FOUNDATIONONE®CDx

PATIENT
Fan, Ching-Ling

TUMOR TYPE
Lung adenocarcinoma

COUNTRY CODE
TW

REPORT DATE
28 Oct 2021

ORDERED TEST #
ORD-1209834-01

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 Fan, Ching-Ling
DATE OF BIRTH 10 June 1947
SEX Female
MEDICAL RECORD # 46384183

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 S110-24691 A (PF21028)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 25 August 2021
SPECIMEN RECEIVED 12 October 2021

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 3 Muts/Mb

Genomic Findings

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

EGFR exon 19 deletion (E746_A750del)
RET ANKRD26-RET fusion
MUTYH splice site 892-2A>G
RB1 splice site 1215+1G>A
TP53 Y205C

6 Disease relevant genes with no reportable alterations: ***KRAS, ALK, BRAF, MET, ERBB2, ROS1***

11 Therapies with Clinical Benefit
0 Therapies with Resistance
20 Clinical Trials

BIOMARKER FINDINGS

Microsatellite status - MS-Stable

Tumor Mutational Burden - 3 Muts/Mb

GENOMIC FINDINGS

***EGFR* -** exon 19 deletion (E746_A750del)

10 Trials *see p. 16*

***RET* -** ANKRD26-RET fusion

10 Trials *see p. 18*

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)	
Afatinib	1	none	
Dacomitinib	1		
Erlotinib	1		
Gefitinib	1		
Osimertinib	1		
Pralsetinib	2A	Cabozantinib	2A
Selpercatinib	2A	Vandetanib	2B
		Lenvatinib	
		Sunitinib	

☐ *NCCN category*

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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.

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

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

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BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors[1-3], including approved therapies nivolumab and pembrolizumab[4]. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, p=0.001)[5].

FREQUENCY & PROGNOSIS

MSI-H is generally infrequent in NSCLC, reported in fewer than 1% of samples across several large studies[6-11], whereas data on the reported incidence of MSI-H in SCLC has been limited and conflicting[12-15]. 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[6]. 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[16]. 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[16-18]. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers[19-21]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[16,18,20-21].

BIOMARKER

Tumor Mutational Burden

RESULT
3 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[22-24], anti-PD-1 therapies[22-25], and combination nivolumab and ipilimumab[26-31]. 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);[22-23,26-28,32-39]. Improved OS of patients with NSCLC treated with pembrolizumab plus chemotherapy relative to chemotherapy only[40], or those treated with nivolumab plus ipilimumab also relative to chemotherapy[41], has been observed across all TMB levels.

FREQUENCY & PROGNOSIS

A large-scale genomic analysis found that unspecified lung non-small cell lung carcinoma (NSCLC), lung adenocarcinoma, and lung squamous cell carcinoma (SCC) samples harbored median TMBs between 6.3 and 9 Muts/Mb, and 12% to 17% of cases had an elevated TMB of greater than 20 Muts/Mb[42]. 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[43]. Although some studies have reported a lack of association between smoking and mutational burden in NSCLC[44-45], several other large studies did find a strong association with increased TMB[46-49]. 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[50]. 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)[44]. 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[51]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[51-52].

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[53-54] and cigarette smoke in lung cancer[32,55], treatment with temozolomide-based chemotherapy in glioma[56-57], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[58-62], and microsatellite instability (MSI)[58,61-62]. This sample harbors a TMB below levels that would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[22-23,26-28,32-39,63].

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GENE
EGFR

ALTERATION
exon 19 deletion (E746_A750del)

TRANSCRIPT ID
NM_005228

CODING SEQUENCE EFFECT
2235_2249delGGAATTAAGAGAAGC

VARIANT ALLELE FREQUENCY (% VAF)
42.2%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

For patients with non-small cell lung cancer, EGFR activating mutations may predict sensitivity to EGFR TKIs, including erlotinib[64], gefitinib[65], afatinib[66], dacomitinib[67], and osimertinib[68]; however, the data for patients with other tumor types are limited[69-74]. 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, including osimertinib-relapsed patients with biomarkers indicating EGFR/MET-based osimertinib resistance[75-77] . 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[78]. 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[79-80]. 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[81]. 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[82]; therefore, the patient's clinical context should be considered.

— Potential Resistance —

Acquired RET rearrangements have been detected in 2 patients with EGFR-mutated NSCLC who had progressed on first-line EGFR inhibitors, suggesting that RET activation may mediate bypass resistance to EGFR-targeted therapy in lung cancer[83]. Case series have reported RET rearrangements for patients with EGFR-mutated NSCLC who progressed on osimertinib, including 7 patients with acquired resistance[84-87]. Patients with EGFR-mutated NSCLC harboring RET rearrangements experienced significantly shorter OS in response to first-line treatment with osimertinib (22.9 vs 59.5 months, p=0.021) and after progressing with osimertinib (2.1 vs 10.0 months, p=0.031) compared with non-RET-rearranged cases[88]. Preclinical studies reported that EGFR-mutated lung cell lines expressing CCDC6–RET rearrangement showed limited response to osimertinib in vitro compared with EGFR-mutated parental cells[85].

FREQUENCY & PROGNOSIS

EGFR mutation has been reported in 12-36% of lung adenocarcinomas[48,89-90] and in 4% of lung squamous cell carcinomas[91]. EGFR protein expression/overexpression has been reported in up to 70% of NSCLC cases[92-97]. In addition, expression of EGFR protein has been shown to be higher in lung squamous cell carcinoma samples as compared to lung adenocarcinoma[98-99]. In the context of metastatic non-small cell lung cancer (NSCLC), patients with EGFR sensitizing mutations and concurrent alterations in both RB1 and TP53 (triple-mutant), as seen here, may be at significantly higher risk of transformation to small cell lung cancer (SCLC), a mechanism of resistance to treatment with EGFR inhibitors; median time from advanced NSCLC diagnosis to SCLC transformation has been reported to be 17.8 months[100-102]. A retrospective study reported SCLC transformation in 18% (7/39) of patients with triple-mutant NSCLC and a shorter time to initial EGFR inhibitor discontinuation in these patients (9.5 months) compared to that in patients with EGFR/TP53-mutant NSCLC (12.3 months) or in patients with NSCLC harboring EGFR mutations only (36.6 months)[102]. In patients with lung adenocarcinoma, EGFR mutation was a predictor of poor overall survival[103-104]. However, EGFR mutations have been reported to predict improved survival in patients with resected Stage 1-3 lung adenocarcinoma[105] or resected Stage 1 NSCLC[106].

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[107]. EGFR exon 19 deletion mutations, such as seen here, have been shown to activate the tyrosine kinase activity of EGFR and to confer sensitivity to EGFR tyrosine kinase inhibitors such as erlotinib, gefitinib[108-110], afatinib[111], osimertinib[112], and dacomitinib[67,113], although limited preclinical data suggest reduced sensitivity to lapatinib[114-115].

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GENE
RET

ALTERATION
ANKRD26-RET fusion

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence, RET activating alterations may predict response to selective RET inhibitors such as pralsetinib[116-118] , selpercatinib[119-120] , and BOS172738[121], as well as the multikinase inhibitors cabozantinib[122-138], lenvatinib[125,139-141], sorafenib[125,142-145], sunitinib[125,146], and vandetanib[125,147-161]. In a Phase 1/1b study for advanced solid tumors, agerafenib (RXDX-105) led to a preliminary ORR of 44% (4/9; 1 CR in colorectal cancer, 3 PRs in non-small cell lung cancer [NSCLC]) for patients with RET-inhibitor-naive, RET-fusion-positive cancer[162]. A Phase 1 study of the selective RET inhibitor BOS172738 reported an ORR of 33% (10/30) across all dose levels for patients with RET-fusion-positive advanced NSCLC[121]. On the basis of limited clinical evidence, RET rearrangements may predict sensitivity to pralsetinib for patients with papillary thyroid carcinoma (PTC), pancreatic adenocarcinoma, or cholangiocarcinoma[163]. RET rearrangements may also predict sensitivity to sorafenib for patients with chronic myelomonocytic leukemia or PTC[144-145]. Three patients with RET-rearranged non-small cell lung cancer who had been previously treated with at least one line of chemotherapy achieved SD following treatment with sorafenib[125,143]. Preclinical studies have presented conflicting data regarding the sensitivity of RET fusions to sorafenib[164-169]. In a Phase 1b study, RET-inhibitor-naive patients with NSCLC were reported to achieve an ORR of 19% (6/31) in response to agerafenib; of note, the ORR was 0% (0/20) for cases harboring the KIF5B-RET fusion compared with 67% (6/9) for non-KIF5B-RET fusions[170]. Phase 1 studies of alectinib for the treatment of patients with RET-rearranged NSCLC have reported limited efficacy with an ORR of 3% (1/33 PR)[171], while case studies have collectively reported 2 PRs in response to higher dose alectinib (and 1 unconfirmed PR) out of 11 patients[125,172-176]. While preclinical data have shown sensitivity, including with gatekeeper V804L/M mutations[177-178], ponatinib has shown limited efficacy in patients with RET-rearranged NSCLC (2/2 SD)[125].

— Potential Resistance —

Acquired RET rearrangements have been detected in 2 patients with EGFR-mutated NSCLC who had progressed on first-line EGFR inhibitors, suggesting that RET activation may mediate bypass resistance to EGFR-targeted therapy in lung cancer[83]. Case series have reported RET rearrangements for patients with EGFR-mutated NSCLC who progressed on osimertinib, including 7 patients with acquired resistance[84-87]. Patients with EGFR-mutated NSCLC harboring RET rearrangements experienced significantly shorter OS in response to first-line treatment with osimertinib (22.9 vs 59.5 months, p=0.021) and after progressing with osimertinib (2.1 vs 10.0 months, p=0.031) compared with non-RET-rearranged cases[88]. Preclinical studies reported that EGFR-mutated lung cell lines expressing CCDC6–RET rearrangement showed limited response to osimertinib in vitro compared with EGFR-mutated parental cells[85].

FREQUENCY & PROGNOSIS

In the TCGA dataset, RET rearrangements were observed in fewer than 1% of lung adenocarcinoma cases[179-180]. Other studies have identified RET rearrangement in 1-2% of cases[124,181-183], and at an incidence of 6% in non-small cell lung cancers lacking other known driver mutations[124]. Multiple activating RET fusions with distinct fusion partners have been described in the context of cancer[179-180], with the KIF5B-RET and CCDC6-RET fusions being the most common variants detected in lung adenocarcinoma[168,182-185]. Multiple studies have suggested that RET fusion in lung cancer correlates with adenocarcinoma histology, younger age, never smoke status and advanced disease[125,183,186].

FINDING SUMMARY

RET (Rearranged during transfection) encodes a receptor tyrosine kinase primarily expressed in cells of the nervous system. It has been identified as a proto-oncogene that results in transformation of cells upon recombination with a partner gene[187]. RET fusions involving an N-terminal partner gene that is predicted to promote dimerization and the kinase domain of RET (exons 12-18)[188] have been characterized as activating and oncogenic[164-165,168,182,184-185,189-193]. Certain other RET rearrangements may retain capacity to dimerize through self-association of the RET transmembrane domain and have been shown to be mildly transforming[194-195]. RET fusions have been shown to be clinically sensitive to RET targeted therapies[116,119,124-125,134,189,196-197]. Rearrangements, such as observed here, are predicted to be activating and oncogenic.

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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)
58.2%

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)[198]. Monoallelic MUTYH mutation occurs in 1-2% of the general population[199-200]. There is conflicting data regarding the impact of monoallelic mutations on the risk of developing CRC[201-203]. Patients with MUTYH-mutant CRC were reported to have significantly improved overall survival compared to patients without MUTYH mutation[204].

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[205]. The two most frequently reported MUTYH loss of function mutations are G382D (also referred to as G396D) and Y165C (also referred to as Y179C)[199-200,206-208]. Numerous other MUTYH mutations have also been shown to result in loss of function[206-209].

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, Mar 2021)[210]. 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)[199,211-213]. MAP accounts for approximately 0.7% of all CRC cases and 2% of early-onset CRC cases[199]. In contrast to CRC, the role of MUTYH mutation in the context of other cancer types is not well established[214-218]. Estimates for the prevalence of MAP in the general population range from 1:5,000-1:10,000[200]. Therefore, in the appropriate clinical context, germline testing of MUTYH is recommended.

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GENE
RB1

ALTERATION
splice site 1215+1G>A

TRANSCRIPT ID
NM_000321

CODING SEQUENCE EFFECT
1215+1G>A

VARIANT ALLELE FREQUENCY (% VAF)
62.5%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of limited clinical data[219] and strong preclinical data[220-222], RB1 inactivation may be associated with sensitivity to inhibitors of Aurora kinase A, particularly in small cell lung cancer. It should be noted that a trial of the Aurora kinase A inhibitor alisertib in advanced prostate cancer did not find an association between RB1 deletion and clinical benefit[223]. Other approaches to target RB1 inactivation under investigation in preclinical studies include inhibitors of BCL-2 family members[224] and activation of the NOTCH pathway[225].

— Potential Resistance —

Rb inactivation may predict resistance to CDK4/6 inhibitors such as palbociclib, abemaciclib, and ribociclib, which act upstream of Rb[226-235].

— Nontargeted Approaches —

Loss of Rb function has been associated with increased sensitivity to cytotoxic agents and chemotherapeutics in both preclinical studies and in patients with bladder or breast cancer[236-237].

FREQUENCY & PROGNOSIS

In the TCGA dataset, RB1 mutation was observed in 5% of lung squamous cell carcinoma cases[91] and 4% of lung adenocarcinoma cases[90]. Loss of Rb protein expression has been reported in 62% of pre-chemotherapy advanced non-small cell lung cancers (NSCLC)[238]. One study found that RB1 expression was correlated with poor prognosis for patients with NSCLC[239]. In the context of metastatic non-small cell lung cancer (NSCLC), patients with EGFR sensitizing mutations and concurrent alterations in both RB1 and TP53 (triple-mutant), as seen here, may be at significantly higher risk of transformation to small cell lung cancer (SCLC), a mechanism of resistance to treatment with EGFR inhibitors; median time from advanced NSCLC diagnosis to SCLC transformation has been reported to be 17.8 months[100-102]. A retrospective study reported SCLC transformation in 18% (7/39) of patients with triple-mutant NSCLC and a shorter time to initial EGFR inhibitor discontinuation in these patients (9.5 months) compared to that in patients with EGFR/TP53-mutant NSCLC (12.3 months) or in patients with NSCLC harboring EGFR mutations only (36.6 months)[102].

FINDING SUMMARY

RB1 encodes the retinoblastoma protein (Rb), a tumor suppressor and negative regulator of the cell cycle[237,240]. Alterations such as seen here may disrupt RB1 function or expression[241-247].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the RB1 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 retinoblastoma (ClinVar, Mar 2021)[210]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Mutations in RB1 underlie the development of retinoblastoma (RB), a rare tumor that arises at a rate of approximately 1:20,000 live births, with nearly 5,000 new cases worldwide per year[248]. Germline mutations in RB1 account for approximately 40% of RB tumors[249] and are associated with an increased risk of developing secondary malignancies that include soft tissue and bone sarcoma and malignant melanoma[250-251]. In the appropriate clinical context, germline testing of RB1 is recommended.

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GENE
TP53

ALTERATION
Y205C

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
614A>G

VARIANT ALLELE FREQUENCY (% VAF)
57.3%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[252-255], or p53 gene therapy and immunotherapeutics such as SGT-53[256-260] and ALT-801[261]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% (17/176) and SDs in 53.4% (94/176) of patients with solid tumors; the response rate was 21.1% (4/19) for patients with TP53 mutations versus 12.1% (4/33) for patients who were TP53 wild-type[262]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 31.9% (30/94, 3 CR) ORR and a 73.4% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[263]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 42.9% (9/21, 1 CR) ORR and a 76.2% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[264]. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[265]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24.0% (6/25) ORR with adavosertib combined with paclitaxel[266]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71.4% (5/7) response rate for patients with TP53 alterations[267]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75.0% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[260]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutated, but not TP53-wild-type, breast cancer xenotransplant mouse model[268]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutated p53 such as APR-246[269-271]. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[272]. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies[273-274]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[275-276]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

TP53 is one of the most commonly mutated genes in lung cancer; mutations have been reported in 43-80% of non-small cell lung cancers (NSCLCs)[90-91,277-282], including 42-52% of lung adenocarcinomas and 58-83% of lung squamous cell carcinomas (cBioPortal, COSMIC, Feb 2021)[48-49,90-91]. TP53 homozygous deletion has been observed in 1.4% of lung adenocarcinoma and <1% of lung squamous cell carcinoma cases (cBioPortal, Feb 2021)[283-284]. In one study of 55 patients with lung adenocarcinoma, TP53 alterations correlated with immunogenic features including PD-L1 expression, tumor mutation burden and neoantigen presentation; likely as a consequence of this association TP53 mutations correlated with improved clinical outcomes to PD-1 inhibitors pembrolizumab and nivolumab in this study[285]. Mutations in TP53 have been associated with lymph node metastasis in patients with lung adenocarcinoma[286]. In the context of metastatic non-small cell lung cancer (NSCLC), patients with EGFR sensitizing mutations and concurrent alterations in both RB1 and TP53 (triple-mutant), as seen here, may be at significantly higher risk of transformation to small cell lung cancer (SCLC), a mechanism of resistance to treatment with EGFR inhibitors; median time from advanced NSCLC diagnosis to SCLC transformation has been reported to be 17.8 months[100-102]. A retrospective study reported SCLC transformation in 18% (7/39) of patients with triple-mutant NSCLC and a shorter time to initial EGFR inhibitor discontinuation in these patients (9.5 months) compared to that in patients with EGFR/TP53-mutant NSCLC (12.3 months) or in patients with NSCLC harboring EGFR mutations only (36.6 months)[102].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[287]. Alterations such as seen here may disrupt TP53 function or expression[288-292].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[293-295], including sarcomas[296-297]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[298] to 1:20,000[297]. For pathogenic TP53 mutations identified during tumor sequencing, the rate of germline mutations was 1% in the overall population and 6% in tumors arising before age 30[299]. In the appropriate clinical context, germline testing of TP53 is recommended.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[300-305]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[300-301]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[306]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[304,307-308]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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Afatinib

Assay findings association

EGFR
exon 19 deletion (E746_A750del)

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[66-67,309-310] , whereas data for patients with other tumor types are limited[69-74,311] .

SUPPORTING DATA

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[66,309,312-315] . 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)[66,309] . 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[111]. 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)[312]. 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[313]. 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[314]. 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[315] 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[316]. 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[317]. 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[318]. 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%[319-324] ; however, DCRs of more than 50% have been observed[323]. 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[325] or osimertinib[326], 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[66,111,309,313,315,317,327] . Afatinib has also shown activity for patients with advanced NSCLC and ERBB2 mutations, most of which were exon 20 insertions[323,328-338] . The randomized Phase 3 LUX-Lung 8 trial comparing afatinib with erlotinib as second-line therapy for advanced lung squamous cell carcinoma (SCC) reported significantly longer 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[327]. For patients who progressed on afatinib monotherapy, additional clinical benefit has been reported from afatinib combined with paclitaxel[339].

Dacomitinib

Assay findings association

EGFR
exon 19 deletion (E746_A750del)

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[66-67,309-310] , whereas data for patients with other tumor types are limited[69-74,311] . Patients with untreated advanced NSCLC and EGFR exon 19 deletions achieved an ORR of 76%[113] and a median OS of 34.1 months with dacomitinib[67].

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)[113,340] ; median OS was 34.1 to 36.7 months and ORR was 74.9% to 79.3%, depending on the dosing regimen[341]. 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)[342]. Reduced efficacy of dacomitinib treatment in patients with NSCLC harboring the EGFR T790M mutation has been reported in multiple studies[343-345] . 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[346]. 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)[344]. In one study, the combination of dacomitinib and crizotinib was ineffective and associated with high toxicity in patients with NSCLC[347].

Erlotinib

Assay findings association

EGFR
exon 19 deletion (E746_A750del)

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[64,348-350] .

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)[64]. A Phase 3 study reported similar efficacy of erlotinib and gefitinib for patients with EGFR-mutated NSCLC[351]. 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[352]. 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)[348]. 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[349]. 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)[353]. 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[354]. In one study, median PFS (4.1 vs. 11.7 months, HR=9.7) and median OS (14.1 vs. 47.0 months, HR=10.2) were significantly shorter for patients with NSCLC harboring EGFR L747_A750>P (n=6) relative to those with deletions affecting EGFR E746_A750 (n=24) treated with first-line erlotinib[355]. 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[356].

Gefitinib

Assay findings association

EGFR
exon 19 deletion (E746_A750del)

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[350,357-362] , and responses have been reported for patients with EGFR-rearranged NSCLC[363-364] .

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)[359] 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)[365]. 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[65]. 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[360,366] . 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[367-368] . 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[369]. 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[370].

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Osimertinib

Assay findings association

EGFR
exon 19 deletion (E746_A750del)

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[68,112,363,371-372] . 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[112]. On the basis of clinical evidence for patients with EGFR-mutated NSCLC, RET rearrangements have been associated with resistance to osimertinib[84-88,373-374] .

SUPPORTING DATA

A patient with 2 primary NSCLC tumors, 1 harboring EGFR L858R and one with KIF5B-RET fusion, initially treated with osimertinib, achieved durable disease control in response to treatment with a combination of alectinib and osimertinib[375]. In a retrospective study of selpercatinib in combination with osimertinib for patients with EGFR-mutant non-small cell lung cancer with acquired RET fusions who progressed after osimertinib, 50% (5/10) of the patients achieved PRs (4 confirmed and 1 unconfirmed), with median treatment duration of 11 months[376]. 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)[112,377] . 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)[378]. 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[68]. 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). 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%[379]. 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[380].

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Pralsetinib

Assay findings association

RET
ANKRD26-RET fusion

AREAS OF THERAPEUTIC USE

Pralsetinib is a RET inhibitor that is FDA approved to treat adult patients with RET fusion-positive non-small cell lung cancer (NSCLC) and adult and pediatric patients with RET fusion-positive thyroid cancer or RET-mutated medullary thyroid cancer (MTC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in RET-fusion-positive NSCLC, thyroid cancer, and other solid malignancies[116-117,381] , RET rearrangements may predict sensitivity to pralsetinib.

SUPPORTING DATA

Pralsetinib has demonstrated clinical benefit for patients with various tumor types harboring RET rearrangements[116,163] as well as for patients with RET-mutated medullary thyroid carcinoma (MTC)[382]. The Phase 1/2 ARROW study of pralsetinib reported ORRs of 73% (12% CR) and 61% (5% CR) for patients with RET-fusion-positive non-small cell lung cancer in the first-line and prior platinum settings, respectively[116]. In this same study, patients with RET-fusion-positive thyroid cancer exhibited an ORR of 91% (10/11; 10 PR), whereas patients with various other RET-fusion-positive solid malignancies achieved an ORR of 50% (6/12; 6 PR); these responses were seen in patients with pancreatic adenocarcinoma (3/3 PR), cholangiocarcinoma (2/2 PR), and unknown primary neuroendocrine cancer (1/1 PR)[163]. The Phase 1/2 ARROW study of pralsetinib reported an ORR of 65% for patients with RET fusion-positive non-small cell lung cancer (NSCLC), including an ORR of 70% (19/27, 3 CRs) for patients who were treatment-naive and 61% (53/87, 5 CRs) for patients previously treated with platinum-based chemotherapy[383]; similar results were shown for a cohort of Chinese patients with an ORR of 80% (24/30) in the first-line setting and an ORR of 67% (11/33) for patients previously treated with platinum-based chemotherapy[384]. The median duration of response was not reached for patients with previously treated disease and was 9 months for patients receiving pralsetinib in the first-line setting[383]. Patients with measurable central nervous system disease experienced an intracranial ORR of 56% (5/9, 3 CRs)[383]. Pralsetinib has also shown clinical benefit as a monotherapy for a patient with RET fusion-positive NSCLC who had progressed on pembrolizumab[385] and in combination with osimertinib for 2 patients with RET fusion-positive NSCLC who had progressed on EGFR inhibitors[85]. No responses were reported among 3 patients with mixed lung sarcoma/adenocarcinoma, mixed SCLC/NSCLC, or lung atypical carcinoid treated with pralsetinib in the Phase 1/2 ARROW study[117].

Selpercatinib

Assay findings association

RET
ANKRD26-RET fusion

AREAS OF THERAPEUTIC USE

Selpercatinib is a RET inhibitor that is FDA approved to treat adult patients with RET fusion-positive non-small cell lung cancer (NSCLC) and adult and pediatric patients with RET fusion-positive thyroid cancer or RET-mutated medullary thyroid cancer (MTC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of a Phase 1/2 study in RET fusion-positive NSCLC[119] or thyroid cancer[196] and additional responses in patients with other RET-rearranged malignancies[386-387] , RET rearrangements may predict sensitivity to selpercatinib.

SUPPORTING DATA

In a retrospective study of selpercatinib in combination with osimertinib for patients with EGFR-mutant non-small cell lung cancer with acquired RET fusions who progressed after osimertinib, 50% (5/10) of the patients achieved PRs (4 confirmed and 1 unconfirmed), with median treatment duration of 11 months[376]. Selpercatinib has demonstrated activity for patients with various tumor types harboring RET rearrangements[196,386,388-389] , and in RET-mutated medullary thyroid cancer[120]. In the Phase 1/2 LIBRETTO-001 study of selpercatinib for RET fusion-positive non-small cell lung cancer (NSCLC), patients who were treatment-naive achieved an ORR of 85% (33/39) and a 1-year PFS rate of 75%, with neither the median duration of response (mDOR) nor median PFS (mPFS) reached; patients previously treated with platinum chemotherapy achieved an ORR of 64% (67/105), mDOR of 17.5 months, 1-year PFS rate of 66%, and mPFS of 16.5 months[388]. Selpercatinib also demonstrated intracranial activity in LIBRETTO-001 with an intracranial ORR of 82% (18/22; 5 CRs) for patients with measurable baseline central nervous system disease and an mPFS of 13.7 months for all patients with intracranial disease; intracranial mDOR was not reached[390]. The Phase 2 LIBRETTO-321 study for Chinese patients with RET fusion-positive NSCLC reported similar activity as reported in LIBRETTO-001 in both the primary analysis set and response-evaluable populations; it also demonstrated intracranial activity[391].

Cabozantinib

Assay findings association

RET
ANKRD26-RET fusion

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

Based on strong clinical evidence demonstrating clinical benefit for patients with RET-rearranged non-small cell lung cancer[123-125] and emerging clinical evidence of responses in patients with RET-rearranged salivary duct carcinoma[134-135] , RET activating rearrangements may predict sensitivity to cabozantinib.

SUPPORTING DATA

A Phase 2 study of cabozantinib in RET-rearranged lung adenocarcinoma reported an ORR of 28% (7 PRs, n=25), a median PFS of 5.5 months, and an OS of 9.9 months[123-124] . In a retrospective analysis of patients with RET-rearranged non-small cell lung cancer treated with various RET inhibitors, of the 19 evaluable patients treated with cabozantinib, 1 CR and 6 PRs were reported, reaching an ORR of 37%[125]. In other studies and case reports, varying degrees of clinical benefit have been reported for patients with RET-rearranged lung cancer treated with cabozantinib[126-133,137,392-397] . 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[398]. 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[399]. 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[127].

Lenvatinib

Assay findings association

RET
ANKRD26-RET fusion

AREAS OF THERAPEUTIC USE

Lenvatinib is a TKI that targets several kinases, including the VEGFRs, FGFRs, PDGFRs, RET, and KIT. It is FDA approved to treat differentiated thyroid cancer (DTC) and hepatocellular carcinoma (HCC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

Activating RET mutations or fusions may predict sensitivity to lenvatinib[400-402] . Clinical responses to lenvatinib have been reported for patients with RET-rearranged non-small cell lung cancer (NSCLC)[125,139,403] and thyroid carcinoma[140,404] .

SUPPORTING DATA

A Phase 2 study of lenvatinib for patients with RET-rearranged lung adenocarcinoma reported an ORR of 16% (4 PRs, n=25) with a median PFS of 7.3 months and median OS not reached[139]. In the Global Multicenter RET Registry (GLORY), 1 PR and 1 PD were reported among the 2 patients with advanced RET-rearranged lung cancer treated with lenvatinib[125]. Another retrospective study identified 1 patient with EGFR-mutated RET-rearranged non-small cell lung cancer (NSCLC) who benefited from lenvatinib[403]. Lenvatinib has primarily been evaluated for the treatment of iodine-131-refractory, differentiated thyroid carcinoma[405] or for patients with advanced renal cell carcinoma[406]. In a Phase 1 trial investigating lenvatinib as a treatment for solid tumors, including two patients with lung cancer, 2/27 of patients experienced partial response (PR), and 11/27 of patients experienced stable disease (SD)[407]. In trials that included patients with NSCLC, the addition of lenvatinib to a carboplatin/paclitaxel regimen led to a complete response (CR) for one patient, PR for 57% (16/24) of patients, and SD for 25% (7/24) of patients[408]; when added to standard-of-care treatment, lenvatinib improved both progression-free survival (PFS; 20.9 months vs. 7.9 months) and overall survival (OS; 38.4 months vs. 24.1 months; p=0.065)[409]. In the latter study, patients achieved an overall response rate (ORR) of 10.1% vs. 2.2% (p=0.1635) and a disease-control rate (DCR) of 42.7 vs. 19.6% (p=0.0079); although response was independent of KRAS mutation, a nonsignificant trend for benefit was observed for patients with wild-type EGFR versus those with EGFR mutation (HR 0.551 vs. 1.3, NS)[409]. In a Phase 1 dose-escalation study of single-agent lenvatinib for patients with advanced solid tumors, confirmed PRs were achieved by 16% (12/77) and unconfirmed PRs by an additional 4% (3/77) of patients; SD was reported for both of the participants with NSCLC[410].

Sunitinib

Assay findings association

RET
ANKRD26-RET fusion

AREAS OF THERAPEUTIC USE

Sunitinib is a small-molecule tyrosine kinase inhibitor that targets PDGFRs, VEGFRs, KIT, FLT3, CSF-1R, and RET. It is FDA approved for the treatment of advanced or metastatic pancreatic neuroendocrine tumors, gastrointestinal stromal tumors (GISTs) in patients who have progressed on or are intolerant to imatinib, and advanced renal cell carcinoma (RCC) as well as for the adjuvant treatment of patients at high risk of recurrent RCC after nephrectomy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data, patients with RET activating mutations[411-412] or RET-rearranged non-small cell lung cancer may respond to sunitinib[125,146,413] .

SUPPORTING DATA

For patients with RET-rearranged non-small cell lung cancer treated with sunitinib, a retrospective study reported 2 PRs and 3 SDs among 9 evaluable patients[125]. Additional studies of heavily pretreated patients with RET-rearranged lung adenocarcinoma have reported 1 PR[146], 1 SD[413], and 1 patient who showed an initial mixed response followed by PD[413]. Sunitinib was shown to have potential value as maintenance therapy in a Phase 2 study of non-small cell lung cancer (NSCLC)[414]. Another Phase 2 study reported an overall response rate of 11% in NSCLC[415]. A Phase 3 study in NSCLC reported that sunitinib plus erlotinib was associated with better response rate and PFS than erlotinib alone[416]. In a Phase 1 dose escalation trial in patients with solid tumors including NSCLC, sunitinib plus pemetrexed and carboplatin was tolerated and demonstrated SD in 3 of 5 evaluable patients[417].

Vandetanib

Assay findings association

RET
ANKRD26-RET fusion

AREAS OF THERAPEUTIC USE

Vandetanib is a multikinase inhibitor that targets RET, VEGFRs, SRC family kinases, and EGFR. It is FDA approved for the treatment of medullary thyroid cancer (MTC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

RET activating alterations may predict sensitivity to vandetanib[125,148,150,156,158,160,418-420] . On the basis of clinical evidence[125,148-150] , patients with RET-rearranged lung cancer may respond to vandetanib. In the Phase 2 LURET study, outcomes were better for patients with CCDC6-RET fusions than for those with KIF5B-RET fusions (ORR, 5/6 vs. 2/10; median PFS, 8.9 vs. 4.2 months; median OS, 10.5 months vs. not reached)[148,418] .

SUPPORTING DATA

Clinical studies indicate that vandetanib is active against RET-rearranged non-small cell lung cancer (NSCLC). The Global Multicenter RET Registry (GLORY) reported an ORR of 18% (2 PRs, n=11), median PFS (mPFS) of 2.9 months, and median OS (mOS) of 10.2 months for patients with advanced RET-rearranged lung cancer treated with vandetanib[125]. Phase 2 studies of vandetanib for patients with previously treated RET-rearranged NSCLC reported ORRs of 18-47% with mPFS of 4.5-6.5 months and mOS of 11.6-13.5 months[148,150] . A retrospective study of vandetanib for Korean patients with RET-rearranged NSCLC reported an ORR of 16% (3 PRs, n=19) with mPFS of 2.9 months and mOS of 9.3 months[149]. A retrospective analysis of the Phase 3 ZODIAC, ZEAL, ZEPHYR, and ZEST studies identified 1 SD and 2 PDs among 3 patients with RET-rearranged NSCLC treated with vandetanib[151]. Multiple case reports have also reported varying degrees of clinical benefit for patients with RET-rearranged lung cancer following treatment with vandetanib[152-156,421] . In a Phase 1 study of vandetanib combined with the mTOR inhibitor everolimus, clinical benefit was observed for 6/6 patients with RET-fusion-positive NSCLC, including 5/6 PRs[422]. This combination has also demonstrated intracranial activity for a patient with RET-rearranged NSCLC and brain metastases[159]. Several Phase 3 studies did not demonstrate significant efficacy of vandetanib for genomically unselected patients with advanced non-small cell lung cancer (NSCLC). Vandetanib alone or added to chemotherapy did not significantly improve OS compared with placebo[423-427] , and vandetanib monotherapy as second-line treatment was not superior to erlotinib (PFS of 2.6 vs. 2.0 months; OS of 6.9 vs. 7.8 months)[428]. Phase 2 trials of vandetanib as maintenance therapy after platinum-doublet chemotherapy reported longer median PFS compared with placebo, although the PFS in 1 study did not exceed the historical control (4.5 vs. 4.6 months)[429-430] .

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.

Electronically signed by Erik Williams, M.D. | 28 October 2021
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ORDERED TEST # ORD-1209834-01

CLINICAL TRIALS

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
exon 19 deletion (E746_A750del)

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. Clinical data suggest that RET rearrangements may confer reduced sensitivity to osimertinib in EGFR-mutated NSCLC.

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)

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)

NCT03720873

PHASE 2

EGFR-TKIs Combine With Anlotinib as First-line Treatment for Patients With Advanced EGFR Mutation-positive NSCLC

TARGETS
EGFR, FGFRs, KIT, VEGFRs

LOCATIONS: Fuzhou (China)

NCT04058704

PHASE 3

A Study to Determine the Efficiency For Brain Metastasis NSCLC Patients Treated With Icotinib Alone or Combined With Radiation Therapy

TARGETS
EGFR

LOCATIONS: Hangzhou (China)

NCT04770688

PHASE 1/2

Advanced Lung Tumor Treated by Osimertinib Plus Anlotinib

TARGETS
EGFR

LOCATIONS: Shanghai (China)

GENE
RET

ALTERATION
ANKRD26-RET fusion

RATIONALE
RET amplification, activating mutations, or activating fusions may confer sensitivity to kinase inhibitors targeting RET. Clinical data suggest that RET rearrangements may confer reduced sensitivity to osimertinib in EGFR-mutated NSCLC.

NCT03157128

PHASE 1/2

Phase 1 Study of LOXO-292 in Patients With Advanced Solid Tumors, RET-Fusion Lung Cancer and Medullary Thyroid Cancer

TARGETS
RET

LOCATIONS: Taipei (Taiwan), Taichung (Taiwan), Hong Kong (Hong Kong), Fukuoka (Japan), Seongnam (Korea, Republic of), Seoul (Korea, Republic of), Goyang-si (Korea, Republic of), Okayama (Japan), Yonago (Japan), Akashi (Japan)

NCT03780517

PHASE 1

Safety, Efficacy, and Tolerability of BOS172738 in Patients With Advanced Rearranged During Transfection (RET) Gene-Altered Tumors

TARGETS
RET

LOCATIONS: Taipei (Taiwan), Taichung (Taiwan), Hong Kong (Hong Kong), Cheongju-si (Korea, Republic of), Gyeonggi-do (Korea, Republic of), Seoul (Korea, Republic of), Leuven (Belgium), Bruxelles (Belgium), Paris (France), Villejuif (France)

NCT04716933

PHASE 3

Safety and Efficacy Study of Pemetrexed + Platinum Chemotherapy + Pembrolizumab (MK-3475) With or Without Lenvatinib (MK-7902/E7080) as First-line Intervention in Adults With Metastatic Nonsquamous Non-small Cell Lung Cancer (MK-7902-006/E7080-G000-315/LEAP-006)-China Extension Study

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

LOCATIONS: Fuzhou (China), Wen Zhou (China), Hangzhou (China), Shanghai (China), Guangzhou (China), Wuhan (China), Zhengzhou (China), Chongqing (China), Tianjin (China), Beijing (China)

NCT04676412

PHASE 3

Efficacy and Safety Study of Pembrolizumab (MK-3475) With or Without Lenvatinib (MK-7902/E7080) in Adults With Programmed Cell Death-Ligand 1 (PD-L1)-Positive Treatment-naïve Non-small Cell Lung Cancer (NSCLC) [MK-7902-007/E7080-G000-314/LEAP-007] - China Extension Study

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

LOCATIONS: Hangzhou (China), Shanghai (China), Nanjing (China), Hefei (China), Changsha (China), Beijing (China), Chang chun (China)

NCT02450123

PHASE NULL

Single-arm Study to Evaluate the Safety and Efficacy of Sunitinib, in Subjects With RET Fusion Positive or FGFR2 Amplification, Refractory Solid Tumors

TARGETS
CSF1R, FLT3, KIT, RET, VEGFRs

LOCATIONS: Seoul (Korea, Republic of)

NCT02691793

PHASE 4

Study to Evaluate the Safety and Efficacy of Sunitinib, in Subject With Refractory Solid Tumors

TARGETS
CSF1R, FLT3, KIT, RET, VEGFRs

LOCATIONS: Seoul (Korea, Republic of)

ORDERED TEST # ORD-1209834-01

CLINICAL TRIALS

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT03564691

PHASE 1

Study of MK-4830 as Monotherapy and in Combination With Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-4830-001)

TARGETS
ITL4, FGFRs, KIT, PDGFRA, RET, VEGFRs, PD-1

LOCATIONS: Seoul (Korea, Republic of), Tokyo (Japan), Haifa (Israel), Petah Tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Warszawa (Poland), Gdansk (Poland), Heraklion (Greece), Washington

NCT04008797

PHASE 1

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

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

LOCATIONS: Osakasayama (Japan), Chuo-Ku (Japan), Kashiwa (Japan)

NCT04200404

PHASE 1/2

A Study of CS1001 in Subjects With Advanced or Refractory Solid Tumors

TARGETS
BRAF, KIT, RET, VEGFRs, PD-L1

LOCATIONS: Kurralta Park (Australia)

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.

ATR
P1438T

CARD11
amplification

CTNNA1
P602A

ERCC4
N738K

FGF10
amplification

IDH1
P149L

MSH6
G355S

NOTCH1
I567V and R912Q

PMS2
amplification

RAC1
amplification

RICTOR
amplification

SDHA
amplification

SNCAIP
amplification

Electronically signed by Erik Williams, M.D. | 28 October 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
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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. The MSI-H/MSS designation by FMI F1CDx test is based on genome wide analysis of 95 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines. The threshold for MSI-H/MSS was determined by analytical concordance to comparator assays (IHC and PCR) using uterine, cecum and colorectal cancer FFPE tissue. The clinical validity of the qualitative MSI designation has not been established. For Microsatellite Instability (MSI) results, confirmatory testing using a validated orthogonal method should be considered.
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%.

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

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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 5.0.0

The median exon coverage for this sample is 568x

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