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 Breast carcinoma (NOS)

DATE OF BIRTH 17 December 1957
SEX Female
MEDICAL RECORD # Not given

PHYSICIAN

MEDICAL FACILITY Arias Stella
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 317319
PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN SITE Breast
SPECIMEN ID BP21 00246 -1 A
SPECIMEN TYPE Block
DATE OF COLLECTION 25 March 2021
SPECIMEN RECEIVED 03 June 2021

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 6 Muts/Mb

Genomic Findings

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

PIK3CA H1047R
MYC amplification - equivocal†
PTEN Y174fs*15
NSD3 (WHSC1L1) amplification - equivocal†
SETD2 R1694fs*17
TET2 H266fs*24
TP53 R209fs*6
ZNF703 amplification - equivocal†

3 Disease relevant genes with no reportable alterations: ***BRCA1, BRCA2, ERBB2***

† See About the Test in appendix for details.

3 Therapies with Clinical Benefit
0 Therapies with Lack of Response
22 Clinical Trials

BIOMARKER FINDINGS	ACTIONABILITY
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section
Tumor Mutational Burden - 6 Muts/Mb	**No therapies or clinical trials.** see Biomarker Findings section

GENOMIC FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
PIK3CA - H1047R	Alpelisib + Fulvestrant [1]	Everolimus [2A]
10 Trials *see p. 15*		Temsirolimus
MYC - amplification - equivocal	none	none
7 Trials *see p. 13*		
PTEN - Y174fs*15	none	none
10 Trials *see p. 17*		

[ ] *NCCN category*

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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.

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIALS 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.

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BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

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

MSI is extremely rare in breast cancer, reported in 0-1% of cases across studies[6-11]. The incidence of MSI is increased in triple-negative breast cancer[9-11] and in tumors with homologous recombination defects, such as mutations in BRCA1/2[9,11]. Notably, in Lynch syndrome–related breast cancer, MSI has been reported in 51-85% of cases[12-17]. A prospective study of 123 patients with breast cancer treated with chemotherapy reported an increase in the incidence of MSI-H following chemotherapy treatment (from 0% pre-treatment to 19% post-treatment) and a significant association between MSI and tumor recurrence[18].

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[19]. 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[19-21]. 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[22-24]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[19,21,23-24].

BIOMARKER

Tumor Mutational Burden

RESULT
6 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[25-27], anti-PD-1 therapies[25-28], and combination nivolumab and ipilimumab[29-34]. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors[25-28,35]. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment of patients with 9 types of advanced tumors[25]. 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[36] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[26]. However, the KEYNOTE 158 trial of pembrolizumab monotherapy in patients with solid tumors found significant improvement in ORR in patients with TMB ≥10 Muts/Mb (based on this assay or others) compared to those with TMB <10 Muts/Mb, in a large cohort that included multiple tumor types; similar findings were observed in the KEYNOTE 028 and 012 trials[28,35]. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors.

FREQUENCY & PROGNOSIS

A study of 3,969 patients with breast cancer reported a median TMB of 2.63 mutations per megabase (Muts/Mb), with 5% of cases harboring TMB ≥10 Muts/Mb; median TMB was significantly higher in hormone receptor (HR)-negative and HER2-negative tumors than HR-positive or HER2-positive tumors[37]. The Breast Invasive Carcinoma TCGA analysis reported an average (non-silent) mutation load of 0.84 Muts/Mb for luminal A tumors, 1.38 Muts/Mb for luminal B tumors, 2.05 Muts/Mb for HER2-enriched tumors, and 1.68 Muts/Mb for basal-like tumors[38]. In breast cancer, TMB is significantly higher in recurrent versus primary tumors, metastatic versus localized cancers, triple-negative versus HR-positive tumors, and CDH1-mutated versus CDH1-wildtype tumors[37,39-40]. Among metastatic tumors, TMB-high samples have been reported more frequently in invasive lobular carcinoma (9-17% of cases, depending on the TMB cutoff to designate TMB-high) than in invasive ductal carcinoma (2-8% of cases, depending on the cutoff), and TMB-high (at either cutoff) has not been observed in papillary carcinoma[37,39-40]. Breast carcinoma harbors a median TMB of 3.8 muts/Mb, and 3.1% of cases have high TMB (>20 muts/Mb)[41]. In a large study of patients with breast cancer, hypermutation was more frequently observed in metastatic tumors than in primary tumors[37]. In a study of 14,867 patients with breast cancer, high TMB was associated with older age and metastatic disease but was not significantly associated with PD-L1 positivity using the TMB cutoff of ≥10 Muts/Mb[40]. In estrogen receptor-positive breast cancer, increased TMB in tissue samples (>mean of 1.25 Muts/Mb) associated with shorter OS (HR=2.02) in an analysis of the TCGA data[42].

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[43-44] and cigarette smoke in lung cancer[45-46], treatment with temozolomide-based chemotherapy in glioma[47-48], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[49-53], and microsatellite instability (MSI)[49,52-53]. 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[26-27,35].

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GENE
PIK3CA

ALTERATION
H1047R

TRANSCRIPT ID
NM_006218

CODING SEQUENCE EFFECT
3140A>G

VARIANT ALLELE FREQUENCY (% VAF)
30.3%

POTENTIAL TREATMENT STRATEGIES

Clinical and preclinical data in various tumor types indicate that PIK3CA activating alterations may predict sensitivity to therapies targeting PI3K[54-56], AKT[57], or mTOR[58-65]. In a Phase 1 trial of the dual PI3K/mTOR kinase inhibitor apitolisib, 79% (11/14) of patients with PIK3CA-mutated advanced solid tumors experienced disease control at the recommended Phase 2 dose (3/14 PRs, 8/14 SDs)[66]. The addition of everolimus to exemestane to treat hormone-receptor-positive (HR+)/HER2-negative advanced breast cancer has shown clinical benefit regardless of PIK3CA status[67-68]. In the BELLE-2 trial for patients with endocrine-resistant HR+ breast cancer, the combination of the pan-PI3K inhibitor buparlisib with fulvestrant resulted in increased ORR (18% vs. 4%), median PFS (7.0 vs. 3.2 months; HR=0.58, p=0.001), and median OS (26.0 vs. 24.8 months; HR=0.81, p=0.127) compared with placebo with fulvestrant for patients with PIK3CA mutation; no significant improvement in ORR, PFS, or OS was observed for patients without PIK3CA mutation[69-70]. In a Phase 1 study, the p110α-selective inhibitor inavolisib (GDC-0077) alone or in combination with endocrine therapy (letrozole or fulvestrant) with or without palbociclib yielded an ORR of 32% (23/73) for patients with PIK3CA-mutated HR+/HER2-negative breast cancer, with an ORR of 40% (6/15) observed for patients who received inavolisib plus palbociclib and fulvestrant[71-72] . A patient with previously treated HER2-negative metastatic breast cancer harboring a PIK3CA H1047R alteration achieved an exceptional response with the pan-class I PI3K inhibitor copanlisib[73]. However, studies of copanlisib and the pan-class I PI3K inhibitor buparlisib have demonstrated limited efficacy against PIK3CA-mutated tumors[70,74-79]. PI3K-alpha-selective inhibitors such as alpelisib or PI3K-beta-sparing inhibitors such as taselisib may have bigger therapeutic windows than pan-PI3K inhibitors[54]. In PIK3CA-mutated advanced solid tumors, alpelisib and taselisib have achieved low ORRs (0% [0/55] to 6% [7/111]) but high DCRs (55% [36/55] to 58% [64/111])[55]. In the Phase 3 SOLAR-1 study, the addition of alpelisib to fulvestrant improved PFS (11.0 vs. 5.7 months, HR=0.65) and ORR (27% vs. 13%) in PIK3CA-mutated HR+/HER2– breast cancer compared with placebo with fulvestrant[57], but not in PIK3CA-wildtype HR+/HER2– breast cancer. In the Phase 3 SANDPIPER study, the addition of taselisib to fulvestrant improved PFS (7.4 vs. 5.4 months, HR=0.70) and ORR (27% vs. 12%) in PIK3CA-mutated HR+/HER2– breast cancer compared with placebo with fulvestrant[80]; additionally, higher ORR was achieved for patients with multiple PIK3CA mutations following treatment with taselisib (30%, n=43) as compared with those treated with placebo (8.7%, n=23) and for patients with single PIK3CA-mutated tumors treated with either taselisib (18%, n=193) or placebo (10%, n=80)[81]. Data from the Phase 2 LOTUS trial reported an improved PFS for patients with PIK3CA/AKT1/PTEN-altered triple negative breast cancer treated with ipatasertib plus paclitaxel compared to paclitaxel alone (9.0 vs 4.9 months)[82]; however, the Phase 3 IPATunity130 trial did not report a significant PFS improvement for first-line ipatasertib in combination with paclitaxel relative to paclitaxel alone (7.4 vs 6.1 months)[83]. AKT inhibitors ipatasertib and capivasertib have also been tested in breast cancer. Two Phase 2 studies have reported improved PFS from the addition of either ipatasertib (9.0 vs. 4.9 months, HR = 0.44) or capivasertib (9.3 vs. 3.7 months, HR = 0.30) to paclitaxel in metastatic triple-negative breast cancer harboring PIK3CA/AKT1/PTEN alterations, compared with paclitaxel and placebo[84]. Responses to capivasertib were also reported in 20% (3/15) of patients with PIK3CA-mutated breast cancer in an earlier study[85]. However, a Phase 1 trial reported no PFS benefit for patients with PIK3CA-mutated, ER+/HER2- metastatic breast cancer from the addition of capivasertib to paclitaxel compared with paclitaxel plus placebo (10.9 vs. 10.8 months)[86]. Activating mutations in PIK3CA may confer resistance to HER2-targeted therapies; combined inhibition of HER2 and the PI3K pathway may be required in HER2-positive tumors with PIK3CA mutation[87-91]. For patients with PIK3CA-mutated breast cancer, PTEN loss or mutation may be associated with resistance to alpelisib in combination with fulvestrant or as a single agent[54,92-93].

FREQUENCY & PROGNOSIS

Mutations in PIK3CA have been reported in 25-40% of breast cancer cases[38,94-98]. In the randomized Phase 2 SAFIR02 trial, PIK3CA mutations were associated with reduced OS in patients with hormone-receptor-positive (HR+)/HER2 negative (HER-) metastatic breast cancer but with improved OS in patients with mTNBC compared to patients with PIK3CA wildtype status[98]. Although double PIK3CA mutations were frequently observed in HR+/HER2- breast cancers, as compared with other receptor subtypes (15.4% vs. 5.4%, p=0.004), this did not impact invasive disease-free survival or OS for patients when compared with single PIK3CA mutations by univariate and multivariate analysis in 1 retrospective study[81]. Mutations in coding exon 20 (H1047R) of PIK3CA have been associated with a better prognosis in breast carcinoma than mutations occurring in coding exon 9 (E542K)[99].

FINDING SUMMARY

PIK3CA encodes p110-alpha, which is the catalytic subunit of phosphatidylinositol 3-kinase (PI3K). The PI3K pathway is involved in cell signaling that regulates a number of critical cellular functions, including cell growth, proliferation, differentiation, motility, and survival[100-101]. PIK3CA alterations that have been characterized as activating, such as observed here, are predicted to be oncogenic[102-122].

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GENE
MYC

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

There are no available therapies that directly target MYC. However, preclinical data indicate that MYC overexpression may predict sensitivity to investigational agents targeting CDK1[123-124], CDK2[125], Aurora kinase A[126-133], Aurora kinase B[134-137], glutaminase[138-141], or BET bromodomain-containing proteins[142-145], as well as agents targeting both HDAC and PI3K[146-148]. 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[149]. A patient with MYC-amplified invasive ductal breast carcinoma experienced a PR to an Aurora kinase inhibitor[150]. 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[151-152] . MYC amplification has also been suggested to predict response to chemotherapy in patients with breast cancer in some studies[153-154]. Preclinical evidence suggests that colon cancer cells with MYC amplification may be more sensitive to 5-fluorouracil and paclitaxel[155-156].

FREQUENCY & PROGNOSIS

In the TCGA dataset, MYC amplification was observed in 15% of breast invasive carcinoma cases[38]. MYC amplification has been associated with an aggressive phenotype, early onset, and poor prognosis in patients with breast cancer, although the data have been conflicting[153,157-159].

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[160]. MYC dysregulation (amplification, overexpression, translocation) has been identified in a number of different cancer types[161]. MYC amplification has been significantly linked with increased mRNA and protein levels and results in the dysregulation of a large number of target genes[160,162-163].

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GENE
PTEN

ALTERATION
Y174fs*15

TRANSCRIPT ID
NM_000314

CODING SEQUENCE EFFECT
518_519insAGGGAGTAACTATTCCCAGTCAGAGGCG

VARIANT ALLELE FREQUENCY (% VAF)
38.5%

POTENTIAL TREATMENT STRATEGIES

PTEN loss or mutation leads to activation of the PI3K-AKT-mTOR pathway and may predict sensitivity to inhibitors of this pathway[75,164-168] such as the mTOR inhibitors temsirolimus and everolimus or the PI3K inhibitor copanlisib. While PTEN loss correlated with longer PFS and response to single-agent everolimus for patients with prostate cancer[164], clinical studies in renal cell carcinoma[169-173], glioblastoma[174-175], cervical carcinoma[176], breast cancer[177-178], endometrial cancer[179-184], urothelial carcinoma[185-187], leiomyosarcoma[188], neuroendocrine tumors[189], gastric cancer[190], and peripheral T-cell lymphomas[191] did not observe a correlation of PTEN deficiency with response to everolimus or temsirolimus. Preclinical studies suggest that PTEN-deficient cancers, in the absence of other oncogenic mutations, depend primarily on the beta isoform of PI3K (PI3K-beta)[192-194], and PI3K-beta-selective inhibitors are in clinical trials for PTEN-deficient tumors. However, the NCI-MATCH Phase 2 study observed limited activity of the PI3K-betaselective inhibitor GSK2636771 as monotherapy in PTEN-deficient cancers, with a median PFS of 1.8 months. The best outcomes were 1 PR (1/22, prostate cancer), SD (7/22) for patients with PTEN deletion/mutation, and SD (9/34) for patients with PTEN protein loss[195]. Clinical data in breast[196-197] and prostate cancer[198-199] suggest that PTEN alterations may predict sensitivity to pan-AKT inhibitors such as ipatasertib or capivasertib. Phase 2 studies have reported improved PFS from the addition of either ipatasertib (9.0 vs. 4.9 months, HR=0.44) or capivasertib (9.3 vs. 3.7 months, HR=0.30) to paclitaxel, compared with paclitaxel and placebo, for patients with metastatic triple-negative breast cancer harboring PIK3CA/AKT1/PTEN alterations[84]. However, data from the Phase 2 LOTUS trial reported an improved PFS for patients with PIK3CA/AKT1/PTEN-altered triple negative breast cancer treated with ipatasertib plus paclitaxel compared to paclitaxel alone (9.0 vs 4.9 months)[82]; however, the Phase 3 IPATunity130 trial did not report a significant PFS improvement for first-line ipatasertib in combination with paclitaxel relative to paclitaxel alone (7.4 vs 6.1 months)[83]. Preclinical data indicate that PTEN loss or inactivation may predict sensitivity to PARP inhibitors[200-204], and clinical benefit has been observed for patients with PTEN-altered breast cancer[205], ovarian cancer[206], endometrial cancer[204], and other tumor types[207] treated with PARP inhibitors. However, several studies have reported a lack of association between PTEN mutation and PARP inhibitor sensitivity[203,208-209]. Limited clinical evidence in glioblastoma[210], leiomyosarcoma[211], NSCLC[212], and melanoma[213] suggests that PTEN alterations may predict a lack of response to anti-PD-1 therapy. In an analysis of 39 patients with metastatic melanoma treated with pembrolizumab or nivolumab, patients with PTEN-expressing tumors achieved significantly greater reduction of tumor size than those with reduction or loss of PTEN expression[213]. In a retrospective analysis of 66 patients with glioblastoma, tumors from nivolumab or pembrolizumab non-responders were significantly enriched for PTEN mutations[210]. In a patient with uterine leiomyosarcoma treated with pembrolizumab monotherapy, a treatment-resistant tumor arose that harbored PTEN loss[211]. A patient with NSCLC whose tumor harbored a PTEN alteration exhibited a lack of response to nivolumab and pembrolizumab[212]. Clinical and preclinical evidence suggests that PTEN loss or mutation may predict resistance to PI3K inhibitors[92,214-215], and to CDK inhibitors such as palbociclib, ribociclib, and abemaciclib[214,216]. For patients with PIK3CA-mutated breast cancer, PTEN loss or mutation may be associated with resistance to alpelisib in combination with fulvestrant or as a single agent[54,92-93].

FREQUENCY & PROGNOSIS

In the TCGA dataset, PTEN mutation has been reported in 4% of breast invasive carcinomas, while putative homozygous deletion of PTEN has been reported in 2% of cases[38]. PTEN mutation has also been observed in 5.3% (1/19) of metaplastic breast cancers[217] and 2% of invasive lobular carcinoma tumors analyzed[218]. PTEN mutations are associated more frequently with triple-negative breast cancer than with HER2- or hormone-positive breast cancer[219-220]. Loss or reduction of PTEN expression has been observed in 28% of invasive ductal breast carcinomas and has been correlated with metastasis and poor patient prognosis, including decreased 2-year disease-free survival[221-223].

FINDING SUMMARY

PTEN encodes an inositol phosphatase that functions as a tumor suppressor by negatively regulating the PI3K-AKT-mTOR pathway; loss of PTEN can lead to uncontrolled cell growth and suppression of apoptosis[167]. Alterations such as seen here may disrupt PTEN function or expression[224-264].

POTENTIAL GERMLINE IMPLICATIONS

PTEN mutations underlie several inherited disorders, collectively termed PTEN hamartoma tumor syndrome (PHTS), which include Cowden syndrome (CS) and its variant Lhermitte-Duclos disease (LD), Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS), and Proteus-like syndrome[265-266]. The mutation rate for PTEN in these disorders ranges from 20 to 85% of patients[265,267]. The estimated incidence of Cowden syndrome is 1/200,000, which may be an underestimate due to the high variability of this disorder[265]. Given the association between PTEN and these inherited syndromes, in the appropriate clinical context, germline testing for mutations affecting PTEN is recommended.

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GENE
NSD3 (WHSC1L1)

ALTERATION
amplification - equivocal

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

FREQUENCY & PROGNOSIS
In TCGA datasets, NSD3 amplification has been most frequently observed in lung squamous cell carcinoma (17%)[268], breast invasive carcinoma (13%)[269], bladder urothelial carcinoma (9%)[270], and head and neck squamous cell carcinoma (9%)[271] samples[272-273]. Amplification of at least one member of the NSD3-CHD8-BRD4 pathway has been associated with worse overall survival in ovarian high-grade serous carcinoma and endometrial cancer[274]. In endometrial cancers, amplification of this pathway was more frequent in endometrial serous and endometrioid serious-like carcinomas compared to low-grade endometrioid endometrial adenocarcinomas[274].

FINDING SUMMARY
NSD3, also known as WHSC1L1, encodes an enzyme that mediates histone methylation[275]. NSD3 has been shown to be amplified in various cancers[276-278].

GENE
SETD2

ALTERATION
R1694fs*17

TRANSCRIPT ID
NM_014159

CODING SEQUENCE EFFECT
5082_5083delAG

VARIANT ALLELE FREQUENCY (% VAF)
8.3%

POTENTIAL TREATMENT STRATEGIES
There are no targeted therapies available to address genomic alterations in SETD2.

FREQUENCY & PROGNOSIS
Somatic inactivating alterations of SETD2 are documented to occur at low frequency in a number of solid tumors, most commonly in renal carcinoma[279]. SETD2 mutations have been detected in 6-12% of acute lymphoblastic leukemias (ALL) and reportedly increase chromosomal abnormalities and contribute to leukemia development[280-282].

FINDING SUMMARY
SETD2 encodes a histone lysine-36 methyltransferase[283] that preferentially interacts with the expanded N-terminal polyglutamine tracts present in mutant huntingtin, implicating it in the pathogenesis of Huntington disease[284]. SETD2 mRNA expression has been observed to be consistently reduced in breast tumors relative to adjacent non-tumor tissue, suggesting a potential tumor suppressor role[285].

GENE
TET2

ALTERATION
H266fs*24

TRANSCRIPT ID
NM_001127208

CODING SEQUENCE EFFECT
797_806delACCCATCGCA

VARIANT ALLELE FREQUENCY (% VAF)
11.7%

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

FREQUENCY & PROGNOSIS
TET2 alterations have been reported at relatively low frequencies in solid tumors and are more prevalent in hematological malignancies (cBioPortal, Jan 2021)[272-273]. Published data investigating the prognostic implications of TET2 alterations in solid tumors are limited (PubMed, Jan 2021).

FINDING SUMMARY
TET2 encodes a tumor suppressor involved in reversing DNA methylation marks, a process critical for proper gene regulation[286-287]. Alterations such as seen here may disrupt TET2 function or expression[288-292].

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[293-298]. 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[293-294]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[299]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[297,300-301]. 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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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
TP53

ALTERATION
R209fs*6

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
626_627delGA

VARIANT ALLELE FREQUENCY (% VAF)
52.0%

POTENTIAL TREATMENT STRATEGIES

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[302-305], or p53 gene therapy and immunotherapeutics such as SGT-53[306-310] and ALT-801[311]. 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) in patients with TP53 mutations versus 12.1% (4/33) in patients who were TP53 wild-type[312]. 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 in patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[313]. 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 in patients with platinum-refractory TP53-mutated ovarian cancer[314]. The combination of adavosertib with paclitaxel and carboplatin in patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[315]. 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[316]. 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[317]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel in 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[310]. 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[318]. 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[319-320]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[321-322]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

TP53 is one of the most commonly mutated genes in breast cancer; mutations in this gene have been identified in 27-37% of breast carcinoma samples[38,323-327]. TP53 mutations that are located within the region encoding the DNA binding domain are associated with poor prognosis in patients with breast cancer[325,328-329]. TP53 mutation is also implicated in breast cancer susceptibility, as TP53 mutation carriers have an 18-60 fold increased risk for early onset breast cancer[330-332].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[333]. Alterations such as seen here may disrupt TP53 function or expression[334-338].

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, Mar 2021)[339]. 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[340-342], including sarcomas[343-344]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[345] to 1:20,000[344]. 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[346]. 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[293-298]. 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[293-294]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[299]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[297,300-301]. 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
ZNF703

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

There are no available targeted therapies to directly address ZNF703 alterations in cancer. One preclinical study suggested that ZNF703 expression in breast cancer cell lines is associated with reduced sensitivity to tamoxifen through AKT-mTOR activation[347], although these findings have not been verified in the clinical setting.

FREQUENCY & PROGNOSIS

Amplification and high expression of ZNF703 has been observed in luminal B breast tumors, a subtype associated with aggressive disease progression and poor patient outcomes[348-350]. ZNF703 expression has also been linked with aggressive tumor characteristics in patients with gastric and colorectal cancers[351-352]. Putative high-level amplification of ZNF703 has been reported with the highest frequency in breast carcinoma, bladder urothelial carcinoma, uterine carcinosarcoma, lung squamous cell carcinoma (SCC), esophageal carcinoma and head and neck SCC (5-13% of samples)(cBioPortal, 2021)[272-273].

FINDING SUMMARY

ZNF703 encodes a transcriptional repressor that plays roles in stem cell proliferation, cell cycle progression, and other key cellular functions[349,353]. Amplification of ZNF703 has been correlated with protein expression[348-349]. ZNF703 was established as a breast cancer oncoprotein by studies showing that ZNF703 expression resulted in transformation and increased proliferation of cultured cells[348-349,354], as well as increased lung metastases in a breast cancer xenograft model[354].

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Alpelisib + Fulvestrant

Assay findings association

PIK3CA
H1047R

AREAS OF THERAPEUTIC USE

Alpelisib is a phosphatidylinositol 3-kinase (PI3K) inhibitor with selective activity against the alpha isoform (PI3K-alpha), and fulvestrant is an estrogen receptor (ER) antagonist and selective estrogen receptor degrader (SERD). The combination is FDA approved to treat men and postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated advanced breast cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of prospective clinical data, PIK3CA mutations including C420R, E542K, E545A, E545G, E545K, E545D, Q546E, Q546R, H1047L, H1047Y, and H1047R are associated with sensitivity to alpelisib in combination with fulvestrant. In ER+/HER2– breast cancer, PFS benefit from the addition of alpelisib to fulvestrant was specifically observed for patients with PIK3CA mutations (11.0 vs. 5.7 months, HR=0.65), including patients with PIK3CA exon 9 or exon 20 mutations[57]. Preclinical and limited clinical evidence suggest that PTEN inactivation may be associated with resistance to PI3K alpha-selective inhibitors[54,92-93] . PTEN mutation or loss has been reported for a small number of patients with PIK3CA-mutated HR+/HER2– breast cancer who progressed on combination treatment with alpelisib and fulvestrant, including as an acquired alteration for 1 patient[93,355] .

SUPPORTING DATA

In the Phase 3 SOLAR-1 study for patients with HR+/HER2– endocrine therapy-resistant advanced breast cancer, addition of alpelisib to fulvestrant significantly improved median PFS (mPFS; 11.0 vs. 5.7 months, HR=0.65), ORR (27% vs. 13%), and clinical benefit rate (CBR; 62% vs. 45%), and numerically improved median OS (39.3 vs. 31.4 months, HR=0.86) for patients with PIK3CA mutation[57,356] . Benefit was observed for patients with PIK3CA exon 9 or exon 20 mutations[57]; for PIK3CA-wildtype patients, the addition of alpelisib to fulvestrant did not significantly improve mPFS (7.4 vs. 5.6 months, HR=0.85)[57]. This trial excluded patients with active brain metastases; however, control of progressive brain metastases (1/4 PR and 2/4 SDs by RANO brain metastases criteria) was reported in a case series of 4 patients with PIK3CA-mutated HR+/HER2– breast cancer treated with alpelisib in combination with either fulvestrant or exemestane[357]. The Phase 2 BYLieve study for previously treated patients with PIK3CA-mutated HR+/HER2– advanced breast cancer reported an ORR of 17%, a CBR of 46%, and mPFS of 7.3 months for patients treated with alpelisib plus fulvestrant following progression on a CDK4/6 inhibitor in combination with an aromatase inhibitor[358] and, similarly in another cohort, an ORR of 16%, CBR of 32%, and mPFS of 5.7 months for patients treated with alpelisib plus letrozole following progression on a CDK4/6 inhibitor in combination with fulvestrant[359].

Everolimus

Assay findings association

PIK3CA
H1047R

AREAS OF THERAPEUTIC USE

Everolimus is an orally available mTOR inhibitor that is FDA approved to treat renal cell carcinoma (RCC) following antiangiogenic therapy; pancreatic neuroendocrine tumors; and well-differentiated non-functional neuroendocrine tumors of the lung or gastrointestinal tract. Everolimus is also approved to treat either renal angiomyolipoma or subependymal giant cell astrocytoma in association with tuberous sclerosis complex (TSC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence[58-65] , PIK3CA activating mutations may predict sensitivity to mTOR inhibitors such as everolimus and temsirolimus. Studies have reported modest activity of these therapies as single agents (ORRs of 0-4%), but improved activity has been observed when they are combined with other agents such as bevacizumab and doxorubicin (ORRs of 25-44%), for patients with PIK3CA-mutated solid tumors[62-65,360-364] .

SUPPORTING DATA

Clinical benefit has been reported for patients with PIK3CA-mutated breast cancer treated with everolimus as a single agent[365] or in combination with gemcitabine and cisplatin[366]. For patients with HR+, HER2– advanced breast cancer, the BOLERO-2, SAFIRTOR, and EVE biomarker studies demonstrated clinical benefit from addition of everolimus to exemestane regardless of baseline PIK3CA mutation status[67-68,367-368] . In the Phase 3 BOLERO-2 study for hormone receptor-positive (HR+), HER2-negative (HER2–) breast cancer, the addition of everolimus to exemestane improved median PFS (mPFS) in both the first-line exploratory cohort (11.5 vs. 4.1 months, HR=0.39)[369] and second-line cohort (7.8 vs. 3.2 months, HR=0.45)[370-372] compared with exemestane alone. Combination everolimus and exemestane modestly improved mPFS compared with everolimus alone in BOLERO-6 (8.4 vs. 6.8 months, HR=0.74)[373]. Patients with HR+, HER2– breast cancer also benefited from everolimus combined with other anti-estrogen therapies, including letrozole, tamoxifen, and anastrozole[374-376] . For patients with HR+, HER2– breast cancer who progressed on anti-estrogen therapies, addition of everolimus to the most recent endocrine therapy elicited mPFS of 6.6 months[377]. For patients with HER2+ breast cancer, everolimus combined with trastuzumab plus paclitaxel did not significantly improve mPFS in the full study population (15.0 months with everolimus vs. 14.5 months with placebo), but increased PFS in the HR-negative subpopulation (20.3 vs. 13.1 months)[378]. For patients with trastuzumab-resistant HER2+ breast cancer, the addition of everolimus to trastuzumab plus vinorelbine prolonged mPFS (7.0 vs. 5.8 months)[379], whereas for HER2– breast cancer, addition of everolimus to vinorelbine in the second-line did not improve mPFS (4.0 vs. 4.1 months)[380]. Patients with metastatic triple-negative breast cancer treated with everolimus plus carboplatin achieved a clinical benefit rate of 36% (9/25)[381]. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[382], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[383].

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Temsirolimus

Assay findings association

PIK3CA
H1047R

AREAS OF THERAPEUTIC USE

Temsirolimus is an intravenous mTOR inhibitor that is FDA approved for the treatment of advanced renal cell carcinoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence[58-65] , PIK3CA activating mutations may predict sensitivity to mTOR inhibitors such as everolimus and temsirolimus. Studies have reported modest activity of these therapies as single agents (ORRs of 0-4%), but improved activity has been observed when they are combined with other agents such as bevacizumab and doxorubicin (ORRs of 25-44%), for patients with PIK3CA-mutated solid tumors[62-65,360-364] .

SUPPORTING DATA

Clinical benefit has been reported for patients with PIK3CA-mutated breast cancer treated with temsirolimus as a single agent[178] or in combination with doxorubicin and bevacizumab[64-65,363,384-386] . A Phase 1 trial examining the combination of temsirolimus, liposomal doxorubicin, and bevacizumab in 74 patients with breast and gynecological malignancies reported that 37.9% of patients experienced either a CR (1.4%), PR (18.9%), or SD (17.6%); among 25 patients with PIK3CA mutation or PTEN loss, 52% experienced a CR, PR (36%), or SD (16%)[65]. Another Phase 1 trial including patients with several types of cancer reported a 42% incidence of complete or partial responses in patients with metastatic breast cancer[63]. However, a Phase 2 study of temsirolimus in pretreated patients with metastatic breast cancer reported minimal clinical activity and no association with PTEN protein or PIK3CA mutation status[178]. A Phase 3 placebo-controlled trial of letrozole plus oral temsirolimus as first-line endocrine therapy in postmenopausal women with locally advanced or metastatic breast cancer was terminated at the second interim since the addition of temsirolimus to letrozole did not improve PFS as a first-line therapy[387]. A study examining the efficacy of temsirolimus-involving regimens in 24 patients with mesenchymal/metaplastic breast cancer (MpBCs) reported 2 CRs, 4 PRs, 2 instances of SD longer than 6 months, and 4 instances of SD shorter than 6 months[363].

NOTE Genomic alterations detected may be associated with activity of certain FDA approved drugs, however, the agents listed in this report may have varied evidence in the patient's tumor type.

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ORDERED TEST # ORD-1110066-01

CLINICAL TRIALS

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
MYC

ALTERATION
amplification - equivocal

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.

NCT03297424

PHASE 1/2

A Study of PLX2853 in Advanced Malignancies.

TARGETS
BRD4

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

NCT03901469

PHASE 2

A Study of ZEN003694 and Talazoparib in Patients With Triple Negative Breast Cancer

TARGETS
BRD2, BRD3, BRD4, BRDT, PARP

LOCATIONS: Texas, Tennessee, Pennsylvania, New York, Kansas, Arizona, Madrid (Spain), Barcelona (Spain), Brussels (Belgium), Leuven (Belgium)

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

NCT02516553

PHASE 1

BI 894999 First in Human Dose Finding Study in Advanced Malignancies

TARGETS
BRD2, BRD3, BRD4, BRDT

LOCATIONS: Texas, New York, Ohio, Massachusetts, California, Madrid (Spain), Nantes (France), Barcelona (Spain), Villejuif (France), Paris (France)

NCT03654547

PHASE 1

Safety of TT-00420 Monotherapy in Patients With Advanced Solid Tumors and Triple Negative Breast Cancer

TARGETS
Aurora kinase A, Aurora kinase B

LOCATIONS: Texas

NCT01434316

PHASE 1

Veliparib and Dinaciclib in Treating Patients With Advanced Solid Tumors

TARGETS
PARP, CDK1, CDK2, CDK5, CDK9

LOCATIONS: Massachusetts

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

GENE
PIK3CA

ALTERATION
H1047R

RATIONALE
PIK3CA activating mutations may lead to activation of the PI3K-AKT-mTOR pathway and may therefore indicate sensitivity to inhibitors of this pathway. Strong clinical data support sensitivity of PIK3CA-mutated solid tumors to the PI3K-alpha inhibitor alpelisib.

NCT04305496

PHASE 3

Capivasertib+Fulvestrant vs Placebo+Fulvestrant as Treatment for Locally Advanced (Inoperable) or Metastatic HR+/HER2– Breast Cancer

TARGETS
ER, AKTs

LOCATIONS: Lima (Peru), Arequipa (Peru), La Rioja (Argentina), Rosario (Argentina), Ciudad Autonoma De Buenos Aire (Argentina), Berazategui (Argentina), Viedma (Argentina), Florida, Georgia

NCT03997123

PHASE 3

Capivasertib+Paclitaxel as First Line Treatment for Patients With Locally Advanced or Metastatic TNBC

TARGETS
AKTs

LOCATIONS: Lima (Peru), Callao (Peru), Rosario (Argentina), Londrina (Brazil), Goiania (Brazil), São José do Rio Preto (Brazil), Mar del Plata (Argentina), Caba (Argentina), Ciudad Autonoma De Buenos Aire (Argentina), Ciudad Autónoma de Bs. As. (Argentina)

NCT04251533

PHASE 3

Study Assessing the Efficacy and Safety of Alpelisib + Nab-paclitaxel in Subjects With Advanced TNBC Who Carry Either a PIK3CA Mutation or Have PTEN Loss Without PIK3CA Mutation

TARGETS
PI3K-alpha

LOCATIONS: Bogota (Colombia), Barretos (Brazil), Caxias do Sul (Brazil), Sao Paulo (Brazil), Florida, Louisiana, Texas

NCT04191499

PHASE 2/3

A Study Evaluating the Efficacy and Safety of GDC-0077 + Palbociclib + Fulvestrant vs Placebo + Palbociclib + Fulvestrant in Patients With PIK3CA-Mutant, Hormone Receptor-Positive, Her2-Negative, Locally Advanced or Metastatic Breast Cancer

TARGETS
PI3K-alpha, CDK4, CDK6, ER

LOCATIONS: Florida, Texas, Georgia

NCT04589845

PHASE 2

Tumor-Agnostic Precision Immuno-Oncology and Somatic Targeting Rational for You (TAPISTRY) Platform Study

TARGETS
ALK, ROS1, TRKA, TRKB, TRKC, RET, PD-L1, AKTs, ERBB2, MDM2, PI3K-alpha

LOCATIONS: Florida, Alabama, Texas, Georgia, Tennessee, Pennsylvania

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

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

LOCATIONS: Florida, Louisiana, Texas

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NCT04632992

PHASE 2

A Study Evaluating Targeted Therapies in Participants Who Have Advanced Solid Tumors With Genomic Alterations or Protein Expression Patterns Predictive of Response

TARGETS
ALK, ROS1, TRKA, TRKB, TRKC, PD-L1, ERBB2, ERBB3, PI3K-alpha, RET, AKTs

LOCATIONS: Florida, Louisiana, Tennessee, Texas, New Jersey

NCT04188548

PHASE 1

A Study of LY3484356 in Participants With Advanced or Metastatic Breast Cancer or Endometrial Cancer

TARGETS
mTOR, Aromatase, CDK4, CDK6, ER, PI3K-alpha, ERBB2

LOCATIONS: Florida, Texas, Georgia, North Carolina, Tennessee, Virginia

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chengdu (China), Chongqing (China)

NCT03280563

PHASE 1/2

A Study of Multiple Immunotherapy-Based Treatment Combinations in Hormone Receptor (HR)-Positive Human Epidermal Growth Factor Receptor 2 (HER2)-Negative Breast Cancer

TARGETS
PD-L1, ER, HDAC, AKTs, CDK4, CDK6

LOCATIONS: North Carolina, Tennessee, Maryland, Pennsylvania, New York, Illinois, California

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GENE
PTEN

ALTERATION
Y174fs*15

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

NCT04305496

PHASE 3

Capivasertib+Fulvestrant vs Placebo+Fulvestrant as Treatment for Locally Advanced (Inoperable) or Metastatic HR+/HER2– Breast Cancer

TARGETS
ER, AKTs

LOCATIONS: Lima (Peru), Arequipa (Peru), La Rioja (Argentina), Rosario (Argentina), Ciudad Autonoma De Buenos Aire (Argentina), Berazategui (Argentina), Viedma (Argentina), Florida, Georgia

NCT03997123

PHASE 3

Capivasertib+Paclitaxel as First Line Treatment for Patients With Locally Advanced or Metastatic TNBC

TARGETS
AKTs

LOCATIONS: Lima (Peru), Callao (Peru), Rosario (Argentina), Londrina (Brazil), Goiania (Brazil), São José do Rio Preto (Brazil), Mar del Plata (Argentina), Caba (Argentina), Ciudad Autonoma De Buenos Aire (Argentina), Ciudad Autónoma de Bs. As. (Argentina)

NCT04191135

PHASE 2/3

Study of Olaparib Plus Pembrolizumab Versus Chemotherapy Plus Pembrolizumab After Induction With First-Line Chemotherapy Plus Pembrolizumab in Triple Negative Breast Cancer (TNBC) (MK-7339-009/KEYLYNK-009)

TARGETS
PD-1, PARP

LOCATIONS: Cali (Colombia), Medellin (Colombia), La Serena (Chile), Monteria (Colombia), Vina del Mar (Chile), Santiago (Chile), Barranquilla (Colombia), Temuco (Chile), Florida, Texas

NCT03598257

PHASE 2

Radiation Therapy With or Without Olaparib in Treating Patients With Inflammatory Breast Cancer

TARGETS
PARP

LOCATIONS: San Juan (Puerto Rico), Florida, Louisiana, Georgia, South Carolina, Texas

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

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

LOCATIONS: Florida, Louisiana, Texas

NCT04632992

PHASE 2

A Study Evaluating Targeted Therapies in Participants Who Have Advanced Solid Tumors With Genomic Alterations or Protein Expression Patterns Predictive of Response

TARGETS
ALK, ROS1, TRKA, TRKB, TRKC, PD-L1, ERBB2, ERBB3, PI3K-alpha, RET, AKTs

LOCATIONS: Florida, Louisiana, Tennessee, Texas, New Jersey

ORDERED TEST # ORD-1110066-01

CLINICAL TRIALS

NCT02498613

PHASE 2

A Phase 2 Study of Cediranib in Combination With Olaparib in Advanced Solid Tumors

TARGETS
PARP, VEGFRs

LOCATIONS: Florida, Texas, Tennessee, Virginia, Connecticut, Massachusetts, Toronto (Canada), California

NCT01042379

PHASE 2

I-SPY 2 TRIAL: Neoadjuvant and Personalized Adaptive Novel Agents to Treat Breast Cancer

TARGETS
PARP, PD-L1, ERBB2, ERBB3, PD-1, TLR9, LAG-3

LOCATIONS: Florida, Georgia, Alabama, North Carolina, Tennessee, District of Columbia, Pennsylvania, New York, Connecticut

NCT03329001

PHASE 1

Crossover Study to Assess the Relative Bioavailability and Bioequivalence of Niraparib Tablet Compared to Niraparib Capsule

TARGETS
PARP

LOCATIONS: Florida, Georgia, Texas, Tennessee, Oklahoma, Connecticut, Michigan, Colorado, California

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chengdu (China), Chongqing (China)

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

BCL6
Q397H

GATA3
amplification

MERTK
P81fs*27

MTOR
G305A

NBN
amplification

RAD21
amplification

TSC1
K587R

XPO1
I87L

Electronically signed by Douglas A. Mata, MD, MPH | 15 June 2021
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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)*	*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	*C11orf30 (EMSY)*	*C17orf39 (GID4)*	*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*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
FAM46C	*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*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*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*	*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*	*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*	*P2RY8*	*PALB2*
PARK2	*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*	*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*	*TET2*	*TGFBR2*	*TIPARP*	*TNFAIP3*	*TNFRSF14*	*TP53*
TSC1	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*	*VHL*	*WHSC1*	*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

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

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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 PRINCIPLES

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 Alterations and Therapies

Biomarker and Genomic Findings

Therapies are ranked based on the following criteria: Therapies with clinical benefit in patient's tumor type (ranked alphabetically within each NCCN category) followed by therapies with clinical benefit in other tumor type (ranked alphabetically within each NCCN category).

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. 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.

Limitations

1. The MSI-H/MSS designation by FMI F1CDx test is based on genome wide analysis of 95 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines. The threshold for MSI-H/MSS was determined by analytical concordance to comparator assays (IHC and PCR) using uterine, cecum and colorectal cancer FFPE tissue. The clinical validity of the qualitative MSI designation has not been established. For Microsatellite Instability (MSI) results, confirmatory testing using a validated orthogonal method should be considered.
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.

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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. 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.
4. 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.
5. 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.
6. 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%.

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 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

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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

MR Suite Version 4.1.0

The median exon coverage for this sample is 685x

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