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)
NAME
DATE OF BIRTH
SEX Female
MEDICAL RECORD #

PHYSICIAN

ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT
MEDICAL FACILITY ID
PATHOLOGIST

SPECIMEN

SPECIMEN SITE
SPECIMEN ID
SPECIMEN TYPE
DATE OF COLLECTION
SPECIMEN RECEIVED

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 1 Muts/Mb

Genomic Findings

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

ERBB2 amplification
FGFR1 amplification
AURKA amplification
MYC amplification
NSD3 (WHSC1L1) amplification
RAD21 amplification
TP53 V216M
ZNF217 amplification
ZNF703 amplification

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

9 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 - 1 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)
ERBB2 **-** amplification	Ado-trastuzumab emtansine [1] Pertuzumab [1] Trastuzumab [1] Lapatinib [2A] Neratinib [2A] Fam-trastuzumab deruxtecan	Afatinib Dacomitinib
10 Trials *see p. 16*		
FGFR1 **-** amplification	none	Pazopanib
10 Trials *see p. 18*		
AURKA **-** amplification	none	none
1 Trial *see p. 15*		
MYC **-** amplification	none	none
7 Trials *see p. 20*		

[ ] *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.

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

No MSI was observed in two large scale analyses of breast cancer samples[6-7]. However, in Lynch syndrome-related breast cancer, MSI has been reported in 51-85% of cases[8-13]. A prospective study observed increased MSI following chemotherapy treatment, and MSI is associated with incidence of secondary tumors[14].

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[15]. 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[15-17]. 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[18-20]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[15,17,19-20].

BIOMARKER

Tumor Mutational Burden

RESULT
1 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[21-23] and anti-PD-1 therapies[21-24]. Higher TMB has corresponded with increased ORR and OS from treatment with immune checkpoint inhibitors in pan-tumor studies[21-24]. Analyses across several solid tumor types have identified that patients with higher TMBs (≥16-20 Muts/Mb) achieved greater clinical benefit using PD-1/PD-L1 monotherapy, compared with patients treated with chemotherapy[25] or those with lower TMBs[22]. Additionally, higher TMB is significantly associated with improved OS with immune checkpoint inhibitor treatment for patients with advanced cancer across 9 solid tumor types[21]. However, the KEYNOTE 158 trial found significant improvement in ORR in a large cohort of patients with a TMB of ≥10 Muts/Mb compared with those with TMBs <10 across multiple solid tumor types, with similar findings observed in the KEYNOTE 028 and 012 trials[24]. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1/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)[26]. 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[27]. In breast cancer, TMB is significantly higher in recurrent versus primary tumors and CDH1-mutated versus CDH1-wildtype tumors[28]. Higher frequencies of TMB high (>20Mut/mb) have also been reported in metastatic invasive lobular carcinomas (8.9%) compared to metastatic invasive ductal carcinomas (1.6%)[28]. In estrogen receptor-positive breast cancer, increased mutation load (> mean of 1.25 muts/Mb) associated with shorter OS (HR of 2.02) in an analysis of the TCGA data[29]. In another study, the number of mutated genes associated with higher tumor grade[30]. Although the number of mutated genes did not correlate with OS by multivariate analysis, cases with 22 or more mutated genes had significantly worse OS than cases with fewer than 22 mutated genes (HR of 4.6)[30].

FINDING SUMMARY

Tumor mutational 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[31-32] and cigarette smoke in lung cancer[33-34], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[35-39], and microsatellite instability (MSI)[35,38-39]. 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[22-23].

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[40-45], pertuzumab in combination with trastuzumab[42,46-48], margetuximab[49], and ZW25[50] as well as antibody-directed conjugates such as ado-trastuzumab emtansine[51] and fam-trastuzumab deruxtecan[52], HER2 kinase inhibitors such as tucatinib[53-55], and dual EGFR/HER2 kinase inhibitors such as lapatinib[56-60], afatinib[45,61-66], neratinib[67-68], dacomitinib[69], and pyrotinib[70]. For patients with HER2-positive metastatic breast cancer, combining margetuximab[71] or pyrotinib[72-73] with chemotherapy significantly improved PFS or ORRs. The Phase 3 SOPHIA study reported improved median PFS (5.8 vs. 4.9 months, HR=0.76) and ORR (22% vs.16%) when combining margetuximab with chemotherapy, as compared with trastuzumab and chemotherapy, for patients who had progressed on ≥2 prior HER2-directed therapies[71]. For patients who had progressed on trastuzumab, the Phase 3 PHENIX study demonstrated improved median PFS (11.1 vs. 4.1 months, HR=0.18) and ORR (69% vs. 16%) for treatment with pyrotinib and capecitabine, as compared with placebo and capecitabine; patients who progressed on the placebo arm and went on to receive single-agent pyrotinib (n=71) achieved median PFS of 5.5 months and ORR of 38%[70].The same combination elicited an ORR of 91% (10/11) for trastuzumab-naive patients, and multiple genetic alterations were significantly associated with poorer PFS compared with none or one genetic alteration (16.8 vs. 29.9 months)[72]. In a randomized Phase 2 trial for previously treated patients, the combination of pyrotinib with capecitabine significantly improved ORR (71% vs. 49%, p=0.01) and median PFS (12.6 vs. 5.6 months, HR=0.37) compared with lapatinib and capecitabine irrespective of prior chemotherapy and trastuzumab treatments[73]. In a Phase 1 trial of margetuximab for HER2-overexpressing solid tumors, 12% (7/60) of patients, including 4 with breast, 2 with gastroesophageal, and 1 with lacrimal gland cancers, experienced PRs, and a further 52% (31/60) of the cohort experienced SD[49]. Early clinical studies aimed at preventing or overcoming resistance to anti-HER2 therapies are underway, including agents targeting the PI3K-AKT pathway or HSP90[74-75].

FREQUENCY & PROGNOSIS

In the TCGA dataset, ERBB2 amplification was detected in 13% of breast invasive carcinoma cases[27]. ERBB2 mutations have been reported in 1-3% of breast invasive carcinoma cases[27,76-77]. The incidence of ERBB2 alterations has been found to be significantly enriched in CDH1-mutated invasive lobular breast cancers[78]. HER2 is predicted to be overexpressed (as assessed by FISH, CNV analysis, or immunohistochemistry) in 12-25% of breast cancers[74,79-80]. Phosphorylated HER2 was expressed in 62.5% (55/88) of HER2-positive breast cancers[81]. Phosphorylated HER2 was associated with development of trastuzumab resistance[81].

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[82].

GENE
FGFR1

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

Tumors with alterations that activate FGFR1 may be sensitive to FGFR family inhibitors[83]. In addition to the pan-FGFR inhibitor erdafitinib[84-85], other FGFR inhibitors such as infigratinib, AZD4547, Debio 1347, TAS-120 and the multikinase inhibitors lenvatinib and lucitanib, are under clinical investigation. Two case studies reported PRs in patients with FGFR1-amplified breast cancer treated with pazopanib[86]. In addition to preclinical evidence supporting the activity of ponatinib for FGFR1 alterations[87-91], limited activity of ponatinib has been demonstrated in patients with FGFR1-rearranged hematological malignancies, including leukemia[92-93] and myeloproliferative neoplasms[94], and SD was reported in 2 of 4 cases of FGFR1-positive lung squamous cell carcinoma[95]. In a Phase 1/2a study of patients with breast carcinoma harboring an amplification of FGFR1, FGF3, FGF4, or FGF19, lucitanib resulted in a disease control rate (DCR) of 100%; 50% (6/12) of patients achieved PR and 50% (6/12) of patients had SD[96]. A Phase 1 study of infigratinib reported a DCR of 50% (18/36), including 4 PRs and 14 SDs, for patients with FGFR1-amplified squamous non-small cell lung carcinoma (NSCLC); although no responses were reported for patients with other tumor types harboring FGFR1 alterations, 32% (10/31) of patients with FGFR1- or FGFR2-amplified breast cancer experienced SD[97]. Preclinical studies suggest that overexpression of FGFR1 may be a mechanism of acquired resistance to gefitinib; addition of an FGFR inhibitor restored gefitinib sensitivity in lung cancer cell lines[98-99].

FREQUENCY & PROGNOSIS

FGFR1 amplification has been reported in 10-27% of breast cancers[27,100-105] and correlated with FGFR1 mRNA overexpression[102-104,106]. FGFR1 amplification correlates with poor prognosis in patients with breast cancer[101-102,107-108], including those with HER2-positive cancer treated with adjuvant trastuzumab[107], and patients with hormone-receptor positive cancer[101,108]. For patients with HR-positive/HER2-negative breast tumors treated with first-line endocrine therapy, FGFR1 amplification associated with a shorter time to progression compared to non-amplified tumors (8.0 vs 13.3 months)[109].

FINDING SUMMARY

FGFR1 encodes the protein fibroblast growth factor receptor 1, which plays key roles in regulation of the cell cycle and angiogenesis and is an upstream regulator of the RAS, MAPK, and AKT signaling pathways[110]. Amplification of FGFR1 has been correlated with protein expression[111-112] and may predict pathway activation and sensitivity to therapies targeting this pathway[83,113].

GENE
AURKA

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES
There are no approved therapies that target Aurora kinase A; however, several inhibitors of Aurora kinase A are in clinical trials[114-115]. The investigational Aurora kinase A inhibitor alisertib has been evaluated in patients with genomically unselected solid tumors and achieved objective response rates of 9% (2/22) in advanced urothelial cancer[116], 18% (9/49) in breast cancer, 21% (10/48) in small cell lung cancer, 4% (1/23) in non-small cell lung cancer, 9% (4/45) in head and neck squamous cell carcinoma, and 9% (4/47) in gastroesophageal adenocarcinoma[117]. However, a high incidence of serious adverse events was reported in urothelial cancer treated with alisertib[116]. In some cancer types, including colorectal cancer, AURKA amplification has been associated with resistance to taxane therapy[118-120].

FREQUENCY & PROGNOSIS
The frequency of AURKA amplification in breast tumors has been reported to range from 3-21%[27,100,105,121]. In patients with some tumor types, such as colon and breast, Aurora kinase A overexpression has been associated with more aggressive disease and poor prognosis, but the earlier studies may have been confounded by the presence of other genes in the amplified chromosome region 20q13[122-124]. In breast cancer, amplified AURKA is likely associated with proliferation, but also with good prognosis (5-year metastasis-free survival, 91%)[124-125].

FINDING SUMMARY
AURKA encodes the protein Aurora A kinase, a serine/threonine kinase that plays a critical role in cell division and maintenance of chromosome structure. AURKA is commonly amplified in cancer, and Aurora kinase A overexpression has been shown to lead to defects in chromosomal stability[120].

GENE
MYC

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES
There are no available therapies that directly target MYC. However, preclinical studies have suggested several synthetic lethal strategies to indirectly target MYC; these studies have shown that cells that overexpress MYC protein may be sensitive to CDK1, CDK2, or Aurora kinase B inhibitors, including those that are under investigation in clinical trials[126-131]. A patient with MYC-amplified invasive ductal breast carcinoma experienced a partial response to an Aurora kinase inhibitor[132]. Furthermore, in numerous preclinical studies, inhibition of BET bromodomain-containing proteins, in particular BRD4, has been reported to downregulate MYC expression and MYC-dependent gene expression programs in a variety of hematopoietic and solid tumor cancer models and primary cells[133-135]. Phase 1 trials of the BET inhibitor OTX015 in patients with hematological malignancies reported clinical activity in patients with acute myeloid leukemia (AML) or lymphoma[136-138] . On the basis of preclinical[139-140] and clinical[141-142] data, MYC alterations that lead to increased MYC expression may predict sensitivity to CUDC-907, a dual inhibitor of HDAC and PI3K, in diffuse large B-cell lymphoma (DLBCL); it is not clear whether this approach would be beneficial in other cancer types. Preclinical evidence suggests that tumors with high MYC expression are dependent on glutaminase metabolism[143-146] and may be more sensitive to glutaminase inhibitors such as telaglenastat[143,147-149], which is in clinical trials for solid and hematological cancers. MYC amplification has also been suggested to predict response to chemotherapy in patients with breast cancer in some studies[150-151]. Preclinical evidence suggests that colon cancer cells with MYC amplification may be more sensitive to 5-fluorouracil and paclitaxel[152-153].

FREQUENCY & PROGNOSIS
In the TCGA dataset, MYC amplification was observed in 15% of breast invasive carcinoma cases[27]. 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[150,154-156].

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[157]. MYC dysregulation (amplification, overexpression, translocation) has been identified in a number of different cancer types[158]. MYC amplification has been significantly linked with increased mRNA and protein levels and results in the dysregulation of a large number of target genes[157,159-160].

GENE
NSD3 (WHSC1L1)

ALTERATION
amplification

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%)[161], breast invasive carcinoma (13%)[162], bladder urothelial carcinoma (9%)[163], and head and neck squamous cell carcinoma (9%)[164] samples. NSD3-NUP98 fusion has been detected in a patient with acute myeloid leukemia (AML)[165], and NUP98 and NSD3 rearrangements have been identified in a patient with radiation-associated myelodysplastic syndrome (MDS)[166]. NSD3-NUT fusion has been reported as a recurrent fusion in midline carcinoma[167-170].

FINDING SUMMARY
NSD3, also known as WHSC1L1, encodes an enzyme that mediates histone methylation[171]. NSD3 has been shown to be amplified in various cancers[172-174].

GENE
RAD21

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES
There are no therapies to target alterations in this gene.

FREQUENCY & PROGNOSIS
RAD21 amplifications, point mutations, and truncating mutations have been reported in various cancers[175]. In the context of breast cancer, increased RAD21 expression has been correlated with poor prognosis in multiple subtypes[176-177], including sporadic Grade 3 but not Grade 1 cancers[176], as well as hereditary BRCA2-mutant and hereditary BRCA-wild-type but not hereditary BRCA1-mutant cancers[176]. Furthermore, SNPs in or near RAD21 have been linked with risk of breast cancer development[178-179]. RAD21 overexpression has also been correlated with poor prognosis in endometrial cancer[180] and in colorectal cancer (CRC), especially in KRAS-mutant CRC[181]. Heterogeneity of RAD21 expression also correlated with aggressive tumor behavior and shorter survival in endometrial cancer[182]. RAD21 amplification has been more frequently reported in hormone-refractory than in treatment-naïve prostate cancer, but RAD21 amplification did not correlate with expression[183]. In the context of ovarian cancer, both RAD21 overexpression and downregulation have been observed, but RAD21 expression was not prognostic[184]. Downregulation of RAD21 expression resulted in sensitization of cultured breast[177,185] and CRC[181] cells to chemotherapy, thereby suggesting that RAD21 overexpression confers resistance to chemotherapy.

FINDING SUMMARY
RAD21 encodes a protein involved in DNA double-strand break repair and sister chromatid cohesion as a part of the cohesin complex[186-189]. In preclinical studies, downregulation of RAD21 or other cohesin components leads to loss of expression from amplified genes, as well as amplifications themselves upon cell passaging[190], but also leads to an increase in deletions, insertions, and other rearrangements[191]. High RAD21 expression has also been associated with increased genomic instability[176]. Cohesin complex also organizes chromatin domains and regulates gene expression[192-193]. Both overexpression and reduction of expression of RAD21 has been reported to alter gene expression[194]. RAD21 amplification has been correlated with increased expression in breast[176-177,195] and endometrial[180] cancers. Other RAD21 alterations, including truncating and point mutations, have been reported in the context of cancer, but the majority have not been characterized.

GENE
TP53

ALTERATION
V216M

TRANSCRIPT NUMBER
NM_000546

CODING SEQUENCE EFFECT
646G>A

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[196-199], or p53 gene therapy and immunotherapeutics such as SGT-53[200-204] and ALT-801[205]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutant p53 such as APR-246[206-208]. In a Phase 1b trial in patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[209]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 10% (17/176) and SDs in 53% (94/176) of patients with solid tumors; the response rate was 21% (4/19) in patients with TP53 mutations versus 12% (4/33) in patients who were TP53 wild-type[210]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR in patients with platinum refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[211]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR in patients with platinum-refractory TP53-mutated ovarian cancer[212]. 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[213]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate in patients with TP53 alterations[214]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel in patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[204]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutant, but not TP53-wild-type, breast cancer xenotransplant mouse model[215].

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[27,76,216-219]. TP53 mutations that are located within the region encoding the DNA binding domain are associated with poor prognosis in patients with breast cancer[217,220-221]. 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[222-224].

FINDING SUMMARY
Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[225]. Any alteration that results in the disruption or partial or complete loss of the region encoding the TP53 DNA-binding domain (DBD, aa 100-292) or the tetramerization domain (aa 325-356), such as observed here, is thought to dysregulate the transactivation of p53-dependent genes and is predicted to promote tumorigenesis[226-228]. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[229-231], including sarcomas[232-233]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[234] to 1:20,000[233]. 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[235]. In the appropriate clinical context, germline testing of TP53 is recommended.

GENE
ZNF217

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

There are no available targeted therapies to address genomic alterations in ZNF217. Expression of ZNF217 may predict relapse of estrogen receptor (ER)-positive breast cancer under hormone therapy through its direct interaction with ER-alpha[236-237]. ZNF217 overexpression has also been associated with resistance to paclitaxel[238] and doxorubicin[239] in breast cancer cell lines. ZNF217 has been suggested as a potential biomarker for treatment with the DNA synthesis inhibitor and AKT inhibitor triciribine in breast cancer based on preclinical findings in cultured cells and xenografts expressing high levels of ZNF217; triciribine treatment also restored sensitivity to doxorubicin in these cells[240].

FREQUENCY & PROGNOSIS

Amplification and/or overexpression of ZNF217 has been reported in breast[241], ovarian[242-243], gastric[244-245], colon[246], prostate[247], esophageal[248], and urothelial carcinomas[249], glioblastoma[250], and ovarian carcinosarcomas[251]. Overexpression in these tumors has generally been linked with aggressive tumor behavior and poor clinical prognosis. High levels of ZNF217 expression result in dysregulation of a broad range of genes that may contribute to tumorigenesis[252-254], and increased expression or activation of ERBB3[241,255], FAK[241], Aurora kinase A[238], AKT[239], and TGF-beta/SMAD signaling[241] has been demonstrated in ZNF217-expressing tumors or cells.

FINDING SUMMARY

ZNF217 encodes a candidate oncogene that has likely roles in histone modification and transcriptional repression[239,256]. ZNF217 amplification has been correlated with protein overexpression in breast carcinoma tumors and cell lines[257]. The role of ZNF217 in promoting tumorigenesis was established in preclinical studies demonstrating that expression of ZNF217 results in the immortalization of both human mammary epithelial cells and ovarian surface epithelial cells in culture[258-259].

GENE
ZNF703

ALTERATION
amplification

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[260], 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[261-263]. ZNF703 expression has also been linked with aggressive tumor characteristics in patients with gastric and colorectal cancers[264-265]. 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, 2020).

FINDING SUMMARY

ZNF703 encodes a transcriptional repressor that plays roles in stem cell proliferation, cell cycle progression, and other key cellular functions[262,266]. Amplification of ZNF703 has been correlated with protein expression[261-262]. ZNF703 was established as a breast cancer oncoprotein by studies showing that ZNF703 expression resulted in transformation and increased proliferation of cultured cells[261-262,267], as well as increased lung metastases in a breast cancer xenograft model[267].

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[268-269] ; it also releases the cytotoxic therapy DM1 into cells, leading to cell death[269-270] . 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.

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)[271] or lapatinib plus capecitabine (9.6 vs. 6.4 months)[51,272-273] . 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[274]; 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[275]. 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[276]. 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[277]. 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[278], paclitaxel and pertuzumab[279], neratinib[280], alpelisib[281], and tucatinib[280]. 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[282].

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[283-284] . Fam-trastuzumab deruxtecan is FDA approved to treat patients with HER2-positive breast cancer 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[52,285] , gastric[286], non-small cell lung[287], and colon[288] 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 HER2-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[52]. A Phase 1 trial for this patient population reported similar results (59.5% ORR, 93.7% DCR, median PFS of 22.1 months)[285].

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 or letrozole for the treatment of HER2-overexpressing (HER2+) metastatic breast cancer.

GENE ASSOCIATION

Activation or amplification of ERBB2 may predict sensitivity to lapatinib. In one study, a patient with inflammatory breast cancer and ERBB2 V777L and S310F activating mutations, but without ERBB2 amplification or protein overexpression, experienced tumor shrinkage in response to combined treatment with lapatinib and trastuzumab[59].

SUPPORTING DATA

Lapatinib as a treatment for HER2+ breast cancer has primarily been investigated in combination with other chemotherapeutic agents, and these combination regimens have been shown to extend PFS and reduce metastases, as well as to extend OS in some instances[56-57,289-292] . As first-line therapy for HER2+ metastatic breast cancer, lapatinib plus taxane resulted in shorter median PFS compared with trastuzumab plus taxane (9.0 vs. 11.3 months, HR of 1.37)[293]. For patients who have progressed on trastuzumab plus taxane, ado-trastuzumab emtansine (T-DM1) was superior to lapatinib plus capecitabine (OS of 30.9 vs. 25.1 months)[51]. Addition of lapatinib to capecitabine had improved PFS compared with capecitabine monotherapy (8.4 vs. 4.4 months) in this setting[57]. Lapatinib plus capecitabine has been reported to reduce the number of newly developed brain metastases[289] and to be active against existing brain metastases (central nervous system [CNS] ORR of 66% [29/44])[294]. However, the incidence of CNS metastases was not significantly different with lapatinib plus capecitabine versus trastuzumab plus capecitabine (3% vs. 5%)[295], and CNS disease progression rates were similar for treatment with T-DM1 and with lapatinib plus capecitabine[296]. Phase 2 and 3 trials comparing the efficacy of lapatinib and trastuzumab for the treatment of HER2+ breast cancer in the neoadjuvant setting reported conflicting results, with the combination of lapatinib and trastuzumab generally achieving slightly higher response rates[290-292] . A Phase 3 trial of patients with HER2+ breast cancer treated with lapatinib, trastuzumab, or a combination of the two, reported 3-year event-free survival rates of 78%, 76%, and 84%, with 3-year OS rates of 93%, 90%, and 95%, respectively[297]. In a Phase 3 study for patients with early HER2+ breast cancer, adjuvant lapatinib (alone, in sequence, or in combination with trastuzumab) did not significantly improve disease-free survival (DFS) and added toxicity compared with adjuvant trastuzumab[298]. Adjuvant lapatinib also did not significantly extend DFS in a placebo-controlled Phase 3 study[299]. In postmenopausal patients with hormone receptor-positive (HR+) HER2+ metastatic breast cancer, lapatinib combined with letrozole increased median PFS compared to letrozole alone (8.2 vs. 3.0 months)[300]. Addition of lapatinib to fulvestrant did not improve outcome for patients with advanced HR+ advanced breast cancer and prior aromatase inhibitor therapy (median PFS of 4.7 vs. 3.8 months), although lapatinib associated with longer median PFS for HER2+ patients in this trial (5.9 vs. 3.3 months)[301]. As neoadjuvant therapy for HR+ HER2-negative breast cancer, lapatinib combined with letrozole did not significantly improve response rates, but showed a trend toward a higher response rate for patients with PIK3CA-mutant tumors[302]. Four patients with HER3-positive and HER2-negative newly diagnosed breast cancer had clinical responses to neoadjuvant lapatinib[303].

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 breast cancer following adjuvant trastuzumab.

GENE ASSOCIATION

On the basis of extensive clinical[68,304-307] and preclinical[308-312] evidence, ERBB2 amplification or activating mutations may confer sensitivity to neratinib.

SUPPORTING DATA

In a Phase 3 study for patients with earlystage HER2-positive (HER2+) breast cancer (BC) previously treated with trastuzumab, adjuvant neratinib significantly improved 2-year invasive disease-free survival (iDFS) compared with placebo (93.9% vs. 91.6%, HR=0.67)[306]. The significant iDFS benefit persisted at year 5 of follow-up (90.2% for neratinib vs. 87.7% for placebo, HR=0.73)[313], including for patients who were also hormone receptor-positive (HR+)[314]; however, the improvement was seen only for those patients who were randomized to neratinib within 12 months of prior trastuzumab treatment[315]. For patients with advanced HER2+ BC previously treated with trastuzumab, a median PFS of 5.6 months from neratinib monotherapy[316], 4.5 months from neratinib plus capecitabine[317], and 6.8 months from neratinib plus lapatinib[317] has been reported in Phase 2 trials; for patients with no prior trastuzumab treatment, neratinib treatment resulted in PFS of 39.6 weeks[316]. For patients with BC and HER2+ brain metastases treated with neratinib, the central nervous system (CNS) ORR was 7.5% (3/40)[318]. The Phase 3 NALA study reported a 24% reduction in risk of disease progression (HR=0.76) with neratinib and capecitabine, as compared with lapatinib and capecitabine, for patients with HER2+ metastatic breast cancer (MBC) and progression on 2 or more prior HER2-directed therapies; neratinib also improved the time to intervention for symptomatic CNS disease compared with lapatinib (overall cumulative incidence 22.8% vs. 29.2%, P=0.043)[319]. Also for patients with HER+ MBC, Phase 1 and Phase 1/2 trials reported an ORR of 73% for neratinib plus paclitaxel[320], an ORR of 38% and a clinical benefit rate of 52% from neratinib with trastuzumab[321], and a higher ORR from neratinib and vinorelbine for patients who were lapatinib-naive (41%) as compared with those patients who had prior lapatinib treatment (8%)[322]. As first-line therapy in HER2+ MBC, PFS or ORR did not significantly differ with neratinib plus paclitaxel compared with trastuzumab plus paclitaxel; however, patients treated with neratinib had a lower incidence of CNS disease recurrence[323]. As neoadjuvant treatment in HER2+, HR-negative BC, the pathologic CR rate was 56% for neratinib plus paclitaxel as compared with 33% for trastuzumab plus paclitaxel[307].

Pertuzumab

Assay findings association

ERBB2
amplification

AREAS OF THERAPEUTIC USE

Pertuzumab is a monoclonal antibody that interferes with the interaction between HER2 and ERBB3. It is FDA approved in combination with trastuzumab and docetaxel to treat patients with HER2-positive (HER2+) metastatic breast cancer who have not received prior chemotherapy or HER2-targeted therapy. It is also approved in combination with trastuzumab and chemotherapy as neoadjuvant treatment for HER2+, locally advanced, inflammatory, or early stage breast cancer and as adjuvant treatment for patients with HER2+ early breast cancer at high risk of recurrence.

GENE ASSOCIATION

On the basis of clinical studies in multiple tumor types, ERBB2 amplification or activating mutations may predict sensitivity to pertuzumab[46-47,324-327] .

SUPPORTING DATA

In the APHINITY trial, addition of pertuzumab to chemotherapy plus trastuzumab as adjuvant treatment for patients with HER2+ early stage breast cancer improved the estimated 3-year rate of invasive disease-free survival compared with placebo (94.1% vs. 93.2%), with greater improvement seen for patients with node-positive [92.0% vs. 90.2%, hazard ratio (HR) = 0.77] than those with node-negative (97.5% vs. 98.4%, HR = 1.13) disease[325]. 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 progression-free survival (PFS; 12.4 vs. 18.7 months) and in median overall survival (OS; 40.8 vs. 56.5 months)[46-47,327] . A Phase 2 study in patients with locally advanced breast cancer (LABC) or HER2+ early stage breast cancer with various combinations of pertuzumab, trastuzumab, and docetaxel reported the greatest benefit when using neoadjuvant pertuzumab combined with trastuzumab and docetaxel (5-year PFS rate of 84)[328-329] . In the KRISTINE Phase 3 trial, patients with HER2+ stage II–III breast cancer treated in the neoadjuvant setting with trastuzumab emtansine plus pertuzumab showed a reduced number of pathological complete responses (44.4%) compared with traditional trastuzumab, pertuzumab, and chemotherapy (55.7%), although more Grade 3-4 and serious adverse events occurred in the chemotherapy plus trastuzumab and pertuzumab group[324]. A study of pertuzumab combined with paclitaxel and ado-trastuzumab emtansine reported an overall response rate of 52.4% in patients with previously treated HER2+ MBC or LABC[279]. In a Phase 3 study of patients with HER2+ MBC failing on first-line trastuzumab, addition of pertuzumab to trastuzumab and capecitabine was reported to increase median PFS (11.1 vs. 9.0 months) and OS (36.1 vs. 28.1 months) when compared with trastuzumab plus capecitabine[330]. A trial of 12 patients with HER2+ MBC progressing on pertuzumab plus trastuzumab reported 1 complete response (CR), 1 partial response (PR), and 5 stable diseases (SD) after treatment with a combination of pertuzumab, trastuzumab, and gemcitabine[331]. A Phase 1 trial of salvage therapy with a combination of pertuzumab, trastuzumab, and gemcitabine for 6 patients with HER2+ MBC after progression on trastuzumab reported 1 PR, 4 SD, 1 progressive disease, and a median PFS of 3.8 months[332].

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 other therapies for HER2-positive (HER2+) metastatic and early breast carcinoma 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[40-41,45,59,326,333-336] .

SUPPORTING DATA

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[337]. Trastuzumab has been approved for patients with HER2+ breast cancer based on multiple Phase 2 and 3 clinical trials[40,46,327] . Trastuzumab biosimilars demonstrated comparable clinical benefit to trastuzumab in patients with HER2+ breast cancer[338-347] . A Phase 3 study of patients with HER2+ breast cancer reported 5-year event-free survival (EFS) in 58% of patients treated with trastuzumab plus neoadjuvant therapy, compared to 43% in patients treated with neoadjuvant therapy alone[333]. A long-term follow-up Phase 2 analysis reported 5-year distant disease-free survival (DFS) rates of 92% in patients with HER2+ breast cancer treated with chemotherapy and trastuzumab and 89% in patients treated with lapatinib and chemotherapy[334]. A Phase 3 trial of patients with HER2+ breast cancer 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[297]. Two Phase 3 studies comparing 6-month to 12-month adjuvant trastuzumab reported similar DFS rates for patients with HER2+ early breast cancer after 5.4 years (89.4% vs. 89.8%, HR=1.07)[348] or 7.5 years median follow-up (78.8% vs. 79.6%, HR=1.08)[349]. A Phase 1b study of trastuzumab in combination with the HER2 TKI tucatinib for patients with HER2+ metastatic breast cancer previously treated with HER2-targeting agents reported a 40% (6/15) ORR and median PFS of 5.5 months; an ORR of 61% (14/23, 1 CR) and median PFS of 7.8 months was reported when capecitabine was added to the combination. In the patients with brain metastases, 42% (5/12, 1 CR) exhibited brain-specific responses[54]. As first-line treatment for patients with HER2+ breast cancer, everolimus combined with trastuzumab plus paclitaxel did not significantly improve median PFS in the full study population (15.0 months with everolimus vs. 14.5 months with placebo) but increased PFS in the HR-negative subpopulation by 7.2 months (20.3 vs. 13.1 months)[350]. For patients with trastuzumab-resistant HER2+ breast cancer, the addition of everolimus to trastuzumab plus vinorelbine prolonged median PFS (7.0 vs. 5.8 months)[351].

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.

GENE ASSOCIATION

Clinical and preclinical data support sensitivity of multiple activating mutations in ERBB2, including A775_G776insYVMA and P780_Y781insGSP, to afatinib[352-359] . Studies have reported DCRs of 54 to 70% for patients with ERBB2-mutated NSCLC treated with afatinib, most of whom harbored exon 20 insertions[352-355] .

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[360]. Afatinib monotherapy achieved an ORR of 11% (4/35) and a median OS of 61 weeks in this setting[62]. 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[361]. 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[362]. In contrast, a Phase 2 trial reported no objective responses for genomically unselected patients with HER2-negative breast cancer[363]. Afatinib plus letrozole achieved SD for 54% (15/28) of patients with estrogen receptor-positive breast cancer who had progressed on single-agent letrozole[364].

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.

GENE ASSOCIATION

On the basis of strong clinical[69,365-368] and preclinical[369-372] 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 2019). 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)[373-374] . 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[375-376]. 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[367]. Studies of dacomitinib in esophageal[377] and cutaneous[378] 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[368] and patients with EGFR-amplified glioblastoma[379] found RRs of fewer than 10% and DCRs of fewer than 50%: 11/27 (41%) DCR in HER2+ gastric cancer[368] and 15/49 (31%) in EGFR-amplified glioblastoma[379].

Pazopanib

Assay findings association

FGFR1
amplification

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

Based on PRs in two patients with FGFR1-amplified breast cancer, pazopanib may be effective in this context[86,380] .

SUPPORTING DATA

A Phase 2 clinical trial of pazopanib in breast cancer reported 55% disease stabilization[381]. A Phase 2 study of heavily pretreated post-menopausal hormone receptor positive (HR+) breast cancer treated with a combination of pazopanib and nonsteroidal aromatase inhibitor reported 7% partial responses (PRs; 2/28) and 18% stable diseases (SDs; 5/28), with 7 patients having progression-free survival (PFS) greater than 6 months[382]. Phase 2 clinical trials of pazopanib with lapatinib in patients with HER2-positive breast cancer reported that the combination was associated with higher response rate than lapatinib alone but did not bring about an increase in PFS[383-384] . A multicenter single-arm Phase 2 study evaluating pazopanib combined with paclitaxel as neoadjuvant following doxorubicin/cyclophosphamide reported complete responses in 9% (6/67) and 38% (10/26) of patients with HR+ and triple-negative locally advanced breast cancer cases, respectively; however, a high level of toxicity led to discontinuation of pazopanib in 61% of patients[385].

NOTE Genomic alterations detected may be associated with activity of certain FDA approved drugs, however the agents listed in this report may have little or no evidence in the patient's tumor type.

IMPORTANT Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months. While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and should be investigated by the physician or research staff. This is not a comprehensive list of all available clinical trials. 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
AURKA

ALTERATION
amplification

RATIONALE
Amplification of AURKA may sensitize cells to inhibitors of Aurora kinase A.

NCT02719691

PHASE 1

Phase I Study of MLN0128 and MLN8237 in Patients With Advanced Solid Tumors and Metastatic Triple-negative Breast Cancer

TARGETS
Aurora kinase A, mTORC1, mTORC2

LOCATIONS: Colorado

GENE
ERBB2

ALTERATION
amplification

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

NCT03529110

PHASE 3

DS-8201a Versus T-DM1 for Human Epidermal Growth Factor Receptor 2 (HER2)-Positive, Unresectable and/or Metastatic Breast Cancer Previously Treated With Trastuzumab and Taxane [DESTINY-Breast03]

TARGETS
ERBB2

LOCATIONS: Calgary (Canada), Salvador (Brazil), L'Hospitalet De Llobregat (Spain), Strasbourg Cedex (France), Beijing (China), Marseille Cedex 20 (France), California, Caen Cedex 05 (France), Plérin (France), Exeter (United Kingdom), District of Columbia, Besançon (France), Florida, Georgia, Aberdeen (United Kingdom), London (United Kingdom), Manchester (United Kingdom), Goyang-si (Korea, Republic of), Seongnam-si (Korea, Republic of), Harbin (China), Montpellier (France), Rennes cedex (France), Illinois, Kentucky, Saint-Herblain (France), Edinburgh (United Kingdom), Maryland, Massachusetts, Monza (Italy), Rozzano (Italy), Missouri, Nebraska, New York, Valenciennes (France), North Carolina, Nottingham (United Kingdom), Ohio, Toronto (Canada), Pennsylvania, Aviano (Italy), Montréal (Canada), Woolloongabba (Australia), Lyon Cedex 08 (France), Pierre Benite Cedex (France), Itajaí (Brazil), São Paulo (Brazil), LeMans Cedex 02 (France), Sevilla (Spain), San Cristobal de la Laguna (Spain), Tennessee, Texas, Utah, Avignon Cedex 9 (France), Saint-Mandé (France), Villejuif cedex (France), Box Hill (Australia), Frankston (Australia), Melbourne (Australia), Washington, Subiaco (Australia), Hangzhou (China), Bruxelles (Belgium), Edegem (Belgium), Gent (Belgium), Leuven (Belgium), Namur (Belgium), Rio De Janeiro (Brazil), Paris (France), Hong Kong (Hong Kong), Shatin (Hong Kong), Bergamo (Italy), Genova (Italy), Lecco (Italy), Messina (Italy), Milano (Italy), Modena (Italy), Napoli (Italy), Torino (Italy), Aichi (Japan), Fukuoka (Japan), Hiroshima (Japan), Hokkaido (Japan), Kanagawa (Japan), Kumamoto (Japan), Niigata (Japan), Osaka (Japan), Saitama (Japan), Tokyo (Japan), Seoul (Korea, Republic of), Badajoz (Spain), Barcelona (Spain), Madrid (Spain), Málaga (Spain), Taichung (Taiwan), Tainan (Taiwan), Taipei (Taiwan)

NCT03523585

PHASE 3

DS-8201a in Pre-treated HER2 Breast Cancer That Cannot be Surgically Removed or Has Spread [DESTINY-Breast02]

TARGETS
ERBB2, EGFR

LOCATIONS: Arizona, Badalona (Spain), L'Hospitalet De Llobregat (Spain), Marseille cedex 20 (France), California, Caen Cedex 05 (France), Cheongju-si (Korea, Republic of), Connecticut, Truro (United Kingdom), Plérin (France), Jerez De La Frontera (Spain), Exeter (United Kingdom), Plymouth (United Kingdom), District of Columbia, Besançon (France), Brest Cedex (France), Florida, Fukushima-shi (Japan), Georgia, Aberdeen (United Kingdom), London (United Kingdom), Incheon (Korea, Republic of), Seongnam-si (Korea, Republic of), Suwon-si (Korea, Republic of), Antony (France), Saint-Cloud (France), Montpellier (France), Rennes cedex (France), Illinois, Indiana, Kentucky, A Coruña (Spain), Edinburgh (United Kingdom), Maine, Maryland, Massachusetts, Michigan, Monza (Italy), Missouri, Darlinghurst (Australia), Liverpool (Australia), Sydney (Australia), Tweed Heads (Australia), New York, Lille cedex (France), Valenciennes (France), Nottingham (United Kingdom), Ohio, Osakasayama-shi (Japan), Ōsakasayama-shi (Japan), Paris Cedex 05 (France), Pennsylvania, Aviano (Italy), Bayonne Cedex (France), Woolloongabba (Australia), Pierre Benite cedex (France), Itajaí (Brazil), Le Mans Cedex 02 (France), Rouen (France), San Cristobal de la Laguna (Spain), Tennessee, Texas, Chuo Ku (Japan), Utah, Avignon Cedex 9 (France), Villejuif cedex (France), Box Hill (Australia), Frankston (Australia), Heidelberg (Australia), Melbourne (Australia), Saint Albans (Australia), Virginia, Washington, Subiaco (Australia), Bruxelles (Belgium), Gent (Belgium), Kortrijk (Belgium), Leuven (Belgium), Namur (Belgium), Rio De Janeiro (Brazil), São Paulo (Brazil), Brno (Czechia), Prague 5 (Czechia), Praha (Czechia), Paris (France), Athens (Greece), Heraklion (Greece), Thessaloníki (Greece), Haifa (Israel), Jerusalem (Israel), Kfar Saba (Israel), Petah tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Bergamo (Italy), Bologna (Italy), Genova (Italy), Lecco (Italy), Messina (Italy), Milano (Italy), Modena (Italy), Napoli (Italy), Padova (Italy), Parma (Italy), Pavia (Italy), Pisa (Italy), Torino (Italy), Ehime (Japan), Fukuoka (Japan), Hiroshima (Japan), Hokkaido (Japan), Hyōgo (Japan), Kanagawa (Japan), Kyoto (Japan), Miyagi (Japan), Nagoya (Japan), Niigata (Japan), Okayama (Japan), Osaka (Japan), Saitama (Japan), Shizuoka (Japan), Tokyo (Japan), Daegu (Korea, Republic of), Goyang-si (Korea, Republic of), Seoul (Korea, Republic of), Badajoz (Spain), Barcelona (Spain), Lleida (Spain), Madrid (Spain), Salamanca (Spain), Sevilla (Spain), Valencia (Spain), Adana (Turkey), Ankara (Turkey), Antalya (Turkey), Istanbul (Turkey), Sakarya (Turkey), Samsun (Turkey), Tekirdağ (Turkey), İzmir (Turkey)

NCT03726879

PHASE 3

A Study To Evaluate the Efficacy and Safety Of Atezolizumab or Placebo in Combination With Neoadjuvant Doxorubicin + Cyclophosphamide Followed By Paclitaxel + Trastuzumab + Pertuzumab In Early Her2-Positive Breast Cancer

TARGETS
PD-L1, ERBB3, ERBB2

LOCATIONS: Calgary (Canada), Salvador (Brazil), Badalona (Spain), Vancouver (Canada), Napoli (Italy), Aviano (Italy), Goiania (Brazil), Obninsk (Russian Federation), Roma (Italy), Monza (Italy), Rozzano (Italy), Missouri, Moskva (Russian Federation), Pamplona (Spain), New York, Candiolo (Italy), Montréal (Canada), Quebec City (Canada), Porto Alegre (Brazil), Sao Paulo (Brazil), Tennessee, Padova (Italy), Olomouc (Czechia), Bad Nauheim (Germany), Essen (Germany), Freiburg (Germany), Hamburg (Germany), Leipzig (Germany), Münster (Germany), Trier (Germany), Ehime (Japan), Fukushima (Japan), Hiroshima (Japan), Hokkaido (Japan), Kanagawa (Japan), Kumamoto (Japan), Niigata (Japan), Osaka (Japan), Tokyo (Japan), Seoul (Korea, Republic of), Gliwice (Poland), Grudziądz (Poland), Kraków (Poland), Warszawa (Poland), Wrocław (Poland), Łódź (Poland), Moscow (Russian Federation), Barcelona (Spain), Burgos (Spain), Granada (Spain), Jaen (Spain), Lerida (Spain), Madrid (Spain), Sevilla (Spain), Taipei (Taiwan), Taipei City (Taiwan), Taoyuan (Taiwan)

NCT03013218

PHASE 1

A Study of ALX148 in Patients With Advanced Solid Tumors and Lymphoma

TARGETS
PD-1, CD47, ERBB2, CD20

LOCATIONS: Colorado, Connecticut, Massachusetts, Michigan, Washington, Seongnam (Korea, Republic of), Seoul (Korea, Republic of)

NCT02892123

PHASE 1

Trial of ZW25 in Patients With Advanced HER2-expressing Cancers

TARGETS
ERBB2

LOCATIONS: Alabama, California, Colorado, Seongnam-si (Korea, Republic of), Illinois, Ottawa (Canada), Toronto (Canada), Montréal (Canada), Tennessee, Texas, Washington, Seoul (Korea, Republic of)

NCT03500380

PHASE 2

A Study of RC48-ADC Administered Intravenously to Patients With HER2-Positive Metastatic Breast Cancer

TARGETS
ERBB2

LOCATIONS: Beijing (China), Shengyang (China), Shenyang (China), Changchun (China), Changsha (China), Chengde (China), Chengdu (China), Dalian (China), Fuzhou (China), Guangzhou (China), Guiyang (China), Hangzhou (China), Harbin (China), Hefei (China), Jinan (China), Linyi (China), Luoyang (China), Nanchang (China), Nanjing (China), Nanning (China), Qingdao (China), Shanghai (China), Shijiazhuang (China), Wuhan (China), Xi'an (China), Xuzhou (China), Yantai (China), Zhengzhou (China)

NCT03264547

PHASE 3

A Study to Compare Eribulin Mesylate + Pertuzumab + Trastuzumab With Paclitaxel or Docetaxel + Pertuzumab + Trastuzumab

TARGETS
ERBB3, ERBB2

LOCATIONS: Ōsaka (Japan)

NCT03989037

PHASE 3

A Study Of SIBP-01 Or CN-Trastuzumab Plus Docetaxel And Carboplatin In HER2 Positive Breast Cancer

TARGETS
ERBB2

LOCATIONS: Shanghai (China)

NCT03772353

PHASE 1/2

Letrozole, Pyrotinib Combined With SHR6390 in Patients With HR+/HER2+ Relapsed/Metastatic Breast Cancer

TARGETS
CDK6, CDK4, EGFR, ERBB2, Aromatase

LOCATIONS: Shanghai (China)

NCT03588091

PHASE 3

Neoadjuvant Study of Pyrotinib in Combination With Trastuzumab in Patients With HER2 Positive Breast Cancer

TARGETS
EGFR, ERBB2

LOCATIONS: Shanghai (China)

GENE
FGFR1

RATIONALE
FGFR inhibitors may be relevant in tumors with alterations that activate FGFR1.

ALTERATION
amplification

NCT03517956

PHASE 1

Phase 1 Study of the Combination of Rogaratinib With Copanlisib in Patients With Fibroblast Growth Factor Receptor (FGFR)-Positive, Locally Advanced or Metastatic Solid Tumors

TARGETS
FGFR1, FGFR2, FGFR3, FGFR4, PI3K

LOCATIONS: California, Frankfurt (Germany), Illinois, Maryland, Massachusetts, Michigan, New York, Köln (Germany), Texas, Bruxelles - Brussel (Belgium), Edegem (Belgium), Liege (Belgium), Würzburg (Germany), Seoul (Korea, Republic of), Singapore (Singapore), Barcelona (Spain), Valencia (Spain)

NCT01948297

PHASE 1

Debio 1347-101 Phase I Trial in Advanced Solid Tumours With Fibroblast Growth Factor Receptor (FGFR) Alterations

TARGETS
FGFR1, FGFR2, FGFR3

LOCATIONS: Massachusetts, New York, Texas, Seoul (Korea, Republic of), Singapore (Singapore), Barcelona (Spain), Taipei (Taiwan)

NCT03235570

PHASE 1

A Safety and Tolerability Study of Pemigatinib in Japanese Subjects With Advanced Malignancies - (FIGHT-102)

TARGETS
FGFR1, FGFR2, FGFR3

LOCATIONS: Aichi (Japan), Chiba (Japan), Kanagawa (Japan), Osaka (Japan), Saitama (Japan), Sapporo (Japan), Shizuoka (Japan), Tokyo (Japan)

NCT03788603

PHASE 1

Rogaratinib (BAY1163877) in Chinese Patients

TARGETS
FGFR1, FGFR2, FGFR3, FGFR4

LOCATIONS: Beijing (China)

NCT03547037

PHASE 1

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

TARGETS
PD-1, FGFRs

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

NCT03879057

PHASE 1

Trial of Sulfatinib Combined With JS001 in the Treatment of Advanced Solid Tumors

TARGETS
PD-1, CSF1R, FGFR1, VEGFRs

LOCATIONS: Beijing (China)

NCT02393248

PHASE 1/2

Open-Label, Dose-Escalation Study of INCB054828 in Subjects With Advanced Malignancies

TARGETS
PD-1, FGFR1, FGFR2, FGFR3

LOCATIONS: Alabama, Florida, Michigan, Missouri, New Jersey, North Carolina, Ohio, South Carolina, Texas, Copenhagen (Denmark)

NCT02549937

PHASE 1/2

A Multi-Center, Open-Label Study of Sulfatinib(HMPL-012) in Patients With Advanced Solid Tumors

TARGETS
CSF1R, FGFR1, VEGFRs

LOCATIONS: California, Colorado, Florida, New York, Tennessee, Texas

NCT02272998

PHASE 2

Ponatinib for Patients Whose Advanced Solid Tumor Cancer Has Activating Mutations Involving the Following Genes: FGFR1, FGFR2, FGFR3, FGFR4, RET, KIT.

TARGETS
ABL, FGFRs, FLT3, KIT, PDGFRs, RET, VEGFRs

LOCATIONS: Ohio

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: Massachusetts, Tennessee, Texas

GENE
MYC

ALTERATION
amplification

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

NCT02964507

PHASE 2

Dose Escalation and Expansion Study of GSK525762 in Combination With Fulvestrant in Subjects With Estrogen Receptor Positive (ER+) Breast Cancer

TARGETS
BRD2, BRD3, BRD4, BRDT, ER

LOCATIONS: Alabama, Arizona, Florida, Georgia, Illinois, Manchester (United Kingdom), Louisiana, Massachusetts, Northwood (United Kingdom), Minnesota, Missouri, Camperdown (Australia), Port Macquarie (Australia), New York, Nottingham (United Kingdom), Ottawa (Canada), Toronto (Canada), Montreal (Canada), Rhode Island, Bedford Park (Australia), Texas, Heidelberg (Australia), Virginia, Washington, Quebec (Canada), Bordeaux Cedex (France), Saint-Herblain (France), Saint-Herblain cedex (France), Gyeonggi-do (Korea, Republic of), Seoul (Korea, Republic of), A Coruna (Spain), Barcelona (Spain), Lerida (Spain), Madrid (Spain), Glasgow (United Kingdom), London (United Kingdom)

NCT02419417

PHASE 1/2

Study of BMS-986158 in Subjects With Select Advanced Solid Tumors

TARGETS
BRD2, BRD3, BRD4, BRDT

LOCATIONS: California, Colorado, Massachusetts, Ottawa (Canada), Oregon, Pennsylvania, South Carolina, Melbourne (Australia), Villejuif (France), Barcelona (Spain), Madrid (Spain), Pamplona (Spain)

NCT03297424

PHASE 1/2

A Study of PLX2853 in Advanced Malignancies.

TARGETS
BRD4

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

NCT02516553

PHASE 1

BI 894999 First in Human Dose Finding Study in Advanced Malignancies

TARGETS
BRD3, BRD4, BRD2, BRDT

LOCATIONS: Massachusetts, Texas, Brussels (Belgium), Bruxelles (Belgium), Gent (Belgium), Leuven (Belgium), Nantes (France), Paris (France), Villejuif (France), Tübingen (Germany)

NCT03205176

PHASE 1

AZD5153 in Patients With Relapsed or Refractory Solid Tumors, Including Lymphomas

TARGETS
BRD4, PARP

LOCATIONS: Toronto (Canada), Florida, Oklahoma, Tennessee

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

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.

ALK
P97S

ATM
A220V

CARD11
amplification

CDK12
amplification

MSH3
T1112M

MSH6
K1358fs*2

MYCL1
T183A

RAD54L
V412I

RARA
amplification

WHSC1 (MMSET)
amplification

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)

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.

NCCN Categorization

Biomarker and genomic findings detected may be associated with certain National Comprehensive Cancer Network (NCCN) Compendium drugs or biologics (www.nccn.org). The NCCN categories 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.

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 defined based on counting the total number of all synonymous and nonsynonymous variants present at 5% allele frequency or greater (after filtering) and reported as mutations per megabase (mut/Mb) unit rounded to the nearest integer. The clinical validity of TMB defined by this panel has not been established.
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.

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

PDF Service version: 2.6.0

The median exon coverage for this sample is 969x

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