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

Companion Diagnostic (CDx) Associated Findings

GENOMIC FINDINGS DETECTED	FDA-APPROVED THERAPEUTIC OPTIONS
PIK3CA E542K	Piqray® (Alpelisib)

For Microsatellite Instability (MSI) results, confirmatory testing using a validated orthogonal method should be performed.

OTHER ALTERATIONS & BIOMARKERS IDENTIFIED

Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapeutic product. See *professional services* section for additional information.

Microsatellite status MS-Stable §
Tumor Mutational Burden 5 Muts/Mb §
CDK4 amplification §
ESR1 Y537S
FGFR2 amplification §
PTEN T319fs*1
TP53 splice site 559+1G>A

§ Refer to appendix for limitation statements related to detection of any copy number alterations, gene rearrangements, BRCA1/2 alterations, LOH, MSI, or TMB results in this section.

Please refer to appendix for Explanation of Clinical Significance Classification and for variants of unknown significance (VUS).

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) and tumor mutational burden (TMB) 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 the targeted therapies listed in Table 1 in accordance with the 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. Genomic findings other than those listed in Table 1 are not prescriptive or conclusive for labeled use of any specific therapeutic product.

The test is also used for detection of genomic loss of heterozygosity (LOH) from FFPE ovarian tumor tissue. Positive homologous recombination deficiency (HRD) status (F1CDx HRD defined as tBRCA-positive and/or LOH high) in ovarian cancer patients is associated with improved progression-free survival (PFS) from Rubraca (rucaparib) maintenance therapy in accordance with the RUBRACA product label.

The F1CDx assay will be performed at Foundation Medicine, Inc. sites located in Cambridge, MA and Morrisville, NC.

TABLE 1: COMPANION DIAGNOSTIC INDICATIONS

INDICATION	BIOMARKER	THERAPY
Non-small cell lung cancer (NSCLC)	*EGFR* exon 19 deletions and *EGFR* exon 21 L858R alterations	Gilotrif® (Afatinib), Iressa® (Gefitinib), Tagrisso® (Osimertinib), or Tarceva® (Erlotinib)
	EGFR exon 20 T790M alterations	Tagrisso® (Osimertinib)
	ALK rearrangements	Alecensa® (Alectinib), Xalkori® (Crizotinib), or Zykadia® (Ceritinib)
	BRAF V600E	Tafinlar® (Dabrafenib) in combination with Mekinist® (Trametinib)
Melanoma	*BRAF* V600E	Tafinlar® (Dabrafenib) or Zelboraf® (Vemurafenib)
	BRAF V600E and V600K	Mekinist® (Trametinib) or Cotellic® (Cobimetinib) in combination with Zelboraf® (Vemurafenib)
Breast cancer	*ERBB2* (HER2) amplification	Herceptin® (Trastuzumab), Kadcyla® (Ado-trastuzumab emtansine), or Perjeta® (Pertuzumab)
	PIK3CA C420R, E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y alterations	Piqray® (Alpelisib)
Colorectal cancer	*KRAS* wild-type (absence of mutations in codons 12 and 13)	Erbitux® (Cetuximab)
	KRAS wild-type (absence of mutations in exons 2, 3, and 4) and *NRAS* wild type (absence of mutations in exons 2, 3, and 4)	Vectibix® (Panitumumab)
Ovarian cancer	*BRCA1/2* alterations	Lynparza® (Olaparib) or Rubraca® (Rucaparib)

ABOUT THE TEST FoundationOne®CDx is the first FDA-approved broad companion diagnostic for solid tumors.

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Note: The intended use (IU) statement and claims made on this sample report may not be up to date. For the latest version of the FoundationOne CDx claims and IU, please see the current label: www.foundationmedicine.com/f1cdx

ABOUT THE TEST FoundationOne®CDx is the first and only FDA-Approved comprehensive companion diagnostic for all solid tumors.

Interpretive content on this page and subsequent pages is provided as a professional service, and is not reviewed or approved by the FDA.

PATIENT

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Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 5 Muts/Mb

Genomic Findings

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

CDK4 amplification
ESR1 Y537S
PIK3CA E542K
PTEN T319fs*1
FGFR2 amplification
TP53 splice site 559+1G>A

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

8 Therapies with Clinical Benefit
3 Therapies with Lack of Response
35 Clinical Trials

BIOMARKER FINDINGS	ACTIONABILITY
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section
Tumor Mutational Burden - 5 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)
CDK4 - amplification	Palbociclib	1	none
10 Trials *see p. 17*	Ribociclib	1	
ESR1 - Y537S	Fulvestrant	1	none
	⚠ Anastrozole[1]		
	⚠ Exemestane[1]		
10 Trials *see p. 19*	⚠ Letrozole[1]		
PIK3CA - E542K	Alpelisib	1	Temsirolimus
10 Trials *see p. 23*	Everolimus	2A	
PTEN - T319fs*1	Everolimus	2A	Temsirolimus
10 Trials *see p. 25*			
FGFR2 - amplification	none		Erdafitinib
9 Trials *see p. 21*			Pazopanib

⚠ *1. Patient may be resistant to indicated therapy*

☐ *NCCN category*

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

For more information regarding biological and clinical significance, including prognostic, diagnostic, germline, and potential chemosensitivity implications, see the Genomic Findings section.

TP53 - splice site 559+1G>A ..... p. 8

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

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.

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BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

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

FREQUENCY & PROGNOSIS

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
5 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 measured in tissue (> 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].

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GENE
CDK4

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES
CDK4 amplification or activation may predict sensitivity to CDK4/6 inhibitors such as abemaciclib, palbociclib, and ribociclib[40-43]. Clinical benefit has been reported for patients with CDK4-amplified solid tumors in response to treatment with palbociclib[40,44] and ribociclib[45]. On the basis of a Phase 1b study, PTEN loss of expression may be associated with resistance to combination therapy with CDK4/6 inhibitors such as ribociclib and aromatase inhibitors such as letrozole[46].

FREQUENCY & PROGNOSIS
Putative high-level amplification of CDK4 occurs in 2% of breast invasive carcinoma cases[27]. CDK4 protein expression has been detected in 70% of breast carcinomas in one study and did not correlate with patient survival[47].

FINDING SUMMARY
CDK4 encodes the cyclin-dependent kinase 4, which regulates the cell cycle, senescence, and apoptosis[48]. CDK4 and its functional homolog CDK6 are activated by D-type cyclins and promote cell cycle progression by inactivating the tumor suppressor Rb[49-50]. Amplification of the chromosomal region that includes CDK4 has been reported in multiple cancer types, including lung cancer, glioblastoma, and liposarcoma, and has been associated with overexpression of CDK4 protein[40,51-57].

GENE
ESR1

ALTERATION
Y537S

TRANSCRIPT NUMBER
NM_000125

CODING SEQUENCE EFFECT
1610A>C

POTENTIAL TREATMENT STRATEGIES
Therapies that directly target ER-alpha, such as selective ER modulators (SERMs) and the selective ER degrader (SERD) fulvestrant, as well as aromatase inhibitors (AIs) that inhibit estrogen production, are approved to treat ER-positive (ER+) and/or hormone receptor-positive (HR+) breast cancer (NCCN Guidelines v1.2019). AI treatment has also been reported to provide clinical benefit in a subset of HR+ gynecologic malignancies[58-62]. Clinical data suggest that ESR1 mutations may confer sensitivity to the first-generation SERD fulvestrant in breast cancer[63-64]. A retrospective analysis of ESR1 mutations in gynecologic malignancies reported clinical benefit for patients with ESR1 mutations and fulvestrant treatment as a monotherapy or in combination, including 1 patient with peritoneal serous carcinoma and an ESR1 Y537N mutation who experienced prolonged clinical benefit (48+ months) from fulvestrant monotherapy[65]. The therapeutic utility of SERMs, including toremifene[66], raloxifene[67], and tamoxifen[68], for ESR1 mutation-positive breast cancer is unclear. Although ESR1 mutations have been reported in patients who progressed on tamoxifen[66,69-70], a retrospective analysis of primary breast tumors reported that patients with non-emergent ESR1 mutations experienced improved (Y537N) or similar (Y537S or D538G) median progression-free survival (PFS) relative to those lacking ESR1 mutation[68]. Preclinical studies suggest that certain ESR1 mutations (Y537S and D538G) may be less sensitive to clinical concentrations of antiestrogens, and higher doses or more potent antiestrogens may be required to inhibit tumors with these mutations[68,71-73]. Clinical data suggest that ESR1 mutations may confer sensitivity to the first-generation SERD fulvestrant[63-64]. In a study of patients with breast cancer treated with fulvestrant as monotherapy or in combination with palbociclib, ESR1 Y537S was the most commonly acquired mutation, suggesting that Y537S may decrease fulvestrant sensitivity[74]. Next-generation SERDs, including AZD9496, elacestrant, GDC-0927, and LSZ102, are in clinical development. A Phase 1 study of elacestrant for the treatment of patients with ER+, HER2– breast cancer reported 1 PR, 1 CR, and a median treatment duration of 18 weeks; 9/16 had at least one ESR1 mutation, and 6/16 were previously treated with fulvestrant[75]. In another Phase 1 study, elacestrant achieved a median PFS of 4.5 months and 5 PRs for heavily pretreated patients with ER+, HER2– breast cancer, 4 of whom harbored ESR1 mutations[76]. A Phase 1 study of GDC-0927 for the treatment of ER+, HER2– metastatic breast cancer reported an unconfirmed ORR of 13% (3/24), 2 of which harbored an ESR1 mutation; a patient with ESR1 D538G had SD on study for over 490 days[77]. Preliminary data from a Phase 1 study of LSZ102 for the treatment of HR+ breast cancer observed SD for 31% (14/45) of cases[78].

FREQUENCY & PROGNOSIS
The most frequent ESR1 mutations include D538G, Y537S, Y537N, and E380Q, with concurrent ESR1 mutations detected in up to 40% of ER+ breast cancer samples harboring an ESR1 alteration[64,71,79-80]. In the TCGA breast invasive carcinoma datasets, ESR1 amplification was observed in 2 to 3% of cases and ESR1 mutation was observed in fewer than 1% of cases[27,81]. Rarely identified in patients with localized disease, ESR1 mutations are more frequently detected in metastatic breast cancers (11–54%)[70,79,82-83], predominantly during progression on hormonal therapy[63,69,79,82,84-87]. ESR1 mutation is associated with shorter median PFS and OS in patients with advanced breast cancer[63,87]. The prevalence, significance, and correlation with protein expression of ESR1 amplification in breast cancer remains controversial[88-96].

FINDING SUMMARY
ESR1 encodes estrogen receptor alpha (ER-alpha), one of the major estrogen receptor isoforms in humans. Along with co-activator proteins, the ER complex promotes transcription of genes involved in cell cycle progression and survival[97]. Alterations that occur within the ligand binding domain of ER-alpha, as seen here, result in ligand-independent activation[82,84-85,98-104]. Emerging clinical[63-64,66,69,82,87,105] and preclinical[64,71,84-85] evidence suggests that these alterations confer resistance to aromatase inhibitors including anastrozole, letrozole, and exemestane.

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GENE
PIK3CA

ALTERATION
E542K

TRANSCRIPT NUMBER
NM_006218

CODING SEQUENCE EFFECT
1624G>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[106-107]. 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[108-113]. 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)[114]. 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[115]. 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[116]. The pan-PI3K inhibitor buparlisib has shown limited activity as monotherapy against PIK3CA-mutated tumors[117-120]. PI3K-alpha-selective inhibitors such as alpelisib or PI3K-beta-sparing inhibitors such as taselisib may have bigger therapeutic windows than pan-PI3K inhibitors[107]. 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])[121]. 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[106]. 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[122]. 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[123]; 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)[124]. 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[125]. Responses to capivasertib were also reported in 20% (3/15) of patients with PIK3CA-mutated breast cancer in an earlier study[126]. 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)[127]. 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[128-132]. In the context of concurrent PIK3CA mutation, PTEN loss or mutation may predict resistance to PI3K-alpha-specific inhibitors[107,133-134].

FREQUENCY & PROGNOSIS

Mutations in PIK3CA have been reported in 25-40% of breast cancer cases[27,135-138]. 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[124]. 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)[139].

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[140-141]. PIK3CA alterations that have been characterized as activating, such as observed here, are predicted to be oncogenic[142-160].

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GENE
PTEN

ALTERATION
T319fs*1

TRANSCRIPT NUMBER
NM_000314

CODING SEQUENCE EFFECT
955_958delACTT

POTENTIAL TREATMENT STRATEGIES

PTEN loss or mutation leads to activation of the PI3K-AKT-mTOR pathway and may predict sensitivity to inhibitors of this pathway[161-165] such as the mTOR inhibitors temsirolimus and everolimus or the PI3K inhibitor copanlisib. Preclinical studies suggest that PTEN-deficient cancers, in the absence of other oncogenic mutations, depend primarily on the beta isoform of PI3K (PI3K-beta)[166-168], and PI3K-beta-selective inhibitors are in clinical trials for PTEN-deficient tumors. However, the NCI-MATCH Phase 2 study observed limited activity of the PI3K-betaselective inhibitor GSK2636771 as monotherapy in PTEN-deficient cancers, with a median PFS of 1.8 months. The best outcomes were 1 PR (1/22, prostate cancer), SD (7/22) for patients with PTEN deletion/mutation, and SD (9/34) for patients with PTEN protein loss[169]. Clinical data in breast[170-171] and prostate cancer[172-173] suggest that PTEN alterations may predict sensitivity to pan-AKT inhibitors such as ipatasertib or capivasertib. Phase 2 studies have reported improved PFS from the addition of either ipatasertib (9.0 vs. 4.9 months, HR=0.44) or capivasertib (9.3 vs. 3.7 months, HR=0.30) to paclitaxel, compared with paclitaxel and placebo, for patients with metastatic triple-negative breast cancer harboring PIK3CA/AKT1/PTEN alterations[125]. Emerging clinical and preclinical data suggest that PTEN alterations may predict sensitivity to PARP inhibitors. Four patients with tumors harboring PTEN mutation or loss but no detected BRCA1/2 alterations experienced clinical benefit from PARP inhibition by olaparib or niraparib[174-175]. However, although multiple preclinical studies have demonstrated sensitivity of PTEN-mutant cell lines to various PARP inhibitors[174,176-179], other studies have observed a lack of association between PTEN mutation and PARP inhibitor sensitivity[179-180]; PTEN association with sensitivity to PARP inhibitors may depend on the cell type or context. Emerging clinical and preclinical data suggest that PTEN alterations may predict a lack of response to anti-PD-1 therapy. In a retrospective analysis of 66 patients with glioblastoma (GBM), tumors from nivolumab or pembrolizumab non-responders were significantly enriched for PTEN mutations[181]. In a patient with uterine leiomyosarcoma treated with pembrolizumab monotherapy, a treatment-resistant tumor arose that harbored PTEN loss[182]. A patient with NSCLC whose tumor harbored PTEN alteration exhibited a lack of response to nivolumab and pembrolizumab[183]. In an analysis of 39 patients with metastatic melanoma treated with pembrolizumab or nivolumab, patients with PTEN-expressing tumors achieved significantly greater reduction of tumor size than those with reduction or loss of PTEN expression[184]. In the context of concurrent PIK3CA mutation, PTEN loss or mutation may predict resistance to PI3K-alpha-specific inhibitors[107,133-134]. On the basis of a Phase 1b study, PTEN loss of expression may be associated with resistance to combination therapy with CDK4/6 inhibitors such as ribociclib and aromatase inhibitors such as letrozole[46].

FREQUENCY & PROGNOSIS

In the TCGA dataset, PTEN mutation has been reported in 4% of breast invasive carcinomas, while putative homozygous deletion of PTEN has been reported in 2% of cases[27]. PTEN mutation has also been observed in 5.3% (1/19) of metaplastic breast cancers[185] and 2% of invasive lobular carcinoma tumors analyzed[186]. PTEN mutations are associated more frequently with triple-negative breast cancer than with HER2- or hormone-positive breast cancer[187-188]. Loss or reduction of PTEN expression has been observed in 28% of invasive ductal breast carcinomas and has been correlated with metastasis and poor patient prognosis, including decreased 2-year disease-free survival[189-191].

FINDING SUMMARY

PTEN encodes an inositol phosphatase that functions as a tumor suppressor by negatively regulating the PI3K-AKT-mTOR pathway; loss of PTEN can lead to uncontrolled cell growth and suppression of apoptosis[163]. PTEN alterations that disrupt the N-terminal PIP2 binding motif[192], the phosphatase domain (amino acids 14-185)[193-222], the C2 domain (amino acids 190-350)[193,195,205,223-229], the C-terminal region[230-231], and/or PTEN localization[232], such as observed here, are predicted to cause a loss of function. One or more of the PTEN variants observed here has been described in the ClinVar database as a pathogenic germline mutation (by an expert panel or multiple submitters with no conflicts) associated with hamartoma tumor syndrome (ClinVar, Nov 2019)[233]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. PTEN mutations underlie several inherited disorders, collectively termed PTEN hamartoma tumor syndrome (PHTS), which include Cowden syndrome (CS) and its variant Lhermitte-Duclos disease (LD), Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS), and Proteus-like syndrome[234-235]. The mutation rate for PTEN in these disorders ranges from 20 to 85% of patients[234,236]. The estimated incidence of Cowden syndrome is 1/200,000, which may be an underestimate due to the high variability of this disorder[234]. Given the association between PTEN and these inherited syndromes, in the appropriate clinical context, germline testing for mutations affecting PTEN is recommended.

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GENE
FGFR2

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

FGFR2 activating mutations, amplification, or fusions may confer sensitivity to FGFR-targeting kinase inhibitors such as erdafitinib[237], pazopanib[238-239], ponatinib[240], AZD4547[241-243], derazantinib[242-243], Debio-1347[244], infigratinib[245], TAS-120[246], pemigatinib[247], and E7090[248]. In the context of FGFR2 amplification, clinical benefit has been reported for patients with breast cancer treated with erdafitinib[249] and infigratinib[245]. In a Phase 2 study of the FGFR inhibitor AZD4547, responses were reported in 33% (3/9) of patients with FGFR2-amplified gastroesophageal cancer; in this study, higher-level amplification correlated with higher likelihood of response to FGFR inhibitors[241]. However, a randomized Phase 2 study of AZD4547 compared with paclitaxel for the treatment of patients with advanced stomach adenocarcinoma harboring FGFR2 amplification or polysomy reported no significant increase in median PFS, median OS, or ORR[242].

FREQUENCY & PROGNOSIS

FGFR2 amplification has been reported in breast cancer at frequencies ranging from 1-12%[250-253]. In the Breast Invasive Carcinoma TCGA dataset, FGFR2 amplification and mutation have been reported in 1.8% and 0.6% of cases, respectively[27]. FGFR2 protein expression has been reported in 13% of triple-negative breast cancer cases[253] and in ~60% of invasive ductal carcinomas[254]. In a study of 125 patients with invasive ductal carcinoma, high-level FGFR2 protein expression was associated with decreased overall and disease-free survival[254] and a meta-analysis of over 11,000 patients with breast cancer showed a significant association between FGFR2/3 expression and reduced overall survival[255]. In contrast, a study of triple-negative breast cancer showed no correlation between FGFR2 amplification or overexpression with survival[253].

FINDING SUMMARY

FGFR2 encodes a tyrosine kinase cell surface receptor, which plays an important role in cell differentiation, growth, and angiogenesis[256-257]. FGFR2 amplification has been reported in a variety of cancer types[258] and has been shown to correlate with increased mRNA and protein expression[241,259]. Higher level, clonal FGFR2 amplification has been reported to correlate with higher response rates to FGFR inhibitors[241,260].

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GENE
TP53

ALTERATION
splice site 559+1G>A

TRANSCRIPT NUMBER
NM_000546

CODING SEQUENCE EFFECT
559+1G>A

POTENTIAL TREATMENT STRATEGIES

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[261-264], or p53 gene therapy and immunotherapeutics such as SGT-53[265-269] and ALT-801[270]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% (17/176) and SDs in 53.4% (94/176) of patients with solid tumors; the response rate was 21.1% (4/19) in patients with TP53 mutations versus 12.1% (4/33) in patients who were TP53 wild-type[271]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 31.9% (30/94, 3 CR) ORR and a 73.4% (69/94) DCR in patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[272]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 42.9% (9/21, 1 CR) ORR and a 76.2% (16/21) DCR in patients with platinum-refractory TP53-mutated ovarian cancer[273]. The combination of adavosertib with paclitaxel and carboplatin in patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[274]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24.0% (6/25) ORR with adavosertib combined with paclitaxel[275]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71.4% (5/7) response rate for patients with TP53 alterations[276]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel in patients with solid tumors, 75.0% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[269]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutated, but not TP53-wild-type, breast cancer xenotransplant mouse model[277]. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies[278-279]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[280-281]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

TP53 is one of the most commonly mutated genes in breast cancer; mutations in this gene have been identified in 27-37% of breast carcinoma samples[27,282-286]. TP53 mutations that are located within the region encoding the DNA binding domain are associated with poor prognosis in patients with breast cancer[284,287-288]. TP53 mutation is also implicated in breast cancer susceptibility, as TP53 mutation carriers have an 18-60 fold increased risk for early onset breast cancer[289-291].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[292]. Any alteration that results in the disruption or partial or complete loss of the region encoding the TP53 DNA-binding domain (DBD, aa 100-292) or the tetramerization domain (aa 325-356), such as observed here, is thought to dysregulate the transactivation of p53-dependent genes and is predicted to promote tumorigenesis[293-295]. One or more of the TP53 variants observed here has been described in the ClinVar database as a pathogenic germline mutation (by an expert panel or multiple submitters with no conflicts) associated with Li-Fraumeni syndrome (ClinVar, Nov 2019)[233]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[296-298], including sarcomas[299-300]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[301] to 1:20,000[300]. For pathogenic TP53 mutations identified during tumor sequencing, the rate of germline mutations was 1% in the overall population and 6% in tumors arising before age 30[302]. In the appropriate clinical context, germline testing of TP53 is recommended.

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Alpelisib

Assay findings association

PIK3CA
E542K

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[106]. Objective responses have also been achieved by patients with several other solid tumor types harboring PIK3CA mutation[121,303] . Preclinical and limited clinical evidence suggest that PTEN inactivation may predict resistance to PI3K-alpha-selective inhibitors[107,133-134] . Acquired PTEN loss or mutation has been identified in patients with breast cancer upon progression on alpelisib[133-134] . Although some patients with PTEN inactivation, with or without concurrent PIK3CA mutation, have not experienced clinical benefit from alpelisib-containing regimens, others have achieved objective response or tumor shrinkage[121-122,304-306] . Preclinical studies suggest combination therapies may be more effective[307-308] .

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[106]. 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)[106]. 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[304]. 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[133-134,159] . 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[309]. 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[310]. 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)[306]. 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[305].

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Everolimus

Assay findings association

PIK3CA
E542K

PTEN
T319fs*1

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[108-109,112] and preclinical[113] evidence in multiple tumor types, PIK3CA activation may predict sensitivity to mTOR inhibitors such as everolimus. PTEN inactivation may predict benefit from mTOR inhibitors, such as everolimus, based on clinical data in various tumor types. For patients with prostate cancer, PTEN loss correlated with response to single-agent everolimus[311]. Retrospective clinical data suggest that patients with advanced breast cancer and PTEN inactivation, particularly in the context of HER2-positive disease, may benefit from everolimus combined with targeted therapy and/or chemotherapy[109,312-313] .

SUPPORTING DATA

In an exploratory cohort of the BOLERO-2 Phase 3 study, the addition of everolimus to exemestane in the first line for hormone receptor-positive (HR+), HER2-negative (HER2-) breast cancer improve the median PFS compared to exemestane alone (11.5 vs. 4.1 months, HR = 0.39)[314]. 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)[315-317] , and modestly improved the median PFS compared with everolimus alone in BOLERO-6 (8.4 vs. 6.8 months, HR = 0.74)[318]. Patients with HR+, HER2- breast cancer also benefited from everolimus combined with other antiestrogen therapies, including letrozole, tamoxifen, and anastrozole[312,319-320] . For patients with HR+, HER- breast cancer who progressed on antiestrogen therapies, addition of everolimus to the most recent endocrine therapy showed efficacy with 8% ORR and median PFS of 6.6 months[321]. 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)[322]. 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)[323]. Patients with metastatic triple-negative breast cancer treated with everolimus plus carboplatin achieved a clinical benefit rate of 36% (9/25)[324]. 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[325], 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[326].

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Fulvestrant

Assay findings association

ESR1
Y537S

AREAS OF THERAPEUTIC USE

Fulvestrant is an estrogen receptor antagonist and selective estrogen receptor degrader (SERD). It is FDA approved as a monotherapy to treat postmenopausal women with hormone receptor (HR)-positive metastatic breast cancer who have progressed on antiestrogen therapy and in combination with palbociclib or abemaciclib to treat patients with HR-positive, HER2-negative, advanced or metastatic breast cancer after progression on endocrine therapy.

GENE ASSOCIATION

On the basis of a prospective-retrospective clinical study[63], activating mutations in ESR1 may predict relative benefit from selective estrogen receptor degraders, such as fulvestrant[64]. Patients with ESR1 mutations experienced an increased median progression-free survival (PFS) on fulvestrant compared to exemestane and greater benefit when palbociclib was added to fulvestrant[63].

SUPPORTING DATA

In an exploratory subgroup analysis for patients with ESR1 mutations treated with fulvestrant (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)[327]. Prospective-retrospective analysis of ESR1 mutational status of 2 Phase 3 studies showed increased median PFS for patients with ESR1 mutations on fulvestrant compared with exemestane [5.7 vs. 2.6 months, HR=0.52, p=0.02] and greater benefit when palbociclib was added to fulvestrant (9.4 vs. 3.6 months)[63]. In the PALOMA Phase 3 study, fulvestrant combined with palbociclib to treat patients with HR+, HER2- breast cancer who progressed on endocrine therapy reported improved median PFS (11.2 vs. 4.6 months) and ORR (25% vs. 11%) compared to placebo with fulvestrant[327-329] ; the combination treatment significantly improved OS relative to the comparator for patients with prior sensitivity to endocrine therapy (39.7 vs. 29.7 months, HR=0.72). A global Phase 3 MONARCH2 study of fulvestrant with the addition of abemaciclib for women with HR+, HER2– advanced breast cancer who had progressed after endocrine therapy showed significantly improved median PFS (16.4 vs. 9.3 months; HR=0.55) and ORR (48% vs. 21%) compared with placebo plus fulvestrant[330], with similar results in the interim analysis of Phase 3 MONARCHplus study of a predominantly Chinese population[331]. A Phase 3 trial of ribociclib in combination with fulvestrant in patients with HR+, HER2- 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[332-333] . For endocrine-therapy naive patients with HR+ advanced or metastatic breast cancer, the FALCON Phase 3 study demonstrated superior median PFS (16.6 vs. 13.8 months) with single-agent fulvestrant compared with anastrozole[334]. A Phase 3 study of fulvestrant in combination with anastrozole to treat patients with HR+ advanced or metastatic breast cancer reported improved median PFS (15.0 vs 13.5 months, HR=0.80, p=0.007) and median OS (49.8 vs. 42.0 months, HR=0.82, p=0.03) relative to anastrozole alone[335-336] and a greater median OS benefit from the combination in patients that had not been previously treated with adjuvant hormonal therapy (52.2 vs. 40.3, HR=0.73) than in those that had been (48.2 vs. 43.5, HR=0.97)[336]. Phase 2 trials have reported increased median PFS and clinical benefit when fulvestrant is combined with everolimus or palbociclib, pertuzumab, and trastuzumab (in neoadjuvant setting) in patients with AI-resistant or treatment naïve breast cancer, respectively[337-338] .

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Palbociclib

Assay findings association

CDK4
amplification

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[40,44-45,339] .

SUPPORTING DATA

In the Phase 3 PALOMA-2 study for postmenopausal patients with newly diagnosed estrogen receptor-positive (ER+)/HER2-negative (HER2-) metastatic breast cancer (MBC), the addition of palbociclib to letrozole significantly improved ORR (42.1% vs. 34.7%) and median PFS (24.8 vs. 14.5 months)[340]; benefit was observed irrespective of cyclin D-CDK4/6-RB pathway gene expression[341]. The Phase 3 PALOMA-3 study reported that addition of palbociclib to fulvestrant improved ORR (24.6% vs. 10.9%), median PFS (11.2 vs. 4.6 months, HR=0.50) and median OS (34.9 vs. 28.0 months, HR=0.81) compared with fulvestrant plus placebo for patients with hormone receptor-positive (HR+)/HER2- breast cancer (BC) who had progressed on endocrine therapy[327-328] ; low tumor CCNE1 expression correlated with improved PFS from the combination therapy (14.1 vs. 7.6 months)[342]. Palbociclib plus fulvestrant compared with fulvestrant alone significantly improved OS for patients with prior sensitivity to endocrine therapy (39.7 vs. 29.7 months, HR=0.72) and patients with ESR1 mutations (35.6 vs. 24.6 months, HR=0.69), but did not significantly improve OS in the overall PALOMA-3 population (34.9 vs. 28.0 months; HR=0.81, p=0.09)[327]. A Phase 2 trial for patients with HR+/HER2- BC previously treated with tamoxifen demonstrated improved median PFS with palbociclib plus exemestane and leuprolide compared with capecitabine (20.1 vs. 14.4 months, HR=0.66)[343]. A Phase 2 study of single-agent palbociclib for Rb+ solid tumors reported a 2.0% (1/50) ORR for patients with HER2- BC, with significantly longer median PFS for patients with HR+ versus HR- disease (4.5 vs. 1.5 months)[344-345] . An additional cohort of HER2+ patients treated with palbociclib plus trastuzumab in this study achieved a 20.0% (2/10) ORR with median PFS of 6.7 months[345]. Palbociclib has also demonstrated clinical activity in combination with hormone therapy and/or HER2-targeted therapy in the neoadjuvant setting[338,346-348] , and with anti-androgen therapy in the metastatic setting[349].

Ribociclib

Assay findings association

CDK4
amplification

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 in sarcomas[40,44-45] , CDK4 amplification may predict sensitivity to CDK4/6 inhibitors such as ribociclib.

SUPPORTING DATA

In the Phase 3 MONALEESA-2 study, postmenopausal patients with hormone-receptor-positive (HR+), HER2– recurrent or metastatic breast cancer treated with first-line ribociclib combined with letrozole experienced improved median PFS (25.3 vs. 16.0 months; HR=0.57) and ORR (55% vs. 39%), versus those treated with letrozole plus placebo[350]. In the Phase 3 MONALEESA-7 trial for premenopausal or perimenopausal women with HR+, HER2– advanced breast cancer (ABC), 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)[351] and estimated 42-month OS (70.2% vs. 46.0%, HR=0.71)[352]. In the Phase 3 MONALEESA-3 study for postmenopausal patients with HR+, HER2– ABC previously treated with up to 1 line of endocrine therapy, the addition of ribociclib to fulvestrant improved median PFS (20.5 vs. 12.8 months, HR=0.59), ORR (41 vs. 29%) and 42-month estimated OS rate (57.8% vs. 45.9%, HR=0.72) compared with fulvestrant plus placebo[332,353] . Treatment with ribociclib combined with everolimus and exemestane elicited a median PFS of 5.7 months and a 24-week clinical benefit rate (CBR) of 41.0% (39/95) in a Phase 1/2 trial for HR+, HER2– ABC after failure on CDK4/6 inhibitors[354]. The same combination led to a 24-week CBR of 56.2% (9/16) and 23.5% (4/17) for postmenopausal patients with HR+, HER2– ABC who were CDK4/6 inhibitor-naive or -refractory, respectively, in a Phase 1b study[355]. Phase 1b studies for HR+, HER2- ABC have reported ORRs from ribociclib plus letrozole of 5.3% (1/19) and 45.8% (11/24) for previously treated and treatment-naive groups, respectively[356-357] , and 22.2% (6/27) from ribociclib in combination with letrozole plus alpelisib[358]. A Phase 1 study of single-agent ribociclib for advanced solid tumors reported a PR for 5.0% (1/20) of patients with HR+ BC[43].

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Anastrozole

Patient may be resistant to Anastrozole

Assay findings association

ESR1
Y537S

AREAS OF THERAPEUTIC USE

Anastrozole is a selective nonsteroidal aromatase inhibitor. It is FDA approved for the adjuvant treatment of postmenopausal women with hormone receptor-positive (HR+) early breast cancer, as first-line treatment for postmenopausal women with locally advanced or metastatic breast cancer HR+ or hormone receptor unknown, and for the treatment of postmenopausal women with advanced breast cancer following disease progression on tamoxifen.

GENE ASSOCIATION

Based on randomized-controlled trials, retrospective studies and case reports, aromatase inhibitors may provide clinical benefit for hormone receptor positive (HR+) breast and gynecologic malignancies[58-62,359-361] . Based on prospective and retrospective studies in breast carcinoma, ESR1 ligand-independent activating alterations, such as seen here, confer resistance of aromatase inhibitors (AIs), particularly for patients who have already received AI treatment[63-64,69,82,105,362-364] .

SUPPORTING DATA

A long-term follow-up of the ATAC Phase 3 clinical trial reported significant improved disease-free survival [hazard ratio (HR) = 0.91, p=0.04], time to recurrence, and time to distant recurrence in postmenopausal women with early stage breast cancer treated with anastrozole as adjuvant therapy compared to tamoxifen[360]; however, patients in the ATAC cohort had not received prior treatment with aromatase inhibitors (AI), and ESR1 mutations are infrequently acquired in the adjuvant setting[87,105,365] . In another study, patients with ESR1 mutations had a substantially shorter progression-free survival on subsequent AI-based therapy compared to patients with wild-type ESR1 (HR = 3.1)[87].

Exemestane

Patient may be resistant to Exemestane

Assay findings association

ESR1
Y537S

AREAS OF THERAPEUTIC USE

Exemestane is a steroidal irreversible aromatase inhibitor that is FDA approved as a monotherapy to treat postmenopausal women with breast cancer who have progressed on tamoxifen and in the adjuvant setting for postmenopausal women with estrogen receptor-positive (ER+) breast cancer who have previously received two or three years of adjuvant tamoxifen. Additionally, exemestane is FDA approved in combination with everolimus to treat hormone receptor-positive (HR+), HER2-negative advanced breast cancer following prior therapy with letrozole or anastrozole.

GENE ASSOCIATION

Based on randomized-controlled trials, retrospective studies and case reports, aromatase inhibitors may provide clinical benefit for hormone receptor positive (HR+) breast and gynecologic malignancies[58-62,359-361] . Based on prospective and retrospective studies in breast carcinoma, ESR1 ligand-independent activating alterations, such as seen here, confer resistance of aromatase inhibitors (AIs), particularly for patients who have already received AI treatment[63-64,69,82,105,362-364] .

SUPPORTING DATA

Retrospective mutational analyses of the Phase 3 SoFEA study demonstrated significantly reduced median progression-free survival [PFS, 2.6 vs. 8.0 months; hazard ratio (HR) = 2.12; p=0.01] and a trend toward decreased overall survival (OS; 12.8 vs. 22.8 months) for patients with hormone receptor-positive (HR+) breast cancer who harbored ESR1 mutations and were treated with exemestane, relative to those with wild-type ESR1 treated similarly[63]. Further, median PFS was significantly shorter for patients harboring ESR1 mutations treated with exemestane than for those treated with a regimen containing the selective ER degrader fulvestrant (2.4 vs. 5.7 months; HR = 0.52; p=0.02); a significant difference between the regimens was not observed among patients with wild-type ESR1 (3.0 vs. 5.4 months, HR = 1.07, p=0.77)[63]. In retrospective mutational analyses of the intent-to-treat cohort of the Phase 3 BOLERO-2 study, both the exemestane plus placebo and exemestane plus everolimus arms demonstrated significantly decreased median OS for patients with HR+ breast cancer harboring ESR1 D538G (25.99 vs. 32.1 months, p=0.03) or Y537S (19.98 vs. 32.1 months, p=0.003), relative to those lacking these mutations[105]. Among the patients with advanced breast cancer in the BOLERO-2 study who were treated with exemestane and placebo, those harboring ESR1 D538G exhibited reduced median PFS relative to those lacking either ESR1 D538G or Y537S (2.69 vs. 3.94 months, HR = 1.71, p=0.02), whereas those harboring ESR1 Y537S did not show a significant difference relative to the Y537S/D538G-negative population (4.14 vs. 3.94 months, HR = 0.95, p=0.86); however, this control population was not analyzed for other ESR1 alterations that may have been present following previous treatment with nonsteroidal aromatase inhibitors[105].

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Letrozole

⚠ Patient may be resistant to Letrozole

Assay findings association

ESR1
Y537S

AREAS OF THERAPEUTIC USE

Letrozole is a selective nonsteroidal aromatase inhibitor. It is FDA approved for the adjuvant treatment of postmenopausal women with hormone receptor-positive (HR+) early breast cancer and for the extended adjuvant treatment of postmenopausal women with early breast cancer who have received prior tamoxifen therapy. Letrozole is also FDA approved to treat postmenopausal women with advanced or metastatic breast cancer, specifically in the first- and second-line setting for treating those with HR+ or hormone unknown advanced breast cancer or in the first-line setting in combination with palbociclib for treating HR+/HER2- advanced or metastatic breast cancer.

GENE ASSOCIATION

Based on randomized-controlled trials, retrospective studies and case reports, aromatase inhibitors may provide clinical benefit for hormone receptor positive (HR+) breast and gynecologic malignancies[58-62,359-361]. Based on prospective and retrospective studies in breast carcinoma, ESR1 ligand-independent activating alterations, such as seen here, confer resistance of aromatase inhibitors (AIs), particularly for patients who have already received AI treatment[63-64,69,82,105,362-364].

SUPPORTING DATA

Follow-up analysis from the Phase 3 Breast International Group (BIG) 1-98 study reported significantly improved intention-to-treat disease-free survival (HR = 0.86), and OS (HR = 0.87) in postmenopausal women with early stage breast cancer treated with letrozole monotherapy compared to tamoxifen monotherapy; sequential treatments involving tamoxifen and letrozole did not improve outcome compared with letrozole monotherapy[359]. For postmenopausal patients with newly diagnosed metastatic estrogen receptor-positive (ER+)/HER2- breast cancer, Phase 2 and 3 studies reported significant clinical benefit from letrozole combined with palbociclib[366-368], with an improved ORR (42% vs. 35%) and median PFS (24.8 vs. 14.5 months) compared with letrozole plus placebo in the Phase 3 PALOMA-2 trial[340,366]. However, patients with ESR1 mutations had a substantially shorter PFS on subsequent AI-based therapy compared to patients with wild-type ESR1 (HR = 3.1)[87], including in the presence of palbociclib (PFS = 3.3 months vs. 9.0 months, p = 0.038)[369].

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Erdafitinib

Assay findings association

FGFR2
amplification

AREAS OF THERAPEUTIC USE

Erdafitinib is a pan-fibroblast growth factor receptor (FGFR) inhibitor. It is FDA approved for the treatment of patients with advanced or metastatic urothelial carcinoma who have FGFR2 or FGFR3 alterations and have progressed after prior chemotherapy.

GENE ASSOCIATION

On the basis of strong clinical evidence for FGFR2 fusions[237,370-371] , limited evidence for FGFR2 mutations[371-372] and limited evidence for FGFR2 amplification[249], and preclinical data[373-374] , FGFR2 activating alterations may confer sensitivity to erdafitinib.

SUPPORTING DATA

Erdafitinib has been primarily studied for the treatment of FGFR-altered urothelial carcinoma. A Phase 2 study evaluating erdafitinib for the treatment of patients with metastatic or unresectable urothelial carcinoma (mUC) previously treated with chemotherapy and harboring FGFR2/3 fusions or FGFR3 activating mutations reported an ORR of 40% (40/99, 3 CR), and a DCR of 80% (79/99)[375]. A Phase 1 trial of erdafitinib reported clinical responses in for patients with various FGFR2- or FGFR3-altered solid tumors[237,372,376-377] , including cholangiocarcinoma (27% ORR, 3/11), NSCLC (5% ORR, 1/21), breast (9% ORR, 3/34), and ovarian (9% ORR, 1/11), while other cancers including endometrial carcinoma and glioblastoma showed a low ORR (2%, 1/58)[249]. Following progression on multiple other lines of therapy, a patient with metastatic FGFR2-fusion-positive NSCLC treated with erdafitinib exhibited an 11-month PR[376].

Pazopanib

Assay findings association

FGFR2
amplification

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

FGFR2 amplification may predict sensitivity to pazopanib. In a Phase 2 study of pazopanib plus capecitabine and oxaliplatin for the treatment of patients with advanced gastric cancer, 6/7 patients with FGFR2 protein expression exhibited a PR, and PFS was significantly improved in patients with FGFR2 expression than in those without (8.5 vs. 5.6 months, p=0.050)[378].

SUPPORTING DATA

A Phase 2 clinical trial of pazopanib in breast cancer reported 55% disease stabilization[379]. A Phase 2 study of heavily pretreated post-menopausal hormone receptor positive (HR+) breast cancer treated with a combination of pazopanib and nonsteroidal aromatase inhibitor reported 7% partial responses (PRs; 2/28) and 18% stable diseases (SDs; 5/28), with 7 patients having progression-free survival (PFS) greater than 6 months[380]. Phase 2 clinical trials of pazopanib with lapatinib in patients with HER2-positive breast cancer reported that the combination was associated with higher response rate than lapatinib alone but did not bring about an increase in PFS[381-382] . A multicenter single-arm Phase 2 study evaluating pazopanib combined with paclitaxel as neoadjuvant following doxorubicin/cyclophosphamide reported complete responses in 9% (6/67) and 38% (10/26) of patients with HR+ and triple-negative locally advanced breast cancer cases, respectively; however, a high level of toxicity led to discontinuation of pazopanib in 61% of patients[383].

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Temsirolimus

Assay findings association

PIK3CA
E542K

PTEN
T319fs*1

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[110-111,384] and preclinical[113] 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%)[110] and 7/23 (30%)[384] were reported in patients with PIK3CA-mutant tumors. PTEN inactivation may predict benefit from mTOR inhibitors, such as temsirolimus, based on clinical data in various tumor types. Out of 10 patients with metaplastic breast cancer and PTEN alterations, 2 cases responded to temsirolimus or everolimus plus doxorubicin and bevacizumab[111,385] . Temsirolimus achieved SD for 6/7 patients with PTEN-deficient cervical carcinoma[386]. Clinical studies in renal cell carcinoma[387-388] , glioblastoma[389-390] , or endometrial cancer[391-394] did not observe a correlation of PTEN deficiency with response to temsirolimus, although several patients with those tumor types and PTEN loss have benefited from mTOR inhibitors.

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%)[395]. 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[396]. 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[397]. 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[398]. 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[111].

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

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CLINICAL TRIALS

NOTE Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months. While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and should be investigated by the physician or research staff. This is not a comprehensive list of all available clinical trials. Foundation Medicine displays a subset of trial options and ranks them in this order of descending priority: Qualification for pediatric trial → Geographical proximity → Later trial phase. Clinical trials listed here may have additional enrollment criteria that may require medical screening to determine final eligibility. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov. Or, visit https://www.foundationmedicine.com/genomic-testing#support-services.

GENE
CDK4

RATIONALE
CDK4 amplification may predict sensitivity to CDK4/6 inhibitors.

ALTERATION
amplification

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: Kuei Shan Hsiang (Taiwan), Virginia, New York, North Carolina, Toronto (Canada), London (Canada), Massachusetts, New Hampshire, Vermont, Michigan

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

NCT02693535

PHASE 2

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

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

LOCATIONS: Virginia, Pennsylvania, North Carolina, Michigan, Indiana, Georgia, Illinois

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

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

LOCATIONS: Virginia, Pennsylvania, New Jersey, New York, North Carolina

NCT03280563

PHASE 1/2

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

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

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

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CLINICAL TRIALS

NCT03573648

PHASE 2

Neoadjuvant Tamoxifen, Palbociclib, Avelumab in Estrogen Receptor Positive Breast Cancer

TARGETS
ER, CDK4, CDK6, PD-L1

LOCATIONS: Maryland

NCT03854903

PHASE 1

WI231696: ASPIRE Bosutinib

TARGETS
CDK4, CDK6, ABL, SRC, ER

LOCATIONS: District of Columbia

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

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: Virginia, Pennsylvania, North Carolina, Ohio, Michigan, Massachusetts, Georgia, Tennessee

NCT04031885

PHASE 4

A Study of Abemaciclib (LY2835219) in Combination With Fulvestrant Compared to Chemotherapy in Women With HR Positive, HER2 Negative Metastatic Breast Cancer

TARGETS
ER, CDK4, CDK6

LOCATIONS: Pennsylvania, New York, Connecticut, Rhode Island, Massachusetts, Michigan, Vermont, Maine, Georgia

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GENE
ESR1

ALTERATION
Y537S

RATIONALE
Tumors with ESR1 activating mutations may be sensitive to selective estrogen receptor degraders (SERDs). Clinical evidence suggests that ESR1 ligand-independent activating alterations reduce the efficacy of AI-containing regimens in breast carcinoma, particularly for patients who have already received AI treatment.

NCT03778931

PHASE 3

Phase 3 Trial of Elacestrant vs. Standard of Care for the Treatment of Patients With ER+/HER2- Advanced Breast Cancer

TARGETS
Aromatase, ER

LOCATIONS: District of Columbia, Virginia, Maryland, Pennsylvania, New Jersey

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: Kuei Shan Hsiang (Taiwan), Virginia, New York, North Carolina, Toronto (Canada), London (Canada), Massachusetts, New Hampshire, Vermont, Michigan

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

NCT03584009

PHASE 2

A Phase II Study Comparing The Efficacy Of Venetoclax + Fulvestrant Vs. Fulvestrant In Women With Estrogen Receptor-Positive, Her2-Negative Locally Advanced Or Metastatic Breast Cancer Who Experienced Disease Recurrence Or Progression During Or After CDK4/6 Inhibitor Therapy

TARGETS
ER, BCL2

LOCATIONS: Maryland, Ohio, Kentucky, Toronto (Canada), Newmarket (Canada), Massachusetts, Ottawa (Canada), Sherbrooke (Canada), Georgia

NCT03280563

PHASE 1/2

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

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

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

NCT03854903

PHASE 1

WI231696: ASPIRE Bosutinib

TARGETS
CDK4, CDK6, ABL, SRC, ER

LOCATIONS: District of Columbia

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CLINICAL TRIALS

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

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: Virginia, Pennsylvania, North Carolina, Ohio, Michigan, Massachusetts, Georgia, Tennessee

NCT04031885

PHASE 4

A Study of Abemaciclib (LY2835219) in Combination With Fulvestrant Compared to Chemotherapy in Women With HR Positive, HER2 Negative Metastatic Breast Cancer

TARGETS
ER, CDK4, CDK6

LOCATIONS: Pennsylvania, New York, Connecticut, Rhode Island, Massachusetts, Michigan, Vermont, Maine, Georgia

NCT04060862

PHASE 3

A Study of Ipatasertib Plus Palbociclib and Fulvestrant Versus Placebo Plus Palbociclib and Fulvestrant in Hormone Receptor Positive and HER2 Negative Locally Advanced Unresectable or Metastatic Breast Cancer

TARGETS
AKTs, CDK4, CDK6, ER

LOCATIONS: New Jersey, Hamilton (Canada), Georgia, Calgary (Canada), Manchester (United Kingdom), London (United Kingdom), Sutton (United Kingdom), Barcelona (Spain), Porto Alegre (Brazil), Malvern (Australia)

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GENE
FGFR2

ALTERATION
amplification

RATIONALE
FGFR inhibitors may be relevant in tumors with alterations that activate FGFR2.

NCT03344536

PHASE 1/2

A Study of Debio 1347 Plus Fulvestrant in Patients With Metastatic Breast Cancer

TARGETS
FGFR1, FGFR2, FGFR3, ER

LOCATIONS: New York

NCT02393248

PHASE 1/2

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

TARGETS
PD-1, FGFR1, FGFR2, FGFR3

LOCATIONS: New Jersey, New York, North Carolina, Ohio, Georgia, Alabama, Missouri, Florida, Texas

NCT02272998

PHASE 2

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

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

LOCATIONS: Ohio

NCT03564691

PHASE 1

Study of MK-4830 as Monotherapy and in Combination With Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-4830-001)

TARGETS
ITL4, FGFRs, KIT, PDGFRA, RET, VEGFRs, PD-1

LOCATIONS: New Jersey, Toronto (Canada), Michigan, Ottawa (Canada), Texas, Madrid (Spain), Hospitalet de Llobregat (Spain), Gdansk (Poland), Warszawa (Poland), Haifa (Israel)

NCT03992131

PHASE 1/2

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

TARGETS
PARP, FGFRs, VEGFRs, TOP1

LOCATIONS: Massachusetts, Tennessee, Texas

NCT04042116

PHASE 1/2

A Study to Evaluate Lucitanib in Combination With Nivolumab in Patients With a Solid Tumor

TARGETS
FGFRs, VEGFRs, PD-1

LOCATIONS: Tennessee, Florida, Oklahoma

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CLINICAL TRIALS

NCT03238196

PHASE 1

Fulvestrant, Palbociclib and Erdafitinib in ER+/HER2-/FGFR-amplified Metastatic Breast Cancer

TARGETS
CDK4, CDK6, FGFRs, ER

LOCATIONS: Tennessee

NCT03235570

PHASE 1

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

TARGETS
FGFR1, FGFR2, FGFR3

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

NCT03547037

PHASE 1

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

TARGETS
PD-1, FGFRs

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

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GENE
PIK3CA

ALTERATION
E542K

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.

NCT03997123

PHASE 3

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

TARGETS
AKTs

LOCATIONS: Maryland, Pennsylvania, Virginia, New York, Ohio, Mississauga (Canada), North York (Canada)

NCT04177108

PHASE 3

A Study Of Ipatasertib in Combination With Atezolizumab and Paclitaxel as a Treatment for Participants With Locally Advanced or Metastatic Triple-Negative Breast Cancer.

TARGETS
PD-L1, AKTs

LOCATIONS: Maryland, Connecticut, Barrie (Canada), South Carolina, Montreal (Canada), Montréal (Canada), Georgia, Tennessee, Quebec (Canada)

NCT03337724

PHASE 2/3

A Study of Ipatasertib in Combination With Paclitaxel as a Treatment for Participants With PIK3CA/AKT1/PTEN-Altered, Locally Advanced or Metastatic, Triple-Negative Breast Cancer or Hormone Receptor-Positive, HER2-Negative Breast Cancer

TARGETS
AKTs

LOCATIONS: Maryland, New Jersey, New York, Massachusetts, Tennessee

NCT01827384

PHASE 2

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

TARGETS
PARP, mTOR, MEK, WEE1

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

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

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

LOCATIONS: Virginia, Pennsylvania, New Jersey, New York, North Carolina

NCT03280563

PHASE 1/2

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

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

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

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CLINICAL TRIALS

NCT03502733

PHASE 1

Copanlisib and Nivolumab in Treating Patients With Metastatic Solid Tumors or Lymphoma

TARGETS
PI3K, PD-1

LOCATIONS: Maryland, Texas

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: Maryland, Virginia, New York, Connecticut, Ohio, Toronto (Canada), Kitchener (Canada), Michigan, Massachusetts

NCT03711058

PHASE 1/2

Study of PI3Kinase Inhibition (Copanlisib) and Anti-PD-1 Antibody Nivolumab in Relapsed/Refractory Solid Tumors With Expansions in Mismatch-repair Proficient (MSS) Colorectal Cancer

TARGETS
PD-1, PI3K

LOCATIONS: Maryland

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

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GENE
PTEN

ALTERATION
T319fs*1

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

NCT03997123

PHASE 3

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

TARGETS
AKTs

LOCATIONS: Maryland, Pennsylvania, Virginia, New York, Ohio, Mississauga (Canada), North York (Canada)

NCT04177108

PHASE 3

A Study Of Ipatasertib in Combination With Atezolizumab and Paclitaxel as a Treatment for Participants With Locally Advanced or Metastatic Triple-Negative Breast Cancer.

TARGETS
PD-L1, AKTs

LOCATIONS: Maryland, Connecticut, Barrie (Canada), South Carolina, Montreal (Canada), Montréal (Canada), Georgia, Tennessee, Quebec (Canada)

NCT03337724

PHASE 2/3

A Study of Ipatasertib in Combination With Paclitaxel as a Treatment for Participants With PIK3CA/AKT1/PTEN-Altered, Locally Advanced or Metastatic, Triple-Negative Breast Cancer or Hormone Receptor-Positive, HER2-Negative Breast Cancer

TARGETS
AKTs

LOCATIONS: Maryland, New Jersey, New York, Massachusetts, Tennessee

NCT03330847

PHASE 2

To Assess Safety and Efficacy of Agents Targeting DNA Damage Repair With Olaparib Versus Olaparib Monotherapy.

TARGETS
ATR, WEE1, PARP

LOCATIONS: Maryland, New Jersey, New York, Connecticut, Toronto (Canada)

NCT02484404

PHASE 1/2

Phase I/II Study of the Anti-Programmed Death Ligand-1 Antibody MEDI4736 in Combination With Olaparib and/or Cediranib for Advanced Solid Tumors and Advanced or Recurrent Ovarian, Triple Negative Breast, Lung, Prostate and Colorectal Cancers

TARGETS
PARP, PD-L1, VEGFRs

LOCATIONS: Maryland

NCT02769962

PHASE 1/2

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

TARGETS
PARP, TOP1

LOCATIONS: Maryland

NCT01827384

PHASE 2

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

TARGETS
PARP, mTOR, MEK, WEE1

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

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CLINICAL TRIALS

NCT03964532

PHASE 1/2

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

TARGETS
PD-L1, PARP

LOCATIONS: District of Columbia, North Carolina

NCT01042379

PHASE 2

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

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

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

NCT03330405

PHASE 2

Javelin Parp Medley: Avelumab Plus Talazoparib In Locally Advanced Or Metastatic Solid Tumors

TARGETS
PD-L1, PARP

LOCATIONS: District of Columbia, New York, Ohio, Toronto (Canada), Massachusetts, Minnesota, Arkansas, Texas

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

APC
K2052T and L662I

CHEK2
S252N

DDR1
R466H

FGFR2
rearrangement

FGFR3
Y337F

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) and tumor mutational burden (TMB) 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 the targeted therapies listed in Table 1 in accordance with the 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. Genomic findings other than those listed in Table 1 are not prescriptive or conclusive for labeled use of any specific therapeutic product.

The test is also used for detection of genomic loss of heterozygosity (LOH) from FFPE ovarian tumor tissue. Positive homologous recombination deficiency (HRD) status (F1CDx HRD defined as tBRCA-positive and/or LOH high) in ovarian cancer patients is associated with improved progression-free survival (PFS) from Rubraca (rucaparib) maintenance therapy in accordance with the RUBRACA product label.

The F1CDx assay will be performed at Foundation Medicine, Inc. sites located in Cambridge, MA and Morrisville, NC.

TABLE 1: COMPANION DIAGNOSTIC INDICATIONS

INDICATION	BIOMARKER	THERAPY
Non-small cell lung cancer (NSCLC)	*EGFR* exon 19 deletions and *EGFR* exon 21 L858R alterations	Gilotrif® (Afatinib), Iressa® (Gefitinib), Tagrisso® (Osimertinib), or Tarceva® (Erlotinib)
	EGFR exon 20 T790M alterations	Tagrisso® (Osimertinib)
	ALK rearrangements	Alecensa® (Alectinib), Xalkori® (Crizotinib), or Zykadia® (Ceritinib)
	BRAF V600E	Tafinlar® (Dabrafenib) in combination with Mekinist® (Trametinib)
Melanoma	*BRAF* V600E	Tafinlar® (Dabrafenib) or Zelboraf® (Vemurafenib)
	BRAF V600E and V600K	Mekinist® (Trametinib) or Cotellic® (Cobimetinib), in combination with Zelboraf® (Vemurafenib)
Breast cancer	*ERBB2* (HER2) amplification	Herceptin® (Trastuzumab), Kadcyla® (Ado-trastuzumab emtansine), or Perjeta® (Pertuzumab)
	PIK3CA C420R, E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y alterations	Piqray® (Alpelisib)
Colorectal cancer	*KRAS* wild-type (absence of mutations in codons 12 and 13)	Erbitux® (Cetuximab)
	KRAS wild-type (absence of mutations in exons 2, 3, and 4) and *NRAS* wild type (absence of mutations in exons 2, 3, and 4)	Vectibix® (Panitumumab)
Ovarian cancer	*BRCA1/2* alterations	Lynparza® (Olaparib) or Rubraca® (Rucaparib)

The median exon coverage for this sample is 685x

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TEST PRINCIPLE

FoundationOne®CDx (F1CDx) is performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The assay employs 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 (refer to Table 2 and Table 3 for complete list of genes included in F1CDx). In total, the assay detects alterations in a total of 324 genes. Using the Illumina® HiSeq 4000 platform, hybrid capture–selected libraries are sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data is then processed using a customized analysis pipeline designed to detect all classes of genomic alterations, including base substitutions, indels, copy number alterations (amplifications and homozygous gene deletions), and selected genomic rearrangements (e.g., gene fusions). Additionally, genomic signatures including microsatellite instability (MSI), tumor mutational burden (TMB), and positive homologous recombination deficiency (HRD) status (tBRCA-positive and/or LOH high) are reported.

PERFORMANCE CHARACTERISTICS

Please refer to product label:
foundationmedicine.com/f1cdx

LIMITATIONS

1. For *in vitro* diagnostic use.
2. For prescription use only. This test must be ordered by a qualified medical professional in accordance with clinical laboratory regulations.
3. A negative result does not rule out the presence of a mutation below the limits of detection of the assay.
4. Samples with <25% tumor may have decreased sensitivity for the detection of CNAs including *ERBB2*.
5. Clinical performance of Tagrisso® (osimertinib) in patients with an *EGFR* exon 20 T790M mutation detected with an allele fraction <5% is ongoing and has not been established.
6. Concordance with other validated methods for CNA (with the exception of *ERBB2*) and gene rearrangement (with the exception of *ALK*) detection has not been demonstrated and will be provided in the post-market setting. Confirmatory testing using a clinically validated assay should be performed for all CNAs and rearrangements not associated with CDx claims noted in Table 1 of the Intended Use, but used for clinical decision making.
7. The MSI-H/MSS designation by FMI FoundationOne®CDx (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. Refer https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf for additional details on methodology. 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. Patients with microsatellite status of "Cannot Be Determined" should be retested with an orthogonal (alternative) method. The clinical validity of the qualitative MSI designation has not been established.
8. TMB by F1CDx is defined based by counting the total number of all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and reported as mutations per megabase (mut/Mb) unit. TMB is a function of the characteristics of a patient's specimen and testing parameters; therefore, TMB may differ among specimens (e.g., primary vs. metastatic, tumor content) and targeted panels. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay LoD, filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has not been established.
9. 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.
10. The test is intended to be performed on specific serial number-controlled instruments by Foundation Medicine, Inc.
11. Alterations in polyT homopolymer runs may not be reliably detected in BRCA1/2.
12. Certain large rearrangements in BRCA1/2 including large scale genomic deletions (affecting at least one whole exon), insertions or other deleterious genomic rearrangements

including inversions or transversion events, may not be detected in an estimated 5% of ovarian cancer patients with BRCA1/2 mutations by F1CDx.

13. Certain potentially deleterious missense or small in-frame deletions in BRCA1/2 may not be reported under the "CDx associated findings" but may be reported in the "Other alterations and biomarkers identified" section in the patient report.
14. Alterations at allele frequencies below the established limit of detection may not be detected consistently.
15. Detection of LOH has been verified only for ovarian cancer patients.
16. Performance of the LOH classification has not been established for samples below 35% tumor content and with LOH scores near the cutoff of 16.
17. 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.

PDF Service Version 2.9.0

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

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

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B)*	*APC*
AR	*ARAF*	*ARFRP1*	*ARID1A*	*ASXL1*	*ATM*	*ATR*	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*
BCOR	*BCORL1*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*	*BTG2*
BTK	*C11orf30 (EMSY)*	*C17orf39 (GID4)*	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	*CCND1*
CCND2	*CCND3*	*CCNE1*	*CD22*	*CD274 (PD-L1)*	*CD70*	*CD79A*	*CD79B*	*CDC73*
CDH1	*CDK12*	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*
CDKN2C	*CEBPA*	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CSF1R*	*CSF3R*
CTCF	*CTNNA1*	*CTNNB1*	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*
DDR2	*DIS3*	*DNMT3A*	*DOT1L*	*EED*	*EGFR*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
FAM46C	*FANCA*	*FANCC*	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*
FGF14	*FGF19*	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*
FGFR4	*FH*	*FLCN*	*FLT1*	*FLT3*	*FOXL2*	*FUBP1*	*GABRA6*	*GATA3*
GATA4	*GATA6*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3F3A*
HDAC1	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*ID3*	*IDH1*	*IDH2*	*IGF1R*
IKBKE	*IKZF1*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JUN	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*	*KIT*	*KLHL6*
KMT2A (MLL)	*KMT2D (MLL2)*	*KRAS*	*LTK*	*LYN*	*MAF*	*MAP2K1 (MEK1)*	*MAP2K2 (MEK2)*	*MAP2K4*
MAP3K1	*MAP3K13*	*MAPK1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*	*MEN1*
MERTK	*MET*	*MITF*	*MKNK1*	*MLH1*	*MPL*	*MRE11A*	*MSH2*	*MSH3*
MSH6	*MST1R*	*MTAP*	*MTOR*	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*
NBN	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2*	*NOTCH3*
NPM1	*NRAS*	*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*	*P2RY8*	*PALB2*
PARK2	*PARP1*	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1 (PD-1)*	*PDCD1LG2 (PD-L2)*	*PDGFRA*
PDGFRB	*PDK1*	*PIK3C2B*	*PIK3C2G*	*PIK3CA*	*PIK3CB*	*PIK3R1*	*PIM1*	*PMS2*
POLD1	*POLE*	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*	*PTCH1*
PTEN	*PTPN11*	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*	*RAD51B*	*RAD51C*
RAD51D	*RAD52*	*RAD54L*	*RAF1*	*RARA*	*RB1*	*RBM10*	*REL*	*RET*
RICTOR	*RNF43*	*ROS1*	*RPTOR*	*SDHA*	*SDHB*	*SDHC*	*SDHD*	*SETD2*
SF3B1	*SGK1*	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*	*SNCAIP*	*SOCS1*
SOX2	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*	*STAT3*	*STK11*	*SUFU*
SYK	*TBX3*	*TEK*	*TET2*	*TGFBR2*	*TIPARP*	*TNFAIP3*	*TNFRSF14*	*TP53*
TSC1	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*	*VHL*	*WHSC1*	*WT1*	*XPO1*
XRCC2	*ZNF217*	*ZNF703*						

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

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

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

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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.

PROFESSIONAL SERVICES FINDINGS

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. 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.

RANKING OF ALTERATIONS AND THERAPIES

Biomarker and Genomic Findings

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

Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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

Foundation Medicine makes no promises or guarantees that a particular drug will be effective in the treatment of disease of 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 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 with the 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.

LOSS OF HETEROZYGOSITY SCORE

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. 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.

MICROSATELLITE STATUS

For Microsatellite Instability (MSI) results, confirmatory testing using a validated orthogonal method should be considered.

TUMOR MUTATIONAL BURDEN

Tumor Mutational Burden (TMB) is determined by measuring the number of somatic mutations in sequenced genes on the FoundationOne CDx test and extrapolating to the genome as a whole. TMB is assayed for all FoundationOne CDx samples and is reported in Professional Services as the number of mutations per megabase (Muts/Mb) rounded to the nearest integer. Tumor Mutational Burden is reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine Tumor Mutational Burden.

Genomic Findings with Evidence of Clinical Significance

Genomic findings listed at Level 2 are associated with clinical significance. Clinical significance may be indicated by evidence of therapeutic sensitivity or resistance and/or diagnostic, prognostic or other clinically relevant implications. Included in this category will be findings associated with clinical validity as supported by professional guidelines and/or peer-reviewed publications.

Genomic Findings with Potential Clinical Significance

Genomic findings listed at Level 3 are cancer-related mutations and biomarkers with potential clinical significance. These include findings in genes known to be associated with cancer and are supported by evidence from publicly available databases, and/or peer-reviewed publications.

A Fluid Approach to Reporting Levels

As additional information becomes available, as recognized by the clinical community (professional guidelines and/or peer-reviewed publications), findings may move between Levels 2 and 3 in accordance with the above descriptions.

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

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1. Gatalica Z, et al. Cancer Epidemiol. Biomarkers Prev. (2014) PMID: 25392179
2. Kroemer G, et al. Oncoimmunology (2015) PMID: 26140250
3. Lal N, et al. Oncoimmunology (2015) PMID: 25949894
4. Le DT, et al. N. Engl. J. Med. (2015) PMID: 26028255
5. Ayers et al., 2016; ASCO-SITC Abstract P60
6. Adem C, et al. Int. J. Cancer (2003) PMID: 14520695
7. Anbazhagan R, et al. Clin. Cancer Res. (1999) PMID: 10213220
8. Walsh MD, et al. Clin. Cancer Res. (2010) PMID: 20215533
9. Risinger JI, et al. Cancer (1996) PMID: 8646682
10. de Leeuw WJ, et al. Cancer Res. (2003) PMID: 12615735
11. Shanley S, et al. Fam. Cancer (2009) PMID: 19123071
12. Buerki N, et al. Genes Chromosomes Cancer (2012) PMID: 22034109
13. Yee CJ, et al. Cancer Res. (1994) PMID: 8137273
14. Kamat N, et al. BMC Cancer (2012) PMID: 22928966
15. Kocarnik JM, et al. Gastroenterol Rep (Oxf) (2015) PMID: 26337942
16. You JF, et al. Br. J. Cancer (2010) PMID: 21081928
17. Bairwa NK, et al. Methods Mol. Biol. (2014) PMID: 24623249
18. Boland CR, et al. Cancer Res. (1998) PMID: 9823339
19. Pawlik TM, et al. Dis. Markers (2004) PMID: 15528785
20. Boland CR, et al. Gastroenterology (2010) PMID: 20420947
21. Samstein RM, et al. Nat. Genet. (2019) PMID: 30643254
22. Goodman AM, et al. Mol. Cancer Ther. (2017) PMID: 28835386
23. Goodman AM, et al. Cancer Immunol Res (2019) PMID: 31405947
24. Cristescu R, et al. Science (2018) PMID: 30309915
25. Legrand et al., 2018; ASCO Abstract 12000
26. Chalmers ZR, et al. Genome Med (2017) PMID: 28420421
27. Nature (2012) PMID: 23000897
28. Sokol ES, et al. Ann. Oncol. (2019) PMID: 30423024
29. Haricharan S, et al. Breast Cancer Res. Treat. (2014) PMID: 24839032
30. Budczies J, et al. J Pathol Clin Res (2015) PMID: 27499907
31. Pfeifer GP, et al. Mutat. Res. (2005) PMID: 15748635
32. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) PMID: 23875803
33. Pfeifer GP, et al. Oncogene (2002) PMID: 12379884
34. Rizvi NA, et al. Science (2015) PMID: 25765070
35. Cancer Genome Atlas Research Network, et al. Nature (2013) PMID: 23636398
36. Briggs S, et al. J. Pathol. (2013) PMID: 23447401
37. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) PMID: 24583393
38. Nature (2012) PMID: 22810696
39. Roberts SA, et al. Nat. Rev. Cancer (2014) PMID: 25568919
40. Dickson MA, et al. J. Clin. Oncol. (2013) PMID: 23569312
41. Flaherty KT, et al. Clin. Cancer Res. (2012) PMID: 22090362
42. Patnaik A, et al. Cancer Discov (2016) PMID: 27217383
43. Infante JR, et al. Clin. Cancer Res. (2016) PMID: 27542767
44. Dickson MA, et al. JAMA Oncol (2016) PMID: 27124835
45. Peguero et al., 2016; ASCO Abstract 2528
46. Costa C, et al. Cancer Discov (2019) PMID: 31594766
47. Peurala E, et al. Breast Cancer Res. (2013) PMID: 23336272
48. Choi YJ, et al. Oncogene (2014) PMID: 23644662
49. Cell (1995) PMID: 7736585
50. Musgrove EA, et al. Nat. Rev. Cancer (2011) PMID: 21734724
51. Wikman H, et al. Genes Chromosomes Cancer (2005) PMID: 15543620
52. Rao SK, et al. J. Neurooncol. (2010) PMID: 19609742
53. Chung L, et al. Am. J. Surg. Pathol. (2009) PMID: 19574885
54. Ragazzini P, et al. Histol. Histopathol. (2004) PMID: 15024701
55. Dujardin F, et al. Mod. Pathol. (2011) PMID: 21336260
56. Zhang K, et al. Cancer Res. (2013) PMID: 23393200
57. Horvai AE, et al. Mod. Pathol. (2009) PMID: 19734852
58. Straubhar A, et al. Gynecol Oncol Rep (2017) PMID: 28560298
59. Thangavelu A, et al. Gynecol. Oncol. (2013) PMID: 24076063
60. Gershenson DM, et al. J. Clin. Oncol. (2017) PMID: 28221866
61. Esfahani K, et al. BMJ Case Rep (2014) PMID: 24925537
62. Ramirez PT, et al. Gynecol. Oncol. (2008) PMID: 18457865
63. Fribbens C, et al. J. Clin. Oncol. (2016) PMID: 27269946
64. Spoerke JM, et al. Nat Commun (2016) PMID: 27174596
65. Gaillard SL, et al. Gynecol. Oncol. (2019) PMID: 30987772
66. Takeshita T, et al. Transl Res (2015) PMID: 26434753
67. Lupien M, et al. Mol. Endocrinol. (2007) PMID: 17299137
68. Gelsomino L, et al. Breast Cancer Res. Treat. (2016) PMID: 27178332
69. Sefrioui D, et al. Int. J. Cancer (2015) PMID: 25994408
70. Niu J, et al. Onco Targets Ther (2015) PMID: 26648736
71. Toy W, et al. Cancer Discov (2017) PMID: 27986707
72. Harrod A, et al. Oncogene (2017) PMID: 27748765
73. Carlson KE, et al. Biochemistry (1997) PMID: 9398213
74. Turner et al., 2018; ASCO Abstract 1001
75. de Vries et al., 2017; SABCS Abstract P1-10-04
76. Bardia et al., 2017; ASCO Abstract 1014
77. Dickler et al., 2017; SABCS Abstract PD5-10
78. Juric et al., 2017; SABCS Abstract P5-21-04
79. Chung JH, et al. Ann. Oncol. (2017) PMID: 28945887
80. Desmedt C, et al. NPJ Breast Cancer (2019) PMID: 30820448
81. Pereira B, et al. Nat Commun (2016) PMID: 27161491
82. Jeselsohn R, et al. Clin. Cancer Res. (2014) PMID: 24398047
83. Zehir A, et al. Nat. Med. (2017) PMID: 28481359
84. Toy W, et al. Nat. Genet. (2013) PMID: 24185512
85. Robinson DR, et al. Nat. Genet. (2013) PMID: 24185510
86. Merenbakh-Lamin K, et al. Cancer Res. (2013) PMID: 24217577
87. Schiavon G, et al. Sci Transl Med (2015) PMID: 26560360
88. World J Clin Oncol (2016) PMID: 27081639
89. Laenkholm AV, et al. Mol Oncol (2012) PMID: 22626971
90. Tsiambas E, et al. Med. Oncol. (2011) PMID: 20458558
91. Lin CH, et al. J. Clin. Pathol. (2013) PMID: 23268322
92. Moelans CB, et al. Cell Oncol (Dordr) (2011) PMID: 21541733
93. Holst F, et al. Nat. Genet. (2007) PMID: 17417639
94. Reis-Filho JS, et al. Nat. Genet. (2008) PMID: 18583966
95. Vincent-Salomon A, et al. Nat. Genet. (2008) PMID: 18583967
96. Chen JR, et al. Virchows Arch. (2014) PMID: 24756215
97. Pearce ST, et al. Crit. Rev. Oncol. Hematol. (2004) PMID: 15094156
98. Pakdel F, et al. Mol. Endocrinol. (1993) PMID: 8114756
99. Lazennec G, et al. Mol. Endocrinol. (1997) PMID: 9259327
100. Li S, et al. Cell Rep (2013) PMID: 24055055
101. Zhang QX, et al. Cancer Res. (1997) PMID: 9102207
102. Weis KE, et al. Mol. Endocrinol. (1996) PMID: 8923465
103. Eng FC, et al. Mol. Cell. Biol. (1997) PMID: 9234721
104. Eng FC, et al. J. Biol. Chem. (1998) PMID: 9774463
105. Chandarlapaty S, et al. JAMA Oncol (2016) PMID: 27532364
106. André F, et al. N. Engl. J. Med. (2019) PMID: 31091374
107. Fritsch C, et al. Mol. Cancer Ther. (2014) PMID: 24608574
108. Park HS, et al. PLoS ONE (2016) PMID: 27105424
109. André F, et al. J. Clin. Oncol. (2016) PMID: 27091708
110. Janku F, et al. Mol. Cancer Ther. (2011) PMID: 21216929
111. Moulder S, et al. Ann. Oncol. (2015) PMID: 25878190
112. Lim SM, et al. Oncotarget (2016) PMID: 26859683
113. Meric-Bernstam F, et al. Clin. Cancer Res. (2012) PMID: 22422409
114. Dolly SO, et al. Clin. Cancer Res. (2016) PMID: 26787751
115. Moynahan ME, et al. Br. J. Cancer (2017) PMID: 28183140
116. Baselga et al., 2015; SABCS Abstract S6-01
117. Rodon J, et al. Invest New Drugs (2014) PMID: 24652201
118. Bendell JC, et al. J. Clin. Oncol. (2012) PMID: 22162589
119. Heudel PE, et al. Br. J. Cancer (2017) PMID: 28072765
120. Vansteenkiste JF, et al. J Thorac Oncol (2015) PMID: 26098748
121. Juric D, et al. J. Clin. Oncol. (2018) PMID: 29401002
122. Mayer IA, et al. Clin. Cancer Res. (2017) PMID: 27126994
123. Baselga et al., 2018; ASCO Abstract LBA1006
124. Vasan N, et al. Science (2019) PMID: 31699932
125. Schmid P, et al. J. Clin. Oncol. (2019) PMID: 31841354
126. Banerji et al., 2015; ASCO Abstract 2500
127. Turner NC, et al. Ann. Oncol. (2019) PMID: 30860570
128. Esteva FJ, et al. Am. J. Pathol. (2010) PMID: 20813970
129. Baselga J, et al. J. Clin. Oncol. (2014) PMID: 25332247
130. Chakrabarty A, et al. Oncogene (2010) PMID: 20581867
131. Kataoka Y, et al. Ann. Oncol. (2010) PMID: 19633047
132. Wang L, et al. BMC Cancer (2011) PMID: 21676217
133. Juric D, et al. Nature (2015) PMID: 25409150
134. Hoste G, et al. Clin Drug Investig (2018) PMID: 30187361
135. Loi S, et al. PLoS ONE (2013) PMID: 23301057
136. Christgen M, et al. Genes Chromosomes Cancer (2013) PMID: 22997091
137. Ramirez-Ardila DE, et al. Breast Cancer Res. Treat. (2013) PMID: 23592373
138. Kalinsky K, et al. Clin. Cancer Res. (2009) PMID: 19671852
139. Barbareschi M, et al. Clin. Cancer Res. (2007) PMID: 17947469
140. Samuels Y, et al. Cancer Cell (2005) PMID: 15950905
141. Nat. Rev. Cancer (2009) PMID: 19629070
142. Kang S, et al. Proc. Natl. Acad. Sci. U.S.A. (2005) PMID: 15647370
143. Ikenoue T, et al. Cancer Res. (2005) PMID: 15930273
144. Gymnopoulos M, et al. Proc. Natl. Acad. Sci. U.S.A. (2007) PMID: 17376864
145. Horn S, et al. Oncogene (2008) PMID: 18317450
146. Rudd ML, et al. Clin. Cancer Res. (2011) PMID: 21266528
147. Hon WC, et al. Oncogene (2012) PMID: 22120714
148. Burke JE, et al. Proc. Natl. Acad. Sci. U.S.A. (2012) PMID: 22949682
149. Wu H, et al. Proc. Natl. Acad. Sci. U.S.A. (2009) PMID: 19915146
150. Laurenti R, et al. Rev Saude Publica (1990) PMID: 2103068
151. Dan S, et al. Cancer Res. (2010) PMID: 20530683
152. Oda K, et al. Cancer Res. (2008) PMID: 18829572
153. Zhao L, et al. Oncogene (2008) PMID: 18794883
154. Lui VW, et al. Cancer Discov (2013) PMID: 23619167

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155. Ross RL, et al. Oncogene (2013) PMID: 22430209
156. Rivière JB, et al. Nat. Genet. (2012) PMID: 22729224
157. Shibata T, et al. Cancer Lett. (2009) PMID: 19394761
158. Dogruluk T, et al. Cancer Res. (2015) PMID: 26627007
159. Croessmann S, et al. Clin. Cancer Res. (2018) PMID: 29284706
160. Ng PK, et al. Cancer Cell (2018) PMID: 29533785
161. Courtney KD, et al. J. Clin. Oncol. (2010) PMID: 20085938
162. Wu R, et al. Clin. Cancer Res. (2011) PMID: 21903772
163. Simpson L, et al. Exp. Cell Res. (2001) PMID: 11237521
164. Dreyling M, et al. Ann. Oncol. (2017) PMID: 28633365
165. Patnaik A, et al. Ann. Oncol. (2016) PMID: 27672108
166. Wee S, et al. Proc. Natl. Acad. Sci. U.S.A. (2008) PMID: 18755892
167. Jia S, et al. Nature (2008) PMID: 18594509
168. Schmit F, et al. Proc. Natl. Acad. Sci. U.S.A. (2014) PMID: 24737887
169. Janku et al., 2018; ESMO Abstract 418PD
170. Dent et al., 2018; ASCO Abstract 1008
171. Schmid et al., 2018; ASCO Abstract 1007
172. de Bono JS, et al. Clin. Cancer Res. (2019) PMID: 30037818
173. Saura C, et al. Cancer Discov (2017) PMID: 27872130
174. Forster MD, et al. Nat Rev Clin Oncol (2011) PMID: 21468130
175. Sandhu SK, et al. Lancet Oncol. (2013) PMID: 23810788
176. Mendes-Pereira AM, et al. EMBO Mol Med (2009) PMID: 20049735
177. Shen Y, et al. Clin. Cancer Res. (2013) PMID: 23881923
178. Chatterjee P, et al. PLoS ONE (2013) PMID: 23565244
179. McCormick A, et al. Int. J. Gynecol. Cancer (2016) PMID: 26905328
180. Ihnen M, et al. Mol. Cancer Ther. (2013) PMID: 23729402
181. Zhao J, et al. Nat. Med. (2019) PMID: 30742119
182. George S, et al. Immunity (2017) PMID: 28228279
183. Parikh AR, et al. Lung Cancer (Auckl) (2018) PMID: 29844707
184. Peng W, et al. Cancer Discov (2016) PMID: 26645196
185. Hennessy BT, et al. Cancer Res. (2009) PMID: 19435916
186. Mercapide J, et al. Mol. Carcinog. (2002) PMID: 12203362
187. Hohensee I, et al. Am. J. Pathol. (2013) PMID: 23665199
188. Perez EA, et al. J. Clin. Oncol. (2013) PMID: 23650412
189. Tsutsui S, et al. Oncology (2005) PMID: 16020969
190. Zhang HY, et al. Oncol Lett (2013) PMID: 23946797
191. Capodanno A, et al. Hum. Pathol. (2009) PMID: 19428048
192. Campbell RB, et al. J. Biol. Chem. (2003) PMID: 12857747
193. Rodríguez-Escudero I, et al. Hum. Mol. Genet. (2011) PMID: 21828076
194. He X, et al. Cancer Res. (2013) PMID: 23475934
195. Han SY, et al. Cancer Res. (2000) PMID: 10866302
196. Myers MP, et al. Proc. Natl. Acad. Sci. U.S.A. (1998) PMID: 9811831
197. Pradella LM, et al. BMC Cancer (2014) PMID: 24498881
198. Kim JS, et al. Mol. Cell. Biol. (2011) PMID: 21536651
199. Denning G, et al. Oncogene (2007) PMID: 17213812
200. Hlobilkova A, et al. Anticancer Res. () PMID: 16619501
201. Redfern RE, et al. Protein Sci. (2010) PMID: 20718038
202. Shenoy S, et al. PLoS ONE (2012) PMID: 22505997
203. Wang Y, et al. Proc. Natl. Acad. Sci. U.S.A. (2009) PMID: 19329485
204. Okumura K, et al. J. Biol. Chem. (2006) PMID: 16829519
205. Lee JO, et al. Cell (1999) PMID: 10555148
206. Maxwell GL, et al. Cancer Res. (1998) PMID: 9635567
207. Risinger JI, et al. Clin. Cancer Res. (1998) PMID: 9865913
208. Kato H, et al. Clin. Cancer Res. (2000) PMID: 11051241
209. Fenton TR, et al. Proc. Natl. Acad. Sci. U.S.A. (2012) PMID: 22891331
210. Ngeow J, et al. J. Clin. Endocrinol. Metab. (2012) PMID: 23066114
211. Lobo GP, et al. Hum. Mol. Genet. (2009) PMID: 19457929
212. Liu J, et al. Oncogene (2014) PMID: 23995781
213. Maehama T, et al. Annu. Rev. Biochem. (2001) PMID: 11395408
214. De Vivo I, et al. J. Med. Genet. (2000) PMID: 10807691
215. Ramaswamy S, et al. Proc. Natl. Acad. Sci. U.S.A. (1999) PMID: 10051603
216. Liu JL, et al. Mol. Cell. Biol. (2005) PMID: 15988030
217. Karoui M, et al. Br. J. Cancer (2004) PMID: 15026806
218. Gil A, et al. PLoS ONE (2015) PMID: 25875300
219. Furnari FB, et al. Cancer Res. (1998) PMID: 9823298
220. Spinelli L, et al. J. Med. Genet. (2015) PMID: 25527629
221. Mingo J, et al. Eur. J. Hum. Genet. (2018) PMID: 29706633
222. Wang Q, et al. J. Mol. Graph. Model. (2010) PMID: 20538496
223. Andrés-Pons A, et al. Cancer Res. (2007) PMID: 17942903
224. Butler MG, et al. J. Med. Genet. (2005) PMID: 15805158
225. Georgescu MM, et al. Proc. Natl. Acad. Sci. U.S.A. (1999) PMID: 10468583
226. Staal FJ, et al. Br. J. Cancer (2002) PMID: 12085208
227. Nguyen HN, et al. Oncogene (2014) PMID: 24292679
228. Rahdar M, et al. Proc. Natl. Acad. Sci. U.S.A. (2009) PMID: 19114656
229. Das S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) PMID: 12808147
230. Wang X, et al. Biochem. J. (2008) PMID: 18498243
231. Valiente M, et al. J. Biol. Chem. (2005) PMID: 15951562
232. Nguyen HN, et al. Oncogene (2015) PMID: 25263454
233. Landrum MJ, et al. Nucleic Acids Res. (2018) PMID: 29165669
234. Blumenthal GM, et al. Eur. J. Hum. Genet. (2008) PMID: 18781191
235. Orloff MS, et al. Oncogene (2008) PMID: 18794875
236. Zbuk KM, et al. Nat. Rev. Cancer (2007) PMID: 17167516
237. Tabernero J, et al. J. Clin. Oncol. (2015) PMID: 26324363
238. Borad MJ, et al. PLoS Genet. (2014) PMID: 24550739
239. Liao RG, et al. Cancer Res. (2013) PMID: 23786770
240. Gozgit JM, et al. Mol. Cancer Ther. (2012) PMID: 22238366
241. Pearson A, et al. Cancer Discov (2016) PMID: 27179038
242. Van Cutsem E, et al. Ann. Oncol. (2017) PMID: 29177434
243. Aggarwal C, et al. J Thorac Oncol (2019) PMID: 31195180
244. Voss MH, et al. Clin. Cancer Res. (2019) PMID: 30745300
245. Nogova L, et al. J. Clin. Oncol. (2017) PMID: 27870574
246. Goyal L, et al. Cancer Discov (2019) PMID: 31109923
247. Hollebecque et al., 2018; ESMO abstract 756
248. Morizane et al., 2020; ASCO GI abstract 538
249. Bahleda R, et al. Clin. Cancer Res. (2019) PMID: 31088831
250. Heiskanen M, et al. Anal Cell Pathol (2001) PMID: 11564899
251. Adnane J, et al. Oncogene (1991) PMID: 1851551
252. Turner N, et al. Oncogene (2010) PMID: 20101236
253. Lee HJ, et al. Ann. Surg. Oncol. (2014) PMID: 24385208
254. Sun S, et al. J Surg Oncol (2012) PMID: 22006548
255. Templeton AJ, et al. Cancer Treat. Rev. (2014) PMID: 25217796
256. Powers CJ, et al. Endocr. Relat. Cancer (2000) PMID: 11021964
257. Turner N, et al. Nat. Rev. Cancer (2010) PMID: 20094046
258. Gao J, et al. Sci Signal (2013) PMID: 23550210
259. Tokunaga R, et al. Oncotarget (2016) PMID: 26933914
260. André F, et al. Clin. Cancer Res. (2013) PMID: 23658459
261. Hirai H, et al. Cancer Biol. Ther. (2010) PMID: 20107315
262. Bridges KA, et al. Clin. Cancer Res. (2011) PMID: 21799033
263. Rajeshkumar NV, et al. Clin. Cancer Res. (2011) PMID: 21389100
264. Osman AA, et al. Mol. Cancer Ther. (2015) PMID: 25504633
265. Xu L, et al. Mol. Cancer Ther. (2002) PMID: 12489850
266. Xu L, et al. Mol. Med. (2001) PMID: 11713371
267. Camp ER, et al. Cancer Gene Ther. (2013) PMID: 23470564
268. Kim SS, et al. Nanomedicine (2015) PMID: 25240597
269. Pirollo KF, et al. Mol. Ther. (2016) PMID: 27357628
270. Hajdenberg et al., 2012; ASCO Abstract e15010
271. Leijen S, et al. J. Clin. Oncol. (2016) PMID: 27601554
272. Moore et al., 2019; ASCO Abstract 5513
273. Leijen S, et al. J. Clin. Oncol. (2016) PMID: 27998224
274. Oza et al., 2015; ASCO Abstract 5506
275. Lee J, et al. Cancer Discov (2019) PMID: 31315834
276. Méndez E, et al. Clin. Cancer Res. (2018) PMID: 29535125
277. Ma CX, et al. J. Clin. Invest. (2012) PMID: 22446188
278. Kwok M, et al. Blood (2016) PMID: 26563132
279. Boudny M, et al. Haematologica (2019) PMID: 30975914
280. Dillon MT, et al. Mol. Cancer Ther. (2017) PMID: 28062704
281. Middleton FK, et al. Cancers (Basel) (2018) PMID: 30127241
282. Banerji S, et al. Nature (2012) PMID: 22722202
283. Stephens PJ, et al. Nature (2012) PMID: 22722201
284. Alsner J, et al. Acta Oncol (2008) PMID: 18465328
285. Alkam Y, et al. Histopathology (2013) PMID: 24004112
286. Uji K, et al. Cancer Lett. (2014) PMID: 23973262
287. Olivier M, et al. Clin. Cancer Res. (2006) PMID: 16489069
288. Végran F, et al. PLoS ONE (2013) PMID: 23359294
289. Walsh T, et al. JAMA (2006) PMID: 16551709
290. Garber JE, et al. J. Clin. Oncol. (2005) PMID: 15637391
291. Apostolou P, et al. Biomed Res Int (2013) PMID: 23586058
292. Brown CJ, et al. Nat. Rev. Cancer (2009) PMID: 19935675
293. Joerger AC, et al. Annu. Rev. Biochem. (2008) PMID: 18410249
294. Kato S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) PMID: 12826609
295. Kamada R, et al. J. Biol. Chem. (2011) PMID: 20978130
296. Bougeard G, et al. J. Clin. Oncol. (2015) PMID: 26014290
297. Sorrell AD, et al. Mol Diagn Ther (2013) PMID: 23355100
298. Nichols KE, et al. Cancer Epidemiol. Biomarkers Prev. (2001) PMID: 11219776
299. Kleihues P, et al. Am. J. Pathol. (1997) PMID: 9006316
300. Gonzalez KD, et al. J. Clin. Oncol. (2009) PMID: 19204208
301. Lalloo F, et al. Lancet (2003) PMID: 12672316
302. Mandelker D, et al. Ann. Oncol. (2019) PMID: 31050713
303. Gallant JN, et al. NPJ Precis Oncol (2019) PMID: 30793038
304. Juric D, et al. JAMA Oncol (2018) PMID: 30543347
305. Jain S, et al. Breast Cancer Res. Treat. (2018) PMID: 29850984
306. Sharma et al., 2018; ASCO Abstract 1018
307. Hosford SR, et al. Clin. Cancer Res. (2017) PMID: 27903677

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308. Wang Q, et al. Oncogene (2016) PMID: 26500061
309. Juric et al., 2016; SABCS Abstract P3-14-01
310. Mayer IA, et al. Clin. Cancer Res. (2019) PMID: 30723140
311. Templeton AJ, et al. Eur. Urol. (2013) PMID: 23582881
312. Wheler JJ, et al. Oncotarget (2014) PMID: 24912489
313. Janku F, et al. Cell Rep (2014) PMID: 24440717
314. Beck JT, et al. Breast Cancer Res. Treat. (2014) PMID: 24362951
315. Yardley DA, et al. Adv Ther (2013) PMID: 24158787
316. Baselga J, et al. N. Engl. J. Med. (2012) PMID: 22149876
317. Piccart M, et al. Ann. Oncol. (2014) PMID: 25231953
318. Jerusalem G, et al. JAMA Oncol (2018) PMID: 29862411
319. Baselga J, et al. J. Clin. Oncol. (2009) PMID: 19380449
320. Bachelot T, et al. J. Clin. Oncol. (2012) PMID: 22565002
321. Yardley DA, et al. Clin. Breast Cancer (2019) PMID: 31932237
322. Hurvitz SA, et al. Lancet Oncol. (2015) PMID: 26092818
323. André F, et al. Lancet Oncol. (2014) PMID: 24742739
324. Singh J, et al. Breast Cancer Res. (2014) PMID: 24684785
325. Tolcher AW, et al. Ann. Oncol. (2015) PMID: 25344362
326. Patterson et al., 2018; AACR Abstract 3891
327. Turner NC, et al. N. Engl. J. Med. (2018) PMID: 30345905
328. Cristofanilli M, et al. Lancet Oncol. (2016) PMID: 26947331
329. Turner NC, et al. N. Engl. J. Med. (2015) PMID: 26030518
330. Sledge GW, et al. J. Clin. Oncol. (2017) PMID: 28580882
331. Jiang et al., 2019; ESMO Abstract LBA25
332. Slamon DJ, et al. J. Clin. Oncol. (2018) PMID: 29860922
333. Slamon et al., 2019; ESMO Abstract LBA7
334. Robertson JFR, et al. Lancet (2016) PMID: 27908454
335. Mehta RS, et al. N. Engl. J. Med. (2012) PMID: 22853014
336. Mehta RS, et al. N. Engl. J. Med. (2019) PMID: 30917258
337. Kornblum N, et al. J. Clin. Oncol. (2018) PMID: 29664714
338. Gianni L, et al. Lancet Oncol. (2018) PMID: 29326029
339. Leonard JP, et al. Blood (2012) PMID: 22383795
340. Finn RS, et al. N. Engl. J. Med. (2016) PMID: 27959613
341. Finn et al., 2017; SABCS Abstract P2-09-10
342. Turner NC, et al. J. Clin. Oncol. (2019) PMID: 30807234
343. Park YH, et al. Lancet Oncol. (2019) PMID: 31668850
344. DeMichele A, et al. Clin. Cancer Res. (2015) PMID: 25501126
345. Clark et al., 2016; SABCS Abstract P4-22-14
346. Johnston S, et al. J. Clin. Oncol. (2019) PMID: 30523750
347. Cottu P, et al. Ann. Oncol. (2018) PMID: 30307466
348. Ma CX, et al. Clin. Cancer Res. (2017) PMID: 28270497
349. Gucalp et al., 2017; SABCS Abstract P3-11-04
350. Hortobagyi GN, et al. Ann. Oncol. (2018) PMID: 29718092
351. Tripathy D, et al. Lancet Oncol. (2018) PMID: 29804902
352. Im SA, et al. N. Engl. J. Med. (2019) PMID: 31166679
353. Slamon DJ, et al. N. Engl. J. Med. (2020) PMID: 31826360
354. Bardia et al., 2019; ASCO Abstract 1016
355. Bardia et al., 2018; AACR Abstract CT069-22
356. Juric et al., 2016; ASCO Abstract 568
357. Munster et al., 2016; SABCS P4-22-18
358. Juric et al, 2015; SABCS P3-14-01
359. Regan MM, et al. Lancet Oncol. (2011) PMID: 22018631
360. Cuzick J, et al. Lancet Oncol. (2010) PMID: 21087898
361. Paridaens RJ, et al. J. Clin. Oncol. (2008) PMID: 18794551
362. Yu M, et al. Science (2014) PMID: 25013076
363. Gellert et al., 2015; SABCS Abstract S6-02
364. Hamadeh IS, et al. Cancer Treat. Rev. (2018) PMID: 30086432
365. Baum M, et al. Lancet (2002) PMID: 12090977
366. Finn et al., 2016; ASCO Abstract 507
367. Finn RS, et al. Lancet Oncol. (2015) PMID: 25524798
368. Finn RS, et al. Breast Cancer Res. (2016) PMID: 27349747
369. Gyanchandani R, et al. Oncotarget (2017) PMID: 28978004
370. Siefker-Radtke et al., 2018; ASCO Abstract 4503
371. Park et al., 2019; ASCO Abstract 4117
372. Soria et al., 2017; ASCO Abstract 4074
373. Perera TPS, et al. Mol. Cancer Ther. (2017) PMID: 28341788
374. Karkera JD, et al. Mol. Cancer Ther. (2017) PMID: 28416604
375. Loriot Y, et al. N. Engl. J. Med. (2019) PMID: 31340094
376. Qin A, et al. J Thorac Oncol (2019) PMID: 30267839
377. Di Stefano AL, et al. Clin. Cancer Res. (2015) PMID: 25609060
378. Kim ST, et al. J. Cancer Res. Clin. Oncol. (2016) PMID: 26983912
379. Taylor SK, et al. Oncologist (2010) PMID: 20682606
380. Majure et al., 2016; ASCO Abstract 560
381. Johnston SR, et al. Breast Cancer Res. Treat. (2013) PMID: 23283526
382. Cristofanilli M, et al. Breast Cancer Res. Treat. (2013) PMID: 23239151
383. Tan AR, et al. Breast Cancer Res. Treat. (2015) PMID: 25542269
384. Janku F, et al. J. Clin. Oncol. (2012) PMID: 22271473
385. Basho et al., 2015; SABCS Abstract P3-14-02
386. Tinker AV, et al. Gynecol. Oncol. (2013) PMID: 23672928
387. Figlin RA, et al. Cancer (2009) PMID: 19526589
388. Cho D, et al. Clin Genitourin Cancer (2007) PMID: 17956710
389. Galanis E, et al. J. Clin. Oncol. (2005) PMID: 15998902
390. Cloughesy TF, et al. PLoS Med. (2008) PMID: 18215105
391. Oza AM, et al. J. Clin. Oncol. (2011) PMID: 21788564
392. Mackay HJ, et al. Cancer (2014) PMID: 24166148
393. Fleming GF, et al. Gynecol. Oncol. (2014) PMID: 24456823
394. Tsoref D, et al. Gynecol. Oncol. (2014) PMID: 25173583
395. Moroney JW, et al. Clin. Cancer Res. (2011) PMID: 21890452
396. Moroney J, et al. Clin. Cancer Res. (2012) PMID: 22927482
397. Fleming GF, et al. Breast Cancer Res. Treat. (2012) PMID: 22245973
398. Wolff AC, et al. J. Clin. Oncol. (2013) PMID: 23233719

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