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

PATIENT

DISEASE Breast carcinoma (NOS)
NAME
DATE OF BIRTH
SEX
MEDICAL RECORD #

PHYSICIAN

ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT
MEDICAL FACILITY ID
PATHOLOGIST

SPECIMEN

SPECIMEN SITE
SPECIMEN ID
SPECIMEN TYPE
DATE OF COLLECTION
SPECIMEN RECEIVED

Genomic Signatures

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

Gene Alterations

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

AKT3 amplification - equivocal†
ERBB2 amplification
RPTOR amplification - equivocal†
TP53 Y220C

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

† See About the Test in appendix for details.

9 Therapies approved in the EU
0 Therapies with Lack of Response
20 Clinical Trials

GENOMIC SIGNATURES

Microsatellite status - MS-Stable

Tumor Mutational Burden - 5 Muts/Mb

GENE ALTERATIONS

***ERBB2* -** amplification

10 Trials *see p. 15*

***AKT3* -** amplification - equivocal

10 Trials *see p. 13*

ACTIONABILITY

No therapies or clinical trials. see Genomic Signatures section

No therapies or clinical trials. see Genomic Signatures section

THERAPIES APPROVED IN THE EU (IN PATIENT'S TUMOR TYPE)		THERAPIES APPROVED IN THE EU (IN OTHER TUMOR TYPE)
Pertuzumab	1	Afatinib
Trastuzumab	1	Dacomitinib
Trastuzumab emtansine	1	
Lapatinib	2A	
Neratinib	2A	
Everolimus		Temsirolimus

☐ *NCCN category*

GENE ALTERATIONS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIALS OPTIONS

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

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

Therapies contained in this report may have been approved through a centralized EU procedure or a national procedure in an EU Member State. Therapies, including but not limited to the following, have been approved nationally and may not be available in all EU Member States: Tretinoin, Anastrozole, Bicalutamide, Cyproterone, Exemestane, Flutamide, Goserelin, Letrozole, Leuprorelin, Triptorelin.

GENOMIC SIGNATURE

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].

GENOMIC SIGNATURE

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 (> mean of 1.25 muts/Mb) associated with shorter OS (HR of 2.02) in an analysis of the TCGA data[29]. In another study, the number of mutated genes associated with higher tumor grade[30]. Although the number of mutated genes did not correlate with OS by multivariate analysis, cases with 22 or more mutated genes had significantly worse OS than cases with fewer than 22 mutated genes (HR of 4.6)[30].

FINDING SUMMARY

Tumor mutational burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[31-32] and cigarette smoke in lung cancer[33-34], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[35-39], and microsatellite instability (MSI)[35,38-39]. This sample harbors a TMB level associated with lower rates of clinical benefit from treatment with PD-1- or PD-L1-targeting immune checkpoint inhibitors compared with patients with tumors harboring higher TMB levels, based on several studies in multiple solid tumor types[22-23].

GENE
AKT3

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES
Activating alterations in AKT3 may predict sensitivity to inhibitors of AKT kinases or the downstream mTOR pathway[40]. Clinical benefit has been achieved in patients with AKT3 amplification treated with an mTOR inhibitor[41].

FREQUENCY & PROGNOSIS
AKT3 amplification has been reported in 5-15% of breast invasive carcinomas[42-44]. AKT3 alterations, including both amplification and deletion, have been reported at higher incidences in triple-negative breast cancer (TNBC, 24%, 20/82) than in ER-positive breast cancers (1%)[45]. AKT3 mRNA is reported to be overexpressed in ER-negative compared to ER-positive breast tumor cell lines, and AKT3 protein and kinase activity were reported to be increased in ER-negative breast cancer cell lines[46]. Increased levels of phosphorylated AKT have been correlated with poor prognosis in patients with breast cancer, especially in the presence of HER2 expression[47]. Additionally, in patients with TNBC, AKT3 amplification and protein expression were negatively associated with recurrence-free survival[45].

FINDING SUMMARY
AKT3 encodes PKB-gamma, an intracellular serine/threonine kinase. AKT3 is one of three members of the AKT gene family, and activation of AKT3 has been implicated in melanoma and breast cancer[48]. AKT3 has been reported to be amplified in cancer[49] and may be biologically relevant in this context[50-51].

GENE
ERBB2

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES
On the basis of extensive clinical evidence, ERBB2 amplification or activating mutation may predict sensitivity to therapies targeting HER2, including antibodies such as trastuzumab[52-57], pertuzumab in combination with trastuzumab[54,58-60], margetuximab[61], and ZW25[62] as well as antibody-directed conjugates such as ado-trastuzumab emtansine[63] and fam-trastuzumab deruxtecan[64], HER2 kinase inhibitors such as tucatinib[65-67], and dual EGFR/HER2 kinase inhibitors such as lapatinib[68-72], afatinib[57,73-78], neratinib[79-80], dacomitinib[81], and pyrotinib[82]. For patients with HER2-positive metastatic breast cancer, combining margetuximab[83] or pyrotinib[84-85] with chemotherapy significantly improved PFS or ORRs. The Phase 3 SOPHIA study reported improved median PFS (5.8 vs. 4.9 months, HR=0.76) and ORR (22% vs.16%) when combining margetuximab with chemotherapy, as compared with trastuzumab and chemotherapy, for patients who had progressed on ≥2 prior HER2-directed therapies[83]. For patients who had progressed on trastuzumab, the Phase 3 PHENIX study demonstrated improved median PFS (11.1 vs. 4.1 months, HR=0.18) and ORR (69% vs. 16%) for treatment with pyrotinib and capecitabine, as compared with placebo and capecitabine; patients who progressed on the placebo arm and went on to receive single-agent pyrotinib (n=71) achieved median PFS of 5.5 months and ORR of 38%[82].The same combination elicited an ORR of 91% (10/11) for trastuzumab-naive patients, and multiple genetic alterations were significantly associated with poorer PFS compared with none or one genetic alteration (16.8 vs. 29.9 months)[84]. In a randomized Phase 2 trial for previously treated patients, the combination of pyrotinib with capecitabine significantly improved ORR (71% vs. 49%, p=0.01) and median PFS (12.6 vs. 5.6 months, HR=0.37) compared with lapatinib and capecitabine irrespective of prior chemotherapy and trastuzumab treatments[85]. In a Phase 1 trial of margetuximab for HER2-overexpressing solid tumors, 12% (7/60) of patients, including 4 with breast, 2 with gastroesophageal, and 1 with lacrimal gland cancers, experienced PRs, and a further 52% (31/60) of the cohort experienced SD[61]. Early clinical studies aimed at preventing or overcoming resistance to anti-HER2 therapies are underway, including agents targeting the PI3K-AKT pathway or HSP90[86-87].

FREQUENCY & PROGNOSIS
In the TCGA dataset, ERBB2 amplification was detected in 13% of breast invasive carcinoma cases[27]. ERBB2 mutations have been reported in 1-3% of breast invasive carcinoma cases[27,88-89]. The incidence of ERBB2 alterations has been found to be significantly enriched in CDH1-mutated invasive lobular breast cancers[90]. HER2 is predicted to be overexpressed (as assessed by FISH, CNV analysis, or immunohistochemistry) in 12-25% of breast cancers[86,91-92]. Phosphorylated HER2 was expressed in 62.5% (55/88) of HER2-positive breast cancers[93]. Phosphorylated HER2 was associated with development of trastuzumab resistance[93].

FINDING SUMMARY
ERBB2 (also known as HER2) encodes a receptor tyrosine kinase which is in the same family as EGFR. Amplification or overexpression of ERBB2 can lead to excessive proliferation and tumor formation[94].

GENE
RPTOR

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

Several therapeutic approaches that target mTORC1 are under clinical and preclinical investigation, including the FDA-approved mTOR inhibitors everolimus and temsirolimus. Dual mTORC1/mTORC2 inhibitors and dual PI3K/mTOR inhibitors are also under investigation in clinical trials[95-96]. However, objective responses were not observed in any of 3 patients with breast carcinomas harboring RPTOR amplification treated with everolimus[97-98] and it is unclear whether mTOR inhibitors may be relevant for tumors with RPTOR alterations.

FREQUENCY & PROGNOSIS

In the Breast Invasive Carcinoma TCGA dataset, putative high-level amplification of RPTOR has been found in 6% of cases[27], whereas RPTOR mutations have been reported in approximately 1% of breast carcinomas analyzed[27,43,88,99-100]. RPTOR and mTOR mRNA expression were reported to be higher in breast carcinoma tissues, whereas expression of the mTORC2 component RICTOR was lower in tumor samples[101]. mTORC1 activity has been shown to be upregulated in models of breast cancer[102-103]. Increased mRNA expression of RPTOR and mTOR in breast cancer was associated with higher tumor grade[101].

FINDING SUMMARY

RPTOR encodes regulatory-associated protein of mTOR, which functions as part of the mTORC1 complex. mTORC1 is activated by growth factors and amino acids and plays a role in activation of cellular protein synthesis and maintenance of cell size[104-105]. RPTOR has been reported to be amplified in cancer[49], and may be biologically relevant in this context[50-51].

GENE
TP53

ALTERATION
Y220C

TRANSCRIPT NUMBER
NM_000546

CODING SEQUENCE EFFECT
659A>G

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[106-109], or p53 gene therapy and immunotherapeutics such as SGT-53[110-114] and ALT-801[115]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutant p53 such as APR-246[116-118]. In a Phase 1b trial in patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[119]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 10% (17/176) and SDs in 53% (94/176) of patients with solid tumors; the response rate was 21% (4/19) in patients with TP53 mutations versus 12% (4/33) in patients who were TP53 wild-type[120]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR in patients with platinum refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[121]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR in patients with platinum-refractory TP53-mutated ovarian cancer[122]. 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[123]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate in patients with TP53 alterations[124]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel in patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[114]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutant, but not TP53-wild-type, breast cancer xenotransplant mouse model[125].

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[27,88,100,126-128]. TP53 mutations that are located within the region encoding the DNA binding domain are associated with poor prognosis in patients with breast cancer[126,129-130]. 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[131-133].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[134]. 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[135-137]. The TP53 variant 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)[138]. 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[139-141], including sarcomas[142-143]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[144] to 1:20,000[143]. 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[145]. In the appropriate clinical context, germline testing of TP53 is recommended.

Everolimus

Assay findings association

AKT3
amplification - equivocal

AREAS OF THERAPEUTIC USE

Everolimus is an orally available mTOR inhibitor. It is available in the EU to treat advanced renal cell carcinoma (RCC) following antiangiogenic therapy; unresectable or metastatic, well- or moderately-differentiated, progressive pancreatic neuroendocrine tumors; unresectable or metastatic, well-differentiated non-functional, progressive 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 available in combination with exemestane to treat postmenopausal women with hormone receptor (HR)-positive, HER2-negative advanced breast cancer following prior therapy with a nonsteroidal aromatase inhibitor.

GENE ASSOCIATION

Alterations that activate AKT3 may predict sensitivity to inhibitors of the AKT-mTOR pathway. A PR and significant symptomatic benefit was observed in a male patient with AKT3-amplified breast cancer who was treated with an mTOR inhibitor[40].

SUPPORTING DATA

In a small study, 1 patient with AKT3-amplified, HR-positive metastatic breast cancer achieved clinical benefit > 6 months following combination treatment with anastrozole and everolimus[146]. 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)[147]. 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)[148-150] , and modestly improved the median PFS compared with everolimus alone in BOLERO-6 (8.4 vs. 6.8 months, HR = 0.74)[151]. Analysis of cell-free DNA revealed a similar benefit for patients with mutant or wild-type PIK3CA (HR = 0.37 vs. 0.43)[152]. Clinical studies for patients with HR+ breast cancer indicate that everolimus may potentiate letrozole or tamoxifen efficacy and can be safely combined with anastrozole[153-155] . Two Phase 3 trials have evaluated whether the addition of everolimus would circumvent or overcome resistance of HER2-positive (HER2+) breast cancer to trastuzumab-based therapy. As first-line treatment for patients with HER2+ breast cancer, everolimus combined with trastuzumab plus paclitaxel did not significantly improve median PFS in the full study population (15.0 months with everolimus vs. 14.5 months with placebo), but increased PFS in the HR-negative subpopulation (20.3 vs. 13.1 months)[156]. 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)[157]. 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)[158]. 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)[158-159] . For patients with metastatic triple-negative breast cancer, everolimus plus carboplatin achieved a clinical benefit rate of 36% (9/25)[160]. 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[161], 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[162].

Lapatinib

Assay findings association

ERBB2
amplification

AREAS OF THERAPEUTIC USE

Lapatinib inhibits the tyrosine kinases EGFR and ERBB2 (HER2). It is available in the EU to treat patients with HER2-positive advanced breast cancer in combination with capecitabine following prior therapy and in combination with trastuzumab for HER2-positive, hormone receptor (HR)-negative metastatic breast cancer following progression on trastuzumab combined with chemotherapy. It is also available in combination with an aromatase inhibitor to treat postmenopausal women with HER2- and HR-positive metastatic breast cancer.

GENE ASSOCIATION

Activation or amplification of ERBB2 may predict sensitivity to lapatinib. In one study, a patient with inflammatory breast cancer and ERBB2 V777L and S310F activating mutations, but without ERBB2 amplification or protein overexpression, experienced tumor shrinkage in response to combined treatment with lapatinib and trastuzumab[71].

SUPPORTING DATA

Lapatinib as a treatment for HER2+ breast cancer has primarily been investigated in combination with other chemotherapeutic agents, and these combination regimens have been shown to extend PFS and reduce metastases, as well as to extend OS in some instances[68-69,163-166] . As first-line therapy for HER2+ metastatic breast cancer, lapatinib plus taxane resulted in shorter median PFS compared with trastuzumab plus taxane (9.0 vs. 11.3 months, HR of 1.37)[167]. 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)[63]. Addition of lapatinib to capecitabine had improved PFS compared with capecitabine monotherapy (8.4 vs. 4.4 months) in this setting[69]. Lapatinib plus capecitabine has been reported to reduce the number of newly developed brain metastases[163] and to be active against existing brain metastases (central nervous system [CNS] ORR of 66% [29/44])[168]. However, the incidence of CNS metastases was not significantly different with lapatinib plus capecitabine versus trastuzumab plus capecitabine (3% vs. 5%)[169], and CNS disease progression rates were similar for treatment with T-DM1 and with lapatinib plus capecitabine[170]. 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[164-166] . A Phase 3 trial of patients with HER2+ breast cancer treated with lapatinib, trastuzumab, or a combination of the two, reported 3-year event-free survival rates of 78%, 76%, and 84%, with 3-year OS rates of 93%, 90%, and 95%, respectively[171]. In a Phase 3 study for patients with early HER2+ breast cancer, adjuvant lapatinib (alone, in sequence, or in combination with trastuzumab) did not significantly improve disease-free survival (DFS) and added toxicity compared with adjuvant trastuzumab[172]. Adjuvant lapatinib also did not significantly extend DFS in a placebo-controlled Phase 3 study[173]. In postmenopausal patients with hormone receptor-positive (HR+) HER2+ metastatic breast cancer, lapatinib combined with letrozole increased median PFS compared to letrozole alone (8.2 vs. 3.0 months)[174]. Addition of lapatinib to fulvestrant did not improve outcome for patients with advanced HR+ advanced breast cancer and prior aromatase inhibitor therapy (median PFS of 4.7 vs. 3.8 months), although lapatinib associated with longer median PFS for HER2+ patients in this trial (5.9 vs. 3.3 months)[175]. As neoadjuvant therapy for HR+ HER2-negative breast cancer, lapatinib combined with letrozole did not significantly improve response rates, but showed a trend toward a higher response rate for patients with PIK3CA-mutant tumors[176]. Four patients with HER3-positive and HER2-negative newly diagnosed breast cancer had clinical responses to neoadjuvant lapatinib[177].

Neratinib

Assay findings association

ERBB2
amplification

AREAS OF THERAPEUTIC USE

Neratinib is an irreversible tyrosine kinase inhibitor that targets EGFR, ERBB2/HER2, and ERBB4. It is available in the EU for the extended adjuvant treatment of patients with early stage HER2-positive breast cancer who are less than 1 year from the completion of prior adjuvant trastuzumab treatment.

GENE ASSOCIATION

On the basis of extensive clinical[80,178-181] and preclinical[182-186] evidence, ERBB2 amplification or activating mutations may confer sensitivity to neratinib.

SUPPORTING DATA

In a Phase 3 study for patients with earlystage HER2-positive (HER2+) breast cancer (BC) previously treated with trastuzumab, adjuvant neratinib significantly improved 2-year invasive disease-free survival (iDFS) compared with placebo (93.9% vs. 91.6%, HR=0.67)[180]. The significant iDFS benefit persisted at year 5 of follow-up (90.2% for neratinib vs. 87.7% for placebo, HR=0.73)[187], including for patients who were also hormone receptor-positive (HR+)[188]; however, the improvement was seen only for those patients who were randomized to neratinib within 12 months of prior trastuzumab treatment[189]. For patients with advanced HER2+ BC previously treated with trastuzumab, a median PFS of 5.6 months from neratinib monotherapy[190], 4.5 months from neratinib plus capecitabine[191], and 6.8 months from neratinib plus lapatinib[191] has been reported in Phase 2 trials; for patients with no prior trastuzumab treatment, neratinib treatment resulted in PFS of 39.6 weeks[190]. For patients with BC and HER2+ brain metastases treated with neratinib, the central nervous system (CNS) ORR was 7.5% (3/40)[192]. The Phase 3 NALA study reported a 24% reduction in risk of disease progression (HR=0.76) with neratinib and capecitabine, as compared with lapatinib and capecitabine, for patients with HER2+ metastatic breast cancer (MBC) and progression on 2 or more prior HER2-directed therapies; neratinib also improved the time to intervention for symptomatic CNS disease compared with lapatinib (overall cumulative incidence 22.8% vs. 29.2%, P=0.043)[193]. Also for patients with HER+ MBC, Phase 1 and Phase 1/2 trials reported an ORR of 73% for neratinib plus paclitaxel[194], an ORR of 38% and a clinical benefit rate of 52% from neratinib with trastuzumab[195], and a higher ORR from neratinib and vinorelbine for patients who were lapatinib-naive (41%) as compared with those patients who had prior lapatinib treatment (8%)[196]. As first-line therapy in HER2+ MBC, PFS or ORR did not significantly differ with neratinib plus paclitaxel compared with trastuzumab plus paclitaxel; however, patients treated with neratinib had a lower incidence of CNS disease recurrence[197]. As neoadjuvant treatment in HER2+, HR-negative BC, the pathologic CR rate was 56% for neratinib plus paclitaxel as compared with 33% for trastuzumab plus paclitaxel[181].

Pertuzumab

Assay findings association

ERBB2
amplification

AREAS OF THERAPEUTIC USE

Pertuzumab is a monoclonal antibody that interferes with the interaction between HER2 and ERBB3. It is available in the EU in combination with trastuzumab and docetaxel to treat patients with HER2-positive (HER2+) metastatic or unresectable breast cancer who have not received prior chemotherapy or HER2-targeted therapy. It is also available in combination with trastuzumab and chemotherapy as neoadjuvant treatment for HER2+; locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence; 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[58-59,198-201] .

SUPPORTING DATA

In the APHINITY trial, addition of pertuzumab to chemotherapy plus trastuzumab as adjuvant treatment for patients with HER2+ early stage breast cancer improved the estimated 3-year rate of invasive disease-free survival compared with placebo (94.1% vs. 93.2%), with greater improvement seen for patients with node-positive [92.0% vs. 90.2%, hazard ratio (HR) = 0.77] than those with node-negative (97.5% vs. 98.4%, HR = 1.13) disease[199]. 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)[58-59,201] . 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)[202-203] . 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[198]. 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[204]. In a Phase 3 study of patients with HER2+ MBC failing on first-line trastuzumab, addition of pertuzumab to trastuzumab and capecitabine was reported to increase median PFS (11.1 vs. 9.0 months) and OS (36.1 vs. 28.1 months) when compared with trastuzumab plus capecitabine[205]. 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[206]. 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[207].

Trastuzumab

Assay findings association

ERBB2
amplification

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical studies in multiple tumor types, ERBB2 amplification, overexpression, or activating mutations may confer sensitivity to trastuzumab[52-53,57,71,200,208-211] .

SUPPORTING DATA

In a study of patients with early breast cancer treated with neoadjuvant trastuzumab, higher ERBB2 copy number (HER2/CEP17 ratio >6) correlated with increased incidence of pathologic CR compared to lower ERBB2 copy number[212]. Trastuzumab has been approved for patients with HER2+ breast cancer based on multiple Phase 2 and 3 clinical trials[52,58,201] . Trastuzumab biosimilars demonstrated comparable clinical benefit to trastuzumab in patients with HER2+ breast cancer[213-222] . A Phase 3 study of patients with HER2+ breast cancer reported 5-year event-free survival (EFS) in 58% of patients treated with trastuzumab plus neoadjuvant therapy, compared to 43% in patients treated with neoadjuvant therapy alone[208]. A long-term follow-up Phase 2 analysis reported 5-year distant disease-free survival (DFS) rates of 92% in patients with HER2+ breast cancer treated with chemotherapy and trastuzumab and 89% in patients treated with lapatinib and chemotherapy[209]. A Phase 3 trial of patients with HER2+ breast cancer treated with lapatinib, trastuzumab, or a combination of both reported 3-year EFS rates of 78%, 76%, and 84%, and 3-year OS rates of 93%, 90%, and 95%, respectively[171]. Two Phase 3 studies comparing 6-month to 12-month adjuvant trastuzumab reported similar DFS rates for patients with HER2+ early breast cancer after 5.4 years (89.4% vs. 89.8%, HR=1.07)[223] or 7.5 years median follow-up (78.8% vs. 79.6%, HR=1.08)[224]. A Phase 1b study of trastuzumab in combination with the HER2 TKI tucatinib for patients with HER2+ metastatic breast cancer previously treated with HER2-targeting agents reported a 40% (6/15) ORR and median PFS of 5.5 months; an ORR of 61% (14/23, 1 CR) and median PFS of 7.8 months was reported when capecitabine was added to the combination. In the patients with brain metastases, 42% (5/12, 1 CR) exhibited brain-specific responses[66]. As first-line treatment for patients with HER2+ breast cancer, everolimus combined with trastuzumab plus paclitaxel did not significantly improve median PFS in the full study population (15.0 months with everolimus vs. 14.5 months with placebo) but increased PFS in the HR-negative subpopulation by 7.2 months (20.3 vs. 13.1 months)[156]. 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)[157].

Trastuzumab emtansine

Assay findings association

ERBB2
amplification

AREAS OF THERAPEUTIC USE

Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate that targets the protein ERBB2/HER2 on the cell surface, inhibiting HER2 signaling; it also releases the cytotoxic therapy DM1 into cells, leading to cell death. T-DM1 is available in the EU to treat patients with HER2-positive (HER2+) advanced breast carcinoma and disease progression on prior therapy.

GENE ASSOCIATION

ERBB2 amplification or activating mutations may predict sensitivity to T-DM1.

SUPPORTING DATA

For patients with HER2+ breast cancer (BC) previously treated with HER2-directed therapies, Phase 3 trials of single-agent T-DM1 have reported significant increases in median PFS as compared with physician's choice of therapy (6.2 vs. 3.3 months)[225] or lapatinib plus capecitabine (9.6 vs. 6.4 months)[63,226-227] . The Phase 3 MARIANNE study for patients with HER2+ advanced BC treated in the first line with T-DM1 reported no significant differences in ORR (60%, 64%, and 68%) or median PFS (14.1, 15.2, and 13.7 months) when comparing T-DM1 combined with placebo, T-DM1 with pertuzumab, and trastuzumab with a taxane, respectively[228]; however, an earlier Phase 2 study reported improved median PFS with T-DM1 as compared with trastuzumab plus docetaxel (14.2 months vs. 9.2 months, HR=0.59) in this setting[229]. In the Phase 3 KATHERINE study, patients with HER2+ early BC with residual invasive disease following completion of neoadjuvant taxane and trastuzumab treated with T-DM1 experienced significantly higher invasive disease-free survival rates at 3 years (88.3% vs.77.0%, HR=0.50) compared with patients treated with trastuzumab[230]. In the neoadjuvant setting, the Phase 3 KRISTINE study for patients with HER2+ BC reported a lower pathologic CR rate (44.4% vs. 55.7%, p=0.016) with T-DM1 plus pertuzumab compared with the combination of trastuzumab, pertuzumab, docetaxel, and carboplatin[231]. Patients with HER2+ locally advanced BC or metastatic BC (MBC) have experienced clinical benefit in Phase 1/2 studies from T-DM1 in combination with docetaxel[232], paclitaxel and pertuzumab[204], neratinib[233], alpelisib[234], and tucatinib[233]. A retrospective analysis found that patients with HER2+ MBC and active central nervous system (CNS) metastases treated with T-DM1 achieved an ORR of 40% (4/10); there was no significant OS difference between patients with and without CNS metastases[235].

Afatinib

Assay findings association

ERBB2
amplification

AREAS OF THERAPEUTIC USE

Afatinib is an irreversible kinase inhibitor that targets the kinase domains of EGFR, ERBB2/HER2, and ERBB4. It is available in the EU to treat patients with advanced non-small cell lung cancer (NSCLC) and activating EGFR mutations and for the treatment of patients with advanced squamous NSCLC after progression on platinum-based chemotherapy.

GENE ASSOCIATION

Clinical and preclinical data support sensitivity of multiple activating mutations in ERBB2, including A775_G776insYVMA and P780_Y781insGSP, to afatinib[236-243] . Studies have reported DCRs of 54 to 70% for patients with ERBB2-mutated NSCLC treated with afatinib, most of whom harbored exon 20 insertions[236-239] .

SUPPORTING DATA

In a Phase 3 study for patients with HER2-positive (HER2+) breast cancer and disease progression on trastuzumab, afatinib plus vinorelbine compared to trastuzumab plus vinorelbine did not improve median PFS (5.5 vs. 5.6 months) or ORR (46% vs. 47%), associated with shorter median OS (20.5 vs. 28.6 months), and was less well tolerated[244]. Afatinib monotherapy achieved an ORR of 11% (4/35) and a median OS of 61 weeks in this setting[74]. 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[245]. 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[246]. In contrast, a Phase 2 trial reported no objective responses for genomically unselected patients with HER2-negative breast cancer[247]. Afatinib plus letrozole achieved SD for 54% (15/28) of patients with estrogen receptor-positive breast cancer who had progressed on single-agent letrozole[248].

Dacomitinib

Assay findings association

ERBB2
amplification

AREAS OF THERAPEUTIC USE

Dacomitinib is a second-generation irreversible tyrosine kinase inhibitor that targets the kinase domains of EGFR, ERBB2/HER2, and ERBB4/HER4. It is available in the EU for first-line treatment of patients with advanced non-small cell lung cancer (NSCLC) with EGFR activating mutations.

GENE ASSOCIATION

On the basis of strong clinical[81,249-252] and preclinical[253-256] data, ERBB2 amplification or activating mutation may indicate sensitivity to dacomitinib.

SUPPORTING DATA

Clinical data on the efficacy of dacomitinib for the treatment of breast carcinoma are limited (PubMed, Aug 2019). Investigations into the efficacy of dacomitinib have primarily been in the context of non-small cell lung cancer (NSCLC). Patients with EGFR-mutant NSCLC treated with dacomitinib exhibited significant improvement in OS compared with gefitinib treatment (median OS, 34.1 vs. 26.8 months)[257-258] . 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[259-260]. 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[251]. Studies of dacomitinib in esophageal[261] and cutaneous[262] SCC reported RRs of 12.5% (6/48) and 28.6% (12/42), respectively, but high DCRs of 73% and 86%, respectively. In contrast, trials of dacomitinib in heavily pretreated patients with HER2+ gastric cancer[252] and patients with EGFR-amplified glioblastoma[263] found RRs of fewer than 10% and DCRs of fewer than 50%: 11/27 (41%) DCR in HER2+ gastric cancer[252] and 15/49 (31%) in EGFR-amplified glioblastoma[263].

Temsirolimus

Assay findings association

AKT3
amplification - equivocal

AREAS OF THERAPEUTIC USE

Temsirolimus is an intravenous mTOR inhibitor. It is available in the EU to treat advanced renal cell carcinoma (RCC) and relapsed or refractory mantle cell lymphoma (MCL).

GENE ASSOCIATION

Alterations that activate AKT3 may predict sensitivity to inhibitors of the AKT-mTOR pathway. A PR and significant symptomatic benefit was observed in a male patient with AKT3-amplified breast cancer who was treated with an mTOR inhibitor[40].

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%)[264]. 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[265]. 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[266]. 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[267]. 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[268].

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 listed in this report may not be complete and exhaustive and the therapeutic agents are not ranked in order of potential or predicted efficacy for this patient or in order of level of evidence for this patient's tumor type.

IMPORTANT Clinical trials are ordered by gene and prioritized in the following descending order: Pediatric trial qualification → Geographical proximity → Trial phase → Trial verification within last 2 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. The clinical trials listed in this report may not be complete and exhaustive or may include trials for which the patient does not meet the clinical trial enrollment criteria. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov or local registries in your region.

GENE
AKT3

ALTERATION
amplification - equivocal

RATIONALE
AKT3 amplification or activating mutations may lead to AKT-mTOR pathway activation and may predict sensitivity to inhibitors of this pathway.

NCT03182634

PHASE 2

The UK Plasma Based Molecular Profiling of Advanced Breast Cancer to Inform Therapeutic CHoices (plasmaMATCH) Trial

TARGETS
ER, EGFR, ERBB2, ERBB4, AKTs, PARP, ATR

LOCATIONS: Sutton (United Kingdom), Bournemouth (United Kingdom), Bristol (United Kingdom), Cambridge (United Kingdom), Cardiff (United Kingdom), Edinburgh (United Kingdom), Exeter (United Kingdom), Glasgow (United Kingdom), Liverpool (United Kingdom), London (United Kingdom), Maidstone (United Kingdom), Manchester (United Kingdom), Oxford (United Kingdom), Plymouth (United Kingdom), Sheffield (United Kingdom), Southampton (United Kingdom), Truro (United Kingdom)

NCT03673787

PHASE 1/2

A Trial of Ipatasertib in Combination With Atezolizumab

TARGETS
AKTs, PD-L1

LOCATIONS: Sutton (United Kingdom)

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

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

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

NCT03366103

PHASE 1/2

Navitoclax and Vistusertib in Treating Patients With Relapsed Small Cell Lung Cancer and Other Solid Tumors

TARGETS
mTORC1, mTORC2, BCL-W, BCL-XL, BCL2

LOCATIONS: Maryland, Massachusetts, New Jersey, New York

NCT01827384

PHASE 2

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

TARGETS
PARP, mTOR, MEK, WEE1

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

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT03154281

PHASE 1

Evaluation of the Safety and Tolerability of Niraparib With Everolimus in Ovarian and Breast

TARGETS
PARP, mTOR

LOCATIONS: South Dakota

NCT02719691

PHASE 1

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

TARGETS
Aurora kinase A, mTORC1, mTORC2

LOCATIONS: Colorado

NCT04032080

PHASE 2

Treatment With Oral LY3023414 To Inhibit Homologous Recombination Followed By Prexasertib

TARGETS
CHK1, mTOR, PI3K

LOCATIONS: Texas

NCT02159989

PHASE 1

Sapanisertib and Ziv-Aflibercept in Treating Patients With Recurrent Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery

TARGETS
PIGF, VEGFA, VEGFB, mTORC1, mTORC2

LOCATIONS: Texas

GENE
ERBB2

ALTERATION
amplification

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

NCT03523585

PHASE 3

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

TARGETS
ERBB2, EGFR

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

NCT03529110

PHASE 3

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

TARGETS
ERBB2

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

NCT03726879

PHASE 3

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

TARGETS
PD-L1, ERBB3, ERBB2

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

NCT03262935

PHASE 3

SYD985 vs. Physician's Choice in Participants With HER2-positive Locally Advanced or Metastatic Breast Cancer

TARGETS
ERBB2, EGFR

LOCATIONS: Alabama, Arizona, California, Florida, Nijmegen (Netherlands), Illinois, Kansas, Maryland, Michigan, Missouri, Amsterdam (Netherlands), North Carolina, Ohio, Oregon, Pennsylvania, Texas, Virginia, Brussel (Belgium), Bruxelles (Belgium), Edegem (Belgium), Gent (Belgium), Kortrijk (Belgium), Leuven (Belgium), Liege (Belgium), Edmonton (Canada), Kelowna (Canada), Montreal (Canada), Ottawa (Canada), Naestved (Denmark), Odense (Denmark), Sønderborg (Denmark), Angers (France), Bordeaux (France), Dijon (France), Lille (France), Metz (France), Nantes (France), Paris (France), Pierre-Benite (France), Rouen (France), Strasbourg (France), Bari (Italy), Bologna (Italy), Catania (Italy), Firenze (Italy), Milano (Italy), Modena (Italy), Monza (Italy), Padova (Italy), Prato (Italy), Roma (Italy), San Giovanni Rotondo (Italy), Groningen (Netherlands), Singapore (Singapore), Alicante (Spain), Barcelona (Spain), Lleida (Spain), Madrid (Spain), Valencia (Spain), Zaragoza (Spain), Gävle (Sweden), Göteborg (Sweden), Stockholm (Sweden), Uppsala (Sweden), Bebington (United Kingdom), Cardiff (United Kingdom), Glasgow (United Kingdom), London (United Kingdom), Manchester (United Kingdom), Oxford (United Kingdom)

NCT03595592

PHASE 3

Neoadjuvant Treatment of HER2 Positive Early High-risk and Locally Advanced Breast Cancer

TARGETS
ERBB3, ERBB2, PD-L1

LOCATIONS: Milano (Italy), Negrar (Italy), Pavia (Italy), Reggio Emilia (Italy), Rimini (Italy), Roma (Italy), Udine (Italy), A Coruña (Spain), Badajoz (Spain), Barcelona (Spain), Madrid (Spain), Málaga (Spain), Valencia (Spain)

NCT02947685

PHASE 3

Randomized, Open Label, Clinical Study of the Targeted Therapy, Palbociclib, to Treat Metastatic Breast Cancer

TARGETS
ERBB2, Aromatase, ER, CDK4, CDK6, ERBB3

LOCATIONS: California, District of Columbia, Florida, Georgia, Illinois, Kansas, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Missouri, Nebraska, New Hampshire, New Jersey, New Mexico, North Carolina, Ohio, Oregon, Pennsylvania, South Carolina, Tennessee, Texas, Utah, Clayton (Australia), Darlinghurst (Australia), Garran (Australia), Melbourne (Australia), Nedlands (Australia), South Brisbane (Australia), Waratah (Australia), Westmead (Australia), Angers (France), Avignon (France), Bordeaux (France), Caen (France), Cholet (France), Clermont-Ferrand (France), Dijon (France), Limoges (France), Lyon (France), Marseille (France), Nice (France), Paris (France), Plerin Cedex (France), Reims (France), Rouen (France), Saint-Cloud (France), Saint-Priest-en-Jarez (France), Strasbourg (France), Toulouse (France), Villejuif (France), Berlin (Germany), Bielefeld (Germany), Bottrop (Germany), Düsseldorf (Germany), Essen (Germany), Frankfurt (Germany), Hameln (Germany), Hannover (Germany), Karlsruhe (Germany), Kiel (Germany), Köln (Germany), Munster (Germany), Münster (Germany), Oldenburg (Germany), Schweinfurt (Germany), Wiesbaden (Germany), Segrate (Italy), Auckland (New Zealand), Barcelona (Spain), Madrid (Spain), Murcia (Spain), Málaga (Spain), Navarro (Spain), Salamanca (Spain), Santiago (Spain), Seville (Spain), Tarragona (Spain), Valencia (Spain)

NCT02627274

PHASE 1

A Study Evaluating Safety, Pharmacokinetics, and Therapeutic Activity of RO6874281 as a Single Agent (Part A) or in Combination With Trastuzumab or Cetuximab (Part B or C)

TARGETS
FAP, ERBB2, EGFR

LOCATIONS: Arizona, Meldola (Italy), Milano (Italy), Missouri, Hamilton (Canada), Toronto (Canada), Edegem (Belgium), Bordeaux (France), Toulouse (France), VILLEJUIF Cedex (France), Amsterdam (Netherlands), Rotterdam (Netherlands), Leicester (United Kingdom), London (United Kingdom), Manchester (United Kingdom)

NCT03523572

PHASE 1/2

Trastuzumab Deruxtecan (DS-8201a) With Nivolumab in Advanced Breast and Urothelial Cancer

TARGETS
PD-1, ERBB2

LOCATIONS: California, Connecticut, London (United Kingdom), Florida, Kentucky, New York, North Carolina, Ohio, Tennessee, Utah, Washington, Brussels (Belgium), Wilrijk (Belgium), Milano (Italy), Siena (Italy), Madrid (Spain), London Borough of Sutton (United Kingdom)

NCT03144947

PHASE 2

Biomarker Study of Immune-mediated Mechanism of Action of Neoadjuvant Trastuzumab in Patients With HER2-positive Breast Cancer

TARGETS
ERBB2, ERBB3

LOCATIONS: Negrar (Italy), Bergamo (Italy), Parma (Italy), Piacenza (Italy), Reggio Emilia (Italy), Rimini (Italy), Verona (Italy)

NCT04132960

PHASE 2

Study of DS-8201a, an Antibody Drug Conjugate for Advanced Breast Cancer Patients, With Biomarkers Analysis

TARGETS
ERBB2

LOCATIONS: Lyon (France), Nice (France), Reims (France), Villejuif (France)

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.

CD22
M600T

FLT1
V278I

IGF1R
P190S

IKZF1
R423C

PDCD1LG2 (PD-L2)
E11fs*7

RARA
amplification

SPOP
amplification

SUFU
S410F

The content provided as a professional service by Foundation Medicine, Inc., has not been reviewed or approved by the FDA.

Electronically signed by J. Keith Killian, M.D. | Julia Elvin, M.D., Ph.D., Laboratory Director | 31 January 2020 | Foundation Medicine, Inc. | Roche Customer Care: +49 7624 14 2098 or europe.foundationmedicine@roche.com

Sample Preparation: FMI Germany GmbH, Nonnenwald 2, 82377 Penzberg, Germany
Sample Analysis: FMI Germany GmbH, Nonnenwald 2, 82377 Penzberg, Germany

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 GENOMIC SIGNATURES

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

FoundationOne CDx fulfills the requirements of the European Directive 98/79 EC for in vitro diagnostic medical devices and is registered as a CE-IVD product by Foundation Medicine's EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium. CE

ABOUT FOUNDATIONONE CDX

FoundationOne CDx was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne CDx may be used for clinical purposes and should not be regarded as purely investigational or for research only. Foundation Medicine's clinical reference laboratories are qualified to perform high-complexity clinical testing.

Please refer to technical information for performance specification details: www.rochefoundationmedicine.com/f1cdxtech.

INTENDED USE

FoundationOne®CDx (F1CDx) is a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI), tumor mutational burden (TMB), and for selected forms of ovarian cancer, loss of heterozygosity (LOH) score, using DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with therapies in accordance with approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms.

TEST PRINCIPLES

FoundationOne CDx will be performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The proposed assay will employ a single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50-1000 ng of which will undergo whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons. The assay therefore includes detection of alterations in a total of 324 genes. Using an Illumina® HiSeq platform, hybrid capture–selected libraries will be sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data will be processed using a customized analysis pipeline designed to accurately detect all classes of genomic alterations, including base substitutions, indels, focal copy number amplifications, homozygous gene deletions, and selected genomic rearrangements (e.g.,gene fusions). Additionally, genomic signatures including loss of heterozygosity (LOH), microsatellite instability (MSI) and tumor mutational burden (TMB) will be reported.

THE REPORT

Incorporates analyses of peer-reviewed studies and other publicly available information identified by Foundation Medicine; these analyses and information may include associations between a molecular alteration (or lack of alteration) and one or more drugs with potential clinical benefit (or potential lack of clinical benefit), including drug candidates that are being studied in clinical research. The F1CDx report may be used as an aid to inform molecular eligibility for clinical trials. Note: The association of a therapy with a genomic alteration or signature does not necessarily indicate pharmacologic effectiveness (or lack thereof); no association of a therapy with a genomic alteration or signature does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness).

Diagnostic Significance

FoundationOne CDx identifies alterations to select cancer-associated genes or portions of genes (biomarkers). In some cases, the Report also highlights selected negative test results regarding biomarkers of clinical significance.

Qualified Alteration Calls (Equivocal and Subclonal)

An alteration denoted as "amplification – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence that the copy number of a gene exceeds the threshold for identifying copy number amplification. The threshold used in FoundationOne CDx for identifying a copy number amplification is four (4) for ERBB2 and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence for homozygous deletion of the gene in question. An alteration denoted as "subclonal" is one that the FoundationOne CDx analytical methodology has identified as being present in <10% of the assayed tumor DNA.

Ranking of Alterations and Therapies

Genomic Signatures and Gene Alterations

Therapies are ranked based on the following criteria: Therapies approved in the EU in patient's tumor type (ranked alphabetically within each NCCN category) followed by therapies approved in the EU in another tumor type (ranked alphabetically within each NCCN category).

Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NCCN Categorization

Genomic signatures and gene alterations detected may be associated with certain National Comprehensive Cancer Network (NCCN) Compendium drugs or biologics (www.nccn.org). The NCCN categories indicated reflect the highest possible category for a given therapy in association with each genomic signature or gene alteration. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories please refer to the NCCN Compendium.

Limitations

1. The MSI-H/MSS designation by FMI F1CDx test is based on genome wide analysis of 95 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines. The threshold for MSI-H/MSS was determined by analytical concordance to comparator assays (IHC and PCR) using uterine, cecum and colorectal cancer FFPE tissue. The clinical validity of the qualitative MSI designation has not been established. For Microsatellite Instability (MSI) results, confirmatory testing using a validated orthogonal method should be considered.
2. TMB by F1CDx is defined based on counting the total number of all synonymous and nonsynonymous variants present at 5% allele frequency or greater (after filtering) and reported as mutations per megabase (mut/Mb) unit rounded to the nearest integer. The clinical validity of TMB defined by this panel has not been established.
3. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH.

Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

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

SELECT ABBREVIATIONS

ABBREVIATION	DEFINITION
CR	Complete response
DCR	Disease control rate
DNMT	DNA methyltransferase
HR	Hazard ratio
ITD	Internal tandem duplication
MMR	Mismatch repair
muts/Mb	Mutations per megabase
NOS	Not otherwise specified
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
SD	Stable disease
TKI	Tyrosine kinase inhibitor

PDF Service version: 2.6.0

The median exon coverage for this sample is 550x

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