FOUNDATIONONE® CDx

PATIENT

TUMOR TYPE
Lung adenocarcinoma

REPORT DATE

COUNTRY CODE
BR

ORDERED TEST #

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

PATIENT	PHYSICIAN	SPECIMEN
DISEASE Lung adenocarcinoma	ORDERING PHYSICIAN	SPECIMEN SITE
NAME	MEDICAL FACILITY	SPECIMEN ID
DATE OF BIRTH	ADDITIONAL RECIPIENT	SPECIMEN TYPE
SEX	MEDICAL FACILITY ID	DATE OF COLLECTION
MEDICAL RECORD #	PATHOLOGIST	SPECIMEN RECEIVED

Biomarker Findings

Microsatellite status - MS-Equivocal [α]
Tumor Mutational Burden - 0 Muts/Mb

Genomic Findings

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

ERBB2 G776>VC
CCND1 amplification
MEN1 D423N - subclonal[†]
MYC amplification
CDKN2A/B CDKN2B loss, CDKN2A loss
FGF19 amplification
FGF3 amplification
FGF4 amplification
TP53 P191fs*56

7 Disease relevant genes with no reportable alterations: ***ALK, BRAF, EGFR, KRAS, MET, RET, ROS1***

† See About the Test in appendix for details.

α Patients with Microsatellite status of MS-Equivocal should be re-tested with an orthogonal (alternative) method.

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Ado-trastuzumab emtansine** (p. 13), **Fam-trastuzumab deruxtecan** (p. 11)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 15)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Microsatellite status - MS-Equivocal	**No therapies or clinical trials.** See Biomarker Findings section
Tumor Mutational Burden - 0 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 **-** G776>VC	Fam-trastuzumab deruxtecan 2A	Ado-trastuzumab emtansine 2A
	Afatinib	Neratinib
	Dacomitinib (?)	Trastuzumab
10 Trials see p. 17		Trastuzumab + Pertuzumab
CCND1 **-** amplification	none	none
7 Trials see p. 15		
MEN1 **-** D423N - subclonal	none	none
7 Trials see p. 19		
MYC **-** amplification	none	none
7 Trials see p. 21		

(?) *Limited evidence showing variant(s) in this sample may confer resistance to this therapy*

☐ *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.

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BIOMARKER

Microsatellite status

RESULT
MS-Equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of prospective clinical evidence in multiple solid tumor types, microsatellite instability (MSI) and associated increased tumor mutational burden (TMB)[1-2] may predict sensitivity to immune checkpoint inhibitors, including the approved PD-1-targeting agents cemiplimab, dostarlimab, nivolumab (alone or in combination with ipilimumab), and pembrolizumab[3-9], as well as PD-L1-targeting agents atezolizumab, avelumab, and durvalumab[10-12] . The efficacy of immune checkpoint inhibitors to treat MS-Equivocal cancers has not been investigated in published studies. Whereas 1 study reported that microsatellite instability-low (MSI-L) tumors, like microsatellite stable (MSS) tumors, have significantly lower expression of a gene signature indicative of immune response compared with microsatellite instability-high (MSI-H) tumors[2], data directly comparing the efficacy of anti-PD-1 immunotherapies in MSI-H and MSI-L tumors are lacking. Therefore, the relevance of these approaches for MSI-L tumors is unclear.

FREQUENCY & PROGNOSIS

MSI-H is generally infrequent in NSCLC, reported in fewer than 1% of samples across several large studies[13-18], whereas data on the reported incidence of MSI-H in SCLC has been limited and conflicting[19-22]. One study reported MSI-H in lung adenocarcinoma patients with smoking history, and 3 of 4 MSI-H patients examined also had metachronous carcinomas in other organs, although this has not been investigated in large scale studies[13]. Published data investigating the prognostic implications of MSI in NSCLC are limited (PubMed, Oct 2022).

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[23]. 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[23-25]. This sample has been characterized to have an equivocal microsatellite status (MS-Equivocal), harboring more instability than microsatellite-stable tumors but less than MSI-high cases. This may represent an MSI-low (MSI-L) tumor: one with mutations in at least 1 but <30% of microsatellite markers[26-28]. MSI-L status indicates low-level deficiency in MMR, also known as a "mild mutator" phenotype[23,27-29]. However, MS-Equivocal status is not identical to the clinical definition of MSI-L. Depending on the clinical context, MSI testing by another methodology could be considered.

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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[30-32], anti-PD-1 therapies[30-33], and combination nivolumab and ipilimumab[34-39]. Multiple clinical trials of PD-1- or PD-L1-targeting immune checkpoint inhibitors or combination of PD-1 and CTLA-4 inhibitors in NSCLC have reported that patients with tumors harboring TMB ≥10 Muts/Mb derive greater clinical benefit from these therapies than those with TMB <10 Muts/Mb (based on this assay or others); similarly, higher efficacy of anti-PD-1 or anti-PD-L1 immunotherapy for treatment of patients with NSCLC, compared with the use of chemotherapy, has been observed more significantly in cases of TMB ≥10 Muts/Mb (based on this assay or others);[8,30-31,34-36,40-46]. Improved OS of patients with NSCLC treated with pembrolizumab plus chemotherapy relative to chemotherapy only[47], or those treated with nivolumab plus ipilimumab also relative to chemotherapy[48], has been observed across all TMB levels.

FREQUENCY & PROGNOSIS

A large-scale genomic analysis found that unspecified lung non-small cell lung carcinoma (NSCLC), lung adenocarcinoma, and lung squamous cell carcinoma (SCC) samples harbored median TMBs between 6.3 and 9 Muts/Mb, and 12% to 17% of cases had an elevated TMB of greater than 20 Muts/Mb[49]. Lower TMB is observed more commonly in NSCLCs harboring known driver mutations (EGFR, ALK, ROS1, or MET) with the exception of BRAF or KRAS mutations, which are commonly observed in elevated TMB cases[50]. Although some studies have reported a lack of association between smoking and mutational burden in NSCLC[51-52], several other large studies did find a strong association with increased TMB[53-56]. TMB >10 muts/Mb was found to be more frequent in NSCLC metastases compared with primary tumors for both adenocarcinoma (38% vs. 25%) and SCC (41% vs. 35%) subtypes[57]. A meta-analysis of 19 studies of immune checkpoint inhibitor-treated NSCLC (n = 2,315 patients) demonstrated that high TMB predicted a significantly longer OS than low TMB (HR = 0.70), and within the high TMB group, immunotherapy was associated with an improved PFS (HR = 0.62, P<0.001), OS (HR = 0.67, P<0.001) and a higher response rate (OR = 2.35, P<0.001) compared to chemotherapy[58]. In contrast, a large study of Chinese patients with untreated lung adenocarcinoma reported a shorter median OS for tumors with a higher number of mutations in a limited gene set compared with a lower mutation number (48.4 vs. 61.0 months)[51]. Another study of patients with NSCLC treated with EGFR inhibitors or platinum doublet chemotherapy found elevated TMB to be correlated with poorer prognosis, as well as finding lower TMB in combination with PD-L1 negative status to be significantly associated with longer median survival in patients with lung adenocarcinoma[59]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[59-60].

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[61-62] and cigarette smoke in lung cancer[8,63], treatment with temozolomide-based chemotherapy in glioma[64-65], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[66-70], and microsatellite instability (MSI)[66,69-70]. This sample harbors a TMB below levels that would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[8,30-31,34-36,40-46,71].

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GENE
ERBB2

ALTERATION
G776>VC

TRANSCRIPT ID
NM_004448.2

CODING SEQUENCE EFFECT
2326_2327insTGT

VARIANT CHROMOSOMAL POSITION
chr17:37880997

VARIANT ALLELE FREQUENCY (% VAF)
39.1%

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[72-77], pertuzumab in combination with trastuzumab[74,78-80], and zanidatamab (ZW25)[81], as well as antibody-directed conjugates such as ado-trastuzumab emtansine (T-DM1)[82] and fam-trastuzumab deruxtecan (T-DXd)[83-85], HER2 kinase inhibitors such as tucatinib[86-89], and dual EGFR/HER2 kinase inhibitors such as lapatinib[90-98], afatinib[77,99-108], neratinib[109-112], dacomitinib[113], and pyrotinib[114-115] . HER2 antibody drug conjugates trastuzumab emtansine[116] and trastuzumab deruxtecan have elicited ORRs of 44-55% among patients with ERBB2-mutated non-small cell lung cancer (NSCLC), including for patients with ERBB2 exon 20 insertions[85]. Tyrosine kinase inhibitors have demonstrated efficacy for patients with HER2 exon 20 insertions including poziotinib (ORR 27-28%)[117-118] and pyrotinib (ORR 30-53%)[119-120]. Other kinase inhibitors have been evaluated for patients with NSCLC harboring exon 20 insertions including afatinib (ORR 8-17%)[104-107], dacomitinib (ORR 12%)[113], and neratinib (ORR 4%)[111].

— Potential Resistance —

Clinical and preclinical data suggest that ERBB2 exon 20 insertions confer resistance to lapatinib and reduced sensitivity to afatinib, dacomitinib, and neratinib[77,105-106,111,113,121-126]. However, it is unclear if ERBB2 exon 20 insertions confer reduced sensitivity to lapatinib in combination with other therapies, such as trastuzumab.

FREQUENCY & PROGNOSIS

ERBB2 mutations have been reported in 2.2–4.2% of lung adenocarcinomas and lung squamous cell carcinomas across several genomic studies[43,55,127-130]. Exon 20 insertions are the most frequently observed ERBB2 alteration in lung adenocarcinomas, representing 61% (72/118) to 96% (24/25) of ERBB2 mutations detected[107,131]. One large study of 20,656 patients with non-small cell lung cancer reported 24% of ERBB2 mutations were exon 20 insertions[132]. Of ERBB2 exon 20 insertions in NSCLC, A775_G776insYVMA is the most common (42–85%), followed by P780_Y781insGSP (9–11%) and G776>VC (8–11%)[106-107,124,131]. Exon 20 insertion mutations are more prevalent in adenocarcinoma histology[106] and are generally mutually exclusive with other common driver alterations in NSCLC[131]. HER2 overexpression has been documented in 11-32% of NSCLC cases, and is generally reported more frequently in non-squamous histologies[133-134]. Expression of HER2 has generally been associated with poor prognosis in NSCLC in several studies[135-139]. In a retrospective study of patients with ERBB2-mutated NSCLC who were treated with afatinib, A775_G776insYVMA predicted inferior PFS when compared with other exon 20 insertions (HR = 0.009) or missense mutations (HR = 0.184), whereas P780_Y781insGSP and G776>VC were associated with improved PFS compared with missense mutations (HR = 0.050)[107].

FINDING SUMMARY

ERBB2 (also known as HER2) encodes a receptor tyrosine kinase which is in the same family as EGFR. ERBB2 exon 20 insertion mutations, such as observed here, are predicted to be activating[123-124,140-142]. The mutation seen here is similar to G776>VC (also known as G776_V777>VCV, G776delinsVC, or G776_V777delinsVCV)[124].

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[143-148], although as monotherapy these agents have shown limited activity in tumor types other than breast cancer[147,149]. 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[150]; 4 patients (13%, 4/36 overall) with squamous cell carcinomas (lung, esophageal, or laryngeal) or adenoid cystic carcinoma experienced prolonged SD in this study[150]. Among 9 patients with CCND1-amplified advanced solid tumors, 1 patient with bladder cancer responded to ribociclib in a Phase 2 trial[151].

FREQUENCY & PROGNOSIS

CCND1 amplification has been reported in 2-25% of lung adenocarcinoma[55,128,152-153] and 6-38% of lung squamous cell carcinoma[130,152-153] cases. Expression of cyclin D1 has been reported in 59% (36/61) of non-small cell lung cancer (NSCLC) tumors analyzed[154]. The prognostic significance of CCND1 amplification in NSCLC is not clear[155]. Cyclin D1 protein expression was not associated with clinicopathologic parameters of NSCLC in one study[154].

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[156] and may lead to excessive proliferation[157-158].

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GENE
MEN1

ALTERATION
D423N - subclonal

TRANSCRIPT ID
NM_130801.2

CODING SEQUENCE EFFECT
1267G>A

VARIANT CHROMOSOMAL POSITION
chr11:64572604

VARIANT ALLELE FREQUENCY (% VAF)
1.2%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies, either approved or in clinical trials, that directly target mutation or loss of MEN1. Preclinical studies in cells and transgenic mice have shown that tumor formation mediated by loss of MEN1 (a direct activator of p18INK4c) is associated with increased expression and activity of CDK4 and that CDK4 knockout abrogates formation of MEN1 loss-driven tumors[159-162]. Therefore, tumors with MEN1 loss or inactivation may be sensitive to CDK4/6 inhibitors, such as ribociclib, abemaciclib, and palbociclib[144-147], although this has not been demonstrated clinically.

FREQUENCY & PROGNOSIS

MEN1 mutations have been reported in 0.4-1.6% of lung adenocarcinomas[54-55,128] and 4% of lung squamous cell carcinomas[130]. Decreased Menin expression has been reported in 23% of lung adenocarcinoma cases and linked with lymph node metastasis[163]. MEN1 has been suggested to act as a tumor suppressor in non-small cell lung cancer (NSCLC)[163-166].

FINDING SUMMARY

MEN1 encodes menin, a tumor suppressor associated with a histone methyltransferase complex that regulates developmental gene expression via chromatin remodeling[167]. Alterations such as seen here may disrupt MEN1 function or expression[168-173].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the MEN1 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 multiple endocrine neoplasia type 1 syndrome (ClinVar, Sep 2022)[174-180]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in MEN1 are associated with multiple endocrine neoplasia (MEN1) syndrome, an autosomal dominant hereditary cancer syndrome characterized most commonly by pancreatic endocrine tumors (in 40-70% of patients), pituitary adenomas (in 30-40% of patients), and parathyroid adenomas[181-182]. In addition, a small subset of breast cancers may be associated with germline MEN1 mutation[182-183]. Prevalence for this disorder in the general population is estimated to be 1:30,000[184], and in the appropriate clinical context, germline testing of MEN1 is recommended.

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[185]. Preclinical data indicate MYC overexpression may predict sensitivity to investigational agents targeting CDK1[186-187], CDK2[188], Aurora kinase A[189-196], Aurora kinase B[197-200], glutaminase[201-204], or BET bromodomain-containing proteins[205-208], as well as agents targeting both HDAC and PI3K[209-211]. 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[212]. A PR was reported for a patient with MYC-amplified invasive ductal breast carcinoma treated with an unspecified Aurora kinase inhibitor and taxol[213].

— Nontargeted Approaches —

MYC amplification has also been suggested to predict response to chemotherapy in patients with breast cancer in some studies[214-215]. Preclinical evidence suggests that colon cancer cells with MYC amplification may be more sensitive to 5-fluorouracil and paclitaxel[216-217].

FREQUENCY & PROGNOSIS

MYC amplification has been reported in 10-50% of non-small cell lung cancer (NSCLC) samples, including adenocarcinoma and/or squamous cell carcinoma subtypes[218-222]. In the Lung Adenocarcinoma TCGA and Lung Squamous Cell Carcinoma TCGA datasets, putative MYC amplification has been reported in 9% and 4.5% of cases, respectively[128,130]. MYC amplification has been associated with metastasis in NSCLC, as well as with poor prognosis in early stage lung adenocarcinoma specifically[218-221].

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[223]. MYC dysregulation (amplification, overexpression, translocation) has been identified in a number of different cancer types[224]. MYC amplification has been significantly linked with increased mRNA and protein levels and results in the dysregulation of a large number of target genes[223,225-226].

GENE
CDKN2A/B

ALTERATION
CDKN2B loss, CDKN2A 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[227-230]. Clinical data in mesothelioma, breast cancer, and uterine leiomyosarcoma indicate that CDKN2A loss may predict sensitivity to abemaciclib[231] and palbociclib treatment[232-233]. However, multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[145-146,151,234-237]; 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[238-239], 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[144-145,151,236,240-241].

FREQUENCY & PROGNOSIS

CDKN2A/B loss and CDKN2A mutation have been reported in approximately 19% and 4% of lung adenocarcinomas, respectively[128]. CDKN2A/B loss and CDKN2A mutation have been reported in 26% and 17% of lung squamous cell carcinoma (SCC) samples analyzed in the TCGA dataset, respectively[130]. Loss of p16INK4a protein expression, through CDKN2A mutation, homozygous deletion, or promoter methylation, has been described in 49-68% of non-small cell lung cancer (NSCLC) samples, whereas low p14ARF protein expression has been detected in 21-72% of NSCLC samples[130,242-247]. In patients with lung SCC, loss of CDKN2B associated with poor survival in one study[248]. Loss of p16INK4a protein as well as CDKN2A promoter hypermethylation correlate with poor survival in patients with NSCLC[244,249-251].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[252-253]. 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[243,254]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[255-256]. One or more alterations observed here are predicted to result in p16INK4a loss of function[257-278]. One or more alterations seen here are predicted to result in p14ARF loss of function[261,278-281]. CDKN2B alterations such as seen here are predicted to inactivate p15INK4b[282].

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[283]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[284-285]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[286-288]. 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[289-291]. In the appropriate clinical context, germline testing of CDKN2A 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)[292]. 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[293]. 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[294]. A retrospective analysis reported that 50% (2/4) of patients with HCC harboring FGF19 amplification experienced a CR to sorafenib[295], 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[296]. 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[297].

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%)[130,298-299]. FGF19 mutations are rare in solid tumors[298]. FGF19 expression or amplification has been associated with poor prognosis in hepatocellular carcinoma (HCC)[300-301], and in prostate cancer following radical prostatectomy[302]. Studies suggest FGF19 expression may also be a poor prognostic indicator in head and neck squamous cell carcinoma (HNSCC)[303] and lung SCC[304].

FINDING SUMMARY

FGF19 encodes fibroblast growth factor 19, an FGFR4 ligand involved with bile acid synthesis and hepatocyte proliferation in the liver[305-306]. 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[307]. Correlation between FGF19 amplification and protein expression has been reported in hepatocellular carcinoma (HCC)[308], lung squamous cell carcinoma[304,309], and head and neck squamous cell carcinoma (HNSCC)[303], but was not observed in other cancers[296,310].

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. 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[311].

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[157].

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[312].

GENE
FGF4

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

FGF4 amplification and overexpression was associated with cell sensitivity to the multikinase inhibitor sorafenib in preclinical studies[313-314] and amplification of FGF4/FGF3 in HCC significantly correlated with patient response to sorafenib (p=0.006)[313]. 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[311].

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[157] 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 2022)[315-316].

FINDING SUMMARY

FGF4 encodes fibroblast growth factor 4, which plays a central role in development of the teeth[317] and acts synergistically with other FGFs and SHH (sonic hedgehog) to regulate limb outgrowth in vertebrate development[318]. 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[157,313,319-322] and may confer sensitivity to the multi-kinase inhibitor sorafenib[313].

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GENE
TP53

ALTERATION
P191fs*56

TRANSCRIPT ID
NM_000546.4

CODING SEQUENCE EFFECT
570delT

VARIANT CHROMOSOMAL POSITION
chr17:7578278-7578279

VARIANT ALLELE FREQUENCY (% VAF)
44.7%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[323-326] or p53 gene therapy such as SGT53[327-331]. 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[332]. 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[333]. 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[334]. 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[335]. 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[336]. 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[337]. 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[338]. 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[331]. 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[339]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[340].

FREQUENCY & PROGNOSIS

TP53 is one of the most commonly mutated genes in lung cancer; mutations have been reported in 43-80% of non-small cell lung cancers (NSCLCs)[128,130,246,341-345], including 42-52% of lung adenocarcinomas and 58-83% of lung squamous cell carcinomas (cBioPortal, COSMIC, Feb 2022)[55-56,128,130]. TP53 homozygous deletion has been observed in 1.4% of lung adenocarcinoma and <1% of lung squamous cell carcinoma cases (cBioPortal, Feb 2022)[315-316]. In one study of 55 patients with lung adenocarcinoma, TP53 alterations correlated with immunogenic features including PD-L1 expression, tumor mutation burden and neoantigen presentation; likely as a consequence of this association TP53 mutations correlated with improved clinical outcomes to PD-1 inhibitors pembrolizumab and nivolumab in this study[346]. Mutations in TP53 have been associated with lymph node metastasis in patients with lung adenocarcinoma[347].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[348]. Alterations such as seen here may disrupt TP53 function or expression[349-353].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[354-356], including sarcomas[357-358]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[359] to 1:20,000[358]. 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[360]. 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[361-366]. 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[361-362]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[367]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[365,368-369]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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Afatinib

Assay findings association

ERBB2
G776>VC

AREAS OF THERAPEUTIC USE

Afatinib is an irreversible kinase inhibitor that targets the kinase domains of EGFR, ERBB2/HER2, and ERBB4. It is FDA approved for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) and nonresistant EGFR mutations and for the treatment of patients with metastatic, squamous NSCLC after progression on platinum-based chemotherapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Clinical and preclinical data support sensitivity of multiple activating mutations in ERBB2, including A775_G776insYVMA and P780_Y781insGSP, to afatinib[104-108,123-126] . Studies have reported DCRs of 54-70% for patients with ERBB2-mutated NSCLC treated with afatinib, most of whom harbored exon 20 insertions[104-108] . Retrospective data suggest that ERBB2 G776>VC or P780_Y781insGSP may predict improved PFS with afatinib in patients with NSCLC as compared with ERBB2 missense mutations (HR = 0.050)[107].

SUPPORTING DATA

The Phase 2 NICHE trial for platinum-refractory non-small cell lung cancer (NSCLC) harboring ERBB2 exon 20 insertions reported a low ORR but a high DCR, with 1 PR and 7 SDs out of 13 patients; the median PFS (mPFS) and OS were 3.7 and 13 months, respectively[104]. A retrospective study of afatinib for patients with ERBB2-mutated NSCLC, most of whom were previously treated, reported an ORR of 16% and a DCR of 69%; the mPFS was 1.2 months for patients with A775_G776insYVMA, 7.6 months for patients with G776>VC or P780_Y781insGSP, and 3.6 months for patients with ERBB2 missense mutations[107]. Other retrospective studies of afatinib for ERBB2-mutated lung cancer have reported similar ORRs of 13–16% and DCRs of 68–70%[105-106] . A case report of a patient with lung adenocarcinoma harboring an ERBB2 V659E activating mutation demonstrated a PR of 9 months in response to afatinib as well as near resolution of a metastatic lesion in the liver[370]. In the LUX-Lung 1 Phase 2b/3 trial for patients with advanced non-small cell lung cancer (NSCLC) who previously progressed on first-generation EGFR tyrosine kinase inhibitors, afatinib treatment resulted in longer median PFS (mPFS; 3.3 vs. 1.1 months, HR=0.38) but no significant difference in median OS (mOS; 10.8 vs. 12.0 months, HR=1.08) when compared with placebo[371]; similar results were observed in the single-arm LUX-Lung 4 trial in the same treatment setting[372]. The randomized Phase 3 LUX-Lung 8 trial comparing afatinib with erlotinib as second-line therapy for advanced lung squamous cell carcinoma (SCC) reported significantly longer mOS (7.9 vs. 6.8 months, HR=0.81), significantly longer mPFS (2.6 vs. 1.9 months, HR=0.81), and higher DCR (51% vs. 40%, p=0.002) for patients treated with afatinib[373]. For patients who progressed on afatinib monotherapy, additional clinical benefit has been reported from afatinib combined with paclitaxel[374].

Fam-trastuzumab deruxtecan

Assay findings association

ERBB2
G776>VC

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 non-small cell lung cancer (NSCLC)[85,375] , ERBB2 missense or exon 20 insertion mutations may predict sensitivity to fam-trastuzumab deruxtecan.

SUPPORTING DATA

The Phase 2 DESTINY-Lung01 study of single-agent fam-trastuzumab deruxtecan for patients with advanced metastatic ERBB2-altered non-small cell lung cancer (NSCLC) predominantly harboring exon 20 insertions reported an ORR of 55% (50/91), median duration of response of 9.3 months, median PFS of 8.2 months, and mOS of 17.8 months[85]. In a similar setting evaluating fam-trastuzumab deruxtecan at a slightly lower dose, the Phase 2 DESTINY-Lung-02 study reported similar efficacy with ORRs of 58% (30/52) and 43% (12/28) and median durations of response of 8.7 months and 5.9 months at doses of 5.4 mg/kg and 6.4 mg/kg, respectively[376]. Fam-trastuzumab deruxtecan achieved a 40% ORR (2/5 PRs) and 80% DCR (4/5) in a retrospective analysis for patients with metastatic ERBB2-mutated/EGFR wildtype NSCLC; patients treated with other trastuzumab regimens had significantly larger tumor sizes (p=0.045)[377].

Dacomitinib

Resistance of variant(s) to associated therapy is unclear

Assay findings association

ERBB2
G776>VC

AREAS OF THERAPEUTIC USE

Dacomitinib is a second generation irreversible tyrosine kinase inhibitor that targets the kinase domains of EGFR, ERBB2/HER2, and ERBB4/HER4. It is FDA approved for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with EGFR exon 19 deletion or exon 21 L858R substitution mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Early phase clinical trials report anti-tumor activity of dacomitinib in advanced solid tumors with ERBB2 activating mutations[113,378] , ERBB2 amplification[379-380] or HER2 overexpression[381]. In a prospective Phase 2 study of dacomitinib in NSCLC, the ORR was 12% in patients with ERBB2 mutations, which were mostly exon 20 insertions; objective response was observed in 2 patients with G778_P780insGSP and 1 patient with M774delinsWLV, but not in patients with other exon 20 insertions[113]. Preclinical data support reduced sensitivity of ERBB2 exon 20 insertions to dacomitinib[124-126] .

SUPPORTING DATA

In a Phase 2 study, 3/26 (12%) of patients with ERBB2 exon 20 mutations experienced PRs to dacomitinib treatment; the median PFS was 3 months and median OS was 9 months in this cohort[113]. In ERBB2-amplified NSCLC, response rates of 0/4 (0%)[113] to 1/3 (33%)[380] have been reported, with disease control (PR or SD) achieved in 4/9 (44%) patients total[113,378,380] . A Phase 1 trial of combination dacomitinib and a MEK1/2 inhibitor for patients with KRAS-mutated CRC, NSCLC, or pancreatic cancer reported 20/36 SDs and 16 PDs, however toxicity from this combination prevented long-term treatment in this patient population[382]. Phase 1/2 studies of dacomitinib for patients with advanced KRAS-wildtype non-small cell lung cancer (NSCLC) who had previously progressed on chemotherapy and erlotinib or gefitinib and were not selected for EGFR mutations reported ORRs of 4.6-17% (3/66-9/53), median PFS of 3-4 months, and median OS of 9-11 months[380,383] .

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Ado-trastuzumab emtansine

Assay findings association

ERBB2
G776>VC

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[82,384-399] . Patients with NSCLC and various ERBB2 exon 20 insertion mutations have benefited from T-DM1[116,387,400] .

SUPPORTING DATA

In a Phase 2 basket trial of T-DM1, patients with ERBB2-mutated and/or -amplified non-small cell lung cancer (NSCLC) achieved an ORR of 51% (25/49) and a median PFS of 5 months. The ERBB2-amplified cohort had an ORR of 55% (6/11), while the ERBB2-mutated cohort had an ORR of 50% (5/10). A subset of patients with tumors harboring both an ERBB2 mutation and amplification had an ORR of 50% (5/10)[386]. Another Phase 2 trial of T-DM1 in chemotherapy-refractory ERBB2-positive NSCLC reported an ORR of 6.7% and a median PFS of 2.0 months; patients with ERBB2 expression experienced an ORR of 0% (0/8) and a DCR of 38% (3/8), whereas patients with ERBB2 exon 20 insertion mutations experienced an ORR of 14% (1/7) and DCR of 71% (5/7)[387]. A patient with ERBB2-amplified and A775_G776insYVMA-mutated NSCLC experienced disease progression on 2 prior lines of chemotherapy but experienced a rapid and durable response to T-DM1[121,400] .

Neratinib

Assay findings association

ERBB2
G776>VC

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[109-112,401-403] and preclinical[142,404-407] evidence, ERBB2 amplification or activating mutations may confer sensitivity to neratinib. A Phase 2 trial of neratinib in patients with solid tumors reported 1 CR, 1 PR, and 14 SD out of 25 evaluable patients with ERBB2 exon 20 insertion mutations, with both objective responses in patients with breast cancer[111]. Preclinical data support reduced sensitivity of ERBB2 exon 20 insertions to neratinib[124-125] .

SUPPORTING DATA

In the Phase 2 SUMMIT trial of neratinib in patients with ERBB2 or ERBB3 mutations, the ORR was 3.8% (1/26) and the median PFS was 5.5 months for patients with NSCLC, most of whom harbored ERBB2 exon 20 insertions; PR was observed in one patient with L755S mutation[111]. A Phase 2 study in ERBB2-mutated NSCLC reported objective response and clinical benefit in 19% (8/43) and 51% (22/43) of patients treated with neratinib plus the mTOR inhibitor temsirolimus, compared with 0% (0/17) and 35% (6/17) for patients treated with single-agent neratinib; exon 20 insertions were the most common ERBB2 mutation[408-409] .

Trastuzumab

Assay findings association

ERBB2
G776>VC

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

Trastuzumab-involving regimens elicited significant responses in patients with certain ERBB2 mutations[76-77,94,121,410-411] . Patients with NSCLC and ERBB2 exon 20 insertions, including A775_G776insYVMA and G776>VC, have benefited from treatment with trastuzumab[76-77,121,411-412] , with reported DCRs of 75–96% for trastuzumab in combination with chemotherapy[77,121] .

SUPPORTING DATA

In a Phase 2a basket trial (MyPathway), trastuzumab plus pertuzumab treatment in non-small cell lung cancer (NSCLC) elicited PRs in 2/16 patients with ERBB2 amplification or overexpression and in 3/14 patients with HER2 mutation[413]. A Phase 2 trial of docetaxel with trastuzumab for the treatment of NSCLC reported PRs for 8% of patients, although the response did not correlate with HER2 status as assessed by immunohistochemistry[414]. Another Phase 2 study of 169 patients with NSCLC reported an ORR of 23% (7/30) with combination therapy of docetaxel and trastuzumab and 32% (11/34) with paclitaxel and trastuzumab; HER2 expression did not impact the results of this study[415]. A patient with lung adenocarcinoma that was HER-positive by FISH and harbored an ERBB2 G776L mutation experienced a PR on trastuzumab and paclitaxel[75]. In a retrospective analysis of patients with NSCLC harboring ERBB2 exon 20 insertion mutations, disease control was reported in 93% of patients (13/14) treated with trastuzumab in combination with chemotherapy[77].

Trastuzumab + Pertuzumab

Assay findings association

ERBB2
G776>VC

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[79,413,416-420] .

SUPPORTING DATA

In the Phase 2a MyPathway basket trial, trastuzumab plus pertuzumab treatment in patients with ERBB2-positive (amplification or overexpression) non-small cell lung cancer (NSCLC) achieved an ORR of 30% (7/27)[413,421] . The combination of trastuzumab, pertuzumab, and docetaxel was evaluated in patients with ERBB2-mutated (missense mutation or exon 20 insertion) NSCLC lacking mutations in known driver genes and reported a 29% (13/45) ORR, 6.8-month median PFS, and 17.6-month median OS[422].

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.

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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.

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: Florida, Virginia, New York, Massachusetts, Texas

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

NCT04553133

PHASE 2

PF-07104091 as a Single Agent and in Combination Therapy

TARGETS
CDK6, Aromatase, CDK4, CDK2

LOCATIONS: Massachusetts, Texas, Michigan

NCT02896335

PHASE 2

Palbociclib In Progressive Brain Metastases

TARGETS
CDK4, CDK6

LOCATIONS: Massachusetts

NCT04000529

PHASE 1

Phase Ib Study of TNO155 in Combination With Spartalizumab or Ribociclib in Selected Malignancies

TARGETS
PD-1, SHP2, CDK6, CDK4

LOCATIONS: Massachusetts, Barcelona (Spain), Bruxelles (Belgium), Westmead (Australia), Singapore (Singapore), Chengdu (China), Hong Kong (Hong Kong), Chuo ku (Japan)

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
ERBB2

ALTERATION
G776>VC

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. Clinical and preclinical data suggest that ERBB2 exon 20 insertions confer resistance to lapatinib and reduced sensitivity to afatinib, dacomitinib, and neratinib. However, it is unclear if ERBB2 exon 20 insertions confer reduced sensitivity to lapatinib in combination with other therapies, such as trastuzumab. Retrospective clinical data suggest that ERBB2 G776>VC or P780_Y781insGSP is associated with improved PFS on afatinib, compared with other ERBB2 mutations or exon 20 insertions. In addition, clinical data suggests reduced sensitivity of ERBB2 G776>VC to dacomitinib. Investigational agents such as poziotinib and pyrotinib, or ERBB2-targeted antibodies such as trastuzumab and T-DM1, may be more effective.

NCT05048797

PHASE 3

A Study to Investigate the Efficacy and Safety of Trastuzumab Deruxtecan as the First Treatment Option for Unresectable, Locally Advanced/Metastatic Non-Small Cell Lung Cancer With HER2 Mutations

TARGETS
PD-1, ERBB2

LOCATIONS: São Paulo (Brazil), Sao Paulo (Brazil), Barretos (Brazil), Blumenau (Brazil), Uberlândia (Brazil), Brasília (Brazil), Salvador (Brazil), New Jersey, New York

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: Sao Paulo (Brazil), Porto Alegre (Brazil), San Juan (Puerto Rico), Florida, Alabama, Georgia, Maryland, Delaware

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: Florida, South Carolina, Georgia

NCT04447118

PHASE 3

Phase 3 Study of Pyrotinib Versus Docetaxel in Patients With Advanced Non-squamous NSCLC Harboring a HER2 Exon 20 Mutation Who Failed Platinum Based Chemotherapy

TARGETS
EGFR, ERBB2

LOCATIONS: Florida, New York, Tennessee, Texas, Malaga (Spain), Madrid (Spain), Valencia (Spain), Kansas, Pamplona (Spain)

NCT04579380

PHASE 2

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

TARGETS
ERBB2, ER

LOCATIONS: Florida, North Carolina, Georgia, South Carolina, District of Columbia, Virginia, New York, Connecticut, Massachusetts

CLINICAL TRIALS

NCT04644068

PHASE 1/2

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

TARGETS
ERBB2, TROP2, PARP

LOCATIONS: New York, Texas, Sevilla (Spain), Málaga (Spain), Montreal (Canada), Toronto (Canada), Madrid (Spain), Oklahoma, Barcelona (Spain), Oxford (United Kingdom)

NCT03066206

PHASE 2

Poziotinib in EGFR Exon 20 Mutant Advanced Non-Small Cell Lung Cancer (NSCLC)

TARGETS
EGFR, ERBB2, ERBB4

LOCATIONS: Texas

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

NCT05246514

PHASE 2

A Single Arm Phase 2 Study to Evaluate Efficacy and Safety of Trastuzumab Deruxtecan for Patients With HER2 Mutant NSCLC

TARGETS
ERBB2

LOCATIONS: Chengdu (China), Chongqing (China), Xi'an (China), Harbin (China), Beijing (China), Baoding (China), Changchun (China), Zhengzhou City (China), Hangzhou (China), Shenyang (China)

NCT03318939

PHASE 2

Phase 2 Study of Poziotinib in Patients With NSCLC With EGFR or HER2 Exon 20 Insertion Mutation

TARGETS
EGFR, ERBB2, ERBB4

LOCATIONS: Florida, North Carolina, Georgia, District of Columbia, Virginia, Maryland, New York

GENE
MEN1

ALTERATION
D423N - subclonal

RATIONALE
Based on limited clinical and preclinical evidence, tumors with MEN1 loss or inactivation may be sensitive to CDK4/6 inhibitors.

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: Florida, Virginia, New York, Massachusetts, Texas

NCT04553133

PHASE 2

PF-07104091 as a Single Agent and in Combination Therapy

TARGETS
CDK6, Aromatase, CDK4, CDK2

LOCATIONS: Massachusetts, Texas, Michigan

NCT02896335

PHASE 2

Palbociclib In Progressive Brain Metastases

TARGETS
CDK4, CDK6

LOCATIONS: Massachusetts

NCT04000529

PHASE 1

Phase Ib Study of TNO155 in Combination With Spartalizumab or Ribociclib in Selected Malignancies

TARGETS
PD-1, SHP2, CDK6, CDK4

LOCATIONS: Massachusetts, Barcelona (Spain), Bruxelles (Belgium), Westmead (Australia), Singapore (Singapore), Chengdu (China), Hong Kong (Hong Kong), Chuo ku (Japan)

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

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)

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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.

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: North Carolina, Virginia, Maryland, Tennessee, Texas, Michigan, Arizona, California

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: Maryland, New York, Pennsylvania, Ohio

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: New Jersey, Texas, Ohio, Illinois, California

NCT04553133

PHASE 2

PF-07104091 as a Single Agent and in Combination Therapy

TARGETS
CDK6, Aromatase, CDK4, CDK2

LOCATIONS: Massachusetts, Texas, Michigan

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

NCT04983810

PHASE 1/2

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

TARGETS
CDK2, CDK9

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

NCT01434316

PHASE 1

Veliparib and Dinaciclib in Treating Patients With Advanced Solid Tumors

TARGETS
PARP, CDK1, CDK9, CDK5, CDK2

LOCATIONS: Massachusetts

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NOTE One or more variants of unknown significance (VUS) were detected in this patient's tumor. These variants may not have been adequately characterized in the scientific literature at the time this report was issued, and/or the genomic context of these alterations makes their significance unclear. We choose to include them here in the event that they become clinically meaningful in the future.

CDK12
S1096P

EGFR
C686Y

GNAS
T415_G423del

POLD1
R1086Q

PRKAR1A
amplification

SOX9
amplification

TSC2
V1298M

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)

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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

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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) 7.5.0

The median exon coverage for this sample is 855x

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