FOUNDATIONONE®CDx

PATIENT
Tsai, Tang-Na

TUMOR TYPE
Lung adenocarcinoma
COUNTRY CODE
TW

REPORT DATE
29 Dec 2021
ORDERED TEST #
ORD-1260175-01

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 adenocarcinoma
NAME Tsai, Tang-Na
DATE OF BIRTH 12 January 1966
SEX Female
MEDICAL RECORD # 23621514

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 S110-38079 B (PF21070)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 06 December 2021
SPECIMEN RECEIVED 17 December 2021

Due to the low tumor purity, sensitivity for the detection of copy number alterations including ERBB2 is reduced due to sample quality. Refer to appendix for limitations statement. Sensitivity for the detection of other alterations and genomic signatures may also be reduced and the TMB score may be underreported.

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.

EGFR T790M, L858R
MUTYH splice site 892-2A>G

7 Disease relevant genes with no reportable alterations: ***ALK, BRAF, ERBB2, KRAS, MET, 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: **Osimertinib** (p. 7)
- Targeted therapies with **potential resistance** based on this patient's genomic findings: **Afatinib** (p. 8), **Dacomitinib** (p. 9), **Erlotinib** (p. 10), **Gefitinib** (p. 11)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 12)
- Variants in select cancer susceptibility genes to consider for possible **follow-up germline testing** in the appropriate clinical context: ***MUTYH* splice site 892-2A>G** (p. 6)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Microsatellite status - Cannot Be Determined	**No therapies or clinical trials.** see Biomarker Findings section
Tumor Mutational Burden - Cannot Be Determined	**No therapies or clinical trials.** see Biomarker Findings section

Electronically signed by Erik Williams, M.D. | 29 December 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
EGFR **-** T790M, L858R	Osimertinib 1	none
	Afatinib ⊗	
	Dacomitinib ⊗	
	Erlotinib ⊗	
10 Trials *see p. 12*	*Gefitinib* ⊗	

⊗ *Extensive evidence showing variant(s) in this sample may confer resistance to this therapy*

☐ *NCCN category*

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

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

MUTYH **-** splice site 892-2A>G ..... p. 6

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

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

MUTYH - splice site 892-2A>G ..... p. 6

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
Cannot Be Determined

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[3-8] and PD-L1-targeting agents atezolizumab, avelumab, and durvalumab[9-11] . 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 2021).

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.

POTENTIAL GERMLINE IMPLICATIONS

While approximately 80% of MSI-H tumors arise due to somatic inactivation of an MMR pathway protein, about 20% arise due to germline mutations in one of the MMR genes[22], which are associated with a condition known as Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC)[25]. Lynch syndrome leads to an increased risk of colorectal, endometrial, gastric, and other cancers[25-27] and has an estimated prevalence in the general population ranging from 1:600 to 1:2000[28-30]. Therefore, in the appropriate clinical context, germline testing of MLH1, MSH2, MSH6, and PMS2 is recommended.

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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[31-33], anti-PD-1 therapies[31-34], and combination nivolumab and ipilimumab[35-40]. 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);[7,31-32,35-37,41-47]. Improved OS of patients with NSCLC treated with pembrolizumab plus chemotherapy relative to chemotherapy only[48], or those treated with nivolumab plus ipilimumab also relative to chemotherapy[49], 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[50]. 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[51]. Although some studies have reported a lack of association between smoking and mutational burden in NSCLC[52-53], several other large studies did find a strong association with increased TMB[54-57]. 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[58]. A large study of Chinese patients with 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)[52]. Another study of patients with NSCLC correlated elevated TMB with poorer prognosis and significantly associated lower TMB in combination with PD-L1 negative status 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[7,63], 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]. 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[32-34,71]. However, the TMB level in this sample could not be determined with confidence.

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GENE
EGFR

ALTERATION
T790M, L858R

TRANSCRIPT ID
NM_005228, NM_005228

CODING SEQUENCE EFFECT
2369C>T, 2573T>G

VARIANT ALLELE FREQUENCY (% VAF)
7.3%, 8.0%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

For patients with non-small cell lung cancer, EGFR activating mutations may predict sensitivity to EGFR TKIs, including erlotinib[72], gefitinib[73], afatinib[74], dacomitinib[75], and osimertinib[76]; however, the data for patients with other tumor types are limited[77-82]. The efficacy of third-generation EGFR inhibitors that selectively target EGFR T790M in non-small cell lung cancer (NSCLC) has been confirmed in osimertinib[76,83-86], D-0316[87], abivertinib[88-89], alflutinib[90], naquotinib[91-94], nazartinib[95], and olmutinib[96-97]. The Phase 1 CHRYSALIS study of amivantamab monotherapy or in combination with lazertinib for the treatment of EGFR-mutated non-small cell lung cancer (NSCLC) has produced encouraging preliminary results for treatment-naive patients and patients who relapsed after treatment with osimertinib with and without chemotherapy, including osimertinib-relapsed patients with biomarkers indicating EGFR/MET-based osimertinib resistance[98-101] . In a Phase 1 trial, the HER3-targeted antibody patritumab deruxtecan elicited an ORR of 39% (22/57, 1 CR) and a median PFS of 8.2 months for patients with non-small cell lung cancer previously treated with an EGFR TKI, many of whom displayed TKI resistance alterations[102]. A Phase 1 trial evaluating the EGFR inhibitor AZD3759 reported a reduction in the volume of brain metastases in 40% (8/20) of patients with previously treated non-small cell lung cancer (NSCLC) harboring either the EGFR L858R alteration or EGFR exon 19 deletion, including 3 confirmed PRs and 3 unconfirmed PRs[103-104]. In a Phase 1/2 trial for advanced NSCLC, the brain-penetrant third-generation EGFR TKI lazertinib enabled ORRs of 54% (69/127) for all evaluable patients and 44% (8/18, intracranial) for patients with brain metastases[105]. The Phase 3 IMpower150 study showed that the addition of atezolizumab to bevacizumab plus chemotherapy treatment also had clinical efficacy for patients with EGFR-mutated or ALK-rearranged metastatic NSCLC[106]; therefore, the patient's clinical context should be considered.

— Potential Resistance —

The EGFR T790M mutation, when co-occurring with an EGFR activating alteration, confers clinical resistance to gefitinib[107-110], erlotinib[107-108,110], afatinib[111-114], and dacomitinib[110,115-117]. Preclinical resistance to lapatinib has also been reported[118-119].

FREQUENCY & PROGNOSIS

EGFR mutation has been reported in 12-36% of lung adenocarcinomas[56,120-121] and in 4% of lung squamous cell carcinomas[122]. EGFR protein expression/overexpression has been reported in up to 70% of NSCLC cases[123-128]. In addition, expression of EGFR protein has been shown to be higher in lung squamous cell carcinoma samples as compared to lung adenocarcinoma[129-130]. In a retrospective study of lung adenocarcinoma treated with surgical resection without neoadjuvant TKIs, significantly shorter OS and recurrence-free survival was observed for patients harboring uncommon EGFR mutations (G719X, T790M, or L861R/Q) compared with those harboring only common mutations (L858R or exon 19 deletion)[131]. In patients with lung adenocarcinoma, EGFR mutation was a predictor of poor overall survival[132-133]. However, EGFR mutations have been reported to predict improved survival in patients with resected Stage 1-3 lung adenocarcinoma[134] or resected Stage 1 NSCLC[135].

FINDING SUMMARY

EGFR encodes the epidermal growth factor receptor, which belongs to a class of proteins called receptor tyrosine kinases. In response to signals from the environment, EGFR passes biochemical messages to the cell that stimulate it to grow and divide[136]. EGFR L858 is located in the kinase domain and is encoded by exon 21. EGFR L858R has been characterized as activating[137-139] and patients with the L858R mutation have been shown to be sensitive to EGFR tyrosine kinase inhibitors, such as erlotinib, gefitinib[137-139], and afatinib[140]. The EGFR T790M mutation, when co-occurring with EGFR activating alterations, has been associated with clinical resistance to gefitinib[107-110], erlotinib[107-108,110], dacomitinib[110,115-117], and afatinib[111-114,141], as well as preclinical resistance to lapatinib[118-119]. Rare cases of EGFR T790M without a concurrent activating alteration have been reported[142] and germline T790M mutations have been reported to predispose to familial lung adenocarcinoma[142-144]. Limited preclinical data suggests T790M alone is weakly activating, and increased EGFR activity is observed when T790M is expressed with certain activating EGFR alterations[145]. Therefore, although this alteration has not been fully characterized, it is likely to result in reduced sensitivity to first- and second-generation EGFR inhibitors.

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GENE
MUTYH

ALTERATION
splice site 892-2A>G

TRANSCRIPT ID
NM_001048171

CODING SEQUENCE EFFECT
892-2A>G

VARIANT ALLELE FREQUENCY (% VAF)
54.2%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies or clinical trials available to address MUTYH alterations in cancer.

FREQUENCY & PROGNOSIS

In general, somatic MUTYH mutations are infrequently reported across cancer types (COSMIC, 2021)[146]. Monoallelic MUTYH mutation occurs in 1-2% of the general population[147-148]. There is conflicting data regarding the impact of monoallelic mutations on the risk of developing CRC[149-151]. Patients with MUTYH-mutant CRC were reported to have significantly improved overall survival compared to patients without MUTYH mutation[152].

FINDING SUMMARY

MUTYH (also known as MYH) encodes an enzyme involved in DNA base excision repair, and loss of function mutations in MUTYH result in increased rates of mutagenesis and promotion of tumorigenesis[153]. The two most frequently reported MUTYH loss of function mutations are G382D (also referred to as G396D) and Y165C (also referred to as Y179C)[147-148,154-156]. Numerous other MUTYH mutations have also been shown to result in loss of function[154-157].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the MUTYH 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 MUTYH-associated polyposis (ClinVar, Sep 2021)[158]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline biallelic MUTYH mutation causes MUTYH-associated polyposis (also known as MYH-associated polyposis or MAP), an autosomal recessive condition characterized by multiple colorectal adenomas and increased lifetime risk of colorectal cancer (CRC)[147,159-161]. MAP accounts for approximately 0.7% of all CRC cases and 2% of early-onset CRC cases[147]. In contrast to CRC, the role of MUTYH mutation in the context of other cancer types is not well established[162-166]. Estimates for the prevalence of MAP in the general population range from 1:5,000-1:10,000[148]. Therefore, in the appropriate clinical context, germline testing of MUTYH is recommended.

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Osimertinib

Assay findings association

EGFR
T790M, L858R

AREAS OF THERAPEUTIC USE

Osimertinib is an irreversible EGFR TKI that is selective for EGFR TKI-sensitizing mutations and the EGFR T790M mutation. It is FDA approved in various treatment settings for patients with non-small cell lung cancer (NSCLC) whose tumors have EGFR exon 19 deletions, exon 21 L858R mutations, or T790M mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

EGFR TKI-sensitizing mutations or rearrangements and/or the EGFR T790M mutation may predict sensitivity to osimertinib in non-small cell lung cancer[76,86,167-169] . Patients with untreated advanced NSCLC and EGFR exon 19 deletions or L858R mutations achieved an ORR of 80% and a median PFS of 21.4 and 14.4 months, respectively[86].

SUPPORTING DATA

The Phase 3 FLAURA study reported that, relative to erlotinib or gefitinib, first-line osimertinib significantly increased both median PFS (18.9 vs. 10.2 months, HR=0.46) and median OS (38.6 vs. 31.8 months; HR=0.80) for patients with advanced NSCLC and activating, sensitizing EGFR mutations (specifically, exon 19 deletion or L858)[86,170] . In the Phase 3 ADAURA study, patients with early Stage (IB/II/IIIA) EGFR-mutated NSCLC experienced longer PFSs on osimertinib compared to placebo in the adjuvant setting (not reached vs. 28.1 months; HR=0.21)[171]. A Phase 1 study reported that T790M-negative patients with acquired EGFR TKI resistance experienced an ORR of 21% and a median PFS of 2.8 months[76]. A Phase 1b/2 study evaluating osimertinib in combination with the CD73 inhibitor oleclumab for patients with advanced EGFR-mutated, T790M-negative NSCLC reported an ORR of 19% (4/19), a DCR of 81%, and mPFS of 11 months (Kim et al., 2021 AACR Abstract CT163). In a Phase 3 study for patients with EGFR T790M-positive advanced NSCLC who progressed on EGFR TKI therapy, osimertinib compared with combination platinum therapy led to longer median PFS (10.1 months vs. 4.4 months), including for patients with central nervous system metastases (8.5 vs. 4.2 months). An ORR of 71% was achieved with osimertinib compared to 31% with combination platinum therapy[172]. The efficacy of osimertinib is confirmed by earlier phase studies in this setting[76,83-85] , and in a real-world setting for patients with T790M-positive advanced NSCLC pretreated with EGFR TKIs[173-174] . Case studies report that 2 patients with T790M-mutated NSCLC achieved durable PRs to osimertinib rechallenge after the adverse events induced by initial osimertinib treatment had been resolved[175-176] . A Phase 1/2 trial of osimertinib in combination with bevacizumab for patients with untreated metastatic EGFR-mutated non-small cell lung cancer (NSCLC) reported an 80% (39/49) ORR, a 100% (6/6, 2 CRs) central nervous system response rate, median PFS of 19 months, and a 1-year PFS rate of 72%[177]. The Phase 1b TATTON study of osimertinib in combination with selumetinib, savolitinib, or durvalumab for patients with previously treated EGFR-mutated NSCLC reported ORRs of 42% (15/36), 44% (8/18), and 44% (10/23), respectively[178].

Afatinib

Resistance of variant(s) to associated therapy is likely

Assay findings association

EGFR
T790M, L858R

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

EGFR activating mutations may indicate sensitivity to afatinib or dacomitinib for patients with non-small cell lung cancer[74-75,179-180] , whereas data for patients with other tumor types are limited[77-82,181] . EGFR T790M, in the presence of a co-occurring activating EGFR alteration, has been associated with clinical resistance to afatinib and has been reported in 33-48% of patients who progressed on the inhibitor across multiple studies[111-114,141] . Although DCRs of more than 50% have been reported for patients with erlotinib- or gefitinib-resistant NSCLC treated with afatinib[182], including T790M-positive patients[183], 1 study observed that overall survival for patients with T790M-positive NSCLC was worse than for patients who were T790M-negative (HR=1.79, p=0.005)[184].

SUPPORTING DATA

Afatinib enabled a DCR of 64.3% (9/14) for patients with advanced T790M-positive NSCLC in a post-hoc analysis of Phase 2 and Phase 3 trials[183]. For T790M-positive patients who were TKI-naive or -pretreated, afatinib treatment resulted in ORRs of 24.0% (6/25) and 18.8% (12/64), respectively, in a large-scale retrospective analysis of EGFR-mutated NSCLC[185]. Another large-scale retrospective study of afatinib administered to Asian patients with NSCLC, 99% of whom were previously treated with erlotinib and/or gefitinib, reported an ORR of 21.1% (4/19) for T790M-positive patients and an ORR of 24.4% (105/431) for the entire cohort[186]. For heavily pre-treated patients with erlotinib- or gefitinib-resistant NSCLC and T790M-positivity, the combination of afatinib with cetuximab enabled an ORR of 31.7% (40/126) in a Phase 1b study[187], and 1/1 PR in a case series[188]. A patient with T790M-positive NSCLC who progressed on erlotinib experienced a PR to afatinib combined with panitumumab in another case series[189]. Afatinib has shown significant clinical activity for patients with NSCLC and the EGFR common sensitizing mutations L858R or exon 19 deletions, based on extensive clinical evidence[74,179,190-193] . Two randomized Phase 3 trials reported significantly improved median PFS from afatinib compared with chemotherapy for patients with EGFR common sensitizing mutations (LUX-Lung 3, 13.6 vs. 6.9 months, HR 0.47, p<0.001; LUX-Lung 6, 11.0 vs. 5.6 months, HR 0.28, p<0.0001)[74,179] . However, while afatinib significantly increased OS relative to chemotherapy for patients with EGFR exon 19 alterations in these two trials (LUX-Lung 3, 33.3 vs. 21.1 months, HR=0.54; LUX-Lung 6, 31.4 vs. 18.4 months, HR=0.64), no significant OS differences were observed in treatment for patients with L858R mutation[140]. A similar alteration-specific difference was observed for EGFR-mutated treatment-naive NSCLC in a retrospective analysis, which reported numerically longer median OS from second- versus first-generation EGFR TKIs (48.8 vs. 26.4 months, HR=0.59) for patients with exon 19 deletions, but no substantial difference for patients with L858R (25.4 vs. 20.6 months, HR=0.90)[190]. A Phase 2b study of first-line afatinib compared with gefitinib, also for NSCLC with exon 19 deletions or L858R, reported similar median OS for the two therapies (27.9 vs. 24.5 months, HR=0.86) but significantly longer time-to-treatment-failure (13.7 vs. 11.5 months, HR=0.75) and higher ORR (73% vs. 56%, p=0.0018) with afatinib[191]. Patients with metastatic NSCLC and common EGFR mutations who progressed on prior chemotherapy experienced an ORR of 50.0% (30/60) from afatinib in a Phase 4 trial[192]. As first-line therapy for NSCLC with EGFR exon 19 deletions or L858R, prospective or randomized Phase 2 trials have reported a median PFS of 10.2 months and OS of 24.8 months for patients unfit for chemotherapy[193] and an ORR of 72.5% (n=40, 1 CR), DCR of 100% (40/40), and median PFS and OS of 15.2 and 30.0 months, respectively, for elderly patients ≥70 years old[194]. A retrospective study of afatinib administered to Asian patients with NSCLC, 99% of whom were previously treated with erlotinib and/or gefitinib, reported an ORR of 27.4% (63/230) for patients with common sensitizing EGFR mutations and an ORR of 24.4% (105/431) for the entire cohort[195]. In a case report, a patient with NSCLC with exon 19 deletion and leptomeningeal metastases experienced an ongoing 16-month PR from afatinib in extracranial, brain, and leptomeningeal lesions[196]. For patients with erlotinib- or gefitinib-resistant NSCLC and EGFR mutations, Phase 2/3 studies of afatinib treatment have generally reported ORRs of only 7 to 9%[182-183,197-200] ; however, DCRs of more than 50% have been observed[182]. In a Phase 1b or observational study, patients with EGFR-mutated NSCLC who progressed on afatinib experienced further clinical benefit from subsequent treatment with afatinib and cetuximab[201] or osimertinib[202], respectively. Extensive clinical data have demonstrated that afatinib is effective for patients with EGFR-mutated advanced NSCLC, including exon 19 deletions and L858 mutations, as well as uncommon sensitizing mutations in exons 18 or 20[74,140,179,191,193,195,203] . Afatinib has also shown activity for patients with advanced NSCLC and ERBB2 mutations, most of which were exon 20 insertions[182,204-214] . The randomized Phase 3 LUX-Lung 8 trial comparing afatinib with erlotinib as second-line therapy for advanced lung

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squamous cell carcinoma (SCC) reported significantly longer median OS (7.9 vs. 6.8 months, HR=0.81), significantly longer median PFS (2.6 vs. 1.9 months, HR=0.81), and higher DCR (51% vs. 40%, p=0.002) for patients treated with afatinib[203]. For patients who progressed on afatinib monotherapy, additional clinical benefit has been reported from afatinib combined with paclitaxel[215].

Dacomitinib

Resistance of variant(s) to associated therapy is likely

Assay findings association

EGFR
T790M, L858R

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

EGFR activating mutations may indicate sensitivity to afatinib or dacomitinib for patients with non-small cell lung cancer[74-75,179-180] , whereas data for patients with other tumor types are limited[77-82,181] . Patients with untreated advanced NSCLC and EGFR L858R mutations achieved an ORR of 73% (68/93)[216] and a median OS of 32.5 months with dacomitinib[75]. EGFR T790M, in the presence of a co-occurring activating EGFR alteration, is associated with clinical resistance to dacomitinib[110,115-116,217-218] .

SUPPORTING DATA

A randomized Phase 3 trial in patients with NSCLC with activating EGFR mutations (primarily L858R or exon 19 deletions) reported improved clinical benefit with first-line dacomitinib compared with gefitinib (median OS, 34.1 vs. 26.8 months, HR=0.760; median PFS, 14.7 vs. 9.2 months, HR=0.59)[216,219] ; median OS was 34.1 to 36.7 months and ORR was 74.9% to 79.3%, depending on the dosing regimen[220]. A pooled subgroup analysis of patients with NSCLC with activating EGFR mutations reported improved clinical efficacy with dacomitinib treatment compared with erlotinib (median PFS, 14.6 vs, 9.6 months, HR=0.717; median OS, 26.6 vs, 23.2 months, HR=0.737)[221]. Reduced efficacy of dacomitinib treatment in patients with NSCLC harboring the EGFR T790M mutation has been reported in multiple studies[110,115-116] . 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[222]. A Phase 2 study of dacomitinib in patients with NSCLC who had been previously treated with chemotherapy or erlotinib and were not selected for EGFR mutations reported an ORR of 4.5% (3/66)[110]. In one study, the combination of dacomitinib and crizotinib was ineffective and associated with high toxicity in patients with NSCLC[223].

Erlotinib

Resistance of variant(s) to associated therapy is likely

Assay findings association

EGFR
T790M, L858R

AREAS OF THERAPEUTIC USE

Erlotinib is a small-molecule inhibitor of EGFR. It is FDA approved as a monotherapy or in combination with ramucirumab for patients with metastatic non-small cell lung cancer (NSCLC) harboring EGFR exon 19 deletions or exon 21 (L858R) mutations. Erlotinib is also FDA approved in combination with gemcitabine as a first-line treatment for advanced pancreatic cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Amplification or activation of EGFR may predict sensitivity to therapies such as erlotinib. For patients with activating mutations in EGFR, treatment with erlotinib has been associated with improved response and lengthened time to progression[72,224-226] . The EGFR T790M mutation, when co-occurring with an EGFR activating alteration, has been associated with resistance to erlotinib and gefitinib[107-110] .

SUPPORTING DATA

For patients with EGFR-mutated NSCLC, the Phase 3 EURTAC trial reported improved PFS with first-line erlotinib relative to platinum-based chemotherapy (9.7 vs. 5.2 months, HR=0.37)[72]. A Phase 3 study reported similar efficacy of erlotinib and gefitinib for patients with EGFR-mutated NSCLC[227]. Meta-analysis of studies comparing erlotinib or gefitinib versus chemotherapy in the first-line setting reported no significant improvement in OS for patients with EGFR-mutated NSCLC; however, the lack of improved OS was attributed to the effectiveness of postprogression salvage therapy[228]. In the maintenance setting, the placebo-controlled Phase 3 SATURN trial reported significantly improved PFS with maintenance erlotinib following first-line platinum-based chemotherapy irrespective of EGFR status; however, the largest effect was seen for patients with EGFR mutations (HR=0.10)[224]. In the neoadjuvant setting, a Phase 2 trial reported a numerically improved ORR and significantly longer PFS with erlotinib compared with chemotherapy for patients with advanced EGFR-mutated NSCLC[225]. In the placebo-controlled Phase 3 RELAY trial, the addition of ramucirumab to erlotinib improved PFS for previously untreated patients with NSCLC harboring EGFR L858R or exon 19 deletion (19.4 vs. 12.4 months, HR=0.59)[229]. In a Phase 2 trial, no clinical benefit was observed from the addition of bevacizumab to erlotinib for patients with NSCLC harboring EGFR exon 19 deletion or L858R mutation[230]. The Phase 3 BR.21 trial demonstrated prolonged OS for genomically unselected patients with NSCLC treated with erlotinib compared with those treated with standard chemotherapy[231].

Electronically signed by Erik Williams, M.D. | 29 December 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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Gefitinib

Resistance of variant(s) to associated therapy is likely

Assay findings association

EGFR
T790M, L858R

AREAS OF THERAPEUTIC USE

Gefitinib targets the tyrosine kinase EGFR and is FDA approved to treat non-small cell lung cancer (NSCLC) harboring exon 19 deletions or exon 21 (L858R) substitution mutations in EGFR. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Activation of EGFR may predict sensitivity to therapies such as gefitinib. Clinical studies have consistently shown significant improvement in response rates and PFS for patients with EGFR-mutated non-small cell lung cancer (NSCLC) treated with gefitinib compared with chemotherapy[226,232-237] , and responses have been reported for patients with EGFR-rearranged NSCLC[169,238] . The EGFR T790M mutation, when co-occurring with an EGFR activating alteration, has been associated with resistance to erlotinib and gefitinib[107-110] .

SUPPORTING DATA

A Phase 3 trial of first-line gefitinib therapy for patients with NSCLC and EGFR exon 19 deletions or L858R mutations reported a longer PFS (9.2 months vs. 6.3 months)[234] but no change in median OS (34.9 months vs. 37.2 months) compared with patients treated with cisplatin plus docetaxel (median OS of 37.2 months)[239]. Gefitinib achieved an ORR of 69.8% and an OS of 19.2 months as first-line treatment for Caucasian patients with non-small cell lung carcinoma (NSCLC) and EGFR sensitizing mutations[73]. In the retrospective analysis of a Phase 3 study for East Asian patients, gefitinib was reported to have a longer PFS for patients with EGFR mutation-positive NSCLC compared with carboplatin/paclitaxel doublet chemotherapy[235,240] . Two Phase 3 trials of gefitinib plus pemetrexed and carboplatin compared with gefitinib alone for patients with advanced NSCLC harboring EGFR activating mutations reported significantly higher ORRs (75.3% and 84% vs. 62.5% and 67%), longer median PFSs (16 and 20.9 months vs. 8 and 11.9 months), and longer median OSs (50.9 months and not reached vs. 17 and 38.8 months) with combination treatment; however, combination treatment was associated with increased Grade 3 or higher adverse events[241-242] . Retrospective analysis of East Asian patients with advanced NSCLC receiving first-line gefitinib therapy reported that patients with EGFR exon 19 mutations experienced a longer median PFS (10.9 months) compared with patients with EGFR mutations in exon 18 (7.9 months), exon 20 (1.2 months), exon 21 (7.7 months), or double mutations (5.7 months); however, no differences in OS were seen between EGFR mutations[243]. In a Phase 1 study for treatment-naive patients with NSCLC, best ORRs of 78% (7/9) were observed in patients treated with combination gefitinib and the PD-L1 inhibitor durvalumab as first-line treatment and of 80% (8/10) in those treated with the combination after gefitinib monotherapy[244].

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

EGFR

ALTERATION

T790M, L858R

RATIONALE

EGFR activating mutations, rearrangements, or amplification may predict sensitivity to EGFR-targeted therapies. Strategies to overcome resistance to current agents include next-generation EGFR inhibitors and combination therapies. In the context of co-occurring activating alterations, EGFR T790M confers clinical resistance to erlotinib, gefitinib, afatinib, lapatinib, and dacomitinib. Other agents may be relevant, including irreversible EGFR inhibitors, and in the context of lung cancer, the ALK/EGFR/ROS1 inhibitor brigatinib.

NCT03521154

PHASE 3

A Global Study to Assess the Effects of Osimertinib Following Chemoradiation in Patients With Stage III Unresectable Non-small Cell Lung Cancer (LAURA)

TARGETS EGFR

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Taichung (Taiwan), Tainan City (Taiwan), Linhai (China), Hangzhou (China), Shanghai (China), Nanjing (China), Beijing (China), Guangzhou (China)

NCT04487080

PHASE 3

A Study of Amivantamab and Lazertinib Combination Therapy Versus Osimertinib in Locally Advanced or Metastatic Non-Small Cell Lung Cancer

TARGETS MET, EGFR

LOCATIONS: New Taipei (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Kaohsiung (Taiwan), Wenzhou (China), Linhai (China), Hangzhou (China), Hang Zhou (China), Shanghai (China), Busan (Korea, Republic of)

NCT04619004

PHASE 2

HERTHENA-Lung01: Patritumab Deruxtecan in Subjects With Metastatic or Locally Advanced EGFR-mutated Non-Small Cell Lung Cancer

TARGETS ERBB3

LOCATIONS: Taipei (Taiwan), Tainan City (Taiwan), Kaohsiung City (Taiwan), Fukuoka (Japan), Daegu (Korea, Republic of), Matsuyama (Japan), Seongnam (Korea, Republic of), Seoul (Korea, Republic of), Akashi (Japan), Ōsaka-sayama (Japan)

NCT02609776

PHASE 1

A Dose Escalation Study of JNJ-61186372 in Participants With Advanced Non-Small Cell Lung Cancer

TARGETS MET, EGFR

LOCATIONS: Taipei (Taiwan), Taipei City (Taiwan), Taichung (Taiwan), Hangzhou (China), Nanchang (China), Nanjing (China), Hefei (China), Guangzhou (China), Changsha (China), Wuhan (China)

NCT03114319

PHASE 1

Dose Finding Study of TNO155 in Adult Patients With Advanced Solid Tumors

TARGETS SHP2, EGFR

LOCATIONS: Taipei (Taiwan), Seoul (Korea, Republic of), Kobe-shi (Japan), Singapore (Singapore), Amsterdam (Netherlands), Rotterdam (Netherlands), Barcelona (Spain), Hospitalet de LLobregat (Spain), Toronto (Canada), Massachusetts

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), Taichung City (Taiwan), Tainan City (Taiwan), Seoul (Korea, Republic of), Chuo-ku (Japan), Kashiwa-shi (Japan), Marseille CEDEX 05 (France), California

NCT04077463

PHASE 1

A Study of Lazertinib as Monotherapy or in Combination With JNJ-61186372 in Japanese Participants With Advanced Non-small Cell Lung Cancer

TARGETS
EGFR, MET

LOCATIONS: Taipei City (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Kaohsiung (Taiwan), Hang Zhou (China), Shanghai (China), Guangzhou (China), Wuhan (China), Jinan (China), Seongnam-si (Korea, Republic of)

NCT04035486

PHASE 3

A Study of Osimertinib With or Without Chemotherapy as 1st Line Treatment in Patients With Mutated Epidermal Growth Factor Receptor Non-Small Cell Lung Cancer (FLAURA2)

TARGETS
EGFR

LOCATIONS: Taichung (Taiwan), Shanghai (China), Nanchang (China), Nanjing (China), Yangzhou (China), Hefei (China), Guangzhou (China), Beijing (China), Urumqi (China), Zhengzhou (China)

NCT04770688

PHASE 1/2

Advanced Lung Tumor Treated by Osimertinib Plus Anlotinib

TARGETS
EGFR

LOCATIONS: Shanghai (China)

NCT04425681

PHASE 2

Osimertinib With Bevacizumab for Leptomeningeal Metastasis From EGFR-mutation Non-Small Cell Lung Cancer

TARGETS
EGFR, VEGFA

LOCATIONS: Nanchang (China)

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

DDR1 D623G	***EGFR*** V651L	***FGFR3*** R158Q	***GATA4*** P15_G16insP
MEN1 G508D	***MTOR*** T1834_T1837del	***PDCD1 (PD-1)*** A202_R203insGA	***RAD51*** Q269K

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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)*	*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	*C11orf30 (EMSY)*	*C17orf39 (GID4)*	*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*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
FAM46C	*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*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*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*	*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*	*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*	*P2RY8*	*PALB2*
PARK2	*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*	*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*	*TET2*	*TGFBR2*	*TIPARP*	*TNFAIP3*	*TNFRSF14*	*TP53*
TSC1	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*	*VHL*	*WHSC1*	*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

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 PRINCIPLES

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

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

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations

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

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. 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.
4. 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.
5. 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.
6. 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

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Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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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

MR Suite Version 5.2.0

The median exon coverage for this sample is 1,014x

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Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
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Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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