Anil Patel

Diagnosis
Metastatic carcinoma, c/w prostatic primary

Accession No.
ABC-12345678

xT

Date of Birth
06/09/1947

Sex
Male

Physician
Rebecca Pryor

Institution
Chicago Cancer Center
CCC12345678

TEMPUS | xT 596 Genes

Tumor specimen:
Lymph node, left inguinal
Chicago Cancer Center
#ABC 123, C2
Collected 3/08/2019
Received 3/18/2019
Tumor Percentage: 70%

Normal specimen:
Blood
Collected 3/20/2019
Received 3/22/2019

Notes

The tumor shows loss of heterozygosity in TP53.

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

GENOMIC VARIANTS

Somatic - Potentially Actionable

		Variant Allele Fraction
TP53	p.R196* Stop gain - LOF	61.4%
AR	Copy number gain	
CDKN2A	Copy number loss	
TMPRSS2 - ERG	Chromosomal rearrangement	

Somatic - Biologically Relevant

CDKN2B	Copy number loss

Germline - Pathogenic / Likely Pathogenic

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

IMMUNOTHERAPY MARKERS

Tumor Mutational Burden

2.1 m/MB 40th percentile

Microsatellite Instability Status

Stable | Equivocal | High

FDA-APPROVED THERAPIES, CURRENT DIAGNOSIS

Anti-androgen	***Abiraterone*** *Already prescribed*	*AR Copy number gain* *Resistance Clinical research, prostate cancer: PMID 26537258*

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.

FDA-APPROVED THERAPIES, OTHER INDICATIONS

CDK4/6 Inhibitor	**Palbociclib**	CDKN2A Copy number loss Loss-of-function Preclinical, renal cell carcinoma: PMID 23898052 Preclinical, melanoma: PMID 24495407
Combination (PARP Inhibitor + Radiotherapy)	**Rucaparib + Radiation**	TMPRSS2-ERG Chromosomal rearrangement Preclinical, prostate cancer: PMID 26026052

WEE1 Inhibitor	**AZD1775**	TP53 p.R196* Loss-of-function Clinical research, solid tumors: PMID 27601554

ADDITIONAL INDICATORS

Diagnostic	TMPRSS2-ERG Chromosomal rearrangement Clinical research, prostate cancer: PMID 16254181

CLINICAL TRIALS

OLAParib COmbinations (NCT02576444)	**Phase II** Cleveland, OH - XX mi ✓ **TP53 mutation** ✓ **CDKN2A deletion** ✓ **CDKN2B deletion**
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** Ann Arbor, MI - XX mi ✓ **CDKN2A deletion**
Study of AG-270 in Subjects With Advanced Solid Tumors or Lymphoma With MTAP Loss (NCT03435250)	**Phase I** Nashville, TN - XX mi ✓ **CDKN2A deletion**

VARIANTS OF UNKNOWN SIGNIFICANCE

Somatic	**Mutation effect**	**Variant allele fraction**
TMPRSS2	c.1339_1424del p.C447fs Frameshift NM_001135099	38.0%
EGF	c.1153G>C p.G385R Missense variant NM_001963	37.3%
FGFR4	c.2273G>A p.R758H Missense variant NM_002011	33.3%
FGFR4	c.1985T>C p.F662S Missense variant NM_002011	29.4%
BCL11B	c.2098G>A p.A700T Missense variant NM_138576	26.5%

Germline	**Mutation effect**	**Condition**
BMPR1A	c.1433G>A p.R478H Missense variant chr10:88683223 NM_004329	Juvenile polyposis

FLT4	GFRA2	NOTCH1	PDPK1	TAF1

SOMATIC VARIANT DETAILS - POTENTIALLY ACTIONABLE

TP53 c.586C>T p.R196* NM_000546 Stop gain - LOF VAF: 61.4%

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.

AR Copy number gain

AR encodes the androgen receptor protein, a hormone receptor important for male sexual development during embryonic development and again at puberty. Binding of androgens, such as testosterone, results in an androgen-receptor complex that binds to DNA and regulates the activity of androgen-responsive genes. Activating mutations and copy number gains of AR are associated with cancer progression.

CDKN2A Copy number loss

CDKN2A encodes two proteins, p16(INK4a) and p14(ARF), that 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. Loss of function mutations, copy number loss, and underexpression of CDKN2A are associated with cancer progression.

TMPRSS2 - ERG Chromosomal rearrangement

ERG is an oncogene and transcription factor in the erythroblast transformation-specific (ETS) family. It normally functions in embryonic development, cell differentiation, apoptosis, and angiogenesis. ERG forms an oncogenic fusion gene with the 5’-UTR of TMPRSS2. The 5'-UTR of TMPRSS2 contains androgen responsive regulatory elements that drive ERG overexpression. In addition to this fusion, amplification and overexpression of ERG are associated with cancer progression.

SOMATIC VARIANT DETAILS - BIOLOGICALLY RELEVANT

CDKN2B Copy number loss

CDKN2B encodes p15(INK4b), a protein that functions in regulating cell growth. The p15(INK4b) protein regulates the cell cycle through the inhibition of CDK4 and CDK6, preventing them from stimulating cell proliferation. Loss of function mutations, copy number loss, epigenetic variation, and underexpression of CDKN2B are associated with cancer progression.

CLINICAL HISTORY

2019

- **Started Docetaxel**
  End date unknown
  03/20/2019

2017

- **Started Enzalutamide**
  End date unknown
  Started Leuprolide
  End date unknown
  11/2017

- **Ended Leuprolide**
  Ended Abiraterone
  09/2017

- **Ended Sipuleucel-T**
  07/2017

- **Started Sipuleucel-T**
  Started Leuprolide
  Started Abiraterone
  06/2017

UNKNOWN DATE

- **Radiotherapy, not otherwise specified**
- **Leuprolide**
- **Surgical procedure, not otherwise specified**

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.)

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.

Assay Description (continued)

When whole transcriptome RNA-Seq is done, expressed fusion transcripts from rearranged genes are detected in an unbiased (non-targeted) fashion. The Tempus RNA whole transcriptome assay uses the IDT xGen Exome Research Panel v1.0 hybridization probes. The fusion transcript detection bioinformatics pipeline analyzes and shows the positions of breakpoint spanning reads and split paired-end reads. This is 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 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

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.

Tempus Disclaimer (continued)

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.