COR2ED

THE HEART OF MEDICAL EDUCATION

DEVELOPED BY BREAST CANCER CONNECT

This programme is developed by BREAST CANCER CONNECT, an international group of experts in the field of breast cancer.

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Acknowledgement and disclosures

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- **Prof. Francois-Clement Bidard** discloses financial support/sponsorship from AstraZeneca, Daiichi-Sankyo, Caris, Exact Sciences, General Electrics Healthcare, GSK, Inatherys, Lilly, Merck KGaA, Menarini Silicon Biosystems, Menarini/Stemline, Novartis, Pfizer, Prolynx, Rain Oncology, Roche, SAGA Diagnostics, Seagen, Sanofi

BREAST CANCER CONNECT ANIMATED VIDEO

OPTIMIZING TREATMENT SELECTION AND MAKE APPROPRIATE SEQUENCING DECISIONS FOR PATIENTS WITH ER+/HER2- MBC PREVIOUSLY TREATED WITH CDK4/6 INHIBITORS[3]

Prof. Francois-Clement Bidard
University of Versailles/Paris-Saclay, Paris, France

September 2023

CDK4/6, Cyclin-Dependent Kinase 4/6; ER+, Estrogen Receptor Positive; HER2-, Human Epidermal Growth Factor Receptor 2 Negative; MBC, Metastatic Breast Cancer

CLINICAL TAKEAWAYS

- To optimize treatment selection, molecular characterization should be conducted for each patient, taking into account 'stable' characteristics and 'labile' traits which are often associated with resistance to endocrine therapy
- *ESR1* mutation testing should be done with a liquid biopsy platform at the time of progression on an aromatase inhibitor as well as after subsequent lines of progression
- Elacestrant was the 1st oral SERD to be FDA approved (January 2023), with optimal efficacy and manageable safety for patients with *ESR1* mutated ER+/HER2- advanced or metastatic breast cancer
- Oral SERDs are being studied as a monotherapy and in combination with targeted therapies (i.e. CDK4/6, PI3K and AKT inhibitors), offering promising prospects for their integration into clinical practice

AKT, Protein Kinase B; CDK4/6, Cyclin-Dependent Kinase 4/6; ESR1, Estrogen Receptor 1; FDA, U.S. Food and Drug Administration; HER2, Human Epidermal Growth Factor Receptor 2; PI3K, Phosphoinositide 3-Kinase; SERD, Selective Estrogen Receptor Degrader.

CLINICAL SCENARIO

PATIENT CASE: *DE NOVO* METASTATIC BREAST CANCER

PATIENT
Monica D.

AGE
54 y.o postmenopausal women

MEDICAL HISTORY
Well controlled hypertension, osteopenia, BMI = 29
+FH of prostate cancer in father, age 80

PRESENTATION
Mild fatigue

JUNE 2021
PRESENTATION

SEP 2023
PROGRESSION

Biopsy
- G2 invasive carcinoma of the left breast, NST
- ER+ (80%), PR+ (0%), HER2- (0)

Imaging: Bone & CT scan
- multiple lytic bone lesions

Diagnosis (June 2021):
- ER+/HER2- *de novo* mBC

1st Line Treatment:
- Letrozole and ribociclib

1st Line Response
- Clinical and radiological response (breast and axilla)
- Densification of bone lesions

Disease Progression
- New liver metastasis and new lytic bone mets
- No re-growth of breast/axillary lesions

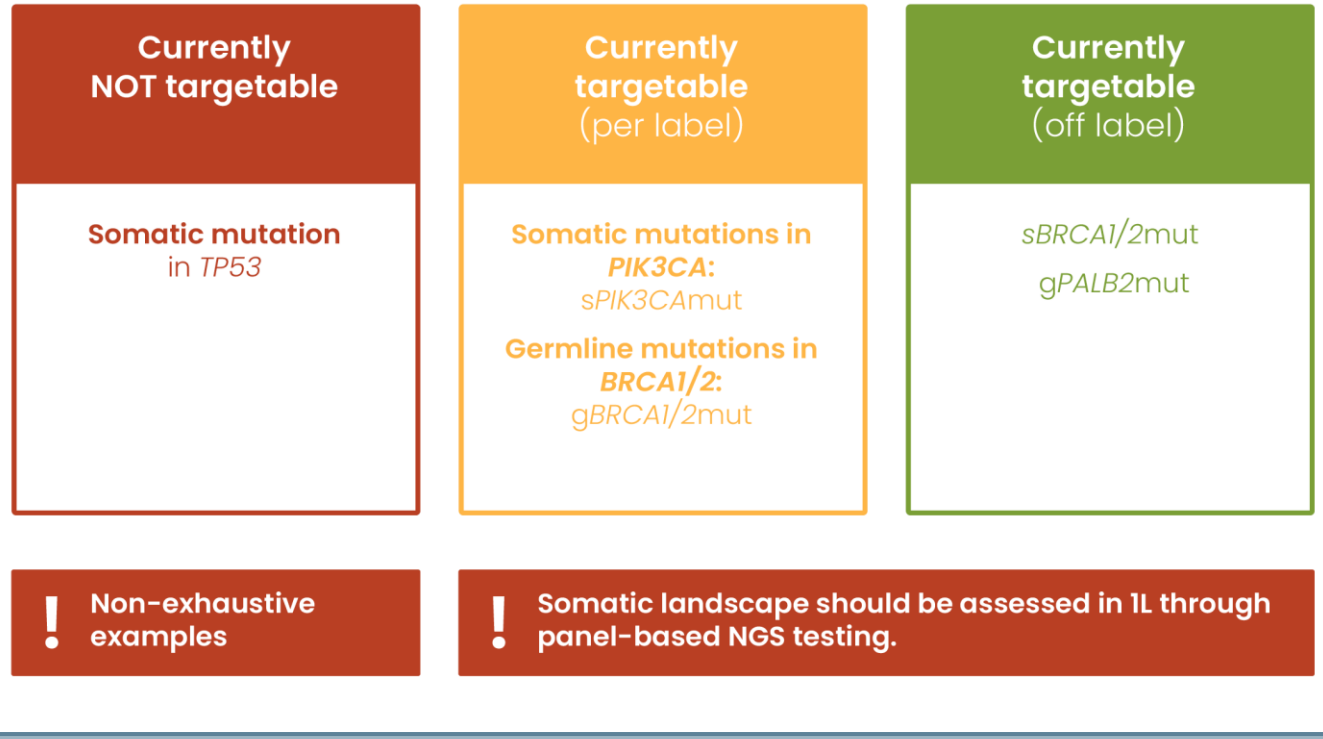
Archived primary tumour tissue
- No *PIK3CA* mutation, no g*BRCA1/2* mutation

BMI, Body Mass Index; ER+, Estrogen Receptor; FH, Family History; HER2, Human Epidermal Growth Factor Receptor 2; NST, No Special Type; y.o, years old

MOLECULAR CHARACTERISATION

MOLECULAR CHARACTERISATION: ‘STABLE’ BC CHARACTERISTICS

‘STABLE’ BC CHARACTERISTICS | **‘LABILE’ BC CHARACTERISTICS**



BRCA1/2, Germline mutations in Breast Cancer Susceptibility Genes 1 and 2; gBRCA1/2mut, Germline mutations in Breast Cancer Susceptibility Genes 1 and 2; gPALB2mut, Germline mutations in Partner and Localizer of BRCA2; PIK3CA, Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (gene); sBRCA1/2mut, Somatic mutations in Breast Cancer Susceptibility Genes 1 and 2; sPIK3CAmut, Somatic mutations in Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (gene); TP53, Tumor Protein 53

MOLECULAR CHARACTERISATION: ‘LABILE’ BC CHARACTERISTICS

‘STABLE’ BC CHARACTERISTICS

‘LABILE’ BC CHARACTERISTICS

➔ **Loss of Estrogen Receptor**

➔ ***ESR1* mutation**

Loss of Estrogen Receptor

New tissue biopsy at progression

18F-FES PET/CT as a possible surrogate

18F-FES PET/CT, 18F-Fluoroestradiol Positron Emission Tomography/Computed Tomography

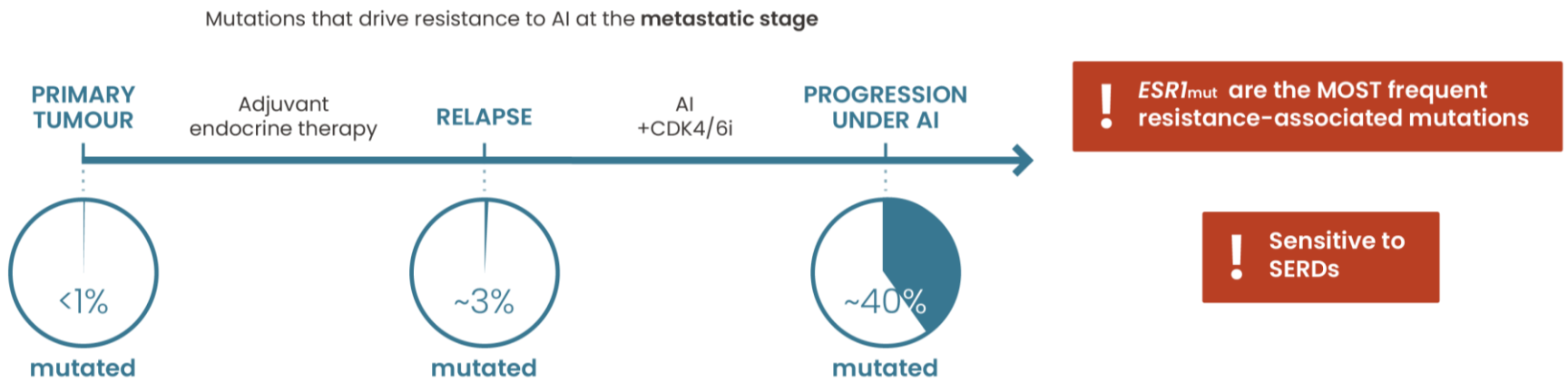
MOLECULAR CHARACTERISATION: ‘LABILE’ BC CHARACTERISTICS

‘STABLE’ BC CHARACTERISTICS | **‘LABILE’ BC CHARACTERISTICS**

- Phenotypic characteristics + genotypic changes associated with resistance to AI and CDK4/6i

➔ Loss of Estrogen Receptor expression by tumor cell

➔ ***ESR1* mutation**



AI, Artificial Intelligence; CDK4/6i: Cyclin-Dependent Kinase 4/6 Inhibitor; ESR1, Estrogen Receptor 1; SERDs, Selective Estrogen Receptor Degraders

MOLECULAR CHARACTERISATION

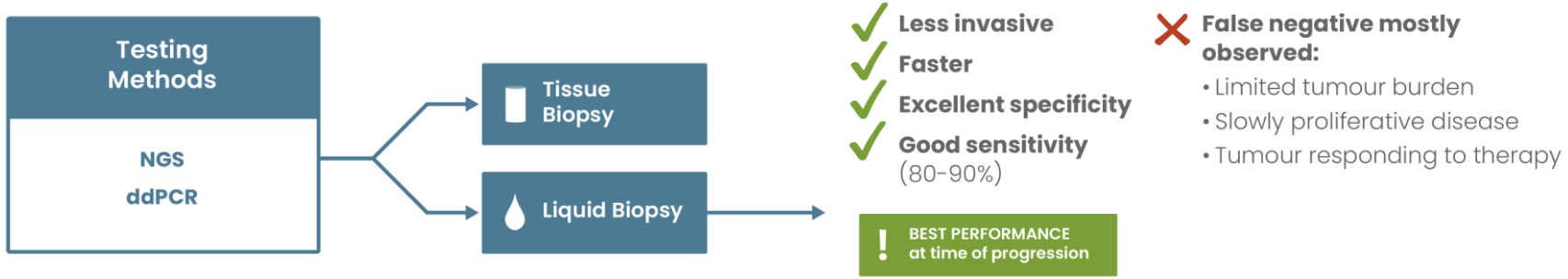
‘STABLE’ BC CHARACTERISTICS

‘LABILE’ BC CHARACTERISTICS

- Phenotypic characteristics + genotypic changes associated with resistance to AI and CDK4/6i

➔ Loss of Estrogen Receptor expression by tumor cell

➔ ***ESR1* mutation**



ctDNA, Circulating Tumor DNA; ddPCR, Digital Droplet Polymerase Chain Reaction; ESR1, Estrogen Receptor 1; NGS, Next-Generation Sequencing

UPDATED CLINICAL SCENARIO

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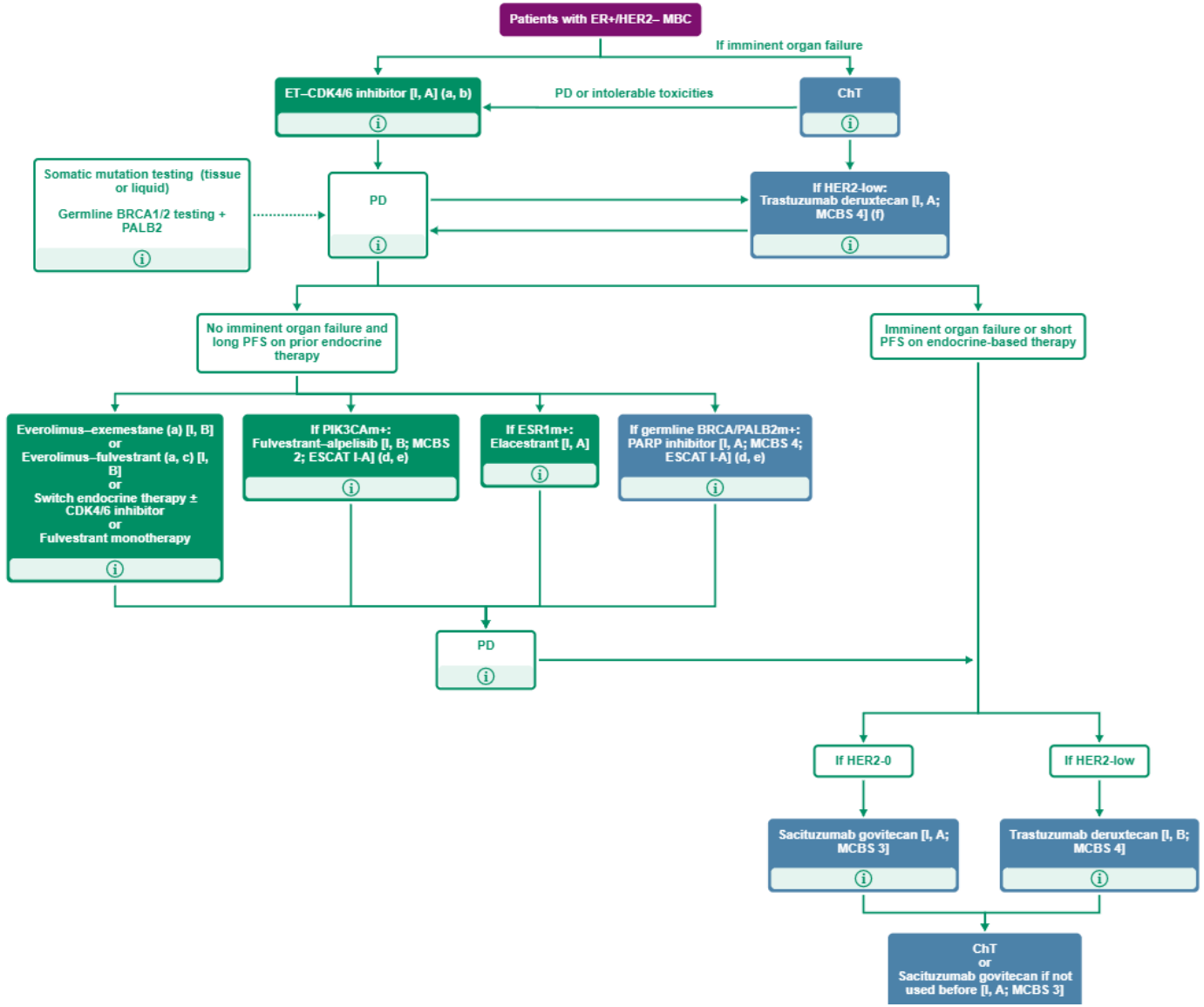
ER+, Estrogen Receptor Positive; ESR1, Estrogen Receptor 1; gBRCA1/2, Germline mutations in Breast Cancer Susceptibility Genes 1 and 2; HER2-, Human Epidermal Growth Factor Receptor 2 Negative; PIK3CA, Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (gene)

TREATMENT OPTIONS: PATIENT CASE SPECIFIC

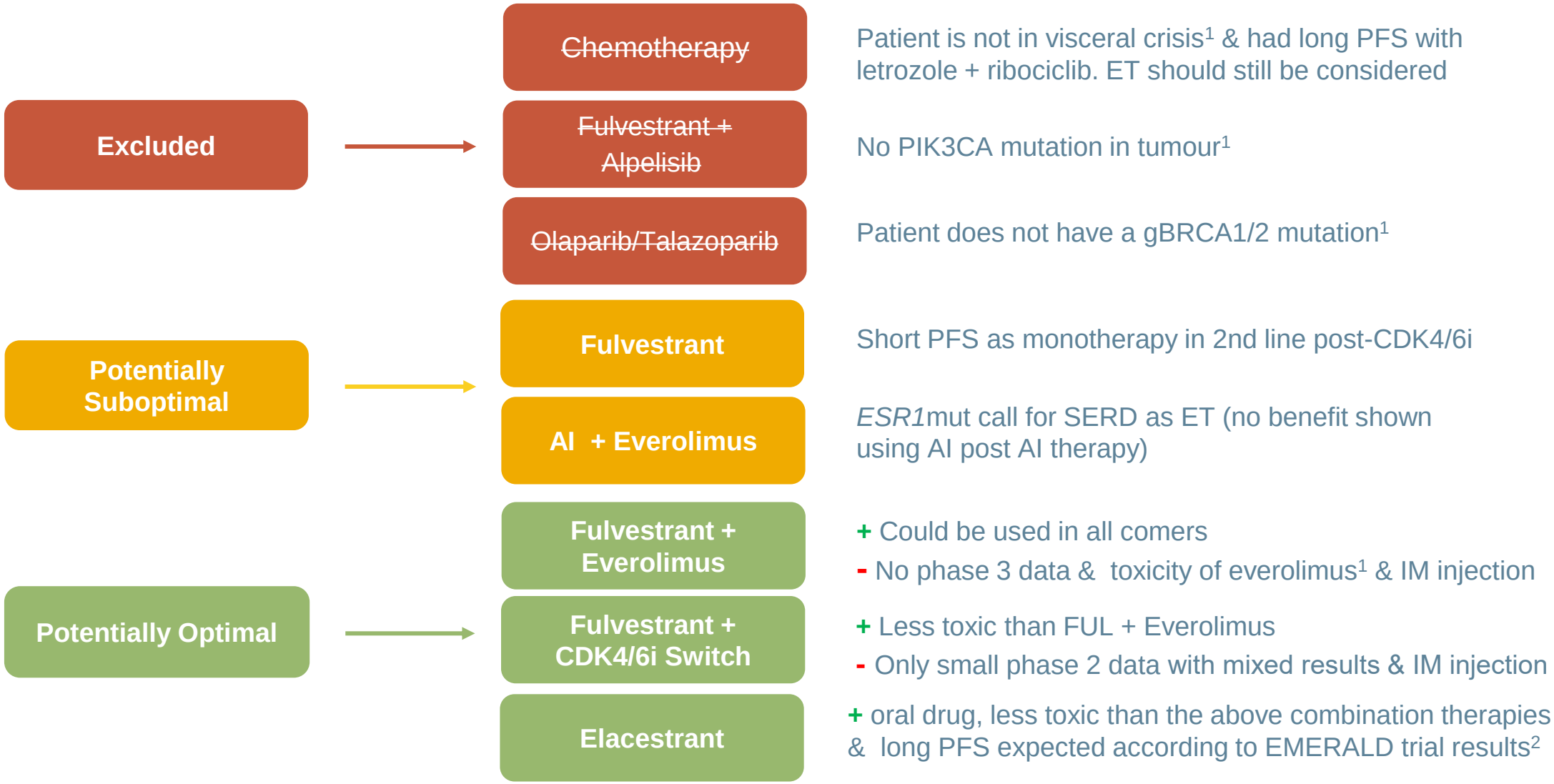
ESMO TREATMENT GUIDELINES FOR ER+/HER2- MBC



ADC, antibody-drug conjugate; BRCA, breast cancer (gene); CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ChT, chemotherapy; ESR1, estrogen receptor 1 (gene); ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor 2 HR, hormone receptor; PALB2, pattern and localizer BRCA2; PARP, poly ADP ribose polymerase; PFS, progression free survival;PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (gene),

https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline/er-positive-her2-negative-breast-cance r (Septembe 2023)

AVAILABLE CURRENT TREATMENT OPTIONS: CASE SPECIFIC



AI, Aromatase Inhibitor; CDK4/6i, Cyclin-Dependent Kinase 4/6 Inhibitor; ESR1, Estrogen Receptor 1; ET, Endocrine Therapy; FUL, Fulvestrant; gBRCA1/2, Germline mutations in Breast Cancer Susceptibility Genes 1 and 2; IM, intramuscular; PFS, Progression-Free Survival; PIK3CA, Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (gene); SERD, Selective Estrogen Receptor Degrader

1. https://www.annalsofoncology.org/article/S0923-7534(21)04498-7/fulltext (Accessed August 08, 2023); 2. Bidard, J Clin Oncol. 2022; PMID: 35584336

ELACESTRANT & THE EMERALD TRIAL

JANUARY 2023: ELACESTRANT (ORSERDU) APPROVAL

FDA approves elacestrant for ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer

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On January 27, 2023, the Food and Drug Administration (FDA) approved elacestrant (Orserdu, Stemline Therapeutics, Inc.) for postmenopausal women or adult men with ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.

FDA also approved the Guardant360 CDx assay as a companion diagnostic device to identify patients with breast cancer for treatment with elacestrant.

ER, estrogen receptor; ESR1, estrogen receptor 1; HER2, human epidermal growth factor receptor 2

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-elacestrant-er-positive-her2-negative-esr1-mutated-advanced-or-metastatic-breast-cancer (accessed May 23, 2023)

PHASE 3 EMERALD: STUDY DESIGN

- A multicentre, international, randomised, open-label, active-controlled phase 3 trial for postmenopausal patients with ER+/HER2- MBC

Key inclusion criteria
Advanced/metastatic ER+/HER2- breast cancer; progressed or relapsed on or after one or two lines of ET, one of which was given in combination with a CDK4/6 inhibitor, for advanced or MBC;
ECOG PS 0 or 1

→ **Elacestrant (400 mg oral QD)**

→ Investigator's choice of fulvestrant, anastrozole, letrozole, exemestane

- Primary end point: assess PFS in all patients and those with m*ESR1*
- Secondary end point: assess OS in all patients and those with m*ESR1*
- Study design considerations:
  - planned sample size: 466 patients (randomised 1:1)
  - planned number of countries/study sites: ~17/215
  - planned study duration: ~30–33 months
  - stratification factors: m*ESR1* status (detected by ctDNA), prior fulvestrant and presence of visceral disease

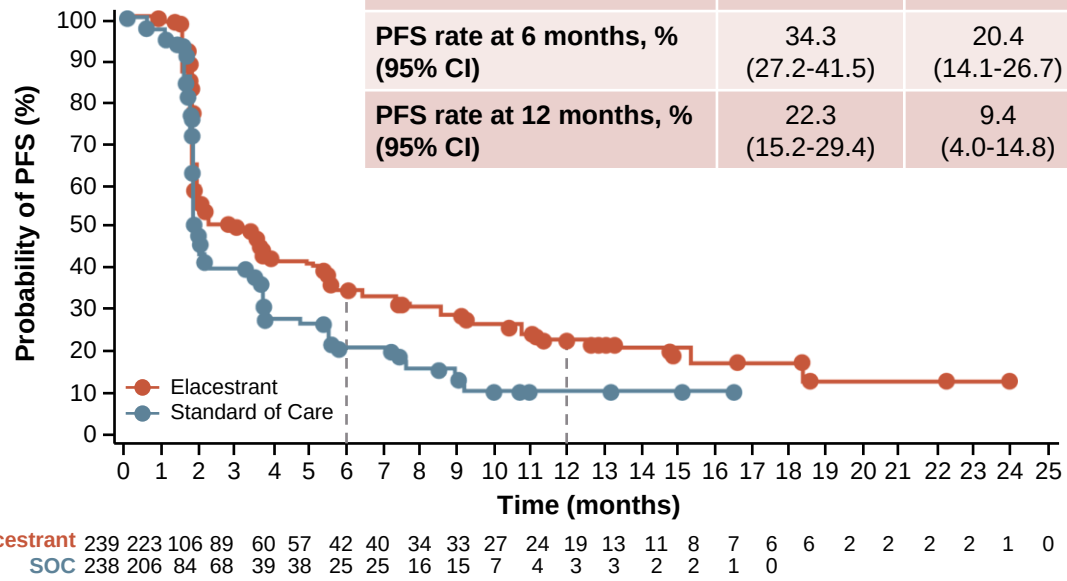
CBR, clinical benefit rate; CDK4/6, cyclin-dependent kinase 4/6; ctDNA, circulating tumour DNA; DoR, duration of response; ECOG PS; Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; ET, endocrine therapy; HER2, hormone epidermal growth factor receptor 2; MBC, metastatic breast cancer; m*ESR1*, estrogen receptor 1 mutation; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PRO patient reported outcome; QD, Use "every day"

Bardia A, et al. SABCS 2021. Abstract GS2-02. Oral presentation

EMERALD: PFS RATE AT 6 & 12 MONTHS ALL PATIENTS AND m*ESR1* GROUP

All patients

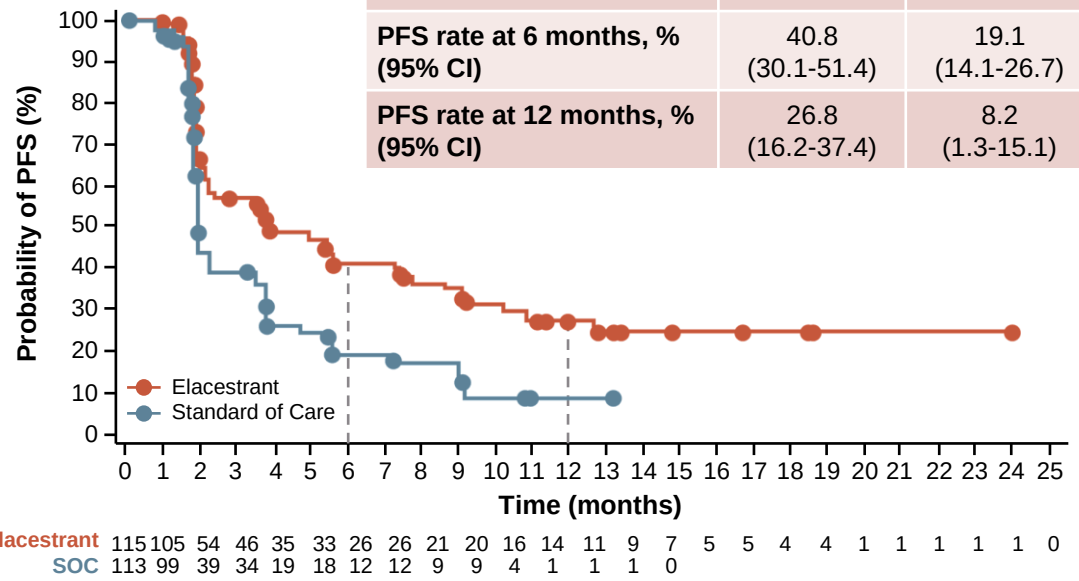
	Elacestrant	SoC
N	**239**	**238**
PFS rate at 6 months, % (95% CI)	34.3 (27.2-41.5)	20.4 (14.1-26.7)
PFS rate at 12 months, % (95% CI)	22.3 (15.2-29.4)	9.4 (4.0-14.8)



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

Patients with tumours harbouring m*ESR1*

	Elacestrant	SoC
N	**115**	**113**
PFS rate at 6 months, % (95% CI)	40.8 (30.1-51.4)	19.1 (14.1-26.7)
PFS rate at 12 months, % (95% CI)	26.8 (16.2-37.4)	8.2 (1.3-15.1)



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										

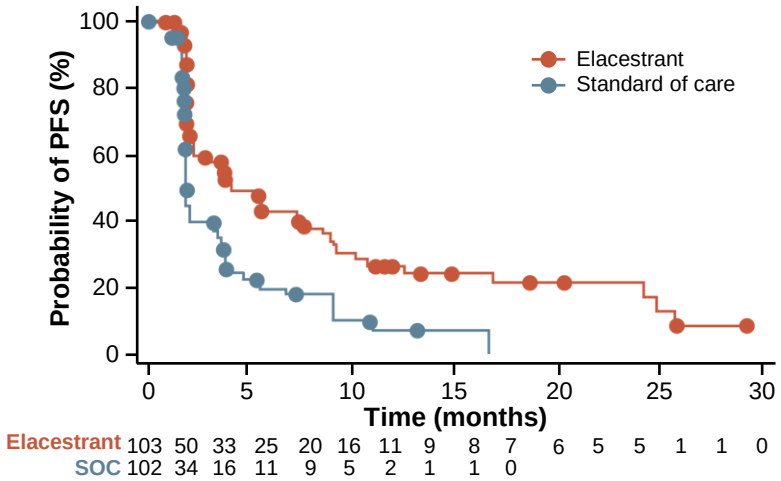
Elacestrant demonstrated a higher PFS rate versus SoC ET at 6 and 12 months in patients with ER+/HER2- advanced/metastatic breast cancer following prior CDK4/6i therapy

CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; m*ESR1*, estrogen receptor 1 mutation; N, sample size; PFS, progression-free survival; SoC, standard of care

Bidard, J Clin Oncol. 2022; PMID: 35584336

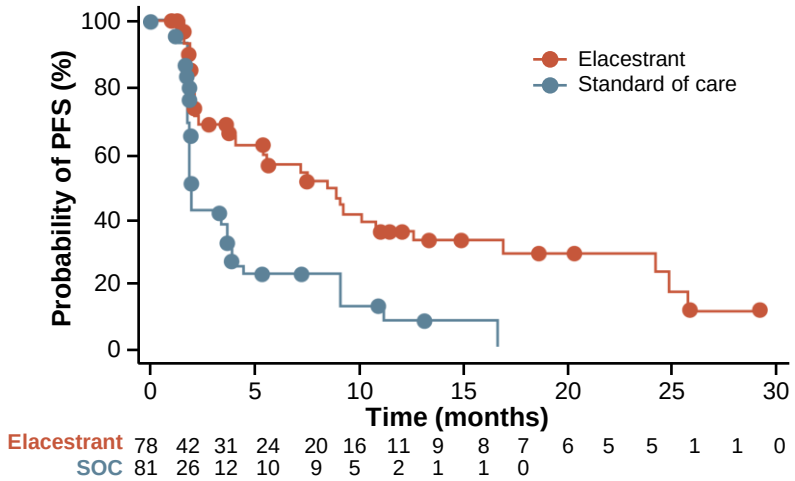
EMERALD: PFS BY DURATION OF CDK4/6i (m*ESR1*)

At least 6 mo CDK4/6i



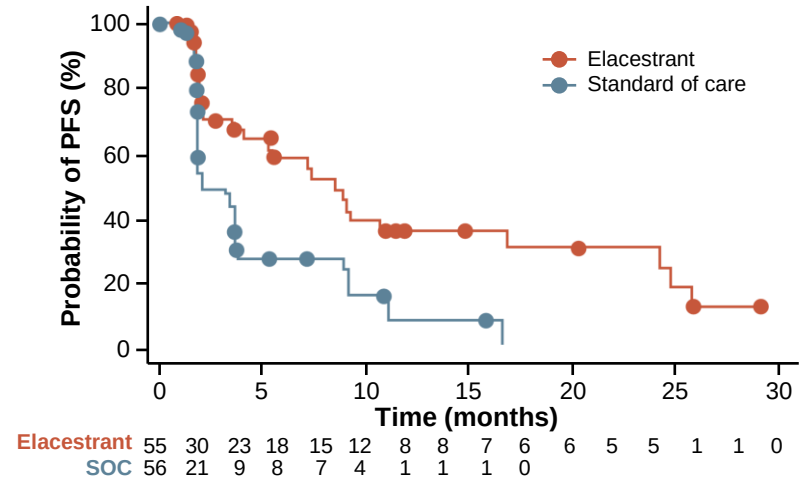
	Elacestrant	SoC Endocrine Therapy
Median PFS, months (95% CI)	**4.14** (2.20-7.79)	**1.87** (1.87-3.29)
PFS rate at 12 months, % (95% CI)	26.02 (15.12-36.92)	6.45 (0.00-13.65)
Hazard ratio (95% CI)	**0.517** (0.361-0.738)	

At least 12 mo CDK4/6i



	Elacestrant	SoC Endocrine Therapy
Median PFS, months (95% CI)	**8.61** (4.14-10.84)	**1.91** (1.87-3.68)
PFS rate at 12 months, % (95% CI)	35.81 (21.84-49.78)	8.39 (0.00-17.66)
Hazard ratio (95% CI)	**0.410** (0.262-0.634)	

At least 18 mo CDK4/6i



	Elacestrant	SoC Endocrine Therapy
Median PFS, months (95% CI)	**8.61** (5.45-16.89)	**2.10** (1.87-3.75)
PFS rate at 12 months, % (95% CI)	35.79 (19.54-52.05)	7.73 (0.00-20.20)
Hazard ratio (95% CI)	**0.466** (0.270-0.791)	

CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; mESR1, estrogen receptor 1 mutation; mo, months; PFS, progression-free survival; SoC; standard of care

Bidard, J Clin Oncol. 2022; PMID: 35584336

ELACESTRANT VS SOC: ADVERSE EVENTS

Event		SoC		
	Elacestrant (N=237)	Total (N=229)	Fulvestrant (N=161)	AI (N=68)
Any AE	218 (92.0)	197 (86.0)	144 (89.4)	53 (77.9)
Grade 3 and 4[a]	64 (27.0)	47 (20.5)	33 (20.5)	14 (20.6)
Grade 5[b]	4 (1.7)	6 (2.6)	5 (3.1)	1 (1.5)
Leading to dose reduction	7 (3.0)	0	0	Not applicable
Leading to study drug discontinuation	15 (6.3)	10 (4.4)	6 (3.7)	4 (5.9)

AEs[c] occurring in ≥10% of patients in any arm	Elacestrant		Total		Fulvestrant		AI	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Nausea	83 (35.0)[d]	6 (2.5)	43 (18.8)	2 (0.9)	26 (16.1)	0	17 (25.0)	2 (2.9)
Fatigue	45 (19.0)	2 (0.8)	43 (18.8)	2 (0.9)	35 (21.7)	1 (0.6)	8 (11.8)	1 (1.5)
Vomiting	45 (19.0)[e]	2 (0.8)	19 (8.3)	0	12 (7.5)	0	7 (10.3)	0
Decreased appetite	35 (14.8)	2 (0.8)	21 (9.2)	1 (0.4)	12 (7.5)	0	9 (13.2)	1 (1.5)
Arthralgia	34 (14.3)	2 (0.8)	37 (16.2)	0	28 (17.4)	0	9 (13.2)	0
Diarrhoea	33 (13.9)	0	23 (10.0)	2 (0.9)	14 (8.7)	1 (0.6)	9 (13.2)	1 (1.5)
Back pain	33 (13.9)	6 (2.5)	22 (9.6)	1 (0.4)	16 (9.9)	1 (0.6)	6 (8.8)	0
AST increased	31 (13.1)	4 (1.7)	28 (12.2)	2 (0.9)	20 (12.4)	2 (1.2)	8 (11.8)	0
Headache	29 (12.2)	4 (1.7)	26 (11.4)	0	18 (11.2)	0	8 (11.8)	0
Constipation	29 (12.2)	0	15 (6.6)	0	10 (6.2)	0	5 (7.4)	0
Hot flush	27 (11.4)	0	19 (8.3)	0	15 (9.3)	0	4 (5.9)	0
Dyspepsia	24 (10.1)	0	6 (2.6)	0	4 (2.5)	0	2 (2.9)	0
ALT increased	22 (9.3)	5 (2.1)	23 (10.0)	1 (0.4)	17 (10.6)	0	6 (8.8)	1 (1.5)

[a] AE severity was graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 5.0. [b] No fatal events were attributed to study drug by the investigator.
[c] Preferred terms were coded using the Medical Dictionary for Regulatory Activities version 23.0. dGrade 1 nausea, n=59 (24.9%); grade 2 nausea, n=18 (7.6%); grade 3 nausea, n= 6 (2.5%); and no patients experienced grade 4 nausea. Percentages reflect maximum grade experienced. eGrade 1 vomiting, n=36 (15.2%); grade 2 vomiting, n=7 (3.0%); grade 3 vomiting, n=2 (0.8%); and no patients experienced grade 4 vomiting. Percentages reflect maximum grade experienced
AE, adverse event; AI, aromatase inhibitor; ALT, alanine transaminase; AST, aspartate transferase; n, sample size; SoC, standard of care
Bidard, J Clin Oncol. 2022; PMID: 35584336

FUTURE PERSPECTIVE & CONCLUSION

FUTURE DIRECTION IN 2ND LINE POST CDK4/6I

CAPITELLO-291[1]

- **Objective:** Investigated Capivesertib as a novel AKT inhibitor
- **Results:** CAPI+ FUL Significantly improved PFS compared to FUL alone. Target Population is TBD

SERENA-6[2]

- **Objective** Assess AZD9833+ CDK4/6i in HR+/HER2-MBC with detectable *ESR1*m Before Progression
- **Primary Outcome:** PFS

evERA[3] & EMBER-3[4]

- **Objective:** Exploring combining oral SERD therapies with everolimus or abemaciclib
- **Primary Outcome:** PFS in ESR1m subpopulation & ITT population

ASCENT-07[5] & DESTINY BREAST-06[6]

- **Objective:** Investigating ADCs as a front-line chemotherapy choice
- **Primary Outcomes:** PFS

ADCs: Antibody-Drug Conjugates; AKT: Protein Kinase B; CAPI: Capivasertib; CDK4/6i: Cyclin-Dependent Kinase 4/6 Inhibitors; ESR1m: Estrogen Receptor 1 Mutations; FUL: Fulvestrant; HR+: Hormone Receptor Positive; ITT: Intent-to-Treat; MBC: Metastatic Breast Cancer; PFS: Progression-Free Survival.

1. Turner N.C, N Engl J Med 2023; 388:2058-2070; 2. https://clinicaltrials.gov/study/NCT04964934?tab=table (Accessed 08 August, 2023);
3. https://classic.clinicaltrials.gov/ct2/show/NCT05306340 (Accessed 08 August, 2023); 4. https://classic.clinicaltrials.gov/ct2/show/NCT04975308 (Accessed 08 August 2023);
5. https://classic.clinicaltrials.gov/ct2/show/NCT05840211 (Accessed 08 August 2023); 6. https://classic.clinicaltrials.gov/ct2/show/NCT04494425 (Accessed 08 August 2023)

CLINICAL TAKEAWAYS

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