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
NAME
DATE OF BIRTH
SEX
MEDICAL RECORD #

PHYSICIAN
ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT
MEDICAL FACILITY ID
PATHOLOGIST

SPECIMEN
SPECIMEN ID
SPECIMEN TYPE
DATE OF COLLECTION
SPECIMEN RECEIVED

Genomic Signatures

Blood Tumor Mutational Burden - 4 Muts/Mb
ctDNA Tumor Fraction - High (6.5%)
Microsatellite status - MSI-High Not Detected

Gene Alterations

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

CCND1 amplification
CHEK2 splice site 1009-1G>A
FGFR1 amplification
PTEN T319fs*2
ATR I774fs*3
EMSY (C11orf30) amplification - equivocal†
FGF19 amplification
FGF3 amplification
FGF4 amplification
INPP4B splice site 2018-1G>A
NSD3 (WHSC1L1) amplification
ZNF703 amplification

† See About the Test in appendix for details.

Report Highlights

- **High ctDNA Tumor Fraction** was detected, indicating a lower risk of false negative results (p. 5)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 12)
- Variants that may represent **clonal hematopoiesis** and may originate from non-tumor sources: ***CHEK2*** **splice site 1009-1G>A** (p. 6)

GENOMIC SIGNATURES	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Blood Tumor Mutational Burden - 4 Muts/Mb	**No therapies or clinical trials. See Genomic Signatures section**
ctDNA Tumor Fraction - High (6.5%)	**High ctDNA Tumor Fraction defined as ≥ 1.0% based on concordance for defined short variants and fusions. See Genomic Signatures Finding Summary.**
Microsatellite status - MSI-High Not Detected	**MSI-High not detected. No evidence of microsatellite instability in this sample (see Appendix section).**

GENE ALTERATIONS	VAF%	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
CCND1 - amplification	-	None	None
10 Trials see p. 12			

GENE ALTERATIONS		VAF%	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
CHEK2 -	splice site 1009-1G>A	0.12%	None	None
10 Trials see p. 14				
FGFR1 -	amplification	-	None	None
10 Trials see p. 16				
PTEN -	T319fs*2	5.9%	None	None
10 Trials see p. 18				

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.

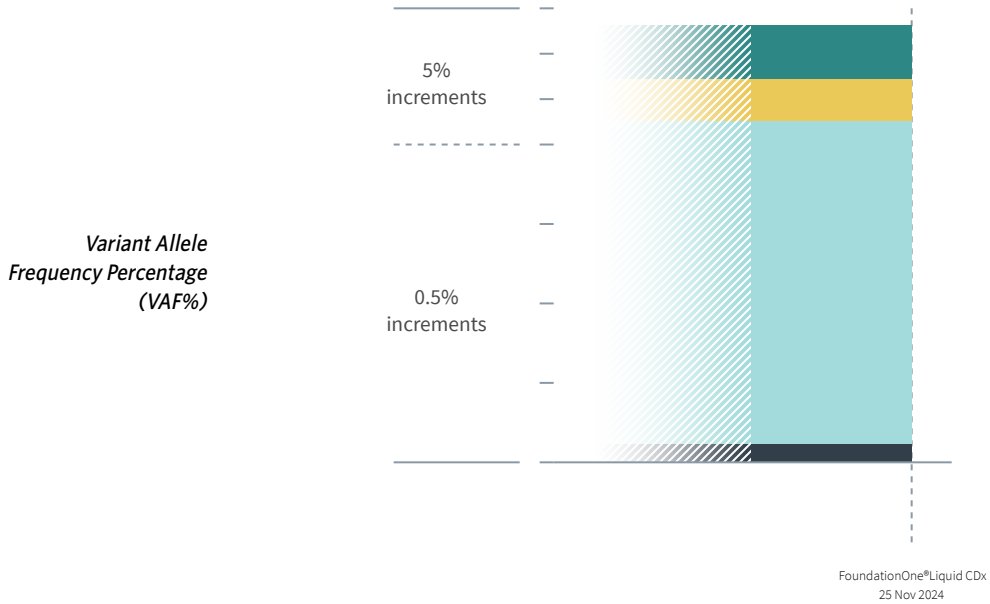
CHEK2 - splice site 1009-1G>A p. 6

GENE ALTERATIONS 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 Gene Alterations 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 through a centralized EU procedure or a national procedure in an EU Member State. Therapies, including but not limited to the following, have been approved nationally in some EU Member States but may not be available in your Member State: Tretinoin, Anastrozole, Bicalutamide, Cyproterone, Exemestane, Flutamide, Goserelin, Letrozole, Leuprorelin, and Triptorelin. The Summary of Product Characteristics of EU-approved therapies are available at https://www.ema.europa.eu/en/medicines. The information available on EMA's website is updated in regular intervals but may not reflect the current status at any time. In the appropriate clinical context, germline testing of *APC, ATM, BAP1, BRCA1, BRCA2, BRIP1, CHEK2, FH, FLCN, MEN1, MLH1, MSH2, MSH6, MUTYH, NF1, NF2, PALB2, PMS2, POLE, PTEN, RAD51C, RAD51D, RB1, RET, SDHA, SDHB, SDHC, SDHD, SMAD4, STK11, TGFBR2, TP53, TSC1, TSC2, VHL,* and *WT1* is recommended.

Variant Allele Frequency is not applicable for copy number alterations.



HISTORIC PATIENT FINDINGS (Genomic Signatures)		ORD-1995151-01
Blood Tumor Mutational Burden		4 Muts/Mb
Microsatellite status		MSI-High Not Detected
ctDNA Tumor Fraction		6.5%
HISTORIC PATIENT FINDINGS (Gene Alterations)		**VAF%**
CCND1	amplification	Detected
CHEK2	● splice site 1009-1G>A	0.12%
FGFR1	amplification	Detected
PTEN	● T319fs*2	5.9%
ATR	● I774fs*3	4.7%
EMSY (C11orf30)	amplification	Detected
FGF19	amplification	Detected
FGF3	amplification	Detected
FGF4	amplification	Detected

HISTORIC PATIENT FINDINGS (Gene Alterations)		VAF%
INPP4B	splice site 2018-1G>A	4.5%
NSD3 (WHSC1L1)	amplification	Detected
ZNF703	amplification	Detected

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

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

ctDNA Tumor Fraction may include previous Tumor Fraction results which reflect reporting practices at the time of reporting. Changes in biomarker reporting may result in the appearance of discrepancies across time points.

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

Tissue Tumor Mutational Burden (TMB) and blood TMB (bTMB) are estimated from the number of synonymous and non-synonymous single-nucleotide variants (SNVs) and insertions and deletions (indels) per area of coding genome sampled, after the removal of known and likely oncogenic driver events and germline SNPs. Tissue TMB is calculated based on variants with an allele frequency of ≥5%, and bTMB is calculated based on variants with an allele frequency of ≥0.5%.

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

Not Detected = baited but not detected on test

Detected = present (VAF% is not applicable)

VAF% = variant allele frequency percentage

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

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

GENOMIC SIGNATURE

Blood Tumor Mutational Burden

RESULT
4 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased blood tumor mutational burden (bTMB) may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[1-5], anti-PD-1[2,5-8], anti-PD-1/CTLA4 therapies[2,7] , anti-PD-L1/CTLA4 therapies[1,9-13]. A Phase 2 multi-solid-tumor trial showed that bTMB ≥16 Muts/Mb (as measured by this assay) was associated with improved survival from treatment with a PD-1 inhibitor alone or in combination with a CTLA-4 inhibitor[7]. 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 Muts/Mb-16 Muts/Mb[3,8,11-13]. In head and neck squamous cell carcinoma (HNSCC), a Phase 3 trial showed that bTMB ≥16 Muts/Mb (approximate equivalency ≥8 Muts/Mb as measured by this assay) was associated with improved survival from treatment with a PD-L1 inhibitor alone or in combination with a CTLA-4 inhibitor[1]. In colorectal cancer (CRC), a Phase 2 study showed that bTMB TMB ≥28 Muts/Mb (approximate equivalency ≥14 Muts/Mb as measured by this assay) was associated with improved OS from a PD-L1 inhibitor alone or in combination with a CTLA-4 inhibitor[9-10].

FREQUENCY & PROGNOSIS

In a genomic study of solid tumors, 12% of samples had a blood tumor mutational burden (bTMB) of >10 Muts/Mb compared with 16% of samples with a tissue TMB >10 Muts/Mb[14]; tumor types where bTMB >10 Muts/Mb was observed most frequently include small cell lung cancer (SCLC; 33%), bladder (30%), melanoma (23%), non-small cell lung cancer (NSCLC; 18%), cervical (15%), head and neck squamous cell carcinoma (HNSCC; 14%) and colorectal cancer (CRC; 15%). Published data investigating the prognostic implications of bTMB levels in SCLC and lung neuroendocrine cancer are limited (PubMed, Oct 2024).

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[15-16] and cigarette smoke in lung cancer[17-18], treatment with temozolomide-based chemotherapy in glioma[19-20], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[21-25], and microsatellite instability (MSI)[21,24-25]. 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[3-4,8,26-27]. Depending on the clinical context, TMB testing of an alternate sample or by another methodology could be considered.

GENOMIC SIGNATURE

ctDNA Tumor Fraction

RESULT
High (6.5%)

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Specimens with high circulating-tumor DNA (ctDNA) tumor fraction have high ctDNA content and thus higher sensitivity for identifying genomic alterations[28-29]. Such specimens are at a lower risk of false-negative results[28-30]. 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 a tumor tissue test that is FDA approved or appropriately validated in other countries, if available. Single observations or changes over time of circulating-tumor DNA (ctDNA) quantity are not part of any clinical decision-making guidelines but may be a useful indicator for future cancer management[31-38].

FREQUENCY & PROGNOSIS

In a large genomic study of 25 solid tumor types, 69% of liquid biopsy samples had ctDNA levels >1% as measured by an investigational composite tumor fraction algorithm with a median tumor fraction of 2.2% across tumor types[29]. Median ctDNA levels were reported to be highest in small cell lung cancer, liver, colon, and bladder tumor types and lowest in glioma and appendiceal cancers[29]. Higher ctDNA levels were reported for patients with metastatic (Stage 4) tumors compared with patients with localized disease (Stages 1 to 3)[39]. Higher ctDNA levels have been reported to be associated with worse prognosis in a variety of advanced solid tumors[40], including non-small cell lung cancer (NSCLC)[41], colorectal cancer (CRC)[41-42], pancreatic cancer[43], Ewing sarcoma and osteosarcoma[44], prostate cancer[32,41,45], breast cancer[41,46], leiomyosarcoma[47], esophageal cancer[48], and gastrointestinal cancer[49].

FINDING SUMMARY

The ctDNA tumor fraction provides an estimate of the percentage of circulating tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample. The ctDNA tumor fraction algorithm utilized for FoundationOne Liquid CDx integrates multiple distinct genomic features, including aneuploidy and the observed allele frequencies of somatic short variants and rearrangements. High ctDNA tumor fraction was detected in this sample. In a study of patients with advanced non-small cell lung cancer (NSCLC), the positive predictive agreement and negative predictive value of liquid biopsy compared with tissue for the detection of targetable driver alterations was 96% and 96%, respectively, when ctDNA tumor fraction was high (greater or equal to 1%)[28].

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[50-58], although as monotherapy these agents have shown limited activity in tumor types other than breast cancer[57,59]. 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[60]; 4 patients (13%, 4/36 overall) with squamous cell carcinomas (lung, esophageal, or laryngeal) or adenoid cystic carcinoma experienced prolonged SD in this study[60]. Among 9 patients with CCND1-amplified advanced solid tumors, 1 patient with bladder cancer responded to ribociclib in a Phase 2 trial[51].

FREQUENCY & PROGNOSIS

CCND1 amplification has been reported in 2-25% of lung adenocarcinoma[61-64] and 6-38% of lung squamous cell carcinoma (SCC)[61-62,65] cases. Overexpression of cyclin D1 was reported in 84% of large cell neuroendocrine tumors, 20% of lung atypical carcinoids, and 15% of lung typical carcinoids[66]. The prognostic significance of CCND1 amplification in NSCLC is not clear[67]. Cyclin D1 protein expression was not associated with clinicopathologic parameters of NSCLC in one study[68].

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[69] and may lead to excessive proliferation[70-71].

GENE
CHEK2

ALTERATION
splice site 1009-1G>A

HGVS VARIANT
NM_007194.3:c.1009-1G>A (p.?)

VARIANT CHROMOSOMAL POSITION
chr22:29092976

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Limited clinical data indicate that CHEK2 inactivation may predict sensitivity to PARP inhibitors. Patients with CHEK2-altered prostate cancer have experienced clinical responses to PARP inhibitors[72-74]. Patients with CHEK2-mutated metastatic castration-resistant prostate cancer treated with niraparib combined with abiraterone as first-line therapy experienced improved radiographic PFS (HR=0.66) and OS (HR=0.44) compared with patients treated with placebo combined with abiraterone in the Phase 3 MAGNITUDE study[75]. Clinical benefit has been observed for patients with ovarian[76-77] and testicular[78] cancers treated with PARP inhibitors. In a study of patients with advanced cancer, clinical benefit was not observed for most patients, although a patient with melanoma and a patient with breast cancer experienced SDs[79]. In a study of patients with metastatic breast cancer, 8 patients with CHEK2 mutations did not respond to olaparib treatment[80]. One study of patients with breast cancer reported that patients carrying the CHEK2 H371Y mutation have a higher likelihood of response to neoadjuvant chemotherapy[81], whereas another study found that those who carry CHEK2 mutations have a lower frequency of objective clinical responses to neoadjuvant therapy[82]. A third study reported that the CHEK2 1100delC mutation is not associated with differential efficacy of chemotherapy and endocrine therapy for patients with metastatic breast cancer[83]. In CHEK2-mutated colorectal cancer (CRC), a basket trial reported PD as best response for a patient treated with olaparib[79]; however, a case study reported a short-term PR for a second patient[84].

FREQUENCY & PROGNOSIS

In the MSK MetTropism genomic study, CHEK2 mutations were seen in the highest frequency in bladder cancer (1.1%), renal cell carcinoma (1%), endometrial cancer (0.9%), and melanoma (0.8%)[85]. In breast cancer, certain CHEK2 mutations are associated with higher grade and larger tumors, as well as bilateral disease[86]. A study in prostate cancer reported that CHEK2 expression is decreased in higher-grade tumors[87].

FINDING SUMMARY

CHEK2 encodes the protein checkpoint kinase 2, a serine/threonine kinase that plays an important role in the DNA-damage response; it is a putative tumor suppressor[88-91]. Alterations such as seen here may disrupt CHEK2 function or expression[92-102].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the CHEK2 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 familial breast cancer (ClinVar, Sep 2024)[103]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline CHEK2 mutation has been associated with cancer susceptibility of low to moderate penetrance, especially in hereditary breast cancer[104]. CHEK2 germline mutation has been identified in approximately 2.5% of familial or high-risk breast cancer cases[105-106]. Although heterozygous germline CHEK2 mutation increases breast cancer risk two- to three-fold, it is not associated with younger age at diagnosis[106-107]. In the appropriate clinical context, germline testing of CHEK2 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[108-113]. Comprehensive genomic profiling of solid tumors may detect nontumor alterations that are due to CH[112,114-115]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

GENE
FGFR1

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Alterations that activate FGFR1 may predict sensitivity to selective FGFR inhibitors, including erdafitinib[116-120], pemigatinib[121-124], infigratinib[125-128], futibatinib[129-131], rogaratinib[132], and derazantinib[133], or to multikinase inhibitors such as pazopanib[134-135] and ponatinib[136-139]. The activity and efficacy of selective FGFR inhibitors for FGFR1-amplified tumors has been modest, with limited responses reported in FGFR1-amplified lung squamous cell carcinoma (SCC) treated with infigratinib[140] or AZD457[141], in FGFR1-amplifed uterine cancer treated with pemigatinib[122], and no responses reported among patients with FGFR1-amplified breast cancer treated with infigratinib[140] or pemigatinib[122]. Two case studies reported PRs in patients with FGFR1-amplified breast cancer treated with pazopanib[134-135].

FREQUENCY & PROGNOSIS

Amplification of FGFR1 has been reported in 3.3-5.6% of small cell lung carcinomas, a type of neuroendocrine tumor[142-143]. In the TCGA datasets, FGFR1 amplification was found in 3% of lung adenocarcinoma cases[64] and 17% of lung squamous cell carcinoma (SCC) cases[65]; FGFR1 mutations and fusions are rare in both lung adenocarcinoma and lung SCC[64-65]. Published data investigating the prognostic implications of FGFR1 alterations in neuroendocrine tumors are limited (PubMed, Mar 2024). The prognostic significance of FGFR1 alteration in lung adenocarcinoma has not been extensively studied; however, 1 analysis of 345 non-small cell lung cancer (NSCLC) cases (48% adenocarcinoma, 39% squamous cell carcinoma [SCC], 7% large cell) suggested that high level amplification of FGFR1 was predictive of shorter survival[144]. The association between FGFR1 amplification and clinical parameters in lung SCC is not clear; some studies have suggested that FGFR1 amplification is associated with poor prognosis, whereas others have reported no association[145-149]. 1 study reported significant association between FGFR1 amplification and improved OS for patients assigned female (p=0.023), but not male (p=0.423), at birth[150].

FINDING SUMMARY

FGFR1 encodes the protein fibroblast growth factor receptor 1, which plays key roles in regulation of the cell cycle and angiogenesis and is an upstream regulator of the RAS, MAPK, and AKT signaling pathways[151]. Amplification of FGFR1 has been correlated with protein expression[146-147] and may predict pathway activation and sensitivity to therapies targeting this pathway[152-153].

GENE
PTEN

ALTERATION
T319fs*2

HGVS VARIANT
NM_000314.4:c.955del (p.T319Lfs*2)

VARIANT CHROMOSOMAL POSITION
chr10:89720803-89720804

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

While most clinical studies of PTEN-deficient cancers have not observed efficacy for inhibitors of the PI3K-AKT-mTOR pathway, clinical benefit has been reported in limited studies in prostate cancer[154-157], renal cell carcinoma (RCC)[158], breast cancer[159-161], and colorectal cancer (CRC)[162]. In the TAPUR study, the mTOR inhibitor temsirolimus met the prespecified threshold of activity for the cohort of solid tumors with PTEN mutations (ORR 7.4%, DCR 26%, n=27)[163]. On the basis of clinical evidence, PTEN loss or inactivation may predict sensitivity to AKT inhibitors[155-156,164-167]. For phosphatidylinositol 3-kinase (PI3K) inhibitors, there is conflicting clinical evidence, with reports of PTEN loss driven resistance to alpelisib[168-169], as well as sensitivity to copanlisib[170-174]. Clinical evidence on the sensitivity of PARP and mTOR inhibitors for PTEN-altered tumors is conflicting; clinical responses have been reported in PTEN-altered solid tumors treated with PARP[78,175-177] and mTOR[154,159,178-179] inhibitors, but some studies have reported a lack of association between PTEN mutation and PARP or mTOR inhibitor sensitivity[180-188]. The Phase 2 NCI-MATCH study of copanlisib for patients with refractory solid tumors harboring PIK3CA mutations with or without PTEN loss met its primary endpoint with an ORR of 16% (4/25 PRs); responses (PR or SD >6 months) were seen for patients with ameloblastoma, liposarcoma, and carcinomas of the endometrium, ovary, esophagus, lung, and prostate[171]. However, the Phase 2 study of copanlisib for patients with endometrial carcinoma harboring PIK3CA hotspot mutations failed to report any objective responses (n=11)[189]. A Phase 2 study of copanlisib combined with nivolumab for patients with solid tumors harboring PIK3CA and PTEN mutations elicited ORRs of 27% (4/15) and 20% (3/15), respectively; all responses were PRs[190]. Two other studies of copanlisib for patients with genomically unselected tumors reported 1 CR and 2 PRs (1 unconfirmed) among 16 total patients with PIK3CA-mutated solid tumors with or without PTEN alterations[172-173].

FREQUENCY & PROGNOSIS

PTEN allelic loss and reduced expression[191-194], and less frequently mutation[195-197], have been reported in a range of neuroendocrine tumors. Loss of PTEN expression was reported in 11-41% of NSCLCs, and was more frequently lost in lung SCC compared with lung adenocarcinoma[198-201], as well as in high-grade large cell neuroendocrine lung cancers (71%) compared with large cell lung cancers without neuroendocrine features (25%) or carcinoid lung tumors (0%)[202]. Loss of PTEN protein expression has been identified as a marker of poor prognosis in NSCLC[198,200].

FINDING SUMMARY

PTEN encodes an inositol phosphatase that functions as a tumor suppressor by negatively regulating the PI3K-AKT-mTOR pathway; loss of PTEN can lead to uncontrolled cell growth and suppression of apoptosis[203]. Alterations such as seen here may disrupt PTEN function or expression[204-245].

POTENTIAL GERMLINE IMPLICATIONS

PTEN mutations underlie several inherited disorders, collectively termed PTEN hamartoma tumor syndrome (PHTS), which include Cowden syndrome (CS) and its variant Lhermitte-Duclos disease (LD), Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS), and Proteus-like syndrome[246-247]. The mutation rate for PTEN in these disorders ranges from 20 to 85% of patients[246,248]. The estimated incidence of Cowden syndrome is 1/200,000, which may be an underestimate due to the high variability of this disorder[246]. Given the association between PTEN and these inherited syndromes, in the appropriate clinical context, germline testing for mutations affecting PTEN is recommended.

GENE
ATR

ALTERATION
I774fs*3

HGVS VARIANT
NM_001184.3:c.2320dup (p.I774Nfs*3)

VARIANT CHROMOSOMAL POSITION
chr3:142274739

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

A Phase 2 study reported talazoparib led to a SD lasting over 6 months for a patient with ATR-mutated breast cancer[78]. Based on preclinical evidence, ATR-deficient tumors may be sensitive to PARP inhibitors[249-250].

FREQUENCY & PROGNOSIS

ATR mutation has been reported in 7.7% (2/26) of large cell lung carcinomas and has not been observed in any of the lung carcinoid-endocrine tumors in COSMIC (Nov 2024)[251]. Published data investigating the prognostic implications of ATR alterations in lung carcinoids, large cell carcinomas, or lung large cell neuroendocrine carcinomas are limited (PubMed, Nov 2024). ATR inactivation, either by mutation or decreased expression, is associated with increased microsatellite instability (MSI) and chromosome instability (CIN) in a variety of tumor types[252-254].

FINDING SUMMARY

ATR encodes the protein ataxia telangiectasia and RAD3 related, which phosphorylates the tumor suppressor BRCA1, and several cell cycle checkpoint proteins including CHK1; it plays a key role in maintaining genome integrity via regulation of DNA repair and replication[255-256]. Alterations such as seen here may disrupt ATR function or expression[257].

GENE
EMSY (C11orf30)

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

EMSY overexpression in breast cancer cell lines has been reported to mimic the effects of inactivating BRCA2 mutations[258]. Unlike BRCA2 inactivation, which predicts sensitivity to DNA-repair-associated inhibitors, such as the PARP inhibitor olaparib[259-260], EMSY amplification in breast cancer lines was not associated with enhanced sensitivity to this drug in 1 preclinical study[261]. In a preclinical study of KEAP1-mutated lung cancer, loss of KEAP1 induced EMSY accumulation and sensitization to PARP inhibitors and stimulator of interferon genes protein agonists[262]. In clinical studies of high-grade serous ovarian cancer, high EMSY expression was associated with greater rates of response to platinum-based chemotherapy and improved clinical outcomes[263-265], although EMSY copy number was found to be a poor predictor of EMSY overexpression[263]. There are no therapies that target EMSY alterations.

FREQUENCY & PROGNOSIS

In the TCGA datasets, EMSY amplification has been most frequently observed in ovarian carcinoma (8%)[266], breast invasive carcinoma (6%)[267], esophageal carcinoma (5%)(cBioPortal, 2024), and head and neck squamous cell carcinoma (HNSCC; 3.5%)[268-270]. EMSY overexpression has been primarily reported in breast and high-grade ovarian cancers, where it is implicated in BRCA2 inactivation and correlates with poor prognosis or advanced disease[261,271-277]. The consequences of EMSY alterations in other solid tumors or hematologic malignancies have not been studied in detail in the scientific literature (PubMed, Jan 2024).

FINDING SUMMARY

EMSY, also known as C11orf30, encodes a BRCA2-interacting protein with roles in transcriptional regulation[277-278]. Preclinical studies have suggested that EMSY binds to and suppresses the function of BRCA2, and EMSY overexpression may therefore mimic BRCA2 inactivation[258,277]. Amplification of the EMSY gene correlates with increased mRNA expression[261,279], although conflicting data have been reported[280]. The functional consequences of other EMSY alterations have not been extensively studied (PubMed, Jan 2024).

GENE
FGF19

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

A Phase 1 study of the FGFR4 inhibitor fisogatinib (BLU-554) for patients with advanced hepatocellular carcinoma (HCC) reported a 17% ORR (11/66, 1 CR, ongoing for >1.5 years) and 3.3-month PFS for FGF19 IHC–positive patients; patients with negative or unknown FGF19 IHC scores experienced poorer outcomes (0% ORR, 2.3-month PFS)[281]. A Phase 1/2 study evaluating another FGFR4 inhibitor, FGF401, demonstrated an ORR of 7.5% (4/53) and SD rate of 53% (28/53) for patients with HCC[282]. A Phase 1 study of the FGFR4 inhibitor H3B-6527 reported a 17% ORR (OS of 10.3 months, 46% clinical benefit rate) among patients with HCC; enrollment of patients with intrahepatic cholangiocarcinoma (ICC) was suspended due to efficacy[283]. A retrospective analysis reported that 50% (2/4) of patients with HCC harboring FGF19 amplification experienced a CR to sorafenib[284], though another retrospective study found patients with higher pretreatment serum levels of FGF19 experienced reduced benefit from sorafenib compared with those with lower serum FGF19 (PFS of 86 vs. 139 days, OS of 353 vs. 494 days); no difference was observed for lenvatinib[285]. A patient with head and neck squamous cell carcinoma (HNSCC) with 11q13 (FGF3, FGF4, FGF19) and 12p13 (FGF6 and FGF23) amplification experienced a CR lasting 9 months from a pan-FGFR inhibitor[286].

FREQUENCY & PROGNOSIS

For patients with solid tumors, FGF19 amplification has been reported most frequently in breast cancer (17%), head and neck cancer (12%), lung squamous cell carcinoma (SCC; 12%), and urothelial carcinoma cancer (11%)[65,287-288]. FGF19 mutations are rare in solid tumors[288]. FGF19 expression or amplification has been associated with poor prognosis in hepatocellular carcinoma (HCC)[289-290], and in prostate cancer following radical prostatectomy[291]. Studies suggest FGF19 expression may also be a poor prognostic indicator in head and neck squamous cell carcinoma (HNSCC)[292] and lung SCC[293].

FINDING SUMMARY

FGF19 encodes fibroblast growth factor 19, an FGFR4 ligand involved with bile acid synthesis and hepatocyte proliferation in the liver[294-295]. FGF19 lies in a region of chromosome 11q13 that also contains FGF3, FGF4, and CCND1; this region is frequently amplified in a diverse range of malignancies[296]. Correlation between FGF19 amplification and protein expression has been reported in hepatocellular carcinoma (HCC)[297], lung squamous cell carcinoma[293,298], and head and neck squamous cell carcinoma (HNSCC)[292], but was not observed in other cancers[285,299].

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. While 1 case study reported radiologic CR for 1 patient with FGF-amplified head and neck squamous cell carcinoma (HNSCC) following treatment with a selective pan-FGFR inhibitor[286], 2 Phase 1/2 studies have reported mixed efficacy for FGFR inhibitor pemigatinib or futibatinib across FGF-amplified solid tumors[122,130].

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[71].

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[300].

GENE
FGF4

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies that target genomic alterations in FGF4. A patient with head and neck squamous cell carcinoma (HNSCC) harboring multiple FGF amplifications experienced a CR when treated with a selective pan-FGF receptor (FGFR) inhibitor[286]. However, 2 phase 1/2 studies have reported mixed efficacy for the FGFR inhibitors pemigatinib and futibatinib across FGF-amplified solid tumors[122,130].

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[71] 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 2024)[268-269].

FINDING SUMMARY

FGF4 encodes fibroblast growth factor 4, which plays a central role in development of the teeth[301] and acts synergistically with other FGFs and SHH (sonic hedgehog) to regulate limb outgrowth in vertebrate development[302]. 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[71,303-307] and may confer sensitivity to the multi-kinase inhibitor sorafenib[306].

GENE
INPP4B

ALTERATION
splice site 2018-1G>A

HGVS VARIANT
NM_003866.2:c.2018-1G>A (p.?)

VARIANT CHROMOSOMAL POSITION
chr4:143043399

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Multiple preclinical studies have shown that loss or inactivation of INPP4B leads to activation of the PI3K-AKT pathway[308-310]. However, sensitivity of tumors harboring INPP4B alterations to inhibitors of this pathway has not been tested clinically. Limited preclinical data indicate that INPP4B loss sensitizes triple-negative breast cancer cell lines to AKT and PI3K inhibition[311].

FREQUENCY & PROGNOSIS

INPP4B alterations have been reported infrequently in various solid tumors (0-2%)[288,312-313]. Loss of heterozygosity at the INPP4B locus in basal-like breast cancer is correlated with reduced OS[308-309]. Reduced expression of INPP4B has been observed in various cancers including lung cancer, prostate cancer, and acute lymphoblastic leukemia (ALL) in children with Down syndrome[314-316] and has been associated with reduced time to recurrence in prostate cancer[315] and reduced OS in ovarian cancer[317]. Collectively, these data suggest a tumor suppressor role for INPP4B.

FINDING SUMMARY

INPP4B encodes an enzyme that negatively regulates the PI3K-AKT pathway and behaves as a tumor suppressor[308-310,318-319].

GENE
NSD3 (WHSC1L1)

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in NSD3.

FREQUENCY & PROGNOSIS

In TCGA datasets, NSD3 amplification has been most frequently observed in lung squamous cell carcinoma (17%), breast invasive carcinoma (13%), bladder urothelial carcinoma (8.8%), gastric carcinoma (8.3%), head and neck squamous cell carcinoma (7.0%), esophageal adenocarcinoma (6.0%), prostate adenocarcinoma (4.7%), and colorectal adenocarcinoma (4.6%) samples (Oct 2024)[268-269]. Amplification of at least 1 member of the NSD3/CHD8/BRD4 pathway has been associated with worse OS in ovarian high-grade serous carcinoma and endometrial cancer[320]. In endometrial cancers, amplification of this pathway was more frequent in endometrial serous and endometrioid serious-like carcinomas compared with low-grade endometrioid endometrial adenocarcinomas[320]. In breast cancers, high NSD3 (WHSC1L1) expression was associated with worse disease-free survival (DFS) and OS[321-322]. Published data investigating the prognostic implications of NSD3 alterations in other solid tumors are limited (PubMed, Oct 2024).

FINDING SUMMARY

NSD3, also known as WHSC1L1, encodes an enzyme that mediates histone methylation[323]. NSD3 has been shown to be amplified in various cancers[324-326].

GENE
ZNF703

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies that directly address genomic alterations in ZNF703. Downregulation of ZNF703 expression using RNA interference and antisense oligonucleotides have been shown to decrease cell proliferation and induce apoptosis in cancer cells[327-329]. One preclinical study suggested that ZNF703 expression in breast cancer cell lines is associated with reduced sensitivity to tamoxifen through AKT-mTOR activation[330]. However, these approaches have not been verified in the clinical setting.

FREQUENCY & PROGNOSIS

ZNF703 amplification has been reported primarily in breast cancer (7%)[331], head and neck squamous cell carcinoma (HNSCC; 19%)[332], and non-small cell lung carcinoma (7%)[65,333-335], whereas ZNF703 mutations have not been observed in solid tumors in the MSK datasets[85,288]. High expression of ZNF703 has been reported in many solid tumor types[331-332,336-338]. Amplification and high expression of ZNF703 has been observed in luminal B breast tumors, a subtype associated with aggressive disease progression and poor patient outcomes[331,339-341]. ZNF703 expression has also been linked with aggressive tumor characteristics for patients with cholangiocarcinoma, gastric cancers, and colorectal cancers (CRC)[336,342-343].

FINDING SUMMARY

ZNF703 encodes a transcriptional repressor that plays roles in stem cell proliferation, cell cycle progression, and other key cellular functions[339,344]. Amplification of ZNF703 has been correlated with protein expression[339-340]. ZNF703 was established as a breast cancer oncoprotein by studies showing that ZNF703 expression resulted in transformation and increased proliferation of cultured cells[339-340,345], as well as increased lung metastases in a breast cancer xenograft model[345].

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.

NCT04116541

PHASE 2

A Study Evaluating the Activity of Anti-cancer Treatments Targeting Tumor Molecular Alterations/ Characteristics in Advanced / Metastatic Tumors.

TARGETS
CDK6, CDK4, MDM2, MET, ROS1, RET, VEGFRs, ALK, BRAF, KIT, MEK, PDGFRA

LOCATIONS: Strasbourg (France), Lyon (France), Marseille (France), Nice (France), Villejuif (France), Bordeaux (France), Toulouse (France)

NCT02925234

PHASE 2

The Drug Rediscovery Protocol (DRUP Trial)

TARGETS
EGFR, PARP, BRAF, ABL, KIT, MEK, ERBB2, SMO, VEGFRs, RET, PD-1, ERBB4, FGFR1, FGFR2, FGFR3, MET, ROS1, PD-L1, VEGFA, TRKB, ALK, TRKC, TRKA, FGFRs, PDGFRA, CDK4, CDK6, AXL, FLT3, CSF1R, CTLA-4, PI3K-alpha

LOCATIONS: Groningen (Netherlands), Hoogeveen (Netherlands), Almelo (Netherlands), Drachten (Netherlands), Leeuwarden (Netherlands), Zwolle (Netherlands), Deventer (Netherlands), Apeldoorn (Netherlands), Arnhem (Netherlands), Venlo (Netherlands)

NCT05252416

PHASE 1/2

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

TARGETS
ER, CDK4, CDK6, CDK2

LOCATIONS: Milano (Italy), Rome (Italy), London (United Kingdom), Massachusetts, New York, Pennsylvania, Maryland, Michigan, Virginia, Illinois

NCT06065592

PHASE 1

Exploring Cancer-Associated Thromboembolism Prognosis Biomarkers and Polymorphisms

TARGETS
CDK4, CDK6

LOCATIONS: Tripoli (Lebanon)

NCT02896335

PHASE 2

Palbociclib In Progressive Brain Metastases

TARGETS
CDK4, CDK6

LOCATIONS: Massachusetts

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)

NCT05953350

PHASE 1/2

A Phase Ib/II Study Confirmed Inhibition of Autophagy Synergizes Anti-tumor Effect of High Dose CDK4/6i

TARGETS
CDK4, CDK6

LOCATIONS: Guangzhou (China)

NCT04693468

PHASE 1

Talazoparib and Palbociclib, Axitinib, or Crizotinib for the Treatment of Advanced or Metastatic Solid Tumors, TalaCom Trial

TARGETS
PARP, CDK4, CDK6, VEGFRs, ALK, ROS1, AXL, TRKA, MET, TRKC

LOCATIONS: Texas

NCT03791112

PHASE 1

A Phase I Study of BPI-16350 in Patients With Advanced Solid Tumor

TARGETS
CDK6, CDK4

LOCATIONS: Hangzhou (China)

NCT03454035

PHASE 1

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

TARGETS
CDK4, CDK6, ERK2, ERK1

LOCATIONS: North Carolina

GENE
CHEK2

ALTERATION
splice site 1009-1G>A

RATIONALE
On the basis of clinical evidence in prostate and other solid cancers, CHEK2 loss or inactivation may confer sensitivity to PARP inhibitors.

NCT04644068

PHASE 1/2

Study of AZD5305 as Monotherapy and in Combination With Anti-cancer Agents in Patients With Advanced Solid Malignancies

TARGETS
ERBB2, TROP2, PARP1

LOCATIONS: Ivano-Frankivsk (Ukraine), Chernivtsi (Ukraine), Warszawa (Poland), Gdańsk (Poland), Gdynia (Poland), Toruń (Poland), Łódź (Poland), Bydgoszcz (Poland), Uzhgorod (Ukraine), Kraków (Poland)

NCT03742895

PHASE 2

Efficacy and Safety of Olaparib (MK-7339) in Participants With Previously Treated, Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD) Positive Advanced Cancer (MK-7339-002 / LYNK-002)

TARGETS
PARP

LOCATIONS: Herlev (Denmark), Edirne (Turkey), Istanbul (Turkey), Izmir (Turkey), Adana (Turkey), Konya (Turkey), Antalya (Turkey), Dublin (Ireland), Barcelona (Spain), Pozuelo de Alarcon (Spain)

NCT05797168

PHASE 1/2

Phase I/IIa Study for AZD5335 as Monotherapy and in Combination With Anti-cancer Agents in Participants With Solid Tumors

TARGETS
PARP1

LOCATIONS: Cambridge (United Kingdom), London (United Kingdom), Sutton (United Kingdom), Glasgow, Scotland (United Kingdom), Haifa (Israel), Ramat Gan (Israel), Barcelona (Spain), Madrid (Spain), Málaga (Spain), Chengdu (China)

NCT02264678

PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1, PARP1

LOCATIONS: Cambridge (United Kingdom), London (United Kingdom), Sutton (United Kingdom), Withington (United Kingdom), Oxford (United Kingdom), Lyon Cedex 08 (France), Villejuif (France), Bordeaux (France), Pennsylvania, Saint Herblain (France)

NCT04817956

PHASE 2

Improving Public Cancer Care by Implementing Precision Medicine in Norway

TARGETS
PD-L1, VEGFA, ERBB2, ALK, RET, PARP, SMO, TRKB, TRKC, ROS1, TRKA, MEK, BRAF, PI3K-alpha, FGFR1, FGFR2, FGFR3, MET, KIT, ABL

LOCATIONS: Fredrikstad (Norway), Hamar (Norway), Oslo (Norway), Drammen (Norway), Skien (Norway), Bodø (Norway), Trondheim (Norway), Kristiansand (Norway), Tromsø (Norway), Førde (Norway)

NCT02925234

PHASE 2

The Drug Rediscovery Protocol (DRUP Trial)

TARGETS
EGFR, PARP, BRAF, ABL, KIT, MEK, ERBB2, SMO, VEGFRs, RET, PD-1, ERBB4, FGFR1, FGFR2, FGFR3, MET, ROS1, PD-L1, VEGFA, TRKB, ALK, TRKC, TRKA, FGFRs, PDGFRA, CDK4, CDK6, AXL, FLT3, CSF1R, CTLA-4, PI3K-alpha

LOCATIONS: Groningen (Netherlands), Hoogeveen (Netherlands), Almelo (Netherlands), Drachten (Netherlands), Leeuwarden (Netherlands), Zwolle (Netherlands), Deventer (Netherlands), Apeldoorn (Netherlands), Arnhem (Netherlands), Venlo (Netherlands)

NCT04497116

PHASE 1/2

Study of RP-3500 in Advanced Solid Tumors

TARGETS
ATR, PARP

LOCATIONS: Manchester (United Kingdom), Rhode Island, Toronto (Canada), New York, Illinois, Texas

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
CDK4, CDK6, FLT3, VEGFRs, CSF1R, KIT, RET, mTOR, ERBB2, MEK, BRAF, PARP, PD-1, CTLA-4, PD-L1, TRKB, ALK, TRKC, ROS1, TRKA, FGFRs

LOCATIONS: Maine

NCT05327010

PHASE 2

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

TARGETS
PARP, BRD4, BRDT, BRD2, BRD3

LOCATIONS: Connecticut, Pennsylvania, Maryland, Virginia, Illinois, North Carolina, Kentucky, Missouri

NCT05898399

PHASE 1/2

Study of ART6043 in Advanced/Metastatic Solid Tumors Patients

TARGETS
PARP

LOCATIONS: Pennsylvania, Michigan, Tennessee, Oklahoma, Texas

GENE
FGFR1

ALTERATION
amplification

RATIONALE
FGFR inhibitors may be relevant in tumors with alterations that activate FGFR1.

NCT04008797

PHASE 1/2

A Study of E7386 in Combination With Other Anticancer Drug in Participants With Solid Tumor

TARGETS
CBP, Beta-catenin, FGFRs, RET, PDGFRA, VEGFRs, KIT

LOCATIONS: Lille (France), Amiens (France), Paris (France), Clichy (France), La Tronche (France), Lyon (France), Villejuif (France), Seodaemun (Korea, Republic of), Jongno-gu (Korea, Republic of), Seoul (Korea, Republic of)

NCT02925234

PHASE 2

The Drug Rediscovery Protocol (DRUP Trial)

TARGETS
EGFR, PARP, BRAF, ABL, KIT, MEK, ERBB2, SMO, VEGFRs, RET, PD-1, ERBB4, FGFR1, FGFR2, FGFR3, MET, ROS1, PD-L1, VEGFA, TRKB, ALK, TRKC, TRKA, FGFRs, PDGFRA, CDK4, CDK6, AXL, FLT3, CSF1R, CTLA-4, PI3K-alpha

LOCATIONS: Groningen (Netherlands), Hoogeveen (Netherlands), Almelo (Netherlands), Drachten (Netherlands), Leeuwarden (Netherlands), Zwolle (Netherlands), Deventer (Netherlands), Apeldoorn (Netherlands), Arnhem (Netherlands), Venlo (Netherlands)

NCT05024214

PHASE 1/2

Phase Ib/II Trial of Envafolimab Plus Lenvatinib for Subjects With Solid Tumors

TARGETS
PD-L1, FGFRs, RET, PDGFRA, VEGFRs, KIT, FLT3, CSF1R

LOCATIONS: Urumqi (China), Taiyuan (China), Beijing (China), Tianjin (China), Zhengzhou (China), Shenyang (China), Jinan (China), Kunming (China), Dalian (China), Benbu (China)

NCT02856425

PHASE 1

Trial Of Pembrolizumab And Nintedanib

TARGETS
FGFR1, LCK, SRC, VEGFRs, FGFR2, FGFR3, FLT3, LYN, PD-1

LOCATIONS: Villejuif (France), Lyon (France), Bordeaux (France), Toulouse (France)

NCT05064280

PHASE 2

Phase II Study of Pembrolizumab in Combination With Lenvatinib in Patients With TNBC, NSCLC, and Other Tumor Types and Brain Metastases

TARGETS
PD-1, KIT, VEGFRs, FGFRs, PDGFRA, RET

LOCATIONS: Texas

CLINICAL TRIALS

NCT05165407

PHASE 2

Sintilimab Combined With IBI310 and Surufatinib for the Treatment of G3-NET and NEC

TARGETS
PD-1, CTLA-4, FGFR1, CSF1R, VEGFRs

LOCATIONS: Beijing (China)

NCT05627427

PHASE 2

Multi-cohort Study of Surufatinib Plus Sintilimab in Metastatic NEN and Pancreatic Carcinoma Who Failed Standard Chemotherapy

TARGETS
FGFR1, CSF1R, VEGFRs, PD-1

LOCATIONS: Tianjin (China)

NCT05740215

PHASE 1/2

Efficacy and Safety Study of F520 Combined With Lenvatinib in the Treatment of Patients With Advanced Solid Tumors

TARGETS
PD-1, FGFRs, RET, PDGFRA, VEGFRs, KIT

LOCATIONS: Chongqing (China)

NCT06081907

PHASE 1/2

The Efficacy and Safety of IBI363 in Solid Tumors.

TARGETS
IL-2R, PD-1, CD73, FGFRs, RET, PDGFRA, VEGFRs, KIT

LOCATIONS: Changsha (China)

NCT04977453

PHASE 1/2

GI-101 as a Single Agent or in Combination With Pembrolizumab, Lenvatinib or Local Radiotherapy in Advanced Solid Tumors

TARGETS
FGFRs, RET, PDGFRA, VEGFRs, KIT, PD-1, CTLA-4

LOCATIONS: Seoul (Korea, Republic of), Suwon-si (Korea, Republic of), Daejeon (Korea, Republic of), New York, North Carolina

GENE
PTEN

ALTERATION
T319fs*2

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

NCT02264678

PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1, PARP1

LOCATIONS: Cambridge (United Kingdom), London (United Kingdom), Sutton (United Kingdom), Withington (United Kingdom), Oxford (United Kingdom), Lyon Cedex 08 (France), Villejuif (France), Bordeaux (France), Pennsylvania, Saint Herblain (France)

NCT04817956

PHASE 2

Improving Public Cancer Care by Implementing Precision Medicine in Norway

TARGETS
PD-L1, VEGFA, ERBB2, ALK, RET, PARP, SMO, TRKB, TRKC, ROS1, TRKA, MEK, BRAF, PI3K-alpha, FGFR1, FGFR2, FGFR3, MET, KIT, ABL

LOCATIONS: Fredrikstad (Norway), Hamar (Norway), Oslo (Norway), Drammen (Norway), Skien (Norway), Bodø (Norway), Trondheim (Norway), Kristiansand (Norway), Tromsø (Norway), Førde (Norway)

NCT02925234

PHASE 2

The Drug Rediscovery Protocol (DRUP Trial)

TARGETS
EGFR, PARP, BRAF, ABL, KIT, MEK, ERBB2, SMO, VEGFRs, RET, PD-1, ERBB4, FGFR1, FGFR2, FGFR3, MET, ROS1, PD-L1, VEGFA, TRKB, ALK, TRKC, TRKA, FGFRs, PDGFRA, CDK4, CDK6, AXL, FLT3, CSF1R, CTLA-4, PI3K-alpha

LOCATIONS: Groningen (Netherlands), Hoogeveen (Netherlands), Almelo (Netherlands), Drachten (Netherlands), Leeuwarden (Netherlands), Zwolle (Netherlands), Deventer (Netherlands), Apeldoorn (Netherlands), Arnhem (Netherlands), Venlo (Netherlands)

NCT04497116

PHASE 1/2

Study of RP-3500 in Advanced Solid Tumors

TARGETS
ATR, PARP

LOCATIONS: Manchester (United Kingdom), Rhode Island, Toronto (Canada), New York, Illinois, Texas

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

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

LOCATIONS: Vermont, Massachusetts, New York, New Jersey, Pennsylvania

NCT05327010

PHASE 2

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

TARGETS
PARP, BRD4, BRDT, BRD2, BRD3

LOCATIONS: Connecticut, Pennsylvania, Maryland, Virginia, Illinois, North Carolina, Kentucky, Missouri

NCT02769962

PHASE 1/2

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

TARGETS
PARP, TOP1

LOCATIONS: Maryland

NCT05700721

PHASE 2

Phase II Trial of the PARP Inhibitor Niraparib and PD-1 Inhibitor Dostarlimab in Patients With Advanced Cancers With Active Progressing Brain Metastases (STARLET)

TARGETS
PD-1, PARP

LOCATIONS: Texas

NCT06077877

PHASE 1/2

A Study to Investigate the Safety, Tolerability, Pharmacokinetics (PK), and Preliminary Anticancer Activity of GSK4524101 Alone or With Niraparib in Participants With Solid Tumors

TARGETS
Pol theta, PARP

LOCATIONS: Ottawa (Canada), Toronto (Canada), Edmonton (Canada), Virginia, Missouri, Florida, Texas, California

NCT04502602

PHASE 1

Niraparib and Neratinib in Advanced Solid Tumors With Expansion Cohort in Advanced Ovarian Cancer

TARGETS
PARP, ERBB2, EGFR, ERBB4

LOCATIONS: Virginia

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.

ATM
NM_000051.3: c.3920G>A
(p.G1307E)
chr11:108155127
0.09% VAF

EPHB4
NM_004444.4: c.983G>A
(p.R328Q)
chr7:100417493
1.8% VAF

IKZF1
NM_006060.3: c.1267C>T
(p.R423C)
chr7:50468032
2.0% VAF

IRS2
NM_003749.2:
c.2701_2709del
(p.L901_S903del)
chr13:110435691-110435700
49.8% VAF

PRDM1
NM_001198.3: c.1877C>T
(p.T626M)
chr6:106554349
0.55% VAF

APPENDIX Genes assayed in FoundationOne®Liquid CDx

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

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

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.

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

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER GENOMIC SIGNATURES

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

FoundationOne Liquid CDx fulfills the requirements of the European Directive 98/79 EC for in vitro diagnostic medical devices and is registered as a CE-IVD product by Foundation Medicine's EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium. Foundation Medicine GmbH is accredited by DAkkS according to DIN EN ISO 15189:2014. The accreditation only applies to the scope of accreditation listed in certificate D-ML-21105-01-00.

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 ctDNA 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 ctDNA 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:* The association of a therapy with a genomic alteration or signature does not necessarily indicate pharmacologic effectiveness (or lack thereof); no association of a therapy with a genomic alteration or signature does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness).

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.

COPY NUMBER LOSS CALLS

The FoundationOne Liquid CDx assay detects copy number loss in the following genes: *BRCA1*, *BRCA2*, and *PTEN*.

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. ctDNA tumor fraction is the percentage of circulating tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample. The ctDNA tumor fraction estimate integrates multiple distinct genomic features, including modeled aneuploidy and the observed allele frequencies of somatic short variants and rearrangements.
9. Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the tumor genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor. The MSI algorithm is based on genome wide analysis of 1765 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines for solid tissue testing.
10. Genomic findings from circulating cell-free

DNA (cfDNA) may originate from circulating tumor DNA fragments, germline alterations, or non-tumor somatic alterations, such as clonal hematopoiesis of indeterminate potential (CHIP). Genes with alterations that may be derived from CHIP include, but are not limited to: *ASXL1*, *ATM*, *CBL*, *CHEK2*, *DNMT3A*, *JAK2*, *KMT2D* (*MLL2*), *MPL*, *MYD88*, *SF3B1*, *TET2*, *TP53*, and *U2AF1*.

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

REPORT HIGHLIGHTS

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

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Genomic signatures and gene alterations 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 genomic signature or gene alteration. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE THE RESPONSIBILITY OF PHYSICIAN

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

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

SELECT ABBREVIATIONS

ABBREVIATION	DEFINITION
CR	Complete response
ctDNA	Circulating tumor DNA
DCR	Disease control rate
DFS	Disease-free survival
DOR	Duration of response
EFS	Event-free survival
EFS	Event-free survival
ER	Estrogen receptor
ER	Estrogen receptor
HR +/-	Hormone-receptor positive/negative
ITD	Internal tandem duplication
MR	Molecular response
MMR	Mismatch repair
Muts/Mb	Mutations per megabase
NOS	Not otherwise specified
ORR	Objective response rate
OS	Overall survival
mOS	Median overall survival
PD	Progressive disease
PFS	Progression-free survival
mPFS	Median progression-free survival
PR	Partial response
PSA	Prostate-specific antigen
R/R	Relapsed or refractory
SD	Stable disease
TKI	Tyrosine kinase inhibitor
CRC	Colorectal cancer
HCC	Hepatocellular carcinoma
HNSCC	Head and neck squamous cell carcinoma
NSCLC	Non-small cell lung cancer
RCC	Renal cell carcinoma
SCC	Squamous cell carcinoma

REFERENCE SEQUENCE INFORMATION

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

SOFTWARE VERSION INFORMATION

MR Suite Version (RG) 8.4.1
MR Reporting Config Version 67
Analysis Pipeline Version v3.38.0
Computational Biology Suite Version 6.34.0

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