Comprehensive Molecular Profiling
Liquid Biopsy Final Report

PATIENT, SAMPLE

Date of Birth: **1950** Gender: **Female**
Report Number: **OR000123456-3021** Report Date: **21-Oct-2022**
Specimen Source/ID: **FFPE**
Ordering Physician: **Dr. First-Name I. Ordering-Physician-Last-Name**
Diagnosis: **Adenocarcinoma of Prostate**

GENETIC RESULT: POSITIVE - CLINICALLY SIGNIFICANT MUTATIONS IDENTIFIED

TMB
7.5 muts/Mb
Medium

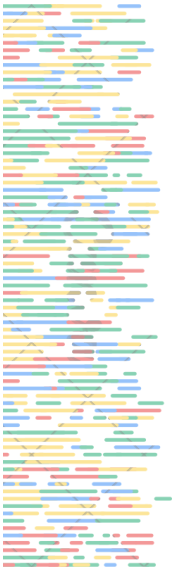
MSI
0.1% Unstable Sites
Stable

PD-L1
CPS %45

IA	IB	IIC	IID
	2 Clinical Trials	3 Clinical Trials	0 Clinical Trials
No Variants Reported	**AR** Copy number gain in AR (3 copies)	**TP53** p.H179R c.536A>G **TP53** p.R248W c.742C>T **ERCC3** p.R109* c.325C>T **ATM** Copy number loss (1 copy) **PTEN** Copy number loss (1 copy) **KIT** Copy number gain (3 copies) **PDGFRA** Copy number gain (3 copies)	**CIC** p.Y770Vfs*1 61 c.2303dupC **MDM4** Copy number gain (4 copies)

REPORT SUMMARY

Comprehensive Genomic Analysis with Liquid Biopsy using cfDNA obtained from our patient's peripheral blood: genomic markers **MSI: Stable (0.1%)**, **TMB: Medium (7.5 muts/mb)** were found. In our patient's plasma, 523 genes and 23 non-coding breakage regions were investigated for genetic changes such as point mutation, in/del changes, amplification, deletion and translocation; pathogenic and driver (driver) considered: ATM and PTEN genes copy number losses (LOH); **AR (3 copies)**, MDM4 (4 copies), KIT (3 copies), PDFRA (3 copies) genes copy number changes; TP53 p.h179r c.536a>g, TP53 p.r248w c.742c>t, CIC p.y770vfs161 c.2303dupc, ercc3 p.r109 c.325c>t mutations were detected. In the same cfdna sample of our patient: AKT2, CCNE1, ERCC1, ERCC2, FGF8, PIK3CB and RET genes copy number losses (LOH); FGF5 (3 copies) and JAK2 (3 copies) genes copy number changes; CDKN2A p.t31m p.t72m (vaf 61%), DNMT3A p.v684i c.2050g>a (vaf 30.9%), DOT1L p.s615 c. 1844c>a (vaf 15.2%), EPHA7 p.a245t c.733g>a (vaf 50.6%), KDM6A p.g291efs34 c.870delc (vaf 0.3%), magi2 p.r839h c. 2516g>a (vaf 47.6%), myod1 p.p186rfs25 c.557delc (vaf 0.4%), tet2 p.q706lfs41 c.2117_2129del13 (vaf 0.1%), ZBTB7A p.a180rfs*14 c.537dupc (vaf 0.7%) variations were detected, but the clinical significance of these variations is unknown (VUS). The primary treatment of metastatic prostate cancer is androgen deprivation therapy (ADT). **AR (Androgen Receptor)** amplification was detected in our patient's plasma sample, and genetic changes such as amplification or mutations in the AR gene have been reported to be responsible for resistance to adt treatment (pmid: 30425524; pmid:36009418; pmid: 24931201). **AR** copy number change indicates that our patient will not benefit from treatments containing Abiraterone, Prednisone and Enzalutamide and their combinations.



No mutation was detected in BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, or RAD54L homologous recombination pathway with dna repair (HRR) genes in our patient's analyzed plasma sample. However, copy number losses (LOH) were observed in the ATM and PTEN genes. In addition, LOH was observed in at least 4 other chromosome regions. Although this test is not a validated test for the gLOH score, due to the number of loh observed, our patient's tumor was evaluated as a gLOH high and HRR defective tumor. Olaparib is one of the treatment options for patients with Metastatic Castration Resistant Prostate Cancer (MCRPC) who have a somatic or germline pathogenic mutation in one of the HRR genes or HRR defective (pmid: 32955174; pmid:34045297). The clinical benefit of Olaparib, a Parp Inhibitor, in MCRPC patients, has been accepted by the FDA and this treatment recommended by the guidelines (NCCN Prostate Cancer v.1 2023). PDGFRA and KIT genes amplification was detected in the plasma sample analyzed by our patient. These genes are located in the 4q12 region and 4q12 amp has been reported in many cancer types (pmid: 31604903). Another Tyrosine Kinase gene KDR gene is also partially located in this amplicon in our patient. Preliminary clinical studies have reported that a multikinase inhibitor such as Pazopanib provided clinical benefit in patients with this co-amplification (pmid: 36139590). Lenvatinib is another multikinase inhibitor and has been reported to provide clinical benefit in the treatment of advanced-stage cancers with an immunotherapy agent such as Pembrolizumab (pmid: 3645727; pmid: 33616314). Clinical trials evaluating the safety and clinical efficacy of the combination of Pembrolizumab and Lenvatinib continue to accept patients with MCRPC and advanced/metastatic Endocrine Prostate Cancer (nct04848337; nct02861573). The NCCN guideline recommends Pembrolizumab treatment for MCRPC patients with MSI-H, dMMR or TMB ≥10 mut/mb.

Clinically Relevant Results

Tier I - Strong Clinical Significance

AR Copy number (3 copies)

B

CLINICAL IMPACT

Not likely to benefit from Abiraterone in combination with Enzalutamide and Prednisone in Metastatic castration-resistant prostate cancer

Interpretation

In our patient, we observed an increased copy number variation (3 copies) in AR gene. AR (also called dihydrotestosterone receptor) functions as a steroid□hormone-activated transcription factor and regulates cell proliferation and differentiation (RefSeq, Jan 2017; UniProt.org). Some evidence indicates that metastatic castration-resistant prostate cancer harboring an AR amplification may not benefit from abiraterone in combination with enzalutamide and prednisone, based on overall survival and time to progression in phase II clinical trial of 202 participants treated with androgen receptor signaling inhibitors (PMID: 34083234). Some clinical studies indicate that castration-resistant adenocarcinoma of the prostate harboring an AR amplification may not benefit from abiraterone in combination with prednisone, based on progression-free survival and overall survival in a prospective study of 109 participants (PMID: 28472366). Some evidence indicates that metastatic castration-resistant adenocarcinoma of prostate harboring an AR amplification may not benefit from abiraterone as first-line therapy based on overall survival and progression-free survival in a retrospective study of 54 participants with ongoing LHRH analog treatment and without prior docetaxel therapy (PMID: 33500577).

Some evidence indicates that metastatic castration-resistant carcinoma of the prostate harboring an AR amplification may not benefit from abiraterone based on progression-free survival in a prospective study of 41 participants (PMID: 32487321). Emerging evidence indicates that metastatic castration-resistant prostate cancer harboring an AR amplification is not likely to benefit from enzalutamide based on overall survival and progression-free survival in a meta-analysis of 630 participants (PMID: 35050750). Some evidence suggests that metastatic castration-resistant prostate cancer harboring an AR amplification may be associated with an unfavorable prognosis based on: a) overall survival and progression-free survival in a prospective study of 106 participants following chemotherapy or androgen receptor signaling inhibitors (PMID: 35331214); b) overall survival in a prospective study of 70 participants following disease progression on androgen-deprivation therapy without prior chemotherapy (PMID: 29858592); c) a retrospective study of 187 participants (PMID: 34157173); and d) progression-free survival in a prospective study of 91 participants (PMID: 34254334).

Tier II - Potential Clinical Significance

CLINICAL IMPACT

TP53 p.H179R c.536A>G

B

Interpretation

TP53 p.H179R is a missense alteration located within the DNA-binding domain (DBD) of the p53 protein (PMID: 18410249), and this mutated amino acid was identified as a recurrent hotspot (statistically significant) in a population-scale cohort of tumor samples of various cancer types (cancerhotspots.org). DBD mutations are thought to result in loss of function via the loss of transactivation of p53-dependent genes (PMID: 12826609). TP53 p.H179R results in a loss of Tp53 protein function as indicated by failure to activate downstream gene transcription and increased survival (PMID: 17361096, PMID: 26585234), and also induces cancer gene signature through activation of Ras signaling (PMID: 22427690). TP53 p.H179R has been reported to result in substantially reduced transactivation capacity, as compared with wild-type TP53, in yeast assays (IARC TP53 Database; PMID: 12826609, PMID: 17311302). Therefore, this alteration is considered oncogenic. In prostate cancer patients carrying defects in at least 2 of PTEN, TP53, and RB1: Cabazitaxel 20 mg/m2 plus carboplatin AUC 4 mg/mL per mon with growth factor support can be considered for fit patients with aggressive variant prostate cancer (visceral metastases, low PSA and bulky disease, high LDH, high CEA, lytic bone metastases, NEPC histology) or unfavorable genomics (defects in at least 2 of PTEN, TP53, and RB1) (PMID: 31515154; NCCN 'Prostate Cancer' v.3.2022). However, no PTEN or RB1 mutations were detected in this sample

TP53 mutations have been reported in 30% of prostate cancer samples in cBioPortal for Cancer Genomics (cBioPortal.org; February 2023). TP53 mutation and nuclear accumulation of p53 protein have been shown to occur late in the development of prostate cancer and be associated with metastasis, advanced disease, and androgen-independent growth (PMID: 7692074, PMID: 18552821, PMID: 25827447, PMID: 26000489, PMID: 28446506). TP53 encodes the p53 tumor suppressor protein, a transcription factor that responds to cellular stresses, including DNA damage and oncogenic activation, by inducing downstream anti-tumor responses such as DNA repair and apoptosis (PMID: 11099028). The p53 protein consists of an N-terminal transactivation domain, a central DNA-binding domain, an oligomerization domain and a C□terminal regulatory domain (PMID: 22713868). Loss of tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers (PMID: 19935675). Carriers of a germline mutation in TP53 have Li-Fraumeni Syndrome, an inherited cancer syndrome resulting in multiple tumors in early adulthood, including breast cancer, brain tumors, and leukemias (PMID: 1978757, PMID: 2259385, PMID: 1683921). Expression of p53 in normal cells is low; however, TP53 alterations, including those that result in loss of p53 tumor suppressor function, may lead to stabilization and increased expression of p53, particularly in the nucleus, and several studies have shown that it may have oncogenic gain-of□function effects (PMID: 15625370, PMID: 11400116, PMID:12826609, PMID: 21760960, PMID: 18802452). Currently, no approved therapies are available that target TP53 alterations, despite their high prevalence in cancer. Therapeutic approaches under investigation include gene therapy for TP53 and (dendritic cell-based) TP53 vaccines (PMID: 24583792, PMID: 21541192, PMID: 24982341). Inhibition of components of the DNA damage checkpoint, including Checkpoint Kinase 1 (Chk1) and Wee1, has been reported to enhance the activity of DNA-damaging agents in preclinical cancer models with deficiency of p53 function (PMID: 21087899, PMID: 20107315, PMID: 21799033). Clinical trials of the Wee1 inhibitor adavosertib (MK-1775) are currently underway for patients with solid tumors and hematologic malignancies. Olaparib in combination with AZD1775 (WEE1 inhibitor) is in phase II clinical trial to determine tumor overall response rate in patients with advanced solid tumors harboring TP53 mutations (NCT02576444, Active, not recruiting).

Studies have reported Aurora kinase A to be activated in cells harboring TP53 mutation, and Aurora kinase A and B inhibitors have been reported to activate wild-type p53 in cellular assays; thus, tumors retaining a wild-type TP53 allele may benefit from Aurora kinase inhibitors (PMID: 25398437, PMID: 25512615, PMID: 21761334, PMID: 25758253, PMID: 22611192, PMID: 23955083). Some studies suggest that Hsp90 inhibitors may be effective in tumors with oncogenic TP53 alterations (PMID: 26009011, PMID: 17982489). Mutations in TP53 may increase resistance to ionizing radiation therapy (PMID: 14576853, PMID: 25913131). TP53 mutations have been significantly associated with platinum resistance in studies of ovarian cancer cases (PMID: 25385265, PMID: 28148293).

Tier II - Potential Clinical Significance

TP53 p.R248W c.742C>T

C

Interpretation

Studies have reported Aurora kinase A to be activated in cells harboring TP53 mutation, and Aurora kinase A and B inhibitors have been reported to activate wild-type p53 in cellular assays; thus, tumors retaining a wild-type TP53 allele may benefit from Aurora kinase inhibitors (PMID: 25398437, PMID: 25512615, PMID: 21761334, PMID: 25758253, PMID: 22611192, PMID: 23955083). Some studies suggest that Hsp90 inhibitors may be effective in tumors with oncogenic TP53 alterations (PMID: 26009011, PMID: 17982489). Mutations in TP53 may increase resistance to ionizing radiation therapy (PMID: 14576853, PMID: 25913131). TP53 mutations have been significantly associated with platinum resistance in studies of ovarian cancer cases (PMID: 25385265, PMID: 28148293).

Some evidence indicates that metastatic castration-resistant prostate cancer harboring a TP53 mutation may not benefit from abiraterone in combination with prednisone, based on overall survival and progression-free survival in a multicenter phase II clinical trial of 116 treatment-naive participants (PMID: 29367197). Some evidence suggests that adenocarcinoma of prostate harboring a somatic TP53 mutation may be associated with an unfavorable prognosis based on: a) overall survival in a retrospective study of 13 participants with metastatic primary and secondary hormone-sensitive disease (PMID: 33955569); and b) progression-free survival, incidence of metastasis, and time to progression in a retrospective study of 294 participants with metastatic or recurrent castration□sensitive disease (PMID: 33419682). The following associations with this genomic finding are from other tumor type contexts: TP53 mutation is deemed as an unfavorable prognostic marker in endometrial carcinoma per ESMO (PMID: 35690222) guidelines. TP53 mutations are associated with an unfavorable prognosis in SHH-activated medulloblastoma per NCCN (Central Nervous System Cancers, 2.2022) guidelines. TP53 mutations are deemed as an unfavorable prognostic marker in squamous cell carcinoma of vulva per NCCN (Vulvar Cancer, 1.2023) guidelines.

CLINICAL IMPACT

Unfavorable Prognosis in
Malignant tumor of unknown origin, Malignant tumor of unknown origin or illdefined site, Squamous cell carcinoma of vulva, Medulloblastoma, or Endometrial carcinoma

Tier II - Potential Clinical Significance

ERCC3 p.R109* c.325C>T

C

Interpretation

ERCC3 p.R109* is expected to truncate the ERCC3 protein at amino acid 109 of 782, which is upstream of the helicase C-terminal domain (aa 551 - 705; UniProt.org). In ClinVar, ERCC3 p.R109* is reported as 'Pathogenic/Likely pathogenic' (Variation ID: 265515). Therefore, this alteration is predicted to be inactivating.

ERCC3 alterations have been reported in 4% of prostate cancer samples in cBioPortal for Cancer Genomics (cBioPortal.org; March 2023). ERCC3 is a tumor suppressor and helicase involved in DNA repair. It is infrequently altered in cancer and germline mutations of ERCC3 are associated with Cockayne's syndrome, xeroderma pigmentosum, and trichothiodystrophy, and may predispose to breast cancer (PMID: 8304337, PMID: 16947863, PMID: 25620205).

ERCC3 (also known as XPB) encodes an ATP-dependent DNA helicase which is an essential component of the transcription factor II H(TFIIH) complex. ERCC3 functions to unwind the DNA double helix which is required as part of the nucleotide-excision repair (NER) pathway (PMID: 21571596). The TFIIH transcriptional complex also requires the activity of ERCC3 for the initiation of transcription (PMID: 8166891). Mutations in ERCC3, likely impairing transcriptional function, have been identified in patients with xeroderma pigmentosum B, a condition resulting in sensitivity to sunlight and increased skin-cancer risk (PMID: 10064601). Loss-of-function ERCC3 truncating mutations have been associated with breast cancer risk, likely due to defects in DNA repair pathways (PMID: 27655433). However, XRCC3 truncations may act epistatically with mutations in other DNA repair genes.

In ERCC3 depleted cells, the CDK4/6 inhibitor palbociclib causes enhanced sensitivity to the PARP superfamily tankyrase enzyme inhibitor MSC2504877, which suppresses Wnt/β-catenin signaling in tumor cells. Indeed, MSC2504877 inhibits the growth of APC mutant colorectal tumor cells. Furthermore, ERCC3 variants are potential therapeutic targets as demonstrated by the enhanced susceptibility of ERCC3 mutant cells to reagents of the fungal sesquiterpene class (PMID: 27655433).

CLINICAL IMPACT

Clinical trials are recruiting patients whose tumors harbor mutations in DDR genes such as ERCC3 (NCT04122625, NCT04095273, NCT04266912, NCT04267939, NCT04693468, NCT04550494, NCT04586335).

Tier II - Potential Clinical Significance

ATM Copy number loss (1 copy)

C

CLINICAL IMPACT

May benefit from
Olaparib in Adenocarcinoma of prostate

Interpretation

ERCC3 p.R109* is expected to truncate the ERCC3 protein at amino acid 109 of 782, which is upstream of the helicase C-terminal domain (aa 551 - 705; UniProt.org). In ClinVar, ERCC3 p.R109* is reported as 'Pathogenic/Likely pathogenic' (Variation ID: 265515). Therefore, this alteration is predicted to be inactivating. ERCC3 alterations have been reported in 4% of prostate cancer samples in cBioPortal for Cancer Genomics (cBioPortal.org; March 2023). ERCC3 is a tumor suppressor and helicase involved in DNA repair. It is infrequently altered in cancer and germline mutations of ERCC3 are associated with Cockayne's syndrome, xeroderma pigmentosum, and trichothiodystrophy, and may predispose to breast cancer (PMID: 8304337, PMID: 16947863, PMID: 25620205). ERCC3 (also known as XPB) encodes an ATP-dependent DNA helicase which is an essential component of the transcription factor II H(TFIIH) complex. ERCC3 functions to unwind the DNA double helix which is required as part of the nucleotide-excision repair (NER) pathway (PMID: 21571596).

The TFIIH transcriptional complex also requires the activity of ERCC3 for the initiation of transcription (PMID: 8166891). Mutations in ERCC3, likely impairing transcriptional function, have been identified in patients with xeroderma pigmentosum B, a condition resulting in sensitivity to sunlight and increased skin-cancer risk (PMID: 10064601). Loss-of-function ERCC3 truncating mutations have been associated with breast cancer risk, likely due to defects in DNA repair pathways (PMID: 27655433). However, XRCC3 truncations may act epistatically with mutations in other DNA repair genes. In ERCC3 depleted cells, the CDK4/6 inhibitor palbociclib causes enhanced sensitivity to the PARP superfamily tankyrase enzyme inhibitor MSC2504877, which suppresses Wnt/β-catenin signaling in tumor cells. Indeed, MSC2504877 inhibits the growth of APC mutant colorectal tumor cells. Furthermore, ERCC3 variants are potential therapeutic targets as demonstrated by the enhanced susceptibility of ERCC3 mutant cells to reagents of the fungal sesquiterpene class (PMID: 27655433). Clinical trials are recruiting patients whose tumors harbor mutations in DDR genes such as ERCC3 (NCT04122625, NCT04095273, NCT04266912, NCT04267939, NCT04693468, NCT04550494, NCT04586335).

Tier II - Potential Clinical Significance

PTEN Copy number loss (1 copy)

C

CLINICAL IMPACT

Unfavorable Prognosis in
Malignant tumor of prostate or Primary malignant neoplasm of prostate

Interpretation

PTEN (phosphatase and tensin homolog) is a tumor suppressor with roles in the cell cycle, growth, DNA repair, cell survival and negative regulation of the AKT/PKB signaling pathway (RefSeq, Feb 2015; PMID: 24656806, 2014). Some evidence indicates that advanced prostate cancer harboring PTEN copy number loss may benefit from everolimus based on progression-free survival in a prospective phase II clinical trial of 89 participants with solid tumors (PMID: 34006291, 2021). Some evidence indicates that metastatic castration-resistant adenocarcinoma of prostate patients harboring PTEN copy number loss may not benefit from abiraterone in combination with prednisone based on overall survival in a prospective study of 62 participants (PMID: 31131348, 2019). Some evidence indicates that metastatic castration-resistant prostate cancer harboring PTEN copy number loss may not benefit from abiraterone based on overall survival in a multicenter phase II clinical trial of 128 participants with no prior chemotherapy (PMID: 33794293, 2021). Some evidence indicates that metastatic castration-resistant adenocarcinoma of prostate patients harboring PTEN copy number loss may not benefit from enzalutamide based on overall survival in a prospective study of 62 participants (PMID: 31131348, 2019). PTEN copy number loss is deemed as an unfavorable prognostic marker in prostate cancer per ASCO (PMID: 31829902, 2019) guidelines.

Tier II - Potential Clinical Significance

CLINICAL IMPACT

KIT Copy number gain (3 copies)

C

Interpretation

KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog, also known as CD117) encodes for the mast/stem cell growth factor receptor Kit protein. It is a receptor tyrosine kinase (RTK) expressed on a wide variety of cell types. The ligand for KIT is stem cell factor (SCF). Binding of the KIT ligand SCF to the KIT RTK activates downstream signaling pathways involved in mediating pro-growth and pro-survival signals within the cell. Mutant KIT has been implicated in the pathogenesis of several cancers including melanoma, acute leukemia, and gastrointestinal stromal tumor (GIST; PMID: 14645423; PMID: 9438854).

KIT Amplification is present in 0.67% of AACR GENIE cases, with conventional glioblastoma multiforme, glioblastoma, breast invasive ductal carcinoma, gastrointestinal stromal tumor, and lung adenocarcinoma having the greatest prevalence (PMID: 28572459).

Tier II - Potential Clinical Significance

CLINICAL IMPACT

PDGFRA Copy number gain (3 copies)

C

Interpretation

PDGFRA (platelet-derived growth factor receptor, alpha polypeptide) encodes the platelet-derived growth factor receptor alpha protein. PDGFRA mutations lead to kinase activation. Mutant PDGFRA has been implicated in the pathogenesis of a number of cancers. For example, mutations are found in gastrointestinal stromal tumors (GIST; PMID: 15928335; PMID: 12522257), and fusions in hypereosinophilic syndrome (PMID: 12660384) and dermatofibrosarcoma protuberans (PMID: 8988177).

PDGFRA amplification is present in 0.75% of AACR GENIE cases, with conventional glioblastoma multiforme, glioblastoma, breast invasive ductal carcinoma, anaplastic astrocytoma, and osteosarcoma having the greatest prevalence (PMID: 28572459).

Tier II - Potential Clinical Significance

CLINICAL IMPACT

CIC p.Y770Vfs*161 c.2303dupC

NM_015125.3 VAF % 44.5 DEPTH 2701

C

Interpretation

CIC p.Y770Vfs*161 is expected to frameshift the CIC protein within the second PRR (aa 508 - 1303) and upstream of the third PRR (aa 1524 - 1601) (cBioPortal.org, UniProt.org). Truncating mutations in CIC are considered to confer loss of function to the CIC tumor suppressor and are thus likely oncogenic (PMID: 21817013). Therefore, this alteration is considered likely oncogenic.

CIC alterations have been reported in 3% of prostate cancer samples in cBioPortal for Cancer Genomics (cBioPortal.org; March, 2023).

CIC (also Capicua) is a transcriptional repressor that is a member of the high mobility (HMG)-box protein family (PMID: 32073140). CIC is expressed in a variety of tissues and is a critical regulator of patterning, differentiation, and signaling (PMID: 32073140). Chromatin modifiers, such as the Sin/HDAC3 histone deacetylase complex, are recruited to sites bound by CIC to inhibit gene expression of target genes (PMID: 29844126). CIC exists in diverse protein complexes including ATXN1, which directly binds CIC and modulates its transcriptional repressor activity (PMID: 17190598). The CIC-ATXN1 complex regulates the expression of several transcription factors, including members of the ETS protein family (PMID: 27869830). Loss of CIC expression results in the derepression of ETS transcriptional regulators, such as ETV4, which can activate extracellular remodeling programs and metastasis (PMID: 22014525). In addition, CIC is a negative regulator of receptor tyrosine kinase (RTK) and MAPK signaling pathways and acts as a transcriptional repressor in the absence of RTK signaling (PMID: 28178529). CIC is recurrently mutated in oligodendrogliomas, including in 1p/19q-deleted cancers (PMID: 22588899). Somatic mutations and deletions have also been found in various other cancer types, including lung and gastric cancers (PMID: 27869830). Chromosomal translocations that produce chimeric CIC proteins fused to several partner proteins, including DUX4 or FOXO4, occur in aggressive round cell sarcomas and result in aberrant CIC-mediated transcriptional activation (PMID: 21813156).

Currently, there are no approved therapies or clinical trials that specifically target CIC alterations in solid tumors.

Tier II - Potential Clinical Significance

CLINICAL IMPACT

MDM4 Copy number gain (4 copies)

C

Interpretation

MDM4, a negative regulator of the p53 tumor suppressor, is altered by amplification and overexpression in various cancer types including breast cancer.

MDM4 amplification is known to be oncogenic. MDM4 maps to a region that is frequently amplified in breast cancers (PMID: 7585611, 9523192). FISH analysis on primary tumors followed by in-situ hybridization analysis on mRNA levels revealed that MDM4 gene copy numbers were elevated with a concomitant increase in MDM4 mRNA expression (19% of breast, 19% of colon, and 18% of lung cancers) (PMID: 15199139).

POTENTIAL CLINICAL TRIALS

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

TITLE	TRIAL IDENTIFIER	PHASE	VARIANT
Pembrolizumab and Lenvatinib in Advanced/Metastatic Neuroendocrine Prostate Cancer	NCT04848337 https://clinicaltrials.gov/ show/NCT04848337	II	**KIT** Copy number gain (3 copies) **PDGFRA** Copy number gain (3 copies)
Niraparib Before Surgery in Treating Patients With High Risk Localized Prostate Cancer and DNA Damage Response Defects	NCT04030559 https://clinicaltrials.gov/ show/NCT04030559	II	**ATM** Copy number loss (1 copy)
Study to Evaluate CCS1477 in Advanced Tumours	NCT03568656 https://clinicaltrials.gov/ show/NCT03568656	I/II	**AR** **Copy number gain(3 copies)**
Safety and Pharmacokinetics of ODM-208 in Patients With Metastatic Castration-resistant Prostate Cancer	NCT03436485 https://clinicaltrials.gov/ show/NCT03436485	I/II	**AR** **Copy number gain(3 copies)**

TIER III - VARIANTS OF UNCERTAIN SIGNIFICANCE

FGF5
Copy number gain (3 copies)

FGF8
Copy number loss (1 copy)

JAK2
Copy number gain (3 copies)

KDM6A
p.G291Efs*34 NM_021140.2 c.870delC
VAF 0.3%
DEPTH 980

MAGI2
p.R839H NM_012301.3 c.2516G>A
VAF 47.6%
DEPTH 5,769

MYOD1
p.P186Rfs*25 NM_002478.4 c.557delC
VAF 0.4 %
DEPTH 1,062

KDM6A
p.G291Efs*34 NM_021140.2 c.870delC
VAF 0.3%
DEPTH 980

MAGI2
p.R839H NM_012301.3 c.2516G>A
VAF 47.6%
DEPTH 5,769

MYOD1
p.P186Rfs*25 NM_002478.4 c.557delC
VAF 0.4 %
DEPTH 1,062

PIK3CB
Copy number loss (1 copy)

RET
Copy number loss (1 copy)

TET2
p.Q706Lfs*41 NM_001127208.2 c.2117_2129del13
VAF 0.1%
DEPTH 1,913

ZBTB7A
p.A180Rfs*14 NM_015898.2 c.537dupC
VAF 0.7%
DEPTH 5,004

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
Variant of strong clinical significance, Level A evidence (FDA approved therapy or practice guideline in patient's tumor type)

IB
Variant of strong clinical significance, Level B Evidence (consensus in the field based on well□powered studies in patient's tumor type)

IIC
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)

IID
Variant of potential clinical significance, Level D evidence (case reports or preclinical studies)

III Variant of uncertain clinical significance

III Benign or likely benign variant

PERTINENT NEGATIVES

Pertinent negatives were not reported for this case.

REPORTED GENES

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

CGW VERSION

CGW_v6.21.1

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
dbSNP: 149
ClinVar: 20210328
dbNSFP: 3.5c
gnomAD: r2.1
ExAC: v1.0
COSMIC: v92
NHLBI ESP: v.0.0.30

METHODOLOGY

Assay Methods: The test was performed using the Illumina TruSight™ Oncology 500 ctDNA (TSO500 ctDNA) panel, a hybrid-capture based liquid biopsy next generation sequencing assay, targeting 523 genes. The assay employs Unique molecular identifiers (UMI) to enable detection of variants present in circulating tumor DNA (ctDNA), found in the cell free DNA (cfDNA), at low frequency with a high degree of sensitivity and specificity. TSO500 ctDNA is designed to detect multiple classes of mutations that includes single-nucleotide variants (SNVs), multi-nucleotide variants (MNVs), small Insertions/Deletions, Fusions and Copy Number Variants (CNVs). The assay also enables quantitative detection of immuno-onco biomarkers such as microsatellite instability (MSI) and tumor mutational burden (TMB). The cfDNA (~30 ng) is extracted from plasma. The regions of interest are hybridized to biotinylated probes, magnetically pulled down with streptavidin-coated beads, and eluted to enrich the library pool. The libraries are then sequenced on the Illumina NovaSeq 6000 system at high depth (~ 35,000x) to enhance sensitivity.

Secondary Analysis Methods: The DNA sequencing data is analyzed using the Illumina Software available on DRAGEN Bio-IT platform that packages enhanced hardware and software for rapid data analysis. This is followed by tertiary analysis performed by customized pipeline on the Clinical Genomics Workspace (CGW) software platform from PierianDx.

Variant Classification: Variants are reported according to HGVS nomenclature (www.hgvs.org/mutnomen) and classified as per the AMP classification system into tiers IA, IB, IIC, IID, III and IV. These tiers are stratified based on clinical utility ('actionability' for clinical decision-making as to diagnosis, prognosis, treatment options, and carrier status) and previously reported data in the medical literature. Variations found in gnomAD (https:// gnomad.broadinstitute.org/) that have ≥ 1% minor allele frequency (except those that are also in ClinVar denoted as clinically relevant, used in a clinical diagnostic assay, or reported as a mutation in a publication) are classified as known polymorphisms.

Notes:

• This assay does not detect complex indels and complex structural alterations. Variants located outside of targeted regions too will not be detected.

• It is possible that pathogenic variants may not be reported by one or more of the tools because of the parameters used. However, tool parameters were optimized to maximize specificity and sensitivity

DISCLAIMER

This Report was generated using the materials and methods described above, which required the use of various reagents, protocols, instruments, software, databases, and other items, some of which were provided or made accessible by third parties. A defect or malfunction in any such reagents, protocols, instruments, software, databases, and/or other items may compromise the quality or accuracy of the Report. The Report has been created based on, or incorporates references to, various scientific manuscripts, references, and other sources of information, including without limitation manuscripts, references, and other sources of information that were prepared by third parties that describe correlations between certain genetic mutations and particular diseases (and/or certain therapeutics that may be useful in ameliorating the effects of such diseases). Such information and correlations are subject to change over time in response to future scientific and medical findings. PierianDx makes no representation or warranty of any kind, expressed or implied, regarding the accuracy of the information provided by or contained in such manuscripts, references, and other sources of information. If any of the information provided by or contained in such manuscripts, references, and other sources is later determined to be inaccurate, the accuracy and quality of the Report may be adversely impacted. PierianDx is not obligated to notify you of any impact that future scientific or medical research findings may have on the Report.

The Report must always be interpreted and considered within the clinical context, and a physician should always consider the Report along with all other pertinent information and data that a physician would prudently consider prior to providing a diagnosis to a patient or developing and implementing a plan of care for a patient. The Report should never be considered or relied upon alone in making any diagnosis or prognosis. The manifestation of many diseases are caused by more than one gene variant, a single gene variant may be relevant to more than one disease, and certain relevant gene variants may not have been considered in the Report. In addition, many diseases are caused or influenced by modifier genes, epigenetic factors, environmental factors, and other variables that are not addressed by the Report (or that are otherwise unknown). This Report is based on a next generation sequencing assay which does not distinguish between somatic and germline variants. If a germline variant is in question, further testing may be recommended. As such, the relevance of the Report should be interpreted in the context of a patient's clinical manifestations. The Report provided by PierianDx is provided on an "AS IS" basis. PierianDx makes no representation or warranty of any kind, expressed or implied, regarding the Report. In no event shall PierianDx be liable for any actual damages, indirect damages, and/or special or consequential damages arising out of or in any way connected with the Report, your use of the Report, your reliance on the Report, or any defect or inaccurate information included within the Report.

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The test performance characteristics were determined by the PierianDx Molecular Laboratory. The Report was generated by the PierianDx Molecular Laboratory as required by the CLIA 1988 regulations. The Report, and the tests used to generate the Report, have not been cleared or approved by the U.S. Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. The test results have been shown to be clinically useful. This laboratory is CLIA certified to perform high complexity testing.

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