FOUNDATIONONE®LIQUID CDx

PATIENT
Lin, Cheng-Hao

TUMOR TYPE
Unknown primary neuroendocrine tumor (NET)

COUNTRY CODE
TW

REPORT DATE
22 December 2022

ORDERED TEST #
ORD-1523476-01

**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** Unknown primary neuroendocrine tumor (NET)
**NAME** Lin, Cheng-Hao
**DATE OF BIRTH** 21 May 1976
**SEX** Male
**MEDICAL RECORD #** 44329557

**PHYSICIAN**
**ORDERING PHYSICIAN** Yeh, Yi-Chen
**MEDICAL FACILITY** Taipei Veterans General Hospital
**ADDITIONAL RECIPIENT** None
**MEDICAL FACILITY ID** 205872
**PATHOLOGIST** Not Provided

**SPECIMEN**
**SPECIMEN ID** 5/21/1976 CHL
**SPECIMEN TYPE** Blood
**DATE OF COLLECTION** 09 December 2022
**SPECIMEN RECEIVED** 12 December 2022

## Biomarker Findings

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

## Genomic Findings

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

***PIK3CA*** E542K
***PTEN*** M35V, G165R
***MLL2*** E830*

## Report Highlights

- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 8)
- Variants that may represent **clonal hematopoiesis** and may originate from non-tumor sources: ***MLL2*** **E830*** (p. 7)

| BIOMARKER FINDINGS | THERAPY AND CLINICAL TRIAL IMPLICATIONS |
|---|---|
| **Blood Tumor Mutational Burden -** 3 Muts/Mb | **No therapies or clinical trials.** See Biomarker Findings section |
| **Microsatellite status -** MSI-High Not Detected | **MSI-High not detected. No evidence of microsatellite instability in this sample (see Appendix section).** |
| **Tumor Fraction -** Elevated Tumor Fraction | **Tumor fraction is considered elevated when ctDNA levels are high enough that aneuploidy can be detected. There is higher sensitivity for identifying genomic alterations and a lower risk of false negative results in specimens with elevated tumor fraction; the positive percent agreement observed between liquid and tissue for defined short variants is ≥ 90% (Li et al., 2021; AACR Abstract 2231) (see Biomarker Findings section).** |

| GENOMIC FINDINGS | | VAF% | THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE) | THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE) |
|---|---|---|---|---|
| ***PIK3CA*** - | E542K | 3.4% | None | None |
| **10 Trials** see p. 8 | | | | |
| ***PTEN*** - | M35V | 0.44% | None | None |
| | G165R | 0.66% | | |
| **10 Trials** see p. 10 | | | | |



Electronically signed by Julie Tse, M.D. | 22 December 2022
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## VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS (CH)

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

***MLL2*** - E830* p. 7

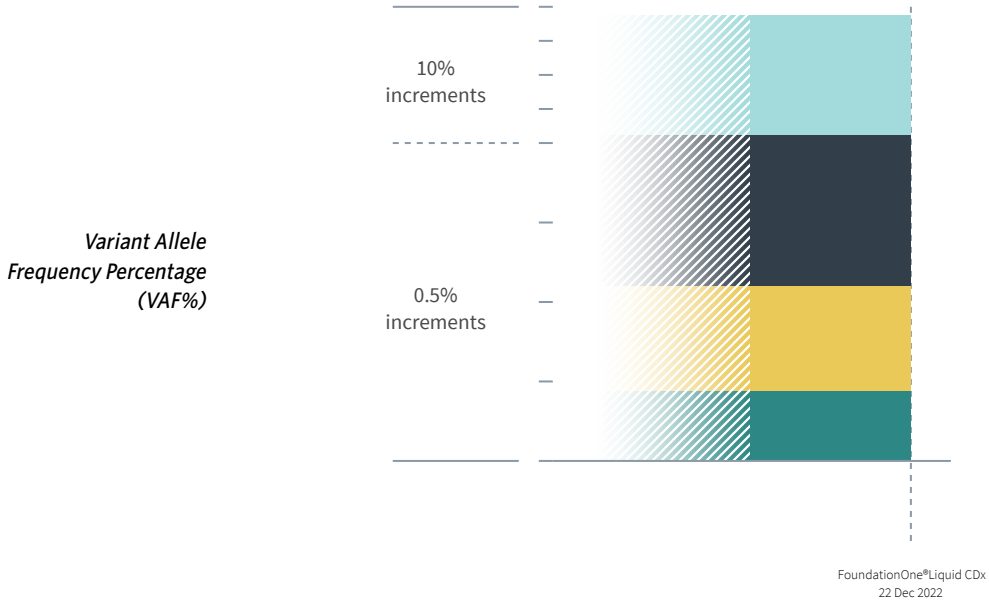
## GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

***MLL2*** - E830* p. 7

**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.




| HISTORIC PATIENT FINDINGS | | ORD-1523476-01 VAF% |
|---|---|---|
| **Blood Tumor Mutational Burden** | | 3 Muts/Mb |
| **Microsatellite status** | | MSI-High Not Detected |
| **Tumor Fraction** | | 67% |
| ***PIK3CA*** | E542K | 3.4% |
| ***PTEN*** | M35V | 0.44% |
| | G165R | 0.66% |
| ***MLL2*** | E830* | 35.1% |

**NOTE** This comparison table refers only to genes and biomarkers assayed by prior FoundationOne®Liquid CDx 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

BIOMARKER

# Blood Tumor Mutational Burden

**RESULT**
3 Muts/Mb

## POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

On the basis of clinical evidence in solid tumors, increased blood tumor mutational burden (bTMB) may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[1-3], anti-PD-1[3-4], anti-PD-1/CTLA4 therapies[5-6] , anti-PD-L1/CTLA4 therapies[7-10]. A Phase 2 multi-solid-tumor trial showed that bTMB ≥16 Muts/Mb (as measured by this assay) was associated with improved survival from treatment with a PD-1 inhibitor alone or in combination with a CTLA-4 inhibitor[5]. In non-small cell lung cancer (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 Muts/Mb-16 Muts/Mb[1,8-10]. In head and neck squamous cell carcinoma (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[11]. In colorectal cancer (CRC), a Phase 2 study showed that bTMB TMB ≥28 Muts/Mb (approximate equivalency ≥14 Muts/Mb as measured by this assay) was associated with improved OS from a PD-L1 inhibitor alone or in combination with a CTLA-4 inhibitor[7].

## FREQUENCY & PROGNOSIS

Average bTMB levels in solid tumors other than NSCLC have not been evaluated (PubMed, Mar 2022). In 1 retrospective study of patients with advanced neuroendocrine tumors not treated with immunotherapy, tumor mutational burden (TMB)-high (≥10 Muts/Mb) was not correlated with any significant difference in OS compared with TMB-low (≤ 10 Muts/Mb) measured in tissue samples (10.4 vs. 6.4 months, adjusted HR = 0.83)[12]. The impact of TMB on the prognosis and clinicopathological features of lung neuroendocrine cancers is unclear; large cell neuroendocrine carcinoma (LCNEC) cases with small cell lung cancer-like molecular features were reported to have significantly higher proliferative activity, as well as a trend toward better clinical benefit from treatment with chemotherapy, than non-small cell lung cancer-like tumors, but the average TMB was not significantly different between the two subsets of LCNEC[13]. MCPyV-negative Merkel cell carcinoma (MCC), associated with higher TMB, has been reported to have a higher number of predicted tumor neoantigens and a significantly higher UV mutation signature than MCPyV-positive MCC[14-15]. Within MCPyV-negative MCC tumors, the mutational burden has been reported to be significantly higher in PD-L1-positive tumors (more than 1% positive tumor and macrophage cells by immunohistochemistry) than in PD-L1-negative tumors[16].

## 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[17-18] and cigarette smoke in lung cancer[19-20], treatment with temozolomide-based chemotherapy in glioma[21-22], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[23-27], and microsatellite instability (MSI)[23,26-27]. 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[1-2,4]. Depending on the clinical context, TMB testing of an alternate sample or by another methodology could be considered.



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BIOMARKER

# Tumor Fraction

**RESULT**
Elevated Tumor Fraction

## POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

Specimens with elevated tumor fraction 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. 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[28-33].

## 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)[34]. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer[35], Ewing sarcoma and osteosarcoma[36], prostate cancer[31], breast cancer[37], leiomyosarcoma[38], esophageal cancer[39], colorectal cancer[40], and gastrointestinal cancer[41].

## 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[42], 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[43-44].

GENE
## *PIK3CA*

**ALTERATION**
E542K

**TRANSCRIPT ID**
NM_006218.2

**CODING SEQUENCE EFFECT**
1624G>A

**VARIANT CHROMOSOMAL POSITION**
chr3:178936082

## POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

Clinical and preclinical data in various tumor types indicate that PIK3CA activating alterations may predict sensitivity to therapies targeting PI3K[45-52], AKT[53-54], or mTOR[55-62]. The Phase 2 NCI-MATCH study of copanlisib for patients with refractory solid tumors harboring PIK3CA mutations with or without PTEN loss met its primary endpoint with an ORR of 16% (4/25 PRs); responses (PR or SD >6 months) were seen in patients with ameloblastoma, liposarcoma, and carcinomas of the endometrium, ovary, esophagus, lung, and prostate[52]. However, the Phase 2 study of copanlisib for patients with endometrial carcinoma harboring PIK3CA hotspot mutations failed to report any objective responses (n=11)[51]. Two other studies of copanlisib for patients with genomically unselected tumors reported 1 CR and 2 PRs (1 unconfirmed) among 16 total patients with PIK3CA-mutated solid tumors with or without PTEN alterations[49-50]. In the Phase 2 MATCH trial for patients with PIK3CA-mutated solid tumors, 28% (18/65) of patients experienced PFS lasting at least 6 months after treatment with taselisib; however, no ORs were observed in this study[63]. A separate Phase 1b study of taselisib in combination with the CDK4/6 inhibitor palbociclib for patients with PIK3CA-mutated solid tumors reported an ORR of 0% (n=12) and a DCR of 17% (2/12)[64]. In a Phase 1 trial of the dual PI3K/mTOR kinase inhibitor apitolisib, 79% (11/14) of patients with PIK3CA-mutated advanced solid tumors experienced disease control (3 PRs, 8 SDs)[65]. The PI3K inhibitor alpelisib is approved as a single agent for the treatment of patients with PIK3CA-related overgrowth spectrum (PROS)[66], but has shown limited activity as monotherapy for PIK3CA-mutated solid tumors with a Phase 1a study reporting an ORR of 6.0% (8/134) and a DCR of 58% (78/134)[46].

## FREQUENCY & PROGNOSIS

PIK3CA mutations have been reported in neuroendocrine carcinomas including pulmonary neuroendocrine tumors (23%), and in Merkel cell carcinomas (4%-10%), but have not been observed in pancreatic neuroendocrine tumors (n=98)[67-70]. p110-alpha has been reported to be overexpressed in 25% of small cell lung carcinomas as compared to normal lung tissue[71]. Published data investigating the prognostic implications of PIK3CA alteration in neuroendocrine carcinoma are limited (PubMed, Jul 2022).

## FINDING SUMMARY

PIK3CA encodes p110-alpha, which is the catalytic subunit of phosphatidylinositol 3-kinase (PI3K). The PI3K pathway is involved in cell signaling that regulates a number of critical cellular functions, including cell growth, proliferation, differentiation, motility, and survival[72-73]. PIK3CA alterations that have been characterized as activating, such as observed here, are predicted to be oncogenic[74-95].

GENE
## *PTEN*

**ALTERATION**
M35V, G165R

**TRANSCRIPT ID**
NM_000314.4, NM_000314.4

**CODING SEQUENCE EFFECT**
103A>G, 493G>A

**VARIANT CHROMOSOMAL POSITION**
chr10:89653805, chr10:89711875

### POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

PTEN loss or mutation leads to activation of the PI3K-AKT-mTOR pathway and may predict sensitivity to inhibitors of this pathway[50,96-98]. Across various tissues, most clinical studies have not observed an association between PTEN deficiency and response to inhibitors of the PI3K-AKT-mTOR pathway. However, limited studies in prostate cancer[99-102], renal cell carcinoma[103], breast cancer[104-105], and colorectal cancer[106] have reported an association between PTEN deficiency and response to inhibitors targeting the PI3K-AKT-mTOR pathway. Preclinical data indicate that PTEN loss or inactivation may predict sensitivity to PARP inhibitors[107-111], and clinical benefit has been observed for patients with PTEN-altered breast cancer including triple negative breast cancer[112], ovarian cancer[113], uterine leiomyosarcoma[114], and endometrial cancer[111] treated with PARP inhibitors. However, some studies have reported a lack of association between PTEN mutation and PARP inhibitor sensitivity[115-116].

### FREQUENCY & PROGNOSIS

PTEN mutations have been reported across solid tumors including endometrial (31%), glioma (21%), thyroid (8.7%), melanoma (8.5%), head and neck carcinoma (6.5%) and colorectal (6.1%)[117]. Loss of PTEN expression has been suggested to be associated with advanced tumor stage and shorter disease-free and overall survival in pancreatic NETs[118-119]. Another study reported that low cytoplasmic PTEN expression is also associated with poor prognosis in pancreatic NETs[120].

### FINDING SUMMARY

PTEN encodes an inositol phosphatase that functions as a tumor suppressor by negatively regulating the PI3K-AKT-mTOR pathway; loss of PTEN can lead to uncontrolled cell growth and suppression of apoptosis[97]. Alterations such as seen here may disrupt PTEN function or expression[121-162]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

### POTENTIAL GERMLINE IMPLICATIONS

One or more of the PTEN 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 hamartoma tumor syndrome (ClinVar, Sep 2022)[163]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. PTEN mutations underlie several inherited disorders, collectively termed PTEN hamartoma tumor syndrome (PHTS), which include Cowden syndrome (CS) and its variant Lhermitte-Duclos disease (LD), Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS), and Proteus-like syndrome[164-165]. The mutation rate for PTEN in these disorders ranges from 20 to 85% of patients[164,166]. The estimated incidence of Cowden syndrome is 1/200,000, which may be an underestimate due to the high variability of this disorder[164]. Given the association between PTEN and these inherited syndromes, in the appropriate clinical context, germline testing for mutations affecting PTEN is recommended.

GENE
## *MLL2*

**ALTERATION**
E830*

**TRANSCRIPT ID**
NM_003482.4

**CODING SEQUENCE EFFECT**
2488G>T

**VARIANT CHROMOSOMAL POSITION**
chr12:49444978

### POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

There are no targeted therapies available to address genomic alterations in MLL2.

### FREQUENCY & PROGNOSIS

MLL2 alterations are observed in a number of solid tumor contexts (COSMIC, 2022)[167], and are especially prevalent in lung squamous cell carcinoma (SCC)[168] and small cell lung carcinoma (SCLC)[169]. MLL2 mutation was found to be an independent prognostic factor of poor PFS and OS in non-small cell lung cancer, but not in SCLC[170]. One study reported that MLL2 truncating mutations were more common in recurrent ovary granulosa cell tumors (GCT) compared with primary GCTs (24% [10/42] vs. 3.0% [1/32])[171]. In a study of esophageal SCC, high MLL2 expression positively correlated with tumor stage, differentiation, and size, and negatively correlated with OS[172].

### FINDING SUMMARY

MLL2 encodes an H3K4-specific histone methyltransferase that is involved in the transcriptional response to progesterone signaling[173]. Germline de novo mutations of MLL2 are responsible for the majority of cases of Kabuki syndrome, a complex and phenotypically distinctive developmental disorder[174]. A significant number of inactivating MLL2 alterations have been observed in multiple tumor types, suggesting a tumor suppressor role[175].

### 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[176-181]. Comprehensive genomic profiling of solid tumors may detect nontumor alterations that are due to CH[180,182-183]. 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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**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**
*PIK3CA*

**ALTERATION**
E542K

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

## NCT04589845

**PHASE 2**

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

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

**LOCATIONS:** Zhongzheng Dist. (Taiwan), Taipei City (Taiwan), Taoyuan County (Taiwan), Tainan (Taiwan), Shanghai City (China), Shanghai (China), Shatin (Hong Kong), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Xi'an (China)

## NCT04341259

**PHASE 1**

A Study Of The Pharmacokinetics And Safety Of Ipatasertib In Chinese Participants With Locally Advanced Or Metastatic Solid Tumors.

**TARGETS**
AKTs

**LOCATIONS:** Shanghai City (China)

## NCT03239015

**PHASE 2**

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

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

**LOCATIONS:** Shanghai (China)

## NCT04337463

**PHASE NULL**

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

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

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

## NCT04803318

**PHASE 2**

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

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

**LOCATIONS:** Guangzhou (China)

## NCT04526470

**PHASE 1/2**

Alpelisib and Paclitaxel in PIK3CA-altered Gastric Cancer

**TARGETS**
PI3K-alpha

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

## NCT05125523

**PHASE 1**

A Study of Sirolimus for Injection (Albumin Bound) in Patients With Advanced Solid Tumors

**TARGETS**
mTOR

**LOCATIONS:** Tianjin (China)

## NCT03772561

**PHASE 1**

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

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

**LOCATIONS:** Singapore (Singapore)

## NCT04801966

**PHASE NULL**

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

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

**LOCATIONS:** Melbourne (Australia)

## NCT03297606

**PHASE 2**

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

**TARGETS**
VEGFRs, ABL, SRC, ALK, ROS1, AXL, TRKA, MET, TRKC, DDR2, KIT, EGFR, PD-1, CTLA-4, PARP, CDK4, CDK6, FLT3, CSF1R, RET, mTOR, ERBB2, MEK, BRAF, SMO

**LOCATIONS:** Vancouver (Canada), Edmonton (Canada), Saskatoon (Canada), Regina (Canada), Ottawa (Canada), Montreal (Canada), Toronto (Canada), Kingston (Canada), London (Canada)

**GENE**
*PTEN*

**ALTERATION**
M35V, G165R

**RATIONALE**
PTEN loss or inactivating mutations may lead to increased activation of the PI3K-AKT-mTOR pathway and may indicate sensitivity to inhibitors of this pathway. PTEN loss or inactivation may also predict sensitivity to PARP inhibitors.

## NCT04341259

**PHASE 1**

A Study Of The Pharmacokinetics And Safety Of Ipatasertib In Chinese Participants With Locally Advanced Or Metastatic Solid Tumors.

**TARGETS**
AKTs

**LOCATIONS:** Shanghai City (China)

## NCT04337463

**PHASE NULL**

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

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

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

## NCT04001569

**PHASE 1/2**

AZD8186 and Paclitaxel in Advanced Gastric Cancer

**TARGETS**
PI3K-beta

**LOCATIONS:** Seongnam-si (Korea, Republic of)

## NCT02264678

**PHASE 1/2**

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

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

**LOCATIONS:** Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Goyang-si (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Coventry (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom)

## NCT05035745

**PHASE 1/2**

Selinexor & Talazoparib in Advanced Refractory Solid Tumors; Advanced/Metastatic Triple Negative Breast Cancer (START)

**TARGETS**
XPO1, PARP

**LOCATIONS:** Singapore (Singapore)

## NCT03772561

**PHASE 1**

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

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

**LOCATIONS:** Singapore (Singapore)

## NCT04801966

**PHASE NULL**

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

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

**LOCATIONS:** Melbourne (Australia)

## NCT04497116

**PHASE 1/2**

Study of RP-3500 in Advanced Solid Tumors

**TARGETS**
ATR, PARP

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

## NCT04972110

**PHASE 1/2**

Study of RP-3500 With Niraparib or Olaparib in Advanced Solid Tumors

**TARGETS**
PARP, ATR

**LOCATIONS:** Utah, Minnesota, Michigan, Connecticut, New York, Maryland, Texas

## NCT04317105

**PHASE 1/2**

Testing the Addition of an Anti-cancer Drug, Copanlisib, to the Usual Immunotherapy (Nivolumab With or Without Ipilimumab) in Patients With Advanced Solid Cancers That Have Changes in the Following Genes: PIK3CA and PTEN

**TARGETS**
PD-1, CTLA-4, PI3K

**LOCATIONS:** Toronto (Canada), Texas, Virginia

**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.

***ALK***
V603M

***ATM***
T2654I

***DNMT3A***
G822V

***DOT1L***
L1006fs*24

***FGFR2***
V463D

***FLCN***
D476E

***NFKBIA***
C167R

***NOTCH2***
G1498E

***NTRK1***
Y729*

***PTPN11***
K131R

***TSC1***
N198S

***VEGFA***
V42M



Electronically signed by Julie Tse, M.D. | 22 December 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
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Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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

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

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

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.

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| *LTK* | *LYN* | *MAF* | ***MAP2K1*** **(MEK1) Exons 2, 3** | ***MAP2K2*** **(MEK2) Exons 2-4, 6, 7** | *MAP2K4* | *MAP3K1* | *MAP3K13* | *MAPK1* |
| *MCL1* | ***MDM2*** | *MDM4* | *MED12* | *MEF2B* | *MEN1* | *MERTK* | ***MET*** | *MITF* |
| *MKNK1* | *MLH1* | ***MPL*** **Exon 10** | *MRE11* (MRE11A) | *MSH2* Intron 5 | *MSH3* | *MSH6* | *MST1R* | *MTAP* |
| ***MTOR*** **Exons 19, 30, 39, 40, 43-45, 47, 48, 53, 56** | *MUTYH* | *MYB** Intron 14 | ***MYC*** **Intron 1** | *MYCL* (MYCL1) | ***MYCN*** | ***MYD88*** **Exon 4** | *NBN* | ***NF1*** |
| *NF2* | *NFE2L2* | *NFKBIA* | *NKX2-1* | *NOTCH1* | *NOTCH2* Intron 26 | *NOTCH3* | ***NPM1*** **Exons 4-6, 8, 10** | ***NRAS*** **Exons 2, 3** |
| *NSD2* (WHSC1 or MMSET) | *NSD3* (WHSC1L1) | *NT5C2* | ***NTRK1*** **Exons 14, 15, Introns 8-11** | *NTRK2* Intron 12 | ***NTRK3*** **Exons 16, 17** | *NUTM1** Intron 1 | *P2RY8* | ***PALB2*** |
| *PARP1* | *PARP2* | *PARP3* | *PAX5* | *PBRM1* | *PDCD1* (PD-1) | ***PDCD1LG2*** **(PD-L2)** | ***PDGFRA*** **Exons 12, 18, Introns 7, 9, 11** | ***PDGFRB*** **Exons 12-21, 23** |
| *PDK1* | *PIK3C2B* | *PIK3C2G* | ***PIK3CA*** **Exons 2, 3, 5-8, 10, 14, 19, 21 (Coding Exons 1, 2, 4-7, 9, 13, 18, 20)** | *PIK3CB* | *PIK3R1* | *PIM1* | *PMS2* | *POLD1* |
| *POLE* | *PPARG* | *PPP2R1A* | *PPP2R2A* | *PRDM1* | *PRKAR1A* | *PRKCI* | *PRKN* (PARK2) | *PTCH1* |
| ***PTEN*** | ***PTPN11*** | *PTPRO* | *QKI* | *RAC1* | *RAD21* | *RAD51* | *RAD51B* | *RAD51C* |
| *RAD51D* | *RAD52* | *RAD54L* | ***RAF1*** **Exons 3, 4, 6, 7, 10, 14, 15, 17,** Introns 4-8 | *RARA* Intron 2 | ***RB1*** | *RBM10* | *REL* | ***RET*** Introns 7, 8, **Exons 11, 13-16, Introns 9-11** |
| *RICTOR* | *RNF43* | ***ROS1*** **Exons 31, 36-38, 40, Introns 31-35** | *RPTOR* | *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* | *TENT5C* (FAM46C) | *TERC** ncRNA | ***TERT**** **Promoter** |
| *TET2* | *TGFBR2* | *TIPARP* | *TMPRSS2** Introns 1-3 | *TNFAIP3* | *TNFRSF14* | ***TP53*** | *TSC1* | *TSC2* |
| *TYRO3* | *U2AF1* | ***VEGFA*** | *VHL* | *WT1* | *XPO1* | *XRCC2* | *ZNF217* | *ZNF703* |

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

Microsatellite (MS) status
Blood Tumor Mutational Burden (bTMB)
Tumor Fraction

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

CE IVD

## ABOUT FOUNDATIONONE LIQUID CDx

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

Please refer to technical information for performance specification details.

## INTENDED USE

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

## TEST PRINCIPLES

The FoundationOne Liquid CDx assay is performed exclusively as a laboratory service using circulating cell-free DNA (cfDNA) isolated from plasma derived from anti-coagulated peripheral whole blood from patients with solid malignant neoplasms. The assay employs a single DNA extraction method to obtain cfDNA from plasma from whole blood. Extracted cfDNA undergoes whole-genome shotgun library construction and hybridization-based capture of 324 cancer-related genes including coding exons and select introns of 309 genes, as well as only select intronic regions or non-coding regions of 15 genes. Hybrid-capture selected libraries are sequenced with deep coverage using the NovaSeq® 6000 platform. Sequence data are processed using a customized analysis pipeline designed to accurately detect genomic alterations, including base substitutions, indels, select copy number variants, and select genomic rearrangements. Substitutions and insertion and deletion alterations (indels) are reported in 311 genes, copy number alterations (CNAs) are reported in 310 genes, and gene rearrangements are reported in 324 genes. The assay also reports tumor fraction, and genomic signatures including MSI and bTMB. A subset of targeted regions in 75 genes is baited for increased sensitivity.

## THE REPORT

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

## QUALIFIED ALTERATION CALLS (EQUIVOCAL)

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

## RANKING OF THERAPIES AND CLINICAL TRIALS

*Ranking of Therapies in Summary Table*

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

*Ranking of Clinical Trials*

Pediatric trial qualification → Geographical proximity → Later trial phase.

## LIMITATIONS

1. For *in vitro* diagnostic use.
2. For prescription use only. This test must be ordered by a qualified medical professional in accordance with clinical laboratory regulations.
3. A negative result does not rule out the presence of a mutation below the limits of detection of the assay. Patients for whom no companion diagnostic alterations are detected should be considered for confirmation with an appropriately validated tumor tissue test, if available.
4. The FoundationOne Liquid CDx assay does not detect heterozygous deletions.
5. The test is not intended to provide information on cancer predisposition.
6. Performance has not been validated for cfDNA input below the specified minimum input.
7. Tissue TMB and blood TMB (bTMB) are estimated from the number of synonymous and nonsynonymous single-nucleotide variants (SNVs) and insertions and deletions (indels) per area of coding genome sampled, after the removal of known and likely oncogenic driver events and germline SNPs. Tissue TMB is calculated based on variants with an allele frequency of ≥5%, and bTMB is calculated based on variants with an allele frequency of ≥0.5%.
8. Tumor fraction is the percentage of circulating tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample. The tumor fraction estimate is computationally derived from the observed level of aneuploidy in the sample. Tumor fraction is considered elevated when ctDNA levels are high enough that aneuploidy can be detected and is significantly distinct from that typically found in non-tumor samples.
9. Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the tumor genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor. The MSI algorithm is based on genome wide analysis of 1765 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines for solid tissue testing.
10. Genomic findings from circulating cell-free DNA (cfDNA) may originate from circulating tumor DNA fragments, germline alterations, or non-tumor somatic alterations, such as clonal hematopoiesis of indeterminate potential (CHIP). Genes with alterations that may be derived from CHIP include, but are not limited to: *ASXL1*, *ATM*, *CBL*, *CHEK2*, *DNMT3A*, *JAK2*,

*KMT2D* (*MLL2*), *MPL*, *MYD88*, *SF3B1*, *TET2*, *TP53*, and *U2AF1*.

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

## REPORT HIGHLIGHTS

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

## VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

The variants indicated for consideration of follow-up germline testing are 1) limited to reportable short variants with a protein effect listed in the ClinVar genomic database (Landrum et al., 2018; 29165669) as Pathogenic, Pathogenic/Likely Pathogenic, or Likely Pathogenic (by an expert panel or multiple submitters), 2) associated with hereditary cancer-predisposing disorder(s), 3) detected at an allele frequency of >30%, and 4) in select genes reported by the ESMO Precision Medicine Working Group (Mandelker et al., 2019; 31050713) to have a greater than 10% probability of germline origin if identified during tumor sequencing. The selected genes are *ATM, BAP1, BRCA1, BRCA2, BRIP1, CHEK2, FH, FLCN, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, POLE, RAD51C, RAD51D, RET, SDHA, SDHB, SDHC, SDHD, TSC2,* and *VHL*, and are not inclusive of all cancer susceptibility genes. The content in this report should not substitute for genetic counseling or follow-up germline testing, which is needed to distinguish whether a finding in this patient's tumor sequencing is germline or somatic. Interpretation should be based on clinical context.

## VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

Variants that may represent clonal hematopoiesis (CH) are limited to select reportable short variants in defined genes identified in solid tumors only. Variant selection was determined based on gene tumor-suppressor or oncogene status, known role in solid tumors versus hematological malignancies, and literature prevalence. The defined genes are *ASXL1, ATM, CBL, CHEK2, DNMT3A, IDH2, JAK2, KMT2D (MLL2), MPL, MYD88, SF3B1, TET2,* and *U2AF1* and are not inclusive of all CH genes. The content in this report should not substitute for dedicated hematological workup. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH. Interpretation should be based on clinical context.

## NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

## LEVEL OF EVIDENCE NOT PROVIDED

Drugs with potential clinical benefit (or potential lack of clinical benefit) are not evaluated for source or level of published evidence.

## NO GUARANTEE OF CLINICAL BENEFIT

This report makes no promises or guarantees that a particular drug will be effective in the treatment of disease in any patient. This report also makes no promises or guarantees that a drug with potential lack of clinical benefit will in fact provide no clinical benefit.

## NO GUARANTEE OF REIMBURSEMENT

Foundation Medicine makes no promises or guarantees that a healthcare provider, insurer or other third party payor, whether private or governmental, will reimburse a patient for the cost of FoundationOne Liquid CDx.

## TREATMENT DECISIONS ARE THE RESPONSIBILITY OF PHYSICIAN

Drugs referenced in this Report may not be suitable for a particular patient. The selection of any, all or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) resides entirely within the discretion of the treating physician. Indeed, the information in this Report must be considered in conjunction with all other relevant information regarding a particular patient, before the patient's treating physician recommends a course of treatment. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this test or the information contained in this report.

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

## SELECT ABBREVIATIONS

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

## REFERENCE SEQUENCE INFORMATION

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

MR Suite Version (RG) 7.4.0

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