PositiveSelect™

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Patient		Physician	
Name : xxxxxxxxxx		Name : xx xxxxxxxxx	
Gender : M	Date of Birth : DD/MM/YYYY	Institute : xxxxxxxxx	

Diagnosis : Lung Adenocarcinoma

Sample Type : FFPE	Sample Collection Date : DD/MM/YYYY		Sample ID : PB_CG_SL_XXXX-XX_XX
Test : PositiveSelect Lite	Technology : Illumina NGS	Coverage : 1000x	Report Date : DD/MM/YYYY

Patient Tumor Type Specific Genes

Gene	Genetic Alteration	Result
AKT1	No alteration detected	Negative
ALK Mutation	No alteration detected	Negative
ALK Translocation	No alteration detected	Negative
BRAF	No alteration detected	Negative
DDR2	No alteration detected	Negative
ERBB2 [HER2]	No alteration detected	Negative
EGFR	Exon 19 deletion [p.Leu747_Thr751del]	Positive
FGFR1 [FLT2]	No alteration detected	Negative
KRAS	No alteration detected	Negative
MAP2K1 [MEK1]	No alteration detected	Negative
MET	No alteration detected	Negative
NRAS	No alteration detected	Negative
PIK3CA [PI3K]	No alteration detected	Negative
PTEN	No alteration detected	Negative
RET	No alteration detected	Negative
RET Rearrangements	No alteration detected	Negative
ROS1	No alteration detected	Negative

Note: Genomic alterations in genes related to cancer type (Lung Cancer) as listed in mycancergenome.org and NCCN guidelines are reported here. Genomic alterations with therapeutic implications are reported in the next page.

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Genomic Aleterations With Therapeutic Implications

Treatment(s)	Gene	Result	Targeted Pathways	Recommendation
First generation tyrosine kinase inhibitors [Gefitinib ± Carboplatin and Paclitaxel] [Erlotinib and Cetuximab] **Second generation tyrosine inhibitors** [Afatinib and Cetuximab] **Third generation tyrosine kinase inhibitors** [Osimertinib and Gefitinib] [Dacomitinib] [NCT01858389] [Neratinib] [NCT00266877] [Rociletinib and Trametinib] [NCT02580708]	EGFR - Exon 19del [p.Leu747_Thr751del]	Positive	EGFR signaling pathway	✓
Cetuximab, Carboplatin and Paclitaxel	EGFR - Exon 19del [p.Leu747_Thr751del]	Positive	EGFR signaling pathway	✓

Note: The NF1 [p.Ser2332Ter] mutation identified in the patient has been regarded pathogenic as per American College of Medical Genetics and Genomics (ACMG). Neurofibromatosis is a condition which is caused due to mutations in the tumor suppressor gene NF1 spanning 59 exons. NF1 gene encodes a RAS GTP-ase activating protein neurofibromin, whose preliminary function is to regulate KRAS mediated cellular activities including cell proliferation and differentiation. Truncation of this protein due to premature stop codons in the coding regions of the gene may hamper the normal functions of the protein resulting in aberrant cell signaling via KRAS/MEK/ERK or KRAS/PI3K/AKT/MTOR signaling pathways (Park, et al. 1998). These truncating mutations in germline or proportionately elevated somatic occurrences may increase the probability of secondary cancer occurrence as well as cancer predispositions (Ponti, et al. 2014). This mutation becomes significant in this patient as the lack of NF1 mediated KRAS regulation may resist the anti-EGFR therapy which could be well addressed at an early stage cautiously utlizing the recommendations. Thus it may be essential to suppress the aberrant signals via KRAS/MEK/ERK by MEK inhibitors and KRAS/PI3K/AKT/MTOR signals by MTOR inhibitors with close monitoring of patient response (Franz, et al. 2012). Though there is no literature support for the particular mutation identified, truncating NF1 mutations still play significant roles in KRAS mediated aberrant signaling in lung cancer (Redig, et al. 2016).

T - Toxicity data

✓ - 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.

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

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References

Christensen, Karen E., et al. "The MTHFD1 p. Arg653Gln variant alters enzyme function and increases risk for congenital heart defects." Human mutation 30.2 (2009): 212-220.

Franz DN, Weiss BD. Molecular therapies for tuberous sclerosis and neurofibromatosis. Current neurology and neuroscience reports. 2012 Jun 1;12(3):294-301.

Goricar, Katja, Viljem Kovac, and Vita Dolzan. "Polymorphisms in folate pathway and pemetrexed treatment outcome in patients with malignant pleural mesothelioma." Radiology and oncology 48.2 (2014): 163-172.

Lopes, Gabriel Lima, Edoardo Filippo de Queiroz Vattimo, and Gilberto de Castro Junior. "Identifying activating mutations in the EGFR gene: prognostic and therapeutic implications in non-small cell lung cancer." Jornal Brasileiro de Pneumologia 41.4 (2015): 365-375.

Okabe T, Okamoto I, Tamura K, Terashima M, Yoshida T, Satoh T, et al. Differential constitutive activation of the epidermal growth factor receptor in non-small cell lung cancer cells bearing EGFR gene mutation and amplification. Cancer Res. 2007;67(5):2046-53.

Park VM, Pivnick EK. Neurofibromatosis type 1 (NF1): a protein truncation assay yielding identification of mutations in 73% of patients. Journal of medical genetics. 1998 Oct 1;35(10):813-20.

Phase II/NCT00266877 - A Phase 2 Study of HKI-272 In Subjects With Advanced Non-Small Cell Lung Cancer.

Phase II/NCT01858389 - Phase 2 Open Label Trial Of Oral Intermittent Dacomitinib In Patients With Advanced NSCLC.

Phase II/NCT03232892 - Phase II Trial to Evaluate Trametinib in Patients With Advanced NF1-mutant Non-small Cell Lung Cancer.

Phase II/NCT02352844 - Phase II Study of Everolimus in Patients With Advanced Solid Malignancies With TSC1, TSC2, NF1, NF2, or STK11 Mutations.

Phase I/II/NCT02580708 - A Phase 1/2 Study of the Safety and Efficacy of Rociletinib When Administered in Combination With Trametinib in Patients With Activating EGFR Mutation-positive Advanced or Metastatic Non-small Cell Lung Cancer (NSCLC).

Ponti G, Martorana D, Pellacani G, Ruini C, Loschi P, Baccarani A, De Santis G, Pollio A, Neri TM, Mandel VD, Maiorana A. NF1 truncating mutations associated to aggressive clinical phenotype with elephantiasis neuromatosa and solid malignancies. Anticancer research. 2014 Jun 1;34(6):3021-30.

Redig AJ, Capelletti M, Dahlberg SE, Sholl LM, Mach SL, Fontes C, Shi Y, Chalasani P, Janne PA. Clinical and molecular characteristics of NF1 mutant lung cancer. Clinical Cancer Research. 2016 Feb 9:clincanres-2377.

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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 Lite covers identification of all four types of genomic alterations viz. Single Nucleotide Variation (SNV), Copy Number Variations (CNV), Indels and Structural Variations (SV). This test also reports on possibility towards usage of off-label drugs and apart from the guideline recommendations and pertinent clinical trials. 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	CYP19A1	ERCC2	JAK2	PARP1
ABCC1	CYP1A1	ERCC3	JAK3	PDCD1
ABCC2	CYP1A2	ERCC4	KDR	PDGFRA
ABCC3	CYP1B1	ERCC5	KIT	PDGFRB
ABCC4	CYP24A1	ESR1	KRAS	PGR
ABCG2	CYP27B1	EWSR1	LINS1	PIK3CA
ABL1	CYP2B6	EZH2	MAP2K1	PTEN
AKT1	CYP2C19	F2R	MAP2K2	REL
ALK	CYP2C9	FGFR1	MAPK1	RET
AR	CYP2E1	FGFR2	MET	ROS1
BCR	CYP3A4	FGFR4	MLH1	RRM1
BRAF	CYP3A5	FLT3	MSH2	STAT3
BRCA1	DCK	GSTA1	MSH6	TERT
BRCA2	DDB1	GSTP1	MTHFD1	TOP1
BTK	DDR2	HIF1A	MTHFR	TP53
CCND1	DYNC2H1	HRAS	MTOR	TSC1
CCND2	EGFR	IDH1	NF1	TSC2
CDA	EML4	IGF1R	NR1I2	VEGFA
CDK4	ERBB2	IL6	NR1I3	VHL
CDK6	ERCC1	JAK1	NRAS	XRCC1

Rearrangements

ALK
FGFR2
RET
ROS1

Amplifications

AR	BRAF
CCND1	CDK4
CCND2	EGFR
ERBB2	FGFR1
FGFR2	KIT
KRAS	MET
PIK3CA	PDGFRA

Insertion/Deletions (Indels)

BRCA1	MTOR
EGFR	NF1
ERBB2	PDGFRA
KIT	PTEN
MET	TP53
MLH1	TSC1
	VHL

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