FOUNDATIONONE®CDx

PATIENT

TUMOR TYPE
Breast carcinoma (NOS)

COUNTRY CODE
JO

REPORT DATE

ORDERED TEST #

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

PATIENT	PHYSICIAN	SPECIMEN
DISEASE Breast carcinoma (NOS)	ORDERING PHYSICIAN	SPECIMEN SITE
NAME	MEDICAL FACILITY	SPECIMEN ID
DATE OF BIRTH	ADDITIONAL RECIPIENT	SPECIMEN TYPE
SEX	MEDICAL FACILITY ID	DATE OF COLLECTION
MEDICAL RECORD #	PATHOLOGIST	SPECIMEN RECEIVED

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 6 Muts/Mb

Genomic Findings

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

BRCA1 K894fs*8
ERBB2 S310Y
FGFR1 amplification - equivocal†
CREBBP Q2199fs*138
MSH6 E1335fs*1
NSD3 (WHSC1L1) amplification - equivocal†
TP53 M246R

2 Disease relevant genes with no reportable alterations: *BRCA2, PIK3CA*

† See About the Test in appendix for details.

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Olaparib** (p. 12), **Talazoparib** (p. 13)
- Variants that may inform **nontargeted treatment approaches** (e.g., chemotherapy) in this tumor type: ***BRCA1*** **K894fs*8** (p. 5)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 18)
- Variants in select cancer susceptibility genes to consider for possible **follow-up germline testing** in the appropriate clinical context: ***BRCA1*** **K894fs*8** (p. 5)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section
Tumor Mutational Burden - 6 Muts/Mb	**No therapies or clinical trials.** see Biomarker Findings section

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
BRCA1 **-** K894fs*8	Olaparib [1]	Niraparib
10 Trials *see p. 18*	Talazoparib [1]	Rucaparib
ERBB2 **-** S310Y	Ado-trastuzumab emtansine	none
	Fam-trastuzumab deruxtecan	
	Lapatinib	
	Neratinib	
	Trastuzumab	
10 Trials *see p. 20*	Trastuzumab + Pertuzumab	
FGFR1 **-** amplification - equivocal	none	Pazopanib
10 Trials *see p. 22*		

[ ] *NCCN category*

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING IN SELECT CANCER SUSCEPTIBILITY GENES

Findings below have been previously reported as pathogenic germline in the ClinVar genomic database and were detected at an allele frequency of >10%. See appendix for details.

BRCA1 **-** K894fs*8 ..... p. 5

This report does not indicate whether variants listed above are germline or somatic in this patient. In the appropriate clinical context, follow-up germline testing would be needed to determine whether a finding is germline or somatic.

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

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.

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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

MSI is extremely rare in breast cancer, reported in 0-1% of cases across studies[6-11]. The incidence of MSI is increased in triple-negative breast cancer[9-11] and in tumors with homologous recombination defects, such as mutations in BRCA1/2[9,11]. Notably, in Lynch syndrome–related breast cancer, MSI has been reported in 51-85% of cases[12-17]. A prospective study of 123 patients with breast cancer treated with chemotherapy reported an increase in the incidence of MSI-H following chemotherapy treatment (from 0% pre-treatment to 19% post-treatment) and a significant association between MSI and tumor recurrence[18].

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[19]. 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[19-21]. 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[22-24]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[19,21,23-24].

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

BIOMARKER

Tumor Mutational Burden

RESULT
6 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[25-27], anti-PD-1 therapies[25-28], and combination nivolumab and ipilimumab[29-34]. In multiple pan-tumor studies, increased tissue tumor mutational burden (TMB) was associated with sensitivity to immune checkpoint inhibitors[25-28,35-39]. In the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors, significant improvement in ORR was observed for patients with TMB ≥10 Muts/Mb (as measured by this assay) compared with those with TMB <10 Muts/Mb in a large cohort that included multiple tumor types[35]; similar findings were observed in the KEYNOTE 028 and 012 trials[28]. At the same TMB cutpoint, retrospective analysis of patients with solid tumors treated with any checkpoint inhibitor identified that tissue TMB scores ≥ 10 Muts/Mb were associated with prolonged time to treatment failure compared with scores <10 muts/Mb (HR=0.68)[39]. For patients with solid tumors treated with nivolumab plus ipilimumab in the CheckMate 848 trial, improved responses were observed in patients with a tissue TMB ≥ 10 Muts/Mb independent of blood TMB at any cutpoint in matched samples[40]. However, support for higher TMB thresholds and efficacy was observed in the prospective Phase 2 MyPathway trial of atezolizumab for patients with pan-solid tumors, where improved ORR and DCR was seen in patients with TMB ≥ 16 Muts/Mb than those with TMB ≥ 10 and <16 Muts/Mb[38]. Similarly, analyses across several solid tumor types reported that patients with higher TMB (defined as ≥16-20 Muts/Mb) achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy compared with patients with higher TMB treated with chemotherapy[41] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[26].

FREQUENCY & PROGNOSIS

A study of 3,969 patients with breast cancer reported a median TMB of 2.63 mutations per megabase (Muts/Mb), with 5% of cases harboring TMB ≥10 Muts/Mb; median TMB was significantly higher in hormone receptor (HR)-negative and HER2-negative tumors than HR-positive or HER2-positive tumors[42]. 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[43]. In breast cancer, TMB is significantly higher in recurrent versus primary tumors, metastatic versus localized cancers, triple-negative versus HR-positive tumors, and CDH1-mutated versus CDH1-wildtype tumors[42,44-45]. Among metastatic tumors, TMB-high samples have been reported more frequently in invasive lobular carcinoma (9-17% of cases, depending on the TMB cutoff to designate TMB-high) than in invasive ductal carcinoma (2-8% of cases, depending on the cutoff), and TMB-high (at either cutoff) has not been observed in papillary carcinoma[42,44-45]. Breast carcinoma harbors a median TMB of 3.8 muts/Mb, and 3.1% of cases have high TMB (>20 muts/Mb)[46]. In a large study of patients with breast cancer, hypermutation was more frequently observed in metastatic tumors than in primary tumors[42]. In a study of 14,867 patients with breast cancer, high TMB was associated with older age and metastatic disease but was not significantly associated with PD-L1 positivity using the TMB cutoff of ≥10 Muts/Mb[45]. In estrogen receptor-positive breast cancer, increased TMB in tissue samples (>mean of 1.25 Muts/Mb) associated with shorter OS (HR=2.02) in an analysis of the TCGA data[47].

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[48-49] and cigarette smoke in lung cancer[50-51], treatment with temozolomide-based chemotherapy in glioma[52-53], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[54-58], and microsatellite instability (MSI)[54,57-58]. 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[26-27,35].

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

GENE
BRCA1

ALTERATION
K894fs*8

TRANSCRIPT ID
NM_007294

CODING SEQUENCE EFFECT
2681_2682delAA

VARIANT ALLELE FREQUENCY (% VAF)
58.3%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Alterations that inactivate BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors[59-76] or ATR inhibitors[77-79]. Clinical responses to PARP inhibitors have been reported for patients with either germline or somatic BRCA1/2 mutations[60,65,68,75-76] and for patients with platinum-resistant or -refractory disease[59,64,71,74]. The PARP inhibitors talazoparib and olaparib have shown significant clinical efficacy for patients with HER2-negative advanced breast cancer and a germline BRCA mutation in Phase 3 studies[62,80]. In the Phase 3 BROCADE3 study for patients with HER2-negative breast cancer harboring deleterious germline BRCA mutations, the addition of veliparib to platinum chemotherapy, which was continued as a monotherapy if chemotherapy was discontinued, improved median PFS compared with placebo plus platinum chemotherapy (14.5 vs. 12.6 months; HR=0.71)[81]. In a Phase 1 trial of monotherapy treatment with the ATR inhibitor BAY1895344, 2 patients with deleterious BRCA1 alterations and platinum-refractory ovarian carcinoma experienced a PR or prolonged SD[77]. In other Phase 1 trials of combination approaches, a patient with BRCA1-mutated ovarian carcinoma experienced prolonged SD from the ATR inhibitor berzosertib combined with topotecan[78]; another patient with platinum- and PARP-inhibitory refractory ovarian cancer and an inactivating germline BRCA1 mutation experienced a PR from berzosertib plus carboplatin[82]; and a third patient with BRCA1-mutated triple-negative breast cancer (TNBC) experienced a PR to the ATR inhibitor ceralasertib combined with olaparib[83]. Preclinical studies of BRCA1/2 inactivation in T-cell acute lymphoblastic leukemia (T-ALL)[84], ovarian carcinoma[85], and TNBC[86] showing reduced cell viability and increased DNA damage during ATR treatment further support the sensitivity of BRCA1-deficient cells to ATR inhibitors. The WEE1 inhibitor adavosertib has been evaluated as a monotherapy and in combination with PARP-inhibitor, olaparib. In a Phase 2 study for patients with PARP-resistant ovarian cancer, the combination of olaparib and adavosertib elicited improved clinical benefit (ORR: 29%; DCR: 89%) compared to adavosertib alone (ORR: 23%; DCR: 63%); however, in the BRCA-mutated cohort, no significant difference in clinical benefit was observed between the combination (ORR: 19%) and monotherapy (ORR: 20%) treatments[87]. In a Phase 1 monotherapy trial of adavosertib that included 9 patients with BRCA1/2-mutated solid tumors, 2 patients with BRCA1-mutated cancers (1 with ovarian serous carcinoma and 1 with oral squamous cell carcinoma) achieved PRs, and a third patient with ovarian serous carcinoma harboring mutations in BRCA1 and TP53 experienced 14% tumor shrinkage prior to disease progression[88].

— Nontargeted Approaches —

Germline BRCA mutations are associated with benefit from platinum chemotherapeutic agents (NCCN Breast Cancer Guidelines, v2.2022). Inactivation of BRCA1 may also predict sensitivity to the DNA-damaging agents trabectedin and lurbinectedin[89-98].

FREQUENCY & PROGNOSIS

In the Breast Invasive Carcinoma TCGA datasets, BRCA1 mutations have been reported in 2-4% of cases[43,99]. A study of patients with sporadic breast cancer identified BRCA1 mutation in 9.3% (4/43) of cases[100]. BRCA1 mutations account for approximately 4.6-7% of breast cancer cases in patients with a family history of breast cancer[101-102]. A study reported decreased nuclear BRCA1 protein expression in breast carcinoma samples (n=22), as compared to normal breast tissue[103]. For BRCA1 and BRCA2 mutation carriers, the risk of developing breast cancer by the age of 70 has been found to be approximately 57-65% and 39-49%, respectively, and a lifetime risk of up to 90% has also been reported[104-106]. One study reported that the presence of germline BRCA2 mutations was significantly associated with inferior PFS for patients with breast cancer treated with first-line CDK4/6 inhibitors plus endocrine combination therapy[107].

FINDING SUMMARY

The protein encoded by BRCA1 is involved in the maintenance of genomic stability, including DNA repair, cell cycle checkpoint, and chromosome segregation[108]. Alterations such as seen here may disrupt BRCA1 function or expression[109-111].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the BRCA1 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with hereditary breast and ovarian cancer syndrome (ClinVar, Mar 2022)[112]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Inactivating germline mutations in BRCA1 or BRCA2 are associated with autosomal dominant hereditary breast and ovarian cancer[113-114], and the lifetime risk of breast and ovarian cancer in BRCA1/2 mutation carriers has been estimated to be as high as 87% and 44%, respectively[115]. Elevated risk for other cancer types, including gastric, pancreatic, prostate, and colorectal, has also been identified, with an increase in risk ranging from 20 to 60%[116]. The estimated prevalence of deleterious germline BRCA1/2 mutations in the general population is between 1:400 and 1:800, with an approximately 10-fold higher prevalence in the Ashkenazi Jewish population[115,117-122]. In the appropriate clinical context, germline testing of BRCA1 is recommended.

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

GENE
ERBB2

ALTERATION
S310Y

TRANSCRIPT ID
NM_004448

CODING SEQUENCE EFFECT
929C>A

VARIANT ALLELE FREQUENCY (% VAF)
19.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of extensive clinical evidence, ERBB2 amplification or activating mutation may predict sensitivity to therapies targeting HER2, including antibodies such as trastuzumab[123-128], pertuzumab in combination with trastuzumab[125,129-131], and zanidatamab (ZW25)[132], as well as antibody-directed conjugates such as ado-trastuzumab emtansine (T-DM1)[133] and fam-trastuzumab deruxtecan[134], HER2 kinase inhibitors such as tucatinib[135-138], and dual EGFR/HER2 kinase inhibitors such as lapatinib[139-147], afatinib[128,148-157], neratinib[158-161], dacomitinib[162], and pyrotinib[163-164] . Patients with ERBB2-mutated breast cancer have benefited from HER2-targeted therapies. In patients with HR+ breast cancer, the triple combination of neratinib plus trastuzumab and fulvestrant achieved an ORR of 42% (14/33, 1CR) and the combination of neratinib plus fulvestrant elicited an ORR of 29% (4/14)[165]. For patients with triple negative breast cancer (TNBC), the combination of neratinib plus trastuzumab achieved an ORR of 33% (6/18, 1 CR)[165]. Pyrotinib has demonstrated an ORR of 40% (4/10) for patients with ERBB2-mutated breast cancer that was not HER2-amplified[166]. Individual patients have benefited from other HER2-targeted regimens including the triple combination of trastuzumab, pertuzumab and fulvestrant[125] and lapatinib plus trastuzumab[143,167].

FREQUENCY & PROGNOSIS

In the TCGA dataset, ERBB2 amplification was detected in 13% of breast invasive carcinoma cases[43]. ERBB2 mutations have been reported in 1-3% of breast invasive carcinoma cases[43,168-169]. The incidence of ERBB2 alterations has been found to be significantly enriched in CDH1-mutated invasive lobular breast cancers[170]. HER2 is predicted to be overexpressed (as assessed by FISH, CNV analysis, or immunohistochemistry) in 12-25% of breast cancers[171-173]. Phosphorylated HER2 was expressed in 62.5% (55/88) of HER2-positive breast cancers[174]. For patients with breast cancer and positive axillary lymph nodes, amplification of HER2 was correlated with shorter time to relapse and overall survival as compared with patients with non-amplified tumors by univariate and multivariate analysis, with greater differences observed in patients whose tumors harbored >5 copies of HER2[175]. Retrospective analysis has reported that patients with low-grade, node-negative, HER2-positive breast cancer have a 5-year survival rate of 68% compared with 96% for patients with HER2-negative tumors[176]. Alterations in ZNF703, ERBB2, MDM2, PALB2, ARFRP1, IRS2, and JAK2 may be associated with resistance to CDK4/6 inhibitors and impaired PFS for patients with HR+ metastatic breast cancer, according to a retroactive study of 131 patients[177]. Acquisition of resistance to trastuzumab was correlated with negativity for pHER2 (p=0.028) for patients with HER2-positive breast cancer[174].

FINDING SUMMARY

ERBB2 (also known as HER2) encodes a receptor tyrosine kinase which is in the same family as EGFR. S310 is located in the HER2 extracellular domain and mutations at this position, including S310F and S310Y, have been reported to be activating[178-179]. In clinical studies, patients with the ERBB2 S310F mutation have benefited from ERBB2-targeted therapies including trastuzumab, pertuzumab, and lapatinib[125,143]; a patient with concurrent EGFR L858R and ERBB2 S310F mutations also reported a complete and durable response to the dual EGFR/ERBB2 inhibitor afatinib[180].

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

GENE
FGFR1

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Alterations that activate FGFR1 may predict sensitivity to selective FGFR inhibitors including erdafitinib[181-183], pemigatinib[184], infigratinib[185-186], rogaratinib[187], Debio 1347[188-189], futibatinib[190], and derazantinib[191], or multikinase inhibitors such as pazopanib[192] and ponatinib[193-195]. The activity and efficacy of selective FGFR inhibitors for FGFR1-amplified tumors has been modest with limited responses reported in FGFR1-amplified lung squamous cell carcinoma (SCC) treated with infigratinib[196] or AZD4547[197] and no responses reported among patients with FGFR1-amplified breast cancer treated with infigratinib[196]. Two case studies reported PRs in patients with FGFR1-amplified breast cancer treated with pazopanib[192]. In a Phase 1/2a study of patients with breast carcinoma harboring an amplification of FGFR1, FGF3, FGF4, or FGF19, lucitanib resulted in a disease control rate (DCR) of 100%; 50% (6/12) of patients achieved PR and 50% (6/12) of patients had SD[198].

— Potential Resistance —

Case series have reported FGFR1 amplification for 10 patients with ER+/HER2– breast cancer who progressed on letrozole[199-201], including 1 patient with acquired resistance[201]. Amplification occurred at significantly higher incidence for resistant patients than for those sensitive to letrozole or with intermediate response (42.9% [9/21] vs. 7.5% [3/40] vs. 9.1% [1/11], p=0.0011) in 1 study[199]. Retrospective studies have reported significantly shorter time to progression (n=56, p=0.05)[202] and OS (n=94, p=0.004)[203] for patients with FGFR1-amplified versus non-amplified HR+ metastatic breast cancers treated with endocrine therapy.

FREQUENCY & PROGNOSIS

FGFR1 amplification has been reported in 10 to 27% of breast cancers[43,203-208] and correlated with FGFR1 mRNA overexpression[200,205-207,209]. FGFR1 amplification correlates with poor prognosis in patients with breast cancer[203,205,210-211], including those with HER2-positive cancer treated with adjuvant trastuzumab[210], and patients with hormone-receptor positive cancer[203,211]. For patients with HR-positive/HER2-negative breast tumors treated with first-line endocrine therapy, FGFR1 amplification associated with a shorter time to progression compared to non-amplified tumors (8.0 vs 13.3 months)[212].

FINDING SUMMARY

FGFR1 encodes the protein fibroblast growth factor receptor 1, which plays key roles in regulation of the cell cycle and angiogenesis and is an upstream regulator of the RAS, MAPK, and AKT signaling pathways[213]. Amplification of FGFR1 has been correlated with protein expression[214-215] and may predict pathway activation and sensitivity to therapies targeting this pathway[216-217].

GENE
CREBBP

ALTERATION
Q2199fs*138

TRANSCRIPT ID
NM_004380

CODING SEQUENCE EFFECT
6596_6608AGCAGCAGCAGCA>TG

VARIANT ALLELE FREQUENCY (% VAF)
14.8%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in CREBBP. The use of histone deacetylase (HDAC) inhibitors are being investigated in clinical trials that are recruiting patients with either lymphoma or urothelial carcinoma harboring CREBBP alterations. However, it has been reported that there is no correlation between CREBBP mutation status and response to HDAC inhibitors in DLBCL[218].

FREQUENCY & PROGNOSIS

CREBBP mutations have been observed at high frequency in follicular lymphoma (FL, 26%) and diffuse large B-cell lymphoma (DLBCL, 16%), and at lower frequency in acute lymphoblastic leukemia (ALL, 7%), and tumors of the urinary tract (15%), skin (12%), liver (9%), stomach (9%), and endometrium (8%)(COSMIC, 2022)[219]. These mutations include missense substitutions clustered in the CREBBP histone acetyltransferase domain and truncating mutations throughout the gene sequence, suggesting a role for CREBBP inactivation in these diseases. CREBBP mutations have been reported to occur in the transition from prostate acinar carcinoma to squamous cell carcinoma (SCC)[220], which may indicate significance for CREBBP in SCC. In two cases of relapsed pediatric B-cell ALL, CREBBP mutation conferred resistance to glucocorticoid therapy[221]. Reports have found CREBBP mutation in 62-68% of patients with FL[222-223], which was associated with immune evasion[222]. AML with MYST3/CREBBP fusion was reported to occur in 60-80% of cases 9-72 months after adjuvant chemotherapy for breast cancer and was associated with a poor prognosis[224-225].

FINDING SUMMARY

CREBBP encodes a ubiquitously expressed transcriptional coregulatory protein that interacts with multiple transcription factors and can couple control of gene expression to chromatin remodeling via its histone acetyltransferase activity. Inherited microdeletions and truncating point mutations in CREBBP are reported to be causal in approximately 20% of cases of Rubinstein-Taybi syndrome[226]. The chromosomal rearrangement t(8;16)(p11;p13) is characteristic of the M4/M5 subtype of acute myeloid leukemia (AML) and results in a chimeric gene fusing MYST3/MOZ (a gene essential for the development of the hematopoietic system and maintenance of hematopoietic stem cells) to CREBBP[227]. CREBBP-BCORL1 fusion has been reported in patients with ossifying fibromyxoid tumors[228-229].

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

GENE
MSH6

ALTERATION
E1335fs*1

TRANSCRIPT ID
NM_000179

CODING SEQUENCE EFFECT
3968_3969insTGAGAAGATGAATCAGTCACTACGATTATTTC
GGTAACTAACTAACTATAATGGAATTATAACTAACTGACCTT
AAGTTTCAAAG

VARIANT ALLELE FREQUENCY (% VAF)
8.9%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Numerous studies in various cancer types have shown that MSH6 loss or inactivation is associated with MSI and increased mutation burden[20,57,230-233]. Clinical studies have shown that MSI is associated with patient responses to anti-programmed death 1 (PD-1) immune checkpoint inhibitors pembrolizumab[4,234] and nivolumab[235]. Higher mutation burden was also reported to be associated with response to pembrolizumab[51]. Furthermore, MSI status correlates with higher PD-1 and PD-L1 expression[1], potential biomarkers of response to PD-1 targeted immunotherapies. Therefore, inactivation of MSH6 may confer sensitivity to anti-PD-1 immune checkpoint inhibitors.

FREQUENCY & PROGNOSIS

MSH6 mutations have been observed in 0-1.5% of breast invasive carcinoma cases, and deletion has not been found in any cases in multiple datasets[43,99,168,236-238]. Published data investigating the prognostic implications of MSH6 alteration in breast cancer are limited (PubMed, Oct 2021).

FINDING SUMMARY

MSH6 encodes MutS homolog 6 protein, a member of the mismatch repair (MMR) gene family. Defective MMR occurring as a result of mutation(s) in the MMR family (MLH1, MSH2, MSH6, or PMS2) can result in microsatellite instability (MSI), common in colon, endometrium, and stomach cancers[20]. Alterations such as seen here may disrupt MSH6 function or expression[239-244].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in MSH6 are associated with both "typical" and "atypical" forms of autosomal dominant Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC), which accounts for 1-7% of all colorectal cancers[245]. Approximately 10% of all Lynch syndrome-associated mutations have been attributed to alterations in MSH6[246]. Carriers of mutations in MSH6 have a 60-80% risk of colorectal cancer[247]. Lynch syndrome has an estimated prevalence in the general population ranging from 1:600 to 1:2000[245,248-249]. Biallelic germline mutation of MSH6 has been shown to account for 20% of cases of the very rare syndrome Constitutional Mismatch Repair Deficiency (CMMRD), which is characterized by a 95% incidence rate of childhood onset lymphoma, leukemia and brain tumors, followed by early-onset colorectal cancer[250-254]. Given the association between MSH6 and these inherited syndromes, in the appropriate clinical context, germline testing of MSH6 is recommended.

GENE
NSD3 (WHSC1L1)

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in NSD3.

FREQUENCY & PROGNOSIS

In TCGA datasets, NSD3 amplification has been most frequently observed in lung squamous cell carcinoma (17%)[255], breast invasive carcinoma (13%)[99], bladder urothelial carcinoma (9%)[256], and head and neck squamous cell carcinoma (9%)[257] samples[258-259]. Amplification of at least one member of the NSD3-CHD8-BRD4 pathway has been associated with worse overall survival in ovarian high-grade serous carcinoma and endometrial cancer[260]. In endometrial cancers, amplification of this pathway was more frequent in endometrial serous and endometrioid serious-like carcinomas compared to low-grade endometrioid endometrial adenocarcinomas[260].

FINDING SUMMARY

NSD3, also known as WHSC1L1, encodes an enzyme that mediates histone methylation[261]. NSD3 has been shown to be amplified in various cancers[262-264].

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

GENE
TP53

ALTERATION
M246R

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
737T>G

VARIANT ALLELE FREQUENCY (% VAF)
20.7%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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[265-268], or p53 gene therapy and immunotherapeutics such as SGT-53[269-273] and ALT-801[274]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% and SDs in 53% of patients with solid tumors; the response rate was 21% (4/19) for patients with TP53 mutations versus 12% (4/33) for patients who were TP53 wildtype[275]. 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 for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[276]. 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 for patients with platinum-refractory TP53-mutated ovarian cancer[277]. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[278]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24% (6/25) ORR with adavosertib combined with paclitaxel[279]. 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 for patients with TP53 alterations[280]. The Phase 2 FOCUS4-C trial for patients with TP53- and RAS-mutated colorectal cancer reported improvement in PFS (3.61 vs. 1.87 months, HR=0.35, p=0.0022), but not OS (14.0 vs 12.8 months, p=0.93), following adavosertib treatment compared with active monitoring[281]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for 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[273]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutated p53 such as APR-246[282-284]. In a Phase 1b trial for 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[285]. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies[286-287]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[288-289]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

TP53 is one of the most commonly mutated genes in breast cancer; mutations in this gene have been identified in 27-37% of breast carcinoma samples[43,168,236,290-292]. TP53 mutations that are located within the region encoding the DNA binding domain are associated with poor prognosis in patients with breast cancer[290,293-294]. 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[295-297].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[298]. Alterations such as seen here may disrupt TP53 function or expression[299-303].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[304-306], including sarcomas[307-308]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[309] to 1:20,000[308]. 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[310]. In the appropriate clinical context, germline testing of TP53 is recommended.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[311-316]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[311-312]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[317]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[315,318-319]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

Ado-trastuzumab emtansine

Assay findings association

ERBB2
S310Y

AREAS OF THERAPEUTIC USE

Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate that targets the protein ERBB2/HER2 on the cell surface, which inhibits HER2 signaling; it also releases the cytotoxic therapy DM1 into cells, leading to cell death. T-DM1 is FDA approved to treat patients with HER2-positive (HER2+) metastatic breast cancer and disease progression on prior therapy as well as patients with HER2+ early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment. Please see the drug label for full prescribing information.

GENE ASSOCIATION

ERBB2 amplification or activating mutations may predict sensitivity to T-DM1[133,320-335] .

SUPPORTING DATA

For patients with HER2-positive breast cancer (BC) previously treated with HER2-directed therapies, Phase 3 trials of single-agent ado-trastuzumab emtansine (T-DM1) have reported significant increases in median PFS (mPFS) compared with the physician's choice of therapy (6.2 vs. 3.3 months)[324] or lapatinib plus capecitabine (9.6 vs. 6.4 months)[133,325,329] . The Phase 3 DESTINY-Breast03 study for patients with HER2-positive metastatic BC (mBC) previously treated with trastuzumab and taxane reported significantly improved mPFS for patients treated with fam-trastuzumab deruxtecan (T-DXd) compared with T-DM1 (not reached vs. 6.8 months, HR=0.28)[336]. The Phase 3 MARIANNE study for patients with HER2-positive advanced BC treated in the first line with T-DM1 reported no significant differences in ORR (60%, 64%, and 68%) or mPFS (14.1, 15.2, and 13.7 months) when comparing T-DM1 combined with placebo, T-DM1 with pertuzumab, and trastuzumab with taxane, respectively[330]; however, an earlier Phase 2 study reported improved mPFS with T-DM1 compared with trastuzumab plus docetaxel (14.2 months vs. 9.2 months, HR=0.59) in this setting[331]. In the Phase 3 KATHERINE study, patients with HER2-positive 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% vs. 77%, HR=0.50) compared with patients treated with trastuzumab[332]. In the neoadjuvant setting, the Phase 3 KRISTINE study for patients with HER2-positive BC reported a lower pathologic CR rate (44% vs. 56%, p=0.016) with T-DM1 plus pertuzumab compared with the combination of trastuzumab, pertuzumab, docetaxel, and carboplatin[333]. Patients with HER2-positive locally advanced BC or mBC have experienced clinical benefit in Phase 1/2 studies from T-DM1 in combination with docetaxel[334], paclitaxel with or without pertuzumab (Krop et al., 2016;), neratinib[337], alpelisib[338], and tucatinib[337]. A retrospective analysis found that patients with HER2-positive 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[339].

Fam-trastuzumab deruxtecan

Assay findings association

ERBB2
S310Y

AREAS OF THERAPEUTIC USE

Fam-trastuzumab deruxtecan is an antibody-drug conjugate that targets the protein ERBB2/HER2 on the cell surface and delivers the cytotoxic payload DXd, which inhibits DNA topoisomerase I to induce DNA damage. Fam-trastuzumab deruxtecan is FDA approved to treat patients with HER2-positive breast cancer and gastric or gastroesophageal junction adenocarcinoma who have received prior HER2-targeted therapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data in non-small cell lung cancer (NSCLC)[340-341] , ERBB2 missense or exon 20 insertion mutations may predict sensitivity to fam-trastuzumab deruxtecan.

SUPPORTING DATA

The Phase 3 DESTINY-Breast03 study for patients with HER2-positive metastatic breast cancer (mBC) previously treated with trastuzumab and taxane reported a significantly improved median PFS (mPFS) for patients treated with fam-trastuzumab deruxtecan (T-DXd) compared with ado-trastuzumab emtansine (T-DM1) (not reached vs. 6.8 months, HR=0.28)[336,342] . The Phase 2 DESTINY-Breast01 study of T-DXd for patients with HER2-positive mBC previously treated with T-DM1 reported a 61% ORR (6.0% CR) and a 97% DCR with a mPFS of 16.4 months[134]. A Phase 1 trial reported similar results (60% ORR, 94% DCR, mPFS of 22.1 months) for patients with pre-treated ERBB2-positive breast cancer[343]. A Phase 1b study evaluating T-DXd to treat patients with heavily pre-treated breast cancer expressing low levels of ERBB2 reported an ORR of 37% (20/54) and a median duration of response of 10.4 months[344].

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

Lapatinib

Assay findings association

ERBB2
S310Y

AREAS OF THERAPEUTIC USE

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 to treat patients with HER2-overexpressing (HER2+) metastatic breast cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Activation or amplification of ERBB2 may predict sensitivity to lapatinib[139-147] .

SUPPORTING DATA

Case reports describe clinical benefit with tumor reduction for a patient with ERBB2 L869Q-positive metastatic lobular breast cancer on lapatinib plus capecitabine[144] and for a patient with inflammatory breast cancer harboring ERBB2 V777L and S310F mutations on lapatinib combined with capecitabine or trastuzumab[143]. Lapatinib as a treatment for HER2+ breast cancer has primarily been investigated in combination with other chemotherapeutic agents; these combination regimens have been shown to extend PFS as well as to extend OS in some instances[140-141,345-348] . However, multiple Phase 3 trials have shown superior clinical outcomes to lapatinib plus capecitabine with other HER2-targeted agents in certain settings, including trastuzumab plus taxane as first-line therapy for HER2+ metastatic breast cancer[349] and ado-trastuzumab emtansine (T-DM1) for patients who have progressed on trastuzumab plus taxane[133]. Phase 3 studies of adjuvant lapatinib have reported no significant disease-free survival benefit compared with placebo[350] or trastuzumab[351]. Phase 2/3 trials in the neoadjuvant setting have found that the combination of lapatinib and trastuzumab may result in numerically improved ORRs compared with either drug alone[346-347,352] .

Neratinib

Assay findings association

ERBB2
S310Y

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 (HER2+) breast cancer following adjuvant trastuzumab. Neratinib is also approved in combination with capecitabine to treat patients with advanced or metastatic HER2+ breast cancer who have been previously treated with 2 or more anti-HER2 regimens. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of extensive clinical[158-161,353-355] and preclinical[356-360] evidence, ERBB2 amplification or activating mutations may confer sensitivity to neratinib.

SUPPORTING DATA

The Phase 2 SUMMIT trial evaluated neratinib for the treatment of patients with ERBB2-mutated metastatic breast cancer determined by immunohistochemistry to be negative for HER2[161,165] . In SUMMIT, for patients with ER-negative tumors, the ORR and median PFS were 36% (4/11) and 2 months for single-agent neratinib[161] and 33% (6/18) and 6.2 months for neratinib in combination with trastuzumab[165]. For patients with ER-positive tumors, the ORR and median PFS were 17% (4/23) and 3.6 months for single-agent neratinib[161], 30-40% and 4-5.4 months for neratinib plus fulvestrant[161,361] , and 42% (14/33) and 7 months for neratinib plus fulvestrant and trastuzumab[165]. For patients with HER2+ metastatic breast cancer who progressed on 2 or more lines of HER2-directed therapies, the Phase 3 NALA study showed improved mean PFS (8.8 vs. 6.6 months, HR=0.76), and fewer interventions for central nervous system (CNS) disease, with neratinib plus capecitabine than with lapatinib plus capecitabine; mean OS did not significantly differ between the treatments (24.0 vs. 22.2 months, HR=0.88)[362]. In a Phase 2 study for patients with advanced HER2+ breast cancer, neratinib monotherapy resulted in median PFS of 22.3 weeks for patients previously treated with trastuzumab (n=63) and 39.6 weeks for patients with no prior trastuzumab treatment (n=64)[363]. Single-agent neratinib showed modest CNS activity (7.5% ORR, 3/40) in a Phase 2 study for patients with breast cancer and HER2+ brain metastases[364]. As first-line therapy in HER2+ metastatic breast cancer, a Phase 2 study for neratinib plus paclitaxel compared with trastuzumab plus paclitaxel reported a lower incidence of CNS disease recurrence[365]. The I-SPY 2 Phase 2 trial reported an estimated pathologic CR rate of 56% for neratinib plus paclitaxel, compared with 33% for trastuzumab plus paclitaxel, as neoadjuvant treatment for patients with HER2+, hormone receptor-negative (HR−) breast cancer[355]. In the placebo-controlled Phase 3 ExteNET study for patients with early-stage HER2+ breast cancer previously treated with trastuzumab, extended adjuvant neratinib for one year, when initiated within a year of prior trastuzumab, significantly improved 5-year invasive disease-free survival (iDFS; 90.8% vs. 85.7%, HR=0.58), and 8-year OS (91.5% vs. 89.4%, HR=0.79)[366]; however, the final OS analysis did not reach statistical significance in the intention-to-treat population (HR=0.95)[367-368] .

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

Olaparib

Assay findings association

BRCA1
K894fs*8

AREAS OF THERAPEUTIC USE

The PARP inhibitor olaparib is FDA approved to treat patients with epithelial ovarian, Fallopian tube, or primary peritoneal cancer, patients with deleterious or suspected deleterious gBRCA-mutated pancreatic adenocarcinoma or HER2-negative breast cancer, and patients with prostate cancer and mutations in homologous recombination repair genes. Olaparib is also approved in combination with bevacizumab to treat patients with ovarian, Fallopian tube, or primary peritoneal cancer with deleterious or suspected deleterious somatic or gBRCA mutation and/or genomic instability. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of extensive clinical evidence in ovarian cancer[69-73] as well as strong clinical evidence in multiple other cancer types[59-61,69,72,76,369] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to olaparib.

SUPPORTING DATA

A Phase 3 study of olaparib monotherapy for patients with germline BRCA1/2 (gBRCA1/2)-mutated HER2–metastatic breast cancer reported a significantly longer median PFS (7.0 vs. 4.2 months, HR=0.58) and a higher ORR (60% vs. 29%) compared with standard chemotherapy[62]. The Phase 3 OlympiA trial of adjuvant olaparib for patients with gBRCA1/2-mutated breast cancer reported significantly increased invasive disease-free survival (IDFS) (HR=0.63), distant DFS (DDFS) (HR=0.61), and OS (HR=0.68; p=0.0091) compared with placebo; 4-year rates of IDFS, DDFS, and OS comparing olaparib with placebo were 83% versus 75%, 87% versus 79%, and 90% versus 86%, respectively[370]. Phase 2 studies of olaparib monotherapy for patients with BRCA-mutated advanced breast cancer reported median PFS of 3.7 to 5.7 months and high clinical benefit rates (60%-85%)[59,61,72] . The Phase 2 MEDIOLA trial of olaparib with durvalumab for patients with gBRCA1/2-mutated metastatic breast cancer reported an ORR of 63%, median PFS of 8.2 months, and median OS of 21.5 months[371]. A Phase 1 trial of olaparib with the PI3K inhibitor buparlisib reported an ORR of 33% (4/12) for patients with gBRCA1/2-mutated breast cancer[372]. A Phase 1 trial of olaparib plus carboplatin for patients with gBRCA1/2-mutated breast cancer reported an ORR of 88% (7/8)[373]. In a Phase 2 study of olaparib plus pembrolizumab for advanced solid tumors, patients with BRCA1 or BRCA2 mutations achieved an ORR of 29% (6/21), whereas patients with mutations in other homologous recombination repair genes achieved an ORR of 6.3% (2/32)[374]. Phase 1 trials of olaparib plus chemotherapy for patients with triple-negative breast cancer (TNBC) reported ORRs of 37-38%[375-376] . A small Phase 1 trial reported a 20% ORR (1/5) for patients with breast cancer and wild-type germline BRCA status following combination treatment with olaparib and buparlisib[372]. A Phase 2 study comparing durvalumab in combination with olaparib and paclitaxel to chemotherapy alone reported pathologic complete response (pCR) for 37% versus 22% of patients with HER2-negative breast cancer, 47% versus 27% of patients with TNBC, and 28% versus 14% of patients with HR-positive HER2-negative breast cancer[377].

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

Talazoparib

Assay findings association

BRCA1
K894fs*8

AREAS OF THERAPEUTIC USE

The PARP inhibitor talazoparib is FDA approved to treat HER2-negative locally advanced or metastatic breast cancer with deleterious or suspected deleterious germline BRCA mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of strong clinical data in breast cancer[80,378-379] and additional clinical evidence in ovarian, pancreatic, and prostate cancer[380-383] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to talazoparib.

SUPPORTING DATA

In the Phase 3 EMBRACA trial, patients with HER2-negative (HER2–) advanced breast cancer and germline BRCA mutations achieved significantly longer median PFS (8.6 vs. 5.6 months, HR=0.54), a higher ORR (63% vs. 27%), and improved quality of life on talazoparib compared with standard chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine)[80,379] . Clinical benefit from talazoparib was observed for patients with either triple-negative or hormone-receptor-positive (HR+) breast cancer, and for those with CNS metastases[80]. Final OS analysis showed that talazoparib did not significantly improve OS compared with chemotherapy (median OS [mOS] 19.3 vs. 19.5 months, HR=0.85) but did significantly delay definitive clinically meaningful deterioration in global health status/quality of life[384]. Retrospective genomic analysis showed that MYC amplification was associated with significantly shorter mOS for patients with triple-negative cancer treated with talazoparib, but not for those treated with chemotherapy; in contrast, for patients with HR+ cancer, MYC amplification was associated with shorter mOS for the chemotherapy treatment group, but not for the talazoparib treatment group[385]. The efficacy of single-agent talazoparib for the treatment of BRCA-mutated advanced breast cancer was also demonstrated in earlier-phase studies, which reported ORRs of 21%-50%[381,386]. As neoadjuvant treatment for early BRCA-mutated HER2 – breast cancer, talazoparib led to a pathologic complete response (pCR) for 46% (22/48) of patients[387]. In the Phase 2 I-SPY2 trial, patients with early-stage, high-risk HER2– breast cancer who received talazoparib with synergy-dosed irinotecan (TI) reported fewer Grade 3/4 adverse events compared with the chemotherapy control arm (paclitaxel with doxorubicin and cyclophosphamide), although a similar pCR rate was observed. Notably, 6 out of 10 patients with germline BRCA mutations achieved a pCR with TI treatment[388]. A Phase 1b/2 trial studying the combination of the BET inhibitor ZEN003694 with talazoparib in patients with TNBC without germline BRCA1/2 mutations reported an ORR of 38% (5/13), including 1 CR and 4 PRs, and a clinical benefit rate of 57% (8/14)[389]. In a Phase 2 study of talazoparib for BRCA1/2-wildtype patients with homologous recombination pathway alterations, those with HER2– advanced breast cancer experienced an ORR of 31% (4/13 PRs), with responses observed for 3 patients with germline PALB2 mutations and for 1 patient with germline CHEK2 and FANCA mutations, as well as somatic PTEN mutation; 3 additional patients with germline PALB2 or somatic ATR or alterations had SD ≥6 months[390].

Trastuzumab

Assay findings association

ERBB2
S310Y

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 chemotherapy for HER2+ metastatic gastric or gastroesophageal adenocarcinoma. Trastuzumab biosimilars are also FDA approved for these indications. Please see the drug label(s) for full prescribing information.

GENE ASSOCIATION

On the basis of clinical studies in multiple tumor types, ERBB2 amplification, overexpression, or activating mutations may confer sensitivity to trastuzumab[123-124,128,143,391-395] .

SUPPORTING DATA

In a case report, a patient with breast cancer and ERBB2 S310F had 12 months of clinical benefit from the combination of trastuzumab, pertuzumab, and fulvestrant[125]. In a second case report, a patient with inflammatory breast cancer and ERBB2 V777L and S310F activating mutations experienced tumor shrinkage in response to combined treatment with lapatinib and trastuzumab[143]. A Phase 3 study of adjuvant trastuzumab with chemotherapy for patients with metastatic HER2-positive breast cancer (HER2+ BC) demonstrated significant improvements in OS, time to progression, and ORR[123]. Trastuzumab biosimilars demonstrated comparable clinical benefit to trastuzumab for patients with HER2+ BC[396-404] . In the Phase 3 NOAH study for patients with HER2+ BC, neoadjuvant trastuzumab plus chemotherapy resulted in improved 5-year event-free survival (EFS) compared with neoadjuvant chemotherapy alone (58% vs. 43%)[391]. The Phase 3 CLEOPATRA study of first-line trastuzumab with pertuzumab and docetaxel for patients with metastatic HER2+ BC reported significantly improved median PFS (18.7 vs. 12.4 months, HR=0.69) and median OS (57.1 vs. 40.8 months, HR=0.69) compared with trastuzumab plus docetaxel[129-130,405-406] . The Phase 3 NeoALTTO trial for patients with early-stage HER2+ BC 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[352]. Two Phase 3 studies comparing 6-month with 12-month adjuvant trastuzumab reported similar disease-free survival (DFS) rates for patients with HER2+ early-stage BC after 5.4 years (89.4% vs. 89.8%, HR=1.07)[407] or 7.5-year median follow-up (78.8% vs. 79.6%, HR=1.08)[408]. The randomized Phase 3 NSABP B-47 study reported that the addition of trastuzumab to adjuvant chemotherapy did not significantly improve invasive disease-free survival (IDFS) for patients with HER2-low BC (defined as IHC score of 1+ or 2+ in the absence of gene amplification) compared with chemotherapy alone (5-year IDFS rates of 89.8% vs. 89.2%, HR=0.98; p=0.85); this response was reported regardless of lymph node involvement or HR status[409]. A Phase 2 analysis reported 5-year distant DFS rates of 92% for patients with HER2+ early-stage BC treated with chemotherapy and trastuzumab, and 89% for patients treated with lapatinib and chemotherapy[392]. In the Phase 3 BOLERO-1 trial, first-line treatment with everolimus and trastuzumab plus paclitaxel versus placebo for patients with HER2+ advanced BC did not significantly improve median PFS (15.0 vs. 14.5 months); however, the regimen increased PFS in the HR-negative subpopulation (20.3 vs. 13.1 months, HR=0.66)[410]. Everolimus plus trastuzumab with vinorelbine prolonged median PFS (7.0 vs. 5.8 months, HR=0.78), relative to the addition of placebo, for patients with trastuzumab-resistant HER2+ BC treated in the Phase 3 BOLERO-3 trial[411]. In a Phase 2 trial for patients with HER2+ metastatic BC previously treated with HER2-targeting agents, tucatinib plus trastuzumab and capecitabine significantly extended median PFS (7.8 vs. 5.6 months) and increased the 1-year median PFS rate (33.1% vs. 12.3%, HR=0.54) and 2-year median OS rate (44.9% vs. 26.6%, HR=0.66) compared with placebo with trastuzumab and capecitabine[135]. For patients with HR+, HER2+ BC who had received prior HER2-targeted therapy, abemaciclib combined with trastuzumab and fulvestrant compared with abemaciclib plus trastuzumab or trastuzumab plus chemotherapy significantly improved median PFS (8.3 vs. 5.7 vs. 5.7 months) and ORR (35.7% vs. 16.2% vs. 15.9%) in Phase 2 monarcHER study[412].

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

Trastuzumab + Pertuzumab

Assay findings association

ERBB2
S310Y

AREAS OF THERAPEUTIC USE

Trastuzumab is a monoclonal antibody that targets ERBB2/HER2, and pertuzumab is a monoclonal antibody that interferes with the interaction between HER2 and ERBB3. These therapies are FDA approved in combination for the treatment of patients with HER2-positive (HER2+) metastatic breast cancer who have not received prior chemotherapy or HER2-targeted therapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical studies in multiple tumor types, ERBB2 amplification or activating mutations may predict sensitivity to trastuzumab in combination with pertuzumab[130,393,413-417] .

SUPPORTING DATA

For patients with HER2+ breast cancer receiving trastuzumab and pertuzumab with chemotherapy, ERBB2 amplification detected by NGS significantly associated with improved PFS (22.8 vs. 9.4 months; HR=1.79)[418]. In a case report, a patient with breast cancer and ERBB2 S310F had 12 months of clinical benefit from the combination of trastuzumab, pertuzumab, and fulvestrant[125]. The CLEOPATRA Phase 3 randomized trial for patients with HER2+ metastatic breast cancer (MBC) reported that the addition of pertuzumab to first-line trastuzumab and docetaxel demonstrated a significant improvement in median PFS (mPFS; 18.7 vs. 12.4 months, HR=0.69) and median OS (mOS; 57.1 vs. 40.8 months, HR=0.69) compared with the addition of placebo to this regimen[129-130,405-406] . Superior clinical benefit has been observed in multiple clinical studies in which pertuzumab was added to the combination of trastuzumab plus chemotherapy, as compared with other combinations of pertuzumab, trastuzumab, and/or chemotherapy, for patients with HER2+ MBC and locally advanced breast cancer (LABC)[416,419-422] . For patients with HER2+ and hormone receptor-positive (HR+) MBC/LABC, addition of pertuzumab to trastuzumab plus an aromatase inhibitor (AI) significantly increased mPFS compared with trastuzumab plus AI alone (20.6 vs. 15.8 months, respectively; HR=0.67) but did not significantly improve mOS (60.2 vs. 57.2 months, respectively; HR=1.05)[423]. In the Phase 3 APHINITY study for patients with HER2+ early-stage breast cancer, the addition of pertuzumab to chemotherapy plus trastuzumab as adjuvant treatment improved the estimated 3-year rate of invasive disease-free survival (IDFS) compared with the addition of placebo to this regimen (94% vs. 93%), with greater improvement seen for patients with node-positive (92% vs. 90%, HR=0.77) versus node-negative (97.5% vs. 98.4%, HR=1.13) disease[414]. Clinical benefit for HER2+ early-stage breast cancer was also reported for patients treated with pertuzumab, trastuzumab, and chemotherapy in the neoadjuvant setting followed by pertuzumab combined with trastuzumab in the adjuvant setting[424]. In the Phase 3 KRISTINE trial, patients with HER2+ Stage 2 to Stage 3 breast cancer treated in the neoadjuvant setting experienced an increased number of pathological CRs (pCRs) when treated with pertuzumab, trastuzumab, and chemotherapy, compared with those treated with trastuzumab emtansine plus pertuzumab (56% vs. 44%, respectively)[413].

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

Niraparib

Assay findings association

BRCA1
K894fs*8

AREAS OF THERAPEUTIC USE

The PARP inhibitor niraparib is FDA approved to treat patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer, with or without homologous recombination deficiency (HRD)-positive status. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in ovarian and breast cancers[63-64,425] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors such as niraparib.

SUPPORTING DATA

In a Phase 1 study of niraparib treatment for patients with solid tumors, 2/4 patients with BRCA1/2-mutated breast cancer experienced PR[64]. A Phase 3 study comparing niraparib monotherapy to physician's choice single-agent chemotherapy for patients with germline BRCA-mutated HER2-negative breast cancer reported an ORR of 35% for the niraparib arm compared with 31% for the chemotherapy arm[426]. However, the trial was unable to accurately assess if PFS was longer for the niraparib arm due to informative censoring for the chemotherapy arm[426]. A Phase 2 study combining the PD-1 inhibitor pembrolizumab with niraparib for patients with triple-negative breast cancer (TNBC) reported an ORR of 21% (10/47) and DCR of 49% (23/47); subgroup analysis showed higher ORR (47% [7/15] vs. 11% [3/27]) and improved median PFS (8.3 vs. 2.1 months) for patients with BRCA1/2-mutated tumors versus BRCA1/2-wildtype tumors[427].

Pazopanib

Assay findings association

FGFR1
amplification - equivocal

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

Based on PRs in two patients with FGFR1-amplified breast cancer, pazopanib may be effective in this context[192,428] .

SUPPORTING DATA

A Phase 2 clinical trial of pazopanib in breast cancer reported 55% disease stabilization[429]. A Phase 2 study of heavily pretreated post-menopausal hormone receptor positive (HR+) breast cancer treated with a combination of pazopanib and nonsteroidal aromatase inhibitor reported 7% PRs (2/28) and 18% SD (5/28), with 7 patients having PFS greater than 6 months[430]. Phase 2 clinical trials of pazopanib with lapatinib in patients with HER2-positive breast cancer reported that the combination was associated with higher response rate than lapatinib alone but did not bring about an increase in PFS[431-432] . A multicenter single-arm Phase 2 study evaluating pazopanib combined with paclitaxel as neoadjuvant following doxorubicin/cyclophosphamide reported CRs in 9% (6/67) and 38% (10/26) of patients with HR+ and triple-negative locally advanced breast cancer cases, respectively; however, a high level of toxicity led to discontinuation of pazopanib in 61% of patients[433].

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

Rucaparib

Assay findings association

BRCA1
K894fs*8

AREAS OF THERAPEUTIC USE

The PARP inhibitor rucaparib is FDA approved to treat patients with metastatic castration-resistant prostate cancer (mCRPC) or epithelial ovarian, Fallopian tube, or primary peritoneal cancer and deleterious somatic or germline BRCA mutations. Rucaparib is also approved as a maintenance treatment of patients with recurrent epithelial ovarian, Fallopian tube, or primary peritoneal cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of strong clinical evidence in ovarian cancer[65-66,276] , as well as clinical data in other cancer types[66,434-435] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to rucaparib.

SUPPORTING DATA

A Phase 2 study evaluating rucaparib for patients with advanced germline BRCA1/2-mutated breast or ovarian cancer reported no responders by ORR (9 SDs) among 23 patients with breast cancer[66]. However, in another Phase 1-2 study of rucaparib for patients with solid tumors, 1 CR and 4 PRs were reported for patients with BRCA1/2-mutated breast cancer[436]. A Phase 2 study for pretreated patients with triple-negative breast cancer (TNBC) or BRCA-mutated BC reported that the addition of rucaparib to cisplatin compared with cisplatin alone did not increase 2-year (64% vs. 54%) or 5-year disease-free survival rates (38% vs. 50%), independent of BRCA status[437]. In a Phase 2 study evaluating rucaparib in combination with chemotherapy for patients with solid tumors, 1 patient with BC experienced a CR and 1 patient with BRCA1-mutated BC achieved a PR[438].

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

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

CLINICAL TRIALS

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

GENE
BRCA1

RATIONALE
BRCA1 loss or inactivating alterations may predict sensitivity to PARP inhibitors or ATR inhibitors.

ALTERATION
K894fs*8

NCT04915755

PHASE 3

Efficacy and Safety Comparison of Niraparib to Placebo in Participants With Either Human Epidermal Growth Factor 2 Negative (HER2-) Breast Cancer Susceptibility Gene Mutation (BRCAmut) or Triple-Negative Breast Cancer (TNBC) With Molecular Disease

TARGETS
PARP

LOCATIONS: Brindisi (Italy), Catania (Italy), Napoli (Italy), Rzeszow (Poland), Krakow (Poland), Meldola (FC) (Italy), Ryazan (Russian Federation), Bologna (Italy), Warszawa (Poland), Padova (Italy)

NCT04644068

PHASE 1/2

Study of AZD5305 as Monotherapy and in Combination With Anti-cancer Agents in Patients With Advanced Solid Malignancies

TARGETS
ERBB2, TROP2, PARP

LOCATIONS: Napoli (Italy), Budapest (Hungary), Roma (Italy), Brno (Czechia), Padova (Italy), Warszawa (Poland), Modena (Italy), Milan (Italy), Gdynia (Poland), Grzepnica (Poland)

NCT04768296

PHASE 2

Berzosertib + Topotecan in Relapsed Platinum-Resistant Small-Cell Lung Cancer (DDRiver SCLC 250)

TARGETS
TOP1, ATR

LOCATIONS: Roma (Italy), Rome (Italy), Meldola (Italy), Pisa (Italy), Milano (Italy), Strasbourg (France), Barcelona (Spain), Arlon (Belgium), Yvoir (Belgium), Brussels (Belgium)

NCT02810743

PHASE 3

Substantially Improving the Cure Rate of High-risk BRCA1-like Breast Cancer

TARGETS
PARP

LOCATIONS: Marseille (France), Maastricht (Netherlands), Enschede (Netherlands), NIjmegen (Netherlands), Groningen (Netherlands), Utrecht (Netherlands), Amsterdam (Netherlands), Rotterdam (Netherlands), Leiden (Netherlands)

NCT04497116

PHASE 1/2

Study of RP-3500 in Advanced Solid Tumors

TARGETS
ATR, PARP

LOCATIONS: Copenhagen (Denmark), London (United Kingdom), Manchester (United Kingdom), Newcastle Upon Tyne (United Kingdom), Massachusetts, Rhode Island, New York, Toronto (Canada), North Carolina, Illinois

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

NCT02264678

PHASE 1/2

Ascending Doses of AZD6738 in Combination With Chemotherapy and/or Novel Anti Cancer Agents

TARGETS
ATR, PARP, PD-L1

LOCATIONS: Villejuif (France), Bordeaux (France), Sutton (United Kingdom), Cambridge (United Kingdom), Oxford (United Kingdom), Coventry (United Kingdom), Manchester (United Kingdom), Withington (United Kingdom), Goyang-si (Korea, Republic of), Seoul (Korea, Republic of)

NCT03907969

PHASE 1/2

A Clinical Trial to Evaluate AZD7648 Alone and in Combination With Other Anti-cancer Agents in Patients With Advanced Cancers

TARGETS
PARP, DNA-PK

LOCATIONS: London (United Kingdom), Newcastle upon Tyne (United Kingdom), Connecticut, Texas

NCT04657068

PHASE 1/2

A Study of ART0380 for the Treatment of Advanced or Metastatic Solid Tumors

TARGETS
ATR

LOCATIONS: London (United Kingdom), Pennsylvania, Tennessee, Florida, Oklahoma, Colorado

NCT04991480

PHASE 1/2

A Study of ART4215 for the Treatment of Advanced or Metastatic Solid Tumors

TARGETS
PARP, Pol theta

LOCATIONS: London (United Kingdom), New York, Tennessee, Florida, Oklahoma, Texas

NCT03150576

PHASE 2/3

Platinum and Polyadenosine 5'Diphosphoribose Polymerisation (PARP) Inhibitor for Neoadjuvant Treatment of Triple Negative Breast Cancer (TNBC) and/or Germline BRCA (gBRCA) Positive Breast Cancer

TARGETS
PARP

LOCATIONS: Cambridge (United Kingdom)

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

GENE
ERBB2

ALTERATION
S310Y

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.

NCT04494425

PHASE 3

Study of Trastuzumab Deruxtecan (T-DXd) vs Investigator's Choice Chemotherapy in HER2-low, Hormone Receptor Positive, Metastatic Breast Cancer

TARGETS
ERBB2

LOCATIONS: Jerusalem (Israel), Petah Tikva (Israel), Kfar-Saba (Israel), Ramat Gan (Israel), Tel-Aviv (Israel), Haifa (Israel), Jeddah (Saudi Arabia), Makkah (Saudi Arabia), Riyadh (Saudi Arabia), Ar Riyā? (Saudi Arabia)

NCT04589845

PHASE 2

Tumor-Agnostic Precision Immuno-Oncology and Somatic Targeting Rational for You (TAPISTRY) Platform Study

TARGETS
TRKB, ALK, TRKC, ROS1, TRKA, RET, PD-L1, AKTs, ERBB2, MDM2, PI3K-alpha

LOCATIONS: Petach Tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Haifa (Israel), Napoli (Italy), Roma (Italy), Firenze (Italy), Warszawa (Poland), Brescia (Italy), München (Germany)

NCT04739761

PHASE 3

A Study of T-DXd in Participants With or Without Brain Metastasis Who Have Previously Treated Advanced or Metastatic HER2 Positive Breast Cancer

TARGETS
ERBB2

LOCATIONS: Catania (Italy), Napoli (Italy), Ancona (Italy), Kraków (Poland), Opole (Poland), Prato (Italy), Padova (Italy), Warszawa (Poland), Bergamo (Italy), München (Germany)

NCT04644068

PHASE 1/2

Study of AZD5305 as Monotherapy and in Combination With Anti-cancer Agents in Patients With Advanced Solid Malignancies

TARGETS
ERBB2, TROP2, PARP

LOCATIONS: Napoli (Italy), Budapest (Hungary), Roma (Italy), Brno (Czechia), Padova (Italy), Warszawa (Poland), Modena (Italy), Milan (Italy), Gdynia (Poland), Grzepnica (Poland)

NCT04579380

PHASE 2

Basket Study of Tucatinib and Trastuzumab in Solid Tumors With HER2 Alterations

TARGETS
ERBB2, ER

LOCATIONS: Milano (Italy), Monza (Italy), Poznan (Poland), Barcelona (Spain), L'Hospitalet de Llobregat (Spain), Liege (Belgium), Charleroi (Belgium), Brussels (Belgium), Edegem (Belgium), Valencia (Spain)

NCT04752059

PHASE 2

Phase II Study of T-DX in HER2-positive Breast Cancer Brain Metastases

TARGETS
ERBB2

LOCATIONS: Vienna (Austria)

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

CLINICAL TRIALS

NCT04042701

PHASE 1

DS8201a and Pembrolizumab in Participants With Locally Advanced/Metastatic Breast or Non-Small Cell Lung Cancer

TARGETS
PD-1, ERBB2

LOCATIONS: Marseille (France), Barcelona (Spain), Toulouse (France), Marsielle (France), Créteil (France), Villejuif (France), Zaragoza (Spain), Bordeaux (France), Sutton (United Kingdom), London (United Kingdom)

NCT04460430

PHASE 2

Targeting EGFR/ERBB2 With Neratinib in Hormone Receptor (HR)-Positive/HER2-negative HER2-enriched Advanced/Metastatic Breast Cancer

TARGETS
ERBB2, EGFR, ERBB4, ER, Aromatase

LOCATIONS: Palma de Mallorca (Spain), Barcelona (Spain), Badalona (Spain), Lleida (Spain), Denia (Spain), Granada (Spain), Madrid (Spain), Jaén (Spain), Sevilla (Spain)

NCT04983238

PHASE 1/2

Evaluation of Safety and Efficacy of Sodium Thiosulfate (BYON5667) Eye Drops to Reduce Ocular Toxicity in Cancer Patients Treated With SYD985

TARGETS
ERBB2

LOCATIONS: Barcelona (Spain), Llobregat (Spain), Lleida (Spain), Leuven (Belgium), Antwerp (Belgium), Paris (France), Lille (France), Bordeaux (France), Madrid (Spain)

NCT03810872

PHASE 2

An Explorative Study of Afatinib in the Treatment of Advanced Cancer Carrying an EGFR, a HER2 or a HER3 Mutation

TARGETS
EGFR, ERBB4, ERBB2

LOCATIONS: Liège (Belgium), Brussels (Belgium), Gent (Belgium)

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

GENE
FGFR1

RATIONALE
FGFR inhibitors may be relevant in tumors with alterations that activate FGFR1.

ALTERATION
amplification - equivocal

NCT03564691

PHASE 1

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

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

LOCATIONS: Petah Tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Haifa (Israel), Heraklion (Greece), Warszawa (Poland), Gdansk (Poland), Hospitalet de Llobregat (Spain), Madrid (Spain), Johannesburg (South Africa)

NCT04024436

PHASE 2

A Study of TAS-120 in Patients With Metastatic Breast Cancer

TARGETS
FGFRs, ER

LOCATIONS: Catania (Italy), Roma (Italy), Pisa (Italy), Modena (Italy), Milano (Italy), Pinerolo (Italy), Lyon (France), Barcelona (Spain), Villejuif (France), Sutton (United Kingdom)

NCT02549937

PHASE 1/2

A Multi-Center, Open-Label Study of Sulfatinib(HMPL-012) in Patients With Advanced Solid Tumors

TARGETS
FGFR1, CSF1R, VEGFRs

LOCATIONS: Milano (Italy), New York, Virginia, Tennessee, Florida, Colorado, Texas, California

NCT04483505

PHASE 1

Rogaratinib, Palbociclib y Fulvestrant in Patients With Breast Cancer.

TARGETS
CDK6, ER, CDK4, FGFR1, FGFR3, FGFR2, FGFR4

LOCATIONS: Hospitalet de Llobregat (Spain), Lleida (Spain), Valencia (Spain), Madrid (Spain), Pozuelo De Alarcón (Spain), Fuenlabrada (Spain)

NCT02856425

PHASE 1

Trial Of Pembrolizumab And Nintedanib

TARGETS
FGFR1, LCK, SRC, VEGFRs, FGFR2, FGFR3, FLT3, LYN, PD-1

LOCATIONS: Villejuif (France)

NCT04977453

PHASE 1/2

GI-101 as a Single Agent or in Combination With Pembrolizumab, Lenvatinib or Local Radiotherapy in Advanced Solid Tumors

TARGETS
FGFRs, RET, PDGFRA, VEGFRs, KIT, PD-1, CTLA-4

LOCATIONS: Seoul (Korea, Republic of), Suwon-si (Korea, Republic of), Daejeon (Korea, Republic of)

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

CLINICAL TRIALS

NCT04962867

PHASE 2

NCCH2006/MK010 Trial (FORTUNE Trial)

TARGETS
FGFR1, FGFR2, FGFR3

LOCATIONS: Higashi-Ku, Fukuoka (Japan), Kita-Ku, Sapporo, Hokkaido (Japan), Sakyo-ku, Kyoto (Japan), Aoba-ku, Sendai, Miyagi (Japan), Chuo-ku, Tokyo (Japan)

NCT04965818

PHASE 1/2

Phase 1b/2 Study of Futibatinib in Combination With Binimetinib in Patients With Advanced KRAS Mutant Cancer

TARGETS
MEK, FGFRs

LOCATIONS: Indiana, Texas, California

NCT04169672

PHASE 2

Study of Surufatinib Combined With Toripalimab in Patients With Advanced Solid Tumors

TARGETS
FGFR1, CSF1R, VEGFRs, PD-1

LOCATIONS: Beijing (China), Shanghai (China)

NCT04803318

PHASE 2

Trametinib Combined With Everolimus and Lenvatinib for Recurrent/Refractory Advanced Solid Tumors

TARGETS
mTOR, FGFRs, RET, PDGFRA, VEGFRs, KIT, MEK

LOCATIONS: Guangzhou (China)

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

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	***CREBBP***	***NOTCH3***	***TEK***
R597C	Q2196L	H170R	T503I

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

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

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B or WTX)*	
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*	*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*	*EMSY (C11orf30)*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
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	*GID4 (C17orf39)*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3-3A (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*	*MRE11 (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*	*NSD2 (WHSC1 or MMSET)*		*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*
P2RY8	*PALB2*	*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*
PRKN (PARK2)	*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*	*TENT5C (FAM46C)*	*TET2*	*TGFBR2*	*TIPARP*
TNFAIP3	*TNFRSF14*	*TP53*	*TSC1*	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*	*VHL*
WT1	*XPO1*	*XRCC2*	*ZNF217*	*ZNF703*				

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	*BCL2*	*BCR*	*BRAF*	*BRCA1*	*BRCA2*	*CD74*	*EGFR*	*ETV1*
ETV4	*ETV5*	*ETV6*	*EWSR1*	*EZR*	*FGFR1*	*FGFR2*	*FGFR3*	*KIT*
KMT2A (MLL)	*MSH2*	*MYB*	*MYC*	*NOTCH2*	*NTRK1*	*NTRK2*	*NUTM1*	*PDGFRA*
RAF1	*RARA*	*RET*	*ROS1*	*RSPO2*	*SDC4*	*SLC34A2*	*TERC**	*TERT***
TMPRSS2								

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

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

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLES

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

Therapies are ranked based on the following criteria: Therapies with clinical benefit (ranked alphabetically within each evidence category), followed by therapies associated with resistance (when applicable).

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations

1. In the fractional-based MSI algorithm, a tumor specimen will be categorized as MSI-H, MSS, or MS-Equivocal according to the fraction of microsatellite loci determined to be altered or unstable (i.e., the fraction unstable loci score). In the F1CDx assay, MSI is evaluated based on a genome-wide analysis across >2000 microsatellite loci. For a given microsatellite locus, non-somatic alleles are discarded, and the microsatellite is categorized as unstable if remaining alleles differ from the reference genome. The final fraction unstable loci score is calculated as the number of unstable microsatellite loci divided by the number of evaluable microsatellite loci. The MSI-H and MSS cut-off thresholds were determined by analytical concordance to a PCR comparator assay using a pan-tumor FFPE tissue sample set. Patients with results categorized as "MS-

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

Stable" with median exon coverage <300X, "MS-Equivocal," or "Cannot Be Determined" should receive confirmatory testing using a validated orthogonal (alternative) method.

2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.
3. Homologous Recombination status may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas (Coleman et al., 2017; 28916367). Samples with deleterious *BRCA1/2* alteration and/or Loss of Heterozygosity (LOH) score ≥ 16% will be reported as "HRD Positive" and samples with absence of these findings will be reported as "HRD Not Detected," agnostic of potential secondary *BRCA1/2* reversion alterations. Certain potentially deleterious missense or small in-frame deletions in *BRCA1/2* may not be classified as deleterious and, in the absence of an elevated LOH profile, samples with such mutations may be classified as "HRD Not Detected." A result of "HRD Not Detected" does not rule out the presence of a *BRCA1/2* alteration or an elevated LOH profile outside the assay performance characteristic limitations.
4. 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.
5. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
6. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
7. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

REPORT HIGHLIGHTS

The Report Highlights includes select genomic and therapeutic information with potential impact on patient care and treatment that is specific to the genomics and tumor type of the sample analyzed. This section may highlight information including targeted therapies with potential sensitivity or resistance; evidence-matched clinical trials; and variants with potential diagnostic, prognostic, nontargeted treatment, germline, or clonal hematopoiesis implications. Information included in the Report Highlights is expected to evolve with advances in scientific and clinical research. Findings included in the Report Highlights should be considered in the context of all other information in this report and other relevant patient information. Decisions on patient care and treatment are the responsibility of the treating physician.

VARIANT ALLELE FREQUENCY

Variant Allele Frequency (VAF) represents the fraction of sequencing reads in which the variant is observed. This attribute is not taken into account for therapy inclusion, clinical trial matching, or interpretive content. Caution is recommended in interpreting VAF to indicate the potential germline or somatic origin of an alteration, recognizing that tumor fraction and tumor ploidy of samples may vary.

Precision of VAF for base substitutions and indels

BASE SUBSTITUTIONS	%CV*
Repeatability	5.11 - 10.40
Reproducibility	5.95 - 12.31
INDELS	**%CV***
Repeatability	6.29 - 10.00
Reproducibility	7.33 - 11.71

**Interquartile Range = 1st Quartile to 3rd Quartile*

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

The variants indicated for consideration of follow-up germline testing are 1) limited to reportable short variants with a protein effect listed in the ClinVar genomic database (Landrum et al., 2018; 29165669) as Pathogenic, Pathogenic/Likely Pathogenic, or Likely Pathogenic (by an expert panel or multiple submitters), 2) associated with hereditary cancer-predisposing disorder(s), 3) detected at an allele frequency of >10%, and 4) in select genes reported by the ESMO Precision Medicine Working Group (Mandelker et al., 2019; 31050713) to have a greater than 10% probability of germline origin if identified during tumor sequencing. The selected genes are *ATM, BAP1, BRCA1, BRCA2, BRIP1, CHEK2, FH, FLCN, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, POLE, RAD51C, RAD51D, RET, SDHA, SDHB, SDHC, SDHD, TSC2,* and *VHL*, and are not inclusive of all cancer susceptibility genes. The content in this report should not substitute for genetic counseling or follow-up germline testing, which is needed to distinguish whether a finding in this patient's tumor sequencing is germline or somatic. Interpretation should be based on clinical context.

VARIANTS THAT MAY REPRESENT

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

CLONAL HEMATOPOIESIS

Variants that may represent clonal hematopoiesis (CH) are limited to select reportable short variants in defined genes identified in solid tumors only. Variant selection was determined based on gene tumor-suppressor or oncogene status, known role in solid tumors versus hematological malignancies, and literature prevalence. The defined genes are *ASXL1, CBL, DNMT3A, IDH2, JAK2, KMT2D (MLL2), MPL, MYD88, SF3B1, TET2,* and *U2AF1* and are not inclusive of all CH genes. The content in this report should not substitute for dedicated hematological workup. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH. Interpretation should be based on clinical context.

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

REFERENCE SEQUENCE INFORMATION

Sequence data is mapped to the human genome, Genome Reference Consortium Human Build 37 (GRCh37), also known as hg19.

MR Suite Version 6.3.0

The median exon coverage for this sample is 785x

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

1. Gatalica Z, et al. Cancer Epidemiol. Biomarkers Prev. (2014) pmid: 25392179
2. Kroemer G, et al. Oncoimmunology (2015) pmid: 26140250
3. Lal N, et al. Oncoimmunology (2015) pmid: 25949894
4. Le DT, et al. N. Engl. J. Med. (2015) pmid: 26028255
5. Ayers et al., 2016; ASCO-SITC Abstract P60
6. Anbazhagan R, et al. Clin. Cancer Res. (1999) pmid: 10213220
7. Adem C, et al. Int. J. Cancer (2003) pmid: 14520695
8. Horimoto Y, et al. Cancer Sci (2020) pmid: 32449246
9. Heeke AL, et al. Breast Cancer Res Treat (2020) pmid: 32776290
10. Kurata K, et al. Breast Cancer (2020) pmid: 31907878
11. Sivapiragasam A, et al. Cancer Med (2020) pmid: 33314633
12. Walsh MD, et al. Clin. Cancer Res. (2010) pmid: 20215533
13. Risinger JI, et al. Cancer (1996) pmid: 8646682
14. de Leeuw WJ, et al. Cancer Res. (2003) pmid: 12615735
15. Shanley S, et al. Fam. Cancer (2009) pmid: 19123071
16. Buerki N, et al. Genes Chromosomes Cancer (2012) pmid: 22034109
17. Yee CJ, et al. Cancer Res. (1994) pmid: 8137273
18. Kamat N, et al. BMC Cancer (2012) pmid: 22928966
19. Kocarnik JM, et al. Gastroenterol Rep (Oxf) (2015) pmid: 26337942
20. You JF, et al. Br. J. Cancer (2010) pmid: 21081928
21. Bairwa NK, et al. Methods Mol. Biol. (2014) pmid: 24623249
22. Boland CR, et al. Cancer Res. (1998) pmid: 9823339
23. Pawlik TM, et al. Dis. Markers (2004) pmid: 15528785
24. Boland CR, et al. Gastroenterology (2010) pmid: 20420947
25. Samstein RM, et al. Nat. Genet. (2019) pmid: 30643254
26. Goodman AM, et al. Mol. Cancer Ther. (2017) pmid: 28835386
27. Goodman AM, et al. Cancer Immunol Res (2019) pmid: 31405947
28. Cristescu R, et al. Science (2018) pmid: 30309915
29. Ready N, et al. J. Clin. Oncol. (2019) pmid: 30785829
30. Hellmann MD, et al. N. Engl. J. Med. (2018) pmid: 29658845
31. Hellmann MD, et al. Cancer Cell (2018) pmid: 29657128
32. Hellmann MD, et al. Cancer Cell (2018) pmid: 29731394
33. Rozeman EA, et al. Nat Med (2021) pmid: 33558721
34. Sharma P, et al. Cancer Cell (2020) pmid: 32916128
35. Marabelle A, et al. Lancet Oncol. (2020) pmid: 32919526
36. Ott PA, et al. J. Clin. Oncol. (2019) pmid: 30557521
37. Cristescu R, et al. J Immunother Cancer (2022) pmid: 35101941
38. Friedman CF, et al. Cancer Discov (2022) pmid: 34876409
39. Sturgill EG, et al. Oncologist (2022) pmid: 35274716
40. Schenker et al., 2022; AACR Abstract 7845
41. Legrand et al., 2018; ASCO Abstract 12000
42. Barroso-Sousa R, et al. Ann. Oncol. (2020) pmid: 32067680
43. Nature (2012) pmid: 23000897
44. Sokol ES, et al. Ann. Oncol. (2019) pmid: 30423024
45. Chumsri S, et al. J Natl Compr Canc Netw (2020) pmid: 32380464
46. Chalmers ZR, et al. Genome Med (2017) pmid: 28420421
47. Haricharan S, et al. Breast Cancer Res. Treat. (2014) pmid: 24839032
48. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
49. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
50. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
51. Rizvi NA, et al. Science (2015) pmid: 25765070
52. Johnson BE, et al. Science (2014) pmid: 24336570
53. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
54. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
55. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
56. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
57. Nature (2012) pmid: 22810696
58. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
59. Kaufman B, et al. J. Clin. Oncol. (2015) pmid: 25366685
60. Mateo J, et al. N. Engl. J. Med. (2015) pmid: 26510020
61. Tutt A, et al. Lancet (2010) pmid: 20609467
62. Robson M, et al. N. Engl. J. Med. (2017) pmid: 28578601
63. Mirza MR, et al. N. Engl. J. Med. (2016) pmid: 27717299
64. Sandhu SK, et al. Lancet Oncol. (2013) pmid: 23810788
65. Swisher EM, et al. Lancet Oncol. (2017) pmid: 27908594
66. Drew Y, et al. Br. J. Cancer (2016) pmid: 27002934
67. Pujade-Lauraine E, et al. Lancet Oncol. (2017) pmid: 28754483
68. Ledermann JA, et al. Lancet Oncol. (2016) pmid: 27617661
69. Fong PC, et al. N. Engl. J. Med. (2009) pmid: 19553641
70. Audeh MW, et al. Lancet (2010) pmid: 20609468
71. Fong PC, et al. J. Clin. Oncol. (2010) pmid: 20406929
72. Gelmon KA, et al. Lancet Oncol. (2011) pmid: 21862407
73. Kaye SB, et al. J. Clin. Oncol. (2012) pmid: 22203755
74. Domchek SM, et al. Gynecol. Oncol. (2016) pmid: 26723501
75. Moore K, et al. N. Engl. J. Med. (2018) pmid: 30345884
76. Golan T, et al. N. Engl. J. Med. (2019) pmid: 31157963
77. Yap TA, et al. Cancer Discov (2021) pmid: 32988960
78. Thomas A, et al. J. Clin. Oncol. (2018) pmid: 29252124
79. Saito YD, et al. Cancer Treat Res Commun (2018) pmid: 31299005
80. Litton JK, et al. N. Engl. J. Med. (2018) pmid: 30110579
81. Diéras V, et al. Lancet Oncol (2020) pmid: 32861273
82. O'Carrigan et al., 2016; ASCO Abstract 2504
83. Yap et al., 2016; AACR-NCI-EORTC Abstract 1LBA
84. Pouliot GP, et al. PLoS ONE (2019) pmid: 31721781
85. Kim H, et al. Clin. Cancer Res. (2017) pmid: 27993965
86. Jin J, et al. Neoplasia (2018) pmid: 29605721
87. Westin et al., 2021; ASCO Abstract 5505
88. Do K, et al. J. Clin. Oncol. (2015) pmid: 25964244
89. Cruz C, et al. J. Clin. Oncol. (2018) pmid: 30240327
90. Poveda A, et al. Ann. Oncol. (2017) pmid: 28368437
91. García MJ, et al. Mol. Cancer Ther. (2013) pmid: 23364677
92. Schöffski P, et al. Eur. J. Cancer (2011) pmid: 21376569
93. Italiano A, et al. Cancer (2011) pmid: 21287534
94. Laroche-Clary A, et al. Br. J. Cancer (2015) pmid: 25602962
95. Ghouadni A, et al. Breast (2017) pmid: 28467918
96. Monk BJ, et al. Ann. Oncol. (2015) pmid: 25722380
97. Monk BJ, et al. Gynecol. Oncol. (2020) pmid: 31924332
98. Yasui H, et al. J Chemother (2016) pmid: 27077926
99. Ciriello G, et al. Cell (2015) pmid: 26451490
100. Al-Moundhri MS, et al. Gulf J Oncolog (2013) pmid: 23996866
101. Ghadirian P, et al. Clin. Genet. (2014) pmid: 23621881
102. Huzarski T, et al. J. Clin. Oncol. (2013) pmid: 23940229
103. Tulchin N, et al. Cancer Cell Int. (2013) pmid: 23855721
104. Gage M, et al. J Surg Oncol (2012) pmid: 22441895
105. Melchor L, et al. Hum. Genet. (2013) pmid: 23552954
106. Oncol Nurs Forum (2013) pmid: 23615136
107. Safonov et al., 2021; SABCS Abstract GS4-08
108. O'Donovan PJ, et al. Carcinogenesis (2010) pmid: 20400477
109. Nelson AC, et al. Radiat. Res. (2010) pmid: 20681793
110. Silver DP, et al. Cancer Discov (2012) pmid: 22843421
111. Ludwig T, et al. Genes Dev. (2001) pmid: 11358863
112. Landrum MJ, et al. Nucleic Acids Res. (2018) pmid: 29165669
113. Miki Y, et al. Science (1994) pmid: 7545954
114. Wooster R, et al. Nature () pmid: 8524414
115. Ford D, et al. Lancet (1994) pmid: 7907678
116. MedGenMed (2005) pmid: 16369438
117. Whittemore AS, et al. Am. J. Hum. Genet. (1997) pmid: 9042908
118. Claus EB, et al. Cancer (1996) pmid: 8635102
119. Struewing JP, et al. N. Engl. J. Med. (1997) pmid: 9145676
120. Oddoux C, et al. Nat. Genet. (1996) pmid: 8841192
121. King MC, et al. Science (2003) pmid: 14576434
122. Hall MJ, et al. Cancer (2009) pmid: 19241424
123. Slamon DJ, et al. N. Engl. J. Med. (2001) pmid: 11248153
124. Bang YJ, et al. Lancet (2010) pmid: 20728210
125. Chumsri S, et al. J Natl Compr Canc Netw (2015) pmid: 26358791
126. Cappuzzo F, et al. N. Engl. J. Med. (2006) pmid: 16775247
127. Falchook GS, et al. J Thorac Oncol (2013) pmid: 23328556
128. Mazières J, et al. J. Clin. Oncol. (2013) pmid: 23610105
129. Baselga J, et al. N. Engl. J. Med. (2012) pmid: 22149875
130. Swain SM, et al. N. Engl. J. Med. (2015) pmid: 25693012
131. Meric-Bernstam F, et al. Lancet Oncol. (2019) pmid: 30857956
132. Meric-Bernstam et al., 2019; ESMO Abstract 453PD
133. Verma S, et al. N. Engl. J. Med. (2012) pmid: 23020162
134. Modi S, et al. N. Engl. J. Med. (2019) pmid: 31825192
135. Murthy RK, et al. N. Engl. J. Med. (2020) pmid: 31825569
136. Borges VF, et al. JAMA Oncol (2018) pmid: 29955792
137. Murthy R, et al. Lancet Oncol. (2018) pmid: 29804905
138. Moulder SL, et al. Clin. Cancer Res. (2017) pmid: 28053022
139. Fan Y, et al. Mol Oncol (2020) pmid: 32478891
140. Cameron D, et al. Oncologist (2010) pmid: 20736298
141. Geyer CE, et al. N. Engl. J. Med. (2006) pmid: 17192538
142. Serra V, et al. Cancer Discov (2013) pmid: 23950206
143. Ali SM, et al. J. Clin. Oncol. (2014) pmid: 24516025
144. Grellety T, et al. Ann. Oncol. (2016) pmid: 26487584
145. Vornicova O, et al. Oncologist (2014) pmid: 25085898
146. Ronellenfitsch MW, et al. J Clin Invest (2020) pmid: 32017710
147. Hou JY, et al. Gynecol Oncol Rep (2020) pmid: 32405522
148. Lin NU, et al. Breast Cancer Res. Treat. (2012) pmid: 22418700
149. Schwab CL, et al. Br. J. Cancer (2014) pmid: 25268372
150. De Grève J, et al. Lung Cancer (2015) pmid: 25682316
151. De Grève J, et al. Lung Cancer (2012) pmid: 22325357
152. Li BT, et al. Lung Cancer (2015) pmid: 26559459
153. Dziadziuszko R, et al. J Thorac Oncol (2019) pmid: 30825613

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

154. Lai WV, et al. Eur. J. Cancer (2019) pmid: 30685684
155. Liu Z, et al. Onco Targets Ther (2018) pmid: 30425522
156. Fang W, et al. Oncologist (2019) pmid: 31748336
157. Yuan B, et al. Front Oncol (2020) pmid: 32477948
158. Ben-Baruch NE, et al. J Natl Compr Canc Netw (2015) pmid: 26358790
159. Ma CX, et al. Clin. Cancer Res. (2017) pmid: 28679771
160. Hyman DM, et al. Nature (2018) pmid: 29420467
161. Smyth LM, et al. Cancer Discov (2019) pmid: 31806627
162. Kris MG, et al. Ann. Oncol. (2015) pmid: 25899785
163. Jiang et al., 2019; ASCO Abstract 1001
164. Xu et al., 2020; ASCO Abstract 1003
165. Jhaveri et al., 2021; SABCS Abstract GS4-10
166. Yi Z, et al. NPJ Breast Cancer (2020) pmid: 33145402
167. Croessmann S, et al. Clin. Cancer Res. (2019) pmid: 30314968
168. Banerji S, et al. Nature (2012) pmid: 22722202
169. Ross JS, et al. Cancer (2016) pmid: 27284958
170. Ross JS, et al. Clin. Cancer Res. (2013) pmid: 23575477
171. Chmielecki J, et al. Oncologist (2015) pmid: 25480824
172. Sci Transl Med (2012) pmid: 22461643
173. Jones KL, et al. Lancet Oncol. (2009) pmid: 19959074
174. Ramić S, et al. Anticancer Res. (2013) pmid: 23749902
175. Slamon DJ, et al. Science (1987) pmid: 3798106
176. Tovey SM, et al. Br. J. Cancer (2009) pmid: 19223897
177. Lee et al., 2021; SABCS Abstract P5-13-35
178. Greulich H, et al. Proc. Natl. Acad. Sci. U.S.A. (2012) pmid: 22908275
179. Lee JC, et al. PLoS Med. (2006) pmid: 17177598
180. Jia Y, et al. Cancer Biol. Ther. (2014) pmid: 24835218
181. Loriot Y, et al. N. Engl. J. Med. (2019) pmid: 31340094
182. Tabernero J, et al. J. Clin. Oncol. (2015) pmid: 26324363
183. Karkera JD, et al. Mol. Cancer Ther. (2017) pmid: 28416604
184. Necchi et al., 2018; ESMO Abstract 900P
185. Pal SK, et al. Cancer Discov (2018) pmid: 29848605
186. Pal SK, et al. Cancer (2020) pmid: 32208524
187. Schuler M, et al. Lancet Oncol. (2019) pmid: 31405822
188. Farouk Sait S, et al. JCO Precis Oncol (2021) pmid: 34250399
189. Voss MH, et al. Clin. Cancer Res. (2019) pmid: 30745300
190. Bahleda R, et al. Ann Oncol (2020) pmid: 32622884
191. Papadopoulos KP, et al. Br. J. Cancer (2017) pmid: 28972963
192. Cheng FT, et al. J Natl Compr Canc Netw (2017) pmid: 29223982
193. Khodadoust MS, et al. Leukemia (2016) pmid: 26055304
194. Tanasi I, et al. Blood (2019) pmid: 31434701
195. Strati P, et al. Leuk. Lymphoma (2018) pmid: 29119847
196. Nogova L, et al. J. Clin. Oncol. (2017) pmid: 27870574
197. Aggarwal C, et al. J Thorac Oncol (2019) pmid: 31195180
198. Soria JC, et al. Ann. Oncol. (2014) pmid: 25193991
199. Formisano L, et al. Clin. Cancer Res. (2017) pmid: 28751448
200. Giltnane JM, et al. Sci Transl Med (2017) pmid: 28794284
201. Mao P, et al. Clin. Cancer Res. (2020) pmid: 32723837
202. Drago et al., 2017; ASCO Abstract 1013
203. Elbauomy Elsheikh S, et al. Breast Cancer Res. (2007) pmid: 17397528
204. Letessier A, et al. BMC Cancer (2006) pmid: 17040570
205. Gelsi-Boyer V, et al. Mol. Cancer Res. (2005) pmid: 16380503
206. Andre F, et al. Clin. Cancer Res. (2009) pmid: 19147748
207. Turner N, et al. Cancer Res. (2010) pmid: 20179196
208. Moelans CB, et al. Mod. Pathol. (2010) pmid: 20473280
209. Reis-Filho JS, et al. Clin. Cancer Res. (2006) pmid: 17121884
210. Hanker AB, et al. Clin. Cancer Res. (2017) pmid: 28381415
211. Jang M, et al. Breast Cancer Res. (2012) pmid: 22863309
212. Drago JZ, et al. Clin. Cancer Res. (2019) pmid: 31371343
213. Turner N, et al. Nat. Rev. Cancer (2010) pmid: 20094046
214. Kohler LH, et al. Virchows Arch. (2012) pmid: 22648708
215. Kim HR, et al. J. Clin. Oncol. (2013) pmid: 23182986
216. André F, et al. Lancet Oncol. (2014) pmid: 24508104
217. Dienstmann R, et al. Ann. Oncol. (2014) pmid: 24265351
218. Mensah AA, et al. Oncotarget (2015) pmid: 25671298
219. Tate JG, et al. Nucleic Acids Res. (2019) pmid: 30371878
220. Grasso CS, et al. Ann. Oncol. (2015) pmid: 25735316
221. Ma X, et al. Nat Commun (2015) pmid: 25790293
222. Green MR, et al. Proc. Natl. Acad. Sci. U.S.A. (2015) pmid: 25713363
223. Loeffler M, et al. Leukemia (2015) pmid: 25027518
224. Gervais C, et al. Leukemia (2008) pmid: 18528428
225. Haferlach T, et al. Leukemia (2009) pmid: 19194466
226. Petrij F, et al. J. Med. Genet. (2000) pmid: 10699051
227. Borrow J, et al. Nat. Genet. (1996) pmid: 8782817
228. Kao YC, et al. Genes Chromosomes Cancer (2017) pmid: 27537276
229. Hofvander J, et al. Mod. Pathol. (2020) pmid: 31932680
230. Joly MO, et al. Hum. Mutat. (2015) pmid: 25504677
231. Pritchard CC, et al. Nat Commun (2014) pmid: 25255306
232. Rosty C, et al. Fam. Cancer (2014) pmid: 25117503
233. McConechy MK, et al. Gynecol. Oncol. (2015) pmid: 25636458
234. Le et al., 2015; ASCO Abstract LBA100
235. Lipson EJ, et al. Clin. Cancer Res. (2013) pmid: 23169436
236. Stephens PJ, et al. Nature (2012) pmid: 22722201
237. Pereira B, et al. Nat Commun (2016) pmid: 27161491
238. Shah SP, et al. Nature (2012) pmid: 22495314
239. Li F, et al. Cell (2013) pmid: 23622243
240. Wu H, et al. PLoS ONE (2011) pmid: 21720545
241. Edelbrock MA, et al. Mutat. Res. () pmid: 23391514
242. Berends MJ, et al. Am. J. Hum. Genet. (2002) pmid: 11709755
243. Warren JJ, et al. Mol. Cell (2007) pmid: 17531815
244. Geng H, et al. J. Biol. Chem. (2012) pmid: 22277660
245. Silva FC, et al. Sao Paulo Med J (2009) pmid: 19466295
246. Raevaara TE, et al. Gastroenterology (2005) pmid: 16083711
247. Kastrinos F, et al. Semin. Oncol. (2007) pmid: 17920897
248. Sehgal R, et al. Genes (Basel) (2014) pmid: 24978665
249. Fam. Cancer (2005) pmid: 16136383
250. Wimmer K, et al. Hum. Genet. (2008) pmid: 18709565
251. Wimmer K, et al. J. Med. Genet. (2014) pmid: 24737826
252. Scott RH, et al. Nat Clin Pract Oncol (2007) pmid: 17259933
253. Ripperger T, et al. Haematologica (2010) pmid: 20015892
254. Baris HN, et al. Pediatr Blood Cancer (2016) pmid: 26544533
255. Nature (2012) pmid: 22960745
256. Nature (2014) pmid: 24476821
257. Nature (2015) pmid: 25631445
258. Cerami E, et al. Cancer Discov (2012) pmid: 22588877
259. Gao J, et al. Sci Signal (2013) pmid: 23550210
260. Jones DH, et al. Mol Clin Oncol (2017) pmid: 28781807
261. Kim SM, et al. Biochem. Biophys. Res. Commun. (2006) pmid: 16682010
262. Kang D, et al. Genes Chromosomes Cancer (2013) pmid: 23011637
263. Chen Y, et al. PLoS ONE (2014) pmid: 24874471
264. Morishita M, et al. Biochim. Biophys. Acta (2011) pmid: 21664949
265. Hirai H, et al. Cancer Biol. Ther. (2010) pmid: 20107315
266. Bridges KA, et al. Clin. Cancer Res. (2011) pmid: 21799033
267. Rajeshkumar NV, et al. Clin. Cancer Res. (2011) pmid: 21389100
268. Osman AA, et al. Mol. Cancer Ther. (2015) pmid: 25504633
269. Xu L, et al. Mol. Cancer Ther. (2002) pmid: 12489850
270. Xu L, et al. Mol. Med. (2001) pmid: 11713371
271. Camp ER, et al. Cancer Gene Ther. (2013) pmid: 23470564
272. Kim SS, et al. Nanomedicine (2015) pmid: 25240597
273. Pirollo KF, et al. Mol. Ther. (2016) pmid: 27357628
274. Hajdenberg et al., 2012; ASCO Abstract e15010
275. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27601554
276. Moore et al., 2019; ASCO Abstract 5513
277. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27998224
278. Oza et al., 2015; ASCO Abstract 5506
279. Lee J, et al. Cancer Discov (2019) pmid: 31315834
280. Méndez E, et al. Clin. Cancer Res. (2018) pmid: 29535125
281. Seligmann JF, et al. J Clin Oncol (2021) pmid: 34538072
282. Lehmann S, et al. J. Clin. Oncol. (2012) pmid: 22965953
283. Mohell N, et al. Cell Death Dis (2015) pmid: 26086967
284. Fransson Å, et al. J Ovarian Res (2016) pmid: 27179933
285. Gourley et al., 2016; ASCO Abstract 5571
286. Kwok M, et al. Blood (2016) pmid: 26563132
287. Boudny M, et al. Haematologica (2019) pmid: 30975914
288. Dillon MT, et al. Mol. Cancer Ther. (2017) pmid: 28062704
289. Middleton FK, et al. Cancers (Basel) (2018) pmid: 30127241
290. Alsner J, et al. Acta Oncol (2008) pmid: 18465328
291. Alkam Y, et al. Histopathology (2013) pmid: 24004112
292. Uji K, et al. Cancer Lett. (2014) pmid: 23973262
293. Olivier M, et al. Clin. Cancer Res. (2006) pmid: 16489069
294. Végran F, et al. PLoS ONE (2013) pmid: 23359294
295. Walsh T, et al. JAMA (2006) pmid: 16551709
296. Garber JE, et al. J. Clin. Oncol. (2005) pmid: 15637391
297. Apostolou P, et al. Biomed Res Int (2013) pmid: 23586058
298. Brown CJ, et al. Nat. Rev. Cancer (2009) pmid: 19935675
299. Joerger AC, et al. Annu. Rev. Biochem. (2008) pmid: 18410249
300. Kato S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12826609
301. Kamada R, et al. J. Biol. Chem. (2011) pmid: 20978130
302. Zerdoumi Y, et al. Hum. Mol. Genet. (2017) pmid: 28472496
303. Yamada H, et al. Carcinogenesis (2007) pmid: 17690113
304. Bougeard G, et al. J. Clin. Oncol. (2015) pmid: 26014290
305. Sorrell AD, et al. Mol Diagn Ther (2013) pmid: 23355100
306. Nichols KE, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11219776
307. Kleihues P, et al. Am. J. Pathol. (1997) pmid: 9006316
308. Gonzalez KD, et al. J. Clin. Oncol. (2009) pmid:

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

19204208
309. Lalloo F, et al. Lancet (2003) pmid: 12672316
310. Mandelker D, et al. Ann. Oncol. (2019) pmid: 31050713
311. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
312. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838
313. Xie M, et al. Nat. Med. (2014) pmid: 25326804
314. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
315. Severson EA, et al. Blood (2018) pmid: 29678827
316. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
317. Hematology Am Soc Hematol Educ Program (2018) pmid: 30504320
318. Chabon JJ, et al. Nature (2020) pmid: 32269342
319. Razavi P, et al. Nat. Med. (2019) pmid: 31768066
320. Jhaveri KL, et al. Ann. Oncol. (2019) pmid: 31504139
321. Li et al., 2018; ASCO Abstract 2502
322. Li BT, et al. Cancer Discov (2020) pmid: 32213539
323. Hotta K, et al. J Thorac Oncol (2018) pmid: 29313813
324. Krop IE, et al. Lancet Oncol. (2014) pmid: 24793816
325. Welslau M, et al. Cancer (2014) pmid: 24222194
326. Krop IE, et al. J. Clin. Oncol. (2012) pmid: 22649126
327. Burris HA, et al. J. Clin. Oncol. (2011) pmid: 21172893
328. Jhaveri et al., 2018; ASCO Abstract 100
329. Baselga J, et al. Clin. Cancer Res. (2016) pmid: 26920887
330. Perez EA, et al. J. Clin. Oncol. (2017) pmid: 28056202
331. Hurvitz SA, et al. J. Clin. Oncol. (2013) pmid: 23382472
332. von Minckwitz G, et al. N. Engl. J. Med. (2019) pmid: 30516102
333. Hurvitz SA, et al. J. Clin. Oncol. (2019) pmid: 31157583
334. Martin M, et al. Ann. Oncol. (2016) pmid: 27052654
335. Mondaca S, et al. JCO Precis Oncol (2019) pmid: 32923849
336. Cortes et al., 2021; ESMO Abstract LBA1
337. Abraham J, et al. J. Clin. Oncol. (2019) pmid: 31442103
338. Jain et al., 2016; ASCO Abstract 588
339. McCabe et al., 2016; ASCO Abstract 582
340. Tsurutani J, et al. Cancer Discov (2020) pmid: 32213540
341. Li BT, et al. N Engl J Med (2021) pmid: 34534430
342. Cortés J, et al. N Engl J Med (2022) pmid: 35320644
343. Tamura K, et al. Lancet Oncol. (2019) pmid: 31047803
344. Modi S, et al. J. Clin. Oncol. (2020) pmid: 32058843
345. Bian L, et al. Tumour Biol. (2013) pmid: 23729232
346. Baselga J, et al. Lancet (2012) pmid: 22257673
347. Robidoux A, et al. Lancet Oncol. (2013) pmid: 24095300
348. Alba E, et al. Br. J. Cancer (2014) pmid: 24457911
349. Gelmon KA, et al. J. Clin. Oncol. (2015) pmid: 25779558
350. Goss PE, et al. Lancet Oncol. (2013) pmid: 23234763
351. Piccart-Gebhart M, et al. J. Clin. Oncol. (2016) pmid: 26598744
352. de Azambuja E, et al. Lancet Oncol. (2014) pmid: 25130998
353. Li et al., 2020; WCLC Abstract FP14.15
354. Chan A, et al. Lancet Oncol. (2016) pmid: 26874901
355. Park JW, et al. N. Engl. J. Med. (2016) pmid: 27406346
356. Schwab CL, et al. Gynecol. Oncol. (2015) pmid: 26260909
357. Menderes G, et al. Med. Oncol. (2017) pmid: 28397106
358. Hu Z, et al. Oncotarget (2015) pmid: 26375550
359. Kavuri SM, et al. Cancer Discov (2015) pmid: 26243863
360. Bose R, et al. Cancer Discov (2013) pmid: 23220880
361. Ma et al., 2021; AACR abstract CT-026
362. Saura C, et al. J Clin Oncol (2020) pmid: 32678716
363. Burstein HJ, et al. J. Clin. Oncol. (2010) pmid: 20142587
364. Freedman RA, et al. J. Clin. Oncol. (2016) pmid: 26834058
365. Awada A, et al. JAMA Oncol (2016) pmid: 27078022
366. Chan A, et al. Clin Breast Cancer (2021) pmid: 33183970
367. Holmes et al., 2020; SABCS Abstract PD3-03
368. Chan et al., 2021; ESMO Abstract 45P
369. Del Conte G, et al. Br. J. Cancer (2014) pmid: 25025963
370. Tutt et al., 2022; ESMO Plenary Abstract VP1-2022
371. Domchek SM, et al. Lancet Oncol (2020) pmid: 32771088
372. Matulonis UA, et al. Ann. Oncol. (2017) pmid: 27993796
373. Lee JM, et al. J. Natl. Cancer Inst. (2014) pmid: 24842883
374. Maio et al., 2021; AACR Abstract CT178
375. Takahashi et al., 2016; ASCO Abstract 1080
376. Dent RA, et al. Breast Cancer Res. (2013) pmid: 24063698
377. Pusztai et al., 2020; AACR Abstract CT011
378. Turner et al., 2017; ASCO Abstract 1007
379. Ettl J, et al. Ann. Oncol. (2018) pmid: 30124753
380. Meehan et al., 2017; AACR Abstract 4687
381. de Bono J, et al. Cancer Discov (2017) pmid: 28242752
382. Lu E, et al. J Natl Compr Canc Netw (2018) pmid: 30099369
383. De Bono et al., 2020; ASCO Abstract 5566
384. Litton JK, et al. Ann Oncol (2020) pmid: 32828825
385. Ettl et al., 2020; SABCS Abstract PS5-07
386. Turner NC, et al. Clin Cancer Res (2019) pmid: 30563931
387. Litton et al., 2021; ASCO abstract 505
388. Schwab et al., 2019; AACR Abstract CT123/2
389. Aftimos et al., 2020; SABCS Abstract PS11-10
390. Gruber et al., 2019; ASCO Abstract 3006
391. Gianni L, et al. Lancet Oncol. (2014) pmid: 24657003
392. Morris PG, et al. Cancer (2013) pmid: 24037735
393. Hainsworth JD, et al. J. Clin. Oncol. (2018) pmid: 29320312
394. Wang K, et al. Clin. Cancer Res. (2016) pmid: 27334835
395. Nishikawa K, et al. Int. J. Cancer (2017) pmid: 27521503
396. von Minckwitz G, et al. Lancet Oncol. (2018) pmid: 29880292
397. Hanes V, et al. Cancer Chemother. Pharmacol. (2017) pmid: 28341959
398. Rugo HS, et al. JAMA (2017) pmid: 27918780
399. Waller CF, et al. Br J Clin Pharmacol (2018) pmid: 29926514
400. Pivot X, et al. J. Clin. Oncol. (2018) pmid: 29373094
401. Pivot X, et al. Eur. J. Cancer (2018) pmid: 29448072
402. Stebbing et al., 2017; 28592386; Esteva et al.
403. Lammers PE, et al. Br. J. Cancer (2018) pmid: 30002437
404. Pegram MD, et al. Br. J. Cancer (2019) pmid: 30568294
405. Swain SM, et al. Lancet Oncol. (2013) pmid: 23602601
406. Swain SM, et al. Lancet Oncol. (2020) pmid: 32171426
407. Earl HM, et al. Lancet (2019) pmid: 31178152
408. Pivot X, et al. Lancet (2019) pmid: 31178155
409. Fehrenbacher L, et al. J. Clin. Oncol. (2020) pmid: 31821109
410. Hurvitz SA, et al. Lancet Oncol. (2015) pmid: 26092818
411. André F, et al. Lancet Oncol. (2014) pmid: 24742739
412. Tolaney SM, et al. Lancet Oncol. (2020) pmid: 32353342
413. Hurvitz SA, et al. Lancet Oncol. (2018) pmid: 29175149
414. von Minckwitz G, et al. N. Engl. J. Med. (2017) pmid: 28581356
415. Swain SM, et al. Ann Oncol (2018) pmid: 29253081
416. Gianni L, et al. Lancet Oncol. (2016) pmid: 27179402
417. Shao Z, et al. JAMA Oncol (2020) pmid: 31647503
418. Ferraro et al., 2021; SABCS Abstract GS3-03
419. Soliman et al., 2016; ASCO Abstract 595
420. Urruticoechea et al., 2016; ASCO Abstract 504
421. Gianni L, et al. Lancet Oncol. (2012) pmid: 22153890
422. Iyengar et al., 2016; ASCO Abstract 611
423. Arpino et al., 2020; SABCS Abstract PD3-02
424. Dang et al., 2021; ESMO Abstract 430
425. Konstantinopolous et al., 2018; ASCO Abstract 106
426. Turner NC, et al. Clin Cancer Res (2021) pmid: 34301749
427. Vinayak S, et al. JAMA Oncol (2019) pmid: 31194225
428. Yuan et al., 2016; SABCS Abstract P6-16-08
429. Taylor SK, et al. Oncologist (2010) pmid: 20682606
430. Majure et al., 2016; ASCO Abstract 560
431. Johnston SR, et al. Breast Cancer Res. Treat. (2013) pmid: 23283526
432. Cristofanilli M, et al. Breast Cancer Res. Treat. (2013) pmid: 23239151
433. Tan AR, et al. Breast Cancer Res. Treat. (2015) pmid: 25542269
434. Kristeleit et al., 2014; ASCO Abstract 2573
435. Domcheck et al., 2016; ASCO Abstract 4110
436. Kristeleit R, et al. Clin. Cancer Res. (2017) pmid: 28264872
437. Kalra M, et al. NPJ Breast Cancer (2021) pmid: 33753748
438. Wilson RH, et al. Br. J. Cancer (2017) pmid: 28222073

Electronically signed by Erik Williams, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531