FOUNDATIONONE®LIQUID CDx

PATIENT
Lin, Hui-Lien

TUMOR TYPE
Unknown primary adenocarcinoma

COUNTRY CODE
TW

REPORT DATE
19 May 2023

ORDERED TEST #
ORD-1627840-01

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 Unknown primary adenocarcinoma
NAME Lin, Hui-Lien
DATE OF BIRTH 15 February 1969
SEX Female
MEDICAL RECORD # 35563429

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 HLL 2/15/1969
SPECIMEN TYPE Blood
DATE OF COLLECTION 09 May 2023
SPECIMEN RECEIVED 12 May 2023

Biomarker Findings

Blood Tumor Mutational Burden - 3 Muts/Mb
Microsatellite status - MSI-High Not Detected
Tumor Fraction - Elevated Tumor Fraction Not Detected

Genomic Findings

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

FGFR2 FGFR2-HK1 fusion
FGFR3 FGFR3-TACC3 fusion
ARID1A Q553*
BAP1 I176fs*3
TP53 P177H

Report Highlights

- Targeted therapies with potential clinical benefit **approved in another tumor type**: **Erdafitinib** (p. 10), **Futibatinib** (p. 10), **Infigratinib** (p. 11), **Pemigatinib** (p. 11)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 12)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Blood Tumor Mutational Burden - 3 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 Not Detected	**Tumor fraction is considered elevated when ctDNA levels are high enough that aneuploidy can be detected. The fact that elevated tumor fraction was not detected in this specimen indicates the possibility of lower levels of ctDNA but does not compromise confidence in any reported alterations. However, in the setting of a negative liquid biopsy result, orthogonal testing of a tissue specimen should be considered if clinically indicated (see Biomarker Findings section).**

GENOMIC FINDINGS		VAF%	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
FGFR2 -	FGFR2-HK1 fusion	2.0%	None	Erdafitinib
				Futibatinib
				Infigratinib
				Pemigatinib
10 Trials see p. 16				
FGFR3 -	FGFR3-TACC3 fusion	0.04%	None	Erdafitinib
10 Trials see p. 18				

Electronically signed by Naomi Lynn Ferguson, M.D. | 19 May 2023
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Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

GENOMIC FINDINGS	VAF%	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
ARID1A - Q553*	2.7%	None	None
6 Trials see p. 12			
BAP1 - I176fs*3	2.8%	None	None
10 Trials see p. 14			

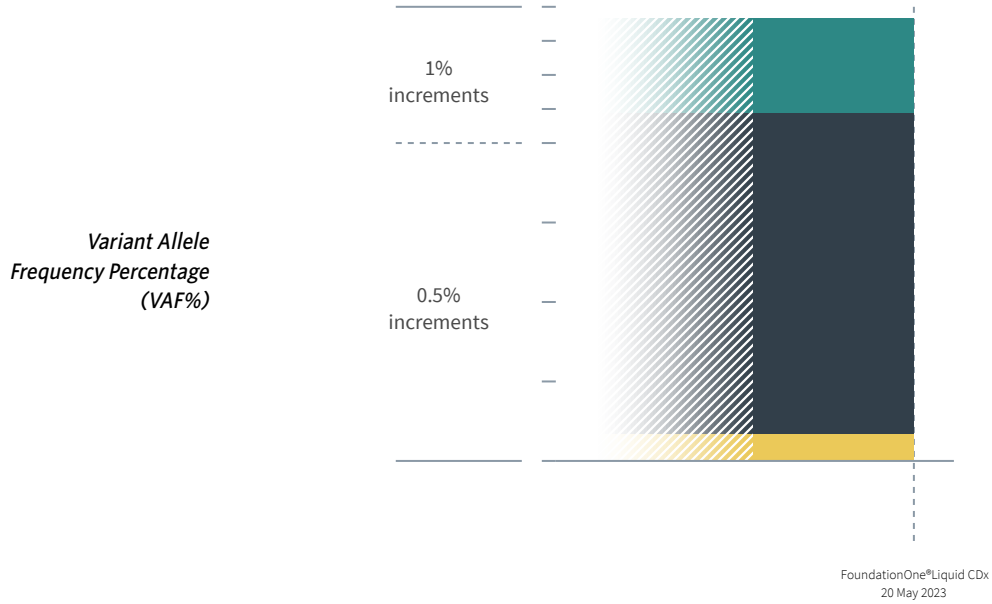
GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

TP53 - P177H ..... p. 9

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

Variant Allele Frequency is not applicable for copy number alterations.



HISTORIC PATIENT FINDINGS		ORD-1627840-01 VAF%
Blood Tumor Mutational Burden		3 Muts/Mb
Microsatellite status		MSI-High Not Detected
Tumor Fraction		Elevated Tumor Fraction Not Detected
FGFR2	FGFR2-HK1 fusion	2.0%
FGFR3	FGFR3-TACC3 fusion	0.04%
ARID1A	● Q553*	2.7%
BAP1	● I176fs*3	2.8%
TP53	● P177H	0.17%

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

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

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

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

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

Not Detected = baited but not detected on test

Detected = present (VAF% is not applicable)

VAF% = variant allele frequency percentage

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

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

BIOMARKER

Blood Tumor Mutational Burden

RESULT
3 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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

FREQUENCY & PROGNOSIS

Average bTMB levels in solid tumors other than NSCLC have not been evaluated (PubMed, Mar 2023). Published data investigating the prognostic implications of TMB have mainly been investigated in the context of tissue TMB. In patients with NSCLC, increased TMB is associated with higher tumor grade and poor prognosis[12], as well as with a decreased frequency of known driver mutations in EGFR, ALK, ROS1, or MET (1% of high-TMB samples each), but not BRAF (10.3%) or KRAS (9.4%)[13]. Although some studies have reported a lack of association between smoking and increased TMB in NSCLC[12,14], several other large studies did find a strong link[15-18]. In CRC, elevated TMB is associated with a higher frequency of BRAF V600E driver mutations[19-20] and with microsatellite instability (MSI)[20], which in turn has been reported to correlate with better prognosis[21-28]. Although increased TMB is associated with increased tumor grade in endometrioid endometrial carcinoma[29-32] and bladder cancer[33], it is also linked with improved prognosis in patients with these tumor types[30].

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[34-35] and cigarette smoke in lung cancer[36-37], treatment with temozolomide-based chemotherapy in glioma[38-39], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[19,30,40-42], and microsatellite instability (MSI)[19,30,42]. High bTMB levels were not detected in this sample. It is unclear whether the bTMB levels in this sample would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[1-2,4]. Depending on the clinical context, TMB testing of an alternate sample or by another methodology could be considered.

BIOMARKER

Tumor Fraction

RESULT
Elevated Tumor Fraction Not Detected

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Specimens with elevated tumor fraction values have high circulating-tumor DNA (ctDNA) content, and thus higher sensitivity for identifying genomic alterations. Such specimens are at a lower risk of false negative results. However, if elevated tumor fraction is not detected, it does not exclude the presence of disease burden or compromise the confidence of reported alterations. Tumor fraction levels currently have limited implications for diagnosis, surveillance, or therapy and should not be overinterpreted or compared from one blood draw to another. There are currently no targeted approaches to address specific tumor fraction levels. In the research setting, changes in tumor fraction estimates have been associated with treatment duration and clinical response and may be a useful indicator for future cancer management[43-48].

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)[49]. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer[50], Ewing sarcoma and osteosarcoma[51], prostate cancer[46], breast cancer[52], leiomyosarcoma[53], esophageal cancer[54], colorectal cancer[55], and gastrointestinal cancer[56].

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[57], 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[58-59].

GENE
FGFR2

ALTERATION
FGFR2-HK1 fusion

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

FGFR2 activating mutations, amplifications, or fusions may confer sensitivity to selective FGFR inhibitors such as erdafitinib[60], pemigatinib[61-63], infigratinib[64], futibatinib[65], RLY-4008[66-67] , E7090[68], AZD4547[69-71], Debio 1347[72-73], rogaratinib[74], ICP192[75], and derazantinib[76] as well as to the multikinase inhibitors pazopanib[77-78] and ponatinib[79]. In the context of FGFR2 fusions and rearrangements, FGFR inhibitors have primarily been investigated in Phase 2 trials for patients with previously treated intrahepatic cholangiocarcinoma[62]. Responses were also reported in gallbladder and pancreatic cancer in a Phase 1/2 study of pemigatinib for patients with FGF/FGFR-altered refractory advanced malignancies[63]. Responses to erdafitinib have been reported in patients with FGFR2 fusion-positive urothelial carcinoma[80] and endometrial carcinoma[60].

FREQUENCY & PROGNOSIS

FGFR2 fusions have been reported in 10-50% of intrahepatic cholangiocarcinoma patients[77,81-82] and have also been observed in colorectal cancer, hepatocellular carcinoma, breast cancer, lung squamous cell cancer, and thyroid cancer[77,83]. Gastric cancer patients with FGFR2 amplification were shown to have shorter overall survival[84]. FGFR2 protein overexpression has been detected in various adenocarcinomas and has been associated with poorly differentiated tumors, aggressive disease, and shorter survival in some tumors[85-88]. FGFR2 signaling has been described as tumorigenic in lung, pancreatic, endometrial, and gastric cancers[89-92]. However, FGFR2 has also been described as a tumor suppressor in the context of other cancers, such as melanoma[93].

FINDING SUMMARY

FGFR2 encodes a tyrosine kinase cell surface receptor, which plays an important role in cell differentiation, growth, and angiogenesis[94-95]. FGFR2 fusions retaining the kinase domain encoded by exons 11-17 have been reported to be activating, oncogenic, and sensitive to FGFR inhibitors[82-83,96-97]. Furthermore, FGFR2 variants lacking a portion of the cytoplasmic domain encoded by exon 18 have been reported to be oncogenic in vitro[83,97-100]. Rearrangements such as observed here are predicted to be activating.

GENE
FGFR3

ALTERATION
FGFR3-TACC3 fusion

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Alterations that activate FGFR3 may predict sensitivity to selective FGFR kinase inhibitors, including erdafitinib[60,101-102], pemigatinib[63], infigratinib[103-104], rogaratinib[74], Debio 1347[72,105], and derazantinib[106]; multikinase inhibitors such as pazopanib[107-108] and ponatinib[78-79]; and vofatamab, an antibody targeting FGFR3[109-111] . In the context of FGFR3 alterations, FGFR inhibitors, such as erdafitinib[101], pemigatinib[63], infigratinib[103], rogaratinib[74], and Debio 1347[112], have predominantly been studied in the context of urothelial carcinoma, resulting in ORRs of 25-40% and DCRs of 64-80%. Clinical benefit has been reported for patients with gliomas harboring FGFR3 fusions treated in a Phase 1 trial of erdafitinib[60,113], and a prolonged SD has been observed in a case study treated with Debio 1347[114]. For infigratinib, activity against non-urothelial tumors harboring FGFR3 alterations are limited[64], with responses reported for individuals with an FGFR3-amplified and -rearranged glioma or FGFR3-mutated head and neck squamous cell carcinoma (HNSCC) with co-occurring FGF amplifications[115].

FREQUENCY & PROGNOSIS

FGFR3-TACC3 fusions are most commonly reported in urothelial cancer[83], non-small cell lung cancer[18,116] and glioblastoma[117-118], but have also been reported in cervical cancer and head and neck squamous cell carcinoma (HNSCC)[119]. FGFR3 mutation has been associated with low tumor stage in bladder tumors and with a lower risk of death in patients with bladder tumors by univariate analysis but not multivariate analysis[120]. One study has associated increased FGFR3 expression with improved survival in glioma[121]. One study reported shorter OS in patients with FGFR alteration-positive lung squamous cell carcinoma (SCC) with disease recurrence after surgery, compared to those with recurrent lung SCC lacking FGFR alterations[122]. Another study found an association between higher FGFR3 expression and shorter OS of patients with lung adenocarcinoma[123].

FINDING SUMMARY

FGFR3 (Fibroblast growth factor receptor 3) encodes a receptor tyrosine kinase that typically promotes cell cycle progression and angiogenesis via activation of downstream signaling pathways, including RAS-MAPK and AKT; gain of function mutations in FGFRs have been reported in several cancer types[94,124-125]. FGFR3 fusions that retain the kinase domain (exons 11-17) have been shown to be activating and oncogenic[96,105]. Additionally, fusions that disrupt a binding site of the regulatory microRNA miR-99a in the FGFR3 3' UTR have been demonstrated to increase FGFR3 expression[118]. Rearrangements that include the N-terminal portion of FGFR3 (exons 1-17), such as observed here, are predicted to be activating and oncogenic.

GENE
ARID1A

ALTERATION
Q553*

HGVS VARIANT
NM_006015.4: c.1657C>T (p.Q553*)

VARIANT CHROMOSOMAL POSITION
chr1:27057949

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies approved to address the mutation or loss of ARID1A in cancer. However, on the basis of limited clinical and preclinical evidence, ARID1A inactivating mutations may lead to sensitivity to ATR inhibitors such as M6620 and ceralasertib[126]. In a Phase 2 study of ceralasertib in solid tumors, 2 patients with endometrial carcinoma in the cohort with loss of ARID1A expression achieved CRs on ceralasertib monotherapy; at least 1 of these 2 patients carried an inactivating ARID1A mutation. In contrast, no responses were observed for patients with normal ARID1A expression treated with ceralasertib combined with olaparib[127]. One patient with small cell lung cancer harboring an ARID1A mutation experienced a PR when treated with M6620 combined with topotecan[128]. In a Phase 1 trial, a patient with metastatic colorectal cancer (CRC) harboring both an ARID1A mutation and ATM loss treated with single-agent M6620 achieved a CR that was ongoing at 29 months[129]. On the basis of limited clinical and preclinical evidence, ARID1A inactivation may predict sensitivity to EZH2 inhibitors[130-131]. A Phase 1 study of EZH2 inhibitor CPI-0209 reported 1 PR for a patient with ARID1A-mutated endometrial cancer[132]. Other studies have reported that the loss of ARID1A may activate the PI3K-AKT pathway and be linked with sensitivity to inhibitors of this pathway[133-135]. Patients with ARID1A alterations in advanced or metastatic solid tumors may derive benefit from treatment with anti-PD-1 or anti-PD-L1 immunotherapy[136]. Loss of ARID1A expression has been associated with chemoresistance to platinum-based therapy for patients with ovarian clear cell carcinoma[137-138] and to 5-fluorouracil in CRC cell lines[139].

FREQUENCY & PROGNOSIS

ARID1A alterations are particularly prevalent in ovarian clear cell carcinoma (46-50%), ovarian and uterine endometrioid carcinomas (24-44%), and cholangiocarcinoma (27%); they are also reported in up to 27% of gastric carcinoma, esophageal adenocarcinoma, Waldenstrom macroglobulinemia, pediatric Burkitt lymphoma, hepatocellular carcinoma, colorectal carcinoma, and urothelial carcinoma samples analyzed (COSMIC, cBioPortal, 2023)[81,140-147]. ARID1A loss is associated with microsatellite instability in ovarian and endometrial endometrioid adenocarcinomas[31,136,148-150], CRC[136,151-153], and gastric cancer[136,154-158]. ARID1A protein loss is associated with tumors of poor histological grade for many tumor types, including colorectal cancer (CRC)[151-153], cervical cancer[159-160], gastric cancer[154-158], urothelial carcinoma[161-163], ovarian and endometrial cancers[31,138,148-150,164-168], breast carcinoma[169-171], and clear cell renal cell carcinoma[172]; ARID1A mutation has been associated with poor outcomes for patients with cholangiocarcinoma[173-176]. However, prognostic data regarding patient survival are often mixed and conflicting.

FINDING SUMMARY

ARID1A encodes the AT-rich interactive domain-containing protein 1A, also known as Baf250a, a member of the SWI/SNF chromatin remodeling complex. Mutation, loss, or inactivation of ARID1A has been reported in many cancers, and the gene is considered a tumor suppressor[144,157,170,177-182]. ARID1A mutations, which are mostly truncating, have been identified along the entire gene and often correlate with ARID1A protein loss[144,155,178-179,183], whereas ARID1A missense mutations are mostly uncharacterized.

GENE
BAP1

ALTERATION
I176fs*3

HGVS VARIANT
NM_004656.2: c.525_549del (p.I176Mfs*3)

VARIANT CHROMOSOMAL POSITION
chr3:52441220-52441245

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Clinical[184] and preclinical[185] evidence in the context of mesothelioma suggests that tumors with BAP1 inactivation may be sensitive to EZH2 inhibitors such as tazemetostat. In a Phase 1 study of the EZH2 inhibitor CPI-0209, 67% (4/6) of patients with mesothelioma had BAP1 loss or alterations, 1 of whom achieved PR[132]. Clinical[186-189] and preclinical[190-193] studies suggest that BAP1 inactivation might be associated with sensitivity to PARP inhibitors. Phase 2, retrospective, and case studies have reported PR or SD for patients with BAP1-deficient cholangiocarcinoma, uveal melanoma, mesothelioma, and clear cell renal cell carcinoma treated with olaparib, rucaparib, niraparib, or veliparib[186-189]. One preclinical study suggests that histone deacetylase inhibitors may be beneficial in BAP1-mutated uveal melanoma; however, it is unclear if these inhibitors are effective in other BAP1-mutated cancers[194].

FREQUENCY & PROGNOSIS

Mutations in BAP1 have been reported in a variety of tumor types, but most frequently in mesothelioma (21%), cholangiocarcinoma (19%), uveal melanoma (16%), kidney renal clear cell carcinoma (9.5%), and uterine corpus endometrial carcinoma (5.6%) (cBioPortal, Feb 2023)[141-142]. Studies reported in the literature confirm the relatively high frequency of BAP1 mutation in clear cell renal cell carcinoma and malignant pleural mesothelioma[195-196]. The chromosomal region where BAP1 is located is subject to frequent deletion in non-small cell lung cancer (NSCLC) and other cancers[197]. High BAP1 protein expression in patients with NSCLC has been associated with increased median survival time as compared to patients with low expression[198]; however, decreases in the expression BAP1 mRNA and protein have been reported in colorectal cancers and have been associated with poor prognosis[199]. In other tumor types, such as clear cell renal cell carcinoma, BAP1 mutations have been associated with high tumor grade, worse cancer-specific survival, and shorter overall survival[192,200-201].

FINDING SUMMARY

BAP1 (BRCA1 associated protein-1) encodes a ubiquitin hydrolase, a protein involved in regulating the availability of target proteins for the ubiquitin-proteasome protein degradation pathway; BAP1 is located on chromosome 3p21.3, in a region of frequent loss of heterozygosity (LOH) in breast and lung cancer, and has been postulated to be a tumor suppressor[197,202]. Alterations such as seen here may disrupt BAP1 function or expression[182,202-210].

POTENTIAL GERMLINE IMPLICATIONS

BAP1 germline inactivating alterations, including mutations and deletions, are associated with BAP1 tumor predisposition syndrome (BAP1-TPDS), an autosomal-dominant syndrome characterized by early onset of benign melanocytic skin tumors[204,211-212]. An estimated 2% of patients with BAP1-inactivated melanocytic tumors display germline BAP1 mutations[213]. Later in life, patients have an increased risk of cancers such as uveal melanoma, mesothelioma, clear cell renal cell carcinoma, basal cell carcinoma, and meningioma[203-207,214]. In small studies, the prevalence of pathogenic germline BAP1 mutation has been reported as 22% in familial uveal melanoma and 4.4% in mesothelioma[215-216]. In the appropriate clinical context, germline testing of BAP1 is recommended.

GENE
TP53

ALTERATION
P177H

HGVS VARIANT
NM_000546.4: c.530C>A (p.P177H)

VARIANT CHROMOSOMAL POSITION
chr17:7578400

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[217-220] or p53 gene therapy such as SGT53[221-225]. 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[226]. 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[227]. 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[228]. 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[229]. 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[230]. 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[231]. 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[232]. 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[225]. Missense mutations leading to TP53 inactivation may be sensitive to therapies that reactivate mutated p53 such as eprenetapopt. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, eprenetapopt combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[233]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[234].

FREQUENCY & PROGNOSIS

Pan-cancer analysis of the TCGA datasets across 12 cancer types identified TP53 as the most frequently mutated gene, with 42% of more than 3,000 tumors harboring a TP53 mutation; in this study TP53 mutation occurred most frequently in ovarian serous carcinoma (95%), lung squamous cell carcinoma (SCC) (79%), head and neck SCC (70%), colorectal adenocarcinoma (59%), lung adenocarcinoma (52%), and bladder urothelial carcinoma (50%)[235]. TP53 loss of heterozygosity (LOH) is frequently seen in tumors and often occurs when one copy of TP53 harbors a mutation; in some tumors, LOH is correlated with progression[236-239]. While the prognostic significance of TP53 alteration or dysregulation varies according to tumor type, studies have shown an association with poor prognosis for patients with breast cancer[240-242], endometrial cancer[243-244], HNSCC[245-247], or urothelial cancer[248-249]. In one study of 55 patients with lung adenocarcinoma, TP53 alterations correlated with immunogenic features including PD-L1 expression, tumor mutation burden and neoantigen presentation; likely as a consequence of this association TP53 mutations correlated with improved clinical outcomes to PD-1 inhibitors pembrolizumab and nivolumab in this study[250]. TP53 mutation has not been consistently demonstrated to be a significant independent prognostic marker in the context of CRC[251].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[252]. Alterations such as seen here may disrupt TP53 function or expression[253-257].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[258-260], including sarcomas[261-262]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[263] to 1:20,000[262]. 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[264]. 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[265-270]. 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[265-266]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[271]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[269,272-273]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

Erdafitinib

Assay findings association

FGFR2
FGFR2-HK1 fusion

FGFR3
FGFR3-TACC3 fusion

AREAS OF THERAPEUTIC USE

Erdafitinib is a pan-fibroblast growth factor receptor (FGFR) inhibitor. It is FDA approved for the treatment of patients with advanced or metastatic urothelial carcinoma who have FGFR2 or FGFR3 alterations and have progressed after prior chemotherapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of strong clinical evidence for FGFR2 fusions[60,80,274] , limited evidence for FGFR2 mutations[274-275] and limited evidence for FGFR2 amplification[276], and preclinical data[102,277] , FGFR2 activating alterations may confer sensitivity to erdafitinib. On the basis of strong clinical evidence, FGFR3 fusions[60,80,113,274] and activating mutations[60,80,101] may confer sensitivity to erdafitinib.

SUPPORTING DATA

Erdafitinib has been primarily studied for the treatment of FGFR-altered urothelial carcinoma. A Phase 2 study evaluating erdafitinib for the treatment of patients with metastatic or unresectable urothelial carcinoma (mUC) previously treated with chemotherapy and harboring FGFR2/3 fusions or FGFR3 activating mutations reported an ORR of 40% (40/99, 3 CR), and a DCR of 80% (79/99)[101]. The interim analysis of the Phase 2 RAGNAR trial reported an ORR of 29% (52/178) for patients with FGFR-altered solid tumors treated with erdafitinib[278]. A Phase 1 trial of erdafitinib reported clinical responses for patients with various FGFR2- or FGFR3-altered solid tumors[60,113,275,279] , including cholangiocarcinoma (27% ORR, 3/11), non-small cell lung cancer (NSCLC) (5% ORR, 1/21), breast (9% ORR, 3/34), and ovarian (9% ORR, 1/11), while other cancers including endometrial carcinoma and glioblastoma showed a low ORR (2%, 1/58)[276].

Futibatinib

Assay findings association

FGFR2
FGFR2-HK1 fusion

AREAS OF THERAPEUTIC USE

Futibatinib is an irreversible pan-fibroblast growth factor receptor (FGFR) inhibitor. It is FDA approved for the treatment of patients with unresectable, locally advanced, or metastatic intrahepatic cholangiocarcinoma harboring FGFR2 fusions or rearrangements that have progressed after prior therapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of strong clinical evidence for patients with FGFR2 fusion- or rearrangement-positive cholangiocarcinoma[65,280] and clinical responses for patients with FGFR2-mutated cholangiocarcinoma or unknown primary carcinoma[65,73,281] , FGFR2 activating fusions, rearrangements, or mutations may confer sensitivity to futibatinib.

SUPPORTING DATA

Futibatinib has been primarily studied for the treatment of patients with FGFR2 fusion- or rearrangement-positive cholangiocarcinoma, with the Phase 2 FOENIX-CCA2 study reporting a 42% ORR for patients with previously treated unresectable or metastatic disease[280]. Phase 1 studies of futibatinib for the treatment of patients with advanced solid tumors and FGF and/or FGFR alterations reported ORRs of 12-14%[65,282] and a DCR of 37%[282]. The Phase 2 FOENIX-CCA2 trial of futibatinib reported a 42% ORR, 83% DCR, and 9.7-month median duration of response for patients with previously treated FGFR2 fusion-positive or FGFR2-rearranged intrahepatic cholangiocarcinoma; the median PFS and median OS were 9.0 months and 21.7 months, respectively[283]. An ORR of 19% was reported in a Phase 1 study for patients with FGFR2 fusion-positive or FGFR2-rearranged cholangiocarcinoma treated with the recommended Phase 2 dose of futibatinib[65]. Responses to futibatinib have been reported for patients with FGFR2 fusion-positive cholangiocarcinoma that have progressed on other FGFR inhibitors[284-285] .

Infigratinib

Assay findings association

FGFR2
FGFR2-HK1 fusion

AREAS OF THERAPEUTIC USE

Infigratinib is a TKI that inhibits FGFR1, FGFR2, and FGFR3. A voluntary withdrawal of the accelerated FDA approval of infigratinib to treat patients with unresectable locally advanced or metastatic cholangiocarcinoma who have FGFR2 rearrangements or fusions and have progressed after prior therapy has been initiated by the manufacturer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in FGFR2-rearranged gallbladder and pancreatic carcinoma treated with pemigatinib and FGFR2-rearranged cholangiocarcinoma treated with pemigatinib or infigratinib[61-63,286-289] , FGFR2 rearrangements may confer sensitivity to the FGFR inhibitors pemigatinib or infigratinib.

SUPPORTING DATA

A Phase 2 study of single-agent infigratinib reported a 23% ORR (1 CR, 24 PR), 5.0-month median duration of response, and 84% DCR for patients with recurrent cholangiocarcinoma harboring an FGFR2 fusion or rearrangement; the median PFS and OS were 7.3 and 12.2 months, respectively[290]. Infigratinib has been primarily studied in the context of FGFR-altered solid tumors. A Phase 2 study of infigratinib reported a 23% ORR (1 CR, 24 PR), 5.0-month median duration of response, and 84% DCR for patients with recurrent cholangiocarcinoma harboring an FGFR2 fusion or rearrangement; the median PFS and OS were 7.3 and 12.2 months, respectively[290]. A Phase 2 study of infigratinib for patients with urothelial carcinoma harboring either FGFR3 mutations or rearrangements reported an ORR of 25% (17/67) and a DCR of 64% (43/67); median PFS and OS were estimated to be 3.75 and 7.75 months, respectively; most responses were reported for patients with FGFR3-mutated tumors; however, a CR was reported for a patient with urothelial carcinoma harboring an FGFR3 rearrangement[103]. A Phase 2 study of infigratinib for patients with recurrent high-grade gliomas harboring FGFR alterations reported a 9.5% (2/21) ORR, 1.7-month median PFS, and 6.7-month median OS[291].

Pemigatinib

Assay findings association

FGFR2
FGFR2-HK1 fusion

AREAS OF THERAPEUTIC USE

Pemigatinib is a small molecule inhibitor of FGFR kinases. It is FDA approved to treat patients with advanced or metastatic cholangiocarcinoma who have FGFR2 rearrangements or fusions and have progressed after prior chemotherapy, as well as for treating patients with relapsed or refractory myeloid/lymphoid neoplasms (MLNs) with FGFR1 rearrangements. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in FGFR2-rearranged gallbladder and pancreatic carcinoma treated with pemigatinib and FGFR2-rearranged cholangiocarcinoma treated with pemigatinib or infigratinib[61-63,286-289] , FGFR2 rearrangements may confer sensitivity to the FGFR inhibitors pemigatinib or infigratinib.

SUPPORTING DATA

Pemigatinib has been primarily studied in the treatment of FGFR2-rearranged cholangiocarcinoma. The Phase 2 FIGHT-202 study of pemigatinib for previously treated patients with FGFR2-rearranged advanced cholangiocarcinoma reported a longer median OS (21.1 vs. 6.7 vs. 4.0 months), longer median PFS (6.9 vs. 2.1 vs. 1.7 months), and a higher ORR (36% [3 CRs] vs. 0% vs. 0%) than those with or without FGF/FGFR alterations[62,288,292-293] . A Phase 1/2 study of pemigatinib for patients with FGFR-altered tumors reported 12 PRs for patients with cholangiocarcinoma (n=5), urothelial carcinoma, recurrent pilocytic astrocytoma, and head and neck, pancreatic, gallbladder, uterine, and non-small-cell lung cancer (NSCLC; each n=1); the ORR was 25% (n=5) and 23% (n=3) for patients with tumors harboring FGFR fusions and/or rearrangements and FGFR mutations, respectively[63].

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

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

GENE
ARID1A

ALTERATION
Q553*

RATIONALE
ARID1A loss or inactivation may predict sensitivity to ATR inhibitors.

NCT02264678

PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1

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

NCT04802174

PHASE 1/2

Lurbinectedin With Berzosertib, an ATR Kinase Inhibitor in Small Cell Cancers and High-Grade Neuroendocrine Cancers

TARGETS
ATR

LOCATIONS: Maryland

NCT04657068

PHASE 1/2

A Study of ART0380 for the Treatment of Advanced or Metastatic Solid Tumors

TARGETS
ATR

LOCATIONS: London (United Kingdom), Colorado, Oklahoma, Texas, Pennsylvania, Tennessee, Florida

NCT04514497

PHASE 1

Testing the Addition of an Anti-cancer Drug, BAY 1895344, to Usual Chemotherapy for Advanced Stage Solid Tumors, With a Specific Focus on Patients With Small Cell Lung Cancer, Poorly Differentiated Neuroendocrine Cancer, and Pancreatic Cancer

TARGETS
TOP1, ATR

LOCATIONS: California, Arizona, Minnesota, Oklahoma, Missouri, Pennsylvania, Connecticut, New York

NCT03669601

PHASE 1

AZD6738 & Gemcitabine as Combination Therapy

TARGETS
ATR

LOCATIONS: Cambridge (United Kingdom)

NCT04616534

PHASE 1

Testing the Addition of an Anti-cancer Drug, BAY 1895344 ATR Inhibitor, to the Chemotherapy Treatment (Gemcitabine) for Advanced Pancreatic and Ovarian Cancer, and Advanced Solid Tumors

TARGETS
ATR

LOCATIONS: Massachusetts, Maryland

GENE
BAP1

ALTERATION
I176fs*3

RATIONALE
BAP1 inactivating alterations may predict sensitivity to PARP inhibitors.

NCT04123366

PHASE 2

Study of Olaparib (MK-7339) in Combination With Pembrolizumab (MK-3475) in the Treatment of Homologous Recombination Repair Mutation (HRRm) and/or Homologous Recombination Deficiency (HRD)-Positive Advanced Cancer (MK-7339-007/KEYLYNK-007)

TARGETS
PARP, PD-1

LOCATIONS: Fukuoka (Japan), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Okayama (Japan), Nagoya (Japan), Tokyo (Japan), Kashiwa (Japan), Sapporo (Japan), Nedlands (Australia), Southport (Australia)

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: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Darlinghurst (Australia), Adana (Turkey), Jerusalem (Israel), Konya (Turkey), Ramat Gan (Israel), Istanbul (Turkey), Antalya (Turkey), Brasov (Romania)

NCT02264678

PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1

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

NCT05035745

PHASE 1/2

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

TARGETS
XPO1, PARP

LOCATIONS: Singapore (Singapore)

NCT03772561

PHASE 1

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

TARGETS
PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

NCT03127215

PHASE 2

Study of Olaparib/Trabectedin vs. Doctor's Choice in Solid Tumors

TARGETS
FUS-DDIT3, PARP

LOCATIONS: Dresden (Germany), München (Germany), Frankfurt (Germany), Essen (Germany), Mainz (Germany), Heidelberg (Germany), Stuttgart (Germany), Tuebingen (Germany), Freiburg (Germany)

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), Kelowna (Canada), Edmonton (Canada), Saskatoon (Canada), Regina (Canada), Ottawa (Canada), Montreal (Canada), Toronto (Canada), Kingston (Canada), London (Canada)

NCT04991480

PHASE 1/2

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

TARGETS
PARP, Pol theta

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

NCT05327010

PHASE 2

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

TARGETS
PARP, BRD4, BRDT, BRD2, BRD3

LOCATIONS: Illinois, Texas, North Carolina, Georgia

NCT04992013

PHASE 2

Niraparib in Tumors Metastatic to the CNS

TARGETS
PARP

LOCATIONS: Massachusetts

GENE
FGFR2

ALTERATION
FGFR2-HK1 fusion

RATIONALE
FGFR inhibitors may be relevant in tumors with alterations that activate FGFR2.

NCT03656536

PHASE 3

A Study to Evaluate the Efficacy and Safety of Pemigatinib Versus Chemotherapy in Unresectable or Metastatic Cholangiocarcinoma - (FIGHT-302)

TARGETS
FGFR1, FGFR2, FGFR3

LOCATIONS: Fuzhou (China), Hangzhou (China), Shanghai (China), SHanghai (China), Nanjing (China), Yangzhou (China), Hefei (China), Guangdong (China), Guangzhou (China), Wuhan (China)

NCT05019794

PHASE 2

Infigratinib in Subjects With GC or GEJ With FGFR2 Amplification or Other Solid Tumors With Other FGFR Alterations

TARGETS
FGFR3, FGFR1, FGFR2

LOCATIONS: Fuzhou (China), Hangzhou (China), Shanghai (China), Changzhou (China), Nanjing (China), Guangzhou (China), Wuan (China), Henan (China), Baoding (China), Taiyuan (China)

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: Hangzhou (China), Shanghai (China), Dongguan (China), Guangzhou (China), Zhuhai (China), Benbu (China), Zhengzhou (China), Jinan (China), Dalian (China), Tianjin (China)

NCT04083976

PHASE 2

A Study of Erdafitinib in Participants With Advanced Solid Tumors and Fibroblast Growth Factor Receptor (FGFR) Gene Alterations

TARGETS
FGFRs

LOCATIONS: Hangzhou (China), Matsuyama (Japan), Hiroshima-shi (Japan), Toyoake (Japan), Chuo-Ku (Japan), Kashiwa (Japan), Hawaii, Warszawa (Poland), Dresden (Germany), Leipzig (Germany)

NCT05098847

PHASE 2

Cryoablation Combined With Sintilimab Plus Lenvatinib In Previously Treated Unresectable Liver Metastasis From Solid Tumors

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

LOCATIONS: Shanghai (China)

NCT03758664

PHASE 1/2

Clinical Study of ICP-192 in Solid Tumors Patients

TARGETS
FGFR2, FGFR1, FGFR3, FGFR4

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

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT04962867

PHASE 2

NCCH2006/MK010 Trial (FORTUNE Trial)

TARGETS
FGFR1, FGFR2, FGFR3

LOCATIONS: Higashi-Ku, Fukuoka (Japan), Sakyo-ku, Kyoto (Japan), Chuo-ku, Tokyo (Japan), Aoba-ku, Sendai, Miyagi (Japan), Kita-Ku, Sapporo, Hokkaido (Japan)

NCT03564691

PHASE 1

Study of MK-4830 as Monotherapy and in Combination With Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-4830-001)

TARGETS
ITL4, FGFRs, RET, PDGFRA, VEGFRs, KIT, PD-1

LOCATIONS: Seoul (Korea, Republic of), Chengdu (China), Brisbane (Australia), Liverpool (Australia), Petah Tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Haifa (Israel), Warszawa (Poland), Gdansk (Poland)

GENE
FGFR3

RATIONALE
FGFR inhibitors may be relevant in tumors with alterations that activate FGFR3.

ALTERATION
FGFR3-TACC3 fusion

NCT03656536

PHASE 3

A Study to Evaluate the Efficacy and Safety of Pemigatinib Versus Chemotherapy in Unresectable or Metastatic Cholangiocarcinoma - (FIGHT-302)

TARGETS
FGFR1, FGFR2, FGFR3

LOCATIONS: Fuzhou (China), Hangzhou (China), Shanghai (China), SHanghai (China), Nanjing (China), Yangzhou (China), Hefei (China), Guangdong (China), Guangzhou (China), Wuhan (China)

NCT05019794

PHASE 2

Infigratinib in Subjects With GC or GEJ With FGFR2 Amplification or Other Solid Tumors With Other FGFR Alterations

TARGETS
FGFR3, FGFR1, FGFR2

LOCATIONS: Fuzhou (China), Hangzhou (China), Shanghai (China), Changzhou (China), Nanjing (China), Guangzhou (China), Wuan (China), Henan (China), Baoding (China), Taiyuan (China)

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: Hangzhou (China), Shanghai (China), Dongguan (China), Guangzhou (China), Zhuhai (China), Benbu (China), Zhengzhou (China), Jinan (China), Dalian (China), Tianjin (China)

NCT04083976

PHASE 2

A Study of Erdafitinib in Participants With Advanced Solid Tumors and Fibroblast Growth Factor Receptor (FGFR) Gene Alterations

TARGETS
FGFRs

LOCATIONS: Hangzhou (China), Matsuyama (Japan), Hiroshima-shi (Japan), Toyoake (Japan), Chuo-Ku (Japan), Kashiwa (Japan), Hawaii, Warszawa (Poland), Dresden (Germany), Leipzig (Germany)

NCT05098847

PHASE 2

Cryoablation Combined With Sintilimab Plus Lenvatinib In Previously Treated Unresectable Liver Metastasis From Solid Tumors

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

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

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT04962867

PHASE 2

NCCH2006/MK010 Trial (FORTUNE Trial)

TARGETS
FGFR1, FGFR2, FGFR3

LOCATIONS: Higashi-Ku, Fukuoka (Japan), Sakyo-ku, Kyoto (Japan), Chuo-ku, Tokyo (Japan), Aoba-ku, Sendai, Miyagi (Japan), Kita-Ku, Sapporo, Hokkaido (Japan)

NCT03564691

PHASE 1

Study of MK-4830 as Monotherapy and in Combination With Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-4830-001)

TARGETS
ITL4, FGFRs, RET, PDGFRA, VEGFRs, KIT, PD-1

LOCATIONS: Seoul (Korea, Republic of), Chengdu (China), Brisbane (Australia), Liverpool (Australia), Petah Tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Haifa (Israel), Warszawa (Poland), Gdansk (Poland)

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)

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.

CREBBP
NM_004380.2: c.5740G>T
(p.V1914L)
chr16:3779308

ERBB3
NM_001982.3: c.1732C>T
(p.H578Y)
chr12:56488213

FANCC
NM_000136.2: c.973G>A
(p.A325T)
chr9:97887391

P2RY8
NM_178129.4: c.968A>G
(p.E323G)
chrX:1584484

PIK3C2B
rearrangement

TIPARP
NM_015508.4: c.398G>T
(p.R133L)
chr3:156395884

ZNF217
NM_006526.2: c.3146G>T
(p.*1049Lext*5)
chr20:52188284

Electronically signed by Naomi Lynn Ferguson, M.D. | 19 May 2023
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
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Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

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

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

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

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

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

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

CE IVD

ABOUT FOUNDATIONONE LIQUID CDx

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

Please refer to technical information for performance specification details.

INTENDED USE

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

TEST PRINCIPLES

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

THE REPORT

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

QUALIFIED ALTERATION CALLS (EQUIVOCAL)

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

RANKING OF THERAPIES AND CLINICAL TRIALS

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

Ranking of Clinical Trials
Pediatric trial qualification → Geographical proximity → Later trial phase.

LIMITATIONS

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

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

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

REPORT HIGHLIGHTS

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

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

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

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE THE RESPONSIBILITY OF PHYSICIAN

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

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

SELECT ABBREVIATIONS

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

REFERENCE SEQUENCE INFORMATION

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

MR Suite Version (RG) 7.8.0

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