FOUNDATIONONE®CDx

PATIENT	TUMOR TYPE	REPORT DATE
Hsu, I Nung	Breast invasive ductal carcinoma (IDC)	16 Jun 2023
	COUNTRY CODE	ORDERED TEST #
	TW	ORD-1648391-01

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 invasive ductal carcinoma (IDC)
NAME Hsu, I Nung
DATE OF BIRTH 01 March 1985
SEX Female
MEDICAL RECORD # 39928002 PF23076

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 S112-81463 F
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 12 April 2023
SPECIMEN RECEIVED 09 June 2023

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 0 Muts/Mb

Genomic Findings

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

CCND1 amplification
PIK3CA H1047R, amplification
FGFR4 FGFR4-RNF130 non-canonical fusion
MYC amplification
NF1 S1140*
FGF19 amplification
FGF3 amplification
FGF4 amplification
RAD21 amplification
TP53 R248Q

3 Disease relevant genes with no reportable alterations: ***BRCA1, BRCA2, ERBB2***

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Abemaciclib** (p. 11), **Alpelisib + Fulvestrant** (p. 12)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 13)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Microsatellite status - MS-Stable	**No therapies or clinical trials.** See Biomarker Findings section
Tumor Mutational Burden - 0 Muts/Mb	**No therapies or clinical trials.** See Biomarker Findings section

GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
CCND1 **-** amplification	Abemaciclib 1	none
10 Trials see p. 13		
PIK3CA **-** H1047R, amplification	Alpelisib + Fulvestrant 1	none
10 Trials see p. 21		
FGFR4 **-** FGFR4-RNF130 non-canonical fusion	none	none
10 Trials see p. 15		

1 *NCCN category*

Electronically signed by Erik Williams, M.D. | 16 June 2023
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Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

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GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
MYC **-** amplification	none	none
10 Trials see p. 17		
NF1 **-** S1140*	none	none
10 Trials see p. 19		

☐ *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.

FGF19 **-** amplification ..... p. 8
FGF3 **-** amplification ..... p. 9
FGF4 **-** amplification ..... p. 9
RAD21 **-** amplification ..... p. 9
TP53 **-** R248Q ..... p. 10

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.

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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
0 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

One study reported that invasive ductal carcinoma (IDC) of the breast has a median TMB of 3.6 mutations per megabase (Muts/Mb), with 1.4% of cases harboring TMB ≥20 Muts/Mb[42]. Another study found that 4% of breast IDC cases have TMB ≥10 Muts/Mb, with a higher frequency of such elevated TMB (7.8%) in metastatic samples[43]. 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[43]. 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[44]. 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[43,45-46]. 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[43,45-46]. Breast carcinoma harbors a median TMB of 3.8 muts/Mb, and 3.1% of cases have high TMB (>20 muts/Mb)[42]. In a large study of patients with breast cancer, hypermutation was more frequently observed in metastatic tumors than in primary tumors[43]. 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[46]. 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].

GENE
CCND1

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Amplification or overexpression of CCND1 may predict sensitivity to CDK4/6 inhibitors, such as abemaciclib, palbociclib, and ribociclib[59-64], although as monotherapy these agents have shown limited activity in tumor types other than breast cancer[63,65]. In refractory advanced solid tumors with CCND1 (n=39) or CCND3 (n=1) amplification and retinoblastoma protein expression, palbociclib resulted in SD for 39% (14/36) of patients and a median PFS of 1.8 months in the NCI-MATCH trial[66]; 4 patients (13%, 4/36 overall) with squamous cell carcinomas (lung, esophageal, or laryngeal) or adenoid cystic carcinoma experienced prolonged SD in this study[66]. Among 9 patients with CCND1-amplified advanced solid tumors, 1 patient with bladder cancer responded to ribociclib in a Phase 2 trial[67].

FREQUENCY & PROGNOSIS

CCND1 amplification occurs in 10-17% of invasive breast cancers, more frequently in estrogen receptor (ER)-positive or BRCA-negative cancers, and correlates with overexpression of cyclin D1[44,68-72]. Meta-analysis showed that both CCND1 amplification (HR=2.5) and cyclin D1 overexpression (HR=1.7) are associated with poor prognosis in patients with ER-positive breast cancer[68,73]. Multiple studies reported that cyclin D1 is associated with resistance to endocrine therapy in patients with breast cancer[74-75]. A multi-arm clinical trial of various therapeutic approaches in patients with high-risk breast cancer reported association between high cyclin D1 expression and worse response to chemotherapy alone or in combination with a PARP inhibitor, or to anti-angiogenic therapy[76]. In addition, variants lacking PEST domain/3' UTR have been reported to be a poor prognostic factor in breast cancer[77], and other studies failed to note prognostic significance of the truncated cyclin D1 variant overexpression in breast cancer[78].

FINDING SUMMARY

CCND1 encodes cyclin D1, a binding partner of the kinases CDK4 and CDK6, that regulates RB activity and cell cycle progression. Amplification of CCND1 has been positively correlated with cyclin D1 overexpression[68] and may lead to excessive proliferation[79-80].

GENE
PIK3CA

ALTERATION
H1047R, amplification

HGVS VARIANT
NM_006218.2:c.3140A>G (p.H1047R)

VARIANT CHROMOSOMAL POSITION
chr3:178952085

VARIANT ALLELE FREQUENCY (% VAF)
91.1%

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[81-88], AKT[89-90], or mTOR[91-98]. A Phase 2 trial of the AKT inhibitor capivasertib with paclitaxel versus paclitaxel alone showed a median OS benefit for the overall population (19.1 vs. 12.6 months; HR=0.61), for patients with AKT1-, PTEN-, or PIK3CA-mutated triple-negative breast cancer (TNBC) (not reached vs. 10.4 months; HR=0.37), and for patients with TNBC without PI3K-pathway mutations (16.6 vs. 13.2 months; HR=0.84)[99]. In a Phase 2 trial, the addition of capivasertib to fulvestrant improved median PFS (mPFS) relative to fulvestrant plus placebo alone for patients with PIK3CA-, AKT1-, and/or PTEN-altered hormone-receptor-positive (HR+), HER2- metastatic breast cancer (12.8 vs. 4.6 months, HR=0.44)[100], although the Phase 3 CAPItello study of capivasertib with fulvestrant for patients with HR+, HER2- metastatic breast cancer reported improved median PFS (mPFS) relative to fulvestrant plus placebo for patients with and without alterations in the AKT pathway (7.3 vs 3.1 months, HR=0.50 and 7.2 vs 3.7 months, HR=0.70, respectively)[101]. In a Phase 2 basket trial of capivasertib monotherapy in AKT1-mutated cancers, 33% (2/6) of patients with HR+, HER2- or TNBC experienced PRs, and 2 other PRs were unconfirmed[102]. Despite promising initial results in earlier trials[103-104], the Phase 3 IPATunity130 trial failed to show improved PFS for first-line ipatasertib in combination with paclitaxel relative to paclitaxel alone for patients with AKT1-, PTEN-, or PIK3CA-mutated TNBC (7.4 vs. 6.1 months)[101] or HR+, HER2- breast cancer[105]. 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[106]. 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)[100,107]. 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[108]. Single-agent capivasertib also demonstrated activity in a Phase 1 study[109]. 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[110]. 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[111-112] . 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[113]. The addition of the mTOR inhibitor everolimus to exemestane to treat HR+, HER2- advanced breast cancer has shown clinical benefit, regardless of PIK3CA status[114-115]. 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[88]. However, the Phase 2 study of copanlisib for patients with endometrial carcinoma harboring PIK3CA hotspot mutations failed to report any objective responses (n=11)[87]. 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[85-86].

— Potential Resistance —

In the context of hormone-receptor-positive HER2-negative breast cancer, retrospective analysis of clinical data showed that MYC alterations were associated with inferior median PFS after treatment with alpelisib plus fulvestrant compared with unaltered MYC in a limited number of patients (HR=1.01 vs. HR=0.49, n=13 vs. 107)[116].

FREQUENCY & PROGNOSIS

PIK3CA amplification has been reported in up to 3% of invasive breast carcinoma cases analyzed[117]. Mutations in PIK3CA have been reported in up to 37% of breast cancer cases[44,118]. 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[119]. 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[120]. 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)[121]. 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)[122].

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[123-124]. PIK3CA amplification has been reported in cancer[125], and correlated with poor prognosis in certain tumor types[126-127]. PIK3CA amplification has also been associated with sensitivity to PI3K-alpha inhibitors in preclinical studies[81]. PIK3CA alterations that have been characterized as activating, such as observed here, are predicted to be oncogenic[128-149].

GENE
FGFR4

ALTERATION
FGFR4-RNF130 non-canonical fusion

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Tumors with FGFR4 amplification or activating mutations may be sensitive to certain pan-FGFR inhibitors, and clinical trials of some of these agents are currently underway in solid tumors, including erdafitinib[150] and LY2874455[151]. The multikinase inhibitor ponatinib has been shown to have substantial activity against all four FGFR kinases[152]. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS

In the Breast Invasive Carcinoma TCGA dataset, putative high-level amplification of FGFR4 was reported in <1% of cases[44]. FGFR4 amplification and gene overexpression have been detected in 10% and 32% of breast tumors, respectively, in the literature[153-154]. One study reported that the putative activating FGFR4 R388 polymorphism correlated with increased metastasis, reduced disease-free survival time, and overall poor prognosis for patients with breast cancer; however, the prognostic implications of FGFR4 amplification were not reported[155-156].

FINDING SUMMARY

FGFR4 encodes fibroblast growth factor receptor 4, a receptor tyrosine kinase that plays a role in regulation of the cell cycle and angiogenesis and is an upstream regulator of the RAS, MAPK, and AKT signaling pathways[157-158]. Missense mutations at residues G388, N535, and V550 of FGFR4 have been shown to be activating[159-162], whereas truncation of the most C-terminal 11 amino acids has been reported to inactivate FGFR4[163]. However, other missense mutations and larger C-terminal truncations have not been functionally characterized, and their effects on FGFR4 function are unknown. Such alterations have been reported in the context of cancer, which may indicate biological relevance.

GENE
MYC

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Limited clinical data indicates that MYC activation may predict sensitivity to the pan-MYC inhibitor OMO-103; a Phase 1 study for patients with solid tumors reported 7 SDs (n=18), including 8% tumor reduction in a patient with pancreas adenocarcinoma[164]. Preclinical data indicate MYC overexpression may predict sensitivity to investigational agents targeting CDK1[165-166], CDK2[167], Aurora kinase A[168-175], Aurora kinase B[176-179], glutaminase[180-183], or BET bromodomain-containing proteins[184-187], as well as agents targeting both HDAC and PI3K[188-190]. Exploratory biomarker analysis in a Phase 2 study reported a PFS benefit associated with a combination of the Aurora A kinase inhibitor alisertib and paclitaxel as second-line therapy for patients with MYC-overexpressed small cell lung cancer, but not for patients without MYC overexpression[191]. A PR was reported for a patient with MYC-amplified invasive ductal breast carcinoma treated with an unspecified Aurora kinase inhibitor and taxol[192].

— Potential Resistance —

In the context of hormone-receptor-positive HER2-negative breast cancer, retrospective analysis of clinical data showed that MYC alterations were associated with inferior median PFS after treatment with alpelisib plus fulvestrant compared with unaltered MYC in a limited number of patients (HR=1.01 vs. HR=0.49, n=13 vs. 107)[116].

— Nontargeted Approaches —

MYC amplification has also been suggested to predict response to chemotherapy in patients with breast cancer in some studies[193-194]. Preclinical evidence suggests that colon cancer cells with MYC amplification may be more sensitive to 5-fluorouracil and paclitaxel[195-196].

FREQUENCY & PROGNOSIS

MYC amplification has been reported in 8.6-26% of breast carcinomas[117-118,197]. MYC amplification has been associated with an aggressive phenotype, early onset, and poor prognosis in patients with breast cancer, although the data have been conflicting[193,198-200].

FINDING SUMMARY

MYC (c-MYC) encodes a transcription factor that regulates many genes related to cell cycle regulation and cell growth. It is an oncogene and may be activated in as many as 20% of cancers[201]. MYC dysregulation (amplification, overexpression, translocation) has been identified in a number of different cancer types[202]. MYC amplification has been significantly linked with increased mRNA and protein levels and results in the dysregulation of a large number of target genes[201,203-204].

GENE
NF1

ALTERATION
S1140*

HGVS VARIANT
NM_001042492.2:c.3419C>A (p.S1140*)

VARIANT CHROMOSOMAL POSITION
chr17:29559822

VARIANT ALLELE FREQUENCY (% VAF)
38.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in neurofibromatosis type 1-associated neurofibroma and malignant peripheral nerve sheath tumors[205-209], central nervous system tumors including glioma and astrocytoma[210-213], limited clinical evidence for MEK inhibitors in non-small cell lung cancer (NSCLC)[213-214], and in combination with chemotherapy for biliary tract cancers[215], NF1 inactivation may predict sensitivity to MEK inhibitors such as cobimetinib, trametinib, binimetinib, and selumetinib. On the basis of limited clinical data[216-218] and preclinical data[219-220], loss or inactivation of NF1 may predict sensitivity to mTOR inhibitors, including everolimus and temsirolimus. A preclinical study suggests that combined mTOR and MEK inhibition is effective in a model of NF1-deficient malignant peripheral nerve sheath tumors (MPNST)[221].

FREQUENCY & PROGNOSIS

NF1 mutations and loss have been reported in 1.9-2.7% and <1% of breast carcinomas, respectively[117-118,197,222]. NF1 alterations are enriched in metastatic breast invasive lobular carcinoma (ILC) compared to metastatic invasive ductal carcinoma (12.2% vs 3.1%), and are often mutually exclusive with ESR1 alterations[45]. NF1 alterations have been reported to arise during endocrine therapy resistance in ILC[45]. Studies have suggested that women with neurofibromatosis type 1, which is associated with germline NF1 mutations, may have an increased risk of breast cancer[223-227]. Published data investigating the prognostic implications of NF1 alteration in breast cancer are limited (PubMed, Jan 2023).

FINDING SUMMARY

NF1 encodes neurofibromin, a GTPase-activating protein (GAP) that is a key negative regulator of the RAS signaling pathway[228]. Neurofibromin acts as a tumor suppressor by repressing RAS signaling[229]. Alterations such as seen here may disrupt NF1 function or expression[229-238].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in NF1 cause the autosomal dominant disorder neurofibromatosis type 1, which is characterized in part by increased risk of developing various tumors, including sarcoma, glioma, breast carcinoma, and neuroendocrine and hematological neoplasms[227,239-240]. Estimates for the prevalence of the disorder in the general population range from 1:2,500 to 1:3,000[241-242], and in the appropriate clinical context, germline testing of NF1 is recommended.

GENE
FGF19

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

A Phase 1 study of the FGFR4 inhibitor fisogatinib (BLU-554) for patients with advanced hepatocellular carcinoma (HCC) reported a 17% ORR (11/66, 1 CR, ongoing for >1.5 years) and 3.3-month PFS for FGF19 IHC–positive patients; patients with negative or unknown FGF19 IHC scores experienced poorer outcomes (0% ORR, 2.3-month PFS)[243]. A Phase 1/2 study evaluating another FGFR4 inhibitor, FGF401, demonstrated an ORR of 7.5% (4/53) and SD rate of 53% (28/53) for patients with HCC[244]. A Phase 1 study of the FGFR4 inhibitor H3B-6527 reported a 17% ORR (OS of 10.3 months, 46% clinical benefit rate) among patients with HCC; enrollment of patients with intrahepatic cholangiocarcinoma (ICC) was suspended due to efficacy[245]. A retrospective analysis reported that 50% (2/4) of patients with HCC harboring FGF19 amplification experienced a CR to sorafenib[246], though another retrospective study found patients with higher pretreatment serum levels of FGF19 experienced reduced benefit from sorafenib compared with those with lower serum FGF19 (PFS of 86 vs. 139 days, OS of 353 vs. 494 days); no difference was observed for lenvatinib[247]. A patient with head and neck squamous cell carcinoma (HNSCC) with 11q13 (FGF3, FGF4, FGF19) and 12p13 (FGF6 and FGF23) amplification experienced a CR lasting 9 months from a pan-FGFR inhibitor[248].

FREQUENCY & PROGNOSIS

For patients with solid tumors, FGF19 amplification has been reported most frequently in breast cancer (17%), head and neck cancer (12%), lung squamous cell carcinoma (SCC; 12%), and urothelial carcinoma cancer (11%)[249-251]. FGF19 mutations are rare in solid tumors[249]. FGF19 expression or amplification has been associated with poor prognosis in hepatocellular carcinoma (HCC)[252-253], and in prostate cancer following radical prostatectomy[254]. Studies suggest FGF19 expression may also be a poor prognostic indicator in head and neck squamous cell carcinoma (HNSCC)[255] and lung SCC[256].

FINDING SUMMARY

FGF19 encodes fibroblast growth factor 19, an FGFR4 ligand involved with bile acid synthesis and hepatocyte proliferation in the liver[257-258]. FGF19 lies in a region of chromosome 11q13 that also contains FGF3, FGF4, and CCND1; this region is frequently amplified in a diverse range of malignancies[259]. Correlation between FGF19 amplification and protein expression has been reported in hepatocellular carcinoma (HCC)[260], lung squamous cell carcinoma[256,261], and head and neck squamous cell carcinoma (HNSCC)[255], but was not observed in other cancers[247,262].

GENE
FGF3

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies that directly address genomic alterations in FGF3. Inhibitors of FGF receptors, however, are undergoing clinical trials in a number of different cancers. While 1 case study reported radiologic CR for 1 patient with FGF-amplified head and neck squamous cell carcinoma (HNSCC) following treatment with a selective pan-FGFR inhibitor[248], 2 Phase 1/2 studies have reported mixed efficacy for FGFR inhibitor pemigatinib or futibatinib across FGF-amplified solid tumors[263-264].

FREQUENCY & PROGNOSIS

FGF3 lies in a region of chromosome 11q13 that also contains FGF19, FGF4, and CCND1, the latter gene encoding cyclin D1, a key regulator of cell cycle progression. This chromosomal region is frequently amplified in a diverse range of malignancies[79].

FINDING SUMMARY

FGF3 encodes fibroblast growth factor 3, a growth factor that plays a central role in development of the inner ear. Germline mutations in FGF3 give rise to an autosomal recessive syndrome characterized by microdontia, deafness, and complete lack of inner ear structures[265].

GENE
FGF4

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies that target genomic alterations in FGF4. A patient with head and neck squamous cell carcinoma (HNSCC) harboring multiple FGF amplifications experienced a CR when treated with a selective pan-FGF receptor (FGFR) inhibitor[248]. However, 2 phase 1/2 studies have reported mixed efficacy for the FGFR inhibitors pemigatinib and futibatinib across FGF-amplified solid tumors[263-264].

FREQUENCY & PROGNOSIS

FGF4 lies in a region of chromosome 11q13 that also contains FGF19, FGF3, and CCND1, the latter gene encoding cyclin D1, a key regulator of cell cycle progression. This chromosomal region is frequently amplified in a diverse range of malignancies[79] including esophageal carcinoma (35%), head and neck squamous cell carcinoma (HNSCC; 24%), breast invasive carcinoma (14%), lung squamous cell carcinoma (13%), cholangiocarcinoma (11%), bladder urothelial carcinoma (10%), stomach adenocarcinoma (7%), skin melanoma (5%), and hepatocellular carcinoma (HCC; 5%), however FGF4 amplification is rare in hematopoietic and lymphoid malignancies, reported in less than 1% of samples analyzed (cBioPortal, Jan 2023)[125,266].

FINDING SUMMARY

FGF4 encodes fibroblast growth factor 4, which plays a central role in development of the teeth[267] and acts synergistically with other FGFs and SHH (sonic hedgehog) to regulate limb outgrowth in vertebrate development[268]. FGF4 lies in a region of chromosome 11q13 that also contains FGF19, FGF3, and CCND1, the latter gene encoding cyclin D1, a key regulator of cell cycle progression. Amplification of FGF4, along with that of FGF3, FGF19, and CCND1, has been reported in a variety of cancers[79,269-273] and may confer sensitivity to the multi-kinase inhibitor sorafenib[272].

GENE
RAD21

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies to target alterations in this gene.

FREQUENCY & PROGNOSIS

RAD21 amplification has been reported in 19% of breast cancers[117]. RAD21 alterations have been associated with inferior OS among patients with HER2+ or HR+/HER2– breast cancer but was not predictive of survival for patients with triple-negative breast cancer[274]. RAD21 expression has been associated with shorter recurrence-free survival (RFS) for patients with breast cancer[275].

FINDING SUMMARY

RAD21 encodes a protein involved in DNA double-strand break repair and sister chromatid cohesion as a part of the cohesin complex[276-279]. Altered RAD21 expression has been associated with increased genomic instability[280-282] and changes to the expression of other genes[283-285]. RAD21 amplification has been correlated with increased RAD21 expression in breast[275,282,286] and endometrial[287] cancers. Other RAD21 alterations, including truncating and point mutations, have been reported in the context of cancer, but the majority have not been characterized.

GENE
TP53

ALTERATION
R248Q

HGVS VARIANT
NM_000546.4:c.743G>A (p.R248Q)

VARIANT CHROMOSOMAL POSITION
chr17:7577538

VARIANT ALLELE FREQUENCY (% VAF)
40.5%

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[288-291] or p53 gene therapy such as SGT53[292-296]. 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[297]. 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[298]. 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[299]. 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[300]. 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[301]. 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[302]. 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[303]. 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[296]. 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[304]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[305].

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[44,222,306-309]. TP53 mutations that are located within the region encoding the DNA binding domain are associated with poor prognosis in patients with breast cancer[307,310-311]. 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[312-314].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[315]. Alterations such as seen here may disrupt TP53 function or expression[316-320].

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, Apr 2023)[321]. 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[322-324], including sarcomas[325-326]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[327] to 1:20,000[326]. 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[328]. 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[329-334]. 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[329-330]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[335]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[333,336-337]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

Abemaciclib

Assay findings association

CCND1
amplification

AREAS OF THERAPEUTIC USE

Abemaciclib inhibits the cyclin-dependent kinases 4 and 6 (CDK4/6) and is FDA approved to treat adults with hormone-receptor-positive (HR+), HER2-negative (HER2-) breast cancer as monotherapy as well as in combination with tamoxifen or an aromatase inhibitor, including anastrozole, letrozole, and exemestane. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data in breast cancer and mantle cell lymphoma[59,63] , CCND1 amplification or activating rearrangement may be associated with response to abemaciclib. In a Phase 1 study, 4 patients with CCND1-amplified breast cancer responded to single-agent abemaciclib, with all the responders having HR+ tumors[63].

SUPPORTING DATA

Biomarker analysis from the Phase 2 nextMONARCH 1 study evaluating abemaciclib monotherapy in patients with heavily pre-treated HR+, HER2-negative metastatic breast cancer revealed that genomic alterations in PIK3CA (3.9 vs. 9.2 months; HR=0.43), TP53 (3.6 vs. 9.0 months; HR=0.66), FGFR1 (3.6 vs. 8.7 months; HR=0.49), MYC (1.9 vs. 9.0 months; HR=0.27), NF1 (3.8 vs. 8.2 months; HR=0.53), EGFR (3.5 vs. 8.8 months; HR=0.4), ERBB2 (4.9 vs. 8.2 months; HR=0.53), or CCNE1 (1.9 vs. 7.4 months; HR=0.35) were associated with a significantly shorter mPFS compared with patients with wildtype status for those genes[338]. As first-line treatment for postmenopausal women with HR+, HER2- advanced breast cancer, the addition of abemaciclib to nonsteroidal aromatase inhibitors significantly increased median PFS (mPFS; 28.1 vs. 14.8 months, HR=0.54) and ORR (61% vs. 46%) in the placebo-controlled Phase 3 MONARCH 3 study[339-340] . The Phase 2 MONARCH 1 study of abemaciclib as a monotherapy for patients with HR+, HER2- metastatic breast cancer refractory to endocrine therapy and chemotherapy observed an mPFS of 6 months, an ORR of 20%, and a median OS of 17.7 months[65]. Abemaciclib also demonstrated clinical benefit for patients with HR+, HER2- breast cancer who progressed on palbociclib or ribociclib[341], for patients with brain metastases[342], and in the neoadjuvant setting[343]. The triplet combination of pembrolizumab, abemaciclib, and anastrozole for postmenopausal patients with HR+, HER2- metastatic breast cancer has been explored in a Phase 1b trial[344]. For pretreated patients with metastatic breast cancer, the combination of abemaciclib and tamoxifen yielded an ORR of 20% (3/15) in a Phase 1b study[345]; however, the randomized Phase 2 nextMONARCH1 study showed that the addition of tamoxifen to abemaciclib did not significantly improve PFS or ORR compared with abemaciclib monotherapy for patients with HR+, HER2- metastatic breast cancer[346]. For patients with HR+, HER2+ breast cancer who had received prior HER2-targeted therapy, abemaciclib combined with trastuzumab and fulvestrant (Arm A) compared with abemaciclib plus trastuzumab (Arm B) or trastuzumab plus chemotherapy (Arm C) significantly increased mPFS (8.3 vs. 5.7 vs. 5.7 months; HR=0.67, A vs. C) and ORR (33% vs. 14% vs. 14%) and numerically increased OS (31.1 vs. 29.2 vs. 20.7 months) in a Phase 2 study[345,347] . In the Phase 3 monarchE study, as adjuvant treatment for patients with HR+, HER2- node-positive early breast cancer at high risk of recurrence, addition of abemaciclib to endocrine therapy improved 4-year invasive disease-free survival (HR=0.664; rates 86% vs. 79%,) and 4-year distant relapse-free survival (HR=0.659; rates 88% vs. 83%) compared with endocrine therapy alone[348]; similar results were reported for patients enrolled in Asia[349].

Alpelisib + Fulvestrant

Assay findings association

PIK3CA
H1047R, amplification

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 postmenopausal patients and patients assigned male at birth with hormone-receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-), 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[89].

SUPPORTING DATA

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[89,106] ; patients with wildtype PIK3CA did not experience significant mPFS benefit (7.4 vs. 5.6 months, HR=0.85)[89]. 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[350]. 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)[351]; 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)[352]. 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[352-353] , 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[354].

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
CCND1

ALTERATION
amplification

RATIONALE
CCND1 amplification or overexpression may activate CDK4/6 and may predict sensitivity to single-agent CDK4/6 inhibitors. CCND1 amplification may activate CDK4/6 and may predict sensitivity to the combination of fulvestrant and abemaciclib in breast cancer.

NCT05169567

PHASE 3

Abemaciclib (LY2835219) Plus Fulvestrant Compared to Placebo Plus Fulvestrant in Previously Treated Breast Cancer

TARGETS
CDK6, ER, CDK4

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), New Taipei City (Taiwan), Tainan City (Taiwan), Kaohsiung (Taiwan), Daegu (Korea, Republic of), Seongnam (Korea, Republic of), Seoul (Korea, Republic of), Diyarbakir (Turkey), Adana (Turkey)

NCT04975308

PHASE 3

Study of LY3484356 Versus Hormone Therapy, in Participants With Estrogen Receptor Positive (ER+), Human Epidermal Growth Factor Receptor 2 Negative (HER2-) Breast Cancer

TARGETS
ER, CDK4, CDK6, Aromatase

LOCATIONS: Taipei (Taiwan), Taichung (Taiwan), Tainan City (Taiwan), Tainan (Taiwan), Ningbo (China), Hangzhou (China), Nanchang (China), Nanjing (China), Guangzhou (China), ChangSha (China)

NCT05501886

PHASE 3

Gedatolisib Plus Fulvestrant With or Without Palbociclib vs Standard-of-Care for the Treatment of Patients With Advanced or Metastatic HR+/HER2- Breast Cancer (VIKTORIA-1)

TARGETS
CDK6, ER, CDK4, PI3K-alpha, PI3K-gamma, mTORC1, mTORC2

LOCATIONS: Kaohsiung (Taiwan), Singapore (Singapore), Nedlands (Australia), Southport (Australia), Woodville (Australia), Adelaide (Australia), Wahroonga (Australia), Fitzroy (Australia), Frankston (Australia), Varna (Bulgaria)

NCT05054751

PHASE 3

GB491 Combined With Fulvestrant for HR+ HER2- Locally Advanced or Metastatic Breast Cancer

TARGETS
CDK6, CDK4, ER

LOCATIONS: Fuzhou (China), Xiamen (China), Meizhou (China), Hangzhou (China), Nanchang (China), Hefei (China), Guangzhou (China), Foshan (China), Wuhan (China), Bengbu (China)

NCT05594095

PHASE 2

SNF Platform Study of HR+/ HER2-advanced Breast Cancer

TARGETS
ER, LHRH, mTOR, Aromatase, PD-1, VEGFR2, VEGFR3, PDGFRB, FLT3, KIT, PDGFRA, FLT1, VEGFR1, CDK6, CDK4, PARP, ERBB2, RET, RAFs, VEGFRs, SRC

LOCATIONS: Shanghai (China)

NCT05438810

PHASE 3

This is a Multicenter, Randomized, Double-blind, Placebo-controlled Phase III Clinical Study Evaluating the Efficacy and Safety of FCN-437c in Combination With Fluvestrant ± Goseraline Versus Placebo Combined With Fulvestrant ± Goserelin in Women With HR+ and HER2- Advanced Breast Cancer.

TARGETS
ER, CDK4, CDK6

LOCATIONS: Shanghai (China)

NCT05640778

PHASE 2

Neoadjuvant Dalpiciclib Plus Aromatase Inhibitors or Chemotherapy in Luminal B/HER2-negative Breast Cancer (DAPATH)

TARGETS
Aromatase, CDK6, CDK4

LOCATIONS: Hangzhou (China)

NCT04858997

PHASE 2

Tumor Response Time of Palbociclib in Combination With AI in Real-world Chinese Patients

TARGETS
Aromatase, CDK4, CDK6

LOCATIONS: Hangzhou (China)

NCT05293964

PHASE 1

Phase I Study to Evaluate SCR-6852 Alone or in Combination in ER+, HER2- Locally Advanced or Metastatic Breast Cancer

TARGETS
CDK4, CDK6

LOCATIONS: Shanghai (China)

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)

GENE
FGFR4

ALTERATION
FGFR4-RNF130 non-canonical fusion

RATIONALE
FGFR inhibitors may be of use in a tumor with FGFR4 amplification or activating mutation. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

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: Taipei (Taiwan), Tainan (Taiwan), Kurume (Japan), Matsuyama (Japan), Seongnamsi Bundang (Korea, Republic of), Songpa-gu (Korea, Republic of), Seodaemun (Korea, Republic of), Seoul (Korea, Republic of), Jongno-gu (Korea, Republic of), Osakasayama (Japan)

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)

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)

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), North Carolina

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)

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), Brisbane (Australia), Liverpool (Australia), Petah Tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Haifa (Israel), Warszawa (Poland), Gdansk (Poland), Thessaloniki (Greece)

NCT05740215

PHASE 1/2

Efficacy and Safety Study of F520 Combined With Lenvatinib in the Treatment of Patients With Advanced Solid Tumors

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

LOCATIONS: Chongqing (China)

NCT05064280

PHASE 2

Phase II Study of Pembrolizumab in Combination With Lenvatinib in Patients With TNBC, NSCLC, and Other Tumor Types and Brain Metastases

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

LOCATIONS: Texas

NCT04565275

PHASE 1/2

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

TARGETS
FGFR2, FGFR1, FGFR3, FGFR4

LOCATIONS: Benowa (Australia), Westmead (Australia), Macquarie Park (Australia), St Leonards (Australia), Melbourne (Australia), Clayton (Australia), Frankston (Australia), California, Colorado, Minnesota

NCT02856425

PHASE 1

Trial Of Pembrolizumab And Nintedanib

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

LOCATIONS: Villejuif (France), Lyon (France), Bordeaux (France), Toulouse (France)

GENE
MYC

ALTERATION
amplification

RATIONALE
MYC overexpression may predict sensitivity to inhibition of CDKs, especially CDK1 and CDK2, of Aurora kinases, including Aurora kinase A and B, and of BET domain proteins, which are reported to downregulate MYC expression and MYC-dependent transcriptional programs.

NCT04553133

PHASE 1/2

PF-07104091 as a Single Agent and in Combination Therapy

TARGETS
CDK6, Aromatase, CDK4, CDK2

LOCATIONS: Shanghai (China), Koto (Japan), Kashiwa (Japan), Iowa, Michigan, Massachusetts, Kentucky, New York

NCT03901469

PHASE 2

A Study of ZEN003694 and Talazoparib in Patients With Triple Negative Breast Cancer

TARGETS
BRD4, BRDT, BRD2, BRD3, PARP

LOCATIONS: Guangzhou (China), Changsha (China), Bengbu (China), Jining (China), Tianjin (China), Neijiang (China), Leuven (Belgium), Anderlecht (Belgium), Barcelona (Spain), Madrid (Spain)

NCT05253053

PHASE 1/2

Study to Evaluate the Efficacy and Safety of TT-00420 as Monotherapy and Combination Therapy in Patients With Advanced Solid Tumors

TARGETS
Aurora kinase A, Aurora kinase B, PD-L1

LOCATIONS: Jinan (China), Beijing (China)

NCT04983810

PHASE 1/2

A Study to Investigate Fadraciclib (CYC065), in Subjects With Advanced Solid Tumors and Lymphoma

TARGETS
CDK2, CDK9

LOCATIONS: Seoul (Korea, Republic of), Barcelona (Spain), California, Texas

NCT05252390

PHASE 1/2

NUV-868 as Monotherapy and in Combination With Olaparib or Enzalutamide in Adult Patients With Advanced Solid Tumors

TARGETS
BRD4, PARP, AR

LOCATIONS: Montana, California, Colorado, Arizona, Michigan, Texas

NCT05327010

PHASE 2

Testing the Combination of the Anti-cancer Drugs ZEN003694 (ZEN-3694) and Talazoparib in Patients With Advanced Solid Tumors, The ComBET Trial

TARGETS
PARP, BRD4, BRDT, BRD2, BRD3

LOCATIONS: Colorado, Illinois, Texas, North Carolina, Georgia

NCT04742959

PHASE 1/2

Crossover Relative Bioavailability and Dose Escalation Study of TT-00420 Tablet in Patients With Advanced Solid Tumors

TARGETS
Aurora kinase A, Aurora kinase B

LOCATIONS: California, Illinois, Ohio, Texas, New Jersey

NCT05053971

PHASE 1/2

Testing A New Anti-cancer Drug Combination, Entinostat and ZEN003694, for Advanced and Refractory Solid Tumors and Lymphomas

TARGETS
BRD3, BRD4, BRD2, BRDT, HDAC

LOCATIONS: Oklahoma, Connecticut, Florida

NCT04840589

PHASE 1

Testing the Combination of ZEN003694 and Nivolumab With or Without Ipilimumab in Solid Tumors

TARGETS
PD-1, CTLA-4, BRD4, BRDT, BRD2, BRD3

LOCATIONS: Ohio, Pennsylvania, New York, Maryland

NCT04555837

PHASE 1/2

Alisertib and Pembrolizumab for the Treatment of Patients With Rb-deficient Head and Neck Squamous Cell Cancer

TARGETS
Aurora kinase A, PD-1

LOCATIONS: Texas

GENE
NF1

ALTERATION
S1140*

RATIONALE
On the basis of clinical evidence and strong preclinical evidence, NF1 inactivation may predict sensitivity to MEK inhibitors. Limited clinical data and strong preclinical data indicate that loss or inactivation of NF1 may also predict sensitivity to mTOR inhibitors.

NCT05501886

PHASE 3

Gedatolisib Plus Fulvestrant With or Without Palbociclib vs Standard-of-Care for the Treatment of Patients With Advanced or Metastatic HR+/HER2- Breast Cancer (VIKTORIA-1)

TARGETS
CDK6, ER, CDK4, PI3K-alpha, PI3K-gamma, mTORC1, mTORC2

LOCATIONS: Kaohsiung (Taiwan), Singapore (Singapore), Nedlands (Australia), Southport (Australia), Woodville (Australia), Adelaide (Australia), Wahroonga (Australia), Fitzroy (Australia), Frankston (Australia), Varna (Bulgaria)

NCT05594095

PHASE 2

SNF Platform Study of HR+/ HER2-advanced Breast Cancer

TARGETS
ER, LHRH, mTOR, Aromatase, PD-1, VEGFR2, VEGFR3, PDGFRB, FLT3, KIT, PDGFRA, FLT1, VEGFR1, CDK6, CDK4, PARP, ERBB2, RET, RAFs, VEGFRs, SRC

LOCATIONS: Shanghai (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)

NCT04818632

PHASE 1

AZD9833 China PK Study

TARGETS
CDK4, CDK6, ER, mTOR

LOCATIONS: Shanghai (China), Beijing (China), Wuhan (China), Chengdu (China)

NCT05306340

PHASE 3

A Study Evaluating the Efficacy and Safety of Giredestrant Plus Everolimus Compared With Exemestane Plus Everolimus in Participants With Estrogen Receptor-Positive, HER2-Negative, Locally Advanced or Metastatic Breast Cancer (evERA Breast Cancer)

TARGETS
ER, mTOR, Aromatase

LOCATIONS: Kumamoto (Japan), Ehime (Japan), Hiroshima (Japan), Osaka (Japan), Kyoto (Japan), Aichi (Japan), Kanagawa (Japan), Tokyo (Japan), Chiba (Japan), Fukushima (Japan)

NCT04802759

PHASE 1/2

A Study Evaluating the Efficacy and Safety of Multiple Treatment Combinations in Participants With Breast Cancer

TARGETS
ER, CDK4, CDK6, AKTs, PI3K-alpha, mTOR

LOCATIONS: Seoul (Korea, Republic of), Goyang-si (Korea, Republic of), Nedlands (Australia), Bedford Park (Australia), Melbourne (Australia), Frankston (Australia), Petach Tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Jerusalem (Israel)

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)

NCT04985604

PHASE 1/2

DAY101 Monotherapy or in Combination With Other Therapies for Patients With Solid Tumors

TARGETS
BRAF, MEK

LOCATIONS: Busan (Korea, Republic of), Seoul (Korea, Republic of), Clayton (Australia), Edegem (Belgium), Oregon, Barcelona (Spain), Madrid (Spain), California, Colorado

NCT05125523

PHASE 1

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

TARGETS
mTOR

LOCATIONS: Tianjin (China)

NCT05580770

PHASE 1/2

Mirdametinib + BGB-3245 in Advanced Solid Tumors

TARGETS
BRAF, MEK

LOCATIONS: Waratah (Australia), Melbourne (Australia), California, Ohio, Massachusetts, Texas, Connecticut, Florida

GENE
PIK3CA

ALTERATION
H1047R, amplification

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.

NCT04191499

PHASE 2/3

A Study Evaluating the Efficacy and Safety of GDC-0077 + Palbociclib + Fulvestrant vs Placebo + Palbociclib + Fulvestrant in Patients With PIK3CA-Mutant, Hormone Receptor-Positive, Her2-Negative, Locally Advanced or Metastatic Breast Cancer

TARGETS
PI3K-alpha, CDK6, ER, CDK4

LOCATIONS: Taipei (Taiwan), Taipei City (Taiwan), Fuzhou City (China), Tainan (Taiwan), Kaohsiung (Taiwan), Shanghai City (China), Shatin (Hong Kong), Nanjing City (China), Hong Kong (Hong Kong), Guangzhou City (China)

NCT05646862

PHASE 3

A Study Evaluating the Efficacy and Safety of Inavolisib Plus Fulvestrant Compared With Alpelisib Plus Fulvestrant in Participants With HR-Positive, HER2-Negative, PIK3CA Mutated, Locally Advanced or Metastatic Breast Cancer Post CDK4/6i and Endocrine Combination Therapy

TARGETS
PI3K-alpha, ER

LOCATIONS: Zhongzheng Dist. (Taiwan), Ankara (Turkey), Edirne (Turkey), Oregon, Ohio, Texas, Guadalajara (Mexico), Mexico City (Mexico), Cdmx (Mexico), Ciudad de México (Mexico)

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: Taipei City (Taiwan), Taoyuan County (Taiwan), Shanghai City (China), Shanghai (China), Shatin (Hong Kong), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Xi'an (China), Tianjin (China), Beijing City (China)

NCT05720260

PHASE 2

Immunotherapy, Hormone Therapy, and AKT Inhibitor for Premenopausal ER Positive MBC

TARGETS
AKTs, ER, PD-L1

LOCATIONS: Taipei City (Taiwan)

NCT05501886

PHASE 3

Gedatolisib Plus Fulvestrant With or Without Palbociclib vs Standard-of-Care for the Treatment of Patients With Advanced or Metastatic HR+/HER2- Breast Cancer (VIKTORIA-1)

TARGETS
CDK6, ER, CDK4, PI3K-alpha, PI3K-gamma, mTORC1, mTORC2

LOCATIONS: Kaohsiung (Taiwan), Singapore (Singapore), Nedlands (Australia), Southport (Australia), Woodville (Australia), Adelaide (Australia), Wahroonga (Australia), Fitzroy (Australia), Frankston (Australia), Varna (Bulgaria)

NCT04544189

PHASE 2

Study Assessing the Efficacy and Safety of Treatment With Alpelisib Plus Fulvestrant Versus Placebo Plus Fulvestrant in Chinese Men and Postmenopausal Women With Advanced Breast Cancer

TARGETS
ER, PI3K-alpha

LOCATIONS: Hangzhou (China), Shanghai (China), Nanchang (China), Shenzhen (China), Nanjing (China), Hefei (China), Guangzhou (China), Changsha City (China), Changsha (China), Wuhan (China)

NCT04524000

PHASE 2

Study Assessing the Efficacy and Safety of Treatment With Alpelisib Plus Fulvestrant in Japanese Men and Postmenopausal Women With Advanced Breast Cancer

TARGETS
ER, PI3K-alpha

LOCATIONS: Naha-city (Japan), Kumamoto City (Japan), Matsuyama (Japan), Hiroshima-city (Japan), Okayama-city (Japan), Akashi (Japan), Osaka (Japan), Osaka-city (Japan), Suita (Japan), Tsu-city (Japan)

NCT05594095

PHASE 2

SNF Platform Study of HR+/ HER2-advanced Breast Cancer

TARGETS
ER, LHRH, mTOR, Aromatase, PD-1, VEGFR2, VEGFR3, PDGFRB, FLT3, KIT, PDGFRA, FLT1, VEGFR1, CDK6, CDK4, PARP, ERBB2, RET, RAFs, VEGFRs, SRC

LOCATIONS: Shanghai (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)

NCT04631835

PHASE 1

Phase I Study of the HS-10352 in Patients With Advanced Breast Cancer

TARGETS
PI3K-alpha

LOCATIONS: Shanghai (China), Guanzhou (China), Changsha (China)

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.

DOT1L
NM_032482.2: c.1764C>G
(p.D588E)
chr19:2213952

HRAS
NM_176795.3: c.488_507del
(p.L163Hfs*30)
chr11:533301-533321

NSD2 (WHSC1 OR MMSET)
rearrangement

PARP1
NM_001618.3: c.14C>G
(p.S5W)
chr1:226595617

SMARCA4
NM_003072.3: c.719C>T
(p.P240L)
chr19:11097228

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. 2023. 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) 7.9.0

The median exon coverage for this sample is 857x

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