Medical Affairs

BY COR2ED

Brought to you by COR2ED Medical Affairs in Collaboration with Menarini Stemline

MENARINI group

Stemline®
A Menarini Group Company

MED--ELA-2400054

CLINICAL TOPIC NEWSLETTER

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

NOVEMBER 2024

This programme has been sponsored by Menarini Stemline and is intended for healthcare professionals only MED--ELA-2400054

ACKNOWLEDGEMENT AND DISCLOSURES

This programme has been sponsored by Menarini Stemline and is intended for healthcare professionals only.

Expert disclosures:

- Dr Virginia Kaklamani has received financial support/sponsorship for research support, consultation, or speaker fees from the following companies:

  Menarini Stemline, Genetech, Lilly, Astrazeneca, Gilead, Novartis, Tersera, Daiichi, and is on the speakers' bureau for Astrazeneca, Lilly, Novartis and Gilead. She has also received funding from Eisai.

TREATMENT LANDSCAPE IN ER+/HER2- MBC

CURRENT FACTORS AFFECTING TREATMENT CHOICES FOR PATIENTS WITH ER+/HER2- MBC

Disease characteristics

ER+/HER2- mBC is a complex, heterogeneous disease[1]

As disease progresses, most tumors develop endocrine resistance[2]

Patient characteristics

Key factors:
performance status, imminent organ failure, menopausal status, prior lines of therapy[1]

Genomic landscape

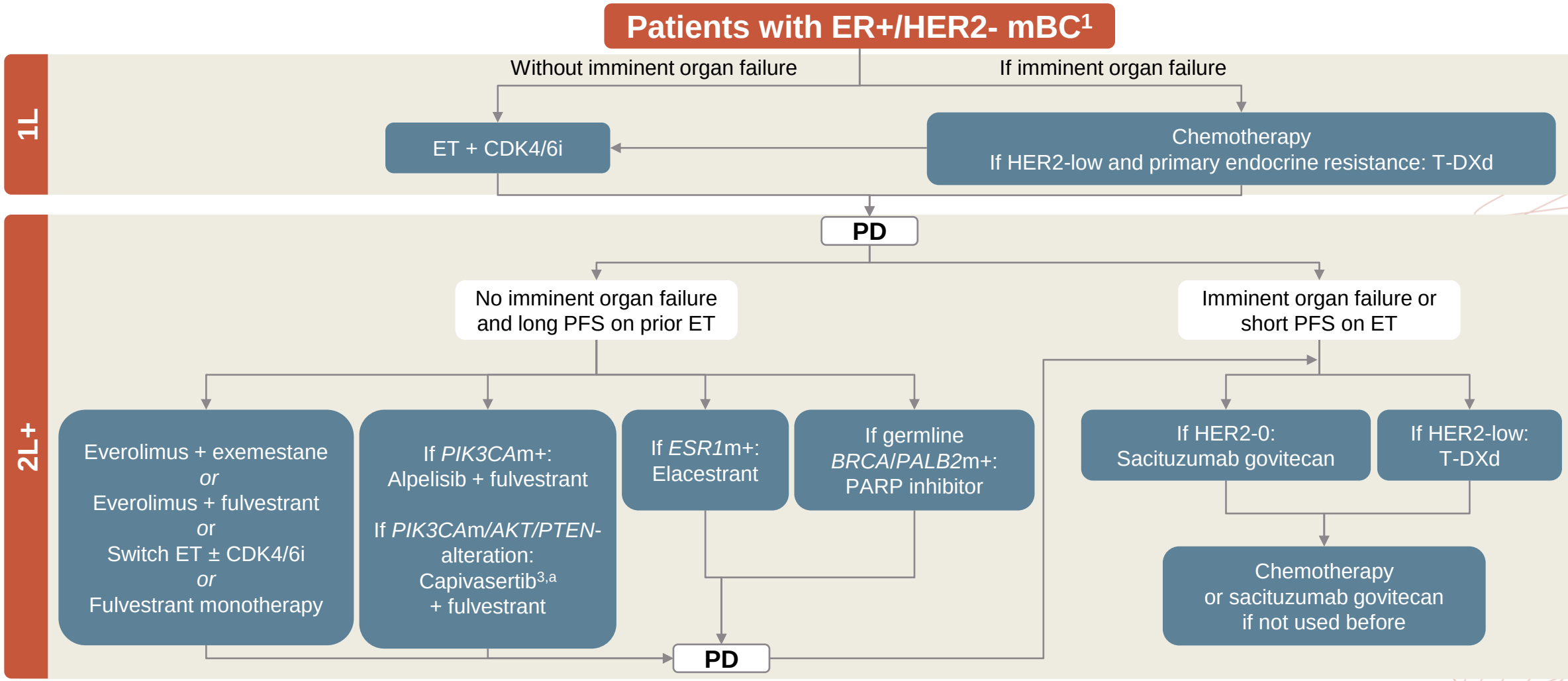
Molecular mechanisms underlying endocrine sensitivity and resistance are multifold[1-3]

Key biomarkers:
PIK3CA, ESR1, BRCA/PALB2[1-3]

mBC, Metastatic breast cancer; *BRCA*, BReast CAncer gene; ER, estrogen receptor; *ESR1*, estrogen receptor 1; HER2, human epidermal growth factor receptor 2; *PALB2*, partner and localizer of BRCA2; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

1. Gennari A, et al. Ann Oncol. 2021;32(12):1475-95. 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

TREATMENT CHOICES FOR PATIENTS WITH ER+/HER2- MBC ARE DRIVEN BY ENDOCRINE SENSITIVITY STATUS AND BIOMARKERS[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, et al. Clin Cancer Res. 2024; Online ahead of print; 3. Truqap (capivasertib) SmPC 2024

EMERALD TRIAL OVERVIEW

EMERALD: PHASE 3 TRIAL OF ELACESTRANT VS SOC ENDOCRINE THERAPY

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

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

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

[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.
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)

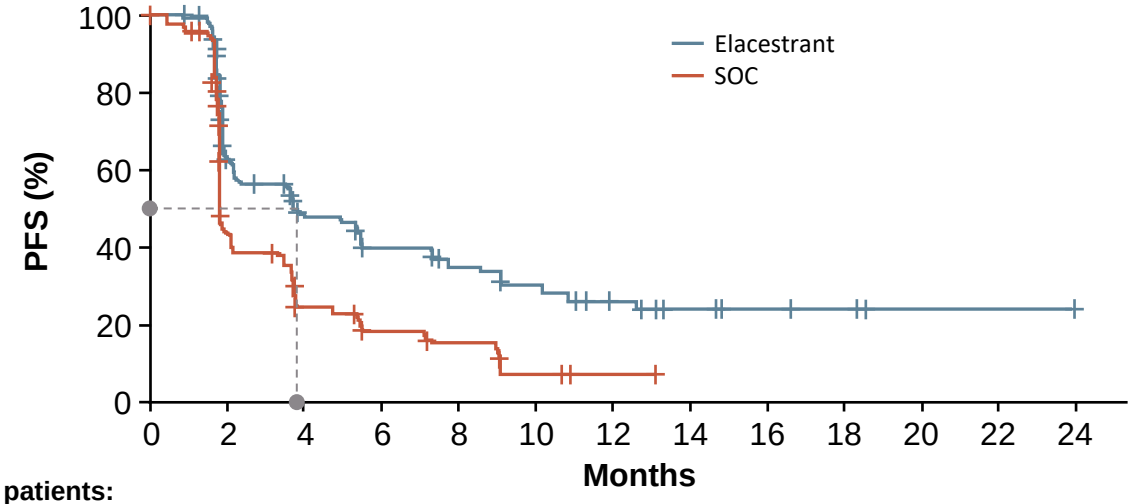
[a] Includes lung, liver, brain, pleural, and peritoneal involvement

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 PROVIDES A 45% REDUCTION IN RISK OF PROGRESSION OR DEATH VS SOC IN PATIENTS WITH *ESR1*-MUT

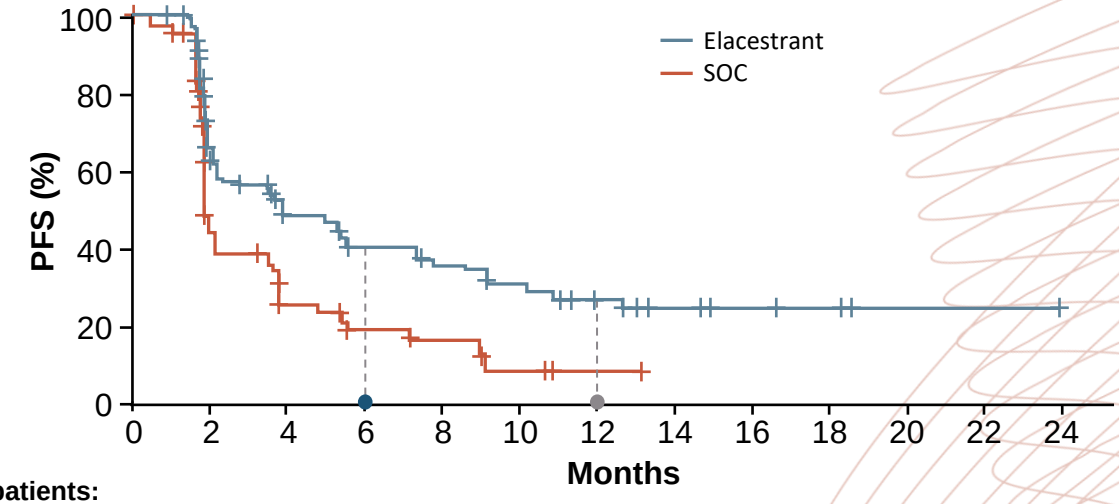
PFS in patients with *ESR1*-mut: Elacestrant vs SOC



No. of patients:

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)
mPFS, months	**3.8**	**1.9**
HR [95% CI]	**0.55** [0.39-0.77]	
p-value	0.0005	



No. of patients:

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**	**19.1**
12-mo PFS, % [95% CI]	**26.8**	**8.2**
HR [95% CI]	**0.55** [0.39-0.77]	
p-value	0.0005	

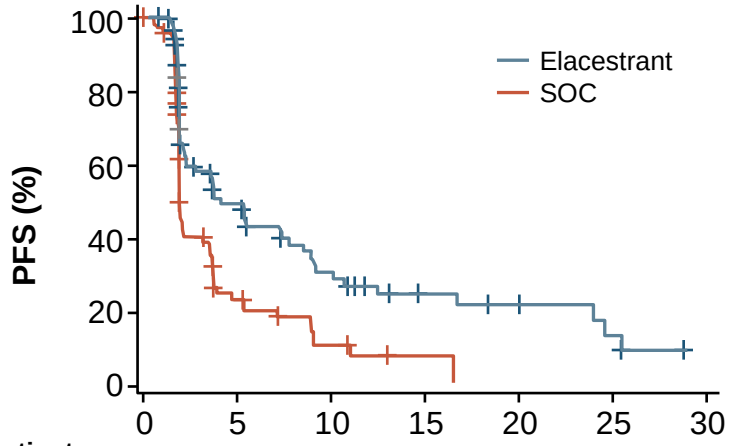
Exploratory analysis; patients without ESR1-mut: n=250, 52% of the ITT population
CI, confidence interval; *ESR1*, estrogen receptor 1; HR, hazard ratio; ITT, intention to treat; mo, months; mut, mutation; (m)PFS, (median) progression-free survival; SOC, standard of care

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

EMERALD TRIAL SUBGROUP ANALYSIS

EMERALD: DURATION OF PRIOR ET + CDK4/6 INHIBITOR THERAPY IS POSITIVELY ASSOCIATED WITH mPFS IN PATIENTS WITH *ESR1*-MUT

≥6 months of prior ET + CDK4/6i[a]

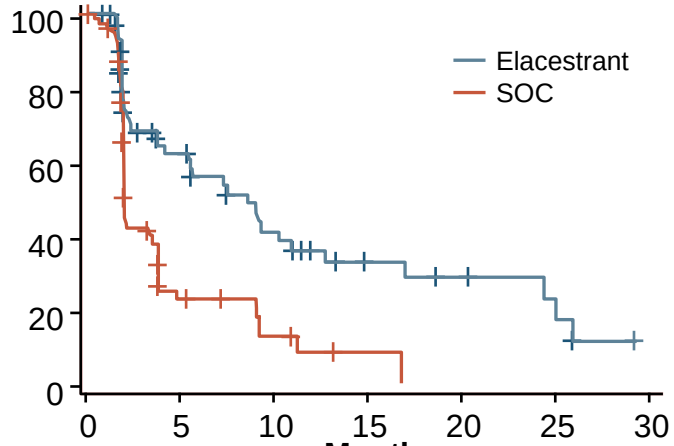


No. of patients:

Elacestrant	103	50	33	25	20	16	11	9	8	7	6	5	5	1	1	0
SOC	102	34	16	11	9	5	2	1	1	0						

	Elacestrant (n=103)	SOC (n=102)
mPFS, mo [95% CI]	**4.14** [2.20-7.79]	**1.87** [1.87-3.29]
12-mo PFS, % [95% CI]	**26.02** [15.12-36.92]	**6.45** [0.00-13.65]
HR [95% CI]	**0.517** [0.361-0.738]	

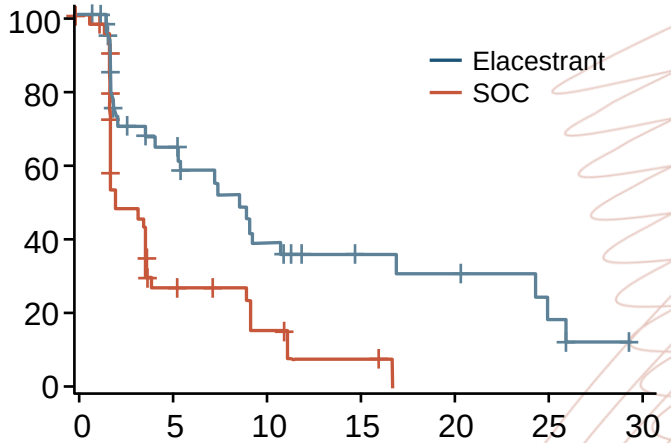
≥12 months of prior ET + CDK4/6i[a]



Elacestrant	78	42	31	24	20	16	11	9	8	7	6	5	5	1	1	0
SOC	81	26	12	10	9	5	2	1	1	0						

	Elacestrant (n=78)	SOC (n=81)
8.61 [4.14-10.84]	**1.91** [1.87-3.68]	
35.81 [21.84-49.78]	**8.39** [0.00-17.66]	
0.410 [0.262-0.634]		

≥18 months of prior ET + CDK4/6i[a]



Elacestrant	55	30	23	18	16	12	8	8	7	6	6	5	5	1	1	0
SOC	56	21	9	8	7	4	1	1	1	0						

	Elacestrant (n=55)	SOC (n=56)
8.61 [5.45-16.89]	**2.10** [1.87-3.75]	
35.79 [19.54-52.05]	**7.73** [0.00-20.20]	
0.466 [0.270-0.791]		

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

CDK4/6(i), cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; *ESR1*, estrogen receptor 1; ET, endocrine therapy; HR, hazard ratio; (m)PFS, (median) progression-free survival; mut, mutation; SOC, standard of care

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

IN TUMOURS WITH RETAINED ENDOCRINE-SENSITIVITY (LONGER EXPOSURE TO PRIOR ET + CDK4/6i), *ESR1* MUTATIONS ARE A MAIN DRIVER OF DISEASE

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** [0.262–0.634]
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]

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

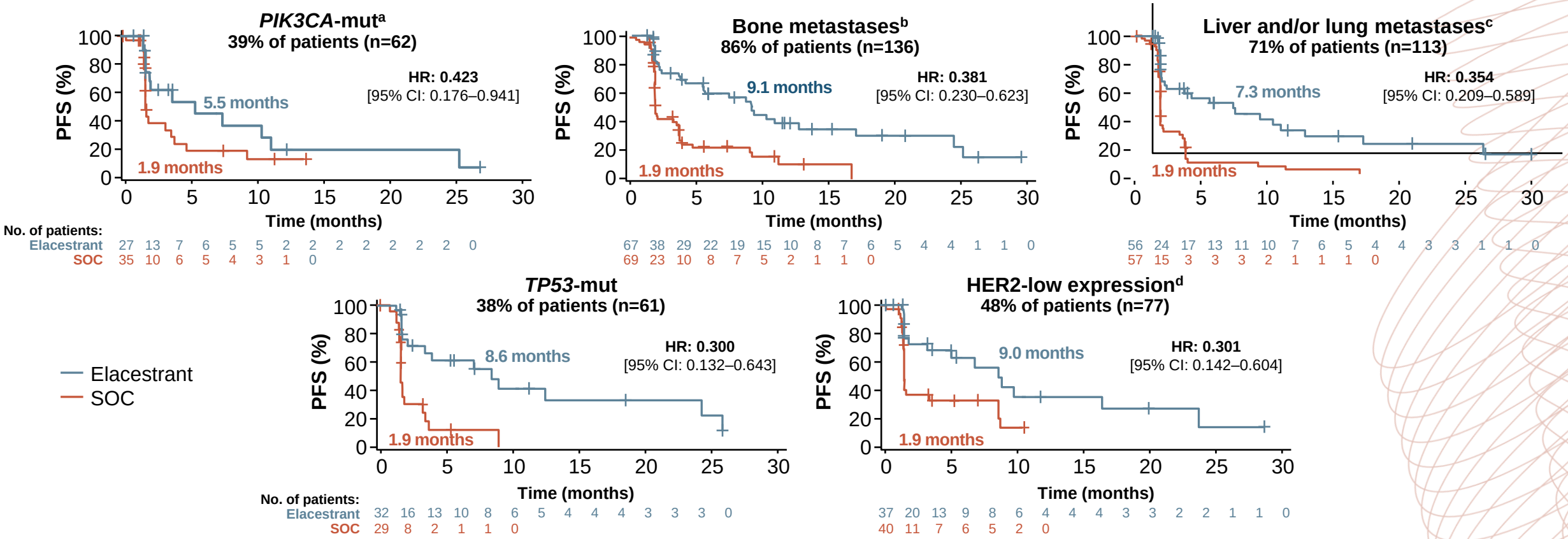
[a] Includes E545K, H1047R, E542K, and others; [b] 85% of patients had bone and other sites of metastases (30% of these patients had no liver or lung involvement); [c] 55% of patients had liver and other sites of metastases (10% of these patients had no lung or bone involvement); 25% of patients had 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

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, tumour protein p53

Bardia A, et al. Clin Cancer Res. 2024; Online ahead of print

IN TUMOURS WITH RETAINED ENDOCRINE-SENSITIVITY (LONGER EXPOSURE TO PRIOR ET + CDK4/6i), *ESR1* MUTATIONS ARE A MAIN DRIVER OF DISEASE

PFS in patients with ≥12 months of prior ET + CDK4/6i and *ESR1*-mut



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. CDK4/6, cyclin dependent kinase 4/6; CI, confidence interval; *ESR1*, estrogen receptor 1; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; mut, mutation; PFS, progression-free survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase; SOC, standard of care; TP53, tumor protein p53.

Bardia A, et al. Clin Cancer Res. 2024; Online ahead of print

IN TUMOURS WITH RETAINED ENDOCRINE-SENSITIVITY (LONGER EXPOSURE TO PRIOR ET + CDK4/6i), *ESR1* MUTATIONS ARE A MAIN DRIVER OF DISEASE

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** [0.262-0.634]
<3 metastatic sites[a]	**52** (82)	**9.0**	**1.9**	**0.41** [0.23-0.75]
≥3 metastatic sites[a]	**33** (53)	**10.8**	**1.8**	**0.31** [0.12-0.79]

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

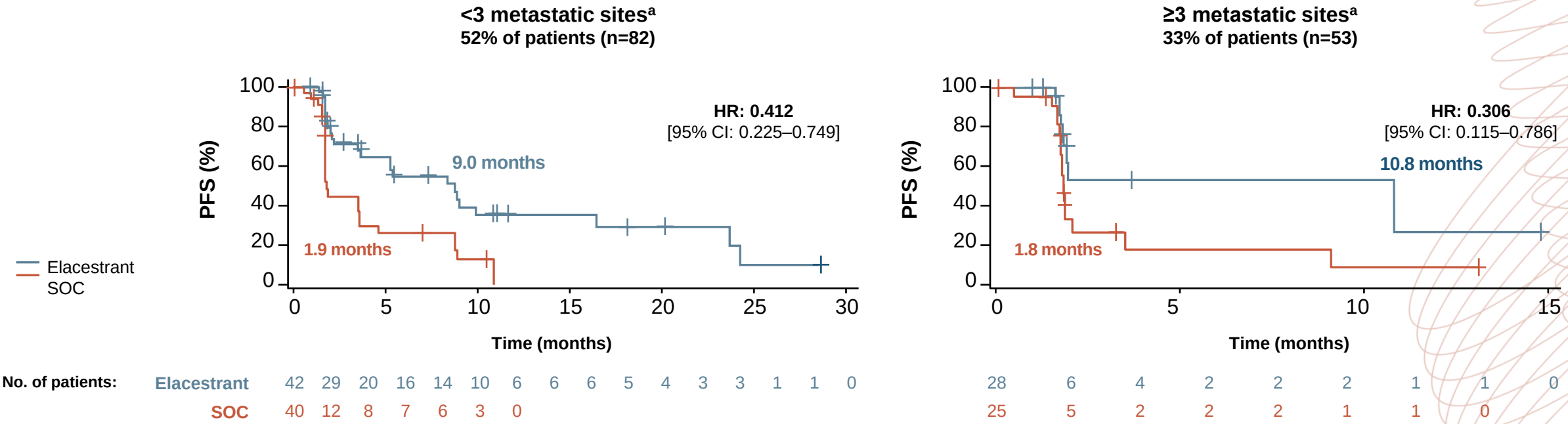
[a] The number of metastatic sites was available for 135 of 159 patients with ESR1-mutated tumours and prior ET+CDK4/6i ≥12 months

CDK4/6, cyclin dependent kinase 4/6; CI, confidence interval; *ESR1*, estrogen receptor 1; ET, endocrine therapy; HR, hazard ratio; mut, mutation; PFS, progression-free survival; SOC, standard of care

Bardia A, et al. Clin Cancer Res. 2024; Online ahead of print

IN TUMOURS WITH RETAINED ENDOCRINE-SENSITIVITY (LONGER EXPOSURE TO PRIOR ET + CDK4/6i), *ESR1* MUTATIONS ARE A MAIN DRIVER OF DISEASE

PFS in patients with ≥12 months of prior ET + CDK4/6i and *ESR1*-mut



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] The number of metastatic sites was available for 135 of 159 patients with ESR1-mutated tumours and prior ET+CDK4/6i ≥12 months

CDK4/6, cyclin dependent kinase 4/6; CI, confidence interval; *ESR1*, estrogen receptor 1; ET, endocrine therapy; HR, hazard ratio; mut, mutation; PFS, progression-free survival; SOC, standard of care

Bardia A, et al. Clin Cancer Res. 2024; Online ahead of print

IN TUMOURS WITH RETAINED ENDOCRINE-SENSITIVITY (LONGER EXPOSURE TO PRIOR ET + CDK4/6i), *ESR1* MUTATIONS ARE A MAIN DRIVER OF DISEASE

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** [0.262-0.634]
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]

90% of patients had one or more *ESR1* mutations detected in the three hot spots presented (D538G, Y537S, and/or Y537N)

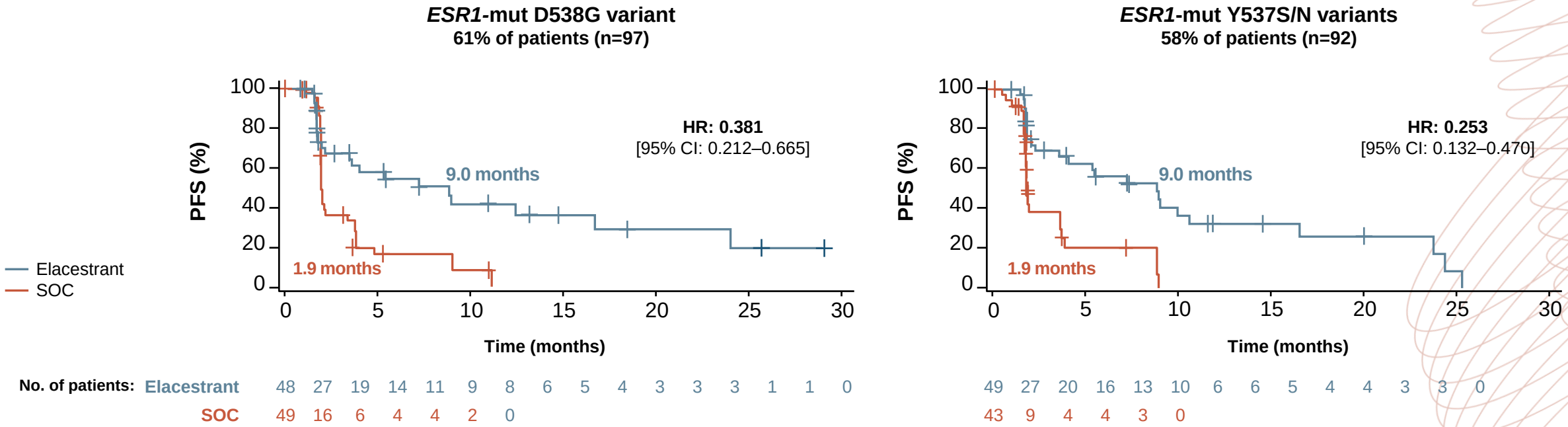
This was an exploratory analysis. Post-hoc analysis results are observational in nature. There was no prespecified statistical procedure controlling for type 1 error

CDK4/6, cyclin dependent kinase 4/6; CI, confidence interval; ER, endocrine receptor; *ESR1*, estrogen receptor 1; ET, endocrine therapy; mut, mutation; PFS, progression-free survival; SOC, standard of care

Bardia A, et al. Clin Cancer Res. 2024; Online ahead of print

IN TUMOURS WITH RETAINED ENDOCRINE-SENSITIVITY (LONGER EXPOSURE TO PRIOR ET + CDK4/6i), *ESR1* MUTATIONS ARE A MAIN DRIVER OF DISEASE

PFS in patients with ≥12 months of prior ET + CDK4/6i and *ESR1*-mut



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

CDK4/6, cyclin dependent kinase 4/6; CI, confidence interval; *ESR1*, estrogen receptor 1; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; mut, mutation; PFS, progression-free survival; SOC, standard of care

Bardia A, et al. Clin Cancer Res. 2024; Online ahead of print

EMERALD: IN THE OVERALL POPULATION, THE MAJORITY OF ADVERSE EVENTS THAT OCCURRED WERE GRADE 1 OR 2[1]

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	NA
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; Online ahead of print; 2. Stemline. ORSERDU (elacestrant) Summary of Product Characteristics. 2024

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

BREAST CANCER IS A DYNAMIC DISEASE WHERE MUTATIONS MAY EMERGE OVER THE COURSE OF 1L 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]

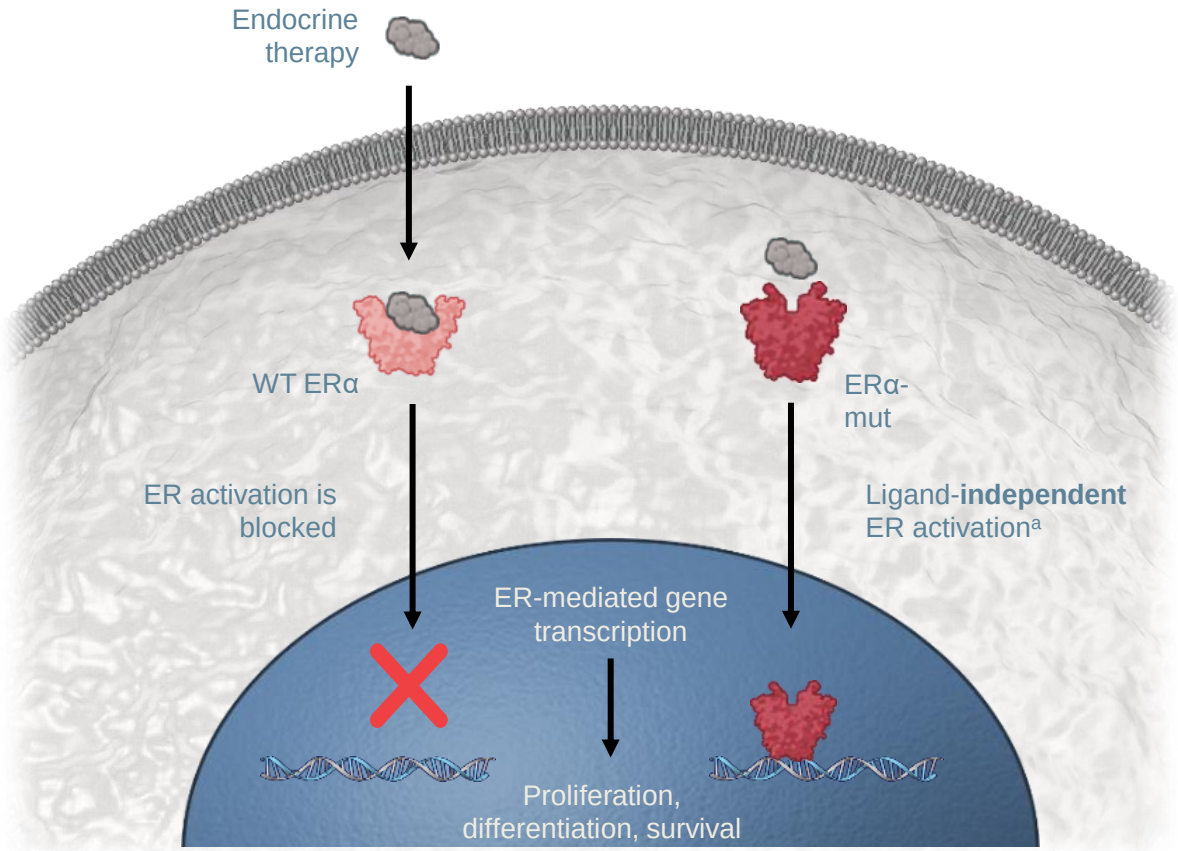
… drive treatment decisions

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

ESR1 MUTATIONS ARE KEY DRIVERS OF RESISTANCE TO ESTABLISHED ENDOCRINE THERAPIES



- ETs exert their anti-tumour activity by binding to the ligand-binding pocket of the ER and inhibiting the activation of downstream targets[1,2]
- By altering the ligand-binding domain, *ESR1* mutations can also cause endocrine resistance to ETs[1,2]

[a] Without the need for estrogen binding

AI, aromatase inhibitor; ER, estrogen receptor; ET, endocrine therapy; LBD, ligand-binding domain; mut, mutant; NGS, next-generation sequencing; NR, nuclear receptor C-terminal domain; SERD, selective estrogen receptor degrader; SERM, selective estrogen receptor modulator; WT, wild-type

Figure adapted from: 1. Bardia A, et al. N Engl J Med. 2018;379:1946–53; 2. Brett JO. Breast Cancer Res. 2021;23:85.

LONGER EXPOSURE TO ET IN MBC INCREASES THE CHANCE OF DEVELOPING *ESR1*-MUT DURING TREATMENT, EMERGING IN UP TO 40% OF PATIENTS[1-10]

Early breast cancer[1-3,5,7] — **Advanced / metastatic breast cancer**[2-9]

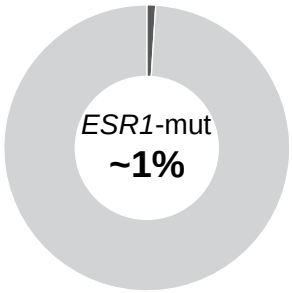
Adjuvant Tx

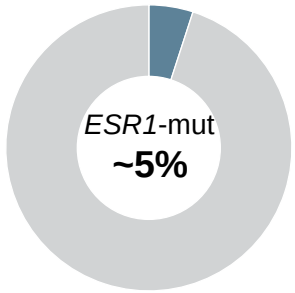
First progression during / after adjuvant therapy

1L mBC Tx
AI + CDK4/6i

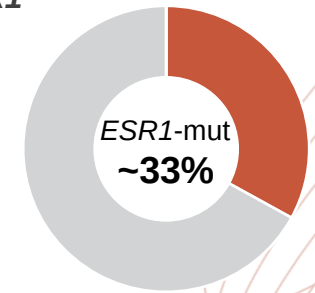
Progression

Tissue biopsy to confirm breast cancer and testing for **intrinsic mutations**
- ***PIK3CA/AKT/PTEN***
- ***BRCA1/2, PALB2***

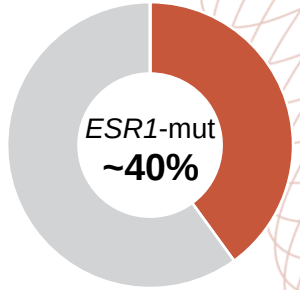




Liquid biopsy
Testing for **acquired mutations**
- ***ESR1***



2L



3L

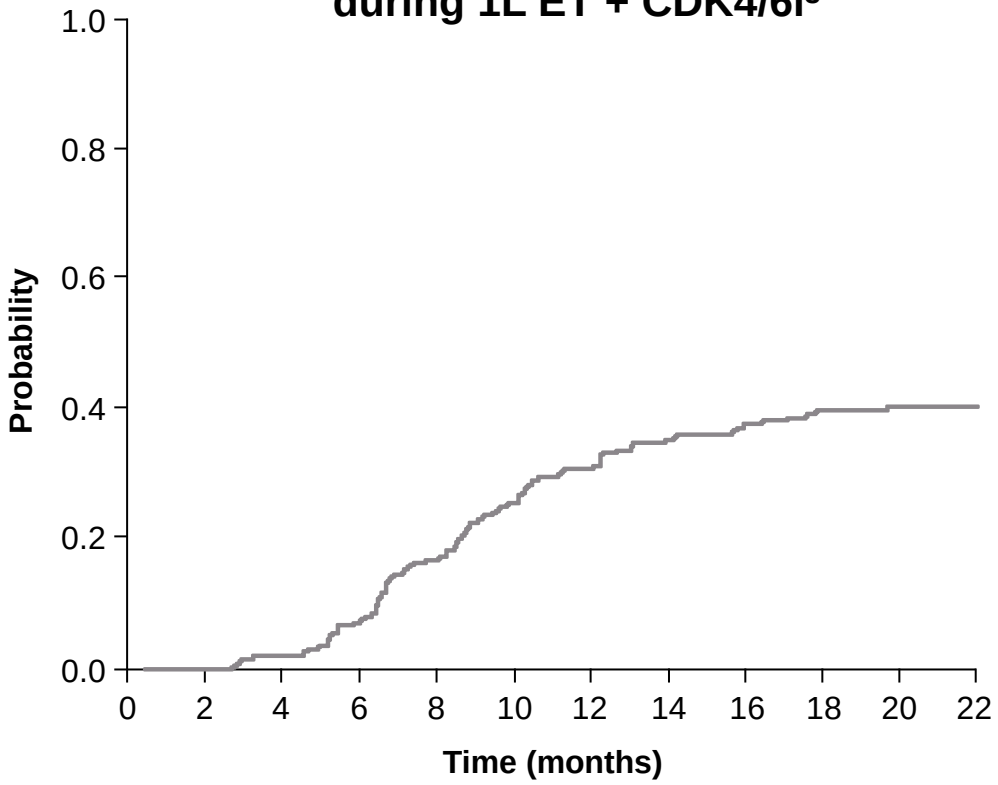
As *ESR1* mutations occur almost exclusively after ET in the mBC setting,[5] testing for *ESR1*-mut should occur at each progression if not detected previously[10-12]

1L, first line; 2L, second line; 3L, third line; *ESR1*, estrogen receptor 1; ET, endocrine therapy; mBC, metastatic breast cancer; mut, mutation; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

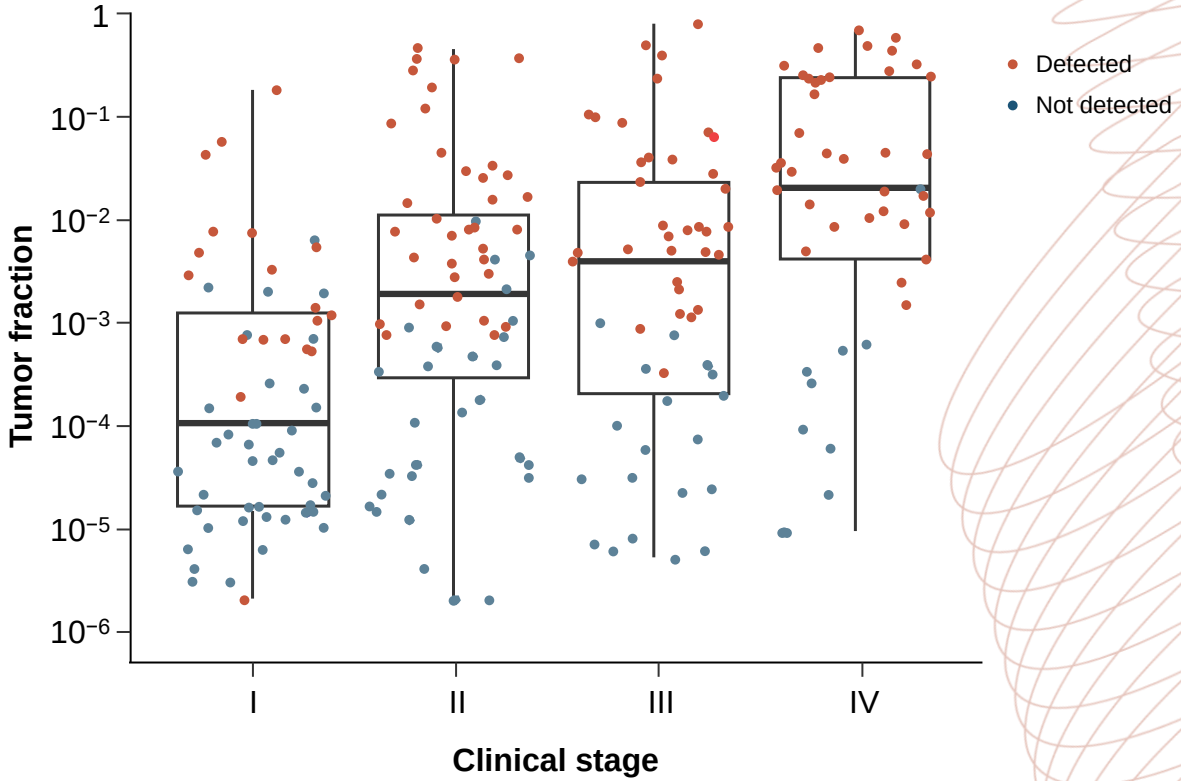
Modified from: 1. Jeselsohn R, et al. Clin Cancer Res. 2014;20:1757-67; 2. Allouchery V, et al. Breast Cancer Res. 2018;20:40; 3. Schiavon G, et al. Sci Transl Med. 2015;7:313ra182; 4. Brett JO, et al. Breast Cancer Res. 2021;23:85; 5. Toy W, et al. Nat Genet. 2013;45:1439-45; 6. Bidard FC, et al. J Clin Oncol. 2022;40:3246-56; 7. Jhaveri et al, Annals of Oncology. 2023;34(suppl_2):S334-S390; 8. Lin, et al, Annals of Oncology. 2023;34(suppl_2):S334-S390; 9. Bhave, et al, SmBCS 2023; Abstract PO2-1605; 10. Lee N, et al Int J Mol Sci. 2020;21:8807; 11. Gennari A, et al. Ann Oncol. 2021;32:1475-95; 12. Burstein HJ, et al J Clin Oncol. 2023;41:3423-5

ESR1-MUT CAN BE IDENTIFIED IN ctDNA AT PROGRESSION[1]
ctDNA TUMOUR ALLELE FRACTION IS ASSOCIATED WITH CANCER AGGRESSIVENESS[2]

ESR1-mut cumulative incidence during 1L ET + CDK4/6i[3]



ctDNA tumour fraction by cancer clinical stage[2]

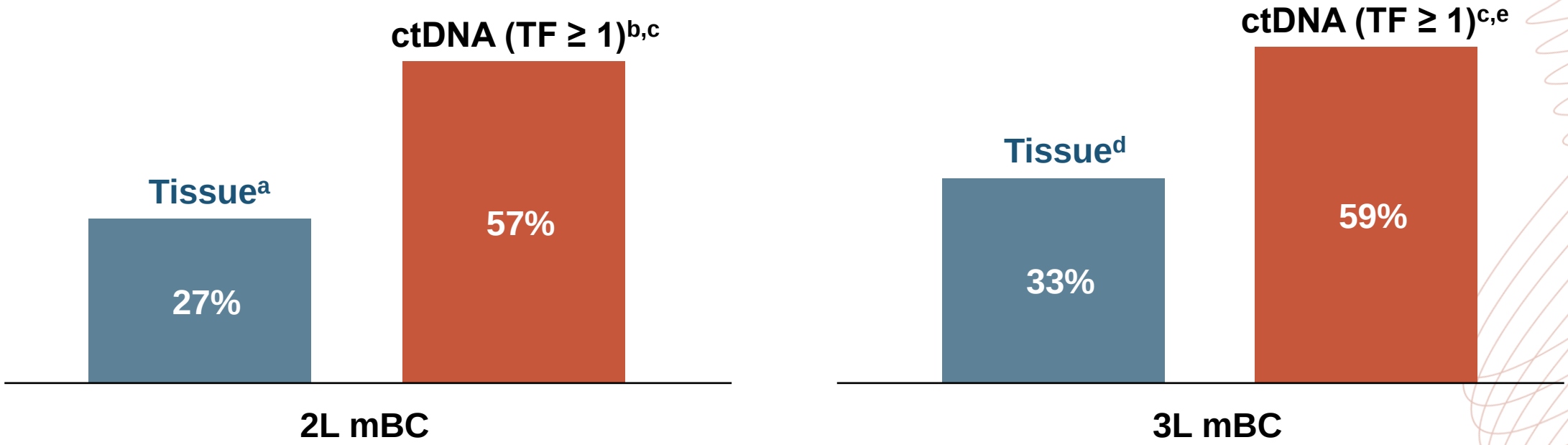


CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ctDNA, circular tumor DNA; *ESR1*, estrogen receptor 1; ET, endocrine therapy; L, line; mut, mutation.

1. Schiavon G, et al. Sci Transl Med. 2015;7:313ra182; 2. Bredno J, et al. Am J Pathol. 2022;192:1368–1378; 3. Adapted from Bidard F-C, ESMO 2019; Poster 307PD.

NOT ALL *ESR1* MUTATIONS WILL BE DETECTED IN A TISSUE BIOPSY. BLOOD-BASED ctDNA IS A PREFERRED TESTING FOR *ESR1*-MUT DUE TO GREATER SENSITIVITY[1,2]

***ESR1*-mut prevalence rate by line in tissue and liquid biopsy[3]**



If *ESR1* mutations are not found when testing on tissue biopsy, ctDNA in liquid biopsy is recommended.[2]

Total sample size: [a] n=269; [b] n=104; [c] ctDNA (TF ≥1%) showed a markedly higher prevalence of any of the genomic alterations assessed. ctDNA (TF <1%) for 2L mBC was 16.1%, and for 3L mBC was 17.2%; ctDNA (regardless of TF) for 2L mBC was 37.6%, and for 3L mBC was 38.7%; [d] n=216; [e] n=61

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

1. Dustin D, et al. Cancer. 2019.1;125:3714-28; 2. Burnstein HJ, et al. J Clin Oncol. 2023;41:3423-5; 3. Adapted from Bhave MA, et al. Breast Cancer Res Treat. Published online: 14 June 2024

ESMO, NCCN AND ASCO RECOMMEND TESTING FOR *ESR1* MUTATIONS AT EACH PROGRESSION, PREFERABLY IN ctDNA, IF NOT DETECTED PREVIOUSLY[1-5]

ESMO[1]

Blood ctDNA or Tissue[1]

- NGS plasma or tissue biopsy

NCCN[3,4]

Blood ctDNA *or Tissue*[3,4]

- NCCN recommends evaluating *ESR1* mutation status using NGS or PCR blood or tissue biopsy[3]
- **NCCN does not recommend testing with primary archived tissue given the acquired nature of *ESR1* mutations during mBC treatment[4]**

ASCO[5]

Blood ctDNA (preferred) or Tissue[5]

- **Testing with a certified assay should be performed at each progression**, on blood or tissue
- **Blood-based ctDNA is preferred** owing to greater sensitivity
- ***ESR1* mutations** develop in response to selection pressure during treatment and are **typically undetectable in the primary tumor**
- Patients whose tumour or ctDNA tests remain ***ESR1* wild-type may warrant retesting at subsequent progression(s)** to determine if an *ESR1* mutation has arisen

ASCO, American Society of Clinical Oncology; ctDNA, circular tumour DNA; ESMO, European Society for Medical Oncology; ESR1, estrogen receptor 1; NCCN, National Comprehensive Cancer Network; PCR, polymerase chain reaction

1. Mosele MF, et al. Ann Oncol. 2024;35:588-606; 2. Pascual J, et al. Ann Oncol. 2022;33:750-68; 3. National Comprehensive Cancer Network. Breast Cancer (Version 4.2024); 4. Gradishar WJ, et al. J Natl Compr Canc Netw. 2023;21:594-608; 5. Burstein HJ, et al. J Clin Oncol. 2023;41:3423-5

CONCLUSION

KEY TAKEAWAYS

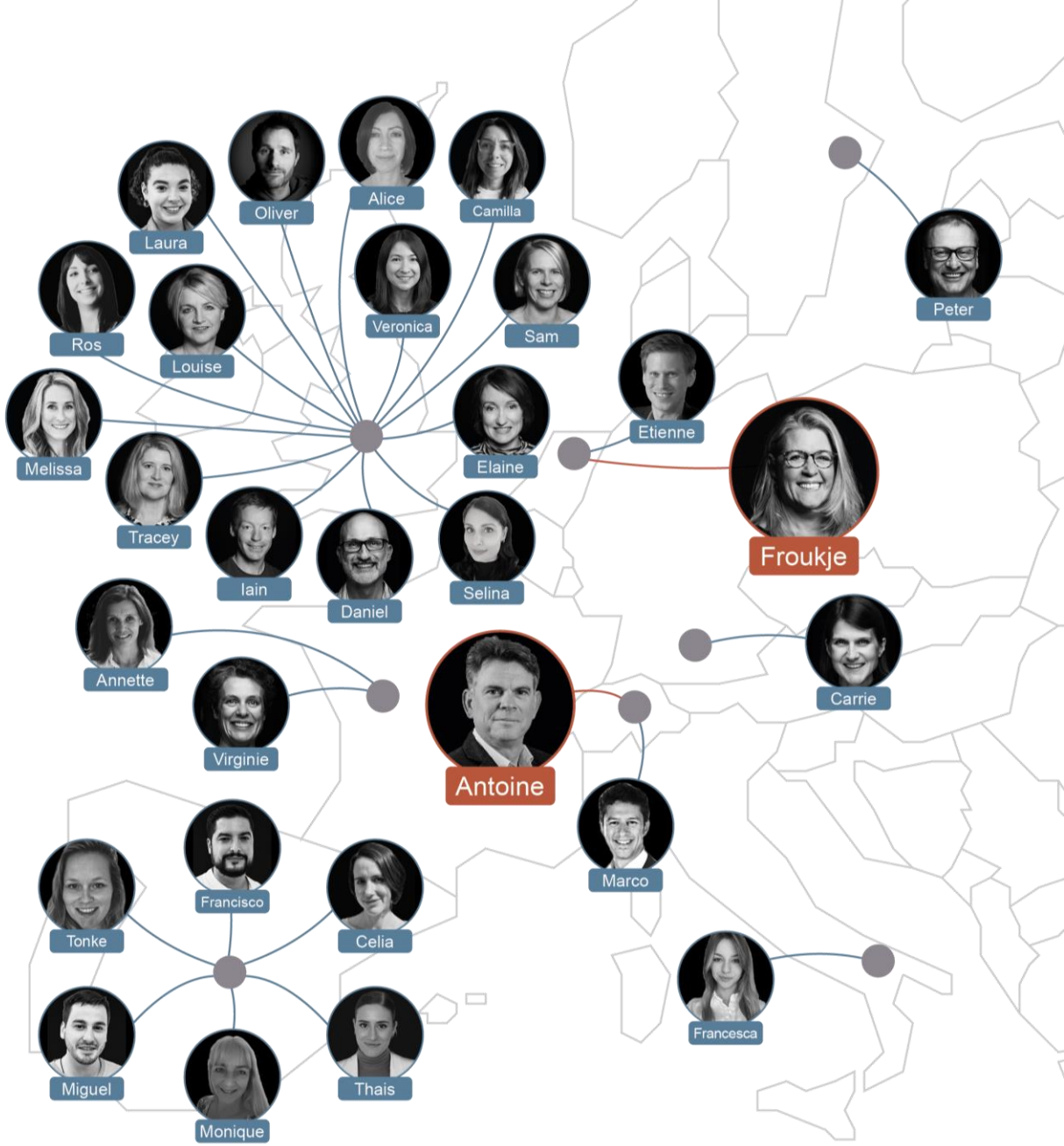
- Treatment choices for patients with ER+/HER2- mBC are driven by endocrine sensitivity status and biomarkers[1,2]
- Elacestrant is indicated for patients with *ESR1*-mut tumours based on its efficacy and safety profiles[3,4]
- Longer duration of prior ET + CDK4/6i is a surrogate for endocrine sensitivity to elacestrant in *ESR1*-mut tumors[2,3,5]
- In tumours retaining endocrine-sensitivity and coexisting *PIK3CA* and *ESR1* mutations, elacestrant monotherapy can be a good option before PI3K/AKT inhibitors, as data suggest the ER pathway may drive disease progression[2]
- *ESR1*-mut emerge over time in up to 40% of patients after initial endocrine therapy in mBC[6-10]
- Testing for *ESR1*-mut should occur at each progression on ET if not detected previously, due to increasing chances of finding it[11-14]
- *ESR1*-mut are subclonal; therefore, not always detected with tissue biopsy. Blood-based ctDNA is considered the preferred testing methodology for *ESR1*-mut[14,15]
- Archival tissue from primary tumour should NOT be used to identify *ESR1*-mut, as *ESR1*-mut develop mainly during 1L metastatic treatment[16]

AKT, protein kinase B; mBC, Metastatic breast cancer; CDK4/6, cyclin-dependent kinase 4/6; ctDNA, circulating tumor DNA; ER, estrogen receptor; *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

1. Gennari A, et al. Ann Oncol. 2021;32(12): 1475-1495. ESMO Metastatic Breast Cancer Living Guidelines. V1.1 May 2023; 2. Bardia, et al. Clin Cancer Res. 2024; Online ahead of print;
3. Bidard FC, et al. J Clin Oncol. 2022;40:3246-56; 4. Orserdu (elacestrant) SmPC 2023. 5. Bardia A, et al. SABCS 2022. Abstract GS3–01; 6. Brett JO, et al. Breast Cancer Res. 2021;23:85;
7. Bidard et al. Lancet Oncol. 2022;23:1367-77; 8. Santiago Novello RG, et al. ESMO Open. 2023;8(suppl 4):104409. Abstract 220P; 9. Lin et al. Annals of Oncology. 2023;34 (suppl_2): S334-S390; 10. Bhave MA, et al. Breast Cancer Res Treat. Published online: 14 June 2024; 11. Jeselsohn R, et al. Clin Cancer Res. 2014;20:1757-67; 12. Jeselsohn R, et al. Cancer Cell. 2018;33:173-86;
13. Allouchery V et al. Breast Cancer Res. 2018;20:40. 14. Burstein HJ, et al J Clin Oncol. 2023;41:3423-5; 15. Turner NC, et al. Lancet Oncol. 2020;21:1296-1308;
16. Gradishar WJ, et al. NCCN Guidelines® Insights: Breast Cancer, Version 4.2023. J Natl Compr Canc Netw. 2023;21:594

Medical Affairs
BY COR2ED

Medical Affairs by COR2ED
Bodenackerstrasse 17
4103 Bottmingen
SWITZERLAND



Connect on
LinkedIn @COR2ED

Watch on
YouTube @COR2ED

Visit us at
https://cor2ed.com/

Follow us on
Twitter @COR2EDMedEd

Email
info@cor2ed.com