FOUNDATIONONE®CDx

PATIENT	TUMOR TYPE	REPORT DATE
Chang, Yu Hsiu	Lung squamous cell carcinoma (SCC)	01 Mar 2023
	COUNTRY CODE TW	ORDERED TEST # ORD-1572622-01

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 Lung squamous cell carcinoma (SCC)
NAME Chang, Yu Hsiu
DATE OF BIRTH 15 March 1954
SEX Female
MEDICAL RECORD # 16469151

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 Lung
SPECIMEN ID S112-04477 A (PF23018)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 07 February 2023
SPECIMEN RECEIVED 22 February 2023

Sample qualified for low tumor purity. Sensitivity for detecting copy-number alterations (including in *ERBB2*), other genomic alterations, and signatures may be reduced and TMB may be underreported. Refer to the appendix for limitations statements.

Biomarker Findings

Microsatellite status - Cannot Be Determined [α]
Tumor Mutational Burden - Cannot Be Determined

Genomic Findings

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

MET exon 14 splice site (3021_3028+29del37)
CDK4 amplification - equivocal[†]
MDM2 amplification
PIK3CA E545K

7 Disease relevant genes with no reportable alterations: ***ALK, BRAF, EGFR, ERBB2, KRAS, RET, ROS1***

† See About the Test in appendix for details.

α Patients with Microsatellite status of Cannot Be Determined should be re-tested with an orthogonal (alternative) method.

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Capmatinib** (p. 8), **Crizotinib** (p. 8), **Tepotinib** (p. 9)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 11)

BIOMARKER FINDINGS

Microsatellite status - Cannot Be Determined

Tumor Mutational Burden - Cannot Be Determined

GENOMIC FINDINGS

***MET* -** exon 14 splice site (3021_3028+29del37)

10 Trials see p. 15

THERAPY AND CLINICAL TRIAL IMPLICATIONS

No therapies or clinical trials. See Biomarker Findings section

No therapies or clinical trials. See Biomarker Findings section

THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)		THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
Capmatinib	2A	Cabozantinib
Crizotinib	2A	
Tepotinib	2A	

☐ *NCCN category*

Electronically signed by Erik Williams, M.D. | 01 March 2023
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Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
CDK4 - amplification - equivocal	none	none
10 Trials see p. 11		
MDM2 - amplification	none	none
7 Trials see p. 13		
PIK3CA - E545K	none	none
10 Trials see p. 17		

☐ *NCCN category*

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

Therapies contained in this report may have been approved by the US FDA.

BIOMARKER

Microsatellite status

RESULT
Cannot Be Determined

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of 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 (alone or in combination with tremelimumab)[10-11]. As the MSI status of this tumor is unknown, the relevance of these therapeutic approaches is unclear.

FREQUENCY & PROGNOSIS

MSI-H is generally infrequent in NSCLC, reported in fewer than 1% of samples across several large studies[12-17], whereas data on the reported incidence of MSI-H in SCLC has been limited and conflicting[18-21]. 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[12]. 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[22]. 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[22-24]. The level of MSI in this sample could not be determined with confidence. Depending on the clinical context, MSI testing of an alternate sample or by another methodology could be considered.

BIOMARKER

Tumor Mutational Burden

RESULT
Cannot Be Determined

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]. 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);[8,25-26,29-31,35-41]. Improved OS of patients with NSCLC treated with pembrolizumab plus chemotherapy relative to chemotherapy only[42], or those treated with nivolumab plus ipilimumab also relative to chemotherapy[43], has been observed across all TMB levels. As the TMB status of this tumor cannot be determined with confidence, the benefit of these therapeutic approaches is unclear.

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[44]. 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[45]. Although some studies have reported a lack of association between smoking and mutational burden in NSCLC[46-47], several other large studies did find a strong association with increased TMB[48-51]. 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[52]. 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[53]. 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)[46]. 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[54]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[54-55].

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[56-57] and cigarette smoke in lung cancer[8,58], treatment with temozolomide-based chemotherapy in glioma[59-60], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[61-65], and microsatellite instability (MSI)[61,64-65]. Elevated TMB has been reported to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors in multiple solid tumor types[26-28,66]. However, the TMB level in this sample could not be determined with confidence.

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GENE
MET

ALTERATION
exon 14 splice site (3021_3028+29del37)

TRANSCRIPT ID
NM_000245.2

CODING SEQUENCE EFFECT
3021_3028+29del37

VARIANT CHROMOSOMAL POSITION
chr7:116412034-116412071

VARIANT ALLELE FREQUENCY (% VAF)
2.9%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of extensive clinical evidence, MET amplification or activating mutations may predict sensitivity to MET-targeting therapies such as kinase inhibitors crizotinib, capmatinib, tepotinib, and cabozantinib. MET inhibitors crizotinib, capmatinib, PF-04217903, tepotinib, glesatinib, savolitinib, and foretinib have provided benefit for patients with MET-mutated papillary renal cell carcinoma (RCC)[67-70], histiocytic sarcoma[71], and non-small cell lung cancer (NSCLC) of varied histologies[72-76]. Patients with MET exon 14 mutated NSCLC who were treated with 1 of several MET inhibitors exhibited superior outcomes (median OS 24.6 vs. 8.1 months; HR=0.11, p=0.04) compared with patients who were not treated with a MET inhibitor[77]. Tepotinib showed durable clinical activity in patients with NSCLC with MET exon 14 skipping mutations[78], and yielded a PR lasting 9 months for a patient with HLA-DRB1-MET fusion-positive NSCLC[79]. In another study, 11 patients with hereditary papillary RCC and germline MET mutations (4 of which were H1094R) experienced 5 PRs and 5 SDs after treatment with foretinib[67]. Savolitinib yielded ORRs of 49% (30/61) in patients with MET exon 14 mutated NSCLC[80] and numerically higher ORR for patients with MET-driven papillary RCC compared to sunitinib (27% [9/33] vs. 7.4% [2/27])[70]. A Phase 1 study for patients with MET-altered NSCLC treated with MET inhibitor bozitinib monotherapy reported an overall ORR of 30.6% (11/36) and DCR of 97.2% (35/36) with MET overexpression, amplification, and exon 14 skipping demonstrating ORRs of 35.7% (5/14), 41.2% (7/17), and 66.7% (10/15), respectively; increased ORRs were observed in patients with both exon 14 skipping and amplification (100%, 4/4) and with both amplification and overexpression (50%, 3/6)[81]. A Phase 2 study evaluating the MET inhibitor savolitinib for patients with MET exon 14 splice site mutation-positive pulmonary sarcomatoid carcinoma and other types of non-small cell lung cancer (NSCLC) reported an ORR of 43% (30/70), median PFS of 6.8 months, and median OS of 12.5 months[82]. In the Phase 1 CHRYSALIS study, patients with NSCLC harboring MET exon 14 skipping mutations treated with amivantamab achieved a 33% (12/36) ORR; 4 out of 19 patients previously treated with MET TKIs responded[83].

FREQUENCY & PROGNOSIS

In the Phase 2 VISION study of patients with non-small cell lung cancer, MET exon 14 skipping alterations were reported in 3.6% of patients[84]. In one study of 4402 lung adenocarcinoma cases, MET mutations (primarily those affecting MET exon 14 splicing) have been reported in 3% of samples[71]. In TCGA datasets, MET mutation has been observed in 8.3% of lung adenocarcinomas and 2.1% of lung squamous cell carcinomas[85-86].

Studies on the effect of MET amplification on prognosis in non-small cell lung cancer (NSCLC) have yielded conflicting results[87-94]. MET exon 14 splice alteration, which has predominantly been observed in lung cancer, was found to be an independent poor prognostic factor in a study of 687 patients with NSCLC[95]. However, other studies did not find MET exon 14 splice alteration to be a major risk factor for OS for patients with NSCLC, although recurrence rate was significantly higher for patients with exon 14 splice alteration compared with those with ALK fusion[96-97]. Among patients with NSCLC and exon 14 alterations who had not been previously treated with a MET inhibitor, a non-significant trend for reduced survival was noted in the context of concurrent MET amplification (5.2 vs. 10.5 months, p=0.06)[77].

FINDING SUMMARY

MET encodes a receptor tyrosine kinase, also known as c-MET or hepatocyte growth factor receptor (HGFR), that is activated by the ligand HGF; MET activation results in signaling mediated partly by the RAS-RAF-MAPK and PI3K pathways to promote proliferation[98-99]. Certain MET alterations have been associated with the removal of exon 14[73,100-104] and/or loss of a binding site for the ubiquitin ligase CBL, an enzyme that targets MET for degradation[100,105-107]. Loss of either MET exon 14 or a CBL binding site increases MET stability, leading to prolonged signaling upon HGF stimulation and increased oncogenic potential[100,104,106-110]; these mutations are expected to be activating. Responses to various MET inhibitors have been reported for multiple patients with alterations in their tumors predicted to lack MET exon 14[71,73,111-115].

GENE
CDK4

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

CDK4 amplification or activation may predict sensitivity to CDK4/6 inhibitors such as abemaciclib, palbociclib, and ribociclib[116-119]. The LungMAP trial evaluated the efficacy of palbociclib for patients with platinum-refractory lung squamous cell carcinoma (SCC) and cell cycle alterations, with CDK4 amplification being present in 6% (2/32) of patients, and reported an ORR of 6% (2/32 PRs overall, 0/2 PRs in CDK4-amplified tumors) and SD rate of 28% (12/32); however, palbociclib compared with docetaxel or durvalumab did not increase median PFS (1.8 vs. 2.7 vs. 2.9 months, respectively) or median OS (7.2 vs. 7.7 vs. 11.6 months, respectively)[120-121] . Other genomically selected trials of ribociclib and palbociclib have not reported any objective responses for patients with lung SCC (n=15 patients overall)[122-124] . As second-line treatment for genomically unselected lung SCC, abemaciclib did not improve outcomes compared with docetaxel (median PFS of 2.5 vs. 4.2 months, ORR of 2.8% vs. 20.8%, and median OS of 7.0 vs. 12.4 months)[125].

FREQUENCY & PROGNOSIS

CDK4 amplification has been reported in 6.5% of lung adenocarcinoma cases and 0.4% of lung squamous cell carcinoma cases[126]. CDK4 amplification correlated with high CDK4 gene and protein expression in lung tumors[127]. High CDK4 protein expression has been detected in 23-47% of non-small cell lung cancers, specifically in 38% (18/47) of lung adenocarcinomas, 44% (4/9) of lung squamous cell carcinomas, and 83% (10/12) of large cell lung cancers[127-129]. High CDK4 protein expression predicted poor OS in patients with lung cancer in one study[129].

FINDING SUMMARY

CDK4 encodes the cyclin-dependent kinase 4, which regulates the cell cycle, senescence, and apoptosis[130]. CDK4 and its functional homolog CDK6 are activated by D-type cyclins and promote cell cycle progression by inactivating the tumor suppressor Rb[131-132]. Amplification of the chromosomal region that includes CDK4 has been reported in multiple cancer types, including lung cancer, glioblastoma, and liposarcoma, and has been associated with overexpression of CDK4 protein[116,127,133-138].

GENE
MDM2

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

MDM2 antagonists disrupt the MDM2-p53 interaction, thereby stabilizing p53[139]. Preclinical studies have suggested that the amplification of MDM2, in the absence of concurrent TP53 mutations, may increase sensitivity to these agents[140-141]. Preliminary Phase 1 studies of the MDM2-p53 antagonist alrizomadlin (APG-115) reported a PR in a patient with liposarcoma harboring an MDM2 amplification and wildtype for TP53 and SD in 21%–38% (6/28 and 5/13, respectively) of patients in genomically unselected solid tumors[142-143] . A Phase 2 trial of alrizomadlin in combination with pembrolizumab reported a PR in 1 of 3 patients with malignant peripheral nerve sheath tumor that had failed standard therapy, as well as PRs in patients with multiple types of solid tumors that had failed immunotherapy, including 1 out of 14 patients with non-small cell lung cancer; 1 out of 5 patients with urothelial carcinoma; and 2 out of5, 1 out of 5, and 1 out of 11 patients with mucosal, uveal, and cutaneous melanoma, respectively[144]. Phase 1b studies of the MDM2 inhibitor idasanutlin for refractory AML in combination with cytarabine or venetoclax reported anti-leukemic response rates of 33% (25/75) and 37% (11/30), respectively[145-146] ; clinical benefit (58% ORR, 7/12) with idasanutlin monotherapy has been reported for patients with polycythemia vera[147]. The dual MDM2/MDM4 inhibitor ALRN-6924 led to an ORR of 27% (4/15) for patients with TP53 wildtype peripheral T-cell lymphoma in a Phase 2 study[148]; responses have also been observed in TP53 wildtype AML, MDS, Merkel cell carcinoma, colorectal cancer, and liposarcoma[149-150] .

FREQUENCY & PROGNOSIS

In the TCGA datasets, amplification of MDM2 has been reported in 7.8% of lung adenocarcinoma cases[85] and 2.3% of lung squamous cell carcinoma (SCC) cases[86]. Separate studies have reported MDM2 amplification at similar incidences of 6-7% in non-small cell lung cancer (NSCLC), mainly in patients with adenocarcinoma, but a higher incidence of 21% (24/116) has also been observed, with amplification found in various NSCLC subtypes[151-153]. The role of MDM2 expression/amplification as a prognostic marker is complex, with some studies showing a negative and others a positive effect on survival in patients with NSCLC[151,153-155].

FINDING SUMMARY

MDM2 encodes an E3 ubiquitin protein ligase, which mediates the ubiquitination and subsequent degradation of p53, Rb1, and other proteins[156-158]. MDM2 acts to prevent the activity of the tumor suppressor p53; therefore, overexpression or amplification of MDM2 may be oncogenic[159-160]. Overexpression or amplification of MDM2 is frequent in cancer[161]. Although two retrospective clinical studies suggest that MDM2 amplification may predict a short time-to-treatment failure on anti-PD-1/PD-L1 immune checkpoint inhibitors, with 4/5 patients with MDM2 amplification[162] and 2/3 patients with MDM2 or MDM4 amplification[163] experiencing tumor hyperprogression, amplification of MDM2 or MDM4 was not associated with shorter progression-free survival (PFS) in a retrospective analysis of non-small cell lung cancer (NSCLC) outcomes with immune checkpoint inhibitors (hazard ratio of 1.4, p=0.44)[38]. The latter study reported PFS of >2 months for 5/8 patients with MDM2/MDM4 amplification[38].

GENE
PIK3CA

ALTERATION
E545K

TRANSCRIPT ID
NM_006218.2

CODING SEQUENCE EFFECT
1633G>A

VARIANT CHROMOSOMAL POSITION
chr3:178936091

VARIANT ALLELE FREQUENCY (% VAF)
1.4%

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[164-171], AKT[172-173], or mTOR[174-181]. A Phase 2 study of buparlisib in NSCLC observed 2 PRs (3.2%; 2/63) in PIK3CA-pathway activated tumors, although the study did not meet its primary endpoint[182]. 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[171]. However, the Phase 2 study of copanlisib for patients with endometrial carcinoma harboring PIK3CA hotspot mutations failed to report any objective responses (n=11)[170]. 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[168-169].

FREQUENCY & PROGNOSIS

In the TCGA datasets, PIK3CA mutation was observed in 8.2% of lung adenocarcinoma cases[126] and in 15.7% of lung squamous cell carcinoma cases[86]. The prognostic significance of PIK3CA mutation or overexpression in NSCLC is unclear, with several studies reporting contradictory data, which may be influenced by the specific PIK3CA mutation, histologic subtype, and the presence of concurrent mutations in oncogenes such as EGFR and KRAS[183-188].

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[189-190]. PIK3CA alterations that have been characterized as activating, such as observed here, are predicted to be oncogenic[191-212].

Capmatinib

Assay findings association

MET
exon 14 splice site
(3021_3028+29del37)

AREAS OF THERAPEUTIC USE

Capmatinib is a selective MET tyrosine kinase inhibitor that is FDA approved to treat patients with non-small cell lung cancer harboring MET exon 14 skipping-associated alterations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Based on extensive clinical data in NSCLC[78,80,213-216] , MET mutations associated with exon 14 skipping may predict sensitivity to selective MET inhibitors.

SUPPORTING DATA

Capmatinib monotherapy has demonstrated clinical activity for patients with advanced non-small cell lung cancer (NSCLC) harboring MET exon 14 skipping alterations or MET amplification and lacking EGFR mutations or ALK rearrangements[217-218] . The retrospective real-world RECAP analysis and the Phase 2 GEOMETRY mono-1 study reported that treatment-naive NSCLC patients with MET exon 14 mutations receiving capmatinib achieved a higher ORR (68% vs. 41%-50%), DCR (96%-84% vs. 77%-78%), and longer median PFS (mPFS; 10.6-12.4 vs. 5.4-9.1 months) compared with patients who were previously treated[217]; higher ORR (40% vs. 29%) and mPFS (4.2 vs. 4.1 months) were also reported for patients with MET amplification (copy number amplification ≥10)[219]. Additionally, the studies recorded an intracranial response rate of 46% (5/11)-54% (7/13) and intracranial DCR of 91% (10/11)-92% (12/13)[217]. A retrospective analysis of the GEOMETRY mono-1 study compared with a cohort of real-world patients with NSCLC harboring MET exon 14 skipping alterations who received first-line chemotherapy and/or immunotherapy reported a longer PFS (mPFS of 12.0 vs. median real-world PFS of 6.2 months)[220].

Crizotinib

Assay findings association

MET
exon 14 splice site
(3021_3028+29del37)

AREAS OF THERAPEUTIC USE

Crizotinib is an inhibitor of the kinases MET, ALK, ROS1, and RON. It is FDA approved to treat patients with ALK rearrangement- or ROS1 rearrangement-positive non-small cell lung cancer (NSCLC), adult and pediatric patients with ALK-positive inflammatory myofibroblastic tumor (IMT), and pediatric and young adult patients with ALK-positive anaplastic large cell lymphoma (ALCL). Please see the drug label for full prescribing information.

GENE ASSOCIATION

Sensitivity of MET alterations to crizotinib is suggested by extensive clinical data in patients with MET-amplified cancers, including non-small cell lung cancer (NSCLC)[221-225] , gastric cancer[226], gastroesophageal cancer[227], glioblastoma[228], and carcinoma of unknown primary[229], as well as in patients with MET-mutated cancers, including NSCLC[71,73-76,230] , renal cell carcinoma (RCC)[69], and histiocytic sarcoma[71]. Crizotinib has also benefited patients with NSCLC or histiocytic sarcoma tumors harboring various alterations associated with MET exon 14 skipping[71,73-77] .

SUPPORTING DATA

The expansion cohort of the PROFILE 1001 study reported a 32.3% (21/65, 3 CRs) ORR, 7.3 month median PFS, and 20.5 month median OS for patients with advanced MET exon 14-altered NSCLC[231]. Other Phase 2 studies have reported ORRs of 20.0% to 35.7%, median PFS of 2.4 to 2.6 months, and median OS of 3.8 to 8.1 months for patients with MET-mutated NSCLC[232-233] . A retrospective study reported median PFS of 7.4 months in patients with MET exon 14-altered NSCLC treated with crizotinib[234]. In a small study for patients with NSCLC and MET overexpression with or without gene amplification, crizotinib elicited 11 PRs and 3 SDs in 19 evaluable patients[222]. Crizotinib has demonstrated efficacy in patients with NSCLC and ALK rearrangements[235-239] , ROS1 rearrangements[233,240-243] , an NTRK1 fusion[244], or MET activation[73-76,103,221-225,230,245-250] .

Tepotinib

Assay findings association

MET
exon 14 splice site
(3021_3028+29del37)

AREAS OF THERAPEUTIC USE

Tepotinib is a selective MET tyrosine kinase inhibitor that is FDA approved to treat patients with non-small cell lung cancer harboring MET exon 14 skipping alterations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Based on extensive clinical data in NSCLC[78,80,213-216] , MET mutations associated with exon 14 skipping may predict sensitivity to selective MET inhibitors.

SUPPORTING DATA

In a combined analysis of the primary and confirmatory cohorts in the Phase 2 VISION study, tepotinib yielded an ORR of 57%, median duration of response (mDOR) of 46.4 months, median PFS (mPFS) of 15.3 months, and median OS (mOS) of 25.9 months for treatment-naive patients with non-small cell lung cancer (NSCLC) and MET exon 14 skipping alterations; an ORR of 50%, mDOR of 10.2 months, mPFS of 11.5 months, and mOS of 20.4 months was achieved for previously treated patients with NSCLC and MET exon 14 skipping alterations[251]. Among patients with CNS metastases, tepotinib treatment resulted in an intracranial DCR of 88% and an intracranial mPFS of 20.9 months; tepotinib treatment yielded an intracranial ORR of 67% (10/15) and DOR not reached for patients with target lesions[251]. Tepotinib has primarily been investigated in non-small cell lung cancer (NSCLC) and has demonstrated efficacy as a single agent for patients with MET amplification[252] and MET exon 14-skipping alterations[78,216,251] . Tepotinib has also been shown to be efficacious in combination with gefitinib for patients with concurrent EGFR mutation and MET amplification or MET overexpression in Phase 2 studies[253-254] . A case study reported 1 PR lasting 9 months for a patient with HLA-DRB1-MET fusion-positive NSCLC metastatic to the brain[79].

Cabozantinib

Assay findings association

MET
exon 14 splice site
(3021_3028+29del37)

AREAS OF THERAPEUTIC USE

Cabozantinib inhibits multiple tyrosine kinases, including MET, RET, VEGFRs, and ROS1. It is FDA approved as monotherapy to treat patients with renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), medullary thyroid cancer (MTC), and differentiated thyroid cancer (DTC). It is also approved in combination with nivolumab to treat RCC. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Sensitivity of MET alterations to cabozantinib is suggested by clinical responses in patients with non-small cell lung cancer (NSCLC) harboring MET mutations associated with MET exon 14 skipping, with or without concurrent MET amplification[73,255] , as well as by extensive preclinical data[256-262] .

SUPPORTING DATA

Cabozantinib elicited a CR in a patient with lung adenocarcinoma harboring a MET amplification and a mutation affecting MET exon 14 splicing[73]. A Phase 2 randomized discontinuation trial of cabozantinib reported a 10.0% (6/60) ORR and a 58.3% (35/60) DCR, with median PFS of 4.2 months, for patients with genomically unselected, heavily pretreated NSCLC[263]. Patients with EGFR wild-type non-squamous NSCLC who had progressed after previous treatment experienced longer median PFS with cabozantinib alone or combined with erlotinib (4.3 and 4.7 months, HR=0.39 and 0.37, respectively) compared with single agent erlotinib (1.8 months) in a randomized Phase 2 trial[264]. A Phase 1 study of cabozantinib for advanced solid tumors reported an ORR of 20.0% (4/20; 4 PRs, all in EGFR-mutated tumors) and DCR of 100% (20/20) in the expansion cohort for Japanese patients with NSCLC[265].

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
CDK4

ALTERATION
amplification - equivocal

RATIONALE
CDK4 amplification may predict sensitivity to CDK4/6 inhibitors.

NCT04000529

PHASE 1

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

TARGETS
PD-1, SHP2, CDK6, CDK4

LOCATIONS: Shanghai (China), Hong Kong (Hong Kong), Chengdu (China), Chuo ku (Japan), Singapore (Singapore), Westmead (Australia), Oslo (Norway), Bruxelles (Belgium), Barcelona (Spain), Valencia (Spain)

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)

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)

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)

NCT02693535

PHASE 2

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

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

LOCATIONS: Hawaii, Washington, Oregon, California

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT04116541

PHASE 2

A Study Evaluating the Activity of Anti-cancer Treatments Targeting Tumor Molecular Alterations/ Characteristics in Advanced / Metastatic Tumors.

TARGETS
CDK6, CDK4, MDM2, MET, ROS1, RET, VEGFRs

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

NCT05252416

PHASE 1/2

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

TARGETS
ER, CDK4, CDK6, CDK2

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

NCT03310879

PHASE 2

Study of the CDK4/6 Inhibitor Abemaciclib in Solid Tumors Harboring Genetic Alterations in Genes Encoding D-type Cyclins or Amplification of CDK4 or CDK6

TARGETS
CDK4, CDK6

LOCATIONS: Massachusetts

NCT05159245

PHASE 2

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

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

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

GENE
MDM2

ALTERATION
amplification

RATIONALE
Inhibitors of the MDM2-p53 interaction are being tested in clinical trials. Overexpression or amplification of MDM2 may increase sensitivity to these agents, but more data are required.

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), Tainan (Taiwan), Shanghai City (China), Shanghai (China), Shatin (Hong Kong), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Xi'an (China), Tianjin (China)

NCT04785196

PHASE 1/2

APG-115 in Combination With PD-1 Inhibitor in Patients With Advanced Liposarcoma or Advanced Solid Tumors

TARGETS
PD-1, MDM2

LOCATIONS: Shanghai (China), Guangzhou (China)

NCT03449381

PHASE 1

This Study Aims to Find the Best Dose of BI 907828 in Patients With Different Types of Advanced Cancer (Solid Tumors)

TARGETS
MDM2

LOCATIONS: Tokyo, Chuo-ku (Japan), Warsaw (Poland), Poznan (Poland), Berlin (Germany), Göttingen (Germany), Köln (Germany), Tübingen (Germany), Leuven (Belgium), Bruxelles (Belgium), Barcelona (Spain)

NCT03964233

PHASE 1

A Study in Patients With Different Types of Advanced Cancer (Solid Tumors) to Test Different Doses of BI 907828 in Combination With Ezabenlimab With or Without BI 754111

TARGETS
MDM2, PD-1

LOCATIONS: Tokyo, Chuo-ku (Japan), Singapore (Singapore), Nedlands (Australia), Budapest (Hungary), Groningen (Netherlands), Ulm (Germany), Leuven (Belgium), London (United Kingdom), Villejuif (France), Lyon (France)

NCT03611868

PHASE 1/2

A Study of APG-115 in Combination With Pembrolizumab in Patients With Metastatic Melanomas or Advanced Solid Tumors

TARGETS
MDM2, PD-1

LOCATIONS: Brisbane (Australia), South Brisbane (Australia), Bedford Park (Australia), Heidelberg (Australia), California, Arizona, Missouri, Arkansas, Ohio, Pennsylvania

NCT05012397

PHASE 2

Milademetan in Advanced/Metastatic Solid Tumors

TARGETS
MDM2

LOCATIONS: California, South Dakota, Missouri, New York, Massachusetts, Tennessee, Texas, North Carolina, Florida

NCT03725436

PHASE 1

ALRN-6924 and Paclitaxel in Treating Patients With Advanced, Metastatic, or Unresectable Solid Tumors

TARGETS
MDM2, MDM4

LOCATIONS: Texas

GENE
MET

RATIONALE
Activating MET alterations may confer sensitivity to MET inhibitors.

ALTERATION
exon 14 splice site (3021_3028+29del37)

NCT03539536

PHASE 2

Study of Telisotuzumab Vedotin (ABBV-399) in Subjects With Previously Treated c-Met+ Non-Small Cell Lung Cancer

TARGETS
MET

LOCATIONS: Taipei (Taiwan), New Taipei City (Taiwan), Taoyuan City (Taiwan), Taipei City (Taiwan), Taichung (Taiwan), Chia-Yi (Taiwan), Fuzhou (China), Tainan (Taiwan), Kaohsiung City (Taiwan), Kaohsiung (Taiwan)

NCT02099058

PHASE 1

A Phase 1/1b Study With ABBV-399, an Antibody Drug Conjugate, in Subjects With Advanced Solid Cancer Tumors

TARGETS
MET, EGFR, PD-1

LOCATIONS: Taipei City (Taiwan), Tainan (Taiwan), Suwon (Korea, Republic of), Seoul (Korea, Republic of), Chuo-ku (Japan), Kashiwa-shi (Japan), Nijmegen (Netherlands), Marseille CEDEX 05 (France), California

NCT03175224

PHASE 1/2

CBT-101 Study for Advanced Solid Tumors and c-Met Dysregulation

TARGETS
MET

LOCATIONS: Taipei City (Taiwan), Taipei (Taiwan), New Taipei City (Taiwan), Taoyuan City (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Singapore (Singapore), Nedlands (Australia), North Adelaide (Australia), Bedford Park (Australia)

NCT04921358

PHASE 3

Tislelizumab in Combination With Sitravatinib in Participants With Locally Advanced or Metastatic Non-Small Cell Lung Cancer

TARGETS
AXL, KIT, DDR2, VEGFRs, PDGFRA, TRKA, MET, FLT3, RET, TRKB, PD-1

LOCATIONS: Fuzhou (China), Xiamen (China), Taizhou (China), Shantou (China), Hangzhou (China), Shanghai (China), Jiangxi (China), Nanchang (China), Suzhou (China), Changzhou (China)

NCT04270591

PHASE 1/2

Assessment of Anti-tumor and Safety in Glumetinib in Patients With c-MET-positive Non-Small Cell Lung Cancer

TARGETS
MET

LOCATIONS: Fuzhou (China), Hangzhou (China), Shanghai (China), Nanchang (China), Nanjing (China), Hefei (China), Guangzhou (China), Changsha (China), Wuhan (China), Fukuoka (Japan)

NCT04677595

PHASE 2

Study of Capmatinib in Chinese Adult Patients With Advanced Non-small Cell Lung Cancer Harboring MET Exon 14 Skipping Mutation

TARGETS
MET

LOCATIONS: Xiamen (China), Hangzhou (China), Shanghai (China), Guangzhou (China), Foshan (China), Changsha (China), Wuhan (China), Zhanjing (China), Zhengzhou (China), Jinan (China)

NCT04923945

PHASE 3

Savolitinib for Treating Locally Advanced or Metastatic Non-small Cell Lung Cancer (NSCLC) Patients

TARGETS
MET

LOCATIONS: Shanghai (China)

NCT05176925

PHASE 2

Tislelizumab Combined With Sitravatinib as Consolidation Treatment Following Concurrent Chemoradiation in Patients With Locally Advanced, Unresectable NSCLC

TARGETS
PD-1, AXL, KIT, DDR2, VEGFRs, PDGFRA, TRKA, MET, FLT3, RET, TRKB

LOCATIONS: Shanghai (China)

NCT05009836

PHASE 3

Clinical Study on Savolitinib + Osimertinib in Treatment of EGFRm+/MET+ Locally Advanced or Metastatic NSCLC

TARGETS
MET, EGFR

LOCATIONS: Guangzhou (China)

NCT04077099

PHASE 1/2

REGN5093 in Patients With MET-Altered Advanced Non-Small Cell Lung Cancer

TARGETS
MET

LOCATIONS: Suwon (Korea, Republic of), Seoul (Korea, Republic of), Gyeonggi do (Korea, Republic of), Dijon Cedex (France), Grenoble (France), Caen cedex (France), Rennes Cedex 9 (France), Texas, New York, Pennsylvania

GENE
PIK3CA

ALTERATION
E545K

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

NCT04589845

PHASE 2

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

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

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

NCT03239015

PHASE 2

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

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

LOCATIONS: Shanghai (China)

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT04526470

PHASE 1/2

Alpelisib and Paclitaxel in PIK3CA-altered Gastric Cancer

TARGETS
PI3K-alpha

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

NCT05125523

PHASE 1

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

TARGETS
mTOR

LOCATIONS: Tianjin (China)

NCT03772561

PHASE 1

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

TARGETS
PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

NCT04801966

PHASE NULL

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

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

LOCATIONS: Melbourne (Australia)

NCT04551521

PHASE 2

CRAFT: The NCT-PMO-1602 Phase II Trial

TARGETS
PD-L1, AKTs, MEK, BRAF, ALK, RET, ERBB2

LOCATIONS: Würzburg (Germany), Mainz (Germany), Heidelberg (Germany), Tübingen (Germany)

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

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.

FANCL
I194V

MDM2
rearrangement

NOTCH3
R1050W

NTRK1
R748W

PDGFRB
S280G

POLE
A724V

PTCH1
E44G and S827G

RPTOR
R34T

TSC1
Q654E

TSC2
A678T and E1360K

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) 7.6.0

The median exon coverage for this sample is 785x

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