

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 Pancreas neuroendocrine carcinoma

NAME Lin, Kuo-Hsiung

DATE OF BIRTH 01 May 1945

SEX Male

MEDICAL RECORD # 6292279

PHYSICIAN

ORDERING PHYSICIAN Chen, Ming-Huang

MEDICAL FACILITY Taipei Veterans General Hospital

ADDITIONAL RECIPIENT None

MEDICAL FACILITY ID 205872

PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN ID KHL 05/01/1945

SPECIMEN TYPE Blood

DATE OF COLLECTION 15 September 2021

SPECIMEN RECEIVED 21 September 2021

Biomarker Findings

Blood Tumor Mutational Burden - 6 Muts/Mb

Microsatellite status - MSI-High Not Detected

Tumor Fraction - 72%

Genomic Findings

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

KRAS G12D

KDM6A Y362fs*2

RB1 L44fs*21

TP53 R282W

0 Therapies with Clinical Benefit

2 Clinical Trials

0 Therapies with Resistance

BIOMARKER FINDINGS

Blood Tumor Mutational Burden - 6 Muts/Mb

Microsatellite status - MSI-High Not Detected

Tumor Fraction - 72%

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 - G12D

59.2%

2 Trials see p. 8

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

None

THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)

None

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.

KDM6A - Y362fs*2 p. 5 **TP53 - R282W** p. 7

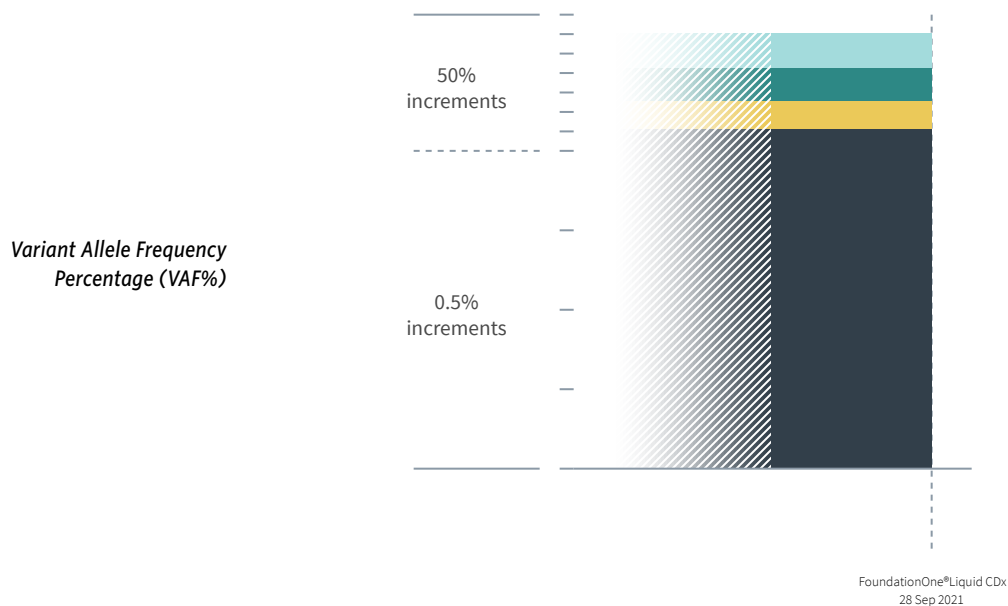
RB1 - L44fs*21 p. 6

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.

ORDERED TEST # ORD-1192856-01



HISTORIC PATIENT FINDINGS

ORD-1192856-01
VAF%

Blood Tumor Mutational Burden

6 Muts/Mb

Microsatellite status

MSI-High Not Detected

Tumor Fraction

72%

KRAS

● G12D

59.2%

KDM6A

● Y362fs*2

84.6%

RB1

● L44fs*21

72.0%

TP53

● R282W

88.3%

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

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

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

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

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

Not Detected = baited but not detected on test

Detected = present (VAF% is not applicable)

VAF% = variant allele frequency percentage

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

ORDERED TEST # ORD-1192856-01

BIOMARKER FINDINGS

BIOMARKER

Blood Tumor Mutational Burden

RESULT

6 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in NSCLC and HSNCC, increased bTMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1¹⁻² and anti-PD-1³ therapies. In NSCLC, multiple clinical trials have shown patients with higher bTMB derive clinical benefit from immune checkpoint inhibitors following single agent or combination treatments with

either CTLA4 inhibitors or chemotherapy, with reported high bTMB cutpoints ranging from 6 to 16 Muts/Mb¹. In 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 inhibitor⁴.

FREQUENCY & PROGNOSIS

Average bTMB levels in solid tumors other than NSCLC have not been evaluated (cBioPortal, COSMIC, PubMed, Mar 2021)⁵⁻⁷. Published data investigating the prognostic implications of tumor mutational burden in pancreas neuroendocrine tumors are limited (PubMed, Apr 2021).

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 melanoma⁸⁻⁹ and cigarette smoke in lung cancer¹⁰⁻¹¹, treatment with temozolomide-based chemotherapy in glioma¹²⁻¹³, mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes¹⁴⁻¹⁸, 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 agents¹⁻³. Depending on the clinical context, TMB testing of an alternate sample or by another methodology could be considered.

BIOMARKER

Tumor Fraction

RESULT

72%

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 results¹⁹. 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 management²⁰⁻²⁵.

FREQUENCY & PROGNOSIS

Detectable ctDNA levels have been reported in a variety of tumor types, with higher tumor fraction levels reported for patients with metastatic (Stage 4) tumors compared with patients with localized disease (Stages 1 to 3)²⁶. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer²⁷, Ewing sarcoma and osteosarcoma²⁸, prostate cancer²³, breast cancer²⁹, leiomyosarcoma³⁰, esophageal cancer³¹, colorectal

cancer³², and gastrointestinal cancer³³.

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 content³⁴, 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 therapy³⁵⁻³⁶.

ORDERED TEST # ORD-1192856-01

GENOMIC FINDINGS

GENE

KRAS

ALTERATION

G12D

TRANSCRIPT ID

NM_004985

CODING SEQUENCE EFFECT

35G>A

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical and clinical data suggest that KRAS mutations may predict clinical benefit from SHP2 inhibitors³⁷⁻³⁸. A Phase 1 study of RMC-4630 for relapsed/refractory solid tumors reported a DCR of 58% (23/40) for patients with NSCLC and KRAS mutations and a DCR of 75% (12/16) for patients with NSCLC and KRAS G12C mutations³⁹. Interim results from a Phase 1/2 study of RMC-4630 plus cobimetinib reported tumor reduction in 3 of 8 patients with KRAS-mutated colorectal cancer⁴⁰. Preclinical evidence suggests that KRAS activation may predict sensitivity to MEK inhibitors, such as trametinib, binimetinib, cobimetinib, and selumetinib⁴¹⁻⁴⁶. While clinical responses have been reported for patients with KRAS-mutated ovarian⁴⁷⁻⁵⁰, cervical small cell neuroendocrine⁵¹, or uterine cancer⁴⁹ treated with MEK inhibitor monotherapy, multiple clinical trials have not demonstrated increased response rates for patients with KRAS-altered tumors including KRAS-mutated CRC⁵²⁻⁵⁵,

pancreatic cancer⁵⁶⁻⁵⁸, and NSCLC^{53,59-60}. A Phase 2 study of trametinib and uprosertib for patients with recurrent cervical cancer reported no responses for patients with KRAS-mutated (2/2 SDs) or KRAS-amplified (1/1 SD) cancer⁶¹. Clinical responses have been reported for combination treatment strategies including MEK inhibitors with PI3K or AKT inhibitors for patients with KRAS-mutated ovarian cancer⁶²⁻⁶⁴ and KRAS-mutated endometrioid adenocarcinoma⁶⁵. Initial Phase 1 monotherapy trials of MEK inhibitors in patients with pancreatic cancer showed promise, with DCR (PR and/or SD) up to 37%⁶⁶, response rates up to 25%^{52,55,66-68}, and prolonged PRs in certain patients^{52,67,69}. However, subsequent clinical trials combining various MEK inhibitors with gemcitabine reported no additional benefit compared to gemcitabine alone irrespective of KRAS mutation status^{56-58,70}, with refametinib and gemcitabine even showing a trend towards worse response and survival in patients with KRAS-mutant pancreatic tumors than in those with KRAS wild-type tumors (OS 6.6 months vs 18.2 months)⁵⁶. Trials combining MEK inhibitors with other targeted therapies, such as EGFR inhibitors⁷¹ or PI3K-AKT pathway inhibitors⁷²⁻⁷³, reported no PRs and frequent adverse events in patients with KRAS-mutant pancreatic cancer. Emerging preclinical studies suggest MEK inhibition downstream of KRAS-mutant pancreatic tumors leads to increased autophagy⁷⁴⁻⁷⁵. Combination MEK/autophagy inhibitors may therefore be more beneficial. A heavily pretreated patient with pancreatic cancer treated with trametinib plus hydroxychloroquine

exhibited a PR⁷⁴. A Phase 2 trial of paclitaxel/carboplatin with or without Reolysin in patients with metastatic pancreatic adenocarcinoma reported no improvement in PFS with addition of Reolysin, regardless of KRAS mutational status⁷⁶; however a Phase 2 study of Reolysin and gemcitabine in patients with pancreatic cancer reported 1 PR, 23 SDs, and 5 PDs in 34 patients with a favorable median OS of 10.2 months⁷⁷.

FREQUENCY & PROGNOSIS

KRAS activating mutation has been reported in pancreatic small cell and large cell neuroendocrine carcinomas (NEC), at incidence of 50% of cases⁷⁸⁻⁷⁹ but was not observed in several studies of other types of pancreatic neuroendocrine tumors (NET)⁷⁸⁻⁸². In the context of pancreatic neuroendocrine carcinomas, KRAS mutation correlated with improved response rate to platinum-based chemotherapy⁷⁸.

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^{42,83}. 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^{42,84-105}.

GENE

KDM6A

ALTERATION

Y362fs*2

TRANSCRIPT ID

NM_021140

CODING SEQUENCE EFFECT

1082_1083insT

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies available to address

KDM6A alterations in cancer.

FREQUENCY & PROGNOSIS

KDM6A mutations have been reported in 3.9% of samples analyzed, with the highest incidence in tumors of the urinary tract (31%), endometrium (7%), and salivary gland (6%) (COSMIC, 2021)⁷. KDM6A mutations or copy number alterations have also been identified in medulloblastoma (8.9%)¹⁰⁶, adenoid cystic carcinoma (6.7%)¹⁰⁷, and metastatic prostate cancer (10%)¹⁰⁸. KDM6A inactivation has been found as a recurrent tumorigenic event in male T-cell acute lymphoblastic leukemia (T-ALL), and loss of KDM6A increased the sensitivity of T-ALL cells to

therapies targeting histone H3 lysine 27 methylation in preclinical assays¹⁰⁹. However, KDM6A overexpression has been noted in breast cancer and renal cell carcinoma, and correlated with inferior prognosis in patients with breast cancer¹¹⁰⁻¹¹².

FINDING SUMMARY

KDM6A encodes a histone H3 lysine 27 demethylase UTX, which functions as a transcriptional regulator¹¹³. A significant number of inactivating KDM6A mutations have been found across multiple tumor types, suggesting a role as a tumor suppressor¹¹³.

ORDERED TEST # ORD-1192856-01

GENOMIC FINDINGS

GENE
RB1

ALTERATION
L44fs*21

TRANSCRIPT ID
NM_000321

CODING SEQUENCE EFFECT
131delT

inhibitors such as palbociclib, abemaciclib, and ribociclib, which act upstream of Rb¹²¹⁻¹³⁰.

with improved response rate to platinum-based chemotherapy in one study¹³⁶.

— Nontargeted Approaches —

Loss of Rb function has been associated with increased sensitivity to cytotoxic agents and chemotherapeutics in both preclinical studies and in patients with bladder or breast cancer¹³¹⁻¹³².

FINDING SUMMARY

RB1 encodes the retinoblastoma protein (Rb), a tumor suppressor and negative regulator of the cell cycle^{132,137}. Alterations such as seen here may disrupt RB1 function or expression¹³⁸⁻¹⁴⁴.

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of limited clinical data¹¹⁴ and strong preclinical data¹¹⁵⁻¹¹⁷, RB1 inactivation may be associated with sensitivity to inhibitors of Aurora kinase A, particularly in small cell lung cancer. It should be noted that a trial of the Aurora kinase A inhibitor alisertib in advanced prostate cancer did not find an association between RB1 deletion and clinical benefit¹¹⁸. Other approaches to target RB1 inactivation under investigation in preclinical studies include inhibitors of BCL-2 family members¹¹⁹ and activation of the NOTCH pathway¹²⁰.

— Potential Resistance —

Rb inactivation may predict resistance to CDK4/6

FREQUENCY & PROGNOSIS

RB1 copy number loss has been found to be common in neuroendocrine tumors, including gastrointestinal neuroendocrine tumors, and high incidences of loss of Rb protein have also been observed in poorly differentiated NECs of the gastrointestinal tract^{79,133-135}. Studies of pancreatic neuroendocrine carcinomas reported that RB expression was abnormal in 50-74% of tumors (both small and large cell NECs), and that loss of expression was correlated with mutation of the RB1 gene; in contrast, this study found that all of the well-differentiated pancreatic neuroendocrine tumors analyzed showed intact expression of Rb protein⁷⁸⁻⁷⁹. Loss of Rb expression in small and large cell NECs correlated with improved response rate to platinum-based chemotherapy but with inferior overall survival to unspecified chemotherapy in multivariate analysis⁷⁸. Rb loss in pancreatic neuroendocrine carcinoma correlated

POTENTIAL DIAGNOSTIC IMPLICATIONS

Mutations in TP53 or RB1 are characteristic of poorly differentiated neuroendocrine carcinomas (NECs) (NCCN Neuroendocrine and Adrenal Tumors, v1.2021)¹⁴⁵⁻¹⁴⁸.

POTENTIAL GERMLINE IMPLICATIONS

Mutations in RB1 underlie the development of retinoblastoma (RB), a rare tumor that arises at a rate of approximately 1:20,000 live births, with nearly 5,000 new cases worldwide per year¹⁴⁹. Germline mutations in RB1 account for approximately 40% of RB tumors¹⁵⁰ and are associated with an increased risk of developing secondary malignancies that include soft tissue and bone sarcoma and malignant melanoma¹⁵¹⁻¹⁵². In the appropriate clinical context, germline testing of RB1 is recommended.

ORDERED TEST # ORD-1192856-01

GENOMIC FINDINGS

GENE

TP53

ALTERATION

R282W

TRANSCRIPT ID

NM_000546

CODING SEQUENCE EFFECT

844C>T

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 adavosertib¹⁵³⁻¹⁵⁶, or p53 gene therapy and immunotherapeutics such as SGT-53¹⁵⁷⁻¹⁶¹ and ALT-801¹⁶². 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-type¹⁶³. 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 cancer¹⁶⁴. 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 cancer¹⁶⁵. The combination of adavosertib with paclitaxel and carboplatin in patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone⁶². 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 paclitaxel¹⁶⁶. 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 alterations¹⁶⁷.

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 shrinkage¹⁶¹. 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 model¹⁶⁸. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutated p53 such as APR-246¹⁶⁹⁻¹⁷¹. 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% DCR¹⁷². 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 studies¹⁷³⁻¹⁷⁴; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies¹⁷⁵⁻¹⁷⁶. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

Although TP53 mutations are rare in pancreatic neuroendocrine tumors (NETs) (3%; 3/100 samples), aberrations in the p53 pathway commonly occur in pancreatic NETs, most often through dysregulation of its negative regulators MDM2, MDM4, and WIP1^{82,177}. Expression of p53 has been associated with aggressive and poorly differentiated gastroenteropancreatic NETs¹⁷⁸. A study of pancreatic NETs reported that increased p53 cytoplasmic protein expression was associated with metastasis¹⁷⁹.

FINDING SUMMARY

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

POTENTIAL DIAGNOSTIC IMPLICATIONS

Mutations in TP53 or RB1 are characteristic of poorly differentiated neuroendocrine carcinomas (NECs) (NCCN Neuroendocrine and Adrenal Tumors, v1.2021)¹⁴⁵⁻¹⁴⁸.

POTENTIAL GERMLINE IMPLICATIONS

One or more of the TP53 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with Li-Fraumeni syndrome (ClinVar, Mar 2021)¹⁸⁶. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers¹⁸⁷⁻¹⁸⁹, including sarcomas¹⁹⁰⁻¹⁹¹. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000¹⁹² to 1:20,000¹⁹¹. 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 30¹⁹³. 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 expansion¹⁹⁴⁻¹⁹⁹. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy¹⁹⁴⁻¹⁹⁵. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease²⁰⁰. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH^{198,201-202}. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

ORDERED TEST # ORD-1192856-01

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
G12D

RATIONALE
 KRAS activating mutations or amplification may predict sensitivity to inhibitors of MAPK pathway components, including MEK inhibitors. Multiple clinical studies have reported lack of efficacy of MEK inhibitors as monotherapy for treatment of

KRAS-mutant pancreatic cancer. Emerging data suggest patients with KRAS-mutant pancreatic cancer may be sensitive to combination MEK/autophagy inhibitors.

NCT04111458
PHASE 1

A Study to Test Different Doses of BI 1701963 Alone and Combined With Trametinib in Patients With Different Types of Advanced Cancer (Solid Tumours With KRAS Mutation)

TARGETS
 KRAS, SOS1, MEK

LOCATIONS: Frankfurt am Main (Germany), Köln (Germany), Utrecht (Netherlands), Rotterdam (Netherlands), Massachusetts, Tennessee, Texas, North Carolina

NCT03825289
PHASE 1

Trametinib and Hydroxychloroquine in Treating Patients With Pancreatic Cancer

TARGETS
 MEK

LOCATIONS: Utah

ORDERED TEST # ORD-1192856-01

APPENDIX
Variants of Unknown Significance

NOTE One or more variants of unknown significance (VUS) were detected in this patient's tumor. These variants may not have been adequately characterized in the scientific literature at the time this report was issued, and/or the genomic context of these alterations makes their significance unclear. We choose to include them here in the event that they become clinically meaningful in the future.

HGF
N398K

PRDM1
G391D

RPTOR
D71H

ORDERED TEST # ORD-1192856-01

APPENDIX

Genes assayed in FoundationOne®Liquid CDx

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

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	ERRF1
ESR1 Exons 4-8	ETV4* Intron 8	ETV5* Introns 6, 7	ETV6* Introns 5, 6	EWSR1* Introns 7-13	EZH2 Exons 4, 16, 17, 18	EZR* Introns 9-11	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
HNFI1A	HRAS Exons 2, 3	HSD3B1	ID3	IDH1 Exon 4	IDH2 Exon 4	IGF1R	IKBKE	IKZF1
INPP4B	IRF2	IRF4	IRS2	JAK1	JAK2 Exon 14	JAK3 Exons 5, 11, 12, 13, 15, 16	JUN	KDMSA
KDMSC	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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ORDERED TEST # ORD-1192856-01

APPENDIX

Genes assayed in FoundationOne®Liquid CDx

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

KRAS	<i>LTK</i>	<i>LYN</i>	<i>MAF</i>	MAP2K1 (MEK1) Exons 2, 3	MAP2K2 (MEK2) Exons 2-4, 6, 7	<i>MAP2K4</i>	<i>MAP3K1</i>	<i>MAP3K13</i>
<i>MAPK1</i>	<i>MCL1</i>	MDM2	<i>MDM4</i>	<i>MED12</i>	<i>MEF2B</i>	<i>MEN1</i>	<i>MERTK</i>	MET
<i>MITF</i>	<i>MKNK1</i>	<i>MLH1</i>	MPL Exon 10	<i>MRE11A</i>	<i>MSH2</i> Intron 5	<i>MSH3</i>	<i>MSH6</i>	<i>MST1R</i>
<i>MTAP</i>	MTOR Exons 19, 30, 39, 40, 43-45, 47, 48, 53, 56	<i>MUTYH</i>	<i>MYB*</i> Intron 14	MYC Intron 1	<i>MYCL</i> (MYCL1)	MYCN	MYD88 Exon 4	<i>NBN</i>
NF1	<i>NF2</i>	<i>NFE2L2</i>	<i>NFKBIA</i>	<i>NKX2-1</i>	<i>NOTCH1</i>	<i>NOTCH2</i> Intron 26	<i>NOTCH3</i>	NPM1 Exons 4-6, 8, 10
NRAS Exons 2, 3	<i>NSD3</i> (WHSC1L1)	<i>NTSC2</i>	NTRK1 Exons 14, 15, Introns 8-11	<i>NTRK2</i> Intron 12	NTRK3 Exons 16, 17	<i>NUTM1*</i> Intron 1	<i>P2RY8</i>	PALB2
<i>PARK2</i>	<i>PARP1</i>	<i>PARP2</i>	<i>PARP3</i>	<i>PAX5</i>	<i>PBRM1</i>	<i>PDCD1</i> (PD-1)	PDCD1LG2 (PD-L2)	PDGFRA Exons 12, 18, Introns 7, 9, 11
PDGFRB Exons 12-21, 23	<i>PDK1</i>	<i>PIK3C2B</i>	<i>PIK3C2G</i>	PIK3CA Exons 2, 3, 5-8, 10, 14, 19, 21 (Coding Exons 1, 2, 4-7, 9, 13, 18, 20) PPP2R2A	<i>PIK3CB</i>	<i>PIK3R1</i>	<i>PIM1</i>	<i>PMS2</i>
<i>POLD1</i>	<i>POLE</i>	<i>PPARG</i>	<i>PPP2R1A</i>		<i>PRDM1</i>	<i>PRKAR1A</i>	<i>PRKCI</i>	<i>PTCH1</i>
PTEN	PTPN11	<i>PTPRO</i>	<i>QKI</i>	<i>RAC1</i>	<i>RAD21</i>	<i>RAD51</i>	<i>RAD51B</i>	<i>RAD51C</i>
<i>RAD51D</i>	<i>RAD52</i>	<i>RAD54L</i>	RAF1 Exons 3, 4, 6, 7, 10, 14, 15, 17, Introns 4-8	<i>RARA</i> Intron 2	RB1	<i>RBM10</i>	<i>REL</i>	RET Introns 7, 8, Exons 11, 13-16, Introns 9-11
<i>RICTOR</i>	<i>RNF43</i>	ROS1 Exons 31, 36-38, 40, Introns 31-35	<i>RPTOR</i>	<i>RSPO2*</i> Intron 1	<i>SDC4*</i> Intron 2	<i>SDHA</i>	<i>SDHB</i>	<i>SDHC</i>
<i>SDHD</i>	<i>SETD2</i>	<i>SF3B1</i>	<i>SGK1</i>	<i>SLC34A2*</i> Intron 4	<i>SMAD2</i>	<i>SMAD4</i>	<i>SMARCA4</i>	<i>SMARCB1</i>
SMO	<i>SNCAIP</i>	<i>SOC1</i>	<i>SOX2</i>	<i>SOX9</i>	<i>SPEN</i>	<i>SPOP</i>	<i>SRC</i>	<i>STAG2</i>
<i>STAT3</i>	STK11	<i>SUFU</i>	<i>SYK</i>	<i>TBX3</i>	<i>TEK</i>	<i>TERC*</i> ncRNA	TERT* Promoter	<i>TET2</i>
<i>TGFBR2</i>	<i>TIPARP</i>	<i>TMPRSS2*</i> Introns 1-3	<i>TNFAIP3</i>	<i>TNFRSF14</i>	TP53	<i>TSC1</i>	<i>TSC2</i>	<i>TYRO3</i>
<i>U2AF1</i>	VEGFA	<i>VHL</i>	<i>WHSC1</i>	<i>WT1</i>	<i>XPO1</i>	<i>XRCC2</i>	<i>ZNF217</i>	<i>ZNF703</i>

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite (MS) status

Blood Tumor Mutational Burden (bTMB)

Tumor Fraction

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ORDERED TEST # ORD-1192856-01

APPENDIX

About FoundationOne® Liquid CDx

FoundationOne Liquid CDx fulfills the requirements of the European Directive 98/79 EC for in vitro diagnostic medical devices and is registered as a CE-IVD product by Foundation Medicine's EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium. The CE-IVD regulatory status of FoundationOne Liquid CDx is applicable in countries that accept and/or recognize the CE mark.



ABOUT FOUNDATIONONE LIQUID CDx

FoundationOne Liquid CDx was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne Liquid CDx may be used for clinical purposes and should not be regarded as purely investigational or for research only. Foundation Medicine's clinical reference laboratories are qualified to perform high-complexity clinical testing.

Please refer to technical information for performance specification details.

INTENDED USE

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

TEST PRINCIPLES

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

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

THE REPORT

Incorporates analyses of peer-reviewed studies and other publicly available information identified by Foundation Medicine; these analyses and information may include associations between a molecular alteration (or lack of alteration) and one or more drugs with potential clinical benefit (or potential lack of clinical benefit), including drug candidates that are being studied in clinical research. *Note:* A finding of biomarker alteration does not necessarily indicate pharmacologic effectiveness (or lack thereof) of any drug or treatment regimen; a finding of no biomarker alteration does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness) of any drug or treatment regimen.

QUALIFIED ALTERATION CALLS (EQUIVOCAL)

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

RANKING OF THERAPIES AND CLINICAL TRIALS

Ranking of Therapies in Summary Table

Therapies are ranked based on the following criteria: Therapies with clinical benefit (ranked alphabetically within each evidence category), followed by therapies associated with resistance (when applicable).

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

LIMITATIONS

- For *in vitro* diagnostic use.
- For prescription use only. This test must be ordered by a qualified medical professional in accordance with clinical laboratory regulations.
- 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.
- The FoundationOne Liquid CDx assay does not detect heterozygous deletions.
- The test is not intended to provide information on cancer predisposition.
- Performance has not been validated for cfDNA input below the specified minimum input.
- Tissue TMB and blood TMB (bTMB) are estimated from the number of synonymous and nonsynonymous single-nucleotide variants (SNVs) and insertions and deletions (indels) per area of coding genome sampled, after the removal of known and likely oncogenic driver events and germline SNPs. Tissue TMB is calculated based on variants with an allele frequency of $\geq 5\%$, and bTMB is calculated based on variants with an allele frequency of $\geq 0.5\%$.
- 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.
- 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.
- 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*.
- Alterations reported may include somatic (not

ORDERED TEST # ORD-1192856-01

APPENDIX

About FoundationOne®Liquid CDx

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

ORDERED TEST # ORD-1192856-01

APPENDIX

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APPENDIX
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