

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 non-small cell lung carcinoma (NOS)

DATE OF BIRTH 05 November 1947

SEX Female

MEDICAL RECORD # Not given

PHYSICIAN

MEDICAL FACILITY Oncologia Patologica

ADDITIONAL RECIPIENT None

MEDICAL FACILITY ID 320946

PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN SITE Lung

SPECIMEN ID 21-3886 (21-9127)

SPECIMEN TYPE Block

DATE OF COLLECTION 12 March 2021

SPECIMEN RECEIVED 14 April 2021

Sensitivity for the detection of copy number alterations is reduced due to sample quality.

Biomarker Findings

Microsatellite status - MS-Stable

Tumor Mutational Burden - 1 Muts/Mb

Genomic Findings

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

EGFR L861Q, R776C

TP53 K305fs*40

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

5 Therapies with Clinical Benefit

10 Clinical Trials

0 Therapies with Lack of Response

BIOMARKER FINDINGS

Microsatellite status - MS-Stable

Tumor Mutational Burden - 1 Muts/Mb

GENOMIC FINDINGS

EGFR - L861Q, R776C

10 Trials see p. 8

ACTIONABILITY

No therapies or clinical trials. see Biomarker Findings section

No therapies or clinical trials. see Biomarker Findings section

THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)

Afatinib

Dacomitinib

Erlotinib

Gefitinib

Osimeertinib

THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)

none

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIALS OPTIONS

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

TP53 - K305fs*40 p. 4

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.

ORDERED TEST # ORD-1069541-01

BIOMARKER FINDINGS

BIOMARKER

Microsatellite status

RESULT

MS-Stable

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors¹⁻³, including approved therapies nivolumab and pembrolizumab⁴. 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 studies⁶⁻¹¹, whereas data on the reported incidence of MSI-H in SCLC has been limited and conflicting¹²⁻¹⁵. 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 studies⁶. The prognostic implications of MSI in NSCLC have not been extensively studied (PubMed, Oct 2020).

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 tumor¹⁶. 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 PMS2¹⁶⁻¹⁸. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers¹⁹⁻²¹. 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

1 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1²²⁻²⁴, anti-PD-1 therapies²²⁻²⁵, and combination nivolumab and ipilimumab²⁶⁻³⁰. 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)^{22-23,26-28,31-38}. Improved OS of patients with NSCLC treated with pembrolizumab plus

chemotherapy relative to chemotherapy only³⁹, or those treated with nivolumab plus ipilimumab also relative to chemotherapy⁴⁰, 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/Mb⁴¹. 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 cases⁴². Although some studies have reported a lack of association between smoking and mutational burden in NSCLC⁴³⁻⁴⁴, several other large studies did find a strong association with increased TMB⁴⁵⁻⁴⁸. 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%) subtypes⁴⁹. 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)⁴³.

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 adenocarcinoma⁵⁰. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC⁵⁰⁻⁵¹.

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 melanoma⁵²⁻⁵³ and cigarette smoke in lung cancer^{31,54}, treatment with temozolomide-based chemotherapy in glioma⁵⁵⁻⁵⁶, mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes⁵⁷⁻⁶¹, and microsatellite instability (MSI)^{57,60-61}. 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^{22-23,26-28,31-38,62}.

ORDERED TEST # ORD-1069541-01

GENOMIC FINDINGS

GENE

EGFR

ALTERATION

L861Q, R776C

TRANSCRIPT ID

NM_005228, NM_005228

CODING SEQUENCE EFFECT

2582T>A, 2326C>T

VARIANT ALLELE FREQUENCY (% VAF)

28.2%, 29.1%

POTENTIAL TREATMENT STRATEGIES

For patients with non-small cell lung cancer, EGFR activating mutations may predict sensitivity to EGFR TKIs, including erlotinib⁶³, gefitinib⁶⁴, afatinib⁶⁵, dacomitinib⁶⁶, and osimertinib⁶⁷; however, the data for patients with other tumor types are limited⁶⁸⁻⁷³. Third-generation EGFR inhibitors, such as osimertinib, selectively target mutated EGFR, including EGFR T790M^{67,74}. Osimertinib achieved a 61% ORR for T790M-positive cases and a 21% ORR for T790M-negative cases⁶⁷. In a Phase 1 study, the third-generation EGFR inhibitor alflutinin achieved a 77% ORR for the dose expansion cohort, as well as a CNS ORR of 58.8% (10/17) for patients with T790M-positive non-small cell lung cancer (NSCLC)⁷⁵. Resistance to EGFR inhibition may arise by reactivation of the MAPK pathway, and preclinical evidence suggests that co-targeting EGFR and MAPK signaling may impede the development of acquired resistance to third-generation EGFR inhibitors⁷⁶⁻⁷⁸. A Phase 1 trial combining third-generation EGFR inhibitor lazertinib with the EGFR/MET bispecific antibody amivantamab for EGFR-mutated NSCLC elicited an ORR of 35.6% (16/45) for the osimertinib-resistant, chemotherapy-naïve cohort, as well as an ORR of 100% (20/20) for the treatment-naïve cohort⁷⁹. Necitumumab is an anti-EGFR antibody that is approved to treat metastatic squamous NSCLC in combination with gemcitabine and cisplatin⁸⁰⁻⁸¹ that has also shown benefit in patients with CRC and melanoma⁸²⁻⁸³. Irreversible EGFR inhibitors, as well as HSP90 inhibitors, may be appropriate for patients with de novo or acquired resistance to EGFR-targeted therapy⁸⁴⁻⁸⁷. Preclinical studies have reported that EGFR-mutant cells⁸⁴⁻⁸⁶, including cells with exon 20 insertions⁸⁸, are sensitive to HSP90 inhibitors. In a Phase 1 trial, the HER3-targeted antibody patritumab

deruxtecan elicited an ORR of 25% (14/56) and a DCR of 69.6% (39/56) for patients with non-small cell lung cancer (NSCLC) previously treated with an EGFR TKI and platinum-based chemotherapy, many of whom displayed TKI resistance alterations⁸⁹. Consistent with preclinical data demonstrating that the EGFR inhibitor AZD3759 is capable of penetrating the blood-brain barrier and reducing the volume of brain and leptomeningeal metastases, preliminary results from a Phase 1 trial evaluating single-agent AZD3759 reported a reduction in the volume of brain metastases in 40.0% (8/20) of patients with previously treated NSCLC harboring either EGFR L858R or EGFR exon 19 deletion, including 3 confirmed PRs and 3 unconfirmed PRs⁹⁰⁻⁹¹. In a Phase 1/2 trial for advanced NSCLC, the brain-penetrant third-generation EGFR TKI lazertinib enabled ORRs of 54.3% (69/127) for all evaluable patients and 44.4% (8/18, intracranial) for patients with brain metastases⁹². The reovirus Reolysin targets cells with activated RAS signaling⁹³⁻⁹⁵ and is in clinical trials in patients with some tumor types. Reolysin has demonstrated mixed clinical efficacy, with the highest rate of response reported for patients with head and neck cancer⁹⁶⁻¹⁰⁴. The role of EGFR or KRAS mutations as biomarkers for response to Reolysin in NSCLC is unclear¹⁰⁵. The Phase 3 IMPower150 study showed that the addition of atezolizumab to bevacizumab plus chemotherapy treatment also had clinical efficacy in patients with untreated EGFR-mutated or ALK-rearranged metastatic NSCLC¹⁰⁶; therefore, the patient's clinical context should be considered.

FREQUENCY & PROGNOSIS

EGFR mutation has been reported in 12-36% of lung adenocarcinomas^{47,107-108} and in 4% of lung squamous cell carcinomas¹⁰⁹. EGFR protein expression/overexpression has been reported in up to 70% of NSCLC cases¹¹⁰⁻¹¹⁵. In addition, expression of EGFR protein has been shown to be higher in lung squamous cell carcinoma samples as compared to lung adenocarcinoma¹¹⁶⁻¹¹⁷. 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)¹¹⁸. In patients with lung adenocarcinoma, EGFR mutation was a predictor of poor overall survival¹¹⁹⁻¹²⁰. However, EGFR mutations have been reported to predict improved

survival in patients with resected Stage 1-3 lung adenocarcinoma¹²¹ or resected Stage 1 NSCLC¹²². Nuclear expression of EGFR in NSCLC has been reported to associate with higher disease stage, shorter progression-free survival, and shorter overall survival¹²³.

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 divide¹²⁴. EGFR R776 mutations, including R776C, G, H and S, have been reported in the context of lung cancer, and have exclusively been reported in the presence of additional, known, activating mutations¹²⁵⁻¹³⁰. R776H compound activating mutations, including L858R and G719S, have demonstrated sensitivity to gefitinib and erlotinib in patients with non-small cell lung cancer (NSCLC), whereas another patient with R776H and L861Q had stable disease following gefitinib treatment^{128,130-131}. In preclinical studies, R776C was shown to be transforming and was sensitive to erlotinib and moderately sensitive to gefitinib¹²⁹. NSCLC patients with R776C and R776S in the presence of additional activating mutations have also responded to erlotinib^{127,130}. One NSCLC patient with L858R and R776G had progressive disease following gefitinib treatment¹²⁸. EGFR mutations affecting amino acids E709, G719, or L861 and EGFR S768I are uncommon activating mutations¹³²⁻¹³⁹ that often occur as compound mutations and predict sensitivity to EGFR tyrosine kinase inhibitors based on substantial clinical data in non-small cell lung cancer (NSCLC)^{128,130,134,140-147}. EGFR G719 mutations or S768I were associated with a response rate (RR) of 78-100% to afatinib¹⁴¹ and 33-53% to erlotinib or gefitinib^{134,145-146}, whereas EGFR exon 21 L861 mutations were associated with an RR of 56% to afatinib¹⁴¹ and 40-60% to erlotinib or gefitinib¹⁴⁵⁻¹⁴⁶. Patients with EGFR G719 or E709 mutations treated with EGFR TKI had a median overall survival of 22 months¹⁴⁷. Patients with EGFR E709 mutations and concurrent G719 or L858R activating mutations had an RR of 67% to erlotinib or gefitinib¹³⁴. Out of 4 patients with the E709_T710>D mutation, one patient achieved a partial response and two patients had stable disease on erlotinib or gefitinib, with one of those two experiencing tumor shrinkage in response to afatinib^{134,145,148}.

ORDERED TEST # ORD-1069541-01

GENOMIC FINDINGS

GENE

TP53

ALTERATION

K305fs*40

TRANSCRIPT ID

NM_000546

CODING SEQUENCE EFFECT

914delA

VARIANT ALLELE FREQUENCY (% VAF)

16.6%

POTENTIAL TREATMENT STRATEGIES

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 adavosertib¹⁴⁹⁻¹⁵², or p53 gene therapy and immunotherapeutics such as SGT-53¹⁵³⁻¹⁵⁷ and ALT-801¹⁵⁸. 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) in patients with TP53 mutations versus 12.1% (4/33) in patients who were TP53 wild-type¹⁵⁹. 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 in patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer¹⁶⁰. 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 in patients with platinum-refractory TP53-mutated ovarian cancer¹⁶¹. The combination of adavosertib with paclitaxel and carboplatin in patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone¹⁶². 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

paclitaxel¹⁶³. 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 alterations¹⁶⁴. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel in 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 shrinkage¹⁵⁷. 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 model¹⁶⁵. 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 studies¹⁶⁶⁻¹⁶⁷; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies¹⁶⁸⁻¹⁶⁹. 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)^{108-109,170-175}, including 42-52% of lung adenocarcinomas and 58-83% of lung squamous cell carcinomas (cBioPortal, COSMIC, Feb 2021)^{47-48,108-109}. TP53 homozygous deletion has been observed in 1.4% of lung adenocarcinoma and <1% of lung squamous cell carcinoma cases (cBioPortal, Feb 2021)¹⁷⁶⁻¹⁷⁷. 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 study¹⁷⁸. Mutations in TP53 have been

associated with lymph node metastasis in patients with lung adenocarcinoma¹⁷⁹.

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers¹⁸⁰. Alterations such as seen here may disrupt TP53 function or expression¹⁸¹⁻¹⁸⁵.

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 cancers¹⁸⁶⁻¹⁸⁸, including sarcomas¹⁸⁹⁻¹⁹⁰. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000¹⁹¹ to 1:20,000¹⁹⁰. 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 30¹⁹². 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 expansion¹⁹³⁻¹⁹⁸. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy¹⁹³⁻¹⁹⁴. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease¹⁹⁹. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH^{197,200-201}. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

ORDERED TEST # ORD-1069541-01

THERAPIES WITH CLINICAL BENEFIT

IN PATIENT'S TUMOR TYPE

Afatinib

Assay findings association

EGFR

L861Q, R776C

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^{65-66,202-203}, whereas data for patients with other tumor types are limited^{68-73,204}.

SUPPORTING DATA

Afatinib has shown clinical activity for patients with NSCLC harboring EGFR uncommon sensitizing mutations. A Phase 2 study assessing first-line afatinib for patients with NSCLC unfit for chemotherapy and rare EGFR mutations in exons 18 or 20 (n=8) reported median PFS of 3.9 months and median OS of 5.7 months²⁰⁵. In a post-hoc analysis of several Phase 2 and Phase 3 trials of afatinib, patients with NSCLC harboring EGFR uncommon sensitizing mutations (alone or in combination with other alterations) had ORRs of 77.8% (14/18) for those with G719 mutations, 56.3% (9/16) for those with L861Q mutations, and 100% (8/8) for those with S768I mutations¹⁴¹. Two large-scale retrospective studies of NSCLC with EGFR uncommon sensitizing mutations reported ORRs of 60% for TKI-naïve patients²⁰⁶⁻²⁰⁷, and in one study, an ORR of 25.0% (8/32) for TKI-pretreated patients²⁰⁶. 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 42.9% (3/7) for patients with the uncommon

sensitizing mutations L861Q, S768I, or G719X, and an ORR of 24.4% (105/431) for the entire cohort²⁰⁸. In case reports of NSCLC with the exon 18 uncommon sensitizing mutation E709_T710>D, 2 patients achieved PRs with afatinib monotherapy²⁰⁹ or afatinib combined with bevacizumab²¹⁰, respectively; 2 additional patients experienced tumor shrinkage and clinical benefit from afatinib monotherapy^{134,211}. In case reports, an elderly patient with L861Q-mutated metastatic lung adenocarcinoma experienced a PR²¹² and a patient with L719A-mutated leptomeningeal metastasis experienced ongoing 7-month PFS²¹³ from afatinib. 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%^{141,214-218}; however, DCRs of more than 50% have been observed²¹⁸. 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 cetuximab²¹⁹ or osimertinib²²⁰, 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^{65,202,205,208,221-223}. Afatinib has also shown activity for patients with advanced NSCLC and ERBB2 mutations, most of which were exon 20 insertions^{218,224-234}. 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 afatinib²²². For patients who progressed on afatinib monotherapy, additional clinical benefit has been reported from afatinib combined with paclitaxel²³⁵.

ORDERED TEST # ORD-1069541-01

THERAPIES WITH CLINICAL BENEFIT

IN PATIENT'S TUMOR TYPE

Dacomitinib

Assay findings association

EGFR

L861Q, R776C

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^{65-66,202-203}, whereas data for patients with other tumor types are limited^{68-73,204}.

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)²³⁶⁻²³⁷; median OS was 34.1 to 36.7 months and ORR was 74.9% to 79.3%, depending on the dosing regimen²³⁸. 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)²³⁹. Reduced efficacy of dacomitinib treatment in patients with NSCLC harboring the EGFR T790M mutation has been reported in multiple studies²⁴⁰⁻²⁴². 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 population²⁴³. 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)²⁴¹. In one study, the combination of dacomitinib and crizotinib was ineffective and associated with high toxicity in patients with NSCLC²⁴⁴.

Erlotinib

Assay findings association

EGFR

L861Q, R776C

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^{63,245-247}. A retrospective study has shown that gefitinib and erlotinib are less effective in lung adenocarcinoma patients with EGFR L861Q, S768I, or alterations at G719, as compared to patients with EGFR L858R or EGFR exon 19 deletions¹⁴⁶.

SUPPORTING DATA

For patients with EGFR-mutated NSCLC, the Phase 3 EORTC trial reported improved PFS with first-line erlotinib relative to platinum-based chemotherapy (9.7 vs. 5.2 months, HR=0.37)⁶³. A Phase 3 study reported similar efficacy of erlotinib and gefitinib for patients with EGFR-

mutated NSCLC²⁴⁸. 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 therapy²⁴⁹. 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)²⁴⁵. 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 NSCLC²⁴⁶. 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)²⁵⁰. In a Phase 2 trial, no clinical benefit was observed from the addition of bevacicumab to erlotinib for patients with NSCLC harboring EGFR exon 19 deletion or L858R mutation²⁵¹. The Phase 3 BR.21 trial demonstrated prolonged OS for genomically unselected patients with NSCLC treated with erlotinib compared with those treated with standard chemotherapy²⁵².

ORDERED TEST # ORD-1069541-01

THERAPIES WITH CLINICAL BENEFIT

IN PATIENT'S TUMOR TYPE

Gefitinib

Assay findings association

EGFR

L861Q, R776C

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^{247,253-258}, and responses have been reported for patients with EGFR-rearranged NSCLC²⁵⁹⁻²⁶⁰. A retrospective study has shown that gefitinib and erlotinib are less effective in lung adenocarcinoma patients with EGFR L861Q, S768I, or alterations at G719, as compared to patients with EGFR L858R or EGFR exon 19 deletions¹⁴⁶.

SUPPORTING DATA

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 mutations⁶⁴. 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^{256,261}. 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 events²⁶²⁻²⁶³. 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 mutations²⁶⁴. In a Phase 1 study for treatment-naïve 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 monotherapy²⁶⁵.

Osimertinib

Assay findings association

EGFR

L861Q, R776C

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^{67,74,259,266-267}.

SUPPORTING DATA

The Phase 3 FLAURA study reported that, relative to erlotinib or gefitinib, first-line osimertinib significantly increased both median PFS (mPFS; 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 non-small cell lung cancer (NSCLC) and activating, sensitizing EGFR mutations (specifically, exon 19 deletion or L858R)^{74,268}. In the Phase 3 ADAURA study, patients with early-stage EGFR-mutated NSCLC receiving adjuvant osimertinib experienced both

longer disease-free survival (DFS; not reached vs. 19.6 months, HR=0.17) and central nervous system DFS (not reached vs. 48.2 months, HR=0.18) than those receiving placebo²⁶⁹. A Phase 1 study reported that T790M-negative patients with acquired EGFR TKI resistance experienced an ORR of 21% and mPFS of 2.8 months⁶⁷. A Phase 2 study of osimertinib for EGFR-TKI-naïve patients with metastatic or recurrent NSCLC and uncommon EGFR mutations reported a 50.0% (18/36) ORR and an 88.9% (32/36) DCR with a median PFS of 8.2 months and a median duration of response of 11.2 months; patients harboring L861Q, G719X, or S768I mutations had ORRs of 77.8% (7/9), 52.6% (10/19), and 37.5% (3/8), respectively²⁷⁰. 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%²⁷¹. 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), respectively²⁷².

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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Electronically signed by Eric Severson, M.D., Ph.D., M.M.Sc. | 21 May 2021
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Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531

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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](https://www.foundationmedicine.com/genomic-testing#support-services). Or visit <https://www.foundationmedicine.com/genomic-testing#support-services>.

GENE **EGFR**

ALTERATION
L861Q, R776C

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.

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: Milano (Italy), Ravenna (Italy), Gauting (Germany), Stuttgart (Germany), Lyon Cedex 8 (France), Marseille (France), Napoli (Italy), Halle (Saale) (Germany), Hemer (Germany), Saint Mande (France)

NCT03944772

PHASE 2

Phase 2 Platform Study in Patients With Advanced Non-Small Lung Cancer Who Progressed on First-Line Osimertinib Therapy (ORCHARD)

TARGETS
EGFR, MET, PD-L1

LOCATIONS: Maastricht (Netherlands), Nijmegen (Netherlands), Barcelona (Spain), Rotterdam (Netherlands), Amsterdam (Netherlands), Odense C (Denmark), Vejle (Denmark), Herlev (Denmark), Madrid (Spain), A Coruña (Spain)

NCT02609776

PHASE 1

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

TARGETS
MET, EGFR

LOCATIONS: Lyon Cedex 8 (France), Dijon (France), Marseille (France), Villejuif Cedex (France), Paris (France), Barcelona (Spain), Bordeaux (France), Saint-Herblain Cedex (France), Sutton (United Kingdom), Manchester (United Kingdom)

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: Marseille CEDEX 05 (France), Massachusetts, New York, New Jersey, Virginia, Michigan, Illinois, Tennessee, Colorado, Texas

NCT03810066

PHASE 2

Exploring the Theragnostic Value of Osimertinib in EGFR-mutated Lung Cancer (THEROS)

TARGETS
EGFR

LOCATIONS: Essen (Germany)

ORDERED TEST # ORD-1069541-01

CLINICAL TRIALS
NCT03804580
PHASE 2

First-line Treatment With Osimertinib in EGFR-mutated Non-small Cell Lung Cancer, Coupled to Extensive Translational Studies

TARGETS
EGFR

LOCATIONS: Odense (Denmark), Copenhagen (Denmark), Aarhus (Denmark), Vilnius (Lithuania), Drammen (Norway), Oslo (Norway), Stockholm (Sweden), Trondheim (Norway)

NCT02664935
PHASE 2

National Lung Matrix Trial: Multi-drug Phase II Trial in Non-Small Cell Lung Cancer

TARGETS
FGFRs, mTORC1, mTORC2, CDK4, CDK6, ALK, AXL, MET, ROS1, TRKA, TRKC, MEK, AKTs, EGFR, PD-L1, DDR2, FLT3, KIT, PDGFRA, RET, TRKB, VEGFRs

LOCATIONS: Maidstone (United Kingdom), Colchester (United Kingdom), London (United Kingdom), Cambridge (United Kingdom), Southampton (United Kingdom), Oxford (United Kingdom), Leicester (United Kingdom), Bristol (United Kingdom), Birmingham (United Kingdom), Exeter (United Kingdom)

NCT02183883
PHASE 2

Deciphering Afatinib Response and Resistance With INtratumour Heterogeneity

TARGETS
EGFR, ERBB2, ERBB4

LOCATIONS: London (United Kingdom), London Borough Of Barnet (United Kingdom), Birmingham (United Kingdom), Manchester (United Kingdom), Glasgow (United Kingdom), Aberdeen (United Kingdom)

NCT02736513
PHASE 2

Intracranial Activity of AZD9291 (TAGRISSO) in Advanced EGFRm NSCLC Patients With Asymptomatic Brain Metastases

TARGETS
EGFR

LOCATIONS: Petach Tikva (Israel), Be'er Sheva (Israel)

NCT03137771
PHASE 2

Maintenance Chemotherapy With or Without Stereotactic Body Radiation Therapy in Treating Patients With Stage IV Non-small Cell Lung Cancer

TARGETS
EGFR, PD-1

LOCATIONS: Tel Hashomer (Israel), New Hampshire, Vermont, Massachusetts, Ottawa (Canada), New York

ORDERED TEST # ORD-1069541-01

APPENDIX
Variants of Unknown Significance

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.

FGFR3
splice site 1413-2A>G

NSD3 (WHSC1L1)
Q141E

RARA
C235W

TSC1
K587R

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APPENDIX
Genes Assayed in FoundationOne®CDx

FoundationOne CDx is designed to include genes known to be somatically altered in human solid tumors that are validated targets for therapy, either approved or in clinical trials, and/or that are unambiguous drivers of oncogenesis based on current knowledge. The current assay interrogates 324 genes as well as introns of 36 genes involved in rearrangements. The assay will be updated periodically to reflect new knowledge about cancer biology.

DNA GENE LIST: ENTIRE CODING SEQUENCE FOR THE DETECTION OF BASE SUBSTITUTIONS, INSERTION/DELETIONS, AND COPY NUMBER ALTERATIONS

ABL1	ACVR1B	AKT1	AKT2	AKT3	ALK	ALOX12B	AMER1 (FAM123B)	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
BTB	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	ERRF1	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	FOXO2	FUBP1	GABRA6	GATA3
GATA4	GATA6	GNAI1	GNAI3	GNAQ	GNAS	GRM3	GSK3B	H3F3A
HDAC1	HGF	HNF1A	HRAS	HSD3B1	ID3	IDH1	IDH2	IGF1R
IKBKE	IKZF1	INPP4B	IRF2	IRF4	IRS2	JAK1	JAK2	JAK3
JUN	KDMSA	KDMS5C	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	NFKB1A	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	SOC3
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	RSP02	SDC4	SLC34A2	TERC*	TERT**	TMPS2

*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)

ORDERED TEST # ORD-1069541-01

APPENDIX
About FoundationOne®CDx

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.


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 Alterations and Therapies
Biomarker and Genomic Findings

Therapies are ranked based on the following criteria: Therapies with clinical benefit in patient's tumor type (ranked alphabetically within each NCCN category) followed by therapies with clinical benefit in other tumor type (ranked alphabetically within each NCCN category).

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.

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APPENDIX

About FoundationOne®CDx

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	
Repeatability	5.11 - 10.40
Reproducibility	5.95 - 12.31
INDELS	
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.

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.

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APPENDIX

About FoundationOne®CDx

SELECT ABBREVIATIONS

ABBREVIATION	DEFINITION
CR	Complete response
DCR	Disease control rate
DNMT	DNA methyltransferase
HR	Hazard ratio
ITD	Internal tandem duplication
MMR	Mismatch repair
mut/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 4.0.0

The median exon coverage for this sample is 1,187x

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APPENDIX

References

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