**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
**NAME** Hsueh, Yao-Yuan
**DATE OF BIRTH** 09 April 1961
**SEX** Male
**MEDICAL RECORD #** 37798713

## PHYSICIAN

**ORDERING PHYSICIAN** Chiang, Chi-Lu
**MEDICAL FACILITY** Taipei Veterans General Hospital
**ADDITIONAL RECIPIENT** None
**MEDICAL FACILITY ID** 205872
**PATHOLOGIST** Not Provided

## SPECIMEN

**SPECIMEN ID** YYH 4/9/1961
**SPECIMEN TYPE** Blood
**DATE OF COLLECTION** 29 September 2021
**SPECIMEN RECEIVED** 01 October 2021

## Biomarker Findings

**Blood Tumor Mutational Burden** - 0 Muts/Mb
**Microsatellite status** - MSI-High Not Detected
**Tumor Fraction** - Cannot Be Determined

## Genomic Findings

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

***EGFR*** exon 19 deletion (E746_A750del)
***PIK3CA*** E726K
***BARD1*** A25fs*41
***DNMT3A*** G543C
***TP53*** K139E

**7** Therapies with Clinical Benefit
**0** Therapies with Resistance
**28** Clinical Trials

# PATHOLOGIST COMMENTS

Brennan Decker, M.D., Ph.D. 8-Oct-2021

The BARD1 variant found in this case has some characteristics suspicious for being a pathogenic germline variant. Please note, however, that this assay is not designed to distinguish germline from somatic variants. Genetic counseling and dedicated germline testing may be helpful, if clinically indicated. See the professional services section for more information.

| BIOMARKER FINDINGS | THERAPY AND CLINICAL TRIAL IMPLICATIONS |
|---|---|
| **Blood Tumor Mutational Burden -** 0 Muts/Mb | **No therapies or clinical trials. See Biomarker Findings section** |
| **Microsatellite status -** MSI-High Not Detected | **MSI-High not detected. No evidence of microsatellite instability in this sample (see Appendix section).** |
| **Tumor Fraction -** Cannot Be Determined | **Tumor fraction is an estimate of the percentage of circulating-tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample based on observed aneuploid instability.** |



Electronically signed by Brennan Decker, M.D., Ph.D. | 08 October 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

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

| GENOMIC FINDINGS | | VAF % | THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE) | THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE) |
|---|---|---|---|---|
| ***EGFR*** - | exon 19 deletion (E746_A750del) | 1.1% | Afatinib 1<br>Dacomitinib 1<br>Erlotinib 1<br>Gefitinib 1<br>Osimertinib 1 | None |
| **10 Trials** see p. 16 | | | | |
| ***PIK3CA*** - | E726K | 0.66% | None | Everolimus<br>Temsirolimus |
| **10 Trials** see p. 18 | | | | |
| ***BARD1*** - | A25fs*41 | 50.5% | None | None |
| **10 Trials** see p. 14 | | | | |

1 *NCCN category*

## VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS (CH)

*Genomic findings below may include nontumor somatic alterations, such as CH. The efficacy of targeting such nontumor somatic alterations is unknown. This content should be interpreted based on clinical context. Refer to appendix for additional information on CH.*

***DNMT3A*** - G543C ..... p. 8

## GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

***DNMT3A*** - G543C ..... p. 8 ***TP53*** - K139E ..... p. 9

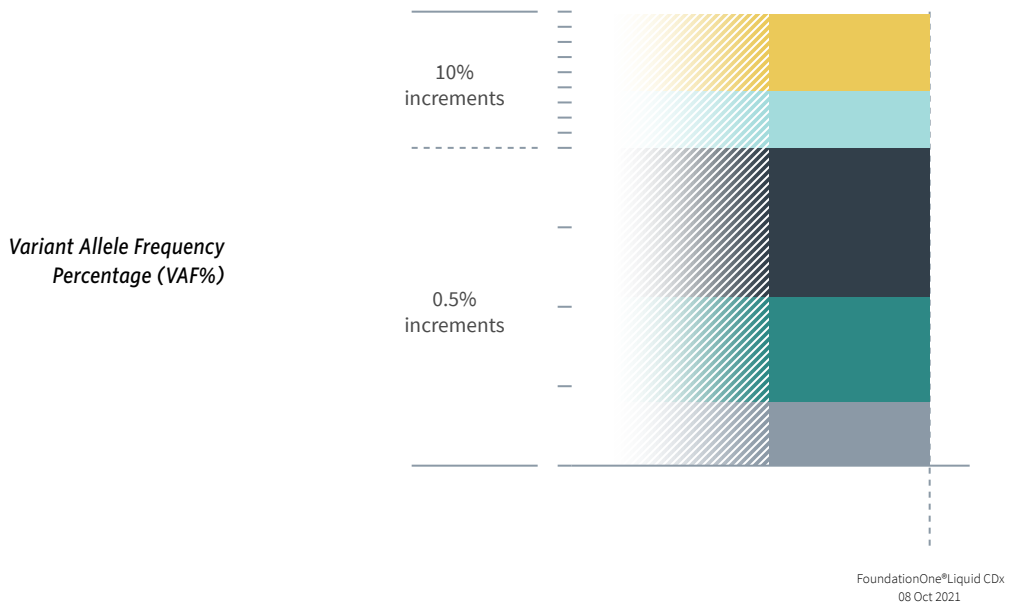
**NOTE** Genomic alterations detected may be associated with activity of certain approved therapies; however, the therapies listed in this report may have varied clinical evidence in the patient's tumor type. Therapies and the clinical trials listed in this report may not be complete and/or exhaustive. 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.



Electronically signed by Brennan Decker, M.D., Ph.D. | 08 October 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

**Sample Preparation:** 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
**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




| HISTORIC PATIENT FINDINGS | | ORD-1203934-01 VAF% |
|---|---|---|
| **Blood Tumor Mutational Burden** | | 0 Muts/Mb |
| **Microsatellite status** | | MSI-High Not Detected |
| **Tumor Fraction** | | Cannot Be Determined |
| ***EGFR*** | exon 19 deletion (E746_A750del) | 1.1% |
| ***PIK3CA*** | E726K | 0.66% |
| ***BARD1*** | A25fs*41 | 50.5% |
| ***DNMT3A*** | G543C | 37.3% |
| ***TP53*** | K139E | 0.40% |

**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 ≥5%, and bTMB is calculated based on variants with an allele frequency of ≥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



Electronically signed by Brennan Decker, M.D., Ph.D. | 08 October 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

**Sample Preparation:** 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
**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

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



Electronically signed by Brennan Decker, M.D., Ph.D. | 08 October 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

**Sample Preparation:** 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
**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

BIOMARKER

# Blood Tumor Mutational Burden

**RESULT**
0 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-L1[1-2] and anti-PD-1[3] 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/Mb[1]. In HNSCC, 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 inhibitor[4].

## 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 docetaxel[5]. 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 chemotherapy[6]. 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)[7]. Another study of patients with NSCLC correlated elevated TMB with poorer prognosis and significantly associated lower TMB in combination with PD-L1 negative status with longer median survival in patients with lung adenocarcinoma[8]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[8-9].

## 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 melanoma[10-11] and cigarette smoke in lung cancer[12-13], treatment with temozolomide-based chemotherapy in glioma[14-15], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[16-20], and microsatellite instability (MSI)[16,19-20]. 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 agents[1-3]. Depending on the clinical context, TMB testing of an alternate sample or by another methodology could be considered.

BIOMARKER

# Tumor Fraction

**RESULT**
Cannot Be Determined

## POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

Specimens with high tumor fraction values have high circulating-tumor DNA (ctDNA) content, and thus higher sensitivity for identifying genomic alterations. Such specimens are at a lower risk of false negative results[21]. However, if tumor fraction is not detected as high, 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 management[22-27].

## FREQUENCY & PROGNOSIS

Detectible 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 cancer[29], Ewing sarcoma and osteosarcoma[30], prostate cancer[25], breast cancer[31], leiomyosarcoma[32], esophageal cancer[33], colorectal cancer[34], and gastrointestinal cancer[35].

## 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 content[36], 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 therapy[37-38]. However, the tumor fraction estimate in this sample could not be determined with confidence.



Electronically signed by Brennan Decker, M.D., Ph.D. | 08 October 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

**Sample Preparation:** 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
**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

GENE
# *EGFR*

**ALTERATION**
exon 19 deletion (E746_A750del)

**TRANSCRIPT ID**
NM_005228

**CODING SEQUENCE EFFECT**
2235_2249delGGAATTAAGAGAAGC

## POTENTIAL TREATMENT STRATEGIES

### — Targeted Therapies —

For patients with non-small cell lung cancer, EGFR activating mutations may predict sensitivity to EGFR TKIs, including erlotinib[39], gefitinib[40], afatinib[41], dacomitinib[42], and osimertinib[43]; however, the data for patients with other tumor types are limited[44-49]. The Phase 1 CHRYSALIS study of amivantamab monotherapy or in combination with lazertinib for the treatment of EGFR-mutated non-small cell lung cancer (NSCLC) has produced encouraging preliminary results for treatment-naive patients and patients who relapsed after treatment with osimertinib, including osimertinib-relapsed patients with biomarkers indicating EGFR/MET-based osimertinib resistance[50-52] . In a Phase 1 trial, the HER3-targeted antibody patritumab deruxtecan elicited an ORR of 39% (22/57, 1 CR) and a median PFS of 8.2 months for patients with non-small cell lung cancer previously treated with an EGFR TKI, many of whom displayed TKI resistance alterations[53]. A Phase 1 trial evaluating the EGFR inhibitor AZD3759 reported a reduction in the volume of brain metastases in 40% (8/20) of patients with previously treated non-small cell lung cancer (NSCLC) harboring either the EGFR L858R alteration or EGFR exon 19 deletion, including 3 confirmed PRs and 3 unconfirmed PRs[54-55]. In a Phase 1/2 trial for advanced NSCLC, the brain-penetrant third-generation EGFR TKI lazertinib enabled ORRs of 54% (69/127) for all evaluable patients and 44% (8/18, intracranial) for patients with brain metastases[56]. The Phase 3 IMpower150 study showed that the addition of atezolizumab to bevacizumab plus chemotherapy treatment also had clinical efficacy for patients with EGFR-mutated or ALK-rearranged metastatic NSCLC[57]; therefore, the patient's clinical context should be considered.

### — Potential Resistance —

For patients with NSCLC treated with EGFR tyrosine kinase inhibitors, PIK3CA mutation is associated with shorter OS in a meta-analysis (pooled HR of 1.83)[58]. Clinical studies of lung cancer have shown that acquired PIK3CA mutation may confer resistance to EGFR inhibitors like osimertinib[59].

## FREQUENCY & PROGNOSIS

EGFR mutation has been reported in 12-36% of lung adenocarcinomas[60-62] and in 4% of lung squamous cell carcinomas[63]. EGFR protein expression/overexpression has been reported in up to 70% of NSCLC cases[64-69]. In addition, expression of EGFR protein has been shown to be higher in lung squamous cell carcinoma samples as compared to lung adenocarcinoma[70-71]. In patients with lung adenocarcinoma, EGFR mutation was a predictor of poor overall survival[72-73]. However, EGFR mutations have been reported to predict improved survival in patients with resected Stage 1-3 lung adenocarcinoma[74] or resected Stage 1 NSCLC[75].

## FINDING SUMMARY

EGFR encodes the epidermal growth factor receptor, which belongs to a class of proteins called receptor tyrosine kinases. In response to signals from the environment, EGFR passes biochemical messages to the cell that stimulate it to grow and divide[76]. EGFR exon 19 deletion mutations, such as seen here, have been shown to activate the tyrosine kinase activity of EGFR and to confer sensitivity to EGFR tyrosine kinase inhibitors such as erlotinib, gefitinib[77-79], afatinib[80], osimertinib[81], and dacomitinib[42,82], although limited preclinical data suggest reduced sensitivity to lapatinib[83-84].



Electronically signed by Brennan Decker, M.D., Ph.D. | 08 October 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

**Sample Preparation:** 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
**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

GENE

## *PIK3CA*

**ALTERATION**
E726K

**TRANSCRIPT ID**
NM_006218

**CODING SEQUENCE EFFECT**
2176G>A

### POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

Clinical and preclinical data in various tumor types indicate that PIK3CA activating alterations may predict sensitivity to therapies targeting PI3K[85-87], AKT[88-89], or mTOR[90-97]. A Phase 2 study of buparlisib in NSCLC observed 2 PRs (3.2%; 2/63) in PIK3CA-pathway activated tumors, although the study did not meet its primary endpoint[98].

**— Potential Resistance —**

Activating mutations in PIK3CA may confer resistance to HER2-targeted therapies; combined inhibition of HER2 and the PI3K pathway may be required in HER2-positive tumors with PIK3CA mutation[99-103]. For patients with NSCLC treated with EGFR tyrosine kinase inhibitors, PIK3CA mutation is associated with shorter OS in a meta-analysis (pooled HR of 1.83)[58]. Clinical studies of lung cancer have shown that acquired PIK3CA mutation may confer resistance to EGFR inhibitors like osimertinib[59].

### FREQUENCY & PROGNOSIS

In the TCGA datasets, PIK3CA mutation was observed in 8.2% of lung adenocarcinoma cases[104] and in 15.7% of lung squamous cell carcinoma cases[63]. Studies have observed PIK3CA amplification and mutation to be far more frequent in lung squamous cell carcinomas than in lung adenocarcinomas, with amplification reported in 34-42% of the former[105-108]. The prognostic significance of PIK3CA mutation or overexpression in NSCLC is unclear, with several studies reporting contradictory data, which may be influenced by the specific PIK3CA mutation, histologic subtype, and the presence of concurrent mutations in oncogenes such as EGFR and KRAS[109-114].

### FINDING SUMMARY

PIK3CA encodes p110-alpha, which is the catalytic subunit of phosphatidylinositol 3-kinase (PI3K). The PI3K pathway is involved in cell signaling that regulates a number of critical cellular functions, including cell growth, proliferation, differentiation, motility, and survival[115-116]. PIK3CA alterations that have been characterized as activating, such as observed here, are predicted to be oncogenic[117-137].

GENE

## *BARD1*

**ALTERATION**
A25fs*41

**TRANSCRIPT ID**
NM_000465

**CODING SEQUENCE EFFECT**
69_70GC>TCCGGGAACGAGCCTCGTTCCGCGT

### POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

Clinical benefit from rucaparib has been observed in a patient with BARD1-mutated ovarian cancer[138]. On the basis of preclinical evidence, tumors with BARD1 inactivation may be sensitive to PARP inhibitors[139-142].

### FREQUENCY & PROGNOSIS

In the TCGA datasets, BARD1 mutation or loss was reported in 4% of lung squamous cell carcinomas and in 1.3% of lung adenocarcinomas[62]. Some BARD1 mutations have been reported to be associated with non-small cell lung cancer development and poor prognosis[143].

### FINDING SUMMARY

BARD1 encodes the BRCA1-associated RING domain 1 protein, which is required for stabilization and nuclear localization of BRCA1 as well as formation of the E3 ubiquitin ligase[144]. The BARD1 ANK repeats and BRCT motifs play important roles in chromosome stability, and both these regions and the RING domain are necessary for homology-directed repair[139,145-146]. Alterations such as seen here may disrupt BARD1 function or expression.



Electronically signed by Brennan Decker, M.D., Ph.D. | 08 October 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

**Sample Preparation:** 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
**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

GENE
# *DNMT3A*

**ALTERATION**
G543C

**TRANSCRIPT ID**
NM_022552

**CODING SEQUENCE EFFECT**
1627G>T

## POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

There are no targeted therapies available to address genomic alterations in DNMT3A in solid tumors.

## FREQUENCY & PROGNOSIS

DNMT3A alterations have been reported at relatively low frequencies in solid tumors and are more prevalent in hematological malignancies (cBioPortal, Feb 2021)[147-148]. Published data investigating the prognostic implications of DNMT3A alterations in solid tumors are limited (PubMed, Feb 2021).

## FINDING SUMMARY

The DNMT3A gene encodes the protein DNA methyltransferase 3A, an enzyme that is involved in the methylation of newly synthesized DNA, a function critical for gene regulation[149-150]. The role of DNMT3A in cancer is uncertain, as some reports describe increased expression and contribution to tumor growth, whereas others propose a role for DNMT3A as a tumor suppressor[151-156]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

## POTENTIAL CLONAL HEMATOPOIESIS

## IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[157-162]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[157-158]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[163]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[161,164-165]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.



Electronically signed by Brennan Decker, M.D., Ph.D. | 08 October 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

**Sample Preparation:** 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
**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

GENE
# *TP53*

**ALTERATION**
K139E

**TRANSCRIPT ID**
NM_000546

**CODING SEQUENCE EFFECT**
415A>G

## POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[166-169], or p53 gene therapy and immunotherapeutics such as SGT-53[170-174] and ALT-801[175]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% (17/176) and SDs in 53.4% (94/176) of patients with solid tumors; the response rate was 21.1% (4/19) for patients with TP53 mutations versus 12.1% (4/33) for patients who were TP53 wild-type[176]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 31.9% (30/94, 3 CR) ORR and a 73.4% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[177]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 42.9% (9/21, 1 CR) ORR and a 76.2% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[178]. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[179]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24.0% (6/25) ORR with adavosertib combined with paclitaxel[180]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71.4% (5/7) response rate for patients with TP53 alterations[181]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75.0% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[174]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutated, but not TP53-wild-type, breast cancer xenotransplant mouse model[182]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutated p53 such as APR-246[183-185]. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[186]. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies[187-188]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[189-190]. 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)[62-63,191-196], including 42-52% of lung adenocarcinomas and 58-83% of lung squamous cell carcinomas (cBioPortal, COSMIC, Feb 2021)[61-63,197]. TP53 homozygous deletion has been observed in 1.4% of lung adenocarcinoma and <1% of lung squamous cell carcinoma cases (cBioPortal, Feb 2021)[147-148]. In one study of 55 patients with lung adenocarcinoma, TP53 alterations correlated with immunogenic features including PD-L1 expression, tumor mutation burden and neoantigen presentation; likely as a consequence of this association TP53 mutations correlated with improved clinical outcomes to PD-1 inhibitors pembrolizumab and nivolumab in this study[198]. Mutations in TP53 have been associated with lymph node metastasis in patients with lung adenocarcinoma[199].

## FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[200]. Alterations such as seen here may disrupt TP53 function or expression[201-205].

## POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[206-208], including sarcomas[209-210]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[211] to 1:20,000[210]. For pathogenic TP53 mutations identified during tumor sequencing, the rate of germline mutations was 1% in the overall population and 6% in tumors arising before age 30[212]. In the appropriate clinical context, germline testing of TP53 is recommended.

## POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[157-162]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[157-158]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[163]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[161,164-165]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.



Electronically signed by Brennan Decker, M.D., Ph.D. | 08 October 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

**Sample Preparation:** 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
**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

# Afatinib

*Assay findings association*

**EGFR**
exon 19 deletion (E746_A750del)

## AREAS OF THERAPEUTIC USE

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

## GENE ASSOCIATION

EGFR activating mutations may indicate sensitivity to afatinib or dacomitinib for patients with non-small cell lung cancer[41-42,213-214] , whereas data for patients with other tumor types are limited[44-49,215] .

## SUPPORTING DATA

Afatinib has shown significant clinical activity for patients with NSCLC and the EGFR common sensitizing mutations L858R or exon 19 deletions, based on extensive clinical evidence[41,213,216-219] . 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)[41,213] . However, while afatinib significantly increased OS relative to chemotherapy for patients with EGFR exon 19 alterations in these two trials (LUX-Lung 3, 33.3 vs. 21.1 months, HR=0.54; LUX-Lung 6, 31.4 vs. 18.4 months, HR=0.64), no significant OS differences were observed in treatment for patients with L858R mutation[80]. A similar alteration-specific difference was observed for EGFR-mutated treatment-naive NSCLC in a retrospective analysis, which reported numerically longer median OS from second- versus first-generation EGFR TKIs (48.8 vs. 26.4 months, HR=0.59) for patients with exon 19 deletions, but no substantial difference for patients with L858R (25.4 vs. 20.6 months, HR=0.90)[216]. A Phase 2b study of first-line afatinib compared with gefitinib, also for NSCLC with exon 19 deletions or L858R, reported similar median OS for the two therapies (27.9 vs. 24.5 months, HR=0.86) but significantly longer time-to-treatment-failure (13.7 vs. 11.5 months, HR=0.75) and higher ORR (73% vs. 56%, p=0.0018) with afatinib[217].

Patients with metastatic NSCLC and common EGFR mutations who progressed on prior chemotherapy experienced an ORR of 50.0% (30/60) from afatinib in a Phase 4 trial[218]. As first-line therapy for NSCLC with EGFR exon 19 deletions or L858R, prospective or randomized Phase 2 trials have reported a median PFS of 10.2 months and OS of 24.8 months for patients unfit for chemotherapy[219] and an ORR of 72.5% (n=40, 1 CR), DCR of 100% (40/40), and median PFS and OS of 15.2 and 30.0 months, respectively, for elderly patients ≥70 years old[220]. A retrospective study of afatinib administered to Asian patients with NSCLC, 99% of whom were previously treated with erlotinib and/or gefitinib, reported an ORR of 27.4% (63/230) for patients with common sensitizing EGFR mutations and an ORR of 24.4% (105/431) for the entire cohort[221]. In a case report, a patient with NSCLC with exon 19 deletion and leptomeningeal metastases experienced an ongoing 16-month PR from afatinib in extracranial, brain, and leptomeningeal lesions[222]. 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%[223-228] ; however, DCRs of more than 50% have been observed[227]. In a Phase 1b or observational study, patients with EGFR-mutated NSCLC who progressed on afatinib experienced further clinical benefit from subsequent treatment with afatinib and cetuximab[229] or osimertinib[230], 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[41,80,213,217,219,221,231] . Afatinib has also shown activity for patients with advanced NSCLC and ERBB2 mutations, most of which were exon 20 insertions[227,232-242] . The randomized Phase 3 LUX-Lung 8 trial comparing afatinib with erlotinib as second-line therapy for advanced lung squamous cell carcinoma (SCC) reported significantly longer median OS (7.9 vs. 6.8 months, HR=0.81), significantly longer median PFS (2.6 vs. 1.9 months, HR=0.81), and higher DCR (51% vs. 40%, p=0.002) for patients treated with afatinib[231]. For patients who progressed on afatinib monotherapy, additional clinical benefit has been reported from afatinib combined with paclitaxel[243].



Electronically signed by Brennan Decker, M.D., Ph.D. | 08 October 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

**Sample Preparation:** 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
**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

# Dacomitinib

*Assay findings association*

**EGFR**
exon 19 deletion (E746_A750del)

### AREAS OF THERAPEUTIC USE

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

### GENE ASSOCIATION

EGFR activating mutations may indicate sensitivity to afatinib or dacomitinib for patients with non-small cell lung cancer[41-42,213-214] , whereas data for patients with other tumor types are limited[44-49,215] . Patients with untreated advanced NSCLC and EGFR exon 19 deletions achieved an ORR of 76%[82] and a median OS of 34.1 months with dacomitinib[42].

### 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)[82,244] ; median OS was 34.1 to 36.7 months and ORR was 74.9% to 79.3%, depending on the dosing regimen[245]. 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)[246]. Reduced efficacy of dacomitinib treatment in patients with NSCLC harboring the EGFR T790M mutation has been reported in multiple studies[247-249] . A Phase 1 trial of combination dacomitinib and a MEK1/2 inhibitor for patients with KRAS-mutated CRC, NSCLC, or pancreatic cancer reported 20/36 SDs and 16 PDs, however toxicity from this combination prevented long-term treatment in this patient population[250]. 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)[248]. In one study, the combination of dacomitinib and crizotinib was ineffective and associated with high toxicity in patients with NSCLC[251].

# Erlotinib

*Assay findings association*

**EGFR**
exon 19 deletion (E746_A750del)

### AREAS OF THERAPEUTIC USE

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

### GENE ASSOCIATION

Amplification or activation of EGFR may predict sensitivity to therapies such as erlotinib. For patients with activating mutations in EGFR, treatment with erlotinib has been associated with improved response and lengthened time to progression[39,252-254] .

### SUPPORTING DATA

For patients with EGFR-mutated NSCLC, the Phase 3 EURTAC trial reported improved PFS with first-line erlotinib relative to platinum-based chemotherapy (9.7 vs. 5.2 months, HR=0.37)[39]. A Phase 3 study reported similar efficacy of erlotinib and gefitinib for patients with EGFR-mutated NSCLC[255]. Meta-analysis of studies comparing erlotinib or gefitinib versus chemotherapy in the first-line setting reported no significant improvement in OS for patients with EGFR-mutated NSCLC; however, the lack of improved OS was attributed to the effectiveness of postprogression salvage therapy[256]. 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)[252]. In the neoadjuvant setting, a Phase 2 trial reported a numerically improved ORR and significantly longer PFS with erlotinib compared with chemotherapy for patients with advanced EGFR-mutated NSCLC[253]. 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)[257]. In a Phase 2 trial, no clinical benefit was observed from the addition of bevacizumab to erlotinib for patients with NSCLC harboring EGFR exon 19 deletion or L858R mutation[258]. In one study, median PFS (4.1 vs. 11.7 months, HR=9.7) and median OS (14.1 vs. 47.0 months, HR=10.2) were significantly shorter for patients with NSCLC harboring EGFR L747_A750>P (n=6) relative to those with deletions affecting EGFR E746_A750 (n=24) treated with first-line erlotinib[259]. The Phase 3 BR.21 trial demonstrated prolonged OS for genomically unselected patients with NSCLC treated with erlotinib compared with those treated with standard chemotherapy[260].

# Gefitinib

*Assay findings association*

**EGFR**
exon 19 deletion (E746_A750del)

### AREAS OF THERAPEUTIC USE

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

### GENE ASSOCIATION

Activation of EGFR may predict sensitivity to therapies such as gefitinib. Clinical studies have consistently shown significant improvement in response rates and PFS for patients with EGFR-mutated non-small cell lung cancer (NSCLC) treated with gefitinib compared with chemotherapy[254,261-266] , and responses have been reported for patients with EGFR-rearranged NSCLC[267-268] .

### SUPPORTING DATA

A Phase 3 trial of first-line gefitinib therapy for patients with NSCLC and EGFR exon 19 deletions or L858R mutations reported a longer PFS (9.2 months vs. 6.3 months)[263] but no change in median OS (34.9 months vs. 37.2 months) compared with patients treated with cisplatin plus docetaxel (median OS of 37.2 months)[269]. Gefitinib achieved an ORR of 69.8% and an OS of 19.2 months as first-line treatment for Caucasian patients with non-small cell lung carcinoma (NSCLC) and EGFR sensitizing mutations[40]. 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[264,270] . Two Phase 3 trials of gefitinib plus pemetrexed and carboplatin compared with gefitinib alone for patients with advanced NSCLC harboring EGFR activating mutations reported significantly higher ORRs (75.3% and 84% vs. 62.5% and 67%), longer median PFSs (16 and 20.9 months vs. 8 and 11.9 months), and longer median OSs (50.9 months and not reached vs. 17 and 38.8 months) with combination treatment; however, combination treatment was associated with increased Grade 3 or higher adverse events[271-272] . Retrospective analysis of East Asian patients with advanced NSCLC receiving first-line gefitinib therapy reported that patients with EGFR exon 19 mutations experienced a longer median PFS (10.9 months) compared with patients with EGFR mutations in exon 18 (7.9 months), exon 20 (1.2 months), exon 21 (7.7 months), or double mutations (5.7 months); however, no differences in OS were seen between EGFR mutations[273]. In a Phase 1 study for treatment-naive patients with NSCLC, best ORRs of 78% (7/9) were observed in patients treated with combination gefitinib and the PD-L1 inhibitor durvalumab as first-line treatment and of 80% (8/10) in those treated with the combination after gefitinib monotherapy[274].

# Osimertinib

*Assay findings association*

**EGFR**
exon 19 deletion (E746_A750del)

### AREAS OF THERAPEUTIC USE

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

### GENE ASSOCIATION

EGFR TKI-sensitizing mutations or rearrangements and/or the EGFR T790M mutation may predict sensitivity to osimertinib in non-small cell lung cancer[43,81,267,275-276] . Patients with untreated advanced NSCLC and EGFR exon 19 deletions or L858R mutations achieved an ORR of 80% and a median PFS of 21.4 and 14.4 months, respectively[81].

### SUPPORTING DATA

The Phase 3 FLAURA study reported that, relative to erlotinib or gefitinib, first-line osimertinib significantly increased both median PFS (18.9 vs. 10.2 months, HR=0.46) and median OS (38.6 vs. 31.8 months; HR=0.80) for patients with advanced NSCLC and activating, sensitizing EGFR mutations (specifically, exon 19 deletion or L858)[81,277] . 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)[278]. A Phase 1 study reported that T790M-negative patients with acquired EGFR TKI resistance experienced an ORR of 21% and a median PFS of 2.8 months[43]. A Phase 1b/2 study evaluating osimertinib in combination with the CD73 inhibitor oleclumab for patients with advanced EGFR-mutated, T790M-negative NSCLC reported an ORR of 19% (4/19), a DCR of 81%, and mPFS of 11 months (Kim et al., 2021 AACR Abstract CT163). A Phase 1/2 trial of osimertinib in combination with bevacizumab for patients with untreated metastatic EGFR-mutated non-small cell lung cancer (NSCLC) reported an 80% (39/49) ORR, a 100% (6/6, 2 CRs) central nervous system response rate, median PFS of 19 months, and a 1-year PFS rate of 72%[279]. The Phase 1b TATTON study of osimertinib in combination with selumetinib, savolitinib, or durvalumab for patients with previously treated EGFR-mutated NSCLC reported ORRs of 42% (15/36), 44% (8/18), and 44% (10/23), respectively[280].

# Everolimus

*Assay findings association*

**PIK3CA**
E726K

### AREAS OF THERAPEUTIC USE

Everolimus is an orally available mTOR inhibitor that is FDA approved to treat renal cell carcinoma (RCC) following antiangiogenic therapy; pancreatic neuroendocrine tumors; and well-differentiated non-functional neuroendocrine tumors of the lung or gastrointestinal tract. Everolimus is also approved to treat either renal angiomyolipoma or subependymal giant cell astrocytoma in association with tuberous sclerosis complex (TSC). Please see the drug label for full prescribing information.

### GENE ASSOCIATION

On the basis of clinical evidence[90-97] , PIK3CA activating mutations may predict sensitivity to mTOR inhibitors such as everolimus and temsirolimus. Studies have reported modest activity of these therapies as single agents (ORRs of 0-4%), but improved activity has been observed when they are combined with other agents such as bevacizumab and doxorubicin (ORRs of 25-44%), for patients with PIK3CA-mutated solid tumors[94-97,281-285] .

### SUPPORTING DATA

A trial of everolimus as a monotherapy in non-small cell lung cancer (NSCLC) showed modest activity[286], but a Phase 2 study of everolimus in combination with docetaxel did not show any added benefit of everolimus in an unselected population[287]. A Phase 1 study evaluated the addition of everolimus to carboplatin and paclitaxel +/- bevacizumab in advanced NSCLC and found the combinations produced 1 CR and 10 PRs (n=52), although treatments were not well tolerated[288]. A Phase 1 study in patients with advanced NSCLC of the combination of everolimus and erlotinib reported 9 objective responses and 28 patients experiencing SD (n=74), but a Phase 2 study found the combination inefficacious at tolerated doses[289-290] . A trial of combination treatment with sorafenib and everolimus reported 1 PR and 1 SD in 2 patients with lung adenocarcinoma, with both patients experiencing progression-free survival of more than 4 months[291]. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[292], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[293].

# Temsirolimus

*Assay findings association*

**PIK3CA**
E726K

### AREAS OF THERAPEUTIC USE

Temsirolimus is an intravenous mTOR inhibitor that is FDA approved for the treatment of advanced renal cell carcinoma. Please see the drug label for full prescribing information.

### GENE ASSOCIATION

On the basis of clinical evidence[90-97] , PIK3CA activating mutations may predict sensitivity to mTOR inhibitors such as everolimus and temsirolimus. Studies have reported modest activity of these therapies as single agents (ORRs of 0-4%), but improved activity has been observed when they are combined with other agents such as bevacizumab and doxorubicin (ORRs of 25-44%), for patients with PIK3CA-mutated solid tumors[94-97,281-285] .

### SUPPORTING DATA

In a Phase 2 clinical trial in non-small cell lung cancer (NSCLC), front-line temsirolimus monotherapy demonstrated some clinical benefit but failed to meet the trial's primary end point[294]. In a Phase 1 trial of temsirolimus and radiation in patients with NSCLC, of 8 evaluable patients, 3 exhibited PR and 2 exhibited SD[295].

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



Electronically signed by Brennan Decker, M.D., Ph.D. | 08 October 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

**Sample Preparation:** 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
**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

**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**
*BARD1*

**ALTERATION**
A25fs*41

**RATIONALE**
Tumors with BARD1 inactivating mutation or loss may be sensitive to PARP inhibitors.

## NCT04380636

**PHASE 3**

Phase 3 Study of Pembrolizumab With Concurrent Chemoradiation Therapy Followed by Pembrolizumab With or Without Olaparib in Stage III Non-Small Cell Lung Cancer (NSCLC) (MK-7339-012/KEYLYNK-012)

**TARGETS**
PD-L1, PARP, PD-1

**LOCATIONS:** Fuzhou (China), Xiamen (China), Hangzhou (China), Shanghai (China), Shangai (China), Nanchang (China), Shenzhen (China), Changsha (China), Wuhan (China), Fukuoka (Japan)

## NCT04123366

**PHASE 2**

Study of Olaparib (MK-7339) in Combination With Pembrolizumab (MK-3475) in the Treatment of Homologous Recombination Repair Mutation (HRRm) and/or Homologous Recombination Deficiency (HRD)-Positive Advanced Cancer (MK-7339-007/KEYLYNK-007)

**TARGETS**
PARP, PD-1

**LOCATIONS:** Fukuoka (Japan), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Okayama (Japan), Nagoya (Japan), Tokyo (Japan), Kashiwa (Japan), Sapporo (Japan), Nedlands (Australia), Southport (Australia)

## NCT03742895

**PHASE 2**

Efficacy and Safety of Olaparib (MK-7339) in Participants With Previously Treated, Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD) Positive Advanced Cancer (MK-7339-002 / LYNK-002)

**TARGETS**
PARP

**LOCATIONS:** Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Chelyabinsk (Russian Federation), Nedlands (Australia), Kazan (Russian Federation), Arkhangelsk (Russian Federation), Port Macquarie (Australia), Ryazan (Russian Federation), Darlinghurst (Australia), Moscow (Russian Federation)

## NCT03739710

**PHASE 1/2**

Platform Trial of Novel Regimens Versus Standard of Care (SoC) in Non-small Cell Lung Cancer (NSCLC)

**TARGETS**
CTLA-4, ICOS, PD-1, TIM-3, PARP

**LOCATIONS:** Cheongju-si, Chungcheongbuk-do (Korea, Republic of), Gyeonggi-do (Korea, Republic of), Seongnam (Korea, Republic of), Seoul (Korea, Republic of), Saint-Petersburg (Russian Federation), Uppsala (Sweden), Solna (Sweden), Otopeni (Romania), Warszawa (Poland), Lodz (Poland)

## NCT02264678

**PHASE 1/2**

Ascending Doses of AZD6738 in Combination With Chemotherapy and/or Novel Anti Cancer Agents

**TARGETS**
ATR, PARP, PD-L1

**LOCATIONS:** Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), London (United Kingdom), Sutton (United Kingdom), Villejuif (France), Saint Herblain (France), California

## NCT04635631

**PHASE 1**

STUDY OF TALAZOPARIB MONOTHERAPY IN CHINESE PARTICIPANTS WITH ADVANCED SOLID TUMORS

**TARGETS**
PARP

**LOCATIONS:** Beijing (China), Changchun (China)

## NCT03772561

**PHASE 1**

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

**TARGETS**
PARP, AKTs, PD-L1

**LOCATIONS:** Singapore (Singapore)

## NCT04801966

**PHASE NULL**

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

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

**LOCATIONS:** Melbourne (Australia)

## NCT04550494

**PHASE 2**

Measuring the Effects of Talazoparib in Patients With Advanced Cancer and DNA Repair Variations

**TARGETS**
PARP

**LOCATIONS:** Maryland

## NCT04497116

**PHASE 1/2**

Study of RP-3500 in Advanced Solid Tumors

**TARGETS**
ATR, PARP

**LOCATIONS:** Copenhagen (Denmark), Newcastle Upon Tyne (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Toronto (Canada), Massachusetts, Rhode Island, New York, Tennessee, Texas



Electronically signed by Brennan Decker, M.D., Ph.D. | 08 October 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

**Sample Preparation:** 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
**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

**GENE**
## *EGFR*

**ALTERATION**
exon 19 deletion (E746_A750del)

**RATIONALE**
EGFR activating mutations, rearrangements, or amplification may predict sensitivity to EGFR-targeted therapies. Strategies to overcome resistance to current agents include next-generation EGFR inhibitors and combination therapies.

### NCT04619004

**PHASE 2**

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

**TARGETS**
ERBB3

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

### NCT03521154

**PHASE 3**

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

**TARGETS**
EGFR

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

### NCT04487080

**PHASE 3**

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

**TARGETS**
MET, EGFR

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

### NCT02609776

**PHASE 1**

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

**TARGETS**
MET, EGFR

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

### NCT02099058

**PHASE 1**

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

**TARGETS**
MET, EGFR, PD-1

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

### NCT04077463

**PHASE 1**

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

**TARGETS**
EGFR, MET

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



Electronically signed by Brennan Decker, M.D., Ph.D. | 08 October 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

**Sample Preparation:** 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
**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

## NCT04035486

**PHASE 3**

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

**TARGETS**
EGFR

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

## NCT03720873

**PHASE 2**

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

**TARGETS**
EGFR, FGFRs, KIT, VEGFRs

**LOCATIONS:** Fuzhou (China)

## NCT04058704

**PHASE 3**

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

**TARGETS**
EGFR

**LOCATIONS:** Hangzhou (China)

## NCT04770688

**PHASE 1/2**

Advanced Lung Tumor Treated by Osimertinib Plus Anlotinib

**TARGETS**
EGFR

**LOCATIONS:** Shanghai (China)



Electronically signed by Brennan Decker, M.D., Ph.D. | 08 October 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

**Sample Preparation:** 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
**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

**GENE**
*PIK3CA*

**ALTERATION**
E726K

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

## NCT04589845

**PHASE 2**

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

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

**LOCATIONS:** Zhongzheng Dist. (Taiwan), Taipei City (Taiwan), Tainan (Taiwan), Seoul (Korea, Republic of), Beijing (China), Woolloongabba (Australia), Darlinghurst (Australia), Randwick (Australia), Melbourne (Australia), Haifa (Israel)

## NCT03239015

**PHASE 2**

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

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

**LOCATIONS:** Shanghai (China)

## NCT04337463

**PHASE NULL**

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

**TARGETS**
mTORC1, mTORC2, PD-1

**LOCATIONS:** Chongqing (China), Chengdu (China)

## NCT02688881

**PHASE 4**

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

**TARGETS**
mTOR

**LOCATIONS:** Seoul (Korea, Republic of)

## NCT04803318

**PHASE 2**

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

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

**LOCATIONS:** Guangzhou (China)

## NCT03772561

**PHASE 1**

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

**TARGETS**
PARP, AKTs, PD-L1

**LOCATIONS:** Singapore (Singapore)



Electronically signed by Brennan Decker, M.D., Ph.D. | 08 October 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

**Sample Preparation:** 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
**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

## NCT04801966

**PHASE NULL**

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

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

**LOCATIONS:** Melbourne (Australia)

## NCT03994796

**PHASE 2**

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

**TARGETS**
ALK, ROS1, TRKA, TRKB, TRKC, CDK4, CDK6, PI3K, mTOR

**LOCATIONS:** Alaska, Washington

## NCT04632992

**PHASE 2**

A Study Evaluating Targeted Therapies in Participants Who Have Advanced Solid Tumors With Genomic Alterations or Protein Expression Patterns Predictive of Response

**TARGETS**
ALK, ROS1, TRKA, TRKB, TRKC, PD-L1, ERBB2, ERBB3, PI3K-alpha, RET, AKTs

**LOCATIONS:** Alaska, Washington, Oregon, California, Montana

## 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:** Aberdeen (United Kingdom), Newcastle (United Kingdom), Glasgow (United Kingdom), Leeds (United Kingdom), Colchester (United Kingdom), Sheffield (United Kingdom), Cambridge (United Kingdom), Manchester (United Kingdom), Leicester (United Kingdom), Maidstone (United Kingdom)

**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.

***FANCA***
G811D

***IGF1R***
G1328S

***MERTK***
N648H

***MLL2***
P2193L

***MSH3***
A58V



Electronically signed by Brennan Decker, M.D., Ph.D. | 08 October 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

**Sample Preparation:** 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
**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

## 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) | ***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** | *C11orf30* (EMSY) | *C17orf39* (GID4) | *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** | *EP300* |
| *EPHA3* | *EPHB1* | *EPHB4* | ***ERBB2*** | ***ERBB3*** **Exons 3, 6, 7, 8, 10, 12, 20, 21, 23, 24, 25** | *ERBB4* | *ERCC4* | *ERG* | ***ERRFI1*** |
| ***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 | *FAM46C* | *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* |
| ***GNA11*** **Exons 4, 5** | *GNA13* | ***GNAQ*** **Exons 4, 5** | ***GNAS*** **Exons 1, 8** | *GRM3* | *GSK3B* | *H3F3A* | *HDAC1* | *HGF* |
| *HNF1A* | ***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) |



Electronically signed by Brennan Decker, M.D., Ph.D. | 08 October 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

**Sample Preparation:** 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
**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

## 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** | *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** | *NSD3* (WHSC1L1) | *NT5C2* | ***NTRK1*** **Exons 14, 15, Introns 8-11** | *NTRK2* Intron 12 | ***NTRK3*** **Exons 16, 17** | *NUTM1** Intron 1 | *P2RY8* | ***PALB2*** |
| *PARK2* | *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)** | *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*** **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* | *RSPO2** Intron 1 | *SDC4** Intron 2 | *SDHA* | *SDHB* | *SDHC* |
| *SDHD* | *SETD2* | *SF3B1* | *SGK1* | *SLC34A2** Intron 4 | *SMAD2* | *SMAD4* | *SMARCA4* | *SMARCB1* |
| ***SMO*** | *SNCAIP* | *SOCS1* | *SOX2* | *SOX9* | *SPEN* | *SPOP* | *SRC* | *STAG2* |
| *STAT3* | ***STK11*** | *SUFU* | *SYK* | *TBX3* | *TEK* | *TERC** ncRNA | ***TERT**** **Promoter** | *TET2* |
| *TGFBR2* | *TIPARP* | *TMPRSS2** Introns 1-3 | *TNFAIP3* | *TNFRSF14* | ***TP53*** | *TSC1* | *TSC2* | *TYRO3* |
| *U2AF1* | ***VEGFA*** | *VHL* | *WHSC1* | *WT1* | *XPO1* | *XRCC2* | *ZNF217* | *ZNF703* |

### ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite (MS) status

Blood Tumor Mutational Burden (bTMB)

Tumor Fraction



Electronically signed by Brennan Decker, M.D., Ph.D. | 08 October 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

**Sample Preparation:** 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
**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

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.

CE IVD

## 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 ≥5%, and bTMB is calculated based on variants with an allele frequency of ≥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 observed aneuploid instability in the sample.
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 to: *ASXL1*, *ATM*, *CBL*, *CHEK2*, *DNMT3A*, *JAK2*, *KMT2D* (*MLL2*), *MPL*, *MYD88*, *SF3B1*, *TET2*, *TP53*, and *U2AF1*.
11. Alterations reported may include somatic (not



Electronically signed by Brennan Decker, M.D., Ph.D. | 08 October 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

**Sample Preparation:** 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
**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

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.

## 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. 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.

## 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.

## SELECT ABBREVIATIONS

| ABBREVIATION | DEFINITION |
|---|---|
| CR | Complete response |
| DCR | Disease control rate |
| DNMT | DNA methyltransferase |
| HR | Hazard ratio |
| ITD | Internal tandem duplication |
| MMR | Mismatch repair |
| Muts/Mb | Mutations per megabase |
| NOS | Not otherwise specified |
| ORR | Objective response rate |
| OS | Overall survival |
| PD | Progressive disease |
| PFS | Progression-free survival |
| PR | Partial response |
| SD | Stable disease |
| TKI | Tyrosine kinase inhibitor |

MR Suite Version 5.0.0



Electronically signed by Brennan Decker, M.D., Ph.D. | 08 October 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

**Sample Preparation:** 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
**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

1. Gandara DR, et al. Nat. Med. (2018) pmid: 30082870
2. Wang Z, et al. JAMA Oncol (2019) pmid: 30816954
3. Aggarwal C, et al. Clin. Cancer Res. (2020) pmid: 32102950
4. Li et al., 2020; ASCO Abstract 6511
5. Nie W, et al. J Natl Compr Canc Netw (2020) pmid: 32380463
6. Ma Y, et al. Front Oncol (2021) pmid: 34055609
7. Xiao D, et al. Oncotarget (2016) pmid: 27009843
8. Chen Y, et al. J. Exp. Clin. Cancer Res. (2019) pmid: 31088500
9. Yu H, et al. J Thorac Oncol (2019) pmid: 30253973
10. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
11. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
12. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
13. Rizvi NA, et al. Science (2015) pmid: 25765070
14. Johnson BE, et al. Science (2014) pmid: 24336570
15. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
16. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
17. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
18. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
19. Nature (2012) pmid: 22810696
20. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
21. Li et al., 2021; AACR Abstract 2231
22. Bronkhorst AJ, et al. Biomol Detect Quantif (2019) pmid: 30923679
23. Raja R, et al. Clin. Cancer Res. (2018) pmid: 30093454
24. Hrebien S, et al. Ann. Oncol. (2019) pmid: 30860573
25. Choudhury AD, et al. JCI Insight (2018) pmid: 30385733
26. Goodall J, et al. Cancer Discov (2017) pmid: 28450425
27. Goldberg SB, et al. Clin. Cancer Res. (2018) pmid: 29330207
28. Bettegowda C, et al. Sci Transl Med (2014) pmid: 24553385
29. Lapin M, et al. J Transl Med (2018) pmid: 30400802
30. Shulman DS, et al. Br. J. Cancer (2018) pmid: 30131550
31. Stover DG, et al. J. Clin. Oncol. (2018) pmid: 29298117
32. Hemming ML, et al. JCO Precis Oncol (2019) pmid: 30793095
33. Egyud M, et al. Ann. Thorac. Surg. (2019) pmid: 31059681
34. Fan G, et al. PLoS ONE (2017) pmid: 28187169
35. Vu et al., 2020; DOI: 10.1200/PO.19.00204
36. Li G, et al. J Gastrointest Oncol (2019) pmid: 31602320
37. Zhang EW, et al. Cancer (2020) pmid: 32757294
38. Butler TM, et al. Cold Spring Harb Mol Case Stud (2019) pmid: 30833418
39. Rosell R, et al. Lancet Oncol. (2012) pmid: 22285168
40. Douillard JY, et al. Br. J. Cancer (2014) pmid: 24263064
41. Sequist LV, et al. J. Clin. Oncol. (2013) pmid: 23816960
42. Mok TS, et al. J. Clin. Oncol. (2018) pmid: 29864379
43. Jänne PA, et al. N. Engl. J. Med. (2015) pmid: 25923549
44. Hong MH, et al. Cancer (2020) pmid: 32749686
45. Kim HS, et al. Oncotarget (2015) pmid: 26462025
46. Kim HS, et al. Clin. Cancer Res. (2015) pmid: 25424851
47. Mondal G, et al. Acta Neuropathol (2020) pmid: 32303840
48. Cavalieri S, et al. Eur. J. Cancer (2018) pmid: 29734047
49. Chi AS, et al. JCO Precis Oncol (2020) pmid: 32923886
50. Haura et al., 2019; ASCO Abstract 9009
51. Cho et al., 2020; ESMO Abstract 1258O
52. Bauml et al., 2021; ASCO Abstract 9006
53. Janne et al., 2021; ASCO Abstract 9007
54. Ahn MJ, et al. Lancet Respir Med (2017) pmid: 29056570
55. Yang Z, et al. Sci Transl Med (2016) pmid: 27928026
56. Ahn MJ, et al. Lancet Oncol (2019) pmid: 31587882
57. Socinski MA, et al. N. Engl. J. Med. (2018) pmid: 29863955
58. Chen JY, et al. Cancer Biol Med (2015) pmid: 26175928
59. Schoenfeld AJ, et al. Clin. Cancer Res. (2020) pmid: 31911548
60. Vallee A, et al. Int. J. Oncol. (2013) pmid: 23934203
61. Imielinski M, et al. Cell (2012) pmid: 22980975
62. Nature (2014) pmid: 25079552
63. Nature (2012) pmid: 22960745
64. Watzka SB, et al. Eur J Cardiothorac Surg (2010) pmid: 20353893
65. Liang Z, et al. BMC Cancer (2010) pmid: 20637128
66. Grob TJ, et al. Lung Cancer (2013) pmid: 23238037
67. Park S, et al. Histol. Histopathol. (2012) pmid: 22207554
68. Dobashi Y, et al. Hum. Pathol. (2011) pmid: 21040950
69. Ludovini V, et al. Cancer Chemother. Pharmacol. (2013) pmid: 23314677
70. Skrzypski M, et al. Clin Lung Cancer (2013) pmid: 23870818
71. Kim SH, et al. Histol. Histopathol. (2012) pmid: 22419022
72. Lee JS, et al. Ann. Surg. Oncol. (2013) pmid: 23525704
73. Oakley GJ, et al. J Thorac Oncol (2011) pmid: 21587084
74. Marks JL, et al. J Thorac Oncol (2008) pmid: 18303429
75. Izar B, et al. Ann. Thorac. Surg. (2013) pmid: 23932319
76. Ciardiello F, et al. N. Engl. J. Med. (2008) pmid: 18337605
77. Lynch TJ, et al. N. Engl. J. Med. (2004) pmid: 15118073
78. Paez JG, et al. Science (2004) pmid: 15118125
79. Pao W, et al. Proc. Natl. Acad. Sci. U.S.A. (2004) pmid: 15329413
80. Yang JC, et al. Lancet Oncol. (2015) pmid: 25589191
81. Soria JC, et al. N. Engl. J. Med. (2018) pmid: 29151359
82. Wu YL, et al. Lancet Oncol. (2017) pmid: 28958502
83. Gilmer TM, et al. Cancer Res. (2008) pmid: 18199554
84. Foster SA, et al. Cancer Cell (2016) pmid: 26996308
85. Fritsch C, et al. Mol. Cancer Ther. (2014) pmid: 24608574
86. Juric D, et al. J. Clin. Oncol. (2018) pmid: 29401002
87. Gallant JN, et al. NPJ Precis Oncol (2019) pmid: 30793038
88. André F, et al. N. Engl. J. Med. (2019) pmid: 31091374
89. Smyth LM, et al. NPJ Breast Cancer (2021) pmid: 33863913
90. Park HS, et al. PLoS ONE (2016) pmid: 27105424
91. Lim SM, et al. Oncotarget (2016) pmid: 26859683
92. Hou MM, et al. Oncotarget (2014) pmid: 25426553
93. Varnier R, et al. Eur J Cancer (2019) pmid: 31351267
94. Janku F, et al. Cell Rep (2014) pmid: 24440717
95. Moroney J, et al. Clin. Cancer Res. (2012) pmid: 22927482
96. Basho RK, et al. JAMA Oncol (2017) pmid: 27893038
97. Moroney JW, et al. Clin. Cancer Res. (2011) pmid: 21890452
98. Vansteenkiste JF, et al. J Thorac Oncol (2015) pmid: 26098748
99. Esteva FJ, et al. Am. J. Pathol. (2010) pmid: 20813970
100. Baselga J, et al. J. Clin. Oncol. (2014) pmid: 25332247
101. Chakrabarty A, et al. Oncogene (2010) pmid: 20581867
102. Kataoka Y, et al. Ann. Oncol. (2010) pmid: 19633047
103. Wang L, et al. BMC Cancer (2011) pmid: 21676217
104. Campbell JD, et al. Nat. Genet. (2016) pmid: 27158780
105. Spoerke JM, et al. Clin. Cancer Res. (2012) pmid: 23136191
106. Wang H, et al. J BUON () pmid: 23335533
107. Ji M, et al. BMC Cancer (2011) pmid: 21507233
108. Massion PP, et al. Cancer Res. (2002) pmid: 12097266
109. Zhao Q, et al. Future Oncol (2014) pmid: 24328409
110. Eng J, et al. J Thorac Oncol (2015) pmid: 26334752
111. Song Z, et al. Cancer Med (2016) pmid: 27554588
112. Zhang L, et al. Onco Targets Ther (2013) pmid: 23674897
113. McGowan M, et al. Lung Cancer (2017) pmid: 28024696
114. Wang Y, et al. Asian Pac. J. Cancer Prev. (2015) pmid: 26107237
115. Samuels Y, et al. Cancer Cell (2005) pmid: 15950905
116. Nat. Rev. Cancer (2009) pmid: 19629070
117. Kang S, et al. Proc. Natl. Acad. Sci. U.S.A. (2005) pmid: 15647370
118. Ikenoue T, et al. Cancer Res. (2005) pmid: 15930273
119. Gymnopoulos M, et al. Proc. Natl. Acad. Sci. U.S.A. (2007) pmid: 17376864
120. Horn S, et al. Oncogene (2008) pmid: 18317450
121. Rudd ML, et al. Clin. Cancer Res. (2011) pmid: 21266528
122. Hon WC, et al. Oncogene (2012) pmid: 22120714
123. Burke JE, et al. Proc. Natl. Acad. Sci. U.S.A. (2012) pmid: 22949682
124. Wu H, et al. Proc. Natl. Acad. Sci. U.S.A. (2009) pmid: 19915146
125. Laurenti R, et al. Rev Saude Publica (1990) pmid: 2103068
126. Dan S, et al. Cancer Res. (2010) pmid: 20530683
127. Oda K, et al. Cancer Res. (2008) pmid: 18829572
128. Zhao L, et al. Oncogene (2008) pmid: 18794883
129. Lui VW, et al. Cancer Discov (2013) pmid: 23619167
130. Ross RL, et al. Oncogene (2013) pmid: 22430209
131. Rivière JB, et al. Nat. Genet. (2012) pmid: 22729224
132. Shibata T, et al. Cancer Lett. (2009) pmid: 19394761
133. Dogruluk T, et al. Cancer Res. (2015) pmid: 26627007
134. Croessmann S, et al. Clin. Cancer Res. (2018) pmid: 29284706
135. Ng PK, et al. Cancer Cell (2018) pmid: 29533785
136. Spangle JM, et al. (2020) pmid: 32929011
137. Chen L, et al. Nat Commun (2018) pmid: 29636477
138. O'Malley et al., 2017; AACR-NCI-EORTC Abstract LB-A12
139. Wu W, et al. Cancer Res. (2015) pmid: 25634209
140. Wang Y, et al. J. Clin. Invest. (2016) pmid: 27454289
141. Ozden O, et al. Sci Rep (2016) pmid: 27197561
142. Zhao W, et al. Nature (2017) pmid: 28976962
143. Zhang YQ, et al. Int. J. Cancer (2012) pmid: 21815143
144. Gynecol. Oncol. (2010) pmid: 19959210
145. Laufer M, et al. J. Biol. Chem. (2007) pmid: 17848578
146. Westermark UK, et al. Mol. Cell. Biol. (2003) pmid: 14560035
147. Cerami E, et al. Cancer Discov (2012) pmid: 22588877
148. Gao J, et al. Sci Signal (2013) pmid: 23550210
149. Trowbridge JJ, et al. Nat. Genet. (2011) pmid: 22200773
150. Prog Mol Biol Transl Sci (2011) pmid: 21507354
151. Yang J, et al. Mol Med Rep () pmid: 21887466
152. Vallböhmer D, et al. Clin Lung Cancer (2006) pmid: 16870044
153. Daskalos A, et al. Cancer (2011) pmid: 21351083
154. Fabbri M, et al. Proc. Natl. Acad. Sci. U.S.A. (2007) pmid: 17890317
155. Gao Q, et al. Proc. Natl. Acad. Sci. U.S.A. (2011) pmid: 22011581
156. Kim MS, et al. APMIS (2013) pmid: 23031157
157. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
158. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838



Electronically signed by Brennan Decker, M.D., Ph.D. | 08 October 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

**Sample Preparation:** 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
**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

159. Xie M, et al. Nat. Med. (2014) pmid: 25326804
160. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
161. Severson EA, et al. Blood (2018) pmid: 29678827
162. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
163. Hematology Am Soc Hematol Educ Program (2018) pmid: 30504320
164. Chabon JJ, et al. Nature (2020) pmid: 32269342
165. Razavi P, et al. Nat. Med. (2019) pmid: 31768066
166. Hirai H, et al. Cancer Biol. Ther. (2010) pmid: 20107315
167. Bridges KA, et al. Clin. Cancer Res. (2011) pmid: 21799033
168. Rajeshkumar NV, et al. Clin. Cancer Res. (2011) pmid: 21389100
169. Osman AA, et al. Mol. Cancer Ther. (2015) pmid: 25504633
170. Xu L, et al. Mol. Cancer Ther. (2002) pmid: 12489850
171. Xu L, et al. Mol. Med. (2001) pmid: 11713371
172. Camp ER, et al. Cancer Gene Ther. (2013) pmid: 23470564
173. Kim SS, et al. Nanomedicine (2015) pmid: 25240597
174. Pirollo KF, et al. Mol. Ther. (2016) pmid: 27357628
175. Hajdenberg et al., 2012; ASCO Abstract e15010
176. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27601554
177. Moore et al., 2019; ASCO Abstract 5513
178. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27998224
179. Oza et al., 2015; ASCO Abstract 5506
180. Lee J, et al. Cancer Discov (2019) pmid: 31315834
181. Méndez E, et al. Clin. Cancer Res. (2018) pmid: 29535125
182. Ma CX, et al. J. Clin. Invest. (2012) pmid: 22446188
183. Lehmann S, et al. J. Clin. Oncol. (2012) pmid: 22965953
184. Mohell N, et al. Cell Death Dis (2015) pmid: 26086967
185. Fransson Å, et al. J Ovarian Res (2016) pmid: 27179933
186. Gourley et al., 2016; ASCO Abstract 5571
187. Kwok M, et al. Blood (2016) pmid: 26563132
188. Boudny M, et al. Haematologica (2019) pmid: 30975914
189. Dillon MT, et al. Mol. Cancer Ther. (2017) pmid: 28062704
190. Middleton FK, et al. Cancers (Basel) (2018) pmid: 30127241
191. Mogi A, et al. J. Biomed. Biotechnol. (2011) pmid: 21331359
192. Tekpli X, et al. Int. J. Cancer (2013) pmid: 23011884
193. Vignot S, et al. J. Clin. Oncol. (2013) pmid: 23630207
194. Maeng CH, et al. Anticancer Res. (2013) pmid: 24222160
195. Cortot AB, et al. Clin Lung Cancer (2014) pmid: 24169260
196. Itakura M, et al. Br. J. Cancer (2013) pmid: 23922113
197. Kim Y, et al. J. Clin. Oncol. (2014) pmid: 24323028
198. Dong ZY, et al. Clin. Cancer Res. (2017) pmid: 28039262
199. Seo JS, et al. Genome Res. (2012) pmid: 22975805
200. Brown CJ, et al. Nat. Rev. Cancer (2009) pmid: 19935675
201. Joerger AC, et al. Annu. Rev. Biochem. (2008) pmid: 18410249
202. Kato S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12826609
203. Kamada R, et al. J. Biol. Chem. (2011) pmid: 20978130
204. Zerdoumi Y, et al. Hum. Mol. Genet. (2017) pmid: 28472496
205. Yamada H, et al. Carcinogenesis (2007) pmid: 17690113
206. Bougeard G, et al. J. Clin. Oncol. (2015) pmid: 26014290
207. Sorrell AD, et al. Mol Diagn Ther (2013) pmid: 23355100
208. Nichols KE, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11219776
209. Kleihues P, et al. Am. J. Pathol. (1997) pmid: 9006316
210. Gonzalez KD, et al. J. Clin. Oncol. (2009) pmid: 19204208
211. Lalloo F, et al. Lancet (2003) pmid: 12672316
212. Mandelker D, et al. Ann. Oncol. (2019) pmid: 31050713
213. Wu YL, et al. Lancet Oncol. (2014) pmid: 24439929
214. Passaro et al., 2019; ELCC Abstract 1150
215. Audet et al., 2013; ASCO Abstract 6041
216. Lau SC, et al. Clin Lung Cancer (2019) pmid: 31178389
217. Paz-Ares L, et al. Ann. Oncol. (2017) pmid: 28426106
218. Thongprasert S, et al. Lung Cancer Manag (2019) pmid: 31807143
219. Januszewski et al., 2018; IASLC WCLC Abstract P1.13-17
220. Suzuki et al., 2018; IASLC WCLC Abstract P1.01-92
221. Chang et al., 2018; IASLC WCLC Abstract P1.01-11
222. Llinás-Quintero N, et al. Case Rep Oncol Med (2019) pmid: 31637072
223. Miller VA, et al. Lancet Oncol. (2012) pmid: 22452896
224. Chen X, et al. Lung Cancer (2013) pmid: 23664448
225. Katakami N, et al. J. Clin. Oncol. (2013) pmid: 23816963
226. Landi L, et al. Clin Lung Cancer (2014) pmid: 25242668
227. De Grève J, et al. Lung Cancer (2015) pmid: 25682316
228. Yang JC, et al. Lancet Oncol. (2015) pmid: 26051236
229. Horn L, et al. Lung Cancer (2017) pmid: 29110849
230. Yamamoto N, et al. Adv Ther (2020) pmid: 31863283
231. Soria JC, et al. Lancet Oncol. (2015) pmid: 26156651
232. Dziadziuszko R, et al. J Thorac Oncol (2019) pmid: 30825613
233. Lai WV, et al. Eur. J. Cancer (2019) pmid: 30685684
234. Greulich H, et al. Proc. Natl. Acad. Sci. U.S.A. (2012) pmid: 22908275
235. Gow CH, et al. J Thorac Oncol (2015) pmid: 26134234
236. Mazières J, et al. Ann. Oncol. (2016) pmid: 26598547
237. Mazières J, et al. J. Clin. Oncol. (2013) pmid: 23610105
238. De Grève J, et al. Lung Cancer (2012) pmid: 22325357
239. Li BT, et al. Lung Cancer (2015) pmid: 26559459
240. Costa DB, et al. J Thorac Oncol (2016) pmid: 26964772
241. Yuan B, et al. Front Oncol (2020) pmid: 32477948
242. Fang W, et al. Oncologist (2019) pmid: 31748336
243. Schuler M, et al. Ann. Oncol. (2016) pmid: 26646759
244. Opsomer RJ, et al. Acta Urol Belg (1985) pmid: 2986437
245. Wu et al., 2018; WCLC abstract MA26.11
246. Ramalingam SS, et al. Ann. Oncol. (2016) pmid: 26768165
247. Yu HA, et al. Lung Cancer (2017) pmid: 29191595
248. Reckamp KL, et al. Cancer (2014) pmid: 24501009
249. Jänne PA, et al. Clin. Cancer Res. (2011) pmid: 21220471
250. van Geel RMJM, et al. Br. J. Cancer (2020) pmid: 32147669
251. Jänne PA, et al. J Thorac Oncol (2016) pmid: 26899759
252. Cappuzzo F, et al. Lancet Oncol. (2010) pmid: 20493771
253. Zhong WZ, et al. J. Clin. Oncol. (2019) pmid: 31194613
254. Petrelli F, et al. Clin Lung Cancer (2012) pmid: 22056888
255. Yang JJ, et al. Br. J. Cancer (2017) pmid: 28103612
256. Lee CK, et al. J. Natl. Cancer Inst. (2017) pmid: 28376144
257. Nakagawa K, et al. Lancet Oncol. (2019) pmid: 31591063
258. Stinchcombe TE, et al. JAMA Oncol (2019) pmid: 31393548
259. Truini A, et al. Clin. Cancer Res. (2019) pmid: 31182434
260. Shepherd FA, et al. N. Engl. J. Med. (2005) pmid: 16014882
261. Han JY, et al. J. Clin. Oncol. (2012) pmid: 22370314
262. Maemondo M, et al. N. Engl. J. Med. (2010) pmid: 20573926
263. Mitsudomi T, et al. Lancet Oncol. (2010) pmid: 20022809
264. Mok TS, et al. N. Engl. J. Med. (2009) pmid: 19692680
265. Qi WX, et al. Curr Med Res Opin (2015) pmid: 25329826
266. Zhao H, et al. J Thorac Oncol (2015) pmid: 25546556
267. Wang J, et al. Int. J. Cancer (2019) pmid: 30255937
268. Baik CS, et al. J Thorac Oncol (2015) pmid: 26398831
269. Yoshioka H, et al. Ann. Oncol. (2019) pmid: 31553438
270. Fukuoka M, et al. J. Clin. Oncol. (2011) pmid: 21670455
271. Noronha V, et al. J. Clin. Oncol. (2019) pmid: 31411950
272. Hosomi Y, et al. J. Clin. Oncol. (2020) pmid: 31682542
273. Sutiman N, et al. J Thorac Oncol (2017) pmid: 27908825
274. Gibbons DL, et al. J Thorac Oncol (2016) pmid: 27198414
275. Alanazi A, et al. Lung Cancer Manag (2020) pmid: 33318755
276. Kim et al., 2021; DOI: 10.1200/PO.20.00296
277. Ramalingam SS, et al. N. Engl. J. Med. (2019) pmid: 31751012
278. Herbst et al., 2020; ASCO Abstract LBA5
279. Yu HA, et al. JAMA Oncol (2020) pmid: 32463456
280. Oxnard GR, et al. Ann. Oncol. (2020) pmid: 32139298
281. Janku F, et al. Cancer Res. (2013) pmid: 23066039
282. Janku F, et al. J. Clin. Oncol. (2012) pmid: 22271473
283. Janku F, et al. Mol. Cancer Ther. (2011) pmid: 21216929
284. Moulder S, et al. Ann. Oncol. (2015) pmid: 25878190
285. Byeon et al., 2020; doi: 10.21037/tcr.2020.04.07
286. Soria JC, et al. Ann. Oncol. (2009) pmid: 19549709
287. Khuri et al., 2011; ASCO Abstract e13601
288. Eberhardt WE, et al. Invest New Drugs (2014) pmid: 23579358
289. Papadimitrakopoulou VA, et al. J Thorac Oncol (2012) pmid: 22968184
290. Besse B, et al. Ann. Oncol. (2014) pmid: 24368400
291. Toffalorio F, et al. Oncologist (2014) pmid: 24674875
292. Tolcher AW, et al. Ann. Oncol. (2015) pmid: 25344362
293. Patterson et al., 2018; AACR Abstract 3891
294. Reungwetwattana T, et al. J Thorac Oncol (2012) pmid: 22722792
295. Waqar SN, et al. Clin Lung Cancer (2014) pmid: 24373609



Electronically signed by Brennan Decker, M.D., Ph.D. | 08 October 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. · 1.888.988.3639

**Sample Preparation:** 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
**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