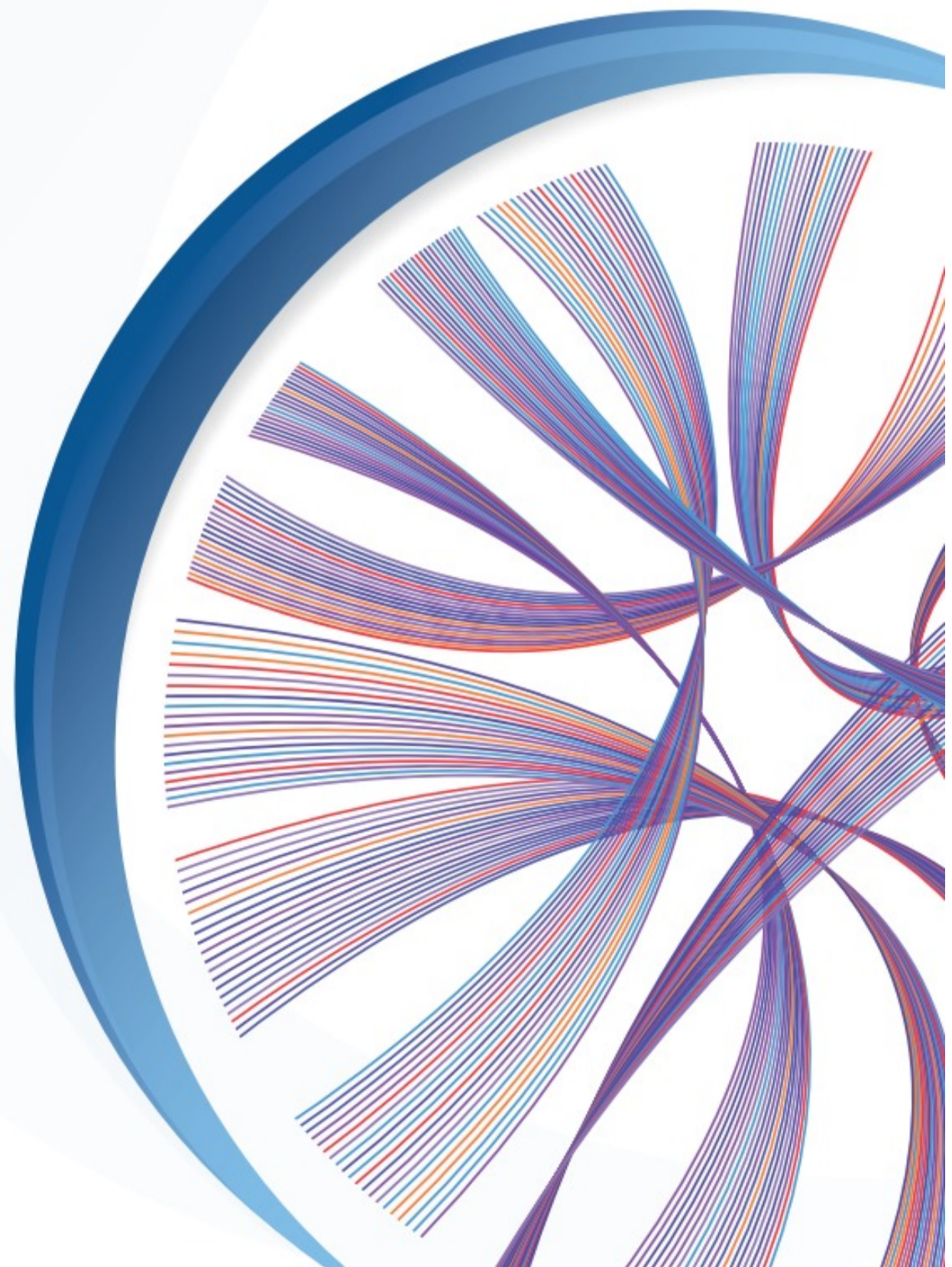


TARGET FIRST

TEST REPORT



SCOPE OF THE TEST

SNVs, InDels, CNAs, Gene Fusions status

CLINICAL INDICATION

Breast Carcinoma

REPORT DETAILS

Name : REKHA DEVI

Gender : Female

Age/DOB : 54 Years

Reporting Date : 20/03/2023

Cancer Celltype : Carcinoma, NOS

Sample Source : B0013691

Tumor content : 40%

Consulting Clinician : Dr. Amit Jain

Hospital : Valentis Cancer Hospital, Mussoorie Mawana Road

RESULTS
GENOMIC FINDINGS FROM TUMOR PROFILING
Genomic Alteration

 PIK3CA Exon 8 (p.Cys420Arg)
 Allelic burden: 25%

Relevant Therapies (in Same Cancer Type)

Therapy	Clinical Relevance
Alpelisib and Fulvestrant	RESPONSIVE

Relevant Therapies (in Different Cancer)

Therapy	Clinical Relevance	Cancer Type
NA	NA	NA

*NA: Not Applicable

STATUS OF VARIANTS IN CANCER RELATED BIOMARKERS

Gene	PIK3CA	ERBB2	BRCA1	BRCA2	ATM	BRIP1	BARD1	CDK12
Status	Pathogenic	Not Detected	VUS	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected

Gene	CHEK1	CHEK2	FANCL	PPP2R2A	RAD51C	RAD54L
Status	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected

VARIANT DETAILS:

Gene	Variant Location	Variant Consequence	Clinical Significance	Variant Type	Reference
<i>PIK3CA</i>	chr3:g.178927980T>C, ENST00000263967, Exon 8	c.1258T>C,p.Cys420Arg , 25%	Pathogenic	Nonsynonymous SNV	rs121913272, VCV000031945.23
<i>PDGFRA</i>	chr4:g.55131142G>A, ENST00000257290, Exon 5	c.685G>A,p.Glu229Lys , 17%	VUS	Nonsynonymous SNV	ACMG Guidelines
<i>ROS1</i>	chr6:g.117725466G>C, ENST00000368508, Exon 5	c.415C>G,p.Leu139Val , 13%	VUS	Nonsynonymous SNV	ACMG Guidelines
<i>BRCA1</i>	chr17:g.41244453C>G, ENST00000471181, Exon 10	c.3095G>C, p.Arg1032Thr , 9%	VUS	Nonsynonymous SNV	ACMG Guidelines

*NA: Not Applicable

ADDITIONAL NOTES:

- The FDA has approved the drug alpelisib in combination with fulvestrant for postmenopausal women and men who have advanced or metastatic breast cancer that is HR-positive/HER2-negative, with mutations in the *PIK3CA* gene. Kindly correlate clinically before making any treatment decisions.
- According to the IHC report dated (02-02-2023) indicating HER2 3+ positive status, we detected a copy number gain in the *ERBB2* gene, which is around our reporting cut-off. This could be due to the inherent nature of FFPE DNA. Hence, we suggest reflex testing on alternate platforms such as FISH before making any treatment related decisions.

VARIANTS WITH CLINICALLY RELEVANT THERAPIES

Gene (Variant) - Drug association

- *PIK3CA* :
Alpelisib and Fulvestrant - RESPONSIVE

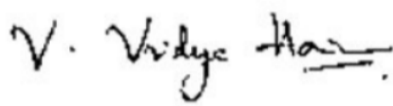
Summary

The drug alpelisib in combination with fulvestrant has been approved for postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen (FDA).

The approval was based on the phase 3 SOLAR-1 (NCT02437318). 341/572 harboured PIK3CA mutation of which 169 were treated with alpelisib+fulvestrant. Investigator led assessment of median progression free survival during a median follow up of 20 months was found to be 11.0 months (95% CI, 7.5, 14.5) with HR 0.65 (95% CI, 0.50, 0.85; p=0.001). Overall response among all the 169 patients was 26.6% (95% CI, 20.1, 34) while for 126 of the patients with measurable disease at baseline was 35.7% (95% CI, 27.4, 44.7).

REFERENCES

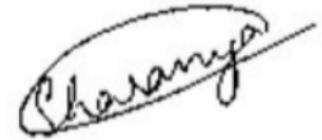
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TEST DESCRIPTION

TARGET First is a Next Generation Sequencing based test which identifies genetic alterations in a comprehensive panel of well curated 53 tumor genes which can impact response to approved therapy for a particular cancer type. Some of the alterations detected may have bearing on prognosis and/or therapeutic options and may provide relevant information that allows oncologists/clinicians to consider various lines of targeted treatment for the patient.

GENES EVALUATED

TARGET First detects mutations (SNVs and Short Indels), Copy Number Variations (CNVs), gene fusions and splice variants in the 53 genes :

SNVs/InDels Covered in TARGET First

ABL1	ALK	AR	ATM	BARD1	BRAF	BRCA1	BRCA2	BRIP1	CDK12
CDK4	CDK6	CDKN2A	CHEK1	CHEK2	EGFR	EPCAM	ERBB2	ERBB3	EZH2
FANCL	FGFR3	GAPDH	IDH1	IDH2	JAK2	KIT	KRAS	MAP2K1	MAP2K2
MDM2	MET	MLH1	MLH3	MSH2	MSH6	NRAS	PALB2	PDGFRA	PDGFRB
PIK3CA	PMS1	PMS2	PPP2R2A	RAD51B	RAD51C	RAD51D	RAD54L	RET	ROS1
STK11	TSC1	TSC2							

CNAs Covered in TARGET First

ABL1	AR	ATM	BARD1	BRCA1	BRCA2	BRIP1	CDK12	CDK4	CDK6
CDKN2A	CHEK1	CHEK2	EGFR	EPCAM	ERBB2	ERBB3	EZH2	FANCL	FGFR3
GAPDH	IDH2	JAK2	KIT	MDM2	NRAS	PALB2	PDGFRA	PDGFRB	PPP2R2A
RAD51B	RAD51C	RAD51D	RAD54L	STK11	TSC1	TSC2			

Gene Fusions Covered in TARGET First

ALK	MET	RET	ROS1
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TEST METHODOLOGY

Sample preparation and Library preparation :

DNA isolated from FFPE, or any other fresh tumor tissue source was used to perform targeted gene capture using a custom capture kit. The libraries were sequenced to mean >250X coverage on Illumina sequencing platform.

Bioinformatics Analysis and Reporting :

The sequences obtained are aligned to human reference genome (GRCh37/hg19) and variant analysis was performed using set of Bioinformatics Pipeline. Only non-synonymous and splice site variants found in the panel consisting of specific set of genes were used for clinical interpretation. Silent variations that do not result in any change in amino acid in the coding region are not reported. Clinically relevant mutations were annotated using published variants in literature and a set of databases – ClinVar, COSMIC and dbSNP. Common variants are filtered based on allele frequency in 1000 Genome Phase 3, ExAC, dbSNP, gnomAD, etc. In the absence of a clinically significant reported known variation(s), pathogenicity will be predicted based on in-silico gene prioritization tools: CADD, SIFT, PolyPhen-2, Condel and Mutation taster and prioritized for clinical correlation. The identified pathogenic variant will be correlated with observed phenotypic features of the patient and interpreted according to American College of Medical Genetics (ACMG) guidelines.

Somatic variants are classified into two tiers based on their level of clinical significance in cancer diagnosis, prognosis, and/or therapeutics as per international guidelines:

ACMG, ASCO, AMP, CAP, NCCN and ESMO

LIMITATIONS AND DISCLAIMER

- DNA studies do not constitute a definitive test for the selected condition(s) in all individuals. It should be realized that there are possible sources of error. Errors can result from trace contamination, rare technical errors, rare genetic variants that interfere with analysis, recent scientific developments, and alternative classification systems. This test should be one of the many aspects used by the healthcare provider to help with a diagnosis and treatment plan.
- We are using the canonical transcript for clinical reporting which is usually the longest coding transcript with strong/multiple supporting evidence. However, in rare cases, clinically relevant variants annotated in alternate complete coding transcripts could also be reported.
- The contents of this test should be carefully assessed by the treating physician and further interpreted along with clinical, histopathological findings, contraindications and guidelines before deciding the course of therapy.
- The chromosomal aberrations like copy number variations and rearrangements may not be reliably detected with this assay and have to be confirmed by alternate method.
- The sensitivity of this assay to detect large deletions/duplications of more than 10 bp or copy number variations (CNV) is 70-75%. The CNVs detected have to be confirmed by alternate method.
- Most recent block is recommended for testing as the mutation profile may change in response to treatment and hence differ at different sampling points.
- TARGT FIRST test has been developed, validated and performed by 4baseCare Genomics Pvt. Ltd and has not been cleared or approved by the FDA.
- The identified pathogenic variant will be correlated with observed phenotypic features of the patient and interpreted according to (ASCO) guidelines.
- Certain genes may not be covered completely, and few mutations could be missed. A negative result cannot rule out the possibility that the tested tumor sample carries mutations not previously associated with cancer and hence not included in the panel.