Marsden360
Developed in partnership with Guardant Health

The ROYAL MARSDEN Clinical Genomics

Consulting physician		Patient		Sample	
Report Date	15/01/2025	Diagnosis	Metastatic breast cancer	Accession Number	21059433_not for reporting
				Collection site	Not provided

Panel Analysis: Somatic cancer

Marsden360 sequences 74 cancer-associated genes to identify somatic alterations. Cell-free circulating DNA (cfDNA) is extracted from plasma, enriched for targeted regions, and sequenced using Illumina platforms and hg19 as the reference genome.

Overall comment

A missense variant was detected in the ESR1 gene; p.(Y537S). Activating variants in ESR1 have been reported in 40% of ER+/HER2- metastatic breast cancers resistant to endocrine therapies.

This patient may benefit from treatment with ESR1 targeted therapy.

MSI high-NOT DETECTED

Analysis results: Clinically relevant variants detected

1 Variant of strong clinical significance, Tier 1	Approved treatments	Trials and Supplementary Information
ESR1, p.Y537S, VAF 1.81%, Pathogenic	Elacestrant	Trials: 2 Phase 1/Phase 2

Interactions

None

Guidelines

Potentially relevant guidelines are reported in the "guidelines" section starting on page 5.

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TREATMENT OPTIONS

Therapies with potential clinical benefit (1)

ELACESTRANT

Elacestrant, an estrogen receptor antagonist, is FDA-approved for treating postmenopausal female patients or adult male patients, with ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.

Sensitive

Gene	Variant	Classification
ESR1	p.Y537S c.1610A>C	Tier 1A Pathogenic

AVAILABLE CLINICAL TRIALS

Phase 1/Phase 2 clinical trials (2)

BLU-222, RIBOCICLIB, FULVESTRANT

A Phase 1/2 Study to Evaluate the Safety, Pharmacokinetics, and Efficacy of BLU-222 as a Single Agent and in Combination Therapy for Patients With Advanced Solid Tumors

NCT05252416

Qualifying variant			Contact
Gene	Variant	Classification	Blueprint Medicines; medinfo@blueprintmedicines.com;
ESR1	p.Y537S c.1610A>C	Tier 1A Pathogenic	617-714-6707;

CAMIZESTRANT, AZD5305

A Modular Phase I/IIa, Open-label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Preliminary Efficacy of Ascending Doses of AZD5305 as Monotherapy and in Combination With Anti-cancer Agents in Patients With Advanced Solid Malignancies

NCT04644068

Qualifying variant			Contact
Gene	Variant	Classification	AstraZeneca Clinical Study Information Center; information.
ESR1	p.Y537S c.1610A>C	Tier 1A Pathogenic	center@astrazeneca.com; 1-877-240-9479;

VARIANT DETAILS

Variant of strong clinical significance (1)

ESR1 Y537S

Gene: ESR1
Nucleotide:
NM_000125.4:
g.152419923A>C
c.1610A>C
Assessment: Pathogenic
Exon: 8
Amino Acid: p.Y537S
Allelic Fraction: 1.81%
Classification: Tier 1A

Treatment options
1 Sensitive
2 Trials

Biomarker summary: *ESR1*-Y537S (NM_001122742) is an activating mutation.

Clinical relevance: *ESR1* encodes estrogen receptor alpha (ER-alpha), one of the major estrogen receptor (ER) isoforms in humans [25]. Activation of *ESR1* through mutation or amplification may result in upregulation of genes involved in cell cycle progression and survival and has been reported as a mechanism of resistance to anti-estrogen therapies [25, 27]. The selective estrogen receptor degrader elacestrant has been approved by the EMA for the treatment of postmenopausal women or adult men with advanced or metastatic ER positive /Her2 negative breast cancer with activating *ESR1* mutations following disease progression on endocrine therapy. Several alterations at Y537, including Y537S, Y537N, and Y537C, have been detected in metastatic and ER positive breast tumors following treatment with aromatase inhibitors, but not in primary or ER negative cases [17, 12, 27, 32].

Disease summary: *ESR1* mutations, particularly those localized to the ligand-binding domain, as well as *ESR1* amplification and certain translocations involving *ESR1*, may result in resistance to anti-estrogen therapy in breast cancer [8, 34, 21, 32, 27, 7, 15].

Molecular function: *ESR1* Y537S is a missense alteration located at a phosphorylated residue within the ligand binding domain (LBD) of the ER-alpha protein [1, 17]. This alteration has been reported to result in constitutive activation of the ER-alpha protein and shown to be enriched in heavily treated ER positive breast cancer patients, with several studies reporting this mutation in metastatic, but not primary, tumors, and in ER positive, but not ER negative, cases [18, 17, 27, 32, 37, 6]. *ESR1* Y537S has also been reported as one of the most commonly acquired *ESR1* mutations following treatment with aromatase inhibitors, with two separate studies citing this mutation in 22% and 25% of *ESR1*-mutant ER positive breast tumors following treatment [4, 12, 32, 27, 17]. Preclinical studies have reported that *ESR1* Y537S confers reduced sensitivity to tamoxifen and fulvestrant as compared with wild-type *ESR1*, as well as increased sensitivity to the BET inhibitor birabresib [10, 13, 33, 12, 36, 14]. However, *ESR1* Y537S has been reported as an acquired alteration in an endometrial stromal sarcoma case following letrozole treatment; subsequent treatment with fulvestrant resulted in no measurable disease for at least 48 months [9]. Positive clonal selection of *ESR1* Y537S has been reported in the PALOMA-3 study of fulvestrant in combination with palbociclib or placebo in 195 patients with breast cancer; a significantly increased median progression-free survival was reported in patients who acquired Y537S as compared with those who had the Y537S alteration at the start of treatment (13.2 vs 3.5 months) [23]. However, fulvestrant has been associated with improved progression-free and overall survival as compared with exemestane in patients with baseline *ESR1* mutation, including Y537 mutation specifically, in analysis of the Phase 3 SoFEA and EFFECT trials, and objective response rates were not significantly different between patients with or without *ESR1* mutation in the PALOMA-3 trial of fulvestrant with or without palbociclib [35, 12]. In preclinical studies, next-generation SERDs such as elacestrant, amcenestrant, and giredestrant, and other agents such as lasofoxifene (SERM) and H3B-6545 (selective estrogen receptor covalent antagonist, SERCA) have shown efficacy in *ESR1* Y537S-mutant xenograft models, and clinical studies have shown benefit from these agents in patients with baseline *ESR1* mutations [26, 29, 22, 19, 24, 2].

Incidence: *ESR1* mutations have been reported in 8.4% (1097/13066) of Breast carcinoma samples analyzed in COSMIC (May 2023). *ESR1* mutations have been reported in 0.0-27% of Breast carcinoma samples (cBioPortal for Cancer Genomics, May 2023). *ESR1* mutations have been reported in 1-12% of breast cancer cases and specifically in 3-20% of ER positive breast cancer cases described in the scientific literature [11, 31, 16, 3, 20, 32, 30, 28]. *ESR1* fusions, exclusively *ESR1-CCDC170* fusions, have been reported in 5% (19/372) of breast cancer samples analyzed in one study [16].

REPORT INFORMATION

Genes tested

Marsden360 reports single nucleotide variants and splice site mutations in all clinically relevant exons in 74 genes and reports other variant types in select genes as indicated below.

AKT1 Ω	ALK #Ω	APC Ω	AR †Ω	ARAF Ω	ARID1A Ω	ATM Ω	BRAF †Ω	BRCA1 Ω
BRCA2 Ω	CCND1 †Ω	CCND2 †Ω	CCNE1 †Ω	CDH1 Ω	CDK12 Ω	CDK4 †Ω	CDK6 †Ω	CDKN2A Ω
CTNNB1 Ω	DDR2 Ω	EGFR †Ω	ERBB2 †Ω	ESR1 Ω	EZH2 Ω	FBXW7 Ω	FGFR1 †Ω	FGFR2 †#Ω
FGFR3 #Ω	GATA3 Ω	GNA11 Ω	GNAQ Ω	GNAS Ω	HNF1A Ω	HRAS Ω	IDH1 Ω	IDH2 Ω
JAK2 Ω	JAK3 Ω	KIT †Ω	KRAS †Ω	MAP2K1 Ω	MAP2K2 Ω	MAPK1 Ω	MAPK3 Ω	MET †Ω
MLH1 Ω	MPL Ω	MTOR Ω	MYC †Ω	NF1 Ω	NFE2L2 Ω	NOTCH1 Ω	NPM1 Ω	NRAS Ω
NTRK1 #Ω	NTRK3 Ω	PDGFRA †Ω	PIK3CA †Ω	PTEN Ω	PTPN11 Ω	RAF1 †Ω	RB1 Ω	RET #Ω
RHEB Ω	RHOA Ω	RIT1 Ω	ROS1 #Ω	SMAD4 Ω	SMO Ω	STK11 Ω	TERT Ω‡	TP53 Ω
TSC1 Ω	VHL Ω							

Ω Marsden360 reports insertion and deletion variants (indels) in this gene.
‡ Marsden360 reports alterations in the promoter region of this gene.
# Marsden360 reports fusion events involving this gene for all known gene partners.
† Marsden360 reports amplifications of this gene.

GUIDELINES

The ESMO Clinical Practice Guidelines for metastatic breast cancer (v1.00, May2022) note that for patients treated with everolimus, substituting the exemestane backbone with fulvestrant is favored in cases with *ESR1* mutation [ESCAT score: II-A; off label] [PMID:34678411].

Methods and limitations

All exons are sequenced in some genes; only clinically significant exons are sequenced in other genes. The types of genomic alterations detected by Marsden360 include single nucleotide variants, gene amplifications, fusions, short insertions/deletions, and splice site-disrupting events. Marsden360 is not validated for detecting other types of genomic alterations, such as complex rearrangements or gene deletions. Microsatellite Instability (MSI) is assessed for all cancer types by evaluating somatic changes in the length of repetitive sequences on the Marsden360 panel. A “Not Detected” result does not preclude MSI-High status in tissue. Marsden360 cannot discern the source of circulating cfDNA, and for some variants in the range of ~40 to 60% cfDNA, the test cannot distinguish germline variants from somatic alterations. Marsden360 is not validated for the detection of germline or de novo variants associated with hereditary cancer risk.
Discrepancies in results between molecular testing on both ctDNA and a tumour biopsy may be observed in 20-30% of patients. In the case of ctDNA, discrepancies may be caused by low circulating tumour DNA, assay limitations in the detection of structural/ copy number variants and non-uniform coverage accross the panel with higher coverage over hotspot regions. In the case of tissue, discrepancies may be caused by low tumour content or extensive necrosis in the biopsy. Tissue testing should be considered when plasma analysis is not informative and if clinically appropriate.

QIAGEN Clinical Insight (QCI™) is a variant analysis, interpretation and decision support tool for research and clinical labs analyzing human genetics data and is not intended to be used for diagnostic purposes. QCI Interpret software includes the following underlying databases, data reference sets and tools: QIAGEN Clinical Insight Interpret (9.3.2.20240813), Ingenuity Knowledge Base (N-release), CADD (v1.6), NCBI Gene (2023-08-25), Allele Frequency Community (2019-09-25), EVS (ESP6500SI-V2), Refseq Gene Model (2023-10-03), JASPAR (2013-11), Ingenuity Knowledge Base Snapshot Timestamp (2024-12-10 12:54:26.108), Vista Enhancer hg18 (2012-07), Vista Enhancer hg19 (2012-07), Clinical Trials (N-release), MITOMAP: A Human Mitochondrial Genome Database. http://www.mitomap.org, 2019 (2020-06-19), PolyPhen-2 (v2.2.2 (HumVar)), 1000 Genome Frequency (phase3v5b), ExAC (0.3.1), TargetScan (7.2), phyloP hg18 (GRCh37 (hg19) 2019-11, GRCh38 2019-11), phyloP hg19 (GRCh37 (hg19) 2019-11, GRCh38 2019-11), GENCODE (Release 44), CentoMD (5.3), dbVar (2021_04), OMIM (October 23, 2023), gnomAD (GRCh37 (hg19) 2.1.1, GRCh38 (hg38) 3.1.2), BSIFT (2016-02-23), TCGA (2013-09-05), Clinvar (2024-11-11), DGV (2016-05-15), COSMIC (v99), HGMD (2024.4), Matched Annotation from NCBI and EMBL-EBI (MANE) (1.2), OncoTree (oncotree_2021_11_02), dbSNP (GRCh37 (hg19) 155, GRCh38 155), SIFT4G (2016-02-23)

Please note that this assay (Marsden360) has not yet been assessed by UKAS for accreditation; an extension to scope applicaton is in progress.

Clinical significance of variants based on AMP / ASCO / CAP guidelines*

Strong clinical significance	Tier 1A	Biomarker predicts response or resistance to an FDA or EMA approved therapy, according to drug label or professional guidelines for this diagnosis Biomarker included in professional guidelines is prognostic or diagnostic for this diagnosis
	Tier 1B	Biomarker predicts response or resistance to a therapy for this diagnosis based on well-powered studies Biomarker is prognostic or diagnostic for this diagnosis based on well-powered studies
Potential clinical significance	Tier 2C	Biomarker is associated with response or resistance to an FDA or EMA approved therapy, according to drug label or professional guidelines but only for different diagnosis Biomarker is an inclusion criterion for an active clinical trial Biomarker is prognostic or diagnostic based on multiple small studies
	Tier 2D	Biomarker shows plausible response or resistance based on case or preclinical studies Biomarker may assist in disease diagnosis or prognosis based on small studies
Uncertain clinical significance	Tier 3	Biomarker has uncertain clinical significance and not known to be likely benign or benign

*Adapted from PMID:27993330 jmd.amjpathol.org/article/S1525-1578(16)30223-9/pdf

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