FOUNDATIONONE®LIQUID CDx

PATIENT
Chang, Hui-Ling

TUMOR TYPE
Pancreas ductal adenocarcinoma

COUNTRY CODE
TW

REPORT DATE
16 January 2024

ORDERED TEST #
ORD-1794437-01

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 Pancreas ductal adenocarcinoma
NAME Chang, Hui-Ling
DATE OF BIRTH 02 May 1965
SEX Female
MEDICAL RECORD # 49908943

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 H.L.C. 5/2/1965
SPECIMEN TYPE Blood
DATE OF COLLECTION 05 January 2024
SPECIMEN RECEIVED 09 January 2024

Biomarker Findings

Blood Tumor Mutational Burden - 0 Muts/Mb
ctDNA Tumor Fraction - Low (< 1.0%)
Microsatellite status - MSI-High Not Detected

Genomic Findings

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

STK11 E33*

This assay tested >300 cancer-related genes, including the following 2 gene(s) routinely assessed in this tumor type: ***BRCA1, BRCA2.***

Report Highlights

- Targeted therapies with potential clinical benefit **approved in another tumor type**: **Everolimus** (p. 6), **Temsirolimus** (p. 6)
- **Low ctDNA Tumor Fraction** was detected; in the absence of actionable driver alterations consider reflex testing to a regulated tissue test, such as FoundationOne®CDx (p. 4)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 7)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Blood Tumor Mutational Burden - 0 Muts/Mb	**No therapies or clinical trials. See Biomarker Findings section**
ctDNA Tumor Fraction - Low (< 1.0%)	**Low ctDNA Tumor Fraction. This result does not compromise confidence in any reported alterations. See Biomarker Finding Summary.**
Microsatellite status - MSI-High Not Detected	**MSI-High not detected. No evidence of microsatellite instability in this sample (see Appendix section).**

GENOMIC FINDINGS		VAF%
STK11 -	E33*	0.10%

7 Trials see p. 7

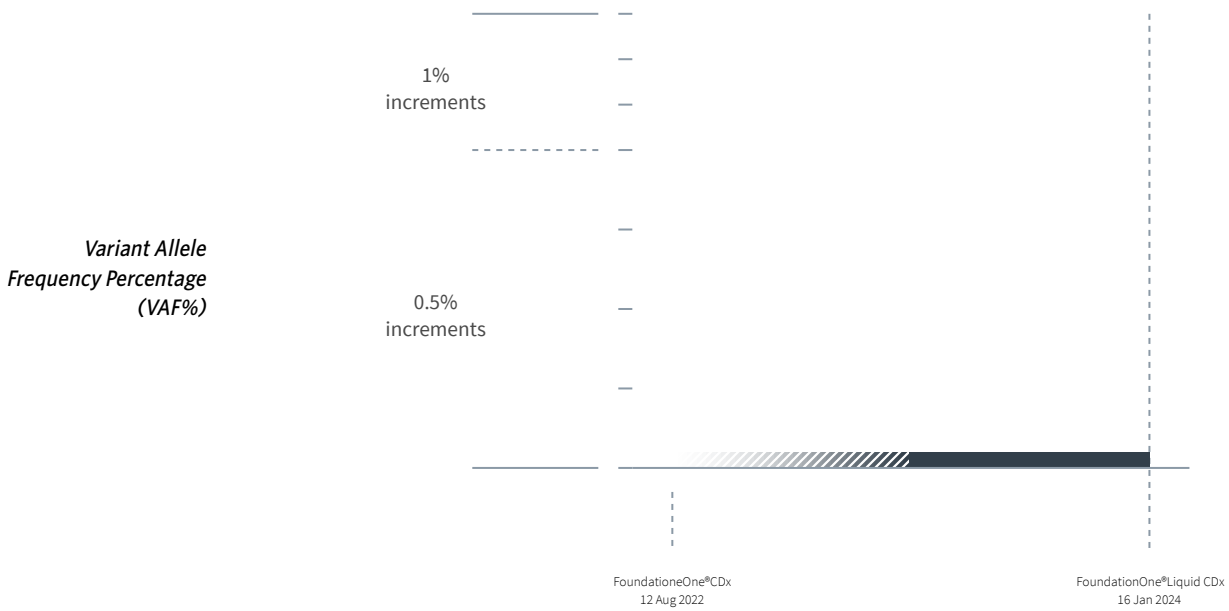
THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
None	Everolimus
	Temsirolimus

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.

Electronically signed by Irene Shyu, M.D. | 16 January 2024
Lauren L. Ritterhouse Casariego, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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



HISTORIC PATIENT FINDINGS (Biomarker Findings)		ORD-1425623-01	ORD-1794437-01
Blood Tumor Mutational Burden		Not Tested	0 Muts/Mb
Tumor Mutational Burden		Cannot Be Determined	Not Tested
Microsatellite status		Cannot Be Determined	MSI-High Not Detected
ctDNA Tumor Fraction		Not Tested	< 1.0%
HISTORIC PATIENT FINDINGS (Genomic Findings)		**VAF%**	**VAF%**
STK11	● E33*	Detected	0.10%
	● N266fs*21	Detected	Not Detected
KRAS	● G12V	Detected	Not Detected

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

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.

ctDNA Tumor Fraction may include previous Tumor Fraction results which reflect reporting practices at the time of reporting. Changes in biomarker reporting may result in the appearance of discrepancies across time points.

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

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

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

Not Detected = baited but not detected on test

Detected = present (VAF% is not applicable)

VAF% = variant allele frequency percentage

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

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

BIOMARKER

Blood Tumor Mutational Burden

RESULT
0 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[1-5], anti-PD-1[2,5-8], anti-PD-1/CTLA4 therapies[2,6] , anti-PD-L1/CTLA4 therapies[1,9-13]. 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[6]. 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[3,11-13]. 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[1]. 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[9-10].

FREQUENCY & PROGNOSIS

Among pancreatic cancer cases profiled by F1LCDx, 2.1% of cases had a blood tumor mutational burden (bTMB) of >10 Muts/Mb[14]. Published data investigating the prognostic implications of bTMB levels in pancreatic carcinoma are limited (PubMed, Jul 2023). A study of patients with pancreatic ductal adenocarcinoma harboring MMR gene mutations reported improved prognosis for patients with high tumor mutational burden (TMB) measured in tissue samples (defined as >50 mutations; survival 69-314 months) compared with patients with lower TMB (average of 5.7 mutations; 10-42 months)[15].

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[16-17] and cigarette smoke in lung cancer[18-19], treatment with temozolomide-based chemotherapy in glioma[20-21], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[22-26], and microsatellite instability (MSI)[22,25-26]. High bTMB levels were not detected in this sample. It is unclear whether the bTMB levels in this sample would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[3-4,8,27-28]. Depending on the clinical context, TMB testing of an alternate sample or by another methodology could be considered.

BIOMARKER

ctDNA Tumor Fraction

RESULT
Low (< 1.0%)

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Specimens with low circulating-tumor DNA (ctDNA) tumor fraction have reduced positive predictive agreement and negative predictive value compared with specimens with high ctDNA tumor fraction[29]. In a study of advanced non-small cell lung cancer (NSCLC), additional follow-up tissue testing identified driver alterations in 51% of patients with a low ctDNA tumor fraction[29]. When high ctDNA tumor fraction is not detected, it does not exclude the presence of disease burden or compromise the confidence of reported alterations. 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 FDA-approved or appropriately validated in other countries tumor tissue test, if available. Single observations or changes over time of circulating-tumor DNA (ctDNA) quantity are not currently part of any clinical decision-making guidelines but may be a useful indicator for future cancer management[30-37].

FREQUENCY & PROGNOSIS

In a large genomic study of 25 solid tumor types, 69% of liquid biopsy samples had ctDNA levels >1% as measured by an investigational composite tumor fraction algorithm with a median tumor fraction of 2.2% across tumor types[38]. Median ctDNA levels were reported to be highest in small cell lung cancer, liver, colon, and bladder tumor types and lowest in glioma and appendiceal cancers[38]. Higher ctDNA levels were reported for patients with metastatic (Stage 4) tumors compared with patients with localized disease (Stages 1 to 3)[39]. Higher ctDNA levels have been reported to be associated with worse prognosis in a variety of advanced solid tumors[40], including non-small cell lung cancer (NSCLC)[41], colorectal cancer (CRC)[41-42], pancreatic cancer[43], Ewing sarcoma and osteosarcoma[44], prostate cancer[35,41,45], breast cancer[41,46], leiomyosarcoma[47], esophageal cancer[48], and gastrointestinal cancer[49].

FINDING SUMMARY

The ctDNA tumor fraction provides an estimate of the percentage of circulating tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample. The ctDNA tumor fraction algorithm utilized for FoundationOne Liquid CDx integrates multiple distinct genomic features, including aneuploidy and the observed allele frequencies of somatic short variants and rearrangements. Low ctDNA tumor fraction (<1.0%) was detected in this sample. For patients with a negative liquid biopsy result with low ctDNA tumor fraction, reflex tissue testing should be considered to confirm tumor mutation status, if feasible[29].

GENE
STK11

ALTERATION
E33*

HGVS VARIANT
NM_000455.4:c.97G>T (p.E33*)

VARIANT CHROMOSOMAL POSITION
chr19:1207009

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Increased mTOR signaling is present in LKB1-deficient tumors, suggesting therapies targeting mTOR may be relevant for tumors with STK11 alterations[50-54]. Case studies reported PRs for 2 patients with STK11-mutated pancreatic cancer following treatment with the mTOR inhibitor everolimus[55-56], with 1 PR of 9 months observed for a patient with Peutz-Jeghers syndrome[56]. However, for patients with endometrial carcinoma, LKB1 (STK11) protein levels were not significantly correlated with response to everolimus[57]. Glutaminase inhibitors targeting GLS1 are under investigation for patients with STK11-mutated tumors[58]. Although 50% (1/2) of patients with STK11-mutated advanced non-small cell lung cancer (NSCLC) experienced an SD of 6 months with the GLS1 inhibitor IPN60090, 100% (2/2) of patients with ovarian cancers did not derive clinical benefit from this therapy[58], and preclinical evidence for this targeted approach is conflicting[59-62]. Preclinical data suggest that the co-repressor of repressor element-1 silencing transcription (CoREST) inhibitor TNG260 may resensitize STK11-mutated tumors to PD-1 ICPIs[63].

FREQUENCY & PROGNOSIS

STK11 mutations have been reported in up to 2.8% of pancreatic adenocarcinomas analyzed in the TCGA dataset[64-66] and in 1-4% of pancreatic carcinoma cases in other studies[67-69]. LKB1 protein expression has been reported to be reduced or absent in 7-20% of pancreatic adenocarcinomas[67-69]. The association between reduced LKB1 protein and prognosis in patients with pancreatic cancer is not clear[69-70]. Patients with Peutz-Jeghers syndrome have been found to have an increased risk for pancreatic cancer, and studies using mouse models have implicated loss of STK11 or LKB1 inhibition in the development of pancreatic cancer[68,71-74].

FINDING SUMMARY

The serine/threonine kinase STK11 (also called LKB1) activates AMPK and negatively regulates the mTOR pathway in response to changes in cellular energy levels[50]. LKB1 acts as a tumor suppressor in cancer, as loss of function promotes proliferation and tumorigenesis[75-76]. Alterations such as seen here may disrupt STK11 function or expression[77-89].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in STK11 underlie Peutz-Jeghers syndrome (PJS), a rare autosomal dominant disorder associated with a predisposition for tumor formation[90]. This disorder has an estimated frequency between 1:29,000 and 1:120,000, although reported rates in the literature vary greatly[90-92]. Although gastrointestinal tumors are the most common malignancies associated with PJS, patients also exhibit an 18-fold increased risk of developing other epithelial cancers[90-92], and individuals with this syndrome have a 30-50% risk of developing breast cancer[90,92]. Given the association with PJS, in the appropriate clinical context testing for the presence of germline mutations in STK11 is recommended.

Everolimus

Assay findings association

STK11
E33*

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

Based on cases of clinical benefit in pancreatic cancer following everolimus treatment[55-56] , STK11 inactivation may confer sensitivity to mTOR inhibitors.

SUPPORTING DATA

A Phase 1 study for patients with metastatic pancreatic adenocarcinoma reported minimal efficacy for the combination of ribociclib and everolimus with 3/12 SD at 8 weeks as the best response[93]. In some tumor types, including pancreatic cancer, it has been observed that monotherapy with mTOR inhibitors can activate a feedback loop involving the PI3K-AKT pathway, sometimes causing rapid progression of the tumor[94]. Treatment with a dual mTOR and PI3K inhibitor, or with a combination of these inhibitors, may circumvent this phenomenon. In a Phase 1/2 study of patients with advanced pancreatic adenocarcinoma, the combination of everolimus, cetuximab, and capecitabine was found to be excessively toxic with minimal efficacy[95]. Early studies with single-agent everolimus in pancreatic cancer also did not show efficacy[96]; however, clinical trials examining mTOR inhibitors in combination with other chemotherapeutics are underway in pancreatic cancer. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[97], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[98].

Temsirolimus

Assay findings association

STK11
E33*

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

Based on cases of clinical benefit in pancreatic cancer following everolimus treatment[55-56] , STK11 inactivation may confer sensitivity to mTOR inhibitors.

SUPPORTING DATA

A Phase 2 clinical trial for patients with pancreatic cancer reported that temsirolimus monotherapy was ineffective and may have contributed to disease progression[94]. While a Phase 2 study for patients with locally advanced or metastatic pancreatic carcinoma treated with temsirolimus in combination with gemcitabine reported a median PFS of 2.7 months and a median OS of 4.95 months, the combination similarly lacks clinical efficacy[99]. A Phase 1 trial of bevacizumab and temsirolimus plus liposomal doxorubicin for patients with advanced solid tumors showed that the combination was well tolerated and resulted in a 6-month SD for 21% of patients with a 21% rate of partial or complete remission[100]. In a Phase 2 clinical trial for non-small cell lung cancer (NSCLC), temsirolimus showed clinical benefit, but further studies are warranted[101]. A Phase 2 study of temsirolimus for patients with KRAS-mutated colorectal cancer (CRC) reported limited efficacy; however, all patients who exhibited tumor reduction were found to have low levels of KRAS mutations in plasma samples[102]. A Phase 2 clinical trial for patients with pancreatic cancer reported that temsirolimus monotherapy had limited efficacy and may have contributed to disease progression[94]. A study examining the efficacy of regimens involving temsirolimus for 24 patients with metaplastic breast cancer reported 2 CRs, 4 PRs, 2 instances of SD longer than 6 months, and 4 instances of SD shorter than 6 months[103].

NOTE Genomic alterations detected may be associated with activity of certain US FDA or other specific country approved therapies; however, the therapies listed in this report may have varied evidence in the patient's tumor type. The listed therapies are not ranked in order of potential or predicted efficacy for this patient or in order of level of evidence for this patient's tumor type. The therapies listed in this report may not be complete and/or exhaustive. Furthermore, the listed therapies are limited to US FDA approved pharmaceutical drug products that are linked to a specific genomic alteration. There may also be US FDA approved pharmaceutical drug products that are not linked to a genomic alteration. Further there may also exist pharmaceutical drug products that are not approved by the US FDA or other national authorities. There may also be other treatment modalities available than pharmaceutical drug products.

IMPORTANT Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months. While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and should be investigated by the physician or research staff. This is not a comprehensive list of all available clinical trials. There may also be compassionate use or early access programs available, which are not listed in this report. Foundation Medicine displays a subset of trial options and ranks them in this order of descending priority: Qualification for pediatric trial → Geographical proximity → Later trial phase. Clinical trials are not ranked in order of potential or predicted efficacy for this patient or in order of level of evidence for this patient's tumor type. Clinical trials listed here may have additional enrollment criteria that may require medical screening to determine final eligibility. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov. However, clinicaltrials.gov does not list all clinical trials that might be available.

GENE
STK11

ALTERATION
E33*

RATIONALE
Increased mTOR signaling is present in LKB1-deficient tumors, suggesting therapies targeting mTOR may be relevant for tumors with STK11 alterations. Preclinical data suggest that the co-repressor of repressor element-1 silencing transcription (CoREST) inhibitor TNG260 may resensitize STK11-mutated tumors to PD-1 ICPIs.

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)

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)

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

TARGETS
ALK, ROS1, AXL, TRKA, MET, TRKC, EGFR, PARP, CDK4, CDK6, mTOR, MEK, BRAF, SMO

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

NCT05887492

PHASE 1/2

Study of TNG260 and an Anti-PD Antibody in STK11 Mutated Solid Tumors

TARGETS
PD-1, CoREST

LOCATIONS: Colorado, Massachusetts, New York, Tennessee, Virginia, Florida

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

NCT05036226

PHASE 1/2

COAST Therapy in Advanced Solid Tumors and Prostate Cancer

TARGETS
DDR2, ABL, SRC, KIT, mTOR

LOCATIONS: South Carolina

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.

EGFR
NM_005228.3: c.1774G>A (p.V592I)
chr7:55233024

EPHB1
NM_004441.4: c.910C>T (p.R304W)
chr3:134825394

NKX2-1
NM_003317.3: c.964G>A (p.G322S)
chr14:36986635

PARP3
NM_005485.4: c.1154G>A (p.G385D)
chr3:51980237

PIK3CA
NM_006218.2: c.1727C>G (p.S576C)
chr3:178937046

SGK1
NM_005627.3: c.599G>A (p.R200H)
chr6:134493863

SPEN
NM_015001.2: c.6915_6917del (p.S2306del)
chr1:16259647-16259650

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)
ctDNA 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 ctDNA 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 ctDNA 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.

COPY NUMBER LOSS CALLS

The FoundationOne Liquid CDx assay detects copy number loss in the following genes: *BRCA1*, *BRCA2*, and *PTEN*.

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. ctDNA tumor fraction is the percentage of circulating tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample. The ctDNA tumor fraction estimate integrates multiple distinct genomic features, including modeled aneuploidy and the observed allele frequencies of somatic short variants and rearrangements.
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.

SOFTWARE VERSION INFORMATION

MR Suite Version (RG) 7.15.0
MR Reporting Config Version Config 49
Analysis Pipeline Version v3.29.0
Computational Biology Suite Version 6.29.0

1. Li et al., 2020; ASCO Abstract 6511
2. Saori et al., 2021; ESMO Abstract 80P
3. Gandara DR, et al. Nat. Med. (2018) pmid: 30082870
4. Wang Z, et al. JAMA Oncol (2019) pmid: 30816954
5. Sturgill EG, et al. Oncologist (2022) pmid: 35274716
6. Schenker et al., 2022; AACR Abstract CT022
7. Peters et al., 2019; AACR Abstract CT074
8. Aggarwal C, et al. Clin. Cancer Res. (2020) pmid: 32102950
9. Loree et al., 2021; ASCO GI Abstract 61
10. Chen EX, et al. JAMA Oncol (2020) pmid: 32379280
11. Rizvi NA, et al. JAMA Oncol (2020) pmid: 32271377
12. Si H, et al. Clin Cancer Res (2021) pmid: 33355200
13. Leighl NB, et al. J Thorac Oncol (2022) pmid: 34800700
14. Mishima et al., 2023; DOI: 10.1016/j.jlb.2023.100003
15. Hu et al., 2017; ASCO Abstract e15791
16. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
17. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
18. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
19. Rizvi NA, et al. Science (2015) pmid: 25765070
20. Johnson BE, et al. Science (2014) pmid: 24336570
21. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
22. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
23. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
24. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
25. Nature (2012) pmid: 22810696
26. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
27. Socinski et al., 2019; ESMO Abstract LBA83
28. Rizvi et al., 2019; ASCO Abstract 9016
29. Rolfo et al., 2023; ASCO Abstract 9076
30. Conteduca et al., 2019; ASCO Abstract 5039
31. Pascual J, et al. Ann Oncol (2022) pmid: 35809752
32. Bronkhorst AJ, et al. Biomol Detect Quantif (2019) pmid: 30923679
33. Raja R, et al. Clin. Cancer Res. (2018) pmid: 30093454
34. Hrebien S, et al. Ann. Oncol. (2019) pmid: 30860573
35. Choudhury AD, et al. JCI Insight (2018) pmid: 30385733
36. Goodall J, et al. Cancer Discov (2017) pmid: 28450425
37. Goldberg SB, et al. Clin. Cancer Res. (2018) pmid: 29330207
38. Husain H, et al. JCO Precis Oncol (2022) pmid: 36265119
39. Bettegowda C, et al. Sci Transl Med (2014) pmid: 24553385
40. Cousin et al., 2023, ASCO Abstract 3005
41. Reichert ZR, et al. Ann Oncol (2023) pmid: 36208697
42. Fan G, et al. PLoS ONE (2017) pmid: 28187169
43. Lapin M, et al. J Transl Med (2018) pmid: 30400802
44. Shulman DS, et al. Br. J. Cancer (2018) pmid: 30131550
45. Conteduca et al., 2019; ASCO abstract 5039
46. Stover DG, et al. J. Clin. Oncol. (2018) pmid: 29298117
47. Hemming ML, et al. JCO Precis Oncol (2019) pmid: 30793095
48. Egyud M, et al. Ann. Thorac. Surg. (2019) pmid: 31059681
49. Vu et al., 2020; DOI: 10.1200/PO.19.00204
50. Shaw RJ, et al. Cancer Cell (2004) pmid: 15261145
51. Ji H, et al. Nature (2007) pmid: 17676035
52. Contreras CM, et al. Cancer Res. (2008) pmid: 18245476
53. Gurumurthy S, et al. Cancer Res. (2008) pmid: 18172296
54. Shackelford DB, et al. Proc. Natl. Acad. Sci. U.S.A. (2009) pmid: 19541609
55. Moreira et al., 2015; ASCO Abstract 315
56. Klümpen HJ, et al. J. Clin. Oncol. (2011) pmid: 21189378
57. Trédan O, et al. Target Oncol (2013) pmid: 23238879
58. Yap et al., 2021; ASCO Abstract 3001
59. Momcilovic M, et al. Cancer Cell (2018) pmid: 29763624
60. Galan-Cobo A, et al. Cancer Res (2019) pmid: 31040157
61. Paik PK, et al. J Thorac Oncol (2022) pmid: 36240971
62. Romero R, et al. Nat. Med. (2017) pmid: 28967920
63. Ahronian et al., 2023; AACR Abstract ND12
64. Witkiewicz AK, et al. Nat Commun (2015) pmid: 25855536
65. Bailey P, et al. Nature (2016) pmid: 26909576
66. Cao L, et al. Cell (2021) pmid: 34534465
67. Sahin F, et al. Mod. Pathol. (2003) pmid: 12861065
68. Yee NS, et al. Cancer Biol. Ther. () pmid: 12673116
69. Morton JP, et al. Gastroenterology (2010) pmid: 20452353
70. Bachet JB, et al. Ann. Oncol. (2012) pmid: 22377565
71. Hezel AF, et al. Mol. Cell. Biol. (2008) pmid: 18227155
72. Lo B, et al. J. Cell Biol. (2012) pmid: 23266956
73. Resta N, et al. Dig Liver Dis (2013) pmid: 23415580
74. Shackelford DB, et al. Nat. Rev. Cancer (2009) pmid: 19629071
75. Carretero J, et al. Cancer Cell (2010) pmid: 20541700
76. Ollila S, et al. J Mol Cell Biol (2011) pmid: 21926085
77. Qiu W, et al. Oncogene (2006) pmid: 16407837
78. Mehenni H, et al. Am. J. Hum. Genet. (1998) pmid: 9837816
79. Karuman P, et al. Mol. Cell (2001) pmid: 11430832
80. Baas AF, et al. EMBO J. (2003) pmid: 12805220
81. Zeng PY, et al. Cancer Res. (2006) pmid: 17108107
82. Boudeau J, et al. J. Cell. Sci. (2004) pmid: 15561763
83. Scott KD, et al. Cancer Res. (2007) pmid: 17575127
84. Xie Z, et al. Mol. Cell. Biol. (2009) pmid: 19414597
85. Boudeau J, et al. Hum. Mutat. (2003) pmid: 12552571
86. Forcet C, et al. Hum. Mol. Genet. (2005) pmid: 15800014
87. Zhang L, et al. Sci Rep (2015) pmid: 25960268
88. Berger AH, et al. Cancer Cell (2016) pmid: 27478040
89. Donnelly LL, et al. Carcinogenesis (2021) pmid: 34849607
90. Amos CI, et al. J. Med. Genet. (2004) pmid: 15121768
91. Hearle N, et al. Clin. Cancer Res. (2006) pmid: 16707622
92. van der Groep P, et al. Cell Oncol (Dordr) (2011) pmid: 21336636
93. Weinberg et al., 2020; AACR Abstract CT116
94. Javle MM, et al. BMC Cancer (2010) pmid: 20630061
95. Kordes S, et al. Invest New Drugs (2013) pmid: 22367239
96. Wolpin BM, et al. J. Clin. Oncol. (2009) pmid: 19047305
97. Tolcher AW, et al. Ann. Oncol. (2015) pmid: 25344362
98. Patterson et al., 2018; AACR Abstract 3891
99. Karavasilis V, et al. Target Oncol (2018) pmid: 30488350
100. Moroney J, et al. Clin. Cancer Res. (2012) pmid: 22927482
101. Reungwetwattana T, et al. J Thorac Oncol (2012) pmid: 22722792
102. Spindler KL, et al. Acta Oncol (2013) pmid: 23514584
103. Moulder S, et al. Ann. Oncol. (2015) pmid: 25878190