**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 cancer (NOS)

**DATE OF BIRTH** 31 December 1940
**SEX** Male
**MEDICAL RECORD #** Not given

## PHYSICIAN

**MEDICAL FACILITY** Arias Stella
**ADDITIONAL RECIPIENT** None
**MEDICAL FACILITY ID** 317319
**PATHOLOGIST** Not Provided

## SPECIMEN

**SPECIMEN ID** HBH 12/31/1940
**SPECIMEN TYPE** Blood
**DATE OF COLLECTION** 23 April 2021
**SPECIMEN RECEIVED** 28 April 2021

## Biomarker Findings

**Blood Tumor Mutational Burden** - 1 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.*

***KRAS*** G12V
***TP53*** C176F, L111M

**0** Therapies with Clinical Benefit
**0** Therapies with Lack of Response
**10** Clinical Trials

## BIOMARKER FINDINGS

**Blood Tumor Mutational Burden -** 1 Muts/Mb

**Microsatellite status -** MSI-High Not Detected

**Tumor Fraction -** Cannot Be Determined

## THERAPY AND CLINICAL TRIAL IMPLICATIONS

**No therapies or clinical trials.** See Biomarker Findings section

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

**Tumor fraction is an estimate of the percentage of circulating-tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample based on observed aneuploid instability.**

| GENOMIC FINDINGS | | VAF % |
|---|---|---|
| ***KRAS*** - | G12V | 1.6% |
| **10 Trials** see p. 6 | | |

| THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE) | THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE) |
|---|---|
| None | None |

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

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

***TP53*** - C176F, L111M ..... p. 5

**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*, *BRCA1*, *BRCA2*, *BRIP1*, *MEN1*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *NF2*, *PALB2*, *PMS2*, *PTEN*, *RAD51C*, *RAD51D*, *RB1*, *RET*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, *SMAD4*, *STK11*, *TGFBR2*, *TP53*, *TSC1*, *TSC2*, *VHL*, and *WT1* is recommended.

Variant Allele Frequency is not applicable for copy number alterations.



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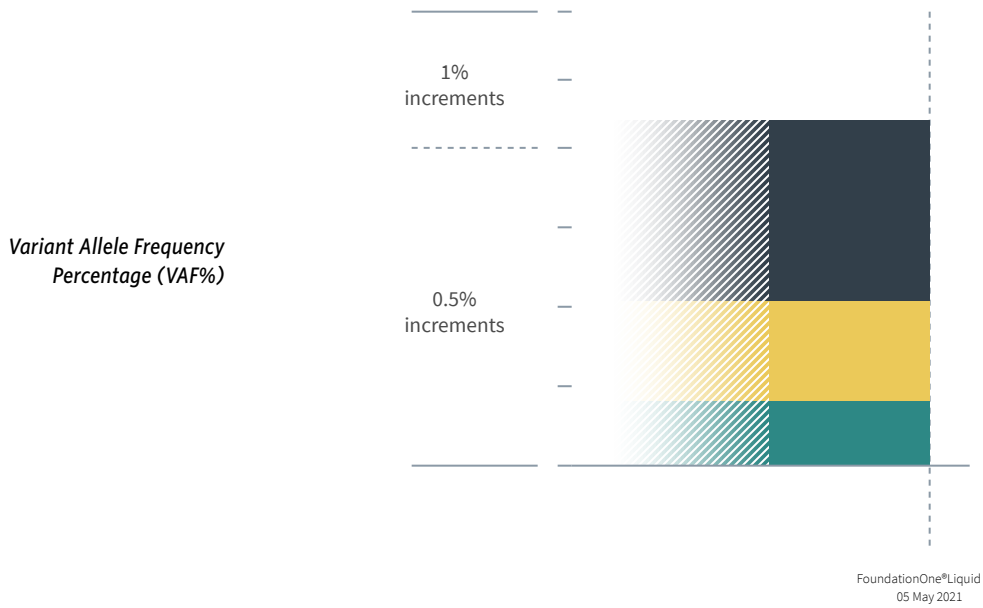


| HISTORIC PATIENT FINDINGS | | ORD-1081686-01 VAF% |
|---|---|---|
| **Blood Tumor Mutational Burden** | | 1 Muts/Mb |
| **Microsatellite status** | | MSI-High Not Detected |
| **Tumor Fraction** | | Cannot Be Determined |
| ***KRAS*** | ● G12V | 1.6% |
| ***TP53*** | ● L111M | 0.41% |
| | ● C176F | 0.63% |

**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

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



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BIOMARKER

# Blood Tumor Mutational Burden

**RESULT**
1 Muts/Mb

## POTENTIAL TREATMENT STRATEGIES

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]. Published data investigating the prognostic implications of bTMB levels in lung cancer are limited (PubMed, Jul 2020). 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)[5]. 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[6]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[6-7].

## 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[8-9] and cigarette smoke in lung cancer[10-11], treatment with temozolomide-based chemotherapy in glioma[12-13], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[14-18], and microsatellite instability (MSI)[14,17-18]. 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

Specimens with high tumor fraction values have high circulating-tumor DNA (ctDNA) content, and thus high sensitivity for identifying genomic alterations. Such specimens are at low risk of false negative results. However, if 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[19-24].

## 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)[25]. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer[26], Ewing sarcoma and osteosarcoma[27], prostate cancer[22], breast cancer[28], leiomyosarcoma[29], esophageal cancer[30], colorectal cancer[31], and gastrointestinal cancer[32].

## 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[33], 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[34-35]. However, the tumor fraction estimate in this sample could not be determined with confidence.



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GENE
# *KRAS*

**ALTERATION**
G12V

**TRANSCRIPT ID**
NM_004985

**CODING SEQUENCE EFFECT**
35G>T

## POTENTIAL TREATMENT STRATEGIES

Preclinical evidence suggests that KRAS activation may predict sensitivity to MEK inhibitors, such as trametinib, binimetinib, cobimetinib, and selumetinib[36-41]. Multiple clinical studies have reported either low response rates or response rates similar to those of chemotherapy in patients with KRAS-mutated NSCLC receiving MEK inhibitors as a monotherapy[42-44]. In a Phase 3 study, the addition of selumetinib to docetaxel did not significantly improve the PFS or OS of patients with KRAS-mutant NSCLC relative to docetaxel alone[45]. In a Phase 1/1b study evaluating trametinib with either docetaxel or pemetrexed, responses were independent of KRAS mutation status[46]. Combinatorial approaches involving MEK inhibitors and other targeted therapies, including PI3K or EGFR inhibitors, have generally had limited clinical efficacy in patients with NSCLC and have been associated with high toxicity[47-49] despite preclinical evidence supporting the effectiveness of combinatorial strategies involving inhibitors of PI3K[50-51], RAF[52], pan-ERBB[53], or BCL2[54-55]. However, a Phase 1 combination trial of the MEK inhibitor PD-0325901 with the CDK4/6 inhibitor palbociclib that included 17 patients with KRAS-mutant NSCLC reported 1 PR, >50% SD, and 5 patients with PFS >6 months; clinical benefit was seen among patients with tumors harboring KRAS mutation alone or together with inactivation of TP53 or CDKN2A/B, but not among patients with tumors harboring KRAS mutation and STK11 inactivation[56]. The CDK4/6 inhibitor abemaciclib demonstrated increased activity in KRAS-mutated NSCLC compared to KRAS-wildtype NSCLC (median PFS of 2.8 vs. 1.9 months) in a Phase 1 trial[57] but did not prolong median OS compared to erlotinib (7.4 vs. 7.8 months, HR=0.97), in spite of improved PFS (3.6 vs. 1.9 months, HR=0.58) and ORR (8.9% vs. 2.7%) relative to erlotinib, in a Phase 3 study for patients with platinum-refractory KRAS-mutated advanced NSCLC[58]. Although some studies have suggested that KRAS mutation status may predict a lack of response to the EGFR inhibitors erlotinib and gefitinib in patients with lung cancer, a retrospective study suggests that there is no statistically significant difference in response to EGFR tyrosine kinase inhibitors among KRAS-wildtype and KRAS-mutated patients[59-62]. A study assessing the immune checkpoint inhibitor nivolumab for pretreated patients with KRAS-mutated (n=206) or KRAS-wildtype (n=324) advanced NSCLC observed a similar ORR (20% vs. 17%), median PFS (4 vs. 3 months) and OS (11.2 vs. 10 months) in both cohorts, although the 3-month PFS rate was significantly longer in KRAS-positive than KRAS-negative patients (53% vs. 42%)[63]. Co-occurring KRAS and STK11 alterations are associated with poorer response to immune checkpoint inhibitors for patients with NSCLC. Following anti-PD-1-based regimens, retrospective analyses have reported shorter OS for patients with KRAS- and STK11-mutated tumors than for those whose KRAS-mutated tumors were STK11-wildtype (6.4 vs. 16.1 months, HR=1.99), as well as markedly fewer objective responses for patients with KRAS-/STK11-mutated versus KRAS-/TP53-mutated tumors in the CheckMate-057 (0% [0/6] vs. 57% [4/7])[64] and GEMINI (0% [0/6], vs. 53% [9/17])[65]. Another study observed that patients with NSCLC and KRAS-mutated tumors without STK11 alteration who were treated with second-line immunotherapy experienced similar median PFS (2.8 vs. 2.2 months, HR = 1.64) and numerically longer median OS (7.7 vs. 3.5 months, HR = 2.3; p=0.09) compared to patients harboring mutations in both KRAS and STK11[66]. Combination of a RAF-MEK inhibitor CH5126766 and FAK inhibitor defactinib elicited clinical responses for patients with low-grade serous ovarian cancer (PR rate 50% [4/8]) and non-small cell lung cancer (PR rate 10% [1/10]) with KRAS mutations[67]. The reovirus Reolysin targets cells with activated RAS signaling[68-70] and is in clinical trials in patients with some tumor types. Reolysin has demonstrated mixed clinical efficacy, with the highest rate of response reported for patients with head and neck cancer[71-79]. The role of EGFR or KRAS mutations as biomarkers for response to Reolysin in NSCLC is unclear[80].

## FREQUENCY & PROGNOSIS

Studies have reported KRAS mutations in 10-38% of non-small cell lung cancers (NSCLC), including 27-37% of lung adenocarcinomas[81-92], 10.5-33% of lung adenosquamous carcinomas[93-95], 22% of lung large cell carcinoma without neuroendocrine features, and 6% of lung large cell neuroendocrine carcinomas[96]. KRAS mutation was associated with shorter PFS (7.0 vs. 8.6 months, p=0.026) and OS (14.2 vs. 21.6 months, p=0.019) with first-line treatment with bevacizumab plus chemotherapy in a retrospective study[97] and a lower major pathological response rate (0% [0/10] vs. 35.5% [11/31]) after neoadjuvant bevacizumab plus chemotherapy followed by adjuvant bevacizumab in a Phase 2 trial[98], relative to those patients lacking KRAS mutation. However, addition of atezolizumab to first-line bevacizumab and chemotherapy improved PFS regardless of KRAS status in the Phase 3 IMpower150 study (HR=0.50 for KRAS mutant vs. 0.47 for KRAS wild-type vs. 0.67 for KRAS unknown)[99]. In one study of 55 patients with lung adenocarcinoma, KRAS mutations, especially in combination with TP53 alterations, correlated with improved clinical outcomes to PD-1 inhibitors pembrolizumab and nivolumab, likely as a consequence of association with some immunogenic features such as tumor mutation burden[100]. KRAS mutation in lung adenocarcinoma has been correlated with disease progression, poorly differentiated tumors, and aggressive tumor behavior[86,92,101]. However, the prognostic value of KRAS mutation in lung adenocarcinoma may differ among ethnic groups and may depend upon the specific allelic variant present[102].

## FINDING SUMMARY

KRAS encodes a member of the RAS family of small GTPases. Activating mutations in RAS genes can cause uncontrolled cell proliferation and tumor formation[37,103]. KRAS alterations affecting amino acids G12, G13, Q22, P34, A59, Q61, and A146, as well as mutations G10_A11insG, G10_A11insAG (also reported as G10_A11dup and G12_G13insAG), A18D, L19F, D33E, G60_A66dup/E62_A66dup, E62K, and K117N have been characterized as activating and oncogenic[37,104-125].



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GENE
# *TP53*

**ALTERATION**
C176F, L111M

**TRANSCRIPT ID**
NM_000546, NM_000546

**CODING SEQUENCE EFFECT**
527G>T, 331C>A

## POTENTIAL TREATMENT STRATEGIES

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[126-129], or p53 gene therapy and immunotherapeutics such as SGT-53[130-134] and ALT-801[135]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% (17/176) and SDs in 53.4% (94/176) of patients with solid tumors; the response rate was 21.1% (4/19) in patients with TP53 mutations versus 12.1% (4/33) in patients who were TP53 wild-type[136]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 31.9% (30/94, 3 CR) ORR and a 73.4% (69/94) DCR in patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[137]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 42.9% (9/21, 1 CR) ORR and a 76.2% (16/21) DCR in patients with platinum-refractory TP53-mutated ovarian cancer[138]. The combination of adavosertib with paclitaxel and carboplatin in patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[139]. 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[140]. 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[141]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel in patients with solid tumors, 75.0% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[134]. 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[142]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutant p53 such as APR-246[143-145]. In a Phase 1b trial in 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[146]. 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[147-148]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[149-150]. 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)[83,151-157], including 42-52% of lung adenocarcinomas and 58-83% of lung squamous cell carcinomas (cBioPortal, COSMIC, Feb 2021)[82-83,151,158]. TP53 homozygous deletion has been observed in 1.4% of lung adenocarcinoma and <1% of lung squamous cell carcinoma cases (cBioPortal, Feb 2021)[159-160]. 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[100]. Mutations in TP53 have been associated with lymph node metastasis in patients with lung adenocarcinoma[161].

## FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[162]. Alterations such as seen here may disrupt TP53 function or expression[163-167].

## 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[168-170], including sarcomas[171-172]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[173] to 1:20,000[172]. 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[174]. 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[175-180]. 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[175-176]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[181]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[179,182-183]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.



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## CLINICAL TRIALS

**IMPORTANT** Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months. While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and should be investigated by the physician or research staff. This is not a comprehensive list of all available clinical trials. There may also be compassionate use or early access programs available, which are not listed in this report. Foundation Medicine displays a subset of trial options and ranks them in this order of descending priority: Qualification for pediatric trial → Geographical proximity → Later trial phase. Clinical trials are not ranked in order of potential or predicted efficacy for this patient or in order of level of evidence for this patient's tumor type. Clinical trials listed here may have additional enrollment criteria that may require medical screening to determine final eligibility. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov. However, clinicaltrials.gov does not list all clinical trials that might be available.

**GENE**
*KRAS*

**ALTERATION**
G12V

**RATIONALE**
KRAS activating mutations or amplification may predict sensitivity to inhibitors of MAPK pathway components, including MEK inhibitors. KRAS alterations are not predictive biomarkers for MEK inhibitor monotherapy in NSCLC and combinatorial approaches may yield improved efficacy. Clinical evidence suggests that patients with KRAS-mutant NSCLC may be sensitive to the CDK4/6 inhibitor abemaciclib.

### NCT03600701

**PHASE 2**

Atezolizumab and Cobimetinib in Treating Patients With Metastatic, Recurrent, or Refractory Non-small Cell Lung Cancer

**TARGETS**
PD-L1, MEK

**LOCATIONS:** Florida, Alabama, North Carolina, Virginia, District of Columbia, Oklahoma, Ohio, Michigan, New Hampshire

### NCT03099174

**PHASE 1**

This Study in Patients With Different Types of Cancer (Solid Tumours) Aims to Find a Safe Dose of Xentuzumab in Combination With Abemaciclib With or Without Hormonal Therapies. The Study Also Tests How Effective These Medicines Are in Patients With Lung and Breast Cancer.

**TARGETS**
CDK4, CDK6, IGF-1, IGF-2, Aromatase, ER

**LOCATIONS:** Florida, North Carolina, Connecticut, Minnesota, Nevada, California, Malaga (Spain), Pozuelo de Alarcón (Spain), Madrid (Spain), Plerin Sur Mer (France)

### NCT03989115

**PHASE 1/2**

Dose-Escalation and Dose-Expansion of RMC-4630 and Cobimetinib in Relapsed/Refractory Solid Tumors

**TARGETS**
SHP2, MEK

**LOCATIONS:** Florida, Georgia, Texas, North Carolina, Tennessee, Virginia, Oklahoma, Maryland, Pennsylvania, Ohio

### NCT03905148

**PHASE 1/2**

Study of the Safety and Pharmacokinetics of BGB-283 and PD-0325901 in Patients With Advanced or Refractory Solid Tumors

**TARGETS**
RAFs, EGFR, MEK

**LOCATIONS:** Texas, Randwick (Australia), Blacktown (Australia), Melbourne (Australia), Nedlands (Australia)

### NCT03581487

**PHASE 1/2**

Durvalumab, Tremelimumab, and Selumetinib in Treating Participants With Recurrent or Stage IV Non-small Cell Lung Cancer

**TARGETS**
MEK, PD-L1, CTLA-4

**LOCATIONS:** Texas



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## CLINICAL TRIALS

### NCT02974725

**PHASE 1**

Study of LXH254 and LTT462 in NSCLC

**TARGETS**
CDK6, CDK4, ERK1, ERK2, ARAF, BRAF, MEK

**LOCATIONS:** Texas, Tennessee, Massachusetts, California, Sevilla (Spain), Madrid (Spain), Valencia (Spain), Pamplona (Spain), Barcelona (Spain)

### NCT02079740

**PHASE 1/2**

Trametinib and Navitoclax in Treating Patients With Advanced or Metastatic Solid Tumors

**TARGETS**
BCL-W, BCL-XL, BCL2, MEK

**LOCATIONS:** Massachusetts

### NCT03170206

**PHASE 1/2**

Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the MEK Inhibitor Binimetinib (MEK162) for Patients With Advanced KRAS Mutant Non-Small Cell Lung Cancer

**TARGETS**
MEK, CDK4, CDK6

**LOCATIONS:** Massachusetts

### 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:** Exeter (United Kingdom), Belfast (United Kingdom), Cardiff (United Kingdom), Bristol (United Kingdom), Wirral (United Kingdom), Southampton (United Kingdom), Glasgow (United Kingdom), Birmingham (United Kingdom), Manchester (United Kingdom), Oxford (United Kingdom)

### NCT03284502

**PHASE 1**

Cobimetinib and HM95573 in Patients With Locally Advanced or Metastatic Solid Tumors

**TARGETS**
MEK, RAFs

**LOCATIONS:** Seoul (Korea, Republic of), Goyang-si (Korea, Republic of), Seongnam (Korea, Republic of), Pusan (Korea, Republic of), Hwasun (Korea, Republic of)

**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.

***BCORL1***
D90E

***DNMT3A***
G532D

***GNAS***
A400_D401insAPA

***JAK3***
L134V

***MAP3K1***
R59W

***POLD1***
D27V

***SDHA***
R352Q

***ZNF703***
A401_H402insPTHLGGSSCST CSA



Electronically signed by Naomi Lynn Ferguson, M.D. | 04 May 2021
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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) |



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## APPENDIX Genes assayed in FoundationOne®Liquid CDx

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

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| ***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



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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 detects select genomic rearrangements, select copy number alterations, 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 ALTERATIONS AND THERAPIES

*Biomarker and Genomic Findings*

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

*Clinical Trials*

Pediatric trial qualification → Geographical proximity → Later trial phase.

## 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



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

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

## 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.

## 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 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 4.0.0



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