

ABOUT THE TEST FoundationOne®Liquid CDx is a next generation sequencing (NGS) assay that identifies clinically relevant genomic alterations in circulating cell-free DNA.

| | | | | | | | | |
|---------|------------------|---------------------|-----------|----------------------|----------------------------------|----------|--------------------|---------------|
| PATIENT | DISEASE | Lung adenocarcinoma | PHYSICIAN | ORDERING PHYSICIAN | Yeh, Yi-Chen | SPECIMEN | SPECIMEN ID | CML 6/26/1961 |
| | NAME | Lin, Chung-Mao | | MEDICAL FACILITY | Taipei Veterans General Hospital | | SPECIMEN TYPE | Blood |
| | DATE OF BIRTH | 26 June 1961 | | ADDITIONAL RECIPIENT | None | | DATE OF COLLECTION | 09 May 2022 |
| | SEX | Male | | MEDICAL FACILITY ID | 205872 | | SPECIMEN RECEIVED | 12 May 2022 |
| | MEDICAL RECORD # | 30120833 | | PATHOLOGIST | Not Provided | | | |

Biomarker Findings

Blood Tumor Mutational Burden - 3 Muts/Mb
Microsatellite status - MSI-High Not Detected
Tumor Fraction - Elevated Tumor Fraction Not Detected

Genomic Findings

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

EGFR T790M, L858R

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Osimertinib** (p. 6)
- Targeted therapies with **potential resistance** based on this patient's genomic findings: **Afatinib** (p. 7), **Dacomitinib** (p. 8), **Erlotinib** (p. 9), **Gefitinib** (p. 9)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 11)

BIOMARKER FINDINGS

Blood Tumor Mutational Burden
- 3 Muts/Mb

Microsatellite status
- MSI-High Not Detected

Tumor Fraction
- Elevated Tumor Fraction Not Detected

THERAPY AND CLINICAL TRIAL IMPLICATIONS

No therapies or clinical trials. See Biomarker Findings section

MSI-High not detected. No evidence of microsatellite instability in this sample (see Appendix section).

Tumor fraction is considered elevated when ctDNA levels are high enough that aneuploidy can be detected. The fact that elevated tumor fraction was not detected in this specimen indicates the possibility of lower levels of ctDNA but does not compromise confidence in any reported alterations. However, in the setting of a negative liquid biopsy result, orthogonal testing of a tissue specimen should be considered if clinically indicated (see Biomarker Findings section).

GENOMIC FINDINGS

VAF %

EGFR - T790M 0.24%
L858R 0.61%

10 Trials see p. 11

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

Osimertinib 1
Afatinib ×
Dacomitinib ×
Erlotinib ×
Gefitinib ×

THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)

None

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

□ NCCN category

NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the therapies listed in this report may have varied clinical evidence in the patient's tumor type. Therapies and the

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clinical trials listed in this report may not be complete and/or exhaustive. Neither the therapies 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 or other national authorities; however, they might not have been approved in your respective country. In the appropriate clinical context, germline testing of *APC*, *ATM*, *BAP1*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *FH*, *FLCN*, *MEN1*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *NF1*, *NF2*, *PALB2*, *PMS2*, *POLE*, *PTEN*, *RAD51C*, *RAD51D*, *RB1*, *RET*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, *SMAD4*, *STK11*, *TGFBR2*, *TP53*, *TSC1*, *TSC2*, *VHL*, and *WT1* is recommended.

Variant Allele Frequency is not applicable for copy number alterations.

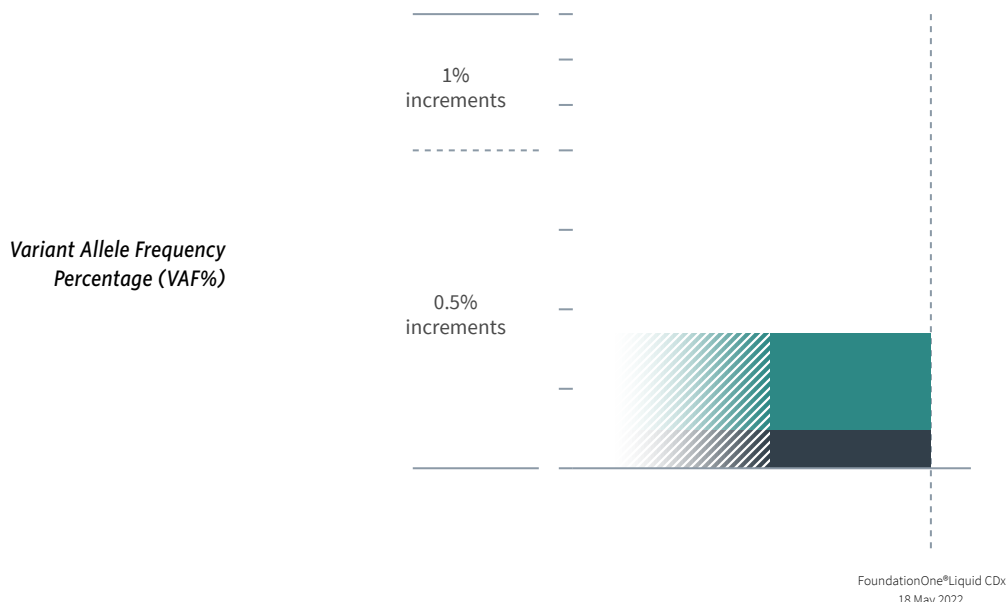
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ORDERED TEST # ORD-1362450-01



HISTORIC PATIENT FINDINGS

ORD-1362450-01
VAF%

Blood Tumor Mutational Burden

3 Muts/Mb

Microsatellite status

MSI-High Not Detected

Tumor Fraction

Elevated Tumor Fraction Not Detected

EGFR

● T790M

0.24%

● L858R

0.61%

NOTE This comparison table refers only to genes and biomarkers assayed by prior FoundationOne®Liquid CDx, FoundationOne®Liquid, FoundationOne®, or FoundationOne®CDx tests. Up to five previous tests may be shown.

For some genes in FoundationOne Liquid CDx, only select exons are assayed. Therefore, an alteration found by a previous test may not have been confirmed despite overlapping gene lists. Please refer to the Appendix for the complete list of genes and exons assayed. The gene and biomarker list will be updated periodically to reflect new knowledge about cancer biology.

As new scientific information becomes available, alterations that had previously been listed as Variants of Unknown Significance (VUS) may become reportable.

Tissue Tumor Mutational Burden (TMB) and blood TMB (bTMB) are estimated from the number of synonymous and non-synonymous single-nucleotide variants (SNVs) and insertions and deletions (indels) per area of coding genome sampled, after the removal of known and likely oncogenic driver events and germline SNPs. Tissue TMB is calculated based on variants with an allele frequency of $\geq 5\%$, and bTMB is calculated based on variants with an allele frequency of $\geq 0.5\%$.

Not Tested = not baited, not reported on test, or test preceded addition of biomarker or gene

Not Detected = baited but not detected on test

Detected = present (VAF% is not applicable)

VAF% = variant allele frequency percentage

Cannot Be Determined = Sample is not of sufficient data quality to confidently determine biomarker status

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BIOMARKER FINDINGS

BIOMARKER

Blood Tumor Mutational Burden

RESULT

3 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in NSCLC and HSNCC, increased bTMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1¹⁻² and anti-PD-1³ therapies. In NSCLC, multiple clinical trials have shown patients with higher bTMB derive clinical benefit from immune checkpoint inhibitors following single agent or combination treatments with either CTLA4 inhibitors or chemotherapy, with reported high bTMB cutpoints ranging from 6 to 16 Muts/Mb¹. In HSNCC, a Phase 3 trial showed that bTMB ≥ 16 Muts/Mb (approximate equivalency ≥ 8 Muts/Mb as measured by this assay) was associated with improved survival from treatment with a PD-L1 inhibitor alone or in combination with a CTLA-4 inhibitor⁴.

FREQUENCY & PROGNOSIS

NSCLC harbors a median bTMB of 16.8 Muts/Mb

(range 1.9–52.5 Muts/Mb)³. Retrospective analysis of the Phase 3 OAK and Phase 2 POPLAR trials for patients with advanced or metastatic non-small cell lung cancer (NSCLC) reported that bTMB ≥ 7 Muts/Mb was associated with shorter PFS (2.8 vs. 4.2 months) and OS (7.4 vs. 11.9 months) compared with bTMB < 7 Muts/Mb for patients treated with docetaxel⁵. In one study of advanced NSCLC in China, bTMB ≥ 6 Muts/Mb was associated with decreased PFS (10 vs. 18 months) and OS (11 vs. 25 months) compared with bTMB < 6 Muts/Mb for patients treated with platinum-based chemotherapy⁶. A meta-analysis of 19 studies of immune checkpoint inhibitor-treated NSCLC (n = 2,315 patients) demonstrated that high TMB predicted a significantly longer OS than low TMB (HR = 0.70), and within the high TMB group, immunotherapy was associated with an improved PFS (HR = 0.62, $P < 0.001$), OS (HR = 0.67, $P < 0.001$) and a higher response rate (OR = 2.35, $P < 0.001$) compared to chemotherapy⁷. In contrast, a large study of Chinese patients with untreated lung adenocarcinoma reported a shorter median OS for tumors with a higher number of mutations in a limited gene set compared with a lower mutation number (48.4 vs. 61.0 months)⁸. Another study of patients with NSCLC treated with EGFR inhibitors or platinum doublet chemotherapy found elevated TMB to be correlated with poorer prognosis, as well as finding lower TMB in combination with PD-L1 negative status to be significantly associated with

longer median survival in patients with lung adenocarcinoma⁹. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC⁹⁻¹⁰.

FINDING SUMMARY

Blood tumor mutational burden (bTMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations from circulating tumor DNA in blood. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma¹¹⁻¹² and cigarette smoke in lung cancer¹³⁻¹⁴, treatment with temozolomide-based chemotherapy in glioma¹⁵⁻¹⁶, mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes¹⁷⁻²¹, and microsatellite instability (MSI)^{17,20-21}. High bTMB levels were not detected in this sample. It is unclear whether the bTMB levels in this sample would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents¹⁻³. Depending on the clinical context, TMB testing of an alternate sample or by another methodology could be considered.

BIOMARKER

Tumor Fraction

RESULT

Elevated Tumor Fraction Not Detected

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Specimens with elevated tumor fraction values have high circulating-tumor DNA (ctDNA) content, and thus high sensitivity for identifying genomic alterations. Such specimens are at low risk of false negative results. However, if elevated tumor fraction is not detected, it does not exclude the presence of disease burden or compromise the confidence of reported alterations. Tumor fraction levels currently have limited implications for diagnosis, surveillance, or therapy and should not

be overinterpreted or compared from one blood draw to another. There are currently no targeted approaches to address specific tumor fraction levels. In the research setting, changes in tumor fraction estimates have been associated with treatment duration and clinical response and may be a useful indicator for future cancer management²²⁻²⁷.

FREQUENCY & PROGNOSIS

Detectable ctDNA levels have been reported in a variety of tumor types, with higher tumor fraction levels reported for patients with metastatic (Stage 4) tumors compared with patients with localized disease (Stages 1 to 3)²⁸. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer²⁹, Ewing sarcoma and osteosarcoma³⁰, prostate cancer²⁵, breast cancer³¹, leiomyosarcoma³², esophageal cancer³³, colorectal

cancer³⁴, and gastrointestinal cancer³⁵.

FINDING SUMMARY

Tumor fraction provides an estimate of the percentage of ctDNA present in a cell-free DNA (cfDNA) sample. The tumor fraction estimate for this sample is based on the observed level of aneuploid instability. The tumor fraction algorithm utilized for FoundationOne Liquid CDx uses the allele frequencies of approximately 1,000 single-nucleotide polymorphism (SNP) sites across the genome. Unlike the maximum somatic allele frequency (MSAF) method of estimating ctDNA content³⁶, the tumor fraction metric does not take into account the allele frequency of individual variants but rather produces a more holistic estimate of ctDNA content using data from across the genome. The amount of ctDNA detected may correlate with disease burden and response to therapy³⁷⁻³⁸.

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ORDERED TEST # ORD-1362450-01

GENOMIC FINDINGS

GENE

EGFR

ALTERATION

T790M, L858R

TRANSCRIPT ID

NM_005228, NM_005228

CODING SEQUENCE EFFECT

2369C>T, 2573T>G

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

For patients with non-small cell lung cancer, EGFR activating mutations may predict sensitivity to EGFR TKIs, including erlotinib³⁹, gefitinib⁴⁰, afatinib⁴¹, dacomitinib⁴², and osimertinib⁴³; however, the data for patients with other tumor types are limited⁴⁴⁻⁴⁹. The efficacy of third-generation EGFR inhibitors that selectively target EGFR T790M in non-small cell lung cancer (NSCLC) has been confirmed in osimertinib^{43,50-53}, D-0316⁵⁴, abivertinib⁵⁵⁻⁵⁶, alflutininib⁵⁷, naquotinib⁵⁸⁻⁶¹, nazartinib⁶², and olmutinib⁶³⁻⁶⁴. 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-naïve patients and patients who relapsed after treatment with osimertinib with and without chemotherapy, including osimertinib-relapsed patients with biomarkers indicating EGFR/MET-based osimertinib resistance⁶⁵⁻⁶⁸. 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 alterations⁶⁹. 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 PRs⁷⁰⁻⁷¹. 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 metastases⁷². A Phase 1 trial evaluating the irreversible pan-HER inhibitor FCN-411 for NSCLC patients who had EGFR mutations and experienced disease progression on standard treatments reported an ORR of 15% with 10/67 patients achieving PR, and a DCR of 73% with 39 additional patients achieving SD⁷³. OR was observed in a numerically higher proportion of patients with the EGFR T790M mutation than those without this mutation⁷³.

— Potential Resistance —

The EGFR T790M mutation, when co-occurring with an EGFR activating alteration, confers clinical resistance to gefitinib⁷⁴⁻⁷⁷, erlotinib^{74-75,77}, afatinib⁷⁸⁻⁸¹, and dacomitinib^{77,82-84}. Preclinical resistance to lapatinib has also been reported⁸⁵⁻⁸⁶.

— Nontargeted Approaches —

Patients with EGFR-mutated non-squamous metastatic non-small cell lung cancer previously treated with EGFR TKI have benefited from immune checkpoint inhibitors combined with anti-angiogenic and chemotherapy, particularly atezolizumab plus bevacizumab plus carboplatin and paclitaxel (OS HR 0.61 compared with bevacizumab/chemotherapy)⁸⁷⁻⁸⁹ or sintilimab plus bevacizumab biosimilar plus cisplatin and pemetrexed (PFS HR 0.46 compared with chemotherapy alone)⁹⁰.

FREQUENCY & PROGNOSIS

EGFR mutation has been reported in 12-36% of lung adenocarcinomas⁹¹⁻⁹³ and in 4% of lung squamous cell carcinomas⁹⁴. EGFR protein expression/overexpression has been reported in up to 70% of NSCLC cases⁹⁵⁻¹⁰⁰. In addition, expression of EGFR protein has been shown to be higher in lung squamous cell carcinoma samples as compared to lung adenocarcinoma¹⁰¹⁻¹⁰². In

patients with lung adenocarcinoma, EGFR mutation was a predictor of poor overall survival¹⁰³⁻¹⁰⁴. However, EGFR mutations have been reported to predict improved survival in patients with resected Stage 1-3 lung adenocarcinoma¹⁰⁵ or resected Stage 1 NSCLC¹⁰⁶. 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)¹⁰⁷.

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 divide¹⁰⁸. EGFR L858 is located in the kinase domain and is encoded by exon 21. EGFR L858R has been characterized as activating¹⁰⁹⁻¹¹¹ and patients with the L858R mutation have been shown to be sensitive to EGFR tyrosine kinase inhibitors, such as erlotinib, gefitinib¹⁰⁹⁻¹¹¹, and afatinib¹¹². The EGFR T790M mutation, when co-occurring with EGFR activating alterations, has been associated with clinical resistance to gefitinib⁷⁴⁻⁷⁷, erlotinib^{74-75,77}, dacomitinib^{77,82-84}, and afatinib^{78-81,113}, as well as preclinical resistance to lapatinib⁸⁵⁻⁸⁶. Rare cases of EGFR T790M without a concurrent activating alteration have been reported¹¹⁴ and germline T790M mutations have been reported to predispose to familial lung adenocarcinoma¹¹⁴⁻¹¹⁶. Limited preclinical data suggests T790M alone is weakly activating, and increased EGFR activity is observed when T790M is expressed with certain activating EGFR alterations¹¹⁷. Therefore, although this alteration has not been fully characterized, it is likely to result in reduced sensitivity to first- and second-generation EGFR inhibitors.

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ORDERED TEST # ORD-1362450-01

THERAPIES WITH CLINICAL BENEFIT
IN PATIENT'S TUMOR TYPE

Osimertinib

Assay findings association

EGFR

T790M, L858R

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

EGFR TKI-sensitizing mutations or rearrangements and/or the EGFR T790M mutation may predict sensitivity to osimertinib in non-small cell lung cancer^{43,53,118-120}. 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, respectively⁵³.

SUPPORTING DATA

The Phase 3 FLAURA study reported that, relative to erlotinib or gefitinib, first-line osimertinib significantly increased both median PFS (18.9 vs. 10.2 months, HR=0.46) and median OS (38.6 vs. 31.8 months; HR=0.80) for patients with advanced NSCLC and activating, sensitizing EGFR mutations (specifically, exon 19 deletion or L858R)^{53,121}. 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)¹²². 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 months⁴³. A Phase 1b/2 study evaluating osimertinib in combination with the CD73 inhibitor oleclumab for patients with advanced EGFR-mutated, T790M-negative NSCLC reported an ORR of 19% (4/19), a DCR of 81%, and mPFS of 11 months (Kim et al., 2021 AACR Abstract CT163). In a Phase 3 study for patients

with EGFR T790M-positive advanced NSCLC who progressed on EGFR TKI therapy, osimertinib compared with combination platinum therapy led to longer median PFS (10.1 months vs. 4.4 months), including for patients with central nervous system metastases (8.5 vs. 4.2 months). An ORR of 71% was achieved with osimertinib compared to 31% with combination platinum therapy¹²³. The efficacy of osimertinib is confirmed by earlier phase studies in this setting^{43,50-52}, and in a real-world setting for patients with T790M-positive advanced NSCLC pretreated with EGFR TKIs¹²⁴⁻¹²⁵. Case studies report that 2 patients with T790M-mutated NSCLC achieved durable PRs to osimertinib rechallenge after the adverse events induced by initial osimertinib treatment had been resolved¹²⁶⁻¹²⁷. A Phase 2 trial of osimertinib in combination with bevacizumab versus osimertinib monotherapy for patients with untreated advanced non-small cell lung cancer (NSCLC) harboring EGFR del19 or L858R reported no difference in ORR (82% vs 86%) and median PFS (22.1 vs 20.2 months, HR 0.862 p=0.213)¹²⁸. The Phase 2 BOOSTER study of osimertinib in combination with bevacizumab versus osimertinib monotherapy for patients with advanced NSCLC with EGFR-sensitizing mutations (exon 19 del or L858R) and L790M at progression on prior EGFR TKI reported no difference in ORR (55% vs 55%), median OS (24.0 vs 24.3 months, HR 1.03 p=0.91), or median PFS (15.4 vs 12.3 months, HR 0.96 p=0.83), although improved PFS was observed for the combination in the subgroup of current or former smokers (16.5 vs 8.4, HR 0.52) while nonsmokers had no benefit (HR 1.47)¹²⁹. 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), respectively¹³⁰.

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ORDERED TEST # ORD-1362450-01

THERAPIES ASSOCIATED WITH RESISTANCE

IN PATIENT'S TUMOR TYPE

Afatinib

Resistance of variant(s) to associated therapy is likely

Assay findings association

EGFR

T790M, L858R

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

EGFR activating mutations may indicate sensitivity to afatinib or dacomitinib for patients with non-small cell lung cancer^{41-42,131-132}, whereas data for patients with other tumor types are limited^{44-49,133}. EGFR T790M, in the presence of a co-occurring activating EGFR alteration, has been associated with clinical resistance to afatinib and has been reported in 33-48% of patients who progressed on the inhibitor across multiple studies^{78-81,113}. Although DCRs of more than 50% have been reported for patients with erlotinib- or gefitinib-resistant NSCLC treated with afatinib¹³⁴, including T790M-positive patients¹³⁵, 1 study observed that overall survival for patients with T790M-positive NSCLC was worse than for patients who were T790M-negative (HR=1.79, p=0.005)¹³⁶.

SUPPORTING DATA

Afatinib enabled a DCR of 64.3% (9/14) for patients with advanced T790M-positive NSCLC in a post-hoc analysis of Phase 2 and Phase 3 trials¹³⁵. For T790M-positive patients who were TKI-naïve or -pretreated, afatinib treatment resulted in ORRs of 24.0% (6/25) and 18.8% (12/64), respectively, in a large-scale retrospective analysis of EGFR-mutated NSCLC¹³⁷. Another large-scale retrospective study of afatinib administered to Asian patients with NSCLC, 99% of whom were previously treated with erlotinib and/or gefitinib, reported an ORR of 21.1% (4/19) for T790M-positive patients and an ORR of 24.4% (105/431) for the entire cohort¹³⁸. For heavily pre-treated patients with erlotinib- or gefitinib-resistant NSCLC and T790M-positivity, the combination of afatinib with cetuximab enabled an ORR of 31.7% (40/126) in a Phase 1b study¹³⁹, and 1/1 PR in a case series¹⁴⁰. A patient with T790M-positive NSCLC who progressed on erlotinib experienced a PR to afatinib combined with panitumumab in another case series¹⁴¹. 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^{41,131,142-145}. 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)^{41,131}. 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 mutation¹¹². A similar alteration-specific difference was observed for EGFR-mutated treatment-naïve 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)¹⁴². 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 afatinib¹⁴³. 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 trial¹⁴⁴. 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 chemotherapy¹⁴⁵ 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 old¹⁴⁶. 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 cohort¹⁴⁷. 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 lesions¹⁴⁸. 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%^{134-135,149-152}; however, DCRs of more than 50% have been observed¹³⁴. 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 cetuximab¹⁵³ or osimertinib¹⁵⁴, 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^{41,112,131,143,145,147,155}. Afatinib has also shown activity for patients with advanced NSCLC and ERBB2 mutations, most of which were exon 20 insertions^{134,156-166}. 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

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THERAPIES ASSOCIATED WITH RESISTANCE

IN PATIENT'S TUMOR TYPE

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 afatinib¹⁵⁵. For patients who

progressed on afatinib monotherapy, additional clinical benefit has been reported from afatinib combined with paclitaxel¹⁶⁷.

Dacomitinib

✗ Resistance of variant(s) to associated therapy is likely

Assay findings association

EGFR

T790M, L858R

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

EGFR activating mutations may indicate sensitivity to afatinib or dacomitinib for patients with non-small cell lung cancer^{41-42,131-132}, whereas data for patients with other tumor types are limited^{44-49,133}. Patients with untreated advanced NSCLC and EGFR L858R mutations achieved an ORR of 73% (68/93)¹⁶⁸ and a median OS of 32.5 months with dacomitinib⁴². EGFR T790M, in the presence of a co-occurring activating EGFR alteration, is associated with clinical resistance to dacomitinib^{77,82-83,169-170}.

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)^{168,171}; median OS was 34.1 to 36.7 months and ORR was 74.9% to 79.3%, depending on the dosing regimen¹⁷². 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)¹⁷³. Reduced efficacy of dacomitinib treatment in patients with NSCLC harboring the EGFR T790M mutation has been reported in multiple studies^{77,82-83}. 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 population¹⁷⁴. 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)⁷⁷. In one study, the combination of dacomitinib and crizotinib was ineffective and associated with high toxicity in patients with NSCLC¹⁷⁵.

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THERAPIES ASSOCIATED WITH RESISTANCE

IN PATIENT'S TUMOR TYPE

Erlotinib

✗ Resistance of variant(s) to associated therapy is likely

Assay findings association

EGFR

T790M, L858R

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

Amplification or activation of EGFR may predict sensitivity to therapies such as erlotinib. For patients with activating mutations in EGFR, treatment with erlotinib has been associated with improved response and lengthened time to progression^{39,176-178}. The EGFR T790M mutation, when co-occurring with an EGFR activating alteration, has been associated with resistance to erlotinib and gefitinib⁷⁴⁻⁷⁷.

SUPPORTING DATA

For patients with EGFR-mutated non-small cell lung cancer (NSCLC), the Phase 3 EURTAC trial improved PFS with first-line erlotinib relative to platinum-based chemotherapy (9.7 vs. 5.2 months, HR=0.37), though OS was not prolonged (22.9 vs 19.6 months, HR=0.92)^{39,179}.

This study and meta-analyses attribute the lack of OS benefit to the effectiveness of post-progression salvage therapy in the control arm¹⁸⁰. A Phase 3 study reported similar efficacy of erlotinib and gefitinib for patients with EGFR-mutated NSCLC¹⁸¹. Patients with EGFR-mutated NSCLC have experienced PFS benefit with the addition of bevacizumab to erlotinib in the first-line setting in Phase 3 trials including the ARTEMIS-CTONG1509 trial for Chinese patients (17.9 vs. 11.2 months, HR=0.55)¹⁸², the NEJ026 trial for Japanese patients (16.9 vs. 13.3 months, HR=0.605)¹⁸³⁻¹⁸⁴, and the international BEVERLY trial (15.4 vs. 9.7 months, HR=0.60)¹⁸⁵; OS benefit has not been observed across these studies. In the maintenance setting, Phase 3 trials have reported significantly improved PFS with maintenance erlotinib following first-line platinum-based chemotherapy, with the largest benefit for patients with EGFR mutations^{176,186}. 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 EGFR-mutated advanced NSCLC¹⁷⁷. 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)¹⁸⁷.

Gefitinib

✗ Resistance of variant(s) to associated therapy is likely

Assay findings association

EGFR

T790M, L858R

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

Activation of EGFR may predict sensitivity to therapies such as gefitinib. Clinical studies have consistently shown significant improvement in response rates and PFS for patients with EGFR-mutated non-small cell lung cancer (NSCLC) treated with gefitinib compared with chemotherapy^{178,188-193}, and responses have been reported for patients with EGFR-rearranged NSCLC^{120,194}. The EGFR T790M mutation, when co-occurring with an EGFR activating alteration, has been associated with resistance to erlotinib and gefitinib⁷⁴⁻⁷⁷.

SUPPORTING DATA

Gefitinib achieved an ORR of 69.8% and OS of 19.2 months as first-line treatment for Caucasian patients with non-small cell lung cancer (NSCLC) and EGFR sensitizing

mutations⁴⁰. Phase 3 studies for Japanese patients^{190,195} and East Asian patients^{191,196} with EGFR-mutated NSCLC reported longer PFS but not longer OS on first-line gefitinib compared with cisplatin and docetaxel or carboplatin and paclitaxel. Retrospective analysis of East Asian patients receiving first-line gefitinib reported greatest PFS benefit among patients with EGFR exon 19 insertions or deletions and shortest PFS for those with exon 20 insertions (1.2 months)¹⁹⁷. Two Phase 3 trials of the combination 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 PFS (16 and 20.9 months vs. 8 and 11.9 months), and longer median OS (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 events¹⁹⁸⁻¹⁹⁹. In a Phase 1 study for treatment-naïve patients with NSCLC, 63% (19/30) of patients experienced PR from the combination of gefitinib and the PD-L1 inhibitor durvalumab²⁰⁰.

NOTE Genomic alterations detected may be associated with activity of certain US FDA or other specific country approved therapies; however, the therapies

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THERAPIES ASSOCIATED WITH RESISTANCE
IN PATIENT'S TUMOR TYPE

listed in this report may have varied evidence in the patient's tumor type. The listed therapies are not ranked in order of potential or predicted efficacy for this patient or in order of level of evidence for this patient's tumor type. The therapies listed in this report may not be complete and/or exhaustive. Furthermore, the listed therapies are limited to US FDA approved pharmaceutical drug products that are linked to a specific genomic alteration. There may also be US FDA approved pharmaceutical drug products that are not linked to a genomic alteration. Further there may also exist pharmaceutical drug products that are not approved by the US FDA or other national authorities. There may also be other treatment modalities available than pharmaceutical drug products.

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CLINICAL TRIALS

IMPORTANT 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. There may also be compassionate use or early access programs available, which are not listed in this report. 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 are not ranked in order of potential or predicted efficacy for this patient or

in order of level of evidence for this patient's tumor type. 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. However, clinicaltrials.gov does not list all clinical trials that might be available.

GENE
EGFR
ALTERATION

T790M, L858R

RATIONALE

EGFR activating mutations, rearrangements, or amplification may predict sensitivity to EGFR-targeted therapies. Strategies to overcome resistance to current agents include next-generation EGFR inhibitors and combination therapies. In the context of co-occurring

activating alterations, EGFR T790M confers clinical resistance to erlotinib, gefitinib, afatinib, lapatinib, and dacomitinib. Other agents may be relevant, including irreversible EGFR inhibitors, and in the context of lung cancer, the ALK/EGFR/ROS1 inhibitor brigatinib.

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: Taipei City (Taiwan), New Taipei (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Kaohsiung (Taiwan), Wenzhou (China), Linhai (China), Hangzhou (China), Hang Zhou (China), Shanghai (China)

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), Kaohsiung (Taiwan), Hangzhou (China), Nanchang (China), Nanjing (China), Hefei (China), Guangzhou (China), Changsha (China)

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), Changsha (China), Wuhan (China), Jinan (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), Tainan (Taiwan), Suwon (Korea, Republic of), Seoul (Korea, Republic of), Chuo-ku (Japan), Kashiwa-shi (Japan), Marseille CEDEX 05 (France), California, Colorado

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CLINICAL TRIALS
NCT04721015
PHASE 1

Study of Intravenous (IV) ABBV-637 Alone or in Combination With IV Docetaxel/Osimertinib to Assess Adverse Events and Change in Disease Activity in Adult Participants With Relapsed/Refractory (R/R) Solid Tumors

TARGETS
 EGFR

LOCATIONS: Taoyuan City (Taiwan), Tainan (Taiwan), Fukuoka-shi (Japan), Seoul (Korea, Republic of), Goyang (Korea, Republic of), Chuo-ku (Japan), Kashiwa-shi (Japan), Wollongong (Australia), Heidelberg (Australia), Ramat Gan (Israel)

NCT03114319
PHASE 1

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

TARGETS
 SHP2, EGFR

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

NCT04636593
PHASE 2

A Phase 2 Trial of Almonertinib With Concurrent Radiotherapy in The Treatment of Local Advanced EGFR-mutant NSCLC

TARGETS
 EGFR

LOCATIONS: Hangzhou (China)

NCT04770688
PHASE 1/2

Advanced Lung Tumor Treated by Osimertinib Plus Anlotinib

TARGETS
 EGFR

LOCATIONS: Shanghai (China)

NCT04425681
PHASE 2

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

TARGETS
 EGFR, VEGFA

LOCATIONS: Nanchang (China)

NCT04816838
PHASE NULL

A Window of Opportunity Study for Investigating Drug Tolerant Persister (DTP) to Neoadjuvant Osimertinib in Resectable Non-small Cell Lung Cancer (NSCLC) Harboring EGFR Mutations

TARGETS
 EGFR

LOCATIONS: Seoul (Korea, Republic of)

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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.

BARD1
G82V

CBL
L857F

IGF1R
A288T

KDR
T442M

MLL2
Y1998C

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APPENDIX
Genes assayed in FoundationOne®Liquid CDx

FoundationOne Liquid CDx interrogates 324 genes, including 309 genes with complete exonic (coding) coverage and 15 genes with only select non-coding coverage (indicated with an *); 75 genes (indicated in bold) are captured with increased sensitivity and have complete exonic (coding) coverage unless otherwise noted.

| | | | | | | | | |
|---------------------------------|--|---|--|---|--|--|---------------------------|----------------------------|
| ABL1 Exons 4-9 | ACVR1B | AKT1 Exon 3 | AKT2 | AKT3 | ALK Exons 20-29, Introns 18, 19 | ALOX12B | AMER1 (FAM123B or WTX) | APC |
| AR | ARAF Exons 4, 5, 7, 11, 13, 15, 16 | ARFRP1 | ARID1A | ASXL1 | ATM | ATR | ATRX | AURKA |
| AURKB | AXIN1 | AXL | BAP1 | BARD1 | BCL2 | BCL2L1 | BCL2L2 | BCL6 |
| BCOR | BCORL1 | BCR* Introns 8, 13, 14 | BRAF Exons 11-18, Introns 7-10 | BRCA1 Introns 2, 7, 8, 12, 16, 19, 20 | BRCA2 Intron 2 | BRD4 | BRIP1 | BTG1 |
| BTG2 | BTK Exons 2, 15 | CALR | CARD11 | CASP8 | CBFB | CBL | CCND1 | CCND2 |
| CCND3 | CCNE1 | CD22 | CD70 | CD74* Introns 6-8 | CD79A | CD79B | CD274 (PD-L1) | CDC73 |
| CDH1 | CDK12 | CDK4 | CDK6 | CDK8 | CDKN1A | CDKN1B | CDKN2A | CDKN2B |
| CDKN2C | CEBPA | CHEK1 | CHEK2 | CIC | CREBBP | CRKL | CSF1R | CSF3R |
| CTCF | CTNNA1 | CTNNB1 Exon 3 | CUL3 | CUL4A | CXCR4 | CYP17A1 | DAXX | DDR1 |
| DDR2 Exons 5, 17, 18 | DIS3 | DNMT3A | DOT1L | EED | EGFR Introns 7, 15, 24-27 | EMSY (C11orf30) | EP300 | EPHA3 |
| EPHB1 | EPHB4 | ERBB2 | ERBB3 Exons 3, 6, 7, 8, 10, 12, 20, 21, 23, 24, 25 | ERBB4 | ERCC4 | ERG | ERRF1 | ESR1 Exons 4-8 |
| ETV4* Intron 8 | ETV5* Introns 6, 7 | ETV6* Introns 5, 6 | EWSR1* Introns 7-13 | EZH2 Exons 4, 16, 17, 18 | EZR* Introns 9-11 | FANCA | FANCC | FANCG |
| FANCL | FAS | FBXW7 | FGF10 | FGF12 | FGF14 | FGF19 | FGF23 | FGF3 |
| FGF4 | FGF6 | FGFR1 Introns 1, 5, Intron 17 | FGFR2 Intron 1, Intron 17 | FGFR3 Exons 7, 9 (alternative designation exon 10), 14, 18, Intron 17 | FGFR4 | FH | FLCN | FLT1 |
| FLT3 Exons 14, 15, 20 | FOXL2 | FUBP1 | GABRA6 | GATA3 | GATA4 | GATA6 | GID4 (C17orf39) | GNA11 Exons 4, 5 |
| GNA13 | GNAQ Exons 4, 5 | GNAS Exons 1, 8 | GRM3 | GSK3B | H3-3A (H3F3A) | HDAC1 | HGF | HNFI1A |
| HRAS Exons 2, 3 | HSD3B1 | ID3 | IDH1 Exon 4 | IDH2 Exon 4 | IGF1R | IKBKE | IKZF1 | INPP4B |
| IRF2 | IRF4 | IRS2 | JAK1 | JAK2 Exon 14 | JAK3 Exons 5, 11, 12, 13, 15, 16 | JUN | KDM5A | KDM5C |
| KDM6A | KDR | KEAP1 | KEL | KIT Exons 8, 9, 11, 12, 13, 17, Intron 16 | KLHL6 | KMT2A (MLL) Introns 6, 8-11, Intron 7 | KMT2D (MLL2) | |

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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

ORDERED TEST # ORD-1362450-01

APPENDIX

Genes assayed in FoundationOne®Liquid CDx

FoundationOne Liquid CDx interrogates 324 genes, including 309 genes with complete exonic (coding) coverage and 15 genes with only select non-coding coverage (indicated with an *); 75 genes (indicated in bold) are captured with increased sensitivity and have complete exonic (coding) coverage unless otherwise noted.

| | | | | | | | | |
|--|---|-------------------|--|---|---|------------------------------|----------------------------|--|
| KRAS | LTK | LYN | MAF | MAP2K1 (MEK1) Exons 2, 3 | MAP2K2 (MEK2) Exons 2-4, 6, 7 | MAP2K4 | MAP3K1 | MAP3K13 |
| MAPK1 | MCL1 | MDM2 | MDM4 | MED12 | MEF2B | MEN1 | MERTK | MET |
| MITF | MKNK1 | MLH1 | MPL Exon 10 | MRE11 (MRE11A) | MSH2 Intron 5 | MSH3 | MSH6 | MST1R |
| MTAP | MTOR Exons 19, 30, 39, 40, 43-45, 47, 48, 53, 56 | MUTYH | MYB* Intron 14 | MYC Intron 1 | MYCL (MYCL1) | MYCN | MYD88 Exon 4 | NBN |
| NF1 | NF2 | NFE2L2 | NFKBIA | NKX2-1 | NOTCH1 | NOTCH2 Intron 26 | NOTCH3 | NPM1 Exons 4-6, 8, 10 |
| NRAS Exons 2, 3 | NSD2 (WHSC1 or MMSET) | NSD3 (WHSC1L1) | NTSC2 | NTRK1 Exons 14, 15, Introns 8-11 | NTRK2 Intron 12 | NTRK3 Exons 16, 17 | NUTM1* Intron 1 | P2RY8 |
| PALB2 | PARP1 | PARP2 | PARP3 | PAX5 | PBRM1 | PDCD1 (PD-1) | PDCD1LG2 (PD-L2) | PDGFRA Exons 12, 18, Introns 7, 9, 11 |
| PDGFRB Exons 12-21, 23 | PDK1 | PIK3C2B | PIK3C2G | PIK3CA Exons 2, 3, 5-8, 10, 14, 19, 21 (Coding Exons 1, 2, 4-7, 9, 13, 18, 20) PPP2R2A | PIK3CB | PIK3R1 | PIM1 | PMS2 |
| POLD1 | POLE | PPARG | PPP2R1A | PPP2R2A | PRDM1 | PRKAR1A | PRKCI | PRKN (PARK2) |
| PTCH1 | PTEN | PTPN11 | PTPRO | QKI | RAC1 | RAD21 | RAD51 | RAD51B |
| RAD51C | RAD51D | RAD52 | RAD54L | RAF1 Exons 3, 4, 6, 7, 10, 14, 15, 17, Introns 4-8 | RARA Intron 2 | RB1 | RBM10 | REL |
| RET Introns 7, 8, Exons 11, 13-16, Introns 9-11 | RICTOR | RNF43 | ROS1 Exons 31, 36-38, 40, Introns 31-35 | RPTOR | RSP02* Intron 1 | SDC4* Intron 2 | SDHA | SDHB |
| SDHC | SDHD | SETD2 | SF3B1 | SGK1 | SLC34A2* Intron 4 | SMAD2 | SMAD4 | SMARCA4 |
| SMARCB1 | SMO | SNCAIP | SOC1 | SOX2 | SOX9 | SPEN | SPOP | SRC |
| STAG2 | STAT3 | STK11 | SUFU | SYK | TBX3 | TEK | TENTSC (FAM46C) | TERC* ncRNA |
| TERT* Promoter | TET2 | TGFBR2 | TIPARP | TMPPRS2* Introns 1-3 | TNFAIP3 | TNFRSF14 | TP53 | TSC1 |
| TSC2 | TYRO3 | U2AF1 | VEGFA | VHL | WT1 | XPO1 | XRCC2 | ZNF217 |

ZNF703

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite (MS) status

Blood Tumor Mutational Burden (bTMB)

Tumor Fraction

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APPENDIX
About FoundationOne® Liquid CDx

FoundationOne Liquid 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. The CE-IVD regulatory status of FoundationOne Liquid CDx is applicable in countries that accept and/or recognize the CE mark.


ABOUT FOUNDATIONONE LIQUID CDx

FoundationOne Liquid CDx was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne Liquid 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.

INTENDED USE

FoundationOne Liquid CDx is a next generation sequencing based *in vitro* diagnostic device that analyzes 324 genes. Substitutions and insertion and deletion alterations (indels) are reported in 311 genes, copy number alterations (CNAs) are reported in 310 genes, and gene rearrangements are reported in 324 genes. The test also detects the genomic signatures blood tumor mutational burden (bTMB), microsatellite instability (MSI), and tumor fraction. FoundationOne Liquid CDx utilizes circulating cell-free DNA (cfDNA) isolated from plasma derived from the anti-coagulated peripheral whole blood of cancer patients. The test is intended to be used as a companion diagnostic to identify patients who may benefit from treatment with targeted therapies in accordance with the approved therapeutic product labeling. Additionally, FoundationOne Liquid CDx 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 malignant neoplasms.

TEST PRINCIPLES

The FoundationOne Liquid CDx assay is performed exclusively as a laboratory service using circulating cell-free DNA (cfDNA) isolated from plasma derived from anti-coagulated peripheral whole blood from patients with solid malignant neoplasms. The assay employs a single DNA extraction method to obtain cfDNA from plasma from whole blood. Extracted

cfDNA undergoes whole-genome shotgun library construction and hybridization-based capture of 324 cancer-related genes including coding exons and select introns of 309 genes, as well as only select intronic regions or non-coding regions of 15 genes. Hybrid-capture selected libraries are sequenced with deep coverage using the NovaSeq® 6000 platform. Sequence data are processed using a customized analysis pipeline designed to accurately detect genomic alterations, including base substitutions, indels, select copy number variants, and select genomic rearrangements. Substitutions and insertion and deletion alterations (indels) are reported in 311 genes, copy number alterations (CNAs) are reported in 310 genes, and gene rearrangements are reported in 324 genes. The assay also reports tumor fraction, and genomic signatures including MSI and bTMB. A subset of targeted regions in 75 genes is baited for increased sensitivity.

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. *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.

QUALIFIED ALTERATION CALLS (EQUIVOCAL)

All equivocal calls, regardless of alteration type, imply that there is adequate evidence to call the alteration with confidence. However, the repeatability of equivocal calls may be lower than non-equivocal calls.

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.

LIMITATIONS

1. For *in vitro* diagnostic use.
2. For prescription use only. This test must be ordered by a qualified medical professional in accordance with clinical laboratory regulations.
3. A negative result does not rule out the presence of a mutation below the limits of detection of the assay. Patients for whom no companion diagnostic alterations are detected should be considered for confirmation with an appropriately validated tumor tissue test, if available.
4. The FoundationOne Liquid CDx assay does not detect heterozygous deletions.
5. The test is not intended to provide information on cancer predisposition.
6. Performance has not been validated for cfDNA input below the specified minimum input.
7. Tissue TMB and blood TMB (bTMB) are estimated from the number of synonymous and nonsynonymous single-nucleotide variants (SNVs) and insertions and deletions (indels) per area of coding genome sampled, after the removal of known and likely oncogenic driver events and germline SNPs. Tissue TMB is calculated based on variants with an allele frequency of $\geq 5\%$, and bTMB is calculated based on variants with an allele frequency of $\geq 0.5\%$.
8. Tumor fraction is the percentage of circulating tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample. The tumor fraction estimate is computationally derived from the observed level of aneuploidy in the sample. Tumor fraction is considered elevated when ctDNA levels are high enough that aneuploidy can be detected and is significantly distinct from that typically found in non-tumor samples.
9. Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the tumor genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor. The MSI algorithm is based on genome wide analysis of 1765 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines for solid tissue testing.
10. Genomic findings from circulating cell-free DNA (cfDNA) may originate from circulating tumor DNA fragments, germline alterations, or non-tumor somatic alterations, such as clonal hematopoiesis of indeterminate potential (CHIP). Genes with alterations that may be derived from CHIP include, but are not limited

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APPENDIX

About FoundationOne®Liquid CDx

to: *ASXL1*, *ATM*, *CBL*, *CHEK2*, *DNMT3A*, *JAK2*, *KMT2D* (*MLL2*), *MPL*, *MYD88*, *SF3B1*, *TET2*, *TP53*, and *U2AF1*.

11. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. If a reported alteration is suspected to be germline, confirmatory testing should be considered in the appropriate clinical context.
12. The test is not intended to replace germline testing or to provide information about cancer predisposition.

REPORT HIGHLIGHTS

The Report Highlights includes select genomic and therapeutic information with potential impact on patient care and treatment that is specific to the genomics and tumor type of the sample analyzed. This section may highlight information including targeted therapies with potential sensitivity or resistance; evidence-matched clinical trials; and variants with potential diagnostic, prognostic, nontargeted treatment, germline, or clonal hematopoiesis implications. Information included in the Report Highlights is expected to evolve with advances in scientific and clinical research. Findings included in the Report Highlights should be considered in the context of all other information in this report and other relevant patient information. Decisions on patient care and treatment are the responsibility of the treating physician.

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 >30%, 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*, *ATM*, *CBL*, *CHEK2*, *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.

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. 2022. 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.

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 Liquid CDx.

TREATMENT DECISIONS ARE THE 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 of variant characteristics may result in reduced sensitivity. These include: low sample quality, deletions and insertions >40bp, or repetitive/high homology sequences. FoundationOne Liquid CDx is performed using cell-free DNA, and as such germline events may not be reported.

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APPENDIX

About FoundationOne®Liquid 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 |
| Muts/Mb | Mutations per megabase |
| NOS | Not otherwise specified |
| ORR | Objective response rate |
| OS | Overall survival |
| PD | Progressive disease |
| PFS | Progression-free survival |
| PR | Partial response |
| SD | Stable disease |
| TKI | Tyrosine kinase inhibitor |

REFERENCE SEQUENCE INFORMATION

Sequence data is mapped to the human genome, Genome Reference Consortium Human Build 37 (GRCh37), also known as hg19.

MR Suite Version 6.2.0

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