

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	Liver cholangiocarcinoma	PHYSICIAN	ORDERING PHYSICIAN	Yeh, Yi-Chen	SPECIMEN	SPECIMEN ID	L.C.H. 11/14/1956
	NAME	Hsiao, Li-Chuan		MEDICAL FACILITY	Taipei Veterans General Hospital		SPECIMEN TYPE	Blood
	DATE OF BIRTH	14 November 1956		ADDITIONAL RECIPIENT	None		DATE OF COLLECTION	30 June 2022
	SEX	Female		MEDICAL FACILITY ID	205872		SPECIMEN RECEIVED	05 July 2022
	MEDICAL RECORD #	26184758		PATHOLOGIST	Not Provided			

Biomarker Findings

Blood Tumor Mutational Burden - 4 Muts/Mb
Microsatellite status - MSI-High Not Detected
Tumor Fraction - Elevated Tumor Fraction Not Detected

Genomic Findings

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

BRCA1 E1222fs*13
CHEK2 M1L
STK11 R297K

Report Highlights

- Targeted therapies with potential clinical benefit approved in another tumor type: Niraparib (p. 8), Olaparib (p. 8), Rucaparib (p. 9), Talazoparib (p. 9)
- Evidence-matched clinical trial options based on this patient's genomic findings: (p. 11)
- Variants that may represent clonal hematopoiesis and may originate from non-tumor sources: **CHEK2** M1L (p. 6)

BIOMARKER FINDINGS

Blood Tumor Mutational Burden
 - 4 Muts/Mb

Microsatellite status
 - MSI-High Not Detected

Tumor Fraction
 - Elevated Tumor Fraction Not Detected

THERAPY AND CLINICAL TRIAL IMPLICATIONS

No therapies or clinical trials. See Biomarker Findings section

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

Tumor fraction is considered elevated when ctDNA levels are high enough that aneuploidy can be detected. The fact that elevated tumor fraction was not detected in this specimen indicates the possibility of lower levels of ctDNA but does not compromise confidence in any reported alterations. However, in the setting of a negative liquid biopsy result, orthogonal testing of a tissue specimen should be considered if clinically indicated (see Biomarker Findings section).

GENOMIC FINDINGS

VAF %

BRCA1 - E1222fs*13 0.30%

10 Trials see p. 11

CHEK2 - M1L 0.19%

10 Trials see p. 13

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

None

THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)

Niraparib

Olaparib

Rucaparib

Talazoparib

None

None

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Electronically signed by Naomi Lynn Ferguson, M.D. | 12 July 2022
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GENOMIC FINDINGS	VAF %	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
STK11 - R297K	0.30%	None	None
1 Trial see p. 15			

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.

CHEK2 - M1L p. 6

NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the therapies listed in this report may have varied clinical evidence in the patient's tumor type. Therapies and the clinical trials listed in this report may not be complete and/or exhaustive. Neither the therapies nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type. This report should be regarded and used as a supplementary source of information and not as the single basis for the making of a therapy decision. All treatment decisions remain the full and final responsibility of the treating physician and physicians should refer to approved prescribing information for all therapies. Therapies contained in this report may have been approved by the US FDA or other national authorities; however, they might not have been approved in your respective country. In the appropriate clinical context, germline testing of APC, ATM, BAP1, BRCA1, BRCA2, BRIP1, CHEK2, FH, FLCN, MEN1, MLH1, MSH2, MSH6, MUTYH, NF1, NF2, PALB2, PMS2, POLE, PTEN, RAD51C, RAD51D, RB1, RET, SDHA, SDHB, SDHC, SDHD, SMAD4, STK11, TGFBR2, TP53, TSC1, TSC2, VHL, and WT1 is recommended.

Variant Allele Frequency is not applicable for copy number alterations.

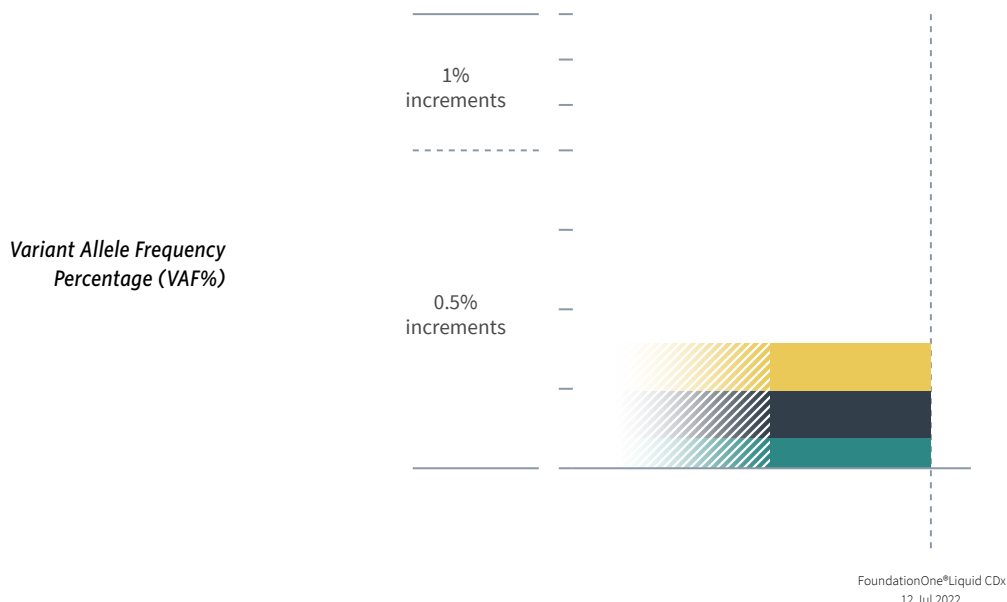
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ORDERED TEST # ORD-1404958-01



HISTORIC PATIENT FINDINGS

ORD-1404958-01
VAF%

Blood Tumor Mutational Burden

4 Muts/Mb

Microsatellite status

MSI-High Not Detected

Tumor Fraction

Elevated Tumor Fraction Not Detected

BRCA1	● E1222fs*13	0.30%
CHEK2	● M1L	0.19%
STK11	● R297K	0.30%

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

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

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

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

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

Not Detected = baited but not detected on test

Detected = present (VAF% is not applicable)

VAF% = variant allele frequency percentage

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

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BIOMARKER FINDINGS

BIOMARKER

Blood Tumor Mutational Burden

RESULT

4 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-L1¹⁻³, anti-PD-1³⁻⁴, and anti-PD-1/CTLA4 therapies⁵⁻⁶. 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 inhibitor⁵. 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/Mb¹. 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 inhibitor⁷.

FREQUENCY & PROGNOSIS

Average bTMB levels in solid tumors other than NSCLC have not been evaluated (cBioPortal, COSMIC, PubMed, Mar 2022)⁸⁻¹⁰. Published data investigating the prognostic implications of bTMB levels in biliary tract cancer are limited (PubMed, Jul 2022). Although cases with hypermutated biliary tract cancer were enriched in a subgroup with poor prognosis in 1 study¹¹, TMB-high (≥ 10 mut/Mb) status in biliary adenocarcinoma not treated with immunotherapy was not significantly associated with OS in another study, in which patients with TMB-high tumors experienced numerically longer OS compared with patients with TMB-low tumors (11.5 vs. 8.4 months,

adjusted HR=0.65)¹².

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 melanoma¹³⁻¹⁴ and cigarette smoke in lung cancer¹⁵⁻¹⁶, treatment with temozolomide-based chemotherapy in glioma¹⁷⁻¹⁸, mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes¹⁹⁻²³, and microsatellite instability (MSI)^{19,22-23}. 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.

BIOMARKER

Tumor Fraction

RESULT

Elevated Tumor Fraction Not Detected

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Specimens with elevated tumor fraction values have high circulating-tumor DNA (ctDNA) content, and thus high sensitivity for identifying genomic alterations. Such specimens are at low risk of false negative results. However, if elevated tumor fraction is not detected, it does not exclude the presence of disease burden or compromise the confidence of reported alterations. Tumor fraction levels currently have limited implications for diagnosis, surveillance, or therapy and should not

be overinterpreted or compared from one blood draw to another. There are currently no targeted approaches to address specific tumor fraction levels. In the research setting, changes in tumor fraction estimates have been associated with treatment duration and clinical response and may be a useful indicator for future cancer management²⁴⁻²⁹.

FREQUENCY & PROGNOSIS

Detectable ctDNA levels have been reported in a variety of tumor types, with higher tumor fraction levels reported for patients with metastatic (Stage 4) tumors compared with patients with localized disease (Stages 1 to 3)³⁰. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer³¹, Ewing sarcoma and osteosarcoma³², prostate cancer²⁷, breast cancer³³, leiomyosarcoma³⁴, esophageal cancer³⁵, colorectal

cancer³⁶, and gastrointestinal cancer³⁷.

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 content³⁸, 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 therapy³⁹⁻⁴⁰.

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ORDERED TEST # ORD-1404958-01

GENOMIC FINDINGS

GENE

BRCA1

ALTERATION

E1222fs*13

TRANSCRIPT ID

NM_007294

CODING SEQUENCE EFFECT

3665delA

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Alterations that inactivate BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors⁴¹⁻⁵⁸ or ATR inhibitors⁵⁹⁻⁶¹. Clinical responses to PARP inhibitors have been reported for patients with either germline or somatic BRCA1/2 mutations^{42,47,50,57-58} and for patients with platinum-resistant or -refractory disease^{41,46,53,56}. In a Phase 1 trial of monotherapy treatment with the ATR inhibitor BAY1895344, 2 patients with deleterious BRCA1 alterations and platinum-refractory ovarian carcinoma experienced a PR or prolonged SD⁵⁹. In other Phase 1 trials of combination approaches, a patient with BRCA1-mutated ovarian carcinoma experienced prolonged SD from the ATR inhibitor berzosertib combined with topotecan⁶⁰; another patient with platinum- and PARP-inhibitory refractory ovarian cancer and an inactivating germline BRCA1 mutation experienced a PR from berzosertib plus carboplatin⁶²; and a third patient with BRCA1-mutated triple-negative breast cancer (TNBC) experienced a PR to the ATR inhibitor ceralasertib combined with olaparib⁶³. Preclinical studies of BRCA1/2 inactivation in T-cell acute lymphoblastic leukemia (T-ALL)⁶⁴, ovarian carcinoma⁶⁵, and TNBC⁶⁶ showing reduced cell viability and increased DNA damage during ATR

treatment further support the sensitivity of BRCA1-deficient cells to ATR inhibitors. The WEE1 inhibitor adavosertib has been evaluated as a monotherapy and in combination with PARP-inhibitor, olaparib. In a Phase 2 study for patients with PARP-resistant ovarian cancer, the combination of olaparib and adavosertib elicited improved clinical benefit (ORR: 29%; DCR: 89%) compared to adavosertib alone (ORR: 23%; DCR: 63%); however, in the BRCA-mutated cohort, no significant difference in clinical benefit was observed between the combination (ORR: 19%) and monotherapy (ORR: 20%) treatments⁶⁷. In a Phase 1 monotherapy trial of adavosertib that included 9 patients with BRCA1/2-mutated solid tumors, 2 patients with BRCA1-mutated cancers (1 with ovarian serous carcinoma and 1 with oral squamous cell carcinoma) achieved PRs, and a third patient with ovarian serous carcinoma harboring mutations in BRCA1 and TP53 experienced 14% tumor shrinkage prior to disease progression⁶⁸.

— Nontargeted Approaches —

Inactivation of BRCA1 may also predict sensitivity to the DNA-damaging agents trabectedin and lurbinectedin⁶⁹⁻⁷⁸.

FREQUENCY & PROGNOSIS

BRCA1 mutations have been reported in 0-2% (1/51) of cholangiocarcinoma cases in several small sequencing studies, while BRCA1 genomic loss was not detected⁷⁹⁻⁸¹. BRCA1 mutation has also been reported in one of 28 intrahepatic cholangiocarcinomas in one study⁸². BRCA1 mutations have been reported in 2.0% of biliary tract carcinomas analyzed in COSMIC, including in 2.8% of gallbladder adenocarcinoma cases (Jan 2022)¹⁰. In a study of pancreaticobiliary cancers in Irish families with pathogenic BRCA variants, biliary tract cancer was reported in 1.7% of

BRCA1-positive pedigrees⁸³. A case study reported 1 patient with gallbladder carcinoma harboring a confirmed BRCA1 germline mutation⁸⁴. Published data investigating the prognostic implications of BRCA1 mutations in biliary tract carcinomas are limited (PubMed, Nov 2021).

FINDING SUMMARY

The protein encoded by BRCA1 is involved in the maintenance of genomic stability, including DNA repair, cell cycle checkpoint, and chromosome segregation⁸⁵. Alterations such as seen here may disrupt BRCA1 function or expression⁸⁶⁻⁸⁸.

POTENTIAL GERMLINE IMPLICATIONS

One or more of the BRCA1 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 hereditary breast and ovarian cancer syndrome (ClinVar, Mar 2022)⁸⁹. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Inactivating germline mutations in BRCA1 or BRCA2 are associated with autosomal dominant hereditary breast and ovarian cancer⁹⁰⁻⁹¹, and the lifetime risk of breast and ovarian cancer in BRCA1/2 mutation carriers has been estimated to be as high as 87% and 44%, respectively⁹². Elevated risk for other cancer types, including gastric, pancreatic, prostate, and colorectal, has also been identified, with an increase in risk ranging from 20 to 60%⁹³. The estimated prevalence of deleterious germline BRCA1/2 mutations in the general population is between 1:400 and 1:800, with an approximately 10-fold higher prevalence in the Ashkenazi Jewish population^{92,94-99}. In the appropriate clinical context, germline testing of BRCA1 is recommended.

ORDERED TEST # ORD-1404958-01

GENOMIC FINDINGS

GENE

CHEK2

ALTERATION

M1L

TRANSCRIPT ID

NM_007194

CODING SEQUENCE EFFECT

1A>T

associated with differential efficacy of chemotherapy and endocrine therapy in patients with metastatic breast cancer¹⁰⁶. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS

Somatic CHEK2 mutations have been reported in 0–3% of various solid tumors, with the highest incidence reported in endometrial, urothelial, and skin tumors (COSMIC, Jan 2022)¹⁰. In breast cancer, certain CHEK2 mutations are associated with higher grade and larger tumors as well as bilateral disease¹⁰⁷. A study reported that a polymorphism in CHEK2 was associated with worse survival of patients with GBM, but this association lost significance after adjusting for other prognostic factors^{108–109}. Another study in prostate cancer reported that CHEK2 expression is decreased in higher grade tumors and that CHEK2 is a tumor suppressor that decreases the growth of prostate cancer cells and regulates androgen receptor signaling¹¹⁰.

FINDING SUMMARY

CHEK2 encodes the protein checkpoint kinase 2, a serine/threonine kinase that plays an important role in the DNA-damage response; it is a putative tumor suppressor^{111–114}. 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

Germline CHEK2 mutation has been associated with cancer susceptibility of low to moderate penetrance, especially in hereditary breast cancer¹¹⁵. CHEK2 germline mutation has been identified in approximately 2.5% of familial or high-risk breast cancer cases^{116–117}. Although heterozygous germline CHEK2 mutation increases breast cancer risk two- to three-fold, it is not associated with younger age at diagnosis^{117–118}. In the appropriate clinical context, germline testing of CHEK2 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^{119–124}. Comprehensive genomic profiling of solid tumors may detect nontumor alterations that are due to CH^{123,125–126}. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Limited clinical data indicate that CHEK2 inactivation may predict sensitivity to PARP inhibitors. Patients with CHEK2-altered prostate cancer have experienced clinical responses to PARP inhibitors^{42,100–101}. Clinical benefit has been observed for patients with ovarian⁴⁷ and testicular¹⁰² cancers treated with PARP inhibitors. In a study of patients with metastatic breast cancer, 8 patients with CHEK2 mutation did not respond to olaparib treatment¹⁰³. One study of patients with breast cancer reported that carriers of the CHEK2 H371Y mutation have a higher likelihood of response to neoadjuvant chemotherapy¹⁰⁴, whereas another study found that those who carry CHEK2 mutations have a lower frequency of objective clinical responses to neoadjuvant therapy¹⁰⁵. A third study reported that the CHEK2 1100delC mutation is not

ORDERED TEST # ORD-1404958-01

GENOMIC FINDINGS

GENE

STK11

ALTERATION

R297K

TRANSCRIPT ID

NM_000455

CODING SEQUENCE EFFECT

890G>A

therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

— Potential Resistance —

STK11 alteration is associated with poorer response to immune checkpoint inhibitors for patients with NSCLC, including those with tumors harboring co-occurring KRAS mutation¹³⁵⁻¹⁴⁷.

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 STK11 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 Peutz-Jeghers syndrome (ClinVar, Mar 2022)⁸⁹. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in STK11 underlie Peutz-Jeghers syndrome (PJS), a rare autosomal dominant disorder associated with a predisposition for tumor formation¹⁵³. This disorder has an estimated frequency between 1:29,000 and 1:120,000, although reported rates in the literature vary greatly^{113,153-154}. Although gastrointestinal tumors are the most common malignancies associated with PJS, patients also exhibit an 18-fold increased risk of developing other epithelial cancers^{113,153-154}, and individuals with this syndrome have a 30-50% risk of developing breast cancer^{113,153}. Given the association with PJS, in the appropriate clinical context testing for the presence of germline mutations in STK11 is recommended.

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Increased mTOR signaling is present in LKB1-deficient tumors, suggesting therapies targeting mTOR may be relevant for tumors with STK11 alterations¹²⁷⁻¹³¹. Case studies have reported PRs for 2 patients with STK11-mutated pancreatic cancer following treatment with the mTOR inhibitor everolimus¹³², with 1 PR observed in a PJS patient for 9 months until progression¹³². However, retrospective analysis of a Phase 2 trial for patients with endometrial carcinoma found LKB1 (STK11) protein levels were not significantly correlated with response to everolimus treatment¹³³. In one preclinical study, STK11 loss was associated with sensitivity to combination treatment including an SRC inhibitor¹³⁴; however, the clinical relevance of these findings has not been established. It is not known whether these

FREQUENCY & PROGNOSIS

STK11 mutations have been reported in 3% of biliary tract carcinomas analyzed in the COSMIC database (Mar 2022)¹⁰. STK11 mutation or loss have also been reported in biliary tract adenocarcinomas in the literature¹⁴⁸⁻¹⁵⁰. Loss of STK11 protein expression in intrahepatic cholangiocarcinoma has been reported as an independent predictor of shorter OS and time to recurrence¹⁵¹.

FINDING SUMMARY

The serine/threonine kinase STK11 (also called LKB1) activates AMPK and negatively regulates the mTOR pathway in response to changes in cellular energy levels¹²⁷. LKB1 acts as a tumor suppressor in cancer, as loss of function promotes proliferation and tumorigenesis^{134,152}. Although alterations such as seen here have not been fully

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THERAPIES WITH CLINICAL BENEFIT

IN OTHER TUMOR TYPE

Niraparib

Assay findings association

BRCA1
E1222fs*13

AREAS OF THERAPEUTIC USE

The PARP inhibitor niraparib is FDA approved to treat patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer, with or without homologous recombination deficiency (HRD)-positive status. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in ovarian and breast cancers^{45-46,155}, loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors such as niraparib.

SUPPORTING DATA

Clinical data on the efficacy of niraparib for the treatment of biliary tract carcinoma are limited (PubMed, Apr 2022). Niraparib has been primarily evaluated in the context of ovarian cancer. In a Phase 3 study of patients with

platinum-sensitive, recurrent ovarian cancer, niraparib significantly increased median PFS, as compared to placebo, in patients with germline BRCA mutations (21 vs. 5.5 months) and in patients without germline BRCA mutations (9.3 vs. 3.9 months) as well as in a subgroup of the patients without germline BRCA mutations with homologous recombination-deficient tumors (12.9 vs. 3.8 months)⁴⁵. In a Phase 1 study of niraparib treatment for patients with solid tumors, 40% (8/20) of patients with ovarian cancer and BRCA mutations and 50% (2/4) of patients with breast cancer and BRCA mutations experienced a PR, and 43% (9/21) of patients with castration-resistant prostate cancer and 100% (2/2) of patients with non-small cell lung cancer achieved SD⁴⁶. A Phase 1 study of the combination of niraparib and bevacizumab in patients with platinum-sensitive, high-grade ovarian cancer reported a DCR of 91% (10/11), with a response rate of 45% (5/11)¹⁵⁶.

Olaparib

Assay findings association

BRCA1
E1222fs*13

AREAS OF THERAPEUTIC USE

The PARP inhibitor olaparib is FDA approved to treat patients with epithelial ovarian, Fallopian tube, or primary peritoneal cancer, patients with deleterious or suspected deleterious gBRCA-mutated pancreatic adenocarcinoma or HER2-negative breast cancer, and patients with prostate cancer and mutations in homologous recombination repair genes. Olaparib is also approved in combination with bevacizumab to treat patients with ovarian, Fallopian tube, or primary peritoneal cancer with deleterious or suspected deleterious somatic or gBRCA mutation and/or genomic instability. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of extensive clinical evidence in ovarian cancer⁵¹⁻⁵⁵ as well as strong clinical evidence in multiple other cancer types^{41-43,51,54,58,157}, loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to

olaparib.

SUPPORTING DATA

In a Phase 2 study of olaparib plus pembrolizumab for advanced solid tumors, patients with BRCA1 or BRCA2 mutations achieved an ORR of 29% (6/21), whereas patients with mutations in other homologous recombination repair genes achieved an ORR of 6.3% (2/32)¹⁵⁸. A disease control rate of 71% (5/7), including 3 PRs, was reported for patients with BRCA2-mutant intrahepatic cholangiocarcinoma (ICC) treated with olaparib following progression on prior chemotherapeutic regimens; the PRs were reported in patients with germline mutations¹⁵⁹. In another study, a heavily pretreated patient with BRCA2-mutant ICC experienced an ongoing PR from olaparib monotherapy¹⁶⁰. A PR was also reported in a patient with gallbladder carcinoma harboring a confirmed BRCA1 germline alteration treated with olaparib⁸⁴.

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THERAPIES WITH CLINICAL BENEFIT

IN OTHER TUMOR TYPE

Rucaparib

Assay findings association

BRCA1
E1222fs*13

AREAS OF THERAPEUTIC USE

The PARP inhibitor rucaparib is FDA approved to treat patients with metastatic castration-resistant prostate cancer (mCRPC) or epithelial ovarian, Fallopian tube, or primary peritoneal cancer and deleterious somatic or germline BRCA mutations. Rucaparib is also approved as a maintenance treatment of patients with recurrent epithelial ovarian, Fallopian tube, or primary peritoneal cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of strong clinical evidence in ovarian cancer^{47-48,161}, as well as clinical data in other cancer types^{48,162-163}, loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to rucaparib.

SUPPORTING DATA

Clinical data on the efficacy of rucaparib for the treatment of biliary tract cancers are limited (PubMed, Jun 2022). Rucaparib has primarily been evaluated in the context of ovarian carcinoma, breast carcinoma, pancreatic carcinoma, and melanoma. In a Phase 2 study of rucaparib for recurrent, platinum-sensitive ovarian, peritoneal, or fallopian tube carcinoma, median PFS was significantly longer in patients with BRCA1/2 mutations (12.8 months) or high loss of heterozygosity (LOH; 5.7 months) compared to patients with low LOH (5.2 months). Objective responses were observed for 80% (32/40) of patients with BRCA1/2 mutations, for 29% (24/82) with high LOH, and for 10% (7/10) with low LOH⁴⁷. In heavily

pretreated patients with a germline BRCA1/2 mutation who had received 2-4 prior chemotherapy treatments and had a progression free interval of greater than 6 months, 65% (17/26) of patients achieved an objective response with rucaparib treatment¹⁶¹. In a Phase 2 study evaluating rucaparib for patients with advanced breast or ovarian cancer and germline BRCA1/2 mutations, disease control was observed in 92% (12/13) of patients with ovarian cancer treated with oral rucaparib dosed continuously, but no objective responses were reported in breast cancer patients (n=23). However, 39% (9/23) of evaluable patients with breast cancer achieved SD lasting 12 weeks or more⁴⁸. In a Phase 1 study of rucaparib treatment in patients with solid tumors, 3/4 patients with ovarian cancer and 1/1 patient with breast cancer given the recommended Phase 2 dose reported objective responses; all responders harbored BRCA1/2 mutations¹⁶². A Phase 2 study of rucaparib treatment for patients with relapsed pancreatic cancer reported 1/19 CR, 2/19 PR (one unconfirmed) and 4/19 SD. Of the 19 patients treated in the study, 15 (79%) had a BRCA2 mutation¹⁶³. In a Phase 2 study of intravenous rucaparib in combination with temozolomide for patients with metastatic melanoma, 8/46 patients achieved a PR and 8/46 had SD¹⁶⁴; a Phase 1 study reported 1 CR, 1 PR, and 4 SD lasting six months or longer in patients with metastatic melanoma¹⁶⁵. A Phase 1 study of intravenous and oral rucaparib in combination with chemotherapy for the treatment of advanced solid tumors reported a disease control rate of 68.8% (53/77), including 1 CR and 9 PRs¹⁶⁶.

Talazoparib

Assay findings association

BRCA1
E1222fs*13

AREAS OF THERAPEUTIC USE

The PARP inhibitor talazoparib is FDA approved to treat HER2-negative locally advanced or metastatic breast cancer with deleterious or suspected deleterious germline BRCA mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of strong clinical data in breast cancer¹⁶⁷⁻¹⁶⁹ and additional clinical evidence in ovarian, pancreatic, and prostate cancer¹⁷⁰⁻¹⁷³, loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to talazoparib.

SUPPORTING DATA

In a basket trial of talazoparib for patients with alterations in homologous repair genes, 1 patient with ATM-mutated cholangiocarcinoma experienced a PR¹⁷⁴. Talazoparib has been studied primarily in the context of BRCA-mutated,

HER2-negative breast cancer, where patients achieved significantly longer median PFS (8.6 vs. 5.6 months, HR=0.54), a higher ORR (62.6% vs. 27.2%), and improved quality of life on talazoparib compared with standard chemotherapy in a Phase 3 study¹⁶⁸⁻¹⁶⁹. In a Phase 2 study of talazoparib for BRCA1/2-wildtype patients with homologous recombination pathway alterations, the best outcome in non-breast tumors was SD ≥ 6 months for 2/7 patients who had colon cancer with germline ATM alteration or testicular cancer with germline CHEK2 and somatic ATM alteration¹⁰². Clinical activity of single-agent talazoparib has been observed in numerous other solid tumors, including responses in BRCA-mutated ovarian, pancreatic, prostate, and ampulla of Vater cancers; PALB2-mutated pancreatic and bladder cancers; ATM-mutated cholangiocarcinoma; and small cell lung cancer^{170-172,174}.

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

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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

ORDERED TEST # ORD-1404958-01

THERAPIES WITH CLINICAL BENEFIT

IN OTHER TUMOR TYPE

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.

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CLINICAL TRIALS

IMPORTANT Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months. While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and should be investigated by the physician or

research staff. This is not a comprehensive list of all available clinical trials. There may also be compassionate use or early access programs available, which are not listed in this report. Foundation Medicine displays a subset of trial options and ranks them in this order of descending priority: Qualification for pediatric trial → Geographical proximity → Later trial phase. Clinical trials are not ranked in order of potential or predicted efficacy for this patient or

in order of level of evidence for this patient's tumor type. Clinical trials listed here may have additional enrollment criteria that may require medical screening to determine final eligibility. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov. However, clinicaltrials.gov does not list all clinical trials that might be available.

GENE
BRCA1
RATIONALE

BRCA1 loss or inactivating alterations may predict sensitivity to PARP inhibitors or ATR inhibitors.

ALTERATION

E1222fs*13

NCT04644068
PHASE 1/2

Study of AZD5305 as Monotherapy and in Combination With Anti-cancer Agents in Patients With Advanced Solid Malignancies

TARGETS
ERBB2, TROP2, PARP

LOCATIONS: Shanghai (China), Seoul (Korea, Republic of), Chuo-ku (Japan), Koto-ku (Japan), Melbourne (Australia), Warszawa (Poland), Gdynia (Poland), Grzegorz (Poland), Budapest (Hungary), Brno (Czechia)

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)

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), Nedlands (Australia), Port Macquarie (Australia), Darlinghurst (Australia), Adana (Turkey), Ankara (Turkey), Jerusalem (Israel), Konya (Turkey), Ramat Gan (Israel)

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ORDERED TEST # ORD-1404958-01

CLINICAL TRIALS
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), Coventry (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom), Villejuif (France)

NCT04298008
PHASE 2

AZD6738 Plus Durvalumab in Biliary Tract Cancer

TARGETS
ATR, PD-L1

LOCATIONS: Seoul (Korea, Republic of)

NCT04298021
PHASE 2

DDR-Umbrella Study of DDR Targeting Agents in Advanced Biliary Tract Cancer

TARGETS
PD-L1, ATR, PARP

LOCATIONS: Seoul (Korea, Republic of)

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)

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ORDERED TEST # ORD-1404958-01

CLINICAL TRIALS
GENE
CHEK2
ALTERATION
M1L
RATIONALE

On the basis of clinical evidence in prostate and other solid cancers, CHEK2 loss or inactivation may confer sensitivity to PARP inhibitors. It is not known whether these therapeutic approaches

would be relevant in the context of alterations that have not been fully characterized, as seen here.

NCT04644068
PHASE 1/2

Study of AZD5305 as Monotherapy and in Combination With Anti-cancer Agents in Patients With Advanced Solid Malignancies

TARGETS
ERBB2, TROP2, PARP

LOCATIONS: Shanghai (China), Seoul (Korea, Republic of), Chuo-ku (Japan), Koto-ku (Japan), Melbourne (Australia), Warszawa (Poland), Gdynia (Poland), Grzegorz (Poland), Budapest (Hungary), Brno (Czechia)

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), Nedlands (Australia), Port Macquarie (Australia), Darlinghurst (Australia), Adana (Turkey), Ankara (Turkey), Jerusalem (Israel), Konya (Turkey), Ramat Gan (Israel)

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), Coventry (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom), Villejuif (France)

NCT04298021
PHASE 2

DDR-Umbrella Study of DDR Targeting Agents in Advanced Biliary Tract Cancer

TARGETS
PD-L1, ATR, PARP

LOCATIONS: Seoul (Korea, Republic of)

NCT05035745
PHASE 1/2

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

TARGETS
XPO1, PARP

LOCATIONS: Singapore (Singapore)

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

NCT02484404
PHASE 1/2

Phase I/II Study of the Anti-Programmed Death Ligand-1 Antibody MEDI4736 in Combination With Olaparib and/or Cediranib for Advanced Solid Tumors and Advanced or Recurrent Ovarian, Triple Negative Breast, Lung, Prostate and Colorectal Cancers

TARGETS
PARP, VEGFRs, PDGFRA, PDGFRB, KIT, PD-L1

LOCATIONS: Maryland

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CLINICAL TRIALS

GENE
STK11
ALTERATION

R297K

RATIONALE

Increased mTOR signaling is present in LKB1-deficient tumors, suggesting therapies targeting mTOR may be relevant for tumors with STK11 alterations. It is not known whether these

therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

NCT04337463
PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS

mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

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ORDERED TEST # ORD-1404958-01

APPENDIX
Variants of Unknown Significance

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

CARD11
A534N

CCND3
R95P

DNMT3A
C710S

ERBB3
G804W

ERBB4
R979Q

FGF14
S49P

GRM3
R235S

IKBKE
A421T

KIT
R634W

P2RY8
T153A

TSC1
Q654E

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APPENDIX
Genes assayed in FoundationOne®Liquid CDx

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

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	ERRF1	ESR1 Exons 4-8
ETV4* Intron 8	ETV5* Introns 6, 7	ETV6* Introns 5, 6	EWSR1* Introns 7-13	EZH2 Exons 4, 16, 17, 18	EZR* Introns 9-11	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	HNFI1A
HRAS Exons 2, 3	HSD3B1	ID3	IDH1 Exon 4	IDH2 Exon 4	IGF1R	IKBKE	IKZF1	INPP4B
IRF2	IRF4	IRS2	JAK1	JAK2 Exon 14	JAK3 Exons 5, 11, 12, 13, 15, 16	JUN	KDMSA	KDMS5C
KDM6A	KDR	KEAP1	KEL	KIT Exons 8, 9, 11, 12, 13, 17, Intron 16	KLHL6	KMT2A (MLL) Introns 6, 8-11, Intron 7	KMT2D (MLL2)	

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KRAS	LTK	LYN	MAF	MAP2K1 (MEK1) Exons 2, 3	MAP2K2 (MEK2) Exons 2-4, 6, 7	MAP2K4	MAP3K1	MAP3K13
MAPK1	MCL1	MDM2	MDM4	MED12	MEF2B	MEN1	MERTK	MET
MITF	MKNK1	MLH1	MPL Exon 10	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)	NTSC2	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) PPP2R2A	PIK3CB	PIK3R1	PIM1	PMS2
POLD1	POLE	PPARG	PPP2R1A	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	SOC1	SOX2	SOX9	SPEN	SPOP	SRC
STAG2	STAT3	STK11	SUFU	SYK	TBX3	TEK	TENT5C (FAM46C)	TERC* ncRNA
TERT* Promoter	TET2	TGFB2	TIPARP	TMPSR2* 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

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APPENDIX

About FoundationOne®Liquid CDx

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



ABOUT FOUNDATIONONE LIQUID CDx

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

Please refer to technical information for performance specification details.

INTENDED USE

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

TEST PRINCIPLES

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

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

THE REPORT

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

QUALIFIED ALTERATION CALLS (EQUIVOCAL)

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

RANKING OF THERAPIES AND CLINICAL TRIALS

Ranking of Therapies in Summary Table

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

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

LIMITATIONS

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 $\geq 5\%$, and bTMB is calculated based on variants with an allele frequency of $\geq 0.5\%$.
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

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APPENDIX

About FoundationOne® Liquid CDx

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.

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About FoundationOne®Liquid CDx

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 6.3.0

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APPENDIX
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APPENDIX

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