# Inside the Issue: Current and Future Management of ER-Positive Metastatic Breast Cancer After Disease Progression on a CDK4/6 Inhibitor

*A CME/MOC-Accredited Live Webinar*

**Thursday, July 20, 2023**
**5:00 PM – 6:00 PM ET**

## Faculty

**Aditya Bardia, MD, MPH**
**Erika Hamilton, MD**

## Moderator

**Neil Love, MD**

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# Faculty

**Aditya Bardia, MD, MPH**
Director, Breast Cancer Research Program
Associate Professor
Harvard Medical School
Attending Physician
Massachusetts General Hospital
Boston, Massachusetts

**Erika Hamilton, MD**
Director, Breast Cancer Research Program
Sarah Cannon Research Institute/Tennessee Oncology
Nashville, Tennessee

**Moderator**
**Neil Love, MD**
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# Commercial Support

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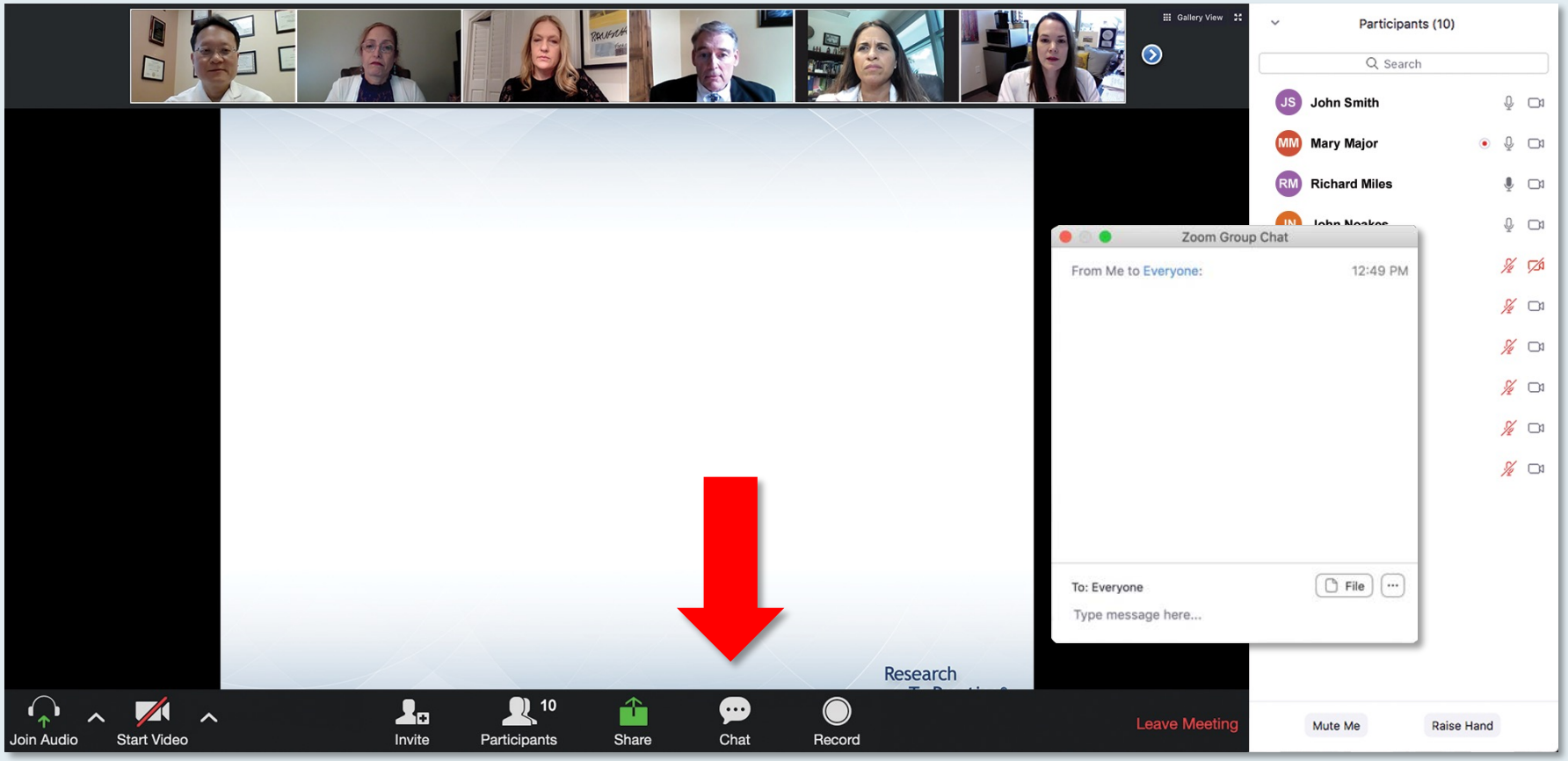


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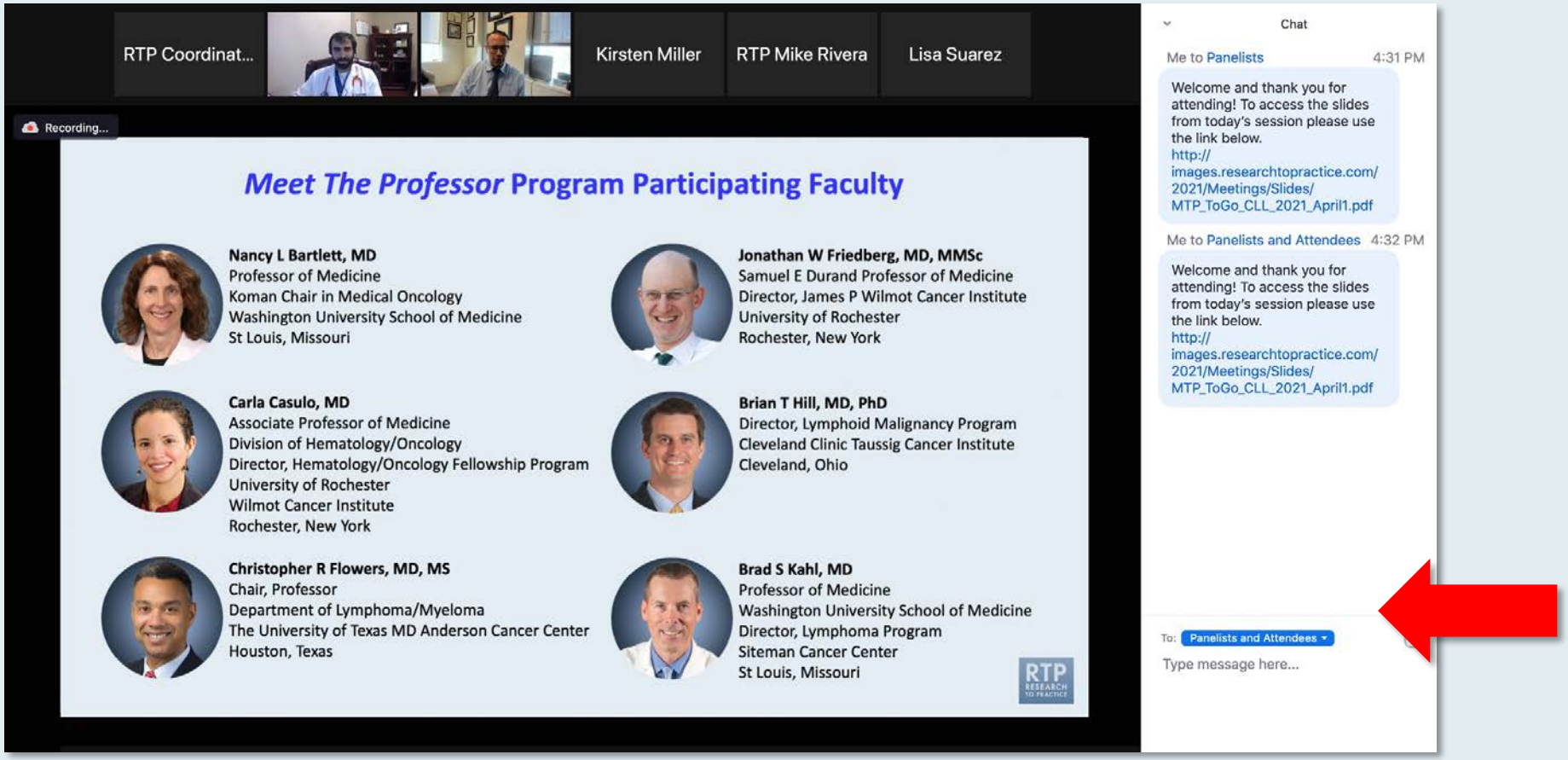


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# Familiarizing Yourself with the Zoom Interface

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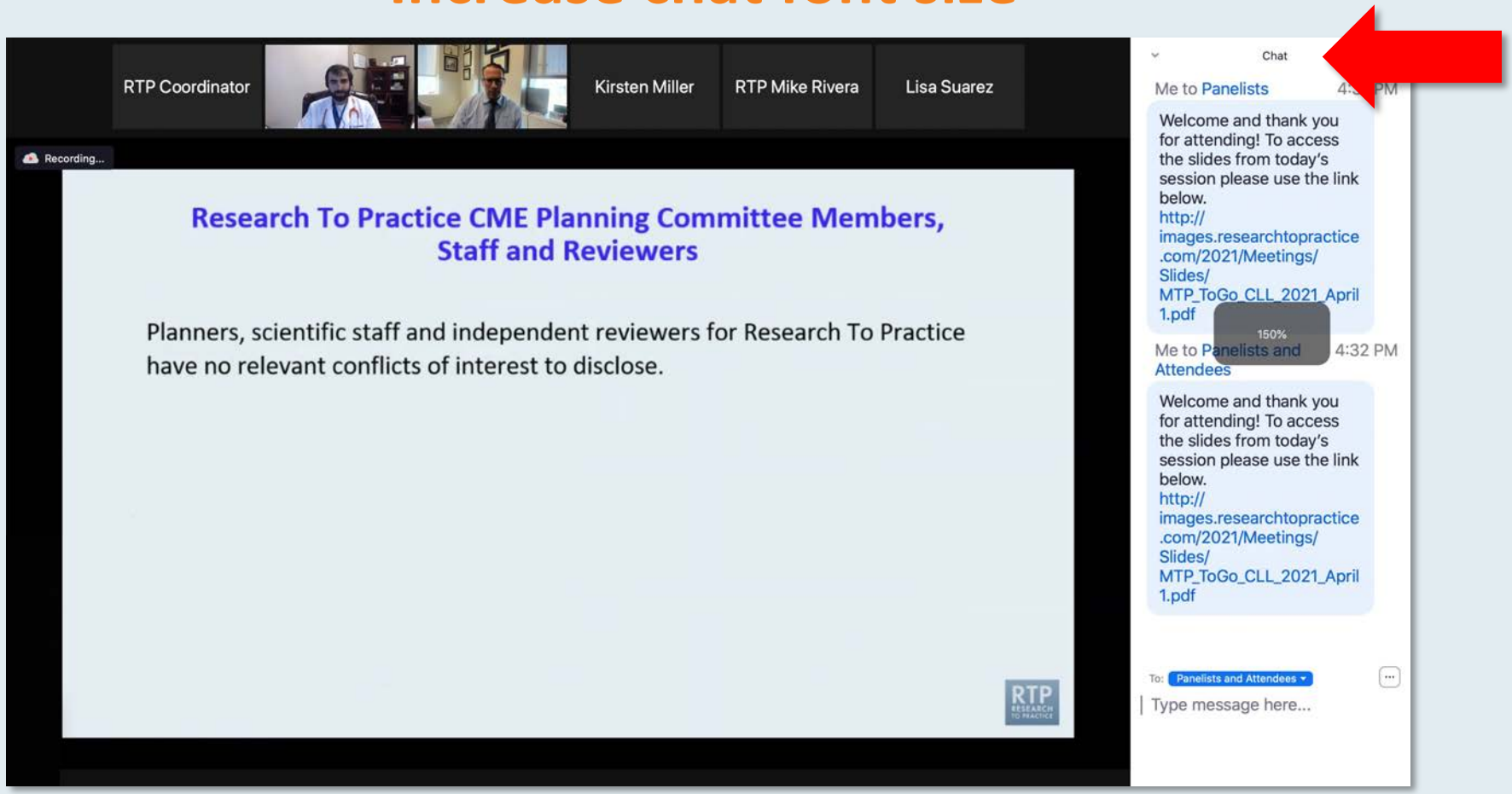


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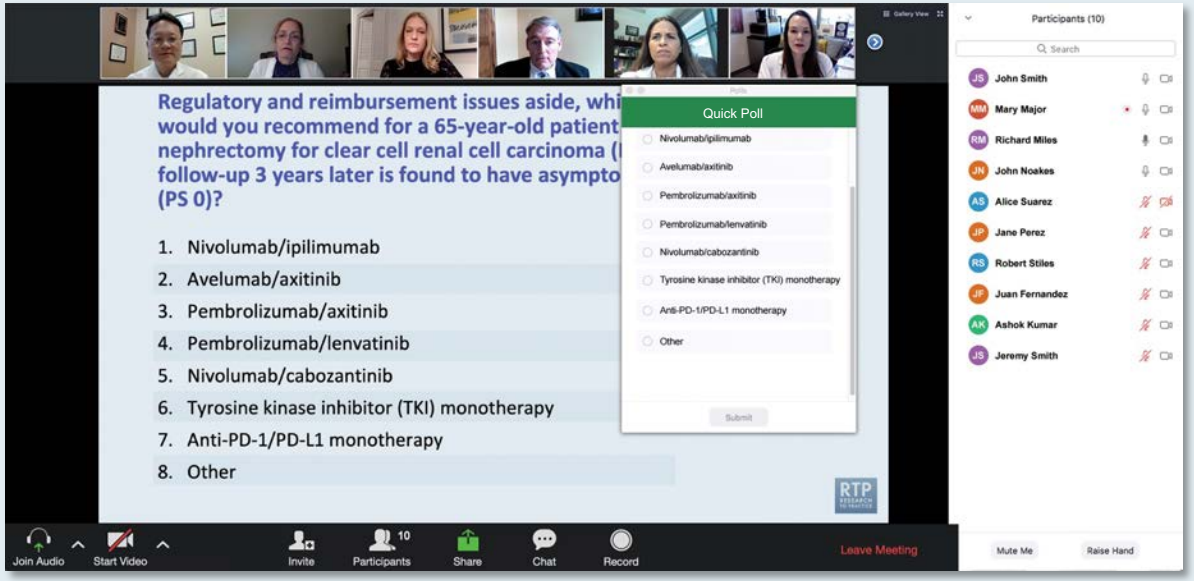


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# HER2-Positive Metastatic Breast Cancer

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# *Meet The Professor*

# Optimizing the Management of Soft Tissue Sarcoma and Related Connective Tissue Disorders

**Tuesday, July 25, 2023**
**5:00 PM – 6:00 PM ET**

## Faculty

**Richard F Riedel, MD**

## Moderator

**Neil Love, MD**

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# The Implications of Recent Data Sets for the Management of Hepatocellular Carcinoma

*A CME/MOC-Accredited Virtual Event*

**Thursday, July 27, 2023**
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## Faculty

**Ghassan Abou-Alfa, MD, MBA**
**Daneng Li, MD**

## Moderator

**Neil Love, MD**

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# Inside the Issue: Exploring the Current and Future Management of High-Risk, Hormone-Sensitive Nonmetastatic Prostate Cancer

*A CME/MOC-Accredited Live Webinar*

**Monday, July 31, 2023**
**5:00 PM – 6:00 PM ET**

## Faculty

**Neal D Shore, MD**
**Mary-Ellen Taplin, MD**

## Moderator

**Neil Love, MD**

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# Inside the Issue: The Current and Future Role of CD20 x CD3 Bispecific Antibodies in the Management of Non-Hodgkin Lymphoma

*A CME/MOC-Accredited Live Webinar*

**Wednesday, August 2, 2023**
**5:00 PM – 6:00 PM ET**

## Faculty

**Martin Hutchings, MD, PhD**
**Loretta J Nastoupil, MD**

## Moderator

**Neil Love, MD**

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# Inside the Issue: Optimizing the Management of Metastatic Pancreatic Cancer

*A CME/MOC-Accredited Live Webinar*

**Tuesday, August 8, 2023**
**5:00 PM – 6:00 PM ET**

## Faculty

**Eileen M O'Reilly, MD**
**Zev Wainberg, MD, MSc**

## Moderator

**Neil Love, MD**

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# *Meet The Professor*

# Optimizing the Management of Melanoma

**Thursday, August 10, 2023**
**5:00 PM – 6:00 PM ET**

## Faculty

**Prof Georgina Long, AO, BSc, PhD, MBBS**

## Moderator

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*Thank you for joining us!*

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Sarah Cannon Research Institute/Tennessee Oncology
Nashville, Tennessee

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**Neil Love, MD**
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# Survey Participants

**Harold J Burstein, MD, PhD**
Institute Physician, Dana-Farber Cancer Institute
Professor of Medicine, Harvard Medical School
Boston, Massachusetts

**Virginia Kaklamani, MD, DSc**
Professor of Medicine
Ruth McLean Bowman Bowers Chair in Breast Cancer Research and Treatment
AB Alexander Distinguished Chair in Oncology
Leader, Breast Oncology Program
UT Health San Antonio MD Anderson Cancer Center
San Antonio, Texas

**Matthew P Goetz, MD**
Erivan K Haub Family Professor of Cancer Research
Honoring Richard F Emslander, MD
Professor of Oncology and Pharmacology
Enterprise Deputy Director, Translational Research
Director, Mayo Clinic Breast Cancer SPORE
Mayo Clinic
Rochester, Minnesota

**Ruth O'Regan, MD**
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Charles A Dewey Professor of Medicine
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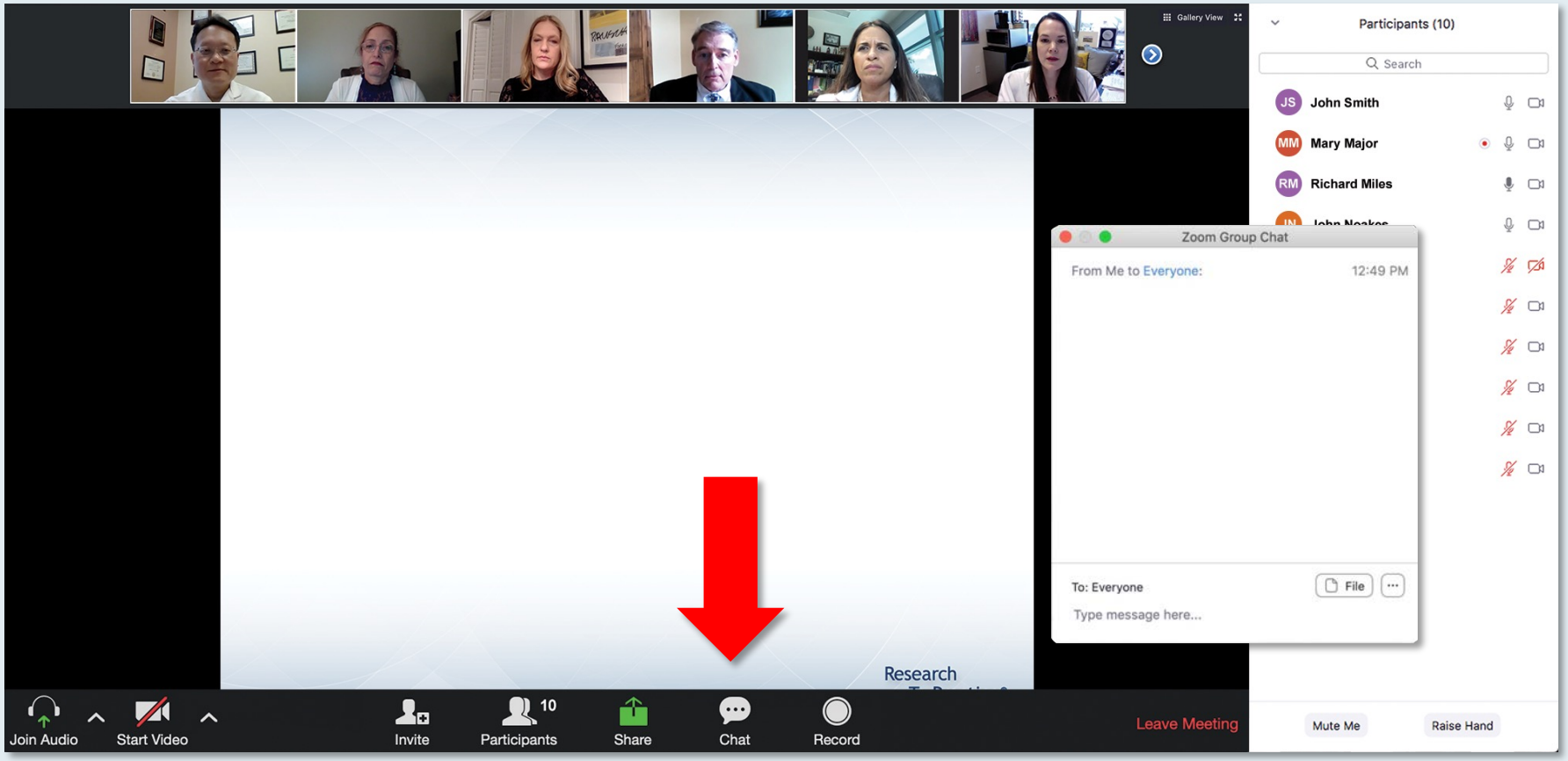


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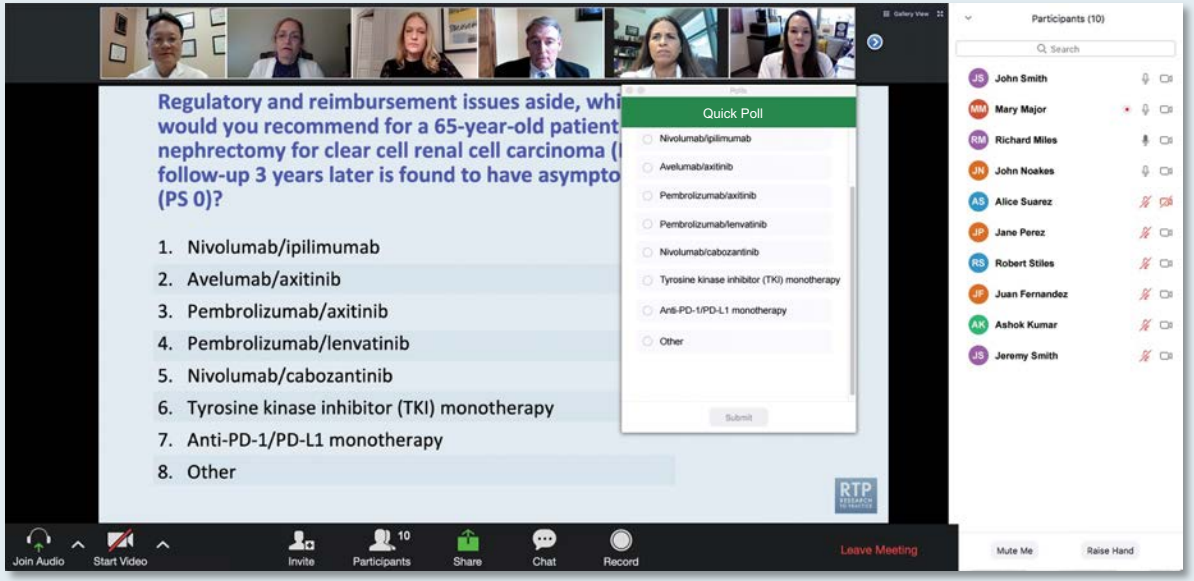


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WITH DR NEIL LOVE

# HER2-Positive Metastatic Breast Cancer

PROFESSOR GIUSEPPE CURIGLIANO
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# Current Strategies for Previously Treated ER-Positive Metastatic Breast Cancer

Aditya Bardia, MD, MPH, FASCO,
Director, Breast Cancer Research,
Associate Professor, Harvard Medical School,
Attending Physician, Mass General Cancer Center.

@DrAdityaBardia

Mass General Brigham
Mass General Cancer Cent

# Future Directions in the Management of ER-Positive mBC

**Erika Hamilton, MD**
Director, Breast Cancer Research Program
Sarah Cannon Research Institute/ Tennessee Oncology
Nashville, TN

SARAH CANNON
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# Key Data Sets

## Aditya Bardia, MD, MPH


- Kalinsky K et al. Randomized phase II trial of endocrine therapy with or without ribociclib after progression on cyclin-dependent kinase 4/6 inhibition in hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer: MAINTAIN trial. *J Clin Oncol* 2023 May 19;[Online ahead of print].
- Mayer EL et al. Palbociclib after CDK4/6i and endocrine therapy (PACE): A randomized phase II study of fulvestrant, palbociclib, and avelumab for endocrine pre-treated ER+/HER2- metastatic breast cancer. SABCS 2022;Abstract GS3-06.
- Bardia A et al. Phase I study of elacestrant (RAD1901), a novel selective estrogen receptor degrader, in ER-positive, HER2-negative advanced breast cancer. *J Clin Oncol* 2021 April 20;39(12):1360-70.
- Bidard F-C et al. Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: Results from the randomized phase III EMERALD trial. *J Clin Oncol* 2022 October 1;40(28):3246-56.

# Key Data Sets

## Aditya Bardia, MD, MPH (continued)


- Bardia A et al. EMERALD phase 3 trial of elacestrant versus standard of care endocrine therapy in patients with ER+/HER2- metastatic breast cancer: Updated results by duration of prior CDK4/6i in metastatic setting. SABCS 2022;Abstract GS3-01.
- Kalinsky K et al. Sacituzumab govitecan in previously treated hormone receptor-positive/HER2-negative metastatic breast cancer: Final results from a phase I/II, single-arm, basket trial. *Ann Oncol* 2020 December;31(12):1709-18.
- Rugo H et al. Sacituzumab govitecan in hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol* 2022 October 10;40(29):3365-76.
- Rugo HS et al. Overall survival (OS) results from the phase 3 TROPiCS-02 study of sacituzumab govitecan (SG) vs treatment of physician's choice (TPC) in patients (pts) with HR+/HER2- metastatic breast cancer (MBC). ESMO 2022;Abstract LBA76.

# Key Data Sets

## Aditya Bardia, MD, MPH (continued)


- Marmé F et al. Sacituzumab govitecan (SG) efficacy in hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2–) metastatic breast cancer (MBC) by HER2 immunohistochemistry (IHC) status in the phase 3 TROPiCS-02 study. *Ann Oncol* 2022;33(Suppl 7):S88-121.
- 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): Results of DESTINY-Breast04, a randomized, phase 3 study. ASCO 2022;Abstract LBA3.
- Modi S et al. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. *N Engl J Med* 2022 July 7;387(1):9-20.

# Key Data Sets

## Erika Hamilton, MD

- Bardia A et al. EMERALD phase 3 trial of elacestrant versus standard of care endocrine therapy in patients with ER+/HER2- metastatic breast cancer: Updated results by duration of prior CDK4/6i in metastatic setting. SABCS 2022;Abstract GS3-01.
- Oliviera M et al. Camizestrant, a next generation oral SERD vs fulvestrant in post-menopausal women with advanced ER-positive HER2-negative breast cancer: Results of the randomized, multi-dose phase 2 SERENA-2 trial. SABCS 2022;Abstract GS3-02.
- Martin M et al. Giredestrant (GDC-9545) vs physician choice of endocrine monotherapy (PCET) in patients (pts) with ER+, HER2- locally advanced/metastatic breast cancer (LA/MBC): Primary analysis of the phase 2 randomised, open-label acelERA BC study. ESMO 2022;Abstract 211MO.
- Hamilton E et al. First-in-human safety and activity of ARV-471, a novel PROTAC estrogen receptor degrader, in ER+/HER2- locally advanced or metastatic breast cancer. SABCS 2021;Abstract PD13-08.

# Key Data Sets

## Erika Hamilton, MD (continued)

- Hurvitz S et al. ARV-471, a PROTAC® estrogen receptor (ER) degrader in advanced ER-positive/human epidermal growth factor receptor 2 (HER2)-negative breast cancer: Phase 2 expansion (VERITAC) of a phase 1/2 study. SABCS 2022;Abstract 205P.
- Turner NC et al. Capivasertib and fulvestrant for patients with aromatase inhibitor-resistant hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer: Results from the Phase III CAPItello-291 trial. SABCS 2022;Abstract GS3-04.
- Oliveira M et al. Capivasertib and fulvestrant for patients with aromatase inhibitor-resistant HR+/HER2– advanced breast cancer: Subgroup analyses from the phase 3 CAPItello-291 trial. ESMO Breast 2023;Abstract 187O.
- Krop I et al. Results from the phase 1/2 study of patritumab deruxtecan, a HER3-directed antibody-drug conjugate (ADC), in patients with HER3-expressing metastatic breast cancer (MBC). ASCO 2022;Abstract 1002.

# Key Data Sets

## Erika Hamilton, MD (continued)

- Pistilli B et al. A phase 2 study of patritumab deruxtecan (HER3-DXd), in patients (pts) with advanced breast cancer (ABC), with biomarker analysis to characterize response to therapy (ICARUS-BREAST01). ESMO Breast 2023;Abstract 189O.
- Hamilton E et al. A phase 2 study of HER3-DXd in patients (pts) with metastatic breast cancer (MBC). ASCO 2023;Abstract 1004.
- Meric-Bernstram F et al. Phase 1 TROPION-PanTumor01 study evaluating datopotamab deruxtecan in unresectable or metastatic hormone receptor positive (HR positive), HER2 negative breast cancer. SABCS 2022;Abstract PD13-08.

# Agenda

**INTRODUCTION: Biopharmacology and Endocrinology of Breast Cancer**

**MODULE 1: Current Strategies for Previously Treated ER-Positive Metastatic Breast Cancer (mBC) — Dr Bardia**

**MODULE 2: Future Directions in the Management of ER-Positive mBC — Dr Hamilton**

**MODULE 3: Clinical Investigator Survey**

# Agenda

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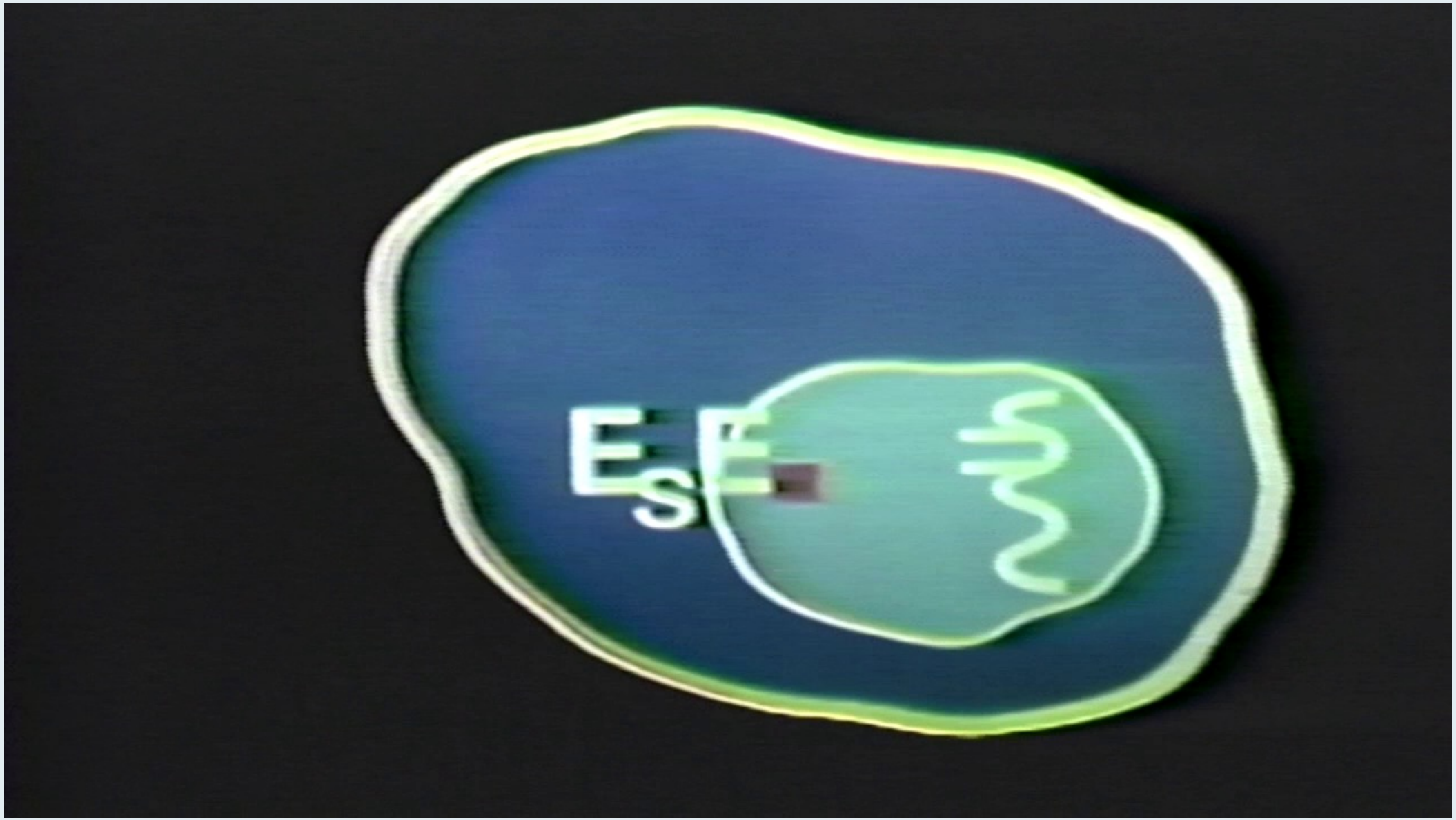
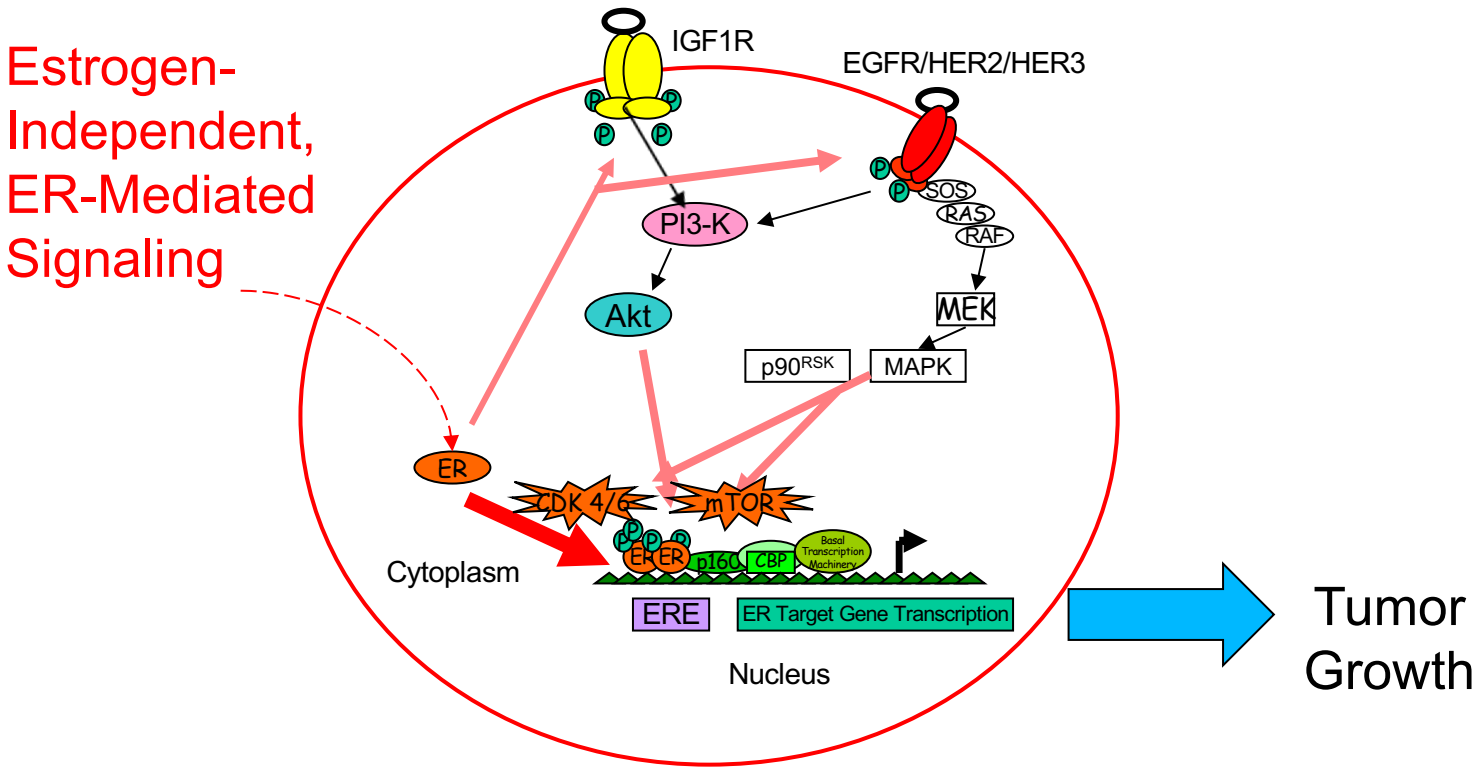
# Hormonal Therapy for the 1980s



# Endocrine Therapy Resistance: Potential Factors to Consider

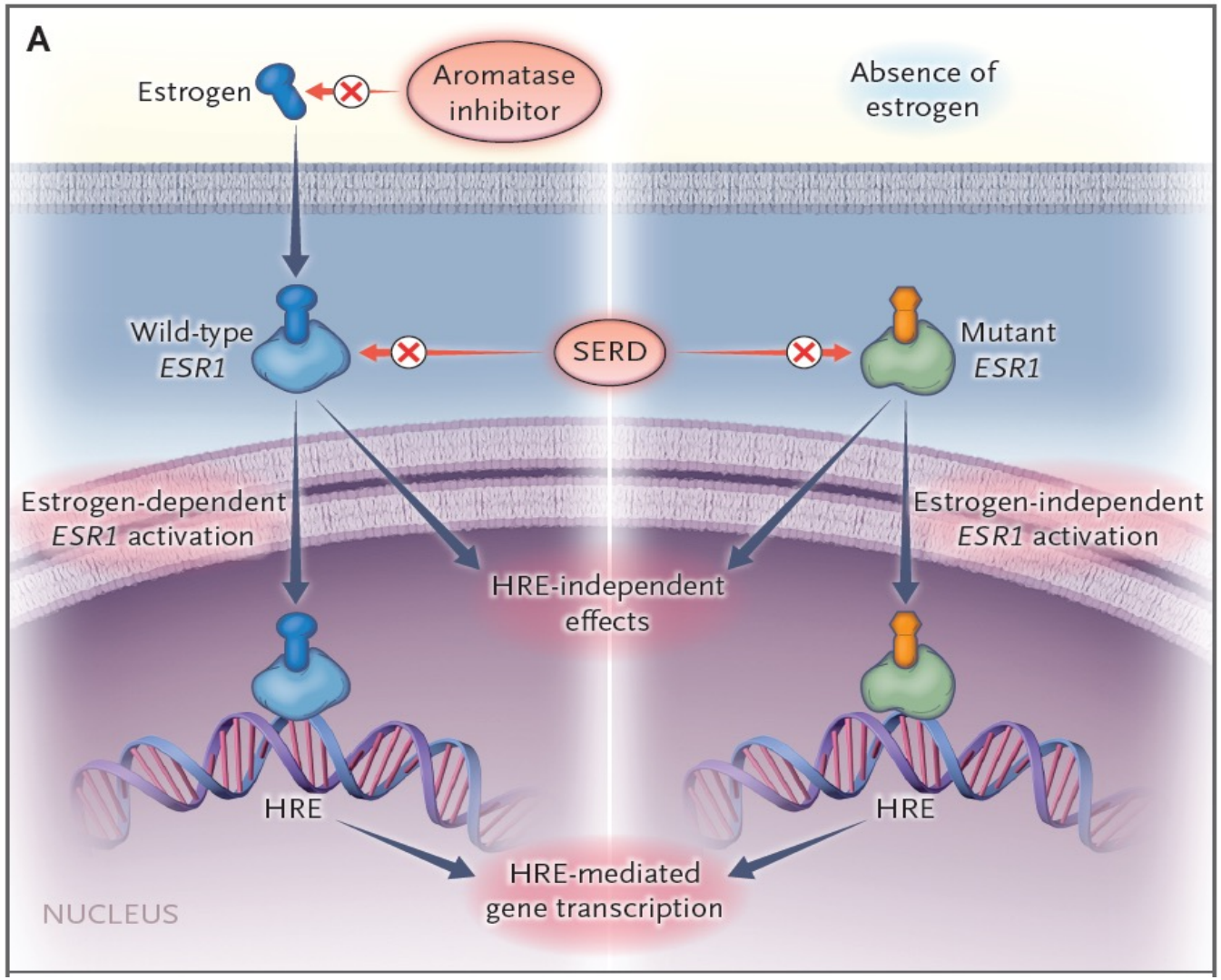



- ER pathway is still active and disease progression due to estrogen-independent but estrogen-receptor mediated signaling...*ESR1* mutations…

Johnston SR. *J Natl Cancer Inst*. 2015;107:djv212.

Courtesy of Aditya Bardia, MD, MPH

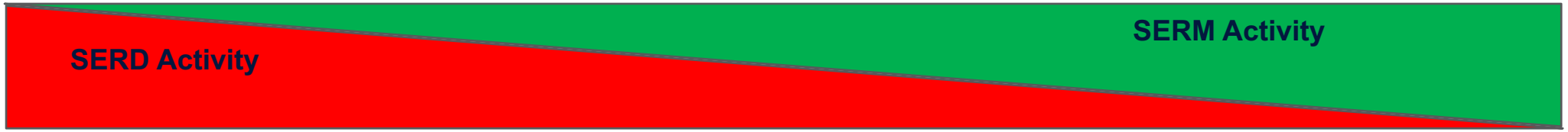
# *ESR1* (Acquired) Mutations: Resistance to AI




Bardia A, et al. *N Engl J Med*. 2018;379:1946-1953.

Courtesy of Aditya Bardia, MD, MPH

# SERM/SERD landscape in breast cancer




| | | | | | | |
|---|---|---|---|---|---|---|
| Fulvestrant | ARV-471 | DPC974 | Bazedoxifene | Elacestrant | Raloxifene | Tamoxifen |
| RU58668 | | | Pipendoxifene | | Lasofoxifene | Toremifene |
| | | | Acolbifene | | Arzoxifene | Endoxifen |
| | | | | | | H3-6545 |
| | | | | | | Idoxifene |
| | | | | | | Droloxifene |

| | |
|---|---|
| D-0502 | Camizestrant |
| SHR9549 | Giresdestrant |
| OP-1250 | Amcenestrant |
| LSZ102 | ZN-c5 |
| GDC810 | Rintodestrant |
| AZD9694 | Imlunestrant |
| GD0927 | AC0682 |

**Red:** First in Class (clinically relevant)
**Red:** FDA approved
**Blue:** Currently in clinical development
**Green**: First in Class (development discontinued)
**Black:** Clinical development discontinued

@ErikaHamilton9

Courtesy of Erika Hamilton, MD

SARAH CANNON Research Institute

Slide credit: D. McDonnell, SABCS 2021

# Agenda

**INTRODUCTION: Biopharmacology and Endocrinology of Breast Cancer**

**MODULE 1: Current Strategies for Previously Treated ER-Positive Metastatic Breast Cancer (mBC) — Dr Bardia**

**MODULE 2: Future Directions in the Management of ER-Positive mBC — Dr Hamilton**

**MODULE 3: Clinical Investigator Survey**

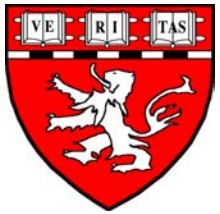
# Current Strategies for Previously Treated ER-Positive Metastatic Breast Cancer

Aditya Bardia, MD, MPH, FASCO,

Director, Breast Cancer Research,

Associate Professor, Harvard Medical School,

Attending Physician, Mass General Cancer Center.




@DrAdityaBardia

Mass General Brigham
Mass General Cancer Center

# Patient Story:
# Endocrine Therapy for HR+ Cancer

65 yo female with:

- 2010: HR+/HER2- breast cancer (localized)
- 2015: Completed adjuvant exemestane
- 2021: Disease recurrence (bone); Started letrozole with CDK4/6i
- 2023: Disease progression (bone)

Which therapy would you consider next?

- Fulvestrant
- Fulvestrant + CDK 4/6i
- Exemestane + everolimus
- Need more information

Courtesy of Aditya Bardia, MD, MPH

# CDK 4/6i after CDK 4/6i

Mixed Results:

- MAINTAIN: Fulvestrant + Ribociclib demonstrated improvement in PFS
- PACE: Fulvestrant + palbociclib demonstrated No improvement in PFS

- postMONARCH: Fulvestrant vs fulvestrant + abemaciclib (NCT05169567): phase 3 trial

Kalinsky K et al. J Clin Oncol. 2023
Mayer E at al. SABCS 2022

Courtesy of Aditya Bardia, MD, MPH

# Patient Story:
# Endocrine Therapy for HR+ Cancer

1st line therapy:

- Endocrine Therapy + CDK 4/6 inhibitor

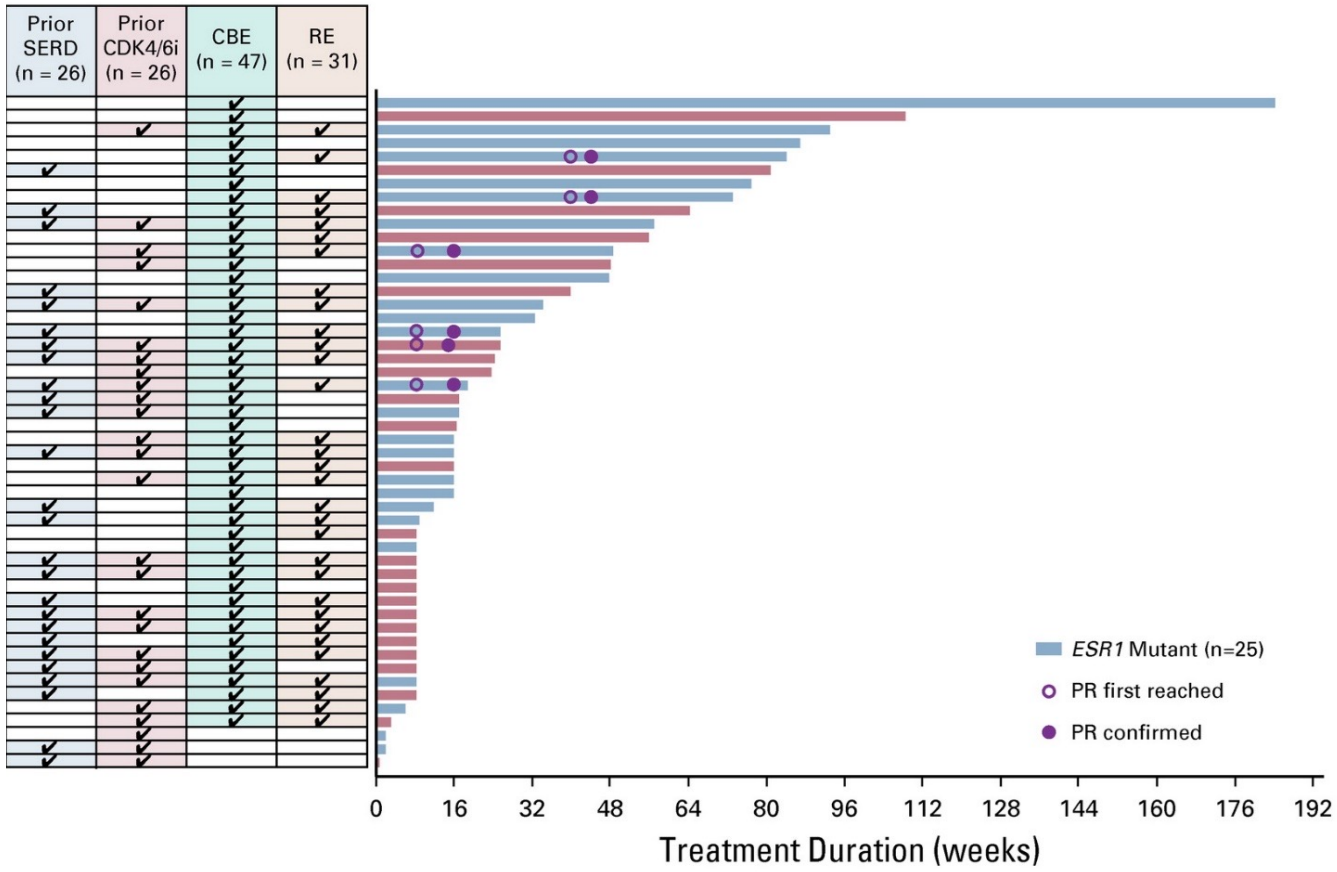
Which therapy would you consider next in 2nd line?

- Fulvestrant
- Fulvestrant + CDK 4/6i
- Exemestane + everolimus
- Need more information

ctDNA analysis revealed *ESR1* mutation

Courtesy of Aditya Bardia, MD, MPH

# Elacestrant Clinical Activity: CBR at 24 Weeks 42.6%



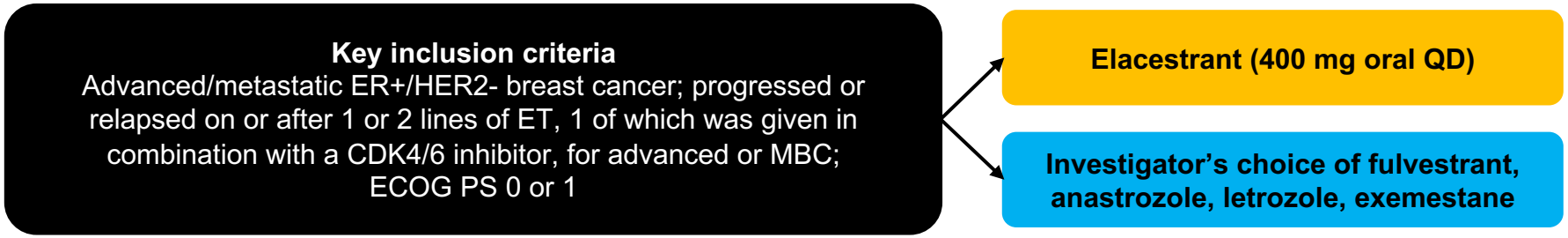

CBE, clinical benefit–evaluable; CBR, clinical benefit rate; PR, partial response; RE, response-evaluable.
Bardia A, et al. *J Clin Oncol*. 2021;39:1360-1370.

Courtesy of Aditya Bardia, MD, MPH

- Median of 3 prior systemic therapies
  - 52% had previously received prior SERD
  - 52% had previously received CDK4/6i therapy
  - 50% had *ESR1* mutation

# Phase 3 EMERALD: Study Design

- A multicenter, international, randomized, open-label, active-controlled phase 3 trial for postmenopausal patients with ER+/HER2- MBC




- Objective: assess PFS in all patients and those with m*ESR1*; OS, ORR, DOR, CBR, safety, PK, PRO

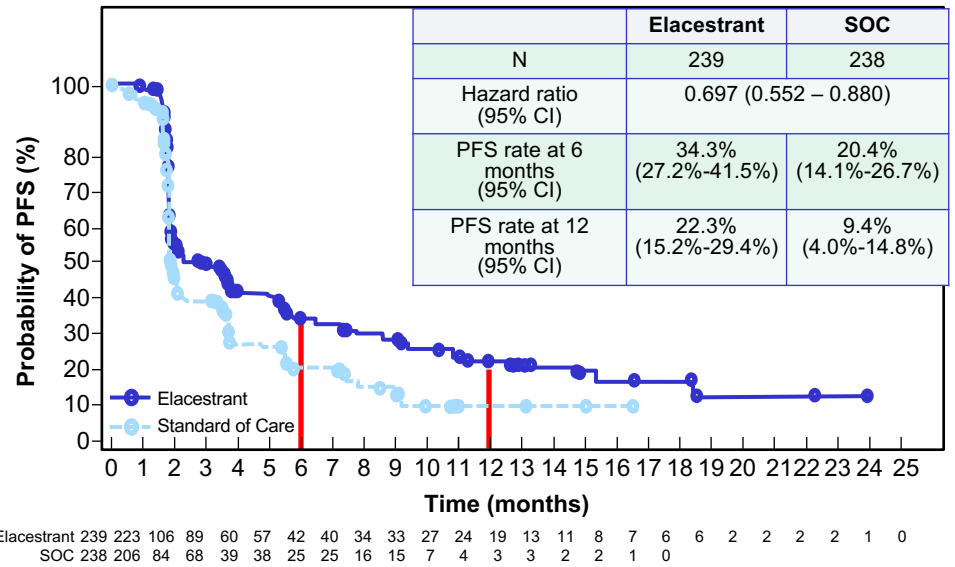
- Study design considerations:
  - planned sample size: 466 patients (randomized 1:1)
  - planned number of countries/study sites: ~17/215
  - planned study duration: ~30–33 months
  - stratification factors: mESR1 status (detected by ctDNA), prior fulvestrant and presence of visceral disease

Bardia A, et al. SABCS 2021. Abstract GS2-02.

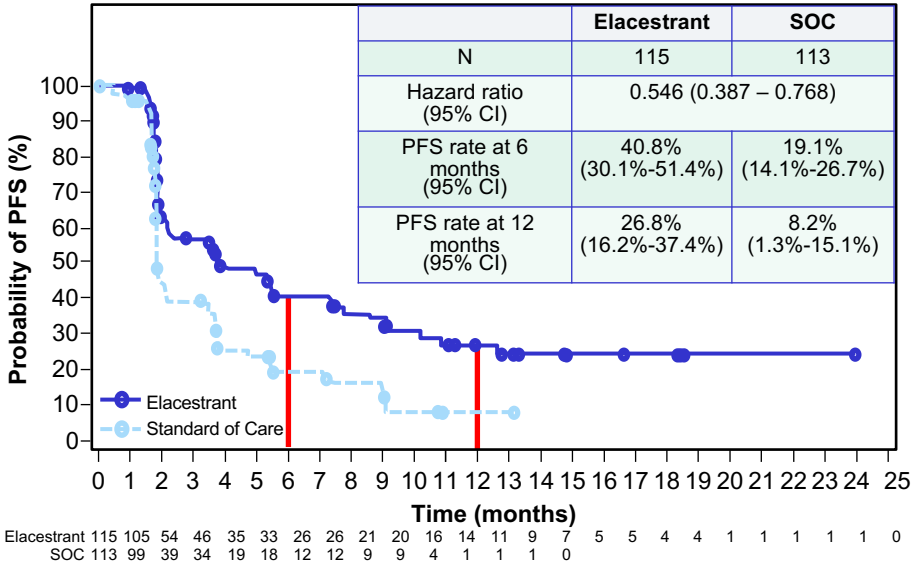
Courtesy of Aditya Bardia, MD, MPH

# EMERALD: PFS Rate at 6 and 12 Months—All Patients and *mESR1* Group

## All Patients




## Patients With Tumors Harboring *mESR1*



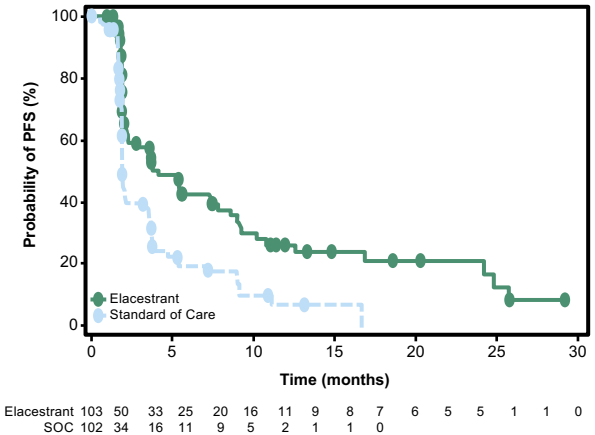

Elacestrant demonstrated a higher PFS rate at 6 and 12 months versus SOC ET in patients with ER+/HER2- advanced/metastatic breast cancer following prior CDK4/6i therapy

Bidard F-C et al. *J Clin Oncol* 2022 Oct 1;40(28):3246–56; Bardia A, et al. SABCS 2021. Abstract GS2-02.

Courtesy of Aditya Bardia, MD, MPH

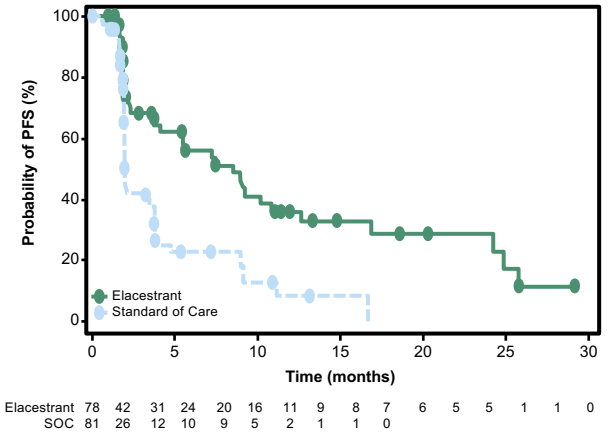
# EMERALD:
# PFS by duration of CDK 4/6i (ESR1m)

## At least 6 mo CDK4/6i



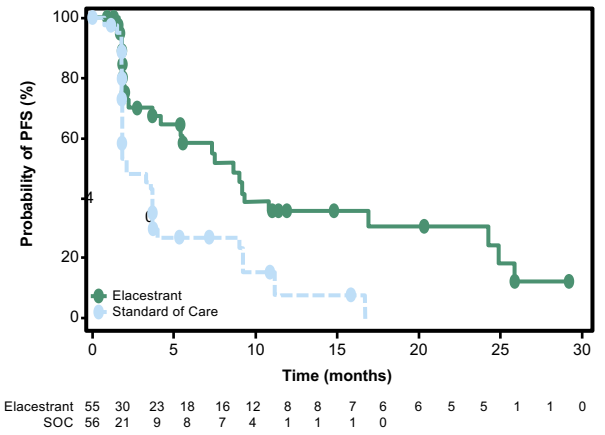

| | Elacestrant | SOC Hormonal Therapy |
|---|---|---|
| Median PFS, months (95% CI) | **4.14** (2.20 - 7.79) | **1.87** (1.87 - 3.29) |
| PFS rate at 12 months, % (95% CI) | 26.02 (15.12 - 36.92) | 6.45 (0.00 - 13.65) |
| Hazard ratio (95% CI) | **0.517** (0.361 - 0.738) | |

## 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 A et al, SABCS, 2022

Courtesy of Aditya Bardia, MD, MPH

# Oral SERD in ER+ MBC: Current Development Status

| Drug name | Current Development Status |
|---|---|
| Elacestrant (RAD1901) | Phase 3 |
| Giredestrant (GDC-9545) | Phase 2/3 |
| *Amcenestrant (SAR439859)* | *Phase 2/3* |
| Imlunestrant | Phase 3 |
| Camizestrant (AZD9833) | Phase 2/3 |

**Need to be careful with cross-study comparisons –**
Differences in prior lines of Rx, endocrine sensitivity, tumor biology

Courtesy of Aditya Bardia, MD, MPH

# Patient Story:
# Endocrine Therapy for HR+ Cancer

1st line therapy:

- Endocrine Therapy + CDK 4/6 inhibitor

Which therapy would you consider next in 2nd line?

- Fulvestrant
- Fulvestrant + CDK 4/6i
- Exemestane + everolimus
- Need more information

ctDNA analysis revealed *ESR1* mutation

Pt started elacestrant. Currently doing well on therapy.

Courtesy of Aditya Bardia, MD, MPH

# Case: 55F with HR+ MBC

55F with metastatic HR+ MBC (HER2 IHC = 0). Disease progression on various endocrine based therapy, and recently capecitabine and paclitaxel. PS = 1. No organ dysfunction. gBRCA = negative. PIK3CA and ESR1 WT.  What therapy would you consider next?

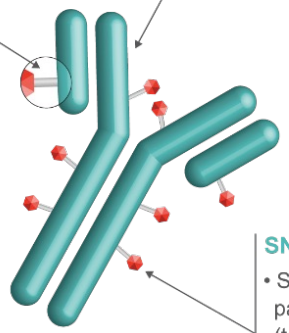
1. Eribulin
2. Vinorelbine
3. Sacituzumab Govitecan
4. Trastuzumab Deruxtecan

Courtesy of Aditya Bardia, MD, MPH

# Trop2 ADC for HR+ MBC: Sacituzumab Govitecan

**Humanized anti–Trop-2 antibody**
- Directed toward Trop-2, an epithelial antigen expressed on many solid cancers

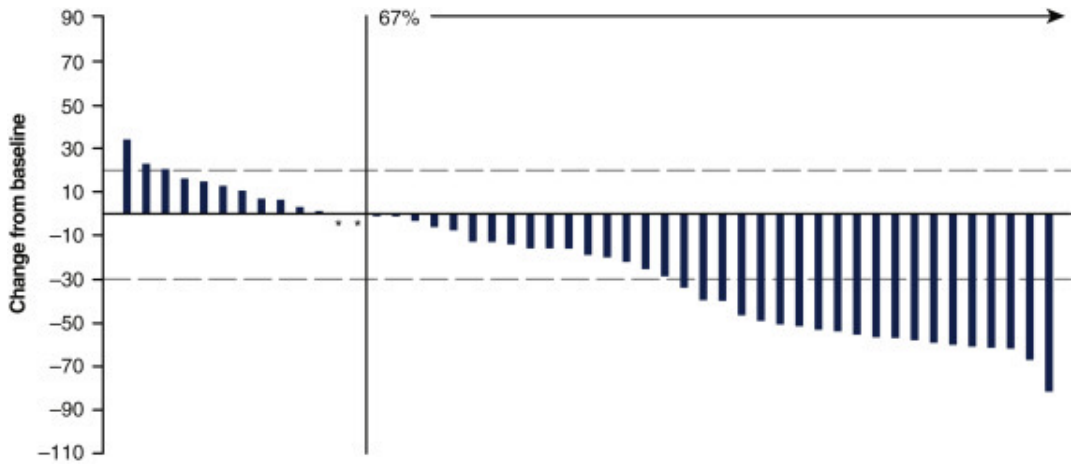
**Linker for SN-38**
- pH-sensitive, hydrolyzable linker for SN-38 release in targeted tumor cells and tumor microenvironment, allowing bystander effect
- High drug-to-antibody ratio (7.6:1)



**SN-38 payload**
- SN-38 more potent than parent compound, irinotecan (topoisomerase I inhibitor)
- SN-38 chosen for its moderate cytotoxicity (with IC50 in the nanomolar range), permitting delivery in high quantity to the tumor

Internalization and enzymatic cleavage by tumor cell not required for SN-38 liberation from antibody

**Confirmed ORR = 31.5%**




**Phase I/II Basket Trial**

**≥3rd Line HR+/HER2- MBC N=54[a]**

**Other Advanced Epithelial Cancers**

- Adults, ≥18 y
- Patients with metastatic epithelial cancers who progressed ≥1 standard therapeutic regimen for their disease
- ECOG performance status 0/1
- Measurable disease by CT/MRI

**Sacituzumab govitecan 10 mg/kg IV**

Days 1 and 8 every 21 days (restaging scans every 8 weeks)

Until progression or unacceptable toxicity

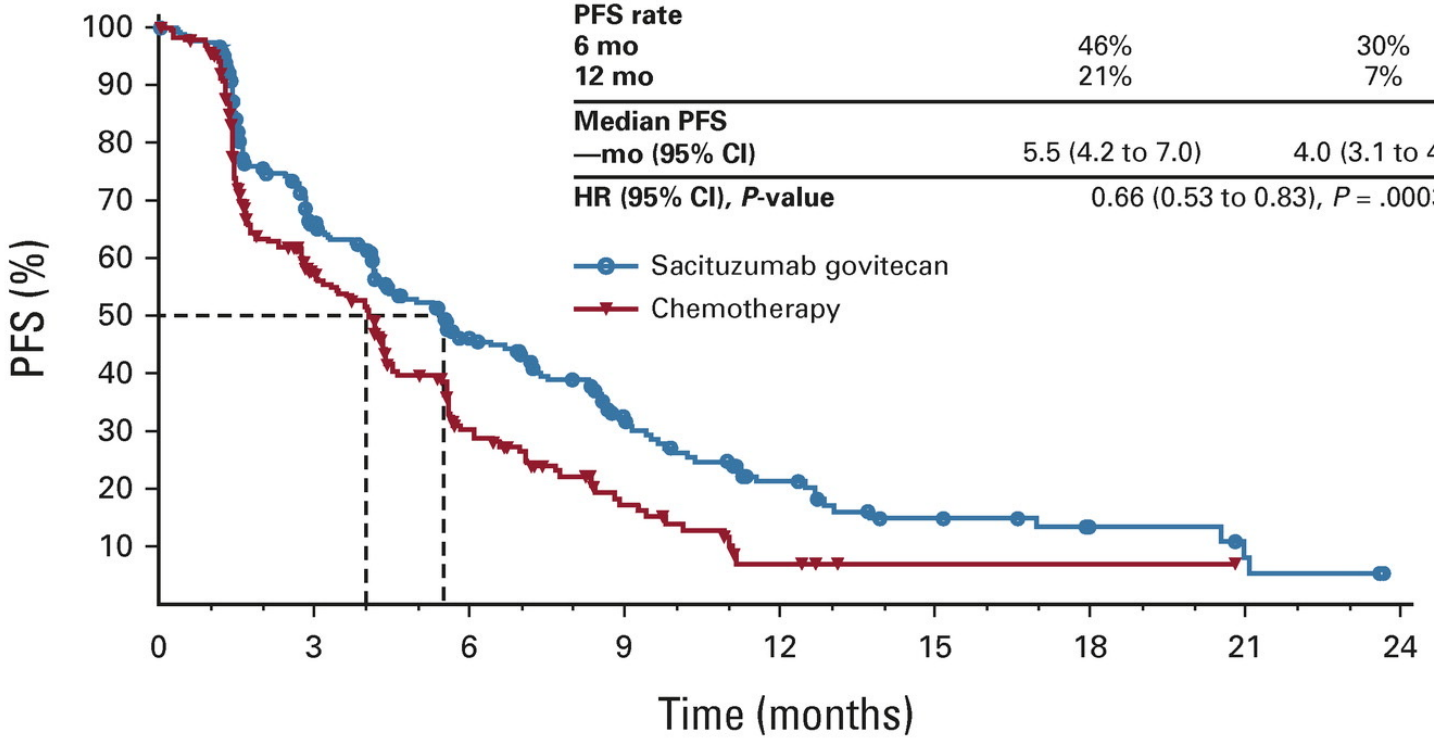
**Endpoints:**
- Response evaluation by investigators according to RECIST 1.1
- Duration of response
- Progression-free survival (PFS)
- Overall survival (OS)
- Safety

Kalinsky K et al. Ann Oncol. 2020

Courtesy of Aditya Bardia, MD, MPH

# Sacituzumab Govitecan vs TPC: PFS (HR+ MBC)

| | Sacituzumab govitecan (n = 272) | Chemotherapy (n = 271) |
|---|---|---|
| **No. of events** | 170 | 159 |
| **PFS rate** | | |
| **6 mo** | 46% | 30% |
| **12 mo** | 21% | 7% |
| **Median PFS —mo (95% CI)** | 5.5 (4.2 to 7.0) | 4.0 (3.1 to 4.4) |
| **HR (95% CI), *P*-value** | 0.66 (0.53 to 0.83), *P* = .0003 | |

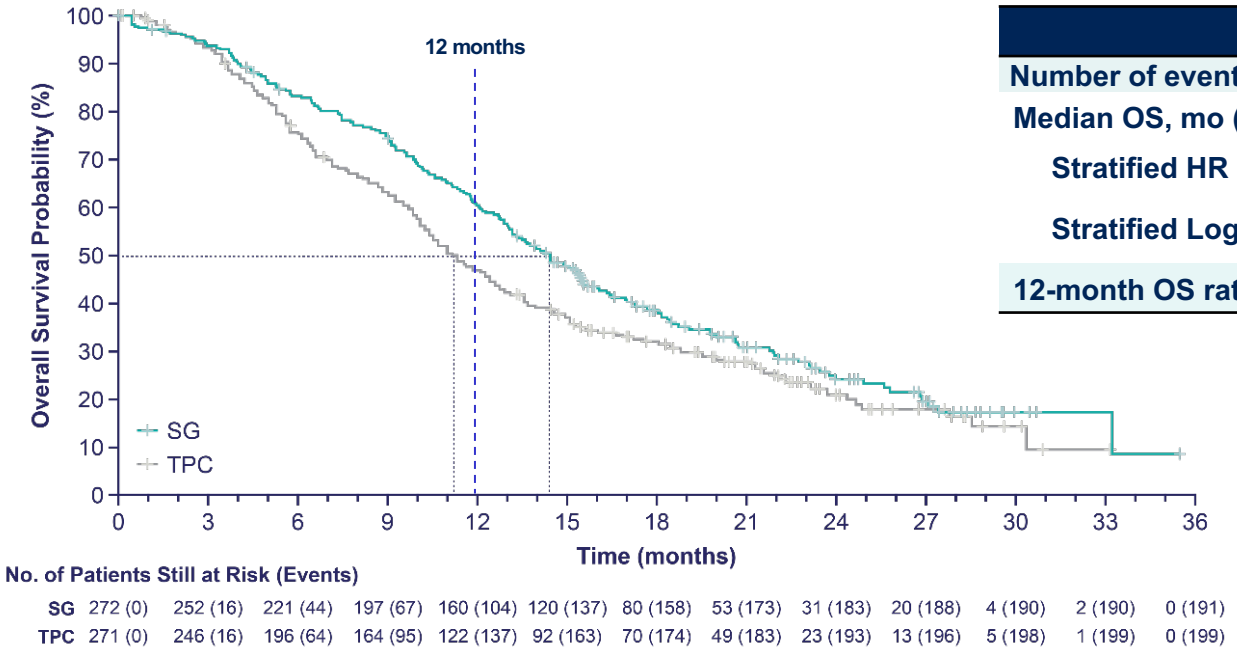



| No. at risk: | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Sacituzumab govitecan | 272 | 148 | 82 | 44 | 22 | 12 | 6 | 3 | 0 |
| Chemotherapy | 271 | 105 | 41 | 17 | 4 | 1 | 1 | 0 | |

Rugo H and Bardia A et al. J Clin Oncol. 2022

Courtesy of Aditya Bardia, MD, MPH

# Sacituzumab Govitecan vs TPC: OS (HR+ MBC)




**No. of Patients Still at Risk (Events)**

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **SG** | 272 (0) | 252 (16) | 221 (44) | 197 (67) | 160 (104) | 120 (137) | 80 (158) | 53 (173) | 31 (183) | 20 (188) | 4 (190) | 2 (190) | 0 (191) |
| **TPC** | 271 (0) | 246 (16) | 196 (64) | 164 (95) | 122 (137) | 92 (163) | 70 (174) | 49 (183) | 23 (193) | 13 (196) | 5 (198) | 1 (199) | 0 (199) |

| | SG (n=272) | TPC (n=271) |
|---|---|---|
| **Number of events** | 191 | 199 |
| **Median OS, mo (95% CI)** | 14.4 (13.0–15.7) | 11.2 (10.1–12.7) |
| **Stratified HR (95% CI)** | **0.79** (0.65–0.96) | |
| **Stratified Log Rank *P* value** | *P*=0.020 | |
| **12-month OS rate, % (95% CI)** | 61 (55–66) | 47 (41–53) |

- SG demonstrated a statistically significant improvement in OS vs TPC with 21% reduction in the risk of death; having met statistical significance, no further formal statistical testing of OS will occur
- Patients who received SG survived a median of ***3.2 months longer*** than those who received TPC

**FDA Approved (Feb 2023)**

Median follow-up was 12.5 months.
OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

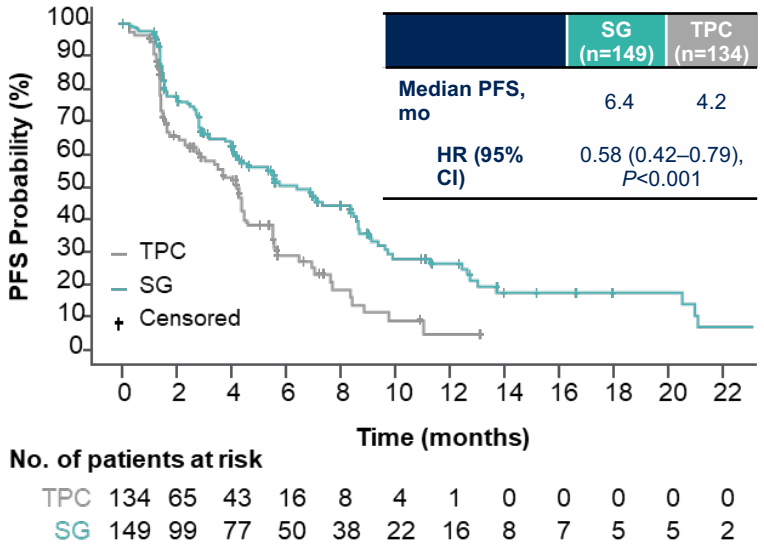
PARIS 2022 ESMO congress

Presented by: Hope S. Rugo, MD

Courtesy of Aditya Bardia, MD, MPH

# Sacituzumab Govitecan vs TPC: Efficacy by HER2 status (TROPiCS-02)

## HER2-Low[a]

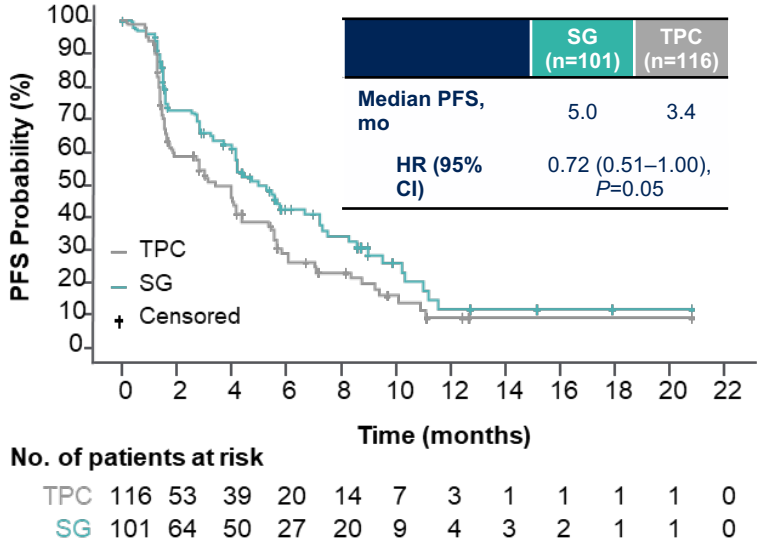



| | SG (n=149) | TPC (n=134) |
|---|---|---|
| Median PFS, mo | 6.4 | 4.2 |
| HR (95% CI) | 0.58 (0.42–0.79), *P*<0.001 | |

No. of patients at risk

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TPC | 134 | 65 | 43 | 16 | 8 | 4 | 1 | 0 | 0 | 0 | 0 | 0 |
| SG | 149 | 99 | 77 | 50 | 38 | 22 | 16 | 8 | 7 | 5 | 5 | 2 |

## HER2 IHC0

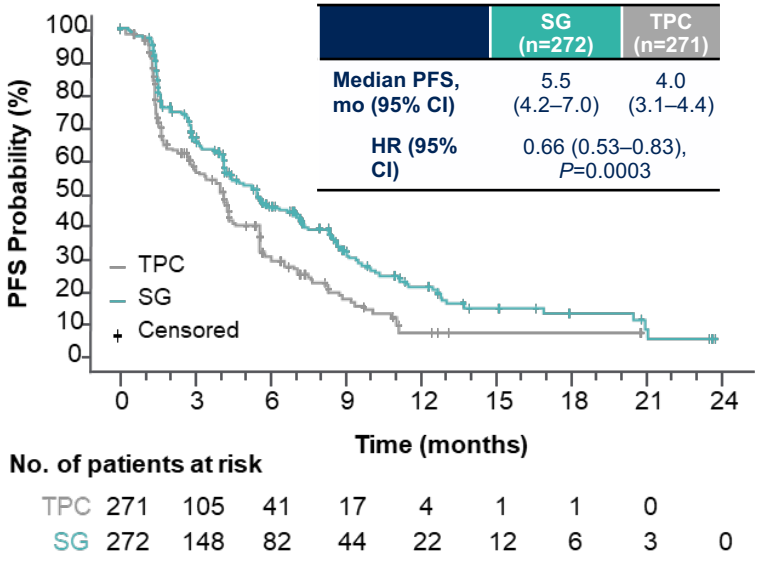



| | SG (n=101) | TPC (n=116) |
|---|---|---|
| Median PFS, mo | 5.0 | 3.4 |
| HR (95% CI) | 0.72 (0.51–1.00), *P*=0.05 | |

No. of patients at risk

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TPC | 116 | 53 | 39 | 20 | 14 | 7 | 3 | 1 | 1 | 1 | 1 | 0 |
| SG | 101 | 64 | 50 | 27 | 20 | 9 | 4 | 3 | 2 | 1 | 1 | 0 |

## ITT[1]




| | SG (n=272) | TPC (n=271) |
|---|---|---|
| Median PFS, mo (95% CI) | 5.5 (4.2–7.0) | 4.0 (3.1–4.4) |
| HR (95% CI) | 0.66 (0.53–0.83), *P*=0.0003 | |

No. of patients at risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TPC | 271 | 105 | 41 | 17 | 4 | 1 | 1 | 0 | |
| SG | 272 | 148 | 82 | 44 | 22 | 12 | 6 | 3 | 0 |

- Within the HER2-Low population, median PFS with SG vs TPC for the IHC1+ and IHC2+ subgroups was 7.0 vs 4.3 (HR, 0.57) and 5.6 vs 4.0 (HR, 0.58) months, respectively
- The hazard ratio for median PFS in a sensitivity analysis of the HER2-Low subgroup (excluding ISH-unverified[b]) was similar (HR, 0.53)

[a]HER2-Low defined as IHC1+, or IHC2+ and ISH-negative/unverified.
[b]39 patients with HER2 IHC2+ did not have ISH data documentation available for verification and were presumed to be HER2-low, consistent with the trial eligibility criteria to enroll HER2-negative patients.
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
1. Rugo HS, et al. *J Clin Oncol*. 2022. doi: 10.1200/JCO.22.01002. (epub ahead of print). Adapted from Rugo HS, et al. Sacituzumab govitecan in hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol*. 2022. doi: 10.1200/JCO.22.01002. Reprinted with permission from American Society of Clinical Oncology.

PARIS 2022 ESMO congress

Presented by: Dr. Frederik Marmé

Courtesy of Aditya Bardia, MD, MPH

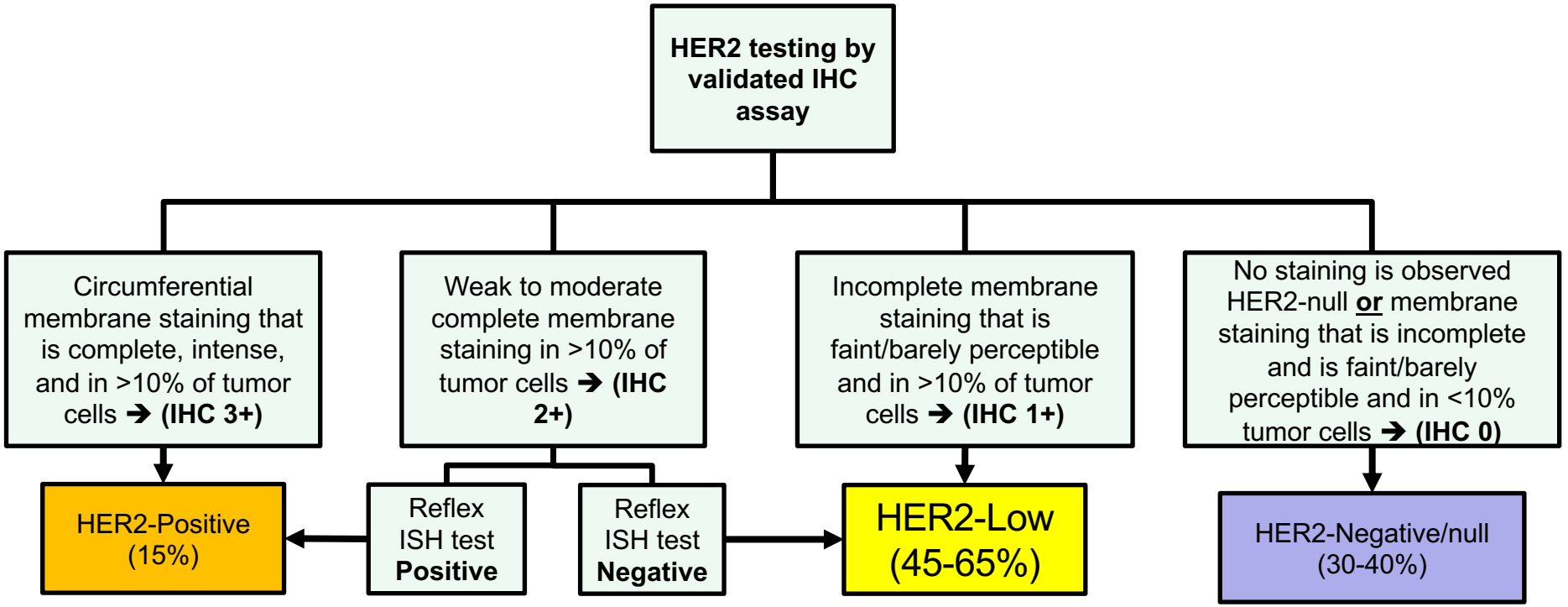
# Case: 55F with HR+ MBC

55F with metastatic HR+ MBC (HER2 IHC = 1). Disease progression on various endocrine based therapy, and recently capecitabine and paclitaxel. PS = 1. No organ dysfunction. gBRCA = negative. PIK3CA and ESR1 WT.  What therapy would you consider next?

1. Eribulin
2. Vinorelbine
3. Sacituzumab Govitecan
4. Trastuzumab Deruxtecan

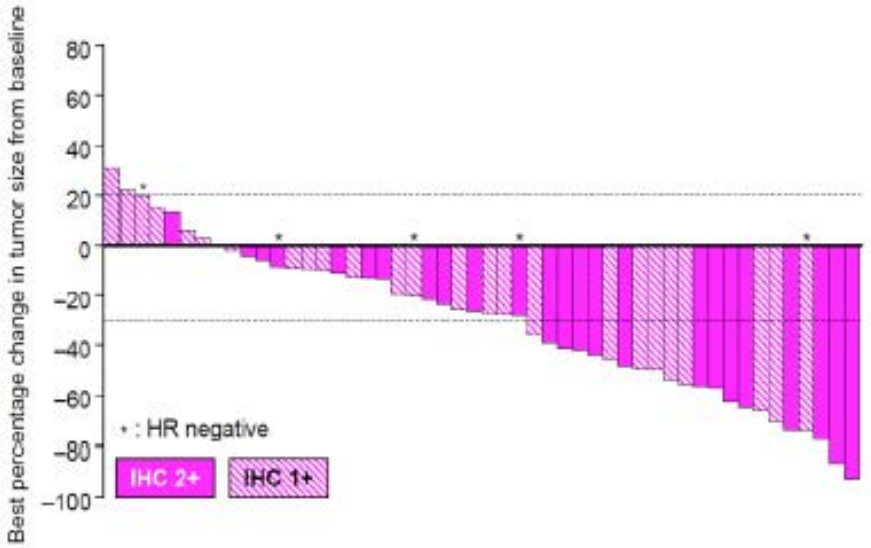
Courtesy of Aditya Bardia, MD, MPH

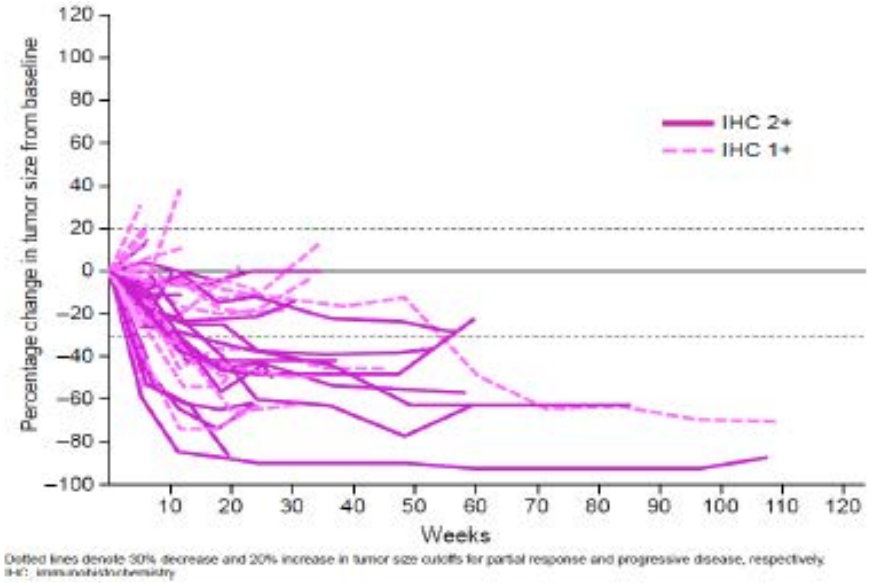
# HER2-Low Breast Cancer: Current Definition




Courtesy of Aditya Bardia, MD, MPH

# Trastuzumab Deruxtecan (T-DXd): HER2 Low Tumors




Dotted lines denote 30% decrease and 20% increase in tumor size cutoffs for partial response and progressive disease, respectively.

| | Confirmed ORR | mDoR | mPFS |
|---|---|---|---|
| All (N = 51) | 44.2% (N=43) | 9.4m | 7.6m |
| IHC 2+ (n = 24) | 54.5% (N=22) | 11.0m | 13.6m |
| IHC 1+ (n = 27) | 33.3% (N=21) | 7.9m | 5.7m |
| HR+ (n = 45) | 47.4% (N=38) | 11.0m | 7.9m |
| Prior CDK4/6 inhibitor (n = 15) | 33.3% (N=12) | NR | 7.1m |

Modi S et al. J Clin Oncol. 2020.

Courtesy of Aditya Bardia, MD, MPH

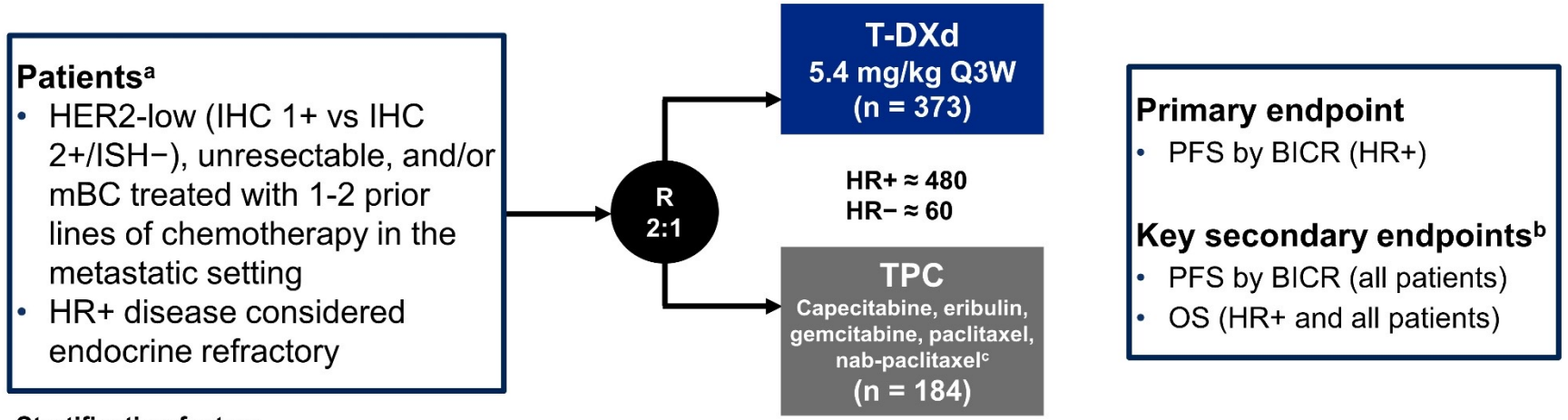
# Trastuzumab Deruxtecan vs TPC: Study Design (DESTINY-Breast04)

DESTINY-Breast04



## DESTINY-Breast04: First Randomized Phase 3 Study of T-DXd for HER2-low mBC

**An open-label, multicenter study (NCT03734029)**




**Stratification factors**

- Centrally assessed HER2 status[d] (IHC 1+ vs IHC 2+/ISH−)
- 1 versus 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR−

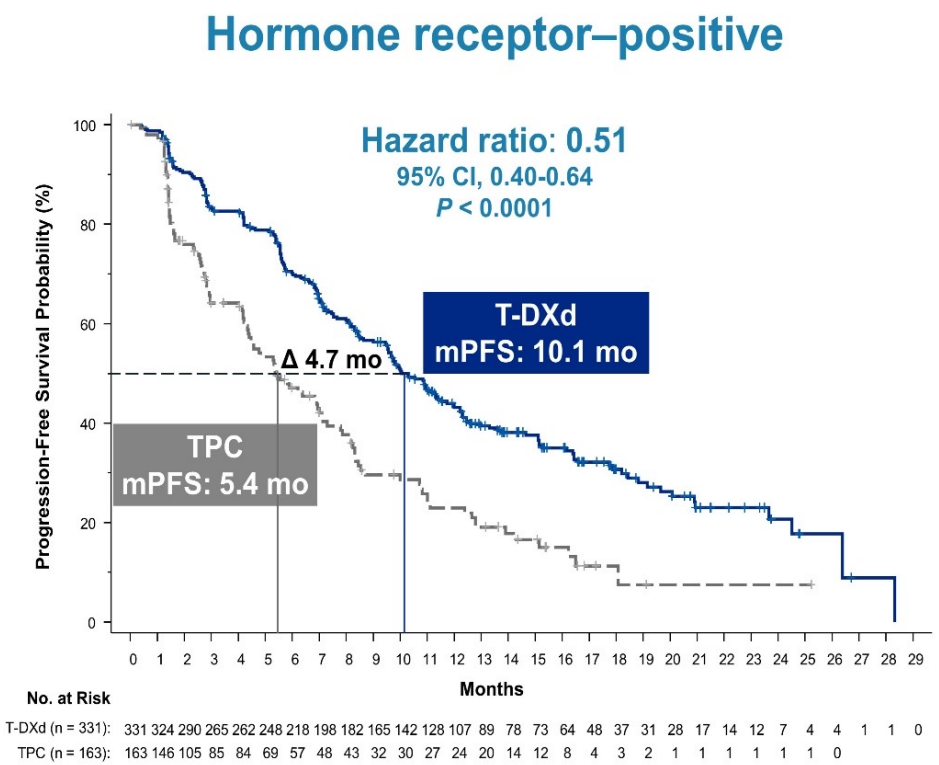
ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CDK, cyclin-dependent kinase; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Other secondary endpoints included ORR (BICR and investigator), DOR (BICR), PFS (investigator), and safety; efficacy in the HR− cohort was an exploratory endpoint. [c]TPC was administered accordingly to the label. [d]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational use only [IUO] Assay system.



Courtesy of Aditya Bardia, MD, MPH

# Trastuzumab Deruxtecan vs TPC: PFS (HR+/HER2 Low BC)

## Progression-Free Survival



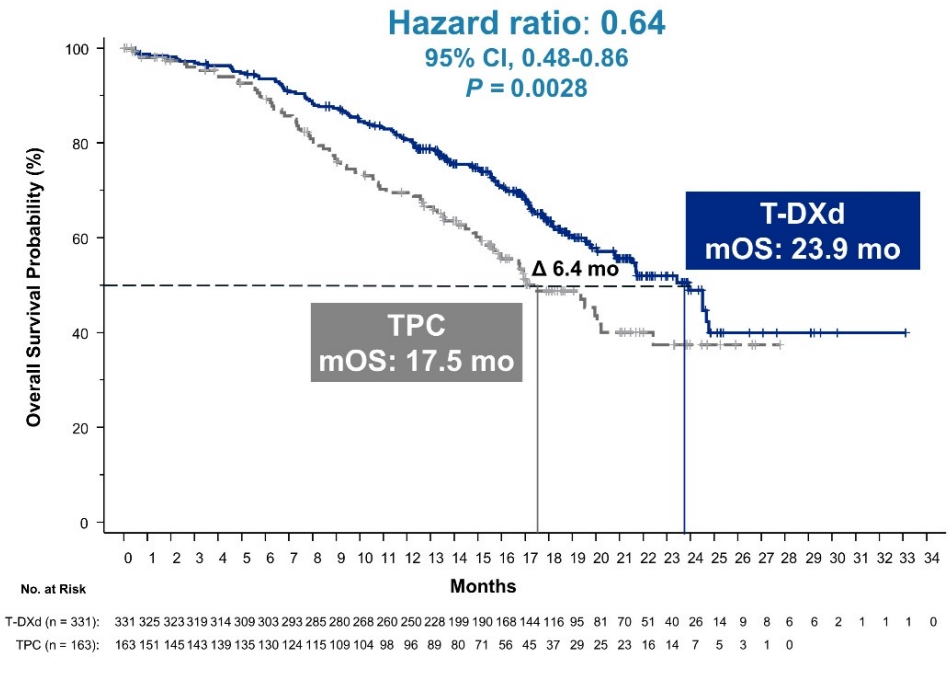

**PFS by blinded independent central review.**
HR, hormone receptor; mPFS, median progression-free survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan;

2022 ASCO ANNUAL MEETING #ASCO22

PRESENTED BY:
Shanu Modi, MD

Modi S et al. ASCO 2022;Abstract LBA3. Modi S et al. *N Engl J Med* 2022;387(1):9-20.

## Overall Survival




Courtesy of Aditya Bardia, MD, MPH

American Society of Clinical Oncology Annual Meeting, 2023

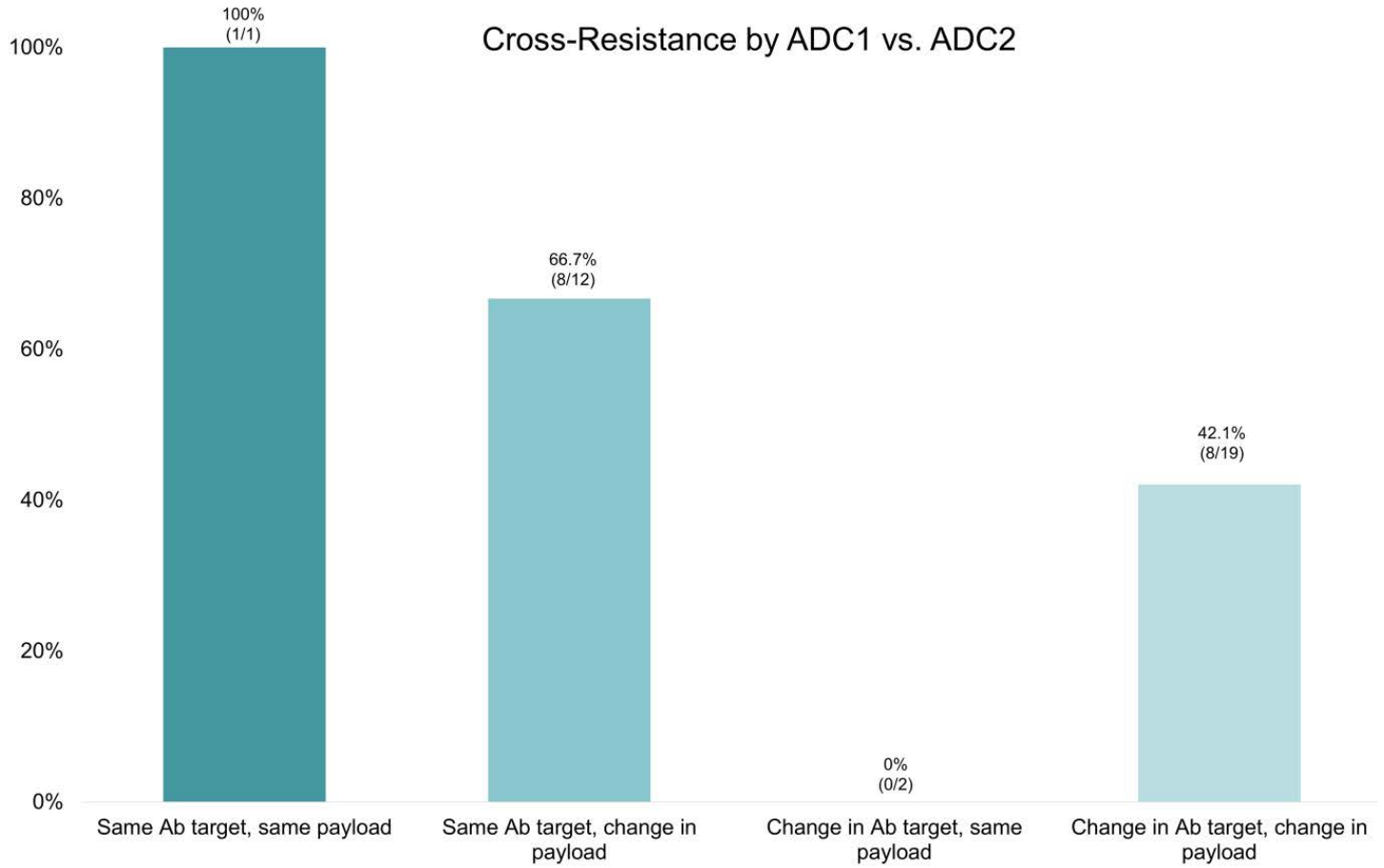
Mass General Brigham
Mass General Cancer Center

CONQUER CANCER® THE ASCO FOUNDATION | MERIT AWARD

# Sequential Use of Antibody-Drug Conjugate after Antibody-Drug Conjugate for Patients with Metastatic Breast Cancer: ADC after ADC (A3) study

Rachel O. Abelman[1], Laura M. Spring[1], Geoffrey Fell[2], Phoebe K Ryan[1], Neelima Vidula[1], Seth Wander[1], Arielle J. Medford[1], Jennifer Shin[1], Elizabeth Abraham[1], Steven J. Isakoff[1], Beverly Moy[1], Leif W. Ellisen[1], Aditya Bardia[1]
[1]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; [2]Dana Farber Cancer Institute, Harvard Medical School, Boston, MA

Harvard Medical School




## Target vs payload: Implications for ADC Sequencing

Courtesy of Aditya Bardia, MD, MPH

# Agenda

**INTRODUCTION: Biopharmacology and Endocrinology of Breast Cancer**

**MODULE 1: Current Strategies for Previously Treated ER-Positive Metastatic Breast Cancer (mBC) — Dr Bardia**

**MODULE 2: Future Directions in the Management of ER-Positive mBC — Dr Hamilton**

**MODULE 3: Clinical Investigator Survey**

# Future Directions in the Management of ER-Positive mBC

**Erika Hamilton, MD**

Director, Breast Cancer Research Program

Sarah Cannon Research Institute/ Tennessee Oncology

Nashville, TN

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# Oral SERDs

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Courtesy of Erika Hamilton, MD

# SERD: Selective estrogen receptor degrader

## Key advantages

- Oral formulation
- Higher potency
- Activity in ESR1 mutant MBC
- Activity in post-ET and CDK4/6i treated pts

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Courtesy of Erika Hamilton, MD

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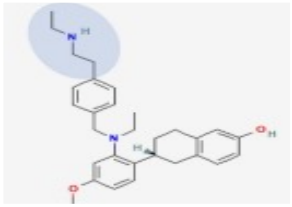
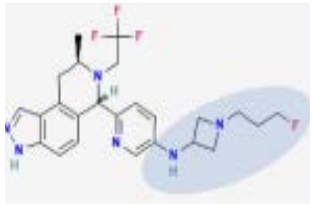
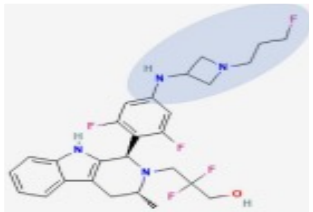
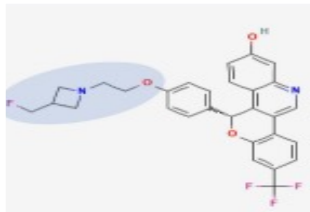
# Comparison of oral SERDs in development

| | Elacestrant* | Camizestrant | Giredestrant | Imlunestrant |
|---|---|---|---|---|
| Structure |  |  |  |  |
| Sidechain | Basic | Basic | Basic | Basic |
| Class | SERM/SERD hybrid** | SERD | SERD | SERD |
| RP2D (monotherapy) | 400mg | 75mg | 30mg | 400mg |
| Adverse events >10% monotherapy | Nausea, fatigue, vomiting, decreased appetite, arthragias | Visual disturbances, bradycardia, nausea, fatigue, dizziness, vomiting, and asthenia | Fatigue, arthralgia, backpain, nausea, diarrhea, cough, constipation | Nausea, diarrhea, fatigue, arthralgia, urinary tract infection, constipation, headache |
| Median PFS (SERD vs ET in post CDK 4/6i) | 2.8 months vs 1.9 months (HR 0.70 p 0.0018) | 7.2 months vs 3.7 months (HR 0.58) statistically significant | 5.6 months vs 5.4 months (HR 0.81, p 0.1757) | NR |
| Activity in ESR1 mutant MBC | Yes | Yes | Yes | NR |

* FDA approved

** lower doses-partial agonist; higher doses - antagonist
As receptor occupancy increases, degradation occurs

@ErikaHamilton9

Courtesy of Erika Hamilton, MD

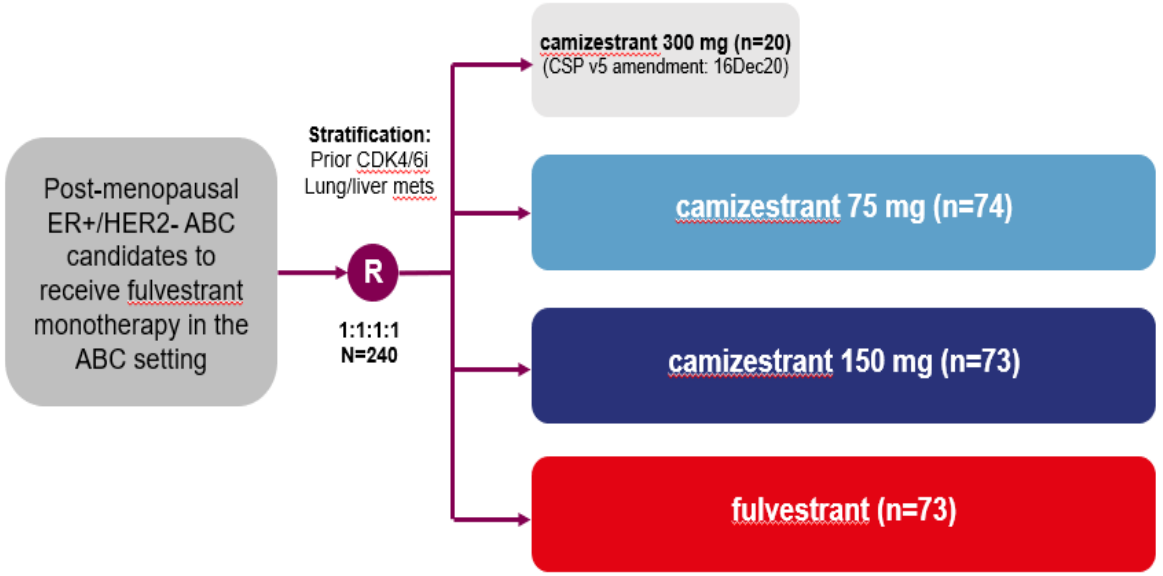
SARAH CANNON Research Institute

Bardia A et al JCO 2022; Oliviera M et al. SABCS 2022; Martin M et al. ESMO 2022

# SERENA-2: Study design and patient population

**Key inclusion/exclusion criteria:**

- Recurrence or progression on at least one line of ET
- No prior fulvestrant or oral SERD in ABC
- No more than one line of ET in ABC setting
- No more than one line CT in ABC setting
- Measurable and non-measurable disease




- **Primary endpoint:** PFS (investigator assessment*)
- **Secondary endpoints:** CBR24, ORR, OS, safety
- **Translational endpoints:** serial ctDNA analysis including *ESR1*m, serial CTCs analysis

**Patient population**

| | C 75 (n=74) | C 150 (n=73) | F (n=73) |
|---|---|---|---|
| Lung/liver mets | 58.1% | 58.9% | 58.9% |
| ESR1m detectable | 29.7% | 35.6% | 47.9% |
| Adjuvant AI | 40.5% | 35.6% | 31.5% |
| AI for MBC | 55.4% | 67.1% | 67.1% |
| Prior CDK 4/6i | 51.4% | 50.7% | 50.7% |

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Courtesy of Erika Hamilton, MD

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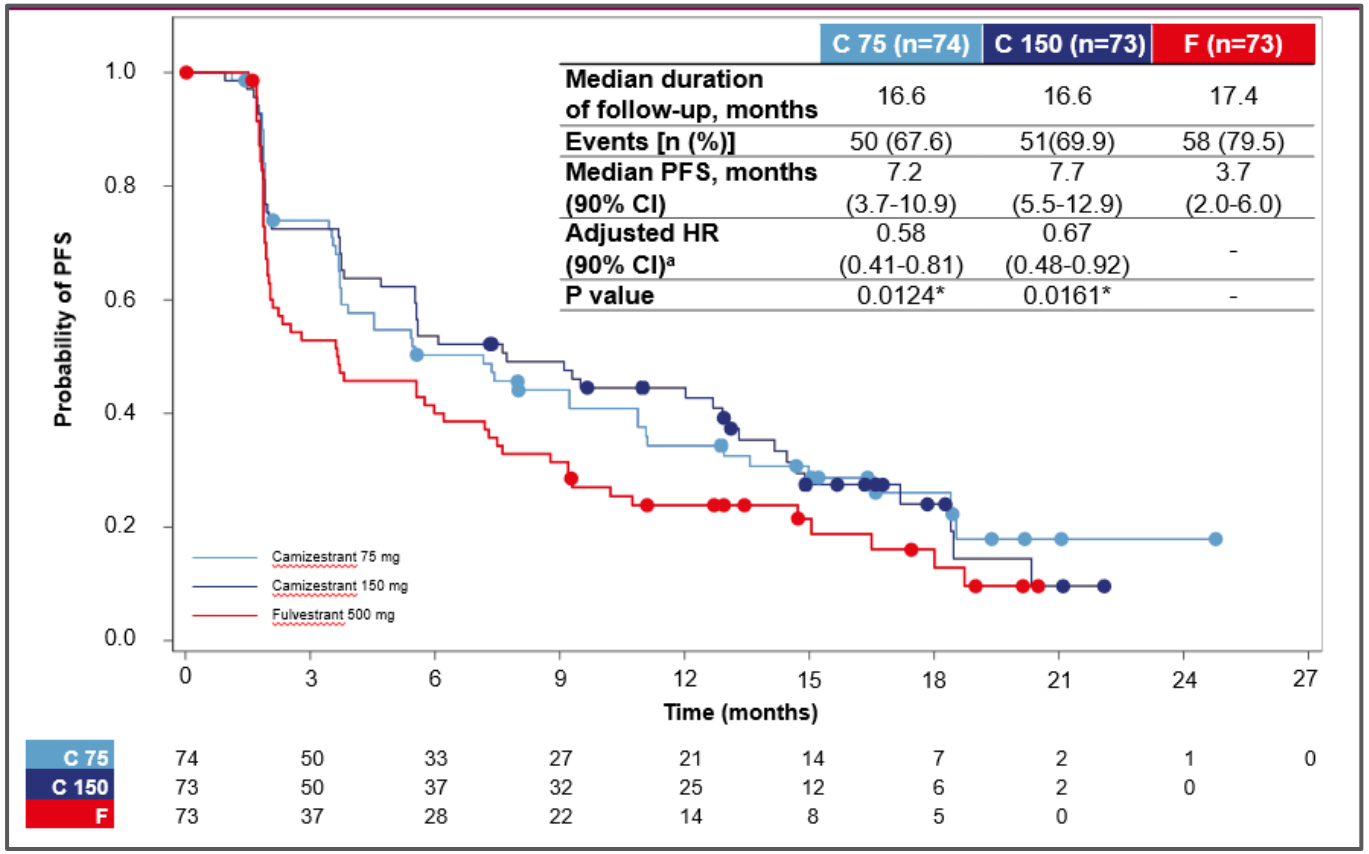
Oliveira M et al. SABCS 2022, GS3-02

# SERENA-2: Progression-free survival

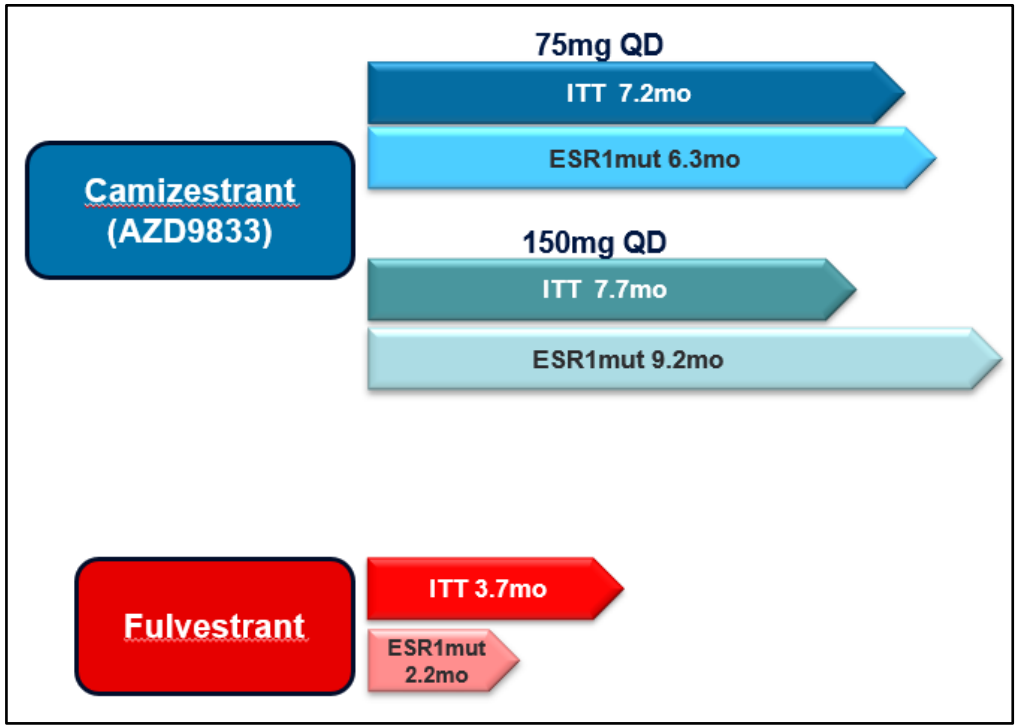
## PFS in overall patient population




| | C 75 (n=74) | C 150 (n=73) | F (n=73) |
|---|---|---|---|
| Median duration of follow-up, months | 16.6 | 16.6 | 17.4 |
| Events [n (%)] | 50 (67.6) | 51(69.9) | 58 (79.5) |
| Median PFS, months (90% CI) | 7.2 (3.7-10.9) | 7.7 (5.5-12.9) | 3.7 (2.0-6.0) |
| Adjusted HR (90% CI)[a] | 0.58 (0.41-0.81) | 0.67 (0.48-0.92) | - |
| P value | 0.0124* | 0.0161* | - |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| C 75 | 74 | 50 | 33 | 27 | 21 | 14 | 7 | 2 | 1 | 0 |
| C 150 | 73 | 50 | 37 | 32 | 25 | 12 | 6 | 2 | 0 | |
| F | 73 | 37 | 28 | 22 | 14 | 8 | 5 | 0 | | |

## PFS in pts based on detectable ESR1mut




**Camizestrant improved PFS over fulvestrant in all patients including those with detectable ESR1 mutations**

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Courtesy of Erika Hamilton, MD

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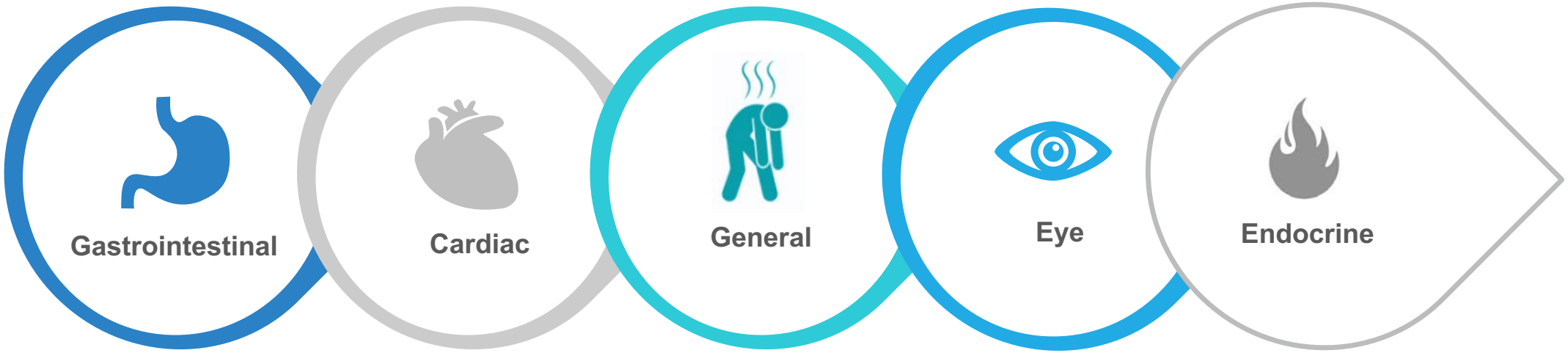
Oliveira M et al. SABCS 2022, GS3-02

# Adverse events with oral SERDs




- Nausea
- Vomiting
- Diarrhea

- G1 bradycardia
- QTc prolongation

- Fatigue

- Visual disturbances

- Hot flashes

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Courtesy of Erika Hamilton, MD

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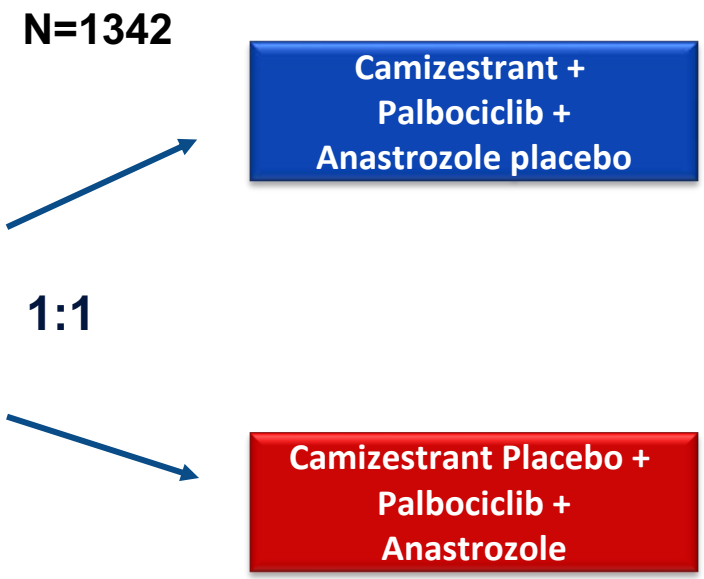
# SERENA-4: Camizestrant + palbociclib as 1L therapy for HR+/HER2- MBC

NCT04711252

- Pre/post menopausal women & male pts with ER+/HER2- MBC
- No prior systemic therapy for metastatic disease
- Recurrence from early stage disease:

-At least 24 months of an AI with a TFI > 12 months **OR**
-At least 24 months of tamoxifen

- Pts with de novo MBC allowed
- Patients with bone only disease must have a lytic or mixed lytic lesion

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# EMBER-3: 1-2L trial for HR+/HER2- MBC with Imlunestrant

- Imlunestrant is an oral SERD (Eli Lilly)
- In a phase 1 trial, Imlunestrant monotherapy led to CBR of 48% in HR+/HER2- MBC treated with fulvestrant and CDK 4/6i

NCT04975308

- **ER+/HER2- LA/MBC**
- **Prior tx with an AI (with or without CDK 4/6i) in adjuvant /met setting**
  - ***Prior tx with CDK 4/6i expected if tx is approved and reimbursed***
- **No other prior therapy for advanced disease**
  - **No prior tx with SERD or chemo or PI3K/AKT/mTOR inhibitor**
- **Measurable or non measurable bone only disease**

**N ~ 800**
**1:1:1**

**Arm A: Imlunestrant**

**Arm B: Fulvestrant or Exemestane**

**Arm C: Imlunestrant + Abemaciclib**

Patients will be randomized 1:1:1 (A:B:C) until the target enrollment is met for either Arm B (n=250) or Arm C (n=180). At that point, the randomization will be 1:1 with Arm A and either Arm B or Arm C, whichever has not met target enrollment.

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Courtesy of Erika Hamilton, MD

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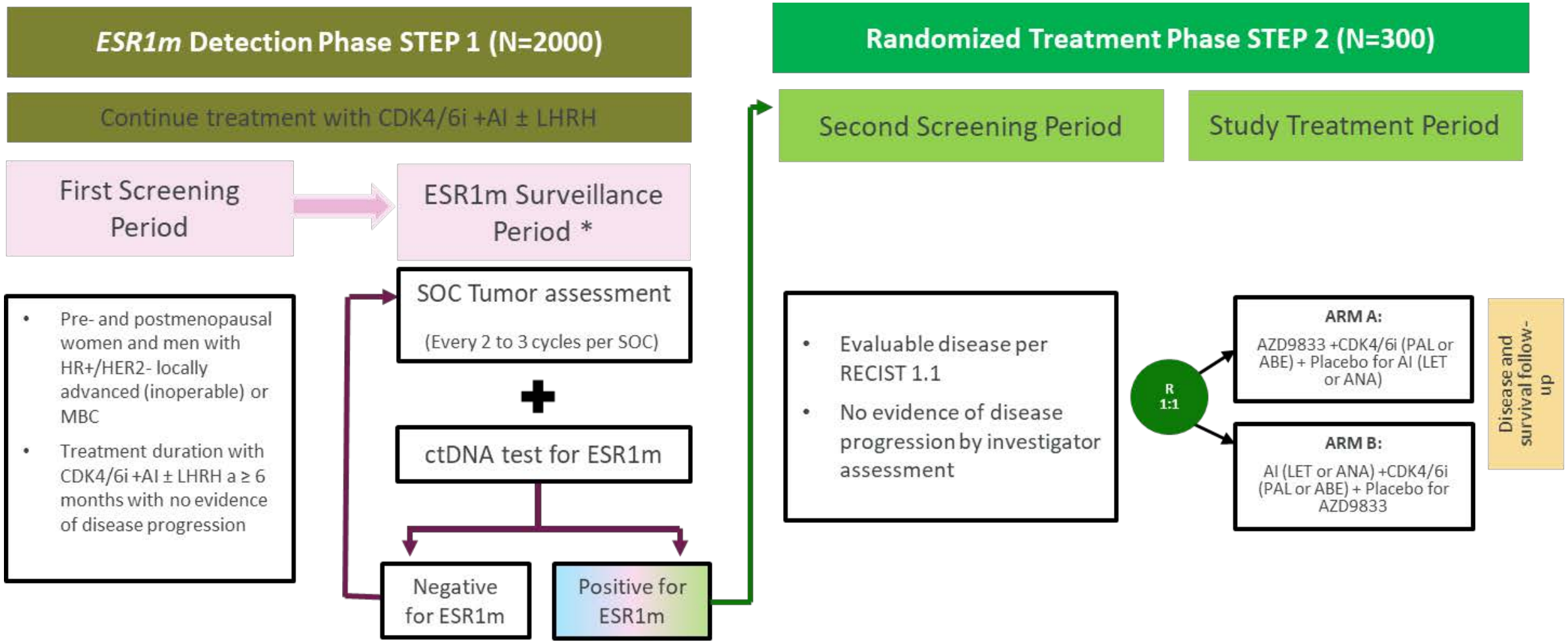
# SERENA-6: Early switch strategy to oral SERD in ESR1-mutant ER+/HER2- MBC

NCT04964934

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# Other ER targeting agents

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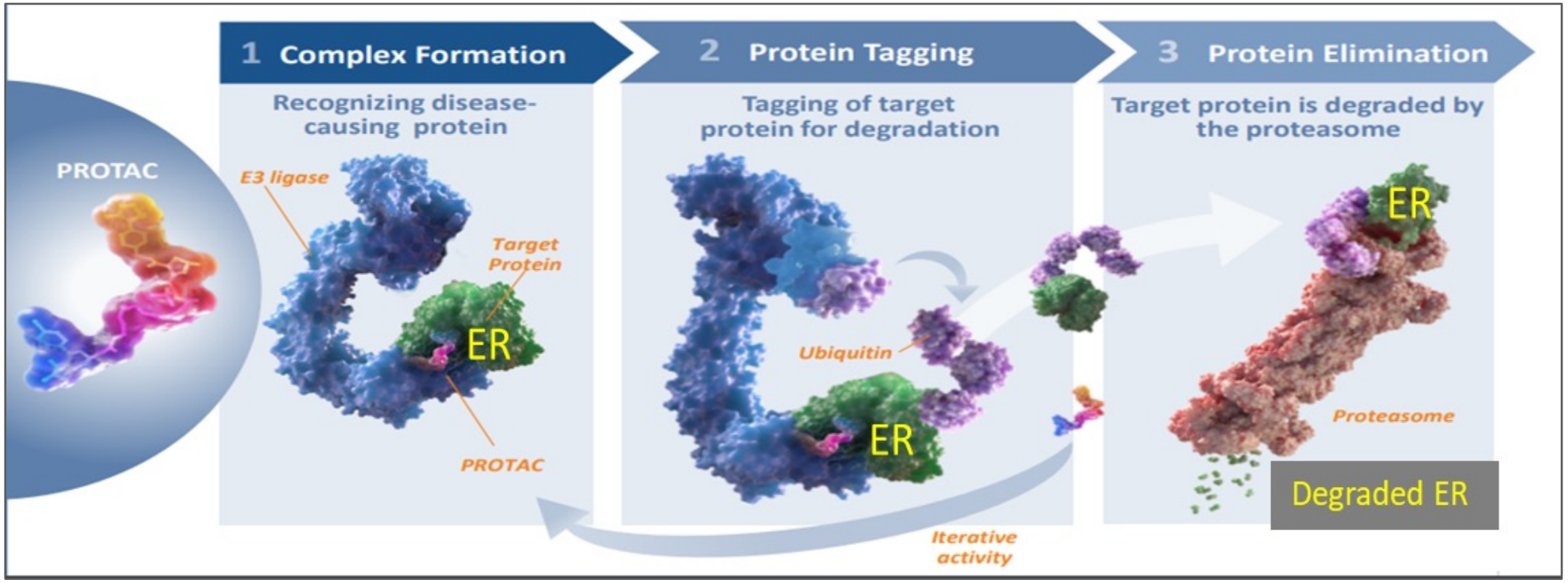
Courtesy of Erika Hamilton, MD

# ARV-471: Proteolysis targeting chimera (PROTAC™)




ARV-471 is a PROTAC™ targeting the WT and ESR1 mutant estrogen receptor (ER)

In a phase 1 dose escalation study:

- ARV-471 was well tolerated all doses with no DLTs
- CBR was 40% (n=47 evaluable); 3 pts had confirmed PRs

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Courtesy of Erika Hamilton, MD

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Hamilton E. et al. SABCS 2021, PD13-08

# ARV-471: Phase 2 (VERITAC) cohort expansion

**Schema**

- ER+/HER2- MBC
- ≥ 1 prior ET line for MBC
- ≥ 1 prior CDK 4/6i
- 0-1 prior chemo for MBC
- Measurable disease per RECIST v1.1

→ ARV 471 200mg PO QD (n=35)

→ ARV 471 500mg PO QD (n=36)

**Patient population**:

- Prior therapies for MBC
  - CDK 4/6i 100%
  - Fulvestrant 30%
  - Chemotherapy 45%
- BL ESR1 mutation 58%

**Primary Endpoint: Clinical benefit rate (CBR)**

| | 200 mg QD (n=35) | 500 mg QD (n=36) | Total (N=71) |
|---|---|---|---|
| CBR, % (95% CI) | 37.1 (21.5–55.1) | 38.9 (23.1–56.5) | 38.0 (26.8–50.3) |
| Patients with mutant *ESR1* | (n=19) | (n=22) | (n=41) |
| CBR, % (95% CI) | 47.4 (24.4–71.1) | 54.5 (32.2–75.6) | 51.2 (35.1–67.1) |

**PFS in ITT vs ESR1 mutant (200mg QD dose)**

| | All patients | | ESR1 mutant | |
|---|---|---|---|---|
| | 200mg QD (n=35) | Total (N=71) | 200mg QD (n=19) | Total (N=41) |
| Median PFS | 3.5 months | 3.7 months | 5.5 months | 5.7 months |

- Robust ER degradation was observed at both doses; mean ER degradation was 71%
- CBR was higher with ARV-471 in ESR1 mutant subset at both doses tested
- Fatigue and nausea were most common AEs, and most AEs were G1/2 events
- 200mg QD was selected as phase 3 dose

VERITAC-2: Phase 3 trial of ARV-471 vs fulvestrant in CDK 4/6i tx HR+/HER2- MBC is ongoing

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Courtesy of Erika Hamilton, MD

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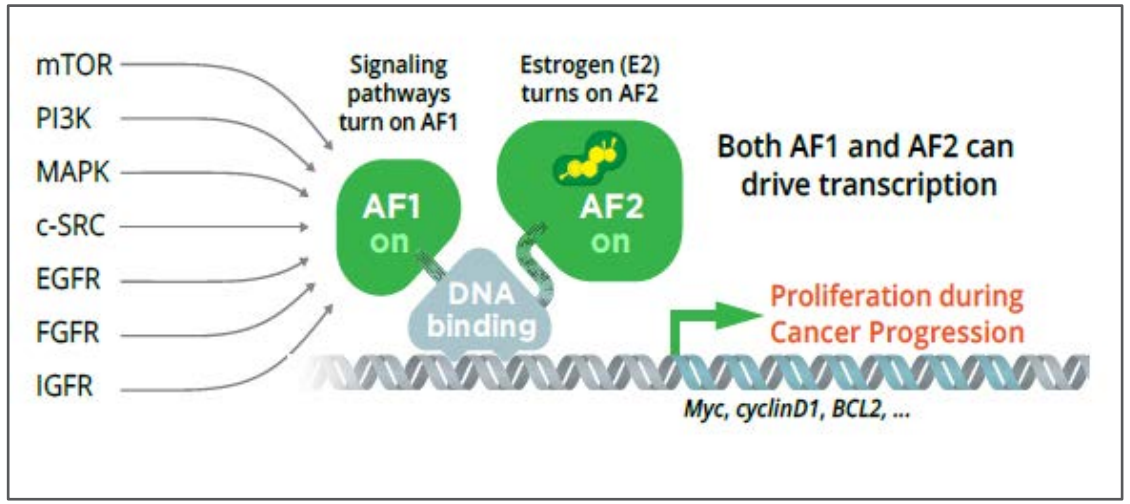
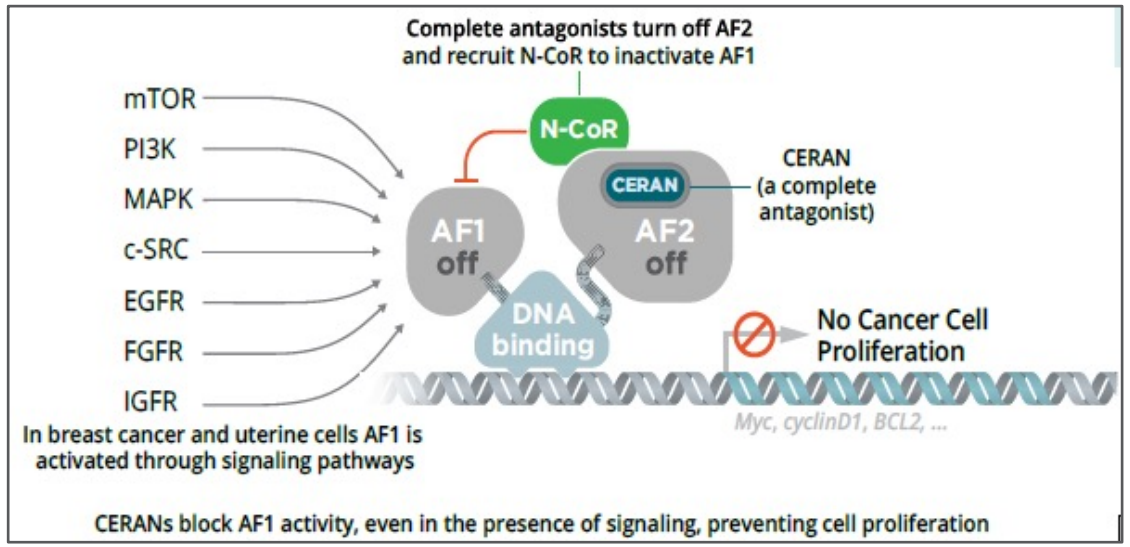
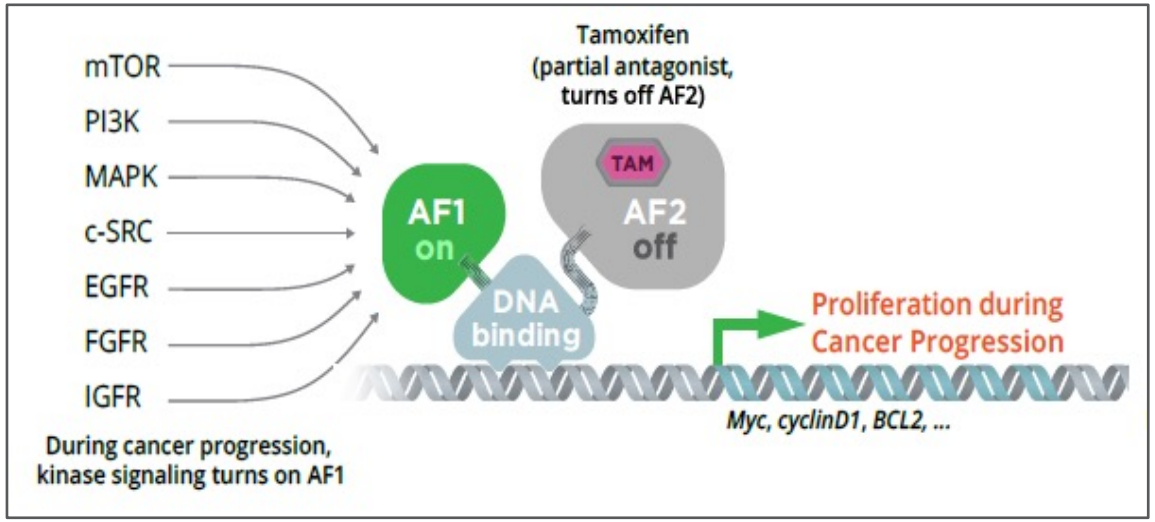
Hurvitz SA et al. SABCS 2022

# Complete ER antagonist (CERAN): MOA




**CERAN shuts down both activation functions (AF1 and AF2) of the ER**

**OP1250 is a CERAN with activity in**

- **WT & ESR1 mutant breast cancer xenografts**
- **Brain mets xenograft model**

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Hodges-Gallaher L et al. ENA (EORTC NCI AACR) 2020
Hodges-Gallagher et al AACR 2021

Courtesy of Erika Hamilton, MD

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# OP-1250 monotherapy and palbociclib combination

## Monotherapy

ER/PR+ MBC treated at doses from 30mg to 300mg (n=40)

- ≥3 prior lines of therapy: 50%
- Prior fulvestrant: 67.5%
- Prior chemo: 75%
- Prior CDK 4/6i: 92.5%

**Efficacy in anticipated RP2D range (60-120mg)**

- ✓ ORR: 8%
- ✓ CBR: 38%

**Safety:**

- ✓ No DLTs observed, MTD not reached
- ✓ Most TEAEs were G1 or G2

## OP-1250 + palbociclib

ER/PR+ MBC treated at doses from 30mg to 120mg OP-1250 + 125 mg palbociclib (n=12)

- ≥1 prior lines of therapy: 58%
- Prior CDK 4/6i: 67%
- Prior fulvestrant: 8%
- Prior chemo: 25%

**Efficacy**

- ✓ SD ≥ 24 weeks : 2 pts and ongoing
- ✓ 8 pts on tx at data cut off; longest duration of tx was 31 weeks

**Safety:**

- ✓ No DLTs observed, MTD not reached
- ✓ Most TEAEs were G1 or G2
- ✓ G3 AEs: Neutropenia (67%), fatigue (8%), WBC count decreased (8%)

**PK analysis:**

- ✓ RP2D - 120mg OP-1250 in combo with 125mg palbociclib
- ✓ No drug-drug interaction observed

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Courtesy of Erika Hamilton, MD

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Patel M et al. SABCS 2021 Abstract # P1-17-12
Chan A et al. SABCS 2022 Abstract # P2-24-07

# Akt inhibition

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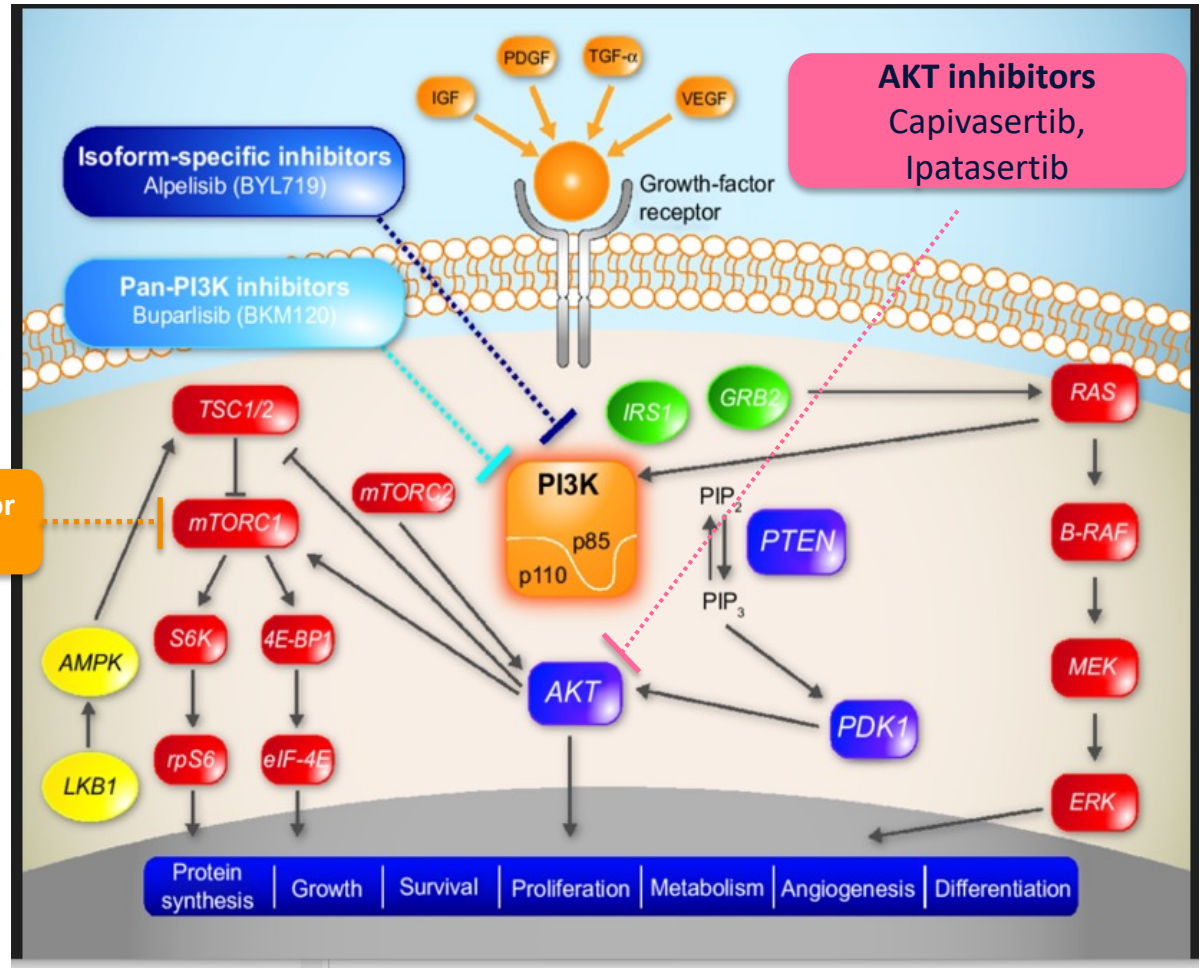
Courtesy of Erika Hamilton, MD

# PI3K/AKT/mTOR pathway




- Capivasertib, a pan-AKT inhibitor demonstrated synergistic activity with fulvestrant in preclinical endocrine sensitive and resistant models

- Ipatasertib is also a pan-AKT inhibitor with demonstrated antitumor activity in preclinical studies

- In phase 1 trials
  - **Capivasertib + fulvestrant** in $AKT^{E17K}$ HR+ MBC – ORR of 20-36% and median PFS of 5-5.6 months depending on prior fulvestrant tx
  - **Ipatasertib + paclitaxel** in HR+/HER2- MBC: 2/15 patients had PR (one with H1047R PIK3CA mutation) and max PFS was 14.2 months in one pt with breast cancer

- Phase 2 FAKTION trial
  - **Capivasertib + fulvestrant** led to significant improvement in PFS vs placebo/fulv irrespective of PI3K/AKT/PTEN pathway activation status

@ErikaHamilton9

Smyth LM et al. 2020; Isakoff SJ et al. 2020
Jones RH et al. ASCO 2019

Courtesy of Erika Hamilton, MD

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Capivasertib in Hormone Receptor–Positive Advanced Breast Cancer

N.C. Turner, M. Oliveira, S.J. Howell, F. Dalenc, J. Cortes, H.L. Gomez Moreno, X. Hu, K. Jhaveri, P. Krivorotko, S. Loibl, S. Morales Murillo, M. Okera, Y.H. Park, J. Sohn, M. Toi, E. Tokunaga, S. Yousef, L. Zhukova, E.C. de Bruin, L. Grinsted, G. Schiavon, A. Foxley, and H.S. Rugo, for the CAPItello-291 Study Group*

2023;388(22):2058-70.

# CAPItello-291: Phase 3 trial with an Akt inhibitor

## 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

## Patient population

| | |
|---|---|
| **Visceral disease** | **66-73%** |
| **AKT pathway alterations** | **38-43%** |
| **Median priors for MBC** | **1** |
| **Prior CDK 4/6i** | **67-72%** |
| **Prior chemo for MBC** | **17-19%** |

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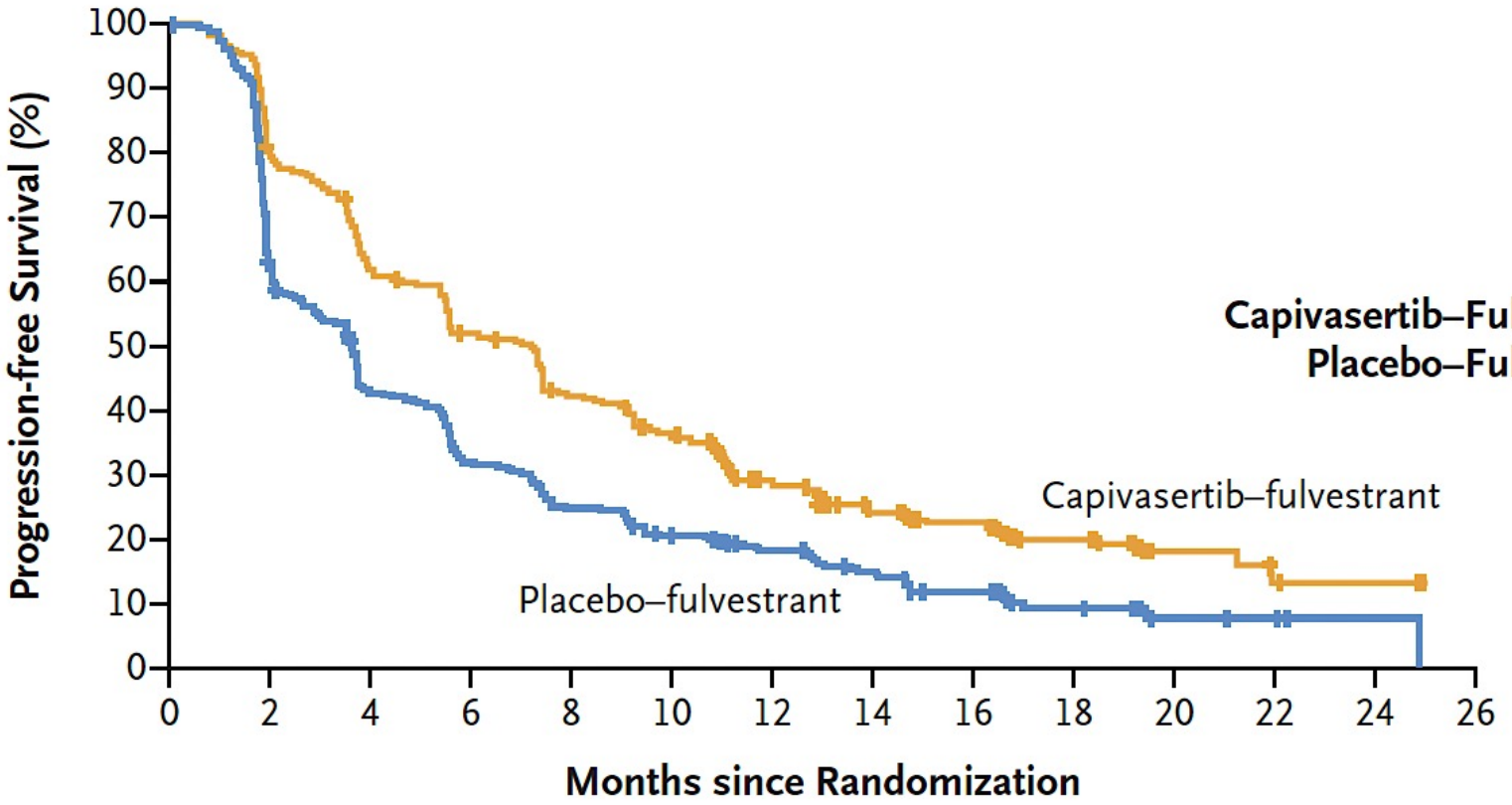
Courtesy of Erika Hamilton, MD

SARAH CANNON Research Institute

Turner NC et al. SABCS 2022, GS3-04

# CAPItello-291: Progression-Free Survival in the Overall Population

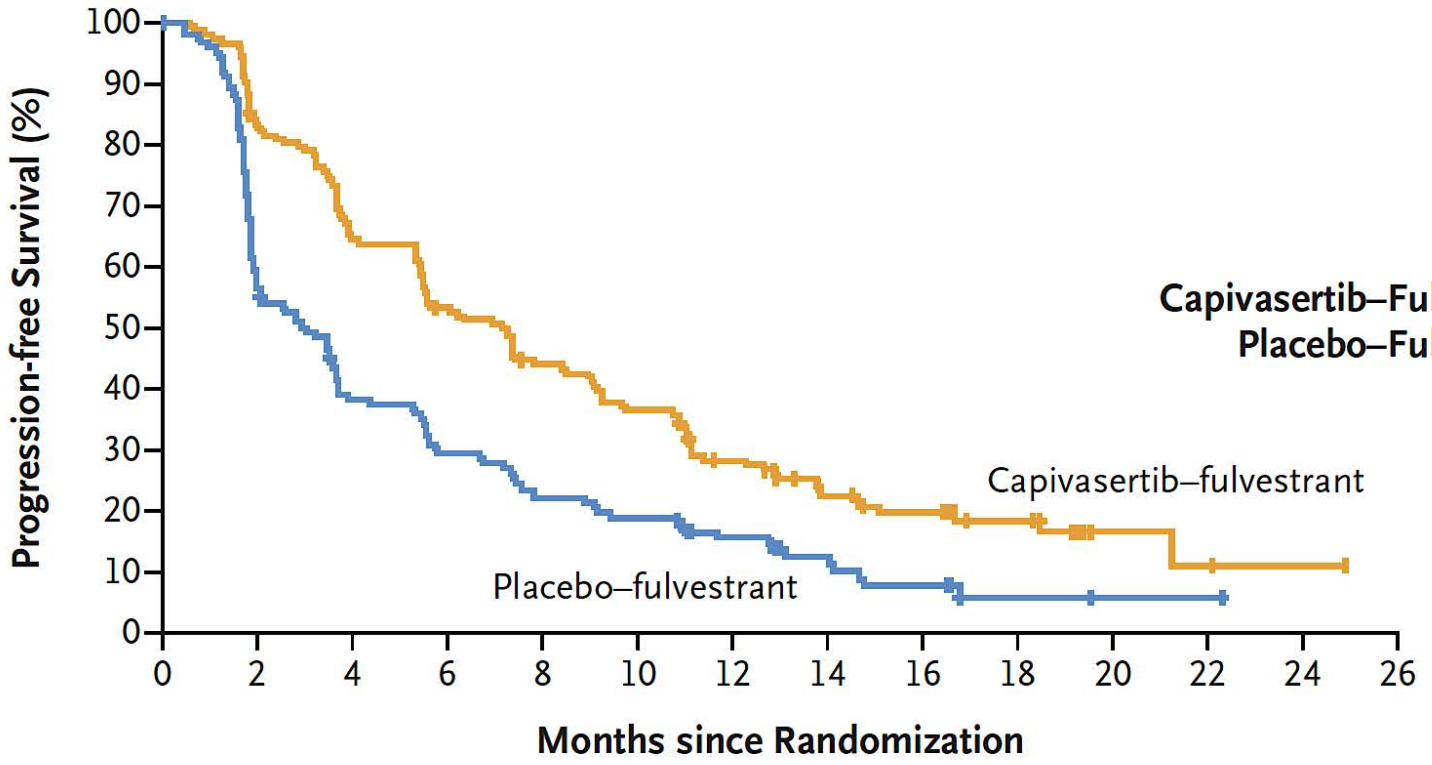



| | No. of Patients | No. of Events | Median Progression-free Survival (95% CI) |
|---|---|---|---|
| | | | *mo* |
| **Capivasertib–Fulvestrant** | 355 | 258 | 7.2 (5.5–7.4) |
| **Placebo–Fulvestrant** | 353 | 293 | 3.6 (2.8–3.7) |

Adjusted hazard ratio for disease progression or death, 0.60 (95% CI, 0.51–0.71)
P<0.001

Turner NC et al. *N Engl J Med* 2023;388(22):2058-70.

# CAPItello-291: Progression-Free Survival for Patients with AKT Pathway-Altered Tumors

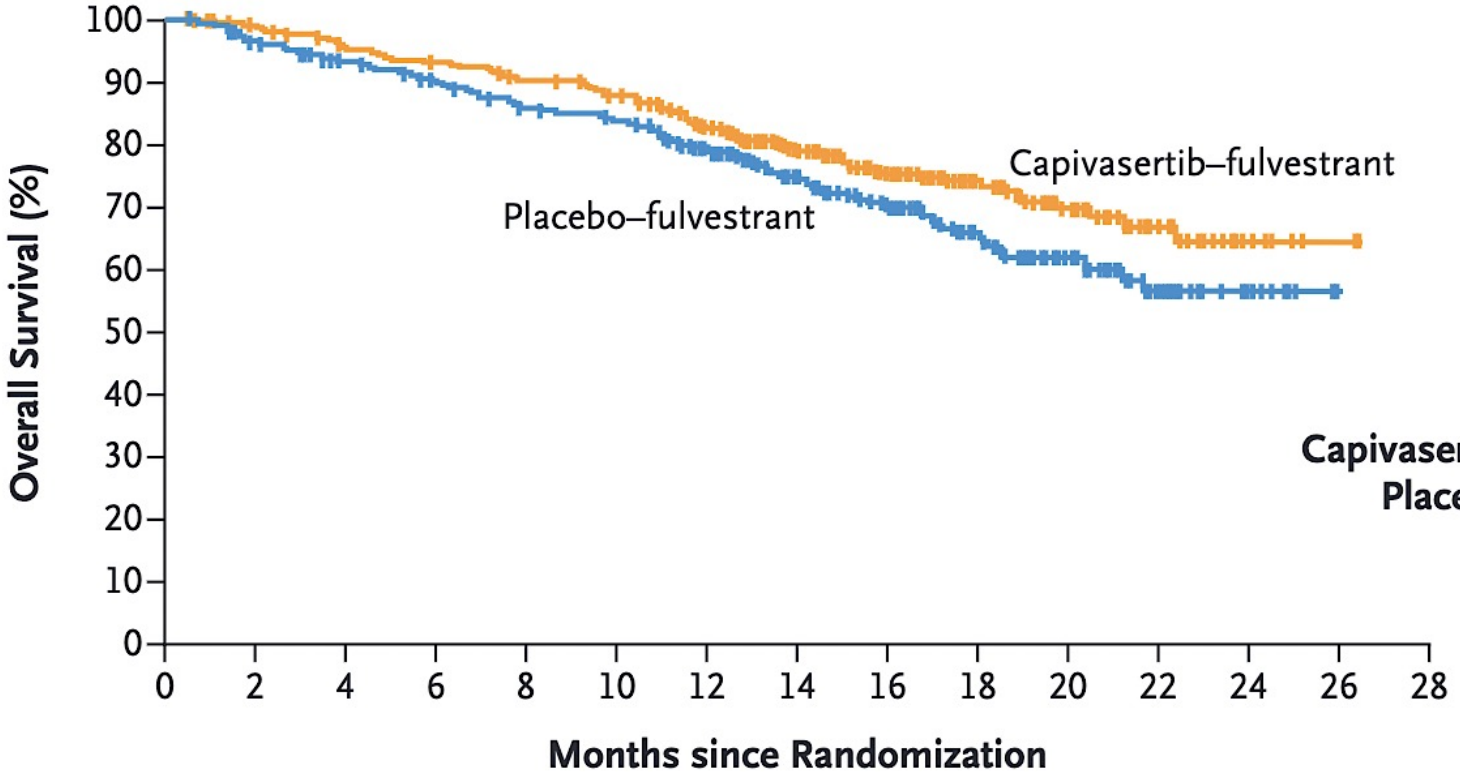



| | No. of Patients | No. of Events | Median Progression-free Survival (95% CI) |
|---|---|---|---|
| | | | *mo* |
| Capivasertib–Fulvestrant | 155 | 121 | 7.3 (5.5–9.0) |
| Placebo–Fulvestrant | 134 | 115 | 3.1 (2.0–3.7) |

Adjusted hazard ratio for disease progression or death, 0.50 (95% CI, 0.38–0.65)
P<0.001

Turner NC et al. *N Engl J Med* 2023;388(22):2058-70.

# CAPItello-291: Overall Survival in the Overall Population

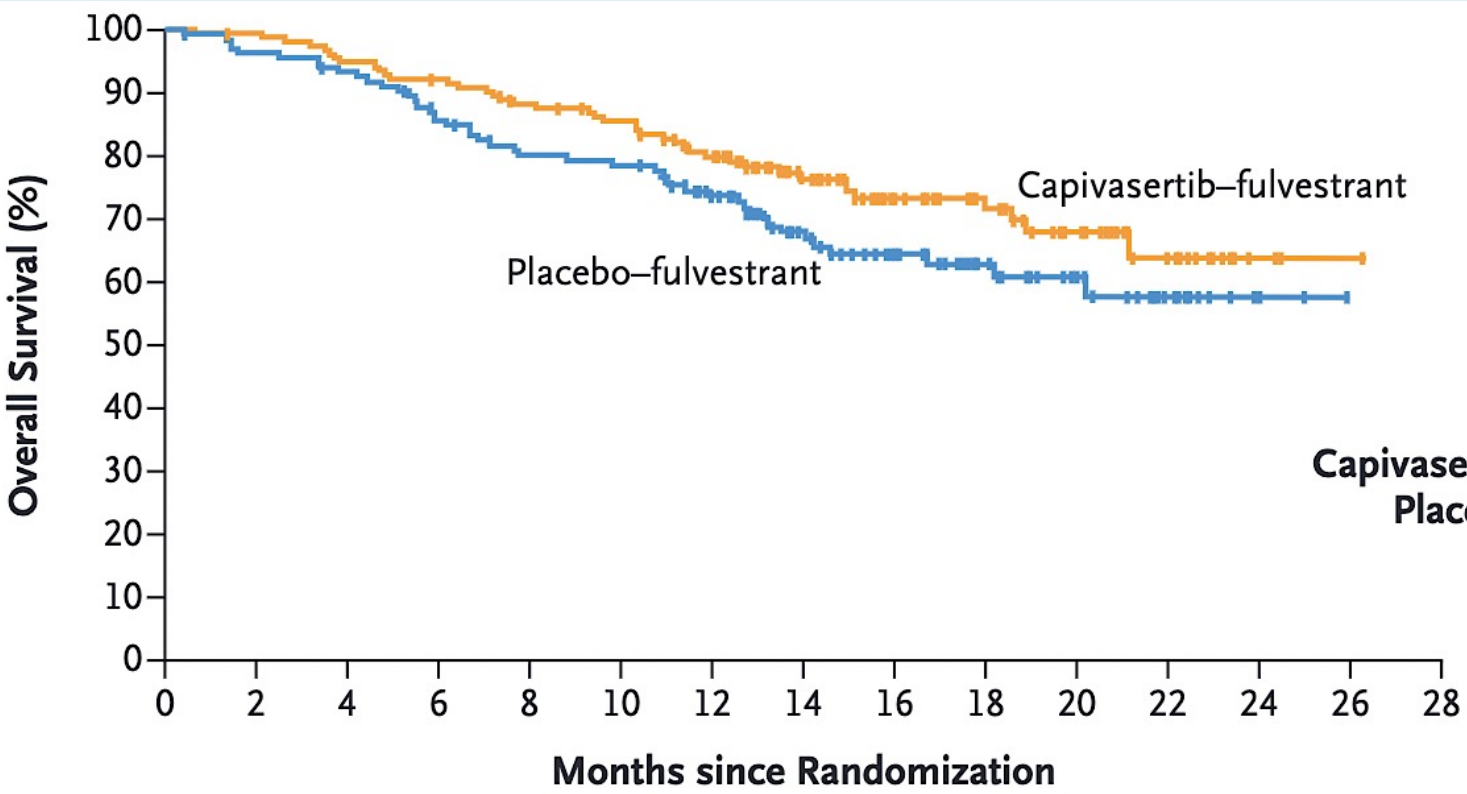



| | No. of Patients | No. of Deaths |
|---|---|---|
| Capivasertib–Fulvestrant | 355 | 87 |
| Placebo–Fulvestrant | 353 | 108 |

Adjusted hazard ratio for death, 0.74 (95% CI, 0.56–0.98)

Turner NC et al. *N Engl J Med* 2023;388(22):2058-70.

# CAPItello-291: Overall Survival for Patients with AKT Pathway-Altered Tumors



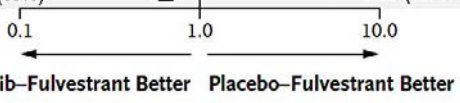

| | No. of Patients | No. of Deaths |
|---|---|---|
| Capivasertib–Fulvestrant | 155 | 41 |
| Placebo–Fulvestrant | 134 | 46 |

Adjusted hazard ratio for death, 0.69 (95% CI, 0.45–1.05)

Turner NC et al. *N Engl J Med* 2023;388(22):2058-70.

# CAPItello-291: Subgroup Analysis

| Subgroup | Capivasertib–Fulvestrant | Placebo–Fulvestrant | Hazard Ratio (95% CI) |
|---|---|---|---|
| | *no. of events/total no. (%)* | | |
| All patients | 258/355 (72.7) | 293/353 (83.0) | 0.60 (0.51–0.71) |
| Age | | | |
| <65 yr | 188/240 (78.3) | 218/251 (86.9) | 0.65 (0.53–0.79) |
| ≥65 yr | 70/115 (60.9) | 75/102 (73.5) | 0.65 (0.47–0.90) |
| Race | | | |
| Asian | 61/95 (64) | 74/94 (79) | 0.62 (0.44–0.86) |
| White | 152/201 (75.6) | 175/206 (85.0) | 0.65 (0.52–0.80) |
| Other | 45/59 (76) | 44/53 (83) | 0.63 (0.42–0.96) |
| Region | | | |
| Australia, Canada, Israel, United States, or Western Europe | 158/197 (80.2) | 174/198 (87.9) | 0.60 (0.48–0.75) |
| Eastern Europe, Latin America, or Russia | 44/68 (65) | 50/68 (74) | 0.77 (0.51–1.16) |
| Asia | 56/90 (62) | 69/87 (79) | 0.60 (0.42–0.85) |
| Menopausal status | | | |
| Pre- or perimenopause | 54/65 (83) | 81/89 (91) | 0.86 (0.60–1.20) |
| Postmenopause | 201/287 (70.0) | 210/260 (80.8) | 0.59 (0.48–0.71) |
| Liver metastases | | | |
| Yes | 130/156 (83.3) | 138/150 (92.0) | 0.61 (0.48–0.78) |
| No | 128/199 (64.3) | 155/203 (76.4) | 0.62 (0.49–0.79) |
| Visceral metastases | | | |
| Yes | 185/237 (78.1) | 205/241 (85.1) | 0.69 (0.56–0.84) |
| No | 73/118 (61.9) | 88/112 (78.6) | 0.54 (0.39–0.74) |
| Bone-only metastases | | | |
| Yes | 32/51 (63) | 42/52 (81) | 0.61 (0.38–0.96) |
| No | 226/304 (74.3) | 251/301 (83.4) | 0.64 (0.54–0.77) |
| Endocrine resistance | | | |
| Primary | 96/127 (75.6) | 113/135 (83.7) | 0.66 (0.50–0.86) |
| Secondary | 162/228 (71.1) | 180/218 (82.6) | 0.64 (0.51–0.79) |
| Previous use of CDK4/6 inhibitor | | | |
| Yes | 194/248 (78.2) | 216/248 (87.1) | 0.62 (0.51–0.75) |
| No | 64/107 (59.8) | 77/105 (73.3) | 0.65 (0.47–0.91) |
| Previous chemotherapy for locally advanced or metastatic disease | | | |
| Yes | 48/65 (74) | 53/64 (83) | 0.61 (0.41–0.91) |
| No | 210/290 (72.4) | 240/289 (83.0) | 0.65 (0.54–0.78) |




Turner NC et al. *N Engl J Med* 2023;388(22):2058-70.

RTP RESEARCH TO PRACTICE

# CAPItello-291: Most Frequent Adverse Events in the Overall Population (Safety Population)

| Event | Capivasertib–Fulvestrant (N=355) | | | | | Placebo–Fulvestrant (N=350) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Any Grade | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Any Grade | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| | *number of patients (percent)* | | | | | | | | | |
| Any adverse event | 343 (96.6) | 52 (14.6) | 139 (39.2) | 139 (39.2) | 9 (2.5) | 288 (82.3) | 115 (32.9) | 118 (33.7) | 44 (12.6) | 10 (2.9) |
| Diarrhea | 257 (72.4) | 164 (46.2) | 60 (16.9) | 33 (9.3) | 0 | 70 (20.0) | 60 (17.1) | 9 (2.6) | 1 (0.3) | 0 |
| Rash† | 135 (38.0) | 57 (16.1) | 35 (9.9) | 43 (12.1) | 0 | 25 (7.1) | 19 (5.4) | 5 (1.4) | 1 (0.3) | 0 |
| Nausea | 123 (34.6) | 85 (23.9) | 35 (9.9) | 3 (0.8) | 0 | 54 (15.4) | 42 (12.0) | 10 (2.9) | 2 (0.6) | 0 |
| Fatigue | 74 (20.8) | 49 (13.8) | 23 (6.5) | 2 (0.6) | 0 | 45 (12.9) | 35 (10.0) | 8 (2.3) | 2 (0.6) | 0 |
| Vomiting | 73 (20.6) | 54 (15.2) | 13 (3.7) | 6 (1.7) | 0 | 17 (4.9) | 10 (2.9) | 5 (1.4) | 2 (0.6) | 0 |
| Headache | 60 (16.9) | 47 (13.2) | 12 (3.4) | 1 (0.3) | 0 | 43 (12.3) | 33 (9.4) | 8 (2.3) | 2 (0.6) | 0 |
| Decreased appetite | 59 (16.6) | 37 (10.4) | 21 (5.9) | 1 (0.3) | 0 | 22 (6.3) | 11 (3.1) | 9 (2.6) | 2 (0.6) | 0 |
| Hyperglycemia | 58 (16.3) | 24 (6.8) | 26 (7.3) | 7 (2.0) | 1 (0.3) | 13 (3.7) | 8 (2.3) | 4 (1.1) | 1 (0.3) | 0 |
| Stomatitis | 52 (14.6) | 24 (6.8) | 21 (5.9) | 7 (2.0) | 0 | 17 (4.9) | 15 (4.3) | 2 (0.6) | 0 | 0 |
| Asthenia | 47 (13.2) | 29 (8.2) | 14 (3.9) | 4 (1.1) | 0 | 36 (10.3) | 31 (8.9) | 3 (0.9) | 2 (0.6) | 0 |
| Pruritus | 44 (12.4) | 32 (9.0) | 10 (2.8) | 2 (0.6) | 0 | 23 (6.6) | 19 (5.4) | 4 (1.1) | 0 | 0 |
| Anemia | 37 (10.4) | 15 (4.2) | 15 (4.2) | 7 (2.0) | 0 | 17 (4.9) | 4 (1.1) | 9 (2.6) | 4 (1.1) | 0 |
| Urinary tract infection | 36 (10.1) | 8 (2.3) | 23 (6.5) | 5 (1.4) | 0 | 23 (6.6) | 2 (0.6) | 21 (6.0) | 0 | 0 |

Turner NC et al. *N Engl J Med* 2023;388(22):2058-70.

# Novel ADCs

SARAH CANNON
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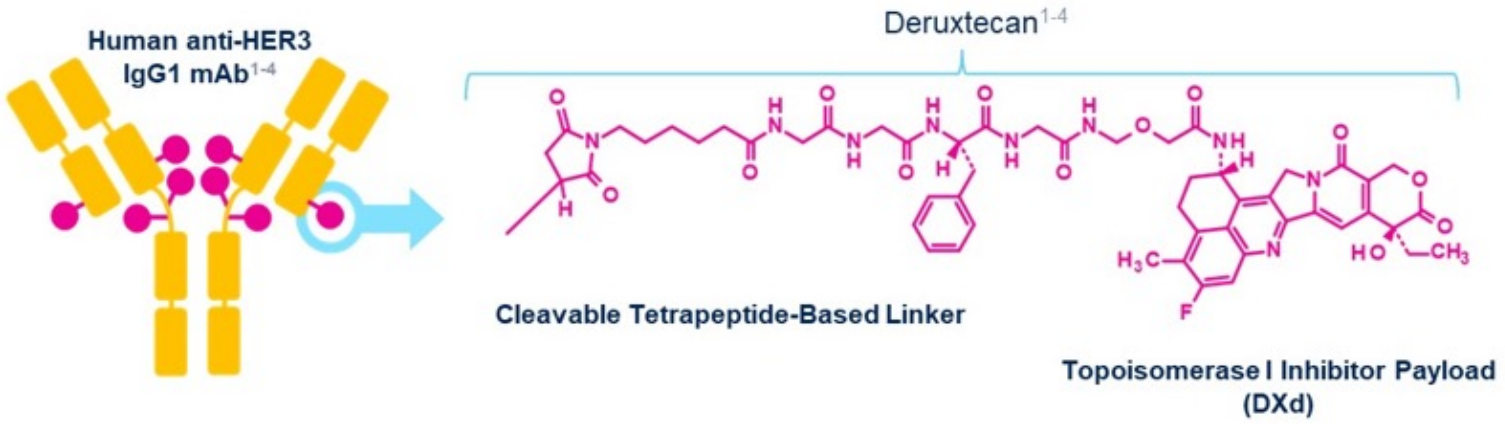
Courtesy of Erika Hamilton, MD

# Patritumab deruxtecan (HER3-DXd)

- HER3-DXd is an ADC with 3 components[1-6]:
  - A fully human anti-HER3 IgG1 mAb (patritumab), covalently linked to
  - A topoisomerase I inhibitor payload, an exatecan derivative, via
  - A tetrapeptide-based cleavable linker




**7 Key Attributes of HER3-DXd**

| |
|---|
| Payload mechanism of action: topoisomerase I inhibitor [a,1-4] |
| High potency of payload [a,1-4] |
| High drug to antibody ratio ≈ 8 [a,1,2] |
| Payload with short systemic half-life [a,b,2,3] |
| Stable linker-payload [a,2-4] |
| Tumor-selective cleavable linker [a,1-5] |
| Bystander antitumor effect [a,2,6] |

HER, human epidermal growth factor receptor; IgG1, immunoglobulin G1; mAb, monoclonal antibody.
[a] The clinical relevance of these features is under investigation. [b] Based on animal data.
1. Hashimoto Y, et al. *Clin Cancer Res*. 2019;25:7151-7161. 2. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67(3):173-185. 3. Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108. 4. Koganemaru S, et al. *Mol Cancer Ther*. 2019;18:2043-2050. 5. Haratani K, et al. *J Clin Invest*. 2020;130(1):374-388. 6. Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046.

@ErikaHamilton9

Courtesy of Erika Hamilton, MD

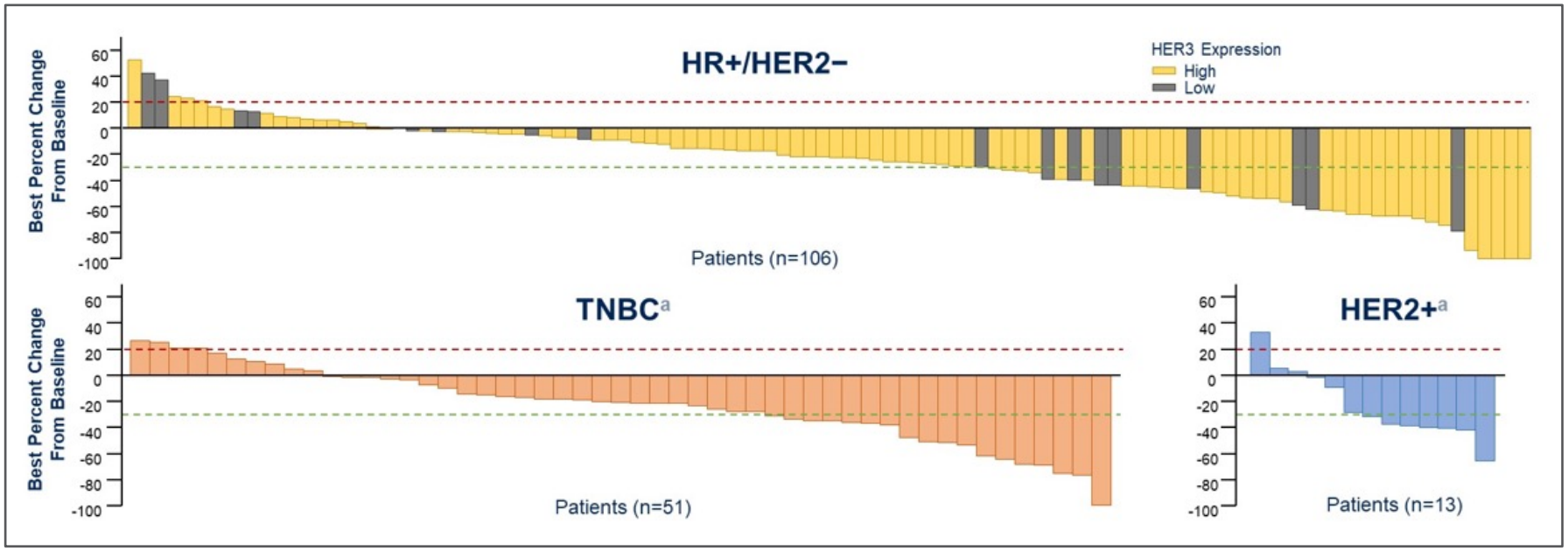
SARAH CANNON Research Institute

Krop I et al. ASCO 2022, Abstract 1002

# Patritumab deruxtecan: Activity in HER3-expressing MBC

- Phase 1/ 2 trial (expansion) in HER3 expressing MBC:
  - Heavily pretreated patient population with median priors ranging from 2-6 depending on subtype

## Change in tumor size from baseline




| Subtype | ORR | Median DoR |
|---|---|---|
| HR+/HER2- | 30% | 7.2 mo |
| HER2+ | 23% | 5.9 mo |
| TNBC | 43% | 8.3 mo |

- ✓ **Durable antitumor activity in all BC subtypes across the range of HER3 expression**
- ✓ **Manageable safety profile with low rates of treatment discontinuation**
- ✓ **Treatment related ILD (6.6%), mostly G1/2; one G5 event**

@ErikaHamilton9

Courtesy of Erika Hamilton, MD

SARAH CANNON Research Institute

Krop I et al. ASCO 2022, Abstract 1002

# ICARUS-Breast01: Phase 2 trial of HER3-DXd in HR+/HER2- MBC

Prospective, multicenter, single-arm study with multiple biomarker analyses

- LA/MBC
- HR+/HER2- or HER2-low
- PD on CDK 4/6i+ET
- PD on 1 prior chemo for MBC
- No prior T-DXd

**N= 56**

**Patritumab deruxtecan**
**5.6mg/kg IV q 3 weeks**

Pre treatment, on tx and EOT biopsy and blood collected

*HER3-expression prescreening (75% of membrane positivity at 10x) was removed by amendment on April 21st, 2022

| Patient population: | |
|---|---|
| Median prior regimens | 2 |
| Prior (neo)adj chemotherapy | 65% |
| Prior everolimus | 32% |
| BL HER3 expression (≥75%) | 51.8% |
| BL HER3 expression unknown | 48.2% |

| Tumor response by 3 months from treatment initiation, n (%) | |
|---|---|
| Partial response* | 16 (28.6)* |
| Stable Disease | 30 (53.6) |
| Progressive Disease | 10 (17.8) |

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Courtesy of Erika Hamilton, MD

SARAH CANNON Research Institute

Pistilli B et al. ESMO Breast 2023

# Phase 2 trial of HER3-DXd in HER2- MBC

- LA/MBC
- TNBC: 1-3 prior lines of chemo for MBC
- HR+: Prior tx with CDK 4/6i +ET; no more than 2 prior chemo for MBC
- Pre- and on-treatment biopsies

**N= 60**

**Patritumab deruxtecan**
**5.6mg/kg IV q 3 weeks**

Pre treatment* biopsy tissue analyzed for ER/PR/HER2 and HER3 expression

| Patient population: | |
|---|---|
| Median prior regimens | 3 |
| Prior chemotherapy | 90% |
| Prior immunotherapy | 20% |
| Prior Sacituzumab | 8.3% |
| BL HER3 expression (≥75%) | 63.8% |
| BL HER3 expression (25-74%) | 27.7% |

| Membrane HER3 expression | ≥75% (N=30) | 25%- 74% (N=13) | <25% (N=4) | Unknown * (N=13) | Total (N=60) N (%) |
|---|---|---|---|---|---|
| ORR, n (%) | 10 (33.3) | 6 (46.2) | 2 (50.0) | 3 (23.1) | 21 (35.0) |
| CBR, n (%)** | 12 (40.0) | 7 (53.8) | 2 (50.0) | 5 (38.5) | 26 (43.3) |
| DoR ≥6 months, n (%)† | 4 (40.0) | 2 (33.3) | 2 (100) | 2 (66.7) | 10 (47.6) |

*HER3 results available for 47 pts. Remaining 13 pts had tissue not available/testing result unevaluable

**All-comer ORR was 35%, overall CBR was 43%, and DoR was at least 6 months in nearly half of all patients who responded**

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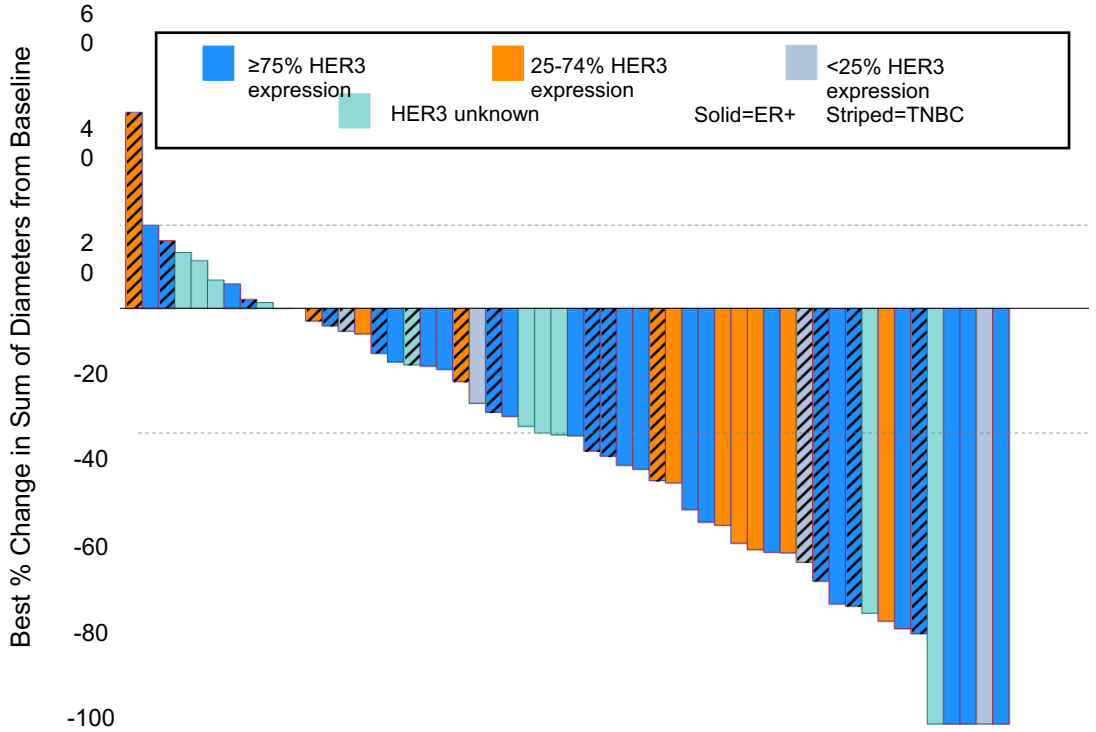
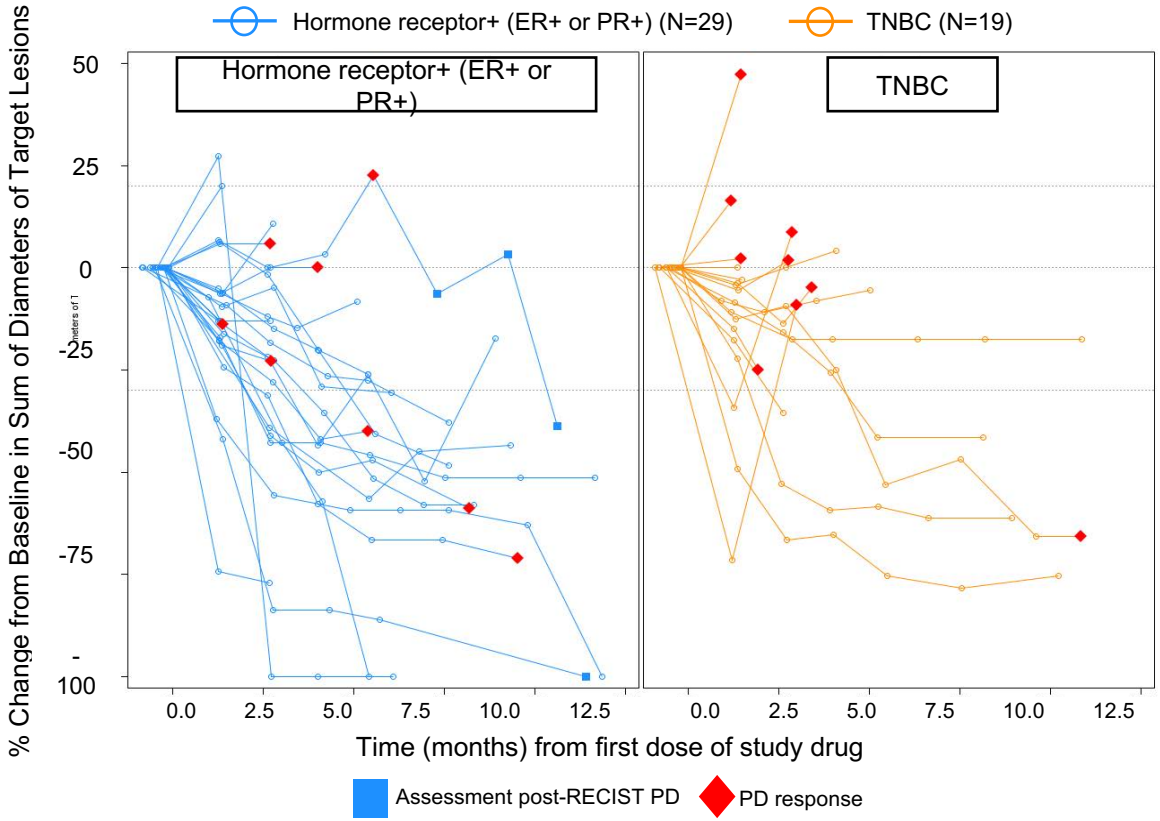
Hamilton E et al. ASCO 2023

# Tumor shrinkage with HER3-DXd

Best Percent Change in Sum of Diameters from Baseline in Target Lesions




Percent Change from Baseline in Sum of Diameters of Target Lesions HR+ vs TNBC




Majority of the patients had tumor shrinkage with HER3-DXd treatment

Courtesy of Erika Hamilton, MD

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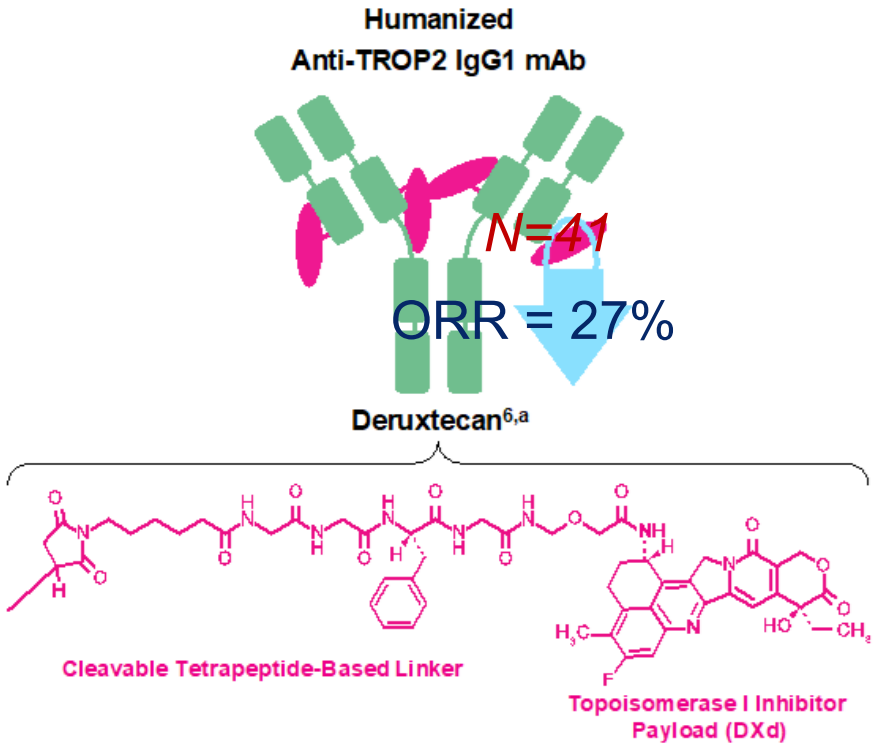
Hamilton E et al. ASCO 2023

# Datopotamab deruxtecan (Dato-DXd): Trop-2 directed ADC




- High-potency TOPO1 payload
- Payload with short systemic half-life
- Optimised DAR ~4
- Tumour-selective cleavable linker
- Bystander anti-tumour effect

**TROPION-PanTumor01**

- Unresectable or metastatic HR+/HER2– (IHC 0/1+ or IHC2+/ISH-) breast cancer
- Progressed on ≥1 endocrine therapy; previously treated with 1-3 prior lines of chemotherapy in the advanced setting
- Unselected for TROP2 expression[a]
- Age ≥18 years (US) or ≥20 years (Japan)
- ECOG PS 0-1
- Measurable disease per RECIST 1.1
- Stable, treated brain metastases allowed

→

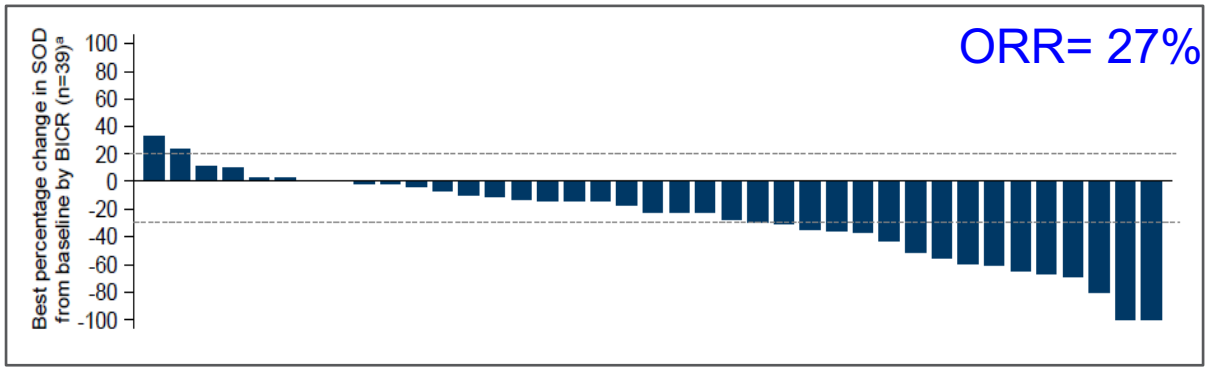
NSCLC[b]
(0.27 to 10 mg/kg IV Q3W)

TNBC[c]
8 mg/kg IV Q3W (n=2); 6 mg/kg IV Q3W (n=42)

**HR+/HER2– breast cancer**
**6 mg/kg IV Q3W (n=41)**

Other tumor types
(SCLC, bladder, gastric, esophageal, CRPC, pancreas)

Patient population (n=41)
- Median prior chemo for MBC = 2 (1-6)
- Prior CDK 4/6i = 95%




Median PFS = 8.3 months
Median OS = NR

Courtesy of Erika Hamilton, MD

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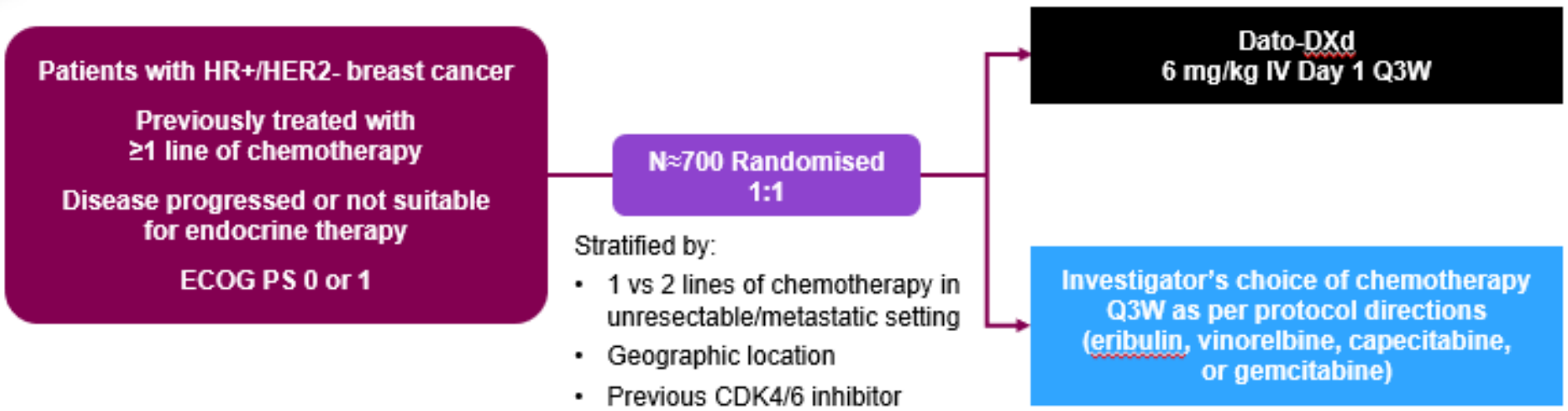
Meric-Bernstram F et al. SABCS 2022; PD13-08

# TROPION-Breast01: Phase 3 trial of Dato-DXd in HR+/HER2- MBC

NCT05104866




**Trial has completed accrual**

Courtesy of Erika Hamilton, MD

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# Case 1 Patient with ER+/HER2- MBC who received an investigational SERD

- Diagnosis of ER+/HER2- BC in 2005
- Lumpectomy- 2.2 cm IDC, G2, ER 100%, PR 80%, HER-2 IHC 0, 0/2 involved SLN
- Adjuvant XRT
- Adjuvant tamoxifen->letrozole for 2005-2013 (8 years)

- Relapsed with lung metastases in 2017
- Received palbociclib + letrozole 2017-2020
- Enrolled on SERENA-2 randomized to camizestrant arm
- Experienced G1 arthralgia and visual disturbances
- Remains on therapy

Courtesy of Erika Hamilton, MD

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# Case 2 Patient with ER+/HER2- MBC who received capivasertib

Diagnosis of ER+/HER2- BC in 2003
- 5.5 cm IDC, grade 3, ER/PR 90%, HER-2 IHC 1+

Neoadjuvant chemotherapy AC->T followed lumpectomy
Bilateral mastectomies 2.2 cm residual IDC, 1+ SLN with 3 mm deposit, 3 additional neg nodes
Adjuvant exemestane/letrozole for 2004-2014 (10 years)

Relapsed with liver metastases in 2018
Received palbociclib + letrozole 2018-2020, needed 1 dose reduction on palbociclib
Progression - appearance of new bone lesions and new lung lesion
Molecular profiling revealed an AKT1 mutation
Patient enrolled on CAPItello-291
- Experienced G2 diarrhea – controlled w/ 3 Imodium daily (2 in am, 1 at lunch)
- G1 hyperglycemia

Courtesy of Erika Hamilton, MD

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# Case 3 Patient with ER+/HER2- MBC who received patritumab deruxtecan

Diagnosis of ER+/HER2- MBC in 2017 denovo with nodal and bone disease
Received palbociclib + letrozole 2017-2021
Exemestane + everolimus, progression at 4 months w/ new liver mets
Received capecitabine for 11 months w/ 1 dose reduction for hand/foot syndrome
Molecular profiling revealed an PIK3CA mutation
Patient received alpelisib + fulvestrant
Developed G2 hyperglycemia; discontinued alpelisib, continued fulvestrant until progression x 4 months
Received Sacituzumab govitecan for 4 months
At progression enrolled on clinical trial with patritumab deruxtecan, ongoing at 5 months

Courtesy of Erika Hamilton, MD

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# Agenda

**INTRODUCTION: Biopharmacology and Endocrinology of Breast Cancer**

**MODULE 1: Current Strategies for Previously Treated ER-Positive Metastatic Breast Cancer (mBC) — Dr Bardia**

**MODULE 2: Future Directions in the Management of ER-Positive mBC — Dr Hamilton**

**MODULE 3: Clinical Investigator Survey**

# In general, which CDK4/6 inhibitor are you most likely to recommend in combination with endocrine therapy for a patient with ER-positive, HER2-negative (IHC 0) metastatic breast cancer?

| | Premenopausal | Postmenopausal |
|---|---|---|
|  Dr Bardia | Ribociclib | Ribociclib |
|  Dr Hamilton | Ribociclib | Ribociclib |
|  Dr Burstein | Palbociclib | Palbociclib |
|  Dr Goetz | Ribociclib | Ribociclib |
|  Dr Kaklamani | Ribociclib | Ribociclib |
|  Dr O'Regan | Ribociclib | Ribociclib |

**A 65-year-old woman with ER-positive, HER2-negative (IHC 0), node-negative breast cancer has developed multiple minimally symptomatic bone metastases 2 years after starting adjuvant anastrozole. Which endocrine-based treatment would you most likely recommend?**

| | |
|---|---|
|  Dr Bardia | Ribociclib + fulvestrant |
|  Dr Hamilton | Ribociclib + fulvestrant |
|  Dr Burstein | Palbociclib + fulvestrant |
|  Dr Goetz | Ribociclib + fulvestrant |
|  Dr Kaklamani | Ribociclib + fulvestrant |
|  Dr O'Regan | Ribociclib + fulvestrant |

RTP RESEARCH TO PRACTICE

A 65-year-old woman with ER-positive, HER2-negative (IHC 0), node-negative breast cancer has developed multiple minimally symptomatic bone metastases 2 years after starting adjuvant anastrozole. She receives a CDK4/6 inhibitor with fulvestrant and initially responds but then experiences disease progression 18 months later. Regulatory and reimbursement issues aside, what would be your most likely next treatment if biomarker evaluation revealed the following results?

| | ESR1-positive, PIK3CA-positive | ESR1-positive, PIK3CA-negative | ESR1-negative, PIK3CA-positive | ESR1-negative, PIK3CA-negative |
|---|---|---|---|---|
|  Dr Bardia | Elacestrant | Elacestrant | Alpelisib/fulvestrant | Exemestane/ everolimus |
|  Dr Hamilton | Elacestrant or camizestrant | Elacestrant or camizestrant | Alpelisib/fulvestrant | Exemestane/ everolimus |
|  Dr Burstein | Elacestrant | Elacestrant or capivasertib/fulvestrant | Capivasertib/ fulvestrant | Capivasertib/ fulvestrant |
|  Dr Goetz | Alpelisib/fulvestrant | Cont fulvestrant, switch to abemaciclib | Alpelisib/fulvestrant | Exemestane/ everolimus |
|  Dr Kaklamani | Elacestrant | Elacestrant | Alpelisib/ exemestane | Exemestane/ everolimus |
|  Dr O'Regan | Elacestrant | Elacestrant | Alpelisib/fulvestrant | Exemestane/ everolimus |

# Have you administered or would you administer a CDK4/6 inhibitor to a patient with ER-positive, HER2-negative (IHC 0) metastatic breast cancer who has experienced disease progression on a CDK4/6 inhibitor?

| | |
|---|---|
|  Dr Bardia | I have not but would for the right patient |
|  Dr Hamilton | I have not but would for the right patient |
|  Dr Burstein | I have |
|  Dr Goetz | I have |
|  Dr Kaklamani | I have not but would for the right patient |
|  Dr O'Regan | I have |

RTP RESEARCH TO PRACTICE

# Should community-based oncologists routinely be testing for the following biomarkers in their patients with ER-positive metastatic breast cancer?

| | ESR1 | PIK3CA |
|---|---|---|
|  Dr Bardia | Yes | Yes |
|  Dr Hamilton | Yes | Yes |
|  Dr Burstein | Yes | No |
|  Dr Goetz | Yes | Yes |
|  Dr Kaklamani | Yes | Yes |
|  Dr O'Regan | Yes | Yes |

# Have you administered or would you administer trastuzumab deruxtecan to a patient with ER-positive, HER2-negative (IHC 0) metastatic breast cancer?

| | |
|---|---|
|  Dr Bardia | I have not but would for the right patient |
|  Dr Hamilton | I have not but would for the right patient |
|  Dr Burstein | I have |
|  Dr Goetz | I have not but would for the right patient |
|  Dr Kaklamani | I have not and would not |
|  Dr O'Regan | I have not and would not |

# Regulatory and reimbursement issues aside, would you offer trastuzumab deruxtecan to a patient with HER2-negative (IHC 0) metastatic breast cancer and a HER2 mutation?

| | |
|---|---|
|  Dr Bardia | Yes |
|  Dr Hamilton | Yes |
|  Dr Burstein | Yes |
|  Dr Goetz | Yes |
|  Dr Kaklamani | Yes |
|  Dr O'Regan | No |

RTP RESEARCH TO PRACTICE

**A 65-year-old woman with ER-positive, HER2-negative (IHC 0) breast cancer experienced disease progression on various endocrine-based therapies and most recently on capecitabine/ paclitaxel. PS 1, no organ dysfunction. Regulatory and reimbursement issues aside what would be your most likely next treatment if biomarker evaluation revealed the following results?**

| | ESR1-positive, PIK3CA-positive | ESR1-positive, PIK3CA-negative | ESR1-negative, PIK3CA-positive | ESR1-negative, PIK3CA-negative |
|---|---|---|---|---|
|  Dr Bardia | Sacituzumab govitecan | Sacituzumab govitecan | Sacituzumab govitecan | Sacituzumab govitecan |
|  Dr Hamilton | Sacituzumab govitecan | Sacituzumab govitecan | Sacituzumab govitecan | Sacituzumab govitecan |
|  Dr Burstein | Sacituzumab govitecan | Sacituzumab govitecan | Sacituzumab govitecan | Sacituzumab govitecan |
|  Dr Goetz | Alpelisib/ fulvestrant | Sacituzumab govitecan | Alpelisib/ fulvestrant | Sacituzumab govitecan |
|  Dr Kaklamani | Sacituzumab govitecan | Sacituzumab govitecan | Sacituzumab govitecan | Sacituzumab govitecan |
|  Dr O'Regan | Alpelisib/ fulvestrant | Elacestrant | Alpelisib/ fulvestrant | Exemestane/ everolimus |

## For a patient with metastatic breast cancer, regulatory and reimbursement issues aside, at what point would you like to use sacituzumab govitecan?

| | ER-positive, HER2-negative | ER-negative, HER2-negative |
|---|---|---|
|  Dr Bardia | After 1 line of chemotherapy | After 1 line of chemotherapy |
|  Dr Hamilton | After 1 line of chemotherapy | After 1 line of chemotherapy |
|  Dr Burstein | After 1 line of chemotherapy | After 1 line of chemotherapy |
|  Dr Goetz | After 1 line of chemotherapy | After 1 line of chemotherapy |
|  Dr Kaklamani | After 1 line of chemotherapy | After 1 line of chemotherapy |
|  Dr O'Regan | After 2 lines of endocrine therapy | After 1 line of chemotherapy |

# If camizestrant were to become available, for which patients with ER-positive, HER2-negative metastatic breast cancer would you prioritize its use?

| | |
|---|---|
|  Dr Bardia | First line as study in 1st-line setting (SERENA-4/6) |
|  Dr Hamilton | Chemo-naïve (both ESR1m and wt) w/ prior benefit from CDK4/6i |
|  Dr Burstein | ESR1 mutation-positive |
|  Dr Goetz | ESR1 mutation-positive |
|  Dr Kaklamani | Depends on ESR1 approval |
|  Dr O'Regan | ESR1 mutation-positive |

Wt = wild type; CDK4/6i = CDK4/6 inhibitor

RTP RESEARCH TO PRACTICE

# If capivasertib were to become available, for which patients with ER-positive, HER2-negative metastatic breast cancer would you prioritize its use?

| | |
|---|---|
|  Dr Bardia | Second-line HR+/HER2- mBC, particularly with PI3K/AKT pathway alteration |
|  Dr Hamilton | Fulvestrant-naïve with prior benefit from CDK4/6i |
|  Dr Burstein | Prior CDK4/6i therapy |
|  Dr Goetz | Disease progression on first-line endocrine therapy, no ESR1 mutation |
|  Dr Kaklamani | After progression on CDK4/6i assuming ESR1 wt |
|  Dr O'Regan | PI3K mutation, access as defined in FAKTION |

CDK4/6i = CDK4/6 inhibitor; wt = wild type

RTP RESEARCH TO PRACTICE

# If datopotamab deruxtecan were to become available, for which patients with ER-positive metastatic breast cancer would you prioritize its use?

| | HER2-negative | HER2-positive |
|---|---|---|
|  Dr Bardia | HR+/HER2- mBC, after 1 prior line of chemotherapy | Unlikely in HER2+ setting w/o data. For HER2 low, after 1 prior line of chemotherapy |
|  Dr Hamilton | Endocrine-resistant disease | No evidence currently |
|  Dr Burstein | Need more data | Need more data |
|  Dr Goetz | After T-DXd and sacituzumab govitecan | I would prioritize it for later lines of therapy |
|  Dr Kaklamani | After currently approved ADCs | After currently approved ADCs |
|  Dr O'Regan | After PD on 2 lines of therapy | After PD on 2 or 3 lines of therapy |

ADC = antibody-drug conjugate; PD = progressive disease

# If patritumab deruxtecan were to become available, for which patients with ER-positive metastatic breast cancer would you prioritize its use?

| | HER2-negative | HER2-positive |
|---|---|---|
|  Dr Bardia | Tough to know without pivotal Phase III trial | Tough to know without pivotal Phase III trial |
|  Dr Hamilton | Endocrine-resistant disease | After THP and T-DXd, likely concurrently |
|  Dr Burstein | Need more data | Need more data |
|  Dr Goetz | After T-DXd and sacituzumab govitecan | After all standard HER2-based therapies |
|  Dr Kaklamani | Depends on the Phase III data | Too early to tell |
|  Dr O'Regan | HER3-positive disease | HER3-positive disease |

THP = docetaxel/trastuzumab/pertuzumab; T-DXd = trastuzumab deruxtecan

**A 65-year-old woman with ER-positive, HER2-low (IHC 1) breast cancer experienced disease progression on various endocrine-based therapies and most recently on capecitabine/paclitaxel. PS 1, no organ dysfunction. Regulatory and reimbursement issues aside, what would be your most likely next treatment if biomarker evaluation revealed the following results?**

| | ESR1-positive, PIK3CA-positive | ESR1-positive, PIK3CA-negative | ESR1-negative, PIK3CA-positive | ESR1-negative, PIK3CA-negative |
|---|---|---|---|---|
|  Dr Bardia | T-DXd | T-DXd | T-DXd | T-DXd |
|  Dr Hamilton | T-DXd | T-DXd | T-DXd | T-DXd |
|  Dr Burstein | Elacestrant or T-DXd* | Elacestrant or T-DXd* | T-DXd | T-DXd |
|  Dr Goetz | T-DXd | T-DXd | T-DXd | T-DXd |
|  Dr Kaklamani | T-DXd | T-DXd | T-DXd | T-DXd |
|  Dr O'Regan | Alpelisib/ fulvestrant | Elacestrant | Alpelisib/ fulvestrant | Exemestane/ everolimus |

T-DXd = trastuzumab deruxtecan; * If not visceral disease, elacestrant

## For a patient with metastatic breast cancer, regulatory and reimbursement issues aside, at what point would you like to use trastuzumab deruxtecan?

| | ER-positive, HER2-low (IHC 1) | ER-negative, HER2-low (IHC 1) |
|---|---|---|
|  Dr Bardia | After 1 line of chemotherapy | After 2 lines of chemotherapy (after SG) |
|  Dr Hamilton | After 1 line of chemotherapy | After 1 line of chemotherapy |
|  Dr Burstein | After 1 line of chemotherapy | After 1 line of chemotherapy |
|  Dr Goetz | After 1 line of chemotherapy | After 2 lines of chemotherapy |
|  Dr Kaklamani | After 1 line of chemotherapy | After 2 lines of chemotherapy |
|  Dr O'Regan | After 2 lines of endocrine therapy | After 2 lines of chemotherapy |

SG = sacituzumab govitecan

# Would you recommend rechallenge with trastuzumab deruxtecan for a patient who previously developed pneumonitis on that treatment and has since recovered?

| | |
|---|---|
|  Dr Bardia | No |
|  Dr Hamilton | Yes, if Grade 1 |
|  Dr Burstein | Yes, if Grade 1 |
|  Dr Goetz | Yes, if Grade 1 |
|  Dr Kaklamani | Yes, if Grade 1 |
|  Dr O'Regan | Yes, if Grade 1 |

RTP RESEARCH TO PRACTICE

**Based on your personal clinical experience and knowledge of available data, please estimate the chance that a patient will experience toxicity requiring a dose hold during treatment with elacestrant. What is the primary toxicity that leads to withholding dosing?**

| | Chance of dose hold | Primary toxicity |
|---|---|---|
|  Dr Bardia | 5% | Nausea |
|  Dr Hamilton | 5% | Fatigue |
|  Dr Burstein | 75% | GI |
|  Dr Goetz | 20% | GI |
|  Dr Kaklamani | 5% | Nausea |
|  Dr O'Regan | <5% | GI |

## Based on your personal clinical experience and knowledge of available data, please estimate the chance that a patient will experience toxicity requiring a dose hold during treatment with camizestrant. What is the primary toxicity that leads to withholding dosing?

| | Chance of dose hold | Primary toxicity |
|---|---|---|
|  Dr Bardia | 10% | Visual toxicity |
|  Dr Hamilton | 5% | Fatigue |
|  Dr Burstein | 75% | GI |
|  Dr Goetz | 20% | Fatigue |
|  Dr Kaklamani | 10% | Nausea |
|  Dr O'Regan | <5% | Vision issues |

**Based on your personal clinical experience and knowledge of available data, please estimate the chance that a patient will experience toxicity requiring a dose hold during treatment with giredestrant held. What is the primary toxicity that leads to withholding dosing?**

| | Chance of dose hold | Primary toxicity |
|---|---|---|
|  Dr Bardia | 5% | Bradycardia |
|  Dr Hamilton | 5% to 10% | GI |
|  Dr Burstein | Not sure | Not sure |
|  Dr Goetz | 20% | GI |
|  Dr Kaklamani | 20% | Nausea |
|  Dr O'Regan | <5% | Hepatotoxicity |

**Based on your personal clinical experience and knowledge of available data, please estimate the chance that a patient will experience toxicity requiring a dose hold during treatment with imlunestrant. What is the primary toxicity that leads to withholding dosing?**

| | Chance of dose hold | Primary toxicity |
|---|---|---|
|  Dr Bardia | 10% | Diarrhea |
|  Dr Hamilton | 5% | Fatigue |
|  Dr Burstein | 75% | GI |
|  Dr Goetz | 20% | GI |
|  Dr Kaklamani | 10% | Nausea |
|  Dr O'Regan | <5% | GI |

**Based on your personal clinical experience and knowledge of available data, please estimate the chance that a patient will experience toxicity requiring a dose hold during treatment with capivasertib. What is the primary toxicity that leads to withholding dosing?**

| | Chance of dose hold | Primary toxicity |
|---|---|---|
|  Dr Bardia | 20% | Diarrhea |
|  Dr Hamilton | 25% | Diarrhea |
|  Dr Burstein | 50% | GI |
|  Dr Goetz | 30% | Diarrhea |
|  Dr Kaklamani | 20% | Diarrhea |
|  Dr O'Regan | 10% to 15% | Rash |

**Based on your personal clinical experience and knowledge of available data, please estimate the chance that a patient will experience toxicity requiring a dose hold during treatment with alpelisib. What is the primary toxicity that leads to withholding dosing?**

| | Chance of dose hold | Primary toxicity |
|---|---|---|
|  Dr Bardia | 25% | Rash, diarrhea |
|  Dr Hamilton | 50% | Hyperglycemia, diarrhea |
|  Dr Burstein | 25% | Hyperglycemia |
|  Dr Goetz | 70% | Hyperglycemia |
|  Dr Kaklamani | 30% | Hyperglycemia |
|  Dr O'Regan | >10% | Hyperglycemia |

**Based on your personal clinical experience and knowledge of available data, please estimate the chance that a patient will experience toxicity requiring a dose hold during treatment with trastuzumab deruxtecan. What is the primary toxicity that leads to withholding dosing?**

| | Chance of dose hold | Primary toxicity |
|---|---|---|
|  Dr Bardia | 30% | Pneumonitis |
|  Dr Hamilton | 20% | Interstitial lung disease, nausea |
|  Dr Burstein | 50% | General fatigue |
|  Dr Goetz | 30% | Neutropenia |
|  Dr Kaklamani | 10% | Nausea |
|  Dr O'Regan | 20% | Interstitial lung disease |

**Based on your personal clinical experience and knowledge of available data, please estimate the chance that a patient will experience toxicity requiring a dose hold during treatment with sacituzumab govitecan. What is the primary toxicity that leads to withholding dosing?**

| | Chance of dose hold | Primary toxicity |
|---|---|---|
|  Dr Bardia | 30% | Myelosuppression |
|  Dr Hamilton | 40% | Neutropenia |
|  Dr Burstein | 25% | Neutropenia |
|  Dr Goetz | 40% | Neutropenia |
|  Dr Kaklamani | 10% | Diarrhea |
|  Dr O'Regan | 15% | Diarrhea |

**Based on your personal clinical experience and knowledge of available data, please estimate the chance that a patient will experience toxicity requiring a dose hold during treatment with datopotamab deruxtecan. What is the primary toxicity that leads to withholding dosing?**

| | Chance of dose hold | Primary toxicity |
|---|---|---|
|  Dr Bardia | 15% | Mucositis |
|  Dr Hamilton | 30% | Stomatitis |
|  Dr Burstein | 25% | General fatigue |
|  Dr Goetz | 30% | Nausea |
|  Dr Kaklamani | 10% | Nausea |
|  Dr O'Regan | 10% | Anemia |

**Based on your personal clinical experience and knowledge of available data, please estimate the chance that a patient will experience toxicity requiring a dose hold during treatment with patritumab deruxtecan. What is the primary toxicity that leads to withholding dosing?**

| | Chance of dose hold | Primary toxicity |
|---|---|---|
|  Dr Bardia | Not sure | Not sure |
|  Dr Hamilton | 15% | Nausea |
|  Dr Burstein | Not sure | Not sure |
|  Dr Goetz | I have not had enough experience with this drug | I have not had enough experience with this drug |
|  Dr Kaklamani | 10% | Nausea |
|  Dr O'Regan | 10% | Hematologic |

**Based on your personal clinical experience and knowledge of available data, please estimate the chance that a patient will experience toxicity requiring a dose hold during treatment with olaparib. What is the primary toxicity that leads to withholding dosing?**

| | Chance of dose hold | Primary toxicity |
|---|---|---|
|  Dr Bardia | 15% | Myelosuppression |
|  Dr Hamilton | ~35% | GI, blood counts |
|  Dr Burstein | 50% | General fatigue |
|  Dr Goetz | 20% | Anemia |
|  Dr Kaklamani | 10% | Blood counts |
|  Dr O'Regan | 10% | Anemia |

**Based on your personal clinical experience and knowledge of available data, please estimate the chance that a patient will experience toxicity requiring a dose hold during treatment with palbociclib. What is the primary toxicity that leads to withholding dosing?**

| | Chance of dose hold | Primary toxicity |
|---|---|---|
|  Dr Bardia | 15% | Myelosuppression |
|  Dr Hamilton | 70% | Transient neutropenia |
|  Dr Burstein | 75% | General fatigue |
|  Dr Goetz | 50% | Neutropenia |
|  Dr Kaklamani | 5% | Infections |
|  Dr O'Regan | 10% | Neutropenia |

**Based on your personal clinical experience and knowledge of available data, please estimate the chance that a patient will experience toxicity requiring a dose hold during treatment with abemaciclib. What is the primary toxicity that leads to withholding dosing?**

| | Chance of dose hold | Primary toxicity |
|---|---|---|
|  Dr Bardia | 20% | Diarrhea |
|  Dr Hamilton | 50% | Diarrhea |
|  Dr Burstein | 50% | GI |
|  Dr Goetz | 50% | Diarrhea |
|  Dr Kaklamani | 20% | Diarrhea |
|  Dr O'Regan | 10% | Diarrhea |

**Based on your personal clinical experience and knowledge of available data, please estimate the chance that a patient will experience toxicity requiring a dose hold during treatment with ribociclib. What is the primary toxicity that leads to withholding dosing?**

| | Chance of dose hold | Primary toxicity |
|---|---|---|
|  Dr Bardia | 20% | LFT increase |
|  Dr Hamilton | 70% | Transient neutropenia |
|  Dr Burstein | 75% | General fatigue |
|  Dr Goetz | 50% | Neutropenia |
|  Dr Kaklamani | 10% | Infections |
|  Dr O'Regan | 10% | Neutropenia |

## Based on your personal clinical experience and knowledge of available data, should olaparib be offered to patients with ER-positive, HER2-negative breast cancer and either a somatic or germline BRCA mutation in the following situations?

| | Any number of positive nodes | Select patients with node-negative disease |
|---|---|---|
|  Dr Bardia | Yes | Yes |
|  Dr Hamilton | Yes | No |
|  Dr Burstein | Yes | Yes |
|  Dr Goetz | Yes | No |
|  Dr Kaklamani | No | No |
|  Dr O'Regan | Yes | Yes |

# *Meet The Professor*

# Optimizing the Management of Soft Tissue Sarcoma and Related Connective Tissue Disorders

**Tuesday, July 25, 2023**
**5:00 PM – 6:00 PM ET**

## Faculty

**Richard F Riedel, MD**

## Moderator

**Neil Love, MD**

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*Please take a moment to complete the survey currently up on Zoom. Your feedback is very important to us. The survey will remain open up to 5 minutes after the meeting ends.*

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