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ctDNA biomarkers to drive therapy

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ISLB
INTERNATIONAL SOCIETY OF LIQUID BIOPSY

SYSTEMIC THERAPY FOR ER- AND/OR PR-POSITIVE RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a]

HER2-Negative and Postmenopausal or Premenopausal Receiving Ovarian Ablation or Suppression

See BINV-P 1 of 3 for general considerations for therapy selection for HR-positive, HER2-negative disease.

First-Line Therapy

Preferred Regimens

- Aromatase inhibitor + CDK4/6 inhibitor[b]
  - Aromatase inhibitor + ribociclib (category 1)[c]
  - Aromatase inhibitor + abemaciclib
  - Aromatase inhibitor + palbociclib

If disease progression on adjuvant endocrine therapy or relapse within 12 months of adjuvant endocrine therapy completion consider:

- Fulvestrant[d] + CDK4/6 inhibitor[b]
  - Fulvestrant + ribociclib (category 1)[e]
  - Fulvestrant + abemaciclib (category 1)[e]
  - Fulvestrant + palbociclib

Useful in Certain Circumstances

- For HER2-negative tumors with *PIK3CA* activating mutations and disease progression on adjuvant endocrine therapy or relapse within 12 months of adjuvant endocrine therapy completion, see BINV-Q (6)

Second- and/or Subsequent-Line Therapy

Preferred Regimens

- Fulvestrant + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) if CKD4/6 inhibitor not previously used (category 1)[f,g]
- For HER2-negative tumors with *PIK3CA* or *AKT1* activating mutations or PTEN alterations, see BINV-Q (6)[h]
- Everolimus + endocrine therapy (exemestane, fulvestrant, tamoxifen)[i,j]
- Targeted therapy, see BINV-Q (6) and BINV-Q (7), and emerging biomarker options, see BINV-Q (8)

Useful in Certain Circumstances

- Megestrol acetate
- Estradiol
- Abemaciclib[l]
- Targeted therapy, see BINV-Q (6) and BINV-Q (7), and emerging biomarker options, see BINV-Q (8)

Other Recommended Regimens for first and/or subsequent lines of therapy

- For HER2-negative disease and *ESR1* mutated tumors and after progression on one or two prior lines of endocrine therapy, including one line containing a CDK4/6 inhibitor, see BINV-Q (6)
- Fulvestrant) + aromatase inhibitor (anastrozole, letrozole) (category 1)[k]
- Fulvestrant
- Anastrozole
- Letrozole
- Tamoxifen
- Exemestane

Footnotes on BINV-P 3 of 3

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inavolisib-Based Therapy in *PIK3CA*-Mutated Advanced Breast Cancer

N.C. Turner, S.-A. Im, C. Saura, D. Juric, S. Loibl, K. Kalinsky, P. Schmid, S. Loi, P. Sunpaweravong, A. Musolino, H. Li, Q. Zhang, Z. Nowecki, R. Leung, E. Thanopoulou, N. Shankar, G. Lei, T.J. Stout, K.E. Hutchinson, J.L. Schutzman, C. Song, and K.L. Jhaveri

FDA approves inavolisib with palbociclib and fulvestrant for endocrine-resistant, PIK3CA-mutated, HR-positive, HER2-negative, advanced breast cancer

U.S. Food and Drug Administration Approves FoundationOne®Liquid CDx as a Companion Diagnostic for Itovebi™ (inavolisib) to Identify Patients with Hormone Receptor-Positive, HER2-Negative Breast Cancer with a PIK3CA Mutation

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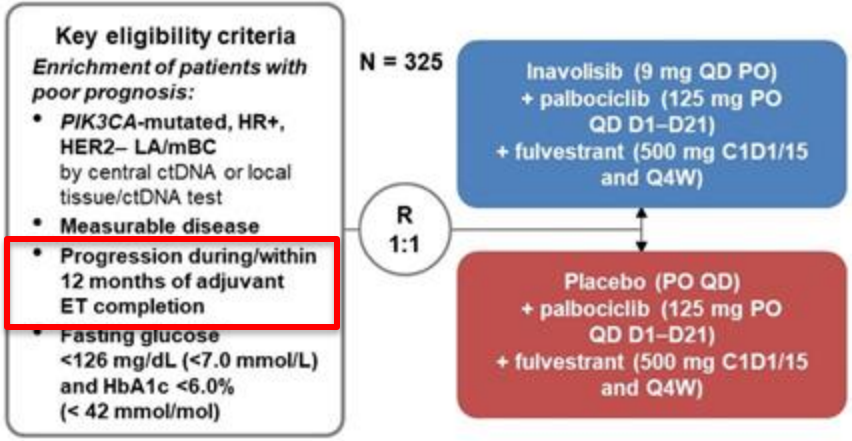
INAVO120: Trial Design



Statistical methods

- For efficacy endpoints and TTCD, hazard ratios were estimated using a Cox proportional hazard model with 95% CI and Kaplan–Meier methodology was used to estimate the medians with the Brookmeyer–Crowley method used for the 95% CI

Efficacy endpoints

- PFS by investigator
- OS
- ORR, BOR, CBR, DOR
- Time from randomization to end or discontinuation of next-line treatment, or death from any cause (proxy for PFS2)
- Time from randomization to first subsequent chemotherapy after treatment discontinuation

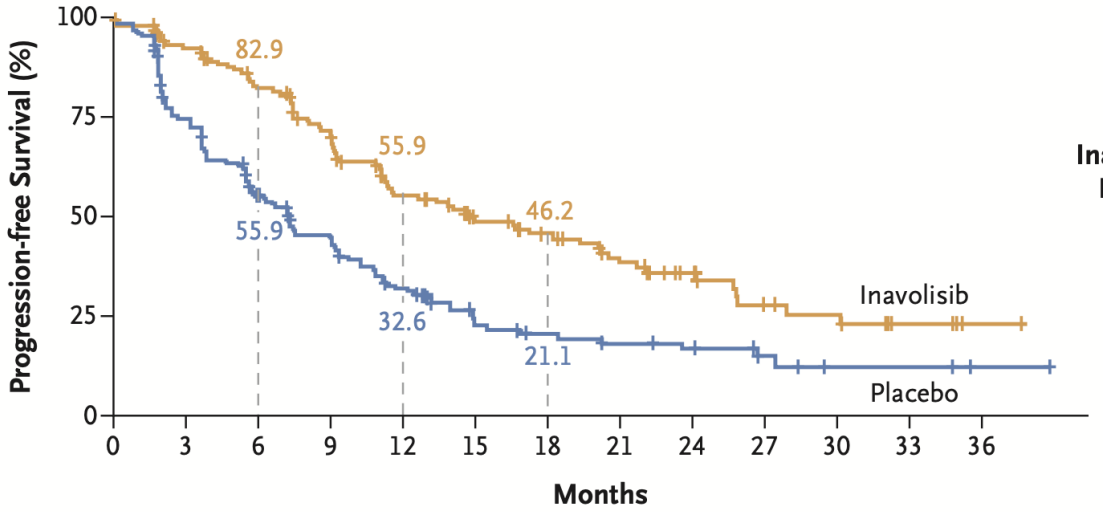
Safety endpoints

Key selected AEs (hyperglycemia, diarrhea, rash, and stomatitis/mucosal inflammation)*

Patient-reported outcomes endpoints†

- BPI-SF: TTCD in worse pain‡§
- EORTC QLQ-C30: mean change from baseline in HRQoL, physical functioning, and role functioning‖
- PRO-CTCAE: presence, frequency of occurrence, severity, and/or degree of interference with daily function of selected symptomatic treatment toxicities
- An overall bother item: overall bother experienced due to side effects of treatment

INAVO120: Progression Free Survival



No. at Risk													
Inavolisib	161	134	111	92	66	48	41	31	22	13	11	5	1
Placebo	164	113	77	59	40	23	19	16	12	6	3	3	1

	No. of Events (%)	Median Progression-free Survival (95% CI)
		mo
Inavolisib (N=161)	82 (50.9)	15.0 (11.3–20.5)
Placebo (N=164)	113 (68.9)	7.3 (5.6–9.3)

Stratified hazard ratio for disease progression or death, 0.43 (95% CI, 0.32–0.59)
P<0.001

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Turner NC et al. NEJM. 2024;391:1584-96.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2025
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

TARGETED THERAPIES AND ASSOCIATED BIOMARKER TESTING FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE

Biomarkers Associated with FDA-Approved Therapies					
Breast Cancer Subtype	**Biomarker**	**Detection[t]**	**FDA-Approved Agents**	**NCCN Category of Evidence**	**NCCN Category of Preference**
HR-positive, HER2-negative	*PIK3CA* activating mutation	NGS, PCR	Inavolisib + palbociclib + fulvestrant[u]	Category 1	Useful in certain circumstances first-line therapy
HR-positive/ HER2-negative	*PIK3CA* activating mutation	NGS, PCR	Alpelisib + fulvestrant[v]	Category 1	Preferred second- or subsequent-line therapy
HR-positive/ HER2-negative	*PIK3CA or AKT1* activating mutations or *PTEN* alterations	NGS, PCR	Capivasertib + fulvestrant[w]	Category 1	Preferred second- or subsequent-line therapy in select patients[w]
HR-positive/ HER2-negative[x]	*ESR1* mutation[x]	NGS, PCR	Elacestrant	Category 2A	Other recommended regimen subsequent-line therapy

Continued

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Capivasertib in Hormone Receptor–Positive Advanced Breast Cancer

N.C. Turner, M. Oliveira, S.J. Howell, F. Dalenc, J. Cortes, H.L. Gomez Moreno, X. Hu, K. Jhaveri, P. Krivorotko, S. Loibl, S. Morales Murillo, M. Okera, Y.H. Park, J. Sohn, M. Toi, E. Tokunaga, S. Yousef, L. Zhukova, E.C. de Bruin, L. Grinsted, G. Schiavon, A. Foxley, and H.S. Rugo, for the CAPItello-291 Study Group*

FDA approves capivasertib with fulvestrant for breast cancer

On November 16, 2023, the Food and Drug Administration approved capivasertib with fulvestrant for adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations, as detected by an FDA-approved test, following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.

FDA also approved the FoundationOne®CDx assay as a companion diagnostic device to identify patients with breast cancer for treatment with capivasertib with fulvestrant.

Post-CDK4/6: HR+ bone only oligometastatic disease

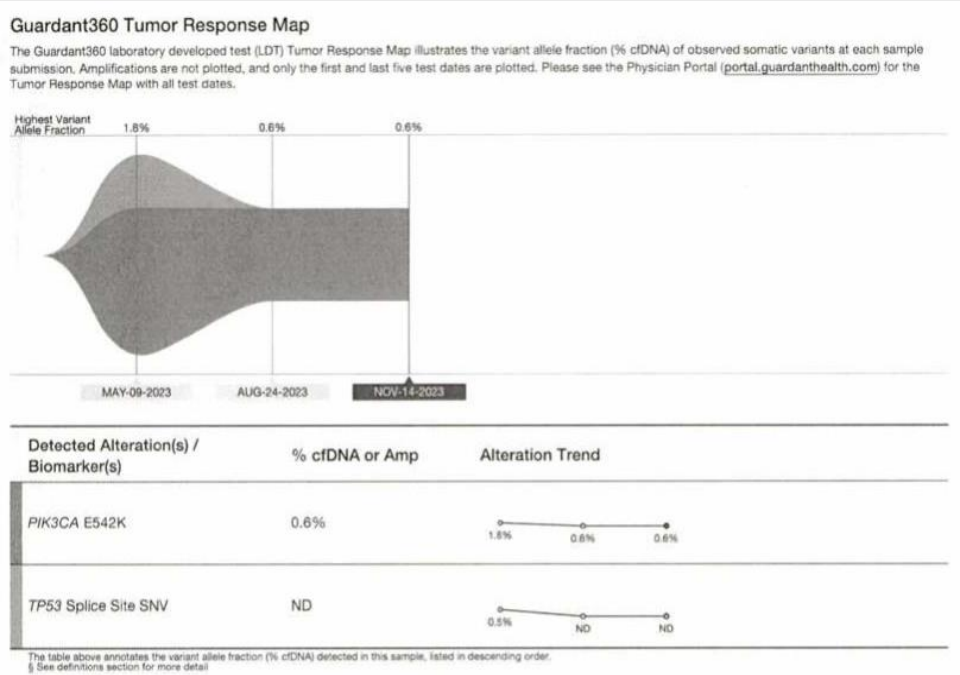
1st line treatment

- ❑ **Fulvestrant 500 mg IM-Alpelisib 300 mg PO daily** since May 2023
- ❑ **Denosumab**
- ❑ OFS with **leuprolide**

August 2023:
PET-CT: showed interval decrease in SUV in the left iliac lesion and no new concerning findings.

Guardant 360: 70% VAF reduction.

Good compliance to the treatment
Still ongoing



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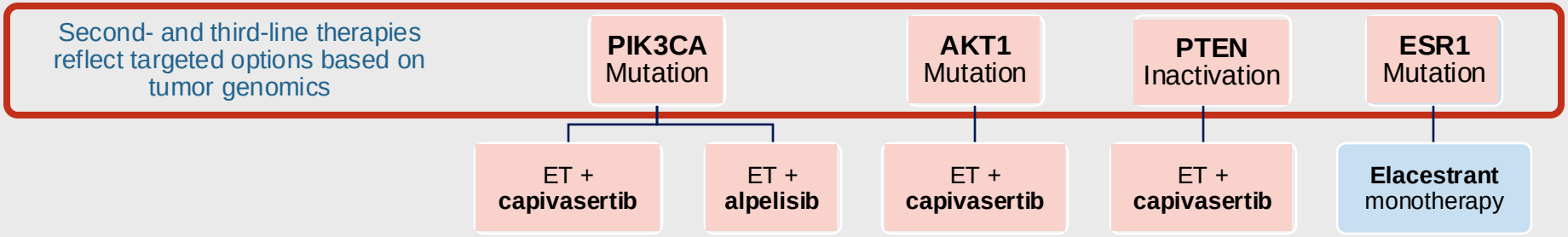
Guidelines for Molecular Testing in HR+/HER2- mBC



- To aid in treatment selection, providers should test for acquired ESR1 mutations **at each recurrence or progression on ET** (with or without CDK4/6i) in patients with ER+/HER2- MBC
- Testing should be performed on blood or tissue obtained **at the time of progression** because 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

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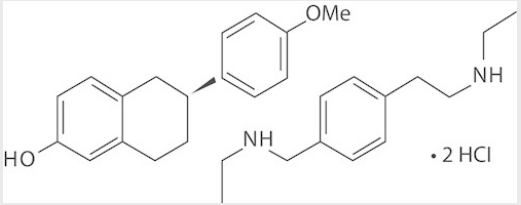
https://society.asco.org/practice-patients/guidelines/breast-cancer#/9676; Burstein HJ et al. *JCO*. 2023; 41(18):3423-3425.



rmation | Approved Drugs / FDA approves elacestrant for ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer

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

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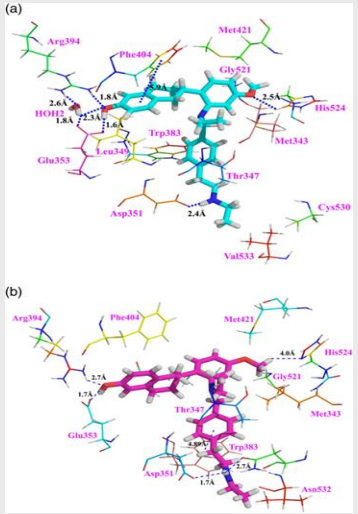
On January 27, 2023, the Food and Drug Administration (FDA) approved elacestrant [redacted] postmenopausal women or adult men with ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.

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

Content current as of:
01/27/2023



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https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-elacestrant-er-positive-her2-negative-esr1-mutated-advanced-or-metastatic-breast-cancer. Accessed September 8, 2024.

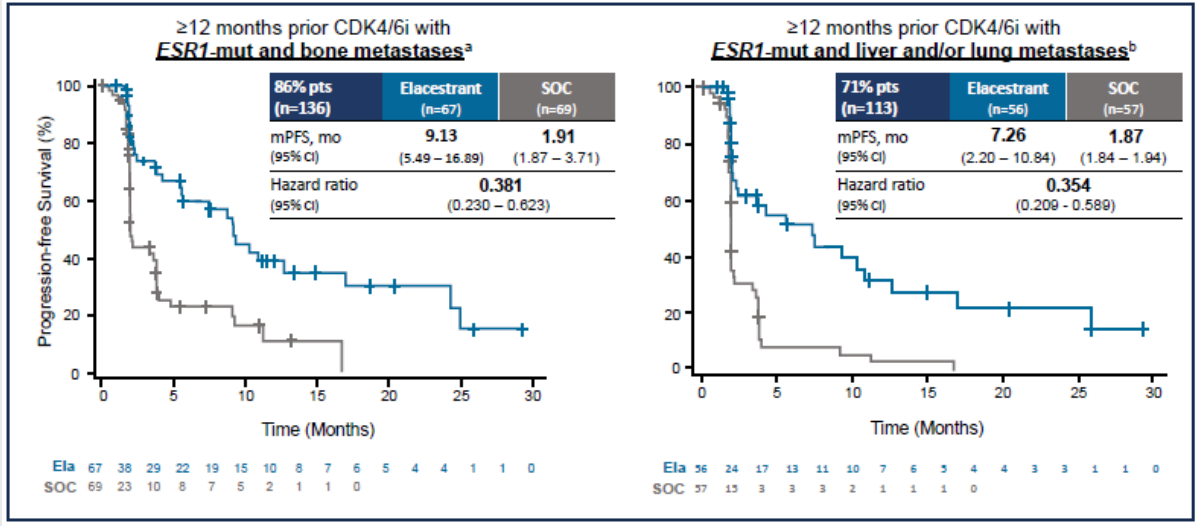
EMERALD: PFS – Subgroup Analysis

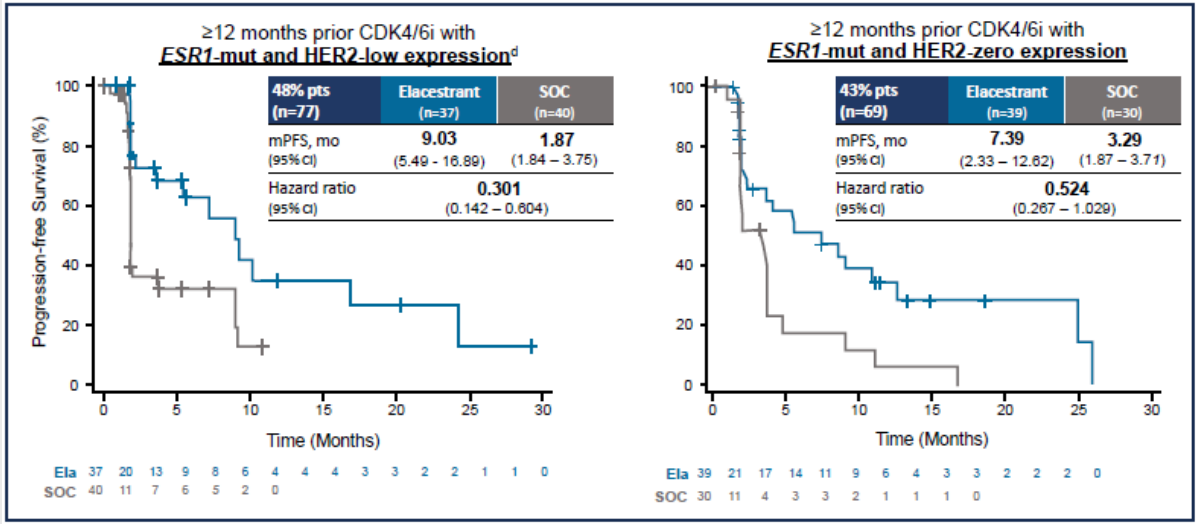
By Site of Metastases:

- Bone
- Liver and/or lung

By HER2 Status:

- HER2-low
- HER2-zero





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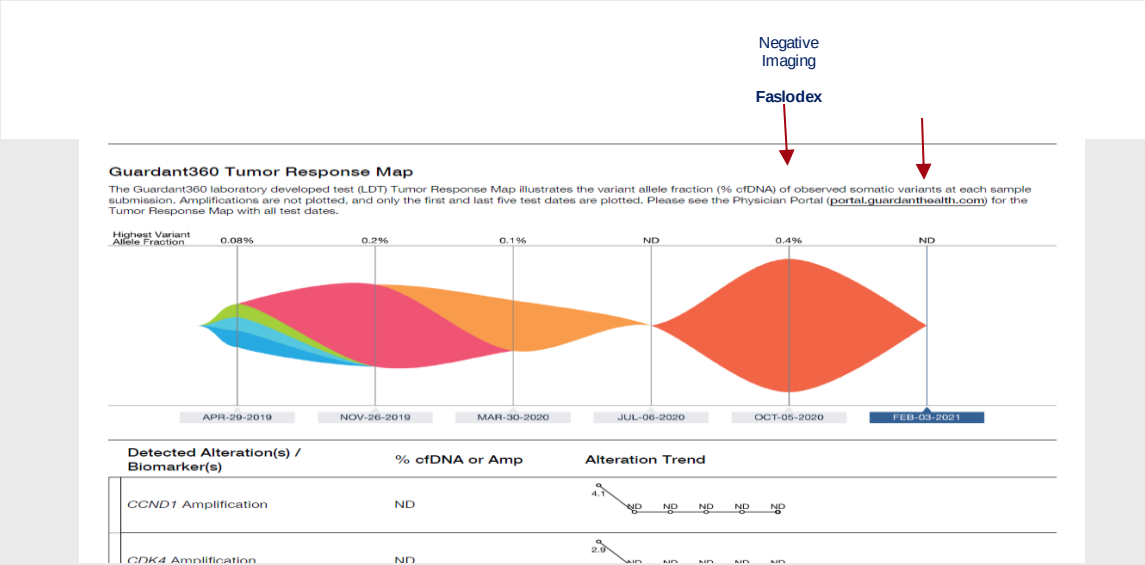
Bardia A et al, SABCS 2023: Abstract PS17-02.

De-Novo stage IV *ESR1*-driven molecular progression

Treatment of molecular PD



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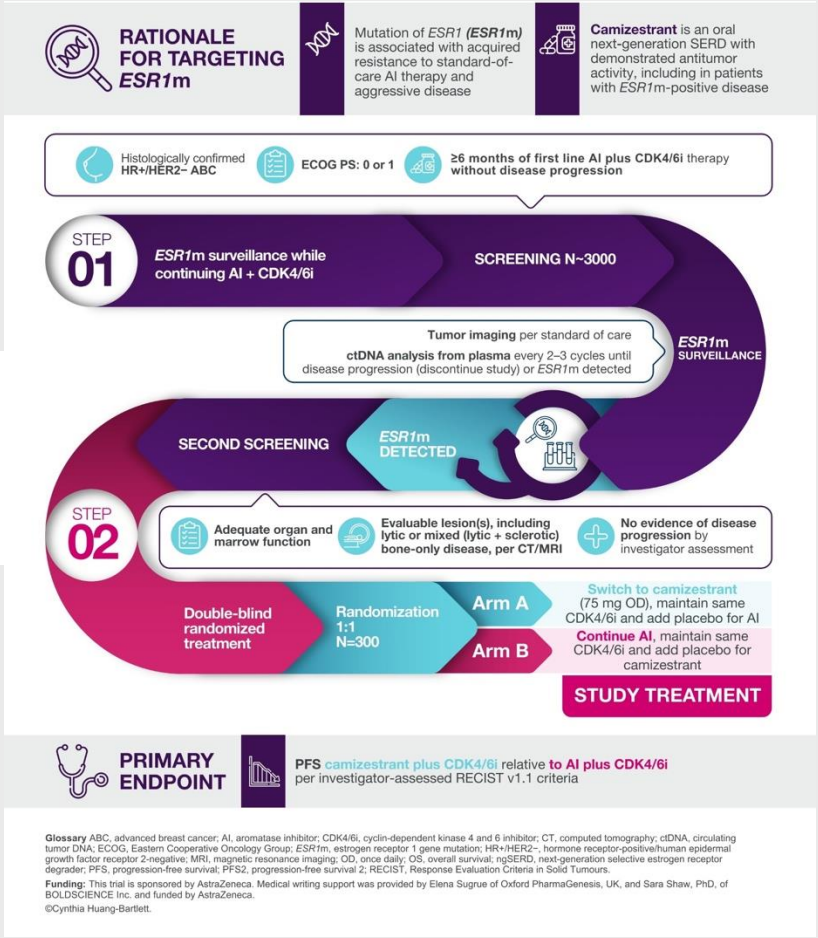
Serial *ESR1* Mutation Testing – SERENA-6

Design of SERENA-6, a Phase 3 switch trial of camizestrant in *ESR1*-mutant breast cancer during first-line treatment

Phase III SERENA-6 study design

Authors: Nicholas Turner, Cynthia Huang-Bartlett, Kevin Kalinsky, Massimo Cristofanilli, Giampaolo Bianchini, Stephen Chia, Hiroji Iwata, Wolfgang Janni, Cynthia X Ma, Erica L Mayer, Yeon Hee Park, Steven Fox, Xiaochun Liu, Sasha McClain & Francois-Clement Bidard.
Article URL https://www.futuremedicine.com/doi/suppl/10.2217/fon-2022-1196 | Trial registration number NCT04964934



Glossary ABC, advanced breast cancer; AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; CT, computed tomography; ctDNA, circulating tumor DNA; ECOG, Eastern Cooperative Oncology Group; *ESR1*m, estrogen receptor 1 gene mutation; HR+/HER2–, hormone receptor-positive/human epidermal growth factor receptor 2-negative; MRI, magnetic resonance imaging; OD, once daily; OS, overall survival; ngSERD, next-generation selective estrogen receptor degrader; PFS, progression-free survival; PFS2, progression-free survival 2; RECIST, Response Evaluation Criteria in Solid Tumours.

Funding: This trial is sponsored by AstraZeneca. Medical writing support was provided by Elena Sugrue of Oxford PharmaGenesis, UK, and Sara Shaw, PhD, of BOLDSCIENCE Inc. and funded by AstraZeneca.

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Camizestrant demonstrated highly statistically significant and clinically meaningful improvement in progression-free survival in 1st-line advanced HR-positive breast cancer with an emergent *ESR1* tumor mutation in SERENA-6 Phase III trial

First and only next-generation oral SERD and complete ER antagonist to demonstrate 1st-line benefit in combination with widely approved CDK4/6 inhibitors

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Conclusions

- **Liquid biopsy is standard of care in MBC**

  - Actionable driver mutations in first and later lines of therapy (*PI3KCA/Akt/PTEN*)

  - Actionable acquired mutations (*ESR1* and *HER2*)

  - Future applications: TMB and Methylation

- **Longitudinal monitoring of ctDNA**

- Response to treatment (change in AF and tumor burden)

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