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.

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SPECIMEN RECEIVED

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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