FOUNDATIONONE®CDx

PATIENT	TUMOR TYPE	REPORT DATE
Liu, Pi Jung	Breast carcinoma (NOS)	17 Dec 2022
	COUNTRY CODE	ORDERED TEST #
	TW	ORD-1521386-01

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

PATIENT
DISEASE Breast carcinoma (NOS)
NAME Liu, Pi Jung
DATE OF BIRTH 02 May 1967
SEX Female
MEDICAL RECORD # 46763502 / PF22141

PHYSICIAN
ORDERING PHYSICIAN Yeh, Yi-Chen
MEDICAL FACILITY Taipei Veterans General Hospital
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 205872
PATHOLOGIST Not Provided

SPECIMEN
SPECIMEN SITE Breast
SPECIMEN ID S111-085971
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 04 March 2022
SPECIMEN RECEIVED 09 December 2022

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 2 Muts/Mb

Genomic Findings

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

ERBB2 amplification - equivocal†
PIK3CA H1047R
FGFR1 amplification
CCND2 amplification
MTAP loss
TSC1 rearrangement intron 3
BAP1 Q456*
BCL2L2 amplification
CDKN2A/B CDKN2A loss, CDKN2B loss
FGF23 amplification
FGF6 amplification
NSD3 (WHSC1L1) amplification
PRDM1 E319*
TP53 splice site 673-1G>A

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

† See About the Test in appendix for details.

Report Highlights

- Variants with **diagnostic implications** that may indicate a specific cancer type: ***ERBB2* amplification** (p. 6)
- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Ado-trastuzumab emtansine** (p. 15), **Fam-trastuzumab deruxtecan** (p. 17), **Trastuzumab** (p. 19), **Trastuzumab + Pertuzumab** (p. 20), **Trastuzumab + Tucatinib** (p. 20), **Lapatinib** (p. 17), **Lapatinib + Letrozole** (p. 18), **Margetuximab** (p. 18), **Neratinib** (p. 18)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 22)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Microsatellite status - MS-Stable	**No therapies or clinical trials.** See Biomarker Findings section
Tumor Mutational Burden - 2 Muts/Mb	**No therapies or clinical trials.** See Biomarker Findings section

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GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
ERBB2 **-** amplification - equivocal	Ado-trastuzumab emtansine 1 Fam-trastuzumab deruxtecan 1 Trastuzumab 1 Trastuzumab + Pertuzumab 1 Trastuzumab + Tucatinib 1 Lapatinib 2A Lapatinib + Letrozole 2A Margetuximab 2A Neratinib 2A	Trastuzumab + Pembrolizumab
10 Trials see p. 24		
PIK3CA **-** H1047R	Alpelisib + Fulvestrant	none
10 Trials see p. 29		
FGFR1 **-** amplification	none	Pazopanib
10 Trials see p. 26		
CCND2 **-** amplification	none	none
10 Trials see p. 22		
MTAP **-** loss	none	none
3 Trials see p. 28		
TSC1 **-** rearrangement intron 3	none	none
8 Trials see p. 31		

NCCN category

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

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.

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].

BIOMARKER

Tumor Mutational Burden

RESULT
2 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].

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GENE
ERBB2

ALTERATION
amplification - equivocal

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[59-64], pertuzumab in combination with trastuzumab[61,65-67], and zanidatamab (ZW25)[68], as well as antibody-directed conjugates such as ado-trastuzumab emtansine (T-DM1)[69] and fam-trastuzumab deruxtecan (T-DXd)[70-72], HER2 kinase inhibitors such as tucatinib[73-76], and dual EGFR/HER2 kinase inhibitors such as lapatinib[77-85], afatinib[64,86-95], neratinib[96-99], dacomitinib[100], and pyrotinib[101-102] . For patients with HER2-positive metastatic breast cancer (mBC), combining tucatinib[73], margetuximab[103], or pyrotinib[104] with chemotherapy or other HER2-targeted agents significantly improved PFS and/or ORR. For patients who progressed on trastuzumab, the combination of pyrotinib with capecitabine elicited improved median PFS (mPFS) compared with lapatinib plus capecitabine (12.5 vs. 6.8 months, HR=0.39) in the Phase 3 PHOEBE study[104] and compared with placebo plus capecitabine (11.1 vs. 4.1 months, HR=0.18) in the Phase 3 PHENIX study[105]; patients with trastuzumab-resistant disease in these studies experienced mPFS of 12.4 months[106]. The Phase 2 PERMEATE study evaluated pyrotinib plus capecitabine for treating patients with HER2-positive mBC and brain metastases, reporting a CNS ORR of 75% (44/59) for radiotherapy-naive patients and 42% (8/19) for patients with prior radiotherapy[107]. For patients with HER2-positive mBC who progressed on HER2-targeted therapy, Phase 2 studies of poziotinib have reported ORRs of 22% (6/27) to 26% (n=102) and PFS rates of 3.0-4.9 months, and 1 study has reported a median OS of 17.7 months[108-109] . For patients with HER2-positive mBC who progressed on previous regimens, including ado-trastuzumab emtansine, treatment with vic-trastuzumab duocarmazine significantly improved mPFS compared with the physician's choice of chemotherapy (7.0 vs. 4.9 months, HR=0.64) in the Phase 3 TULIP trial[110]. A Phase 1 study evaluating the bispecific HER2 antibody KN026 for patients with previously treated HER2-positive mBC reported an ORR of 28% (16/57) and mPFS of 6.8 months with the recommended Phase 2 dose[111]. For patients with HER2-positive metastatic breast cancer, the combination of lapatinib with letrozole[112] or other aromatase inhibitors[113] significantly improved PFS and/or ORR.

— Potential Resistance —

In the context of HER2-positive breast cancer, retrospective[114-119] and Phase 2 or 3[120-121] clinical studies suggest that concurrent PTEN inactivation or PIK3CA alterations leading to PI3K pathway activation promote resistance to therapies targeting HER2[122-123]; however, one retrospective study did not support this association[124]. Combined inhibition of HER2 and the PI3K pathway may be required in HER2-positive tumors with PIK3CA mutation[119,121,123,125-126].

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[43,127-128]. The incidence of ERBB2 alterations has been found to be significantly enriched in CDH1-mutated invasive lobular breast cancers[129]. HER2 is predicted to be overexpressed (as assessed by FISH, CNV analysis, or immunohistochemistry) in 12-25% of breast cancers[130-132]. Phosphorylated HER2 was expressed in 62.5% (55/88) of HER2-positive breast cancers[133]. HER2 overexpression is associated with poor prognosis in invasive breast cancer (NCCN Breast Cancer Guidelines, v4.2022). 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[134]. 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[135]. 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 retrospective study of 131 patients[136]. Acquisition of resistance to trastuzumab was correlated with negativity for pHER2 (p=0.028) for patients with HER2-positive breast cancer[133].

FINDING SUMMARY

ERBB2 (also known as HER2) encodes a receptor tyrosine kinase which is in the same family as EGFR. Amplification or overexpression of ERBB2 can lead to excessive proliferation and tumor formation[137].

POTENTIAL DIAGNOSTIC IMPLICATIONS

HER2 overexpression as assessed by immunohistochemistry or FISH is diagnostic of HER2-positive breast cancer (NCCN Breast Cancer Guidelines, v4.2022).

GENE
PIK3CA

ALTERATION
H1047R

TRANSCRIPT ID
NM_006218.2

CODING SEQUENCE EFFECT
3140A>G

VARIANT CHROMOSOMAL POSITION
chr3:178952085

VARIANT ALLELE FREQUENCY (% VAF)
49.7%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Clinical and preclinical data in various tumor types indicate that PIK3CA activating alterations may predict sensitivity to therapies targeting PI3K[138-145], AKT[146-147], or mTOR[148-155]. In the Phase 3 SOLAR-1 study, the addition of alpelisib to fulvestrant statistically improved PFS (11.0 vs. 5.7 months, HR=0.65) and ORR (27% vs. 13%) and numerically improved median OS (mOS; 39.3 vs. 31.4 months, HR=0.86) in PIK3CA-mutated hormone-receptor-positive (HR+), HER2- breast cancer compared with placebo with fulvestrant, but not in PIK3CA-wildtype HR+, HER2- breast cancer[156]. In a Phase 2 trial, the addition of the AKT inhibitor capivasertib to fulvestrant improved median PFS (mPFS) for patients with PIK3CA-, AKT1-, and/or PTEN-altered HR+, HER2- metastatic breast cancer (12.8 vs. 4.6 months, HR=0.44)[157-158]. A Phase 2 study of alpelisib monotherapy for patients harboring PIK3CA-mutated HR+, HER2- breast cancer reported an ORR of 38% (10/26), mPFS of 5.4 months, median OS of 18.8 months, and median duration of response of 5.6 months; no responses (0% ORR [0/7]) were reported for PIK3CA-mutated triple negative breast cancer (TNBC) patients[159]. Single-agent capivasertib also demonstrated activity in a Phase 1 study[160]. In trials of AKT inhibitors with paclitaxel, neither capivasertib nor ipatasertib showed significant mPFS benefit for patients with PI3K pathway-mutated HR+, HER2- metastatic breast cancer compared with paclitaxel plus placebo[161]. In a Phase 1 study, the PIK3CA-selective inhibitor inavolisib (GDC-0077) alone or in combination with endocrine therapy (letrozole or fulvestrant) with or without palbociclib yielded an ORR of 32% (23/73) for patients with PIK3CA-mutated HR+, HER2- breast cancer, with an ORR of 40% (6/15) observed for patients who received inavolisib plus palbociclib and fulvestrant[162-163] . A Phase 1 study of combination palbociclib, fulvestrant, and the pan-PIK3CA inhibitor taselisib reported an ORR of 38% (9/24), DCR of 58% (14/24), and mPFS of 7.2 months for patients with PIK3CA-mutated ER+, HER2- breast cancer[164]. The addition of the mTOR inhibitor everolimus to exemestane to treat HR+, HER2- advanced breast cancer has shown clinical benefit, regardless of PIK3CA status[165-166]. A Phase 2 trial of capivasertib with paclitaxel versus paclitaxel alone showed a median OS benefit (19.1 vs. 13.5 months) both for patients with AKT1, PTEN, or PIK3CA-mutated triple-negative breast cancer (TNBC; HR=0.58, 95% CI 0.2-1.6) and for patients with TNBC without PI3K-pathway mutations (HR=0.74, 95% CI 0.47-1.18)[167]. Despite promising initial results in earlier trials, the Phase 3 IPATunity130 trial for patients with AKT1, PTEN, or PIK3CA-mutated TNBC failed to show improved PFS for first-line ipatasertib in combination with paclitaxel relative to paclitaxel alone (7.4 vs. 6.1 months)[168]. The Phase 2 NCI-MATCH study of copanlisib for patients with refractory solid tumors harboring PIK3CA mutations with or without PTEN loss met its primary endpoint with an ORR of 16% (4/25 PRs); responses (PR or SD >6 months) were seen in patients with ameloblastoma, liposarcoma, and carcinomas of the endometrium, ovary, esophagus, lung, and prostate[145]. However, the Phase 2 study of copanlisib for patients with endometrial carcinoma harboring PIK3CA hotspot mutations failed to report any objective responses (n=11)[144]. Two other studies of copanlisib for patients with genomically unselected tumors reported 1 CR and 2 PRs (1 unconfirmed) among 16 total patients with PIK3CA-mutated solid tumors with or without PTEN alterations[142-143].

— Potential Resistance —

In the context of HER2-positive breast cancer, retrospective[114-119] and Phase 2 or 3[120-121] clinical studies suggest that concurrent PTEN inactivation or PIK3CA alterations leading to PI3K pathway activation promote resistance to therapies targeting HER2[122-123]; however, one retrospective study did not support this association[124]. Combined inhibition of HER2 and the PI3K pathway may be required in HER2-positive tumors with PIK3CA mutation[119,121,123,125-126]. Limited clinical and preclinical evidence suggests that FGFR1 amplification may be associated with reduced sensitivity to alpelisib in breast cancer[169]. However, for patients with HR+, HER2– breast cancer with PIK3CA alterations, retrospective analysis reported increased clinical benefit following treatment with alpelisib plus fulvestrant for those with FGFR1 alterations versus wildtype FGFR1, with median PFS of 12.7 vs. 11.0 months and HR against placebo of 0.36 versus 0.54[170].

FREQUENCY & PROGNOSIS

Mutations in PIK3CA have been reported in up to 37% of breast cancer cases[43,171]. In the randomized Phase 2 SAFIR02 trial, PIK3CA mutations were associated with reduced OS in patients with hormone-receptor-positive (HR+)/HER2 negative (HER-) metastatic breast cancer but with improved OS in patients with mTNBC compared to patients with PIK3CA wildtype status[172]. Although double PIK3CA mutations were frequently observed in HR+/HER2- breast cancers, as compared with other receptor subtypes (15% vs. 5.4%, p=0.004), this did not impact invasive disease-free survival or OS for patients when compared with single PIK3CA mutations by univariate and multivariate analysis in 1 retrospective study[173]. For patients with HER2+ breast cancer receiving trastuzumab and pertuzumab with chemotherapy, PIK3CA mutations significantly associated with shorter PFS (13 vs. 23 months; HR=1.98)[174]. Mutations in coding exon 20 (H1047R) of PIK3CA have been associated with a better prognosis in breast carcinoma than mutations occurring in coding exon 9 (E542K)[175].

FINDING SUMMARY

PIK3CA encodes p110-alpha, which is the catalytic subunit of phosphatidylinositol 3-kinase (PI3K). The PI3K pathway is involved in cell signaling that regulates a number of critical cellular functions, including cell growth, proliferation, differentiation, motility, and survival[176-177]. PIK3CA alterations that have been characterized as activating, such as observed here, are predicted to be oncogenic[178-199].

GENE
FGFR1

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Alterations that activate FGFR1 may predict sensitivity to selective FGFR inhibitors including erdafitinib[200-202], pemigatinib[203], infigratinib[204-205], futibatinib[206-208], rogaratinib[209], Debio 1347[210-211], and derazantinib[212], or multikinase inhibitors such as pazopanib[213] and ponatinib[214-216]. 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[217] or AZD4547[218] and no responses reported among patients with FGFR1-amplified breast cancer treated with infigratinib[217]. Two case studies reported PRs in patients with FGFR1-amplified breast cancer treated with pazopanib[213]. Exploratory biomarker analysis in the Phase 2 FINESSE study of lucitanib for the treatment of patients with HR+/HER2- metastatic breast cancer reported higher ORR in patients with FGFR1 high-amplified (copy number at least 4) tumors than in those with FGFR1 low- or non-amplified tumors (22% vs. 9%)[219]. A Phase 1/2a study of lucitanib for the treatment of patients with breast carcinoma harboring amplifications of FGFR1, FGF3, FGF4, or FGF19 reported a DCR of 100% (12/12), including 6 PRs with several in FGFR1-amplified tumors[220]. In an arm of the Phase 2 TAPUR study in which 27 patients with FGFR1-altered (predominantly amplification) metastatic breast cancer treated with the multi-kinase inhibitor sunitinib were evaluable for efficacy, 2 PRs and 5 SDs lasting 16 weeks or longer were reported[221].

— Potential Resistance —

Case series have reported FGFR1 amplification for 10 patients with ER+/HER2− breast cancer who progressed on letrozole[222-224], including 1 patient with acquired resistance[224]. 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[222]. Retrospective studies have reported significantly shorter time to progression (n=56, p=0.05)[225] and OS (n=94, p=0.004)[226] for patients with FGFR1-amplified versus non-amplified HR+ metastatic breast cancers treated with endocrine therapy. Limited clinical and preclinical evidence suggests that FGFR1 amplification may be associated with reduced sensitivity to alpelisib in breast cancer[169]. However, for patients with HR+, HER2− breast cancer with PIK3CA alterations, retrospective analysis reported increased clinical benefit following treatment with alpelisib plus fulvestrant for those with FGFR1 alterations versus wildtype FGFR1, with median PFS of 12.7 vs. 11.0 months and HR against placebo of 0.36 versus 0.54[170].

FREQUENCY & PROGNOSIS

FGFR1 amplification has been reported in 10 to 27% of breast cancers[43,226-231] and correlated with FGFR1 mRNA overexpression[223,228-230,232]. FGFR1 amplification correlates with poor prognosis in patients with breast cancer[226,228,233-234], including those with HER2-positive cancer treated with adjuvant trastuzumab[233], and patients with hormone-receptor positive cancer[226,234]. 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)[235].

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[236]. Amplification of FGFR1 has been correlated with protein expression[237-238] and may predict pathway activation and sensitivity to therapies targeting this pathway[239-240].

GENE
CCND2

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Although preclinical studies suggest that cyclin D2 activates CDK4/6[241-242], it is unknown whether CCND2 amplification or activating mutation predicts response to CDK4/6 inhibitors such as abemaciclib, palbociclib, and ribociclib. Clinical studies of CDK4/6 inhibitors have shown the most promise for estrogen receptor-positive breast cancer[243-244].

FREQUENCY & PROGNOSIS

In the TCGA dataset, CCND2 amplification was observed in 1.5% of breast invasive carcinoma cases[43]. Additionally, several studies in breast cancer have demonstrated promoter hypermethylation and subsequent repression of CCND2 expression, and this effect is potentiated in BRCA-negative tumors[245-247]. CCND2 has been reported to be one of the most frequently methylated genes in premalignant and malignant breast lesions, and this study suggests that methylation of a group of genes, including CCND2, may play an important role in the development of breast cancer driven by precursor columnar cell lesions[248]. Low CCND2 expression is associated with unfavorable OS in breast cancer (HR = 0.173)[249].

FINDING SUMMARY

CCND2 encodes the protein cyclin D2, which binds and regulates the cyclin-dependent kinases that control cell cycle progression, and is a downstream target of cancer signaling pathways including hedgehog and PI3K[250-251]. CCND2 has been reported to be amplified in cancer[252], and may be biologically relevant in this context[253-254].

GENE
MTAP

ALTERATION
loss

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

MTAP inactivation produces specific metabolic vulnerabilities that may be sensitive to MAT2A[255-256] or PRMT5 inhibition[256-258]. A Phase 1 trial of MAT2A inhibitor AG-270 reported 1 PR and 2 SDs lasting longer than 6 months for patients with advanced solid tumors displaying MTAP loss[259]. Preclinical data suggest that MTAP loss sensitizes cells to S-adenosyl-L-methionine (SAM)-competitive PRMT5 inhibitors[260], dual PRMT1 and PRMT5 inhibitors[261-263], and PRMT5 inhibitors that selectively bind the PRMT5 when complexed with S-methyl-5'-thioadenosine (MTA), such as MRTX1719, TNG908, and AMG193[264]. In preclinical models, MTAP inactivation showed increased sensitivity to inhibitors of purine synthesis or purine analogs, especially upon addition of exogenous MTA[265-275]. A Phase 2 study of L-alanosine, an inhibitor of adenine synthesis, as a monotherapy for 65 patients with MTAP-deficient cancers reported no responses and SD for 24% (13/55) of patients[276]. Preclinical and limited clinical evidence suggest MTAP deficiency may confer sensitivity to pemetrexed[277].

FREQUENCY & PROGNOSIS

MTAP loss/homozygous deletion as well as loss of expression has been reported in a wide variety of solid tumors and hematologic cancers[278-279]; such events have been correlated with poor prognosis in a variety of cancer types, including hepatocellular carcinoma[280], gastrointestinal stromal tumors[281], mantle cell lymphoma (MCL)[282], melanoma[283-284], gastric cancer[285], myxofibrosarcoma[286], nasopharyngeal carcinoma[287], ovarian carcinoma[278] and non-small cell lung cancer[288]. MTAP loss was not prognostic in pediatric B-cell acute lymphocytic leukemia[289] or in astrocytoma[290]. However, MTAP has also been reported to be overexpressed in colorectal cancer (CRC) samples[291], and MTAP retention is thought to be important for prostate cancer growth due to continuous supply of SAM[292]. Germline SNPs in MTAP have been correlated with the development of cutaneous melanoma[293-294], esophageal cancer[295-296], osteosarcoma[297], and CRC[298].

FINDING SUMMARY

MTAP encodes S-methyl-5'-thioadenosine (MTA) phosphorylase, a tumor suppressor involved in polyamine metabolism and methionine synthesis, although its enzymatic function is dispensable for its tumor suppressor activity[299-300]. Decreased expression of MTAP leads to MTA accumulation within tumor cells and their microenvironment[280,301-302], thereby reducing intracellular arginine methylation[256-258] and altering cell signaling[302-303]. MTAP is located at 9p21, adjacent to CDKN2A and CDKN2B, with which it is frequently co-deleted in various cancers. Other alterations in MTAP are rare and have not been extensively characterized.

GENE
TSC1

ALTERATION
rearrangement intron 3

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Loss or inactivation of TSC1 can activate mTOR signaling[304-305]; however, response rates for patients with TSC1-mutated solid tumors treated with MTOR inhibitors such as everolimus and temsirolimus have been low[306-308]. In the prospective NCI-MATCH study, the ORR for patients with various TSC1-mutated solid tumors treated with everolimus was 7.7% (1/13); the single response was reported for a patient with urothelial cancer[306]. In TSC1-mutated renal cell carcinoma (RCC), although responses to MTOR inhibitors have been described in multiple case series and reports[309-313], retrospective analysis of a broader cohort showed no responses in TSC1-mutated RCC (0/7)[307]. Retrospective analyses of the RECORD-3, GRANITE-1, and EVOLVE-1 studies of everolimus to treat patients with RCC, gastric cancer, or hepatocellular carcinoma, respectively, showed no significant association between alterations in MTOR, TSC1, or TSC2 and median PFS[308]. PRs have been reported for patients with TSC1-altered perivascular epithelioid cell tumors[314-315] and epithelial ovarian carcinoma[316] treated with nab-sirolimus.

FREQUENCY & PROGNOSIS

TSC1 mutations have been reported in 0-1.5% of breast carcinomas[43,127,317-319]. One study has reported decreased Hamartin protein expression in invasive breast carcinoma samples, as compared to normal epithelial breast tissue[320]. Decreased Hamartin expression has been associated with poor prognosis in breast cancer patients[320].

FINDING SUMMARY

TSC1 encodes the protein Hamartin, which interacts with Tuberin, the gene product of TSC2, to inhibit and regulate mTOR activity[304,321]. Alterations such as seen here may disrupt TSC1 function or expression[322-324].

POTENTIAL GERMLINE IMPLICATIONS

Inactivating germline mutations in TSC1 are associated with the autosomal dominant disorder tuberous sclerosis complex, which results in the development of hamartomas in multiple organ systems and an increased risk of developing renal cell carcinoma[325-326]. TSC1 mutations account for approximately 10 to 30% of reported sporadic cases[327]. Prevalence for this disorder in the general population is estimated to be 1/6,000 from birth and 1/12,000 to 1/14,000 in children under 10 years of age[328]. In the appropriate clinical context, germline testing of TSC1 is recommended.

GENE
BAP1

ALTERATION
Q456*

TRANSCRIPT ID
NM_004656.2

CODING SEQUENCE EFFECT
1366C>T

VARIANT CHROMOSOMAL POSITION
chr3:52437795

VARIANT ALLELE FREQUENCY (% VAF)
62.8%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Clinical[329] and preclinical[330] evidence in the context of mesothelioma suggests that tumors with BAP1 inactivation may be sensitive to EZH2 inhibitors such as tazemetostat. Preclinical studies suggest that BAP1 is involved in the DNA damage response[331-334], and BAP1 inactivation might be associated with sensitivity to PARP inhibitors[332-333]. One preclinical study suggests that HDAC inhibitors may be beneficial in BAP1-mutated uveal melanoma; however, it is unclear if these inhibitors are effective in other BAP1-mutated cancers[335].

— Potential Resistance —

One preclinical study suggests that BAP1 inactivation in breast cancer may be associated with resistance to tamoxifen[336].

FREQUENCY & PROGNOSIS

BAP1 somatic mutations are reported to be rare in breast cancer[337], and have been reported in 0.4-2% of breast invasive carcinoma cases[43,317-319]. BAP1 has been suggested to play a tumor suppressive role in breast cancer cells by regulating genomic stability; high BAP1 expression was significantly associated with improved overall survival in patients with breast cancer, and with prolonged progression-free survival in patients with basal or luminal breast cancer[338].

FINDING SUMMARY

BAP1 (BRCA1 associated protein-1) encodes a ubiquitin hydrolase, a protein involved in regulating the availability of target proteins for the ubiquitin-proteasome protein degradation pathway; BAP1 is located on chromosome 3p21.3, in a region of frequent loss of heterozygosity (LOH) in breast and lung cancer, and has been postulated to be a tumor suppressor[339-340]. Alterations such as seen here may disrupt BAP1 function or expression[340-349].

POTENTIAL GERMLINE IMPLICATIONS

BAP1 germline inactivating alterations, including mutations and deletions, are associated with BAP1 tumor predisposition syndrome (BAP1-TPDS), an autosomal-dominant syndrome characterized by early onset of benign melanocytic skin tumors[343,350-351]. An estimated 2% of patients with BAP1-inactivated melanocytic tumors display germline BAP1 mutations[352]. Later in life, patients have an increased risk of cancers such as uveal melanoma, mesothelioma, clear cell renal cell carcinoma, basal cell carcinoma, and meningioma[342-346,353]. In small studies, the prevalence of pathogenic germline BAP1 mutation has been reported as 22% in familial uveal melanoma and 4.4% in mesothelioma[354-355]. In the appropriate clinical context, germline testing of BAP1 is recommended.

GENE
BCL2L2

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies that target BCL2L2 amplification or overexpression. Small-molecule inhibitors of BCL-W, such as navitoclax, are under investigation in preclinical and clinical studies[356-358].

FREQUENCY & PROGNOSIS

BCL2L2 amplification has been observed in 4% of prostate adenocarcinomas[359], 3.7% of pancreatic cancer[360], 2.9% of sarcomas[361], 2.2% of lung adenocarcinomas[362-363], and 2.2% of ovarian serous cystadenocarcinomas[364], with amplification rarer in other tumor types such as breast carcinoma (0.4-1.2%)[43,319,365]. Overexpression of BCL-W has been reported to be associated with tumor stage, differentiation status, and a poorer patient prognosis in multiple tumor types, including lung, gastric, ovarian, and colorectal tumors[366-369].

FINDING SUMMARY

BCL2L2 encodes the pro-survival protein BCL-W, which mediates apoptosis, the biological cell death process[370]. BCL2L2 has been reported to be amplified in cancer[252] and may be biologically relevant in this context[253-254].

GENE
CDKN2A/B

ALTERATION
CDKN2A loss, CDKN2B loss

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib[371-374]. Clinical data in mesothelioma, breast cancer, and uterine leiomyosarcoma indicate that CDKN2A loss may predict sensitivity to abemaciclib[375] and palbociclib treatment[376-377]. However, multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[243-244,378-382]; it is not known whether CDK4/6 inhibitors would be beneficial in this case. Although preclinical studies have suggested that loss of p14ARF function may be associated with reduced sensitivity to MDM2 inhibitors[383-384], the clinical relevance of p14ARF as a predictive biomarker is not clear. Because the p15INK4b protein encoded by CDKN2B is known to inhibit CDK4, tumors with CDKN2B mutation or loss may predict sensitivity to CDK4/6 inhibitors, such as ribociclib, abemaciclib, and palbociclib[243-244,379,385-387].

FREQUENCY & PROGNOSIS

CDKN2A/B loss or mutation occurs in 4% and 1% of breast invasive carcinoma cases, respectively[43,388]. CDKN2B is deleted in 33% of early-onset breast cancers (n=47), compared to 14% of late-onset breast cancers (n=59)[389]. Expression of the mRNA transcripts encoding p16INK4a and p14ARF has been reported to be variable in breast carcinoma[390]. CDKN2B and CDKN2A methylation, including hypermethylation of the p16INK4a and p14ARF promoters, in breast tumors has been reported in 4-40% of breast carcinomas[389-395]. Loss of p16INK4a protein expression has been reported in breast carcinoma, including lobular and ductal carcinoma samples[396-397], and one study did not detect p14ARF protein in 21% of invasive ductal breast carcinomas[398]. However, other studies report p16INK4a expression in 26-50% of breast cancer samples while p14ARF expression has been reported in 24% of breast tumors[398-401]. Methylation of the CDKN2A promoter has been shown to increase with tumor grade in ductal carcinoma in-situ (DCIS)[392,402], and is associated with increased breast cancer-specific mortality[395]. There have been conflicting reports about the association between p16INK4a or p14ARF expression and prognosis. Some studies have showed that the overexpression of p16INK4a may play a role in the progression of breast tumors[403]. Increased expression of p16INK4a in basal-like tumors has been suggested to be involved in the poor prognosis of this tumor type[404]. However, p16INK4a expression has also been correlated with prolonged breast cancer-specific survival and disease-free survival[399-400,405]. Increased p14 expression were associated better overall and disease-free survival; p16 expression was not found to be associated with clinical outcome in this study[406]. Analysis of the expression and mutational profile of CDKN2B suggests that loss of CDKN2B may play a role in the loss of control of growth but not in the progression of tumors[407]. Loss of p16INK4a may also associate with HER2 positivity and be less frequent in triple-negative breast carcinomas, which often inactivate Rb[399,405].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[408-409]. Both p15INK4b and p16INK4a bind to and inhibit CDK4 and CDK6, thereby maintaining the growth-suppressive activity of the Rb tumor suppressor; loss or inactivation of either p15INK4b or p16INK4a contributes to dysregulation of the CDK4/6-cyclin-Rb pathway and loss of cell cycle control[410-411]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[412-413]. One or more alterations observed here are predicted to result in p16INK4a loss of function[414-435]. One or more alterations seen here are predicted to result in p14ARF loss of function[418,435-438]. CDKN2B alterations such as seen here are predicted to inactivate p15INK4b[439].

POTENTIAL GERMLINE IMPLICATIONS

Germline CDKN2A mutation is associated with melanoma-pancreatic cancer syndrome, a condition marked by increased risk of developing malignant melanoma and/or pancreatic cancer[440]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[441-442]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[443-445]. CDKN2A alteration has also been implicated in familial melanoma-astrocytoma syndrome, an extremely rare tumor association characterized by dual predisposition to melanoma and nervous system tumors[446-448]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

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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
FGF23

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies that directly address genomic alterations in FGF23. Inhibitors of FGF receptors, however, are undergoing clinical trials in a number of different cancers. Limited data suggest that pan-FGFR inhibitors show activity in FGF amplified cancers; following treatment with a selective pan-FGFR inhibitor, a patient with head and neck squamous cell carcinoma (HNSCC) and amplification of 11q13 (FGF3, FGF4, FGF19) and 12p13 (FGF6 and FGF23) experienced a radiologic CR[449].

FREQUENCY & PROGNOSIS

FGF23 alterations have been reported with highest incidence in uterine carcinosarcoma (7.0%), ovarian carcinoma (6.5%), testicular germ cell cancer (5.4%), cutaneous melanoma (5.0%), low-grade glioma (4.9%), lung squamous cell carcinoma (4.5%), sarcoma (4.3%), colorectal adenocarcinoma (4.2%), lung adenocarcinoma (3.7%), and head and neck squamous cell carcinoma (3.4%) (cBioPortal, 2022)[252,450].

FINDING SUMMARY

FGF23 encodes a member of the fibroblast growth factor protein family that plays a central role in phosphate homeostasis[451]. Overexpression of FGF23 by tumor cells can cause hypophosphatemia through excessive renal phosphate clearance[452], while germline gain-of-function (protein stabilizing) mutations in FGF23 cause autosomal dominant hypophosphatemic rickets[453].

GENE
FGF6

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies that directly address genomic alterations in FGF6. Inhibitors of FGF receptors, however, are undergoing clinical trials in a number of different cancers. Limited data suggest that pan-FGFR inhibitors show activity in FGF amplified cancers; following treatment with a selective pan-FGFR inhibitor, a patient with head and neck squamous cell carcinoma (HNSCC) and amplification of 11q13 (FGF3, FGF4, FGF19) and 12p13 (FGF6 and FGF23) experienced a radiologic CR[449].

FREQUENCY & PROGNOSIS

Somatic alterations affecting FGF6 are infrequently documented, with the highest rates reported in penile cancer (4%), cutaneous melanoma (1-3%), stomach carcinoma (1-3%) and colorectal cancer (1%) (cBioPortal, COSMIC, Jan 2022)[252,450,454]. Amplification of FGF6 has been frequently observed in testicular germ cell cancer (5%) and ovarian serous cystadenocarcinoma (5%), and in 2-6% of lower-grade gliomas, glioblastomas, sarcomas, breast invasive carcinomas, uterine carcinosarcomas, lung squamous cell carcinomas (SCC), head and neck SCC, pancreatic adenocarcinomas, and esophageal carcinomas (cBioPortal, Jan 2022)[252,450]. FGF6 is co-localized with FGF23 and CCND2 at chromosomal locus 12p13 and has been reported to be co-amplified with these genes in 1.3% of patients with breast cancer[455]. FGF6 expression has been reported in 54% (14/26) of prostate cancer samples, which also frequently express FGFR4[456]. FGF6 expression has also been observed in 71% (12/17) of patients with childhood acute lymphoblastic leukemia[457].

FINDING SUMMARY

FGF6 (also known as HST-2) encodes a member of the fibroblast growth factor protein family and is hypothesized to play a role in muscle tissue regeneration[458] by signaling through FGFR4, and to a lesser extent FGFR1 and FGFR2[459]. FGF6 expression has been observed in several cancers[456-457,460] and was shown to be oncogenic in preclinical models[460-461]. FGF6 has been reported as amplified in cancer[252] and may be biologically relevant in this context[253-254].

GENE
NSD3 (WHSC1L1)

ALTERATION
amplification

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%)[462], breast invasive carcinoma (13%)[319], bladder urothelial carcinoma (9%)[463], and head and neck squamous cell carcinoma (9%)[464] samples[252,450]. 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[465]. 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[465].

FINDING SUMMARY

NSD3, also known as WHSC1L1, encodes an enzyme that mediates histone methylation[466]. NSD3 has been shown to be amplified in various cancers[467-469].

GENE
PRDM1

ALTERATION
E319*

TRANSCRIPT ID
NM_001198.3

CODING SEQUENCE EFFECT
955G>T

VARIANT CHROMOSOMAL POSITION
chr6:106552990

VARIANT ALLELE FREQUENCY (% VAF)
37.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in PRDM1.

FREQUENCY & PROGNOSIS

Inactivating somatic alterations of PRDM1 have been shown to occur in approximately one quarter of activated B-cell type diffuse large B-cell lymphomas (ABC-DLBCL) but not in other DLBCL subtypes[470]. In contrast to this tumor suppressor role in lymphoma, BLIMP-1 activity has been hypothesized to promote cell migration and invasion based on cell culture models of lung cancer[471].

FINDING SUMMARY

PRDM1 encodes the transcriptional repressor protein BLIMP-1, which antagonizes expression of beta-interferon, among other genes[472]. BLIMP-1 plays a key role in mediating terminal differentiation of myeloid cells and B-lymphocytes, in part through repression of c-MYC transcription[473].

GENE
TP53

ALTERATION
splice site 673-1G>A

TRANSCRIPT ID
NM_000546.4

CODING SEQUENCE EFFECT
673-1G>A

VARIANT CHROMOSOMAL POSITION
chr17:7577609

VARIANT ALLELE FREQUENCY (% VAF)
64.4%

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[474-477] or p53 gene therapy such as SGT53[478-482]. 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[483]. 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[484]. 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[485]. 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[486]. 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[487]. 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[488]. 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[489]. 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[482]. Missense mutations leading to TP53 inactivation may be sensitive to therapies that reactivate mutated p53 such as eprenetapopt. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, eprenetapopt combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[490]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[491].

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[43,127,318,492-494]. TP53 mutations that are located within the region encoding the DNA binding domain are associated with poor prognosis in patients with breast cancer[492,495-496]. 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[497-499].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[500]. Alterations such as seen here may disrupt TP53 function or expression[501-505].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the TP53 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 Li-Fraumeni syndrome (ClinVar, Sep 2022)[506]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[507-509], including sarcomas[510-511]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[512] to 1:20,000[511]. 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[513]. 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[514-519]. 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[514-515]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[520]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[518,521-522]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

Ado-trastuzumab emtansine

Assay findings association

ERBB2
amplification - equivocal

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[69,523-538] .

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)[527] or lapatinib plus capecitabine (9.6 vs. 6.4 months)[69,528,532] . 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)[539]. 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[533]; 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[534]. 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[535]. 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[536]. 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[537], paclitaxel with or without pertuzumab (Krop et al., 2016;), neratinib[540], alpelisib[541], and tucatinib[540]. 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[542].

Alpelisib + Fulvestrant

Assay findings association

PIK3CA
H1047R

AREAS OF THERAPEUTIC USE

Alpelisib is a phosphatidylinositol 3-kinase (PI3K) inhibitor with selective activity against the alpha isoform (PI3K-alpha), and fulvestrant is an estrogen receptor (ER) antagonist and selective estrogen receptor degrader (SERD). The combination is FDA approved to treat men and postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated advanced breast cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of prospective clinical data, PIK3CA mutations including C420R, E542K, E545A, E545G, E545K, E545D, Q546E, Q546R, H1047L, H1047Y, and H1047R are associated with sensitivity to alpelisib in combination with fulvestrant. In ER+/HER2– breast cancer, PFS benefit from the addition of alpelisib to fulvestrant was specifically observed for patients with PIK3CA mutations (11.0 vs. 5.7 months, HR=0.65), including patients with PIK3CA exon 9 or exon 20 mutations[146].

SUPPORTING DATA

Biomarker analysis of the SOLAR-1 trial showed that the addition of alpelisib to fulvestrant improved median PFS relative to placebo for patients with PIK3CA-mutated, HR+, HER2- breast cancer and either co-occurring FGFR1 (12.7 vs. 3.8 months, HR=0.36) or FGFR2 (9.6 vs. 2.8 months, HR=0.28) alteration[170]. In the Phase 3 SOLAR-1 study for patients with HR+, HER2- endocrine-therapy-resistant advanced breast cancer, the addition of alpelisib to fulvestrant significantly improved median PFS (mPFS; 11.0 vs. 5.7 months, HR=0.65), ORR (27% vs. 13%), clinical benefit rate (62% vs. 45%), and numerically improved median OS (mOS; 39.3 vs. 31.4 months, HR=0.86) for patients with PIK3CA mutations[146,156] ; patients with wildtype PIK3CA did not experience significant mPFS benefit (7.4 vs. 5.6 months, HR=0.85)[146]. This trial excluded patients with active brain metastases; however, control of progressive brain metastases (1/4 PR and 2/4 SDs by response assessment in neuro-oncology brain metastases criteria) was reported in a case series of 4 patients with PIK3CA-mutated HR+, HER2- breast cancer treated with alpelisib in combination with either fulvestrant or exemestane[543]. The Phase 2 BYLieve study for previously treated patients with PIK3CA-mutated HR+, HER2- advanced breast cancer reported an ORR of 19%, an mPFS of 7.3 months, and an mOS of 26.4 months for patients treated with alpelisib plus fulvestrant following progression on a CDK4/6 inhibitor in combination with an aromatase inhibitor (AI)[544]; patients who progressed more quickly on their prior CDK4/6 inhibitor plus AI regimen (<6 months) experienced greater mPFS benefit from alpelisib plus fulvestrant (12.0 vs. 6.2 months) than patients who experienced delayed progression (>6 months)[545]. The Phase 2 BYLieve trial also reported an ORR of 16% and an mPFS of 5.7 months for patients treated with alpelisib plus letrozole following progression on a CDK4/6 inhibitor in combination with fulvestrant, benefit did not differ by duration of prior treatment[545-546] , and an ORR of 24% and an mPFS of 5.6 months for patients treated with alpelisib plus fulvestrant who had previously progressed on aromatase inhibitors and received chemotherapy or endocrine therapy[547].

Fam-trastuzumab deruxtecan

Assay findings association

ERBB2
amplification - equivocal

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. It is also approved for patients with HER2-low advanced breast cancer who have previously been treated with chemotherapy, as well as for patients with advanced ERBB2-mutated non-small cell lung cancer (NSCLC) who have received systemic therapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data in solid cancers, including breast[70,548] , gastric[71,549] , non-small cell lung[550-551] , and colon[552] cancers, ERBB2 amplification may predict sensitivity to fam-trastuzumab deruxtecan.

SUPPORTING DATA

The Phase 3 DESTINY-Breast03 study for patients with HER2+ metastatic breast cancer (mBC) previously treated with trastuzumab and taxane reported 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)[539,553] . The Phase 2 DESTINY-Breast01 study of T-DXd for patients with HER2+ mBC previously treated with T-DM1 reported a 61% ORR (6.0% CR) and a 97% DCR with mPFS of 16.4 months[70]. T-DXd has also demonstrated efficacy against active brain metastases; a Phase 2 study reported a 73% (11/15) intracranial response rate and 14-month PFS[554]. The Phase 3 DESTINY-Breast04 study reported that T-DXd improved outcomes for patients with HER2-low (IHC 1+ or IHC 2+/ISH−) metastatic breast cancer compared with physician's choice chemotherapy, with improved median OS (23.4 vs. 16.8 months, HR=0.64) and mPFS (9.9 vs. 5.1 months, HR=0.50); benefit was observed among HR+ and HR− cohorts[555]. A Phase 1b trial evaluating T-DXd in combination with nivolumab for patients with HER2+ or HER2-low breast cancer reported ORRs of 66% (21/32) and 50% (8/16), respectively[556].

Lapatinib

Assay findings association

ERBB2
amplification - equivocal

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[77-85] .

SUPPORTING DATA

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[78-79,557-560] . 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[561] and ado-trastuzumab emtansine (T-DM1) for patients who have progressed on trastuzumab plus taxane[69]. Phase 3 studies of adjuvant lapatinib have reported no significant disease-free survival benefit compared with placebo[562] or trastuzumab[563]. 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[558-559,564] .

Lapatinib + Letrozole

Assay findings association

ERBB2
amplification - equivocal

AREAS OF THERAPEUTIC USE

Lapatinib is a tyrosine kinase inhibitor that targets EGFR and ERBB2 (HER2) and letrozole is an aromatase inhibitor. The combination is FDA approved for the treatment of HER2-overexpressing (HER2+) metastatic breast cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Clinical benefit with lapatinib combined with letrozole has been observed for patients with breast cancer harboring ERBB2 amplification[112].

SUPPORTING DATA

The combination of lapatinib with letrozole[112] significantly improved PFS (8.2 vs 3.0 months) and ORR (28% vs 15%) for patients with HR+, HER2+ breast cancer compared to letrozole + placebo but did not improve PFS for patients with HR+, HER2-negative breast cancer.

Margetuximab

Assay findings association

ERBB2
amplification - equivocal

AREAS OF THERAPEUTIC USE

Margetuximab is an Fc-engineered antibody targeting ERBB2/HER2 that was designed to enhance the anti-tumor immune response. Margetuximab is FDA approved for the treatment of patients with HER2-positive breast cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical studies in multiple tumor types, ERBB2 amplification may predict sensitivity to margetuximab[565-568] .

SUPPORTING DATA

The Phase 3 SOPHIA trial of margetuximab for HER2-positive metastatic breast cancer, reported improved median PFS (5.8 vs. 4.9 months, HR=0.76) and ORR (22% vs. 16%) when combining margetuximab with chemotherapy, compared with trastuzumab and chemotherapy, for patients who had progressed on ≥2 prior HER2-directed therapies[565]. A Phase 1 trial for HER2-positive solid tumors reported 4 PRs in patients with breast cancer[566]. In a study of margetuximab for HER2-positive cancers, 2/10 patients with breast cancer reported PRs[567].

Neratinib

Assay findings association

ERBB2
amplification - equivocal

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[96-99,569-571] and preclinical[572-576] evidence, ERBB2 amplification or activating mutations may confer sensitivity to neratinib.

SUPPORTING DATA

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)[577]. 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)[578]. 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[579]. 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[580]. 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[571]. 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)[581]; however, the final OS analysis did not reach statistical significance in the intention-to-treat population (HR=0.95)[582-583] .

Trastuzumab

Assay findings association

ERBB2
amplification - equivocal

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[59-60,64,81,584-588] .

SUPPORTING DATA

Follow-up exploratory analysis of these studies showed that patients with PIK3CA alterations achieved extended median PFS with everolimus compared with placebo (HR=0.69), when combined with trastuzumab plus paclitaxel (12.0 vs. 7.6 months) or vinorelbine (6.9 vs. 5.7 months)[589]. In a retrospective study for patients with HER2-positive breast cancer treated with neoadjuvant chemotherapy with or without trastuzumab, patients with non-inflammatory breast cancer reported a significant association between elevated HER2 FISH ratio and increased pathologic CR rate and longer OS, compared with patients with inflammatory breast cancer (IBC)[590]. In a study of patients with early breast cancer treated with neoadjuvant trastuzumab, higher ERBB2 copy number (HER2/CEP17 ratio >6) correlated with increased incidence of pathologic CR compared to lower ERBB2 copy number[591]. A Phase 3 study of adjuvant trastuzumab with chemotherapy for patients with metastatic HER2+ breast cancer (BC) demonstrated significant improvements in OS, time to progression, and ORR[59]. 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 6.1 or 7.5 years of median follow-up[592-593] . 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 immunohistochemistry [IHC] score of 1+ or 2+ in the absence of gene amplification) compared with chemotherapy alone, regardless of lymph node involvement or hormone receptor status[594]. Trastuzumab biosimilars demonstrated comparable clinical benefit to trastuzumab for patients with HER2+ BC[595-603] . 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%)[584]. The Phase 3 neoadjuvant NeoALTTO trial reported numerically improved 6-year EFS from the combination of lapatinib plus trastuzumab (74%) compared with lapatinib or trastuzumab alone (both 67%)[604]. The Phase 3 CLEOPATRA study of first-line trastuzumab with pertuzumab and docetaxel for patients with metastatic HER2+ BC reported significantly improved 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 trastuzumab plus docetaxel[65-66,605-606] . The first-line Phase 3 PHILA study also supports dual-HER2 targeting, reporting improved PFS (33.0 vs 10.4 months, HR=0.35) from the addition of pyrotinib to trastuzumab plus docetaxel[607]. 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 mPFS (15.0 vs. 14.5 months); however, the regimen increased PFS in the HR- subpopulation (20.3 vs. 13.1 months, HR=0.66)[608]. Everolimus plus trastuzumab with vinorelbine prolonged mPFS (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[609]. In a Phase 2 trial for patients with HER2+ metastatic BC previously treated with HER2-targeting agents, tucatinib plus trastuzumab and capecitabine significantly extended mPFS (7.8 vs. 5.6 months) and increased the 1-year mPFS rate (33% vs. 12%, HR=0.54) and 2-year mOS rate (45% vs. 27%, HR=0.66) compared with placebo with trastuzumab and capecitabine[73]. 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 mPFS (8.3 vs. 5.7 vs. 5.7 months) and ORR (33% vs. 14% vs. 14%), and numerically improved OS (31.1 vs. 29.2 vs. 20.7 months) in the Phase 2 monarcHER study[610-611] .

Trastuzumab + Pertuzumab

Assay findings association

ERBB2
amplification - equivocal

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[66,586,612-616] .

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)[174]. 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[65-66,605-606] . 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)[615,617-620] . 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)[621]. 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[613]. 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[622]. 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)[612].

Trastuzumab + Tucatinib

Assay findings association

ERBB2
amplification - equivocal

AREAS OF THERAPEUTIC USE

Trastuzumab is a monoclonal antibody that targets ERBB2/HER2, and tucatinib is a reversible TKI targeting ERBB2/HER2. These therapies are FDA approved in combination for the treatment of patients with previously treated advanced HER2-positive breast cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data in breast cancer[73-76] and colorectal cancer[623], ERBB2 amplification may predict sensitivity to trastuzumab plus tucatinib.

SUPPORTING DATA

In the Phase 2 HER2CLIMB trial for patients with HER2+ metastatic breast cancer previously treated with HER2-targeting agents, the combination of tucatinib with trastuzumab and capecitabine significantly extended median PFS (7.6 vs. 4.9 months, HR=0.57) and median OS (24.7 vs. 19.2 months, HR=0.73) compared with placebo plus trastuzumab and capecitabine[73,624] . For Interim results from HER2CLIMB for patients with brain metastases, showed that the tucatinib-containing combination improved intracranial ORR (47% vs. 20%), central nervous system-specific PFS (CNS-PFS; 9.9 vs. 4.2 months, HR=0.32), and OS (18.1 vs. 12.0 months, HR=0.58)[625]; final analysis showed improved 1-year CNS-PFS (40% vs. 0%)[624].

Pazopanib

Assay findings association

FGFR1
amplification

AREAS OF THERAPEUTIC USE

Pazopanib is a tyrosine kinase inhibitor that targets VEGFRs, PDGFRs, FGFRs, KIT, ITK, LCK, and c-FMS. It is FDA approved for the treatment of advanced renal cell carcinoma and soft tissue sarcomas that have progressed after prior chemotherapy. 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[213,626] .

SUPPORTING DATA

A Phase 2 clinical trial of pazopanib in breast cancer reported 55% disease stabilization[627]. 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[628]. 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[629-630] . 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[631].

Trastuzumab + Pembrolizumab

Assay findings association

ERBB2
amplification - equivocal

AREAS OF THERAPEUTIC USE

Trastuzumab is a monoclonal antibody that targets ERBB2/HER2, and pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor. These therapies are FDA approved in combination with chemotherapy for HER2-positive gastric or gastroesophageal junction adenocarcinoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in gastric and esophagogastric cancer[632-633] and additional limited clinical evidence in breast cancer[634], ERBB2 amplification may predict sensitivity to trastuzumab combined with pembrolizumab.

SUPPORTING DATA

In the Phase 1b/2 PANACEA study, addition of pembrolizumab to trastuzumab for treatment of patients with HER2-positive, PD-L1-positive breast cancer who had previously progressed on trastuzumab elicited an ORR of 15% (2/46 CRs, 5/46 PRs), median DOR of 11.1 months, and median PFS of 2.7 months; none of the 12 patients with PD-L1-negative tumors (CPS <1%) experienced objective response or disease control[634].

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.

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
CCND2

ALTERATION
amplification

RATIONALE
CCND2 amplification or activation may predict sensitivity to CDK4/6 inhibitors.

NCT04282031

PHASE 1/2

A Study of BPI-1178 in Patients With Advanced Solid Tumor and HR+/HER2- Breast Cancer

TARGETS
CDK6, CDK4, ER, Aromatase

LOCATIONS: Shanghai (China)

NCT04801966

PHASE NULL

Safety and Oversight of the Individually Tailored Treatment Approach: A Novel Pilot Study

TARGETS
CDK4, CDK6, PI3K-alpha, PD-L1, MEK, PARP, PD-1, BRAF

LOCATIONS: Melbourne (Australia)

NCT05252416

PHASE 1/2

(VELA) Study of BLU-222 in Advanced Solid Tumors

TARGETS
ER, CDK4, CDK6, CDK2

LOCATIONS: Massachusetts, New York, Virginia, Texas, Florida

NCT05159245

PHASE 2

The Finnish National Study to Facilitate Patient Access to Targeted Anti-cancer Drugs

TARGETS
BRAF, VEGFRs, RET, KIT, ERBB2, TRKB, ALK, TRKC, ROS1, TRKA, SMO, PD-L1, MEK, CDK4, CDK6

LOCATIONS: Kuopio (Finland), Helsinki (Finland), Tampere (Finland), Turku (Finland)

NCT04603183

PHASE 2

ABemaciclib, ET ± paclItaxel in aGgressive HR+/HER2- MBC trIaL

TARGETS
CDK4, Aromatase, CDK6, ER

LOCATIONS: Piacenza (Italy), Girona (Spain), Manresa (Spain), Lleida (Spain), Reus (Spain), Pamplona (Spain), Zaragoza (Spain), Bilbao (Spain), Castellón De La Plana (Spain), Valencia (Spain)

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

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

LOCATIONS: Washington, Oregon, Idaho, Montana

NCT03573648

PHASE 2

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

TARGETS
ER, CDK4, CDK6, PD-L1

LOCATIONS: Pennsylvania, Maryland, District of Columbia, Alabama

NCT02896335

PHASE 2

Palbociclib In Progressive Brain Metastases

TARGETS
CDK4, CDK6

LOCATIONS: Massachusetts

NCT04352777

PHASE 2

Impact of Endocrine Therapy and Abemaciclib on Host and Tumor Immune Cell Repertoire/Function in Advanced ER+/HER2- Breast Cancer

TARGETS
CDK4, Aromatase, CDK6, ER

LOCATIONS: North Carolina

NCT04360941

PHASE 1

PAveMenT: Palbociclib and Avelumab in Metastatic AR+ Triple Negative Breast Cancer

TARGETS
PD-L1, CDK4, CDK6

LOCATIONS: London (United Kingdom)

GENE
ERBB2

ALTERATION
amplification - equivocal

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. ERBB2 amplification may confer sensitivity to the combination of lapatinib with aromatase inhibitors.

NCT04622319

PHASE 3

A Study of Trastuzumab Deruxtecan (T-DXd) Versus Trastuzumab Emtansine (T-DM1) in High-risk HER2-positive Participants With Residual Invasive Breast Cancer Following Neoadjuvant Therapy (DESTINY-Breast05)

TARGETS
ERBB2

LOCATIONS: Beitou (Taiwan), Taipei (Taiwan), Taichung (Taiwan), Chang Hua (Taiwan), Tainan (Taiwan), Kaohsiung (Taiwan), Xiamen (China), Hangzhou (China), Shanghai (China), Nanchang (China)

NCT04873362

PHASE 3

A Study Evaluating the Efficacy and Safety of Adjuvant Atezolizumab or Placebo and Trastuzumab Emtansine for Participants With HER2-Positive Breast Cancer at High Risk of Recurrence Following Preoperative Therapy

TARGETS
ERBB2, PD-L1

LOCATIONS: Taipei (Taiwan), Taichung (Taiwan), Taipei 100 (Taiwan), Tainan (Taiwan), Zhejiang (China), Shanghai (China), Hong Kong (Hong Kong), Guangzhou City (China), Guangzhou (China), Wuhan City (China)

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: Taipei (Taiwan), Tao-Yuan (Taiwan), Taichung (Taiwan), Fuzhou (China), Tainan (Taiwan), Hangzhou (China), Naha-shi (Japan), Shanghai (China), Nanchang (China), Nanjing (China)

NCT05132582

PHASE 3

A Study of Tucatinib or Placebo With Trastuzumab and Pertuzumab for Metastatic HER2+ Breast Cancer

TARGETS
ERBB2

LOCATIONS: Taipei (Taiwan), New Taipei City (Taiwan), Kaohsiung (Taiwan), Hangzhou (China), Hangzhou City (China), Nanchang (China), Nanchang City (China), Hefei (China), Wuhan (China), Liuzhou (China)

NCT05113251

PHASE 3

Trastuzumab Deruxtecan (T-DXd) Alone or in Sequence With THP, Versus Standard Treatment (ddAC-THP), in HER2-positive Early Breast Cancer

TARGETS
ERBB2

LOCATIONS: Taipei (Taiwan), Taipei 112 (Taiwan), Taipei City (Taiwan), Taoyuan (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Kaohsiung (Taiwan), Shanghai (China), Guangzhou (China), Beijing (China)

NCT04538742

PHASE 1/2

A Phase 1b/2 Study of T-DXd Combinations in HER2-positive Metastatic Breast Cancer

TARGETS
PD-L1, ERBB2

LOCATIONS: Taipei (Taiwan), Taipei City (Taiwan), Taoyuan City (Taiwan), Tainan (Taiwan), Busan (Korea, Republic of), Seoul (Korea, Republic of), Gurgaon (India), Delhi (India), Madurai (India), Mumbai (India)

NCT04188548

PHASE 1

A Study of LY3484356 in Participants With Advanced or Metastatic Breast Cancer or Endometrial Cancer

TARGETS
mTOR, Aromatase, CDK4, CDK6, ER, PI3K-alpha, ERBB2

LOCATIONS: Taipei (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Kaohsiung (Taiwan), Seoul (Korea, Republic of), Akashi (Japan), Chuo-ku (Japan), Nedlands (Australia), Kurralta Park (Australia), Waratah (Australia)

NCT05296798

PHASE 3

A Study to Evaluate the Efficacy and Safety of Giredestrant in Combination With Phesgo (Pertuzumab, Trastuzumab, and Hyaluronidase-zzxf) Versus Phesgo in Participants With Locally Advanced or Metastatic Breast Cancer (heredERA Breast Cancer)

TARGETS
ER, Aromatase, ERBB2

LOCATIONS: Taichung (Taiwan), Taipei 100 (Taiwan), Changhua (Taiwan), Taipei (Taiwan), Tainan (Taiwan), Hangzhou City (China), Bengbu City (China), Jinan (China), Nanning (China), Daegu (Korea, Republic of)

NCT03500380

PHASE 2/3

A Study of RC48-ADC Administered Intravenously to Patients With HER2-Positive Metastatic Breast Cancer

TARGETS
ERBB2

LOCATIONS: Fuzhou (China), Taizhou (China), Shantou (China), Hangzhou (China), Shanghai (China), Shaoguan (China), Nanjing (China), Hefei (China), Guangzhou (China), Changsha (China)

NCT04281641

PHASE NULL

Markers to Evaluate the Efficacy of PH-based Regimen as a Neoadjuvant Therapy for Operable HER2 Positive Breast Cancer

TARGETS
ERBB2

LOCATIONS: Shanghai (China)

GENE
FGFR1

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

ALTERATION
amplification

NCT05098847

PHASE 2

Cryoablation Combined With Sintilimab Plus Lenvatinib In Previously Treated Unresectable Liver Metastasis From Solid Tumors

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

LOCATIONS: Shanghai (China)

NCT05024214

PHASE 1/2

Phase Ib/II Trial of Envafolimab Plus Lenvatinib for Subjects With Solid Tumors

TARGETS
PD-L1, FGFRs, RET, PDGFRA, VEGFRs, KIT, FLT3, CSF1R

LOCATIONS: Hangzhou (China), Shanghai (China), Dongguan (China), Guangzhou (China), Zhuhai (China), Benbu (China), Zhengzhou (China), Jinan (China), Dalian (China), Tianjin (China)

NCT04169672

PHASE 2

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

TARGETS
FGFR1, CSF1R, VEGFRs, PD-1

LOCATIONS: Shanghai (China), Beijing (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)

NCT05077384

PHASE 1/2

Open-label Study of Surufatinib in Japanese Patients

TARGETS
FGFR1, CSF1R, VEGFRs

LOCATIONS: Sendai (Japan), Fukuoka (Japan), Kagawa (Japan), Osaka (Japan), Nagoya (Japan), Tokyo (Japan), Yokohama (Japan), Mitaka (Japan), Kashiwa-shi (Japan), Sapporo (Japan)

NCT04008797

PHASE 1

A Study of E7386 in Combination With Other Anticancer Drug in Participants With Solid Tumor

TARGETS
CBP, Beta-catenin, FGFRs, RET, PDGFRA, VEGFRs, KIT

LOCATIONS: Kurume (Japan), Matsuyama (Japan), Osakasayama (Japan), Nagoya (Japan), Chuo-Ku (Japan), Chiba (Japan), Kashiwa (Japan)

NCT04962867

PHASE 2

NCCH2006/MK010 Trial (FORTUNE Trial)

TARGETS
FGFR1, FGFR2, FGFR3

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

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

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: Seoul (Korea, Republic of), Liverpool (Australia), Petah Tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Haifa (Israel), Warszawa (Poland), Gdansk (Poland), Thessaloniki (Greece), Heraklion (Greece)

NCT04565275

PHASE 1/2

A Study of ICP-192 in Patients With Advanced Solid Tumors

TARGETS
FGFR2, FGFR1, FGFR3, FGFR4

LOCATIONS: Macquarie Park (Australia), Melbourne (Australia), Clayton (Australia), Frankston (Australia), Colorado, Minnesota, Arizona, Ohio, Florida

GENE
MTAP

ALTERATION
loss

RATIONALE
MTAP loss may predict sensitivity to MAT2A inhibitors, or to inhibitors that target PRMT5 when in complex with MTA.

NCT05094336

PHASE 1/2

AMG 193, Methylthioadenosine (MTA) Cooperative Protein Arginine Methyltransferase 5 (PRMT5) Inhibitor, Alone and in Combination With Docetaxel in Advanced Methylthioadenosine Phosphorylase (MTAP)-Null Solid Tumors

TARGETS
PRMT5-MTA

LOCATIONS: Hong Kong (Hong Kong), Nagoya-shi (Japan), Chuo-ku (Japan), Kashiwa-shi (Japan), Camperdown (Australia), Halle (Saale) (Germany), Salzburg (Austria), Wuerzburg (Germany), Ulm (Germany), Heidelberg (Germany)

NCT05275478

PHASE 1/2

Safety and Tolerability of TNG908 in Patients With MTAP-deleted Solid Tumors

TARGETS
PRMT5-MTA

LOCATIONS: Lyon (France), Missouri, Massachusetts, Tennessee, Texas, Virginia

NCT05245500

PHASE 1/2

Phase 1/2 Study of MRTX1719 in Solid Tumors With MTAP Deletion

TARGETS
PRMT5-MTA

LOCATIONS: Colorado, Massachusetts, New York, Tennessee, Texas

GENE
PIK3CA

ALTERATION
H1047R

RATIONALE
PIK3CA activating mutations may lead to activation of the PI3K-AKT-mTOR pathway and may therefore indicate sensitivity to inhibitors of this pathway. Strong clinical data support sensitivity of PIK3CA-mutated solid tumors to the PI3K-alpha inhibitor alpelisib.

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, RAFs, NRAS

LOCATIONS: Zhongzheng Dist. (Taiwan), Taipei City (Taiwan), Taoyuan County (Taiwan), Tainan (Taiwan), Shanghai City (China), Shanghai (China), Shatin (Hong Kong), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Xi'an (China)

NCT04341259

PHASE 1

A Study Of The Pharmacokinetics And Safety Of Ipatasertib In Chinese Participants With Locally Advanced Or Metastatic Solid Tumors.

TARGETS
AKTs

LOCATIONS: Shanghai City (China)

NCT03239015

PHASE 2

Efficacy and Safety of Targeted Precision Therapy in Refractory Tumor With Druggable Molecular Event

TARGETS
EGFR, ERBB4, ERBB2, PARP, mTOR, MET, ROS1, RET, VEGFRs, BRAF, CDK4, CDK6

LOCATIONS: Shanghai (China)

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (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)

NCT04526470

PHASE 1/2

Alpelisib and Paclitaxel in PIK3CA-altered Gastric Cancer

TARGETS
PI3K-alpha

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of)

NCT05125523

PHASE 1

A Study of Sirolimus for Injection (Albumin Bound) in Patients With Advanced Solid Tumors

TARGETS
mTOR

LOCATIONS: Tianjin (China)

NCT03772561

PHASE 1

Phase I Study of AZD5363 + Olaparib + Durvalumab in Patients With Advanced or Metastatic Solid Tumor Malignancies

TARGETS
PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

NCT04801966

PHASE NULL

Safety and Oversight of the Individually Tailored Treatment Approach: A Novel Pilot Study

TARGETS
CDK4, CDK6, PI3K-alpha, PD-L1, MEK, PARP, PD-1, BRAF

LOCATIONS: Melbourne (Australia)

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

GENE
TSC1

RATIONALE
Inactivating TSC1 alterations may lead to increased mTOR activation and predict sensitivity to mTOR inhibitors.

ALTERATION
rearrangement intron 3

NCT03239015

PHASE 2

Efficacy and Safety of Targeted Precision Therapy in Refractory Tumor With Druggable Molecular Event

TARGETS
EGFR, ERBB4, ERBB2, PARP, mTOR, MET, ROS1, RET, VEGFRs, BRAF, CDK4, CDK6

LOCATIONS: Shanghai (China)

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (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)

NCT05125523

PHASE 1

A Study of Sirolimus for Injection (Albumin Bound) in Patients With Advanced Solid Tumors

TARGETS
mTOR

LOCATIONS: Tianjin (China)

NCT02693535

PHASE 2

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

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

LOCATIONS: Hawaii, Washington, Oregon, California

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT01582191

PHASE 1

A Phase 1 Trial of Vandetanib (a Multi-kinase Inhibitor of EGFR, VEGFR and RET Inhibitor) in Combination With Everolimus (an mTOR Inhibitor) in Advanced Cancer

TARGETS
mTOR, EGFR, SRC, RET, VEGFRs

LOCATIONS: Texas

NCT03203525

PHASE 1

Combination Chemotherapy and Bevacizumab With the NovoTTF-100L(P) System in Treating Participants With Advanced, Recurrent, or Refractory Hepatic Metastatic Cancer

TARGETS
VEGFA, mTOR

LOCATIONS: Texas

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.

DIS3 K396Q	***FH*** T474R	***PTCH1*** Q413R	***SNCAIP*** S496N
SPOP amplification	***STK11*** F354L	***TEK*** loss	***TSC1*** K1085E and amplification

ORDERED TEST # ORD-1521386-01

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*	*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)

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 PRINCIPLE

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 fraction-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-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 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 (RG) 7.4.0

The median exon coverage for this sample is 883x

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