FOUNDATIONONE®LIQUID CDx

PATIENT
Hung Wang, Ai-Yu

TUMOR TYPE
Liver mixed hepatocellular cholangiocarcinoma

COUNTRY CODE
TW

REPORT DATE
17 Nov 2021

ORDERED TEST #
ORD-1235216-01

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 Liver mixed hepatocellular cholangiocarcinoma
NAME Hung Wang, Ai-Yu
DATE OF BIRTH 12 June 1946
SEX Female
MEDICAL RECORD # 31965090

PHYSICIAN

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

SPECIMEN

SPECIMEN ID AYHW 6/12/1946
SPECIMEN TYPE Blood
DATE OF COLLECTION 08 November 2021
SPECIMEN RECEIVED 10 November 2021

Biomarker Findings

Blood Tumor Mutational Burden - 6 Muts/Mb
Microsatellite status - MSI-High Not Detected
Tumor Fraction - Cannot Be Determined

Genomic Findings

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

FBXW7 E287fs*55
IDH1 R132C
ERRFI1 L164fs*2
TSC2 D1690fs*27
DNMT3A S352fs*55, L653*, R635W
TP53 C238Y

3 Therapies with Clinical Benefit
0 Therapies with Resistance
22 Clinical Trials

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Blood Tumor Mutational Burden - 6 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 - Cannot Be Determined	**Tumor fraction is an estimate of the percentage of circulating-tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample based on observed aneuploid instability.**

GENOMIC FINDINGS		VAF %	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
FBXW7 -	E287fs*55	2.2%	None	Everolimus Temsirolimus
10 Trials see p. 13				
IDH1 -	R132C	2.3%	None	Ivosidenib
10 Trials see p. 15				
ERRFI1 -	L164fs*2	0.87%	None	None
1 Trial see p. 12				
TSC2 -	D1690fs*27	30.1%	None	None
10 Trials see p. 17				

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VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS (CH)

Genomic findings below may include nontumor somatic alterations, such as CH. The efficacy of targeting such nontumor somatic alterations is unknown. This content should be interpreted based on clinical context. Refer to appendix for additional information on CH.

DNMT3A - S352fs*55, L653*, R635W ..... p. 8

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.

DNMT3A - S352fs*55, L653*, R635W ..... p. 8 ***TP53*** - C238Y ..... p. 9

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.

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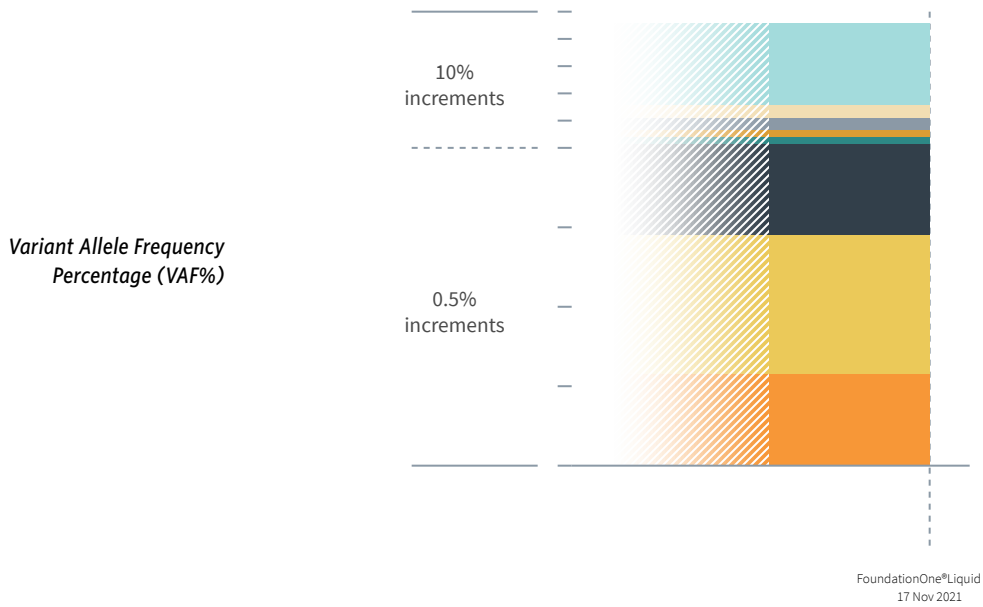

HISTORIC PATIENT FINDINGS		ORD-1235216-01 VAF%
Blood Tumor Mutational Burden		6 Muts/Mb
Microsatellite status		MSI-High Not Detected
Tumor Fraction		Cannot Be Determined
FBXW7	E287fs*55	2.2%
IDH1	R132C	2.3%
ERRFI1	L164fs*2	0.87%
TSC2	D1690fs*27	30.1%
DNMT3A	S352fs*55	4.3%
	L653*	0.58%
	R635W	4.7%
TP53	C238Y	2.8%

NOTE This comparison table refers only to genes and biomarkers assayed by prior FoundationOne®Liquid CDx, FoundationOne®Liquid, FoundationOne®, 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. 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.

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

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BIOMARKER

Blood Tumor Mutational Burden

RESULT
6 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in NSCLC and HSNCC, increased bTMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[1-2] and anti-PD-1[3] therapies. In 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 to 16 Muts/Mb[1]. In 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[4].

FREQUENCY & PROGNOSIS

Average bTMB levels in solid tumors other than NSCLC have not been evaluated (cBioPortal, COSMIC, PubMed, Mar 2021)[5-7]. Published data investigating the prognostic implications of bTMB levels in biliary tract cancer are limited (PubMed, Jul 2021). Published data investigating the prognostic implications of bTMB levels in HCC are limited (PubMed, Jul 2021). Although cases with hypermutated biliary tract cancer were enriched in a subgroup with poor prognosis in 1 study[8], TMB-high (≥10 mut/Mb) status in biliary adenocarcinoma not treated with immunotherapy was not significantly associated with OS in another study, in which patients with TMB-high tumors experienced numerically longer OS compared with patients with TMB-low tumors (11.5 vs. 8.4 months, adjusted HR=0.65)[9]. In an analysis of the TCGA Liver HCC dataset, high TMB was associated with reduced PFS and OS[10]. A retrospective study of 128 patients with HCC who underwent curative resection reported decreased recurrence-free survival for patients with high TMB (>4.8 Muts/Mb) compared to those with low TMB (≤4.8 Muts/Mb) measured in tissue samples[11].

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[12-13] and cigarette smoke in lung cancer[14-15], treatment with temozolomide-based chemotherapy in glioma[16-17], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[18-22], and microsatellite instability (MSI)[18,21-22]. 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[1-3]. Depending on the clinical context, TMB testing of an alternate sample or by another methodology could be considered.

BIOMARKER

Tumor Fraction

RESULT
Cannot Be Determined

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Specimens with high tumor fraction values 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[23]. However, if tumor fraction is not detected as high, it does not exclude the presence of disease burden or compromise the confidence of reported alterations. 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[24-29].

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)[30]. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer[31], Ewing sarcoma and osteosarcoma[32], prostate cancer[27], breast cancer[33], leiomyosarcoma[34], esophageal cancer[35], colorectal cancer[36], and gastrointestinal cancer[37].

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[38], 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[39-40]. However, the tumor fraction estimate in this sample could not be determined with confidence.

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GENE
FBXW7

ALTERATION
E287fs*55

TRANSCRIPT ID
NM_033632

CODING SEQUENCE EFFECT
858delA

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

FBXW7 inactivating alterations may indicate sensitivity to mTOR inhibitors[41-42]. Several case studies reported clinical benefit for patients with FBXW7-mutated cancers, including lung adenocarcinoma[43], renal cell carcinoma[44], and cervical squamous cell carcinoma[45].

— Nontargeted Approaches —

FBXW7 inactivation may also result in resistance to anti-tubulin chemotherapies based on results from preclinical studies[46].

FREQUENCY & PROGNOSIS

FBXW7 amplification and mutation have been observed in 0.5% (2/370) and in up to 1.6%, respectively, of hepatocellular carcinoma (HCC) samples (cBioPortal, COSMIC, Nov 2021)[5-7]. FBXW7 mutations were found in 35% (7/20) of cholangiocarcinomas in one study[47] and in 15% (3/20) of extrahepatic, compared to 5.5% (3/55) of intrahepatic cholangiocarcinomas in another[48]. Protein and mRNA expression of FBXW7 has been reported to be significantly downregulated in HCC tumors compared to the adjacent normal tissue, and lower FBXW7 protein levels were associated with high histological grade and advanced tumor–node–metastasis stage[49-50]. Low FBXW7 protein expression was associated with increased metastasis or inferior survival in patients with cholangiocarcinoma[48,51]. Positive FBXW7 protein expression independently predicted better 5-year overall survival in two studies of patients with surgically resected HCC[52-53].

FINDING SUMMARY

FBXW7 encodes the F-box protein subunit of the SCF ubiquitin ligase complex, which targets proteins for degradation[54]. FBXW7 inactivation is associated with chromosomal instability and with stabilization of proto-oncogenes, such as mTOR, MYC, cyclin E, NOTCH, and JUN; FBXW7 is therefore considered a tumor suppressor[47,54]. Alterations such as seen here may disrupt FBXW7 function or expression[47,55-61].

GENE
IDH1

ALTERATION
R132C

TRANSCRIPT ID
NM_005896

CODING SEQUENCE EFFECT
394C>T

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

IDH1 mutations that lead to production of 2-HG, most commonly R132 alterations, may predict sensitivity to IDH1-mutation-specific inhibitors such as ivosidenib[62]. A Phase 1b/2 study of the IDH1 inhibitor olutasidenib for patients with IDH1-mutated glioma reported a DCR of 50% (n=24) with 1 PR[63]. A Phase 1 study of the pan-IDH1/IDH2 inhibitor vorasidenib for patients with IDH1- or IDH2-mutated glioma reported an ORR of 18.2% (4/22; RANO criteria) and median PFS of 31.4 months for non-enhancing cases and median PFS of 7.5 months for the overall glioma population (n=52)[64]. Preclinical studies suggested that IDH1 neomorphic mutations may also confer sensitivity to PARP inhibitors[65-68].

FREQUENCY & PROGNOSIS

In the literature, IDH1 or IDH2 mutations have been observed in 11-35% of combined HCC and cholangiocarcinoma cases[69-70]. IDH1 or IDH2 mutation has been reported in 10-23% of cholangiocarcinoma cases and has been found to be more prevalent in intrahepatic (22-28%) than extrahepatic (0-7%) cholangiocarcinomas[71-76]. While frequent in cholangiocarcinoma, IDH1 mutations (predominantly at codon R132)[74], have either been infrequently detected or undetected in gallbladder or pancreatic carcinomas[77-80]. IDH1/2 mutations in combined HCC and cholangiocarcinoma did not correlate with any clinicopathological features[70]. In patients with intrahepatic cholangiocarcinoma, IDH1/2 mutations are associated with longer OS and increased time to tumor recurrence[76]. A preclinical study observed that mutant IDH can block hepatocyte differentiation and cooperate with oncogenic KRAS to drive cholangiocarcinoma development[81].

FINDING SUMMARY

The isocitrate dehydrogenases IDH1 and IDH2 encode highly homologous enzymes that are involved in the citric acid (TCA) cycle and other metabolic processes, playing roles in normal cellular metabolism and in protection against oxidative stress and apoptosis[82]. R132 is located within the active site of IDH1 and is a hotspot for mutations in cancer[82-86]. Substitutions at IDH1 R132 alter the enzymatic activity of IDH1, resulting in the production of the oncometabolite, D-2-hydroxyglutarate (2-HG)[84-88], which promotes tumorigenesis[84,89-92].

GENE
ERRFI1

ALTERATION
L164fs*2

TRANSCRIPT ID
NM_018948

CODING SEQUENCE EFFECT
490_491delCT

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

ERRFI1 loss or inactivating mutations may result in EGFR activation and predict sensitivity to ERBB tyrosine kinase inhibitors such as erlotinib, gefitinib, afatinib, and lapatinib, which are approved to treat lung or breast cancers. One patient with cholangiocarcinoma and an ERRFI1 loss of function mutation was reported to have a partial response to the EGFR inhibitor erlotinib[93]. In preclinical studies, the EGFR inhibitor gefitinib was reported to cause regression of tumors in ERRFI1 knockout mice[94] and inhibit signaling downstream EGFR in ERRFI1-depleted human cell lines[95].

FREQUENCY & PROGNOSIS

ERRFI1 mutations were not detected in several cholangiocarcinoma sequencing studies and in <1% of biliary tract carcinomas (COSMIC, Feb 2021)[7,96-98]. ERRFI1 mutations have been reported in 1-10% of hepatocellular carcinoma (HCC) cases in the TCGA datasets[99-100]. In the literature, ERRFI1 has been reported in 3-13% of HCC cases and ERRFI1 expression loss has been associated with hepatocyte proliferation[101]. One study reports that higher ERRFI1 expression is associated with longer OS amongst patients with hepatocellular carcinoma ($P < 0.05$) [49].

FINDING SUMMARY

The ERRFI1 gene (also known as MIG6 or RALT) encodes a tumor suppressor that negatively regulates the ERBB family of receptors[102-105], and is transcriptionally activated by RAS-RAF-ERK signaling[106]. ERRFI1 directly binds to the kinase domain of ERBB proteins and consequently antagonizes their oncogenic signaling and cell proliferation[102-105]. ERRFI1 also negatively regulates signaling by promoting EGFR endocytosis and degradation[107-108]. Knockout or depletion of ERRFI1 was shown to result in EGFR and ERBB2/ERBB3 activation[94,106,108-109], and disruption of the ERRFI1 gene promoted tumorigenesis in mice[94,110], whereas overexpression of ERRFI1 inhibited EGFR- or ERBB2-mediated signaling and oncogenic transformation in vitro[108,111-112]. Alterations such as seen here may disrupt ERRFI1 function or expression[102,104].

GENE
TSC2

ALTERATION
D1690fs*27

TRANSCRIPT ID
NM_000548

CODING SEQUENCE EFFECT
5050_5051insCCCTGCAGTGCAGGAAAGGTAGGGCCGGGT GGGG

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Loss or inactivation of TSC2 can activate mTOR signaling[113-114]. MTOR inhibitors such as everolimus, temsirolimus, and sirolimus have shown activity against tumors associated with the genetic disease tuberous sclerosis complex (TSC), including subependymal giant-cell astrocytomas and renal angiomyolipomas[115-119]. In the context of TSC2-altered malignancies unrelated to TSC, MTOR inhibitor activity has been limited[120-122], with the exception of perivascular epithelioid cell tumors (PEComas)[123-124] and anecdotal reports across various solid tumors including anaplastic thyroid cancer[125], renal cell carcinoma (RCC)[126-127], glioblastoma[128], and CNS embryonal tumor[129], as well as a case of Hodgkin lymphoma[130]. In the prospective NCI-MATCH study, only 6.7% (1/15) of patients with TSC2-mutated solid tumors responded to everolimus, with the single response reported for a patient with uterine leiomyosarcoma[120]. Retrospective analyses of the RECORD-3, GRANITE-1, and EVOLVE-1 studies of everolimus to treat patients with RCC, gastric cancer, or hepatocellular carcinoma, respectively, showed no significant association between alterations in MTOR, TSC1, or TSC2 and median PFS[131].

FREQUENCY & PROGNOSIS

TSC2 mutation has been reported in 2.4% of ampullary adenocarcinomas and 2.2% of biliary tract tumors analyzed in the COSMIC database, including 2.2% gallbladder adenocarcinomas and 1.8% bile duct carcinomas (Oct 2021)[7]. TSC2 mutation was also detected in one cholangiocarcinoma sample in a genomic profiling study of 28 cholangiocarcinomas[74]. Published data investigating the prognostic implications of TSC2 alteration in biliary tract carcinomas are limited (PubMed, Sep 2021).

FINDING SUMMARY

The tumor suppressor protein Tuberin (TSC2) binds with Hamartin (TSC1) to inhibit mTOR signaling and cell growth[113,132]. Alterations such as seen here may disrupt TSC2 function or expression[133-135].

POTENTIAL GERMLINE IMPLICATIONS

Inactivating germline mutations in TSC2 are associated with the autosomal dominant disorder tuberous sclerosis complex, which results in the development of hamartomas in multiple organ systems and an increased risk of developing renal cell carcinoma (RCC)[136-138]. TSC2 mutations account for approximately 75 to 80% of reported sporadic cases[139]. Prevalence for this disorder in the general population is estimated to be 1/6,000 from birth and 1/12,000 to 1/14,000 in children under 10 years of age[139]. In the appropriate clinical context, germline testing of TSC2 is recommended.

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GENE
DNMT3A

ALTERATION
S352fs*55, L653*, R635W

TRANSCRIPT ID
NM_022552, NM_022552, NM_022552

CODING SEQUENCE EFFECT
1054delA, 1958T>A, 1903C>T

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in DNMT3A in solid tumors.

FREQUENCY & PROGNOSIS

DNMT3A alterations have been reported at relatively low frequencies in solid tumors and are more prevalent in hematological malignancies (cBioPortal, Feb 2021)[5-6]. Published data investigating the prognostic implications of DNMT3A alterations in solid tumors are limited (PubMed, Feb 2021).

FINDING SUMMARY

The DNMT3A gene encodes the protein DNA methyltransferase 3A, an enzyme that is involved in the methylation of newly synthesized DNA, a function critical for gene regulation[140-141]. The role of DNMT3A in cancer is uncertain, as some reports describe increased expression and contribution to tumor growth, whereas others propose a role for DNMT3A as a tumor suppressor[142-147]. Alterations such as seen here may disrupt DNMT3A function or expression[148-151]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

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[152-157]. 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[152-153]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[158]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[156,159-160]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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GENE
TP53

ALTERATION
C238Y

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
713G>A

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[161-164], or p53 gene therapy and immunotherapeutics such as SGT-53[165-169] and ALT-801[170]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% (17/176) and SDs in 53.4% (94/176) of patients with solid tumors; the response rate was 21.1% (4/19) for patients with TP53 mutations versus 12.1% (4/33) for patients who were TP53 wild-type[171]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 31.9% (30/94, 3 CR) ORR and a 73.4% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[172]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 42.9% (9/21, 1 CR) ORR and a 76.2% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[173]. 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[174]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24.0% (6/25) ORR with adavosertib combined with paclitaxel[175]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71.4% (5/7) response rate for patients with TP53 alterations[176]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75.0% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[169]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutated, but not TP53-wild-type, breast cancer xenotransplant mouse model[177]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutated p53 such as APR-246[178-180]. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[181]. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies[182-183]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[184-185]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

Inactivation of p53, through mutation, deletion, or loss of heterozygosity (LOH), has been observed in 25-63% of gallbladder carcinomas and 10-61% of cholangiocarcinomas[8,74-75,77,96-98,186-188]. TP53 mutations occur more frequently in tumors caused by liver fluke (O. viverrini) infection (40%) than in cholangiocarcinoma cases not related to infection (9%)[96]. TP53 mutations have been reported in 30-31% of hepatocellular carcinoma (HCC) cases[99,189]. TP53 has been reported to be the most frequently mutated tumor suppressor in HCC, with mutations identified in 16-35% of cases[190-192]. Significantly higher rates of TP53 mutation have been reported in HCC associated with Hepatitis B or Hepatitis C infections compared to other types of HCC[193-195]. TP53 mutations have been reported in 5-44% of cholangiocarcinomas[74-75,77,96,98,186-187]. Expression of p53 has been variously identified in 35-96% of HCC cases[191,196]. Data regarding the prognostic significance of TP53 mutation in cholangiocarcinoma are conflicting[48,197-204]. Overexpression of p53 protein has been associated with reduced patient survival in poorly differentiated gallbladder adenocarcinomas and biliary tract cancers[205-206]; however, another study did not find such a correlation[199]. Studies have reported that patients with HCC harboring TP53 mutation and/or p53 upregulation experienced significantly shorter recurrence-free survival and overall survival[191,196,207-208].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[209]. Alterations such as seen here may disrupt TP53 function or expression[210-214].

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 2021)[215]. 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[216-218], including sarcomas[219-220]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[221] to 1:20,000[220]. 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[222]. 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[152-157]. 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[152-153]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[158]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[156,159-160]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

Electronically signed by Erik Williams, M.D. | 17 November 2021
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Everolimus

Assay findings association

FBXW7
E287fs*55

AREAS OF THERAPEUTIC USE

Everolimus is an orally available mTOR inhibitor that is FDA approved to treat renal cell carcinoma (RCC) following antiangiogenic therapy; pancreatic neuroendocrine tumors; and well-differentiated non-functional neuroendocrine tumors of the lung or gastrointestinal tract. Everolimus is also approved to treat either renal angiomyolipoma or subependymal giant cell astrocytoma in association with tuberous sclerosis complex (TSC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of several case reports describing clinical benefit for patients with FBXW7-mutated cancers treated with mTOR inhibitors, including lung adenocarcinoma[43], renal cell carcinoma[44], and cervical squamous cell carcinoma[223], FBXW7 loss or inactivation may predict sensitivity to everolimus or temsirolimus.

SUPPORTING DATA

A Phase 2 study of everolimus in patients with advanced biliary tract cancer showed 2.6% (1/38) PR and 42.1% (16/38) SD, and a median PFS of 3.2 months[224]. Another Phase 2 study of everolimus in patients with biliary tract cancer reported 7.4% (2/27) PR, 48.1% (13/27) SD, and a median PFS of 6 months[225]. An observational study of everolimus in biliary tract cancer reported a disease control rate of 50%, but a high incidence (64%) of severe toxicities in patients with biliary tract cancer[226]. A Phase 1 trial of everolimus combined with sorafenib reported SD >10 weeks in 62% of cholangiocarcinoma patients[227]. A Phase 1 trial evaluating everolimus in combination with gemcitabine and/or cisplatin for the treatment of patients with solid tumors reported 0% PR, 60% SD, and 40% PD in an expansion cohort of 10 patients with cholangiocarcinoma or gallbladder carcinoma[228]. Although Phase 1/2 studies of everolimus in hepatocellular carcinoma (HCC) reported that everolimus was well tolerated and had preliminary anti-tumor activity[229-230] , the EVOLVE-1 Phase 3 trial of single-agent everolimus in patients with HCC who had failed sorafenib treatment reported that everolimus did not significantly extend overall survival, median time to progression, or disease control rate in comparison with placebo[231]. Everolimus-based immunosuppression significantly extended survival and decreased rate of recurrence in patients with HCC who had undergone liver transplant[232-233] . Studies of everolimus in combination with sorafenib for the treatment of HCC showed limited efficacy, and one study reported considerable adverse effects[234-235] . 15 patients with HCC and low TSC2 expression tended to have a longer overall survival in response to everolimus (9.5-32.7 months) when compared to placebo (1.3-5.6 months)[236]. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[237], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[238].

Ivosidenib

Assay findings association

IDH1
R132C

AREAS OF THERAPEUTIC USE

Ivosidenib is an isocitrate dehydrogenase 1 (IDH1) inhibitor that is FDA approved to treat patients with a susceptible IDH1 mutation in relapsed or refractory acute myeloid leukemia (AML) or previously treated locally advanced or metastatic cholangiocarcinoma. It is also approved as a first-line treatment for patients with AML and a susceptible IDH1 mutation who are not eligible for intensive induction chemotherapy or who are ≥75 years old. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of extensive clinical evidence in AML[239] and cholangiocarcinoma[240-241] and limited clinical data in myelodysplastic syndrome (MDS)[239] and glioma[62,242] , IDH1 R132 mutation may confer sensitivity to ivosidenib.

SUPPORTING DATA

In the Phase 3 ClarIDHy trial for patients with previously treated IDH1 R132-mutated cholangiocarcinoma, ivosidenib significantly increased PFS (2.7 vs. 1.4 months, HR=0.37, p <0.001) as well as PFS rates compared with placebo (6-month: 32% vs. 0%, 12-month: 22% vs. 0%) and reported numerically increased OS (10.3 vs. 7.5 months, HR=0.79, p=0.09), which reached statistical significance once adjusted for crossover (10.3 vs. 5.1 months, HR=0.49, p <0.0001)[241,243] . A Phase 1 study reported an ORR of 5.6% (4/72, all PRs), SD rate of 56% (40/72), median PFS of 3.8 months, and median OS of 13.8 months for patients with IDH1-mutated cholangiocarcinoma treated with ivosidenib[240].

Temsirolimus

Assay findings association

FBXW7
E287fs*55

AREAS OF THERAPEUTIC USE

Temsirolimus is an intravenous mTOR inhibitor that is FDA approved for the treatment of advanced renal cell carcinoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of several case reports describing clinical benefit for patients with FBXW7-mutated cancers treated with mTOR inhibitors, including lung adenocarcinoma[43], renal cell carcinoma[44], and cervical squamous cell carcinoma[223], FBXW7 loss or inactivation may predict sensitivity to everolimus or temsirolimus.

SUPPORTING DATA

A Phase 1/2 trial of temsirolimus in patients with hepatocellular carcinoma (HCC) reported 2.9% (1/35) partial responses (PR) and 57% (20/35) stable disease (SD), with a greater level of disease stabilization (PR+SD; 70%) in tumors with higher activated mTOR[244]. A trial of temsirolimus in combination with bevacizumab reported 5 confirmed and 1 unconfirmed partial response (PR) in a cohort of 26 patients with HCC[245]. Out of 18 evaluable patients treated with a combination of temsirolimus and doxorubicin in a Phase 1 trial, two achieved a PR (one in a patient with HCC) and 6 achieved stable disease (SD) (one in a patient with HCC)[246]. A Phase 1 trial of 25 patients with HCC treated with sorafenib and temsirolimus reported 2 (8%) patients with a confirmed PR and 15 (60%) with SD, warranting further study of the combination treatment[247].

NOTE Genomic alterations detected may be associated with activity of certain US FDA or other specific country approved therapies; however, the therapies listed in this report may have varied evidence in the patient's tumor type. The listed therapies 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. The therapies listed in this report may not be complete and/or exhaustive. Furthermore, the listed therapies are limited to US FDA approved pharmaceutical drug products that are linked to a specific genomic alteration. There may also be US FDA approved pharmaceutical drug products that are not linked to a genomic alteration. Further there may also exist pharmaceutical drug products that are not approved by the US FDA or other national authorities. There may also be other treatment modalities available than pharmaceutical drug products.

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
ERRFI1

ALTERATION
L164fs*2

RATIONALE
ERRFI1 loss or inactivating mutations may result in EGFR activation and predict sensitivity to ERBB tyrosine kinase inhibitors.

NCT03768375

PHASE 2

Molecularly Target Therapy With FORFIRINOX in Advanced or Recurrent Extrahepatic Cholangiocarcinoma and Gallbladder Carcinoma

TARGETS
EGFR, mTOR, ERBB2

LOCATIONS: Shanghai (China)

GENE
FBXW7

ALTERATION
E287fs*55

RATIONALE
Loss or inactivation of FBXW7 may lead to increased mTOR activation and may predict sensitivity to mTOR inhibitors.

NCT03591965

PHASE 2

Dual TORC1/TORC2 Inhibitor ATG-008 (CC-223) in HBV Positive Advanced Hepatocellular Carcinoma (HCC) Subjects

TARGETS
mTORC1, mTORC2

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Taichung (Taiwan), Fuzhou (China), Hangzhou (China), Shanghai (China), Nanjing (China), Hefei (China), Guangzhou (China), Changsha (China)

NCT03239015

PHASE 2

Efficacy and Safety of Targeted Precision Therapy in Refractory Tumor With Druggable Molecular Event

TARGETS
EGFR, ERBB2, ERBB4, PARP, mTOR, MET, RET, ROS1, VEGFRs, BRAF, CDK4, CDK6

LOCATIONS: Shanghai (China)

NCT03768375

PHASE 2

Molecularly Target Therapy With FORFIRINOX in Advanced or Recurrent Extrahepatic Cholangiocarcinoma and Gallbladder Carcinoma

TARGETS
EGFR, mTOR, ERBB2

LOCATIONS: Shanghai (China)

NCT04803318

PHASE 2

Trametinib Combined With Everolimus and Lenvatinib for Recurrent/Refractory Advanced Solid Tumors

TARGETS
mTOR, FGFRs, KIT, PDGFRA, RET, VEGFRs, MEK

LOCATIONS: Guangzhou (China)

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

TARGETS
VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, DDR2, KIT, EGFR, PD-1, CTLA-4, PARP, CDK4, CDK6, CSF1R, FLT3, RET, mTOR, ERBB2, ERBB3, MEK, BRAF, SMO

LOCATIONS: Vancouver (Canada), Edmonton (Canada), Saskatoon (Canada), Regina (Canada), Ottawa (Canada), Montreal (Canada), Toronto (Canada), Kingston (Canada), London (Canada)

NCT03190174

PHASE 1/2

Nivolumab (Opdivo®) Plus ABI-009 (Nab-rapamycin) for Advanced Sarcoma

TARGETS
mTOR, PD-1

LOCATIONS: California

NCT03217669

PHASE 1

Epacadostat (INCB24360) in Combination With Sirolimus in Advanced Malignancy

TARGETS
IDO1, mTOR

LOCATIONS: Kansas

NCT03065062

PHASE 1

Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the PI3K/mTOR Inhibitor Gedatolisib (PF-05212384) for Patients With Advanced Squamous Cell Lung, Pancreatic, Head & Neck and Other Solid Tumors

TARGETS
PI3K-alpha, PI3K-gamma, mTORC1, mTORC2, CDK4, CDK6

LOCATIONS: Massachusetts

NCT01582191

PHASE 1

A Phase 1 Trial of Vandetanib (a Multi-kinase Inhibitor of EGFR, VEGFR and RET Inhibitor) in Combination With Everolimus (an mTOR Inhibitor) in Advanced Cancer

TARGETS
mTOR, EGFR, RET, SRC, VEGFRs

LOCATIONS: Texas

NCT02159989

PHASE 1

Sapanisertib and Ziv-Aflibercept in Treating Patients With Recurrent Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery

TARGETS
PIGF, VEGFA, VEGFB, mTORC1, mTORC2

LOCATIONS: Texas

GENE
IDH1

ALTERATION
R132C

RATIONALE
IDH1 mutations may predict sensitivity to IDH1 inhibitors. On the basis of preclinical data, IDH1 mutations may also confer sensitivity to PARP inhibitors in solid tumors.

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), Cambridge (United Kingdom), Withington (United Kingdom), London (United Kingdom), Sutton (United Kingdom), Villejuif (France), Saint Herblain (France), California

NCT04298021

PHASE 2

DDR-Umbrella Study of DDR Targeting Agents in Advanced Biliary Tract Cancer

TARGETS
PD-L1, ATR, PARP

LOCATIONS: Seoul (Korea, Republic of)

NCT04635631

PHASE 1

STUDY OF TALAZOPARIB MONOTHERAPY IN CHINESE PARTICIPANTS WITH ADVANCED SOLID TUMORS

TARGETS
PARP

LOCATIONS: Beijing (China), Changchun (China)

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)

NCT04801966

PHASE NULL

Safety and Oversight of the Individually Tailored Treatment Approach: A Novel Pilot Study

TARGETS
CDK4, CDK6, PI3K-alpha, PD-L1, MEK, PARP, PD-1, BRAF

LOCATIONS: Melbourne (Australia)

NCT04497116

PHASE 1/2

Study of RP-3500 in Advanced Solid Tumors

TARGETS
ATR, PARP

LOCATIONS: Copenhagen (Denmark), Newcastle Upon Tyne (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Toronto (Canada), Massachusetts, Rhode Island, New York, Tennessee, Texas

NCT03907969

PHASE 1/2

A Clinical Trial to Evaluate AZD7648 Alone and in Combination With Other Anti-cancer Agents in Patients With Advanced Cancers

TARGETS
PARP, DNA-PK

LOCATIONS: Newcastle upon Tyne (United Kingdom), London (United Kingdom), Connecticut, Texas

NCT03878095

PHASE 2

Testing Olaparib and AZD6738 in IDH1 and IDH2 Mutant Tumors

TARGETS
ATR, PARP

LOCATIONS: Utah, Wisconsin, Michigan, Ohio, Connecticut, Maryland, Texas, Florida

NCT03830918

PHASE 1/2

Niraparib and Temozolomide in Treating Patients With Extensive-Stage Small Cell Lung Cancer With a Complete or Partial Response to Platinum-Based First-Line Chemotherapy

TARGETS
PARP

LOCATIONS: California

NCT03212274

PHASE 2

Olaparib in Treating Patients With Advanced Glioma, Cholangiocarcinoma, or Solid Tumors With IDH1 or IDH2 Mutations

TARGETS
PARP

LOCATIONS: California, Wisconsin, Missouri, Kansas

GENE
TSC2

ALTERATION
D1690fs*27

RATIONALE
Inactivating TSC2 alterations may lead to increased mTOR activation and predict sensitivity to mTOR inhibitors.

NCT03591965

PHASE 2

Dual TORC1/TORC2 Inhibitor ATG-008 (CC-223) in HBV Positive Advanced Hepatocellular Carcinoma (HCC) Subjects

TARGETS
mTORC1, mTORC2

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Taichung (Taiwan), Fuzhou (China), Hangzhou (China), Shanghai (China), Nanjing (China), Hefei (China), Guangzhou (China), Changsha (China)

NCT03239015

PHASE 2

Efficacy and Safety of Targeted Precision Therapy in Refractory Tumor With Druggable Molecular Event

TARGETS
EGFR, ERBB2, ERBB4, PARP, mTOR, MET, RET, ROS1, VEGFRs, BRAF, CDK4, CDK6

LOCATIONS: Shanghai (China)

NCT03768375

PHASE 2

Molecularly Target Therapy With FORFIRINOX in Advanced or Recurrent Extrahepatic Cholangiocarcinoma and Gallbladder Carcinoma

TARGETS
EGFR, mTOR, ERBB2

LOCATIONS: Shanghai (China)

NCT04803318

PHASE 2

Trametinib Combined With Everolimus and Lenvatinib for Recurrent/Refractory Advanced Solid Tumors

TARGETS
mTOR, FGFRs, KIT, PDGFRA, RET, VEGFRs, MEK

LOCATIONS: Guangzhou (China)

NCT02693535

PHASE 2

TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer

TARGETS
VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, CDK4, CDK6, CSF1R, FLT3, KIT, RET, mTOR, EGFR, ERBB2, ERBB3, MEK, BRAF, SMO, DDR2, PARP, PD-1, CTLA-4, ERBB4

LOCATIONS: Hawaii, Washington, Oregon, California

NCT04185831

PHASE 2

A MolEcularly Guided Anti-Cancer Drug Off-Label Trial

TARGETS
PD-L1, MEK

LOCATIONS: Uppsala (Sweden), Gothenburg (Sweden)

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

TARGETS
VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, DDR2, KIT, EGFR, PD-1, CTLA-4, PARP, CDK4, CDK6, CSF1R, FLT3, RET, mTOR, ERBB2, ERBB3, MEK, BRAF, SMO

LOCATIONS: Vancouver (Canada), Edmonton (Canada), Saskatoon (Canada), Regina (Canada), Ottawa (Canada), Montreal (Canada), Toronto (Canada), Kingston (Canada), London (Canada)

NCT03190174

PHASE 1/2

Nivolumab (Opdivo®) Plus ABI-009 (Nab-rapamycin) for Advanced Sarcoma

TARGETS
mTOR, PD-1

LOCATIONS: California

NCT03217669

PHASE 1

Epacadostat (INCB24360) in Combination With Sirolimus in Advanced Malignancy

TARGETS
IDO1, mTOR

LOCATIONS: Kansas

NCT03065062

PHASE 1

Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the PI3K/mTOR Inhibitor Gedatolisib (PF-05212384) for Patients With Advanced Squamous Cell Lung, Pancreatic, Head & Neck and Other Solid Tumors

TARGETS
PI3K-alpha, PI3K-gamma, mTORC1, mTORC2, CDK4, CDK6

LOCATIONS: Massachusetts

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.

BARD1 R529Q	***ERBB3*** G316E	***FGFR3*** L164V	***GATA6*** M197L
GNAS E105K	***KDR*** splice site 1091+1G>C	***MAF*** E156D	***MLH1*** Y379S
PDGFRA A401D	***PTCH1*** E44G and S827G	***SYK*** D612N	***TSC2*** D529A

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Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

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)	***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**	*C11orf30* (EMSY)	*C17orf39* (GID4)	*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**	*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	*FAM46C*	*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*
GNA11 **Exons 4, 5**	*GNA13*	***GNAQ*** **Exons 4, 5**	***GNAS*** **Exons 1, 8**	*GRM3*	*GSK3B*	*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)

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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.

KRAS	*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**	*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**	*NSD3* (WHSC1L1)	*NT5C2*	***NTRK1*** **Exons 14, 15, Introns 8-11**	*NTRK2* Intron 12	***NTRK3*** **Exons 16, 17**	*NUTM1** Intron 1	*P2RY8*	***PALB2***
PARK2	*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*	*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*	*TERC** ncRNA	***TERT**** **Promoter**	*TET2*
TGFBR2	*TIPARP*	*TMPRSS2** Introns 1-3	*TNFAIP3*	*TNFRSF14*	***TP53***	*TSC1*	*TSC2*	*TYRO3*
U2AF1	***VEGFA***	*VHL*	*WHSC1*	*WT1*	*XPO1*	*XRCC2*	*ZNF217*	*ZNF703*

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite (MS) status

Blood Tumor Mutational Burden (bTMB)

Tumor Fraction

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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 observed aneuploid instability in the sample.
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.

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. 2021. 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

MR Suite Version 5.1.1

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