Medical Affairs

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ANIMATED VIDEO

ELACESTRANT IN ER+/HER2- MBC WITH *ESR1*-MUT TUMORS: OVERVIEW OF THE EMERALD SUBGROUP ANALYSIS

APRIL 2025

This programme has been sponsored by Menarini Stemline and is intended for healthcare professionals only
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ACKNOWLEDGEMENT AND DISCLOSURES

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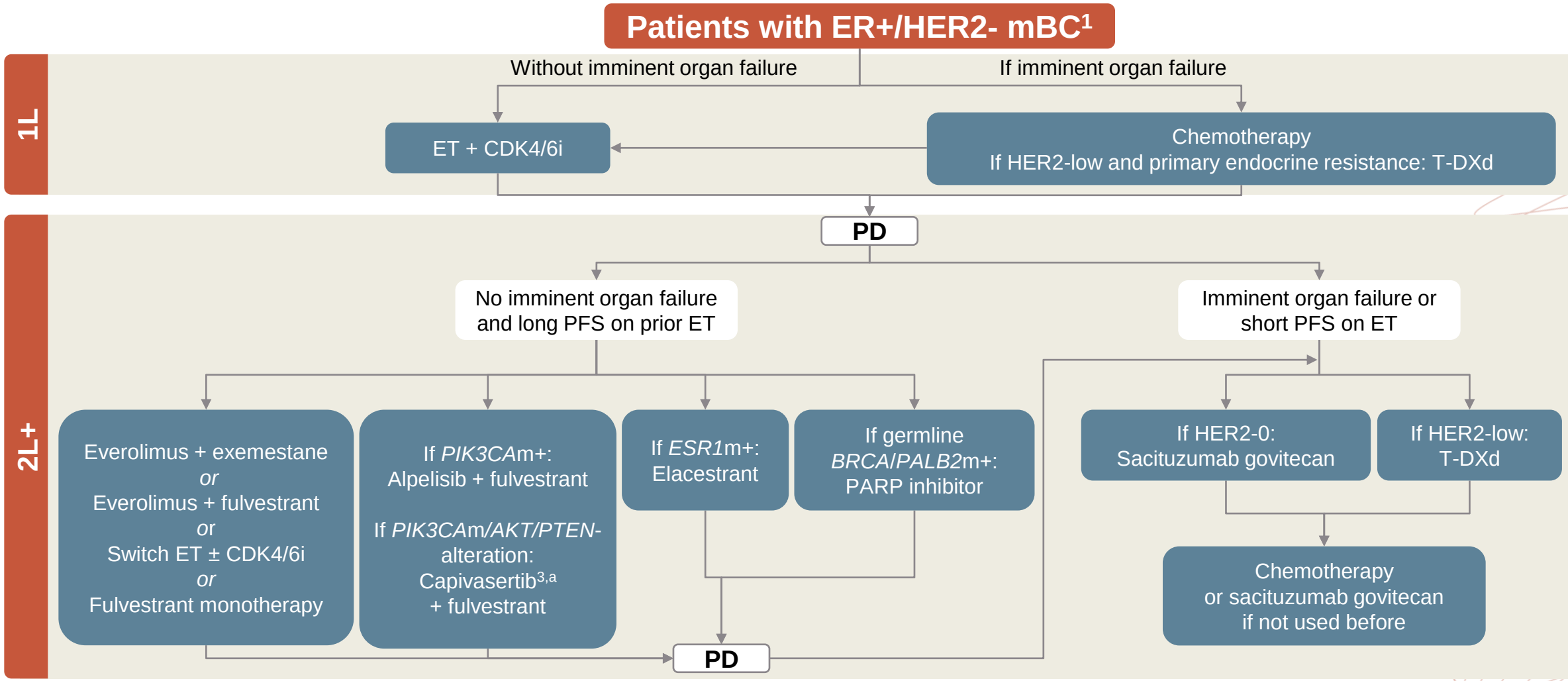
CLINICAL TAKEAWAYS

- Elacestrant provides clinically meaningful improvements in PFS for patients with ER+/HER2- mBC who received at least 12 months of ET + CDK4/6i in 1st line and whose tumors harbor *ESR1*-mut.
- The PFS benefit associated with elacestrant was consistent across clinically relevant subgroups including tumors harboring coexisting *ESR1* and *PIK3CA*-mut, indicating that disease progression after ET + CDK4/6i in this subgroup may remain ER-driven.
- Safety analyses demonstrated that elacestrant had a manageable safety profile similar to other ETs and without evidence of some of the toxicities associated with other drug classes, such as CDK4/6i and PI3K/AKT/mTOR inhibitors.
- *ESR1*-mut testing should be done at 1st line progression via liquid biopsy due to disease subclonality; if negative, repeat at each progression. Archival tissue should not be used for testing due to the acquired nature of *ESR1*-mut.

AKT, protein kinase B; CDK4/6i, cyclin dependent kinase 4/6 inhibitor; ER, estrogen receptor; *ESR1*, estrogen receptor 1; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; mTOR, mammalian target of rapamycin; PI3K, Phosphoinositide 3-kinases.

TREATMENT LANDSCAPE IN ER+/HER2- MBC

TREATMENT CHOICES FOR PATIENTS WITH ER+/HER2- MBC ARE DRIVEN BY ENDOCRINE SENSITIVITY STATUS AND BIOMARKERS[1,2]



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Adapted from: 1. Gennari A, et al. Ann Oncol. 2021;32(12):1475-95. ESMO Metastatic Breast Cancer Living Guidelines. V1.1 May 2023; 2. Bardia A, et al. *Clin Cancer Res.* 2024;30(19):4299–4309; 3. Truqap (capivasertib) SmPC 2024.

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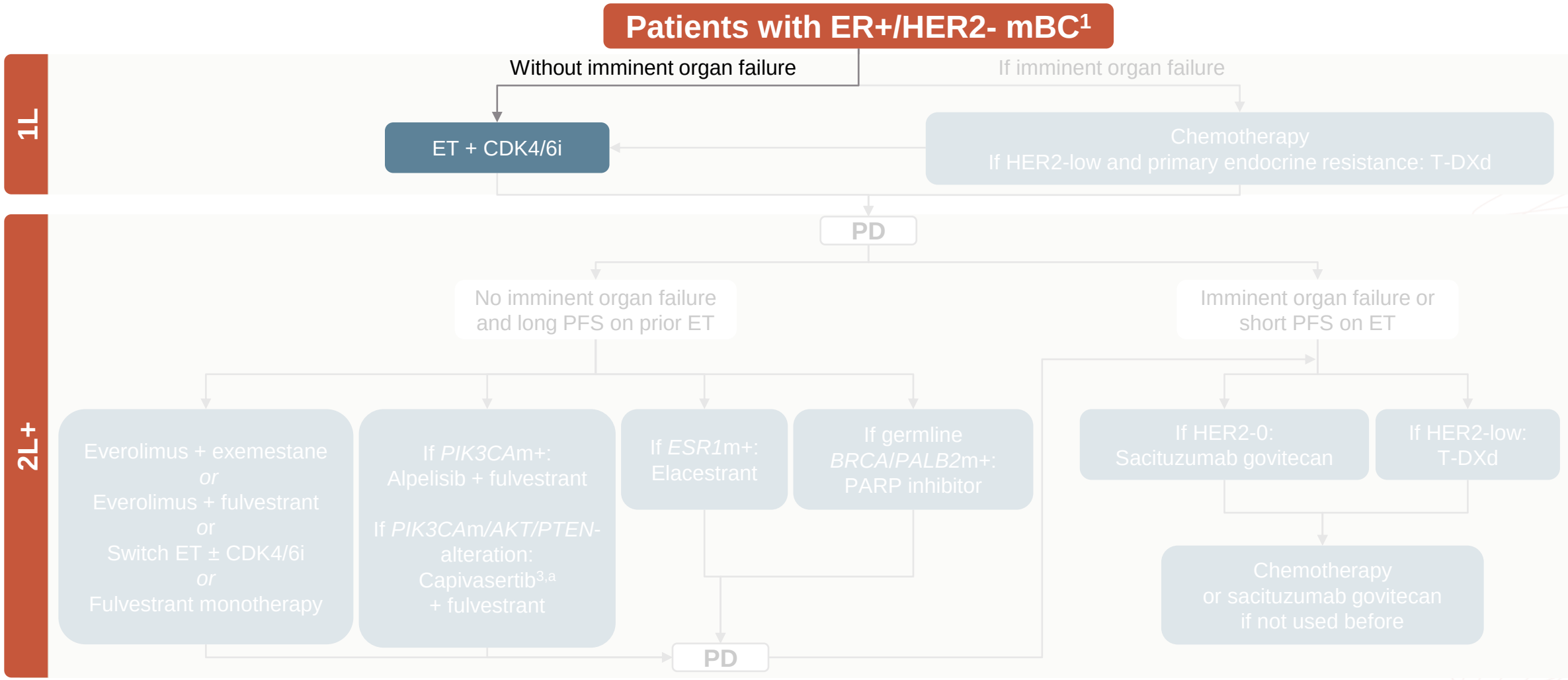

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ET + CDK4/6i IS THE 1ST LINE STANDARD OF CARE IN ER+/HER2- MBC[1-3]

Median duration of treatment with endocrine therapy + CDK4/6 inhibition based on pivotal trials is ~15-21 months[4-6]

	PALOMA-2[7]	MONALEESA-2[8]	MONARCH-2[9]	MONARCH-3[10]	MONALEESA-3[a 11]	MONALEESA-7[b 6]
Phase (n)	Ph3 (666)	Ph3 (668)	Ph3 (669)	Ph3 (493)	Ph3 (726)	Ph3 (672)
CDK4/6i	Palbociclib	Ribociclib	Abemaciclib	Abemaciclib	Ribociclib	Ribociclib
Endocrine partner	Letrozole	Letrozole	Fulvestrant	Letrozole or anastrozole	Fulvestrant	Tamoxifen, letrozole, or anastrozole
Patient population	Post-menopausal	Post-menopausal	Pre/post-menopausal	Post-menopausal	Post-menopausal	Pre/peri-menopausal
mPFS, mo	24.8 vs 14.5	25.3 vs 16.0	16.4 vs 9.3	28.2 vs 14.8	20.5 vs 12.8	23.8 vs 13.0
HR (95% CI)	0.58 (0.46-0.72)	0.57 (0.46-0.70)	0.55 (0.45-0.68)	0.54 (0.42-0.70)	0.59[c] (0.48-0.73)	0.55 (0.44-0.69)

Comparisons of efficacy and safety should not be drawn or inferred in the absence of head-to-head studies

[a]Includes first and second line; [b]First-line ET; up to 1 previous CT line permitted in advanced setting (14% had received CT); [c]Descriptive analysis. CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; mBC, metastatic breast cancer; mPFS, median progression free survival; Ph, phase.

1. Burstein HJ, et al. *J Clin Oncol*. 2021;39:3959-77; 2. Cardoso F, et al. *Ann Oncol.* 2020;31:1623-49; 3. Gennari et al. *Ann Oncol.* 2021;32:1475-95; 4. Pfizer. Ibrance (palbociclib) Summary of Product Characteristics. 2024; 5. Hortobagyi GN, et al. *Ann Oncol*. 2018;29:1541-7; 6. Tripathy D, et al. *Lancet Oncol*. 2018;19:904-15; 7.Finn, et al. *NEJM.* 2016;375-1925; 8.Hortobagyi, et al. *NEJM*. 2016;375-1738; 9. Sledge, et al. *J Clin Oncol*. 2017 Sep 1;35(25):2875-84. 6:116; 10. Johnston S, et al. *NPJ Breast Cancer*. 2019;7:5:5; 11. Goetz, et al. *JCO*. 2017;35:3638.

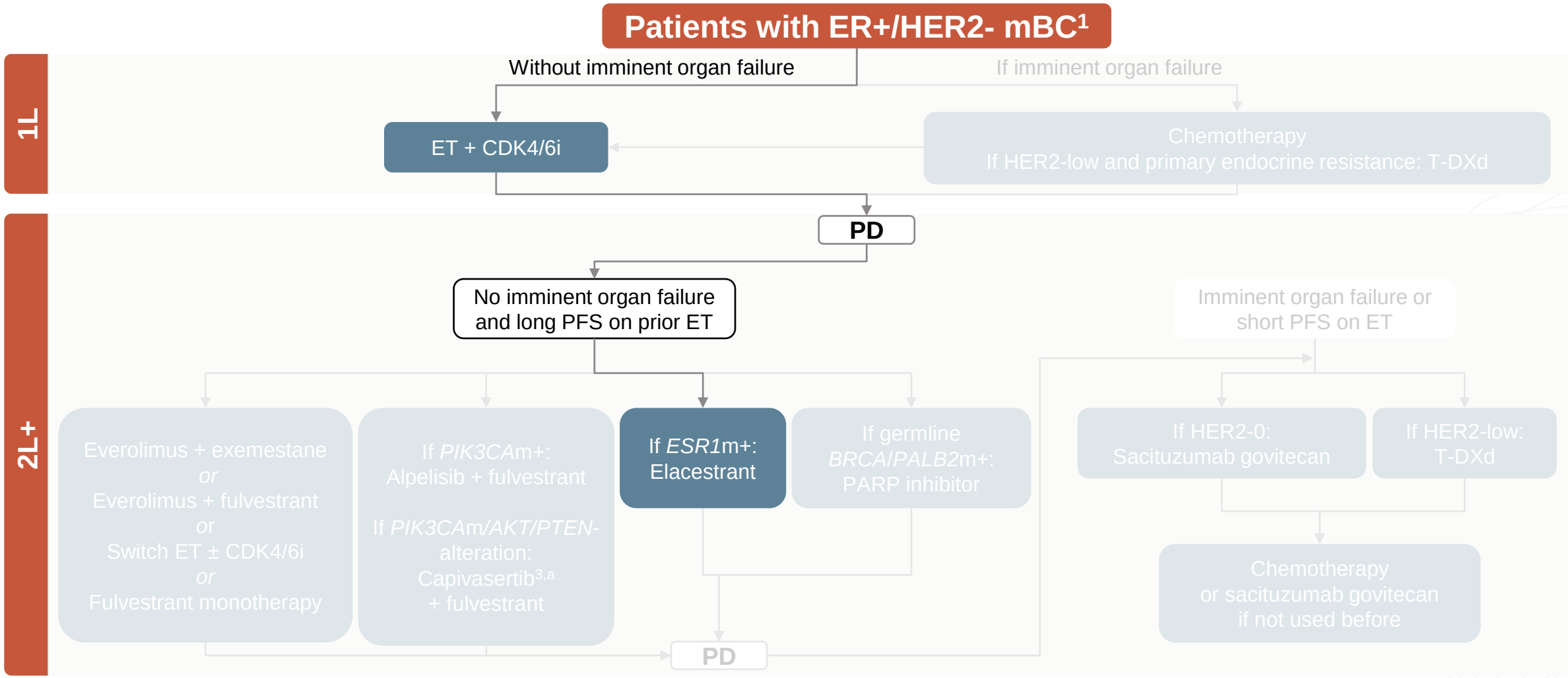
RESISTANCE TO ET IN ER+/HER2− mBC CAN BE CLASSIFIED BY CLINICAL AND MOLECULAR VARIABLES[1-5]

Clinical definition	**Primary endocrine resistance**	**Secondary endocrine resistance**
	PD within first 6 months of 1L ET-based therapy, while on ET (regardless of CDK4/6i use)[1]	PD after ≥6 months of 1L ET[1] *or* PD after any duration of 2L+ ET-based therapy[1]
Molecular definition	**Intrinsic**	**Acquired**
	Alterations of the PI3K/AKT/mTOR, RAS-MAPK, FGFR1 pathways, *BRCA1/2* mutations, *RB1* loss, *TP53* activation, etc.[2–4]	Mechanisms of resistance, such as *ESR1* mutations, occurring after prior endocrine therapy in mBC[3,5]

1L, first line; 2L+ second line and above; mBC, Metastatic breast cancer; ET, endocrine therapy; PD, progressive disease.

1. Cardoso F, et al. *The Breast*. 2024; [ePub ahead of print]; 2. Rani A, et al. *Front Endocrinol.* (Lausanne) 2019;10:245; 3. Xu P, et al. *Acta Pharmacol Sin.* 2021;42:171-8; 4. Karlsson E, et al. SABCS. 2023.PO5-13-02; 5. Brett JO, et al. *Breast Cancer Res*. 2021;23:85.

2ND LINE TREATMENT CHOICES FOR PATIENTS WITH ER+/HER2- MBC ARE DRIVEN BY BIOMARKER STATUS[1,2]



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EMERALD TRIAL OVERVIEW

EMERALD: PHASE 3 TRIAL OF ELACESTRANT VS SOC ENDOCRINE THERAPY[1]

100% of patients HAD received prior CDK4/6 inhibitor therapy

- Men and postmenopausal women with advanced/metastatic breast cancer
- ER+/HER2-
- Progressed or relapsed on or after one or two lines of endocrine therapy for advanced disease, one of which was given in combination with a CDK4/6i
- ≤1 line of chemotherapy for metastatic disease
- ECOG PS 0 or 1

Stratification factors
- *ESR1*-mut status
- Presence of visceral metastases
- Prior treatment with fulvestrant

R 1:1
(N=478)

Elacestrant
345 mg daily[a]

Investigator's choice (SOC)
- Fulvestrant
- Anastrozole
- Letrozole
- Exemestane

PD
Follow-up

Primary endpoints:
- PFS in *ESR1*-mut
- PFS in all patients

[a] 345 mg of elacestrant is equivalent to 400 mg of elacestrant dihydrochloride.
mBC, Metastatic breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; ESR1, estrogen receptor 1 mutation; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; PD, progressive disease; PFS, progression-free survival; R, randomization; SOC, standard of care.
1.Bidard FC, et al. *J Clin Oncol.* 2022;40:3246-56.

EMERALD TRIAL BASELINE CHARACTERISTICS[1,2]

	Elacestrant		SOC	
	All (N=239)	*ESR1*-mut (N=115)	All (N=239)	*ESR1*-mut (N=113)
Median age, years (range)	63 (24-89)	64 (28-89)	63 (32-83)	63 (32-83)
Female, n (%)	233 (97.5)	115 (100)	238 (99.6)	113 (100)
ECOG PS, n (%)				
0	143 (59.8)	67 (58.3)	135 (56.5)	62 (54.9)
1	96 (40.2)	48 (41.7)	103 (43.1)	51 (45.1)
Visceral metastasis[a], n (%)	163 (68.2)	81 (70.4)	170 (71.1)	84 (74.3)
Prior CDK4/6 inhibitor, n %)	239 (100)	115 (100)	239 (100)	113 (100)
No. of prior lines of endocrine therapy in the advanced or metastatic setting, n (%)				
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)
Prior therapies for advanced or metastatic disease, n (%)				
Fulvestrant	70 (29.3)	27 (23.5)	75 (31.4)	28 (24,8)
Aromatase inhibitor	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)
No. of prior lines of chemotherapy in the advanced or metastatic setting, n (%)				
0	191 (79.9)	89 (77.4)	180 (75.3)	81 (71.7)
1	26 (20.1)	26 (22.6)	59 (24.7)	32 (28.3)

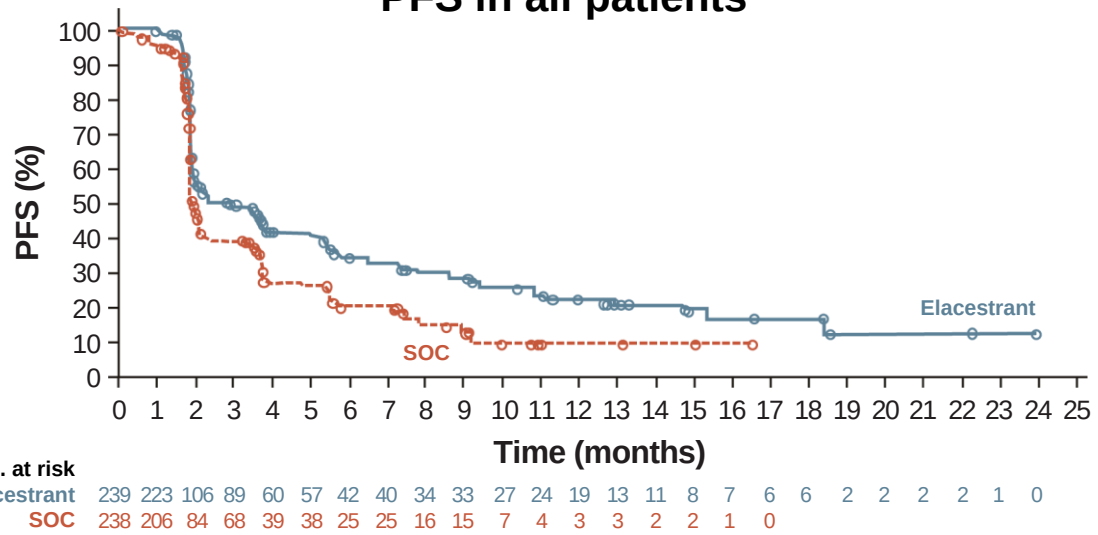
[a] Includes lung, liver, brain, pleural, and peritoneal involvement.

mBC, Metastatic breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; *ESR1*, estrogen receptor 1 mutation; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; PD, progressive disease; PFS, progression-free survival; R, randomization; SOC, standard of care

1. Orserdu (elacestrant) SmPC 2023; 2023; 2. Bardia A, et al. SABCS 2022. Abstract GS3-01.

EMERALD: ELACESTRANT DEMONSTRATED PFS IMPROVEMENT VERSUS SOC BOTH IN THE OVERALL POPULATION AND IN PATIENTS WITH *ESR1* MUTATIONS[1]

PFS in all patients

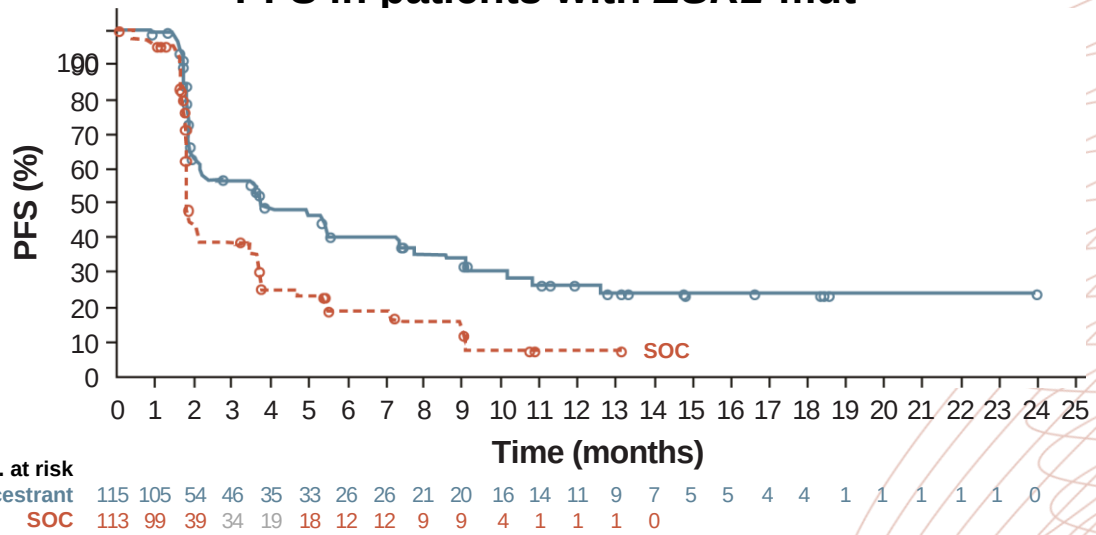


No. at risk

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							

	Elacestrant (n=239)	SOC (n=238)
6-mo PFS, % [95% CI]	**34.3** [27.2-41.5]	**20.4** [14.1-26.7]
12-mo PFS,% [95% CI]	**22.3** [15.2-29.4]	**9.4** [4.0-14.8]
HR [95% CI]	**0.70** [0.55–0.88]	
p-value	0.0018	

PFS in patients with *ESR1*-mut



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										

	Elacestrant (n=115)	SOC (n=113)
6-mo PFS, % [95% CI]	**40.8** [30.1-51.4]	**19.1** [10.5-15.1]
12-mo PFS,% [95% CI]	**26.8** [16.2-37.4]	**8.2** [1.3-15.1]
HR [95% CI]	**0.55** [0.39–0.77]	
p-value	0.0005	

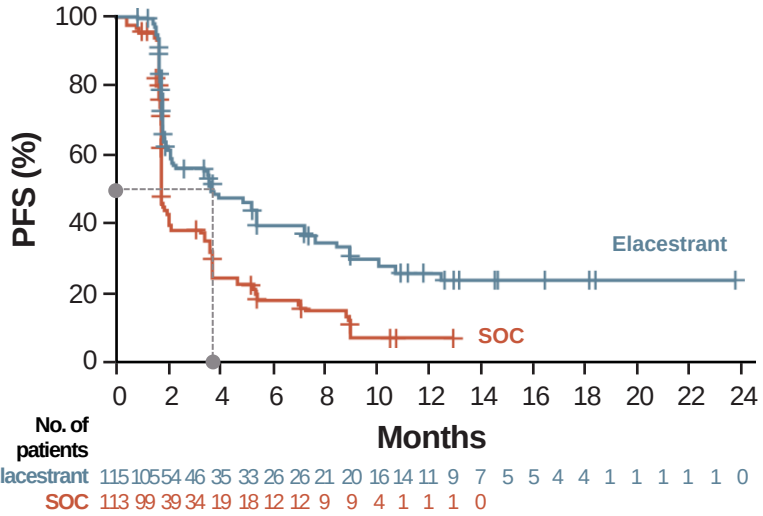
CI, confidence interval; *ESR1*, estrogen receptor 1; HR, hazard ratio; ITT, intent-to-treat; mo, months; mPFS,median progression-free survival; mut, mutated; PFS, progression-free survival.

1.Bidard FC, et al. *J Clin Oncol*. 2022;40:3246-56.

EMERALD TRIAL SUBGROUP ANALYSES

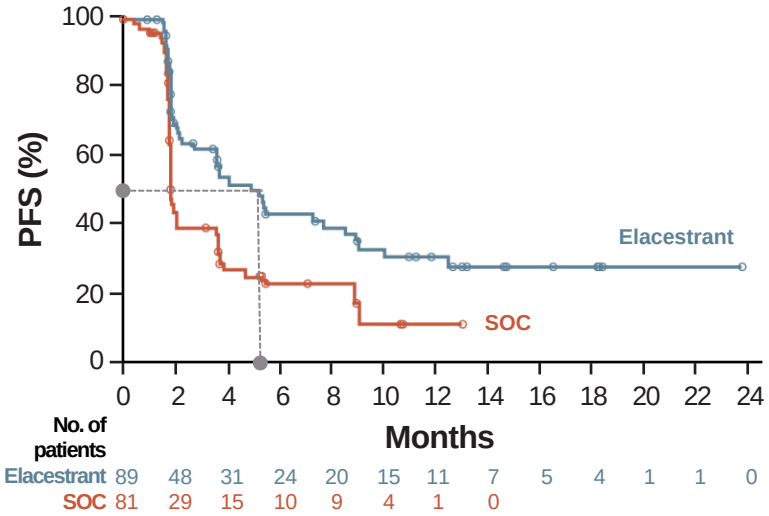
EMERALD: ELACESTRANT PROVIDES IMPROVED PFS RESULTS VS SOC IN PATIENTS WITH *ESR1* MUTATIONS

45% reduction in risk of progression or death[1]



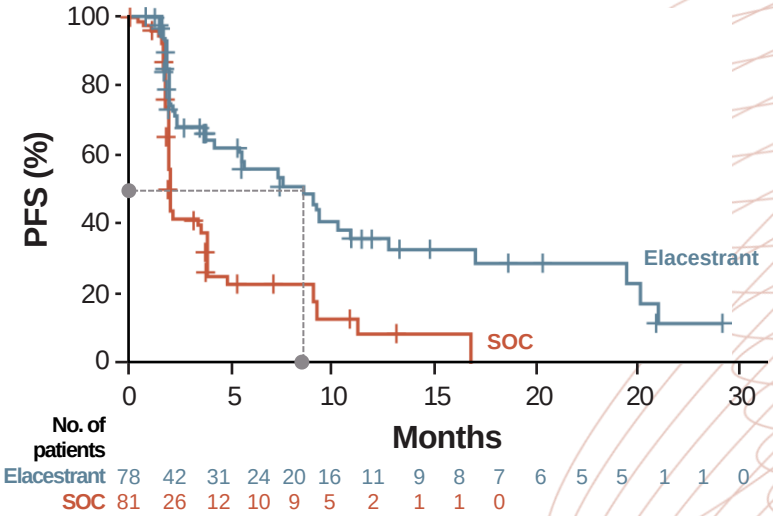
	Elacestrant (n=115)	SOC (n=113)
mPFS, mo	**3.8**	**1.9**
HR [95% CI]	**0.55** [0.39–0.77]	
p-value	0.0005	

Significant PFS improved in patients who did not receive prior chemotherapy[2]



	Elacestrant (n=89)	SOC (n=81)
mPFS, mo [range]	**5.3** [3.7–9.0]	**1.9** [1.9–3.7]
HR [95% CI]	**0.54** [0.36–0.80]	
p-value	0.00235	

≥12 months duration of prior ET + CDK4/6i therapy is positively associated with mPFS[a,3]



	Elacestrant (n=78)	SOC (n=81)
mPFS, mo [95% CI]	**8.6** [4.1–10.8]	**1.9** [1.9–3.7]
12-mo PFS, % [95% CI]	**35.8** [21.8–49.8]	**8.39** [0.0–17.7]
HR [95% CI]	**0.41** [0.26–0.63]	

[a] Post-hoc analysis results are observational in nature. There was no prespecified statistical procedure controlling for type 1 error.

CI, confidence interval; HR, hazard ratio; *ESR1*, estrogen receptor 1; mo, months; mPFS, median progression-free survival; mut, mutated; No, number; PFS, progression-free survival; SOC, standard of care.

1.Bidard FC, et al. *J Clin Oncol*. 2022;40:3246-56; 2.Kaklamani V, et al. *J Clin Oncol*. 2022;40(16_suppl):Abstract 1100; 3.Bardia A, et al. SABCS 2022. Abstract GS3-01.

IN TUMORS WITH RETAINED ENDOCRINE-SENSITIVITY (LONGER EXPOSURE TO PRIOR ET + CDK4/6i), *ESR1* MUTATIONS MAY BE A MAIN DRIVER OF DISEASE[1,2]

Patients with ≥12 months of prior ET + CDK4/6i	**% (n)**	**Elacestrant** mPFS, months	**SOC** mPFS, months	**HR** [95% CI]
All *ESR1*-mut patients	**100** (159)	**8.61**	**1.91**	**0.41** [0.26-0.63]
PIK3CA-mut[a]	**39** (62)	**5.5**	**1.9**	**0.42** [0.18-0.94]
Bone metastases[b]	**86** (136)	**9.1**	**1.9**	**0.38** [0.23-0.62]
Liver and/or lung metastases[c]	**71** (113)	**7.3**	**1.9**	**0.35** [0.21-0.59]
TP53-mut	**38** (61)	**8.6**	**1.9**	**0.30** [0.13-0.64]
HER2-low expression[d]	**48** (77)	**9.0**	**1.9**	**0.30** [0.14-0.60]
<3 metastatic sites[e]	**52** (82)	**9.0**	**1.9**	**0.41** [0.23-0.75]
≥3 metastatic sites[e]	**33** (53)	**10.8**	**1.8**	**0.31** [0.12-0.79]
ESR1 D538G-mut	**61** (97)	**9.0**	**1.9**	**0.38** [0.21-0.67]
ESR1 Y537S/N-mut	**58** (92)	**9.0**	**1.9**	**0.25** [0.13-0.47]

This was an exploratory analysis. Post-hoc analysis results are observational in nature. There was no prespecified statistical procedure controlling for type 1 error.

[a] Includes E545K, H1047R, E542K, and others; [b] 85% of patients had bone and other sites of metastases (30% of these patients had no liver or lung involvement); [c] 55% of patients had liver and other sites of metastases (10% of these patients had no lung or bone involvement); 25% of patients had lung and other sites of metastases (2% of these patients had no liver or bone involvement); [d] Locally assessed HER2 immunohistochemistry 1+, and 2+ with no *in situ* hybridization amplification; Data not available for all patients. [e] The number of metastatic sites was available for 135 of 159 patients with ESR1-mutated tumors and prior ET+CDK4/6i ≥12 month. CDK4/6, cyclin dependent kinase 4/6; CI, confidence interval; *ESR1*, estrogen receptor 1; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; mut, mutation; PIK3CA , phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; SOC, standard of care; TP53, tumor protein p53.

1.Bardia A, et al. *Clin Cancer Res.* 2024;30(19):4299–4309; 2.Bardia et al SABCS 2024. P1-01-25.

EMERALD: SAFETY

Most common adverse events ≥10% in either arm in the overall population[1]

	Elacestrant (n=237)		SOC (n=230)	
Adverse events[1,a]	**All grades (%)**	**Grade ≥3 (%)**	**All grades (%)**	**Grade ≥3 (%)**
Nausea	35	2.5	19	0.9
Vomiting[b]	19	0.8	9	0
Diarrhoea	13	0	10	1
Constipation	12	0	6	0
Abdominal pain[b]	11	1	10	0.9
Dyspepsia	10	0	2.6	0
Fatigue[b]	26	2	27	1
Decreased appetite	15	0.8	10	0.4
Headache	12	2	12	0
Hot flush	11	0	8	0

Nausea summary[1]	Elacestrant (n=237)	SOC (n=230)
Grade 3 nausea, %	2.5	0.9
Dose-reduction rate due to nausea, %	1.3	N/A
Discontinuation rate due to nausea, %	1.3	0
Antiemetic use*, %	8.0	10.3 (AI) 3.7 (fulvestrant)

Nausea was generally reported early, with a median time to first onset of 14 days.[2]
* Patients may have been on antiemetics prior to enrollment.[1]

- No grade 4 treatment-related AEs were reported[1]
- Treatment-related AEs leading to discontinuation were 3.4% and 0.9% in the elacestrant and SOC arms, respectively[1]
- No hematologic safety signal was observed, and none of the patients in either treatment arm had sinus bradycardia[1]

[a] Adverse events were graded using NCI CTCAE version 5.0; [b] Includes other related terms.

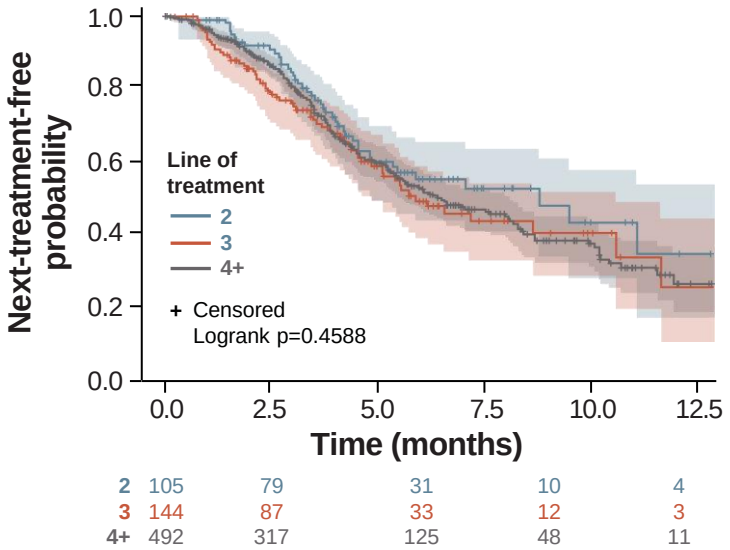
AI, aromatase inhibitor; AE, adverse event; ER, estrogen receptor; FUL, fulvestrant; HER2, human epidermal growth factor receptor 2; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; SOC, standard of care (fulvestrant or aromatase inhibitor).

1.Bardia A, et al. *Clin Cancer Res.* 2024;30(19):4299–4309; 2. Stemline. ORSERDU (elacestrant) Summary of Product Characteristics. 2024.

ELACESTRANT AND REAL-WORLD ANALYSES

ELACESTRANT SHOWED CONSISTENT REAL-WORLD TTNT AND PFS BENEFIT AMONG CLINICALLY RELEVANT SUBGROUPS

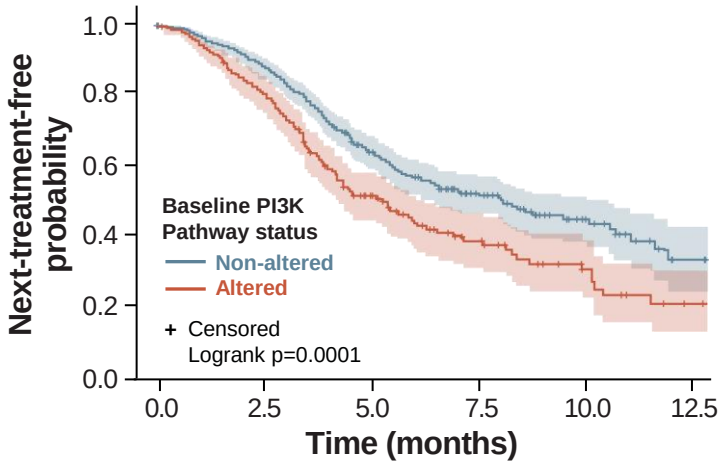
rwTTNT since elacestrant initiation by line of treatment[1]



2	105	79	31	10	4
3	144	87	33	12	3
4+	492	317	125	48	11

	2	3	4+
Subjects	104	144	492
Event	42	62	208
Censored	62	82	284
Median survival	8.8	5.9	6.4
95% CI	4.8-	4.6-10.6	5.5-8.1

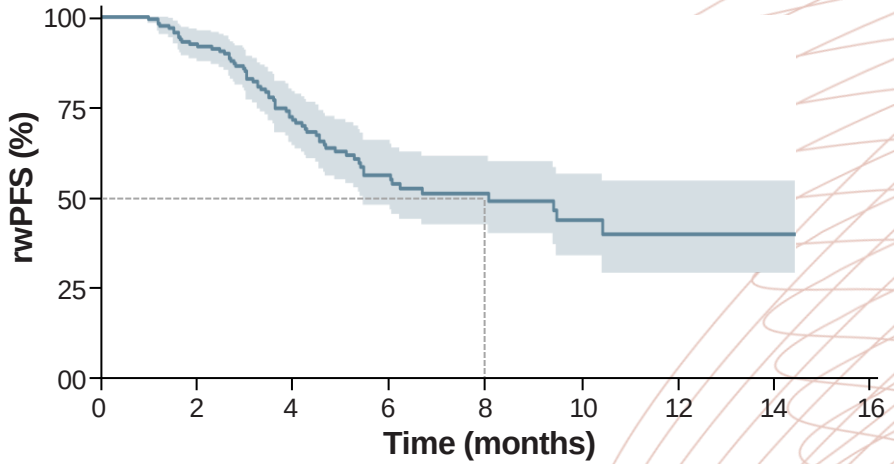
rwTTNT since elacestrant initiation by baseline PI3K* pathway status[1]



Non-altered	508	344	139	48	12
Altered	234	141	50	21	6

	Non-altered	Altered
Subjects	508	234
Event	191	121
Censored	317	113
Median survival	8.0	5.2
95% CI	6.2–10.1	4.2–6.0

rwPFS: 1-2 prior lines of ET[2]



Events	0	12	41	57	61	64	65	65	65

	Elacestrant (n=166)
Events, n (%)	**65 (39)**
Median rwPFS, mo [95% CI]	**8.0** [5.5-NR]
12 mo rwPFS, % [95% CI]	**40** [29-54]

* Oncogenic alterations in *AKT1*, *PTEN*, and *PIK3CA* with an FDA approved targeted therapeutic indication were included as PI3K pathway alterations: *PIK3CA* (n=197), *AKT1* (n=30), and/or *PTEN* (n=15).

2L, second line; 3L, third line; 4L, fourth line; AKT, protein kinase B; CI, confidence interval; CL, confidence limits; HR, hazard ratio; mo, months, PI3K, phosphoinositide 3-kinase; *PIK3CA*, phosphatidylinositol 3-kinase catalytic subunit alpha; *PTEN*, phosphatase and tensin homolog rw, real-world; TTNT, time to next treatment.

1. Lloyd M, et al. SABCS 2024. Abstract PS7-05; 2.Swallow et al. SABCS 2024. Abstract P3 10-08.

ELACESTRANT SHOWS CONSISTENT ~8-9 MONTHS BENEFIT IN NEARLY 1200 PATIENTS WITH PRIOR EXPOSURE TO CDK4/6i, AS DEMONSTRATED BY EMERALD AND RWE ANALYSES

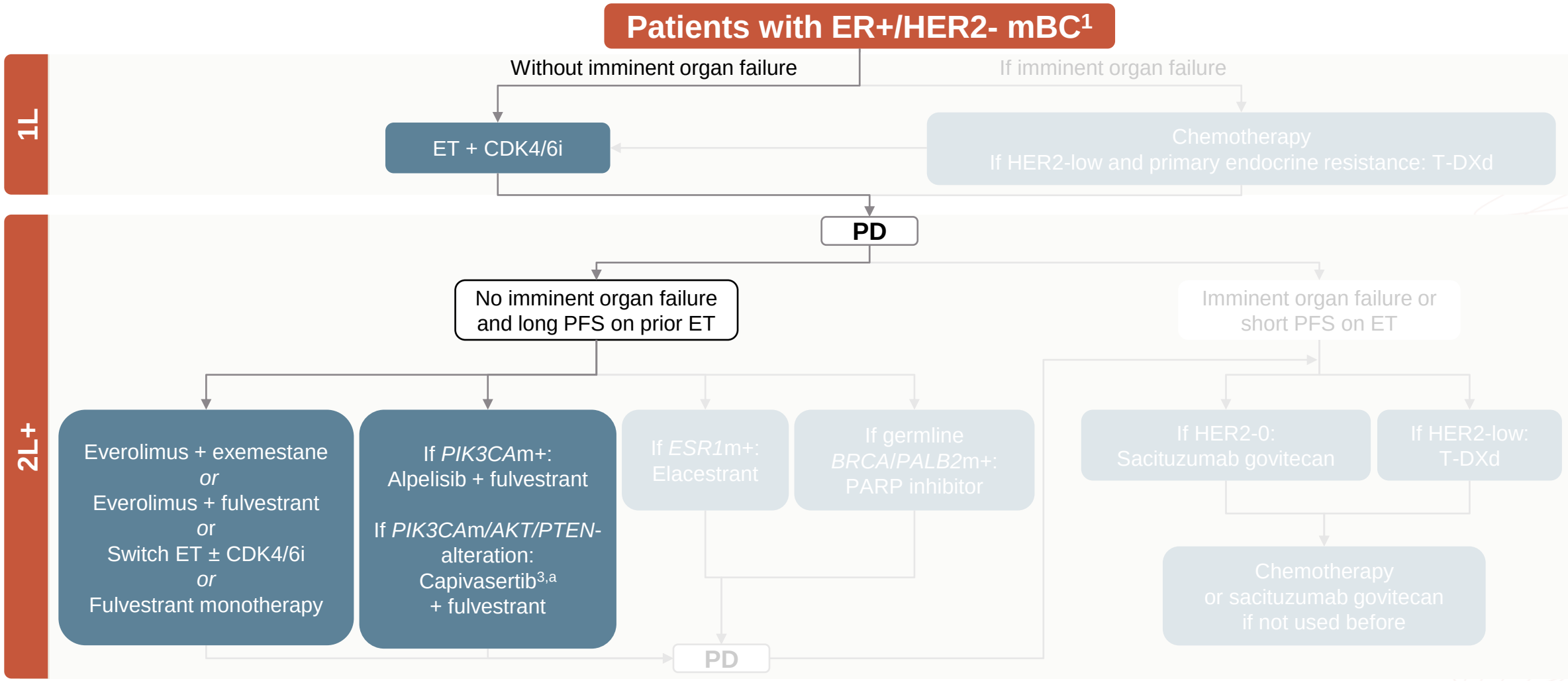
	Bardia et al, EMERALD CCR (n=159)[1]	**Lloyd et al, Guardant** Inform (n=742)[2]	**Swallow et al, Komodo** Calims (n=276)[3]
Baseline Characteristics			
Prior CDK4/6i mBC	100%	83%	90%
Prior CDK4/6i >12 mo	100%	–	88%
Prior fulvestrant in mBC	23%	53%	61%
Prior chemo in mBC	20%	41%	33%
mPFS / rwPFS / TTNT			
2L	–	8.8	–
2-3L	8.6	–	8.0

2L, second line; 3L, third line; CDK4/6i, cyclin dependent kinase 4/6 inhibitor; mBC; metastatic breast cancer; mo, months; mPFS, median progression free survival; RWE, real world evidence; rwPFS, real world progression free survival; TTNT, time to next treatment.

1. Bardia A, et al. *Clin Cancer Res.* 2024;30(19):4299–4309; 2.Llyod, *SABCS* 2024. Abstract PS7-05; 3.Swallow et al, *SABCS* 2024. Abstract P3 10-08.

ALTERNATIVE SECOND LINE THERAPY REGIMENS

2ND LINE TREATMENT CHOICES FOR PATIENTS WITH ER+/HER2- MBC ARE DRIVEN BY BIOMARKER STATUS[1,2]



[a] Capivasertib may be used following recurrence or progression on or after an ET-based regimen. mBC, Metastatic breast cancer; *BRCA*, BReast CAncer gene; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER, estrogen receptor; *ESR1*, estrogen receptor 1; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; m, mutation; *PALB2*, partner and localizer of BRCA2; PARP, poly(ADP-ribose) polymerase; PD, progressive disease; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; T-DXd, trastuzumab deruxtecan.

Adapted from: 1. Gennari A, et al. *Ann Oncol.* 2021;32(12):1475-95. ESMO Metastatic Breast Cancer Living Guidelines. V1.1 May 2023; 2. Bardia A, et al. *Clin Cancer Res.* 2024;30(19):4299–4309; 3. Truqap (capivasertib) SmPC 2024.

mTOR INHIBITOR PLUS ET HAS BEEN ASSOCIATED WITH SHORTER mPFS IN PATIENTS WITH PRIOR CDK4/6i AND *ESR1* MUTATION TUMORS

	BOLERO-2[1–3]	RWD Rozenblit et al.[4]	RWD Vasseur et al.[5]	TRINITI-1[6]
Phase (n)	Ph3 (724)	N/A (246)	N/A (57)	Ph1/2 (95)
Experimental arm	Everolimus + exemestane	Everolimus + ET	Everolimus + fulvestrant	Everolimus + exemestane + ribociclib
Control arm	Placebo + exemestane	N/A	N/A	N/A
Previous CDK4/6i Yes *No*	 – 100%	 22% 78%	 100% –	 100% –
***ESR1*-mut (%)**	30%	N/A	N/A	34%
mPFS all patients mPFS, months HR (95% CI)	**7.8 vs 3.2** 0.45 (0.38-0.54)	**mTTNT** *Prior CDK4/6i:* **4.3** *No prior CDK4/6i:* **6.2**	**6.8**	**5.7**
mPFS *ESR1*-mut mPFS, months HR (95% CI)	**5.4 vs 2.8** 0.52 (0.36-0.75)	**N/A**	**N/A**	**3.5[a]**

Comparisons of efficacy and safety should not be drawn or inferred in the absence of head-to-head studies

[a] N=89 patients had a baseline ctDNA biomarker assessment.

2L, second line; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; ESR1, estrogen receptor 1 gene; ET, endocrine therapy; HR, hazard ratio; (m)PFS, (median) progression-free survival; mTOR, mammalian target of rapamycin; mTTNT, median time to next therapy; mut, mutation; N/A not available; NS, not significant; PBO, placebo; PFS, progression-free survival; RWD, real-world data.

1. Yardley DA, et al. *Adv Ther.* 2013;30:870-84; 2. Cook M, et al. *Oncologist*. 2021;26:101-6; 3. Chandarlapaty S, et al. *JAMA Oncol*. 2016;2:1310-5; 4. Rozenblit, et al. *Breast Cancer Res*. 2021;23:14; 5. Vasseur, et al. *Oncogene*. 2024;43:1214-22, incl Suppl; 6. Bardia A, et al. *Clin Cancer Res*. 2021;27:4177-85.

PIK3CA/AKT-PATHWAY INHIBITORS + ET SHOW BENEFIT IN AKT-PATHWAY ALTERED TUMORS, BUT MAY BE LIMITED IN ENDOCRINE SENSITIVE TUMORS WHERE ER IS THE DRIVER

	SOLAR-1[1]	BYLieve[2,3]	Capitello 291[4]
Phase (n)	Ph3 (572)	Ph2 (336)	Ph3 (708)
Cohort (n)	*PIK3CA*-mutant (341)	Cohort A (127)	AKT pathway altered (289)
Experimental arm	Alpelisib + fulvestrant	Alpelisib + fulvestrant	Capivasertib + fulvestrant
Control arm	Placebo + fulvestrant	N/A	Placebo + fulvestrant
Previous CDK4/6i Yes *No*	 **6%** **94%**	 **100%** **–**	 **72%** **28%**
***ESR1*-mut (%)**	Data not available	21%	Data not available
mPFS all patients mPFS, months HR (95% CI)	**11 vs 5.7** 0.65 (0.50-0.85)	**8.0** (5.6-8.6)	**7.3 vs 3.1** 0.50 (0.38-0.65)
mPFS prior CDK4/6i mPFS, months HR (95% CI)i	**Data not available**	**8.0** (5.6-8.6)	**5.5 vs 2.0** 0.59 (0.48-0.72)
mPFS *ESR1*-mut mPFS, months HR (95% CI)	**Data not available**	**5.6** (3.8-12.0)	**Data not available**

Comparisons of efficacy and safety should not be drawn or inferred in the absence of head-to-head studies

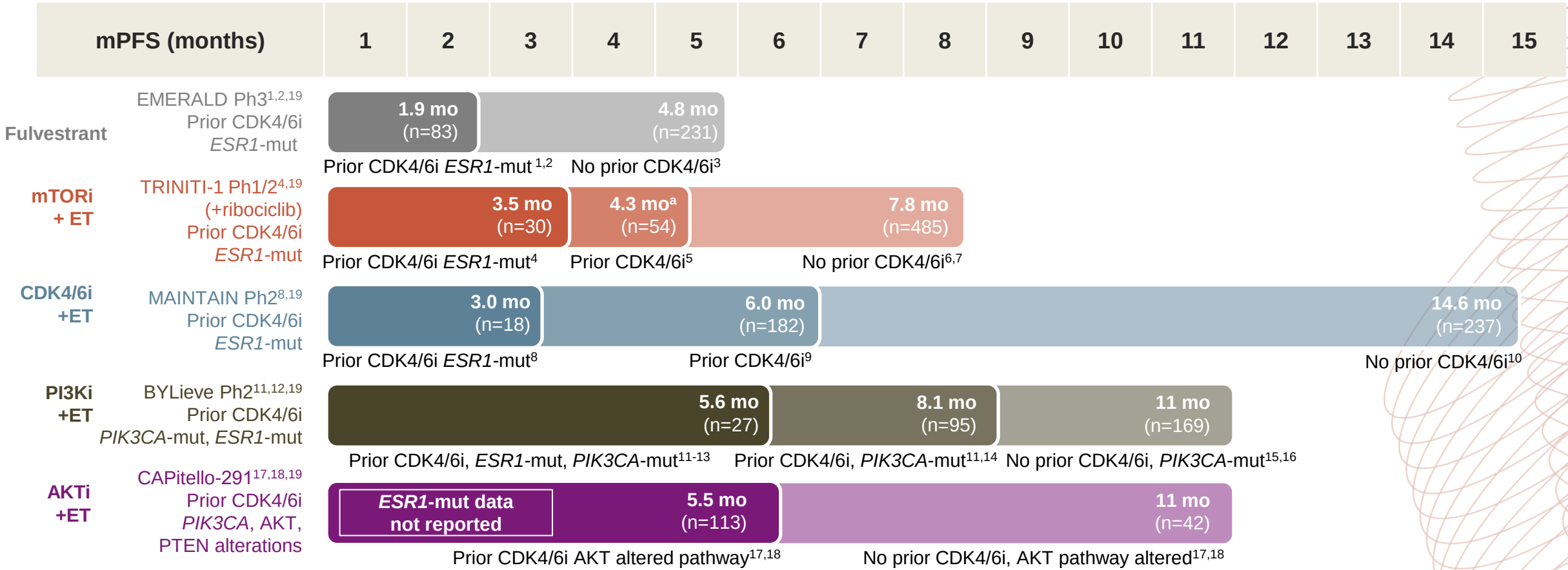
AKT, protein kinase B; CDK4/6, cyclin-dependent kinase 4/6; CI, confidence interval; *ESR1*, estrogen receptor 1; HR, hazard ratio; N/A not available; mPFS, median PFS; mut, mutation; PFS, progression-free survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TP53, tumor protein p53.

1. André F, et al. *N Engl J Med.* 2019;380:1929-40; 2. Chia S, et al. ASCO 2023. Abstract P1078; 3. Turner S, et al. *SABCS 2021.* PD15-01; 4 Turner NC, et al. *N Engl J Med.* 2023;388:2058-70.

SUMMARY: PFS DURATION IS CONSISTENTLY LOWER IN PATIENTS WITH PRIOR CDK4/6 INHIBITOR THERAPY AND *ESR1*-MUT

Prior ET + CDK4/6i AND *ESR1*-mut

Comparisons of efficacy and safety should not be drawn or inferred in the absence of head-to-head studies



mPFS of studies represent n of intervention group; [a] Time to next treatment. 2L, second line; ET, endocrine therapy; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*-mut, estrogen receptor 1 mutated; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

1. Orserdu (elacestrant) SmPC 2023; 2. Bidard FC, et al. *J Clin Oncol.* 2022;40:3246-56; 3. Johnston SR, et al. *Lancet Oncol*. 2013;14:989-98; 4. Bardia A, et al. *Clin Cancer Res*. 2021;27:4177-85; 5. Rozenblit M, et al. *Breast Cancer Res.* 2021;23:14; 6. Afinitor (everolimus). SmPC 2022; 7. Baselga J, et al. *N Engl J Med.* 2012;366:520-9; 8. Kalinsky K, et al. *J Clin Oncol*. 2023;41:4004-13; 9. Kalinsky K, et al. ASCO 2024. Abstract LBA1001; 10. Slamon DJ, et al. *N Engl J Med. 2020;* 382:514-524; 11. Rugo HS, et al. *Lancet Oncol*. 2021;22:489-98; 12. Turner N, et al. SABCS. 2021; Abstract PD15-01; 13. Fillbrunn M, et al. *BMC*. 2022;22:1002. 14. Chia S, et al. *J Clin Oncol*. 2023;41(suppl 16; abstr 1078); 15. Piqray (alpelisib). SmPC 2023; 16. Andre F, et al. *N Engl J Med*. 2019; 380:1929-40; 17. Oliveira M., et al. *Ann Oncol*. 2023;8:101223–101223. Poster 187O; 18. Turner NC, et al. *N Engl J Med.* 2023;388:2058-70; 19. Bardia A, et al. *Clin Cancer Res.* 2024;30(19):4299–4309.

SAFETY OF ET COMBINATION REGIMENS FOR 2ND LINE+, ER+/HER2− MBC

Comparisons of efficacy and safety should not be drawn or inferred in the absence of head-to-head studies

	CDK4/6 inhibitors + ET		mTOR inhibitors + ET		*PIK3CA* inhibitors + ET		AKT-pathway[a] inhibitors + ET	
	Palbociclib,[1] ribociclib,[2] abemaciclib[3,4]		Everolimus[5]		Alpelisib[6]		Capivasertib[7]	
	All grades	Grade 3-4	All grades	Grade 3-4	All grades	Grade 3-4	All grades	Grade 3-4
Adverse event incidence for combinations, %								
Neutropenia	**45-81**	**25-74**	–	–	–	–	–	–
Leukopenia	**26-45**	**9-31**	–	–	–	–	–	–
Anemia	**19-44**	**3-8**	16	6	–	–	10	2
Stomatitis	14-29	0-1	56	8	25	3	15	2
Rash	13-18	1-2	36	1	36	10	38	12
Diarrhea	**25-86**	**1-12**	30	2	58	7	72	9
Hyperglycemia	–	–	13	4	64	33	16	2
Fatigue	33-41	2-3	33	4	24	4	21	1
Nausea	34-49	0-2	29	0	45	3	35	1
Discontinuation rate, %	**2-15**		**19**		**25**		**13**	

CDK4/6 inhibitors are associated with myelosuppression (neutropenia, leukopenia, anemia) and diarrhea

[a] *PIK3CA/AKT1/PTEN*; 2L, second line; AKT, protein kinase B; CDK4/6, cyclin-dependent kinase 4/6; ET, endocrine therapy; mBC, metastatic breast cancer; mTOR, mammalian target of rapamycin; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

1. Dieras V, et al. *J Natl Cancer Inst*. 2018;111:419-30; 2. Burris HA, et al. *Br J Cancer*. 2021;125:679-86; 3. Rugo HS, et al. *Oncologist*. 2021;26:e53-e65; 4. Jhavieri KL et al. *N Engl J Med* . 2024. doi: 10.1056/NEJMoa2410858. Online ahead of print. 5. Baselga J, et al.*N Engl J Med*. 2012;366:520-9; 6. Andre F, et al. *N Engl J Med*. 2019;380:1929-40; 7. Turner NC, et al. *N Engl J Med*. 2023;388:2058-70.

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	CDK4/6 inhibitors + ET		mTOR inhibitors + ET		*PIK3CA* inhibitors + ET		AKT-pathway[a] inhibitors + ET	
	Palbociclib,[1] ribociclib,[2] abemaciclib[3,4]		Everolimus[5]		Alpelisib[6]		Capivasertib[7]	
	All grades	Grade 3-4	All grades	Grade 3-4	All grades	Grade 3-4	All grades	Grade 3-4
Adverse event incidence for combinations, %								
Neutropenia	45-81	25-74	–	–	–	–	–	–
Leukopenia	26-45	9-31	–	–	–	–	–	–
Anemia	19-44	3-8	16	6	–	–	10	2
Stomatitis	14-29	0-1	**56**	**8**	**25**	**3**	**15**	**2**
Rash	13-18	1-2	**36**	**1**	**36**	**10**	**38**	**12**
Diarrhea	25-86	1-12	**30**	**2**	**58**	**7**	**72**	**9**
Hyperglycemia	–	–	**13**	**4**	**64**	**33**	**16**	**2**
Fatigue	33-41	2-3	33	4	24	4	21	1
Nausea	34-49	0-2	29	0	45	3	35	1
Discontinuation rate, %	2-15		19		25		13	

PI3K/AKT/mTOR pathway inhibitors are associated with Grade 3/4 diarrhea, rash, hyperglycemia and stomatitis

[a] *PIK3CA/AKT1/PTEN*; 2L, second line; AKT, protein kinase B; CDK4/6, cyclin-dependent kinase 4/6; ET, endocrine therapy; mBC, metastatic breast cancer; mTOR, mammalian target of rapamycin; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

1. Dieras V, et al. *J Natl Cancer Inst*. 2018;111:419-30; 2. Burris HA, et al. *Br J Cancer*. 2021;125:679-86; 3. Rugo HS, et al. *Oncologist*. 2021;26:e53-e65; 4. Jhavieri KL et al. *N Engl J Med* . 2024. doi: 10.1056/NEJMoa2410858. Online ahead of print. 5. Baselga J, et al.*N Engl J Med*. 2012;366:520-9; 6. Andre F, et al. *N Engl J Med*. 2019;380:1929-40; 7. Turner NC, et al. *N Engl J Med*. 2023;388:2058-70.

ESR1 MUTATION: WHY, WHAT, WHEN AND HOW TO TEST

BREAST CANCER IS A DYNAMIC DISEASE WHERE MUTATIONS MAY EMERGE OVER THE COURSE OF 1ST LINE MBC TREATMENT

- *ESR1* mutations:

… are acquired

Breast cancer is a dynamic disease: new mutations develop over the course of treatment[1,2]

… are subclonal

Molecular profile can vary between and within tumour sites, with a heterogeneous distribution in tissue[2,3]

… drive treatment decisions

Biomarker profile influences choice of therapy in 2L+[1]

1L, first line; 2L, second line; ESR1, estrogen receptor 1; mBC, metastatic breast cancer.

1. Gennari A, et al. *Ann Oncol* 2021;32(12): 1475-1495. ESMO Metastatic Breast Cancer Living Guidelines. V1.1 May 2023; 2. Hartkopf A, et al. *Breast Care (Basel)*. 2020;15:347-54; 3. Bennett C, et al. *Cancers (Basel).* 2022;14:3046.

LONGER EXPOSURE TO ET IN MBC INCREASES THE CHANCE OF DEVELOPING *ESR1*-MUT DURING TREATMENT[1-10]

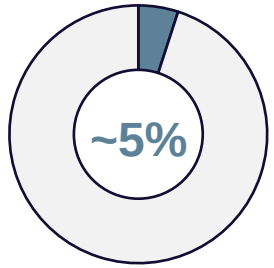
Early Breast Cancer[1-3,5,7]

Metastatic Breast Cancer[2-9]

Adjuvant Treatment (Tx)

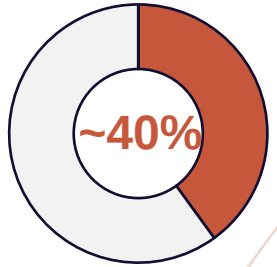
% *ESR1*-mut

1st Progression During/After Adjuvant Tx

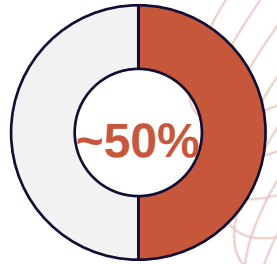


1L mBC Treatment AI + CDK4/6i

Progression



2L



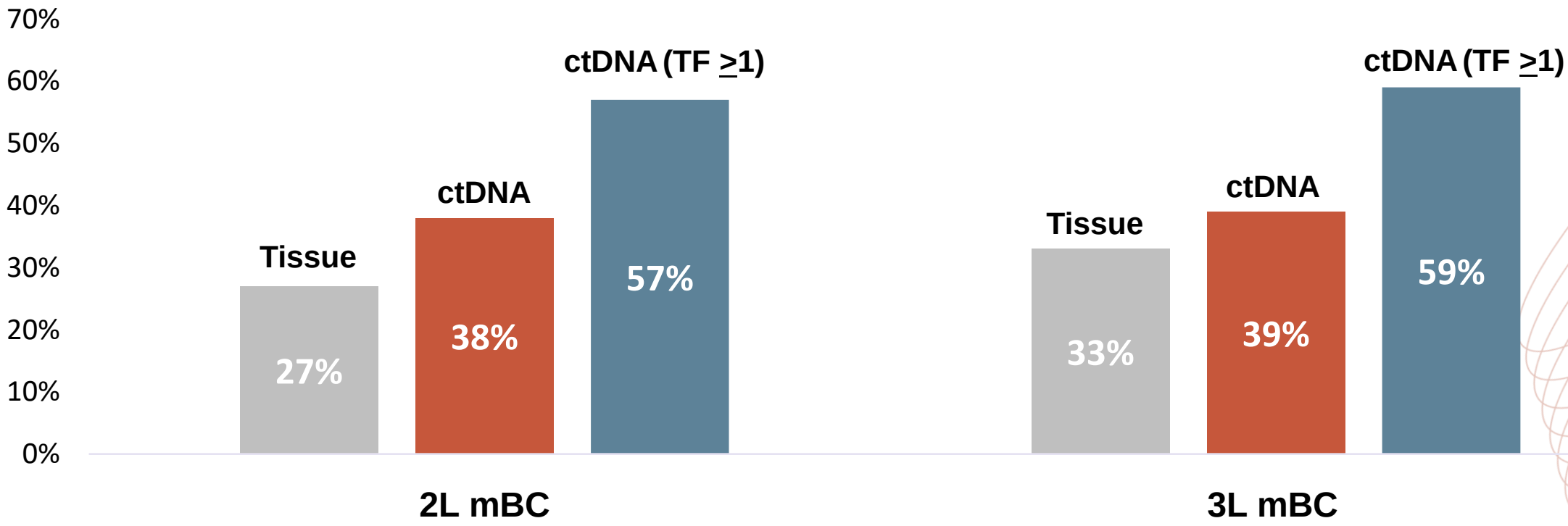
3L

1L, first line; 2L, second line; 3L, third line; AI, aromatase inhibitor; AKT, protein kinase B; BC, breast cancer; *BRCA1/2*, breast cancer gene 1/2; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ctDNA, circulating tumor DNA; *ESR1*, oestrogen receptor 1; ET, endocrine therapy; mBC, metastatic breast cancer; *mut*, mutation; *PALB2*, partner and localizer of *BRCA2*; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; *PTEN*, phosphatase and tensin homolog; Tx, treatment.

1.Jeselsohn R, et al. *Clin. Cancer Res.* 2014;20:1757–1767; 2.Allouchery V, et al. *Breast Cancer Res.* 2018;20:40; 3.Schiavon G, et al. *Sci. Transl. Med.* 2015;7(313):313ra182; 4.Brett JO, et al. *Breast Cancer Res.* 2021;23(1):85; 5.Toy W, et al. *Nat. Genet.* 2013;45(12):1439–1445; 6.Bidard FC, et al. *J. Clin. Oncol.* 2022;40:3246–3256; 7.Jhaveri K, et al. *Ann. Oncol.* 2023;34(suppl_2):S334–S390; 8.Lin N, et al. *Ann. Oncol.* 2023;34(suppl_2):S334–S390; 9.Bhave MA, et al. *Breast Cancer Res. Treat.* 2024; 10.Lee N, et al. *Int. J. Mol. Sci.* 2020;21(22):8807.

ESR1 MUTATIONS ARE SUBCLONAL AND HETEROGENOUS WITHIN THE TUMOR[1,2]

ESR1-mut prevalence rate in mBC by line in tissue and liquid biopsies[3]



2L, second line; 3L, third line; ctDNA, circulating tumor DNA; *ESR1*, estrogen receptor 1; mBC, metastatic breast cancer; mut, mutation; TF, tumor fraction.

1. Dustin D, et al. *Cancer*. 2019.1;125(21):3714-3728. 2. Burstein HJ, et al. *J Clin Oncol.* 2023;41(18):3423-3425. 3. Adapted from: Bhave MA, et al. *Breast Cancer Res Treat*. 2024;207:599-609.

WHEN TO TEST

Patients should get tested for *ESR1*-mut at each progression on their metastatic treatment, if not detected previously.[1-5]

ESMO

European Society of Medical Oncology[1,2]

- NGS of plasma or tissue biopsy should be carried out after resistance to ET in order to optimize the likelihood of **detecting *ESR1*-mut**

NCCN[3]

National Comprehensive Cancer Network® (NCCN®)[3,4]

- **Detection of *ESR1*-mut:** NGS or PCR (ctDNA preferred)
- Given the acquired nature of *ESR1*-mut during metastatic breast cancer treatment, **primary archived breast cancer tissue should NOT be used** as a source of tumor tissue for *ESR1*-mut testing

ASCO

American Society of Clinical Oncology (ASCO)[5]

- **Detection of *ESR1*-mut:** Blood-based ctDNA is preferred owing to greater sensitivity
- *ESR1*-mut develop in response to selection pressure during ET and are typically undetectable in the primary tumor
- Patients whose tumor or ctDNA tests remain *ESR1*-WT may warrant re-testing at subsequent progression(s) to determine if an *ESR1*-mut has arisen

ctDNA, circulating tumor DNA; *ESR1*, estrogen receptor 1; ET, endocrine therapy; mBC, metastatic breast cancer; mut, mutation; NGS, next generation sequencing; PCR, polymerase chain reaction; WT, wild-type.

1. Mosele MF, et al. *Ann Oncol*. 2024;35(7):588-606; 2. Pascual J, et al. *Ann Oncol.* 2022;33(8):750-768; 3. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.3.2025. © *National Comprehensive Cancer Network*, Inc. 2024. All rights reserved. Accessed March 18, 2025. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way; 4. Gradishar WJ, et al. *J Natl Compr Canc Netw*. 2023;21(6):594-608; 5. Burstein HJ, et al. J Clin Oncol. 2023;41(18):3423-3425.

CLINICAL TAKEAWAYS

CLINICAL TAKEAWAYS

- Elacestrant provides clinically meaningful improvements in PFS for patients with ER+/HER2- mBC who received at least 12 months of ET + CDK4/6i in 1st line and whose tumors harbor *ESR1*-mut
- The PFS benefit associated with elacestrant was consistent across clinically relevant subgroups including tumors harboring coexisting *ESR1* and *PIK3CA*-mut, indicating that disease progression after ET + CDK4/6i in this subgroup may remain ER-driven
- Safety analyses demonstrated that elacestrant had a manageable safety profile similar to other ETs and without evidence of some of the toxicities associated with other drug classes, such as CDK4/6i and PI3K/AKT/mTOR inhibitors
- *ESR1*-mut testing should be done at 1st line progression via liquid biopsy due to disease subclonality; if negative, repeat at each progression. Archival tissue should not be used for testing due to the acquired nature of *ESR1*-mut

AKT, protein kinase B; CDK4/6i, cyclin dependent kinase 4/6 inhibitor; ER, estrogen receptor; *ESR1*, estrogen receptor 1; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; mTOR, mammalian target of rapamycin; PI3K, Phosphoinositide 3-kinases.

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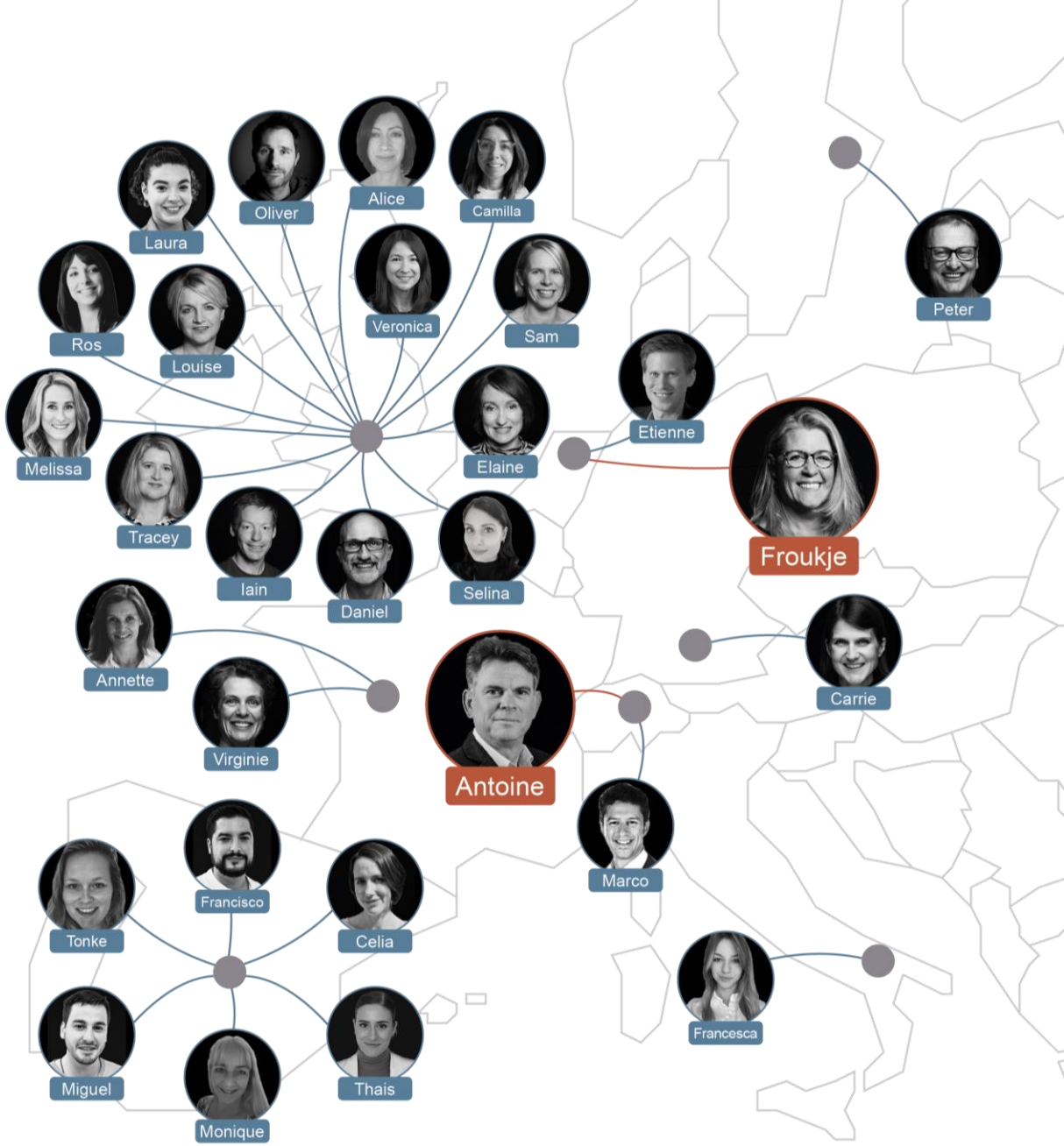

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