Dwayne Holder

Diagnosis
Pancreatic Ductal Adenocarcinoma

Accession No.
ABC - 12345678

xT

Date of Birth
8/8/1971

Sex
Male

Physician
Dr. David Patel

Institution
Northwestern University Medical Center
NW-12345-DH6

TEMPUS | xT 596 Genes

Tumor specimen:
Lung, core needle biopsy
Case #ABC 123, B1
Collected on 2/28/2019
Received on 3/2/2019
Tumor percentage: **40%**

Normal specimen:
Blood
Collected on 2/28/2019
Received on 3/1/2019

Notes

This patient has a pathogenic germline BRCA2 mutation combined with somatic loss of heterozygosity, indicating that this is a BRCA2 driven tumor, therefore, PARP inhibitor therapy is suggested. Genetic counseling is recommended for this patient and potentially affected family members.

RNA analysis is being performed and will be reported in the Tempus online portal when complete.

GENOMIC VARIANTS

Somatic - Clinically Actionable

		Variant Allele Fraction
CDKN2A	c.225delC p.A76fs Loss-of-Function	40.7%
KRAS	c.35G>T p.G12V Gain-of-Function	22.0%
BRCA2	Copy Number Loss Loss-of-Function	

Germline

		Clinical Significance
BRCA2	c.1832C>A p.S611* chr13:32907447	Pathogenic Hereditary breast and ovarian cancer

IMMUNOTHERAPY MARKERS

Tumor Mutational Burden

4.7 m/MB 79th percentile

Microsatellite Instability Status

Stable | Equivocal | High

FDA-APPROVED THERAPIES, CURRENT DIAGNOSIS

Combination (EGFR inhibitor + Anti-metabolite)	**Erlotinib + Gemcitabine**	KRAS p.G12V Gain-of-Function Resistance Clinical research, pancreatic cancer: PMID 21862683

FDA-APPROVED THERAPIES, OTHER INDICATIONS

PARP inhibitors	**Olaparib, Rucaparib, Niraparib**	BRCA2 Copy Number Loss Loss-of-Function BRCA2 p.S611* Loss-of-Function GERMLINE Consensus, ovarian cancer: NCCN
	Olaparib	BRCA2 Copy Number Loss Loss-of-Function BRCA2 p.S611* Loss-of-Function GERMLINE Consensus, breast cancer: NCCN
CDK4/6 inhibitor	***Palbociclib*** *Already prescribed*	*CDKN2A p.A76fs Loss-of-Function* *Clinical research, breast cancer: PMID 26715889*
Pan-RAF Inhibitor	**Verteporfin**	KRAS p.G12V Gain-of-Function Preclinical, pancreatic cancer: PMID 28576749

Tempus can only report already prescribed therapies based on the clinical documents we receive and have abstracted, which may not reflect the complete treatment history.

Gemcitabine hydrochloride and cisplatin with or without veliparib or veliparib alone in treating patients with locally advanced or metastatic pancreatic cancer	✓ **BRCA2** Phase II: NCT01585805 University of Chicago, 6 mi
Genetic analysis-guided dosing of FOLFIRABAX in treating patients with advanced gastrointestinal cancer	Phase I/II: NCT02333188 University of Chicago, 6 mi
Study of PD1 Blockade by Pembrolizumab With Stereotactic Body Radiotherapy in Advanced Solid Tumors	Phase I: NCT02608385 University of Chicago, 6 mi

VARIANTS OF UNKNOWN SIGNIFICANCE

Somatic variant	Mutation effect		Variant allele fraction
ARHGAP5	c.1441G>T	p.E481*	18.6%
ARHGAP5	c.1465G>A	p.E489K	22.1%
CCT6A	c.725+1G>A	Splice-Donor	21%

LOW COVERAGE REGIONS

CDKN1C	GFRA2	NOTCH1	PDPK1	RECQL4
FLT4	MTAP	NOTCH2	PIK3R2	ZNRF3

SOMATIC VARIANT DETAILS - CLINICALLY ACTIONABLE

CDKN2A c.225delC p.A76fs Frameshift - Loss of Function — Variant Allele Fraction: 40.7%

CDKN2A encodes two proteins, p16(INK4A) and p14(ARF) which function in regulating cell growth. The p16(INK4A) protein regulates the cell cycle through the inhibition of CDK4 and CDK6, preventing them from stimulating cell proliferation. The p14(ARF) protein binds to MDM2 to keep p53 intact and stimulate the p53-dependent cell cycle arrest and apoptosis. Deleterious single nucleotide variants, copy number loss and underexpression of CDKN2A are associated with cancer progression.

KRAS c.35G>T p.G12V Gain of Function — Variant Allele Fraction: 22.0%

KRAS encodes 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 MAPK cascade. Activating mutations in KRAS are associated with cancer progression.

BRCA2 Copy Number Loss Loss of Function

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.

BRCA2 chr13:32907447 c.1832C>A p.S611*

Clinical Significance: ● Pathogenic

This patient has a heterozygous germline pathogenic variant in BRCA2, therefore, PARP inhibitor therapy is recommended. 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. 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.

CLINICAL HISTORY

2018

- **Release from Northwestern ICU**
  1/6/2018

2017

- **Biopsy: Lung**
  MRI: Abdomen
  12/29/2017
- **Admitted to Northwestern ICU**
  12/27/2017
- **Started Palbociclib**
  Ended Gemcitabine
  9/10/2017
- **CT: Chest**
  9/2/2017
- **Started Gemcitabine**
  6/23/2017
- **Diagnosis: Pancreatic ductal adenocarcinoma T2 N0 M0**
  CT: Chest
  Pancreaticoduodenectomy
  Northwestern University Medical Center
  Comorbidity: Diabetes
  6/19/2017

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, 30% VAF with sensitivity of 95.7% for CNVs, and 99.9% sensitivity for translocations. (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 the patient has consented to receive germline findings).

Tumor mutational burden (TMB) measures the quantity of somatic mutations, of any pathogenicity, including benign, detected in the tumor as the number of single nucleotide protein-altering mutations per million base pairs. TMB is calculated using variants with an alternate allele fraction greater than or equal to 5%, therefore the limit of detection is 5% VAF. 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. The limit of detection for MSI status is 30% tumor sample with a sensitivity of 99.9%. If MSI status will affect clinical management, immunohistochemical staining for DNA mismatch repair proteins, or another method of ascertaining MSI status, is recommended.

When there is sufficient quantity and quality of nucleic acid, whole transcriptome RNA-Seq is done for the tumor sample using IDT xGen Exome Research Panel v1.0 hybridization probes. Then fusion transcripts are detected by the bioinformatics pipeline which shows the positions of breakpoint spanning reads and split paired-end reads. These data are compared to the Tempus knowledge database of previously reported fusion transcripts. Non-canonical fusion transcripts may be reported at the discretion of the medical director.

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 sequence-specific alterations can be affected in many ways, related and unrelated to the tumor DNA. First, the quality of tumor DNA obtained from formalin-fixed samples is generally poor and can result in degraded and damaged DNA. Second, the quantity of DNA obtained can be very low, limiting the amount of DNA that can be successfully analyzed by next generation sequencing. Third, the purity of tumor DNA can be a factor, as a significant portion of the DNA analyzed in the tumor sample may be derived from contaminated normal tissues. These three aspects can reduce the chance of detecting somatic sequence alterations. Additionally, next generation sequencing approaches may provide incorrect sequence or mutational data due to insuffi cient coverage in specific regions of the genome an inability to distinguish highly related human sequences, and sequencing errors.

Sequence mutations, including single base and small insertions/deletions, are evaluated where the allele frequency is > 5.0%, and amplifications are evaluated when change is 4 fold or greater. These numbers are subject to change based on the depth and quality of the sequencing.

Genetic alterations are defined as clinically significant based on study results in peer-reviewed published literature and other authoritative sources. These references are not comprehensive, therefore clinically unknown findings may occur.

The results of the Tempus Test are intended for use solely by the patient's clinical care team. In making any diagnosis, counseling, or treatment decisions, qualified health professionals should evaluate these results in the context of other individual patient health information, including clinical presentation and other test reports.

As requested by the ordering physician/institution, and in accordance with the recommendations of the ACMG, [1] Tempus has also included as secondary findings in this report sequencing results for variants in 59 genes that are associated with serious conditions unrelated the the patient's current cancer diagnosis and that are considered medically actionable. The clinical significance of specific variants is based on germline classification criteria created by the ACMG [2].

Results of germline genetic testing may have implications for both the patient and family members. Tempus does not provide genetic counseling. If genetic counseling is desired, the ordering physician or the patient is responsible for contacting a genetic counselor to discuss test results.

These test results and Information contained within the report is 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. Tempus is not liable for medical judgment with regards to diagnosis, prognosis or treatment in connection with the test results. The results in this report should be interpreted in the context of the patient's clinical profile and family history.

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.