FOUNDATIONONE®LIQUID CDx

PATIENT
Chen, Li-Fen

TUMOR TYPE
Breast carcinoma (NOS)
COUNTRY CODE
TW

REPORT DATE
10 February 2023
ORDERED TEST #
ORD-1558827-01

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 Breast carcinoma (NOS)
NAME Chen, Li-Fen
DATE OF BIRTH 28 December 1944
SEX Female
MEDICAL RECORD # 46795613

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 LFC 12/28/1944
SPECIMEN TYPE Blood
DATE OF COLLECTION 30 January 2023
SPECIMEN RECEIVED 03 February 2023

Biomarker Findings

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

Genomic Findings

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

PIK3CA H1047R, E453K
NF1 W425*
AKT1 E17K
FGFR4 V550L
DNMT3A S663*
LYN amplification
MAP3K1 T1145fs*6, Q1425fs*7
RAD21 amplification

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Alpelisib + Fulvestrant** (p. 11)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 14)
- Variants that may represent **clonal hematopoiesis** and may originate from non-tumor sources: ***DNMT3A* S663*** (p. 9)

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

GENOMIC FINDINGS		VAF%
PIK3CA -	H1047R	21.5%
	E453K	21.1%

10 Trials see p. 20

THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)		THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
Alpelisib + Fulvestrant	1	None

1 *NCCN category*

Electronically signed by Naomi Lynn Ferguson, M.D. | 10 February 2023
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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

GENOMIC FINDINGS		VAF%	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
NF1 -	W425*	24.2%	None	Cobimetinib Selumetinib Trametinib
10 Trials see p. 18				
AKT1 -	E17K	14.3%	None	None
10 Trials see p. 14				
FGFR4 -	V550L	15.2%	None	None
10 Trials see p. 16				

☐ *NCCN category*

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.

DNMT3A - S663* ..... p. 9

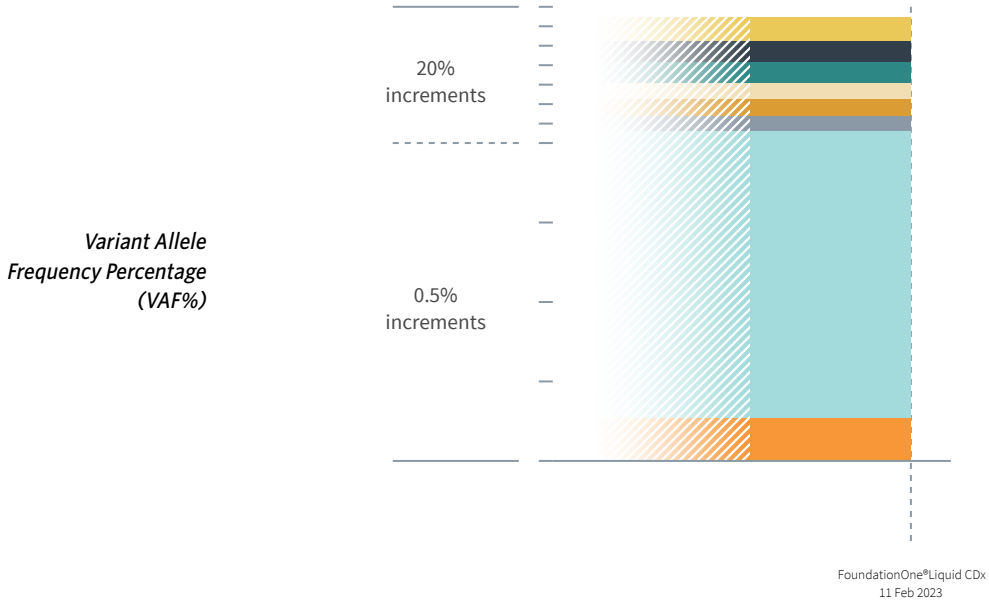
GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

DNMT3A - S663* ..... p. 9
LYN - amplification ..... p. 10
MAP3K1 - T1145fs*6, Q1425fs*7 ..... p. 10
RAD21 - amplification ..... p. 10

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-1558827-01 VAF%
Blood Tumor Mutational Burden		3 Muts/Mb
Microsatellite status		MSI-High Not Detected
Tumor Fraction		21%
PIK3CA	● H1047R	21.5%
	● E453K	21.1%
NF1	● W425*	24.2%
AKT1	● E17K	14.3%
FGFR4	● V550L	15.2%
DNMT3A	● S663*	0.27%
LYN	amplification	Detected
MAP3K1	● T1145fs*6	17.3%
	● Q1425fs*7	17.3%
RAD21	amplification	Detected

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.

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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
3 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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

FREQUENCY & PROGNOSIS

Average bTMB levels in solid tumors other than NSCLC have not been evaluated (PubMed, Mar 2022). Published data investigating the prognostic implications of bTMB levels in breast cancer are limited (PubMed, Jul 2022). In a large study of patients with breast cancer, hypermutation was more frequently observed in metastatic tumors than in primary tumors[12]. In a study of 14,867 patients with breast cancer, high TMB was associated with older age and metastatic disease but was not significantly associated with PD-L1 positivity using the TMB cutoff of ≥10 Muts/Mb[13]. In estrogen receptor-positive breast cancer, increased TMB in tissue samples (>mean of 1.25 Muts/Mb) associated with shorter OS (HR=2.02) in an analysis of the TCGA data[14].

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[15-16] and cigarette smoke in lung cancer[17-18], treatment with temozolomide-based chemotherapy in glioma[19-20], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[21-25], and microsatellite instability (MSI)[21,24-25]. 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

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Specimens with elevated tumor fraction have high circulating-tumor DNA (ctDNA) content, and thus high sensitivity for identifying genomic alterations. Such specimens are at low risk of false negative results. Tumor fraction levels currently have limited implications for diagnosis, surveillance, or therapy and should not be overinterpreted or compared from one blood draw to another. There are currently no targeted approaches to address specific tumor fraction levels. In the research setting, changes in tumor fraction estimates have been associated with treatment duration and clinical response and may be a useful indicator for future cancer management[26-31].

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)[32]. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer[33], Ewing sarcoma and osteosarcoma[34], prostate cancer[29], breast cancer[35], leiomyosarcoma[36], esophageal cancer[37], colorectal cancer[38], and gastrointestinal cancer[39].

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[40], 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[41-42].

GENE
PIK3CA

ALTERATION
H1047R, E453K

TRANSCRIPT ID
NM_006218.2, NM_006218.2

CODING SEQUENCE EFFECT
3140A>G, 1357G>A

VARIANT CHROMOSOMAL POSITION
chr3:178952085, chr3:178928079

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Clinical and preclinical data in various tumor types indicate that PIK3CA activating alterations may predict sensitivity to therapies targeting PI3K[43-50], AKT[51-52], or mTOR[53-60]. A Phase 2 trial of the AKT inhibitor capivasertib with paclitaxel versus paclitaxel alone showed a median OS benefit for the overall population (19.1 vs. 12.6 months; HR=0.61), for patients with AKT1-, PTEN-, or PIK3CA-mutated triple-negative breast cancer (TNBC) (not reached vs. 10.4 months; HR=0.37), and for patients with TNBC without PI3K-pathway mutations (16.6 vs. 13.2 months; HR=0.84)[61]. In a Phase 2 trial, the addition of capivasertib to fulvestrant improved median PFS (mPFS) relative to fulvestrant plus placebo alone for patients with PIK3CA-, AKT1-, and/or PTEN-altered hormone-receptor-positive (HR+), HER2- metastatic breast cancer (12.8 vs. 4.6 months, HR=0.44)[62], although the Phase 3 CAPItello study of capivasertib with fulvestrant for patients with HR+, HER2- metastatic breast cancer reported improved median PFS (mPFS) relative to fulvestrant plus placebo for patients with and without alterations in the AKT pathway (7.3 vs 3.1 months, HR=0.50 and 7.2 vs 3.7 months, HR=0.70, respectively)[63]. In a Phase 2 basket trial of capivasertib monotherapy in AKT1-mutated cancers, 33% (2/6) of patients with HR+, HER2- or TNBC experienced PRs, and 2 other PRs were unconfirmed[64]. Despite promising initial results in earlier trials[65-66], the Phase 3 IPATunity130 trial failed to show improved PFS for first-line ipatasertib in combination with paclitaxel relative to paclitaxel alone for patients with AKT1-, PTEN-, or PIK3CA-mutated TNBC (7.4 vs. 6.1 months)[63] or HR+, HER2- breast cancer[67]. In the Phase 3 SOLAR-1 study, the addition of alpelisib to fulvestrant statistically improved PFS (11.0 vs. 5.7 months, HR=0.65) and ORR (27% vs. 13%) and numerically improved median OS (mOS; 39.3 vs. 31.4 months, HR=0.86) in PIK3CA-mutated hormone-receptor-positive (HR+), HER2- breast cancer compared with placebo with fulvestrant, but not in PIK3CA-wildtype HR+, HER2- breast cancer[68]. In a Phase 2 trial, the addition of the AKT inhibitor capivasertib to fulvestrant improved median PFS (mPFS) for patients with PIK3CA-, AKT1-, and/or PTEN-altered HR+, HER2- metastatic breast cancer (12.8 vs. 4.6 months, HR=0.44)[62,69]. A Phase 2 study of alpelisib monotherapy for patients harboring PIK3CA-mutated HR+, HER2- breast cancer reported an ORR of 38% (10/26), mPFS of 5.4 months, median OS of 18.8 months, and median duration of response of 5.6 months; no responses (0% ORR [0/7]) were reported for PIK3CA-mutated triple negative breast cancer (TNBC) patients[70]. Single-agent capivasertib also demonstrated activity in a Phase 1 study[71]. In trials of AKT inhibitors with paclitaxel, neither capivasertib nor ipatasertib showed significant mPFS benefit for patients with PI3K pathway-mutated HR+, HER2- metastatic breast cancer compared with paclitaxel plus placebo[72]. In a Phase 1 study, the PIK3CA-selective inhibitor inavolisib (GDC-0077) alone or in combination with endocrine therapy (letrozole or fulvestrant) with or without palbociclib yielded an ORR of 32% (23/73) for patients with PIK3CA-mutated HR+, HER2- breast cancer, with an ORR of 40% (6/15) observed for patients who received inavolisib plus palbociclib and fulvestrant[73-74] . A Phase 1 study of combination palbociclib, fulvestrant, and the pan-PIK3CA inhibitor taselisib reported an ORR of 38% (9/24), DCR of 58% (14/24), and mPFS of 7.2 months for patients with PIK3CA-mutated ER+, HER2- breast cancer[75]. The addition of the mTOR inhibitor everolimus to exemestane to treat HR+, HER2- advanced breast cancer has shown clinical benefit, regardless of PIK3CA status[76-77]. The Phase 2 NCI-MATCH study of copanlisib for patients with refractory solid tumors harboring PIK3CA mutations with or without PTEN loss met its primary endpoint with an ORR of 16% (4/25 PRs); responses (PR or SD >6 months) were seen in patients with ameloblastoma, liposarcoma, and carcinomas of the endometrium, ovary, esophagus, lung, and prostate[50]. However, the Phase 2 study of copanlisib for patients with endometrial carcinoma harboring PIK3CA hotspot mutations failed to report any objective responses (n=11)[49]. Two other studies of copanlisib for patients with genomically unselected tumors reported 1 CR and 2 PRs (1 unconfirmed) among 16 total patients with PIK3CA-mutated solid tumors with or without PTEN alterations[47-48].

FREQUENCY & PROGNOSIS

Mutations in PIK3CA have been reported in up to 37% of breast cancer cases[78-79]. In the randomized Phase 2 SAFIR02 trial, PIK3CA mutations were associated with reduced OS in patients with hormone-receptor-positive (HR+)/HER2 negative (HER-) metastatic breast cancer but with improved OS in patients with mTNBC compared to patients with PIK3CA wildtype status[80]. Although double PIK3CA mutations were frequently observed in HR+/HER2- breast cancers, as compared with other receptor subtypes (15% vs. 5.4%, p=0.004), this did not impact invasive disease-free survival or OS for patients when compared with single PIK3CA mutations by univariate and multivariate analysis in 1 retrospective study[81]. For patients with HER2+ breast cancer receiving trastuzumab and pertuzumab with chemotherapy, PIK3CA mutations significantly associated with shorter PFS (13 vs. 23 months; HR=1.98)[82]. Mutations in coding exon 20 (H1047R) of PIK3CA have been associated with a better prognosis in breast carcinoma than mutations occurring in coding exon 9 (E542K)[83].

FINDING SUMMARY

PIK3CA encodes p110-alpha, which is the catalytic subunit of phosphatidylinositol 3-kinase (PI3K). The PI3K pathway is involved in cell signaling that regulates a number of critical cellular functions, including cell growth, proliferation, differentiation, motility, and survival[84-85]. PIK3CA alterations that have been characterized as activating, such as observed here, are predicted to be oncogenic[86-107].

GENE
NF1

ALTERATION
W425*

TRANSCRIPT ID
NM_001042492.2

CODING SEQUENCE EFFECT
1275G>A

VARIANT CHROMOSOMAL POSITION
chr17:29533272

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in neurofibromatosis Type 1-associated neurofibroma[108-111], glioma or glioblastoma[111-115], and non-small cell lung cancer[116], NF1 inactivation may predict sensitivity to MEK inhibitors such as cobimetinib, trametinib, binimetinib, and selumetinib. On the basis of limited clinical data[117-119] and preclinical data[120-121], loss or inactivation of NF1 may predict sensitivity to mTOR inhibitors, including everolimus and temsirolimus. A preclinical study suggests that combined mTOR and MEK inhibition is effective in a model of NF1-deficient malignant peripheral nerve sheath tumors (MPNST)[122].

FREQUENCY & PROGNOSIS

NF1 mutations and loss have been reported in 1.9-2.7% and <1% of breast carcinomas, respectively[78,123-125]. NF1 alterations are enriched in metastatic breast invasive lobular carcinoma (ILC) compared to metastatic invasive ductal carcinoma (12.2% vs 3.1%), and are often mutually exclusive with ESR1 alterations[126]. NF1 alterations have been reported to arise during endocrine therapy resistance in ILC[126]. Studies have suggested that women with neurofibromatosis type 1, which is associated with germline NF1 mutations, may have an increased risk of breast cancer[127-131]. Published data investigating the prognostic implications of NF1 alteration in breast cancer are limited (PubMed, Jan 2023).

FINDING SUMMARY

NF1 encodes neurofibromin, a GTPase-activating protein (GAP) that is a key negative regulator of the RAS signaling pathway[132]. Neurofibromin acts as a tumor suppressor by repressing RAS signaling[133]. Alterations such as seen here may disrupt NF1 function or expression[133-142].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in NF1 cause the autosomal dominant disorder neurofibromatosis type 1, which is characterized in part by increased risk of developing various tumors, including sarcoma, glioma, breast carcinoma, and neuroendocrine and hematological neoplasms[131,143-144]. Estimates for the prevalence of the disorder in the general population range from 1:2,500 to 1:3,000[145-146], and in the appropriate clinical context, germline testing of NF1 is recommended.

GENE
AKT1

ALTERATION
E17K

TRANSCRIPT ID
NM_001014431.1

CODING SEQUENCE EFFECT
49G>A

VARIANT CHROMOSOMAL POSITION
chr14:105246551

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

A Phase 2 basket trial of ipatasertib reported an ORR of 22% (7/32) for patients with AKT1 E17K-mutated solid tumors, including 4 breast cancer, 1 endometrioid adenocarcinoma, 1 anal squamous cell carcinoma, and 1 salivary gland cancer[147]. On the basis of clinical evidence, activating AKT1 alterations in hormone-receptor-positive (HR+) and triple-negative breast cancer (TNBC) may predict sensitivity to AKT inhibitors. An expanded Phase 1 study of the AKT inhibitor capivasertib with fulvestrant or capivasertib monotherapy for patients with heavily pretreated AKT1-mutated HR+ breast cancer reported a PR rate of 36% (10/28) for patients with previous fulvestrant exposure who received the combination therapy; in fulvestrant-naive patients, PR rates of 20% were reported for both the monotherapy (4/20) and combination therapy (3/15) subgroups[148]. In an NCI-MATCH subprotocol study of capivasertib in AKT1-mutated solid tumors, 47% (7/15) of patients with HR+, HER2- breast cancer experienced PRs[149]. In a Phase 2 basket trial of capivasertib plus fulvestrant, 4 confirmed and 4 unconfirmed PRs were experienced among the group of 18 patients with AKT1-mutated HR+ breast cancer[64]. A Phase 2 trial of the AKT inhibitor capivasertib with paclitaxel versus paclitaxel alone showed a median OS benefit for the overall population (19.1 vs. 12.6 months; HR=0.61), for patients with AKT1-, PTEN-, or PIK3CA-mutated triple-negative breast cancer (TNBC) (not reached vs. 10.4 months; HR=0.37), and for patients with TNBC without PI3K-pathway mutations (16.6 vs. 13.2 months; HR=0.84)[61]. In a Phase 2 trial, the addition of capivasertib to fulvestrant improved median PFS (mPFS) relative to fulvestrant plus placebo alone for patients with PIK3CA-, AKT1-, and/or PTEN-altered hormone-receptor-positive (HR+), HER2- metastatic breast cancer (12.8 vs. 4.6 months, HR=0.44)[62], although the Phase 3 CAPItello study of capivasertib with fulvestrant for patients with HR+, HER2- metastatic breast cancer reported improved median PFS (mPFS) relative to fulvestrant plus placebo for patients with and without alterations in the AKT pathway (7.3 vs 3.1 months, HR=0.50 and 7.2 vs 3.7 months, HR=0.70, respectively)[63]. In a Phase 2 basket trial of capivasertib monotherapy in AKT1-mutated cancers, 33% (2/6) of patients with HR+, HER2- or TNBC experienced PRs, and 2 other PRs were unconfirmed[64]. Despite promising initial results in earlier trials[65-66], the Phase 3 IPATunity130 trial failed to show improved PFS for first-line ipatasertib in combination with paclitaxel relative to paclitaxel alone for patients with AKT1-, PTEN-, or PIK3CA-mutated TNBC (7.4 vs. 6.1 months)[63] or HR+, HER2- breast cancer[67]. On the basis of clinical data in solid tumors, AKT1 activating mutations may be sensitive to mTOR inhibitors such as everolimus and temsirolimus[150-153]. In an exploratory analysis, a study for patients with AKT1-mutated hormone-receptor-positive (HR+), HER2-negative breast cancer treated with the investigational ATP-competitive MTOR inhibitor sapanisertib and exemestane or fulvestrant reported a positive association between best overall response (CR+PR) and AKT1-mutated status (n=11) compared with patients with AKT1-wildtype status (n=42) (p<0.03)[154]. In a retrospective analysis of clinical outcomes for patients with HR+ breast cancer, AKT1 E17K was associated with significantly increased median duration of treatment with everolimus-containing regimens[155].

FREQUENCY & PROGNOSIS

In the TCGA dataset, AKT1 mutations have been reported in approximately 2% of all breast carcinomas; the E17K mutation accounts for the majority of these mutations[79]. In one study of breast carcinomas, AKT1 mutations were detected in 3% (1/31) of invasive ductal carcinomas but not in any invasive mucinous carcinomas (0/35)[156]. Another study reported AKT1 mutations in 7% (8/108) of patients with metastatic breast cancer[157]. A clinicogenomic registry study for patients with estrogen receptor-positive metastatic breast cancer reported increased rates of metastasis to the liver (32.7% vs. 22.8%, p<0.001) and lymph node (31.4% vs. 24.8%, p=0.026) for patients with AKT1 E17K-mutated tumors relative to wild-type AKT1 tumors; however, median OS did not significantly differ with respect to AKT1 mutation status (24.1 vs. 29.9 months, p=0.98, HR=1.0)[155]. A retrospective study reported a significant association of reduced survival and AKT1 copy number gain (HR=3.89) or high AKT1 mRNA expression (HR=3.93-6.1) for patients with triple-negative breast cancer basal-like 2 subtype[158].

FINDING SUMMARY

AKT1 encodes an intracellular serine/threonine kinase and is one of three members of the AKT gene family. AKT activation promotes cell survival via inhibition of apoptosis and also contributes to cell proliferation through several interactions with the cell cycle machinery; inappropriate activation of AKT can therefore lead to tumor formation[159]. Missense mutations and in-frame duplications that occur in the pleckstrin homology (PH) domain of AKT1, as seen here, have been shown to transform cells and activate AKT signaling and are therefore considered to be oncogenic[160-166].

GENE
FGFR4

ALTERATION
V550L

TRANSCRIPT ID
NM_213647.3

CODING SEQUENCE EFFECT
1648G>C

VARIANT CHROMOSOMAL POSITION
chr5:176522551

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Tumors with FGFR4 amplification or activating mutations may be sensitive to certain pan-FGFR inhibitors, and clinical trials of some of these agents are currently underway in solid tumors, including erdafitinib[167] and LY2874455[168]. The multikinase inhibitor ponatinib has been shown to have substantial activity against all four FGFR kinases[169].

— Potential Resistance —

Preclinical studies of FGFR4 V550 mutant sensitivity to ponatinib treatment are conflicting. Mutations of the corresponding residue in other FGFRs has been shown to confer resistance to several FGFR kinase inhibitors including ponatinib[170-171] and V550E/L mutations have been shown to confer resistance to ponatinib[172]. However, a subsequent study demonstrated that, although in vitro experiments only suggested activity at doses beyond what is clinically achievable, reduced tumor growth was observed after treating a mouse rhabdomyosarcoma xenograft model harboring the V550E mutation with ponatinib[173]. Therefore, the relevance of ponatinib for mutation at this position is unclear. A Phase 1 study reported the emergence of FGFR4 V550L during progression on fisogatinib in a patient with FGF19-overexpressing liver cancer, although additional FGFR4 resistance mutations also co-emerged, making the relevance of clinical resistance to fisogatinib for V550L unclear[174]. This and other V550 mutations (V550M/E) emerged in in vitro and in vivo resistance screens in cells expressing a TEL-FGFR4 fusion. In other preclinical studies, V550 mutations (E/L/M) markedly reduced sensitivity to the FGFR inhibitors infigratinib, erdafitinib, and LY2874455[174].

FREQUENCY & PROGNOSIS

In the Breast Invasive Carcinoma TCGA dataset, putative high-level amplification of FGFR4 was reported in <1% of cases[79]. FGFR4 amplification and gene overexpression have been detected in 10% and 32% of breast tumors, respectively, in the literature[175-176]. One study reported that the putative activating FGFR4 R388 polymorphism correlated with increased metastasis, reduced disease-free survival time, and overall poor prognosis for patients with breast cancer; however, the prognostic implications of FGFR4 amplification were not reported[177-178].

FINDING SUMMARY

FGFR4 encodes fibroblast growth factor receptor 4, a receptor tyrosine kinase that plays a role in regulation of the cell cycle and angiogenesis and is an upstream regulator of the RAS, MAPK, and AKT signaling pathways[179-180]. FGFR4 V550 is located at the 'gatekeeper' position in the kinase domain[181-182], and FGFR4 variants V550E/L were reported to promote autophosphorylation, STAT3 signaling, tumor proliferation, and metastatic potential in murine cells[181,183]. Other alterations at this position are likely activating.

GENE
DNMT3A

ALTERATION
S663*

TRANSCRIPT ID
NM_022552.3

CODING SEQUENCE EFFECT
1988C>A

VARIANT CHROMOSOMAL POSITION
chr2:25464525

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in DNMT3A in solid tumors.

FREQUENCY & PROGNOSIS

DNMT3A alterations have been reported at relatively low frequencies in solid tumors and are more prevalent in hematological malignancies (cBioPortal, COSMIC, PubMed, Feb 2023)[184-186]. Published data investigating the prognostic implications of DNMT3A alterations in solid tumors are limited (PubMed, Feb 2023).

FINDING SUMMARY

The DNMT3A gene encodes the protein DNA methyltransferase 3A, an enzyme that is involved in the methylation of newly synthesized DNA, a function critical for gene regulation[187-188]. The role of DNMT3A in cancer is uncertain, as some reports describe increased expression and contribution to tumor growth, whereas others propose a role for DNMT3A as a tumor suppressor[189-194]. Alterations such as seen here may disrupt DNMT3A function or expression[195-198].

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[199-204]. 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[199-200]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[205]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[203,206-207]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

GENE
LYN

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Dasatinib is a kinase inhibitor that targets the BCR-ABL fusion protein, SRC family kinases including LYN (specifically at low nanomolar concentration)[208-209], and other kinases, and has been approved to treat chronic myelocytic leukemia (CML) and acute lymphoblastic leukemia (ALL). A pediatric patient with relapsed B-cell acute lymphoblastic leukemia and an NCOR1-LYN fusion achieved complete remission after 2 weeks of treatment with dasatinib[210]. Similarly, a preclinical study showed that treatment with dasatinib significantly increased survival in a xenograft model of leukemic blast cells harboring NCOR1-LYN[211]. In preclinical studies of LYN-expressing breast and prostate cancer, dasatinib has been reported to inhibit cell migration and invasion[208,212]. However, amplification or other genomic alterations in LYN in solid tumors, and their potential predictive value for sensitivity of these tumors to dasatinib and other kinase inhibitors, remains poorly understood.

FREQUENCY & PROGNOSIS

LYN alterations are rare in solid tumors[213-214]. However, LYN amplification has been reported more frequently, including in ovarian (3.1%), melanoma (2.3%), prostate (2.2%), breast (1.9%), and endometrial (1.6%) cancers[213-214]. LYN expression and activation have also been reported in several types of solid tumors, including glioblastoma[215], prostate cancer[216], head and neck squamous cell carcinoma (HNSCC)[217], Ewing sarcoma[218], and breast cancer[212]. High LYN expression was associated with lower survival rates for patients with breast, colorectal, and renal cancers[212,219-220].

FINDING SUMMARY

LYN encodes a SRC family intracellular membrane-associated tyrosine protein kinase. LYN is expressed predominantly in hematopoietic cells and conveys signals from the B-cell receptor (BCR) and other receptors to activate the PI3K, STAT, and other signaling pathways[221-222].

GENE
MAP3K1

ALTERATION
T1145fs*6, Q1425fs*7

TRANSCRIPT ID
NM_005921.1, NM_005921.1

CODING SEQUENCE EFFECT
3433_3434insA, 4272_4273insA

VARIANT CHROMOSOMAL POSITION
chr5:56178459, chr5:56184065

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in MAP3K1.

FREQUENCY & PROGNOSIS

Somatic alterations of MAP3K1, including missense mutations, truncating alterations, and loss, are most frequent in breast cancer (8-14%) and present at lower frequencies in various solid tumor types[213,223]. MAP3K1 mutations are enriched in PIK3CA-mutated hormone-receptor-positive (HR-positive) breast cancer (15%)[80,224], and the co-occurrence of MAP3K1 and PIK3CA mutations correlated with the luminal A molecular subtype and favorable prognosis[224-226]. MAP3K1 mutations alone may also implicate lower risk of distant disease in HR-positive early breast cancer[223].

FINDING SUMMARY

MAP3K1 encodes a multifunctional protein kinase and E3 ubiquitin ligase involved in several signal transduction pathways central to cancer cell biology[227]. Different MAP3K1 protein isoforms have been suggested to exert both pro- and anti-apoptotic influences[228-229]. Germline polymorphism in MAP3K1 has been hypothesized to associate with risk for at least some subtypes of breast carcinoma[230], but the extent of effect is small and experimental results have been inconsistently replicated[231].

GENE
RAD21

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies to target alterations in this gene.

FREQUENCY & PROGNOSIS

RAD21 amplification has been reported in 19% of breast cancers[124]. RAD21 alterations have been associated with inferior OS among patients with HER2+ or HR+/HER2− breast cancer but was not predictive of survival for patients with triple-negative breast cancer[232]. RAD21 expression has been associated with shorter recurrence-free survival (RFS) for patients with breast cancer[233].

FINDING SUMMARY

RAD21 encodes a protein involved in DNA double-strand break repair and sister chromatid cohesion as a part of the cohesin complex[234-237]. Altered RAD21 expression has been associated with increased genomic instability[238-240] and changes to the expression of other genes[241-243]. RAD21 amplification has been correlated with increased RAD21 expression in breast[233,240,244] and endometrial[245] cancers. Other RAD21 alterations, including truncating and point mutations, have been reported in the context of cancer, but the majority have not been characterized.

Alpelisib + Fulvestrant

Assay findings association

PIK3CA
H1047R, E453K

AREAS OF THERAPEUTIC USE

Alpelisib is a phosphatidylinositol 3-kinase (PI3K) inhibitor with selective activity against the alpha isoform (PI3K-alpha), and fulvestrant is an estrogen receptor (ER) antagonist and selective estrogen receptor degrader (SERD). The combination is FDA approved to treat men and postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated advanced breast cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of prospective clinical data, PIK3CA mutations including C420R, E542K, E545A, E545G, E545K, E545D, Q546E, Q546R, H1047L, H1047Y, and H1047R are associated with sensitivity to alpelisib in combination with fulvestrant. In ER+/HER2– breast cancer, PFS benefit from the addition of alpelisib to fulvestrant was specifically observed for patients with PIK3CA mutations (11.0 vs. 5.7 months, HR=0.65), including patients with PIK3CA exon 9 or exon 20 mutations[51].

SUPPORTING DATA

In the Phase 3 SOLAR-1 study for patients with HR+, HER2- endocrine-therapy-resistant advanced breast cancer, the addition of alpelisib to fulvestrant significantly improved median PFS (mPFS; 11.0 vs. 5.7 months, HR=0.65), ORR (27% vs. 13%), clinical benefit rate (62% vs. 45%), and numerically improved median OS (mOS; 39.3 vs. 31.4 months, HR=0.86) for patients with PIK3CA mutations[51,68] ; patients with wildtype PIK3CA did not experience significant mPFS benefit (7.4 vs. 5.6 months, HR=0.85)[51]. This trial excluded patients with active brain metastases; however, control of progressive brain metastases (1/4 PR and 2/4 SDs by response assessment in neuro-oncology brain metastases criteria) was reported in a case series of 4 patients with PIK3CA-mutated HR+, HER2- breast cancer treated with alpelisib in combination with either fulvestrant or exemestane[246]. The Phase 2 BYLieve study for previously treated patients with PIK3CA-mutated HR+, HER2- advanced breast cancer reported an ORR of 19%, an mPFS of 7.3 months, and an mOS of 26.4 months for patients treated with alpelisib plus fulvestrant following progression on a CDK4/6 inhibitor in combination with an aromatase inhibitor (AI)[247]; patients who progressed more quickly on their prior CDK4/6 inhibitor plus AI regimen (<6 months) experienced greater mPFS benefit from alpelisib plus fulvestrant (12.0 vs. 6.2 months) than patients who experienced delayed progression (>6 months)[248]. The Phase 2 BYLieve trial also reported an ORR of 16% and an mPFS of 5.7 months for patients treated with alpelisib plus letrozole following progression on a CDK4/6 inhibitor in combination with fulvestrant, benefit did not differ by duration of prior treatment[248-249] , and an ORR of 24% and an mPFS of 5.6 months for patients treated with alpelisib plus fulvestrant who had previously progressed on aromatase inhibitors and received chemotherapy or endocrine therapy[250].

Cobimetinib

Assay findings association

NF1
W425*

AREAS OF THERAPEUTIC USE

Cobimetinib is a MEK inhibitor that is FDA approved to treat patients with histiocytic neoplasms. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in neurofibromatosis type 1 (NF1)-associated neurofibroma[108-111,251-255] , glioma[111-115,256] , and non-small cell lung cancer[116], NF1 inactivation may predict sensitivity to MEK inhibitors.

SUPPORTING DATA

As first-line treatment for advanced triple-negative breast cancer, addition of cobimetinib to paclitaxel was associated with a trend toward improved median PFS (mPFS; 5.5 vs. 3.8 months, HR=0.73, p=0.25) and a higher confirmed ORR (18/47 vs. 9/43, all PRs) in a placebo-controlled Phase 2 study[257]. In the same setting, the combination of cobimetinib with the anti-PD-L1 immunotherapy atezolizumab and paclitaxel or nab-paclitaxel, respectively, resulted in an ORR of 34% (11/32) and 29% (9/31), median duration of response of 5.8 months and 11.0 months, and mPFS of 3.8 months and 7.0 months[257]. The study observed a trend toward higher ORR for patients with PD-L1 expression on tumor-infiltrating immune cells compared with patients with PD-L1-negative disease (ORR of 39% [12/31] vs. 19% [4/21])[257].

Selumetinib

Assay findings association

NF1
W425*

AREAS OF THERAPEUTIC USE

Selumetinib is a MEK inhibitor that is FDA approved to treat pediatric patients with neurofibromatosis type 1 (NF1)-associated plexiform neurofibromas (PNs). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in neurofibromatosis type 1 (NF1)-associated neurofibroma[108-111,251-255] , glioma[111-115,256] , and non-small cell lung cancer[116], NF1 inactivation may predict sensitivity to MEK inhibitors.

SUPPORTING DATA

In a Phase 2 study for post-menopausal patients with endocrine sensitive breast cancer who had progressed after aromatase inhibitor therapy, the addition of selumetinib to fulvestrant did not improve survival compared to placebo plus fulvestrant[258]. Selumetinib has demonstrated efficacy in NF1-associated neurofibroma in Phase 2 studies[109,251-252] and a Phase 1 study[108]. Phase 2 studies reported clinical responses in low-grade glioma[112,259] , melanoma[260-264] , and in lung[116,265-266] and endometrial cancer[267]. A Phase 2 study of selumetinib for patients with activating alterations in the MAPK pathway reported a DCR of 15% (3/20), with no objective responses observed[268]. Phase 1 studies of selumetinib to treat patients with solid tumors reported 1/15 PR for a patient with colorectal cancer (CRC) and 5/15 SDs for patients with tonsil squamous cell carcinoma (SCC), non-small cell lung cancer (NSCLC), and CRC[269]; 2/39 PRs (for patients with CRC) and 18/39 SDs were achieved when selumetinib was administered in combination with cyclosporin A[270]. Multiple Phase 1 studies combining selumetinib with erlotinib or temsirolimus[271], docetaxel or dacarbazine[272], AKT inhibitors[273], or cixutumumab (an anti-IGF-1R antibody)[274] reported clinical responses for patients with advanced solid tumors including NSCLC, thyroid carcinoma, tongue SCC, and ovarian cancer.

Trametinib

Assay findings association

NF1
W425*

AREAS OF THERAPEUTIC USE

Trametinib is a MEK inhibitor that is FDA approved as a monotherapy to treat patients with melanoma with BRAF V600E or V600K mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in neurofibromatosis type 1 (NF1)-associated neurofibroma[108-111,251-255] , glioma[111-115,256] , and non-small cell lung cancer[116], NF1 inactivation may predict sensitivity to MEK inhibitors.

SUPPORTING DATA

In the Phase 2 NCI-MATCH study Subprotocol R evaluating trametinib in solid tumors, 1 patient with breast ductal adenocarcinoma and a BRAF G569E and an NF1 inactivating mutation had a transient PR[275]. In a Phase 2 study for patients with triple negative breast cancer (TNBC) treated with trametinib (Part 1) followed by trametinib in combination with AKT inhibitor GSK2141795 (Part 2), 6.5% (2/31) of the patients in Part 1 achieved PRs and 6.3% (1/16) of the patients in Part 2 had an unconfirmed PR[276]. A Phase 1 study of trametinib combined with AKT inhibitor uprosertib for patients with solid tumors reported a CR for a patient with TNBC[277]. A Phase 1b trial of trametinib in combination with gemcitabine in solid tumors showed a CR from 6 patients with breast cancer[278]. Another patient with TNBC achieved a clinical response upon single-agent trametinib treatment[279]. No responses were reported for patients with breast cancer in early phase studies of trametinib combined with everolimus[280], PI3K inhibitor buparlisib[281], PI3K/mTOR inhibitor GSK2126458[282], or AKT inhibitor afuresertib[283]. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[280], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[284].

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
AKT1

ALTERATION
E17K

RATIONALE
AKT1 amplification or mutation may lead to activation of AKT signaling and therefore may result in sensitivity to AKT pathway inhibitors. Inhibitors of AKT and the downstream protein mTOR are under investigation in clinical trials.

NCT04589845

PHASE 2

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

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

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

NCT04188548

PHASE 1

A Study of LY3484356 in Participants With Advanced or Metastatic Breast Cancer or Endometrial Cancer

TARGETS
mTOR, Aromatase, CDK4, CDK6, ER, PI3K-alpha, ERBB2

LOCATIONS: Taipei (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Kaohsiung (Taiwan), Seoul (Korea, Republic of), Akashi (Japan), Chuo-ku (Japan), Nedlands (Australia), Kurralta Park (Australia), Waratah (Australia)

NCT04556773

PHASE 1

A Phase 1b Study of T-DXd Combinations in HER2-low Advanced or Metastatic Breast Cancer

TARGETS
PD-L1, ERBB2, AKTs, Aromatase

LOCATIONS: Taipei (Taiwan), Taipei City (Taiwan), Taoyuan (Taiwan), Taichung (Taiwan), Kaohsiung (Taiwan), Seoul (Korea, Republic of), Westmead (Australia), East Melbourne (Australia), Edegem (Belgium), Antwerpen (Belgium)

NCT03997123

PHASE 3

Capivasertib+Paclitaxel as First Line Treatment for Patients With Locally Advanced or Metastatic TNBC

TARGETS
AKTs

LOCATIONS: Tainan City (Taiwan), Wenzhou (China), Shanghai (China), Nanchang (China), Nanjing (China), Hefei (China), Changchun (China), Guangzhou (China), Urumqi (China), Zhengzhou (China)

NCT04818632

PHASE 1

AZD9833 China PK Study

TARGETS
CDK4, CDK6, ER, mTOR

LOCATIONS: Shanghai (China), Beijing (China), Wuhan (China), Chengdu (China)

NCT04802759

PHASE 1/2

A Study Evaluating the Efficacy and Safety of Multiple Treatment Combinations in Participants With Breast Cancer

TARGETS
ER, CDK4, CDK6, AKTs, PI3K-alpha, mTOR

LOCATIONS: Seoul (Korea, Republic of), Goyang-si (Korea, Republic of), Nedlands (Australia), Bedford Park (Australia), Melbourne (Australia), Frankston (Australia), Jerusalem (Israel), Petach Tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel)

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT04862663

PHASE 3

Capivasertib + Palbociclib + Fulvestrant for HR+/HER2- Advanced Breast Cancer (CAPItello-292).

TARGETS
AKTs, CDK6, ER, CDK4

LOCATIONS: Chuo-ku (Japan), Koto-ku (Japan), Nedlands (Australia), Darlinghurst (Australia), Miranda (Australia), Solna (Sweden), Warszawa (Poland), Bydgoszcz (Poland), Kraków (Poland), Odense C (Denmark)

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)

NCT04650581

PHASE 3

Fulvestrant and Ipatasertib for Advanced HER-2 Negative and Estrogen Receptor Positive (ER+) Breast Cancer Following Progression on First Line CDK 4/6 Inhibitor and Aromatase Inhibitor

TARGETS
ER, AKTs

LOCATIONS: Murdoch (Australia), Bunbury (Australia), Birtinya (Australia), Toowoomba (Australia), Herston (Australia), Gateshead (Australia), Gosford (Australia), Macquarie University (Australia), Randwick (Australia), Bowral (Australia)

GENE
FGFR4

ALTERATION
V550L

RATIONALE
FGFR inhibitors may be of use in a tumor with FGFR4 amplification or activating mutation. However, preclinical studies have reported somewhat discordant data regarding the sensitivity of V550E/L mutations to ponatinib. In preclinical studies, the sensitivity of V550L/E is unclear; these mutations are associated with reduced sensitivity to pan-FGFR inhibitors and the specific FGFR4 inhibitor fisogatinib.

NCT05024214

PHASE 1/2

Phase Ib/II Trial of Envafolimab Plus Lenvatinib for Subjects With Solid Tumors

TARGETS
PD-L1, FGFRs, RET, PDGFRA, VEGFRs, KIT, FLT3, CSF1R

LOCATIONS: Hangzhou (China), Shanghai (China), Dongguan (China), Guangzhou (China), Zhuhai (China), Benbu (China), Zhengzhou (China), Jinan (China), Dalian (China), Tianjin (China)

NCT05098847

PHASE 2

Cryoablation Combined With Sintilimab Plus Lenvatinib In Previously Treated Unresectable Liver Metastasis From Solid Tumors

TARGETS
FGFRs, RET, PDGFRA, VEGFRs, KIT, PD-1

LOCATIONS: Shanghai (China)

NCT03564691

PHASE 1

Study of MK-4830 as Monotherapy and in Combination With Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-4830-001)

TARGETS
ITL4, FGFRs, RET, PDGFRA, VEGFRs, KIT, PD-1

LOCATIONS: Shanghai (China), Seoul (Korea, Republic of), Brisbane (Australia), Liverpool (Australia), Petah Tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Haifa (Israel), Warszawa (Poland), Gdansk (Poland)

NCT04977453

PHASE 1/2

GI-101 as a Single Agent or in Combination With Pembrolizumab, Lenvatinib or Local Radiotherapy in Advanced Solid Tumors

TARGETS
FGFRs, RET, PDGFRA, VEGFRs, KIT, PD-1, CTLA-4

LOCATIONS: Daejeon (Korea, Republic of), Suwon-si (Korea, Republic of), Seoul (Korea, Republic of), North Carolina

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

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), Chuo-Ku (Japan), Koto-ku (Japan), Chiba (Japan), Kashiwa (Japan), Hidaka (Japan)

NCT04565275

PHASE 1/2

A Study of ICP-192 in Patients With Advanced Solid Tumors

TARGETS
FGFR2, FGFR1, FGFR3, FGFR4

LOCATIONS: Macquarie Park (Australia), Melbourne (Australia), Clayton (Australia), Frankston (Australia), Colorado, Minnesota, Arizona, Ohio, Florida

NCT04729348

PHASE 2

Pembrolizumab And Lenvatinib In Leptomeningeal Metastases

TARGETS
PD-1, KIT, VEGFRs, FGFRs, PDGFRA, RET

LOCATIONS: Massachusetts

NCT05064280

PHASE 2

Phase II Study of Pembrolizumab in Combination With Lenvatinib in Patients With TNBC, NSCLC, and Other Tumor Types and Brain Metastases

TARGETS
PD-1, KIT, VEGFRs, FGFRs, PDGFRA, RET

LOCATIONS: Texas

NCT02856425

PHASE 1

Trial Of Pembrolizumab And Nintedanib

TARGETS
FGFR1, LCK, SRC, VEGFRs, FGFR2, FGFR3, FLT3, LYN, PD-1

LOCATIONS: Villejuif (France)

GENE
NF1

ALTERATION
W425*

RATIONALE
On the basis of clinical evidence and strong preclinical evidence, NF1 inactivation may predict sensitivity to MEK inhibitors. Limited clinical data and strong preclinical data indicate that loss or inactivation of NF1 may also predict sensitivity to mTOR inhibitors.

NCT04188548

PHASE 1

A Study of LY3484356 in Participants With Advanced or Metastatic Breast Cancer or Endometrial Cancer

TARGETS
mTOR, Aromatase, CDK4, CDK6, ER, PI3K-alpha, ERBB2

LOCATIONS: Taipei (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Kaohsiung (Taiwan), Seoul (Korea, Republic of), Akashi (Japan), Chuo-ku (Japan), Nedlands (Australia), Kurralta Park (Australia), Waratah (Australia)

NCT04818632

PHASE 1

AZD9833 China PK Study

TARGETS
CDK4, CDK6, ER, mTOR

LOCATIONS: Shanghai (China), Beijing (China), Wuhan (China), Chengdu (China)

NCT04985604

PHASE 1/2

DAY101 Monotherapy or in Combination With Other Therapies for Patients With Solid Tumors

TARGETS
BRAF, MEK

LOCATIONS: Busan (Korea, Republic of), Seoul (Korea, Republic of), Clayton (Australia), Edegem (Belgium), Oregon, Barcelona (Spain), Madrid (Spain), California, Colorado

NCT04802759

PHASE 1/2

A Study Evaluating the Efficacy and Safety of Multiple Treatment Combinations in Participants With Breast Cancer

TARGETS
ER, CDK4, CDK6, AKTs, PI3K-alpha, mTOR

LOCATIONS: Seoul (Korea, Republic of), Goyang-si (Korea, Republic of), Nedlands (Australia), Bedford Park (Australia), Melbourne (Australia), Frankston (Australia), Jerusalem (Israel), Petach Tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel)

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

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)

NCT04551521

PHASE 2

CRAFT: The NCT-PMO-1602 Phase II Trial

TARGETS
PD-L1, AKTs, MEK, BRAF, ALK, RET, ERBB2

LOCATIONS: Würzburg (Germany), Mainz (Germany), Heidelberg (Germany), Tübingen (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)

NCT03911973

PHASE 1/2

Gedatolisib Plus Talazoparib in Advanced Triple Negative or BRCA1/2 Positive, HER2 Negative Breast Cancers

TARGETS
PI3K-gamma, mTORC1, mTORC2, PI3K-alpha, PARP

LOCATIONS: Wisconsin, Iowa, Illinois, Indiana

NCT03905148

PHASE 1/2

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

TARGETS
RAFs, EGFR, MEK

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

GENE
PIK3CA

ALTERATION
H1047R, E453K

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

NCT04191499

PHASE 2/3

A Study Evaluating the Efficacy and Safety of GDC-0077 + Palbociclib + Fulvestrant vs Placebo + Palbociclib + Fulvestrant in Patients With PIK3CA-Mutant, Hormone Receptor-Positive, Her2-Negative, Locally Advanced or Metastatic Breast Cancer

TARGETS
PI3K-alpha, CDK6, ER, CDK4

LOCATIONS: Taipei (Taiwan), Fuzhou City (China), Tainan (Taiwan), Kaohsiung (Taiwan), Shanghai City (China), Shatin (Hong Kong), Nanjing City (China), Hong Kong (Hong Kong), Guangzhou City (China), Hefei (China)

NCT04589845

PHASE 2

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

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

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

NCT04188548

PHASE 1

A Study of LY3484356 in Participants With Advanced or Metastatic Breast Cancer or Endometrial Cancer

TARGETS
mTOR, Aromatase, CDK4, CDK6, ER, PI3K-alpha, ERBB2

LOCATIONS: Taipei (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Kaohsiung (Taiwan), Seoul (Korea, Republic of), Akashi (Japan), Chuo-ku (Japan), Nedlands (Australia), Kurralta Park (Australia), Waratah (Australia)

NCT04556773

PHASE 1

A Phase 1b Study of T-DXd Combinations in HER2-low Advanced or Metastatic Breast Cancer

TARGETS
PD-L1, ERBB2, AKTs, Aromatase

LOCATIONS: Taipei (Taiwan), Taipei City (Taiwan), Taoyuan (Taiwan), Taichung (Taiwan), Kaohsiung (Taiwan), Seoul (Korea, Republic of), Westmead (Australia), East Melbourne (Australia), Edegem (Belgium), Antwerpen (Belgium)

NCT03997123

PHASE 3

Capivasertib+Paclitaxel as First Line Treatment for Patients With Locally Advanced or Metastatic TNBC

TARGETS
AKTs

LOCATIONS: Tainan City (Taiwan), Wenzhou (China), Shanghai (China), Nanchang (China), Nanjing (China), Hefei (China), Changchun (China), Guangzhou (China), Urumqi (China), Zhengzhou (China)

NCT04544189

PHASE 2

Study Assessing the Efficacy and Safety of Treatment With Alpelisib Plus Fulvestrant Versus Placebo Plus Fulvestrant in Chinese Men and Postmenopausal Women With Advanced Breast Cancer

TARGETS
ER, PI3K-alpha

LOCATIONS: Hangzhou (China), Shanghai (China), Nanchang (China), Shenzhen (China), Nanjing (China), Hefei (China), Guangzhou (China), Changsha City (China), Changsha (China), Wuhan (China)

NCT04524000

PHASE 2

Study Assessing the Efficacy and Safety of Treatment With Alpelisib Plus Fulvestrant in Japanese Men and Postmenopausal Women With Advanced Breast Cancer

TARGETS
ER, PI3K-alpha

LOCATIONS: Naha-city (Japan), Kumamoto City (Japan), Matsuyama (Japan), Hiroshima-city (Japan), Okayama-city (Japan), Akashi (Japan), Osaka (Japan), Osaka-city (Japan), Tsu-city (Japan), Nagoya-city (Japan)

NCT04818632

PHASE 1

AZD9833 China PK Study

TARGETS
CDK4, CDK6, ER, mTOR

LOCATIONS: Shanghai (China), Beijing (China), Wuhan (China), Chengdu (China)

NCT05504213

PHASE 1

A Phase Ib Study of HS-10352 Plus Fulvestrant in Patients With Advanced Breast Cancer

TARGETS
PI3K-alpha, ER

LOCATIONS: Shanghai (China)

NCT04802759

PHASE 1/2

A Study Evaluating the Efficacy and Safety of Multiple Treatment Combinations in Participants With Breast Cancer

TARGETS
ER, CDK4, CDK6, AKTs, PI3K-alpha, mTOR

LOCATIONS: Seoul (Korea, Republic of), Goyang-si (Korea, Republic of), Nedlands (Australia), Bedford Park (Australia), Melbourne (Australia), Frankston (Australia), Jerusalem (Israel), Petach Tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel)

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 S1252T	***BRCA2*** S450C	***BRD4*** A1307T	***CTCF*** C271F
FGF3 T140M	***KMT2A (MLL)*** S206P	***MLL2*** G1316E	***NBN*** amplification
NF2 T251I	***NSD3 (WHSC1L1)*** rearrangement	***NTRK3*** V21F	***RPTOR*** K272T

ORDERED TEST # ORD-1558827-01

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***

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) 7.5.0

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