FOUNDATIONONE®LIQUID CDx

PATIENT
Lo, Shun-Hsing

TUMOR TYPE
Stomach adenocarcinoma (NOS)

COUNTRY CODE
TW

REPORT DATE
25 May 2023

ORDERED TEST #
ORD-1632719-01

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 Stomach adenocarcinoma (NOS)
NAME Lo, Shun-Hsing
DATE OF BIRTH 25 February 1955
SEX Male
MEDICAL RECORD # 26689974

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 SHL 02/25/1955
SPECIMEN TYPE Blood
DATE OF COLLECTION 16 May 2023
SPECIMEN RECEIVED 18 May 2023

Biomarker Findings

Blood Tumor Mutational Burden - 14 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.

CTNNB1 D32N
KEAP1 P322L
RET T636M
PBRM1 I404fs*1
TP53 R282W

Report Highlights

- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 10)

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
Blood Tumor Mutational Burden - 14 Muts/Mb	None	None
10 Trials see p. 10		
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)
CTNNB1 - D32N	72.4%	None	None
4 Trials see p. 12			
KEAP1 - P322L	0.79%	None	None
1 Trial see p. 13			
RET - T636M	34.6%	None	None
10 Trials see p. 14			

Electronically signed by J. Keith Killian, M.D. | 25 May 2023
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
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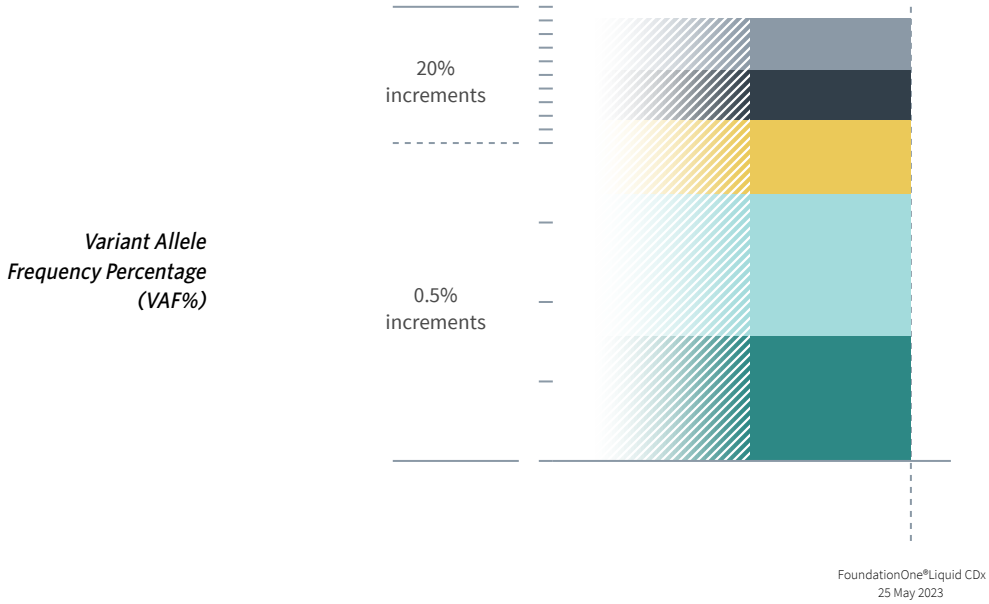
Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

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

Variant Allele Frequency is not applicable for copy number alterations.



HISTORIC PATIENT FINDINGS		ORD-1632719-01 VAF%
Blood Tumor Mutational Burden		14 Muts/Mb
Microsatellite status		MSI-High Not Detected
Tumor Fraction		69%
CTNNB1	D32N	72.4%
KEAP1	P322L	0.79%
RET	T636M	34.6%
PBRM1	I404fs*1	0.89%
TP53	R282W	75.9%

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

For some genes in FoundationOne Liquid CDx, only select exons are assayed. Therefore, an alteration found by a previous test may not have been confirmed despite overlapping gene lists. Please refer to the Appendix for the complete list of genes and exons assayed. Variants reported for prior time points reflect reporting practices at the time of the historical test(s). Changes in variant reporting nomenclature, classification, or handling may result in the appearance of discrepancies across time points. The gene and biomarker list will be updated periodically to reflect new knowledge about cancer biology.

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

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

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

Not Detected = baited but not detected on test

Detected = present (VAF% is not applicable)

VAF% = variant allele frequency percentage

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

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

BIOMARKER

Blood Tumor Mutational Burden

RESULT
14 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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

FREQUENCY & PROGNOSIS

Average bTMB levels in solid tumors other than NSCLC have not been evaluated (PubMed, Mar 2023). For patients with gastric cancer, increased TMB is reported to be associated with prolonged OS[12-14]. One study observed that the OS and disease-free survival (DFS) benefits of postoperative chemotherapy were more pronounced in patients with TMB-low gastric cancer (stage Ib/II) compared to those with TMB-high; however, patients with stage III gastric cancer benefitted regardless of TMB level[15]. In esophageal cancer, patients with TMB-high who had not received radiotherapy had significantly reduced OS (p=0.038) compared to those with TMB-low[16].

FINDING SUMMARY

Blood tumor mutational burden (bTMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations from circulating tumor DNA in blood. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[17-18] and cigarette smoke in lung cancer[19-20], treatment with temozolomide-based chemotherapy in glioma[21-22], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[23-27], and microsatellite instability (MSI)[23,26-27]. 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 higher sensitivity for identifying genomic alterations. Such specimens are at a lower risk of false negative results. Tumor fraction levels currently have limited implications for diagnosis, surveillance, or therapy and should not be overinterpreted or compared from one blood draw to another. There are currently no targeted approaches to address specific tumor fraction levels. In the research setting, changes in tumor fraction estimates have been associated with treatment duration and clinical response and may be a useful indicator for future cancer management[28-33].

FREQUENCY & PROGNOSIS

Detectible ctDNA levels have been reported in a variety of tumor types, with higher tumor fraction levels reported for patients with metastatic (Stage 4) tumors compared with patients with localized disease (Stages 1 to 3)[34]. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer[35], Ewing sarcoma and osteosarcoma[36], prostate cancer[31], breast cancer[37], leiomyosarcoma[38], esophageal cancer[39], colorectal cancer[40], and gastrointestinal cancer[41].

FINDING SUMMARY

Tumor fraction provides an estimate of the percentage of ctDNA present in a cell-free DNA (cfDNA) sample. The tumor fraction estimate for this sample is based on the observed level of aneuploid instability. The tumor fraction algorithm utilized for FoundationOne Liquid CDx uses the allele frequencies of approximately 1,000 single-nucleotide polymorphism (SNP) sites across the genome. Unlike the maximum somatic allele frequency (MSAF) method of estimating ctDNA content[42], the tumor fraction metric does not take into account the allele frequency of individual variants but rather produces a more holistic estimate of ctDNA content using data from across the genome. The amount of ctDNA detected may correlate with disease burden and response to therapy[43-44].

GENE
CTNNB1

ALTERATION
D32N

HGVS VARIANT
NM_001904.3:c.94G>A (p.D32N)

VARIANT CHROMOSOMAL POSITION
chr3:41266097

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Mutation or activation of CTNNB1 signaling has been shown to increase mTOR signaling, promote tumorigenesis, and respond to mTOR inhibition in preclinical studies[45-47]. Small studies have reported clinical benefit following treatment of everolimus combined with other targeted agents for patients with CTNNB1-mutated hepatocellular carcinoma[48-49] or endometrial carcinoma[50]. In preclinical studies, CTNNB1 activating mutations have been shown to increase expression of WNT pathway member DKK1, which may promote tumor cell proliferation and immune evasion[51-53]. A Phase 1 trial of DKK1-targeting antibody DKN-01 in combination with paclitaxel in esophageal cancer reported a 50% (2/4) PR rate and 25% (1/4) SD rate in patients with CTNNB1 activating mutations, compared with 24% (10/41) PR and 37% (15/41) SD in unselected patients[54]. Multiple preclinical studies in cancer models harboring CTNNB1 mutation or beta-catenin pathway activation have reported activation of the NOTCH pathway and sensitivity to pharmacologic inhibition of NOTCH signaling by gamma-secretase inhibitors[55-58]. Clinical trials of gamma-secretase inhibitor nirogacestat have shown high response rates in patients with desmoid tumors, which are driven by activating CTNNB1 mutations in the majority of cases[59], suggesting CTNNB1-mutated tumors may be sensitive to gamma-secretase inhibitors. Although WNT pathway inhibitors have been explored preclinically in CTNNB1-mutated cells, clinical data supporting this therapeutic approach are lacking[46,60-62].

FREQUENCY & PROGNOSIS

CTNNB1 mutations have been identified in 1.3-2.5% of esophageal cancers[63-64], 1.7-8.0% of gastric cancers[63,65-66], and 0.0-2.2% of gastroesophageal cancers[66-67]. Expression of beta-catenin has been reported in 69-78% of gastric carcinoma cases[68-69]. Activated, nuclear beta-catenin has been reported in high-grade dysplasia, but not in Barrett metaplasia, which is a precursor to esophageal adenocarcinoma; the authors suggest that activation of WNT signaling may be involved in the progression but not in the initiation of Barrett esophagus[70-71]. One study reported that expression of beta-catenin correlated with longer overall survival in gastric cancer patients, and dual loss of E-cadherin and beta-catenin has been correlated with lymph node metastasis[68,72]. Solid tumors with WNT/beta-catenin pathway alterations, as seen here, were observed to have significantly less T-cell inflammation in one study[73].

FINDING SUMMARY

CTNNB1 encodes beta-catenin, a key downstream component of the WNT signaling pathway. Beta-catenin interacts with cadherin to regulate cell-cell adhesion; as a component of the WNT pathway, it also plays a role in development, cell proliferation, and cell differentiation[74]. CTNNB1 exon 3 mutations are activating in that they lead to increased beta-catenin protein stability and activation of the WNT pathway[75-93]. One or more of the CTNNB1 exon 3 mutations seen here are expected to be activating.

GENE
KEAP1

ALTERATION
P322L

HGVS VARIANT
NM_012289.3:c.965C>T (p.P322L)

VARIANT CHROMOSOMAL POSITION
chr19:10602613

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

A study of patients with localized non-small cell lung cancer (NSCLC) identified pathogenic KEAP1 and NFE2L2 mutations as predictors of local recurrence following radiotherapy but not surgery; limited preclinical data also showed that treatment with a glutaminase inhibitor sensitized KEAP1-mutated NSCLC cells to radiation[94]. In other preclinical studies, treatment with AKT inhibitors sensitized lung cancer cells harboring KEAP1 or NFE2L2 mutations to both chemotherapy and radiation therapy[95-96]. Mixed clinical data have been reported for the association between KEAP1 mutations and the response to immunotherapy. A pan-cancer study of immunotherapy showed that patients with KEAP1 mutations had shorter OS (10 vs. 20 months) than those without[97]. However, another study across solid tumors showed that KEAP1 mutations were associated with higher tumor mutational burden (TMB) and PD-L1 expression, as well as improved survival outcomes with immunotherapy compared with other treatments (20.0 vs. 11.5 months)[98]. For patients with non-small cell lung cancer (NSCLC), a study of PD-L1 inhibitors showed that patients with concurrent mutations of STK11 and KEAP1 (n=39) experienced significantly shorter PFS (1.6 vs. 2.5 months, HR=1.5) and OS (4 vs. 11 months, HR=1.9) compared with patients with STK11- and KEAP1-wildtype tumors (n=210) despite significantly higher TMB in the group harboring STK11 and KEAP1 mutations (median 9.4 vs. 6.1 Muts/Mb)[99]. Retrospective analyses of patients with NSCLC who received immunotherapy reported reduced OS (p=0.040) for patients harboring KEAP1- or NFE2L2-mutated tumors[100] or STK11- or KEAP1-mutated tumors (p <0.001)[101] compared with those without. Studies of immune checkpoint inhibitors for patients with lung adenocarcinoma showed that coexisting mutations between KEAP1, PBRM1, SMARCA4, STK11, and KRAS were associated with worse OS[102]. An exploratory analysis of a subset of patients with PD-L1-positive NSCLC treated in the first-line setting with pembrolizumab showed similar ORR, PFS, and OS when comparing patients with STK11 or KEAP1 mutations and those without[103]. In addition, preclinical data suggest that KEAP1 inactivation increases tumor demand for glutamine and increases tumor sensitivity to glutaminase inhibitors like telaglenastat[104-106]. Limited clinical data suggest that KEAP1 mutations may predict improved clinical benefit from combinations of glutaminase inhibitors and anti-PD-1 inhibitors[107]; a Phase 1/2 study of the glutaminase inhibitor telaglenastat (CB-839) plus nivolumab to treat advanced NSCLC reported better clinical benefit rates and median PFS for patients with KEAP1 mutations (75% [3/4] vs. 15% [2/13], 6.4 vs. 3.7 months), KRAS mutations (38% [3/8] vs. 20% [2/10], 4.5 vs. 3.7 months), or KEAP1 and KRAS concurrent mutations (100% [2/2] vs. 13% [1/8], 7.2 vs. 3.7 months) compared with patients without these mutations[107]. The KEAP1 mutation has also been identified as a potential biomarker for sensitivity to combined AKT and TXNRD1 inhibition in lung cancer[108].

FREQUENCY & PROGNOSIS

Somatic mutation of KEAP1 occurs in a range of solid tumors, including gastric, hepatocellular, colorectal, and lung cancers[109]. KEAP1 mutations are rare in hematological malignancies, occurring in fewer than 1% of samples analyzed (COSMIC, 2023)[110]. In a retrospective analysis of the pan-solid MSKCC dataset, KEAP1 mutation correlated with reduced OS (13.28 vs. 26.53 months)[98].

FINDING SUMMARY

KEAP1 encodes a substrate adaptor protein that regulates the cellular response to oxidative stress by providing substrate specificity for a CUL3-dependent ubiquitin ligase[111]. KEAP1 exerts anti-tumor effects through negative regulation of NRF2, a transcription factor encoded by NFE2L2[112-114]; KEAP1 inactivation promotes cancer progression through NRF2-mediated chemoresistance and cell growth[113-114].

GENE
RET

ALTERATION
T636M

HGVS VARIANT
NM_020975.4:c.1907C>T (p.T636M)

VARIANT CHROMOSOMAL POSITION
chr10:43609955

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence, RET activating alterations may predict response to selective RET inhibitors such as pralsetinib[115-117] , selpercatinib[118-119] , and BOS172738[120], as well as the multikinase inhibitors cabozantinib[121-137], lenvatinib[124,138-140], sorafenib[124,141-144], sunitinib[124,145], and vandetanib[124,146-160]. In the context of RET mutation, these therapies have primarily been investigated for the treatment of patients with medullary thyroid carcinoma (MTC) where pralsetinib[117,161] , selpercatinib[162], cabozantinib[135,137,163-164], lenvatinib[165], sorafenib[166], sunitinib[167], and vandetanib[159,164] were reported to achieve clinical benefit. However, small studies of lenvatinib showed no significant difference in efficacy between patients with RET-mutated and RET-wildtype MTC[140] or melanoma[168]. A Phase 1 study of the selective RET inhibitor BOS172738 reported an ORR of 44% (7/16) across all dose levels for patients with RET-mutated advanced MTC[120]. In a Phase 1/1b study of RXDX-105 for advanced solid tumors, a patient with MTC harboring RET M918T experienced an ongoing PR[169]. Preclinical studies have shown that RET mutation may confer sensitivity to ponatinib[170-171].

FREQUENCY & PROGNOSIS

RET mutations have been observed in 1.6-4.0% of gastric, esophageal, and gastroesophageal carcinoma samples (cBioPortal, COSMIC, Oct 2022)[110,172-177]. Published data investigating the prognostic implications of RET alterations in gastric, esophageal, or gastroesophageal adenocarcinoma are limited (PubMed, Oct 2022).

FINDING SUMMARY

RET (Rearranged during transfection) encodes a receptor tyrosine kinase primarily expressed in cells of the nervous system. It has been identified as a proto-oncogene that results in transformation of cells upon recombination with a partner gene[178]. The RET alteration observed here has been characterized as activating and is predicted to be oncogenic[179-184].

POTENTIAL GERMLINE IMPLICATIONS

Activating heterozygous germline mutations in RET may be associated with multiple endocrine neoplasia type 2 (MEN2), an uncommon autosomal dominant disorder with an estimated prevalence of 1:30,000-1:200,000[185-188]. MEN2 is comprised of 3 subtypes, MEN2A, MEN2B and familial medullary thyroid carcinoma (FMTC). Additionally, inactivating germline mutations of RET have been associated with Hirschsprung disease, which has an estimated prevalence of 1:5,000-1:10,000[189-190]. Subtypes of MEN2 and Hirschsprung disease may result in medullary thyroid cancer (MTC), pheochromocytomas, neuroganglionomas, and other tumors[191]. Therefore, in the appropriate clinical context, germline testing of RET is recommended.

GENE
PBRM1

ALTERATION
I404fs*1

HGVS VARIANT
NM_018313.4:c.1209_1213del (p.I404*)

VARIANT CHROMOSOMAL POSITION
chr3:52668705-52668710

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of significant clinical data from prospective studies, PBRM1 inactivation may predict benefit from PD-1-targeting immune checkpoint inhibitors, such as nivolumab, pembrolizumab, cemiplimab, or dostarlimab, for patients with clear cell renal cell carcinoma and prior anti-angiogenic therapy[192-194]. However, multiple retrospective analyses report that PBRM1 mutation status is not associated with clinical benefit from various immune checkpoint inhibitors in other solid tumor types, including non-small cell lung cancer, urothelial carcinoma, melanoma, or esophagogastric cancer, suggesting that the impact of PBRM1 loss of function may depend on tumor type[195-198].

FREQUENCY & PROGNOSIS

Somatic mutations in PBRM1 are prevalent in clear cell renal cell carcinomas (ccRCC) (41%)[199], intrahepatic cholangiocarcinomas (9-13%)[200-203], and bladder urothelial carcinomas (6-14%)[204-206]. PBRM1 mutations are detected in other tumor types, including in 37% (11/30) of papillary meningiomas and 4% (2/54) of thymic carcinomas[207-208] and in tumors of the skin (7.2%), stomach (5.7%), large intestine (4.8%), lung (2.7%), and soft tissue (2.4%) (COSMIC, Jan 2023)[110]. Preclinical studies have shown that PBRM1 loss increases the proliferation of clear cell renal cell carcinoma (ccRCC) cell lines[199]. PBRM1 protein loss or mutations are correlated with late tumor stage, low differentiation grade, and/or poor patient prognosis in ccRCC[209-211], extrahepatic cholangiocarcinoma[202], and pancreatic cancer[212]. However, 1 ccRCC study reported no correlation between PBRM1 mutations and cancer-specific survival[213]. In ccRCC, PBRM1 alterations are generally observed to be mutually exclusive with BAP1 alterations[199,214]; a retrospective analysis of 145 primary ccRCCs found a decreased median OS for patients with mutations in both BAP1 and PBRM1 compared with patients having either mutated gene alone[215]. A trend toward worse survival was also seen for patients with intrahepatic cholangiocarcinoma harboring mutations in chromatin modifiers, including BAP1, ARID1A, or PBRM1[201].

FINDING SUMMARY

PBRM1 (Polybromo-1), also known as BAF180, encodes a subunit of ATP-dependent chromatin-remodeling complexes and a required cofactor for ligand-dependent transactivation by nuclear hormone receptors[216]. Mutation, loss, or inactivation of PBRM1 has been reported in several cancers, suggesting PBRM1 is a tumor suppressor[199,201,217]. Alterations such as seen here may disrupt PBRM1 function or expression[218-223].

GENE
TP53

ALTERATION
R282W

HGVS VARIANT
NM_000546.4:c.844C>T (p.R282W)

VARIANT CHROMOSOMAL POSITION
chr17:7577094

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[224-227] or p53 gene therapy such as SGT53[228-232]. 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[233]. 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[234]. 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[235]. 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[236]. 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[237]. 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[238]. 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[239]. 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[232]. 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[240]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[241].

FREQUENCY & PROGNOSIS

TP53 is frequently mutated in cancers of the gastrointestinal tract, with alterations reported in 34–72% of esophageal, gastroesophageal junction, and gastric adenocarcinomas[175,242-244]. Overexpression of p53 protein, which may occur as a result of mutation, has been reported in approximately 36% of gastric cancers, with p53 expression reported to be more frequent in intestinal-type compared with diffuse-type gastric cancer[245-248]. While some studies have reported no association between TP53 mutation status and prognosis in patients with esophageal carcinoma or gastroesophageal junction adenocarcinoma[243-244] others have associated TP53 mutation and elevated p53 expression with poor prognosis for patients with esophageal squamous cell carcinoma[249-250] or stomach cancer[251-253].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[254]. Alterations such as seen here may disrupt TP53 function or expression[255-259].

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, Apr 2023)[260]. 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[261-263], including sarcomas[264-265]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[266] to 1:20,000[265]. 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[267]. 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[268-273]. 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[268-269]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[274]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[272,275-276]. 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

14 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

NCT03281369

PHASE 1/2

A Study of Multiple Immunotherapy-Based Treatment Combinations in Patients With Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction Cancer (G/GEJ) (Morpheus-Gastric Cancer)

TARGETS
MEK, CXCR4, VEGFRs, PD-L1

LOCATIONS: Taipei City (Taiwan), Zhongzheng Dist. (Taiwan), Tainan (Taiwan), Suwon-si (Korea, Republic of), Seodaemun-Gu (Korea, Republic of), Seoul (Korea, Republic of), Blacktown (Australia), Melbourne (Australia), Clayton (Australia), Haifa (Israel)

NCT03829501

PHASE 1/2

Safety and Efficacy of KY1044 and Atezolizumab in Advanced Cancer

TARGETS
ICOS, PD-L1

LOCATIONS: Taipei (Taiwan), Changhua City (Taiwan), Siedlce (Poland), Nyíregyháza (Hungary), Budapest (Hungary), Meldola (Italy), Roma (Italy), Milano (Italy), Manchester (United Kingdom), London (United Kingdom)

NCT05007106

PHASE 2

MK-7684A With or Without Other Anticancer Therapies in Participants With Selected Solid Tumors (MK-7684A-005)

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

LOCATIONS: Taoyuan (Taiwan), Taipei (Taiwan), Tainan (Taiwan), Seoul (Korea, Republic of), Osaka (Japan), Nagoya (Japan), Tokyo (Japan), Kashiwa (Japan), Alaska, Adana (Turkey)

NCT03674567

PHASE 1/2

Dose Escalation and Expansion Study of FLX475 Monotherapy and in Combination With Pembrolizumab

TARGETS
PD-1, CCR4

LOCATIONS: Taipei (Taiwan), Tainan (Taiwan), Busan (Korea, Republic of), Shatin (Hong Kong), High West (Hong Kong), Chungbuk (Korea, Republic of), Seoul (Korea, Republic of), Gyeonggi-do (Korea, Republic of), Bangkok (Thailand), Nedlands (Australia)

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), Hefei (China), Guangdong (China), Changsha (China)

NCT05166577

PHASE 1/2

Nanatinostat Plus Valganciclovir in Patients With Advanced EBV+ Solid Tumors, and in Combination With Pembrolizumab in EBV+ RM-NPC

TARGETS
HDAC, PD-1

LOCATIONS: Taipei City (Taiwan), Taipei (Taiwan), Taoyuan City (Taiwan), Sha Tin (Hong Kong), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Kuching (Malaysia), Kuala Lumpur (Malaysia), Singapore (Singapore), Blacktown (Australia)

NCT05489211

PHASE 2

Study of Dato-Dxd as Monotherapy and in Combination With Anti-cancer Agents in Patients With Advanced Solid Tumours (TROPION-PanTumor03)

TARGETS
TROP2, PD-L1, PARP1, PD-1

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Liou Ying Township (Taiwan), Shanghai (China), Seoul (Korea, Republic of), Seodaemun-gu (Korea, Republic of), Suita-shi (Japan), Chuo-ku (Japan), Koto-ku (Japan), Kashiwa (Japan)

NCT03530397

PHASE 1

A Study to Evaluate MEDI5752 in Subjects With Advanced Solid Tumors

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

LOCATIONS: Taipei (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), Meldola (Italy)

NCT04879368

PHASE 3

RegoNivo vs Standard of Care Chemotherapy in AGOC

TARGETS
PD-1, BRAF, VEGFRs, RET, KIT

LOCATIONS: Kaohsiung (Taiwan), Jinju (Korea, Republic of), Busan (Korea, Republic of), Anyang (Korea, Republic of), Seoul (Korea, Republic of), Sapporo (Japan), Tiwi (Australia), Douglas (Australia), Subiaco (Australia), Nedlands (Australia)

GENE
CTNNB1

ALTERATION
D32N

RATIONALE
Based on clinical and preclinical evidence, tumors with activating CTNNB1 alterations may be sensitive to mTOR inhibitors.

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)

NCT05036226

PHASE 1/2

COAST Therapy in Advanced Solid Tumors and Prostate Cancer

TARGETS
DDR2, ABL, SRC, KIT, mTOR

LOCATIONS: South Carolina

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

GENE
KEAP1

ALTERATION
P322L

RATIONALE
KEAP1 inactivation may predict sensitivity to glutaminase inhibitors.

NCT05039801

PHASE 1

IACS-6274 With or Without Pembrolizumab for the Treatment of Advanced Solid Tumors

TARGETS
GLS, PD-1

LOCATIONS: Texas

GENE
RET

ALTERATION
T636M

RATIONALE
RET activating mutations, or activating fusions may confer sensitivity to kinase inhibitors targeting RET.

NCT04008797

PHASE 1

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

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

LOCATIONS: Taipei (Taiwan), Tainan (Taiwan), Kurume (Japan), Matsuyama (Japan), Seongnamsi Bundang (Korea, Republic of), Songpa-gu (Korea, Republic of), Seodaemun (Korea, Republic of), Seoul (Korea, Republic of), Jongno-gu (Korea, Republic of), Osakasayama (Japan)

NCT05024214

PHASE 1/2

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

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

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

NCT05098847

PHASE 2

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

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

LOCATIONS: Shanghai (China)

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)

NCT05171530

PHASE 1

Lenvatinib With Taxane Drugs Treatment for Advanced Gastric Cancer

TARGETS
FGFRs, RET, PDGFRA, VEGFRs, KIT

LOCATIONS: Shanghai (China)

NCT04977453

PHASE 1/2

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

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

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

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT03564691

PHASE 1

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

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

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

NCT05740215

PHASE 1/2

Efficacy and Safety Study of F520 Combined With Lenvatinib in the Treatment of Patients With Advanced Solid Tumors

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

LOCATIONS: Chongqing (China)

NCT05221775

PHASE 1

Safety of XELOX Combined With GLS-010 and Lenvatinib in Advanced AFP-positive Gastric Cancer Patients

TARGETS
FGFRs, RET, PDGFRA, VEGFRs, KIT

LOCATIONS: Tianjin (China)

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

APC
NM_000038.4: c.266C>T
(p.S89L)
chr5:112102931

ATM
NM_000051.3: c.6187G>A
(p.G2063R)
chr11:108186829

ERBB4
NM_005235.2:
c.3727_3728delinsCT
(p.W1243L)
chr2:212248539-212248540

FBXW7
NM_033632.3: c.463C>T
(p.H155Y)
chr4:153332493

GABRA6
NM_000811.2: c.802T>A
(p.S268T)
chr5:161117335

GNAS
NM_080425.2: c.1063G>C
(p.E355Q)
chr20:57429383

IRF2
NM_002199.3: c.974G>A
(p.R325Q)
chr4:185309988

LYN
NM_002350.2: c.252C>A
(p.F84L)
chr8:56860250

MAP3K1
NM_005921.1: c.3706C>T
(p.P1236S)
chr5:56179393 and
NM_005921.1: c.536G>A
(p.R179H)
chr5:56152480

MSH2
NM_000251.1: c.2425G>A
(p.E809K)
chr2:47705625

NOTCH3
NM_000435.2: c.1261C>T
(p.R421C)
chr19:15299917

NTRK1
NM_002529.3: c.453C>G
(p.H151Q)
chr1:156837920

REL
NM_002908.2: c.1306C>G
(p.L436V)
chr2:61149116

RET
NM_020975.4: c.2531G>C
(p.R844P)
chr10:43615117

RICTOR
NM_152756.3: c.2198C>G
(p.T733R)
chr5:38958914

SMAD4
NM_005359.5: c.182T>C
(p.I61T)
chr18:48573598

SNCAIP
NM_005460.2: c.2266G>A
(p.E756K)
chr5:121786808

SRC
rearrangement

TENT5C (FAM46C)
NM_017709.3: c.211C>A
(p.L71M)
chr1:118165701

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

ABL1 **Exons 4-9**	*ACVR1B*	***AKT1*** **Exon 3**	*AKT2*	*AKT3*	***ALK*** **Exons 20-29, Introns 18, 19**	*ALOX12B*	*AMER1* (FAM123B or WTX)	***APC***
AR	***ARAF*** **Exons 4, 5, 7, 11, 13, 15, 16**	*ARFRP1*	*ARID1A*	*ASXL1*	***ATM***	***ATR***	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*
BCOR	*BCORL1*	*BCR** Introns 8, 13, 14	***BRAF*** **Exons 11-18,** Introns 7-10	***BRCA1*** Introns 2, 7, 8, 12, 16, 19, 20	***BRCA2*** Intron 2	*BRD4*	*BRIP1*	*BTG1*
BTG2	***BTK*** **Exons 2, 15**	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	***CCND1***	*CCND2*
CCND3	*CCNE1*	*CD22*	*CD70*	*CD74** Introns 6-8	*CD79A*	*CD79B*	***CD274*** **(PD-L1)**	*CDC73*
CDH1	***CDK12***	***CDK4***	***CDK6***	*CDK8*	*CDKN1A*	*CDKN1B*	***CDKN2A***	*CDKN2B*
CDKN2C	*CEBPA*	*CHEK1*	***CHEK2***	*CIC*	*CREBBP*	***CRKL***	*CSF1R*	*CSF3R*
CTCF	*CTNNA1*	***CTNNB1*** **Exon 3**	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*
DDR2 **Exons 5, 17, 18**	*DIS3*	*DNMT3A*	*DOT1L*	*EED*	***EGFR*** **Introns 7,** 15, **24-27**	*EMSY* (C11orf30)	*EP300*	*EPHA3*
EPHB1	*EPHB4*	***ERBB2***	***ERBB3*** **Exons 3, 6, 7, 8, 10, 12, 20, 21, 23, 24, 25**	*ERBB4*	*ERCC4*	*ERG*	***ERRFI1***	***ESR1*** **Exons 4-8**
*ETV4** Intron 8	*ETV5** Introns 6, 7	***ETV6**** **Introns 5, 6**	*EWSR1** Introns 7-13	***EZH2*** **Exons 4, 16, 17, 18**	*EZR** Introns 9-11	*FANCA*	*FANCC*	*FANCG*
FANCL	*FAS*	*FBXW7*	*FGF10*	*FGF12*	*FGF14*	*FGF19*	*FGF23*	*FGF3*
FGF4	*FGF6*	***FGFR1*** Introns 1, 5, **Intron 17**	***FGFR2*** Intron 1, **Intron 17**	***FGFR3*** **Exons 7, 9 (alternative designation exon 10), 14, 18, Intron 17**	*FGFR4*	*FH*	*FLCN*	*FLT1*
FLT3 **Exons 14, 15, 20**	***FOXL2***	*FUBP1*	*GABRA6*	*GATA3*	*GATA4*	*GATA6*	*GID4* (C17orf39)	***GNA11*** **Exons 4, 5**
GNA13	***GNAQ*** **Exons 4, 5**	***GNAS*** **Exons 1, 8**	*GRM3*	*GSK3B*	*H3-3A* (H3F3A)	*HDAC1*	*HGF*	*HNF1A*
HRAS **Exons 2, 3**	*HSD3B1*	*ID3*	***IDH1*** **Exon 4**	***IDH2*** **Exon 4**	*IGF1R*	*IKBKE*	*IKZF1*	*INPP4B*
IRF2	*IRF4*	*IRS2*	*JAK1*	***JAK2*** **Exon 14**	***JAK3*** **Exons 5, 11, 12, 13, 15, 16**	*JUN*	*KDM5A*	*KDM5C*
KDM6A	*KDR*	*KEAP1*	*KEL*	***KIT*** **Exons 8, 9, 11, 12, 13, 17,** Intron 16	*KLHL6*	*KMT2A* (MLL) Introns 6, 8-11, Intron 7	*KMT2D* (MLL2)	***KRAS***

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

LTK	*LYN*	*MAF*	***MAP2K1*** **(MEK1) Exons 2, 3**	***MAP2K2*** **(MEK2) Exons 2-4, 6, 7**	*MAP2K4*	*MAP3K1*	*MAP3K13*	*MAPK1*
MCL1	***MDM2***	*MDM4*	*MED12*	*MEF2B*	*MEN1*	*MERTK*	***MET***	*MITF*
MKNK1	*MLH1*	***MPL*** **Exon 10**	*MRE11* (MRE11A)	*MSH2* Intron 5	*MSH3*	*MSH6*	*MST1R*	*MTAP*
MTOR **Exons 19, 30, 39, 40, 43-45, 47, 48, 53, 56**	*MUTYH*	*MYB** Intron 14	***MYC*** **Intron 1**	*MYCL* (MYCL1)	***MYCN***	***MYD88*** **Exon 4**	*NBN*	***NF1***
NF2	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2* Intron 26	*NOTCH3*	***NPM1*** **Exons 4-6, 8, 10**	***NRAS*** **Exons 2, 3**
NSD2 (WHSC1 or MMSET)	*NSD3* (WHSC1L1)	*NT5C2*	***NTRK1*** **Exons 14, 15, Introns 8-11**	*NTRK2* Intron 12	***NTRK3*** **Exons 16, 17**	*NUTM1** Intron 1	*P2RY8*	***PALB2***
PARP1	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1* (PD-1)	***PDCD1LG2*** **(PD-L2)**	***PDGFRA*** **Exons 12, 18, Introns 7, 9, 11**	***PDGFRB*** **Exons 12-21, 23**
PDK1	*PIK3C2B*	*PIK3C2G*	***PIK3CA*** **Exons 2, 3, 5-8, 10, 14, 19, 21 (Coding Exons 1, 2, 4-7, 9, 13, 18, 20)**	*PIK3CB*	*PIK3R1*	*PIM1*	*PMS2*	*POLD1*
POLE	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*	*PRKN* (PARK2)	*PTCH1*
PTEN	***PTPN11***	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*	*RAD51B*	*RAD51C*
RAD51D	*RAD52*	*RAD54L*	***RAF1*** **Exons 3, 4, 6, 7, 10, 14, 15, 17,** Introns 4-8	*RARA* Intron 2	***RB1***	*RBM10*	*REL*	***RET*** Introns 7, 8, **Exons 11, 13-16, Introns 9-11**
RICTOR	*RNF43*	***ROS1*** **Exons 31, 36-38, 40, Introns 31-35**	*RPTOR*	*RSPO2** Intron 1	*SDC4** Intron 2	*SDHA*	*SDHB*	*SDHC*
SDHD	*SETD2*	*SF3B1*	*SGK1*	*SLC34A2** Intron 4	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*
SMO	*SNCAIP*	*SOCS1*	*SOX2*	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*
STAT3	***STK11***	*SUFU*	*SYK*	*TBX3*	*TEK*	*TENT5C* (FAM46C)	*TERC** ncRNA	***TERT**** **Promoter**
TET2	*TGFBR2*	*TIPARP*	*TMPRSS2** Introns 1-3	*TNFAIP3*	*TNFRSF14*	***TP53***	*TSC1*	*TSC2*
TYRO3	*U2AF1*	***VEGFA***	*VHL*	*WT1*	*XPO1*	*XRCC2*	*ZNF217*	*ZNF703*

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite (MS) status
Blood Tumor Mutational Burden (bTMB)
Tumor Fraction

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

CE IVD

ABOUT FOUNDATIONONE LIQUID CDx

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

Please refer to technical information for performance specification details.

INTENDED USE

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

TEST PRINCIPLES

The FoundationOne Liquid CDx assay is performed exclusively as a laboratory service using circulating cell-free DNA (cfDNA) isolated from plasma derived from anti-coagulated peripheral whole blood from patients with solid malignant neoplasms. The assay employs a single DNA extraction method to obtain cfDNA from plasma from whole blood. Extracted cfDNA undergoes whole-genome shotgun library construction and hybridization-based capture of 324 cancer-related genes including coding exons and select introns of 309 genes, as well as only select intronic regions or non-coding regions of 15 genes. Hybrid-capture selected libraries are sequenced with deep coverage using the NovaSeq® 6000 platform. Sequence data are processed using a customized analysis pipeline designed to accurately detect genomic alterations, including base substitutions, indels, select copy number variants, and select genomic rearrangements. Substitutions and insertion and deletion alterations (indels) are reported in 311 genes, copy number alterations (CNAs) are reported in 310 genes, and gene rearrangements are reported in 324 genes. The assay also reports tumor fraction, and genomic signatures including MSI and bTMB. A subset of targeted regions in 75 genes is baited for increased sensitivity.

THE REPORT

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

QUALIFIED ALTERATION CALLS (EQUIVOCAL)

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

RANKING OF THERAPIES AND CLINICAL TRIALS

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

Ranking of Clinical Trials
Pediatric trial qualification → Geographical proximity → Later trial phase.

LIMITATIONS

1. For *in vitro* diagnostic use.
2. For prescription use only. This test must be ordered by a qualified medical professional in accordance with clinical laboratory regulations.
3. A negative result does not rule out the presence of a mutation below the limits of detection of the assay. Patients for whom no companion diagnostic alterations are detected should be considered for confirmation with an appropriately validated tumor tissue test, if available.
4. The FoundationOne Liquid CDx assay does not detect heterozygous deletions.
5. The test is not intended to provide information on cancer predisposition.
6. Performance has not been validated for cfDNA input below the specified minimum input.
7. Tissue TMB and blood TMB (bTMB) are estimated from the number of synonymous and nonsynonymous single-nucleotide variants (SNVs) and insertions and deletions (indels) per area of coding genome sampled, after the removal of known and likely oncogenic driver events and germline SNPs. Tissue TMB is calculated based on variants with an allele frequency of ≥5%, and bTMB is calculated based on variants with an allele frequency of ≥0.5%.
8. Tumor fraction is the percentage of circulating tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample. The tumor fraction estimate is computationally derived from the observed level of aneuploidy in the sample. Tumor fraction is considered elevated when ctDNA levels are high enough that aneuploidy can be detected and is significantly distinct from that typically found in non-tumor samples.
9. Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the tumor genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor. The MSI algorithm is based on genome wide analysis of 1765 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines for solid tissue testing.
10. Genomic findings from circulating cell-free DNA (cfDNA) may originate from circulating tumor DNA fragments, germline alterations, or non-tumor somatic alterations, such as clonal hematopoiesis of indeterminate potential (CHIP). Genes with alterations that may be derived from CHIP include, but are not limited to: *ASXL1*, *ATM*, *CBL*, *CHEK2*, *DNMT3A*, *JAK2*,

KMT2D (*MLL2*), *MPL*, *MYD88*, *SF3B1*, *TET2*, *TP53*, and *U2AF1*.

11. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. If a reported alteration is suspected to be germline, confirmatory testing should be considered in the appropriate clinical context.
12. The test is not intended to replace germline testing or to provide information about cancer predisposition.

REPORT HIGHLIGHTS

The Report Highlights includes select genomic and therapeutic information with potential impact on patient care and treatment that is specific to the genomics and tumor type of the sample analyzed. This section may highlight information including targeted therapies with potential sensitivity or resistance; evidence-matched clinical trials; and variants with potential diagnostic, prognostic, nontargeted treatment, germline, or clonal hematopoiesis implications. Information included in the Report Highlights is expected to evolve with advances in scientific and clinical research. Findings included in the Report Highlights should be considered in the context of all other information in this report and other relevant patient information. Decisions on patient care and treatment are the responsibility of the treating physician.

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE THE RESPONSIBILITY OF PHYSICIAN

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

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

SELECT ABBREVIATIONS

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

REFERENCE SEQUENCE INFORMATION

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

MR Suite Version (RG) 7.9.0

1. Gandara DR, et al. Nat. Med. (2018) pmid: 30082870
2. Wang Z, et al. JAMA Oncol (2019) pmid: 30816954
3. Sturgill EG, et al. Oncologist (2022) pmid: 35274716
4. Aggarwal C, et al. Clin. Cancer Res. (2020) pmid: 32102950
5. Schenker et al., 2022; AACR Abstract CT022
6. Saori et al., 2021; ESMO Abstract 80P
7. Chen EX, et al. JAMA Oncol (2020) pmid: 32379280
8. Rizvi NA, et al. JAMA Oncol (2020) pmid: 32271377
9. Si H, et al. Clin Cancer Res (2021) pmid: 33355200
10. Leighl NB, et al. J Thorac Oncol (2022) pmid: 34800700
11. Li et al., 2020; ASCO Abstract 6511
12. Cai L, et al. Cancer Commun (Lond) (2020) pmid: 32141230
13. Zhao DY, et al. World J Gastrointest Oncol (2021) pmid: 33510848
14. Wei XL, et al. Ther Adv Med Oncol (2021) pmid: 33613701
15. Wang D, et al. Gastric Cancer (2021) pmid: 33687617
16. Yuan C, et al. Aging (Albany NY) (2020) pmid: 32165590
17. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
18. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
19. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
20. Rizvi NA, et al. Science (2015) pmid: 25765070
21. Johnson BE, et al. Science (2014) pmid: 24336570
22. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
23. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
24. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
25. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
26. Nature (2012) pmid: 22810696
27. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
28. Bronkhorst AJ, et al. Biomol Detect Quantif (2019) pmid: 30923679
29. Raja R, et al. Clin. Cancer Res. (2018) pmid: 30093454
30. Hrebien S, et al. Ann. Oncol. (2019) pmid: 30860573
31. Choudhury AD, et al. JCI Insight (2018) pmid: 30385733
32. Goodall J, et al. Cancer Discov (2017) pmid: 28450425
33. Goldberg SB, et al. Clin. Cancer Res. (2018) pmid: 29330207
34. Bettegowda C, et al. Sci Transl Med (2014) pmid: 24553385
35. Lapin M, et al. J Transl Med (2018) pmid: 30400802
36. Shulman DS, et al. Br. J. Cancer (2018) pmid: 30131550
37. Stover DG, et al. J. Clin. Oncol. (2018) pmid: 29298117
38. Hemming ML, et al. JCO Precis Oncol (2019) pmid: 30793095
39. Egyud M, et al. Ann. Thorac. Surg. (2019) pmid: 31059681
40. Fan G, et al. PLoS ONE (2017) pmid: 28187169
41. Vu et al., 2020; DOI: 10.1200/PO.19.00204
42. Li G, et al. J Gastrointest Oncol (2019) pmid: 31602320
43. Zhang EW, et al. Cancer (2020) pmid: 32757294
44. Butler TM, et al. Cold Spring Harb Mol Case Stud (2019) pmid: 30833418
45. Tanwar PS, et al. Biol. Reprod. (2009) pmid: 19403928
46. Tanwar PS, et al. PLoS ONE (2011) pmid: 21695255
47. Fujishita T, et al. Proc. Natl. Acad. Sci. U.S.A. (2008) pmid: 18768809
48. Bhoori S, et al. J. Hepatol. (2010) pmid: 20347502
49. Janku F, et al. Oncotarget (2014) pmid: 24931142
50. Slomovitz BM, et al. J. Clin. Oncol. (2015) pmid: 25624430
51. Niida A, et al. Oncogene (2004) pmid: 15378020
52. Chamorro MN, et al. EMBO J. (2005) pmid: 15592430
53. Kagey MH, et al. Br. J. Pharmacol. (2017) pmid: 28574171
54. Kagey et al., 2017; AACR Abstract 369
55. Kwon C, et al. Nat. Cell Biol. (2011) pmid: 21841793
56. Arcaroli JJ, et al. Br. J. Cancer (2013) pmid: 23868008
57. Shang H, et al. Cancer (2015) pmid: 26349011
58. Kode A, et al. Nature (2014) pmid: 24429522
59. Messersmith WA, et al. Clin. Cancer Res. (2015) pmid: 25231399
60. Zhu J, et al. Carcinogenesis (2012) pmid: 22964660
61. Kogan Y, et al. Biochem. J. (2012) pmid: 22356261
62. Lachenmayer A, et al. Clin. Cancer Res. (2012) pmid: 22811581
63. Busch EL, et al. Oncotarget (2017) pmid: 29156750
64. Maeng CH, et al. PLoS ONE (2012) pmid: 22870241
65. Ge S, et al. Am J Cancer Res (2017) pmid: 28744403
66. Li-Chang HH, et al. BMC Cancer (2015) pmid: 25656989
67. Borger DR, et al. Oncologist (2012) pmid: 22180306
68. Ayed-Guerfali DB, et al. Tumour Biol. (2014) pmid: 24197976
69. Sun GY, et al. Chin. J. Cancer Res. (2012) pmid: 23359759
70. Moyes LH, et al. J. Pathol. (2012) pmid: 22653845
71. Krishnan K, et al. Dig. Dis. Sci. (2012) pmid: 21948356
72. Yoshii T, et al. Tumori () pmid: 23748820
73. Luke JJ, et al. Clin Cancer Res (2019) pmid: 30635339
74. Biochem. Biophys. Res. Commun. (2000) pmid: 10679188
75. Anastas JN, et al. Nat. Rev. Cancer (2013) pmid: 23258168
76. Fukuchi T, et al. Cancer Res. (1998) pmid: 9721853
77. Cancer Sci. (2003) pmid: 12824913
78. Takahashi Y, et al. Virchows Arch. (2006) pmid: 16523258
79. Tanaka Y, et al. Cancer Res. (2001) pmid: 11731417
80. Abraham SC, et al. Am. J. Pathol. (2002) pmid: 11943721
81. Austinat M, et al. Mol. Cancer (2008) pmid: 18282277
82. Wu G, et al. Mol. Cell (2003) pmid: 12820959
83. Provost E, et al. Oncogene (2005) pmid: 15829978
84. Curr. Opin. Genet. Dev. (1999) pmid: 10072352
85. Segditsas S, et al. Oncogene (2006) pmid: 17143297
86. Barth AI, et al. J. Cell Biol. (1997) pmid: 9024698
87. Harada N, et al. EMBO J. (1999) pmid: 10545105
88. Hsu SC, et al. Mol. Cell. Biol. (1998) pmid: 9671490
89. Breuhahn K, et al. J. Pathol. (2008) pmid: 18491352
90. Soon PS, et al. Oncologist (2008) pmid: 18515740
91. Tacon LJ, et al. Oncologist (2011) pmid: 21212436
92. Simon DP, et al. Mol. Cell. Endocrinol. (2012) pmid: 22266195
93. Hirotsu Y, et al. Hepatol. Res. (2016) pmid: 26850916
94. Binkley MS, et al. Cancer Discov (2020) pmid: 33071215
95. Chowdhry S, et al. Oncogene (2013) pmid: 22964642
96. Abazeed ME, et al. Cancer Res. (2013) pmid: 23980093
97. Chen X, et al. Ann Transl Med (2020) pmid: 32175433
98. Xu X, et al. Oncologist (2020) pmid: 32272498
99. Arbour et al., 2018; IASLC WCLC Abstract MA19.09
100. Zhang C, et al. J Thorac Oncol (2020) pmid: 32471565
101. Shang et al., 2020; WCLC Abstract P75.02
102. Marinelli D, et al. Ann Oncol (2020) pmid: 32866624
103. Cho et al., 2020; AACR Abstract CT084
104. Gwinn DM, et al. Cancer Cell (2018) pmid: 29316436
105. Sayin VI, et al. Elife (2017) pmid: 28967864
106. Romero R, et al. Nat. Med. (2017) pmid: 28967920
107. Skoulidis et al., 2021; ASCO Abstract TPS9627
108. Dai B, et al. Cancer Res. (2013) pmid: 23824739
109. Yoo NJ, et al. Histopathology (2012) pmid: 22348534
110. Tate JG, et al. Nucleic Acids Res. (2019) pmid: 30371878
111. Lo SC, et al. J. Biol. Chem. (2006) pmid: 17046835
112. Wakabayashi N, et al. Nat. Genet. (2003) pmid: 14517554
113. Kansanen E, et al. Redox Biol (2013) pmid: 24024136
114. Hast BE, et al. Cancer Res. (2013) pmid: 23382044
115. Gainor et al., 2020; ASCO Abstract 9515
116. Subbiah et al., 2020; ASCO Abstract 109
117. Hu et al., 2020; ESMO Abstract 1913O
118. Drilon et al., 2019; WCLC Abstract PL02.08
119. Wirth et al., 2019; ESMO Abstract LBA93
120. Schoffski et al., 2021; Abstract 3008
121. Chen L, et al. Open Med (Wars) (2021) pmid: 33869783
122. Drilon A, et al. Lancet Oncol. (2016) pmid: 27825636
123. Drilon A, et al. Cancer Discov (2013) pmid: 23533264
124. Gautschi O, et al. J. Clin. Oncol. (2017) pmid: 28447912
125. Mukhopadhyay S, et al. J Thorac Oncol (2014) pmid: 25436805
126. Nokihara H, et al. Clin Lung Cancer (2019) pmid: 30718102
127. Wang Y, et al. Medicine (Baltimore) (2019) pmid: 30653139
128. Sarfaty M, et al. Clin Lung Cancer (2017) pmid: 28082048
129. Zheng Q, et al. J Thorac Oncol (2020) pmid: 32718536
130. Chae YK, et al. JCO Precis Oncol (2019) pmid: 32914006
131. Abbar B, et al. J Thorac Oncol (2019) pmid: 31668323
132. Drilon A, et al. Clin. Cancer Res. (2015) pmid: 25567908
133. Wang K, et al. Clin. Cancer Res. (2016) pmid: 27334835
134. Ross JS, et al. Ann. Oncol. (2017) pmid: 28961851
135. Elisei R, et al. J. Clin. Oncol. (2013) pmid: 24002501
136. Michels S, et al. J Thorac Oncol (2016) pmid: 26762747
137. Sherman SI, et al. Cancer (2016) pmid: 27525386
138. Hida T, et al. Lung Cancer (2019) pmid: 31710864
139. Chu YH, et al. Mod Pathol (2020) pmid: 32737449
140. Schlumberger M, et al. Clin. Cancer Res. (2016) pmid: 26311725
141. Jones SJ, et al. Genome Biol. (2010) pmid: 20696054
142. Horiike A, et al. Lung Cancer (2016) pmid: 26898613
143. Chen L, et al. Thyroid (2011) pmid: 21186953
144. Ballerini P, et al. Leukemia (2012) pmid: 22513837
145. Wu H, et al. J Thorac Oncol (2015) pmid: 26291023
146. Moore A, et al. Head Neck (2020) pmid: 31762146
147. Yoh K, et al. Lung Cancer (2021) pmid: 33725547
148. Lee J, et al. Jpn J Clin Oncol (2020) pmid: 32083304
149. Lee SH, et al. Ann. Oncol. (2017) pmid: 27803005
150. Platt A, et al. BMC Cancer (2015) pmid: 25881079
151. Gautschi O, et al. J Thorac Oncol (2013) pmid: 23584301
152. Drilon A, et al. J Thorac Oncol (2018) pmid: 30017832
153. Dagogo-Jack I, et al. J Thorac Oncol (2018) pmid: 30368414
154. Loh Z, et al. Intern Med J (2019) pmid: 31808254
155. Falchook GS, et al. J. Clin. Oncol. (2016) pmid: 25366691
156. Davis JL, et al. Histopathology (2020) pmid: 31994201
157. Dermatol Pract Concept (2015) pmid: 26693082
158. Subbiah V, et al. Lung Cancer (2015) pmid: 25982012
159. Wells SA, et al. J. Clin. Oncol. (2012) pmid: 22025146
160. Yoh K, et al. Lancet Respir Med (2017) pmid: 27825616
161. Taylor et al., 2019; ASCO Abstract 6018
162. Sherman et al., 2021; ASCO Abstract 6073

163. Schlumberger M, et al. Ann. Oncol. (2017) pmid: 29045520
164. Koehler VF, et al. Thyroid (2021) pmid: 32781914
165. Sato H, et al. Tokai J Exp Clin Med (2020) pmid: 32219805
166. Lam ET, et al. J. Clin. Oncol. (2010) pmid: 20368568
167. De Souza et al., 2010; ASCO Abstract 5504
168. Sachdev et al., 2013; ASCO Abstract 9058
169. Drilon et al., 2016; EORTC-NCI-AACR Abstract 437
170. Dabir S, et al. J Thorac Oncol (2014) pmid: 25122427
171. Mologni L, et al. Mol. Cell. Endocrinol. (2013) pmid: 23811235
172. Cerami E, et al. Cancer Discov (2012) pmid: 22588877
173. Gao J, et al. Sci Signal (2013) pmid: 23550210
174. Lin DC, et al. Nat. Genet. (2014) pmid: 24686850
175. Dulak AM, et al. Nat. Genet. (2013) pmid: 23525077
176. Cancer Genome Atlas Research Network, et al. Nature (2017) pmid: 28052061
177. Janjigian YY, et al. Cancer Discov (2018) pmid: 29122777
178. Takahashi M, et al. Cell (1985) pmid: 2992805
179. Asai N, et al. Biochem. Biophys. Res. Commun. (1999) pmid: 10049754
180. Cordella D, et al. Endocr Relat Cancer (2006) pmid: 16954442
181. Muzza M, et al. Eur. J. Endocrinol. (2010) pmid: 20103606
182. Silva AL, et al. Endocrine (2015) pmid: 25725622
183. Krampitz GW, et al. Cancer (2014) pmid: 24699901
184. Fazioli F, et al. Thyroid (2008) pmid: 18631007
185. American Thyroid Association Guidelines Task Force, et al. Thyroid (2009) pmid: 19469690
186. Romei C, et al. J Oncol (2012) pmid: 23209466
187. Taïeb D, et al. Clin. Endocrinol. (Oxf) (2014) pmid: 24889858
188. Moline J, et al. Genet. Med. (2011) pmid: 21552134
189. Best KE, et al. Birth Defects Res. Part A Clin. Mol. Teratol. (2014) pmid: 25066220
190. Int J Epidemiol (1984) pmid: 6240474
191. Salehian B, et al. J Clin Res Pediatr Endocrinol (2013) pmid: 23455356
192. Braun DA, et al. JAMA Oncol (2019) pmid: 31486842
193. Braun DA, et al. Nat Med (2020) pmid: 32472114
194. Miao D, et al. Science (2018) pmid: 29301960
195. Abou Alaiwi S, et al. Cancer Immunol Res (2020) pmid: 32321774
196. Hakimi AA, et al. Nat Commun (2020) pmid: 32820162
197. Miao D, et al. Nat. Genet. (2018) pmid: 30150660
198. Yang Q, et al. Ann Transl Med (2021) pmid: 33850862
199. Varela I, et al. Nature (2011) pmid: 21248752
200. Fujimoto A, et al. Nat Commun (2015) pmid: 25636086
201. Jiao Y, et al. Nat. Genet. (2013) pmid: 24185509
202. Churi CR, et al. PLoS ONE (2014) pmid: 25536104
203. Simbolo M, et al. Oncotarget (2014) pmid: 24867389
204. Nature (2014) pmid: 24476821
205. Robertson AG, et al. Cell (2017) pmid: 28988769
206. Pietzak EJ, et al. Eur. Urol. (2017) pmid: 28583311
207. Williams EA, et al. Acta Neuropathol. (2020) pmid: 32405805
208. Petrini I, et al. Nat. Genet. (2014) pmid: 24974848
209. da Costa WH, et al. BJU Int. (2014) pmid: 24053427
210. Pawłowski R, et al. Int. J. Cancer (2013) pmid: 22949125
211. Hakimi AA, et al. Eur. Urol. (2013) pmid: 23036577
212. Numata M, et al. Int. J. Oncol. (2013) pmid: 23229642
213. Hakimi AA, et al. Clin. Cancer Res. (2013) pmid: 23620406
214. Peña-Llopis S, et al. Nat. Genet. (2012) pmid: 22683710
215. Kapur P, et al. Lancet Oncol. (2013) pmid: 23333114
216. Lemon B, et al. Nature () pmid: 11780067
217. Xia W, et al. Cancer Res. (2008) pmid: 18339845
218. Hopson S, et al. ACS Chem. Biol. (2017) pmid: 28921948
219. Porter EG, et al. J. Biol. Chem. (2017) pmid: 28053089
220. Niimi A, et al. Mutat. Res. (2015) pmid: 26117423
221. Brownlee PM, et al. Cell Rep (2014) pmid: 24613357
222. Kakarougkas A, et al. Mol. Cell (2014) pmid: 25066234
223. Gao W, et al. Proc. Natl. Acad. Sci. U.S.A. (2017) pmid: 28082722
224. Hirai H, et al. Cancer Biol. Ther. (2010) pmid: 20107315
225. Bridges KA, et al. Clin. Cancer Res. (2011) pmid: 21799033
226. Rajeshkumar NV, et al. Clin. Cancer Res. (2011) pmid: 21389100
227. Osman AA, et al. Mol. Cancer Ther. (2015) pmid: 25504633
228. Xu L, et al. Mol. Cancer Ther. (2002) pmid: 12489850
229. Xu L, et al. Mol. Med. (2001) pmid: 11713371
230. Camp ER, et al. Cancer Gene Ther. (2013) pmid: 23470564
231. Kim SS, et al. Nanomedicine (2015) pmid: 25240597
232. Pirollo KF, et al. Mol. Ther. (2016) pmid: 27357628
233. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27601554
234. Moore et al., 2019; ASCO Abstract 5513
235. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27998224
236. Oza et al., 2015; ASCO Abstract 5506
237. Lee J, et al. Cancer Discov (2019) pmid: 31315834
238. Méndez E, et al. Clin. Cancer Res. (2018) pmid: 29535125
239. Seligmann JF, et al. J Clin Oncol (2021) pmid: 34538072
240. Gourley et al., 2016; ASCO Abstract 5571
241. Park H, et al. ESMO Open (2022) pmid: 36084396
242. Nature (2014) pmid: 25079317
243. Sengpiel C, et al. Cancer Invest. (2009) pmid: 19160092
244. Pühringer-Oppermann F, et al. J. Cancer Res. Clin. Oncol. (2006) pmid: 16538517
245. Lee HE, et al. Pathobiology (2014) pmid: 23969480
246. Sezer C, et al. J BUON () pmid: 23613399
247. Victorzon M, et al. Eur. J. Cancer (1996) pmid: 8664030
248. Gonçalves AR, et al. Pathol. Oncol. Res. (2011) pmid: 21116760
249. Han U, et al. Dis. Esophagus (2007) pmid: 17760650
250. Yamasaki M, et al. Ann. Surg. Oncol. (2010) pmid: 19941080
251. Liu X, et al. PLoS ONE (2012) pmid: 23285001
252. Wiksten JP, et al. Anticancer Res. () pmid: 18751407
253. Migliavacca M, et al. J. Cell. Physiol. (2004) pmid: 15254976
254. Brown CJ, et al. Nat. Rev. Cancer (2009) pmid: 19935675
255. Joerger AC, et al. Annu. Rev. Biochem. (2008) pmid: 18410249
256. Kato S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12826609
257. Kamada R, et al. J. Biol. Chem. (2011) pmid: 20978130
258. Zerdoumi Y, et al. Hum. Mol. Genet. (2017) pmid: 28472496
259. Yamada H, et al. Carcinogenesis (2007) pmid: 17690113
260. Landrum MJ, et al. Nucleic Acids Res. (2018) pmid: 29165669
261. Bougeard G, et al. J. Clin. Oncol. (2015) pmid: 26014290
262. Sorrell AD, et al. Mol Diagn Ther (2013) pmid: 23355100
263. Nichols KE, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11219776
264. Kleihues P, et al. Am. J. Pathol. (1997) pmid: 9006316
265. Gonzalez KD, et al. J. Clin. Oncol. (2009) pmid: 19204208
266. Lalloo F, et al. Lancet (2003) pmid: 12672316
267. Mandelker D, et al. Ann. Oncol. (2019) pmid: 31050713
268. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
269. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838
270. Xie M, et al. Nat. Med. (2014) pmid: 25326804
271. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
272. Severson EA, et al. Blood (2018) pmid: 29678827
273. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
274. Hematology Am Soc Hematol Educ Program (2018) pmid: 30504320
275. Chabon JJ, et al. Nature (2020) pmid: 32269342
276. Razavi P, et al. Nat. Med. (2019) pmid: 31768066

Electronically signed by J. Keith Killian, M.D. | 25 May 2023
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