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

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Faculty

Francois-Clement Bidard, MD, PhD
Medical Oncologist
Institut Curie, Inserm CIC1428
Professor, Versailles/Paris-Saclay University
Vice-Chair, Unicancer Breast Group (UCBG)
Paris, France

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

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

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

Hope S Rugo, MD
Professor of Medicine
Winterhof Family Professor of Breast Cancer Director
Breast Oncology and Clinical Trials Education
Medical Director
Cancer Infusion Services
University of California, San Francisco
Helen Diller Family Comprehensive Cancer Center
San Francisco, California

Moderator

Neil Love, MD
Research To Practice
Miami, Florida

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Prof Bidard — Disclosures

Consulting Agreements	AstraZeneca Pharmaceuticals LP, Caris Life Sciences, Exact Sciences Corporation, GE Healthcare, Gilead Sciences Inc, GSK, Lilly, Menarini Group, Novartis, Pfizer Inc, Rain Oncology, Sanofi
Contracted Research	GE Healthcare, Menarini Silicon Biosystems, Merck KGaA, Novartis, Pfizer Inc, ProLynx Inc
Speakers Bureau	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Lilly, Menarini Group, Novartis, Pfizer Inc, Rain Oncology, Roche Laboratories Inc, Stemline Therapeutics Inc

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Dr Hamilton — Disclosures

Advisory Committee and Consulting Agreements	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Ellipses Pharma, Genentech, a member of the Roche Group, Gilead Sciences Inc, Greenwich LifeSciences Inc, Janssen Biotech Inc, Jazz Pharmaceuticals Inc, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Medical Pharma Services sro, Mersana Therapeutics Inc, Novartis, Olema Oncology, Orum Therapeutics, Pfizer Inc, Relay Therapeutics, Seagen Inc, Stemline Therapeutics Inc, Theratechnologies, Tubulis, Zentalis Pharmaceuticals
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Nonrelevant Financial Relationship	Dana-Farber Cancer Institute, Verascity Science

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Dr Jhaveri — Disclosures

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Dr Kaklamani — Disclosures

Consulting Agreements	AstraZeneca Pharmaceuticals LP, Gilead Sciences Inc, Puma Biotechnology Inc, TerSera Therapeutics LLC
Contracted Research	Eisai Inc
Data and Safety Monitoring Board/Committee	Bristol Myers Squibb
Speakers Bureau	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Exact Sciences Corporation, Genentech, a member of the Roche Group, Gilead Sciences Inc, Novartis, Pfizer Inc, Seagen Inc

Dr Rugo — Disclosures

Consultancy/Advisory Support	Daiichi Sankyo Inc, Napo Pharmaceuticals Inc, Puma Biotechnology Inc, Viatris
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Travel Support to Academic Meetings	AstraZeneca Pharmaceuticals LP, Gilead Sciences Inc, Merck

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Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Localized HER2-Negative Breast Cancer

Part 2 of a 3-Part CME Satellite Symposium Series in Partnership with the 2023 San Antonio Breast Cancer Symposium®

Wednesday, December 6, 2023

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

Faculty

Harold J Burstein, MD, PhD
Matthew P Goetz, MD
Sara A Hurvitz, MD, FACP
Joyce O'Shaughnessy, MD
Lajos Pusztai, MD, DPhil, FASCO

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of HER2-Low Breast Cancer

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

Thursday, December 7, 2023

7:15 PM – 8:45 PM CT (8:15 PM – 9:45 PM ET)

Faculty

Aditya Bardia, MD, MPH

Lisa A Carey, MD, ScM, FASCO

Shanu Modi, MD

Professor Peter Schmid, FRCP, MD, PhD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Hematologic Cancers

A 4-Part CME Friday Satellite Symposium Series Preceding the 65th ASH Annual Meeting and Exposition

Friday, December 8, 2023

Follicular, Mantle Cell and Hodgkin Lymphoma
7:30 AM – 10:00 AM PT

Chronic Lymphocytic Leukemia
3:15 PM – 5:15 PM PT

Diffuse Large B-Cell Lymphoma
11:30 AM – 1:30 PM PT

Multiple Myeloma
7:00 PM – 9:00 PM PT

Moderator
Neil Love, MD

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Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Follicular, Mantle Cell and Hodgkin Lymphoma (Part 1 of a 4-Part Series)

A CME Friday Satellite Symposium and Virtual Event Preceding the 65th ASH Annual Meeting

Friday, December 8, 2023

7:30 AM – 10:00 AM PT (10:30 AM – 1:00 PM ET)

Faculty

Jeremy S Abramson, MD, MMSc
Stephen M Ansell, MD, PhD
Nancy L Bartlett, MD
Jonathon B Cohen, MD
Jonathan W Friedberg, MD, MMSc
Brad S Kahl, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Diffuse Large B-Cell Lymphoma (Part 2 of a 4-Part Series)

A CME Friday Satellite Symposium and Virtual Event Preceding the 65th ASH Annual Meeting

Friday, December 8, 2023

11:30 AM – 1:30 PM PT (2:30 PM – 4:30 PM ET)

Faculty

Michael Dickinson, MD
Grzegorz S Nowakowski, MD
Gilles Salles, MD, PhD
Laurie H Sehn, MD, MPH
Jason Westin, MD, MS

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Chronic Lymphocytic Leukemia (Part 3 of a 4-Part Series)

A CME Friday Satellite Symposium and Virtual Event Preceding the 65th ASH Annual Meeting

Friday, December 8, 2023

3:15 PM – 5:15 PM PT (6:15 PM – 8:15 PM ET)

Faculty

Farrukh T Awan, MD
Matthew S Davids, MD, MMSc
Stephen J Schuster, MD
William G Wierda, MD, PhD
Jennifer Woyach, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Multiple Myeloma (Part 4 of a 4-Part Series)

A CME Friday Satellite Symposium and Virtual Event Preceding the 65th ASH Annual Meeting

Friday, December 8, 2023

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

Faculty

Amrita Krishnan, MD
Sagar Lonial, MD
Robert Z Orlowski, MD, PhD
Noopur Raje, MD
Paul G Richardson, MD

Moderator

Neil Love, MD

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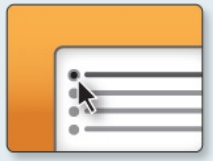
Clinicians in the Meeting Room

Networked iPads are available.

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



Answer Survey Questions: Complete the premeeting survey.

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

Complete Your Evaluation: Tap the CME/NCPD Evaluation button to complete your evaluation electronically to receive credit for your participation.

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

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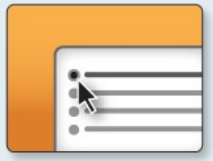
Clinicians Attending via Zoom

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



Answer Survey Questions: Complete the premeeting survey at the beginning of each module.

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

Get CME/NCPD Credit: CME and NCPD credit links will be provided in the chat room at the conclusion of the program. MOC and ONCC credit information will be emailed to attendees within the next 2-3 business days.

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

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Hope S Rugo, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Agenda

Module 1: Optimal Integration of CDK4/6 Inhibitors into the Management of ER-Positive Metastatic Breast Cancer (mBC) — Dr Kaklamani

Module 2: Novel Strategies to Overcome Resistance to Endocrine Therapy — Dr Jhaveri

Module 3: Current Role of Antibody-Drug Conjugates in the Management of ER-Positive mBC — Dr Rugo

Module 4: Current and Future Role of Selective Estrogen Receptor Degraders (SERDs) in the Management of ER-Positive mBC — Prof Bidard

Module 5: Novel Therapies Under Investigation for Patients with ER-Positive mBC — Dr Hamilton

Breast Cancer Survey Respondents

Aditya Bardia, MD, MPH
François-Clément Bidard, MD, PhD
Adam Brufsky, MD, PhD
Harold J Burstein, MD, PhD
Lisa A Carey, MD, ScM, FASCO
Matthew P Goetz, MD
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Mark Pegram, MD
Lajos Pusztai, MD, DPhil, FASCO
Hope S Rugo, MD
Paolo Tarantino, MD
Prof Peter Schmid, FRCP, MD, PhD
Priyanka Sharma, MD
Eric P Winer, MD

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Consulting Faculty

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Pittsburgh, Pennsylvania

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Division of Medical Oncology
Department of Internal Medicine
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Associate Vice Chair of Faculty Development and Promotions
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Paolo Tarantino, MD
Medical Oncologist
Advanced Research Fellow
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Mark D Pegram, MD
Susy Yuan-Huey Hung Endowed Professor of Oncology
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Stanford, California

Eric P Winer, MD
Alfred Gilman Professor of Medicine and Pharmacology
Director, Yale Cancer Center
President and Physician-in-Chief
Smilow Cancer Hospital
New Haven, Connecticut

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Analysis of Time to Recurrence in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) Trial According to Estrogen Receptor and Progesterone Receptor Status

Dowsett M, on behalf of the ATAC Trialists' Group.

SABCS 2003;Abstract 4.

GENERAL SESSION 1 | WEDNESDAY, DECEMBER 3 | 10:15 AM CT

Final Overall Survival Analysis from the MONARCH 3 Study of Abemaciclib to be Presented at the 2023 San Antonio Breast Cancer Symposium

Press Release – December 5, 2023

Results from the MONARCH 3 clinical trial will be presented in a late-breaking presentation during the 2023 San Antonio Breast Cancer Symposium (SABCS).

"MONARCH 3 evaluated abemaciclib in combination with an aromatase inhibitor (AI) compared to an AI alone as initial endocrine-based therapy for post-menopausal patients with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced or metastatic breast cancer. At eight years of follow-up, MONARCH 3 showed women taking abemaciclib and an AI had a median overall survival (OS) of more than 5.5 years – an increase of 13.1 months compared to the control arm in the intent-to-treat (ITT) population (66.8 vs 53.7 months), although statistical significance for the OS outcome was not reached (HR, 0.804; 95% CI, 0.637-1.015; p = 0.0664).

For women with visceral organ metastases, data showed a median OS of more than five years, with an increase in median OS of 14.9 months in the abemaciclib arm compared to the control arm (63.7 vs 48.8 months). [...] Patients with visceral disease are at an increased risk of disease progression and death compared to metastatic breast cancer (MBC) patients without visceral metastases. The OS results for this subpopulation were also not statistically significant (HR, 0.758; 95% CI, 0.558-1.030; p = 0.0757)."

https://investor.lilly.com/news-releases/news-release-details/lilly-present-final-overall-survival-analysis-monarch-3-study

Positive Phase III Results for Inavolisib Combination in People with Advanced Hormone Receptor-Positive, HER2-Negative Breast Cancer with a PIK3CA Mutation

Press Release – December 5, 2023

Positive results were announced from the Phase III INAVO120 study of the investigational therapy inavolisib in combination with palbociclib and fulvestrant as a potential first-line treatment option for people with PIK3CA-mutated, hormone receptor-positive, HER2-negative, endocrine-resistant, locally advanced or metastatic breast cancer.

"The study met its primary endpoint of progression-free survival (PFS), demonstrating a statistically significant and clinically meaningful improvement compared to palbociclib and fulvestrant alone. Overall survival data were immature at this time, but a clear positive trend has been observed. Follow-up will continue to the next analysis. [...]

The inavolisib combination was well tolerated and adverse events were consistent with the known safety profiles of the individual study treatments, with no new safety signals observed."

https://www.roche.com/media/releases/med-cor-2023-12-05

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Agenda

Module 1: Optimal Integration of CDK4/6 Inhibitors into the Management of ER-Positive Metastatic Breast Cancer (mBC) — Dr Kaklamani

Module 2: Novel Strategies to Overcome Resistance to Endocrine Therapy — Dr Jhaveri

Module 3: Current Role of Antibody-Drug Conjugates in the Management of ER-Positive mBC — Dr Rugo

Module 4: Current and Future Role of Selective Estrogen Receptor Degraders (SERDs) in the Management of ER-Positive mBC — Prof Bidard

Module 5: Novel Therapies Under Investigation for Patients with ER-Positive mBC — Dr Hamilton

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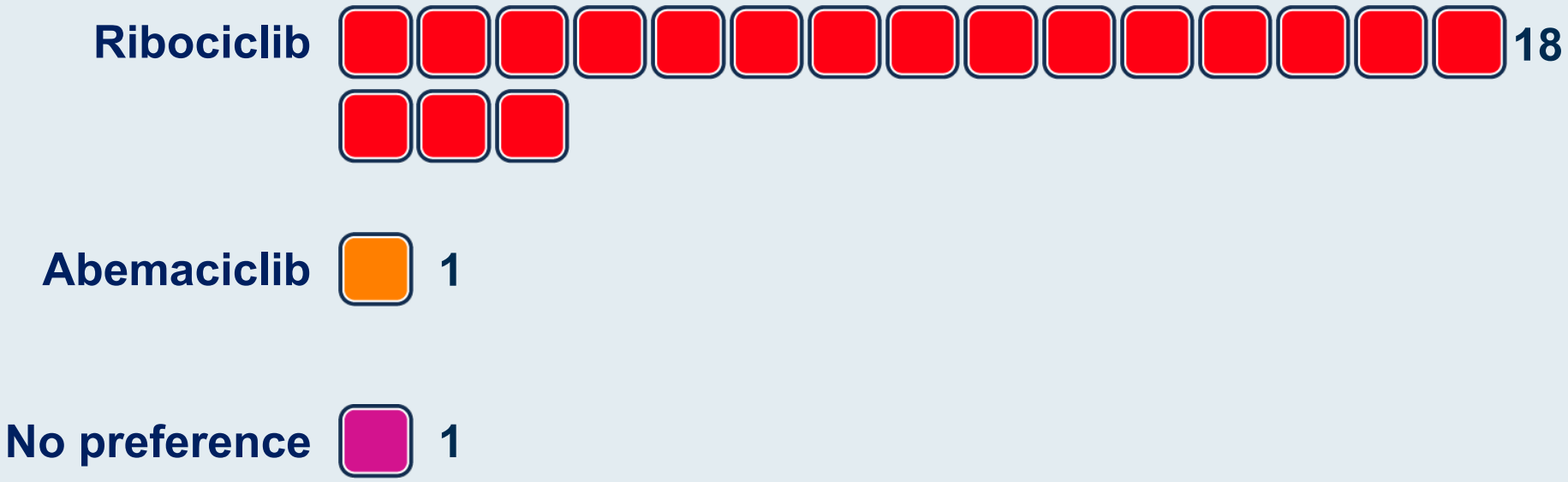
In general, which CDK4/6 inhibitor are you most likely to recommend in combination with endocrine therapy for a premenopausal patient with ER-positive, HER2-negative metastatic breast cancer?



Survey of 20 US-based clinical investigators November 2023

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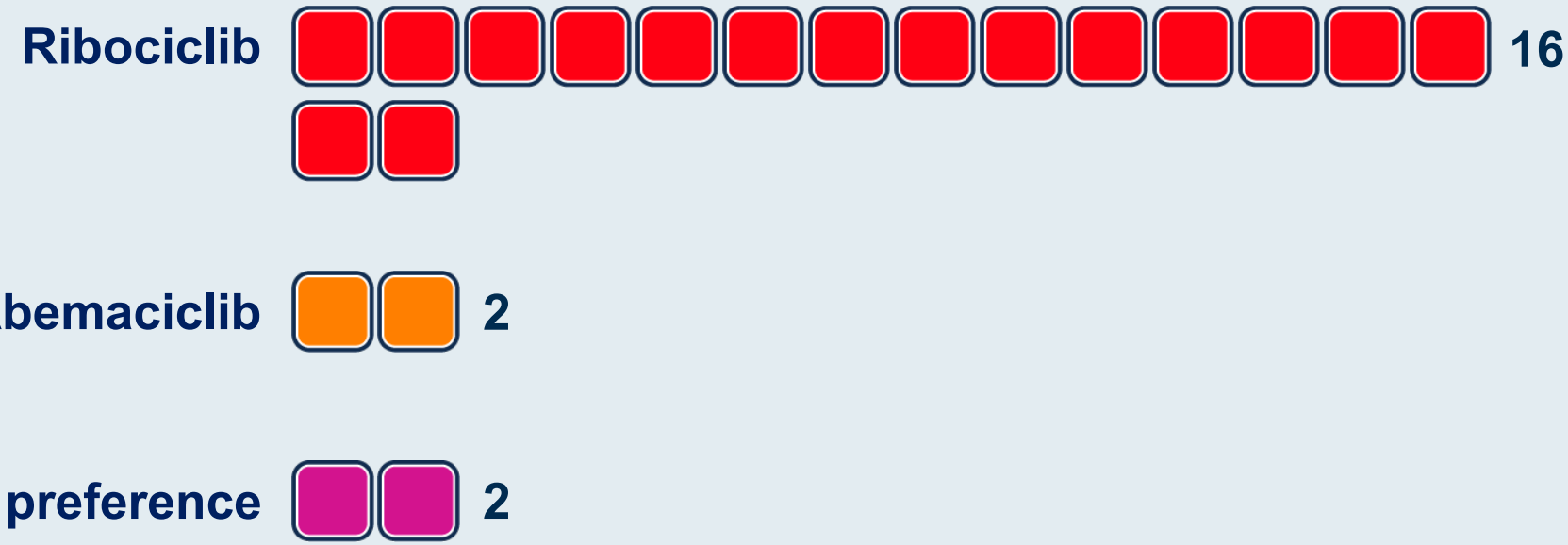
In general, which CDK4/6 inhibitor are you most likely to recommend in combination with endocrine therapy for a postmenopausal patient with ER-positive, HER2-negative metastatic breast cancer?



Survey of 20 US-based clinical investigators November 2023

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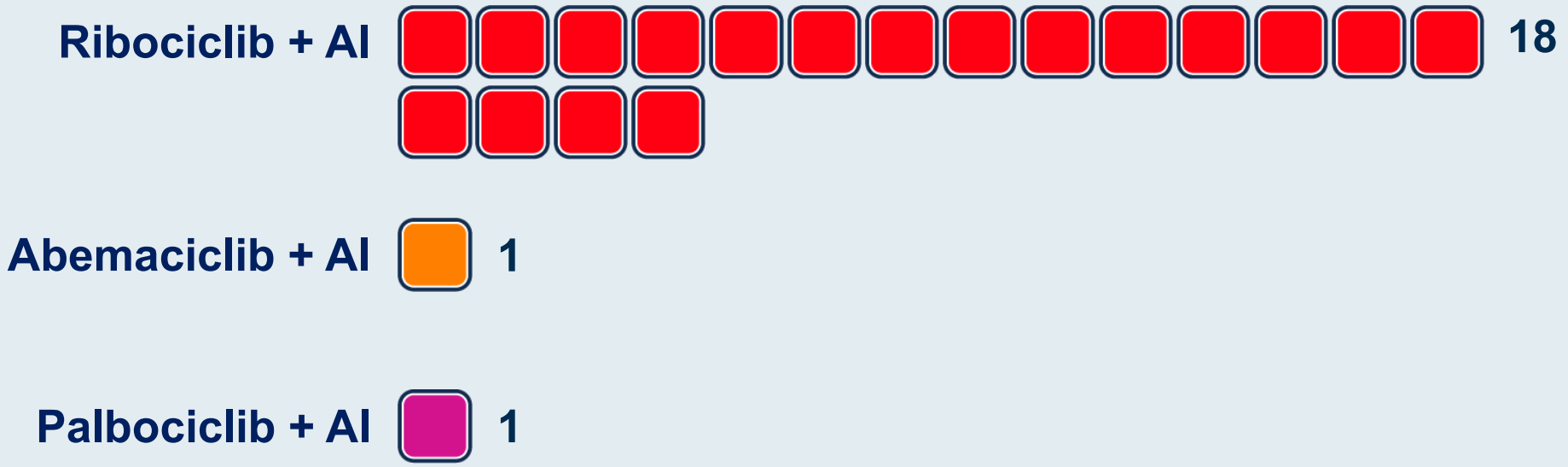
A 65-year-old woman presents with de novo ER-positive, HER2-negative metastatic breast cancer. Which endocrine-based treatment would you most likely recommend?



AI = aromatase inhibitor

Survey of 20 US-based clinical investigators November 2023

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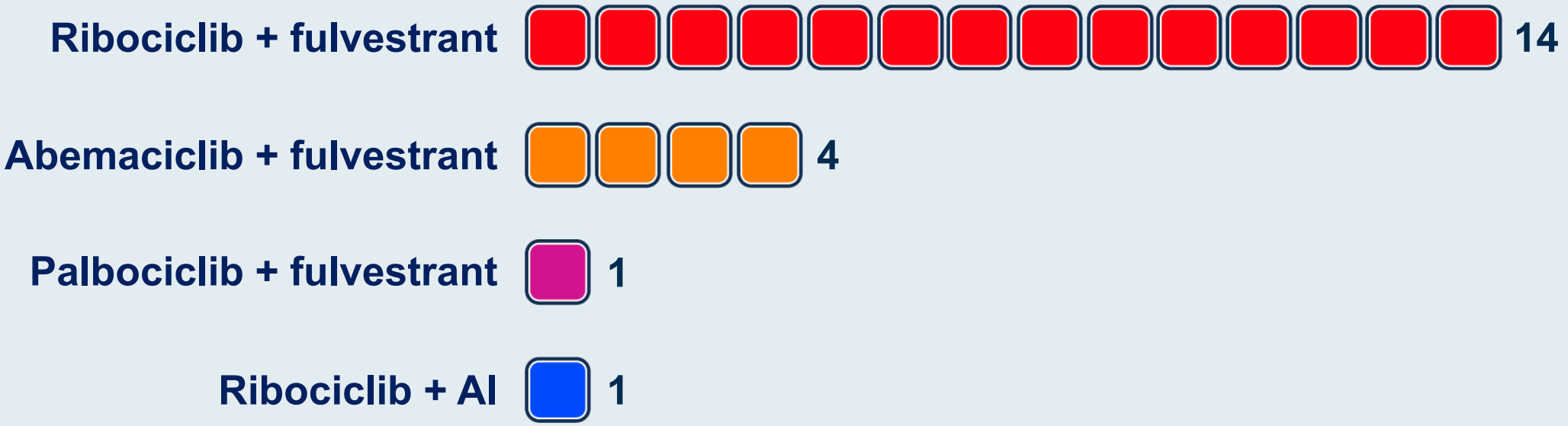
A 65-year-old woman with ER-positive, HER2-negative, node-negative breast cancer has developed multiple metastases 2 years after starting adjuvant anastrozole. Which endocrine-based treatment would you most likely recommend?



Survey of 20 US-based clinical investigators November 2023

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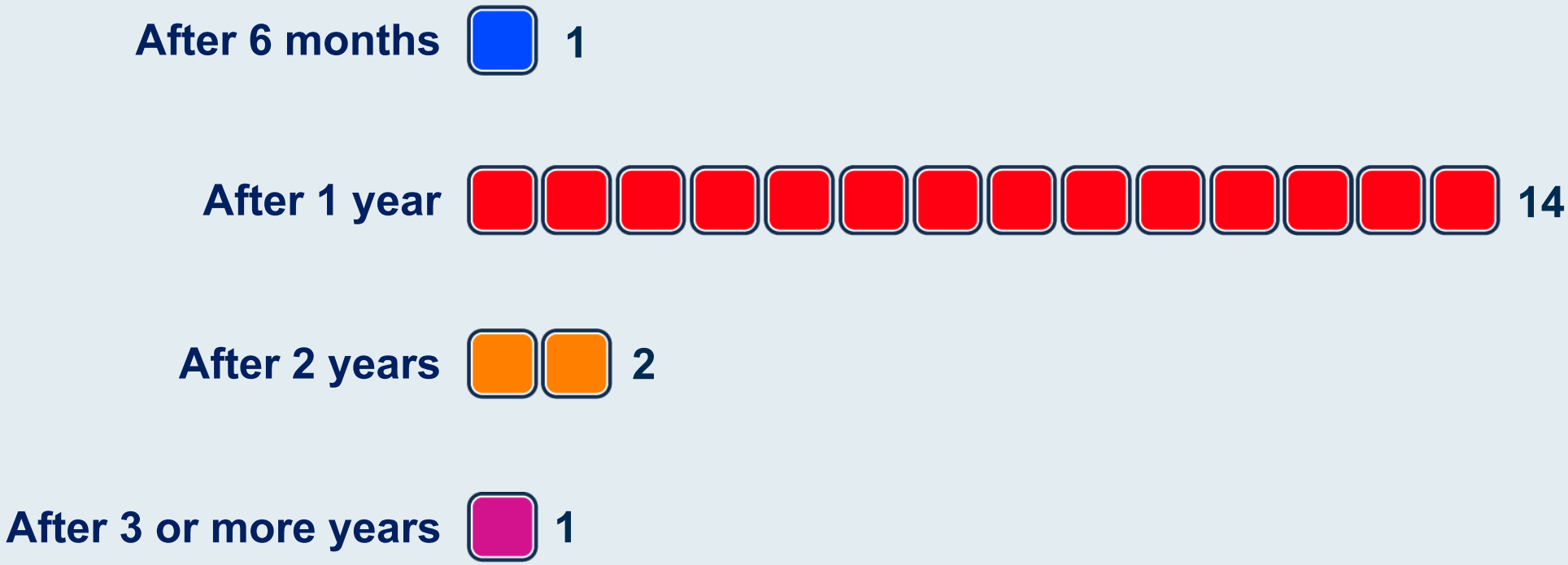
For a patient with ER-positive, HER2-negative breast cancer who receives a CDK4/6 inhibitor in the adjuvant setting and responds, at what time point, if any, would you be comfortable rechallenging with a CDK4/6 inhibitor in the metastatic setting?



Survey of 20 US-based clinical investigators November 2023

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Choice of CDK4/6 inhibitor in the metastatic setting

Priyanka Sharma, MD

Jane Lowe Meisel, MD

Paolo Tarantino, MD

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Selection of therapy for ER-positive metastatic breast cancer progressing on a CDK4/6 inhibitor and endocrine treatment

Adam M Brufsky, MD, PhD

Jane Lowe Meisel, MD

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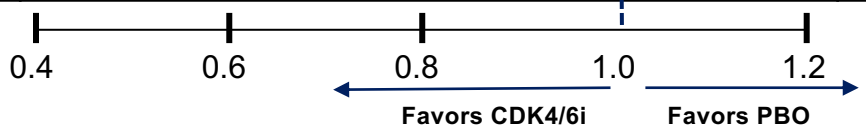
Optimal Integration of CDK4/6 Inhibitors into the Management of ER-Positive MBC

Virginia Kaklamani, MD DSc
Professor of Medicine
Leader, Breast Oncology Program

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	SABCS tomorrow					
RIBO	MONALEESA-2[4,5] Ribociclib + letrozole	63.9	51.4		0.76 (0.63-0.93)	.008	✓
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	✓

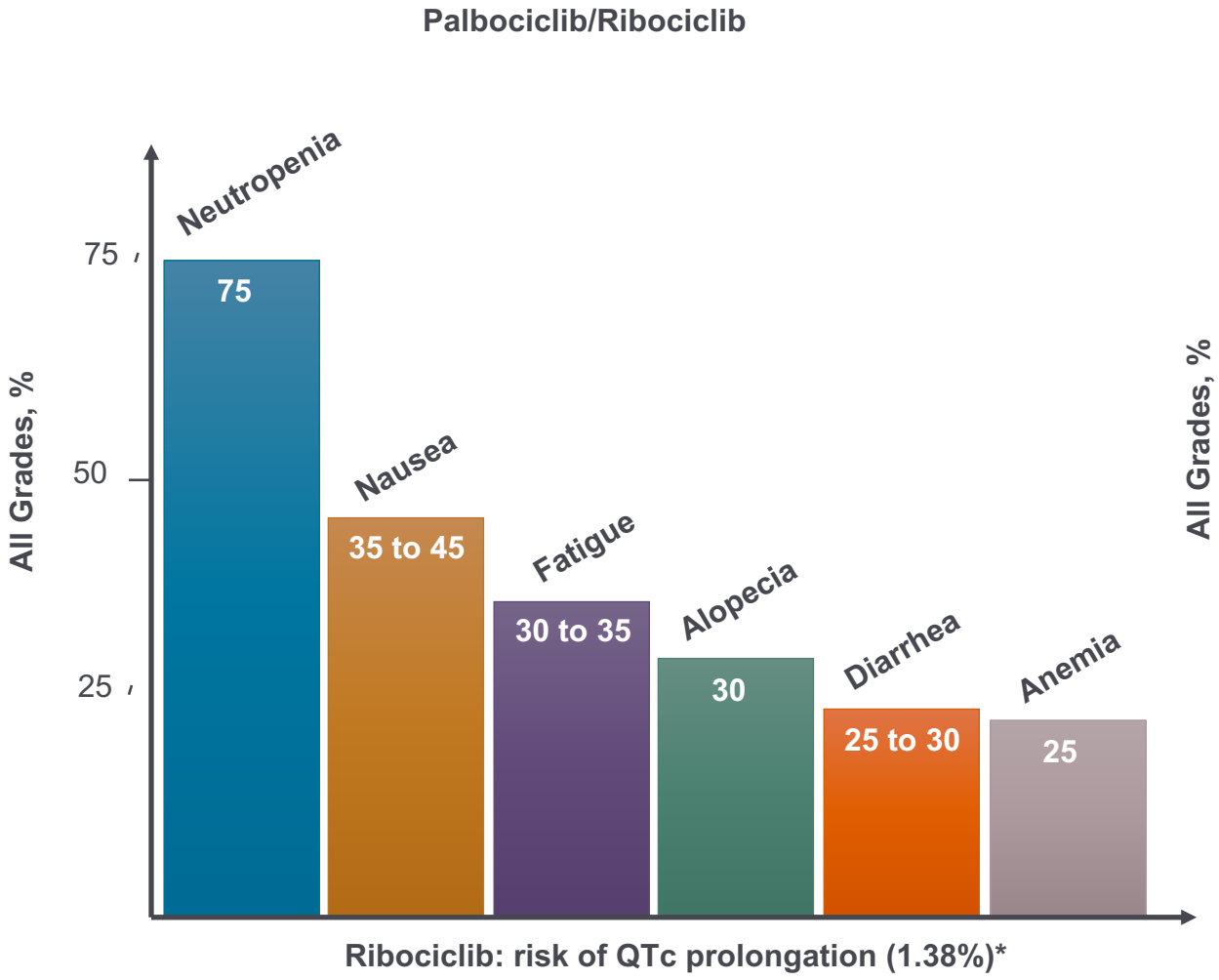


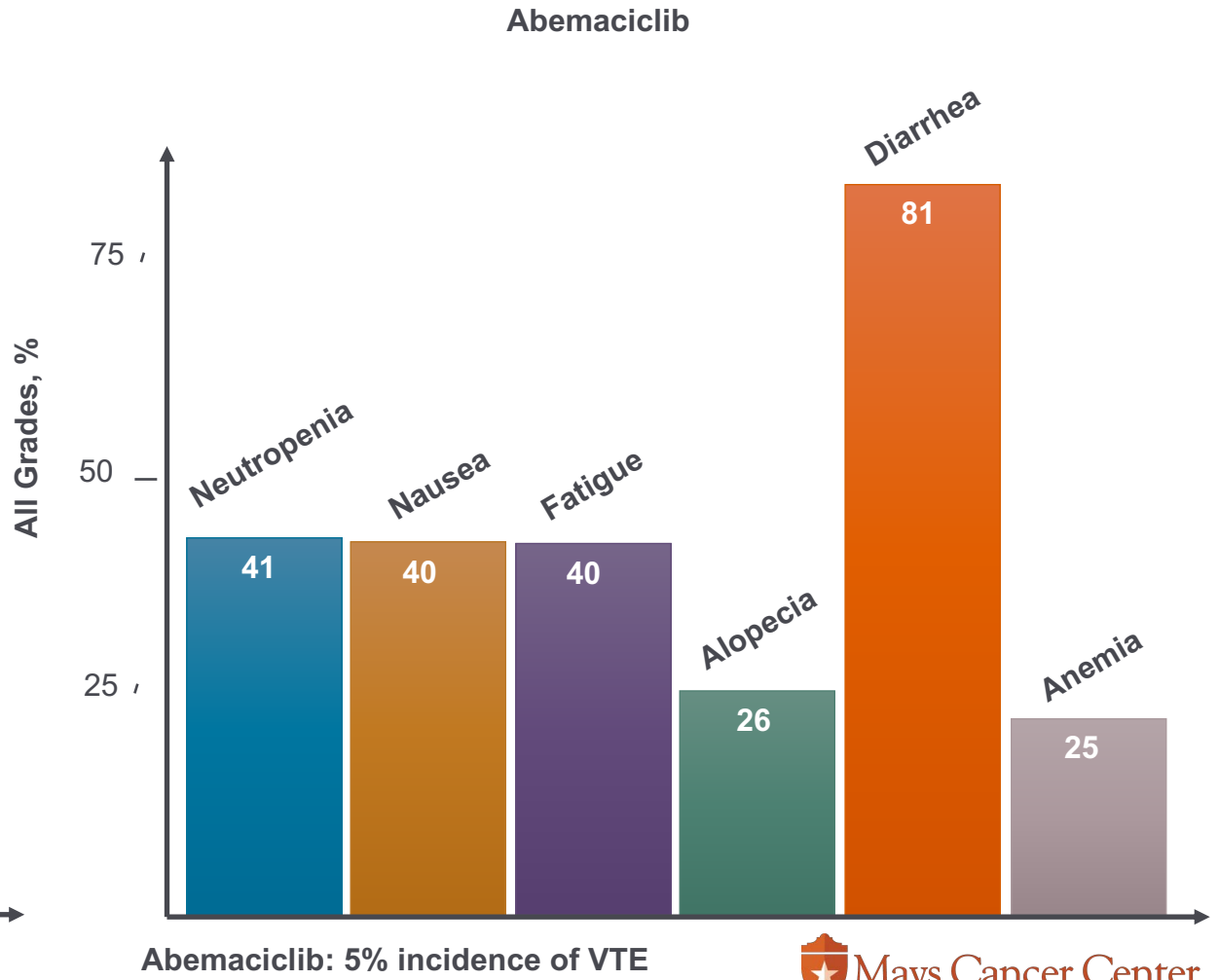
[a] The red × denotes trials that did not report significant median OS compared with placebo.

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.

Side Effect Profile of CDK 4/6i + ET

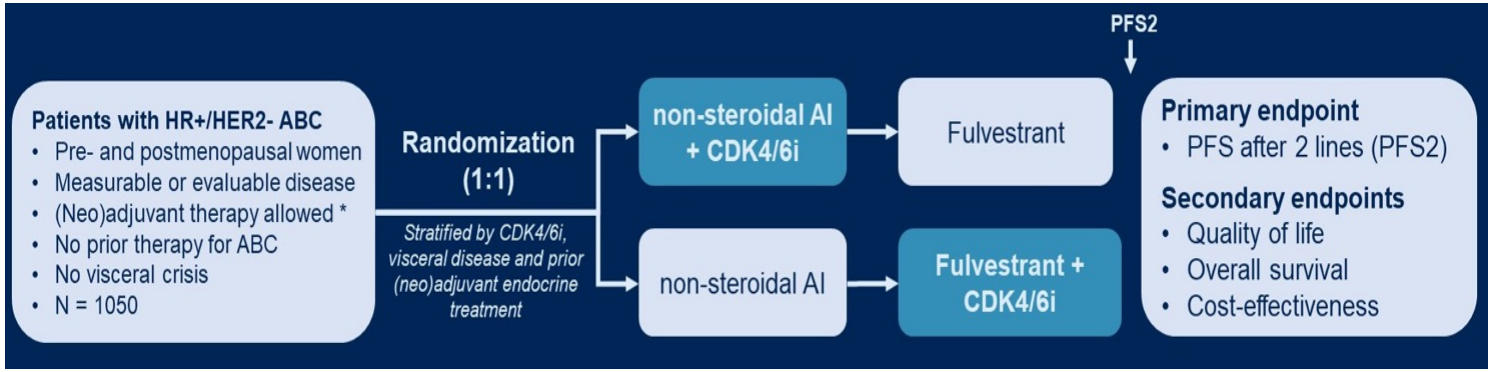


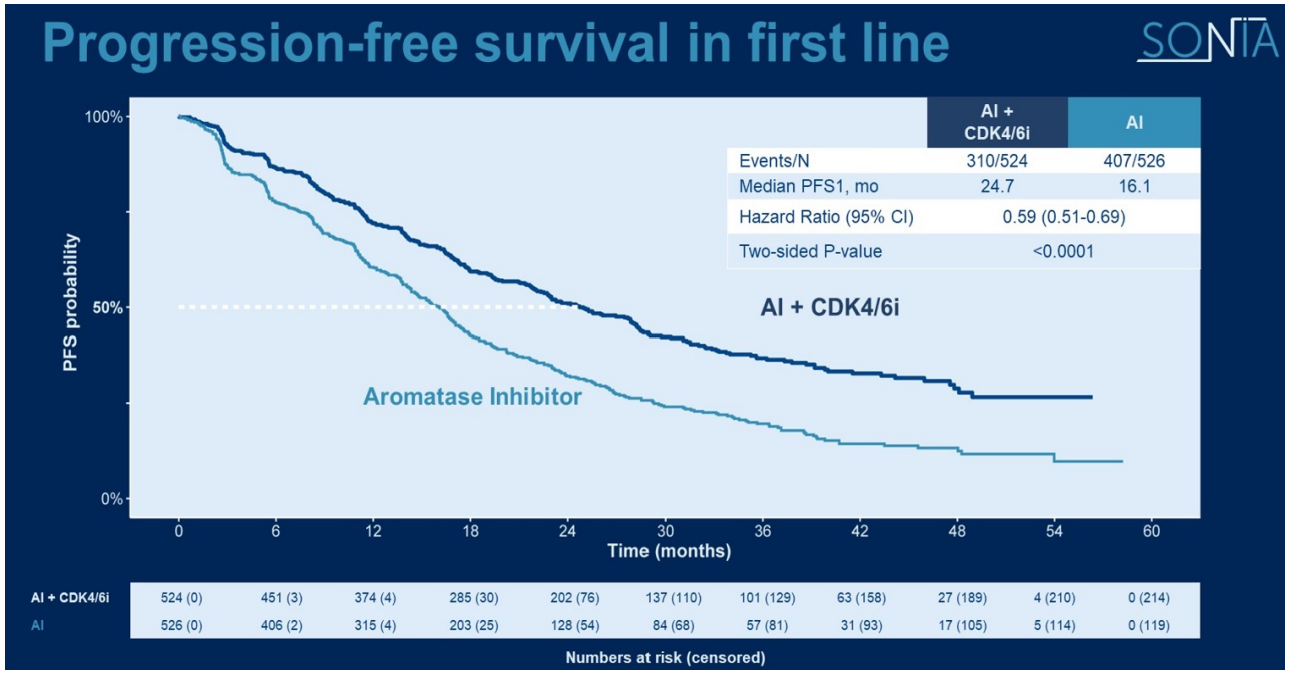


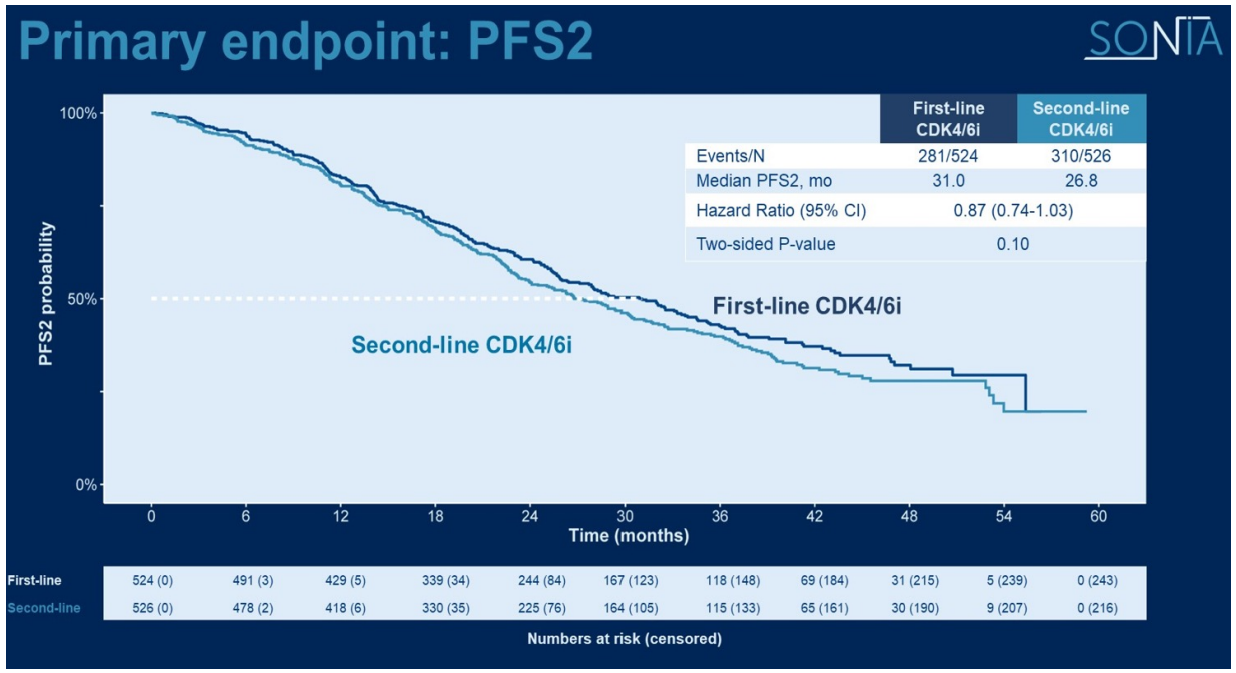
Mays Cancer Center
UT Health San Antonio MD Anderson Cancer Center

Thein KZ, et al. JNCCN, 2019;17(3.5):CLO19-052.
CDK, cyclin-dependent kinase; VTE, venous thromboembolism.

SONIA TRIAL







Sonke et al ASCO 2023

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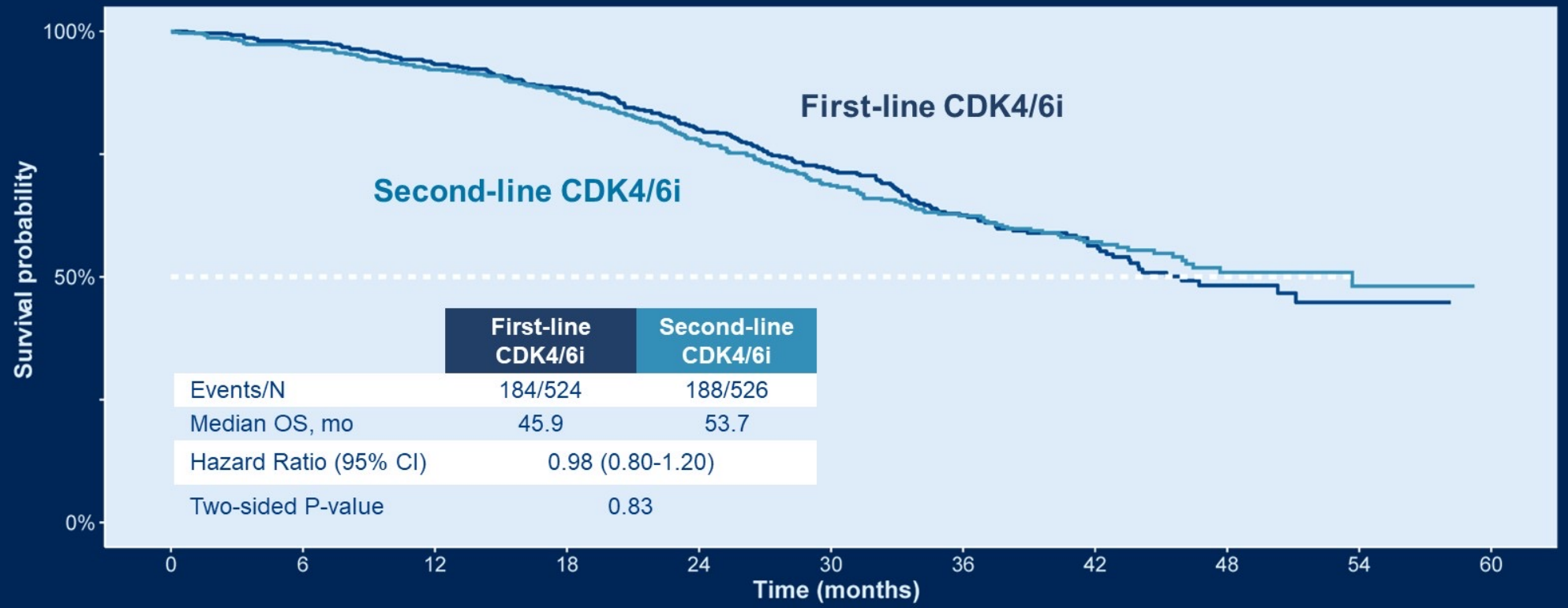
Overall survival

SONIA



	First-line CDK4/6i	Second-line CDK4/6i
Events/N	184/524	188/526
Median OS, mo	45.9	53.7
Hazard Ratio (95% CI)	0.98 (0.80-1.20)	
Two-sided P-value	0.83	

Numbers at risk (censored)											
First-line	524 (0)	510 (3)	485 (4)	427 (37)	324 (103)	240 (157)	171 (197)	104 (250)	42 (300)	7 (333)	0 (340)
Second-line	526 (0)	506 (2)	483 (2)	426 (32)	328 (89)	242 (139)	175 (186)	112 (236)	52 (287)	16 (322)	0 (338)

The Phase II RIGHT Choice Trial

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

R 1:1

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

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

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

Primary endpoint
- PFS (locally assessed per RECIST 1.1)

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

Exploratory endpoints
- Biomarker analyses
- Healthcare resource utilization

Demographics

Median age: 44

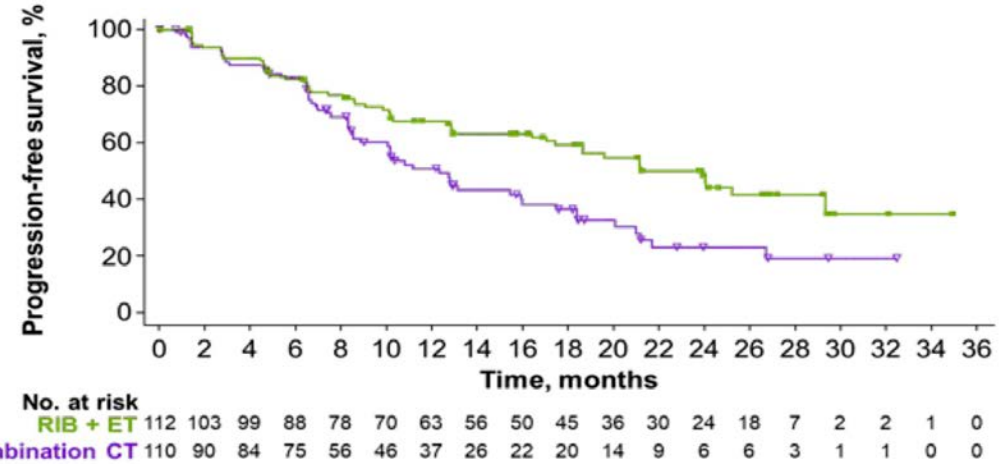
De novo MBC: 65%

Visceral mets: 78%

Visceral crisis: 52%

Symptomatic visceral mets: ~67%

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



	RIB + ET	Combo CT
Events/n	52/112	58/110
Median PFS, mo	24.0	12.3
HR (95% CI)	0.54 (0/36-0.79)	

P value .0007

Lu YS, et al. SABCS 2022. Abstract GS1-10.
ABC, advanced breast cancer; CBR, clinical benefit rate; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; QoL, quality of life; TFR, treatment-free remission; TTF, time to treatment failure; TTR, time to recurrence.

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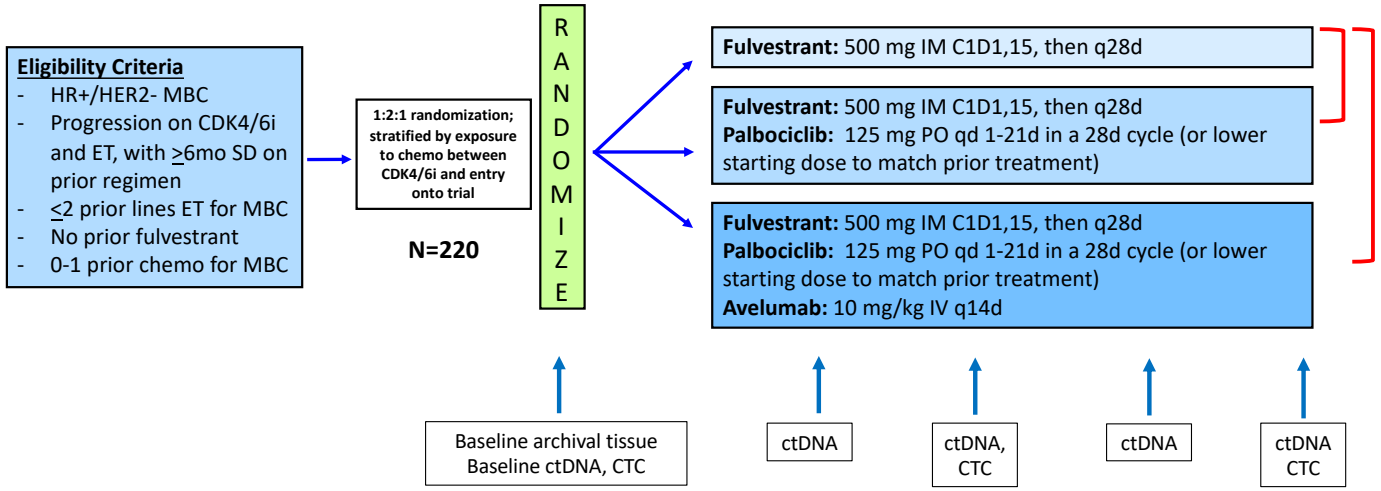
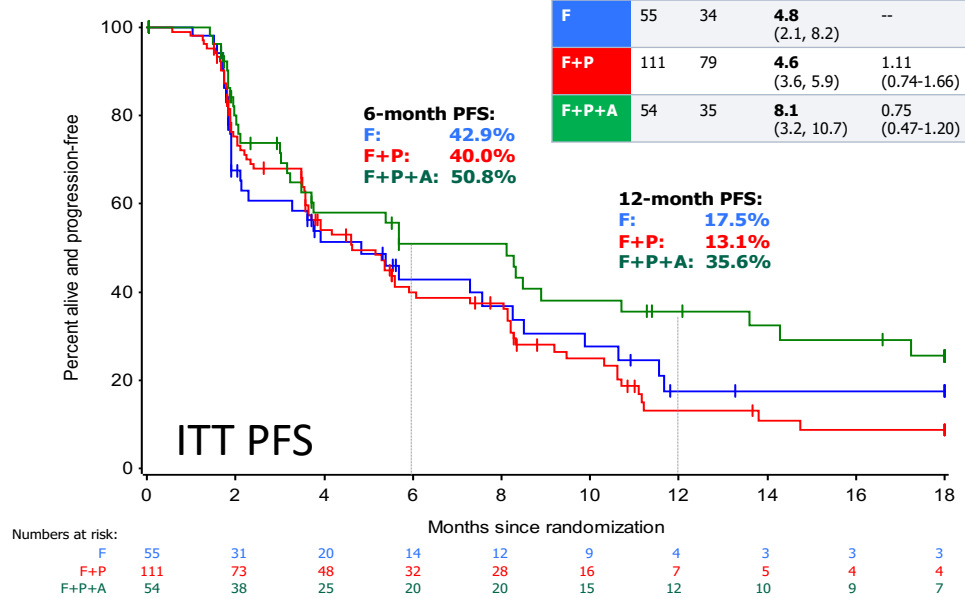
Phase 2 PACE: Palbociclib After CDK Inhibitor and Endocrine Therapy



Primary objective: To compare PFS (RECIST-confirmed) for fulvestrant+palbociclib vs fulvestrant alone
Secondary objectives: To compare PFS for fulvestrant+palbociclib+avelumab vs fulvestrant alone, response endpoints, Safety, outcomes in predefined molecular subgroups including ESR1, PIK3CA, and Rb

	Pts	PFS Events	Median PFS, mo (90% CI)	HR vs F (90% CI)	P-value
F	55	34	**4.8** (2.1, 8.2)	--	--
F+P	111	79	**4.6** (3.6, 5.9)	1.11 (0.74-1.66)	P=0.62
F+P+A	54	35	**8.1** (3.2, 10.7)	0.75 (0.47-1.20)	P=0.23



Demographics

- 81% post menopausal
- 40% de novo MBC
- 60% visceral disease
- 68% measurable disease
- 90.9% prior palbociclib, 4.5% ribociclib, 4.1% abemaciclib
- 76% prior ET > 12 months
- 77% second line

Other endpoints

- ORR (n=149): 10.8 v 13.7 v 17.9%
- Med OS: 27.5 v 24.6 v 42.5 months
- Rare immune-related AEs
- Suggestion of improved efficacy of FP over F in ESR1 and PIK3CA mutations

Mays Cancer Center
UT Health San Antonio MD Anderson Cancer Center

Mayer et al. SABCS 2022. Abstract GS3-06.
AE, adverse event; CDK, cyclin-dependent kinase; CTC, circulating tumor cells; ctDNA, circulating tumor DNA; ET, endocrine therapy; HER2, human epidermal growth factor receptor; HR, hormone receptor; ITT, intent to treat; MBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

PALMIRA Study Design (NCT03809988)

Key Eligibility Criteria

1. Patients with HR[+]/HER2[-] ABC*
2. PD on a 1L of palbociclib plus ET (AI or fulvestrant) after clinical benefit, or
   - PD on palbociclib–based adjuvant regimen after at least 12 months of treatment but no more than 12 months following completion
3. No other prior treatment for ABC

Stratification Factors

- Prior ET (fulvestrant *vs.* AIs)
- Site of disease (visceral *vs.* non-visceral)

R 2:1 N = 198

N = 136

- **Fulvestrant‡** 500 mg IM, on day 1, 15, 29 and monthly thereafter
- OR
- **Letrozole‡** 2.5 mg PO, once daily, continuously
- ✚
- **Palbociclib†** 75/100/125 mg PO, once daily, 3 weeks on, 1 week off

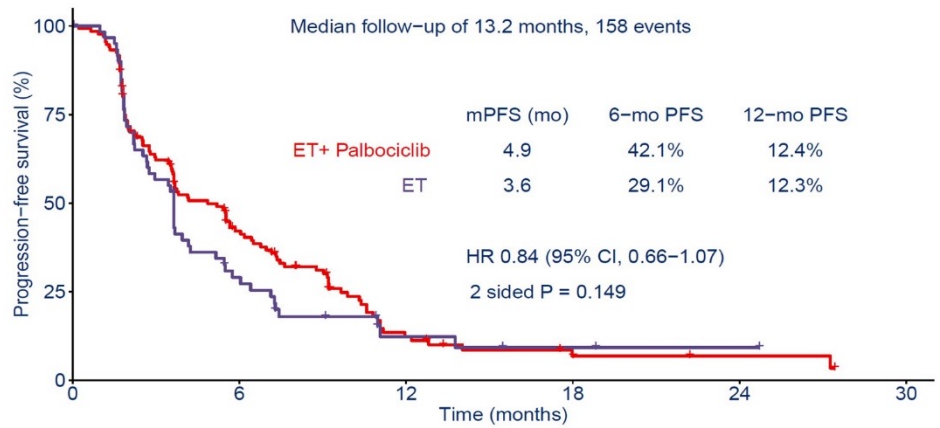
N = 62

- **Fulvestrant‡** 500 mg IM, on day 1, 15, 29 and monthly thereafter
- OR
- **Letrozole‡** 2.5 mg PO, once daily, continuously

→ **Treatment until progressive disease, unacceptable toxicity, or study withdrawal**

1L: First–line; ABC: Advanced breast cancer; AI: Aromatase inhibitors; ET: Endocrine therapy; HER2[-]: Human Epidermal Growth Factor Receptor 2-negative; HR[+]: Hormone receptor-positive; IM: Intramuscular injection; PO: oral administration; PD: Progressive disease; R: Randomization.
*If pre-menopausal, ovarian function suppression method required.
†Palbociclib dose could be reduced until 75 mg. If a dose reduction below 75 mg is required, treatment must be discontinued.
‡Administration of endocrine therapy was chosen depending on the prior administered agent.

Primary Objective: Investigator-assessed PFS (ITT Population)



CI: Confidence interval; HR: Hazard ratio; ITT: Intention to treat; mo: Months; mPFS: Median progression-free survival; PFS: Progression-free survival.

Llombart-Cussac et al. ASCO 2023. Abstract 1001.

2022 ASCO ANNUAL MEETING

A randomized phase II trial of fulvestrant or exemestane with or without ribociclib after progression on anti-estrogen therapy plus cyclin-dependent kinase 4/6 inhibition in patients with unresectable or metastatic hormone receptor positive, HER2 negative breast cancer: MAINTAIN Trial

Schema

Key Entry Criteria
- Men or Women age ≥ 18 yrs
- ER and/or PR ≥ 1%, HER2- MBC
- Progression on ET + any CDK 4/6 inhibitor
- ≤ 1 line of chemotherapy for MBC
- Measurable or non-measurable
- PS 0 or 1
- Postmenopausal
  - GnRH agonist allowed if premenopausal
- Stable brain metastases allowed

1:1, N=120

Arm 1
Ribociclib + Switch Endocrine Therapy*

Arm 2
Placebo + Switch Endocrine Therapy*

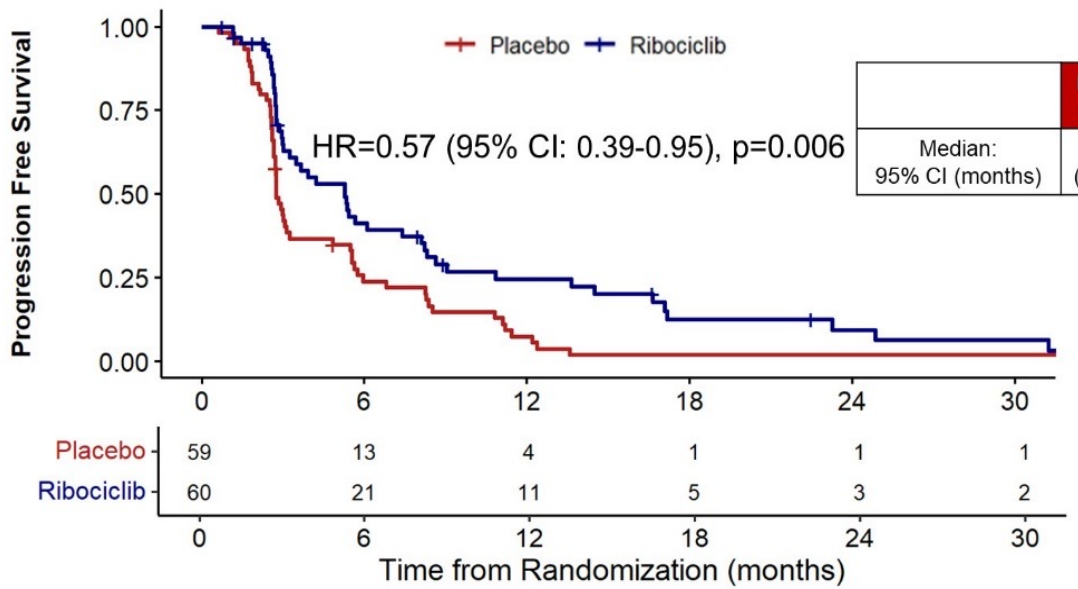
Primary Endpoint
- Progression free survival
  - Locally assessed per RECIST 1.1

Secondary Endpoints
- Overall response rate
- Clinical benefit rate
- Safety
- Tumor and blood markers, including circulating tumor DNA

- Fulvestrant as endocrine therapy in pts with progression on a prior aromatase inhibitor for MBC and no prior fulvestrant; Protocol amended to allow exemestane as endocrine therapy if progression on prior fulvestrant (September 2018); Ribociclib 600 mg administered 3 weeks on/1 week off

#ASCO22 PRESENTED BY: Kevin Kalinsky, MD, M Abstract LBA1004 ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

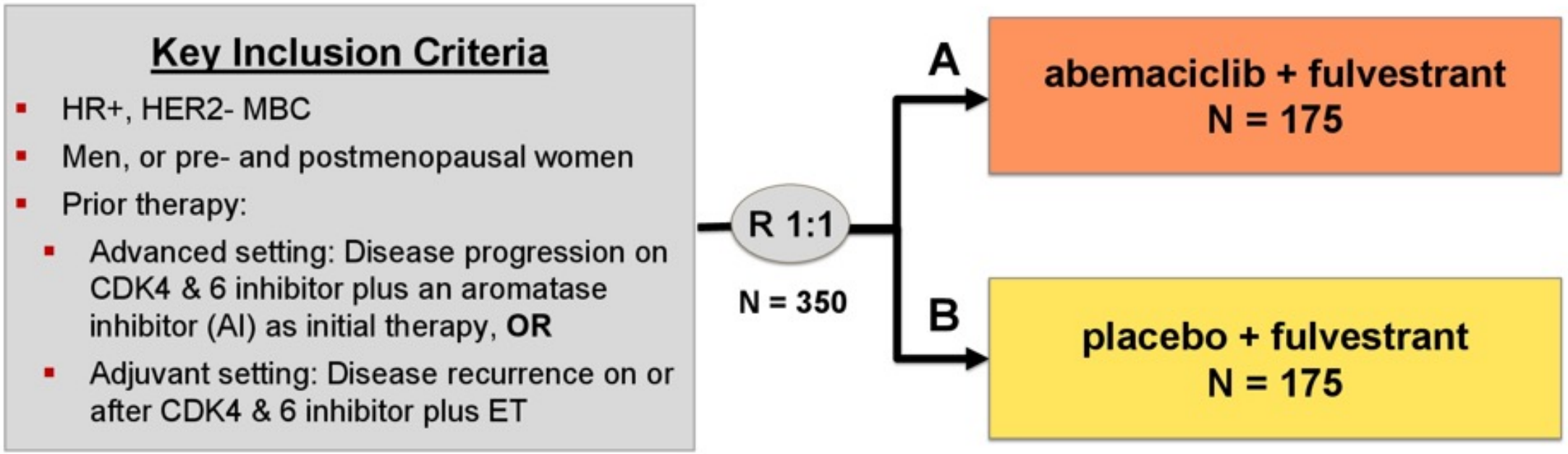
Primary Endpoint: Progression Free Survival (PFS)



	Placebo + ET (n=59)	Ribociclib + ET (n=60)
Median: 95% CI (months)	**2.76** (2.66-3.25)	**5.29** (3.02-8.12)

Kalinsky et al. *J Clin Oncol* 2023;41(24):4004-13.

Ongoing postMONARCH study (NCT05169567; PI: Kalinsky)



Conclusions

First line CDK4/6i should be considered SOC

CDK after CDK: let's wait for more data

Agenda

Module 1: Optimal Integration of CDK4/6 Inhibitors into the Management of ER-Positive Metastatic Breast Cancer (mBC) — Dr Kaklamani

Module 2: Novel Strategies to Overcome Resistance to Endocrine Therapy — Dr Jhaveri

Module 3: Current Role of Antibody-Drug Conjugates in the Management of ER-Positive mBC — Dr Rugo

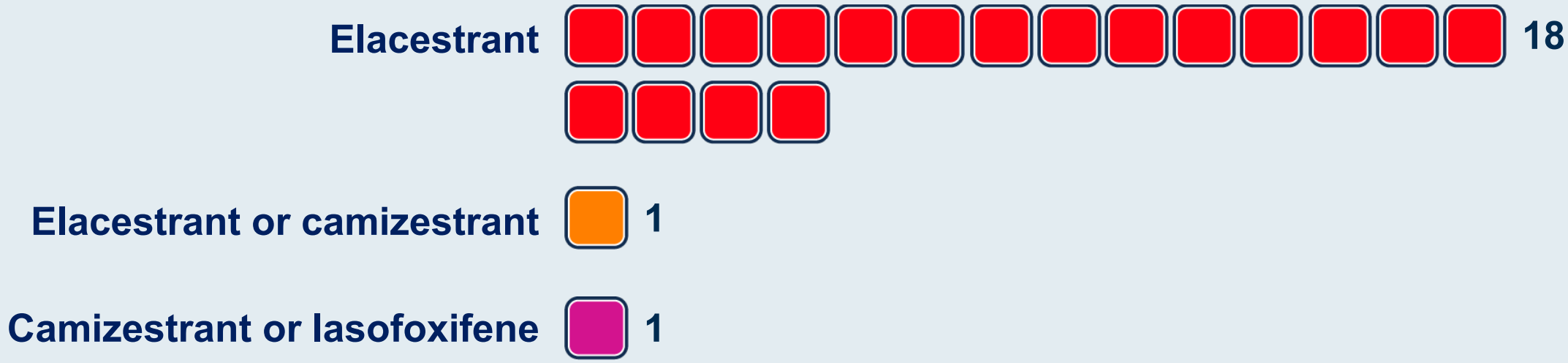
Module 4: Current and Future Role of Selective Estrogen Receptor Degraders (SERDs) in the Management of ER-Positive mBC — Prof Bidard

Module 5: Novel Therapies Under Investigation for Patients with ER-Positive mBC — Dr Hamilton

A 65-year-old woman with ER-positive, HER2-negative, node-negative breast cancer has developed multiple 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 results were as follows?

A 65-year-old woman with ER-positive, HER2-negative, node-negative breast cancer has developed multiple 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.

ESR1-positive **PIK3CA-negative** **AKT- and PTEN-negative**



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

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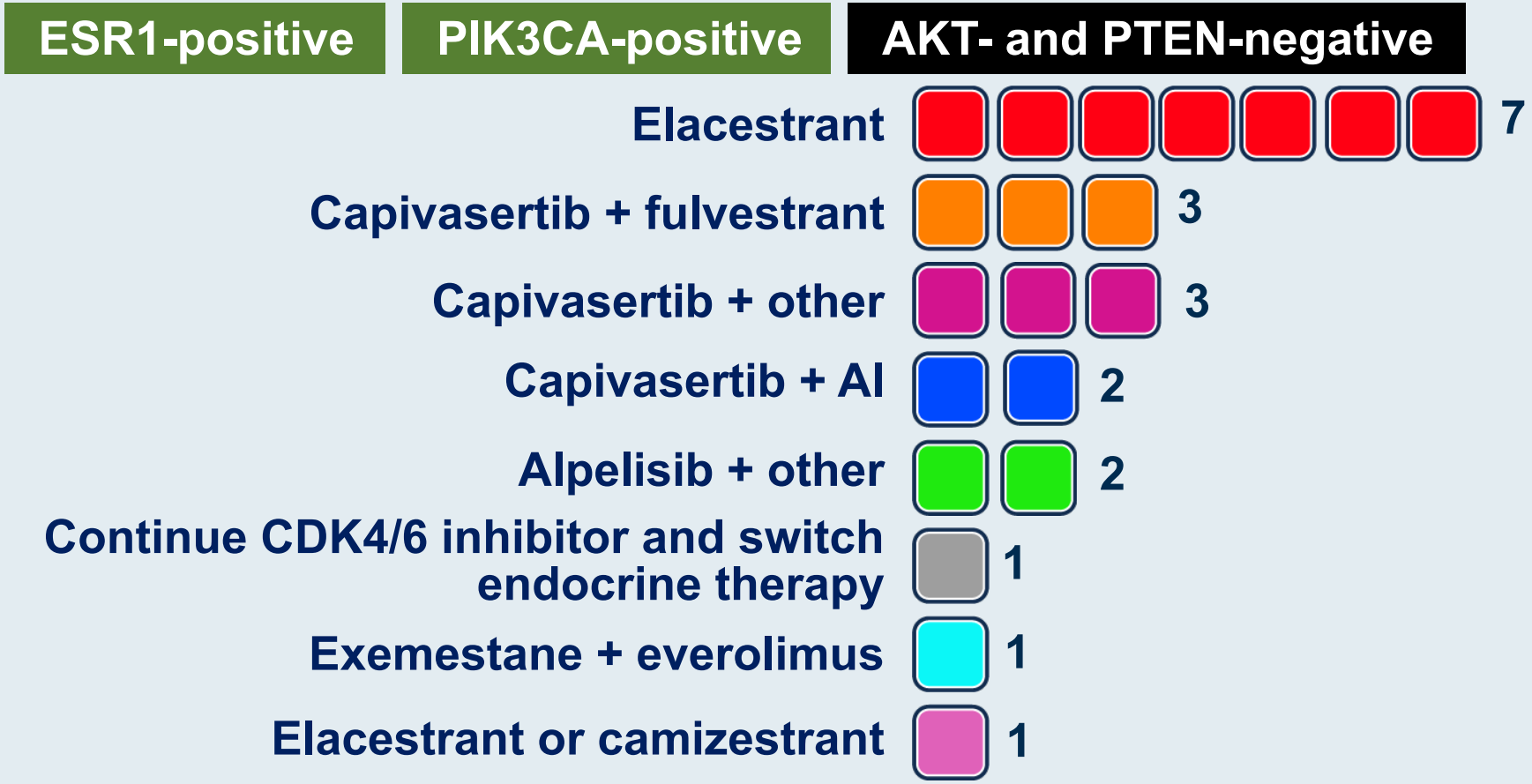

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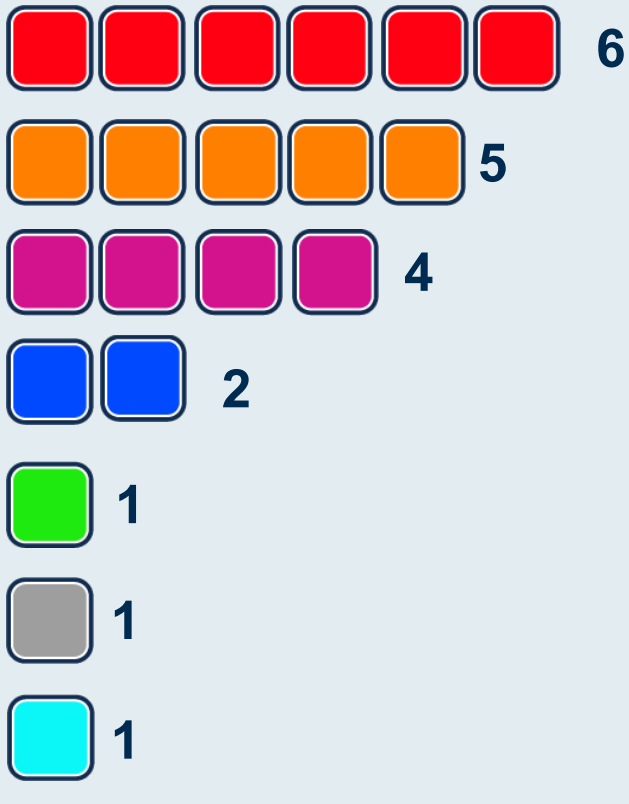
ESR1-positive	PIK3CA-positive	AKT- or PTEN-positive



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ESR1-negative | **PIK3CA-negative** | **AKT- and PTEN-negative**

Survey of 20 US-based clinical investigators November 2023

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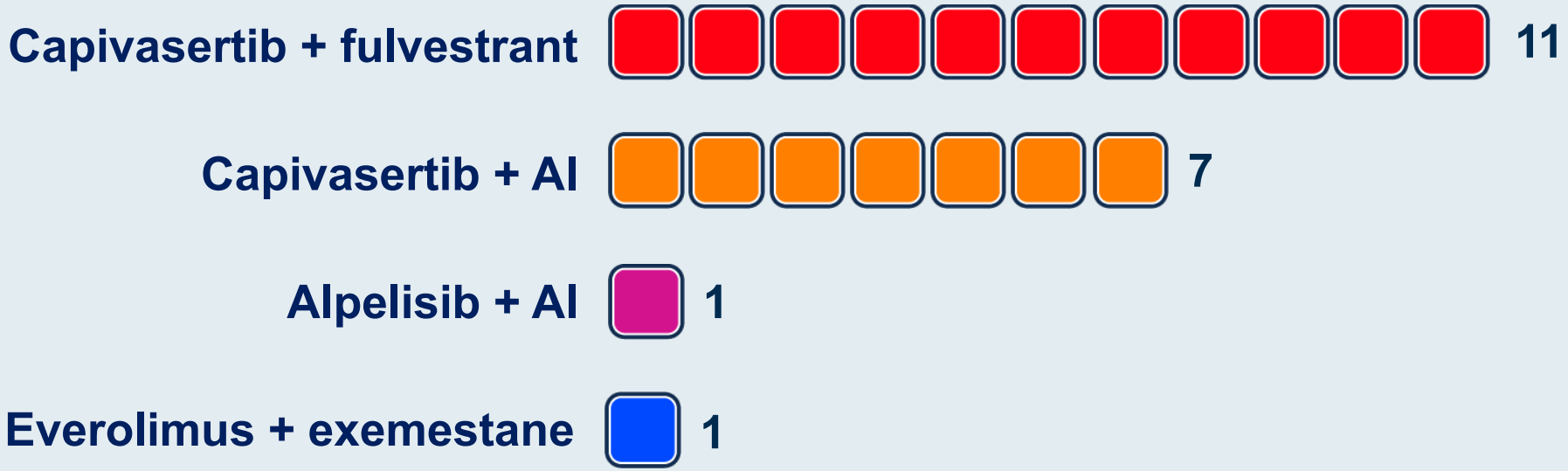
ESR1-negative **PIK3CA-positive** **AKT- or PTEN-positive**



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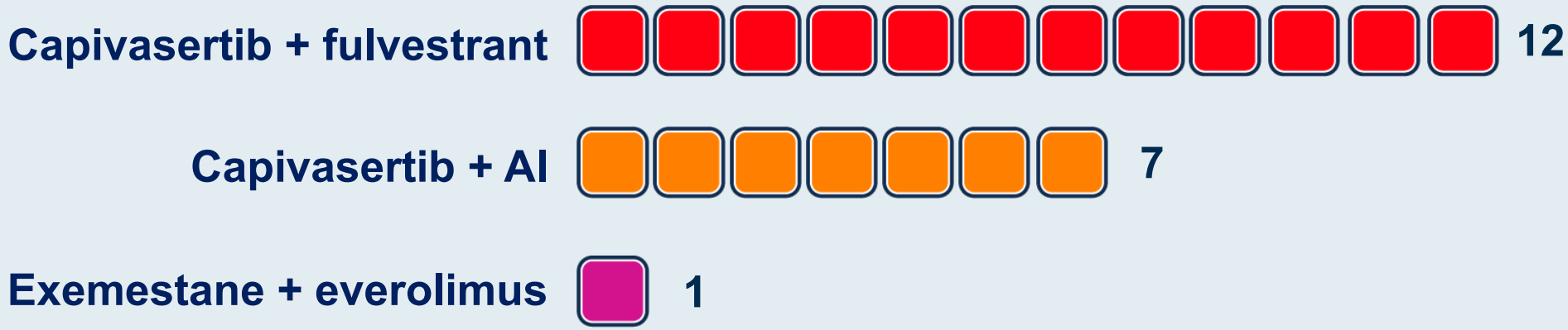
ESR1-negative **PIK3CA-negative** **AKT- or PTEN-positive**



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ESR1-positive | **PIK3CA-negative** | **AKT- or PTEN-positive**

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Selection of second-line endocrine therapy for ER-positive metastatic breast cancer

Priyanka Sharma, MD

RTP
RESEARCH
TO PRACTICE

Elacestrant, PI3K/AKT pathway inhibitors for the treatment of recurrent ER-positive metastatic breast cancer

Adam M Brufsky, MD, PhD

RTP
RESEARCH
TO PRACTICE

Prevention and management of side effects associated with alpelisib

Priyanka Sharma, MD

RTP
RESEARCH
TO PRACTICE

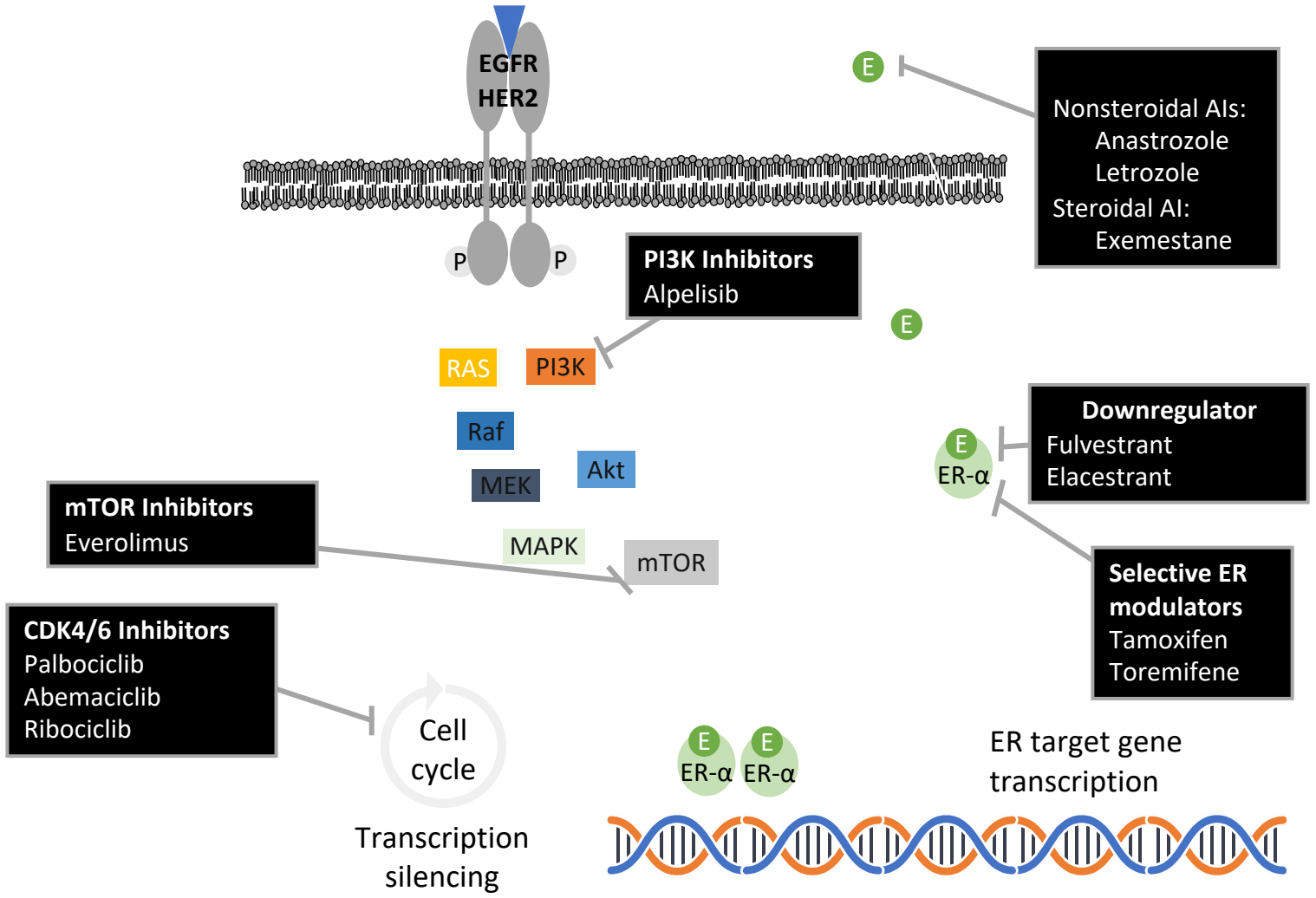
Novel Strategies to Overcome Resistance to Endocrine Therapy

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

Associate Professor
Weill Cornell Medical College
New York, New York

@jhaveri_komal

Targeted Strategies to Overcome Resistance in HR+/HER2- MBC

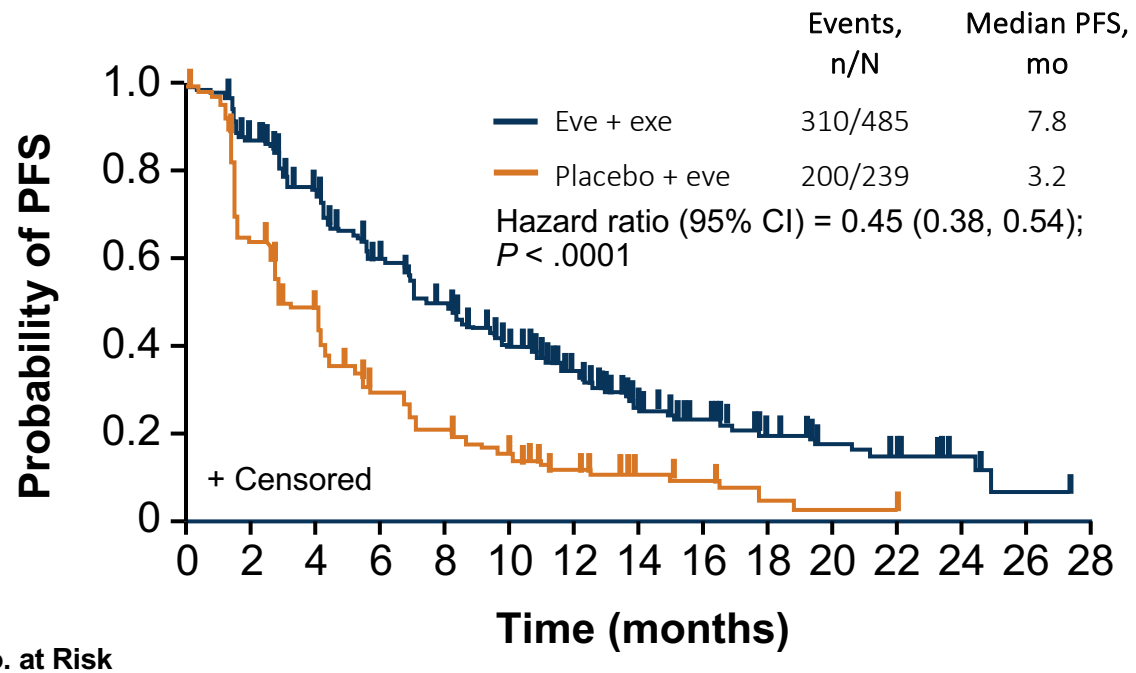


- **Mechanisms of Endocrine Resistance**
  - Alteration of cell survival and cell cycle pathways
  - Activation of growth factor signaling pathways
  - Deregulation of the ER pathway
- PI3K/AKT/mTOR pathway is frequently altered (~40%) in HR+ BC, implicated in resistance to endocrine therapies
- PI3K signaling promotes estrogen-independent growth of ER+ BC, and can be inhibited by the addition of agents targeting PI3K pathway to antiestrogens

Miller TW et al. *J Clin Oncol*. 2011;29:4452-4461. Bosch A et al. *Sci Transl Med.* 2015;7283ra51. Mayer IA et al. *Clin Cancer Res*. 2017;23:26-34. Loi S et al. *Proc Natl Acad Sci*. 2010;107:10208-10213. Stemke-Hale K et al. *Cancer Res.* 2008;68:6084-6091. Miller TW et al. *JCI.* 2010;120:2406-2413. Crowder RJ et al. *Cancer Res.* 2009;69:3955-3962. Miller TW et al. *Cancer Discovery*. 2011;1:338-351. Hennessy BT et al. *Nat Rev Drug Discov*. 2005;4:988-1004. Brufsky. Oncologist. 2018;23:528. AlFakeeh. Curr Oncol. 2018;25:S18. Di Cosimo. Nat Rev Clin Oncol. 2010;7:139.

Improved PFS With mTOR Inhibition
BOLERO-2 and PrE0102 Trials

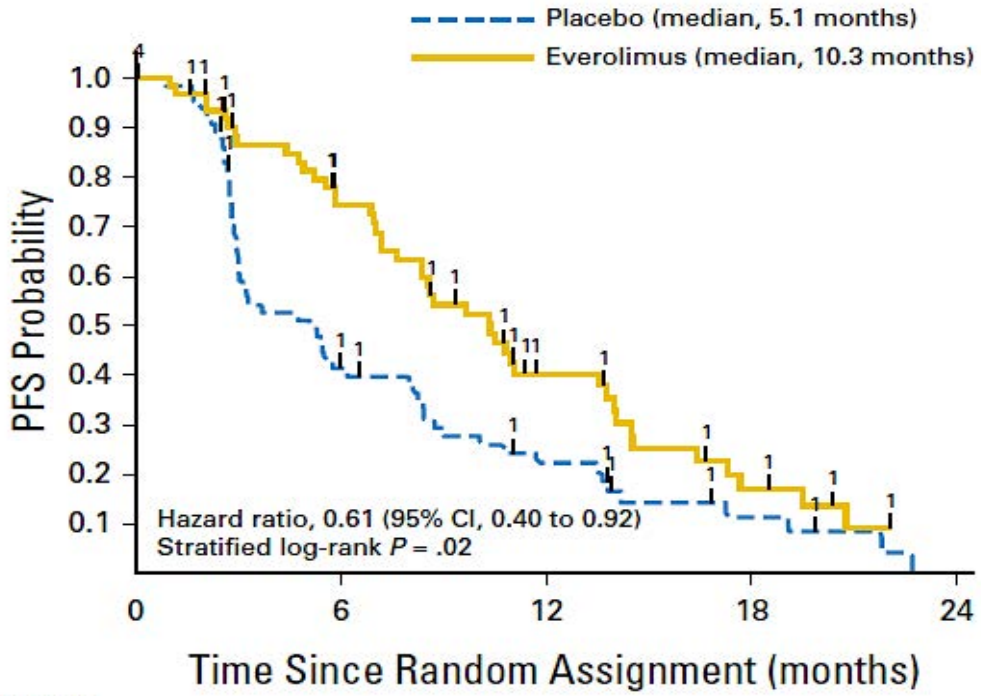
Local Assessment[a,b]



No. at Risk

Eve + exe	485	394	318	236	194	147	99	57	42	23	13	10	4	1	0
Placebo + eve	239	146	103	61	42	27	17	9	6	2	1	1	0	0	0

Investigator-Assessed PFS[c]



No. at risk:

Placebo	65	25	12	4	0
Everolimus	66	41	17	6	1

Improved PFS with mTOR inhibition regardless of *PIK3CA* mutation[a-c]; similar results with tamoxifen + everolimus[d]; no OS benefit

a. Yardley DA, et al. Adv Ther. 2013;30:870-884; b. Baselga J, et al. N Engl J Med. 2012;366:520-529; c. Kornblum N, et al. J Clin Oncol. 2018;36:1556-1563; d. Bachelot T, et al. J Clin Oncol. 2012;30:2718-2724.

BOLERO-2 Toxicity

Table 2. Adverse Events Irrespective of Relationship to Study Treatment (with at Least 10% Incidence in the Everolimus–Exemestane Group).

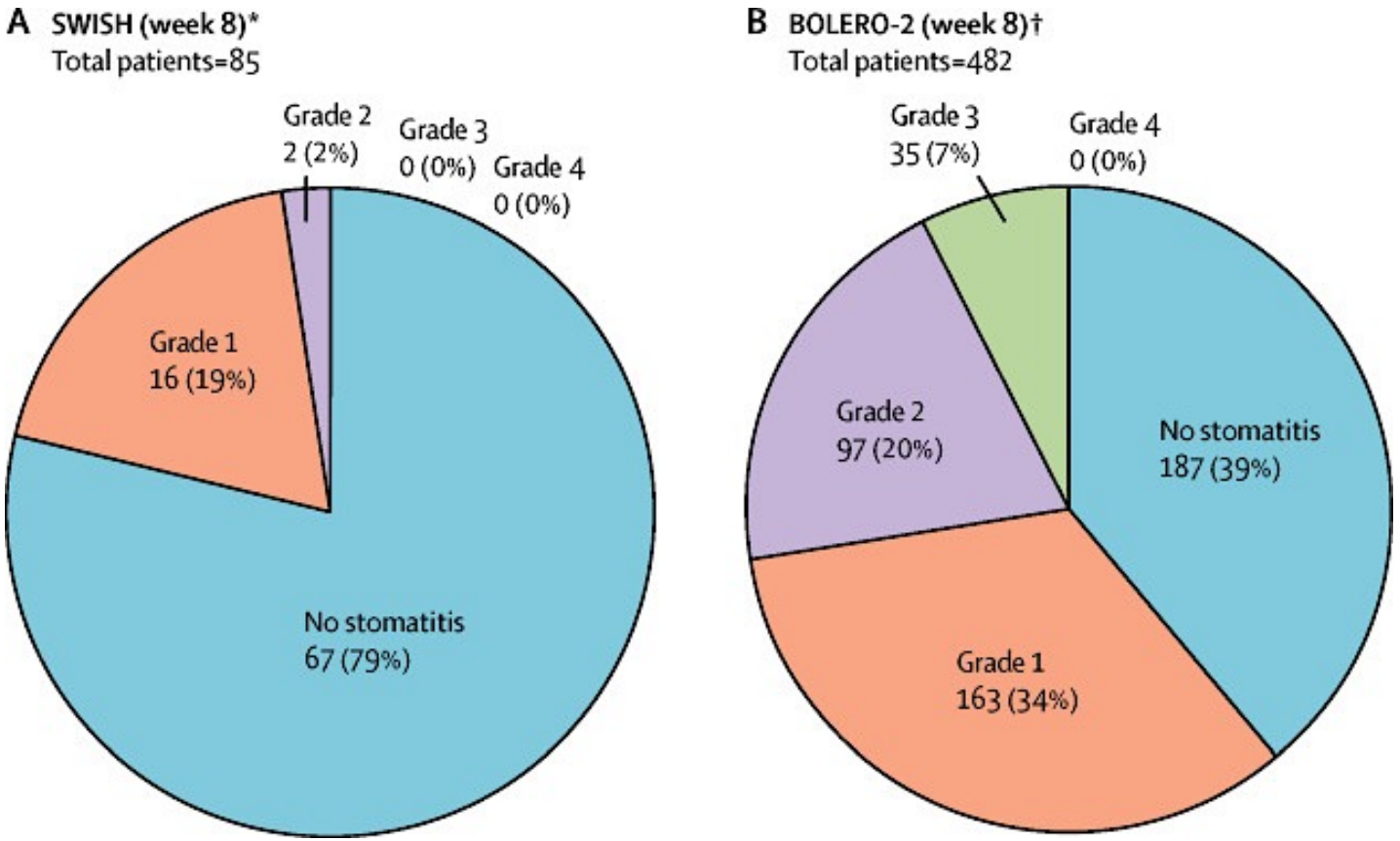
Adverse Event	Everolimus and Exemestane (N=482)			Placebo and Exemestane (N=238)		
	Any Event	Grade 3 Event	Grade 4 Event	Any Event	Grade 3 Event	Grade 4 Event
	percent					
Stomatitis	56	8	0	11	1	0
Rash	36	1	0	6	0	0
Fatigue	33	3	<1	26	1	0
Diarrhea	30	2	<1	16	1	0
Decreased appetite	29	1	0	10	0	0
Nausea	27	<1	<1	27	1	0
Cough	22	1	0	11	0	0
Dysgeusia	21	<1	0	5	0	0
Headache	19	<1	0	13	0	0
Decreased weight	19	1	0	5	0	0
Dyspnea	18	4	0	9	1	<1
Arthralgia	16	1	0	16	0	0
Anemia	16	5	1	4	<1	<1
Epistaxis	15	0	0	1	0	0
Vomiting	14	<1	<1	11	<1	0
Peripheral edema	14	1	0	6	<1	0
Pyrexia	14	<1	0	6	<1	0
Aspartate aminotransferase level increased	13	3	<1	6	1	0
Constipation	13	<1	0	11	<1	0
Hyperglycemia	13	4	<1	2	<1	0
Pneumonitis	12	3	0	0	0	0
Thrombocytopenia	12	2	1	<1	0	<1
Asthenia	12	2	0	3	0	0
Alanine aminotransferase level increased	11	3	<1	3	2	0
Pruritus	11	<1	0	3	0	0
Insomnia	11	<1	0	8	0	0
Back pain	11	0	0	8	1	0

Discontinuation rate: 19% vs 4%

Baselga et al NEJM 2012

SWISH: Phase 2 Trial to Prevent Everolimus Related Stomatitis

Prophylactic use of dexamethasone oral solution substantially reduced the incidence and severity of stomatitis in patients receiving everolimus and exemestane

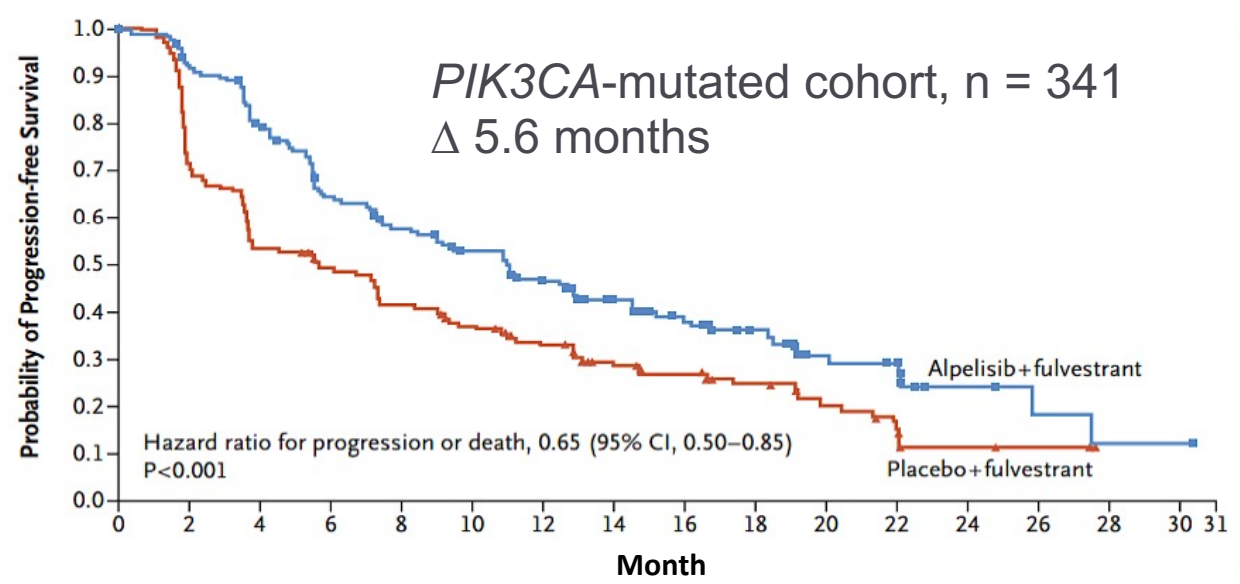


Rugo et al. Lancet Oncology 2017

Option for Patients Whose Tumors Harbor *PIK3CA* Mutations
Fulvestrant + *Alpelisib*

SOLAR-1 (Phase 3): Fulvestrant ± Alpelisib

(Progression on or after AI)



- Numerical improvement in median OS of 7.9 months in the mutated cohort[b]
- Discontinuation rate was 25% in FUL + ALP arm vs 4.2% in the FUL arm[a]
- Most common side effects (grade 3): hyperglycemia (36%), rash (10%), and diarrhea (7%)[a]
- **6% had prior CDK4/6 inhibitor**

Median PFS[a]

- 11.0 months (ALP + FUL) vs 5.7 months (FUL)
- HR = 0.65 (95% CI: 0.50, 0.85); *P* < .001

- ALP, alpelisib; FUL, fulvestrant.

a. Andre F, et al. N Engl J Med. 2019;380:1929-1940; b. Andre F, et al. Ann Oncol. 2021;32:208-217

SOLAR-1: Adverse Events of Alpelisib

AEs ≥20% in Either Arm, n (%)	Alpelisib + Fulvestrant (n = 284)			Placebo + Fulvestrant (n = 287)		
	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Any AE	282 (99.3)	183 (64.4)	33 (11.6)	264 (92.0)	87 (30.3)	15 (5.2)
Hyperglycemia	181 (63.7)	93 (32.7)	11 (3.9)	28 (9.8)	1 (0.3)	1 (0.3)
Diarrhea	164 (57.7)	19 (6.7)	0	45 (15.7)	1 (0.3)	0
Nausea	127 (44.7)	7 (2.5)	0	64 (22.3)	1 (0.3)	0
Decreased appetite	101 (35.6)	2 (0.7)	0	30 (10.5)	1 (0.3)	0
Rash[a]	101 (35.6)	28 (9.9)	0	17 (5.9)	1 (0.3)	0
Vomiting	77 (27.1)	2 (0.7)	0	28 (9.8)	1 (0.3)	0
Decreased weight	76 (26.8)	11 (3.9)	0	6 (2.1)	0	0
Stomatitis	70 (24.6)	7 (2.5)	0	18 (6.3)	0	0
Fatigue	69 (24.3)	10 (3.5)	0	49 (17.1)	3 (1.0)	0
Asthenia	58 (20.4)	5 (1.8)	0	37 (12.9)	0	0

- 25% of patients discontinued alpelisib: 18 patients (6.3%) for hyperglycemia, 9 patients (3.2%) for rash; no patients discontinued placebo due to either hyperglycemia or rash
- Maculopapular rash, all grade (grade 3): 14.1% (8.8%) with alpelisib vs 1.7% (0.3%) with placebo
- Safety similar in *PIK3CA*-mutant and *PIK3CA*-nonmutant cohorts

Rugo et al Ann Oncology 2020

Activity With PI3K Inhibitors and Various Endocrine Partners

PFS benefit in 2L metastatic setting after progression on CDK4/6i is ~ 5 to 7 months

	BYLieve: PI3Ki + ET in HR+/HER2– BC With *PIK3CA* Mutation and PD on CDK4/6 Inhibition		
	Cohort A[a] (n = 121)	Cohort B[b] (n = 115)	Cohort C[c] (n = 115)
Cohort population	CDK4/6i + AI as immediate prior tx	CDK4/6i + fulvestrant as immediate prior tx	Chemo or ET as immediate prior tx
Endocrine partner	Fulvestrant	Letrozole	Fulvestrant
PI3Ki	Alpelisib	Alpelisib	Alpelisib
Median PFS, mo	7.3	5.7	5.6
HR (PI3Ki vs control)	NA	NA	NA

- PD, progressive disease; tx, treatment.

a. Rugo HS, et al. Lancet Oncol. 2021;22:489-498; b. Rugo HS, et al. Presented at: San Antonio Breast Cancer Symposium (SABCS) 2020; December 8-11, 2020; Virtual. Presentation PD2-07; c. Rugo HS, et al. Presented at: San Antonio Breast Cancer Symposium (SABCS) 2021; December 7-10, 2021; San Antonio, TX. Presentation PD13-05.

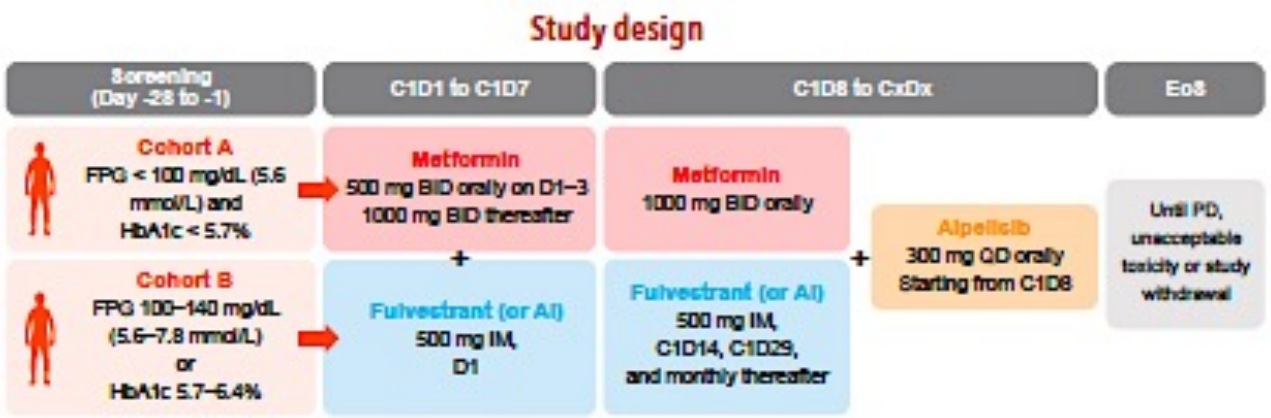
Lessons Learned From SOLAR-1 and BYLieve Trials

	SOLAR-1[a] Fulvestrant + Alpelisib	BYLieve Cohort A[b] Fulvestrant + Alpelisib	BYLieve Cohort B[c] Letrozole + Alpelisib
Prior Rx in metastatic setting, %			
First line	52	70.1	52.4
Second line	47	16.5	44.4
Third line	-	1.6	1.6
Prior CDK4/6i, %	5.3	100	100
Median PFS, months	11.0	7.3	5.7
ORR, % (measurable disease)	36	21	18
CBR, % (measurable disease)	57	42	32
Decrease in best % change from baseline	75.9	70.1	66.3
Median relative dose intensity, %	82.7	89.9	87.6
AEs leading to discontinuation (≥ 1.5%), %	25	20.5	14.3
Hyperglycemia	6.3	1.6	0.8
Rash	3.2	3.9	3.2

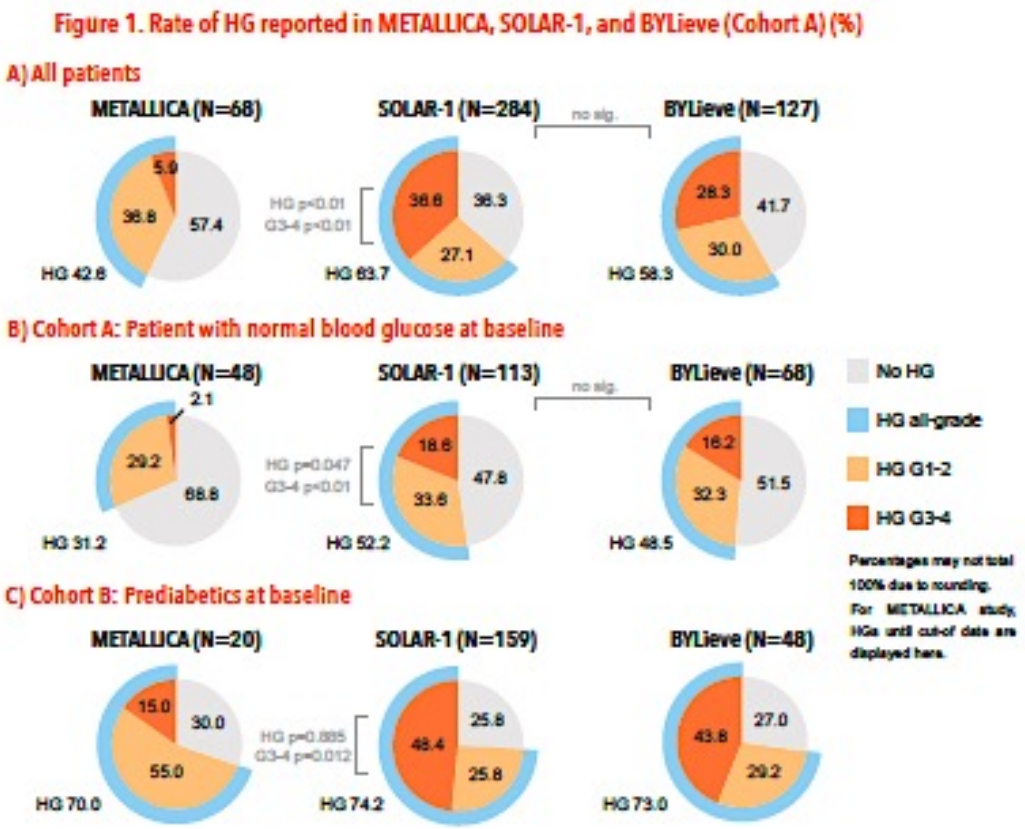
- AE, adverse event; CBR, clinical benefit rate; ORR, overall response rate.

a. André F, et al. N Engl J Med. 2019;380:1929-1940; b. Rugo H, et al. Presented at: 2020 ASCO Annual Meeting; May 29 to May 31, 2020; Virtual. Abstract 1006; c. Rugo H, et al. Presented at: San Antonio Breast Cancer Symposium (SABCS) 2020; December 8-11, 2020; Virtual. Presentation PD2-07.

METALLICA Study:
Metformin prophylaxis to prevent hyperglycemia with alpelisib



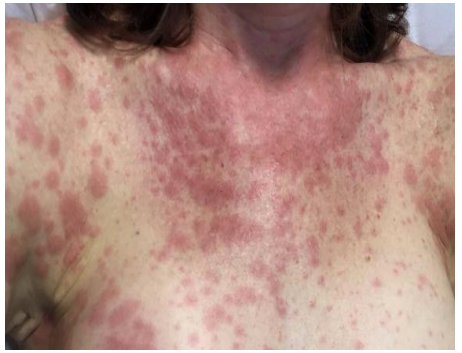
- Use of prophylactic metformin substantially reduced incidence of severe hyperglycemia with alpelisib exposure
- G3 hyperglycemia 5.9% (METALLICA) versus 36.6% (SOLAR-1)



Llombart-Cussac et al, SABCS 2022

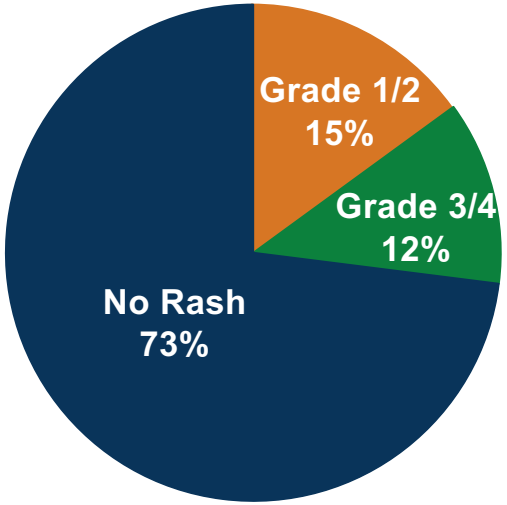
Understanding and Modifying Toxicity Associated With Alpelisib

- In SOLAR-1, median time to onset for grade ≥3 rash: 13 days
- Discontinuation rate due to any grade rash: 3.2%

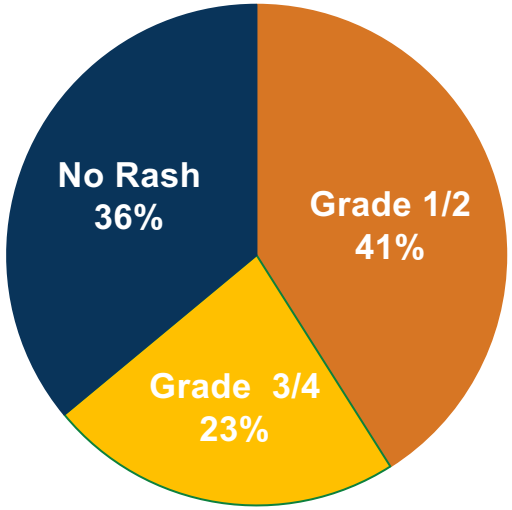


- For patients who received alpelisib + fulvestrant, antihistamine prophylaxis reduced rash
  - Of patients who received anti-rash prophylaxis
    - 69.8% received antihistamines
    - Rash occurred in 26.7% with prophylaxis and 64.1% without
    - Grade 3/4 incidence reduced by 50%

Alpelisib + Fulvestrant
Prophylactic Anti-rash Medication
(n = 86)



Alpelisib + Fulvestrant
No Prophylactic Anti-rash Medication
(n = 198)



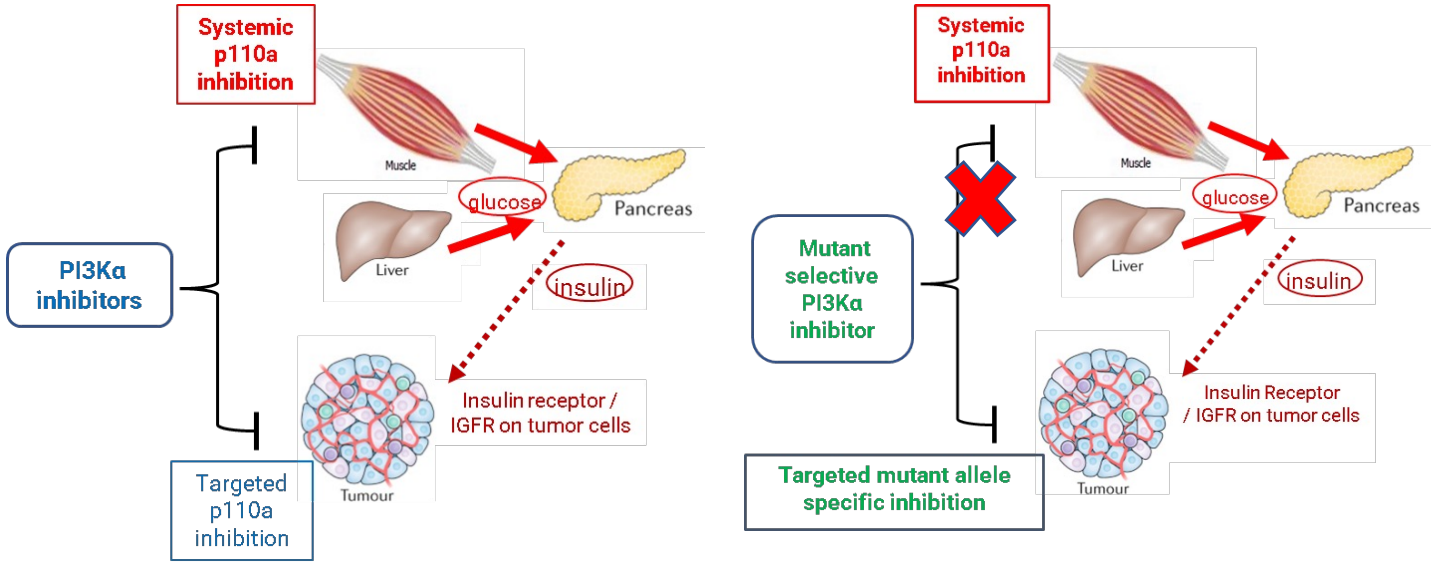
Rugo et al Ann Oncology 2020

How can we harness the power of PIK3CA inhibition with improved tolerability?

- WT PI3Kα inhibition leads to dose-limiting toxicities, which may limit efficacy
  - -Hyperglycemia (65% all gr)
  - -Diarrhea (60% all gr)
  - -Rash (36% all gr)

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

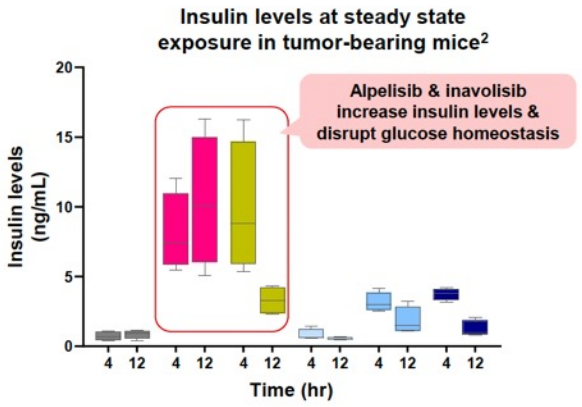
Agent	Trial
LOXO-783	Phase 1 trial LOXO-783 for *PIK3CA*1047R mutant cancer: PIKASSO-01 NCT05307705
RLY-2608	ReDiscover: First-in-Human Study of RLY-2608; NCT05216432
STX-478	Study of STX-478 as Monotherapy and in Combination With Other Antineoplastic Agents in Patients With Advanced Solid Tumors NCT05768139



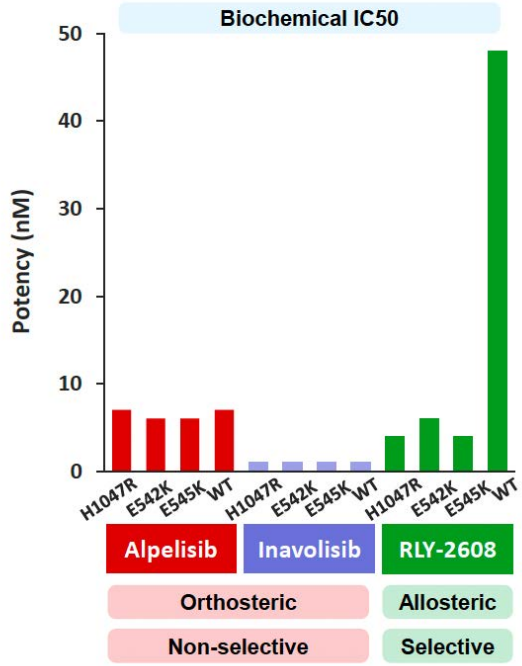
Dent R. Presented at: ESMO Breast Cancer 2021; May 5-8, 2021; Virtual; Kalinsky K, et al. Clin Cancer Res. 2009;15:5049-5059.

ReDiscover: First-in-Human Study of RLY-2608

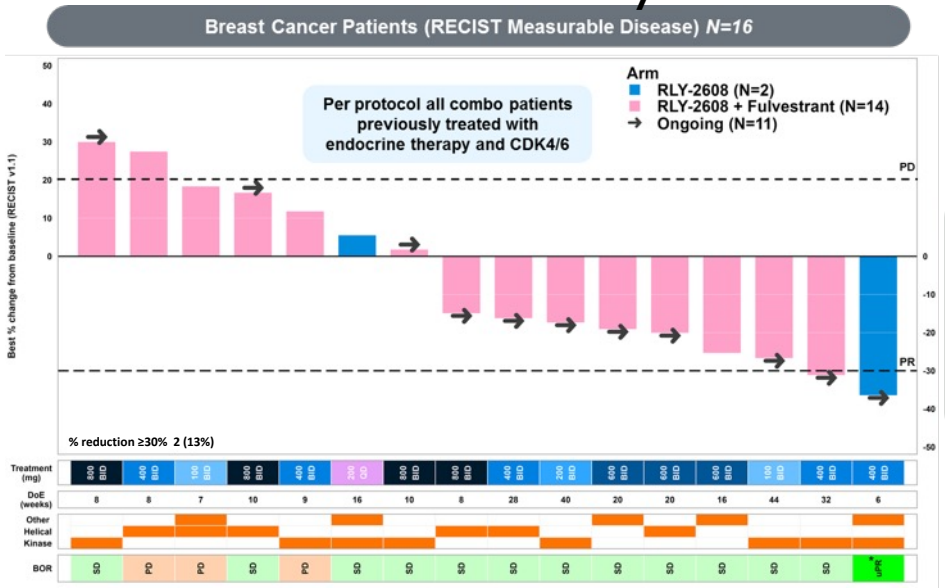
Minimal perturbation of insulin levels



RLY-2608 selectively inhibits mutant PI3Kα



Efficacy



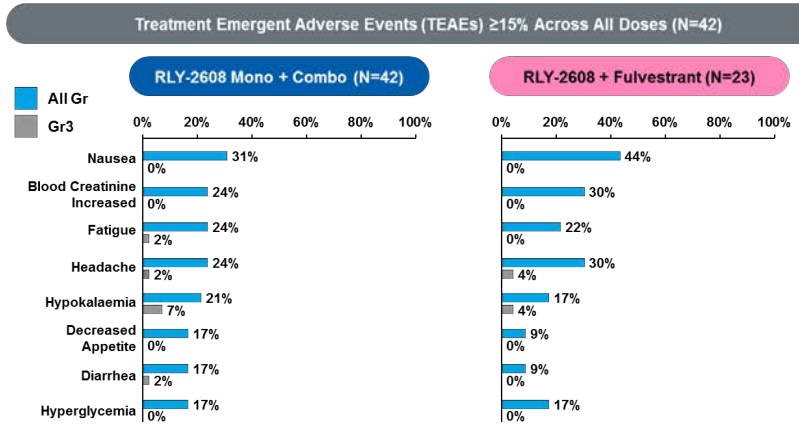
56% of patients (9/16) exhibit radiographic tumor reductions

81% of patients (13/16) with SD/uPR* across genotypes

11/16 patients ongoing

Median duration on treatment: 16 weeks

Safety



AEs leading to alpelisib discontinuation observed with RLY-2608
(for 400mg BID mono, ≥600mg BID combo; N=17)

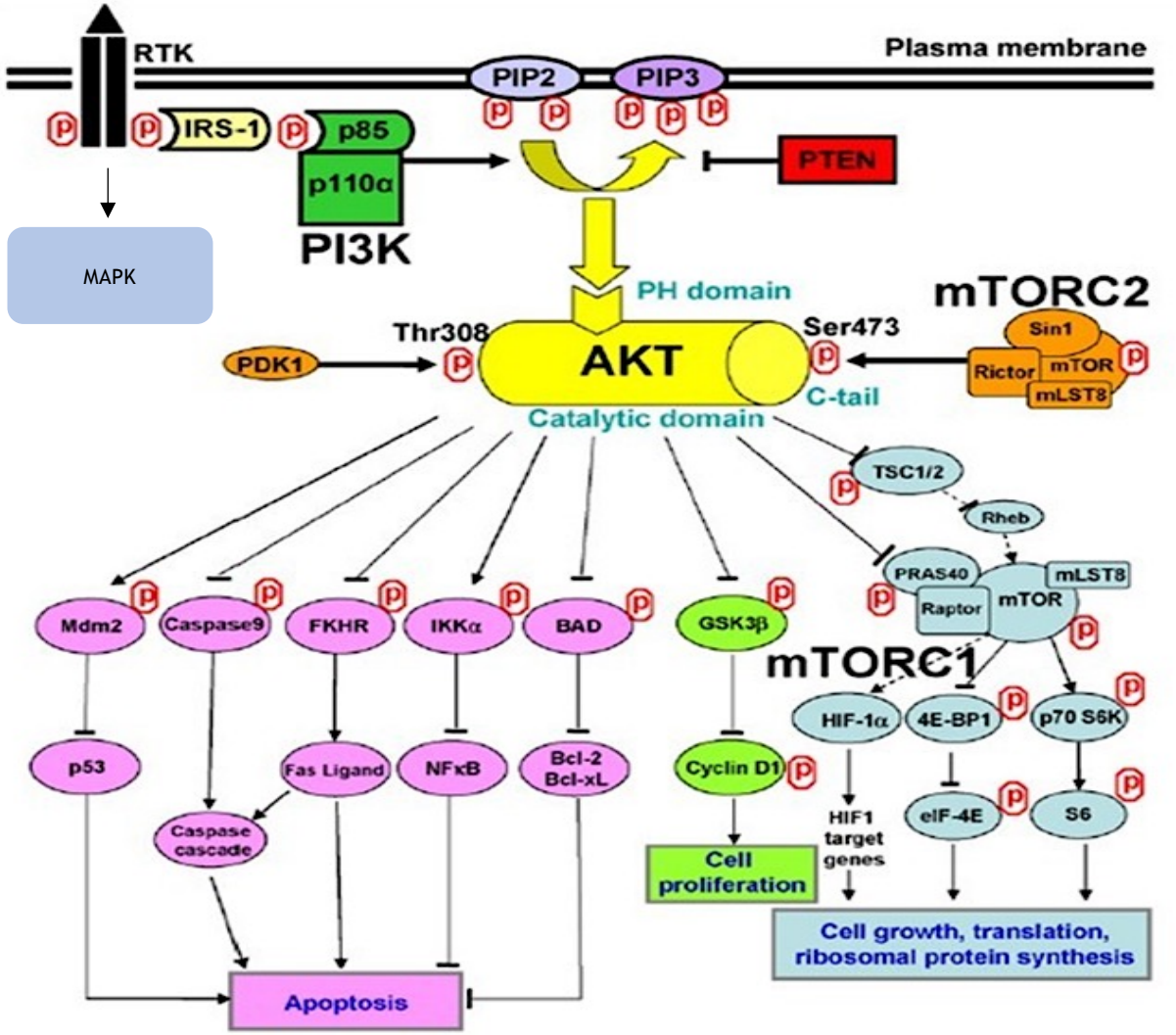
AE	All Gr (Gr3+)
Hyperglycemia	18% (0%)
Diarrhea	0%
Rash	12% (0%)

Most AEs low grade, manageable, reversible
Grade 3 TEAEs 10/42 (24%); No Grade 4-5 AEs
Dose modifications due to AE: Interruptions 31%; Reductions 2%; Discontinuations 0%
Median Relative Dose Intensity: 98%

NCT05216432

Varkaris et al AACR 2023

AKT is a central node in PI3K/Akt/mTOR pathway



Source data: TCGA; except *SU23/PCF Dream Team

Tumour type	PIK3CA mutation (%)	PTEN mutation or loss (%)	AKT1 mutation (%)
Breast	35	11	3
Prostate (metastatic)*	5	40	1
Bladder	22	9	1
Endometrial	53	66	2
Glioblastoma	9	30	<1
Head and Neck	18	2	<1
Lung: squamous	11	18	<1
Gastric-esophageal	5	9	1
Ovarian	<1	6	<1

- **AKT is a central node in the PI3K-AKT-mTOR pathway**
- **Pathway activated by multiple mechanisms (tumour-dependent),**
  - **activating mutations in *PIK3CA* (PI3K catalytic sub-unit) and *AKT1*;**
  - **loss of function alterations in *PTEN***
- **AKT activation mediates resistance to inhibitors of RTKs, anti-hormonal agents and chemotherapy**

Yap TA, et al. Curr Opin Pharmacol 2008; 8(4):393-412; Manning BD and Toker A. Cell. 2017;169(3):381-405

Capivasertib in Advanced ER+ Breast Cancer: Phase 2 FAKTION Trial

- >50% of ER+ MBC tumours have activated PI3K/AKT/PTEN pathway
- Capivasertib is a potent and selective inhibitor of all 3 isoforms of AKT
- In Phase II FAKTION trial, addition of capivasertib to fulvestrant doubled median PFS (10.3 vs 4.8 mo, HR 0.58)

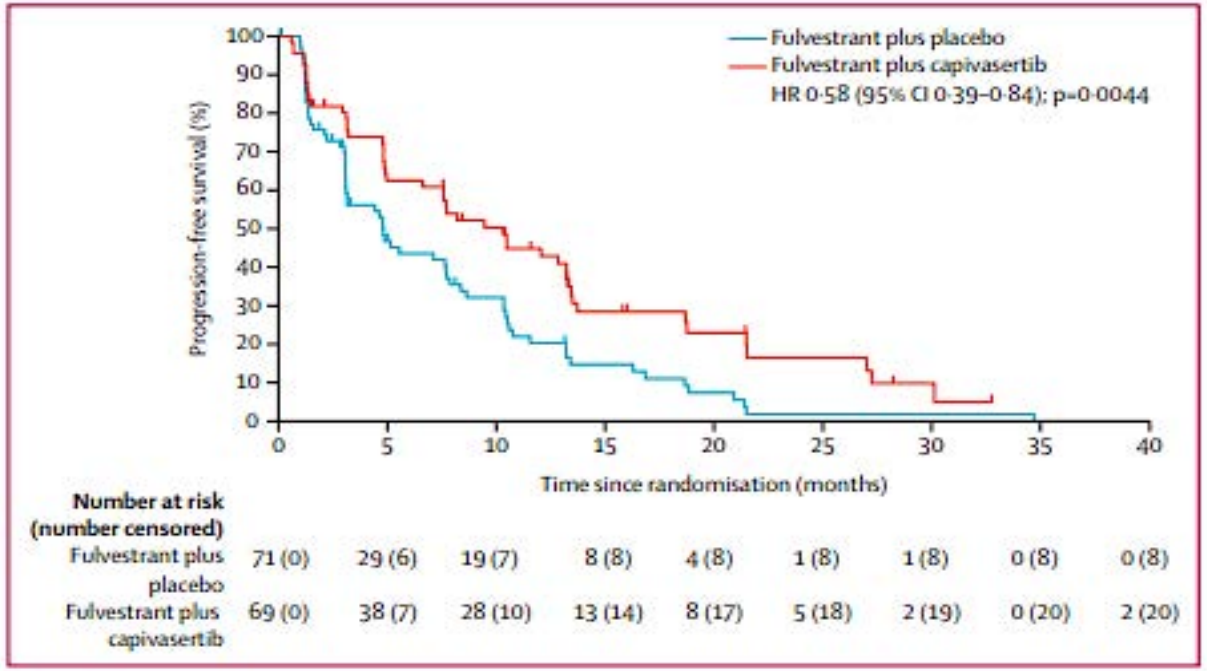
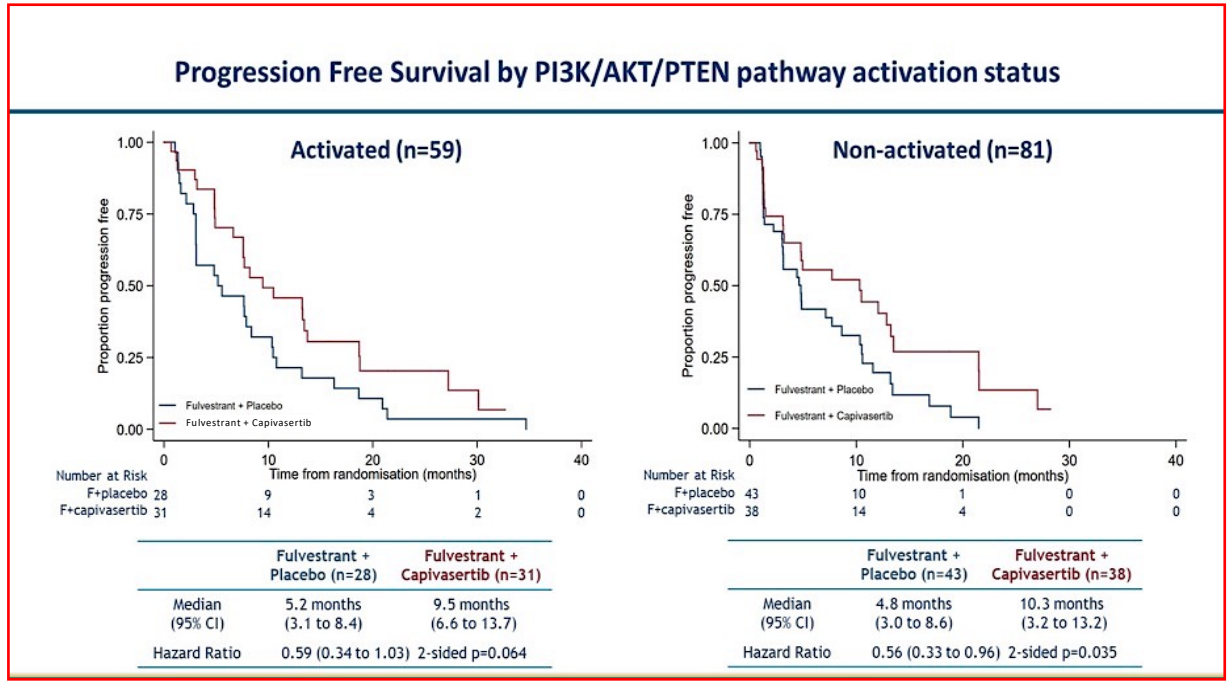


Figure 2: **Progression-free survival**
HR=hazard ratio.



	Fulvestrant + Placebo (n=28)	Fulvestrant + Capivasertib (n=31)
Median (95% CI)	5.2 months (3.1 to 8.4)	9.5 months (6.6 to 13.7)
Hazard Ratio	0.59 (0.34 to 1.03)	2-sided p=0.064

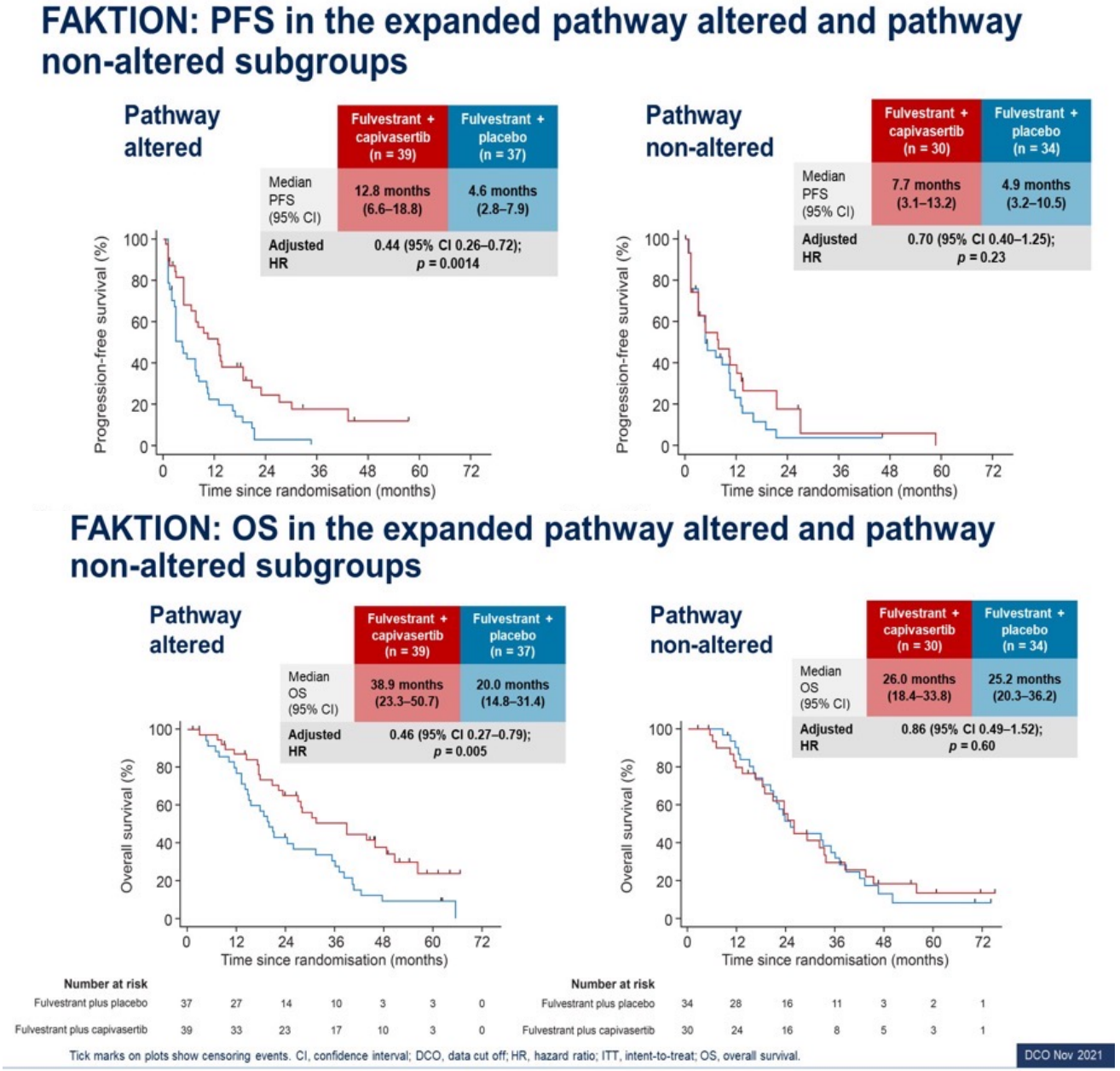
	Fulvestrant + Placebo (n=43)	Fulvestrant + Capivasertib (n=38)
Median (95% CI)	4.8 months (3.0 to 8.6)	10.3 months (3.2 to 13.2)
Hazard Ratio	0.56 (0.33 to 0.96)	2-sided p=0.035

- Benefit appeared independent of activated pathway, albeit only tested for limited *PIK3CA* mutations by ddPCR and PTEN protein loss by IHC
- *AKT1* not examined

Jones RL et al, Lancet Oncol 2020;21:345-57

Capivasertib in Advanced ER+ Breast Cancer: Phase 2 FAKTION Trial

- Updated efficacy data after median 60 mo follow-up
- Expanded NGS testing used to identify *AKT1* E17K mutation, additional activating *PIK3CA* mutations, and *PTEN* alterations predicted to result in loss of function
- PI3K/AKT/PTEN alterations found in 54% of participants in ITT population (vs 42% using original ddPCR / IHC methods)
- PFS and OS data indicated that capivasertib mainly benefited the pathway altered subgroup
  - Median PFS 12.8 mo vs 4.6 mo (HR 0.44; p = 0.0014)
  - Median OS 39.8 mo vs 20.0 mo (HR 0.46; p = 0.005)



Howell S et al, Lancet Oncol 2022

CAPItello-291: A Global Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial of Patients with HR+/HER2− aBC or mBC Following Recurrence or Progression On or After AI-based Regimen[1,2]

Patients with HR+/HER2− aBC or mBC

- 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 or mBC
- ≤2 lines of prior endocrine therapy for aBC or mBC
- ≤1 line of chemotherapy for aBC or mBC
- 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)

Capivasertib	400 mg (two 200-mg tablets) twice daily, 4 days on, 3 days off, weekly
Fulvestrant	500 mg: Days 1, 15, 29 and once monthly thereafter
Placebo	Two tablets Twice daily, 4 days on, 3 days off, weekly
Fulvestrant	500 mg: Days 1, 15, 29 and once monthly thereafter

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

Dual primary endpoints

PFS by investigator assessment
- Overall population
- PI3K/AKT/PTEN pathway-altered tumors (≥1 qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration)

Key secondary endpoints

- Overall survival
- Objective response rate
- Safety

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. Pre- or peri-menopausal women also received a luteinizing hormone-releasing hormone agonist for the duration of the study treatment.

- aBC, locally advanced breast cancer; AI, aromatase inhibitor; AKT, serine/threonine protein kinase; CDK4/6, cyclin-dependent kinase 4/6; FFPE, formalin-fixed, paraffin-embedded; HER2−, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; mBC, metastatic breast cancer; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; PTEN, Phosphatase and tensin homolog; PFS, progression-free survival; SERD, selective estrogen receptor degrader.

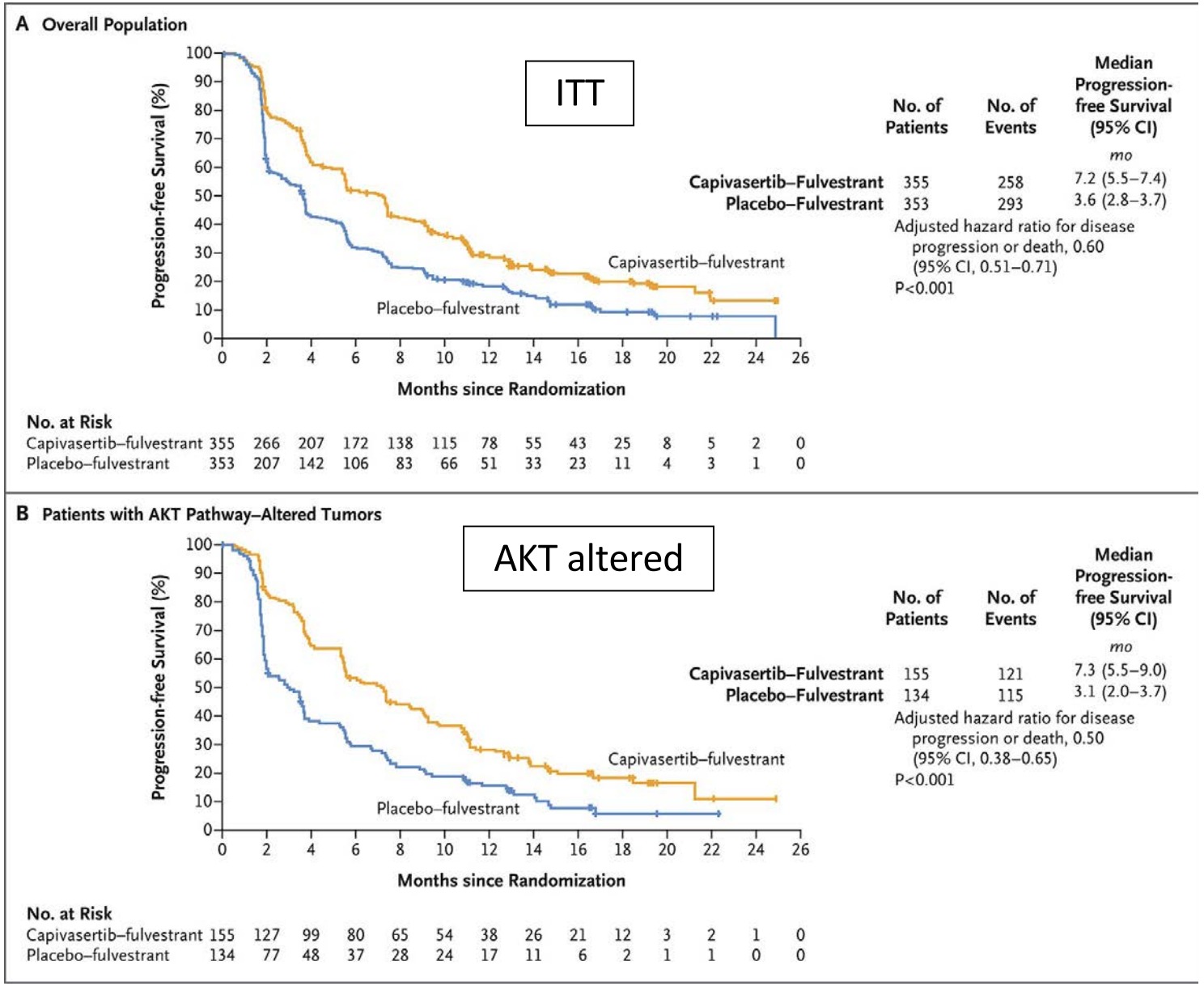
Turner NC et al. N Engl J Med. 2023;388(22):2058-2070

CAPItello-291:

- 69% prior CDK4/6i
- 18% prior chemotherapy
- Study met dual primary endpoints, showing significantly prolonged PFS with capivasertib + FULV vs placebo + FULV in overall and AKT pathway–altered populations (41% AKT altered)

  -HR 0.60 (ITT)

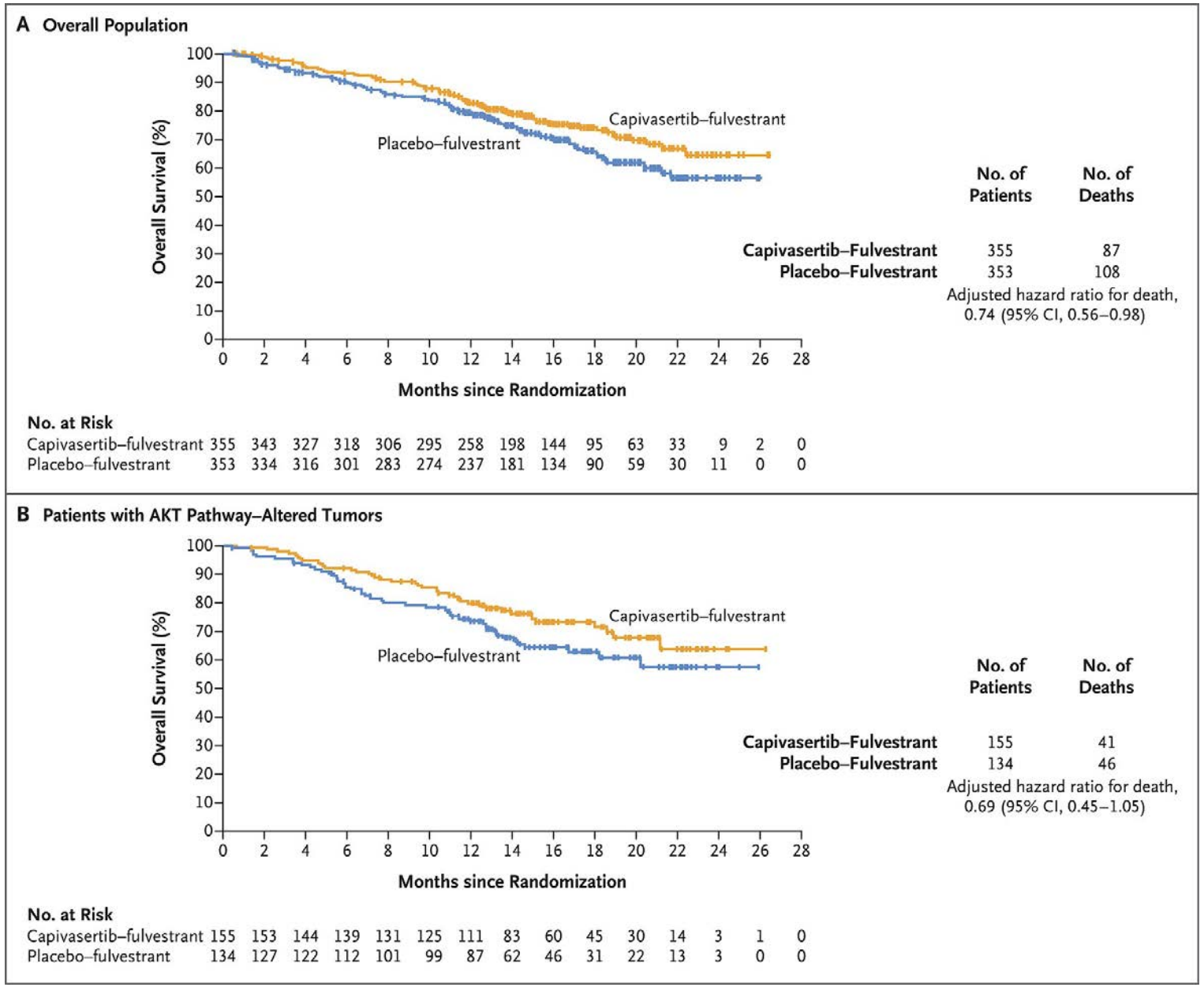
  -HR 0.50 (AKT altered)



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

OS in Overall Population and AKT-Pathway Altered

- OS is immature
- OS at 18 months:
  - Overall population: 73.9% capi vs. 65% placebo
  - AKT-pathway altered: 73.2% capi vs. 62.9% placebo

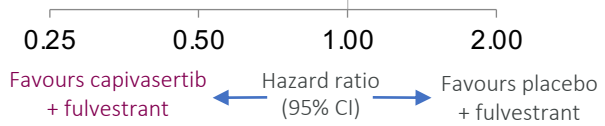


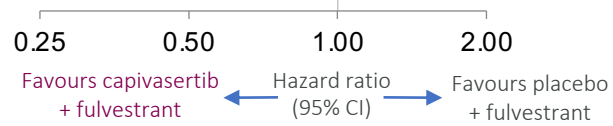
Turner NC, et al. N Engl J Med. 2023;388(22):2058-2070.

CAPItello-291: Summary of PFS by subgroups

Consistent benefit with capivasertib + fulvestrant was observed across clinically relevant subgroups in both the overall population and AKT pathway-altered population

		Overall population				AKT pathway-altered population			
			Median PFS, months				Median PFS, months		
		n	Capivasertib + fulvestrant	Placebo + fulvestrant		n	Capivasertib + fulvestrant	Placebo + fulvestrant	
Overall[a]		708	7.2	3.6		289	7.3	3.1	
Prior CDK4/6 inhibitor[b]	Yes	496	5.5	2.6		208	5.5	2.0	
	No	212	10.9	7.2		81	11.0	7.4	
Prior chemotherapy for ABC[b]	Yes	129	3.8	2.1		53	4.0	2.0	
	No	579	7.3	3.7		236	7.4	3.5	
Liver metastases at baseline[b]	Yes	306	3.8	1.9		123	5.5	1.8	
	No	402	9.2	5.5		166	9.1	3.7	





[a]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. [b]HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases and geographic region (prior CDK4/6 inhibitor subgroup), the presence of liver metastases and prior use of CDK4/6 inhibitor (prior chemotherapy for ABC subgroup [overall population]) and prior use of CDK4/6 inhibitor only (prior chemotherapy for ABC subgroup [AKT pathway-altered population] and liver metastases subgroup).

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

CAPItello-291: Efficacy

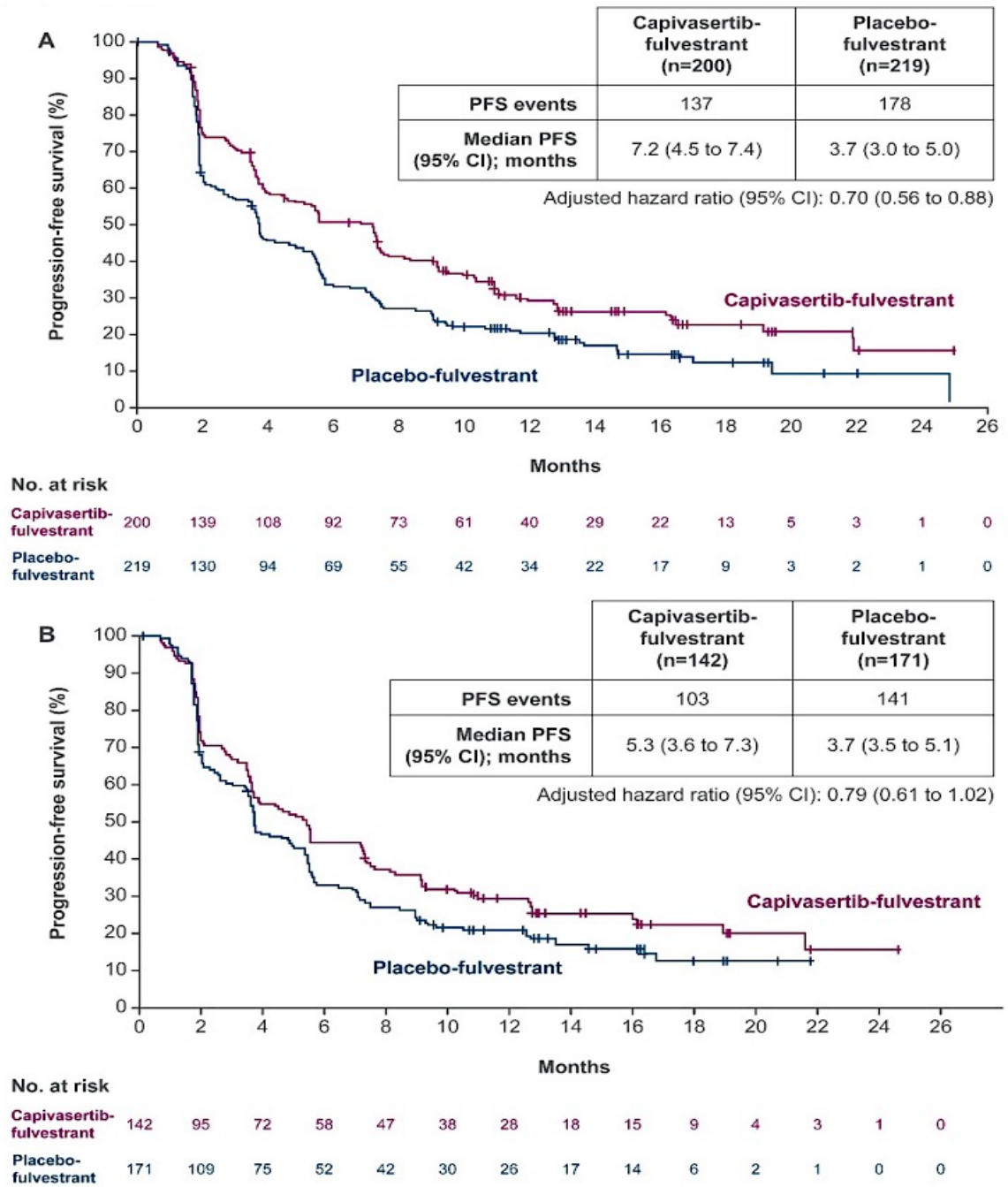
Exploratory Analyses

- 44% had alterations in *PIK3CA/PTEN/AKT*
- 16% unknown

PFS in patients with AKT pathway non-altered tumors, including unknown NGS result (per protocol)

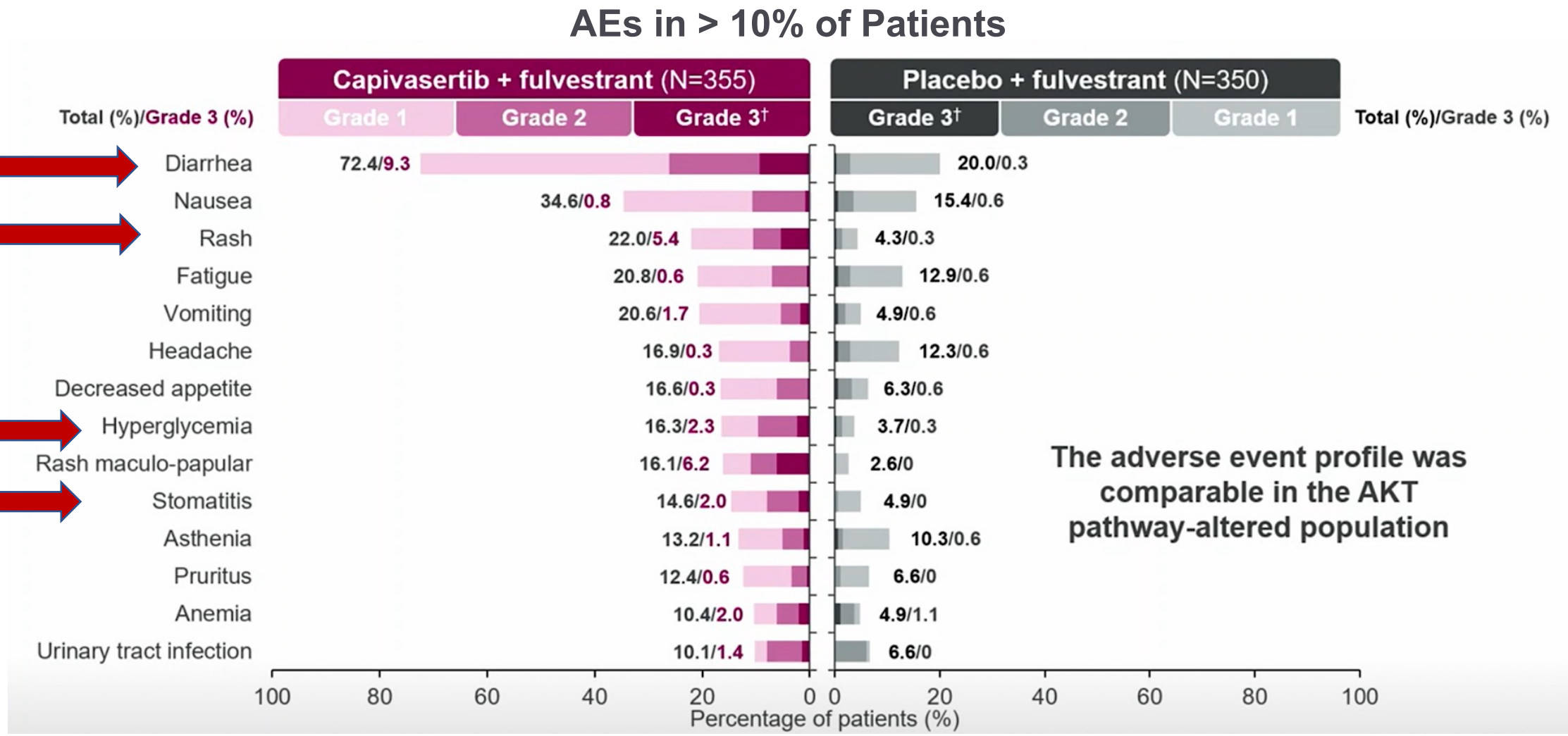
US FDA approval is for PI3K/AKT1/PTEN pathway altered group FoundationOne®CDx: companion diagnostic assay

PFS in patients with AKT pathway non-altered tumors, excluding unknown NGS result (exploratory analysis)



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

CAPItello-291: Capivasertib, AKT inhibitor
Adverse Events



35% dose interruption; 20% dose reduction and Discontinuation rate 13%; 9% due to capivasertib

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

Toxicity Summary: Everolimus, Capivasertib, Alpelisib

	Alpelisib (PI3Ki)		Capivasertib (AKTi)		Everolimus (mTORi)	
Toxicity	**All grades**	**Grade 3+**	**All grades**	**Grade 3+**	**All grades**	**Grade 3+**
Diarrhea %	57.7	6.7	72.4	9.3	30	2
Rash %	35.6	9.9	38	12.1	36	1
Hyperglycemia %	63.7	36.6	16.9	2	13	4
Stomatitis %	24.6	2.5	14.6	2	56	8
Discontinuation rate	**25%**		**13%**		**19%**	

Rugo et al Ann Oncology 2020; Rugo et al ASCO 2023; Baselga et al NEJM 2012

Agenda

Module 1: Optimal Integration of CDK4/6 Inhibitors into the Management of ER-Positive Metastatic Breast Cancer (mBC) — Dr Kaklamani

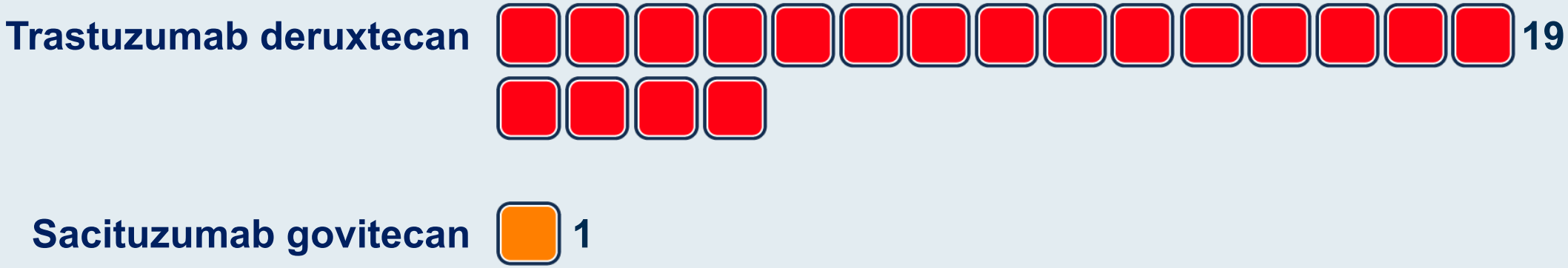
Module 2: Novel Strategies to Overcome Resistance to Endocrine Therapy — Dr Jhaveri

Module 3: Current Role of Antibody-Drug Conjugates in the Management of ER-Positive mBC — Dr Rugo

Module 4: Current and Future Role of Selective Estrogen Receptor Degraders (SERDs) in the Management of ER-Positive mBC — Prof Bidard

Module 5: Novel Therapies Under Investigation for Patients with ER-Positive mBC — Dr Hamilton

A 65-year-old woman with ER-positive, HER2-low (IHC = 2) metastatic breast cancer has exhausted all available endocrine therapy options and experienced disease progression on capecitabine. Regulatory and reimbursement issues aside, would you most likely use trastuzumab deruxtecan or sacituzumab govitecan as the next line of treatment?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

How do you generally sequence the following agents for a patient with HER2-low metastatic breast cancer who is eligible to receive both?

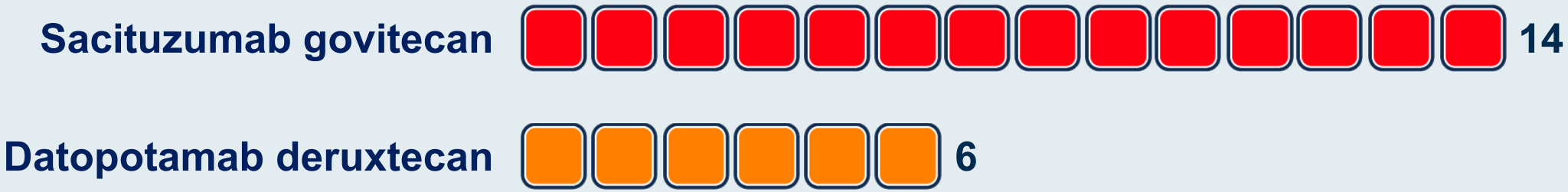
ER-Positive

ER-Negative

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

A 65-year-old woman with ER-positive, HER2-negative (IHC = 0) metastatic breast cancer has exhausted all available endocrine therapy options and experienced disease progression on capecitabine. Regulatory and reimbursement issues aside, would you most likely use sacituzumab govitecan or datopotamab deruxtecan as the next line of treatment?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Based on your personal clinical experience and knowledge of available data, for each of the following agents please estimate the chance that a patient will experience toxicity during treatment that will require withholding administration. What is the primary toxicity patients experience that leads to withholding the drug?

	Chance of withholding*	Primary toxicity
Trastuzumab deruxtecan	15% (10% - 50%)	Pneumonitis/ILD
Sacituzumab govitecan	20% (5% - 50%)	Neutropenia, diarrhea

ILD = interstitial lung disease
*** Median (Range)**

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Antibody-drug conjugates in the management of recurrent hormone receptor-positive, HER2-low or HER2-negative metastatic breast cancer

Paolo Tarantino, MD

RTP
RESEARCH
TO PRACTICE

Therapy options for patients with HER2-low metastatic breast cancer after capecitabine; ILD associated with trastuzumab deruxtecan

Eric P Winer, MD

RTP
RESEARCH
TO PRACTICE

Tolerability profile of sacituzumab govitecan; datopotamab deruxtecan, sacituzumab govitecan for hormone receptor-positive, HER2-low or HER2-negative metastatic breast cancer

Priyanka Sharma, MD

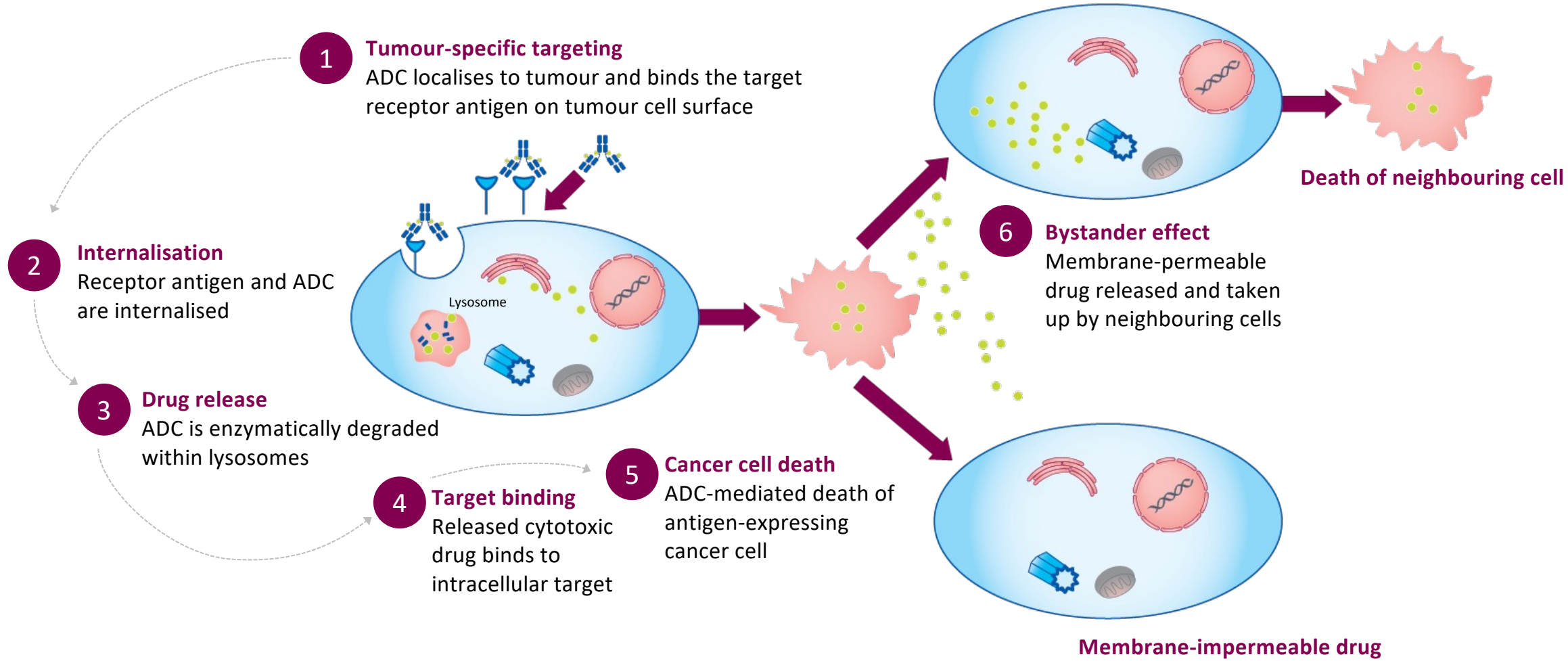
RTP
RESEARCH
TO PRACTICE

UCSF Helen Diller Family Comprehensive Cancer Center

Current Role of Antibody-Drug Conjugates in the Management of HR-Positive mBC

Hope S. Rugo, MD
Professor of Medicine and Winterhof Famly Professor of Breast Oncology
Director, Breast Oncology and Clinical Trials Education
University of California San Francisco Comprehensive Cancer Center

ADC technology enables tumour-specific targeting



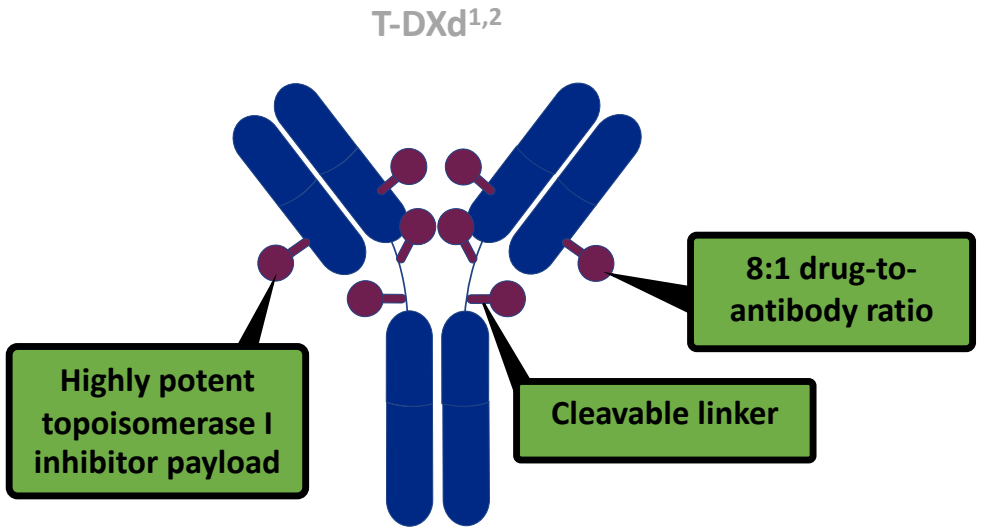
ADC=antibody-drug conjugate

Adapted from: Trail PA, et al. *Pharmacol Ther.* 2018;181:126–142.

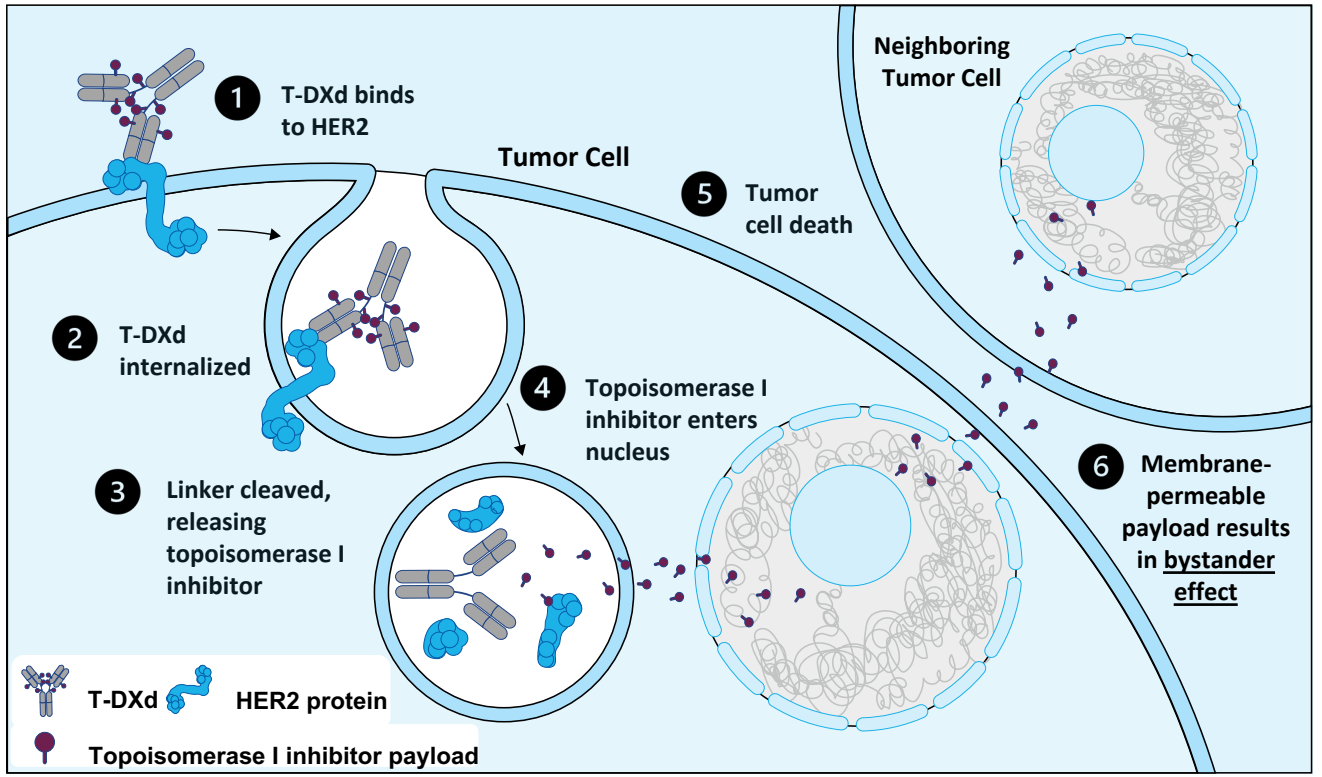
Current Clinical Evidence: Antibody Drug Conjugates

- **An exciting and effective drug delivery system for the treatment of multiple subtypes of mBC – it's still chemotherapy!**
- **Remarkable efficacy and established role in HER2+ disease**
- **Established role in TNBC**
  - Sacituzumab govitecan is a new standard of care for mTNBC
- **Established role in HER2 low and HR+ disease**
  - T-DXd is a new standard of care for HER2 'low' disease
  - Sacituzumab govitecan is an effective treatment option for pre-treated HR+ disease
- **Ongoing trials in earlier lines, early-stage disease, and new ADCs in phase III trials**
- **Many questions remain!**
  - Defining HER2 low
  - Sequencing of ADCs
  - Mechanisms of resistance
- **Toxicity management is critical**

T-DXd MOA, Bystander Effect, and Rationale for Targeting HER2-low mBC



Internalization of T-DXd leads to release of the DXd payload and subsequent cell death in the target tumor cell and neighboring tumor cells through the bystander effect[1,2]



Adapted with permission from Modi S, et al. *J Clin Oncol* 2020;38:1887-96. CC BY ND 4.0.

- **Results from a phase 1b study have reported efficacy of T-DXd in heavily pretreated patients (N = 54) with HER2-low mBC, with a mPFS of 11.1 months and an ORR of 37.0%[3]**

HER2, human epidermal growth factor receptor 2; MOA, mechanism of action; mBC, metastatic breast cancer; mPFS, median progression-free survival; ORR, objective response rate; T-DXd, trastuzumab deruxtecan.

1. Nakada T, et al. *Chem Pharm Bull*. 2019;67:173-185. 2. Ogitani Y, et al. *Clin Cancer Res.* 2016;22:5097-5108. 3. Modi S, et al. *J Clin Oncol.* 2020;38:1887-1896.

DESTINY-Breast04: Updated Survival Results of T-DXd in HER2-low Metastatic Breast Cancer

An open-label, multicenter study (NCT03734029)[1-3]

Patients[a]
- HER2-low (IHC 1+ or IHC 2+/ISH−), unresectable, and/or mBC treated with 1-2 prior lines of chemotherapy in the metastatic setting
- HR+ disease considered endocrine refractory

Stratification factors
- Centrally assessed HER2 status[b] (IHC 1+ vs IHC 2+/ISH−)
- 1 vs 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6i) vs HR−

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 373)

N=557

TPC
Capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel[c]
(n = 184)

Primary endpoint
- PFS by BICR (HR+)

Key secondary endpoints[d]
- PFS by BICR (all patients)
- **OS (HR+ and all patients)**

Secondary endpoints[d]
- **PFS by investigator**
- ORR by BICR and investigator
- DOR by BICR
- **Safety**
- Patient-reported outcomes (HR+)[e]

Chemotherapy, n (%)	
Eribulin	94 (51.1)
Capecitabine	37 (20.1)
Nab-paclitaxel	19 (10.3)
Gemcitabine	19 (10.3)
Paclitaxel	15 (8.2)

At the updated data cutoff (March 1, 2023), median follow-up was 32.0 months (95% CI, 31.0-32.8 months)

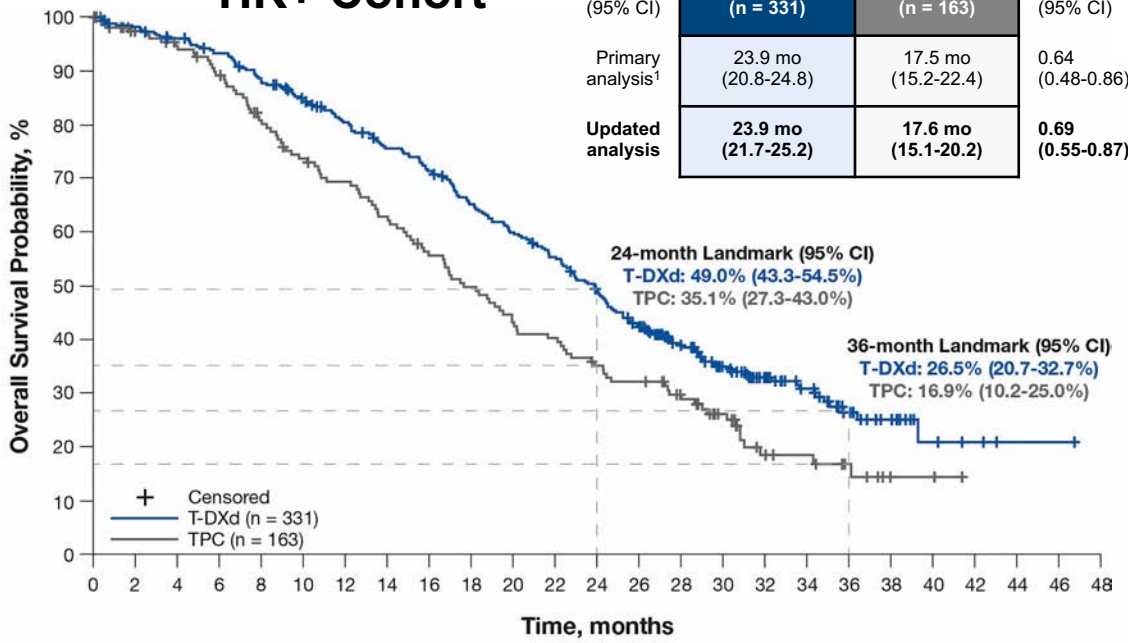
- At the primary analysis (data cutoff, January 11, 2022), median follow-up was 18.4 months
- The primary analysis of PFS was by BICR; this is comparing investigator assessment
- Patient population: Median one line of chemotherapy for mBC, 65-70% prior CDKi, 70% liver mets

Modi et al, NEJM 2022; ESMO 2023

Updated Overall Survival

HR+ Cohort

Median (95% CI)	T-DXd (n = 331)	TPC (n = 163)	Hazard ratio (95% CI)
Primary analysis[1]	23.9 mo (20.8-24.8)	17.5 mo (15.2-22.4)	0.64 (0.48-0.86)
Updated analysis	**23.9 mo (21.7-25.2)**	**17.6 mo (15.1-20.2)**	**0.69 (0.55-0.87)**



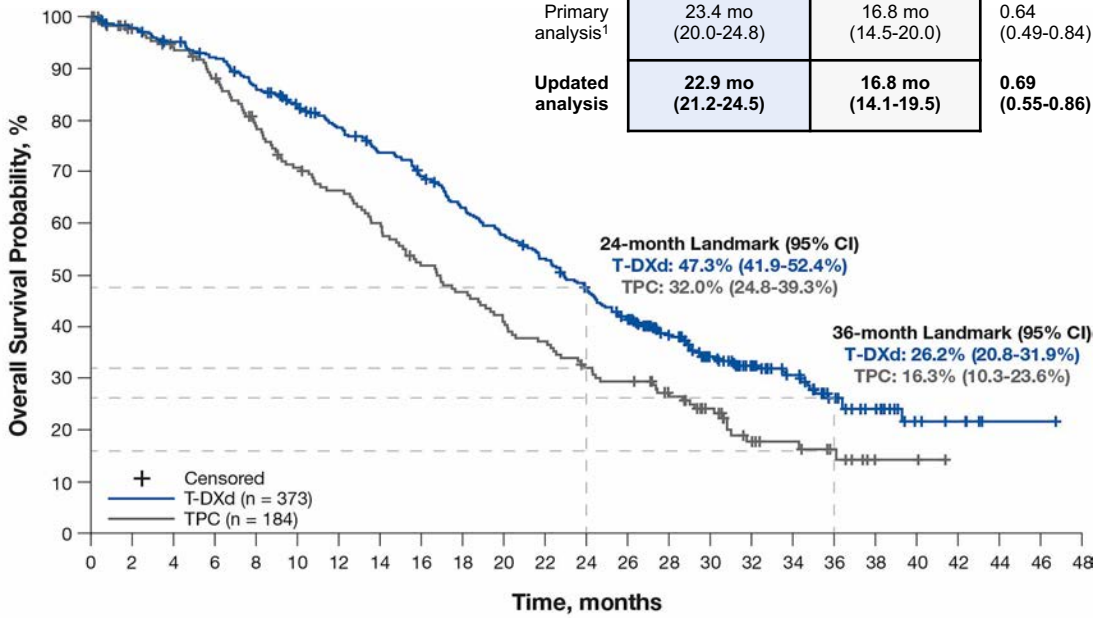
Patients still at risk:

T-DXd (n = 331) 331 325 323 317 313 307 302 292 284 279 267 258 250 243 233 230 220 212 199 189 183 176 168 155 147 135 124 109 94 81 72 66 54 46 42 34 23 17 14 7 5 4 3 2 1 1 1 0

TPC (n = 163) 163 150 144 142 138 134 129 123 114 108 103 97 96 92 87 82 76 71 68 64 59 56 55 50 47 43 43 42 35 31 25 16 13 11 11 9 7 5 2 2 2 1 0

All Patients

Median (95% CI)	T-DXd (n = 373)	TPC (n = 184)	Hazard ratio (95% CI)
Primary analysis[1]	23.4 mo (20.0-24.8)	16.8 mo (14.5-20.0)	0.64 (0.49-0.84)
Updated analysis	**22.9 mo (21.2-24.5)**	**16.8 mo (14.1-19.5)**	**0.69 (0.55-0.86)**



Patients still at risk:

T-DXd (n = 373) 373 366 363 355 350 342 337 325 314 308 295 285 276 269 257 254 240 231 217 205 199 191 182 168 160 148 137 122 107 94 81 75 62 52 48 39 28 21 18 11 7 6 5 3 1 1 1 0

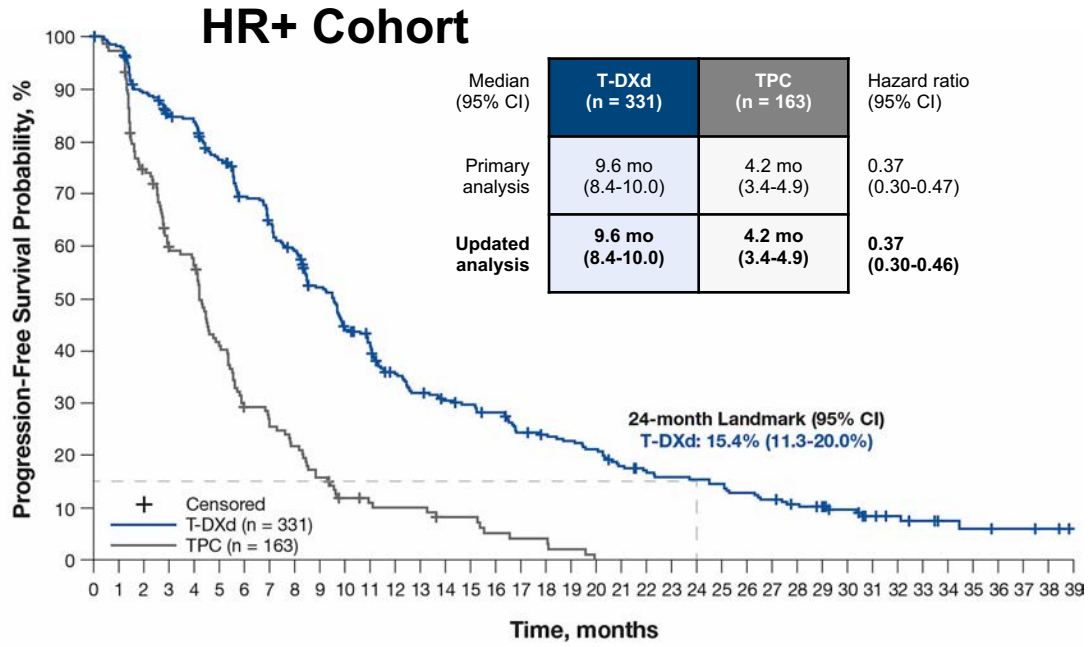
TPC (n = 184) 184 170 165 160 156 152 145 137 127 119 113 107 105 100 95 88 81 76 73 69 64 59 58 53 49 45 45 44 37 33 27 18 15 12 12 10 8 5 2 2 2 1 0

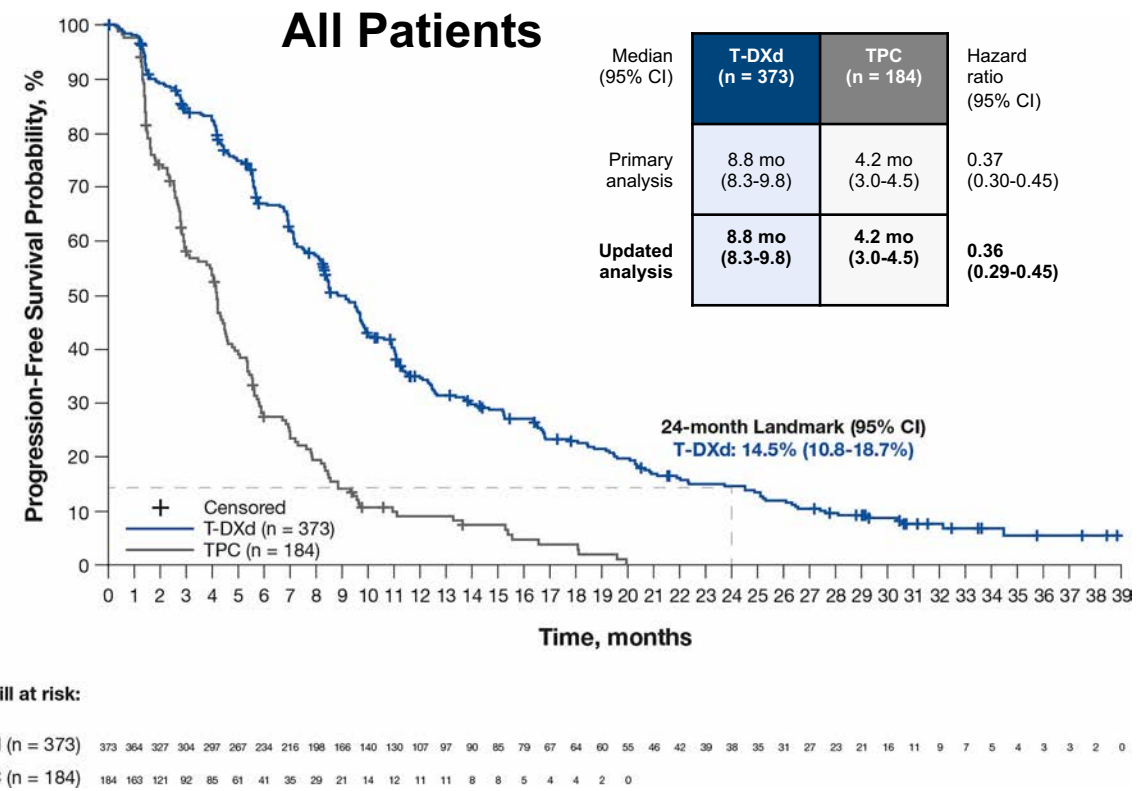
Primary Analysis (BICR)

OS	HR+		HR-		All Patients	
	T-DXd (n=331)	TPC (n=163)	T-DXd (n=40)	TPC (n=18)	T-DXd (n=373)	TPC (n=184)
Median OS, months	23.9	17.5	18.2	8.3	23.4	16.8
HR (95% CI); *P* value	HR 0.64 (0.48-0.86); 0.0028		0.48 (0.24-0.95)		HR 0.64 (0.49-0.84); 0.0010	

Modi et al, NEJM 2022; ESMO 2023

Updated Progression-Free Survival (Investigator Assessed)





Primary Analysis (BICR)

PFS	HR+		HR-		All Patients	
	T-DXd (n=331)	TPC (n=163)	T-DXd (n=40)	TPC (n=18)	T-DXd (n=373)	TPC (n=184)
Median PFS, months	10.1	5.4	8.5	2.9	9.9	5.1
HR (95% CI); *P* value	0.51 (0.40-0.64); <0.0001		0.46 (0.24-0.89)		HR 0.50 (0.40-0.63); <0.0001	

Modi et al, NEJM 2022; ESMO 2023

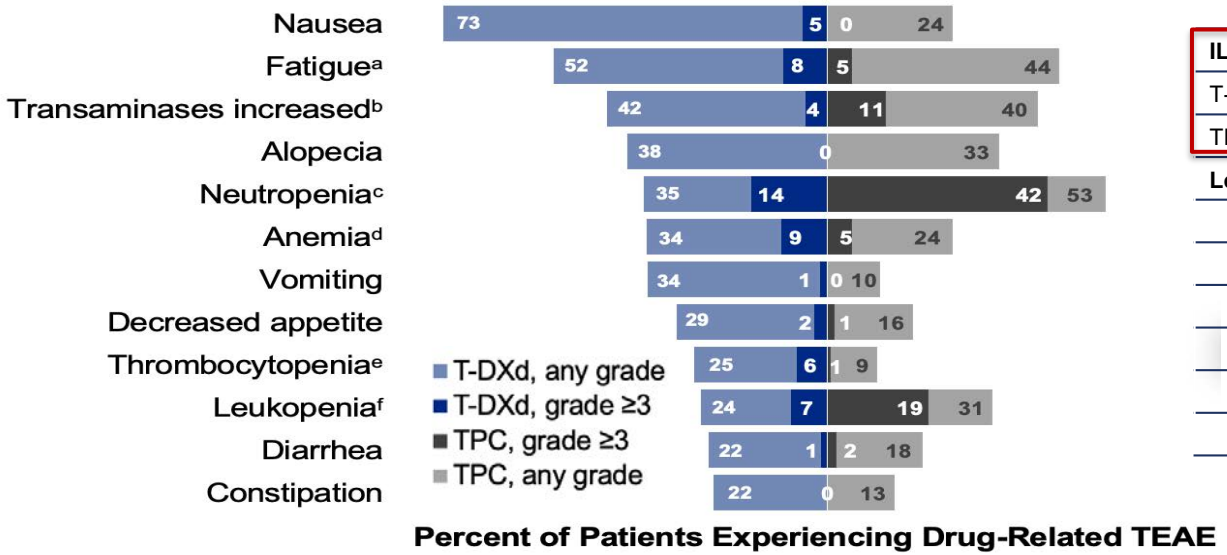
Subgroup analyses: OS in the HR+ Cohort

	No. of Events/No. of Patients		OS, median (95% CI), mo		Hazard Ratio for Death (95% CI)
	T-DXd	TPC	T-DXd	TPC	
Prior CDK4/6 inhibitors					
Yes	156/233	78/115	22.3 (19.8-24.3)	16.8 (13.6-19.5)	0.71 (0.54-0.94)
No	53/96	31/47	30.3 (23.0-35.1)	22.4 (15.6-27.2)	0.63 (0.41-0.99)
IHC status					
IHC 1+	121/192	67/96	22.9 (20.8-25.2)	16.9 (13.5-22.4)	0.67 (0.50-0.91)
IHC 2+/ISH−	90/139	43/67	24.2 (20.8-26.5)	19.1 (15.1-22.3)	0.73 (0.51-1.05)
Prior lines of chemotherapy					
1	118/203	63/93	25.5 (23.9-28.8)	19.4 (16.7-23.9)	0.66 (0.48-0.89)
≥2	93/127	47/69	19.0 (16.7-22.7)	14.0 (10.8-20.0)	0.76 (0.53-1.08)
Age					
<65 years	164/260	81/120	23.0 (20.8-24.8)	17.6 (14.8-20.0)	0.67 (0.52-0.88)
≥65 years	47/71	29/43	25.5 (21.0-28.8)	19.5 (9.2-30.6)	0.72 (0.45-1.15)
Race					
White	104/156	51/78	23.9 (19.8-24.8)	15.1 (12.3-19.9)	0.65 (0.47-0.91)
Asian	80/131	46/66	23.9 (21.7-28.7)	19.9 (16.7-27.2)	0.75 (0.52-1.07)
Other	25/37	12/16	21.5 (15.0-30.4)	15.2 (6.2-23.9)	0.56 (0.28-1.12)
Region					
Asia	80/128	42/60	23.4 (21.0-27.4)	19.9 (16.7-27.2)	0.76 (0.53-1.11)
Europe and Israel	102/149	49/73	23.9 (20.8-25.7)	17.6 (12.3-20.2)	0.66 (0.47-0.93)
North America	29/54	19/30	24.5 (15.8-28.9)	16.0 (8.8-22.3)	0.59 (0.33-1.06)
ECOG performance status					
0	109/187	59/95	26.0 (23.0-29.6)	20.2 (16.7-24.4)	0.68 (0.49-0.93)
1	102/44	51/68	21.4 (17.9-23.9)	14.9 (12.6-18.4)	0.70 (0.50-0.99)
Visceral disease at baseline					
Yes	201/298	99/146	22.9 (21.4-24.5)	17.5 (14.8-20.2)	0.73 (0.57-0.93)
No	10/33	11/17	NE (20.4-NE)	18.4 (13.5-NE)	0.34 (0.14-0.81)

OS in all Patients

	No. of Events/No. of Patients		OS, median (95% CI), mo		Hazard Ratio for Death (95% CI)
	T-DXd	TPC	T-DXd	TPC	
Prior CDK4/6 inhibitors					
Yes	158/235	81/118	22.3 (19.7-24.2)	16.7 (14.0-19.4)	0.71 (0.54-0.92)
No	55/98	32/48	29.6 (22.9-35.1)	22.4 (15.6-27.2)	0.64 (0.41-0.99)
IHC status					
IHC 1+	137/214	77/107	22.7 (20.3-24.7)	15.7 (13.5-19.9)	0.65 (0.49-0.86)
IHC 2+/ISH−	105/159	51/77	23.6 (20.0-26.0)	17.1 (13.1-21.7)	0.72 (0.51-1.01)
Prior lines of chemotherapy					
1	129/221	69/100	25.5 (23.4-28.9)	18.2 (15.6-22.5)	0.62 (0.46-0.83)
≥2	113/151	59/83	18.1 (16.1-21.5)	14.0 (10.8-19.1)	0.78 (0.57-1.07)
Age					
<65 years	185/290	95/136	22.7 (20.3-24.4)	16.7 (14.0-19.1)	0.64 (0.50-0.82)
≥65 years	57/83	33/48	24.4 (18.4-28.0)	19.5 (11.1-30.2)	0.77 (0.50-1.19)
Race					
White	123/176	62/91	22.0 (18.2-24.2)	14.5 (10.7-19.4)	0.68 (0.50-0.93)
Asian	90/151	51/72	25.2 (21.7-29.6)	19.1 (15.7-24.3)	0.68 (0.48-0.96)
Other	26/38	13/17	21.2 (17.0-28.9)	15.2 (6.2-23.9)	0.55 (0.28-1.07)
Region					
Asia	90/147	47/66	24.0 (21.7-29.3)	19.1 (15.7-24.3)	0.69 (0.49-0.98)
Europe and Israel	118/166	59/85	22.3 (19.0-24.2)	14.8 (10.7-19.9)	0.67 (0.49-0.91)
North America	34/60	22/33	20.6 (13.6-25.9)	14.9 (10.5-19.5)	0.66 (0.38-1.13)
ECOG performance status					
0	117/200	68/105	25.9 (23.0-29.3)	19.4 (15.1-22.8)	0.62 (0.46-0.83)
1	125/173	60/79	20.6 (17.2-22.7)	14.5 (12.3-18.4)	0.74 (0.54-1.01)
Visceral disease at baseline					
Yes	227/332	109/157	22.4 (20.0-24.0)	16.9 (14.0-20.0)	0.71 (0.57-0.90)
No	15/41	19/27	NE (28.0-NE)	15.7 (12.9-20.6)	0.35 (0.18-0.70)

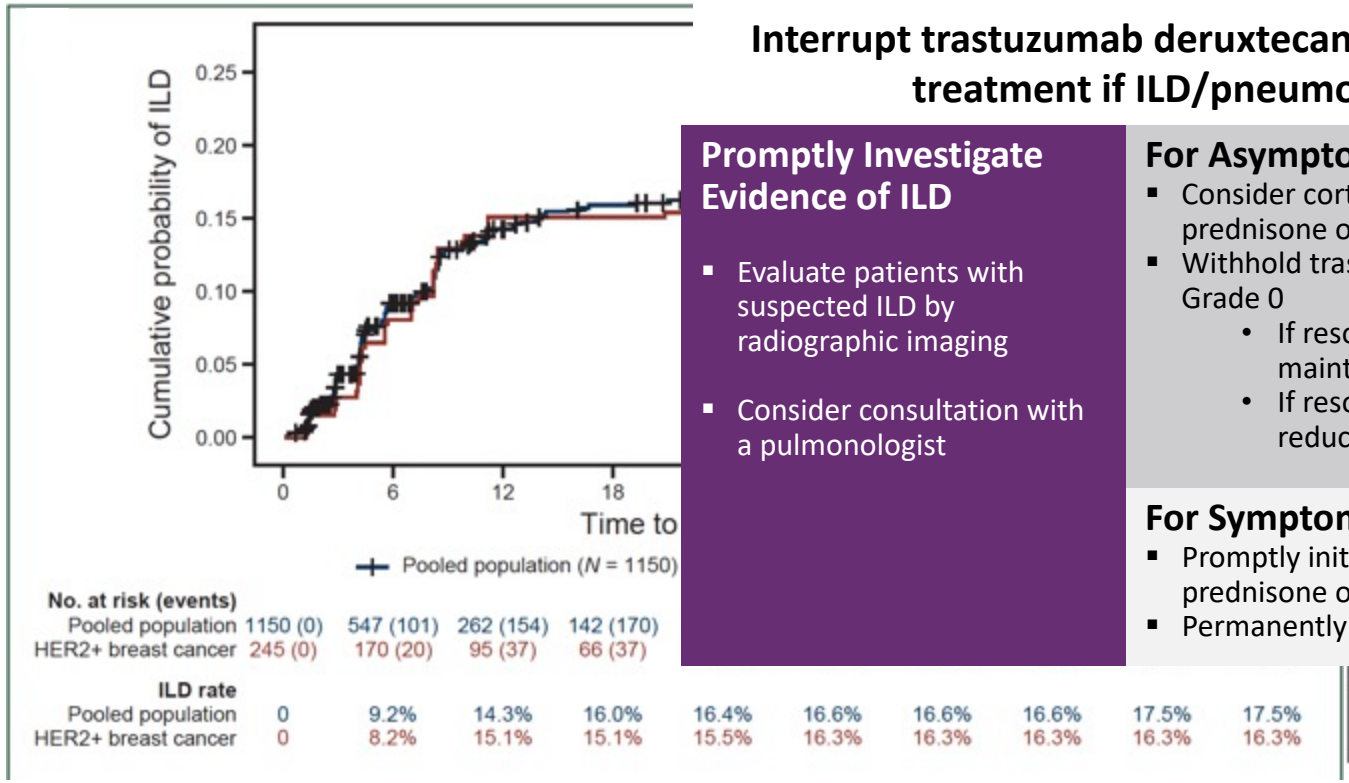
Adverse Events



	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
ILD/pneumonitis (adjudicated, drug-related), n (%)						
T-DXd (n = 371)	13 (3.5)	24 (6.5)	4 (1.1)[a]	0	4 (1.1)[a]	45 (12.1)
TPC (n = 172)	1 (0.6)	0	0	0	0	1 (0.6)
Left ventricular dysfunction						
Ejection fraction decreased, n (%)						
T-DXd (n = 371)	2 (0.5)	15 (4.0)	1 (0.3)	0	0	18 (4.9)
TPC (n = 172)	0	0	0	0	0	0
Cardiac failure, n (%)						
T-DXd (n = 371)	0	1 (0.3)	1 (0.3)	0	0	2 (0.5)
TPC (n = 172)	0	0	0	0	0	0

Modi et al, NEJM 2022; ESMO 2023

Pooled Analysis of ILD/Pneumonitis in 9 Trastuzumab deruxtecan Monotherapy Studies



Interrupt trastuzumab deruxtecan and initiate corticosteroid treatment if ILD/pneumonitis is suspected

Promptly Investigate Evidence of ILD

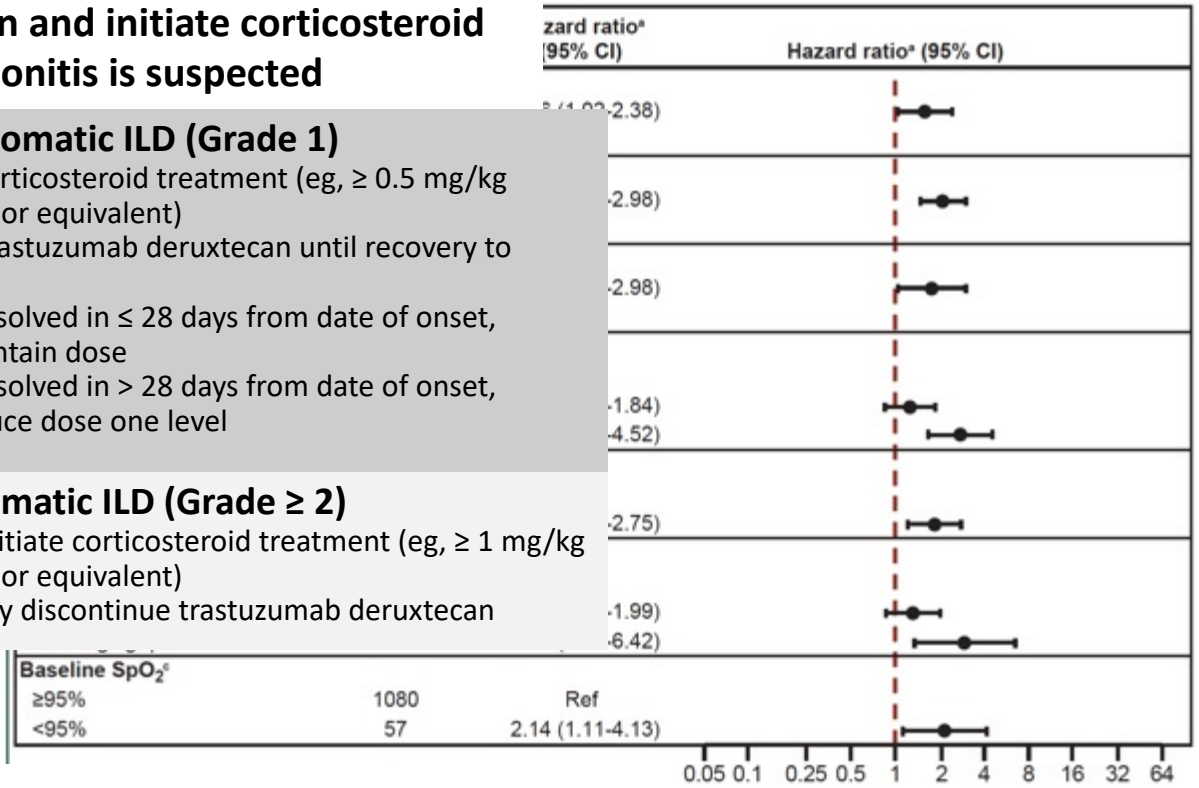
- Evaluate patients with suspected ILD by radiographic imaging
- Consider consultation with a pulmonologist

For Asymptomatic ILD (Grade 1)

- Consider corticosteroid treatment (eg, ≥ 0.5 mg/kg prednisone or equivalent)
- Withhold trastuzumab deruxtecan until recovery to Grade 0
  - If resolved in ≤ 28 days from date of onset, maintain dose
  - If resolved in > 28 days from date of onset, reduce dose one level

For Symptomatic ILD (Grade ≥ 2)

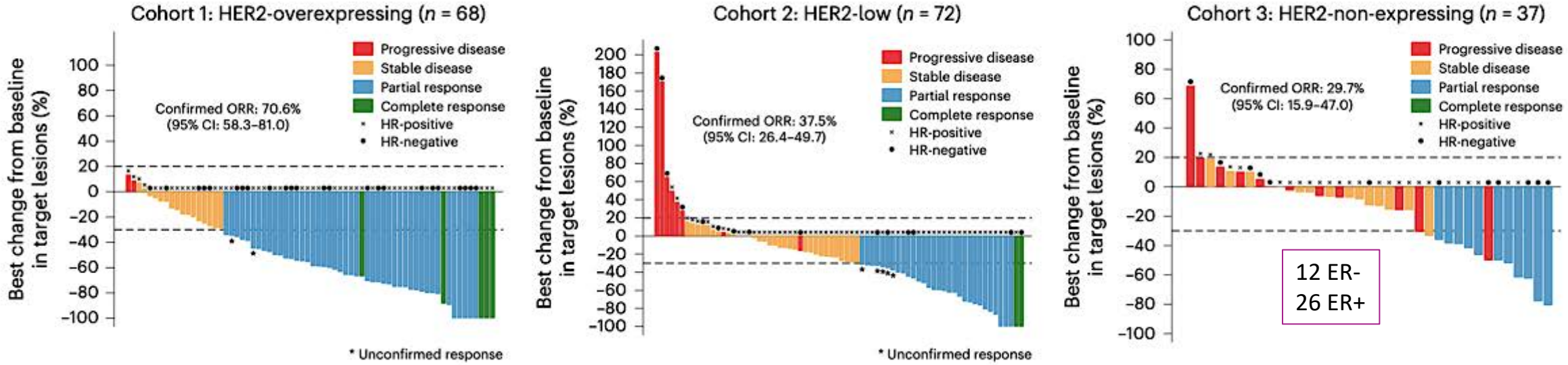
- Promptly initiate corticosteroid treatment (eg, ≥ 1 mg/kg prednisone or equivalent)
- Permanently discontinue trastuzumab deruxtecan



- 1150 pts (44.3% breast cancer) with a median treatment duration 5.8 mo (0.7-56.3)
- Overall incidence: 15.4% (grade 5: 2.2%); grade 1-2: 77.4%
- 87% had their first event within 12 months of their first dose

Powell et al, ESMO Open 2022

Can Use of T-DXd be Expanded? The DAISY Trial



mPFS, mo. **95% CI**	**11.1** **(8.5-14.4)**	**6.7** **(4.4-8.3)**	**4.2 (2.1 in ER-)** **(2.0-5.7)**

PFS was longer in cohort 1 (adj HR: 0.53, 95% CI 0.34–0.84, *P* = 0.007) and shorter in cohort 3 (adj HR: 1.96 95% CI 1.21–3.15, *P* = 0.006) comp to cohort 2.

Mosele et al, Nature Med 2023; 29:2110-2120

Testing Trastuzumab Deruxtecan in HER2 'Ultralow' DESTINY-Breast06

Key differences with DB-04:

- Includes IHC0 (ultralow, n=150)
- Larger (n=850)
- Restricted to HR+ disease
- Chemo-naïve patients

Status: Completed accrual

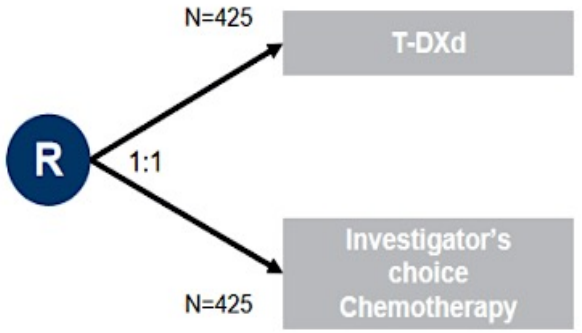
POPULATION

- Advanced/metastatic breast cancer after progression on 2 prior ETs
- HR+
- HER2 IHC 0+ or 1+ or 2+ (determined based on central IHC assessment of archival tissue collected at time of diagnosis of first metastatic disease or later)

Stratification factors:

- Prior CDK4/6 inhibitor
- HER2 IHC 2+ v. 1+ v. 0+
- Prior taxane in non-metastatic setting

TREATMENT



- Chemotherapy options: capecitabine, paclitaxel, nAb-paclitaxel
- Treatment continues until progressive disease or toxicity
- HER2 IHC 0+ defined by any IHC staining up to 10% of tumor cells
- Futility analysis in HER2 IHC 0+ cohort will be done

ENDPOINTS

Primary:

- PFS (BICR) in HER2 IHC 1+/2+ population

Key Secondary:

- OS in HER2 IHC 1+/2+ population
- PFS in ITT population
- OS in ITT population

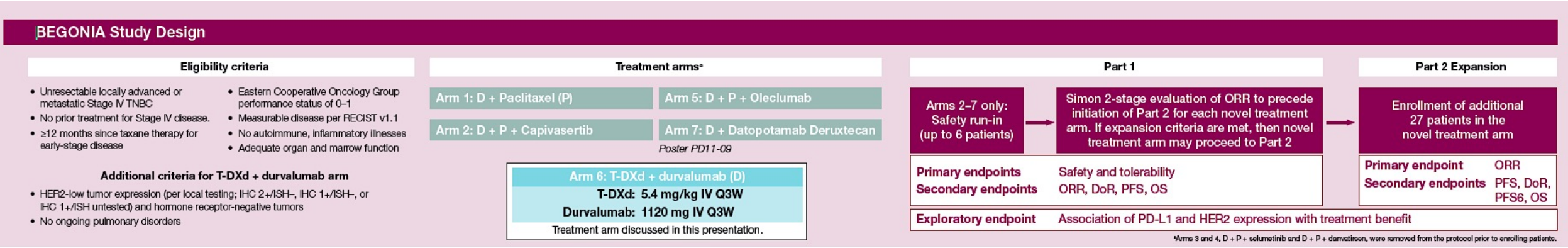
Secondary:

- PFS (investigator assessed) in HER2 IHC 1+/2+
- ORR and DOR of HER2 IHC 1+/2+ and ITT populations
- Safety and tolerability
- Symptoms, functioning and HRQoL

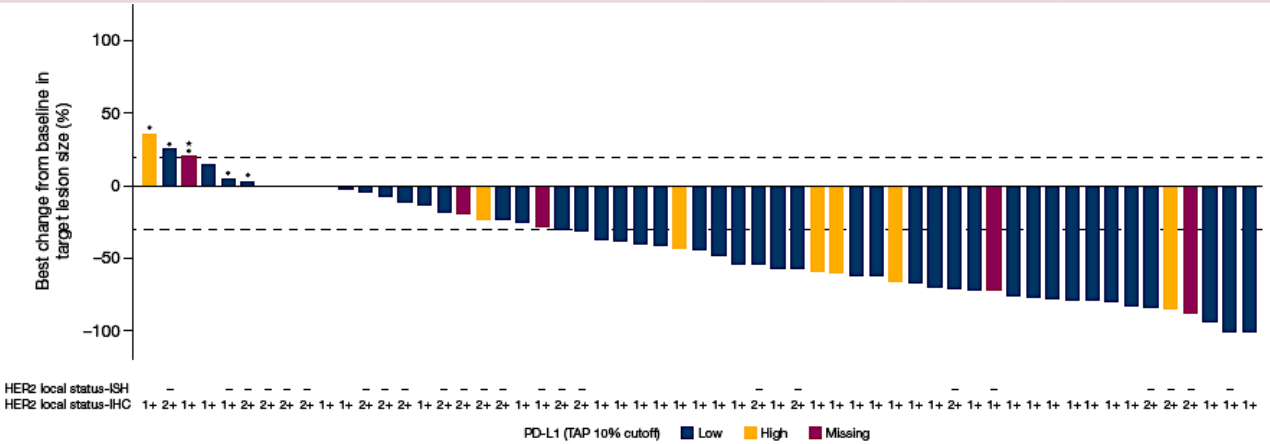
Exploratory:

- PRO
- Pharmacodynamic biomarkers

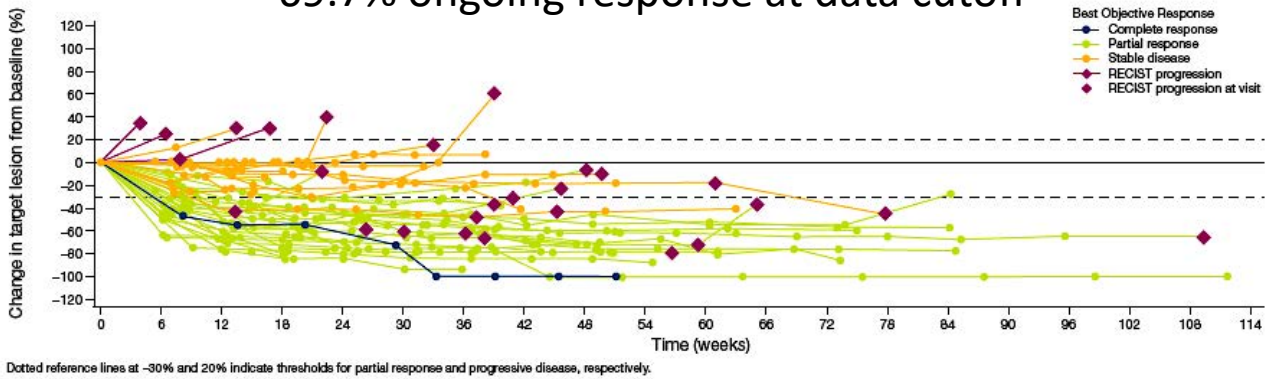
T-DXd + Durvalumab: The BEGONIA Trial



- First-line basket trial for HER2-low mTNBC
  - Arm 6 (n=58)
    - PD-L1 testing using SP263
    - ORR 56.9% (n=33)
    - PFS 12.6 mo (8.3-NC)
  - Safety
    - **8 cases of adjudicated ILD, 2 more pending review**
      - Grade 1 (3), grade 2 (2), grade 3 (1), grade 5 (1, Covid related)
      - 17% stopped rx due to AEs

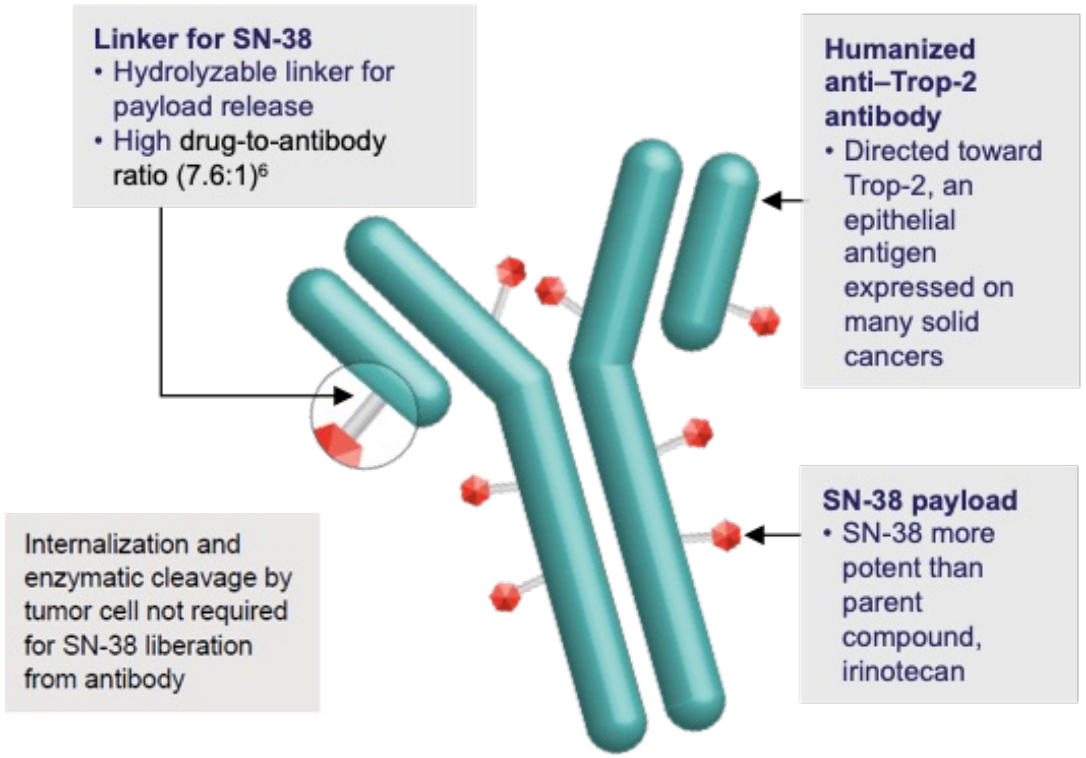


69.7% ongoing response at data cutoff

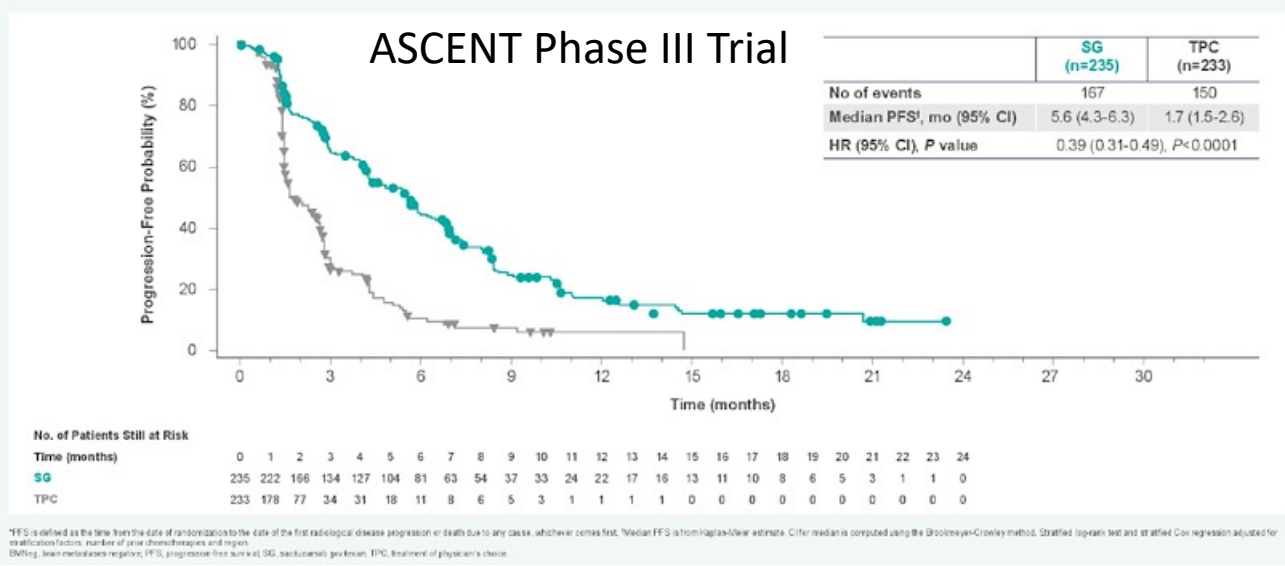


Schmid et al, SABCS 2022; PD11-08

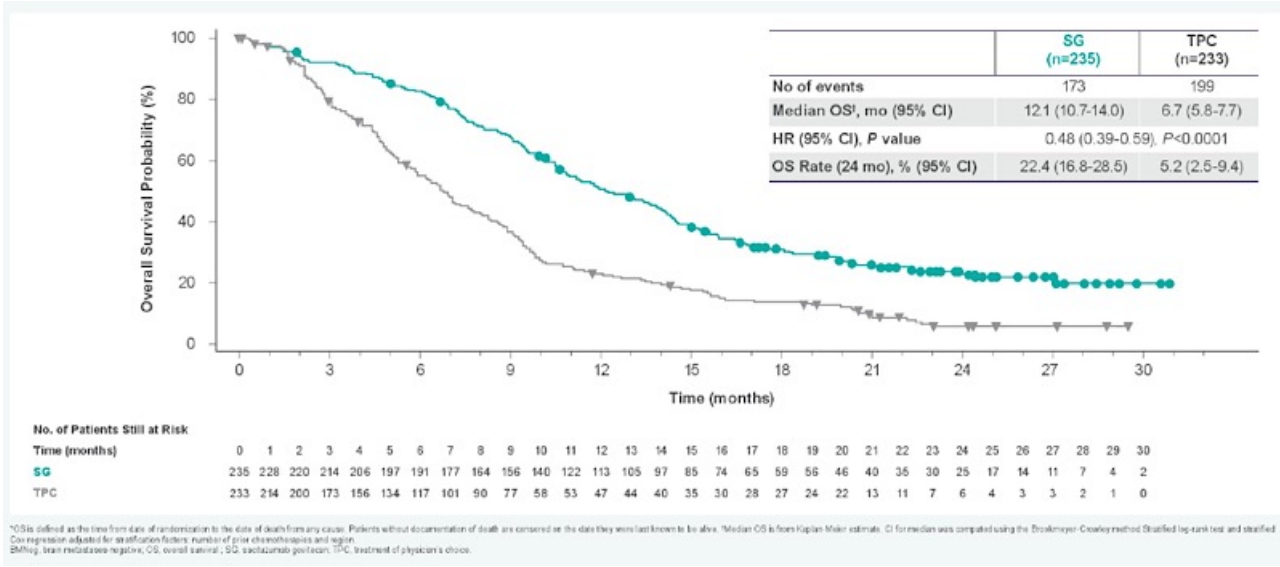
Sacituzumab Govitecan (SG): First-in-Class Trop-2–Directed ADC



ASCENT Phase III Trial



	SG (n=235)	TPC (n=233)
No of events	167	150
Median PFS[1], mo (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
HR (95% CI), *P* value	0.39 (0.31-0.49), *P*<0.0001	



	SG (n=235)	TPC (n=233)
No of events	173	199
Median OS[1], mo (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
HR (95% CI), *P* value	0.48 (0.39-0.59), *P*<0.0001	
OS Rate (24 mo), % (95% CI)	22.4 (16.8-28.5)	5.2 (2.5-9.4)

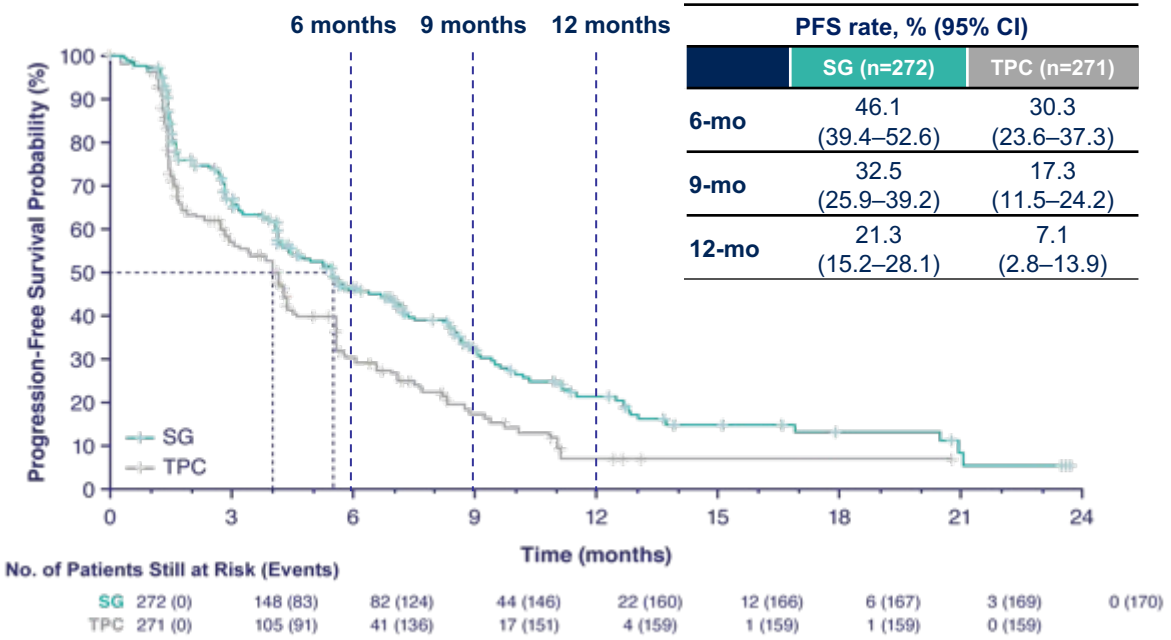
- Trop-2 is expressed in all subtypes of breast cancer and linked to poor prognosis
- **Key grade ≥3 TRAEs (SG vs TPC): neutropenia (51% vs 33%), diarrhea (10% vs <1%), leukopenia (10% vs 5%), anemia (8% vs 5%), FN (6% vs 2%)**
  - G-CSF: 49% in the SG arm vs 23% in the TPC arm
  - Dose reductions due to TRAEs were similar (22% SG vs 26% TPC)
  - No severe CV toxicity, no grade >2 neuropathy or grade >3 ILD with SG

Bardia et al. *NEJM*, 2021.

TROPiCS-02 for HR+/HER2- Disease: PFS & OS in the ITT Population

PFS[1]

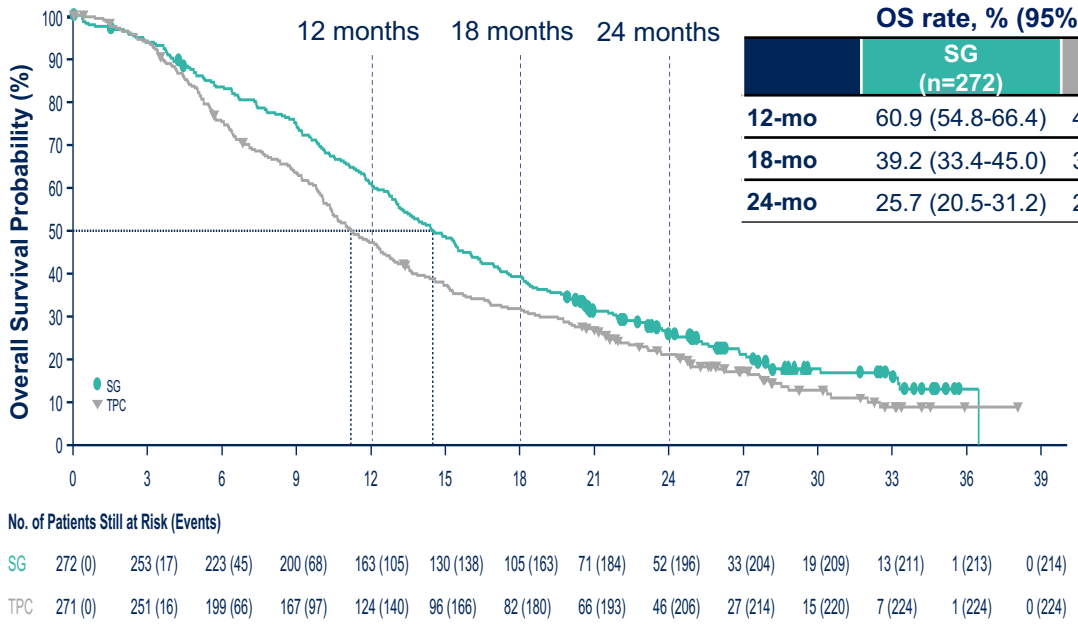
BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
Stratified HR (95% CI)	**0.66** (0.53–0.83)	
Stratified Log Rank *P* value	*P*=0.0003	



PFS rate, % (95% CI)	SG (n=272)	TPC (n=271)
6-mo	46.1 (39.4–52.6)	30.3 (23.6–37.3)
9-mo	32.5 (25.9–39.2)	17.3 (11.5–24.2)
12-mo	21.3 (15.2–28.1)	7.1 (2.8–13.9)

OS[2,3]

	SG (n=272)	TPC (n=271)
Median OS, mo (95% CI)	14.5 (13.0–16.0)	11.2 (10.2–12.6)
Stratified HR (95% CI)	**0.79** (0.65–0.95)	
Nominal *P* value	*P*=0.0133	



OS rate, % (95% CI)	SG (n=272)	TPC (n=271)
12-mo	60.9 (54.8-66.4)	47.1 (41.0-53.0)
18-mo	39.2 (33.4-45.0)	31.7 (26.2-37.4)
24-mo	25.7 (20.5-31.2)	21.1 (16.3-26.3)

SG demonstrated a statistically significant improvement in PFS and OS vs TPC

Median follow-up was 10.2 months.

BICR, blinded independent central review; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

1. Rugo HS, et al. *J Clin Oncol.* 2022;40:3365-3376. 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. 2. Rugo H, et al. ESMO 2022. Oral LBA76. 3. Tolaney et al, ASCO Abstract 1003; Rugo et al, Lancet 2023

No new toxicity signals compared to ASCENT

TROPiCS-02: PFS and OS by Trop-2 Expression Level and HER2 IHC Status

PFS

	Status	Median PFS, months (95% CI)		HR (95% CI)
		SG	TPC	
Trop-2	H-score <100	5.0 (4.1, 6.0) n=96	4.0 (2.7, 5.6) n=96	**0.79** (0.56, 1.12)
	H-score ≥100	5.8 (4.0, 8.3) n=142	4.1 (2.3, 4.5) n=128	**0.61** (0.45, 0.83)
HER2	IHC1+, IHC2+/ISH−	5.8 (4.1, 8.4) n=149	4.2 (2.8, 5.5) n=134	**0.60** (0.44, 0.62)
	IHC0	5.0 (3.9, 7.2) n=101	3.4 (1.8, 4.2) n=116	**0.70** (0.51, 0.98)

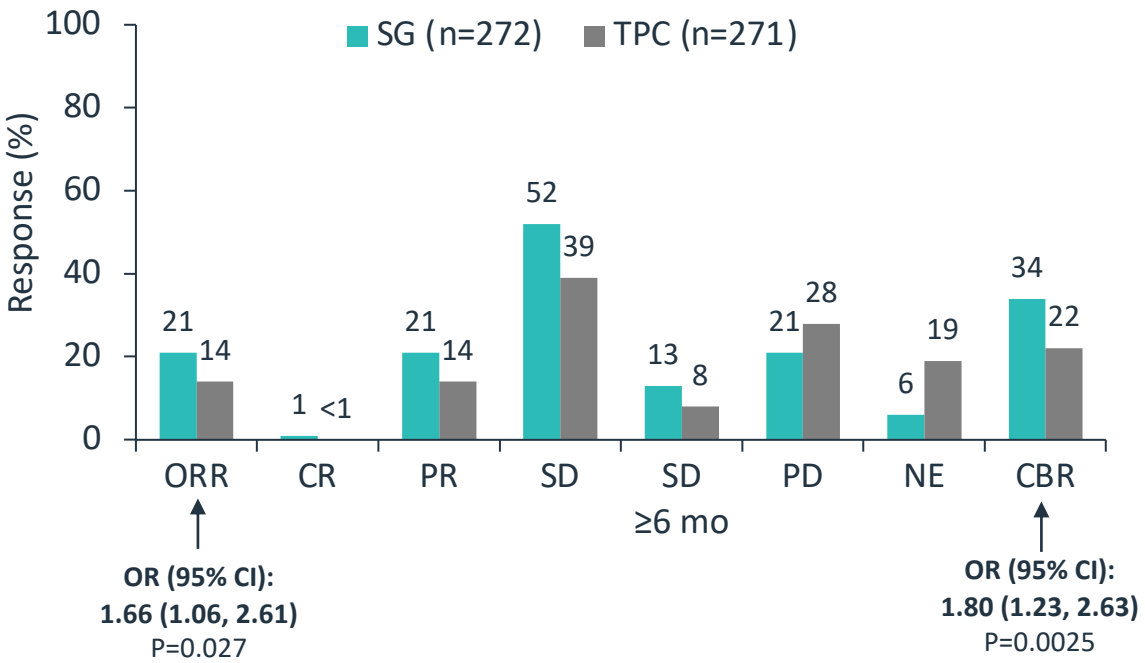
OS

	Status	Median OS, months (95% CI)		HR (95% CI)
		SG	TPC	
Trop-2	H-score <100	14.9 (12.7, 18.1) n=96	11.3 (10.0, 13.3) n=96	**0.78** (0.57, 1.06)
	H-score ≥100	14.4 (12.7, 17.0) n=142	11.2 (9.9, 12.7) n=128	**0.82** (0.63, 1.08)
HER2	IHC1+, IHC2+/ISH−	15.4 (13.5, 19.1) n=149	11.5 (10.1, 12.9) n=134	**0.75** (0.57, 0.97)
	IHC0	13.6 (12.1, 16.0) n=101	10.8 (9.2, 14.2) n=116	**0.85** (0.63, 1.14)

Tolaney et al. ASCO 2023. Abstract 1003; updated from Rugo et al, ESMO 2022 and Rugo et al, SABCS 2022; Rugo et al, Lancet 2023

TROPiCS-02: Responses and Safety Summary

Tumor response



Median DoR, months (95% CI): 8.1 (6.7, 8.9) vs **5.6** (3.8, 7.9)

Safety summary

n (%)		SG (n=268)		TPC (n=249)	
AE Grade ≥3		199 (74)		149 (60)	
AEs → discontinuation		17 (6)		11 (4)	
AEs → dose delay		178 (66)		109 (44)	
AEs → dose reductions		91 (34)		82 (33)	
SAEs		74 (28)		48 (19)	
AEs → death[a]		6 (2)		0	
		Any grade	Grade ≥3	Any grade	Grade ≥3
Hematologic	Neutropenia	189 (71)	140 (52)	136 (55)	97 (39)
	Anemia	98 (37)	20 (7)	69 (28)	8 (3)
	Thrombocytopenia	17 (6)	1 (<1)	41 (16)	9 (4)
GI	Diarrhea	166 (62)	27 (10)	57 (23)	3 (1)
	Nausea	157 (59)	3 (1)	87 (35)	7 (3)
	Constipation	93 (35)	1 (<1)	61 (24)	0
	Vomiting	64 (24)	3 (1)	39 (16)	4 (2)
	Abdominal pain	53 (20)	10 (4)	34 (14)	2 (1)
Other	Alopecia	128 (48)	0	46 (18)	0
	Fatigue	105 (39)	16 (6)	82 (33)	9 (4)
	Asthenia	62 (23)	6 (2)	50 (20)	5 (2)
	Decreased appetite	57 (21)	4 (1)	52 (21)	2 (1)
	Dyspnea	49 (18)	5 (2)	39 (16)	11 (4)
	Headache	44 (16)	1 (<1)	36 (14)	2 (1)
	Pyrexia	39 (15)	2 (1)	45 (18)	0
	AST increased	33 (12)	4 (1)	44 (18)	8 (3)

[a]Of 6 AEs leading to death, 1 (septic shock due to neutropenic colitis) was considered treatment related by investigator

Rugo et al, JCO 2022; Rugo et al, ESMO 2022; Rugo et al, SABCS 2022; Tolaney et al. ASCO 2023. Abstract 1003; Rugo et al, Lancet 2023

ASCENT and TROPiCS-02: Safety Outcomes by UGT1A1 Status

UGT1A1

- ✓ Variants affect enzymatic function, causing reduced metabolic capacity
- ✓ Over 50% of individuals may harbor an UTG1A1 polymorphism, dependent on genetic ancestry

	ASCENT		TROPiCS-02	
SG patients (n=250)	UGT1A1 Status n(%)	Dose Intensity (%)	UGT1A1 Status n(%)	Dose Intensity (%)
***1/*1 (wt)**	113 (44)	99.8	104 (38)	99
***1/*28**	96 (37)	99.5	119 (44)	98
***28/*28**	34 (13)	99.8	25 (9)	94

Grade ≥3 TEAEs Overall (%)	SG (n=268)
Neutropenia	52
Diarrhea	10
Anemia	8
Febrile neutropenia	6

	ASCENT			TROPiCS-02		
Grade ≥3 TEAEs By UGT1A1 Status (%)	*1/*1 (wt)	*1/*28	*28/*28	*1/*1 (wt)	*1/*28	*28/*28
Neutropenia	53	47	59	45	57	64
Diarrhea	10	9	15	6	13	24
Anemia	4	6	15	6	8	8
Febrile neutropenia	3	5	18	6	7	4
Growth factor for neutropenia (initiated on/after first dose) overall 54%						
				33	49	11

ASCENT: Treatment discontinuation due to TRAEs more common in *28 homozygous genotype

Nelson, RS, et al. *Cancers.* 2021;13:1566.
Rugo, HS, et al. *npj Breast Cancer.* 2022;8:98.
Marmé, F, et al. *Annals of Oncol.* 2023;8(1suppl_4):101223-101223.
Rugo et al. *Lancet* 2023

ASCENT-03 (NCT05382299): PD-L1 negative
N=540

First-line therapy
- PD-L1 neg TNBC
- TNBC Rxd with IO in early stage

→ Sacituzumab govitecan

→ TPC: paclitaxel, nab-paclitaxel, gem/carbo

ASCENT-04 (NCT05382286): PD-L1 positive
N=570

1L mTNBC PD-L1+
- Previously untreated, inoperable, locally advanced, OR metastatic TNBC
- PD-L1+ (CPS ≥10, IHC 22C3 assay)
- PD-L1 and TNBC status centrally confirmed
- Prior anti-PD-(L)1 allowed in the curative setting
- ≥6 months since treatment in curative setting

1:1

N=570
(≤25% *de novo*)

→ SG + pembrolizumab
(SG: 10 mg/kg IV on days 1 and 8 of 21-day cycles; Pembro: 200 mg IV on day 1 of 21-day cycles)

→ TPC chemotherapy + pembrolizumab
(Pembro dosed as above. TPC: gem 1000 mg/m² with carbo AUC 2 IV on days 1 and 8 of 21-day cycles OR paclitaxel 90 mg/m² IV on days 1, 8, and 15 of 28-day cycles OR nab-paclitaxel: 100 mg/m² IV on days 1, 8, and 15 of 28-day cycles)

SACI-IO TNBC and HR+: Sacituzumab govitecan +/− pembrolizumab in 1L PD-L1− mTNBC and HR+

Garrido-Castro/Tolaney

mTNBC
- No prior chemo
  No prior PD-1/L1
- PD-L1 <1% by SP-142
  ER ≤5%
  PR ≤5%
  HER2-
- Stable brain mets
- Exclude prior: PD-1/L1, SG, Irinotecan

mHR+/HER2-
- ≥ 1 Hormonal
- 0-1 Prior Chemo
- Exclude prior: PD-1/L1, SG, Irinotecan

N=110

1:1

N=110

→ Sacituzumab govitecan 10 mg/kg IV d1, 8 q21 days + pembrolizumab 200 mg/kg d1 q21 days

→ Sacituzumab govitecan 10 mg/kg d1,8 q21 days

Endpoints
Primary
- PFS

Secondary
- OS, ORR
- Duration and time to objective response, time to progression, CBR
- Safety and tolerability

80% power to detect PFS improvement from 5.5 months (Arm B) to 8.5 months (Arm A)

ASCENT-07:
First-line Chemotherapy in HR+

Key eligibility criteria:
- HR+/HER2* negative, locally advanced and unresectable, or metastatic breast cancer
- Eligible for first chemotherapy for advanced mBC
- Progressed after 1 or more ET for mBC, or relapsed within 12 months of completing adjuvant ET or while receiving adjuvant ET
- No prior treatment with a topoisomerase I inhibitor
- Measurable disease per RECIST v1.1
- Prior CDK 4/6i not required (no prior CDK 4/6i capped at 30%)

N = 654

2:1 randomization

→ Sacituzumab govitecan 10 mg/kg IV Days 1 and 8, every 21 days

→ Treatment of physician's choice (capecitabine, paclitaxel, nab-paclitaxel)

Stratification:
- Duration of prior CDK 4/6i in metastatic setting (none/≤12 mos vs >12 mos)
- HER2 IHC (HER2 IHC 0 vs HER2 IHC-low ([IHC 1+; 2+/ISH-])
- Geographic region (US/CAN/EU vs. ROW)

Primary Endpoint
- PFS by BICR

Key Secondary Endpoints
- OS
- ORR by BICR
- TTDD to Physical functioning

Secondary Endpoints
- PFS by investigator
- ORR by investigator
- DOR
- Safety

GBG: SASCIA Post-Neoadjuvant Trial
NCT04595565

N=1200
HER2-negative early breast cancer

- At least 16 weeks of taxane-based NACT
- No pCR:
  - TNBC
  - HR-positive and CPS-EG score ≥3 or 2 and ypN+

R 1:1

→ Sacituzumab govitecan (8 cycles d1, 8 q3w)

→ Treatment of physician´s choice*

Follow-up

Stratification factors:
- HR-positive vs HR-negative
- ypN+ vs ypN-0

Phase III Trial: OptimICE-RD/ASCENT-05
Residual disease in TNBC

Residual invasive TNBC disease in breast or positive node(s) after anthracycline, taxane, and checkpoint inhibitor-based neoadjuvant therapy
N = 1514

R 1:1

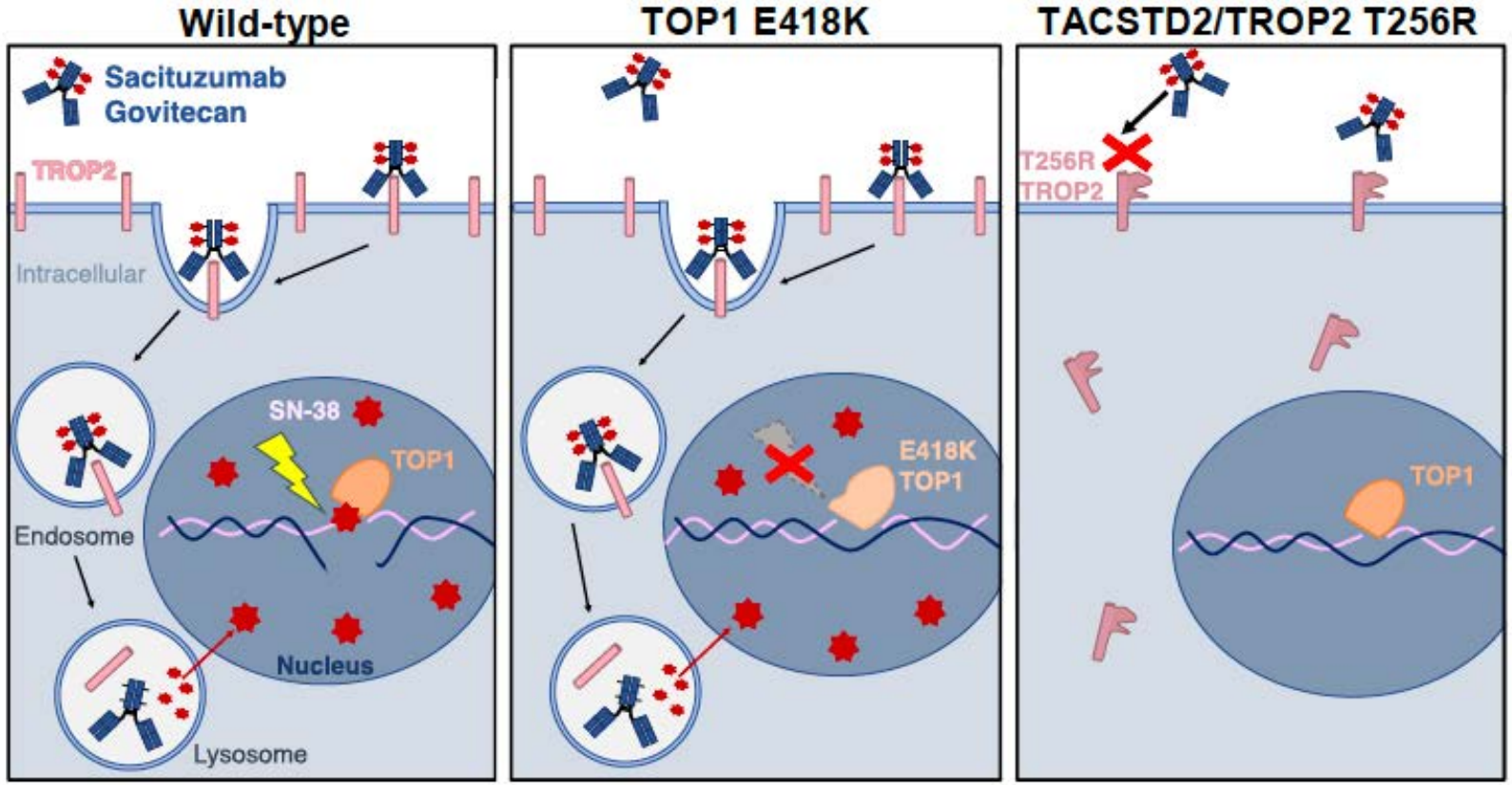
→ A: Sacituzumab Govitecan x 8 cycles + Pembrolizumab x 8 cycles

→ B: Pembrolizumab x 8 cycles (add-on capecitabine per physician's choice)

Follow-up

PI: Sara Tolaney; Alliance Foundation Trial

Mechanisms of Resistance to TROP2 ADC



- Analysis of tumor tissue from 3 patients pre- and post-Sacituzumab treatment
- Two acquired resistance mechanisms identified
  - Mutations in TOP1 leading to decreased binding of SN38 with topoisomerase I
  - Mutation in TROP2 leading to decreased binding of SG and decreased cell surface expression

Failed SN38/TOP1 Binding → Resistance to payload

Altered TROP2 Localization and Binding → Resistance to antibody target

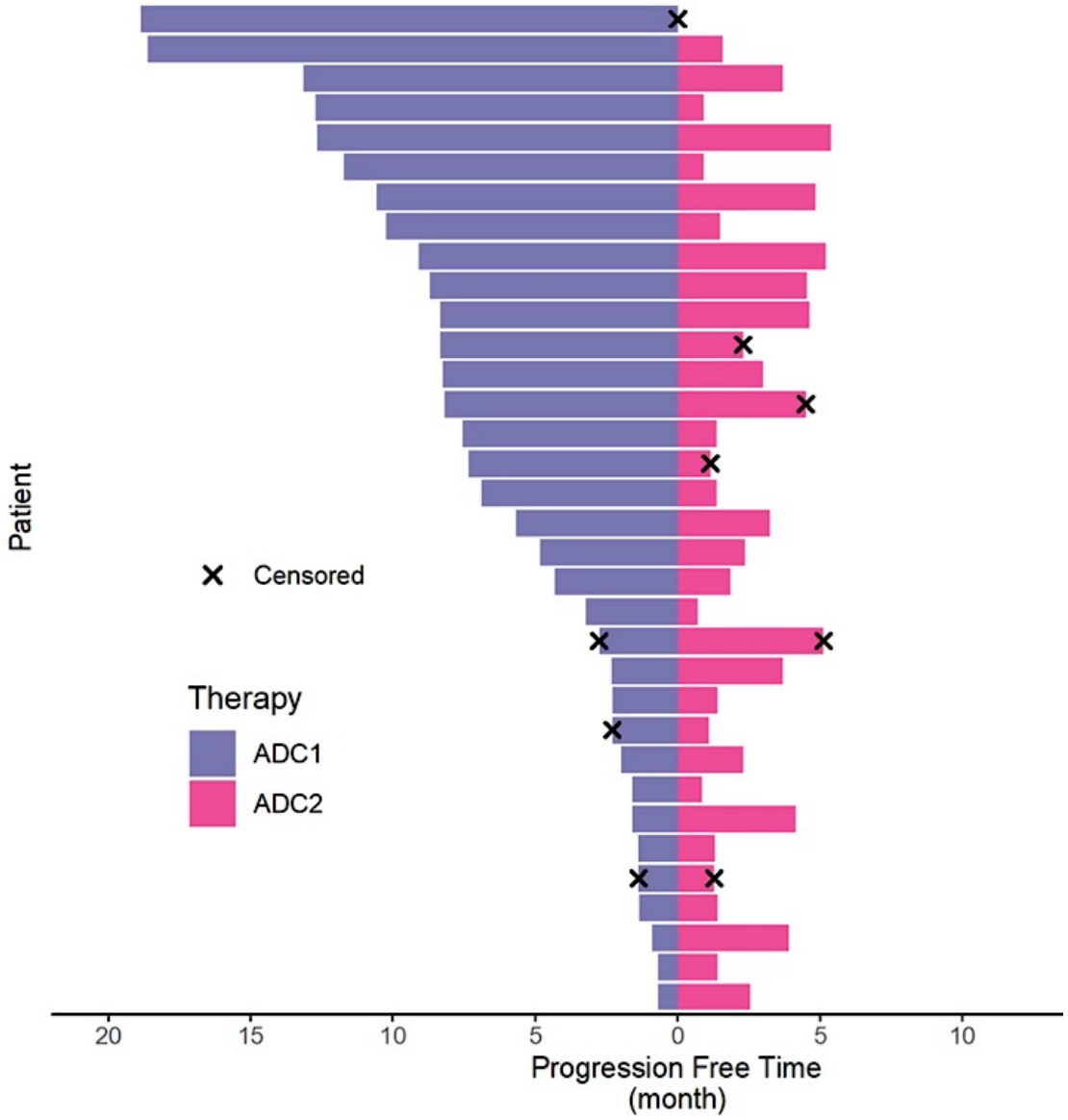
Coates et al. Cancer Discov 2021; courtesy of Elison

Single center study of sequential use of ADC after ADC for patients with MBC

Key Eligibility Criteria

- HER2– MBC (HR+/HER2– or TNBC)
- Treated with 2+ ADCs for MBC at a single institution

Patient Characteristics		n=35
Breast cancer subtype, n (%)	HR+/HER2–	15 (42.9)
	TNBC	20 (57.1)
	HER2-low	24 (68.6)
Median age at second ADC, years		56
Median prior lines of treatment, n	HR+/HER2–	7
	TNBC	3
Antibody target of ADC1, n (%)	HER2	8 (22.9)
	Trop-2	26 (74.3)
	Other	1 (2.9)
Antibody target of ADC2, n (%)	HER2	14 (40.0)
	Trop-2	19 (54.3)
	Other	2 (5.7)
Payload of ADC1	TOP-1 inhibitor	35 (100)
Payload of ADC2	TOP-1 inhibitor	31 (88.6)
	Microtubule inhibitor	2 (5.7)
	Other	2 (5.7)



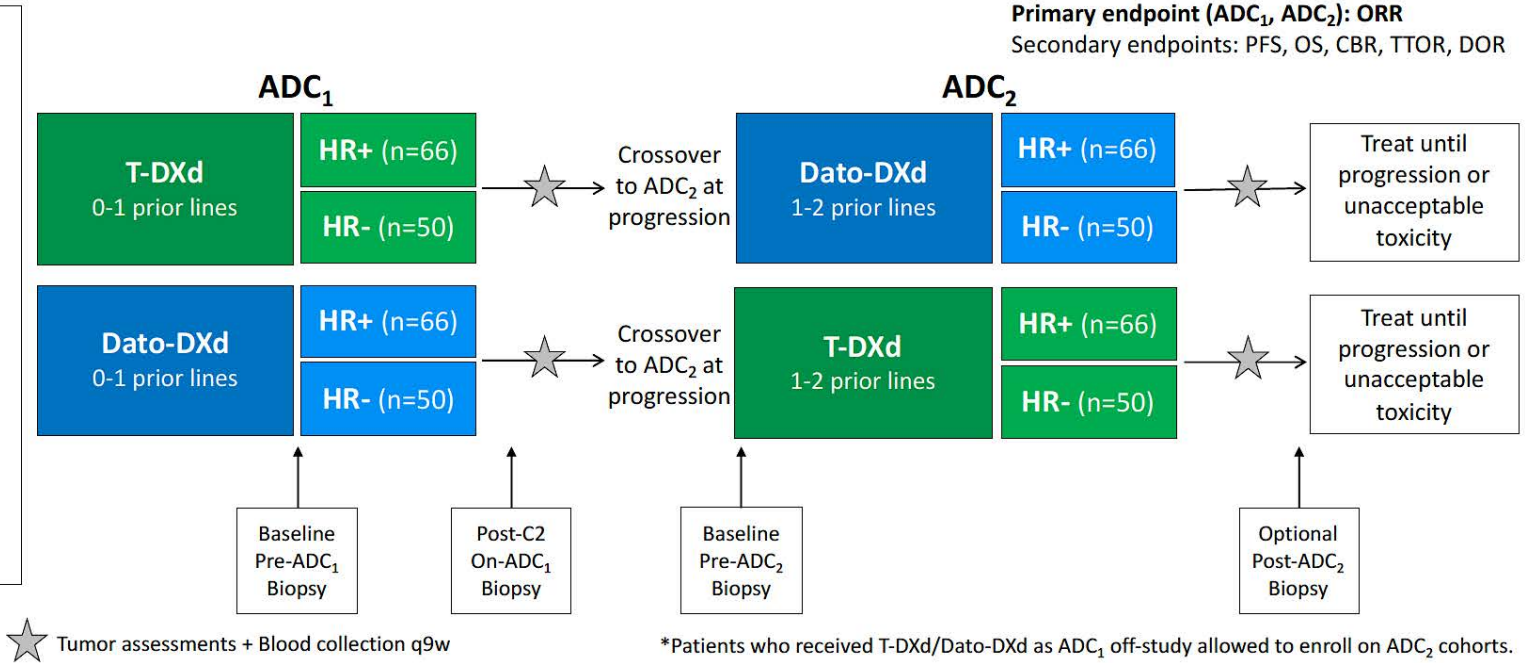
Abelman et. al. ASCO 2023

TBCRC 064: TReatment of ADC-Refractory Breast CancEr with Dato-DXd or T-DXd (TRADE-DXd).
PI: Ana Garrido-Castro

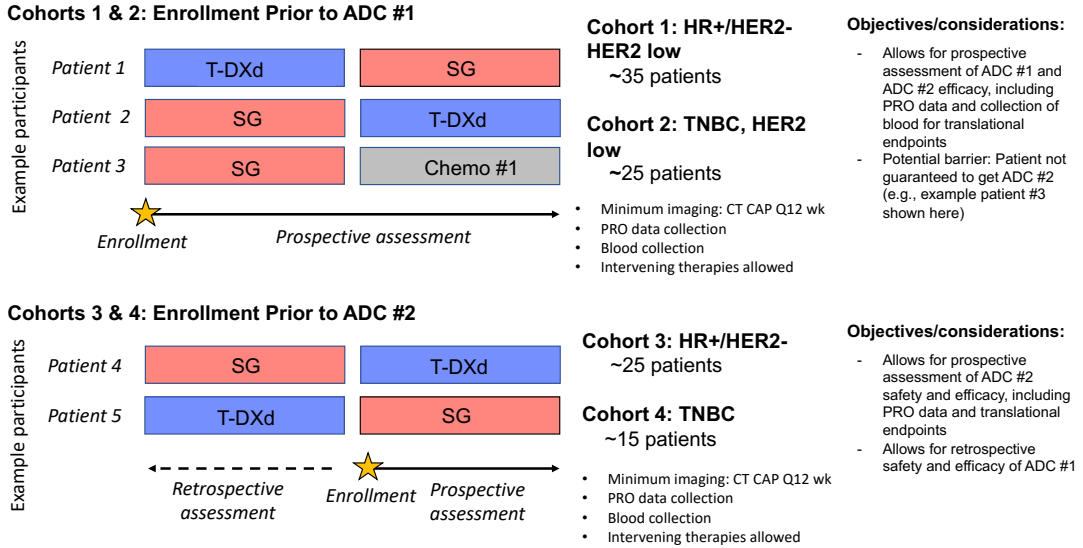
Eligibility:

- Confirmed unresectable locally advanced or metastatic disease
- History of HER2-low BC: IHC 1+ or 2+/ISH- (any sample: primary or met)
- Measurable disease
- Prior endocrine therapy and CDK4/6 inhibitor for HR+ MBC
- Prior topo-I inhibitor allowed only in neo-/adjuvant setting(s) and if ≥12m elapsed since last dose to metastatic recurrence

*Randomization 1:1 to T-DXd or Dato-DXd as ADC_1 for allocation purposes.

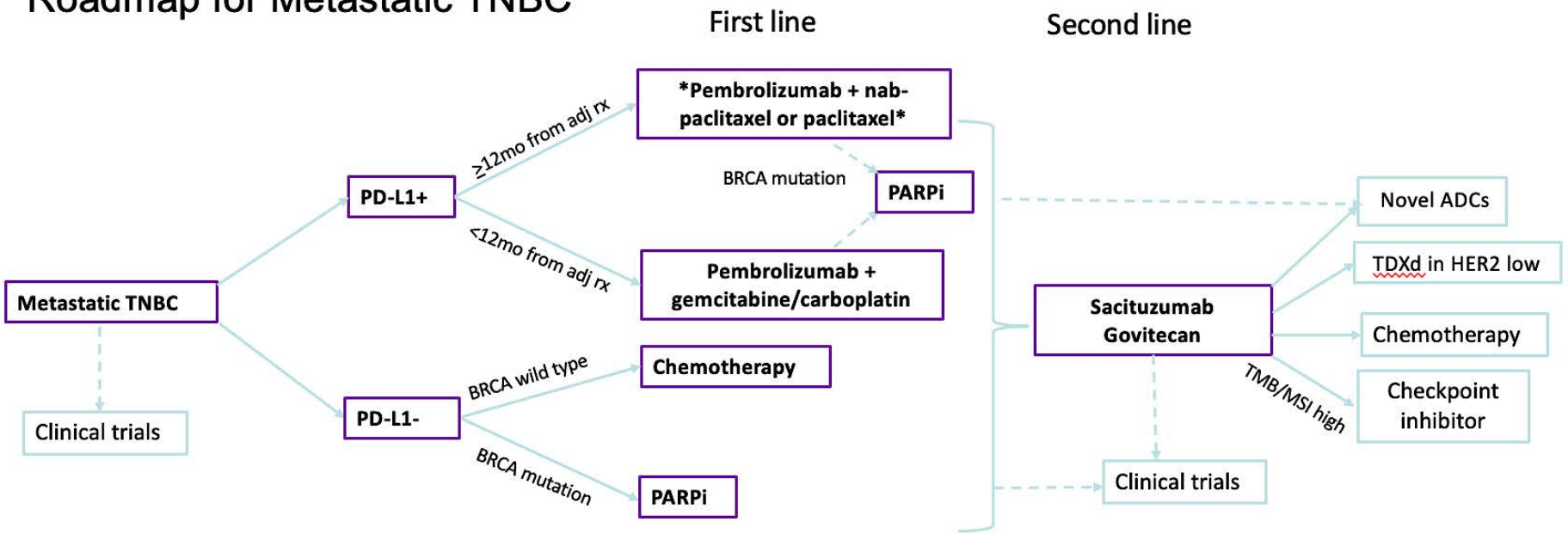


Registry Sequencing Study: Laura Huppert UCSF

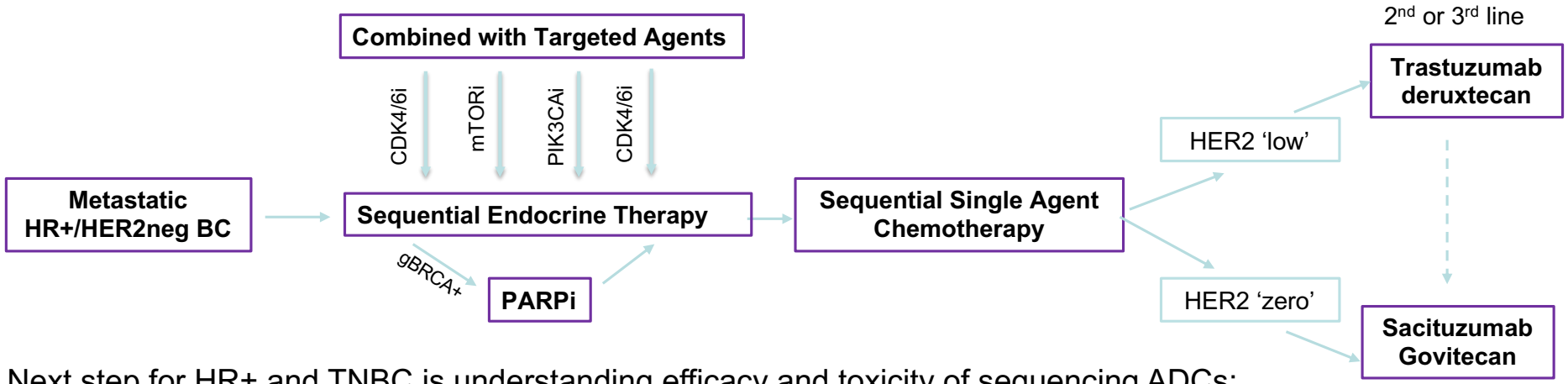


Stay tuned for more data on sequencing:
PS-08
Wednesday 5:30pm
PS08-02-04

Roadmap for Metastatic TNBC



Roadmap for HR+/HER2- Metastatic Breast Cancer



Next step for HR+ and TNBC is understanding efficacy and toxicity of sequencing ADCs:

- TRADE-DXd (DFCI): DATO-Dxd and TDXd
- Sacituzumab sequenced registry trial (UCSF): SG and TDXd

Agenda

Module 1: Optimal Integration of CDK4/6 Inhibitors into the Management of ER-Positive Metastatic Breast Cancer (mBC) — Dr Kaklamani

Module 2: Novel Strategies to Overcome Resistance to Endocrine Therapy — Dr Jhaveri

Module 3: Current Role of Antibody-Drug Conjugates in the Management of ER-Positive mBC — Dr Rugo

Module 4: Current and Future Role of Selective Estrogen Receptor Degraders (SERDs) in the Management of ER-Positive mBC — Prof Bidard

Module 5: Novel Therapies Under Investigation for Patients with ER-Positive mBC — Dr Hamilton

RTP
RESEARCH
TO PRACTICE

Based on your personal clinical experience and knowledge of available data, for each of the following agents please estimate the chance that a patient will experience toxicity during treatment that will require withholding administration. What is the primary toxicity patients experience that leads to withholding the drug?

	Chance of withholding*	Primary toxicity
Elacestrant	5% (5% - 25%)	Nausea/GI toxicity
Camizestrant	7% (2% - 20%)	Photopsia, bradycardia
Imlunestrant	5% (2% - 20%)	Nausea/GI toxicity
Capivasertib	13% (5% - 40%)	Rash, GI toxicity

*** Median (Range)**

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

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

- Certainly for patients with metastatic ER+ breast cancer who had ESR1 mutations and had progressed on prior endocrine therapy but were still felt to be endocrine sensitive
- ESR1-mutant pts — toss up between camizestrant and elacestrant — they could be sequenced
- Patients with ESR1 mutation being detected while on 1st line AI+CDK4/6i
- The SERENA-2 patient population: post-menopausal patients with estrogen receptor (ER)-positive locally advanced or metastatic breast cancer, previously treated with endocrine therapy for advanced disease
- Depends on whether it is restricted to only ESR1, if it isn't I would use for all pts post AI + CDK4/6
- Patients with ESR1 mutant disease and indolent pace of progression

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

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

- ESR1mt tumors esp if had >12m PFS on ET + CDK4/6i although might be harder drug than Elacestrant
- Depends on if label extends beyond ESR1 mutation.Probably would be alternative to fulvestrant.
- We need more data to make this decision as we do not have phase III data yet. So we dont know if it will work for all or only those with ESR1 mutations.
- Not sure
- ESR1 mutant after fulvestrant

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Elacestrant for recurrent ER-positive metastatic breast cancer harboring an ESR1 mutation; management of recurrent ER-positive metastatic breast cancer

Jane Lowe Meisel, MD

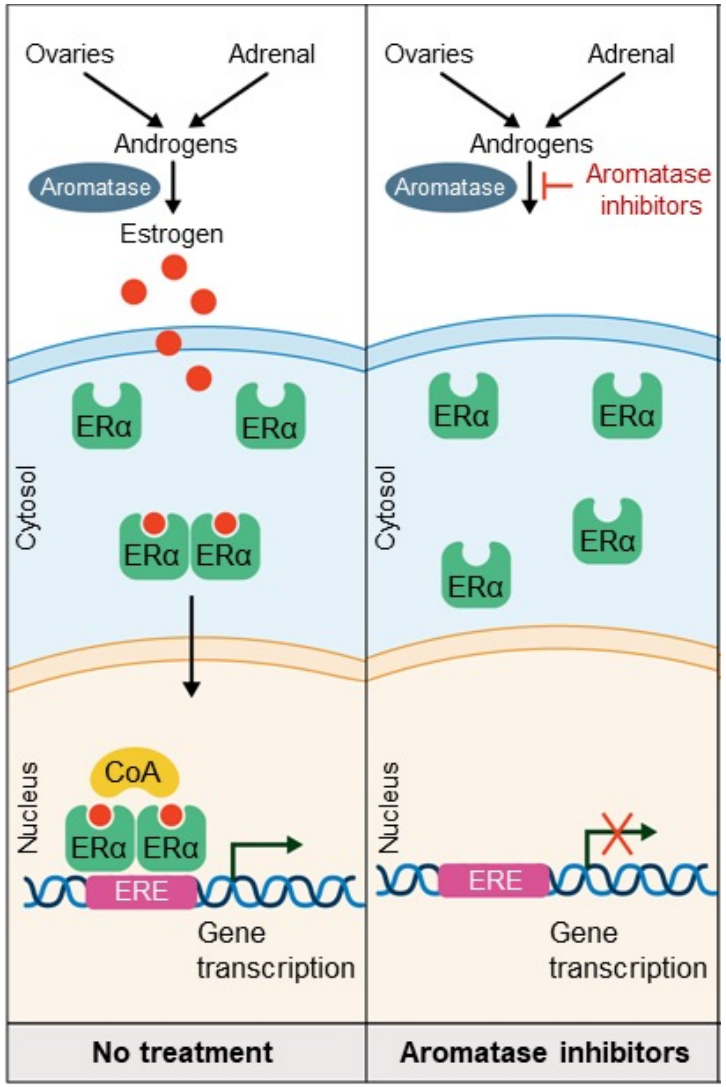
RTP
RESEARCH
TO PRACTICE

Current and Future Role of Selective Estrogen Receptor Degraders (SERDs) in the Management of ER-Positive mBC

Francois-Clement Bidard, MD PhD

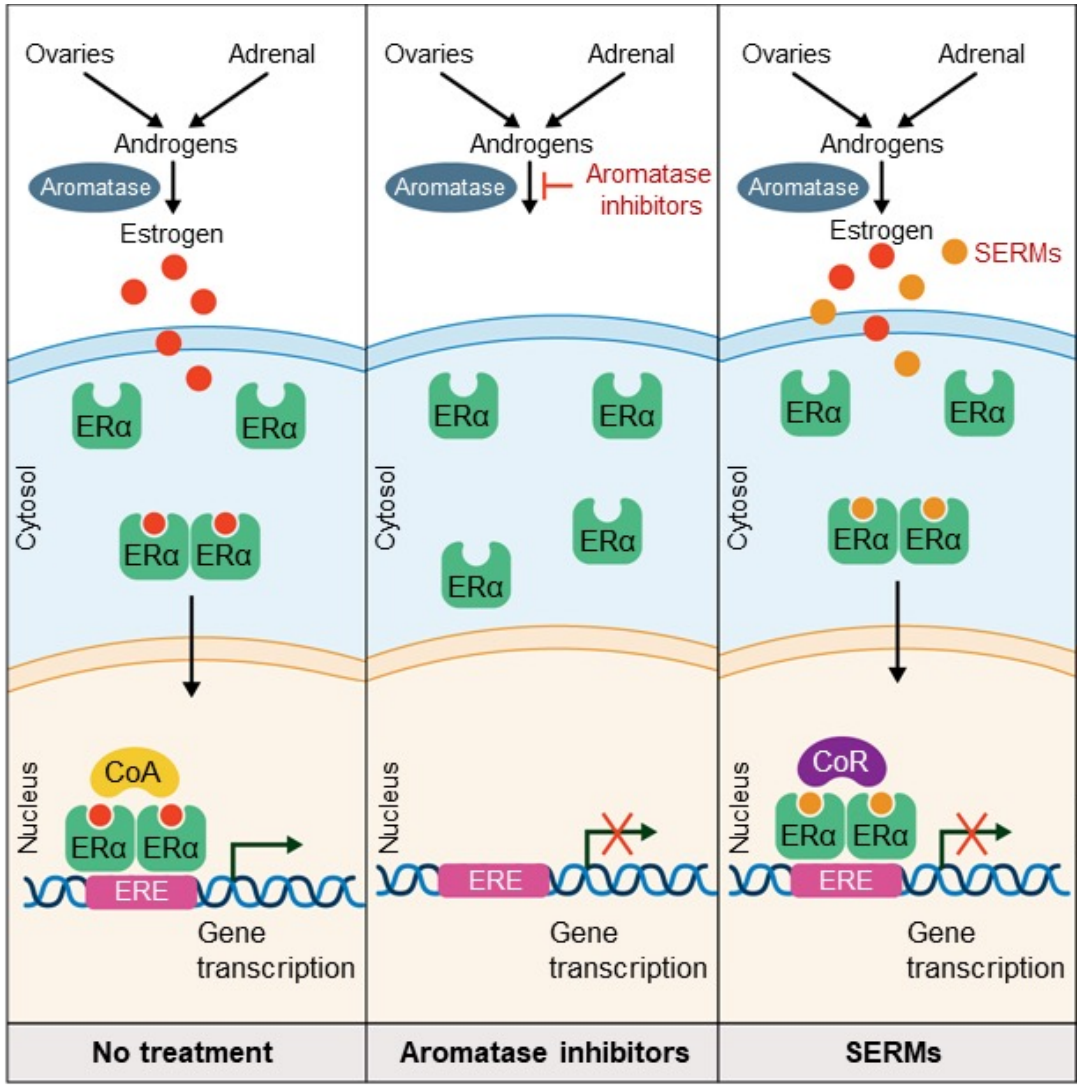
Institut Curie & Université de Versailles / Paris-Saclay

Mechanisms of action of endocrine therapies



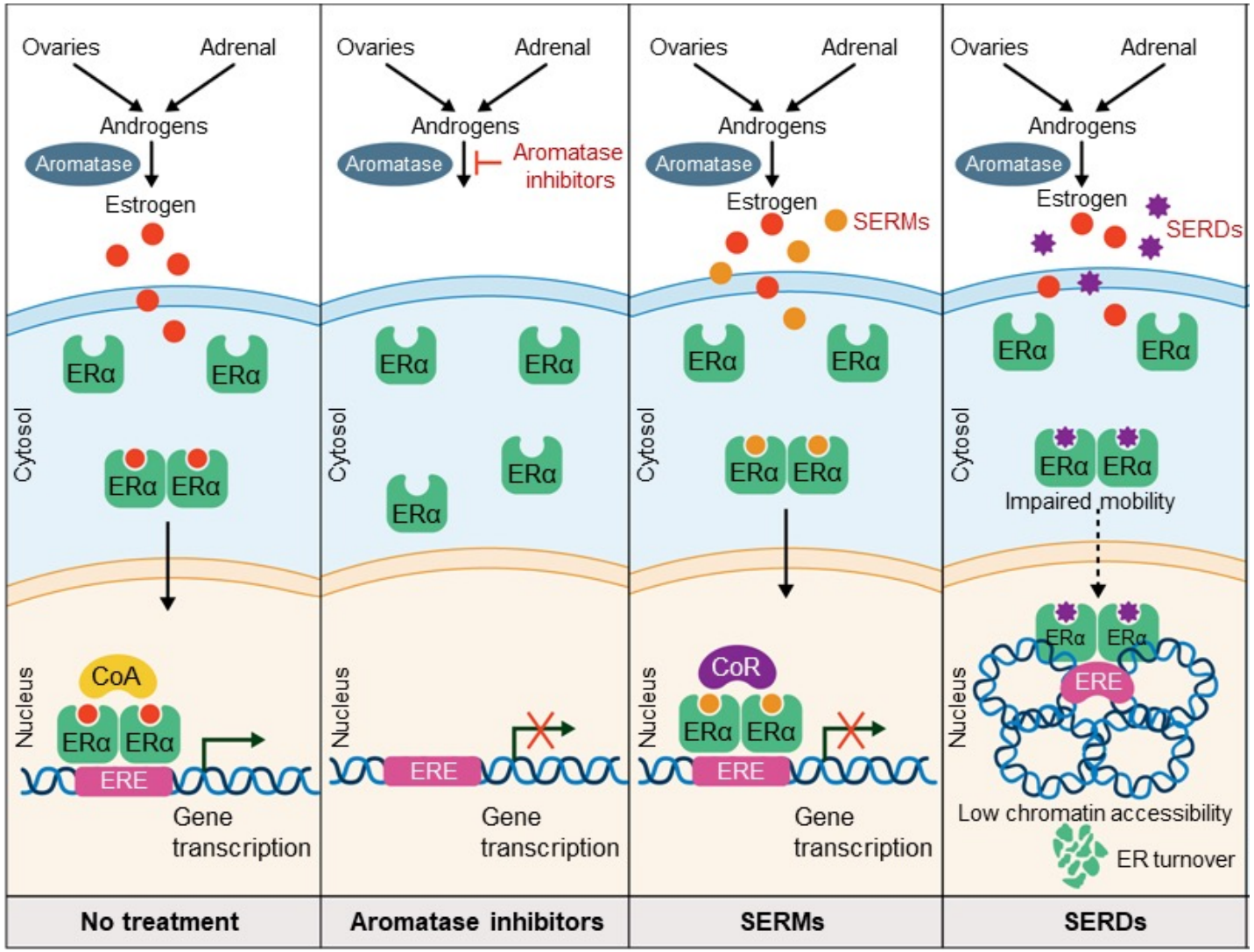
1. Hanker AB et al. *Cancer Cell*. 2020;37:496-513.

Mechanisms of action of endocrine therapies



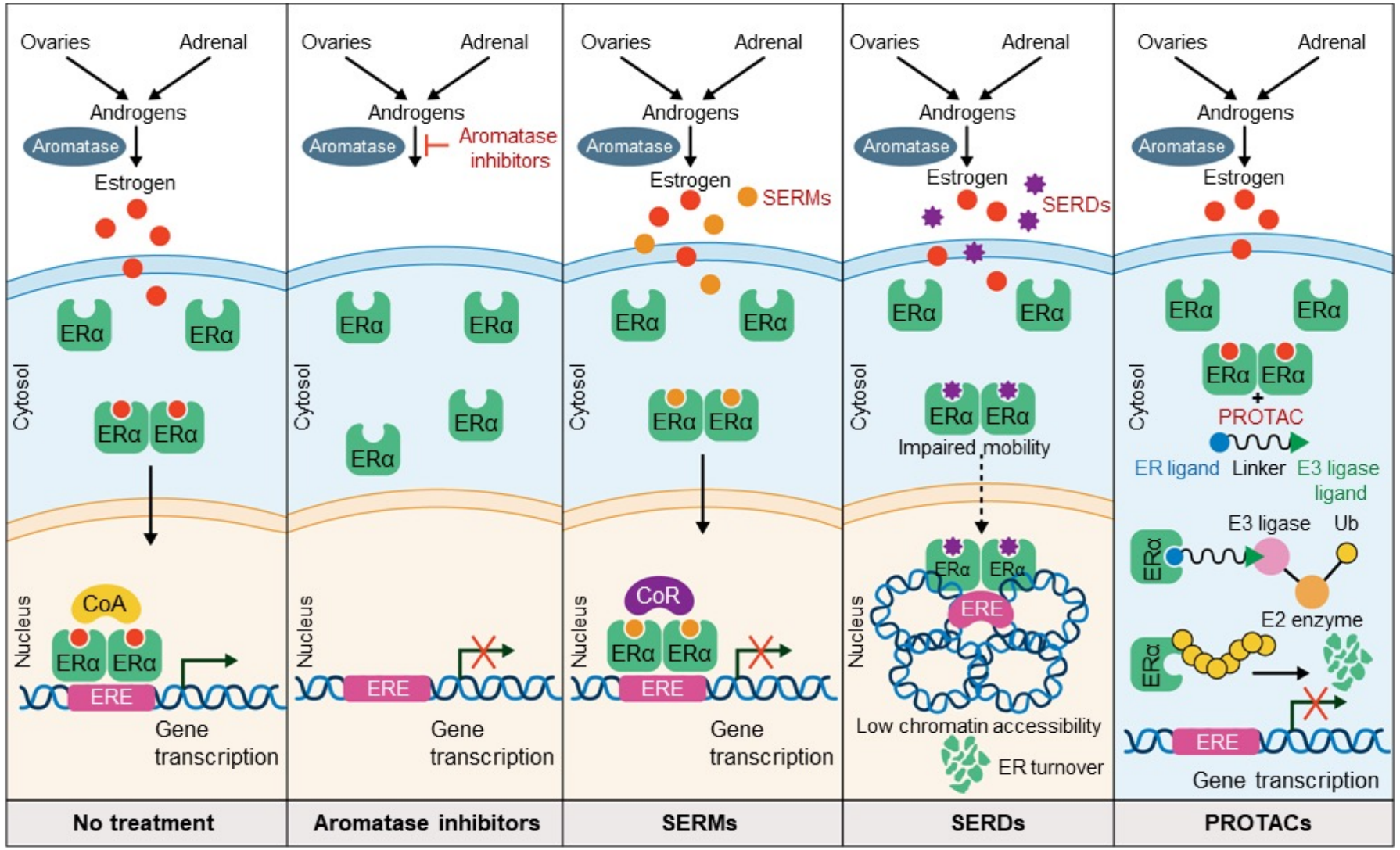
1. Hanker AB et al. *Cancer Cell*. 2020;37:496-513.

Mechanisms of action of endocrine therapies



1. Hanker AB et al. *Cancer Cell*. 2020;37:496-513.

Mechanisms of action of endocrine therapies



Estrogen Receptor therapeutic ligands

Estrogen Receptor therapeutic ligands

All these drugs target ER-dependent tumor growth

Different MoA can have implications on:

- Clinical efficacy
- Safety
- Predictive biomarkers

1. Hanker AB et al. *Cancer Cell*. 2020;37:496-513.

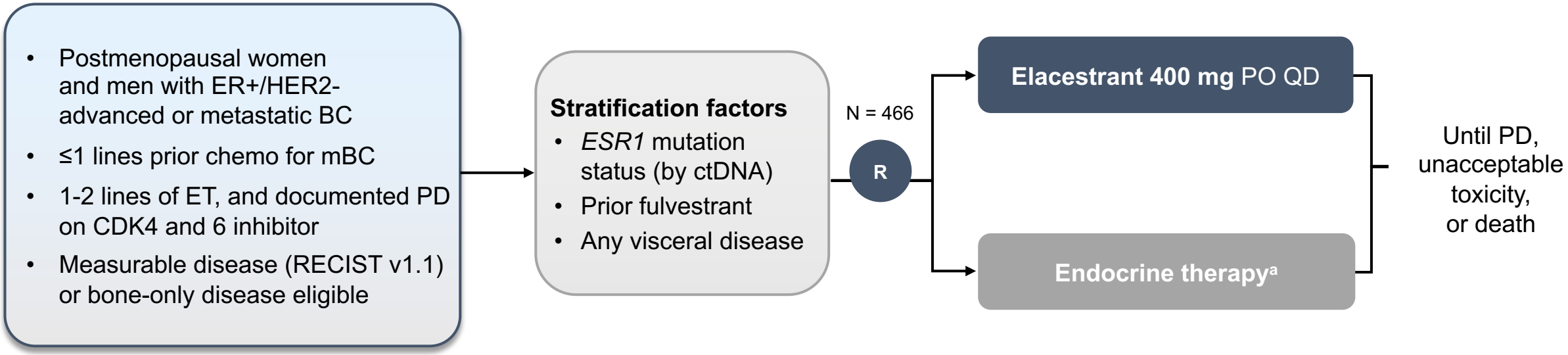
Current landscape of registrational trials with next generation SERDs & PROTAC

	2nd-3rd line Single agent	2nd line Combo	1st line HER2+ ER+ Combo with trastu/pertu.	*ESR1*$_{mut}$+ 1.5th line Combo with CDK4/6i	1st line Combo with CDK4/6i	Adjuvant late switch Single agent	Adjuvant frontline Single agent
Elacestrant	**EMERALD**					Treat ctDNA	
Giredestrant	**acelERA**	**evERA** (everolimus)	**heredERA**		**perservERA**		lidERA
Camizestrant	SERENA-2 (*)			**SERENA-6**	**SERENA-4**	CAMBRIA-1	CAMBRIA-2
Imlunestrant	**EMBER-3** (+/- abemaciclib)					EMBER-4	
Vepdegestrant (PROTAC)	**VERITAC-2**				**VERITAC-3**		

Source: clinicaltrials.gov, accessed on nov 15, 2023
(*) SERENA-2 was a non- registrational phase 2

EMERALD trial: study design

Randomized, Open-Label Phase 3 Study



- **Primary endpoint:** PFS by BICR in all patients and in patients with mutant *ESR1*
  - Overall population (power ≥90% for HR of 0.667) or *ESR1*-mutated subset (power ≥80% for HR of 0.610) at an overall α level of 5%
- **Secondary endpoints:** OS, PFS by BICR in patients with WT *ESR1*, PFS by investigator review, ORR, DOR, CBR, safety, PK, and QoL

[a] Investigator's choice of fulvestrant 500 mg IM on days 1 and 15 of cycle 1 and then on day 1 of 28-day cycles or an AI (continuous dosing of anastrozole 1 mg/day, letrozole 2.5 mg/day, or exemestane 25 mg/day).

1. Bardia A et al. ASCO 2019. Abstract TPS1104.

EMERALD trial: population

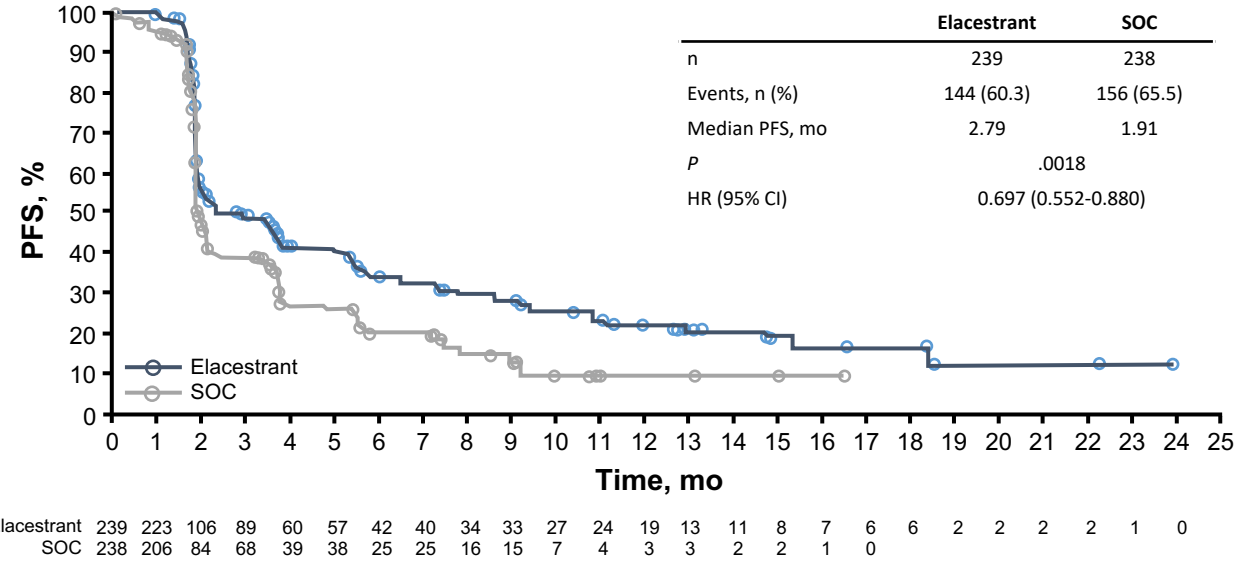
Parameter	Elacestrant		SOC	
	All (n = 239)	*ESR1*mut (n = 115)	All (n = 238)	*ESR1*mut (n = 113)
Median age, years (range)	63.0 (24-89)	64.0 (28-89)	63.5 (32-83)	63.0 (32-83)
Gender, n % Female Male	 233 (97.5) 6 (2.5)	 115 (100) 0	 237 (99.6) 1 (0.4)	 113 (100) 0
ECOG PS, n (%) 0 1 >1	 143 (59.8) 96 (40.2) 0	 67 (58.3) 48 (41.7) 0	 135 (56.7) 102 (42.9) 1 (0.4)	 62 (54.9) 51 (45.1) 0
Visceral metastasis[a], n (%)	163 (68.2)	81 (70.4)	168 (70.6)	83 (73.5)
Bone-only disease, n (%)	38 (15.9)	14 (12.2)	29 (12.2)	14 (12.4)
Prior adjuvant therapy, n (%)	158 (66.1)	62 (53.9)	141 (59.2)	65 (57.5)
Number of prior lines of endocrine therapy[b], n (%) 1 2	 129 (54.0) 110 (46.0)	 73 (63.5) 42 (36.5)	 141 (59.2) 97 (40.8)	 69 (61.1) 44 (38.9)
Number of prior lines of chemotherapy[b], n (%) 0 1	 191 (79.9) 48 (20.1)	 89 (77.4) 26 (22.6)	 180 (75.6) 58 (24.4)	 81 (71.7) 32 (28.3)

[a] Includes lung, liver, brain, pleural, and peritoneal involvement. [b] In the advanced/metastatic setting.

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

EMERALD trial: results

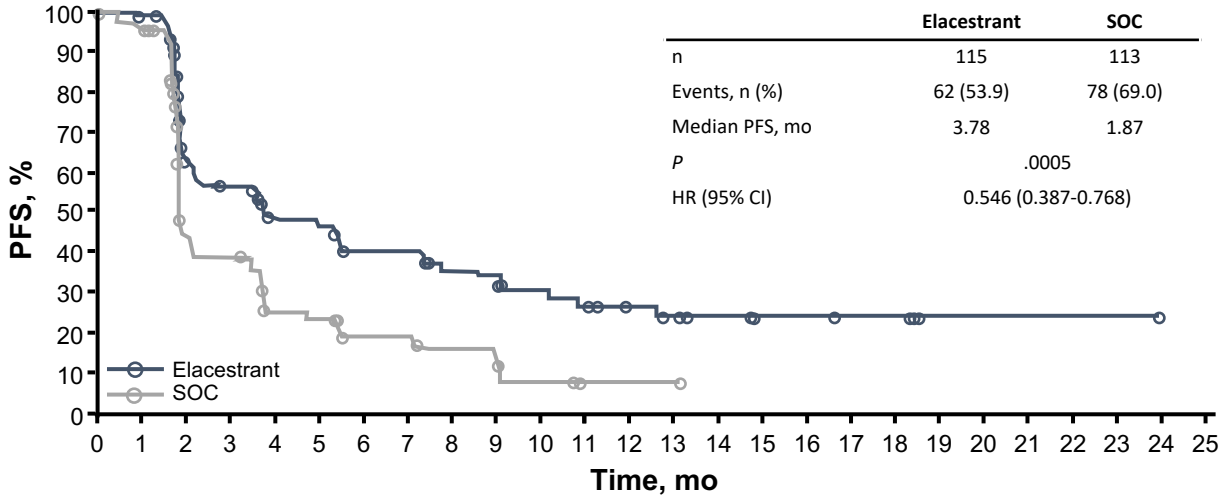
All Patients (ITT)



	Elacestrant	SOC
n	239	238
Events, n (%)	144 (60.3)	156 (65.5)
Median PFS, mo	2.79	1.91
P	.0018	
HR (95% CI)	0.697 (0.552-0.880)	

Elacestrant is associated with a 30% reduction in the risk of progression or death in all patients with ER+/HER2- mBC

Patients With Tumors Harboring *ESR1*mut



	Elacestrant	SOC
n	115	113
Events, n (%)	62 (53.9)	78 (69.0)
Median PFS, mo	3.78	1.87
P	.0005	
HR (95% CI)	0.546 (0.387-0.768)	

Elacestrant is associated with a 45% reduction in the risk of progression or death in patients harboring *ESR1*mut

Bidard FC et al .J Clin Oncol 2022

Subgroup analysis of EMERALD

Patients with *ESR1*-mut Tumors: PFS by Duration of CDK4/6i

Magnitude of Benefit is Greater With Longer Exposure to CDK4/6i

Duration on CDK4/6i in the metastatic setting

	At Least 6 Months (92.3%)		At Least 12 Months (71.6%)		At Least 18 Months (50.0%)	
	Elacestrant (n=103)	SOC Hormonal Therapy (n=102)	Elacestrant (n=78)	SOC Hormonal Therapy (n=81)	Elacestrant (n=55)	SOC Hormonal Therapy (n=56)
Median PFS, months (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)
PFS rate at 6 months, % (95% CI)	42.43 (31.15 - 53.71)	19.15 (9.95 - 28.35)	55.81 (42.69 - 68.94)	22.66 (11.63 - 33.69)	58.57 (43.02 - 74.12)	27.06 (13.05 - 41.07)
PFS rate at 12 months, % (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)
PFS rate at 18 months, % (95% CI)	20.70 (9.77 - 31.63)	0.00 (. - .)	28.49 (14.08 - 42.89)	0.00 (. - .)	30.68 (13.94 - 47.42)	0.00 (. - .)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)		**0.410** (0.262 - 0.634)		**0.466** (0.270 - 0.791)	

Kaklamani et al, SABCS 2022, Abstract GS3-01.

EMERALD trial: Toxicity

- Most adverse events (AEs), including nausea, were grade 1 and 2, and no grade 4 treatment-related AEs (TRAEs) were reported.
- Only 3.4% of patients receiving elacestrant and 0.9% receiving SOC discontinued therapy due to any TRAE.
- No deaths assessed as treatment-related were reported in either arm.
- No hematologic safety signal was observed, and none of the patients in either treatment arm had sinus bradycardia.
- Dyslipidemia was infrequent, mostly grade 1, there were no discontinuations, and it was similar to SoC.

Nausea Summary	Elacestrant (n=237)	SOC (n=230)
Grade 3 nausea, n (%)	6 (2.5%)	2 (0.9%)
Dose-reduction rate due to nausea, n (%)	3 (1.3%)	Not applicable
Discontinuation rate due to nausea, n (%)	3 (1.3%)	0 (0%)
Antiemetic use	8%	10.3% (AI) 1.3% (Ful)

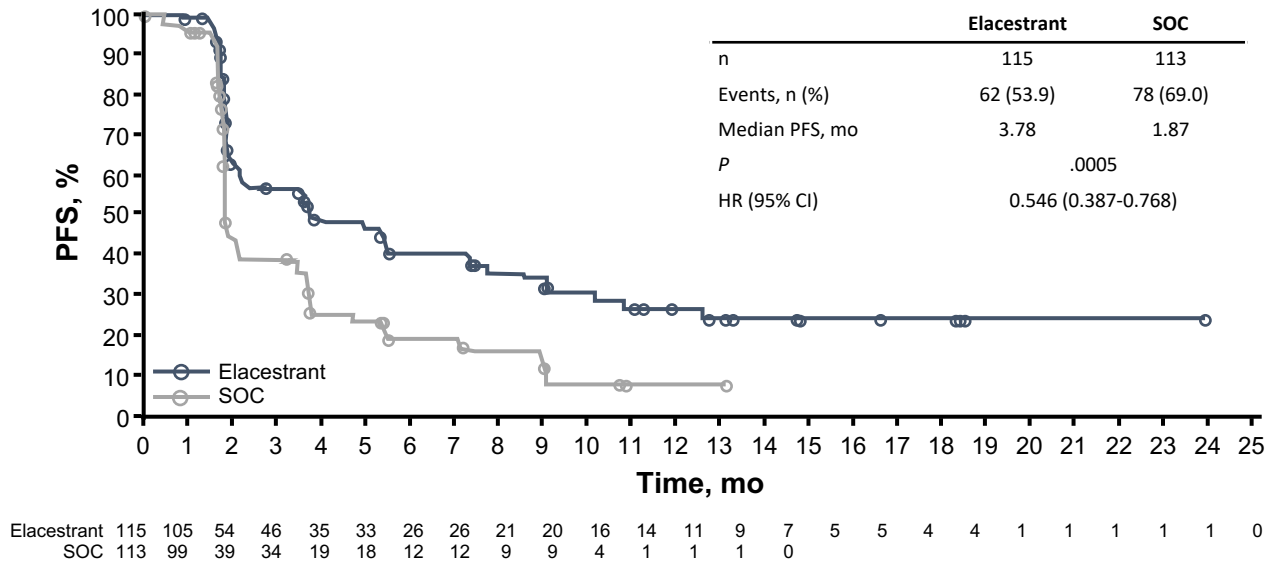
Bardia A et al. SABCS 2022 Abstract GS3-01.

EMERALD trial results led to FDA and EMA approvals in 2023

FDA label postmenopausal women or adult men with ER+, HER2-, **ESR1-mutated** advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.

EMA label: Elacestrant monotherapy is indicated for the treatment of postmenopausal women, and men, with ER+, HER2-locally advanced or metastatic breast cancer with an **activating ESR1 mutation** who have disease progression following at least one line of endocrine therapy including a CDK4/6 inhibitor

Patients With Tumors Harboring *ESR1*mut



	Elacestrant	SOC
n	115	113
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Median PFS, mo	3.78	1.87
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HR (95% CI)	0.546 (0.387-0.768)	

Elacestrant is associated with a 45% reduction in the risk of progression or death in patients harboring *ESR1*mut

Phase 2 trials with other ngSERD confirmed the exquisite sensitivity of ESR1mut+ mBC

	PFS HR ngSERD vs SoC in mBC pts (all comers)	PFS HR ngSERD vs SoC in $ESR1_{mut}$ not detected mBC pts	PFS HR ngSERD vs SoC in $ESR1_{mut}$+ mBC pts
AcelERA (giredestrant) [1]	0.81 95%CI [0.60, 1.10]	N/A	0.60 95%CI [0.35, 1.03]
SERENA-2 (camizestrant) [2]	0.58 * 90%CI [0.41, 0.81]	0.76 * 90%CI [0.50, 1.22]	0.33 * 90%CI [0.18, 0.58]

Grade 3-4 adverse events were observed in 17% and 12% of patients receiving ngSERD in the acelERA and SERENA-2 trials, respectively.

* 75mg cohort

[1] Martin Jimenez, ESMO 2022
[2] Oliveira, SABCS 2022

Future challenges in ER+ HER2- mBC

Elacestrant is approved in 2+ line

- Implementing *ESR1$_{mut}$* testing on ctDNA in routine
- (bio)markers to predict long PFS ?

	2nd-3rd line Single agent	2nd line Combo	1st line HER2+ ER+ Combo with trastu/pertu.	*ESR1$_{mut}$*+ 1.5th line Combo with CDK4/6i	1st line Combo with CDK4/6i
Elacestrant	**EMERALD**				
Giredestrant	**acelERA**	**evERA** (everolimus)	**heredERA**		**perservERA**
Camizestrant	**SERENA-2** (*)			**SERENA-6**	**SERENA-4**
Imlunestrant	**EMBER-3** (+/- abemaciclib)				
Vepdegestrant (PROTAC)	**VERITAC-2**				**VERITAC-3**

Source: clinicaltrials.gov, accessed on nov 15, 2023

(*) SERENA-2 was a non- registrational phase 2

Future + HER2- mBCchallenges in ER

Elacestrant is approved in 2+ line

- Implementing *ESR1$_{mut}$* testing on ctDNA in routine
- (bio)markers to predict long PFS ?

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Imlunestrant	**EMBER-3** (+/- abemaciclib)				
Vepdegestrant (PROTAC)	**VERITAC-2**				**VERITAC-3**

Combination with targeted therapies

- Can it expand further the survival benefit ?
- Only in *ESR1$_{mut}$*+ or in all comers ?

Source: clinicaltrials.gov, accessed on nov 15, 2023
(*) SERENA-2 was a non- registrational phase 2

MADRID 2023 ESMO congress

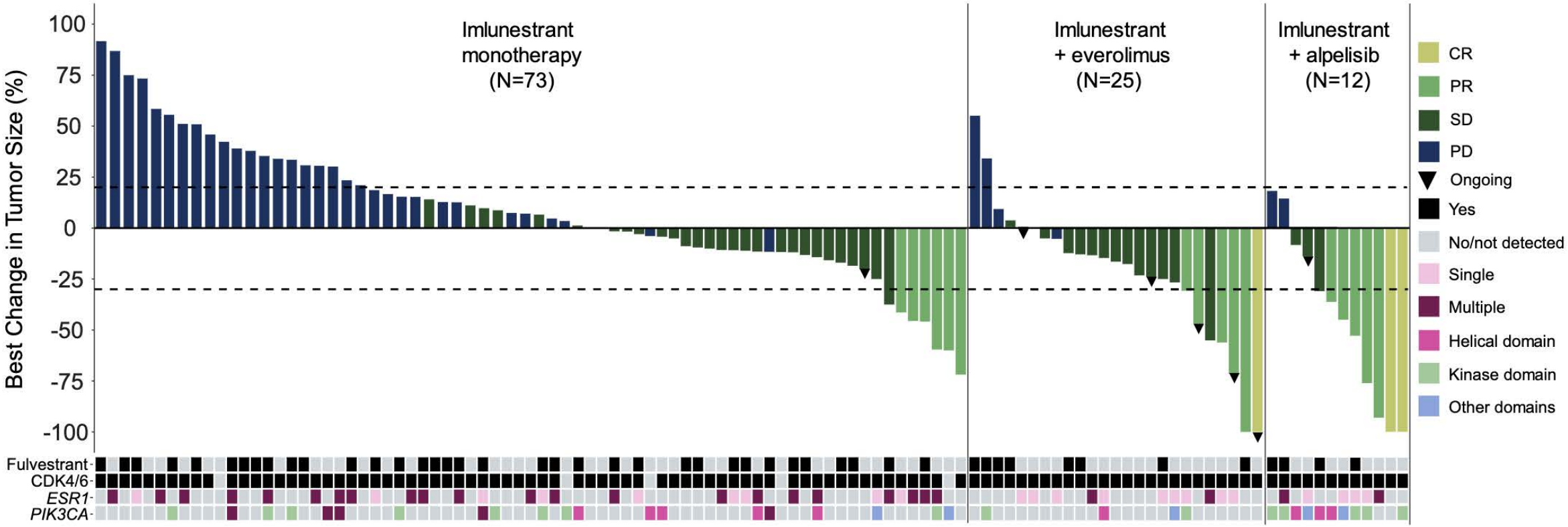
Imlunestrant, with or without everolimus or alpelisib, in ER+, HER2- advanced breast cancer (aBC): Results from the phase 1a/b EMBER study

Komal L. Jhaveri, Rinath Jeselsohn, Cynthia X. Ma, Elgene Lim, Kan Yonemori, Erika P. Hamilton, Kathleen Harnden, Seock-Ah Im, J. Thaddeus Beck, Sarah Sammons, Manali Bhave, Peter A. Kaufman, Cristina Saura, Tarek Meniawy, Francesca Bacchion, Roohi Ismail-Khan, Yujia Li, Shawn T. Estrem, Bastien Nguyen, Muralidhar Beeram.

Komal L. Jhaveri

New York, USA. 22nd October 2023

EMBER: Tumor Response in Patients with Measurable Disease



	Imlunestrant monotherapy (n=114)	Imlunestrant + everolimus (n=42)	Imlunestrant + alpelisib (n=21)
Objective Response Rate, n/N (%)	6/76 (8)	6/28 (21)	7/12 (58)
Clinical Benefit Rate, n (%)	48 (42)	26 (62)	13 (62)

Jhaveri K et al. ESMO 2023;Abstract 383MO.

EMBER: Safety

AE Term % [a]	Imlunestrant (n=114)		Imlunestrant + everolimus (n=42)		Imlunestrant + alpelisib (n=21)	
	Grade		Grade		Grade	
	All	≥3	All	≥3	All	≥3
Patients with ≥1 TEAE	93	21	100	43	100	81
Nausea	41	1	26	2	57	5
Fatigue	33	2	48	0	57	5
Diarrhea	31	2	57	2	86	10
AST increased	11	0	38	10	5	0
Decreased appetite	11	0	12	0	43	5
Vomiting	11	0	14	2	33	0
Rash	9	0	24	0	67	48
Hyperglycemia	5	0	19	0	62	10
Stomatitis	1	0	31	0	33	0
Hypercholesterolemia	1	0	33	0	0	0
Discontinuations due to TRAE, %	**0**		**7 [b]**		**34 [c]**	

[a] TEAEs occurring in ≥30% of at least one treatment cohort; [b] 5% everolimus alone; 2% everolimus and imlunestrant; 0% imlunestrant alone
[c] 29% alpelisib alone; 5% alpelisib and imlunestrant; 0% imlunestrant alone

Jhaveri K et al. ESMO 2023;Abstract 383MO.

Future challenges in ER+ HER2- mBC

Elacestrant is approved in 2+ line
- Implementing *ESR1*$_{mut}$ testing on ctDNA in routine
- (bio)markers to predict long PFS ?

	2nd-3rd line Single agent	2nd line Combo	1st line HER2+ ER+ Combo with trastu/pertu.	*ESR1*$_{mut}$+ 1.5th line Combo with CDK4/6i	1st line Combo with CDK4/6i
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Giredestrant	acelERA	evERA (everolimus)	heredERA		perservERA
Camizestrant	SERENA-2 (*)			SERENA-6	SERENA-4
Imlunestrant	EMBER-3 (+/- abemaciclib)				
Vepdegestrant (PROTAC)	VERITAC-2				VERITAC-3

Targeting *ESR1*$_{mut}$ as soon as they appear
- Building on PADA-1 results, with a more active drug

Combination with targeted therapies
- Can it expand further the survival benefit ?
- Only in *ESR1*$_{mut}$+ or in all comers ?

Source: clinicaltrials.gov, accessed on nov 15, 2023
(*) SERENA-2 was a non- registrational phase 2

Future challenges in ER+ HER2- mBC

Elacestrant is approved in 2+ line
- Implementing *ESR1$_{mut}$* testing on ctDNA in routine
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Imlunestrant	EMBER-3 (+/- abemaciclib)				
Vepdegestrant (PROTAC)	VERITAC-2				VERITAC-3

Frontline use in 1st line
- Preventing the onset of *ESR1$_{mut}$?*
- And more ?

Combination with targeted therapies
- Can it expand further the survival benefit ?
- Only in *ESR1$_{mut}$*+ or in all comers ?

Source: clinicaltrials.gov, accessed on nov 15, 2023
(*) SERENA-2 was a non- registrational phase 2

Future challenges in ER+ HER2- mBC

Elacestrant is approved in 2+ line
- Implementing *ESR1$_{mut}$* testing on ctDNA in routine
- (bio)markers to predict long PFS ?

Differences between drugs
- Toxicities
- (bio)markers

	2nd-3rd line Single agent	2nd line Combo	1st line HER2+ ER+ Combo with trastu/pertu.	*ESR1$_{mut}$*+ 1.5th line Combo with CDK4/6i	1st line Combo with CDK4/6i
Elacestrant	EMERALD				
Giredestrant	acelERA	evERA (everolimus)	heredERA		perservERA
Camizestrant	SERENA-2 (*)			SERENA-6	SERENA-4
Imlunestrant	EMBER-3 (+/- abemaciclib)				
Vepdegestrant (PROTAC)	VERITAC-2				VERITAC-3

Targeting *ESR1$_{mut}$* as soon as they appear
- Early intervention delayed tumor resistance [PADA-1] [1]
- Now tested with a more active drug

Frontline use in 1st line
- Preventing the onset of *ESR1$_{mut}$* ?
- And more ?

Combination with targeted therapies
- Can it expand further the survival benefit ?
- Only in *ESR1$_{mut}$*+ or in all comers ?

Source: clinicaltrials.gov, accessed on nov 15, 2023
(*) SERENA-2 was a nonregistrational phase 2 trial

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 RESEARCH TO PRACTICE

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

Mafalda Oliveira, MD, PhD[1], Denys Pominchuk, PhD[2], Zbigniew Nowecki MD[3], Erika Hamilton, MD[4], Yaroslav Kulyaba, MD[5], Timur Andabekov, PhD[6], Yevhen Hotko, MD[7], Tamar Melkadze, MD[8], Gia Nemsadze, MD, PhD[9], Patrick Neven, MD[10], Yuriy Semegen, MD[11], Vladimir Vladimirov, MD[12], Claudio Zamagni, MD[13], Hannelore Denys, MD, PhD[14], Frédéric Forget, MD[15], Zsolt Horvath, MD, PhD[16], Alfiya Nesterova, MD, PhD[17], Maxine Bennett, PhD[18], Bistra Kirova, MBChB, MSc[19], Teresa Klinowska, PhD[20], Justin P O Lindemann, MBChB, MB[18], Delphine Lissa, PharmD, PhD[18], Alastair Mathewson, PhD[18], Christopher J Morrow, PhD[18], Zuzana Traugottova, MD[21], Ruaan van Zyl, PhD[22], Ekaterine Arkania, MD[23]

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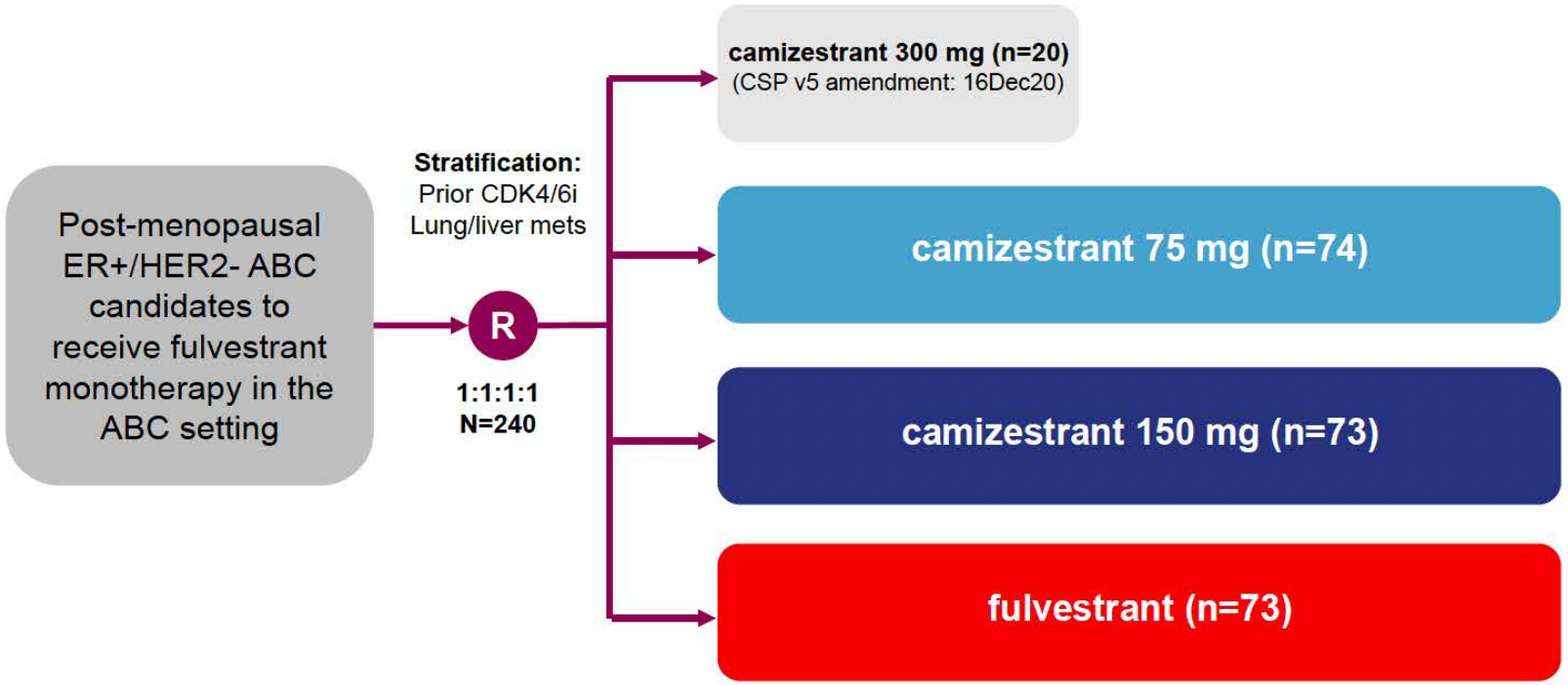
Oliveira M et al. SABCS 2022; Abstract GS3-02.

SERENA-2: Study Overview

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

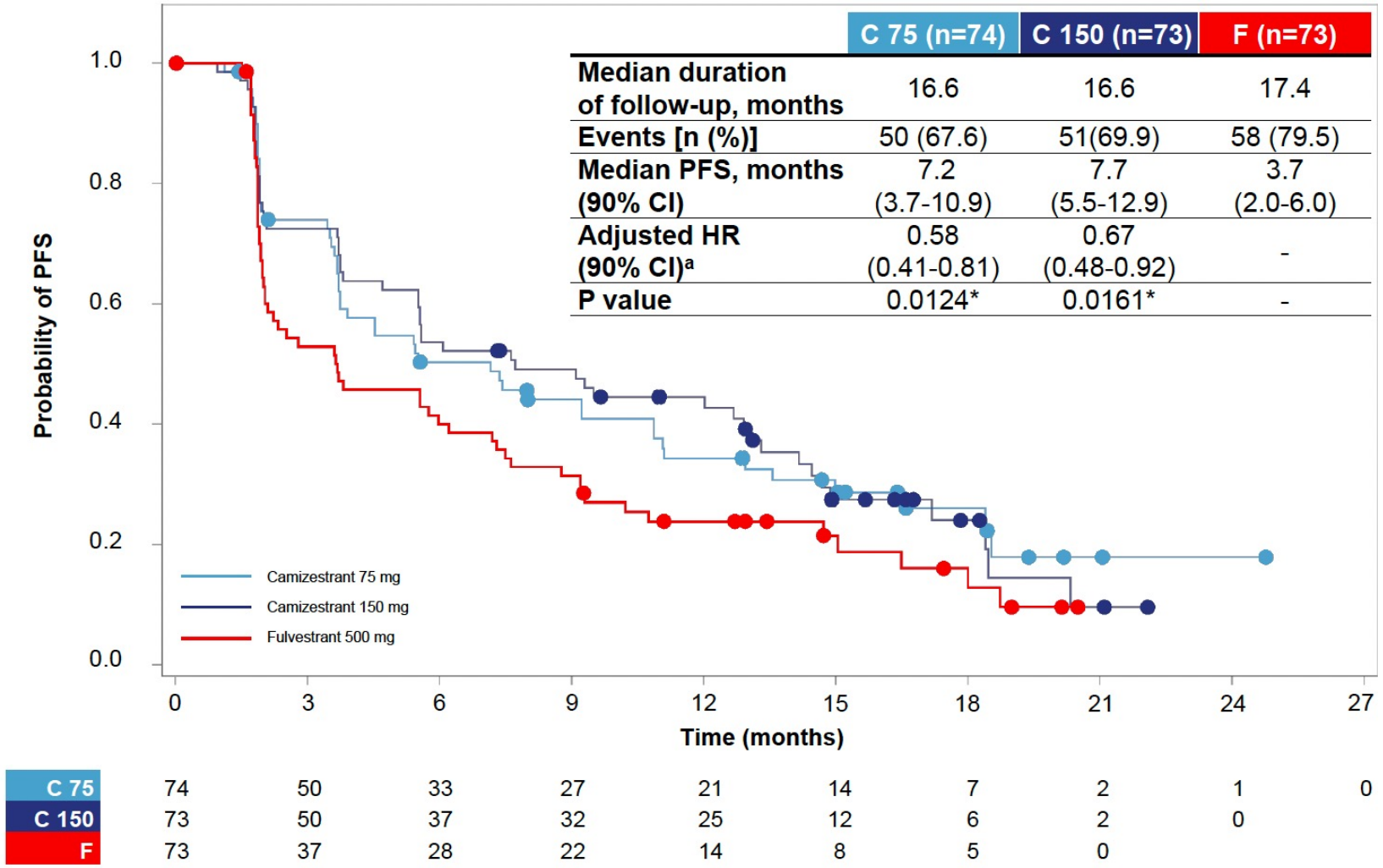


- **Primary endpoint:** PFS (investigator assessment*)
- **Secondary endpoints:** CBR24, ORR, OS, safety
- **Translational endpoints:** serial ctDNA analysis including *ESR1*m, serial CTCs analysis

*disease progression assessed by the Investigator and defined using RECIST, version 1.1
ABC: advanced breast cancer; CBR24: clinical benefit rate at 24 weeks; CDK4/6i: CDK4/6 inhibitor; CT: chemotherapy; CTC: circulating tumor cells; ctDNA: circulating tumor DNA; ER: estrogen receptor; *ESR1*m: mutation in estrogen receptor 1 gene; ET: endocrine therapy; HER2: human epidermal growth factor; PFS: progression-free survival; R: randomization; RECIST: Response Evaluation Criteria for Solid Tumors; SERD: selective estrogen receptor degrader

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

SERENA-2: PFS by Investigator Assessment



	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		

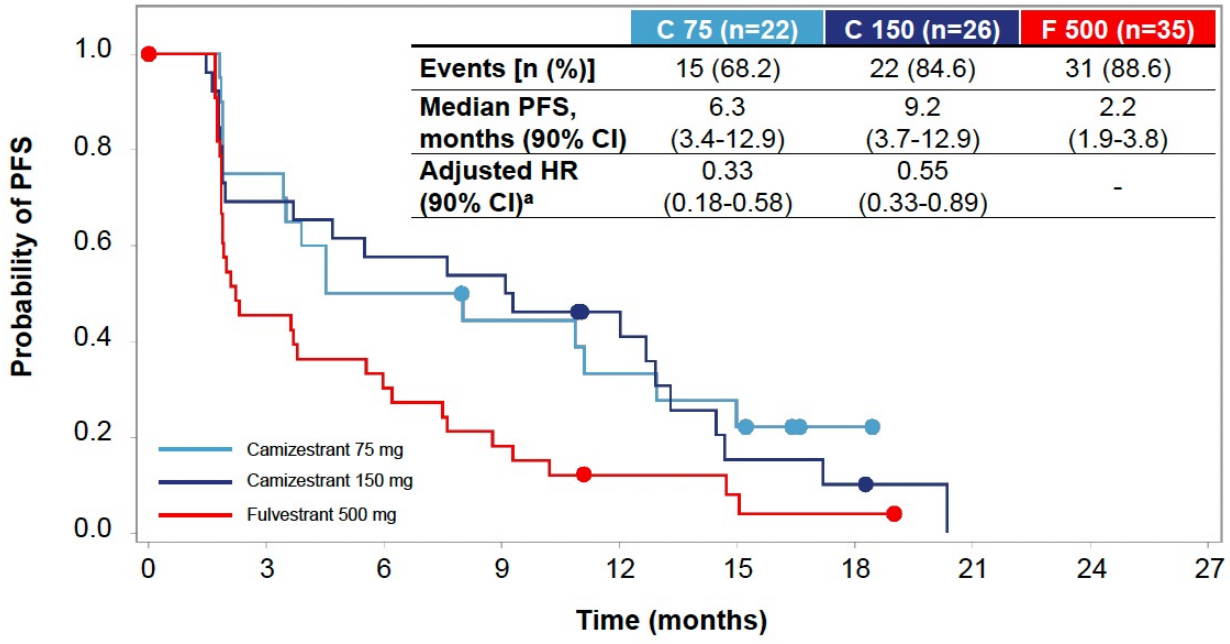
In the overall population, camizestrant produces a statistically significant and clinically meaningful improvement in PFS for both 75 and 150 mg camizestrant doses over fulvestrant

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

RTP RESEARCH TO PRACTICE

SERENA-2: PFS in Patients by Detectable *ESR1*m

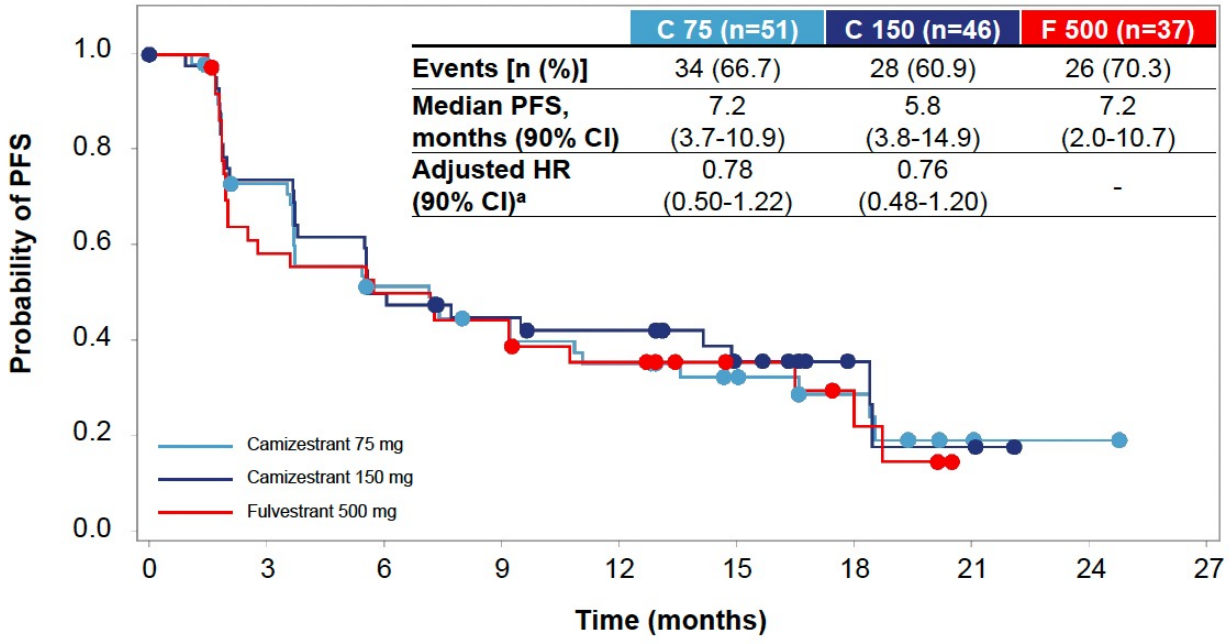
*ESR1*m detectable at baseline



	C 75 (n=22)	C 150 (n=26)	F 500 (n=35)
Events [n (%)]	15 (68.2)	22 (84.6)	31 (88.6)
Median PFS, months (90% CI)	6.3 (3.4-12.9)	9.2 (3.7-12.9)	2.2 (1.9-3.8)
Adjusted HR (90% CI)[a]	0.33 (0.18-0.58)	0.55 (0.33-0.89)	-

C 75	22	15	10	8	6	4	1	0	
C 150	26	18	15	14	9	3	2	0	
F	35	15	10	6	3	2	1	0	

*ESR1*m not detectable at baseline



	C 75 (n=51)	C 150 (n=46)	F 500 (n=37)
Events [n (%)]	34 (66.7)	28 (60.9)	26 (70.3)
Median PFS, months (90% CI)	7.2 (3.7-10.9)	5.8 (3.8-14.9)	7.2 (2.0-10.7)
Adjusted HR (90% CI)[a]	0.78 (0.50-1.22)	0.76 (0.48-1.20)	-

C 75	51	34	23	19	15	10	6	2	1	0
C 150	46	31	21	17	15	9	4	2	0	
F	37	21	18	16	11	6	4	1	0	

- In the sub-population of patients with detectable *ESR1*m at baseline, camizestrant at both doses produces a clinically meaningful improvement in PFS over fulvestrant

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

RTP RESEARCH TO PRACTICE

Agenda

Module 1: Optimal Integration of CDK4/6 Inhibitors into the Management of ER-Positive Metastatic Breast Cancer (mBC) — Dr Kaklamani

Module 2: Novel Strategies to Overcome Resistance to Endocrine Therapy — Dr Jhaveri

Module 3: Current Role of Antibody-Drug Conjugates in the Management of ER-Positive mBC — Dr Rugo

Module 4: Current and Future Role of Selective Estrogen Receptor Degraders (SERDs) in the Management of ER-Positive mBC — Prof Bidard

Module 5: Novel Therapies Under Investigation for Patients with ER-Positive mBC — Dr Hamilton

RTP RESEARCH TO PRACTICE

Based on your personal clinical experience and knowledge of available data, for each of the following agents please estimate the chance that a patient will experience toxicity during treatment that will require withholding administration. What is the primary toxicity patients experience that leads to withholding the drug?

	Chance of withholding*	Primary toxicity
Datopotamab deruxtecan	15% (5% - 30%)	Stomatitis, neutropenia
Patritumab deruxtecan	13% (2% - 30%)	Cytopenias

*** Median (Range)**

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

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

- Patients with HER2-0 MBC that have progressed already on chemotherapy
- Would likely pick between saci and dato based on side effect profile, efficacy, and dosing schedule
- After all endocrine options, HER2 IHC=0; or salvage setting after TDX-d in ER+/HER2-low.
- Vs other Trop2 ADC (SG): less pretreated setting, similar PFS delta, but SG has OS advantage. Vs other deruxtecan ADC (TDXd): not need HER2-low, less ILD. Not clearly advantageous over either SG or T-DXd.
- 2 or 3L line IHC 0; would discuss Sacituzumab vs Datopotamab- schedule and toxicity profile
- Patients with ER+ disease who had exhausted endocrine therapy

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

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

- After exhaustion of endocrine therapy options, after 1 or 2 lines of chemotherapy, after T-DXd if HER2-low, and after SG unless there is a good reason not to use SG first (contra-indication, tumor biomarker landscape, etc)
- Those that progress on sacituzumab govitecan
- Unclear that it is better than TDXd or SG
- Not sure
- 2L after capecitabine

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

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

- At this point, HER3+ after T-DXd and SG, or after SG if high risk of ILD. How much HER3 expression is unknown (in lung cancer doesn't seem to matter).
- Highly pretreated patients with progression on several chemotherapies
- After exhaustion of endocrine therapy options, after 1 or 2 lines of chemotherapy, after T-DXd if HER2-low, and I would consider the tumor biomarker landscape (HER3 expression on most recent tissue ?)
- Likely post TDXd and TROP-2
- After all endocrine options, after TDX-d (if HER2 low); and after sacituzumab govitecan.

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

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

- If HER2 low then post TDXD; if HER2 0 then post sacituzumab
- After exhaustion of all ET options and one line of chemotherapy and HER3 +
- Unclear that it is better than TDXd or SG
- Not sure I would use, would need to see phase III data to try to gauge relative benefits and would only use for those not a candidate of T-DXd.
- We just do not have enough data as yet. Likely later line given lack of current data except in the pre-treated setting.
- Probably 3rd line unless good data emerges for earlier lines

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Tolerability profile of datopotamab deruxtecan and potential integration into the treatment algorithm for ER-positive metastatic breast cancer

Paolo Tarantino, MD

Adam M Brufsky, MD, PhD

Patritumab deruxtecan; HER3 as a cellular signaling intermediate; zanidatamab and other promising investigational agents under clinical development

Mark D Pegram, MD

RTP RESEARCH TO PRACTICE

Novel therapies under investigation for patients with ER-Positive mBC

Erika Hamilton, MD

Director, Breast Cancer Research Program

Sarah Cannon Research Institute

Nashville, TN

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Datopotamab deruxtecan (Dato-DXd)

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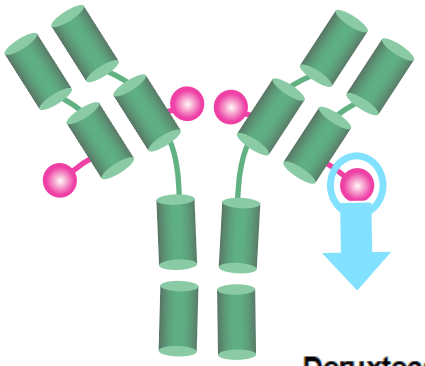
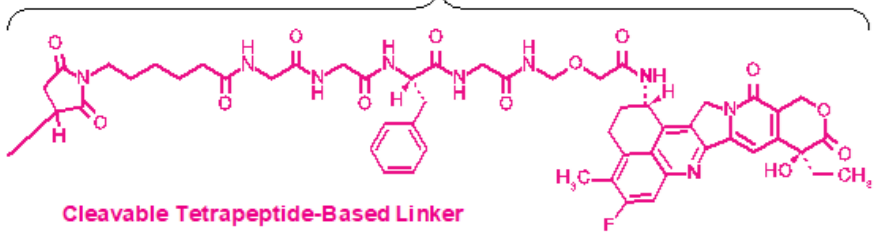
Datopotamab deruxtecan (Dato-DXd): Trop-2 directed ADC

Dato-DXd: Humanised anti-TROP2 monoclonal antibody



Deruxtecan[6,a]



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

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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

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

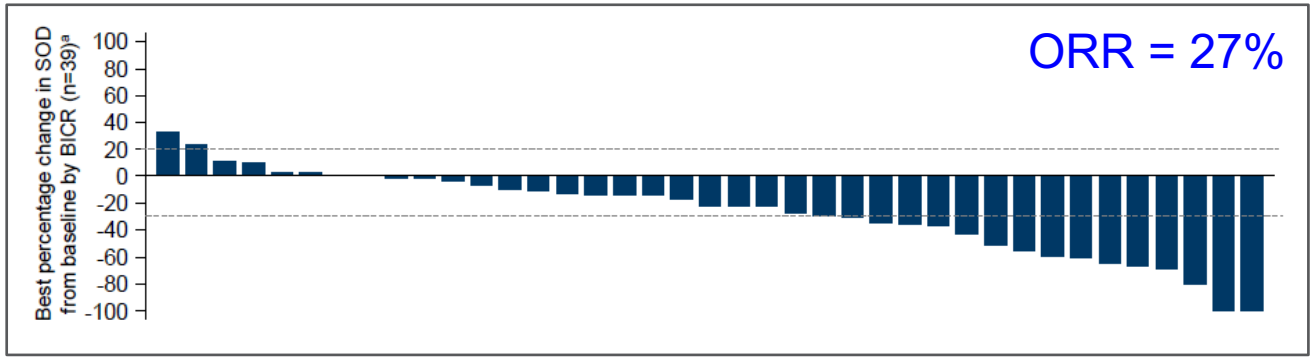
NSCLC[b]
(0.27 to 10 mg/kg IV Q3W)

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

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

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Meric-Bernstram F et al. SABCS 2022

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

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)

ICC
Q3W as per protocol directions† (eribulin mesylate, vinorelbine, capecitabine, or gemcitabine)
(n=367)

Endpoints:

- **Dual primary:** PFS by BICR per RECIST v1.1, and OS
- **Key secondary:** ORR, PFS (investigator assessed) and safety

Patient population

	Dato-DXd	ICC
Prior CDK 4/6 inhibitor	82%	78%
1 prior line of chemo	63%	61%
2 prior lines of chemo	37%	38%
Prior taxane alone	22%	19%
Prior taxane and anthracyclines	65%	67%

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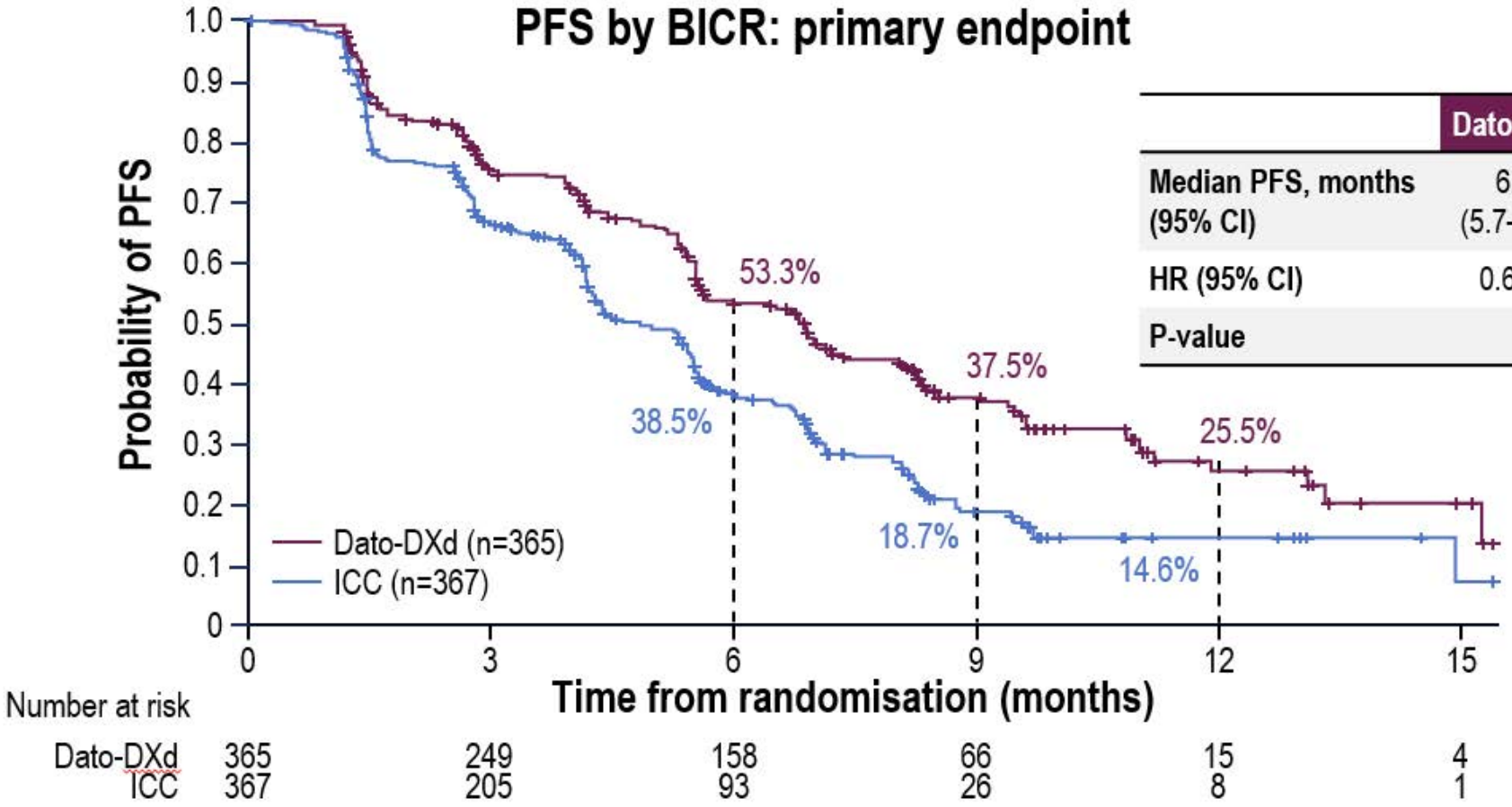
Bardia A et al. ESMO 2023, LBA11

TROPION-Breast01: Progression-free survival



	Dato-DXd	ICC
Median PFS, months (95% CI)	6.9 (5.7–7.4)	4.9 (4.2–5.5)
HR (95% CI)	0.63 (0.52–0.76)	
P-value	<0.0001	

PFS by investigator assessment: Median 6.9 vs 4.5 months; HR 0.64 (95% CI 0.53–0.76)

Subgroup analysis: Consistent benefit across all subgroups with Dato-DXd

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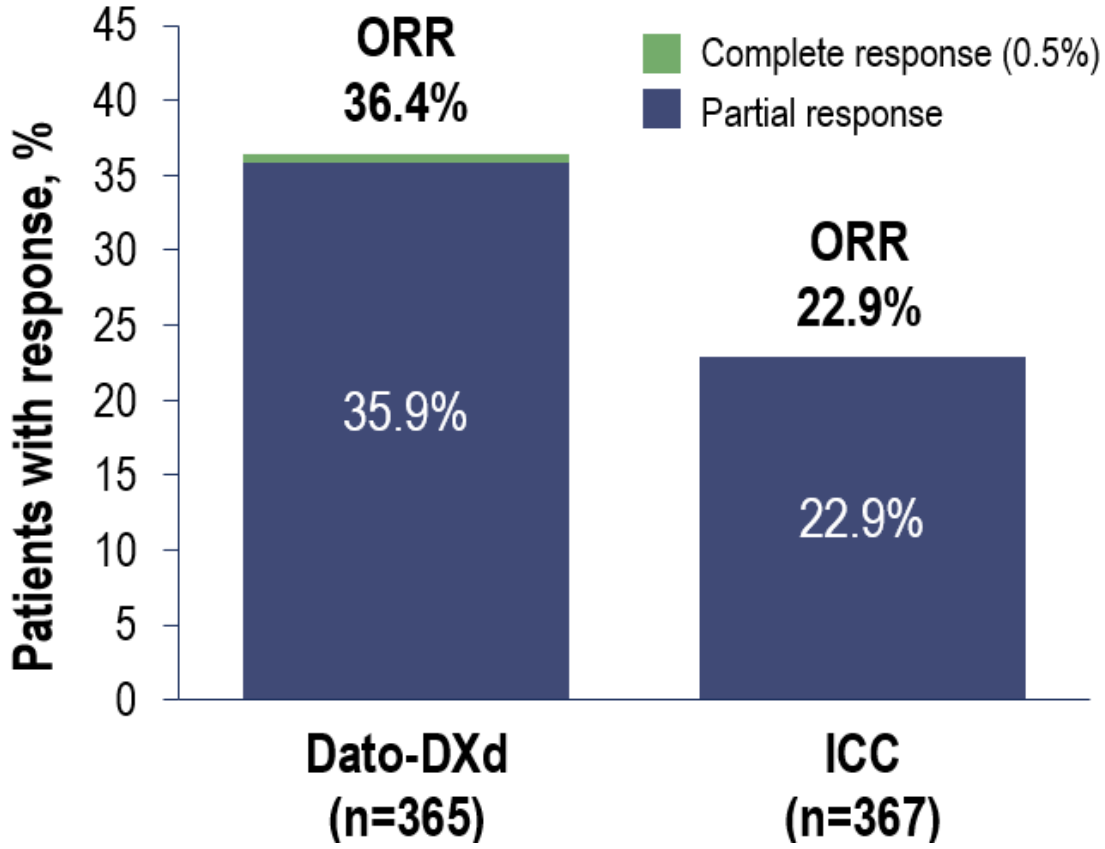
Bardia A et al. ESMO 2023, LBA11

TROPION-Breast01: ORR and interim OS

Response rate



OS: dual primary endpoint

- OS data were not mature:*
  - Median follow-up 9.7 months
- A trend favouring Dato-DXd was observed:
  - HR 0.84 (95% CI 0.62–1.14)
- The study is continuing to the next planned analysis for OS

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Bardia A et al. ESMO 2023, LBA11

TROPION-Breast01: Safety and summary

- Most frequent TRAEs with Dato-DXd were nausea (51%) and stomatitis (50%)
- Most common TRAEs with ICC were neutropenia (42%) and nausea (24%)

Adverse events of special interest

All-cause events, n (%)	Dato-DXd (n=360)	ICC (n=351)
Oral mucositis/stomatitis*		
All grades	211 (59)	61 (17)
Grade 3†	25 (7)	9 (3)
Ocular events‡		
All grades	175 (49)	81 (23)
Grade 3†	3 (1)	0
Adjudicated drug-related ILD§		
All grades	9 (3)	0
Grade ≥3	2 (1)	0
Infusion-related reactions		
All grades	32 (9)	12 (3)
Grade 3†	1 (0.3)	0

- Median treatment duration: **6.7** (Dato-DXd) and **4.1** months (ICC)
- Rate of grade ≥3 TRAEs in the Dato-DXd group was less than half that in the ICC group
- Fewer TRAEs leading to dose reductions or interruptions with Dato-DXd compared with ICC

- ✓ Significant improvement in PFS with Dato-DXd in pre-treated HR+/HER2- MBC
- ✓ Trend towards OS benefit with Dato-DXd at interim analysis
- ✓ No new safety signals observed with Dato-DXd
- ✓ Data suggest promise of a new treatment option for pts with HR+/HER2- MBC who have been treated with prior chemo

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Bardia A et al. ESMO 2023, LBA11

SKB264 (MK-2870): another novel TROP2 ADC

- SKB264 (MK-2870) comprises
  - a TROP2 antibody
  - a belotecan-derivative topo I inhibitor
  - a sulfonyl pyrimidine-CL2A-carbonate linker

to achieve an average DAR of 7.4

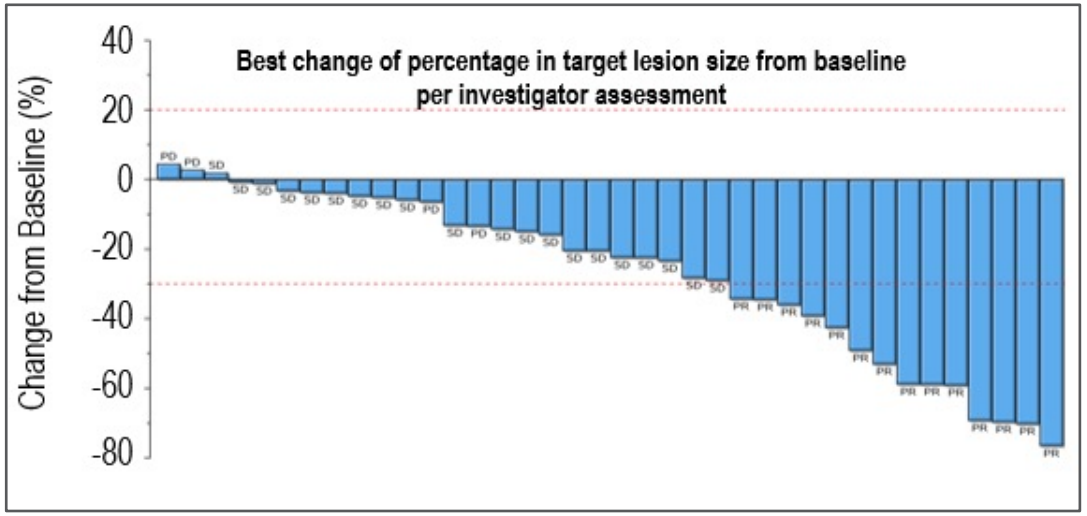
- The design was to achieve a more effective balance between stability in circulation and release of the ADC payload in tumor cells

- **Phase 1/ 2 basket study** in adv solid tumors included

  Pts with HR+/HER2- MBC, 66% treated with prior CDK 4/6i and a median of 2 prior chemo received SKB264 5mg/kg every 2weeks

  Safety: Mainly heme tox, mostly within first 2 months of tx and pts recovered following G-CSF tx

  No neuropathy, ocular toxicity, or drug-related ILD/pneumonitis reported



	All patients (N=38)[a]
ORR, n (%)	**14 (36.8)**
Confirmed PR	12
DCR, n (%)	**34 (89.5)**
DoR	
Median (Range), mo	7.4 (4.2~14.9+)
6-mon DoR rate, % (95% CI)	80.0 (40.9, 94.6)
PFS	
Median (95% CI), mo	11.1 (5.4, 13.1)
6-mon PFS rate, % (95% CI)	61.2 (41.3, 76.1)
OS	
Median (95% CI), mo	NE (10.71, NE)
9-mon OS rate (95% CI), %	81.4 (57.1, 92.7)

a. Of patients enrolled, 38 patients were evaluable for response assessment (defined as ≥1 on-study scan).

Yin Y et al. ESMO 2023

Patritumab deruxtecan (HER3-DXd)

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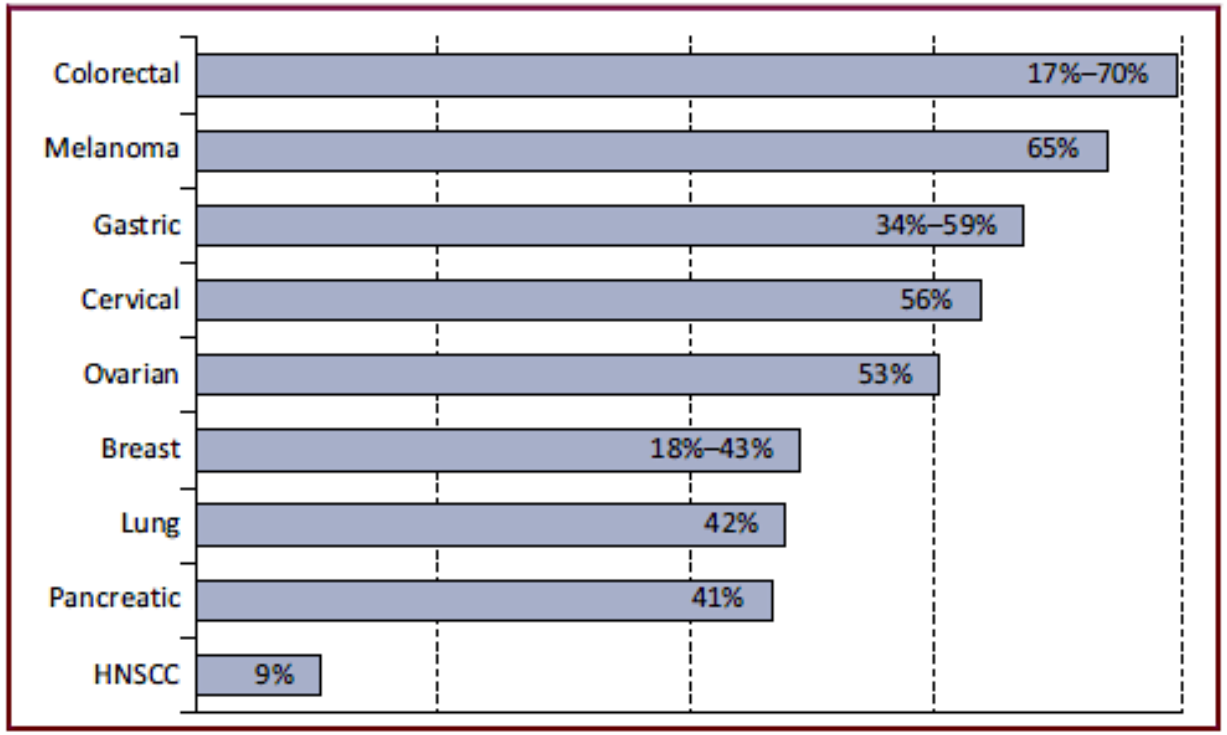
HER3 - role in cancer

Rate of HER3 expression in different tumor types



- HER3 is a tyrosine kinase receptor belonging to the HER family of receptors
  - has poor if no intracellular kinase activity
  - forms heterodimers preferentially with HER2 and/or EGFR leading to activation of the downstream signaling pathways promoting oncogenesis
  - is overexpressed in many types of cancers including ~20-50% of breast cancers
  - Overexpression of HER3 in breast cancer is associated with poor prognosis

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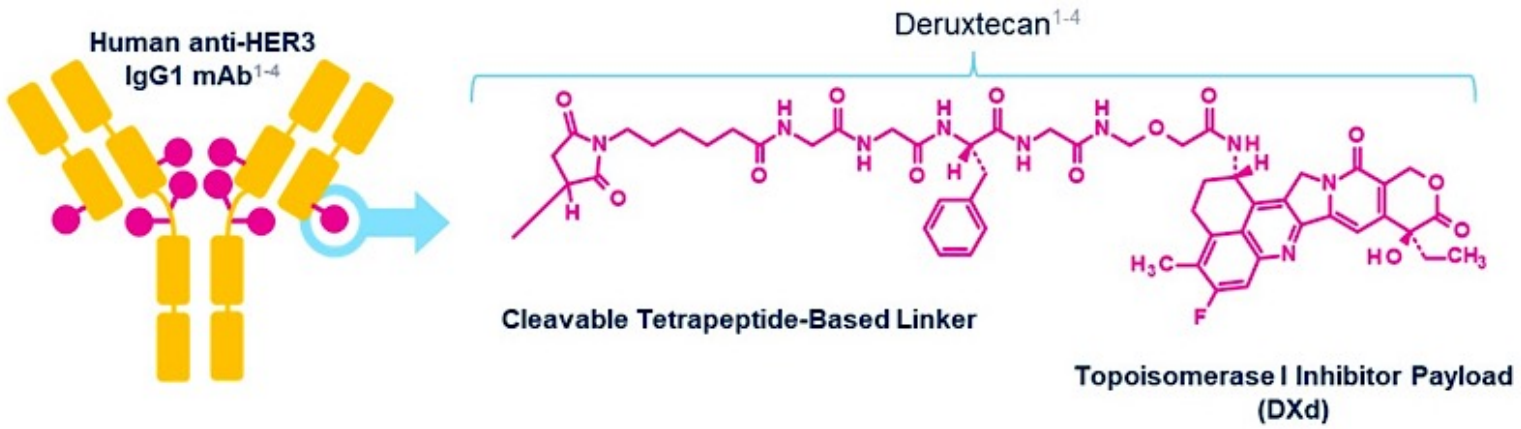
Uliano J et al. 2023; Weng W et al. 2023

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.

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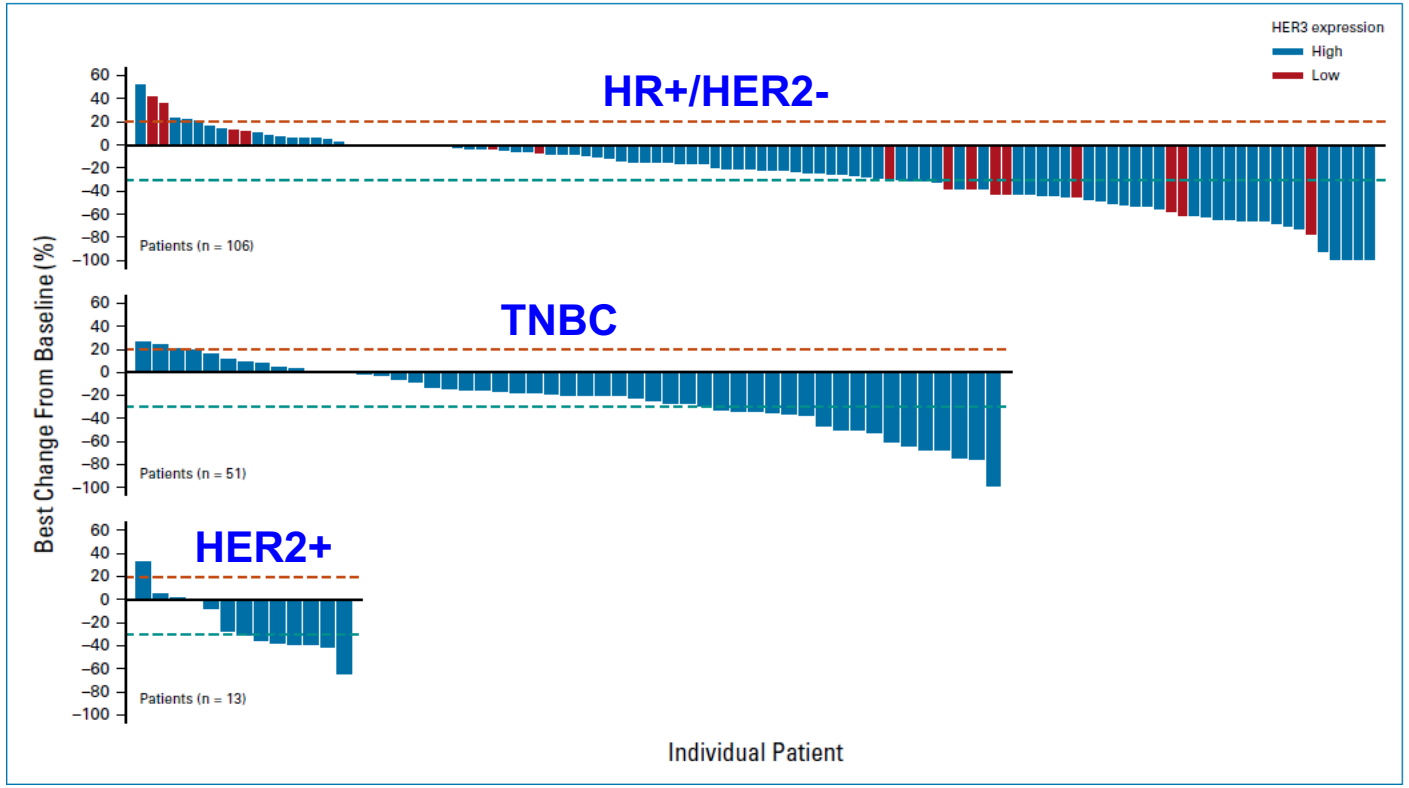
Krop I et al. ASCO 2022, Abstract 1002

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%	7.4 mo
HER2+	43%	11 mo
TNBC	23%	5.5 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**

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Krop I et al. JCO 2023

ICARUS-BREAST01: Phase 2 trial of HER3-DXd (Patritumab deruxtecan) 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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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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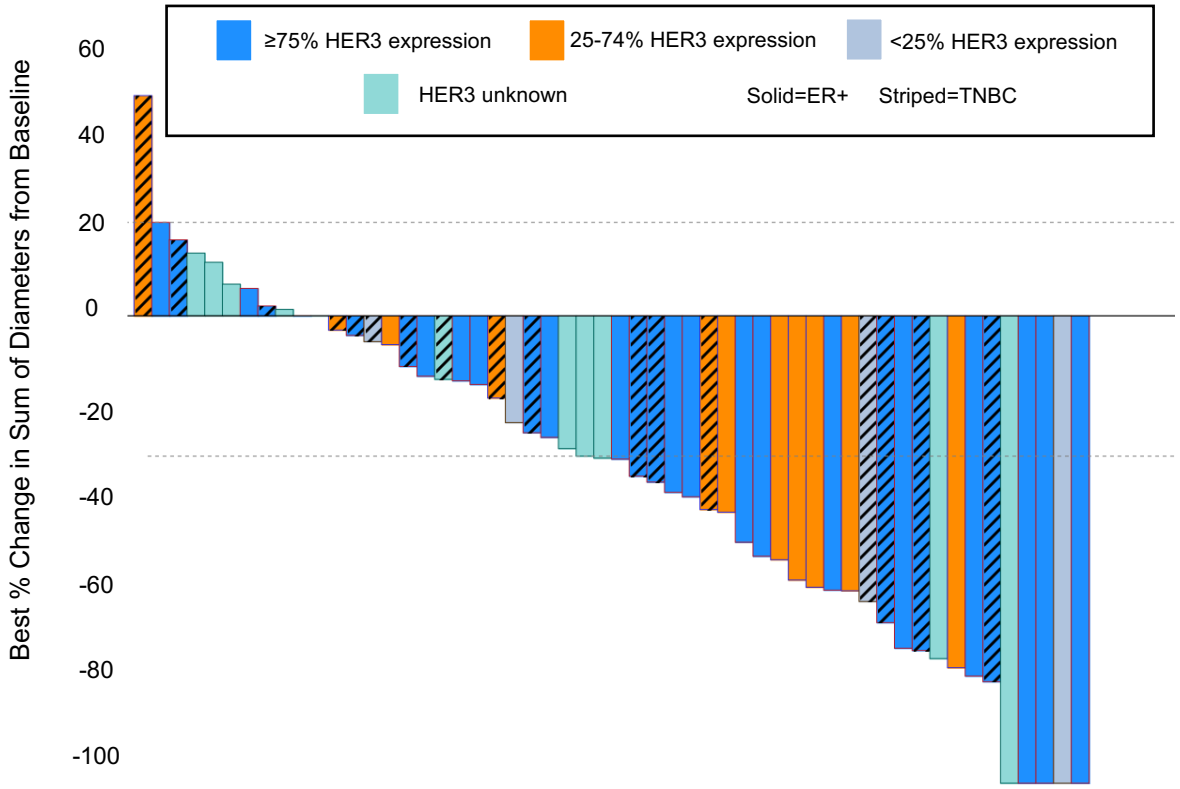
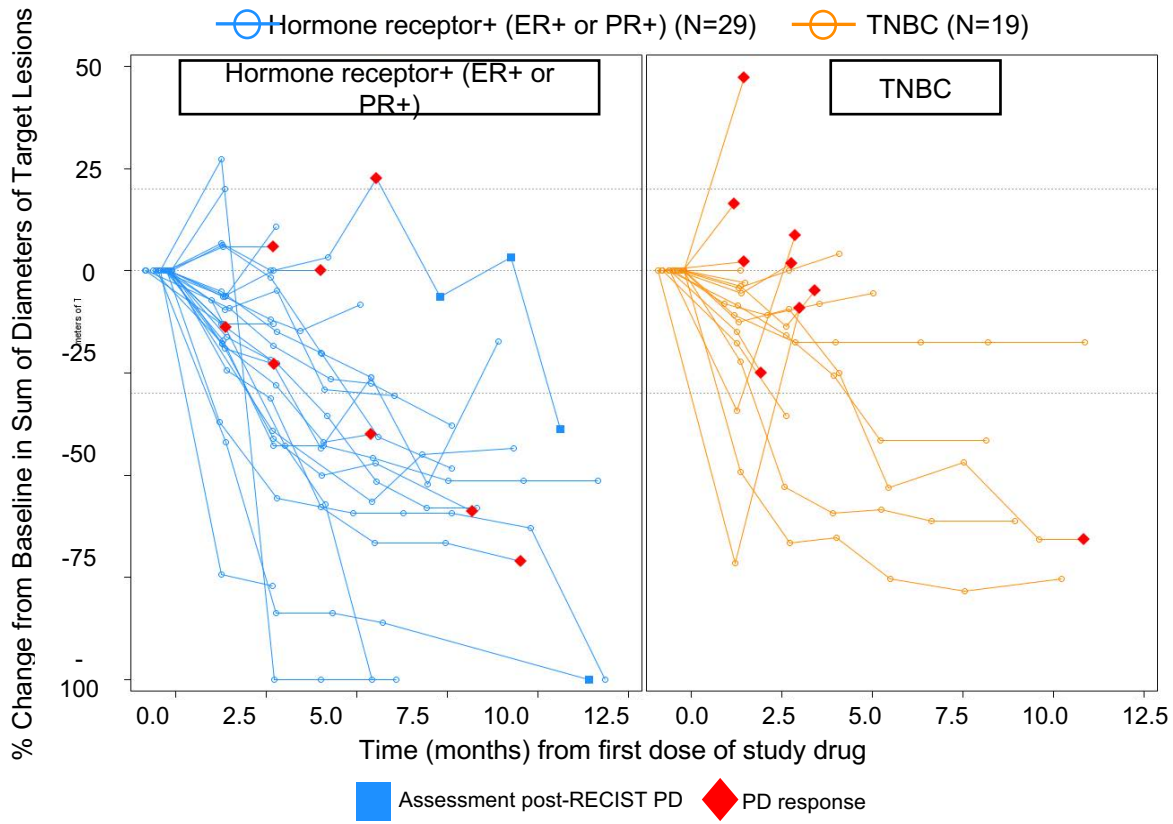
Hamilton E et al. ASCO 2023

Tumor shrinkage with HER3-DXd (Patritumab deruxtecan)

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

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Hamilton E et al. ASCO 2023

HER3-DXd (Patritumab deruxtecan) for HR+/HER2- MBC: Key takeaways

- ✓ HER3-DXd is active in HR+/HER2- MBC, irrespective of level of HER3 expression
  - ORR 30-35% across both trials

- ✓ Biomarker analyses (ICARUS-BREAST01):
  - clinical activity seen regardless of most frequent genomic alterations
  - RNAseq showed a higher modulation of gene expression in early responders as compared to non-responders: is primary resistance more related to reduced ADC internalization/binding?

- ✓ Fatigue and GI toxicity were the most common AEs

- ✓ Rate of ILD was low (1.8%)

- ✓ These data warrant further exploration of HER3-DXD in HR+/HER2- MBC

SHR-A2009: Another novel HER3 ADC

SHR-A2009: novel ADC composed of fully human anti-HER3 IgG1 mAb, covalently linked to a DNA topoisomerase I inhibitor via a cleavable peptide linker (DAR=4)

FIH trial in patients with advanced solid tumors (NCT05114759)

- Majority of pts enrolled had NSCLC (36/42)
- No DLTs reported (up to dose level 10.5mg/kg q 3 weeks
- Most common toxicities: anemia, neutropenia and nausea
- ORR: 25% (all tumors); 30% (NSCLC)
- Median DoR: 7 months

Trial ongoing to assess higher doses of SHR-A2009

Other novel agents for HR+/HER2- MBC

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Novel agents under evaluation in ER+/HER2- MBC

ER-PROTAC: heterobifunctional molecules that degrade ER via the ubiquitin proteasome system
Catalytic in their MOA; can promote target degradation at low concentrations; less toxicity & higher therapeutic index
ARV-471 (Vepdegestrant) single agent in phase 3 trials in ER+/HER2- MBC NCT05654623; NCT05909397
AC0699 : Chimeric ER degrader in phase 1 trials NCT05654532

CERAN: shuts down both activation functions (AF1 and AF2) of the ER
OP-1250 (Palazestrant) in phase 3 trial in ER+/HER2- MBC NCT06016738

Novel SERM: Modulate ER by altering its conformation and thus its interaction with ER coactivators and co-repressors
Lasofoxifene: Phase 3 trial in combination with abemaciclib NCT05696626

SARM: Selective AR modulator. AR is expressed in 70-95% of ER+ BC
it is a tumor suppressor & its expression is associated with improved prognosis in ER+ BC
RAD140: oral breast-tissue selective AR agonist; preliminary activity in phase 1 trial in ER+/HER2- MBC NCT03088527
EP0062 (Vosilasarm- AR agonist): Phase 1 trial ongoing in AR+/ER+/HER2- MBC NCT05573126
Enobosarm: (AR agonist) Phase 3 trial in AR+/ER+/HER2- MBC NCT04869943

CDK4 inhibitor: Selective inhibition of CDK4 with significant sparing of CDK6 reduces neutropenia and enables higher doses to be administered
PF-07220060: Phase 3 trial in combination with fulvestrant planned NCT06105632

CDK2 inhibitor: CDK2 inhibition effective in tumors with cyclinE overexpression/amplification, a key CDK4/6i resistance mechanism
BLU-222: Phase 1/ 2 trial ongoing with preliminary antitumor activity in heavily pretreated ER+/HER2- MBC reported recently NCT05252416
ARTS-021: First-in-human study ongoing in CCNE1 altered malignancies including ER+/HER2- MBC NCT05867251

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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 RESEARCH TO PRACTICE

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Localized HER2-Negative Breast Cancer

Part 2 of a 3-Part CME Satellite Symposium Series in Partnership with the 2023 San Antonio Breast Cancer Symposium®

Wednesday, December 6, 2023

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

Faculty

Harold J Burstein, MD, PhD
Matthew P Goetz, MD
Sara A Hurvitz, MD, FACP
Joyce O'Shaughnessy, MD
Lajos Pusztai, MD, DPhil, FASCO

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Thank you for joining us!
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Please complete the survey currently up on the iPads for attendees in the room and on Zoom for those attending virtually. The survey will remain open up to 5 minutes after the meeting ends.

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Online/Zoom attendees: The CME credit link is posted in the chat room.

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