FOUNDATIONONE®LIQUID CDx

PATIENT
Wang, Chien-Fa

TUMOR TYPE
Esophagus cancer (NOS)
COUNTRY CODE
TW

REPORT DATE
11 May 2023
ORDERED TEST #
ORD-1623178-01

ABOUT THE TEST FoundationOne®Liquid CDx is a next generation sequencing (NGS) assay that identifies clinically relevant genomic alterations in circulating cell-free DNA.

PATIENT
DISEASE Esophagus cancer (NOS)
NAME Wang, Chien-Fa
DATE OF BIRTH 05 October 1958
SEX Male
MEDICAL RECORD # 49225287

PHYSICIAN
ORDERING PHYSICIAN Yeh, Yi-Chen
MEDICAL FACILITY Taipei Veterans General Hospital
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 205872
PATHOLOGIST Not Provided

SPECIMEN
SPECIMEN ID CFW 10/5/1958
SPECIMEN TYPE Blood
DATE OF COLLECTION 01 May 2023
SPECIMEN RECEIVED 04 May 2023

Biomarker Findings

Blood Tumor Mutational Burden - 4 Muts/Mb
Microsatellite status - MSI-High Not Detected
Tumor Fraction - Elevated Tumor Fraction

Genomic Findings

For a complete list of the genes assayed, please refer to the Appendix.

CCND2 amplification
PTEN C218*
KDM5A amplification
NFKBIA amplification
NOTCH3 rearrangement exon 6
TP53 R273C
WT1 Q490_K491>H*

Report Highlights

- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 11)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Blood Tumor Mutational Burden - 4 Muts/Mb	**No therapies or clinical trials. See Biomarker Findings section**
Microsatellite status - MSI-High Not Detected	**MSI-High not detected. No evidence of microsatellite instability in this sample (see Appendix section).**
Tumor Fraction - Elevated Tumor Fraction	**Tumor fraction is considered elevated when ctDNA levels are high enough that aneuploidy can be detected. There is higher sensitivity for identifying genomic alterations and a lower risk of false negative results in specimens with elevated tumor fraction; the positive percent agreement observed between liquid and tissue for defined short variants is ≥ 90% (Li et al., 2021; AACR Abstract 2231) (see Biomarker Findings section).**

GENOMIC FINDINGS		VAF%	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
CCND2 -	amplification	-	None	None
7 Trials see p. 11				
PTEN -	C218*	0.82%	None	None
10 Trials see p. 13				

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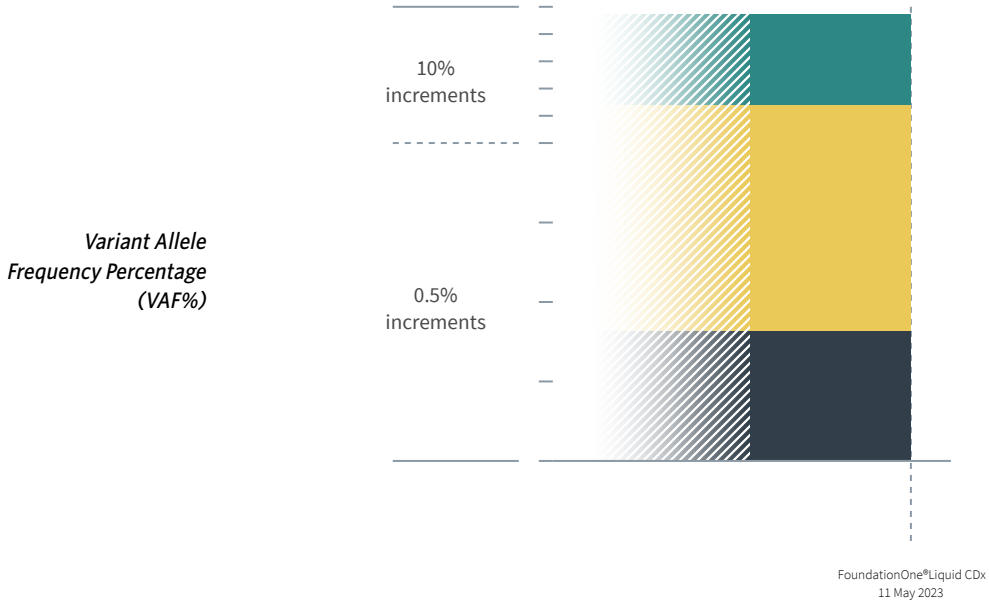
GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

For more information regarding biological and clinical significance, including prognostic, diagnostic, germline, and potential chemosensitivity implications, see the Genomic Findings section.

NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the therapies listed in this report may have varied clinical evidence in the patient's tumor type. Therapies and the clinical trials listed in this report may not be complete and/or exhaustive. Neither the therapies nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type. This report should be regarded and used as a supplementary source of information and not as the single basis for the making of a therapy decision. All treatment decisions remain the full and final responsibility of the treating physician and physicians should refer to approved prescribing information for all therapies. Therapies contained in this report may have been approved by the US FDA or other national authorities; however, they might not have been approved in your respective country. In the appropriate clinical context, germline testing of *APC, ATM, BAP1, BRCA1, BRCA2, BRIP1, CHEK2, FH, FLCN, MEN1, MLH1, MSH2, MSH6, MUTYH, NF1, NF2, PALB2, PMS2, POLE, PTEN, RAD51C, RAD51D, RB1, RET, SDHA, SDHB, SDHC, SDHD, SMAD4, STK11, TGFBR2, TP53, TSC1, TSC2, VHL,* and *WT1* is recommended.

Variant Allele Frequency is not applicable for copy number alterations.



HISTORIC PATIENT FINDINGS		ORD-1623178-01 VAF%
Blood Tumor Mutational Burden		4 Muts/Mb
Microsatellite status		MSI-High Not Detected
Tumor Fraction		38%
CCND2	amplification	Detected
PTEN	● C218*	0.82%
KDM5A	amplification	Detected
NFKBIA	amplification	Detected
NOTCH3	rearrangement exon 6	13.1%
TP53	● R273C	33.1%
WT1	● Q490_K491>H*	15.4%

IMPORTANT NOTE This comparison table refers only to genes and biomarkers assayed by prior FoundationOne®Liquid CDx or FoundationOne®CDx tests. Up to five previous tests may be shown.

For some genes in FoundationOne Liquid CDx, only select exons are assayed. Therefore, an alteration found by a previous test may not have been confirmed despite overlapping gene lists. Please refer to the Appendix for the complete list of genes and exons assayed. Variants reported for prior time points reflect reporting practices at the time of the historical test(s). Changes in variant reporting nomenclature, classification, or handling may result in the appearance of discrepancies across time points. The gene and biomarker list will be updated periodically to reflect new knowledge about cancer biology.

As new scientific information becomes available, alterations that had previously been listed as Variants of Unknown Significance (VUS) may become reportable or reportable variants may become VUS.

Tissue Tumor Mutational Burden (TMB) and blood TMB (bTMB) are estimated from the number of synonymous and non-synonymous single-nucleotide variants (SNVs) and insertions and deletions (indels) per area of coding

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genome sampled, after the removal of known and likely oncogenic driver events and germline SNPs. Tissue TMB is calculated based on variants with an allele frequency of ≥5%, and bTMB is calculated based on variants with an allele frequency of ≥0.5%.

Not Tested = not baited, not reported on test, or test preceded addition of biomarker or gene

Not Detected = baited but not detected on test

Detected = present (VAF% is not applicable)

VAF% = variant allele frequency percentage

Cannot Be Determined = Sample is not of sufficient data quality to confidently determine biomarker status

Please note that other aspects of this table may have changed from the previous version to reflect the most up-to-date reporting information.

BIOMARKER

Blood Tumor Mutational Burden

RESULT
4 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased blood tumor mutational burden (bTMB) may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[1-3], anti-PD-1[3-4], anti-PD-1/CTLA4 therapies[5-6] , anti-PD-L1/CTLA4 therapies[7-10]. A Phase 2 multi-solid-tumor trial showed that bTMB ≥16 Muts/Mb (as measured by this assay) was associated with improved survival from treatment with a PD-1 inhibitor alone or in combination with a CTLA-4 inhibitor[5]. In non-small cell lung cancer (NSCLC), multiple clinical trials have shown patients with higher bTMB derive clinical benefit from immune checkpoint inhibitors following single-agent or combination treatments with either CTLA4 inhibitors or chemotherapy, with reported high bTMB cutpoints ranging from 6 Muts/Mb-16 Muts/Mb[1,8-10]. In head and neck squamous cell carcinoma (HNSCC), a Phase 3 trial showed that bTMB ≥16 Muts/Mb (approximate equivalency ≥8 Muts/Mb as measured by this assay) was associated with improved survival from treatment with a PD-L1 inhibitor alone or in combination with a CTLA-4 inhibitor[11]. In colorectal cancer (CRC), a Phase 2 study showed that bTMB TMB ≥28 Muts/Mb (approximate equivalency ≥14 Muts/Mb as measured by this assay) was associated with improved OS from a PD-L1 inhibitor alone or in combination with a CTLA-4 inhibitor[7].

FREQUENCY & PROGNOSIS

Average bTMB levels in solid tumors other than NSCLC have not been evaluated (PubMed, Mar 2023). For patients with gastric cancer, increased TMB is reported to be associated with prolonged OS[12-14]. One study observed that the OS and disease-free survival (DFS) benefits of postoperative chemotherapy were more pronounced in patients with TMB-low gastric cancer (stage Ib/II) compared to those with TMB-high; however, patients with stage III gastric cancer benefitted regardless of TMB level[15]. In esophageal cancer, patients with TMB-high who had not received radiotherapy had significantly reduced OS (p=0.038) compared to those with TMB-low[16].

FINDING SUMMARY

Blood tumor mutational burden (bTMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations from circulating tumor DNA in blood. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[17-18] and cigarette smoke in lung cancer[19-20], treatment with temozolomide-based chemotherapy in glioma[21-22], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[23-27], and microsatellite instability (MSI)[23,26-27]. High bTMB levels were not detected in this sample. It is unclear whether the bTMB levels in this sample would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[1-2,4]. Depending on the clinical context, TMB testing of an alternate sample or by another methodology could be considered.

BIOMARKER

Tumor Fraction

RESULT
Elevated Tumor Fraction

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Specimens with elevated tumor fraction have high circulating-tumor DNA (ctDNA) content, and thus higher sensitivity for identifying genomic alterations. Such specimens are at a lower risk of false negative results. Tumor fraction levels currently have limited implications for diagnosis, surveillance, or therapy and should not be overinterpreted or compared from one blood draw to another. There are currently no targeted approaches to address specific tumor fraction levels. In the research setting, changes in tumor fraction estimates have been associated with treatment duration and clinical response and may be a useful indicator for future cancer management[28-33].

FREQUENCY & PROGNOSIS

Detectible ctDNA levels have been reported in a variety of tumor types, with higher tumor fraction levels reported for patients with metastatic (Stage 4) tumors compared with patients with localized disease (Stages 1 to 3)[34]. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer[35], Ewing sarcoma and osteosarcoma[36], prostate cancer[31], breast cancer[37], leiomyosarcoma[38], esophageal cancer[39], colorectal cancer[40], and gastrointestinal cancer[41].

FINDING SUMMARY

Tumor fraction provides an estimate of the percentage of ctDNA present in a cell-free DNA (cfDNA) sample. The tumor fraction estimate for this sample is based on the observed level of aneuploid instability. The tumor fraction algorithm utilized for FoundationOne Liquid CDx uses the allele frequencies of approximately 1,000 single-nucleotide polymorphism (SNP) sites across the genome. Unlike the maximum somatic allele frequency (MSAF) method of estimating ctDNA content[42], the tumor fraction metric does not take into account the allele frequency of individual variants but rather produces a more holistic estimate of ctDNA content using data from across the genome. The amount of ctDNA detected may correlate with disease burden and response to therapy[43-44].

GENE

CCND2

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Although preclinical studies suggest that cyclin D2 activates CDK4/6[45-46], it is unknown whether CCND2 amplification or activating mutation predicts response to CDK4/6 inhibitors such as abemaciclib, palbociclib, and ribociclib. Clinical studies of CDK4/6 inhibitors have shown the most promise for estrogen receptor-positive breast cancer[47-48].

FREQUENCY & PROGNOSIS

Putative high-level amplification of CCND2 has been reported in 2% of gastric carcinomas and in 1% of esophageal carcinomas, whereas CCND2 mutation has only been reported in 0.5% of esophageal carcinomas[49]. Published data investigating the prognostic implications of CCND2 alterations in esophageal carcinoma are limited (PubMed, Nov 2022).

FINDING SUMMARY

CCND2 encodes the protein cyclin D2, which binds and regulates the cyclin-dependent kinases that control cell cycle progression, and is a downstream target of cancer signaling pathways including hedgehog and PI3K[50-51]. CCND2 has been reported to be amplified in cancer[52], and may be biologically relevant in this context[53-54].

GENE

PTEN

ALTERATION
C218*

HGVS VARIANT
NM_000314.4: c.654C>A (p.C218*)

VARIANT CHROMOSOMAL POSITION
chr10:89717629

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

PTEN loss or mutation leads to activation of the PI3K-AKT-mTOR pathway and may predict sensitivity to inhibitors of this pathway[55-58]. Clinical studies in gastric cancer have not observed an association between PTEN deficiency and response to the mTOR inhibitor everolimus[59] or ipatasertib[60]. Preclinical data indicate that PTEN loss or inactivation may predict sensitivity to PARP inhibitors[61-65], and clinical benefit has been observed for patients with PTEN-altered breast cancer including triple negative breast cancer[66], ovarian cancer[67], uterine leiomyosarcoma[68], and endometrial cancer[65] treated with PARP inhibitors. However, some studies have reported a lack of association between PTEN mutation and PARP inhibitor sensitivity[69-70].

FREQUENCY & PROGNOSIS

In the Esophageal Adenocarcinoma dataset, PTEN mutations have been reported in 2.7% of tumors[71]. PTEN loss has been reported in 14% of esophageal adenocarcinoma samples[72]. Loss of PTEN has been observed primarily in advanced stage esophageal tumors, where it was associated with shorter disease-free and overall patient survival[72]. In addition, absence of nuclear PTEN expression has been correlated with decreased survival in esophageal adenocarcinoma[73]. Another study reports that negative PTEN nuclear staining was associated with poor 10-year survival of patients with ESCC[73]. Activation of the PI3K-AKT-mTOR pathway, including through reduced expression of PTEN, is a common contributor to esophageal cancer, in both squamous cell and adenocarcinoma tumor types[73-74].

FINDING SUMMARY

PTEN encodes an inositol phosphatase that functions as a tumor suppressor by negatively regulating the PI3K-AKT-mTOR pathway; loss of PTEN can lead to uncontrolled cell growth and suppression of apoptosis[56]. Alterations such as seen here may disrupt PTEN function or expression[75-116].

POTENTIAL GERMLINE IMPLICATIONS

PTEN mutations underlie several inherited disorders, collectively termed PTEN hamartoma tumor syndrome (PHTS), which include Cowden syndrome (CS) and its variant Lhermitte-Duclos disease (LD), Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS), and Proteus-like syndrome[117-118]. The mutation rate for PTEN in these disorders ranges from 20 to 85% of patients[117,119]. The estimated incidence of Cowden syndrome is 1/200,000, which may be an underestimate due to the high variability of this disorder[117]. Given the association between PTEN and these inherited syndromes, in the appropriate clinical context, germline testing for mutations affecting PTEN is recommended.

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GENE
KDM5A

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to directly address genomic alterations in KDM5A. However, multiple preclinical studies have identified potential targets in KDM5A amplified or activated cells that may respond to therapy. KDM5A-mediated chromatin remodeling induces CCND1 expression and represses CDKI expression[120-124]; therefore, KDM5A activation or amplification may sensitize cells to CDK4/CDK6 inhibitors. Drug-resistant cell populations, characterized by elevated KDM5A expression, responded to histone deacetylase (HDAC) inhibition[125], suggesting that HDAC inhibitors may be a potential therapeutic option. KDM5A also induces expression of VEGF and promotes angiogenesis, oncogenic transformation, and tumorigenesis, which can be inhibited by KDM5A knockdown[126-127], suggesting that tumors harboring KDM5A amplification may be sensitive to angiogenesis inhibitors, including kinase inhibitors that target the VEGF receptors, such as sunitinib, sorafenib, vandetanib, ponatinib, cabozantinib, regorafenib, pazopanib, and axitinib. However, these inhibitors have yet to be extensively tested in the context of KDM5A amplification or activation; therefore, it is not known if these therapeutic strategies are relevant.

FREQUENCY & PROGNOSIS

KDM5A amplification has been reported with the highest incidence in TCGA datasets in ovarian serous cystadenocarcinoma (7.2%), testicular germ cell cancer (5.8%), pancreatic adenocarcinoma (4.3%), and lung squamous cell carcinoma (3.9%) (cBioPortal, Jan 2023)[52,128]. Elevated levels of KDM5A expression have also been reported in a range of solid tumor types[121-122,124,126,129-130], and fusion of KDM5A to NUP98 has been documented in acute myeloid leukemia[131-132]. KDM5A expression is significantly correlated with HIF-1alpha and VEGF expression, as well as tumor size, angiogenesis, and poor patient prognosis in lung cancer[127].

FINDING SUMMARY

KDM5A encodes a lysine-specific histone demethylase that potentiates the expression of genes involved in cellular proliferation, senescence, angiogenesis, and migration[120-121,126,133-134]. KDM5A overexpression alters the transcriptional regulation of cell cycle genes, including CCND1, and a variety of cyclin-dependent kinase inhibitors (CDKIs), including CDKN1A, CDKN1B, and CDKN2A, and results in cell cycle progression[120-124,126]. Additionally, elevated KDM5A expression and associated chromatin remodeling has been implicated in resistance to various tyrosine kinase inhibitors in vitro, including erlotinib and gefitinib[125,129,135].

GENE
NFKBIA

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies that directly target NFKBIA amplification or expression.

FREQUENCY & PROGNOSIS

In the TCGA datasets, amplification of NFKBIA has been reported with the highest incidence in lung adenocarcinoma (11.7%)[136], esophageal carcinoma (3.8%), prostate adenocarcinoma (3.4%)[137], lung squamous cell carcinoma (2.8%)[138], and ovarian serous cystadenocarcinoma (2.6%) (cBioPortal, Jan 2023)[52,128]. Amplification or increased expression of NFKBIA in EGFR-mutant lung cancer has been reported to predict improved response to EGFR tyrosine kinase inhibitors[139-140]. Certain NFKBIA polymorphisms, which may affect IkBa expression levels, have been studied as risk factors for some cancer types, although the data are mixed and conflicting[141-143].

FINDING SUMMARY

NFKBIA encodes IkBa, an inhibitor of the NF-kappaB (NFkB)/REL complex. It has been reported to act as a tumor suppressor in Hodgkin's lymphoma[144-148] and in glioblastoma[141,149-150]. NFKBIA has been reported to be amplified in cancer[52] and may be biologically relevant in this context[53-54]. In contrast, truncating mutations that result in loss of the majority of the IkBa protein are predicted to be inactivating.

GENE
NOTCH3

ALTERATION
rearrangement exon 6

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Several approaches for inhibiting NOTCH3 signaling are being developed, including neutralizing NOTCH antibodies such as tarextumab (OMP-59R5)[151], which targets NOTCH2 and NOTCH3, and pan-NOTCH inhibitors, such as gamma-secretase inhibitors (GSI)[152-154]. In a Phase 2 study, the GSI AL101 (BMS-906024) elicited PR in 15% (6/39) and SD in 54% (21/39) of patients with metastatic adenoid cystic carcinoma harboring NOTCH activating alterations[155]. Phase 2 studies have evaluated the efficacy of tarextumab in combination with chemotherapy in metastatic pancreatic cancer or extensive-stage small cell lung cancer, though NOTCH3 expression was not found to be a predictor of OS or PFS in either study[156]. As it is unclear if the rearrangement seen here results in expression of an oncogenic protein, it is not known whether these therapeutic approaches would be relevant.

FREQUENCY & PROGNOSIS

NOTCH3 mutation has been observed in 0-2.3% of esophageal squamous cell carcinomas[157-158]. In the Broad Esophageal Adenocarcinoma dataset, NOTCH3 mutations have been reported in 1% of tumors[71]. In other studies, NOTCH3 mutations were reported in 1/11 esophageal adenocarcinomas and 6-8% of esophageal squamous cell carcinomas[159-160]. In a study of esophageal squamous cell carcinoma, increased NOTCH3 expression was identified as an adverse prognostic marker in multivariate analysis (HR=2.38, p=0.047)[161]. A study reported increased expression of NOTCH3, as well as NOTCH1, JAGGED1, and JAGGED2, in gastric cancer tissue compared to normal tissue, and an association of NOTCH3 overexpression with intestinal-type gastric cancer and with better patient prognosis[162]. However, a meta-analysis of 15 studies encompassing a total of 1547 gastric cancer cases reported significantly higher expression of NOTCH3 in diffuse type gastric cancer[163]. A preclinical study also found that NOTCH3 expression increased in gastric cancer cell lines treated with 5-fluorouracil chemotherapy, suggesting that NOTCH3 may be a biomarker of drug resistance[164].

FINDING SUMMARY

NOTCH3 encodes a member of the NOTCH family of receptors, which are involved in cell fate determination and various developmental processes. Upon binding of membrane-bound ligands, NOTCH signaling involves cleavage of the NOTCH intracellular domain (NICD), which subsequently forms part of a transcription factor complex that regulates downstream target genes[165-166]. Although internal deletions that remove EGF repeats (7-10 and 21-22) have been shown in vitro to negatively affect ligand binding and reduce NOTCH3 transcriptional activity[167], NOTCH1 and NOTCH2 rearrangements that eliminate the extracellular domain (ECD) have been observed in patients with breast cancer[168-169] and T-cell acute lymphoblastic leukemia (T-ALL)[170], resulting in ligand-independent activation of NOTCH transcriptional activity and sensitivity to gamma-secretase inhibitors[169-173]. NOTCH3 intracellular domain (NICD) has also been shown to increase cell proliferation in vitro and tumorigenesis in vivo[174], and a fusion of MIR143 to NOTCH3 NICD has been observed in benign glomus tumor, with a similar fusion involving NOTCH2 reported to upregulate NOTCH expression[175]. However, as it is unknown whether such alterations, as observed here, would lead to expression of NICD, the functional effect is unclear.

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GENE
TP53

ALTERATION
R273C

HGVS VARIANT
NM_000546.4: c.817C>T (p.R273C)

VARIANT CHROMOSOMAL POSITION
chr17:7577121

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[176-179] or p53 gene therapy such as SGT53[180-184]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% and SDs in 53% of patients with solid tumors; the response rate was 21% (4/19) for patients with TP53 mutations versus 12% (4/33) for patients who were TP53 wildtype[185]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[186]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[187]. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[188]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24% (6/25) ORR with adavosertib combined with paclitaxel[189]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate for patients with TP53 alterations[190]. The Phase 2 FOCUS4-C trial for patients with TP53- and RAS-mutated colorectal cancer reported improvement in PFS (3.61 vs. 1.87 months, HR=0.35, p=0.0022), but not OS (14.0 vs 12.8 months, p=0.93), following adavosertib treatment compared with active monitoring[191]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[184]. Missense mutations leading to TP53 inactivation may be sensitive to therapies that reactivate mutated p53 such as eprenetapopt. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, eprenetapopt combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[192]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[193].

FREQUENCY & PROGNOSIS

TP53 is frequently mutated in cancers of the gastrointestinal tract, with alterations reported in 34–72% of esophageal, gastroesophageal junction, and gastric adenocarcinomas[71,194-196]. TP53 mutations have been observed in 61-93% of esophageal squamous cell carcinoma samples[157-158,197]. While some studies have reported no association between TP53 mutation status and prognosis in patients with esophageal carcinoma or gastroesophageal junction adenocarcinoma[195-196] others have associated TP53 mutation and elevated p53 expression with poor prognosis for patients with esophageal squamous cell carcinoma[198-199] or stomach cancer[200-202].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[203]. Alterations such as seen here may disrupt TP53 function or expression[204-208].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the TP53 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with Li-Fraumeni syndrome (ClinVar, Sep 2022)[209]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[210-212], including sarcomas[213-214]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[215] to 1:20,000[214]. For pathogenic TP53 mutations identified during tumor sequencing, the rate of germline mutations was 1% in the overall population and 6% in tumors arising before age 30[216]. In the appropriate clinical context, germline testing of TP53 is recommended.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[217-222]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[217-218]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[223]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[221,224-225]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

GENE
WT1

ALTERATION
Q490_K491>H*

HGVS VARIANT
NM_024426.4: c.1470_1471delinsTT
(p.Q490_K491delinsH*)

VARIANT CHROMOSOMAL POSITION
chr11:32410687-32410688

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies that target WT1 mutation. Preclinical studies in acute myeloid leukemia (AML) have shown that WT1 loss may disrupt interactions with the TET2 enzyme[226-228] and, based on one clinical study, may confer sensitivity to the DNA methyltransferase (DNMT) inhibitor azacitidine in AML and myelodysplastic syndrome patients[229]. However, it is not known if this approach would be beneficial for solid tumors or in the context of WT1 mutation. WT1 peptide-based vaccines are being investigated in hematopoietic malignancies and solid cancers, although their relevance to WT1 mutation is unknown[230-234].

FREQUENCY & PROGNOSIS

WT1 alterations have been reported in Wilms tumors at frequencies ranging from 9% to 81%, with higher rates in bilateral Wilms tumors[235-239], and at lower frequencies (<8%) in various other solid tumors (COSMIC, Jan 2023)[240]. Reduced expression or aberrant methylation of WT1 has been reported in a variety of cancers including breast cancer, colorectal cancer, testicular germ cell tumors, and non-small cell lung carcinoma (NSCLC)[241-245], and low expression of WT1 in NSCLC was predictive of poor patient prognosis in one study[246]. However, the majority of solid tumors examined have been reported to overexpress WT1[247-254]. In several tumor types, overexpression of WT1 has been associated with poor prognosis[254-256].

FINDING SUMMARY

The WT1 gene encodes a zinc finger transcription factor, which has been described as both a tumor suppressor and oncogene in a variety of cancers, including Wilms tumor (nephroblastoma), a malignant tumor of the kidney found most commonly in children[257]. WT1 alterations that disrupt the N-terminal region (amino acids 74–244, also 6–180 in alternate transcripts) and/or zinc finger domain (amino acids 391–506, also 323–438 in alternate transcripts) are predicted to be inactivating[258-262]. Missense mutations at codons 404, 462, and 464 (336, 394, and 396 in alternate transcripts) have been observed in patients with T-cell acute lymphoblastic leukemia (T-ALL)[263], acute myeloid leukemia (AML) post myelodysplastic syndrome[264-265], Wilms tumor or the disorder Denys-Drash syndrome[262-263,266-268]. Germline mutations in WT1 are associated with several rare genitourinary developmental and cancer syndromes, including Wilms tumor, WAGR syndrome, Denys-Drash syndrome, Frasier syndrome, nephrotic syndrome type 4, and Meacham syndrome[269-274]. Wilms tumor, the most common of these, occurs in approximately 1:10,000 children and accounts for 7–8% of childhood cancers[269-270,275], and in the appropriate clinical context, germline testing of WT1 is recommended.

IMPORTANT Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months. While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and should be investigated by the physician or research staff. This is not a comprehensive list of all available clinical trials. There may also be compassionate use or early access programs available, which are not listed in this report. Foundation Medicine displays a subset of trial options and ranks them in this order of descending priority: Qualification for pediatric trial → Geographical proximity → Later trial phase. Clinical trials are not ranked in order of potential or predicted efficacy for this patient or in order of level of evidence for this patient's tumor type. Clinical trials listed here may have additional enrollment criteria that may require medical screening to determine final eligibility. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov. However, clinicaltrials.gov does not list all clinical trials that might be available.

GENE

CCND2

ALTERATION

amplification

RATIONALE

CCND2 amplification or activation may predict sensitivity to CDK4/6 inhibitors.

NCT04282031

PHASE 1/2

A Study of BPI-1178 in Patients With Advanced Solid Tumor and HR+/HER2- Breast Cancer

TARGETS

CDK6, CDK4, ER, Aromatase

LOCATIONS: Shanghai (China)

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

TARGETS

TRKB, ALK, TRKC, ROS1, TRKA, CDK4, CDK6, PI3K, mTOR

LOCATIONS: Washington, Oregon, Idaho, Montana

NCT05252416

PHASE 1/2

(VELA) Study of BLU-222 in Advanced Solid Tumors

TARGETS

ER, CDK4, CDK6, CDK2

LOCATIONS: Illinois, Massachusetts, Arkansas, New York, Virginia, Texas, Florida

NCT02896335

PHASE 2

Palbociclib In Progressive Brain Metastases

TARGETS

CDK4, CDK6

LOCATIONS: Massachusetts

NCT05159245

PHASE 2

The Finnish National Study to Facilitate Patient Access to Targeted Anti-cancer Drugs

TARGETS

BRAF, VEGFRs, RET, KIT, ERBB2, TRKB, ALK, TRKC, ROS1, TRKA, SMO, PD-L1, MEK, CDK4, CDK6

LOCATIONS: Kuopio (Finland), Helsinki (Finland), Tampere (Finland), Turku (Finland)

NCT03310879

PHASE 2

Study of the CDK4/6 Inhibitor Abemaciclib in Solid Tumors Harboring Genetic Alterations in Genes Encoding D-type Cyclins or Amplification of CDK4 or CDK6

TARGETS
CDK4, CDK6

LOCATIONS: Massachusetts

NCT03454035

PHASE 1

Ulixertinib/Palbociclib in Patients With Advanced Pancreatic and Other Solid Tumors

TARGETS
CDK4, CDK6, ERK2, ERK1

LOCATIONS: North Carolina

GENE
PTEN

ALTERATION
C218*

RATIONALE
PTEN loss or inactivating mutations may lead to increased activation of the PI3K-AKT-mTOR pathway and may indicate sensitivity to inhibitors of this pathway. PTEN loss or inactivation may also predict sensitivity to PARP inhibitors.

NCT02264678

PHASE 1/2

Ascending Doses of AZD6738 in Combination With Chemotherapy and/or Novel Anti Cancer Agents

TARGETS
ATR, PARP, PD-L1

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Goyang-si (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Coventry (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom)

NCT05035745

PHASE 1/2

Selinexor & Talazoparib in Advanced Refractory Solid Tumors; Advanced/Metastatic Triple Negative Breast Cancer (START)

TARGETS
XPO1, PARP

LOCATIONS: Singapore (Singapore)

NCT03772561

PHASE 1

Phase I Study of AZD5363 + Olaparib + Durvalumab in Patients With Advanced or Metastatic Solid Tumor Malignancies

TARGETS
PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

NCT04551521

PHASE 2

CRAFT: The NCT-PMO-1602 Phase II Trial

TARGETS
PD-L1, AKTs, MEK, BRAF, ALK, RET, ERBB2

LOCATIONS: Lübeck (Germany), Würzburg (Germany), Mainz (Germany), Heidelberg (Germany), Tübingen (Germany)

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

TARGETS
TRKB, ALK, TRKC, ROS1, TRKA, CDK4, CDK6, PI3K, mTOR

LOCATIONS: Washington, Oregon, Idaho, Montana

NCT04991480

PHASE 1/2

A Study of ART4215 for the Treatment of Advanced or Metastatic Solid Tumors

TARGETS
PARP, Pol theta

LOCATIONS: London (United Kingdom), Oklahoma, Connecticut, New York, Pennsylvania, Tennessee, Texas, Florida

NCT05327010

PHASE 2

Testing the Combination of the Anti-cancer Drugs ZEN003694 (ZEN-3694) and Talazoparib in Patients With Advanced Solid Tumors, The ComBET Trial

TARGETS
PARP, BRD4, BRDT, BRD2, BRD3

LOCATIONS: Illinois, Texas, North Carolina, Georgia

NCT04317105

PHASE 1/2

Testing the Addition of an Anti-cancer Drug, Copanlisib, to the Usual Immunotherapy (Nivolumab With or Without Ipilimumab) in Patients With Advanced Solid Cancers That Have Changes in the Following Genes: PIK3CA and PTEN

TARGETS
PD-1, CTLA-4, PI3K

LOCATIONS: Toronto (Canada), Texas, Virginia

NCT02769962

PHASE 1/2

Trial of CRLX101, a Nanoparticle Camptothecin With Olaparib in People With Relapsed/Refractory Small Cell Lung Cancer

TARGETS
PARP, TOP1

LOCATIONS: Maryland

NCT05142241

PHASE 2

Testing the Combination of Anti-Cancer Drugs Talazoparib and Temozolomide in Patients >= 18 Years Old With Advanced Stage Rare Cancers, RARE 2 Study

TARGETS
PARP

LOCATIONS: Maryland

NOTE One or more variants of unknown significance (VUS) were detected in this patient's tumor. These variants may not have been adequately characterized in the scientific literature at the time this report was issued, and/or the genomic context of these alterations makes their significance unclear. We choose to include them here in the event that they become clinically meaningful in the future.

ATR
NM_001184.3: c.4951T>G
(p.Y1651D)
chr3:142226853

BRCA2
NM_000059.3: c.7522G>A
(p.G2508S)
chr13:32930651

CBFB
amplification

CD22
amplification

FGFR2
NM_000141.4: c.1388T>A
(p.V463D)
chr10:123263355

FOXL2
NM_023067.3: c.1024G>A
(p.G342S)
chr3:138664541

GABRA6
NM_000811.2: c.251G>A
(p.R84H)
chr5:161115980

GATA4
NM_002052.3: c.482C>G
(p.P161R)
chr8:11566303

KLHL6
NM_130446.2: c.1235G>A
(p.W412*)
chr3:183211982

MAP3K1
NM_005921.1: c.364G>T
(p.A122S)
chr5:56111764

PIK3C2G
NM_004570.4: c.2638C>A
(p.P880T)
chr12:18644460

PIK3CB
NM_006219.1:
c.1664_1665delinsGT
(p.M555S)
chr3:138417854-138417855

PIK3R1
NM_181523.3: c.1355A>G
(p.Y452C)
chr5:67589592

PTEN
NM_000314.4:
c.383_384delinsGT (p.K128S)
chr10:89692899-89692900

RAD52
amplification

REL
NM_002908.2: c.1808T>A
(p.M603K)
chr2:61149618

ROS1
NM_002944.2: c.6639C>A
(p.D2213E)
chr6:117622231

SGK1
amplification

TNFRSF14
amplification

TP53
NM_000546.4: c.1066G>A
(p.G356R)
chr17:7573961

TYRO3
NM_006293.3: c.1164G>T
(p.K388N)
chr15:41861132

ORDERED TEST # ORD-1623178-01

APPENDIX Genes assayed in FoundationOne®Liquid CDx

FoundationOne Liquid CDx interrogates 324 genes, including 309 genes with complete exonic (coding) coverage and 15 genes with only select non-coding coverage (indicated with an *) ; 75 genes (indicated in bold) are captured with increased sensitivity and have complete exonic (coding) coverage unless otherwise noted.

ABL1 **Exons 4-9**	*ACVR1B*	***AKT1*** **Exon 3**	*AKT2*	*AKT3*	***ALK*** **Exons 20-29, Introns 18, 19**	*ALOX12B*	*AMER1* (FAM123B or WTX)	***APC***
AR	***ARAF*** **Exons 4, 5, 7, 11, 13, 15, 16**	*ARFRP1*	*ARID1A*	*ASXL1*	***ATM***	***ATR***	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*
BCOR	*BCORL1*	*BCR** Introns 8, 13, 14	***BRAF*** **Exons 11-18,** Introns 7-10	***BRCA1*** Introns 2, 7, 8, 12, 16, 19, 20	***BRCA2*** Intron 2	*BRD4*	*BRIP1*	*BTG1*
BTG2	***BTK*** **Exons 2, 15**	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	***CCND1***	*CCND2*
CCND3	*CCNE1*	*CD22*	*CD70*	*CD74** Introns 6-8	*CD79A*	*CD79B*	***CD274*** **(PD-L1)**	*CDC73*
CDH1	***CDK12***	***CDK4***	***CDK6***	*CDK8*	*CDKN1A*	*CDKN1B*	***CDKN2A***	*CDKN2B*
CDKN2C	*CEBPA*	*CHEK1*	***CHEK2***	*CIC*	*CREBBP*	***CRKL***	*CSF1R*	*CSF3R*
CTCF	*CTNNA1*	***CTNNB1*** **Exon 3**	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*
DDR2 **Exons 5, 17, 18**	*DIS3*	*DNMT3A*	*DOT1L*	*EED*	***EGFR*** **Introns 7,** 15, **24-27**	*EMSY* (C11orf30)	*EP300*	*EPHA3*
EPHB1	*EPHB4*	***ERBB2***	***ERBB3*** **Exons 3, 6, 7, 8, 10, 12, 20, 21, 23, 24, 25**	*ERBB4*	*ERCC4*	*ERG*	***ERRFI1***	***ESR1*** **Exons 4-8**
*ETV4** Intron 8	*ETV5** Introns 6, 7	***ETV6**** **Introns 5, 6**	*EWSR1** Introns 7-13	***EZH2*** **Exons 4, 16, 17, 18**	*EZR** Introns 9-11	*FANCA*	*FANCC*	*FANCG*
FANCL	*FAS*	*FBXW7*	*FGF10*	*FGF12*	*FGF14*	*FGF19*	*FGF23*	*FGF3*
FGF4	*FGF6*	***FGFR1*** Introns 1, 5, **Intron 17**	***FGFR2*** Intron 1, **Intron 17**	***FGFR3*** **Exons 7, 9 (alternative designation exon 10), 14, 18, Intron 17**	*FGFR4*	*FH*	*FLCN*	*FLT1*
FLT3 **Exons 14, 15, 20**	***FOXL2***	*FUBP1*	*GABRA6*	*GATA3*	*GATA4*	*GATA6*	*GID4* (C17orf39)	***GNA11*** **Exons 4, 5**
GNA13	***GNAQ*** **Exons 4, 5**	***GNAS*** **Exons 1, 8**	*GRM3*	*GSK3B*	*H3-3A* (H3F3A)	*HDAC1*	*HGF*	*HNF1A*
HRAS **Exons 2, 3**	*HSD3B1*	*ID3*	***IDH1*** **Exon 4**	***IDH2*** **Exon 4**	*IGF1R*	*IKBKE*	*IKZF1*	*INPP4B*
IRF2	*IRF4*	*IRS2*	*JAK1*	***JAK2*** **Exon 14**	***JAK3*** **Exons 5, 11, 12, 13, 15, 16**	*JUN*	*KDM5A*	*KDM5C*
KDM6A	*KDR*	*KEAP1*	*KEL*	***KIT*** **Exons 8, 9, 11, 12, 13, 17,** Intron 16	*KLHL6*	*KMT2A* (MLL) Introns 6, 8-11, Intron 7	*KMT2D* (MLL2)	***KRAS***

FoundationOne Liquid CDx interrogates 324 genes, including 309 genes with complete exonic (coding) coverage and 15 genes with only select non-coding coverage (indicated with an *) ; 75 genes (indicated in bold) are captured with increased sensitivity and have complete exonic (coding) coverage unless otherwise noted.

LTK	*LYN*	*MAF*	***MAP2K1*** **(MEK1) Exons 2, 3**	***MAP2K2*** **(MEK2) Exons 2-4, 6, 7**	*MAP2K4*	*MAP3K1*	*MAP3K13*	*MAPK1*
MCL1	***MDM2***	*MDM4*	*MED12*	*MEF2B*	*MEN1*	*MERTK*	***MET***	*MITF*
MKNK1	*MLH1*	***MPL*** **Exon 10**	*MRE11* (MRE11A)	*MSH2* Intron 5	*MSH3*	*MSH6*	*MST1R*	*MTAP*
MTOR **Exons 19, 30, 39, 40, 43-45, 47, 48, 53, 56**	*MUTYH*	*MYB** Intron 14	***MYC*** **Intron 1**	*MYCL* (MYCL1)	***MYCN***	***MYD88*** **Exon 4**	*NBN*	***NF1***
NF2	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2* Intron 26	*NOTCH3*	***NPM1*** **Exons 4-6, 8, 10**	***NRAS*** **Exons 2, 3**
NSD2 (WHSC1 or MMSET)	*NSD3* (WHSC1L1)	*NT5C2*	***NTRK1*** **Exons 14, 15, Introns 8-11**	*NTRK2* Intron 12	***NTRK3*** **Exons 16, 17**	*NUTM1** Intron 1	*P2RY8*	***PALB2***
PARP1	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1* (PD-1)	***PDCD1LG2*** **(PD-L2)**	***PDGFRA*** **Exons 12, 18, Introns 7, 9, 11**	***PDGFRB*** **Exons 12-21, 23**
PDK1	*PIK3C2B*	*PIK3C2G*	***PIK3CA*** **Exons 2, 3, 5-8, 10, 14, 19, 21 (Coding Exons 1, 2, 4-7, 9, 13, 18, 20)**	*PIK3CB*	*PIK3R1*	*PIM1*	*PMS2*	*POLD1*
POLE	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*	*PRKN* (PARK2)	*PTCH1*
PTEN	***PTPN11***	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*	*RAD51B*	*RAD51C*
RAD51D	*RAD52*	*RAD54L*	***RAF1*** **Exons 3, 4, 6, 7, 10, 14, 15, 17,** Introns 4-8	*RARA* Intron 2	***RB1***	*RBM10*	*REL*	***RET*** Introns 7, 8, **Exons 11, 13-16, Introns 9-11**
RICTOR	*RNF43*	***ROS1*** **Exons 31, 36-38, 40, Introns 31-35**	*RPTOR*	*RSPO2** Intron 1	*SDC4** Intron 2	*SDHA*	*SDHB*	*SDHC*
SDHD	*SETD2*	*SF3B1*	*SGK1*	*SLC34A2** Intron 4	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*
SMO	*SNCAIP*	*SOCS1*	*SOX2*	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*
STAT3	***STK11***	*SUFU*	*SYK*	*TBX3*	*TEK*	*TENT5C* (FAM46C)	*TERC** ncRNA	***TERT**** **Promoter**
TET2	*TGFBR2*	*TIPARP*	*TMPRSS2** Introns 1-3	*TNFAIP3*	*TNFRSF14*	***TP53***	*TSC1*	*TSC2*
TYRO3	*U2AF1*	***VEGFA***	*VHL*	*WT1*	*XPO1*	*XRCC2*	*ZNF217*	*ZNF703*

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite (MS) status
Blood Tumor Mutational Burden (bTMB)
Tumor Fraction

FoundationOne Liquid CDx fulfills the requirements of the European Directive 98/79 EC for in vitro diagnostic medical devices and is registered as a CE-IVD product by Foundation Medicine's EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium. The CE-IVD regulatory status of FoundationOne Liquid CDx is applicable in countries that accept and/or recognize the CE mark.

CE IVD

ABOUT FOUNDATIONONE LIQUID CDx

FoundationOne Liquid CDx was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne Liquid CDx may be used for clinical purposes and should not be regarded as purely investigational or for research only. Foundation Medicine's clinical reference laboratories are qualified to perform high-complexity clinical testing.

Please refer to technical information for performance specification details.

INTENDED USE

FoundationOne Liquid CDx is a next generation sequencing based *in vitro* diagnostic device that analyzes 324 genes. Substitutions and insertion and deletion alterations (indels) are reported in 311 genes, copy number alterations (CNAs) are reported in 310 genes, and gene rearrangements are reported in 324 genes. The test also detects the genomic signatures blood tumor mutational burden (bTMB), microsatellite instability (MSI), and tumor fraction. FoundationOne Liquid CDx utilizes circulating cell-free DNA (cfDNA) isolated from plasma derived from the anti-coagulated peripheral whole blood of cancer patients. The test is intended to be used as a companion diagnostic to identify patients who may benefit from treatment with targeted therapies in accordance with the approved therapeutic product labeling. Additionally, FoundationOne Liquid CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with malignant neoplasms.

TEST PRINCIPLES

The FoundationOne Liquid CDx assay is performed exclusively as a laboratory service using circulating cell-free DNA (cfDNA) isolated from plasma derived from anti-coagulated peripheral whole blood from patients with solid malignant neoplasms. The assay employs a single DNA extraction method to obtain cfDNA from plasma from whole blood. Extracted cfDNA undergoes whole-genome shotgun library construction and hybridization-based capture of 324 cancer-related genes including coding exons and select introns of 309 genes, as well as only select intronic regions or non-coding regions of 15 genes. Hybrid-capture selected libraries are sequenced with deep coverage using the NovaSeq® 6000 platform. Sequence data are processed using a customized analysis pipeline designed to accurately detect genomic alterations, including base substitutions, indels, select copy number variants, and select genomic rearrangements. Substitutions and insertion and deletion alterations (indels) are reported in 311 genes, copy number alterations (CNAs) are reported in 310 genes, and gene rearrangements are reported in 324 genes. The assay also reports tumor fraction, and genomic signatures including MSI and bTMB. A subset of targeted regions in 75 genes is baited for increased sensitivity.

THE REPORT

Incorporates analyses of peer-reviewed studies and other publicly available information identified by Foundation Medicine; these analyses and information may include associations between a molecular alteration (or lack of alteration) and one or more drugs with potential clinical benefit (or potential lack of clinical benefit), including drug candidates that are being studied in clinical research. *Note:* A finding of biomarker alteration does not necessarily indicate pharmacologic effectiveness (or lack thereof) of any drug or treatment regimen; a finding of no biomarker alteration does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness) of any drug or treatment regimen.

QUALIFIED ALTERATION CALLS (EQUIVOCAL)

All equivocal calls, regardless of alteration type, imply that there is adequate evidence to call the alteration with confidence. However, the repeatability of equivocal calls may be lower than non-equivocal calls.

RANKING OF THERAPIES AND CLINICAL TRIALS

Ranking of Therapies in Summary Table

Therapies are ranked based on the following criteria: Therapies with clinical benefit (ranked alphabetically within each evidence category), followed by therapies associated with resistance (when applicable).

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

LIMITATIONS

1. For *in vitro* diagnostic use.
2. For prescription use only. This test must be ordered by a qualified medical professional in accordance with clinical laboratory regulations.
3. A negative result does not rule out the presence of a mutation below the limits of detection of the assay. Patients for whom no companion diagnostic alterations are detected should be considered for confirmation with an appropriately validated tumor tissue test, if available.
4. The FoundationOne Liquid CDx assay does not detect heterozygous deletions.
5. The test is not intended to provide information on cancer predisposition.
6. Performance has not been validated for cfDNA input below the specified minimum input.
7. Tissue TMB and blood TMB (bTMB) are estimated from the number of synonymous and nonsynonymous single-nucleotide variants (SNVs) and insertions and deletions (indels) per area of coding genome sampled, after the removal of known and likely oncogenic driver events and germline SNPs. Tissue TMB is calculated based on variants with an allele frequency of ≥5%, and bTMB is calculated based on variants with an allele frequency of ≥0.5%.
8. Tumor fraction is the percentage of circulating tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample. The tumor fraction estimate is computationally derived from the observed level of aneuploidy in the sample. Tumor fraction is considered elevated when ctDNA levels are high enough that aneuploidy can be detected and is significantly distinct from that typically found in non-tumor samples.
9. Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the tumor genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor. The MSI algorithm is based on genome wide analysis of 1765 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines for solid tissue testing.
10. Genomic findings from circulating cell-free DNA (cfDNA) may originate from circulating tumor DNA fragments, germline alterations, or non-tumor somatic alterations, such as clonal hematopoiesis of indeterminate potential (CHIP). Genes with alterations that may be derived from CHIP include, but are not limited to: *ASXL1*, *ATM*, *CBL*, *CHEK2*, *DNMT3A*, *JAK2*,

KMT2D (*MLL2*), *MPL*, *MYD88*, *SF3B1*, *TET2*, *TP53*, and *U2AF1*.

11. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. If a reported alteration is suspected to be germline, confirmatory testing should be considered in the appropriate clinical context.
12. The test is not intended to replace germline testing or to provide information about cancer predisposition.

REPORT HIGHLIGHTS

The Report Highlights includes select genomic and therapeutic information with potential impact on patient care and treatment that is specific to the genomics and tumor type of the sample analyzed. This section may highlight information including targeted therapies with potential sensitivity or resistance; evidence-matched clinical trials; and variants with potential diagnostic, prognostic, nontargeted treatment, germline, or clonal hematopoiesis implications. Information included in the Report Highlights is expected to evolve with advances in scientific and clinical research. Findings included in the Report Highlights should be considered in the context of all other information in this report and other relevant patient information. Decisions on patient care and treatment are the responsibility of the treating physician.

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

The variants indicated for consideration of follow-up germline testing are 1) limited to reportable short variants with a protein effect listed in the ClinVar genomic database (Landrum et al., 2018; 29165669) as Pathogenic, Pathogenic/Likely Pathogenic, or Likely Pathogenic (by an expert panel or multiple submitters), 2) associated with hereditary cancer-predisposing disorder(s), 3) detected at an allele frequency of >30%, and 4) in select genes reported by the ESMO Precision Medicine Working Group (Mandelker et al., 2019; 31050713) to have a greater than 10% probability of germline origin if identified during tumor sequencing. The selected genes are *ATM, BAP1, BRCA1, BRCA2, BRIP1, CHEK2, FH, FLCN, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, POLE, RAD51C, RAD51D, RET, SDHA, SDHB, SDHC, SDHD, TSC2,* and *VHL*, and are not inclusive of all cancer susceptibility genes. The content in this report should not substitute for genetic counseling or follow-up germline testing, which is needed to distinguish whether a finding in this patient's tumor sequencing is germline or somatic. Interpretation should be based on clinical context.

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

Variants that may represent clonal hematopoiesis (CH) are limited to select reportable short variants in defined genes identified in solid tumors only. Variant selection was determined based on gene tumor-suppressor or oncogene status, known role in solid tumors versus hematological malignancies, and literature prevalence. The defined genes are *ASXL1, ATM, CBL, CHEK2, DNMT3A, IDH2, JAK2, KMT2D (MLL2), MPL, MYD88, SF3B1, TET2,* and *U2AF1* and are not inclusive of all CH genes. The content in this report should not substitute for dedicated hematological workup. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH. Interpretation should be based on clinical context.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

LEVEL OF EVIDENCE NOT PROVIDED

Drugs with potential clinical benefit (or potential lack of clinical benefit) are not evaluated for source or level of published evidence.

NO GUARANTEE OF CLINICAL BENEFIT

This report makes no promises or guarantees that a particular drug will be effective in the treatment of disease in any patient. This report also makes no promises or guarantees that a drug with potential lack of clinical benefit will in fact provide no clinical benefit.

NO GUARANTEE OF REIMBURSEMENT

Foundation Medicine makes no promises or guarantees that a healthcare provider, insurer or other third party payor, whether private or governmental, will reimburse a patient for the cost of FoundationOne Liquid CDx.

TREATMENT DECISIONS ARE THE RESPONSIBILITY OF PHYSICIAN

Drugs referenced in this Report may not be suitable for a particular patient. The selection of any, all or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) resides entirely within the discretion of the treating physician. Indeed, the information in this Report must be considered in conjunction with all other relevant information regarding a particular patient, before the patient's treating physician recommends a course of treatment. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this test or the information contained in this report.

Certain sample of variant characteristics may result in reduced sensitivity. These include: low sample quality, deletions and insertions >40bp, or repetitive/high homology sequences. FoundationOne Liquid CDx is performed using cell-free DNA, and as such germline events may not be reported.

SELECT ABBREVIATIONS

ABBREVIATION	DEFINITION
CR	Complete response
DCR	Disease control rate
DNMT	DNA methyltransferase
HR	Hazard ratio
ITD	Internal tandem duplication
MMR	Mismatch repair
Muts/Mb	Mutations per megabase
NOS	Not otherwise specified
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
SD	Stable disease
TKI	Tyrosine kinase inhibitor

REFERENCE SEQUENCE INFORMATION

Sequence data is mapped to the human genome, Genome Reference Consortium Human Build 37 (GRCh37), also known as hg19.

MR Suite Version (RG) 7.8.0

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