TruSight™ Oncology 500

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Peter MacCallum Cancer Centre
305 Grattan Street
Melbourne Victoria, 3000
Australia

Peter Mac
Peter MacCallum Cancer Centre
Victoria Australia

PATIENT	DOB	DISEASE	MRN	REPORT DATE	REPORT STATUS
[redacted]	[redacted]	Large cell neuroendocrine carcinoma	[redacted]	[redacted]/2020	Final

REPORT SUMMARY

Executive Summary

TMPRSS2-ERG fusion was detected. *TMPRSS2-ERG* fusions are most frequently found in prostate carcinoma. Please correlate with pathological, radiological, and clinical features.

PTEN copy number loss with potential clinical significance was detected.

Discussed at Variant Review Meeting on [redacted]-2020.

Other Biomarkers

BIOMARKER	LEVEL
TMB	Low
MSI	Stable

Genomic Findings

IA	IB	IIC	IID
No variants reported.	No variants reported.	***TMPRSS2, ERG*** *TMPRSS2-ERG* fusion transcript **0** Clinical Trials	***PTEN*** Copy number loss in *PTEN* (0 copies) **0** Clinical Trials

CLINICALLY RELEVANT RESULTS

Tier I - Strong Clinical Significance

No variants were reported for this classification tier.

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Tier II - Potential Clinical Significance

VARIANT	CLINICAL IMPACT

TMPRSS2, ERG

TMPRSS2-ERG fusion transcript

C

INTERPRETATION

A rearrangement involving *TMPRSS2 and ERG* genes predicts an in-frame gene fusion. *TMPRSS2* and *ERG* are located in close proximity on 12q22.13. *TMPRSS2* is a prostate-specific and androgen-responsive gene that encodes a transmembrane serine protease 2, a member of the serine protease family. *ERG* is an oncogene that encodes a member of the erythroblast transformation-specific family of transcription factors. *ERG* functions in key cellular processes, including cell proliferation, differentiation, angiogenesis, and apoptosis [PMID: 25915839]. In the Catalogue of Somatic Mutations in Cancer database (https://cancer.sanger.ac.uk/cosmic), *TMPRSS2-ERG* gene fusions are found exclusively in prostate cancer (>2000 occurrences). Clinically, the presence of the *TMPRESS2-ERG* fusion is regarded as pathognomomic for prostatic origin [PMID: 29629426]. The fusion has been reported in both primary and castration-resistant prostate carcinoma with comparable frequencies of 40-50% [PMID: 20303538, 31748536]. The *TMPRSS2-ERG* fusion leads to overexpression of *ERG* in a hormone-dependent manner through androgen-responsive promoter elements of *TMPRSS2*, promoting cell proliferation [PMID: 23264855]. Elevated ERG protein or mRNA expression has been shown to be associated with high Gleason score and increased tumour stage in prostate carcinoma [PMID: 30658688]. There are currently no therapies directly targeting *ERG* alterations in cancer.

PTEN

Copy number loss in *PTEN* (0 copies)

D

Unfavorable Prognosis in

— Malignant tumor of prostate or Primary malignant neoplasm of prostate

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VARIANT	CLINICAL IMPACT

INTERPRETATION

PTEN (phosphatase and tensin homologue) is a tumour suppressor and functions as a core inhibitory component of the phosphoinositide 3-kinase (PI3K) signalling pathway. *PTEN* inactivation by either genomic deletion or point mutations occurs in a broad spectrum of tumour types and is typically mutually exclusive with *PIK3CA* activating alterations [PMID: 28481359, 24132290]. Loss of PTEN function results in primarily activation of the PI3K/AKT/mTOR pathway, and also increases the activity of other kinases such as JNK, MAPK, STAT, and FAK [PMID: 21430697]. Preclinical studies show that PTEN loss is associated with elevated PI3K-β expression, providing a rational basis for targeting the PI3K/AKT/mTOR pathway in *PTEN*-mutated tumours [PMID: 21430697, 27621407, 24440717]. Loss of *PTEN* has been shown to promote tumour progression in prostate tumours harbouring *TMPRSS2-ERG* fusion [PMID: 19396168]. *PTEN* deficiency has recently been described as a mechanism of resistance to immune checkpoint blockade in a case study of uterine leiomysarcoma and in patients with metastatic melanoma [PMID: 26645196, 28228279].

Other Biomarkers

BIOMARKER	CLINICAL IMPACT
TMB Low 1.6 muts/Mb	**Not likely to benefit from** — Immune checkpoint inhibitors *in Tumours with low TMB*

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BIOMARKER CLINICAL IMPACT

INTERPRETATION

The tumour mutation burden (TMB) in this tumour is less than 10 mutations/Mb (TMB-L). In the phase II basket study KEYNOTE-158 (NCT02628067), of 102 patients with TMB-H tumours given pembrolizumab, 30 responded (ORR 29%, 95% CI, 21-39) with 4% having a complete response and 50% having ongoing responses after 24 months. In June 2020, US FDA gave accelerated approval for pembrolizumab in patients with unresectable or metastatic solid tumours that have progressed on prior treatment or have no other treatments options, if TMB is ≥10 mutations/Mb measured by an approved test, regardless of histological type.

MSI

Stable

2.0%
Unstable Sites

Not likely to benefit from

— Immune checkpoint inhibitors *in Mismatch repair-proficient cancer*

INTERPRETATION

Mismatch repair-deficient cancers are likely to benefit from immune checkpoint blockade regardless of tissue of origin [PMID: 28596308].

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POTENTIAL CLINICAL TRIALS

Clinical Trials associated with this patient's genomic profile and tumor type are displayed below.

TITLE	TRIAL IDENTIFIER	PHASE	VARIANT
[redacted]	[redacted]	[redacted]	

TIER III - VARIANTS OF UNCERTAIN SIGNIFICANCE

ERG, IFNAR1	*FOXL2*	*IFNAR1, TMPRSS2*
ERG-IFNAR1 fusion transcript	p.S372* NM_023067.3 c.1115C>A	*IFNAR1-TMPRSS2* fusion transcript

CLASSIFICATION AND LEVELS OF EVIDENCE

The variant classification system used in this report is based on joint consensus recommendations of the Association for Molecular Pathology, American Society of Clinical Oncology, and the College of American Pathologists (J Mol Diagn 2017, 19:4-23). Tiers IA, IB, IIC, IID, III and IV describe variant categories of descending clinical significance in the patient. Variants in Tier IV are not reported in accordance with the consensus recommendations.

IA	IB	IIC	IID
Variant of strong clinical significance, Level A evidence (FDA approved therapy or practice guideline in patient's tumor type)	Variant of strong clinical significance, Level B Evidence (consensus in the field based on well-powered studies in patient's tumor type)	Variant of potential clinical significance, Level C evidence (FDA approved therapy or practice guideline in other tumor type(s), evidence from multiple small published studies, or based on availability of investigational therapies)	Variant of potential clinical significance, Level D evidence (case reports or preclinical studies)

III	Variant of uncertain clinical significance
IV	Benign or likely benign variant

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OTHER TEST RESULTS

No other test results related to this episode are available.

TEST DETAILS

REPORTED GENES

A total of 523 genes were subjected to targeted next generation sequencing analysis. Details available upon request.

CGW VERSION

CGW_v6.13

DATABASE DETAILS

The versions, releases, builds, dates of the following databases were used to generate this report.

- Genomic Build: GRCh37.p13
- Genomic Annotation Sources: NCBI RefSeq v105
- NHLBI ESP: v.0.0.30
- dbSNP: 149
- dbNSFP: 3.5c
- gnomAD: r2.1
- ExAC: v1.0
- COSMIC: v89
- ClinVar: 20190603

CODING EXON COVERAGE METRICS

Level 2 metrics are not available.

METHODOLOGY

Targeted sequencing of 523 cancer genes from DNA and 55 cancer genes from RNA was performed using the Illumina TruSight ™ Oncology 500 assay (TSO500). DNA and RNA were extracted from the submitted formalin-fixed paraffin-embedded (FFPE) tumour sample using the Qiagen AllPrep DNA/RNA FFPE kit. RNA was reverse transcribed to cDNA. DNA was sheared to an appropriate size range. Unique Molecular Identifier (UMI) containing libraries were prepared and enriched with magnetic streptavidin beads following targeted hybridisation to biotinylated probes. Pooled, normalised libraries were sequenced to an approximate target mean coverage on an Illumina NextSeq500 instrument.

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Illumina Software TSO500 v2.0.0 Local App was used to generate aligned reads and call variants against the hg38 human reference genome. Clinical Genomics Workspace (CGW) software platform from PierianDx was used to annotate, filter and report clinically relevant findings.

TSO500 DNA analysis detects single-nucleotide and multi-nucleotide variants <3nt (SNV), small Insertions up to 18nt and Deletions up to 27nt (Indels), Copy Number Variants (CNVs), Microsatellite Instability (MSI) and tumour mutational burden (TMB). TSO500 RNA analysis detects gene fusions and splice variants. Variants are described according to HGVS nomenclature (http://varnomen.hgvs.org/) and classified as per AMP/ASCO/CAP guidelines for the interpretation of somatic variants (Li et al., J Mol Diagn. 2017;19(1):4-23). Variations found in gnomAD (https://gnomad.broadinstitute.org/) with ≥ 1% minor allele frequency (except those regarded as clinically relevant) are classified as polymorphisms. Some exons found in minor transcripts of certain genes are not targeted by TSO500. Some variants in genes with sequence homology to multiple genomic locations are excluded from reporting. This assay does not detect complex structural variations and large or complex Indels and is unable to discriminate between somatic and germline variants.

Please contact the laboratory on (03) 8559 8401 if you wish to discuss the performance characteristics of this assay.

DISCLAIMER

A Peter Mac pathologist HAS NOT reassessed the original diagnosis. Tumour cell purity within the area selected for analysis was estimated but no formal pathology review was conducted. This test result is based solely on an H&E prepared from the tissue provided and not from the original diagnostic slides. The Peter Mac pathologist did not have access to the original H&E, special stains or other ancillary and clinical information. This pathology assessment is not a confirmation of malignancy but verifies the presence of atypical cells consistent with tumour as diagnosed by the reporting pathologist. Peter Mac assumes sample identification, family relationships, and clinical diagnoses are as stated on the request form. Our clinical recommendations may be based on evidence from third-party data sources and should be interpreted in the context of all other clinical and laboratory information for this patient.

The test performance characteristics were determined by Peter Mac. This laboratory is accredited by NATA to perform NGS targeted panel testing on somatic tissue

Accreditation:
NATA & RCPA Accredited Laboratory Number 2465
Accredited for Technical Compliance
Accredited for Compliance with NPAAC Standards and ISO 15189

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PATIENT AND ORDER DETAILS

PATIENT

DATE OF BIRTH
[redacted]

SEX
Male

ETHNICITY
Not Reported

RACE
Not Reported

AGE
[redacted]

PHYSICIAN

ORDERING PHYSICIAN
[redacted]

FACILITY
Private Provider

COPY TO

SPECIMEN

DATE COLLECTED
[redacted]/2020

DATE RECEIVED
[redacted]/2020

EXT. SPECIMEN ID
[redacted] 1A

SPECIMEN TYPE
Formalin-fixed paraffin-embedded tissue specimen

ANATOMICAL SITE
R iliac node

% TUMOR CELL NUCLEI IN THE SELECTED AREA
80

CASE

ACCESSION NUMBER
[redacted]

DATE ACCESSIONED
[redacted]/2020

DATE REPORTED
[redacted]/2020

REVIEW STATUS
Final

Report electronically reviewed and signed out by

Andrew Fellowes

Date Reported: [redacted]/2020