FOUNDATIONONE®LIQUID CDx

PATIENT
Ting, Chen-Chiu

TUMOR TYPE
Liver hepatocellular carcinoma (HCC)

COUNTRY CODE
TW

REPORT DATE
15 Mar 2022

ORDERED TEST #
ORD-1319654-01

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 hepatocellular carcinoma (HCC)
NAME Ting, Chen-Chiu
DATE OF BIRTH 08 August 1970
SEX Female
MEDICAL RECORD # 25325819

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 CCT 8/AUG/1970
SPECIMEN TYPE Blood
DATE OF COLLECTION 04 March 2022
SPECIMEN RECEIVED 09 March 2022

Biomarker Findings

Blood Tumor Mutational Burden - 1 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.

MET amplification
CCND1 amplification
FGF19 amplification
FGF3 amplification
FGF4 amplification
TET2 A277T
TP53 N131I

† See About the Test in appendix for details.

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Cabozantinib** (p. 10)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 13)
- Variants that may represent **clonal hematopoiesis** and may originate from non-tumor sources: ***TET2* A277T** (p. 8)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Blood Tumor Mutational Burden - 1 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 %
MET -	amplification	-

10 Trials see p. 15

THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)		THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
Cabozantinib	1	Capmatinib
		Crizotinib
		Tepotinib

☐ *NCCN category*

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GENOMIC FINDINGS	VAF %	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
CCND1 **-** amplification	-	None	None
6 Trials see p. 13			

☐ *NCCN category*

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.

TET2 **-** A277T ..... 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.

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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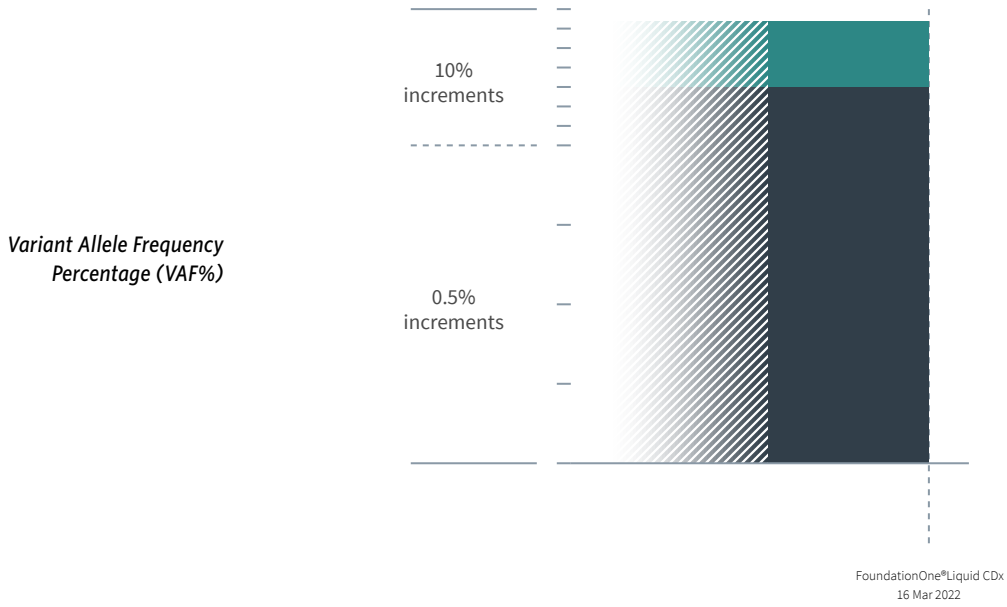

HISTORIC PATIENT FINDINGS		ORD-1319654-01 VAF%
Blood Tumor Mutational Burden		1 Muts/Mb
Microsatellite status		MSI-High Not Detected
Tumor Fraction		41%
MET	amplification	Detected
CCND1	amplification	Detected
FGF19	amplification	Detected
FGF3	amplification	Detected
FGF4	amplification	Detected
TET2	● A277T	32.1%
TP53	● N131I	33.7%

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 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%.

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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
1 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 2022)[5-7]. Published data investigating the prognostic implications of bTMB levels in HCC are limited (PubMed, Jul 2021). In an analysis of the TCGA Liver HCC dataset, high TMB was associated with reduced PFS and OS[8]. 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[9].

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[10-11] and cigarette smoke in lung cancer[12-13], treatment with temozolomide-based chemotherapy in glioma[14-15], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[16-20], and microsatellite instability (MSI)[16,19-20]. 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
Elevated Tumor Fraction

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Specimens with elevated tumor fraction have high circulating-tumor DNA (ctDNA) content, and thus high sensitivity for identifying genomic alterations. Such specimens are at low 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[21-26].

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)[27]. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer[28], Ewing sarcoma and osteosarcoma[29], prostate cancer[24], breast cancer[30], leiomyosarcoma[31], esophageal cancer[32], colorectal cancer[33], and gastrointestinal cancer[34].

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[35], 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[36-37].

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GENE
MET

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of extensive clinical evidence, MET amplification or activating mutations may predict sensitivity to MET-targeting therapies such as kinase inhibitors crizotinib, capmatinib, tepotinib, and cabozantinib. In a Phase 2 study, patients with advanced hepatocellular carcinoma (HCC) and high MET expression achieved a 30.0% ORR (3/10, 1 CR) when treated with capmatinib; no responses (n=20) were observed for patients with lower MET expression[38]. A Phase 1 capmatinib trial reported SD as the best response for patients with MET-amplified advanced HCC[39]. Crizotinib has benefited patients with MET-amplified non-small cell lung cancer (NSCLC) of varied histologies[40-43], gastroesophageal cancer[44], glioblastoma[45], and carcinoma of unknown primary[46]. Capmatinib has demonstrated clinical efficacy for patients with MET-amplified NSCLC both as a monotherapy[47-48] and in combination with an EGFR-TKI for patients with concurrent activating EGFR mutations[49-51]. Tepotinib has demonstrated efficacy for patients with MET-amplified hepatocellular carcinoma[52] and NSCLC[53] as a monotherapy, as well as in combination with gefitinib for patients with MET-amplified and EGFR-mutated NSCLC[54-56] . Savolitinib elicited responses in patients with MET-amplified papillary renal cell carcinoma[57] and gastric cancer either alone or in combination with docetaxel[58-59]. AMG 337 elicited an ORR of 50% (5/10), including 1 CR, for patients with MET-amplified gastric, esophageal, or gastroesophageal junction cancer[60]. Patients with MET-amplified NSCLC[61] or MET-amplified gastric cancer[62] treated with the MET-targeting antibody onartuzumab (MetMAb) achieved clinical responses. In addition, high MET expression has been suggested to predict patient response to therapies such as the monoclonal HGF-targeting antibody rilotumumab, as well as the combination of ramucirumab and the monoclonal MET-targeting antibody emibetuzumab[63]. A first-in-human Phase 1 trial of telisotuzumab vedotin (teliso-V), a MET antibody-drug conjugate, reported activity in a subset of patients with MET-positive NSCLC, with an ORR of 19% (3/16) and a DCR of 56% (9/16); no responses were observed in any other patients[64]. A subsequent Phase 2 trial of teliso-V in patients with MET-positive NSCLC reported a 35% (13/37) ORR in patients with non-squamous, EGFR-wildtype tumors, which met the prespecified criteria for transition to the next stage; lower ORRs were observed in patients with squamous (14%; 3/21) or non-squamous EGFR-mutated (13%; 4/30) tumors[65].

FREQUENCY & PROGNOSIS

MET amplification has been reported at frequencies ranging from 3% to 25% of hepatocellular carcinoma (HCC) cases[66-71]. MET mutation has been reported much more rarely, in 0-1% of cases[66,72]. Overexpression of MET at protein and mRNA levels is common in HCC and has been found in 27.9%-80.6% of samples[71,73-74]. However, MET overexpression has demonstrated low level of correlation with MET amplification[70-71]. Multiple studies have reported that alteration or expression of MET is not associated with overall survival in HCC[70-71,74-76].

FINDING SUMMARY

MET encodes a receptor tyrosine kinase, also known as c-MET or hepatocyte growth factor receptor (HGFR), that is activated by the ligand HGF; MET activation results in signaling mediated partly by the RAS-RAF-MAPK and PI3K pathways to promote proliferation[77-78]. MET has been reported to be amplified in cancer[6], with amplification positively correlating with protein expression in some cancer types[74,79-82] and associating with therapeutic response to MET inhibitors in a variety of cancer types[40-42,44-46,83-84].

GENE
CCND1

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Amplification or overexpression of CCND1 may predict sensitivity to CDK4/6 inhibitors, such as abemaciclib, palbociclib, and ribociclib[85-90], although as monotherapy these agents have shown limited activity in tumor types other than breast cancer[89,91]. In refractory advanced solid tumors with CCND1 (n=39) or CCND3 (n=1) amplification and retinoblastoma protein expression, palbociclib resulted in SD for 39% (14/36) of patients and a median PFS of 1.8 months in the NCI-MATCH trial[92]; 4 patients (13%, 4/36 overall) with squamous cell carcinomas (lung, esophageal, or laryngeal) or adenoid cystic carcinoma experienced prolonged SD in this study[92]. Among 9 patients with CCND1-amplified advanced solid tumors, 1 patient with bladder cancer responded to ribociclib in a Phase 2 trial[93].

— Potential Resistance —

CCND1 amplification may predict worse outcomes on immune checkpoint inhibitors (anti-PD-1/PD-L1/CTLA-4) in solid tumors on the basis of 2 meta-analyses[94-95]; in these studies, CCND1 amplification was associated with significantly decreased response rate[95] and OS (HR=1.6-2.0)[94-95] across various tumor types and significantly shorter OS specifically in urothelial carcinoma (HR=2.2-3.6), melanoma (HR=1.6-2.5), and solid tumors harboring elevated TMB (HR=2.8)[94-95].

FREQUENCY & PROGNOSIS

CCND1 amplification has been reported in 5-7% of hepatocellular carcinomas (HCC) in several studies (cBioPortal, Feb 2022)[5-6]. Published data investigating the prognostic implications of CCND1 alterations in HCC are limited (PubMed, Feb 2022).

FINDING SUMMARY

CCND1 encodes cyclin D1, a binding partner of the kinases CDK4 and CDK6, that regulates RB activity and cell cycle progression. Amplification of CCND1 has been positively correlated with cyclin D1 overexpression[96] and may lead to excessive proliferation[97-98].

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GENE
FGF19

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies that directly address genomic alterations in FGF19. However, FGF19 amplification predicts sensitivity to FGFR4 inhibitors in liver cancer cell lines[99-100]; selective FGFR4 inhibition reduced tumor burden in an FGF19-amplified HCC xenograft model[101]. A Phase 1 study of the FGFR4 inhibitor fisogatinib (BLU-554) for patients with previously treated hepatocellular carcinoma (HCC), most of whom had received prior sorafenib treatment, reported a 16.7% ORR (11/66, 1 CR, ongoing for >1.5 years) and a median PFS of 3.3 months for FGF19-IHC-positive patients; poorer outcomes (0% ORR, PFS of 2.3 months) were observed for patients with negative or unknown FGF19 IHC scores[102]. Acquisition of FGFR4 mutations may represent a mechanism of resistance for patients with FGF19 overexpression who initially responded but then progressed on fisogatinib[100]. Preliminary results from the dose escalation part of a Phase 1/2 study evaluating another FGFR4 inhibitor, FGF401, showed an ORR of 7.6% (4/53), SD rate of 52.8% (28/53), and a median time to progression of 4.1 months; responses were observed in both FGF19-positive and FGF19-negative cases[103]. In a retrospective analysis, a trend toward response to sorafenib treatment and FGF19 copy number gain was observed in patients with HCC, and 2 patients harboring FGF19 copy number gain experienced a CR[104]. A case study reported activity of pan-FGFR inhibitors in FGF-amplified cancers; following treatment with a selective pan-FGFR inhibitor, a patient with head and neck squamous cell carcinoma (HNSCC) and amplification of 11q13 (FGF3, FGF4, FGF19) and 12p13 (FGF6 and FGF23) experienced a radiologic CR[105]. Other therapies targeting FGF19 or FGFR4 signaling are in development[106].

FREQUENCY & PROGNOSIS

In the TCGA datasets, FGF19 amplification has been reported in esophageal carcinoma (34%), head and neck squamous cell carcinoma (23%), breast carcinoma (15%), lung squamous cell carcinoma (13%), and cholangiocarcinoma (11%) (cBioPortal, Jan 2022)[5-6]. In HCC, FGF19 is an important driver gene[101,107-108], and FGF19 protein expression correlates with tumor progression and poorer prognosis[109]. Exogenous FGF19 has been shown to promote prostate cancer tumorigenesis in a preclinical study[110], and the presence of FGF19-positive tissues is an independent factor for worse prognosis following radical prostatectomy[111].

FINDING SUMMARY

FGF19 encodes fibroblast growth factor 19, an FGFR4 ligand involved with bile acid synthesis and hepatocyte proliferation in the liver[101,112]. FGF19 lies in a region of chromosome 11q13 frequently amplified in a diverse range of malignancies that also contains FGF3, FGF4, and CCND1[113]. Correlation between FGF19 amplification and protein expression has been demonstrated in hepatocellular carcinoma (HCC)[114] but was not observed in several other tumor types[108].

GENE
FGF3

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies that directly address genomic alterations in FGF3. Inhibitors of FGF receptors, however, are undergoing clinical trials in a number of different cancers. Limited data suggest that pan-FGFR inhibitors show activity in FGF amplified cancers; following treatment with a selective pan-FGFR inhibitor, a patient with head and neck squamous cell carcinoma (HNSCC) and amplification of 11q13 (FGF3, FGF4, FGF19) and 12p13 (FGF6 and FGF23) experienced a radiologic CR[115].

FREQUENCY & PROGNOSIS

FGF3 lies in a region of chromosome 11q13 that also contains FGF19, FGF4, and CCND1, the latter gene encoding cyclin D1, a key regulator of cell cycle progression. This chromosomal region is frequently amplified in a diverse range of malignancies[97].

FINDING SUMMARY

FGF3 encodes fibroblast growth factor 3, a growth factor that plays a central role in development of the inner ear. Germline mutations in FGF3 give rise to an autosomal recessive syndrome characterized by microdontia, deafness, and complete lack of inner ear structures[116].

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GENE
FGF4

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

FGF4 amplification and overexpression was associated with cell sensitivity to the multikinase inhibitor sorafenib in preclinical studies[117-118] and amplification of FGF4/FGF3 in HCC significantly correlated with patient response to sorafenib (p=0.006)[117]. Limited data suggest that pan-FGFR inhibitors show activity in FGF amplified cancers; following treatment with a selective pan-FGFR inhibitor, a patient with head and neck squamous cell carcinoma (HNSCC) and amplification of 11q13 (FGF3, FGF4, FGF19) and 12p13 (FGF6 and FGF23) experienced a radiologic CR[115].

FREQUENCY & PROGNOSIS

FGF4 lies in a region of chromosome 11q13 that also contains FGF19, FGF3, and CCND1, the latter gene encoding cyclin D1, a key regulator of cell cycle progression. This chromosomal region is frequently amplified in a diverse range of malignancies[97] including esophageal carcinoma (35%), head and neck squamous cell carcinoma (HNSCC; 24%), breast invasive carcinoma (14%), lung squamous cell carcinoma (13%), cholangiocarcinoma (11%), bladder urothelial carcinoma (10%), stomach adenocarcinoma (7%), skin melanoma (5%), and hepatocellular carcinoma (HCC; 5%), however FGF4 amplification is rare in hematopoietic and lymphoid malignancies, reported in less than 1% of samples analyzed (cBioPortal, Jan 2022)[5-6].

FINDING SUMMARY

FGF4 encodes fibroblast growth factor 4, which plays a central role in development of the teeth[119] and acts synergistically with other FGFs and SHH (sonic hedgehog) to regulate limb outgrowth in vertebrate development[120]. FGF4 lies in a region of chromosome 11q13 that also contains FGF19, FGF3, and CCND1, the latter gene encoding cyclin D1, a key regulator of cell cycle progression. Amplification of FGF4, along with that of FGF3, FGF19, and CCND1, has been reported in a variety of cancers[97,117,121-124] and may confer sensitivity to the multi-kinase inhibitor sorafenib[117].

GENE
TET2

ALTERATION
A277T

TRANSCRIPT ID
NM_001127208

CODING SEQUENCE EFFECT
829G>A

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in TET2 in solid tumors.

FREQUENCY & PROGNOSIS

TET2 alterations have been reported at relatively low frequencies in solid tumors and are more prevalent in hematological malignancies (cBioPortal, Jan 2022)[5-6]. Published data investigating the prognostic implications of TET2 alterations in solid tumors are limited (PubMed, Jan 2022).

FINDING SUMMARY

TET2 encodes a tumor suppressor involved in reversing DNA methylation marks, a process critical for proper gene regulation[125-126]. 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[127-132]. 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[127-128]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[133]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[131,134-135]. 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
N131I

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
392A>T

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[136-139], or p53 gene therapy and immunotherapeutics such as SGT-53[140-144] and ALT-801[145]. 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[146]. 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[147]. 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[148]. 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[149]. 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[58]. 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[150]. 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[151]. 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[144]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutated p53 such as APR-246[152-154]. 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[155]. 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[156-157]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[158-159]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

TP53 mutations have been reported in 30-31% of hepatocellular carcinoma (HCC) cases[66,160]. TP53 has been reported to be the most frequently mutated tumor suppressor in HCC, with mutations identified in 16-35% of cases[114,161-162]. 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[163-165]. Expression of p53 has been variously identified in 35-96% of HCC cases[161,166]. Studies have reported that patients with HCC harboring TP53 mutation and/or p53 upregulation experienced significantly shorter recurrence-free survival and overall survival[161,166-168].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[169]. Alterations such as seen here may disrupt TP53 function or expression[170-174].

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)[175]. 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[176-178], including sarcomas[179-180]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[181] to 1:20,000[180]. 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[182]. 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[127-132]. 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[127-128]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[133]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[131,134-135]. 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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Cabozantinib

Assay findings association

MET
amplification

AREAS OF THERAPEUTIC USE

Cabozantinib inhibits multiple tyrosine kinases, including MET, RET, VEGFRs, and ROS1. It is FDA approved as monotherapy to treat patients with renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), medullary thyroid cancer (MTC), and differentiated thyroid cancer (DTC). It is also approved in combination with nivolumab to treat RCC. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Sensitivity of MET alterations to cabozantinib is suggested by clinical responses in patients with non-small cell lung cancer (NSCLC) harboring MET mutations associated with MET exon 14 skipping, with or without concurrent MET amplification[183-184] , as well as by extensive preclinical data[185-191] .

SUPPORTING DATA

The randomized Phase 3 CELESTIAL study for patients with advanced hepatocellular carcinoma (HCC) previously treated with sorafenib reported improved OS (10.2 vs. 8.0 months, HR=0.76), median PFS (mPFS; 5.2 vs. 1.9 months, HR=0.44), and ORR (3.8% vs. 0.4%) with cabozantinib compared with placebo[192]. A Phase 2 study for patients with previously treated HCC reported a 4.9% (2/41) ORR with cabozantinib and numerically improved mPFS compared with placebo (2.5 vs. 1.4 months)[193]. In a cohort from the Phase 1/2 CheckMate-040 trial for patients with advanced HCC who were previously treated or untreated with sorafenib, the triplet combination of nivolumab, cabozantinib, and ipilimumab reported improved ORR (28.6% vs. 19.4%), median PFS (6.8 vs. 5.4 months), and OS (not reached vs. 21.5 months) compared with the doublet combination of nivolumab and cabozantinib[194].

Capmatinib

Assay findings association

MET
amplification

AREAS OF THERAPEUTIC USE

Capmatinib is a selective MET tyrosine kinase inhibitor that is FDA approved to treat patients with non-small cell lung cancer harboring MET exon 14 skipping-associated alterations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data in non-small cell lung cancer[47,53-56,195] , hepatocellular carcinoma[52], renal cell carcinoma[57], and gastric cancer[58], MET amplification may predict sensitivity to selective MET inhibitors.

SUPPORTING DATA

A Phase 2 study evaluating capmatinib in hepatocellular carcinoma reported an ORR of 30% (3/10, 1 CR, 2 PR) for patients with MET amplification or overexpression compared with an ORR of 0% (0/20) for patients without[38].

Crizotinib

Assay findings association

MET
amplification

AREAS OF THERAPEUTIC USE

Crizotinib is an inhibitor of the kinases MET, ALK, ROS1, and RON. It is FDA approved to treat patients with ALK rearrangement- or ROS1 rearrangement-positive non-small cell lung cancer (NSCLC), and to treat pediatric and young adult patients with ALK rearrangement-positive anaplastic large cell lymphoma (ALCL). Please see the drug label for full prescribing information.

GENE ASSOCIATION

Sensitivity of MET alterations to crizotinib is suggested by extensive clinical data in patients with MET-amplified cancers, including non-small cell lung cancer (NSCLC)[40-42,196-197] , gastric cancer[83], gastroesophageal cancer[44], glioblastoma[45], and carcinoma of unknown primary[46], as well as in patients with MET-mutated cancers, including NSCLC[183,198-202] , renal cell carcinoma (RCC)[203], and histiocytic sarcoma[198]. Crizotinib has also benefited patients with NSCLC or histiocytic sarcoma tumors harboring various alterations associated with MET exon 14 skipping[183,198,200-202,204] .

SUPPORTING DATA

A patient with MET-amplified hepatocellular carcinoma experienced a reduction in tumor volume after treatment with crizotinib[205]. Crizotinib has demonstrated efficacy in patients with NSCLC and ALK rearrangements[206-210] , ROS1 rearrangements[211-215] , an NTRK1 fusion[216], or MET activation[40-42,183,196-197,199-202,217-223] . Crizotinib has also benefited patients with MET-mutated renal cell carcinoma[224] and patients with MET-amplified gastroesophageal cancer, glioblastoma, and carcinoma of unknown primary[44-46] . While a Phase 1b study evaluating crizotinib for the treatment of patients with ALK-positive malignancies, reported ORR of 52.9% (9/17) and 66.7% (6/9) in patients with lymphoma and inflammatory myofibroblastic tumors (IMT), respectively, an ORR of 11.8% (2/17) was reported for patients with other types of tumors[225]. Whereas median PFS and median OS were not reached for patients with lymphoma or IMT, median PFS was 1.3 months and median OS was 8.3 months for patients with other tumor types, and the median duration of treatment was ~1 month relative to 1-3 years for patients with lymphoma or IMT[225]. A Phase 1 clinical trial of crizotinib in pediatric solid tumors reported objective responses in 14/79 patients, including nine CRs and five PRs; response was enriched in patients with activating alterations in ALK[226].

Tepotinib

Assay findings association

MET
amplification

AREAS OF THERAPEUTIC USE

Tepotinib is a selective MET tyrosine kinase inhibitor that is FDA approved to treat patients with non-small cell lung cancer harboring MET exon 14 skipping alterations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data in non-small cell lung cancer[47,53-56,195] , hepatocellular carcinoma[52], renal cell carcinoma[57], and gastric cancer[58], MET amplification may predict sensitivity to selective MET inhibitors.

SUPPORTING DATA

For patients with MET-amplified advanced hepatocellular carcinoma (HCC), Phase 1b/2 studies showed that tepotinib yielded ORRs of 44% (4/9) in the first-line setting and 20% (1/5) in the second-line setting[52]. In the first-line setting, a Phase 2 study showed that tepotinib significantly improved ORR (11% [4/38] vs. 0% [0/37]) and median PFS (2.8 vs. 1.4 months, HR=0.53), and numerically increased median OS (9.3 vs. 8.6 months, HR=0.73) compared with sorafenib for patients with MET-overexpressing advanced hepatocellular carcinoma (HCC)[52,227-228] . For sorafenib-pretreated patients, a Phase 2 study of tepotinib reported an ORR of 8.2% (4/49, 1 CR, 3 PR), a DCR of 57% (28/49), a median PFS of 3.4 months, and a median OS of 5.6 months for patients with MET-overexpressing advanced HCC[52,229] . A Phase 1b study reported an ORR of 29% (2/7, 2 PR) with tepotinib treatment for patients with MET-overexpressing HCC[230-231] .

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.

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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
CCND1

ALTERATION
amplification

RATIONALE
CCND1 amplification or overexpression may activate CDK4/6 and may predict sensitivity to single-agent 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)

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)

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT02896335

PHASE 2

Palbociclib In Progressive Brain Metastases

TARGETS
CDK4, CDK6

LOCATIONS: Massachusetts

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

NCT02897375

PHASE 1

Palbociclib With Cisplatin or Carboplatin in Advanced Solid Tumors

TARGETS
CDK4, CDK6

LOCATIONS: Georgia

GENE
MET

RATIONALE
Activating MET alterations may confer sensitivity to MET inhibitors.

ALTERATION
amplification

NCT03175224

PHASE 1/2

CBT-101 Study for Advanced Solid Tumors and c-Met Dysregulation

TARGETS
MET

LOCATIONS: Taipei City (Taiwan), Taipei (Taiwan), New Taipei City (Taiwan), Taoyuan City (Taiwan), Tainan (Taiwan), Singapore (Singapore), Nedlands (Australia), Saransk (Russian Federation), North Adelaide (Australia), Bedford Park (Australia)

NCT03755791

PHASE 3

Study of Cabozantinib in Combination With Atezolizumab Versus Sorafenib in Subjects With Advanced HCC Who Have Not Received Previous Systemic Anticancer Therapy

TARGETS
PD-L1, MET, ROS1, RET, VEGFRs, KIT, RAFs, FLT3

LOCATIONS: Fuzhou (China), Xiamen (China), Hangzhou (China), Shanghai (China), Nanchang (China), Jiangyin (China), Nanjing (China), Hefei (China), Changsha (China), Linyi (China)

NCT04588051

PHASE 2

Cabozantinib in Hepatocellular Carcinoma

TARGETS
MET, ROS1, RET, VEGFRs

LOCATIONS: Hong Kong (Hong Kong), Seoul (Korea, Republic of)

NCT03899428

PHASE 2

Immune Checkpoint Therapy vs Target Therapy in Reducing Serum HBsAg Levels in Patients With HBsAg+ Advanced Stage HCC

TARGETS
PD-L1, FGFRs, RET, PDGFRA, VEGFRs, KIT, BRAF, RAFs, FLT3, MET, ROS1

LOCATIONS: Hong Kong (Hong Kong)

NCT04647838

PHASE 2

Tepotinib in Solid Tumors Harboring MET Alterations

TARGETS
MET

LOCATIONS: Cheonan (Korea, Republic of), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of)

NCT03170960

PHASE 1/2

Study of Cabozantinib in Combination With Atezolizumab to Subjects With Locally Advanced or Metastatic Solid Tumors

TARGETS
PD-L1, MET, ROS1, RET, VEGFRs

LOCATIONS: Gosford (Australia), North Ryde (Australia), Camperdown (Australia), Randwick (Australia), Albury (Australia), St Albans (Australia), Düsseldorf (Germany), Nijmegen (Netherlands), Tübingen (Germany), Meldola (Italy)

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NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT04497038

PHASE 1/2

Cabozantinib in Patients With Advanced Hepatocellular Carcinoma With Child Pugh Class B Cirrhosis After First-Line Therapy

TARGETS
MET, ROS1, RET, VEGFRs

LOCATIONS: Illinois, Michigan, Texas

NCT04522908

PHASE 2

Dose Escalation Study of Cabozantinib for Advanced HCC Patients With Compensated Liver Cirrhosis

TARGETS
MET, ROS1, RET, VEGFRs

LOCATIONS: Bad Saarow (Germany), Dresden (Germany), Leipzig (Germany), Müchen (Germany), Frankfurt (Germany), Essen (Germany)

NCT04511455

PHASE 2

A Phase II, Non-randomized, Single Arm, Translational Study of Cabozantinib for Patients With Hepatocellular Carcinoma (HCC) Refractory to Lenvatinib Treatment

TARGETS
MET, ROS1, RET, VEGFRs

LOCATIONS: Lübeck (Germany)

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.

ALK
S737L

ARAF
E578D

CUL4A
G35R

HRAS
L163fs*30

IGF1R
T500M

JAK2
V392M

RAD51D
A52V

TET2
P1544T

TSC2
A1141T

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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 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

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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. 2022. 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.

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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 6.0.0

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