ONCOLOGY genpath an OPKO Health Company

OnkoSight™ Advanced Lung Cancer NGS Report

Final Report

SAMPLE, PHYSICIAN
ONCOLOGY HOSPITAL

Acct#: XXXXX
P: (555) 555-5555 F: (555) 555-5555

Patient Name: SAMPLE, PATIENT
DOB: 01/02/1934 **Age:** 87 Y **Sex:** F
Surgical #:

Specimen ID: XXXXXXXXX
Date of Report: 04/29/2021 06:39 PM EDT
Date Collected: 04/16/2021
Date Received: 04/22/2021
Specimen Source: Solid Tumor
Specimen Tumor %: 20-50%

TUMOR MUTATION BURDEN: **HIGH**

RESULT SUMMARY: ABNORMAL

DETECTED GENOMIC ALTERATIONS:

Tier II: Variants of Potential Clinical Significance

KRAS Amplification

BRAF p.(Gly596Arg)

TP53 p.(Cys141Tyr)

Tier III: Variants of Unknown Clinical Significance

POLE p.(Asp1783Asn)

TUMOR TYPE: Neoplasm

CLINICAL INFORMATION:

Right iliac bone lytic lesion fine needle aspiration showed malignant cells, favor metastatic lung adenocarcinoma (Testing performed on # 76-FN-21-492-1A).

IMMUNOTHERAPY BIOMARKERS:

TUMOR MUTATION BURDEN: HIGH **(19.6 MUTATIONS / MB)**

MICROSATELLITE INSTABILITY: MSI NEGATIVE

PERTINENT NEGATIVE RESULTS:

The following genes are NEGATIVE for clinically relevant mutations. Mutational hotspots and surrounding exonic regions were interrogated for DNA level point mutations and indels (fusions not assayed).

AKT1, ALK, DDR2, EGFR, ERBB2, FGFR1, MAP2K1, MET, NRAS, NTRK1, PIK3CA, POLD1, STK11, TERT

TECHNICAL SUMMARY

Gene	Alteration	AMP Tier	Chr	Pos	Ref	Alt	Coverage	Allele Freq. or Fold Change	cDNA Change	Exon
KRAS	Amplification	II	0	0	-	-	-	2.679x	-	-
BRAF	p.(Gly596Arg)	II	7	140453149	C	G	275	22%	c.1786G>C	15
TP53	p.(Cys141Tyr)	II	17	7578508	C	T	471	64%	c.422G>A	5
POLE	p.(Asp1783Asn)	III	12	133218264	C	T	597	43%	c.5347G>A	39

THERAPEUTIC ASSOCIATIONS

In Other Tumor Type

	Gene / Locus	Alteration	Potential Therapeutic Response / Drug Class	Disease Association
✓	TMB	High	High Level TMB may represent a positive molecular biomarker indication for immunotherapeutic agents including Pembrolizumab, among others.	Colon Adenocarcinoma

INTERPRETATION SUMMARY

High level Tumor Mutation Burden (TMB) is POSITIVE in this patient's sample, and microsatellite instability was NOT detected.

The present sample analysis is positive for high level Tumor Mutation Burden. Presence of >10 mutations / megabase has been reported to be therapeutically predictive of favorable clinical outcomes and responsiveness to immune checkpoint inhibitors, according to some studies (29658845; 30395155). TMB is an evolving biomarker, and consensus standardization for this biomarker remains an ongoing imperative (30664300; NCCN Guidelines, Non-Small Cell Lung Cancer, Version 2.2021). To date, the median TMB for all tumor types tested by OnkoSight Advanced in general, is approximately 3.9 mutations / megabase, and 9.4 mutations / megabase for Lung Cancers, in particular. According to some large scale cohorts published in the primary literature, a median TMB value of 7.5 mutations / megabase has been reported for non-small cell lung cancer, NOS (28420421).

The present sample analysis is negative for high level microsatellite instability.

A mutation in BRAF p.(Gly596Arg) was detected in this patient's sample.

Most studies of BRAF-mutated cancers are based on tumors harboring common BRAF V600 mutations (22663011; 25265492). BRAF non-V600E mutations are frequent and recurrent in NSCLC, however the therapeutically predictive significance of these alterations is not well established and remains under investigation; BRAF non-V600 mutations have not been explicitly or formally incorporated into diagnostic, prognostic, or therapeutic algorithms for NSCLC (NCCN Guidelines, Non-Small Cell Lung Cancer, Version 4.2021).

An amplification in KRAS was detected in this patient's sample.

KRAS amplification is a common molecular alteration in NSCLC, characterizing ~15% of tumors. This alteration is associated with indicators of local aggressiveness, and may act synergistically with KRAS mutations to promote tumor progression (21477882). However, KRAS amplification has not been explicitly or formally incorporated into diagnostic, prognostic, or therapeutic algorithms for non-small cell lung cancer (NCCN Guidelines, Non-Small Cell Lung Cancer, Version 4.2021).

A mutation in TP53 (p.(Cys141Tyr)) was detected in this patient's sample.

TP53 mutations are highly recurrent in non-small cell lung cancer (NSCLC). The impact of TP53 mutational status on clinical outcomes in NSCLC is the subject of ongoing investigations (22980975; 24696321). Evidence for the prognostic or therapeutically predictive significance of TP53 mutations in NSCLC is insufficient, and, at present time, TP53 mutational status is not formally incorporated in diagnostic or therapeutic algorithms for NSCLC (24916693; NCCN Guidelines, Non-Small Cell Lung Cancer, Version 4.2021).

An unclear variant in POLE p.(Asp1783Asn) was detected in this patient's sample.

This variant has been reported in a limited number of tumor samples (COSMIC). It has also been observed as an extremely rare population variant in publicly available databases (GnomAD). This variant has been documented also in the ClinVar public germline database with an interpretation of variant of unknown significance. Therefore, due to the paucity of functional and clinical evidence, its significance is currently unclear.

Clinical and pathologic correlation is required to interpret these findings.

LEGEND:	Likely Response for defined therapy	Unlikely Response for defined therapy	Unknown therapeutic response	Associated with increased survival	Associated with decreased survival	Investigational agent available
	✓	✗	?	↑	↓	

DETAILED GENETIC INTERPRETATION

Alteration	Interpretation
KRAS **Amplification** **-** **2.679x fold change** **Exon -**	The KRAS gene (Kirsten rat sarcoma viral oncogene homolog) is located on chromosome 12p12.1. The gene is a member of the Ras oncogene family and encodes a GTPase. RAS proteins are involved in regulation of cell proliferation and cell survival pathways. Somatic missense KRAS mutations are most commonly found in exons 2 and 3 (codons 12, 13 and 61), promote constitutive activation of the protein in the GTP-bound state, and result in increased signaling (17384584; 19349489; 18372904; 23622131; 22898602).
BRAF **p.(Gly596Arg)** **c.1786G>C** **22% allele frequency** **Exon 15**	p.Gly596Arg represents a missense mutation in exon 15 of BRAF converting the wild type amino acid Glycine, into amino acid Arginine at residue 596. The G596R mutation exhibits reduced kinase activity towards MEK and no transforming activity in vitro (15035987; 19735675; 14678966), which is in contrast to other strong activating BRAF mutations. However, despite impaired kinase activity, this mutation was shown to activate downstream ERK signaling in vivo, likely through an alternate mechanism involving CRAF-dependent activation of ERK signaling, as opposed to direct MEK activation (15035987; 16364920). This mutation has been reported in melanoma, colorectal, lung and other tumors in public databases and in the literature (12438234; 24297085; 22154054; 21726664), and may predict response to RAF inhibitors. The V-Raf murine sarcoma viral oncogene homolog B (BRAF) is located on chromosome 7q34. The gene encodes a member of the raf/mil family of serine/threonine protein kinases, and is involved in the MAP kinase/ERKs signaling pathway. BRAF mutations have been identified in a wide range of cancers, including colorectal cancer, malig-t melanoma, papillary thyroid cancer, non-small cell lung carcinoma and hairy cell leukemia, among other tumors (12068308; 12460918; 21663470; 23668556). Most BRAF mutations destabilize the interaction between two regions of the kinase domain (Glycine rich loop and activation segment), resulting in constitutive increase in kinase activity (24388103; 21388974; 15035987). The most common BRAF missense mutation (V600E) accounts for over 90% of all reported somatic BRAF mutations, and consists of a single base substitution in exon 15 (c.1799T>A), leading to a substitution of Valine by a Glutamic acid at position 600.
TP53 **p.(Cys141Tyr)** **c.422G>A** **64% allele frequency** **Exon 5**	p.Cys141Tyr represents a missense mutation in exon 5 of TP53 converting the wild type amino acid Cysteine, into amino acid Tyrosine at residue 141. This mutation occurs within the DNA binding domain and has been described as a somatic mutation across a wide variety of tumor types (COSMIC). TP53 p.Cys141Tyr has also been reported as a likely pathogenic germline mutation inÂ two individuals with a personal and family history of Li-Fraumeni syndrome (ClinVar).Â The tumor protein p53 (TP53) is located on chromosome 17p13.1, and encodes a tumor suppressor protein. The TP53 protein mediates cellular response to DNA damage and is involved in a wide range of cellular processes, including transcriptional regulation, cell cycle control, apoptosis, and DNA repair. The TP53 gene is the most frequently mutated gene in human cancers, with somatic mutations associated with unfavorable prognosis in many tumor types (24132290; 21045690). Majority of the inactivating mutations are missense mutations that target the core DNA-binding domain (DBD), disrupting the DNA-binding capacity of p53 protein and leading to loss of function of the wild-type protein (24651012). Nonsense mutations, frameshift mutations, and deletions have also been reported in various tumor types. Some TP53 mutations are thought to result in domi-t negative inhibition of wild-type p53 protein activity including inhibition of apoptosis, or in gain of function leading to increased proliferation, migration, and genomic instability (24916693; 24651012). Somatic mutations in TP53 are associated with leukemic transformation, complex karyotype, and adverse outcome in a number of hematological malig-cies, including chronic myeloproliferative neoplasms (MPN) (21288114; 24478400), myelodysplastic syndrome (MDS) (21714648), and acute myeloid leukemia (AML)

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Alteration	Interpretation
	(22186996). Somatic TP53 mutations are independently associated with inferior prognosis in acute lymphoblastic leukemia (ALL) (25013160; 24829203; 25790293). TP53 mutations also have prognostic value in common solid tumors (21045690). Pathogenic germline mutations in TP53 are associated with Li Fraumeni syndrome.
POLE **p.(Asp1783Asn)** **c.5347G>A** **43% allele frequency** **Exon 39**	p.(Asp1783Asn) represents a missense variant in exon 39 of POLE at amino acid 1783 converting the wild type residue, Aspartic Acid, into an Asparagine. This variant has been reported in a limited number of tumor samples (COSMIC). It has also been observed as an extremely rare population variant in publicly available databases (GnomAD). This variant has been documented also in the ClinVar public germline database with an interpretation of variant of unknown significance. Therefore, due to the paucity of functional and clinical evidence, its significance is currently unclear.

CLINICAL TRIALS

Context	NCTID	Title	Conditions	Location	Sponsor
BRAF	NCT03042221	Early Rebiopsy to Identify Biomarkers of Tumor Cell Survival Following EGFR, ALK, ROS1 or BRAF TKI Therapy	Multiple Disease Types	Aurora, Colorado, United States	University of Colorado, Denver
	NCT04302025	A Study of Alectinib, Entrectinib, or Vemurafenib Plus Cobimetinib in Participants With Stages I-III Non-Small Cell Lung Cancer With ALK, ROS1, NTRK, or BRAF v600E Molecular Alterations	Non-small Cell Lung Cancer	Multiple locations in United States	Genentech, Inc.
	NCT03220035	Vemurafenib in Treating Patients With Relapsed or Refractory Advanced Solid Tumors, Non-Hodgkin Lymphoma, or Histiocytic Disorders With BRAF V600 Mutations (A Pediatric MATCH Treatment Trial)	Multiple Disease Types	Multiple locations in Puerto Rico, United States	National Cancer Institute (NCI)
	NCT04190628	Safety of ABM-1310 Monotherapy in Patients With Advanced Solid Tumors	Multiple Disease Types	Multiple locations in United States	ABM Therapeutics, Inc.
	NCT03839342	Binimetinib and Encorafenib for the Treatment of Advanced Solid Tumors With Non-V600E BRAF Mutations	Solid Tumor	Toronto, Ontario, Canada	University Health Network, Toronto
TP53	NCT01443468	Clinical and Genetic Studies of Li-Fraumeni Syndrome	Multiple Disease Types	Bethesda, Maryland, United States	National Cancer Institute (NCI)
	NCT03654716	Phase 1 Study of the Dual MDM2/MDMX Inhibitor ALRN-6924 in Pediatric Cancer	Multiple Disease Types	Multiple locations in United States	Dana-Farber Cancer Institute
	NCT03406715	Combination Immunotherapy-Ipilimumab-Nivolumab-Dendritic Cell p53 Vac - Patients With Small Cell Lung Cancer (SCLC)	Multiple Disease Types	Tampa, Florida, United States	H. Lee Moffitt Cancer Center and Research Institute

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Context	NCTID	Title	Conditions	Location	Sponsor
General Consideration	NCT04029688	A Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Preliminary Activity of Idasanutlin in Combination With Either Chemotherapy or Venetoclax in the Treatment of Pediatric and Young Adult Participants With Relapsed/Refractory Acute Leukemias or Solid Tumors	Multiple Disease Types	Multiple locations in Canada, France, Netherlands, Spain, United Kingdom, United States	Hoffmann-La Roche
	NCT04289259	Tumor Mutational Burden in Lung Cancer Patients	Multiple Disease Types	Multiple locations in France	Assistance Publique - Hôpitaux de Paris
	NCT03911557	Durvalumab and Tremelimumab Combination in Somatically Hypermutated Recurrent Solid Tumors	Tumor, Solid	Lexington, Kentucky, United States	John L. Villano, MD, PhD

METHODS

Tissue microdissection and DNA isolation from tumor enriched areas are based on histologic review by an appropriately board certified pathologist; specimens with minimal tumor cellularity may be rejected. DNA is extracted and fragmented by Covaris shearing. DNA molecules from each sample are uniquely identified by ligation of a short oligonucleotide, sample specific barcodes. Each genomic DNA fragment is also tagged with a unique molecular identifier sequence (UMI) to collapse PCR duplicates and facilitate error corrected sequencing. Exons of 523 genes are enriched by hybridization to oligonucleotide synthetic probes, and PCR is performed to further amplify captured sequences. Amplified DNA is sequenced using Illumina sequencing-by-synthesis methodology. The assay interrogates whole exons and selected intronic regions across 523 genes to detect single base substitutions, insertion/deletions, and gene amplifications, targeting 1.94 million bases, encompassing 1.28 Mb of exonic sequence. The software requires a minimum number of 100 unique reads (after removal of PCR duplicates) to detect a mutation. An automated process that takes into account statistical confidence of base calling, alignment, and mapping quality, identifies variants (TSO500 Local App Software Release Notes V2.1.0; April 17, 2020). Following mapping of the read data to the human genome (reference build GRCh37/hg19), single nucleotide variants (SNVs), and insertion deletion events (Indels) with an allele frequency greater than 4% are detected. Detection of Insertions and Deletions larger than 29 bases have not been validated. 1.5x, 3x, and 5x fold changes have been validated with this assay to correspondent to high level FISH amplification for ERBB2, MET, and EGFR, respectively; fold changes for other genes are reported if in excess of 2.5x. Reported variants include known disease associated mutations and unclear variants with little or no literature support. Benign population polymorphisms or likely benign variants are not included in the report. Variant Tier categorizations are clinically reported in accordance with the AMP/ASCO/CAP consensus recommendations indicated in Li et. al. (27993330). Tumor Mutation Burden (TMB) is calculated as the number of mutations / megabase, and 1.94 megabases of genomic coding sequence are targeted for analysis. A cutoff of 10 mutations / MB is employed to report TMB as either high or low. Standardization for this biomarker remains an ongoing imperative, and further generation of assay specific, laboratory specific percentile cutoffs for individual tumor types has not yet been established. Median tumor mutation burden specific for tumor type is referenced from large scale patient cohorts in published studies (28420421). The assay interrogates 130 microsatellite regions to determine microsatellite instability class (MSI-Positive or MSI-Negative). Data from a minimum of 40 regions is needed to calculate an MSI score. A sample is classified as MSI-POSITIVE if 30% or more of the microsatellite regions are unstable (24310308; 29665853). Reportable Range: For full listings of interrogated genes please refer to: https://www.genpathdiagnostics.com/oncology/ngspersonalized-medicine/.

OnkoSight Advanced was developed and its performance characteristics were determined by GenPath, a division of BioReference Laboratories. This test has not been cleared or approved by the US Food and Drug Administration (FDA). The FDA has determined that such a clearance or approval is not necessary. Pursuant to the requirements of CLIA88, this laboratory has established and verified the test's accuracy and precision. However, a false positive or false negative result incurred during any phase of the testing cannot be completely excluded. Large insertion/deletion events may not be detected by this assay due to the limit of sequencing read length and bioinformatics processing. This assay does not detect translocation/gene fusion. This assay does not determine variant causality, or whether a variant is inherited or somatically acquired. These results may be used for clinical or research purposes and therefore should be carefully considered within the context of other clinical and laboratory data. In the absence of an appropriate clinical context, the clinical utility of OnkoSight ™ testing is not clearly defined. The information contained in this report reflects the current interpretation of the findings as of the date of the report, based on the available scientific information. This information, which comes from numerous sources, is subject to change over time in response to future scientific and medical findings and correlations. BioReference Laboratories, Inc. makes no representation or warranty of any kind regarding the accuracy of information provided or contained in these manuscripts, references or other sources of information. If any of the information provided by or contained in the referenced material is later deemed to be inaccurate, this may impact the accuracy of this report and interpretation of the findings. BioReference Laboratories, Inc. is not obligated to notify you of any impact that additional or modified information, or future scientific or medical research may have on this report. The laboratory is not responsible for reanalysis of the data or updated classification of this report or past reports' findings as the knowledge evolves. A medical provider can request a reassessment of clinical significance of variants and/or re-review of the clinical interpretation of the findings. Additional charges may apply for the updated report.Please contact the laboratory for more information if update is requested.This assay has been approved by the NYS DOH based on initial validation; orthogonal testing for full validation is currently ongoing. Please contact the laboratory for more information if update is requested.

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