QUESITO CLINICO 1:
In pazienti con carcinoma mammario HR-positivo/HER2-negativo, metastatico, con mutazione ESR1, dopo almeno una linea di ormonoterapia (comprendente CDK 4/6i), è raccomandabile elacestrant?

Quale impatto nella pratica clinica?

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Roma, 23 March 2024

Disclosure Information

Luisa Carbognin, MD PhD

I have the following relevant financial relationships to disclose:

- Honoraria from: Novartis, Eli Lilly, Astrazeneca
- Grant/Research support from: AIRC

Topics

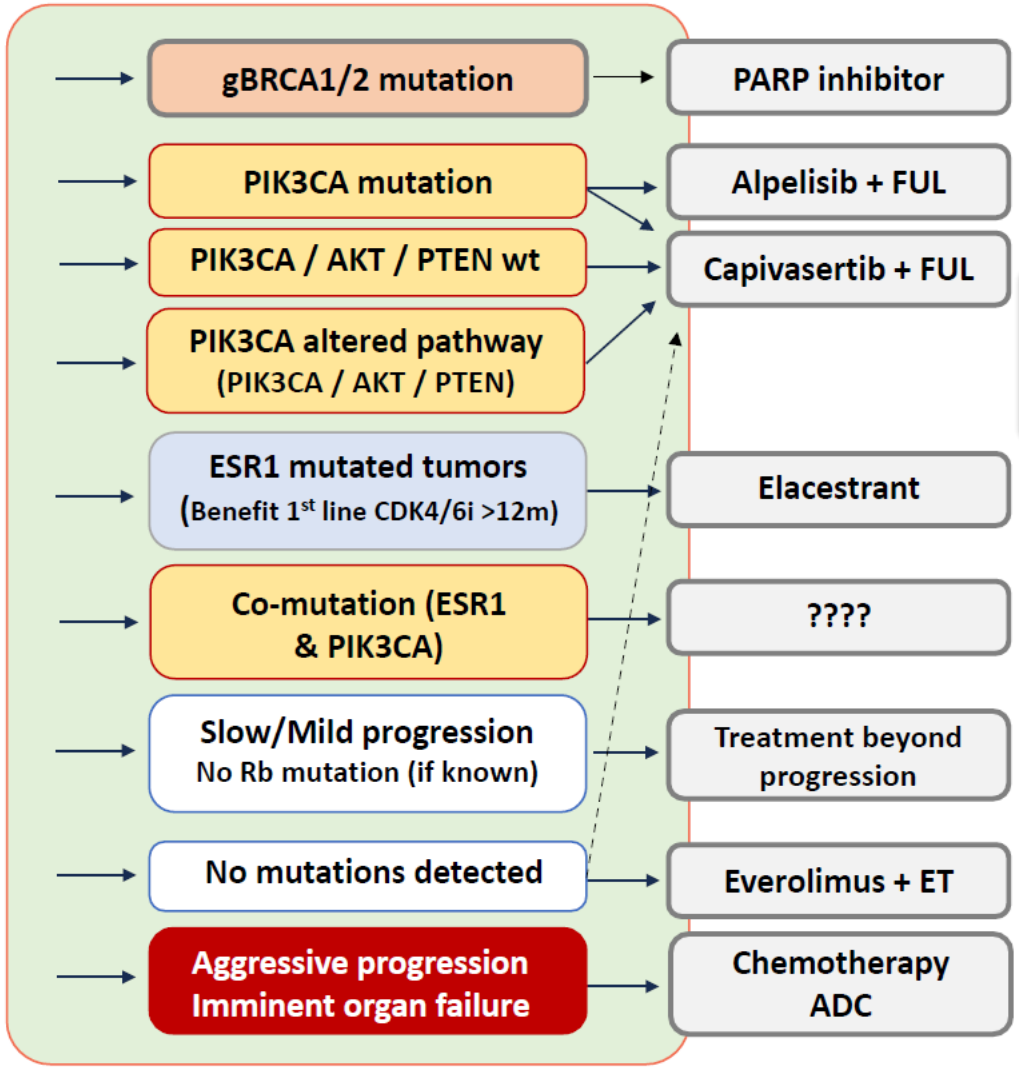
- **Background**
- **Elacestrant Approval**
- ***mESR1* & Companion Diagnostic**
- **Conclusions & Future perspectives**

What to do at the time of CDK4/6i Progression?

First line AI + CDK4/6i

Post-progression on CDK4/6i: defining the playing field

- Prior ET, response duration, Disease Free Interval (ET sensitivity)
- Somatic mutations - ESR1, PIK3CA, AKT, PTEN, others…
- Germline mutations - BRCA1/2, others…
- Biology of the disease (rapid vs. slow progression, oligoprogression)
- Clinical factors, toxicity, comorbidities, patient preferences



Potential Strategy:

Novel ER-targeting Agent?

CDK4/6i beyond progression?

Combinations?

CT/ADC?

Barrios CH, author's slide 2023

Modified from Barrios, SABCS 2023

The four oral SERD (monotherapy) Phase II/III Trials

EMERALD	SERENA-2	AMEERA-3	acelERA
ELACESTRANT*	CAMIZESTRANT*	AMCENESTRANT	GIREDESTRANT
vs Fulvestrant/AI	*vs* Fulvestrant	*vs* Fulvestrant/AI/tam	*vs* Fulvestrant/AI
Phase III (478)	Phase II (240)	Phase II (367)	Phase II (303)
I[ary]: PFS in ITT/ESR1+	I[ary]: PFS in ITT	I[ary]: PFS in ITT	I[ary]: PFS in ITT
Prior CDK4/6i 100%	**Prior CDK4/6i 46.6%**	**Prior CDK4/6i 78.9%**	**Prior CDK4/6i 42%**
Prior Fulvestrant 30.3%	Prior Fulvestrant 0%	Prior Fulvestrant 9.6%	Prior Fulvestrant 19%
Prior CT (≤1) 22.3%	Prior CT (≤1) 19.2%	Prior CT (≤1) 11.4%	Prior CT (≤1) 32%
Visceral 69.7%	Visceral 58.3%**	Visceral 63.8%	Visceral 68%
ESR1mut: 47.7%**	**ESR1mut***: 36.7%**	**ESR1mut*: 41.4%**	**ESR1mut: 39%**
POSITIVE (median PFS: 2.8 vs 1.9 mos)	POSITIVE (median PFS: 7.2-7.7 vs 3.7 mos)	NEGATIVE (median PFS: 3.6 vs 3.7 mos)	NEGATIVE (median PFS: 5.6 vs 5.4 mos)
*Elacestrant is both a ER degrader and inhibithor of estradiol-dependent ER-directed gene trascription **Gaurdant 360	*The dose of 75 mg will go forward **lung and/or liver disease ***GuardantOMNI™	*digital PCR *AMCENESTRANT DEVELOPMENT: STOPPED*	*FoundationOne liquid CDx

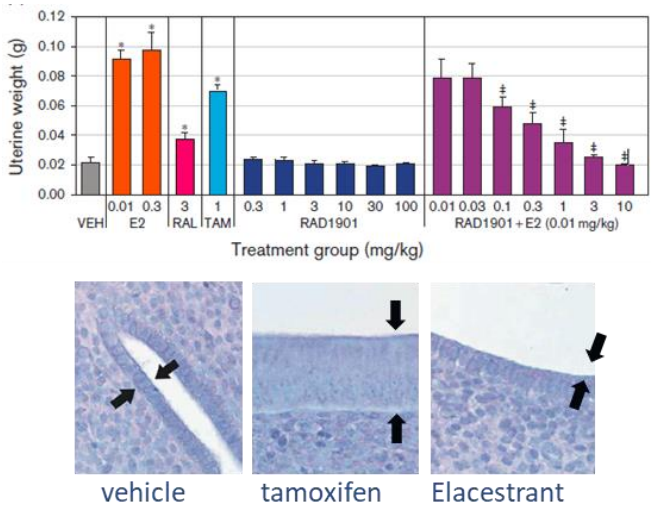
Bidard et al, JCO 2022; Bardia et al, SABCS2022; Oliveira et al, SABCS2022; Tolaney et al, ESMO 2022; Martin et al, ESMO 2022

Miglietta F, CANOA 2023

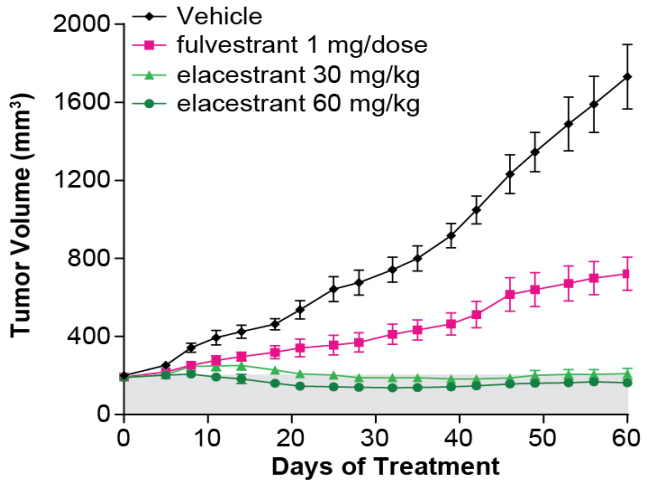
Elacestrant

- Elacestrant is a nonsteroidal, **oral SERD and ER antagonist** that in preclinical studies induced the **degradation of ER** and prevented bone loss in a osteopenic rat model with negligible SERM-like activity detected at the uterine level in *in vitro* and *in vivo* models of BC.[1,2,3]
- In preclinical studies, elacestrant **degraded ER alpha in a dose-dependent manner and disrupted ER signaling**, significantly inhibiting proliferation of BC cells in vitro and in vivo BC models, including those harboring ESR1 mutations.[2,3,4]
- Elacestrant demonstrated antitumor activity and tolerability in a **phase I** trial of heavily pretreated patients with advanced ER+/HER2- BC, including patients with ESR1-mutated tumors[5]

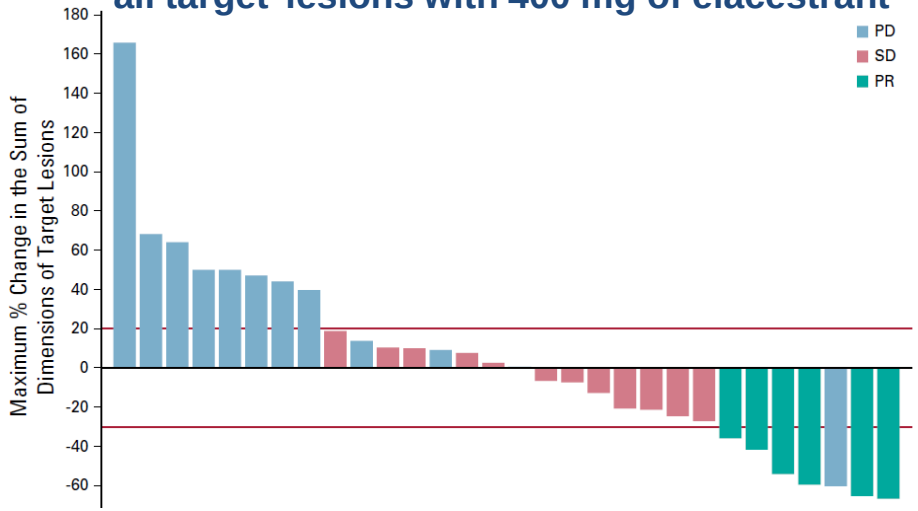
No stimulation in the immature rat model[2]



***In vivo* efficacy of elacestrant in tumors expressing *ESR1* mutations[1]**



Maximum percent change in sum of diameters of all target lesions with 400 mg of elacestrant[5]



1. Bihani T, et al. Clin Cancer Res. 2017; 2. Wardell SE, et al. Endocr Relat Cancer. 2015; 3. Patel HK, et al. Pharmacol Ther. 2018; 4. Garner F, et al. Anticancer Drugs. 2015; 5. Patel HK, et al. Breast Cancer Res. 2019;. 5. Bardia A, et al. J Clin Oncol. 2021

EMERALD Trial

Inclusion Criteria
- Men and postmenopausal women with advanced/metastatic breast cancer
- ER-positive,[a] HER2-negative
- Progressed or relapsed on or after 1 or 2 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
- ECOG PS 0 or 1

N = 477[b]

R

1:1

Elacestrant 400 mg daily[c]

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

PD or withdrawal criterion[f]

Follow Up

Co-Primary Endpoints:[d]
- PFS in all pts
- PFS in m*ESR1*

Key Secondary Endpoint:
- Overall Survival

Stratification Factors:
- *ESR1*-mutation status[e]
- Prior treatment with fulvestrant
- Presence of visceral metastases

Prior Adjuvant Therapy: ~ 65%

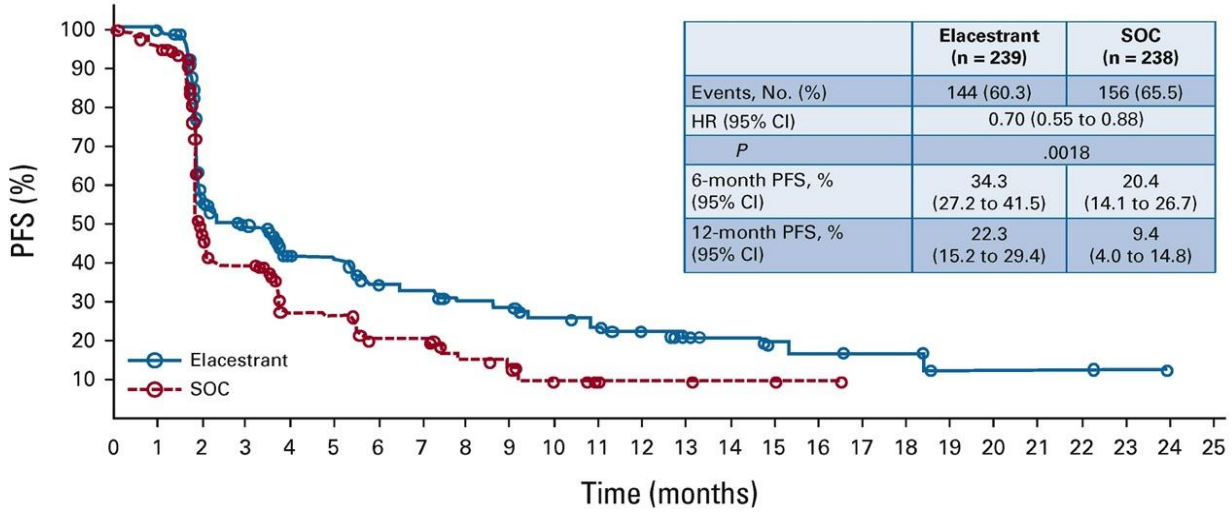
Prior CT for ABC: ~ 20%

Visceral metastasis: ~ 70%

Prior Target Therapy for ABC: ~ 4% mTOR inhibitor; ~ 1% PI3K inhibitor

2 prior endocrine therapies in Fulvestrant-treated patients (27.3%)

All Patients (ITT)

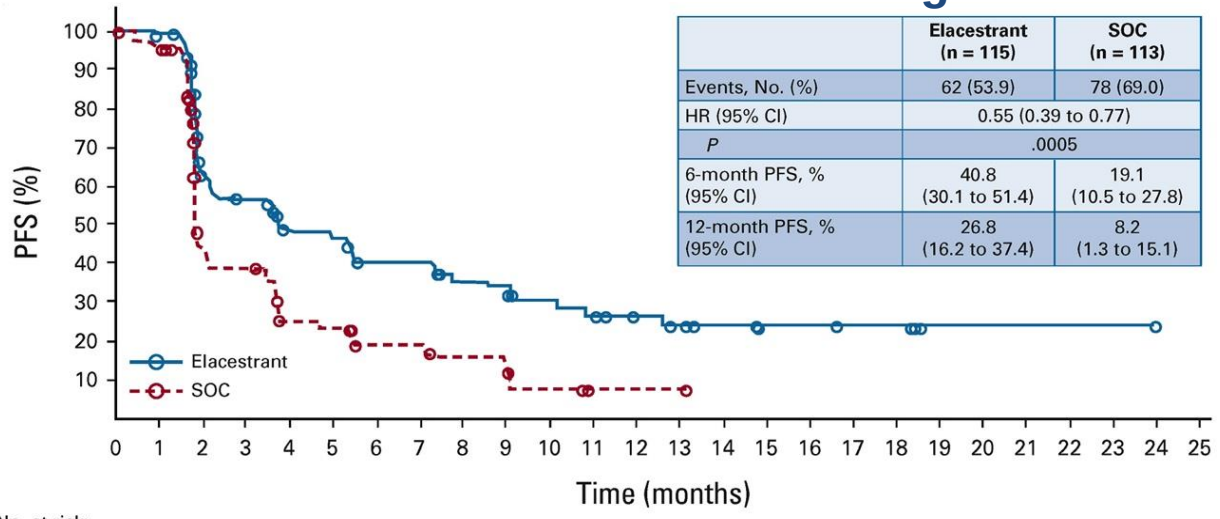


	Elacestrant (n = 239)	SOC (n = 238)
Events, No. (%)	144 (60.3)	156 (65.5)
HR (95% CI)	0.70 (0.55 to 0.88)	
P	.0018	
6-month PFS, % (95% CI)	34.3 (27.2 to 41.5)	20.4 (14.1 to 26.7)
12-month PFS, % (95% CI)	22.3 (15.2 to 29.4)	9.4 (4.0 to 14.8)

No. at risk:

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

Patients with Tumors Harboring m*ESR1*



	Elacestrant (n = 115)	SOC (n = 113)
Events, No. (%)	62 (53.9)	78 (69.0)
HR (95% CI)	0.55 (0.39 to 0.77)	
P	.0005	
6-month PFS, % (95% CI)	40.8 (30.1 to 51.4)	19.1 (10.5 to 27.8)
12-month PFS, % (95% CI)	26.8 (16.2 to 37.4)	8.2 (1.3 to 15.1)

No. at risk:

Elacestrant	115	105	54	46	35	33	26	26	21	20	16	14	11	9	7	5	5	4	4	1	1	1	1	1	0
SOC	113	99	39	34	19	18	12	12	9	9	4	1	1	1	0										

Bidard FC, JCO 2022

Elacestrant: ESMO-Magnitude of Clinical Benefit Scale

Monthly compilation of approvals by the EMA and the FDA, either new cancer medicines and/or extension of therapeutic indication

MEDICINES APPROVAL

TRIAL DETAILS

The pivotal trial data required for scoring are gathered

Key evaluators, including bio-statisticians, score the cancer medicines. QoL evaluations are sent to the ESMO-MCBS WG QoL experts for their review

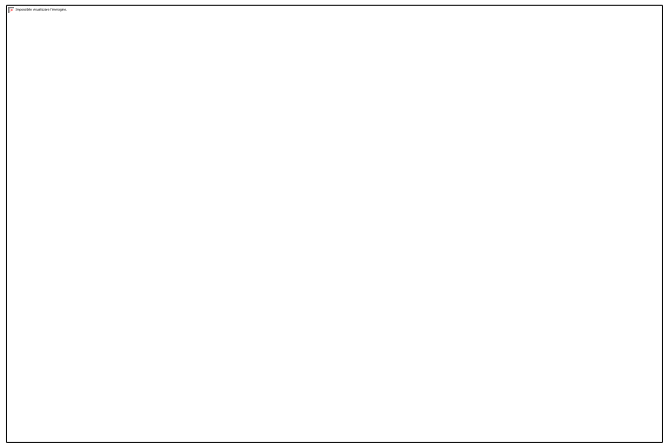
SCORING

SCORECARDS

On completion and validation of scoring, Scorecards are created or updated and published on the ESMO website

Scorecards are regularly updated for example when mature OS or QoL data are available

UPDATES



Elacestrant EMERALD

PRELIMINARY SCORE

CURATIVE

NON-CURATIVE

PFS

ADJUSTMENTS

Quality of life

Serious and disabling adverse effects

Other adjustments

Elacestrant EMERALD

FINAL SCORE

CURATIVE

Overall Survival / Disease-Free Survival / Pathological Complete Response

NON-CURATIVE

Overall Survival

3

Progression-Free Survival

Non-inferiority (Improved Quality of Life or Reduced Adverse Events) / Response Rate

Overall Response Rate / Duration of Response

Overall Survival / Disease-Free Survival / Pathological Complete Response

INFORMATION

Therapeutic Indication: Treatment of postmenopausal women, and men, with estrogen receptor (ER)-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor
Experimental Arm: Elacestrant
Control Arm: Standard-of-care endocrine therapy

ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale

SCORECARDS

Topics

- **Background**
- **Elacestrant Approval**
- ***mESR1* & Companion Diagnostic**
- **Conclusions & Future perspectives**

Elacestrant Approval

- On January 27, 2023, the **FDA** approved Elacestrant 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.

- On September 2023, the **EMA** Commission approved Elacestrant for the treatment of postmenopausal women and men with ER–positive, HER2-negative, locally advanced, or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK4/6 inhibitor.

- On December 2023, the **AIFA** approved Elacestrant with the same indication of EMA.

European EAP - Elacestrant

Inclusion Criteria

Subject must have a histologically- or cytologically proven diagnosis of adenocarcinoma of ER+ and HER2- ABC and must be appropriate candidates for endocrine monotherapy.
Post-menopausal women or man ≥ 18 years of age.
Disease progression following at least one but no more than two lines of endocrine therapy, including CDK4/6 inhibitors.
Activating mutations of the estrogen receptor 1 (ESR1) gene
Adequate organ function and ECOG 0-1
All toxic effects of prior therapies or surgical procedures resolved to Grade ≤ 1 (except alopecia and peripheral neuropathy).
Ability to understand the protocol and provide informed consent
Active contraception (male subjects)

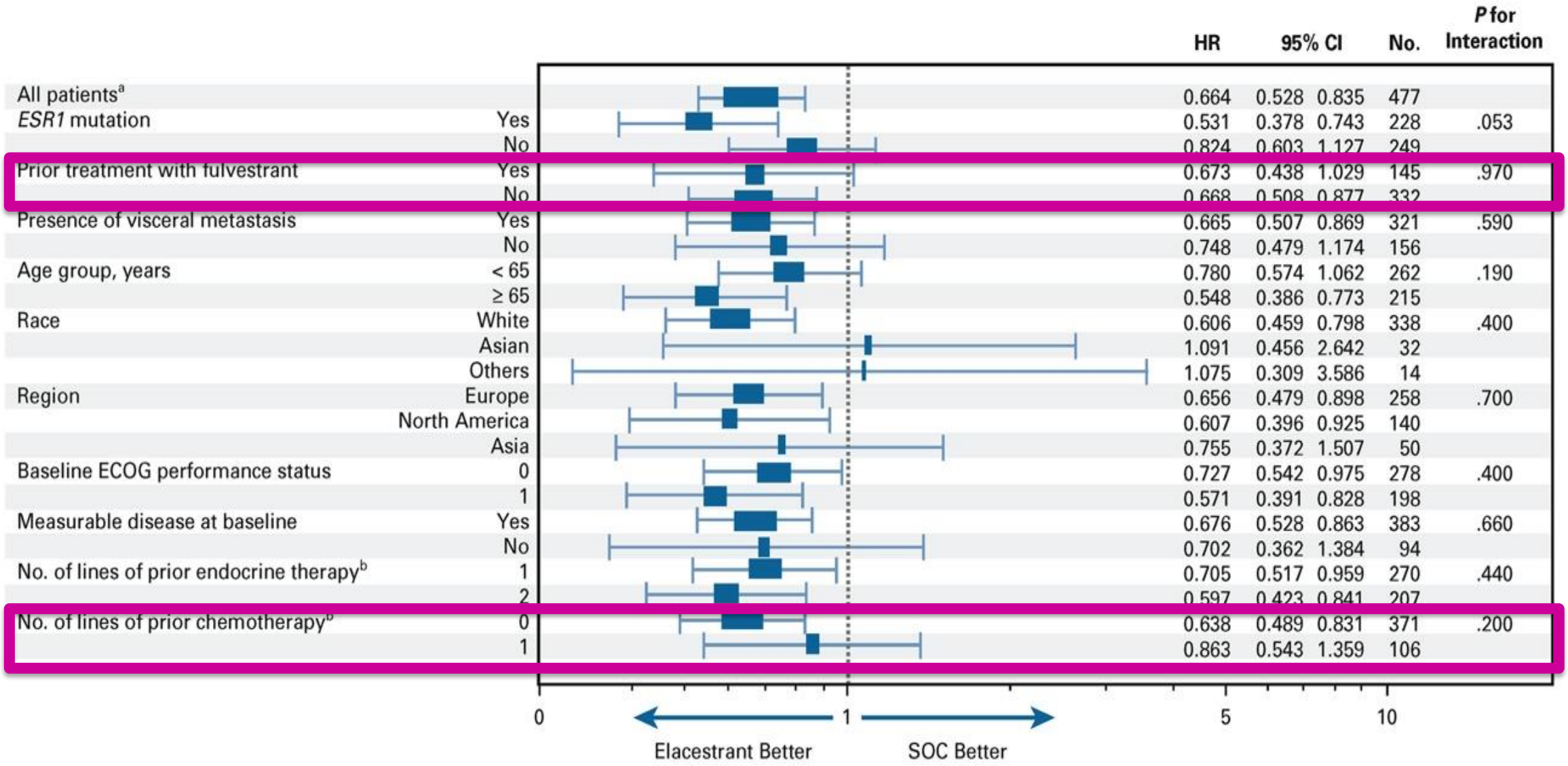
Countries:

European EAP - Elacestrant

Exclusion Criteria

Prior treatment with elacestrant or other SERD or ER antagonist (e.g. in clinical trials)
Fulvestrant treatment (last injection) < 28 days before first dose of drug.
Any other endocrine therapy < 14 days before first dose of drug.
Radiation therapy within 14 days before the first dose of elacestrant
Chemotherapy-based regimens (including ADCs) in metastatic or advanced setting.
Any investigational anti-cancer drug therapy < 28 days or 5 half-lives (whichever is shorter) before first dose of drug.
Major surgery < 28 days before the first dose of elacestrant
Presence of symptomatic metastatic visceral disease, including but not limited to, extensive hepatic involvement, untreated or progressive central nervous system (CNS) metastases, or symptomatic pulmonary lymphangitic spread.
Intact uterus with a history of endometrial intraepithelial neoplasia (atypical endometrial hyperplasia or higher-grade lesion).
Major Cardiovascular conditions/events
Child-Pugh Score greater than Class A (ie, score >6).
Coagulopathy or any history of coagulopathy within the past 6 months, including history of deep vein thrombosis or pulmonary embolism.
Known difficulty in tolerating oral medications or conditions which would impair absorption of oral medications such as: uncontrolled nausea or vomiting (ie, CTCAE ≥ Grade 3 despite antiemetic therapy), ongoing gastrointestinal obstruction/motility disorder, malabsorption syndrome, or prior gastric bypass
Unable or unwilling to avoid other medications/supplements
Known hypersensitivity reaction to drugs chemically related to elacestrant or their excipients

EMERALD - Subgroup Analysis of PFS (all patients)



Bidard FC, JCO 2022

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Unable or unwilling to avoid other medications/supplements
Known hypersensitivity reaction to drugs chemically related to elacestrant or their excipients

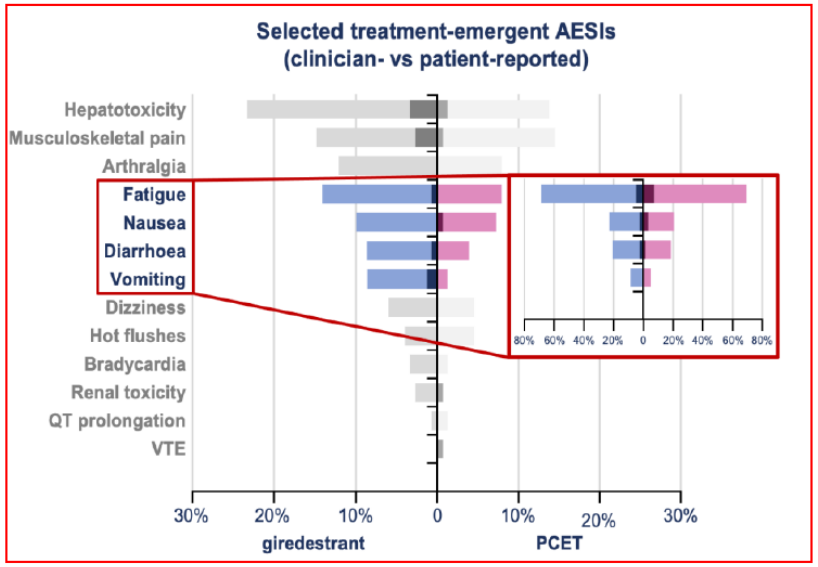
Safety of Oral SERD

Elacestrant

Adverse events, n (%)	Elacestrant N=237	SOC All N=229	SOC Fulvestrant N=161	SOC AI N=68
Any treatment-emergent AE	218 (92.0)	197 (86.0)	144 (89.4)	53 (77.9)
Treatment-emergent Grade 3 AE	64 (27.0)	47 (20.5)	33 (20.5)	14 (20.6)
Any treatment-related AE	150 (63.3)	100 (43.7)	72 (44.7)	28 (41.2)
Treatment-related Grade 3 AE	17 (7.2)	7 (3.1)	5 (3.1)	2 (2.9)
Any treatment-related serious AE	3 (1.3)	0	0	0
AE leading to discontinuation of therapy	15 (6.3)	10 (4.4)	6 (3.7)	4 (5.9)
Treatment-emergent AE occurring in >15% of patients[a]				
Nausea	83 (35.0)	43 (18.8)	26 (16.1)	17 (25.0)
Fatigue	45 (19.0)	43 (18.8)	35 (21.7)	8 (11.8)
Vomiting	45 (19.0)	19 (8.3)	12 (7.5)	7 (10.3)
Arthralgia	34 (14.3)	37 (16.2)	28 (17.4)	9 (13.2)

Bidard FC, JCO 2022

Giredestrant



Martin M, ESMO 2022

Camizestrant

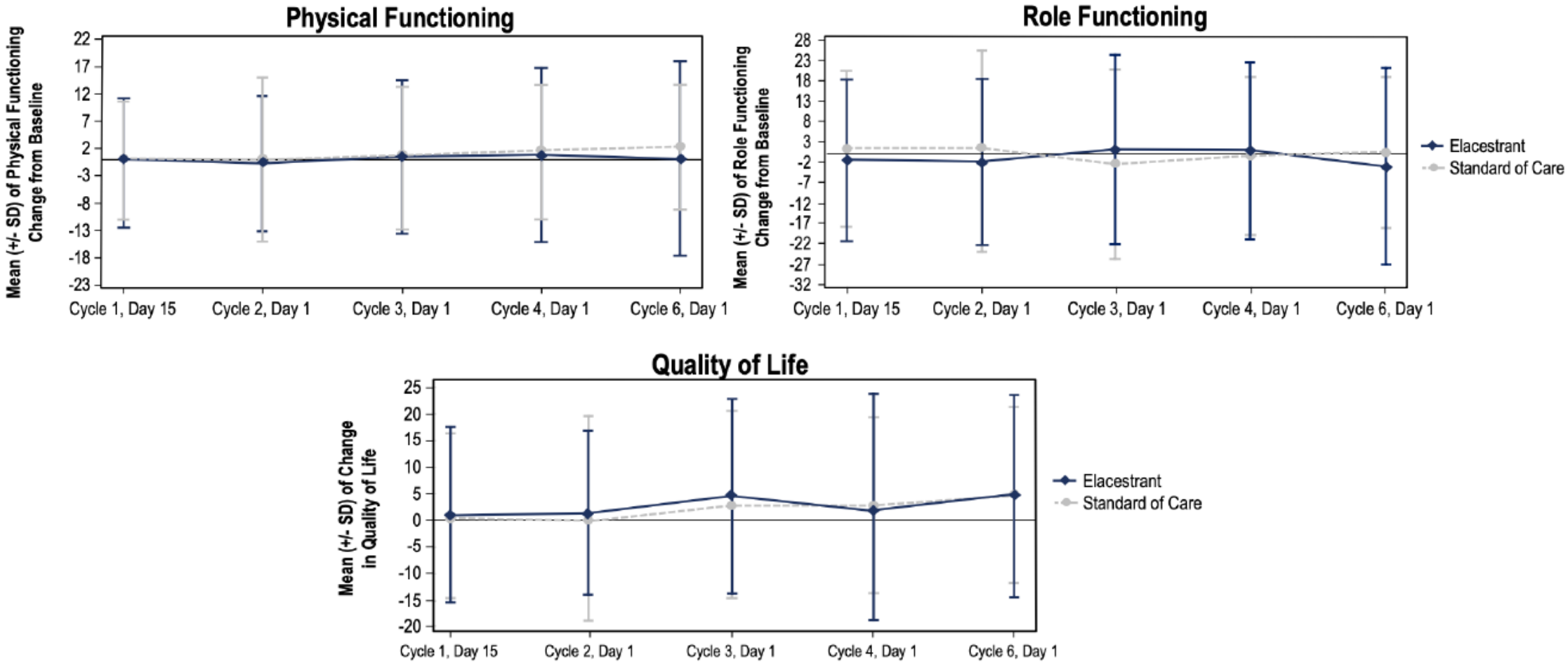
AE, n (%)	C 75 (n=74) All grades	C 75 (n=74) Grade ≥3	C 150 (n=73) All grades	C 150 (n=73) Grade ≥3	C 300 (n=20) All grades	C 300 (n=20) Grade ≥3	F 500 (n=73) All grades	F 500 (n=73) Grade ≥3
Any AE	57 (77.0)	9 (12.2)	66 (90.4)	16 (21.9)	19 (95.0)	3 (15)	50 (68.5)	10 (13.7)
Photopsia	9 (12.2)	0	18 (24.7)	0	7 (35.0)	0	0	0
(Sinus) bradycardia	4 (5.4)	0	19 (26.0)	0	8 (40.0)	0	0	0
Fatigue	4 (5.4)	0	13 (17.8)	1 (1.4)	4 (20.0)	0	3 (4.1)	0
Anemia	8 (10.8)	0	11 (15.1)	1 (1.4)	1 (5.0)	0	5 (6.8)	2 (2.7)
Asthenia	6 (8.1)	0	11 (15.1)	0	2 (10.0)	0	4 (5.5)	0
Arthralgia	3 (4.1)	0	9 (12.3)	1 (1.4)	2 (10.0)	0	2 (2.7)	0

Oliveira M, SABCS 2022

EMERALD - Quality of Life Results

EORTC QLQ-C30 scores were similar for **elacestrant and SoC**, with no differences across all time points for functional, symptom, and global health status/QoL domains

There were no differences between subgroups (*ESR1*-mut and all patients)

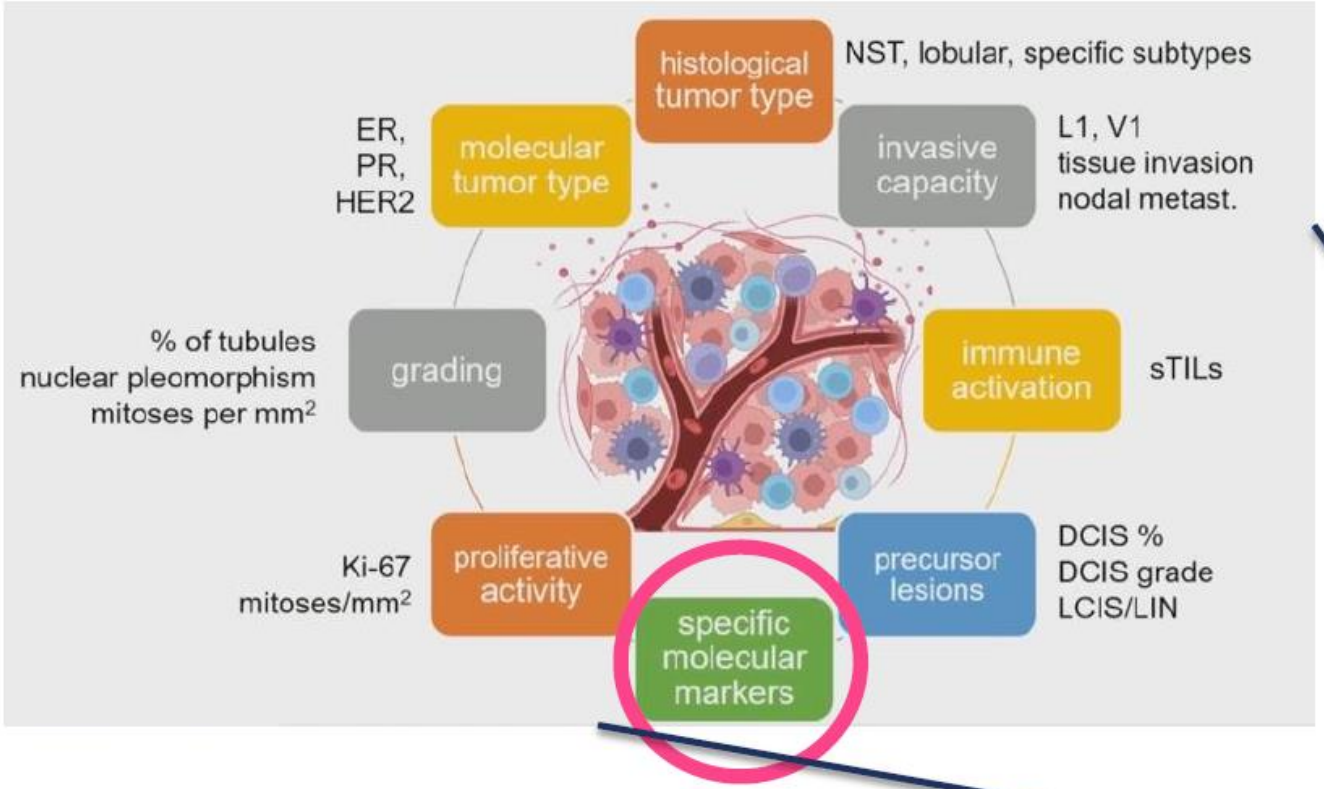


Cortes J et al, SABCS 2023

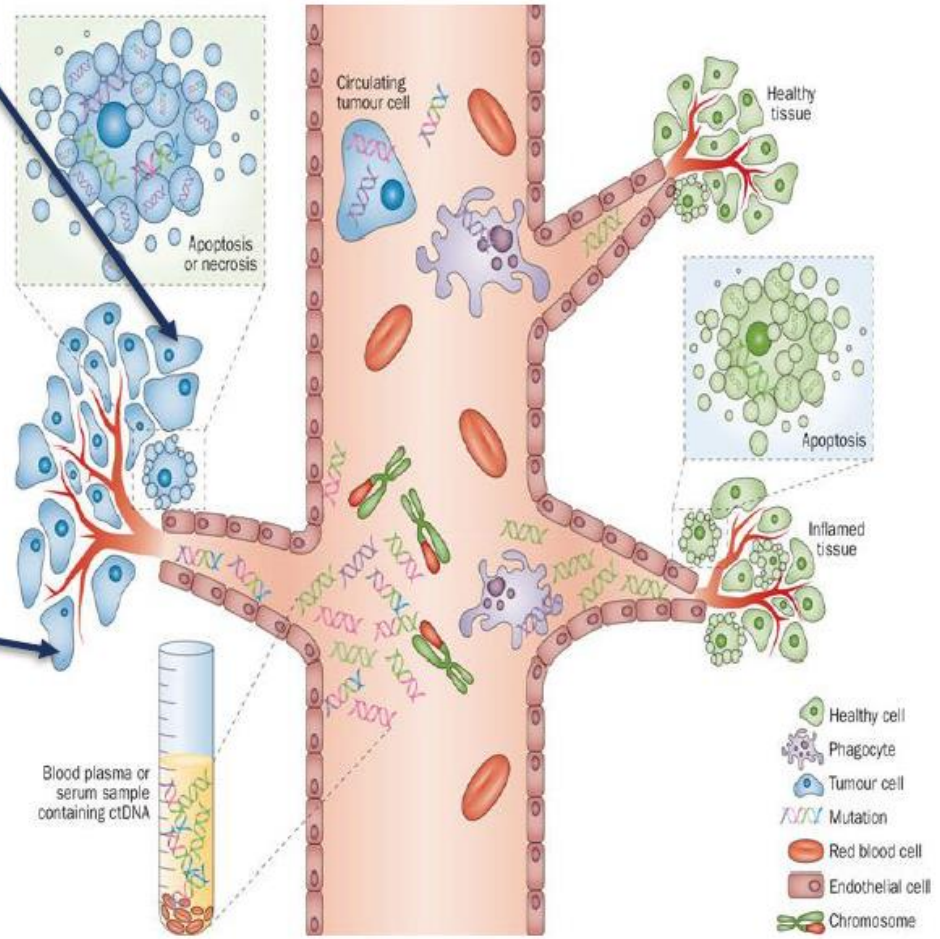
Topics

- **Background**
- **Elacestrant Approval**
- ***mESR1* & Companion Diagnostic**
- **Conclusions & Future perspectives**

Which Factors are relevant for Clinical Decisions?



TUMOR → LIQUID



Liquid biopsy, shed from tumors

- Non-invasive, serial assessment
- May overcome heterogeneity (spatial, temporal)
- Lack spatial analyses, unable to visualize
- Molecular profiling (ctDNA, CTC)

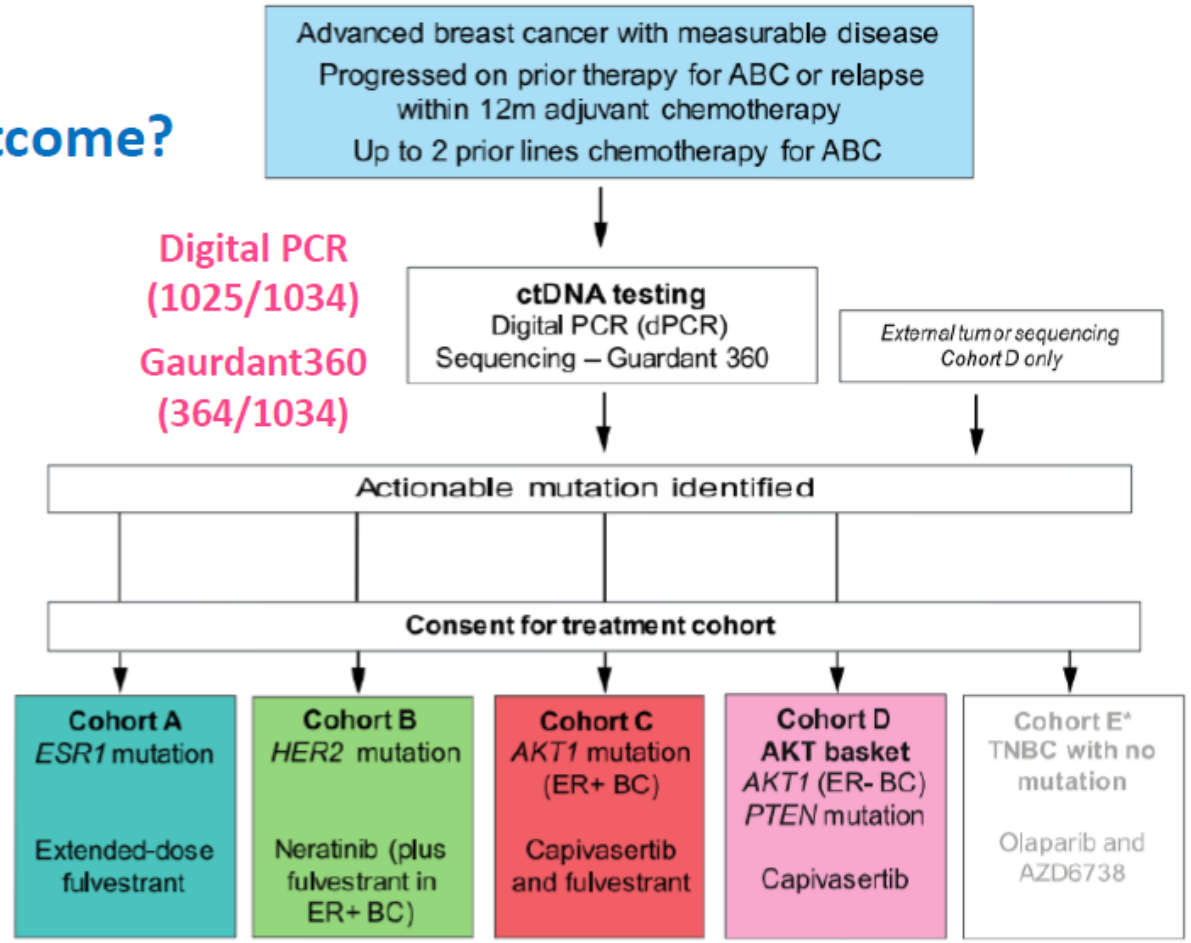
Adapted from C Denkert et al. SGBCC 2023, Crowley et al. Nat Rev Clin Oncol 2013

Plasma-MATCH Trial: Liquid Biopsy

Plasma-MATCH

Does ctDNA guided therapy lead to better outcome?

- ctDNA genomic alteration driven BASKET trial
- Primary endpoint
  - Objective response rate
- 2ndary endpoints
  - Duration of response
  - Clinical benefit rate
  - Accuracy of ctDNA testing by agreement btw ctDNA and tissue mutation



N Turner et al. Lancet Oncol 2020

Modified from Kim J, ESMO BC 2023

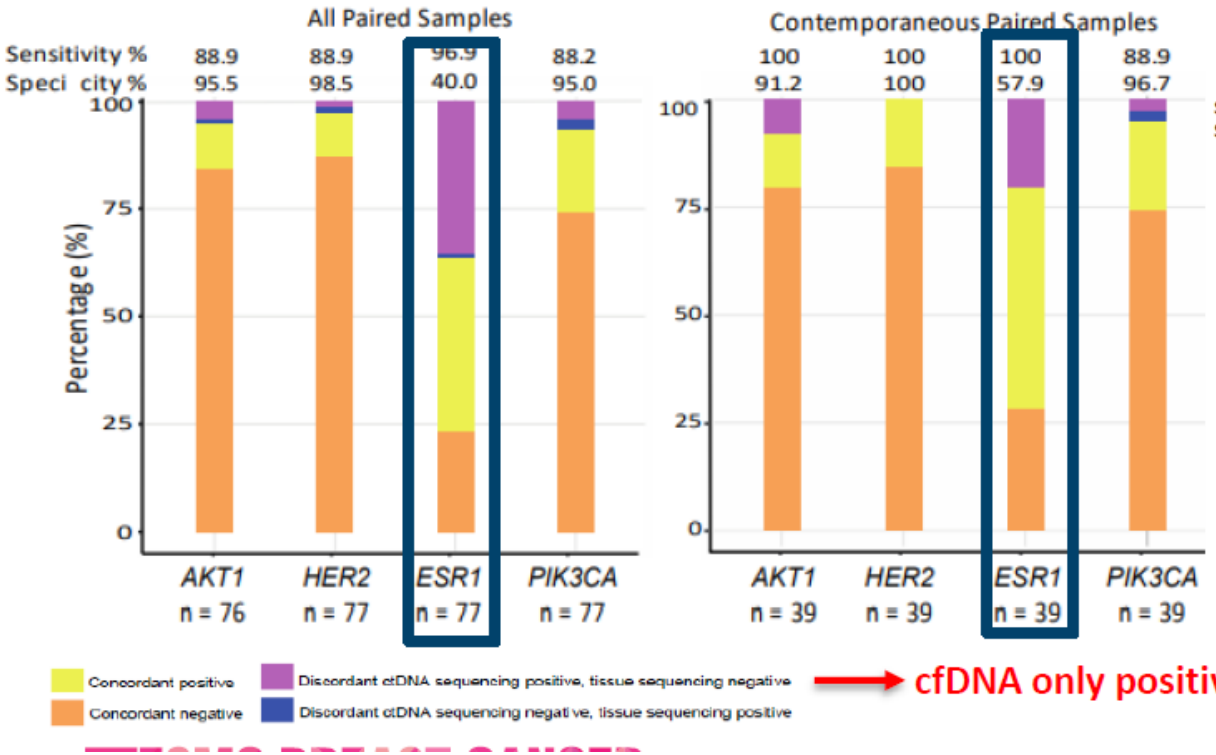
CONCORDANCE BETWEEN TISSUE AND LIQUID

Plasma-MATCH

96-99% Gene-level agreement for mutation identification between ctDNA digital PCR and targeted sequencing (n=800)

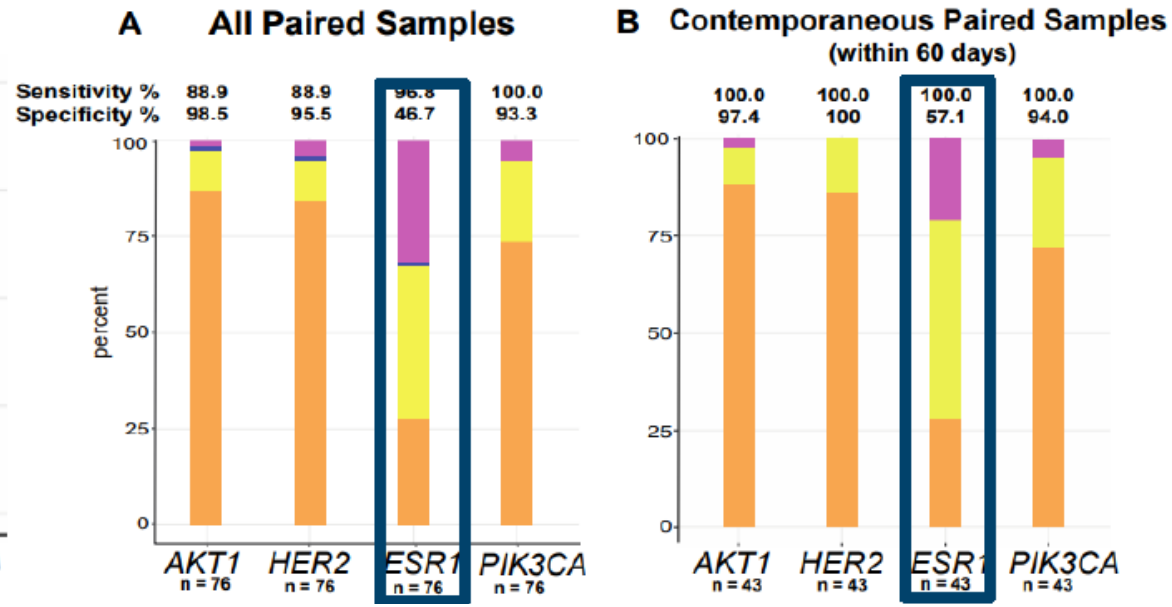
AKT1 kappa 0·93 (95% CI 0·87–0·99), *HER2* kappa 0.89 (0·79–0·98), *ESR1* kappa 0·90 (0·86–0·93), *PIK3CA* kappa 0·92 (0·89–0·95).

Tissue vs cfDNA digital PCR (n=77)



→ cfDNA only positive

Tissue vs cfDNA NGS (n=77)



Advantage of combined testing

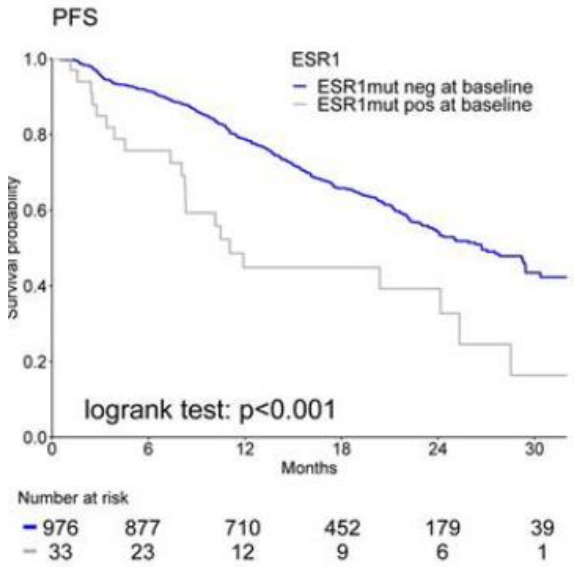
- All ESR1 variants more likely to be detected in cfDNA than tissue (cf. PIK3CA H1047X, ts>>)

NC Turner et al. Lancet Oncol 2021

ESR1m as a Prognostic Factor

PADA-1 Trial

PFS by ESR1mut status (ddPCR) at baseline



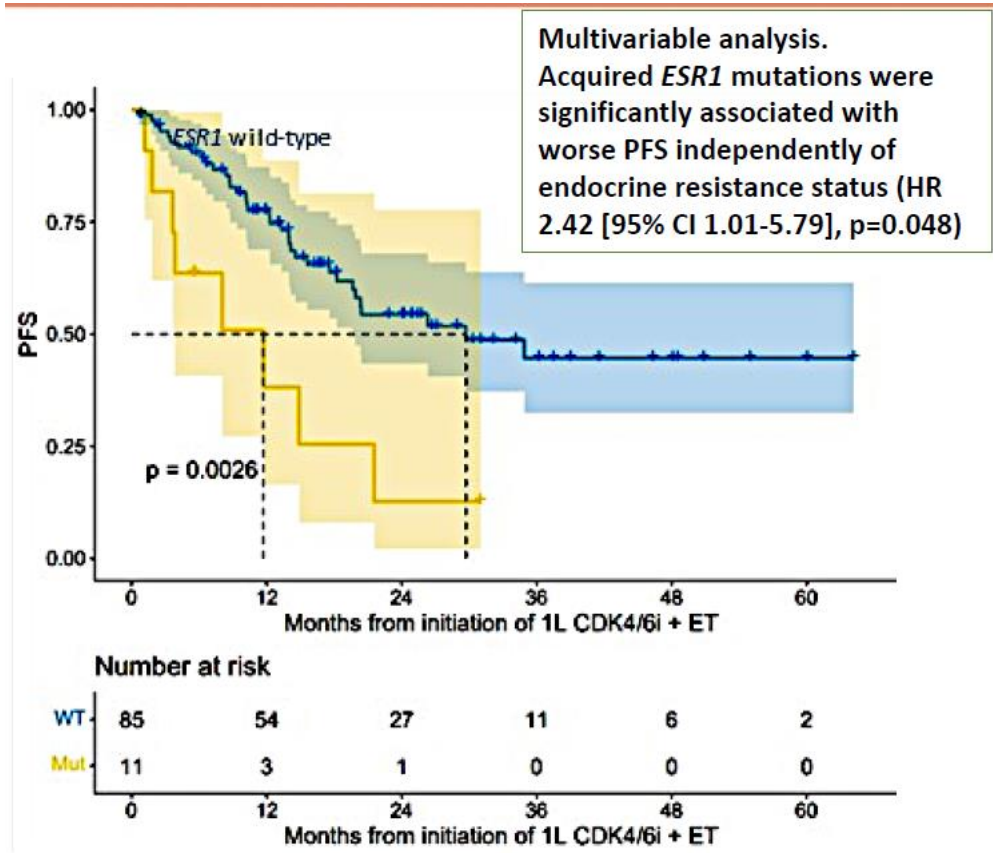
Median FU = 21.2 months (0-34.5)

Estimated PFS[1]:

ESR1$_{mut}$ (N=33 pts)
Median PFS: **11.0 mo**, 95%CI=[8.3-NR]

ESR1$_{wt}$ (N=976 pts)
Median PFS: **26.7 mo**, 95%CI=[24.1-29.4]

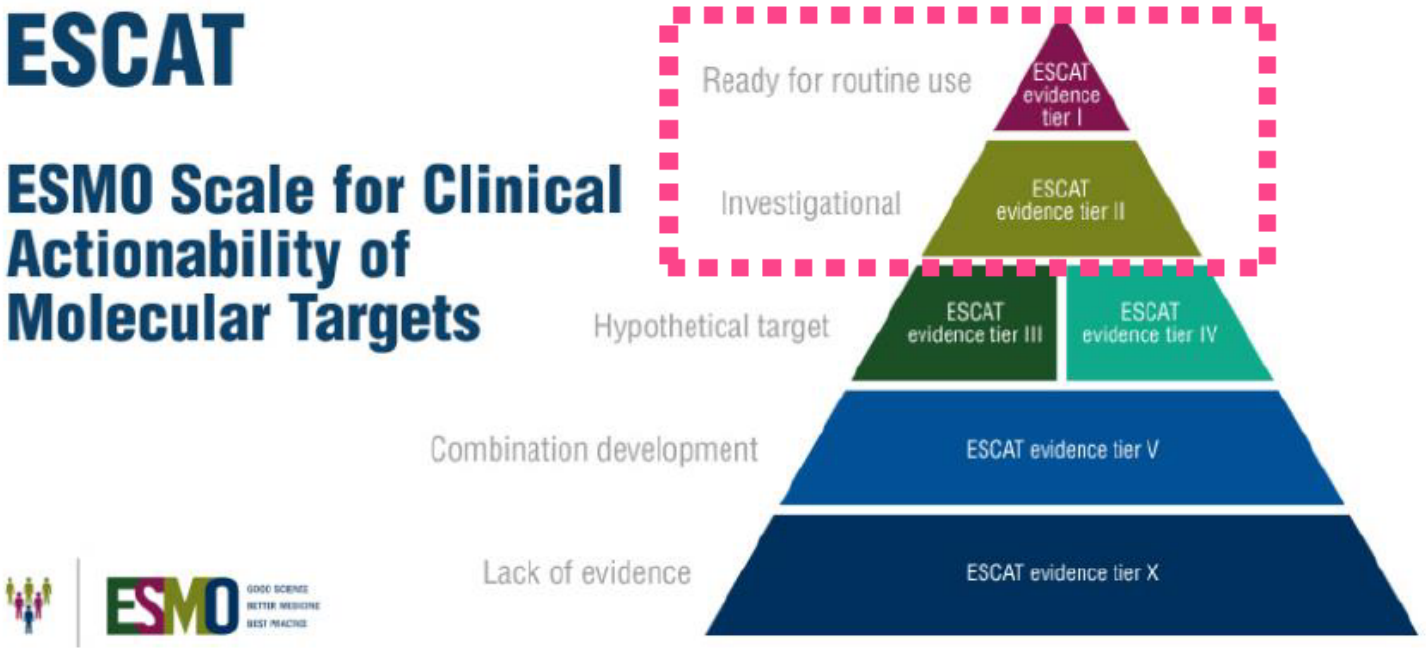
HR= 2.3 95%CI=[1.5;3.6]



Bidard FC et al, ASCO 2020

Agostinetto E et al, ASCO 2023

Genomic driven Therapy – Clinical Relevance in ABC



ESMO recommendations on the use of circulating tumour DNA assays for patients with cancer: a report from the ESMO Precision Medicine Working

Tumour type	Indications	ESCAT tier and level of evidence	Recommendation
Breast cancer	*PIK3CA* mutations	IA[140]	*ESR1* mutations should preferentially be tested in ctDNA. *ERBB2* amplification and *NTRK* fusions only when advanced tissue biopsy not available.
	ERBB2 amplification	IA[141,142]	
	*BRCA*1/2 mutations	IA[143,144]	
	ESR1 mutations	IB[145,146]	
	MSI-H	IC[147]	
	NTRK 1/2/3 fusions	IC[134]	

Pascual J et al, Ann. Oncol. 2022 & Modified from Kim J, ESMO BC 2023

Ranking Genomic Alterations as Targets for Cancer Precision Medicine

NOT Subject of MTBs [*Clinical Practice, Disease-TBs*]

Subject of MTBs

ESCAT		JCR		OncoKB	
ESCAT I	Ready for routine use A: Prospective randomized trials B: Prospective nonrandomized trials C: Basket trials and trials across tumor types	Tier 1	Strong clinical impact A: FDA approved therapy/professional guidelines B: Well-powered studies with expert consensus	Level of actionability	
				Level 1	FDA approval FDA-recognized biomarker predictive of response to an FDA-approved drug in this indication
ESCAT II	Investigational therapeutic options A: Retrospective studies B: Retrospective studies trial; endpoints not currently available	Tier 2	Potential clinical impact C: FDA approval in different tumors/inclusion in clinical trial/multiple small studies with some consensus D: Preclinical trials/case reports	Level 2	Standard care biomarker predictive of response to approved drug[a] A: In this indication B: In another indication
ESCAT III	Hypothetical targets A: As ESCAT I but in other tumor types B: Alteration with predicted impact in same pathways			Level 3	Compelling clinical evidence supports the biomarker as being predictive of response to a drug A: In this indication B: In another indication
ESCAT IV	Preclinical evidences A: *In vivo* or *in vitro* evidences B: *In silico* evidences			Level 4	Compelling biological evidence supports the biomarker as being predictive of response to a drug
ESCAT V	Combination development Objective response but not improved outcomes	Tier 3	Unknown clinical significance		
ESCAT X	Benign variants	Tier 4	Benign variants		
				Level of resistance	
				Level R1	Standard care biomarker predictive of resistance to an FDA-approved drug in this indication
				Level R2	Compelling clinical evidence supports the biomarker as being predictive of resistance to a drug
				Level R3	Compelling biological evidence supports the biomarker as being predictive of resistance to a drug

Luchini C et al, Trends in Cancer 2020

ASCO Guidelines for HR+ HER2- Metastatic Breast Cancer

Journal of Clinical Oncology®

ASCO special articles

Endocrine Treatment and Targeted Therapy for Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer: ASCO Guideline Update

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abstract

PURPOSE To update recommendations of the ASCO systemic therapy for hormone receptor (HR)-positive metastatic breast cancer (MBC) guideline.

METHODS An Expert Panel conducted a systematic review to identify new, potentially practice-changing data.

RESULTS Fifty-one articles met eligibility criteria and form the evidentiary basis for the recommendations.

RECOMMENDATIONS Alpelisib in combination with endocrine therapy (ET) should be offered to postmenopausal patients, and to male patients, with HR-positive, human epidermal growth factor receptor 2 (HER2)-negative, *PIK3CA*-mutated, ABC, or MBC following prior endocrine therapy with or without a cyclin-dependent kinase (CDK) 4/6 inhibitor. Clinicians should use next-generation sequencing in tumor tissue or cell-free DNA in plasma to detect *PIK3CA* mutations. If no mutation is found in cell-free DNA, testing in tumor tissue, if available, should be used as this will detect a small number of additional patients with *PIK3CA* mutations. There are insufficient data at present to recommend routine testing for *ESR1* mutations to guide therapy for HR-positive, HER2-negative MBC. For *BRCA1* or *BRCA2* mutation carriers with metastatic HER2-negative breast cancer, olaparib or talazoparib should be offered in the 1st-line through 3rd-line setting. A nonsteroidal aromatase inhibitor (AI) and a CDK4/6 inhibitor should be offered to postmenopausal women with treatment-naïve HR-positive MBC. Fulvestrant and a CDK4/6 inhibitor should be offered to patients with progressive disease during treatment with AIs (or who develop a recurrence within 1 year of adjuvant AI therapy) with or without one line of prior chemotherapy for metastatic disease, or as first-line therapy. Treatment should be limited to those without prior exposure to CDK4/6 inhibitors in the metastatic setting.

Additional information can be found at www.asco.org/breast-cancer-guidelines.

Insufficient data for routine ESR1 mutation testing?

Burstein HJ et al, J. Clin. Oncol. 2021;39(35):3959-3977.

Testing for *ESR1* Mutations to Guide Therapy for Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer: ASCO Guideline Rapid Recommendation Update

UPDATED RECOMMENDATIONS

- **…. the Expert Panel recommends routine testing for emergence of ESR1 mutations at recurrence or progression on ET (given with or without CDK4/6 inhibitor) in patients with ER+, HER2-MBC.** Testing with a Clinical Laboratory Improvement Amendments–certified assay should be performed on blood or tissue obtained at the time of progression, as ESR1 mutations develop in response to selection pressure during treatment and are typically undetectable in the primary tumor.
- **Blood-based ctDNA is preferred owing to greater sensitivity.** If not performed earlier, testing for PIK3CA mutations should also be performed to guide further therapy. Patients whose tumor or ctDNA tests remain ESR1 wild-type may warrant retesting at subsequent progression(s) to determine if an ESR1 mutation has arisen *(Type: Evidence-based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong).*

Burstein HJ et al, JCO 2023

Conclusions & Future Perspectives

- **Elacestrant approval due to better efficacy compared to Fulvestrant (bioavalaibility)**
  - **No incidence of bradycardia or ocular toxicity**
  - **Dose: 345 mg/die (one dose reduction to 258 mg/die: 3x86 mg); hepatic metabolism (CYP3A4)**
- **How to identify patients with potential benefit to Elacestrant after CDK4/6i?**
  - **There are patients that remain sensible to ET and do derive benefit from single agent ET**
  - **Duration of CDK4/6i & *ESR1m* were associated with PFS**
  - **Nevertheless, a subset of patients with *mESR1* presents primary resistant to Elacestrant**
  - **Better setting?: 2nd line (after CDK4/6i progression and previous benefit from CDK5/6i), without previous CT or target agents**
- **Increase of *mESR1* during ET (+CDK4/6i) treatment up to 40%**
  - **Need to perform a real-time (ctDNA) test (NGS/ddPCR) to asses *mESR1*: possibility to perform the *ESR1* test in the EAP**
- **In patients with PIK3CA altered pathway? Capivasertib (plus Fulvestrant) is FDA approval**
- **Additional data with other SERDs & more potent ER-inhibitors are coming (EMBER3 - pre-treated ABC; SERENA-4 1st line) also including other settings (early BC). Also other genomic driven strategy are ongoing (SERENA-6)**

Thank you for your attention