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
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.

CCND1 amplification - equivocal†
PIK3CA N345K
AURKA amplification - equivocal†
MDM2 amplification
ACVR1B M121fs*6
GATA3 G335fs*18
GNAS amplification - equivocal†
RAD21 amplification - equivocal†
ZNF217 amplification - equivocal†

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

† See About the Test in appendix for details.

6 Therapies with Clinical Benefit
0 Therapies with Lack of Response
23 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)
***CCND1* -** amplification - equivocal	Abemaciclib	1	none
	Palbociclib	1	
10 Trials *see p. 16*	Ribociclib	1	
***PIK3CA* -** N345K	Alpelisib	1	Temsirolimus
10 Trials *see p. 20*	Everolimus	2A	
***AURKA* -** amplification - equivocal	none		none
1 Trial *see p. 15*			
***MDM2* -** amplification	none		none
5 Trials *see p. 19*			

☐ *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
CCND1

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

Amplification or overexpression of CCND1 may predict sensitivity to CDK4/6 inhibitors, such as abemaciclib, palbociclib, and ribociclib[40-44], although as monotherapy these agents have shown limited activity in tumor types other than breast cancer[43,45]. In refractory advanced solid tumors with CCND1 (n=39) or CCND3 (n=1) amplification and retinoblastoma protein expression, palbociclib resulted in SD for 39% (14/36) of patients and a median PFS of 1.8 months in the NCI-MATCH trial[46]; 4 patients (13%, 4/36 overall) with squamous cell carcinomas (lung, esophageal, or laryngeal) or adenoid cystic carcinoma experienced prolonged SD in this study[46]. Among 9 patients with CCND1-amplified advanced solid tumors, 1 patient with bladder cancer responded to ribociclib in a Phase 2 trial[47].

FREQUENCY & PROGNOSIS

CCND1 amplification occurs in 10-17% of invasive breast cancers, more frequently in estrogen receptor (ER)-positive or BRCA-negative cancers, and correlates with overexpression of cyclin D1[27,48-52]. Both CCND1 amplification and cyclin D1 overexpression predict poor prognosis in patients with ER-positive breast cancer (hazard ratio of 2.5 and 1.7, respectively)[48,53]. Overexpression of cyclin D1 has also been associated with resistance to endocrine therapy in patients with breast cancer[54-55].

FINDING SUMMARY

CCND1 encodes cyclin D1, a binding partner of the kinases CDK4 and CDK6, that regulates RB activity and cell cycle progression. Amplification of CCND1 has been positively correlated with cyclin D1 overexpression[48] and may lead to excessive proliferation[56-57].

GENE
PIK3CA

ALTERATION
N345K

TRANSCRIPT NUMBER
NM_006218

CODING SEQUENCE EFFECT
1035T>A

POTENTIAL TREATMENT STRATEGIES

Clinical and preclinical data in various tumor types indicate that PIK3CA activating alterations may predict sensitivity to therapies targeting PI3K or AKT[58-59]. On the basis of clinical benefit for patients with PIK3CA mutations and preclinical evidence, PIK3CA-mutated tumors may also respond to mTOR inhibitors, including everolimus and temsirolimus[60-65]. In a Phase 1 trial of the dual PI3K/mTOR kinase inhibitor apitolisib, 79% (11/14) of patients with PIK3CA-mutated advanced solid tumors experienced disease control at the recommended Phase 2 dose (3/14 PRs, 8/14 SDs)[66]. The addition of everolimus to exemestane for the treatment of hormone-receptor-positive (HR+)/HER2-negative advanced breast cancer has shown clinical benefit regardless of PIK3CA status[67]. In the BELLE-2 trial for patients with endocrine-resistant HR+ breast cancer, the combination of the pan-PI3K inhibitor buparlisib with fulvestrant resulted in increased PFS (7.0 vs. 3.2 months) and ORR (18% vs. 4%) compared to placebo with fulvestrant in patients with PIK3CA mutation; no significant improvement in PFS or ORR was observed in patients without PIK3CA mutation[68]. The pan-PI3K inhibitor buparlisib has shown limited activity as monotherapy against PIK3CA-mutated tumors[69-72]. PI3K-alpha-selective inhibitors such as alpelisib or PI3K-beta-sparing inhibitors such as taselisib may have bigger therapeutic windows than pan-PI3K inhibitors[59]. In PIK3CA-mutated advanced solid tumors, alpelisib and taselisib have achieved low ORRs (0% [0/55] to 6% [7/111]) but a high DCR (55% [36/55] to 58% [64/111])[73]. In the Phase 3 SOLAR-1 study, the addition of alpelisib to fulvestrant improved PFS (11.0 vs. 5.7 months, HR=0.65) and ORR (26.6 vs. 12.8%) in PIK3CA-mutated HR+/HER2– breast cancer compared with placebo with fulvestrant[58]. Combination of alpelisib with letrozole in advanced HR+/HER2– breast cancer achieved an ORR of 25% (4/16) and a DCR of 62% (10/16) in patients with PIK3CA-mutated tumors and an ORR of 10% (1/10) and a DCR of 70% (7/10) in patients with PIK3CA-wild-type tumors[74]. In the Phase 3 SANDPIPER study, the addition of taselisib to fulvestrant improved PFS (7.4 vs. 5.4 months, HR=0.70) and ORR (27.3 vs. 11.9%) in PIK3CA-mutated HR+/HER2– breast cancer compared with placebo with fulvestrant[75]; additionally, patients with multiple PIK3CA mutations achieved a higher ORR following treatment with taselisib (30.2%, n=43) as compared with those treated with placebo (8.7%, n=23) or with patients with single PIK3CA-mutated tumors treated with either taselisib (18.1%, n=193) or placebo (10.0%, n=80)[76]. AKT inhibitors ipatasertib and capivasertib have also been tested in breast cancer. Two Phase 2 studies have reported improved PFS from the addition of either ipatasertib (9.0 vs. 4.9 months, HR = 0.44) or capivasertib (9.3 vs. 3.7 months, HR = 0.30) to paclitaxel in metastatic triple-negative breast cancer harboring PIK3CA/AKT1/PTEN alterations, compared with paclitaxel and placebo[77]. Responses to capivasertib were also reported in 20% (3/15) of patients with PIK3CA-mutated breast cancer in an earlier study[78]. However, a Phase 1 trial reported no PFS benefit for patients with PIK3CA-mutated, ER+/HER2- metastatic breast cancer from the addition of capivasertib to paclitaxel compared with paclitaxel plus placebo (10.9 vs. 10.8 months)[79]. Activating mutations in PIK3CA may confer resistance to HER2-targeted therapies; combined inhibition of HER2 and the PI3K pathway may be required in HER2-positive tumors with PIK3CA mutation[80-84].

FREQUENCY & PROGNOSIS

Mutations in PIK3CA have been reported in 25-40% of breast cancer cases[27,85-88]. Although double PIK3CA mutations are frequently observed in hormone-receptor-positive, HER2-negative breast cancers, as compared with other receptor subtypes (15.4% vs. 5.4%, p=0.004), this did not impact invasive disease-free survival or OS for patients when compared with single PIK3CA mutations by univariate and multivariate analysis in 1 retrospective study[76]. Mutations in coding exon 20 (H1047R) of PIK3CA have been associated with a better prognosis in breast carcinoma than mutations occurring in coding exon 9 (E542K)[89].

FINDING SUMMARY

PIK3CA encodes p110-alpha, which is the catalytic subunit of phosphatidylinositol 3-kinase (PI3K). The PI3K pathway is involved in cell signaling that regulates a number of critical cellular functions, including cell growth, proliferation, differentiation, motility, and survival[90-91]. PIK3CA alterations that have been characterized as activating, such as observed here, are predicted to be oncogenic[92-110].

GENE
AURKA

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

There are no approved therapies that target Aurora kinase A; however, several inhibitors of Aurora kinase A are in clinical trials[111-112]. 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[113], 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[114]. However, a high incidence of serious adverse events was reported in urothelial cancer treated with alisertib[113]. In some cancer types, including colorectal cancer, AURKA amplification has been associated with resistance to taxane therapy[115-117].

FREQUENCY & PROGNOSIS

The frequency of AURKA amplification in breast tumors has been reported to range from 3-21%[27,118-120]. 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[121-123]. In breast cancer, amplified AURKA is likely associated with proliferation, but also with good prognosis (5-year metastasis-free survival, 91%)[123-124].

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[117].

GENE
MDM2

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

MDM2 antagonists disrupt the MDM2-p53 interaction, thereby stabilizing p53[125]. Preclinical studies have suggested that amplification of MDM2, in the absence of concurrent TP53 mutations, may increase sensitivity to these agents[126-127]. Preliminary Phase 1 studies of the MDM2-p53 antagonist APG-115 reported a PR in a patient with liposarcoma harboring a MDM2 amplification and wild-type for TP53 and SD in 21.4%–38.5% (5/13 and 6/28) of patients in genomically unselected solid tumors[128-129] . Phase 1b studies of the MDM2 inhibitor idasanutlin for refractory AML in combination with cytarabine or venetoclax reported anti-leukemic response rates of 33% (25/75) and 37% (11/30), respectively[130-131] ; clinical benefit (58% ORR, 7/12) with idasanutlin monotherapy has been reported for patients with polycythemia vera[132]. The dual MDM2/MDM4 inhibitor ALRN-6924 led to an ORR of 27% (4/15) for patients with TP53 wild-type peripheral T-cell lymphoma in a Phase 2 study[133]; responses have also been observed in TP53 wild-type AML, MDS, Merkel cell carcinoma, colorectal cancer, and liposarcoma[134-135] .

FREQUENCY & PROGNOSIS

MDM2 amplification has been reported in 3-7% of breast carcinomas[27,136-137] and has been associated with high tumor grade in patients with breast cancer. The effect of MDM2 amplification on breast carcinoma prognosis is unclear[136-137].

FINDING SUMMARY

MDM2 encodes an E3 ubiquitin protein ligase, which mediates the ubiquitination and subsequent degradation of p53, Rb1, and other proteins[138-140]. MDM2 acts to prevent the activity of the tumor suppressor p53; therefore, overexpression or amplification of MDM2 may be oncogenic[141-142]. Overexpression or amplification of MDM2 is frequent in cancer[143]. Although two retrospective clinical studies suggest that MDM2 amplification may predict a short time-to-treatment failure on anti-PD-1/PD-L1 immune checkpoint inhibitors, with 4/5 patients with MDM2 amplification[144] and 2/3 patients with MDM2 or MDM4 amplification[145] experiencing tumor hyperprogression, amplification of MDM2 or MDM4 was not associated with shorter progression-free survival (PFS) in a retrospective analysis of non-small cell lung cancer (NSCLC) outcomes with immune checkpoint inhibitors (hazard ratio of 1.4, p=0.44)[146]. The latter study reported PFS of >2 months for 5/8 patients with MDM2/MDM4 amplification[146].

GENE
ACVR1B

ALTERATION
M121fs*6

TRANSCRIPT NUMBER
NM_020328

CODING SEQUENCE EFFECT
363_369delGTGGGGC

POTENTIAL TREATMENT STRATEGIES

There are no approved therapies available to address genomic alterations in ACVR1B. Several ALK4 inhibitors are in development[147-149], and inhibitors of Activin A, a ligand for ALK4 and other ALK-family receptors, are in clinical trials. However, further study is required to delineate the respective oncogenic and tumor-suppressive functions of ALK4 and to determine any associations between genomic alterations in ACVR1B and the potential clinical benefit of ALK4 signaling inhibitors.

FREQUENCY & PROGNOSIS

Consistent with its potential for both oncogenic and tumor-suppressive functions, mutations and deletions of ACVR1B have been reported in about 5% of gastric, colorectal, and adenoid cystic carcinoma samples, whereas amplification has been reported in more than 5% of prostate neuroendocrine cancer, adrenocortical carcinoma, and uterine carcinosarcoma samples (cBioPortal, 2020). Deletion or loss of heterozygosity of ACVR1B has been reported in 20-34% of pancreatic cancer samples[150-151]; in most cases, tumors with ACVR1B deletion harbored concurrent deletion or inactivation of SMAD4[150-151]. ACVR1B deletion associated with a trend toward shorter progression-free and overall survival for patients with pancreatic cancer, but the trend did not reach statistical significance[151]. One study reported significant downregulation of ACVR1B, as well as other Activin receptors, in thyroid cancer samples relative to non-cancerous thyroid tissues[152].

FINDING SUMMARY

ACVR1B encodes ALK4, also known as activin receptor 1B, which mediates TGF-beta signaling, including for ligands such as Activin and Nodal, through regulation of SMAD transcription factors[150,153-155]. ACVR1B is reported to have potential oncogenic roles in some cancer types, such as prostate cancer[156], and potential tumor-suppressive functions in others, such as thyroid[152] and pancreatic[150-151] cancers; however, one preclinical study suggested that signaling through ALK4 may promote pancreatic cancer stem cell functions[154]. A single-nucleotide polymorphism in ACVR1B was associated with risk of lung cancer in never smokers exposed to second-hand smoke[157].

GENE
GATA3

ALTERATION
G335fs*18

TRANSCRIPT NUMBER
NM_001002295

CODING SEQUENCE EFFECT
1002_1003insT

POTENTIAL TREATMENT STRATEGIES

There are no targeted therapies available to address genomic alterations in GATA3.

FREQUENCY & PROGNOSIS

Somatic mutation of GATA3 has been reported at modest frequency in several solid tumor types: breast carcinoma (4-15%)[27,158-160], cutaneous melanoma (2-6%)[161-163], gastric carcinoma (0-6%)[164-167], uterine carcinosarcoma (18%)[168], and lung carcinoma (1-3%)[169-170].

FINDING SUMMARY

GATA3 encodes a zinc-finger transcription factor involved in a range of developmental pathways. Along with GATA2, it participates in control of adipocyte differentiation[171], and through control of cytokine expression it acts along with TBET as a master regulator of T-cell Th1/Th2 lineage determination[172]. Germline inactivating mutations in GATA3 result in a developmental disorder characterized by hypoparathyroidism, sensorineural deafness, and renal insufficiency (HDRS)[173]. GATA3 has been hypothesized to be required for BRCA1-mediated repression of proliferation-associated genes in breast tissue and in triple-negative breast tumors[174].

GENE
GNAS

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES
There are no therapies targeted to GNAS mutation in cancer. However, there is limited data indicating that a patient with appendiceal adenocarcinoma and a GNAS mutation (R201H) benefited from trametinib for 4 months[175]. Additionally, a patient with GNAS-mutated Erdheim-Chester disease exhibited a PR following treatment with single-agent trametinib[176].

FREQUENCY & PROGNOSIS
The highest incidences of GNAS mutations have been reported in intraductal papillary mucinous neoplasms (40-66%)[177-178] and appendiceal mucinous neoplasms (50-72%)[179-180] as well as in tumors affecting the peritoneum (23%), pituitary gland (20%), pancreas (12%), small intestine (16%), and bone (15%) (COSMIC, 2020). Amplification of GNAS has been reported in ovarian epithelial carcinomas (12-30%)[181-183], colorectal adenocarcinoma (9%)[38], stomach adenocarcinoma (7%)[166], lung adenocarcinoma (6.5%)[170], breast invasive carcinoma (6.5%)[27], pancreatic adenocarcinoma (6%)[184], and sarcomas (5.8%)[185]. GNAS mutations are rare in hematological malignancies generally (COSMIC, 2020)[186-187]. Activating GNAS mutations have been identified in gastrointestinal polyps in 75% (3/4) of patients with McCune-Albright syndrome[188]. Amplification of GNAS has been associated with shorter progression-free survival in patients with ovarian cancer[182-183], while activating GNAS mutations have been correlated with tumor progression and poor prognosis in patients with gastric cancer[189].

FINDING SUMMARY
GNAS encodes the alpha subunit of the stimulatory G protein (Gs-alpha)[190]. Gs-alpha is a guanine-nucleotide binding protein (G protein) that is involved in hormonal regulation of adenylate cyclase[190]. GNAS has been reported to be amplified in cancer[191] and may be biologically relevant in this context[143,192]. GNAS alterations that have been shown to result in constitutive activation of adenylyl cyclase and an increase in cellular cAMP concentration[193-198] are predicted to be activating. Mutations at R201 specifically are commonly associated with McCune-Albright syndrome, a disease that can co-occur with various cancers in patients with GNAS activating mutations[199-201].

GENE
RAD21

ALTERATION
amplification - equivocal

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[202]. In the context of breast cancer, increased RAD21 expression has been correlated with poor prognosis in multiple subtypes[203-204], including sporadic Grade 3 but not Grade 1 cancers[203], as well as hereditary BRCA2-mutant and hereditary BRCA-wild-type but not hereditary BRCA1-mutant cancers[203]. Furthermore, SNPs in or near RAD21 have been linked with risk of breast cancer development[205-206]. RAD21 overexpression has also been correlated with poor prognosis in endometrial cancer[207] and in colorectal cancer (CRC), especially in KRAS-mutant CRC[208]. Heterogeneity of RAD21 expression also correlated with aggressive tumor behavior and shorter survival in endometrial cancer[209]. RAD21 amplification has been more frequently reported in hormone-refractory than in treatment-naïve prostate cancer, but RAD21 amplification did not correlate with expression[210]. In the context of ovarian cancer, both RAD21 overexpression and downregulation have been observed, but RAD21 expression was not prognostic[211]. Downregulation of RAD21 expression resulted in sensitization of cultured breast[204,212] and CRC[208] 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[213-216]. 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[217], but also leads to an increase in deletions, insertions, and other rearrangements[218]. High RAD21 expression has also been associated with increased genomic instability[203]. Cohesin complex also organizes chromatin domains and regulates gene expression[219-220]. Both overexpression and reduction of expression of RAD21 has been reported to alter gene expression[221]. RAD21 amplification has been correlated with increased expression in breast[203-204,222] and endometrial[207] 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
ZNF217

ALTERATION
amplification - equivocal

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[223-224]. ZNF217 overexpression has also been associated with resistance to paclitaxel[225] and doxorubicin[226] 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[227].

FREQUENCY & PROGNOSIS

Amplification and/or overexpression of ZNF217 has been reported in breast[228], ovarian[229-230], gastric[231-232], colon[233], prostate[234], esophageal[235], and urothelial carcinomas[236], glioblastoma[237], and ovarian carcinosarcomas[238]. 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[239-241], and increased expression or activation of ERBB3[228,242], FAK[228], Aurora kinase A[225], AKT[226], and TGF-beta/SMAD signaling[228] 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[226,243]. ZNF217 amplification has been correlated with protein overexpression in breast carcinoma tumors and cell lines[244]. 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[245-246].

Abemaciclib

Assay findings association

CCND1
amplification - equivocal

AREAS OF THERAPEUTIC USE

Abemaciclib inhibits the cyclin-dependent kinases 4 and 6 (CDK4/6) and is FDA approved to treat hormone receptor-positive (HR+), HER2-negative (HER2–) advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine-based therapy for postmenopausal women, in combination with fulvestrant for women who have progressed on endocrine therapy, or as monotherapy for adults who have progressed on endocrine therapy and chemotherapy in the metastatic setting. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data in breast cancer and mantle cell lymphoma[43,247], CCND1 amplification or activation may be associated with response to abemaciclib. In a Phase 1 study, 4/10 patients with CCND1-amplified breast cancer responded to single-agent abemaciclib, with all of the responders having HR+ tumors[43].

SUPPORTING DATA

As first-line treatment for postmenopausal women with HR+, HER2– advanced breast cancer, the addition of abemaciclib to nonsteroidal aromatase inhibitors significantly increased median PFS (28.1 vs. 14.8 months; hazard ratio [HR]=0.54) and ORR (61% vs. 46%) in a placebo-controlled Phase 3 study[248-249]. Abemaciclib as monotherapy for HR+, HER2– metastatic breast cancer refractory to endocrine therapy and chemotherapy achieved an ORR of 20%, a median PFS of 6.0 months, and a median OS of 17.7 months[45]. For women with HR+, HER2– recurrent or metastatic breast cancer who had progressed after endocrine therapy, abemaciclib combined with fulvestrant significantly improved median PFS (16.4 vs. 9.3 months; HR=0.55) and ORR (48% vs. 21%) compared with placebo plus fulvestrant[250]. However, patients in this study with PIK3CA or ESR1 mutations, detected in ctDNA, exhibited a greater clinical benefit than patients without PIK3CA or ESR1 mutations (PIK3CA HR=0.46 vs. 0.68; ESR1 HR = 0.49 vs 0.69); this clinical benefit was not observed for patients with PIK3CA or ESR1 mutations detected from FFPE samples[251]. A Phase 1 trial of abemaciclib monotherapy for patients with heavily treated advanced breast cancer observed a higher DCR in HR+ tumors (81%, 29/36) than in HR– tumors (33%, 3/9), with radiographic responses occurring exclusively in the HR+ cohort[43]. In patients with brain metastases originating from HR+, HER2– breast cancer, single-agent abemaciclib has shown an intracranial clinical benefit rate of 25% (3/52 PR and 10/52 SD of ≥6 months)[252]. As neoadjuvant treatment for early stage HR+, HER2– breast cancer, abemaciclib in combination with anastrozole led to radiologic responses in 46% of patients[253]. Preliminary data suggest that in patients with HR+, HER2– breast cancer who have progressed on palbociclib or ribociclib, additional clinical benefit may be derived from abemaciclib alone or in combination with antiestrogen therapy[254].

Alpelisib

Assay findings association

PIK3CA
N345K

AREAS OF THERAPEUTIC USE

Alpelisib inhibits phosphatidylinositol-3-kinase (PI3K) with selective activity against the alpha isoform (PI3K-alpha). Alpelisib is FDA approved in combination with fulvestrant for postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated advanced breast cancer following progression on or after endocrine therapy.

GENE ASSOCIATION

On the basis of prospective clinical data, PIK3CA mutations including C420R, E542K, E545A, E545G, E545K, E545D, Q546E, Q546R, H1047L, H1047Y, and H1047R are associated with sensitivity to alpelisib. In ER+/HER2– breast cancer, PFS benefit from the addition of alpelisib to fulvestrant was specifically observed for patients with PIK3CA mutations (11.0 vs. 5.7 months, HR=0.65), including patients with PIK3CA exon 9 or exon 20 mutations[58]. Objective responses have also been achieved by patients with several other solid tumor types harboring PIK3CA mutation[73,255] .

SUPPORTING DATA

The Phase 3 SOLAR-1 study in ER+/HER2– endocrine therapy-resistant advanced breast cancer reported that the addition of alpelisib to fulvestrant improved median PFS (11.0 vs. 5.7 months, HR=0.65), ORR (26.6% vs. 12.8%), and clinical benefit rate (61.5% vs. 45.3%) for patients with PIK3CA mutation; benefit was observed for patients with PIK3CA exon 9 and exon 20 mutations[58]. For PIK3CA-wild-type patients, addition of alpelisib to fulvestrant did not significantly improve median PFS (7.4 vs. 5.6 months, HR=0.85)[58]. Similarly, a Phase 1b study of alpelisib and fulvestrant for patients with ER+/HER2– endocrine therapy-resistant breast cancer reported improved median PFS (9.1 vs. 4.7 months) and ORR (32%, 14/49 vs. 0%, 0/32) in PIK3CA-mutated tumors compared with PIK3CA-wild-type tumors[256]. Case studies have reported durable responses (>6 months) from alpelisib alone or combined with endocrine therapy in patients with advanced or metastatic breast cancer previously treated with endocrine therapy[109,257-258] . In combination with letrozole and the CDK4/6 inhibitor ribociclib, alpelisib resulted in objective responses for 7% (2/27) and unconfirmed PRs for 15% (4/27) of patients with HR+/HER2– advanced breast cancer[259]. As neoadjuvant therapy for postmenopausal women with HR+/HER2– early breast cancer, alpelisib added to letrozole did not increase ORR for patients with (45% vs. 43%) or without (61% vs. 63%) PIK3CA mutation in a placebo-controlled Phase 2 trial[260]. A Phase 1/2 study of alpelisib and nab-paclitaxel in patients with HER2– metastatic breast cancer previously treated with chemotherapy reported a 57% ORR (24/42, 2 CR) and a median PFS of 9 months, with improved median PFS in patients with PIK3CA pathway activation (13 vs. 7 months, HR=0.39)[261]. For patients with HER2+ advanced breast cancer who progressed on trastuzumab and/or a taxane, alpelisib combined with ado-trastuzumab emtansine yielded a 43% ORR (6/14, 1 CR), including responses for patients with high AKT expression or PTEN loss[262].

Everolimus

Assay findings association

PIK3CA
N345K

AREAS OF THERAPEUTIC USE

Everolimus is an orally available mTOR inhibitor that is FDA approved to treat renal cell carcinoma (RCC) following antiangiogenic therapy; pancreatic neuroendocrine tumors and well-differentiated non-functional neuroendocrine tumors of the lung or gastrointestinal tract; and, in association with tuberous sclerosis complex (TSC), renal angiomyolipoma and subependymal giant cell astrocytoma. Everolimus is also approved to treat hormone receptor-positive, HER2-negative advanced breast cancer in combination with exemestane following prior therapy with letrozole or anastrozole, as well as in combination with the multikinase inhibitor lenvatinib to treat advanced RCC following prior antiangiogenic therapy.

GENE ASSOCIATION

On the basis of extensive clinical[60-61,64] and preclinical[65] evidence in multiple tumor types, PIK3CA activation may predict sensitivity to mTOR inhibitors such as everolimus.

SUPPORTING DATA

In an exploratory cohort of the BOLERO-2 Phase 3 study, the addition of exemestane to everolimus in the first line for hormone receptor-positive (HR+), HER2-negative breast cancer was shown to improve the median PFS compared to exemestane alone (11.5 vs. 4.1 months, HR = 0.39)[263]. Everolimus combined with exemestane as second-line therapy in the same setting also improved the median PFS compared with exemestane in BOLERO-2 (7.8 vs. 3.2 months, HR = 0.45)[264-266] , and modestly improved the median PFS compared with everolimus alone in BOLERO-6 (8.4 vs. 6.8 months, HR = 0.74)[267]. Analysis of cell-free DNA revealed a similar benefit for patients with mutant or wild-type PIK3CA (HR = 0.37 vs. 0.43)[67]. Clinical studies for patients with HR+ breast cancer indicate that everolimus may potentiate letrozole or tamoxifen efficacy and can be safely combined with anastrozole[268-270] . Two Phase 3 trials have evaluated whether the addition of everolimus would circumvent or overcome resistance of HER2-positive (HER2+) breast cancer to trastuzumab-based therapy. 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 (20.3 vs. 13.1 months)[271]. 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)[272]. Follow-up exploratory analysis in patients with PIK3CA alterations showed longer median PFS from addition of everolimus to trastuzumab plus either paclitaxel (12.0 vs. 7.6 months) or vinorelbine (6.9 vs. 5.7 months), compared with the addition of placebo to trastuzumab plus either paclitaxel or vinorelbine (HR = 0.69)[273]. Low PTEN expression or PTEN loss also was significantly associated with benefit from added everolimus in the combined analysis of both studies (HR = 0.50), whereas PIK3CA mutation was significantly associated with benefit in HR-negative (HR = 0.43) but not HR+ disease (HR = 0.93)[61,273] . For patients with metastatic triple-negative breast cancer, everolimus plus carboplatin achieved a clinical benefit rate of 36% (9/25)[274]. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[275], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[276].

Palbociclib

Assay findings association

CCND1
amplification - equivocal

AREAS OF THERAPEUTIC USE

Palbociclib inhibits the cyclin-dependent kinases 4 and 6 (CDK4/6) and is FDA approved to treat hormone receptor (HR)-positive/HER2-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor as first-line therapy for postmenopausal women or in combination with fulvestrant following progression on endocrine therapy.

GENE ASSOCIATION

Clinical studies in liposarcoma and mantle cell lymphoma as well as responses in patients with breast cancer or melanoma indicate that activation of cyclin D-CDK4/6 may predict sensitivity to therapies such as palbociclib[44,47,277-278] .

SUPPORTING DATA

The Phase 3 PALOMA-3 study reported that addition of palbociclib to fulvestrant improved median PFS (11.2 vs. 4.6 months) and ORR (25% vs. 11%) compared with fulvestrant plus placebo in patients with hormone receptor-positive (HR+)/HER2-negative breast cancer who had progressed on endocrine therapy, regardless of menopausal status; luminal status; PIK3CA and ESR1 mutation status; CDK4, CDK6, cyclin D1, and RB1 expression status; HR expression level; or the number of previous endocrine therapies[273,279-283] . PALOMA-3 demonstrated that the combination of palbociclib and fulvestrant significantly improved OS relative to the comparator for patients with prior sensitivity to endocrine therapy (39.7 vs. 29.7 months, HR=0.72) and in an exploratory subgroup analysis for patients with ESR1 mutations (35.6 vs. 24.6 months, HR=0.69); statistical significance was not reached for the overall population (34.9 vs. 28.0 months; HR=0.81, p=0.09)[283]. Retrospective analysis of the PALOMA-3 overall population found that low tumor CCNE1 expression correlated with improved PFS from palbociclib plus fulvestrant versus high tumor CCNE1 expression (14.1 vs. 7.6 months)[280]. For postmenopausal patients with newly diagnosed estrogen receptor-positive (ER+)/HER2-negative metastatic breast cancer (MBC), the addition of palbociclib to letrozole significantly improved ORR (42% vs. 35%) and median PFS (24.8 vs. 14.5 months); benefit was irrespective of expression of genes within the cyclin D-CDK4/6-RB pathway[284]. For patients with breast cancer, HR positivity appears to be the best biomarker for response to CDK4/6 inhibition; CCND1 amplification or CDKN2A loss failed to correlate with sensitivity in an unselected breast cancer cohort and did not improve the selection of HR+ patients experiencing clinical benefit[41,285] . However, a Phase 1 study of the CDK4/6 inhibitor ribociclib in Rb+ tumors reported 2 patients with PRs, and both responding tumors had CCND1 amplification[42]. In a Phase 1 trial of palbociclib in combination with bicalutamide for patients with androgen receptor-positive, HER2-negative MBC, 3/8 patients with HR+ disease and 1/7 patients with triple-negative breast cancer were treated for >30 weeks, with treatment still ongoing for one patient for more than a year[286]. A Phase 2 study of single-agent palbociclib for Rb+ breast cancer reported that 3.8% (2/52) of patients experienced a PR and 15.3% (8/52) of patients had prolonged SD; median PFS was significantly longer for patients with HR+ versus HR- disease (4.5 vs. 1.5 months); a subcohort of HER2+ patients treated with palbociclib plus trastuzumab in this study achieved 20% (2/10) PRs and 10% (1/10) prolonged SD, with median PFS of 6.7 months[285,287-288] . Palbociclib has also demonstrated clinical activity in combination with hormonal therapy and/or HER2-targeted therapy in the neoadjuvant setting[289-290] . In the single-arm Phase 2 trial combining palbociclib, trastuzumab, pertuzumab, and fulvestrant as neoadjuvant therapy for previously untreated HER2+, ER+ invasive breast cancer, an objective response prior to surgery was observed for 97% (29/30) of patients and, at surgery, 27% (8/30) had achieved a pathologic CR in breast tissue and axillary nodes[291].

Ribociclib

Assay findings association

CCND1
amplification - equivocal

AREAS OF THERAPEUTIC USE

Ribociclib inhibits the cyclin-dependent kinases 4 and 6 (CDK4/6) and is FDA approved in combination with an aromatase inhibitor as first-line therapy to treat women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) advanced or metastatic breast cancer. Ribociclib is also approved in combination with fulvestrant to treat postmenopausal women with HR+, HER2– advanced or metastatic breast cancer, either as first-line therapy or following disease progression on endocrine therapy.

GENE ASSOCIATION

On the basis of clinical responses for 3 patients with bladder cancer, BRAF/NRAS-wild-type melanoma, or ER-positive breast cancer[42,47], CCND1 amplification or expression may predict sensitivity to CDK4/6 inhibitors such as ribociclib. In a prospective trial, 1 out of 12 patients with CCND1-amplified solid tumors responded to ribociclib[47].

SUPPORTING DATA

In the Phase 3 MONALEESA-2 study, the addition of ribociclib to letrozole as first-line therapy for postmenopausal patients with HR+, HER2– recurrent or metastatic breast cancer improved median PFS (25.3 vs. 16.0 months; hazard ratio [HR]=0.57) and ORR (55% vs. 39%) when compared to placebo[292]. In a Phase 3 trial for premenopausal or perimenopausal women with HR+, HER2– advanced breast cancer, the addition of ribociclib in the first-line setting to tamoxifen or a nonsteroidal aromatase inhibitor plus goserelin compared with the addition of placebo significantly improved median PFS (23.8 vs. 13.0 months, HR=0.55)[293] and estimated 42-month OS (70.2% vs. 46.0%, HR=0.71)[294]. In the Phase 3 MONALEESA-3 study, ribociclib in combination with fulvestrant treatment in postmenopausal patients with HR+, HER2- advanced breast cancer previously treated with up to 1 line of endocrine therapy improved median PFS (20.5 vs. 12.8 months, HR=0.59 and 33.6 vs 19.2, HR=0.55 in first line setting), ORR (41 vs. 29% in patients with measurable disease), and OS (not reached vs 45.1 months, HR=0.73 as first line and 40.2 vs 32.5 months, HR=0.73 as second line) as compared to placebo with fulvestrant[295-296] . Phase 1 and 2 studies of ribociclib monotherapy or in combination for patients with breast cancer have reported efficacy and clinical benefit[297-299] .

Temsirolimus

Assay findings association

PIK3CA
N345K

AREAS OF THERAPEUTIC USE

Temsirolimus is an intravenous mTOR inhibitor that is FDA approved for the treatment of advanced renal cell carcinoma.

GENE ASSOCIATION

On the basis of extensive clinical[62-63,300] and preclinical[65] evidence, PIK3CA activation may predict sensitivity to mTOR inhibitors such as temsirolimus. In two studies of temsirolimus-containing treatment regimens in a variety of cancer types, response rates of 4/16 (25%)[62] and 7/23 (30%)[300] were reported in patients with PIK3CA-mutant tumors.

SUPPORTING DATA

A Phase 1 trial examining the combination of temsirolimus, liposomal doxorubicin, and bevacizumab in 74 patients with breast and gynecological malignancies reported that 37.9% of patients experienced either a CR (1.4%), PR (18.9%), or SD (17.6%); among 25 patients with PIK3CA mutation or PTEN loss, 52% experienced a CR, PR (36%), or SD (16%)[301]. Another Phase 1 trial including patients with several types of cancer reported a 42% incidence of complete or partial responses in patients with metastatic breast cancer[302]. However, a Phase 2 study of temsirolimus in pretreated patients with metastatic breast cancer reported minimal clinical activity and no association with PTEN protein or PIK3CA mutation status[303]. A Phase 3 placebo-controlled trial of letrozole plus oral temsirolimus as first-line endocrine therapy in postmenopausal women with locally advanced or metastatic breast cancer was terminated at the second interim since the addition of temsirolimus to letrozole did not improve PFS as a first-line therapy[304]. A study examining the efficacy of temsirolimus-involving regimens in 24 patients with mesenchymal/metaplastic breast cancer (MpBCs) reported 2 CRs, 4 PRs, 2 instances of SD longer than 6 months, and 4 instances of SD shorter than 6 months[63].

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.

CLINICAL TRIALS

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

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

ALTERATION
amplification - equivocal

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
CCND1

ALTERATION
amplification - equivocal

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

NCT03701334

PHASE 3

A Trial to Evaluate Efficacy and Safety of Ribociclib With Endocrine Therapy as Adjuvant Treatment in Patients With HR+/HER2- Early Breast Cancer

TARGETS
Aromatase, ER, CDK6, CDK4

LOCATIONS: Alabama, Edmonton (Canada), Elche (Spain), Nice Cedex 2 (France), Cordoba (Spain), Granada (Spain), Huelva (Spain), Jaen (Spain), Malaga (Spain), Sevilla (Spain), Edegem (Belgium), Arizona, Bergamo (Italy), Brindisi (Italy), Kelowna (Canada), North Vancouver (Canada), Surrey (Canada), Vancouver (Canada), California, Avila (Spain), Burgos (Spain), Salamanca (Spain), Badalona (Spain), Barcelona (Spain), Manresa (Spain), Cheongju si (Korea, Republic of), Colorado, Alicante (Spain), Valencia (Spain), Connecticut, Wilton (Ireland), Truro (United Kingdom), Dijon Cedex (France), Dublin 9 (Ireland), Seoul (Korea, Republic of), Badajoz (Spain), Caceres (Spain), Florida, A Coruna (Spain), La Coruna (Spain), Wonju-si (Korea, Republic of), Georgia, Bundang Gu (Korea, Republic of), Limoges cedex (France), Saint-Cloud (France), Rennes Cedex (France), Illinois, Indiana, Kansas, Maidstone (United Kingdom), Suwon (Korea, Republic of), Rozzano (Italy), Fuenlabrada (Spain), Maryland, Massachusetts, Michigan, Minnesota, Missouri, Montana, El Palmar (Spain), Madrid (Spain), Nebraska, Nevada, New Jersey, Campbelltown (Australia), Coffs Harbour (Australia), Darlinghurst (Australia), Kingswood (Australia), Kogarah (Australia), Liverpool (Australia), North Ryde (Australia), St Leonards (Australia), Wahroonga (Australia), Westmead (Australia), New York, North Carolina, Halifax (Canada), Kitchener (Canada), Newmarket (Canada), Oshawa (Canada), Sault Ste Marie (Canada), Sudbury (Canada), Toronto (Canada), Windsor (Canada), Oregon, Aviano (Italy), San Sebastian (Spain), Vitoria-Gasteiz (Spain), Pennsylvania, Vigo (Spain), Greenfield Park (Canada), Montreal (Canada), St-Jerome (Canada), Auchenflower (Australia), Birtinya (Australia), Wooloongabba (Australia), Roma (Italy), Porto Alegre (Brazil), Leningrad Region (Russian Federation), Sao Paulo (Brazil), Rosario (Argentina), Bedford Park (Australia), Graz (Austria), Tennessee, Texas, San Miguel De Tucuman (Argentina), Innsbruck (Austria), Warsaw (Poland), Utah, Bendigo (Australia), East Melbourne (Australia), Epping (Australia), Fitzroy (Australia), Franston (Australia), Heidelberg (Australia), Melbourne (Australia), Shepparton (Australia), Rio Negro (Argentina), Virginia, Washington, Murdoch (Australia), Nedlands (Australia), Wisconsin, Zalaegerszeg (Hungary), Caba (Argentina), Jujuy (Argentina), La Rioja (Argentina), Santa Fe (Argentina), Linz (Austria), Salzburg (Austria), Wien (Austria), Bruxelles (Belgium), Charleroi (Belgium), Hasselt (Belgium), Leuven (Belgium), Libramont (Belgium), Liege (Belgium), Namur (Belgium), Wilrijk (Belgium), Yvoir (Belgium), Caxias do Sul (Brazil), Ijui (Brazil), Passo Fundo (Brazil), Quebec (Canada), Amiens (France), Angers Cedex 02 (France), Argenteuil (France), Avignon Cedex (France), Besancon cedex (France), Bobigny Cedex (France), Bordeaux Cedex (France), Caen Cedex (France), Grenoble cedex (France), Le Mans (France), Lyon (France), Marseille (France), Montpellier (France), Montpellier Cedex 5 (France), Nantes cedex 2 (France), Paris (France), Pierre Benite Cedex (France), Rouen Cedex 1 (France), Saint Herblain cedex (France), Strasbourg (France), Toulouse Cedex 9 (France), Vandoeuvre-les-Nancy cedex (France), Villejuif Cedex (France), Budapest (Hungary), Debrecen (Hungary), Kecskemet (Hungary), Pecs (Hungary), Szeged (Hungary), Szekszard (Hungary), Szombathely (Hungary), Tatabanya (Hungary), County Limerick (Ireland), Dublin (Ireland), Dublin 4 (Ireland), Dublin 7 (Ireland), Waterford (Ireland), Bologna (Italy), Napoli (Italy), Incheon (Korea, Republic of), Seongnam Si Gyeonggi Do (Korea, Republic of), Ulsan (Korea, Republic of), Bialystok (Poland), Gdynia (Poland), Krakow (Poland), Lodz (Poland), Lublin (Poland), Opole (Poland), Ostroleka (Poland), Otwock (Poland), Wieliszew (Poland), Wroclaw (Poland), Kazan (Russian Federation), Kostroma (Russian Federation), Krasnoyarsk (Russian Federation), Kursk (Russian Federation), Moscow (Russian Federation), Nizhny Novgorod (Russian Federation), Novosibirsk (Russian Federation), Obninsk (Russian Federation), Omsk (Russian Federation), Orenburg (Russian Federation), Rostov-na-Donu (Russian Federation), Ryazan (Russian Federation), St Petersburg (Russian Federation), St- Petersburg (Russian Federation), Tyumen (Russian Federation), Ufa (Russian Federation), Yaroslavl (Russian Federation), Bilbao (Spain), Castellon (Spain), Murcia (Spain), Navarra (Spain), Sabadell (Spain), Zaragoza (Spain), Changhua (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Taipei (Taiwan), Taoyuan (Taiwan), Cardiff (United Kingdom), London (United Kingdom), Nottingham (United Kingdom), Oxford (United Kingdom), Preston (United Kingdom), Stoke-on-Trent (United Kingdom)

NCT02107703

PHASE 3

A Study of Abemaciclib (LY2835219) Combined With Fulvestrant in Women With Hormone Receptor Positive HER2 Negative Breast Cancer

TARGETS
CDK4, CDK6, ER

LOCATIONS: Calgary (Canada), Arkansas, California, Colorado, Florida, Georgia, Illinois, Indiana, Massachusetts, Michigan, Minnesota, Missouri, Montana, Nebraska, New Hampshire, New York, North Carolina, North Dakota, Oklahoma, London (Canada), Toronto (Canada), Tennessee, Texas, Utah, Vermont, Virginia, Washington, Chungbuk (Korea, Republic of), Gyeonggi-Do (Korea, Republic of), Incheon (Korea, Republic of), Seoul (Korea, Republic of), Ulsan-Si (Korea, Republic of), Leon (Mexico), Mexico (Mexico), Mexico City (Mexico), Monterrey (Mexico), Nuevo Leon (Mexico), Tijuana (Mexico), Bialystok (Poland), Wieliszew (Poland), Bayamon (Puerto Rico), Cluj-Napoca (Romania), Barcelona (Spain), Elche (Spain), Lleida (Spain), Madrid (Spain), Murcia (Spain), Valencia (Spain), Kaohsiung (Taiwan), Kuei Shan Hsiang (Taiwan), Taichung (Taiwan), Taipei (Taiwan)

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

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

LOCATIONS: Alaska, Arkansas, California, Colorado, Connecticut, Florida, Georgia, Idaho, Illinois, Iowa, Kentucky, Louisiana, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, New Jersey, New York, North Carolina, Ohio, Oklahoma, Oregon, Pennsylvania, Texas, Utah, Vermont, Virginia, Washington, Wisconsin, Wyoming

NCT03284957

PHASE 1/2

Phase 1 / 2 Study of SAR439859 Single Agent and in Combination With Palbociclib in Postmenopausal Women With Estrogen Receptor Positive Advanced Breast Cancer

TARGETS
ER, CDK4, CDK6

LOCATIONS: Colorado, Massachusetts, New York, Pennsylvania, South Carolina, Texas, Washington, Leuven (Belgium), Wilrijk (Belgium), Edmonton (Canada), Montreal (Canada), Toronto (Canada), Vancouver (Canada), Brno (Czechia), Hradec Kralove (Czechia), Praha 2 (Czechia), Praha 4 (Czechia), Bordeaux Cedex (France), Lille (France), Lyon (France), Saint-Herblain (France), Villejuif Cedex (France), Milano (Italy), Napoli (Italy), Negrar (Italy), Gdynia (Poland), Warsaw (Poland), Lisboa (Portugal), Porto (Portugal), Madrid (Spain), Cardiff (United Kingdom), Glasgow (United Kingdom), Oxford (United Kingdom)

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT02738866

PHASE 2

Palbociclib With Fulvestrant for Metastatic Breast Cancer After Treatment With Palbociclib and an Aromatase Inhibitor

TARGETS
ER, CDK4, CDK6

LOCATIONS: District of Columbia, Maryland, Pennsylvania

NCT02734615

PHASE 1

Phase I/Ib Trial of LSZ102 Single Agent or LSZ102 + LEE011 or LSZ102 + BYL719 in ER+ Breast Cancers

TARGETS
ER, CDK6, CDK4, PI3K-alpha

LOCATIONS: California, Barcelona (Spain), Milano (Italy), Maryland, Massachusetts, New York, North Carolina, Toronto (Canada), Texas, Koto ku (Japan), Singapore (Singapore), Madrid (Spain)

NCT02668666

PHASE 2

Palbociclib in Combination With Tamoxifen as First Line Therapy for Metastatic Hormone Receptor Positive Breast Cancer

TARGETS
CDK4, CDK6, ER

LOCATIONS: Illinois, Michigan, Minnesota, Nebraska, Pennsylvania, Wisconsin

NCT02684032

PHASE 1

A Study To Assess The Tolerability And Clinical Activity Of Gedatolisib In Combination With Palbociclib/Letrozole Or Palbociclib/Fulvestrant In Women With Metastatic Breast Cancer

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

LOCATIONS: Alabama, California, Colorado, Florida, Georgia, Massachusetts, Michigan, North Carolina, Ohio, Pennsylvania, Tennessee, Texas, Virginia, Washington

NCT01037790

PHASE 2

PHASE II TRIAL OF THE CYCLIN-DEPEDENT KINASE INHIBITOR PD 0332991 IN PATIENTS WITH CANCER

TARGETS
CDK4, CDK6

LOCATIONS: Pennsylvania

GENE
MDM2

ALTERATION
amplification

RATIONALE
Inhibitors of the MDM2-p53 interaction are being tested in clinical trials. Overexpression or amplification of MDM2 may increase sensitivity to these agents, but more data are required.

NCT04029688

PHASE 1/2

A Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Preliminary Activity of Idasanutlin in Combination With Either Chemotherapy or Venetoclax in the Treatment of Pediatric and Young Adult Participants With Relapsed/Refractory Acute Leukemias or Solid Tumors

TARGETS
MDM2, BCL2

LOCATIONS: Arkansas, Florida, Pennsylvania, Texas, Madrid (Spain)

NCT03449381

PHASE 1

This Study Aims to Find the Best Dose of BI 907828 in Patients With Different Types of Advanced Cancer (Solid Tumors)

TARGETS
MDM2

LOCATIONS: Connecticut, Florida, New York, Ottawa (Canada), Tennessee, Tokyo, Chuo-ku (Japan)

NCT02935907

PHASE 1

APG-115 in Patients With Advanced Solid Tumors or Lymphomas

TARGETS
MDM2

LOCATIONS: Michigan, Texas

NCT03611868

PHASE 1/2

A Study of APG-115 in Combination With Pembrolizumab in Patients With Metastatic Melanomas or Advanced Solid Tumors

TARGETS
MDM2, PD-1

LOCATIONS: Arkansas, Tennessee, Texas

NCT03725436

PHASE 1

ALRN-6924 and Paclitaxel in Treating Patients With Advanced, Metastatic, or Unresectable Solid Tumors

TARGETS
MDM2, MDM4

LOCATIONS: Texas

GENE
PIK3CA

ALTERATION
N345K

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

NCT03056755

PHASE 2

Efficacy and Safety of Treatment With Alpelisib Plus Endocrine Therapy in Patients With HR+, HER2-negative aBC, With PIK3CA Mutations, Whose Disease Has Progressed on or After CDK 4/6 Treatment With an Aromatase Inhibitor (AI) or Fulvestrant

TARGETS
ER, PI3K-alpha, Aromatase

LOCATIONS: Maastricht (Netherlands), Nice Cedex 2 (France), Malaga (Spain), Sevilla (Spain), Temuco (Chile), Arizona, Bergamo (Italy), Vancouver (Canada), Caba (Argentina), California, Salamanca (Spain), Barcelona (Spain), Hospitalet de LLobregat (Spain), Castellon (Spain), Connecticut, Mexico D F (Mexico), Florida, Saint-Cloud (France), Iowa, Kansas, Kentucky, Milano (Italy), Maryland, Massachusetts, Michigan, Missouri, Montana, New Mexico, New York, Halifax (Canada), Ohio, Kitchener (Canada), Toronto (Canada), Osaka-city (Japan), Suita city (Japan), San Sebastian (Spain), Roma (Italy), Rosario (Argentina), Sutton (United Kingdom), Texas, Bunkyo ku (Japan), Koto ku (Japan), Shinjuku-ku (Japan), Virginia, Washington, Kolkata (India), La Rioja (Argentina), San Juan (Argentina), Leuven (Belgium), Liege (Belgium), Santiago (Chile), Odense C (Denmark), Vejle (Denmark), Bordeaux (France), Caen Cedex (France), Lille Cedex (France), Lyon (France), Montpellier Cedex 5 (France), Saint Herblain cedex (France), Strasbourg Cedex (France), Toulouse Cedex 9 (France), Augsburg (Germany), Berlin (Germany), Dresden (Germany), Erlangen (Germany), Essen (Germany), Heidelberg (Germany), Kiel (Germany), Troisdorf (Germany), Tübingen (Germany), Ulm (Germany), Delhi (India), Kfar Saba (Israel), Petach Tikva (Israel), Ramat Gan (Israel), Rehovot (Israel), Tel Aviv (Israel), Bologna (Italy), Napoli (Italy), Seoul (Korea, Republic of), Jalisco (Mexico), Singapore (Singapore), Madrid (Spain), Tainan (Taiwan), Taipei (Taiwan), Edinburgh (United Kingdom), Leicester (United Kingdom), London (United Kingdom), Nottingham (United Kingdom)

NCT03997123

PHASE 3

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

TARGETS
AKTs

LOCATIONS: Arizona, Victoria (Canada), California, Florida, Illinois, Kansas, New York, Ohio, Kitchener (Canada), Mississauga (Canada), North York (Canada), Pennsylvania, Tennessee, Texas, Utah, Virginia, Caba (Argentina), Ciudad Autonoma De Buenos Aire (Argentina), Mar del Plata (Argentina), Florianópolis (Brazil), Londrina (Brazil), Sao Paulo (Brazil), São José do Rio Preto (Brazil), São Paulo (Brazil), Chomutov (Czechia), Hradec Kralove (Czechia), Jihlava (Czechia), Praha 10 (Czechia), Praha 2 (Czechia), Brest Cedex (France), Montpellier (France), Nice (France), Paris (France), Saint Herblain (France), Villejuif (France), Bangalore (India), Gurgaon (India), Hyderabad (India), Kolkata (India), Nagpur (India), Nasik (India), Fukuoka-shi (Japan), Hidaka-shi (Japan), Hiroshima-shi (Japan), Kagoshima-shi (Japan), Kitaadachi-gun (Japan), Koto-ku (Japan), Kumamoto-shi (Japan), Nagoya-shi (Japan), Osaka-shi (Japan), Ota-shi (Japan), Sapporo-shi (Japan), Shinagawa-ku (Japan), Shinjuku-ku (Japan), Sunto-gun (Japan), Tsu-shi (Japan), Yokohama-shi (Japan), Cheongju-si (Korea, Republic of), Daegu (Korea, Republic of), Goyang-si (Korea, Republic of), Incheon (Korea, Republic of), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Cebu City (Philippines), Davao City (Philippines), Iloilo (Philippines), Las Pinas (Philippines), San Juan (Philippines), Bydgoszcz (Poland), Grudziądz (Poland), Konin (Poland), Ostrołęka (Poland), Poznan (Poland), Racibórz (Poland), Radom (Poland), Tomaszów Mazowiecki (Poland), Warszawa (Poland), Wroclaw (Poland), Arkhangelsk (Russian Federation), Moscow (Russian Federation), Saint-Petersburg (Russian Federation), Volgograd (Russian Federation), Yaroslavl (Russian Federation), Dammam (Saudi Arabia), Makkah (Saudi Arabia), Riyadh (Saudi Arabia), Barcelona (Spain), Hospitalet deLlobregat (Spain), Madrid (Spain), Málaga (Spain), Sevilla (Spain), Valencia (Spain), Zaragoza (Spain), Göteborg (Sweden), Linköping (Sweden), Stockholm (Sweden), Uppsala (Sweden), Changhua (Taiwan), Kaohsiung (Taiwan), Tainan (Taiwan), Taipei (Taiwan), Ankara (Turkey), Istanbul (Turkey), Izmir (Turkey), Malatya (Turkey), Mersin (Turkey), Edinburgh (United Kingdom), London (United Kingdom), Sheffield (United Kingdom), York (United Kingdom)

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

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

LOCATIONS: Alaska, Arkansas, California, Colorado, Connecticut, Florida, Georgia, Idaho, Illinois, Iowa, Kentucky, Louisiana, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, New Jersey, New York, North Carolina, Ohio, Oklahoma, Oregon, Pennsylvania, Texas, Utah, Vermont, Virginia, Washington, Wisconsin, Wyoming

NCT01827384

PHASE 2

Molecular Profiling-Based Targeted Therapy in Treating Patients With Advanced Solid Tumors

TARGETS
PARP, mTOR, MEK, WEE1

LOCATIONS: Colorado, Kentucky, Maryland, Missouri, New Jersey, Pennsylvania, Texas

NCT03280563

PHASE 1/2

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

TARGETS
PD-L1, ER, HDAC, AKTs

LOCATIONS: Alabama, California, Illinois, Maryland, New York, North Carolina, Oregon, Pennsylvania, Tennessee, Haifa (Israel), Jerusalem (Israel), Petah Tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Gyeonggi-do (Korea, Republic of), Seoul (Korea, Republic of)

NCT03424005

PHASE 1/2

A Study Evaluating the Efficacy and Safety of Multiple Immunotherapy-Based Treatment Combinations in Patients With Metastatic Triple-Negative Breast Cancer (Morpheus-TNBC)

TARGETS
PD-L1, AKTs, MEK, VEGFA

LOCATIONS: California, Florida, New York, Pennsylvania, Tennessee, Melbourne (Australia), Lyon (France), Toulouse (France), Villejuif CEDEX (France), Erlangen (Germany), Essen (Germany), Seoul (Korea, Republic of), Barcelona (Spain), Madrid (Spain), Glasgow (United Kingdom), London (United Kingdom)

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

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)

NCT02890069

PHASE 1

A Study of PDR001 in Combination With LCL161, Everolimus or Panobinostat

TARGETS
mTOR, PD-1, CXCR2, HDAC, MDM2, IAPs

LOCATIONS: California, Barcelona (Spain), Seoul (Korea, Republic of), Maryland, Massachusetts, Michigan, Pamplona (Spain), Sutton (United Kingdom), Texas, Utah, Washington, Jena (Germany), Ulm (Germany), Wuerzburg (Germany), Amsterdam (Netherlands), Leiden (Netherlands), Rotterdam (Netherlands), Utrecht (Netherlands), Madrid (Spain), Taipei (Taiwan), Manchester (United Kingdom)

NCT02734615

PHASE 1

Phase I/Ib Trial of LSZ102 Single Agent or LSZ102 + LEE011 or LSZ102 + BYL719 in ER+ Breast Cancers

TARGETS
ER, CDK6, CDK4, PI3K-alpha

LOCATIONS: California, Barcelona (Spain), Milano (Italy), Maryland, Massachusetts, New York, North Carolina, Toronto (Canada), Texas, Koto ku (Japan), Singapore (Singapore), 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.

BCORL1	*CREBBP*	*PIK3CB*	*RICTOR*
C1101Y	S128C	R276K	A713G

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 862x

117. Anand S, Penrhyn-Lowe S, Venkitaraman AR 3 (1):51-62 (2003) PMID: 12559175

119. Letessier A, Sircoulomb F, Ginestier C, et al. ePub Oct 2006 (2006) PMID: 17040570

120. Staff S, Isola J, Jumppanen M, et al. ePub Feb 2010 (2010) PMID: 20043089

27. null ePub Oct 2012 (2012) PMID: 23000897

121. Zhang C, Fang Z, Xiong Y, et al. ePub Nov 2010 (2010) PMID: 20929925

122. Tanaka T, Kimura M, Matsunaga K, et al. 59 (9):2041-4 (1999) PMID: 10232583

123. Ginestier C, Cervera N, Finetti P, et al. 12 (15):4533-44 (2006) PMID: 16899599

124. Haibe-Kains B, Desmedt C, Loi S, et al. ePub Feb 2012 (2012) PMID: 22262870

111. Lens SM, Voest EE, Medema RH ePub Dec 2010 (2010) PMID: 21102634

112. Boss DS, Beijnen JH, Schellens JH ePub Aug 2009 (2009) PMID: 19684075

113. Necchi A, Lo Vullo S, Mariani L, et al. ePub Apr 2016 (2016) PMID: 26873642

114. Melichar B, Adenis A, Lockhart AC, et al. ePub Apr 2015 (2015) PMID: 25728526

115. Swanton C, Tomlinson I, Downward J ePub Apr 2006 (2006) PMID: 16628000

116. McGrogan BT, Gilmartin B, Carney DN, et al. 1785 (2):96-132 (2008) PMID: 18068131

15. Kocarnik JM, Shiovitz S, Phipps AI 3 (4):269-76 (2015) PMID: 26337942

16. You JF, Buhard O, Ligtenberg MJ, et al. ePub Dec 2010 (2010) PMID: 21081928

17. Bairwa NK, Saha A, Gochhait S, et al. ePub 2014 (2014) PMID: 24623249

18. Boland CR, Thibodeau SN, Hamilton SR, et al. 58 (22):5248-57 (1998) PMID: 9823339

19. Pawlik TM, Raut CP, Rodriguez-Bigas MA 20 (4-5):199-206 (2004) PMID: 15528785

20. Boland CR, Goel A ePub Jun 2010 (2010) PMID: 20420947

6. Adem C, Soderberg CL, Cunningham JM, et al. 107 (4):580-2 (2003) PMID: 14520695

7. Anbazhagan R, Fujii H, Gabrielson E 5 (4):839-44 (1999) PMID: 10213220

8. Walsh MD, Buchanan DD, Cummings MC, et al. 16 (7):2214-24 (2010) PMID: 20215533

9. Risinger JI, Barrett JC, Watson P, et al. 77 (9):1836-43 (1996) PMID: 8646682

10. de Leeuw WJ, van Puijenbroek M, Tollenaar RA, et al. 63 (5):1148-9 (2003) PMID: 12615735

11. Shanley S, Fung C, Milliken J, et al. ePub 2009 (2009) PMID: 19123071

12. Buerki N, Gautier L, Kovac M, et al. ePub Jan 2012 (2012) PMID: 22034109

13. Yee CJ, Roodi N, Verrier CS, et al. 54 (7):1641-4 (1994) PMID: 8137273

14. Kamat N, Khidhir MA, Jaloudi M, et al. ePub Aug 2012 (2012) PMID: 22928966

1. Gatalica Z, Snyder C, Maney T, et al. ePub Dec 2014 (2014) PMID: 25392179

2. Kroemer G, Galluzzi L, Zitvogel L, et al. 4 (7):e1058597 (2015) PMID: 26140250

3. Lal N, Beggs AD, Willcox BE, et al. 4 (3):e976052 (2015) PMID: 25949894

4. Le DT, Uram JN, Wang H, et al. ePub Jun 2015 (2015) PMID: 26028255

90. Samuels Y, Diaz LA, Schmidt-Kittler O, et al. 7 (6):561-73 (2005) PMID: 15950905

91. null ePub Aug 2009 (2009) PMID: 19629070

92. Kang S, Bader AG, Vogt PK 102 (3):802-7 (2005) PMID: 15647370

93. Ikenoue T, Kanai F, Hikiba Y, et al. 65 (11):4562-7 (2005) PMID: 15930273

94. Gymnopoulos M, Elsliger MA, Vogt PK 104 (13):5569-74 (2007) PMID: 17376864

95. Horn S, Bergholz U, Jücker M, et al. ePub Jul 2008 (2008) PMID: 18317450

96. Rudd ML, Price JC, Fogoros S, et al. 17 (6):1331-40 (2011) PMID: 21266528

97. Hon WC, Berndt A, Williams RL ePub Aug 2012 (2012) PMID: 22120714

98. Burke JE, Perisic O, Masson GR, et al. ePub Sep 2012 (2012) PMID: 22949682

99. Wu H, Shekar SC, Flinn RJ, et al. ePub Dec 2009 (2009) PMID: 19915146

100. Laurenti R, Buchalla CM, de Lolio CA, et al. 24 (6):468-72 (1990) PMID: 2103068

101. Dan S, Okamura M, Seki M, et al. ePub Jun 2010 (2010) PMID: 20530683

102. Oda K, Okada J, Timmerman L, et al. ePub Oct 2008 (2008) PMID: 18829572

103. Zhao L, Vogt PK ePub Sep 2008 (2008) PMID: 18794883

104. Lui VW, Hedberg ML, Li H, et al. ePub Jul 2013 (2013) PMID: 23619167

105. Ross RL, Askham JM, Knowles MA ePub Feb 2013 (2013) PMID: 22430209

106. Rivière JB, Mirzaa GM, O'Roak BJ, et al. ePub Jun 2012 (2012) PMID: 22729224

107. Shibata T, Kokubu A, Tsuta K, et al. ePub Oct 2009 (2009) PMID: 19394761

108. Dogruluk T, Tsang YH, Espitia M, et al. ePub Dec 2015 (2015) PMID: 26627007

109. Croessmann S, Sheehan JH, Lee KM, et al. 24 (6):1426-1435 (2018) PMID: 29284706

110. Ng PK, Li J, Jeong KJ, et al. ePub 03 2018 (2018) PMID: 29533785

85. Loi S, Michiels S, Baselga J, et al. ePub 2013 (2013) PMID: 23301057

86. Christgen M, Noskowicz M, Schipper E, et al. ePub Jan 2013 (2013) PMID: 22997091

87. Ramirez-Ardila DE, Helmijr JC, Look MP, et al. ePub May 2013 (2013) PMID: 23592373

88. Kalinsky K, Jacks LM, Heguy A, et al. 15 (16):5049-59 (2009) PMID: 19671852

76. Vasan N, Razavi P, Johnson JL, et al. ePub 11 2019 (2019) PMID: 31699932

89. Barbareschi M, Buttitta F, Felicioni L, et al. 13 (20):6064-9 (2007) PMID: 17947469

58. André F, Ciruelos E, Rubovszky G, et al. ePub 05 2019 (2019) PMID: 31091374

59. Fritsch C, Huang A, Chatenay-Rivauday C, et al. ePub May 2014 (2014) PMID: 24608574

60. Park HS, Lim SM, Kim S, et al. ePub 2016 (2016) PMID: 27105424

61. André F, Hurvitz S, Fasolo A, et al. ePub Jun 2016 (2016) PMID: 27091708

62. Janku F, Tsimberidou AM, Garrido-Laguna I, et al. ePub Mar 2011 (2011) PMID: 21216929

63. Moulder S, Helgason T, Janku F, et al. ePub Jul 2015 (2015) PMID: 25878190

64. Lim SM, Park HS, Kim S, et al. ePub Mar 2016 (2016) PMID: 26859683

65. Meric-Bernstam F, Akcakanat A, Chen H, et al. 18 (6):1777-89 (2012) PMID: 22422409

66. Dolly SO, Wagner AJ, Bendell JC, et al. 22 (12):2874-84 (2016) PMID: 26787751

67. Moynahan ME, Chen D, He W, et al. ePub Mar 2017 (2017) PMID: 28183140

69. Rodon J, Braña I, Siu LL, et al. ePub Aug 2014 (2014) PMID: 24652201

70. Bendell JC, Rodon J, Burris HA, et al. ePub Jan 2012 (2012) PMID: 22162589

71. Heudel PE, Fabbro M, Roemer-Becuwe C, et al. ePub 01 2017 (2017) PMID: 28072765

72. Vansteenkiste JF, Canon JL, De Braud F, et al. ePub Sep 2015 (2015) PMID: 26098748

73. Juric D, Rodon J, Tabernero J, et al. ePub May 2018 (2018) PMID: 29401002

74. Mayer IA, Abramson VG, Formisano L, et al. 23 (1):26-34 (2017) PMID: 27126994

77. Schmid P, Abraham J, Chan S, et al. ePub Dec 2019 (2019) PMID: 31841354

79. Turner NC, Alarcón E, Armstrong AC, et al. ePub May 2019 (2019) PMID: 30860570

80. Esteva FJ, Guo H, Zhang S, et al. ePub Oct 2010 (2010) PMID: 20813970

81. Baselga J, Cortés J, Im SA, et al. ePub Nov 2014 (2014) PMID: 25332247

82. Chakrabarty A, Rexer BN, Wang SE, et al. ePub Sep 2010 (2010) PMID: 20581867

83. Kataoka Y, Mukohara T, Shimada H, et al. ePub Feb 2010 (2010) PMID: 19633047

84. Wang L, Zhang Q, Zhang J, et al. ePub Jun 2011 (2011) PMID: 21676217

48. Elsheikh S, Green AR, Aleskandarany MA, et al. 109 (2):325-35 (2008) PMID: 17653856

56. Fu M, Wang C, Li Z, et al. 145 (12):5439-47 (2004) PMID: 15331580

57. Takahashi-Yanaga F, Sasaguri T 20 (4):581-9 (2008) PMID: 18023328

49. Hadzisejdić I, Mustać E, Jonjić N, et al. ePub Mar 2010 (2010) PMID: 20062009

50. Bane AL, Mulligan AM, Pinnaduwage D, et al. ePub Jun 2011 (2011) PMID: 21327470

51. Holm K, Staaf J, Jönsson G, et al. ePub Jun 2012 (2012) PMID: 22002566

52. Peurala E, Koivunen P, Haapasaari KM, et al. ePub Jan 2013 (2013) PMID: 23336272

53. Xu XL, Chen SZ, Chen W, et al. ePub Jun 2013 (2013) PMID: 23670132

54. Lange CA, Yee D ePub Aug 2011 (2011) PMID: 21613412

55. Musgrove EA, Sutherland RL ePub Sep 2009 (2009) PMID: 19701242

40. Flaherty KT, Lorusso PM, Demichele A, et al. 18 (2):568-76 (2012) PMID: 22090362

41. Finn RS, Crown JP, Lang I, et al. ePub Jan 2015 (2015) PMID: 25524798

42. Infante JR, Cassier PA, Gerecitano JF, et al. 22 (23):5696-5705 (2016) PMID: 27542767

43. Patnaik A, Rosen LS, Tolaney SM, et al. ePub 07 2016 (2016) PMID: 27217383

44. Leonard JP, LaCasce AS, Smith MR, et al. ePub May 2012 (2012) PMID: 22383795

45. Dickler MN, Tolaney SM, Rugo HS, et al. 23 (17):5218-5224 (2017) PMID: 28533223

138. Sdek P, Ying H, Chang DL, et al. 20 (5):699-708 (2005) PMID: 16337594

139. Brady M, Vlatkovic N, Boyd MT 25 (2):545-53 (2005) PMID: 15632057

140. Li M, Brooks CL, Kon N, et al. 13 (6):879-86 (2004) PMID: 15053880

141. Brown CJ, Lain S, Verma CS, et al. ePub Dec 2009 (2009) PMID: 19935675

142. Cordon-Cardo C, Latres E, Drobnjak M, et al. 54 (3):794-9 (1994) PMID: 8306343

143. Beroukhim R, Mermel CH, Porter D, et al. ePub Feb 2010 (2010) PMID: 20164920

144. Kato S, Goodman A, Walavalkar V, et al. 23 (15):4242-4250 (2017) PMID: 28351930

146. Rizvi H, Sanchez-Vega F, La K, et al. ePub Mar 2018 (2018) PMID: 29337640

136. Choschzick M, Heilenkötter U, Lebeau A, et al. ePub (null) PMID: 21896991

137. Al-Kuraya K, Schraml P, Torhorst J, et al. 64 (23):8534-40 (2004) PMID: 15574759

125. Cheok CF, Verma CS, Baselga J, et al. ePub Jan 2011 (2011) PMID: 20975744

126. Ohnstad HO, Castro R, Sun J, et al. ePub Mar 2013 (2013) PMID: 23165797

127. Gamble LD, Kees UR, Tweddle DA, et al. ePub Feb 2012 (2012) PMID: 21725357

226. Huang G, Krig S, Kowbel D, et al. 14 (21):3219-25 (2005) PMID: 16203743

243. Banck MS, Li S, Nishio H, et al. ePub Feb 2009 (2009) PMID: 19242095

244. Collins C, Rommens JM, Kowbel D, et al. 95 (15):8703-8 (1998) PMID: 9671742

245. Nonet GH, Stampfer MR, Chin K, et al. 61 (4):1250-4 (2001) PMID: 11245413

246. Li P, Maines-Bandiera S, Kuo WL, et al. 120 (9):1863-73 (2007) PMID: 17266044

228. Vendrell JA, Thollet A, Nguyen NT, et al. ePub Jul 2012 (2012) PMID: 22593193

229. Li J, Song L, Qiu Y, et al. ePub 2014 (2014) PMID: 25031722

230. Rahman MT, Nakayama K, Rahman M, et al. ePub Aug 2012 (2012) PMID: 22843878

231. Yang SH, Seo MY, Jeong HJ, et al. 11 (2 Pt 1):612-20 (2005) PMID: 15701848

232. Shida A, Fujioka S, Kurihara H, et al. ePub Sep 2014 (2014) PMID: 25202062

233. Rooney PH, Boonsong A, McFadyen MC, et al. 204 (3):282-8 (2004) PMID: 15476264

234. Szczyrba J, Nolte E, Hart M, et al. ePub Feb 2013 (2013) PMID: 22815235

235. Geppert CI, Rümmele P, Sarbia M, et al. ePub Jun 2014 (2014) PMID: 24853183

236. Toncheva D, Zaharieva B 26 (2):88-93 (null) PMID: 15897688

237. Mao XG, Yan M, Xue XY, et al. ePub Jul 2011 (2011) PMID: 21483406

238. Schipf A, Mayr D, Kirchner T, et al. 452 (3):259-68 (2008) PMID: 18193277

239. Quinlan KG, Verger A, Yaswen P, et al. 1775 (2):333-40 (2007) PMID: 17572303

240. Krig SR, Jin VX, Bieda MC, et al. 282 (13):9703-12 (2007) PMID: 17259635

241. Cowger JJ, Zhao Q, Isovic M, et al. 26 (23):3378-86 (2007) PMID: 17130829

242. Krig SR, Miller JK, Frietze S, et al. ePub Oct 2010 (2010) PMID: 20661224

225. Thollet A, Vendrell JA, Payen L, et al. ePub Nov 2010 (2010) PMID: 21059223

223. Nguyen NT, Vendrell JA, Poulard C, et al. ePub Dec 2014 (2014) PMID: 24973012

224. Frietze S, O'Geen H, Littlepage LE, et al. ePub Jun 2014 (2014) PMID: 24962896

227. Littlepage LE, Adler AS, Kouros-Mehr H, et al. ePub Jul 2012 (2012) PMID: 22728437

190. Hayward BE, Moran V, Strain L, et al. 95 (26):15475-80 (1998) PMID: 9860993

191. Gao J, Aksoy BA, Dogrusoz U, et al. ePub Apr 2013 (2013) PMID: 23550210

192. Zack TI, Schumacher SE, Carter SL, et al. ePub Oct 2013 (2013) PMID: 24071852

193. Masters SB, Miller RT, Chi MH, et al. 264 (26):15467-74 (1989) PMID: 2549064

194. Graziano MP, Gilman AG 264 (26):15475-82 (1989) PMID: 2549065

195. Jang IS, Juhnn YS 33 (1):37-45 (2001) PMID: 11322485

196. Landis CA, Masters SB, Spada A, et al. 340 (6236):692-6 (1989) PMID: 2549426

197. Tobar-Rubin R, Sultan D, Janevska D, et al. ePub Apr 2013 (2013) PMID: 23288949

198. Mariot V, Wu JY, Aydin C, et al. ePub Feb 2011 (2011) PMID: 20887824

199. Weinstein LS, Shenker A, Gejman PV, et al. 325 (24):1688-95 (1991) PMID: 1944469

200. Collins MT, Sarlis NJ, Merino MJ, et al. 88 (9):4413-7 (2003) PMID: 12970318

201. Nault JC, Fabre M, Couchy G, et al. ePub Jan 2012 (2012) PMID: 21835143

177. Furukawa T, Kuboki Y, Tanji E, et al. ePub 2011 (2011) PMID: 22355676

178. Wu J, Matthaei H, Maitra A, et al. ePub Jul 2011 (2011) PMID: 21775669

118. Moelans CB, de Weger RA, Monsuur HN, et al. ePub Jul 2010 (2010) PMID: 20473280

180. Singhi AD, Davison JM, Choudry HA, et al. ePub Aug 2014 (2014) PMID: 24925222

181. null ePub Jun 2011 (2011) PMID: 21720365

182. Kan Z, Jaiswal BS, Stinson J, et al. ePub Aug 2010 (2010) PMID: 20668451

183. Tominaga E, Tsuda H, Arao T, et al. ePub Aug 2010 (2010) PMID: 20537689

38. null ePub Jul 2012 (2012) PMID: 22810696

166. null ePub Sep 2014 (2014) PMID: 25079317

170. null ePub Jul 2014 (2014) PMID: 25079552

184. Witkiewicz AK, McMillan EA, Balaji U, et al. ePub Apr 2015 (2015) PMID: 25855536

185. Barretina J, Taylor BS, Banerji S, et al. ePub Aug 2010 (2010) PMID: 20601955

186. Lohr JG, Stojanov P, Carter SL, et al. ePub Jan 2014 (2014) PMID: 24434212

187. Chapman MA, Lawrence MS, Keats JJ, et al. ePub Mar 2011 (2011) PMID: 21430775

188. Zacharin M, Bajpai A, Chow CW, et al. ePub Jul 2011 (2011) PMID: 21357941

189. Alakus H, Mönig SP, Warnecke-Eberz U, et al. ePub Dec 2009 (2009) PMID: 20027678

175. Ang C, Stollman A, Zhu H, et al. 10 (2):548-552 (null) PMID: 28868010

176. Saunders IM, Goodman AM, Kurzrock R ePub Nov 2019 (2019) PMID: 31740567

150. Su GH, Bansal R, Murphy KM, et al. 98 (6):3254-7 (2001) PMID: 11248065

153. Vo BT, Khan SA ePub Jul 2011 (2011) PMID: 21557273

154. Lonardo E, Hermann PC, Mueller MT, et al. ePub Nov 2011 (2011) PMID: 22056140

155. Tykwinska K, Lauster R, Knaus P, et al. ePub 2013 (2013) PMID: 23950971

156. Nomura M, Tanaka K, Wang L, et al. ePub Jan 2013 (2013) PMID: 23159635

152. Schulte KM, Jonas C, Krebs R, et al. 11 (1):3-14 (2001) PMID: 11272093

151. Togashi Y, Sakamoto H, Hayashi H, et al. ePub May 2014 (2014) PMID: 24886203

157. Spitz MR, Gorlov IP, Amos CI, et al. ePub Oct 2011 (2011) PMID: 22586632

147. Inman GJ, Nicolás FJ, Callahan JF, et al. 62 (1):65-74 (2002) PMID: 12065756

148. DaCosta Byfield S, Major C, Laping NJ, et al. 65 (3):744-52 (2004) PMID: 14978253

149. Jin CH, Krishnaiah M, Sreenu D, et al. ePub May 2014 (2014) PMID: 24786585

31. Pfeifer GP, You YH, Besaratinia A 571 (1-2):19-31 (2005) PMID: 15748635

32. Hill VK, Gartner JJ, Samuels Y, et al. ePub 2013 (2013) PMID: 23875803

33. Pfeifer GP, Denissenko MF, Olivier M, et al. 21 (48):7435-51 (2002) PMID: 12379884

34. Rizvi NA, Hellmann MD, Snyder A, et al. ePub Apr 2015 (2015) PMID: 25765070

35. Cancer Genome Atlas Research Network, Kandoth C, Schultz N, et al. ePub May 2013 (2013) PMID: 23636398

36. Briggs S, Tomlinson I ePub Jun 2013 (2013) PMID: 23447401

37. Heitzer E, Tomlinson I ePub Feb 2014 (2014) PMID: 24583393

39. Roberts SA, Gordenin DA ePub 12 2014 (2014) PMID: 25568919

22. Goodman AM, Kato S, Bazhenova L, et al. ePub 11 2017 (2017) PMID: 28835386

23. Goodman AM, Sokol ES, Frampton GM, et al. ePub Oct 2019 (2019) PMID: 31405947

26. Chalmers ZR, Connelly CF, Fabrizio D, et al. ePub 04 2017 (2017) PMID: 28420421

28. Sokol ES, Feng YX, Jin DX, et al. ePub 01 2019 (2019) PMID: 30423024

29. Haricharan S, Bainbridge MN, Scheet P, et al. ePub Jul 2014 (2014) PMID: 24839032

30. Budczies J, Bockmayr M, Denkert C, et al. 1 (4):225-38 (2015) PMID: 27499907

21. Samstein RM, Lee CH, Shoushtari AN, et al. ePub 02 2019 (2019) PMID: 30643254

24. Cristescu R, Mogg R, Ayers M, et al. ePub 10 2018 (2018) PMID: 30309915

213. Xu H, Tomaszewski JM, McKay MJ ePub 03 2011 (2011) PMID: 21326324

214. Hill VK, Kim JS, Waldman T 1866 (1):1-11 (2016) PMID: 27207471

215. Solomon DA, Kim JS, Waldman T ePub Jun 2014 (2014) PMID: 24856830

216. Bauerschmidt C, Arrichiello C, Burdak-Rothkamm S, et al. ePub Jan 2010 (2010) PMID: 19906707

217. Yun J, Song SH, Kang JY, et al. ePub Jan 2016 (2016) PMID: 26420833

218. Gelot C, Guirouilh-Barbat J, Lopez BS ePub Jul 2016 (2016) PMID: 27326661

203. Yan M, Xu H, Waddell N, et al. ePub Apr 2012 (2012) PMID: 22537934

219. Sofueva S, Yaffe E, Chan WC, et al. ePub Dec 2013 (2013) PMID: 24185899

220. Deng Z, Wang Z, Stong N, et al. ePub Nov 2012 (2012) PMID: 23010778

221. Yun J, Song SH, Kim HP, et al. ePub 09 2016 (2016) PMID: 27466323

204. Xu H, Yan M, Patra J, et al. ePub Jan 2011 (2011) PMID: 21255398

222. Mahmood SF, Gruel N, Chapeaublanc E, et al. ePub Mar 2014 (2014) PMID: 24148822

207. Supernat A, Lapińska-Szumczyk S, Sawicki S, et al. 4 (4):727-732 (2012) PMID: 23205091

202. Zehir A, Benayed R, Shah RH, et al. ePub Jun 2017 (2017) PMID: 28481359

205. Stevens KN, Wang X, Fredericksen Z, et al. ePub Sep 2011 (2011) PMID: 21607584

206. Sehl ME, Langer LR, Papp JC, et al. 15 (6):2192-203 (2009) PMID: 19276285

208. Deb S, Xu H, Tuynman J, et al. ePub Mar 2014 (2014) PMID: 24548858

209. Supernat A, Lapińska-Szumczyk S, Majewska H, et al. 7 (5):613-9 (2014) PMID: 25048628

210. Porkka KP, Tammela TL, Vessella RL, et al. 39 (1):1-10 (2004) PMID: 14603436

211. Davis SJ, Sheppard KE, Anglesio MS, et al. ePub Jun 2015 (2015) PMID: 25852062

212. Atienza JM, Roth RB, Rosette C, et al. 4 (3):361-8 (2005) PMID: 15767545

171. Tong Q, Dalgin G, Xu H, et al. 290 (5489):134-8 (2000) PMID: 11021798

172. Fields PE, Kim ST, Flavell RA 169 (2):647-50 (2002) PMID: 12097365

173. Van Esch H, Groenen P, Nesbit MA, et al. 406 (6794):419-22 (2000) PMID: 10935639

174. Tkocz D, Crawford NT, Buckley NE, et al. ePub Aug 2012 (2012) PMID: 22120723

158. Banerji S, Cibulskis K, Rangel-Escareno C, et al. ePub Jun 2012 (2012) PMID: 22722202

159. Stephens PJ, Tarpey PS, Davies H, et al. ePub May 2012 (2012) PMID: 22722201

160. Ciriello G, Gatza ML, Beck AH, et al. ePub Oct 2015 (2015) PMID: 26451490

161. Krauthammer M, Kong Y, Ha BH, et al. ePub Sep 2012 (2012) PMID: 22842228

162. Hodis E, Watson IR, Kryukov GV, et al. ePub Jul 2012 (2012) PMID: 22817889

163. Berger MF, Hodis E, Heffernan TP, et al. ePub May 2012 (2012) PMID: 22622578

164. Wang K, Kan J, Yuen ST, et al. ePub Oct 2011 (2011) PMID: 22037554

165. Kakiuchi M, Nishizawa T, Ueda H, et al. ePub Jun 2014 (2014) PMID: 24816255

167. Wang K, Yuen ST, Xu J, et al. ePub Jun 2014 (2014) PMID: 24816253

168. Jones S, Stransky N, McCord CL, et al. ePub Sep 2014 (2014) PMID: 25233892

169. Imielinski M, Berger AH, Hammerman PS, et al. ePub Sep 2012 (2012) PMID: 22980975

292. Hortobagyi GN, Stemmer SM, Burris HA, et al. ePub Jul 2018 (2018) PMID: 29718092

293. Tripathy D, Im SA, Colleoni M, et al. ePub Jul 2018 (2018) PMID: 29804902

294. Im SA, Lu YS, Bardia A, et al. ePub 07 2019 (2019) PMID: 31166679

295. Slamon DJ, Neven P, Chia S, et al. ePub Aug 2018 (2018) PMID: 29860922

277. Dickson MA, Schwartz GK, Keohan ML, et al. ePub Jul 2016 (2016) PMID: 27124835

278. Dickson MA, Tap WD, Keohan ML, et al. ePub Jun 2013 (2013) PMID: 23569312

281. Cristofanilli M, Turner NC, Bondarenko I, et al. ePub Apr 2016 (2016) PMID: 26947331

282. Turner NC, Ro J, André F, et al. ePub Jul 2015 (2015) PMID: 26030518

283. Turner NC, Slamon DJ, Ro J, et al. ePub 11 2018 (2018) PMID: 30345905

285. DeMichele A, Clark AS, Tan KS, et al. 21 (5):995-1001 (2015) PMID: 25501126

288. Finn RS, Dering J, Conklin D, et al. ePub 2009 (2009) PMID: 19874578

290. Ma CX, Gao F, Luo J, et al. 23 (15):4055-4065 (2017) PMID: 28270497

291. Gianni L, Bisagni G, Colleoni M, et al. ePub Feb 2018 (2018) PMID: 29326029

263. Beck JT, Hortobagyi GN, Campone M, et al. ePub Feb 2014 (2014) PMID: 24362951

264. Yardley DA, Noguchi S, Pritchard KI, et al. ePub Oct 2013 (2013) PMID: 24158787

265. Baselga J, Campone M, Piccart M, et al. ePub Feb 2012 (2012) PMID: 22149876

266. Piccart M, Hortobagyi GN, Campone M, et al. ePub Dec 2014 (2014) PMID: 25231953

267. Jerusalem G, de Boer RH, Hurvitz S, et al. ePub Jun 2018 (2018) PMID: 29862411

268. Baselga J, Semiglazov V, van Dam P, et al. ePub Jun 2009 (2009) PMID: 19380449

269. Bachelot T, Bourgier C, Cropet C, et al. ePub Aug 2012 (2012) PMID: 22565002

270. Wheler JJ, Moulder SL, Naing A, et al. ePub May 2014 (2014) PMID: 24912489

271. Hurvitz SA, Andre F, Jiang Z, et al. ePub Jul 2015 (2015) PMID: 26092818

272. André F, O'Regan R, Ozguroglu M, et al. ePub May 2014 (2014) PMID: 24742739

274. Singh J, Novik Y, Stein S, et al. ePub Mar 2014 (2014) PMID: 24684785

275. Tolcher AW, Bendell JC, Papadopoulos KP, et al. ePub Jan 2015 (2015) PMID: 25344362

255. Gallant JN, Sewell A, Almodovar K, et al. 3 :5 (2019) PMID: 30793038

256. Juric D, Janku F, Rodón J, et al. ePub Dec 2018 (2018) PMID: 30543347

257. Hoste G, Slembrouck L, Jongen L, et al. ePub Nov 2018 (2018) PMID: 30187361

258. Juric D, Castel P, Griffith M, et al. ePub Feb 2015 (2015) PMID: 25409150

260. Mayer IA, Prat A, Egle D, et al. 25 (10):2975-2987 (2019) PMID: 30723140

262. Jain S, Shah AN, Santa-Maria CA, et al. ePub Sep 2018 (2018) PMID: 29850984

249. Goetz MP, Toi M, Campone M, et al. ePub Nov 2017 (2017) PMID: 28968163

250. Sledge GW, Toi M, Neven P, et al. ePub Sep 2017 (2017) PMID: 28580882

300. Janku F, Wheler JJ, Westin SN, et al. ePub Mar 2012 (2012) PMID: 22271473

301. Moroney JW, Schlumbrecht MP, Helgason T, et al. 17 (21):6840-6 (2011) PMID: 21890452

302. Moroney J, Fu S, Moulder S, et al. 18 (20):5796-805 (2012) PMID: 22927482

303. Fleming GF, Ma CX, Huo D, et al. ePub Nov 2012 (2012) PMID: 22245973

304. Wolff AC, Lazar AA, Bondarenko I, et al. ePub Jan 2013 (2013) PMID: 23233719

46. Clark et al., 2019; AACR Abstract LB-010/2

47. Peguero et al., 2016; ASCO Abstract 2528

145. Singavi et al., 2017; ESMO Abstract 1140PD

128. Zhang et al., 2019; ASCO Abstract 3124

129. Rasco et al., 2019; ASCO Abstract 3126

130. Martinelli et al., 2016; EHA21 Abstract S504

131. Daver et al., 2018; ASH Abstract 767

132. Mascarenhas et al., 2019; ASH Abstract 134

133. Shustov et al., 2018; ASH Abstract 1623

134. Sallman et al., 2018; ASH Abstract 4066

135. Meric-Bernstam et al., 2017; ASCO Abstract 2505

68. Baselga et al., 2015; SABCS Abstract S6-01

75. Baselga et al., 2018; ASCO Abstract LBA1006

78. Banerji et al., 2015; ASCO Abstract 2500

5. Ayers et al., 2016; ASCO-SITC Abstract P60

25. Legrand et al., 2018; ASCO Abstract 12000

273. Turner et al., 2016; ASCO Abstract 512

279. Loibl et al., 2016; ASCO Abstract 524

280. Turner et al., 2018; AACR abstract CT039

284. Finn et al., 2017; SABCS Abstract P2-09-10

286. Gucalp et al., 2017; SABCS Abstract P3-11-04

287. Clark et al., 2016; SABCS Abstract P4-22-14

289. Gianni et al., 2016; SABCS Abstract P4-21-39

276. Patterson et al., 2018; AACR Abstract 3891

259. Juric et al., 2016; SABCS Abstract P3-14-01

261. Sharma et al., 2018; ASCO Abstract 1018

247. Morschhauser et al., 2014; ASH Abstract 3067

248. Goetz et al., 2018; AACR Abstract CT040

251. Tolaney et al., 2019; AACR Abstract 4458

252. Anders et al., 2019; ASCO Abstract 1017

253. Hurvitz et al., 2017; SABCS Abstract PD5-01

254. Wander et al., 2019; ASCO Abstract 1057

296. Slamon et al., 2019; ESMO Abstract LBA7

297. Infante et al., 2016; 27542767; Juric et al

179. Nishikawa G, Sekine S, Ogawa R, et al. ePub Mar 2013 (2013) PMID: 23403822