MRS.A.M.M.S.A. Munawwara

AGE: 51 years | **Gender:** Female | **Coupon/UID:** NA / AOMG007

Diagnosis: Carcinoma, Non-Small-Cell Lung

MGM1493 : Lung Cancer gene Panel by NGS (SNVs, InDels & Fusions) + PD-L1 (SP263) by IHC

Report Details		Specimen Information		Ordering Clinician	
Sample ID / Order ID:	8690104 / 1042104	**Specimen Site:**	Lung	**Clinician:**	Dr. Senaka Kandegedara
Collection Date:	NA	**Specimen Received:**	FFPE Tissue Blocks [3]	**Affiliation:**	Aegle Omics Private Limited
Date Received:	4th September 2024	**Specimen Tested:**	SWH 1257 (A, B, C) block	**Serviced By:**	18718
Report Date & Time:	19th Sep 2024 21:47 PM	**Tumor Content:**	60	**Report Status:**	Final

Clinical Summary: Lung mass biopsy: Squamous cell carcinoma

TEST RESULT SUMMARY

PD-L1 IHC (SP263)

TPS - 1 %

Kindly refer to the complete PD-L1 IHC reports below.

Next Generation Sequencing (NGS) Results

POSITIVE

Gene	Findings	Gene	Findings
ALK	Not Detected	*BRAF*	Not Detected
EGFR	**p.L858R**	*ERBB2*	Not Detected
KRAS	Not Detected	*MET*	Not Detected
NTRK1	Not Detected	*NTRK2*	Not Detected
NTRK3	Not Detected	*RET*	Not Detected
ROS1	Not Detected		

Please refer to the complete variant details in the result table in page 2.

Next Generation Sequencing (NGS) Test Result

Result - POSITIVE

CLINICALLY RELEVANT VARIANT/S DETECTED

AMP Classification ^	CDS variant details	Interpretation	Treatment Recommendations	$Treatment Response
***EGFR* p.Leu858Arg (MISSENSE)** Variant Allele Frequency - 43.8%				
Tier I	c.2573T>G (ENST00000275493.7)	Oncogenic	Sensitive to EGFR TKIs	Effective

No clinically significant fusion has been detected in this sample

^Refer to Glossary section for the classification criteria details.

$Drug Approvals are based on US-FDA Guidelines. Kindly refer to local guidelines if required.

Please refer to the appendix section for the complete list of genes covered in this assay.

ADDITIONAL BIOMARKERS DETECTED

This section provides information about variants that do not have any therapeutic value. However, these variants may or may not have a likely oncogenic effect.

No other biomarkers that warrants to be reported was detected

ACTIONABLE BIOMARKER DETAILS

EGFR (p.Leu858Arg) - MISSENSE

Gene: *EGFR*	**Exon:** 21	**Variant Allele Frequency:** 43.8%
Nucleotide change: chr7:g.55191822T>G	**Protein change:** p.Leu858Arg	**Population MAF:** 0 (1000G);0(gnomAD);
cDNA change: c.2573T>G	**Variant Type:** MISSENSE	**In-silico Predictions:** D_lc(SIFT); D(LRT); PrD(Polyphen2)
Transcript ID: ENST00000275493.7	**Variant Allele Depth/Total depth:** 900/2055x	**Gene Function:** Oncogene

Gene Summary: The protein encoded by *EGFR* is a transmembrane glycoprotein that is a member of the protein kinase superfamily. This protein is a receptor for members of the epidermal growth factor family. EGFR is a cell surface protein that binds to epidermal growth factor, thus inducing receptor dimerization and tyrosine autophosphorylation leading to cell proliferation. Mutations in *EGFR* are associated with lung cancer.

Clinical and Therapeutic Relevance:

EGFR is a receptor tyrosine kinase that regulates the PI3K and RAS/MAPK pathways. The missense mutation L858R of *EGFR* is a well-known driver mutation shown in preclinical studies to activate the PI3K and RAS/MAPK pathways. The tyrosine kinase inhibitors (TKI) erlotinib (alone or in combination with ramucirumab), osimertinib (alone or in combination with pemetrexed and platinum-based chemotherapy), gefitinib, dacomitinib, and afatinib, are indicated for first-line treatment of L858R mutated lung adenocarcinoma. Icotinib is only approved in China. Also, the bispecific antibody ivonescimab (ak-112) targeting PD-1 and VEGFA is approved in China for the treatment of *EGFR*-mutated locally advanced or metastatic NSCLC progressed after TKI therapy. In phase III clinical trials, lazertinib (LASER301), aumolertinib (AENEAS), and alflutinib (furmonertinib) (FURLONG) showed superior efficacy compared to gefitinib in NSCLC patients with *EGFR*-activating mutations. The progression-free survival (PFS) for lazertinib vs. gefitinib was 17.8 vs. 9.6 months, and the objective response rate (ORR) was 76% for both. PFS for aumolertinib vs. gefitinib was 19.3 vs. 9.9 months; the ORR was 73.8% vs. 72.1%, respectively. PFS for alflutinib vs. gefitinib was 20.8 vs. 11.1 months, and the ORR was 89% vs. 84%, respectively. In patients with brain metastases, alflutinib as a first-line treatment had superior efficacy in CNS with PFS 20.8 vs. 9.8 months, and CNS ORR was 91% vs. 65%. A phase III clinical trial for befotertinib vs. icotinib showed a PFS of 22.1 vs. 13.8 months; the ORR was 67% and 64.4%. The intracranial PFS was 24.9 vs. 15.2 months, and the intracranial ORR was 92.3% vs. 55.6%. The phase III trial MARIPOSA-2 compared amivantamab-chemotherapy and amivantamab-lazertinib-chemotherapy vs. chemotherapy with an ORR of 64% and 63% vs. 36% and PFS of 6.3 and 8.3 vs. 4.2 months respectively. In phase II clinical studies, mefatinib, rezivertinib, zorifertinib, and nazartinib demonstrated promising clinical efficacy. Zorifertinib has a good blood-brain barrier penetration and showed activity in brain metastases with *EGFR*-activating mutations. Also, patritumab deruxtecan, an ERBB3 antibody-drug conjugate, showed an ORR of 35.4% (29/82) in the subgroup of L858R mutated patients in a phase II trial (HERTHENA-Lung01). Ba/F3 cells overexpressing this mutation are sensitive to avitinib, lazertinib, zipalertinib (TAS6417), sunvozertinib (DZD-9008), nazartinib, zorifertinib and mobocertinib. The TKI oritinib is under clinical investigation for NSCLC with this mutation.

PubMed References: 39073550, 37937763, 37879444, 37689979, 37244266, 36617560, 35932953, 35810553, 35662408, 35580297, 35425698, 35404393, 34719670, 33395611, 31591063, 31564835, 31467113, 30670498, 29285266, 29056570, 27928026, 27573423, 26980062, 25261231, 24868098, 23982599, 23816960, 22285168

AMP-ASCO-CAP CLASSIFICATION CRITERIA

Genetic test results are reported based on the somatic variant classification recommendations of College of American Pathologists (CAP) /American society for Clinical Oncology (ASCO)/Association of Molecular Pathologists (AMP) [PMID: 27993330] as described in the table below:

Tier	Criteria
Tier I	Variants of strong clinical significance.
Tier II	Variants of potential clinical significance.
Tier III	Variants of unknown clinical significance
Tier IV	Benign or likely benign variants

DISCLAIMER

- **Decisions regarding treatment action plan should not be solely based on these test results. These findings are highly recommended to be correlated with the patient's clinical, pathological, radiological and family history for decisions on diagnosis, prognosis, or therapeutics.**
- The therapy information provided in this report is based on FDA approved drugs data, NCCN guidelines, peer-reviewed published literature, standard clinical databases, and strength of biomarker results. These therapies may or may not be suitable/beneficial to a particular patient. This clinical report summarizes potentially effective medications, potentially ineffective medications, and medications that may pose a higher risk of adverse reactions by mapping the patient's genetic alterations to the biomedical reference information. The report may also provide prognostic and diagnostic biomarkers detected or shown for the given disease context. The treatment recommendations for the variants classified in Tier II are not provided.
- The clinical trials information provided in this report is compiled from www.clinicaltrials.gov as per currently available data, however completeness of information provided herein cannot be guaranteed. This information should only be used as a guide and specific eligibility criteria should be reviewed thoroughly for the concerned patient. MedGenome Labs does not guarantee or promise an enrolment in any clinical trials.
- The identification of a genomic biomarker does not necessarily imply pharmacological effectiveness or ineffectiveness. The medications identified by the treating physician may or may not be suitable for use on a particular patient. Thus, the clinical report does not guarantee that any particular agent will be effective in the treatment of any particular condition. Also, the absence of a treatment option does not determine the effectiveness or predict an ineffective or safety-relevant effect of a medication selected by the treating physician.
- The classification and clinically relevant information for the reported variants is based on peer-reviewed publications, public clinical databases, medical guidelines (WHO, NCCN, ASCO, AMP) or other publicly available information and it has been ensured that the information provided is up to date at the time of report generated, however continuous updates may happen in public domains. Also, the classification of variants can change based on the updated literature evidence. Re-analysis of the results can be requested at additional cost.
- This test is performed on the patient's tumor sample without a paired blood sample; therefore, it may include variations which may be of germline origin. However, this test is designed and validated for the detection and reporting of somatic genomic variants only and does not discriminate between germline and somatic variants. If clinically warranted, appropriate germline testing and

genetic counselling for the patient should be considered for further evaluation.

- Due to poor quality of FFPE tissue blocks, the QC parameters for extracted RNA may not pass to proceed further with the testing, therefore there is a possibility of assay failure at various steps (RNA QC, Library QC, Bioinformatics QC) or compromised results that include low gene coverage and low variant depth. However, sample status in such scenarios shall be sent through mail to the ordering clinician.
- This test has been validated at MedGenome Labs and the limit of detection (LOD) of allele fraction for SNVs and InDels is ≥5% and for fusions is ≥10 spanning reads. However, the report may include, at the discretion of laboratory director, the variants with lower allele burden (3-5%) having strong or potential clinical significance or those have been reported earlier in the patient. Variants with <1% allele fraction and variants of uncertain significance with <5% allele fraction are not routinely reported. However, possibility of false negative or false positive below the limit of detection of this assay cannot be ruled out.
- Large deletions and deep intronic variations are not detected in this assay.
- Copy Number Variations (CNVs) are based on the RNA expression data using a CNV prediction model developed with control samples. Hence, the chromosome coordinates and size of the CNV can not be determined. It is recommended to confirm the CNVs by alternate methods, such as FISH as the sensitivity of NGS for detecting CNVs is not 100%.
- **Additional case specific disclaimer : None**

TEST DESCRIPTION

The MedGenome's lung cancer panel is a high throughput next-generation sequencing based single assay that may provide treatment benefit to the patients. This next-generation sequencing based multi-gene lung cancer test is developed to sequence and identify genomic alterations associated with genes having therapeutic, prognostic and diagnostic implications. This panel covers key lung cancer genes for the assessment of various classes of genomic alterations (SNVs, InDels, CNVs and Fusions). *MET* gene is primarily tested for variations that lead to exon 14 skipping.

TEST METHODOLOGY

Sample type:FFPE Specimen; A histopathologic review is performed to determine the tumor content in the FFPE block/curls.
Extraction and Library Preparation: Tumor nucleic acid is extracted from FFPE (Formalin fixed) tissue block and used to perform targeted gene capture using a custom hybrid capture kit.
Sequencing: The QC passed libraries are sequenced to a minimum depth of 250X on validated Illumina sequencing platform.
Data Analysis: The sequences are processed using a customized and validated analysis pipeline designed to accurately detect all classes of genomic alterations (SNVs, InDels, CNVs and Fusions).
Variant Annotation and Reporting: The variants are annotated using our in-house annotation pipeline. Reportable genomic alterations and fusions are prioritized, classified, and reported based on AMP-ASCO-CAP guidelines [PMID:27993330] and NCCN guidelines.
Limit of Detection (LOD): The LOD for SNVs and InDels is 5% Variant allele Frequency (VAF) and for Fusions is >10 spanning reads.
The transcript used for clinical reporting generally represents the canonical transcript (according to Ensembl release 99 human gene model), which is usually the longest coding transcript with strong/multiple supporting evidence. However, clinically relevant variants annotated in alternate complete coding transcripts could also be reported. Variants annotated on incomplete, and nonsense mediated decay transcripts are not reported.
§This test is developed, and its performance characteristics is determined by MedGenome Labs Ltd.

GENES ANALYSED

SNVs/InDels					
BRAF	*EGFR*	*ERBB2*	*KRAS*	*MET*	*RET*

Note: *MET* exon 14 skipping mutations included.

CNVs		
EGFR	*ERBB2*	*MET*

FUSIONS					
ALK	*NTRK1*	*NTRK2*	*NTRK3*	*RET*	*ROS1*

CLINICAL TRIALS

The following trials are potentially best suited for your patient's indication, considering all reported treatment recommendations. See https://clinicaltrials.gov (clinical trials from NCT) or https://trialsearch.who.int (clinical trials from other registries) for more information.

Clinical trials in total : 0 **Trial countries :** IN-India, US-United States

S.No	Title	Phase and ID	Intervention	Disease	Age & Sex
No Clinical Trials.					

Aparna Natarajan, Ph.D
Lead - Genome Analyst (Oncology)

Dr. Syed Muqlisur Rehman, MD Path
Molecular Pathologist
KMC Registration No. 71468

END OF REPORT

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Attibele Hobli, Electronic City, Phase-1, Bangalore,
Karnataka, 560100.

PD-L1 (SP263) - IHC Test Report

Patient Name	MRS.A.M.M.S.A. Munawwara	Order ID	1042104
Age / Gender	51 Years / Female	Sample ID	8690104
Physician	Dr. Senaka Kandegedara	Collection Date	NA
Customer	MCC18718-Aegle Omics Private Limited	Sample Received Date	04-09-2024 03:30 PM
Report Date	11-09-2024 05:40 PM	Report Status	Final

Lab/Biopsy No : MBI-4572-24

Clinical Details : Lung mass biopsy - Squamous cell carcinoma

Specimen received : Three blocks and slides

Gross Examination : Three blocks and slides labelled as SWH-1257-A, B & C. Test done on SWH-1257-B block

Test interpretation/Result:

IHC Markers	Tumor cell proportion score (TPS)	Result
PD-L1 IHC	1 %	1 % of tumor cells show membranous staining of weak intensity

Note:

A sample from this individual was referred to our laboratory for "Combo Test" (Two different tests were performed & two different reports shall be sent). Results of these two reports have to be interpreted while making a clinical decision.
Report 1 of 2 (Report 2 of 2 is due for release).

Comments:

1. PD-L1 testing done by ventana PD-L1 (SP263) assay using rabbit anti-human PD-L1/CD274 monoclonal antibody (clone SP 263) on Ventana benchmark autostainer with optiview DAB IHC detection kit.

2. PD-L1 staining / expression is defined as complete or partial circumferential linear plasma membrane staining at any intensity that can be differentiated from background and diffuse cytoplasmic staining. Only cytoplasmic staining is not considered significant.

3. Roche's Ventana PD-L1 (SP263) assay is CE (European Conformity) labelled to inform treatment decisions in lung cancer patients being considered for keytruda (pembrolizumab) immunotherapy as a first line of treatment for high PD-L1 expressors.

4. Recommended positive cut off for PD-L1 (clone SP 263) in lung cancer(NSCLC) : > or = 50% of tumor cells. Studies showed superior progression free survival and overall survival in first-line treatment of mNSCLC with PD-L1 expression > or = 50% of tumor cells. There is also high degree of concordance between SP 263 (CE marked) and 22c3 assays (FDA approved) if a 50 % cut off point is applied in both cases.

5. Recommended positive cut off of PD-L1 (clone SP 263) for metastatic urothelial carcinoma is > or = 25% of tumor cells.

6. Clinical utility of this PD-L1 clone SP 263 assay needs to be verified in clinical studies for tumors other than NSCLC and urothelial carcinoma.

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Report Date	11-09-2024 05:40 PM	Report Status	Final

Note:

System level Controls (internal & or external) run with the test are satisfactory. Reagents used are the complimentary diagnostic assay consisting of primary antibody PD-L1 clone SP 263 and Optiview DAB detection on a Ventana Benchmark autostainer. This assay has not been validated on decalcified tissue and result should be interpreted with caution given the likelihood of false negativity of decalcified specimen. Specimen should be processed by routine tissue processing method. Inappropriate fixation (nonformalin) and processing may give erroneous result.

The performance characteristics of this assay has been determined by MedGenome. Performance characteristics refer to the analytical performance of the test.

Please correlate the block# given with that of its HPE report.

References:

1. Kerr K. M., Nicolson. M.C.; Non-small cell lung cancer, PDL-1 and the Pathologist. Arch Pathol Lab Med. 2016;140:249-254.
2. Fred . Hirsch , McElhinny A, Dave Stanforth D. PD-L1 Immunohistochemistry Assays for Lung Cancer: Results from Phase 1 of the Blueprint PD-L1 IHC Assay Comparison Project. Journal of Thoracic Oncology. 2017; 12: 208–22.
3. Scholl L.M. et al. 2016. Programmed Death Ligand-1 Immunohistochemistry—A New Challenge for Pathologists. A Perspective From Members of the Pulmonary Pathology Society Arch Pathol Lab Med. 140: 341-344.
4. Ratcliffe et al. Agreement between Programmed Cell Death Ligand-1 Diagnostic Assays across Multiple Protein Expression Cutoffs in Non–Small Cell Lung Cancer. Clin Cancer Res July 15 2017 (23) (14) 35853591; DOI: 10.1158/1078-0432.

Enclosed : Three blocks and slides

Verified By

Dr. Rumana Tasneem
Junior Pathologist, MBBS, MD
KMC Reg No. 96079

Approved By

Dr. Syed Muqlisur Rehman, MD (Path)
Molecular Pathologist
KMC Reg No. - 71468

*****End of Report*****

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CONDITIONS OF LABORATORY TESTING AND REPORTING

Medgenome Labs Ltd, Bangalore, Karnataka, India

- Laboratory results should be used with other clinical information to determine a final diagnosis.
- In case of unexpected test results please contact the laboratory. We will investigate and repeat analysis if possible.
- The medical report must be viewed and reproduced as a whole
- This medical report is not intended for medico-legal purposes.
- The medical report is to be interpreted and used by medical personnel only
- Assays are performed and reported in accordance with the stated schedule.
- There may be circumstances beyond our control that delay results, e.g., invalid assay run.
- The results of a laboratory test are dependent on the quality of the sample as well as the assay procedure.
- A requested test may not be carried out if:
- Sample is insufficient or inappropriate
- Sample quality is unsatisfactory
- Request for testing is withdrawn by the ordering doctor or patient
- There is discord between the labelling of the sample container and the name on the test requisition.
- For any query contact customer support : +91(0)8067154932/33
