Final Report

CARIS LIFE SCIENCES

Patient

Name: MOYE, SHONA
Date of Birth: 12/03/1976
Sex: Female
Case Number: TN21-188895
Diagnosis: Adenocarcinoma, NOS

Specimen Information

Primary Tumor Site: Upper lobe, lung
Specimen Site: Lung, NOS
Specimen ID: TL-4425-SU21-D-4
Specimen Collected: 07-Dec-2021
Test Report Date: 28-Dec-2021

Ordered By

Scott A. Tetreault, MD
Florida Cancer Specialists - Tallahassee Cancer Center
2351 Phillips Road
Tallahassee, FL 32308 USA
(850) 877-8166

Results with Therapy Associations

PD-L1 (22c3)	**IHC**	**Protein**	**Positive, TPS: 95%**	[redacted]	**cemiplimab, pembrolizumab**	**Level 1**
PD-L1 (28-8)	**IHC**	**Protein**	**Positive | 3+, 95%**	[redacted]	**nivolumab/ipilimumab combination**	**Level 1**
PD-L1 (SP142)	**IHC**	**Protein**	**Positive, TC: 3+, 90%**	[redacted]	**atezolizumab**	**Level 1**
TMB	**Seq**	**DNA-Tumor**	**High, 23 mut/Mb**	[redacted]	**pembrolizumab**	**Level 2**
ALK	IHC	Protein	Negative | 0	[redacted]	alectinib, ceritinib, crizotinib, lorlatinib	Level 1
					brigatinib	Level 2
	Seq	RNA-Tumor	Fusion Not Detected		alectinib, brigatinib, ceritinib, crizotinib, lorlatinib	Level 2
BRAF	Seq	DNA-Tumor	Mutation Not Detected	[redacted]	dabrafenib and trametinib combination therapy, vemurafenib	Level 2
EGFR	Seq	DNA-Tumor	Mutation Not Detected	[redacted]	erlotinib, gefitinib	Level 2
KRAS	Seq	DNA-Tumor	Pathogenic Variant Exon 2 | p.G12V			
ROS1	Seq	RNA-Tumor	Fusion Not Detected	[redacted]	ceritinib, crizotinib, entrectinib, lorlatinib	Level 2
MET	CNA-Seq	DNA-Tumor	Amplification Not Detected	[redacted]	crizotinib	Level 3
	Seq	DNA-Tumor	Mutation Not Detected			

* Biomarker reporting classification: Level 1 – Companion diagnostic (CDx); Level 2 – Strong evidence of clinical significance or is endorsed by standard clinical guidelines; Level 3 – Potential clinical significance. Bolded benefit therapies, if present, highlight the most clinically significant findings.

Important Note

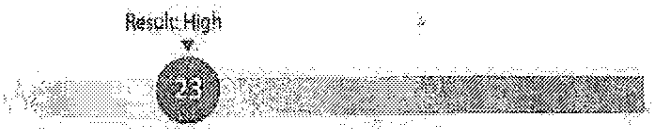
This report includes IHC and/or CISH results from FDA-approved and laboratory-developed tests performed on tissue preserved with an unknown fixative. Caris and the manufacturer of these tests have validated their use only with formalin-fixed, paraffin-embedded tissues. The use of these stains on tissues processed with other fixatives is not recommended. IHC/CISH results should be interpreted with caution given the potential for false negative results.

TMB-High status should only be used to guide pembrolizumab treatment when no satisfactory alternative treatment options are available.

Cancer-Type Relevant Biomarkers

RET	**Seq**	**DNA-Tumor**	**Pathogenic Variant Exon 11 | p.C634F**
		RNA-Tumor	Fusion Not Detected
TP53	**Seq**	**DNA-Tumor**	**Pathogenic Variant Exon 5 | p.R158G**
MSI	Seq	DNA-Tumor	Stable
Mismatch Repair Status	IHC	Protein	Proficient
NTRK1/2/3	Seq	RNA-Tumor	Fusion Not Detected
ALK	Seq	DNA-Tumor	Mutation Not Detected
BRAF	Seq	RNA-Tumor	Fusion Not Detected
ERBB2 (Her2/Neu)	Seq	DNA-Tumor	Mutation Not Detected
FGFR3	Seq	RNA-Tumor	Fusion Not Detected
KEAP1	Seq	DNA-Tumor	Mutation Not Detected
KRAS	CNA-Seq	DNA-Tumor	Amplification Not Detected
MET	Seq	RNA-Tumor	Variant Transcript Not Detected
MTAP	CNA-Seq	DNA-Tumor	Deletion Not Detected
NFE2L2	Seq	DNA-Tumor	Mutation Not Detected
NRG1	Seq	RNA-Tumor	Fusion Not Detected
PD-L1 (SP142)	IHC	Protein	Negative, IC: 0%
RB1	Seq	DNA-Tumor	Mutation Not Detected
STK11	Seq	DNA-Tumor	Mutation Not Detected

Genomic Signatures

Microsatellite Instability (MSI)	Seq	DNA-Tumor	Stable
Tumor Mutational Burden (TMB)	Seq	DNA-Tumor	Result: High 
Genomic Loss of Heterozygosity (LOH)	Seq	DNA-Tumor	Low - 0% of tested genomic segments exhibited LOH (assay threshold is ≥ 16%)

Genes Tested with Pathogenic or Likely Pathogenic Alterations

BRCA1	CNA-Seq	DNA-Tumor	Deleted	-	-	-	-
KRAS	Seq	DNA-Tumor	Pathogenic Variant	p.G12V	2	c.35G>T	10
NF1	Seq	DNA-Tumor	Pathogenic Variant	p.M968fs	22	c.2903_2904 insA	14
RET	Seq	DNA-Tumor	Pathogenic Variant	p.C634F	11	c.1901G>T	7
SMAD4	Seq	DNA-Tumor	Pathogenic Variant	p.S344fs	9	c.1030delA	8
TP53	Seq	DNA-Tumor	Pathogenic Variant	p.R158G	5	c.472C>G	12

Unclassified alterations for DNA and RNA sequencing can be found in the MI Portal.
Formal nucleotide nomenclature and gene reference sequences can be found in the Appendix of this report.

Genes Tested with Variants of Uncertain Significance

BRCA2	Seq	DNA-Tumor	Variant of Uncertain Significance	p.F439L	10	c.1317T>G	46
NTRK3	Seq	DNA-Tumor	Variant of Uncertain Significance	p.R121T	5	c.362G>C	8
ROS1	Seq	DNA-Tumor	Variant of Uncertain Significance	p.E290Q	9	c.868G>C	42

Additional Variants of Uncertain Significance can be found in the MI Portal.

Human Leukocyte Antigen (HLA) Genotype Results

The impact of HLA genotypes on drug response and prognosis is an active area of research. These results can help direct patients to clinical trials recruiting for specific genotypes. Please see www.clinicaltrials.gov for more information.

HLA-A	Seq	RNA-Tumor	A*74:01,A*23:01
HLA-B	Seq	RNA-Tumor	B*14:02,B*53:01
HLA-C	Seq	RNA-Tumor	C*04:01,C*08:02

Please note that the HLA sequencing data above was obtained from expressed RNA transcripts and not from DNA sequencing reads.
HLA sequencing data from DNA may be different from what is reported here.
HLA genotypes with only one allele are either homozygous or have loss-of-heterozygosity at that position.

Immunohistochemistry Results

ALK	Negative | 0	PD-L1 (28-8)	Positive | 3+, 95%
MLH1	Positive | 1+, 90%	PD-L1 (SP142)	Negative, IC: 0% Positive, TC: 3+, 90%
MSH2	Positive | 2+, 95%	PMS2	Positive | 1+, 60%
MSH6	Positive | 1+, 90%	PTEN	Positive | 1+, 100%
PD-L1 (22c3)	Positive, TPS: 95%		

Genes Tested with Indeterminate Results by Tumor DNA Sequencing

COL2A1	NOTCH1	PIK3CB	PLCB4	PTPN11	BAC1	RASA1	RPA1	STAG2	TRAF7	XRCC1	XRCC2
MED12	NPM1	PIK3R2	PRKACA	PTPRO							

Genes in this table were ruled indeterminate due to low coverage for some or all exons.

The results in this report were curated to represent biomarkers most relevant for the submitted cancer type. These include results important for therapeutic decision-making, as well as notable alterations in other biomarkers known to be involved in oncogenesis. Additional results, including genes with normal findings, additional variants of uncertain significance and unclassified alterations can be found in the MI Portal at **miportal.carismolecularintelligence.com.** If you do not have an MI Portal account, or need assistance accessing it, please contact Caris Customer Support at (888) 979-8669.

Notes of Significance

Clinical Trials Connector ™ opportunities based on biomarker expression: 201 Chemotherapy Trials | 742 Targeted Therapy Trials. See page 6 for details.

Note regarding tissue preparation: This report includes IHC and/or CISH results from FDA-approved and laboratory-developed tests performed on tissue preserved with an unknown fixative. Caris and the manufacturer of these tests have validated their use only with formalin-fixed, paraffin-embedded tissues. The use of these stains on tissues processed with other fixatives is not recommended. IHC/CISH results should be interpreted with caution given the potential for false negative results.

Specimen Information

Specimen ID: TL-4425-SU21-D-4

Specimen Collected: 12/07/2021

Specimen Received: 12/16/2021

Testing Initiated: 12/20/2021

Gross Description: 1 (A) Paraffin Block - Client ID(TL-4425-SU21-D-4) from HCA - Integrated Regional Laboratories - North Florida, Alachua, FL, with the corresponding pathology report labeled "SU21-TL-4425".

Pathologic Diagnosis: Lung, right, pneumonectomy: Invasive solid adenocarcinoma, poorly differentiated.

Dissection Information: Molecular testing of this specimen was performed after harvesting of targeted tissues with an approved manual microdissection technique. Candidate slides were examined under a microscope and areas containing tumor cells (and separately normal cells, when necessary for testing) were circled. A laboratory technician harvested targeted tissues for extraction from the marked areas using a dissection microscope.

Clinical Trials Connector℠

For a complete list of open, enrolling clinical trials visit MI Portal to access the **Clinical Trials Connector**. This personalized, real-time web-based service provides additional clinical trial information and enhanced searching capabilities, including, but not limited to:

- Location: filter by geographic area
- Biomarker(s): identify specific biomarkers associated with open clinical trials to choose from
- Drug(s): search for specific therapies
- Trial Sponsor: locate trials based on the organization supporting the trial(s)

The Clinical Trials Connector lists agents that are matched to available clinical trials according to biomarker status. In some instances, older-generation agents may still be relevant in the context of new combination strategies and, therefore, will still appear on this report.

Visit www.CarisMolecularIntelligence.com to view all matched trials. Therapeutic agents listed below may or may not be currently FDA approved for the tumor type tested.

DNA minor groove binding agents (6)	BRCA1	CNA-NGS	DNA-Tumor	lurbinectedin, trabectedin
Platinum compounds (196)	BRCA1	CNA-NGS	DNA-Tumor	carboplatin, cisplatin, oxaliplatin

ATR inhibitors (15)	BRCA1	CNA-NGS	DNA-Tumor	AZD6738, BAY1895344, berzosertib
Cancer vaccines (1)	KRAS	NGS	DNA-Tumor	V941
ERK inhibitors (5)	KRAS	NGS	DNA-Tumor	LTT462, LY3214996, pexmetinib, ulixertinib
	NF1	NGS	DNA-Tumor	
Glutaminase inhibitor (5)	NF1	NGS	DNA-Tumor	DRP-104, IPN60090, sirpiglenastat, telaglenastat
Immunomodulatory agents (672)	TMB	NGS	DNA-Tumor	BAY1905254, CDX-527, INBRX-105, M7824, atezolizumab, avelumab, camrelizumab, cemiplimab, dostarlimab, durvalumab, efineptakin alfa, ipilimumab, nivolumab, pembrolizumab, retifanlimab, sintilimab, spartalizumab, tislelizumab, toripalimab, tremelimumab
	PD-L1	IHC	Protein	
MEK inhibitors (36)	NF1	NGS	DNA-Tumor	binimetinib, mirdametinib, selumetinib, trametinib
	KRAS	NGS	DNA-Tumor	
Multikinase RET inhibitors (53)	RET	NGS	DNA-Tumor	cabozantinib, lenvatinib, regorafenib, sitravatinib, sorafenib, sunitinib
PARP inhibitors (45)	BRCA1	CNA-NGS	DNA-Tumor	BGB-290, niraparib, olaparib, pamiparib, rucaparib, talazoparib, veliparib
Selective RET inhibitors (10)	RET	NGS	DNA-Tumor	pralsetinib, selpercatinib

() = represents the total number of clinical trials identified by the Clinical Trials Connector for the provided drug class or table.

The Clinical Trials Connector may include trials that enroll patients with additional screening of molecular alterations. In some instances, only specific gene variants may be eligible.

Pathogen Identification

HPV16	0	Negative	≥100 Reads
HPV18	0	Negative	≥100 Reads

HPV 16/18-detection by Whole Exome Sequencing (WES) Methods:
The DNA of human papilloma virus (HPV) types 16 or 18 must be detected for a tumor to be considered positive for HPV. This WES-based HPV-detection assay determines HPV-status using the MI Exome assay to enumerate the number of sequencing reads specific to either HPV 16 or HPV 18. Reads greater than or equal to 100 are deemed positive. There is no intermediate range. The MI Exome assay for HPV-detection is reliable down to tumor percentages of 20%. Concordance data showed that this WES HPV-detection assay was able to detect HPV status with a positive percent agreement of 97%, a negative percent agreement of 93%, and an overall percent agreement of 95% with samples confirmed as positive by ISH analysis.

HPV types 16 and 18, are two of the most prevalent high-risk HPV genotypes detected in HPV-associated cancers. Tumors commonly ascribed to HPV etiology are most common in squamous cell carcinomas including cervical, vulvar, anal, penile and oropharyngeal. If positive, HPV has been associated with improved prognosis, de-intensified treatment protocols and tumor subclassification.

1p/19q Co-deletion

Co-deletion Not Detected

1p/19q by Whole Exome Sequencing (WES) Methods:
The entire short and long arms of chromosomes 1 and 19, respectively, must be confirmed deleted for a tumor to be considered positive for 1p/19q codeletion. This WES-based 1p/19q co-deletion assay determines deletion status using CNVKit (via Python 3.7, version 0.9.6) to examine tens of thousands of data points across the entirety of 1p and 19q using evenly-spaced SNP probes. Deletion status is based on consecutive measurements of the presence or absence of DNA. CNVKit for 1p/19q co-deletion is reliable down to tumor percentages of 20%. Concordance data showed that this WES 1p/19q codeletion assay was able to detect 1p/19q co-deletion with 100% sensitivity for samples confirmed as positive by either FISH or array CGH analysis. No false negatives were detected.

1p/19q co-deletion is strongly associated with oligodendroglial histology and helps confirm the oligodendroglial character of tumors with equivocal or mixed histologic features.

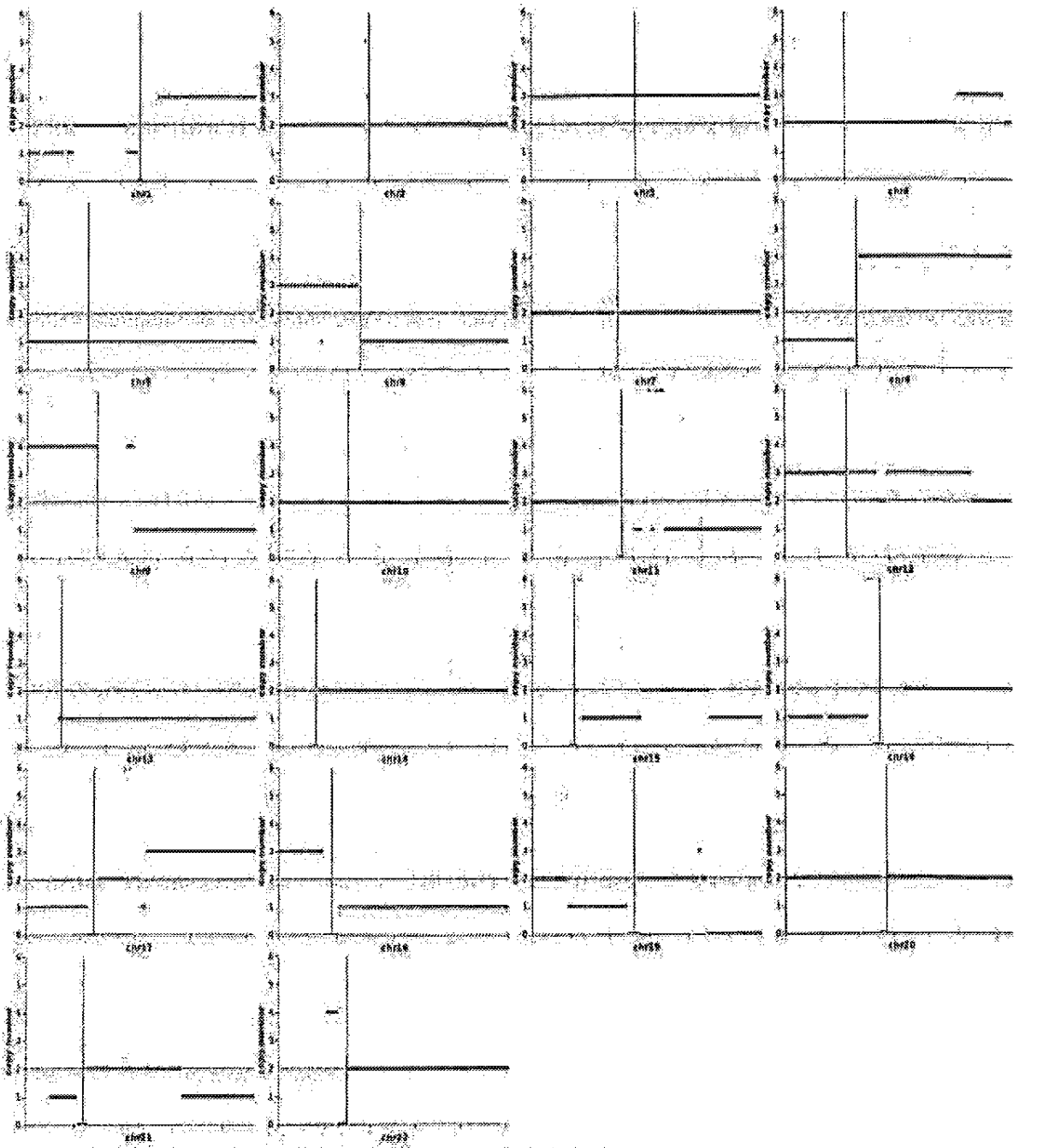
Gene Expression

ALK	<1 | 42	EZH2	13 | 46	NRG1	3 | 45
AURKA	10 | 30	FGFR1	58 | 55	NTRK1	2 | 85
AXL	10 | 60	FGFR3	1 | 24	NTRK2	<1 | 18
BRAF	22 | 36	HGF	9 | 56	NTRK3	<1 | 48
CCND1	2755 | 98	IGF1R	20 | 20	PTEN	71 | 44
CCND2	18 | 80	KEAP1	20 | 66	RET	<1 | 30
CCND3	37 | 79	KL	<1 | 34	ROR1	4 | 62
CCNE1	6 | 76	KRAS	31 | 55	ROS1	23 | 68
CD274	53 | 96	LAG3	5 | 94	SMARCB1	43 | 62

CD276	19|55	MAPRE1	15|54	STK11	3|80
CD38	49|98	MCL1	56|92	TACSTD2	111|66
CDKN2A	3|28	MDM2	113|58	TF	<1|29
CDR1	173|56	MET	161|78	TNFRSF10B	36|71
EGFR	23|38	MSLN	23|69	TNFRSF9	6|93
EPHA2	19|44	MTAP	4|18	TP53	54|46
ERBB2	24|50	MUC1	217|58	XPO1	117|38
ERBB3	28|29	MYC	18|76		

Gene Expression of Selected Genes by Whole Transcriptome Sequencing (WTS) Methods:
Whole transcriptome sequencing was performed and sequences aligned to human reference genome hg19. Transcript level of genes is presented as TPM, or Transcript per Million Molecules and, if available, accompanied by a percentile in Caris' cohort of the tumor type profiled. Expression of genes reported in this section are selected for their importance in the tumor type profiled for matching to clinical trials, or tumor type subclassification.

Karyotype



Karyotyping using Copy Number Analysis by Whole Exome Sequencing (WES) Methods:
Copy-number alterations (CNA) associated with human cancers range from chromosomal aneuploidy, to microduplication and microdeletion syndromes, and include smaller structural variants (SVs) that affect single genes and exons. In traditional cytogenetics, the comprehensive analysis of all structural aberrations in a given sample required chromosomal karyotyping, fluorescence in situ hybridization and CNV microarrays. WES allows a visualization of cytogenetic aberrations across the entire genome. The copy number is a smoothed non-log representation of the estimated ploidy across arm-level parts of the genome.

Somatic structural variants like whole or partial chromosome duplications or deletion, are important for cancer development and progression, and may identify alterations for matching to therapies in clinical trials.

Disclaimer

Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all available information concerning the patient's condition, the FDA prescribing information for any therapeutic, and in accordance with the applicable standard of care. Drug associations provided in this report do not guarantee that any particular agent will be effective for the treatment of any patient or for any particular condition. Caris Life Sciences expressly disclaims and makes no representation or warranty whatsoever relating, directly or indirectly, to the performance of services, including any information provided and/or conclusions drawn from therapies that are included or omitted from this report. Whether or not a particular patient will benefit from a selected therapy is based on many factors and can vary significantly. The selection of therapy, if any, resides solely in the discretion of the treating physician.

Individual assays that are available through Caris Molecular Intelligence® include both Laboratory Developed Tests (LDT) and U.S. Food and Drug Administration (FDA) approved or cleared tests. Caris MPI, Inc. d/b/a Caris Life Sciences® is certified under the Clinical Laboratory Improvement Amendments (CLIA) as qualified to perform high complexity clinical laboratory testing, including all of the assays that comprise the Caris Molecular Intelligence®. The LDTs were developed and their performance characteristics determined by Caris. The LDTs have not been cleared or approved by the U.S. Food and Drug Administration. Caris' CLIA certification number is located at the bottom of each page of this report. Certain tests have not been cleared or approved by the FDA. The FDA has determined that clearance or approval is not necessary for certain laboratory developed tests. Caris LDTs are used for clinical purposes. They are not investigational or for research.

The information presented in the Clinical Trials Connector™ section of this report, if applicable, is compiled from sources believed to be reliable and current. However, the accuracy and completeness of the information provided herein cannot be guaranteed. The clinical trials information present in the biomarker description was compiled from www.clinicaltrials.gov. The contents are to be used only as a guide, and health care providers should employ their best comprehensive judgment in interpreting this information for a particular patient. Specific eligibility criteria for each clinical trial should be reviewed as additional inclusion criteria may apply.

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Caris Molecular Intelligence is subject to Caris' intellectual property. Patent www.carislifesciences.com/ip.

Amy L Adams, MD

Electronic Signature
Amy Adams, MD
12/28/2021

For full biomarker assay results, including cutoffs, unit of measure, methods, etc., please visit MI Portal to access complete report details. Please contact Client Services at (888)979-8669 for questions or assistance.