FOUNDATIONONE®CDx

PATIENT
Chen, Hsiu Ching

TUMOR TYPE
Pancreas ductal adenocarcinoma

COUNTRY CODE
TW

REPORT DATE
09 May 2023

ORDERED TEST #
ORD-1620416-01

ABOUT THE TEST FoundationOne®CDx is a next-generation sequencing (NGS) based assay that identifies genomic findings within hundreds of cancer-related genes.

PATIENT
DISEASE Pancreas ductal adenocarcinoma
NAME Chen, Hsiu Ching
DATE OF BIRTH 01 March 1950
SEX Male
MEDICAL RECORD # 48576961

PHYSICIAN
ORDERING PHYSICIAN Yeh, Yi-Chen
MEDICAL FACILITY Taipei Veterans General Hospital
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 205872
PATHOLOGIST Not Provided

SPECIMEN
SPECIMEN SITE Pancreas
SPECIMEN ID S112-04080 F (PF23043)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 04 February 2023
SPECIMEN RECEIVED 01 May 2023

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 6 Muts/Mb

Genomic Findings

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

ARID1A R376fs*15
KRAS G12V
PDGFRB V823I
CDKN2A/B CDKN2B loss, CDKN2A loss
TP53 R342*

2 Disease relevant genes with no reportable alterations: ***BRCA1, BRCA2***

Report Highlights

- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 9)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** See Biomarker Findings section	
Tumor Mutational Burden - 6 Muts/Mb	**No therapies or clinical trials.** See Biomarker Findings section	
GENOMIC FINDINGS	**THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)**	**THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)**
***ARID1A* -** R376fs*15	none	none
6 Trials see p. 9		
***KRAS* -** G12V	none	none
4 Trials see p. 11		
***PDGFRB* -** V823I	none	none
4 Trials see p. 12		

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.

CDKN2A/B - CDKN2B loss, CDKN2A loss ..... p. 7
TP53 - R342* ..... p. 8

Electronically signed by Julie Tse, M.D. | 09 May 2023
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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

NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the agents 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 exhaustive. Neither the therapeutic agents 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.

BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors[1-3], including approved therapies nivolumab and pembrolizumab[4]. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, p=0.001)[5].

FREQUENCY & PROGNOSIS

MSI is rare in pancreatic carcinoma, reported in less than 1% of samples (n=>1,000)[6-10]. The prognostic significance of MSI in pancreatic cancer is unknown (PubMed, Aug 2022).

FINDING SUMMARY

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor[11]. Defective MMR and consequent MSI occur as a result of genetic or epigenetic inactivation of one of the MMR pathway proteins, primarily MLH1, MSH2, MSH6, or PMS2[11-13]. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers[14-16]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[11,13,15-16].

BIOMARKER

Tumor Mutational Burden

RESULT
6 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[17-19], anti-PD-1 therapies[17-20], and combination nivolumab and ipilimumab[21-26]. In multiple pan-tumor studies, increased tissue tumor mutational burden (TMB) was associated with sensitivity to immune checkpoint inhibitors[17-20,27-31]. In the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors, significant improvement in ORR was observed for patients with TMB ≥10 Muts/Mb (as measured by this assay) compared with those with TMB <10 Muts/Mb in a large cohort that included multiple tumor types[27]; similar findings were observed in the KEYNOTE 028 and 012 trials[20]. At the same TMB cutpoint, retrospective analysis of patients with solid tumors treated with any checkpoint inhibitor identified that tissue TMB scores ≥ 10 Muts/Mb were associated with prolonged time to treatment failure compared with scores <10 muts/Mb (HR=0.68)[31]. For patients with solid tumors treated with nivolumab plus ipilimumab in the CheckMate 848 trial, improved responses were observed in patients with a tissue TMB ≥ 10 Muts/Mb independent of blood TMB at any cutpoint in matched samples[32]. However, support for higher TMB thresholds and efficacy was observed in the prospective Phase 2 MyPathway trial of atezolizumab for patients with pan-solid tumors, where improved ORR and DCR was seen in patients with TMB ≥ 16 Muts/Mb than those with TMB ≥ 10 and <16 Muts/Mb[30]. Similarly, analyses across several solid tumor types reported that patients with higher TMB (defined as ≥16-20 Muts/Mb) achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy compared with patients with higher TMB treated with chemotherapy[33] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[18].

FREQUENCY & PROGNOSIS

Pancreatic carcinomas, including ductal and acinar subtypes, have been reported to harbor a median TMB of 2-3 mutations per megabase (muts/Mb), and 0-2% of cases have high TMB (>20 muts/Mb)[34]; TMB has not been assessed in pancreatic mucinous neoplasms (PubMed, Oct 2022). A study of patients with pancreatic ductal adenocarcinoma harboring mismatch repair gene mutations reported improved prognosis for patients with high TMB measured in tissue samples (defined as >50 mutations; survival 69-314 months) compared to those with lower TMB (average of 5.7 mutations; 10-42 months)[35].

FINDING SUMMARY

Tumor mutation burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[36-37] and cigarette smoke in lung cancer[38-39], treatment with temozolomide-based chemotherapy in glioma[40-41], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[42-46], and microsatellite instability (MSI)[42,45-46]. This sample harbors a TMB level associated with lower rates of clinical benefit from treatment with PD-1- or PD-L1-targeting immune checkpoint inhibitors compared with patients with tumors harboring higher TMB levels, based on several studies in multiple solid tumor types[18-19,27].

GENE
ARID1A

ALTERATION
R376fs*15

HGVS VARIANT
NM_006015.4: c.1126del (p.R376Gfs*15)

VARIANT CHROMOSOMAL POSITION
chr1:27024017-27024018

VARIANT ALLELE FREQUENCY (% VAF)
13.0%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies approved to address the mutation or loss of ARID1A in cancer. However, on the basis of limited clinical and preclinical evidence, ARID1A inactivating mutations may lead to sensitivity to ATR inhibitors such as M6620 and ceralasertib[47]. In a Phase 2 study of ceralasertib in solid tumors, 2 patients with endometrial carcinoma in the cohort with loss of ARID1A expression achieved CRs on ceralasertib monotherapy; at least 1 of these 2 patients carried an inactivating ARID1A mutation. In contrast, no responses were observed for patients with normal ARID1A expression treated with ceralasertib combined with olaparib[48]. One patient with small cell lung cancer harboring an ARID1A mutation experienced a PR when treated with M6620 combined with topotecan[49]. In a Phase 1 trial, a patient with metastatic colorectal cancer (CRC) harboring both an ARID1A mutation and ATM loss treated with single-agent M6620 achieved a CR that was ongoing at 29 months[50]. On the basis of limited clinical and preclinical evidence, ARID1A inactivation may predict sensitivity to EZH2 inhibitors[51-52]. A Phase 1 study of EZH2 inhibitor CPI-0209 reported 1 PR for a patient with ARID1A-mutated endometrial cancer[53]. Other studies have reported that the loss of ARID1A may activate the PI3K-AKT pathway and be linked with sensitivity to inhibitors of this pathway[54-56]. Patients with ARID1A alterations in advanced or metastatic solid tumors may derive benefit from treatment with anti-PD-1 or anti-PD-L1 immunotherapy[57]. Loss of ARID1A expression has been associated with chemoresistance to platinum-based therapy for patients with ovarian clear cell carcinoma[58-59] and to 5-fluorouracil in CRC cell lines[60].

FREQUENCY & PROGNOSIS

ARID1A alterations are particularly prevalent in ovarian clear cell carcinoma (46-50%), ovarian and uterine endometrioid carcinomas (24-44%), and cholangiocarcinoma (27%); they are also reported in up to 27% of gastric carcinoma, esophageal adenocarcinoma, Waldenstrom macroglobulinemia, pediatric Burkitt lymphoma, hepatocellular carcinoma, colorectal carcinoma, and urothelial carcinoma samples analyzed (COSMIC, cBioPortal, 2023)[61-69]. ARID1A loss is associated with microsatellite instability in ovarian and endometrial endometrioid adenocarcinomas[57,70-73], CRC[57,74-76], and gastric cancer[57,77-81]. ARID1A protein loss is associated with tumors of poor histological grade for many tumor types, including colorectal cancer (CRC)[74-76], cervical cancer[82-83], gastric cancer[77-81], urothelial carcinoma[84-86], ovarian and endometrial cancers[59,70-73,87-91], breast carcinoma[92-94], and clear cell renal cell carcinoma[95]; ARID1A mutation has been associated with poor outcomes for patients with cholangiocarcinoma[96-99]. However, prognostic data regarding patient survival are often mixed and conflicting.

FINDING SUMMARY

ARID1A encodes the AT-rich interactive domain-containing protein 1A, also known as Baf250a, a member of the SWI/SNF chromatin remodeling complex. Mutation, loss, or inactivation of ARID1A has been reported in many cancers, and the gene is considered a tumor suppressor[65,80,93,100-105]. ARID1A mutations, which are mostly truncating, have been identified along the entire gene and often correlate with ARID1A protein loss[65,78,101-102,106], whereas ARID1A missense mutations are mostly uncharacterized.

Electronically signed by Julie Tse, M.D. | 09 May 2023
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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

GENE
KRAS

ALTERATION
G12V

HGVS VARIANT
NM_004985.3: c.35G>T (p.G12V)

VARIANT CHROMOSOMAL POSITION
chr12:25398284

VARIANT ALLELE FREQUENCY (% VAF)
22.8%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical evidence suggests that KRAS activation may predict sensitivity to MEK inhibitors, such as trametinib, binimetinib, cobimetinib, and selumetinib[107-112]. For patients with pancreatic cancer, MEK inhibitor combinations are under investigation. A Phase 2 study of trametinib with pembrolizumab versus gemcitabine after stereotactic body radiotherapy (SBRT) reported increased median OS (mOS, 14.9 months vs. 12.8 months, HR=0.69) benefit for patients with KRAS-mutated, PD-L1 positive disease[113]. Combination MEK/autophagy inhibitors are also under investigation based on preclinical evidence of increased autophagy downstream of KRAS-mutated pancreatic tumors[114-115]. A heavily pretreated patient with pancreatic cancer treated with trametinib plus hydroxychloroquine experienced a PR[114]. A Phase 2 study of the reoviral agent pelareorep with gemcitabine for patients with pancreatic cancer reported 1 PR, 23 SDs, and 5 PDs for 34 patients with a favorable median OS of 10.2 months[116]. A Phase 1b study of second-line pelareorep with pembrolizumab and chemotherapy reported 1 PR of 17.4 months and a DCR of 30% (3/10)[117]; an earlier study reported no benefit from pelareorep in combination with paclitaxel/carboplatin[118]. Trials combining MEK inhibitors with other targeted therapies, such as EGFR inhibitors[119] or PI3K-AKT pathway inhibitors[120-121], reported no PRs and frequent adverse events for patients with KRAS-mutated pancreatic cancer. Clinical trials combining various MEK inhibitors with gemcitabine reported no additional benefit compared to gemcitabine alone irrespective of KRAS mutation status[122-125], despite promising results in earlier trials of MEK inhibitor monotherapies[126-131]. In a Phase 1 study evaluating the MEK-pan-RAF dual inhibitor CH5126766, 6 patients harboring KRAS mutations experienced PRs, including 3 with non-small cell lung cancer (NCSLC), 1 with low-grade serous ovarian carcinoma (LGSOC), 1 with endometrial adenocarcinoma, and 1 with multiple myeloma[132]. Combination of CH5126766 with the FAK inhibitor defactinib elicited PR rates of 50% (4/8) for patients with KRAS-mutated LGSOC and 12% (2/17) for patients with KRAS-mutated NSCLC in a Phase 1 study[133-134] . Preclinical and clinical data suggest that KRAS mutations may predict clinical benefit from SHP2 inhibitors[135-136]. A Phase 1 study of RMC-4630 for relapsed/refractory solid tumors reported a DCR of 58% (23/40) for patients with NSCLC and KRAS mutations and a DCR of 75% (12/16) for patients with NSCLC and KRAS G12C mutations[137]. Interim results from a Phase 1/2 study of RMC-4630 plus cobimetinib reported tumor reduction in 3 of 8 patients with KRAS-mutated colorectal cancer[138]. Preclinical studies suggest that KRAS activating mutations may confer sensitivity to SOS1 inhibitors such as BI-3406, MRTX0902, BI-1701963, and BAY-293 as single agents[139-144] or in combination with covalent KRAS G12C inhibitors[144] and MEK inhibitors[145-146].

FREQUENCY & PROGNOSIS

KRAS mutations have been observed in 91-95% of pancreatic ductal adenocarcinoma cases[147-148], with the majority of mutations found at codon 12[149-152]. KRAS mutations, particularly G12D, have been associated with decreased median survival time in patients with pancreatic ductal adenocarcinoma[150].

FINDING SUMMARY

KRAS encodes a member of the RAS family of small GTPases. Activating mutations in RAS genes can cause uncontrolled cell proliferation and tumor formation[108,153]. KRAS alterations affecting amino acids G12, G13, Q22, P34, A59, Q61, and A146, as well as mutations G10_A11insG, G10_A11insAG (also reported as G10_A11dup and G12_G13insAG), A18D, L19F, D33E, G60_A66dup/E62_A66dup, E62K, E63K, R68S, K117R, and K117N have been characterized as activating and oncogenic[108,154-176].

GENE
PDGFRB

ALTERATION
V823I

HGVS VARIANT
NM_002609.3: c.2467G>A (p.V823I)

VARIANT CHROMOSOMAL POSITION
chr5:149500570

VARIANT ALLELE FREQUENCY (% VAF)
50.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical benefit for patients with renal cell carcinoma[177-180] or solitary fibrous tumor[181-182], as well as for a patient with urothelial carcinoma[183] and a patient with clear cell sarcoma[184], PDGFRB expression is associated with sensitivity to sorafenib and sunitinib. PDGFRB fusions in myeloid neoplasms have been shown to be exquisitely sensitive to PDGFR-targeting therapies[185-186]. Significant clinical benefit has also been achieved with dasatinib or imatinib in PDGFRB fusion-positive acute lymphoblastic leukemia[187-190], chronic eosinophilic leukemia[191-193], and various other hematologic malignancies[194-198]. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS

PDGFRB amplification was reported in 3% of samples in a study of pancreatic ductal adenocarcinoma[148]. However, active (phosphorylated) PDGFR-beta was reported in 93.5% (29/31) of pancreatic carcinoma samples in another study[199]. PDGFRB mutations have been found in up to 1.1% of pancreatic adenocarcinoma cases (cBioPortal, COSMIC, Nov 2021)[61-63]. High expression of PDGFR-beta has been reported to be associated with worse metastasis-free and postoperative survival of patients with pancreatic cancer[200-201].

FINDING SUMMARY

PDGFRB (Platelet-derived growth factor receptor, beta) encodes PDGFR-beta, a receptor tyrosine kinase that binds growth factors of the platelet-derived growth factor (PDGF) family. It is located on chromosome 5q33, and rearrangements involving this gene that result in its constitutive activation have been found in chronic myeloproliferative diseases[194,202-205]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

GENE
CDKN2A/B

ALTERATION
CDKN2B loss, CDKN2A loss

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib[206-209]. Clinical data in mesothelioma, breast cancer, and uterine leiomyosarcoma indicate that CDKN2A loss may predict sensitivity to abemaciclib[210] and palbociclib treatment[211-212]. However, multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[213-219]; it is not known whether CDK4/6 inhibitors would be beneficial in this case. The p15INK4b protein encoded by CDKN2B is known to inhibit CDK4, and although concomitant loss of CDKN2A and CDKN2B may predict sensitivity to CDK4/6 inhibitors, such as ribociclib, abemaciclib, and palbociclib[216-217,220-221], direct supporting data for CDKN2B alteration as a predictive biomarker for these therapies are limited[222-223]. Although preclinical studies have suggested that loss of p14ARF function may be associated with reduced sensitivity to MDM2 inhibitors[224-225], the clinical relevance of p14ARF as a predictive biomarker is not clear.

FREQUENCY & PROGNOSIS

CDKN2A/B loss has been reported in 36% of pancreatic ductal carcinomas[148]. CDKN2A loss has been reported in 25-100% of pancreatic ductal adenocarcinomas analyzed, with a portion of those due to gene deletion[150,226-228]. A study of multiple pancreatic cancer subtypes reported no CDKN2A mutations (0/6 samples) and loss of heterozygosity in only one of four samples of pancreatic acinar carcinomas, compared to mutation or loss of heterozygosity in 38% and 67% of pancreatic ductal carcinomas, respectively[229]. Promoter methylation affecting p16INK4a and p14ARF has been reported in 43% (16/37) and 20.6% (7/34), respectively, of pancreatic fluid specimens of patients with pancreatic carcinoma[230]. The loss or decrease of p16INK4a expression levels in pancreatic ductal adenocarcinoma has been reported in 32-80% of samples analyzed and one study reported concurrent loss of p16INK4a and p14ARF protein expression in 68% (19/28) of cases[226,231-232]. p16INK4a expression has been associated with improved OS in pancreatic adenocarcinoma patients in univariate and multivariate analysis[233]. Furthermore, CDKN2A alterations (deletion or mutation) in the presence of concomitant KRAS mutation may correlate with shorter survival in patients with pancreatic ductal adenocarcinoma[231].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[234-235]. Both p15INK4b and p16INK4a bind to and inhibit CDK4 and CDK6, thereby maintaining the growth-suppressive activity of the Rb tumor suppressor; loss or inactivation of either p15INK4b or p16INK4a contributes to dysregulation of the CDK4/6-cyclin-Rb pathway and loss of cell cycle control[236-237]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[238-239]. One or more alterations observed here are predicted to result in p16INK4a loss of function[240-261]. One or more alterations seen here are predicted to result in p14ARF loss of function[244,261-264]. CDKN2B alterations such as seen here are predicted to inactivate p15INK4b[265].

POTENTIAL GERMLINE IMPLICATIONS

Germline CDKN2A mutation is associated with melanoma-pancreatic cancer syndrome, a condition marked by increased risk of developing malignant melanoma and/or pancreatic cancer[266]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[267-268]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[269-271]. CDKN2A alteration has also been implicated in familial melanoma-astrocytoma syndrome, an extremely rare tumor association characterized by dual predisposition to melanoma and nervous system tumors[272-274]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

GENE
TP53

ALTERATION
R342*

HGVS VARIANT
NM_000546.4: c.1024C>T (p.R342*)

VARIANT CHROMOSOMAL POSITION
chr17:7574003

VARIANT ALLELE FREQUENCY (% VAF)
26.7%

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[275-278] or p53 gene therapy such as SGT53[279-283]. 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[284]. 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[285]. 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[286]. 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[287]. 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[288]. 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[289]. 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[290]. 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[283]. 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[291]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[292].

FREQUENCY & PROGNOSIS

TP53 mutations have been reported in 33-75% of pancreatic carcinomas, with the majority occurring as missense mutations, while deletion of TP53 has been found in 66% of pancreatic ductal adenocarcinoma cases[147,293-295]. TP53 mutations are common in pancreatic ductal adenocarcinomas and are known to occur in the process of pancreatic carcinogenesis[296-297]. Additionally, aberrant expression of p53 has been found in 54-81% of pancreatic ductal adenocarcinoma cases[231,294,298-299]. Studies have found inconsistent results regarding the prognostic significance of p53 expression in pancreatic ductal adenocarcinoma, although one study correlated low levels of TP53 mRNA with poor patient prognosis[231,300-301].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[302]. Alterations such as seen here may disrupt TP53 function or expression[303-307].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the TP53 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with Li-Fraumeni syndrome (ClinVar, Sep 2022)[308]. 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[309-311], including sarcomas[312-313]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[314] to 1:20,000[313]. 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[315]. 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[316-321]. 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[316-317]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[322]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[320,323-324]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

NOTE 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. 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 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. Or, visit https://www.foundationmedicine.com/genomic-testing#support-services.

GENE
ARID1A

ALTERATION
R376fs*15

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

NCT02264678

PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1

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

NCT04802174

PHASE 1/2

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

TARGETS
ATR

LOCATIONS: Maryland

NCT04657068

PHASE 1/2

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

TARGETS
ATR

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

NCT04514497

PHASE 1

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

TARGETS
TOP1, ATR

LOCATIONS: California, Arizona, Minnesota, Oklahoma, Missouri, Pennsylvania, Connecticut, New York

NCT03669601

PHASE 1

AZD6738 & Gemcitabine as Combination Therapy

TARGETS
ATR

LOCATIONS: Cambridge (United Kingdom)

NCT04616534

PHASE 1

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

TARGETS
ATR

LOCATIONS: Massachusetts, Maryland

GENE
KRAS

ALTERATION
G12V

RATIONALE
Multiple clinical studies have reported lack of efficacy of MEK inhibitors as monotherapy for treatment of KRAS-mutant pancreatic cancer. Emerging data suggest patients with KRAS-mutant pancreatic cancer may be sensitive to MEK-pan-RAF dual inhibitors or combination MEK/autophagy inhibitors. Preclinical evidence suggests that KRAS activating mutations may predict sensitivity to SOS1 inhibitors.

NCT05669482

PHASE 1/2

Study of Avutometinib (VS-6766) +Defactinib With Gemcitabine and Nab-paclitaxel in Patients With Pancreatic Cancer

TARGETS
RAFs, MEK, FAK

LOCATIONS: Missouri, New York

NCT04892017

PHASE 1/2

A Safety, Tolerability and PK Study of DCC-3116 in Patients With RAS or RAF Mutant Advanced or Metastatic Solid Tumors.

TARGETS
ULK1, ULK2, MEK

LOCATIONS: Massachusetts, New York, Texas, Pennsylvania

NCT03825289

PHASE 1

Trametinib and Hydroxychloroquine in Treating Patients With Pancreatic Cancer

TARGETS
MEK

LOCATIONS: Utah

NCT04132505

PHASE 1

Binimetinib and Hydroxychloroquine in Treating Patients With KRAS Mutant Metastatic Pancreatic Cancer

TARGETS
MEK

LOCATIONS: Texas

GENE
PDGFRB

ALTERATION
V823I

RATIONALE
PDGFRB amplification or activating mutations may predict sensitivity to certain PDGFRB-targeted therapies. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

NCT02693535

PHASE 2

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

TARGETS
CDK4, CDK6, FLT3, VEGFRs, CSF1R, KIT, RET, mTOR, ERBB2, MEK, BRAF, PARP, PD-1, CTLA-4, PD-L1, TRKB, ALK, TRKC, ROS1, TRKA, FGFRs

LOCATIONS: Hawaii, Washington, Oregon, California

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT04817956

PHASE 2

Improving Public Cancer Care by Implementing Precision Medicine in Norway

TARGETS
PD-L1, VEGFA, ERBB2, ALK, RET, PARP, SMO, TRKB, TRKC, ROS1, TRKA, MEK, BRAF, PI3K-alpha, FGFR1, FGFR2, FGFR3, MET, KIT, ABL

LOCATIONS: Tromsø (Norway), Bodø (Norway), Hamar (Norway), Oslo (Norway), Fredrikstad (Norway), Drammen (Norway), Trondheim (Norway), Skien (Norway), Førde (Norway), Bergen (Norway)

NCT01738139

PHASE 1

Ipilimumab and Imatinib Mesylate in Advanced Cancer

TARGETS
KIT, ABL, CTLA-4

LOCATIONS: Texas

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

ABL1
NM_005157.4: c.2470G>A
(p.V824M)
chr9:133760147

AR
NM_000044.2: c.528C>A
(p.S176R)
chrX:66765516

ATRX
NM_000489.3: c.6035A>T
(p.E2012V)
chrX:76849241

CARD11
NM_032415.4: c.2009C>T
(p.T670M)
chr7:2962899

CSF3R
NM_156039.3: c.1348G>T
(p.E450*)
chr1:36935379

ERBB3
NM_001982.3: c.1463G>A
(p.R488Q)
chr12:56487317

FH
NM_000143.3: c.797T>C
(p.M266T)
chr1:241669410

HSD3B1
amplification

MAP2K4
NM_003010.2: c.557A>G
(p.D186G)
chr17:12011150

NFE2L2
NM_006164.4: c.78_86dup
(p.I28_D29insEDI)
chr2:178098958

PDGFRA
NM_006206.4: c.101A>G
(p.E34G)
chr4:55127313

PTCH1
NM_001083603.1: c.131A>G
(p.E44G)
chr9:98278972

SGK1
NM_005627.3: c.1174G>C
(p.E392Q)
chr6:134491528

FoundationOne CDx is designed to include genes known to be somatically altered in human solid tumors that are validated targets for therapy, either approved or in clinical trials, and/or that are unambiguous drivers of oncogenesis based on current knowledge. The current assay interrogates 324 genes as well as introns of 36 genes involved in rearrangements. The assay will be updated periodically to reflect new knowledge about cancer biology.

DNA GENE LIST: ENTIRE CODING SEQUENCE FOR THE DETECTION OF BASE SUBSTITUTIONS, INSERTION/DELETIONS, AND COPY NUMBER ALTERATIONS

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B or WTX)*	
APC	*AR*	*ARAF*	*ARFRP1*	*ARID1A*	*ASXL1*	*ATM*	*ATR*	*ATRX*
AURKA	*AURKB*	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*
BCL6	*BCOR*	*BCORL1*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*
BTG2	*BTK*	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	*CCND1*	*CCND2*
CCND3	*CCNE1*	*CD22*	*CD274 (PD-L1)*	*CD70*	*CD79A*	*CD79B*	*CDC73*	*CDH1*
CDK12	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*	*CDKN2C*
CEBPA	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CSF1R*	*CSF3R*	*CTCF*
CTNNA1	*CTNNB1*	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*	*DDR2*
DIS3	*DNMT3A*	*DOT1L*	*EED*	*EGFR*	*EMSY (C11orf30)*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
FANCA	*FANCC*	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*	*FGF14*
FGF19	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*	*FGFR4*
FH	*FLCN*	*FLT1*	*FLT3*	*FOXL2*	*FUBP1*	*GABRA6*	*GATA3*	*GATA4*
GATA6	*GID4 (C17orf39)*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3-3A (H3F3A)*
HDAC1	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*ID3*	*IDH1*	*IDH2*	*IGF1R*
IKBKE	*IKZF1*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JUN	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*	*KIT*	*KLHL6*
KMT2A (MLL)	*KMT2D (MLL2)*	*KRAS*	*LTK*	*LYN*	*MAF*	*MAP2K1 (MEK1)*	*MAP2K2 (MEK2)*	*MAP2K4*
MAP3K1	*MAP3K13*	*MAPK1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*	*MEN1*
MERTK	*MET*	*MITF*	*MKNK1*	*MLH1*	*MPL*	*MRE11 (MRE11A)*	*MSH2*	*MSH3*
MSH6	*MST1R*	*MTAP*	*MTOR*	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*
NBN	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2*	*NOTCH3*
NPM1	*NRAS*	*NSD2 (WHSC1 or MMSET)*		*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*
P2RY8	*PALB2*	*PARP1*	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1 (PD-1)*	*PDCD1LG2 (PD-L2)*
PDGFRA	*PDGFRB*	*PDK1*	*PIK3C2B*	*PIK3C2G*	*PIK3CA*	*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*	*RARA*	*RB1*	*RBM10*
REL	*RET*	*RICTOR*	*RNF43*	*ROS1*	*RPTOR*	*SDHA*	*SDHB*	*SDHC*
SDHD	*SETD2*	*SF3B1*	*SGK1*	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*
SNCAIP	*SOCS1*	*SOX2*	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*	*STAT3*
STK11	*SUFU*	*SYK*	*TBX3*	*TEK*	*TENT5C (FAM46C)*		*TET2*	*TGFBR2*
TIPARP	*TNFAIP3*	*TNFRSF14*	*TP53*	*TSC1*	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*
VHL	*WT1*	*XPO1*	*XRCC2*	*ZNF217*	*ZNF703*			

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	*BCL2*	*BCR*	*BRAF*	*BRCA1*	*BRCA2*	*CD74*	*EGFR*	*ETV4*
ETV5	*ETV6*	*EWSR1*	*EZR*	*FGFR1*	*FGFR2*	*FGFR3*	*KIT*	*KMT2A (MLL)*
MSH2	*MYB*	*MYC*	*NOTCH2*	*NTRK1*	*NTRK2*	*NUTM1*	*PDGFRA*	*RAF1*
RARA	*RET*	*ROS1*	*RSPO2*	*SDC4*	*SLC34A2*	*TERC**	*TERT***	*TMPRSS2*

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Homologous Recombination status
Loss of Heterozygosity (LOH) score
Microsatellite (MS) status
Tumor Mutational Burden (TMB)

FoundationOne 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. CE

ABOUT FOUNDATIONONE CDX

FoundationOne CDx was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne 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: www.rochefoundationmedicine.com/f1cdxtech.

INTENDED USE

FoundationOne®CDx (F1CDx) is a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI), tumor mutational burden (TMB), and for selected forms of ovarian cancer, loss of heterozygosity (LOH) score, using DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with therapies in accordance with approved therapeutic product labeling. Additionally, F1CDx 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 solid malignant neoplasms.

TEST PRINCIPLE

FoundationOne CDx will be performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The proposed assay will employ a single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50-1000 ng of which will undergo whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons. The assay therefore includes detection of alterations in a total of 324 genes.

Using an Illumina® HiSeq platform, hybrid capture–selected libraries will be sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data will be processed using a customized analysis pipeline designed to accurately detect all classes of genomic alterations, including base substitutions, indels, focal copy number amplifications, homozygous gene deletions, and selected genomic rearrangements (e.g.,gene fusions). Additionally, genomic signatures including loss of heterozygosity (LOH), microsatellite instability (MSI) and tumor mutational burden (TMB) will be reported.

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. The F1CDx report may be used as an aid to inform molecular eligibility for clinical trials. 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.

Diagnostic Significance

FoundationOne CDx identifies alterations to select cancer-associated genes or portions of genes (biomarkers). In some cases, the Report also highlights selected negative test results regarding biomarkers of clinical significance.

Qualified Alteration Calls (Equivocal and Subclonal)

An alteration denoted as "amplification – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence that the copy number of a gene exceeds the threshold for identifying copy number amplification. The threshold used in FoundationOne CDx for identifying a copy number amplification is four (4) for *ERBB2* and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence for homozygous deletion of the gene in question. An alteration denoted as "subclonal" is one that the FoundationOne CDx analytical methodology has identified as being present in <10% of the assayed tumor DNA.

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.

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.

Limitations

1. In the fraction-based MSI algorithm, a tumor specimen will be categorized as MSI-H, MSS, or MS-Equivocal according to the fraction of microsatellite loci determined to be altered or unstable (i.e., the fraction unstable loci score). In the F1CDx assay, MSI is evaluated based on a genome-wide analysis across >2000 microsatellite loci. For a given microsatellite locus, non-somatic alleles are discarded, and the microsatellite is categorized as unstable if remaining alleles differ from the reference genome. The final fraction unstable loci score is calculated as the number of unstable microsatellite loci divided by the number of evaluable microsatellite loci. The MSI-H and MSS cut-off thresholds were determined by

analytical concordance to a PCR comparator assay using a pan-tumor FFPE tissue sample set. Patients with results categorized as "MS-Stable" with median exon coverage <300X, "MS-Equivocal," or "Cannot Be Determined" should receive confirmatory testing using a validated orthogonal (alternative) method.

2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.
3. Homologous Recombination status may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas (Coleman et al., 2017; 28916367). Samples with deleterious *BRCA1/2* alteration and/or Loss of Heterozygosity (LOH) score ≥ 16% will be reported as "HRD Positive" and samples with absence of these findings will be reported as "HRD Not Detected," agnostic of potential secondary *BRCA1/2* reversion alterations. Certain potentially deleterious missense or small in-frame deletions in *BRCA1/2* may not be classified as deleterious and, in the absence of an elevated LOH profile, samples with such mutations may be classified as "HRD Not Detected." A result of "HRD Not Detected" does not rule out the presence of a *BRCA1/2* alteration or an elevated LOH profile outside the assay performance characteristic limitations.
4. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.
5. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
6. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
7. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

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.

VARIANT ALLELE FREQUENCY

Variant Allele Frequency (VAF) represents the fraction of sequencing reads in which the variant is observed. This attribute is not taken into account for therapy inclusion, clinical trial matching, or interpretive content. Caution is recommended in interpreting VAF to indicate the potential germline or somatic origin of an alteration, recognizing that tumor fraction and tumor ploidy of samples may vary.

Precision of VAF for base substitutions and indels

BASE SUBSTITUTIONS	%CV*
Repeatability	5.11 - 10.40
Reproducibility	5.95 - 12.31
INDELS	**%CV***
Repeatability	6.29 - 10.00
Reproducibility	7.33 - 11.71

**Interquartile Range = 1st Quartile to 3rd Quartile*

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 >10%, 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, CBL, 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.

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 CDx.

TREATMENT DECISIONS ARE 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 or variant characteristics may result in reduced sensitivity. FoundationOne CDx is performed using DNA derived from tumor, 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) 7.8.0

The median exon coverage for this sample is 907x

1. Gatalica Z, et al. Cancer Epidemiol. Biomarkers Prev. (2014) pmid: 25392179
2. Kroemer G, et al. Oncoimmunology (2015) pmid: 26140250
3. Lal N, et al. Oncoimmunology (2015) pmid: 25949894
4. Le DT, et al. N. Engl. J. Med. (2015) pmid: 26028255
5. Ayers et al., 2016; ASCO-SITC Abstract P60
6. Hu ZI, et al. Clin. Cancer Res. (2018) pmid: 29367431
7. Campbell BB, et al. Cell (2017) pmid: 29056344
8. Pihlak R, et al. Cancers (Basel) (2018) pmid: 29329208
9. Salem ME, et al. Mol. Cancer Res. (2018) pmid: 29523759
10. Laghi L, et al. PLoS ONE (2012) pmid: 23029359
11. Kocarnik JM, et al. Gastroenterol Rep (Oxf) (2015) pmid: 26337942
12. You JF, et al. Br. J. Cancer (2010) pmid: 21081928
13. Bairwa NK, et al. Methods Mol. Biol. (2014) pmid: 24623249
14. Boland CR, et al. Cancer Res. (1998) pmid: 9823339
15. Pawlik TM, et al. Dis. Markers (2004) pmid: 15528785
16. Boland CR, et al. Gastroenterology (2010) pmid: 20420947
17. Samstein RM, et al. Nat. Genet. (2019) pmid: 30643254
18. Goodman AM, et al. Mol. Cancer Ther. (2017) pmid: 28835386
19. Goodman AM, et al. Cancer Immunol Res (2019) pmid: 31405947
20. Cristescu R, et al. Science (2018) pmid: 30309915
21. Ready N, et al. J. Clin. Oncol. (2019) pmid: 30785829
22. Hellmann MD, et al. N. Engl. J. Med. (2018) pmid: 29658845
23. Hellmann MD, et al. Cancer Cell (2018) pmid: 29657128
24. Hellmann MD, et al. Cancer Cell (2018) pmid: 29731394
25. Rozeman EA, et al. Nat Med (2021) pmid: 33558721
26. Sharma P, et al. Cancer Cell (2020) pmid: 32916128
27. Marabelle A, et al. Lancet Oncol. (2020) pmid: 32919526
28. Ott PA, et al. J. Clin. Oncol. (2019) pmid: 30557521
29. Cristescu R, et al. J Immunother Cancer (2022) pmid: 35101941
30. Friedman CF, et al. Cancer Discov (2022) pmid: 34876409
31. Sturgill EG, et al. Oncologist (2022) pmid: 35274716
32. Schenker et al., 2022; AACR Abstract 7845
33. Legrand et al., 2018; ASCO Abstract 12000
34. Chalmers ZR, et al. Genome Med (2017) pmid: 28420421
35. Hu et al., 2017; ASCO Abstract e15791
36. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
37. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
38. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
39. Rizvi NA, et al. Science (2015) pmid: 25765070
40. Johnson BE, et al. Science (2014) pmid: 24336570
41. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
42. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
43. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
44. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
45. Nature (2012) pmid: 22810696
46. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
47. Williamson CT, et al. Nat Commun (2016) pmid: 27958275
48. Aggarwal et al., 2021; ESMO Abstract 5120
49. Thomas A, et al. J. Clin. Oncol. (2018) pmid: 29252124
50. Yap TA, et al. J Clin Oncol (2020) pmid: 32568634
51. Bitler BG, et al. Nat. Med. (2015) pmid: 25686104
52. Kim KH, et al. Nat. Med. (2015) pmid: 26552009
53. Papadopoulos et al., 2022; ENA Abstract 188
54. Wiegand KC, et al. BMC Cancer (2014) pmid: 24559118
55. Huang HN, et al. Mod. Pathol. (2014) pmid: 24336158
56. Samartzis EP, et al. Oncotarget (2014) pmid: 24979463
57. Okamura R, et al. J Immunother Cancer (2020) pmid: 32111729
58. Yokoyama Y, et al. J Gynecol Oncol (2014) pmid: 24459582
59. Katagiri A, et al. Mod. Pathol. (2012) pmid: 22101352
60. Xie C, et al. Tumour Biol. (2014) pmid: 24833095
61. Tate JG, et al. Nucleic Acids Res. (2019) pmid: 30371878
62. Cerami E, et al. Cancer Discov (2012) pmid: 22588877
63. Gao J, et al. Sci Signal (2013) pmid: 23550210
64. Wu RC, et al. Cancer Biol. Ther. (2014) pmid: 24618703
65. Jones S, et al. Hum. Mutat. (2012) pmid: 22009941
66. Dulak AM, et al. Nat. Genet. (2013) pmid: 23525077
67. Streppel MM, et al. Oncogene (2014) pmid: 23318448
68. Jiao Y, et al. J. Pathol. (2014) pmid: 24293293
69. Ross JS, et al. Oncologist (2014) pmid: 24563076
70. Huang HN, et al. Histopathology (2015) pmid: 25195947
71. Hussein YR, et al. Mod. Pathol. (2015) pmid: 25394778
72. Bosse T, et al. Mod. Pathol. (2013) pmid: 23702729
73. Allo G, et al. Mod. Pathol. (2014) pmid: 23887303
74. Chou A, et al. Hum. Pathol. (2014) pmid: 24925223
75. Ye J, et al. Hum. Pathol. (2014) pmid: 25311944
76. Wei XL, et al. World J. Gastroenterol. (2014) pmid: 25561809
77. Chen K, et al. Proc. Natl. Acad. Sci. U.S.A. (2015) pmid: 25583476
78. Wang K, et al. Nat. Genet. (2011) pmid: 22037554
79. Abe H, et al. Virchows Arch. (2012) pmid: 22915242
80. Wang DD, et al. PLoS ONE (2012) pmid: 22808142
81. Wiegand KC, et al. Hum. Pathol. (2014) pmid: 24767857
82. Katagiri A, et al. Int. J. Gynecol. Cancer (2012) pmid: 22274316
83. Cho H, et al. Hum. Pathol. (2013) pmid: 23427874
84. Gui Y, et al. Nat. Genet. (2011) pmid: 21822268
85. Balbás-Martínez C, et al. PLoS ONE (2013) pmid: 23650517
86. Faraj SF, et al. Hum. Pathol. (2014) pmid: 25175170
87. Rahman M, et al. Hum. Pathol. (2013) pmid: 22939958
88. Maeda D, et al. Int J Mol Sci (2010) pmid: 21614196
89. Lowery WJ, et al. Int. J. Gynecol. Cancer (2012) pmid: 22193641
90. Fadare O, et al. Mod. Pathol. (2013) pmid: 23524907
91. Mao TL, et al. Am. J. Surg. Pathol. (2013) pmid: 24076775
92. Zhang X, et al. Cancer Epidemiol (2012) pmid: 21889920
93. Mamo A, et al. Oncogene (2012) pmid: 21892209
94. Zhao J, et al. Tumour Biol. (2014) pmid: 24430365
95. Lichner Z, et al. Am. J. Pathol. (2013) pmid: 23416164
96. Feng F, et al. Int J Clin Oncol (2021) pmid: 33387086
97. Conci S, et al. Updates Surg (2020) pmid: 32020551
98. Simbolo M, et al. Sci Rep (2018) pmid: 29740198
99. Ruzzenente A, et al. Ann. Surg. Oncol. (2016) pmid: 26717940
100. Guan B, et al. Cancer Res. (2011) pmid: 21900401
101. Wiegand KC, et al. N. Engl. J. Med. (2010) pmid: 20942669
102. Jones S, et al. Science (2010) pmid: 20826764
103. Yan HB, et al. Carcinogenesis (2014) pmid: 24293408
104. Huang J, et al. Nat. Genet. (2012) pmid: 22922871
105. Chan-On W, et al. Nat. Genet. (2013) pmid: 24185513
106. Zang ZJ, et al. Nat. Genet. (2012) pmid: 22484628
107. Nakano H, et al. Proc. Natl. Acad. Sci. U.S.A. (1984) pmid: 6320174
108. Pylayeva-Gupta Y, et al. Nat. Rev. Cancer (2011) pmid: 21993244
109. Yamaguchi T, et al. Int. J. Oncol. (2011) pmid: 21523318
110. Watanabe M, et al. Cancer Sci. (2013) pmid: 23438367
111. Gilmartin AG, et al. Clin. Cancer Res. (2011) pmid: 21245089
112. Yeh JJ, et al. Mol. Cancer Ther. (2009) pmid: 19372556
113. Zhu X, et al. Lancet Oncol (2022) pmid: 35240087
114. Kinsey CG, et al. Nat. Med. (2019) pmid: 30833748
115. Bryant KL, et al. Nat. Med. (2019) pmid: 30833752
116. Mahalingam D, et al. Cancers (Basel) (2018) pmid: 29799479
117. Mahalingam D, et al. Clin. Cancer Res. (2019) pmid: 31694832
118. Noonan AM, et al. Mol. Ther. (2016) pmid: 27039845
119. Ko AH, et al. Clin. Cancer Res. (2016) pmid: 26251290
120. Chung V, et al. JAMA Oncol (2017) pmid: 27978579
121. Bedard PL, et al. Clin. Cancer Res. (2015) pmid: 25500057
122. Van Laethem JL, et al. Target Oncol (2017) pmid: 27975152
123. Infante JR, et al. Eur. J. Cancer (2013) pmid: 23583440
124. Infante JR, et al. Eur. J. Cancer (2014) pmid: 24915778
125. Van Cutsem E, et al. Int. J. Cancer (2018) pmid: 29756206
126. Bodoky G, et al. Invest New Drugs (2012) pmid: 21594619
127. Rinehart J, et al. J. Clin. Oncol. (2004) pmid: 15483017
128. Lorusso PM, et al. J. Clin. Oncol. (2005) pmid: 16009947
129. Infante JR, et al. Lancet Oncol. (2012) pmid: 22805291
130. Weekes CD, et al. Clin. Cancer Res. (2013) pmid: 23434733
131. Garrido-Laguna I, et al. Oncoscience (2015) pmid: 25897431
132. Guo C, et al. Lancet Oncol (2020) pmid: 33128873
133. Krebs et al., 2021; AACR Abstract CT019
134. Shinde et al., 2020; AACR Abstract CT143
135. Lu H, et al. Mol Cancer Ther (2019) pmid: 31068384
136. Mainardi S, et al. Nat Med (2018) pmid: 29808006
137. Koczywas et al., 2021; AACR Abstract LB001
138. Bendell et al., 2020; EORTC-NCI-AACR Abstract 5
139. Hofmann MH, et al. Cancer Discov (2021) pmid: 32816843
140. He H, et al. J Med Chem (2022) pmid: 36173339
141. Zhang S, et al. J Med Chem (2022) pmid: 36384290
142. Liu M, et al. ACS Med Chem Lett (2023) pmid: 36793426
143. Ramharter J, et al. J Med Chem (2021) pmid: 33719426
144. Ketcham JM, et al. J Med Chem (2022) pmid: 35833726
145. Plangger A, et al. Discov Oncol (2022) pmid: 36048281
146. Ma Y, et al. Cancers (Basel) (2022) pmid: 36139627
147. Biankin AV, et al. Nature (2012) pmid: 23103869
148. Witkiewicz AK, et al. Nat Commun (2015) pmid: 25855536
149. Feldmann G, et al. J Hepatobiliary Pancreat Surg (2007) pmid: 17520196
150. Rachakonda PS, et al. PLoS ONE (2013) pmid: 23565280
151. Hruban RH, et al. Am. J. Pathol. (1993) pmid: 8342602
152. Maitra A, et al. Best Pract Res Clin Gastroenterol (2006) pmid: 16549325
153. Kahn S, et al. Anticancer Res. () pmid: 3310850
154. Akagi K, et al. Biochem. Biophys. Res. Commun. (2007)

pmid: 17150185
155. Bollag G, et al. J. Biol. Chem. (1996) pmid: 8955068
156. Buhrman G, et al. Proc. Natl. Acad. Sci. U.S.A. (2010) pmid: 20194776
157. Sci. STKE (2004) pmid: 15367757
158. Edkins S, et al. Cancer Biol. Ther. (2006) pmid: 16969076
159. Feig LA, et al. Mol. Cell. Biol. (1988) pmid: 3043178
160. Gremer L, et al. Hum. Mutat. (2011) pmid: 20949621
161. Janakiraman M, et al. Cancer Res. (2010) pmid: 20570890
162. Kim E, et al. Cancer Discov (2016) pmid: 27147599
163. Lukman S, et al. PLoS Comput. Biol. (2010) pmid: 20838576
164. Naguib A, et al. J Mol Signal (2011) pmid: 21371307
165. Prior IA, et al. Cancer Res. (2012) pmid: 22589270
166. Privé GG, et al. Proc. Natl. Acad. Sci. U.S.A. (1992) pmid: 1565661
167. Scheffzek K, et al. Science (1997) pmid: 9219684
168. Scholl C, et al. Cell (2009) pmid: 19490892
169. Smith G, et al. Br. J. Cancer (2010) pmid: 20147967
170. Tyner JW, et al. Blood (2009) pmid: 19075190
171. Valencia A, et al. Biochemistry (1991) pmid: 2029511
172. White Y, et al. Nat Commun (2016) pmid: 26854029
173. Wiest JS, et al. Oncogene (1994) pmid: 8058307
174. Angeles AKJ, et al. Oncol Lett (2019) pmid: 31289513
175. Tong JH, et al. Cancer Biol. Ther. (2014) pmid: 24642870
176. Loree JM, et al. Clin Cancer Res (2021) pmid: 34117033
177. Ornstein et al., 2015; ASCO GU Abstract 450
178. Dornbusch J, et al. PLoS ONE (2013) pmid: 24086736
179. Garcia-Donas J, et al. Ann. Oncol. (2013) pmid: 23788753
180. Ma X, et al. Sci Rep (2016) pmid: 27488093
181. Stacchiotti S, et al. Mol. Cancer Ther. (2010) pmid: 20457621
182. Stacchiotti S, et al. Ann. Oncol. (2012) pmid: 22711763
183. Shah CH, et al. Anticancer Drugs (2013) pmid: 23542751
184. Stacchiotti S, et al. Ann. Oncol. (2010) pmid: 20093352
185. Jawhar M, et al. Ann. Hematol. (2017) pmid: 28725989
186. Appiah-Kubi K, et al. Crit. Rev. Oncol. Hematol. (2017) pmid: 28010895
187. Kobayashi K, et al. Pediatr Blood Cancer (2015) pmid: 25400122
188. Lengline E, et al. Haematologica (2013) pmid: 24186319
189. Roberts KG, et al. N. Engl. J. Med. (2014) pmid: 25207766
190. Weston BW, et al. J. Clin. Oncol. (2013) pmid: 23835704
191. Chang et al., 2016; DOI 10.1016/j.jcrpr.2015.10.003
192. Li Z, et al. Pediatr Blood Cancer (2011) pmid: 21072821
193. Metzgeroth G, et al. Br. J. Haematol. (2008) pmid: 18950453
194. Apperley JF, et al. N. Engl. J. Med. (2002) pmid: 12181402
195. Cornfield D, et al. J. Clin. Oncol. (2012) pmid: 22331939
196. David M, et al. Blood (2007) pmid: 16960151
197. Walz C, et al. Haematologica (2007) pmid: 17296564
198. Winkelmann N, et al. Leuk. Lymphoma (2013) pmid: 23186533
199. Hwang RF, et al. Clin. Cancer Res. (2003) pmid: 14695158
200. Weissmueller S, et al. Cell (2014) pmid: 24725405
201. Kurahara H, et al. World J Surg (2016) pmid: 26940582
202. Roberts KG, et al. Cancer Cell (2012) pmid: 22897847
203. Chmielecki J, et al. Genes Chromosomes Cancer (2012) pmid: 21938754
204. Vizmanos JL, et al. Cancer Res. (2004) pmid: 15087377
205. Kobayashi K, et al. Br. J. Haematol. (2014) pmid: 24628626
206. Konecny GE, et al. Clin. Cancer Res. (2011) pmid: 21278246
207. Katsumi Y, et al. Biochem. Biophys. Res. Commun. (2011) pmid: 21871868
208. Cen L, et al. Neuro-oncology (2012) pmid: 22711607
209. Logan JE, et al. Anticancer Res. (2013) pmid: 23898052
210. Fennell DA, et al. Lancet Oncol (2022) pmid: 35157829
211. Elvin JA, et al. Oncologist (2017) pmid: 28283584
212. Gao J, et al. Curr Oncol (2015) pmid: 26715889
213. Gopalan et al., 2014; ASCO Abstract 8077
214. Peguero et al., 2016; ASCO Abstract 2528
215. Konecny et al., 2016; ASCO Abstract 5557
216. DeMichele A, et al. Clin. Cancer Res. (2015) pmid: 25501126
217. Finn RS, et al. Lancet Oncol. (2015) pmid: 25524798
218. Infante JR, et al. Clin. Cancer Res. (2016) pmid: 27542767
219. Johnson DB, et al. Oncologist (2014) pmid: 24797823
220. Flaherty KT, et al. Clin. Cancer Res. (2012) pmid: 22090362
221. Dickson MA, et al. J. Clin. Oncol. (2013) pmid: 23569312
222. Su D, et al. Nat Commun (2019) pmid: 31700061
223. Tramontana TF, et al. JCO Precis Oncol (2020) pmid: 32923894
224. Van Maerken T, et al. Mol. Cancer Ther. (2011) pmid: 21460101
225. Gamble LD, et al. Oncogene (2012) pmid: 21725357
226. Tsiambas E, et al. J BUON () pmid: 17600882
227. Bergmann F, et al. J. Clin. Pathol. (2006) pmid: 16497872
228. Attri J, et al. BMC Gastroenterol (2005) pmid: 15985168
229. Moore PS, et al. Br. J. Cancer (2001) pmid: 11161385
230. Klump B, et al. Br. J. Cancer (2003) pmid: 12610506
231. Oshima M, et al. Ann. Surg. (2013) pmid: 23470568
232. Geradts J, et al. Mod. Pathol. (2001) pmid: 11706079
233. Chang DT, et al. Cancer (2010) pmid: 20665497
234. Quelle DE, et al. Cell (1995) pmid: 8521522
235. Mutat. Res. (2005) pmid: 15878778
236. Gazzeri S, et al. Oncogene (1998) pmid: 9484839
237. Oncogene (1999) pmid: 10498883
238. Sherr CJ, et al. Cold Spring Harb. Symp. Quant. Biol. (2005) pmid: 16869746
239. Ozenne P, et al. Int. J. Cancer (2010) pmid: 20549699
240. Ruas M, et al. Oncogene (1999) pmid: 10498896
241. Jones R, et al. Cancer Res. (2007) pmid: 17909018
242. Haferkamp S, et al. Aging Cell (2008) pmid: 18843795
243. Huot TJ, et al. Mol. Cell. Biol. (2002) pmid: 12417717
244. Rizos H, et al. J. Biol. Chem. (2001) pmid: 11518711
245. Gombart AF, et al. Leukemia (1997) pmid: 9324288
246. Yang R, et al. Cancer Res. (1995) pmid: 7780957
247. Parry D, et al. Mol. Cell. Biol. (1996) pmid: 8668202
248. Greenblatt MS, et al. Oncogene (2003) pmid: 12606942
249. Yarbrough WG, et al. J. Natl. Cancer Inst. (1999) pmid: 10491434
250. Poi MJ, et al. Mol. Carcinog. (2001) pmid: 11255261
251. Byeon IJ, et al. Mol. Cell (1998) pmid: 9660926
252. Kannengiesser C, et al. Hum. Mutat. (2009) pmid: 19260062
253. Lal G, et al. Genes Chromosomes Cancer (2000) pmid: 10719365
254. Koh J, et al. Nature (1995) pmid: 7777061
255. McKenzie HA, et al. Hum. Mutat. (2010) pmid: 20340136
256. Miller PJ, et al. Hum. Mutat. (2011) pmid: 21462282
257. Kutscher CL, et al. Physiol. Behav. (1977) pmid: 905385
258. Scaini MC, et al. Hum. Mutat. (2014) pmid: 24659262
259. Jenkins NC, et al. J. Invest. Dermatol. (2013) pmid: 23190892
260. Walker GJ, et al. Int. J. Cancer (1999) pmid: 10389768
261. Rutter JL, et al. Oncogene (2003) pmid: 12853981
262. Itahana K, et al. Cancer Cell (2008) pmid: 18538737
263. Zhang Y, et al. Mol. Cell (1999) pmid: 10360174
264. Zhang Y, et al. Cell (1998) pmid: 9529249
265. Jafri M, et al. Cancer Discov (2015) pmid: 25873077
266. Whelan AJ, et al. N Engl J Med (1995) pmid: 7666917
267. Adv Exp Med Biol (2010) pmid: 20687502
268. Hogg D, et al. J Cutan Med Surg (1998) pmid: 9479083
269. De Unamuno B, et al. Melanoma Res (2018) pmid: 29543703
270. Soura E, et al. J Am Acad Dermatol (2016) pmid: 26892650
271. Huerta C, et al. Acta Derm Venereol (2018) pmid: 29405243
272. Kaufman DK, et al. Neurology (1993) pmid: 8414022
273. Bahuau M, et al. Cancer Res (1998) pmid: 9622062
274. Chan AK, et al. Clin Neuropathol () pmid: 28699883
275. Hirai H, et al. Cancer Biol. Ther. (2010) pmid: 20107315
276. Bridges KA, et al. Clin. Cancer Res. (2011) pmid: 21799033
277. Rajeshkumar NV, et al. Clin. Cancer Res. (2011) pmid: 21389100
278. Osman AA, et al. Mol. Cancer Ther. (2015) pmid: 25504633
279. Xu L, et al. Mol. Cancer Ther. (2002) pmid: 12489850
280. Xu L, et al. Mol. Med. (2001) pmid: 11713371
281. Camp ER, et al. Cancer Gene Ther. (2013) pmid: 23470564
282. Kim SS, et al. Nanomedicine (2015) pmid: 25240597
283. Pirollo KF, et al. Mol. Ther. (2016) pmid: 27357628
284. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27601554
285. Moore et al., 2019; ASCO Abstract 5513
286. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27998224
287. Oza et al., 2015; ASCO Abstract 5506
288. Lee J, et al. Cancer Discov (2019) pmid: 31315834
289. Méndez E, et al. Clin. Cancer Res. (2018) pmid: 29535125
290. Seligmann JF, et al. J Clin Oncol (2021) pmid: 34538072
291. Gourley et al., 2016; ASCO Abstract 5571
292. Park H, et al. ESMO Open (2022) pmid: 36084396
293. Morton JP, et al. Proc. Natl. Acad. Sci. U.S.A. (2010) pmid: 20018721
294. Scarpa A, et al. Am. J. Pathol. (1993) pmid: 8494051
295. Luo Y, et al. Pathol. Oncol. Res. (2013) pmid: 22782330
296. Iacobuzio-Donahue CA, et al. Clin. Cancer Res. (2012) pmid: 22896692
297. Macgregor-Das AM, et al. J Surg Oncol (2013) pmid: 22806689
298. Ottenhof NA, et al. Cell Oncol (Dordr) (2012) pmid: 22351431
299. Tsiambas E, et al. J BUON () pmid: 20414934
300. Ansari D, et al. Br J Surg (2011) pmid: 21644238
301. Grochola LF, et al. Pancreas (2011) pmid: 21404460
302. Brown CJ, et al. Nat. Rev. Cancer (2009) pmid: 19935675
303. Joerger AC, et al. Annu. Rev. Biochem. (2008) pmid: 18410249
304. Kato S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12826609
305. Kamada R, et al. J. Biol. Chem. (2011) pmid: 20978130
306. Zerdoumi Y, et al. Hum. Mol. Genet. (2017) pmid: 28472496

307. Yamada H, et al. Carcinogenesis (2007) pmid: 17690113
308. Landrum MJ, et al. Nucleic Acids Res. (2018) pmid: 29165669
309. Bougeard G, et al. J. Clin. Oncol. (2015) pmid: 26014290
310. Sorrell AD, et al. Mol Diagn Ther (2013) pmid: 23355100
311. Nichols KE, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11219776
312. Kleihues P, et al. Am. J. Pathol. (1997) pmid: 9006316
313. Gonzalez KD, et al. J. Clin. Oncol. (2009) pmid: 19204208
314. Lalloo F, et al. Lancet (2003) pmid: 12672316
315. Mandelker D, et al. Ann. Oncol. (2019) pmid: 31050713
316. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
317. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838
318. Xie M, et al. Nat. Med. (2014) pmid: 25326804
319. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
320. Severson EA, et al. Blood (2018) pmid: 29678827
321. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
322. Hematology Am Soc Hematol Educ Program (2018) pmid: 30504320
323. Chabon JJ, et al. Nature (2020) pmid: 32269342
324. Razavi P, et al. Nat. Med. (2019) pmid: 31768066