ONCOLOGY genpath an OPKO Health Company

OnkoSight Advanced™ NGS Lung Tumor Sequencing Report

Final Report

PATIENT NAME
REFERRAL INSTITUTION
123 ROAD
SAINT LOUIS, MO 63131
Acct#: xxxxxx MO
P: (xxx)-xxx-xxxx F: (xxx)-xxx-xxxx

Patient Name: XXXXX
DOB: XXXX
Age: 59 Y **Sex:** M **Surgical #:**
Patient ID: XXXXX

Specimen ID: XXXXX
Date of Report: XXXXX 05:10 PM EDT
Date Collected: 09/03/2019
Date Received: 09/13/2019
Specimen Source: Solid Tumor
Specimen Tumor %: >50%

RESULT SUMMARY: ABNORMAL

DETECTED GENOMIC ALTERATIONS:

Variants of Strong Clinical Significance (AMP Tier 1)

EGFR p.Leu747_Pro753delinsSer EGFR

p.Thr790Met

TUMOR TYPE: Non-Small Cell Carcinoma (NSCLC)

CLINICAL INFORMATION:

Left lower lung lobe mass transbronchial biopsy showed non-small cell carcinoma.

IMMUNOTHERAPY BIOMARKERS:

MICROSATELLITE INSTABILITY: MSI-POSITIVE

TUMOR MUTATION BURDEN: HIGH (30.0 MUTATIONS / MB)

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, BRAF, DDR2, ERBB2, FGFR1, KRAS, MAP2K1, MET, NRAS, NTRK1, PIK3CA, POLD1, POLE, STK11, TERT, TP53

TECHNICAL SUMMARY

Gene	Alteration	Variant Category	Chr	Pos	Ref	Alt	Coverage	Allele Freq. or Fold Change	cDNA Change	Transcript
EGFR	p.Leu747_Pro753delinsSer	Disease Associated	7	55242469	*	T	7503	51%	c.2240_2257del	NM_005228.3
*Ref: TTAAGAGAAGCAACATCTC										
EGFR	p.Thr790Met	Disease Associated	7	55249071	C	T	10078	70%	c.2369C>T	NM_005228.3

THERAPEUTIC ASSOCIATIONS

In Patient's Tumor Type

	Gene / Locus	Alteration	Potential Therapeutic Response / Drug Class	Disease Association
✓	EGFR	Exon 19 Deletion	Confers Sensitivity to First, Second and Third Generation EGFR Tyrosine Kinase Inhibitors (TKIs)	Lung Adenocarcinoma
✓	HIGH TMB / MICROSATELLITE INSTABILITY		Immune CheckPoint Inhibitors (e.g. Pembrolizumab, Nivolumab/ Ipilimumab)	Lung Adenocarcinoma
✗	EGFR	Thr790Met	Associated with resistance to 1st and 2nd generation anti EGFR TKI agents	Lung Adenocarcinoma

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

James Weisberger M.D.
Laboratory Director

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Electronically signed by xxx MD PhD

Created 09/18/2019 05:10 PM EDT

Patient Name: _____ **Specimen ID:**

INTERPRETATION SUMMARY

Immunotherapy Biomarkers:

Positive microsatellite instability status has been associated with favorable responses to immune checkpoint inhibitors, irrespective of solid tumor type (30787022).

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 (31562796). Consensus standardization for TMB remains an ongoing imperative (30664300). Of note, as per one large scale published cohort, median tumor mutation burden specific for NSCLC has been noted as 8.1 mutations / MB (28420421).

Mutations in EGFR (p.Leu747_Pro753delinsSer and p.Thr790Met) are detected in this patient's sample.

Activating EGFR exon 19 mutations are in-frame deletions or in-frame deletion/insertions occurring in the kinase domain of EGFR that result in increased signaling by the protein. These mutations are associated with sensitivity to first, second and third generation EGFR tyrosine kinase inhibitors (TKIs) such as afatinib, erlotinib, gefitinib, neratinib, dacomitinib, and osimertinib (NCCN Guidelines, Non-Small Cell Lung Cancer, Version 5.2020). Per NCCN guidelines, osimertinib can be used as the first line therapy for patients with sensitizing EGFR mutations regardless of the stage of the non-small cell lung cancer (NSCLC) (NCCN Guidelines, Non-Small Cell Lung Cancer, Version 5.2020). This mutation is associated with primary and secondary resistance to EGFR TKIs, even in the presence of activating EGFR mutations (15737014). It should be noted that a third generation EGFR TKI, osimertinib (tagrisso), has been approved as a category 1 treatment for EGFR T790M-mutated, metastatic non-small cell lung cancer (NCCN Guidelines, Non-Small Cell Lung Cancer, Version 5.2020). Per NCCN guidelines, osimertinib can be used as the first line therapy for patients with sensitizing EGFR mutations regardless of the stage of the NSCLC (NCCN Guidelines, Non-Small Cell Lung Cancer, Version 5.2020).

Clinical and pathologic correlation is required to interpret these findings.

DETAILED GENETIC INTERPRETATION

Alteration	Interpretation
EGFR **p.Leu747_Pro753delinsSer** **c.2240_2257del** **51% allele frequency**	p.Leu747_Pro753delinsSer represents a deletion of 18 nucleotides, TAAGAGAAGCAACATCTC, in exon 19 of EGFR. This variation results in an in-frame deletion of seven amino acids (Leucine, Arginine, Glutamic Acid, Alanine, Threonine, Serine, Proline) along with the insertion of one amino acid (Serine). EGFR exon 19 deletions occur as in-frame activating mutations within the tyrosine kinase domain (15118073; 15284455; 22190593; 24828672). EGFR exon 19 deletions confers sensitivity to EGFR tyrosine kinase inhibitors such as afatinib, getfitinib and erlotinib (15118073; 15284455; 19692680; 22285168). EGFR exon 19 deletions accompanied by small in-frame insertions have been described in non-small cell lung cancer and are thought to have a similar effect as simple deletions (22848739; 24828672). The epidermal growth factor receptor gene (EGFR) is located on chromosome 7p11.2. It encodes a receptor tyrosine kinase (RTK) of the ErbB family which activates several downstream signaling pathways that regulate apoptosis and cell proliferation. Most tumor-associated EGFR mutations are missense mutations and small deletions that occur within exons 18-21, result in amino acid changes in the tyrosine kinase domain (15329413; 15118073; 15118125) and frequently involve deletions within exon 19 and point mutations targeting L858 (18437168). Most point mutations and deletions in the EGFR gene are thought to result in increased tyrosine kinase activity and confer sensitivity to tyrosine kinase inhibitors (TKI) (15118073; 15284455), while some mutations (exon 20 insertions, T790M point mutations) have been associated with primary and secondary TKI resistance (15737014; 15728811; 18437168).
EGFR **p.Thr790Met** **c.2369C>T** **70% allele frequency**	p.Thr790Met represents a hotspot missense mutation in exon 20 of EGFR converting the wild type amino acid Threonine, into amino acid Methionine at residue 790. p.Thr790Met affects the residue located in the hydrophobic ATP-binding pocket of the catalytic region within the EGFR kinase domain. Substitution of Threonine by a larger residue, such as Methionine, likely results in steric hindrance with the tyrosine kinase inhibitors' binding to the catalytic site (15737014; 15728811). The EGFR (p.Thr790Met) T790M mutation is the most common acquired resistance mutation in tumors treated with EGFR tyrosine kinase inhibitors (TKIs) and has been associated with primary and secondary resistance to EGFR tyrosine kinase inhibitors (TKIs)

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Alteration	Interpretation
	(15737014; 15728811; 18437168). The epidermal growth factor receptor gene (EGFR) is located on chromosome 7p11.2. It encodes a receptor tyrosine kinase (RTK) of the ErbB family which activates several downstream signaling pathways that regulate apoptosis and cell proliferation. Most tumor-associated EGFR mutations are missense mutations and small deletions that occur within exons 18-21, result in amino acid changes in the tyrosine kinase domain (15329413; 15118073; 15118125) and frequently involve deletions within exon 19 and point mutations targeting L858 (18437168). Most point mutations and deletions in the EGFR gene are thought to result in increased tyrosine kinase activity and confer sensitivity to tyrosine kinase inhibitors (TKI) (15118073; 15284455), while some mutations (exon 20 insertions, T790M point mutations) have been associated with primary and secondary TKI resistance (15737014; 15728811; 18437168).

CLINICAL TRIALS

Context	NCTID	Title	Conditions	Location	Sponsor
TMB / MSI	NCT03683407	Effect of Chemotherapy on TMB in NSCLC	Non Small Cell Lung Cancer	Multiple locations in Australia, France, Germany, Italy, Netherlands, Singapore, Spain, Switzerland, United States	Novartis Pharmaceuticals
	NCT03668119	A Study of Nivolumab Combined With Ipilimumab and Nivolumab Alone in Patients With Advanced or Metastatic Solid Tumors of High Tumor Mutational Burden (TMB-H)	Non-small Cell Lung Cancer	Multiple locations in Spain, United Kingdom, United States	Bristol-Myers Squibb
	NCT03236935	Phase Ib of L-NMMA and Pembrolizumab	Multiple Disease Types	Houston, Texas, 77030, United States	Jorge G. Darcourt
EGFR	NCT02143466	AZD9291 in Combination With Ascending Doses of Novel Therapeutics	Advanced NSCLC	Multiple locations in Canada, Japan, Korea, Republic of, Poland, Russian Federation, Taiwan, Ukraine, United States	AstraZeneca
	NCT02411448	A Study of Ramucirumab (LY3009806) in Combination With Erlotinib in Participants With EGFR Mutation-Positive Metastatic NSCLC	Metastatic Non-Small Cell Lung Cancer	Multiple locations in Canada, France, Germany, Greece, Hong Kong, Italy, Japan, Korea, Republic of, Romania, Spain, Taiwan, Turkey, United Kingdom, United States	Eli Lilly and Company
	NCT03292133	A Study of EGF816 and Gefitinib in TKI-naïve EGFR-mutant Non-Small Cell Lung Cancer	Lung Cancer	Boston, Massachusetts, United States	Massachusetts General Hospital

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Patient Name: **Specimen ID:**

Context	NCTID	Title	Conditions	Location	Sponsor
	NCT03255083	DS-1205c With Osimertinib for Metastatic or Unresectable Epidermal Growth Factor Receptor (EGFR)-Mutant Non-Small Cell Lung Cancer	Non-small Cell Lung Cancer (NSCLC)	Multiple locations in United States	Daiichi Sankyo, Inc.
	NCT02716116	A Trial of AP32788 in Non-Small Cell Lung Cancer	Carcinoma, Non-Small-Cell Lung	Multiple locations in United States	Ariad Pharmaceuticals
	NCT02535338	Erlotinib Hydrochloride and Onalespib Lactate in Treating Patients With Recurrent or Metastatic EGFR-Mutant Non-small Cell Lung Cancer	Multiple Disease Types	Multiple locations in United States	National Cancer Institute (NCI)
	NCT02496663	Osimertinib and Necitumumab in Treating Patients With EGFR-Mutant Stage IV or Recurrent Non-small Cell Lung Cancer Who Have Progressed on a Previous EGFR Tyrosine Kinase Inhibitor	Multiple Disease Types	Multiple locations in United States	National Cancer Institute (NCI)
	NCT02864251	A Study of Nivolumab + Chemotherapy or Nivolumab + Ipilimumab Versus Chemotherapy in Patients With EGFR Mutation, T790M Negative NSCLC Who Have Failed 1L EGFR TKI Therapy	Non-Small-Cell Lung Carcinoma	Multiple locations in China, France, Hong Kong, Japan, Korea, Republic of, Singapore, Spain, Taiwan, United States	Bristol-Myers Squibb

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 molecules from each sample are uniquely identified by ligation of a short oligonucleotide barcode. Each genomic DNA fragment is also tagged with a unique molecular identifier sequence (UMI), used after sequencing to collapse PCR duplicates and enable accurate counting of variant allelic frequencies. Exons of 523 genes are enriched by hybridization to oligonucleotide synthetic probes and PCR is performed to amplified 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. Tumor Mutation Burden (TMB) is calculated as the number of mutations / megabase, and 1.94 megabase of genomic coding sequence is 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 patient percentile cutoffs for individual tumor types has not yet been established. 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 MSI score. A sample is classify as MSI-POSITIVE if 30% or more of the microsatellite regions are unstable (24310308; 29665853). An automated process that takes into account statistical confidence of base calling and alignment and mapping quality identifies variants (TSO500 Local App Software Release Notes V2.1.0; April 17, 2020). Reported variants include known disease associated mutations and unclear variants with little or no literature support. Benign population polymorphisms are not included in the report. Reportable Range: For full list of interrogated genes please refer to: https://www.genpathdiagnostics.com/oncology/ngspersonalized-medicine/. Variant Tier categorizations are clinically reported in accordance with the AMP/ASCO/CAP consensus recommendations indicated in Li et. al. (27993330).

Onkosight™ 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 CLIA'88, 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 (eg. FLT3-ITD aberrations) 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.

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