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 23 October 1970
SEX Female
MEDICAL RECORD # Not given

PHYSICIAN

MEDICAL FACILITY Clinica Internacional
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 316373
PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN SITE Lymph Node
SPECIMEN ID H20-26368 (473-4-20)
SPECIMEN TYPE Block
DATE OF COLLECTION 28 December 2020
SPECIMEN RECEIVED 11 January 2021

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 3 Muts/Mb

Genomic Findings

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

ERBB2 amplification
CDK12 rearrangement exon 4
RICTOR amplification
CDKN2A/B p16INK4a G89V
FAM123B G605D
TP53 loss exons 10-11

3 Disease relevant genes with no reportable alterations: ***BRCA1, BRCA2, PIK3CA***

11 Therapies with Clinical Benefit
0 Therapies with Lack of Response
28 Clinical Trials

BIOMARKER FINDINGS	ACTIONABILITY
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section
Tumor Mutational Burden - 3 Muts/Mb	**No therapies or clinical trials.** see Biomarker Findings section

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GENOMIC FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)		THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
ERBB2 **-** amplification	Ado-trastuzumab emtansine	1	Afatinib
	Trastuzumab	1	Dacomitinib
	Trastuzumab + Pertuzumab	1	
	Trastuzumab + Tucatinib	1	
	Fam-trastuzumab deruxtecan	2A	
	Lapatinib	2A	
	Lapatinib + Letrozole	2A	
10 Trials *see p. 15*	Neratinib	2A	
	Margetuximab		
CDK12 **-** rearrangement exon 4	none		none
10 Trials *see p. 13*			
RICTOR **-** amplification	none		none
8 Trials *see p. 17*			

☐ *NCCN category*

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
3 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[29-33]. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors[25-28,34]. 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[35] 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[28,34]. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors.

FREQUENCY & PROGNOSIS

Breast carcinoma harbors a median TMB of 3.8 muts/Mb, and 3.1% of cases have high TMB (>20 muts/Mb)[36]. 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]. 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[41].

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[42-43] and cigarette smoke in lung cancer[44-45], treatment with temozolomide-based chemotherapy in glioma[46-47], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[48-52], and microsatellite instability (MSI)[48,51-52]. 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[26-27,34].

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GENE
ERBB2

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

On the basis of extensive clinical evidence, ERBB2 amplification or activating mutation may predict sensitivity to therapies targeting HER2, including antibodies such as trastuzumab[53-58], pertuzumab in combination with trastuzumab[55,59-61], and ZW25[62], as well as antibody-directed conjugates such as ado-trastuzumab emtansine (T-DM1)[63] and fam-trastuzumab deruxtecan[64], HER2 kinase inhibitors such as tucatinib[65-68], and dual EGFR/HER2 kinase inhibitors such as lapatinib[69-73], afatinib[58,74-78], neratinib[79-80], dacomitinib[81], and pyrotinib[82-83] . For patients with HER2-positive metastatic breast cancer (mBC), combining tucatinib[65], margetuximab[84], or pyrotinib[82-83] with chemotherapy or other HER2-targeted agents significantly improved PFS and/or ORR. For patients who progressed on trastuzumab, the combination of pyrotinib with capecitabine elicited improved median PFS (mPFS) compared with lapatinib and capecitabine (12.5 vs. 6.8 months, HR=0.39) in the Phase 3 PHOEBE study[83] and compared with placebo and capecitabine (11.1 vs. 4.1 months, HR=0.18) in the Phase 3 PHENIX study[82]; patients with trastuzumab-resistant disease in these studies experienced mPFS of 12.4 months[85]. For patients with HER2-positive mBC who progressed on HER2-targeted therapy, treatment with 16-mg or 24-mg doses of poziotinib elicited ORRs of 22% (6/27) and 23% (7/30) and PFS rates of 4.9 and 3.0 months, respectively[86]. Early clinical studies aimed at preventing or overcoming resistance to anti-HER2 therapies are underway, including agents targeting the PI3K-AKT pathway or HSP90[87-88]. For patients with HER2-positive metastatic breast cancer, the combination of lapatinib with letrozole[89] or other aromatase inhibitors[90] significantly improved PFS and/or ORR.

FREQUENCY & PROGNOSIS

In the TCGA dataset, ERBB2 amplification was detected in 13% of breast invasive carcinoma cases[38]. ERBB2 mutations have been reported in 1-3% of breast invasive carcinoma cases[38,91-92]. The incidence of ERBB2 alterations has been found to be significantly enriched in CDH1-mutated invasive lobular breast cancers[93]. HER2 is predicted to be overexpressed (as assessed by FISH, CNV analysis, or immunohistochemistry) in 12-25% of breast cancers[87,94-95]. Phosphorylated HER2 was expressed in 62.5% (55/88) of HER2-positive breast cancers[96]. For patients with breast cancer and positive axillary lymph nodes, amplification of HER2 was correlated with shorter time to relapse and overall survival as compared with patients with non-amplified tumors by univariate and multivariate analysis, with greater differences observed in patients whose tumors harbored >5 copies of HER2[97]. Retrospective analysis has reported that patients with low-grade, node-negative, HER2-positive breast cancer have a 5-year survival rate of 68% compared with 96% for patients with HER2-negative tumors[98]. Acquisition of resistance to trastuzumab was correlated with negativity for pHER2 (p=0.028) for patients with HER2-positive breast cancer[96].

FINDING SUMMARY

ERBB2 (also known as HER2) encodes a receptor tyrosine kinase which is in the same family as EGFR. Amplification or overexpression of ERBB2 can lead to excessive proliferation and tumor formation[99].

GENE
CDK12

ALTERATION
rearrangement exon 4

POTENTIAL TREATMENT STRATEGIES

CDK12 inactivation in cancer is associated with genomic instability characterized by tandem duplications[100-104] and has been shown to increase tumor immunogenicity in advanced prostate cancer[101]. On the basis of preclinical and limited clinical evidence in advanced prostate cancer, CDK12 inactivation may predict benefit from immune checkpoint inhibitors[101]. Retrospective studies have observed clinical benefit, including prostate-specific antigen (PSA) responses, for patients with CDK12-mutated castration-resistant prostate cancer treated with anti-PD-1 immunotherapy[101]. Preclinical studies suggest that CDK12 truncations and inactivating mutations impair homologous recombination and sensitize cells to PARP inhibitors[105-110]. Preclinical data suggest CDK12 inactivating alterations may sensitize cells to PARP inhibitors[105-110], and the Phase 3 PROfound study reported numerically improved PFS for patients with CDK12-altered castration-resistant prostate cancer (CRPC) treated with olaparib compared to control androgen deprivation therapy (5.1 vs. 2.2 months)[111]. However, multiple clinical studies have observed no radiographic responses in patients with CDK12-altered CRPC treated with PARP inhibitors[112-113]. A patient with ovarian cancer and a CDK12 frameshift mutation experienced a PR to rucaparib[114]. Cells lacking CDK12 incur spontaneous DNA damage and exhibit heightened sensitivity to DNA-damaging agents[105-110].

FREQUENCY & PROGNOSIS

CDK12 mutation has been reported in up to 2.4% of breast cancer cases (cBioPortal, COSMIC, Jul 2020)[104,115-120]. CDK12 rearrangements resulting in truncation have been reported in 13% of HER2-positive breast cancers[106]. Published data investigating the prognostic implications of CDK12 alterations in breast cancer are limited (PubMed, Jul 2020). One study reported that CDK12 protein expression was not independently associated with outcomes for patients with breast cancer[121].

FINDING SUMMARY

CDK12 encodes a cyclin-dependent kinase that interacts with cyclin K to regulate the phosphorylation of RNA polymerase II and the expression of genes involved in maintaining genomic stability, including BRCA1 and ATR[122]. Alterations such as seen here may disrupt CDK12 function or expression[108,123-125].

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GENE
RICTOR

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES
RICTOR amplification may indicate sensitivity to mTORC1/2 inhibitors[126] or dual PI3K/mTOR inhibitors[127]. A patient with RICTOR-amplified lung adenocarcinoma experienced SD for >18 months upon treatment with the dual mTORC1/2 inhibitor CC-223[126], and a patient with RICTOR-amplified metastatic thymic carcinoma achieved a PR upon treatment with a pan-PI3K/mTORC1/2 inhibitor PQR309[127]. However, 4/4 patients with small cell lung cancer and RICTOR amplification did not achieve an objective response or SD (PFS of 1.25 months) from treatment with vistusertib[128], and additional trials of vistusertib were terminated due to lack of efficacy[129]. RICTOR alterations, including amplification, have been implicated in resistance to the EGFR tyrosine kinase inhibitor erlotinib in patients with non-small cell lung carcinoma[130].

FREQUENCY & PROGNOSIS
In the Breast Invasive Carcinoma TCGA dataset, amplification of RICTOR has been reported in 1% of cases, and RICTOR mutation was observed in fewer than 1% of cases[38]. In one study, RICTOR protein expression was reported to be decreased in breast cancer tissue compared with normal breast tissue[131]. Studies have associated RICTOR amplification or overexpression with disease progression and therapy resistance in triple-negative or HER2-amplified breast cancer[132-134], whereas RICTOR expression has been inversely correlated with tumor grade, and has been associated with better overall and disease-free survival in other studies of breast carcinoma[131,135].

FINDING SUMMARY
RICTOR encodes an mTOR-binding protein that forms part of the rapamycin-insensitive mTORC2 complex, a regulator of cell metabolism and the cytoskeleton[136-138]. RICTOR amplification has been reported in cancer[139] and has been associated with clinical response to mTORC1/2 inhibition[140-141] .

GENE
CDKN2A/B

ALTERATION
p16INK4a G89V

TRANSCRIPT ID
NM_000077

CODING SEQUENCE EFFECT
266G>T

VARIANT ALLELE FREQUENCY (% VAF)
59.6%

POTENTIAL TREATMENT STRATEGIES
Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib[142-145]. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment[146-147], multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[148-154]; it is not known whether CDK4/6 inhibitors would be beneficial in this case. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS
CDKN2A/B loss or mutation occurs in 4% and 1% of breast invasive carcinoma cases, respectively[38,118]. CDKN2B is deleted in 33% of early-onset breast cancers (n=47), compared to 14% of late-onset breast cancers (n=59)[155].

Expression of the mRNA transcripts encoding p16INK4a and p14ARF has been reported to be variable in breast carcinoma[156]. CDKN2B and CDKN2A methylation, including hypermethylation of the p16INK4a and p14ARF promoters, in breast tumors has been reported in 4-40% of breast carcinomas[155-161]. Loss of p16INK4a protein expression has been reported in breast carcinoma, including lobular and ductal carcinoma samples[162-163], and one study did not detect p14ARF protein in 21% of invasive ductal breast carcinomas[164]. However, other studies report p16INK4a expression in 26-50% of breast cancer samples while p14ARF expression has been reported in 24% of breast tumors[164-167]. Methylation of the CDKN2A promoter has been shown to increase with tumor grade in ductal carcinoma in-situ (DCIS)[158,168], and is associated with increased breast cancer-specific mortality[161]. There have been conflicting reports about the association between p16INK4a or p14ARF expression and prognosis. Some studies have showed that the overexpression of p16INK4a may play a role in the progression of breast tumors[169]. Increased expression of p16INK4a in basal-like tumors has been suggested to be involved in the poor prognosis of this tumor type[170]. However, p16INK4a expression has also been correlated with prolonged breast cancer-specific survival and disease-free survival[165-166,171]. Increased p14 expression were associated better overall and disease-free survival; p16 expression was not found to be associated with clinical outcome in this study[172]. Analysis of the expression and mutational profile of CDKN2B suggests that loss of CDKN2B may play a role in the loss of control of growth but not in the progression of tumors[173]. Loss of p16INK4a may also associate with HER2 positivity and be less frequent in triple-negative breast carcinomas, which often inactivate Rb[165,171].

FINDING SUMMARY
CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[174-175]. Both p15INK4b and p16INK4a bind to and inhibit CDK4 and CDK6, thereby maintaining the growth-suppressive activity of the Rb tumor suppressor; loss or inactivation of either p15INK4b or p16INK4a contributes to dysregulation of the CDK4/6-cyclin-Rb pathway and loss of cell cycle control[176-177]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[178-179]. One or more alterations seen here have been observed in the context of cancer but have not been characterized and their effect on p16INK4a function is unclear. Germline CDKN2A mutation is associated with melanoma-pancreatic cancer syndrome, a condition marked by increased risk of developing malignant melanoma and/or pancreatic cancer[180]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[181-182]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[183-185]. CDKN2A alteration has also been implicated in familial melanoma-astrocytoma syndrome, an extremely rare tumor association characterized by dual predisposition to melanoma and nervous system tumors[186-188]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

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GENE
FAM123B

ALTERATION
G605D

TRANSCRIPT ID
NM_152424

CODING SEQUENCE EFFECT
1814G>A

VARIANT ALLELE FREQUENCY (% VAF)
30.6%

POTENTIAL TREATMENT STRATEGIES
There are no targeted therapies available to address genomic alterations in FAM123B.

FREQUENCY & PROGNOSIS
Somatic mutation of FAM123B is rare in most cancers (COSMIC, 2021)[117], but is observed at rates ranging from 5-30% in Wilms tumor[189-191]. No association between FAM123B alteration and clinical features or outcomes of Wilms tumor has been documented.

FINDING SUMMARY
FAM123B, also known as AMER1, encodes the protein WTX, which binds to beta-catenin, enhancing its proteasomal degradation and thereby exerting a repressive effect on WNT pathway signaling[192]. Germline mutation or deletion of FAM123B causes osteopathia striata with cranial sclerosis[193-194].

GENE
TP53

ALTERATION
loss exons 10-11

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[195-198], or p53 gene therapy and immunotherapeutics such as SGT-53[199-203] and ALT-801[204]. 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[205]. 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[206]. 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[207]. 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[208]. 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[129]. 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[209]. 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[203]. 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[210]. 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[211-212]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[213-214]. 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[38,91,215-218]. TP53 mutations that are located within the region encoding the DNA binding domain are associated with poor prognosis in patients with breast cancer[216,219-220]. 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[221-223].

FINDING SUMMARY
Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[224]. Alterations such as seen here may disrupt TP53 function or expression[225-229]. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[230-232], including sarcomas[233-234]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[235] to 1:20,000[234]. 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[236]. In the appropriate clinical context, germline testing of TP53 is recommended.

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Ado-trastuzumab emtansine

Assay findings association

ERBB2
amplification

AREAS OF THERAPEUTIC USE

Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate that targets the protein ERBB2/HER2 on the cell surface, which inhibits HER2 signaling; it also releases the cytotoxic therapy DM1 into cells, leading to cell death. T-DM1 is FDA approved to treat patients with HER2-positive (HER2+) metastatic breast cancer and disease progression on prior therapy as well as patients with HER2+ early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment. Please see the drug label for full prescribing information.

GENE ASSOCIATION

ERBB2 amplification or activating mutations may predict sensitivity to T-DM1.

SUPPORTING DATA

For patients with HER2+ breast cancer (BC) previously treated with HER2-directed therapies, Phase 3 trials of single-agent T-DM1 have reported significant increases in median PFS as compared with physician's choice of therapy (6.2 vs. 3.3 months)[237] or lapatinib plus capecitabine (9.6 vs. 6.4 months)[63,238-239] . The Phase 3 MARIANNE study for patients with HER2+ advanced BC treated in the first line with T-DM1 reported no significant differences in ORR (60%, 64%, and 68%) or median PFS (14.1, 15.2, and 13.7 months) when comparing T-DM1 combined with placebo, T-DM1 with pertuzumab, and trastuzumab with a taxane, respectively[240]; however, an earlier Phase 2 study reported improved median PFS with T-DM1 as compared with trastuzumab plus docetaxel (14.2 months vs. 9.2 months, HR=0.59) in this setting[241]. In the Phase 3 KATHERINE study, patients with HER2+ early BC with residual invasive disease following completion of neoadjuvant taxane and trastuzumab treated with T-DM1 experienced significantly higher invasive disease-free survival rates at 3 years (88.3% vs.77.0%, HR=0.50) compared with patients treated with trastuzumab[242]. In the neoadjuvant setting, the Phase 3 KRISTINE study for patients with HER2+ BC reported a lower pathologic CR rate (44.4% vs. 55.7%, p=0.016) with T-DM1 plus pertuzumab compared with the combination of trastuzumab, pertuzumab, docetaxel, and carboplatin[243]. Patients with HER2+ locally advanced BC or metastatic BC (MBC) have experienced clinical benefit in Phase 1/2 studies from T-DM1 in combination with docetaxel[244], paclitaxel and pertuzumab[245], neratinib[246], alpelisib[247], and tucatinib[246]. A retrospective analysis found that patients with HER2+ MBC and active central nervous system (CNS) metastases treated with T-DM1 achieved an ORR of 40% (4/10); there was no significant OS difference between patients with and without CNS metastases[248].

Fam-trastuzumab deruxtecan

Assay findings association

ERBB2
amplification

AREAS OF THERAPEUTIC USE

Fam-trastuzumab deruxtecan is an antibody-drug conjugate that targets the protein ERBB2/HER2 on the cell surface and delivers the cytotoxic payload DXd, which inhibits DNA topoisomerase I to induce DNA damage. Fam-trastuzumab deruxtecan is FDA approved to treat patients with HER2-positive breast cancer and gastric or gastroesophageal junction adenocarcinoma who have received prior HER2-targeted therapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data in solid cancers, including breast[64,249] , gastric[250-251] , non-small cell lung[252], and colon[253] cancers, ERBB2 amplification may predict sensitivity to fam-trastuzumab deruxtecan.

SUPPORTING DATA

The Phase 2 DESTINY-Breast01 study of fam-trastuzumab deruxtecan for patients with ERBB2-positive breast cancer previously treated with ado-trastuzumab emtansine reported a 60.9% ORR (6% CR) and a 97.3% DCR with a median PFS of 16.4 months[64]. A Phase 1 trial reported similar results (59.5% ORR, 93.7% DCR, median PFS of 22.1 months) for previously treated patients with ERBB2-positive breast cancer[249]. A Phase 1b study evaluating fam-trastuzumab deruxtecan for the treatment of patients with heavily pre-treated breast cancer expressing low levels of ERBB2 reported an ORR of 37.0% (20/54) and a median duration of response of 10.4 months[254].

Lapatinib

Assay findings association

ERBB2
amplification

AREAS OF THERAPEUTIC USE

Lapatinib is a tyrosine kinase inhibitor that targets EGFR, ERBB2/HER2, and to a lesser degree, ERBB4. It is FDA approved in combination with capecitabine to treat patients with HER2-overexpressing (HER2+) metastatic breast cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Activation or amplification of ERBB2 may predict sensitivity to lapatinib[69-73] .

SUPPORTING DATA

Lapatinib as a treatment for HER2+ breast cancer has primarily been investigated in combination with other chemotherapeutic agents; these combination regimens have been shown to extend PFS as well as to extend OS in some instances[69-70,255-258] . However, multiple Phase 3 trials have shown superiority of other HER2-targeted agents in certain settings, including trastuzumab plus taxane as first-line therapy for HER2+ metastatic breast cancer[259] and ado-trastuzumab emtansine (T-DM1) for patients who have progressed on trastuzumab plus taxane[63]. Phase 3 studies of adjuvant lapatinib have reported no significant disease-free survival benefit compared with placebo[260] or trastuzumab[261]. Phase 2/3 trials in the neoadjuvant setting have found that the combination of lapatinib and trastuzumab may result in numerically improved ORRs compared with either drug alone[256-257,262] .

Lapatinib + Letrozole

Assay findings association

ERBB2
amplification

AREAS OF THERAPEUTIC USE

Lapatinib is a tyrosine kinase inhibitor that targets EGFR and ERBB2 (HER2) and letrozole is an aromatase inhibitor. The combination is FDA approved for the treatment of HER2-overexpressing (HER2+) metastatic breast cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Clinical benefit with lapatinib combined with letrozole has been observed for patients with breast cancer harboring ERBB2 amplification[89].

SUPPORTING DATA

The combination of lapatinib with letrozole[89] significantly improved PFS (8.2 vs 3.0 months) and ORR (28% vs 15%) for patients with HR+, HER2+ breast cancer compared to letrozole + placebo but did not improve PFS for patients with HR+, HER2-negative breast cancer.

Margetuximab

Assay findings association

ERBB2
amplification

AREAS OF THERAPEUTIC USE

Margetuximab is an Fc-engineered antibody targeting ERBB2/HER2 that was designed to enhance the anti-tumor immune response. Margetuximab is FDA approved for the treatment of patients with HER2-positive breast cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical studies in multiple tumor types, ERBB2 amplification may predict sensitivity to margetuximab[84,263-265] .

SUPPORTING DATA

The Phase 3 SOPHIA trial of margetuximab for HER2-positive metastatic breast cancer, reported improved median PFS (5.8 vs. 4.9 months, HR=0.76) and ORR (22% vs. 16%) when combining margetuximab with chemotherapy, compared with trastuzumab and chemotherapy, for patients who had progressed on ≥2 prior HER2-directed therapies[84]. A Phase 1 trial for HER2-positive solid tumors reported 4 PRs in patients with breast cancer[263]. In a study of margetuximab for HER2-positive cancers, 2/10 patients with breast cancer reported PRs[264].

Neratinib

Assay findings association

ERBB2
amplification

AREAS OF THERAPEUTIC USE

Neratinib is an irreversible tyrosine kinase inhibitor that targets EGFR, ERBB2/HER2, and ERBB4. It is FDA approved for the extended adjuvant treatment of early-stage HER2-positive (HER2+) breast cancer following adjuvant trastuzumab. Neratinib is also approved in combination with capecitabine to treat patients with advanced or metastatic HER2+ breast cancer who have been previously treated with 2 or more anti-HER2 regimens. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of extensive clinical[80,266-269] and preclinical[270-274] evidence, ERBB2 amplification or activating mutations may confer sensitivity to neratinib.

SUPPORTING DATA

For patients with HER2+ metastatic breast cancer following progression on 2 or more lines of HER2-directed therapies, the Phase 3 NALA study showed improved mean PFS (8.8 vs. 6.6 months, HR=0.76) and fewer interventions for CNS disease with neratinib plus capecitabine than with lapatinib plus capecitabine; mean OS did not significantly differ between the treatments (24.0 vs. 22.2 months, HR=0.88)[275]. In a Phase 2 study for patients with advanced HER2+ breast cancer, neratinib monotherapy resulted in a median PFS of 22.3 weeks for patients previously treated with trastuzumab (n=63) and 39.6 weeks for patients with no prior trastuzumab treatment (n=64)[276]. Single-agent neratinib showed modest CNS activity (7.5% ORR, 3/40) in a Phase 2 study for patients with breast cancer and HER2+ brain metastases[277]. As first-line therapy in HER2+ metastatic breast cancer, a Phase 2 study for neratinib plus paclitaxel compared with trastuzumab plus paclitaxel reported a lower incidence of CNS disease recurrence[278]. The I-SPY2 Phase 2 trial reported, as neoadjuvant treatment in HER2+, HR- breast cancer, the estimated pathologic CR rate was 56% for neratinib plus paclitaxel compared with 33% for trastuzumab plus paclitaxel[269]. In the placebo-controlled Phase 3 ExteNET study for patients with early stage HER2+ breast cancer previously treated with trastuzumab, extended adjuvant neratinib for one year significantly improved 2-year invasive disease-free survival (iDFS; 93.9% vs. 91.6%, HR=0.67)[268] and 5-year iDFS (90.2% vs. 87.7%, HR=0.73)[279]. Final OS analysis of this study did not reach statistical significance in the ITT population (HR=0.95)[280].

Trastuzumab

Assay findings association

ERBB2
amplification

AREAS OF THERAPEUTIC USE

Trastuzumab is a monoclonal antibody that targets the protein ERBB2/HER2. It is FDA approved as monotherapy and in combination with chemotherapy for HER2+ metastatic gastric or gastroesophageal adenocarcinoma. Trastuzumab biosimilars are also FDA approved for these indications. Please see the drug label(s) for full prescribing information.

GENE ASSOCIATION

On the basis of clinical studies in multiple tumor types, ERBB2 amplification, overexpression, or activating mutations may confer sensitivity to trastuzumab[53-54,58,72,281-285].

SUPPORTING DATA

In a retrospective study for patients with HER2-positive breast cancer treated with neoadjuvant chemotherapy with or without trastuzumab, patients with non-inflammatory breast cancer reported a significant association between elevated HER2 FISH ratio and increased pathologic CR rate and longer OS, compared with patients with inflammatory breast cancer (IBC)[286]. In a study of patients with early breast cancer treated with neoadjuvant trastuzumab, higher ERBB2 copy number (HER2/CEP17 ratio >6) correlated with increased incidence of pathologic CR compared to lower ERBB2 copy number[287]. A Phase 3 study of adjuvant trastuzumab with chemotherapy for patients with metastatic HER2-positive breast cancer (HER2+ BC) demonstrated significant improvements in OS, time to progression, and ORR[53]. Trastuzumab biosimilars demonstrated comparable clinical benefit to trastuzumab for patients with HER2+ BC[288-296]. In the Phase 3 NOAH study for patients with HER2+ BC, neoadjuvant trastuzumab plus chemotherapy resulted in improved 5-year event-free survival (EFS) compared with neoadjuvant chemotherapy alone (58% vs. 43%)[281]. The Phase 3 CLEOPATRA study of first-line trastuzumab with pertuzumab and docetaxel for patients with metastatic HER2+ BC reported significantly improved median PFS (18.7 vs. 12.4 months, HR=0.69) and median OS (57.1 vs. 40.8 months, HR=0.69) compared with trastuzumab plus docetaxel[59-60,297-298]. The Phase 3 NeoALTTO trial for patients with early-stage HER2+ BC treated with lapatinib, trastuzumab, or a combination of both reported 3-year EFS rates of 78%, 76%, and 84%, and 3-year OS rates of 93%, 90%, and 95%, respectively[262]. Two Phase 3 studies comparing 6-month with 12-month adjuvant trastuzumab reported similar disease-free survival (DFS) rates for patients with HER2+ early-stage BC after 5.4 years (89.4% vs. 89.8%, HR=1.07)[299] or 7.5-year median follow-up (78.8% vs. 79.6%, HR=1.08)[300]. The randomized Phase 3 NSABP B-47 study reported that the addition of trastuzumab to adjuvant chemotherapy did not significantly improve invasive disease-free survival (IDFS) for patients with HER2-low BC (defined as IHC score of 1+ or 2+ in the absence of gene amplification) compared with chemotherapy alone (5-year IDFS rates of 89.8% vs. 89.2%, HR=0.98; p=0.85); this response was reported regardless of lymph node involvement or HR status[301]. A Phase 2 analysis reported 5-year distant DFS rates of 92% for patients with HER2+ early-stage BC treated with chemotherapy and trastuzumab, and 89% for patients treated with lapatinib and chemotherapy[282]. In the Phase 3 BOLERO-1 trial, first-line treatment with everolimus and trastuzumab plus paclitaxel versus placebo for patients with HER2+ advanced BC did not significantly improve median PFS (15.0 vs. 14.5 months); however, the regimen increased PFS in the HR-negative subpopulation (20.3 vs. 13.1 months, HR=0.66)[302]. Everolimus plus trastuzumab with vinorelbine prolonged median PFS (7.0 vs. 5.8 months, HR=0.78), relative to the addition of placebo, for patients with trastuzumab-resistant HER2+ BC treated in the Phase 3 BOLERO-3 trial[303]. In a Phase 2 trial for patients with HER2+ metastatic BC previously treated with HER2-targeting agents, tucatinib plus trastuzumab and capecitabine significantly extended median PFS (7.8 vs. 5.6 months) and increased the 1-year median PFS rate (33.1% vs. 12.3%, HR=0.54) and 2-year median OS rate (44.9% vs. 26.6%, HR=0.66) compared with placebo with trastuzumab and capecitabine[65]. For patients with HR+, HER2+ BC who had received prior HER2-targeted therapy, abemaciclib combined with trastuzumab and fulvestrant compared with abemaciclib plus trastuzumab or trastuzumab plus chemotherapy significantly improved median PFS (8.3 vs. 5.7 vs. 5.7 months) and ORR (35.7% vs. 16.2% vs. 15.9%) in Phase 2 monarcHER study[304].

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Trastuzumab + Pertuzumab

Assay findings association

ERBB2
amplification

AREAS OF THERAPEUTIC USE

Trastuzumab is a monoclonal antibody that targets ERBB2/HER2, and pertuzumab is a monoclonal antibody that interferes with the interaction between HER2 and ERBB3. These therapies are FDA approved in combination for the treatment of patients with HER2-positive (HER2+) metastatic breast cancer who have not received prior chemotherapy or HER2-targeted therapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical studies in multiple tumor types, ERBB2 amplification or activating mutations may predict sensitivity to trastuzumab in combination with pertuzumab[60,283,305-309] .

SUPPORTING DATA

The CLEOPATRA Phase 3 randomized trial for patients with HER2+ metastatic breast cancer (MBC) reported that compared to placebo, addition of pertuzumab to first-line trastuzumab and docetaxel demonstrated a significant improvement in median PFS (18.7 vs. 12.4 months, HR=0.69) and median OS (57.1 vs. 40.8 months, HR=0.69)[59-60,297-298] . Superior clinical benefit has been observed in multiple clinical studies where pertuzumab was added to the combination of trastuzumab plus chemotherapy as compared to other combinations of pertuzumab, trastuzumab, and/or chemotherapy in patients with HER2+ MBC and locally advanced breast cancer (LABC)[308,310-313] . In the large-scale randomized Phase 3 APHINITY study for patients with HER2+ early-stage breast cancer, the addition of pertuzumab to chemotherapy plus trastuzumab as adjuvant treatment improved the estimated 3-year rate of invasive disease-free survival (IDFS) compared with placebo (94.1% vs. 93.2%), with greater improvement seen for patients with node-positive (92.0% vs. 90.2%, HR=0.77) than those with node-negative (97.5% vs. 98.4%, HR=1.13) disease[306]. In the randomized large-scale Phase 3 KRISTINE trial, patients with HER2+ Stage 2 to Stage 3 breast cancer treated in the neoadjuvant setting experienced an increased number of pathological CRs (pCRs) when treated with pertuzumab, trastuzumab, and chemotherapy, as compared to trastuzumab emtansine plus pertuzumab (55.7% vs. 44.4%, respectively)[305].

Trastuzumab + Tucatinib

Assay findings association

ERBB2
amplification

AREAS OF THERAPEUTIC USE

Trastuzumab is a monoclonal antibody that targets ERBB2/HER2, and tucatinib is a reversible TKI targeting ERBB2/HER2. These therapies are FDA approved in combination for the treatment of patients with previously treated advanced HER2-positive breast cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data in breast cancer[65-68] and colorectal cancer[314], ERBB2 amplification may predict sensitivity to trastuzumab plus tucatinib.

SUPPORTING DATA

In the Phase 2 HER2CLIMB trial for patients with HER2+ metastatic BC previously treated with HER2-targeting agents, the combination of tucatinib with trastuzumab and capecitabine significantly extended median PFS (7.8 vs. 5.6 months, HR=0.54) and median OS (21.9 vs. 17.4 months, HR=0.66) compared with placebo plus trastuzumab and capecitabine[65]. For HER2CLIMB patients with brain metastases, the tucatinib-containing combination improved intracranial ORR (47% vs. 20%), central nervous system-specific PFS (9.9 vs. 4.2 months, HR=0.32), and OS (18.1 vs. 12.0 months, HR=0.58)[315].

Afatinib

Assay findings association

ERBB2
amplification

AREAS OF THERAPEUTIC USE

Afatinib is an irreversible kinase inhibitor that targets the kinase domains of EGFR, ERBB2/HER2, and ERBB4. It is FDA approved for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) and nonresistant EGFR mutations and for the treatment of patients with metastatic, squamous NSCLC after progression on platinum-based chemotherapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Clinical and preclinical data support sensitivity of multiple activating mutations in ERBB2, including A775_G776insYVMA and P780_Y781insGSP, to afatinib[316-323] . Studies have reported DCRs of 54 to 70% for patients with ERBB2-mutated NSCLC treated with afatinib, most of whom harbored exon 20 insertions[316-319] .

SUPPORTING DATA

In a Phase 3 study for patients with HER2-positive (HER2+) breast cancer and disease progression on trastuzumab, afatinib plus vinorelbine compared to trastuzumab plus vinorelbine did not improve median PFS (5.5 vs. 5.6 months) or ORR (46% vs. 47%), associated with shorter median OS (20.5 vs. 28.6 months), and was less well tolerated[324]. Afatinib monotherapy achieved an ORR of 11% (4/35) and a median OS of 61 weeks in this setting[74]. For patients with progressive brain metastases after HER2-targeted therapy, treatment with afatinib alone, afatinib combined with vinorelbine, or investigator's choice did not increase patient benefit (12/40 vs. 13/38 vs. 18/43) and caused frequent adverse events[325]. As neoadjuvant treatment for HER2+ breast cancer, afatinib demonstrated a comparable or higher ORR (80%, 8/10) than lapatinib (75%, 6/8) or trastuzumab (36%, 4/11); however, adverse events were more frequent than with lapatinib or trastuzumab[326]. In contrast, a Phase 2 trial reported no objective responses for genomically unselected patients with HER2-negative breast cancer[327]. Afatinib plus letrozole achieved SD for 54% (15/28) of patients with estrogen receptor-positive breast cancer who had progressed on single-agent letrozole[328].

Dacomitinib

Assay findings association

ERBB2
amplification

AREAS OF THERAPEUTIC USE

Dacomitinib is a second generation irreversible tyrosine kinase inhibitor that targets the kinase domains of EGFR, ERBB2/HER2, and ERBB4/HER4. It is FDA approved for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with EGFR exon 19 deletion or exon 21 L858R substitution mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of strong clinical[81,329-332] and preclinical[333-336] data, ERBB2 amplification or activating mutation may indicate sensitivity to dacomitinib.

SUPPORTING DATA

Clinical data on the efficacy of dacomitinib for the treatment of breast carcinoma are limited (PubMed, Aug 2020). Investigations into the efficacy of dacomitinib have primarily been in the context of non-small cell lung cancer (NSCLC). Patients with EGFR-mutant NSCLC treated with dacomitinib exhibited significant improvement in OS compared with gefitinib treatment (median OS, 34.1 vs. 26.8 months)[337-338] . A Phase 2 study of dacomitinib in patients with advanced penile squamous cell carcinoma (SCC) reported an ORR of 32% (1 CR, 8 PR), including a 100% DCR (1 CR, 1 PR, 2 SD) in four patients with EGFR amplification[339-340]. A Phase 2 study of dacomitinib in patients with recurrent or metastatic head and neck SCC reported clinical benefit (defined as PFS>4 months) in 13/31 (42%) of patients[331]. Studies of dacomitinib in esophageal[341] and cutaneous[342] SCC reported RRs of 12.5% (6/48) and 28.6% (12/42), respectively, but high DCRs of 73% and 86%, respectively. In contrast, trials of dacomitinib in heavily pretreated patients with HER2+ gastric cancer[332] and patients with EGFR-amplified glioblastoma[343] found RRs of fewer than 10% and DCRs of fewer than 50%: 11/27 (41%) DCR in HER2+ gastric cancer[332] and 15/49 (31%) in EGFR-amplified glioblastoma[343].

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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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
CDK12

ALTERATION
rearrangement exon 4

RATIONALE
Preclinical and clinical data suggest that tumors with CDK12 mutation or loss may be sensitive to PARP inhibitors.

NCT03742895

PHASE 2

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

TARGETS
PARP

LOCATIONS: Lima (Peru), Trujillo (Peru), Cali (Colombia), Bogota (Colombia), Medellin (Colombia), Monteria (Colombia), Valledupar (Colombia), Barranquilla (Colombia), Buenos Aires (Argentina), Ciudad de Buenos Aires (Argentina)

NCT04123366

PHASE 2

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

TARGETS
PARP, PD-1

LOCATIONS: Lima (Peru), Bellavista (Peru), Cuzco (Peru), Cali (Colombia), Medellin (Colombia), Bucaramanga (Colombia), Barranquilla (Colombia), Buenos Aires (Argentina), Ciudad de Buenos Aires (Argentina), Guatemala (Guatemala)

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, Texas, South Carolina

NCT03992131

PHASE 1/2

A Study to Evaluate Rucaparib in Combination With Other Anticancer Agents in Patients With a Solid Tumor (SEASTAR)

TARGETS
PARP, FGFRs, VEGFRs, TOP1

LOCATIONS: Texas, Tennessee, Massachusetts

NCT02769962

PHASE 1/2

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

TARGETS
PARP, TOP1

LOCATIONS: Maryland

NCT02264678

PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1

LOCATIONS: New York, Massachusetts, California, Saint Herblain (France), Withington (United Kingdom), Sutton (United Kingdom), London (United Kingdom), Villejuif (France), Seoul (Korea, Republic of)

NCT02286687

PHASE 2

Phase II Study of BMN 673

TARGETS
PARP

LOCATIONS: Texas

NCT03842228

PHASE 1

Copanlisib, Olaparib, and Durvalumab in Treating Patients With Metastatic or Unresectable Solid Tumors

TARGETS
PI3K, PD-L1, PARP

LOCATIONS: Texas, Massachusetts

NCT04267939

PHASE 1

ATR Inhibitor BAY 1895344 Plus Niraparib Phase 1b Study in Advanced Solid Tumors and Ovarian Cancer

TARGETS
ATR, PARP

LOCATIONS: Texas, New York, Massachusetts

NCT03964532

PHASE 1/2

TALAVE: Induction Talazoparib Followed by Combination of Talazoparib and Avelumab in Advanced Breast Cancer

TARGETS
PD-L1, PARP

LOCATIONS: North Carolina, District of Columbia

GENE
ERBB2

ALTERATION
amplification

RATIONALE
ERBB2 amplification may confer sensitivity to the combination of lapatinib with aromatase inhibitors. ERBB2 amplification or activating mutation may confer sensitivity to HER2-targeted and dual EGFR/HER2-directed therapies, and may enhance efficacy of HSP90 inhibitors.

NCT03387553

PHASE NULL

HER2 Directed Dendritic Cell Vaccine During Neoadjuvant Therapy of HER2+Breast Cancer

TARGETS
ERBB2, ERBB3

LOCATIONS: Florida

NCT03975647

PHASE 3

A Study of Tucatinib vs. Placebo in Combination With Trastuzumab Emtansine (T-DM1) for Patients With Advanced or Metastatic HER2+ Breast Cancer

TARGETS
ERBB2

LOCATIONS: Florida, Louisiana, Alabama, Texas

NCT03199885

PHASE 3

Paclitaxel, Trastuzumab, and Pertuzumab With or Without Atezolizumab in Treating Patients With Metastatic Breast Cancer

TARGETS
PD-L1, ERBB2, ERBB3

LOCATIONS: Florida, Mississippi

NCT02947685

PHASE 3

Randomized, Open Label, Clinical Study of the Targeted Therapy, Palbociclib, to Treat Metastatic Breast Cancer

TARGETS
ERBB2, ERBB3, ER, Aromatase, CDK4, CDK6

LOCATIONS: Florida, Louisiana, Texas, South Carolina, Georgia, North Carolina

NCT02693535

PHASE 2

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

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

LOCATIONS: Florida, Texas, Georgia, Alabama, North Carolina, Virginia, Oklahoma, Pennsylvania, Indiana

NCT03377387

PHASE 1/2

Capecitabine 7/7 Schedule With Neratinib in Patients With Metastatic HER2-Positive Breast Cancer

TARGETS
EGFR, ERBB2, ERBB4

LOCATIONS: Florida, New Jersey, Pennsylvania, New York, Connecticut

NCT03179904

PHASE 2

FASN Inhibitor TVB-2640, Paclitaxel, and Trastuzumab in Treating Patients With HER2 Positive Advanced Breast Cancer

TARGETS
FASN, ERBB2

LOCATIONS: Florida, Arizona, Minnesota

NCT03523572

PHASE 1

Trastuzumab Deruxtecan (DS-8201a) With Nivolumab in Advanced Breast and Urothelial Cancer

TARGETS
PD-1, ERBB2

LOCATIONS: Florida, North Carolina, Tennessee, Kentucky, New York, Connecticut, California, Utah, Washington, Madrid (Spain)

NCT03219268

PHASE 1

A Study of MGD013 in Patients With Unresectable or Metastatic Neoplasms

TARGETS
LAG-3, PD-1, ERBB2

LOCATIONS: Florida, Texas, North Carolina, Tennessee, Oklahoma, Maryland, Ohio, Pennsylvania, Massachusetts

NCT01042379

PHASE 1

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, District of Columbia, Pennsylvania, New York, Connecticut, Illinois

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GENE
RICTOR

ALTERATION
amplification

RATIONALE
RICTOR amplification may predict sensitivity to dual mTORC1/mTORC2 inhibitors, as well as dual PI3K/mTOR inhibitors.

NCT04032080

PHASE 2

Treatment With Oral LY3023414 To Inhibit Homologous Recombination Followed By Prexasertib

TARGETS
CHK1, mTOR, PI3K

LOCATIONS: Texas

NCT03366103

PHASE 1/2

Navitoclax and Vistusertib in Treating Patients With Relapsed Small Cell Lung Cancer and Other Solid Tumors

TARGETS
mTORC1, mTORC2, BCL-W, BCL-XL, BCL2

LOCATIONS: Maryland, New Jersey, New York

NCT02159989

PHASE 1

Sapanisertib and Ziv-Aflibercept in Treating Patients With Recurrent Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery

TARGETS
PIGF, VEGFA, VEGFB, mTORC1, mTORC2

LOCATIONS: Texas

NCT03017833

PHASE 1

Sapanisertib and Metformin in Treating Patients With Advanced or Metastatic Relapsed or Refractory Cancers

TARGETS
mTORC1, mTORC2

LOCATIONS: Texas

NCT03430882

PHASE 1

Sapanisertib, Carboplatin, and Paclitaxel in Treating Patients With Recurrent or Refractory Malignant Solid Tumors

TARGETS
mTORC1, mTORC2

LOCATIONS: Texas

NCT03065062

PHASE 1

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

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

LOCATIONS: Massachusetts

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chengdu (China)

NCT03154294

PHASE 1

Evaluation of the Safety and Tolerability of TAK-228 With TAK-117 and Paclitaxel in Advanced Solid Tumors

TARGETS
PI3K-alpha, mTORC1, mTORC2

LOCATIONS: South Dakota

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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.

CDK12
amplification

ID3
K114E

KEAP1
amplification

MAP3K1
amplification

POLE
V134D

RAD51D
amplification

RET
D567N

SDHC
I58M

SPEN
S2306del

SPOP
amplification

TP53
rearrangement

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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. 2020. All rights reserved. To view the most recent and complete version of the guideline, 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. Observed TMB is dependent on characteristics

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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.

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*

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

MR Suite Version 2.1.0

The median exon coverage for this sample is 565x

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