Lung Sample Patient 22024

Diagnosis
Adenocarcinoma

Accession No.
Lung 22024

xT

Date of Birth
11/22/1961

Sex
Male

Physician
Dr. Patel

Institution
Chicago Cancer Center

TEMPUS | xT
648 gene panel

Tumor specimen:
Lung, right upper lobe

Collected 3/3/2022
Received 3/16/2022
Tumor Percentage: 40%

Normal specimen:
Blood
Collected 3/9/2022
Received 3/11/2022

GENOMIC VARIANTS

Somatic - Potentially Actionable		Variant Allele Fraction
KRAS	p.G12C Missense variant (exon 2) - GOF	23.8%

Somatic - Biologically Relevant		
ARID2	p.W266* Stop gain - LOF	26.7%
RBM10	p.E808* Stop gain - LOF	25.5%
STK11	p.R331fs Frameshift - LOF	15.7%
NFE2L2	p.G81V Missense variant - GOF	12.6%
FAT1	c.13139-1G>T Splice region variant - LOF	10.7%
BCL11B	p.T502fs Frameshift - LOF	8.0%

Germline - Pathogenic / Likely Pathogenic

No germline pathogenic variants were found in the limited set of genes on which we report.

Pertinent Negatives

No pathogenic single nucleotide variants, indels, or copy number changes found in:

EGFR | BRAF | ALK | ROS1 | RET | MET | ERBB2 (HER2)

IMMUNOTHERAPY MARKERS

Tumor Mutational Burden

7.4 m/MB — 76th percentile

Microsatellite Instability Status

Stable | Equivocal | High

FDA-APPROVED THERAPIES, CURRENT DIAGNOSIS

KRAS G12C Inhibitor	**Sotorasib**	NCCN, Consensus, Non-Small Cell Lung Cancer MSK OncoKB, Level 1 KRAS p.G12C G12C - GOF

Unfavorable prognosis

NCCN, Consensus, Non-Small Cell Lung Cancer

KRAS p.G12C Gain-of-function

None of the therapies on this report were identified in the clinical notes received and abstracted by Tempus, which may not reflect the complete treatment history.

CLINICAL TRIALS

A Study of VS-6766 v. VS-6766 + Defactinib in Recurrent G12V, Other KRAS and BRAF Non-Small Cell Lung Cancer (NCT04620330)	**Phase II** City, State - x mi ✓ **KRAS mutation**
Phase 1/2 Study of MRTX849 in Patients With Cancer Having a KRAS G12C Mutation KRYSTAL-1 (NCT03785249)	**Phase I/II** City, State - x mi ✓ **KRAS mutation** ✓ **STK11 mutation**
First-in-human Study of DRP-104 (Sirpiglenastat) as Single Agent and in Combination With Atezolizumab in Patients With Advanced Solid Tumors. (NCT04471415)	**Phase I/II** City, State - x mi ✓ **NFE2L2 mutation** ✓ **STK11 mutation**

VARIANTS OF UNKNOWN SIGNIFICANCE

Somatic	Mutation effect	Variant allele fraction
AR	c.20G>T p.S7I Splice region variant NM_001011645	24.8%
PDGFRB	c.3268C>T p.P1090S Missense variant NM_002609	19.1%
PRDM1	c.1499G>A p.G500E Missense variant NM_001198	17.4%
STK11	c.889A>G p.R297G Missense variant NM_000455	15.7%
ERG	c.527G>A p.C176Y Missense variant NM_001243428	15.0%
PAX5	c.911-4T>A Splice region variant NM_016734	14.8%
APOB	c.11500G>A p.G3834S Missense variant NM_000384	14.5%
AXIN1	c.691G>A p.G231R Missense variant NM_003502	14.3%
PREX2	c.2324C>A p.P775H Missense variant NM_024870	12.7%
RBM10	c.1700G>T p.G567V Missense variant NM_001204468	11.0%

Somatic	Mutation effect	Variant allele fraction
RBM10	c.1707_1709delinsCCT p.AP569AL Missense variant NM_001204468	9.2%
ATP7B	c.3472G>A p.G1158S Missense variant NM_000053	9.1%

LOW COVERAGE REGIONS

PMS2

SOMATIC VARIANT DETAILS - POTENTIALLY ACTIONABLE

KRAS c.34G>T p.G12C NM_033360 Missense variant (exon 2) - GOF VAF: 23.8%

KRAS is a GDP/GTP binding protein that acts as an intracellular signal transducer. KRAS is involved in several pathways involved in cellular proliferation and survival, including the PI3K-AKT-mTOR pathway and the Ras-Raf-MEK-ERK pathway. Activating mutations, copy number gains, and overexpression of KRAS are associated with cancer progression.

SOMATIC VARIANT DETAILS - BIOLOGICALLY RELEVANT

ARID2 c.798G>A p.W266* NM_152641 Stop gain - LOF VAF: 26.7%

ARID2 encodes a protein that is a subunit of the SWI/SNF chromatin remodeling complex SWI/SNF-B or PBAF. This complex functions in ligand-dependent transcriptional activation. Loss of function mutations and copy number loss of ARID2 are associated with cancer progression.

RBM10 c.2422G>T p.E808* NM_001204468 Stop gain - LOF VAF: 25.5%

RBM10 encodes a protein that contains a RNA-binding motif and interacts with RNA homopolymers, and is thought to function in regulating alternative splicing. Loss of function mutations and copy number loss of RBM10 are associated with cancer progression.

STK11 c.991_992insA p.R331fs NM_000455 Frameshift - LOF VAF: 15.7%

STK11 (LKB1) encodes an enzyme in the serine/threonine kinase family that is responsible for maintaining energy metabolism and cellular polarization through the activation of AMP-activated protein kinase and other members of the AMPK family. The enzyme also acts as a tumor suppressor by regulating cell growth. Loss of function mutations, copy number loss, epigenetic variation, and underexpression of STK11 are associated with cancer progression.

NFE2L2 c.242G>T p.G81V NM_006164 Missense variant - GOF VAF: 12.6%

NFE2L2 acts as a transcription factor for proteins that contain an antioxidant response element (ARE) within their promoter sequence. Genes that contain ARE are involved in injury and inflammation response. Activating mutations and overexpression of NFE2L2 are associated with cancer progression.

FAT1 c.13139-1G>T NM_005245 Splice region variant - LOF VAF: 10.7%

FAT1 encodes a transmembrane protein involved in tumor suppressor signaling. FAT1 protein can regulate transcriptional activity by sequestering beta-catenin, thereby preventing it from entering the nucleus. Loss of function mutations and copy number loss of FAT1 are associated with cancer progression.

BCL11B c.1505_1506del p.T502fs NM_138576 Frameshift - LOF VAF: 8.0%

BCL11B encodes a C2H2-type zinc finger protein that functions as a transcriptional repressor and plays a role in T-cell development and survival. Loss of function mutations, copy number loss, and fusions resulting in the underexpression of BCL11B are associated with cancer progression.

CLINICAL HISTORY

DIAGNOSIS

Diagnosed on
03/02/2022

Assay Description

The Tempus xT(version 4) assay is a custom oncology testing panel consisting of 648 genes with single nucleotide variants, indels and translocations measured by hybrid capture next-generation sequencing (NGS). A complete gene list can be found at the end of this assay description. This assay has 98.2% sensitivity for single nucleotide variants (SNV) above 5% variant allele fraction (VAF), 91.8% sensitivity for indels above 5% VAF and 91.7% sensitivity for reported translocations. The assay has 91.3% sensitivity for copy number alterations for samples with the copy number gain limit of detection (LOD) set as 30% tumor purity and copy number loss at 40% tumor purity. (Certain driver or resistance genes may be reported to lower VAFs when technically possible.)

Potentially Actionable alterations are protein-altering variants with an associated therapy based on evidence from the medical literature. **Biologically Relevant** alterations are protein-altering variants that may have functional significance or have been observed in the medical literature but are not associated with a specific therapy in the Tempus knowledge database. **Variants of Unknown Significance (VUSs)** are protein-altering variants exhibiting an unclear effect on function and/or without sufficient evidence to determine their pathogenicity. **Benign variants** are not reported. Variants are identified through aligning the patient's DNA sequence to the human genome reference sequence version hg19 (GRCh37). The clinical summary (first page of the report) shows actionable and biologically relevant somatic variants, and certain pathogenic or likely pathogenic inherited variants that are reported as incidental findings (if a matched normal sample was provided and analyzed). Reportable secondary/incidental findings are limited to genes and variants associated with inherited cancer syndromes.

Tumor mutational burden (TMB) measures the quantity of somatic SNVs and indels, of any pathogenicity, including benign, carried in a tumor as the number of protein-altering mutations per million coding base pairs. TMB is calculated at the time of initial report delivery. Accordingly, the TMB calculation is based upon (a) both the tumor and normal sample if Tempus had analyzed both at the time of the initial report, or (b) the tumor sample only if no normal sample had been analyzed at the time of the initial report. Please note that tumor only calculations are not updated or amended even if a normal sample is subsequently analyzed. Studies have shown that tumors with higher TMB have an increased likelihood of response to immunotherapy [1, 2].

Microsatellite instability (MSI) refers to hypermutability caused by genetic or acquired defects in the DNA mismatch repair pathway. MSI status is divided into **MSI-high (MSI-H)** tumors, which have changes in microsatellite repeat lengths due to defective DNA mismatch repair activity. **Microsatellite stable (MSS)** tumors do not have detectable defects in DNA mismatch repair. **Microsatellite equivocal (MSE)** tumors have an intermediate phenotype which cannot be clearly classified as MSI-H or MSS based on the statistical cutoff used to define those categories. If MSI status will affect clinical management, immunohistochemical staining for DNA mismatch repair proteins, or another method of ascertaining MSI status, is recommended.

Assay Description (continued)

The Tempus 2nd generation RNA whole-transcriptome assay (RS.v2) uses IDT xGen Exome Research Panel v2 probe set as backbone, which consists of >415K individually synthesized probes and spans 34 Mb target region (19,433 genes) of the human genome. Additional Tempus-specific custom spike-ins probes are added to enhance target region detection (e.g., fusion and viral probes). When whole transcriptome RNA-Seq is performed, expressed fusion transcripts from rearranged genes specifically targeted by the assay will be detected. In addition to this, expressed fusion transcripts from rearranged genes not targeted by the assay may also be detected. A list of targeted fusion transcripts can be made available upon request. The fusion transcript detection bioinformatics pipeline identifies and analyzes the positions of breakpoint spanning reads and split paired-end reads. Non-canonical fusion transcripts may be reported at the discretion of the medical director. This assay has >99% sensitivity for targeted fusion and 97% sensitivity for untargeted fusions.

1. Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden. https://www.ncbi.nlm.nih.gov/pubmed/29658845

2. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. https://www.ncbi.nlm.nih.gov/pubmed/25765070

Gene List

A-B
ABCB1, ABCC3, ABL1, ABL2, ABRAXAS1, ACTA2, ACVR1 (ALK2), ACVR1B, AGO1, AJUBA, AKT1, AKT2, AKT3, ALK, AMER1, APC, APLNR, APOB, AR, ARAF, ARHGAP26, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASNS, ASPSCR1, ASXL1, ATIC, ATM, ATP7B, ATR, ATRX, AURKA, AURKB, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1, BCL10, BCL11B, BCL2, BCL2L1, BCL2L11, BCL6, BCL7A, BCLAF1, BCOR, BCORL1, BCR, BIRC3, BLM, BMPR1A, BRAF, BRCA1, BRCA2, BRD4, BRIP1, BTG1, BTK, BUB1B

C-D
C11orf65, C3orf70, C8orf34, CALR, CARD11, CARM1, CASP8, CASR, CBFB, CBL, CBLB, CBLC, CBR3, CCDC6, CCND1, CCND2, CCND3, CCNE1, CD19, CD22, CD274 (PD-L1), CD40, CD70, CD79A, CD79B, CDC73, CDH1, CDK12, CDK4, CDK6, CDK8, CDKN1A, CDKN1B, CDKN1C, CDKN2A, CDKN2B, CDKN2C, CEBPA, CEP57, CFTR, CHD2, CHD4, CHD7, CHEK1, CHEK2, CIC, CIITA, CKS1B, CREBBP, CRKL, CRLF2, CSF1R, CSF3R, CTC1, CTCF, CTLA4, CTNNA1, CTNNB1, CTRC, CUL1, CUL3, CUL4A, CUL4B, CUX1, CXCR4, CYLD, CYP1B1, CYP2D6, CYP3A5, CYSLTR2, DAXX, DDB2, DDR2, DDX3X, DICER1, DIRC2, DIS3, DIS3L2, DKC1, DNM2, DNMT3A, DOT1L, DPYD, DYNC2H1

E-F
EBF1, ECT2L, EGF, EGFR, EGLN1, EIF1AX, ELF3, ELOC (TCEB1), EMSY, ENG, EP300, EPCAM, EPHA2, EPHA7, EPHB1, EPHB2, EPOR, ERBB2 (HER2), ERBB3, ERBB4, ERCC1, ERCC2, ERCC3, ERCC4, ERCC5, ERCC6, ERG, ERRFI1, ESR1, ETS1, ETS2, ETV1, ETV4, ETV5, ETV6, EWSR1, EZH2, FAM46C, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAS, FAT1, FBXO11, FBXW7, FCGR2A, FCGR3A, FDPS, FGF1, FGF10, FGF14, FGF2, FGF23, FGF3, FGF4, FGF5, FGF6, FGF7, FGF8, FGF9, FGFR1, FGFR2, FGFR3, FGFR4, FH, FHIT, FLCN, FLT1, FLT3, FLT4, FNTB, FOXA1, FOXL2, FOXO1, FOXO3, FOXP1, FOXQ1, FRS2, FUBP1, FUS

G-H
G6PD, GABRA6, GALNT12, GATA1, GATA2, GATA3, GATA4, GATA6, GEN1, GLI1, GLI2, GNA11, GNA13, GNAQ, GNAS, GPC3, GPS2, GREM1, GRIN2A, GRM3, GSTP1, H19, H3F3A, HAS3, HAVCR2, HDAC1, HDAC2, HDAC4, HGF, HIF1A, HIST1H1E, HIST1H3B, HIST1H4E, HLA-A, HLA-B, HLA-C, HLA-DMA, HLA-DMB, HLA-DOA, HLA-DOB, HLA-DPA1, HLA-DPB1, HLA-DPB2, HLA-DQA1, HLA-DQA2, HLA-DQB1, HLA-DQB2, HLA-DRA, HLA-DRB1, HLA-DRB5, HLA-DRB6, HLA-E, HLA-F, HLA-G, HNF1A, HNF1B, HOXA11, HOXB13, HRAS, HSD11B2, HSD3B1, HSD3B2, HSP90AA1, HSPH1

I-K
IDH1, IDH2, IDO1, IFIT1, IFIT2, IFIT3, IFNAR1, IFNAR2, IFNGR1, IFNGR2, IFNL3, IKBKE, IKZF1, IL10RA, IL15, IL2RA, IL6R, IL7R, ING1, INPP4B, IRF1, IRF2, IRF4, IRS2, ITPKB, JAK1, JAK2, JAK3, JUN, KAT6A, KDM5A, KDM5C, KDM5D, KDM6A, KDR, KEAP1, KEL, KIF1B, KIT, KLF4, KLHL6, KLLN, KMT2A, KMT2B, KMT2C, KMT2D, KRAS

L-M
L2HGDH, LAG3, LATS1, LCK, LDLR, LEF1, LMNA, LMO1, LRP1B, LYN, LZTR1, MAD2L2, MAF, MAFB, MAGI2, MALT1, MAP2K1, MAP2K2, MAP2K4, MAP3K1, MAP3K7, MAPK1, MAX, MC1R, MCL1, MDM2, MDM4, MED12, MEF2B, MEN1, MET, MGMT, MIB1, MITF, MKI67, MLH1, MLH3, MLLT3, MN1, MPL, MRE11, MS4A1, MSH2, MSH3, MSH6, MTAP, MTHFD2, MTHFR, MTOR, MTRR, MUTYH, MYB, MYC, MYCL, MYCN, MYD88, MYH11

N-O
NBN, NCOR1, NCOR2, NF1, NF2, NFE2L2, NFKBIA, NHP2, NKX2-1, NOP10, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NPM1, NQO1, NRAS, NRG1, NSD1, NSD2, NT5C2, NTHL1, NTRK1, NTRK2, NTRK3, NUDT15, NUP98, OLIG2

P-Q
P2RY8, PAK1, PALB2, PALLD, PAX3, PAX5, PAX7, PAX8, PBRM1, PCBP1, PDCD1, PDCD1LG2, PDGFRA, PDGFRB, PDK1, PHF6, PHGDH, PHLPP1, PHLPP2, PHOX2B, PIAS4, PIK3C2B, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R1, PIK3R2, PIM1, PLCG1, PLCG2, PML, PMS1, PMS2, POLD1, POLE, POLH, POLQ, POT1, POU2F2, PPARA, PPARD, PPARG, PPM1D, PPP1R15A, PPP2R1A, PPP2R2A, PPP6C, PRCC, PRDM1, PREX2, PRKAR1A, PRKDC, PRKN, PRSS1, PTCH1, PTCH2, PTEN, PTPN11, PTPN13, PTPN22, PTPRD, PTPRT, QKI

Assay Description (continued)

R-S
RAC1, RAD21, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD54L, RAF1, RANBP2, RARA, RASA1, RB1, RBM10, RECQL4, RET, RHEB, RHOA, RICTOR, RINT1, RIT1, RNF139, RNF43, ROS1, RPL5, RPS15, RPS6KB1, RPTOR, RRM1, RSF1, RUNX1, RUNX1T1, RXRA, SCG5, SDHA, SDHAF2, SDHB, SDHC, SDHD, SEC23B, SEMA3C, SETBP1, SETD2, SF3B1, SGK1, SH2B3, SHH, SLC26A3, SLC47A2, SLC9A3R1, SLIT2, SLX4, SMAD2, SMAD3, SMAD4, SMARCA1, SMARCA4, SMARCB1, SMARCE1, SMC1A, SMC3, SMO, SOCS1, SOD2, SOX10, SOX2, SOX9, SPEN, SPINK1, SPOP, SPRED1, SRC, SRSF2, STAG2, STAT3, STAT4, STAT5A, STAT5B, STAT6, STK11, SUFU, SUZ12, SYK, SYNE1

T-U
TAF1, TANC1, TAP1, TAP2, TARBP2, TBC1D12, TBL1XR1, TBX3, TCF3, TCF7L2, TCL1A, TERT, TET2, TFE3, TFEB, TFEC, TGFBR1, TGFBR2, TIGIT, TMEM127, TMEM173, TMPRSS2, TNF, TNFAIP3, TNFRSF14, TNFRSF17, TNFRSF9, TOP1, TOP2A, TP53, TP63, TPM1, TPMT, TRAF3, TRAF7, TSC1, TSC2, TSHR, TUSC3, TYMS, U2AF1, UBE2T, UGT1A1, UGT1A9, UMPS

V-Z
VEGFA, VEGFB, VHL, VSIR, WEE1, WNK1, WNK2, WRN, WT1, XPA, XPC, XPO1, XRCC1, XRCC2, XRCC3, YEATS4, ZFHX3, ZMYM3, ZNF217, ZNF471, ZNF620, ZNF750, ZNRF3, ZRSR2

Gene Rearrangements Found by DNA Sequencing

ABL1, ALK, BCR, BRAF, EGFR, ETV6, EWSR1, FGFR2, FGFR3, MYB, NRG1, NTRK1, NTRK2, NTRK3, PAX8, PDGFRA, PML, RARA, RET, ROS1, TFE3, TMPRSS2

Germline Genes

APC, ATM, AXIN2, BAP1, BARD1, BLM, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CEBPA, CHEK2, DICER1, EGFR, EPCAM, ETV6, FH, FLCN, GATA2, KIT, MAX, MEN1, MET, MLH1, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NF2, NTHL1, PALB2, PDGFRA, PHOX2B, PMS2, POLD1, POLE, PRKAR1A, PTCH1, PTEN, RAD51C, RAD51D, RB1, RET, RUNX1, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMAD4, SMARCA4, SMARCB1, STK11, SUFU, TMEM127, TP53, TSC1, TSC2, VHL, WT1

RNA Fusion Analysis

RNA transcriptome analysis for fusion detection will be attempted on all samples. If fusions are identified via RNA sequencing, they will be added to the report or issued as an addendum.

Tempus Disclaimer

The analysis of nucleic acids by next-generation sequencing (NGS) can be affected by multiple factors including formalin-fixation degrading DNA and RNA quality, and low tumor purity limiting sensitivity. Additionally, the chance of detecting genetic alterations may be reduced in regions of the genome which are structurally difficult to sequence, in homologous genes, or due to low complexity regions prone to sequencing error.

Genetic alterations are defined as clinically significant based on peer-reviewed published literature and other authoritative sources such as NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). These references are not comprehensive, therefore clinically unknown findings may occur.

These test results and information contained within the report are current as of the report date. Tempus will not update reports or send notification regarding reclassification of genomic alterations. This test was developed and its performance characteristics determined by Tempus. It has not been cleared or approved by the FDA. The laboratory is CLIA certified to perform high-complexity testing. Any decisions related to patient care and treatment choices should be based on the independent judgment of the treating physician and should take into account all information related to the patient, including without limitation, the patient and family history, direct physical examination and other tests. Tempus is not liable for medical judgment with regards to diagnosis, prognosis or treatment in connection with the test results.

Tempus may report certain germline secondary/incidental findings as part of these test results. The reportable secondary/incidental findings for the genes included on these panels include genes recommended for testing by the ACMG [1], the NCCN, and other published literature and are associated with inherited cancer syndromes. These secondary/incidental findings may or may not be related to the patient's current cancer diagnosis. The clinical significance of any such reported variants are based on germline classification criteria created by the ACMG [2]. Variants that are classified as pathogenic, likely pathogenic, or as a risk allele may be reported. Variants of uncertain significance (VUS), likely benign, and benign variants are not reported. Classifications are provided based on evidence evaluated at the time of reporting. When a variant is detected in both the somatic and germline samples, the variant is reported only under the "germline" section of genomic variants, unless otherwise noted. Tempus does not notify physicians or patients of updated variant classifications.

Tempus Disclaimer (continued)

This is not a stand alone germline test, and as such the rate of false positives and false negatives has not been assessed and certain alterations, such as exon level rearrangements may be missed. Additionally, detection of genetic variation in genes with high homology to other regions of the genome may be decreased or not reliably detected by NGS (including but not limited to these genes: NF1, PMS2, SBDS, and SUZ12) and large insertions and deletions may also not be detected by NGS. Because of these limitations, these germline test results cannot be used to definitively rule out cancer or other genetic predisposition syndromes. Unless Tempus has provided a separate report indicating that a specific germline finding is validated, the incidental germline finding results set forth herein should not be used as a substitute for tests validated to determine genetic risk; additional validated hereditary testing may be recommended for incidental germline findings not validated in a separate report from Tempus.

Results of genetic testing, including the incidental germline findings described above, may have implications for both the patient and family members. Tempus does not provide genetic counseling; however, genetic counseling is strongly suggested, based on the patient's clinical history and/or genetic test results. The ordering physician or the patient is responsible for contacting a genetic counselor to discuss test results.

1. Miller DT, Lee K, Chung WK, Gordon AS, Herman GE, Klein TE, Stewart DR, Amendola LM, Adelman K, Bale SJ, Gollob MH, Harrison SM, Hershberger RE, McKelvey K, Richards CS, Vlangos CN, Watson MS, Martin CL; ACMG Secondary Findings Working Group. ACMG SF v3.0 list for reporting of secondary findings in clinical exome and genome sequencing: a policy statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021 Aug;23(8):1381-1390. doi: 10.1038/s41436-021-01172-3. Epub 2021 May 20. Erratum in: Genet Med. 2021 Aug 3;: PMID: 34012068.

2. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. ACMG Laboratory Quality Assurance Committee. Genet Med. 2015 May;17(5):405-24. DOI: 10.1038/gim.2015.30.

Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Lymphoblastic Leukemia V.4.2021, Acute Myeloid Leukemia V.1.2022, Ampullary Adenocarcinoma V.1.2022, Anal Carcinoma V.1.2022, Basal Cell Skin Cancer V.1.2022, B-Cell Lymphomas V.1.2022, Bladder Cancer V.1.2022, Bone Cancer V.2.2022, Breast Cancer V.2.2022, Central Nervous System Cancers V.2.2021, Cervical Cancer V.1.2022, Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma V.2.2022, Chronic Myeloid Leukemia V.3.2022, Colon Cancer V.1.2022, Dermatofibrosarcoma Protuberans V.1.2022, Esophageal and Esophagogastric Junction Cancers V.2.2022, Gastric Cancer V.2.2022, Gastrointestinal Stromal Tumors (GIST) V.1.2022, Gestational Trophoblastic Neoplasia V.1.2022, Hairy Cell Leukemia V.1.2022, Head and Neck Cancers V.1.2022, Hepatobiliary Cancers V.5.2021, Histiocytic Neoplasms V.2.2021, Hodgkin Lymphoma V.2.2022, Kaposi Sarcoma V.1.2022, Kidney Cancer V.4.2022, Malignant Peritoneal Mesothelioma V.1.2022, Malignant Pleural Mesothelioma V.1.2022, Melanoma: Cutaneous V.2.2022, Melanoma: Uveal V.2.2021, Merkel Cell Carcinoma V.1.2022, Multiple Myeloma V.5.2022, Myelodysplastic Syndromes V.3.2022, Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes V.4.2021, Myeloproliferative Neoplasms V.1.2022, Neuroendocrine and Adrenal Tumors V.4.2021, Non-Small Cell Lung Cancer V.3.2022, Occult Primary V.1.2022, Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer V.1.2022, Pancreatic Adenocarcinoma V.1.2022, Pediatric Acute Lymphoblastic Leukemia V.1.2022, Pediatric Aggressive Mature B-Cell Lymphomas, V.3.2021, Pediatric Hodgkin Lymphoma, V.3.2021, Penile Cancer, V.2.2022, Primary Cutaneous Lymphomas V.1.2022, Prostate Cancer V.3.2022, Rectal Cancer V.1.2022, Small Bowel Adenocarcinoma V.1.2022, Small Cell Lung Cancer V.2.2022, Soft Tissue Sarcoma V.3.2021, Squamous Cell Skin Cancer V.1.2022, Systemic Light Chain Amyloidosis V.1.2022, Systemic Mastocytosis V.3.2021, T-Cell Lymphomas V.2.2022, Testicular Cancer V.2.2022, Thymomas and Thymic Carcinomas V.1.2022, Thyroid Carcinoma V.3.2021, Uterine Neoplasms V.1.2022, Vulvar Cancer V.1.2022, Waldenström Macroglobulinemia / Lymphoplasmacytic Lymphoma V.2.2022, Wilms Tumor (Nephroblastoma) V.2.2021. Accessed March 17, 2022. To view the most recent and complete version of the guideline, go online to NCCN.org. The NCCN Guidelines® and other content provided by NCCN are works in progress that may be refined as often as new significant data becomes available. They are statements of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® or other NCCN Content is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. Therapeutic options are not applicable in all disease settings.

The OncoKB™ precision oncology knowledge base was made available under license from Memorial Sloan Kettering Cancer Center. See terms here.

For therapy entries designating that genes are wild-type, no activating variants were detected in the specified genes.

Dates and times are represented in the coordinated universal time zone (UTC) unless otherwise specified. However, dates that are provided to Tempus without a timestamp (e.g., sample collection date) are listed as provided.

Lung Sample
Patient 22024

Diagnosis
Adenocarcinoma

Accession No.
Lung 22024

xF

Date of Birth
11/22/1961

Sex
Male

Physician
Dr. Patel

Institution
Chicago Cancer Center

TEMPUS| xF
105 gene liquid biopsy

cfDNA specimen:
Peripheral Blood
Collected 3/9/2022
Received 3/11/2022

GENOMIC VARIANTS

Potentially Actionable — **Variant Allele Fraction**

ATM	p.S2306fs	Frameshift - LOF	1.0%

Median Variant Allele Fraction

1.0%

IMMUNOTHERAPY MARKERS

Microsatellite Instability Status

MSI-High not detected

FDA-APPROVED THERAPIES, OTHER INDICATIONS

PARP Inhibitor	**Olaparib**	**NCCN, Consensus, Prostate Cancer** ATM p.S2306fs Loss-of-function

None of the therapies on this report were identified in the clinical notes received and abstracted by Tempus, which may not reflect the complete treatment history.

CLINICAL TRIALS

TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer (NCT02693535)	**Phase II** City, State - x mi ✓ **ATM mutation**
A Study Investigating DNA-damage Response Agents in Molecularly Altered Advanced Cancer (NCT04564027)	**Phase II** City, State - x mi ✓ **ATM mutation**
M6620 and Irinotecan Hydrochloride in Treating Patients With Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery (NCT02595931)	**Phase I** City, State - x mi ✓ **ATM mutation**

Gene	Mutation effect	Variant allele fraction
TSC1	c.3059C>G p.T1020S Missense variant NM_000368	0.7%

LOW COVERAGE REGIONS

ERRFI1 KMT2A MSH3 TERT TSC2

VARIANT DETAILS - POTENTIALLY ACTIONABLE

ATM c.6915del p.S2306fs NM_000051 Frameshift - LOF VAF: 1.0%

ATM is a member of the PI3/PI4-kinase gene family. ATM functions as a cell cycle checkpoint kinase, controlling the rate of cell growth and division. Additionally, it assists in the repair of damaged DNA. Loss of function mutations, copy number loss, and underexpression of ATM are associated with cancer progression.

CLINICAL HISTORY

DIAGNOSIS

Diagnosed on
03/02/2022

Assay Description

The Tempus xF assay is a next-generation sequencing (NGS) cell-free DNA liquid biopsy tumor profiling assay for identifying genomic alterations derived from solid tumors but circulating in the blood. The 105 gene panel includes single nucleotide variants (SNVs), insertions and deletions (indels), copy number variants (CNVs) and chromosomal rearrangements (translocations) detected by hybrid capture NGS using custom designed IDT probes. The assay typically (but see below) uses 30 to 50 ng of input DNA, and at 30 ng of input material, the technical sensitivity is >99% for SNVs and CNV amplifications at ≥0.5% variant allele fraction (VAF), and >98% for indels and >97% for translocations at >0.5% VAF. The assay spans clinically relevant coding exons for 35 genes and covers recurrent hotspot mutations in 70 genes. Insertions and deletions will be reported down to the lower limit of detection (LLOD) in clinically relevant regions in 97 genes (list available upon request). BRCA1 and BRCA2 copy number losses are reported when detected. *At the discretion of the attending pathologists, the assay may be run at 10 to <30 ng of input DNA, but in such a case, the report will indicate reduced sensitivity and consideration should be given to additional testing. Please see the Tempus website for a complete gene list and performance specifications.

Potentially Actionable variants have associated therapeutic, prognostic or diagnostic evidence from the medical literature. **Biologically Relevant** variants have functional significance or an association with the disease state in the medical literature, but do not have relevant therapeutic, prognostic or diagnostic evidence in the Tempus knowledge database. **Variants of Unknown Significance (VUSs)** exhibit an unclear effect on function and/or do not have sufficient evidence to determine their pathogenicity. **Benign variants** are not reported. Variants are identified through aligning the patient's DNA sequence to the human genome reference sequence version hg19 (GRCh37). The clinical summary shows actionable and biologically relevant variants. Because sequencing is performed without a matched normal sample, it is not possible to distinguish whether reported variants are germline or somatic.

The xF assay evaluates alterations in 105 genes including the following guideline-recommended genes for:

Non-small cell lung cancer: EGFR, KRAS, BRAF, ALK, ROS1, RET, MET, ERBB2 (HER2)

Breast cancer: ERBB2 (HER2), ESR1, PIK3CA

Colorectal cancer: KRAS, BRAF, NRAS

Assay Description (continued)

Gastroesophageal adenocarcinoma: ERBB2 (HER2)

Gastrointestinal stromal tumor: KIT, PDGFRA

Cutaneous melanoma: BRAF, NRAS, KIT

Uveal melanoma: GNAQ, GNA11

DISCLAIMER: Note that certain tumor type-, sample- or variant-related characteristics, such as low cell-free DNA concentration, may result in reduced analytic sensitivity of the xF test for detection of alterations in the covered genes, including the above mentioned guideline-recommended genes.

Complete Gene List

A-C
AKT1, AKT2, ALK, APC, AR, ARAF, ARID1A, ATM, ATR, B2M, BAP1, BRAF, BRCA1, BRCA2, BTK, CCND1, CCND2, CCND3, CCNE1, CD274 (PD-L1), CDH1, CDK4, CDK6, CDKN2A, CTNNB1

D-F
DDR2, DPYD, EGFR, ERBB2 (HER2), ERRFI1, ESR1, EZH2, FBXW7, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FOXL2

G-M
GATA3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK1, JAK2, JAK3, KDR, KEAP1, KIT, KMT2A, KRAS, MAP2K1, MAP2K2, MAPK1, MET, MLH1, MPL, MSH2, MSH3, MSH6, MTOR, MYC, MYCN

N-R
NF1, NF2, NFE2L2, NOTCH1, NPM1, NRAS, NTRK1, PALB2, PBRM1, PDCD1LG2, PDGFRA, PDGFRB, PIK3CA, PIK3R1, PMS2, PTCH1, PTEN, PTPN11, RAD51C, RAF1, RB1, RET, RHEB, RHOA, RIT1, RNF43, ROS1

S-Z
SDHA, SMAD4, SMO, SPOP, STK11, TERT, TP53, TSC1, TSC2, UGT1A1, VHL

Gene Rearrangements
ALK, BRAF, FGFR2, FGFR3, NTRK1, RET, ROS1

Copy Number Gains
CCNE1, CD274 (PD-L1), EGFR, ERBB2 (HER2), MET, MYC

Copy Number Losses
BRCA1 and BRCA2

Tempus Disclaimer

The analysis of nucleic acids by next-generation sequencing (NGS) can be affected by multiple factors including DNA quality, hemolysis of the peripheral blood sample, and low amounts of circulating cell-free DNA limiting sensitivity. Tempus may report findings below our sensitivity threshold due to reduced sample quality and/or quantity. For samples flagged as falling below this threshold, Tempus advises resequencing in order to provide more accurate results. Additionally, the chance of detecting genetic alterations may be reduced in regions of the genome which are structurally difficult to sequence, in homologous genes, or due to sequencing errors.

Genetic alterations are defined as clinically significant based on peer-reviewed published literature and other authoritative sources such as NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). These references are not comprehensive, therefore clinically unknown findings may occur.

These test results and information contained within the report are current as of the report date. Tempus will not update reports or send notification regarding reclassification of genomic alterations. This test was developed and its performance characteristics determined by Tempus. It has not been cleared or approved by the FDA. The laboratory is CLIA certified to perform high-complexity testing. Any decisions related to patient care and treatment choices should be based on the independent judgment of the treating physician and should take into account all information related to the patient, including without limitation, the patient and family history, direct physical examination and other tests. Tempus is not liable for medical judgment with regards to diagnosis, prognosis or treatment in connection with the test results.

Tempus Disclaimer (continued)

Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Lymphoblastic Leukemia V.4.2021, Acute Myeloid Leukemia V.1.2022, Ampullary Adenocarcinoma V.1.2022, Anal Carcinoma V.1.2022, Basal Cell Skin Cancer V.1.2022, B-Cell Lymphomas V.1.2022, Bladder Cancer V.1.2022, Bone Cancer V.2.2022, Breast Cancer V.2.2022, Central Nervous System Cancers V.2.2021, Cervical Cancer V.1.2022, Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma V.2.2022, Chronic Myeloid Leukemia V.3.2022, Colon Cancer V.1.2022, Dermatofibrosarcoma Protuberans V.1.2022, Esophageal and Esophagogastric Junction Cancers V.2.2022, Gastric Cancer V.2.2022, Gastrointestinal Stromal Tumors (GIST) V.1.2022, Gestational Trophoblastic Neoplasia V.1.2022, Hairy Cell Leukemia V.1.2022, Head and Neck Cancers V.1.2022, Hepatobiliary Cancers V.5.2021, Histiocytic Neoplasms V.2.2021, Hodgkin Lymphoma V.2.2022, Kaposi Sarcoma V.1.2022, Kidney Cancer V.4.2022, Malignant Peritoneal Mesothelioma V.1.2022, Malignant Pleural Mesothelioma V.1.2022, Melanoma: Cutaneous V.2.2022, Melanoma: Uveal V.2.2021, Merkel Cell Carcinoma V.1.2022, Multiple Myeloma V.5.2022, Myelodysplastic Syndromes V.3.2022, Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes V.4.2021, Myeloproliferative Neoplasms V.1.2022, Neuroendocrine and Adrenal Tumors V.4.2021, Non-Small Cell Lung Cancer V.3.2022, Occult Primary V.1.2022, Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer V.1.2022, Pancreatic Adenocarcinoma V.1.2022, Pediatric Acute Lymphoblastic Leukemia V.1.2022, Pediatric Aggressive Mature B-Cell Lymphomas, V.3.2021, Pediatric Hodgkin Lymphoma, V.3.2021, Penile Cancer, V.2.2022, Primary Cutaneous Lymphomas V.1.2022, Prostate Cancer V.3.2022, Rectal Cancer V.1.2022, Small Bowel Adenocarcinoma V.1.2022, Small Cell Lung Cancer V.2.2022, Soft Tissue Sarcoma V.3.2021, Squamous Cell Skin Cancer V.1.2022, Systemic Light Chain Amyloidosis V.1.2022, Systemic Mastocytosis V.3.2021, T-Cell Lymphomas V.2.2022, Testicular Cancer V.2.2022, Thymomas and Thymic Carcinomas V.1.2022, Thyroid Carcinoma V.3.2021, Uterine Neoplasms V.1.2022, Vulvar Cancer V.1.2022, Waldenström Macroglobulinemia / Lymphoplasmacytic Lymphoma V.2.2022, Wilms Tumor (Nephroblastoma) V.2.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed March 17, 2022. To view the most recent and complete version of the guideline, go online to NCCN.org. The NCCN Guidelines® and other content provided by NCCN are works in progress that may be refined as often as new significant data becomes available. They are statements of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® or other NCCN Content is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. Therapeutic options are not applicable in all disease settings.

The OncoKB™ precision oncology knowledge base was made available under license from Memorial Sloan Kettering Cancer Center. See terms here.

Dates and times are represented in the coordinated universal time zone (UTC) unless otherwise specified. However, dates that are provided to Tempus without a timestamp (e.g., sample collection date) are listed as provided.