Satellite Symposium

Current and Upcoming Treatment Strategies After CDK4/6 Inhibitors for Patients With ER+/HER2- Advanced Breast Cancer

21st March 2024, 12:45-13:45 Red Room

Disclosures

Acknowledgement and disclosures

This Symposium has been sponsored by Stemline and is intended for healthcare professionals only

Expert disclosures:

- **Prof. Valentina Guarneri** has received financial support/sponsorship for research support, consultation, or speaker fees from the following companies: Eisai, Eli Lilly, Exact Sciences, Gilead, MSD, Novartis, Olema Oncology, GSK, AstraZeneca, Daiichi Sankyo, Roche, Novartis, Zentiva, Menarini Stemline.
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Agenda

Current and upcoming treatment strategies after CDK4/6 inhibitors for patients with ER+/HER2- advanced breast cancer

Time (CEST)	Topic	Facilitator
12:45-12:55	Opening by the Chairman	Prof. Valentina Guarneri
12:55-13:05	Overview of ESMO Breast Cancer Living Guidelines in the ER+/HER2- metastatic breast cancer setting	Prof. Matteo Lambertini
13:05-13:20	The current and future treatment landscape for ER+/HER2- metastatic breast cancer	Prof. Valentina Guarneri
13:20-13:30	Emerging biomarkers in BC: Implementing liquid biopsy *ESR1* mutation testing	Prof. Federico Rojo
13:30-13:45	Key takeaways Q&A	All

BC, breast cancer; CDK4/6, cyclin dependent kinase 4/6; HR, hormone recept, HER2, human epidermal growth factor 2

Programme Developed by Experts

Prof. Matteo Lambertini
University of Genoa, Italy

Prof. Valentina Guarneri
University of Padua, Italy

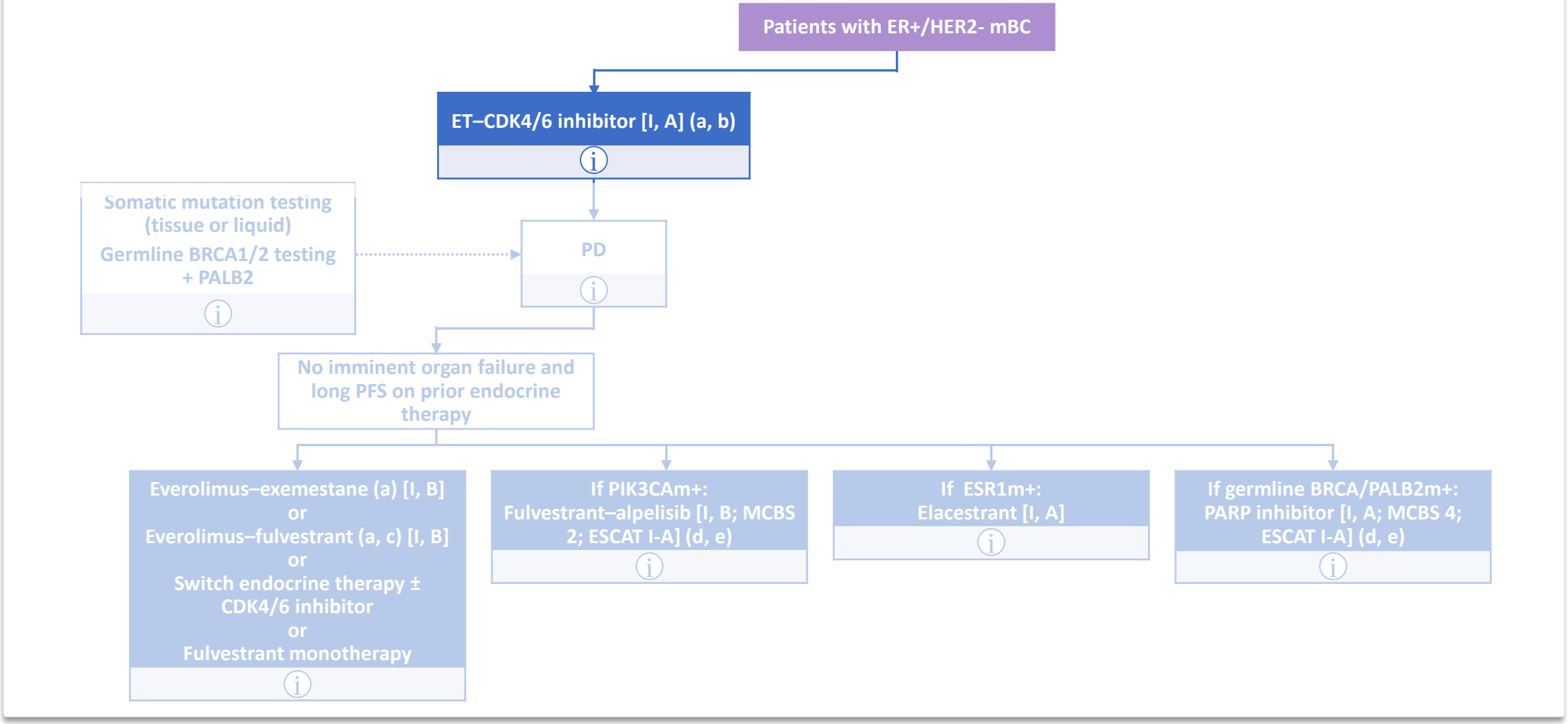
Prof. Federico Rojo,
Fundación Jiménez Díaz
University Hospital, Spain

Overview of ESMO Breast Cancer Living Guidelines in the ER+/HER2- Metastatic Breast Cancer Setting

Prof. Matteo Lambertini
Associate *Professor in Medical Oncology at University of Genoa, Italy*

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2

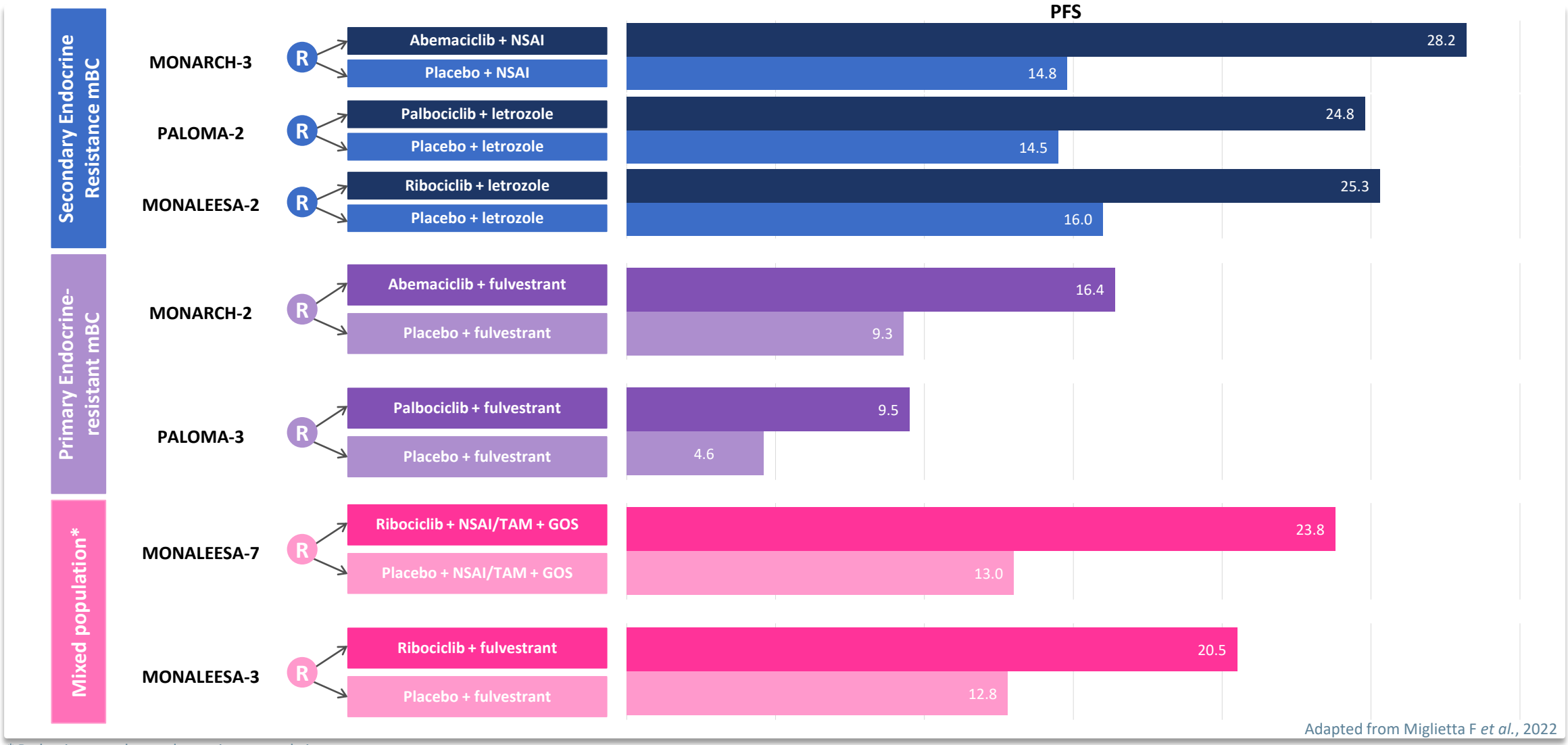
ESMO mBC Living Guidelines: Adding CDK4/6 inhibitors to ET is the global SoC in first-line ER+/HER2- mBC treatment



BRCA 1/2, BReast CAncer gene 1 or 2; CDK4/6i cyclin-dependent kinase 4/6; ESCAT, ESMO scale for clinical actionability of molecular targets; ER, estrogen receptor; *ESR1*, estrogen receptor 1; ESMO, European Society of Medical Oncology; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; m, mutation; mBC, metastatic breast cancer; MCBS, magnitude of clinical benefit scale; PALB2, partner and localizer of BRCA2; PARP, poly(ADP-ribose) polymerase; PD, progressive disease; PFS, progression free survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase; SoC, standard of care

ESMO metastatic breast cancer living guidelines: https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline/er-positive-her2-negative-breast-cancer (accessed March 2024)

Endocrine resistance/sensitivity in eBC will impact on the CDK4/6 inhibitor selection



Adapted from Miglietta F *et al.*, 2022

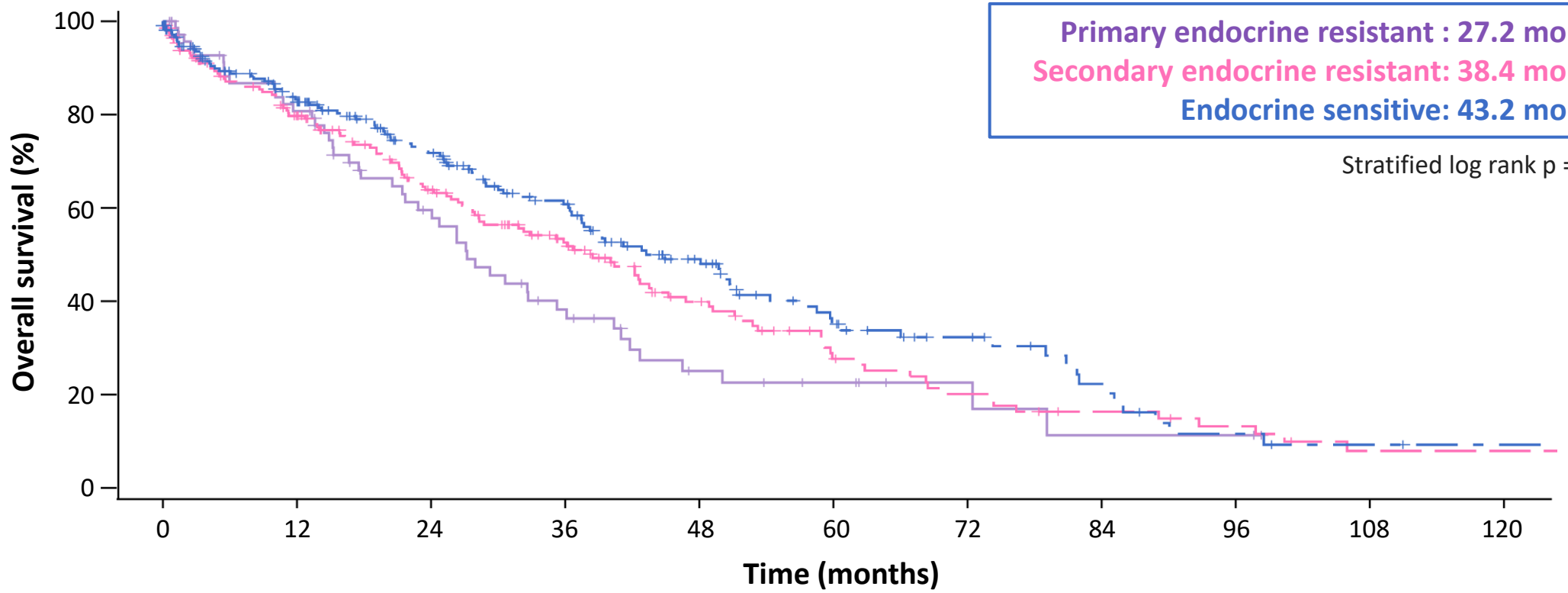
* Both primary and secondary resistant population

CDK4/6i, cyclin dependent kinase 4/6 inibition; eBC, early breast cancer GOS, goserilin; mBC, metastatic breast cancer; NSAI, non-steroidal aromatase inhibitor; PFS, progression free survival; R, randomization; TAM, tamoxifen

Miglietta F *et al.* ESMO Open. 2022 Apr;7(2):100409.

Endocrine resistance/sensitivity in eBC will impact on the CDK4/6 inhibitor selection

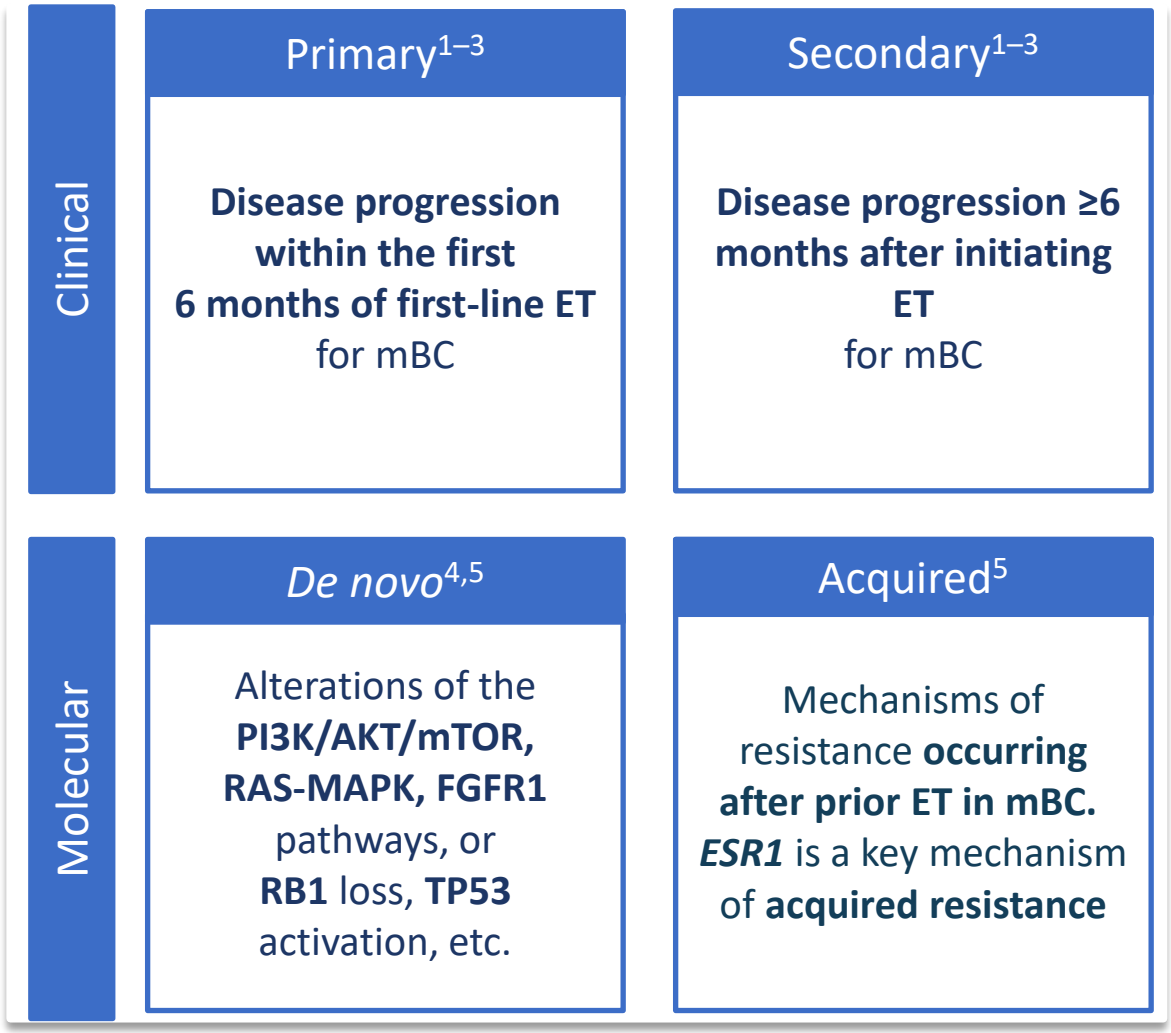
mOS (from diagnosis of mBC)



CDK4/6, cyclin dependent kinase 4/6; eBC, early breast cancer; ES, endocrine sensitive; ER, endocrine resistant; mBC, metastatic breast cancer; mOS, median overall survival

Lambertini M. et al. eClinicalMedicine. 2023;59:101931.

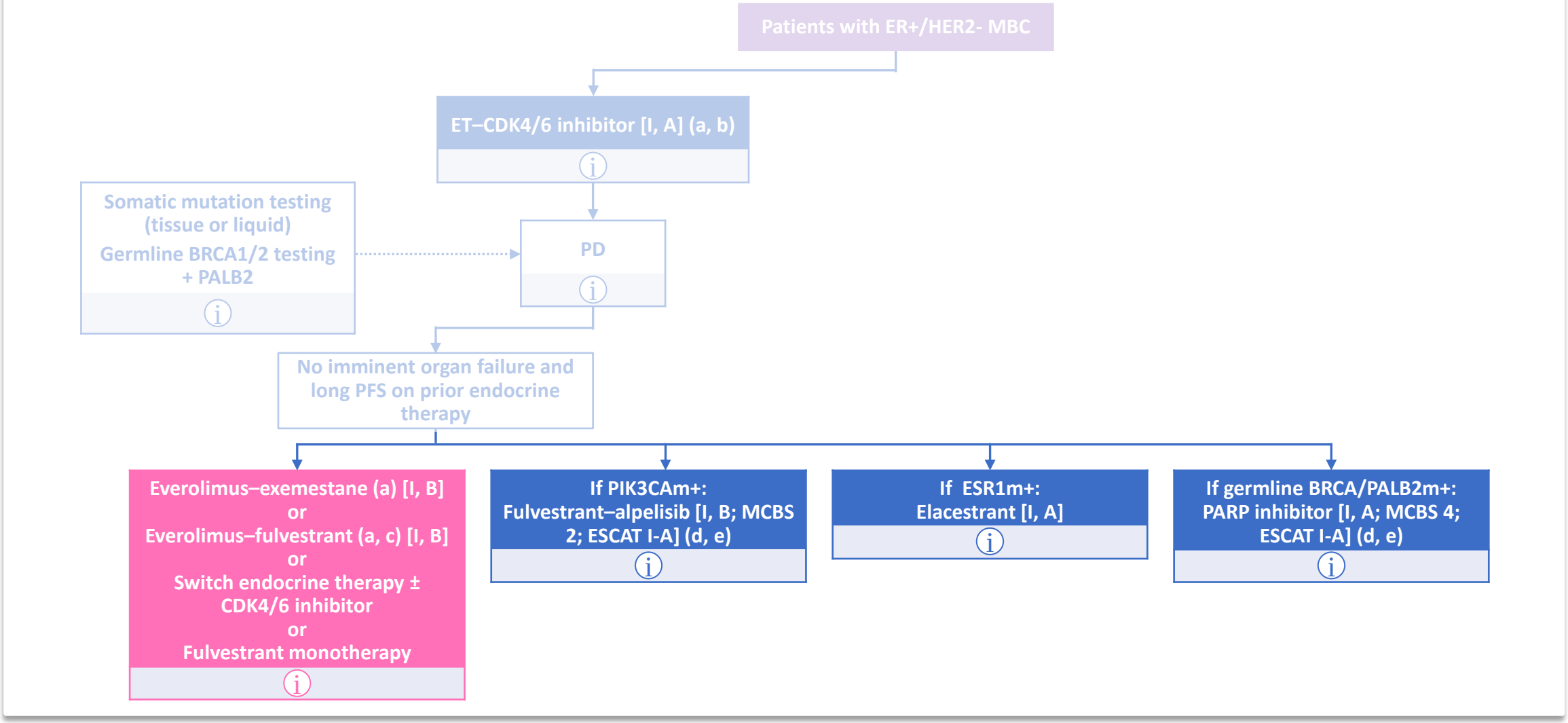
Integrating clinical and molecular variables in the endocrine resistance classification



AKT, protein kinase B; *ESR1,* estrogen receptor 1; ET, endocrine therapy; FGFR1, fibroblast growth factor receptor 1; mBC, metastic breast cancer; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; RAS-MAPK, rat sarcoma-mitogen-activated protein kinase; RB1, retinoblastoma protein; TP53, tumour protein p53.

1. Gennari A, et al. Ann Oncol 2021;12:1475–1495; 2. Rasha F, et al. Mol Cell Endocrinol 2021;532:111322; 3. Patel R, et al. NPJ Breast Cancer 2023;9:20; 4. Rani A, et al. Front Endocrinol (Lausanne) 2019;10:245; 5. Xu P, et al. Acta Pharmacol Sin 2021;42:171-178.

ESMO mBC Living Guidelines: The second-line treatment landscape for the ER+/HER2- mBC population is evolving



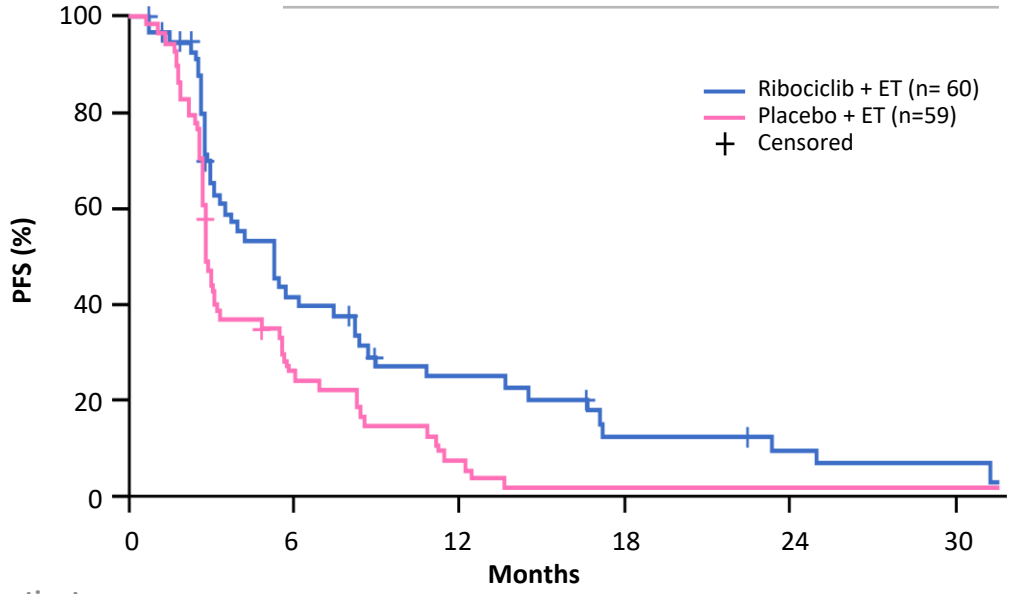
BRCA 1/2, BReast CAncer gene 1 or 2; CDK4/6i cyclin-dependent kinase 4/6; ESCAT, ESMO scale for clinical actionability of molecular targets; ER, estrogen receptor; *ESR1*, estrogen receptor 1; ESMO, European Society of Medical Oncology; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; m, mutation; mBC, metastatic breast cancer; MCBS, magnitude of clinical benefit scale; PALB2, partner and localizer of BRCA2; PARP, poly(ADP-ribose) polymerase; PD, progressive disease; PFS, progression free survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase; SoC, standard of care

ESMO metastatic breast cancer living guidelines: https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline/er-positive-her2-negative-breast-cancer (accessed March 2024).

MAINTAIN: Fulvestrant monotherapy is associated with lower benefit after CDK4/6 inhibitor therapy

All patients

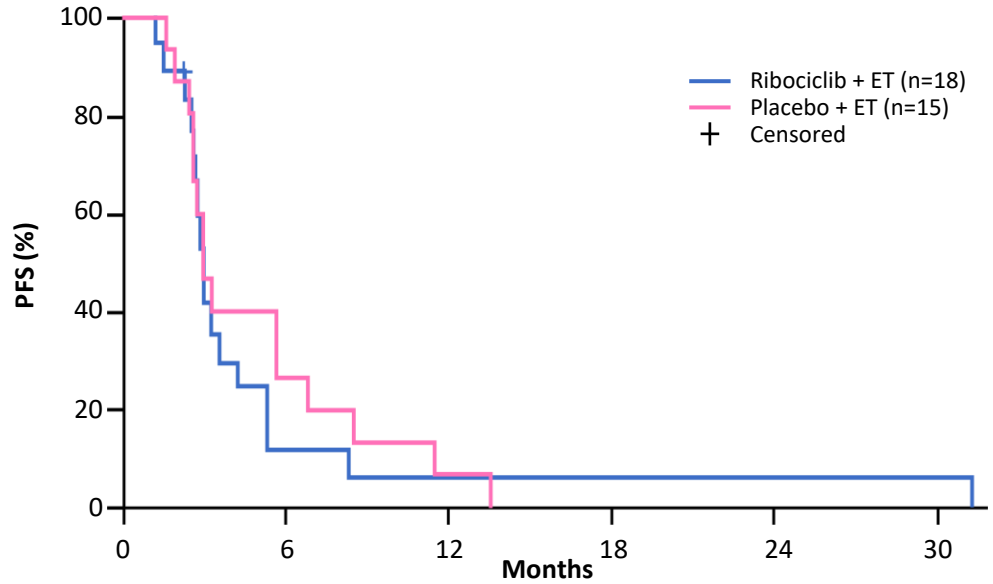
	RIBO + ET	PBO + ET
mPFS, months (95% CI)	**5.26** (3.02-8.12)	**2.76** (2.66-3.25)
HR (95% CI)	**0.57** (0.39-0.85)	
P-value	**0.006**	



No. of patients						
RIBO + ET	60	21	11	5	3	2
PBO + ET	59	13	4	1	1	1

PFS in patients with *ESR1*-mut

	RIBO + ET	PBO + ET
mPFS, months (95% CI)	**2.96** (2.66-4.21)	**3.02** (2.53-5.62)
HR (95% CI)	**1.22** (0.59-2.49) NS*	



No. of patients						
RIBO + ET	18	2	1	1	1	1
PBO + ET	15	4	1	0	0	0

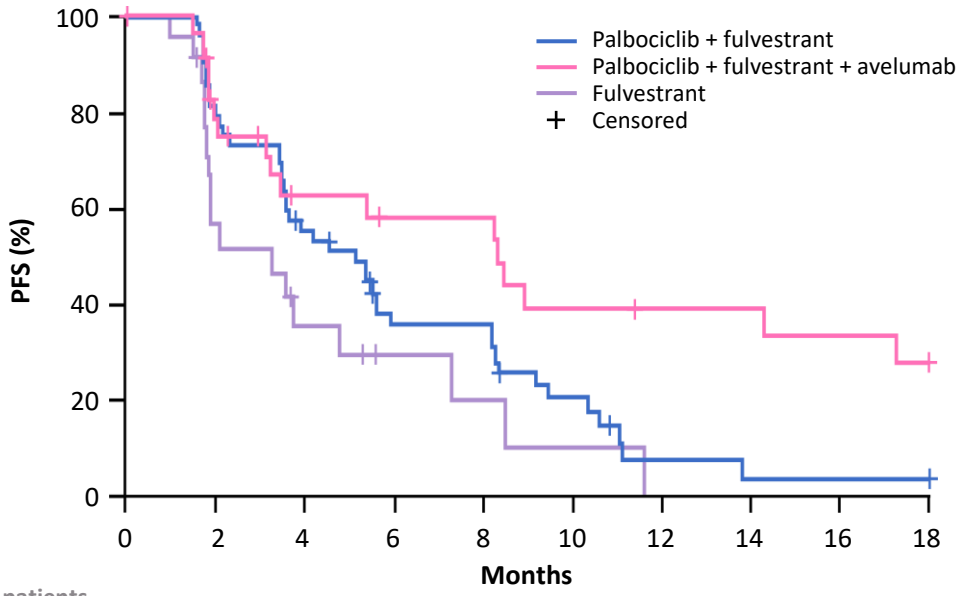
*No statistically significant difference observed between treatment groups

2L, second line; CDK4/6, cyclin-dependent kinase 4/6; CI, confidence interval; *ESR1*, estrogen receptor 1; ET, endocrine therapy; HR, hazard ratio; (m)PFS, (median) progression-free survival; mut, mutation; NS, not significant; Kalinsky K, et al. J Clin Oncol. 2023;41:4004-4013.

PACE/PALMIRA: Fulvestrant monotherapy is associated with lower benefit after CDK4/6 inhibitor therapy

PACE study: Patients with *ESR1*-mut[1,a]

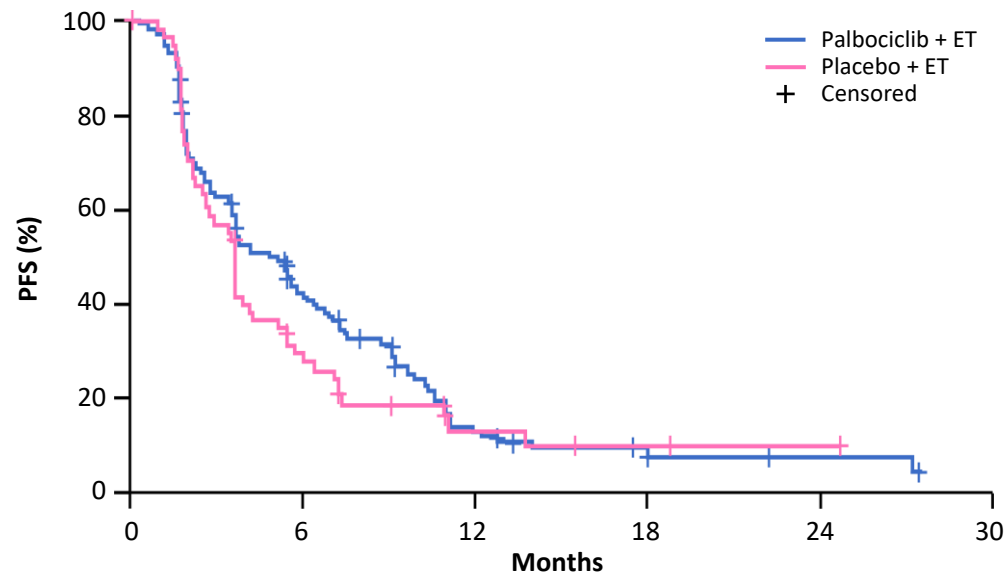
	PALBO + FUL	PALBO + FUL + AVE	FUL
mPFS, months (90% CI)	**5.2** (3.5-5.9)	**8.3** (3.2-17.2)	**3.3** (1.8-7.3)
HR P+F vs F (90% CI)		**0.68** (0.42-1.09) NS*	



No. of patients									
PALBO + FUL	55	41	27	15	15	7	2	1	1	1
PALBO + FUL + AVE	30	21	14	12	12	8	7	7	6	5
FUL	23	12	6	3	2	1	0	0	0	0

PALMIRA study: *ESR1* status unknown[2]

	PALBO + ET	PBO + ET
mPFS, months	**4.9**	**3.6**
HR (95% CI)	**0.84** (0.66-1.07) NS*	
Two-sided p-value	**0.149**	



No. of patients						
PALBO + ET	136	47	11	4	2	0
PBO + ET	62	16	4	2	1	0

[a]All patients had received at least 6 months of CDK4/6 inhibitor therapy prior to joining the trial, with 76% of patients having received ≥12 months of prior CDK4/6 inhibitor therapy; 91% had received palbociclib previously. *No statistically significant difference observed between treatment groups

CDK4/6, cyclin-dependent kinase 4/6; CI, confidence interval; *ESR1*, estrogen receptor 1; F, fulvestrant; HR, hazard ratio; (m)PFS, (median) progression-free survival; mut, mutation; NS, not significant; P, palbociclib

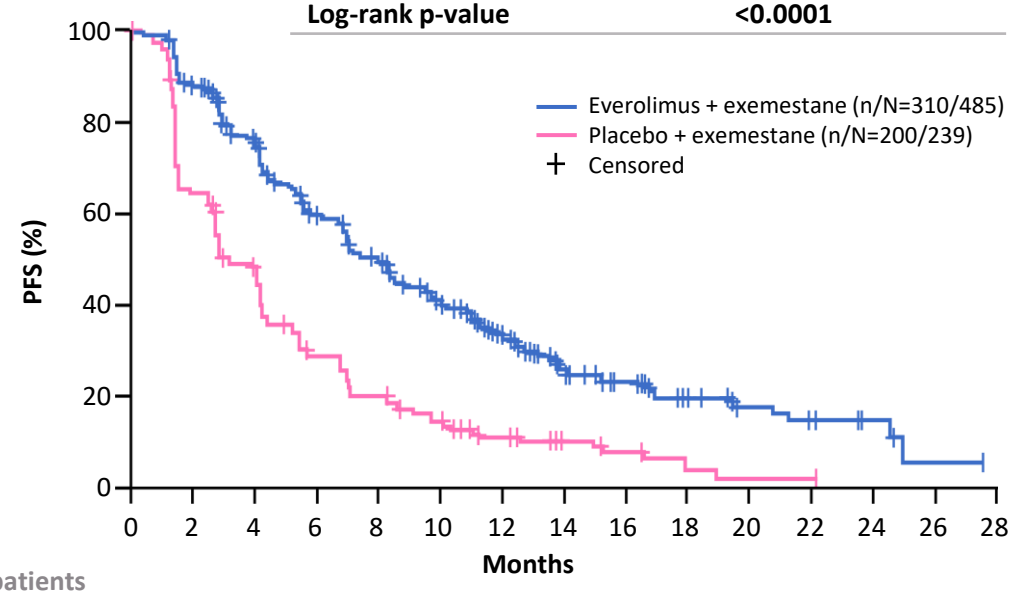
1. Mayer EL, et al. SABCS 2022. Oral GS3-06; 2. Llombart-Cussac A, et al. J Clin Oncol. 2023;41(suppl 16; abstr 1001).

Everolimus + exemestane in patients with ER+/HER2- mBC

BOLERO-2 [1]

Patients had not received prior CDK4/6 inhibitor therapy

	EVE + EXE	PBO + EXE
mPFS, months	7.8	3.2
HR (95% CI)	0.45 (0.38-0.54)	
Log-rank p-value	<0.0001	

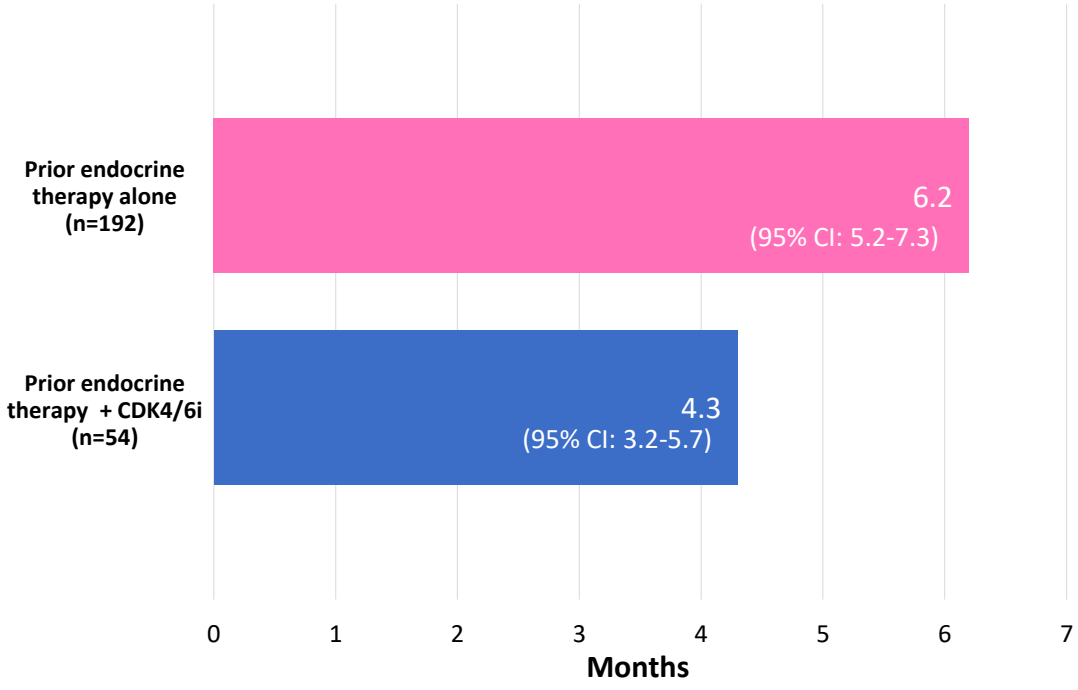


No. of patients														
EVE + EXE	485	394	318	236	194	147	99	57	42	23	13	10	4	1	0
PBO + EXE	239	146	103	61	42	27	17	9	6	2	1	1	0	0	0

Real-world study (Rozenblit)[2]

Patients had received prior CDK4/6 inhibitor therapy

Median time to next treatment for patients treated with everolimus + exemestane in the second line setting



CDK4/6(i), cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; mBC, metastatic breast cancer; (m)PFS, (median) progression-free survival

1. Yardley DA, et al. Adv Ther. 2013;30:870–884; 2. Rozenblit M, et al. Breast Cancer Res. 2021;23:14.

Key considerations and uncovering unmet needs of second-line classical therapies in ER+/HER2- mBC

- Adding a CDK4/6i to ET is the global SoC in first-line mBC treatment in both endocrine sensitive and endocrine resistant settings
- Classical endocrine therapies are a suboptimal treatment after progression on CDK4/6i + ET, particularly in patient with actionable genomic alternations
- Additional biomarkers other than ER and HER2 status need to be identified to properly select second-line therapy
- Among the biomarkers needed, *ESR1*-mut are frequently observed in patients progressing on AI-based therapy

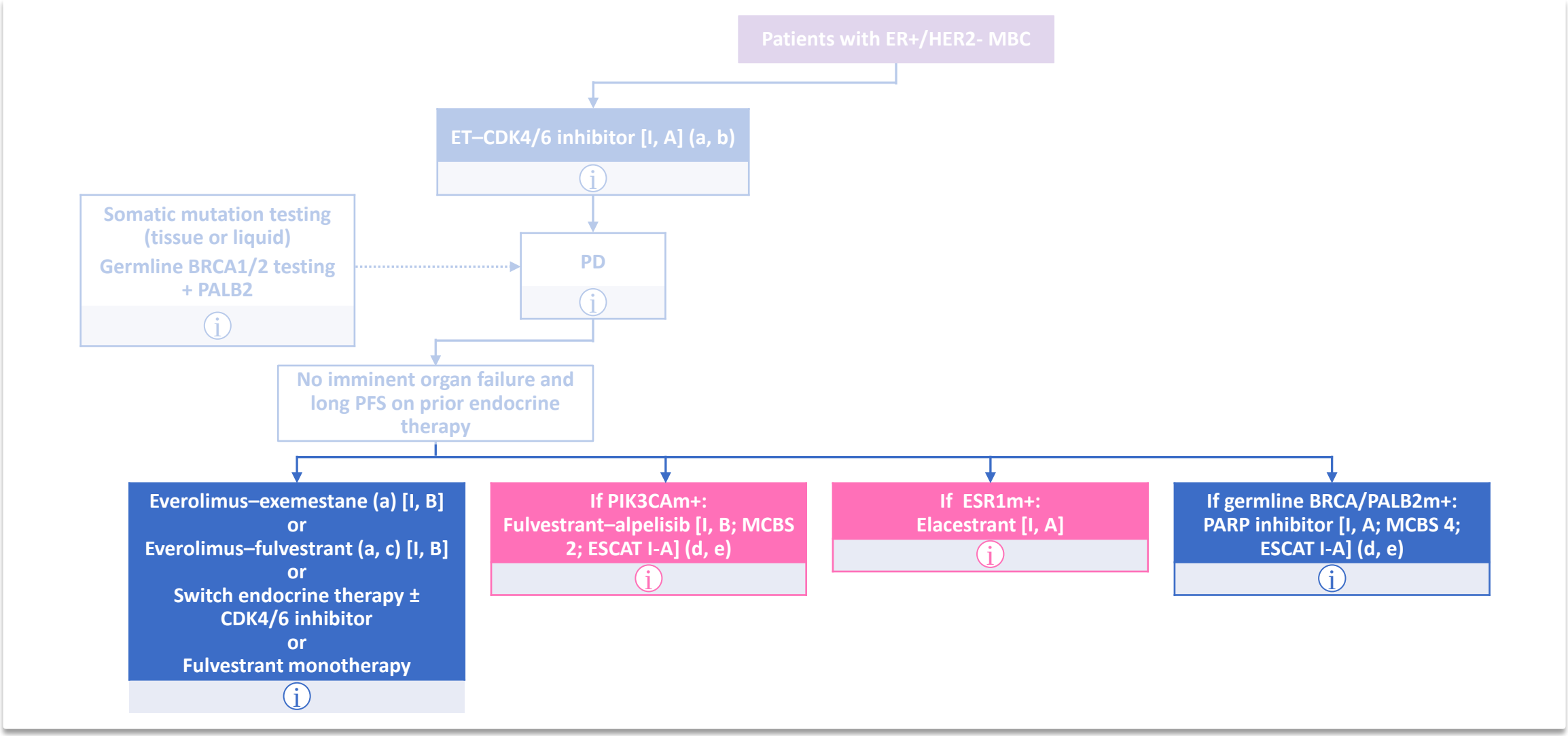
AI, aromatase inhibitor; CDK4/6i, cyclin dependent kinase 4/6 inhibitor; ER, estrogen receptor; ESR1 (-mut), estrogen receptor 1 (mutation); ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; SoC, standard of care

The Current and Future Treatment Landscape for ER+/HER2- Metastatic Breast Cancer

Prof. Valentina Guarneri
Professor of Oncology at University of Padua, Italy

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2

ESMO mBC Living Guidelines: The second-line treatment landscape for the ER+/HER2- mBC population is evolving



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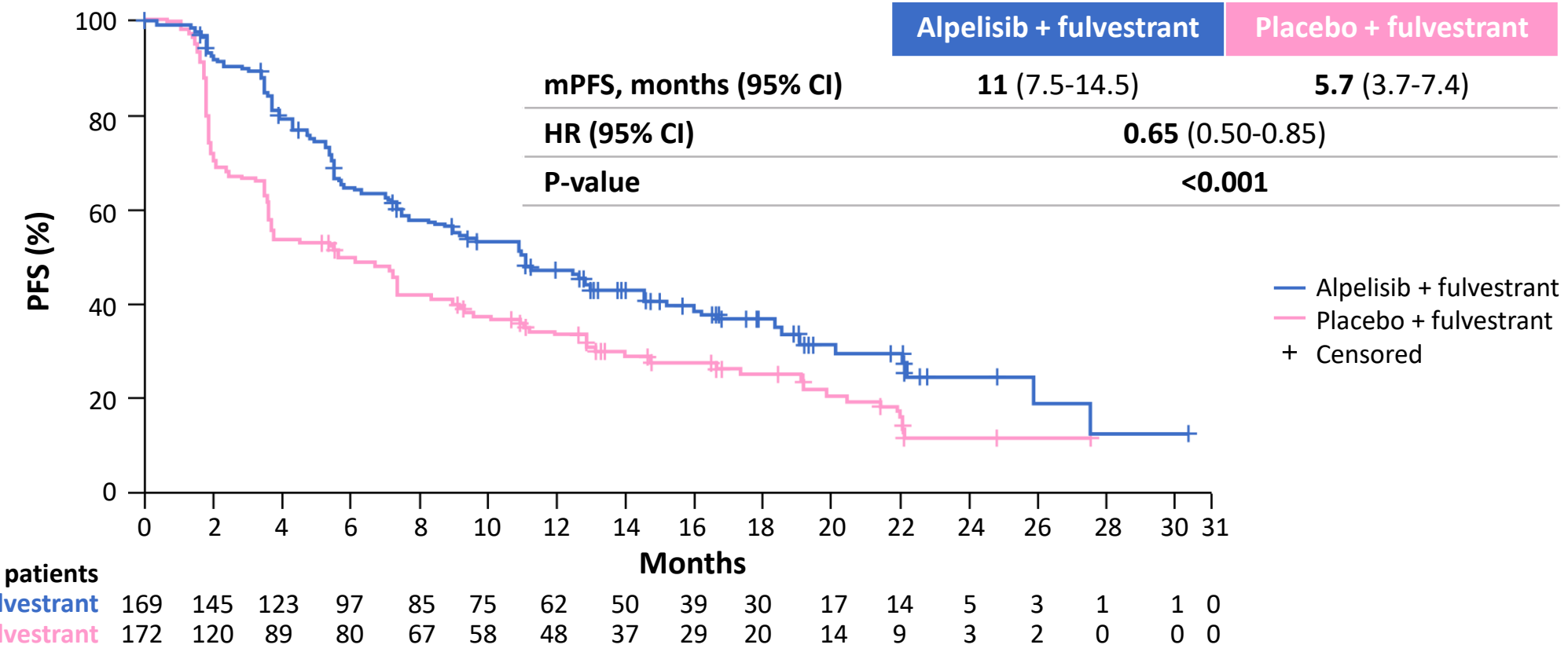
Alpelisib + fulvestrant in patients with ER+/HER2– and *PIK3CA*-mut mBC

SOLAR-1 study: patients with *PIK3CA*-mut

Patients had not received prior CDK4/6 inhibitor therapy*



	Alpelisib + fulvestrant	Placebo + fulvestrant
mPFS, months (95% CI)	**11** (7.5-14.5)	**5.7** (3.7-7.4)
HR (95% CI)	**0.65** (0.50-0.85)	
P-value	**<0.001**	

No. of patients																	
Alpelisib + fulvestrant	169	145	123	97	85	75	62	50	39	30	17	14	5	3	1	1	0
Placebo + fulvestrant	172	120	89	80	67	58	48	37	29	20	14	9	3	2	0	0	0

*5.9% of patients had received prior CDK4/6 inhibitor therapy for mBC.

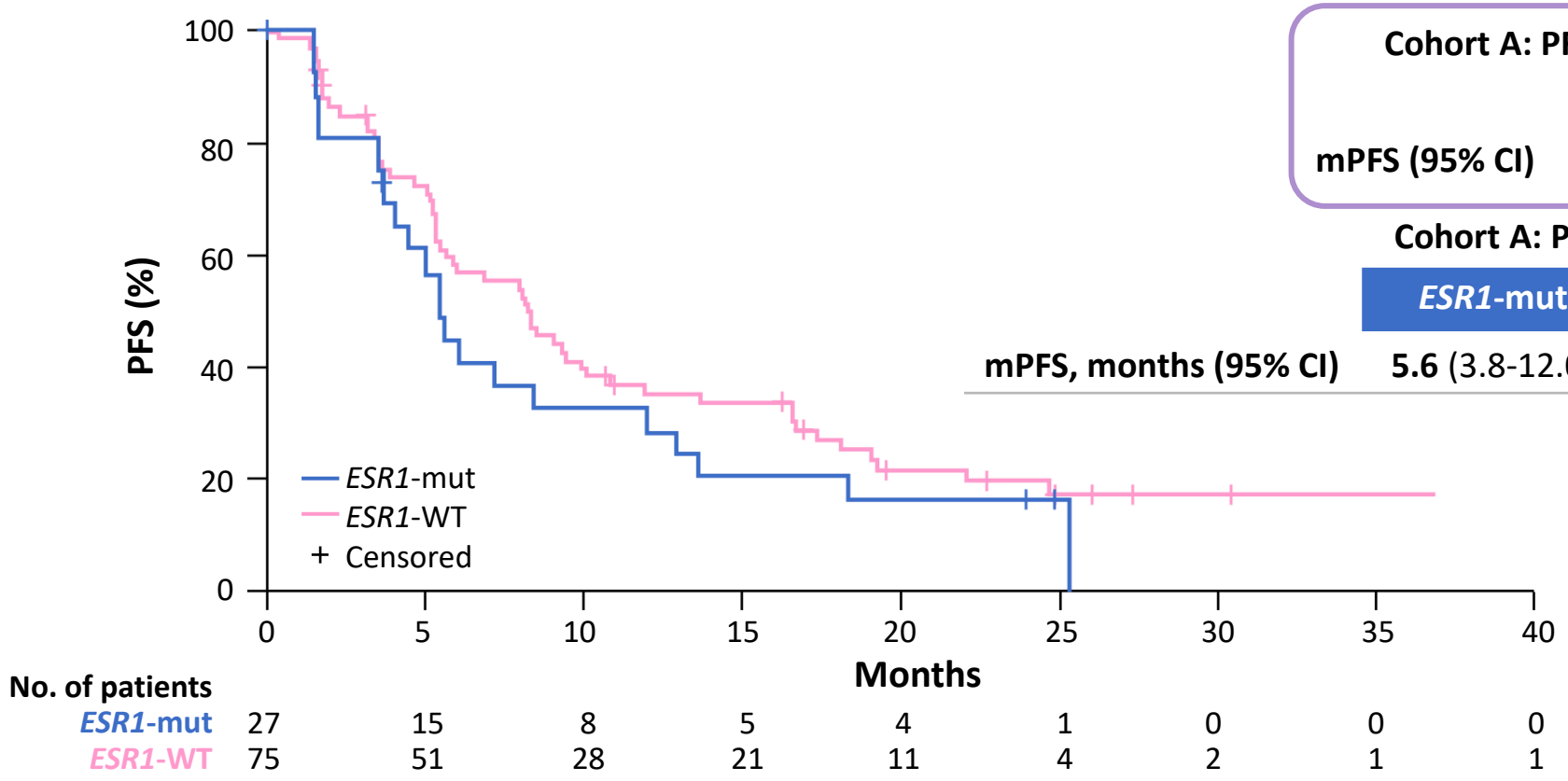
CDK4/6, cyclin-dependent kinase 4/6; CI, confidence interval; HR, hazard ratio; mBC, metastatic breast cancer; mPFS, median PFS; PFS, progression-free survival; WT, wild type.

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

Alpelisib + fulvestrant in patients with ER+/HER2– and *PIK3CA*-mut mBC

BYLieve study[1]: patients with *PIK3CA*-mut

Patients had received prior CDK4/6 inhibitor therapy



No. of patients								
ESR1-mut	27	15	8	5	4	1	0	0	0
ESR1-WT	75	51	28	21	11	4	2	1	1

Cohort A: PFS Total Population[1]

	Cohort A (n=119)
mPFS (95% CI)	**8.0** (5.6-8.6)

Cohort A: PFS *ESR1*-mut status[2]

	ESR1-mut	*ESR1*-WT
mPFS, months (95% CI)	**5.6** (3.8-12.0)	**8.3** (5.5-10.1)

*5.9% of patients had received prior CDK4/6 inhibitor therapy for aBC.

CDK4/6, cyclin-dependent kinase 4/6; CI, confidence interval; HR, hazard ratio; mBC, metastatic breast cancer; mPFS, median PFS; PFS, progression-free survival; mut, mutant; WT, wild type.

1. Chia S, et al. ASCO 2023. P1078; 2. Turner S, et al. SABCS 2021. PD15-01.

SOLAR-1 trial safety profile: With the exclusion of hyperglycemia, most adverse events are of low grade

Most frequent adverse events, according to single preferred term and regardless of relationship to intervention, in the overall patient population

	Alpelisib–Fulvestrant Group (N=284)		Placebo–Fulvestrant Group (N=287)	
Adverse event, %	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Hyperglycemia[a]	63.7	36.6	9.8	0.6
Diarrhea[b]	57.7	6.7	15.7	0.3
Nausea[b]	44.7	2.5	22.3	0.3
Decreased appetite	35.6	0.7	10.5	0.3
Rash[c]	35.6	9.9	5.9	0.3
Vomiting[b]	27.1	0.7	9.8	0.3
Weight loss	26.8	3.9	2.1	0
Stomatitis	24.6	2.5	6.3	0
Fatigue	24.3	3.5	17.1	1.0
Asthenia	20.4	1.8	12.9	0
Alopecia	19.7	0	2.4	0
Mucosal inflammation	18.3	2.1	1.0	0
Pruritus	18.0	0.7	5.6	0
Headache	17.6	0.7	13.2	0
Dysgeusia	16.5	0	3.5	0
Arthralgia	11.3	0.4	16.4	1.0

[a]Adverse events of any grade related to were reported in 65.8% of the patients in the alpelisib–fulvestrant group (grade ≥3 in 38.0%) and in 10.5% of those in the placebo–fulvestrant group (grade ≥3 in 0.7%). [b]Gastrointestinal toxic effects of any grade (including nausea, vomiting, and diarrhea were reported in 75.4% of the patients in the alpelisib–fulvestrant group (grade ≥3 in 8.8%) and in 34.8% of those in the placebo–fulvestrant group (grade ≥3 in 1.0%). Diarrhea was assessed at a maximum grade 2 severity in 18.3% of the patients. [c]Adverse events of any grade related to were reported in 53.9% of the patients in the alpelisib– fulvestrant group (grade ≥3 in 20.1%) and in 8.4% of those in the placebo–fulvestrant group (grade ≥3 in 0.3%).

André F. *et al.* N Engl J Med. 2019.380(20):1929-1940.

CAPItello-291: Phase 3 trial comparing capivasertib + fulvestrant vs PBO + fulvestrant

CAPItello-291 study design

69% of patients had received prior CDK4/6 inhibitor therapy

Patients with HR+/HER2- aBC

- Men and pre-/post-menopausal women
- Recurrence while on or <12 months from end of adjuvant AI, or PD while on prior AI for aBC
- ≤2 lines of prior endocrine therapy for aBC
- ≤1 line of chemotherapy for aBC
- FFPE tumor sample from the primary/recurrent cancer available for retrospective central molecular testing

R 1:1 (N=708)

Capivasertib 400 mg twice daily, 4 days on, 3 days off + fulvesrant

PBO Twice daily, 4 days on, 3 days off + fulvesrant

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

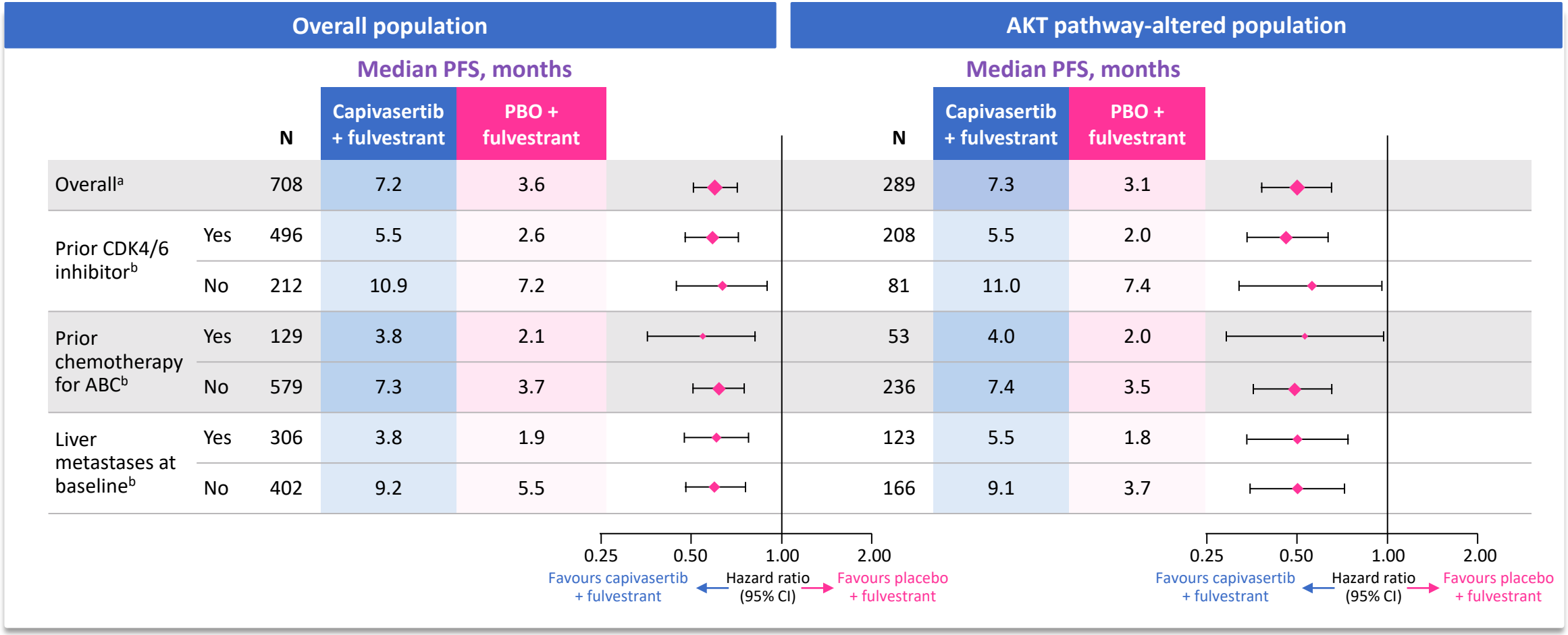
Dual primary endpoints

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

*Region 1: United States, Canada, Western Europe, Australia, and Israel, Region 2: Latin America, Eastern Europe and Russia vs Region 3: Asia. aBC, advanced (locally advanced [inoperable] or metastatic) breast cancer.

aBC, advanced breast cancer; AI, aromatase inhibitor; AKT, protein kinase B; CDK4/6, cyclin-dependent kinase 4/6; FFPE, formalin-fixed paraffin-embedded; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridisation; PBO, placebo; PD, progressive disease; PFS, progression-free survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase; PTEN, phosphatase and tensin homologue; R, randomisationTurner NC, et al. Cancer Res. 2023; 83 (5_Supplement): GS3-04

CAPitello-291: mPFS capivasertib + fulvestrant vs placebo + fulvestrant[1,2]



The CAPItello-291 study design included the overall population
Capivasertib has been approved by the FDA for the AKT pathway-altered population
As of March 2024, capivasertib is not yet approved by the European Commission

aBC, advanced breast cancer; AKT, protein kinase B; CDK4/6, cyclin-dependent kinase 4/6; CI, confidence interval; (m)PFS, (median) progression-free survival

1. Turner NC, et al. Ann Oncol. 2023;8 (1suppl_4): 101223-101223 (poster 187O); 2. Turner NC, et al. N Engl J Med. 2023;388:2058–2070

CAPitello-291 trial safety profile: Most common AE of any grade reported in CAPI + FUL were diarrhea, rash and nausea

Adverse Reactions, %	CAPI + FUL (N=355)		PBO + FUL (N=350)	
	Grade 1 or 2	Grade 3 or 4	Grade 1 or 2	Grade 3 or 4
Diarrhea	63.1	9.3	19.7	0.3
Rasha	25.9	12.1	6.9	0.3
Nausea	33.8	0.8	14.9	0.6
Fatigue	20.3	0.6	12.3	0.6
Vomiting	18.9	1.7	4.3	0.6
Headache	16.6	0.3	11.7	0.6
Decreased appetite	16.3	0.3	5.7	0.6
Hyperglycemia	14.1	2.3	3.4	0.3
Stomatitis	12.7	2.0	4.9	0
Asthenia	12.1	1.1	9.7	0.6
Pruritus	11.8	0.6	6.6	0
Anemia	8.5	2.0	3.7	1.1
UTI	8.7	1.4	6.6	0

[a]The group term of rash includes the preferred terms of rash, rash macular, maculopapular rash, rash papular, and rash pruritic.

AE, adverse events; CAPI, capivasertib; FUL, fulvestrant; UTI, uinary tract infection

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

The CAPItello-291 study design included the overall population
Capivasertib has been approved by the FDA for the AKT pathway-altered population
As of March 2024, capivasertib is not yet approved by the European Commission

EMERALD: Phase 3 trial of elacestrant vs SoC endocrine therapy

EMERALD study design

Visceral metastasis[b]: ~70 %
Prior ChT[b]: ~22%

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 advanced disease permitted
- 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

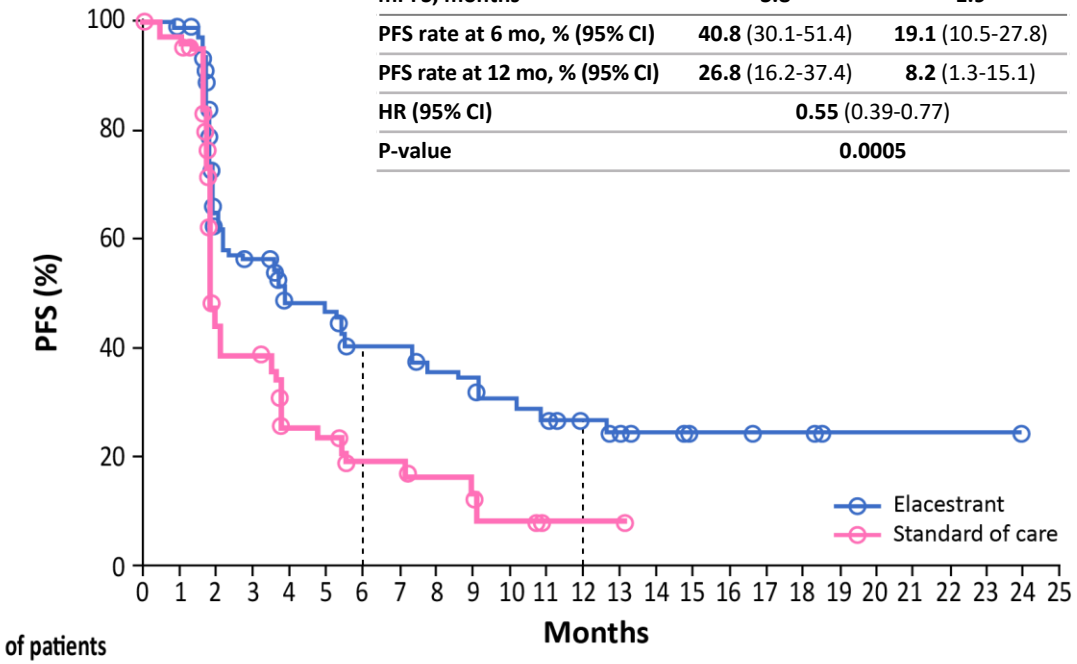
Stratification factors
- *ESR1*-mut status
- Presence of visceral metastases
- Prior treatment with fulvestrant

[a]345 mg of elacestrant is equivalent to 400 mg of elacestrant dihydrochloride. [b]*ESR1*-mut population in elacestrant arm
CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; *ESR1*(-mut), estrogen receptor 1 (mutation); ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PD, progressive disease; PFS, progression-free survival; R, randomization; SoC, standard of care.
Bidard FC, et al. J Clin Oncol. 2022;40:3246-3256.

EMERALD: 45% reduction in risk of progression in patients with *ESR1*-mut

PFS in patients with *ESR1*-mut: elacestrant vs SoC

	Elacestrant (n=115)	SoC (n=113)
mPFS, months	**3.8**	**1.9**
PFS rate at 6 mo, % (95% CI)	**40.8** (30.1-51.4)	**19.1** (10.5-27.8)
PFS rate at 12 mo, % (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**	

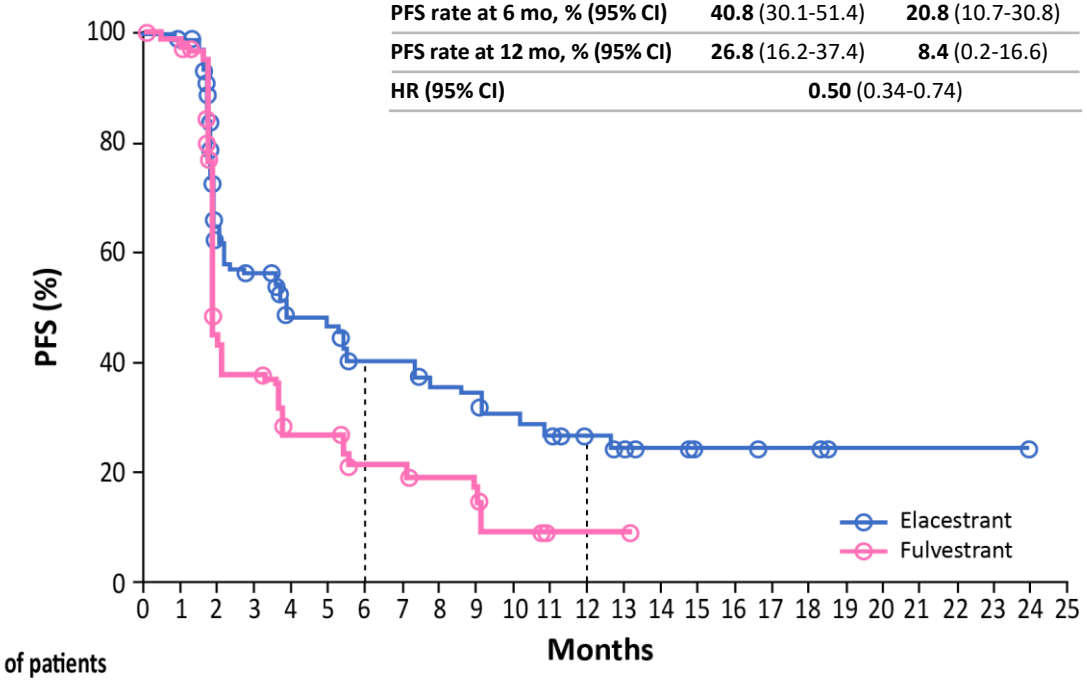


No. of patients

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										

PFS in patients with *ESR1*-mut: elacestrant vs fulvestrant*

	Elacestrant (n=115)	Fulvestrant (n=83)
PFS rate at 6 mo, % (95% CI)	**40.8** (30.1-51.4)	**20.8** (10.7-30.8)
PFS rate at 12 mo, % (95% CI)	**26.8** (16.2-37.4)	**8.4** (0.2-16.6)
HR (95% CI)	**0.50** (0.34-0.74)	



No. of patients

Elacestrant	115	54	35	26	21	16	11	7	5	4	1	1	0
Fulvestrant	83	29	16	10	8	3	1	0					

Elacestrant has been approved by the FDA and European Commission for *ESR1*-mut population

*Exploratory analysis; patients without *ESR1*-mut: n=250, 52% of the ITT population.

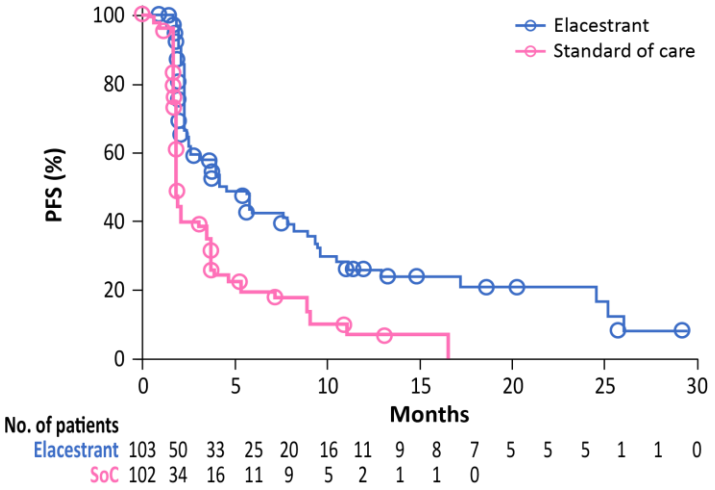
CI, confidence interval; HR, hazard ratio; ITT, intention to treat; PFS, progression-free survival; SoC, standard of care.

Bidard FC, et al. J Clin Oncol. 2022;40:3246-3256.

EMERALD: Duration of prior CDK4/6 inhibitor therapy is positively associated with mPFS in patients with *ESR1*-mut

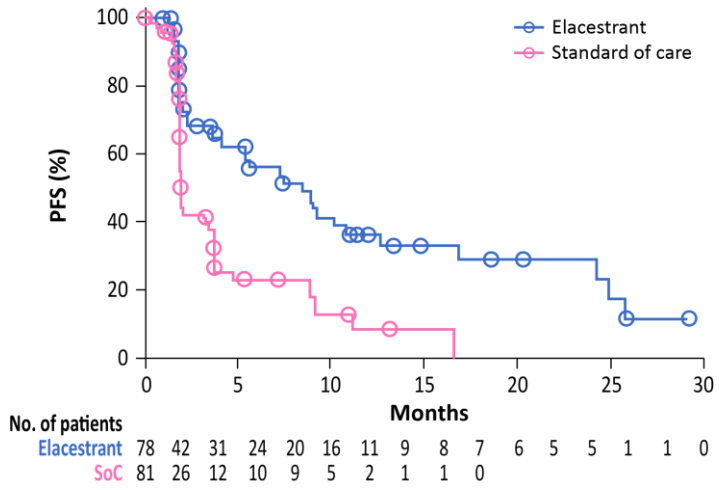
At least 6 months of prior CDK4/6i

	Elacestrant	SoC
mPFS, months (95% CI)	**4.14** (2.20-7.79)	**1.87** (1.87-3.29)
PFS rate at 12 mo, % (95% CI)	**26.02** (15.12-36.92)	**6.45** (0.00-13.65)
HR (95% CI)	**0.517** (0.361-0.738)	



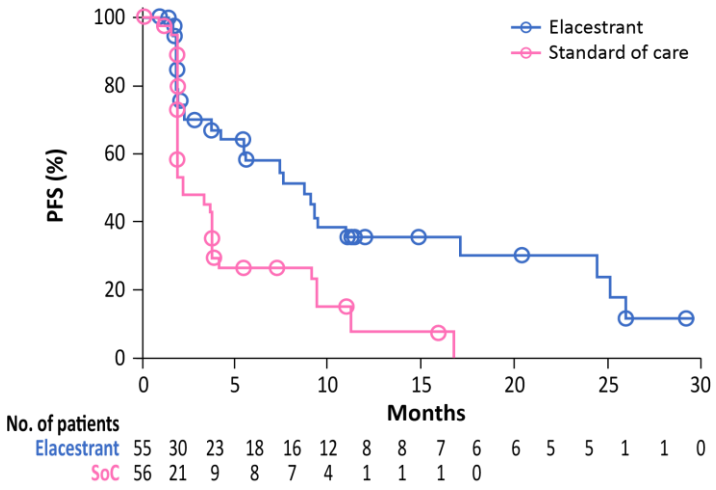
At least 12 months of prior CDK4/6i

	Elacestrant	SoC
mPFS, months (95% CI)	**8.61** (4.14-10.84)	**1.91** (1.87-3.68)
PFS rate at 12 mo, % (95% CI)	**35.81** (21.84-49.78)	**8.39** (0.00-17.66)
HR (95% CI)	**0.410** (0.262-0.634)	



At least 18 months of prior CDK4/6i

	Elacestrant	SoC
mPFS, months (95% CI)	**8.61** (5.45-16.89)	**2.10** (1.87-3.75)
PFS rate at 12 mo, % (95% CI)	**35.79** (19.54-52.05)	**7.73** (0.00-20.20)
HR (95% CI)	**0.466** (0.270-0.791)	



Results are observational in nature. There was no prespecified statistical procedure controlling for type 1 errorCDK4/6(i), cyclin-dependent kinase 4/6 (inhibitor); CI, confidence interval; ESR1, estrogen receptor 1; HR, hazard ratio; (m)PFS, (median) progression-free survival; SoC, standard of care

Bardia A, et al. Cancer Res. 2023;83 (5_Supplement): GS3-01

EMERALD subgroup analysis: PFS consistent across relevant subgroups in patients with endocrine-sensitive *ESR1*-mut tumors

PFS summary in *ESR1*-mut patients with ≥12 months of prior CDK4/6 inhibitor

Patients	% (n)	Median PFS, months (95% CI)		Hazard ratio (95% CI)
		Elacestrant	SOC	
All *ESR1*-mut patients[9]	100 (159)	8.61 (4.14–10.84)	1.91 (1.87–3.68)	0.410 (0.262–0.634)
ESR1-mut and bone metastases[a]	86 (136)	9.13 (5.49–16.89)	1.91 (1.87–3.71)	0.381 (0.230–0.623)
ESR1-mut and liver and/or lung metastases[b]	71 (113)	7.26 (2.20–10.84)	1.87 (1.84–1.94)	0.354 (0.209–0.589)
ESR1-mut and *PIK3CA*-mut[c]	39 (62)	5.45 (2.14–10.84)	1.94 (1.84–3.94)	0.423 (0.176–0.941)
ESR1-mut and HER2-low expression[d]	48 (77)	9.03 (5.49–16.89)	1.87 (1.84–3.75)	0.301 (0.142–0.604)
ESR1-mut and *TP53*-mut	38 (61)	8.61 (3.65–24.25)	1.87 (1.84–3.52)	0.300 (0.132–0.643)

[a]85% of patients had bone and other sites of metastases (30% of these patients had no liver or lung involvement); [b]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); [c]Includes E545K, H1047R, E542K amongst others;
[d]HER2 IHC 1+, and 2+ with no ISH amplification. Data not available for all patients

Bardia A, et al. SABCS 2023. PS17-02.

EMERALD: >10% adverse events were low grade; no Grade 4 treatment-related AEs were reported with elacestrant[1,2]

	Elacestrant (n=237)		SoC (n=230)	
	All grades	Grade 3 or 4[c]	All grades	Grade 3 or 4[c]
AEs, %[1,2,a]				
Musculoskeletal pain[a]	41	7	39	1
Nausea	**35**	**2.5**	**19**	**0.9**
Fatigue[b]	26	2	27	1
Vomiting[b]	19	0.8	9	0
Decreased appetite	15	0.8	10	0.4
Diarrhea	13	0	10	1
Constipation	12	0	6	0
Headache	12	2	12	0
Abdominal pain[b]	11	1	10	0.9
Hot flush	11	0	8	0
Dyspepsia	10	0	2.6	0
AEs leading to discontinuation, %[2]				
	3.4		0.9	

Nausea summary[1,2]	Elacestrant (n=237)	SoC (n=230)
Grade 3 nausea, %	**2.5**	**0.9**
Dose-reduction rate due to nausea, %	1.7	NA
Discontinuation rate due to nausea, %	1.3	0.0
Antiemetic use, %*	**8.0**	**10.3 (AI) 3.7 (fulvestrant)**

*Patients may have been on antiemetics prior to enrollment.

[a]Adverse reactions were graded using NCI CTCAE version 5.0; [b]Includes other related terms; [c]Only includes Grade 3 adverse reactions;
AE, adverse event; AI, aromatase inhibitor; NA, not available; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; SoC, standard of care.

1. Stemline Therapeutics. Orserdu (elacestrant). Prescribing Information. 2023; 2. Bardia A, et al. Cancer Res 2023;83:Abstract GS3-01.

Key considerations: The importance of delivering personalized care for patients with ER+/HER2– mBC

- ET in 2L is SoC for patient with no imminent organ failure and long PFS on prior ET[1]
- Data suggest that greater PFS benefit is achieved in patient subgroups with biomarker selected endocrine based therapies[2–5]
- A biomarker-driven treatment algorithm is needed to ensure optimal treatment selection for patients[2–5]
- Biomarker testing is essential during the metastatic treatment course to ensure that patients who are most likely to respond to targeted treatments are identified[6–10]

2L, second line; CDK4/6, cyclin-dependent kinase 4/6; ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; PFS, progression-free survival; SoC, standard of care.

1. Gennari A, et al. Ann Oncol. 2021;32(12):1475-1495; 2. Burstein HJ, et al. J Clin Oncol 2021;39:3959-3977; 3. Turner S, et al. Cancer Res. 2022;82 (4_Supplement): PD15-01; 4. Bidard FC, et al. J Clin Oncol. 2022;40:3246-3256; 5. Turner NC, et al. N Engl J Med. 2023;388:2058-2070; 6. Jeselsohn R, et al. Clin Cancer Res. 2014;20:1757-1767; 7. Jeselsohn R, et al. Cancer Cell. 2018;33:173-186; 8. Allouchery V, et al. Breast Cancer Res. 2018;20:40; 9. Schiavon G, et al. Sci Transl Med. 2015;7;313ra182; 10. Brett JO, et al. Breast Cancer Res. 2021;23:85

Emerging Biomarkers in BC: Implementing Liquid Biopsy *ESR1* Mutation Testing

Prof. Federico Rojo
Head of Pathology
Fundación Jiménez Díaz University Hospital, Spain

BC, breast cancer; *ESR1,* estrogen recceptor 1

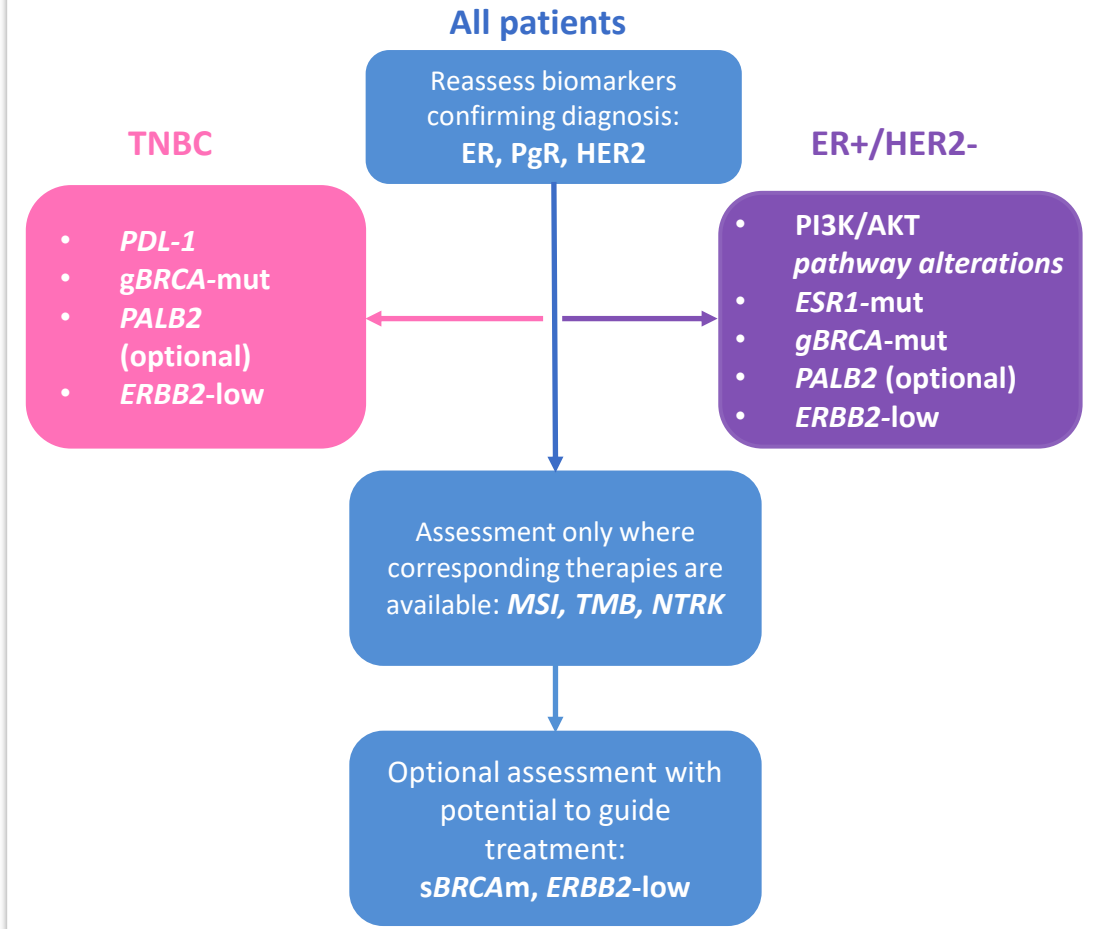
Genomic alteration as target for mBC precision medicine

Biomarker Ranked by ESCAT Score[1]

- **ESCAT Level I :** Ready for clinical use
- **ESCAT level II** : Investigational

Gene	Alteration	Prevalence	ESCAT score
ERBB2	Amplification	15-20%	IA
	Hotspot mutations	4%	IIB
PIK3CA	Hotspot mutations	30-40%	IA
ESR1	Mutations	30-40%	**IA**
BRCA1/2	Germline pathogenic/likely pathogenic variants	4%	IA
	Somatic mutations	3%	**IIB**
PTEN	Mutations	7%	IIA
AKT^{E17K}	Mutations	5%	IIB
PALB2	Germline pathogenic/likely pathogenic variants	1%	**IIB**
NTRK	Fusions	<1%	IC
	MSI-H/dMMR	1%	IC
TMB-H	TMB-H		IC

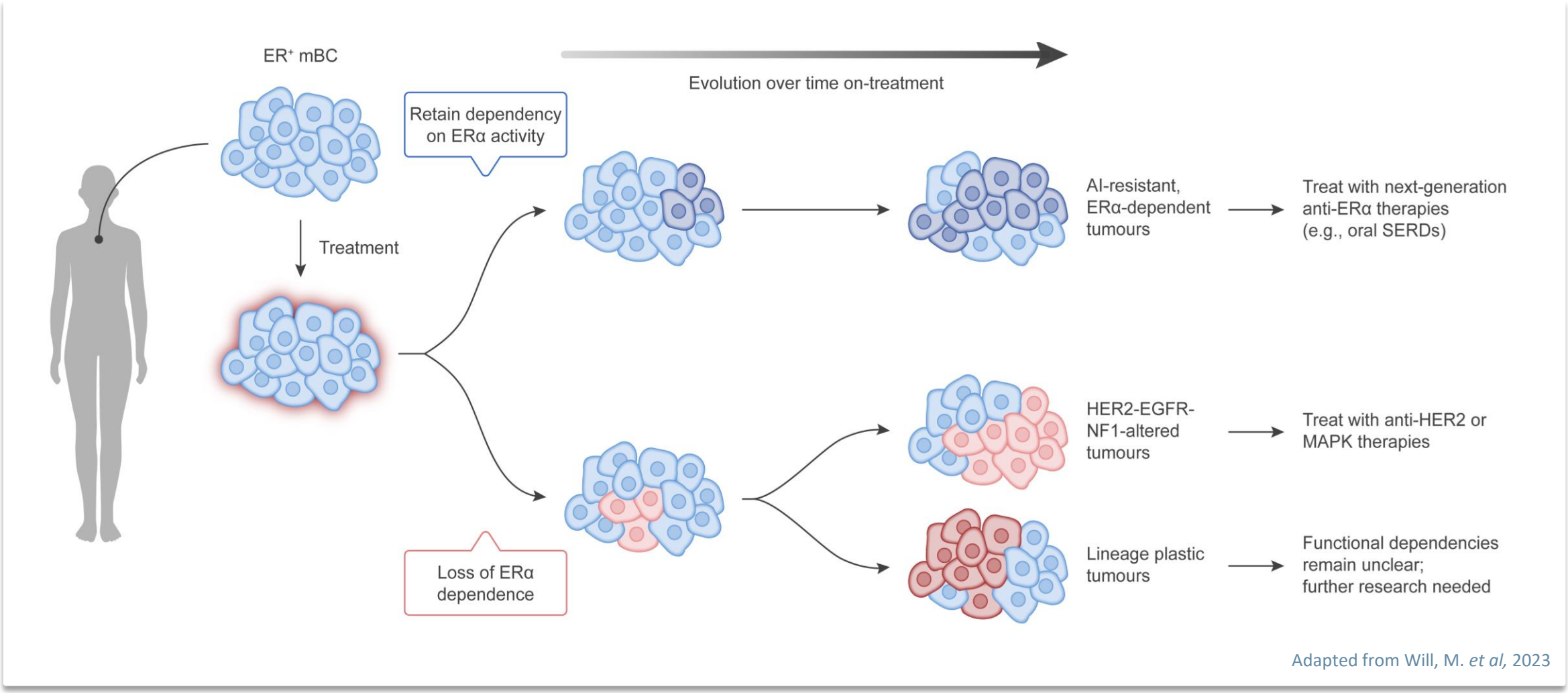
Biomarker Testing Guideline in mBC[2]



AKT, protein kinase B; BRCA, BReast CAncer gene; dMMR, mismatch repair deficiency; ERBB2, Erb-B2 receptor tyrosine kinase 2; ER, estrogen receptor; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; ESR1, estrogen receptor 1; g, germline; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; mut, mutation; MSI(-H), microsatellite instability(-high); NTRK, neurotrophic tyrosine receptor kinase; PALB2, partner and localiser of BRCA2; PD-L1, programmed death-ligand 1; PgR, progesterone receptor; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN, phosphatase and tensin homolog; s, somatic; TMB(-H), tumour mutational burden(-high)

1. Andre F, Mosele F and Westphalen B. NGS use in metastatic cancer. ESMO Webinar Series. 2023. Available at: https://www.esmo.org/meeting-calendar/past-meetings/precision-oncology-genomics-guided-care-update-of-the-recommendations-for-the-use-of-next-generation-sequencing-ngs-for-patients-with-metastatic-cancer (accessed March 2024); 2. ESMO metastatic breast cancer living guidelines, diagnosis and staging, 2023. Available at: https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline/diagnosis-and-staging (accessed March 2024)

Treatment creates selective pressure driving tumour evolution categorized by their dependency on ERα signalling

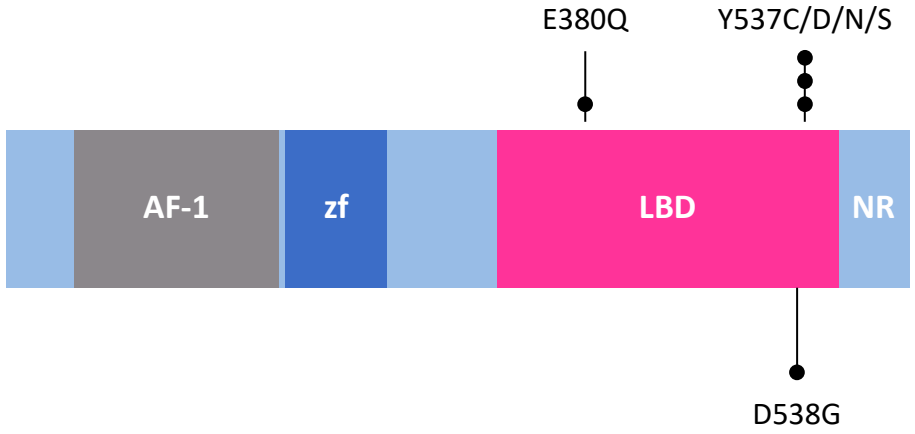


Adapted from Will, M. *et al,* 2023

EGFR, epidermal growth factor receptor; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; MAPK; mitogen-activate protein kinase; mBC, metastatic breast cancer; NF1, neurofibromatosis type 1; SERD, selective estrogen receptor degradors;
Will M, et al. Nat Rev Cancer. 2023;23(10):673-685.

A deep-dive into the ligand binding domain

ESR1-mut stabilizes active ER conformation without the need of a ligand



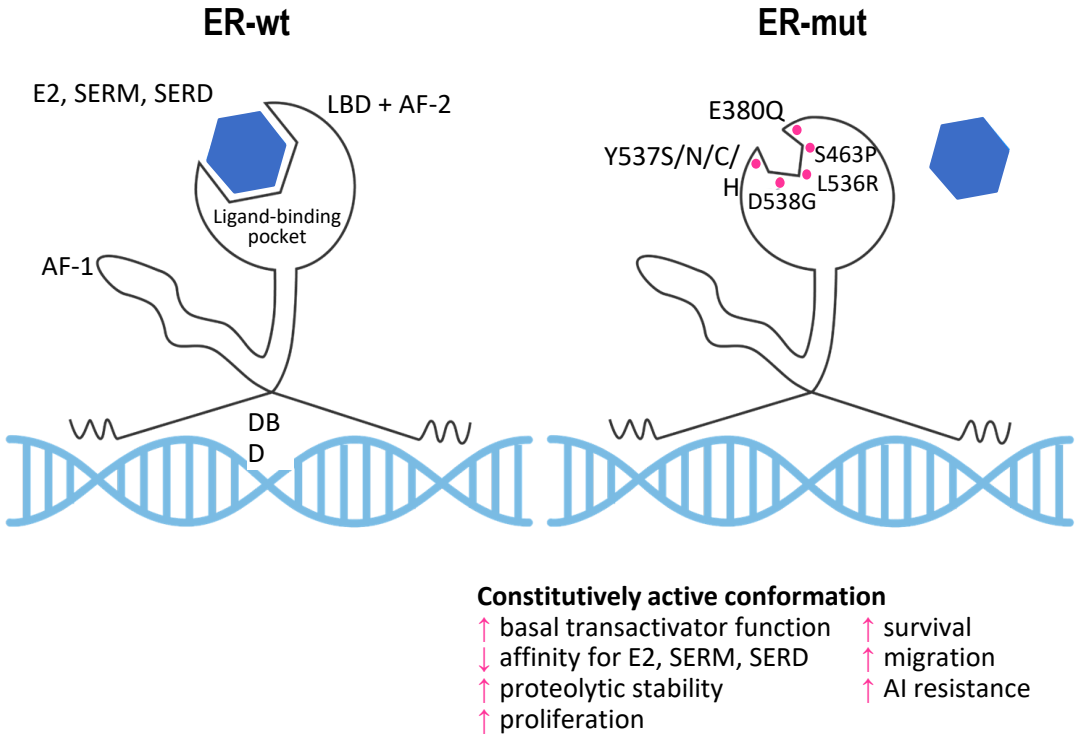
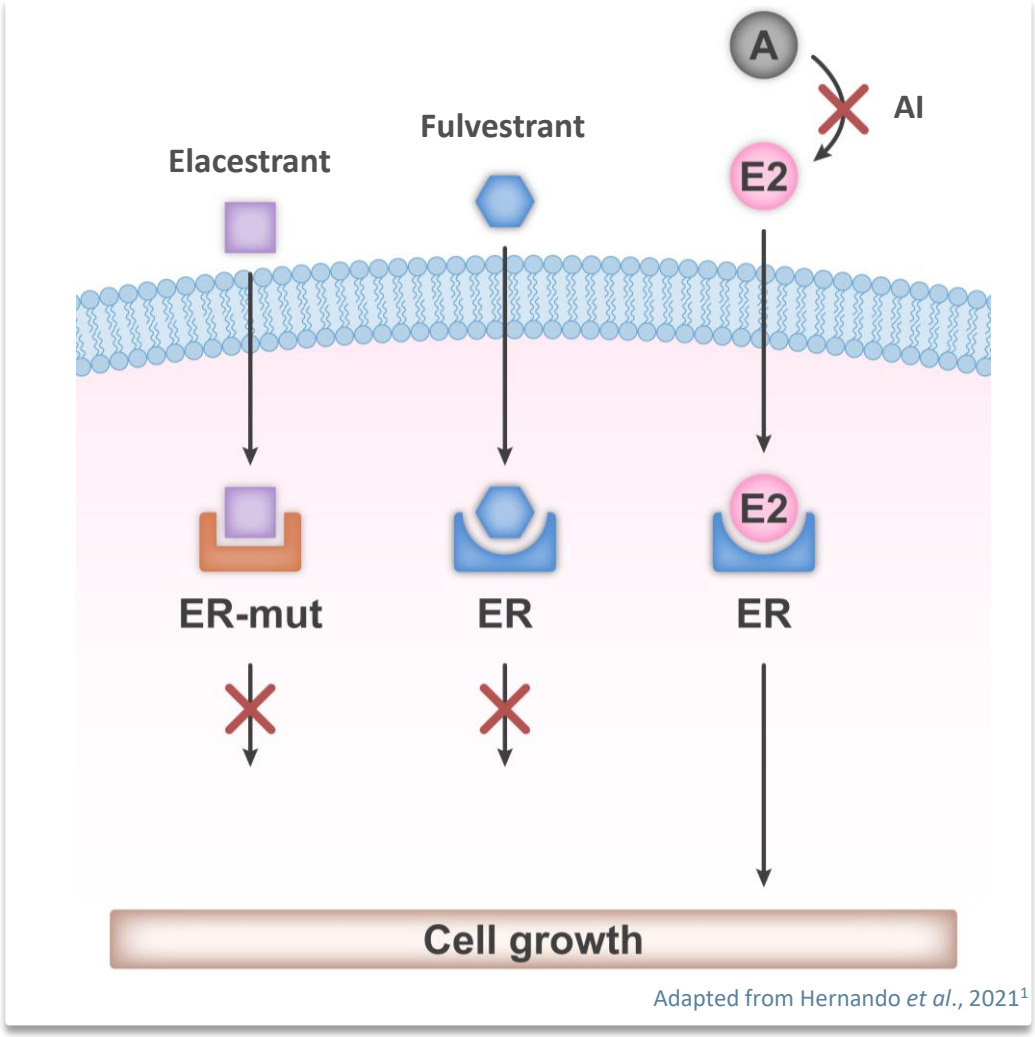


Figure adapted from Piscuoglio S, et al. 2018[3] and Brett JO, et al. 2021.[4]

AF, activating function; AI, aromatase inhibitor; DBD, DNA binding domain; E2, estrogen; *ESR1,* estrogen receptor 1; ER, estrogen receptor; LBD, ligand binding domain; mut; mutations; NR; nuclear receptor C-terminal domain; SERD, selective estrogen receptor degrador; SERM, selective estrogen receptor modulator; wt, wild type; zf, zinc-finger

1.Piscuoglio S. et al. Ann Oncol. 2018.29(4):787-789. 29522117; 2. Brett J. et al. Breast Cancer Res. 2021.23(1):85. 34392831.

Estrogen receptor-α signalling and modes of inhibition



Adapted from Hernando *et al*., 2021[1]

AI block the conversion of androgens (A) to estrogens (E2) decreasing E2 levels needed to activate cell proliferation[1,2]

SERDs (i.e. fulvestrant & elacestrant) act by **binding to ER** accelerating its **degradation**[1,2]

ESR1-mut **decreases** binding **affinity** to **estrogen and fulvestrant**[3]

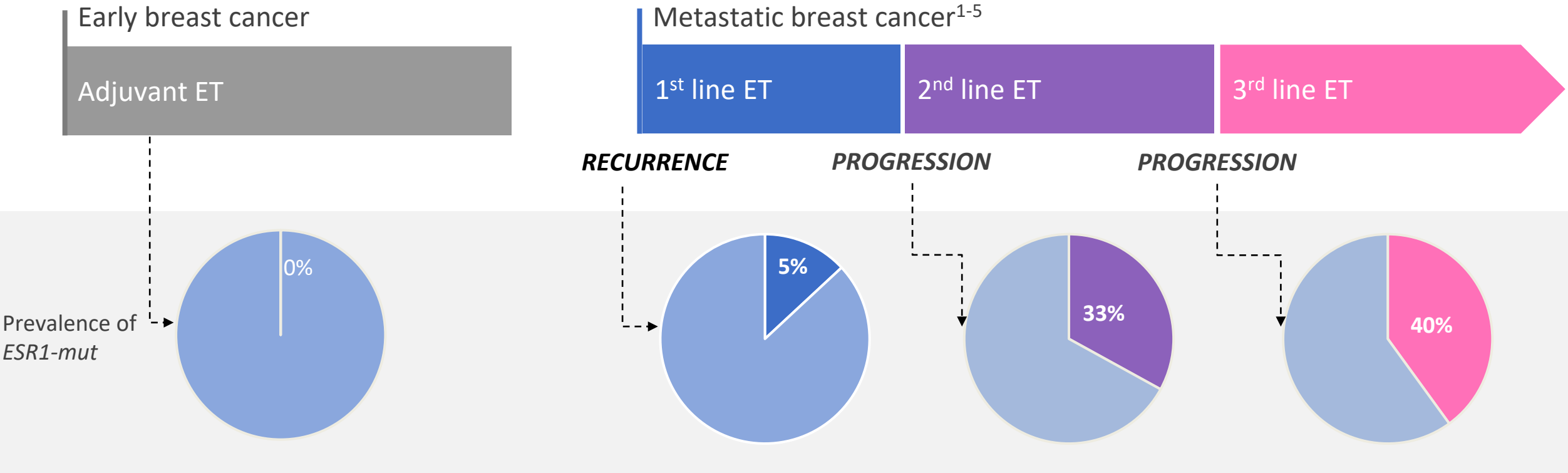
Mutated receptor has an optimal **affinity** to **elacestrant**[2]

AI, aromatase inhibitor; ESR1, estrogen receptor 1; ER, estrogen receptor; mut, mutant; SERDs, selective estrogen receptor degrador; SoC, standard of care

1. Hernando C. et al. Int J Mol Sci. 2021;22(15):7812; 2.Lloyd MR, et al. Ther Adv Med Oncol. 2022;14:17588359221113694; 3. Raheem F, et al. Int J Mol Sci. 2023;24(22):16198.

Prevalence of *ESR1*-mut in tissue and liquid specimens collected in the first three metastatic lines of therapy

Acquired mechanisms of resistance **occurs after prior endocrine therapy in mBC**



Testing for *ESR1*-mut should occur at each progession during the metastatic treatment course, if not detected previously

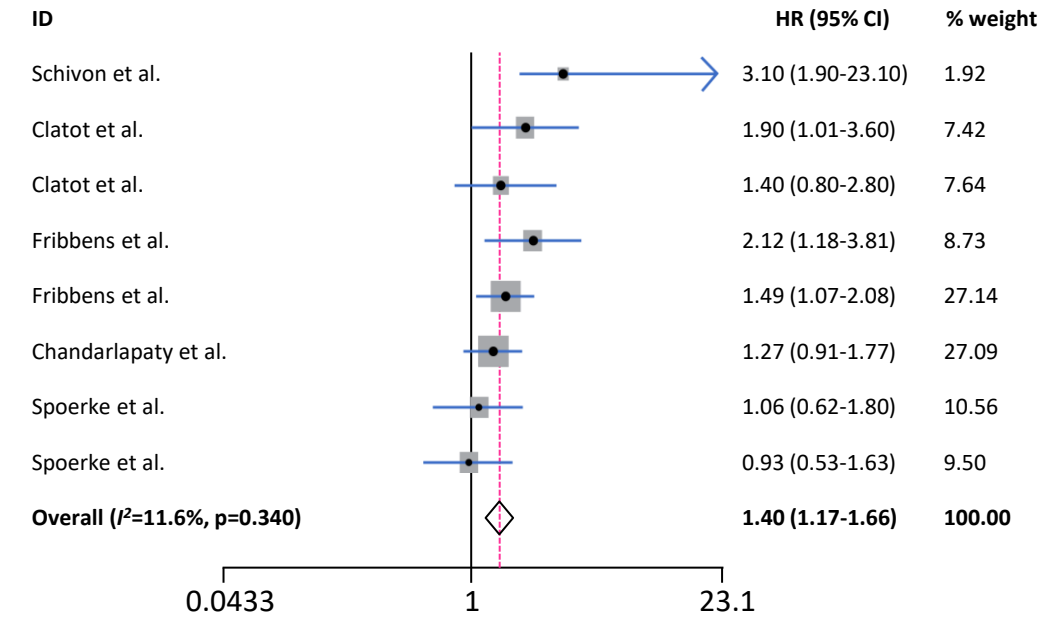
ESR1, estrogen receptor 1; ET, endocrine therapy; mut; mutation

1. Jeselsohn R, et al. Clin Cancer Res. 2014;20:1757-1767; 2. Jeselsohn R, et al. Cancer Cell. 2018;33:173-186.e5; 3. Allouchery V, et al. Breast Cancer Res. 2018;20:40; 4. Schiavon G, et al. Sci Transl Med. 2015;7;313ra182; 5. Brett JO, et al. Breast Cancer Res. 2021;23:85

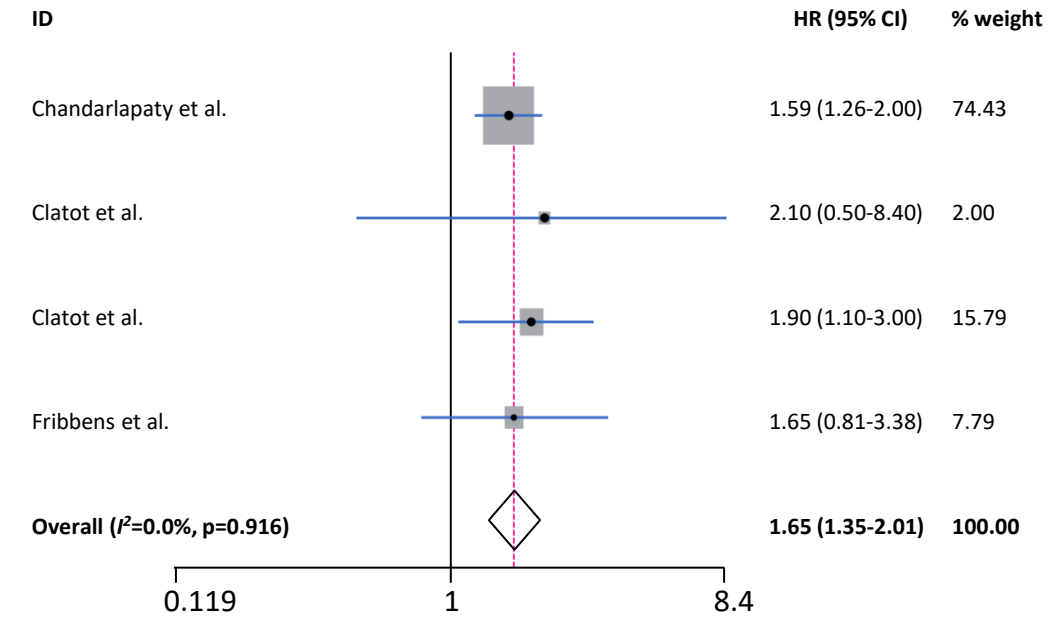
ESR1-mut as a prognostic and predictive biomarker

- Meta-analysis: 5 studies (1530 patients with ER+/HER2- mBC)
- Plasma *ESR1*-mut were significantly associated with worse PFS (p<0.0001) and OS (p<0.001) compared with *ESR1*-wt
- The predictive value of *ESR1*-mut has been demonstrated in the EMERALD trial[2]

Plot for PFS



Plot for OS



CI, confidence interval; ER, estrogen receptor; *ESR1,* estrogen receptor 1; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; mBC, metastatic breast cancer; mut; mutation; OS, overall survival; PFS, progression free survival; wt, wild type

1. Zhang K, et al. Cancer Manag Res. 2018;10:2573-2580 2. Bidard FC, et al. J Clin Oncol. 2022;40:3246-3256.

How to design *ESR1*-mut testing in ER+/HER2- mBC

Specimen types and collection considerations

Guidelines recommend *ESR1*-mut testing at recurrence or progression on ET using tissue or liquid biopsy (ASCO, NCCN, ESMO guidelines) [1,2,3]

Tissue biopsy

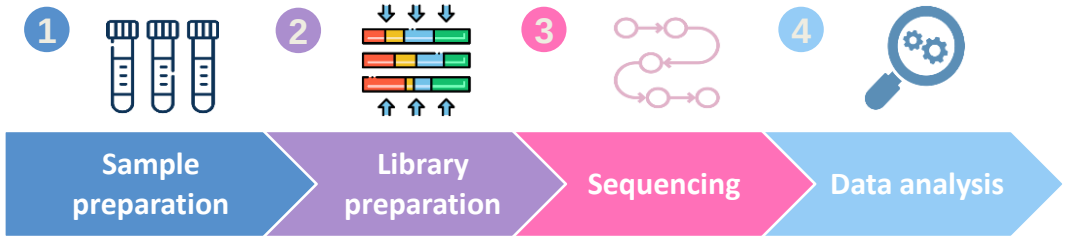
1. Sample collection **timing**
2. Tumour **burden**
3. Tumor sample **content**
4. Availability and DNA quality of **bone metastasis** samples

Liquid biopsy

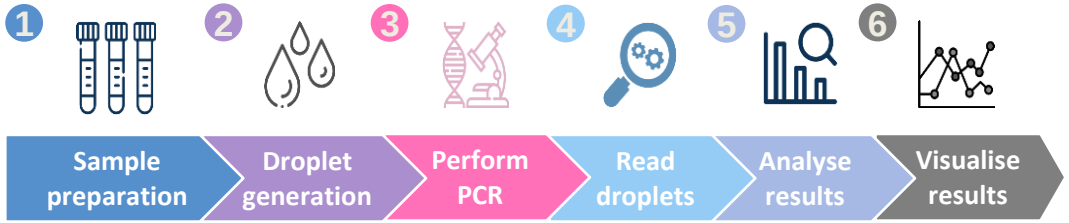
1. Sample collection **timing**
2. Presence (proportion) of **ctDNA** in plasma
3. Sensitivity of method to detect mutant DNA
4. **Pre-analytic** conditions

Techniques workflow

NGS offers a broad coverage of different genes[5,6]



ddPCR can be used to quantify specific genes[7–9]



ASCO, American Society of Clinical Oncology; ctDNA, circulating tumour DNA; ddPCR, droplet digital polymerase chain reaction; DNA, deoxyribonucleic acid; ER, estrogen receptor; *ESR1*, estrogen receptor 1; ESMO, European Society for Medical Oncology; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; mut, mutation; NCCN, National Comprehensive Cancer Network; NGS, next generation sequencing; PCR, polymerase chain reaction

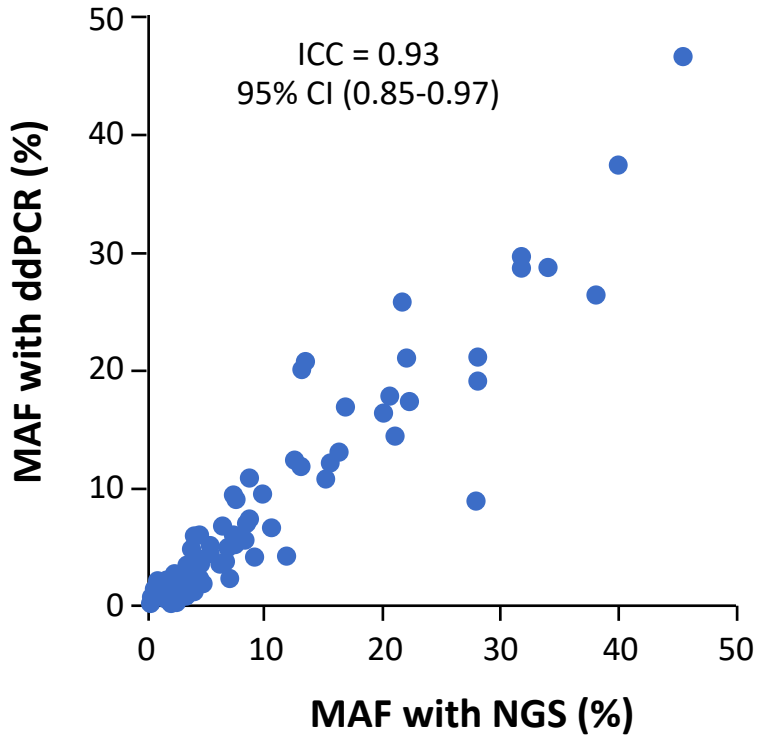
1. Burstein HJ, et al. J Clin Oncol. 2023;41(18):3423-3425; 2.ESMO metastatic breast cancer living guidelines. Available at: https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline/er-positive-her2-negative-breast-cancer (accessed March 2024); 3. NCCN clinical practice guidelines in oncology (NCCN Guidelines) Breast Cancer Version 1.2024-Jan 25, 2024; 4. Pascual J, et al. Ann Oncol. 2022;33(8):750-768; 5. BIORAD. Next-Generation Sequencing Technology. Available at: https://www.bio-rad.com/en-uk/applications-technologies/next-generation-sequencing-technology?ID=Q106XPE08O1Y (accessed March 2024); 6. BIORAD. Droplet Digital PCR (ddPCR) Technology. Available at: https://www.bio-rad.com/en-uk/life-science/learning-center/introduction-to-digital-pcr/what-is-droplet-digital-pcr?ID=MDV31M4VY (accessed March 2024)

Detection of *ESR1*-mut: Concordance between ddPCR and NGS

The use of **ddPCR** for detection of *ESR1*-mut in mBC cancer has been cross **validated** against **NGS**[1]

Good concordance in *ESR1* MAF **between ddPCR** and **NGS**, both in patients receiving **1L therapy*** and in **≥2L** patients, **resistant to AI**

Correlation of *ESR1* MAF by ddPCR and NGS in patients undergoing 1L AI + CDK4/6i therapy (n=200)

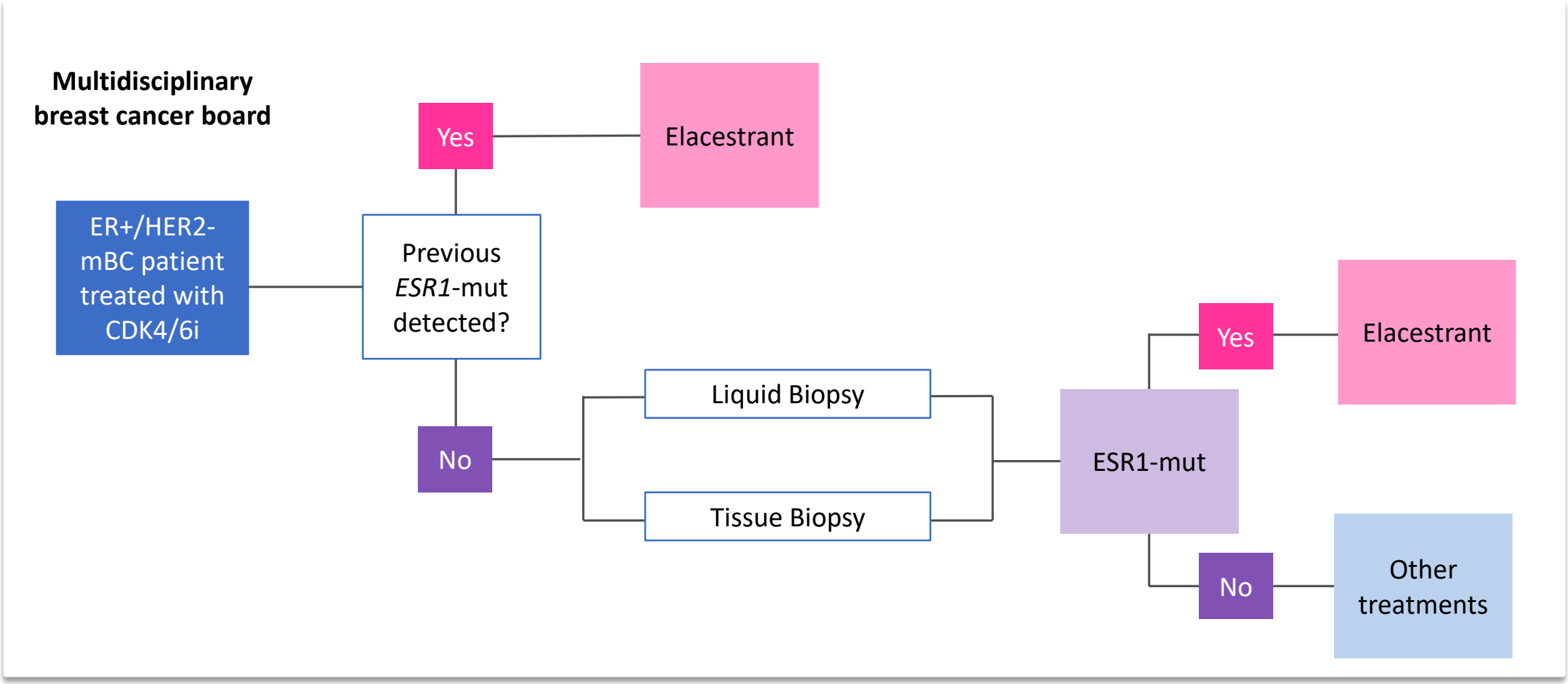


*AI + CDK4/6 inhibitor

1L, first line; 2L, second line; AI, aromatase inhibitor; CDK4/6(i), cyclin-dependent kinase 4/6 (inhibitor); CI, confidence interval; ddPCR, droplet digital polymerase chain reaction; *ESR1*, estrogen receptor 1; ICC, intraclass correlation coefficient; MAF, mutant allele frequency; mBC, metastatic breast cancer; mut, mutation; NGS, next-generation sequencing

Callens C, et al. Anal Chem. 2022;94:6297-6303

My thoughts about *ESR1*-mut testing with liquid and tissue biopsy



CDK4/6i, cyclin dependent kinase 4/6 inhibitor; ER, estrogen receptor; *ESR1,* estrogen receptor 1; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; mut, mutation

Proposed by Prof. Rojo F. , 2024

Summary

1	**Whom** to test?	In patients with ER+/HER2- mBC who experienced progression on prior CDK4/6i therapy
2	**When** to test?	At relapse on a CDK4/6i and subsequent lines, if not previously detected
3	**Where** to test?	Blood or tissue In plasma, methods with sufficient sensitivity for ctDNA analysis: NGS or ddPCR
4	**How** to test?	Universalization of this prognostic and predictive biomarker in clinical routine requires diagnostic laboratories that ensure the quality of results

CDK4/6i, cyclin dependent kinase 4/6 inhibitor; ctDNA, circulating tumour DNA; ddPCR, droplet digital PCR; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; NGS, next-generation sequencing.