FoundationOne®CDx is a next-generation sequencing (NGS) based assay that identifies genomic findings within hundreds of cancer-related genes.

**PATIENT**
- DISEASE: Breast carcinoma (NOS)
- NAME: Not Given
- DATE OF BIRTH: Not Given
- SEX: Not Given
- MEDICAL RECORD #: Not Given

**PHYSICIAN**
- ORDERING PHYSICIAN: Not Given
- MEDICAL FACILITY: Not Given
- ADDITIONAL RECIPIENT: Not Given
- MEDICAL FACILITY ID: Not Given
- PATHOLOGIST: Not Given

**SPECIMEN**
- SPECIMEN SITE: Not Given
- SPECIMEN ID: Not Given
- SPECIMEN TYPE: Not Given
- DATE OF COLLECTION: Not Given
- SPECIMEN RECEIVED: Not Given

**PATIENT**
- Sample, Jane

**TUMOR TYPE**
- Breast carcinoma (NOS)

**REPORT DATE**
- 01 Jan 2018

**QRF#**
- XXXXXXXX

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**ABOUT THE TEST**

### Biomarker Findings

**Microsatellite status • MS-Stable**

**Tumor Mutational Burden • TMB-Low (3 Muts/Mb)**

### Genomic Findings

**ERBB2 • amplification**

**PIK3CA • H1047R**

**CDK12 • rearrangement exon 5**

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**BIOMARKER FINDINGS**

**Microsatellite status • MS-Stable**

**Tumor Mutational Burden • TMB-Low (3 Muts/Mb)**

**GENOMIC FINDINGS**

**ERBB2 • amplification**

- 10 Trials see p. 16

**PIK3CA • H1047R**

- 7 Trials see p. 18

**CDK12 • rearrangement exon 5**

- 9 Trials see p. 20

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**THERAPIES WITH CLINICAL BENEFIT (IN PATIENT’S TUMOR TYPE)**

- Ado-trastuzumab emtansine
- Lapatinib
- Neratinib
- Pertuzumab
- Trastuzumab
- Trastuzumab-dkst

**THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)**

- Afatinib
- Dacomitinib
- Everolimus
- Temsirolimus

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No therapies or clinical trials. see Biomarker Findings section

No therapies or clinical trials. see Biomarker Findings section
For more information regarding biological and clinical significance, including prognostic, diagnostic, germline, and potential chemosensitivity implications, see the Genomic Findings section.

**CCNE1** - amplification .................................................. p. 6   **TP53** - T253fs*11 .......................................................... p. 7

**NOTCH3** - AKAP8-NOTCH3 fusion .................................. p. 7

**NOTE** Genomic alterations detected may be associated with activity of certain approved therapies; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Therapies and the clinical trials listed in this report may not be complete and exhaustive. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type. This report should be regarded and used as a supplementary source of information and not as the single basis for the making of a therapy decision. All treatment decisions remain the full and final responsibility of the treating physician and physicians should refer to approved prescribing information for all therapies.

Therapies contained in this report may have been approved by the US FDA.
Microsatellite status

CATEGORY
MS-Stable

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 tumors. 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. These tumors may also have increased MSI following chemotherapy treatment, and MSI is associated with incidence of secondary tumors.

FREQUENCY & PROGNOSIS
The frequency of MSI in breast cancer varies widely due to differences in patient characteristics and sample size. In a few studies of Lynch syndrome-related breast cancer patients with small sample sizes (n<10), MSI was observed in 60%-85% of patients. However, no MSI was observed in a few larger scale analysis of breast cancer samples. MSI was reported in 51% of patients with MMR deficient breast cancer. Furthermore, a prospective study observed increased MSI following chemotherapy treatment, and MSI is associated with incidence of secondary tumors.

POTENTIAL TREATMENT STRATEGIES
On the basis of clinical evidence, microsatellite stable (MSS) tumors are significantly less likely than MSI-high (MSI-H) tumors to respond to anti-PD-1 immune checkpoint inhibitors, including approved therapies nivolumab and pembrolizumab. Pembrolizumab therapy resulted in a significantly lower objective response rate (ORR) in MSS colorectal cancer (CRC) compared with MSI-H CRC (0% vs. 40%). Similarly, a clinical study of nivolumab, alone or in combination with ipilimumab, in patients with CRC reported a significantly higher response rate in patients with MSI-H tumors than those without.
On the basis of emerging clinical evidence, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-CTLA-4, anti-PD-L1, and anti-PD-1 therapies including ipilimumab, atezolizumab, avelumab, durvalumab, pembrolizumab, cemiplimab-rwlc, and nivolumab. In multiple solid tumor types, higher mutational burden has corresponded with response and improved prognosis. Pembrolizumab improved progression-free survival (14.5 vs. 3.4-3.7 months) for patients with non-small cell lung cancer (NSCLC) and higher mutational load (greater than 200 nonsynonymous mutations; hazard ratio = 0.19) compared to nonresponders (6.4 muts/Mb) and mutational load of 16 muts/Mb or higher was associated with significantly longer overall survival. In a retrospective analysis of 17 solid tumor types (comprised of 47% NSCLC, 40% mUC, and 13% encompassing 15 other solid tumors), a TMB of ≥16 muts/Mb associated with an objective response rate to atezolizumab of 30% vs. 14% for chemotherapy alone.

**FINDING SUMMARY**

Tumor mutation burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma and cigarette smoke in lung cancer and mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes. The tumor seen here harbors a low TMB. Compared to patients with tumors harboring higher TMB levels, patients with tumors harboring low TMB levels have experienced lower rates of clinical benefit from treatment with immune checkpoint inhibitors, including anti-CTLA-4 therapy in melanoma, anti-PD-L1 therapy in urothelial carcinoma, and anti-PD-1 therapy in non-small cell lung cancer and colorectal cancer.

**TUMOR MUTATIONAL BURDEN**

**CATEGORY**

TMB-Low (3 Muts/Mb)

**POTENTIAL TREATMENT STRATEGIES**

On the basis of emerging clinical evidence, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-CTLA-4, anti-PD-L1, and anti-PD-1 therapies including ipilimumab, atezolizumab, avelumab, durvalumab, pembrolizumab, cemiplimab-rwlc, and nivolumab. In multiple solid tumor types, higher mutational burden has corresponded with response and improved prognosis. Pembrolizumab improved progression-free survival (14.5 vs. 3.4-3.7 months) for patients with non-small cell lung cancer (NSCLC) and higher mutational load (greater than 200 nonsynonymous mutations; hazard ratio = 0.19) compared to nonresponders (6.4 muts/Mb) and mutational load of 16 muts/Mb or higher was associated with significantly longer overall survival. In a retrospective analysis of 17 solid tumor types (comprised of 47% NSCLC, 40% mUC, and 13% encompassing 15 other solid tumors), a TMB of ≥16 muts/Mb associated with an objective response rate to atezolizumab of 30% vs. 14% for chemotherapy alone.

**FREQUENCY & PROGNOSIS**

The Breast Invasive Carcinoma TCGA analysis reported an average (non-silent) mutation load of 0.84 mutations per megabase (muts/Mb) for Luminal A tumors, 1.98 muts/Mb for Luminal B tumors, 2.05 muts/Mb for HER2-enriched tumors, and 1.68 muts/Mb for Basal-like tumors. In estrogen receptor-positive breast cancer, increased mutation load (> mean of 1.25 muts/Mb) associated with shorter overall survival (hazard ratio [HR] of 2.02) in an analysis of the TCGA data. In another study, the number of mutated genes associated with higher tumor grade. Although the number of mutated genes did not correlate with overall survival by multivariate analysis, cases with 22 or more mutated genes had significantly worse overall survival than cases with fewer than 22 mutated genes (HR of 4.6).

**TUMOR**

**TUMOR TYPE**

Breast carcinoma (NOS)

**PATIENT**

Sample, Jane

**REPORT DATE**

01 Jan 2018
**GENE**

**ERBB2**

**ALTERATION**

amplification

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**GENE**

**PIK3CA**

**ALTERATION**

H1047R

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**FINDING SUMMARY**

ERBB2 encodes the receptor tyrosine kinase ER2, which is in the same family as EGFR. Amplification or overexpression of ERBB2 can lead to excessive proliferation and tumor formation.

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**POTENTIAL TREATMENT STRATEGIES**

On the basis of extensive clinical evidence, ERBB2 amplification or activating mutation may predict sensitivity to therapies targeting HER2, including antibodies such as trastuzumab47-52, pertuzumab in combination with trastuzumab49,53-54, and ado-trastuzumab emtansine (T-DM1)55, as well as dual EGFR/HER2 kinase inhibitors such as lapatinib56-60, afatinib52,61-65, neratinib66-71, and dacomitinib72. In patients with breast cancer, concurrent PIK3CA or PTEN alterations that activate the PI3K pathway have been associated with resistance to therapies that target HER2, including trastuzumab and lapatinib73-77. However, other studies have reported conflicting results, with one study suggesting that neither PIK3CA nor PTEN alteration is associated with trastuzumab resistance78 and another study reporting a correlation between PIK3CA mutation and increased clinical response to the combination of letrozole and lapatinib79. Clinical trials of agents aimed at preventing or overcoming resistance to anti-HER2 therapies are under way, including agents targeting the PI3K-akt pathway or HSF9080-81.

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**FREQUENCY & PROGNOSIS**

In the TCGA dataset, ERBB2 amplification was observed in 13% of breast invasive carcinoma cases65. HER2 is predicted to be overexpressed (as assessed by FISH, CNV analysis, or immunohistochemistry) in 12-25% of breast cancers80-82. The incidence of ERBB2 alterations has been found to be significantly enriched in CDH1-mutated invasive lobular breast cancers84. Phosphorylated HER2 (pHER2) was expressed in 62.6% (55/88) of HER2-positive breast cancers, and phosphoHER2 expression was associated with development of trastuzumab resistance85.

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**POTENTIAL TREATMENT STRATEGIES**

Clinical and preclinical data in various tumor types indicate that PIK3CA activating alterations may predict sensitivity to therapies targeting PI3K or AKT87-88 89. 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 temsirolimus90-95. In addition to mTOR inhibitors, PIK3CA-mutated solid tumors; similar ORR (4.3%, 1/23) and DCR (61%, 14/23) were reported for PIK3CA-wild-type, HR+/HER2-negative breast cancer 99. Combination of alpelisib with letrozole in advanced HR+/HER2-negative breast cancer achieved an ORR of 25% (4/16) and a DCR of 62% (10/16) in PIK3CA-mutant patients, and an ORR of 10% (1/10) and a DCR of 70% (7/10) in PIK3CA-wildtype patients100. The pan-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 101-102. Responses to capivasertib have also been reported in patients with PIK3CA-mutated breast cancer (3/16) in an earlier study 103. A Phase 1 trial of the dual PI3K/mTOR kinase inhibitor apitolisib reported disease control in 79% (14/16) of patients with PIK3CA-mutated advanced solid tumors at the recommended Phase 2 dose (3/14 PRs, 8/ 14 SDs)104. Activating mutations in PIK3CA may confer resistance to HER2-targeted therapies; combined inhibition of HER2 and the PI3K pathway may be required in tumors with ERBB2 amplification and PIK3CA mutation105-107.

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**FREQUENCY & PROGNOSIS**

Mutations in PIK3CA have been reported in 25-40% of breast cancer cases80-81. Mutations in exon 20 (H1047R) of PIK3CA have been associated with a better prognosis than mutations occurring in exon 9 (E542K, E545K)112.

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**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 survival113-114. PIK3CA alterations that have been characterized as activating, such as observed here, are predicted to be oncogenic115-116.
**GENE**  
**CDK12**  
**ALTERATION**  
rearrangement exon 5  

**POTENTIAL TREATMENT STRATEGIES**  
Preclinical studies suggest that CDK12 truncations and inactivating mutations that affect the kinase domain (amino acids 719-1051) impair homologous recombination and sensitize cells to PARP inhibitors. PARP inhibitors have been shown to be an effective treatment for ovarian, breast, pancreatic, and prostate tumors with BRCA1/2 alterations, indicating that this approach may be relevant for tumors with defects in homologous recombination. Although CDK12 amplification has also been reported in several cancer types, it is unlikely that PARP inhibitors would be relevant in tumors with CDK12 amplification.

**FREQUENCY & PROGNOSIS**  
Homozygous mutations in CDK12 have been identified in approximately 3% of ovarian carcinomas, supporting a role for CDK12 as a tumor suppressor in this tumor type. CDK12 rearrangements resulting in truncation have also been reported in 15% of HER2-positive breast cancers and CDK12-ERBB2 fusions leading to truncation of CDK12 have been identified in gastric cancers.

**GENE**  
**CCNE1**  
**ALTERATION**  
amplification  

**POTENTIAL TREATMENT STRATEGIES**  
There are no approved therapies that directly target CCNE1 alterations. Because amplification or overexpression of CCNE1 leads to increased genomic instability through the ATR-CHK1 pathway, clinical studies have investigated inhibitors of CHK1, ATR, and CDK2 as potential therapeutic approaches for tumors with CCNE1 activation. Clinical benefit has been reported for patients with recurrent high-grade ovarian carcinoma with CCNE1 amplification or expression in response to treatment with the CHK1 inhibitor prexasertib. Preclinical studies have demonstrated that cell lines with CCNE1 amplification or overexpression were sensitive to inhibitors of ATR (G1S) or CDK213. However, other studies have shown that sensitivity of various cell lines to CDK2 inhibitors, including SNS-052, dinaciclib, and seliciclib, at clinically achievable doses, is largely independent of CCNE1 copy number or expression. One study has reported a reduction in tumor cell number in lung and esophageal cancer cases following treatment with the HDAC inhibitor vorinostat, paralleling findings from a CCNE1-driven mouse model of lung cancer, where vorinostat treatment led to tumor reduction and a decrease in CCNE1 levels. CCNE1 amplification has been linked to inferior clinical benefit rate and progression-free survival in patients with HER2-positive breast cancer who were treated with trastuzumab and has also been implicated in resistance to platinum-based therapies in patients with ovarian carcinoma. CCNE1 amplification correlates with inferior survival in this population. CCNE1 amplification has been linked to resistance to CDK4/6 inhibition. Furthermore, a retrospective analysis of a study evaluating palbociclib in combination with fulvestrant in patients with breast cancer has reported that CCNE1 gene overexpression correlated with resistance to CDK4/6 inhibition. Another study has identified two patients with CCNE1-amplified breast cancer who progressed on the CDK4/6 inhibitor abemaciclib.

**FREQUENCY & PROGNOSIS**  
In the Breast Invasive Carcinoma TCGA dataset, putative high-level amplification of CCNE1 has been reported in 2.8% of cases. An analysis of HER2-positive breast cancer samples found CCNE1 amplification in 28-35% of patients. However, a separate study reported that CCNE1 gene overexpression occurred mainly in basal-like breast cancer, whereas overexpression of CCNE2 was associated with HER2-positive and luminal B breast cancer subtypes. CCNE1 amplification and cyclin E1 overexpression have been correlated with poor prognosis in patients with breast cancer.
POTENTIAL TREATMENT STRATEGIES
Several approaches for inhibiting NOTCH3 signaling are being developed, including neutralizing NOTCH antibodies such as OMP-59R5, which targets NOTCH2 and NOTCH3, and pan-NOTCH inhibitors, such as gamma-secretase inhibitors (GSIs)176-178. A Phase 1b study of OMP-59R5 in combination with gemcitabine and nab-paclitaxel has shown promising efficacy (up to 50% partial response) in patients with untreated metastatic pancreatic cancer179. Preliminary results from a Phase 1b study of OMP-59R5 in combination with etoposide and cisplatin has shown promising efficacy in small cell lung cancer180. The GSI BMS-966245 inhibits NOTCH activity in vitro and exhibits anti-tumor activity in xenograft models of leukemia and triple negative breast cancer harboring NOTCH1 and NOTCH3 activating mutations or overexpression181. These agents are being investigated in preclinical studies and early clinical trials in various tumor types182. While activating mutations may be targeted via gamma-secretase inhibitors, there are currently no therapies available to address NOTCH3 inactivation.

FREQUENCY & PROGNOSIS
In the TCGA dataset, NOTCH3 mutation was observed in fewer than 1% of breast invasive carcinoma cases; homozygous deletion was not observed in any of 778 cases but amplification was observed in 2% of cases. NOTCH3 amplification and/or overexpression has been infrequently (<3%) reported in breast carcinoma, with amplification not always correlating with overexpression183-185. However, NOTCH3 expression was noted in 9/34 (26.5%) HER2-negative breast cancers compared to 0/14 of HER2-positive tumors186. In cell-based and xenograft breast cancer models, NOTCH3 signaling has been reported to facilitate cell proliferation, invasion, and tumor growth176,184,187-188.

FINDING SUMMARY
NOTCH3 encodes a member of the NOTCH family of receptors, which are involved in cell fate determination and various developmental processes. Upon binding of membrane-bound ligands, NOTCH signaling involves cleavage of the Notch intracellular domain (NICD), which subsequently forms part of a transcription factor complex that regulates downstream genes. Inhibitors of NOTCH3 signaling are being developed, including small molecule inhibitors, gamma-secretase inhibitors, and NOTCH3-specific antibodies. Clinical trials of these agents are under way in various solid tumors, with promising efficacy in small cell lung cancer and breast cancer187-188. However, NOTCH3 mutation is more frequent in rare disease Li-Fraumeni syndrome and the frequent mutational hotspots in NOTCH3 are also observed in breast cancer189-193. Mutations in NOTCH3 are associated with overexpression181.

TP53 mutation is also implicated in breast cancer susceptibility, as TP53 mutation carriers have a 18-60 fold increased risk for early onset breast cancer193. TP53 mutation is also associated with aggressive disease, including poor prognosis in patients with breast cancer193-195. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:2,000 to 1:20,000, and are lower than the prevalence of TP53 mutations in breast cancer195.

FINDING SUMMARY
Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers196. 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 tumorigenesis177-179. Germline mutations in TP53 are associated with the very rare disorder Li-Fraumeni syndrome and the early onset of many cancers198-201. Germline mutations in TP53 are associated with the very rare disorder Li-Fraumeni syndrome and the early onset of many cancers198-201. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:1,000 to 1:10,000197, and in the appropriate clinical context, germline testing of TP53 is recommended.
Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate that targets the protein ERBB2/HER2 on the cell surface, which inhibits HER2 signaling227-228; it also releases the cytotoxic therapy DM1 into cells, leading to cell death228-229. T-DM1 is FDA approved to treat patients with HER2-positive (HER2+) metastatic breast cancer and disease progression on prior therapy.

ERBB2 amplification or activating mutations may predict sensitivity to T-DM1. A patient with non-small cell lung cancer, disease progression on two prior lines of chemotherapy, and an activating ERBB2 exon 20 insertion mutation (A775_G776insYVMA) with concurrent ERBB2 amplification experienced a rapid and durable response to T-DM1230-231. A heavily pretreated patient with metastatic salivary duct ex pleomorphic carcinoma and ERBB2 amplification achieved tumor reduction of 70%, and a partial response ongoing for 36 weeks, following treatment with T-DM1232.

Although a Phase 2 study reported improved median progression-free survival (PFS) for patients with HER2+ advanced breast cancer treated in the first line with TDM1 as compared with trastuzumab plus docetaxel (14.2 months vs. 9.2 months, hazard ratio of 0.59)233, the Phase 3 MARIANNE study reported no significant differences in overall response rate (ORR; 60%, 64%, and 68%) or median PFS (14.1, 15.4, and 13.7 months) when comparing T-DM1 combined with placebo, T-DM1 with pertuzumab, and trastuzumab with taxane, respectively, in this same setting234. For patients with HER2+ breast cancer previously treated with HER2-directed therapies, Phase 3 trials of single-agent T-DM1 have reported significant increases in median PFS as compared with physician's choice of therapy (6.2 vs. 3.3 months)235 or lapatinib plus capecitabine (9.6 vs. 6.4 months)55,236-237. These results are comparable to previous Phase 2 studies in patients with HER2+ metastatic breast cancer (MBC) previously treated with HER2-directed therapies with or without chemotherapy238-239; although another Phase 2 study reported a lower response rate for T-DM1 after trastuzumab and pertuzumab, one-third of patients received therapy for more than 6 months, thereby suggesting some clinical benefit.40 Treatment of MBC with T-DM1 in combination with docetaxel was reported to achieve an ORR of 80% and median PFS of 13.8 months241. A similar study of T-DM1 combined with paclitaxel and pertuzumab reported an ORR of 54.4%242. Patients with newly diagnosed HER2+ locally advanced breast cancer treated with T-DM1 plus docetaxel and with or without pertuzumab achieved pathologic complete response rates of 60.6% and 60.0%, respectively243. Treatment of MBC with T-DM1 in combination with the PI3Kalpha inhibitor alpelisib for patients with HER2+ MBC reported a median PFS of 5.6 and 9.8 months for those with or without prior T-DM1 monotherapy treatment243. Patients with HER2+ MBC and active central nervous system (CNS) metastases treated with T-DM1 achieved an ORR of 40% (4/10); there was no significant difference in OS between patients with and without CNS metastases244. A retrospective study of patients with breast cancer and brain metastases treated with T-DM1, chemotherapy, and radiotherapy reported 44% (17/39) partial responses, 15% (6/39) stable disease, and a median PFS of 6.1 months245.
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 nonfunctional 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 clinical90-91,94 and preclinical95 evidence in multiple tumor types, PIK3CA activation may predict sensitivity to mTOR inhibitors such as everolimus.

**SUPPORTING DATA**

In an exploratory cohort of the BOLERO-2 Phase 3 study, the addition of exemestane to everolimus in the first line for hormone receptor-positive (HR+), HER2-negative breast cancer was shown to improve the median PFS compared to exemestane alone (11.5 vs. 4.1 months, HR = 0.39) 246. 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)247-249, and modestly improved the median PFS compared with everolimus alone in BOLERO-6 (8.4 vs. 6.8 months, HR = 0.74) 250. Analysis of cell-free DNA revealed a similar benefit for patients with mutant or wild-type PIK3CA (HR = 0.37 vs. 0.43) 96. Clinical studies for patients with HR+ breast cancer indicate that everolimus may potentiate letrozole or tamoxifen efficacy and can be safely combined with anastrozole251-253. Two Phase 3 trials have evaluated whether the addition of everolimus would circumvent or overcome resistance of HER2-positive (HER2+) breast cancer to trastuzumab-based therapy. As first-line treatment for patients with HER2+ breast cancer, everolimus combined with trastuzumab plus paclitaxel did not significantly improve median PFS in the full study population (15.0 months with everolimus vs. 14.5 months with placebo), but increased PFS in the HR-negative subpopulation (203 vs. 13.1 months) 254. 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) 255. Follow-up exploratory analysis in patients with PIK3CA alterations showed longer median PFS from addition of everolimus to trastuzumab plus either paclitaxel (12.0 vs. 7.6 months) or vinorelbine (6.9 vs. 5.7 months), compared with the addition of placebo to trastuzumab plus either paclitaxel or vinorelbine (HR = 0.69)256. Low PTEN expression or PTEN loss also was significantly associated with benefit from added everolimus in the combined analysis of both studies (HR = 0.50), whereas PIK3CA mutation was significantly associated with benefit in HR-negative (HR = 0.43) but not HR+ disease (HR = 0.93)256. For patients with metastatic triple-negative breast cancer, everolimus plus carboplatin achieved a clinical benefit rate of 36% (9/ 25)257. A Phase 1b trial of a combination of everolimus and the MEK inhibitor trametinib in patients with solid tumors reported frequent adverse events, and the study was unable to identify a recommended Phase 2 dose and schedule for the combination258.
Lapatinib is a tyrosine kinase inhibitor that targets EGFR, ERBB2/HER2, and to a lesser degree, ERBB4. It is FDA approved in combination with capecitabine or letrozole for the treatment of HER2-overexpressing (HER2+) metastatic breast cancer.

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

Lapatinib as a treatment for HER2+ breast cancer has primarily been investigated in combination with other chemotherapeutic agents, and these combination regimens have been shown to extend progression-free survival (PFS) and reduce metastases, as well as to extend overall survival (OS) in some instances. As first-line therapy for HER2+ metastatic breast cancer, lapatinib plus taxane resulted in shorter median PFS compared with trastuzumab plus taxane (9.0 vs. 11.3 months). For patients who have progressed on trastuzumab plus taxane, ado-trastuzumab emtansine (T-DM1) was superior to lapatinib plus capecitabine (OS of 30.9 vs. 25.1 months). Addition of lapatinib to capecitabine had improved PFS compared with capecitabine monotherapy (8.4 vs. 4.4 months) in this setting. Lapatinib plus capecitabine has been reported to reduce the number of newly developed brain metastases and to be active against existing brain metastases (objective central nervous system [CNS] response rate of 66% [29/44]). However, the incidence of CNS metastases was not significantly different with lapatinib plus capecitabine versus trastuzumab plus capecitabine (3% vs. 5%). CNS disease progression rates were similar for treatment with T-DM1 and with lapatinib plus capecitabine. Phase 2 and 3 trials comparing the efficacy of lapatinib and trastuzumab for the treatment of HER2+ breast cancer in the neoadjuvant setting reported conflicting results, with the combination of lapatinib and trastuzumab generally achieving slightly higher response rates.

SUPPORTING DATA
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**AREAS OF THERAPEUTIC USE**
Lapatinib has been approved by the FDA for the treatment of HER2+ metastatic breast cancer. It is used in combination with capecitabine or letrozole for the treatment of HER2+ breast cancer.

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

**SUPPORTING DATA**
Lapatinib is a tyrosine kinase inhibitor that targets EGFR, ERBB2/HER2, and to a lesser degree, ERBB4. It is FDA approved in combination with capecitabine or letrozole for the treatment of HER2-overexpressing (HER2+) metastatic breast cancer.

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

**AREAS OF THERAPEUTIC USE**
Neratinib is an irreversible tyrosine kinase inhibitor that targets EGFR, ERBB2/HER2, and ERBB4. It is FDA approved for the extended adjuvant treatment of early stage HER2-positive breast cancer following adjuvant trastuzumab.

**GENE ASSOCIATION**
On the basis of extensive clinical67-70,273 and preclinical274-278 evidence, ERBB2 amplification or activating mutations may confer sensitivity to neratinib.

**SUPPORTING DATA**
In a Phase 3 study for patients with early stage HER2-positive (HER2+) breast cancer previously treated with trastuzumab, adjuvant neratinib significantly improved the two-year invasive disease-free survival (iDFS) compared with placebo (94% vs. 92%; hazard ratio, HR, of 0.67)69. The significant iDFS benefit persisted at 5 years of follow up (90% for neratinib vs. 88% for placebo, HR= 0.73)279, including for patients who were also hormone receptor-positive (HR+)280; however, the improvement was seen only for those patients who were randomized to neratinib within 12 months of prior trastuzumab treatment281. For patients with advanced HER2+ breast cancer previously treated with trastuzumab, neratinib resulted in a progression-free survival (PFS) of 22.3 weeks; for those with no prior trastuzumab treatment, PFS of 39.6 weeks was observed71. In Phase 2 trials for patients with ERBB2-mutated, nonamplified, metastatic breast cancer (MBC), a clinical benefit rate (CBR) of 31—40% and median PFS of 3.5—4 months were achieved with neratinib68,282. For patients with breast cancer and HER2+ brain metastases treated with neratinib, the central nervous system (CNS) objective response rate (ORR) was 8% (3/40)283. The therapeutic efficacy of neratinib in combination with other targeted or chemotherapies is also under investigation. Preliminary data from a Phase 2 trial of patients with ERBB2-mutated, ER-positive MBC treated with neratinib plus fulvestrant reported an ORR of 55% (including 2 complete responses and 4 partial responses)284. In a Phase 2 study for patients with HER2+ MBC previously treated with trastuzumab, the ORR was 63%285. For this population, PFS with neratinib plus capecitabine was 4.5 months, compared to 6.8 months with lapatinib plus capecitabine286. Neratinib plus paclitaxel resulted in an ORR of 73% for patients with HER+ MBC,287. Neratinib and vinorelbine resulted in a higher ORR for patients who were lapatinib-naive (41%) as compared with those patients who had prior lapatinib (8%)288. In a Phase 1 study of neratinib with trastuzumab and paclitaxel for patients with HER2+ MBC, an ORR of 38% and a CBR of 52% was reported289. As first-line therapy in HER2+ MBC, PFS or ORR did not significantly differ with neratinib plus paclitaxel compared with trastuzumab plus paclitaxel; however, patients treated with neratinib had a lower incidence of CNS recurrences290. As neoadjuvant treatment in HER2+, HR-negative breast cancer, the pathologic complete response rate was 56% with neratinib plus paclitaxel as compared with 33% with trastuzumab plus paclitaxel270.
Pertuzumab

**AREAS OF THERAPEUTIC USE**

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

**GENE ASSOCIATION**

On the basis of clinical studies in multiple tumor types, ERBB2 amplification or activating mutations may predict sensitivity to pertuzumab.

**SUPPORTING DATA**

In the APHINITY trial, addition of pertuzumab to chemotherapy plus trastuzumab as adjuvant treatment for patients with HER2+ early stage breast cancer improved the estimated 3-year rate of invasive disease-free survival compared with placebo (94.1% vs. 93.2%), with greater improvement seen for patients with node-negative (92.0% vs. 90.2%, hazard ratio (HR) = 0.77) than those with node-negative (97.5% vs. 98.4%, HR = 1.13) disease. The CLEOPATRA Phase 3 randomized trial for patients with HER2+ metastatic breast cancer (MBC) reported that, compared to placebo, addition of pertuzumab to first-line trastuzumab and docetaxel demonstrated a significant improvement in progression-free survival (PFS; 12.4 vs. 18.7 months) and in median overall survival (OS; 40.8 vs. 56.5 months).

A Phase 2 study in patients with locally advanced breast cancer (LABC) or HER2+ early stage breast cancer with various combinations of pertuzumab, trastuzumab, and docetaxel reported the greatest benefit when using neoadjuvant pertuzumab combined with trastuzumab and docetaxel (5-year PFS rate of 84.29% vs. 70.45%). In the KRISTINE Phase 3 trial, patients with HER2+ stage II-III breast cancer treated in the neoadjuvant setting with trastuzumab emtansine plus pertuzumab showed a reduced number of pathological complete responses (44.4%) compared with traditional trastuzumab, pertuzumab, and chemotherapy (55.7%), although more Grade 3-4 and serious adverse events occurred in the chemotherapy plus trastuzumab and pertuzumab group. A study of pertuzumab combined with paclitaxel and ado-trastuzumab emtansine reported an overall response rate of 52.4% in patients with previously treated HER2+ MBC or LABC. In a Phase 3 study of patients with HER2+ MBC failing on first-line trastuzumab, addition of pertuzumab to trastuzumab and capecitabine was reported to increase median PFS (11.1 vs. 9.0 months) and OS (36.1 vs. 28.1 months) when compared with placebo plus capecitabine. A trial of 12 patients with HER2+ MBC progressing on pertuzumab plus trastuzumab reported 1 complete response (CR), 1 partial response (PR), and 5 stable diseases (SD) after treatment with a combination of pertuzumab, trastuzumab, and gemcitabine. A Phase 1 trial of salvage therapy with a combination of pertuzumab, trastuzumab, and gemcitabine for 6 patients with HER2+ MBC after progression on trastuzumab reported 1 PR, 4 SD, 1 progressive disease, and a median PFS of 3.8 months.
**Trastuzumab**

**AREAS OF THERAPEUTIC USE**

Trastuzumab is a monoclonal antibody that targets the protein ERBB2/HER2. It is FDA approved as monotherapy and in combination with other therapies for HER2-positive (HER2+) metastatic and early breast carcinoma and in combination with chemotherapy for HER2+ metastatic gastric or gastroesophageal adenocarcinoma.

**GENE ASSOCIATION**

On the basis of clinical studies in multiple tumor types, ERBB2 amplification, overexpression, or activating mutations may confer sensitivity to trastuzumab.

**SUPPORTING DATA**

Trastuzumab has been approved for breast cancer based on a Phase 3 randomized clinical trial comparing treatment with trastuzumab and chemotherapy to treatment with chemotherapy alone, which showed that the addition of trastuzumab was associated with significant improvements in time to progression, objective response rate, response duration, and overall survival. A subsequent Phase 3 study of patients with HER2-positive (HER2+) breast cancer reported 3-year event-free survival in 58% of patients treated with trastuzumab plus neoadjuvant therapy, compared to 43% in patients treated with neoadjuvant therapy alone. Long-term follow-up Phase 2 analysis reported a 5-year distant disease-free survival rate of 92% in patients with HER2+ breast cancer treated with dose-dense chemotherapy and trastuzumab and 89% in patients treated with lapatinib and dose-dense chemotherapy. In one study of patients with early breast cancer treated with neoadjuvant trastuzumab, higher ERBB2 copy number (HER2/CEP17 ratio >6) correlated with increased incidence of pathologic complete response compared to lower ERBB2 copy number. A Phase 3 trial of patients with HER2+ breast cancer treated with lapatinib, trastuzumab, or a combination of the two, reported 3-year event-free survival rates of 78%, 76%, and 84%, and 3-year overall survival rates of 93%, 90%, and 95%, respectively. Trastuzumab is also approved in combination with pertuzumab and docetaxel for the first-line treatment of metastatic HER2+ breast cancer. Two Phase 3 studies have evaluated whether addition of the mTOR inhibitor everolimus would circumvent or overcome resistance of HER2-positive breast cancer to trastuzumab-based therapy. As first-line treatment for patients with HER2-positive breast cancer, everolimus combined with trastuzumab plus paclitaxel did not significantly improve median progression-free survival (PFS) in the full study population (15.0 months with everolimus vs. 14.5 months with placebo) but increased PFS in the hormone receptor-negative subpopulation by 7.2 months (20.3 months vs. 13.1 months). For patients with trastuzumab-resistant HER2-positive breast cancer, the addition of everolimus to trastuzumab plus vinorelbine prolonged median PFS (7.0 vs. 5.8 months). Follow-up exploratory analysis of these studies showed that patients with PIK3CA alterations achieved extended median PFS with everolimus compared to placebo (hazard ratio [HR] = 0.69), when combined with trastuzumab plus paclitaxel (12.0 vs. 7.6 months) or vinorelbine (6.9 vs. 5.7 months). Low PTEN expression or PTEN loss also significantly associated with benefit from added everolimus in the combined analysis of both studies (HR = 0.50).

**Trastuzumab-dkst**

**AREAS OF THERAPEUTIC USE**

Trastuzumab-dkst is FDA approved as a biosimilar therapy to trastuzumab. Trastuzumab-dkst is a monoclonal antibody that targets the protein ERBB2/HER2, and is FDA approved as monotherapy and in combination with chemotherapy for HER2-positive (HER2+) metastatic and early breast carcinoma and in combination with chemotherapy for HER2+ metastatic gastric or gastroesophageal junction adenocarcinoma.

**GENE ASSOCIATION**

On the basis of clinical studies in multiple tumor types, ERBB2 amplification, overexpression, or activating mutations may confer sensitivity to anti-HER2 therapies such as trastuzumab-dkst.

In patients with HER2+ metastatic breast cancer, first-line trastuzumab-dkst with taxane elicited an objective response rate of 69.6%.

**SUPPORTING DATA**

The Phase 3 Heritage study demonstrated comparable 24-week objective response rates (69.6% vs. 64.9%) and progression-free survival for patients with treatment-naive HER2+ metastatic breast cancer treated with either trastuzumab-dkst or trastuzumab in combination with taxane. In both patients with HER2+ breast cancer and in healthy adults, trastuzumab-dkst demonstrated comparable pharmacokinetic, safety, and immunomodulation profiles to trastuzumab.
Afatinib

**AREAS OF THERAPEUTIC USE**
Afatinib is an irreversible kinase inhibitor that targets the kinase domains of EGFR, ERBB2/HER2, and ERBB4. It is FDA approved for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) and non-resistant EGFR mutations and for the treatment of patients with metastatic, squamous NSCLC after progression on platinum-based chemotherapy.

**GENE ASSOCIATION**
ERBB2 amplification or activating mutations may indicate sensitivity to afatinib on the basis of clinical evidence in various solid tumors.

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

**Dacomitinib**

**AREAS OF THERAPEUTIC USE**
Dacomitinib is a second generation irreversible tyrosine kinase inhibitor that targets the kinase domains of EGFR, ERBB2/HER2, and ERBB4/HER4. It is FDA approved for the first-line treatment of patients with metastatic nonsmall cell lung cancer (NSCLC) with EGFR exon 19 deletion or exon 21 L858R substitution mutations.

**GENE ASSOCIATION**
ERBB2 amplification or activating mutations may indicate sensitivity to dacomitinib.

**SUPPORTING DATA**
Investigations into the efficacy of dacomitinib have primarily been in the context of non-small cell lung cancer (NSCLC). Patients with EGFR-mutant NSCLC treated with dacomitinib exhibited significant improvement in OS compared with gefitinib treatment (median OS, 34.1 vs. 26.8 months). A Phase 2 study of dacomitinib in patients with advanced penile squamous cell carcinoma (SCC) reported an ORR of 32% (1 CR, 8 PR), including a 100% DCR (1 CR, 1 PR, 2 SD) in four patients with EGFR amplification. A Phase 2 study of dacomitinib in patients with recurrent or metastatic head and neck SCC reported clinical benefit (defined as PFS>4 months) in 13/31 (42%) of patients. Studies of dacomitinib in esophageal and cutaneous SCC reported RRs of 12-15% (6/48 and 28.6% (12/42), respectively, but high DCRs of 73% and 86%, respectively. On the other hand, trials of dacomitinib in heavily pretreated patients with HER2+ gastric cancer reported RRs of fewer than 10% and DCRs of fewer than 50%. A Phase 2 study in HER2+ gastric cancer reported RRs of 12-15% in EGFR-amplified gastric cancer.
**Temsirolimus**

**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 and preclinical 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%) and 7/23 (30%) were reported in patients with PIK3CA-mutant tumors.

**SUPPORTING DATA**

A Phase 1 trial examining the combination of temsirolimus, liposomal doxorubicin, and bevacizumab in 74 patients with breast and gynecological malignancies reported that 37.9% of patients experienced either a complete response (1.4%), partial response (18.9%), or stable disease (17.6%); among 25 patients with PIK3CA mutation or PTEN loss, 52% experienced a complete or partial response (36%) or stable disease (16%).

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. 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. Another 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 progression-free survival as a first-line therapy.

A study examining the efficacy of temsirolimus-involving regimens in 24 patients with mesenchymal/metaplastic breast cancer (MpBCs) reported 2 complete responses, 4 partial responses, 2 instances of stable disease longer than 6 months, and 4 instances of stable disease shorter than 6 months.

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

#### NCT02614794

**Phase 2 Randomized, Double-Blinded, Controlled Study of Tucatinib vs Placebo in Combination With Capecitabine and Trastuzumab in Patients With Pretreated Unresectable Locally Advanced or Metastatic HER2+ Breast Carcinoma (HER2CLIMB)**

**TARGETS**

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**LOCATIONS:**

- Missouri, Wisconsin, Santiago de Compostela (Spain), Tennessee, Palma (Spain), Offenbach (Germany), New Jersey, Sutton (United Kingdom), Brussels (Belgium), Colchester (United Kingdom), Halle (Germany), Málaga (Spain), Lyon (France), Peterborough (United Kingdom), Louisiana, Cáceres (Spain), London (United Kingdom), Toulouse (France), Texas, Namur (Belgium), District of Columbia, Minnesota, Hannover (Germany), Linz (Austria), Indiana, Koeln (Germany), Nedlands (Australia), Essen (Germany), Connecticut, Libramont (Belgium), Sydney (Australia), Grenoble (France), Heidelberg (Australia), Capri (Italy), Zaragoza (Spain), Washington, Paris (France), Salzburg (Austria), Saskatoon (Canada), Marseille (France), Jerusalem (Israel), St. John’s (Canada), Alabama, Aalborg (Denmark), Berlin (Germany), Hradec Králové (Czechia), Michigan, Cremona (Italy), Halifax (Canada), Be’er Sheva (Israel), Toronto (Canada), Munich (Germany), Montreal (Canada), Pierre-Bénite (France), Koblenz (Germany), Kiel (Germany), Oregon, Illinois, Nottingham (United Kingdom), Reims (France), Edmonton (Canada), Copenhagen (Denmark), Maryland, Sheffield (United Kingdom), Hamburg (Germany), Rechovot (Israel), Kansas, Virginia, North Carolina, New York, Braschaat (Belgium), New Hampshire, Bologna (Italy), Northwood (United Kingdom), Rennes (France), Strasbourg (France), Pennsylvania, Le Mans (France), Regina (Canada), Besançon (France), Massachusetts, Tel Aviv (Israel), León (Spain), Tours (France), Herlev (Denmark), Madrid (Spain), Barcelona (Spain), Mons (Belgium), Truro (United Kingdom), Milan (Italy), Melbourne (Australia), South Carolina, St. Albans (Australia), Pardubice (Czechia), Manchester (United Kingdom), Georgia, Haifa (Israel), South Brisbane (Australia), Freiburg (Germany), Valencia (Spain), Colorado, Düsseldorf (Germany), Québec (Canada), Kfar Saba (Israel), Lisboa (Portugal), Nantes (France), Graz (Austria), Prague (Czechia), Vejle (Denmark), Malvern (Australia), Ohio, Innsbruck (Austria), Arizona, Odense (Denmark), Florida, Westmead (Australia), Charleroi (Belgium), Nebraska, California

#### NCT02400476

**An Open-Label Study to Characterize the Incidence and Severity of Diarrhea in Patients With Early-Stage HER2+ Breast Cancer Treated With Neratinib and Intensive Loperamide Prophylaxis**

**TARGETS**

| EGFR, ERBB2, ERBB4 |

**LOCATIONS:**

- Virginia, Missouri, Pennsylvania, Nedlands (Australia), Maryland, Kentucky, Madrid (Spain), Texas, Illinois, Utah, Mississippi, Florida, Oregon, Georgia, Kurralta Park (Australia), New Jersey, South Carolina, Maine, Nebraska, Sevilla (Spain), New York, Montreal (Canada), California, Wahroonga (Australia), Toronto (Canada)

#### NCT01920061

**A Phase I/II Open-label Three-arm Multi-center Study To Assess The Safety And Tolerability Of PFI-05212384 (pi3k/Mtor Inhibitor) In Combination With Other Anti-tumor Agents**

**TARGETS**

| EGFR, mTORC1, ERBB2, PI3K-gamma, mTORC2, PI3K-alpha, ERBB4 |

**LOCATIONS:**

- London (United Kingdom), Massachusetts, South Carolina, California, Milan (Italy), Vancouver (Canada), Pennsylvania, Toronto (Canada), Barcelona (Spain), Michigan, Roma (Italy)
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<td>Targeted Agent and Profiling Utilization Registry (TAPUR) Study</td>
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<td>Phase II Prospective Open Label Study of Pertuzumab, Trastuzumab, and Nab-Paclitaxel in Patients With HER-2 Positive Advanced Breast Cancer</td>
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<td>A Phase 2 Study of Pzoziotinib in Patients With HER2-Positive Metastatic Breast Cancer (MBC) Who Have Received Prior HER2 Regimens for MBC</td>
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<td>A Phase 1b Study of Pzoziotinib in Combination With T-DM1 in Women With Advanced or Metastatic HER2-Positive Breast Cancer</td>
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PIK3CA activating mutations or amplification may lead to activation of the PI3K-AKT-mTOR pathway, and may therefore indicate sensitivity to inhibitors of PI3K, AKT, and/or mTOR. Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the trial website clinicaltrials.gov using keyword terms such as "PI3K", "mTOR", "AKT", "everolimus", "temsirolimus", "copanlisib", "breast carcinoma", "solid tumor", and/or "advanced cancer".

### NCT01920061
**A Phase 1b Open-label Three-arm Multi-center Study To Assess The Safety And Tolerability Of PF-05212384 (pi3k/Mtor Inhibitor) In Combination With Other Anti-tumor Agents**

**TARGETS**
EGFR, mTORC1, ERBB2, PI3K-gamma, mTORC2, PI3K-alpha, ERBB4

**LOCATIONS:**
London (United Kingdom), Massachusetts, South Carolina, California, Milan (Italy), Vancouver (Canada), Pennsylvania, Toronto (Canada), Barcelona (Spain), Michigan, Roma (Italy)

### NCT01226316
**A Phase I, Open-label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumour Activity of Ascending Doses of AZD5363 Under Adaptable Dosing Schedules in Patients With Advanced Solid Malignancies.**

**TARGETS**
AKTs

**LOCATIONS:**
Milano (Italy), København Ø (Denmark), Amsterdam (Netherlands), Oklahoma, Napoli (Italy), Connecticut, Kashiwa (Japan), París Cedex 5 (France), Barcelona (Spain), California, Sapporo-shi (Japan), Pierre Benite Cedex (France), Chuo-ku (Japan), Koto-ku (Japan), Tennessee, Valencia (Spain), Montreal (Canada), Prato (Italy), Colorado, Toronto (Canada), París (France), Madrid (Spain), Vancouver (Canada), South Carolina, New York, Texas, Singapore (Singapore), Pennsylvania

### NCT02734615
**A Phase I/ib, Open label Study of LSZ102 Single Agent and LSZ102 in Combination With Either LEE011 (LSZ102 + LEE011) or BYL719 (LSZ102 + BYL719) in Patients With Advanced or Metastatic ER+ Breast Cancer Who Have Progressed After Endocrine Therapy**

**TARGETS**
CDK4, ER, PI3K-alpha, CDK6

**LOCATIONS:**
Barcelona (Spain), Maryland, Bruxelles (Belgium), Koto-ku (Japan), Lyon Cedex (France), Milano (Italy), Singapore (Singapore), Massachusetts, Texas, Toronto (Canada), New York

### NCT02719691
**A Phase Ib Study of the Combination of MLN0128 (Dual TORC1/2 Inhibitor) and MLN8237 (Aurora A Inhibitor, Alisertib) in Patients With Advanced Solid Tumors With an Expansion Cohort in Metastatic Triple-negative Breast Cancer (TNBC)**

**TARGETS**
Aurora kinase A, mTORC1, mTORC2

**LOCATIONS:**
Colorado

### NCT02124148
**A Phase 1b Trial of LY2606368 in Combination With Chemotherapy or Targeted Agents in Advanced and/or Metastatic Tumors**

**TARGETS**
PI3K, EGFR, DNA-PK, mTOR, CHK1

**LOCATIONS:**
Texas, Oklahoma, Florida, Tennessee

### NCT02476955
**An Open-label Phase 1b Study of ARQ 092 in Combination With Carboplatin Plus Paclitaxel, in Combination With Paclitaxel, or in Combination With Anastrozole in Subjects With Selected Solid Tumors**

**TARGETS**
AKTs, Aromatase

**LOCATIONS:**
New York, Michigan, Texas
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<tr>
<td>A Phase 1 Dose Escalation Study of ARQ 751 in Adult Subjects With Advanced Solid Tumors With AKT1, 2, 3 Genetic Alterations, Activating PI3K Mutations or PTEN-null</td>
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**LOCATIONS:** Texas, Tennessee
CDK12

rearrangement exon 5

Tumors with CDK12 mutation or loss may be sensitive to PARP inhibitors. Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the trial website clinicaltrials.gov using keyword terms such as "CDK12", "PARP", "olaparib", "rucaparib", "BMN 673", "ABT-888", "veliparib", "E7449", "niraparib", "breast carcinoma", "solid tumor", and/or "advanced cancer".

**NCT02921919**
A Single-arm, Open-label, Multicenter, Extended Treatment, Safety Study In Patients Treated With Talazoparib

**PHASE 2**

**TARGETS**
PARP

**LOCATIONS:** New Jersey, Michigan, Warszawa (Poland), Hamilton (Canada), Budapest (Hungary), Moscow (Russian Federation), Florida, Indiana, Edmonton (Canada), Sutton (United Kingdom), Chisinau (Moldova, Republic of), Saint-Petersburg (Russian Federation), Montreal (Canada), California, Texas

**NCT02264678**
A Modular Phase I, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumour Activity of AZD6738 in Combination With Cytotoxic Chemotherapy and/or DNA Damage Repair/Novel Anti-cancer Agents in Patients With Advanced Solid Malignancies.

**PHASE 1 / 2**

**TARGETS**
PARP, PD-L1, ATR

**LOCATIONS:** Villejuif (France), London (United Kingdom), New York, Seongnam-si (Korea, Republic of), Saint Herblain (France), Cambridge (United Kingdom), Sutton (United Kingdom), California, Manchester (United Kingdom), Seoul (Korea, Republic of)

**NCT02511795**
A Phase Ib Study of AZD1775 and Olaparib in Patients With Refractory Solid Tumours

**PHASE 1**

**TARGETS**
PARP, WEE1

**LOCATIONS:** New York, Florida, Texas, Tennessee, Toronto (Canada), Colorado

**NCT02997163**
A Phase I Open-label Pharmacokinetics And Safety Study Of Talazoparib (mdv3800) In Patients With Advanced Solid Tumors And Normal Or Varying Degrees Of Renal Impairment

**PHASE 1**

**TARGETS**
PARP

**LOCATIONS:** Indiana, Montreal (Canada), Hamilton (Canada), Massachusetts, Michigan, California, Texas, Edmonton (Canada)

**NCT02997176**
A Phase I Open-label Pharmacokinetics And Safety Study Of Talazoparib (mdv3800) In Patients With Advanced Solid Tumors And Normal Or Varying Degrees Of Hepatic Impairment

**PHASE 1**

**TARGETS**
PARP

**LOCATIONS:** California, Texas

**NCT01042379**
I-SPY 2 Trial (Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging And molecular Analysis 2)

**PHASE 2**

**TARGETS**
PARP, TOP1, ERBB2, PD-1, ERBB3

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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.

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**APPENDIX**
Genes assayed in FoundationOne®CDx

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

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### APPENDIX: Genes assayed in FoundationOne®CDx

**DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS**

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<td>TERT**</td>
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**TERC** is an ncRNA

**Promoter region of TERT is interrogated**

### ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

- **Microsatellite (MS) status**
- **Tumor Mutational Burden (TMB)**
Sequence data will be processed using a customized analysis pipeline designed to accurately detect all classes of genomic alterations, including base substitutions, indels, focal copy number amplifications, homologous gene deletions, and selected genomic rearrangements (e.g., gene fusions). Additionally, genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) will be reported.

Genomic Findings
Therapies with Clinical Benefit In Patient’s Tumor Type → Therapies with Clinical Benefit In Other Tumor Type → Clinical Trial Options → No Known Options (If multiple findings exist within any of these categories, the results are listed alphabetically by gene name.)

Therapies
Sensitizing therapies → Resistant therapies.
(If multiple therapies exist within any of these categories, they are listed alphabetically by therapy name.)

Clinical Trials
Pediatric trial qualification → Geographical proximity → Later trial phase.

Limitations
1. The MSI-H/MSS designation by FMI F1CDx test is based on genome wide analysis of 95 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines. The threshold for MSI-H/MSS was determined by analytical concordance to comparator assays (IHC and PCR) using uterine, cecum and colorectal cancer FFPE tissue. The clinical validity of the qualitative MSI designation has not been established.

2. TMB by F1CDx is defined based on counting the total number of all synonymous and nonsynonymous variants present at 5% allele frequency or greater (after filtering) and reported as mutations per megabase (mut/Mb) unit rounded to the nearest integer. The clinical validity of TMB defined by this panel has not been established.
LEVEL OF EVIDENCE NOT PROVIDED

Drugs with potential clinical benefit (or potential lack of clinical benefit) are not evaluated for source or level of published evidence.

NO GUARANTEE OF CLINICAL BENEFIT

This Report makes no promises or guarantees that a particular drug will be effective in the treatment of disease in any patient. This Report also makes no promises or guarantees that a drug with potential lack of clinical benefit will in fact provide no clinical benefit.

NO GUARANTEE OF REIMBURSEMENT

Foundation Medicine makes no promises or guarantees that a healthcare provider, insurer or other third party payer, whether private or governmental, will reimburse a patient for the cost of FoundationOne CDx.

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

Drugs referenced in this Report may not be suitable for a particular patient. The selection of any, all or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) resides entirely within the discretion of the treating physician. Indeed, the information in this Report must be considered in conjunction with all other relevant information regarding a particular patient, before the patient's treating physician recommends a course of treatment. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this Test, or the information contained in this Report. Certain sample or variant characteristics may result in reduced sensitivity. FoundationOne CDx is performed using DNA derived from tumor, and as such germline events may not be reported.

SELECT ABBREVIATIONS

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<td>CR</td>
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<td>Disease control rate</td>
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<td>DNA methyltransferase</td>
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<td>Hazard ratio</td>
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<td>Mismatch repair</td>
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<td>Stable disease</td>
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<td>TKI</td>
<td>Tyrosine kinase inhibitor</td>
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The median exon coverage for this sample is 733X


4. Overman et al., 2016; ASCO Abstract 3501


6. ASCO-CTC 2016: Abstract P60


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


91. Hor WC, Berndt A, Williams RL (2012) Regulation of lipid binding underlies the activation mechanism of class IA PI3-kinases. Oncogene 31(32):3655-66


Cyclin K/Cdk12 complex maintains genomic stability via structural variation in the gastric cancer kinome revealed.

240. Jain et al., 2016; ASCO Abstract 588
241. McCabe et al., 2016; ASCO Abstract 582


Hyman et al., 2016; San Antonio Breast Cancer Symposium Abstract PD2-08


Chia et al., 2017; SABCS Abstract P1-13-03

Ejertsen et al., 2017; SABCS Abstract P1-13-05

Hyman et al., 2016; SABCS Abstract PD2-08


Ururucocechea et al., 2016; ASCO Abstract 504

Iyengar et al., 2016; ASCO Abstract 611

Salimian et al., 2016; ASCO Abstract 595


Rugo et al., 2016; ASCO Abstract LB503

Wallner et al., 2016; ASCO Abstract 538

Audian et al., 2017; ASCO-SITC Clinical Immun- Oncology Symposium Abstract 207


References

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[36x39]Electronically Signed by Julia A. Elvin, M.D., Ph.D. • Jeffrey S. Ross, M.D., Medical Director • 01 January 2018

[36x709]QRF#


