Patient

Name:
Date of Birth:
Sex: Female
Case Number: TN23-
Diagnosis: Carcinoma, metastatic, NOS

Specimen Information

Primary Tumor Site: Lower lobe, lung
Specimen Site: Mediastinal lymph node
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: 80%**	**BENEFIT**	**cemiplimab, pembrolizumab**	**Level 1**
PD-L1 (28-8)	**IHC**	**Protein**	**Positive | 1+, 60%**	**BENEFIT**	**nivolumab/ipilimumab combination**	**Level 1**
PD-L1 (SP263)	**IHC**	**Protein**	**Positive, TC: 1+, 60%**	**BENEFIT**	**atezolizumab (adjuvant)**	**Level 1**
KRAS	**Seq**	**DNA-Tumor**	**Pathogenic Variant Exon 2 | p.G12C**	**BENEFIT**	**adagrasib, sotorasib**	**Level 2**
				LACK OF BENEFIT	erlotinib, gefitinib	Level 2
TMB	**Seq**	**DNA-Tumor**	**High, 14 mut/Mb**	**BENEFIT**	**pembrolizumab**	**Level 2**
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 and trametinib combination therapy, vemurafenib	Level 2
EGFR	Seq	DNA-Tumor	Mutation Not Detected	LACK OF BENEFIT	erlotinib, gefitinib	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	Level 2
MET	CNA-Seq	DNA-Tumor	Amplification Not Detected	LACK OF BENEFIT	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.

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Important Note

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.

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

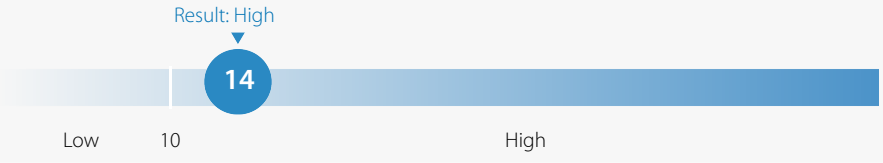
MI GPSai was performed on this case. Please see *Page 5* for results.

Cancer-Type Relevant Biomarkers

Biomarker	Method	Analyte	Result
IDH1	**Seq**	**DNA-Tumor**	**Pathogenic Variant Exon 4 | p.R132C**
MSI	Seq	DNA-Tumor	Stable
Mismatch Repair Status	IHC	Protein	Proficient (Intact)
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	CNA-Seq	DNA-Tumor	Deletion Not Detected
	Seq	DNA-Tumor	Mutation Not Detected
KRAS	CNA-Seq	DNA-Tumor	Amplification Not Detected
MET	Seq	RNA-Tumor	Variant Transcript Not Detected

Biomarker	Method	Analyte	Result
MTAP	CNA-Seq	DNA-Tumor	Deletion Not Detected
NFE2L2	CNA-Seq	DNA-Tumor	Deletion Not Detected
	Seq	DNA-Tumor	Mutation Not Detected
NRG1	Seq	RNA-Tumor	Fusion Not Detected
PD-L1 (SP142)	IHC	Protein	Negative, IC: 5% Negative, TC: 1+, 10%
PTEN	IHC	Protein	Positive | 1+, 90%
	CNA-Seq	DNA-Tumor	Deletion Not Detected
RB1	CNA-Seq	DNA-Tumor	Deletion Not Detected
	Seq	DNA-Tumor	Mutation Not Detected
STK11	CNA-Seq	DNA-Tumor	Deletion Not Detected
	Seq	DNA-Tumor	Mutation Not Detected
TP53	CNA-Seq	DNA-Tumor	Deletion Not Detected
	Seq	DNA-Tumor	Mutation Not Detected

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	Low - 4% of tested genomic segments exhibited LOH (assay threshold is ≥ 16%)

PATIENT: **TN23-** **PHYSICIAN:**

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Genes Tested with Pathogenic or Likely Pathogenic Alterations

Gene	Method	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %
ARID1A	Seq	DNA-Tumor	Pathogenic Variant	p.Y788*	7	c.2364C>A	24
IDH1	Seq	DNA-Tumor	Pathogenic Variant	p.R132C	4	c.394C>T	45
JAK2	Seq	DNA-Tumor	Pathogenic Variant	c.2762-1G>C	21	c.2762-1G>C	15
KMT2C	Seq	DNA-Tumor	Pathogenic Variant	p.Q1719*	35	c.5155C>T	44
KRAS	Seq	DNA-Tumor	Pathogenic Variant	p.G12C	2	c.34G>T	44

Unclassified alterations for DNA 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

Gene	Method	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %
ATM	Seq	DNA-Tumor	Variant of Uncertain Significance	p.E2499G	50	c.7496A>G	51

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.

Gene	Method	Analyte	Genotype
MHC CLASS I			
HLA-A	Seq	DNA-Tumor	A*03:01, A*31:01
HLA-B	Seq	DNA-Tumor	B*07:02, B*40:01
HLA-C	Seq	DNA-Tumor	C*03:04, C*07:02

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

PATIENT: **TN23-** **PHYSICIAN:**

Immunohistochemistry Results

Biomarker	Result	Biomarker	Result
ALK	Negative | 0	PD-L1 (28-8)	Positive | 1+, 60%
Mismatch Repair Status	Proficient (Intact)	PD-L1 (SP142)	Negative, IC: 5% Negative, TC: 1+, 10%
MLH1	Intact nuclear expression	PD-L1 (SP263)	Positive, TC: 1+, 60%
MSH2	Intact nuclear expression	PMS2	Intact nuclear expression
MSH6	Intact nuclear expression	PTEN	Positive | 1+, 90%
PD-L1 (22c3)	Positive, TPS: 80%		

Genes Tested with Indeterminate Results by Tumor DNA Sequencing

ACVR1B	COL2A1	MED12	NPM1	PIK3R2	PRKACA	PTPN11	RAC1	RASA1	STAG2	TRAF7	XRCC1
AXIN1	ELOC	NOTCH3	PIK3CB	PLCB4							

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.

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MI GPSai™

The MI GPSai™ (MI Genomic Prevalence Score - Artificial Intelligence) is a cancer-type similarity assessment which compares the characteristics of a patient's tumor against other tumors in the Caris database. MI GPSai analyzes a tumor's molecular signature and provides the prevalence of that signature in the Caris Life Sciences genomic and transcriptomic database across 21 distinct cancer categories.

Cancer Category	Prevalence
Lung Adenocarcinoma	99 %
Squamous Cell Carcinoma	<1 %
Breast Adenocarcinoma	0 %
Central Nervous System Cancer	0 %
Cervical Adenocarcinoma	0 %
Cholangiocarcinoma	0 %
Colon Adenocarcinoma	0 %
Gastroesophageal Adenocarcinoma	0 %
GIST	0 %
Hepatocellular carcinoma	0 %
Melanoma	0 %
Meningioma	0 %
Ovarian, Fallopian Tube Adenocarcinoma	0 %
Ovarian Granulosa Cell Tumor	0 %
Pancreas Adenocarcinoma	0 %
Prostate Adenocarcinoma	0 %
Renal Cell Carcinoma	0 %
Thyroid Cancer	0 %
Urothelial Carcinoma	0 %
Uterine Endometrial Adenocarcinoma	0 %
Uterine Sarcoma	0 %

Methods

MI GPSai™ is a machine learning platform that was trained on genomic data from 34,352 cases and transcriptomic data from over 11,000 cases. In a validation set of over 12,000 additional cases, MI GPSai accurately predicted the cancer category in the labeled data set with an accuracy of over 93%. The accuracy increased to 97% when the second highest ranking predicted cancer type was included. The profile has been validated to differentiate among 21 distinct cancer types. MI GPSai prevalence tables were produced at or above the required confidence level for 93% of samples in the validation set. Samples that do not generate a score at or above this confidence level will not receive a MI GPSai result.

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Notes of Significance

SEE APPENDIX FOR DETAILS

Clinical Trials Connector ™ opportunities based on biomarker expression: 14 Chemotherapy Trials | 773 Targeted Therapy Trials. See page 7 for details.

Specimen Information

Specimen ID:

Specimen Collected:

Specimen Received:

Testing Initiated:

Gross Description: 1 (A) Paraffin Block - Client ID

Pathologic Diagnosis: Nodes, level VII #3, biopsy: Multiple fragments of soft tissue containing carcinoma as well as one lymph node containing metastatic carcinoma (1/1).

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™

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.

CHEMOTHERAPY CLINICAL TRIALS (14)				
Drug Class	**Biomarker**	**Method**	**Analyte**	**Investigational Agent(s)**
Alkylating agents (9)	IDH1	NGS	DNA-Tumor	dacarbazine, temozolomide
Hypomethylating agents (5)	IDH1	NGS	DNA-Tumor	azacitidine, decitabine

TARGETED THERAPY CLINICAL TRIALS (773)				
Drug Class	**Biomarker**	**Method**	**Analyte**	**Investigational Agent(s)**
ATR inhibitors (18)	ARID1A	NGS	DNA-Tumor	AZD6738, BAY1895344, berzosertib
BET bromodomain inhibitors (3)	ARID1A	NGS	DNA-Tumor	CPI-0610, tazemetostat
Dual IDH1/2 inhibitors (1)	IDH1	NGS	DNA-Tumor	HMPL-306
ERK inhibitors (5)	KRAS	NGS	DNA-Tumor	LY3214996, pexmetinib, ulixertinib
Glutaminase Inhibitor (4)	IDH1	NGS	DNA-Tumor	DRP-104, IPN60090, telaglenastat
IDH1 inhibitors (2)	IDH1	NGS	DNA-Tumor	LY3410738, ivosidenib
Immunomodulatory agents (619)	TMB	NGS	DNA-Tumor	INBRX-105, M7824, MGD019, atezolizumab, avelumab, camrelizumab, cemiplimab, dostarlimab, durvalumab, efineptakin alfa, ipilimumab, nivolumab, pembrolizumab, retifanlimab, sintilimab, spartalizumab, tislelizumab, toripalimab, tremelimumab
	PD-L1	IHC	Protein	
JAK2-targeted therapy (1)	JAK2	NGS	DNA-Tumor	pacritinib
JAK inhibitors (2)	JAK2	NGS	DNA-Tumor	ruxolitinib
KRAS G12C inhibitors (23)	KRAS	NGS	DNA-Tumor	GDC-6036, adagrasib, sotorasib
MEK inhibitors (36)	KRAS	NGS	DNA-Tumor	binimetinib, mirdametinib, selumetinib, trametinib
PARP inhibitors (51)	IDH1	NGS	DNA-Tumor	2X-121, BGB-290, niraparib, olaparib, pamiparib, rucaparib, talazoparib, veliparib
	ARID1A	NGS	DNA-Tumor	

( ) = 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.

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

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TARGETED THERAPY CLINICAL TRIALS (773)				
Drug Class	**Biomarker**	**Method**	**Analyte**	**Investigational Agent(s)**
SHP2 inhibitors (8)	KRAS	NGS	DNA-Tumor	RLY-1971, RMC-4630, TNO155

( ) = 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, 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.

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Electronic Signature

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Gene Expression

Gene	TPM | Percentile in Cancer Type	Gene	TPM | Percentile in Cancer Type	Gene	TPM | Percentile in Cancer Type
ALK	<1 | 3	EZH2	9 | 28	NRG1	2 | 34
AURKA	4 | 15	FGFR1	56 | 54	NTRK1	<1 | 35
AXL	13 | 74	FGFR3	<1 | 14	NTRK2	2 | 50
BRAF	27 | 47	HGF	4 | 30	NTRK3	<1 | 14
CCND1	840 | 75	IGF1R	24 | 24	PTEN	58 | 34
CCND2	11 | 63	KEAP1	12 | 34	RET	<1 | 18
CCND3	11 | 24	KL	<1 | 28	ROR1	4 | 55
CCNE1	<1 | 14	KRAS	34 | 60	ROS1	50 | 82
CD274	11 | 67	LAG3	<1 | 40	SMARCB1	29 | 37
CD276	24 | 73	MAPRE1	11 | 35	STK11	1 | 43
CD38	3 | 36	MCL1	17 | 26	TACSTD2	73 | 50
CDKN2A	9 | 51	MDM2	152 | 73	TF	<1 | 13
CDR1	59 | 26	MET	121 | 70	TNFRSF10B	42 | 78
EGFR	24 | 38	MSLN	60 | 82	TNFRSF9	2 | 68
EPHA2	28 | 60	MTAP	5 | 31	TP53	33 | 26
ERBB2	95 | 96	MUC1	801 | 94	XPO1	120 | 39
ERBB3	60 | 58	MYC	8 | 42		

Gene Expression of Selected Genes by Whole Transcriptome Sequencing (WTS) Methods:
Gene expression is derived from whole transcriptome sequencing. Relative expression of genes are presented as normalized values using Transcripts per Million Molecules or TPM. If available, TPM values are accompanied by 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:	TN23-	PHYSICIAN:

Mutational Analysis by Next-Generation Sequencing (NGS)

TUMOR MUTATIONAL BURDEN	
Mutations / Megabase	**Result**
14	High

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 within 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)	Low - 4% 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)

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
ARID1A	DNA-Tumor	Pathogenic Variant	p.Y788*	7	c.2364C>A	24	NM_006015.5

Interpretation: A pathogenic mutation was detected in ARID1A.

This gene encodes a member of the SWI/SNF family, whose members have helicase and ATPase activities and are thought to regulate transcription of certain genes by altering the chromatin structure around those genes. Inactivating mutations of ARID1A, a member of the SWI/SNF chromatin-remodeling complex, have been identified in a long list of cancers, including ovarian clear-cell carcinoma, gastric, hepatocellular, breast and so on. Mutational and functional data suggest ARID1A is a bona fide tumor suppressor. ARID1A may contribute to tumor suppression via effects on the SWI/SNF complex, control of cell proliferation and differentiation, and/or effects on histone ubiquitylation.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
ATM	DNA-Tumor	Variant of Uncertain Significance	p.E2499G	50	c.7496A>G	51	NM_000051.3

Interpretation: A variant with no known clinical or functional significance was detected in ATM.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
IDH1	DNA-Tumor	Pathogenic Variant	p.R132C	4	c.394C>T	45	NM_005896.3

Interpretation: A gain of function IDH1 mutation was detected in this sample. Tumors with this mutation tend to exhibit hypermethylation secondary to an accumulation of D-2-hydroxyglutarate. High concentrations of D-2-hydroxyglutarate inhibit alpha-ketoglutarate-dependent enzymes such as histone lysine demethylases (PMID: 269207730, 20171147).

IDH1 encodes for isocitrate dehydrogenase in cytoplasm and is found to be mutated in 60-90% of secondary gliomas, 75% of cartilaginous tumors, 17% of thyroid tumors, 15% of cholangiocarcinoma, 12-18% of patients with acute myeloid leukemia, 5% of primary gliomas, 3% of prostate cancer, as well as in less than 2% in paragangliomas, colorectal cancer and melanoma. Mutated IDH1 results in impaired catalytic function of the enzyme, thus altering normal physiology of cellular respiration and metabolism. IDH1 mutation can also cause overproduction of onco-metabolite 2-hydroxy-glutarate, which can extensively alter the methylation profile in cancer.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
JAK2	DNA-Tumor	Pathogenic Variant	Intron Splice Variant	21	c.2762-1G>C	15	NM_004972.3

Interpretation: A pathogenic mutation that disrupts an intron splice site was detected in JAK2

JAK2 or Janus kinase 2 is a part of the JAK/STAT pathway which mediates multiple cellular responses to cytokines and growth factors including proliferation and cell survival. It is also essential for numerous developmental and homeostatic processes, including hematopoiesis and immune cell development. Mutations in the JAK2 kinase domain result in constitutive activation of the kinase and the development of chronic myeloproliferative neoplasms such as polycythemia vera (95%), essential thrombocythemia (50%) and myelofibrosis (50%). JAK2 mutations were also found in BCR-ABL1-negative acute lymphoblastic leukemia patients and the mutated patients show a poor outcome.Germline mutations in JAK2 have been associated with myeloproliferative neoplasms and thrombocythemia.

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
KMT2C	DNA-Tumor	Pathogenic Variant	p.Q1719*	35	c.5155C>T	44	NM_170606.2

Interpretation: A pathogenic mutation was detected in KMT2C.

This gene is a member of the myeloid/lymphoid or mixed-lineage leukemia (MLL) family and encodes a nuclear protein with an AT hook DNA-binding domain, a DHHC-type zinc finger, six PHD-type zinc fingers, a SET domain, a post-SET domain and a RING-type zinc finger. This protein is a member of the ASC-2/NCOA6 complex (ASCOM), which possesses histone methylation activity and is involved in transcriptional coactivation.

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
KRAS	DNA-Tumor	Pathogenic Variant	p.G12C	2	c.34G>T	44	NM_004985.4

Interpretation: A pathogenic codon 12 mutation was detected in KRAS.

KRAS or V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog encodes a signaling intermediate involved in many signaling cascades including the EGFR pathway. KRAS somatic mutations have been found in pancreatic (57%), colon (35%), lung (16%), biliary tract (28%), and endometrial (15%) cancers. Several germline mutations of KRAS (V14I, T58I, and D153V amino acid substitutions) are associated with Noonan syndrome.

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					
ACVR1B	ELOC	NPM1	PLCB4	RAC1	TRAF7
AXIN1	MED12	PIK3CB	PRKACA	RASA1	XRCC1
COL2A1	NOTCH3	PIK3R2	PTPN11	STAG2	

*** 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 HLA genotypes. 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. HLA results are not available in New York State.

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Copy Number Alterations by Next-Generation Sequencing (NGS)

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
PTEN	1 +	90	Positive	Intensity ≥1+ and ≥1% of cells stained

MISMATCH REPAIR (MMR) PROTEINS	
Biomarker	Result
MLH1	Intact nuclear expression
MSH2	Intact nuclear expression
MSH6	Intact nuclear expression
PMS2	Intact nuclear expression
Mismatch Repair Protein Status	**Proficient (Intact)**

Mismatch Repair Protein Status result interpretation: Proficient (Intact) – No evidence of deficient mismatch repair (no loss of nuclear expression of any MMR protein); Deficient (Loss) – Loss of nuclear expression of one or more MMR proteins

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 (28-8)	1 +	60%	Positive	Intensity ≥1+ and ≥1% of cells stained
PD-L1 (SP142)	1 +	10%	Negative	Intensity ≥1+ and ≥50% of cells stained
PD-L1 (SP263)	1 +	60%	Positive	Intensity ≥1+ and ≥1% 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	80%	TPS ≥1 %

PD-L1 22c3: Scoring was based on the percentage of viable tumor cells showing partial or complete membrane staining. There are three categories of PD-L1 expression defined by the PD-L1 22c3 IHC pharmDx NSCLC interpretation guide: TPS < 1% (negative), TPS ≥ 1% and TPS ≥ 50%.

PD-L1 IMMUNE CELL (IC) SCORE			
Biomarker	Result	IC	Threshold
PD-L1 (SP142)	Negative	5%	≥10%

Additional IHC results continued on the next page. >

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Protein Expression by Immunohistochemistry (IHC)

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: MLH1 (M1), MSH2 (G219-1129), MSH6 (SP93), PMS2 (A16-4), PD-L1 (SP263), PD-L1 (SP142), PD-L1 (22c3), PTEN (6H2.1), ALK (D5F3), PD-L1 (28-8).

Electronic Signature

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 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), PR (CONFIRM anti-Progesterone Receptor (PR) (1E2), Ventana), HER2/neu (PATHWAY anti-HER-2/neu (4B5), Ventana), Ki-67 (MIB-1 pharmaDx, Dako), PD-L1 22c3 (pharmDx, Dako), PD-L1 SP142 (VENTANA, Ventana in urothelial carcinomas and non-small cell lung cancer; drug association only in urothelial and 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.

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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	National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer Version 1.2020
4	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
5	entrectinib	ROS1	Desai AV, Brodeur GM, Foster J, et al. Phase I study of entrectinib (RXDX-101), a TRK, ROS1, and ALK inhibitor, in children, adolescents, and young adults with recurrent or refractory solid tumors. J Clin Oncol. 2018;36 (suppl;abstr 10536). doi: 10.1200/JCO.2018.36.15_suppl.10536. View Citation Online
6	entrectinib	ROS1	Demetri, G.D., R.D., Doebele, et al. (2018). "Efficacy and safety of entrectinib in patients with NTRK fusion-positive tumors: pooled analysis of STARTRK-2, STARTRK-1 and ALKA-372-001. Presented at: 2018 ESMO Congress; October 19-23, 2018; Munich, Germany. Abstract LBA17. View Citation Online
7	crizotinib	MET	Wang, S.X.Y., J.W. Neal, et al. (2019). "Case series of MET exon 14 skipping mutation-positive non-small-cell lung cancers with response to crizotinib and cabozantinib." Anticancer Drugs 30(5):537-541. View Citation Online
8	crizotinib	MET	Paik, P.K., M. Ladanyi, et al. (2015). "Response to MET inhibitors in patients with stage IV lung adenocarcinomas harboring MET mutations causing exon 14 skipping". Cancer Discov. Published online May 13, 2015. View Citation Online
9	crizotinib	MET	Noonan, S.A., D.R.Camidge, et al. (2016). "Identifying the Appropriate FISH Criteria for Defining MET Copy Number-Driven Lung Adenocarcinoma through Oncogene Overlap Analysis." J Thorac Oncol 11(8): 1293-1304. View Citation Online
10	crizotinib	MET	Camidge, D.R., L. C. Villaruz, et al. (2018). "Crizotinib in patients (pts) with MET-amplified non-small cell lung cancer (NSCLC): Updated safety and efficacy findings from a phase 1 trial." J Clin Oncol 36(15s):9062-9062. View Citation Online
11	crizotinib	ALK	Solomon, B. J., T. S. Mok, et al. (2018). "Final overall survival analysis from a study comparing first-line crizotinib versus chemotherapy in ALK-mutation positive Non-small-cell-lung cancer." J Clin Oncol 36: 2251-2258. View Citation Online
12	crizotinib	ALK	van der Wekken, A. J., H.J.M Groen, et al. (2017). "Dichotomous ALK IHC is a better predictor for ALK inhibition outcome than traditional ALK FISH in advanced Non-small cell lung cancer." Clin Cancer Res 23(15): 4251-4258. View Citation Online
13	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
14	crizotinib	ROS1	Shaw, A.T., S.-H. I. Ou, et al. (2019). "Crizotinib in ROS1-rearranged advanced non-small-cell lung cancer (NSCLC): updated results, including overall survival, from PROFILE 1001." Ann Oncol 30(7): 1121-1126. View Citation Online
15	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

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16	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
17	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
18	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
19	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
20	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
21	ceritinib, lorlatinib	ROS1	Lim SM, BC Cho, et al. (2017). "Open-Label, Multicenter, Phase II Study of Ceritinib in Patients With Non-Small-Cell Lung Cancer Harboring ROS1 Rearrangement". J Clin Oncol. May 18:JCO2016713701. View Citation Online
22	ceritinib, lorlatinib	ROS1	Shaw, A.T., S.-H. I. Ou, et al. (2019). "Lorlatinib in advanced ROS-1 positive non-small-cell lung cancer: a multicentre, open-label, single-arm, phase 1-2 trial." Lancet Oncol pii: S1470-2045(19)30655-2. View Citation Online
23	nivolumab/ipilimumab combination	PD-L1 (28-8)	Hellmann, M.D., S.S. Ramalingam, et al., (2019). "Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer." N Engl J Med 381:2020-31. View Citation Online
24	pralsetinib, selpercatinib	RET	National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer Version 6.2020 View Citation Online
25	selpercatinib	RET	Drilon, A., V. Subbiah, et al. (2020). "Efficacy of Selpercanib in RET Fusion-Positive Non-Small-Cell Lung Cancer." N Engl J Med. 383 (9): 813-824. View Citation Online
26	pralsetinib	RET	Gainor J.F., V. Subbiah, et al. (2020). "Registrational dataset from the phase I/II ARROW trial of pralsetinib (BLU-667) in patients (pts) with advanced RET fusion+ non-small cell lung cancer (NSCLC)." J Clin Oncol. 38(suppl):9515. View Citation Online
27	cemiplimab	PD-L1 (22c3)	Sezer, A., P. Rietschel, et al., (2020). "EMPOWER-Lung 1: Phase III first-line (1L) cemiplimab monotherapy vs platinum-doublet chemotherapy (chemo) in advanced non-small cell lung cancer (NSCLC) with programmed cell death-ligand 1 (PD-L1) ≥50%." Ann Oncol 31 (suppl_4): S1142-S1215 View Citation Online
28	dabrafenib and trametinib combination therapy, vemurafenib	BRAF	Hyman, D.H., J. Baselga, et al. (2015). "Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations." NEJM 373(8):726-736. View Citation Online
29	dabrafenib and trametinib combination therapy, vemurafenib	BRAF	Planchard, D., B.E. Johnson, et al. (2016). "An open-label phase II trial of dabrafenib (D) in combination with trametinib (T) in patients (pts) with previously treated BRAF V600E-mutant advanced non-small cell lung cancer (NSCLC; BRF113928)." J Clin Oncol 34: 15_suppl, 107-107. View Citation Online
30	dabrafenib and trametinib combination therapy, vemurafenib	BRAF	Planchard, D., B.E. Johnson, et al. (2017). "Dabrafenib plus trametinib in patients with previously untreated BRAFV600E-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial." Lancet Oncol 18(1):1307-1316. View Citation Online
31	dabrafenib and trametinib combination therapy, vemurafenib	BRAF	Subbiah, V., D.M. Hyman, et al. (2019). "Efficacy of Vemurafenib in Patients With Non-Small-Cell Lung Cancer With BRAF V600 Mutation: An Open-Label, Single-Arm Cohort of the Histology-Independent VE-BASKET Study." JCO Precis Oncol 2019: 3, 1-9. View Citation Online

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References

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33	pembrolizumab	PD-L1 (22c3)	Gadgeel, S., C. Garassino, et al. (2020). "Updated Analysis From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non-Small-Cell Lung Cancer" J Clin Oncol. 2020 Mar 9:JCO1903136. doi: 10.1200/JCO.19.03136 View Citation Online
34	pembrolizumab	PD-L1 (22c3)	Reck, M., JR Brahmer, et al. (2019). "Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater." J Clin Oncol. 37(7):537-546 View Citation Online
35	pembrolizumab	PD-L1 (22c3)	Mok, T.S., KEYNOTE-042 Investigators, et al. (2019). "Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial." Lancet. 393(10183):1819-1830 View Citation Online
36	pembrolizumab	TMB	Marabelle, A., Y.J. Bang, et al., (2019). "Association of Tumor Mutational Burden with Outcomes in Patients with Select Advanced Solid Tumors Treated with Pembrolizumab in KEYNOTE-158." AnnOncol 30(suppl_5): v475-v532 View Citation Online
37	atezolizumab (adjuvant)	PD-L1 (SP263)	Felip, E., Altorki N, et al. (2021). "Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label,phase 3 trial." Lancet 398: 1344-57. View Citation Online
38	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
39	erlotinib, gefitinib	EGFR, KRAS	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
40	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
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42	erlotinib, gefitinib	KRAS	Sacher, A. G., G. R. Oxnard, et al. (2016). "Prospective Validation of Rapid Plasma Genotyping for the Detection of EGFR and KRAS Mutations in Advanced Lung Cancer." JAMA Oncol. 2 (8): 1014-22 View Citation Online
43	erlotinib, gefitinib	KRAS	Mack, P. C., D. R. Bandara, et al. (2020). "Spectrum of driver mutations and clinical impact of circulating tumor DNA analysis in non-small cell lung cancer: Analysis of over 8000 cases." Cancer. 126 (14): 3219-3228 View Citation Online
44	erlotinib, gefitinib	KRAS	Nardo, G., E. Zulato, et al. (2021). "Detection of Low-Frequency KRAS Mutations in cfDNA From EGFR-Mutated NSCLC Patients After First-Line EGFR Tyrosine Kinase Inhibitors." Front Oncol. 10: 607840 View Citation Online
45	erlotinib, gefitinib	KRAS	Zhu, C.Q., M.S. Tsao, et. al. (2008). "Role of KRAS and EGFR as biomarkers of response to erlotinib in National Cancer Institute of Canada Clinical Trials Group Study BR.21." J. Clin. Oncol. 26:4268-4275. View Citation Online

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References

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46	adagrasib, sotorasib	KRAS	Hong, D.S., B.T. Li, et al. (2020). "KRAS G12C Inhibition with Sotorasib in Advanced Solid Tumors." N Engl J Med. 383(13): 1207-1217. View Citation Online
47	adagrasib, sotorasib	KRAS	Li, B.T, J. Wolf, et al. (2021). "CodeBreaK 100: Registrational Phase 2 Trial of Sotorasib in KRAS p.G12C Mutated Non-small Cell Lung Cancer". J Thorac Oncol. 16 (3): S61. View Citation Online
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