CARIS® ASSURE

Final Report

Patient
Name:
Date of Birth:
Sex:
Case Number:
Diagnosis:

Specimen Information
Primary Tumor Site: Lung, NOS
Specimen Site:
Specimen ID:
Specimen Collected:
Test Report Date:

Ordered By

Results with Therapy Associations

Biomarker	Results	Therapy Association		Biomarker Level*
EGFR	Pathogenic Variant Exon 19 | p.L747 _P753 delinsS	BENEFIT	afatinib, dacomitinib, erlotinib¶, gefitinib, osimertinib	Level 2

*Level 1: Companion diagnostic (CDx); Level 2: Strong evidence of clinical significance or endorsed by clinical guidelines; Level 3: Potential clinical significance.

IMPORTANT NOTE(S): Osimertinib is the NCCN-preferred agent for first-line setting of advanced or metastatic NSCLC patients harboring sensitizing EGFR mutations.

¶ Erlotinib combinations with VEGF receptor (VEGFR) inhibitors utilized in the first-line setting for metastatic NSCLC include:
- erlotinib + ramucirumab (FDA-approved, Nakagawa, et al., 2019)
- erlotinib + bevacizumab (NCCN-guidelines, Saito, et al., 2019)
Osimertinib and VEGFR inhibitor combinations have not been evaluated.

Tumor Associated Findings

Biomarker	Protein Change	DNA Change	Variant Frequency	Interpretation
CTNNB1	S37F	c.110C>T	0.7 %	Pathogenic Variant
EGFR	L747_P753delinsS	c.2240 _2257del18	0.7 %	Pathogenic Variant
PIK3CA	M1043I	c.3129G>A	1.8 %	Pathogenic Variant

Other Results

BLOOD TMB (mut/Mb) : 1

MICROSATELLITE INSTABILITY : Not Detected

TUMOR FRACTION : 1.8 %

Incidental Findings* (Pathogenic & Likely Pathogenic Variants)

Incidental Germline Variants

Biomarker	Protein Change	DNA Change	Variant Frequency	Interpretation
None Detected				

Incidental Findings continued on the next page. >

Clonal Hematopoiesis (CH)

Biomarker	Protein Change	DNA Change	Variant Frequency	Interpretation
None Detected				

*Incidental findings section reports variants characterized as non-tumor derived. These results are not a replacement for comprehensive germline testing. Incidental germline pathogenic alterations in ACMG-recognized & additional selected cancer genes are reported (see reportable gene list). Negative results do not imply the patient does not harbor a germline mutation. CH refers to mutations in cancer-associated genes in white blood cells (WBC) and not of solid tumor origin. Incidental CH variants are reported but may not comprehensively detect all CH variants. These mutations occur naturally and increase with age or may be smoking - or therapy-related. Although CH is considered a benign state, there is a risk of progression to hematological malignancy and thus appropriate clinical correlation is recommended. Variants characterized as indeterminant origin, if reported, are likely characterized as high-level CH variants or potential mosaic. Categorization of incidental pathogenic and likely pathogenic variants are based on the observed allele frequency in the buffy coat, such that, for the majority of cases: ≥ 30% is germline; 20%-30% is indeterminant origin; ≤20% is clonal hematopoiesis, though some rare exceptions may exist.

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.

Gene	Method	Analyte	Genotype
		MHC CLASS I	
HLA-A	Seq	gDNA	A*11:01;A*11:01
HLA-B	Seq	gDNA	B*13:01;B*51:01
HLA-C	Seq	gDNA	C*03:04;C*14:02

gDNA = genomic DNA extracted from the buffy coat
HLA genotypes with only one allele are either homozygous or have loss-of-heterozygosity at that position.

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Specimen Information

Specimen ID:

Specimen Collected:

Specimen Received:

Testing Initiated:

Test Ordered: Caris Assure

Gross Description: 2 (T1-T2) Peripheral Blood PAXgene Tubes from patient (**xxxx**).

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Clinical Trials Connector™

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.

Therapeutic agents listed below may or may not be currently FDA approved for the tumor type tested.

Please see https://clinicaltrials.gov/ for more information.

TARGETED THERAPY CLINICAL TRIALS (20)

Drug Class	Biomarker	Analyte	Investigational Agent(s)
EGFR TKIs (1)	EGFR	DNA-Tumor	CLN-081
PI3K/Akt/mTOR inhibitors (18)	PIK3CA	DNA-Tumor	CYH33, afuresertib, capivasertib, copanlisib, everolimus, inavolisib, ipatasertib
Wnt pathway inhibitors (1)	CTNNB1	DNA-Tumor	CGX1321

( ) = 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.

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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, 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 and the tests should not be considered a companion diagnostic.

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. Individual assays that are available through Caris molecular profiling include both Laboratory Developed Tests (LDT) and U.S. Food and Drug Administration (FDA) approved or cleared tests. 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. 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. Caris' CLIA certification number is located at the bottom of each page of this report.

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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Mutational Analysis by Tumor and Germline Next Generation Sequencing

BLOOD TUMOR MUTATIONAL BURDEN

Mutations / Megabase: 1

MICROSATELLITE INSTABILITY

Result: Not Detected

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
CTNNB1	DNA-Tumor	Pathogenic Variant	p.S37F	3	c.110C>T	0.69	NM_001904.3

Interpretation: A pathogenic mutation was detected in CTNNB1 (beta-catenin).

CTNNB1 or cadherin-associated protein, beta 1, encodes for β-catenin, a central mediator of the Wnt signaling pathway which regulates cell growth, migration, differentiation and apoptosis. Mutations in CTNNB1 (often occurring in exon 3) prevent the breakdown of β-catenin, which allows the protein to accumulate resulting in persistent transactivation of target genes, including c-myc and cyclin-D1. Somatic CTNNB1 mutations occur in 1-4% of colorectal cancers, 2-3% of melanomas, 25-38% of endometrioid ovarian cancers, 84-87% of sporadic desmoid tumors, as well as the pediatric cancers, hepatoblastoma, medulloblastoma and Wilms' tumors.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
EGFR	DNA-Tumor	Pathogenic Variant	p.L747_P753 delinsS	19	c.2240 _2257del18	0.72	NM_005228.4

Interpretation: A pathogenic exon 19 deletion mutation was detected in EGFR.

EGFR or epidermal growth factor receptor, is a transmembrane receptor tyrosine kinase belonging to the ErbB family of receptors. Upon ligand binding, the activated receptor triggers a series of intracellular pathways (Ras/MAPK, PI3K/Akt, JAK-STAT) that result in cell proliferation, migration and adhesion. EGFR mutations have been observed in 20-25% of non-small cell lung cancer (NSCLC), 10% of endometrial and peritoneal cancers. Somatic gain-of-function EGFR mutations, including in-frame deletions in exon 19 or point mutations in exon 21, confer sensitivity to first- and second-generation tyrosine kinase inhibitors (TKIs), whereas the secondary mutation, T790M in exon 20, confers reduced response. Germline mutations and polymorphisms of EGFR have been associated with familial lung adenocarcinomas.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
PIK3CA	DNA-Tumor	Pathogenic Variant	p.M1043I	21	c.3129G>A	1.8	NM_006218.3

Interpretation: A pathogenic mutation was detected in PIK3CA.

PIK3CA or phosphoinositide-3-kinase catalytic alpha polypeptide encodes a protein in the PI3 kinase pathway. This pathway is an active target for drug development. PIK3CA somatic mutations have been found in breast (26%), endometrial (23%), urinary tract (19%), colon (13%), and ovarian (11%) cancers. Somatic mosaic activating mutations in PIK3CA are said to cause CLOVES syndrome.

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NGS Methods:

Next-generation sequencing analysis of DNA and RNA extracted from plasma and white blood cells (buffy coat) was performed using Illumina NovaSeq 6000 sequencers. A hybrid pull-down panel of baits was used to capture DNA and reverse-transcribed RNA from >20,000 genes. Sequence data was analyzed using a custom bioinformatics pipeline to detect variants as well as the characterization of the source of genomic findings (e.g. somatic tumor, germline, or non-tumor derived mutations that result from clonal hematopoiesis). Only likely pathogenic or pathogenic alterations are reported. The ACMG SF v3.0 (Miller, et al. (2021) Genet Med 23(8):1381-1390) guidelines were followed for reporting of alterations identified in cancer-associated genes determined to have originated from the patient's germline. This assay cannot detect all likely pathogenic or pathogenic germline alterations nor all carriers of germline cancer predisposition alterations. A positive germline or suspected germline result is an indication that the patient may be predisposed to cancer and patients may consider further independent testing, consult with their physician, or obtain genetic counseling.

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Genes Reported:

This test assays for variants in >20,000 genes (exome). To provide a succinct report, clinical reporting focuses on 275 genes with known clinical associations with cancer therapies, prognosis, or etiology. Of note, calculation of blood tumor mutational burden (bTMB) utilizes the entire exome. Alterations reported include single nucleotide variants (SNVs) and insertion/deletions (indels) in all 275 genes and reports other variant types in certain genes as indicated by the following: incidental germline variants (bolded), fusion events (§) and amplifications (▲).

ABL1	BTK	CYSLTR2	FGFR4	KMT2D	NOTCH1	PTCH1	SMARCE1
ACD	CALR	DDR2	FH	KRAS ▲	NOTCH2	**PTEN**	SMO
ACVR1	CARD11	DICER1	**FLCN**	LZTR1	NPM1	PTPN11	SOCS1
ACVR1B	CASP8	DNMT3A	FLT1	MAP2K1 (MEK1)	NRAS	PTPRD	SOS1
AIP	CBFB	EED	FLT3	MAP2K2 (MEK2)	NSD1	RABL3	SOX9
AJUBA	CBL	EGFR	FOXA1	MAP2K4	NSD2	RAC1	SPEN
AKT1	CCDC6	EIF1AX	FOXL2	MAP3K1	NT5C2	RAD50	SPOP
AKT2	CCND1 ▲	ELF3	FUBP1	MAPK1	NTHL1	RAD51B	SRC
AKT3	CCND2	ELOC	GATA3	**MAX**	NTRK1 §	**RAD51C**	STAG2
ALK §	CCND3 ▲	EP300	GNA11	MED12	NTRK2 §	**RAD51D**	STAT3
AMER1	CD79B	EPHA2	GNA13	MEF2B	NTRK3 §	RAD54L	STAT5B
AR	CDC73	ERBB2 ▲	GNAQ	**MEN1**	**PALB2**	RAF1	**STK11**
APC	**CDH1**	ERBB3	GNAS	MGA	PARP1	RASA1	SUFU
ARAF	CDK12	ERBB4	GRIN2A	MITF	PBRM1	**RB1**	SUZ12
ARHGAP35	CDK4	ERCC2	GRM3	**MLH1**	PDGFRA	RBM10	TCF7L2
ARID1A	CDKN1A	ESR1	H3F3A	MLH3	PDGFRB	**RET §**	TERT
ARID2	CDKN1B	EXT1	H3F3B	MPL	PIK3CA	RHEB	TET2
ASXL1	**CDKN2A**	EZH2	HIST1H3B	MRE11	PIK3CB	RHOA	TGFBR1
ATM	CEBPA	FANCA	HNF1A	**MSH2**	PIK3R1	RIT1	TGFBR2
ATRX	CHEK1	FANCB	HOXB13	MSH3	PIK3R2	RNF43	**TMEM127**
AXIN1	**CHEK2**	FANCC	HRAS	**MSH6**	PIM1	ROS1 §	TNFAIP3
AXIN2	CIC	FANCD2	IDH1	MTOR	PLCB4	RRAS2	TNFRSF14
B2M	c-KIT	FANCE	IDH2	**MUTYH**	**PMS2**	RUNX1	**TP53**
BAP1	cMET	FANCF	IRF4	MYC	POLD1	SDHA	TRAF3
BARD1	CNOT3	FANCG	JAK1	MYCN	POLE	**SDHAF2**	TRAF7
BCL2	COL2A1	FANCI	JAK2	MYD88	POT1	**SDHB**	TRRAP
BCL9	CREBBP	FANCL	JAK3	MYOD1	PPM1D	**SDHC**	**TSC1**
BCOR	CSF3R	FANCM	KDM5C	NBN	PPP2R1A	**SDHD**	**TSC2**
BLM	CTCF	FAS	KDM6A	NF1	PPP2R2A	SETD2	U2AF1
BMPR1A	CTNNA1	FAT1	KDR	**NF2**	PPP6C	SF3B1	**VHL**
BRAF	CTNNB1	FBXW7	KEAP1	NFE2L2	PRDM1	SMAD2	WRN
BRCA1	CUL3	FGFR1	KLF4	NFKBIA	PRKACA	**SMAD4**	**WT1**
BRCA2	CXCR4	FGFR2 §	KMT2A	NFKBIE	PRKAR1A	SMARCA4	XPO1
BRIP1	CYLD	FGFR3 §	KMT2C	NKX2-1	PRKDC	SMARCB1	XRCC1

Additional Biomarkers:

Blood Tumor Mutational Burden (bTMB, mutations/Mb)
Blood Microsatellite Instability
Human Leukocyte Antigen (HLA) genotypes for HLA-A, HLA-B and HLA-C
Tumor Fraction

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References

#	Drug	Biomarker	Reference
1	afatinib, dacomitinib	EGFR	Yang, J.C., et al. (2015). "Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6." Lancet Oncol; (7):830-838. View Citation Online
2	afatinib, dacomitinib	EGFR	Yang, J.C., et al. (2013). "Symptom control and quality of life in LUX-Lung 3: a phase III study of afatinib or cisplatin/pemetrexed in patients with advanced lung adenocarcinoma with EGFR mutations." J Clin Oncol 31:3342-3350. View Citation Online
3	afatinib, dacomitinib	EGFR	Wu, Y-L, T.S. Mok, et al (2017). "Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomized, open-label, phase III trial." Lancet Oncol. 2017;18(11):1454-1466. View Citation Online
4	afatinib, dacomitinib	EGFR	Sequist, L.V., M. Schuler, et al. (2013). "Phase III Study of Afatinib or Cisplatin Plus Pemetrexed in Patients with Metastatic Lung Adenocarcinoma With EGFR Mutations." J Clin Oncol ahead of print July 1, 2013, doi: 10.1200/JCO.2012.44.2806 View Citation Online
5	erlotinib, gefitinib	EGFR	Brugger, W., F. Cappuzzo, et. al. (2011). "Prospective molecular marker analyses of EGFR and KRAS from a randomized, placebo-controlled study of erlotinib maintenance therapy in advanced non-small-cell lung cancer." J. Clin. Oncol. 29:4113-4120. View Citation Online
6	erlotinib, gefitinib	EGFR	Fukuoka, M., T.S.K. Mok, et. al. (2011). "Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). J. Clin. Oncol. DOI: 10.1200/JCO.2010.33.4235. View Citation Online
7	erlotinib, gefitinib	EGFR	Keedy, V.L., G. Gianconne, et. al. (2011). "American Society of Clinical Oncology Provisional Clinical Opinion: epidermal growth factor receptor (EGFR) mutation testing for patients with advanced non-small cell lung cancer considering first-line EGFR tyrosine kinase inhibitor therapy." J. Clin. Oncol. 29(15):2121-2127. View Citation Online
8	erlotinib, gefitinib	EGFR	Maemondo, M., T. Nukiwa, et. al. (2010). "Gefitinib or chemotherapy for non-small cell lung cancer with mutated EGFR." N. Engl. J. Med. 362:2380-8. View Citation Online
9	osimertinib	EGFR	Ramalingam, S.S., P.A., Janne, et al. (2017). "Osimertinib As First-Line Treatment of EGFR Mutation-Positive Advanced Non-SmallCell Lung Cancer." J Clin Oncol . doi: 10.1200/JCO.2017.74.7576. View Citation Online
10	osimertinib	EGFR	Soria, J.-C., S.S. Ramalingam, et al. (2017). "Osimertinib in Untreated EGFR-Mutated Advanced Non-Small Cell Lung Cancer." N Eng J Med. doi:10.1056/NEJMoa1713137. View Citation Online

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