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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

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

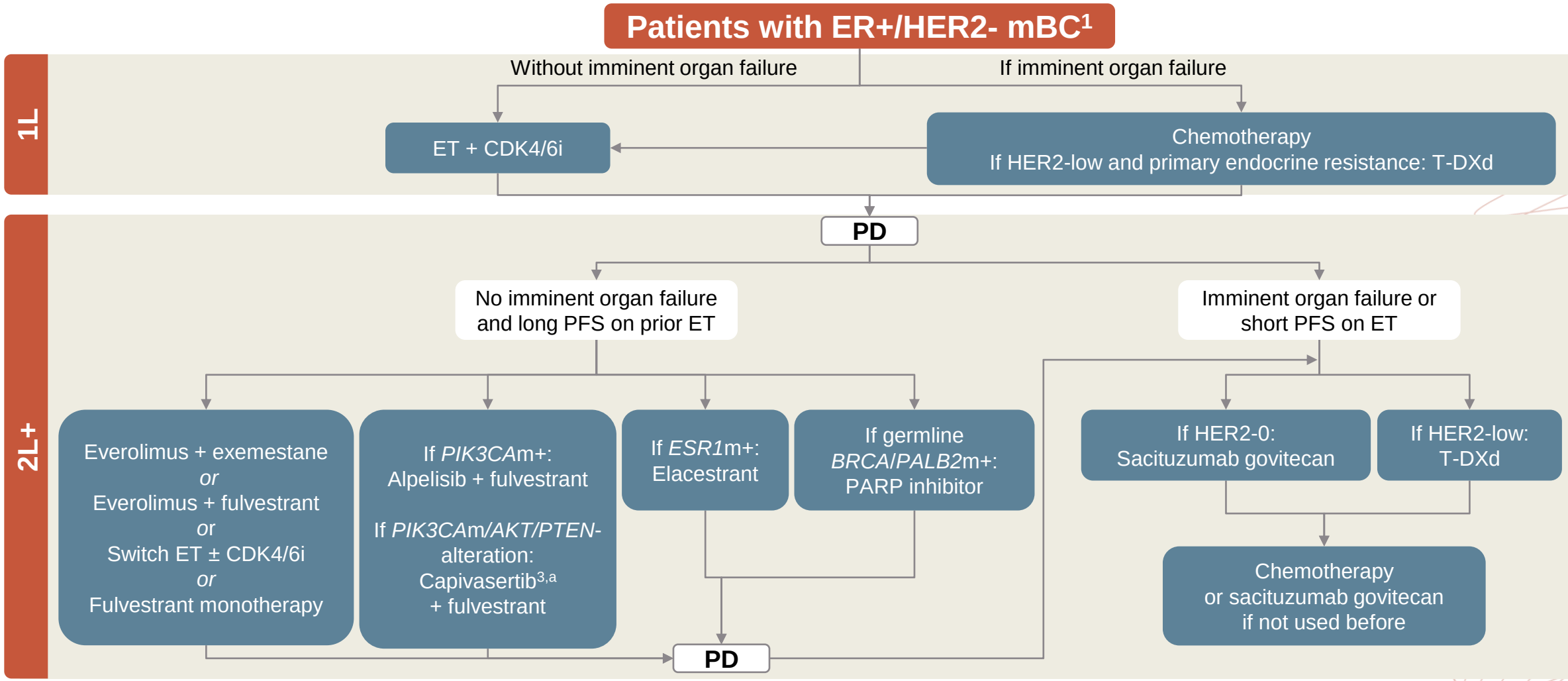
Molecular mechanisms underlying endocrine sensitivity and resistance are multifold[1-3]

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 1	 143 (59.8) 96 (40.2)	 67 (58.3) 48 (41.7)	 135 (56.5) 103 (43.1)	 62 (54.9) 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 2	 129 (54.0) 110 (46.0)	 73 (63.5) 42 (36.5)	 142 (59.4) 97 (40.6)	 69 (61.1) 44 (38.9)
Prior therapies for advanced or metastatic disease, n (%) Fulvestrant Aromatase inhibitor Tamoxifen	 70 (29.3) 193 (80.8) 19 (7.9)	 27 (23.5) 101 (87.8) 9 (7.8)	 75 (31.4) 194 (81.2) 15 (6.3)	 28 (24,8) 96 (85.0) 9 (8.0)
No. of prior lines of chemotherapy in the advanced or metastatic setting, n (%) 0 1	 191 (79.9) 26 (20.1)	 89 (77.4) 26 (22.6)	 180 (75.3) 59 (24.7)	 81 (71.7) 32 (28.3)

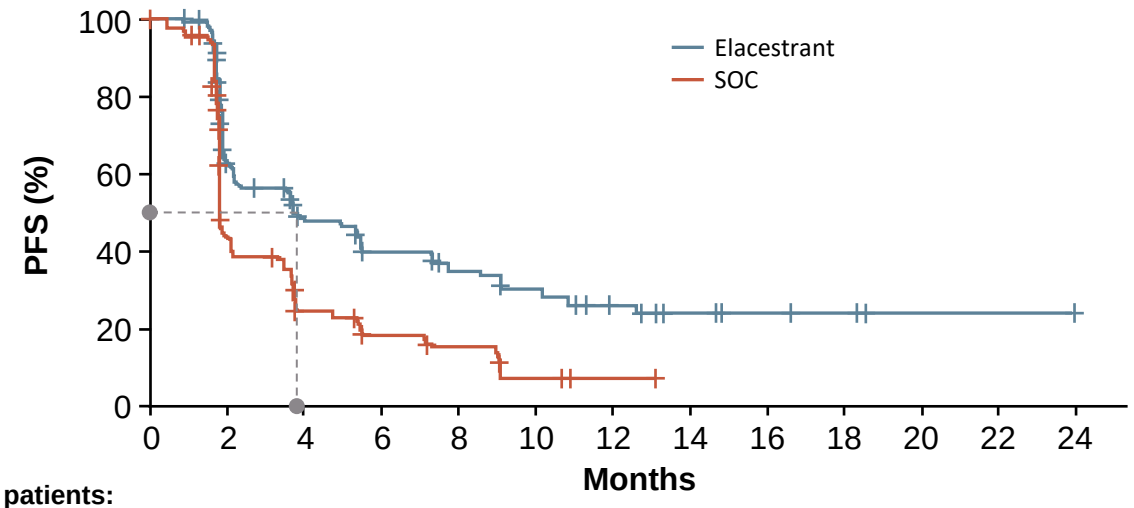
[a] Includes lung, liver, brain, pleural, and peritoneal involvement

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

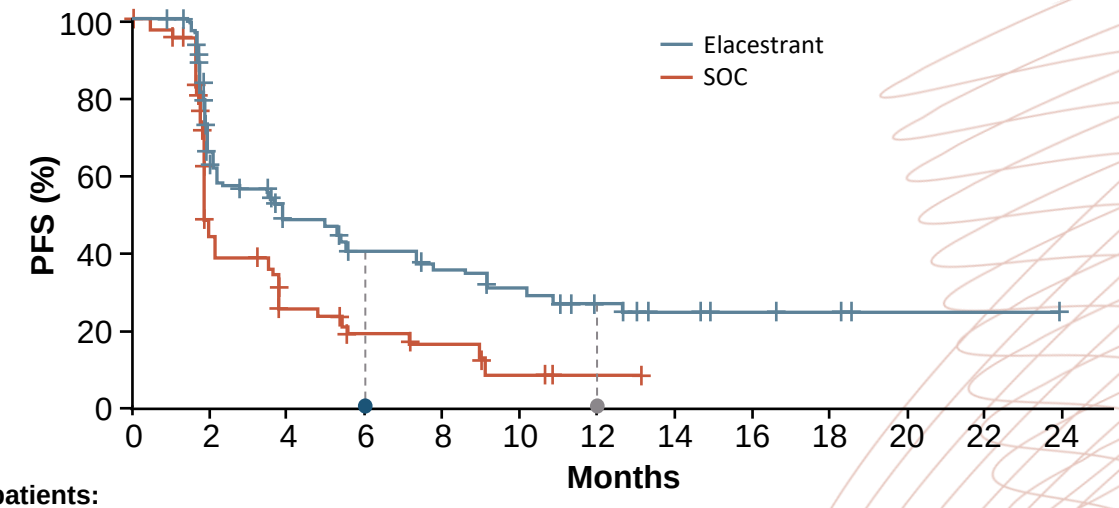
PFS in patients with *ESR1*-mut: Elacestrant vs SOC



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	



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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	

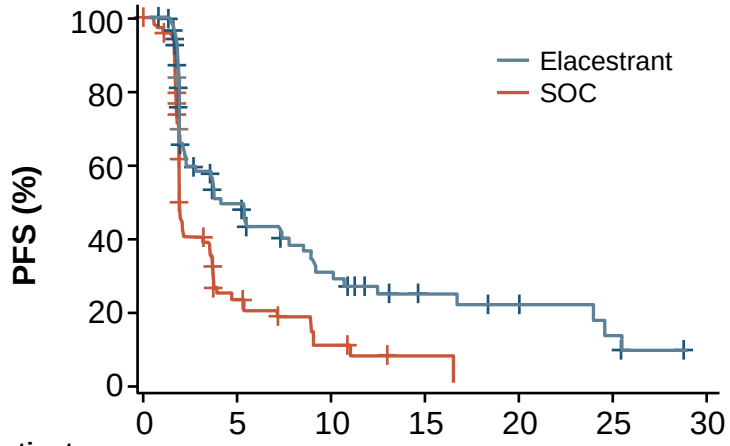
Exploratory analysis; patients without ESR1-mut: n=250, 52% of the ITT population
CI, confidence interval; *ESR1*, estrogen receptor 1; HR, hazard ratio; ITT, intention to treat; mo, months; mut, mutation; (m)PFS, (median) progression-free survival; SOC, standard of care

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]

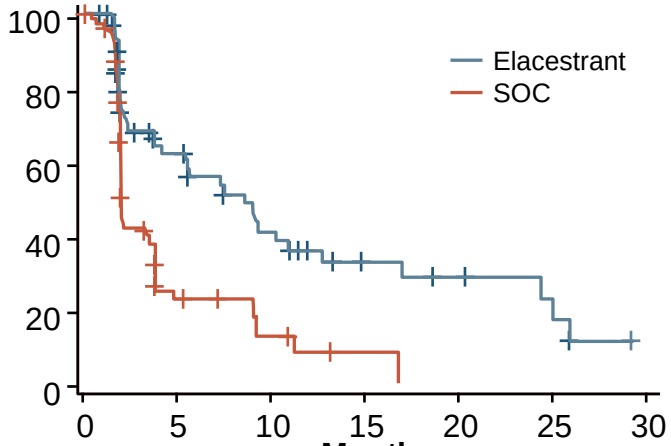


No. of patients:

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]	

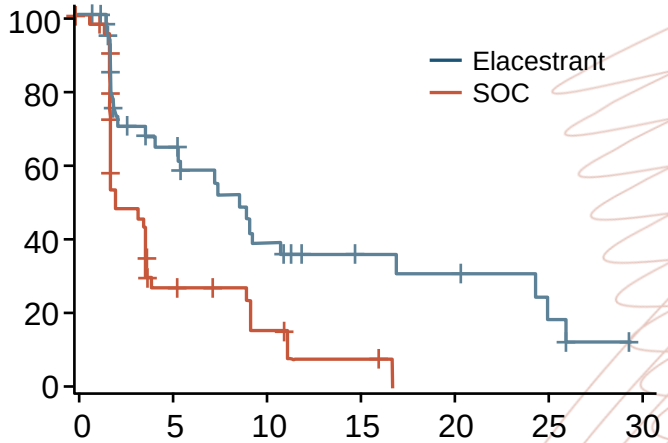
≥12 months of prior ET + CDK4/6i[a]



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

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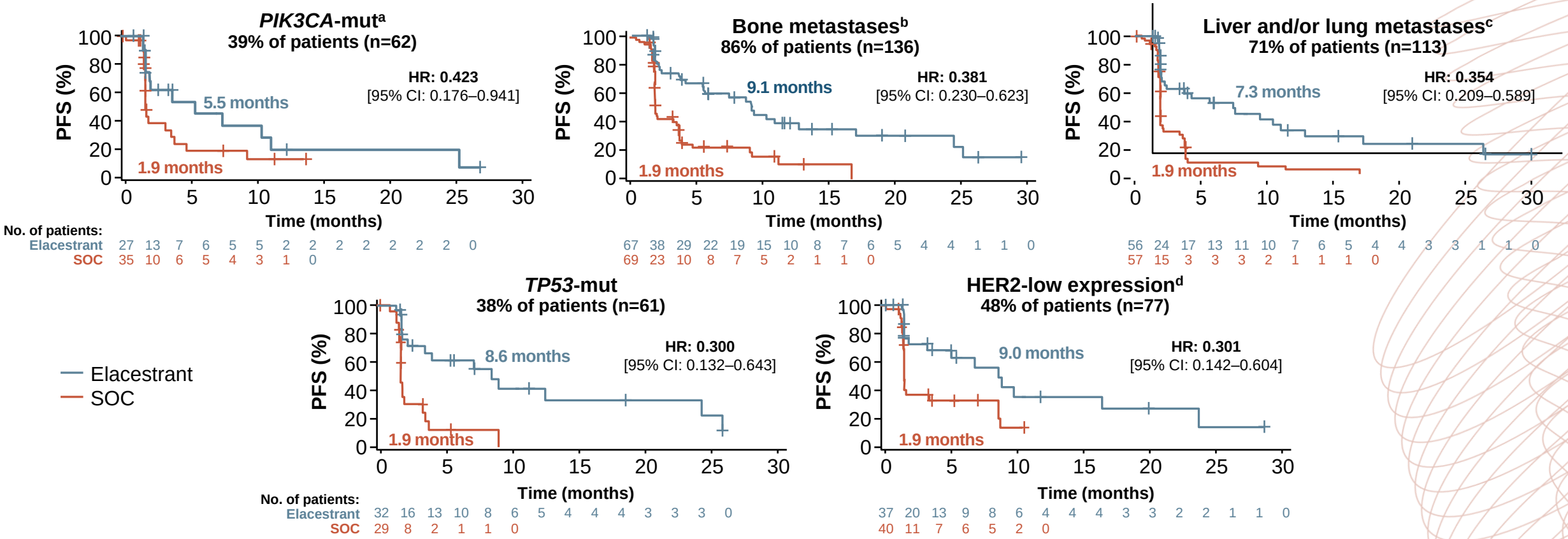

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Patients with ≥12 months of prior ET + CDK4/6i	% (n)	Elacestrant mPFS, months	SOC mPFS, months	HR [95% CI]
All *ESR1*-mut patients	**100** (159)	**8.61**	**1.91**	**0.41** [0.262-0.634]
<3 metastatic sites[a]	**52** (82)	**9.0**	**1.9**	**0.41** [0.23-0.75]
≥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

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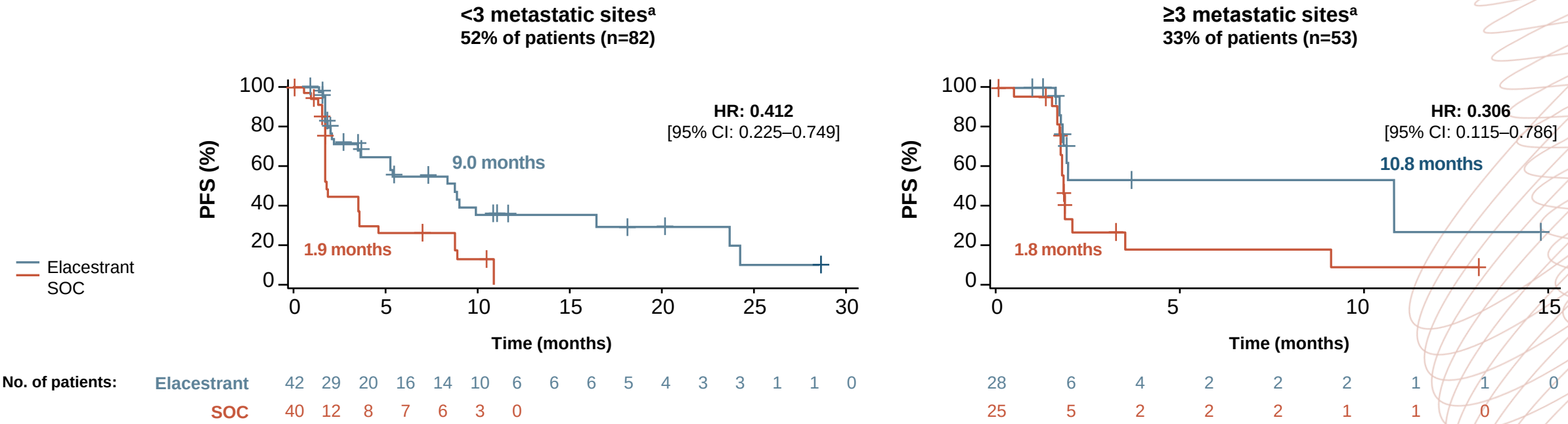

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All *ESR1*-mut patients	**100** (159)	**8.61**	**1.91**	**0.41** [0.262-0.634]
ESR1 D538G-mut	**61** (97)	**9.0**	**1.9**	**0.38** [0.21-0.67]
ESR1 Y537S/N-mut	**58** (92)	**9.0**	**1.9**	**0.25** [0.13-0.47]

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

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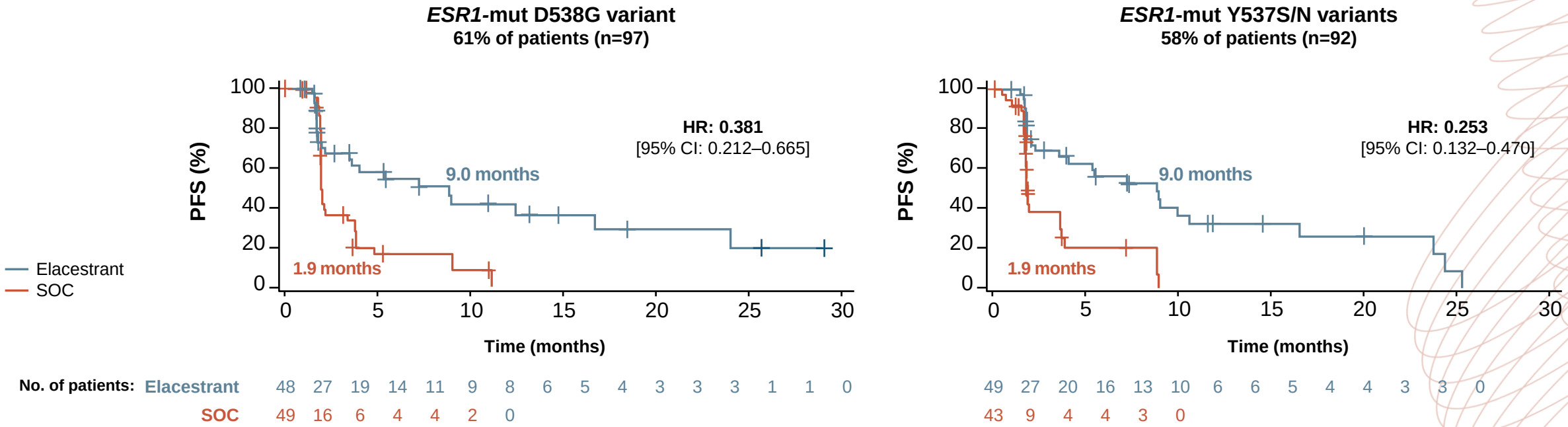
PFS in patients with ≥12 months of prior ET + CDK4/6i and *ESR1*-mut



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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]

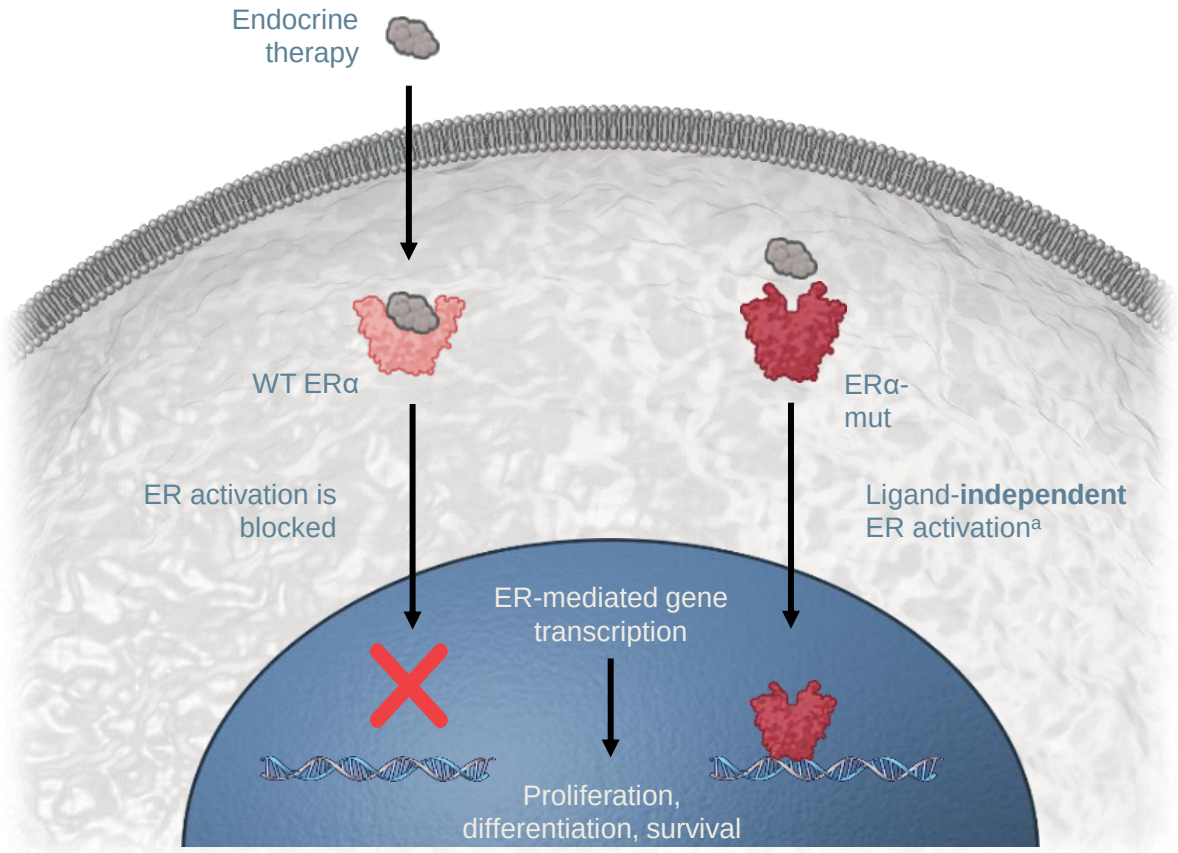
… drive treatment decisions

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]

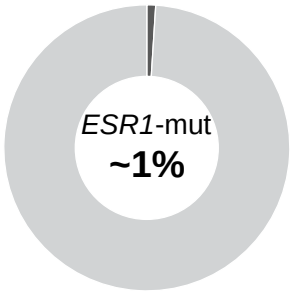
Adjuvant Tx

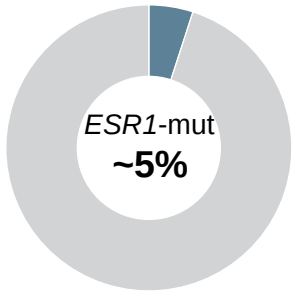
First progression during / after adjuvant therapy

1L mBC Tx
AI + CDK4/6i

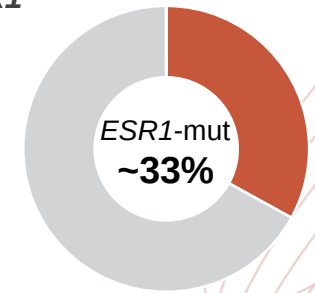
Progression

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

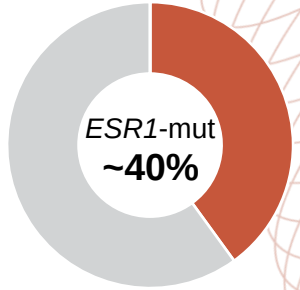




Liquid biopsy
Testing for **acquired mutations**
- ***ESR1***



2L



3L

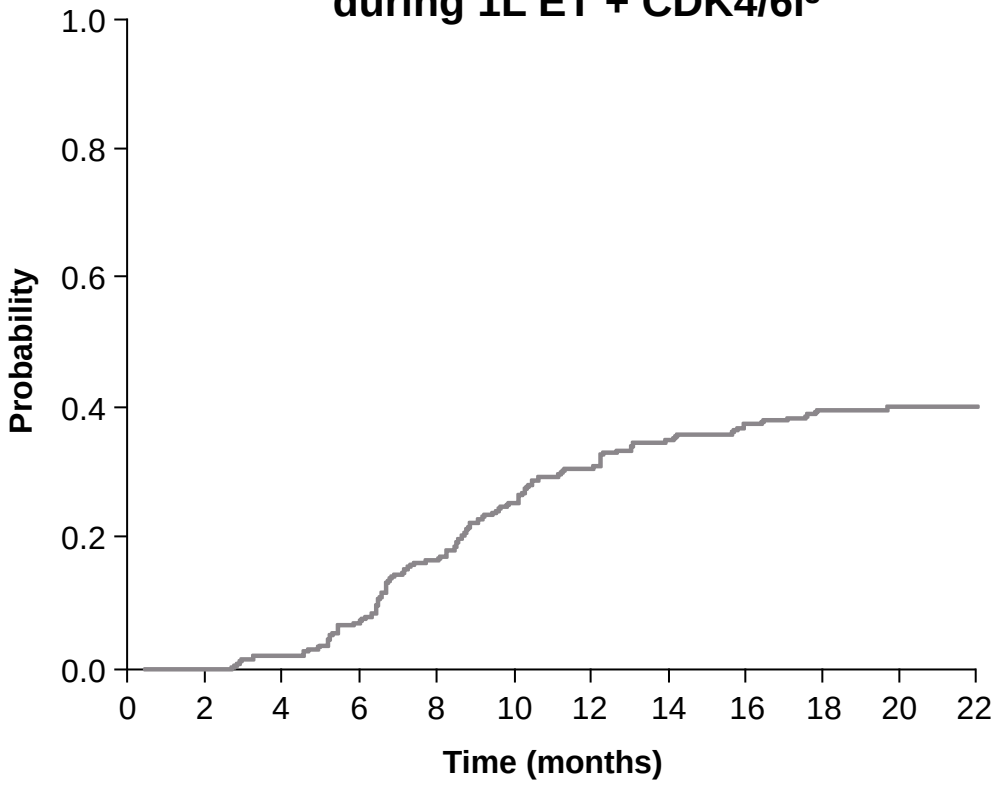
As *ESR1* mutations occur almost exclusively after ET in the mBC setting,[5] testing for *ESR1*-mut should occur <u>at each progression</u> if not detected previously[10-12]

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.

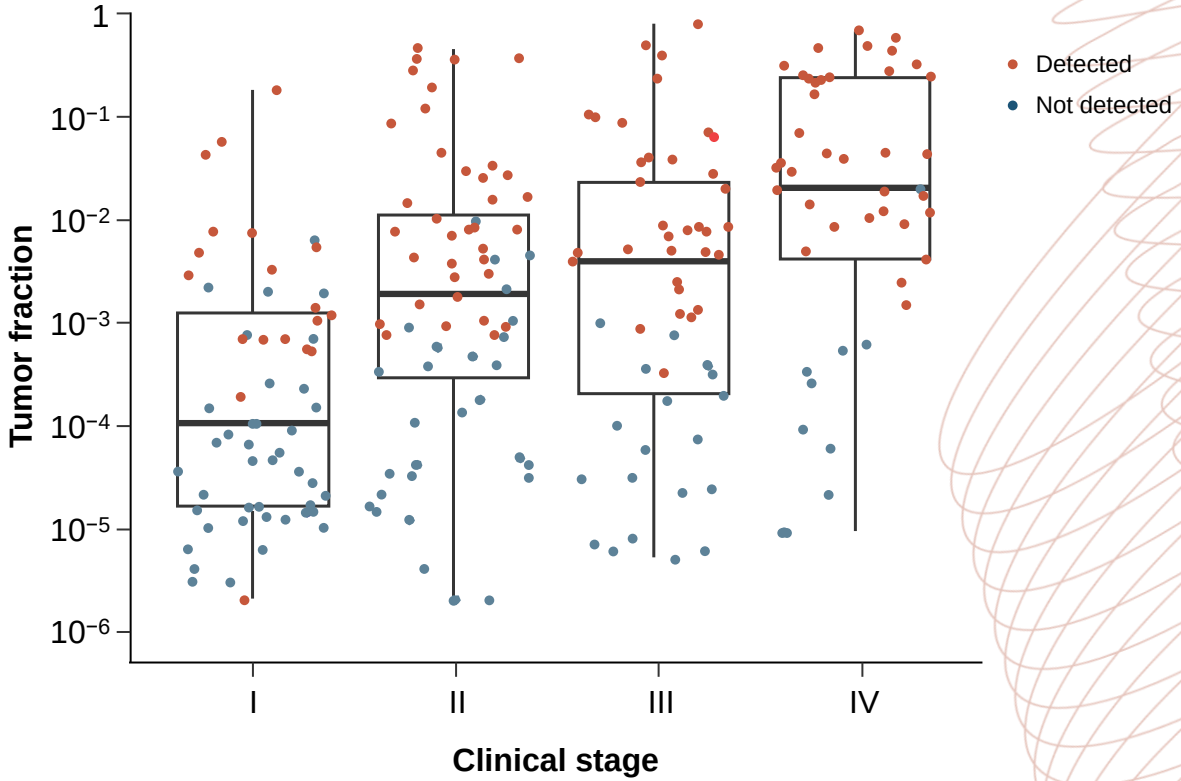
Modified from: 1. Jeselsohn R, et al. Clin Cancer Res. 2014;20:1757-67; 2. Allouchery V, et al. Breast Cancer Res. 2018;20:40; 3. Schiavon G, et al. Sci Transl Med. 2015;7:313ra182; 4. Brett JO, et al. Breast Cancer Res. 2021;23:85; 5. Toy W, et al. Nat Genet. 2013;45:1439-45; 6. Bidard FC, et al. J 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]

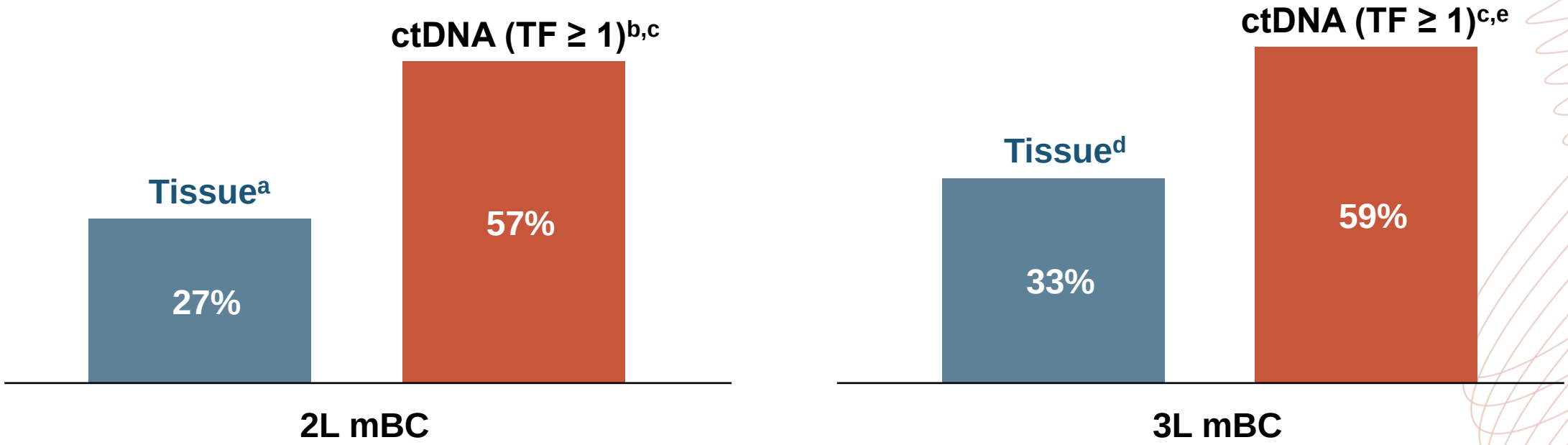


CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ctDNA, circular tumor DNA; *ESR1*, estrogen receptor 1; ET, endocrine therapy; L, line; mut, mutation.

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

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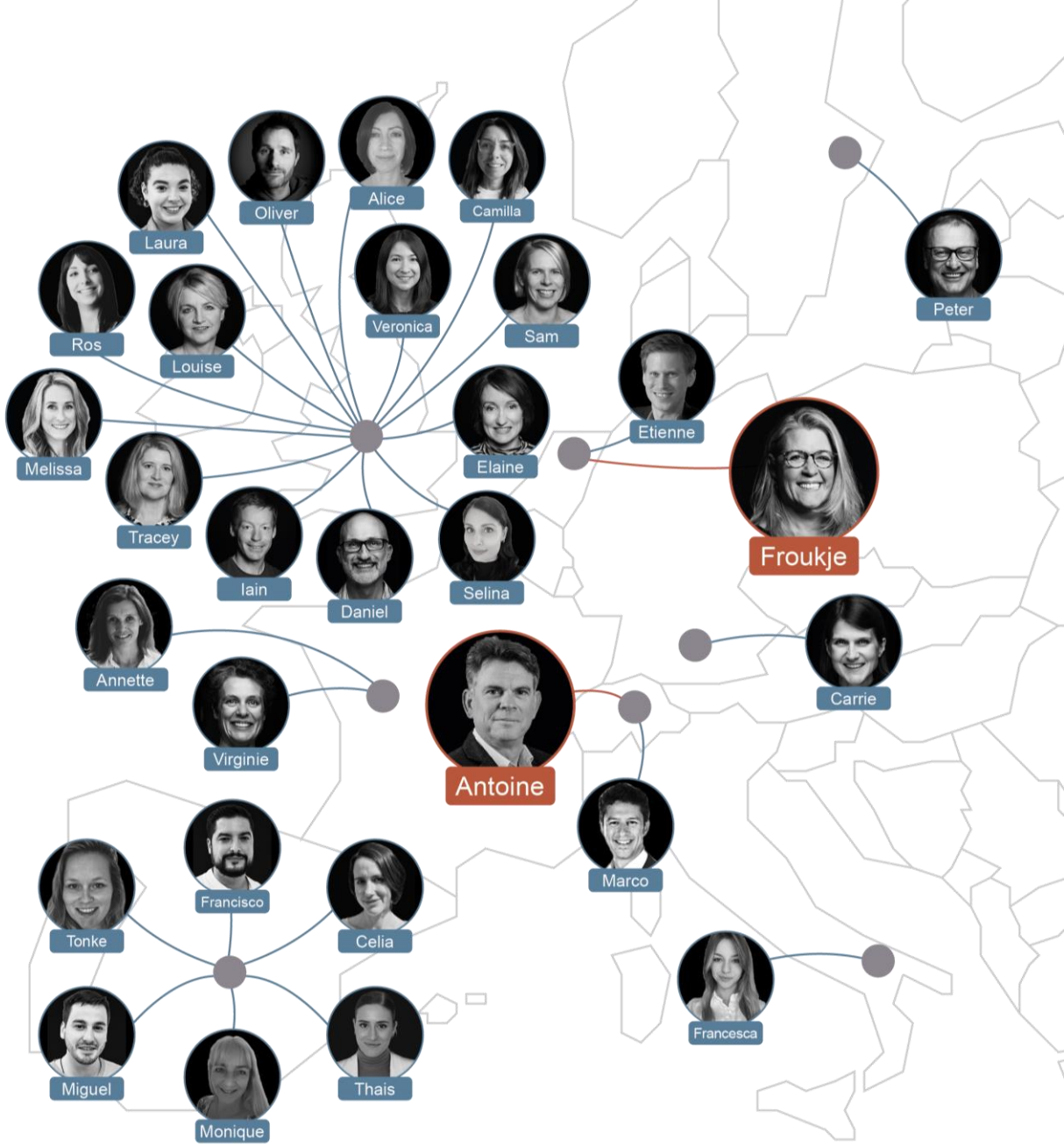

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