FOUNDATIONONE®CDx

PATIENT	TUMOR TYPE	REPORT DATE
Wu, Chih-Liang	Anus squamous cell carcinoma	10 Sep 2022
	COUNTRY CODE	ORDERED TEST #
	TW	ORD-1445643-01

ABOUT THE TEST FoundationOne®CDx is a next-generation sequencing (NGS) based assay that identifies genomic findings within hundreds of cancer-related genes.

PATIENT
DISEASE Anus squamous cell carcinoma
NAME Wu, Chih-Liang
DATE OF BIRTH 12 March 1950
SEX Male
MEDICAL RECORD # 8879161

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

SPECIMEN
SPECIMEN SITE Anus
SPECIMEN ID S111-31320 A (PF22097)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 12 August 2022
SPECIMEN RECEIVED 30 August 2022

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 0 Muts/Mb

Genomic Findings

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

CCND1 amplification - equivocal†
C11orf30 (EMSY) amplification
CUL4A amplification - equivocal†
FGF19 amplification - equivocal†
FGF3 amplification - equivocal†
FGF4 amplification - equivocal†
GATA6 amplification - equivocal†

† See About the Test in appendix for details.

Report Highlights

- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 8)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Microsatellite status - MS-Stable	**No therapies or clinical trials.** See Biomarker Findings section
Tumor Mutational Burden - 0 Muts/Mb	**No therapies or clinical trials.** See Biomarker Findings section

GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
CCND1 **-** amplification - equivocal	none	none
6 Trials see p. 8		

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2022 Foundation Medicine, Inc. All rights reserved.

Electronically signed by Giles Maule, M.D., Ph.D | 10 September 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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 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 agents 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 exhaustive. Neither the therapeutic agents 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.

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2022 Foundation Medicine, Inc. All rights reserved.

BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors[1-3], including approved therapies nivolumab and pembrolizumab[4]. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, p=0.001)[5].

FREQUENCY & PROGNOSIS

A study of 8 patients with anal squamous cell carcinoma (SCC), 4 who experienced CR to chemoradiotherapy (CRT) and 4 whose tumors were CRT resistant, reported MSI-low in 2 cases (1 CRT-sensitive and 1 CRT-resistant) and MSS in the other 6; both MSI-low cases were HIV-positive[6]. A larger study also did not find MSI-high in any of 40 anal carcinoma cases[7]. Published data investigating the prognostic implications of MSI in anal cancer are limited (PubMed, Jul 2022).

FINDING SUMMARY

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor[8]. Defective MMR and consequent MSI occur as a result of genetic or epigenetic inactivation of one of the MMR pathway proteins, primarily MLH1, MSH2, MSH6, or PMS2[8-10]. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers[11-13]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[8,10,12-13].

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2022 Foundation Medicine, Inc. All rights reserved.

Electronically signed by Giles Maule, M.D., Ph.D | 10 September 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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

BIOMARKER

Tumor Mutational Burden

RESULT
0 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[14-16], anti-PD-1 therapies[14-17], and combination nivolumab and ipilimumab[18-23]. In multiple pan-tumor studies, increased tissue tumor mutational burden (TMB) was associated with sensitivity to immune checkpoint inhibitors[14-17,24-28]. In the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors, significant improvement in ORR was observed for patients with TMB ≥10 Muts/Mb (as measured by this assay) compared with those with TMB <10 Muts/Mb in a large cohort that included multiple tumor types[24]; similar findings were observed in the KEYNOTE 028 and 012 trials[17]. At the same TMB cutpoint, retrospective analysis of patients with solid tumors treated with any checkpoint inhibitor identified that tissue TMB scores ≥ 10 Muts/Mb were associated with prolonged time to treatment failure compared with scores <10 muts/Mb (HR=0.68)[28]. For patients with solid tumors treated with nivolumab plus ipilimumab in the CheckMate 848 trial, improved responses were observed in patients with a tissue TMB ≥ 10 Muts/Mb independent of blood TMB at any cutpoint in matched samples[29]. However, support for higher TMB thresholds and efficacy was observed in the prospective Phase 2 MyPathway trial of atezolizumab for patients with pan-solid tumors, where improved ORR and DCR was seen in patients with TMB ≥ 16 Muts/Mb than those with TMB ≥ 10 and <16 Muts/Mb[27]. Similarly, analyses across several solid tumor types reported that patients with higher TMB (defined as ≥16-20 Muts/Mb) achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy compared with patients with higher TMB treated with chemotherapy[30] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[15]. In the Phase 2 POD1UM-202 study of retifanlimab, an investigational anti-PD-1 antibody, patients with squamous carcinoma of the anal canal experienced an ORR of 14% (13/94, 1 CR), median PFS of 2.3 months, and median OS of 10.1 months[31].

FREQUENCY & PROGNOSIS

Squamous cell carcinoma (SCC) of unknown primary harbors a median tumor mutational burden (TMB) of 7.6 Muts/Mb, and 22% of cases have high TMB (>20 Muts/Mb)[32]. High TMB has been reported frequently in skin SCC (67% of cases)[32-33]; in 10% of lung SCC[33]; 8-13% of head and neck SCC cases and non-small cell lung carcinoma, including lung SCC cases[32]; and in additional SCC cases, including urothelial (12%), cervical (6.5%), anal (3.8%), and esophageal (2.1%)[33]. One study of anal carcinomas reported a median tumor mutational burden (mTMB) of 4.4 Muts/Mb, with 14% of cases (17/125) harboring a TMB ≥10 Muts/Mb[34]. Similarly, another study reported that anal squamous cell carcinoma harbors an mTMB of 5.4 Muts/Mb, with 5.6% of cases possessing high TMB (>20 Muts/Mb)[32]. For patients with squamous cell carcinoma (SCC) treated with PD-L1/PD-1 inhibitors, a Kaplan-Meier analysis showed a significant association for patients with high tumor mutational burden (TMB) with longer time to treatment failure (9.9 vs. 4.4 months)[33]. In the majority of cutaneous SCC cases, high mutational burden has been attributed to UV exposure rather than defective DNA mismatch repair or polymerase activity[35-36], although one study reported a small number of cutaneous SCC cases (4/39) harboring a mutation signature similar to that of human papillomavirus-positive head and neck SCC[36]. In patients with non-small cell lung cancer (NSCLC), TMB is similar between cases with squamous and non-squamous histology[37], and increased TMB is associated with higher tumor grade and poor prognosis[38], 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%) or KRAS (9.4%)[37]. Although some studies have reported a lack of association between smoking and increased TMB in NSCLC[38-39], several other large studies did find a strong prognostic association[40-43]. In 1 study, OS did not differ between patients with advanced anal cancer harboring tumor mutational burden (TMB)-high (≥10 Muts/Mb) or TMB-low (<10 Muts/Mb) who were not previously treated with immunotherapy[34].

FINDING SUMMARY

Tumor mutation burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[44-45] and cigarette smoke in lung cancer[46-47], treatment with temozolomide-based chemotherapy in glioma[48-49], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[50-54], and microsatellite instability (MSI)[50,53-54]. This sample harbors a TMB level associated with lower rates of clinical benefit from treatment with PD-1- or PD-L1-targeting immune checkpoint inhibitors compared with patients with tumors harboring higher TMB levels, based on several studies in multiple solid tumor types[15-16,24].

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2022 Foundation Medicine, Inc. All rights reserved.

Electronically signed by Giles Maule, M.D., Ph.D | 10 September 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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

GENE
CCND1

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Amplification or overexpression of CCND1 may predict sensitivity to CDK4/6 inhibitors, such as abemaciclib, palbociclib, and ribociclib[55-60], although as monotherapy these agents have shown limited activity in tumor types other than breast cancer[59,61]. In refractory advanced solid tumors with CCND1 (n=39) or CCND3 (n=1) amplification and retinoblastoma protein expression, palbociclib resulted in SD for 39% (14/36) of patients and a median PFS of 1.8 months in the NCI-MATCH trial[62]; 4 patients (13%, 4/36 overall) with squamous cell carcinomas (lung, esophageal, or laryngeal) or adenoid cystic carcinoma experienced prolonged SD in this study[62]. Among 9 patients with CCND1-amplified advanced solid tumors, 1 patient with bladder cancer responded to ribociclib in a Phase 2 trial[63].

FREQUENCY & PROGNOSIS

The 11q13 amplicon, containing CCND1, FGF3, FGF4, and FGF10, was detected in 9% of anal squamous cell carcinomas (SCCs) in one study involving 70 patients[64]. Another study did not detect CCND1 amplification in any of 24 anal SCCs analyzed; however, weak cyclin D1 expression was observed in 8% of cases[65]. Other studies have reported cyclin D1 expression in approximately 33% (7/21) to 34% (33/98) of anal carcinoma samples[66-67]. Published data investigating the prognostic implications of CCND1 alterations in anal carcinoma are limited (PubMed, Jul 2022).

FINDING SUMMARY

CCND1 encodes cyclin D1, a binding partner of the kinases CDK4 and CDK6, that regulates RB activity and cell cycle progression. Amplification of CCND1 has been positively correlated with cyclin D1 overexpression[68] and may lead to excessive proliferation[69-70].

GENE
C11orf30 (EMSY)

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

EMSY overexpression in breast cancer cell lines has been reported to mimic the effects of inactivating BRCA2 mutations[71]. Unlike BRCA2 inactivation, which predicts sensitivity to DNA repair-associated inhibitors such as the PARP inhibitor olaparib[72-73], EMSY amplification in breast cancer lines was not associated with enhanced sensitivity to this drug in one preclinical study[74]. There are no therapies that target EMSY alterations.

FREQUENCY & PROGNOSIS

In the TCGA datasets, EMSY amplification has been most frequently observed in ovarian carcinoma (8%)[75], breast invasive carcinoma (6%)[76], esophageal carcinoma (5%)(cBioPortal, 2022), and head and neck squamous cell carcinoma (3.5%)[77-79]. EMSY overexpression has been primarily reported in breast and high grade ovarian cancers, where it is implicated in BRCA2 inactivation and correlates with poor prognosis or advanced disease[74,80-86]. The consequences of EMSY alterations in other solid tumors or hematologic malignancies have not been studied in detail in the scientific literature (PubMed, 2022).

FINDING SUMMARY

EMSY, also known as C11orf30, encodes a BRCA2-interacting protein with roles in transcriptional regulation[86-87]. Preclinical studies have suggested that EMSY binds to and suppresses the function of BRCA2, and EMSY overexpression may therefore mimic BRCA2 inactivation[71,86]. Amplification of the EMSY gene correlates with increased mRNA expression[74,88], although conflicting data have been reported[89]. The functional consequences of other EMSY alterations have not been extensively studied (PubMed, 2022).

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2022 Foundation Medicine, Inc. All rights reserved.

GENE
CUL4A

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies available to target CUL4A alterations in cancer. Preclinical studies have suggested association of CUL4A expression in cancer cell lines with increased sensitivity to trabectedin[90] or thalidomide[91] and reduced sensitivity to cisplatin[92-93]; gemcitabine[94-95]; or P-gp substrate drugs paclitaxel, vincristine, and adriamycin[96], but clinical data supporting these findings are limited.

FREQUENCY & PROGNOSIS

CUL4A amplification and/or overexpression has been reported in breast carcinoma[97-102], lung carcinoma[103-105], gastric carcinoma[101,106-107], colorectal carcinoma (CRC)[101,108-109], hepatocellular carcinoma (HCC)[110-111], intrahepatic cholangiocarcinoma[112-113], malignant pleural mesothelioma[114-115], ovarian carcinoma[101,116], osteosarcoma[117-118], and other tumor types[91,119-120]. In several of these studies, increased CUL4A mRNA and/or protein expression was significantly associated with adverse clinicopathologic features, such as clinical stage, pathological grade, or distant metastasis[91,101,105-106,108-109,111,117-119]. High CUL4A expression has been associated with inferior survival in patients with breast cancer [overall survival (OS), hazard ratio (HR) = 2.10; disease-free survival (DFS), HR = 1.92][99], lung cancer [OS, HR = 1.610; progression-free survival (PFS), HR = 1.739][105], intrahepatic cholangiocarcinoma (DFS, HR = 1.688)[113], or invasive ovarian cancer (OS, HR = 2.387; DFS, HR = 3.5)[116] in multivariate analyses.

FINDING SUMMARY

CUL4A encodes cullin 4A, a core component of an E3 ubiquitin ligase complex that targets proteins for ubiquitin-mediated degradation, regulating critical processes such as cell cycle progression and maintenance of genomic stability[121-123]. CUL4A overexpression increases cell proliferation and transformation[91,101,109,114,124-126]. Amplification of CUL4A or the 13q34 genomic region encompassing CUL4A has been correlated with increased CUL4A mRNA and/or protein expression in several cancer types[100,103,105,112,114-115].

GENE
FGF19

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

A Phase 1 study of the FGFR4 inhibitor fisogatinib (BLU-554) for patients with advanced hepatocellular carcinoma (HCC) reported a 17% ORR (11/66, 1 CR, ongoing for >1.5 years) and 3.3-month PFS for FGF19 IHC–positive patients; patients with negative or unknown FGF19 IHC scores experienced poorer outcomes (0% ORR, 2.3-month PFS)[127]. A Phase 1/2 study evaluating another FGFR4 inhibitor, FGF401, demonstrated an ORR of 7.5% (4/53) and SD rate of 53% (28/53) for patients with HCC[128]. A Phase 1 study of the FGFR4 inhibitor H3B-6527 reported a 17% ORR (OS of 10.3 months, 46% clinical benefit rate) among patients with HCC; enrollment of patients with intrahepatic cholangiocarcinoma (ICC) was suspended due to efficacy[129]. A retrospective analysis reported that 50% (2/4) of patients with HCC harboring FGF19 amplification experienced a CR to sorafenib[130], though another retrospective study found patients with higher pretreatment serum levels of FGF19 experienced reduced benefit from sorafenib compared with those with lower serum FGF19 (PFS of 86 vs. 139 days, OS of 353 vs. 494 days); no difference was observed for lenvatinib[131]. A patient with head and neck squamous cell carcinoma (HNSCC) with 11q13 (FGF3, FGF4, FGF19) and 12p13 (FGF6 and FGF23) amplification experienced a CR lasting 9 months from a pan-FGFR inhibitor[132].

FREQUENCY & PROGNOSIS

For patients with solid tumors, FGF19 amplification has been reported most frequently in breast cancer (17%), head and neck cancer (12%), lung squamous cell carcinoma (SCC; 12%), and urothelial carcinoma cancer (11%)[133-135]. FGF19 mutations are rare in solid tumors[133]. FGF19 expression or amplification has been associated with poor prognosis in hepatocellular carcinoma (HCC)[136-137], and in prostate cancer following radical prostatectomy[138]. Studies suggest FGF19 expression may also be a poor prognostic indicator in head and neck squamous cell carcinoma (HNSCC)[139] and lung SCC[140].

FINDING SUMMARY

FGF19 encodes fibroblast growth factor 19, an FGFR4 ligand involved with bile acid synthesis and hepatocyte proliferation in the liver[141-142]. FGF19 lies in a region of chromosome 11q13 that also contains FGF3, FGF4, and CCND1; this region is frequently amplified in a diverse range of malignancies[143]. Correlation between FGF19 amplification and protein expression has been reported in hepatocellular carcinoma (HCC)[144], lung squamous cell carcinoma[140,145], and head and neck squamous cell carcinoma (HNSCC)[139], but was not observed in other cancers[131,146].

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2022 Foundation Medicine, Inc. All rights reserved.

GENE
FGF3

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies that directly address genomic alterations in FGF3. Inhibitors of FGF receptors, however, are undergoing clinical trials in a number of different cancers. Limited data suggest that pan-FGFR inhibitors show activity in FGF amplified cancers; following treatment with a selective pan-FGFR inhibitor, a patient with head and neck squamous cell carcinoma (HNSCC) and amplification of 11q13 (FGF3, FGF4, FGF19) and 12p13 (FGF6 and FGF23) experienced a radiologic CR[147].

FREQUENCY & PROGNOSIS

FGF3 lies in a region of chromosome 11q13 that also contains FGF19, FGF4, and CCND1, the latter gene encoding cyclin D1, a key regulator of cell cycle progression. This chromosomal region is frequently amplified in a diverse range of malignancies[69].

FINDING SUMMARY

FGF3 encodes fibroblast growth factor 3, a growth factor that plays a central role in development of the inner ear. Germline mutations in FGF3 give rise to an autosomal recessive syndrome characterized by microdontia, deafness, and complete lack of inner ear structures[148].

GENE
FGF4

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

FGF4 amplification and overexpression was associated with cell sensitivity to the multikinase inhibitor sorafenib in preclinical studies[149-150] and amplification of FGF4/FGF3 in HCC significantly correlated with patient response to sorafenib (p=0.006)[149]. Limited data suggest that pan-FGFR inhibitors show activity in FGF amplified cancers; following treatment with a selective pan-FGFR inhibitor, a patient with head and neck squamous cell carcinoma (HNSCC) and amplification of 11q13 (FGF3, FGF4, FGF19) and 12p13 (FGF6 and FGF23) experienced a radiologic CR[147].

FREQUENCY & PROGNOSIS

FGF4 lies in a region of chromosome 11q13 that also contains FGF19, FGF3, and CCND1, the latter gene encoding cyclin D1, a key regulator of cell cycle progression. This chromosomal region is frequently amplified in a diverse range of malignancies[69] including esophageal carcinoma (35%), head and neck squamous cell carcinoma (HNSCC; 24%), breast invasive carcinoma (14%), lung squamous cell carcinoma (13%), cholangiocarcinoma (11%), bladder urothelial carcinoma (10%), stomach adenocarcinoma (7%), skin melanoma (5%), and hepatocellular carcinoma (HCC; 5%), however FGF4 amplification is rare in hematopoietic and lymphoid malignancies, reported in less than 1% of samples analyzed (cBioPortal, Jan 2022)[78-79].

FINDING SUMMARY

FGF4 encodes fibroblast growth factor 4, which plays a central role in development of the teeth[151] and acts synergistically with other FGFs and SHH (sonic hedgehog) to regulate limb outgrowth in vertebrate development[152]. FGF4 lies in a region of chromosome 11q13 that also contains FGF19, FGF3, and CCND1, the latter gene encoding cyclin D1, a key regulator of cell cycle progression. Amplification of FGF4, along with that of FGF3, FGF19, and CCND1, has been reported in a variety of cancers[69,149,153-156] and may confer sensitivity to the multi-kinase inhibitor sorafenib[149].

GENE
GATA6

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in GATA6. Patients with GATA6-high pancreatic tumors exhibited better clinical outcomes following treatment with adjuvant chemotherapy (p=0.003) or first-line folfirinox (HR=1.90, p=0.025) treatment compared with low GATA6 expressing tumors, while no difference was observed for patients treated with gemcitabine[157-158].

FREQUENCY & PROGNOSIS

Amplification of the GATA6 locus, 18q11.2, has been reported with highest incidences in esophageal adenocarcinomas (21%, 18/85) and pancreatobiliary carcinomas (19%, 7/37)[159-160], and at lower rates in small intestine cancer (5.5%)[161], urothelial bladder carcinoma (3.9%), lung adenocarcinoma (1.7%), and ovarian carcinoma (1.8%)[75,162-163]. While low GATA6 expression correlated with poor prognosis for patients with non-small cell lung cancer (NSCLC)[164], gastric cancer[165], bladder cancer[166], or esophageal adenocarcinomas without neoadjuvant treatment[167], high GATA6 expression has been associated with poor outcome for patients with colon cancer[168], breast cancer[169], ovarian cancer[170], cholangiocarcinoma[171], and NSCLC following EGFR-TKI treatment[172].

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[173]. GATA6 has been described as both a tumor suppressor and an oncogene, which may be dependent on the tumor type.

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2022 Foundation Medicine, Inc. All rights reserved.

NOTE 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. 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 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. Or, visit https://www.foundationmedicine.com/genomic-testing#support-services.

GENE
CCND1

ALTERATION
amplification - equivocal

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

NCT04282031

PHASE 1/2

A Study of BPI-1178 in Patients With Advanced Solid Tumor and HR+/HER2- Breast Cancer

TARGETS
CDK6, CDK4, ER, Aromatase

LOCATIONS: Shanghai (China)

NCT04801966

PHASE NULL

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

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

LOCATIONS: Melbourne (Australia)

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT04116541

PHASE 2

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

TARGETS
CDK6, CDK4, MDM2, MET, ROS1, RET, VEGFRs

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

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2022 Foundation Medicine, Inc. All rights reserved.

NCT05252416

PHASE 1/2

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

TARGETS
ER, CDK4, CDK6, CDK2

LOCATIONS: Massachusetts, Texas, Florida

NCT02896335

PHASE 2

Palbociclib In Progressive Brain Metastases

TARGETS
CDK4, CDK6

LOCATIONS: Massachusetts

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2022 Foundation Medicine, Inc. All rights reserved.

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.

EED
amplification

IRS2
A512T

MEN1
amplification

MKNK1
R443H

POLD1
V124A

SPEN
S2306del

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2022 Foundation Medicine, Inc. All rights reserved.

FoundationOne CDx is designed to include genes known to be somatically altered in human solid tumors that are validated targets for therapy, either approved or in clinical trials, and/or that are unambiguous drivers of oncogenesis based on current knowledge. The current assay interrogates 324 genes as well as introns of 36 genes involved in rearrangements. The assay will be updated periodically to reflect new knowledge about cancer biology.

DNA GENE LIST: ENTIRE CODING SEQUENCE FOR THE DETECTION OF BASE SUBSTITUTIONS, INSERTION/DELETIONS, AND COPY NUMBER ALTERATIONS

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B or WTX)*	
APC	*AR*	*ARAF*	*ARFRP1*	*ARID1A*	*ASXL1*	*ATM*	*ATR*	*ATRX*
AURKA	*AURKB*	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*
BCL6	*BCOR*	*BCORL1*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*
BTG2	*BTK*	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	*CCND1*	*CCND2*
CCND3	*CCNE1*	*CD22*	*CD274 (PD-L1)*	*CD70*	*CD79A*	*CD79B*	*CDC73*	*CDH1*
CDK12	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*	*CDKN2C*
CEBPA	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CSF1R*	*CSF3R*	*CTCF*
CTNNA1	*CTNNB1*	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*	*DDR2*
DIS3	*DNMT3A*	*DOT1L*	*EED*	*EGFR*	*EMSY (C11orf30)*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
FANCA	*FANCC*	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*	*FGF14*
FGF19	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*	*FGFR4*
FH	*FLCN*	*FLT1*	*FLT3*	*FOXL2*	*FUBP1*	*GABRA6*	*GATA3*	*GATA4*
GATA6	*GID4 (C17orf39)*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3-3A (H3F3A)*
HDAC1	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*ID3*	*IDH1*	*IDH2*	*IGF1R*
IKBKE	*IKZF1*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JUN	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*	*KIT*	*KLHL6*
KMT2A (MLL)	*KMT2D (MLL2)*	*KRAS*	*LTK*	*LYN*	*MAF*	*MAP2K1 (MEK1)*	*MAP2K2 (MEK2)*	*MAP2K4*
MAP3K1	*MAP3K13*	*MAPK1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*	*MEN1*
MERTK	*MET*	*MITF*	*MKNK1*	*MLH1*	*MPL*	*MRE11 (MRE11A)*	*MSH2*	*MSH3*
MSH6	*MST1R*	*MTAP*	*MTOR*	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*
NBN	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2*	*NOTCH3*
NPM1	*NRAS*	*NSD2 (WHSC1 or MMSET)*		*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*
P2RY8	*PALB2*	*PARP1*	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1 (PD-1)*	*PDCD1LG2 (PD-L2)*
PDGFRA	*PDGFRB*	*PDK1*	*PIK3C2B*	*PIK3C2G*	*PIK3CA*	*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*	*RARA*	*RB1*	*RBM10*
REL	*RET*	*RICTOR*	*RNF43*	*ROS1*	*RPTOR*	*SDHA*	*SDHB*	*SDHC*
SDHD	*SETD2*	*SF3B1*	*SGK1*	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*
SNCAIP	*SOCS1*	*SOX2*	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*	*STAT3*
STK11	*SUFU*	*SYK*	*TBX3*	*TEK*	*TENT5C (FAM46C)*		*TET2*	*TGFBR2*
TIPARP	*TNFAIP3*	*TNFRSF14*	*TP53*	*TSC1*	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*
VHL	*WT1*	*XPO1*	*XRCC2*	*ZNF217*	*ZNF703*			

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	*BCL2*	*BCR*	*BRAF*	*BRCA1*	*BRCA2*	*CD74*	*EGFR*	*ETV4*
ETV5	*ETV6*	*EWSR1*	*EZR*	*FGFR1*	*FGFR2*	*FGFR3*	*KIT*	*KMT2A (MLL)*
MSH2	*MYB*	*MYC*	*NOTCH2*	*NTRK1*	*NTRK2*	*NUTM1*	*PDGFRA*	*RAF1*
RARA	*RET*	*ROS1*	*RSPO2*	*SDC4*	*SLC34A2*	*TERC**	*TERT***	*TMPRSS2*

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Homologous Recombination status
Loss of Heterozygosity (LOH) score
Microsatellite (MS) status
Tumor Mutational Burden (TMB)

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2022 Foundation Medicine, Inc. All rights reserved.

FoundationOne 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. CE

ABOUT FOUNDATIONONE CDX

FoundationOne CDx was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne 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: www.rochefoundationmedicine.com/f1cdxtech.

INTENDED USE

FoundationOne®CDx (F1CDx) is a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI), tumor mutational burden (TMB), and for selected forms of ovarian cancer, loss of heterozygosity (LOH) score, using DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with therapies in accordance with approved therapeutic product labeling. Additionally, F1CDx 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 solid malignant neoplasms.

TEST PRINCIPLE

FoundationOne CDx will be performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The proposed assay will employ a single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50-1000 ng of which will undergo whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons. The assay therefore includes detection of alterations in a total of 324 genes.

Using an Illumina® HiSeq platform, hybrid capture–selected libraries will be sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data will be processed using a customized analysis pipeline designed to accurately detect all classes of genomic alterations, including base substitutions, indels, focal copy number amplifications, homozygous gene deletions, and selected genomic rearrangements (e.g.,gene fusions). Additionally, genomic signatures including loss of heterozygosity (LOH), microsatellite instability (MSI) and tumor mutational burden (TMB) will be reported.

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. The F1CDx report may be used as an aid to inform molecular eligibility for clinical trials. 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.

Diagnostic Significance

FoundationOne CDx identifies alterations to select cancer-associated genes or portions of genes (biomarkers). In some cases, the Report also highlights selected negative test results regarding biomarkers of clinical significance.

Qualified Alteration Calls (Equivocal and Subclonal)

An alteration denoted as "amplification – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence that the copy number of a gene exceeds the threshold for identifying copy number amplification. The threshold used in FoundationOne CDx for identifying a copy number amplification is four (4) for *ERBB2* and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence for homozygous deletion of the gene in question. An alteration denoted as "subclonal" is one that the FoundationOne CDx analytical methodology has identified as being present in <10% of the assayed tumor DNA.

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.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations

1. In the fractional-based MSI algorithm, a tumor specimen will be categorized as MSI-H, MSS, or MS-Equivocal according to the fraction of microsatellite loci determined to be altered or unstable (i.e., the fraction unstable loci score). In the F1CDx assay, MSI is evaluated based on a genome-wide analysis across >2000 microsatellite loci. For a given microsatellite locus, non-somatic alleles are discarded, and the microsatellite is categorized as unstable if remaining alleles differ from the reference genome. The final fraction unstable loci score is calculated as the number of unstable microsatellite loci divided by the number of evaluable microsatellite loci. The MSI-H and MSS cut-off thresholds were determined by

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2022 Foundation Medicine, Inc. All rights reserved.

analytical concordance to a PCR comparator assay using a pan-tumor FFPE tissue sample set. Patients with results categorized as "MS-Stable" with median exon coverage <300X, "MS-Equivocal," or "Cannot Be Determined" should receive confirmatory testing using a validated orthogonal (alternative) method.

2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.
3. Homologous Recombination status may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas (Coleman et al., 2017; 28916367). Samples with deleterious *BRCA1/2* alteration and/or Loss of Heterozygosity (LOH) score ≥ 16% will be reported as "HRD Positive" and samples with absence of these findings will be reported as "HRD Not Detected," agnostic of potential secondary *BRCA1/2* reversion alterations. Certain potentially deleterious missense or small in-frame deletions in *BRCA1/2* may not be classified as deleterious and, in the absence of an elevated LOH profile, samples with such mutations may be classified as "HRD Not Detected." A result of "HRD Not Detected" does not rule out the presence of a *BRCA1/2* alteration or an elevated LOH profile outside the assay performance characteristic limitations.
4. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.
5. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
6. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
7. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

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.

VARIANT ALLELE FREQUENCY

Variant Allele Frequency (VAF) represents the fraction of sequencing reads in which the variant is observed. This attribute is not taken into account for therapy inclusion, clinical trial matching, or interpretive content. Caution is recommended in interpreting VAF to indicate the potential germline or somatic origin of an alteration, recognizing that tumor fraction and tumor ploidy of samples may vary.

Precision of VAF for base substitutions and indels

BASE SUBSTITUTIONS	%CV*
Repeatability	5.11 - 10.40
Reproducibility	5.95 - 12.31
INDELS	**%CV***
Repeatability	6.29 - 10.00
Reproducibility	7.33 - 11.71

**Interquartile Range = 1st Quartile to 3rd Quartile*

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 >10%, 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

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2022 Foundation Medicine, Inc. All rights reserved.

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, CBL, 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.

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 CDx.

TREATMENT DECISIONS ARE 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 or variant characteristics may result in reduced sensitivity. FoundationOne CDx is performed using DNA derived from tumor, 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) 7.1.0

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of data conversion. It is suggested the hospital to verify the output and validate the suitability of use.

The median exon coverage for this sample is 862x

© 2022 Foundation Medicine, Inc. All rights reserved.

1. Gatalica Z, et al. Cancer Epidemiol. Biomarkers Prev. (2014) pmid: 25392179
2. Kroemer G, et al. Oncoimmunology (2015) pmid: 26140250
3. Lal N, et al. Oncoimmunology (2015) pmid: 25949894
4. Le DT, et al. N. Engl. J. Med. (2015) pmid: 26028255
5. Ayers et al., 2016; ASCO-SITC Abstract P60
6. Gervaz P, et al. Dis. Colon Rectum (2001) pmid: 11598481
7. Steiniche T, et al. Future Sci OA (2020) pmid: 32983568
8. Kocarnik JM, et al. Gastroenterol Rep (Oxf) (2015) pmid: 26337942
9. You JF, et al. Br. J. Cancer (2010) pmid: 21081928
10. Bairwa NK, et al. Methods Mol. Biol. (2014) pmid: 24623249
11. Boland CR, et al. Cancer Res. (1998) pmid: 9823339
12. Pawlik TM, et al. Dis. Markers (2004) pmid: 15528785
13. Boland CR, et al. Gastroenterology (2010) pmid: 20420947
14. Samstein RM, et al. Nat. Genet. (2019) pmid: 30643254
15. Goodman AM, et al. Mol. Cancer Ther. (2017) pmid: 28835386
16. Goodman AM, et al. Cancer Immunol Res (2019) pmid: 31405947
17. Cristescu R, et al. Science (2018) pmid: 30309915
18. Ready N, et al. J. Clin. Oncol. (2019) pmid: 30785829
19. Hellmann MD, et al. N. Engl. J. Med. (2018) pmid: 29658845
20. Hellmann MD, et al. Cancer Cell (2018) pmid: 29657128
21. Hellmann MD, et al. Cancer Cell (2018) pmid: 29731394
22. Rozeman EA, et al. Nat Med (2021) pmid: 33558721
23. Sharma P, et al. Cancer Cell (2020) pmid: 32916128
24. Marabelle A, et al. Lancet Oncol. (2020) pmid: 32919526
25. Ott PA, et al. J. Clin. Oncol. (2019) pmid: 30557521
26. Cristescu R, et al. J Immunother Cancer (2022) pmid: 35101941
27. Friedman CF, et al. Cancer Discov (2022) pmid: 34876409
28. Sturgill EG, et al. Oncologist (2022) pmid: 35274716
29. Schenker at al., 2022; AACR Abstract 7845
30. Legrand et al., 2018; ASCO Abstract 12000
31. Rao et al., 2020; ESMO Abstract LBA42
32. Chalmers ZR, et al. Genome Med (2017) pmid: 28420421
33. Goodman AM, et al. Cancer Immunol Res (2019) pmid: 31003990
34. Shao C, et al. JAMA Netw Open (2020) pmid: 33119110
35. South AP, et al. J. Invest. Dermatol. (2014) pmid: 24662767
36. Pickering CR, et al. Clin. Cancer Res. (2014) pmid: 25303977
37. Spigel et al., 2016; ASCO Abstract 9017
38. Xiao D, et al. Oncotarget (2016) pmid: 27009843
39. Shim HS, et al. J Thorac Oncol (2015) pmid: 26200269
40. Govindan R, et al. Cell (2012) pmid: 22980976
41. Ding L, et al. Nature (2008) pmid: 18948947
42. Imielinski M, et al. Cell (2012) pmid: 22980975
43. Kim Y, et al. J. Clin. Oncol. (2014) pmid: 24323028
44. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
45. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
46. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
47. Rizvi NA, et al. Science (2015) pmid: 25765070
48. Johnson BE, et al. Science (2014) pmid: 24336570
49. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
50. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
51. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
52. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
53. Nature (2012) pmid: 22810696
54. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
55. Morschhauser F, et al. Haematologica (2020) pmid: 32381571
56. Flaherty KT, et al. Clin. Cancer Res. (2012) pmid: 22090362
57. Finn RS, et al. Lancet Oncol. (2015) pmid: 25524798
58. Infante JR, et al. Clin. Cancer Res. (2016) pmid: 27542767
59. Patnaik A, et al. Cancer Discov (2016) pmid: 27217383
60. Leonard JP, et al. Blood (2012) pmid: 22383795
61. Dickler MN, et al. Clin. Cancer Res. (2017) pmid: 28533223
62. Clark et al., 2019; AACR Abstract LB-010/2
63. Peguero et al., 2016; ASCO Abstract 2528
64. Chung JH, et al. Ann. Oncol. (2016) pmid: 27052656
65. Sheyn I, et al. Hum. Pathol. (1997) pmid: 9042789
66. Lê LH, et al. Am. J. Clin. Pathol. (2005) pmid: 15923158
67. Allal AS, et al. Br. J. Cancer (2004) pmid: 15292923
68. Elsheikh S, et al. Breast Cancer Res. Treat. (2008) pmid: 17653856
69. Fu M, et al. Endocrinology (2004) pmid: 15331580
70. Takahashi-Yanaga F, et al. Cell. Signal. (2008) pmid: 18023328
71. Cousineau I, et al. Mol. Genet. Genomics (2011) pmid: 21409565
72. Dedes KJ, et al. Cell Cycle (2011) pmid: 21487248
73. Ihnen M, et al. Mol. Cancer Ther. (2013) pmid: 23729402
74. Wilkerson PM, et al. J. Pathol. (2011) pmid: 21735447
75. Nature (2011) pmid: 21720365
76. Nature (2012) pmid: 23000897
77. Nature (2015) pmid: 25631445
78. Cerami E, et al. Cancer Discov (2012) pmid: 22588877
79. Gao J, et al. Sci Signal (2013) pmid: 23550210
80. Brown LA, et al. Genes Chromosomes Cancer (2008) pmid: 18314909
81. Brown LA, et al. Breast Cancer Res. Treat. (2010) pmid: 19636701
82. Altinisik J, et al. Mol. Biol. Rep. (2011) pmid: 20349280
83. Madjd Z, et al. Asian Pac. J. Cancer Prev. (2014) pmid: 24641409
84. Bane AL, et al. Breast Cancer Res. Treat. (2011) pmid: 21327470
85. Rodriguez C, et al. Clin. Cancer Res. (2004) pmid: 15355907
86. Hughes-Davies L, et al. Cell (2003) pmid: 14651845
87. Varier RA, et al. J. Biol. Chem. (2016) pmid: 26841866
88. van Hattem WA, et al. Int J Clin Exp Pathol (2008) pmid: 18787609
89. Shih IeM, et al. Proc. Natl. Acad. Sci. U.S.A. (2005) pmid: 16172393
90. García MJ, et al. Mol. Cancer Ther. (2013) pmid: 23364677
91. Ren S, et al. J. Mol. Med. (2012) pmid: 22422151
92. Yang YL, et al. J. Pathol. (2014) pmid: 24648314
93. Englinger B, et al. Br. J. Cancer (2017) pmid: 28095394
94. Hung MS, et al. J. Cell. Mol. Med. (2016) pmid: 26969027
95. Hung MS, et al. Oncol. Rep. (2015) pmid: 26503734
96. Wang Y, et al. Molecules (2013) pmid: 24368600
97. Chen LC, et al. Cancer Res. (1998) pmid: 9721878
98. Abba MC, et al. Cancer Res. (2007) pmid: 17483321
99. Schindl M, et al. Anticancer Res. () pmid: 17465225
100. Melchor L, et al. Breast Cancer Res. (2009) pmid: 19995430
101. Wang Y, et al. Cancer Res. (2014) pmid: 24305877
102. Pfefferle AD, et al. Dis Model Mech (2016) pmid: 27149990
103. Castillo SD, et al. J. Pathol. (2010) pmid: 20556744
104. Wang Y, et al. Mol. Cancer (2014) pmid: 25413624
105. Jia L, et al. J. Biol. Chem. (2017) pmid: 27974468
106. Deng J, et al. Oncotarget (2016) pmid: 26840256
107. Gong Y, et al. Biologics (2017) pmid: 28442889
108. Ren W, et al. Arch. Med. Res. (2016) pmid: 27418574
109. Sui X, et al. Onco Targets Ther (2017) pmid: 28223829
110. Yasui K, et al. Hepatology (2002) pmid: 12029633
111. Pan Y, et al. Sci Rep (2015) pmid: 26593394
112. Liu TT, et al. PLoS ONE (2015) pmid: 26684807
113. Huang G-, et al. BMC Cancer (2017) pmid: 28576144
114. Hung MS, et al. J. Cell. Mol. Med. (2011) pmid: 19929949
115. Yang YL, et al. J. Cell. Mol. Med. (2015) pmid: 26218750
116. Birner P, et al. J. Clin. Pathol. (2012) pmid: 22447918
117. Song J, et al. Int J Immunopathol Pharmacol (2015) pmid: 26055549
118. Li X, et al. Tumour Biol. (2016) pmid: 26715273
119. Xu Y, et al. J. Neurooncol. (2014) pmid: 24420924
120. Yang Y, et al. Tumour Biol. (2017) pmid: 28677427
121. Sang Y, et al. Oncotarget (2015) pmid: 26460955
122. Hannah J, et al. Gene (2015) pmid: 26344709
123. Sharma P, et al. Open Biol (2014) pmid: 24522884
124. Gupta A, et al. Int. J. Radiat. Oncol. Biol. Phys. (2002) pmid: 11849807
125. Li B, et al. Blood (2003) pmid: 12393421
126. Saucedo-Cuevas LP, et al. Oncotarget (2014) pmid: 24870930
127. Kim RD, et al. Cancer Discov (2019) pmid: 31575541
128. Chan et al., 2017; AACR Abstract CT106
129. Macarulla et al., 2021; ASCO Abstract 4090
130. Kaibori M, et al. Oncotarget (2016) pmid: 27384874
131. Kanzaki H, et al. Sci Rep (2021) pmid: 33674622
132. Dumbrava EI, et al. JCO Precis Oncol (2018) pmid: 31123723
133. Zehir A, et al. Nat. Med. (2017) pmid: 28481359
134. Nature (2012) pmid: 22960745
135. Robertson AG, et al. Cell (2017) pmid: 28988769
136. Miura S, et al. BMC Cancer (2012) pmid: 22309595
137. Kang HJ, et al. Liver Cancer (2019) pmid: 30815392
138. Nagamatsu H, et al. Prostate (2015) pmid: 25854696
139. Gao L, et al. Oncogene (2019) pmid: 30518874
140. Li F, et al. Oncogene (2020) pmid: 32111983
141. Xie MH, et al. Cytokine (1999) pmid: 10525310
142. Hagel M, et al. Cancer Discov (2015) pmid: 25776529
143. Int. J. Oncol. (2002) pmid: 12429977
144. Kan Z, et al. Genome Res. (2013) pmid: 23788652
145. Caruso S, et al. Gastroenterology (2019) pmid: 31063779
146. Sawey ET, et al. Cancer Cell (2011) pmid: 21397858
147. Dumbrava et al., 2018; doi/full/10.1200/PO.18.00100
148. Tekin M, et al. Am. J. Hum. Genet. (2007) pmid: 17236138
149. Arao T, et al. Hepatology (2013) pmid: 22890726
150. Yamada T, et al. BMC Cancer (2015) pmid: 25885470
151. Kratochwil K, et al. Genes Dev. (2002) pmid: 12502739
152. Scherz PJ, et al. Science (2004) pmid: 15256670

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2022 Foundation Medicine, Inc. All rights reserved.

153. Zaharieva BM, et al. J. Pathol. (2003) pmid: 14648664
154. Arai H, et al. Cancer Genet. Cytogenet. (2003) pmid: 14499691
155. Ribeiro IP, et al. Tumour Biol. (2014) pmid: 24477574
156. Schulze K, et al. Nat. Genet. (2015) pmid: 25822088
157. Duan K, et al. Sci Rep (2021) pmid: 34294813
158. Martinelli P, et al. Gut (2017) pmid: 27325420
159. Lin L, et al. Proc Natl Acad Sci U S A (2012) pmid: 22375031
160. Kwei KA, et al. PLoS Genet. (2008) pmid: 18535672
161. Takeda et al., 2022; ASCO GI Abstract 642
162. Nature (2014) pmid: 24476821
163. Nature (2014) pmid: 25079552
164. Chen W, et al. Front Oncol (2020) pmid: 32596145
165. Liu H, et al. Cell Death Dis (2019) pmid: 30674866
166. Wang C, et al. FASEB J (2020) pmid: 32103545
167. Plum PS, et al. J Cancer Res Clin Oncol (2021) pmid: 33300112
168. Shen F, et al. Oncol. Rep. (2013) pmid: 23784465
169. Song Y, et al. Exp Mol Pathol (2015) pmid: 26505174
170. Shen W, et al. Hum Pathol (2019) pmid: 30633927
171. Tian F, et al. Eur J Cancer (2013) pmid: 23313142
172. Ma R, et al. Cancer Biol Ther (2019) pmid: 31092103
173. Zheng R, et al. Genes Cancer (2010) pmid: 21779441

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2022 Foundation Medicine, Inc. All rights reserved.