

Com|Pl|i|t DX

ΠΛΗΡΟΦΟΡΙΕΣ

Εξεταζόμενος	-	Ημ. Συλλογής Δείγμ.	-
ΑΜΚΑ	-	Παραπέμπων	-
Ημερ. Γέννησης	-	Barcode	26xxxxxxGR
Τύπος Δείγμ. #1	ΙΣΤΟΣ ΕΓΚΛΕΙΣΜΕΝΟΣ ΣΕ ΜΠΛΟΚ ΠΑΡΑΦΙΝΗΣ	Ημερ. Παρ. Δειγμ.	-
Τύπος Δείγμ. #2	-	Ημερ. Αποτελ.	-
Κωδικός Δείγμ. #1	-	Τύπος όγκου	ΚΑΡΚΙΝΟΣ ΜΑΣΤΟΥ

Com.Pl.i.t. Dx (23 genes, 7 fusions) | Comprehensive Panel for Individualized Treatment

Αποτελέσματα και ερμηνεία*

Βιοδείκτης	Αποτέλεσμα	Θεραπείες με ισχυρή κλινική σημασία		Θεραπείες με πιθανή κλινική σημασία	Θεραπείες με πιθανή αντίσταση
		Εγκεκριμένες/ βάσει οδηγιών θεραπείες για την ένδειξη (Level A)	Θεραπείες σε ισχυρές μελέτες (Level B)	Εκτός ένδειξης θεραπείες (Level C)	
PIK3CA	Wild-Type	**Gedatolisib+Fulvestrant+Palbociclib Gedatolisib+Fulvestrant			-
ESR1	Exon 10 p.Y537S VAF: 18.3%	Elacestrant Imlunestrant Vepdegestrant	Fulvestrant	-	Aromatase Inhibitors
Μικροδορυφορική Αστάθεια (MSI)	χωρίς μικροδορυφορική αστάθεια (MSS)	-	-	-	-

*Σημείωση: Το επίπεδο σημαντικότητας των παραλλαγών (Level of Evidence, LoE) (π.χ. A, B, C κλπ) βασίζονται στις οδηγίες για την αναφορά γενετικών παραλλαγών στον καρκίνο που δόθηκαν με κοινή συναίνεση των AMP, ACMG, ASCO και CAP. Για λεπτομερή περιγραφή των οδηγιών αυτών, ανατρέξτε στην Εικόνα 1.

^ Η ανάλυση συγκεκριμένων βιοδεικτών του παρόντος πολυγονιδιακού πάνελ πραγματοποιείται στο πλαίσιο διαπίστευσης κατά ΕΛΟΤ EN ISO 15189:2022 (βλ. ενότητα «Methodology»). Η διαπίστευση κατά ΕΛΟΤ EN ISO 15189:2022 αφορά αποκλειστικά τον αναλυτικό προσδιορισμό των εν λόγω βιοδεικτών. Οι ερμηνείες που σχετίζονται με την πρόβλεψη ανταπόκρισης σε θεραπεία δεν περιλαμβάνονται στο πεδίο διαπίστευσης.

** ενδείκνυται για καρκίνο του μαστού HR+/HER2 και PIK3CA wild-type (χωρίς ανιχνεύσιμη PIK3CA παραλλαγή).



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SAMPLE INFORMATION

Name	-	Date Sp. Extracted	-
ID/Medical ID	-	Req. Physician	-
Date of Birth	-	Report No	26xxxxxxGR
Material #1	PARAFFIN EMBEDDED TISSUE-BLOCK	Date Received	-
Material #2	-	Date of Report	-
Sample #1 ID	-	Tumor type	BREAST CANCER

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1. Clinically Significant Biomarkers*

Biomarker	Result	Therapies with strong clinical significance		Therapies with potential significance	Therapies with potential resistance
		Approved/ Standard of care therapies (Level A)	Therapies in well powered studies (Level B)	Off label/ Investigational therapies (Level C)	
PIK3CA	Wild-Type	**Gedatolisib+Fulvestrant+Palbociclib Gedatolisib+Fulvestrant			-
ESR1	Exon 10 p.Y537S VAF: 18.3%	Elacestrant Imlunestrant Vepdegestrant	Fulvestrant	-	Aromatase Inhibitors
Microsatellite Instability (MSI)	Stable (MSS)	-	-	-	-

*Note: Variants' Level of Evidence (LoE) (e.g. A, B, C etc) are based on the Joint consensus recommendation of AMP, ACMG, ASCO and CAP for reporting genetic variants in cancer. For a detailed description of the recommendation please refer to Fig. 1

^ The analysis of selected biomarkers included in the present multigene panel is performed within the scope of accreditation according to ELOT EN ISO 15189:2022 (see «Methodology» section). Accreditation according to ELOT EN ISO 15189:2022 applies exclusively to the analytical determination of the selected biomarkers. Interpretations related to the prediction of therapeutic response are not included in the scope of accreditation.

** indicated for HR+/HER2- breast cancer with PIK3CA wild-type status (no detectable PIK3CA mutation).



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George Nasioulas, PhD Molecular Biologist, Scientific Director, Medical ID:26025301255

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Name

-

Report No

26xxxxxxGR

1. [Clinically Significant Biomarkers](#)
2. [Methodology](#)
3. [Quality Control Results](#)
4. [Important biomarkers findings](#)
5. [Immune Checkpoint inhibitors biomarkers](#)
6. [Interpretations for targeted therapies](#)
7. [Clinical Trials to consider](#)
8. [Appendix](#)
9. [Biomarker findings across all Levels of evidence \(A-D\)](#)
10. [References](#)



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Name

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Report No

26xxxxxxGR

2. Methodology

NGS analysis

DNA is extracted from the sample under investigation using the Qiaamp DNA FFPE Kit (Qiagen). A capture based targeted next generation sequencing (NGS) analysis was performed, using the Oncology 188-Gene Variant Assay (GenePlus) which is a qualitative test which enables the simultaneous detection of single nucleotide variants (SNVs), insertions and deletions (InDels), fusions and copy number variations (CNVs) as well as microsatellite instability (MSI) in a single workflow.

Sequencing was carried out on the DNBSEQ-T7 NGS platform (MGI). The analysis of 23 genes includes the entire exon regions and CNVs of 15 genes, partial exon regions of 8 genes and introns/promoters/fusion breakpoint regions of 7 genes. The test also reports on Microsatellite Instability (MSI) status.

Sequencing data are analyzed through bioinformatics pipeline for variant calling and interpretation using the Gene+Box data analysis and management system. Alteration- and tumor type-specific therapeutic implications are classified using the OncoKB™ Levels of Evidence system, which assigns clinical actionability to individual mutational events. For additional details about the OncoKB™ curation process, please refer to the version-controlled OncoKB™ Curation Standard Operating Procedure.

Genes Analyzed

23 Gene Alterations									
AKT1	BRCA1*	BRCA2*	CDH1	CDK4*	CDK6*	CCND1*	EGFR*	ERBB2*(HER2)	ERBB3
ESR1	FBXW7	FGFR1	FGFR2*	FGFR3*	GATA3	KRAS*	NF1	PALB2*	PIK3CA*
PTEN*	RB1*	TP53*							
7 Fusion Genes									
FGFR1	FGFR2	FGFR3	NTRK1	NTRK2	NTRK3	RET			
MSI									

*CNV (amplification/deletion) analysis is included for these genes

Biomarkers within the scope of accreditation (ISO15189:2022)

-BRCA1, BRCA2 (SNV/indel detection by NGS)

-MSI (NGS)

Sensitivity: Positive reference standards are tested with the assay, all corresponding mutation sites can be accurately detected, and the positive percent agreement (PPA) for all variants (SNVs, Indels, fusions and CNVs) assessed was 95%.



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Name

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Report No

26xxxxxxGR

Specificity: Negative reference standards are tested with the assay, and the negative percent agreement (NPA) of SNVs, Indels, fusions and CNVs was 99%.

Limit of Detection (LoD): The detection limit of the method is 1-2% of mutant allelic content, depending on the genomic region. DNA variations detected at frequencies of less than 5% are confirmed using NGS or an alternative method (Real-Time PCR). All fusions detected are confirmed with an alternative method (Real-Time PCR or FISH).

The performance characteristics of the assay are summarized in the following table:

Variant Type	Limit of Detection
Single nucleotide variations (SNV)	VAF $\geq$ 2-5%
Insertions/deletions (Indel)	VAF $\geq$ 2-5%
Fusion (or rearrangement)	VAF $\geq$ 2%
Copy number (CNV)	$\geq$ 3 copies

Disclaimer

1. This test is mainly used to assist clinical decision-making, and the result does not represent clinical decision.
2. The test should be interpreted by combining the actual patient context. The medication information provided only on the basis of genetic test results, and the actual medication should follow the physician's instructions.
3. The clinical trials only present partial relevant clinical recruitment trials. For more comprehensive and updated information, please refer to the website: <https://clinicaltrials.gov/>.
4. As evidence on variants and drugs evolves, previous classifications may later be modified. The interpretation of a variant is based on current available evidence.
5. Sequence variants were reported using Human Genome Variation Society (HGVS) nomenclature. Classification and interpretation of variants follow guidelines of American College of Medical Genetics and Genomics (ACMG), Association of Molecular Pathology (AMP), American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP).
6. Database and references used: Reference genome (GRCh37), annotation using A Locus Reference Genomic (LRG), database referencing 1000G (phaseIII-ucsc), EXAC (0.3.1), dbSNP (147), PolyPhen2/SIFT (ensdb v73), PhyloP (2013-12-06), Clinvar (2018-8) and Cosmic(V80).

Limitations

1. The test is limited to test genomic variations on DNA level and does not involve RNA level or protein level.
2. Limited tissue detection may not represent the whole DNA variations of lesions because of tumor heterogeneity.
3. Scientific data show that not all patients carry genomic variations that are associated with targeted drug, therefore not all subjects can be matched with targeted therapies or clear resistance mechanism.



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Name

-

Report No

26xxxxxxGR

4. Genetic variation beyond the detection range of this test or some non-gene mutation related factors such as drug interactions may affect the clinical effects of drugs.
5. The detection method cannot distinguish between somatic mutations and germline mutations effectively without control sample analysis.
6. Every molecular test has an internal 0.5-1% chance of failure. This is due to rare molecular events and factors related to the preparation and analysis of the samples.
7. Improper sample collection, transportation and storage may lead to compromised or invalid results.



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Name

-

Report No

26xxxxxxGR

3. Quality Control Results

Quality Control Index	Result	Criterion
Average effective sequencing depth ¹	6315	≥ 500
Tumor cell content ²	60%	≥20%
Overall Assessment ³	PASS	

Note :

1. Average effective sequencing depth: Average sequencing depth on target with duplicated reads.
2. An overall tumor cell content percentage of $\geq 20\%$ is recommended for the efficient detection of somatic alterations in the sample analyzed.
3. Overall Assessment: The quality control overall assessment results are divided into two levels: "PASS" and "RISK". When the overall quality assessment result is "RISK", 94-96% of coverage was achieved in the genes analysed, hence there is a small range where clinical actionable variations could be undetected.



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Name - Report No 26xxxxxxGR

4. Important biomarkers findings

Gene	Finding (VAF)	Gene	Finding (VAF)
AKT1	Not Detected	PIK3CA	(%)
BRCA1/2	Not Detected	PTEN	Not Detected
ERBB2	Not Detected	NTRK1/2/3 rearrangement	Not Detected
ESR1	p.Y537S (18.3%)		

5. Immune Checkpoint inhibitors biomarkers

Biomarker/Variant	Result	Clinical Interpretation
Treatment effect - positive correlation		
TP53 mutation	Not Detected	-
KRAS mutation	Not Detected	-
BRCA1/2 mutation	Not Detected	-
Treatment effect - negative correlation		
PTEN inactivating mutation	Not Detected	-
EGFR mutation (L858R/EX19del)	Not Detected	-



Name - Report No 26xxxxxxGR

6. Interpretations for targeted therapies

Genetic Variation:	PIK3CA: Wild-Type ()	OncoKB
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Treatment Information

The FDA has approved gedatolisib in combination with fulvestrant and palbociclib, or in combination with fulvestrant alone, for the treatment of adults with hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2–), PIK3CA wild-type locally advanced or metastatic breast cancer following progression on or after a CDK4/6 inhibitor and an aromatase inhibitor. The approval marks the first regulatory authorization of a multitarget PI3K/AKT/mTOR (PAM) pathway inhibitor for patients with PIK3CA wild-type disease, a population representing approximately 60% of patients with HR+/HER2– advanced breast cancer who lack the mutation targeted by currently approved PI3K isoform–specific inhibitors. The approval is supported by data from the PIK3CA wild-type cohort of the phase 3 VIKTORIA-1 trial (NCT05501886), a randomized, open-label study that met both primary end points of progression-free survival (PFS) improvement with the gedatolisib-based triplet and doublet regimens vs fulvestrant monotherapy.

Gene information

Phosphatidylinositol-3-kinase (PI3K) is comprised of a regulatory subunit (p85α) as well as a catalytic subunit (p110α) and it is the catalytic subunit that is encoded by the PIK3CA gene. PIK3CA is among the most commonly mutated genes in cancer and aberrant activation of PI3K is a transforming event (PMID: [17376864](#)). Multiple receptor tyrosine kinases, including EGFR, ERBB2 (HER2), RET, MET, and VEGFR, among others, convert extracellular cues into intracellular signals and recruit PI3K to the plasma membrane via scaffold proteins such as IRS1 or by activating RAS. Upon stimulation, PI3K-110α converts its lipid substrate PIP2 (phosphatidylinositol - 4,5 - biphosphate) to PIP3 (phosphatidylinositol - 3,4,5 - biphosphate), which activates several signaling cascades, including the well-characterized AKT-mTOR pathway. Once activated, AKT-mTOR downstream signaling promotes cell survival, proliferation, growth and motility (PMID: [16341083](#)). Adding to this complexity, exposure to some PI3K/mTOR pathway-targeted drugs relieves cancer cells of self-regulatory properties inherent in the PI3K-AKT-mTOR pathway thereby promoting tumor resistance to these agents (PMID: [22576208](#)).

Genetic Variation:	ESR1: c.1610A>C (p.Y537S)	VAF*: 18.3%	OncoKB
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Treatment Information

- On May 1, 2026, the Food and Drug Administration approved vepdegestrant, a heterobifunctional protein degrader, for adults with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, ESR1-mutated advanced or metastatic breast cancer, as detected by an FDA-authorized test, with disease progression following at least one line of endocrine therapy.
- Recently, the Food and Drug Administration approved imlunestran, an estrogen receptor antagonist, for adults with estrogen receptor (ER)-positive, human epidermal growth factor 2 (HER2)-negative, estrogen receptor-1 (ESR1)-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy. Efficacy was evaluated in EMBER-3 (NCT04975308), a randomized, open-label, active-controlled, multicenter trial that enrolled 874 patients with ER-positive, HER2-negative locally advanced or metastatic breast cancer previously treated with an aromatase inhibitor either alone or in combination





Name

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Report No

26xxxxxxGR

with a CDK4/6 inhibitor. In the ESR1 mutated population (n=256), a statistically significant difference in investigator-assessed PFS for imlunestrant compared to investigator's choice of endocrine therapy was observed. The median PFS was 5.5 months in the imlunestrant arm and 3.8 months in the investigator's choice arm. The ORR was 14.3% in the imlunestrant arm and 7.7% in the investigator's choice arm.

- The FDA has granted an accelerated approval to elacestrant for the treatment of patients with estrogen receptor-positive, HER2-negative advanced or metastatic breast cancer following at least 1 prior lines of endocrine therapy. The approval is supported by data from the phase 3 EMERALD study (NCT03778931). The investigational oral selective estrogen receptor degrader (SERD) was evaluated among patients with ESR1-mutant disease (n = 115) vs standard-of-care (SOC) endocrine therapy (n = 113) of either fulvestrant or an aromatase inhibitor. The median progression-free survival was 3.8 months (95% CI, 2.2-7.3) vs 1.9 months (95% CI, 1.9-2.1) with the SERD and SOC, respectively (HR, 0.55; 95% CI, 0.39-0.77; P = .0005).² The overall survival outcomes were not statically significant (HR, 0.90; 95% CI, 0.63-1.30). Results presented during the 2022 SABCS showed that the duration of prior CDK4/6 inhibition played a role for patients who received elacestrant. Among those with ESR1-mutant disease who received at least 12 months of CDK4/6 inhibition (n = 78), the median PFS was 8.61 months vs 1.91 months with SOC (n = 81; HR, 0.410; 95% CI, 0.262-0.634). The 6-, 12-, and 18-month PFS rates were 55.81%, 35.81%, and 28.49% with elacestrant vs 22.66%, 8.39%, and 0% with SOC. Fulvestrant has been approved for women with breast cancer: as a standalone treatment for postmenopausal women with HR-positive metastatic breast cancer whose disease progressed after treatment with other antiestrogen therapy, in combination with the CDK4/6 inhibitor Palbociclib for the treatment of women with advanced or metastatic HR-positive, HER2-negative breast cancer that has progressed after endocrine therapy and as a standalone treatment, or monotherapy, for postmenopausal women with advanced hormone receptor (HR)-positive, HER2-negative breast cancer who have not undergone endocrine therapy previously. Turner et al (2020) have shown that the detection of ESR1 mutations in baseline ctDNA is associated with inferior progression free survival (PFS) and overall survival (OS) in patients treated with exemestane versus fulvestrant (PMID: [32546646](#)).

Gene information

ESR1 is a nuclear receptor that encodes the estrogen receptor alpha (ERα) protein. ERα plays a major role in sexual reproductive development and maintenance, specifically in the female reproductive organs (PMID: [10368776](#)). Binding of the hormone estrogen, the ERα ligand, induces conformational changes to ERα, which allows the receptor to dissociate from HSP90 and dimerize with itself or ERβ. The dimer then translocates to the nucleus where it binds to promoters and enhancers of target genes either directly, via Estrogen Responsive Elements (ERE) in the DNA, or via other transcription factor complexes such as FOS/JUN/SP-1 (PMID: [11162939](#), [10681512](#)). Once bound, the estrogen receptor recruits co-regulators that modulate the transcription of ESR1 target genes, resulting in changes in proliferation, migration and differentiation (PMID: [21779010](#)). Lack of ERα delays the development of WNT1- and ERBB2 mutant-induced mouse mammary tumors (PMID: [10213494](#), [12019156](#)) and reduces the occurrence of estrogen and carcinogen-induced mouse mammary tumors (PMID: [20181624](#), [11156389](#)), indicating the involvement of ERα in tumorigenesis. While mutations in ESR1 are generally very rare in primary cancers (<5%), a number of mutations occurring in the ligand-binding domain (LBD) of the receptor were identified in ~12-25% of hormone-resistant metastatic breast cancer patients (PMID: [24398047](#), [24185512](#), [24185510](#), [24217577](#)). The most recurrent mutations, Y537S and D538G, result in a constitutively active receptor, which is shown to confer acquired resistance to estrogen deprivation therapies.

Variant Information

The ESR1 Y537S mutation is located in the ligand-binding domain of the protein. This mutation has been found in breast cancer (PMID: [24185512](#)). Expression of this mutation in breast cancer cell lines demonstrated that it is activating as measured by increased



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Name

-

Report No

26xxxxxxGR

protein activity, cell proliferation and tumor growth in a xenograft model compared to wildtype (PMID: [8923465](#), [9398213](#), [11914066](#), [26836308](#), [24185512](#), [30733228](#)). In vitro and in vivo studies demonstrated that this mutation is resistant to the ESR1 inhibitors tamoxifen and fulvestrant, but is sensitive to AZD9496 when expressed in embryonic kidney and breast cancer cell lines as measured by protein activity, cell proliferation, and tumor growth upon drug treatment (PMID: [24185512](#), [24185510](#), [27986707](#)). Among 195 patients with estrogen-receptor-positive breast cancer who were treated with the CDK4/6 inhibitor palbociclib plus fulvestrant, the ESR1 Y537S mutation was found at a significantly higher percentage in post-treatment samples compared to pre-treatment samples (PMID: [30206110](#)). The ESR1 Y537S mutation is known to be pathogenic.

Elacestrant

[DrugBank](#)

Elacestrant is an oral, estrogen receptor antagonist that is FDA-approved for the treatment of postmenopausal adult patients with ER+/HER2-, ESR1-mutated advanced or metastatic breast cancer. Oncogenic ESR1 ligand-binding domain missense mutations for treatment with elacestrant were detected with the Guardant360 CDx assay. FDA approval was based on the results of the Phase III EMERALD (NCT03778931) trial of elacestrant versus standard-of-care endocrine monotherapy in 477 patients with ER+/HER2- advanced breast cancer who had received one or two lines of endocrine therapy (n=228, patients with ESR1 missense mutations in codons 310-547).

In the Phase III EMERALD (NCT03778931) trial, the ESR1-mutated cohort had a six-month progression-free survival (PFS) of 40.8% (95% CI=30.1-51.4) versus 19.1% (95% CI=10.5-27.8) and a twelve-month progression-free survival of 26.8% (95% CI=16.2-37.4) versus 8.2% (95% CI=1.3-15.1) for the elacestrant versus standard-of-care arm, respectively (PMID: [35584336](#)). In the updated results from the Phase III EMERALD (NCT03778931) trial based on the duration of prior CDK4/6i treatment, the ESR1-mutated cohort previously treated with CDK4/6i for ≥ 6.0 months (n=103 elacestrant arm; n=102 stand-of-care arm), ≥ 12.0 months (n=78 elacestrant arm; n=81 stand-of-care arm) or ≥ 18.0 months (n=55 elacestrant arm; n=56 stand-of-care arm) demonstrated a median PFS of 4.1 months, 8.6 months and 8.6 months with elacestrant versus 1.9 months (HR=0.52 [95% CI=0.36-0.74]), 1.9 months (HR=0.41 [95% CI=0.26-0.63]) and 2.1 months (HR=0.47 [95% CI=0.20-0.79]) with standard-of-care treatment (PMID: [39087959](#)).

Imlunestrant

[DrugBank](#)

Imlunestrant is an orally available, small-molecule estrogen receptor (ER) antagonist that is FDA-approved for the treatment of adults with ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy. ESR1 mutations for treatment with imlunestrant were detected by the Guardant360 CDx assay. FDA approval was based on the results of the Phase III EMBER-3 (NCT04975308) trial of imlunestrant versus standard-of-care (SOC) treatment in 256 patients with ER-positive, HER2-negative locally advanced or metastatic breast cancer previously treated with an aromatase inhibitor either alone or in combination with a CDK4/6 inhibitor. Patients were excluded from the trial if they were eligible to receive a PARP inhibitor.

In the Phase III EMBER-3 (NCT04975308) trial, the imlunestrant monotherapy cohort (n=138) demonstrated a clinical benefit rate of 43.5% (n=60), an objective response rate (ORR) of 14.3% (95% CI=7.8-20.8), with a 0.9% complete response (CR) rate and 13.4% partial response (PR) rate, a median duration of response (DOR) of thirteen months (range=2-20), an estimated restricted mean survival time at 19.4 months of 7.9 months (95% CI=6.8-9.1) and a median progression-free survival (PFS) of 5.5 months (95% CI=3.9-7.4) (PMID: [39087959](#)).



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Name	Report No
-	26xxxxxxGR
39660834). The SOC monotherapy (fulvestrant or exemestane) (n=118) cohort demonstrated a clinical benefit rate of 33.1% (n=39), an ORR of 7.7% (95% CI=2.2-13.2), with a 7.7% PR rate, a median DOR of seven months (range=4-16), an estimated restricted mean survival time at 19.4 months of 5.4 months (95% CI=4.6-6.2) and a median PFS of 3.8 months (95% CI=3.7-5.5) (HR=0.62 [95% CI=0.46-0.82]; p=0.0008) (PMID: 39660834).	
Vepdegestrant	DrugBank
Vepdegestrant is an orally bioavailable, proteolysis-targeting chimera (PROTAC) estrogen receptor (ER) degrader that is FDA approved for the treatment of adults with ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer, as detected by an FDA-authorized test, with disease progression following at least one line of endocrine therapy. Select ESR1 mutations for treatment with vepdegestrant are detected by the Guardant360 CDx. FDA approval was based on the results of the Phase III VERITAC-2 (NCT05654623) trial of vepdegestrant versus fulvestrant in patients with previously treated, ESR1-mutated advanced or metastatic breast cancer. In the Phase III VERITAC-2 (NCT05654623) trial, the vepdegestrant cohort harboring ESR1 mutations (n=136) demonstrated a median progression-free survival of 5.0 months (95% CI=3.7-7.4) and an overall response rate (ORR) of 19% (95% CI=12-27) (PMID: 40454645). The fulvestrant cohort harboring ESR1 mutations (n=134) demonstrated a median PFS of 2.1 months (95% CI=1.9-3.5) (HR=0.58 [95% CI=0.43-0.78]; p<0.001) and an ORR of 4% (95% CI=1.6-10) (PMID: 40454645).	
Fulvestrant	DrugBank
Fulvestrant is an intramuscularly injected, steroidal selective estrogen receptor degrader (SERD) that is an estrogen receptor (ER) antagonist and results in ER degradation. There are promising clinical data of response to fulvestrant in patients with ESR1-mutant breast cancer. In a retrospective analysis of the Phase III SoFEA (NCT00253422) trial of fulvestrant or exemestane in patients with hormone receptor-positive breast cancer, patients who had ER mutations had a significantly longer median progression-free survival (PFS) when treated with fulvestrant (5.7 months) versus exemestane (2.6 months) (HR, 0.52; P = 0.02), while patients without ER mutations had no significant difference in median PFS between the two treatment arms (P = 0.77) (PMID: 27269946). The addition of abemaciclib to fulvestrant in patients with hormone receptor-positive breast cancer (abemaciclib plus fulvestrant, n=446; placebo plus fulvestrant, n=223) further increased overall survival in these patients (46.7 months versus 37.3 months; HR= 0.757; 95% CI [0.606-0.945]; P = .01) (PMID: 31563959). In the Phase III PADA-1 (NCT03079011) trial of combination fulvestrant and palbociclib in 172 patients with estrogen receptor-positive, HER2-negative advanced breast cancer with rising ESR1 mutation in blood, median PFS was 11.9 months (95% CI= 9.1-13.6) in the fulvestrant and palbociclib experimental group versus 5.7 months (95% CI= 3.9-7.5) in the aromatase inhibitor and palbociclib control group (PMID: 36183733).	

*VAF: Variant Allele Frequency



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7. Clinical Trials to consider

PIK3CA associated clinical trials

[NCT06757634](#)

PHASE3

Title	Phase 3 Study of Gedatolisib as First-Line Treatment for Patients With HR-Positive, HER2-Negative Advanced Breast Cancer (VIKTORIA-2)
Treatment	Arm A: Gedatolisib + Palbociclib + Fulvestrant Arm B: Ribociclib + Fulvestrant Arm C: Gedatolisib + Palbociclib + Letrozole Arm D: Ribociclib + Letrozole
Location	Argentina, Australia, Belgium, Brazil, Bulgaria, Czechia, France, Germany, Greece, Hungary, Italy, Malaysia, Mexico, Poland, Portugal, Romania, South Korea, Spain, Taiwan, Thailand, Turkey (Türkiye), United States

Press [here](#) for a live search of clinical trials for PIK3CA

ESR1 associated clinical trials

[NCT07062965](#)

PHASE3

Title	A Study to Learn About the Study Medicine Called PF-07248144 in Combination With Fulvestrant in People With HR-positive, HER2-negative Advanced or Metastatic Breast Cancer Who Progressed After a Prior Line of Treatment.
Treatment	PF-07248144 Fulvestrant Everolimus Exemestane
Location	Australia, Belgium, Brazil, Bulgaria, Canada, China, Czechia, Finland, France, Germany, Greece, Hungary, India, Israel, Italy, Japan, Mexico, Netherlands, Poland, Slovakia, South Korea, Spain, Sweden, Taiwan, Turkey (Türkiye), United Kingdom, United States

[NCT06380751](#)

PHASE3

Title	Saruparib (AZD5305) Plus Camizestrant or Plus Endocrine Therapy, Compared With CDK4/6 Inhibitor Plus Endocrine Therapy or Plus Camizestrant in HR-Positive, HER2-Negative (IHC 0, 1+, 2+/ ISH Non-amplified), BRCA1, BRCA2, or PALB2m Advanced Breast Cancer
Treatment	Saruparib (AZD5305) Camizestrant Abemaciclib Ribociclib Palbociclib Fulvestrant Letrozole Anastrozole Exemestane
Location	Argentina, Australia, Austria, Brazil, Bulgaria, Canada, Chile, China, Czechia, France, Germany, Hong Kong, Hungary, India, Israel, Italy, Japan, Malaysia, Peru, Poland, Portugal, Puerto Rico, South Korea, Spain, Taiwan, Thailand, Turkey (Türkiye), United Kingdom, United States



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Name		-	Report No	26xxxxxxGR
NCT06065748			PHASE3	
Title	A Study to Evaluate Efficacy and Safety of Giredestrant Compared With Fulvestrant (Plus a CDK4/6 Inhibitor), in Participants With ER-Positive, HER2-Negative Advanced Breast Cancer Resistant to Adjuvant Endocrine Therapy (pionERA Breast Cancer)			
Treatment	Giredestrant Fulvestrant Abemaciclib Palbociclib Ribociclib LHRH Agonist FoundationOne Liquid CDx Assay (F1LCDx)			
Location	Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, China, Colombia, Costa Rica, Finland, France, Germany, Greece, Guatemala, Hong Kong, Hungary, India, Israel, Italy, Kenya, Mexico, New Zealand, Peru, Poland, Portugal, Puerto Rico, Romania, Singapore, Slovenia, South Africa, South Korea, Spain, Taiwan, Thailand, Turkey (Türkiye), United States			

NCT05816655		PHASE2
Title	Comparison of Clinical Efficacy Between Letrozole + Ribociclib and Fulvestrant + Letrozole + Ribociclib in Hormone Receptor Positive, HER2 Negative Metastatic Breast Cancer	
Treatment	Fulvestrant plus AI plus ribociclib AI plus ribociclib	
Location	South Korea	

NCT06062498		PHASE2
Title	Elacestrant vs Elacestrant Plus a CDK4/6 Inhibitor in Patients With ERpositive/HER2-negative Advanced or Metastatic Breast Cancer	
Treatment	elacestrant, palbociclib, abemaciclib, ribociclib	
Location	United States	

NCT06067503		PHASE2
Title	Biomarkers to Detect Endocrine Therapy Resistance	
Treatment	18F-fluorofuranylnorprogesterone Liquid Biopsy Positron Emission Tomography/Computed Tomography	
Location	United States	

NCT06195306		PHASE2
Title	Low Dose Tamoxifen With or Without Omega-3 Fatty Acids for Breast Cancer Risk Reduction	



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Name	-	Report No	26xxxxxxGR
Treatment	Biospecimen Collection Mammography Omega-3-Acid Ethyl Esters Questionnaire Administration Random Periareolar Fine-Needle Aspiration Tamoxifen		
Location	United States		

NCT06064812		PHASE1 PHASE2
Title	A Phase I/II Study of FWD1802 in Patients With ER+/HER2- Advanced BC.	
Treatment	FWD1802	
Location	China	

NCT04174352		EARLY_PHASE1
Title	FES Imaging to Optimize Tamoxifen for Metastatic Breast Cancer	
Treatment	Tamoxifen FES PET/CT	
Location	United States	

Press [here](#) for a live search of clinical trials for ESR1



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8. Appendix

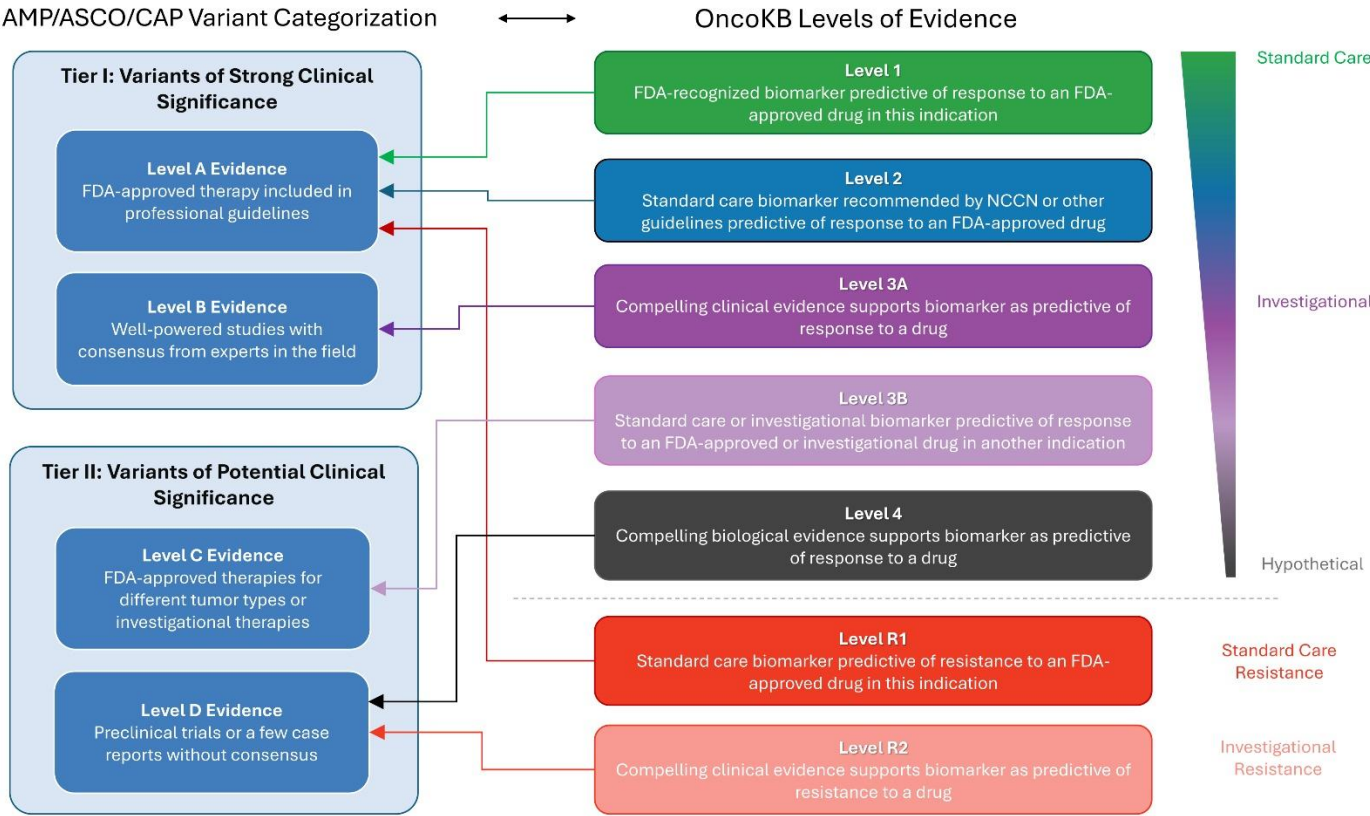


Figure 1. Joint consensus recommendation of AMP, ACMG, ASCO and CAP for reporting genetic variants in cancer. [1-2]

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Report No

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Microsatellite Instability (MSI)

Microsatellite instability (MSI) is a condition of genetic hypermutability resulting from impaired DNA mismatch repair (MMR) mechanisms. It is characterized by the accumulation of mutations in short repetitive DNA sequences known as microsatellites. MSI-H is found across multiple cancer types, most notably in colorectal, endometrial, gastric, and ovarian cancer. It can arise sporadically or as part of Lynch syndrome, a hereditary condition caused by germline mutations in MMR genes (MLH1, MSH2, MSH6, PMS2).

The results of MSI are divided into three types: MSI-H, which means microsatellites are highly unstable; MSS, which means microsatellites are stable; MSI-U, which means that the sample does not meet the MSI evaluation conditions (tissues or pleural fluid samples may not have passed the MSI indicator calculation quality control due to the low DNA and/or content of tumor cells).

Pembrolizumab has received full FDA approval for adult and pediatric patients with unresectable or metastatic MSI-H or dMMR solid tumors (PMID: 35680043, 33264544) — representing the first full approval for an immunotherapy based on a predictive biomarker, regardless of solid tumor type. This approval applies to patients who have progressed after prior treatment and have no satisfactory alternative options. Beyond the tumor-agnostic indication, specific approvals have been granted for tumor types such as endometrial and colorectal cancer.



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9. Biomarker findings across all Levels of evidence (A-D)

Biomarker	Result	Therapies with strong clinical significance		Therapies with potential significance		Therapies with potential resistance
		Approved/ Standard of care therapies (Level A)	Therapies in well powered studies (Level B)	Off label/ Investigational therapies (Level C)	Therapies in pre-clinical trials (Level D)	
PIK3CA	Wild-Type	**Gedatolisib+Fulvestrant+Palbociclib Gedatolisib+Fulvestrant			-	-
ESR1	Exon 10 c.1610A>C (p.Y537S) VAF: 18.3%	Elacestrant Imlunestrant Vepdegestrant	Fulvestrant	-	-	Aromatase Inhibitors



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