FOUNDATIONONE®LIQUID CDx

PATIENT
Lan, Kai-Ting

TUMOR TYPE
Unknown primary adenocarcinoma

COUNTRY CODE
TW

REPORT DATE
29 Nov 2021

ORDERED TEST #
ORD-1241589-01

ABOUT THE TEST FoundationOne®Liquid CDx is a next generation sequencing (NGS) assay that identifies clinically relevant genomic alterations in circulating cell-free DNA.

PATIENT

DISEASE Unknown primary adenocarcinoma
NAME Lan, Kai-Ting
DATE OF BIRTH 22 September 1981
SEX Female
MEDICAL RECORD # 33574366

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 KTL 09/22/1981
SPECIMEN TYPE Blood
DATE OF COLLECTION 15 November 2021
SPECIMEN RECEIVED 18 November 2021

Biomarker Findings

Blood Tumor Mutational Burden - 1 Muts/Mb
Microsatellite status - MSI-High Not Detected
Tumor Fraction - Cannot Be Determined

Genomic Findings

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

PIK3CA Q546K
ARID1A R1446*
BRAF G466A
FGFR4 amplification - equivocal†
KRAS G12D
CRKL amplification - equivocal†

† See About the Test in appendix for details.

2 Therapies with Clinical Benefit
0 Therapies with Resistance
32 Clinical Trials

BIOMARKER FINDINGS
Blood Tumor Mutational Burden - 1 Muts/Mb
Microsatellite status - MSI-High Not Detected
Tumor Fraction - Cannot Be Determined

THERAPY AND CLINICAL TRIAL IMPLICATIONS
No therapies or clinical trials. See Biomarker Findings section
MSI-High not detected. No evidence of microsatellite instability in this sample (see Appendix section).
Tumor fraction is an estimate of the percentage of circulating-tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample based on observed aneuploid instability.

GENOMIC FINDINGS		VAF %	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
PIK3CA -	Q546K	0.68%	None	Everolimus Temsirolimus
10 Trials see p. 19				
ARID1A -	R1446*	1.9%	None	None
5 Trials see p. 12				
BRAF -	G466A	0.49%	None	None
10 Trials see p. 13				
FGFR4 -	amplification - equivocal	-	None	None
8 Trials see p. 15				

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GENOMIC FINDINGS		VAF %	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
KRAS -	G12D	0.64%	None	None
10 Trials see p. 17				

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.

CRKL - amplification - equivocal p. 9

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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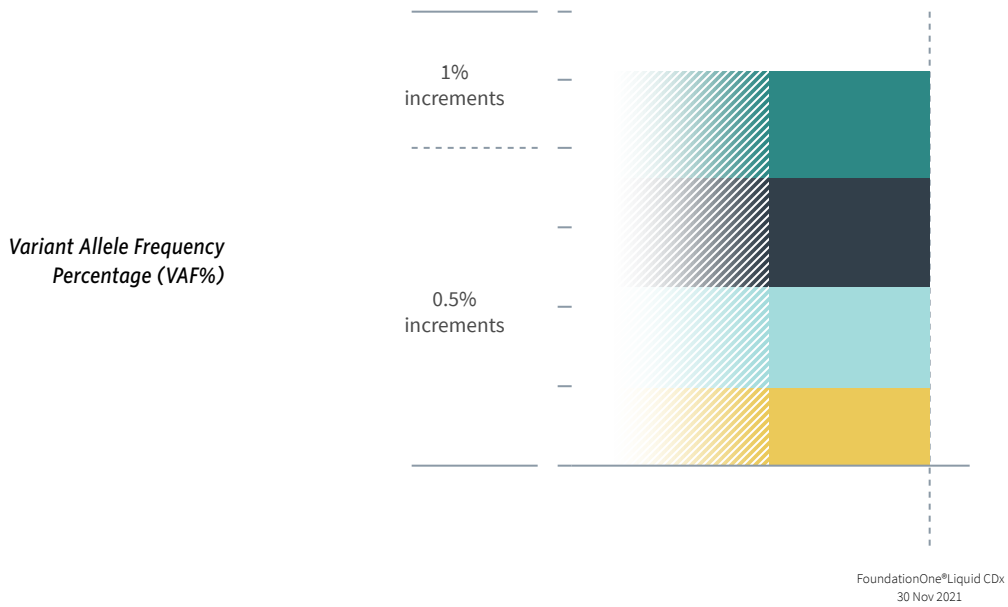

HISTORIC PATIENT FINDINGS		ORD-1241589-01 VAF%
Blood Tumor Mutational Burden		1 Muts/Mb
Microsatellite status		MSI-High Not Detected
Tumor Fraction		Cannot Be Determined
PIK3CA	● Q546K	0.68%
ARID1A	● R1446*	1.9%
BRAF	● G466A	0.49%
FGFR4	amplification	Detected
KRAS	● G12D	0.64%
CRKL	amplification	Detected

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 ≥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)

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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

Blood Tumor Mutational Burden

RESULT
1 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in NSCLC and HSNCC, increased bTMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[1-2] and anti-PD-1[3] therapies. In NSCLC, multiple clinical trials have shown patients with higher bTMB derive clinical benefit from immune checkpoint inhibitors following single agent or combination treatments with either CTLA4 inhibitors or chemotherapy, with reported high bTMB cutpoints ranging from 6 to 16 Muts/Mb[1]. In HNSCC, a Phase 3 trial showed that bTMB ≥16 Muts/Mb (approximate equivalency ≥8 Muts/Mb as measured by this assay) was associated with improved survival from treatment with a PD-L1 inhibitor alone or in combination with a CTLA-4 inhibitor[4].

FREQUENCY & PROGNOSIS

Average bTMB levels in solid tumors other than NSCLC have not been evaluated (cBioPortal, COSMIC, PubMed, Mar 2021)[5-7]. Published data investigating the prognostic implications of TMB have mainly been investigated in the context of tissue TMB. In patients with NSCLC, increased TMB is associated with higher tumor grade and poor prognosis[8], as well as with a decreased frequency of known driver mutations in EGFR, ALK, ROS1, or MET (1% of high-TMB samples each), but not BRAF (10.3%) or KRAS (9.4%)[9]. Although some studies have reported a lack of association between smoking and increased TMB in NSCLC[8,10], several other large studies did find a strong link[11-14]. In CRC, elevated TMB is associated with a higher frequency of BRAF V600E driver mutations[15-16] and with microsatellite instability (MSI)[16], which in turn has been reported to correlate with better prognosis[17-24]. Although increased TMB is associated with increased tumor grade in endometrioid endometrial carcinoma[25-28] and bladder cancer[29], it is also linked with improved prognosis in patients with these tumor types[26].

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[30-31] and cigarette smoke in lung cancer[32-33], treatment with temozolomide-based chemotherapy in glioma[34-35], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[15,26,36-38], and microsatellite instability (MSI)[15,26,38]. 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[1-3]. Depending on the clinical context, TMB testing of an alternate sample or by another methodology could be considered.

BIOMARKER

Tumor Fraction

RESULT
Cannot Be Determined

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Specimens with high tumor fraction values have high circulating-tumor DNA (ctDNA) content, and thus higher sensitivity for identifying genomic alterations. Such specimens are at a lower risk of false negative results[39]. However, if tumor fraction is not detected as high, it does not exclude the presence of disease burden or compromise the confidence of reported alterations. Tumor fraction levels currently have limited implications for diagnosis, surveillance, or therapy and should not be overinterpreted or compared from one blood draw to another. There are currently no targeted approaches to address specific tumor fraction levels. In the research setting, changes in tumor fraction estimates have been associated with treatment duration and clinical response and may be a useful indicator for future cancer management[40-45].

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)[46]. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer[47], Ewing sarcoma and osteosarcoma[48], prostate cancer[43], breast cancer[49], leiomyosarcoma[50], esophageal cancer[51], colorectal cancer[52], and gastrointestinal cancer[53].

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[54], 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[55-56]. However, the tumor fraction estimate in this sample could not be determined with confidence.

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GENE
PIK3CA

ALTERATION
Q546K

TRANSCRIPT ID
NM_006218

CODING SEQUENCE EFFECT
1636C>A

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[57-59], AKT[60-61], or mTOR[62-69]. In the Phase 2 MATCH trial for patients with PIK3CA-mutated solid tumors, 28% (18/65) of patients experienced PFS lasting at least 6 months after treatment with taselisib; however, no ORs were observed in this study[70]. A separate Phase 1b study of taselisib in combination with the CDK4/6 inhibitor palbociclib for patients with PIK3CA-mutated solid tumors reported an ORR of 0% (n=12) and a DCR of 17% (2/12)[71]. In a Phase 1 trial of the dual PI3K/mTOR kinase inhibitor apitolisib, 79% (11/14) of patients with PIK3CA-mutated advanced solid tumors experienced disease control (3 PRs, 8 SDs)[72]. The PI3K inhibitor alpelisib demonstrated an ORR of 6.0% (8/134) and a DCR of 58% (78/134) in a study for patients with PIK3CA-mutated solid tumors[73]. However, the PI3K inhibitor copanlisib exhibited limited efficacy in PIK3CA-mutated tumors[74-75].

— Potential Resistance —

Activating mutations in PIK3CA may confer resistance to HER2-targeted therapies; combined inhibition of HER2 and the PI3K pathway may be required in HER2-positive tumors with PIK3CA mutation[76-80].

FREQUENCY & PROGNOSIS

PIK3CA mutations have been reported in various malignancies, with the highest incidences in carcinomas of the uterus (53%)[26], breast (35%)[81-83], cervix (25%)(cBioPortal, Nov 2021)[5-6], bladder (23%)[84-87], head and neck (21%)[88], and stomach (20%)[89]. The prognostic significance of PIK3CA alteration is uncertain in many tumor types[90-95].

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[96-97]. PIK3CA alterations that have been characterized as activating, such as observed here, are predicted to be oncogenic[98-118].

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GENE
ARID1A

ALTERATION
R1446*

TRANSCRIPT ID
NM_006015

CODING SEQUENCE EFFECT
4336C>T

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies approved to address the mutation or loss of ARID1A in cancer. However, on the basis of limited clinical and preclinical evidence, ARID1A inactivating mutations may lead to sensitivity to ATR inhibitors such as M6620 and ceralasertib[119]. In a Phase 2 study of ceralasertib in solid tumors, 2 patients with endometrial carcinoma in the cohort with loss of ARID1A expression achieved CRs on ceralasertib monotherapy; at least 1 of these 2 patients carried an inactivating ARID1A mutation. In contrast, no responses were observed for patients with normal ARID1A expression treated with ceralasertib combined with olaparib[120]. One patient with small cell lung cancer harboring an ARID1A mutation experienced a PR when treated with M6620 combined with topotecan[121]. In a Phase 1 trial, a patient with metastatic colorectal cancer harboring both an ARID1A mutation and ATM loss treated with single-agent M6620 achieved a CR that was ongoing at 29 months[122]. On the basis of limited preclinical evidence from studies in ovarian cancer, ARID1A inactivation may predict sensitivity to EZH2 inhibitors[123-124], which are under investigation in clinical trials. Other studies have reported that the loss of ARID1A may activate the PI3K-AKT pathway and be linked with sensitivity to inhibitors of this pathway[125-127]. Patients with ARID1A alterations in advanced or metastatic solid tumors may derive benefit from treatment with anti-PD-1 or anti-PD-L1 immunotherapy[128]. Loss of ARID1A expression has been associated with chemoresistance to platinum-based therapy for patients with ovarian clear cell carcinoma[129-130] and to 5-fluorouracil in colorectal cancer cell lines[131].

FREQUENCY & PROGNOSIS

ARID1A alterations are particularly prevalent in ovarian clear cell carcinoma (46-50%), ovarian and uterine endometrioid carcinomas (24-44%), and cholangiocarcinoma (27%); they are also reported in up to 27% of gastric carcinoma, esophageal adenocarcinoma, Waldenstrom macroglobulinemia, pediatric Burkitt lymphoma, hepatocellular carcinoma, colorectal carcinoma, and urothelial carcinoma samples analyzed (COSMIC, cBioPortal, 2021)[5-7,132-137]. ARID1A loss is associated with microsatellite instability in ovarian and endometrial endometrioid adenocarcinomas[27,128,138-140], CRC[128,141-143], and gastric cancer[128,144-148]. ARID1A protein loss is associated with tumors of poor histological grade for many tumor types, including colorectal cancer (CRC)[141-143], cervical cancer[149-150], gastric cancer[144-148], urothelial carcinoma[151-153], ovarian and endometrial cancers[27,130,138-140,154-158], breast carcinoma[159-161], and clear cell renal cell carcinoma[162]; ARID1A mutation has been associated with poor outcomes for patients with cholangiocarcinoma[163-166]. However, prognostic data regarding patient survival are often mixed and conflicting.

FINDING SUMMARY

ARID1A encodes the AT-rich interactive domain-containing protein 1A, also known as Baf250a, a member of the SWI/SNF chromatin remodeling complex. Mutation, loss, or inactivation of ARID1A has been reported in many cancers, and the gene is considered a tumor suppressor[133,147,160,167-172]. ARID1A mutations, which are mostly truncating, have been identified along the entire gene and often correlate with ARID1A protein loss[133,145,168-169,173], whereas ARID1A missense mutations are mostly uncharacterized.

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GENE
BRAF

ALTERATION
G466A

TRANSCRIPT ID
NM_004333

CODING SEQUENCE EFFECT
1397G>C

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

In 2 Phase 1 studies evaluating the MEK-pan-RAF dual inhibitor CH5126766, 3 patients harboring BRAF V600E mutations experienced PRs, including 2 patients with melanoma[174] and 1 patient with low-grade serous ovarian carcinoma[175]. BRAF and MEK inhibitors have shown efficacy for patients with activating BRAF alterations at the V600 codon; clinical outcomes are more limited for class 2 alterations in BRAF such as one or more of the alterations seen here. A retrospective study of immunotherapies in NSCLC reported a 69% DCR (9/13) for patients with class 2 mutations[176]. MEK inhibitors alone or in combination with RAF inhibitors also may be of benefit in these alterations[177-180]. Doublet RAF- and MEK-directed therapy may be more efficacious relative to either monotherapy; a retrospective analysis of BRAF-mutated melanoma observed 5/16 patient responses to BRAF inhibitor with MEK inhibitor therapy in BRAF class 2 tumors and 0/13 responses to BRAF inhibitor monotherapy[181]. A basket trial of single-agent BRAF-inhibitor vemurafenib (n=11)[182] and a trial in NSCLC (n=9)[183] also did not yield any responses for patients with class 2 tumors. In a basket trial of single-agent MEK-inhibitor trametinib, no responses were observed for patients with class 2 tumors (3 SDs, n=5)[184]. Investigational ERK inhibitors are also in development; a basket trial of ulixertinib reported 3 PRs for patients across class 2-mutated tumors[185]. A basket trial of second-generation investigational BRAF inhibitor PLX8394 reported 3 SDs and 4 PDs for patients with class 2 tumors[186]. 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

BRAF mutation has been most extensively studied in melanoma, where it has been reported in 37-66% of cases[187-190]. BRAF mutation also occurs at high frequencies in patients with papillary craniopharyngiomas (95%)[191], metanephric kidney adenomas (90%)[192], and papillary thyroid carcinoma (45%)[193-195], and has also been reported in lung adenocarcinoma (10%)[196] and colorectal cancer (9%)[15]. Studies on the effect of BRAF alteration on prognosis are conflicting with reports of association with poor prognosis in cholangiocarcinoma[197-199] and colorectal cancer[200-207], improved prognosis in ovarian cancer[208], or no association in NSCLC[209-210] and pancreatic ductal adenocarcinoma[211]. BRAF mutation in papillary thyroid carcinoma have been reported to correlate with poor prognosis in some studies[193,195,212-216], but not in other studies[217-218]. There are similarly conflicting reports regarding the prognostic significance of BRAF mutation in the context of melanoma[219-222].

FINDING SUMMARY

BRAF encodes a member of the RAF family of protein kinases, which includes ARAF, BRAF, and CRAF. These kinases function downstream of RAS as part of the MAPK (RAF-MEK-ERK) signaling cascade that facilitates cell proliferation, survival and transformation[223-224]. BRAF mutations have been reported in up to 20% of all cancers, with the majority of mutations occurring at the V600 position[187,225]. Efforts to characterize this mutation as BRAF Class 2 kinase-activating or RAS-dependent Class 3 have yielded mixed findings, with increased BRAF kinase activity and enhanced ERK activation reported in some[226], but not other[227-229] studies. Although the functional effect of this alteration is unclear, it has been previously reported in the context of cancer, which may indicate biological relevance.

GENE
FGFR4

ALTERATION
amplification - equivocal

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[230] and LY2874455[231]. The multikinase inhibitor ponatinib has been shown to have substantial activity against all four FGFR kinases[232].

FREQUENCY & PROGNOSIS

Putative high-level amplification of FGFR4 has been identified in a number of tumor types, with the highest incidences being seen in kidney renal clear cell carcinoma (7.5%), prostate carcinoma (6%, 4/65), pancreatic cancer (6%), uterine carcinosarcoma (2%, 1/56), ovarian serous cystadenocarcinoma (1.5%), adrenocortical carcinoma (4.5%, 4/89), with lower incidences in other tumor types (cBioPortal, Jan 2020). In the scientific literature, FGFR4 amplification has been reported in 14.3% (2/14) of ovarian carcinomas and in 54.5% (6/11) of adult adrenocortical carcinomas, where it was highly correlated with FGFR4 mRNA expression[233-234]. FGFR4 expression has also been reported in gastric carcinoma, lung cancer, cholangiocarcinoma, and rhabdomyosarcoma[235-239]. Increasing FGFR4 expression has been correlated with tumor grade in prostate tumors, ovarian carcinomas, and astrocytomas[240-242]. Similarly, FGFR4 expression has been correlated with poor patient prognosis in many tumor types[239,241-244].

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[245-246]. FGFR4 has been reported to be amplified in cancer[6], and may be biologically relevant in this context[247-248].

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GENE
KRAS

ALTERATION
G12D

TRANSCRIPT ID
NM_004985

CODING SEQUENCE EFFECT
35G>A

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

In a Phase 1 study evaluating the MEK-pan-RAF dual inhibitor CH5126766, 6 patients harboring KRAS mutations experienced PRs, including 3 with non-small cell lung cancer (NCSLC), 1 with low-grade serous ovarian carcinoma (LGSOC), 1 with endometrial adenocarcinoma, and 1 with multiple myeloma[175]. Another Phase 1 study of CH5126766 combined with the FAK inhibitor defactinib reported 4 PRs in KRAS-mutated LGSOC[249]. Preclinical and clinical data suggest that KRAS mutations may predict clinical benefit from SHP2 inhibitors[250-251]. A Phase 1 study of RMC-4630 for relapsed/refractory solid tumors reported a DCR of 58% (23/40) for patients with NSCLC and KRAS mutations and a DCR of 75% (12/16) for patients with NSCLC and KRAS G12C mutations[252]. Interim results from a Phase 1/2 study of RMC-4630 plus cobimetinib reported tumor reduction in 3 of 8 patients with KRAS-mutated colorectal cancer[253]. Preclinical evidence suggests that KRAS activation may predict sensitivity to MEK inhibitors, such as trametinib, binimetinib, cobimetinib, and selumetinib[254-259]. Preclinical data suggest that KRAS mutation may confer sensitivity to SOS1 inhibitors[260-261]. Phase 1 studies of the SOS1 inhibitor BI 1701963 alone or in combination with MEK inhibitors, KRAS G12C inhibitors, or irinotecan are recruiting for patients with solid tumors harboring KRAS mutations[262-263] . While clinical responses have been reported for patients with KRAS-mutated ovarian[264-267], cervical small cell neuroendocrine[268], or uterine cancer[266] treated with MEK inhibitor monotherapy, multiple clinical trials have not demonstrated increased response rates for patients with KRAS-altered tumors including KRAS-mutated CRC[269-272], pancreatic cancer[273-275], and NSCLC[270,276-277]. A Phase 2 study of trametinib and uprosertib for patients with recurrent cervical cancer reported no responses for patients with KRAS-mutated (2/2 SDs) or KRAS-amplified (1/1 SD) cancer[278]. Clinical responses have been reported for combination treatment strategies including MEK inhibitors with PI3K or AKT inhibitors for patients with KRAS-mutated ovarian cancer[279-281] and KRAS-mutated endometrioid adenocarcinoma[282].

FREQUENCY & PROGNOSIS

KRAS mutations have been observed in 18% of tumor samples analyzed in the COSMIC database, including 53% of pancreatic, 45% of peritoneal, 32% of colorectal, 21% of small intestinal, 18% of biliary tract, and 15% of lung tumors (Jul 2021)[7]. Mutations in KRAS have been reported in 32-54% of colorectal cancer cases, with the G12C, G12V, and G13D mutations specifically identified in 7-11%, 26-32%, and 16-24% of cases, respectively[283-288]. Additionally, an activating KRAS mutation has been reported in more than 80% of pancreatic adenocarcinomas, with the majority of mutations found at codon 12[289-292]. KRAS mutations, particularly G12D, have been associated with decreased median survival time in patients with pancreatic ductal adenocarcinoma[290]. KRAS mutation in lung adenocarcinoma has been correlated with disease progression, poorly differentiated tumors, and aggressive tumor behavior (NCCN NSCLC Guidelines, v4.2021)[293-295]. However, the prognostic value of KRAS mutation in lung adenocarcinoma may differ among ethnic groups and may depend upon the specific allelic variant present[296].

FINDING SUMMARY

KRAS encodes a member of the RAS family of small GTPases. Activating mutations in RAS genes can cause uncontrolled cell proliferation and tumor formation[255,297]. KRAS alterations affecting amino acids G12, G13, Q22, P34, A59, Q61, and A146, as well as mutations G10_A11insG, G10_A11insAG (also reported as G10_A11dup and G12_G13insAG), A18D, L19F, D33E, G60_A66dup/E62_A66dup, E62K, R68S, and K117N have been characterized as activating and oncogenic[255,298-320].

GENE
CRKL

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies that directly target CRKL[321-322]. Preclinical studies report that some cancer cell lines with CRKL amplification are sensitive to tyrosine kinase inhibitor (TKI) dasatinib[321-323]. However, a patient with CRKL-amplified pancreatic cancer did not respond to dasatinib[324]. CRKL amplification has been shown to be a mechanism of acquired resistance to EGFR TKIs[322,325].

FREQUENCY & PROGNOSIS

CRKL amplification has been identified in various solid tumor types, including uterine carcinosarcoma (7%), pancreatic ductal adenocarcinoma (5.5%)[326], lung squamous cell carcinoma (4.5%)[327], sarcoma (4%), ovarian serous cystadenocarcinoma (3.8%), bladder urothelial carcinoma (3%)[84], and melanoma (3%)(cBioPortal, 2021)[5-6]. Increased CRKL expression has been reported in many tumor types, including lung[328-329], breast[330-331], ovarian[331-332], pancreatic[333], skin[331], colon[331,334], hepatocellular[335], and gastric cancers[321]. CRKL overexpression has been shown to significantly correlate with reduced OS for patients with NSCLC or hepatocellular carcinoma[329,335] and with tumor size and metastasis for patients with breast cancer[330].

FINDING SUMMARY

CRKL encodes an adaptor protein that has been shown to mediate growth, motility, and adhesion in solid tumor cells[336]. Studies in non-small cell lung cancer (NSCLC) and pancreatic cancer cells have linked CRKL amplification and overexpression with increased cell proliferation and with tumorigenesis[322,328-329,333].

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Everolimus

Assay findings association

PIK3CA
Q546K

AREAS OF THERAPEUTIC USE

Everolimus is an orally available mTOR inhibitor that is FDA approved to treat renal cell carcinoma (RCC) following antiangiogenic therapy; pancreatic neuroendocrine tumors; and well-differentiated non-functional neuroendocrine tumors of the lung or gastrointestinal tract. Everolimus is also approved to treat either renal angiomyolipoma or subependymal giant cell astrocytoma in association with tuberous sclerosis complex (TSC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence[62-69] , PIK3CA activating mutations may predict sensitivity to mTOR inhibitors such as everolimus and temsirolimus. Studies have reported modest activity of these therapies as single agents (ORRs of 0-4%), but improved activity has been observed when they are combined with other agents such as bevacizumab and doxorubicin (ORRs of 25-44%), for patients with PIK3CA-mutated solid tumors[66-69,337-341] .

SUPPORTING DATA

In a Phase 1 study to assess the safety and pharmacokinetics of everolimus and paclitaxel in patients with advanced solid tumors, 6/16 patients exhibited SD for more than 4 months[342]. A Phase 1 study to assess the safety and pharmacokinetics of everolimus, bevacizumab, and panobinostat (LBH-589) in patients with advanced solid tumors reported a PR in 1/9 patients and SD in 2/9 patients, but the safety and tolerability profiles were not acceptable and the authors of the study did not recommend further study[343]. In a Phase 1 study of the combination of everolimus and cetuximab in patients with advanced cancer, 5/16 evaluable patients exhibited SD for at least four months (4-19 months)[344]. A Phase 1 study of the combination of everolimus and lapatinib reported 17% (13/78) of patients exhibited PR or SD for at least four months[345]. A Phase 1b study of everolimus with lenvatinib in patients with metastatic renal cell carcinoma identified PR in 6/18 and SD in 9/18 patients[346]. A Phase 2 study of everolimus in combination with bevacizumab in advanced colorectal cancer reported modest activity for the combination[347]. A Phase 2 study of two cohorts of 71 patients with colorectal cancer treated with everolimus reported OS rates of 4.9 months and 5.9 months; patients with KRAS mutation had a decreased OS rate as compared to patients with wild-type KRAS[348]. 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[349], 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[350].

Temsirolimus

Assay findings association

PIK3CA
Q546K

AREAS OF THERAPEUTIC USE

Temsirolimus is an intravenous mTOR inhibitor that is FDA approved for the treatment of advanced renal cell carcinoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence[62-69] , PIK3CA activating mutations may predict sensitivity to mTOR inhibitors such as everolimus and temsirolimus. Studies have reported modest activity of these therapies as single agents (ORRs of 0-4%), but improved activity has been observed when they are combined with other agents such as bevacizumab and doxorubicin (ORRs of 25-44%), for patients with PIK3CA-mutated solid tumors[66-69,337-341] .

SUPPORTING DATA

A Phase 1 trial of bevacizumab and temsirolimus plus liposomal doxorubicin in patients with advanced solid tumors showed that the combination was well tolerated and resulted in six-month SD in 21% of patients, with a 21% rate of partial or complete remission[67]. In a Phase 2 clinical trial in non-small cell lung cancer (NSCLC), temsirolimus showed clinical benefit, but further studies are warranted[351]. A Phase 2 study of temsirolimus in patients with KRAS-mutant colorectal cancer reported limited efficacy; however, all patients who exhibited tumor reduction were found to have low levels of mutated KRAS in plasma samples[352]. A Phase 2 clinical trial in patients with pancreatic cancer reported that temsirolimus monotherapy had limited efficacy, and may have contributed to disease progression[353]. A study examining the efficacy of temsirolimus-involving regimens in 24 patients with mesenchymal/metaplastic breast cancer (MpBCs) reported 2 CRs, 4 PRs, 2 instances of SD longer than 6 months, and 4 instances of SD shorter than 6 months[340].

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

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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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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
ARID1A

RATIONALE
ARID1A loss or inactivation may predict sensitivity to ATR inhibitors.

ALTERATION
R1446*

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), Cambridge (United Kingdom), Withington (United Kingdom), London (United Kingdom), Sutton (United Kingdom), Villejuif (France), Saint Herblain (France), California

NCT02630199

PHASE 1

Study of AZD6738, DNA Damage Repair/Novel Anti-cancer Agent, in Combination With Paclitaxel, in Refractory Cancer

TARGETS
ATR

LOCATIONS: Seoul (Korea, Republic of)

NCT03641547

PHASE 1

M6620 Plus Standard Treatment in Oesophageal and Other Cancer

TARGETS
ATR

LOCATIONS: Glasgow (United Kingdom), Manchester (United Kingdom), Oxford (United Kingdom), Cardiff (United Kingdom)

NCT03669601

PHASE 1

AZD6738 & Gemcitabine as Combination Therapy

TARGETS
ATR

LOCATIONS: Cambridge (United Kingdom)

NCT02595931

PHASE 1

ATR Kinase Inhibitor VX-970 and Irinotecan Hydrochloride in Treating Patients With Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery

TARGETS
ATR

LOCATIONS: California, Missouri, Pennsylvania, Massachusetts, Connecticut, Tennessee, Florida

GENE
BRAF

ALTERATION
G466A

RATIONALE
BRAF activating alterations may predict sensitivity to inhibitors of BRAF, MEK, or ERK. Limited clinical and preclinical studies indicate BRAF mutations may predict sensitivity to MEK-pan-RAF dual 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.

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT03498521

PHASE 2

A Phase II Randomized Study Comparing the Efficacy and Safety of Targeted Therapy or Cancer Immunotherapy Versus Platinum-Based Chemotherapy in Patients With Cancer of Unknown Primary Site

TARGETS
ALK, RET, SMO, AKTs, PARP, PD-L1, EGFR, VEGFA, MEK, BRAF, ERBB2, ERBB3, ROS1, TRKA, TRKB, TRKC

LOCATIONS: Fukuoka (Japan), Ehime (Japan), Seoul (Korea, Republic of), Aichi (Japan), Tokyo (Japan), Chiba (Japan), Bangkok (Thailand), Blacktown (Australia), St Leonards (Australia), Helsinki (Finland)

NCT03989115

PHASE 1/2

Dose-Escalation and Dose-Expansion of RMC-4630 and Cobimetinib in Relapsed/Refractory Solid Tumors

TARGETS
SHP2, MEK

LOCATIONS: Seoul (Korea, Republic of), Oregon, California, Colorado, Arizona, Wisconsin, Illinois

NCT03284502

PHASE 1

Cobimetinib and HM95573 in Patients With Locally Advanced or Metastatic Solid Tumors

TARGETS
MEK, RAFs

LOCATIONS: Hwasun (Korea, Republic of), Pusan (Korea, Republic of), Seongnam (Korea, Republic of), Seoul (Korea, Republic of), Goyang-si (Korea, Republic of)

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)

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), Texas

NCT02428712

PHASE 1/2

A Study of PLX8394 as a Single Agent in Patients With Advanced Unresectable Solid Tumors

TARGETS
BRAF, CRAF

LOCATIONS: Arizona, New York, Texas, Florida

NCT03839342

PHASE 2

Binimetinib and Encorafenib for the Treatment of Advanced Solid Tumors With Non-V600E BRAF Mutations

TARGETS
MEK, BRAF

LOCATIONS: Toronto (Canada)

NCT02407509

PHASE 1

Phase I Trial of RO5126766

TARGETS
RAFs, MEK, mTOR

LOCATIONS: London (United Kingdom), Sutton (United Kingdom)

NCT02070549

PHASE 1

Trametinib in Treating Patients With Advanced Cancer With or Without Hepatic Dysfunction

TARGETS
MEK

LOCATIONS: Toronto (Canada)

GENE
FGFR4

RATIONALE
FGFR inhibitors may be of use in a tumor with FGFR4 amplification or activating mutation.

ALTERATION
amplification - equivocal

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (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, KIT, PDGFRA, RET, VEGFRs, PD-1

LOCATIONS: Seoul (Korea, Republic of), Tokyo (Japan), Haifa (Israel), Petah Tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Warszawa (Poland), Gdansk (Poland), Heraklion (Greece), Washington

NCT04008797

PHASE 1

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

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

LOCATIONS: Osakasayama (Japan), Chuo-Ku (Japan), Kashiwa (Japan)

NCT03547037

PHASE 1

A Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of JNJ-63723283, an Anti-Programmed Cell Death (PD)-1 Monoclonal Antibody, as Monotherapy or in Combination With Erdafitinib in Japanese Participants With Advanced Solid Cancers

TARGETS
PD-1, FGFRs

LOCATIONS: Chuo-Ku (Japan), Kashiwa (Japan)

NCT04042116

PHASE 1/2

A Study to Evaluate Lucitanib in Combination With Nivolumab in Patients With a Solid Tumor

TARGETS
FGFRs, VEGFRs, PD-1

LOCATIONS: Innsbruck (Austria), Essen (Germany), Bologna (Italy), Naples (Italy), Leuven (Belgium), Brussels (Belgium), Ghent (Belgium), Washington, Barcelona (Spain), Madrid (Spain)

NCT04565275

PHASE 1/2

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

TARGETS
FGFR1, FGFR2, FGFR3, FGFR4

LOCATIONS: Colorado, Minnesota, Arizona, Florida

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NCT04729348

PHASE 2

Pembrolizumab And Lenvatinib In Leptomeningeal Metastases

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

LOCATIONS: Massachusetts

NCT02856425

PHASE 1

Trial Of Pembrolizumab And Nintedanib

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

LOCATIONS: Villejuif (France)

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GENE
KRAS

ALTERATION
G12D

RATIONALE
KRAS activating mutations or amplification may predict sensitivity to inhibitors of MAPK pathway components, including MEK inhibitors. Limited clinical and preclinical studies indicate KRAS mutations may predict sensitivity to MEK-pan-RAF dual inhibitors.

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT03498521

PHASE 2

A Phase II Randomized Study Comparing the Efficacy and Safety of Targeted Therapy or Cancer Immunotherapy Versus Platinum-Based Chemotherapy in Patients With Cancer of Unknown Primary Site

TARGETS
ALK, RET, SMO, AKTs, PARP, PD-L1, EGFR, VEGFA, MEK, BRAF, ERBB2, ERBB3, ROS1, TRKA, TRKB, TRKC

LOCATIONS: Fukuoka (Japan), Ehime (Japan), Seoul (Korea, Republic of), Aichi (Japan), Tokyo (Japan), Chiba (Japan), Bangkok (Thailand), Blacktown (Australia), St Leonards (Australia), Helsinki (Finland)

NCT03989115

PHASE 1/2

Dose-Escalation and Dose-Expansion of RMC-4630 and Cobimetinib in Relapsed/Refractory Solid Tumors

TARGETS
SHP2, MEK

LOCATIONS: Seoul (Korea, Republic of), Oregon, California, Colorado, Arizona, Wisconsin, Illinois

NCT03284502

PHASE 1

Cobimetinib and HM95573 in Patients With Locally Advanced or Metastatic Solid Tumors

TARGETS
MEK, RAFs

LOCATIONS: Hwasun (Korea, Republic of), Pusan (Korea, Republic of), Seongnam (Korea, Republic of), Seoul (Korea, Republic of), Goyang-si (Korea, Republic of)

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)

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), Texas

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NCT02079740

PHASE 1/2

Trametinib and Navitoclax in Treating Patients With Advanced or Metastatic Solid Tumors

TARGETS
BCL-W, BCL-XL, BCL2, MEK

LOCATIONS: Massachusetts

NCT04111458

PHASE 1

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

TARGETS
KRAS, SOS1, MEK

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

NCT02407509

PHASE 1

Phase I Trial of RO5126766

TARGETS
RAFs, MEK, mTOR

LOCATIONS: London (United Kingdom), Sutton (United Kingdom)

NCT04800822

PHASE 1

PF-07284892 in Participants With Advanced Solid Tumors

TARGETS
SHP2, ROS1, ALK, BRAF, EGFR, MEK

LOCATIONS: California, Michigan, New York, Tennessee, Texas

GENE
PIK3CA

ALTERATION
Q546K

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

NCT04589845

PHASE 2

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

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

LOCATIONS: Zhongzheng Dist. (Taiwan), Taipei City (Taiwan), Tainan (Taiwan), Seoul (Korea, Republic of), Beijing (China), Woolloongabba (Australia), Darlinghurst (Australia), Randwick (Australia), Melbourne (Australia), Haifa (Israel)

NCT03239015

PHASE 2

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

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

LOCATIONS: Shanghai (China)

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

NCT02688881

PHASE 4

Study to Evaluate the Safety and Efficacy of Sirolimus, in Subject With Refractory Solid Tumors

TARGETS
mTOR

LOCATIONS: Seoul (Korea, Republic of)

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT03498521

PHASE 2

A Phase II Randomized Study Comparing the Efficacy and Safety of Targeted Therapy or Cancer Immunotherapy Versus Platinum-Based Chemotherapy in Patients With Cancer of Unknown Primary Site

TARGETS
ALK, RET, SMO, AKTs, PARP, PD-L1, EGFR, VEGFA, MEK, BRAF, ERBB2, ERBB3, ROS1, TRKA, TRKB, TRKC

LOCATIONS: Fukuoka (Japan), Ehime (Japan), Seoul (Korea, Republic of), Aichi (Japan), Tokyo (Japan), Chiba (Japan), Bangkok (Thailand), Blacktown (Australia), St Leonards (Australia), Helsinki (Finland)

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)

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

TARGETS
ALK, ROS1, TRKA, TRKB, TRKC, CDK4, CDK6, PI3K, mTOR

LOCATIONS: Alaska, Washington

NCT04632992

PHASE 2

A Study Evaluating Targeted Therapies in Participants Who Have Advanced Solid Tumors With Genomic Alterations or Protein Expression Patterns Predictive of Response

TARGETS
ALK, ROS1, TRKA, TRKB, TRKC, PD-L1, ERBB2, ERBB3, PI3K-alpha, RET, AKTs

LOCATIONS: Alaska, Washington, Oregon, California, Montana

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.

LTK	*MST1R*	*STK11*	*TGFBR2*
G213_A214insGGG	V1341M	F354L	K291del

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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)	***APC***
AR	***ARAF*** **Exons 4, 5, 7, 11, 13, 15, 16**	*ARFRP1*	*ARID1A*	*ASXL1*	***ATM***	***ATR***	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*
BCOR	*BCORL1*	*BCR** Introns 8, 13, 14	***BRAF*** **Exons 11-18,** Introns 7-10	***BRCA1*** Introns 2, 7, 8, 12, 16, 19, 20	***BRCA2*** Intron 2	*BRD4*	*BRIP1*	*BTG1*
BTG2	***BTK*** **Exons 2, 15**	*C11orf30* (EMSY)	*C17orf39* (GID4)	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*
CCND1	*CCND2*	*CCND3*	*CCNE1*	*CD22*	*CD70*	*CD74** Introns 6-8	*CD79A*	*CD79B*
CD274 **(PD-L1)**	*CDC73*	***CDH1***	***CDK12***	***CDK4***	***CDK6***	*CDK8*	*CDKN1A*	*CDKN1B*
CDKN2A	*CDKN2B*	*CDKN2C*	*CEBPA*	*CHEK1*	***CHEK2***	*CIC*	*CREBBP*	***CRKL***
CSF1R	*CSF3R*	*CTCF*	*CTNNA1*	***CTNNB1*** **Exon 3**	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*
DAXX	*DDR1*	***DDR2*** **Exons 5, 17, 18**	*DIS3*	*DNMT3A*	*DOT1L*	*EED*	***EGFR*** **Introns 7,** 15**, 24-27**	*EP300*
EPHA3	*EPHB1*	*EPHB4*	***ERBB2***	***ERBB3*** **Exons 3, 6, 7, 8, 10, 12, 20, 21, 23, 24, 25**	*ERBB4*	*ERCC4*	*ERG*	***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	*FAM46C*	*FANCA*
FANCC	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*	*FGF14*	*FGF19*
FGF23	*FGF3*	*FGF4*	*FGF6*	***FGFR1*** Introns 1, 5, **Intron 17**	***FGFR2*** Intron 1, **Intron 17**	***FGFR3*** **Exons 7, 9 (alternative designation exon 10), 14, 18, Intron 17**	*FGFR4*	*FH*
FLCN	*FLT1*	***FLT3*** **Exons 14, 15, 20**	***FOXL2***	*FUBP1*	*GABRA6*	*GATA3*	*GATA4*	*GATA6*
GNA11 **Exons 4, 5**	*GNA13*	***GNAQ*** **Exons 4, 5**	***GNAS*** **Exons 1, 8**	*GRM3*	*GSK3B*	*H3F3A*	*HDAC1*	*HGF*
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)

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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**	*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**	*NSD3* (WHSC1L1)	*NT5C2*	***NTRK1*** **Exons 14, 15, Introns 8-11**	*NTRK2* Intron 12	***NTRK3*** **Exons 16, 17**	*NUTM1** Intron 1	*P2RY8*	***PALB2***
PARK2	*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*	*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*	*TERC** ncRNA	***TERT**** **Promoter**	*TET2*
TGFBR2	*TIPARP*	*TMPRSS2** Introns 1-3	*TNFAIP3*	*TNFRSF14*	***TP53***	*TSC1*	*TSC2*	*TYRO3*
U2AF1	***VEGFA***	*VHL*	*WHSC1*	*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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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 observed aneuploid instability in the sample.
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

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inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. If a reported alteration is suspected to be germline, confirmatory testing should be considered in the appropriate clinical context.

12. The test is not intended to replace germline testing or to provide information about cancer predisposition.

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE THE RESPONSIBILITY OF PHYSICIAN

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

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

SELECT ABBREVIATIONS

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

MR Suite Version 5.1.1

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