS assay (Huidu). † Defined per 4th European School of Oncology (ESO)–European Society for Medical Oncology (ESMO) International Consensus Guidelines for Advanced Breast Cancer.[1] Primary: relapse while on the first 2 years of adjuvant ET; Secondary: relapse while on adjuvant ET after at least 2 years or relapse within 12 months of completing adjuvant ET. ‡ OS testing only if PFS is positive; interim OS analysis at primary PFS analysis; **Pre-menopausal women received ovarian suppression. ctDNA, circulating tumor DNA; R, randomized. 1. Cardoso F, *et al. Ann Oncol* 2018;**29:**1634–1657.

INAVO120: Primary endpoint: PFS (investigator assessed)



	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
No. of events, n (%)	82 (50.9)	113 (68.9)
Median (95% CI), mo	15.0 (11.3, 20.5)	7.3 (5.6, 9.3)
Stratified hazard ratio (95% CI)	**0.43 (0.32, 0.59) p<0.0001**	

Patients at risk:

Inavo+Palbo+Fulv	161	134	111	92	66	48	41	31	22	13	11	5	1
Pbo+Palbo+Fulv	164	113	77	59	40	23	19	16	12	6	3	3	1

Median follow-up:
21.3 months

CCOD: 29th September 2023

CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; mo, months; Palbo, palbociclib; Pbo, placebo; PFS, progression-free survival.

INAVO120: Adverse events with any grade AEs ≥20% incidence in either treatment group

Adverse Events	Inavo+Palbo+Fulv (N=162)		Pbo+Palbo+Fulv (N=162)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Neutropenia	**144 (88.9%)**	**130 (80.2%)**	**147 (90.7%)**	**127 (78.4%)**
Thrombocytopenia	78 (48.1%)	23 (14.2%)	73 (45.1%)	7 (4.3%)
Stomatitis/Mucosal inflammation	**83 (51.2%)**	**9 (5.6%)**	**43 (26.5%)**	**0**
Anemia	60 (37.0%)	10 (6.2%)	59 (36.4%)	3 (1.9%)
Hyperglycemia	**95 (58.6%)**	**9 (5.6%)**	**14 (8.6%)**	**0**
Diarrhea	**78 (48.1%)**	**6 (3.7%)**	**26 (16.0%)**	**0**
Nausea	**45 (27.8%)**	**1 (0.6%)**	**27 (16.7%)**	**0**
Rash	**41 (25.3%)**	**0**	**28 (17.3%)**	**0**
Decreased Appetite	38 (23.5%)	<2%	14 (8.6%)	<2%
Fatigue	38 (23.5%)	<2%	21 (13.0%)	<2%
COVID-19	37 (22.8%)	<2%	17 (10.5%)	<2%
Headache	34 (21.0%)	<2%	22 (13.6%)	<2%
Leukopenia	28 (17.3%)	11 (6.8%)	40 (24.7%)	17 (10.5%)
Ocular Toxicities	36 (22.2%)	0	21 (13.0%)	0

Key AEs are shown in **bold.** AES were assessed per CTCAE V5**.** Neutropenia, thromb ash were assessed as medical concepts using grouped terms

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Fulv, fulvestrant; Inavo, inavolisib; Palbo, palbociclib; Pbo, placebo.

No toxicity prophylaxis used in this trial

INAVO120: Inavolisib

- Reassuring to see improved outcomes in a very high-risk cohort of patients with HR+ MBC.
- Supports need to know PIK3CA mutation status from time of diagnosis of MBC, in 1L setting.
- Palbociclib remains a CDK4/6i option for MBC; may be best tolerated of the agents and easiest to combine in a triplet.
- Population had low BMI and was not diverse; toxicity profile including hyperglycemia and mucositis, may be different in a more “real world” group of patients.
- Next generation mutant specific PIK3CA inhibitors may offer efficacy with minimal hyperglycemia

Courtesy of Erica Mayer, MD, MPH, FASCO

Agenda

INTRODUCTION: Endocrinology and Pharmacology of Hormonal Therapy for Breast Cancer

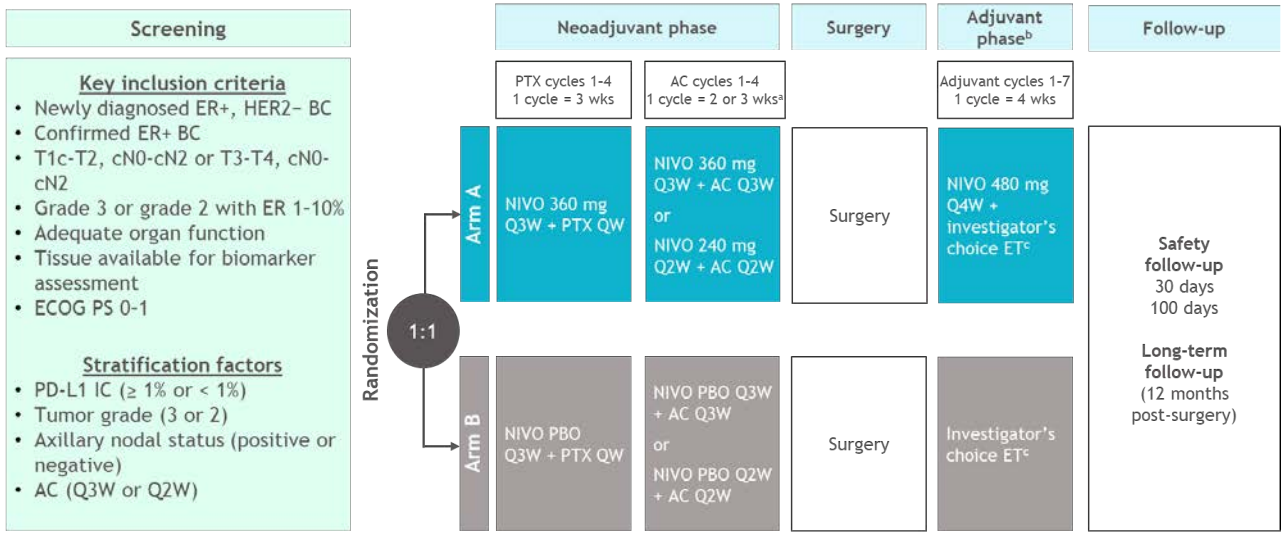
MODULE 1: Current and Emerging Strategies for Localized Hormonal Receptor (HR)-Positive Breast Cancer — Dr Graff

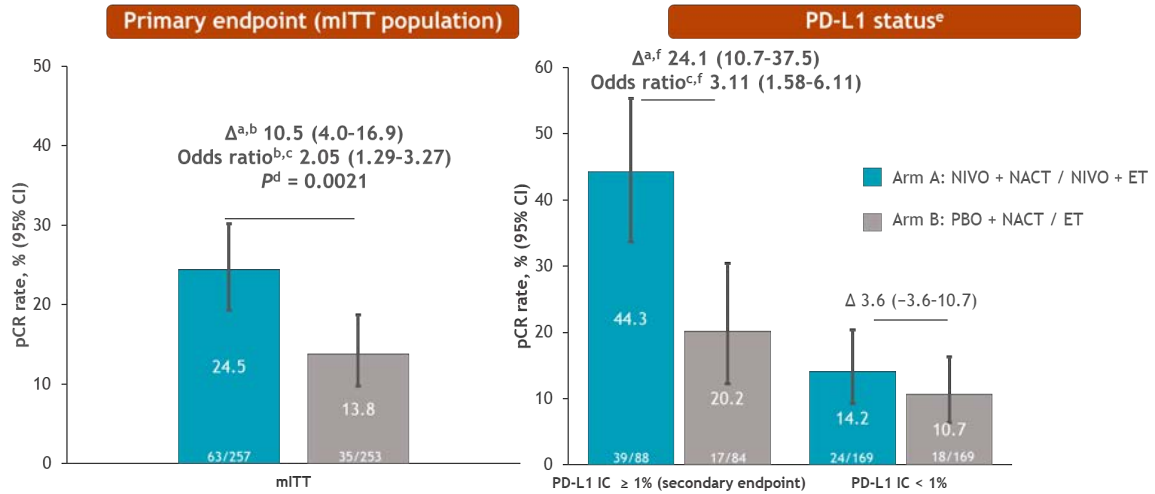
MODULE 2: Advances in the Care of Patients with HR-Positive Metastatic Breast Cancer — Dr Mayer

Neoadjuvant Immunotherapy

- Loi S et al. A randomized, double-blind trial of **nivolumab (NIVO)** vs placebo (PBO) with **neoadjuvant chemotherapy** (NACT) followed by **adjuvant endocrine therapy (ET) ± NIVO** in patients (pts) with **high-risk**, ER+ HER2– **primary breast cancer** (BC). ESMO 2023;Abstract LBA20.
- Cardoso F et al. **KEYNOTE-756**: **Phase III** study of **neoadjuvant pembrolizumab** (pembro) or placebo (pbo) + **chemotherapy** (chemo), followed by **adjuvant pembro** or pbo + **endocrine therapy** (ET) for **early-stage high-risk** ER+/HER2– breast cancer. ESMO 2023;Abstract LBA21.

CheckMate 7FL: A randomized, double-blind trial of nivolumab vs placebo with neoadjuvant chemotherapy followed by adjuvant endocrine therapy ± NIVO in patients with high-risk, ER+ HER2– primary breast cancer



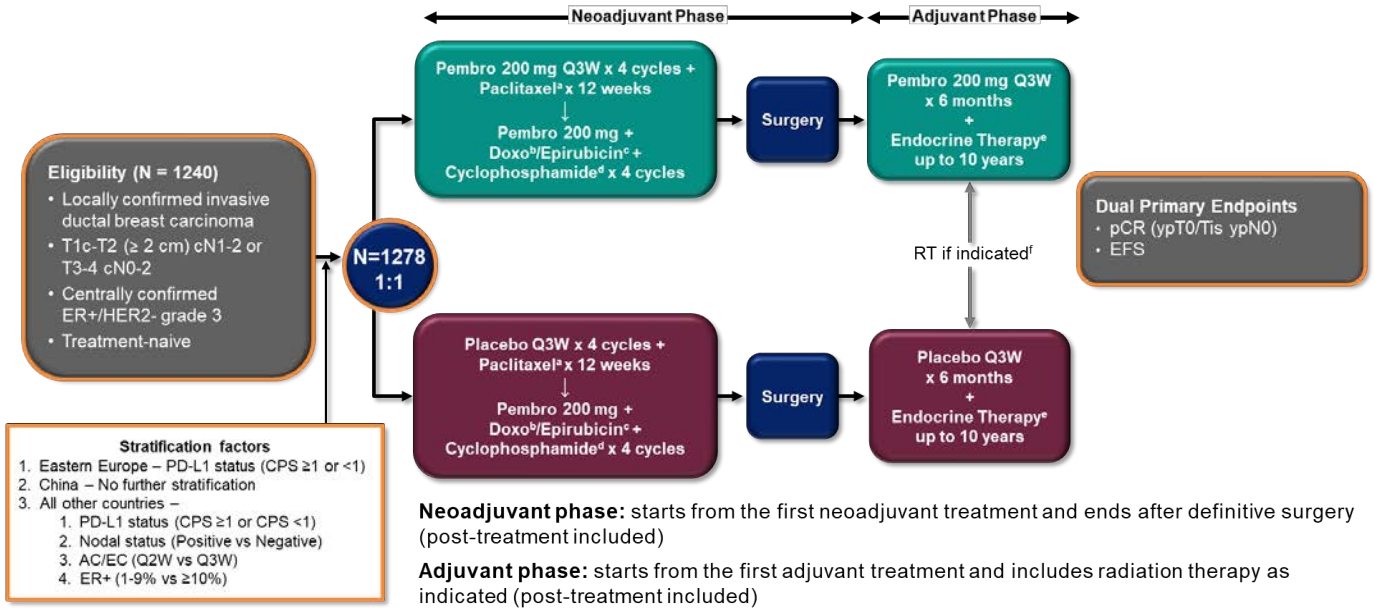


- Study population: median age 50, 98% G3, ~45% Stage III, AC dosing 50/50 Q3 vs DD
- The addition of NIVO to NACT/ET increased pCR by **10.5%** (24.5% in arm A and 13.8% in arm B)
- The benefit from NIVO was more pronounced in patients with **PD-L1 IC ≥ 1% (SP142)**
  - Δ pCR of **24.1%** (44.3% in arm A and 20.2% in arm B)
  - Δ RCB 0-1 of **28.5%** (54.5% in arm A and 26.2% in arm B)

Courtesy of Stephanie L Graff, MD, FACP

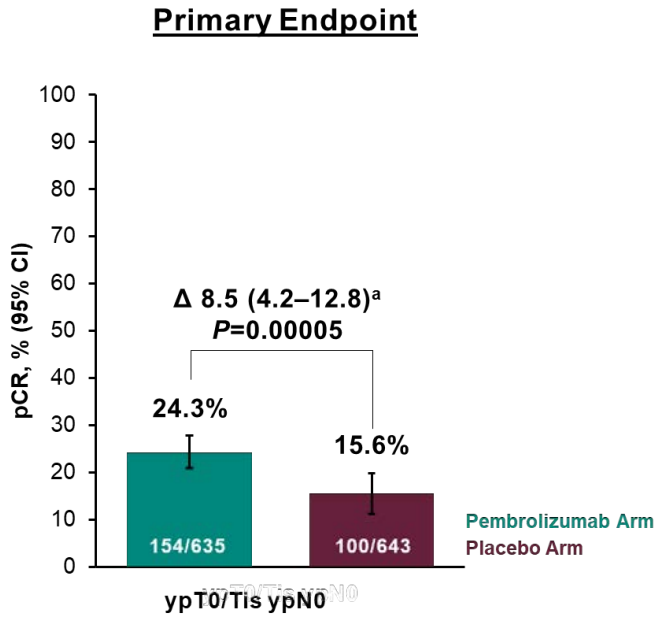
Loi S et al. A randomized, double-blind trial of nivolumab (NIVO) vs placebo (PBO) with neoadjuvant chemotherapy (NACT) followed by adjuvant endocrine therapy (ET) ± NIVO in patients (pts) with high-risk, ER+ HER2− primary breast cancer (BC). ESMO 2023;Abstract LBA20.

KEYNOTE-756: Phase 3 Study of Neoadjuvant Pembrolizumab or Placebo + Chemotherapy Followed by Adjuvant Pembrolizumab or Placebo + Endocrine Therapy for Early-Stage High-Risk ER+/HER2– Breast Cancer



Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post-treatment included)

Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post-treatment included)



- Study population: median age 49, 100% G3, 90% node positive, 35% T3/T4, AC dosing ~65 Q3 weeks
- The addition of PEMBRO to NACT/ET increased pCR by **8.5%**
- Presenter's conclusion: Pembro benefit was “regardless of PD-L1 status”; but magnitude of benefit smaller in PD-L1 negative population (Δ 4.5% vs 9.8%)
- Rate of Grade 3-5 TRAE Δ 6.1%, and serious TRAE Δ 8.2% in pembro arm
- **Will await Event Free Survival before KEYNOTE-756 informs practice**

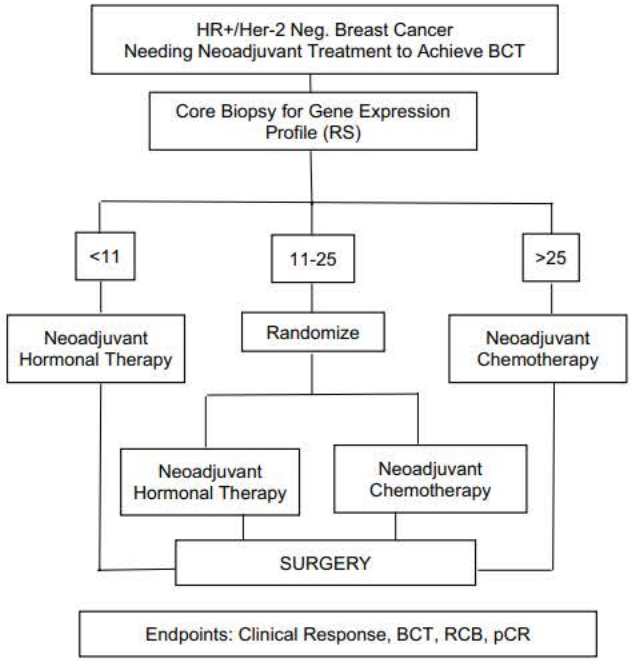
Courtesy of Stephanie L Graff, MD, FACP

Cardoso F et al. KEYNOTE-756: Phase III study of neoadjuvant pembrolizumab (pembro) or placebo (pbo) + chemotherapy (chemo), followed by adjuvant pembro or pbo + endocrine therapy (ET) for early-stage high-risk ER+/HER2– breast cancer. ESMO 2023;Abstract LBA21.

Use of Onco*type* DX® to Define the Role of Neoadjuvant Therapy

- Taylor C et al. Using Onco*type* DX breast Recurrence Score® assay to define the **role of neoadjuvant endocrine therapy** in **early-stage** hormone receptor-positive breast cancer. *Breast Cancer Res Treat* 2023;199(1):91-8.
- Trapani D et al. Identifying **patterns** and **barriers** in **Onco*type* DX** Recurrence Score testing in **older patients with early-stage**, estrogen receptor-positive breast cancer: Implications for guidance and reimbursement. *JCO Oncol Pract* 2023;19(8):560-70.

Using Onco*type* DX breast Recurrence Score® assay to define the role of neoadjuvant endocrine therapy in early-stage hormone receptor-positive breast cancer



Variable	Group A ($N=21$)	Group B ($N=23$)	Group C ($N=22$)	Group D ($N=37$)	P value (a)
pCR Breast	1 (4.8%)	0 (0.0%)	0 (0.0%)	8 (21.6%)	0.0059
pCR Nodes	0 (0.0%)	1 (4.3%)	3 (13.6%)	2 (5.6%)	0.2977
pCR Breast + Nodes	1 (4.8%)	0 (0.0%)	0 (0.0%)	7 (18.9%)	0.0143

(a) Fisher's exact test was used for categorical variables with cell counts < 5

Group A = Recurrence Score < 11, Group B = Recurrence Score 11–24 (Emory) or 11–25 (VCU) receiving NET, Group C = Recurrence Score 11–24 (Emory) or 11–25 (VCU) receiving NCT, and Group D = Recurrence Score > 24 (Emory) or > 25 (VCU)

- Further supports TAILORx and RxPONDER
- Two cohorts received significantly different lengths of neoadjuvant endocrine therapy (median 10 months versus 5.5), with no significant differences in pCR across RS result groups between the two institutions

Courtesy of Stephanie L Graff, MD, FACP

Taylor C et al. Using Oncotype DX breast Recurrence Score® assay to define the role of neoadjuvant endocrine therapy in early-stage hormone receptor-positive breast cancer. Breast Cancer Res Treat 2023;199(1):91-8.

Identifying Patterns & Barriers in Oncotype DX Recurrence Score Testing in Older Patients With Early-Stage, Estrogen Receptor–Positive Breast Cancer: Implications for Guidance, Reimbursement, Trapani JCO-OP

TABLE A1. Updated Consensus Statements for Surgeon-Triggered OncotypeDX Reflex Testing

Reflex Testing Criteria	
2019-2021	2022-2024
Age ≤65 years, AND pT1c G2-3 pN0 tumors grade II-III pT2 pN0 tumors of any grade pT1-T2 pN1 tumors of any grade pT3 pN0-N1 tumors any grade Pre- and postmenopausal status	Patient's age ≤65 years, AND pT1c-T3, G1-3, pN0-1 tumors Pre- and postmenopausal status
Additional settings to consider RS testing	
Per physician's choice	Recurrent scenarios Patients aged 66-72 years pT1b pN0 G2-3 Per physician's choice

- Authors created cohort of patients >65 years who did not have RS testing for comparison
  - Were older (median age 73 v 69 years)
  - More likely G1 tumors (43.9% v 15.1%)
  - More likely to have not undergone SLNB/ALND (48% v 9.3%)

Courtesy of Stephanie L Graff, MD

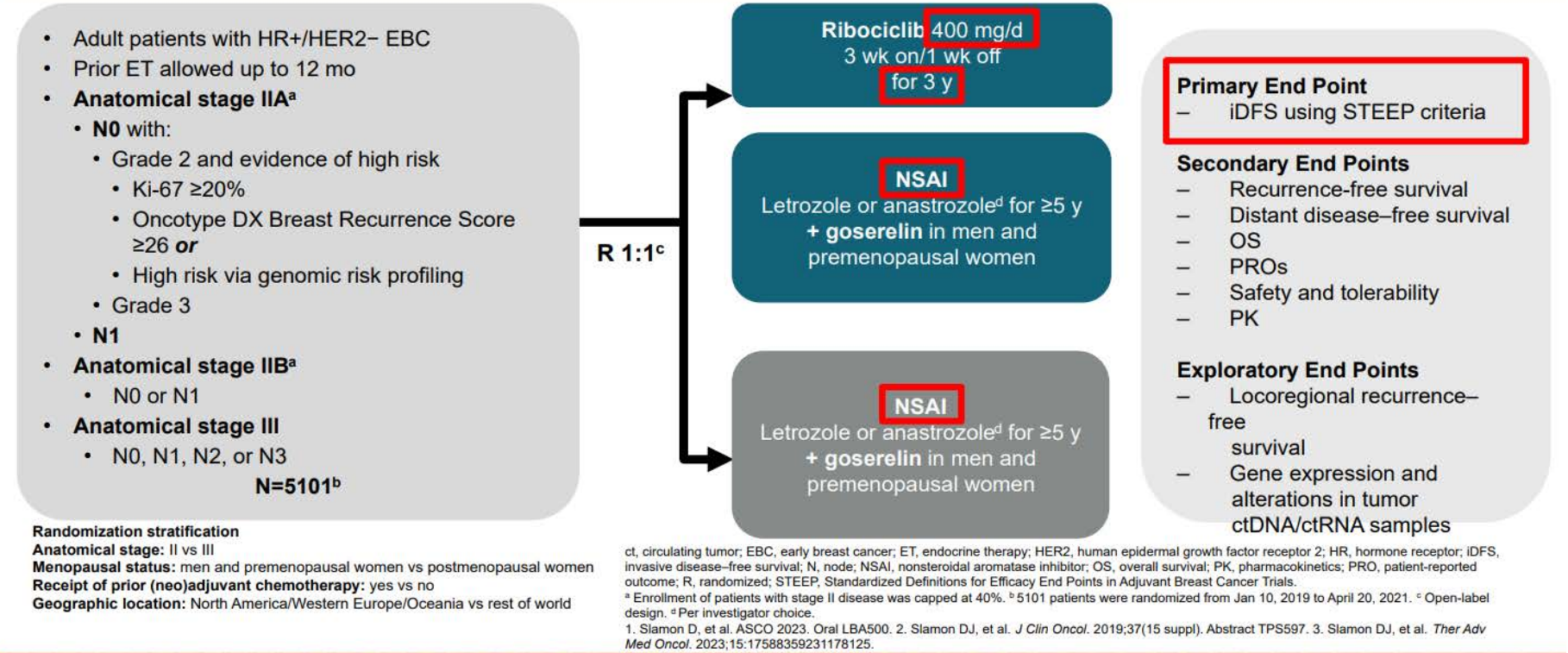
	Cohort A (Reflex) n=1087 (64.4%)	Cohort B (Case-by-Case) n=600 (35.6%)	Cohort B + Age>65 n=279 (46.5% of Cohort B)
RS Range	0-74 (median 16)	0-62 (median 17)	NR
Low	205 (18.9%)	130 (21.7%)	70 (25.1%)
Intermediate	711 (67.5%)	357 (59.7%)	156 (55.9%)
High	167 (15.4%)	111 (18.6%)	52 (18.6%)
Received Chemotherapy	20.5%	21.8%	15.4%

Trapani D et al. Identifying patterns and barriers in OncotypeDX Recurrence Score testing in older patients with early-stage, estrogen receptor-positive breast cancer: Implications for guidance and reimbursement. JCO Oncol Pract 2023;19(8):560-70.

Adjuvant CDK4/6 Inhibition

- Hortobagyi G et al. **Ribociclib (RIB) + nonsteroidal aromatase inhibitor** (NSAI) as **adjuvant** treatment in patients with HR+/HER2− **early breast cancer**: **Final invasive disease–free survival** (iDFS) analysis from the **NATALEE** trial. San Antonio Breast Cancer Symposium 2023;Abstract GS03-03.
- Johnston SRD et al. **Abemaciclib** plus **endocrine therapy** for hormone receptor-positive, HER2-negative, node-positive, **high-risk early breast cancer (monarchE):** Results from a preplanned interim analysis of a randomised, open-label, phase 3 trial. *Lancet Oncol* 2023;24(1):77-90.
- Harbeck N et al. **Adjuvant abemaciclib** plus **endocrine therapy** for HR+, HER2-, **high-risk early breast cancer**: Results from a preplanned **monarchE overall survival interim analysis**, including 5-year efficacy outcomes. ESMO 2023;Abstract LBA17.
- Robertson J et al. **SERENA-3**: A randomized pre-surgical window of opportunity study assessing dose and duration of **camizestrant** treatment in **post-menopausal** women with ER-positive, HER2-negative **primary breast cancer**. San Antonio Breast Cancer Symposium 2023;Abstract RF01-01.

Ribociclib + Nonsteroidal Aromatase Inhibitor as Adjuvant Treatment in Patients With HR+/HER2− Early Breast Cancer: Final Invasive Disease–Free Survival Analysis From the NATALEE Trial



ct, circulating tumor; EBC, early breast cancer; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; iDFS, invasive disease–free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PK, pharmacokinetics; PRO, patient-reported outcome; R, randomized; STEEP, Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials.
[a] Enrollment of patients with stage II disease was capped at 40%. [b] 5101 patients were randomized from Jan 10, 2019 to April 20, 2021. [c] Open-label design. [d] Per investigator choice.
1. Slamon D, et al. ASCO 2023. Oral LBA500. 2. Slamon DJ, et al. *J Clin Oncol*. 2019;37(15 suppl). Abstract TPS597. 3. Slamon DJ, et al. *Ther Adv Med Oncol*. 2023;15:17588359231178125.

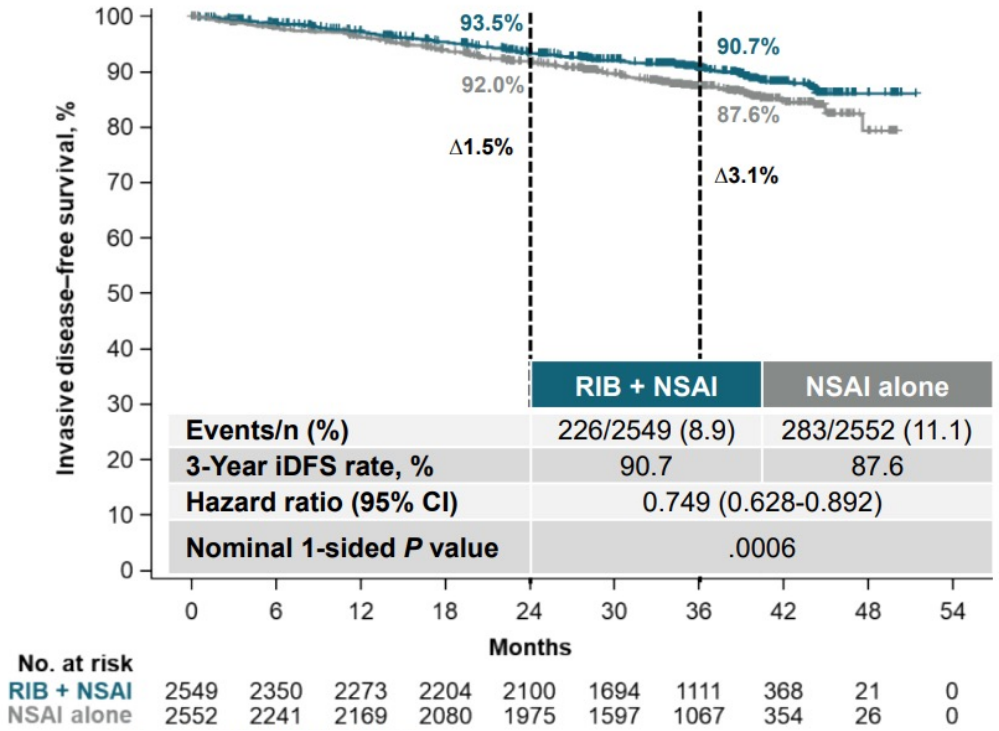
- Second IE Analysis 1/11/23 = 426 iDFS events, 54% stopped Ribo including 20% completing 3 years and 33% stopping early vs Final IDFS Analysis 7/21/23 = 509 iDFS events, 78.3% stopped Ribo including 42.8% completing 3 years and 35.5% stopping early
- Median follow-up for IDFS was 33.3 mos (max 51 mos)—5.6 mos more than second IE analysis

Courtesy of Stephanie L Graff, MD, FACP

Hortobagyi G et al. Ribociclib (RIB) + nonsteroidal aromatase inhibitor (NSAI) as adjuvant treatment in patients with HR+/HER2− early breast cancer: Final invasive disease–free survival (iDFS) analysis from the NATALEE trial. San Antonio Breast Cancer Symposium 2023;Abstract GS03-03.

Ribociclib + Nonsteroidal Aromatase Inhibitor as Adjuvant Treatment in Patients With HR+/HER2− Early Breast Cancer: Final Invasive Disease–Free Survival Analysis From the NATALEE Trial

Invasive Disease-Free Survival



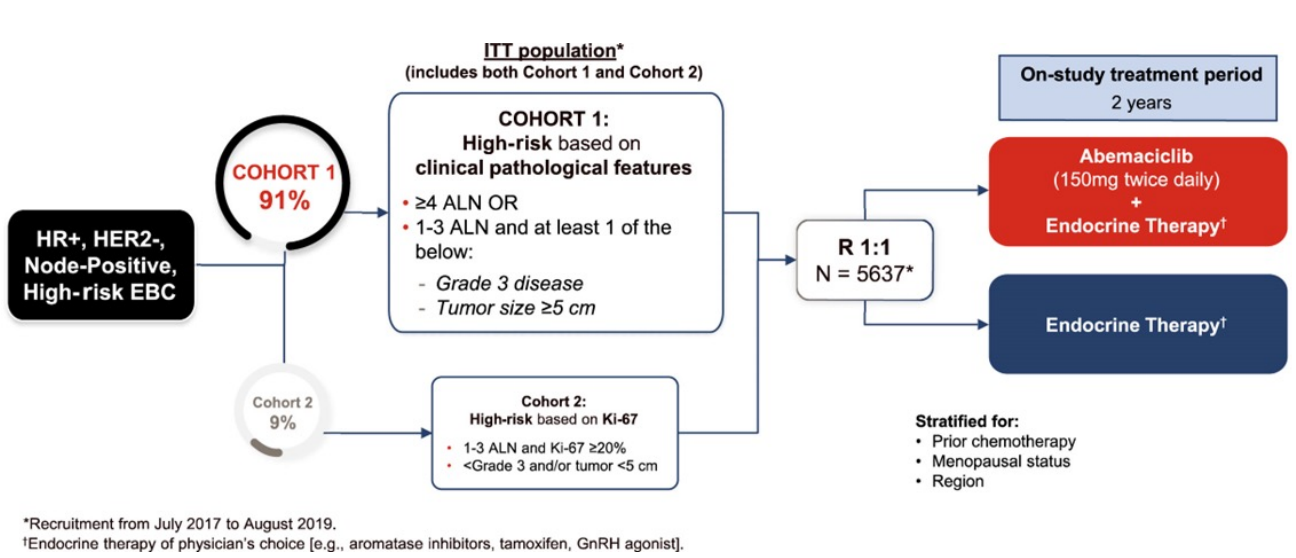
	RIBO + NSAI	NSAI Alone
STAGE II		
Events/n (%)	55/1011 (5.44)	80/1034 (7.74)
3-year IDFS rate, %	94.2	92.6
Hazard ratio (95% CI)	0.700 (0.496-0.986)	
STAGE III		
Events/n (%)	170/1528 (11.1)	203/1512 (13.4)
3-year IDFS rate, %	88.1	83.8
Hazard ratio (95% CI)	0.755 (0.616-0.926)	
N0		
Events/n (%)	20/285 (7.0)	31/328 (9.5)
3-year IDFS rate, %	93.2	90.6
Hazard ratio (95% CI)	0.723 (0.412-1.268)	
N1- N3		
Events/n (%)	206/2261 (9.1)	251/2219 (11.3)
3-year IDFS rate, %	90.3	87.1
Hazard ratio (95% CI)	0.759 (0.631-0.912)	

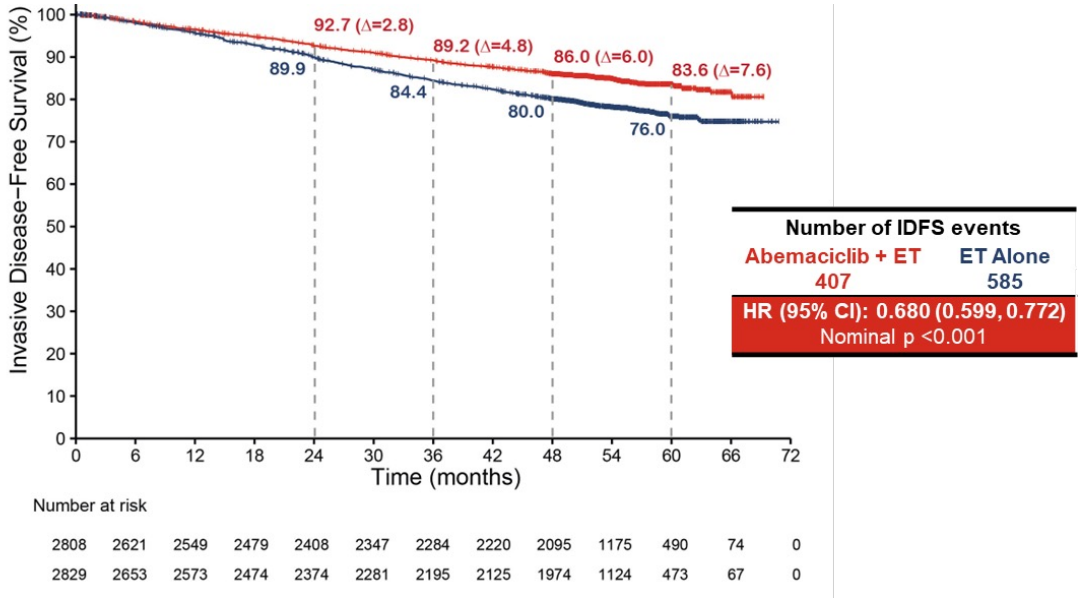
- Absolute iDFS benefit with Ribo plus NSAI was 3.1% at 3 years, a 25.1% relative risk reduction
- iDFS benefit consistent across prespecified subgroups, including patients with stage II, III, node-negative, and node-positive disease

Courtesy of Stephanie L Graff, MD, FACP

Hortobagyi G et al. Ribociclib (RIB) + nonsteroidal aromatase inhibitor (NSAI) as adjuvant treatment in patients with HR+/HER2− early breast cancer: Final invasive disease–free survival (iDFS) analysis from the NATALEE trial. San Antonio Breast Cancer Symposium 2023;Abstract GS03-03.

Adjuvant abemaciclib plus endocrine therapy for HR+, HER2-, high-risk early breast cancer: results from a preplanned monarchE overall survival interim analysis, including 5-year efficacy outcomes



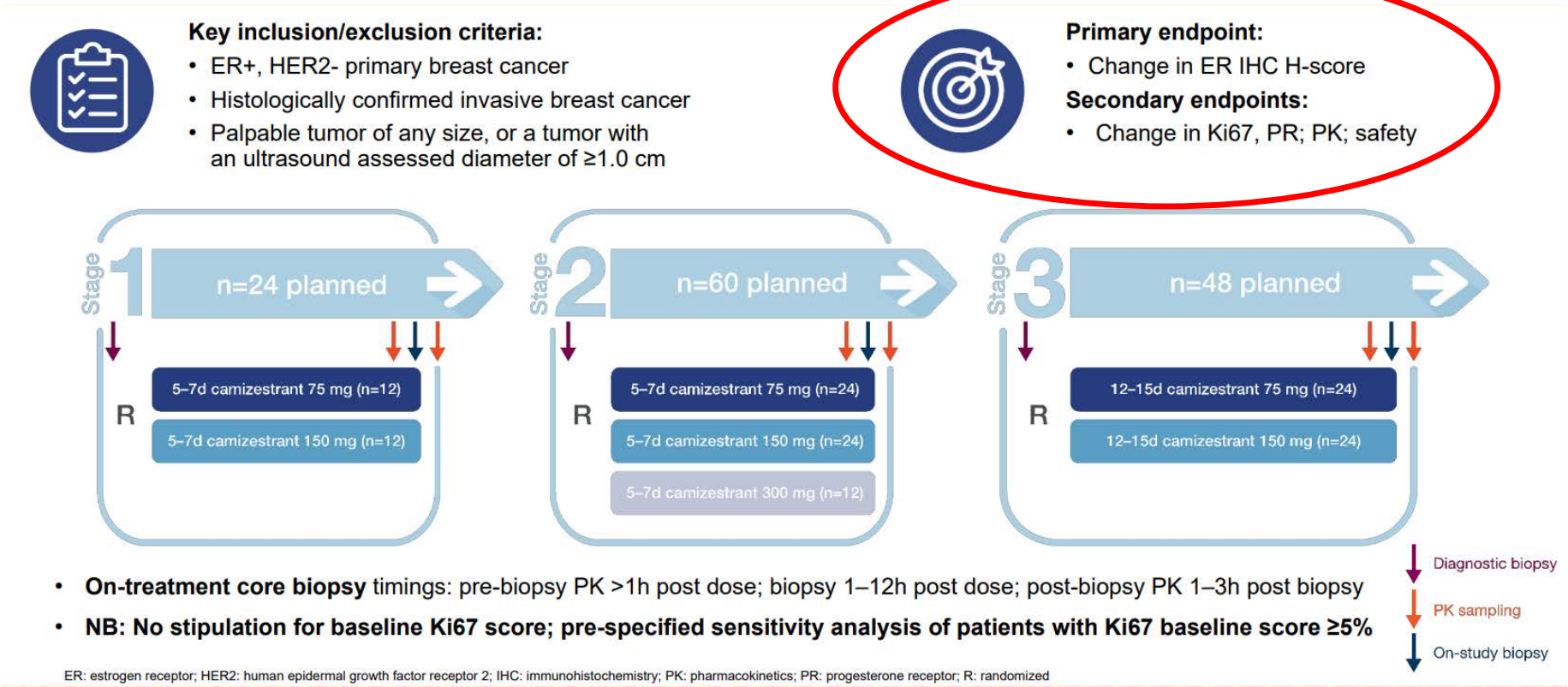


- Overall Survival Interim Analysis 3 (OS IA3) 7/3/2023= Median follow up 4.5 years (54 mos); all patients completed abemaciclib, with 80% followed 2 years since completion
- 32% risk reduction in IDFS, absolute difference of 7.6% at 5 years
  - 48 mos (Lancet, Jan 2023): 4-year IDFS rate abema + ET 85.8% (95% CI 84.2–87.3) vs. ET alone 79.4% (77.5–81.1), absolute Δ 6.4%
- 32.5% risk reduction in DRFS, absolute difference of 6.7% at 5 years *(not shown)*

Courtesy of Stephanie L Graff, MD, FACP

Johnston SRD et al. Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): Results from a preplanned interim analysis of a randomised, open-label, phase 3 trial. Lancet Oncol 2023;24(1):77-90.
Harbeck N et al. Adjuvant abemaciclib plus endocrine therapy for HR+, HER2-, high-risk early breast cancer: Results from a preplanned monarchE overall survival interim analysis, including 5-year efficacy outcomes. ESMO 2023;Abstract LBA17.

SERENA-3: A randomized pre-surgical window of opportunity study assessing dose and duration of camizestrant treatment in post-menopausal women with ER-positive, HER2-negative primary breast cancer



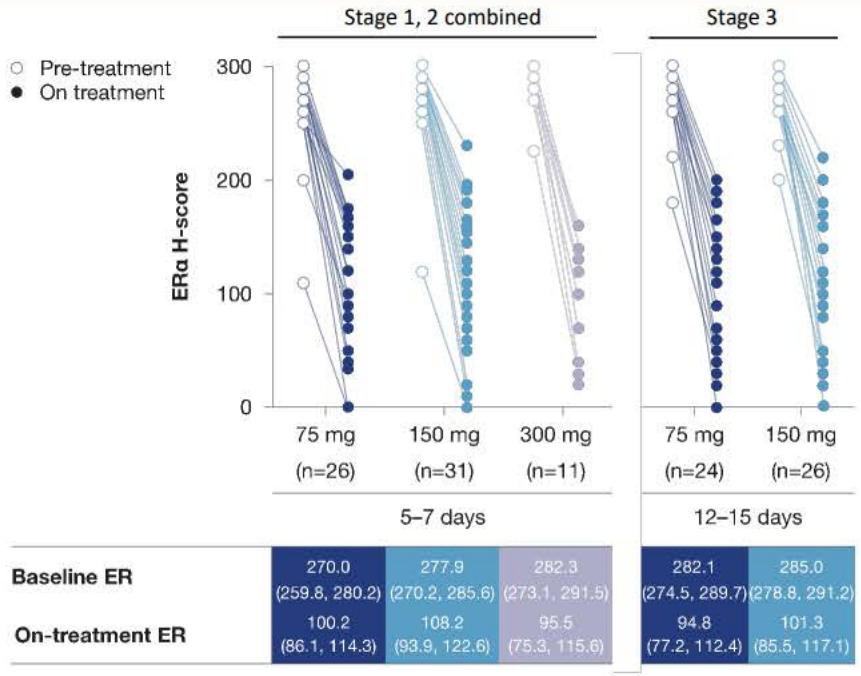
Enrolled

- 92.6% Ductal
- Stage I (34.8%) or Stage II (57.8%)
- Mostly G2 (66.7%)
- N0 (69.6%) or N1 (26.7%)

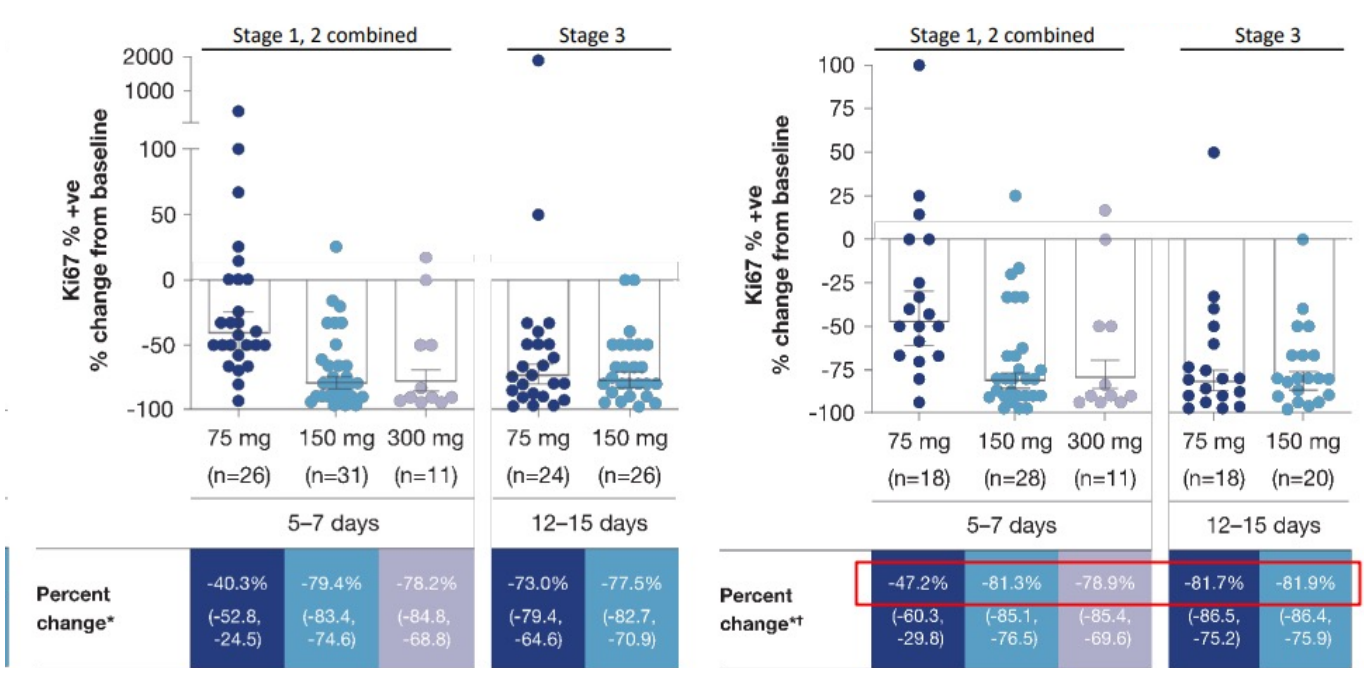
Courtesy of Stephanie L Graff, MD, FACP

Robertson J et al. SERENA-3: A randomized pre-surgical window of opportunity study assessing dose and duration of camizestrant treatment in post-menopausal women with ER-positive, HER2-negative primary breast cancer. San Antonio Breast Cancer Symposium 2023;Abstract RF01-01.

SERENA-3: A randomized pre-surgical window of opportunity study assessing dose and duration of camizestrant treatment in post-menopausal women with ER-positive, HER2-negative primary breast cancer



Camizestrant effectively degrades ERα on treatment across stages, treatment doses & duration of exposure



After 5-7 days of exposure, ki-67 is reduced; more effectively at 150 and 300 mg than at 75 mg. After 12-15 days of exposure, ki-67 reduced ~82% for both 75 and 150 mg doses

Courtesy of Stephanie L Graff, MD, FACP

Robertson J et al. SERENA-3: A randomized pre-surgical window of opportunity study assessing dose and duration of camizestrant treatment in post-menopausal women with ER-positive, HER2-negative primary breast cancer. San Antonio Breast Cancer Symposium 2023;Abstract RF01-01.

Agenda

INTRODUCTION: Endocrinology and Pharmacology of Hormonal Therapy for Breast Cancer

MODULE 1: Current and Emerging Strategies for Localized Hormonal Receptor (HR)-Positive Breast Cancer — Dr Graff

MODULE 2: Advances in the Care of Patients with HR-Positive Metastatic Breast Cancer — Dr Mayer

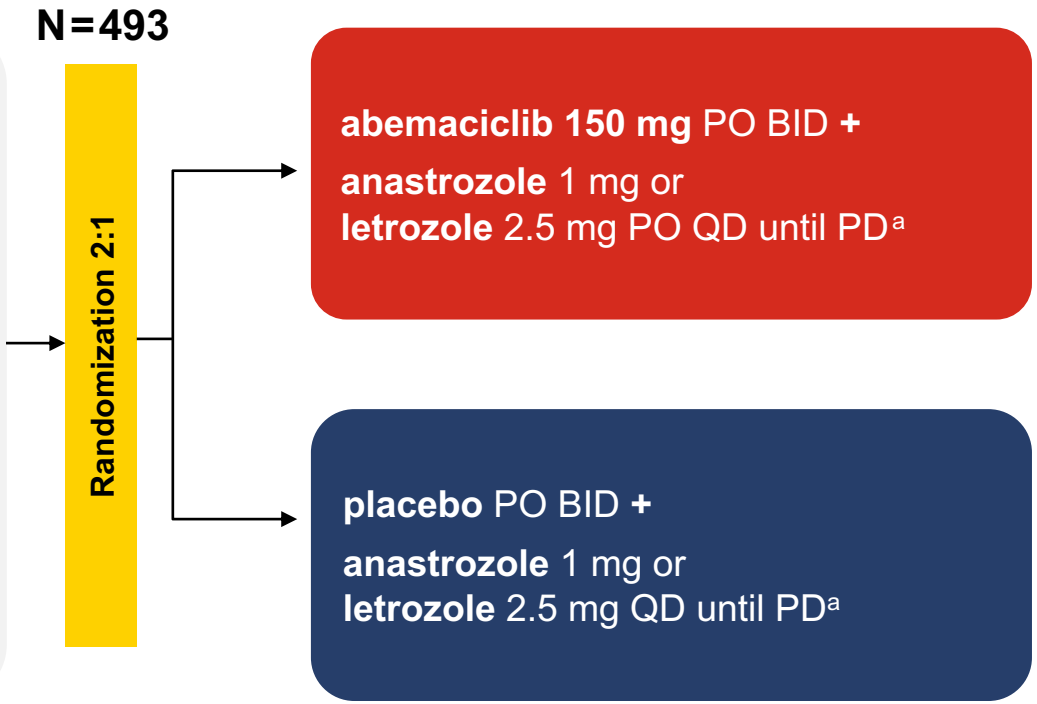
Choice of First-Line CDK4/6 Inhibitor

- Goetz M et al. **MONARCH 3: Final overall survival** results of **abemaciclib** plus a nonsteroidal aromatase inhibitor **as first-line therapy** for HR+, HER2- **advanced breast cancer**. San Antonio Breast Cancer Symposium 2023;Abstract GS01-12.

MONARCH 3 Study Design

Eligibility Criteria:

- HR+, HER2- ABC
- Postmenopausal
- Metastatic or locoregionally recurrent disease with no prior systemic therapy in this setting
- If (neo)adjuvant ET administered, a disease-free interval of >12 months since completion of ET
- ECOG PS ≤1



Primary Endpoint[5]
Investigator-assessed PFS

Key Secondary Endpoints
Overall survival, response rates, safety

Exploratory Endpoint
Chemotherapy-free survival

Stratification Factors

- Metastatic site (visceral, bone only, or other)
- Prior ET (AI, no ET, or other)

MONARCH 3 enrolled from November 2014 to November 2015 in 158 centers from 22 countries

[a]per physician's choice: 79.1% received letrozole, 19.9% received anastrozole
[5]Goetz MP, et al. *J Clin Oncol.* 2017;35(32):3638-3646

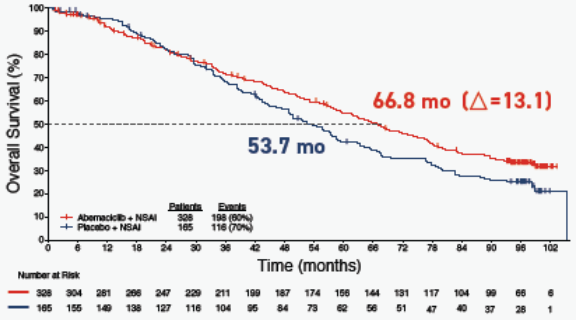
Courtesy of Erica Mayer, MD, MPH, FASCO

MONARCH 3 Final OS results of abemaciclib plus AI as first-line therapy for HR+, HER2- advanced breast cancer

OS in the ITT Population

	Abemaciclib + NSAI	Placebo + NSAI
Median OS (months)	66.8	53.7
Hazard ratio (95% CI)	0.804 (0.637-1.015)	
2-sided *P* value	p=0.0664*	

*P-value did not reach threshold (0.034) for statistical significance at this final analysis



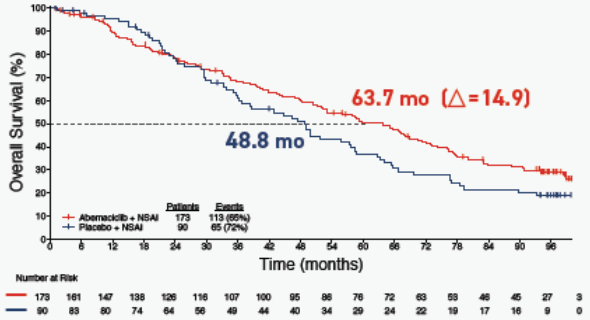
Abemaciclib + NSAI resulted in a numerically longer OS vs. NSAI alone, however statistical significance was not reached

The observed difference in median OS was 13.1 months

OS in the Subgroup with Visceral Disease

	Abemaciclib + NSAI	Placebo + NSAI
Median OS (months)	63.7	48.8
Hazard ratio (95% CI)	0.758 (0.558-1.030)	
2-sided *P* value	p=0.0757*	

*P-value did not reach threshold (0.009) for statistical significance at this final analysis



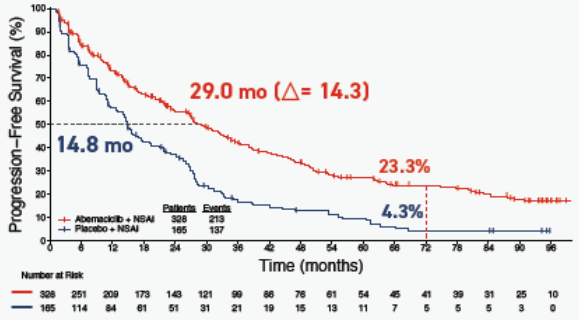
Abemaciclib + NSAI resulted in a numerically longer OS vs. NSAI alone in the subgroup with visceral disease, however statistical significance was not reached

The observed difference in median OS was 14.9 months

Updated PFS in the ITT Population

	Abemaciclib + NSAI	Placebo + NSAI
Median PFS (months)	29.0	14.8
Hazard ratio (95% CI)	0.535 (0.429-0.668)	
2-sided *P* value	nominal p=<0.0001*	

*Statistical significance was reached at the interim PFS analysis



Continued separation of curves at this longer follow-up

The observed improvement in median PFS was 14.3 months

Courtesy of Erica Mayer, MD, MPH, FASCO

Overall Survival in Patients Treated with CDK4/6i for Metastatic Disease

		Treatment Arm: OS, Median, Mo	Placebo Arm: OS, Median, Mo	Hazard Ratio	Hazard Ratio (95% CI)	*P* Value	Significance reached vs placebo[a]
PAL	PALOMA-2[1] Palbociclib + letrozole	53.9	51.2		0.956 (0.777-1.177)	0.3378	✗
PAL	PALOMA-3[2] Palbociclib + fulvestrant	34.9	28.0		0.81 (0.64-1.03)	.09	✗
ABE	MONARCH 2[3] Abemaciclib + fulvestrant	46.7	37.3		0.76 (0.61-0.95)	.01	✓
ABE	MONARCH 3 Abemaciclib + NSAI	66.8	53.7		0.804 (0.637-1.015)	.0664	✗
RIBO	MONALEESA-2[4,5] Ribociclib + letrozole	63.9	51.4		0.76 (0.63-0.93)	.004	✓
RIBO	MONALEESA-7[6] Ribociclib + goserelin + tamoxifen/NSAI	NR	40.9		0.71 (0.54-0.95)	.00973	✓
RIBO	MONALEESA-3[7] Ribociclib + fulvestrant	NR	40.0		0.72 (0.57-0.92)	.00455	✓

PARSIFAL-LONG: mOS 65 months

[a] The red × denotes trials that did not report significant median OS compared with placebo. ABC, advanced breast cancer; ABE, abemaciclib; NR, not reached; NSAI, non-steroidal aromatase inhibitor; OS, overall survival; RIBO, ribociclib; PAL, palbociclib.

1. Finn RS, et al. J Clin Oncol. 2022; 40 (suppl 17; abstr LBA1003). 2. Turner NC, et al. *N Engl J Med*. 2018;379:1926-1936. 3. Sledge GW, et al. *JAMA Oncol*. 2020;6:116-124. 4. Hortobagyi GN, et al. *N Engl J Med*. 2022;386:942-950. 5. Hortobagyi GN, et al. ESMO 2021. Oral LBA17_PR. 6. Im SA, et al. *N Engl J Med*. 2019;381:307-316. 7. Slamon DJ, et al. *N Engl J Med*. 2020;382:514-524.

Courtesy of Erica Mayer, MD, MPH, FASCO

MONARCH 3 OS

- Smaller trial than other 1L CDK4/6i trials: 2:1 randomization and split alpha create statistical challenges versus the other larger trials
- OS benefits are somewhat washed out with subsequent therapies
- 1 in 5 patients without progression at 8 years
- PARSIFAL-LONG – 65-month median OS for palbociclib, may revive interest in the agent
- For now, tend to select ribociclib, but abemaciclib is a reasonable alternative, especially if ribociclib not feasible

Courtesy of Erica Mayer, MD, MPH, FASCO

Capivasertib

- Turner NC et al. **Capivasertib** in hormone receptor-positive **advanced breast cancer**. *N Engl J Med* 2023;388(22):2058-70.
- Howell S et al. **Capivasertib** and **fulvestrant** for patients with **aromatase inhibitor-resistant** HR positive/HER2-negative **advanced breast cancer**: Exploratory analysis of PFS by AKT pathway gene from the Phase 3 **CAPItello-291** trial. San Antonio Breast Cancer Symposium 2023;Abstract PS17-03.

CAPItello-291: Study overview

Phase III, randomized, double-blind, placebo-controlled study (NCT04305496)

Patients with HR+/HER2– ABC

- Men and pre-/post-menopausal women
- Recurrence or progression 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 sample from the primary/recurrent cancer available for retrospective central molecular testing

R1:1 (N=708)

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

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

Dual primary endpoints

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

Key secondary endpoints

Overall survival
- Overall
- AKT pathway–altered s

Objective response rate
- Overall
- AKT pathway–altered s

.

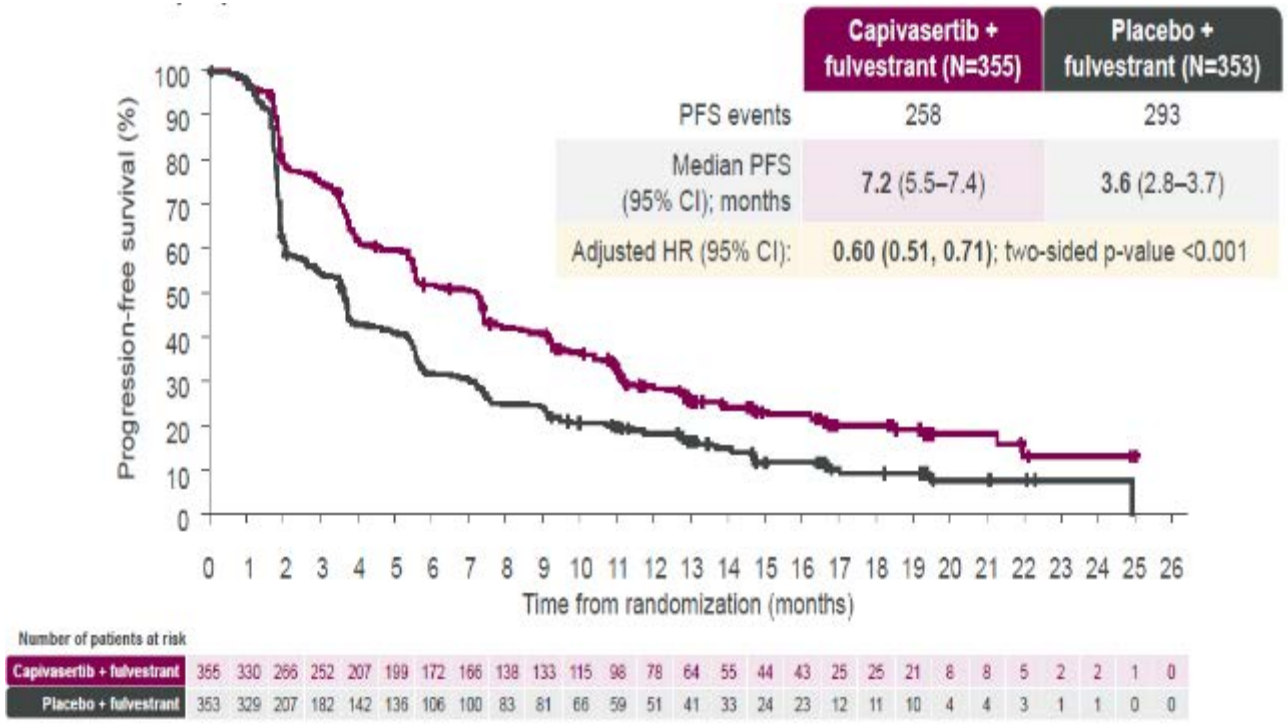
HER2– was defined as IHC 0 or 1+, or IHC 2+/ISH–. *Region 1: United States, Canada, Western Europe, Australia, and Israel, Region 2: Latin America, Eastern Europe and Russia vs Region 3: Asia.
ABC, advanced (locally advanced [inoperable] or metastatic) breast cancer.
Pre- or peri-menopausal women also received a luteinizing hormone-releasing hormone agonist for the duration of the study treatment
Turner NC, et al. SABCS 2022. Abstract GS3-04.

Courtesy of Erica Mayer, MD, MPH, FASCO

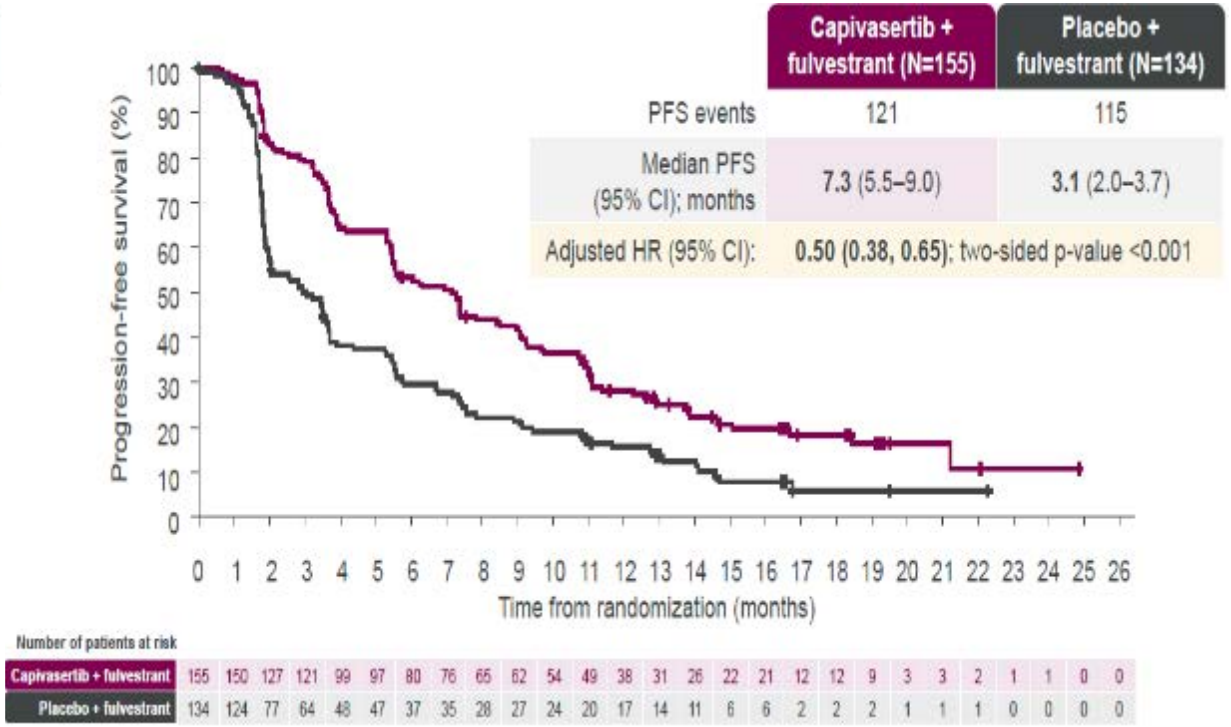
CAPItello-291 Dual Primary Endpoints: PFS in Overall and AKT Pathway-altered Populations

Capivasertib plus fulvestrant provides a statistically significant and clinically meaningful improvement in PFS in the overall and the AKT pathway-altered populations

PFS in Overall: 7.2 vs 3.6 *HR: 0.60*



PFS in AKT Altered: 7.3 vs 3.1 *HR: 0.50*

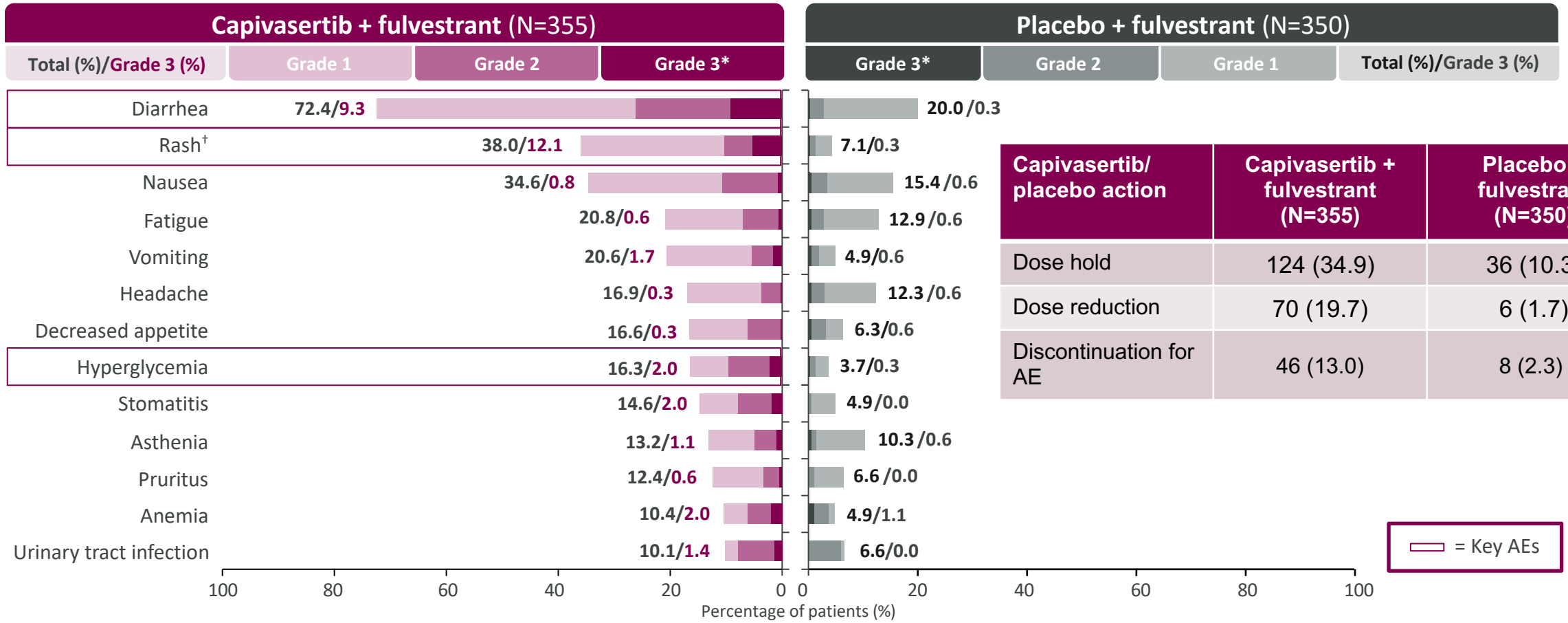


+ indicates a censored observation. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases, prior use of CDK4/6 inhibitor, and geographic region.
Turner NC, et al. SABCS 2022. Abstract GS3-04.

Courtesy of Erica Mayer, MD, MPH, FASCO

CAPItello-291 Adverse Event Profile

AEs (>10% of patients) – overall population



Capivasertib/ placebo action	Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=350)
Dose hold	124 (34.9)	36 (10.3)
Dose reduction	70 (19.7)	6 (1.7)
Discontinuation for AE	46 (13.0)	8 (2.3)

*All events shown were Grade 3 except 1 case of Grade 4 hyperglycemia in the capivasertib + fulvestrant arm.

†The collective term rash includes the preferred terms of rash, rash macular, maculopapular rash, rash papular, and rash pruritic.

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

Courtesy of Erica Mayer, MD, MPH, FASCO

CAPItello-291 - capivasertib

- The combination of capivasertib and fulvestrant is now an approved therapy for pretreated HR+/HER2- MBC with a PIK3CA/AKT1/PTEN-alteration.
- Supports need for tumor genomic profiling; ctDNA may be preferred
- Toxicity profile may be a differentiator:
  - Notable for diarrhea and rash; nausea and fatigue also observed.
  - Less hyperglycemia than seen with alpelisib in a population including diabetics, although glucose monitoring is necessary.
  - Consider prophylactic antihistamine for rash; educate patients about antidiarrheal use.
  - May be a preferred choice compared to alpelisib, especially if concerned about hyperglycemia.

Courtesy of Erica Mayer, MD, MPH, FASCO

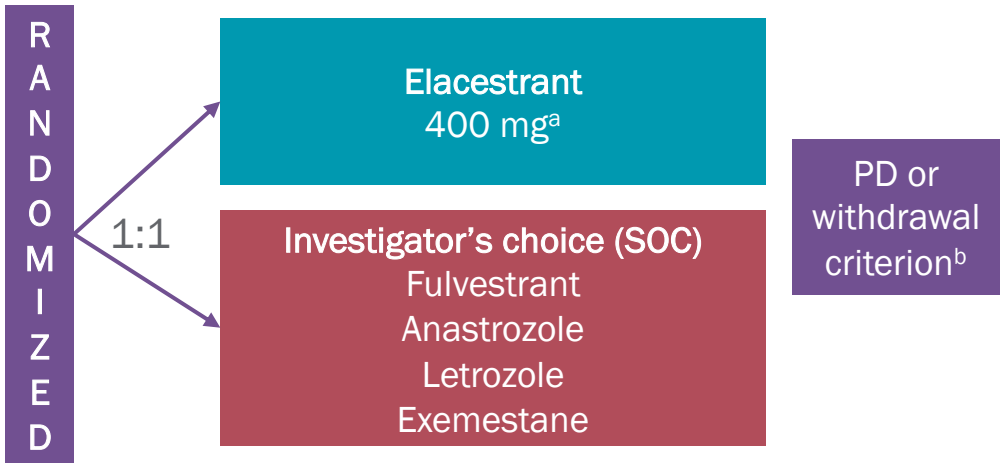
Oral SERDs

- Lu J et al. **Elacestrant** vs standard-of-care in ER+/HER2- advanced or metastatic breast cancer **(mBC)** with **ESR1 mutation**: Key biomarkers and clinical subgroup analyses from the phase 3 **EMERALD** trial. San Antonio Breast Cancer Symposium 2023;Abstract PS17-02.
- Burstein HJ et al. **Testing** for **ESR1** mutations to guide therapy for hormone receptor-positive, human epidermal growth factor receptor 2-negative **metastatic breast cancer: ASCO guideline** Rapid Recommendation Update. *J Clin Oncol* 2023;41(18):3423-5.
- Oliveira M et al. Clinical activity of **camizestrant**, a next-generation SERD, versus **fulvestrant** in patients with a **detectable ESR1 mutation**: Exploratory analysis of the **SERENA-2** phase 2 trial. ASCO 2023;Abstract 1066.
- Jhaveri K et al. **Imlunestrant monotherapy** and in combination with **abemaciclib**, with or without an aromatase inhibitor, in estrogen receptor-positive (ER+), HER2-negative (HER2-) **advanced breast cancer** (aBC): Updated results from the **EMBER** study. San Antonio Breast Cancer Symposium 2023;Abstract PS15-09.

EMERALD Phase 3 Trial of Elacestrant vs SOC in ER+/HER2– MBC: Study Design and Patients[1,2]

Key Eligibility Criteria

- ER+/HER2– MBC
- 1-2 prior lines of ET, one of which in combination with CDK4/6i
- ≤1 line of chemotherapy for advanced disease
- ECOG PS 0-1



Primary endpoints[c]: PFS in all, PFS in *ESR1*mut patients
Secondary endpoints: OS, safety

Patient Characteristics, n (%)		Elacestrant		SOC	
		All (n=239)	*ESR1*mut (n=115)	All (n=239)	*ESR1*mut (n=115)
Median age (range), years		63 (24-89)	64 (28-89)	63 (32-83)	63 (32-83)
ECOG PS	0	143 (59.8)	67 (58.3)	135 (56.5)	61 (54.9)
	1	96 (40.2)	48 (41.7)	103 (43.1)	51 (45.1)
Visceral metastasis, %		163 (68.2)	81 (70.4)	170 (71.1)	84 (74.3)
Prior CDK4/6i		239 (100)	115 (100)	239 (100)	113 (100)
Prior lines of ET	1	129 (54.0)	73 (63.5)	142 (59.4)	69 (61.1)
	2	110 (46.0)	42 (36.5)	97 (40.6)	44 (38.9)
Type of prior ET	Fulvestrant	70 (29.3)	27 (23.5)	75 (31.4)	28 (24.8)
	AI	193 (80.8)	101 (87.8)	194 (81.2)	96 (85.0)
	Tamoxifen	19 (7.9)	9 (7.8)	15 (6.3)	9 (8.0)
Prior lines of Chemo	0	191 (79.9)	89 (77.4)	180 (75.3)	81 (71.7)
	1	48 (20.1)	26 (22.6)	59 (24.7)	32 (28.3)

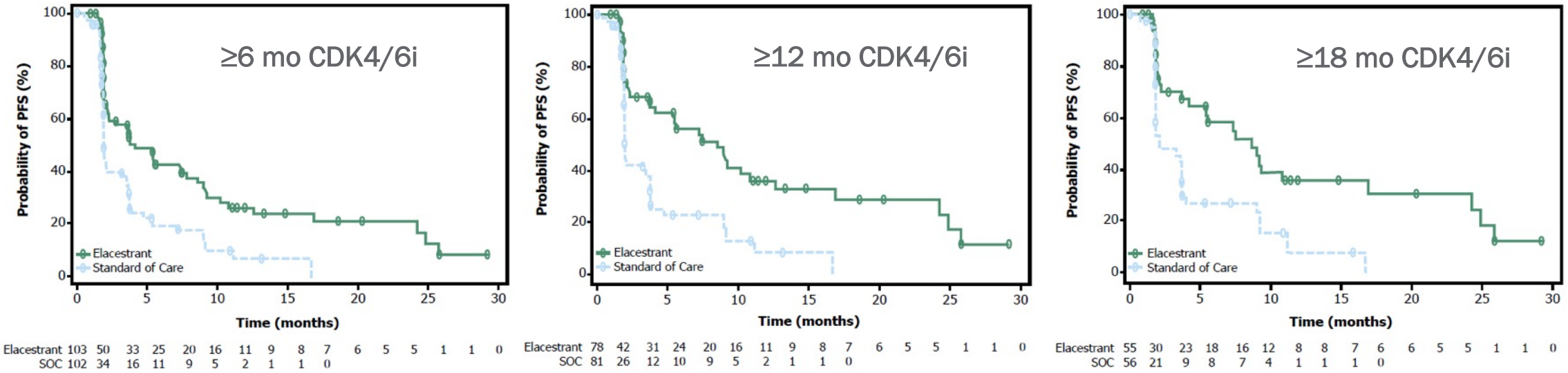
[a] Protocol-defined dose reductions permitted. [b] Restaging CT scans every 8 weeks. [c] By BICR.

1. Bidard F, et al. *J Clin Oncol*. 2022;40(28):3246-3256. **2.** Bardia A, et al. SABCS 2022. Abstract GS3-01.

Courtesy of Erica Mayer, MD, MPH, FASCO

EMERALD: PFS in *ESR1*mut Population by Duration of Prior CDK4/6i

PFS by Duration of CDK4/6i in Patients With *ESR1*mut Tumors



PFS by Duration of CDK4/6i	≥6 Months		≥12 Months		≥18 Months	
	Elacestrant (n=103)	SOC (n=102)	Elacestrant (n=78)	SOC (n=81)	Elacestrant (n=55)	SOC (n=56)
mPFS, mo (95% CI)	4.14 (2.20-7.79)	1.87 (1.87-3.29)	8.61 (4.14-10.84)	1.91 (1.87-3.68)	8.61 (5.45-16.89)	2.10 (1.87-3.75)
12-mo PFS rate, % (95% CI)	26.02 (15.12-36.92)	6.45 (0.00-13.65)	35.81 (21.84-49.78)	8.39 (0.00-17.66)	35.79 (19.54-52.05)	7.73 (0.00-20.20)
HR (95% CI)	**0.517** (0.361-0.738)		**0.410** (0.262-0.634)		**0.466** (0.270-0.791)	

Bardia A, et al. SABCS 2022. Abstract GS3-01

Courtesy of Erica Mayer, MD, MPH, FASCO

Phase 3 EMERALD Biomarker & Subgroup Analysis

- Subgroup analysis (by sites of metastases, common coexisting mutations [*PIK3CA, TP53*], and HER2-low status) of patients with endocrine sensitive (CDK4/6i for ≥12 mos) HR+ MBC with *ESR1* mutations, revealed clinically meaningful improvement in PFS favoring elacestrant vs SOC was consistent across all relevant subgroups

Improvement in PFS Favoring Elacestrant Compared With SOC Was Consistent Across All Relevant Subgroups in Patients With *ESR1-mut*

PFS Summary in *ESR1*-mut Patients With ≥12 Months of Prior CDK4/6 Inhibitor

		Median PFS, months (95% CI)		
Patients	**% (n)**	**Elacestrant**	**SOC**	**HR (95% CI)**
All *ESR1*-mut patients[9]	**100** (159)	**8.61** (4.14–10.84)	**1.91** (1.87–3.68)	**0.410** (0.262–0.634)
ESR1-mut and bone metastases[a]	**86** (136)	**9.13** (5.49–16.89)	**1.91** (1.87–3.71)	**0.381** (0.230–0.623)
ESR1-mut and liver and/or lung metastases[b]	**71** (113)	**7.26** (2.20–10.84)	**1.87** (1.84–1.94)	**0.354** (0.209–0.589)
ESR1-mut and *PIK3CA*-mut[c]	**39** (62)	**5.45** (2.14–10.84)	**1.94** (1.84–3.94)	**0.423** (0.176–0.941)
ESR1-mut and HER2-low expression[d]	**48** (77)	**9.03** (5.49–16.89)	**1.87** (1.84–3.75)	**0.301** (0.142–0.604)
ESR1-mut and *TP53*-mut	**38** (61)	**8.61** (3.65–24.25)	**1.87** (1.84–3.52)	**0.300** (0.132–0.643)

[a]85% of patients had bone and other sites of metastases (30% of these patients had no liver or lung involvement); [b]55% of patients had liver and other sites of metastases (10% of these patients had no lung or bone involvement); 25% of patients had lung and other sites of metastases (2% of these patients had no liver or bone involvement); [c]Includes E545K, H1047R, E542K amongst others; [d]HER2 IHC 1+, and 2+ with no ISH amplification. Data not available for all patients

Lu et al. SABCS 2023. Abstract PS-17-02.

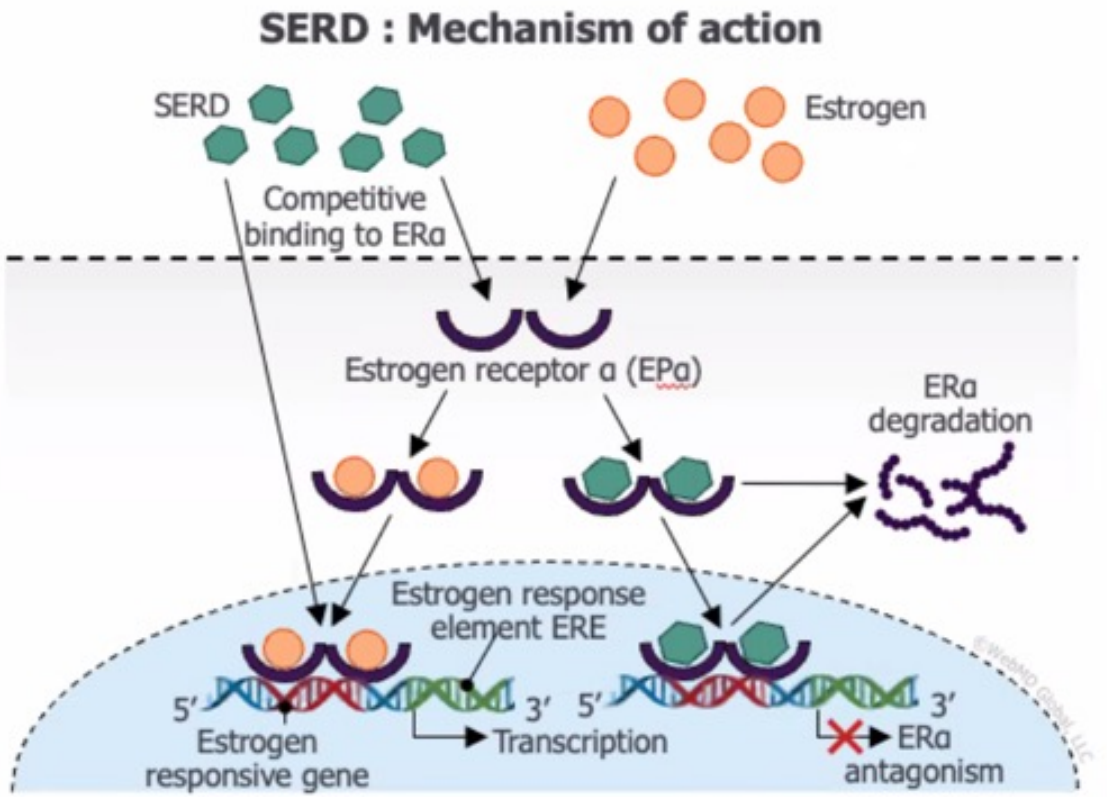
Courtesy of Erica Mayer, MD, MPH, FASCO

EMERALD Subgroup Analysis

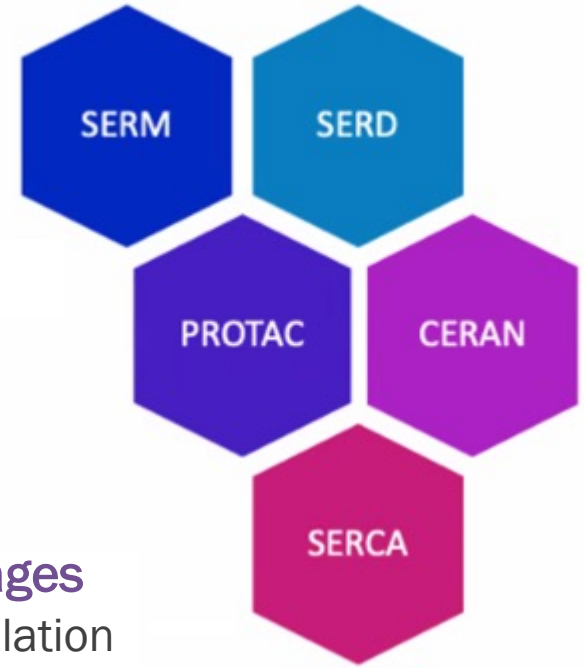
- Elacestrant monotherapy is an option in MBC with ESR1 mutation and retained endocrine sensitivity (eg, prior CDK4/6 inhibitor duration ≥12 months)
- In that situation, the ER pathway could be the main driver of disease, regardless of the metastatic site or coexistence of PIK3CA-mut, TP53-mut, or HER2-low expression.
- If there are both ESR1 and PIK3CA mutations or HER2-low, could prioritize elacestrant as a well tolerated option before moving to capivasertib, alpelisib, or T-DXd.
- Await results of studies of elacestrant combinations.
- ESR1 is a kinetic mutation that develops over time; supports need to check ESR1 status at time of PD.

Courtesy of Erica Mayer, MD, MPH, FASCO

Novel Endocrine Therapies May Address Endocrine Resistance in MBC



Hernando et al. Int J Mol Sci. 2021; slide adapted from Erika Hamilton.



Key Advantages

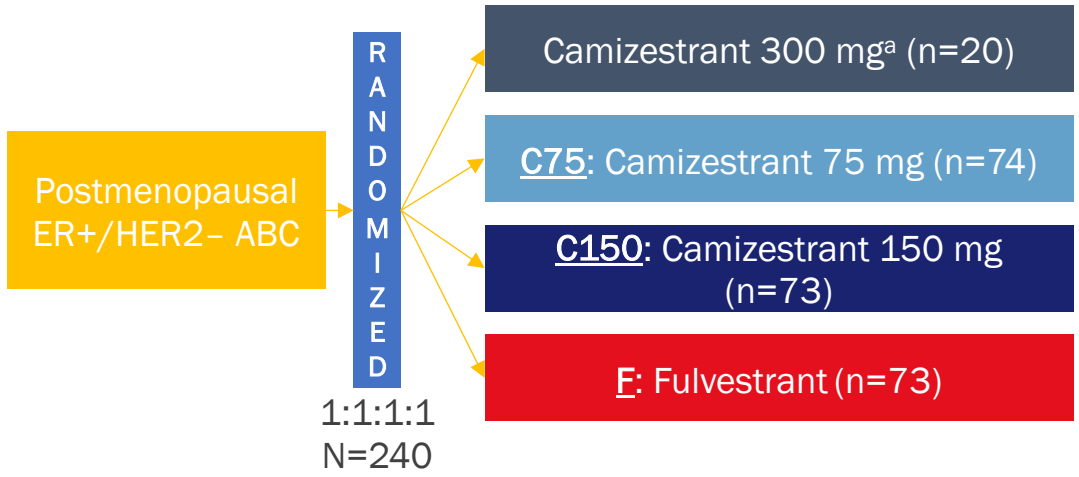
- Oral formulation
- Higher potency
- Activity in ESR1mut MBC
- Activity in post-ET and CDK4/6i treated pts
- Can be well tolerated

Courtesy of Erica Mayer, MD, MPH, FASCO

SERENA-2: Phase 2 Trial of Camizestrant vs Fulvestrant in ER+/HER2– MBC: Study Design and Patients

Key Eligibility Criteria

- Recurrence or progression on ≥1 line of ET
- No prior fulvestrant or oral SERD in ABC
- ≤1 line of ET in ABC setting
- ≤1 line chemotherapy in ABC setting
- Measurable and nonmeasurable disease



Primary endpoint: PFS by investigator[b]
Secondary endpoints: CBR24, ORR, OS, safety
Translational endpoints: Serial CTC and ctDNA (*ESR1*mut) analyses

Patient Characteristics, %		C75 (n=74)	C150 (n=73)	F (n=73)
Median age (range), years		61 (37-79)	60 (42-84)	60 (35-84)
ER+		100	100	100
ECOG PS 0		62.2	57.5	58.9
Lung/liver metastasis		58.1	58.9	58.9
Liver metastasis		31.1	41.1	47.9
*ESR1*mut detectable[c]		29.7	35.6	47.9
Chemotherapy in ABC		21.6	12.3	26.0
ET adjuvant	AI	40.5	35.6	31.5
	SERM	32.4	45.2	43.8
ET in ABC	0 lines	37.8	28.8	26.0
	1 line	62.2	71.2	74.0
	AI	55.4	67.1	67.1
	SERM	6.8	2.7	6.8
Prior CDK4/6i[d]		51.4	50.7	50.7
Palbociclib		21.6	31.5	30.1
Ribociclib		23.0	19.2	16.4
Abemaciclib		5.4	1.4	4.1

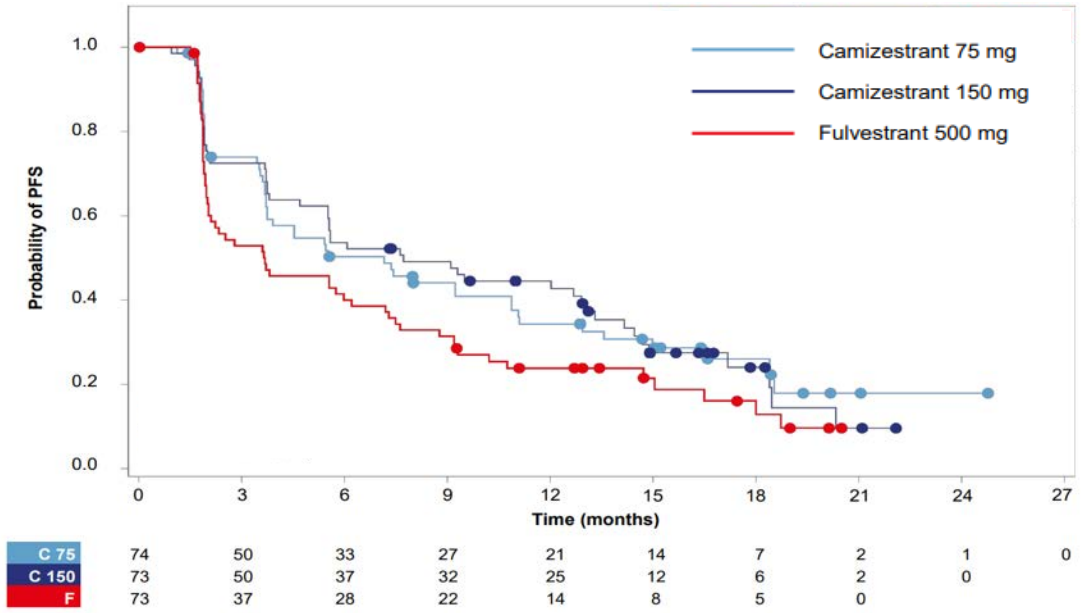
[a] CSP v5 amendment: December 16, 2020. [b] Disease progression defined using RECIST v1.1. [c] *ESR1*mut assessed in plasma samples at screening and C1D1; *ESR1*mut defined as E380Q, V422del, S463P, L536H/P/R, Y537C/D/N/S, D538G, individual mutations present in >2% total cases reported. [d] Missing or not specified in 3 patients.

Oliveira M et al. SABCS 2022. Abstract GS3-02.

Courtesy of Erica Mayer, MD, MPH, FASCO

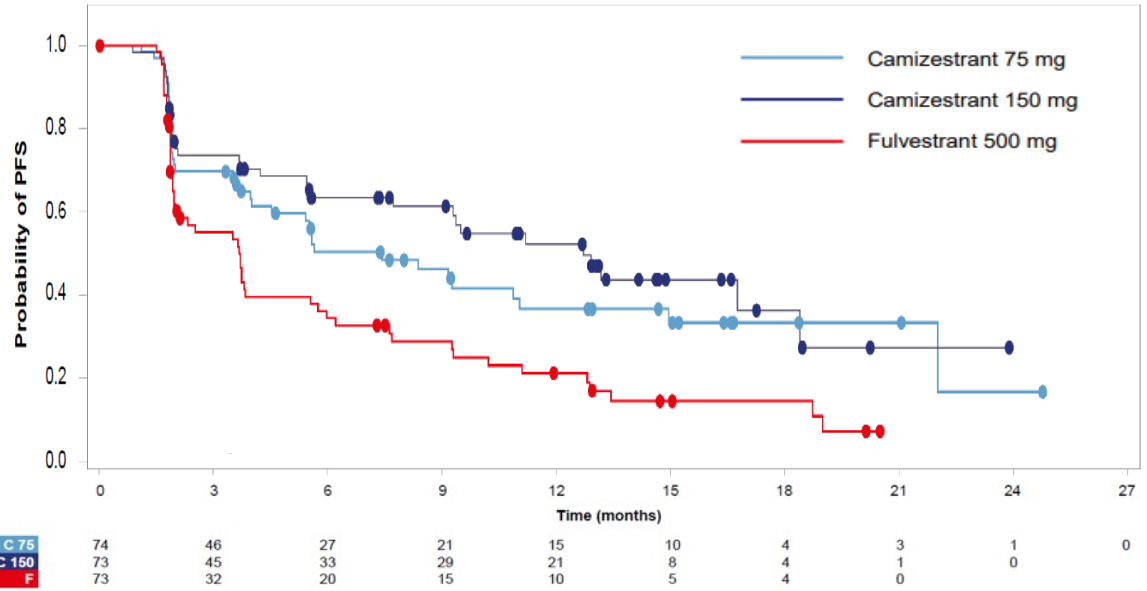
SERENA-2: PFS in ITT

Primary Endpoint: PFS by Investigator Assessment



	C75 (n=74)	C150 (n=73)	F (n=73)
Median follow-up, mo	16.6	16.6	17.4
Events, n (%)	50 (67.6)	51 (69.9)	58 (79.5)
mPFS, mo (90% CI)	7.2 (3.7-10.9)	7.7 (5.5-12.9)	3.7 (2.0-6.0)
Adjusted HR[a] (90% CI)	0.58 (0.41-0.81)	0.67 (0.48-0.92)	-
P value	0.0124[b]	0.0161[b]	-

PFS by BICR



	C75 (n=74)	C150 (n=73)	F (n=73)
Events, n (%)	39 (52.7)	33 (45.2)	53 (72.6)
mPFS, mo (90% CI)	7.4 (4.5-10.9)	12.7 (9.3-18.4)	3.7 (2.0-3.8)
Adjusted HR[a] (90% CI)	0.56 (0.39-0.80)	0.47 (0.33-0.68)	-
P value	0.0079[b]	0.0004[b]	-

[a] HR adjusted for prior use of CDK4/6i and liver/lung metastases. [b] Statistically significant.

Oliveira M et al. SABCS 2022. Abstract GS3-02.

Courtesy of Erica Mayer, MD, MPH, FASCO

SERENA-2: Exploratory Analysis

- Camizestrant monotherapy has shown promising data over fulvestrant in patients with HR+/HER2- MBC and an ESR1 mutation
- The agent retains activity regardless of number or type of ESR1 mutations
- Ongoing studies are looking at:
  - Camizestrant combinations
  - Other oral SERDs in combinations: giredestrant, imlunestrant
  - ARV-471 (vepdegestrant, PROTAC), OP-1250 (CERAN)
- Likely will be a rapidly expanding space in the next 1-2 years

Courtesy of Erica Mayer, MD, MPH, FASCO

Novel Oral Endocrine Therapies: SERD, CERAN, PROTAC

Agent	Disease setting	Select ongoing trials
ORAL SERDs		
Elacestrant (RAD1901)	Advanced/Metastatic	EMERALD, ELEVATE
Giredestrant (GDC-9545)	Advanced/Metastatic	persevERA, acelERA, evERA. pionERA
	Neoadjuvant	coopERA
	Adjuvant	lidERA
Camizestrant (AZD9833)	Advanced/Metastatic	SERENA-1,-2,-4, -6
	Neoadjuvant	SERENA-3
	Adjuvant	CAMBRIA, CAMBRIA-2
Imlunestrant (LY3484356)	Advanced/Metastatic	EMBER
	Neoadjuvant	EMBER-2
	Adjuvant	EMBER-4
Other novel agents		
ARV-471	Advanced/Metastatic	NCT04072952
OP-1250	Advanced/Metastatic	NCT04505826

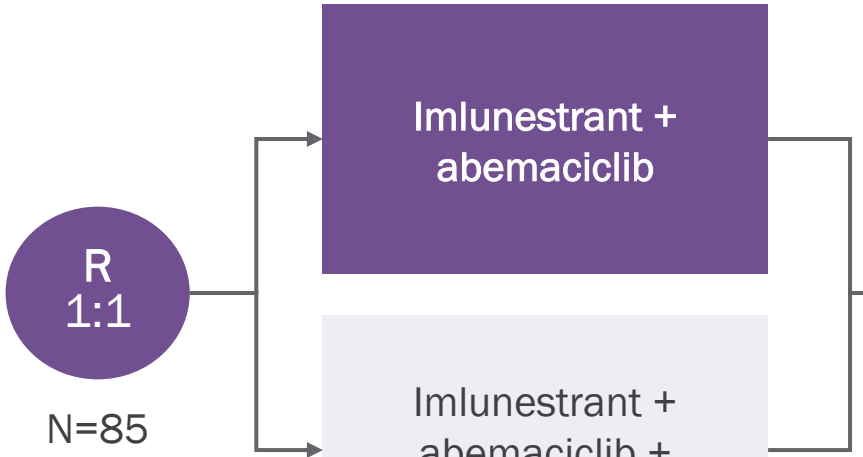
Courtesy of Erica Mayer, MD, MPH, FASCO

EMBER: Phase 1a/b Study of Imlunestrant With Abemaciclib ± AI in ER+ ABC: Study Design

Key Eligibility Criteria

- ER+/HER2– ABC
- ≤1 line of prior therapy of ABC
- No prior CDK4/6i
- Demonstrated prior sensitivity to ET or have untreated de novo ABC

- Imlunestrant PO qd with abemaciclib (150 mg bid) ± AI in 28-day cycles
- Men and premenopausal women received concomitant GnRH agonist
- Cutoff date Oct 6, 2022



Stratification Factors

- Menopausal status
- Visceral metastases

Primary Endpoint

- Determine RP2D

Secondary Endpoints

- Safety
- PK
- Antitumor activity (ORR, CBR, TTR, PFS)

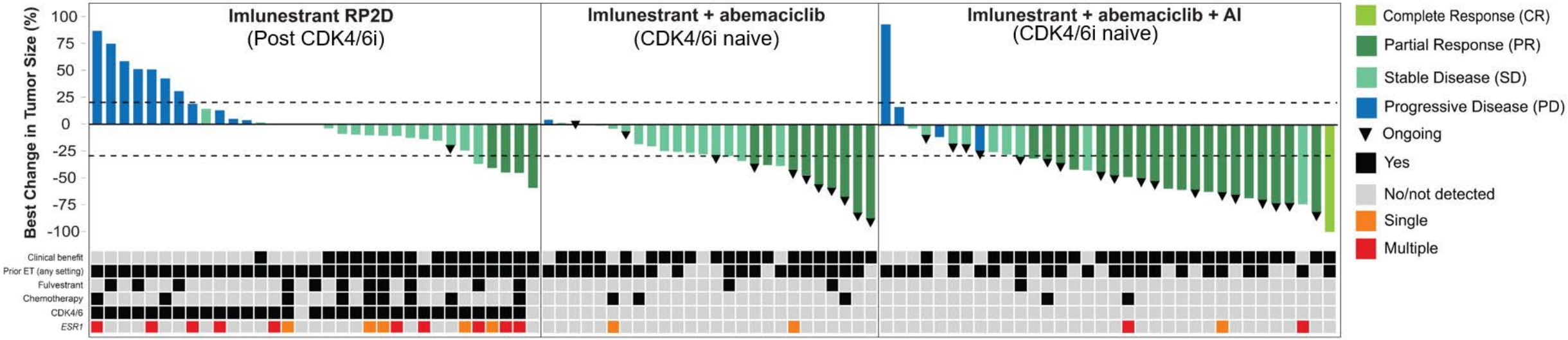
RP2D imlunestrant combination with abemaciclib: imlunestrant 400 mg qd (same as monotherapy)

[a] AI was physician's choice of anastrozole, letrozole, or exemestane at standard doses.

Jhaveri KL, et al SABCS 2023. Abstract PS15-09.

Courtesy of Erica Mayer, MD, MPH, FASCO

EMBER: Imlunestrant With Abemaciclib ± AI: Efficacy & Safety Summary



	Imlunestrant RP2D 400 mg (n=51)		Imlunestrant + abemaciclib (n=42)		Imlunestrant + abemaciclib + AI (n=43)	
ORR in patients with measurable disease, n/N (%)	**4/34 (12)**		**9/28 (32)**		**21/34 (62)**	
CBR (CR+PR+SD ≥ 24 weeks), n (%)	**28 (55)**		**30 (71)**		**34 (79)**	
Median TTR, months (min-max)	**3.6 (1.6, 5.4)**		**5.5 (1.6, 10.9)**		**3.7 (1.7, 8.5)**	
Median PFS, months (95% CI)	**7.2 (3.7, 8.3)**		**19.2 (13.8, NA)**		**NA (18.9, NA)**	
12-month PFS, % (95% CI)	22.2 (11.3, 35.3)		74.2 (56.2, 85.7)		80.7 (65.1, 89.9)	
Treatment Related Adverse Events (TRAEs), n (%)	**All grade**	**Grade ≥3**	**All grade**	**Grade ≥3**	**All grade**	**Grade ≥3**
Patients with ≥1 TRAE	**36 (71)**	**5 (10)**	**41 (98)**	**15 (36)**	**40 (93)**	**17 (40)**
Nausea	14 (28)	0	21 (50)	0	21 (49)	0
Diarrhea	10 (20)	1 (2)	40 (95)	4 (10)	31 (72)	3 (7)
Fatigue	11 (22)	2 (4)	14 (33)	3 (7)	21 (49)	1 (2)
Neutropenia	3 (6)	2 (4)	15 (36)	4 (10)	19 (44)	8 (19)
Discontinuations due to TRAE, n (%)	**0**		**0**		**1 (2)**	

CBR, clinical benefit rate; NA, not available; ORR, objective response rate; PFS, progression free-survival; TTR, time to response

Jhaveri KL, et al SABCS 2023. Abstract PS15-09

Courtesy of Erica Mayer, MD, MPH, FASCO

EMBER: Imlunestrant With Abemaciclib ± AI: Summary

- Imlunestrant monotherapy was well tolerated; no new safety signals observed
  - RP2D was determined as 400mg QD
- Combination with abemaciclib ± AI revealed no new safety signals and no drug-drug interactions
- Clinical activity is encouraging with imlunestrant monotherapy, especially at the RP2D and particularly in the 2L post-CDK4/6i setting. Robust efficacy is observed with imlunestrant in combination with abemaciclib ± AI
- Pivotal Phase 3, randomized, open-label registration trials of imlunestrant are ongoing:
  - EMBER-3 (NCT04975308): Imlunestrant, investigator's choice ET (fulvestrant or AI), and imlunestrant + abemaciclib in ER+/HER2- ABC previously treated with ET
  - EMBER-4 (NCT05514054): Adjuvant imlunestrant vs. adjuvant ET in patients who have previously received 2 to 5 years of adjuvant ET for ER+/HER2- early BC with an increased risk of recurrence

Jhaveri KL, et al SABCS 2023. Abstract PS15-09

Courtesy of Erica Mayer, MD, MPH, FASCO

Antibody-Drug Conjugates

- Modi S et al. **Trastuzumab deruxtecan (T-DXd)** versus treatment of physician's choice (TPC) in patients (pts) with **HER2-low** unresectable and/or metastatic breast cancer (mBC): **Updated survival** results of the randomized, phase III **DESTINY-Breast04 study.** ESMO 2023;Abstract 376O.
- Bardia A et al. Randomized phase 3 study of **datopotamab deruxtecan vs chemotherapy** for patients with **previously-treated inoperable or metastatic** hormone receptor-positive, HER2-negative breast cancer: Results from **TROPION-Breast01**. San Antonio Breast Cancer Symposium 2023;Abstract GS02-01.
- Hamilton EP et al. A phase 2 study of **HER3-DXd** in patients (pts) with metastatic breast cancer (MBC). ASCO 2023;Abstract 1004.
- Krop IE et al. **Patritumab deruxtecan (HER3-DXd),** a human epidermal growth factor receptor 3-directed antibody-drug conjugate, in patients with previously treated human epidermal growth factor receptor 3-expressing metastatic breast cancer: A multicenter, Phase I/II trial. *J Clin Oncol* 2023;41(36):5550-60.

Antibody-drug conjugates in breast cancer

	Trastuzumab emtansine (T-DM1)	Trastuzumab deruxtecan (T-DXd)	Trastuzumab duocarmazine (SYD985)	Disitamab vedotin (RC48-ADC)	Sacituzumab govitecan	Datopotamab deruxtecan (Dato-DXd)	Patritumab deruxtecan (U3-1402)	Ladiratuzumab vedotin (SGN-LIV1A)
Target	**HER2**	**HER2**	**HER2**	**HER2**	**TROP2**	**TROP2**	**HER3**	**LIV1A**
Payload	Microtubule inhibitor (DM1)	Topoisomerase I inhibitor (DXd)	DNA alkylation (duocarmazine)	Microtubule inhibitor (MMAE)	Topoisomerase I inhibitor (SN38)	Topoisomerase I inhibitor (DXd)	Topoisomerase I inhibitor (DXd)	Microtubule inhibitor (MMAE)
Linker cleavage	No	Enzymatic (peptidase)	Enzymatic (peptidase)	Enzymatic (peptidase)	Enzymatic and pH-dependent	Enzymatic (peptidase)	Enzymatic (peptidase)	Enzymatic (peptidase)
Bystander effect	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
DAR	3.5	~8	~2.8	4	7.6	4	7.8	4
Dosing	D1 (Q3W)	D1 (Q3W)	D1 (Q3W)	D1 (Q2W)	D1, D8 (Q3W)	D1 (Q3W)	D1 (Q3W)	D1 (Q1W or Q3W)

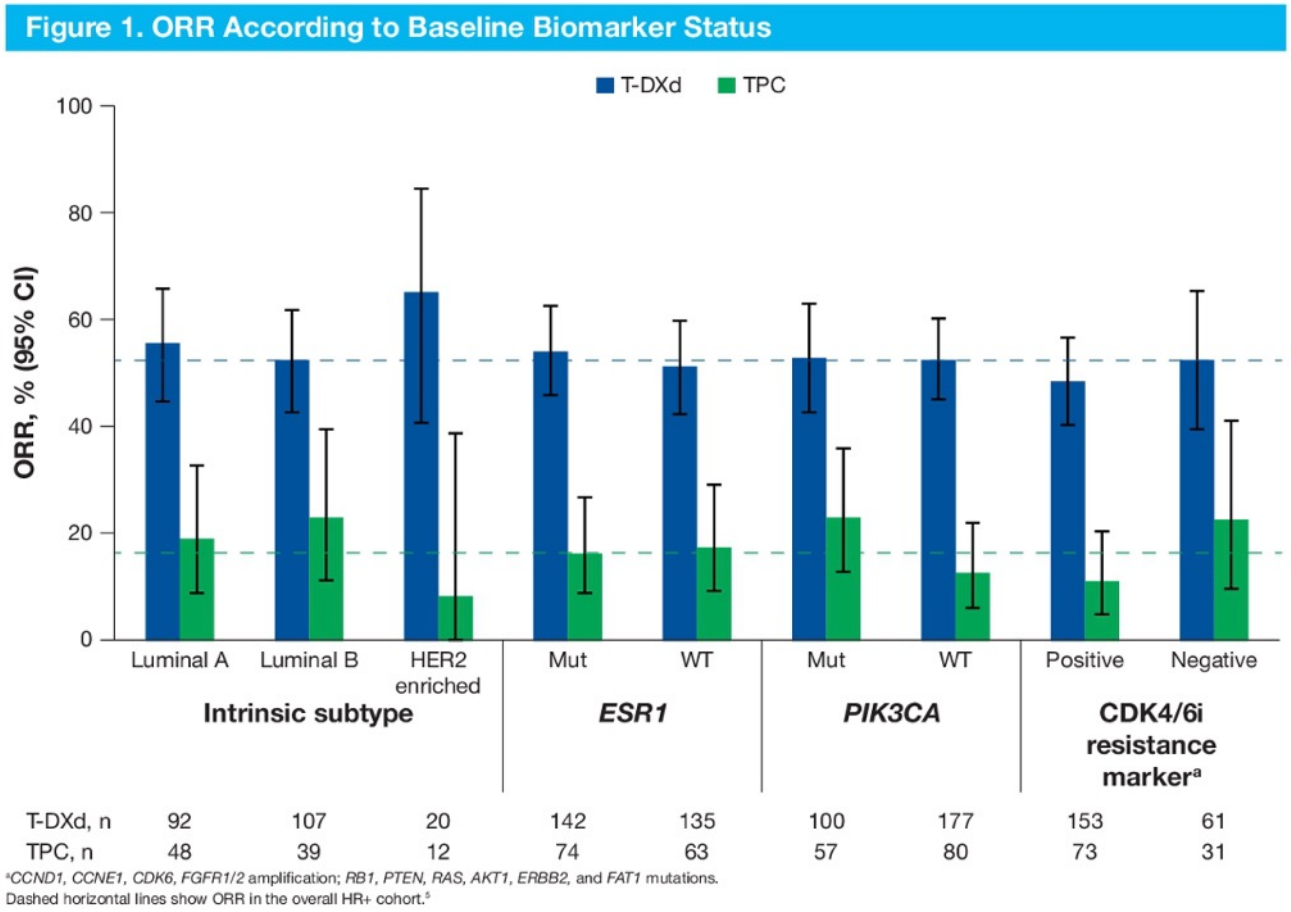
Courtesy of Erica Mayer, MD, MPH, FASCO

T-DXd versus TPC in HER2-low MBC: Updated survival results of the Phase III DESTINY-Breast04 study.

- Preserved clinical benefit for T-DXd over TPC therapy was observed regardless of biomarker status including intrinsic subtype, ESR1 mutation, PIK3CA mutation, or CDK4/6i resistance marker status

PFS according to baseline biomarker status

Biomarker	Status	Median PFS (95% CI)		HR (95% CI)
		T-DXd	TPC	
PIK3CA	WT	10.0 (8.5–12.2) n=177	4.8 (2.9–8.3) n=80	**0.50** (0.35–0.70)
	Mut	9.7 (7.5–12.3) n=100	6.2 (5.3–7.8) n=57	**0.60** (0.40–0.91)
ESR1	WT	10.0 (8.3–12.6) n=135	5.3 (4.0–7.8) n=63	**0.43** (0.29–0.62)
	Mut	9.8 (8.2–12.0) n=142	6.9 (4.3–10.7) n=74	0.67 (0.47–0.97)
Intrinsic subtype	HER2	11.0 (6.6–NA) n=20	2.7 (1.4–5.9) n=12	**0.15** (0.05–0.40)
	Luminal A	13.0 (10.1–16.4) n=92	7.8 (5.4–12.4) n=48	**0.57** (0.36–0.89)
	Luminal B	8.7 (6.9–11.1) n=107	4.8 (2.7–8.3) n=39	**0.60** (0.40–0.92)



Modi S et al. ESMO 2023;Abstract 376O

Courtesy of Erica Mayer, MD, MPH, FASCO

TROPION-Breast01 Study Design[1]

Randomized, phase 3, open-label, global study (NCT05104866)

Key inclusion criteria:

- Patients with HR+/HER2– breast cancer* (HER2– defined as IHC 0/1+/2+; ISH negative)
- Previously treated with 1–2 lines of chemotherapy (inoperable/metastatic setting)
- Experienced progression on ET and for whom ET was unsuitable
- ECOG PS 0 or 1

1:1

Dato-DXd
6 mg/kg IV Day 1 Q3W
(n=365)

Investigator's choice of chemotherapy (ICC)
as per protocol directions†
(eribulin mesylate D1,8 Q3W; vinorelbine D1,8 Q3W; gemcitabine D1,8 Q3W; capecitabine D1–14 Q3W)
(n=367)

Endpoints:

- **Dual primary:** PFS by BICR per RECIST v1.1, and OS
- **Secondary endpoints included:** ORR, PFS (investigator assessed), TFST, safety, PROs

Randomization stratified by:

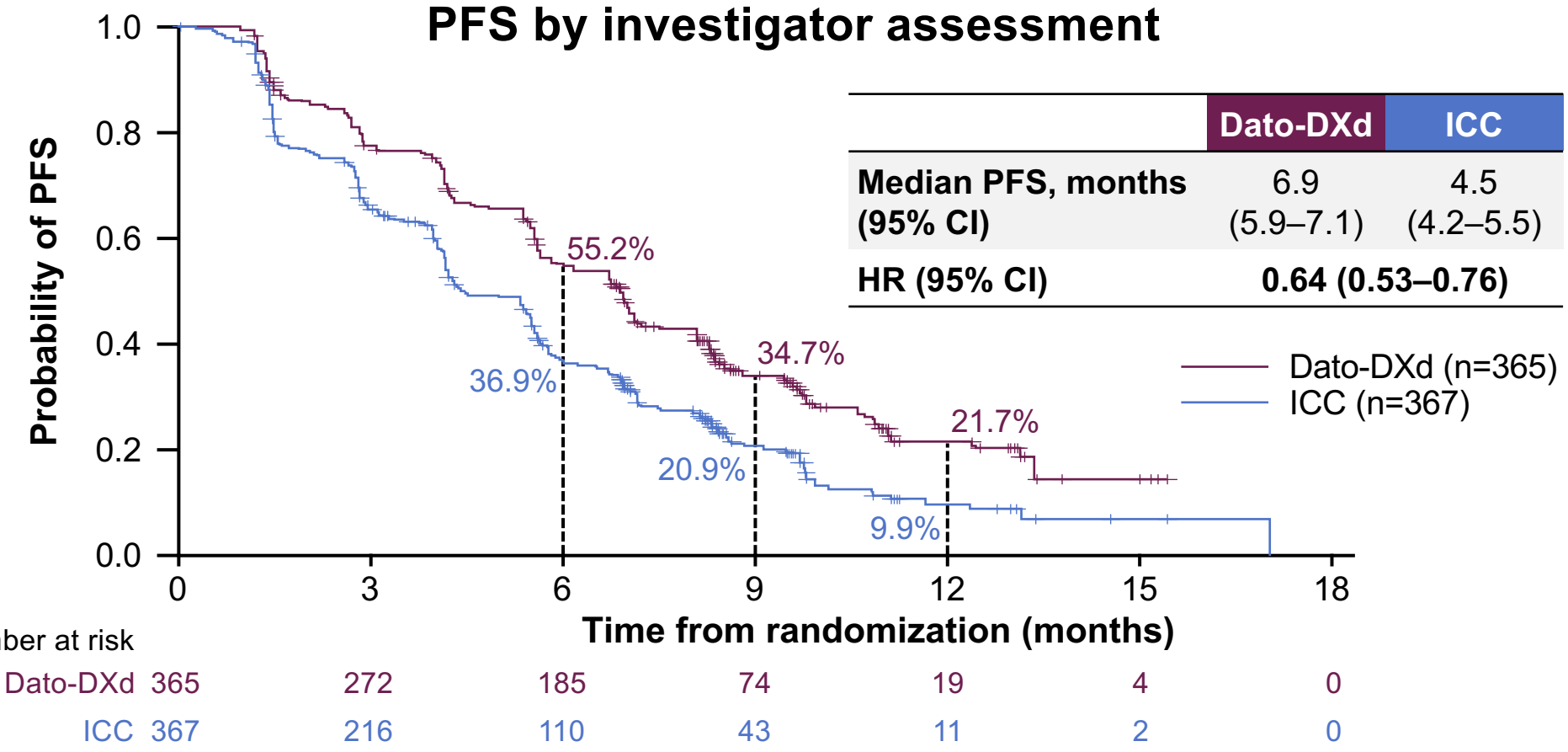
- **Lines of chemotherapy** in unresectable/metastatic setting (1 vs 2)
- **Geographic location** (US/Canada/Europe vs ROW)
- **Previous CDK4/6 inhibitor** (yes vs no)

- Treatment continued until PD, unacceptable tolerability, or other discontinuation criteria

Detailed description of the statistical methods published previously.[1] *Per American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines. †ICC was administered as follows: eribulin mesylate, 1.4 mg/m^2 IV on Days 1 and 8, Q3W; vinorelbine, 25 mg/m^2 IV on Days 1 and 8, Q3W; or gemcitabine, 1000 mg/m^2 IV on Days 1 and 8, Q3W; capecitabine, 1000 or 1250 mg/m^2 orally twice daily on Days 1 to 14, Q3W (dose per standard institutional practice). CDK4/6, cyclin-dependent kinase 4/6; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; IHC, immunohistochemistry; ISH, in-situ hybridization; IV, intravenous; PD, progressive disease; PROs, patient-reported outcomes; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; ROW, rest of world; TFST, time to first subsequent therapy.

1. Bardia A, et al. *Future Oncol* 2023; doi: 10.2217/fon-2023-0188.

TROPION-Breast01: Progression-Free Survival



	Dato-DXd	ICC
Median PFS, months (95% CI)	6.9 (5.9–7.1)	4.5 (4.2–5.5)
HR (95% CI)	**0.64 (0.53–0.76)**	

PFS by BICR (primary endpoint)[1]: Median 6.9 vs 4.9 months; HR 0.63 (95% CI 0.52–0.76); P<0.0001

Data cut-off: 17 July 2023.

1. Bardia A, et al. Oral Presentation at ESMO 2023; Abstract LBA11.

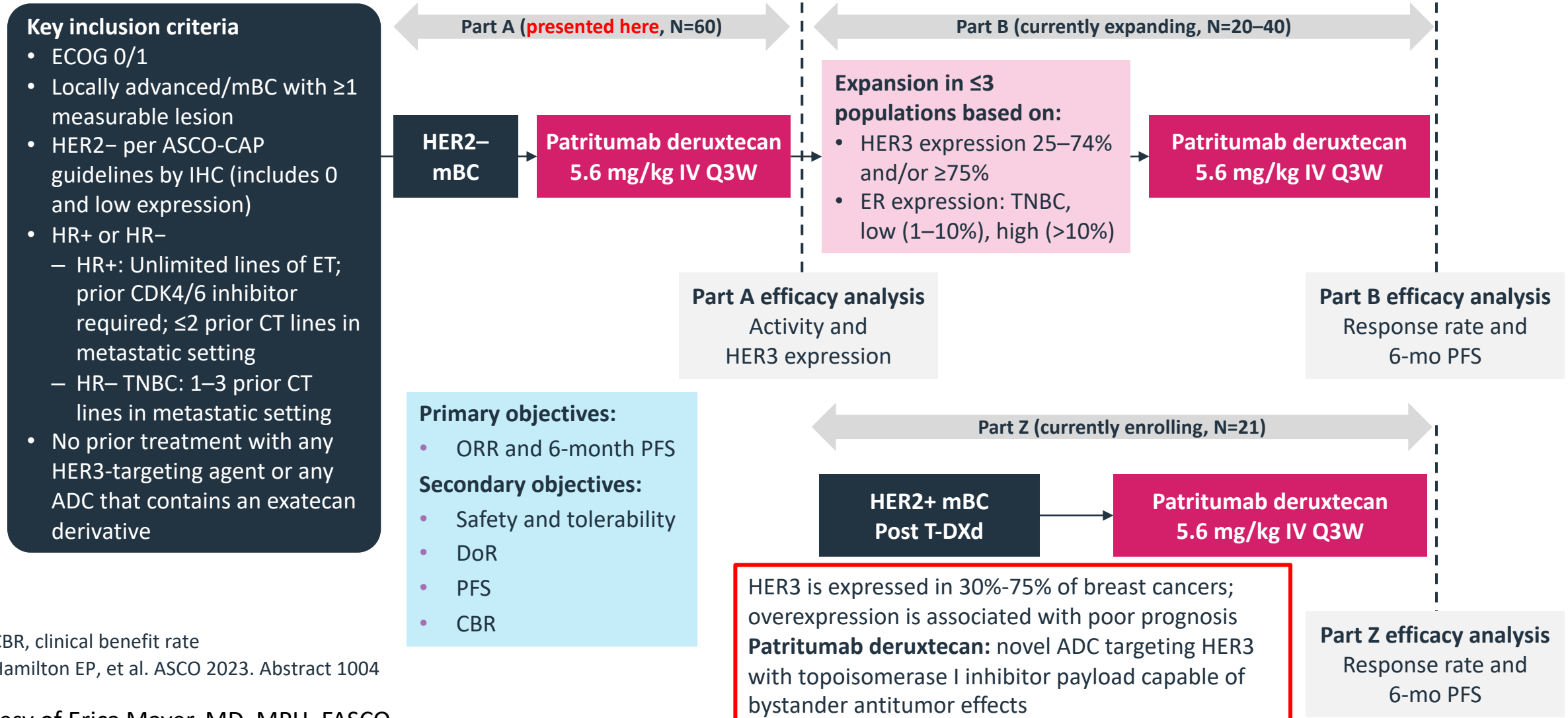
TROPION-Breast01: Adverse Events of Clinical Interest

Neutropenia*	Dato-DXd (n=360)	ICC (n=351)
Treatment-related neutropenia*, n (%)		
Any grade	39 (11)	149 (42)
Grade ≥3	4 (1)	108 (31)
Leading to dose interruption	0	60 (17)
Leading to dose reduction	1 (0.3)	45 (13)
Leading to dose discontinuation	0	1 (0.3)
G-CSF usage, n (%)		
On treatment	10 (3)	81 (22)
Post-treatment†	1 (0.3)	30 (8)

Stomatitis‡	Dato-DXd (n=360)	ICC (n=351)
Treatment-related stomatitis‡, n (%)		
Any grade	180 (50)	46 (13)
Grade 3	23 (6)	9 (3)
Leading to dose interruption	5 (1)	3 (1)
Leading to dose reduction	44 (12)	5 (1)
Leading to dose discontinuation	1 (0.3)	0

*Neutropenia includes the preferred terms neutropenia and neutrophil count decreased. Treatment-related febrile neutropenia occurred in 0 patients in the Dato-DXd arm and 8 patients (2.3%; all grade ≥3) in the ICC arm.
†Administered after discontinuation of study treatment.
‡As part of the Oral Care Protocol specified in the study protocol, daily use of prophylaxis with a steroid-containing mouthwash (e.g., dexamethasone oral solution or a similar mouthwash regimen using an alternative steroid advocated by institutional/local guidelines) was highly recommended.
G-CSF, granulocyte colony stimulating factor.

Phase 2 trial of HER3-DXd in patients with metastatic breast cancer



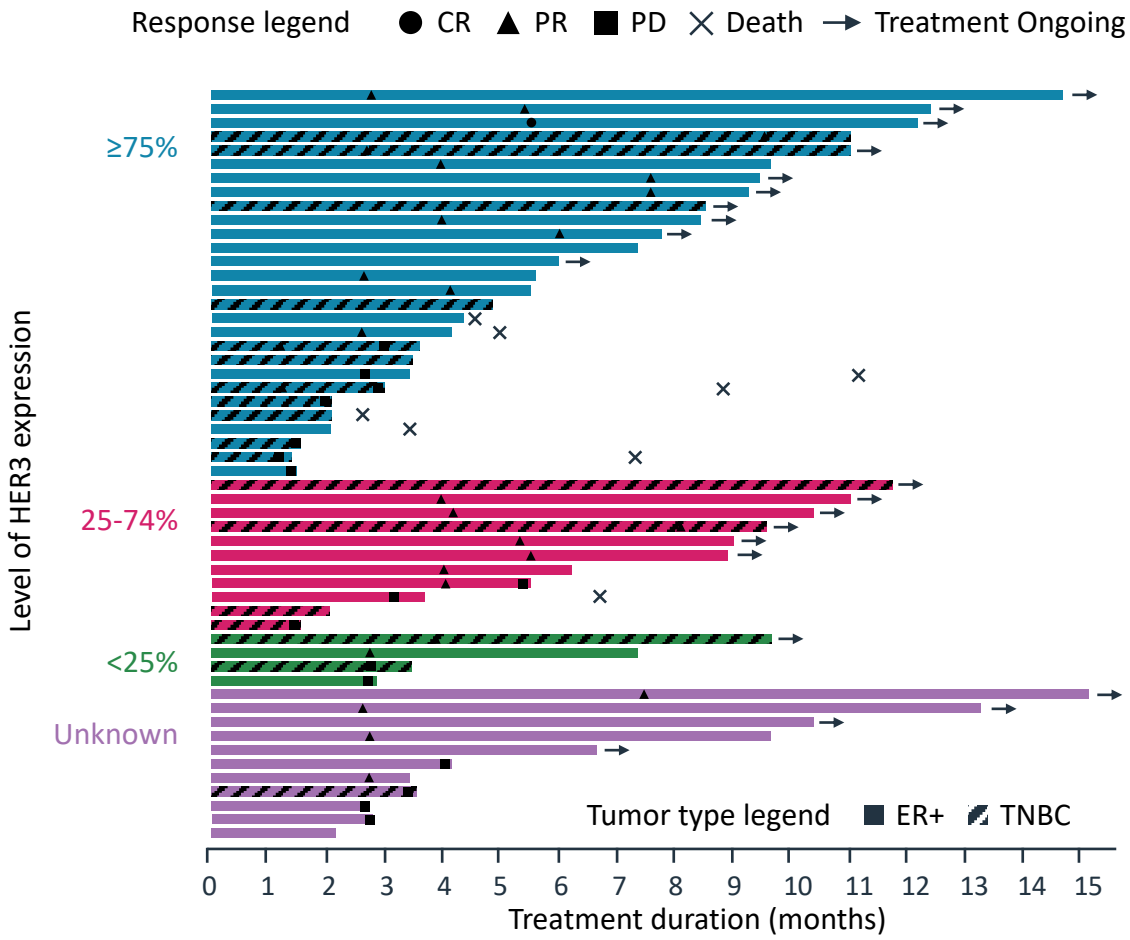
CBR, clinical benefit rate

Hamilton EP, et al. ASCO 2023. Abstract 1004

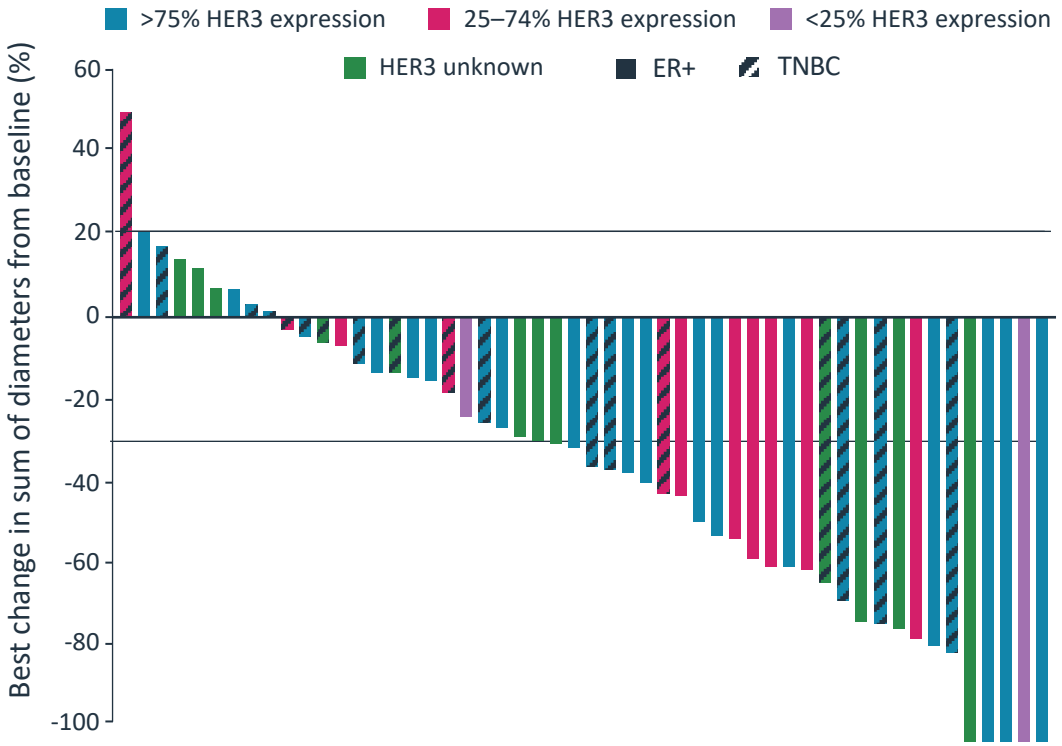
Courtesy of Erica Mayer, MD, MPH, FASCO

Phase 2 trial of HER3-DXd: Efficacy

Duration on study treatment by HER3 membrane expression



Best percentage change in sum of diameters from baseline in target lesions



Hamilton EP, et al. ASCO 2023. Abstract 1004

Courtesy of Erica Mayer, MD, MPH, FASCO

Phase 2 trial of HER3-DXd: Safety and Conclusions

Safety summary

TRAEs occurring in ≥10% of patients by highest reported grade[a]	Any grade (N=60)	Grade 3/4 (N=60)
Any AE	56 (93.3)	19 (31.7)
Nausea	30 (50.0)	2 (3.3)
Fatigue	27 (45.0)	4 (6.7)
Diarrhea	22 (36.7)	3 (5.0)
Vomiting	19 (31.7)	1 (1.7)
Anemia	18 (30.0)	0
Alopecia	17 (28.3)	N/A
Hypokalemia	9 (15.0)	1 (1.7)
Decreased appetite	8 (13.3)	0
Neutrophil count decreased	7 (11.7)	3 (5.0)
WBC count decreased	7 (11.7)	1 (1.7)
Treatment-related SAEs	**N=60**	
Interstitial lung disease	1 (1.7)	
Nausea/vomiting	1 (1.7)	
Pneumonitis	1 (1.7)	
Thrombocytopenia	1 (1.7)	
Unrelated SAEs		
Dyspnea	1 (1.7)	
Pneumocystis jirovecii pneumonia	1 (1.7)	
Pneumothorax	1 (1.7)	

[a]No Grade 5 AEs recorded prior to data cutoff

Hamilton EP, et al. ASCO 2023. Abstract 1004

- Patritumab is active, regardless of level of HER3 expression in HER2-non-amplified MBC, more so in HR+ than in TNBC pts
- Responses are durable in most patients. Safety is also reasonable with nausea, diarrhea, and fatigue the main toxicities and very little ILD to date
- Unclear how patients will respond to patritumab following treatment and progression on T-DXd with shared payload
- Should patritumab be developed to follow T-DXd, or in patients with HER2 ultralow or 0 IHC pts, instead of T-DXd?

Courtesy of Erica Mayer, MD, MPH, FASCO

Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Management of Gastroesophageal Cancers

Part 1 of a 2-Part CME Symposium Series Held in Conjunction with the 2024 ASCO Gastrointestinal Cancers Symposium

Thursday, January 18, 2024

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

Faculty

David H Ilson, MD, PhD

Professor Markus Moehler, MD

Rutika Mehta, MD, MPH

Manish A Shah, MD

Moderator

Harry H Yoon, MD, MHS

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