PositiveSelect™

Positive Bioscience

Patient		Physician	
Name : xxxxxxxxxx		Name : xx xxxxxxxxxx	
Gender : F	Date of Birth : DD/MM/YYYY	**Institute :** xxxxxxxxxx	

Diagnosis : Breast cancer

Sample Type : Plasma and Blood	Sample Collection Date : DD/MM/YYYY		Sample ID : PB_CG_SU_XXXX-XX_XX
Test : PositiveSelect Ultimate	Technology : Illumina NGS	Coverage : 1000x	Report Date : DD/MM/YYYY

Expert Commentary

The patient was diagnosed with Stage IV breast cancer with metastasis and has undergone chemotherapy.

We identified two clinically actionable genomic alterations in PIK3CA [p.Asn345Lys]; ESR1 [p.Glu380Gln]. The PIK3CA mutation identified is present at the C2 PI3K-type domain of the PIK3CA protein and has been studied to result in increased phosphorylation of Akt, thereby showing oncogenic transformations invitro. This mutation has also been studied in cell cultures to display strong oncogenic activities. This mutation has also been studied in patients with aggressive tumors. Due to oncogenic properties, we infer beneficial effects from PIK3CA inhibitors and mTOR inhibitors. The ESR1 mutation has also been well established in breast cancer and has been identified to show elevated downstream activities. Also, studies show that breast cancer cells with this mutation may increase resistance to tamoxifen and fulvestrant (Antiestrogen therapy) as they can grow significantly in hormone depleted conditions.ESR1 and PIK3CA mutations have been identified together in many HER2 negative breast cancer, elevating the oncogenic activities.The identified mutation has shown increased progression free survival when administered with fulvestrant and palbociclib than fulvestrant alone.

Further analysis identified low tumor mutation burden and stable MS regions.

Note: Complimentary call for consultation is available.

Genomic Highlights

2 Pathways driving cancer	• PIK3CA/AKT/MTOR signaling pathway • ESR1 mediated signaling pathway
2 Genomic alterations	• PIK3CA [p.Asn345Lys] • ESR1 [p.Glu380Gln]
2 Genomic alterations with clinical actionability	
2 Genomic alteration (related to drug response) with clinical lack of benefit	
1 Clinical trial	

Implications To Immunotherapy

Microsatellite status	MS - Stable
Tumor Mutation Burden	TMB - Low

Note: TMB-Low :- ≤ 19 mutations/MB, TMB-High - ≥ 20 mutations/MB; MS-Stable <20% unstable sites, MS-Unstable ≥ 20% unstable sites

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Therapeutic Implications

Treatment(s)	Gene	Result	Targeted Pathways	Recommendation
Buparlisib and Cisplatin/Carboplatin [NCT02439489] * MTOR inhibitors [Everolimus]	PIK3CA [p.Asn345Lys] (p.N345K)	Positive	PIK3CA/AKT/ MTOR signaling pathway	✓
* CDK4/6 inhibitors [Palbociclib]	ESR1 [p.Glu380Gln] (p.E380Q)	Positive	ESR1 mediated signaling pathway	✓

* Note : Everolimus has been approved for stage IV recurrent breast cancers which can effectively be administered in combination with exmestane and other hormonal therapeutic drugs (Yi Z, et al. 2017). Palbociclib is approved as systemic therapy for HER2 negative, ER/PR positive recurrent or stage IV breast cancer.The drug has been recommended on the basis of patient's molecular profile only. Combination strategies of palbociclib with hormone therapy could prove beneficial in patient's condition (Kuang, et al. 2018).

Note: Though all the genes mentioned in the appendix have been analyzed, only those which have clinically actionable information have been highlighted in this report.

Note: This report is meant to be used only by the clinicians. Therapeutic indications mentioned here in are to be practised as per clinicians discretion depending on the pathophysiological status of the patient and prior clinical history.

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preTADME

Treatment(s)	Gene - Genotype	Inference	Recommendation
5-Fluorouracil	MTHFR [p. E429A]	Better response	✓
Cyclophosphamide	CYP2B6 [p. Q172H]	Poor response	✗
Docetaxel	CYP1B1 [p.V432L]	Poor response	✗

✓ - Better Response, Better Prognosis

✗ - Poor Response, Poor Prognosis, Resistance

Note: Though all the genes mentioned in the appendix have been analyzed, only those which have clinically actionable information have been highlighted in this report.

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Mutation Status

Gene	Genetic Alteration	Result
AKT1	No alteration detected	Negative
AR	No alteration detected	Negative
ERBB2 [HER2]	No alteration detected	Negative
ESR1 [ER1]	[p.Glu380Gln]	Positive
FGFR1	No alteration detected	Negative
FGFR2	No alteration detected	Negative
FGFR3	No alteration detected	Negative
PGR [PR]	No alteration detected	Negative
PIK3CA [PI3K]	[p.Asn345Lys]	Positive
PTEN	No alteration detected	Negative
BRCA1	No alteration detected	Negative
BRCA2	No alteration detected	Negative

Note: Genomic alterations in genes related to cancer type (Breast cancer) as listed in mycancer genome and NCCN guidelines are reported here.

Mutation Signature

Gene	Genetic Alteration	Germline	True Somatic
PIK3CA	[p.Asn345Lys]		✓
ESR1	[p.Glu380Gln]		✓

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About PositiveSelect

PositiveSelect is a range of comprehensive genomics test offering definitive clinical as well as prognostic markers from deep analysis of Next Generation Sequencing (NGS) data delivering clinically relevant actionable recommendations. This complete genomics test begins with sample collection, through DNA isolation followed by sequencing and data processing finally towards analysis and expert personalized recommendations. Following are some highlights of the PositiveSelect test significance.

Test Significance : PositiveSelect Ultimate covers identification of all four types of genomic alterations viz. Single Nucleotide Variations (SNV), Copy Number Variations (CNV), Indels and Structural Variations (SV) apart from Tumor Mutation Burden (TMB) and Microsatellite Instability (MSI). This test also reports on possibility towards usage of off-label drugs and immunotherapeutics apart from the guideline recommendations and pertinent clinical trials. This matched-normal test ensures reporting on true somatic and germline variants to identify genomic alterations driving cancer. Reporting on germline variants also aid in identifying inherited risks. The test does not report on large SV and we do not include reporting on Variants of Unknown Significance (VUS). However the same can be provided on request if detected.

Analyzed by:	Verified by:
Scientific Officer	Sr. Scientific Officer

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Gene List

Single Nucleotide Variations

ABCB1	BCL2	CDKN1A	DNMT3B	FGF3	IDH2	MAP2K2	MYD88	PDGFRA	RAD51B	SF3B1	TNFRSF14
ABCC1	BCL2L1	CDKN1B	DOT1L	FGF4	IFNGR1	MAP2K4	MYOD1	PDGFRB	RAD51C	SH2D1A	TOP1
ABCC2	BCL2L11	CDKN2A	E2F3	FGFR1	IGF1	MAP3K1	NBN	PDPK1	RAD51D	SLC22A1	TP53
ABCC4	BCL6	CDKN2B	EGFL7	FGFR2	IGF1R	MAP3K13	NCOR1	PGR	RAD52	SMAD2	TP63
ABCG2	BCOR	CDKN2C	EGFR	FGFR3	IGF2	MAPK1	NF1	PIK3C2G	RAD54L	SMAD3	TRAF7
ABL1	BCR	CHEK1	EML4	FGFR4	IKBKE	MAX	NF2	PIK3C3	RAF1	SMAD4	TSC1
AKT1	BLM	CHEK2	EP300	FH	IKZF1	MCL1	NFE2L2	PIK3CA	RARA	SMARCA4	TSC2
AKT2	BRAF	CREBBP	EPCAM	FLCN	IL10	MDC1	NKX2-1	PIK3CB	RASA1	SMARCB1	TSHR
AKT3	BRCA1	CRKL	EPHA3	FLT1	IL7R	MDM2	NKX3-1	PIK3CD	RB1	SMO	TSPY4
ALK	BRCA2	CRLF2	EPHA5	FLT3	INSR	MDM4	NOTCH1	PIK3CG	RECQL4	SOCS1	TTTY23
ALOX12B	BRD4	CSF1R	EPHB1	FLT4	IRF4	MED12	NOTCH2	PIK3R1	REL	SOX17	TYMS
AMELY	BRIP1	CTCF	ERBB2	FOXA1	IRS1	MEF2B	NOTCH3	PIK3R2	RET	SOX2	U2AF1
APC	BTK	CTLA4	ERBB3	FOXL2	IRS2	MEN1	NOTCH4	PIK3R3	RFWD2	SOX9	USP9Y
AR	CARD11	CTNNB1	ERBB4	FOXP1	JAK1	MET	NPM1	PIM1	RHOA	SPOP	VHL
ARAF	CASP8	CUL3	ERCC2	FUBP1	JAK2	MITF	NR1I2	PLK2	RICTOR	SRC	WT1
ARID1A	CBFB	CYP19A1	ERCC3	GATA1	JAK3	MLH1	NRAS	PMAIP1	RIT1	SRY	XIAP
ASXL1	CBL	CYP1A1	ERCC4	GATA2	JUN	MLL	NSD1	PMS1	RNF43	STAG2	XPO1
ASXL2	CCND1	CYP1A2	ERCC5	GATA3	KDM5A	MLL2	NTRK1	PMS2	ROS1	STK11	YAP1
ATM	CCND2	CYP1B1	ERG	GNA11	KDM5C	MLL3	NTRK2	PNRC1	RPS4Y2	STK40	YES1
ATR	CCND3	CYP2A4	ESR1	GNAQ	KDM5D	MPL	NTRK3	POLE	RPS6KA4	SUFU	ZFY
ATRX	CCNE1	CYP2A6	ETV1	GNAS	KDM6A	MSH2	NUTM1	PPP2R1A	RPS6KB2	SYK	
AURKA	CD274	CYP2B6	ETV6	GSK3B	KDR	MSH6	PAK1	PRDM1	RPTOR	TBX3	
AURKB	CD276	CYP2E1	EWSR1	GSTA1	KEAP1	MTHFD1	PAK7	PRKAR1A	RUNX1	TERT	
AXIN1	CD79B	DAXX	EZH2	GSTP1	KIT	MTHFD1L	PALB2	PRKY	RYBP	TET1	
AXIN2	CDC73	DAZ1	FAM123B	HGF	KLF4	MTHFR	PARK2	PTCH1	SDHA	TET2	
AXL	CDH1	DDR2	FANCA	HIF1A	KRAS	MTOR	PARP1	PTEN	SDHAF2	TGFBR1	
B2M	CDK12	DICER1	FANCC	HIST1H3B	LATS1	MUTYH	PAX5	PTPN11	SDHB	TGFBR2	
BAP1	CDK4	DIS3	FAT1	HNF1A	LATS2	MYC	PAX8	RAC1	SDHC	TMEM127	
BARD1	CDK6	DNMT1	FBXW7	HRAS	LMO1	MYCL1	PBRM1	RAD50	SDHD	TMPRSS2	
BBC3	CDK8	DNMT3A	FGF19	IDH1	MAP2K1	MYCN	PDCD1	RAD51	SETD2	TNFAIP3	

Rearrangements

ALK	
FGFR2	
FGFR3	
RET	
ROS1	
NTRK1	

Amplifications

AR	BRAF
CCNE1	CDK4
CCND1	CDK6
CCND2	EGFR
ERBB2	FGFR1
FGFR2	KIT
KRAS	MET
PIK3CA	PDGFRA
MYC	RAF1

Insertions/Deletions (Indels)

ATM	GATA3	SMAD4
APC	KIT	STK11
ARID1A	MET	TP53
BRCA1	MLH1	TSC1
BRCA2	MTOR	VHL
CDH1	NF1	
CDKN2A	PDGFRA	
EGFR	PTEN	
ERBB2	RB1	

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