Precision Panel- 50 Genes

Test Description

The MolQ Precision Panel includes 50 genes, involving hotspot regions and 3159 unique variants, applicable to a wide range of tumor types for detection of SNV (single and multiple nucleotide variation), Insertion-Deletion, Copy Number Variation (CNV), and gene Fusions. Fusion and splice variants are detected in RNA.

Patient Demographic

Name: Mr. Niranjan Swarup
Sex: Male
Date of Birth/Age: 57 years
Disease: Transitional Cell Carcinoma of the Bladder

Clinician

Clinician Name: Dr Amit Verma
Medical Facility: Dr AV Institute of Personalized Cancer Therapy and Research
Pathologist: Not Provided

Specimen

Booking ID: 012306050041
Sample Type: FFPE
Tumor Content Percentage:60%
Date of Collection: 06-06-2023
Date of Booking: 06-06-2023

CLINICAL SYNOPSIS

Niranjan Swarup, is a known case of transitional cell carcinoma of the bladder. He has been evaluated for pathogenic variations in the genes listed in Appendix 2.

RESULT SUMMARY

The assay has detected ***FGFR3*** (**p.Ser249Cys, VAF=24.7%**) and ***AKT1*** (**p.Glu17Lys, VAF=25.05%**) mutations in this sample. Multiple drugs under clinical trials are available to target these alterations. *FGFR3* (p.S249C) mutation promotes chemoresistance in bladder cancer cells by activating the Akt signaling pathway[1].

RESULTS

Variants in *FGFR3* and *AKT1* genes were detected.

Gene/ Transcript (Locus)	Variant ID	Variant	Allele Frequency	Variant Effect	*Relevant Therapies (In this cancer type)	*Relevant Therapies (In other cancer type)	Tier[2]
FGFR3 NM_000142.4 (chr4:1803568)	COSM715	c.746C>G (p. Ser249Cys)	24.70%	Missense	None	erdafitinib[i]	IIc
AKT1 NM_001014431.2 (chr14:105246551)	COSM33765	c.49G>A (p.Glu17Lys)	25.05%	Missense	None	None	IIc

* Public data sources included in relevant therapies: FDA[i], NCCN, EMA[ii], ESMO

CLINICAL CORRELATION AND VARIANT INTERPRETATION

AKT1 **p.Glu17Lys**

Gene description: The *AKT1* gene encodes Protein Kinase B, a serine/threonine kinase, that belongs to a family of closely related protein kinases that also includes AKT2 and AKT3. Growth factor signaling leads to the activation of phosphatidylinositol 3-kinase (PI3K), recruitment of AKT to the plasma membrane, and subsequent activation of downstream effectors including MTOR. The PI3K/AKT/MTOR pathway is central to the regulation of cancer cell proliferation, survival, and metabolism[3,4].

Alterations and prevalence: *AKT1* encodes a proto-oncogene that is the target of recurrent somatic mutations in cancer[5]. The most common recurrent mutation is E17K, which is located in the N-terminal pleckstrin homology (PH) domain. E17K is a gain-of-function activating mutation that constitutively targets *AKT1* to the plasma membrane and leads to downstream signaling[6,7]. Other recurrent activating mutations include L52H, Q79K, and D323Y/G/N, which disrupt negative regulatory interactions between the PH domain and the kinase domain[8]. *AKT1* mutations in cancer are common in breast and endometrial cancers, where they occur at a prevalence of 2-5%[9]. *AKT1* mutations are observed at a prevalence of 1-2% in bladder, colorectal, melanoma, and thyroid cancers[9,10]. AKT1 is overexpressed via gene amplification in ovarian cancer, lung squamous cell cancer, and sarcoma at a prevalence of 2-5%[9,10].

Potential relevance: Currently no therapies are approved for *AKT1* aberrations. However, in the phase II NCI-MATCH trial, the pan-AKT inhibitor capivasertib (AZD5363) demonstrated a partial response in 23% (8/35) of *AKT1* E17K mutated solid tumor patients[11]. Results from a phase I clinical trial of capivasertib demonstrated partial responses in 9/52 heavily pre-treated patients with *AKT1* E17K mutated solid tumors, with a median progression-free survival (PFS) of 5.5 months in ER positive breast cancer, 6.6 months in gynecologic cancers, and 4.2 months in other solid tumors[12]. In the same phase I study, an ovarian cancer patient with an *AKT1* Q79K mutation demonstrated stable disease lasting 14 months[12].

FGFR3 **p. Ser249Cys**

Gene description: The *FGFR3* gene encodes fibroblast growth receptor 3, a member of the fibroblast growth-factor receptor (FGFR) family that also includes FGFR1, 2, and 4. These proteins are single-transmembrane receptors composed of three extracellular immunoglobulin (Ig)-type domains and an intracellular kinase domain. Upon FGF-mediated stimulation, FGFRs activate several oncogenic signaling pathways, including the RAS/RAF/MEK/ERK, PI3K/AKT/MTOR, PLC/PKC, and JAK/STAT pathways influencing cell proliferation, migration, and survival[13-15].

Alterations and prevalence: Aberrations most common to the FGFR family are amplifications, followed by mutations and fusions. The majority of these aberrations result in gain of function[16]. *FGFR3* amplification is observed in up to 19% of uterine carcinoma, with somatic mutations occurring in 10-20% of bladder cancer[9,10,17]. Missense mutations that occur in the extracellular immunoglobulin-like and transmembrane domains of FGFR3, including S249C, R248C, and Y375C, cause ligand-independent dimerization and constitutive activation of FGFR3[18-20].

Potential relevance: The pan-FGFR inhibitor, erdafitinib[21], received FDA approval (2019) for the treatment of locally advanced or metastatic urothelial cancer that is positive for *FGFR2* fusions, *FGFR3* fusions including *FGFR3-TACC3* and *FGFR3-BAIAP2L1*, and *FGFR3* gene mutations including R248C, S249C, G370C, and Y373C. The *FGFR3* monoclonal antibody, vofatamab[22] was granted fast-track designation (2019) by the FDA, for the treatment of advanced or metastatic bladder urothelial cell carcinoma that harbors *FGFR3* mutations or fusions. The FDA also granted fast track designation (2018) to Debio 1347[23] for solid tumors harboring *FGFR1*, *FGFR2*, or *FGFR3* aberrations. Unregulated activation of *FGFR3* has been associated with resistance to tamoxifen in ER-positive breast cancer[24].

RECOMMENDATIONS

- Validation of the variant(s) by Sanger sequencing is recommended to rule out false positives.
- Genetic counselling is advised for interpretation on the consequences of the variant(s).
- If results obtained do not match the clinical findings, additional testing should be considered as per referring clinician's recommendations.

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APPENDIX 1: TEST METHODOLOGY

Method

DNA and RNA were extracted from samples using the Qiagen FFPE DNA kit and Promega ReliaPrep FFPE Total RNA Miniprep system. Isolated DNA/RNA was directly loaded on Genexus Next Generation Sequencer and subjected to automated library preparation and template preparation followed by sequencing at average depth of ~4000X.
It utilizes unique molecular tags to enable high sensitivity detection of variants. Analysis is done using Ion Torrent Reporter Software, the data is visualized on Integrative Genomics Viewer (IGV) and analyzed. The final report is generated using Oncomine curated knowledgebase reporter and includes clinical trials information continuously being updated for the best of the patient management as per clinical guidelines.

DISCLAIMER

- This report was generated using the materials and methods as recommended which required the use of quality reagents, protocols, instruments, software, databases and other items, some of which were provided or made accessible by third parties. A defect or malfunction in any such reagents, protocols, instruments, software, databases and/or other items may compromise the quality or accuracy of the report.
- The report has been created based on, or incorporated inferences to, various scientific manuscripts, references, and other sources of information, including without limitation manuscripts, references, and other sources of information that were prepared by third parties that describe correlations between certain genetic mutations and particular diseases (and/or certain therapeutics that may be useful in ameliorating the effects of such diseases). Such information and correlations are subject to change over time in response to future scientific and medical findings. MolQ Laboratory makes no representation or warranty of any kind, expressed or implied, regarding the accuracy of the information provided by or contained in such manuscripts, references, and other sources is later determined to be inaccurate, the accuracy and quality of the Report may be adversely impacted. MolQ Laboratory is not obligated to notify you of any of the impact that future scientific or medical findings may have on the report.
- The report must always be interpreted and considered within the clinical context, and a physician should always consider the report along with all other pertinent information and data that a physician would prudently consider prior to providing a diagnosis or developing and implementing a plan of care for the patient. The report should never be considered or relied upon alone in making any diagnosis or prognosis. The manifestations of many diseases are caused by more than one gene variant, a single gene variant may be relevant to more than one disease, and certain relevant gene variants may not have been considered in the report. In addition, many diseases are caused or influenced by modifier genes, epigenetic factors, environmental factors, and other variables that are not addressed by the report. This report is based on a Next Generation Assay which does not distinguish between a somatic and a germline variant. If germline variant is in question, further testing is recommended. The report provided by MolQ Laboratory is on a "as is" basis. MolQ Laboratory makes no representation or warranty of any kind, expressed or implied, regarding the report. In no event will MolQ Laboratory be liable for any actual damages, indirect damages, and/or special or consequential damages arising out of or in any way connected with the Report, your use of the report, your reliance on the report, or any defect or inaccurate information included within the report.
- Medical knowledge and annotation are constantly updated and reflects the current knowledge at the time.
- Due to inherent technology limitations of the assay, not all bases of the exome can be covered by this test. Accordingly, variants in regions of insufficient coverage may not be identified and/or interpreted. Therefore, it is possible that certain variants are present in one or more of the genes analyzed, but have not been detected. The variants not detected by the assay that was performed may/ may not impact the phenotype.
- It is also possible that a pathogenic variant is present in a gene that was not selected for analysis and/or interpretation in cases where insufficient phenotypic information is available.
- The report shall be generated within turnaround time (TAT), however, such TAT may vary depending upon the complexity of test(s) requested. MolQ Laboratory under no circumstances will be liable for any delay beyond afore mentioned TAT.
- It is hereby clarified that the report(s) generated from the test(s) do not provide any diagnosis or opinion or recommends any cure in any manner. MolQ Laboratory hereby recommends the patient and/or the guardians of the patients, as the case may be, to take assistance of the clinician or a certified physician or doctor, to interpret the report(s) thus generated. MolQ Laboratory hereby disclaims all liability arising in connection with the report(s).
- In a very few cases genetic test may not show the correct results, e.g. because of the quality of the material provided to MolQ Laboratory. In case where any test provided by MolQ Laboratory fails for unforeseeable or unknown reasons that cannot be influenced by MolQ Laboratory in advance, MolQ Laboratory shall not be responsible for the incomplete, potentially misleading or even wrong result of any testing if such could not be recognized by MolQ Laboratory in advance.

- This is a laboratory developed test and the development and the performance characteristics of this test was determined by reference laboratory as required by the CLIA 1988 regulations. The report, and the tests used to generate the Report have not been cleared or approved by the US Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. The test results have scientifically shown to be clinically useful.

APPENDIX 2: GENE LIST WITH COVERAGE

DNA Hotspots					
AKT1	*AKT2*	*AKT3*	*ALK*	*AR*	*ARAF*
BRAF	*CDK4*	*CDKN2A*	*CHEK2*	*CTNNB1*	*EGFR*
ERBB2	*ERBB3*	*ERBB4*	*ESR1*	*FGFR1*	*FGFR2*
FGFR3	*FGFR4*	*FLT3*	*GNA11*	*GNAQ*	*GNAS*
HRAS	*IDH1*	*IDH2*	*KIT*	*KRAS*	*MAPK1*
MAPK2	*MET*	*MTOR*	*NRAS*	*NTRK1*	*NTRK2*
NTRK3	*PDGFRA*	*PIK3CA*	*PTEN*	*RAF1*	*RET*
ROS1	*SMO*	*TP53*			
CNVs					
ALK	*AR*	*CD274*	*CDKN2A*	*EGFR*	*ERBB2*
ERBB3	*FGFR1*	*FGFR2*	*FGFR3*	*KRAS*	*MET*
PIK3CA	*PTEN*				
Inter-genetic Fusions					
ALK	BRAF	*ESR1*	*FGFR1*	*FGFR2*	*FGFR3*
MET	*NRG1*	*NTRK1*	*NTRK2*	*NTRK3*	*NUTM1*
RET	*ROS1*	*RSPO2*	*RSPO3*		
Intra-genetic Fusions					
AR	*EGFR*	*MET*			