Patient

Name:
Date of Birth:
Sex:
Case Number: TN26-
Diagnosis: Adenocarcinoma, NOS

Specimen Information

Primary Tumor Site: Upper lobe, lung
Specimen Site: Upper lobe, lung
Specimen ID:
Specimen Collected:
Test Report Date:

Ordered By

Results with Therapy Associations

BIOMARKER	METHOD	ANALYTE	RESULT	THERAPY ASSOCIATION		BIOMARKER LEVEL*
PD-L1 (22c3)	**IHC**	**Protein**	**Positive, TPS: 95%**	**BENEFIT**	**cemiplimab, pembrolizumab**	**Level 1**
					atezolizumab (adjuvant)	**Level 2**
					nivolumab + ipilimumab	**Level 2**
EGFR	**Seq**	**DNA-Tumor**	**Pathogenic Variant Exon 20 | p.V769 _D770 insGVV**	**BENEFIT**	**amivantamab, amivantamab + carboplatin/ pemetrexed, sunvozertinib**	**Level 2**
					datopotamab deruxtecan	**Level 2**
				LACK OF BENEFIT	erlotinib, gefitinib	Level 2
BRCA2	Seq	DNA-Tumor	Pathogenic Variant Exon 11 | p.S871*	BENEFIT	olaparib, talazoparib	Level 3
ALK	IHC	Protein	Negative | 0	LACK OF BENEFIT	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	LACK OF BENEFIT	dabrafenib, dabrafenib + trametinib, encorafenib + binimetinib, vemurafenib	Level 2
KRAS	Seq	DNA-Tumor	Mutation Not Detected	LACK OF BENEFIT	adagrasib, sotorasib	Level 2
MET	Seq	RNA-Tumor	Variant Transcript Not Detected	LACK OF BENEFIT	capmatinib, tepotinib	Level 2
					crizotinib	Level 2
RET	Seq	RNA-Tumor	Fusion Not Detected	LACK OF BENEFIT	pralsetinib, selpercatinib	Level 2
ROS1	Seq	RNA-Tumor	Fusion Not Detected	LACK OF BENEFIT	ceritinib, crizotinib, entrectinib, lorlatinib, repotrectinib, taletrectinib	Level 2

* Biomarker reporting classification - Level 1 – MI Cancer Seek™ or other companion diagnostic (CDx) performed as part of professional services; 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.

The selection of any, all, or none of the matched therapies resides solely with the discretion of the treating physician. 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. Whether or not a particular patient will benefit from a selected therapy is based on many factors and can vary significantly. All trademarks and registered trademarks are the property of their respective owners.

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Important Note

This content is provided as part of the professional services. For MI Cancer Seek™ results, see CDx Associated Findings.

A pathogenic nonsense mutation was detected in BRCA2. Germline pathogenic variants in this gene are causal for hereditary cancers of the breast, ovaries, pancreas, and prostate. Confirmation of the patient's carrier status should be considered.

Datopotamab deruxtecan is FDA-approved for patients with locally advanced or metastatic EGFR-mutated NSCLC who have received prior EGFR-directed therapy and platinum-based chemotherapy.

For patients with advanced or metastatic NSCLC harboring EGFR exon 20 insertion mutations, amivantamab plus chemotherapy is FDA-approved in the first-line setting. In the second-line setting, either amivantamab or sunvozertinib may be used as FDA-approved single-agent options following progression on platinum-based chemotherapy.

This patient's tumor has an EGFR exon 20 insertion mutation and is positive for PD-L1 expression. Please note that associations for immune checkpoint inhibitors are based on PD-L1 positivity, however, recent data show mixed results with immune checkpoint inhibitors for patients with exon 20 insertion mutations (PMID:33582070, 32336530, 33946594).

Please note that multiple companion diagnostic assays (antibodies) have been utilized to assess PD-L1 expression. Each test has different performance characteristics, therefore, the results will not always be concordant.

Cancer-Type Relevant Biomarkers

Biomarker	Method	Analyte	Result
MET	**IHC**	**Protein**	**Positive | 3+, 60%**
	CNA-Seq	DNA-Tumor	Amplification Not Detected
	Seq	DNA-Tumor	Mutation Not Detected
TP53	**Seq**	**DNA-Tumor**	**Likely Pathogenic Variant Exon 5 | p.E171_S183del**
MSI	Seq	DNA-Tumor	Stable
NTRK1/2/3	Seq	RNA-Tumor	Fusion Not Detected
Tumor Mutational Burden	Seq	DNA-Tumor	Low, 7 mut/Mb
ALK	Seq	DNA-Tumor	Mutation Not Detected
BRAF	Seq	RNA-Tumor	Fusion Not Detected
ERBB2 (Her2/Neu)	CNA-Seq	DNA-Tumor	Amplification Not Detected
	IHC	Protein	Negative | Score 0
	Seq	DNA-Tumor	Mutation Not Detected
EGFR3	Seq	RNA-Tumor	Fusion Not Detected
KEAP1	Seq	DNA-Tumor	Mutation 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: 3% Negative, TC: 1+, 5%
RB1	Seq	DNA-Tumor	Indeterminate
RET	Seq	DNA-Tumor	Mutation Not Detected
STK11	Seq	DNA-Tumor	Mutation Not Detected
Tobacco Airway Signature	Seq	DNA-Tumor	Not Detected

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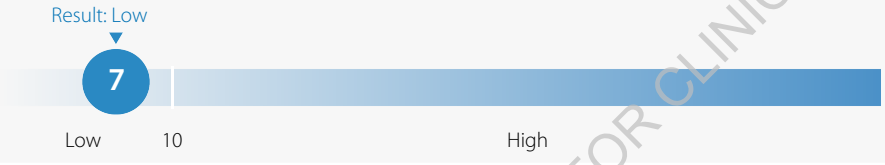
Genomic Signatures

Biomarker	Method	Analyte	Result
Microsatellite Instability (MSI)	Seq	DNA-Tumor	Stable
Tumor Mutational Burden (TMB)	Seq	DNA-Tumor	
Genomic Loss of Heterozygosity (LOH)	Seq	DNA-Tumor	Equivocal - 12% of tested genomic segments exhibited LOH (assay threshold is ≥ 16%)
Tobacco Airway Signature	Seq	DNA-Tumor	Not Detected

Genes Tested with Pathogenic or Likely Pathogenic Alterations

Gene	Method	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %
BRCA2	Seq	DNA-Tumor	Pathogenic Variant	p.S871*	11	c.2612C>G	66
DNMT3A	Seq	DNA-Tumor	Pathogenic Variant	c.2083-1G>A	18	c.2083-1G>A	25
EGFR	Seq	DNA-Tumor	Pathogenic Variant	p.V769 _D770 insGVV	20	c.2308 _2309 ins9	35
TP53	Seq	DNA-Tumor	Likely Pathogenic Variant	p.E171 _S183del	5	c.513 _551del39	24

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

PATIENT: **TN26-** **PHYSICIAN:**

Predicted Human Leukocyte Antigen (HLA) Genotype Results

The predicted HLA genotype results are summarized in the table below. Please note that HLA typing via tumor tissue sequencing is not a substitute for histocompatibility testing performed using peripheral blood. It is recommended to confirm the patient's HLA type with an appropriate assay.

Gene	Method	Analyte	Genotype
MHC CLASS I			
HLA-A	Seq	DNA-Tumor	A*11:02, A*33:03
HLA-B	Seq	DNA-Tumor	B*58:01, B*35:89
HLA-C	Seq	DNA-Tumor	C*03:02, C*04:01

HLA genotypes with only one allele are either homozygous or have loss-of-heterozygosity at that position.

Biomarker	Result	Interpretation
HLA-A LOH	Negative	HLA-A loss of heterozygosity (LOH) is not detected

Immunohistochemistry Results

Biomarker	Result	Biomarker	Result
ALK	Negative | 0	PD-L1 (22c3)	Positive, TPS: 95%
ERBB2 (Her2/Neu)	Negative | Score 0	PD-L1 (SP142)	Negative, IC: 3% Negative, TC: 1+, 5%
MET	Positive | 3+, 60%		

Genes Tested with Indeterminate Results by Tumor DNA Sequencing

AKT3	CDC73	CYSLTR2	ELOC	FYN	LYN	MSH3	PMS1	PTEN	RHEB	SMARCE1	TGFBR2
APC	CDK6	DACH1	EXO1	GRIN2A	MAP2K4	NF1	POLD3	PTPRD	ROS1	SOS1	TRIM28
ARID2	CHEK1	DGCR8	FANCC	GRM3	MAP3K1	NOTCH2	POLQ	RABL3	RPA2	SPEN	TRRAP
ATM	CHEK2	DICER1	FANCL	JAK2	MDH2	NPM1	PRDM6	RAD50	RPA3	SSBP1	WRN
ATP6AP2	COL2A1	EED	FAS	KDM6A	MDM2	PARP1	PREX2	RASA1	RRAS2	STAG2	XPO1
ATR	CREBBP	EGLN1	FBXW7	KIF1B	MGA	PIK3R1	PRKD1	RB1	RUNX1	SUZ12	XRCC2
B2M	CUL3	EIF1AX	FUBP1	KMT2C	MRE11	PLCB4	PRKDC	REST	SMARCA2	TCF7L2	YES1
CBL	CYLD										

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

Genes Tested with Intermediate CNA Results by Tumor DNA Sequencing

EGFR	RAC1										

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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, variants of uncertain significance, or 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.

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Notes of Significance

SEE APPENDIX FOR DETAILS

CDx reports are generated through automated bioinformatics processing of a pre-defined list of genes and variants. Pathogenic or likely pathogenic variants identified outside the FDA-approved list will not be included in the CDx report. In addition, downgrading of variants approved by board-eligible/board-certified geneticists and pathologists may have occurred through manual variant annotation carried out by Caris' professional services. To ensure optimal coverage, multiple sequencing runs may be performed for a given case. This may account for some discrepancies observed between CDx reports and professional services.

Clinical Trials Connector ™ opportunities based on biomarker expression: 43 Targeted Therapies. See page 7 for details.

Please Note: A pathogenic nonsense mutation was detected in BRCA2. Germline pathogenic variants in this gene are causal for hereditary cancers of the breast, ovaries, pancreas, and prostate. Confirmation of the patient's carrier status should be considered.

Specimen Information

Specimen ID:

Specimen Collected:

Specimen Received:

Testing Initiated:

Test Ordered*: MI Profile™ (MI Cancer Seek™ + IHCs and Other Tests by Tumor Type)
* If the submitted specimen is inadequate, only a subset of the ordered testing may be reported.

Gross Description: 1 (A) Paraffin Block

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.

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Clinical Trials Connector™

The Clinical Trials Connector identifies clinical trials by matching reported biomarker status and tumor type to studies listed on ClinicalTrials.gov using internally curated matching logic. Trials listed below are within ~250 miles of the ordering physician's location and were active at the time this report was generated. Trial identification relies on information on http://clinicaltrials.gov/ and may be affected by missing or inaccurate trial information. Therefore, results may not include every potentially relevant study and some listed trials may not apply to an individual patient. For access to the entire list of trials matched based on biomarker and tumor type status, or to query the clinical trials connector at a later time point, visit: https://ctc.caris.ai/public/FH1__db7.

Biomarker Directed Clinical Trials

Biomarker(s)	Investigational Agent(s)	NCT ID	Study Title	Trial Phase	Locations
BRCA2	ART0380	NCT04657068	A Study of ART0380 for the Treatment of Advanced or Metastatic Solid Tumors	PHASE 1/2	Alabama (1), Tennessee (2)
	BET Bromodomain Inhibitor ZEN-3694	NCT05327010	Testing the Combination of the Anti-cancer Drugs ZEN003694 (ZEN-3694) and Talazoparib in Patients With Advanced Solid Tumors, The ComBET Trial	PHASE 2	Georgia (1)
		NCT05803382	Testing the Addition of an Anti-Cancer Drug, ZEN003694, to the Usual Chemotherapy Treatment (Capecitabine) for Metastatic or Unresectable Cancers	PHASE 1	Tennessee (2)
	AMXI-5001:Dose Escalation Phase I	NCT04503265	A Trial of AMXI-5001 for Treatment in Patients With Advanced Malignancies	PHASE 1/2	Tennessee (1)
	MOMA-313	NCT06545942	Study of Orally Administered MOMA-313 in Participants With Advanced or Metastatic Solid Tumors	PHASE 1	Tennessee (1)
	IDE-161	NCT05787587	A Study of PARG Inhibitor IDE161 in Participants With Advanced Solid Tumors	PHASE 1	Tennessee (1)
	XL309	NCT05932862	A Phase 1 Study of XL309 (ISM3091) Alone and in Combination in Participants With Advanced Solid Tumors	PHASE 1	Tennessee (1)
EGFR	osimertinib	NCT06538038	Prospective Non-Interventional Study Comparing Osimertinib +/- Chemotherapy for EGFR-Mutated NSCLC Patients	N/A	Alabama (1), Georgia (3), North Carolina (1), South Carolina (2), Tennessee (1)
	Iza-bren	NCT07100080	Study of Izalontamab Brengitecan (BMS-986507) Versus Platinum-Pemetrexed for EGFR-mutated Non-small Cell Lung Cancer After Failure of EGFR TKI Therapy (IZABRIGHT-Lung01)	PHASE 2/3	Tennessee (1)
	telisotuzumab adizutecan	NCT07155187	A Study to Assess Adverse Events and Change in Disease Activity of Intravenous (IV) Telisotuzumab Adizutecan Compared to Standard of Care in Adult Participants With Locally Advanced or Metastatic EGFR-Mutated Non-Squamous Non-Small Cell Lung Cancer	PHASE 2/3	Tennessee (2)
	amivantamab	NCT06667076	A Study of Amivantamab in Combination With Lazertinib, or Amivantamab in Combination With Platinum-Based Chemotherapy, for Common Epidermal Growth Factor Receptor (EGFR)-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)	PHASE 2	Alabama (1), Georgia (6), North Carolina (1), South Carolina (1), Tennessee (5)

Additional Clinical Trials Connector results continued on the next page. >

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Clinical Trials Connector™

Biomarker Directed Clinical Trials *(continued)*					
Biomarker(s)	**Investigational Agent(s)**	**NCT ID**	**Study Title**	**Trial Phase**	**Locations**
EGFR	Sutetinib Maleate Capsule	NCT05168566	Study to Evaluate Sutetinib Maleate Capsule in Locally Advanced or Metastatic Non-small Cell Lung Cancer	PHASE 2	Georgia (1)
		NCT06010329	A Study to Evaluate the Efficacy and Safety of Sutetinib Maleate Capsule in Locally Advanced or Metastatic NSCLC	PHASE 2	Georgia (1)
	BH-30643	NCT06706076	A Study of BH-30643 in Subjects With Locally Advanced or Metastatic NSCLC Harboring EGFR and/or HER2 Mutations	PHASE 1/2	Tennessee (1)
	TAS6417	NCT05967689	A Study of Zipalertinib in Patients With Advanced Non-Small Cell Lung Cancer With Epidermal Growth Factor Receptor (EGFR) Exon 20 Insertions or Other Uncommon Mutation.	PHASE 2	Tennessee (1)
	DB-1310	NCT05785741	A Study of DB-1310 in Advanced/Metastatic Solid Tumors	PHASE 1/2	Georgia (1), Tennessee (1)
	HER3-Dxd	NCT06172478	A Study of HER3-DXd in Subjects With Locally Advanced or Metastatic Solid Tumors	PHASE 2	Tennessee (1)
	PLB1004	NCT06046495	A Study of the Oral EGFR Inhibitor PLB1004 in Non-Small Cell Lung Cancer	PHASE 1	Tennessee (1)
	CPO301	NCT05948865	A Phase 1 Study of CPO301 in Adult Patients With Advanced or Metastatic Solid Tumors	PHASE 1	Tennessee (1)
MET	telisotuzumab adizutecan	NCT07155187	A Study to Assess Adverse Events and Change in Disease Activity of Intravenous (IV) Telisotuzumab Adizutecan Compared to Standard of Care in Adult Participants With Locally Advanced or Metastatic EGFR-Mutated Non-Squamous Non-Small Cell Lung Cancer	PHASE 2/3	Tennessee (2)
	telisotuzumab vedotin	NCT04928846	A Study to Assess Disease Activity and Adverse Events of Intravenous (IV) Telisotuzumab Vedotin Compared to IV Docetaxel in Adult Participants With Previously Treated Non-Squamous Non-Small Cell Lung Cancer (NSCLC)	PHASE 3	North Carolina (1), South Carolina (1)
		NCT06568939	A Study to Assess Adverse Events and How Intravenously (IV) Infused Telisotuzumab Vedotin (ABBV-399) Moves Through the Body as a Monotherapy in Adult Participants With Previously Treated Non-Squamous Non-Small Cell Lung Cancer (NSCLC)	PHASE 2	Georgia (3), South Carolina (2), Tennessee (1)
	cabozantinib	NCT03611595	Cabozantinib in Combination With 13-cis-Retinoic Acid in Children With Relapsed or Refractory Solid Tumors	PHASE 1	Georgia (1)

Additional Clinical Trials Connector results continued on the next page. >

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Biomarker Directed Clinical Trials *(continued)*					
Biomarker(s)	**Investigational Agent(s)**	**NCT ID**	**Study Title**	**Trial Phase**	**Locations**
PD-L1	balstilimab	NCT05572970	Expanded Access for Cancer Treatment With Balstilimab (AGEN2034) and Zalifrelimab (AGEN1884)	N/A	Alabama (1)
	PF-08046054	NCT07144280	A Study to Learn About the Study Medicine Called PF-08046054/SGN-PDL1V Versus Docetaxel in Adult Participants With Previously-Treated Programmed Cell Death Ligand 1 (PD-L1) Positive Non-Small-Cell Lung Cancer (NSCLC)	PHASE 3	Alabama (7), Tennessee (1)
		NCT05208762	A Study of PF-08046054/SGN-PDL1V in Advanced Solid Tumors	PHASE 1	Alabama (4)
	rilvegostomig	NCT06627647	A Global Phase III Study of Rilvegostomig or Pembrolizumab Plus Chemotherapy for First-Line Treatment of Metastatic Non-squamous NSCLC	PHASE 3	Tennessee (2)
		NCT06692738	A Global Phase III Study of Rilvegostomig or Pembrolizumab Plus Chemotherapy for First-Line Treatment of Metastatic Squamous Non-small Cell Lung Cancer (NSCLC)	PHASE 3	Georgia (1), Tennessee (2)
		NCT04541108	Phase 0 Master Protocol for CIVO Intratumoral Microdosing of Anti-Cancer Therapies	PHASE 1	Georgia (1), South Carolina (1)
	pumitamig	NCT07361510	A Study to Evaluate the Efficacy of Pumitamig Versus Pembrolizumab in Participants With Previously Untreated Advanced Non-Small Cell Lung Cancer and PD-L1 ≥ 50%. (ROSETTA Lung-202)	PHASE 3	Georgia (1)
		NCT07361497	A Study to Evaluate Pumitamig Versus Durvalumab Following Concurrent Chemoradiation Therapy in Participants With Unresectable Stage III Non-small Cell Lung Cancer (NSCLC) (ROSETTA Lung-201)	PHASE 3	Tennessee (1)
		NCT06712316	Safety, Efficacy, and Pharmacokinetics of BNT327 in Combination With Chemotherapy and Other Investigational Agents for Lung Cancer	PHASE 2/3	North Carolina (1), Tennessee (1)
		NCT06841055	Safety and Preliminary Efficacy of Pumitamig (BNT327), an Investigational Therapy for Patients With Non-small Cell Lung Cancer in Combination With Chemotherapy as First-line or Second-line Treatment	PHASE 2	Alabama (1)

For remaining trial matches, visit the link listed at the start of the CTC section.

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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, including all Caris molecular profiling assays. 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. In addition, certain tests have been CE-marked as a general IVD under the In Vitro Diagnostic Directive (IVDD) 98/79/EC. Offered LDTs were developed and their performance characteristics determined by Caris. Certain tests have not been cleared or approved by the FDA. 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.

All materials, documents, data, data software, information and/or inventions supplied to customers by or on behalf of Caris or created by either party relating to the services shall be and remain the sole and exclusive property of Caris. Customer shall not use or disclose the information provided by Caris through the services or related reports except in connection with the treatment of the patient for whom the services were ordered and shall not use such property for, or disseminate such property to, any third parties without expressed written consent from Caris. Customer shall deliver all such property to Caris immediately upon demand or upon Caris ceasing to provide the services. The technical and professional component of all testing was performed at the laboratory location displayed in the footer unless otherwise notated in the report.

Caris molecular testing is subject to Caris' intellectual property. Patent www.CarisLifeSciences.com/ip.

Professional Component Performed: -

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CARIS | MI CANCER SEEK

Patient

Name:
Date of Birth:
Sex:
Case Number: TN26-
CDx Report Generated:

Specimen Information

Diagnosis and Tumor Type: Adenocarcinoma, NOS, Upper lobe, lung
Specimen Site: Upper lobe, lung
Specimen ID:
Specimen Type: Formalin-fixed paraffin embedded
Specimen Collected:

Ordered By

CDx Associated Findings

Genomic Findings Detected	FDA-approved Therapeutic Options
Findings did not yield any biomarker results with Companion Diagnostic (CDx) Claims.	
EGFR exon 19 deletions	Not Detected
EGFR L858R	Not Detected
Microsatellite Instability (MSI)	Not MSI-H

Tumor Profiling Results

MI Cancer Seek is FDA-approved to provide tumor mutation profiling results for previously diagnosed oncology patients with solid tumors.

Other Alterations and Biomarkers Identified

Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapeutic product.
Confirmation of tumor mutation status using an FDA-approved CDx test is needed for therapeutic use.

Tumor Mutational Burden (TMB)	7 mut/Mb	***EGFR***	V769_D770insGVV
BRCA2	S871*	***TP53***	E171_S183del
DNMT3A	c.2083-1G>A		

CARIS | MI CANCER SEEK

MI Cancer Seek™

Intended Use:

MI Cancer Seek is a next-generation sequencing (NGS) based in vitro diagnostic (IVD) device using total nucleic acid (TNA) isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue specimens for the detection of single nucleotide variants (SNVs) and insertions and deletions (indels) in 228 genes, microsatellite instability (MSI), tumor mutational burden (TMB) in patients with previously diagnosed solid tumors, and copy number amplification (CNA) in one gene in patients with breast cancer.

MI Cancer Seek is intended as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies listed in Table 1 below, in accordance with the approved therapeutic product labeling.

Additionally, MI Cancer Seek is intended to provide tumor mutational profiling to be used by qualified healthcare professionals in accordance with professional oncology guidelines for cancer patients with previously diagnosed solid malignant neoplasms. Genomic findings other than those listed in Table 1 are not prescriptive or conclusive for labeled use of any specific therapeutic product.

Table 1. MI Cancer Seek Companion Diagnostic Indications

INDICATION	BIOMARKER	THERAPY
Breast Cancer	PIK3CA (C420R, E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R, H1047L, H1047R, H1047Y)	PIQRAY® (alpelisib)
Colorectal Cancer (CRC)	KRAS wild-type (absence of mutations in exons 2, 3, and 4) and NRAS wild-type (absence of mutations in exons 2, 3, and 4)	VECTIBIX® (panitumumab)
	BRAF V600E	BRAFTOVI® (encorafenib) in combination with ERBITUX® (cetuximab)
Melanoma	BRAF V600E	BRAF Inhibitors approved by FDA*
	BRAF V600E or BRAF V600K	MEKINIST® (trametinib) or BRAF/MEK Inhibitor Combinations approved by FDA*
Non-small cell lung cancer (NSCLC)	EGFR exon 19 deletions and exon 21 L858R alterations	EGFR Tyrosine Kinase Inhibitors approved by FDA*
Solid Tumors	MSI-H	KEYTRUDA® (pembrolizumab), JEMPERLI® (dostarlimab-gxly)
Endometrial Carcinoma	Not MSI-H	KEYTRUDA® (pembrolizumab) in combination with LENVIMA® (lenvatinib)

* For the most current information about the therapeutic products in this group, go to:

www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools#Group_Labeling

MI Cancer Seek™ is a single-site assay performed at Caris Life Sciences, Phoenix, AZ.

Contraindications:

There are no known contraindications.

Warnings and Precautions:

Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.

Limitations:

- For in vitro diagnostic use.
- CAUTION: Federal law restricts this device to sale by or on the order of a physician.
- The acceptable preparation method for MI Cancer Seek CDx specimens is FFPE. Other preparations have not been evaluated.
- The test is designed to report out somatic variants and is not intended to report germline variants.
- MI Cancer Seek requires a minimum tumor percentage of 20% for detection of alterations, with tumor content enrichment recommended for specimens with tumor percentage lower than 20%.

- Genomic findings other than those listed in the Companion Diagnostic Indications table are not prescriptive or conclusive for labeled use of any specific therapeutic product. Confirmation of tumor mutation status using an FDA-approved CDx test is needed for therapeutic use.
- A negative result does not rule out the presence of a mutation below the limits of detection of the assay.
- MI Cancer Seek is only approved for use with Caris Life Sciences pre-qualified Illumina NovaSeq 6000 instruments.
- The test is intended to be performed on specific serial number-controlled instruments by Caris Life Sciences.
- MI Cancer Seek does not report TMB for values lower than 3 mut/Mb as the accuracy of TMB values below 3 mut/Mb are unreliable.
- Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community.
- Based on the low positive percent agreement (PPA) in the accuracy study for ERBB2 copy number amplifications (CNAs) in breast cancer patients, this alteration may not be detected. Additional clinical investigation to confirm the presence of ERBB2 CNAs in the breast cancer patient's tumor with another FDA approved or cleared test is strongly recommended.
- Patients with breast cancer whose specimens have intermediate ERBB2 CNA status should be tested with another FDA approved or cleared test to ascertain ERRB2 CNA status in their tumor.
- Test may have reduced sensitivity and may yield false negative results in samples where necrotic tissue is >15%, melanin is >5%, fat cells are >10%.

Test Principle:

MI Cancer Seek is a single-site assay performed at Caris Life Sciences located at 4610 South 44th Place, Phoenix, AZ 85040. The test includes reagents, software, and procedures for testing of total nucleic acid (TNA) from formalin fixed paraffin embedded (FFPE) tumor tissue. The test uses a custom bait panel to measure all coding regions of the exome to detect and report SNVs and indels within 228 genes outlined in Table 2 across solid tumors and amplifications in ERBB2 in patients with breast cancer only. The test also detects MSI (determined from 3,210 genes) and whole exome based TMB in patients with solid tumors.

Table 2. MI Cancer Seek Reportable Gene List for SNVs and indels

ABL1	BARD1	CDH1	EP300	FAT1	H3F3B	KMT2D	MSH3	NTRK2	PRKAR1A	SDHA	STAT3
ACVR1	BCL2	CDK12	EPHA2	FBXW7	HIST1H3B	KRAS	MSH6	NTRK3	PRKDC	SDHAF2	STK11
AIP	BCL9	CDK4	ERBB2	FGFR1	HNF1A	LZTR1	MTOR	PALB2	PTCH1	SDHB	SUFU
AKT1	BCOR	CDKN1B	ERBB3	FGFR2	HOXB13	MAP2K1	MUTYH	PBRM1	PTEN	SDHC	TCF7L2
AKT2	BLM	CDKN2A	ERBB4	FGFR3	HRAS	MAP2K2	MYC	PDGFRA	PTPN11	SDHD	TERT
AKT3	BMPR1A	CHEK1	ERCC2	FGFR4	IDH1	MAP2K4	MYCN	PDGFRB	RAC1	SETD2	TET2
ALK	BRAF	CHEK2	ESR1	FH	IDH2	MAP3K1	MYD88	PIK3CA	RAD50	SF3B1	TMEM127
AMER1	BRCA1	CIC	EZH2	FLCN	IRF4	MAPK1	NBN	PIK3CB	RAD51B	SMAD2	TNFAIP3
APC	BRCA2	CREBBP	FANCA	FLT1	JAK1	MAX	NF1	PIK3R1	RAD51C	SMAD4	TNFRSF14
AR	BRIP1	CSF1R	FANCB	FLT3	JAK2	MED12	NF2	PIK3R2	RAD51D	SMARCA4	TP53
ARAF	BTK	CTCF	FANCC	FOXA1	JAK3	MEF2B	NFE2L2	PIM1	RAD54L	SMARCB1	TRAF7
ARID1A	CALR	CTNNA1	FANCD2	FOXL2	KDM5C	MEN1	NFKBIA	PMS2	RAF1	SMARCE1	TSC1
ARID2	CARD11	CTNNB1	FANCE	FUBP1	KDM6A	MET	NOTCH1	POLD1	RASA1	SMO	TSC2
ASXL1	CBFB	CXCR4	FANCF	GATA3	KDR	MITF	NPM1	POLE	RB1	SOCS1	U2AF1
ATM	CCND1	CYLD	FANCG	GNA11	KEAP1	MLH1	NRAS	POT1	RET	SOS1	VHL
ATRX	CCND2	DDR2	FANCI	GNA13	KIT	MLH3	NSD1	PPP2R1A	RHOA	SPEN	WRN
AXIN2	CCND3	DICER1	FANCL	GNAQ	KLF4	MPL	NSD2	PPP2R2A	RNF43	SPOP	WT1
B2M	CD79B	DNMT3A	FANCM	GNAS	KMT2A	MRE11	NTHL1	PRDM1	ROS1	SRC	XPO1
BAP1	CDC73	EGFR	FAS	H3F3A	KMT2C	MSH2	NTRK1	PRKACA	RUNX1	STAG2	XRCC1

FDA Evidence Levels:

Genomic findings other than those listed in the Intended Use are not prescriptive or conclusive for labeled use of any specif ic therapeutic product. Test results should be interpreted in the context of pathological evaluation of tumors, treatment history, clinical findings, and other laboratory data. The test report includes genomic findings reported in the following levels (Table 3).

Table 3. Classification Criteria for FDA Evidence Levels

LEVEL	CRITERIA
Level 1	Biomarker is FDA-approved as a companion diagnostic as part of MI Cancer Seek™
Level 2	Cancer alterations that are well-established with strong clinical evidence that the clinician must know according to professional consensus guidelines in the specific tumor type.
Level 3	Cancer alterations with potential clinical significance, e.g., biomarkers deemed useful for directing patients to a clinical trial or simply for informational purposes. i. Clinical data such as case reports, single or several case series, or Phase I/II clinical trial data that support the utility of specific biomarker alteration to direct a patient to clinical trials, or ii Pre-clinical and/or in vitro studies provide structural analysis of the mutation, fusion, or isoform to confirm pathogenicity (tumor-promoting), sensitivity, or resistance through colony forming assays, growth inhibition or drug sensitivity assays, etc.

Gene Expression

Gene	Percentile in Cancer Type	Gene	Percentile in Cancer Type	Gene	Percentile in Cancer Type
ADAM9	90	FGFR1	80	NTRK1	42
ADORA2A	48	FGFR2	18	NTRK2	10
ALK	55	FGFR3	24	NTRK3	48
ASCL1	8	FN1	85	PDCD1	50
ATM	9	FOLR1	38	PDCD1LG2	86
AURKA	61	GPC3	20	PIK3CA	16
BRAF	2	HGF	27	POU3F2	24
BRCA1	28	HRAS	36	PRAME	36
BRCA2	18	IGF1R	72	PTEN	75
BRD4	69	ITGB6	96	RB1	52
CCND1	96	KDM1A	90	RET	51
CCND2	96	KDR	44	ROR1	76
CCNE1	50	KEAP1	78	ROR2	61
CD274	80	KRAS	12	ROS1	76
CD276	91	LAG3	50	SLFN11	42
CDH17	19	MAGEA4	15	SRC	69
CDH3	96	MDM2	9	SSTR2	50
CDH6	14	MET	77	SSTR3	22
CDKN2A	18	MKI67	42	SSTR5	10
CEACAM5	48	MSLN	42	STK11	67
CLDN18	48	MTAP	32	TACSTD2	72
CLDN4	81	MTOR	43	TGFB1	90
CLDN6	26	MUC1	68	TNFRSF1B	84
CTLA4	64	MUC16	51	TOP1	5
DLL3	22	MYC	54	TP53	83
EGFR	98	NECTIN4	16	TSC1	73
EPHA2	88	NEUROD1	32	TSC2	47
EPHA5	86	NF1	10	VEGFA	88
ERBB2	32	NRAS	18	XPO1	30
ERBB3	30	NRG1	24	YAP1	72

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Gene Expression of Selected Genes by Whole Transcriptome Sequencing (WTS) Methods:
Gene expression is derived from whole transcriptome sequencing. Relative expression of genes are calculated as normalized values using Transcripts per Million Molecules or TPM. TPM is presented as a percentile derived by comparison to a distribution of Caris' internal cohort of the tumor-type profiled. Selected genes reported in this section were chosen based on their tumor-type specific relevance for matching to clinical trials, or tumor type subclassification.

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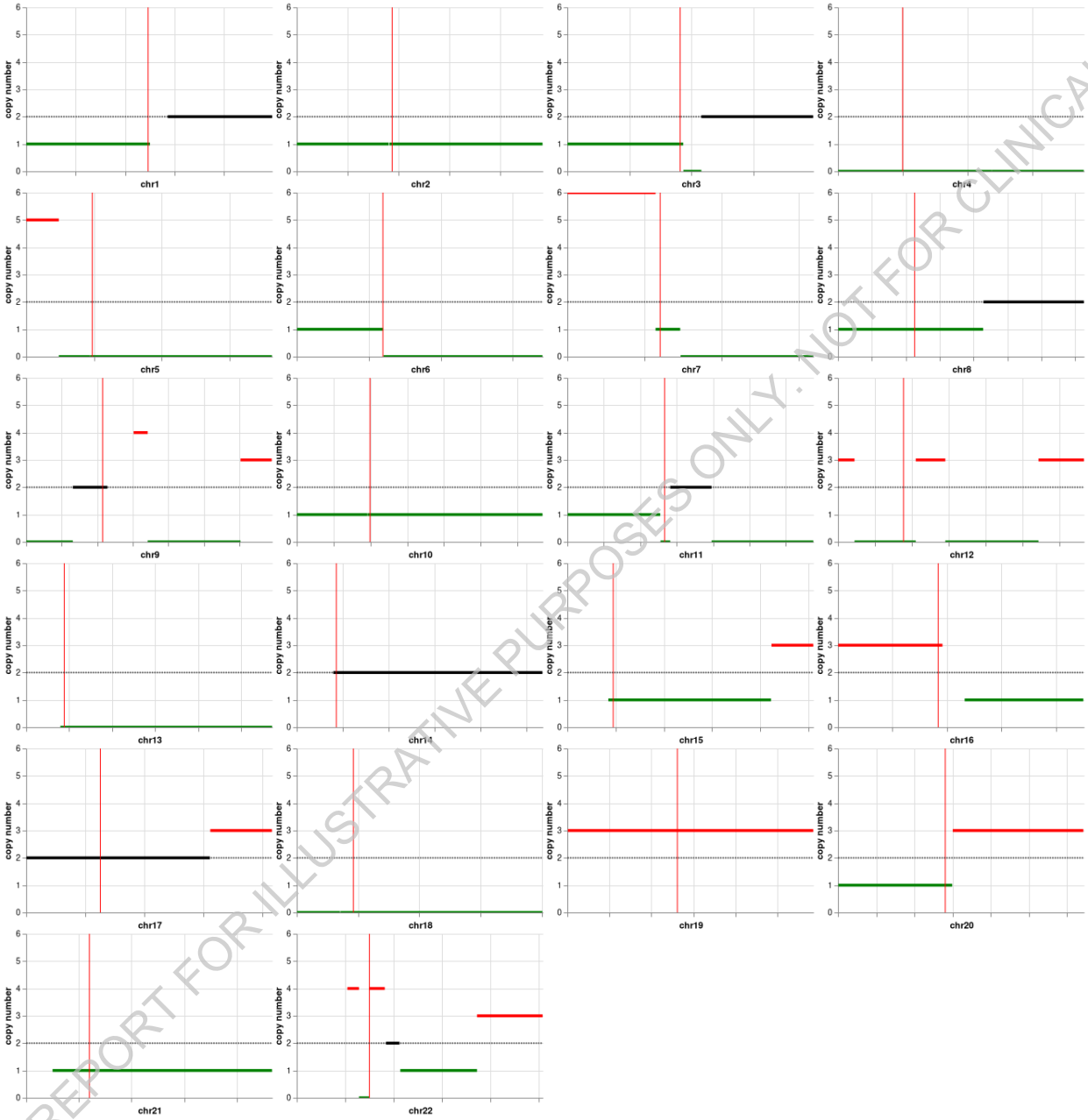
Karyotype



Karyotyping using Copy Number Analysis by Whole Exome Sequencing (WES) Methods:
Whole exome sequencing in combination with interrogation of single nucleotide polymorphisms (SNPs) tiled throughout the genome, allows for the identification and visualization of cytogenetic aberrations.

Somatic structural variants like whole or partial chromosome duplications or deletions, are important for cancer development and progression, and may identify clinically actionable alterations.

PATIENT:	TN26-	PHYSICIAN:

Mutational Analysis by Next-Generation Sequencing (NGS)

TUMOR MUTATIONAL BURDEN	
Mutations / Megabase	**Result**
7	Low

TMB

Tumor Mutational Burden (TMB) is defined as the number of somatic non-synonymous mutations per million bases of sequenced DNA in a tumor sample. Tumors with high TMB may increase the number of neoantigens which is hypothesized to increase T-cell reactivity and potential for response to immune checkpoint inhibitors. TMB analysis was performed based on next generation sequencing analysis of genomic DNA isolated from a tumor sample.

MICROSATELLITE INSTABILITY ANALYSIS	
Test	**Result**
MSI	Stable

MSI

Microsatellite instability (MSI) status is a measure of the number of somatic mutations with in short, repeated sequences of DNA (microsatellites). MSI-High status can indicate that the tumor has a defect in mismatch repair (MMR) abrogating the ability to correct mistakes during DNA replication. Tumors with MSI-high status may increase the number of neoantigens which is hypothesized to increase T-cell reactivity and potential for response to immune checkpoint inhibitors. Tumor-only microsatellite instability status by NGS (MSI-NGS) is measured by the direct analysis of known microsatellite regions sequenced in the CMI NGS panel.

GENOMIC LOSS OF HETEROZYGOSITY	
Test	**Result**
Genomic Loss of Heterozygosity (LOH)	Equivocal - 12% of tested genomic segments exhibited LOH (assay threshold is ≥ 16%)

LOH

To calculate genomic loss-of-heterozygosity (LOH), the 22 autosomal chromosomes are split into 552 segments and the LOH of single nucleotide polymorphisms (SNPs) within each segment is calculated. Caris WES data consist of approximately 250k SNPs spread across the genome. SNP alleles with frequencies skewed towards 0 or 100% indicate LOH (heterozygous SNP alleles have a frequency of 50%). The final call of genomic LOH is based on the percentage of all 552 segments with observed LOH.

Additional Next-Generation Sequencing results continued on the next page. >

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Mutational Analysis by Next-Generation Sequencing (NGS)

MUTATIONAL SIGNATURES	
Test	**Result**
Tobacco Airway Signature	Not Detected

MUTATIONAL SIGNATURES

Mutational signatures are characteristic patterns of somatic mutations that reflect underlying mutational processes driven by endogenous mechanisms or environmental exposures. Signatures are used clinically to inform tumor etiology and support diagnostic interpretation. Signature definitions and interpretation follow the Catalogue of Somatic Mutations in Cancer (COSMIC) database framework (PMIDs 30371878, 32025018). For each tumor, mutational data is decomposed into contributions from known signatures, yielding a per-signature contribution score. A signature is reported as "Detected" when all the following are met: TMB ≥ 5 mut/Mb, contribution score ≥ 0.4, and model reconstruction accuracy ≥ 0.85. A result of "Not Detected" indicates that the signature's contribution did not meet thresholds but does not exclude a minor contribution.

Signatures were validated to support diagnostic use:

Tobacco Airway: Sensitivity 26.5%, Specificity 99.9%, PPV 99.2%

Additional Next-Generation Sequencing results continued on the next page. >

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Mutational Analysis by Next-Generation Sequencing (NGS)

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
BRCA2	DNA-Tumor	Pathogenic Variant	p.S871*	11	c.2612C>G	66	NM_000059.3

Interpretation: A pathogenic nonsense mutation was detected in BRCA2. Germline pathogenic variants in this gene are causal for hereditary cancers of the breast, ovaries, pancreas, and prostate.

BRCA2 or breast cancer type 2 susceptibility gene encodes a protein involved in cell growth, cell division, and DNA-damage repair. It is a tumor suppressor gene which plays an important role in mediating double-strand DNA breaks by homologous recombination (HR). Tumors with BRCA2 mutation may be more sensitive to platinum agents and PARP inhibitors.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
DNMT3A	DNA-Tumor	Pathogenic Variant	c.2083-1G>A	18	c.2083-1G>A	25	NM_022552.4

Interpretation: A pathogenic mutation that disrupts an intron splice site was detected in DNMT3A

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
EGFR	DNA-Tumor	Pathogenic Variant	p.V769_D770 insGVV	20	c.2308 _2309 ins9	35	NM_005228.4

Interpretation: A pathogenic exon 20 insertion 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
TP53	DNA-Tumor	Likely Pathogenic Variant	p.E171 _S183del	5	c.513 _551del39	24	NM_000546.5

Interpretation: An inframe deletion mutation was found in TP53. This mutation deletes several amino acids that have been found to be frequently mutated in cancer, therefore, is presumed pathogenic.

TP53, or p53, plays a central role in modulating response to cellular stress through transcriptional regulation of genes involved in cell-cycle arrest, DNA repair, apoptosis, and senescence. Inactivation of the p53 pathway is essential for the formation of the majority of human tumors. Mutation in p53 (TP53) remains one of the most commonly described genetic events in human neoplasia, estimated to occur in 30-50% of all cancers. Generally, presence of a disruptive p53 mutation is associated with a poor prognosis in all types of cancers, and diminished sensitivity to radiation and chemotherapy. Germline p53 mutations are associated with the Li-Fraumeni syndrome (LFS) which may lead to early-onset of several forms of cancer currently known to occur in the syndrome, including sarcomas of the bone and soft tissues, carcinomas of the breast and adrenal cortex (hereditary adrenocortical carcinoma), brain tumors and acute leukemias.

Additional Next-Generation Sequencing results continued on the next page. >

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Mutational Analysis by Next-Generation Sequencing (NGS)

GENES TESTED WITH INDETERMINATE* RESULTS BY TUMOR DNA SEQUENCING					
AKT3	CYLD	FYN	NF1	RABL3	SSBP1
APC	CYSLTR2	GRIN2A	NOTCH2	RAD50	STAG2
ARID2	DACH1	GRM3	NPM1	RASA1	SUZ12
ATM	DGCR8	JAK2	PARP1	RB1	TCF7L2
ATP6AP2	DICER1	KDM6A	PIK3R1	REST	TGFBR2
ATR	EED	KIF1B	PLCB4	RHEB	TRIM28
B2M	EGLN1	KMT2C	PMS1	ROS1	TRRAP
CBL	EIF1AX	LYN	POLD3	RPA2	WRN
CDC73	ELOC	MAP2K4	POLQ	RPA3	XPO1
CDK6	EXO1	MAP3K1	PRDM6	RRAS2	XRCC2
CHEK1	FANCC	MDH2	PREX2	RUNX1	YES1
CHEK2	FANCL	MDM2	PRKD1	SMARCA2	
COL2A1	FAS	MGA	PRKDC	SMARCE1	
CREBBP	FBXW7	MRE11	PTEN	SOS1	
CUL3	FUBP1	MSH3	PTPRD	SPEN	

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

For a complete list of genes tested, visit www.CarisMolecularIntelligence.com/profilemenu.

NGS Methods

Direct sequence analysis was performed on genomic DNA isolated from a micro-dissected tumor sample using Illumina NovaSeq 6000 sequencers. A hybrid pull-down panel of baits was used to enrich more than 700 clinically relevant genes along with > 20,000 other genes. Sequence data is analyzed using a customized bioinformatics pipeline to detect sequencing variants, copy number alterations (amplifications and deletions) indels and predicted HLA genotypes, including copy number estimation of HLA LOH. In addition, genomic signatures for tumor mutational burden (TMB), microsatellite instability (MSI), genomic loss-of-heterozygosity (LOH) or HRD-Genomic Scar Score (HRD-GSS), and homologous recombination deficiency (HRD) are reported when applicable. For a complete list of what is covered by the assay, and genes with partial coverage, please contact Caris Customer Support.

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Copy Number Alterations by Next-Generation Sequencing (NGS)

GENES TESTED WITH INTERMEDIATE CNA RESULTS					
EGFR	RAC1				

GENES WITH INDETERMINATE CNA RESULTS					
AFDN	CDKN1B	ETV6	JAK2	PDCD1LG2	SMAD4
ARID1B	CDKN2A	EZR	KRAS	PRDM1	SMARCA2
BCL2	CDX2	FGFR1OP	LHFPL6	RB1	TNFAIP3
BRCA2	ECT2L	FLT1	MLLT3	ROS1	WISP3
CD274 (PD-L1)	ERCC5	FLT3	MYB	SETBP1	ZNF521
CDK8	ESR1	FOXO1	NFIB	SMAD2	

CNA Methods

The copy number alteration (CNA) of each exon is determined by a calculation using the average sequencing depth of the sample along with the sequencing depth of each exon and comparing this calculated result to a pre-calibrated value. A complete list of genes for reporting copy number alterations, including amplifications and deletions, is available upon request.

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Gene Fusion and Transcript Variant Detection by RNA Sequencing

Whole Transcriptome Sequencing (WTS) Methods

Gene fusion and variant transcript detection were performed on RNA isolated from a tumor sample using next generation sequencing. The assay also detects fusions occurring at known and novel breakpoints within genes. The genes included in this report represent the subset of genes associated with cancer. The complete list of unclassified alterations is available by request.

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Protein Expression by Immunohistochemistry (IHC)

Biomarker	Patient Tumor			Thresholds
	Staining Intensity (0, 1+, 2+, 3+)	Percent of cells	Result	Conditions for a Positive Result:
ALK	0	100	Negative	Intensity ≥3+ and ≥1% of cells stained
MET	3 +	60	Positive	Intensity ≥3+ and ≥50% of cells stained

PD-L1 TUMOR CELL STAINING				
Biomarker	Patient Tumor			Thresholds
	Staining Intensity (0, 1+, 2+, 3+)	Percent of cells	Result	Conditions for a Positive Result:
PD-L1 (SP142)	1 +	5%	Negative	Intensity ≥1+ and ≥50% of cells stained

PD-L1 (28-8): Scoring was based on percentage of viable tumor cells showing partial or complete membrane staining at any intensity.
PD-L1 (SP142): TC scoring was based on the presence of discernible PD-L1 membrane staining of any intensity in ≥ 50% of viable tumor cells.
PD-L1 (SP263): Scoring was based on percentage of viable tumor cells showing partial or complete membrane staining at any intensity.

PD-L1 TUMOR PROPORTION SCORE (TPS)			
Biomarker	Result	TPS	Threshold
PD-L1 (22c3)	Positive	95%	TPS ≥1 %

PD-L1 22c3: Scoring was based on the percentage of viable tumor cells showing partial or complete membrane staining. In non-small cell lung cancer, there are three categories of expression defined, TPS < 1% (negative), TPS ≥ 1% and TPS ≥ 50%. Thresholds for clinical interpretation of PD-L1 TPS in other tumor types have not been established.

Her-2 IHC: Biopsy	
Final Score	Threshold for Positive Result
Negative | Score 0	Intensity =3+ and ≥5 tumor cells staining

PD-L1 IMMUNE CELL (IC) SCORE			
Biomarker	Result	IC	Threshold
PD-L1 (SP142)	Negative	3%	≥10%

PD-L1 (SP142): IC scoring was based on discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering ≥ 10% of tumor area occupied by tumor cells, associated intratumoral or contiguous peritumoral stroma.

Clones used: ALK (D5F3), ERBB2 (Her2/Neu) (4B5), MET (SP44), PD-L1 (22c3), PD-L1 (SP142).

Additional IHC results continued on the next page. >

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Protein Expression by Immunohistochemistry (IHC)

IHC Methods

The Laboratory Developed Tests (LDT) immunohistochemistry (IHC) assays were developed and their performance characteristics determined by Caris Life Sciences. These tests have not been cleared or approved by the US Food and Drug Administration. The FDA has determined that such clearance or approval is not currently necessary. Interpretations of all immunohistochemistry (IHC) assays were performed manually or with the assistance of an AI-based image analysis tool by a board certified pathologist using a microscope and/or digital whole slide image(s).

The following IHC assays were performed using FDA-approved companion diagnostic or FDA-cleared tests consistent with the manufacturer's instructions: ALK (VENTANA ALK (D5F3) CDx Assay, Ventana), ER (CONFIRM anti-Estrogen Receptor (ER) (SP1), Ventana), FOLR1 (VENTANA FOLR1-2.1 RxDx, Ventana), CLDN18 (VENTANA, 43-14A RxDx Assay, Gastric/GEJ), PR (CONFIRM anti-Progesterone Receptor (PR) (1E2), Ventana), HER2/neu (PATHWAY anti-HER-2/neu (4B5), Ventana), Ki-67 (MIB-1 pharmaDx, Dako), MAGE-A4 1F9 (pharmDx, Dako), MET (VENTANA, SP44, RxDx Assay), PD-L1 22c3 (pharmDx, Dako), PD-L1 SP142 (VENTANA, non-small cell lung cancer), PD-L1 28-8 (pharmDx, Dako, Gastric/GEJ, non-small cell lung cancer), PD-L1 SP263 (Ventana, non-small cell lung cancer), and Mismatch Repair (MMR) proteins (MLH1, MSH2, MSH6, and PMS2; VENTANA MMR RxDx Panel, Ventana).

HER2 results and interpretation follow the ASCO/CAP scoring criteria. Bartley, A.N., J.A. Ajani, et al. (2016). "HER2 testing and clinical decision making in gastroesophageal adenocarcinoma: guideline from the College of American Pathologists, American Society for Clinical Pathology, and the American Society of Clinical Oncology". J Clin Oncol. 35(4):446-464.

Professional Component Performed:

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References

#	Drug	Biomarker	Reference
1	alectinib	ALK	Camidge, D.R., A.T. Shaw, et al. (2019). "Updated Efficacy and Safety Data and Impact of the EML4-ALK Fusion Variant on the Efficacy of Alectinib in Untreated ALK-Positive Advanced Non–Small Cell Lung Cancer in the Global Phase III ALEX Study." J Thorac Oncol 14(7): 1233-1243. View Citation Online
2	alectinib	ALK	Gadgeel, S., D.R. Camidge, et al. (2018). "Alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive (ALK+) non-small-cell lung cancer: CNS efficacy results from the ALEX study." Ann Oncol 29 (11): 2214-2222. View Citation Online
3	alectinib, brigatinib, ceritinib, crizotinib, lorlatinib	ALK	Lindeman, N.I., Y. Yatabe, et al. (2018). "Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology." J Thorac Oncol 13(3): 323-358. View Citation Online
4	alectinib, brigatinib, ceritinib, crizotinib, lorlatinib	ALK	National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer Version 1.2020
5	brigatinib	ALK	Camidge, D.R., S. Popat, et al. (2018). "Brigatinib versus Crizotinib in ALK-Positive Non-Small-Cell Lung Cancer." N Engl J Med 379(21): 2027-2039. View Citation Online
6	brigatinib	ALK	Lin, J.L., G.J. Riely, et al. (2018). "Brigatinib in Patients with Alectinib-refractory ALK-positive NSCLC." J Thorac Onc 13(10): 1530-1538. View Citation Online
7	brigatinib	ALK	Reckamp, K., J. Lee, et al. (2019). "Comparative efficacy of brigatinib versus ceritinib and alectinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non-small cell lung cancer." Curr Med Res Opin 35(4):569-576. View Citation Online
8	brigatinib, crizotinib	ALK	Thorne-Nuzzo, T., P. Towne, et al. (2017). "A Sensitive ALK Immunohistochemistry Companion Diagnostic Test Identifies Patients Eligible for Treatment with Crizotinib." J Thorac Oncol 12(5): 804-813 View Citation Online
9	ceritinib, lorlatinib	ALK	Shaw, A.T., E. Felip, et al. (2017). "Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial." Lancet Oncol 18 (7):874-886. View Citation Online
10	ceritinib, lorlatinib	ALK	Solomon, B. J., A. T. Shaw, et al. (2018). "Lorlatinib in patients with ALK-positive non-small cell lung cancer: results from a global phase 2 study." Lancet Oncol 19:1654-1667. View Citation Online
11	ceritinib, lorlatinib	ALK	Soria, J.C., de Castro G., et al. (2017). "First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study." Lancet 389: 917-929. View Citation Online
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