FOUNDATIONONE®LIQUID CDx

PATIENT
Hsu, Wen-Hsiung

TUMOR TYPE
Colon adenocarcinoma (CRC)
COUNTRY CODE
TW

REPORT DATE
19 May 2023
ORDERED TEST #
ORD-1628850-01

**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** Colon adenocarcinoma (CRC)
**NAME** Hsu, Wen-Hsiung
**DATE OF BIRTH** 08 April 1959
**SEX** Male
**MEDICAL RECORD #** 49487765

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** WHH 04/8/1959
**SPECIMEN TYPE** Blood
**DATE OF COLLECTION** 10 May 2023
**SPECIMEN RECEIVED** 12 May 2023

## Biomarker Findings

**Blood Tumor Mutational Burden** - 8 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.*

***MET*** amplification
***APC*** R499*, R1450*
***ATM*** rearrangement intron 44
***RAD54L*** C391fs*1
***BCL2L1*** amplification - equivocal†
***SRC*** amplification - equivocal†
***TP53*** R175H

† See About the Test in appendix for details.

## Report Highlights

- Targeted therapies with potential clinical benefit **approved in another tumor type**: **Cabozantinib** (p. 11), **Capmatinib** (p. 11), **Crizotinib** (p. 12), **Tepotinib** (p. 12)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 13)

| BIOMARKER FINDINGS | THERAPY AND CLINICAL TRIAL IMPLICATIONS |
|---|---|
| **Blood Tumor Mutational Burden -** 8 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% |
|---|---|---|
| ***MET*** - | amplification | - |

**10 Trials** see p. 16

| THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE) | THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE) |
|---|---|
| None | Cabozantinib |
| | Capmatinib |
| | Crizotinib |
| | Tepotinib |



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| GENOMIC FINDINGS | | VAF% | THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE) | THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE) |
|---|---|---|---|---|
| ***APC*** - | R499* | 2.2% | None | None |
| | R1450* | 71.8% | | |
| **3 Trials** see p. 13 | | | | |
| ***ATM*** - | rearrangement intron 44 | 0.51% | None | None |
| **10 Trials** see p. 14 | | | | |
| ***RAD54L*** - | C391fs*1 | 27.7% | None | None |
| **10 Trials** see p. 18 | | | | |

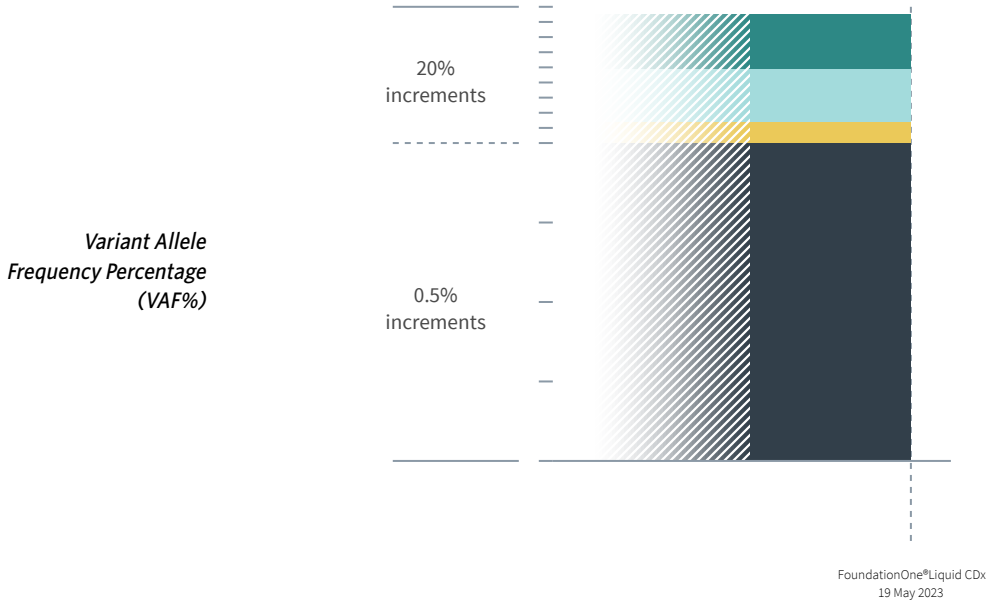
## GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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



**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-1628850-01 VAF% |
|---|---|---|
| **Blood Tumor Mutational Burden** | | 8 Muts/Mb |
| **Microsatellite status** | | MSI-High Not Detected |
| **Tumor Fraction** | | 68% |
| ***MET*** | amplification | Detected |
| ***APC*** | ● R499* | 2.2% |
| | ● R1450* | 71.8% |
| ***ATM*** | rearrangement intron 44 | 0.51% |
| ***RAD54L*** | ● C391fs*1 | 27.7% |
| ***BCL2L1*** | amplification | Detected |
| ***SRC*** | amplification | Detected |
| ***TP53*** | ● R175H | 70.7% |

**IMPORTANT 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. Variants reported for prior time points reflect reporting practices at the time of the historical test(s). Changes in variant reporting nomenclature, classification, or handling may result in the appearance of discrepancies across time points. 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 or reportable variants may become VUS.

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

Please note that other aspects of this table may have changed from the previous version to reflect the most up-to-date reporting information.

BIOMARKER

# Blood Tumor Mutational Burden

**RESULT**
8 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

In 1 study, the median plasma TMB for 163 patients with metastatic CRC was 16.3 muts/Mb (approximately 8 muts/Mb as measured by this assay)[12]. The prognostic value of tumor mutational burden (TMB) in colorectal cancer (CRC) is context- and therapy-dependent. A study of tissue TMB (tTMB) in 145 CRC samples showed longer OS in TMB-high samples compared with TMB-low ones[13]. Similarly, for patients with metastatic CRC treated with first-line chemotherapy combined with bevacizumab or cetuximab, high tissue TMB (tTMB-H) was associated with longer OS[14]. For patients treated with adjuvant chemotherapy, tTMB-H was associated with better 5-year relapse-free survival[15]. However, for patients with EGFR/BRAF-inhibitor-treated, BRAF-mutated microsatellite stable (MSS) metastatic CRC, intermediate tTMB was associated with significantly poorer PFS and OS compared with TMB-low status; patients with primary resistance to EGFR/BRAF blockage had higher TMB than those sensitive to these therapies[16]. In a study for 61 patients with metastatic, MSS CRC treated with best standard of care, plasma TMB scores ≥28 Muts/Mb (approximately 14 Muts/Mb as measured by this assay) were associated with reduced OS compared with plasma TMB scores <28 Muts/Mb (3.0 vs. 5.3 months, HR=0.76, p=0.007), whereas tTMB was not found to be prognostic in this population[7].

## FINDING SUMMARY

Blood tumor mutational burden (bTMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations from circulating tumor DNA in blood. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[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 higher sensitivity for identifying genomic alterations. Such specimens are at a lower 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
## *MET*

ALTERATION
amplification

### POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of extensive clinical evidence, MET amplification or activating mutations may predict sensitivity to MET-targeting therapies such as kinase inhibitors crizotinib, capmatinib, tepotinib, and cabozantinib. Crizotinib has benefited patients with MET-amplified non-small cell lung cancer (NSCLC) of varied histologies[45-48], gastroesophageal cancer[49], glioblastoma[50], and carcinoma of unknown primary[51]. Capmatinib has demonstrated clinical efficacy for patients with MET-amplified cholangiocarcinoma[52], as well as MET-amplified NSCLC, both as a monotherapy[53] and in combination with an EGFR TKI for patients with concurrent activating EGFR mutations[54-56]. Tepotinib has demonstrated efficacy for patients with MET-amplified hepatocellular carcinoma[57] and NSCLC[58] as a monotherapy as well as in combination with gefitinib for patients with MET-amplified and EGFR-mutated NSCLC[59]. Savolitinib elicited responses for patients with MET-amplified gastric cancer either alone or in combination with docetaxel[60-61]. AMG 337 elicited an ORR of 50% (5/10), including 1 CR, for patients with MET-amplified gastric, esophageal, or gastroesophageal junction cancer[62]. Patients with MET-amplified NSCLC[63] or MET-amplified gastric cancer[64] treated with the MET-targeting antibody onartuzumab (MetMAb) achieved clinical responses. In addition, high MET expression has been suggested to predict patient response to therapies such as the monoclonal HGF-targeting antibody rilotumumab as well as the combination of ramucirumab and the monoclonal MET-targeting antibody emibetuzumab[65]. The Phase 2 LUMINOSITY study of the MET antibody drug conjugate telisotuzumab vedotin (teliso-V) reported a 37% (19/52) ORR for patients with non-squamous EGFR-wildtype tumors; lower ORRs were observed for patients with squamous (11%, 3/27) or non-squamous EGFR-mutated (12%, 5/43) tumors[66]. A Phase 1 study showed that teliso-V plus osimertinib yielded an ORR of 56% (10/18) for patients with EGFR-mutated MET-overexpressing NSCLC who progressed on osimertinib, including ORRs of 56% (5/9) for patients with an EGFR L858R mutation and 67% (6/9) for those with an EGFR exon 19 deletion[67].

### FREQUENCY & PROGNOSIS

MET amplification is relatively uncommon in CRC, with reported incidences of 0-12%, and has been found to increase with advancing stage[68-70]. However, low-level copy number gains of genomic regions that include MET have been reported in up to 30% of CRC cases[70]. MET overexpression has been reported in 72% of CRCs, and several studies have observed an association between MET expression, alone and/or with other factors, and prognosis, but not all studies agree[71-73].

### FINDING SUMMARY

MET encodes a receptor tyrosine kinase, also known as c-MET or hepatocyte growth factor receptor (HGFR), that is activated by the ligand HGF; MET activation results in signaling mediated partly by the RAS-RAF-MAPK and PI3K pathways to promote proliferation[74-75]. MET has been reported to be amplified in cancer[76], with amplification positively correlating with protein expression in some cancer types[77-81] and associating with therapeutic response to MET inhibitors in a variety of cancer types[45-47,49-51,82-83].

GENE
## *APC*

ALTERATION
R499*, R1450*

HGVS VARIANT
NM_000038.4: c.1495C>T (p.R499*),
NM_000038.4: c.4348C>T (p.R1450*)

VARIANT CHROMOSOMAL POSITION
chr5:112162891, chr5:112175639

### POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved drugs targeting APC inactivation in cancer. Loss of APC function leads to accumulation of beta-catenin and upregulation of WNT pathway transcription programs[84], and potential therapeutic approaches to target this pathway include CBP/beta-catenin antagonists, which interfere with the ability of beta-catenin to interact with transcriptional co-activator CBP[85-86]. In a Phase 1 trial of the CBP/beta-catenin antagonist E7386, 1 patient with APC-mutated small bowel adenocarcinoma achieved a PR with tumor shrinkage of -69% and response duration of 165 days[87]; preclinical data support sensitivity of APC-deficient gastric or colorectal cancer models to E7386[88-89].

### FREQUENCY & PROGNOSIS

APC mutations have been found in 73% of tumors in the colorectal adenocarcinoma TCGA dataset[26]. In 1 study, loss of heterozygosity (LOH) of APC was observed in 32% of colorectal cancer (CRC) samples[90]. The prognostic significance of APC mutations in sporadic CRC remains unclear[91]. Solid tumors with WNT/beta-catenin pathway alterations, as seen here, were observed to have significantly less T-cell inflammation in one study[92].

### FINDING SUMMARY

APC (adenomatous polyposis coli) encodes a tumor suppressor with critical roles in regulating cell division and adhesion. APC interacts with beta-catenin and controls signaling in the WNT pathway, which regulates embryonic development and cell differentiation[93]. Alterations such as seen here may disrupt APC function or expression[94-98].

### POTENTIAL GERMLINE IMPLICATIONS

One or more of the APC 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 familial adenomatous polyposis (ClinVar, Sep 2022)[99]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in APC are found in more than 90% of patients with familial adenomatous polyposis (FAP)[100-102]. The prevalence for FAP in the general population is estimated to be 1:8,300 from birth[103], and in the appropriate clinical context germline testing of APC is recommended.

GENE
## *ATM*

**ALTERATION**
rearrangement intron 44

### POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

Loss of functional ATM results in a defective DNA damage response and homologous recombination-mediated DNA repair and may predict sensitivity to PARP inhibitors[104-105]. Clinical responses have been reported for patients with ATM-mutated prostate cancer treated with PARP inhibitors[106-108] and PARP inhibitors have shown limited clinical benefit for patients with other ATM-mutated solid tumors including pancreatic cancer[109-110] , colorectal cancer[111], papillary renal cell carcinoma[112], ovarian cancer[113], small cell bowel cancer,[110], and biliary tract cancer[114]. In Phase 1 trials of ATR inhibitors, a heavily pretreated patient with colorectal cancer who achieved a CR to berzosertib[115] and 4 out of 4 patients with diverse solid tumors who achieved PRs to BAY1895344[116] harbored ATM inactivation or protein loss. In a Phase 2 study of a combination of the ATR inhibitor ceralasertib and durvalumab for patients with advanced gastric cancer, objective responses (ORs) were experienced by 50% (4/8) of patients with loss of ATM expression, compared with 14% (3/21) patients with intact ATM[117]. Studies showing reduced cell viability and increased DNA damage in preclinical models of solid tumors[118-120] and hematologic malignancies[118,121] also support the increased sensitivity of ATM-deficient cells to ATR inhibitors. Preclinical experiments also indicate that loss of ATM causes dependency on DNA-PKcs in cancer cells; DNA-PKcs inhibitors promoted apoptosis in ATM-deficient cells and were active in a lymphoma mouse model lacking ATM activity[122].

### FREQUENCY & PROGNOSIS

In the Colorectal Adenocarcinoma TCGA dataset, ATM mutations have been reported in 11% of cases[26]. Loss of heterozygosity (LOH) of ATM has been observed in 23-31% of distal colon cancers, but not in proximal colon tumors[123]. ATM expression or mutation has been associated with longer survival for patients with CRC[124-125].

### FINDING SUMMARY

ATM encodes the protein ataxia telangiectasia mutated, which is a serine/threonine protein kinase that plays a key role in the DNA damage response[126]. Loss of functional ATM promotes tumorigenesis[127]. Alterations such as seen here may disrupt ATM function or expression[128-130].

### POTENTIAL GERMLINE IMPLICATIONS

ATM mutation carriers have increased cancer risk, with carriers assigned female at birth displaying a 38% lifetime risk of breast cancer[131]. Biallelic mutations in ATM underlie the rare autosomal-recessive inherited disorder ataxia-telangiectasia (A-T), also referred to as genome instability or DNA damage response syndrome[132]. This disease is characterized by genomic instability, sensitivity to DNA-damaging agents, and increased risk of developing cancer[126,132]. The prevalence of A-T is estimated at 1:40,000 to 1:100,000 worldwide[132]. In the appropriate clinical context, germline testing of ATM is recommended.

GENE
## *RAD54L*

**ALTERATION**
C391fs*1

**HGVS VARIANT**
NM_003579.3: c.1093_1169+15dup (p.C391*)

**VARIANT CHROMOSOMAL POSITION**
chr1:46736380

### POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

There are no therapies available that directly target RAD54L. Limited clinical evidence in ovarian cancer[133] and prostate cancer[134] indicates that RAD54L inactivation may confer sensitivity to PARP inhibitors.

### FREQUENCY & PROGNOSIS

RAD54L alterations are rare in cancer[135]. Loss of heterozygosity (LOH) at chromosomal region 1p32-34, in which RAD54L resides, has been reported as a frequent event in breast cancer[136], oligodendroglioma[137], nontypical meningioma[138-141], and parathyroid adenoma[142], but it is not clear whether RAD54L loss of function is pathogenic in these cases. Increased RAD54L expression was reported in NSCLC samples in response to increased mutation rate[143] and also in castration-resistant prostate cancer (CRPC) cells[144]. RAD54L polymorphisms have been associated with increased risk of developing meningioma[145], glioma[146], and decreased OS ($p<0.004$) in patients with potentially resectable pancreatic adenocarcinoma[147]. Germline mutations of RAD54L has been associated with increased risk of gastric cancer[148] but not lymphoid malignancies[149].

### FINDING SUMMARY

RAD54L encodes a member of the SNF2/SWI2 superfamily and forms part of the RAD52 complex involved in recombination and DNA repair in response to ionizing radiation[150-153]. Alterations leading to disruption of critical domains with RAD54L are predicted to enhance genomic instability[154]. Alterations such as seen here may disrupt RAD54L function or expression[154-159].



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GENE

## *BCL2L1*

**ALTERATION**
amplification - equivocal

### POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

Multiple investigational therapies that target BCL-2 family members, including ABT-737, navitoclax, pelcitoclax, A-1331852, and obatoclax, have been studied in preclinical studies or early-stage clinical trials[160-161]; clinical studies have been conducted in genomically unselected populations. Single-agent navitoclax has been evaluated in Phase 1 and Phase 2 studies where it demonstrated limited efficacy (ORR 2.6%, SD rate 20-23%); 2 patients achieved PRs, including a patient with small cell lung cancer who benefited for over 2 years[162-163]. Navitoclax has also been evaluated in combination with the EGFR TKI erlotinib, though no ORs were observed (27% SD rate, [3/11])[164]. In a Phase 1 trial for patients with advanced non-small cell lung cancer (NSCLC), the combination of pelcitoclax and EGFR TKI osimertinib resulted in an ORR of 15% (3/20)[165].

### FREQUENCY & PROGNOSIS

BCL2L1 amplification has been observed in 1-6% of solid tumor samples, including colorectal (5%) and ovarian (6%) cancers[135,166]. Studies suggest that expression of BCL-XL may be associated with poor prognosis for patients with ovarian cancer[167], pleural mesothelioma[168], and colorectal cancer (CRC)[169]. Elevated BCL-XL levels protect cancer cells against apoptosis in multiple cancer types, and has been associated with chemotherapy resistance for patients with ovarian cancer[167,170] and resistance to radiation and targeted therapies in preclinical studies[168,171-175].

### FINDING SUMMARY

BCL2L1 encodes BCL-XL, an anti-apoptotic member of the BCL-2 protein family that is frequently overexpressed in cancer[176-178]. In colorectal cancer (CRC), 20q gain has been associated with BCL-XL protein overexpression[179].

GENE

## *SRC*

**ALTERATION**
amplification - equivocal

### POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

Dasatinib, a SRC and tyrosine kinase inhibitor, is approved for use in Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) and Ph+ acute lymphoblastic leukemia (ALL). Bosutinib, which targets both ABL and SRC kinases, is approved to treat Ph+ CML with resistance or intolerance to prior therapy. Clinical trials of these agents and other SRC inhibitors are in progress in various cancer types[180-181].

**— Nontargeted Approaches —**

Overexpression of SRC in colorectal carcinoma may be associated with resistance to chemotherapy[182].

### FREQUENCY & PROGNOSIS

In the Colorectal Adenocarcinoma TCGA dataset, putative high-level amplification of SRC has been found in 12% of cases[26]. Dysregulation of the SRC family of kinases (SFK) in general has been reported in 80% of colorectal tumors, with 5-10-fold increases of SFK activity[183-185]. Increased SFK expression and activity, including that of SRC, has been shown to occur early in colon carcinogenesis and play a role in colorectal tumor progression, with one study reporting strong SRC expression in 95% of adenomatous colon tissue[186-190]. Increased SRC activity has been correlated with more aggressive CRC, shorter OS, and general poor patient prognosis[182,184-185,188-189]. In contrast, one study of patients with CRC reported that amplification of chromosome 20q, which includes SRC, is significantly associated with wildtype KRAS/NRAS/BRAF, microsatellite stability, and improved OS in patients with metastatic disease[191].

### FINDING SUMMARY

The protein encoded by SRC belongs to a family of related non-receptor tyrosine kinases, members of which have been implicated in the growth and progression of a number of tumors, including breast, colon, and pancreatic cancer[192-194]. SRC has been reported to be amplified in cancer[76] and may be biologically relevant in this context[195-196].

GENE
## *TP53*

**ALTERATION**
R175H

**HGVS VARIANT**
NM_000546.4: c.524G>A (p.R175H)

**VARIANT CHROMOSOMAL POSITION**
chr17:7578406

## POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[197-200] or p53 gene therapy such as SGT53[201-205]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% and SDs in 53% of patients with solid tumors; the response rate was 21% (4/19) for patients with TP53 mutations versus 12% (4/33) for patients who were TP53 wildtype[206]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[207]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[208]. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[209]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24% (6/25) ORR with adavosertib combined with paclitaxel[60]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate for patients with TP53 alterations[210]. The Phase 2 FOCUS4-C trial for patients with TP53- and RAS-mutated colorectal cancer reported improvement in PFS (3.61 vs. 1.87 months, HR=0.35, p=0.0022), but not OS (14.0 vs 12.8 months, p=0.93), following adavosertib treatment compared with active monitoring[211]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[205]. Missense mutations leading to TP53 inactivation may be sensitive to therapies that reactivate mutated p53 such as eprenetapopt. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, eprenetapopt combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[212]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[213].

## FREQUENCY & PROGNOSIS

TP53 mutations have been reported in up to 75% of colorectal cancer cases[26,214-219]. A study reported p53 expression in 49% of analyzed colorectal cancer cases[220]. TP53 mutation has not been consistently demonstrated to be a significant independent prognostic marker in the context of CRC[221].

## FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[222]. Alterations such as seen here may disrupt TP53 function or expression[223-227].

## 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, Sep 2022)[99]. 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 cancers[228-230], including sarcomas[231-232]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[233] to 1:20,000[232]. For pathogenic TP53 mutations identified during tumor sequencing, the rate of germline mutations was 1% in the overall population and 6% in tumors arising before age 30[234]. In the appropriate clinical context, germline testing of TP53 is recommended.

## POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[235-240]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[235-236]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[241]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[239,242-243]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

## Cabozantinib

*Assay findings association*

**MET**
amplification

### AREAS OF THERAPEUTIC USE

Cabozantinib inhibits multiple tyrosine kinases, including MET, RET, VEGFRs, and ROS1. It is FDA approved as monotherapy to treat patients with renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), medullary thyroid cancer (MTC), and differentiated thyroid cancer (DTC). It is also approved in combination with nivolumab to treat RCC. Please see the drug label for full prescribing information.

### GENE ASSOCIATION

Sensitivity of MET alterations to cabozantinib is suggested by clinical responses in patients with non-small cell lung cancer (NSCLC) harboring MET mutations associated with MET exon 14 skipping, with or without concurrent MET amplification[244-245] , as well as by extensive preclinical data[246-252] .

### SUPPORTING DATA

A Phase 1 ascending dose study of cabozantinib for patients with advanced solid tumors, including 1 patient with colorectal adenocarcinoma (CRC), reported early indications of drug response and prolonged SD, with no dose-limiting toxicities or serious adverse events[253]. A Phase 1b study evaluating cabozantinib plus panitumumab for patients with KRAS-wildtype metastatic CRC reported a median PFS of 3.7 months and a median OS of 7.5 months, with PRs for 14% (2/14) of patients; 36% (5/14) of patients had PFS >6 months[254]. Preclinical studies have shown that treatment of CRC patient-derived xenografts with cabozantinib significantly inhibited tumor growth[255-257] and in some cases resulted in tumor regression[257]. Phase 2 studies of cabozantinib reported antitumor activity in renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), and breast cancer and a safety profile similar to that of other TKIs[258-260] .

## Capmatinib

*Assay findings association*

**MET**
amplification

### AREAS OF THERAPEUTIC USE

Capmatinib is a selective MET tyrosine kinase inhibitor that is FDA approved to treat patients with non-small cell lung cancer harboring MET exon 14 skipping-associated alterations. Please see the drug label for full prescribing information.

### GENE ASSOCIATION

On the basis of clinical data in non-small cell lung cancer[58,261-265] , hepatocellular carcinoma[57], renal cell carcinoma[266], and gastric cancer[60], MET amplification may predict sensitivity to selective MET inhibitors.

### SUPPORTING DATA

A Phase 1b study of capmatinib in combination with cetuximab reported a 0% ORR and 46% (6/13) DCR for patients with MET-positive colorectal cancer[267]. Capmatinib has been investigated primarily for the treatment of NSCLC, demonstrating efficacy as monotherapy for patients with MET amplification[268-270] or MET exon 14 skipping alterations[53,269] as well as in combination with EGFR inhibitors for patients with MET amplification[54-56] . Multiple Phase 1 and 2 clinical studies have reported limited efficacy for capmatinib monotherapy in non-NSCLC indications, with no responses observed for patients with MET-amplified glioblastoma (n=10)[271], MET-overexpressing gastric cancer (n=9)[272], or other advanced solid tumors with MET amplification or overexpression (n=11)[272-273] .

## Crizotinib

*Assay findings association*

**MET**
amplification

### AREAS OF THERAPEUTIC USE

Crizotinib is an inhibitor of the kinases MET, ALK, ROS1, and RON. It is FDA approved to treat patients with ALK rearrangement- or ROS1 rearrangement-positive non-small cell lung cancer (NSCLC), adult and pediatric patients with ALK-positive inflammatory myofibroblastic tumor (IMT), and pediatric and young adult patients with ALK-positive anaplastic large cell lymphoma (ALCL). Please see the drug label for full prescribing information.

### GENE ASSOCIATION

Sensitivity of MET alterations to crizotinib is suggested by extensive clinical data in patients with MET-amplified cancers, including non-small cell lung cancer (NSCLC)[45-47,274-275] , gastric cancer[82], gastroesophageal cancer[49], glioblastoma[50], and carcinoma of unknown primary[51], as well as in patients with MET-mutated cancers, including NSCLC[244,276-280] , renal cell carcinoma (RCC)[281], and histiocytic sarcoma[276]. Crizotinib has also benefited patients with NSCLC or histiocytic sarcoma tumors harboring various alterations associated with MET exon 14 skipping[244,276,278-280,282] .

### SUPPORTING DATA

Out of 10 patients with MET-amplified colorectal cancer (CRC) treated with crizotinib in a Phase 2 study, 2 achieved SD[274]. A Phase 1b study evaluating crizotinib for the treatment of patients with ALK-positive malignancies reported a lower ORR for patients with various solid tumors relative to those with either lymphoma or inflammatory myofibroblastic tumors; however, a PR was reported for a patient with CRC[283]. In a case report, a patient with metastatic colon cancer harboring a GOPC-ROS1 fusion experienced a PR following treatment with crizotinib[284].

## Tepotinib

*Assay findings association*

**MET**
amplification

### AREAS OF THERAPEUTIC USE

Tepotinib is a selective MET tyrosine kinase inhibitor that is FDA approved to treat patients with non-small cell lung cancer harboring MET exon 14 skipping alterations. Please see the drug label for full prescribing information.

### GENE ASSOCIATION

On the basis of clinical data in non-small cell lung cancer[58,261-265] , hepatocellular carcinoma[57], renal cell carcinoma[266], and gastric cancer[60], MET amplification may predict sensitivity to selective MET inhibitors.

### SUPPORTING DATA

In a Phase 1 study of advanced solid tumors, tepotinib yielded an ORR of 20% (1/5) for patients with CRC, including 1 unconfirmed PR for a patient with MET amplification[285]. Tepotinib has primarily been investigated in non-small cell lung cancer and has demonstrated efficacy as a single agent for patients with MET amplification[58] and MET exon 14-skipping alterations[286-287] . Tepotinib has also been shown to be efficacious in combination with gefitinib for patients with concurrent EGFR mutation and MET amplification or MET overexpression in Phase 2 studies[264-265] . In advanced hepatocellular carcinoma, Phase 2 studies of tepotinib reported improved ORR and PFS for both treatment-naive and previously treated patients with MET protein overexpression[57,288-290] . In a Phase 1 study of advanced solid tumors, tepotinib monotherapy yielded an ORR of 1.3% and a DCR of 24%, with 2 confirmed PRs observed for patients with esophageal or lung cancer and 2 unconfirmed PRs for patients with colorectal or nasopharyngeal cancer[285]. In another Phase 1 study of solid tumors, tepotinib yielded a DCR of 17% (2/12), with 2 SD of ≥12 weeks observed in a patient with gastric cancer and another with urachal cancer[291].

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

**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**

*APC*

**ALTERATION**

R499*, R1450*

**RATIONALE**

Based on preclinical and limited clinical data, APC inactivation may be associated with sensitivity to CBP/beta-catenin interaction inhibitors.

## NCT05091346

**PHASE 1/2**

A Study of E7386 in Combination With Pembrolizumab in Previously Treated Participants With Selected Solid Tumors

**TARGETS**

CBP, Beta-catenin, PD-1

**LOCATIONS:** Fukuoka (Japan), Osaka (Japan), Shizouka (Japan), Tokyo (Japan), Chiba-shi (Japan), Kashiwa (Japan), Sapporo shi (Japan), Glasgow (United Kingdom), Manchester (United Kingdom), London (United Kingdom)

## NCT04008797

**PHASE 1**

A Study of E7386 in Combination With Other Anticancer Drug in Participants With Solid Tumor

**TARGETS**

CBP, Beta-catenin, FGFRs, RET, PDGFRA, VEGFRs, KIT

**LOCATIONS:** Kurume (Japan), Matsuyama (Japan), Seodaemun (Korea, Republic of), Osakasayama (Japan), Nagoya (Japan), Kawasaki (Japan), Chuo-Ku (Japan), Koto-ku (Japan), Chiba (Japan), Kashiwa (Japan)

## NCT03264664

**PHASE 1**

Study of E7386 in Participants With Selected Advanced Neoplasms

**TARGETS**

CBP, Beta-catenin

**LOCATIONS:** Glasgow (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Sutton (United Kingdom)

**GENE**
*ATM*

**ALTERATION**
rearrangement intron 44

**RATIONALE**
Loss or inactivation of ATM may increase sensitivity to PARP inhibitors, ATR inhibitors, or DNA-PKcs inhibitors.

## NCT04123366

**PHASE 2**

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

**TARGETS**
PARP, PD-1

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

## NCT03742895

**PHASE 2**

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

**TARGETS**
PARP

**LOCATIONS:** Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Darlinghurst (Australia), Adana (Turkey), Jerusalem (Israel), Konya (Turkey), Ramat Gan (Israel), Istanbul (Turkey), Antalya (Turkey), Brasov (Romania)

## 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)

## NCT05514132

**PHASE 1**

A Study to Evaluate the Safety and Pharmacokinetics of Ceralasertib in Combination With Durvalumab in Chinese Patients With Advanced Solid Tumours

**TARGETS**
PD-L1, ATR

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

## NCT05035745

**PHASE 1/2**

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

**TARGETS**
XPO1, PARP

**LOCATIONS:** Singapore (Singapore)

## NCT03188965

**PHASE 1**

First-in-human Study of ATR Inhibitor BAY1895344 in Patients With Advanced Solid Tumors and Lymphomas

**TARGETS**
ATR

**LOCATIONS:** Kashiwa (Japan), Singapore (Singapore), Bellinzona (Switzerland)

## 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)

## NCT02693535

**PHASE 2**

TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer

**TARGETS**
CDK4, CDK6, FLT3, VEGFRs, CSF1R, KIT, RET, mTOR, ERBB2, MEK, BRAF, PARP, PD-1, CTLA-4, PD-L1, TRKB, ALK, TRKC, ROS1, TRKA, FGFRs

**LOCATIONS:** Hawaii, Washington, Oregon, California

## NCT03127215

**PHASE 2**

Study of Olaparib/Trabectedin vs. Doctor's Choice in Solid Tumors

**TARGETS**
FUS-DDIT3, PARP

**LOCATIONS:** Dresden (Germany), München (Germany), Frankfurt (Germany), Essen (Germany), Mainz (Germany), Heidelberg (Germany), Stuttgart (Germany), Tuebingen (Germany), Freiburg (Germany)

## 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), Kelowna (Canada), Edmonton (Canada), Saskatoon (Canada), Regina (Canada), Ottawa (Canada), Montreal (Canada), Toronto (Canada), Kingston (Canada), London (Canada)

**GENE**
*MET*

**ALTERATION**
amplification

**RATIONALE**
Activating MET alterations may confer sensitivity to MET inhibitors.

## NCT03175224

**PHASE 1/2**

CBT-101 Study for Advanced Solid Tumors and c-Met Dysregulation

**TARGETS**
MET

**LOCATIONS:** Taipei City (Taiwan), Taipei (Taiwan), New Taipei City (Taiwan), Taoyuan City (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Singapore (Singapore), Nedlands (Australia), North Adelaide (Australia), Bedford Park (Australia)

## NCT04647838

**PHASE 2**

Tepotinib in Solid Tumors Harboring MET Alterations

**TARGETS**
MET

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

## NCT05439993

**PHASE 1/2**

Tepotinib Plus Paclitaxel in MET Amplified or MET Exon 14 Alterated Gastric and GEJ Carcinoma

**TARGETS**
MET

**LOCATIONS:** Gyeonggi-do (Korea, Republic of)

## 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), Kelowna (Canada), Edmonton (Canada), Saskatoon (Canada), Regina (Canada), Ottawa (Canada), Montreal (Canada), Toronto (Canada), Kingston (Canada), London (Canada)

## NCT04817956

**PHASE 2**

Improving Public Cancer Care by Implementing Precision Medicine in Norway

**TARGETS**
PD-L1, VEGFA, ERBB2, ALK, RET, PARP, SMO, TRKB, TRKC, ROS1, TRKA, MEK, BRAF, PI3K-alpha, FGFR1, FGFR2, FGFR3, MET, KIT, ABL

**LOCATIONS:** Tromsø (Norway), Bodø (Norway), Hamar (Norway), Oslo (Norway), Fredrikstad (Norway), Drammen (Norway), Trondheim (Norway), Skien (Norway), Førde (Norway), Bergen (Norway)

## NCT04116541

**PHASE 2**

A Study Evaluating the Activity of Anti-cancer Treatments Targeting Tumor Molecular Alterations/ Characteristics in Advanced / Metastatic Tumors.

**TARGETS**
CDK6, CDK4, MDM2, MET, ROS1, RET, VEGFRs

**LOCATIONS:** Villejuif (France), Nice (France), Lyon (France), Marseille (France), Toulouse (France), Bordeaux (France)

## NCT04963283

**PHASE 2**

Study of Cabozantinib and Nivolumab in Refractory Metastatic Microsatellite Stable (MSS) Colorectal Cancer

**TARGETS**
PD-1, MET, ROS1, RET, VEGFRs

**LOCATIONS:** Colorado

## NCT03539822

**PHASE 1/2**

Cabozantinib in Combination With Durvalumab in Patients With Gastroesophageal Cancer and Other Gastrointestinal Malignancies (CAMILLA)

**TARGETS**
PD-L1, MET, ROS1, RET, VEGFRs

**LOCATIONS:** Kansas

## NCT04868773

**PHASE 1**

Study of Cabozantinib Plus TAS102 in mCRC as Salvage Therapy

**TARGETS**
MET, ROS1, RET, VEGFRs

**LOCATIONS:** California

## NCT04693468

**PHASE 1**

Talazoparib and Palbociclib, Axitinib, or Crizotinib for the Treatment of Advanced or Metastatic Solid Tumors, TalaCom Trial

**TARGETS**
PARP, CDK4, CDK6, VEGFRs, ALK, ROS1, AXL, TRKA, MET, TRKC

**LOCATIONS:** Texas

**GENE**
*RAD54L*

**ALTERATION**
C391fs*1

**RATIONALE**
RAD54L inactivation may predict sensitivity to PARP inhibitors.

## NCT04123366

**PHASE 2**

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

**TARGETS**
PARP, PD-1

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

## NCT03742895

**PHASE 2**

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

**TARGETS**
PARP

**LOCATIONS:** Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Darlinghurst (Australia), Adana (Turkey), Jerusalem (Israel), Konya (Turkey), Ramat Gan (Israel), Istanbul (Turkey), Antalya (Turkey), Brasov (Romania)

## 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)

## NCT03127215

**PHASE 2**

Study of Olaparib/Trabectedin vs. Doctor's Choice in Solid Tumors

**TARGETS**
FUS-DDIT3, PARP

**LOCATIONS:** Dresden (Germany), München (Germany), Frankfurt (Germany), Essen (Germany), Mainz (Germany), Heidelberg (Germany), Stuttgart (Germany), Tuebingen (Germany), Freiburg (Germany)

## 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), Kelowna (Canada), Edmonton (Canada), Saskatoon (Canada), Regina (Canada), Ottawa (Canada), Montreal (Canada), Toronto (Canada), Kingston (Canada), London (Canada)

## NCT04991480

**PHASE 1/2**

A Study of ART4215 for the Treatment of Advanced or Metastatic Solid Tumors

**TARGETS**
PARP, Pol theta

**LOCATIONS:** London (United Kingdom), Oklahoma, Connecticut, New York, Pennsylvania, Tennessee, Texas, Florida

## NCT05327010

**PHASE 2**

Testing the Combination of the Anti-cancer Drugs ZEN003694 (ZEN-3694) and Talazoparib in Patients With Advanced Solid Tumors, The ComBET Trial

**TARGETS**
PARP, BRD4, BRDT, BRD2, BRD3

**LOCATIONS:** Illinois, Texas, North Carolina, Georgia

## NCT04992013

**PHASE 2**

Niraparib in Tumors Metastatic to the CNS

**TARGETS**
PARP

**LOCATIONS:** Massachusetts

**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.

***APC***
NM_000038.4: c.2174C>A (p.A725D)
chr5:112173465 and
NM_000038.4: c.1750A>C (p.T584P)
chr5:112170654

***ASXL1***
amplification

***BTG2***
NM_006763.2: c.287T>C (p.L96P)
chr1:203276376

***CDK12***
NM_016507.2: c.2244C>A (p.D748E)
chr17:37649139

***GNAS***
NM_080425.2: c.395A>C (p.E132A)
chr20:57428715

***MET***
NM_000245.2: c.3650C>T (p.T1217I)
chr7:116423375

***MRE11 (MRE11A)***
NM_005590.3: c.1412A>G (p.E471G)
chr11:94192662

***MSH2***
NM_000251.1: c.2197G>A (p.A733T)
chr2:47703697

***MSH3***
NM_002439.3: c.3181A>G (p.R1061G)
chr5:80168985

***NOTCH3***
NM_000435.2: c.3523C>T (p.R1175W)
chr19:15290031

***PALB2***
NM_024675.3: c.1818T>A (p.F606L)
chr16:23641657

***PRKN (PARK2)***
NM_004562.2: c.1187G>C (p.R396T)
chr6:161781218

***PTPRO***
NM_030667.1: c.1720A>T (p.T574S)
chr12:15669831

***RET***
NM_020975.4: c.2234_2238delinsTTTTT (p.H745_L746delinsLF)
chr10:43612129-43612133

***SMAD2***
NM_005901.4: c.1247T>G (p.M416R)
chr18:45371744

***SOX2***
NM_003106.2: c.213C>G (p.I71M)
chr3:181430361

ORDERED TEST # ORD-1628850-01

## 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 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*** |

ORDERED TEST # ORD-1628850-01

## 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.

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| *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. 2023. 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) 7.8.0

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