

Date of Birth
10/25/1990

Sex
Female

Physician
Benjamin Folger

Institution
Chicago Cancer Center
CCC1234567

TEMPUS | xT 596 Genes

Tumor specimen:
Liver
Chicago Cancer Center,
ABC-123, A2
Collected 3/4/2019
Received 3/8/2019
Tumor Percentage: 50%

Normal specimen:
Blood
Collected 3/4/2019
Received 3/5/2019

Notes

Per Chicago Cancer Center, pathology report (ABC-123), the tumor is ER negative, PR negative, and HER2 equivocal (2+) by IHC.

The tumor shows loss of heterozygosity in NF1.

This patient has a pathogenic germline variant in BRCA2 with somatic loss of heterozygosity. Genetic counseling is recommended. For additional detail, please see the Somatic Variant Details and Germline Variant Details sections of this report.

No pathogenic alterations were found in ERBB2 (HER2) or ESR1.

RNA expression analysis has been performed and is reported in the Tempus online portal.

GENOMIC VARIANTS

Somatic - Potentially Actionable		Variant Allele Fraction
PIK3CA	p.E545K Missense variant (exon 10) - GOF	45.2%
NF1	p.K1036fs Frameshift - LOF	28.5%
MAP2K4	p.K114fs Frameshift - LOF	21.2%
TP53	Copy number loss	
BRCA2	Copy number loss	
Somatic - Biologically Relevant		
STAG2	Copy number loss	
Germline - Pathogenic / Likely Pathogenic		Clinical Significance
BRCA2	p.V220fs Chr13:32903604	Pathogenic Hereditary breast and ovarian cancer

IMMUNOTHERAPY MARKERS

Tumor Mutational Burden	Microsatellite Instability Status
4.2 m/MB 64th percentile	Stable Equivocal High

FDA-APPROVED THERAPIES, CURRENT DIAGNOSIS

PARP Inhibitor	Olaparib, Talazoparib	BRCA2 p.V220fs Loss-of-function BRCA2 Copy number loss Loss-of-function Consensus, HER2 negative breast cancer: NCCN
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PARP Inhibitor	Niraparib, Rucaparib	BRCA2 p.V220fs Loss-of-function <div>GERMLINE</div> BRCA2 Copy number loss Loss-of-function Consensus, ovarian cancer: NCCN
Anti-PD-1 MAb	Nivolumab, Pembrolizumab	NF1 p.K1036fs Loss-of-function Clinical research, melanoma: PMID 27671167 BRCA2 p.V220fs Loss-of-function <div>GERMLINE</div> BRCA2 Copy number loss Loss-of-function Case study, melanoma: PMID 26997480
mTOR Inhibitor	Everolimus	NF1 p.K1036fs Loss-of-function Case study, head and neck cancer: PMID 26859683
EGFR Inhibitor	Dacomitinib	MAP2K4 p.K114fs Loss-of-function Preclinical, solid tumors: PMID 29795445
MEK Inhibitor	Trametinib	MAP2K4 p.K114fs Loss-of-function Preclinical, solid tumors: PMID 29795445

INVESTIGATIONAL THERAPIES

PI3K Inhibitor	Alpelisib	PIK3CA p.E545K Gain-of-function Clinical research, ER+ HER2- breast cancer: PMID 29401002
Combination (Estrogen Receptor Antagonist + PI3K Inhibitor)	Fulvestrant + Alpelisib	PIK3CA p.E545K Gain-of-function Clinical research, ER+ breast cancer: PMID 30543347
WEE1 Inhibitor	AZD1775	TP53 Copy number loss Loss-of-function Clinical research, solid tumors: PMID 27601554
Combination (PI3K Inhibitor + CDK4/6 Inhibitor)	Pictilisib, Alpelisib + Ribociclib	PIK3CA p.E545K Gain-of-function Preclinical, breast cancer: PMID 25002028

CLINICAL TRIALS

Dose Escalation of RMC-4630 Monotherapy in Relapsed/Refractory Solid Tumors (NCT03634982)	Phase I Duarte, CA - XX mi ✔ NF1 mutation
Javelin BRCA/ATM: Avelumab Plus Talazoparib in Patients With BRCA or ATM Mutant Solid Tumors (NCT03565991)	Phase II Palo Alto, CA - XX mi ✔ BRCA2 mutation ✔ BRCA2 deletion
Phase I Study of LXH254 in Patients With Advanced Solid Tumors Harboring MAPK Pathway Alterations (NCT02607813)	Phase I Houston, TX - XX mi ✔ MAP2K4 mutation

To Evaluate the Safety, Tolerability, and Pharmacokinetics of GDC-0077 Single Agent in Participants With Solid Tumors and in Combination With Endocrine and Targeted Therapies in Participants With Breast Cancer (NCT03006172)

Phase I
Nashville, TN - XX mi
✓ PIK3CA mutation

OLAParib COmbinations (NCT02576444)

Phase II
Cleveland, OH - XX mi
✓ TP53 deletion
✓ PIK3CA mutation

VARIANTS OF UNKNOWN SIGNIFICANCE

Somatic	Mutation effect	Variant allele fraction
ARHGAP35	c.2594C>A p.A865D Missense variant NM_004491	50.3% <div></div>
SEMA3C	c.1981G>C p.V661L Missense variant NM_006379	39.6% <div></div>
TMED1	c.515_530delTCACGCTACTGCGGGC p.L172fs Frameshift NM_006858	31.6% <div></div>
APOB	c.5098G>C p.D1700H Missense variant NM_000384	29.4% <div></div>
BARD1	c.2001+1_2001+6delGTATTT Splice region variant NM_000465	23.1% <div></div>
LRP1B	c.5612G>A p.R1871H Missense variant NM_018557	21.4% <div></div>
POLE	c.6757G>A p.E2253K Missense variant NM_006231	19.1% <div></div>
IL6R	c.953C>A p.S318Y Missense variant NM_000565	13.1% <div></div>
ELF3	c.381C>G p.D127E Missense variant NM_004433	10.7% <div></div>

LOW COVERAGE REGIONS

AREG	FLT4	GFRA2	NOTCH1	OR4F5	PDPK1
SEMA3C					

SOMATIC VARIANT DETAILS - POTENTIALLY ACTIONABLE

⬅️ PIK3CA

c.1633G>A p.E545K NM_006218 Missense variant (exon 10) - GOF

VAF: 45.2%

PIK3CA encodes the catalytic subunit, p110 alpha protein, of the phosphatidylinositol 3-kinase (PI3K) enzyme. The p110 subunit is responsible for the enzyme's phosphorylation activity, and is involved in the PI3K-AKT-mTOR and the Ras-Raf-MEK-ERK pathways that mediate cellular growth and survival. Activating mutations, copy number gains, and overexpression of PIK3CA are associated with cancer progression.

⊕

NF1

c.3107_3113+16del p.K1036fs NM_001042492 Frameshift - LOF

VAF: 28.5%

NF1 is a tumor suppressor that plays a role in cellular growth and differentiation through the regulation of the Ras protein. Loss of function mutations and copy number loss of NF1 are associated with cancer progression.

⊕

MAP2K4

c.339_370del p.K114fs NM_001281435 Frameshift - LOF

VAF: 21.2%

MAP2K4 encodes a protein within the MAP kinase family and functions as a signaling molecule in the Ras-Raf-MEK-ERK pathway. Loss of function mutations, copy number loss, and underexpression of MAP2K4 are associated with cancer progression.

⊖

TP53

Copy number loss

TP53 encodes a tumor suppressor that is commonly disabled across cancer types. It normally functions to activate cellular DNA repair mechanisms, plays a role in cell cycle progression in response to DNA damage, and can initiate apoptosis. Loss of function mutations, copy number loss, and epigenetic modifications resulting in underexpression of TP53 are associated with cancer progression.

⊖

BRCA2

Copy number loss

BRCA2 encodes a nuclear phosphoprotein which helps maintain DNA stability through homologous recombination based DNA double stranded break repair and involvement in DNA damage checkpoint control. The double strand break repair phenotype is associated with tumorigenesis. In addition to a germline BRCA2 pathogenic variant (see below), this tumor shows somatic loss of heterozygosity of BRCA2. These findings suggest that this may be a BRCA2 driven tumor, therefore, PARP inhibitor therapy is suggested. Loss of function mutations and copy number loss of BRCA2 are associated with cancer progression.

SOMATIC VARIANT DETAILS - BIOLOGICALLY RELEVANT

⊖

STAG2

Copy number loss

STAG2 encodes a protein that is a subunit of the cohesin complex, a complex that is required for the process of separating sister chromatids during cell division. Loss of function mutations and copy number loss of STAG2 are associated with cancer progression.

GERMLINE VARIANT DETAILS

⊕

BRCA2

c.658_659delGT p.V220fs NM_000059 Chr13:32903604 Frameshift

Clinical Significance: Pathogenic

This patient has a heterozygous germline pathogenic variant in BRCA2. Germline pathogenic variants in BRCA2 are associated with an increased risk of development of breast, ovarian and fallopian tube cancers in women. Men with pathogenic variants in BRCA2 are at an increased risk to develop breast and prostate cancer, and both men and women are at an increased risk to develop pancreatic cancer. Genetic counseling and appropriate cancer screening are recommended for this patient and any potentially affected family members.

Assay Description

The Tempus xT assay is a custom oncology testing panel consisting of 596 genes with single nucleotide variants, indels and translocations measured by hybrid capture next-generation sequencing (NGS). For the complete gene list, see the [Tempus website](#). The limit of detection of the assay is 5% variant allele fraction (VAF) with sensitivity of 99.1% for single nucleotide variants, 10% VAF with sensitivity of 98.1% for indels and 99.9% sensitivity for translocations. (Certain driver or resistance genes may be reported to lower VAFs when technically possible.)

Assay Description (continued)

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 the patient has consented to receive germline findings).

Tumor mutational burden (TMB) measures the quantity of somatic mutations, of any pathogenicity, including benign, carried in a tumor as the number of single nucleotide protein-altering mutations per million base pairs. 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.

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>

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 sequencing errors.

Genetic alterations are defined as clinically significant based on peer-reviewed published literature and other authoritative sources such as 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.

If the patient has consented to germline reporting, then consistent with the recommendations of the ACMG [1], Tempus reports certain germline secondary/incidental findings. These incidental findings include germline sequencing results associated with serious conditions that may or may not be related to the patient’s current cancer diagnosis but are considered medically actionable. The clinical significance of reported variants is based on germline classification criteria created by the ACMG [2].

Since these are incidental findings and not a stand alone germline test, the rate of false negatives has not been assessed and certain mutations, 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 tests results cannot be used to definitively rule out cancer or other genetic predisposition syndromes, and the results set forth herein should not be used as a substitute for tests validated to determine genetic risk.

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, particularly in the event that deleterious mutations are reported. The ordering physician or the patient is responsible for contacting a genetic counselor to discuss test results.

Tempus Insights

Tempus Disclaimer (continued)

If this report includes a section titled “Tempus Insights”, then in addition to the limitations above in this Disclaimer, the “Tempus Insights” are also subject to certain additional limitations, as described below.

Tempus may, in its sole discretion, populate patient reports with informational “Tempus Insights.” Tempus Insights are observations that may be relevant to a specific patient based upon the similarity of the patient’s clinical or molecular attributes with a subset of patients whose clinical and/or molecular data has been included in an internal Tempus database. Where appropriate (and/or available), the Tempus Insights have been presented with material information (e.g., supporting PubMed citation, size of the population underlying the Insight) and/or statistical analyses (e.g., p-values, confidence intervals) intended to give the ordering physician adequate context to evaluate the potential relevance of the Insight to the patient.

Tempus derives the "Tempus Insights" from the analysis of Tempus' own internal dataset. The data that populate this dataset are, in many cases, gathered from real-world settings (as opposed to within controlled clinical trials), and as such, the analyses run thereon may be subject to certain biases that restrict their generalizability or applicability to individual patients. The data that comprise the Tempus dataset may not be representative of patient populations as a whole, nor relevant to this patient specifically.

The Tempus Insights are current as of the date provided, and reflect the analysis of the patient’s specific data and the internal Tempus database as of the date thereof. Tempus' dataset grows over time and, as a result, the Insight(s) generated from the analysis of the Tempus dataset may (or may not) change as the Tempus dataset includes additional data. Tempus will not update the Tempus Insights, even insofar as subsequent changes to the Tempus dataset would have led to additional and/or contradictory Insights if the Tempus database were to be re-queried with the patient’s information.

Tempus provides the “Tempus Insights” for informational purposes only, and strongly encourages the patient’s physician to consider all available information and options for obtaining additional information before making any patient-specific management or treatment decisions. All context should be taken into account when making a decision for any patient, and in no case should the Tempus Insights be cited as sufficient evidence in any clinical decision.

Any language specific to the insight(s) generated for the patient will be noted below.

1. Kalia SS, Adelman K, Bale SJ, Chung WK, Eng C, Evans JP, Herman GE, Hufnagel SB, Klein TE, Korf BR, McKelvey KD, Ormond KE, Richards CS, Vlangos CN, Watson M, Martin CL, Miller DT., Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Genet Med. 2016 Nov 17. DOI: 10.1038/gim.2016.190.

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.