Fourth Annual
National General Medical Oncology Summit

A Multitumor CME/MOC-, NCPD- and ACPE-Accredited Educational Conference Developed in Partnership with

Florida Cancer Specialists & Research Institute

Friday, February 28, 2025

Moderator

Neil Love, MD

Faculty

Aditya Bardia, MD, MPH
Virginia F Borges, MD, MMSc
Harold J Burstein, MD, PhD
Joyce O'Shaughnessy, MD

Disclosures for Moderator Neil Love, MD

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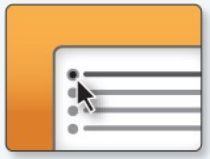
Clinicians in the Meeting Room

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.

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

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.

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

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

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

About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from this weekend 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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Hormone Receptor-Positive Metastatic Breast Cancer

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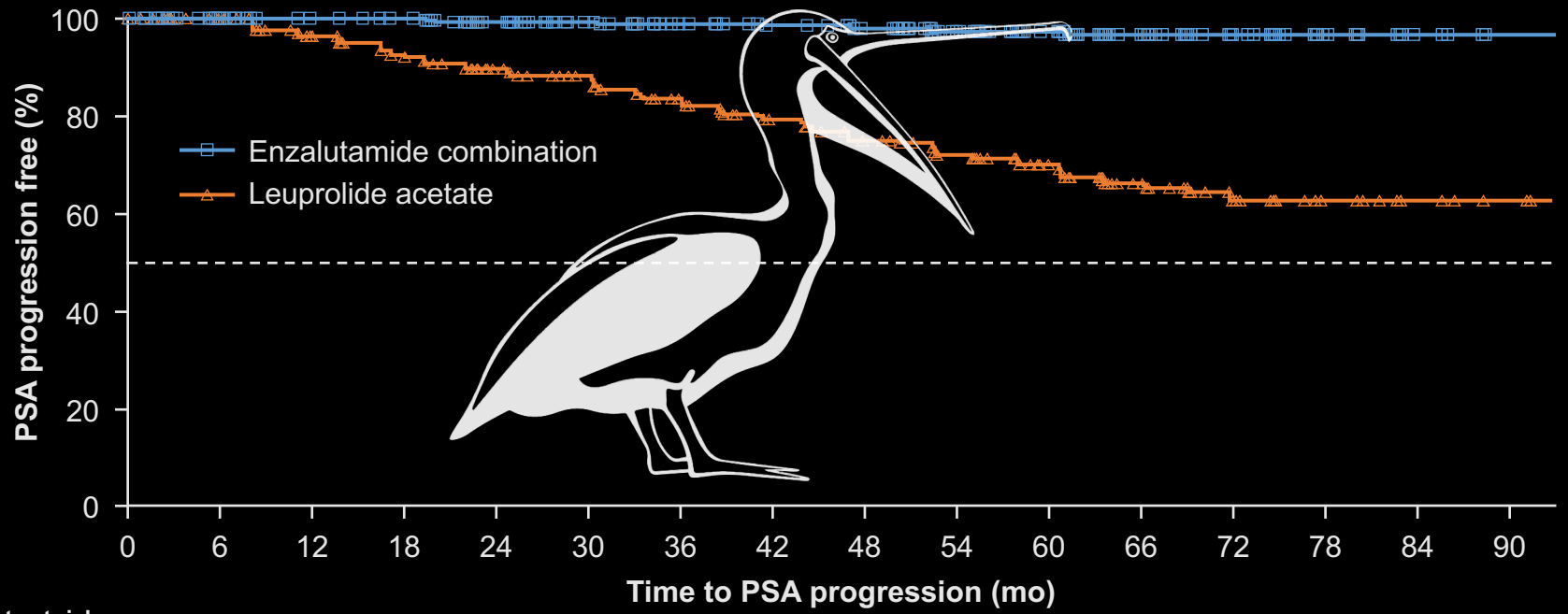
AUA 2023
CHICAGO ✶ APR 28-MAY 1

Key secondary endpoint — Time to PSA progression with enzalutamide combination vs leuprolide acetate



Patients at risk

Enzalutamide combination	355	337	326	319	302	286	270	260	247	230	175	119	75	37	12	0
Leuprolide acetate	358	341	314	293	268	253	223	201	182	168	128	83	42	20	7	3

	Enzalutamide combination (n = 355)	Leuprolide acetate (n = 358)
Events, n (%)	8 (2)	93 (26)
Median time to PSA progression (95% CI), mo	NR (NR)	NR (NR)

HR (95% CI): 0.07 (0.03–0.14); *P*<0.0001[a]

Data cutoff: January 31, 2023. Symbols indicate censored data. [a]The HR was based on a Cox regression model with treatment as the only covariate stratified by screening PSA, PSADT, and prior hormonal therapy as reported in the IWRS; relative to leuprolide acetate <1 favoring enzalutamide combination; the two-sided *P*-value is based on a stratified log-rank test.

Shore N et al. AUA 2023;Abstract LBA02-09.

First-Line Camizestrant Demonstrated a Statistically Significant and Clinically Meaningful Improvement in PFS for Advanced HR-Positive Breast Cancer with an Emergent ESR1 Tumor Mutation in the Phase III SERENA-6 Trial

Press Release: February 26, 2025

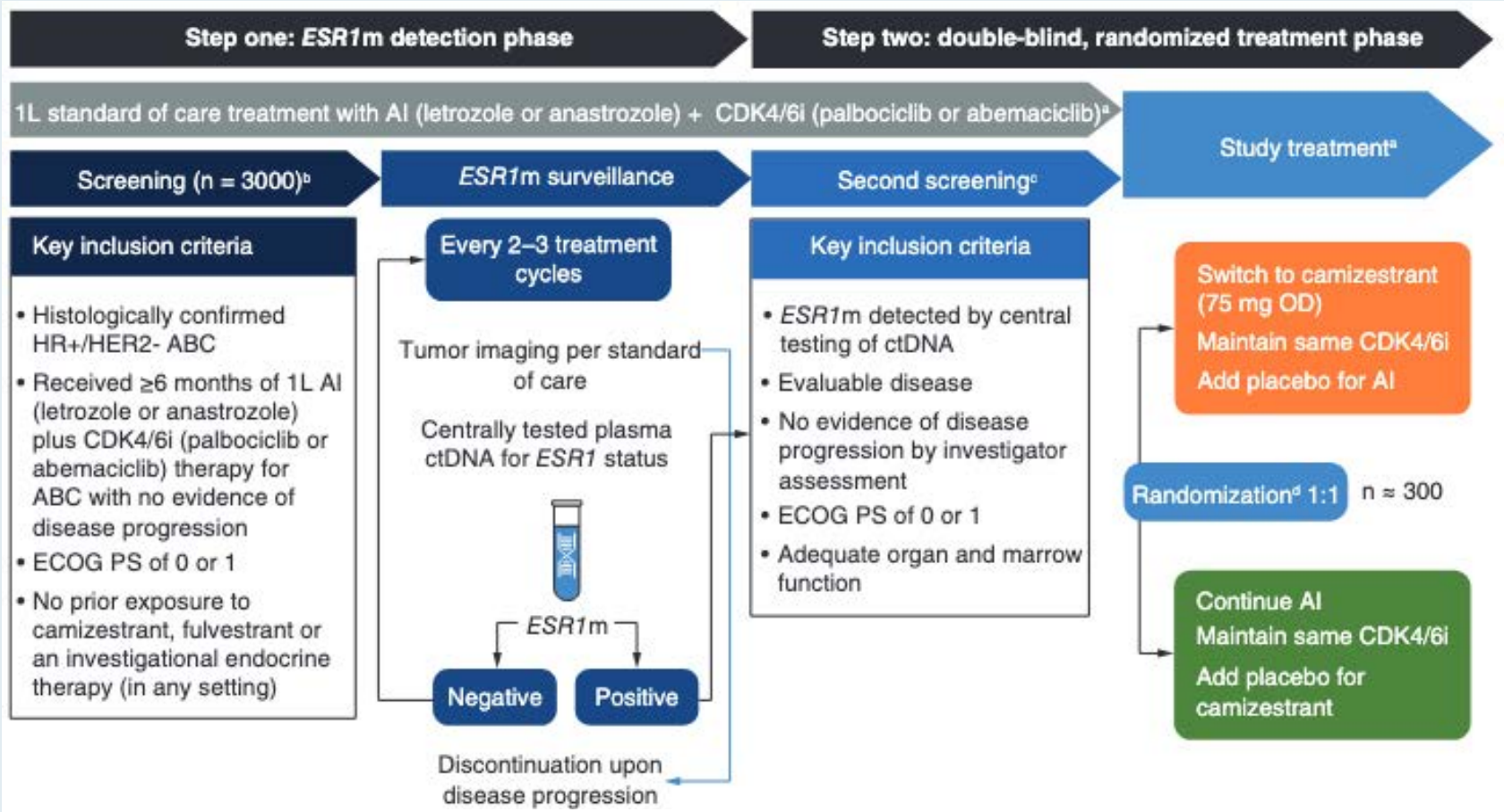
"Positive high-level results from a planned interim analysis of the SERENA-6 Phase III trial showed that camizestrant in combination with a cyclin-dependent kinase (CDK) 4/6 inhibitor (palbociclib, ribociclib or abemaciclib) demonstrated a highly statistically significant and clinically meaningful improvement in the primary endpoint of progression-free survival (PFS). The trial evaluated switching to the camizestrant combination versus continuing standard-of-care treatment with an aromatase inhibitor (AI) (anastrozole or letrozole) in combination with a CDK4/6 inhibitor in the 1st-line treatment of patients with hormone receptor (HR)-positive, HER2-negative advanced breast cancer whose tumours have an emergent *ESR1* mutation.

The key secondary endpoints of time to second disease progression (PFS2) and overall survival (OS) were immature at the time of this interim analysis. However, the camizestrant combination demonstrated a trend toward improvement in PFS2. The trial will continue as planned to further assess key secondary endpoints."

https://www.astrazeneca.com/media-centre/press-releases/2025/camizestrant-improved-pfs-in-1l-hr-breast-cancer.html.

RTP RESEARCH TO PRACTICE

SERENA-6 Phase III Study Design



[a]Premenopausal/perimenopausal women or male participants (if medically indicated) receive a concurrent monthly luteinizing-hormone-releasing hormone agonist (goserelin or leuprorelin).
[b]Patients who are screen failures for STEP 1 can be rescreened.
[c]Patients who are screen failures for STEP 2 can be rescreened after consultation with the Global Study Team.
[d]Randomization will be stratified by: disease site (visceral disease vs non-visceral disease); *ESR1*m status (detectable at first versus subsequent ctDNA tests); time from initiation of CDK4/6i + AI to randomization (<18 months vs ≥18 months); CDK4/6i.

Turner N et al. *Future Oncol* 2023;19(8):559-73.

RTP RESEARCH TO PRACTICE

Keynote Session: Hormone Receptor-Positive Metastatic Breast Cancer

CDK4/6 Inhibitors for HR-Positive Metastatic Breast Cancer (mBC) — Dr Borges

Targeting the PTEN/PI3K/AKT Pathway in HR-Positive mBC — Dr Burstein

Role of Oral Selective Estrogen Receptor Degraders (SERDs) in the Management of HR-Positive mBC — Dr O'Shaughnessy

Antibody-Drug Conjugates for HR-Positive mBC — Dr Bardia

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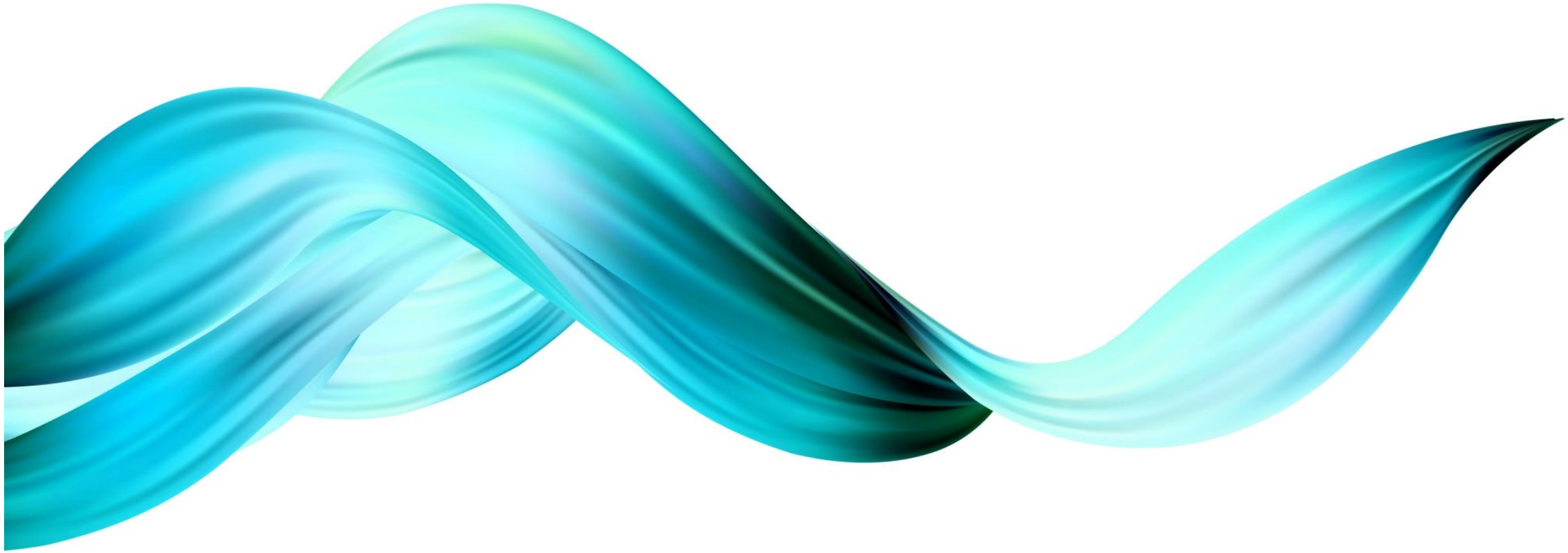
CDK4/6 Inhibitors for Hormone Receptor (HR)-Positive Metastatic Breast Cancer

Virginia F. Borges, MD, MMSc

University of Colorado Cancer Center



Disclosures

Advisory Committees	AstraZeneca Pharmaceuticals LP, Gilead Sciences Inc, Olema Oncology, Pfizer Inc, Seagen Inc
Consulting Agreements	Gilead Sciences Inc, Olema Oncology
Contracted Research	Agendia Inc, AstraZeneca Pharmaceuticals LP, Genentech, a member of the Roche Group, Gilead Sciences Inc, Olema Oncology, Pfizer Inc, Seagen Inc
Data and Safety Monitoring Boards/Committees	Pfizer Inc, Seagen Inc (HER2CLIMB-02 trial)
Nonrelevant Financial Relationships	Pearl Scientific LLC

Agenda

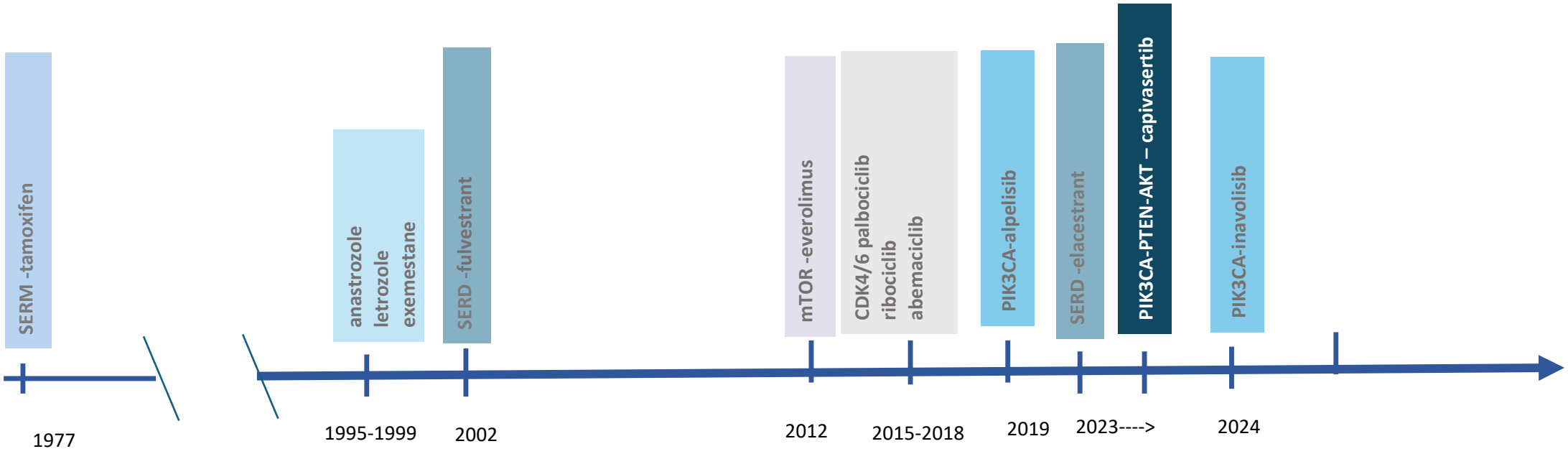
1. Review the pivotal CDK4/6 inhibitor trials for HR+ MBC
2. Discuss how to decide first line therapy options for HR+ MBC
3. Relevant toxicities and management strategies for CDK4/6 inhibitors
4. Sequencing of CDK4/6 inhibitors as a treatment option

First line therapy decision making

HR+, HER2 neg MBC

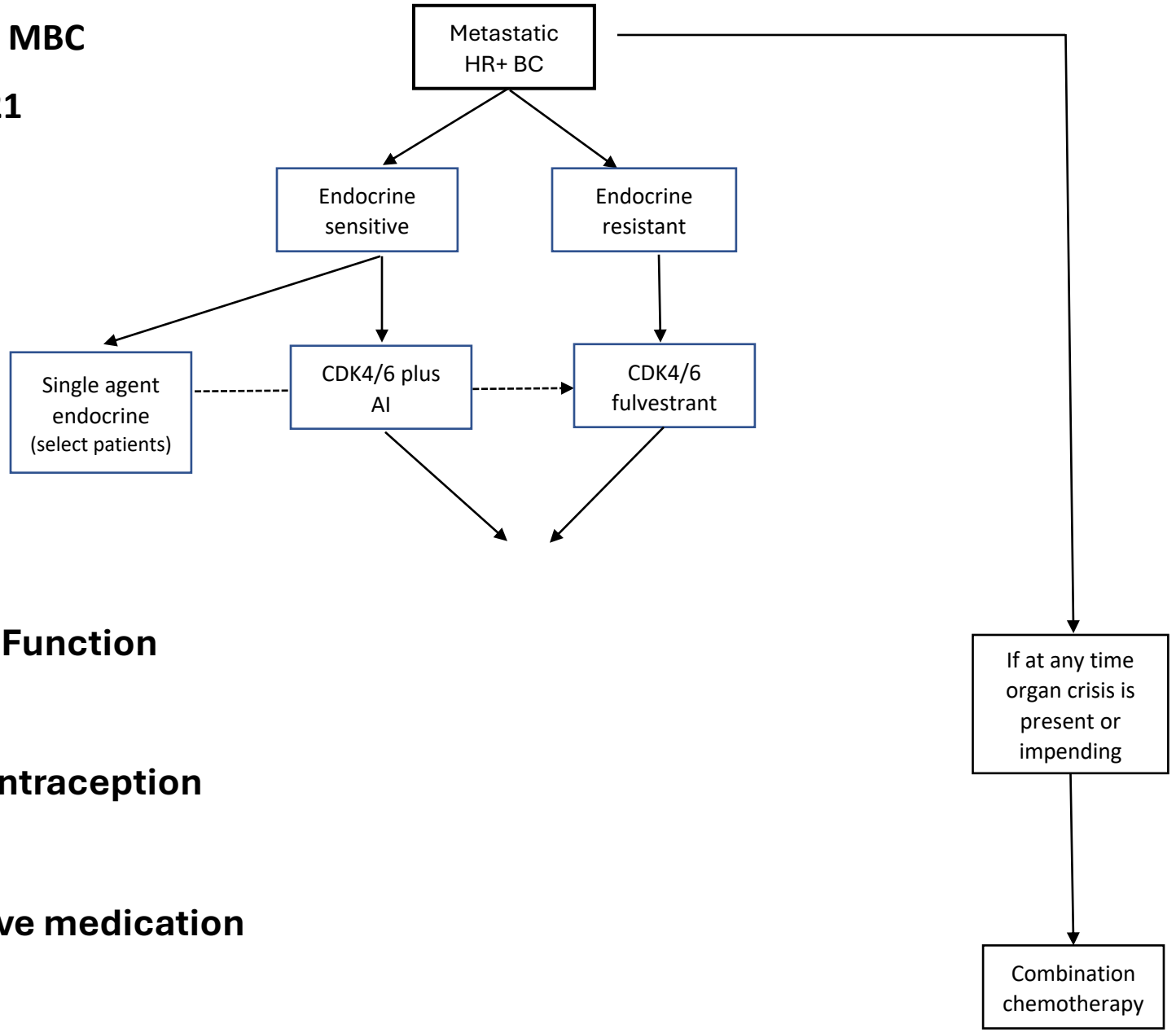
- Is there a role for front line chemo in 2025?
- Best ET choices – monotherapy v. combination with CDK4/6 inhibitors?

Timeline of initial novel drug approvals for HR+ HER2- metastatic breast cancer



Borges, JCO, Dec 2021- updated

Flow diagram for ER+/HER2- MBC treatment decisions 2021



- **Re-initiate the Ovarian Function Suppression**
- **Check for adequate contraception method**
- **Re-start bone supportive medication**

Borges, JCO, Dec 2021

CDK 4/6 inhibitor	Study	ET partner	Menopausal Status	Disease Status	PFS[4] Exp v control (HR)
palbociclib	PALOMA-1	letrozole	Pre/post	AI sens	20.2 v 10.2 (0.48)
	PALOMA-2				27.6 v 14.5 (0.56)
	PALOMA-3	fulvestrant		AI resis	9.5 v 4.6 (0.46)
ribociclib	MONALEESA-2	letrozole	Post	AI sens	25.3 v 16 (0.56)
	MONALEESA-3	fulvestrant		AI mixed	20.5 v 12.8 (0.59)
	MONALEESA-7	Tam/NSAI	Pre	AI sens	23.8 v 13.3 (0.55)
abemaciclib	MONARCH 1	None (phase II)	Pre/post	AI resis	6.0 (single arm)
	MONARCH 2	fulvestrant		AI resis	16.4 v 9.3 (0.55)
	MONARCH 3	NSAI		AI sens	28.1 v 14.7 (0.54)

Borges, JCO, Dec 2021

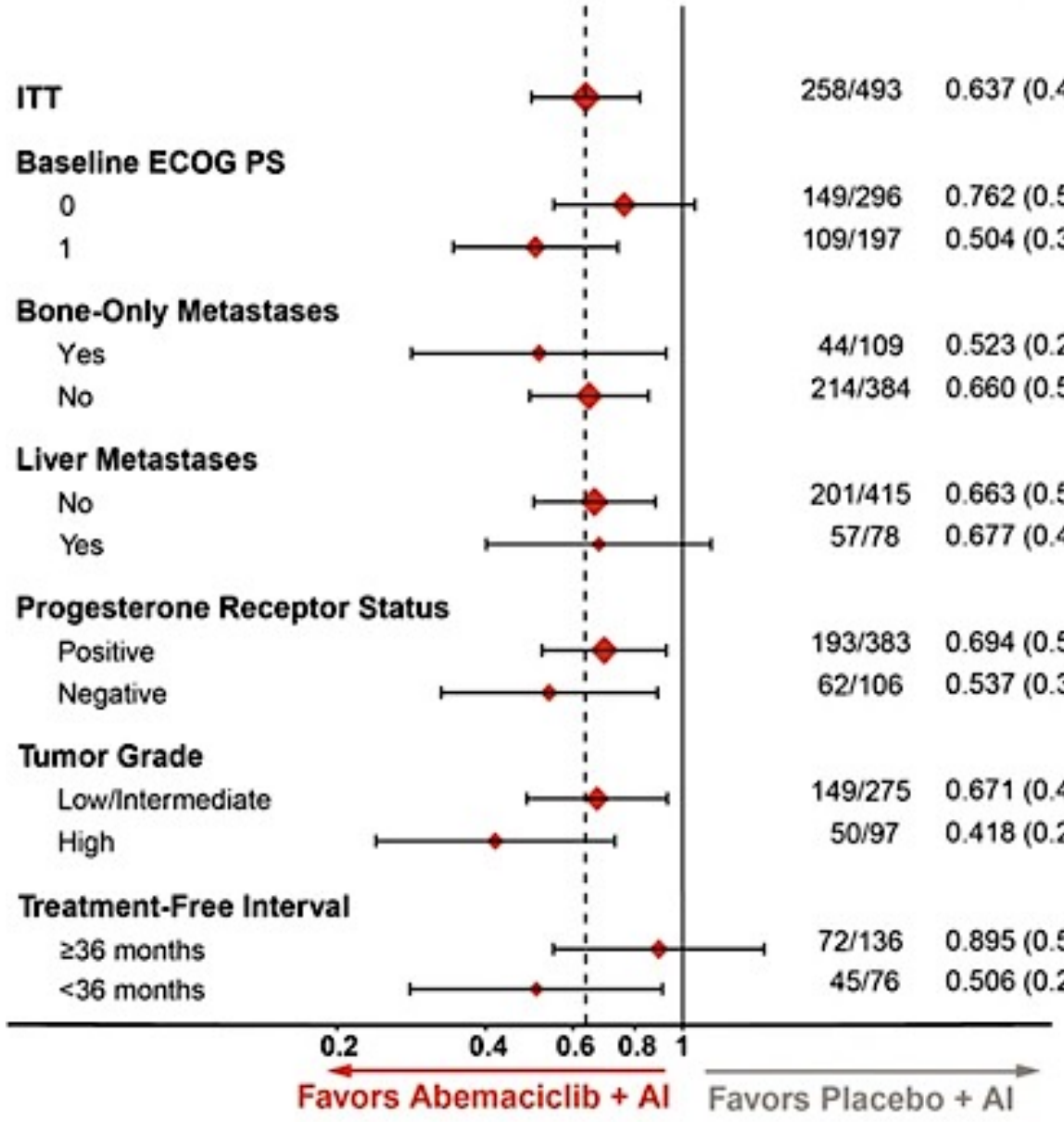
Study characteristics	CDK4/6i with AI or tamoxifen				CDK4/6i with fulvestrant		
	PALOMA-2	MONALEESA-2	MONALEESA-7	MONARCH 3	PALOMA-3	MOLANEESA-3	MONARCH 2
Year of initial publication	2015	2016	2018	2017	2016	2018	2017
Year of updated data	2022	2022	2022	2023	2021	2021	2020
Total number of patients	666	668	672	493	521	726	669
Line	1st	1st	1st and 2nd line (after chemotherapy)	1st	Progression after ET (adjuvant or 1st line)	1st and 2nd line	Progression after ET (neo/adjuvant or 1st line)
Menopausal status	Post	Post	Pre	Post	Pre/post	Post	Pre/post
Median follow-up (months)	90	80	53.5	97.2	73.3	56.3	48.7
CDK4/6i	Palbociclib	Ribociclib	Ribociclib	Abemaciclib	Palbociclib	Ribociclib	Abemaciclib
Median OS in placebo + endocrine arm (months)	51.2	51.4	48.0	54.5	28	41.5	37.3
Median OS in CDK4/6I + endocrine arm (months)	53.9	63.9	58.7	66.8	34.8	53.7	46.7
Reported HR for OS	0.956	0.76	0.76	0.804	0.814	0.73	0.757
Reported 95% CI for HR of OS	0.777–1.177	0.63–0.93	0.61–0.96	0.637–1.015	0.644–1.029	0.59–0.90	0.606–0.945

Kappel, C. Sci Rep 2024. https://doi.org/10.1038/s41598-024-53151-8

	Overall N (%) 205	Palbociclib N (%) 120	Ribociclib N (%) 32	Abemaciclib N (%) 53
All grade toxicity				
Neutropenia	69 (33.7)	53 (44)	10 (31)	6 (11.3)
Mucositis	30 (14.6)	21 (17.5)	3 (9.4)	6 (11.3)
Fatigue	61 (29.8)	35 (29.2)	13 (40.6)	13 (24.5)
Nausea	51 (24.9)	24 (20.0)	9 (28.1)	18 (24.5)
Thrush	3 (1.5)	2 (1.7)	1 (3.1)	0 (0.0)
Hot flushes	14 (6.8)	11 (9.2)	2 (6.3)	1 (1.9)
Diarrhoea	53 (25.9)	14 (11.7)	8 (25.0)	31 (58.5)
Vomiting	16 (7.8)	8 (6.7)	2 (6.3)	6 (11.3)
Hair thinning	7 (3.4)	5 (4.2)	1 (3.1)	1 (1.9)
Headache	8 (3.9)	7 (5.8)	1 (3.1)	0 (0.0)
Watery eyes	4 (2.0)	2 (1.7)	0 (0.0)	2 (3.8)
Dry eyes	3 (1.5)	1 (0.8)	1 (3.1)	1 (1.9)
Abdominal pain	5 (2.4)	3 (2.5)	0 (0.0)	2 (3.8)
Pruritus	9 (4.4)	5 (4.2)	0 (0.0)	4 (7.5)
Dry skin	7 (3.4)	6 (5.0)	0 (0.0)	1 (1.9)
Pneumonitis	4 (2.0)	0 (0.0)	0 (0.0)	4 (7.5)
Hepatic transaminitis	4 (2.0)	2 (1.7)	0 (0.0)	2 (3.8)
Epistaxis	4 (2.0)	3 (2.5)	0 (0.0)	1 (1.9)
Neuropathy	1 (0.5)	1 (0.8)	0 (0.0)	0 (0.0)
Grade 3 or above toxicity				
Neutropenia	44 (21)	37 (31)	6 (19)	1 (1.9)
Thrombocytopenia	1 (0.5)	1 (0.8)	0 (0.0)	0 (0.0)
Myelosuppression[a]	1 (0.5)	1 (0.8)	0 (0.0)	0 (0.0)
Nausea	1 (0.5)	1 (0.8)	0 (0.0)	0 (0.0)
General deterioration	1 (0.5)	1 (0.8)	0 (0.0)	0 (0.0)
Nausea, vomiting, acute kidney injury	1 (0.5)	1 (0.8)	0 (0.0)	0 (0.0)
Diarrhoea	1 (0.5)	0 (0.0)	0 (0.0)	1 (1.9)
Hepatic transaminitis	1 (0.5)	0 (0.0)	0 (0.0)	1 (1.9)

Buller W, J Oncol Pharmacy Practice 2023
doi:10.1177/10781552231163121

MONARCH 3 updated results in prognostic subgroups



	Events/N	HR (95% CI)	p value	Median (months) Abema +AI	Median (months) Placebo +AI
ITT	258/493	0.637 (0.495, 0.819)		36.9	25.6
Baseline ECOG PS					
0	149/296	0.762 (0.549, 1.059)	.108	36.9	30.6
1	109/197	0.504 (0.344, 0.740)		38.9	20.6
Bone-Only Metastases					
Yes	44/109	0.523 (0.289, 0.945)	.484	42.4	33.6
No	214/384	0.660 (0.501, 0.871)		34.2	23.0
Liver Metastases					
No	201/415	0.663 (0.500, 0.881)	.948	39.2	28.9
Yes	57/78	0.677 (0.401, 1.142)		18.6	14.8
Progesterone Receptor Status					
Positive	193/383	0.694 (0.520, 0.927)	.386	38.6	27.2
Negative	62/106	0.537 (0.325, 0.889)		32.3	24.1
Tumor Grade					
Low/Intermediate	149/275	0.671 (0.484, 0.931)	.164	34.9	25.6
High	50/97	0.418 (0.240, 0.730)		38.6	18.3
Treatment-Free Interval					
≥36 months	72/136	0.895 (0.548, 1.461)	.437	33.0	28.3
<36 months	45/76	0.506 (0.281, 0.910)		31.6	22.5

Johnston, S, O'Shaughnessy, J *npj Breast Cancer* (2021). https://doi.org/10.1038/s41523-021-00289-7

Sequencing of CDK4/6 Inhibitor Studies

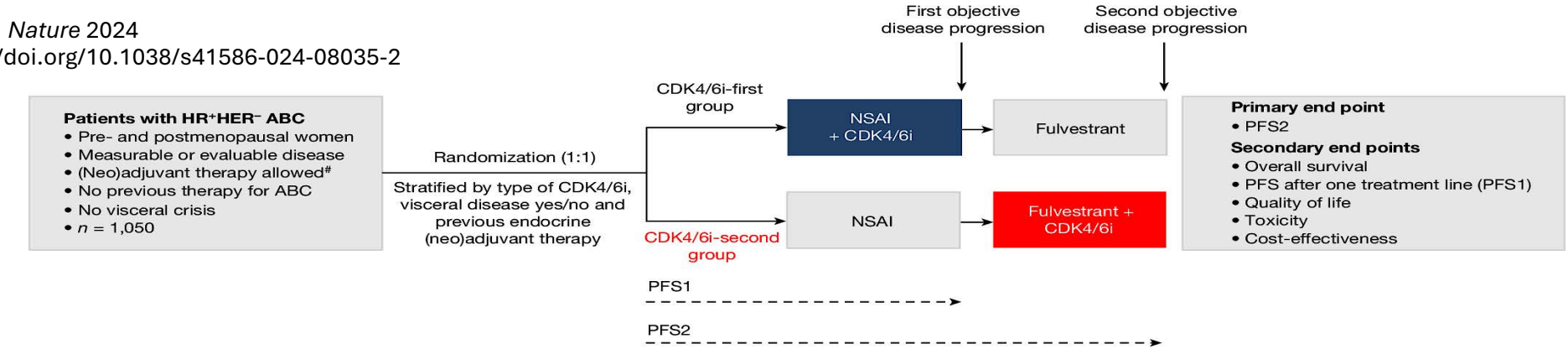
SONIA trial: Patients with MBC were randomized to AI alone vs AI + CDK4/6 inhibitor; patients who were on AI as a first line received CDK4/6 inhibitor as a second line. No difference in PFS. (*Gabe S. Sonke et al, JCO 41, LBA1000-LBA1000, 2023*).

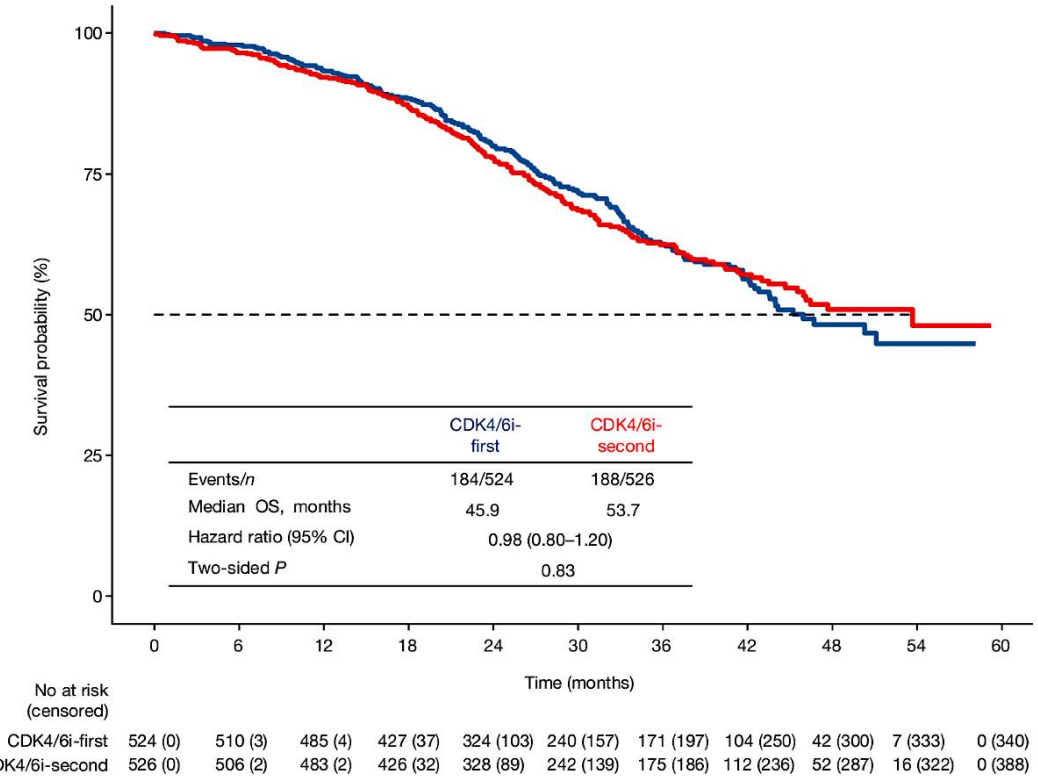
RIGHT Choice trial: first line ribociclib with endocrine therapy vs chemotherapy for patients with HR+ breast cancer with aggressive first-line ribociclib plus endocrine therapy showed better PFS, similar response rates, and better tolerability (*Yen-Shan Lu et al, JCO 42, 2812-2821, 2024*).

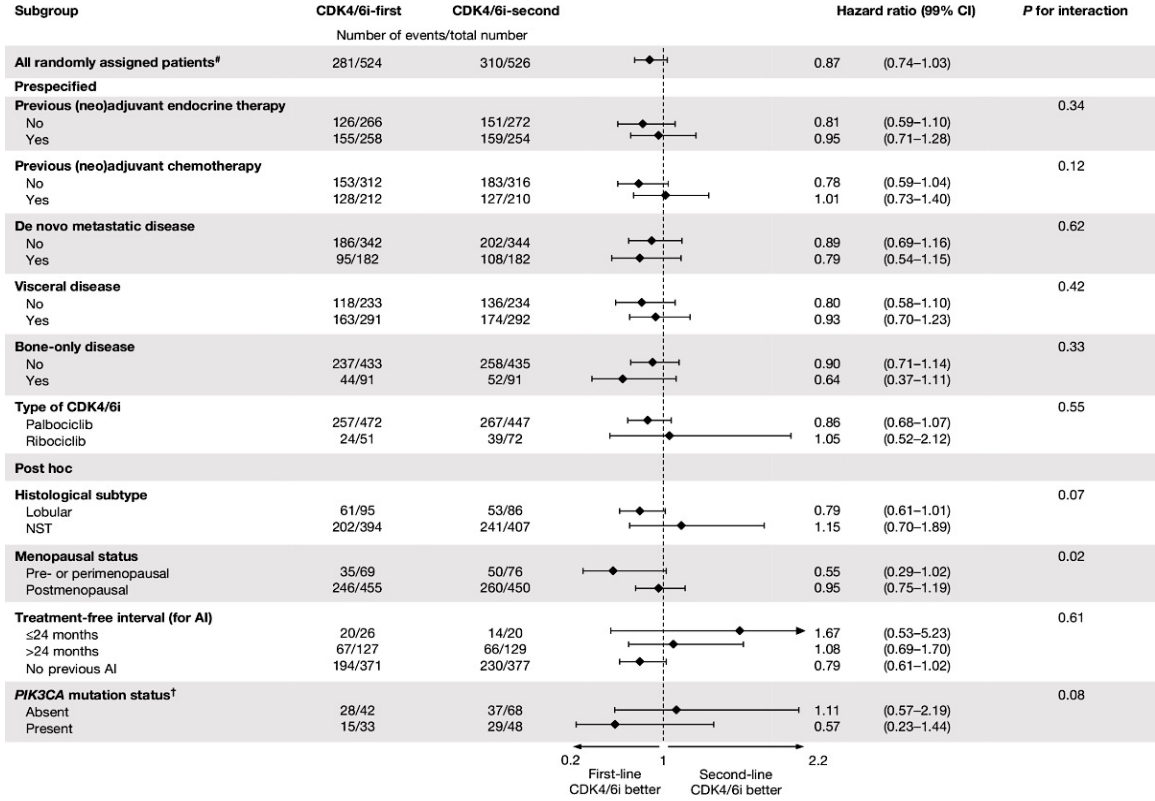
postMONARCH trial: Abemaciclib Plus Fulvestrant in Advanced Breast Cancer After Progression on CDK4/6 Inhibition: Results From the Phase III postMONARCH Trial

Primary outcome analysis of the phase 3 SONIA trial (BOOG 2017-03) on selecting the optimal position of cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors for patients with hormone receptor-positive (HR+), HER2-negative (HER2-) advanced breast cancer (ABC)

Sonke, *Nature* 2024
https://doi.org/10.1038/s41586-024-08035-2







SONIA: Financial comparison of Up-front v delayed CDK4/6 inhibition

Sonke, *Nature* 2024
https://doi.org/10.1038/s41586-024-08035-2

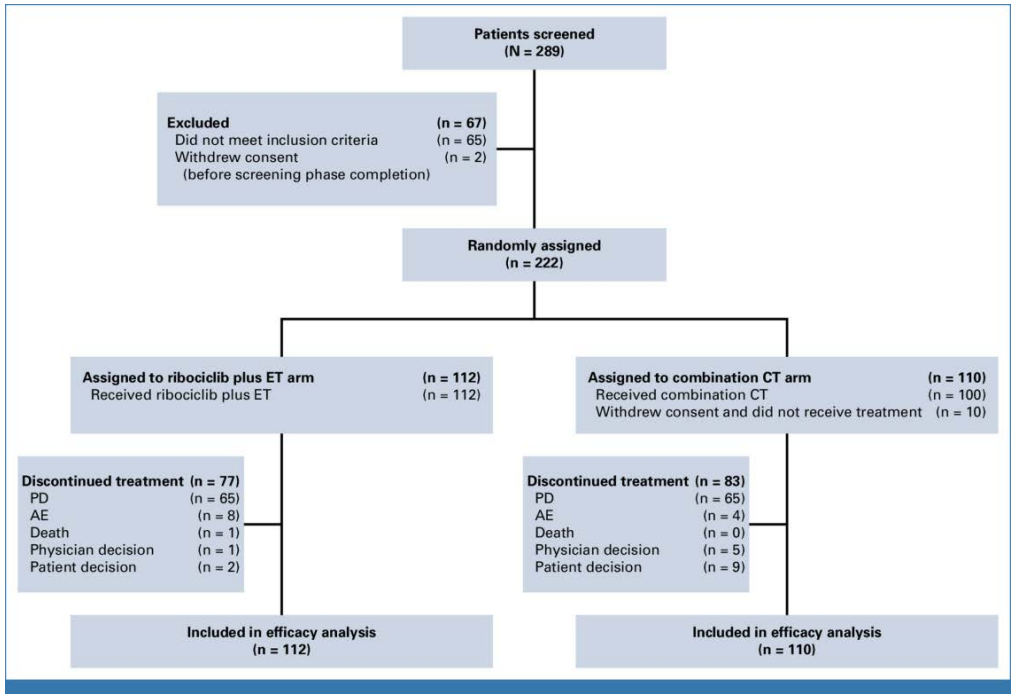
Costs by drug:

d. Input drug costs	Mg	Price US 2022[22]
Abemaciclib	50	$259
Abemaciclib	100	$259
Abemaciclib	150	$259
Palbociclib	75	$694
Palbociclib	100	$694
Palbociclib	125	$694
Ribociclib	200	$272

c. US list price of 2022	CDK4/6i-first group *n*=524	CDK4/6i-second group *n*=526	Incremental differences
Number of patients with CDK4/6i use at data cut-off	519	345	
Total costs	$170,792,867	$49,783,721	$121,009,146
Average costs per patient	$329,081	$144301	$184,780
Minimum costs per patient	$5,552	$4,164	$1,388
Maximum costs per patient	$909,644	$670,346	$239,298

Spares select patients ~15.6 months on CDK4/6 without loss of long-term benefit

RIGHT Choice: Ribociclib Plus Endocrine Therapy Versus Combination Chemotherapy in Premenopausal Women With Clinically Aggressive Hormone Receptor–Positive/Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer



Characteristics	Ribociclib + ET (n = 112)	Combination CT (n = 110)
Age, years, median (range)	44.0 (26-58)	43.0 (26-55)
Disease-free interval,[a] No. (%)		
De novo disease	70 (62.5)	73 (66.4)
Relapsed from early breast cancer	42 (37.5)	37 (33.6)
≤12 months	6 (5.4)	2 (1.8)
>12 and ≤24 months	8 (7.1)	7 (6.4)
>24 months	28 (25.0)	28 (25.5)
HER2 receptor negative, No. (%)	112 (100.0)	110 (100.0)
Estrogen receptor positive,[b] No. (%)	112 (100.0)	110 (100.0)
≥50%	95 (84.8)	96 (87.3)
<50%	8 (7.1)	4 (3.6)
Progesterone receptor positive,[c] No. (%)	99 (88.4)	102 (92.7)
Disease history, No. (%)		
Rapid progression	23 (20.5)	18 (16.4)
Symptomatic nonvisceral disease	15 (13.4)	16 (14.5)
Symptomatic visceral metastases	74 (66.1)	76 (69.1)
Visceral crisis status, No. (%)		
Yes	57 (50.9)	49 (44.5)
Metastatic sites,[d] No. (%)		
Bone	60 (53.6)	68 (61.8)
Bone only	5 (4.5)	4 (3.6)
CNS	1 (0.9)	3 (2.7)
Liver	54 (48.2)	53 (48.2)
Liver or lung	87 (77.7)	82 (74.5)
Lung	62 (55.4)	55 (50.0)
Lymph node	74 (66.1)	75 (68.2)
Other	46 (41.1)	38 (34.5)
Skin	9 (8.0)	2 (1.8)
Soft tissue	3 (2.7)	5 (4.5)
Metastatic sites, No. (%)		
1	19 (17.0)	11 (10.0)
2	29 (25.9)	39 (35.5)
≥3	64 (57.1)	60 (54.5)

Lu, J Clin Oncol, JCO 2024 https://doi.org/10.1200/JCO.24.0014

RIGHT Choice: Ribociclib Plus Endocrine Therapy Versus Combination Chemotherapy in Premenopausal Women With Clinically Aggressive Hormone Receptor–Positive/Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer

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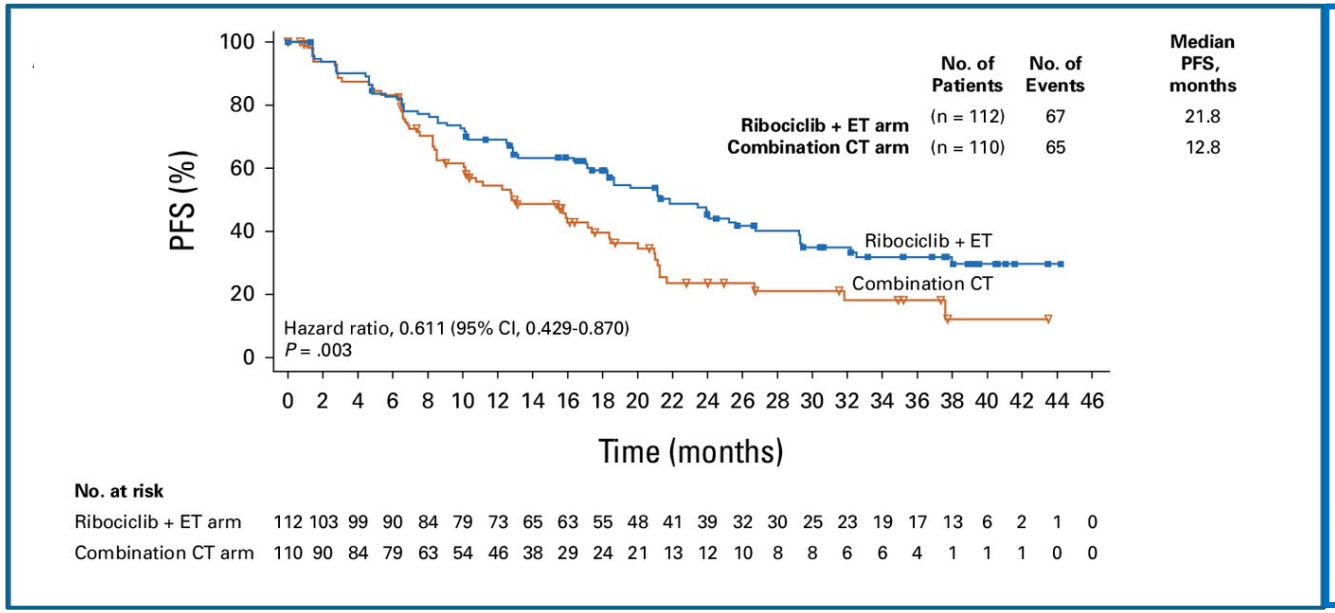
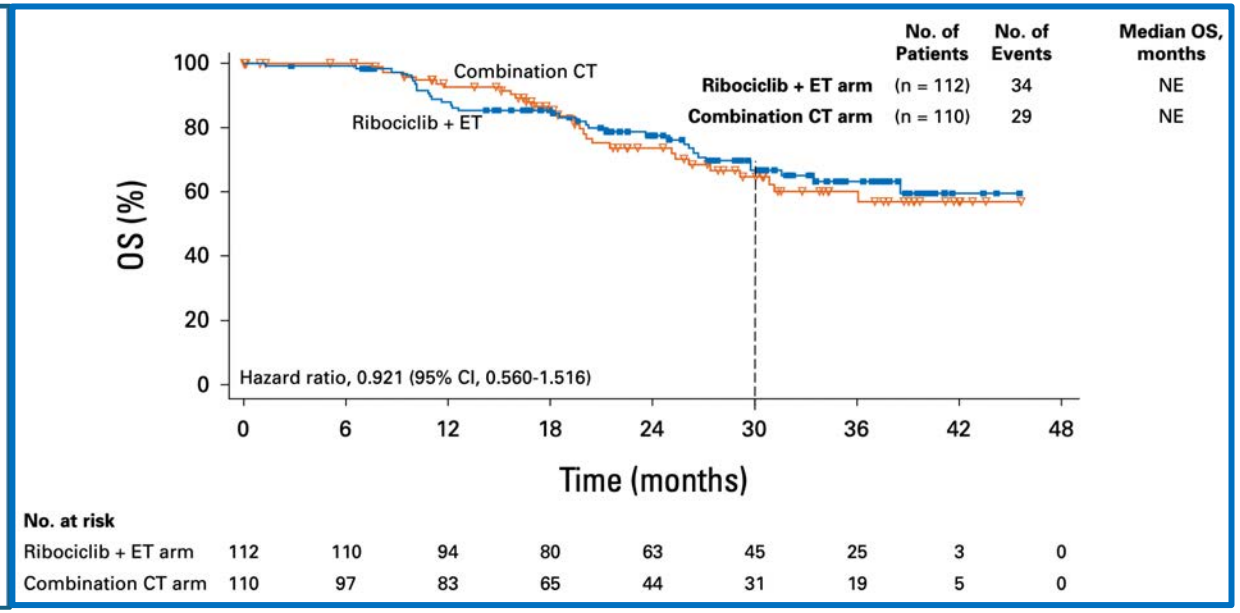
Rapid progression	23 (20.5)	18 (16.4)
Symptomatic nonvisceral disease	15 (13.4)	16 (14.5)
Symptomatic visceral metastases	74 (66.1)	76 (69.1)
Visceral crisis status, No. (%)		
Yes	57 (50.9)	49 (44.5)
Metastatic sites,[d] No. (%)		
Bone	60 (53.6)	68 (61.8)
Bone only	5 (4.5)	4 (3.6)
CNS	1 (0.9)	3 (2.7)
Liver	54 (48.2)	53 (48.2)
Liver or lung	87 (77.7)	82 (74.5)
Lung	62 (55.4)	55 (50.0)
Lymph node	74 (66.1)	75 (68.2)
Other	46 (41.1)	38 (34.5)
Skin	9 (8.0)	2 (1.8)
Soft tissue	3 (2.7)	5 (4.5)
Metastatic sites, No. (%)		
1	19 (17.0)	11 (10.0)
2	29 (25.9)	39 (35.5)
≥3	64 (57.1)	60 (54.5)

Lu, J Clin Oncol, JCO 2024 https://doi.org/10.1200/JCO.24.00144

RIGHT Choice: Ribociclib Plus Endocrine Therapy Versus Combination Chemotherapy in Premenopausal Women With Clinically Aggressive Hormone Receptor–Positive/Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer

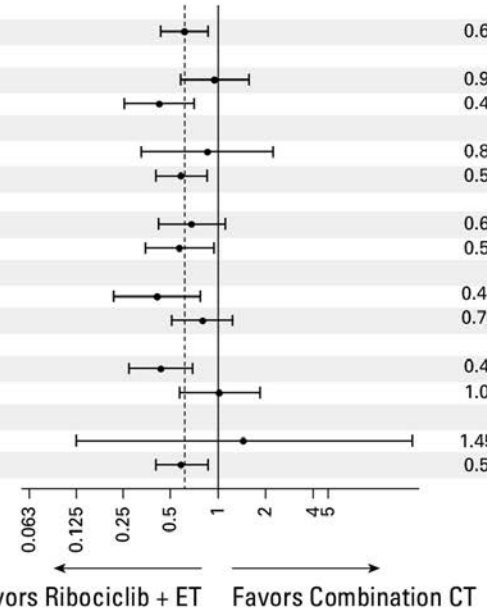


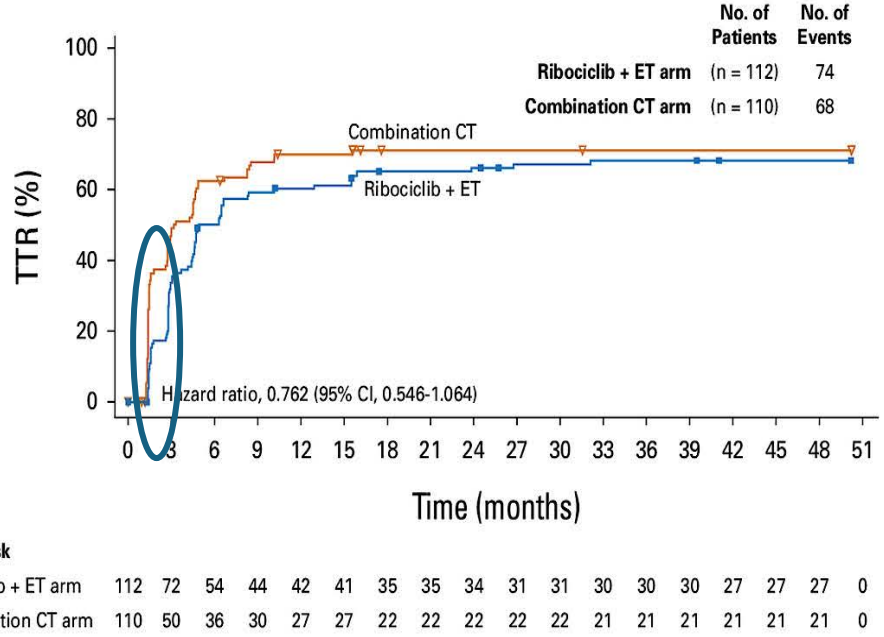


Lu, J Clin Oncol, JCO 2024 https://doi.org/10.1200/JCO.24.0014

RIGHT Choice: Ribociclib Plus Endocrine Therapy Versus Combination Chemotherapy in Premenopausal Women With Clinically Aggressive Hormone Receptor–Positive/Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer

Subgroup	Ribociclib + ET Arm n/N	Combination CT Arm n/N	Hazard Ratio (95% CI)
All patients	67/112	65/110	0.611 (0.429, 0.870)
Visceral crisis status (yes *v* no)			
Yes	37/57	27/49	0.953 (0.574, 1.582)
No	30/55	38/61	0.423 (0.254, 0.704)
Disease-free interval, years			
<2	11/14	8/9	0.851 (0.325, 2.231)
≥2	56/98	57/101	0.581 (0.398, 0.847)
Presence of liver metastasis (yes *v* no)			
Yes	35/54	32/53	0.681 (0.420, 1.106)
No	32/58	33/57	0.565 (0.343, 0.933)
Age, years			
<40	19/32	28/38	0.410 (0.217, 0.776)
≥40	48/80	37/72	0.789 (0.505, 1.232)
De novo (yes *v* no)			
Yes	36/70	45/73	0.432 (0.270, 0.689)
No	31/42	20/37	1.016 (0.562, 1.836)
Estrogen receptor status			
<50	4/8	3/4	1.457 (0.124, 17.079)
≥50	57/95	56/96	0.585 (0.398, 0.860)



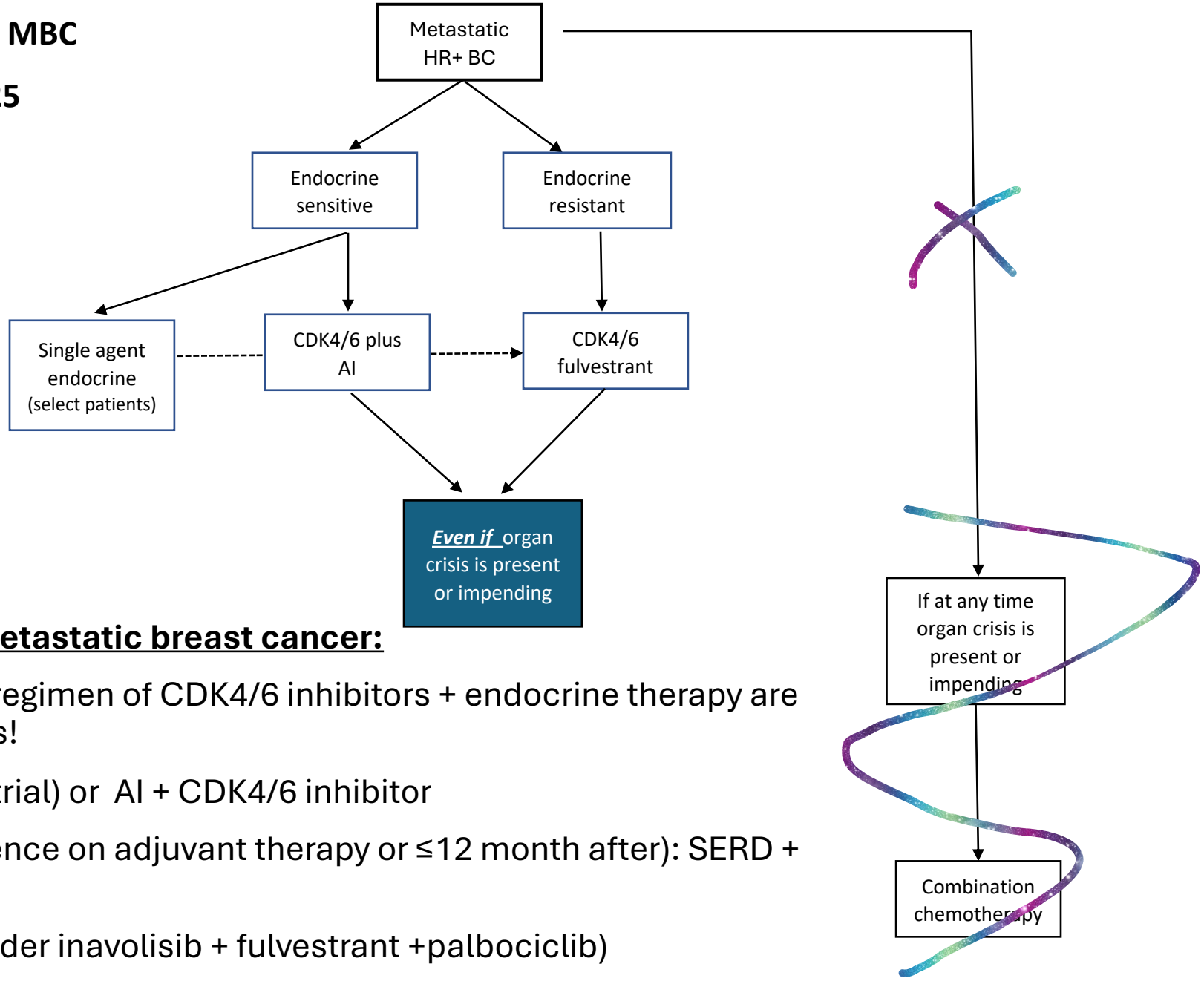


Ribociclib + ET offers fast early response within 1-2 months, equal to chemo and sufficient to rescue from visceral crisis

Lu, J Clin Oncol, JCO 2024 https://doi.org/10.1200/JCO.24.0014

Flow diagram for ER+/HER2- MBC

treatment decisions 2025



<u>Front line therapy for HR+ metastatic breast cancer:</u>

<u>Do not give chemotherapy:</u> regimen of CDK4/6 inhibitors + endocrine therapy are superior even in visceral crisis!

AI sensitive: AI alone (SONIA trial) or AI + CDK4/6 inhibitor

Endocrine resistance (recurrence on adjuvant therapy or ≤12 month after): SERD + CDK4/6

(PIK3CA + can consider inavolisib + fulvestrant +palbociclib)

What about after a CDK4/6 inhibitor?

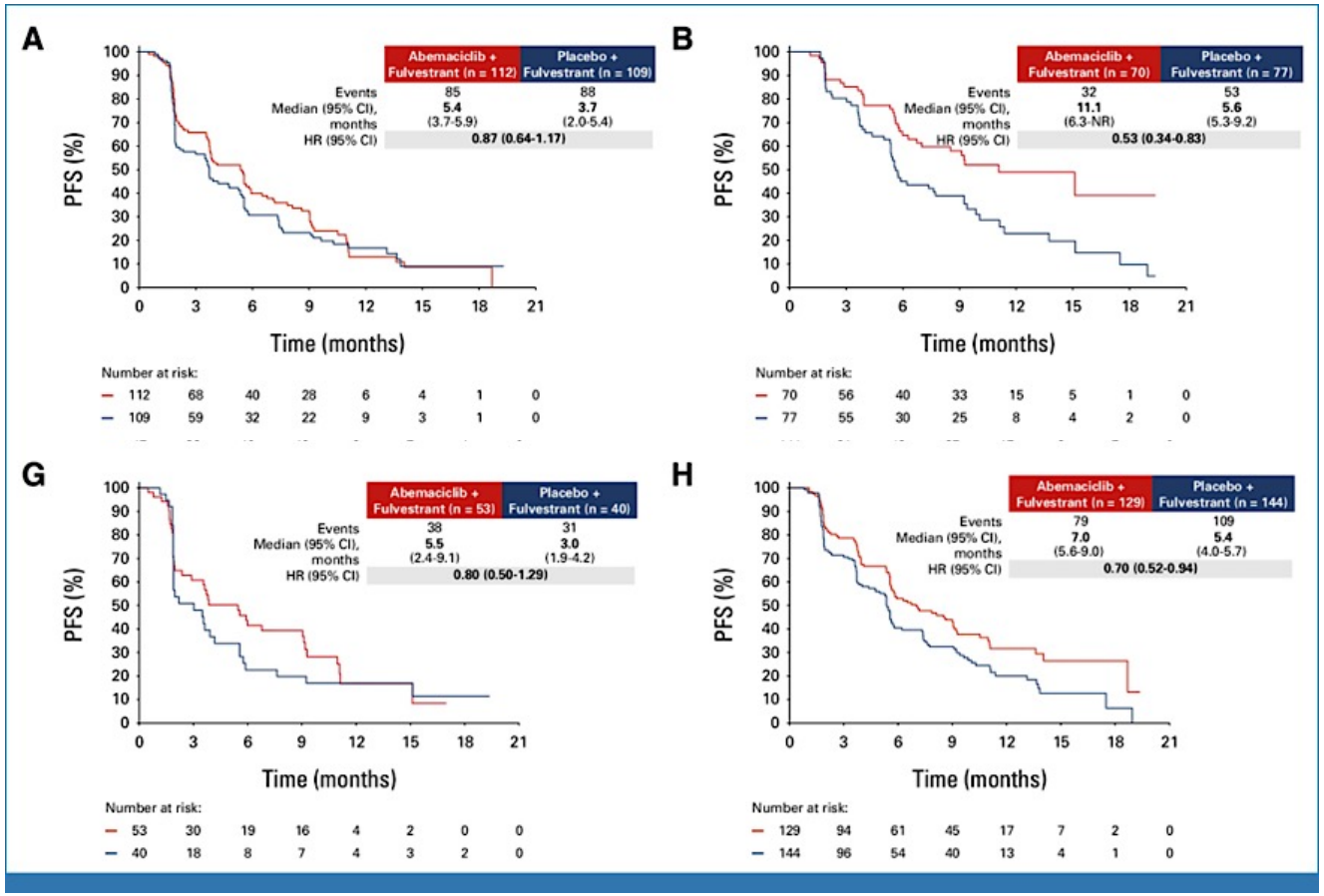
Can sequencing be used?

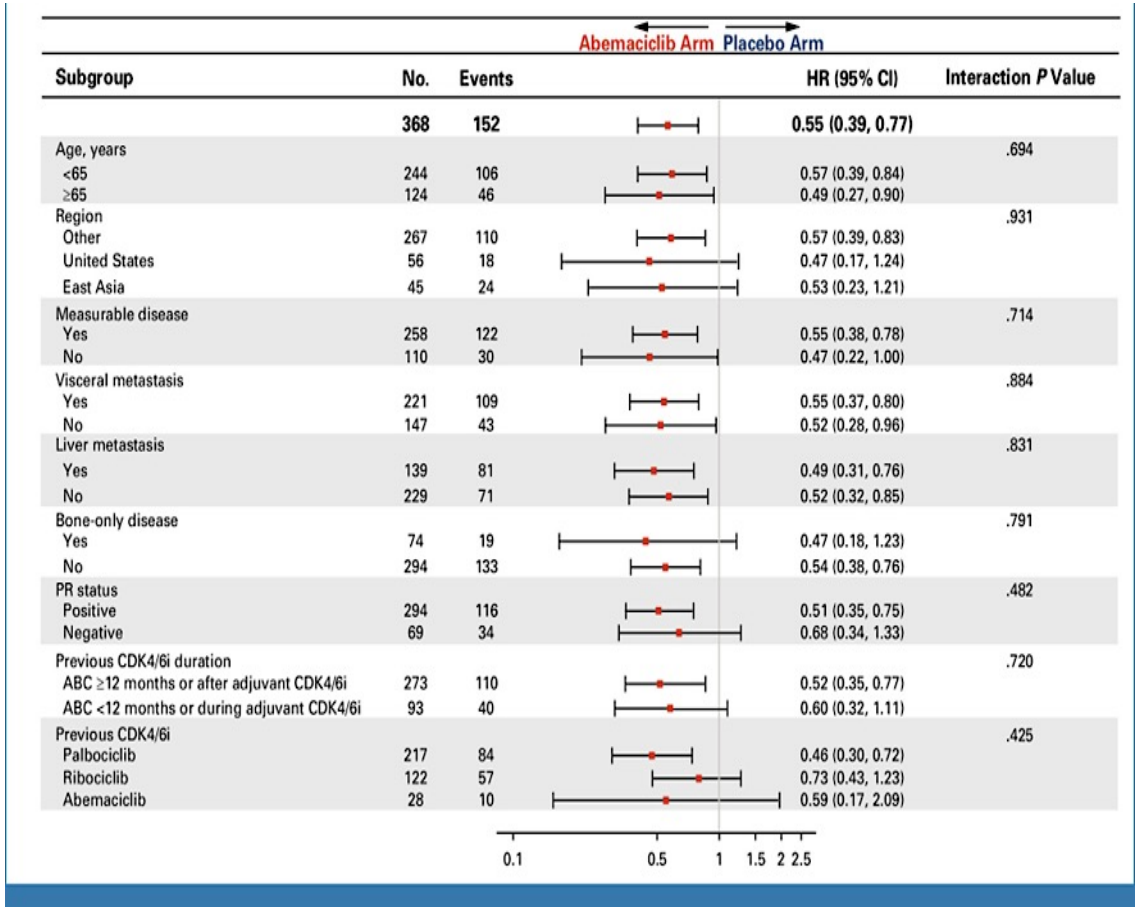
Abemaciclib Plus Fulvestrant in Advanced Breast Cancer After Progression on CDK4/6 Inhibition: Results From the Phase III postMONARCH Trial

Characteristic	Abemaciclib + Fulvestrant (n = 182)	Placebo + Fulvestrant (n = 186)	Total (N = 368)
Age, years			
Median	58.0	61.0	59.0
<65, No. (%)	126 (69.2)	118 (63.4)	244 (66.3)
ECOG performance status, No. (%)			
0	104 (57.1)	107 (57.5)	211 (57.3)
1	78 (42.9)	79 (42.5)	157 (42.7)
Site of metastasis, No. (%)			
Visceral	112 (61.5)	109 (58.6)	221 (60.1)
Liver	68 (37.4)	71 (38.2)	139 (37.8)
Bone only	32 (17.6)	42 (22.6)	74 (20.1)
Stage IV at initial diagnosis	75 (41.2)	74 (39.8)	149 (40.5)
Previous CDK4/6i setting,[b] No. (%)			
ABC	182 (100)	182 (97.8)	364 (98.9)
Adjuvant	0	3 (1.6)	3 (0.8)
Previous CDK4/6i, No. (%)			
Palbociclib	107 (58.8)	110 (59.1)	217 (59.0)
Ribociclib	61 (33.5)	61 (32.8)	122 (33.2)
Abemaciclib	14 (7.7)	14 (7.5)	28 (7.6)
Duration of previous CDK4/6i, months,[c] No. (%)			
≥12	129 (70.9)	141 (75.8)	270 (73.4)
<12	53 (29.1)	40 (21.5)	93 (25.3)
Duration of previous CDK4/6i,[c] months, median			
All	19	21	20
Palbociclib	19	23	21
Ribociclib	15	18	17
Abemaciclib	26	17	22

Kalinsky, JCO 2024.
https://doi.org/10.1200/JCO-24-02086

Outcomes for clinically relevant subgroups





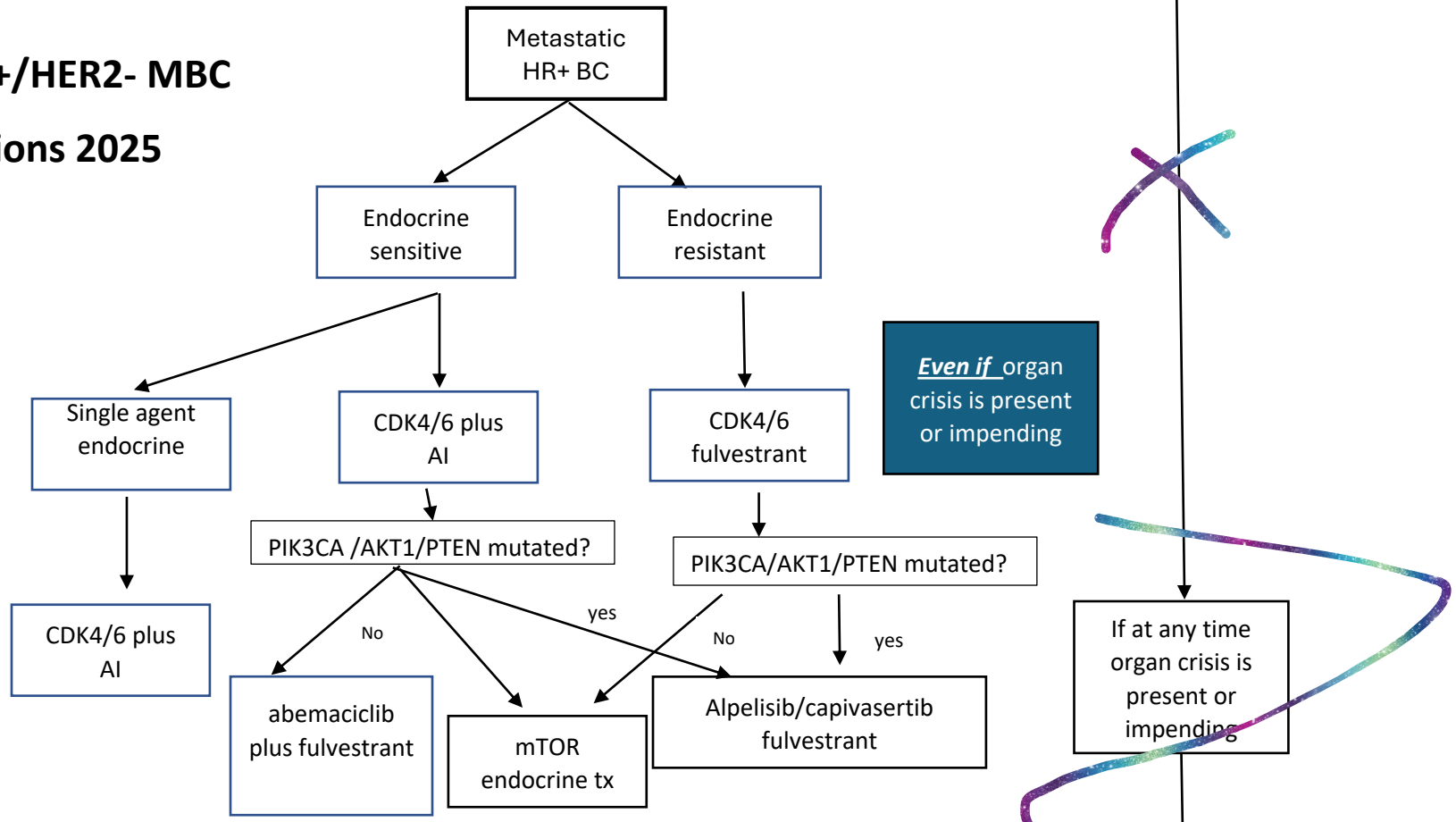
Subgroup	No.	Events	HR (95% CI)	Interaction *P* Value
	368	152	0.55 (0.39, 0.77)	
Age, years				.694
<65	244	106	0.57 (0.39, 0.84)	
≥65	124	46	0.49 (0.27, 0.90)	
Region				.931
Other	267	110	0.57 (0.39, 0.83)	
United States	56	18	0.47 (0.17, 1.24)	
East Asia	45	24	0.53 (0.23, 1.21)	
Measurable disease				.714
Yes	258	122	0.55 (0.38, 0.78)	
No	110	30	0.47 (0.22, 1.00)	
Visceral metastasis				.884
Yes	221	109	0.55 (0.37, 0.80)	
No	147	43	0.52 (0.28, 0.96)	
Liver metastasis				.831
Yes	139	81	0.49 (0.31, 0.76)	
No	229	71	0.52 (0.32, 0.85)	
Bone-only disease				.791
Yes	74	19	0.47 (0.18, 1.23)	
No	294	133	0.54 (0.38, 0.76)	
PR status				.482
Positive	294	116	0.51 (0.35, 0.75)	
Negative	69	34	0.68 (0.34, 1.33)	
Previous CDK4/6i duration				.720
ABC ≥12 months or after adjuvant CDK4/6i	273	110	0.52 (0.35, 0.77)	
ABC <12 months or during adjuvant CDK4/6i	93	40	0.60 (0.32, 1.11)	
Previous CDK4/6i				.425
Palbociclib	217	84	0.46 (0.30, 0.72)	
Ribociclib	122	57	0.73 (0.43, 1.23)	
Abemaciclib	28	10	0.59 (0.17, 2.09)	

(A) patients with liver metastasis (B) patients without visceral metastasis (G) patients who received previous CDK4/6i for <12 months; and (H) patients who received previous CDK4/6i for ≥12 months.

Kalinsky, JCO 2024.
https://doi.org/10.1200/JCO-24-02086

Sequencing of CDK4/6 inhibitor data in context

Flow diagram for ER+/HER2- MBC treatment decisions 2025



Second line therapy

<u>Second line therapy for HR+ metastatic breast cancer:</u>

SERD + CDK4/6 and sequencing of CDK4/6 to second line abemaciclib appropriate

PIK3CA/AKT1/PTEN+ consider alpelisib or capivasertib + fulvestrant

ESR1+ consider elacestrant or clinical trial of oral SERD

Sequencing of CDK4/6 inhibitor data in context

Front line therapy for HR+ metastatic breast cancer:

Do not give chemotherapy: regimen of CDK4/6 inhibitors + endocrine therapy are superior even in visceral crisis!

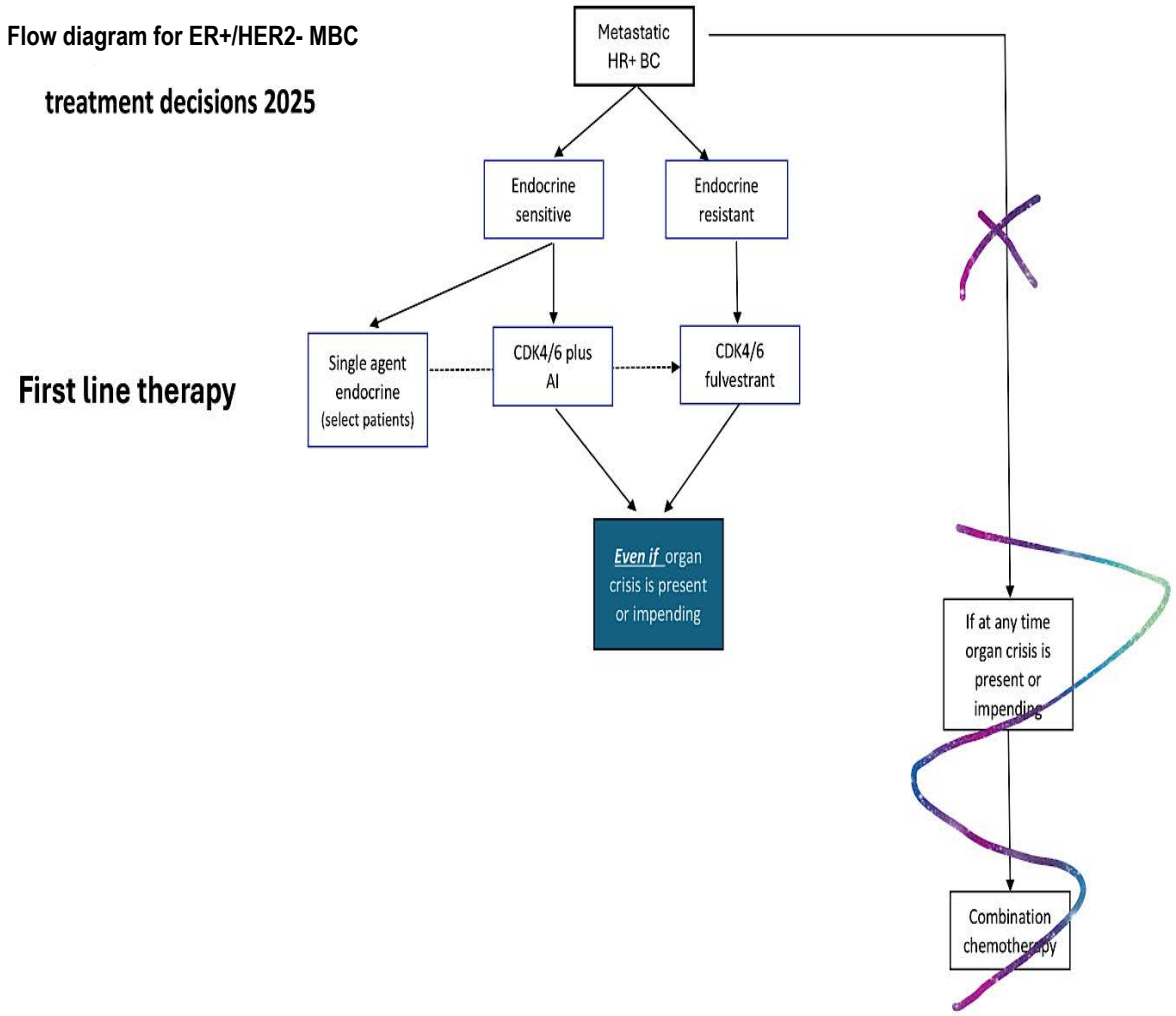
AI sensitive: AI alone (SONIA trial) or AI + CDK4/6 inhibitor

Consider types of metastasis, performance status, prior treatment results and treatment course

Favors using CDK4/6: Visceral/liver mets, rapid recurrence on or shortly after EBC ET, poor performance status

Endocrine resistance (recurrence on adjuvant therapy or ≤12 month after): SERD + CDK4/6 (PIK3CA+ can consider inavolisib + fulvestrant + palbociclib)

Second line therapy for HR+ metastatic breast cancer



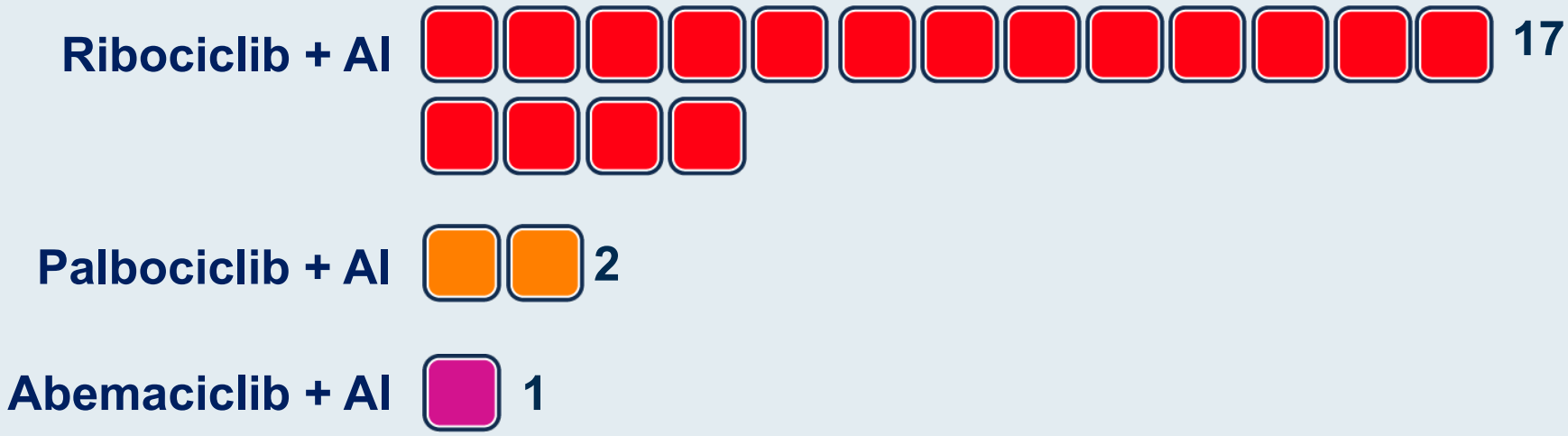
Discussion Questions and Faculty Case Presentations

Clinical Factors Affecting Clinical Investigators' (CIs) Selection of CDK4/6 Inhibitors (CDKis) for Patients with Hormone Receptor-Positive Metastatic Breast Cancer (HR+ mBC)

Abstract Submitted: ASCO 2025

A woman presents with de novo ER-positive, PR-positive, HER2-negative, BRCA WT metastatic breast cancer. Which endocrine-based treatment would you most likely recommend for the scenario below?

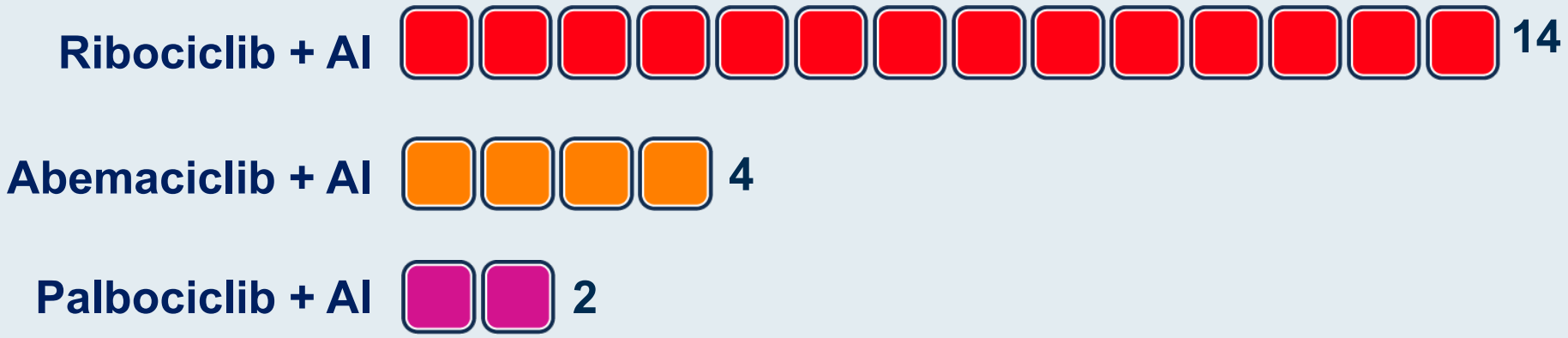
Age 65, PS 0
Asymptomatic bone metastases



Survey of 20 Breast Cancer Clinical Investigators

A woman presents with de novo ER-positive, PR-negative, HER2-negative, BRCA WT metastatic breast cancer. Which endocrine-based treatment would you most likely recommend for the scenario below?

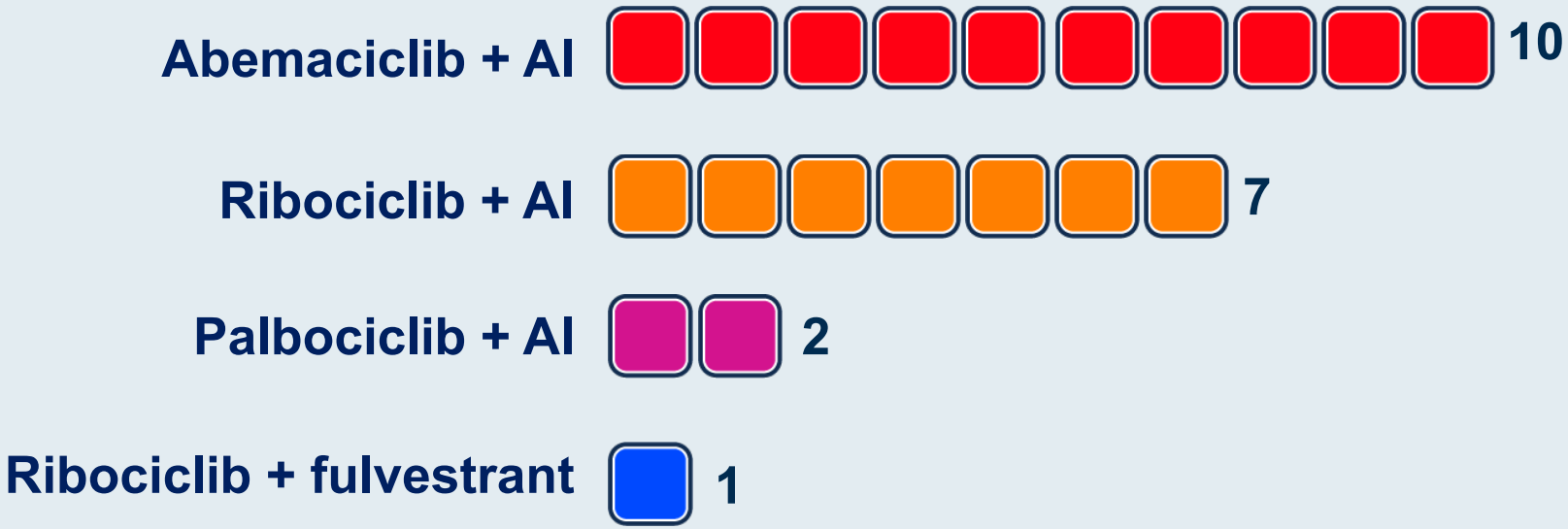
Age 65, PS 0
Symptomatic visceral (including liver) metastases



Survey of 20 Breast Cancer Clinical Investigators

A woman presents with de novo ER-positive, PR-positive, HER2-negative, BRCA WT metastatic breast cancer. Which endocrine-based treatment would you most likely recommend for the scenario below?

Age 65, PS 0
Multiple asymptomatic brain metastases that require WBRT



Survey of 20 Breast Cancer Clinical Investigators

An 85-year-old woman with multiple comorbidities who has a difficult time managing polypharmacy presents with de novo ER-positive, PR-positive, HER2-negative, BRCA WT breast cancer and symptomatic visceral metastases. Which endocrine-based treatment would you most likely recommend?

Survey of 20 Breast Cancer Clinical Investigators

Case Presentation: Dr O'Shaughnessy

- 36 yo woman interrupted adjuvant ET for 2+ years to have 2nd child
- Initial disease was grade 2 T2 N0 M0 ER/PR++ HER2-; bilat mastectomy
- Treated with adjuvant AC/T then leuprolide + tamoxifen
- After 2 years stopped ET and proceeded to have 2nd child and to nurse for 1 year
- Resumed leuprolide + tamoxifen
- 1 year later recurred with right pleural disease only – ER/PR++ HER2-
- Treated with leuprolide, letrozole, ribociclib
- CA27.29 stable for few months then steadily increased and chest CT showed increased pleural thickening
- Ribociclib was changed to abemaciclib and her disease responded for 2 years then progressed in the pleura

Case Presentation: Dr Bardia

55 yo Female with:

- 2008: HR+/HER2- breast cancer (localized)
- 2018: Completed adjuvant tamoxifen
- 2022: Disease recurrence (bone):

  ER+/HER2 low (IHC = 1+). Started letrozole with ribociclib
- 2025: Disease progression (bone)

ctDNA analysis revealed no actionable mutations

Pt started fulvestrant and abemaciclib

Case Presentation: Dr Burstein (Part 1)

- A 59 year old woman has been receiving treatment for advanced breast cancer.
- In 2015, she was diagnosed with screening mammogram findings and was found to have ER positive, PR positive, HER2 negative breast cancer, with nodal involvement. She received adjuvant TC chemotherapy, OFS, and AI treatment.
- In February 2021, she had metastatic disease to bone diagnosed after presenting with lower back pain. T11 vertebral body biopsy disclosed ER pos 90%, PR negative, HER2 +1 breast cancer.
- She began fulvestrant and palbociclib.

Keynote Session: Hormone Receptor-Positive Metastatic Breast Cancer

CDK4/6 Inhibitors for HR-Positive Metastatic Breast Cancer (mBC) — Dr Borges

Targeting the PTEN/PI3K/AKT Pathway in HR-Positive mBC — Dr Burstein

Role of Oral Selective Estrogen Receptor Degraders (SERDs) in the Management of HR-Positive mBC — Dr O'Shaughnessy

Antibody-Drug Conjugates for HR-Positive mBC — Dr Bardia

Targeting the PTEN-PI3K-AKT Pathway In ER+ Advanced Breast Cancer

Harold J. Burstein, MD, PhD

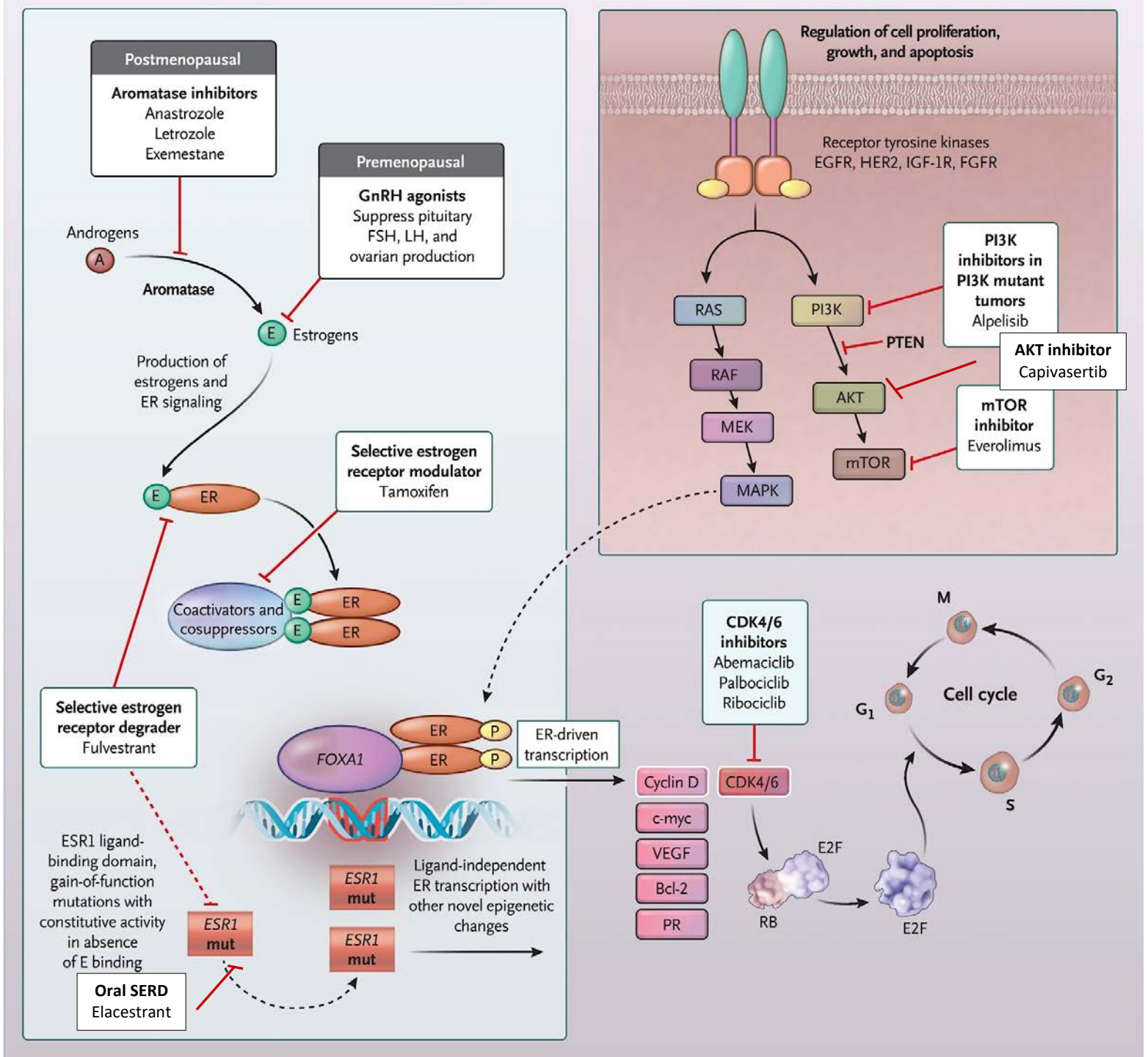
Dana-Farber
Cancer Institute

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Disclosures

No relevant conflicts of interest to disclose.

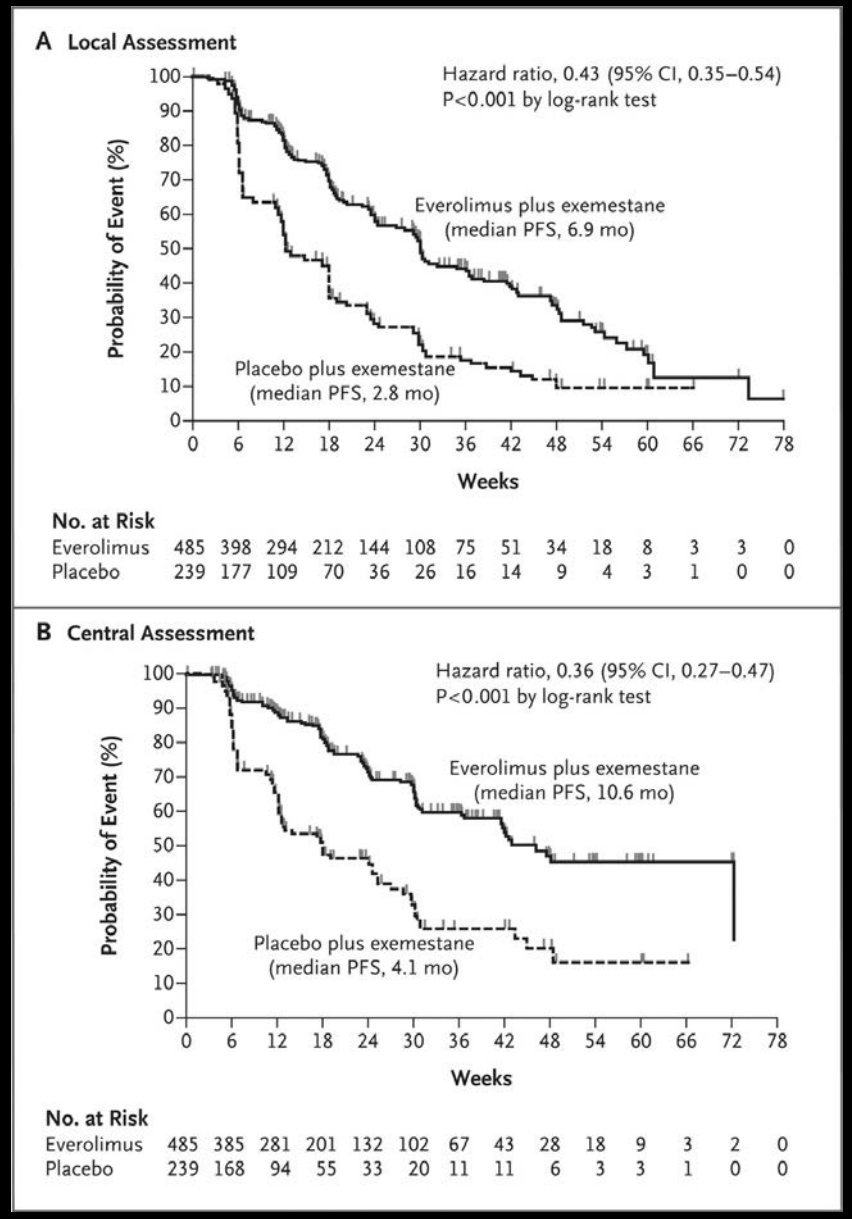
Targeting ER or E2



Targeting Other Growth Factor Paths

Adapted from
N Engl J Med 2020;383:2557.

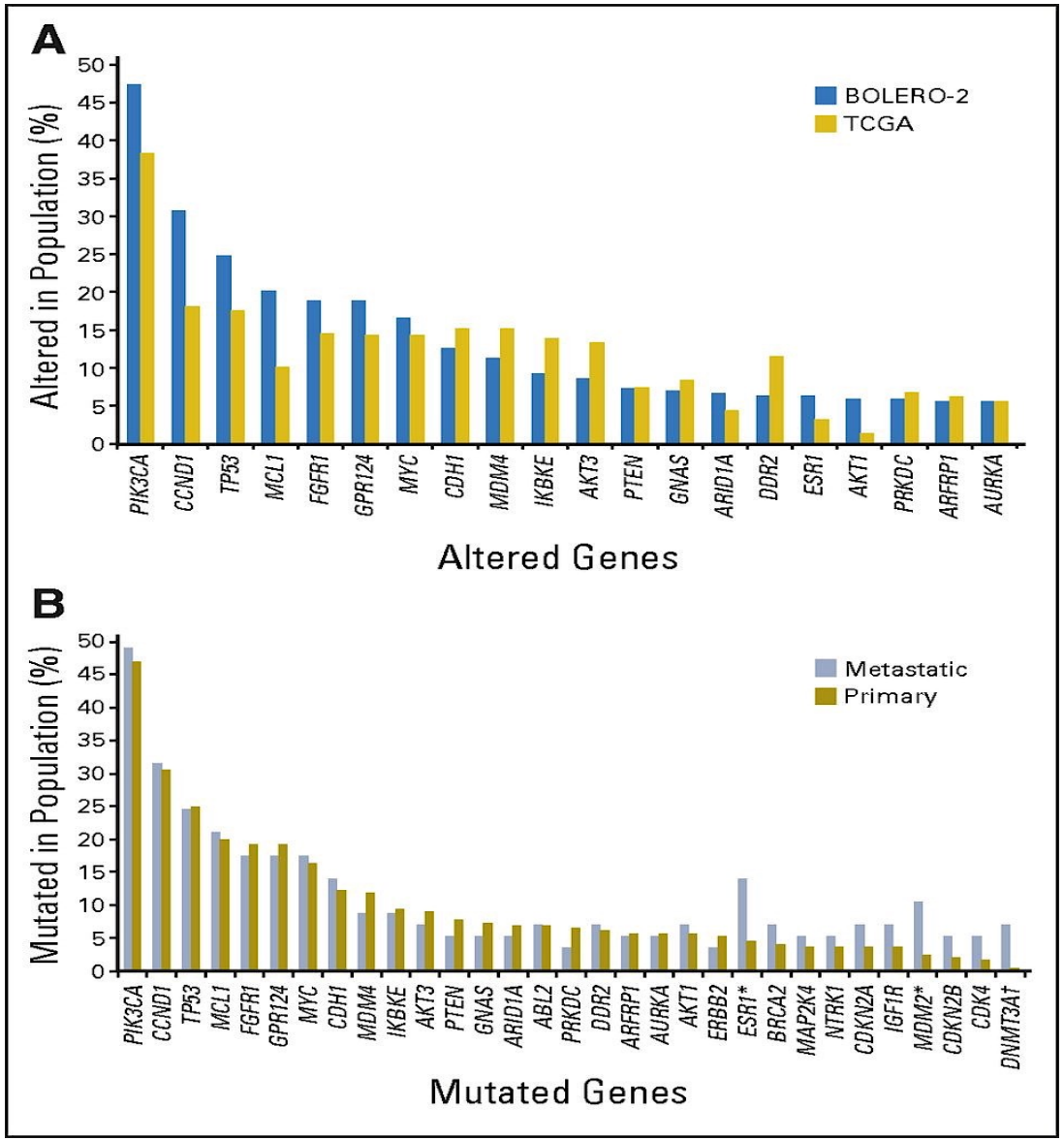
AI +/- everolimus in ER+ breast cancer



Baselga J et al. N Engl J Med 2012;366:520-529

The NEW ENGLAND JOURNAL of MEDICINE

GENE MUTATION FREQUENCIES IN ER+ MBC



Gabriel N. Hortobagyi; et al. *Journal of Clinical Oncology* 2016 34419-426.

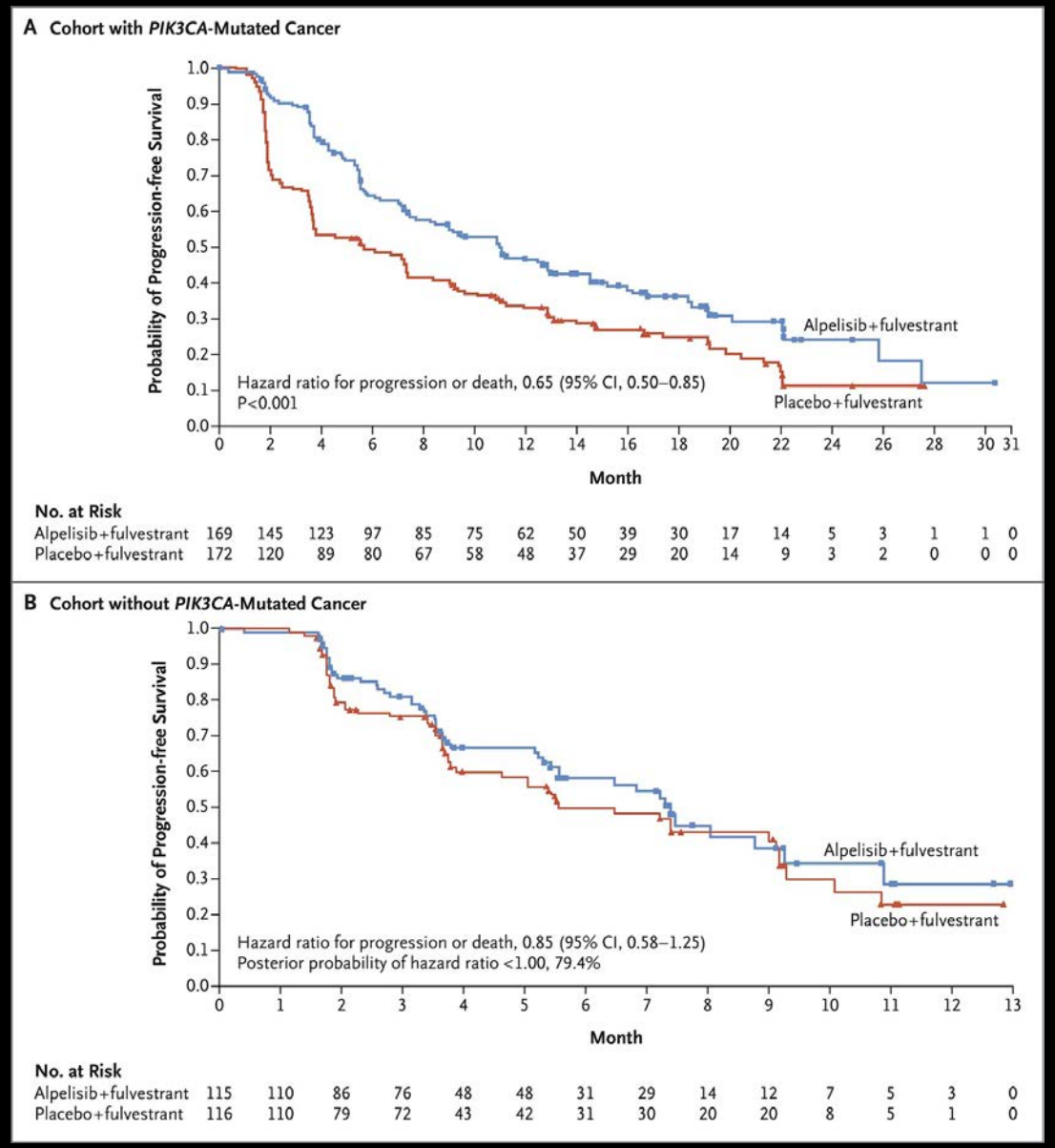
PI3K pathway alteration and BC subtype

	PIK3CA mut	AKT1 mut	PTEN mut	PTEN protein loss	PDK1 amp	INPP4B del	RAS/RAF mut	P53 mut
Breast (total)	339/1261 **(26.9%)**	27/1008 (2.6%)	6/209 (2.3%)	25/110 **(22.7%)**	27/129 **(20.9%)**	**≈ 20%**	2/406 (0.5%)	46/121 **(38%)**
Breast HR+	101/305 **(33.1%)**	6/232 (2.6%)	4/131 (3.4%)	10/69 (14.5%)	16/79 **(23.2%)**	Rare		18/73 **(24.6%)**
Breast HER2+	24/98 **(24.5%)**	0/75	0/33	2/18 (11%)	5/19 **(26.3%)**	Rare		14/23 **(60.9%)**
Breast TNBC	21/262 (8%)	0/111	0/41	11/21 **(52%)**	2/15 (13.3%)	**≈ 60%**		12/22 **(63.6%)**
Ovarian	*2/332 (0.6%)*	*2/332 (0.6%)*	*4/132 (3%)*	***≈ 40%***	*Rare*	*≈ 20%*	*12/428 (2.8%)*	*90/132* ***(68%)***
Endometrial	*73/246* ***(30%)***	*3/150 (2%)*	*20/76* ***(26%)***	*≈ 50%*	*Rare*	*≈ 8%*	*44/206* ***(21%)***	*9/96 (9%)*

Not included: PIK3CA amp

Unpublished data: SU2C

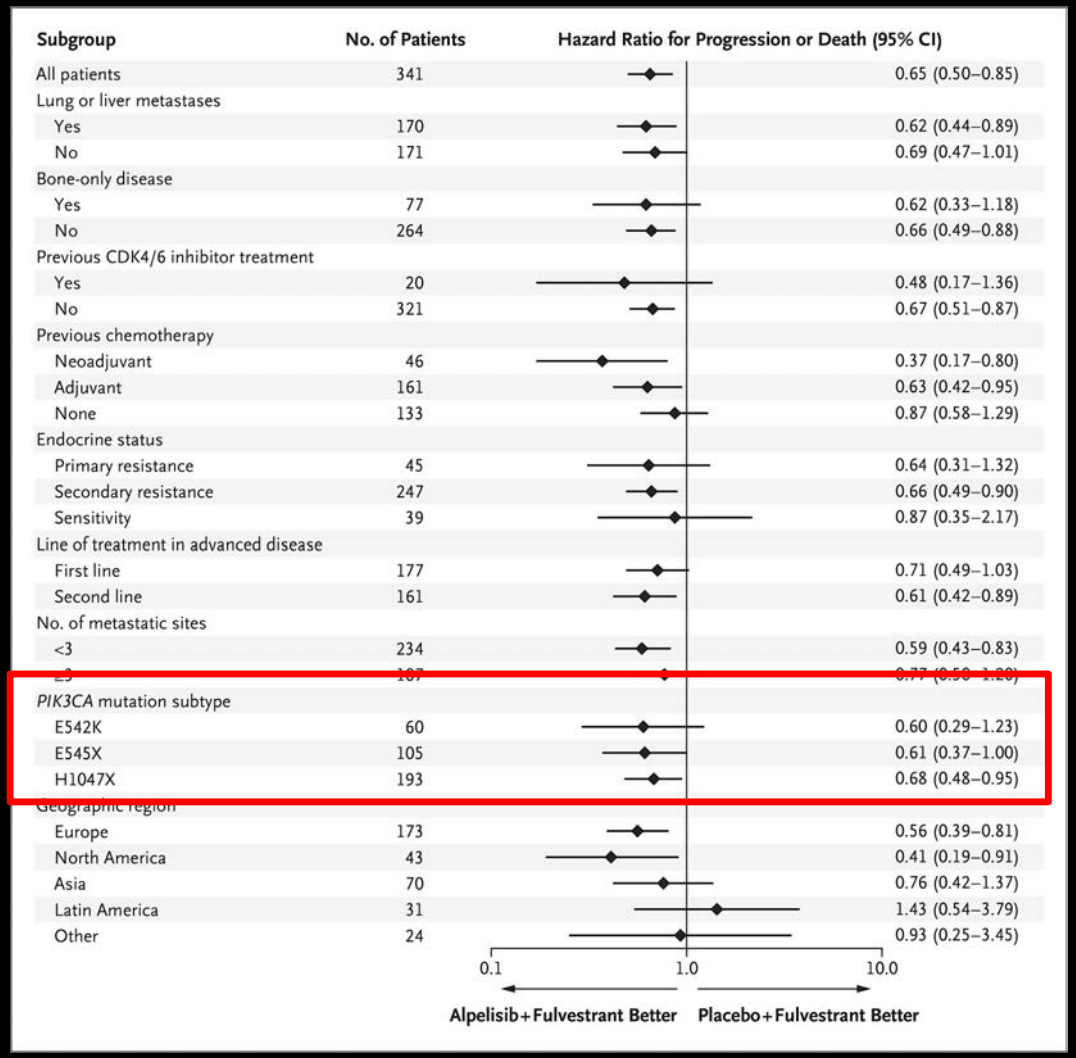
Alpelisib in ER+ MBC



André F et al. N Engl J Med 2019;380:1929-1940

The NEW ENGLAND JOURNAL of MEDICINE

Subgroup Analysis of Progression-free Survival in the Cohort with PIK3CA-Mutated Cancer.



André F et al. N Engl J Med 2019;380:1929-1940

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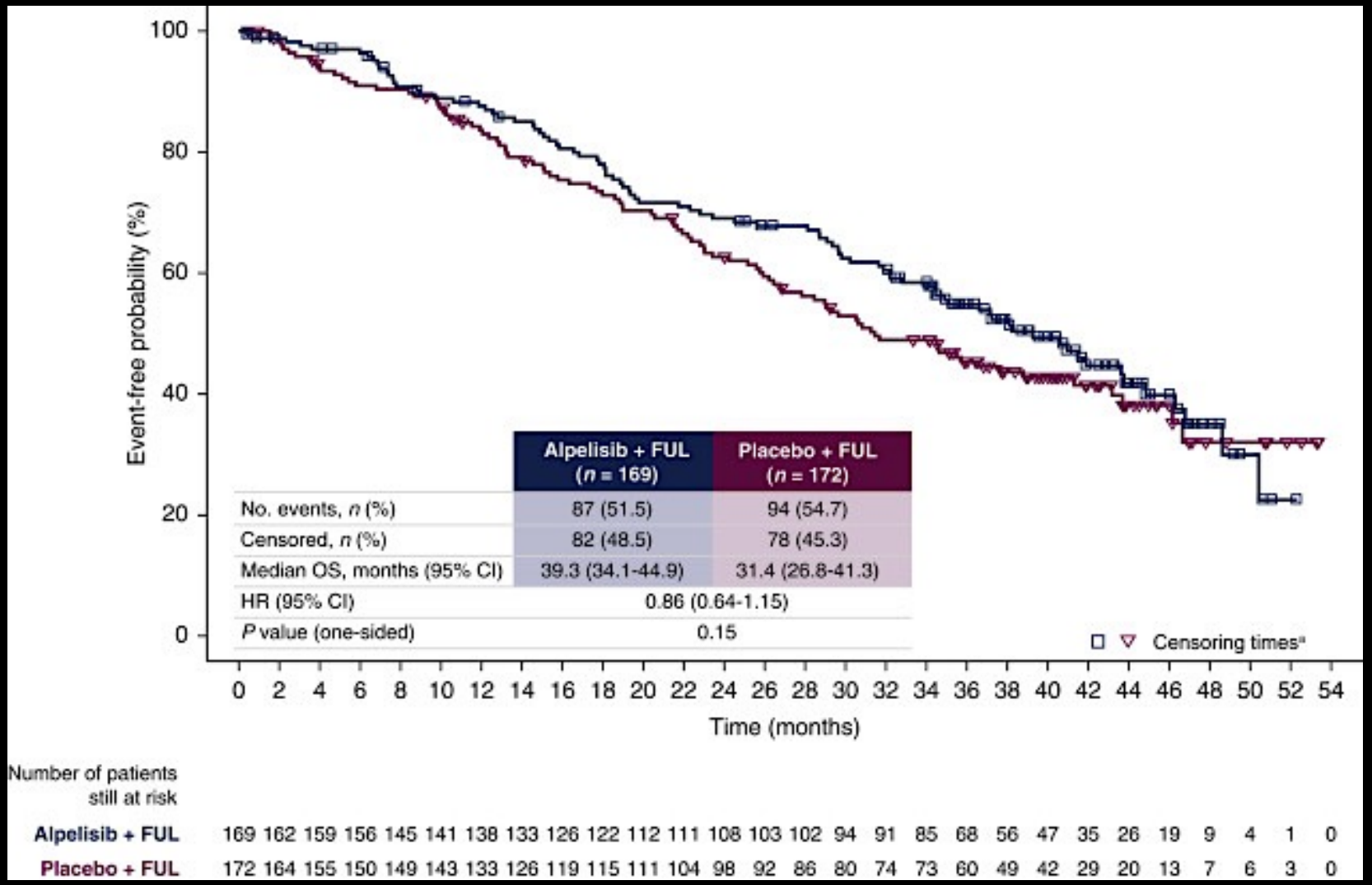
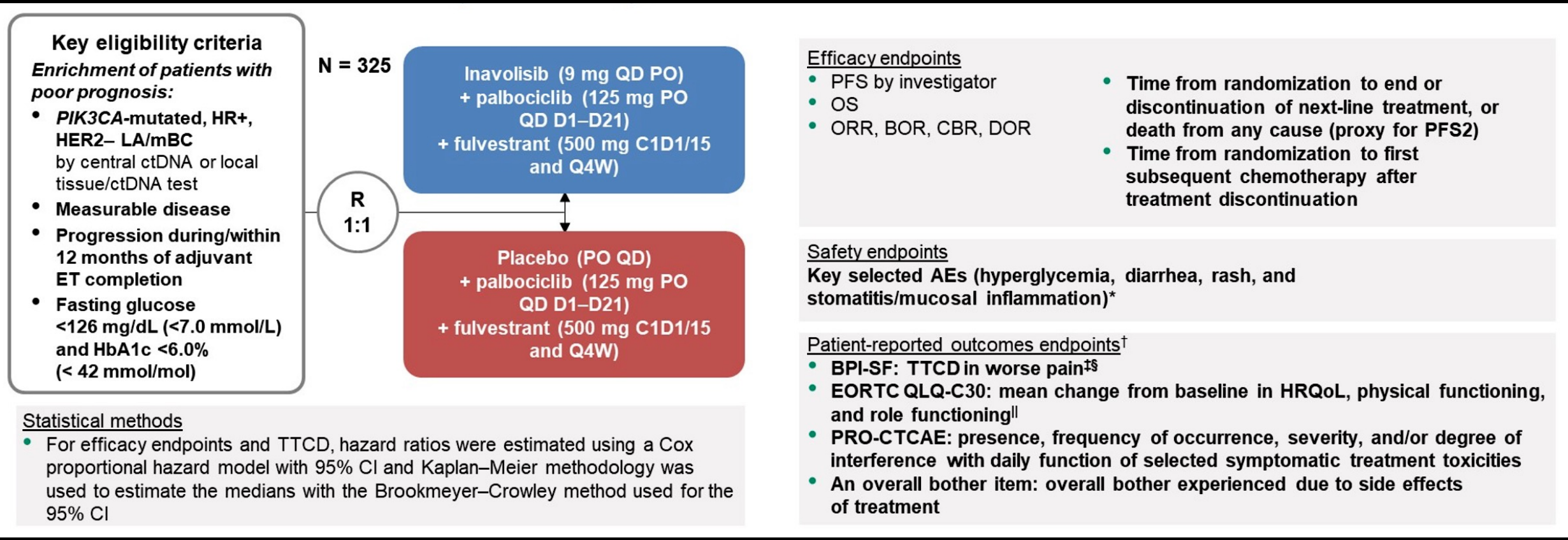
Overall Survival in SOLAR-1 Trial



Andre, et al. Ann Oncol 2021

INAVO120 Study Design



Juric D et al. ASCO 2024;Abstract 1003.

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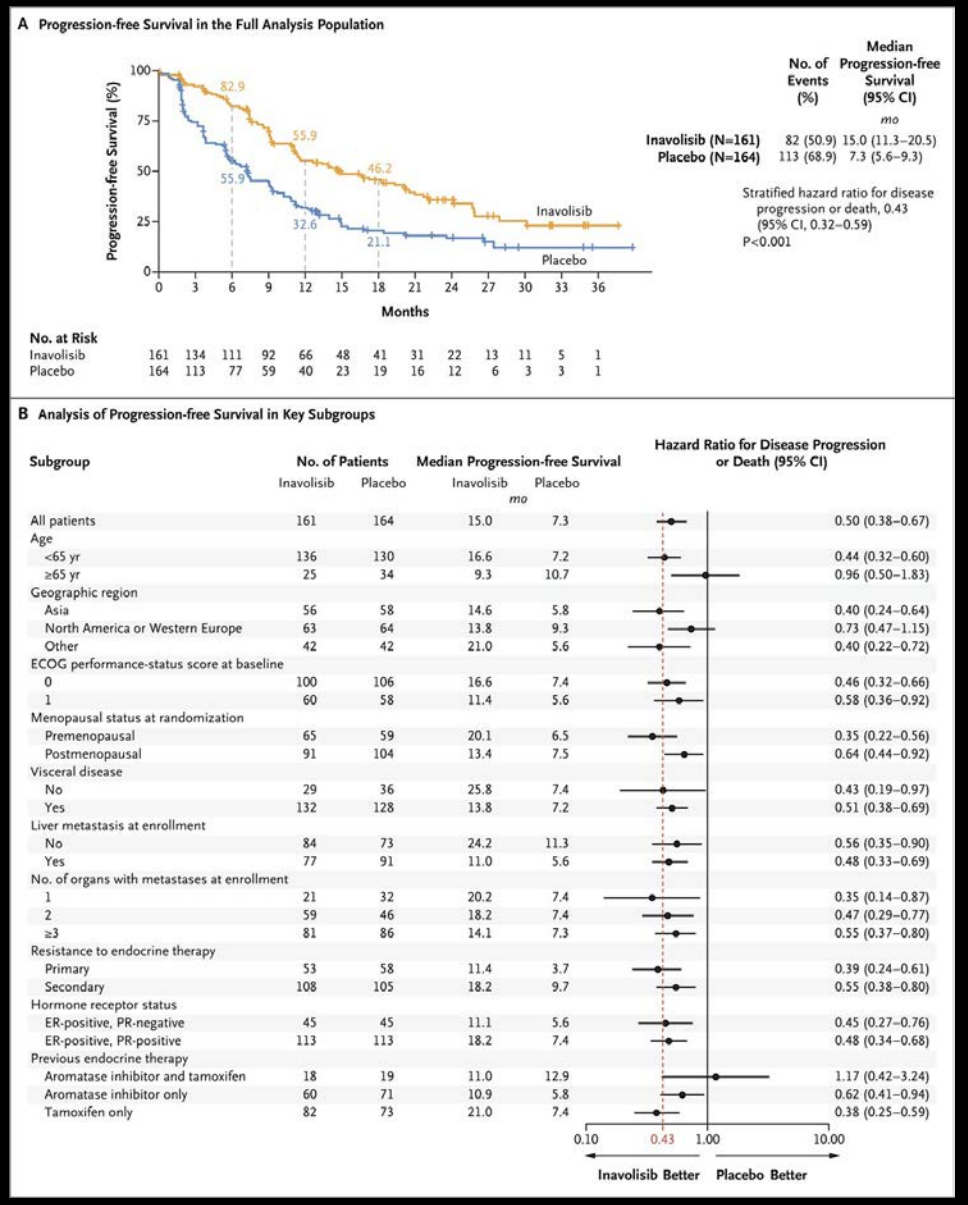
INAVO120 Progression-free Survival.



Turner NC et al. N Engl J Med 2024;391:1584-1596

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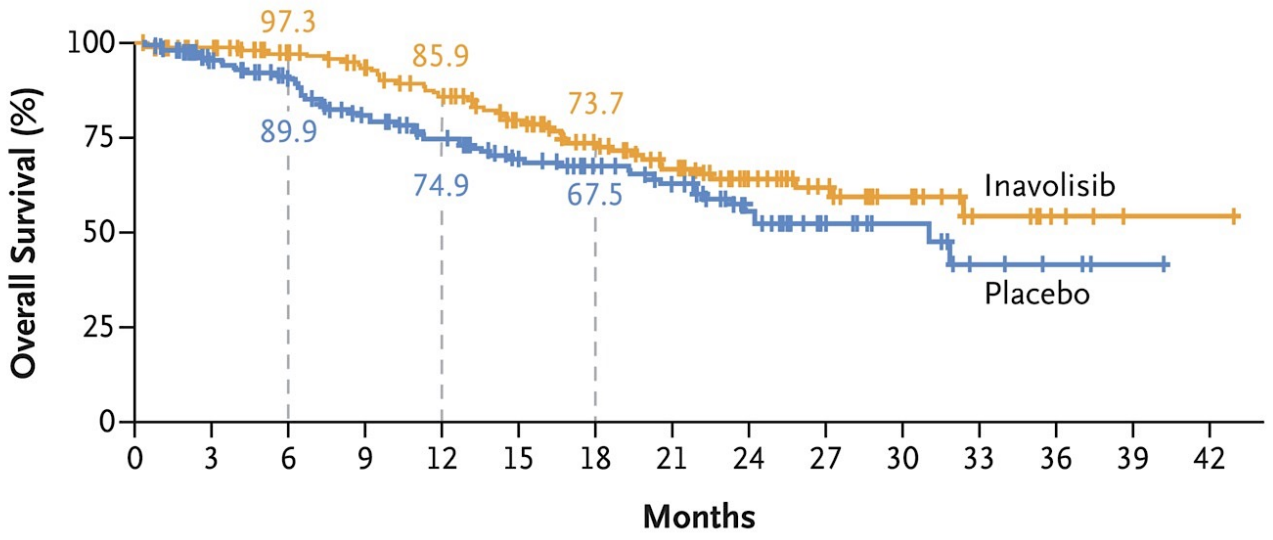
Overall Survival.



No. at Risk

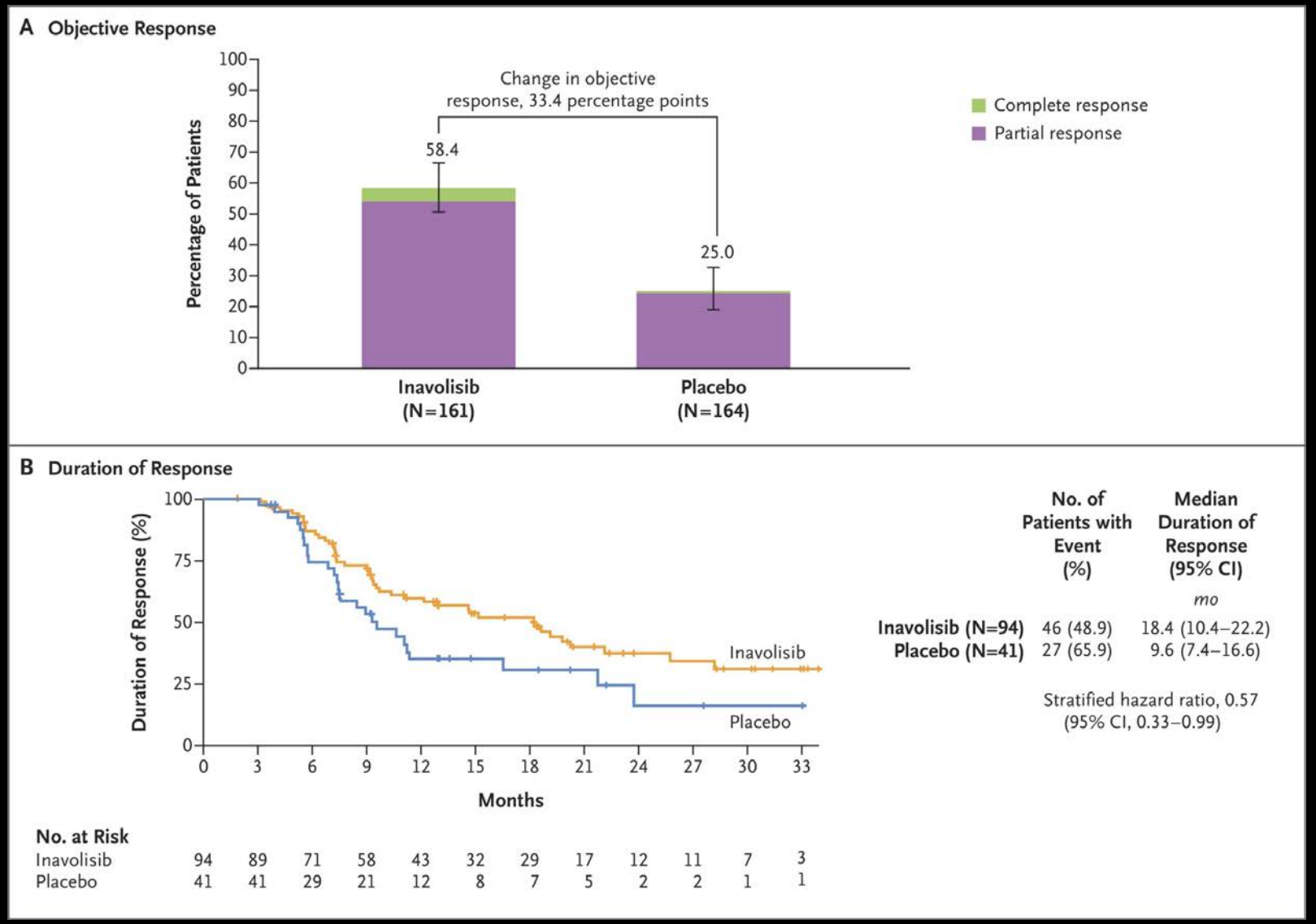
Inavolisib	161	143	127	114	101	85	69	56	38	26	17	8	4	1	1
Placebo	164	139	120	98	87	72	61	52	33	19	11	5	3	1	0

	No. of Deaths (%)	Median Overall Survival (95% CI)
		mo
Inavolisib (N=161)	42 (26.1)	NR (27.3–NR)
Placebo (N=164)	55 (33.5)	31.1 (22.3–NR)

Stratified hazard ratio for death, 0.64 (95% CI, 0.43–0.97)
P=0.03

Turner NC et al. N Engl J Med 2024;391:1584-1596

Objective Response and Response Duration.



Turner NC et al. N Engl J Med 2024;391:1584-1596

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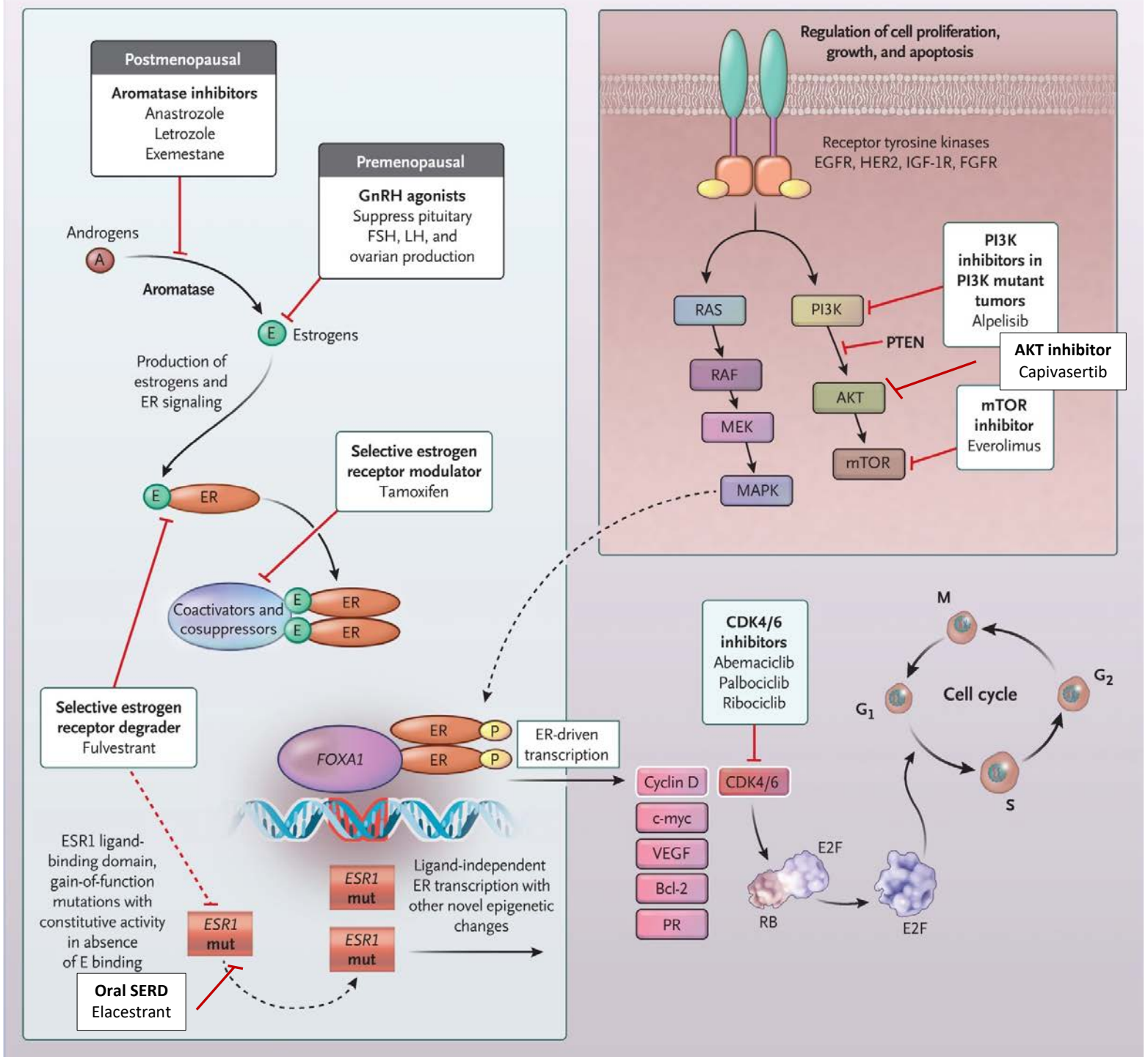
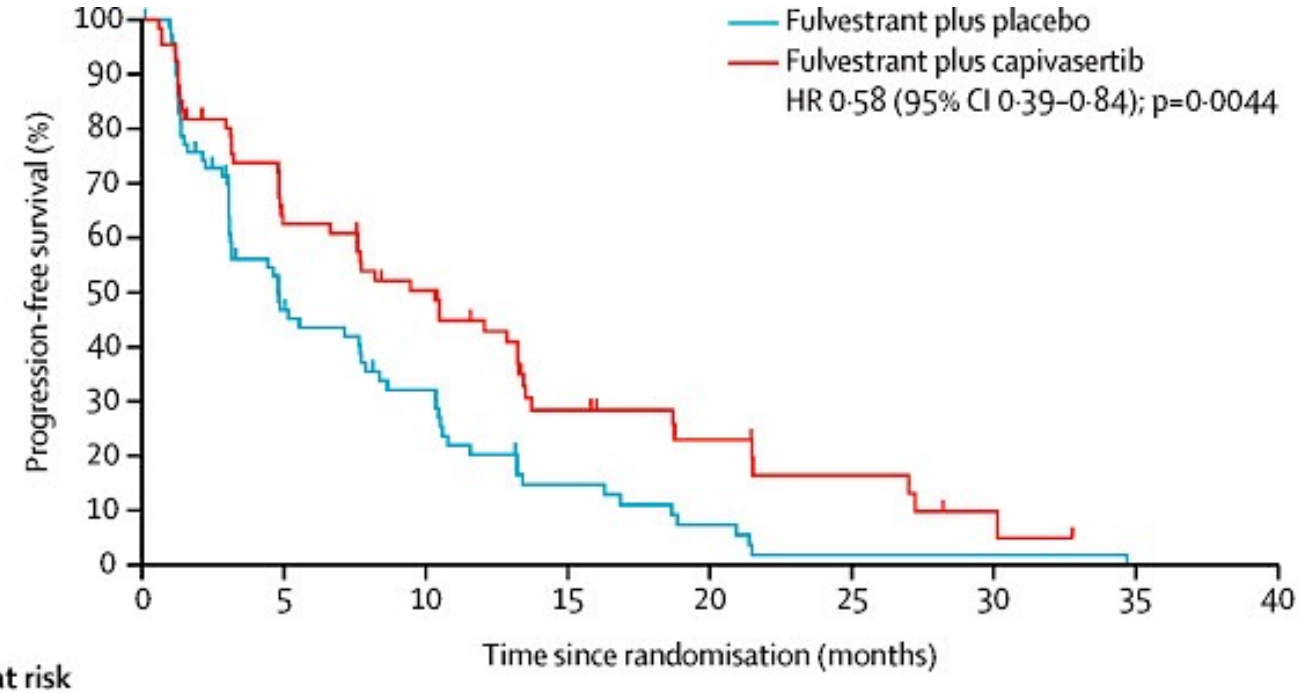
Targeting ER or E2



Targeting Other Growth Factor Paths

Adapted from
N Engl J Med 2020;383:2557.

FAKTION: RP2 fulvestrant +/- capivasertib



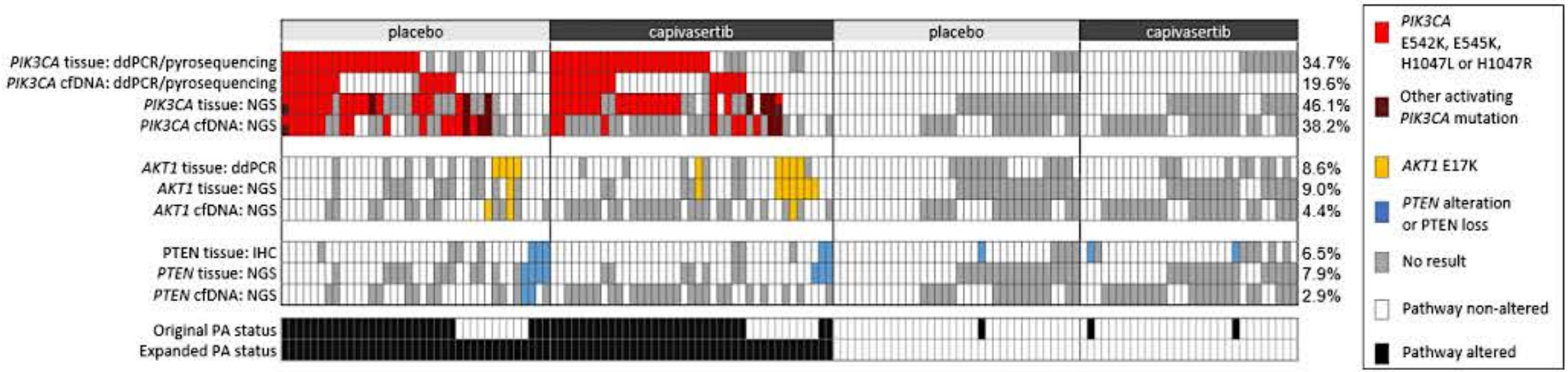
Number at risk (number censored)									
Fulvestrant plus placebo	71 (0)	29 (6)	19 (7)	8 (8)	4 (8)	1 (8)	1 (8)	0 (8)	0 (8)
Fulvestrant plus capivasertib	69 (0)	38 (7)	28 (10)	13 (14)	8 (17)	5 (18)	2 (19)	0 (20)	2 (20)

Response Rates

F	8%
F + C	29%

Jones RH, et al. Lancet Oncol 2020;21:345

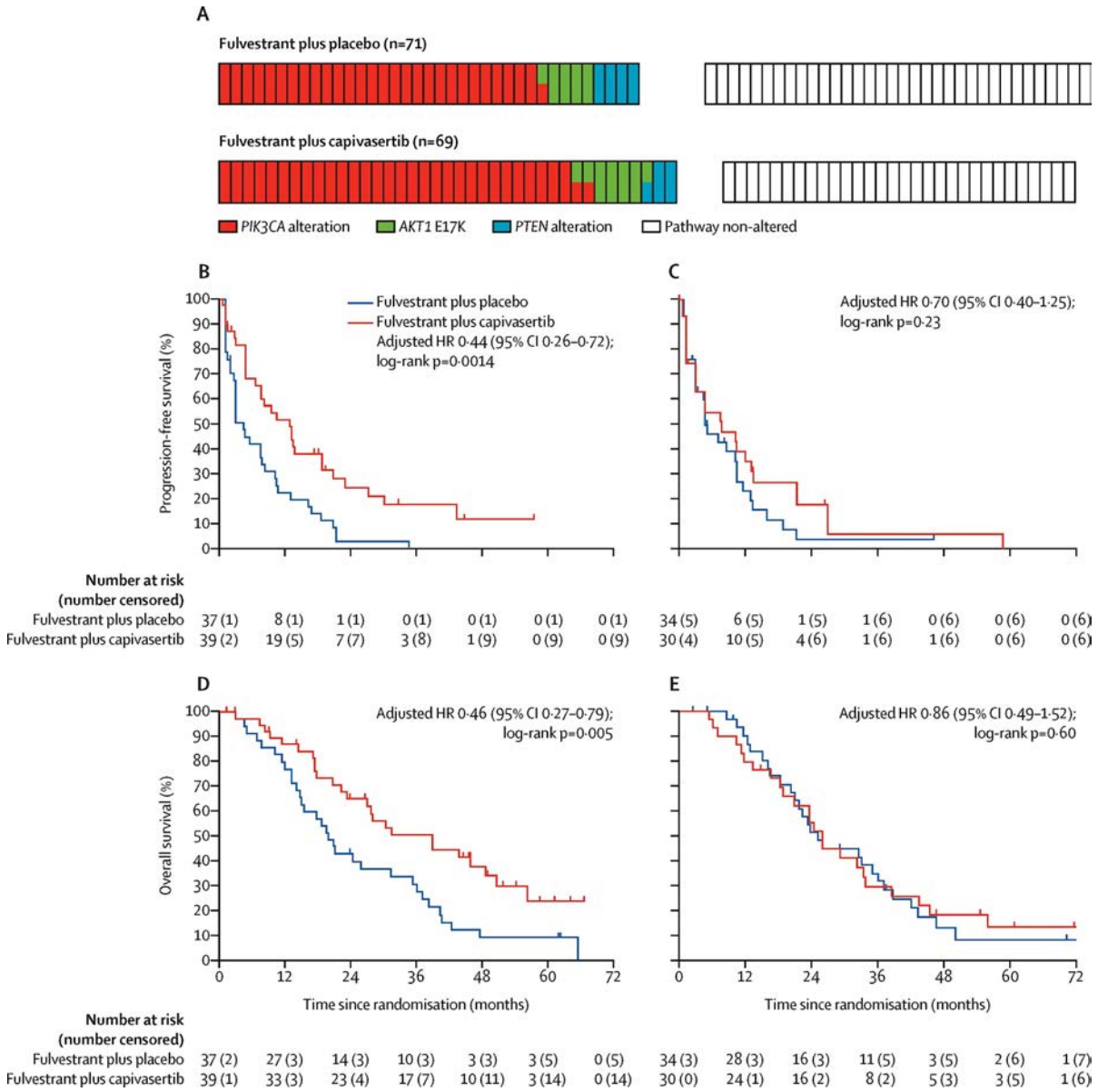
***Supplemental Figure 1*: Concordance between ddPCR/pyrosequencing, next-generation sequencing and immunohistochemical identification of PI3K/AKT/PTEN pathway altered and non-altered tumours**



Tumour testing results and subgroup assignments of individual participants are arranged as columns, with each box indicating the result of a specific test (upper panel) or subgroup assignment (lower panel). Upper Panel: Red/burgundy, amber and blue boxes indicate that the assay identified a *PIK3CA*, *AKT1* or *PTEN* alteration (or PTEN loss), respectively. Multiple colours reflect that a tumour carried two types of *PIK3CA* alteration. White boxes indicate that the test did not detect an alteration. Grey boxes indicate that there was no test result, either because no additional tumour biopsy or plasma sample was available, or there was a test failure. Percentages (right) show how frequently each test (when it returned a result) identified each genetic alteration or PTEN deficiency. Lower panel: Participant subgroup assignments based on the original testing results and the expanded testing results. Black boxes indicate a participant was in the pathway altered subgroup and white boxes indicate that a participant was in the pathway non-altered subgroup.

Howell SJ, et al. Lancet Oncol 2022;23:851

FAKTION: RP2 fulvestrant +/- capivasertib—Expanded Analyses



Howell SJ, et al. Lancet Oncol 2022;23:851

CAPItello-291: Study Design

- Phase III, randomized, double-blind, placebo-controlled study

Patients with HR+/HER2*– ABC

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

R1:1 (N=708)

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

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

Dual primary endpoints

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

Preplanned exploratory PFS analyses

Subgroups: prior use of CDK4/6 inhibitor (yes/no), prior chemotherapy for ABC (yes/no) and presence of liver metastases at baseline (yes/no)
- Overall
- AKT pathway-altered tumours

Oliveira M et al. ESMO Breast Cancer 2023

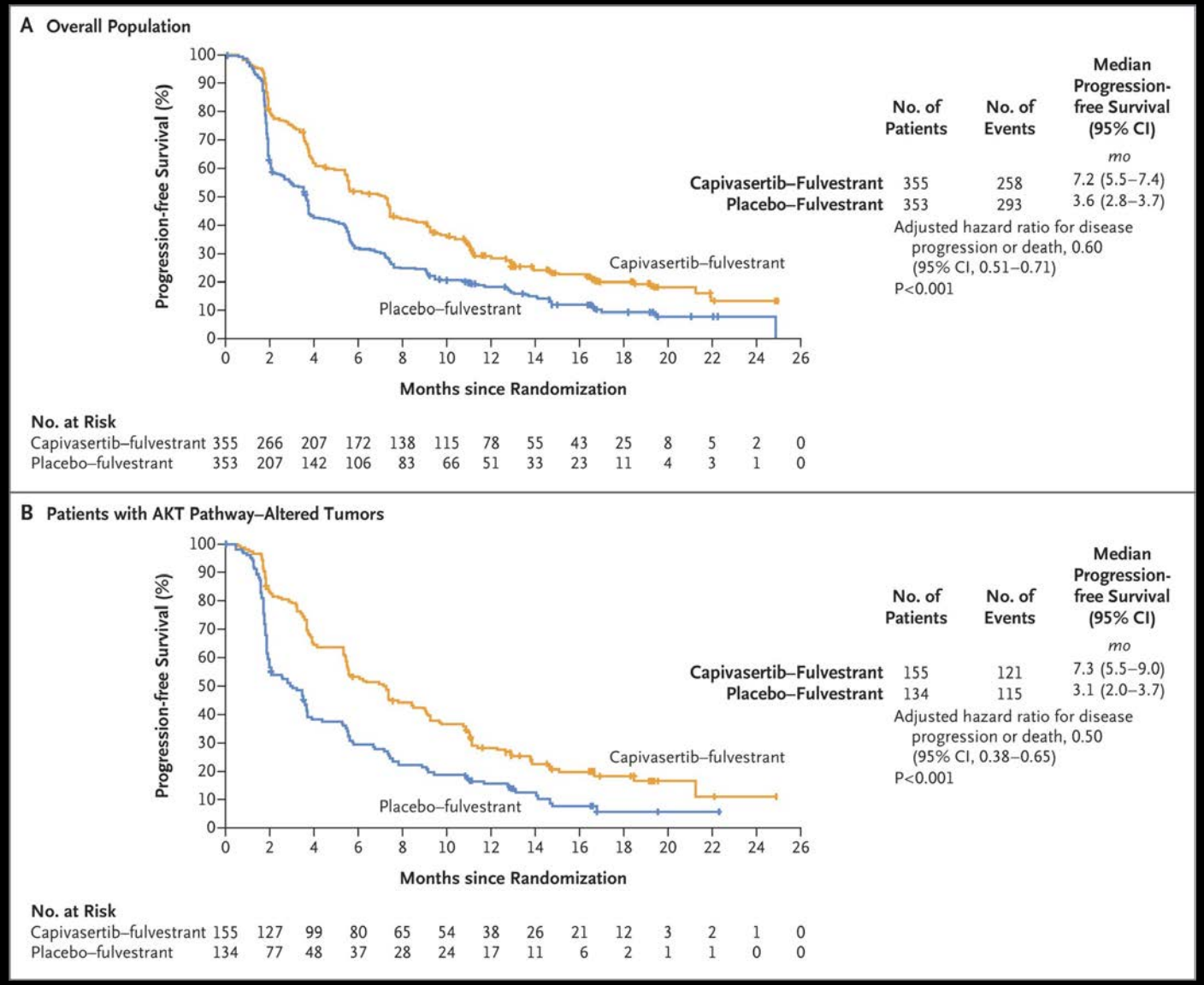
AKT pathway alteration status by NGS

Alteration; n (%)		Capivasertib-fulvestrant (n=355)	Placebo-fulvestrant (n=353)
Any AKT pathway alteration		155 (43.7)	134 (38.0)
PIK3CA	Any	116 (32.7)	103 (29.2)
	PIK3CA only	110 (31.0)	92 (26.1)
	PIK3CA and *AKT1*	2 (0.6)	2 (0.6)
	PIK3CA and *PTEN*	4 (1.1)	9 (2.5)
AKT1 only		18 (5.1)	15 (4.2)
PTEN only		21 (5.9)	16 (4.5)
AKT pathway non-altered		200 (56.3)	219 (62.0)
AKT pathway alteration not detected		142 (40.0)	171 (48.4)
Unknown		58 (16.3)	48 (13.6)
No sample available		10 (2.8)	4 (1.1)
Pre-analytical failure		39 (11.0)	34 (9.6)
Post-analytical failure		9 (2.5)	10 (2.8)

Table S1

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

Investigator-Assessed Progression-free Survival in the Overall Population and in Patients with AKT Pathway–Altered Tumors.



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

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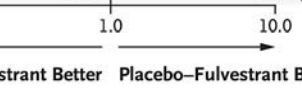
Subgroup Analysis of Investigator-Assessed Progression-free Survival in the Overall Population.

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



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

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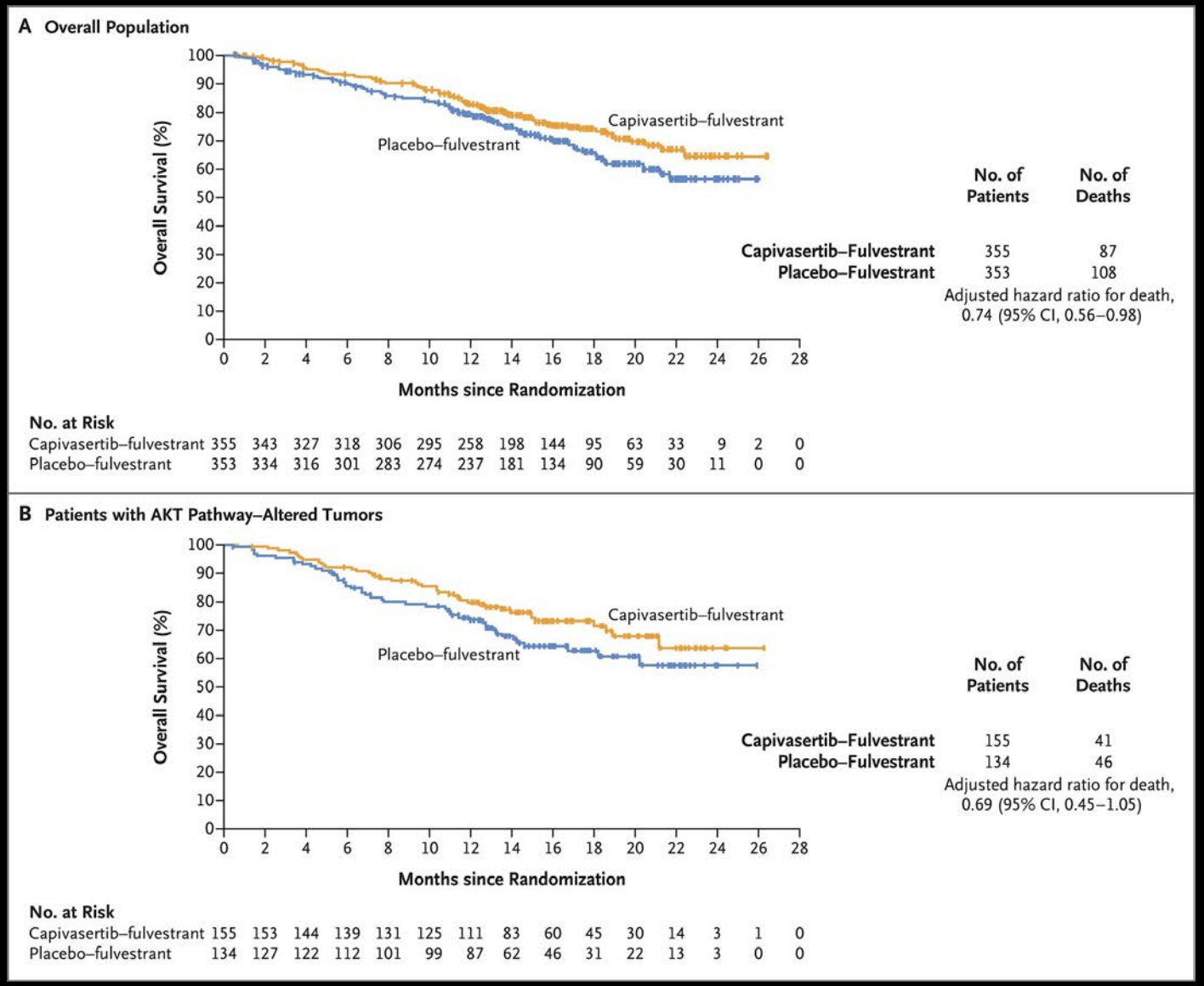
Overall Survival in the Overall Population and among Patients with AKT Pathway–Altered Tumors.



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

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Investigator-Assessed PFS in Patients with AKT Pathway-Altered Tumors

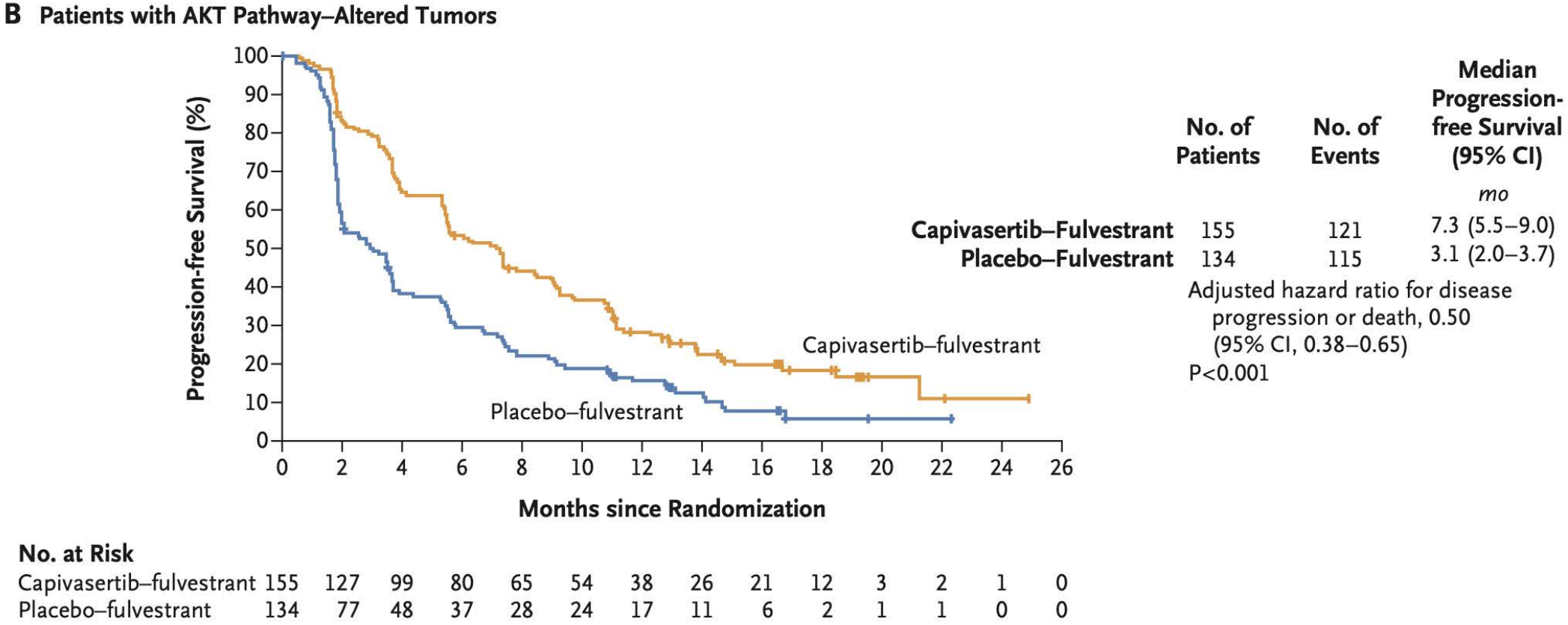
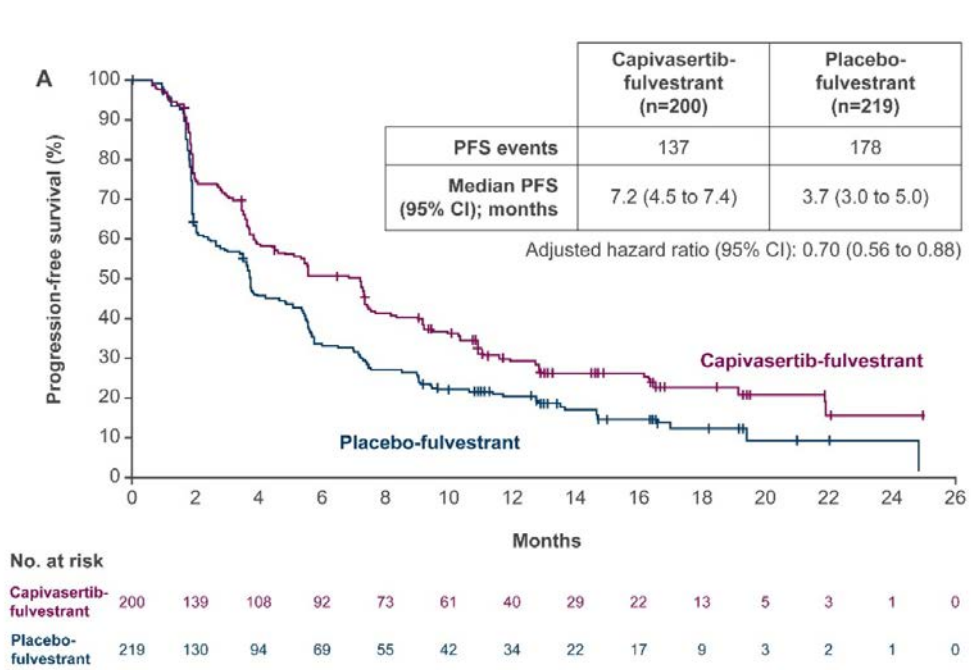


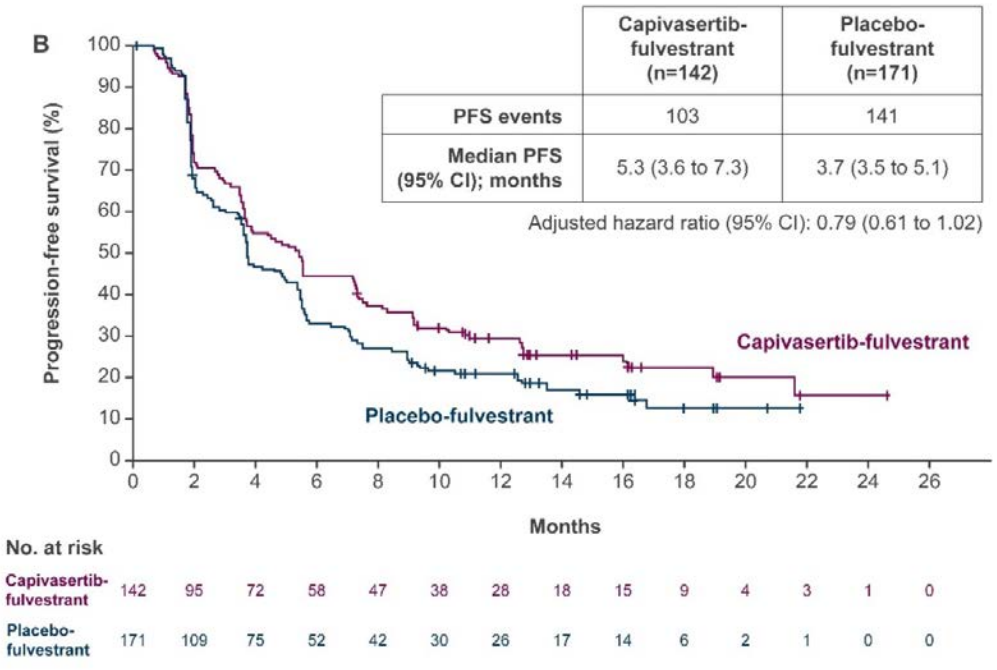
Figure 1B

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

Investigator-Assessed PFS in Patients with AKT Pathway Non-Altered Tumors



Patients with AKT pathway non-altered tumors including unknown NGS result (per protocol)

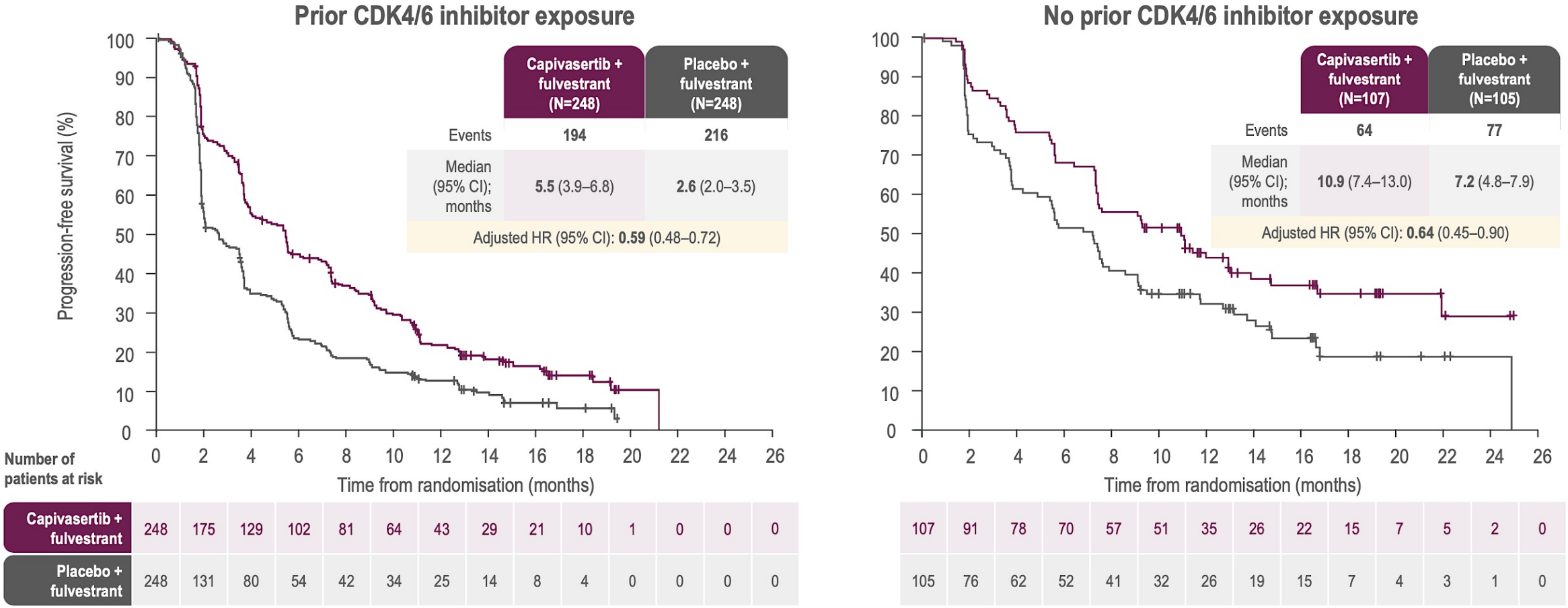


Patients with AKT pathway non-altered tumors excluding unknown NGS result (exploratory analysis)

Figure S2

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

PFS by prior CDK4/6 inhibitor (overall population)



Number of patients at risk

Capivasertib + fulvestrant	248	175	129	102	81	64	43	29	21	10	1	0	0	0
Placebo + fulvestrant	248	131	80	54	42	34	25	14	8	4	0	0	0	0

Capivasertib + fulvestrant	107	91	78	70	57	51	35	26	22	15	7	5	2	0
Placebo + fulvestrant	105	76	62	52	41	32	26	19	15	7	4	3	1	0

+ indicates a censored observation. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases and geographic region. n=22 patients received >1 prior CDK4/6 inhibitor.

Oliveira M et al. ESMO Breast Cancer 2023

Response Rates

- Fulvestrant +/- alpelisib 12% vs 26%
- Fulvestrant +/- capivasertib 12% vs 23%
- Fulvestrant + palbociclib +/- inavolisib 25% vs 58%

André F et al. N Engl J Med 2019;380:1929-1940
Turner NC et al. N Engl J Med 2023;388:2058-2070
Turner NC et al. N Engl J Med 2024;391:1584-1596

Major side effects of this class of drugs

- Mucositis, rash, diarrhea, asthenia
- Hyperglycemia – grade 3 or 4
  - Alpelisib 36.6%
  - Capivasertib 2.3%
  - Inavolisib 5.6%

André F et al. N Engl J Med 2019;380:1929-1940
Turner NC et al. N Engl J Med 2023;388:2058-2070
Turner NC et al. N Engl J Med 2024;391:1584-1596

Key Questions

- Is one of these agents fundamentally better than others?
- Is sequencing / timing of treatment important?
- Will next-wave mutant-selective agents prove active with fewer side effects?

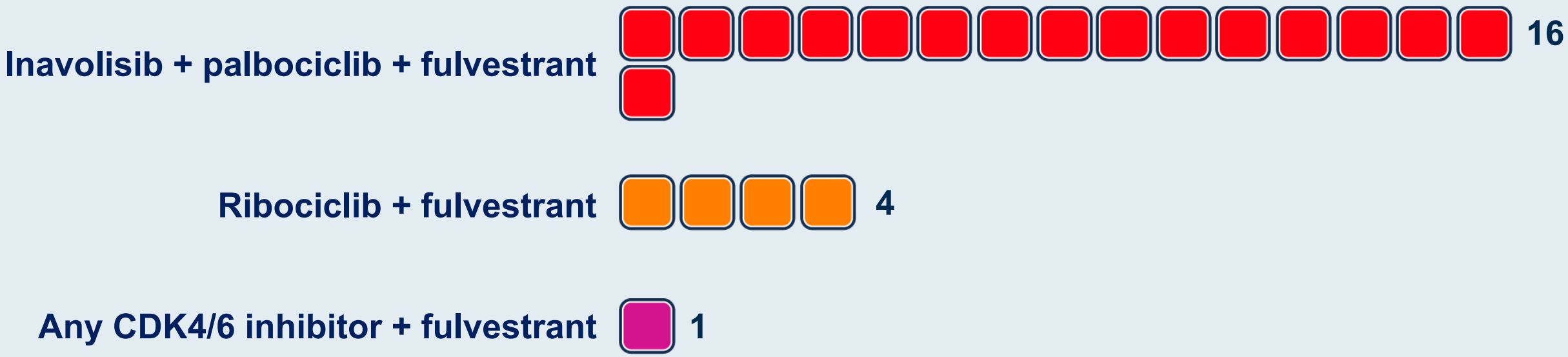
Discussion Questions and Faculty Case Presentations

Clinical Investigators' (CIs) Practice Patterns for Patients with Hormone Receptor-Positive Metastatic Breast Cancer (HR+ mBC) Harboring PI3K/AKT/PTEN Pathway Abnormalities (PAPm)

Abstract Submitted: ASCO 2025

A 65-year-old woman with ER-positive, HER2-negative (HER2 IHC 0), node-negative breast cancer has developed multiple metastases 2 years after starting adjuvant anastrozole.

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

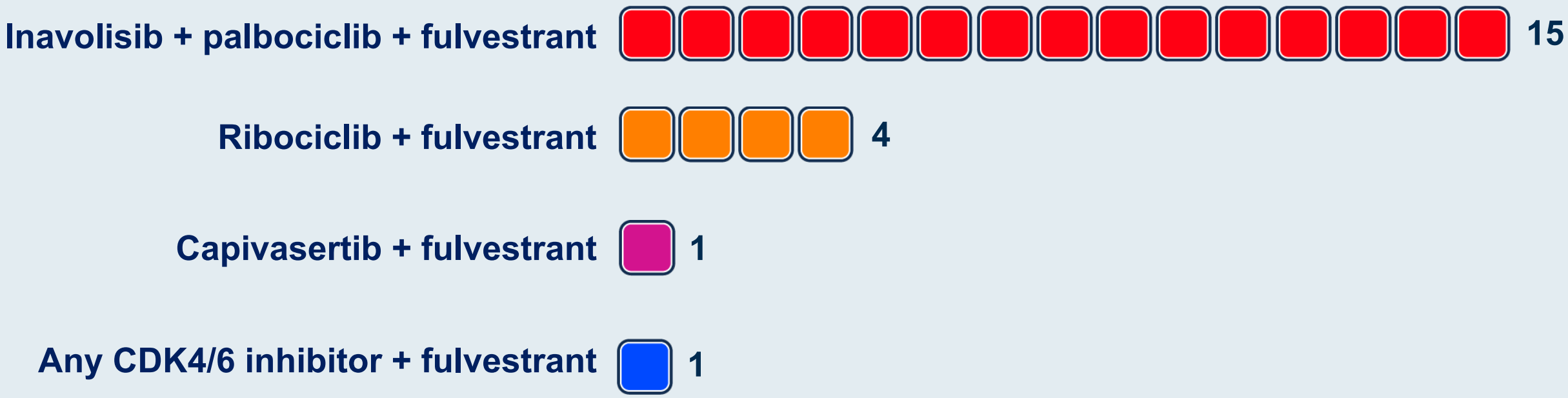


Survey of 21 US-based breast cancer clinical investigators, October 2024

RTP RESEARCH TO PRACTICE

A 65-year-old woman with ER-positive, HER2-negative (HER2 IHC 0), node-negative breast cancer has developed multiple metastases 2 years after starting adjuvant anastrozole.

ESR1 mutation-positive | **PIK3CA mutation-positive** | **AKT1 and PTEN mutation-negative**

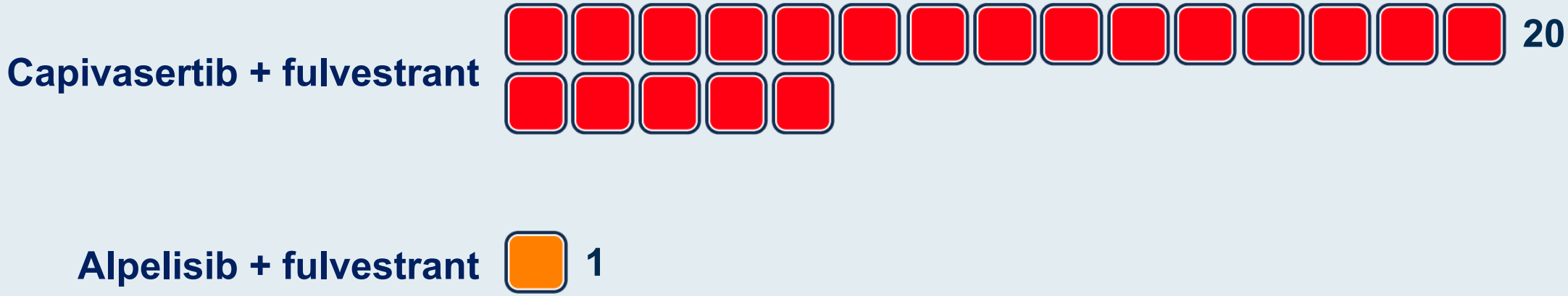


Survey of 21 US-based breast cancer clinical investigators, October 2024

RTP RESEARCH TO PRACTICE

A 65-year-old woman with ER-positive, HER2-negative (HER2 IHC 0), node-negative mBC receives a CDK4/6 inhibitor with an AI and initially responds but then experiences disease progression 18 months later.

ESR1 mutation-negative | **PIK3CA mutation-positive** | **AKT1 and PTEN mutation-negative**



Survey of 21 US-based breast cancer clinical investigators, October 2024

RTP RESEARCH TO PRACTICE

A 65-year-old woman with ER-positive, HER2-negative (HER2 IHC 0), node-negative mBC receives a CDK4/6 inhibitor with an AI and initially responds but then experiences disease progression 18 months later.

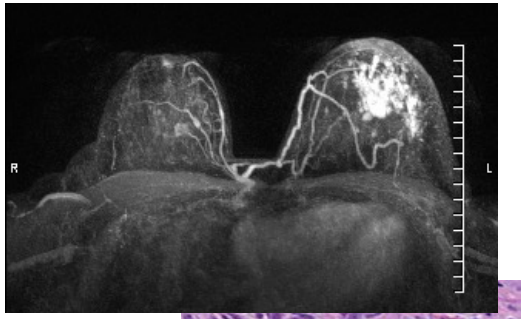
ESR1 mutation-negative | **PIK3CA mutation-negative** | **AKT1 or PTEN mutation-positive**

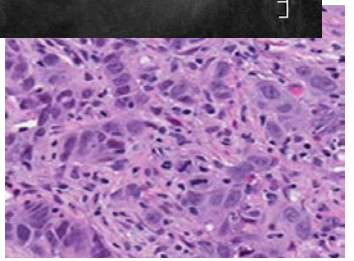
Capivasertib + fulvestrant

Survey of 21 US-based breast cancer clinical investigators, October 2024

RTP RESEARCH TO PRACTICE

Case Presentation: Dr Borges





35-year-old woman presented in 10/2022 with a palpable mass in her L breast noted for 8 weeks prior to presentation.

She is G2P2, youngest child 5 years old. She is complete in her childbearing and her husband has had a vasectomy. She has a maternal grandmother with breast cancer at age 72 and no other cancers in the family. She is a pediatric surgery NP.

- Ultrasound notes a 2.3cm hypoechoic mass. No abnormal axillary lymph nodes.
- Mammogram shows markedly dense breast tissue and vague density in the area of the palpable mass.
- MRI confirms a 2.0 solid mass within a 4.0 area of non-mass like enhancement. No abnormal LN seen.
- Biopsy diagnoses an invasive ductal carcinoma, grade 3, ER 3+ 90%, PR 2+ 80%, HER2 IHC 0, Ki-67% 30%

Testing for a cancer predisposing mutation is negative on a 70 gene panel.

She is taken to surgery first with bilateral mastectomies and reconstruction.

Final surgical pathology confirms a T2 (2.1cm), N0 tumor, grade 3. Markers remain the same. The 21-gene assay returns a Recurrence Score® of 28. She is given adjuvant chemotherapy with 4 cycles of docetaxel and cyclophosphamide with concomitant goserelin for ovarian protection.

Afterwards, she is continued on goserelin and letrozole is added. She also initiates zoledronic acid q 6 months IV.

Case Presentation: Dr Borges (Con't)

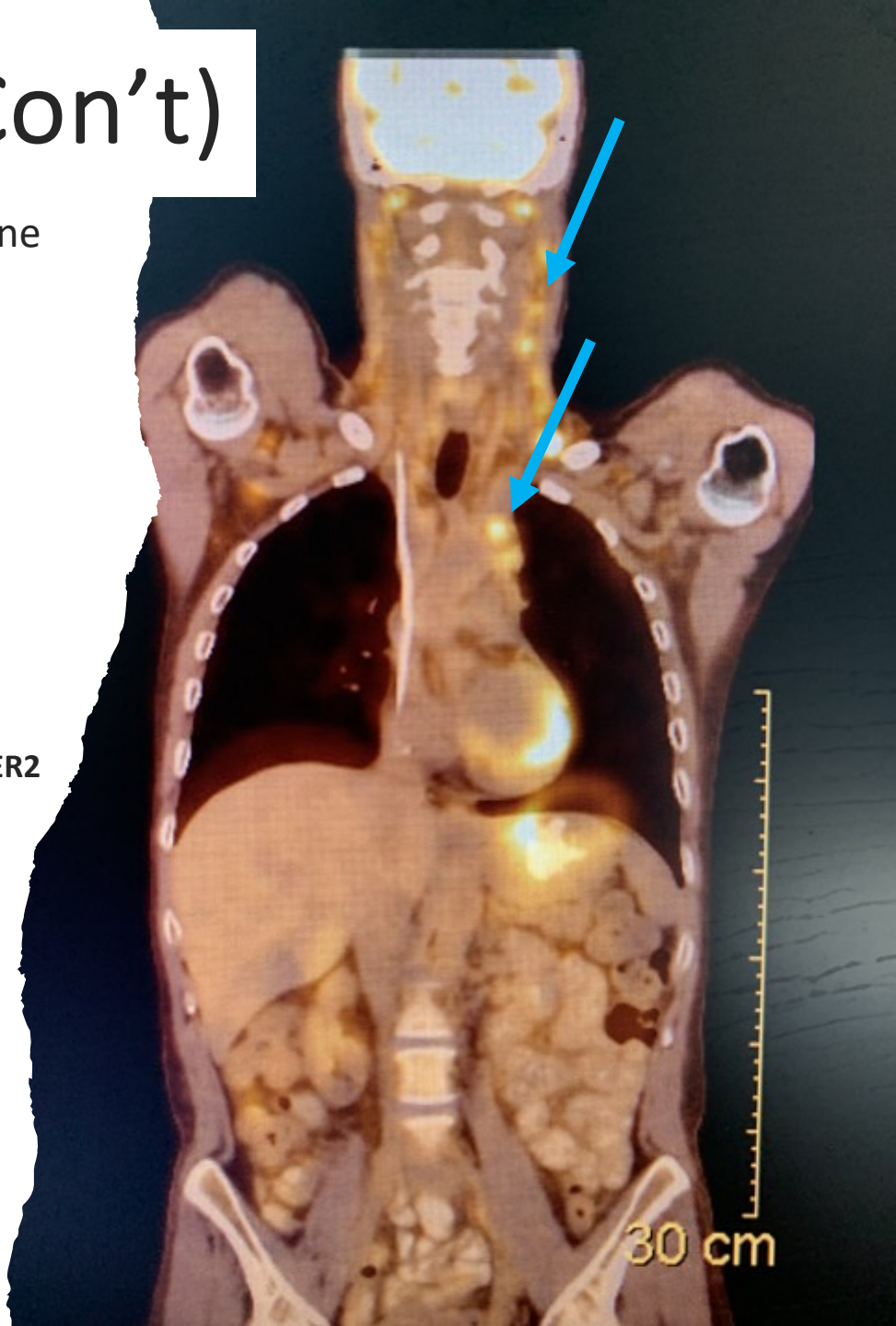
Our patient is now 37 and has been compliant on her OFS and AI for endocrine therapy

January 2025: Notices enlarged cervical nodes and comes in to be seen. On exam, there are firm enlarged LN in the L cervical chain and supraclavicular fossa. She otherwise feels well though on discussion has been more easily fatigued lately, which she attributed to work and the kids.

A PET CT is ordered.

- **Widespread metastatic breast cancer**
  - **Extensive neck and mediastinal LAD**
  - **Bone metastasis in the T Spine, pelvis and R acetabulum**
  - **Biopsy of the cervical LN shows adenocarcinoma, GATA3 positive, ER positive, PR negative, HER2 IHC 1+.**
  - **A genomic test is performed and the tumor is ESR1 WT, BRCA WT, and PIK3CA mutated.**

What should her first line treatment should be?



Case Presentation: Dr Bardia

55 yo Female with:

- 2008: HR+/HER2- breast cancer (localized)
- 2018: Completed adjuvant tamoxifen
- 2022: Disease recurrence (bone):

  ER+/HER2 low (IHC = 1+). Started letrozole with ribociclib
- 2025: Disease progression (bone)

ctDNA analysis revealed PIK3CA and ESR1 mutation

Case Presentation: Dr Bardia (continued)

Pt started Elacestrant. Tolerated therapy well. Disease progression after 9 months with new mets in liver. Relatively asymptomatic. No liver dysfunction. What would you consider next?

ctDNA analysis revealed ESR1 and PIK3CA mutation

Pt started fulvestrant and alpelisib

Case Presentation: Dr O'Shaughnessy

- 36 yo woman received adjuvant AC/T then LHRH agonist + AI for grade 3 2+ nodes, ER++ PR+ HER2 1+ EBC.
- She stopped ET for toxicity and declined tamoxifen
- Recurred 3 years later in bone with destructive, painful, lytic disease – ER++ PR 0 HER2 1+ and was treated with LHRH agonist, ribociclib + AI
- Progressed in bone and new liver mets after 12 mos and required L spine and hip RT
- ctDNA showed AKT mutation and no ESR1mutation
- No response to capecitabine and T-DXd; response to sacituzumab for 9 mos
- PS 2 due to bone pain with increasing liver mets and mildly elevated LFTs
- Had immediate improvement in bone pain and PS within 1 mo of starting fulvestrant + capivasertib and responded for 10 mos

Keynote Session: Hormone Receptor-Positive Metastatic Breast Cancer

CDK4/6 Inhibitors for HR-Positive Metastatic Breast Cancer (mBC) — Dr Borges

Targeting the PTEN/PI3K/AKT Pathway in HR-Positive mBC — Dr Burstein

Role of Oral Selective Estrogen Receptor Degraders (SERDs) in the Management of HR-Positive mBC — Dr O'Shaughnessy

Antibody-Drug Conjugates for HR-Positive mBC — Dr Bardia

Role of Oral Selective Estrogen Receptor Degraders (SERDs) in HR-Positive mBC

Joyce O'Shaughnessy, MD
Baylor University Medical Center
Texas Oncology
Sarah Cannon Research Institute

Disclosures

Advisory Committees and Consulting Agreements	Aadi Bioscience, Agendia Inc, Amgen Inc, Aptitude Health, AstraZeneca Pharmaceuticals LP, BioNTech SE, Bristol Myers Squibb, Daiichi Sankyo Inc, Duality Biologics, Eisai Inc, Ellipses Pharma, Exact Sciences Corporation, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Guardant Health, HiberCell, Jazz Pharmaceuticals Inc, Johnson & Johnson Pharmaceuticals, Lilly, Merck, Mersana Therapeutics Inc, Natera Inc, Novartis, Pfizer Inc, Pierre Fabre, Puma Biotechnology Inc, Roche Laboratories Inc, Sanofi, Seagen Inc, Stemline Therapeutics Inc, Summit Therapeutics, Tempus, TerSera Therapeutics LLC

ESR1 as an Acquired Mutation[1]

- In ER+/HER2- mBC, **mutations in the *ESR1* gene** are one of the main molecular mechanisms of **acquired endocrine resistance**[1-4]
- *ESR1* mutations are most frequently **acquired under the selective pressure of endocrine therapy (ET)**, especially with AIs[5]
- ***ESR1* mutations** in mBC cause estrogen receptors to be active, even without estrogen[6]
- *ESR1* mutations **differ from somatic mutations**, such as *PIK3CA*, which are stable mutations that rarely change over the course of the disease[1,7-9]

Development of *ESR1* Mutations in mBC Tumors in Response to ET Exposure[10]

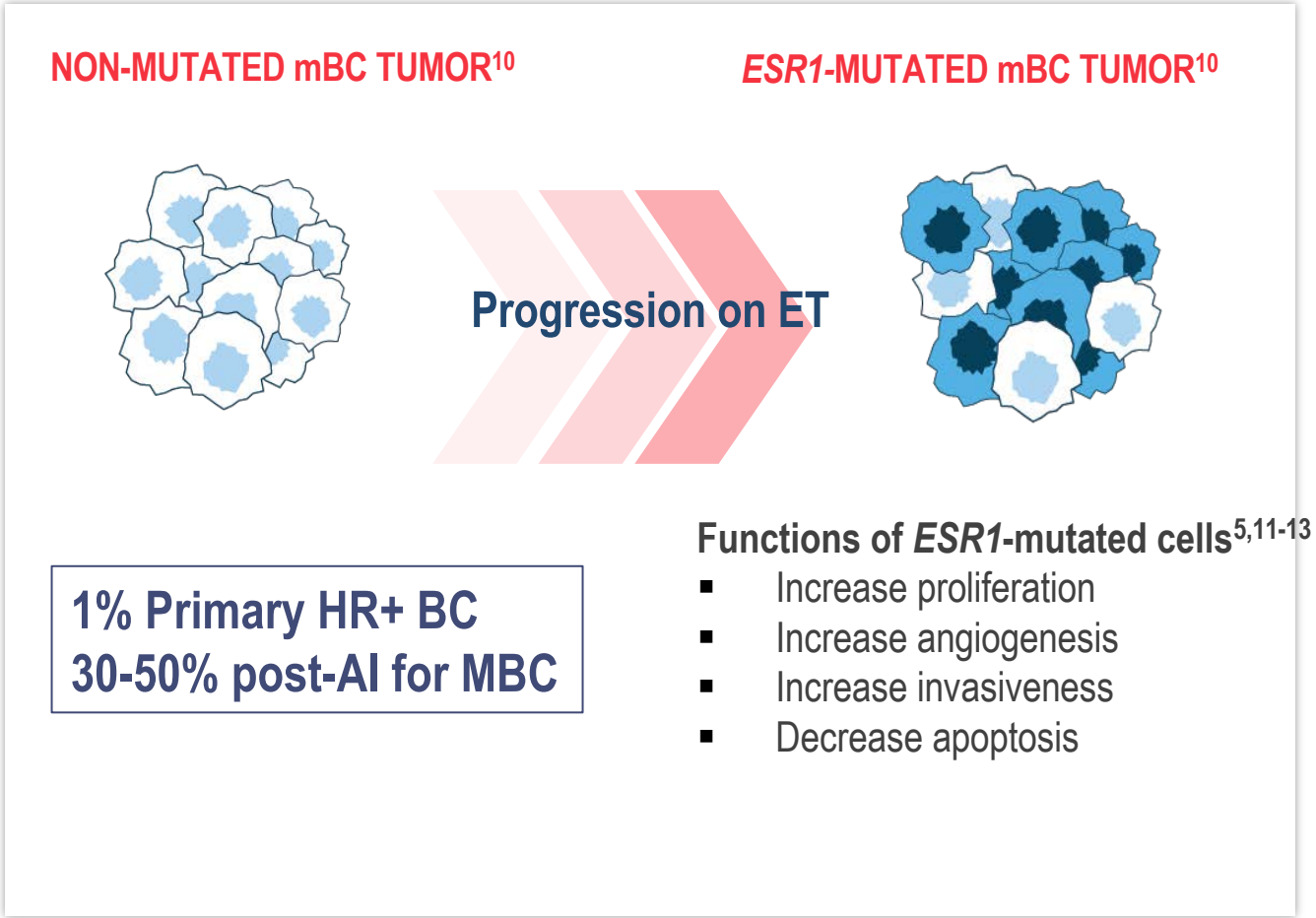
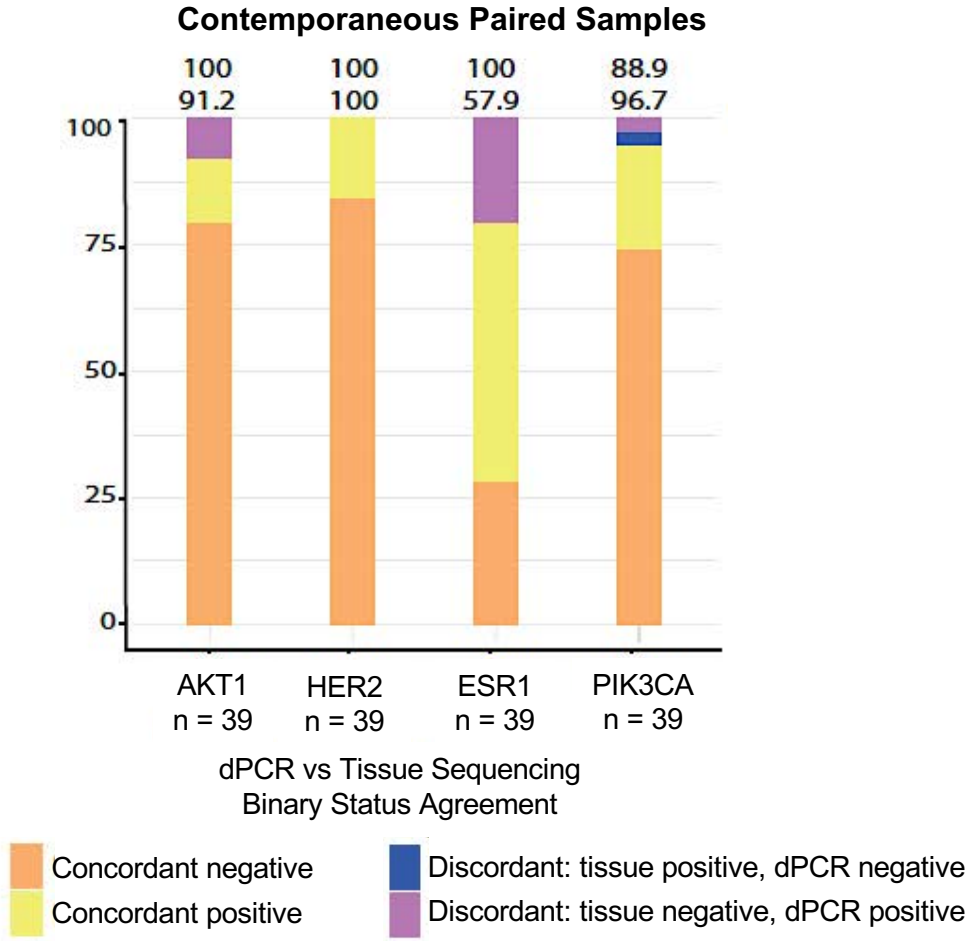


Figure adapted from Lloyd MR, et al.[10]

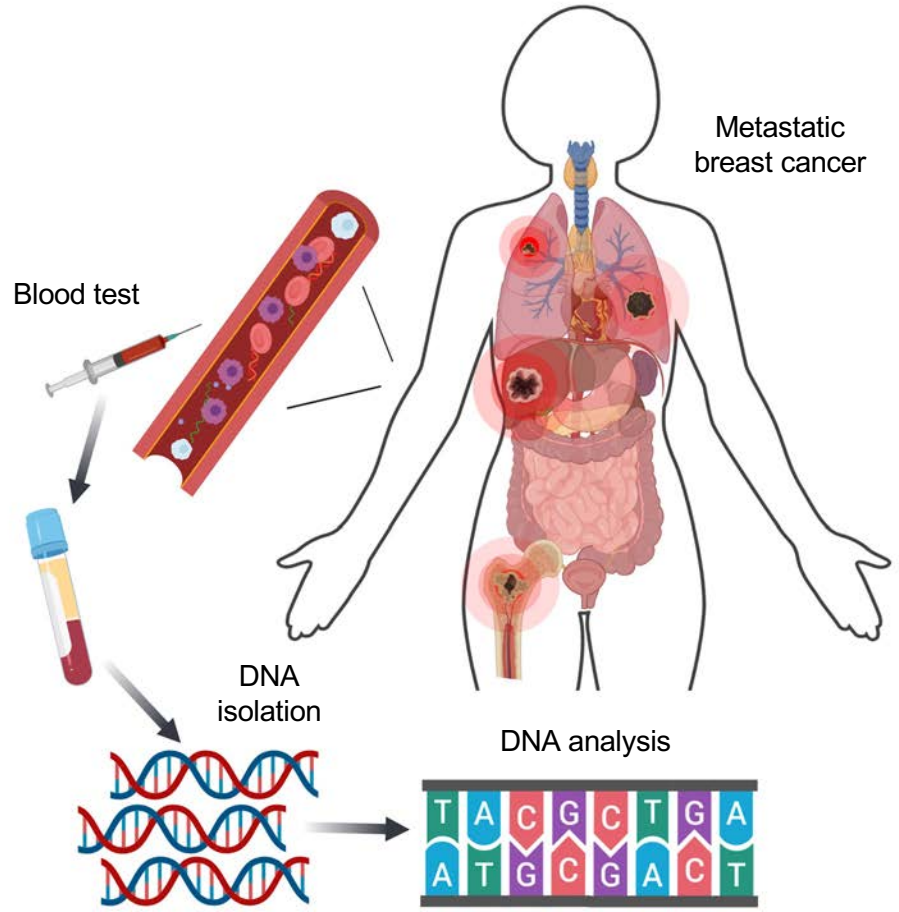
1. Clatot F, et al. *Breast Cancer Res*. 2020;22(1):56. **2.** Chandarlapaty S, et al. *JAMA Oncol*. 2016;2(10):1310-1315. **3.** Turner NC, et al. *Clin Cancer Res*. 2020;26(19):5172-5177. **4.** Zundelevich A, et al. *Breast Cancer Res*. 2020;22(1):16. **5.** Dustin D, et al. *Cancer*. 2019;125(21):3714-3728. **6.** Stallard J. Memorial Sloan Kettering Cancer Center. May 3, 2023. Accessed July 17, 2023. https://www.mskcc.org/news/msk-discovery-of-esr1-gene-mutation-leads-to-approval-of-breast-cancer-drug-elacestrant **7.** Mankoo PK, et al. *Proteins*. 2009;75(2):499-508. **8.** Casaubon JT, et al. StatPearls Publishing; Last updated: July 23, 2023. https://www.ncbi.nlm.nih.gov/books/NBK470239/ **9.** Arthur LM, et al. *Breast Cancer Res Treat*. 2014;147(1):211-219. **10.** Lloyd MR, et al. *Ther Adv Med Oncol*. 2022;14:17588359221113694. **11.** Brett JO, et al. *Breast Cancer Res*. 2021;23(1):85. **12.** Fatima LA, et al. *Sci Rep* 7, 16716 (2017). **13.** Zhang K, et al. *Cancer Manag Res*. 2018;10:2573-2580.

ESR1 Mutations Often Subclinical: Liquid Biopsy Testing Is the Standard[1]

ctDNA testing identified more *ESR1* mutations than contemporaneous biopsy

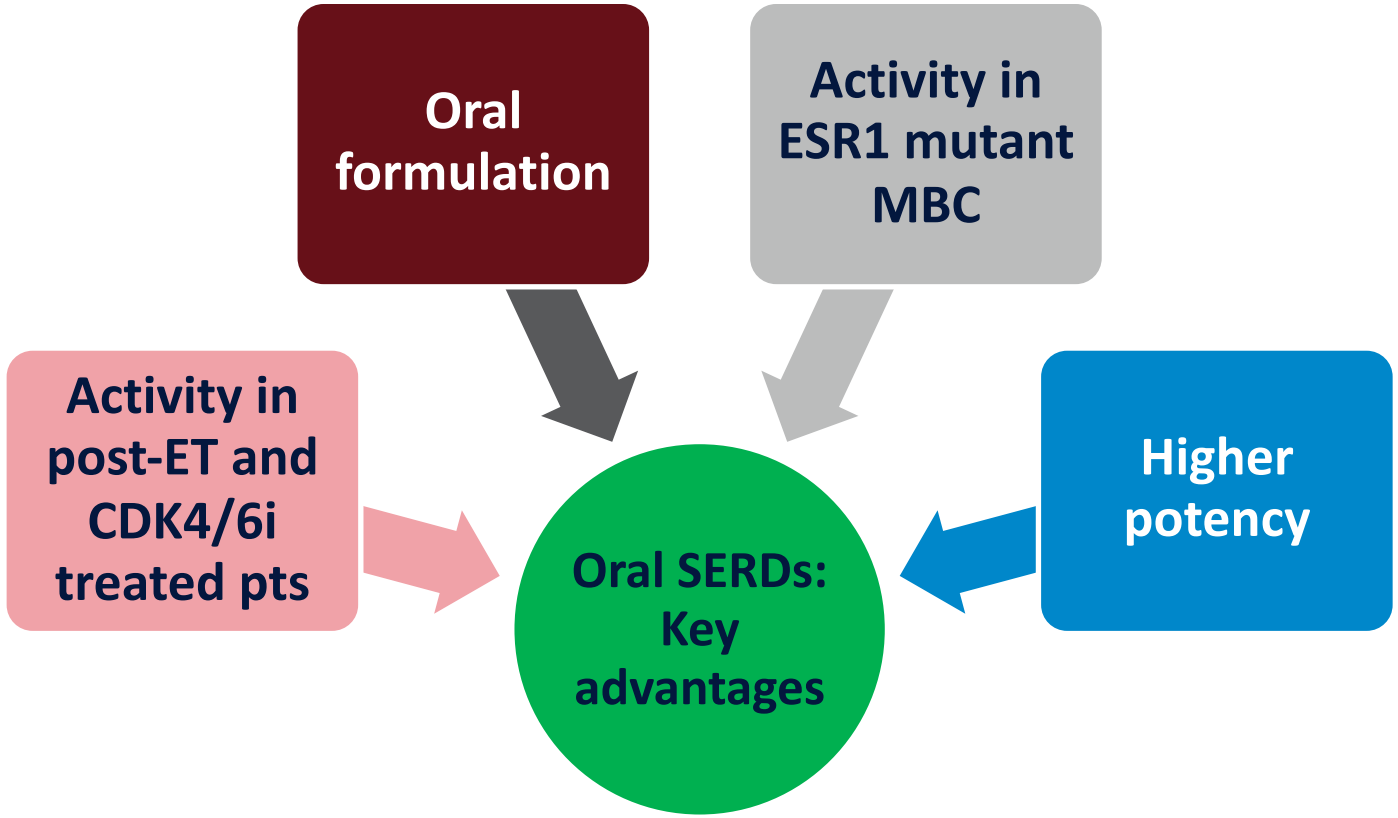


Different metastases may develop different resistance mutations



1. Turner NC et al. *Lancet Oncol*. 2020;21:1296-1308.

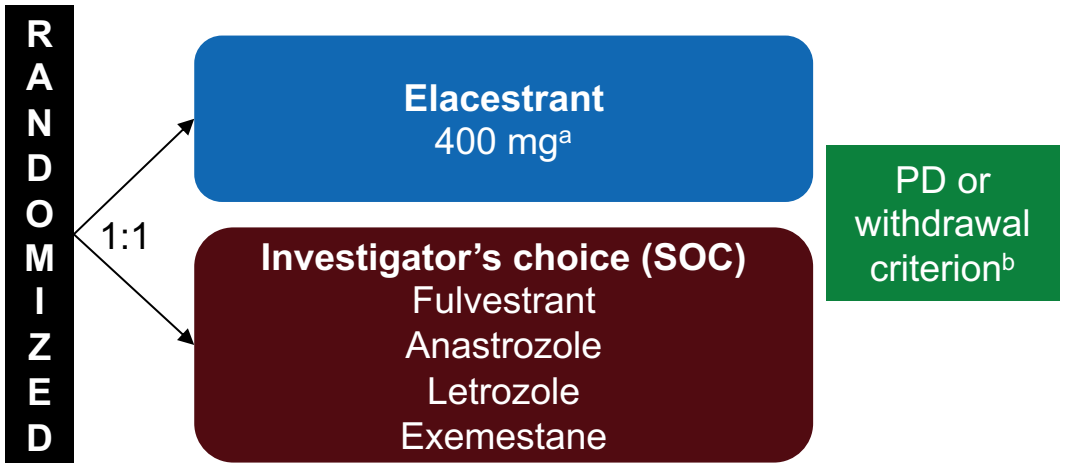
SERD: Selective estrogen receptor degrader



SARAH CANNON Research Institute

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

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



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

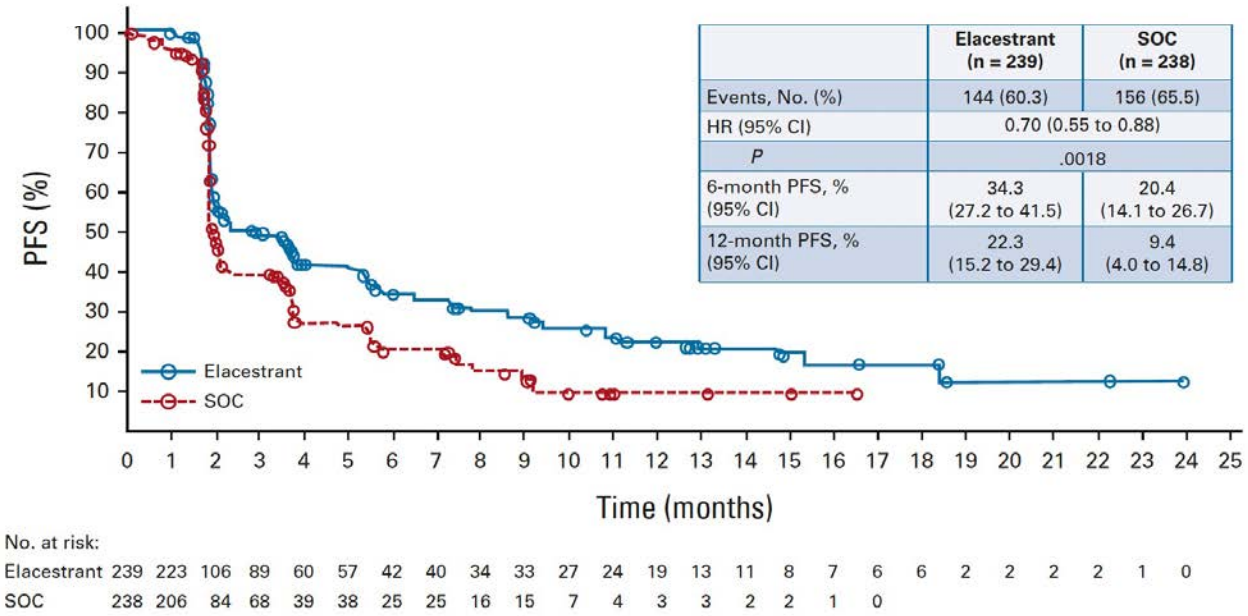
Patient Characteristics,[d] n (%)		Elacestrant		SOC	
		All (n = 239)	*ESR1*mut (n = 115)	All (n = 239)	*ESR1*mut (n = 115)
Median age (range), years		63 (24-89)	64 (28-89)	63 (32-83)	63 (32-83)
Female		233 (97.5)	115 (100)	238 (99.6)	113 (100)
ECOG PS	0	143 (59.8)	67 (58.3)	135 (56.5)	61 (54.9)
	1	96 (40.2)	48 (41.7)	103 (43.1)	51 (45.1)
Visceral metastasis, %		163 (68.2)	81 (70.4)	170 (71.1)	84 (74.3)
Prior CDK4/6i		239 (100)	115 (100)	239 (100)	113 (100)
Prior lines of ET	1	129 (54.0)	73 (63.5)	142 (59.4)	69 (61.1)
	2	110 (46.0)	42 (36.5)	97 (40.6)	44 (38.9)
Type of prior ET	Fulvestrant	70 (29.3)	27 (23.5)	75 (31.4)	28 (24.8)
	AI	193 (80.8)	101 (87.8)	194 (81.2)	96 (85.0)
	Tamoxifen	19 (7.9)	9 (7.8)	15 (6.3)	9 (8.0)
Prior lines of CT	0	191 (79.9)	89 (77.4)	180 (75.3)	81 (71.7)
	1	48 (20.1)	26 (22.6)	59 (24.7)	32 (28.3)

[a] Protocol-defined dose reductions permitted. [b] Restaging CT scans every 8 weeks. [c] By BICR. [d] Patient characteristics are updated from 2022 SGO presentation.

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

EMERALD: PFS With Elacestrant vs SOC in ITT and *ESR1*mut Populations[1]

PFS in All Patients

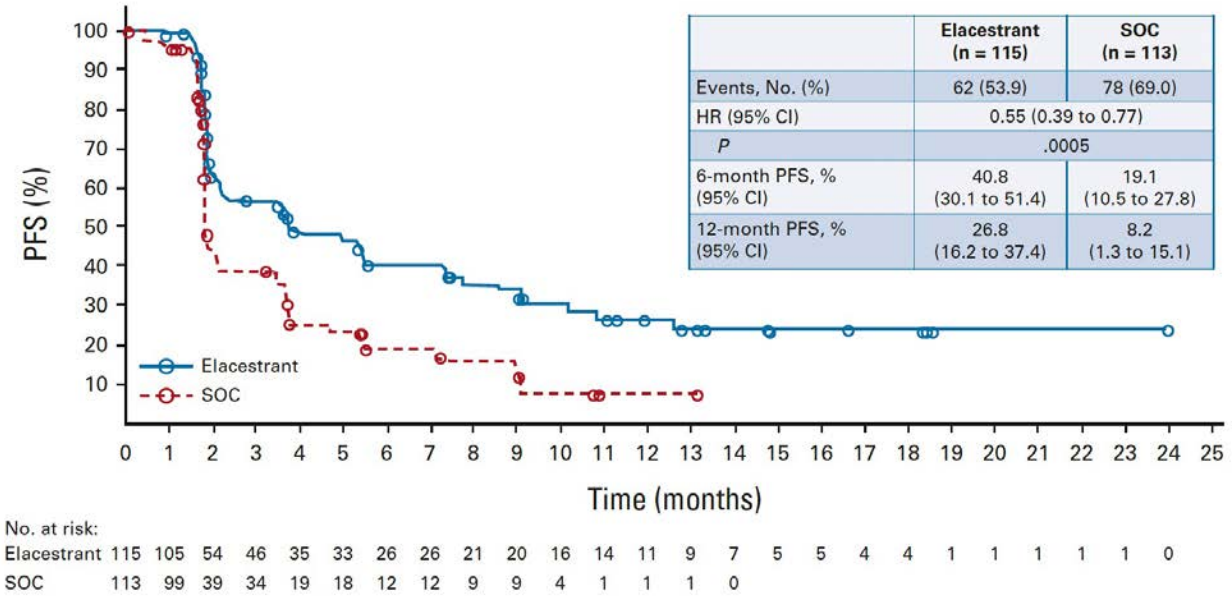


	Elacestrant (n = 239)	SOC (n = 238)
Events, No. (%)	144 (60.3)	156 (65.5)
HR (95% CI)	0.70 (0.55 to 0.88)	
P	.0018	
6-month PFS, % (95% CI)	34.3 (27.2 to 41.5)	20.4 (14.1 to 26.7)
12-month PFS, % (95% CI)	22.3 (15.2 to 29.4)	9.4 (4.0 to 14.8)

No. at risk:

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

PFS in Patients With *ESR1*mut Tumors



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

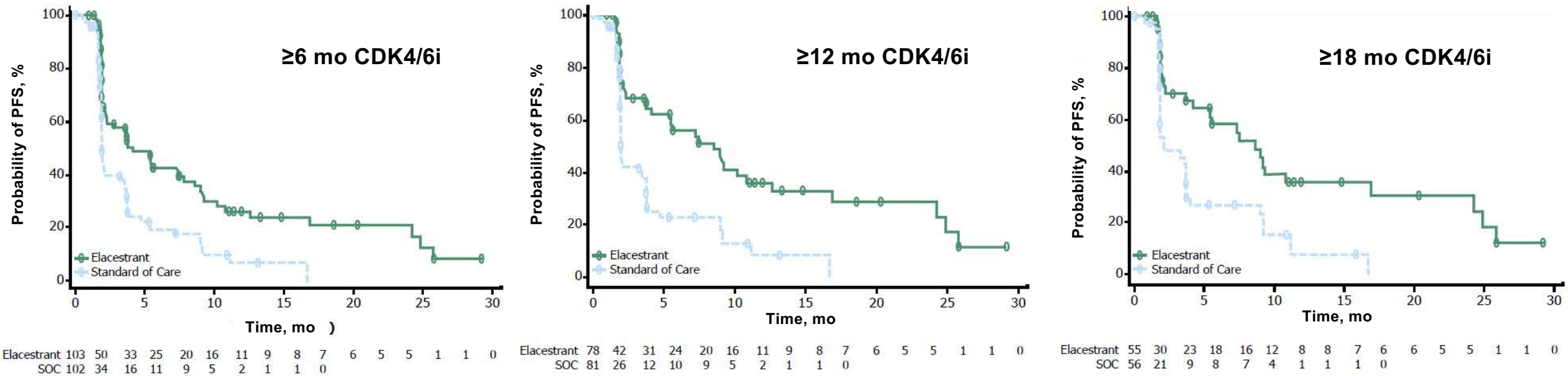
No. at risk:

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

1. Bidard F et al. *J Clin Oncol*. 2022;40:3246-3256.

EMERALD: PFS in *ESR1*mut by Duration of Prior CDK4/6i[1]

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

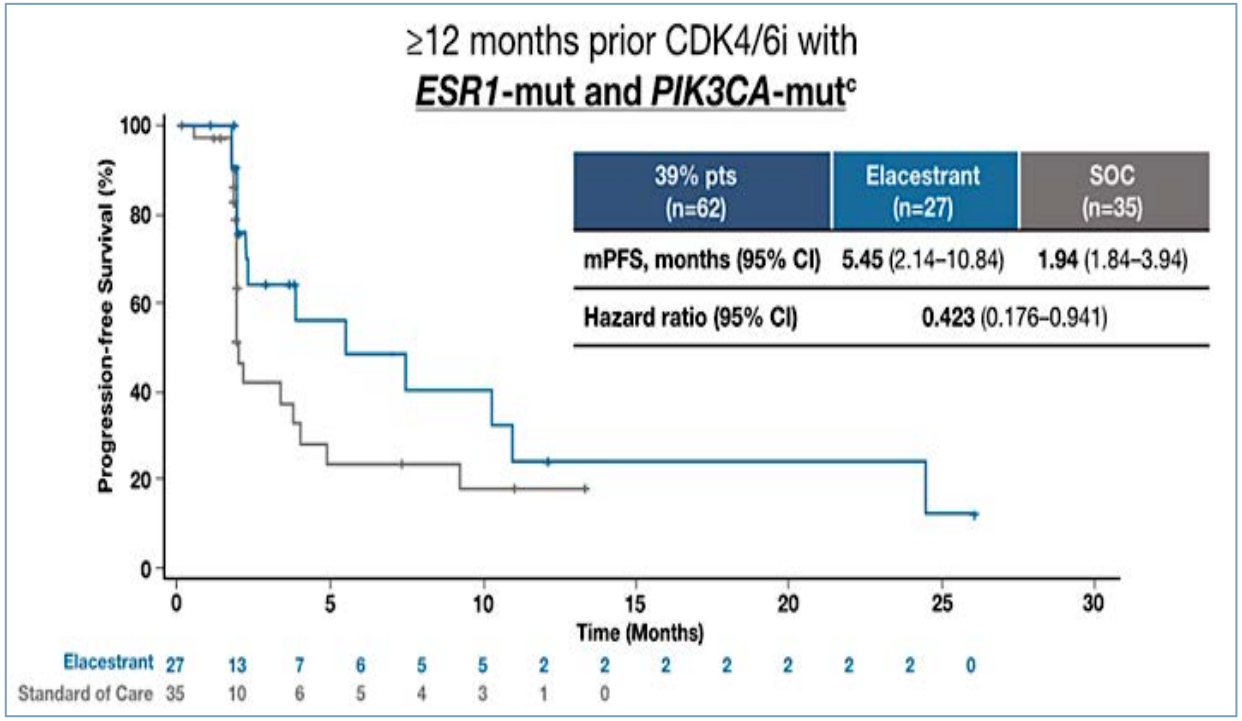


PFS by Duration of CDK4/6i	≥6 Months		≥12 Months		≥18 Months	
	Elacestrant (n = 103)	SOC (n = 102)	Elacestrant (n = 78)	SOC (n = 81)	Elacestrant (n = 55)	SOC (n = 56)
mPFS, mo (95% CI)	4.14 (2.20-7.79)	1.87 (1.87-3.29)	8.61 (4.14-10.84)	1.91 (1.87-3.68)	8.61 (5.45-16.89)	2.10 (1.87-3.75)
12-mo PFS rate,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

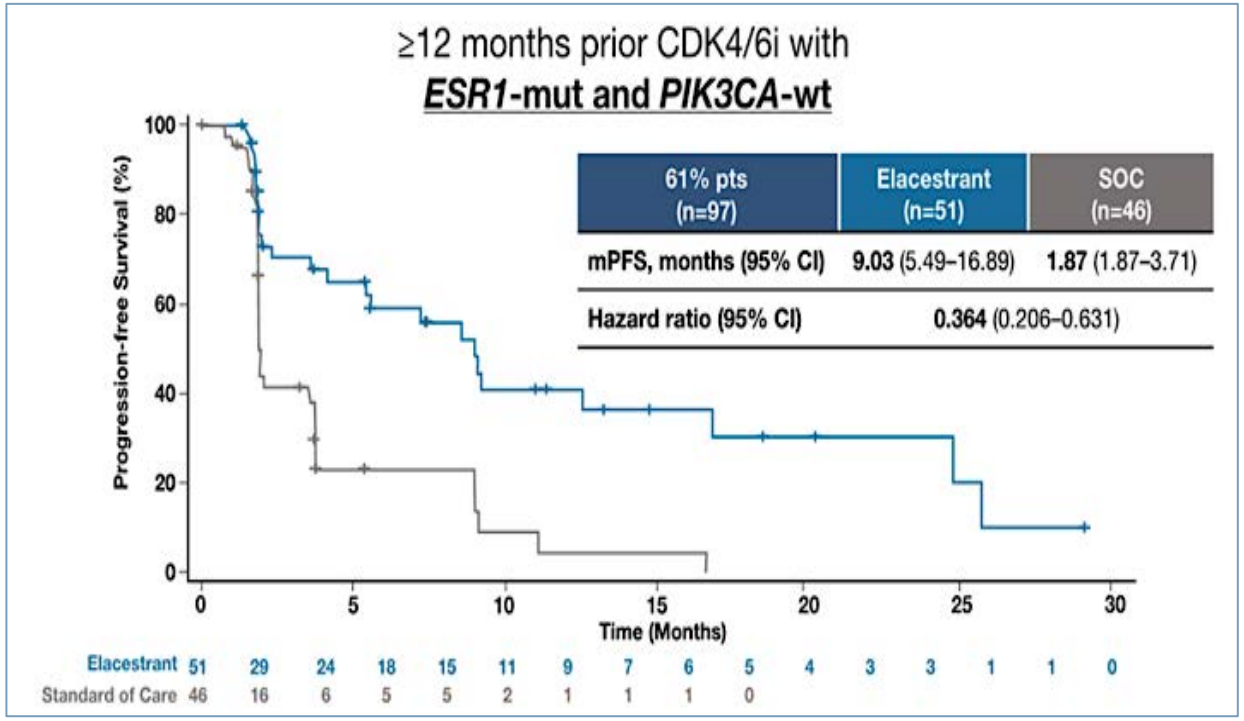
Kaklamani VG et al. ASCO 2023. Abstract 1070. Bardia A, Cortés J, Bidard FC, et al. *Clin Cancer Res*. 2024;30(19):4299-4309.

EMERALD: Improvement in PFS Across All Subgroups[1]

PIK3CA-mut



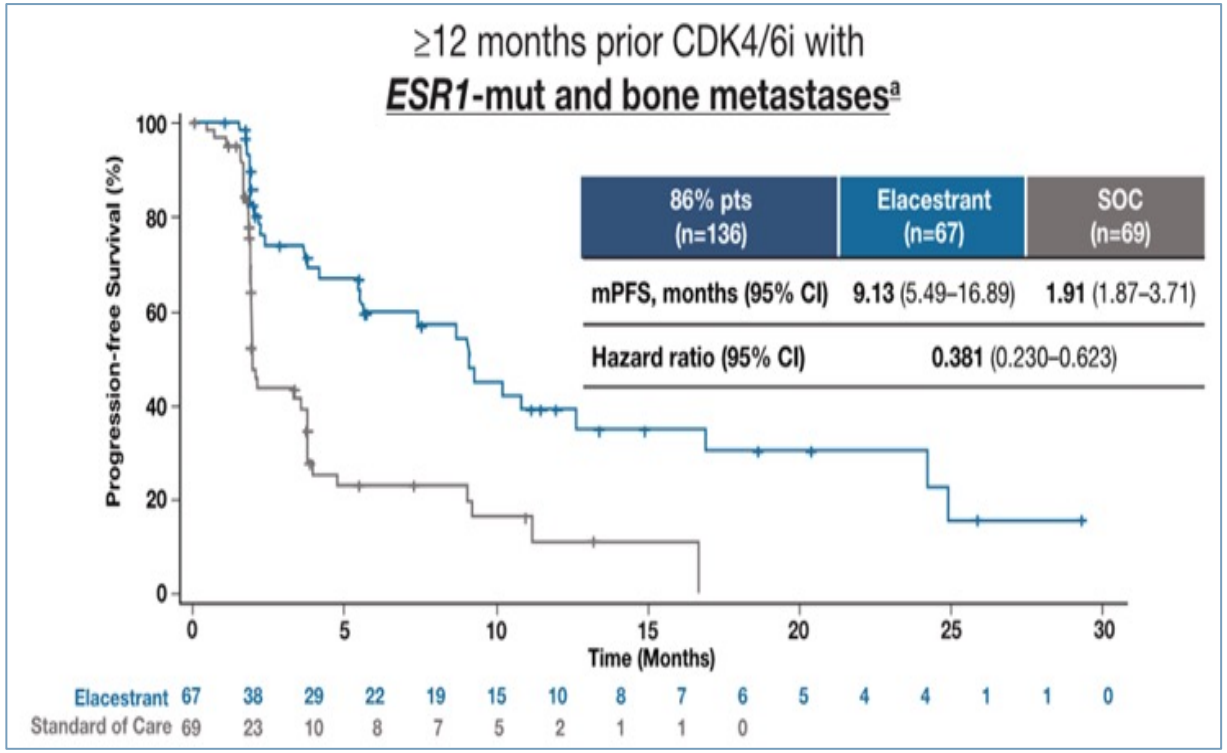
PIK3CA-wt



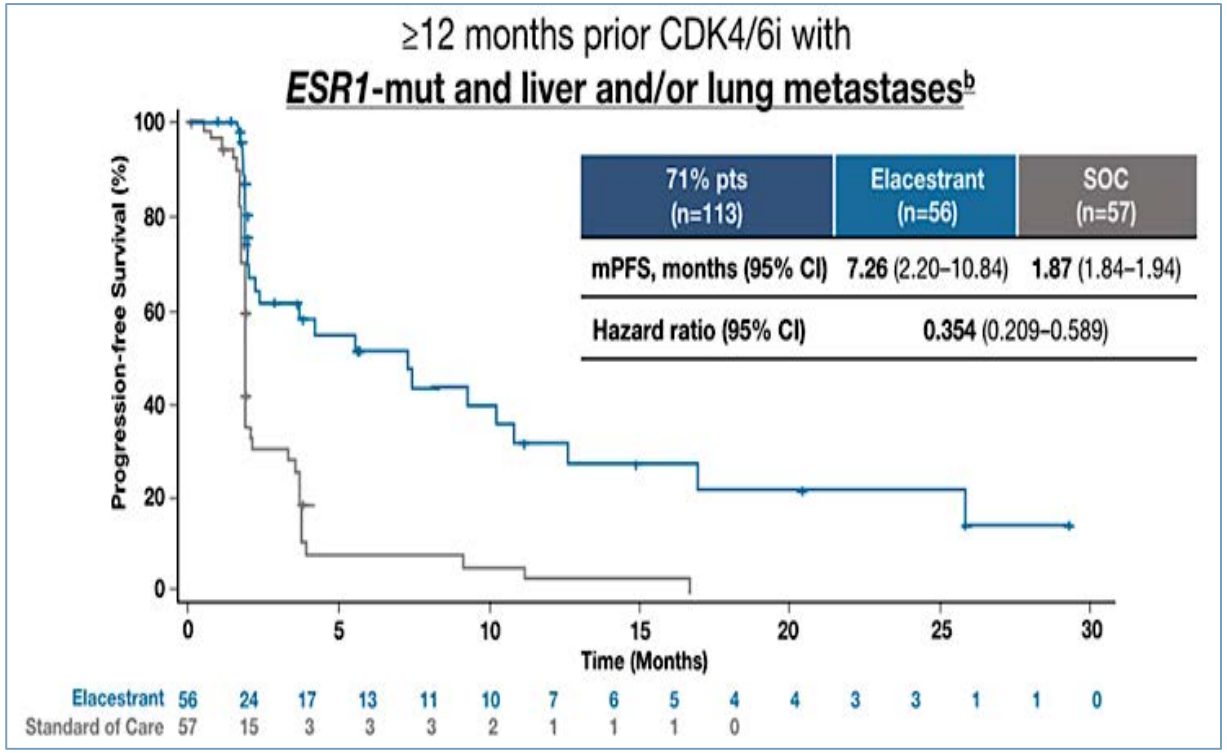
1. Bardia A et al. SABCS 2023. Abstract PS16-01. Bardia A, Cortés J, Bidard FC, et al. *Clin Cancer Res*. 2024;30(19):4299-4309.

EMERALD: Clinically Meaningful Improvement in PFS Across All Subgroups

Bone Metastases



Liver and/or Lung Metastases



Bardia A, O'Shaughnessy J, Bidard F-C, et al. San Antonio Breast Cancer Symposium 2023;San Antonio, Texas; Friday, December 8th:PS16-01. Bardia A, Cortés J, Bidard FC, et al. *Clin Cancer Res*. 2024;30(19):4299-4309.

EMERALD: Adverse Events (≥ 10%)

Adverse Event, n (%)	Elacestrant		ET (All Types)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Nausea	83 (35.0)	6 (2.5)	43 (18.8)	2 (0.9)
Fatigue	45 (19.0)	2 (0.8)	43 (18.8)	2 (0.9)
Vomiting	45 (19.0)	2 (0.8)	19 (8.3)	0
Decreased appetite	35 (14.8)	2 (0.8)	21 (9.2)	1 (0.4)
Arthralgia	34 (14.3)	2 (0.8)	37 (16.2)	0
Diarrhea	33 (13.9)	0	23 (10.0)	2 (0.9)
Back pain	33 (13.9)	6 (2.5)	22 (9.6)	1 (0.4)
Increased aspartate aminotransferase	31 (13.1)	4 (1.7)	28 (12.2)	2 (0.9)
Headache	29 (12.2)	4 (1.7)	26 (11.4)	0
Constipation	29 (12.2)	0	15 (6.6)	0
Hot flush	27 (11.4)	0	19 (8.3)	0
Dyspepsia	24 (10.1)	0	6 (2.6)	0
Increased alanine aminotransferase	22 (9.3)	5 (2.1)	23 (10.0)	1 (0.4)

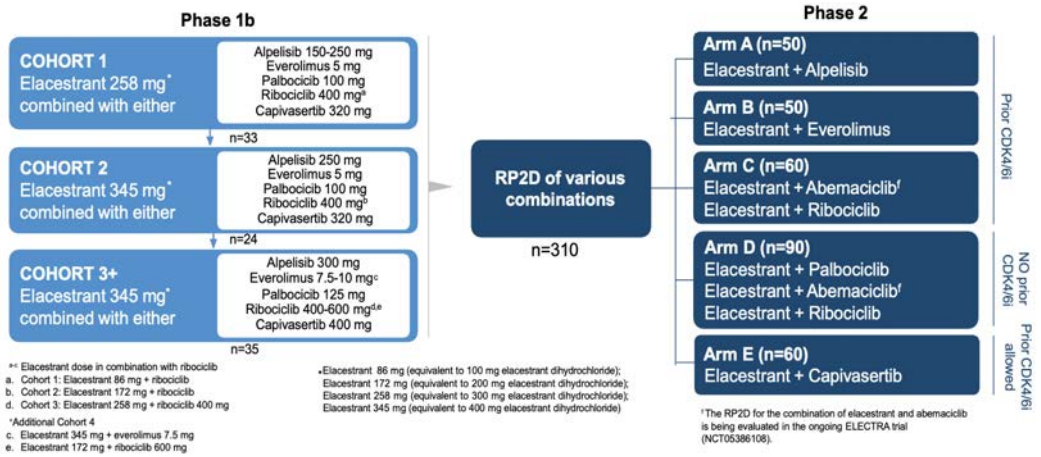
SABCS 2022: Updated Safety Data were Consistent with Prior Reports

Bardia A, Cortés J, Bidard FC, et al. *Clin Cancer Res*. 2024;30(19):4299-4309.

Bidard F, et al. *J Clin Oncol*. 2022;40:3246-3256.
Bardia A, et al. *Cancer Res.* 2023;83(5_Supplement): Abstract GS3-01.
https://doi.org/10.1158/1538-7445.SABCS22-GS3-01.

ELEVATE Trial: Elacestrant Combinations in HR+ MBC

ELEVATE Study Design



*,< Elacestrant dose in combination with ribociclib
a. Cohort 1: Elacestrant 86 mg + ribociclib
b. Cohort 2: Elacestrant 172 mg + ribociclib
d. Cohort 3: Elacestrant 258 mg + ribociclib 400 mg
*Additional Cohort 4
c. Elacestrant 345 mg + everolimus 7.5 mg
e. Elacestrant 172 mg + ribociclib 600 mg

*Elacestrant 86 mg (equivalent to 100 mg elacestrant dihydrochloride); Elacestrant 172 mg (equivalent to 200 mg elacestrant dihydrochloride); Elacestrant 258 mg (equivalent to 300 mg elacestrant dihydrochloride); Elacestrant 345 mg (equivalent to 400 mg elacestrant dihydrochloride)

[f]The RP2D for the combination of elacestrant and abemaciclib is being evaluated in the ongoing ELECTRA trial (NCT05386108).

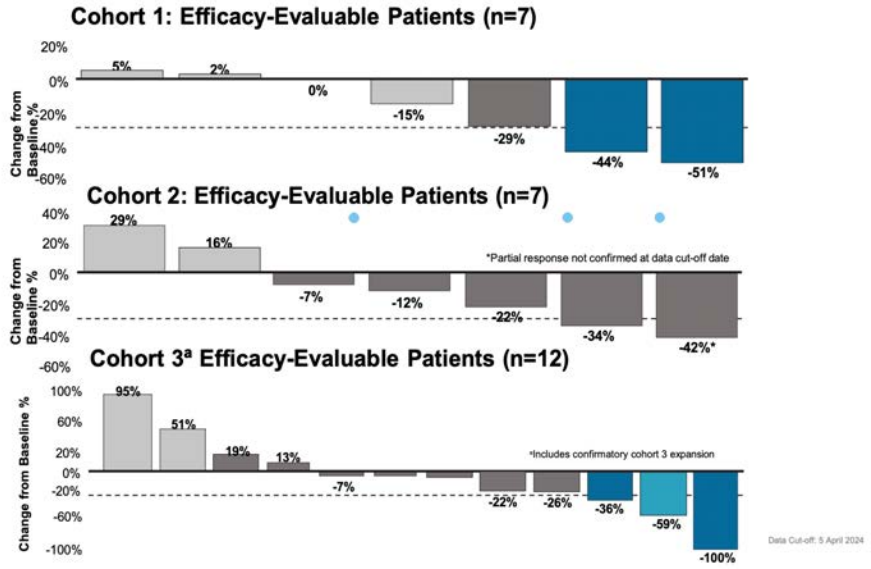
Phase 1b primary objective
- Determine RP2D of elacestrant in combination with each of the other study drugs

Phase 2 primary objective
- Evaluate the PFS of elacestrant in combination with each of the other study drugs
- Further evaluate efficacy and safety of elacestrant in combination with each of the other drugs

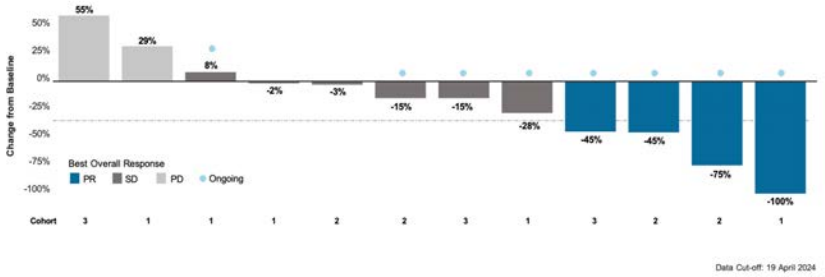
Clinical Trial: NCT05563220

Rugo et al., *ASCO 2024*

Best Tumor Response: Elacestrant + Abemaciclib



Efficacy: Elacestrant + Everolimus



acelERA Phase 2 trial of giredestrant vs ET in ER+/HER2- MBC

Giredestrant is a highly potent, non-steroidal, oral selective SERD

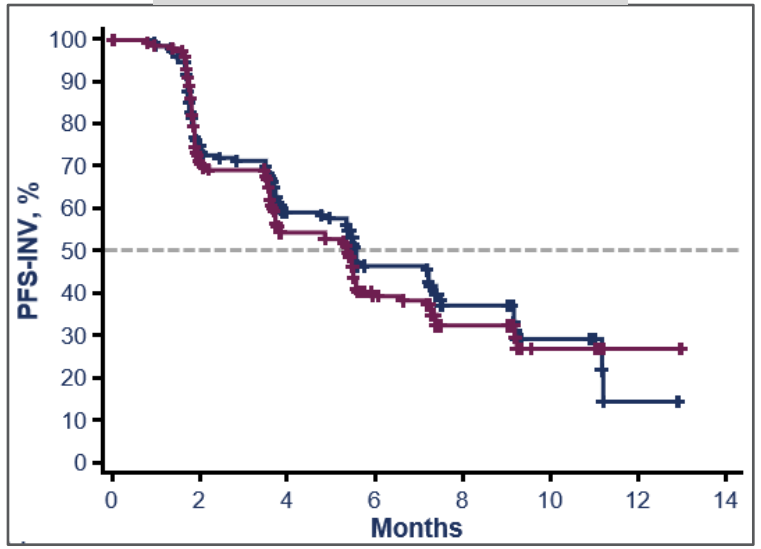
- ER+/HER2– LA/mBC
- Post- or pre-/peri-menopausal women, and men*
- 1 or 2 prior lines of systemic therapy for LA/mBC:
  - 1 must be ET (≥ 6 months)
  - ≤ 1 targeted agent
  - ≤ 1 chemotherapy allowed

N = 303

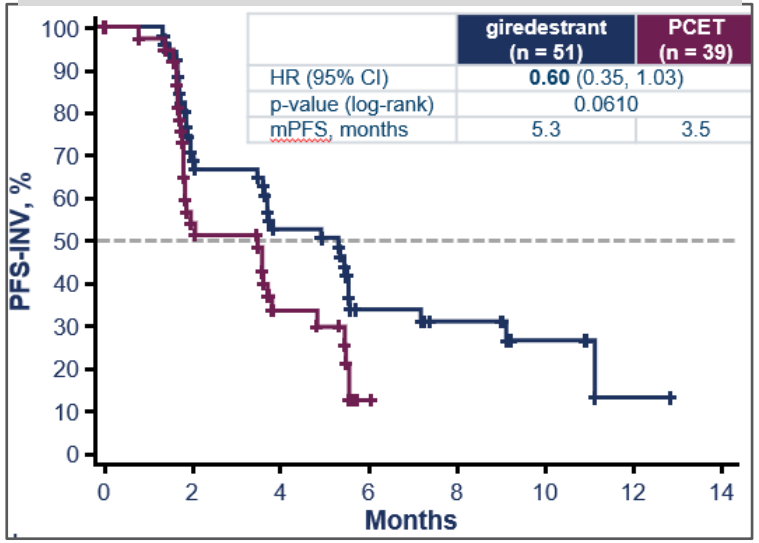
R 1:1

- giredestrant 30 mg PO QD
- Physician's choice of mono ET (fulvestrant or AI)

Primary EP: PFS in ITT population



Secondary EP: PFS in ESR1 mutant subgroup



Pt population:

Prior CDK 4/6i -42%; prior FULV -19%; prior chemo -32%.
ESR1 mutations: 40%

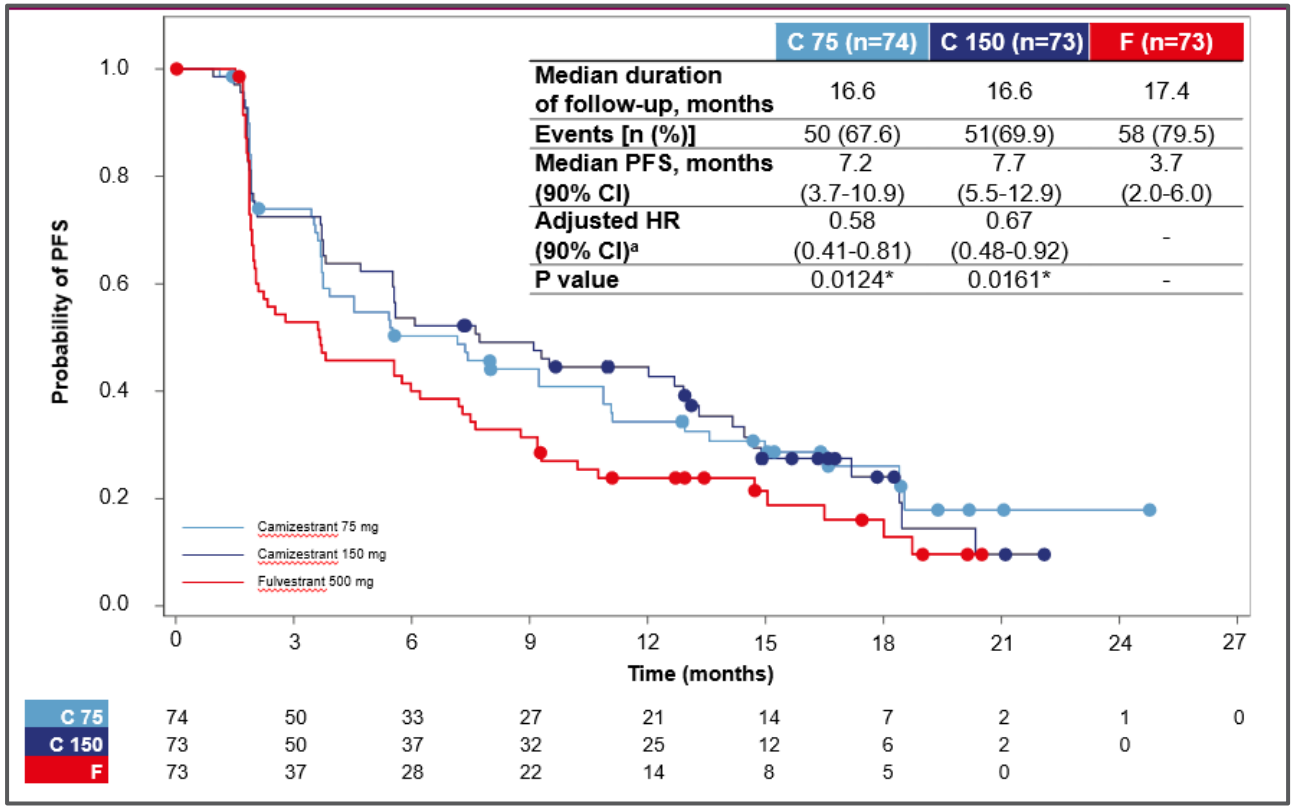
There was no improvement in PFS in the ITT populations and a modest improvement in the ESR1 mutant subset.

@ErikaHamilton9

Martin M et al. ESMO 2022 Martín M, Lim E, Chavez-MacGregor M, et al. *J Clin Oncol*. 2024;42(18):2149-2160.

SERENA-2: Progression-free survival

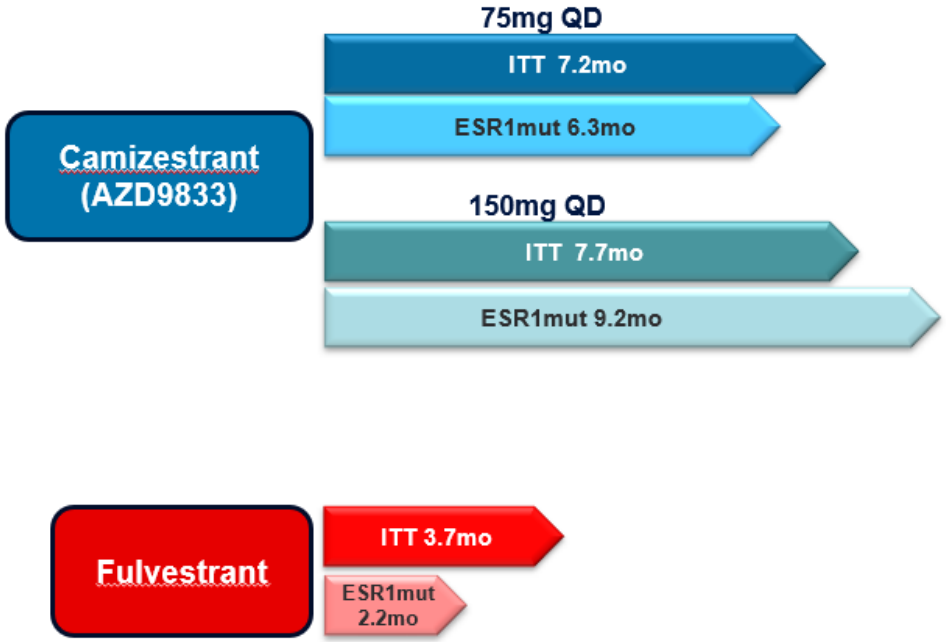
PFS in overall patient population



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

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

PFS in pts based on detectable ESR1mut



Patient population

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

Oliveira M et al. SABCS 2022, GS3-02

Oliveira M, Pominchuk D, Nowecki Z, et al. Lancet Oncol. 2024;25(11):1424-1439.

Selection of Additional Phase 3 SERD Trials in MBC

EMBER-3

1:1:1 Randomization
N = ~860

ER+, HER2-, Advanced Breast Cancer

- Relapsed on (neo) adjuvant/within 1 year of adjuvant AI, alone or in combination with a CDK4/6 inhibitor
  OR
- Progressed on 1L AI, alone or in combination with a CDK4/6 inhibitor
- Prior CDK4/6i treatment is expected if approved and reimbursed

Stratified for:
- Prior CDK4 & 6 inhibitor therapy
- Presence of visceral metastases
- Region

- Imlunestrant 400 mg PO QD (Arm A)
- Investigator's choice ET Fulvestrant or Exemestane (Arm B)
- Imlunestrant 400 mg PO QD + Abemaciclib 150 mg PO BID (Arm C)

Primary Objectives:
- Investigator-assessed PFS for A vs B
- Investigator-assessed PFS for A vs B in the *ESR1*-mutation detected population
- Investigator-assessed PFS for C vs A (gated, i.e. only tested if A vs B is stat sig)

Secondary Objectives:
- OS (gated), PFS by BICR, ORR, CBR, DoR, PRO's

persevERA

N=978
- ER+/HER2- LA/ABC
- No prior systemic tx for ABC

R 1:1

- Giredestrant 30mg QD Palbociclib 125mg Letrozole-matched PLA
- Letrozole 2.5mg Palbociclib 125mg Giradestrant-matched PLA

PFS

Recruiting

NCT04546009

SERENA-4

N=1342
- ER+/HER2- LA/ABC
- No prior systemic tx for ABC

R 1:1

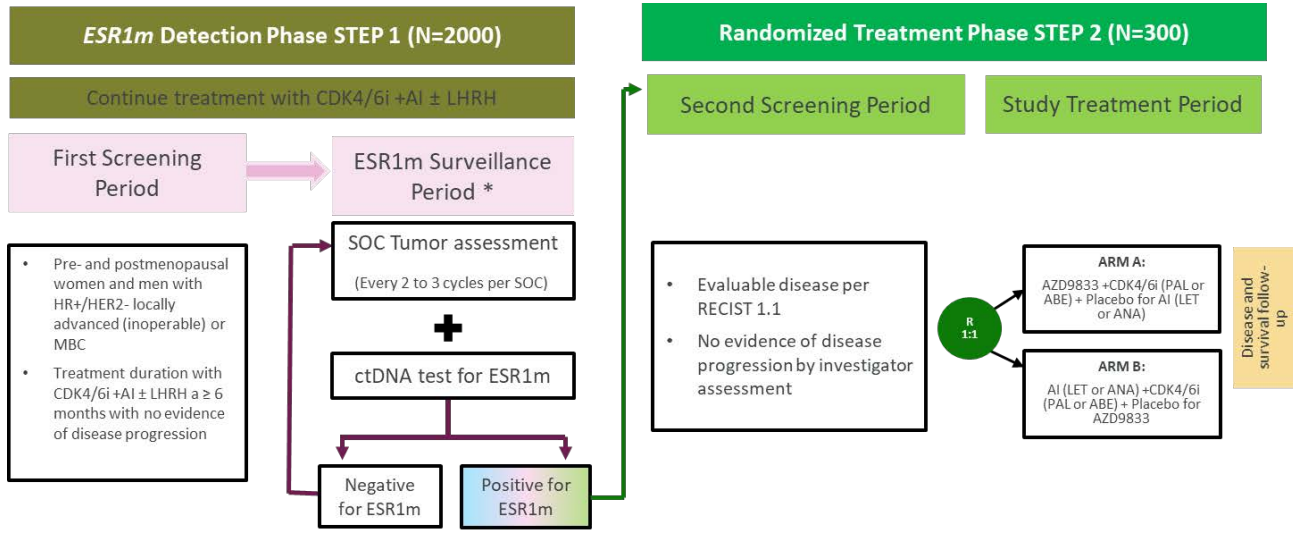
- Camizestrant 75mg QD Palbociclib 125mg Anastrozole-matched PLA
- Anastrozole 1mg Palbociclib 125mg Camizestrant-matched PLA

PFS

Recruiting

NCT04711252

SERENA-6



EMBER-3 (Phase 3): Imlunestrant ± abemaciclib for ER+, HER2– advanced breast cancer pretreated with endocrine therapy

Key eligibility

ER+, HR2- ABC

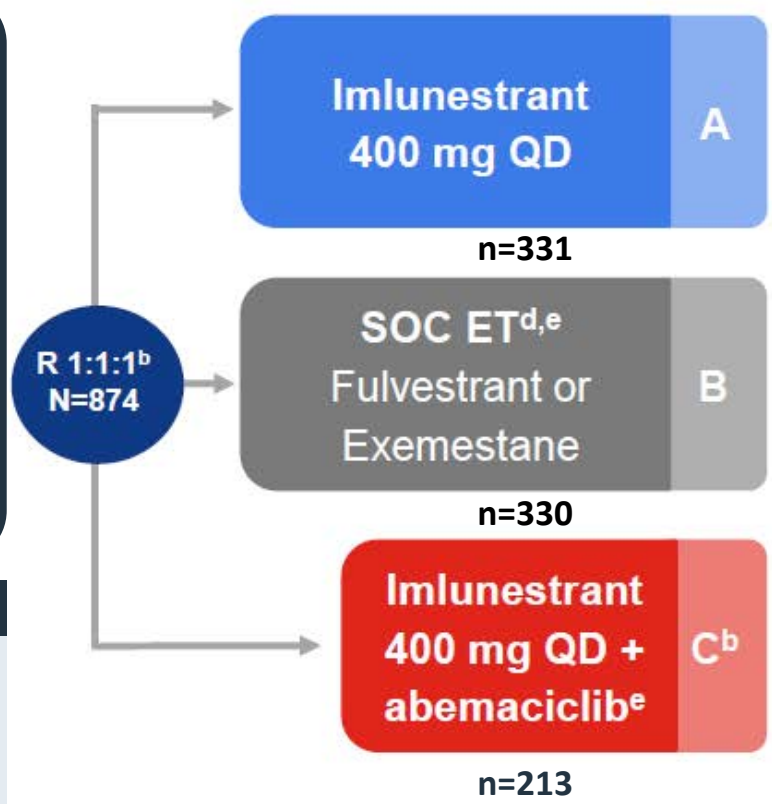
- Men and Pre-[a]/Post-menopausal women

Prior therapy:

- Adjuvant: Recurrence on or within 12 months of completion of AI ± CDK4/6i
- **ABC**: Progression on first-line AI ± CDK4/6i
- No other therapy for ABC

Stratification factors

- Prior CDK4/6i therapy (Y/N)
- Visceral metastases (Y/N)
- Region[c]



Primary endpoints

- **Investigator-assessed PFS for[f]:**
  - A vs B in patients with *ESR1*m[g]
  - A vs B in all patients
  - C vs A in all[h] patients

Key secondary endpoints

- OS, PFS by BICR, and ORR
- Safety

Exploratory endpoints

- PFS and OS for C vs B in all[h] patients

- The primary reason for study treatment discontinuation was progressive disease in all arms

[a]GnRH agonist was required in men and premenopausal women; [b]Enrollment into Arm C started with Protocol Amendment A (at which point 122 patients had been randomized across Arms A and B); [c]East Asia vs United States/European Union vs others; [d]Investigator's choice; [e]Labeled dose; [f]Scans every 8 weeks for the first 12 months, then every 12 weeks; [g]ESR1m status was centrally determined in baseline plasma by the Guardant 360 ctDNA assay and OncoCompass Plus assay (Burning Rock Biotech) for patients from China; [h]Analysis conducted in all concurrently randomized patients.

Jhaveri K, et al. SABCS 2024. Abstract GS1-01

EMBER-3 (Phase 3): Baseline characteristics

Characteristic		Imlunestrant n=331	SOC ET n=330	Imlunestrant + abemaciclib n=213
Median age, years (range)		61 (28-87)	62 (27-89)	62 (36-87)
Female, %		99	99	99
Post-menopausal, %		84	86	86
Race, %	White	56	58	52
	Asian	28	29	34
	Black or African American	3	2	4
Region, %	East Asia	25	26	31
	North America/ Western Europe	38	39	45
	Other	37	36	24
PR-positive, %		78	79	74
***ESR1* mutation, %[a]**		42	36	32
PI3K pathway mutations, %[b]		39	39	41

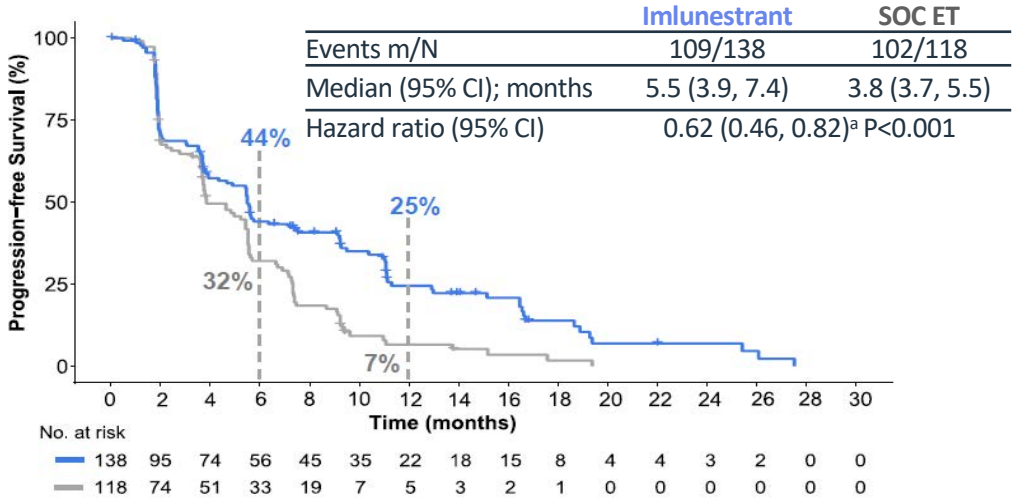
Characteristic		Imlunestrant n=331	SOC ET n=330	Imlunestrant + abemaciclib n=213
Site of metastases, %	Visceral	57	54	56
	Liver	32	30	27
	Bone-only	22	26	24
Endocrine resistance, %[c]	Primary	8	11	8
	Secondary	92	89	93
Most recent ET, %[d]	Adjuvant	32	34	30
	ABC	63	63	68
Previous CDK4/6i, %	Overall	59	57	65
	Adjuvant	4	5	3
	ABC	55	53	62
Previous CDK4/6i therapy, %[e]	Palbociclib	61	69	65
	Ribociclib	29	27	27
	Abemaciclib	10	4	7

[a]Samples were analyzed by Guardant360 CDx, except for patients from China where samples were analyzed by OncoCompass Target assay, Burning Rock Biotech; [b]Includes single nucleotide variants and insertions/deletions of PIK3CA, AKT1 or PTEN analyzed by Guardant 360 ctDNA assay. This analysis excludes patients from China or with unknown ESR1m status; [c]Per ESO-ESMO International Consensus Guidelines for ABC (ABC 6 and 7); [d]Adjuvant ET = First-line; ABC = Second-line; [e]Percentages calculated based on the numbers of patients who received prior CDK4/6i therapy (imlunestrant, n=195; SOC ET, n=189; imlunestrant + abemaciclib, n=139); [f]Data available in the online supplementary slides.

Jhaveri K, et al. SABCS 2024. Abstract GS1-01

EMBER-3 (Phase 3): Primary endpoints, imlunestrant vs SOC ET

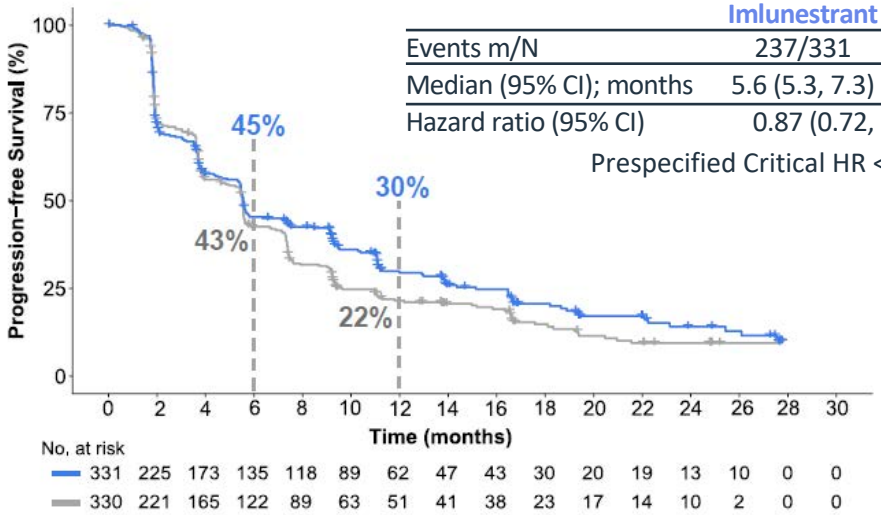
Investigator-Assessed PFS in patients with *ESR1* mutations



	Imlunestrant	SOC ET
Events m/N	109/138	102/118
Median (95% CI); months	5.5 (3.9, 7.4)	3.8 (3.7, 5.5)
Hazard ratio (95% CI)	0.62 (0.46, 0.82)[a] P<0.001	

- Imlunestrant led to a 38% reduction in the risk of progression or death in patients with *ESR1*m
- Consistent imlunestrant benefit across subgroups in patients with *ESR1*m

Investigator-Assessed PFS in all patients



	Imlunestrant	SOC ET
Events m/N	237/331	253/330
Median (95% CI); months	5.6 (5.3, 7.3)	5.5 (4.6, 5.6)
Hazard ratio (95% CI)	0.87 (0.72, 1.04); P=0.12	
Prespecified Critical HR < 0.84[b]		

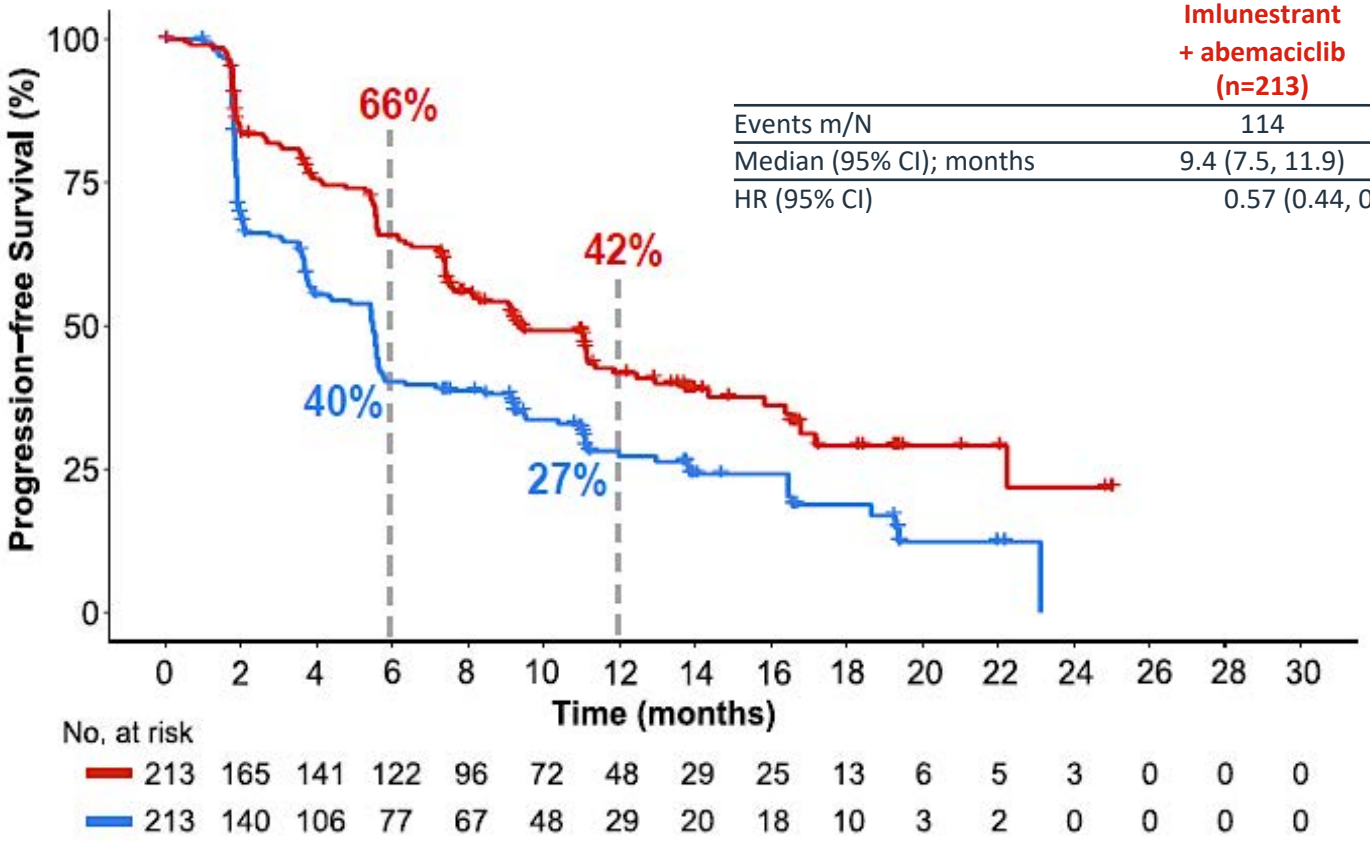
- PFS difference of imlunestrant vs SOC ET in all patients did not reach significance
  - The majority subgroup of patients without *ESR1*m showed no difference in PFS (HR=1.00; 95% CI, 0.79, 1.27)

[a]Due to evidence of non-proportional hazards, a sensitivity analysis of PFS using RMST was conducted. Estimated RMST at 19.4 months was 7.9 months (95% CI 6.8, 9.1) in the imlunestrant arm vs 5.4 months (95% CI 4.6, 6.2) in the SOC ET arm [difference 2.6 months (1.2 to -3.9)]; [b]At full alpha.

Jhaveri K, et al. SABCS 2024. Abstract GS1-01

EMBER-3 (Phase 3): Primary endpoints, imlunestrant + abemaciclib vs imlunestrant

Imlunestrant + abemaciclib vs imlunestrant: Investigator-assessed PFS in all patients



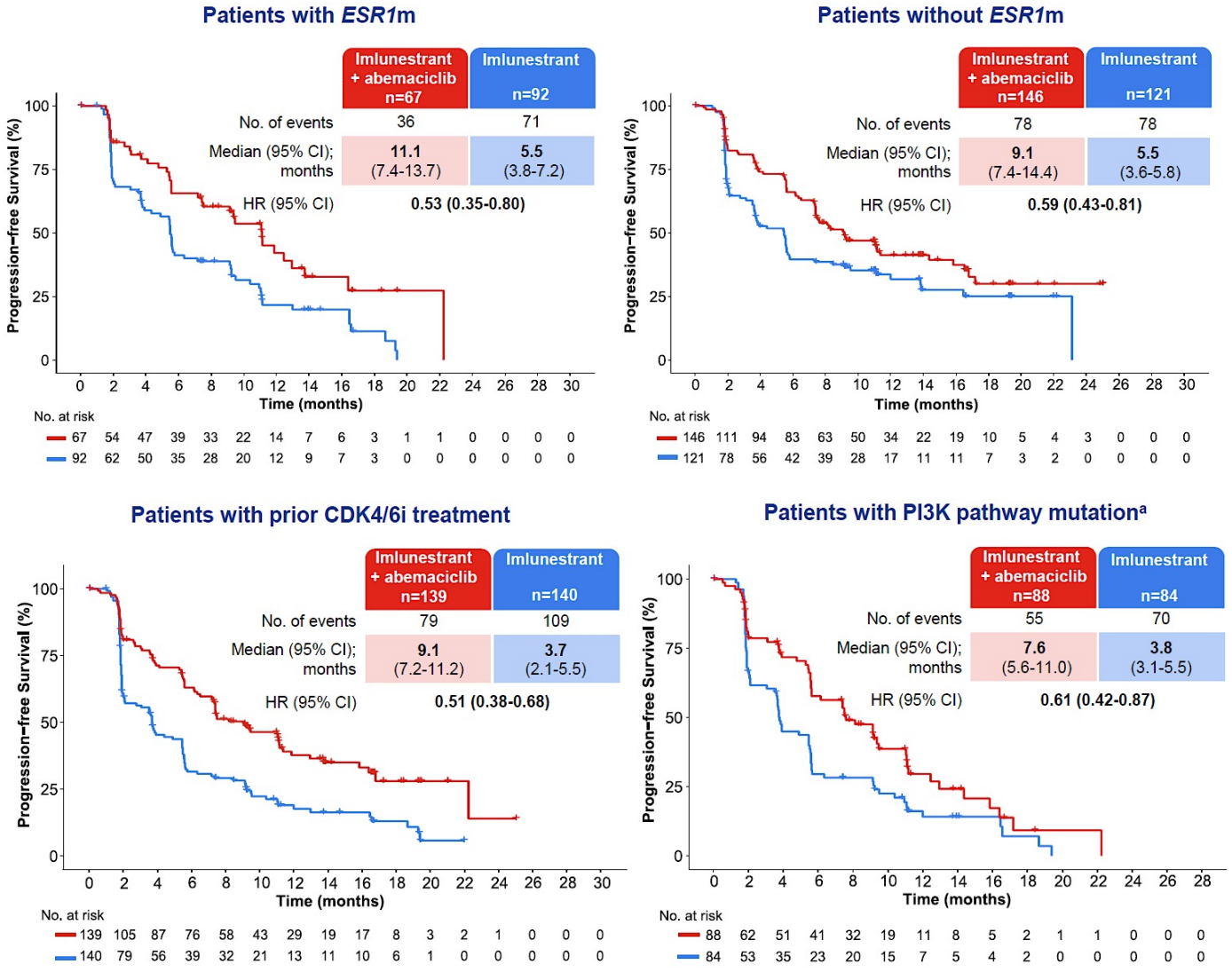
	Imlunestrant + abemaciclib (n=213)	Imlunestrant (n=213)[a]
Events m/N	114	149
Median (95% CI); months	9.4 (7.5, 11.9)	5.5 (3.8, 5.6)
HR (95% CI)	0.57 (0.44, 0.73); P <0.001	

- Imlunestrant + abemaciclib led to a 43% reduction in the risk of progression or death over imlunestrant alone in all patients
- Consistent imlunestrant + abemaciclib benefit observed across key clinical subgroups and regardless of *ESR1m* status

[a]Efficacy analyses confined to the imlunestrant population concurrently randomized to imlunestrant + abemaciclib treatment arm. The median follow-up was 13.5 months in the imlunestrant + abemaciclib arm and 13.7 months in the imlunestrant arm.

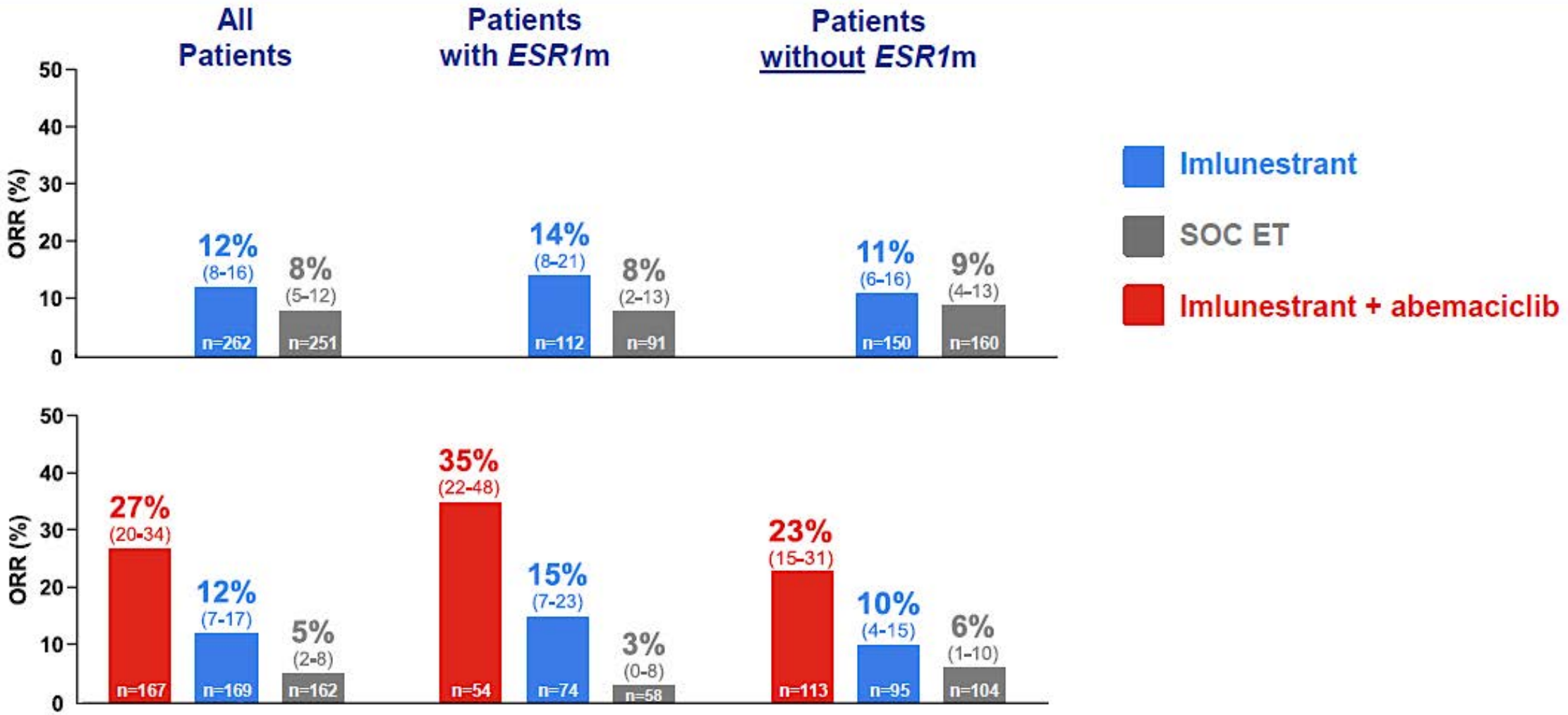
Jhaveri K, et al. SABCS 2024. Abstract GS1-01

EMBER-3 (Phase 3): Investigator-assessed PFS by subgroup, imlunestrant + abemaciclib vs imlunestrant



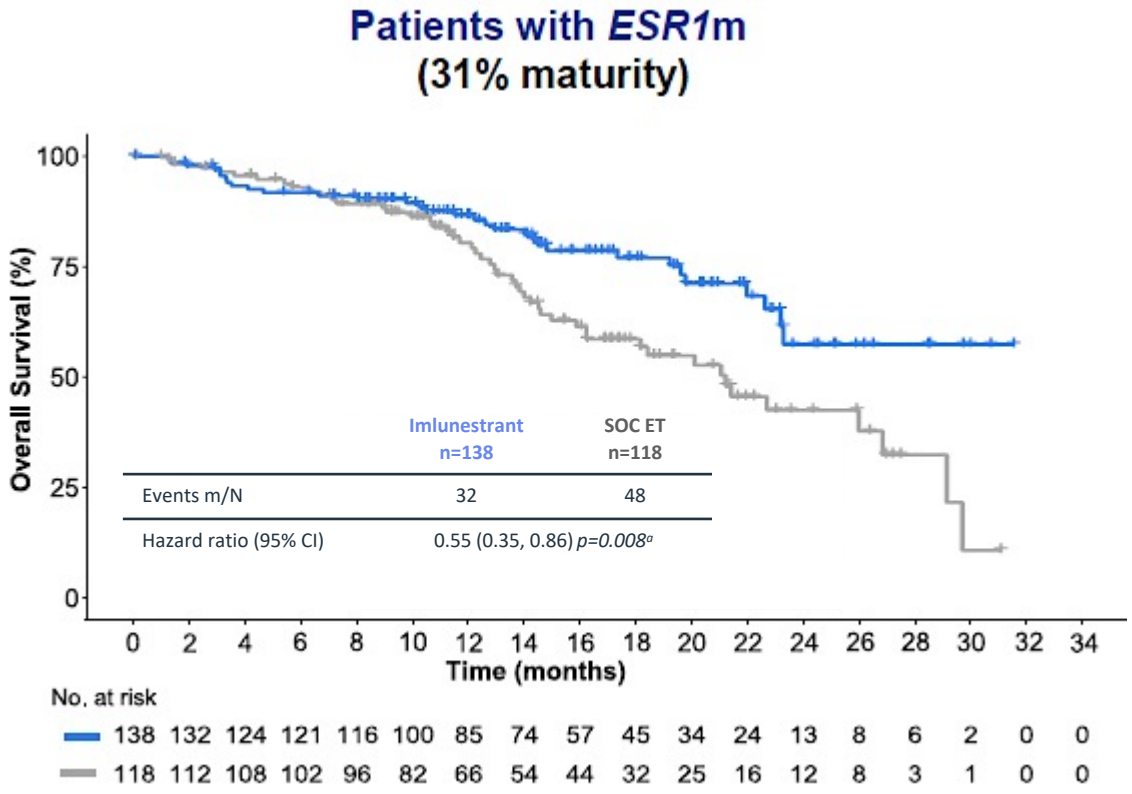
Jhaveri K, et al. SABCS 2024. Abstract GS1-01

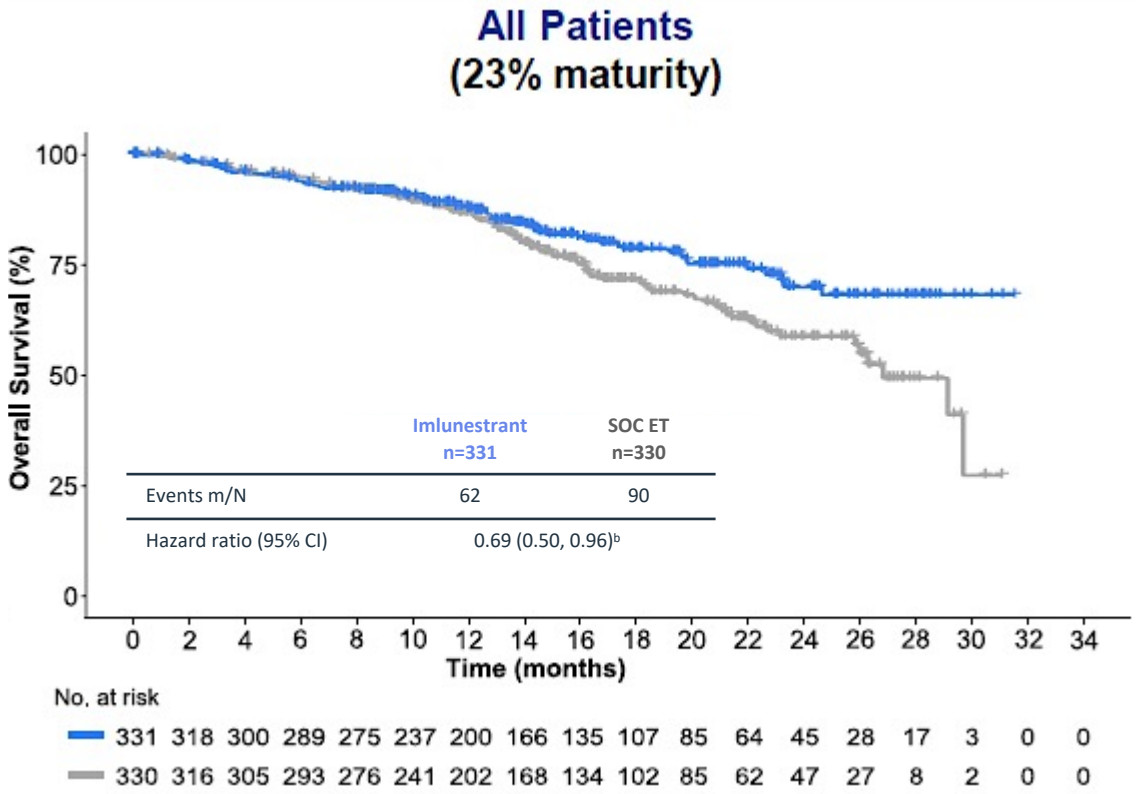
EMBER-3 (Phase 3): Secondary endpoints, treatment response



Jhaveri K, et al. SABCS 2024. Abstract GS1-01

EMBER-3 (Phase 3): Interim overall survival





- In patients without ESR1m: maturity 18% (HR=0.87; 95% CI, 0.54-1.40)[c]
- In all patients within the combination therapy comparison: maturity 15% (HR=1.34; 95% CI, 0.81-2.21)[c]

[a]Did not meet prespecified boundary for statistical significance; [b]Statistical significance was not inferentially tested due to not meeting the PFS endpoint; [c]Prespecified subgroup analysis, not inferentially tested, data available in the online supplementary slides.

Jhaveri K, et al. SABCS 2024. Abstract GS1-01.

EMBER-3 (Phase 3): Safety and tolerability

TEAEs in ≥ 10% of Patients, %	Imlunestrant n=327		SOC ET n=324	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Patients with ≥ 1 TEAE	83	17	84	21
Fatigue[a]	23	<1	13	1
Diarrhea	21	<1	12	0
Nausea	17	<1	13	0
Arthralgia	14	1	14	<1
AST increased	13	1	13	1
Back pain	11	1	7	<1
ALT increased	10	<1	10	1
Anemia[a]	10	2	13	3
Constipation	10	0	6	<1

Patients with ≥ 1 SAE, %		10	12
Dose reductions due to AE, %		2	0
Discontinuations due to AE, %		4	1
Deaths due to AE on study, %		2	1
Injection Site Reaction[a]	TEAE, n/N (%)[b]	NA	27/292 (9%)
	PRO-CTCAE, n/N (%)[c]	NA	201/278 (72%)

- Generally favorable safety profile

TEAEs in ≥ 20% of Patients, %	Imlunestrant + abemaciclib n=208	
	Any Grade	Grade ≥3
Patients with ≥ 1 TEAE	98	49
Diarrhea	86	8
Nausea	49	2
Neutropenia[a]	48	20
Anemia[a]	44	8
Fatigue[a]	39	5
Vomiting	31	1
Leukopenia[a]	26	4
Hypercreatinemia[a]	22	1
Abdominal pain[a]	20	2
Decreased appetite	20	1

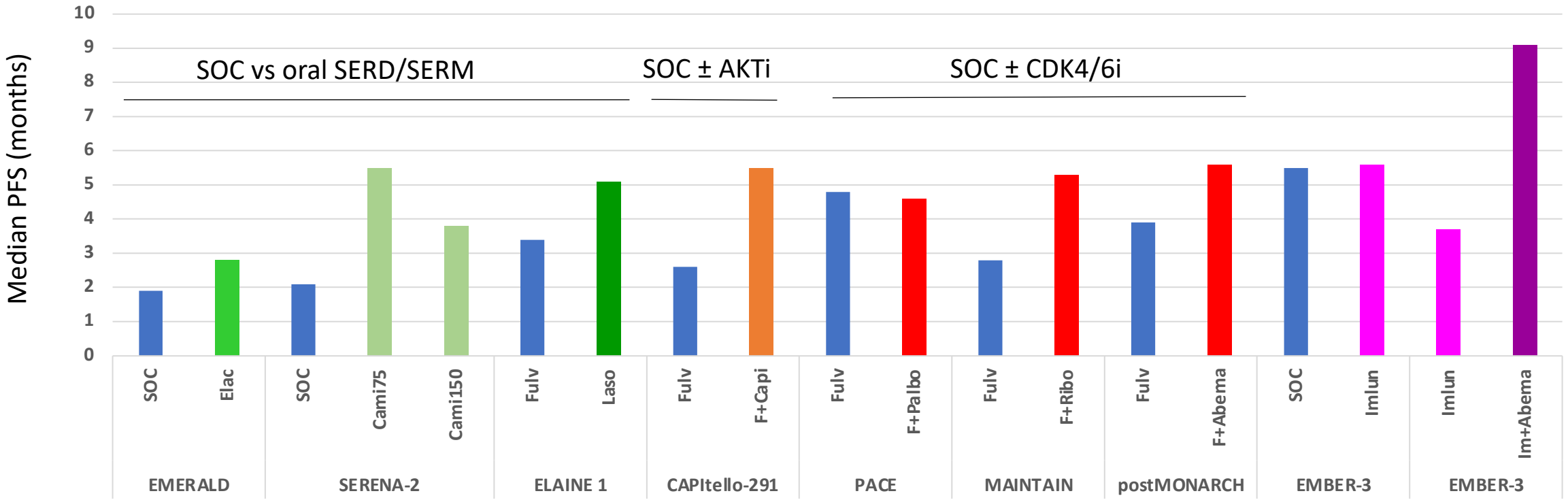
Patients with ≥ 1 SAE, %	17
Dose reductions due to AE, %[d]	39
Discontinuations due to AE, %	6
Deaths due to AE on study, %	1

- Safety consistent with the known abemaciclib profile

[a]Consolidated term; [b]N is the number of evaluable patients who received fulvestrant; [c]N is the number of evaluable patients who completed the PRO-CTCAE survey (answered "yes" or "no" to injection site pain, swelling, or redness); [d]Dose reduction of imlunestrant alone: 2%; abemaciclib alone: 23%; both drugs: 14%.

Jhaveri K, et al. SABCS 2024. Abstract GS1-01

Median Progression Free Survival in Recent Randomized Trials of Endocrine Therapy:
*Outcomes among patients with prior CDK4/6 inhibitor treatment**

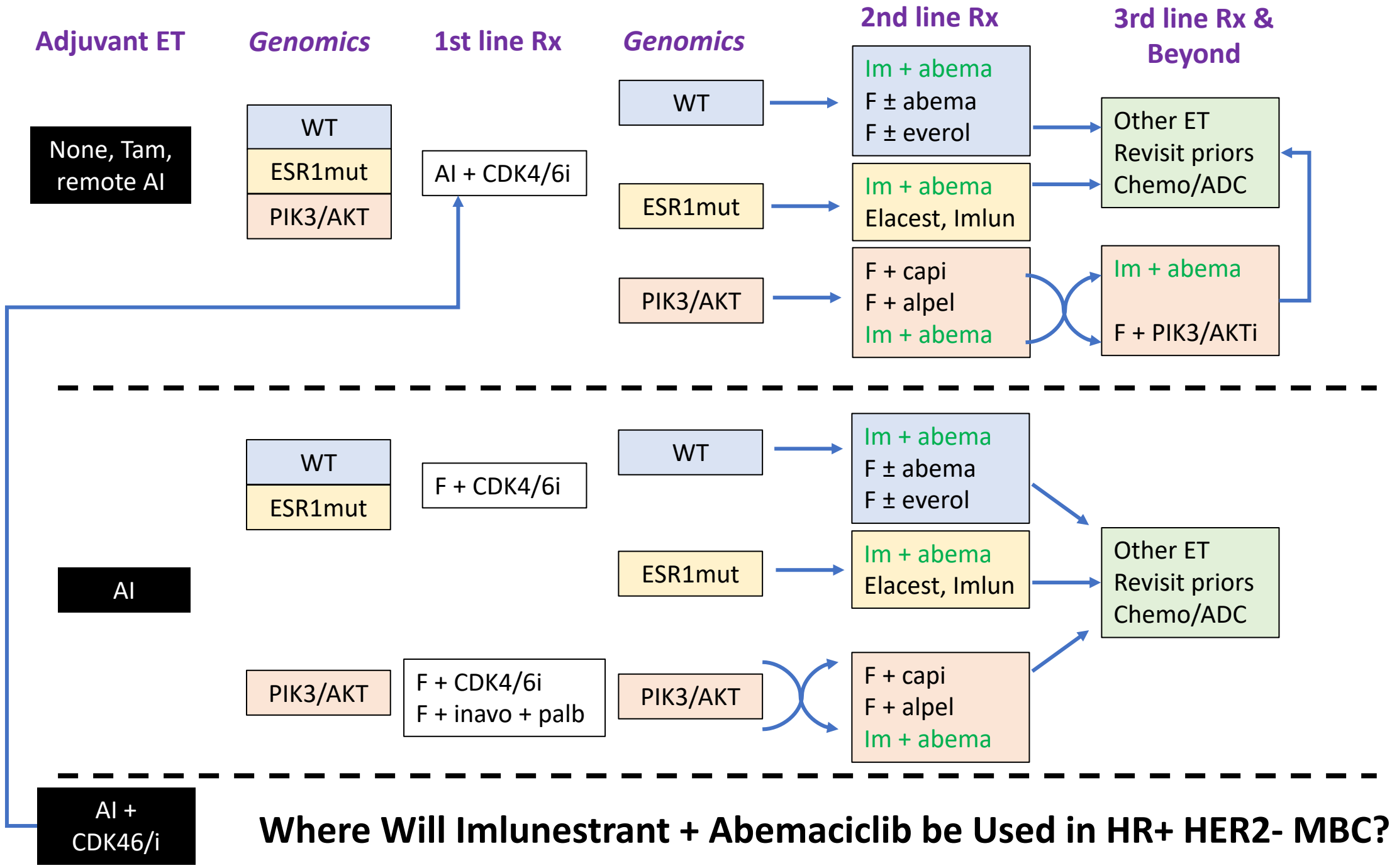


Prior CDK46i	100%	100%**	100%	100%**	100%	100%	100%	58%	100%**

*there are a lot of problems with cross study comparisons, especially in unplanned subset analyses:
extent/types of prior therapy, variable tumor genomics/biomarker profile,
SOC options, sample size, exposure vs resistance, investigator vs BICR, etc.

** Denotes subset of larger study cohort

Harold Burstein, MD, PhD, SABCS 2024


Adjuvant ET
Genomics
1st line Rx
Genomics
2nd line Rx
3rd line Rx & Beyond
None, Tam, remote AI
WT
ESR1mut
PIK3/AKT
AI + CDK4/6i
WT
ESR1mut
PIK3/AKT
Im + abema
F ± abema
F ± everol
Im + abema
Elacest, Imlun
F + capi
F + alpel
Im + abema
Other ET
Revisit priors
Chemo/ADC
Im + abema
F + PIK3/AKTi
AI
WT
ESR1mut
F + CDK4/6i
WT
ESR1mut
PIK3/AKT
Im + abema
F ± abema
F ± everol
Im + abema
Elacest, Imlun
Other ET
Revisit priors
Chemo/ADC
PIK3/AKT
F + CDK4/6i
F + inavo + palb
PIK3/AKT
F + capi
F + alpel
Im + abema
AI + CDK46/i
Where Will Imlunestrant + Abemaciclib be Used in HR+ HER2- MBC?

Discussion Questions and Faculty Case Presentations

Second-Line, Post-CDKi Treatment of Metastatic ER+ HER2-Negative Breast Cancer (ER+ mBC): The Impact of a 30-Minute CME Video on Treatment Choices of Community-Based General Medical Oncologists (GMOs)

Abstract: P4-08-12

Thursday, December 12, 2024
5:30 PM – 7:00 PM

Key Factors Affecting Clinical Investigators' Use of Oral SERDs in Current Management of ER-Positive, HER2-Negative, ESR1-Mutated (ER+/HER2-/ESR1+) Metastatic Breast Cancer That Has Relapsed After Treatment with a CDK4/6 Inhibitor/Endocrine Therapy

Abstract: P4-12-15

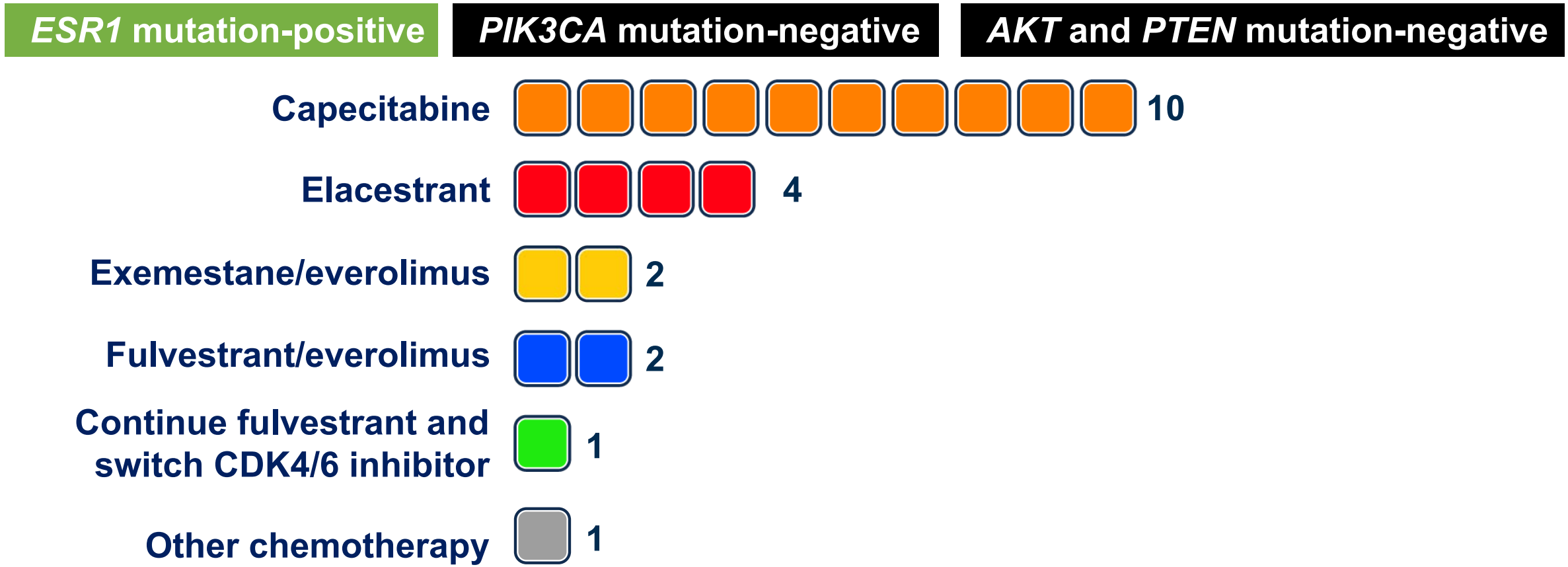
Thursday, December 12, 2024
5:30 PM – 7:00 PM

A 65-year-old woman with ER-positive, HER2-negative, node-negative breast cancer who developed multiple minimally symptomatic bone metastases 2 years after starting adjuvant anastrozole receives a CDK4/6 inhibitor with fulvestrant and initially responds but then experiences disease progression 18 months later.

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

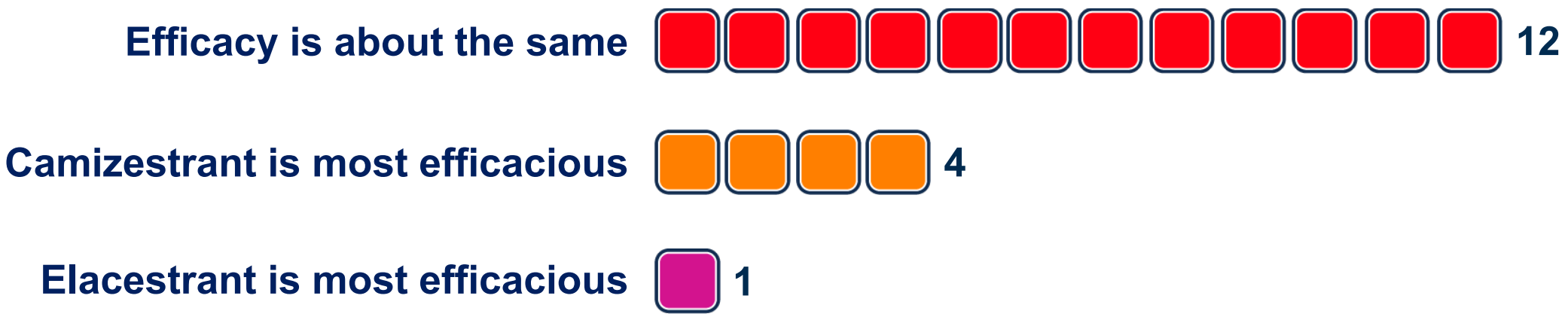
Survey of 20 US-based clinical investigators, January 2024

A 65-year-old woman with ER-positive, HER2-negative, node-negative breast cancer who developed multiple minimally symptomatic bone metastases 2 years after starting adjuvant anastrozole receives a CDK4/6 inhibitor with fulvestrant and initially responds but then experiences disease progression 6 months later.



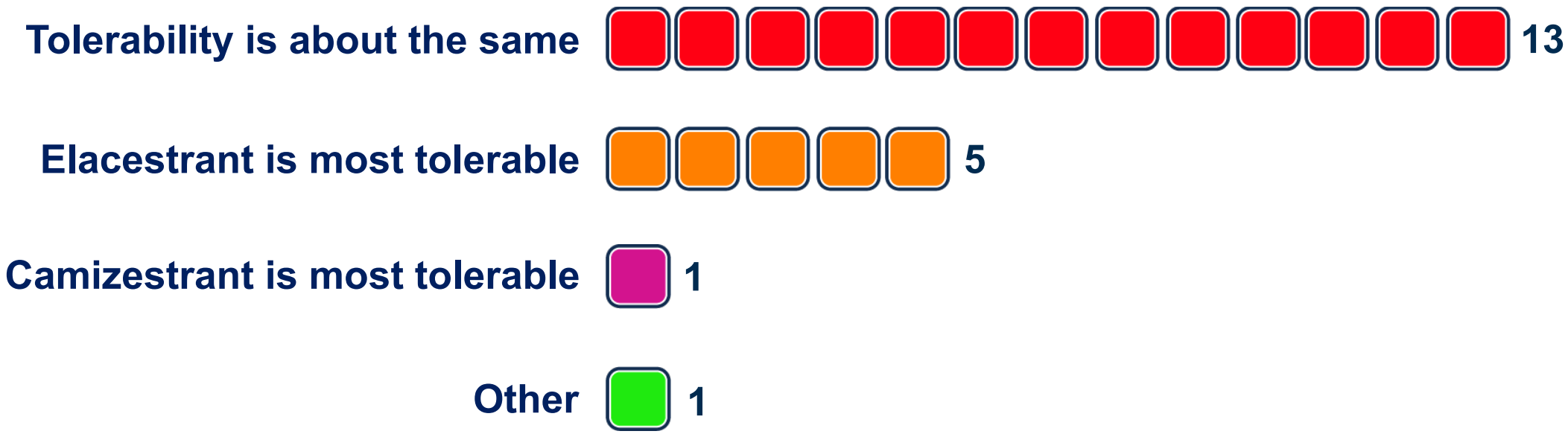
Survey of 20 US-based clinical investigators

Based on current available data and/or your personal clinical experience, how would you compare the global efficacy of the oral selective estrogen receptor degraders (SERDs) elacestrant, camizestrant and imlunestrant?



Survey of 20 US-based clinical investigators

Based on current available data and/or your personal clinical experience, how would you compare the global tolerability of the oral SERDs elacestrant, camizestrant and imlunestrant?



Survey of 20 US-based clinical investigators

Case Presentation: Dr Burstein

- A 65 yo woman was diagnosed with advanced breast cancer in 2022. She presented with a R breast mass, and biopsy confirmed ER pos 90%, PR pos 40%, HER2 +1 invasive ductal carcinoma.
- A staging work up disclosed metastatic disease in the bone.
- April 2022. She received palliative radiation to a lesion in the iliac crest, and began ribociclib and letrozole.
- August 2024. Restaging scans showed tumor progression with new liver lesions. She began trastuzumab deruxtecan.
- December 2024. Scans show enlarging liver metastasis and progression in L acetabular lesion.
- She was treated with radiation to acetabulum, and radiofrequency ablation of prominent liver lesion.
- A repeat liver biopsy done at time of RFA showed metastatic carcinoma, ER pos 100%, PR pos 10%, and HER2 0.
- Genomic testing shows an ESR1 mutation D538G. TMB 5.6 mut/Mb.
- Recommendation: elacestrant

Case Presentation: Dr Borges

44-year-old woman initially diagnosed 2020 with a clinical stage IIb (T2N1M0) multicentric invasive carcinoma right breast with ductal and lobular features, grade 3, ER 3+ 90% PR 2+ 40% HER2 1+/ negative, Ki-67 40%. Biopsy-proven positive right axillary lymph node. Staging studies: 1/7/2020 CT scan of chest, abdomen, and pelvis and whole-body bone scan negative for metastasis.

She is nulliparous, retired military, currently fosters service dogs. Partnered. Does not desire childbearing. Cancer predisposing gene testing was uninformative.

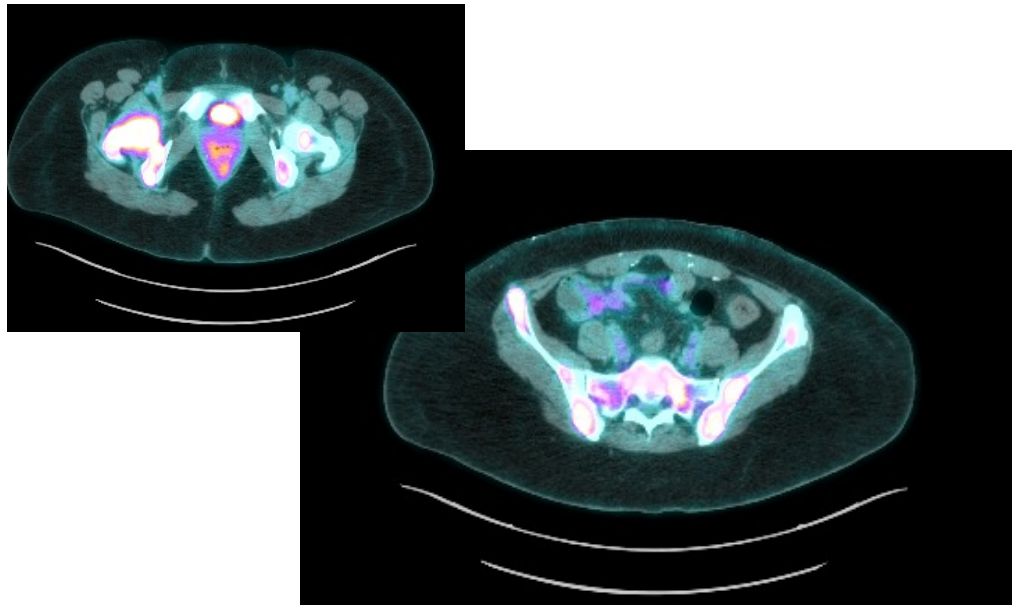
Systemic therapy given with neoadjuvant dose dense AC/T. Last cycle on 5/28/2020.

Post-treatment pathologic stage IIIc/prognostic stage IIIa (ypT3N3aM0) grade 2 invasive ductal carcinoma. Surgical pathology revealed residual multifocal invasive ductal carcinoma measuring 8.4 cm with metastasis to 14 axillary lymph nodes with isolated tumor cells in an additional lymph node. Mastectomy specimen positive for lymphovascular space invasion. Nodes positive for extranodal extension.

Adjuvant therapy: Completed adjuvant radiation to the right chest wall, axillary, supraclavicular and internal mammary nodes to 4005cGy in 15 fx followed by a right chest wall scar boost to 1068cGy in 4 fractions. Endocrine therapy: ovarian suppression for a year, anastrozole for 18 months and abemaciclib - 8 months. Tolerance is a struggle, and she is switched to tamoxifen. She has regular menses and feels well on current therapy.

She is well until 2/2024 when she presents with intense L hip pain.

Case Presentation: Dr Borges (Con't)

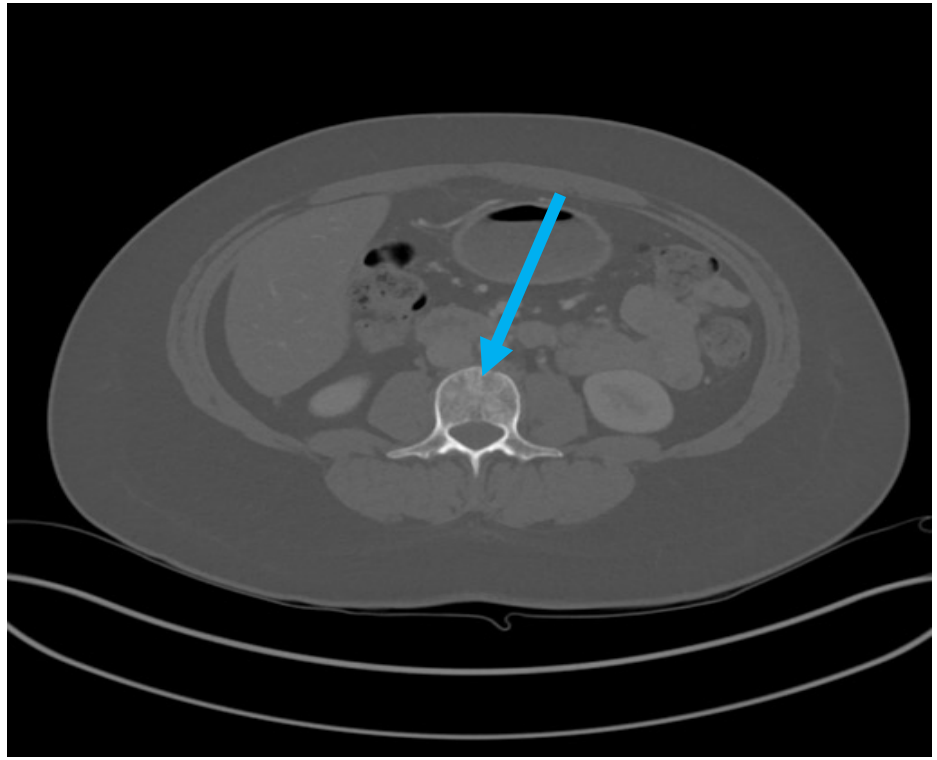


PET CT is obtained revealing extensive bone metastasis included her L hip. Bone biopsy is positive for breast cancer metastasis. ER positive, HER2 1+/negative.

She comes to the University for consideration of clinical trials.
Diagnostic CT shows extensive lytic bone metastasis, no visceral disease.
Serum CA 27-29 is 385.
Her L hip is evaluated.

Ortho-oncology recommends radiation and systemic therapy with careful follow up.

Radiation is given 2000Gy in 5 fractions.



Her best treatment options would be?

Case Presentation: Dr Borges (Con’t)

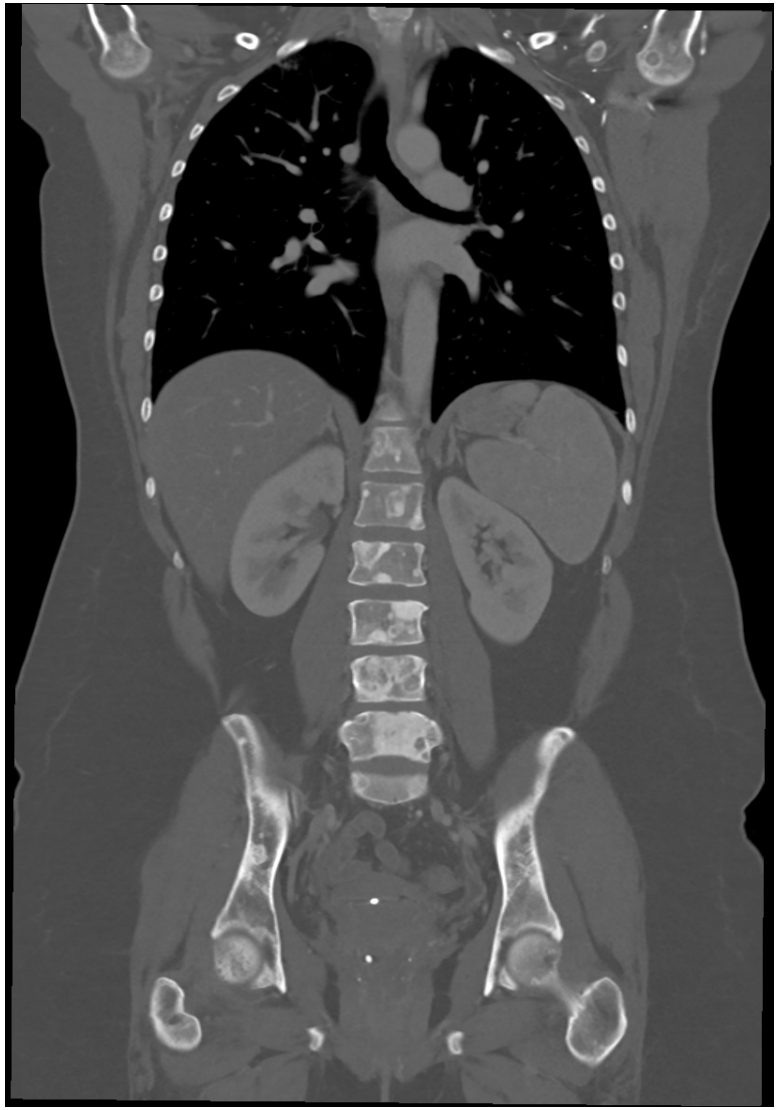
She opts to enroll in a first line study of palazestrant and ribociclib.

3 and 6 month follow-up CT and bone scans show marked sclerosis in all bony lesions.

She is able to come off all pain medications.
She returns to normal functioning, hiking and enjoying life with return to her usual activities.

Her CA27-29 drops to 64 and levels off.

The response is enduring until January 7, 2025.



January 7, 2025, on routine follow up and imaging for her trial participation, she reports her R hip is hurting her now as are a few areas in her back.

CT CAP shows new small pulmonary nodules, largest 13mm, and progression of her bone disease, including a new soft tissue mass growing from her L iliac wing.

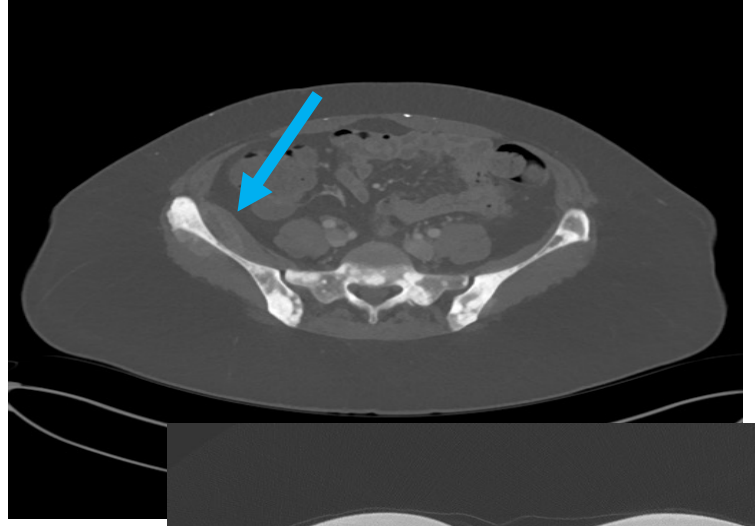
By liquid genomic ctDNA analysis, her tumor is genomically ESR1 WT, PIK3CA WT, BRCA WT, p53 mutated, FGFR amplified.

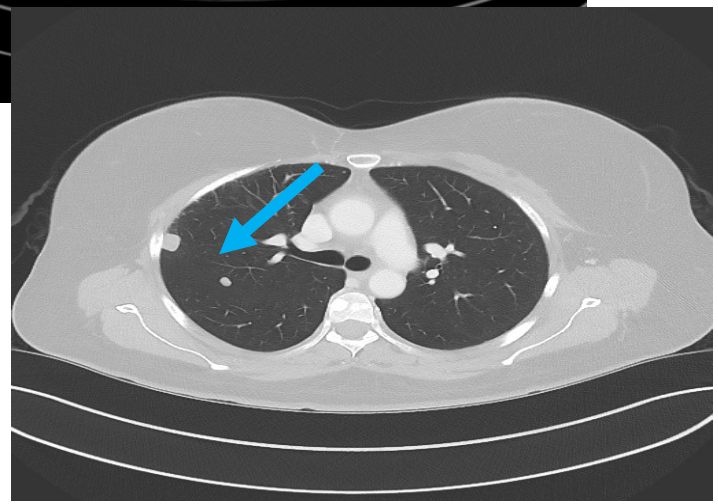
She is interested in having more freedom to travel and declines the next currently available clinical trial.

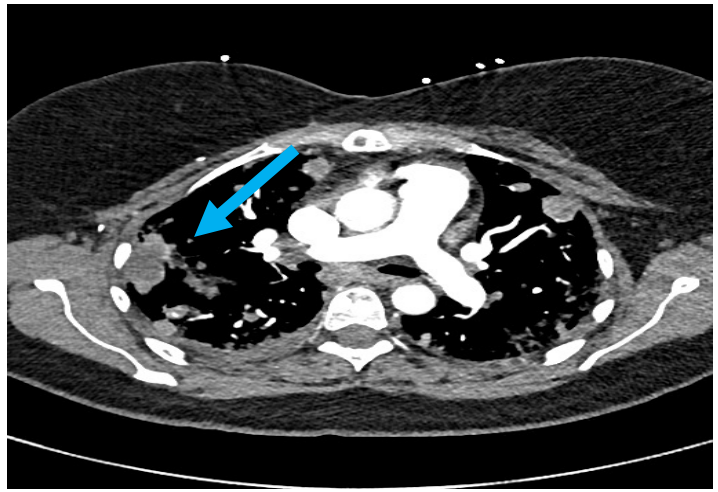
After weighing her SOC options, and in light of some of the difficulties with menopausal symptoms on endocrine therapy, she opts to start capecitabine monotherapy.

Within three weeks, she presents with worsening shortness of breath, rapidly increasing bone pain and is admitted to the hospital. Respiratory infectious panel is negative. CT PE is performed.

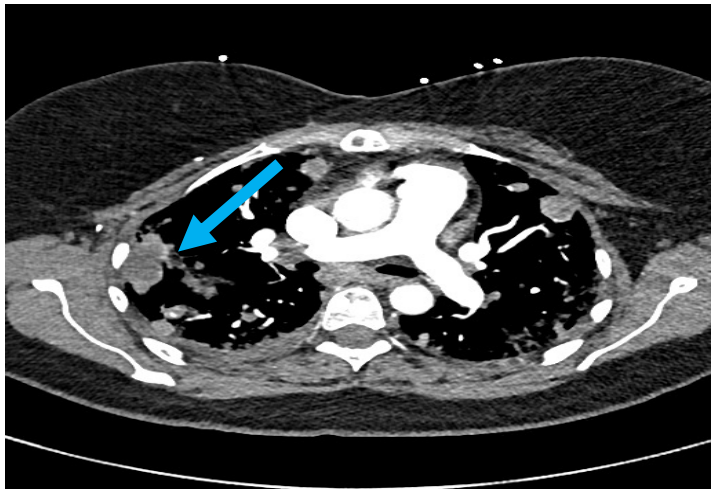
There is marked progression of pulmonary disease, prior 13mm lesion is now 36mm and multiple new lesions. No PE is seen.







Case Presentation: Dr Borges (Con't)



How would you opt to treat her?

She spends 22 days admitted with increasing respiratory support, requiring step-down level care and pain control.
Her pelvic mass and R hip are radiated.
On day 19-22 her O2 requirement goes from 45% heated high-flow to 2L NC at rest, 4L with ambulation.
She comes off IV narcotics and is well controlled on oral twice daily oxycodone alone.
She is discharged and sees you on day 23 for her second cycle of treatment.

Keynote Session: Hormone Receptor-Positive Metastatic Breast Cancer

CDK4/6 Inhibitors for HR-Positive Metastatic Breast Cancer (mBC) — Dr Borges

Targeting the PTEN/PI3K/AKT Pathway in HR-Positive mBC — Dr Burstein

Role of Oral Selective Estrogen Receptor Degraders (SERDs) in the Management of HR-Positive mBC — Dr O'Shaughnessy

Antibody-Drug Conjugates for HR-Positive mBC — Dr Bardia

Antibody-Drug Conjugates (ADCs) for HR-Positive Metastatic Breast Cancer

Aditya Bardia, MD, MPH

Program Director, Breast Medical Oncology, UCLA,
Assistant Chief, Hem Onc (Translational Research),
Director of Translational Research Integration,
Jonsson Comprehensive Cancer Center, Los Angeles

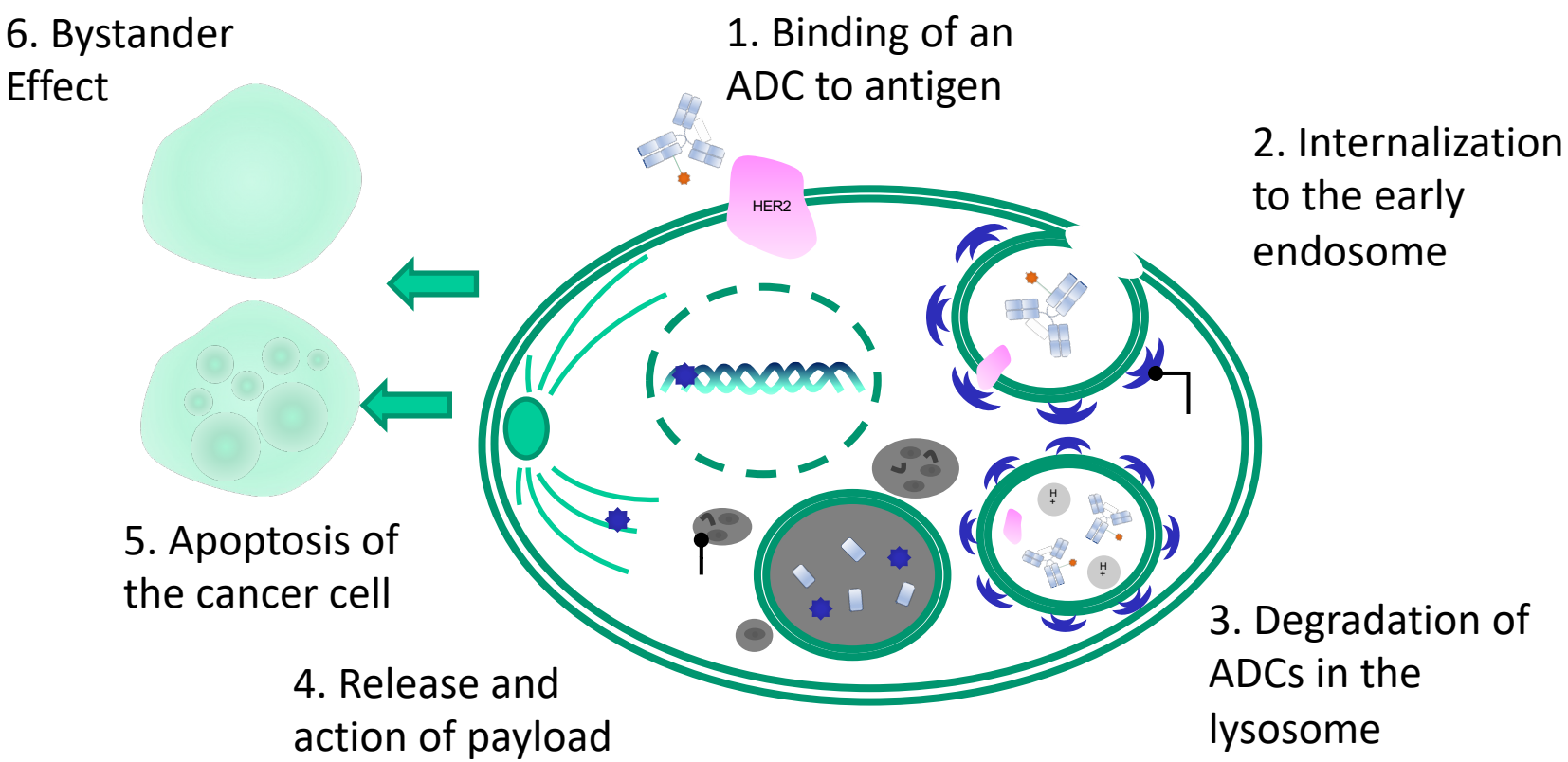
UCLA Health
Jonsson Comprehensive Cancer Center

David Geffen School of Medicine

Disclosures

Consulting Agreements and Contracted Research	Alyssum Therapeutics, AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Lilly, Menarini Group, Merck, Novartis, Pfizer Inc, Sanofi

Selective delivery of toxic payload

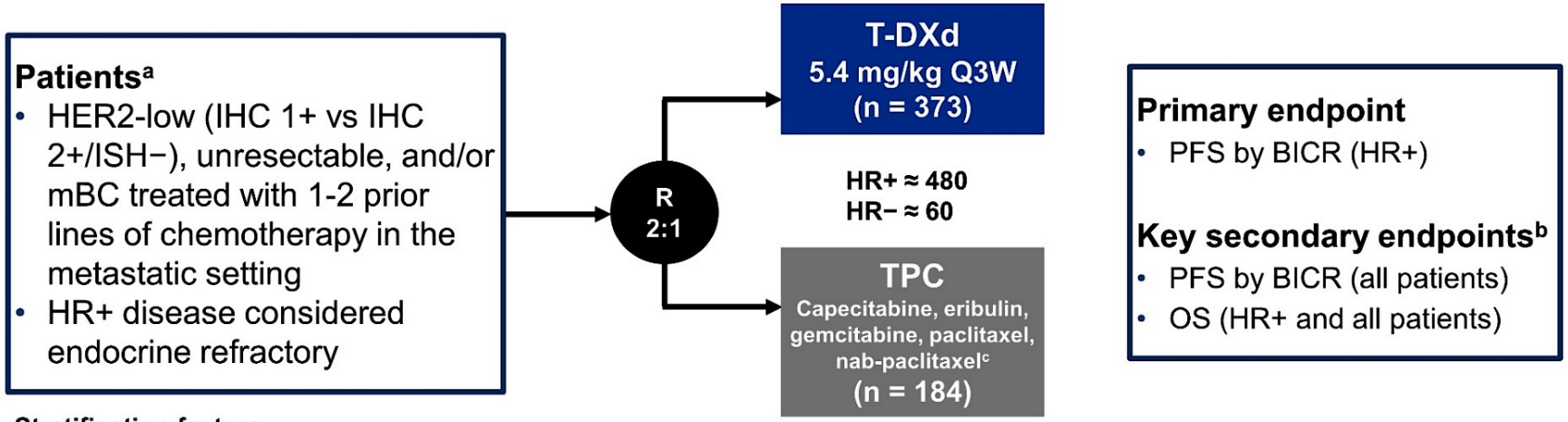


Nagayama, A, Ellisen L, Chabner B, Bardia A. Target Oncol. 2017

T-DXd vs TPC in HER2 low MBC: Study Design (DESTINY-Breast04)

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

An open-label, multicenter study (NCT03734029)



Stratification factors

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

ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CDK, cyclin-dependent kinase; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Other secondary endpoints included ORR (BICR and investigator), DOR (BICR), PFS (investigator), and safety; efficacy in the HR− cohort was an exploratory endpoint. [c]TPC was administered accordingly to the label. [d]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational use only [IUO] Assay system.

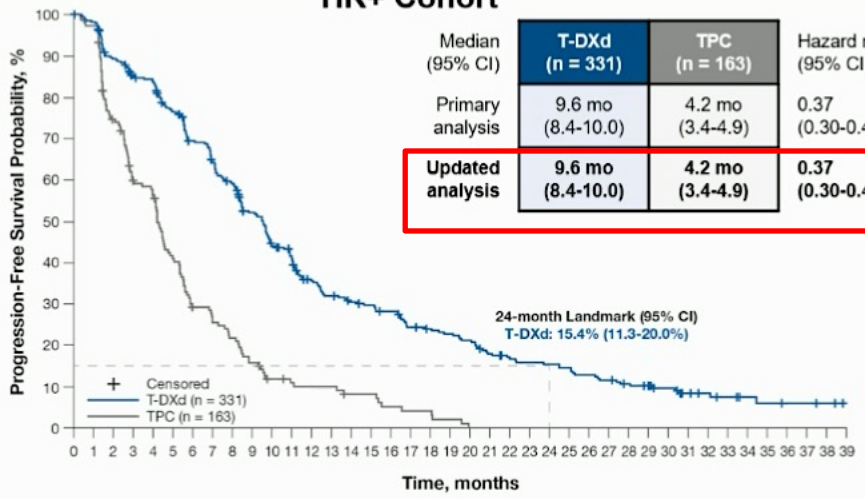
Modi S et al. ASCO 2022

T-DXd vs TPC in HER2 low: Efficacy (DESTINY-Breast04)

Progression-Free Survival (by Investigator[a])

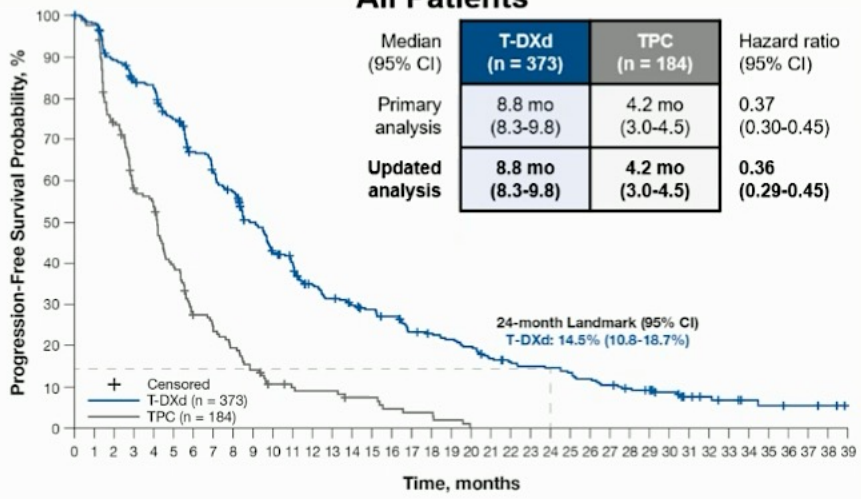
HR+ Cohort

	T-DXd (n = 331)	TPC (n = 163)	Hazard ratio (95% CI)
Median (95% CI)			
Primary analysis	9.6 mo (8.4-10.0)	4.2 mo (3.4-4.9)	0.37 (0.30-0.47)
Updated analysis	**9.6 mo (8.4-10.0)**	**4.2 mo (3.4-4.9)**	**0.37 (0.30-0.46)**



All Patients

	T-DXd (n = 373)	TPC (n = 184)	Hazard ratio (95% CI)
Median (95% CI)			
Primary analysis	8.8 mo (8.3-9.8)	4.2 mo (3.0-4.5)	0.37 (0.30-0.45)
Updated analysis	**8.8 mo (8.3-9.8)**	**4.2 mo (3.0-4.5)**	**0.36 (0.29-0.45)**



Patients still at risk:

T-DXd (n = 331)
TPC (n = 163)

Patients still at risk:

T-DXd (n = 373)
TPC (n = 184)

- Median PFS was consistent with results from the primary analysis,[1] showing a reduction in risk of disease progression or death of 63% and 64% in the HR+ cohort and all patients, respectively, for the T-DXd arm compared with the TPC arm

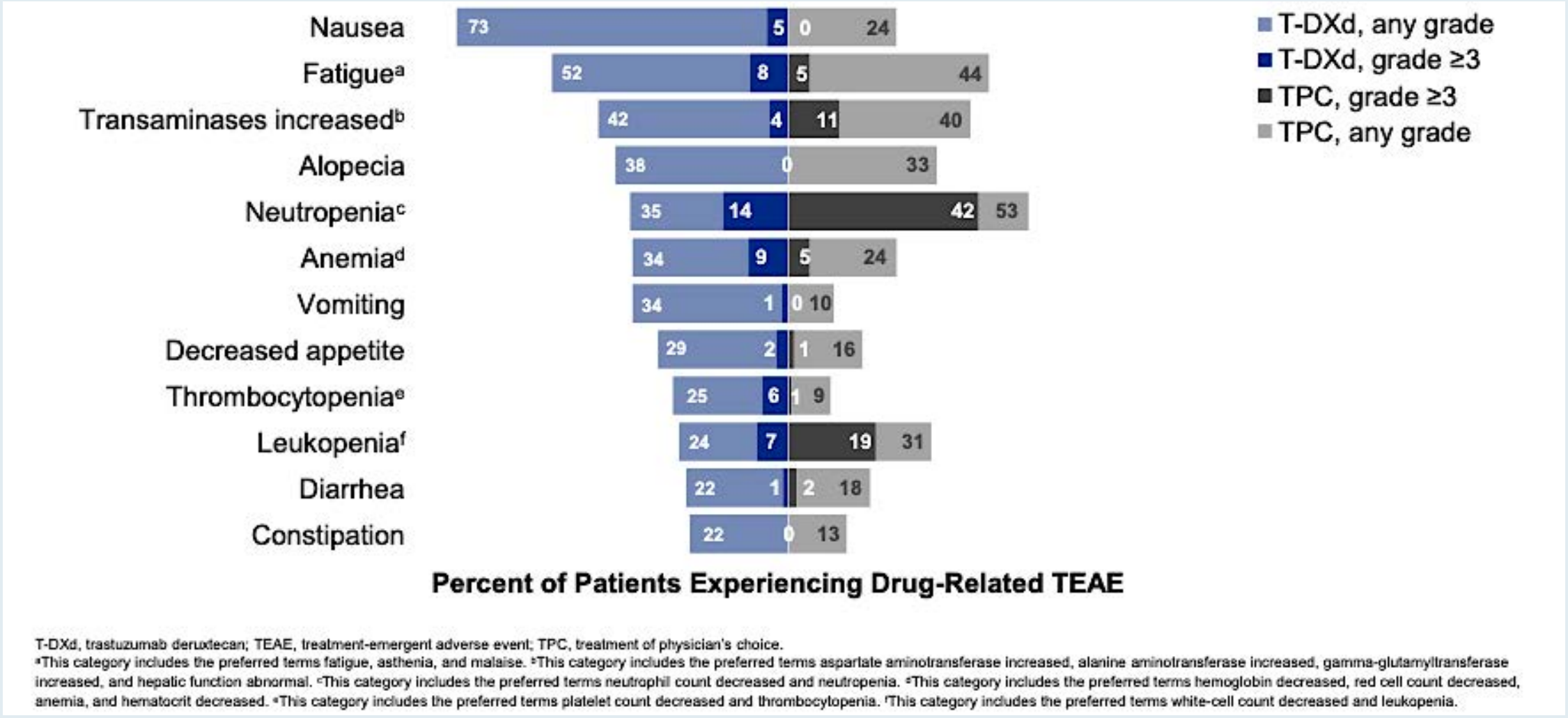
BICR, blinded independent central review; HR, hormone receptor; mo, month; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]PFS by BICR was stopped after the primary analysis as final PFS by BICR was achieved. At primary analysis, PFS by BICR for HR+ cohort was 10.1 mo and 5.4 mo for T-DXd and TPC, respectively (hazard ratio, 0.51). For all patients, the PFS by BICR was 9.9 mo and 5.1 mo for T-DXd and TPC, respectively (hazard ratio, 0.50). The updated analysis is based on PFS by investigator.

1. Modi S et al. *N Engl J Med*. 2022;387:9-20.

Efficacy seen across all pre-defined subgroups

Modi S et al. ESMO 2023

DESTINY-Breast04: Drug-Related TEAEs with T-DXd in ≥20% of Patients



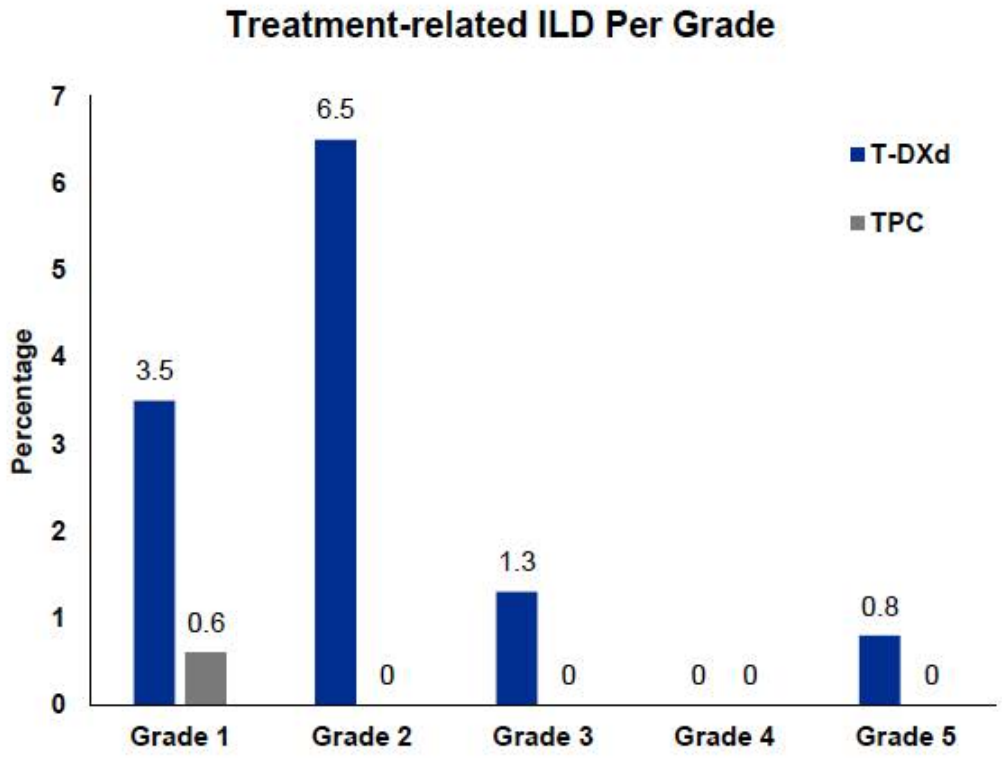
T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.
[a]This category includes the preferred terms fatigue, asthenia, and malaise. [b]This category includes the preferred terms aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, and hepatic function abnormal. [c]This category includes the preferred terms neutrophil count decreased and neutropenia. [d]This category includes the preferred terms hemoglobin decreased, red cell count decreased, anemia, and hematocrit decreased. [e]This category includes the preferred terms platelet count decreased and thrombocytopenia. [f]This category includes the preferred terms white-cell count decreased and leukopenia.

Modi S et al. ESMO 2023;Abstract 376O.

RTP RESEARCH TO PRACTICE

DESTINY-Breast04: Adjudicated Drug-Related ILD

- Adjudicated ILD occurred in 45 patients (12.1%) in the T-DXd arm versus in 1 patient (0.6%) in the TPC arm
- Most ILD events were low in grade; 3 patients (0.8%) had grade 5 ILD in the T-DXd arm
- At DCO, 31 patients (68.9%) in the T-DXd arm recovered, were recovering, or recovered with sequalae and 10 patients (22.2%) in the T-DXd arm had not yet recovered



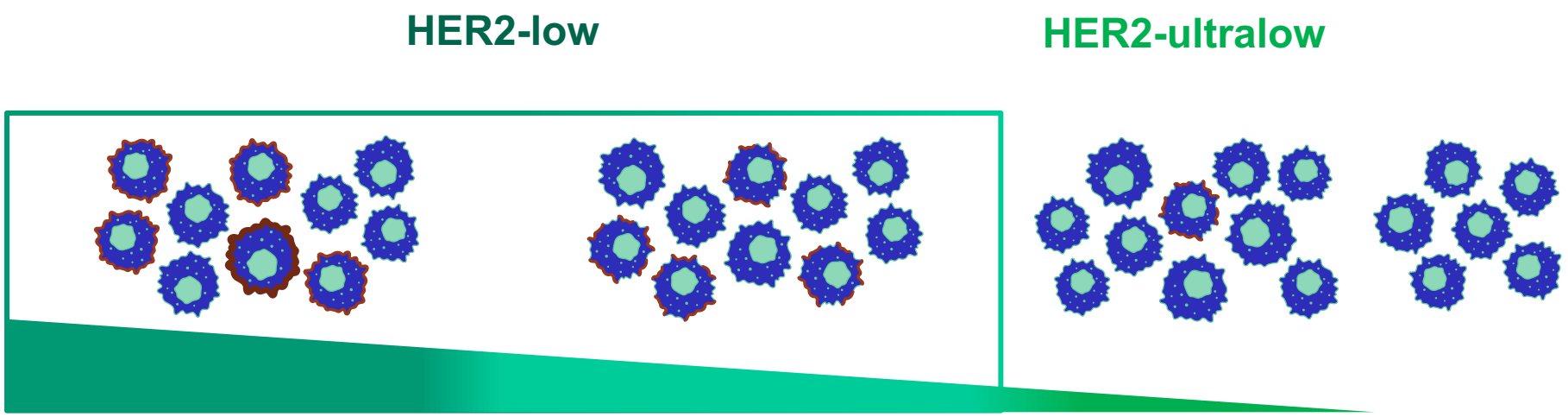
DCO, data cutoff; ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Rugo HS et al. ESMO Breast Cancer Congress 2023;Abstract 185O.

How about lower HER2 expression?

What is HER2 low and ultra-low?

HER2 IHC categories within HR+, HER2− mBC (per ASCO/CAP guidelines[1])



- HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan

Images adapted from Venetis K, et al. *Front Mol Biosci.* 2022; 1. Wolff A, et al. *J Clin Oncol.* 2023;41:3867–3872

Trastuzumab Deruxtecan vs TPC: Study Design (DESTINY-Breast06)

DESTINY-Breast06: a Phase 3, randomized, multicenter, open-label study (NCT04494425)

PATIENT POPULATION

- HR+ mBC
- HER2-low (IHC 1+ or IHC 2+/ISH−) or HER2-ultralow (IHC 0 with membrane staining)*
- **Chemotherapy naïve in the mBC setting**

Prior lines of therapy

- ≥2 lines of ET ± targeted therapy for mBC
  OR
- 1 line for mBC **AND**
  - Progression ≤6 months of starting first-line ET + CDK4/6i
    OR
  - Recurrence ≤24 months of starting adjuvant ET

Stratification factors

- Prior CDK4/6i use (yes vs no)
- HER2 expression (IHC 1+ vs IHC 2+/ISH− vs IHC 0 with membrane staining)
- Prior taxane in the non-metastatic setting (yes vs no)

R 1:1

T-DXd
5.4 mg/kg Q3W
(n=436)

HER2-low = 713
HER2-ultralow = 153†

TPC
(n=430)

Options: capecitabine, nab-paclitaxel, paclitaxel

ENDPOINTS

Primary

- PFS (BICR) in HER2-low

Key secondary

- PFS (BICR) in ITT (HER2-low + ultralow)
- OS in HER2-low
- OS in ITT (HER2-low + ultralow)

Other secondary

- PFS (INV) in HER2-low
- ORR (BICR/INV) and DOR (BICR/INV) in HER2-low and ITT (HER2-low + ultralow)
- Safety and tolerability
- Patient-reported outcomes‡

Three important differences from DB-04:

- Included HER2 ultra-low breast cancer
- No prior chemotherapy required
- Pts with rapid progression on 1st line therapy eligible

*Determined based on the most recent evaluable HER2 IHC sample prior to randomization; HER2-ultralow defined as faint, partial staining of the membrane in ≤10% of the cancer cells (also known as IHC >0<1+); †as determined by IRT (note: efficacy analyses in the HER2-ultralow subgroup were based on n=152 by central laboratory testing); ‡to be presented separately

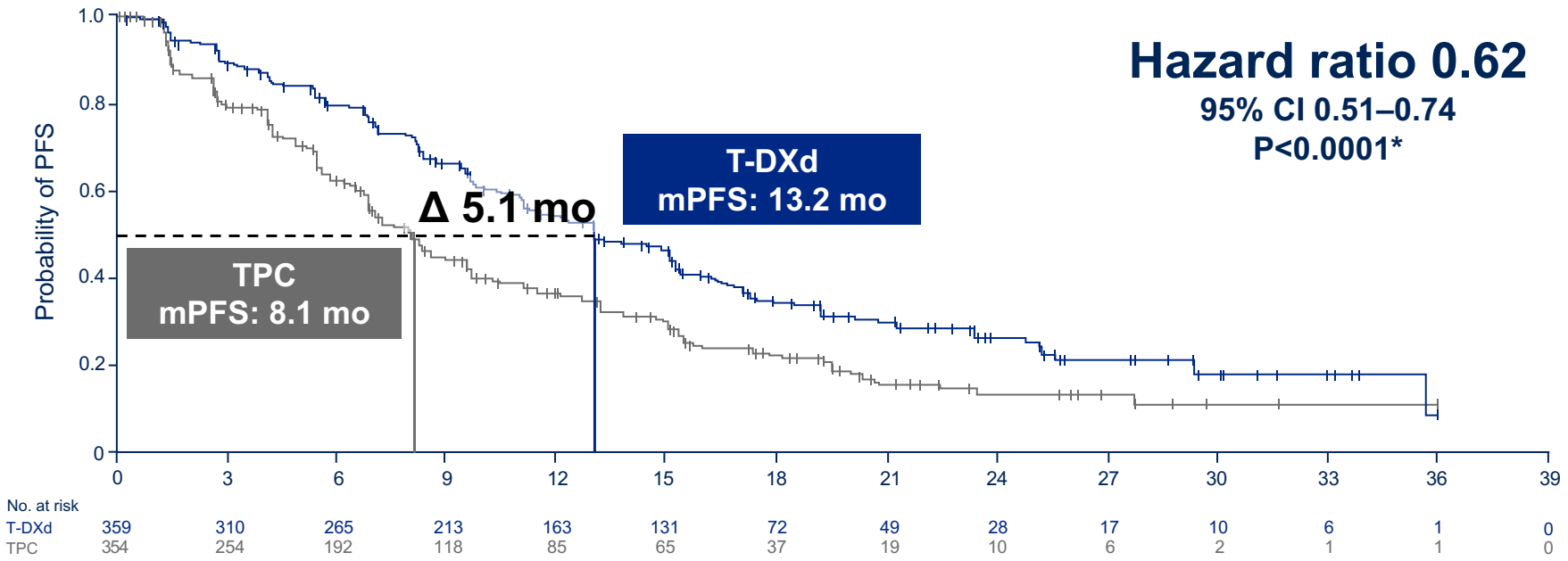
BICR, blinded independent central review; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DOR, duration of response; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; IHC, immunohistochemistry; INV, investigator assessed; IRT, interactive response technology; ISH, in situ hybridization; ITT, intent-to-treat; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

NCT04494425. Updated April 12, 2024. Available from: https://clinicaltrials.gov/study/NCT04494425 (Accessed May 13, 2024)

Curigliano G et al. ASCO 2024

T-DXd vs TPC in HER2 low: Efficacy (DESTINY-Breast06)

PFS (BICR) in HER2-low: primary endpoint



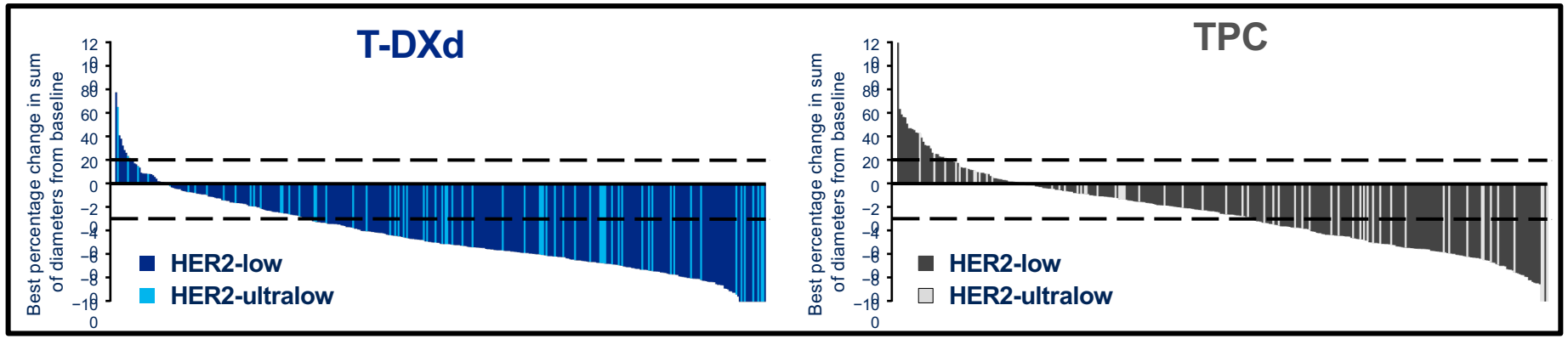
T-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with standard-of-care chemotherapy in HER2-low

*P-value of <0.05 required for statistical significance
BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

Similar results in HER2 ultra-low MBC

Curigliano G et al. ASCO 2024; Bardia A et al NEJM 2024

ORR in HER2-low and ultralow: T-DXd vs TPC (DESTINY-Breast06)



	HER2-low*		ITT		HER2-ultralow*	
	T-DXd (n=359)	TPC (n=354)	T-DXd (n=436)	TPC (n=430)	T-DXd (n=76)	TPC (n=76)
Confirmed ORR, n (%)	203 (56.5)	114 (32.2)	250 (57.3)	134 (31.2)	47 (61.8)	20 (26.3)
Best overall response, n (%)						
Complete response	9 (2.5)	0	13 (3.0)	0	4 (5.3)	0
Partial response	194 (54.0)	114 (32.2)	237 (54.4)	134 (31.2)	43 (56.6)	20 (26.3)
Stable disease	125 (34.8)	170 (48.0)	148 (33.9)	212 (49.3)	22 (28.9)	42 (55.3)
Clinical benefit rate, n (%)†	275 (76.6)	190 (53.7)	334 (76.6)	223 (51.9)	58 (76.3)	33 (43.4)
Duration of response, median, mo	14.1	8.6	14.3	8.6	14.3	14.1

Activity seen in both HER2-low and ultra-low MBC

Curigliano G et al. ASCO 2024; Bardia A et al NEJM 2024

FDA Approves Trastuzumab Deruxtecan for Unresectable or Metastatic HR-Positive, HER2-Low or HER2-Ultralow Breast Cancer

Press Release: January 25, 2025

"On January 27, 2025, the Food and Drug Administration approved fam-trastuzumab deruxtecan-nxki for unresectable or metastatic hormone receptor (HR)-positive, HER2-low (IHC 1+ or IHC 2+/ISH-) or HER2-ultralow (IHC 0 with membrane staining) breast cancer, as determined by an FDA-approved test, that has progressed on one or more endocrine therapies in the metastatic setting.

FDA also approved the Ventana's PATHWAY anti-HER-2 (4B5) Rabbit Monoclonal Primary Antibody assay as a companion diagnostic device to identify patients with HER2-ultralow (IHC 0 with membrane staining) breast cancer for treatment with fam-trastuzumab deruxtecan-nxki. This assay was previously approved to identify patients with HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer for treatment with fam-trastuzumab deruxtecan-nxki."

Approval was based on results from the DESTINY-Breast06 trial.

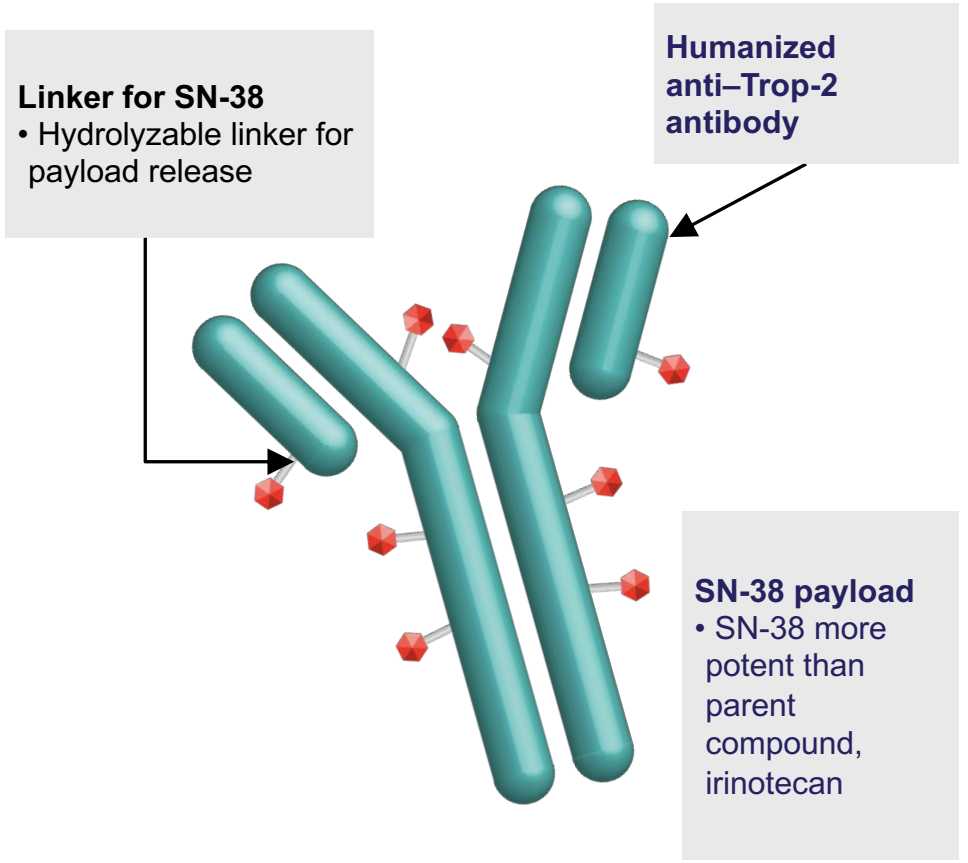
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-fam-trastuzumab-deruxtecan-nxki-unresectable-or-metastatic-hr-positive-her2-low-or-her2

RTP RESEARCH TO PRACTICE

Sacituzumab Govitecan: First-in-class Trop2 ADC

SG is distinct from other ADCs

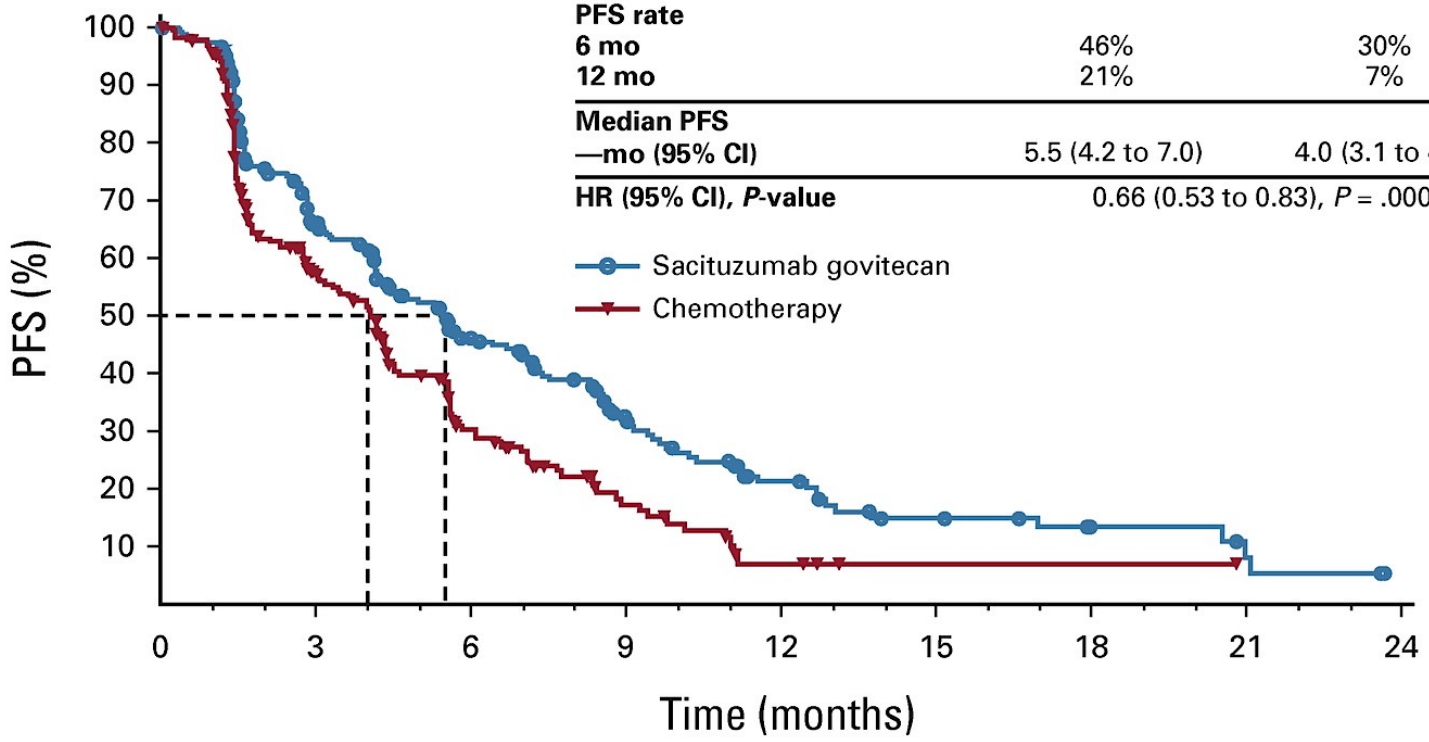
- Antibody highly specific for Trop-2
- High drug-to-antibody ratio (7.6:1)
- Internalization and enzymatic cleavage by tumor cell not required for the liberation of SN-38 from the antibody
- Hydrolysis of the linker also releases the SN-38 cytotoxic extracellularly in the tumor microenvironment, providing a bystander effect



Nagayama A et al. *Ther Adv Med Oncol*. 2020; Cardillo TM et al. *Bioconjugate Chem.* 2015.

Sacituzumab Govitecan vs TPC: PFS (HR+ MBC)

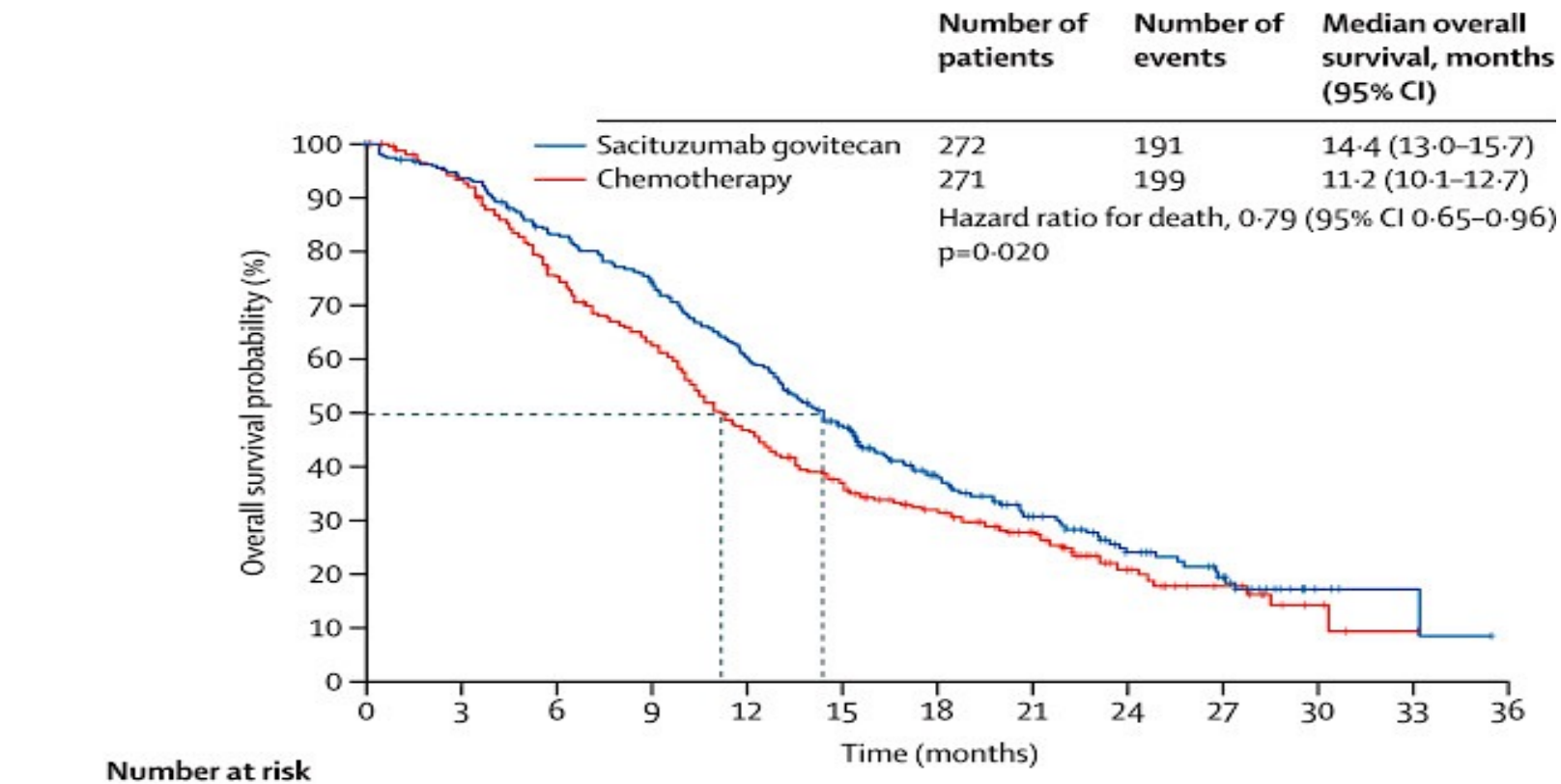
	Sacituzumab govitecan (n = 272)	Chemotherapy (n = 271)
No. of events	170	159
PFS rate		
6 mo	46%	30%
12 mo	21%	7%
Median PFS —mo (95% CI)	5.5 (4.2 to 7.0)	4.0 (3.1 to 4.4)
HR (95% CI), *P*-value	0.66 (0.53 to 0.83), *P* = .0003	



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

Rugo HS, et al. *J Clin Oncol.* 2022;40(20):3365-3376.

Sacituzumab Govitecan vs TPC: Overall Survival



Number at risk (events)													
Sacituzumab govitecan	272 (0)	252 (16)	221 (44)	197 (67)	160 (104)	120 (137)	80 (158)	53 (173)	31 (183)	20 (188)	4 (190)	2 (190)	0 (191)
Chemotherapy	271 (0)	246 (16)	196 (64)	164 (95)	122 (137)	92 (163)	70 (174)	49 (183)	23 (193)	13 (196)	5 (198)	1 (199)	0 (199)

Rugo H and Bardia A et al. Lancet 2023

TROPiCS-02 Trial: Treatment-Emergent Events Summary

	Sacituzumab govitecan (n=268)	Chemotherapy (n=249)
Grade 3 or higher	198 (74%)	150 (60%)
Leading to treatment discontinuation	17 (6%)	11 (4%)
Leading to dose delay	178 (66%)	109 (44%)
Leading to dose reduction	90 (34%)	82 (33%)
Serious events	74 (28%)	48 (19%)
Leading to death*	6 (2%)	0
Treatment-related death	1 (<1%)	0

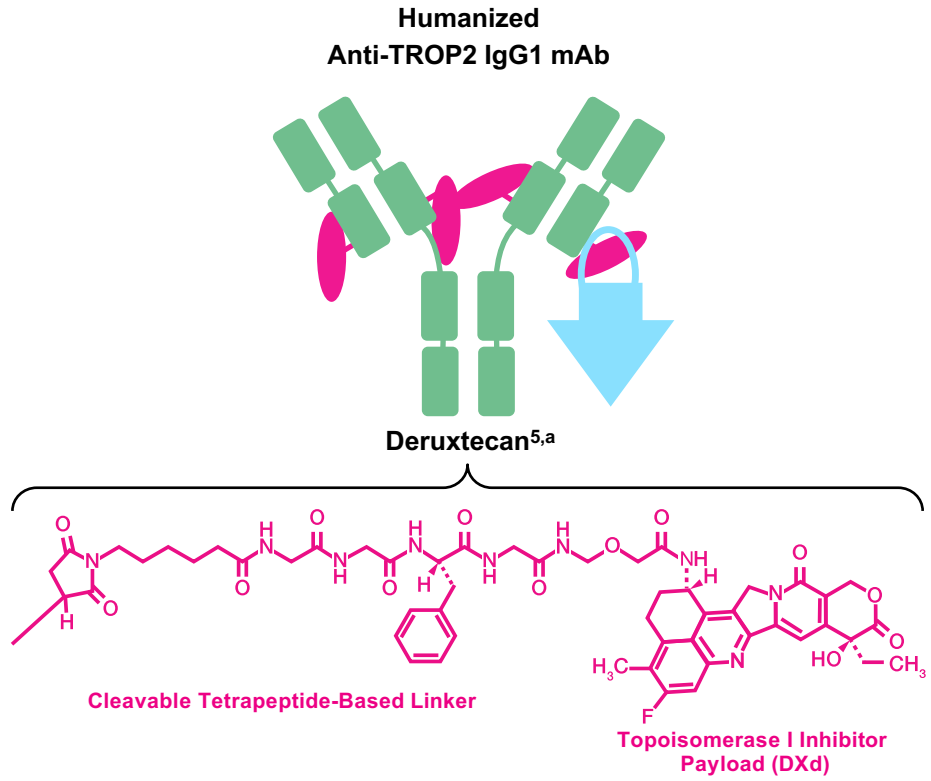
Treatment-emergent adverse events were defined as any adverse event that began or worsened on or after the start of the study drug until 30 days after the last dose of the study drug. *Of six treatment-emergent adverse events leading to death, only one was considered by the investigator to be treatment related (septic shock caused by neutropenic colitis). The other five deaths were caused by COVID-19 pneumonia, pulmonary embolism, pneumonia, nervous system disorder, and arrhythmia. Upon detailed review of the treatment-emergent adverse events leading to death, no patterns were identified.

- The most frequent treatment-emergent adverse events of any grade with sacituzumab govitecan versus chemotherapy were:
  - Neutropenia (189 [71%] versus 136 [55%])
  - Diarrhea (166 [62%] versus 57 [23%])
  - Nausea (157 [59%] versus 87 [35%])
  - Alopecia (128 [48%] versus 46 [18%])
  - Anemia (98 [37%] versus 69 [28%])
- The most common Grade 3 or worse treatment-emergent adverse events were neutropenia (138 [51%] versus 97 [39%]) and diarrhea (27 [10%] versus 3 [1%])

Rugo HS et al. *Lancet* 2023;402:1423-33.

Datopotamab Deruxtecan

- Patients with relapsed/refractory advanced or metastatic TNBC have poor clinical outcomes[1]
- Dato-DXd is a differentiated TROP2-directed ADC designed with 3 components[2,3]:
  - A humanized anti-TROP2 IgG1 mAb
  - A topoisomerase I inhibitor payload (exatecan derivative, DXd)
  - A tetrapeptide-based cleavable linker
- Dato-DXd has demonstrated highly encouraging antitumor activity and manageable AEs in the NSCLC cohort[4]
  - 6 mg/kg has been selected as the dose for expansion into other advanced tumor types

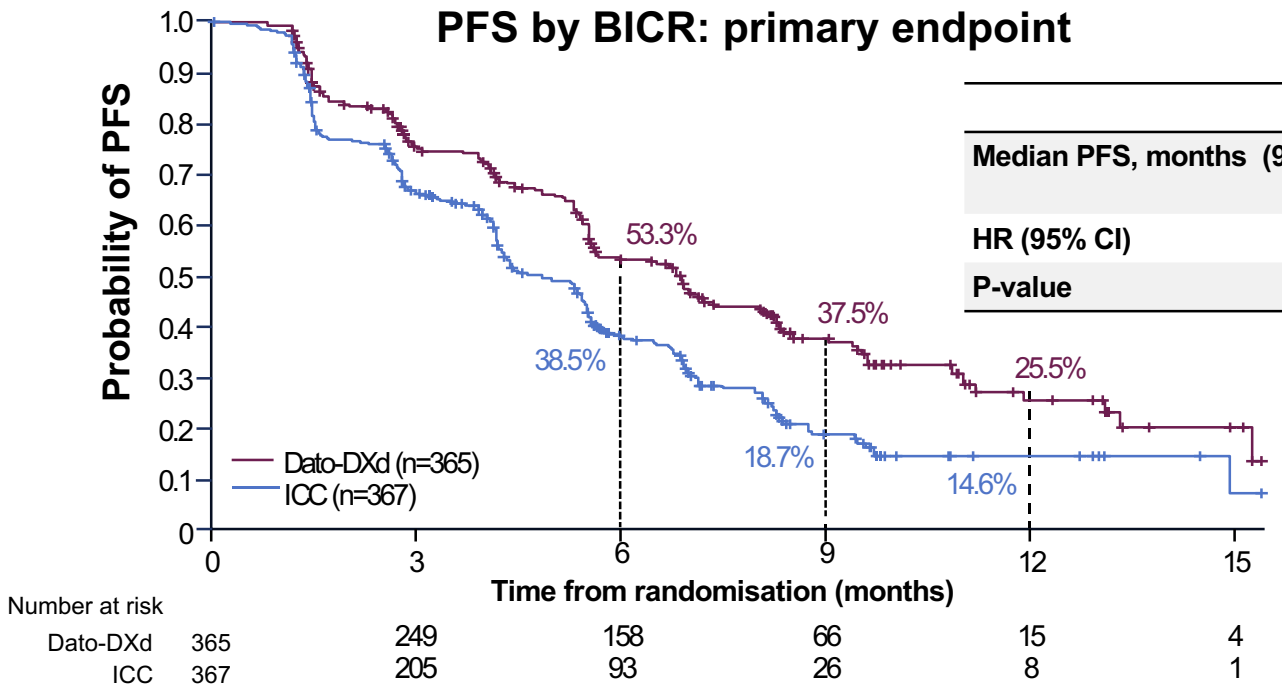


ADC, antibody drug conjugate; AE, adverse event; IgG1, immunoglobulin G1; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; TNBC, triple negative breast cancer; TROP2, trophoblast cell surface antigen.

[a] Actual drug positions may vary.

1. Bardia A, et al. *N Engl J Med.* 2021;384(16):1529-1541.; 2. Okajima D, et al. AACR-NCI-EORTC 2019 [Abstract C026]; 3. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67(3):173-185; 5. Spira A et al. WCLC 2020 [Abstract 3407]; 6. Krop I, et al. SABCS 2019 [Abstract GS1-03].

Dato-DXd in HR+ MBC (TROPION-Breast01)



	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	

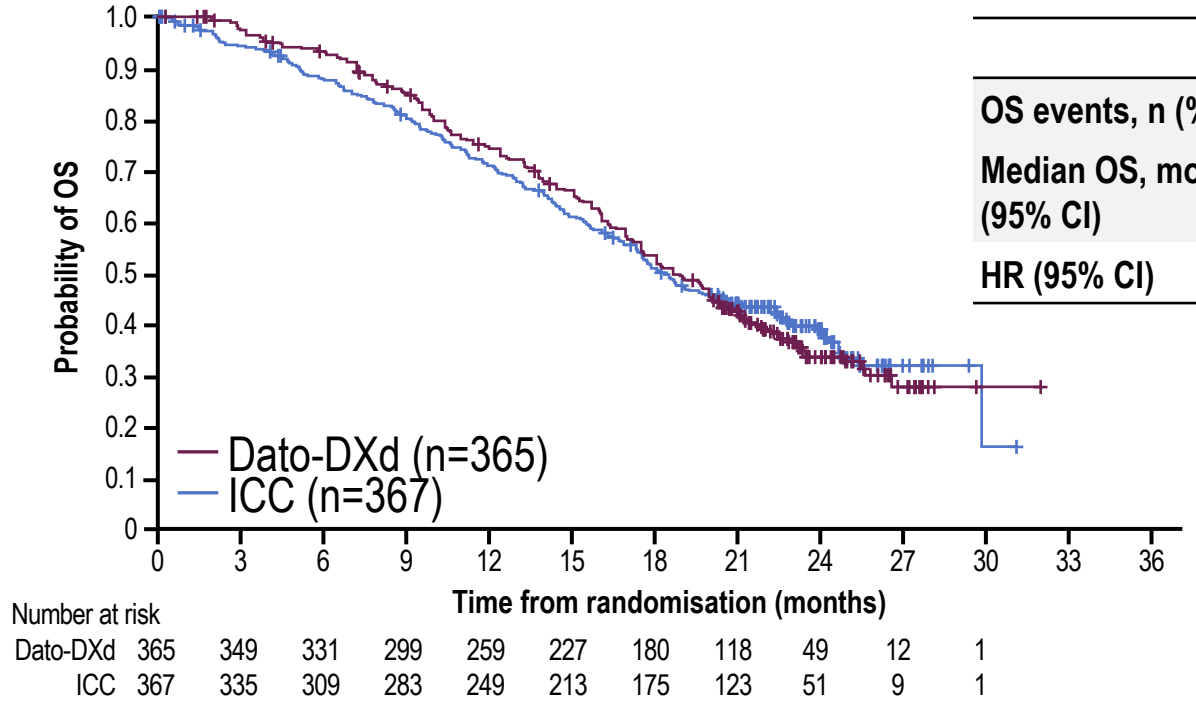
PFS by investigator assessment: Median 6.9 vs 4.5 months; HR 0.64 (95% CI 0.53–0.76)

CI, confidence interval;
HR, hazard ratio

MADRID 2023 ESMO congress

Bardia A, et al. ESMO 2023. Abstract LBA11; Bardia A, et al. *J Clin Oncol* 2025.

Dato-DXd in HR+ MBC: Overall Survival (TROPION-Breast01)

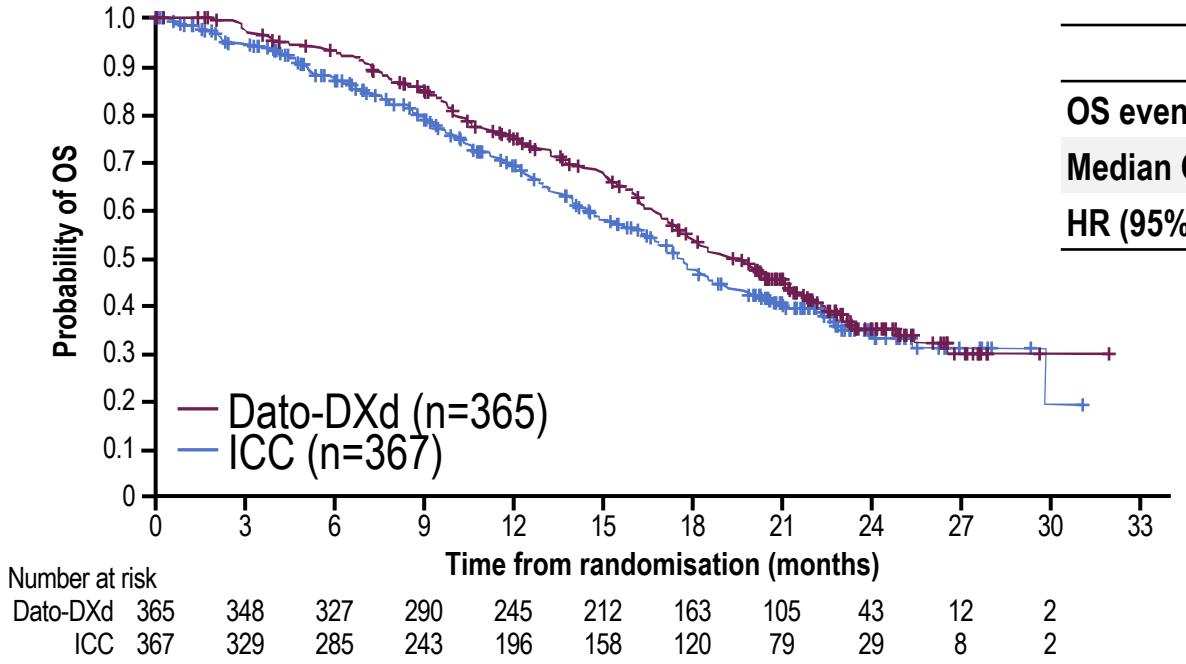


	Dato-DXd	ICC
OS events, n (%)	223 (61)	213 (58)
Median OS, months (95% CI)	18.6 (17.3–20.1)	18.3 (17.3–20.5)
HR (95% CI)	**1.01 (0.83–1.22)**	

Data cutoff: 24 July 2024. Pre-specified P-value boundary for OS analysis: α=0.0427.
*Mis-stratification between interactive response technology (where data entered could not be changed by the site) and eCRF (where data could be corrected by sites) was <5%.
eCRF, electronic case report form.

Overall Survival Adjusted for Subsequent ADC Therapy

Post-hoc Sensitivity Analysis Using IPCW Method



	Dato-DXd	ICC
OS events, n (%)	195 (53)	177 (48)
Median OS, months	19.1	17.5
HR (95% CI)	0.86 (0.70–1.06)	

Data cutoff: 24 July 2024.
IPCW, Inverse Probability Censoring Weighting

1. Robins JM. Proceedings of the Biopharmaceutical Section (American Statistical Association) 1993:24–33;
2. Robins JM, Finkelstein DM. Biometrics 2000;56:779–88;
3. Sherry AD, et al. BMJ Oncology 2024;3:e000322.

Dato-DXd in HR+ MBC: Safety Summary (TROPION-Breast01)

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

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

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

Bardia A, et al. ESMO 2023; Bardia A, et al. *J Clin Oncol* 2025.

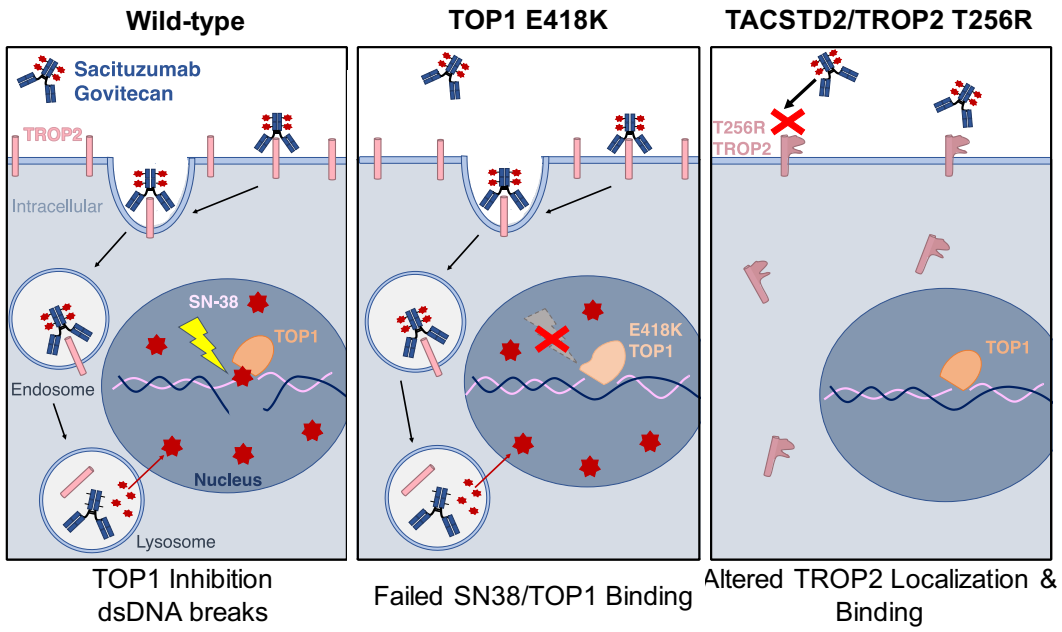
ADCs to target MBC: Multiple Agents in Development

Antibody Drug Conjugate	Target	Payload
Trastuzumab deruxtecan (DS-8201a)	HER2	Topo-1 inhibitor
Sacituzumab govitecan (IMMU-132)	Trop-2	Topo-1 inhibitor
Datopotamab deruxtecan (DS-1062)	Trop-2	Topo-1 inhibitor
Sacituzumab Tirumotecan (Sac-TMT)	Trop-2	Topo-1 inhibitor
Patritumab deruxtecan (U3-1402)	HER3	Topo-1 inhibitor
BB1701	HER2	Microtubule inhibitor
Disitimab Vedotin	HER2	Microtubule inhibitor

Besides target, type of payload might impact ADC success in advanced setting

How to sequence the different ADCs?

Implications of resistance mechanisms for ADC sequencing



TROP2 mutation

TROP2-targeted ADC → No Response

Non-TROP2-targeted ADC → Response

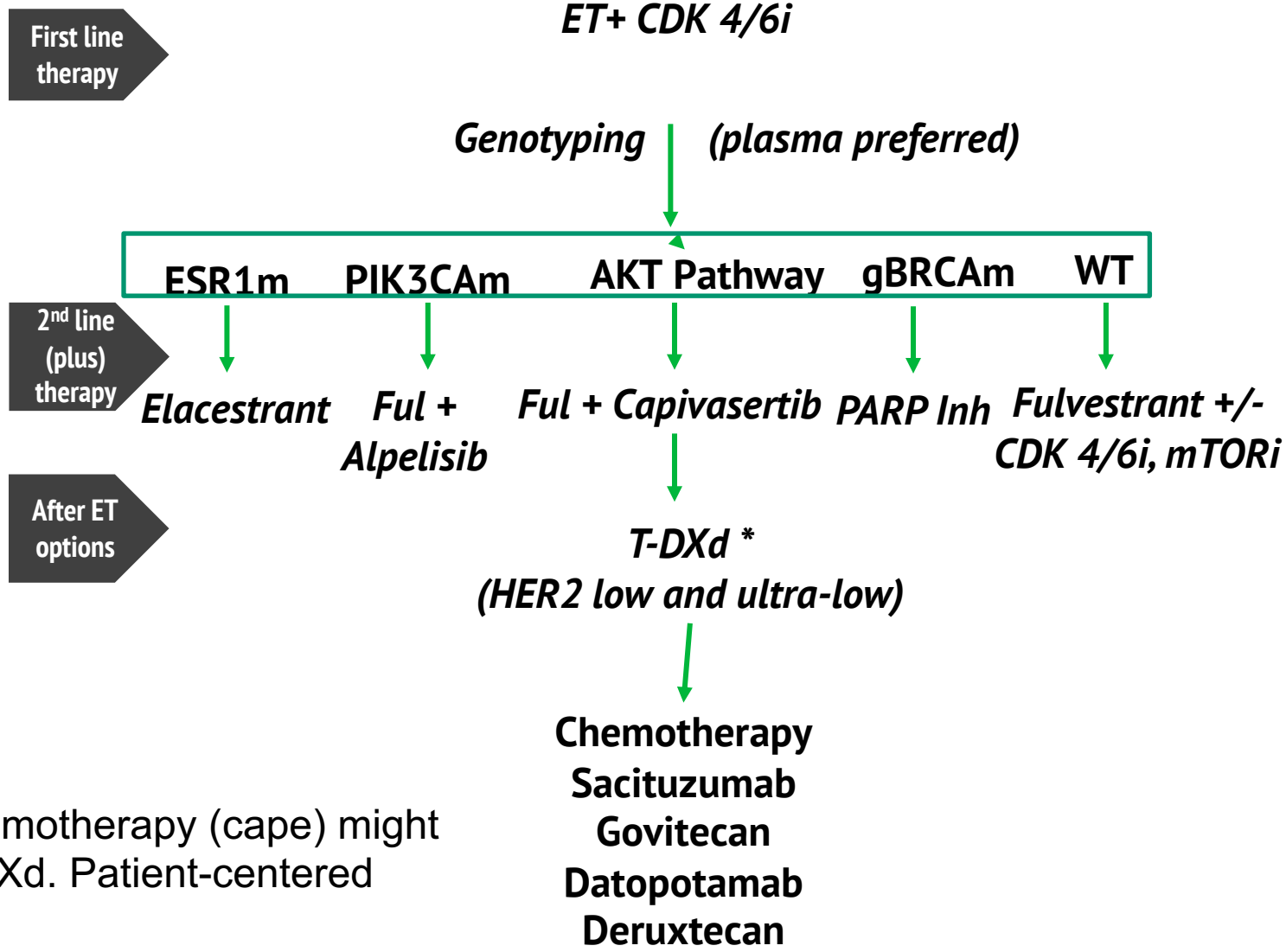
TOP1 mutation

TOP1i payload ADC → No Response

Non-TOP1i-payload ADC → Response

Coates JT, et al. *Cancer Discov.* 2021;11(10):2436-2445.

Management of HR+/HER2- MBC: General Guideline



*For some patients, chemotherapy (cape) might be preferred before T-DXd. Patient-centered discussion

Summary

- Trastuzumab deruxtecan: currently approved for HER2 low and HER2 ultra-low MBC. No prior line of chemotherapy required.
- Datopotamab deruxtecan approved for HR+/HER2- MBC after 1 prior line of chemotherapy.
- Sacituzumab govitecan approved for metastatic HR+ breast cancer after 2 prior lines of systemic therapy.
- There are multiple other ADCs in development to target antigens overexpressed in MBC.
- Additional studies evaluating efficacy of ADCs alone and in combination as well as other indications in breast cancer could redefine the receptor classification of breast cancer.

Discussion Questions and Faculty Case Presentations

Case Presentation: Dr O'Shaughnessy

- 76 yo woman from rural TX with h/o idiopathic sensory neuropathy in her feet developed indolent, bone only HR+ HER2 0 de novo MBC
- Over 5 years responded to palbociclib + letrozole, everolimus + exemestane, then tamoxifen
- ctDNA showed no actionable mutations. Germline testing negative
- Disease progressed in bone and with small volume liver mets but she remained asymptomatic. Liver biopsy ER++ PR 0 and HER2 0 and NGS – no actionable mutations
- Treated with capecitabine for 18 mos. Could tolerate only 1000mg bid 7on/7off due to diarrhea
- Has no symptoms from cancer. PS 1 (fatigue)
- She is a good candidate for datopotamab over sacituzumab and fulvestrant/abemaciclib due to diarrhea and over a taxane due to neuropathy

Case Presentation: Dr Burstein (Part 2)

- A 59 year old woman has been receiving treatment for advanced breast cancer.
- In 2015, she was diagnosed with screening mammogram findings and was found to have ER positive, PR positive, HER2 negative breast cancer, with nodal involvement. She received adjuvant TC chemotherapy, OFS, and AI treatment.
- In February 2021, she had metastatic disease to bone diagnosed after presenting with lower back pain. T11 vertebral body biopsy disclosed ER pos 90%, PR negative, HER2 +1 breast cancer.
- She began fulvestrant and palbociclib.
- In January 2024, she had tumor progression with mediastinal lymph nodes and worsening bone lesions. Liquid biopsy was ‘bland’ for actionable mutations. She started capecitabine.
- In August 2024, she had tumor progression, and began trastuzumab deruxtecan.
- In February 2025, scans showed new liver lesions.

Discussion Question

- A 65-year-old woman presents with de novo HR-positive, HER2-low (IHC 1+) metastatic breast cancer, receives ribociclib with anastrozole and initially responds but then experiences disease progression 5 months later. Biomarker evaluation is negative for ESR1 mutations and PIK3CA/AKT1/PTEN alterations. Regulatory and reimbursement issues aside, what would be your most likely next treatment?

Discussion Question

- A 65-year-old woman with ER-positive, HER2-negative (IHC 0) mBC has disease progression on capecitabine after exhausting all available endocrine therapy options. Regulatory and reimbursement issues aside, which systemic therapy would you most likely recommend next?

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Moderator

Neil Love, MD

Faculty

Aditya Bardia, MD, MPH
Virginia F Borges, MD, MMSc
Harold J Burstein, MD, PhD
Joyce O'Shaughnessy, MD

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