FOUNDATIONONE®LIQUID CDx

PATIENT Hsiao, I-Wen

TUMOR TYPE
Unknown primary undifferentiated neuroendocrine carcinoma

COUNTRY CODE
TW

REPORT DATE
04 October 2022

ORDERED TEST #
ORD-1462448-01

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 undifferentiated neuroendocrine carcinoma
NAME Hsiao, I-Wen
DATE OF BIRTH 26 January 1978
SEX Female
MEDICAL RECORD # 45969184

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 IWH 1/26/1978
SPECIMEN TYPE Blood
DATE OF COLLECTION 19 September 2022
SPECIMEN RECEIVED 21 September 2022

Biomarker Findings

Blood Tumor Mutational Burden - 13 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.

ARID1A Q543*, Y215fs*17
PTEN R130Q, Y29*
TSC1 splice site 2391+2T>C
DNMT3A R882H
GNAQ R181T
TP53 R158P

Report Highlights

- Variants with **diagnostic implications** that may indicate a specific cancer type: ***TP53*** **R158P** (p. 10)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 11)
- Variants that may represent **clonal hematopoiesis** and may originate from non-tumor sources: ***DNMT3A*** **R882H** (p. 8)

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
Blood Tumor Mutational Burden - 13 Muts/Mb	None	None
10 Trials see p. 11		
Microsatellite status - MSI-High Not Detected	**MSI-High not detected. No evidence of microsatellite instability in this sample (see Appendix section).**	
Tumor Fraction - Elevated Tumor Fraction	**Tumor fraction is considered elevated when ctDNA levels are high enough that aneuploidy can be detected. There is higher sensitivity for identifying genomic alterations and a lower risk of false negative results in specimens with elevated tumor fraction; the positive percent agreement observed between liquid and tissue for defined short variants is ≥ 90% (Li et al., 2021; AACR Abstract 2231) (see Biomarker Findings section).**	

GENOMIC FINDINGS		VAF%	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
ARID1A -	Q543*	11.6%	None	None
	Y215fs*17	52.7%		
8 Trials see p. 13				

Electronically signed by Douglas A. Mata, MD, MPH | 04 October 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
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Foundation Medicine, Inc. | 1.888.988.3639

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)
PTEN -	R130Q	2.5%	None	None
	Y29*	0.36%		
10 Trials see p. 15				
TSC1 -	splice site 2391+2T>C	4.2%	None	None
9 Trials see p. 17				

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 - R882H ..... p. 8

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 - R882H ..... p. 8
GNAQ - R181T ..... p. 9
TP53 - R158P ..... 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.

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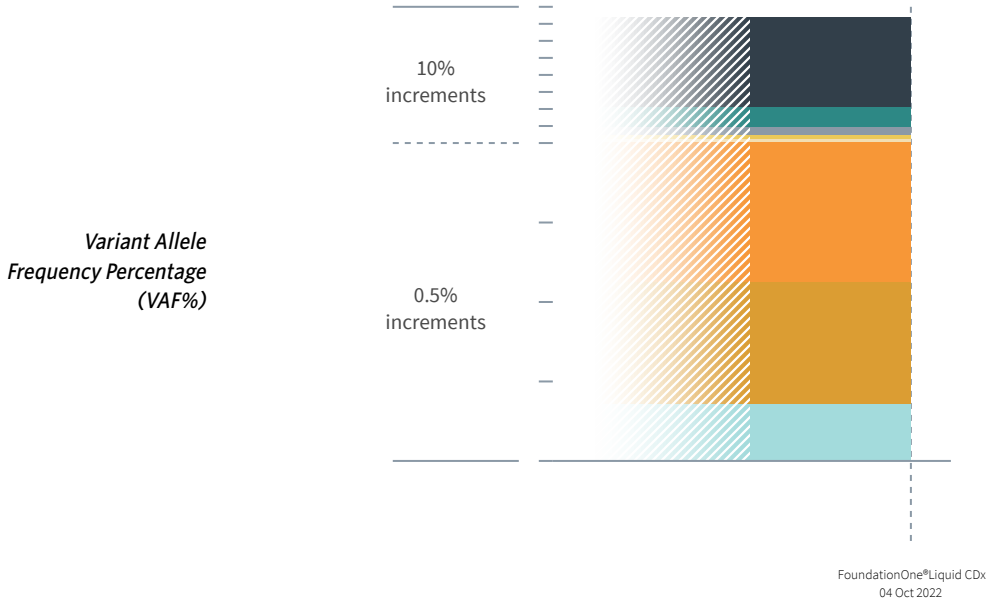

HISTORIC PATIENT FINDINGS		ORD-1462448-01 VAF%
Blood Tumor Mutational Burden		13 Muts/Mb
Microsatellite status		MSI-High Not Detected
Tumor Fraction		57%
ARID1A	Y215fs*17	52.7%
	Q543*	11.6%
PTEN	R130Q	2.5%
	Y29*	0.36%
TSC1	splice site 2391+2T>C	4.2%
DNMT3A	R882H	1.5%
GNAQ	R181T	2.1%
TP53	R158P	0.77%

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

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

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

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

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

Not Detected = baited but not detected on test

Detected = present (VAF% is not applicable)

VAF% = variant allele frequency percentage

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

BIOMARKER

Blood Tumor Mutational Burden

RESULT
13 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], and anti-PD-1/CTLA4 therapies[5-6] . A Phase 2 multi-solid-tumor trial showed that bTMB ≥16 Muts/Mb (as measured by this assay) was associated with improved survival from treatment with a PD-1 inhibitor alone or in combination with a CTLA-4 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]. 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[7].

FREQUENCY & PROGNOSIS

Average bTMB levels in solid tumors other than NSCLC have not been evaluated (PubMed, Mar 2022). In 1 retrospective study of patients with advanced neuroendocrine tumors not treated with immunotherapy, tumor mutational burden (TMB)-high (≥10 Muts/Mb) was not correlated with any significant difference in OS compared with TMB-low (≤ 10 Muts/Mb) measured in tissue samples (10.4 vs. 6.4 months, adjusted HR = 0.83)[8]. The impact of TMB on the prognosis and clinicopathological features of lung neuroendocrine cancers is unclear; large cell neuroendocrine carcinoma (LCNEC) cases with small cell lung cancer-like molecular features were reported to have significantly higher proliferative activity, as well as a trend toward better clinical benefit from treatment with chemotherapy, than non-small cell lung cancer-like tumors, but the average TMB was not significantly different between the two subsets of LCNEC[9]. MCPyV-negative Merkel cell carcinoma (MCC), associated with higher TMB, has been reported to have a higher number of predicted tumor neoantigens and a significantly higher UV mutation signature than MCPyV-positive MCC[10-11]. Within MCPyV-negative MCC tumors, the mutational burden has been reported to be significantly higher in PD-L1-positive tumors (more than 1% positive tumor and macrophage cells by immunohistochemistry) than in PD-L1-negative tumors[12].

FINDING SUMMARY

Blood tumor mutational burden (bTMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations from circulating tumor DNA in blood. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[13-14] and cigarette smoke in lung cancer[15-16], treatment with temozolomide-based chemotherapy in glioma[17-18], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[19-23], and microsatellite instability (MSI)[19,22-23]. This sample harbors a bTMB level that may be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[1-2,4].

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[24-29].

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)[30]. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer[31], Ewing sarcoma and osteosarcoma[32], prostate cancer[27], breast cancer[33], leiomyosarcoma[34], esophageal cancer[35], colorectal cancer[36], and gastrointestinal cancer[37].

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[38], 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[39-40].

GENE
ARID1A

ALTERATION
Q543*, Y215fs*17

TRANSCRIPT ID
NM_006015, NM_006015

CODING SEQUENCE EFFECT
1627C>T, 642delC

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[41]. 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[42]. One patient with small cell lung cancer harboring an ARID1A mutation experienced a PR when treated with M6620 combined with topotecan[43]. 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[44]. On the basis of limited preclinical evidence from studies in ovarian cancer, ARID1A inactivation may predict sensitivity to EZH2 inhibitors[45-46], 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[47-49]. Patients with ARID1A alterations in advanced or metastatic solid tumors may derive benefit from treatment with anti-PD-1 or anti-PD-L1 immunotherapy[50]. Loss of ARID1A expression has been associated with chemoresistance to platinum-based therapy for patients with ovarian clear cell carcinoma[51-52] and to 5-fluorouracil in colorectal cancer cell lines[53].

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, Jan 2022)[54-62]. ARID1A loss is associated with microsatellite instability in ovarian and endometrial endometrioid adenocarcinomas[50,63-66], CRC[50,67-69], and gastric cancer[50,70-74]. ARID1A protein loss is associated with tumors of poor histological grade for many tumor types, including colorectal cancer (CRC)[67-69], cervical cancer[75-76], gastric cancer[70-74], urothelial carcinoma[77-79], ovarian and endometrial cancers[52,63-66,80-84], breast carcinoma[85-87], and clear cell renal cell carcinoma[88]; ARID1A mutation has been associated with poor outcomes for patients with cholangiocarcinoma[89-92]. 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[58,73,86,93-98]. ARID1A mutations, which are mostly truncating, have been identified along the entire gene and often correlate with ARID1A protein loss[58,71,94-95,99], whereas ARID1A missense mutations are mostly uncharacterized.

GENE
PTEN

ALTERATION
R130Q, Y29*

TRANSCRIPT ID
NM_000314, NM_000314

CODING SEQUENCE EFFECT
389G>A, 87T>G

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

PTEN loss or mutation leads to activation of the PI3K-AKT-mTOR pathway and may predict sensitivity to inhibitors of this pathway[100-103]. Across various tissues, most clinical studies have not observed an association between PTEN deficiency and response to inhibitors of the PI3K-AKT-mTOR pathway. However, limited studies in prostate cancer[104-107], renal cell carcinoma[108], breast cancer[109-110], and colorectal cancer[111] have reported an association between PTEN deficiency and response to inhibitors targeting the PI3K-AKT-mTOR pathway. Preclinical data indicate that PTEN loss or inactivation may predict sensitivity to PARP inhibitors[112-116], and clinical benefit has been observed for patients with PTEN-altered breast cancer including triple negative breast cancer[117], ovarian cancer[118], uterine leiomyosarcoma[119], and endometrial cancer[116] treated with PARP inhibitors. However, some studies have reported a lack of association between PTEN mutation and PARP inhibitor sensitivity[120-121].

FREQUENCY & PROGNOSIS

PTEN mutations have been reported across solid tumors including endometrial (31%), glioma (21%), thyroid (8.7%), melanoma (8.5%), head and neck carcinoma (6.5%) and colorectal (6.1%)[122]. Loss of heterozygosity of the genomic region that includes PTEN (10q23) has been reported in 53% (8/15) of pancreatic endocrine tumors, and in 80% (4/5) gastrointestinal neuroendocrine tumors[123-124]. Reports in the literature also associate PTEN mutation with neuroendocrine tumors[125-127]. One study reported loss of Pten expression in 63% (17/27) of prostate small cell carcinomas, with 38% (5/13) displaying allelic loss[128]. Furthermore, one study reports that most of the 72 pancreatic endocrine tumors analyzed showed reduced PTEN expression[129]. Loss of PTEN expression has been suggested to be associated with advanced tumor stage and shorter disease-free and overall survival in pancreatic NETs[130-131]. Another study reported that low cytoplasmic PTEN expression is also associated with poor prognosis in pancreatic NETs[129].

FINDING SUMMARY

PTEN encodes an inositol phosphatase that functions as a tumor suppressor by negatively regulating the PI3K-AKT-mTOR pathway; loss of PTEN can lead to uncontrolled cell growth and suppression of apoptosis[101]. Alterations such as seen here may disrupt PTEN function or expression[132-173].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the PTEN variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with hamartoma tumor syndrome (ClinVar, Sep 2022)[174]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. PTEN mutations underlie several inherited disorders, collectively termed PTEN hamartoma tumor syndrome (PHTS), which include Cowden syndrome (CS) and its variant Lhermitte-Duclos disease (LD), Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS), and Proteus-like syndrome[175-176]. The mutation rate for PTEN in these disorders ranges from 20 to 85% of patients[175,177]. The estimated incidence of Cowden syndrome is 1/200,000, which may be an underestimate due to the high variability of this disorder[175]. Given the association between PTEN and these inherited syndromes, in the appropriate clinical context, germline testing for mutations affecting PTEN is recommended.

GENE
TSC1

ALTERATION
splice site 2391+2T>C

TRANSCRIPT ID
NM_000368

CODING SEQUENCE EFFECT
2391+2T>C

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Loss or inactivation of TSC1 can activate mTOR signaling[178-179]; however, response rates for patients with TSC1-mutated solid tumors treated with MTOR inhibitors such as everolimus and temsirolimus have been low[108,180-181]. In the prospective NCI-MATCH study, the ORR for patients with various TSC1-mutated solid tumors treated with everolimus was 7.7% (1/13); the single response was reported for a patient with urothelial cancer[180]. In TSC1-mutated renal cell carcinoma (RCC), although responses to MTOR inhibitors have been described in multiple case series and reports[182-186], retrospective analysis of a broader cohort showed no responses in TSC1-mutated RCC (0/7)[181]. Retrospective analyses of the RECORD-3, GRANITE-1, and EVOLVE-1 studies of everolimus to treat patients with RCC, gastric cancer, or hepatocellular carcinoma, respectively, showed no significant association between alterations in MTOR, TSC1, or TSC2 and median PFS[108]. PRs have been reported for patients with TSC1-altered perivascular epithelioid cell tumors[187-188] and epithelial ovarian carcinoma[189] treated with nab-sirolimus.

FREQUENCY & PROGNOSIS

TSC1 mutations have been observed at varying frequency in neuroendocrine tumors, including 3.8% of pancreatic and 1.5% of lung neuroendocrine tumors, but have not ben observed in any of 212 small intestine, 23 large intestine, or 9 stomach neuroendocrine tumors analyzed in COSMIC (Apr 2022)[54]. In one study, low expression of TSC1 and TSC2 was more common in pancreatic neuroendocrine tumors (NET) than in small intestinal NET, however no correlation between TSC1 expression levels and overall survival was reported[190]. Published data investigating the prognostic implications of TSC1 alterations in neuroendocrine tumors are limited (PubMed, Nov 2021). In the scientific literature, there is speculation that neuroendocrine tumors may be a feature of tuberous sclerosis, caused by TSC1 and TSC2 mutations[191-193].

FINDING SUMMARY

TSC1 encodes the protein Hamartin, which interacts with Tuberin, the gene product of TSC2, to inhibit and regulate mTOR activity[178,194]. Alterations such as seen here may disrupt TSC1 function or expression[195-197].

POTENTIAL GERMLINE IMPLICATIONS

Inactivating germline mutations in TSC1 are associated with the autosomal dominant disorder tuberous sclerosis complex, which results in the development of hamartomas in multiple organ systems and an increased risk of developing renal cell carcinoma[198-199]. TSC1 mutations account for approximately 10 to 30% of reported sporadic cases[200]. Prevalence for this disorder in the general population is estimated to be 1/6,000 from birth and 1/12,000 to 1/14,000 in children under 10 years of age[201]. In the appropriate clinical context, germline testing of TSC1 is recommended.

GENE
DNMT3A

ALTERATION
R882H

TRANSCRIPT ID
NM_022552

CODING SEQUENCE EFFECT
2645G>A

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, Feb 2022)[55-56]. Published data investigating the prognostic implications of DNMT3A alterations in solid tumors are limited (PubMed, Feb 2022).

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[202-203]. 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[204-209]. Mutations at codon 882, including R882S, R882H, and R882C, have demonstrated reduced methyltransferase activity in vitro, with R882H and R882C conferring increased cell proliferation[210-212]. About half of all DNMT3A mutations in AML are R882H, which leads to a partially defective enzyme and altered oligomerization behavior, although the effect on global methylation remains to some extent controversial; in addition, at least one report suggests that mutation of R882 is associated with sensitivity to DNA methyltransferase inhibitors[210-213]. On the basis of this, any alteration at R882 is likely to promote tumorigenesis, although the efficacy of DNMT inhibitors may not be consistent for all mutations.

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[214-219]. 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[214-215]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[220]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[218,221-222]. 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
GNAQ

ALTERATION
R181T

TRANSCRIPT ID
NM_002072

CODING SEQUENCE EFFECT
542G>C

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical studies have reported that tumors with GNAQ mutation may be sensitive to inhibitors of PKC or MEK, particularly MEK inhibitors in combination with other targeted agents[223-227]. Clinical benefit has been observed in patients with uveal melanoma harboring GNA11 or GNAQ mutations treated with selumetinib[228], although conflicting data have also been reported[229]. Phase 1 trials of single-agent PKC inhibitors sotrastaurin and IDE196 in metastatic uveal melanoma have yielded DCRs of 52.2% to 77.3%[230]; treatment with sotrastaurin resulted in 4 PRs, with 1 PR observed in a patient harboring a GNAQ mutation[230]. A preclinical study showed strong synergy between MEK and PKC inhibitors against melanoma cells harboring activating mutations in GNAQ or GNA11; the combined treatment, much more than treatment with either inhibitor alone, inhibited proliferation and induced apoptosis of melanoma cells in vitro and caused regression of uveal melanoma xenografts in vivo[231]. 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

GNAQ mutations have been reported in fewer than 1% of lung small cell carcinomas and have not been reported in any of the 15 ovary small cell carcinoma, 8 cervical small cell carcinoma, 1 cervical neuroendocrine carcinoma, or 1 head and neck neuroendocrine carcinoma samples analyzed in COSMIC (Jul 2022)[54]. Published data investigating the prognostic implications of GNAQ alterations in neuroendocrine cancers are limited (PubMed, Jul 2022).

FINDING SUMMARY

GNAQ encodes the protein guanine nucleotide-binding protein G(q) subunit alpha (Gq-alpha), a G protein that acts as a modulator of transmembrane signaling and activates phospholipase C[232]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

GENE
TP53

ALTERATION
R158P

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
473G>C

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[233-236] or p53 gene therapy such as SGT53[237-241]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% and SDs in 53% of patients with solid tumors; the response rate was 21% (4/19) for patients with TP53 mutations versus 12% (4/33) for patients who were TP53 wildtype[242]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[243]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[244]. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[245]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24% (6/25) ORR with adavosertib combined with paclitaxel[246]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate for patients with TP53 alterations[247]. The Phase 2 FOCUS4-C trial for patients with TP53- and RAS-mutated colorectal cancer reported improvement in PFS (3.61 vs. 1.87 months, HR=0.35, p=0.0022), but not OS (14.0 vs 12.8 months, p=0.93), following adavosertib treatment compared with active monitoring[248]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[241]. Missense mutations leading to TP53 inactivation may be sensitive to therapies that reactivate mutated p53 such as eprenetapopt. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, eprenetapopt combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[249]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[250].

FREQUENCY & PROGNOSIS

TP53 mutation has been reported in a number of carcinoid-endocrine cases, including 48% (15/31) of the stomach, 9.1% of large intestine, 6.8% of pancreatic, 5.8% of lung, and 4.8% of small intestine origin; TP53 mutations were also observed in 19% of Merkel cell carcinomas, 41% (9/22) of prostate small cell carcinomas, 14% (10/72) of cervical endocrine tumors, and 63% of small cell lung cancer samples (COSMIC, Jan 2022)[54,128,251-257]. The frequency of TP53 mutation or loss and altered p53 levels in neuroendocrine lung tumors has been correlated with the degree of malignancy, as TP53 alterations are more frequent in the most malignant tumor types, including SCLC and large cell neuroendocrine carcinoma[258-260]. Within neuroendocrine tumors, expression of p53 has been associated with aggressive and poorly differentiated gastroenteropancreatic neuroendocrine tumors and with shorter survival in patients with high-grade neuroendocrine carcinomas[261-264].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[265]. Alterations such as seen here may disrupt TP53 function or expression[266-270].

POTENTIAL DIAGNOSTIC IMPLICATIONS

Mutations in TP53 or RB1 are characteristic of poorly differentiated neuroendocrine carcinomas (NECs) (NCCN Neuroendocrine and Adrenal Tumors, v1.2022)[271-274].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the TP53 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with Li-Fraumeni syndrome (ClinVar, Sep 2022)[174]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[275-277], including sarcomas[278-279]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[280] to 1:20,000[279]. For pathogenic TP53 mutations identified during tumor sequencing, the rate of germline mutations was 1% in the overall population and 6% in tumors arising before age 30[281]. In the appropriate clinical context, germline testing of TP53 is recommended.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[214-219]. 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[214-215]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[220]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[218,221-222]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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.

BIOMARKER

Blood Tumor Mutational Burden

RESULT

13 Muts/Mb

RATIONALE

Increased tumor mutational burden may predict response to anti-PD-1 (alone or in combination with anti-CTLA-4) or anti-PD-L1 immune checkpoint inhibitors.

NCT04237649

PHASE NULL

KAZ954 Alone and With PDR001, NZV930 and NIR178 in Advanced Solid Tumors

TARGETS
ADORA2A, CD73, PD-1

LOCATIONS: Taipei (Taiwan), Shatin, New Territories (Hong Kong), Sunto Gun (Japan), Singapore (Singapore), Milano (Italy), Barcelona (Spain), California, Illinois, Toronto (Canada), Missouri

NCT03396445

PHASE 1

Safety and Pharmacokinetics Study of MK-5890 as Monotherapy and in Combination With Pembrolizumab (MK-3475) in Adults With Advanced Solid Tumors (MK-5890-001)

TARGETS
PD-1, CD27

LOCATIONS: Taipei (Taiwan), Seoul (Korea, Republic of), Be'er Sheva (Israel), Amsterdam (Netherlands), Rotterdam (Netherlands), Barcelona (Spain), Madrid (Spain), Pozuelo de Alarcon (Spain), Santiago (Chile)

NCT03530397

PHASE 1

A Study to Evaluate MEDI5752 in Subjects With Advanced Solid Tumors

TARGETS
PD-L1, PD-1, CTLA-4

LOCATIONS: Taipei (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Cheongju-si (Korea, Republic of), Incheon (Korea, Republic of), Seoul (Korea, Republic of), Gyeonggi-do (Korea, Republic of), Melbourne (Australia), Amsterdam (Netherlands), Ravenna (Italy)

NCT03861793

PHASE 1/2

A Dose Escalation and Cohort Expansion Study of Subcutaneously-Administered Cytokine (ALKS 4230) as a Single Agent and in Combination With Anti-PD-1 Antibody (Pembrolizumab) in Subjects With Select Advanced or Metastatic Solid Tumors (ARTISTRY-2)

TARGETS
PD-1

LOCATIONS: Taipei (Taiwan), Tainan (Taiwan), Suwon (Korea, Republic of), Incheon (Korea, Republic of), Seoul (Korea, Republic of), Edmonton (Canada), Badalona (Spain), Rotterdam (Netherlands), Valencia (Spain), Madrid (Spain)

NCT04047862

PHASE 1

Study of BGB-A1217 in Combination With Tislelizumab in Advanced Solid Tumors

TARGETS
PD-1, TIGIT

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Hualien City (Taiwan), Taichung (Taiwan), Fujian (China), Hangzhou (China), Shanghai (China), Guangdong (China), Changsha (China), Wuhan (China)

NCT04261439

PHASE 1

A Phase I/Ib Study of NIZ985 Alone and in Combination With Spartalizumab

TARGETS
PD-1

LOCATIONS: Taipei (Taiwan), Chuo ku (Japan), Essen (Germany), Napoli (Italy), Leuven (Belgium), Barcelona (Spain), California, Texas

NCT04892498

PHASE 2

Hypofractionated Radiotherapy Combined With PD-1 Inhibitor Sequential GM-CSF and IL-2 for the Treatment of Advanced Refractory Solid Tumors (PRaG2.0)

TARGETS
PD-1

LOCATIONS: Hangzhou (China), Suzhou (China), Wuxi (China), Hefei (China), Xuzhou (China)

NCT04785196

PHASE 1/2

APG-115 in Combination With PD-1 Inhibitor in Patients With Advanced Liposarcoma or Advanced Solid Tumors

TARGETS
PD-1, MDM2

LOCATIONS: Shanghai (China), Guangzhou (China)

NCT05113355

PHASE 2

Chidamide Plus Sintilimab for Chemotherapy-refractory Advanced High-grade Neuroendocrine Neoplasm

TARGETS
HDAC, PD-1

LOCATIONS: Xiamen (China), Harbin (China)

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)

GENE
ARID1A

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

ALTERATION
Q543*, Y215fs*17

NCT02264678

PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1

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

NCT04657068

PHASE 1/2

A Study of ART0380 for the Treatment of Advanced or Metastatic Solid Tumors

TARGETS
ATR

LOCATIONS: London (United Kingdom), Colorado, Oklahoma, Texas, Pennsylvania, Tennessee, Florida

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

NCT04514497

PHASE 1

Testing the Addition of an Anti-cancer Drug, BAY 1895344, to Usual Chemotherapy for Advanced Stage Solid Tumors, With a Specific Focus on Patients With Small Cell Lung Cancer, Poorly Differentiated Neuroendocrine Cancer, and Pancreatic Cancer

TARGETS
ATR, TOP1

LOCATIONS: Arizona, Minnesota, Oklahoma, Pennsylvania, Connecticut, Tennessee, Florida

NCT04616534

PHASE 1

Testing the Addition of an Anti-cancer Drug, BAY 1895344 ATR Inhibitor, to the Chemotherapy Treatment (Gemcitabine) for Advanced Pancreatic and Ovarian Cancer, and Advanced Solid Tumors

TARGETS
ATR

LOCATIONS: Massachusetts, Maryland

NCT04802174

PHASE 1/2

Lurbinectedin With Berzosertib, an ATR Kinase Inhibitor in Small Cell Cancers and High-Grade Neuroendocrine Cancers

TARGETS
ATR

LOCATIONS: Maryland

NCT04266912

PHASE 1/2

Avelumab and M6620 for the Treatment of DDR Deficient Metastatic or Unresectable Solid Tumors

TARGETS
ATR, PD-L1

LOCATIONS: Texas

NCT03669601

PHASE 1

AZD6738 & Gemcitabine as Combination Therapy

TARGETS
ATR

LOCATIONS: Cambridge (United Kingdom)

GENE
PTEN

ALTERATION
R130Q, Y29*

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

NCT04644068

PHASE 1/2

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

TARGETS
ERBB2, TROP2, PARP

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

NCT04341259

PHASE 1

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

TARGETS
AKTs

LOCATIONS: Shanghai City (China)

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

NCT02264678

PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1

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

NCT04001569

PHASE 1/2

AZD8186 and Paclitaxel in Advanced Gastric Cancer

TARGETS
PI3K-beta

LOCATIONS: Seongnam-si (Korea, Republic of)

NCT05035745

PHASE 1/2

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

TARGETS
XPO1, PARP

LOCATIONS: Singapore (Singapore)

NCT03772561

PHASE 1

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

TARGETS PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

NCT04801966

PHASE NULL

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

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

LOCATIONS: Melbourne (Australia)

NCT04497116

PHASE 1/2

Study of RP-3500 in Advanced Solid Tumors

TARGETS ATR, PARP

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

NCT04991480

PHASE 1/2

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

TARGETS PARP, Pol theta

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

GENE
TSC1

RATIONALE
Inactivating TSC1 alterations may lead to increased mTOR activation and predict sensitivity to mTOR inhibitors.

ALTERATION
splice site 2391+2T>C

NCT03239015

PHASE 2

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

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

LOCATIONS: Shanghai (China)

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT05125523

PHASE 1

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

TARGETS
mTOR

LOCATIONS: Tianjin (China)

NCT02693535

PHASE 2

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

TARGETS
ALK, ROS1, AXL, TRKA, MET, TRKC, CDK4, CDK6, FLT3, VEGFRs, CSF1R, KIT, RET, mTOR, ERBB2, MEK, BRAF, PARP, PD-1, CTLA-4, EGFR, ERBB4

LOCATIONS: Hawaii, Washington, Oregon, California

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT04185831

PHASE 2

A MolEcularly Guided Anti-Cancer Drug Off-Label Trial

TARGETS
PD-L1, MEK, mTOR

LOCATIONS: Uppsala (Sweden), Gothenburg (Sweden)

NCT01582191

PHASE 1

A Phase 1 Trial of Vandetanib (a Multi-kinase Inhibitor of EGFR, VEGFR and RET Inhibitor) in Combination With Everolimus (an mTOR Inhibitor) in Advanced Cancer

TARGETS
mTOR, EGFR, SRC, RET, VEGFRs

LOCATIONS: Texas

NCT03203525

PHASE 1

Combination Chemotherapy and Bevacizumab With the NovoTTF-100L(P) System in Treating Participants With Advanced, Recurrent, or Refractory Hepatic Metastatic Cancer

TARGETS
VEGFA, mTOR

LOCATIONS: Texas

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

ALK
P278L

APC
P1440Q

AR
D496N

ATM
D1080G and H2208Y

BCOR
V450I

BRCA1
T1675A

C11ORF30 (EMSY)
P1006R

CREBBP
L1296del

DAXX
E457del

KEAP1
M409V

LTK
C759Y

MAP3K1
T426A

NF1
K1099E and L552R

NTRK1
V211M

PIK3CA
Q958R

POLD1
A692V, G237fs*39 and S766P

PTEN
A39T

REL
P329L

SMARCA4
R1189L

Electronically signed by Douglas A. Mata, MD, MPH | 04 October 2022
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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

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. 2022. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE THE RESPONSIBILITY OF PHYSICIAN

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

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

SELECT ABBREVIATIONS

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

REFERENCE SEQUENCE INFORMATION

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

MR Suite Version (RG) 7.1.0

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

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