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 Stomach adenocarcinoma (NOS)
NAME Chang, Chi-Chun
DATE OF BIRTH 01 July 1940
SEX Female
MEDICAL RECORD # 26693243

PHYSICIAN

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

SPECIMEN

SPECIMEN ID CCC 7/1/1940
SPECIMEN TYPE Blood
DATE OF COLLECTION 22 October 2021
SPECIMEN RECEIVED 26 October 2021

Biomarker Findings

Blood Tumor Mutational Burden - 20 Muts/Mb
Microsatellite status - MSI-High Not Detected
Tumor Fraction - 50%

Genomic Findings

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

FGFR2 amplification, rearrangement intron 17
CDK6 amplification - equivocal†
MYC amplification
DNMT3A F732fs*8
EPHB4 amplification
GATA6 amplification - equivocal†
GNAS Q227E
TP53 H214R, L206fs*3

† See About the Test in appendix for details.

2 Therapies with Clinical Benefit
0 Therapies with Resistance
33 Clinical Trials

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
Blood Tumor Mutational Burden - 20 Muts/Mb **10 Trials** see p. 12	None	None
Microsatellite status - MSI-High Not Detected	MSI-High not detected. No evidence of microsatellite instability in this sample (see Appendix section).	
Tumor Fraction - 50%	Tumor fraction is an estimate of the percentage of circulating-tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample based on observed aneuploid instability.	

GENOMIC FINDINGS		VAF %	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
FGFR2 -	amplification	-	None	Erdafitinib
	rearrangement intron 17	17.0%		Pazopanib
10 Trials see p. 16				
CDK6 -	amplification - equivocal	-	None	None
10 Trials see p. 14				

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GENOMIC FINDINGS	VAF %	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
MYC - amplification	-	None	None
4 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.

DNMT3A - F732fs*8 p. 7

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

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

Variant Allele Frequency is not applicable for copy number alterations.

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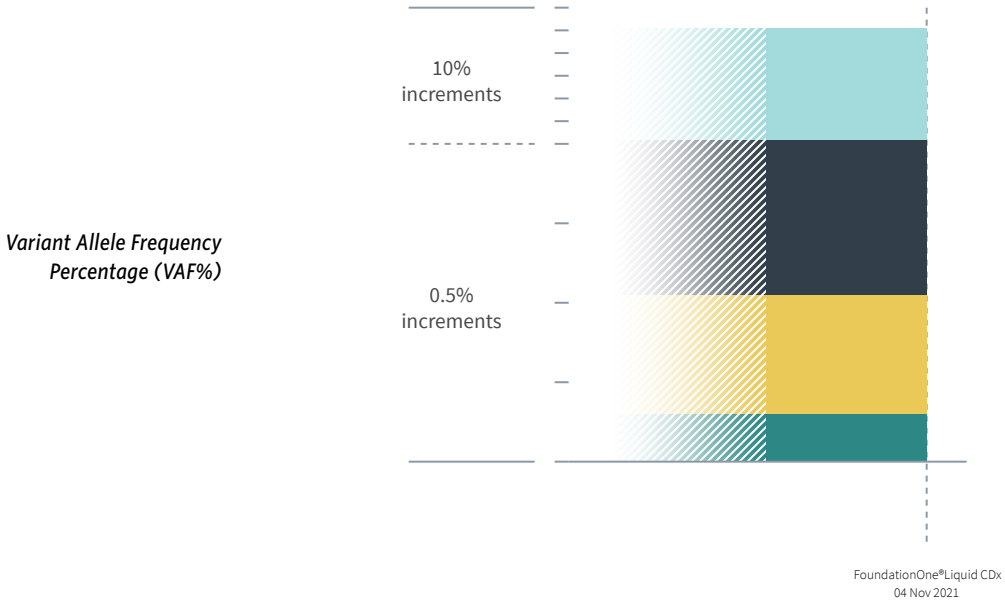

HISTORIC PATIENT FINDINGS		ORD-1223719-01 VAF%
Blood Tumor Mutational Burden		20 Muts/Mb
Microsatellite status		MSI-High Not Detected
Tumor Fraction		50%
FGFR2	amplification	Detected
CDK6	amplification	Detected
MYC	amplification	Detected
DNMT3A	● F732fs*8	2.9%
EPHB4	amplification	Detected
GATA6	amplification	Detected
GNAS	● Q227E	0.30%
TP53	● L206fs*3	0.75%
	● H214R	49.2%

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

For some genes in FoundationOne Liquid CDx, only select exons are assayed. Therefore, an alteration found by a previous test may not have been confirmed despite overlapping gene lists. Please refer to the Appendix for the complete list of genes and exons assayed. The gene and biomarker list will be updated periodically to reflect new knowledge about cancer biology.

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

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

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

Not Detected = baited but not detected on test

Detected = present (VAF% is not applicable)

VAF% = variant allele frequency percentage

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

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BIOMARKER

Blood Tumor Mutational Burden

RESULT
20 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in NSCLC and HSNCC, increased bTMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[1-2] and anti-PD-1[3] therapies. In NSCLC, multiple clinical trials have shown patients with higher bTMB derive clinical benefit from immune checkpoint inhibitors following single agent or combination treatments with either CTLA4 inhibitors or chemotherapy, with reported high bTMB cutpoints ranging from 6 to 16 Muts/Mb[1]. In HNSCC, a Phase 3 trial showed that bTMB ≥16 Muts/Mb (approximate equivalency ≥8 Muts/Mb as measured by this assay) was associated with improved survival from treatment with a PD-L1 inhibitor alone or in combination with a CTLA-4 inhibitor[4].

FREQUENCY & PROGNOSIS

Average bTMB levels in solid tumors other than NSCLC have not been evaluated (cBioPortal, COSMIC, PubMed, Mar 2021)[5-7]. For patients with gastric cancer, increased TMB is reported to be associated with prolonged OS[8-10]. One study observed that the OS and disease-free survival (DFS) benefits of postoperative chemotherapy were more pronounced in patients with TMB-low gastric cancer (stage Ib/II) compared to those with TMB-high; however, patients with stage III gastric cancer benefitted regardless of TMB level[11]. In esophageal cancer, patients with TMB-high who had not received radiotherapy had significantly reduced OS (p=0.038) compared to those with TMB-low[12].

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[13-14] and cigarette smoke in lung cancer[15-16], treatment with temozolomide-based chemotherapy in glioma[17-18], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[19-23], and microsatellite instability (MSI)[19,22-23]. This sample harbors a bTMB level that may be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[1-3].

BIOMARKER

Tumor Fraction

RESULT
50%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Specimens with high tumor fraction values have high circulating-tumor DNA (ctDNA) content, and thus higher sensitivity for identifying genomic alterations. Such specimens are at a lower risk of false negative results[24]. However, if tumor fraction is not detected as high, it does not exclude the presence of disease burden or compromise the confidence of reported alterations. Tumor fraction levels currently have limited implications for diagnosis, surveillance, or therapy and should not be overinterpreted or compared from one blood draw to another. There are currently no targeted approaches to address specific tumor fraction levels. In the research setting, changes in tumor fraction estimates have been associated with treatment duration and clinical response and may be a useful indicator for future cancer management[25-30].

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)[31]. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer[32], Ewing sarcoma and osteosarcoma[33], prostate cancer[28], breast cancer[34], leiomyosarcoma[35], esophageal cancer[36], colorectal cancer[37], and gastrointestinal cancer[38].

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[39], 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[40-41].

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GENE

FGFR2

ALTERATION

amplification, rearrangement intron 17

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

FGFR2 activating mutations, amplifications, or fusions may confer sensitivity to selective FGFR inhibitors such as erdafitinib[42], pemigatinib[43-44], infigratinib[45], E7090[46], AZD4547[47-49], Debio 1347[50-51], rogaratinib[52], futibatinib[53], and derazantinib[54] as well as to the multikinase inhibitors pazopanib[55-56] and ponatinib[57]. In a Phase 2 study of the FGFR inhibitor AZD4547, responses were reported in 33% (3/9) of patients with FGFR2-amplified gastroesophageal cancer; in this study, higher-level amplification correlated with higher likelihood of response to FGFR inhibitors[47]. However, a randomized Phase 2 study of AZD4547 compared with paclitaxel for the treatment of patients with advanced stomach adenocarcinoma harboring FGFR2 amplification or polysomy reported no significant increase in median PFS, median OS, or ORR[48]. Bemarituzumab, a monoclonal antibody against the FGFR2 splice variant FGFR2b, has been evaluated to treat patients with gastroesophageal junction (GEJ) adenocarcinoma expressing FGFR2b[58]. In a Phase 1 study of single-agent bemarituzumab, the ORR was higher for patients with GEJ adenocarcinoma and high FGFR2b expression (all FGFR2-amplified) than for those with low FGFR2b expression (none FGFR2-amplified) (18% [5/28] vs. 8% [1/12])[58]. The addition of bemarituzumab to modified FOLFOX6 as first-line treatment in a Phase 2 study for patients with FGFR2b-positive, HER2-negative gastric or GEJ adenocarcinoma improved median OS (19.2 vs. 13.5 months, HR=0.60) with 12.5 months of follow-up, median PFS (9.5 vs. 7.4 months, HR=0.68, p=0.0727), and ORR (47% vs. 33%)[59-60] . In the context of FGFR2 rearrangement, FGFR inhibitors have primarily been investigated for patients with previously treated intrahepatic cholangiocarcinoma (ICC), with the Phase 2 FIGHT-202 trial for pemigatinib[44] and a Phase 2 trial for infigratinib[61] respectively reporting ORRs of 36% (38/107) and 23% (25/108). Responses to erdafitinib have been reported in patients with FGFR2 fusion-positive urothelial carcinoma[62] and endometrial carcinoma[42].

FREQUENCY & PROGNOSIS

FGFR2 mutations have been reported in 0-4% of gastric adenocarcinoma cases[63-66]. In the Stomach Adenocarcinoma TCGA dataset, putative high-level amplification of FGFR2 has been reported in 5% of cases[63]. Studies have reported FGFR2 amplification in 2-9% of gastric cancer samples analyzed[67-70]. FGFR2 protein expression and pathway alteration has been associated with diffuse-type gastric cancer and not with the intestinal type[71-73]. However, one study did report FGFR2 protein overexpression in intestinal-type gastric cancer[74]. High FGFR2 protein expression or FGFR2 gene amplification in patients with gastric carcinoma has been correlated with worse prognosis, tumor infiltration, and a more advanced disease state[67-72].

FINDING SUMMARY

FGFR2 encodes a tyrosine kinase cell surface receptor, which plays an important role in cell differentiation, growth, and angiogenesis[75-76]. FGFR2 amplification has been reported in a variety of cancer types[6] and has been shown to correlate with increased mRNA and protein expression[47,77]. Higher level, clonal FGFR2 amplification has been reported to correlate with higher response rates to FGFR inhibitors[47,78]. FGFR2 fusions retaining the kinase domain encoded by exons 11-17 have been reported to be activating, oncogenic, and sensitive to FGFR inhibitors[79-82]. Furthermore, FGFR2 variants lacking a portion of the cytoplasmic domain encoded by exon 18 have been reported to be oncogenic in vitro[80-81,83-85]. FGFR2 variants truncated after exon 17, as observed here, have been reported to be oncogenic, efficiently transforming cultured cells and driving xenograft growth in mice with higher potency than full-length FGFR2[83-86].

GENE

CDK6

ALTERATION

amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Tumors with CDK6 activation may be sensitive to CDK4/6 inhibitors, such as abemaciclib, palbociclib, and ribociclib[87-90]. Clinical benefit has been reported for patients with CDK6-amplified or mutated solid tumors in response to treatment with ribociclib[91-92] .

FREQUENCY & PROGNOSIS

In the TCGA dataset, amplification of CDK6 was found in 8% of stomach adenocarcinoma cases[63]. High-level amplification or copy number gain of CDK6 has been observed in 35.5% (11/31) of gastric cancer cell lines and was associated with increased CDK6 mRNA levels[93]. CDK6 overexpression has also been reported in patients with gastric cancer, and was found to be significantly associated with metastasis, poor differentiation, and poor survival[94].

FINDING SUMMARY

CDK6 encodes cyclin-dependent kinase 6, which regulates the cell cycle, differentiation, senescence, and apoptosis[95-97]. CDK6 and its functional homolog CDK4 are activated by D-type cyclins and promote cell cycle progression by inactivating the tumor suppressor Rb[98-99]. Amplification of the chromosomal region that includes CDK6 has been reported in multiple cancer types, and has been associated with overexpression of CDK6 protein[100-101].

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GENE
MYC

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no available therapies that directly target MYC. However, preclinical data indicate that MYC overexpression may predict sensitivity to investigational agents targeting CDK1[102-103], CDK2[104], Aurora kinase A[105-112], Aurora kinase B[113-116], glutaminase[117-120], or BET bromodomain-containing proteins[121-124], as well as agents targeting both HDAC and PI3K[125-127]. A Phase 2 study reported a PFS benefit associated with a combination of the Aurora A kinase inhibitor alisertib and paclitaxel as second-line therapy for patients with MYC-overexpressed small cell lung cancer but not for patients without MYC overexpression[128]. A patient with MYC-amplified invasive ductal breast carcinoma experienced a PR to an Aurora kinase inhibitor[129]. The glutaminase inhibitor CB-839, in combination with either everolimus or cabozantinib, has demonstrated encouraging efficacy in Phase 1 and 2 studies enrolling patients with pretreated advanced renal cell carcinoma[130-131] .

— Nontargeted Approaches —

MYC amplification has also been suggested to predict response to chemotherapy in patients with breast cancer in some studies[132-133]. Preclinical evidence suggests that colon cancer cells with MYC amplification may be more sensitive to 5-fluorouracil and paclitaxel[134-135].

FREQUENCY & PROGNOSIS

MYC amplification has been reported in 9-51% of gastric adenocarcinomas, although gains of chromosome 8q, where the MYC gene resides, have been identified in up to 78% of gastric adenocarcinomas[63,136-139]. MYC dysregulation, especially MYC amplification, has been suggested to play a role in gastric carcinogenesis[140]. Overexpression of MYC protein and mRNA has been associated with tumor metastasis, particularly in intestinal type gastric adenocarcinoma, and high MYC expression has been observed in gastric cancer samples from patients with poor disease-free survival[141-145].

FINDING SUMMARY

MYC (c-MYC) encodes a transcription factor that regulates many genes related to cell cycle regulation and cell growth. It is an oncogene and may be activated in as many as 20% of cancers[146]. MYC dysregulation (amplification, overexpression, translocation) has been identified in a number of different cancer types[147]. MYC amplification has been significantly linked with increased mRNA and protein levels and results in the dysregulation of a large number of target genes[146,148-149].

GENE
DNMT3A

ALTERATION
F732fs*8

TRANSCRIPT ID
NM_022552

CODING SEQUENCE EFFECT
2196_2197delTG

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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

FREQUENCY & PROGNOSIS

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

FINDING SUMMARY

The DNMT3A gene encodes the protein DNA methyltransferase 3A, an enzyme that is involved in the methylation of newly synthesized DNA, a function critical for gene regulation[150-151]. The role of DNMT3A in cancer is uncertain, as some reports describe increased expression and contribution to tumor growth, whereas others propose a role for DNMT3A as a tumor suppressor[152-157]. Alterations such as seen here may disrupt DNMT3A function or expression[158-161].

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[162-167]. 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[162-163]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[168]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[166,169-170]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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GENE
EPHB4

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies available to target EPHB4 alterations in cancer. sEPHB4 is a soluble monomeric extracellular domain of EPHB4 that functions as an antagonist of EphrinB2-EPHB4 interaction[171], and fusion of sEPHB4 with human serum albumin (HSA) increases its stability[172]. Recombinant sEPHB4-HSA is under investigation in clinical trials. Preclinical studies have demonstrated that sEPHB4-HSA inhibits cell proliferation and xenograft tumor growth, including for cells expressing cancer-associated EPHB4 mutants or overexpressing wild-type EPHB4[171,173-177]. In addition, small-molecule inhibitors targeting multiple tyrosine kinases including EPHB4, such as JI-101 and XL647, have been under preclinical and clinical investigation[178-180].

FREQUENCY & PROGNOSIS

Increased EPHB4 mRNA and/or protein expression has been reported in a variety of cancer types, including head and neck squamous cell carcinoma (HNSCC)[181-184], gastric and esophageal[185-189], colorectal carcinoma (CRC)[190-196], breast[197-201], ovarian[201-203], endometrial[204-206], thyroid[207-209], lung[210-211], glioma[212-213], and other solid tumors[173,214-221]. In several of these studies, increased EPHB4 expression has been associated with clinicopathologic features, including disease stage[173,181,197,202-203,211,214,216], histological grade[187,197,204,213], and hormone receptor status[200,205]. High EPHB4 expression has been associated with inferior survival in multivariate analyses for patients with CRC treated with bevacizumab [hazard ratio (HR) = 5.95][195], HNSCC (HR = 2.95)[184], epithelial ovarian cancer (HR = 4.53)[201], or glioma (HR = 3.21)[213].

FINDING SUMMARY

EPHB4 encodes a member of the EPH family of receptor tyrosine kinases[222]. Ephrin signaling has been implicated in multiple processes, including cell adhesion, cytoskeletal organization, and cell migration[223], and signaling between EPHB4 and its ligand EphrinB2 is particularly important for angiogenesis[224-225]. EPHB receptors, including EPHB4, have been shown to undergo dysregulation (amplification, mutation, under- or overexpression) in a number of different cancer types[226]. EPHB4 amplification has been reported in several solid tumor types[181-182,187,227-228] and was associated with advanced disease stage in head and neck squamous cell carcinoma (HNSCC)[181]. Activating missense mutations in or near the tyrosine kinase domain, including G723S, A742V, and P881S, have also been identified in lung cancer[177].

GENE
GATA6

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in GATA6.

FREQUENCY & PROGNOSIS

GATA6 was identified as a tumor suppressor in a preclinical model of astrocytoma and verified in human samples; GATA6 mutations, loss of GATA6 expression, or loss of heterozygosity were discovered in glioblastomas, but not in lower grade astrocytomas, and restoration of GATA6 inhibited glioblastoma cell line growth[229]. However, overexpression of GATA6 has been detected in pancreatic and bile duct carcinoma and is associated with increased proliferation, cell cycle progression, and colony formation, which have been shown to be inhibited by GATA6 siRNA knockdown in pancreatic carcinoma cell lines[230-231]. GATA6 overexpression in colorectal carcinoma is also associated with poor prognosis and metastasis[232].

FINDING SUMMARY

GATA6 encodes a zinc finger transcription factor, which is involved in the development of several tissues and is expressed in proliferating cells throughout the intestinal tract[233]. GATA6 has been described as both a tumor suppressor and an oncogene, which may be dependent on the tumor type.

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GENE
GNAS

ALTERATION
Q227E

TRANSCRIPT ID
NM_000516

CODING SEQUENCE EFFECT
679C>G

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies targeted to GNAS mutation in cancer. However, there is limited data indicating that a patient with appendiceal adenocarcinoma and a GNAS mutation (R201H) benefited from trametinib for 4 months[234]. Additionally, a patient with GNAS-mutated Erdheim-Chester disease exhibited a PR following treatment with single-agent trametinib[235].

FREQUENCY & PROGNOSIS

The highest incidences of GNAS mutations have been reported in intraductal papillary mucinous neoplasms (40-66%)[236-237] and appendiceal mucinous neoplasms (50-72%)[238-239] as well as in tumors affecting the peritoneum (22%), pituitary gland (20%), bone (15%), pancreas (12%), and small intestine (12%)(COSMIC, 2021)[7]. Amplification of GNAS has been reported in ovarian epithelial carcinomas (12-30%)[240-242], colorectal adenocarcinoma (9%)[22], stomach adenocarcinoma (7%)[63], lung adenocarcinoma (6.5%)[243], breast invasive carcinoma (6.5%)[244], pancreatic adenocarcinoma (6%)[245], and sarcomas (5.8%)[246]. GNAS mutations are rare in hematological malignancies generally (COSMIC, 2021)[7,247-248]. Activating GNAS mutations have been identified in gastrointestinal polyps in 75% (3/4) of patients with McCune-Albright syndrome[249]. Amplification of GNAS has been associated with shorter progression-free survival in patients with ovarian cancer[241-242], while activating GNAS mutations have been correlated with tumor progression and poor prognosis in patients with gastric cancer[250].

FINDING SUMMARY

GNAS encodes the alpha subunit of the stimulatory G protein (Gs-alpha)[251]. Gs-alpha is a guanine-nucleotide binding protein (G protein) that is involved in hormonal regulation of adenylate cyclase[251]. GNAS has been reported to be amplified in cancer[6] and may be biologically relevant in this context[252-253]. GNAS alterations that have been shown to result in constitutive activation of adenylyl cyclase and an increase in cellular cAMP concentration[254-259] are predicted to be activating. Mutations at R201 specifically are commonly associated with McCune-Albright syndrome, a disease that can co-occur with various cancers in patients with GNAS activating mutations[260-262].

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GENE
TP53

ALTERATION
H214R, L206fs*3

TRANSCRIPT ID
NM_000546, NM_000546

CODING SEQUENCE EFFECT
641A>G, 617_618insT

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[263-266], or p53 gene therapy and immunotherapeutics such as SGT-53[267-271] and ALT-801[272]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% (17/176) and SDs in 53.4% (94/176) of patients with solid tumors; the response rate was 21.1% (4/19) for patients with TP53 mutations versus 12.1% (4/33) for patients who were TP53 wild-type[273]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 31.9% (30/94, 3 CR) ORR and a 73.4% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[274]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 42.9% (9/21, 1 CR) ORR and a 76.2% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[275]. 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[276]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24.0% (6/25) ORR with adavosertib combined with paclitaxel[277]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71.4% (5/7) response rate for patients with TP53 alterations[278]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75.0% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[271]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutated, but not TP53-wild-type, breast cancer xenotransplant mouse model[279]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutated p53 such as APR-246[280-282]. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[283]. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies[284-285]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[286-287]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

TP53 is frequently mutated in cancers of the gastrointestinal tract, with alterations reported in 34–72% of esophageal, gastroesophageal junction, and gastric adenocarcinomas[63,288-290]. Overexpression of p53 protein, which may occur as a result of mutation, has been reported in approximately 36% of gastric cancers, with p53 expression reported to be more frequent in intestinal-type compared with diffuse-type gastric cancer[291-294]. While some studies have reported no association between TP53 mutation status and prognosis in patients with esophageal carcinoma or gastroesophageal junction adenocarcinoma[289-290] others have associated TP53 mutation and elevated p53 expression with poor prognosis for patients with esophageal squamous cell carcinoma[295-296] or stomach cancer[297-299].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[300]. Alterations such as seen here may disrupt TP53 function or expression[301-305].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the TP53 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with Li-Fraumeni syndrome (ClinVar, Sep 2021)[306]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[307-309], including sarcomas[310-311]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[312] to 1:20,000[311]. 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[313]. 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[162-167]. 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[162-163]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[168]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[166,169-170]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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Erdafitinib

Assay findings association

FGFR2
amplification, rearrangement
intron 17

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[42,62,314] , limited evidence for FGFR2 mutations[314-315] and limited evidence for FGFR2 amplification[316], and preclinical data[317-318] , FGFR2 activating alterations may confer sensitivity to erdafitinib.

SUPPORTING DATA

Clinical data on the efficacy of erdafitinib for the treatment of gastric or esophageal carcinomas are limited (PubMed, Oct 2021). 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)[319]. A Phase 1 trial of erdafitinib reported clinical responses in for patients with various FGFR2- or FGFR3-altered solid tumors[42,315,320-321] , including cholangiocarcinoma (27% ORR, 3/11), 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)[316]. Following progression on multiple other lines of therapy, a patient with metastatic FGFR2-fusion-positive NSCLC treated with erdafitinib exhibited an 11-month PR[320].

Pazopanib

Assay findings association

FGFR2
amplification, rearrangement
intron 17

AREAS OF THERAPEUTIC USE

Pazopanib is a tyrosine kinase inhibitor that targets VEGFRs, PDGFRs, FGFRs, KIT, ITK, LCK, and c-FMS. It is FDA approved for the treatment of advanced renal cell carcinoma and soft tissue sarcomas that have progressed after prior chemotherapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Analysis of a single-arm Phase 2 study in advanced gastric cancer suggests that patients with FGFR2 protein overexpression may benefit from the addition of pazopanib to chemotherapy[322]. Based on a PR in a patient with FGFR2-rearranged cholangiocarcinoma[55], FGFR2 fusions may predict sensitivity to pazopanib.

SUPPORTING DATA

In a Phase 2 study of pazopanib plus capecitabine and oxaliplatin for the treatment of patients with advanced gastric cancer, 85.7% (6/7) of the patients with FGFR2 protein expression exhibited a PR, and PFS was significantly improved for patients with FGFR2 expression compared to those without (8.5 vs. 5.6 months, p=0.050)[322]. In a Phase 2 study comparing pazopanib in combination with fluorouracil, leukovorin, and oxaliplatin (FLO) to treatment with FLO alone in 87 patients with HER2-negative gastric or gastroesophageal junction cancer, pazopanib showed marginal efficacy, and both the pazopanib and control cohorts experienced inferior PFS compared to previous studies[323]. A Phase 1 study of pazopanib in combination with paclitaxel and carboplatin for patients with advanced solid tumors (n=34) reported CRs for 2 of 4 patients with esophageal cancer and a PR for 1 of 2 patients with gastroesophageal junction cancer[324].

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

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

BIOMARKER

Blood Tumor Mutational Burden

RESULT

20 Muts/Mb

RATIONALE

Increased tumor mutational burden may predict response to anti-PD-1 (alone or in combination with anti-CTLA-4) or anti-PD-L1 immune checkpoint inhibitors.

NCT04237649

PHASE NULL

KAZ954 Alone and With PDR001, NZV930 and NIR178 in Advanced Solid Tumors

TARGETS
ADORA2A, CD73, PD-1

LOCATIONS: Taipei (Taiwan), Sunto Gun (Japan), Singapore (Singapore), Milano (Italy), Barcelona (Spain), California, Illinois, Missouri, Connecticut, Texas

NCT04592913

PHASE 3

Assessing Durvalumab and FLOT Chemotherapy in Resectable Gastric and Gastroesophageal Junction Cancer

TARGETS
PD-L1

LOCATIONS: Taipei (Taiwan), Taoyuan City (Taiwan), Taichung (Taiwan), Tainan City (Taiwan), Kaohsiung (Taiwan), Hwasun-gun (Korea, Republic of), Anyang-si (Korea, Republic of), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Suita-shi (Japan)

NCT03281369

PHASE 1/2

A Study of Multiple Immunotherapy-Based Treatment Combinations in Patients With Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction Cancer (G/GEJ) (Morpheus-Gastric Cancer)

TARGETS
MEK, CXCR4, VEGFRs, PD-L1

LOCATIONS: Taipei City (Taiwan), Zhongzheng Dist. (Taiwan), Tainan (Taiwan), Suwon-si, (Korea, Republic of), Seodaemun-Gu (Korea, Republic of), Seoul (Korea, Republic of), Songpa-gu (Korea, Republic of), Blacktown (Australia), Melbourne (Australia), Clayton (Australia)

NCT03674567

PHASE 1/2

Dose Escalation and Expansion Study of FLX475 Monotherapy and in Combination With Pembrolizumab

TARGETS
PD-1, CCR4

LOCATIONS: Taipei (Taiwan), Tainan (Taiwan), Shatin (Hong Kong), High West (Hong Kong), Ulsan (Korea, Republic of), Chungbuk (Korea, Republic of), Seoul (Korea, Republic of), Bangkok (Thailand), Nedlands (Australia), Heidelberg (Australia)

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NCT04181788

PHASE 1/2

Sasanlimab (PF-06801591, PD-1 Inhibitor) in Participants With Advanced Malignancies

TARGETS
PD-1

LOCATIONS: Taipei (Taiwan), Kaohsiung (Taiwan), Shanghai (China), Nanjing (China), Incheon (Korea, Republic of), Seoul (Korea, Republic of), Chongqing (China), Beijing (China), Chuo-ku (Japan), Kopeysk (Russian Federation)

NCT02829723

PHASE 1/2

Phase I/II Study of BLZ945 Single Agent or BLZ945 in Combination With PDR001 in Advanced Solid Tumors

TARGETS
PD-1, CSF1R

LOCATIONS: Taipei (Taiwan), Tainan (Taiwan), Nagoya (Japan), Koto ku (Japan), Singapore (Singapore), Tel Aviv (Israel), Zurich (Switzerland), Rozzano (Italy), Barcelona (Spain), Hospitalet de LLobregat (Spain)

NCT03797326

PHASE 2

Efficacy and Safety of Pembrolizumab (MK-3475) Plus Lenvatinib (E7080/MK-7902) in Previously Treated Participants With Select Solid Tumors (MK-7902-005/E7080-G000-224/LEAP-005)

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

LOCATIONS: Taipei (Taiwan), Tainan (Taiwan), Seoul (Korea, Republic of), Songpagu (Korea, Republic of), Bangkok (Thailand), Nedlands (Australia), Kazan (Russian Federation), Herston (Australia), Arkhangelsk (Russian Federation), Moscow (Russian Federation)

NCT03829501

PHASE 1/2

Safety and Efficacy of KY1044 and Atezolizumab in Advanced Cancer

TARGETS
ICOS, PD-L1

LOCATIONS: Taipei (Taiwan), Napoli (Italy), Milano (Italy), Manchester (United Kingdom), Sutton (United Kingdom), Connecticut, Tennessee, Texas, Florida

NCT03530397

PHASE 1

A Study to Evaluate MEDI5752 in Subjects With Advanced Solid Tumors

TARGETS
PD-L1, PD-1, CTLA-4

LOCATIONS: Taipei (Taiwan), Cheongju-si (Korea, Republic of), Incheon (Korea, Republic of), Seoul (Korea, Republic of), Gyeonggi-do (Korea, Republic of), Amsterdam (Netherlands), Napoli (Italy), Roma (Italy), Villejuif Cedex (France), Barcelona (Spain)

NCT03192345

PHASE 1

A First-in-human Study of the Safety, Pharmacokinetics, Pharmacodynamics and Anti-tumor Activity of SAR439459 Monotherapy and Combination of SAR439459 and Cemiplimab in Patients With Advanced Solid Tumors

TARGETS
PD-1, TGF-beta

LOCATIONS: Taipei 100 (Taiwan), Tainan (Taiwan), Kaohsiung (Taiwan), Seoul (Korea, Republic of), Heidelberg West (Australia), Melbourne (Australia), Tallinn (Estonia), Hannover (Germany), Essen (Germany), Utrecht (Netherlands)

GENE
CDK6

RATIONALE
Tumors with CDK6 amplification may be sensitive to CDK4/6 inhibitors.

ALTERATION
amplification - equivocal

NCT04594005

PHASE 1/2

CDK4/6 Tumor, Abemaciclib, Paclitaxel

TARGETS
CDK4, CDK6

LOCATIONS: Seoul (Korea, Republic of)

NCT03099174

PHASE 1

This Study in Patients With Different Types of Cancer (Solid Tumours) Aims to Find a Safe Dose of Xentuzumab in Combination With Abemaciclib With or Without Hormonal Therapies. The Study Also Tests How Effective These Medicines Are in Patients With Lung and Breast Cancer.

TARGETS
CDK4, CDK6, IGF-1, IGF-2, Aromatase, ER

LOCATIONS: Seoul (Korea, Republic of), Goyang (Korea, Republic of), Aichi, Nagoya (Japan), Kanagawa, Isehara (Japan), Tokyo, Chuo-ku (Japan), Tokyo, Koto-ku (Japan), Chiba, Kashiwa (Japan), Helsinki (Finland), Tampere (Finland), Turku (Finland)

NCT04801966

PHASE NULL

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

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

LOCATIONS: Melbourne (Australia)

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

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

LOCATIONS: Alaska, Washington

NCT02693535

PHASE 2

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

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

LOCATIONS: Hawaii, Washington, Oregon, California

NCT02896335

PHASE 2

Palbociclib In Progressive Brain Metastases

TARGETS
CDK4, CDK6

LOCATIONS: Massachusetts

NCT03310879

PHASE 2

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

TARGETS
CDK4, CDK6

LOCATIONS: Massachusetts

NCT03065062

PHASE 1

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

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

LOCATIONS: Massachusetts

NCT03454035

PHASE 1

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

TARGETS
MAPK3, MAPK1, CDK4, CDK6

LOCATIONS: North Carolina

NCT02897375

PHASE 1

Palbociclib With Cisplatin or Carboplatin in Advanced Solid Tumors

TARGETS
CDK4, CDK6

LOCATIONS: Georgia

GENE
FGFR2

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

ALTERATION
amplification, rearrangement intron 17

NCT04083976

PHASE 2

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

TARGETS
FGFRs

LOCATIONS: Taipei (Taiwan), Taoyuan City (Taiwan), Taichung (Taiwan), Changhua (Taiwan), Tainan (Taiwan), Kaohsiung City (Taiwan), Kaohsiung (Taiwan), Hangzhou (China), Shanghai (China), Nanjing (China)

NCT03797326

PHASE 2

Efficacy and Safety of Pembrolizumab (MK-3475) Plus Lenvatinib (E7080/MK-7902) in Previously Treated Participants With Select Solid Tumors (MK-7902-005/E7080-G000-224/LEAP-005)

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

LOCATIONS: Taipei (Taiwan), Tainan (Taiwan), Seoul (Korea, Republic of), Songpagu (Korea, Republic of), Bangkok (Thailand), Nedlands (Australia), Kazan (Russian Federation), Herston (Australia), Arkhangelsk (Russian Federation), Moscow (Russian Federation)

NCT02450136

PHASE NULL

Single-arm Study to Evaluate the Safety and Efficacy of Pazopanib, in Subjects With FGFR2 Amplification, FGFR2 Mutation Refractory Solid Tumors

TARGETS
FGFR1, FGFR2, FGFR3, KIT, VEGFRs

LOCATIONS: Seoul (Korea, Republic of)

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT04189445

PHASE 2

Futibatinib in Patients With Specific FGFR Aberrations

TARGETS
FGFRs

LOCATIONS: Seul (Korea, Republic of), Sapporo-shi (Japan), London (United Kingdom), California, Arizona, Wisconsin, Texas

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

LOCATIONS: Seoul (Korea, Republic of), Tokyo (Japan), Haifa (Israel), Petah Tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Warszawa (Poland), Gdansk (Poland), Heraklion (Greece), Washington

NCT04008797

PHASE 1

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

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

LOCATIONS: Osakasayama (Japan), Chuo-Ku (Japan), Kashiwa (Japan)

NCT03547037

PHASE 1

A Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of JNJ-63723283, an Anti-Programmed Cell Death (PD)-1 Monoclonal Antibody, as Monotherapy or in Combination With Erdafitinib in Japanese Participants With Advanced Solid Cancers

TARGETS
PD-1, FGFRs

LOCATIONS: Chuo-Ku (Japan), Kashiwa (Japan)

NCT04042116

PHASE 1/2

A Study to Evaluate Lucitanib in Combination With Nivolumab in Patients With a Solid Tumor

TARGETS
FGFRs, VEGFRs, PD-1

LOCATIONS: Innsbruck (Austria), Essen (Germany), Bologna (Italy), Naples (Italy), Leuven (Belgium), Brussels (Belgium), Ghent (Belgium), Washington, Barcelona (Spain), Madrid (Spain)

NCT04565275

PHASE 1/2

A Study of ICP-192 in Patients With Advanced Solid Tumors

TARGETS
FGFR1, FGFR2, FGFR3, FGFR4

LOCATIONS: Colorado, Minnesota, Arizona, Florida

GENE
MYC

ALTERATION
amplification

RATIONALE
MYC overexpression may predict sensitivity to inhibition of CDKs, especially CDK1 and CDK2, of Aurora kinases, including Aurora kinase A and B, and of BET domain proteins, which are reported to downregulate MYC expression and MYC-dependent transcriptional programs.

NCT03220347

PHASE 1

A Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of CC-90010 in Subjects With Advanced Solid Tumors and Relapsed/Refractory Non-Hodgkin's Lymphomas

TARGETS
BRD2, BRD3, BRD4, BRDT

LOCATIONS: Kashiwa (Japan), Meldola (Italy), Napoli, Campania (Italy), Rozzano (MI) (Italy), Villejuif (France), Bordeaux (France), Barcelona (Spain), Madrid (Spain)

NCT03297424

PHASE 1/2

A Study of PLX2853 in Advanced Malignancies.

TARGETS
BRD4

LOCATIONS: Arizona, New York, Texas, Virginia, Florida

NCT04555837

PHASE 1/2

Alisertib and Pembrolizumab for the Treatment of Patients With Rb-deficient Head and Neck Squamous Cell Cancer

TARGETS
Aurora kinase A, PD-1

LOCATIONS: Texas

NCT01434316

PHASE 1

Veliparib and Dinaciclib in Treating Patients With Advanced Solid Tumors

TARGETS
PARP, CDK1, CDK2, CDK5, CDK9

LOCATIONS: Massachusetts

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

AKT1
K377T

ATM
S2141T

AXL
N814I

BRCA1
K1207T

BRCA2
S662A

BRD4
A1301P

CCNE1
P396L

CD22
K707T

CREBBP
E43A

DNMT3A
V897G and W409L

ERBB4
K191T

FANCA
Q376E

FGFR2
K196T, L647R, S299C and rearrangement

GABRA6
V32I

GATA4
amplification

HNF1A
D80E

IDH2
amplification

MAP3K13
L606V

MET
K80T

NOTCH2
N570T

NTRK2
L584V

NTRK3
amplification

PALB2
A900V

PTCH1
R1319C

RAD21
amplification

TSC1
E1101V

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APPENDIX Genes assayed in FoundationOne®Liquid CDx

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

ABL1 **Exons 4-9**	*ACVR1B*	***AKT1*** **Exon 3**	*AKT2*	*AKT3*	***ALK*** **Exons 20-29, Introns 18, 19**	*ALOX12B*	*AMER1* (FAM123B)	***APC***
AR	***ARAF*** **Exons 4, 5, 7, 11, 13, 15, 16**	*ARFRP1*	*ARID1A*	*ASXL1*	***ATM***	***ATR***	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*
BCOR	*BCORL1*	*BCR** Introns 8, 13, 14	***BRAF*** **Exons 11-18,** Introns 7-10	***BRCA1*** Introns 2, 7, 8, 12, 16, 19, 20	***BRCA2*** Intron 2	*BRD4*	*BRIP1*	*BTG1*
BTG2	***BTK*** **Exons 2, 15**	*C11orf30* (EMSY)	*C17orf39* (GID4)	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*
CCND1	*CCND2*	*CCND3*	*CCNE1*	*CD22*	*CD70*	*CD74** Introns 6-8	*CD79A*	*CD79B*
CD274 **(PD-L1)**	*CDC73*	***CDH1***	***CDK12***	***CDK4***	***CDK6***	*CDK8*	*CDKN1A*	*CDKN1B*
CDKN2A	*CDKN2B*	*CDKN2C*	*CEBPA*	*CHEK1*	***CHEK2***	*CIC*	*CREBBP*	***CRKL***
CSF1R	*CSF3R*	*CTCF*	*CTNNA1*	***CTNNB1*** **Exon 3**	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*
DAXX	*DDR1*	***DDR2*** **Exons 5, 17, 18**	*DIS3*	*DNMT3A*	*DOT1L*	*EED*	***EGFR*** **Introns 7,** 15**, 24-27**	*EP300*
EPHA3	*EPHB1*	*EPHB4*	***ERBB2***	***ERBB3*** **Exons 3, 6, 7, 8, 10, 12, 20, 21, 23, 24, 25**	*ERBB4*	*ERCC4*	*ERG*	***ERRFI1***
ESR1 **Exons 4-8**	*ETV4** Intron 8	*ETV5** Introns 6, 7	***ETV6**** **Introns 5, 6**	*EWSR1** Introns 7-13	***EZH2*** **Exons 4, 16, 17, 18**	*EZR** Introns 9-11	*FAM46C*	*FANCA*
FANCC	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*	*FGF14*	*FGF19*
FGF23	*FGF3*	*FGF4*	*FGF6*	***FGFR1*** Introns 1, 5, **Intron 17**	***FGFR2*** Intron 1, **Intron 17**	***FGFR3*** **Exons 7, 9 (alternative designation exon 10), 14, 18, Intron 17**	*FGFR4*	*FH*
FLCN	*FLT1*	***FLT3*** **Exons 14, 15, 20**	***FOXL2***	*FUBP1*	*GABRA6*	*GATA3*	*GATA4*	*GATA6*
GNA11 **Exons 4, 5**	*GNA13*	***GNAQ*** **Exons 4, 5**	***GNAS*** **Exons 1, 8**	*GRM3*	*GSK3B*	*H3F3A*	*HDAC1*	*HGF*
HNF1A	***HRAS*** **Exons 2, 3**	*HSD3B1*	*ID3*	***IDH1*** **Exon 4**	***IDH2*** **Exon 4**	*IGF1R*	*IKBKE*	*IKZF1*
INPP4B	*IRF2*	*IRF4*	*IRS2*	*JAK1*	***JAK2*** **Exon 14**	***JAK3*** **Exons 5, 11, 12, 13, 15, 16**	*JUN*	*KDM5A*
KDM5C	*KDM6A*	*KDR*	*KEAP1*	*KEL*	***KIT*** **Exons 8, 9, 11, 12, 13, 17,** Intron 16	*KLHL6*	*KMT2A* (MLL) Introns 6, 8-11, Intron 7	*KMT2D* (MLL2)

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APPENDIX Genes assayed in FoundationOne®Liquid CDx

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

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

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite (MS) status

Blood Tumor Mutational Burden (bTMB)

Tumor Fraction

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

CE IVD

ABOUT FOUNDATIONONE LIQUID CDx

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

Please refer to technical information for performance specification details.

INTENDED USE

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

TEST PRINCIPLES

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

THE REPORT

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

QUALIFIED ALTERATION CALLS (EQUIVOCAL)

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

RANKING OF THERAPIES AND CLINICAL TRIALS

Ranking of Therapies in Summary Table

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

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

LIMITATIONS

1. For *in vitro* diagnostic use.
2. For prescription use only. This test must be ordered by a qualified medical professional in accordance with clinical laboratory regulations.
3. A negative result does not rule out the presence of a mutation below the limits of detection of the assay. Patients for whom no companion diagnostic alterations are detected should be considered for confirmation with an appropriately validated tumor tissue test, if available.
4. The FoundationOne Liquid CDx assay does not detect heterozygous deletions.
5. The test is not intended to provide information on cancer predisposition.
6. Performance has not been validated for cfDNA input below the specified minimum input.
7. Tissue TMB and blood TMB (bTMB) are estimated from the number of synonymous and nonsynonymous single-nucleotide variants (SNVs) and insertions and deletions (indels) per area of coding genome sampled, after the removal of known and likely oncogenic driver events and germline SNPs. Tissue TMB is calculated based on variants with an allele frequency of ≥5%, and bTMB is calculated based on variants with an allele frequency of ≥0.5%.
8. Tumor fraction is the percentage of circulating-tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample. The tumor fraction estimate is computationally derived from observed aneuploid instability in the sample.
9. Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the tumor genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor. The MSI algorithm is based on genome wide analysis of 1765 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines for solid tissue testing.
10. Genomic findings from circulating cell-free DNA (cfDNA) may originate from circulating tumor DNA fragments, germline alterations, or non-tumor somatic alterations, such as clonal hematopoiesis of indeterminate potential (CHIP). Genes with alterations that may be derived from CHIP include, but are not limited to: *ASXL1*, *ATM*, *CBL*, *CHEK2*, *DNMT3A*, *JAK2*, *KMT2D* (*MLL2*), *MPL*, *MYD88*, *SF3B1*, *TET2*, *TP53*, and *U2AF1*.
11. Alterations reported may include somatic (not

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inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. If a reported alteration is suspected to be germline, confirmatory testing should be considered in the appropriate clinical context.

12. The test is not intended to replace germline testing or to provide information about cancer predisposition.

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE THE RESPONSIBILITY OF PHYSICIAN

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

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

SELECT ABBREVIATIONS

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

MR Suite Version 5.0.0

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Electronically signed by Erik Williams, M.D. | 04 November 2021
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Electronically signed by Erik Williams, M.D. | 04 November 2021
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