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 Colon adenocarcinoma (CRC)
NAME Li, Tien-Shih
DATE OF BIRTH 22 January 1959
SEX Male
MEDICAL RECORD # 46613278

PHYSICIAN

ORDERING PHYSICIAN Cheng, Hou-Hsuan
MEDICAL FACILITY Taipei Veterans General Hospital
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 205872
PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN SITE Colon
SPECIMEN ID S110-21825F (PF21013)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 03 September 2021
SPECIMEN RECEIVED 14 September 2021

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 4 Muts/Mb

Genomic Findings

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

BRAF V600E, amplification - equivocal†
MYC amplification
RNF43 A193fs*6
KEL amplification - equivocal†
KRAS wildtype
MTAP P41fs*20
NRAS wildtype
SMAD4 R361H
TP53 D228fs*1

2 Disease relevant genes with no reportable alterations: ***KRAS, NRAS***

† See About the Test in appendix for details.

8 Therapies with Clinical Benefit
0 Therapies with Resistance
17 Clinical Trials

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section
Tumor Mutational Burden - 4 Muts/Mb	**No therapies or clinical trials.** see Biomarker Findings section

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GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
BRAF **-** V600E, amplification - equivocal	Encorafenib + Cetuximab 2A	Dabrafenib
		Dabrafenib + Trametinib
		Encorafenib + Binimetinib
		Selumetinib
		Trametinib
		Vemurafenib
		Vemurafenib + Cobimetinib
10 Trials *see p. 16*		
MYC **-** amplification	none	none
4 Trials *see p. 18*		
RNF43 **-** A193fs*6	none	none
3 Trials *see p. 19*		

☐ *NCCN category*

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the 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.

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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]. For patients with chemotherapy-refractory metastatic colorectal cancer, 92% of which were MSS or MSI-Intermediate, a Phase 3 trial reported no OS advantage from the combination of the PD-L1 inhibitor atezolizumab plus cobimetinib relative to regorafenib (8.9 vs. 8.5 months, HR=1.00); atezolizumab monotherapy similarly did not prolong OS (7.1 vs. 8.5 months, HR=1.19)[6].

— Nontargeted Approaches —

MSI has not been found to be a predictive biomarker for combination chemotherapy regimens, including FOLFOX[7-8] and FOLFIRI[9-10]. Patients with MSS CRC are more likely to benefit from postsurgical fluorouracil (FU)-based adjuvant therapy[11-12] but less likely to benefit from irinotecan chemotherapy[13].

FREQUENCY & PROGNOSIS

MSS colorectal cancers (CRCs) make up 70-85% of CRC cases[3,14-18]. MSS colorectal cancers are molecularly heterogeneous, driven by diverse mechanisms such as extensive DNA methylation, oncogenic mutations in KRAS or BRAF, or chromosomal instability[18]. Multiple studies have shown that MSS CRCs have a worse prognosis than MSI-high tumors[14,19-25].

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[16]. 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[16,26-27]. 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[15,28-29]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[15-16,27,29].

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BIOMARKER

Tumor Mutational Burden

RESULT
4 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[30-32], anti-PD-1 therapies[30-33], and combination nivolumab and ipilimumab[34-39]. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors[30-33,40]. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment for patients with 9 types of advanced tumors[30]. 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[41] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[31]. However, the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors found significant improvement in ORR for patients with TMB ≥10 Muts/Mb (based on this assay or others) compared to those with TMB <10 Muts/Mb, in a large cohort that included multiple tumor types; similar findings were observed in the KEYNOTE 028 and 012 trials[33,40]. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors. In CRC specifically, a retrospective analysis of immune checkpoint inhibitor efficacy reported significantly improved OS for patients with tumors harboring TMB ≥9.8 Muts/MB compared with those with tumors with TMB <9.8 Muts/Mb (~ equivalency <12 Muts/Mb as measured by this assay)[30]. Another retrospective study reported that a TMB ≥12 Muts/Mb cutoff identifies >99% of MSI-High CRC cases but only 3% of MSS cases, indicating the utility of this cutoff for identification of patients with CRC likely to benefit from treatment with immune checkpoint inhibitors[42].

FREQUENCY & PROGNOSIS

Elevated TMB has been reported in 8-25% of colorectal cancer (CRC) samples[17,43-45]. Multiple studies have reported that the majority (up to 90%) of hypermutant CRC cases exhibit high levels of microsatellite instability (MSI-H) and mismatch repair deficiency (MMR-D)[17,45]. Increased TMB is significantly associated with MSI-H and MMR-D, with studies reporting that 100% of MSI-H CRCs harbor elevated TMB and, conversely, that 100% of tumors with low TMB harbor intact MMR[43-45]. A subset of CRCs that harbor increased TMB but not MSI-H are driven by mutations in POLE, which lead to an "ultramutated" phenotype with especially high TMB[17,45]. Tumors with increased TMB harbor BRAF V600E mutations more frequently than those with low TMB[17,45], whereas TMB-low tumors more frequently harbor mutations in TP53 and APC[17]. In a study for 61 patients with metastatic, microsatellite stable (MSS) CRC treated with best standard of care, plasma TMB scores ≥28 muts/Mb (approximately 14 muts/Mb as measured by this assay) were associated with reduced OS as compared with plasma TMB scores <28 muts/Mb (3.0 vs. 5.3 months, HR 0.76, p=0.007), whereas tissue TMB was not found to be prognostic in this population[46].

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[47-48] and cigarette smoke in lung cancer[49-50], treatment with temozolomide-based chemotherapy in glioma[51-52], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[17,53-56], and microsatellite instability (MSI)[17,53,56]. This sample harbors a TMB below levels that 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[30,40,42].

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GENE
BRAF

ALTERATION
V600E, amplification - equivocal

TRANSCRIPT ID
NM_004333

CODING SEQUENCE EFFECT
1799T>A

VARIANT ALLELE FREQUENCY (% VAF)
38.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Significant benefit for patients with BRAF V600-mutated colorectal cancers (CRC) has been achieved with combinatorial approaches involving BRAF inhibitors, EGF-targeting antibodies, and MEK inhibitors[57-60]. In a Phase 3 study for patients with metastatic CRC on second- or third-line treatments, doublet therapy with the RAF inhibitor encorafenib and the EGFR antibody cetuximab showed superior mOS to cetuximab plus chemotherapy (9.3 vs. 5.9 months, HR=0.61, n=220 and n=221), and similar benefit was seen for a triplet therapy cohort adding the MEK inhibitor binimetinib (OS of 9.3 months, n=224)[61]. Combinations of other RAF inhibitors such as dabrafenib or vemurafenib with EGFR antibodies such as panitumumab have also resulted in clinical benefit for similar patient populations in Phase 1 and 2 studies. A trial of dabrafenib and panitumumab with or without the MEK inhibitor trametinib reported a 21% ORR and 86% DCR (n=91) for the triplet combination and a 10% ORR and 90% DCR (n=20) for the doublet therapy[57]. Multiple similar studies of vemurafenib with panitumumab or cetuximab doublet therapy have also reported a benefit[58-59]. In a randomized Phase 2 study for patients with 0-4 previous lines of therapy, the addition of vemurafenib to cetuximab and irinotecan significantly improved ORR (17% vs. 4.2%, n=50 and n=50) and DCR (65% vs. 21%)[60]. A Phase 2 trial evaluating the investigational agent spartalizumab, an anti-PD-1 antibody, with dabrafenib and trametinib reported an ORR of 35% (n=20) and DCR of 75%[62]. Extensive clinical evidence also supports a significant benefit in BRAF-inhibitor and MEK-inhibitor doublet therapy for patients with BRAF V600E-mutated metastatic CRC. A Phase 2 study of vemurafenib plus cobimetinib for patients with advanced BRAF V600E-mutated CRC reported an ORR of 29% (n=28) and DCR of 57%[63], and a similar trial of dabrafenib and trametinib reported a 12% ORR (n=43) and 67% DCR[64]. A basket trial of the combination of encorafenib and binimetinib for patients with BRAF V600-mutated solid cancers elicited 1 PR and 1 SD for 3 patients with CRC[65]. Outcomes for patients with BRAF amplifications have been studied almost exclusively in the context of concurrent activating alterations and resistance mechanisms[66-68]; the evidence that BRAF amplification without a concurrent activating mutation is responsive to BRAF-pathway-targeting MEK or RAF inhibitors is very limited. A patient with triple-negative breast cancer with a high-level BRAF amplification and loss of PTEN and INPP4B achieved a major response to a combination of a MEK inhibitor and an AKT inhibitor[69]. Investigational ERK[70] and second-generation BRAF inhibitors[71] are also in development; however, it is uncertain whether these strategies would be of benefit for patients with BRAF amplifications.

— Potential Resistance —

On the basis of extensive clinical data, BRAF V600 mutation does not generally associate with significant clinical benefit from addition of cetuximab or panitumumab to chemotherapy (NCCN Colon Cancer Guidelines, v2.2021)[72-81]. Low response rates to cetuximab or panitumumab monotherapy or combination with chemotherapy have been frequently observed among patients with BRAF V600-mutated CRC, although similarly low response rates in this patient population were also often observed to chemotherapy alone; additionally, response rates were generally lower for patients with BRAF-mutated tumors than for those whose tumors were BRAF-wild-type[74,77-78,81-84]. In a limited number of patients with CRC treated with cetuximab- or panitumumab-containing chemotherapy regimens, BRAF V600E was found to be present at the time of progression[85-90], to be a mechanism of acquired[91-92] or primary[93] resistance, or to be enriched in nonresponders versus responders[88].

FREQUENCY & PROGNOSIS

BRAF mutations have been reported in approximately 5-19% of colorectal cancer samples[82,94-97]. BRAF V600E is a strong adverse prognostic marker in colorectal cancer (NCCN Colon Cancer Guidelines, v2.2021). BRAF mutations have been associated with poor prognosis and shorter survival in patients with colorectal cancer, particularly those with metastatic disease, as well as with smoking history[8,74,76,98-104]. Analysis of individual BRAF mutations in 2127 patients with advanced colorectal cancer treated with chemotherapy with or without cetuximab revealed that BRAF V600E associated with poor prognosis (HR 2.60, P=1.0e-15, with median reduction of survival being 320 days) and distinct clinicopathological features, including correlation with increased peritoneal metastases compared to BRAF wild-type tumors (24% vs. 12%, P=0.0015), while BRAF D594G inactivating mutation was not prognostic (HR 1.30, P=0.37) and had similar clinicopathologic features as BRAF wild-type tumors[105].

FINDING SUMMARY

BRAF encodes a member of the RAF family of protein kinases, which includes ARAF, BRAF, and CRAF. These kinases function downstream of RAS as part of the MAPK (RAF-MEK-ERK) signaling cascade that facilitates cell proliferation, survival and transformation[106-107]. BRAF mutations have been reported in up to 20% of all cancers, with the majority of mutations occurring at the V600 position[108-109]. BRAF amplification has been reported and correlated with overexpression of the BRAF protein in various tumor types[110-113]. Among the V600 mutations, V600E accounts for 70-80% of observations, V600K for 10-30%, and V600R for 5-7%, with V600D comprising the majority of the rest[108,114-115]. Mutations at V600 have been shown to constitutively activate BRAF kinase and hyperactivate the downstream MEK-ERK signaling, promoting oncogenic transformation[108,116]. In multiple cancer types, multiple mutations at V600, including V600E, V600K, V600R, V600D, and V600M exhibited sensitivity to V600-targeted therapies[115,117-127]; other mutations at this position are predicted to behave similarly.

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GENE
MYC

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no available therapies that directly target MYC. However, preclinical data indicate that MYC overexpression may predict sensitivity to investigational agents targeting CDK1[128-129], CDK2[130], Aurora kinase A[131-138], Aurora kinase B[139-142], glutaminase[143-146], or BET bromodomain-containing proteins[147-150], as well as agents targeting both HDAC and PI3K[151-153]. A Phase 2 study reported a PFS benefit associated with a combination of the Aurora A kinase inhibitor alisertib and paclitaxel as second-line therapy for patients with MYC-overexpressed small cell lung cancer but not for patients without MYC overexpression[154]. A patient with MYC-amplified invasive ductal breast carcinoma experienced a PR to an Aurora kinase inhibitor[155]. The glutaminase inhibitor CB-839, in combination with either everolimus or cabozantinib, has demonstrated encouraging efficacy in Phase 1 and 2 studies enrolling patients with pretreated advanced renal cell carcinoma[156-157] .

— Nontargeted Approaches —

MYC amplification has also been suggested to predict response to chemotherapy in patients with breast cancer in some studies[158-159]. Preclinical evidence suggests that colon cancer cells with MYC amplification may be more sensitive to 5-fluorouracil and paclitaxel[160-161].

FREQUENCY & PROGNOSIS

Mutation and amplification of MYC have been observed in up to 2% and 5% of patients with colorectal cancer, respectively (cBioPortal, COSMIC, Sep 2021)[110,162-163]. Overexpression of MYC in colorectal carcinoma has been reported to occur in the absence of MYC amplification[164-166].

MYC is a target gene of beta-catenin and may be upregulated by aberrant WNT signaling in colorectal cancer[167]. MYC overexpression has been reported in 62-91% of colorectal carcinomas studied[164,166,168-169]. MYC protein overexpression was reported to be a favorable prognostic biomarker in patients with colorectal cancer, and patients with low-level MYC amplification have been found to have significantly longer survival[169-170]. However, MYC amplification and high expression have been associated with metastatic and aggressive colorectal tumors[166,171].

FINDING SUMMARY

MYC (c-MYC) encodes a transcription factor that regulates many genes related to cell cycle regulation and cell growth. It is an oncogene and may be activated in as many as 20% of cancers[172]. MYC dysregulation (amplification, overexpression, translocation) has been identified in a number of different cancer types[173]. MYC amplification has been significantly linked with increased mRNA and protein levels and results in the dysregulation of a large number of target genes[172,174-175].

GENE
RNF43

ALTERATION
A193fs*6

TRANSCRIPT ID
NM_017763

CODING SEQUENCE EFFECT
575_576insC

VARIANT ALLELE FREQUENCY (% VAF)
38.0%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical studies have reported that RNF43 is a negative regulator of WNT signaling, and RNF43 loss or inactivation leads to WNT activation and confers sensitivity to WNT pathway inhibitors, particularly Porcupine inhibitors, in multiple tumor types[176-180]. Therefore, patients whose tumors harbor inactivating alterations in RNF43 may benefit from WNT pathway inhibitors, which are under investigation in clinical trials.

FREQUENCY & PROGNOSIS

Mutations in RNF43 have been reported in 18-27% of endometrial cancers[181-182], 3-5% of pancreatic cancers[183], 21% of ovarian mucinous carcinomas[184], 9% of liver fluke-associated cholangiocarcinomas[185], and up to 18% of colorectal cancers[17,182]. RNF43 mutations are associated with mismatch repair deficiency and microsatellite instability (MSI) in colorectal[182], endometrial[182], and gastric cancers[186-187]; one study reported RNF43 alterations in more than 50% of MSI gastric carcinomas[186].

FINDING SUMMARY

RNF43 encodes a ubiquitin ligase[188] that was discovered because it is overexpressed in colon cancer[189]. RNF43 and the homologous E3 ubiquitin ligase ZNRF3 are tumor suppressors that function as negative regulators of WNT signaling[176-180]. An additional tumor-suppressor-like role for RNF43 in colon cancer is hypothesized to occur via its interaction with the ubiquitin-protein ligase NEDL1, which is predicted to enhance the pro-apoptotic effects of p53[190].

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GENE
KEL

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies available to target genomic alterations in KEL.

FREQUENCY & PROGNOSIS

KEL mutations have been reported in tumors of the skin, lung, endometrium, stomach, large intestine, soft tissue, and liver at rates of 1.9-8.4%; up to 1.2% of acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and chronic lymphocytic leukemia-small lymphocytic lymphoma (CLL/SLL) samples (COSMIC, 2021)[163]. However, the mechanism by which KEL mutations contribute to tumor formation is not known.

FINDING SUMMARY

KEL encodes a transmembrane glycoprotein with similarities to zinc-dependent metalloproteases; this glycoprotein is highly polymorphic and forms the Kell blood group antigen[191].

GENE
KRAS

ALTERATION
wildtype

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Lack of mutations in KRAS or NRAS is associated with clinical benefit of treatment with EGFR-targeting antibodies cetuximab[74,192-194] or panitumumab[76,195-196] for patients with CRC. Therefore, these agents are indicated to treat patients with CRC lacking such mutations (NCCN Guidelines v2.2021).

FREQUENCY & PROGNOSIS

Approximately 50-65% of colorectal cancers (CRCs) have been reported to lack KRAS mutations[94,197-204]. Numerous studies have reported that KRAS wild-type status is associated with decreased metastasis, better clinicopathological features, and longer survival of patients with CRC[198-201,205-206].

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[207-208]. No alterations in KRAS were identified in this case.

GENE
MTAP

ALTERATION
P41fs*20

TRANSCRIPT ID
NM_002451

CODING SEQUENCE EFFECT
91_92insAAAAATATGTGGATACTCCATTTGGCAAGGTTAATATCCAACTTGTGGAGAC

VARIANT ALLELE FREQUENCY (% VAF)
9.8%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical and limited clinical evidence indicate that MTAP inactivation produces specific metabolic vulnerabilities. MTAP inactivation may confer sensitivity to MAT2A inhibitors[209]. A Phase 1 trial of MAT2A inhibitor AG-270 reported 1 PR and 2 SDs lasting longer than 6 months for patients with advanced solid tumors displaying MTAP loss[210]. Although preclinical data have suggested that MTAP loss sensitizes cells to PRMT5 inhibition[209,211-212], MTAP loss may not be a biomarker of response to previously developed small-molecule SAM-uncompetitive PRMT5 inhibitors[213]; dual PRMT1 and PRMT5 inhibition may be more effective[214-216]. In preclinical cancer models, MTAP inactivation showed increased sensitivity to inhibitors of purine synthesis or purine analogs, especially upon addition of exogenous MTA, which is converted to adenine in normal cells, thereby providing competition to purine poisons lacking in MTAP-deficient cells[217-227]. A Phase 2 study of L-alanosine, an inhibitor of adenine synthesis, as a monotherapy for 65 patients with MTAP-deficient cancers reported no responses and stable disease in 23.6% (13/55) of patients[228].

FREQUENCY & PROGNOSIS

MTAP loss/homozygous deletion as well as loss of expression has been reported in a wide variety of solid tumors and hematologic cancers[229-230]; such events have been correlated with poor prognosis in a variety of cancer types, including hepatocellular carcinoma[231], gastrointestinal stromal tumors[232], mantle cell lymphoma (MCL)[233], melanoma[234-235], gastric cancer[236], myxofibrosarcoma[237], nasopharyngeal carcinoma[238], ovarian carcinoma[229] and non-small cell lung cancer[239]. MTAP loss was not prognostic in pediatric B-cell acute lymphocytic leukemia[240] or in astrocytoma[241]. However, MTAP has also been reported to be overexpressed in colorectal cancer (CRC) samples[242], and MTAP retention is thought to be important for prostate cancer growth due to continuous supply of SAM[243]. Germline SNPs in MTAP have been correlated with the development of cutaneous melanoma[244-245], esophageal cancer[246-247], osteosarcoma[248], and CRC[249].

FINDING SUMMARY

MTAP encodes S-methyl-5'-thioadenosine (MTA) phosphorylase, a tumor suppressor involved in polyamine metabolism and methionine synthesis, although its enzymatic function is dispensable for its tumor suppressor activity[250-251]. Decreased expression of MTAP leads to MTA accumulation within tumor cells and their microenvironment[231,252-253], thereby reducing intracellular arginine methylation[209,211,254] and altering cell signaling[253,255]. MTAP is located at 9p21, adjacent to CDKN2A and CDKN2B, with which it is frequently co-deleted in various cancers. Other alterations in MTAP are rare and have not been extensively characterized.

GENE
NRAS

ALTERATION
wildtype

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Lack of mutations in KRAS or NRAS is associated with clinical benefit of treatment with EGFR-targeting antibodies cetuximab[74,192-194] or panitumumab[76,195-196] for patients with CRC. Therefore, these agents are indicated to treat patients with CRC lacking such mutations (NCCN Guidelines v2.2021).

FREQUENCY & PROGNOSIS

The majority of colorectal cancers (CRCs) (91-98%) have been reported to lack NRAS mutations[17,204,256-261]. NRAS wild-type status has been reported to be associated with decreased frequency of metastasis[204] and longer survival[261-262] of patients with CRC.

FINDING SUMMARY

NRAS encodes a member of the RAS family of small GTPases that mediate transduction of growth signals. Activation of RAS signaling causes cell growth, differentiation, and survival by activating the RAF-MAPK-ERK, PI3K, and other pathways[207]. No alterations in NRAS were identified in this case.

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GENE
SMAD4

ALTERATION
R361H

TRANSCRIPT ID
NM_005359

CODING SEQUENCE EFFECT
1082G>A

VARIANT ALLELE FREQUENCY (% VAF)
26.9%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies to address SMAD4 alterations in cancer. Preclinical studies[263-264] and a clinical study of pancreatic cancer suggest that low SMAD4 expression exhibit increased responsiveness to chemotherapeutic agents such as cisplatin and irinotecan[265].

FREQUENCY & PROGNOSIS

SMAD4 mutation or homozygous deletion is most frequently observed in pancreatic adenocarcinoma (43%)[266], pancreatic acinar cell carcinoma[267], cholangiocarcinoma (25%)[268], appendiceal adenocarcinoma (14-20% mutation; 57% deletion)[269-270], colorectal adenocarcinoma (CRC; 14%)[17], esophageal adenocarcinoma (14%)[271], and stomach adenocarcinoma (13%)[187]. In preclinical studies, SMAD4 loss of function has been implicated in the development of mucinous neoplasms of the pancreas, including mucinous cystic neoplasms (MCN)[272] and intraductal papillary mucinous neoplasms (IPMN)[273]; in clinical samples, SMAD4 homozygous deletion has been observed in 10% of IPMNs and 8% of MCNs, and mutation was also observed in 5% of IPMNs[274]. SMAD4 gene alterations have been associated with reduced overall survival for patients with pancreatic adenocarcinoma[275]. Reduced SMAD4 expression has been associated with worse prognosis in various cancer types, including CRC[276-278], appendiceal mucinous neoplasm[279], gastric adenocarcinoma[280-281], esophageal adenocarcinoma[282], esophageal squamous cell carcinoma[283], breast cancer[284], and prostate cancer[285].

FINDING SUMMARY

SMAD4, also known as DPC4, encodes a tumor suppressor that regulates transcriptional activity downstream of TGF-beta receptor signaling[286-287]. SMAD4 alterations that result in loss or disruption of the MH1 domain (aa 18-142), MH2 domain (aa 323-552), or SAD domain (aa 275-320) are predicted to be inactivating[288-301].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the SMAD4 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 juvenile polyposis syndrome (ClinVar, Mar 2021)[302]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline SMAD4 mutations, including those at the R361 hotspot, have been observed in patients with juvenile polyposis syndrome[303-305], which is associated with an increased risk of gastrointestinal cancers[306]. The penetrance of deleterious SMAD4 mutations in patients with colon cancer is estimated at 20% by age 35 and 70% by age 65[307]. In the appropriate clinical context, germline testing of SMAD4 is recommended.

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GENE
TP53

ALTERATION
D228fs*1

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
681_682insT

VARIANT ALLELE FREQUENCY (% VAF)
38.4%

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[308-311], or p53 gene therapy and immunotherapeutics such as SGT-53[312-316] and ALT-801[317]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% (17/176) and SDs in 53.4% (94/176) of patients with solid tumors; the response rate was 21.1% (4/19) in patients with TP53 mutations versus 12.1% (4/33) in patients who were TP53 wild-type[318]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 31.9% (30/94, 3 CR) ORR and a 73.4% (69/94) DCR in patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[319]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 42.9% (9/21, 1 CR) ORR and a 76.2% (16/21) DCR in patients with platinum-refractory TP53-mutated ovarian cancer[320]. The combination of adavosertib with paclitaxel and carboplatin in patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[321]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24.0% (6/25) ORR with adavosertib combined with paclitaxel[322]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71.4% (5/7) response rate for patients with TP53 alterations[323]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel in patients with solid tumors, 75.0% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[316]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutated, but not TP53-wild-type, breast cancer xenotransplant mouse model[324]. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies[325-326]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[327-328]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

TP53 mutations have been reported in up to 60% of colorectal cancer cases[17,78,329-333]. A study reported p53 expression in 49% of analyzed colorectal cancer cases[334]. TP53 mutation has not been consistently demonstrated to be a significant independent prognostic marker in the context of CRC[335].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[336]. Alterations such as seen here may disrupt TP53 function or expression[337-341].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[342-344], including sarcomas[345-346]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[347] to 1:20,000[346]. 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[348]. 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[349-354]. 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[349-350]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[355]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[353,356-357]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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Encorafenib + Cetuximab

Assay findings association

BRAF
V600E, amplification - equivocal

AREAS OF THERAPEUTIC USE

Encorafenib is an inhibitor of BRAF, and cetuximab is a monoclonal antibody that targets EGFR. The combination is FDA approved to treat patients with BRAF V600E-mutated colorectal cancer (CRC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

Patients with BRAF V600-mutated CRC are considered unlikely to benefit from cetuximab, alone or in combination with chemotherapy, unless combined with BRAF inhibitors (NCCN Guidelines, Colon Cancer, v.2.2020). Response rates to cetuximab, both as monotherapy and in combination with chemotherapy, have generally been found to be low for patients with BRAF V600-mutated CRC, independent of treatment line and chemotherapy backbone[74,77,82-84,86,90,104,259,358-362] . However, significant clinical responses have been reported for patients with BRAF V600-mutated CRC treated with cetuximab in combination with the BRAF inhibitor vemurafenib[58], the 2 in combination with irinotecan[363], or cetuximab in combination with BRAF inhibitor encorafenib[364-365] .

SUPPORTING DATA

The Phase 3 BEACON study for previously treated patients with BRAF V600E-mutated metastatic colorectal cancer (CRC) demonstrated significantly improved efficacy of encorafenib and cetuximab doublet therapy over standard irinotecan and cetuximab therapy (median OS [mOS] of 9.3 vs. 5.9 months, HR=0.61; median PFS [mPFS] of 4.3 vs. 1.5 months, HR=0.44; and ORR of 19.5% vs. 1.8%)[364,366] . The triplet therapy of encorafenib and cetuximab combined with the MEK inhibitor binimetinib resulted in similar efficacy as the doublet therapy, compared with standard therapy in the BEACON study (mOS of 9.3 vs. 5.9 months, HR=0.60; mPFS of 4.5 vs. 1.5 months, HR=0.42; and ORR of 26.8% vs. 1.8%)[366].

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Dabrafenib

Assay findings association

BRAF
V600E, amplification - equivocal

AREAS OF THERAPEUTIC USE

Dabrafenib is a BRAF V600-selective inhibitor that is FDA approved as a monotherapy to treat melanoma with BRAF V600E or V600K mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Mutations at BRAF V600, including V600E, V600K, V600R, V600D, and V600M, have been reported to exhibit clinical sensitivity to V600-targeted therapies[115,117-126,367] ; therefore, this tumor may be sensitive to V600-targeted therapy such as dabrafenib.

SUPPORTING DATA

Dabrafenib and vemurafenib have primarily been studied in the context of BRAF V600E-positive melanoma and NSCLC[115,117-126,367] . Clinical trials of single-agent dabrafenib for the treatment of BRAF-mutated colorectal cancers (CRCs) have shown a very low frequency of objective responses[95,368-369] , but combination regimens with other agents have shown improved efficacy. In patients with BRAF V600E-mutated CRC, a combination of dabrafenib and panitumumab resulted in an ORR of 10% (2/20)[370]. Dabrafenib can induce adverse effects such as the development of cutaneous squamous cell carcinomas and keratoacanthomas caused by inactivation of wildtype BRAF that leads to paradoxical activation of the MAPK pathway, but it has been reported to be well tolerated in patients with BRAF V600E-mutated thyroid cancer[117,371-372] . Patients with melanoma harboring BRAF V600E or V600K mutation treated with a combination of dabrafenib and trametinib experienced significantly lower rates of cutaneous squamous cell carcinoma and regression of established BRAF inhibitor-induced skin lesions[373-377] .

Dabrafenib + Trametinib

Assay findings association

BRAF
V600E, amplification - equivocal

AREAS OF THERAPEUTIC USE

Dabrafenib is a BRAF V600-selective inhibitor and trametinib is a MEK inhibitor. These two therapies are FDA approved in combination to treat patients with melanoma with BRAF V600E or BRAF V600K mutations. This combination is also approved to treat patients with non-small cell lung cancer (NSCLC) with a BRAF V600E mutation, and to treat patients with BRAF V600E-positive anaplastic thyroid cancer (ATC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in various solid tumors and hematologic malignancies, BRAF activating alterations may confer sensitivity to the combination of BRAF V600-targeted therapies and MEK inhibitors such as dabrafenib and trametinib[64,376-383] .

SUPPORTING DATA

The combination of BRAF inhibitors with MEK inhibitors has shown clinical activity for patients with BRAF V600-mutated metastatic colorectal carcinoma (mCRC). A Phase 1/2 open-label trial combining dabrafenib and trametinib for BRAF V600-mutated mCRC reported an ORR of 12% (5/43, including 1 CR with a response duration >36 months)[64]. For patients with BRAF V600E-mutated mCRC, a combination of dabrafenib, trametinib, and panitumumab resulted in an ORR of 26% (9/35)[370]. A Phase 2 trial evaluating dabrafenib and trametinib in combination with the anti-PD-1 immune checkpoint inhibitor spartalizumab reported an ORR of 33% (7/21) for patients with BRAF V600-mutated mCRC, with a median duration of response of 5.6 months[62]. One case report describes a patient with colon adenocarcinoma who responded to a combination of dabrafenib, trametinib, and oxaliplatin[384]. Dabrafenib can induce adverse effects such as the development of cutaneous squamous cell carcinomas and keratoacanthomas caused by inactivation of wildtype BRAF that leads to paradoxical activation of the MAPK pathway, but it has been reported to be well tolerated in patients with BRAF V600E-mutated thyroid cancer[117,371-372] . Patients with melanoma harboring BRAF V600E or V600K mutation treated with a combination of dabrafenib and trametinib experienced significantly lower rates of cutaneous squamous cell carcinoma and regression of established BRAF inhibitor-induced skin lesions[373-377] .

Encorafenib + Binimetinib

Assay findings association

BRAF
V600E, amplification - equivocal

AREAS OF THERAPEUTIC USE

The combination of the BRAF inhibitor encorafenib and MEK inhibitor binimetinib is FDA approved to treat patients with melanoma with BRAF V600E or BRAF V600K mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical efficacy in the treatment of patients with BRAF V600-mutated melanoma[385-388] , and activity in colorectal, thyroid, and lung cancer[388-390] , activating alterations affecting BRAF predict sensitivity to the combination of encorafenib and binimetinib.

SUPPORTING DATA

A Phase 1/2 trial of encorafenib combined with binimetinib for patients with BRAF V600E- or BRAF V600K-mutated solid tumors reported an ORR of 18.2% (2/11) for the subset of patients with metastatic colorectal cancer[388]. The combination of encorafenib and binimetinib has been reported to provide clinical benefit for patients with various solid tumors harboring BRAF V600 activating alterations[385,388-390] , and has been studied primarily in the context of BRAF V600-mutated melanoma where patients treated with this combination achieved greater PFS and OS compared with encorafenib or vemurafenib monotherapy[385-386,391] . A combination of encorafenib, binimetinib, and the CDK4/6 inhibitor ribociclib in a Phase 1b trial for patients with BRAF V600-mutant cancers elicited responses in melanoma, astrocytoma, unknown carcinoma, and in 1 of 3 patients with colorectal cancer; a Phase 2 study of this combination in V600-mutant melanoma reported an ORR of 52.4% (22/42), including 5 CRs, median PFS of 9.2 months, and median OS of 19.4 months[65].

Selumetinib

Assay findings association

BRAF
V600E, amplification - equivocal

AREAS OF THERAPEUTIC USE

Selumetinib is a MEK inhibitor that is FDA approved to treat pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PNs). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence demonstrating the efficacy of selumetinib in patients with BRAF V600-mutated papillary thyroid cancer[392], melanoma,[393-397] and low grade glioma[398], as well as in patients with BRAF fusion-positive glioma[398-399] , BRAF activating alterations may predict sensitivity to selumetinib.

SUPPORTING DATA

A Phase 2 study for selumetinib in patients with CRC showed similar efficacy (10/34 SD) to capecitabine (1/35 PR and 15/35 SD) and a median PFS of 81 days and 88 days, respectively[400]. A Phase 2 study evaluating the combination of MK-2206, an allosteric AKT 1/2/3 inhibitor, and selumetinib, did not report objective responses for 21 CRC patients[401]. The combination of selumetinib plus irinotecan has been evaluated in a Phase 2 study for patients with KRAS-mutated CRC and achieved 3/31 PR and 16/21 SD[402]. A Phase 1 study for selumetinib in patients with advanced solid tumors reported 1/15 PR and 3/15 SD, followed by 5/18 SD in an extended cohort of KRAS-mutated CRC patients[403], and an additional Phase 1 study evaluating the combination of selumetinib with rectal chemoradiotherapy (CRT) for CRC patients reported a low tolerance[404].

Trametinib

Assay findings association

BRAF
V600E, amplification - equivocal

AREAS OF THERAPEUTIC USE

Trametinib is a MEK inhibitor that is FDA approved as a monotherapy to treat patients with melanoma with BRAF V600E or V600K mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Activating BRAF alterations may predict sensitivity to MEK inhibitors such as trametinib. Significant clinical responses to trametinib have been achieved by patients with melanoma harboring BRAF V600E[405-406], V600K[405], V600R[406], K601E[406-407], L597V[405], L597Q[407-408], or L597S[409] mutations; by a patient with histiocytosis harboring an activating N486_P490del alteration[127]; as well as by patients with tumors harboring BRAF fusions[410-415].

SUPPORTING DATA

Preclinical studies have reported that trametinib shows some activity in colorectal cancer (CRC) cells alone and enhances antitumor effects in cells treated with 5-fluorouracil[416-417]. In addition, preclinical investigations have shown sensitivity to trametinib in cell lines with activating KRAS mutations in codons 12, 13, and 61[418]. Phase 1 and Phase 1b studies of trametinib, alone or in combination with gemcitabine, reported some activity in several types of solid tumors[419-420]. However, Phase 1 monotherapy trials of RO4987655, another MEK inhibitor, have shown no responses and only 1 incidence of stable disease in 31 evaluable patients with CRC, including an expansion cohort of 24 patients with KRAS mutations[421-422]. In contrast, a trial of combination treatment with selumetinib (another MEK inhibitor) and irinotecan in patients with KRAS-mutated CRC reported confirmed partial responses (PR) in 3/31 (10%) patients, an unconfirmed PR in one patient (3%), and stable disease in 15/31 (48%) patients, improving upon historical clinical trial data of irinotecan single-agent treatment; longer progression-free survival compared to historical controls was also achieved[423]. A Phase 1b trial of combination treatment with the MEK inhibitor MEK162 and the PI3K-alpha inhibitor BYL719 reported stable disease in 43% of patients with KRAS-mutated CRC, with responses independent of PIK3CA mutation status[424]. Another Phase 1b combination trial of trametinib and the CDK4/6 inhibitor palbociclib in solid tumors observed ongoing partial responses in 2/28 (7%) of patients, including one patient with CRC harboring a NRAS Q61K mutation[425]. Although the presence of a KRAS mutation in CRC has been associated with lack of efficacy to monotherapy MEK inhibitors[400,420,422,426], the extent to which other alterations affecting this pathway, such as observed here, confers sensitivity to MEK inhibitors is unclear[427]. 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[428], 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[429].

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Vemurafenib

Assay findings association

BRAF
V600E, amplification - equivocal

AREAS OF THERAPEUTIC USE

Vemurafenib is a selective inhibitor of BRAF with V600 mutations and is FDA approved to treat melanoma as monotherapy for patients with the BRAF V600E mutation. It is also approved to treat patients with Erdheim-Chester Disease (ECD) with BRAF V600 mutation. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of strong clinical data, BRAF V600E mutations may confer sensitivity to V600-targeted therapies such as vemurafenib[58,118-119,124,430-435] .

SUPPORTING DATA

Vemurafenib monotherapy in patients with BRAF V600-mutated colorectal cancer (CRC) has shown limited efficacy[58,436-437] . A study of vemurafenib plus panitumumab reported an ORR of 13% (2/15), median PFS of 3.2 months, and median OS of 7.6 months[59], whereas a study of vemurafenib plus cetuximab reported an ORR of 3.7% (1/27), median PFS of 3.7 months, and median OS of 7.1 months[58]. In a randomized Phase 2 study of cetuximab and irinotecan with or without vemurafenib for patients with BRAF V600-mutated, RAS-wildtype metastatic CRC, the addition of vemurafenib improved median PFS (4.4 vs. 2.0 months, HR=0.42) and ORR (16% vs. 4.2%, p=0.08)[438-439] . Dabrafenib and vemurafenib have primarily been studied in the context of BRAF V600E-positive melanoma and NSCLC[115,117-126,367] . Vemurafenib can induce adverse effects, such as the development of cutaneous squamous cell carcinomas, keratoacanthomas, and new primary melanomas caused by inactivation of wildtype BRAF and leading to paradoxical activation of the MAPK pathway[118,371] . In a Phase 1b trial, patients with BRAF V600E-mutated melanoma treated with a combination of vemurafenib and cobimetinib had increased RR (87%) and PFS (13.7 months) compared to the RR and PFS values previously reported for vemurafenib or MEK inhibitor monotherapy; this combination also resulted in lower rates of cutaneous SCC[440].

Vemurafenib + Cobimetinib

Assay findings association

BRAF
V600E, amplification - equivocal

AREAS OF THERAPEUTIC USE

Vemurafenib is a selective inhibitor of BRAF with V600 mutations and cobimetinib is a MEK inhibitor. The combination is FDA approved to treat patients with melanoma with BRAF V600E or V600K mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in melanoma and colorectal carcinoma, BRAF activating alterations may confer sensitivity to the combination of BRAF V600-targeted therapies and MEK inhibitors such as vemurafenib and cobimetinib[63,441-442] .

SUPPORTING DATA

The Phase 2 TAPUR study of vemurafenib plus cobimetinib for patients with advanced BRAF V600E-mutated CRC reported an ORR of 28.6% (8/28), median PFS of 15.8 weeks, and median OS of 38.9 weeks[63]. Vemurafenib can induce adverse effects, such as the development of cutaneous squamous cell carcinomas, keratoacanthomas, and new primary melanomas caused by inactivation of wildtype BRAF and leading to paradoxical activation of the MAPK pathway[118,371] . In a Phase 1b trial, patients with BRAF V600E-mutated melanoma treated with a combination of vemurafenib and cobimetinib had increased RR (87%) and PFS (13.7 months) compared to the RR and PFS values previously reported for vemurafenib or MEK inhibitor monotherapy; this combination also resulted in lower rates of cutaneous SCC[440].

NOTE Genomic alterations detected may be associated with activity of certain FDA approved drugs, however, the agents listed in this report may have varied evidence in the patient's tumor type.

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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

BRAF

ALTERATION

V600E, amplification - equivocal

RATIONALE

BRAF activating alterations may predict sensitivity to inhibitors of BRAF, MEK, or ERK. Response rates to cetuximab or panitumumab, as monotherapies or in combination with chemotherapy, have generally been found to be low for patients with BRAF V600-mutated CRC; however, improved clinical benefit has been reported from combinations of these EGFR antibodies with BRAF inhibitors, alone or in combination with inhibitors of MEK or PI3K-alpha.

NCT03239015

PHASE 2

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

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

LOCATIONS: Shanghai (China)

NCT03727763

PHASE 2

FIVC in Advanced Colorectal Cancer Patients With BRAF V600E Mutation.

TARGETS
EGFR, BRAF

LOCATIONS: Shanghai (China)

NCT03781219

PHASE 1

A Phasel Study of HL-085 Plus Vemurafenib in Solid Tumor With BRAF V600 Mutation

TARGETS
MEK, BRAF

LOCATIONS: Hangzhou (China), Zhengzhou (China), Beijing (China)

NCT04607421

PHASE 3

BRAF V600E-mutant Colorectal Cancer Study of Encorafenib Taken With Cetuximab Plus or Minus Chemotherapy (BREAKWATER)

TARGETS
VEGFA, BRAF, EGFR, MEK

LOCATIONS: Seoul (Korea, Republic of), Nagoya (Japan), Kashiwa (Japan), Herston (Australia), Adelaide (Australia), Melbourne (Australia), Clayton (Australia), Padova (Italy), Utrecht (Netherlands), Barcelona (Spain)

NCT04790448

PHASE 1/2

Efficacy of VIC Regimen in BRAF Mutant Metastatic Colorectal Cancer

TARGETS
EGFR, BRAF, TOP1

LOCATIONS: Guangzhou (China)

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT03989115

PHASE 1/2

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

TARGETS
SHP2, MEK

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

NCT03284502

PHASE 1

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

TARGETS
MEK, RAFs

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

NCT04294160

PHASE 1

A Study of Select Drug Combinations in Adult Patients With Advanced/Metastatic BRAF V600 Colorectal Cancer

TARGETS
ERK1, ERK2, SHP2, ARAF, BRAF, MEK, PD-1

LOCATIONS: Singapore (Singapore), Westmead (Australia), Tel Aviv (Israel), Dresden (Germany), Essen (Germany), Ulm (Germany), Amsterdam (Netherlands), Leuven (Belgium), Bruxelles (Belgium), Manchester (United Kingdom)

NCT04801966

PHASE NULL

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

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

LOCATIONS: Melbourne (Australia)

GENE
MYC

ALTERATION
amplification

RATIONALE
MYC overexpression may predict sensitivity to inhibition of CDKs, especially CDK1 and CDK2, of Aurora kinases, including Aurora kinase A and B, and of BET domain proteins, which are reported to downregulate MYC expression and MYC-dependent transcriptional programs.

NCT03220347

PHASE 1

A Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of CC-90010 in Subjects With Advanced Solid Tumors and Relapsed/Refractory Non-Hodgkin's Lymphomas

TARGETS
BRD2, BRD3, BRD4, BRDT

LOCATIONS: Kashiwa (Japan), Meldola (Italy), Napoli, Campania (Italy), Rozzano (MI) (Italy), Villejuif (France), Bordeaux (France), Barcelona (Spain), Madrid (Spain)

NCT03297424

PHASE 1/2

A Study of PLX2853 in Advanced Malignancies.

TARGETS
BRD4

LOCATIONS: Arizona, New York, Texas, Virginia, Florida

NCT04555837

PHASE 1/2

Alisertib and Pembrolizumab for the Treatment of Patients With Rb-deficient Head and Neck Squamous Cell Cancer

TARGETS
Aurora kinase A, PD-1

LOCATIONS: Texas

NCT01434316

PHASE 1

Veliparib and Dinaciclib in Treating Patients With Advanced Solid Tumors

TARGETS
PARP, CDK1, CDK2, CDK5, CDK9

LOCATIONS: Massachusetts

GENE
RNF43

ALTERATION
A193fs*6

RATIONALE
Based on preclinical evidence, tumors with loss or inactivation of RNF43 may be sensitive to inhibitors of the WNT signaling pathway.

NCT02521844

PHASE 1

A Study to Evaluate the Safety and Tolerability of ETC-1922159 in Advanced Solid Tumours

TARGETS
PORCN

LOCATIONS: Singapore (Singapore), Colorado, Missouri, Texas, North Carolina

NCT01351103

PHASE 1

A Study of LGK974 in Patients With Malignancies Dependent on Wnt Ligands

TARGETS
PORCN, PD-1

LOCATIONS: Utrecht (Netherlands), Rotterdam (Netherlands), Barcelona (Spain), Hospitalet de LLobregat (Spain), Valencia (Spain), Madrid (Spain), California, Michigan, Massachusetts, New York

NCT03447470

PHASE 1

Study to Evaluate the Safety and Tolerability of RXC004 in Advanced Malignancies

TARGETS
PORCN

LOCATIONS: Newcastle (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom)

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.

CASP8
rearrangement

ERCC4
E145K

HNF1A
T82M

IRS2
Q1269P

LYN
amplification

MAP2K2 (MEK2)
P298L

MTOR
T1834_T1837del

NBN
amplification

NTRK1
R49G

P2RY8
D162E

PMS2
V816M

RAD21
amplification

Electronically signed by J. Keith Killian, M.D. | 21 September 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
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APPENDIX Genes Assayed in FoundationOne®CDx

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)*	*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	*C11orf30 (EMSY)*	*C17orf39 (GID4)*	*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*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
FAM46C	*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*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*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*	*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*	*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*	*P2RY8*	*PALB2*
PARK2	*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*	*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*	*TET2*	*TGFBR2*	*TIPARP*	*TNFAIP3*	*TNFRSF14*	*TP53*
TSC1	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*	*VHL*	*WHSC1*	*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

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

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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 PRINCIPLES

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. 2021. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations

1. The MSI-H/MSS designation by FMI F1CDx test is based on genome wide analysis of 95 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines. The threshold for MSI-H/MSS was determined by analytical concordance to comparator assays (IHC and PCR) using uterine, cecum and colorectal cancer FFPE tissue. The clinical validity of the qualitative MSI designation has not been established. For Microsatellite Instability (MSI) results, confirmatory testing using a validated orthogonal method should be considered.
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. 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.
4. 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.
5. 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.
6. 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%.

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

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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

MR Suite Version 5.0.0

The median exon coverage for this sample is 896x

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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. Ciardiello et al., 2018; ESMO Abstract LBA-004
7. Sinicrope FA, et al. J. Clin. Oncol. (2013) pmid: 24019539
8. Gavin PG, et al. Clin. Cancer Res. (2012) pmid: 23045248
9. Bertagnolli MM, et al. J. Clin. Oncol. (2009) pmid: 19273709
10. Van Cutsem E, et al. J. Clin. Oncol. (2009) pmid: 19451425
11. Ribic CM, et al. N. Engl. J. Med. (2003) pmid: 12867608
12. Sargent DJ, et al. J. Clin. Oncol. (2010) pmid: 20498393
13. Fallik D, et al. Cancer Res. (2003) pmid: 14522894
14. Guastadisegni C, et al. Eur. J. Cancer (2010) pmid: 20627535
15. Pawlik TM, et al. Dis. Markers (2004) pmid: 15528785
16. Kocarnik JM, et al. Gastroenterol Rep (Oxf) (2015) pmid: 26337942
17. Nature (2012) pmid: 22810696
18. Histopathology (2007) pmid: 17204026
19. Samowitz WS, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11535541
20. Elsaleh H, et al. Clin Colorectal Cancer (2001) pmid: 12445368
21. Brueckl WM, et al. Anticancer Res. () pmid: 12820457
22. Guidoboni M, et al. Am. J. Pathol. (2001) pmid: 11438476
23. Gryfe R, et al. N. Engl. J. Med. (2000) pmid: 10631274
24. Sinicrope FA, et al. Gastroenterology (2006) pmid: 16952542
25. Laghi L, et al. Dig Dis (2012) pmid: 22722556
26. You JF, et al. Br. J. Cancer (2010) pmid: 21081928
27. Bairwa NK, et al. Methods Mol. Biol. (2014) pmid: 24623249
28. Boland CR, et al. Cancer Res. (1998) pmid: 9823339
29. Boland CR, et al. Gastroenterology (2010) pmid: 20420947
30. Samstein RM, et al. Nat. Genet. (2019) pmid: 30643254
31. Goodman AM, et al. Mol. Cancer Ther. (2017) pmid: 28835386
32. Goodman AM, et al. Cancer Immunol Res (2019) pmid: 31405947
33. Cristescu R, et al. Science (2018) pmid: 30309915
34. Ready N, et al. J. Clin. Oncol. (2019) pmid: 30785829
35. Hellmann MD, et al. N. Engl. J. Med. (2018) pmid: 29658845
36. Hellmann MD, et al. Cancer Cell (2018) pmid: 29657128
37. Hellmann MD, et al. Cancer Cell (2018) pmid: 29731394
38. Rozeman EA, et al. Nat Med (2021) pmid: 33558721
39. Sharma P, et al. Cancer Cell (2020) pmid: 32916128
40. Marabelle A, et al. Lancet Oncol. (2020) pmid: 32919526
41. Legrand et al., 2018; ASCO Abstract 12000
42. Fabrizio DA, et al. J Gastrointest Oncol (2018) pmid: 30151257
43. George et al., 2016; ASCO Abstract 3587
44. Nagahashi et al., 2016; ASCO Abstract e15103
45. Stadler ZK, et al. J. Clin. Oncol. (2016) pmid: 27022117
46. Chen EX, et al. JAMA Oncol (2020) pmid: 32379280
47. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
48. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
49. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
50. Rizvi NA, et al. Science (2015) pmid: 25765070
51. Johnson BE, et al. Science (2014) pmid: 24336570
52. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
53. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
54. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
55. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
56. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
57. Corcoran RB, et al. Cancer Discov (2018) pmid: 29431699
58. Hyman DM, et al. N. Engl. J. Med. (2015) pmid: 26287849
59. Yaeger R, et al. Clin. Cancer Res. (2015) pmid: 25589621
60. Kopetz S, et al. J Clin Oncol (2021) pmid: 33356422
61. Kopetz et al., 2020; ASCO Abstract 4001
62. Corcoran et al., 2020; ESMO GI Abstract SO-26
63. Klute et al., 2020; ASCO Abstract 122
64. Corcoran RB, et al. J. Clin. Oncol. (2015) pmid: 26392102
65. Ascierto et al., 2017; ASCO Abstract 9518
66. Rizos H, et al. Clin. Cancer Res. (2014) pmid: 24463458
67. Stagni C, et al. Mol Cancer Ther (2018) pmid: 29626128
68. Wilson MA, et al. Clin. Cancer Res. (2016) pmid: 26307133
69. O'Shaughnessy et al., 2011; SABC Abstract S3-5
70. Sullivan RJ, et al. Cancer Discov (2018) pmid: 29247021
71. Janku et al., 2021; AACR Abstract CT212
72. Pietrantonio F, et al. Eur. J. Cancer (2015) pmid: 25673558
73. Rowland A, et al. Br. J. Cancer (2015) pmid: 25989278
74. Van Cutsem E, et al. J. Clin. Oncol. (2011) pmid: 21502544
75. Smith CG, et al. Clin. Cancer Res. (2013) pmid: 23741067
76. Douillard JY, et al. N. Engl. J. Med. (2013) pmid: 24024839
77. Karapetis CS, et al. Clin. Cancer Res. (2014) pmid: 24218517
78. Peeters M, et al. Clin. Cancer Res. (2013) pmid: 23325582
79. Peeters M, et al. Clin. Cancer Res. (2015) pmid: 26341920
80. Guren TK, et al. Br. J. Cancer (2017) pmid: 28399112
81. Seymour MT, et al. Lancet Oncol. (2013) pmid: 23725851
82. Di Nicolantonio F, et al. J. Clin. Oncol. (2008) pmid: 19001320
83. Stintzing S, et al. Eur. J. Cancer (2017) pmid: 28463756
84. Tol J, et al. N. Engl. J. Med. (2009) pmid: 19571295
85. Freeman DJ, et al. Clin Colorectal Cancer (2008) pmid: 18621636
86. Gao J, et al. Chin. J. Cancer Res. (2011) pmid: 23357879
87. Soeda H, et al. Int. J. Clin. Oncol. (2013) pmid: 22638623
88. Molinari F, et al. Clin. Cancer Res. (2011) pmid: 21632860
89. André T, et al. Ann. Oncol. (2013) pmid: 23041588
90. Benvenuti S, et al. Cancer Res. (2007) pmid: 17363584
91. Arena S, et al. Clin. Cancer Res. (2015) pmid: 25623215
92. Montagut C, et al. Nat. Med. (2012) pmid: 22270724
93. Toledo RA, et al. Oncotarget (2017) pmid: 27852040
94. De Roock W, et al. Lancet Oncol. (2011) pmid: 21163703
95. Dienstmann R, et al. Mol. Cancer Ther. (2012) pmid: 22723336
96. Safaee Ardekani G, et al. PLoS ONE (2012) pmid: 23056577
97. Guedes JG, et al. BMC Cancer (2013) pmid: 23548132
98. Sinicrope et al., 2012; ASCO Abstract 3514
99. Hassabo et al., 2014; ASCO Gastrointestinal Cancers Symposium Abstract 473
100. Bokemeyer C, et al. Eur. J. Cancer (2012) pmid: 22446022
101. Laurent-Puig P, et al. J. Clin. Oncol. (2009) pmid: 19884556
102. Ogino S, et al. Clin. Cancer Res. (2012) pmid: 22147942
103. Roth AD, et al. J. Clin. Oncol. (2010) pmid: 20008640
104. Hsu HC, et al. Oncotarget (2016) pmid: 26989027
105. Summers MG, et al. Clin. Cancer Res. (2017) pmid: 27815357
106. Holderfield M, et al. Nat. Rev. Cancer (2014) pmid: 24957944
107. Burotto M, et al. Cancer (2014) pmid: 24948110
108. Davies H, et al. Nature (2002) pmid: 12068308
109. Kandoth C, et al. Nature (2013) pmid: 24132290
110. Gao J, et al. Sci Signal (2013) pmid: 23550210
111. Tanami H, et al. Oncogene (2004) pmid: 15467732
112. Modrek B, et al. Mol. Cancer Res. (2009) pmid: 19671679
113. Ciampi R, et al. Endocr. Pathol. (2005) pmid: 16199894
114. Greaves WO, et al. J Mol Diagn (2013) pmid: 23273605
115. Klein O, et al. Eur. J. Cancer (2013) pmid: 23237741
116. Wellbrock C, et al. Cancer Res. (2004) pmid: 15059882
117. Hauschild A, et al. Lancet (2012) pmid: 22735384
118. McArthur GA, et al. Lancet Oncol. (2014) pmid: 24508103
119. Fisher R, et al. Cancer Manag Res (2012) pmid: 22904646
120. Yang H, et al. Cancer Res. (2010) pmid: 20551065
121. Gentilcore G, et al. BMC Cancer (2013) pmid: 23317446
122. van den Brom RR, et al. Eur. J. Cancer (2013) pmid: 23473613
123. Klein O, et al. Eur. J. Cancer (2013) pmid: 23490649
124. Ponti G, et al. J. Clin. Pathol. (2013) pmid: 23463675
125. Ponti G, et al. J Hematol Oncol (2012) pmid: 23031422
126. Parakh S, et al. J Clin Pharm Ther (2015) pmid: 25382067
127. Lee LH, et al. JCI Insight (2017) pmid: 28194436
128. Horiuchi D, et al. J. Exp. Med. (2012) pmid: 22430491
129. Goga A, et al. Nat. Med. (2007) pmid: 17589519
130. Molenaar JJ, et al. Proc. Natl. Acad. Sci. U.S.A. (2009) pmid: 19525400
131. Dammert MA, et al. Nat Commun (2019) pmid: 31375684
132. Mollaoglu G, et al. Cancer Cell (2017) pmid: 28089889
133. Cardnell RJ, et al. Oncotarget (2017) pmid: 29088717
134. Wang L, et al. Mol Oncol (2017) pmid: 28417568
135. Takahashi Y, et al. Ann. Oncol. (2015) pmid: 25632068
136. Li Y, et al. Thyroid (2018) pmid: 30226440
137. Mahadevan D, et al. PLoS ONE (2014) pmid: 24893165
138. Park SI, et al. Target Oncol (2019) pmid: 31429028
139. Helfrich BA, et al. Mol. Cancer Ther. (2016) pmid: 27496133
140. Hook KE, et al. Mol. Cancer Ther. (2012) pmid: 22222631
141. Yang D, et al. Proc. Natl. Acad. Sci. U.S.A. (2010) pmid: 20643922
142. He J, et al. Anticancer Drugs (2019) pmid: 30540594
143. Shroff EH, et al. Proc. Natl. Acad. Sci. U.S.A. (2015) pmid: 25964345
144. Effenberger M, et al. Oncotarget (2017) pmid: 29156762
145. Qu X, et al. Biochem. Biophys. Res. Commun. (2018) pmid: 30103944
146. Xiang Y, et al. J. Clin. Invest. (2015) pmid: 25915584
147. Delmore JE, et al. Cell (2011) pmid: 21889194

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148. Bandopadhayay P, et al. Clin. Cancer Res. (2014) pmid: 24297863
149. Lovén J, et al. Cell (2013) pmid: 23582323
150. Otto C, et al. Neoplasia (2019) pmid: 31734632
151. Dong LH, et al. J Hematol Oncol (2013) pmid: 23866964
152. Pei Y, et al. Cancer Cell (2016) pmid: 26977882
153. Fu XH, et al. Acta Pharmacol. Sin. (2019) pmid: 30224636
154. Owonikoko TK, et al. J Thorac Oncol (2020) pmid: 31655296
155. Ganesan P, et al. Mol. Cancer Ther. (2014) pmid: 25253784
156. Tannir et al., 2018; ASCO GU Abstract 603
157. Motzer et al., 2019; ESMO Abstract LBA54
158. Pereira CB, et al. PLoS ONE (2013) pmid: 23555992
159. Yasojima H, et al. Eur. J. Cancer (2011) pmid: 21741827
160. Arango D, et al. Cancer Res. (2001) pmid: 11406570
161. Bottone MG, et al. Exp. Cell Res. (2003) pmid: 14516787
162. Cerami E, et al. Cancer Discov (2012) pmid: 22588877
163. Tate JG, et al. Nucleic Acids Res. (2019) pmid: 30371878
164. Erisman MD, et al. Mol. Cell. Biol. (1985) pmid: 3837853
165. Erisman MD, et al. Oncogene (1988) pmid: 3283655
166. Wang J, et al. Chin. Med. Sci. J. (1994) pmid: 8086630
167. Herbst A, et al. BMC Genomics (2014) pmid: 24467841
168. Huang MY, et al. Cancer Biomark (2013) pmid: 24240588
169. Toon CW, et al. PLoS ONE (2014) pmid: 24503701
170. Augenlicht LH, et al. Cancer Res. (1997) pmid: 9135021
171. Monnat M, et al. Int. J. Cancer (1987) pmid: 3040597
172. Dang CV, et al. Semin. Cancer Biol. (2006) pmid: 16904903
173. Nesbit CE, et al. Oncogene (1999) pmid: 10378696
174. Blancato J, et al. Br. J. Cancer (2004) pmid: 15083194
175. Fromont G, et al. Hum. Pathol. (2013) pmid: 23574779
176. Hao HX, et al. Nature (2012) pmid: 22575959
177. Koo BK, et al. Nature (2012) pmid: 22895187
178. Jiang X, et al. Proc. Natl. Acad. Sci. U.S.A. (2013) pmid: 23847203
179. Koo BK, et al. Proc. Natl. Acad. Sci. U.S.A. (2015) pmid: 26023187
180. Tsukiyama T, et al. Mol. Cell. Biol. (2015) pmid: 25825523
181. Kinde I, et al. Sci Transl Med (2013) pmid: 23303603
182. Giannakis M, et al. Nat. Genet. (2014) pmid: 25344691
183. Madan B, et al. Mol. Cancer Ther. (2015) pmid: 25901018
184. Ryland GL, et al. J. Pathol. (2013) pmid: 23096461
185. Ong CK, et al. Nat. Genet. (2012) pmid: 22561520
186. Wang K, et al. Nat. Genet. (2014) pmid: 24816253
187. Nature (2014) pmid: 25079317
188. Sugiura T, et al. Exp. Cell Res. (2008) pmid: 18313049
189. Yagyu R, et al. Int. J. Oncol. (2004) pmid: 15492824
190. Shinada K, et al. Biochem. Biophys. Res. Commun. (2011) pmid: 21108931
191. Clapéron A, et al. J. Biol. Chem. (2005) pmid: 15769748
192. Bokemeyer C, et al. Ann. Oncol. (2011) pmid: 21228335
193. Karapetis CS, et al. N. Engl. J. Med. (2008) pmid: 18946061
194. De Roock W, et al. Ann. Oncol. (2008) pmid: 17998284
195. Douillard JY, et al. Ann. Oncol. (2014) pmid: 24718886
196. Amado RG, et al. J. Clin. Oncol. (2008) pmid: 18316791
197. Lièvre A, et al. Cancer Res. (2006) pmid: 16618717
198. Chen J, et al. BMC Cancer (2014) pmid: 25367198
199. Li W, et al. BMC Cancer (2015) pmid: 25929517
200. Hu J, et al. Medicine (Baltimore) (2016) pmid: 27977612
201. Zekri J, et al. Genet. Mol. Res. (2017) pmid: 28218784
202. Staudacher JJ, et al. Clin Transl Gastroenterol (2017) pmid: 29048416
203. Wang Y, et al. Virchows Arch. (2018) pmid: 29705968
204. Guo F, et al. Sci Rep (2018) pmid: 29666387
205. Mármol I, et al. Int J Mol Sci (2017) pmid: 28106826
206. Kwak MS, et al. Medicine (Baltimore) (2017) pmid: 28858102
207. Pylayeva-Gupta Y, et al. Nat. Rev. Cancer (2011) pmid: 21993244
208. Kahn S, et al. Anticancer Res. () pmid: 3310850
209. Marjon K, et al. Cell Rep (2016) pmid: 27068473
210. Heist et al., 2019; AACR-NCI-EORTC Abstract B116
211. Mavrakis KJ, et al. Science (2016) pmid: 26912361
212. Endoscopy (1989) pmid: 2691236
213. Guccione E, et al. Nat. Rev. Mol. Cell Biol. (2019) pmid: 31350521
214. Fedoriw A, et al. Cancer Cell (2019) pmid: 31257072
215. Srour N, et al. Cancer Cell (2019) pmid: 31287990
216. Gao G, et al. Nucleic Acids Res. (2019) pmid: 30916320
217. Hansen LJ, et al. Cancer Res. (2019) pmid: 31040154
218. Tang B, et al. Cancer Res. (2018) pmid: 29844120
219. Munshi PN, et al. Oncologist (2014) pmid: 24928612
220. de Oliveira SF, et al. PLoS ONE (2016) pmid: 26751376
221. Lubin M, et al. PLoS ONE (2009) pmid: 19478948
222. Tang B, et al. Cancer Biol. Ther. (2012) pmid: 22825330
223. Collins CC, et al. Mol. Cancer Ther. (2012) pmid: 22252602
224. Bertino JR, et al. Cancer Biol. Ther. (2011) pmid: 21301207
225. Coulthard SA, et al. Mol. Cancer Ther. (2011) pmid: 21282358
226. Miyazaki S, et al. Int. J. Oncol. (2007) pmid: 17912432
227. Efferth T, et al. Blood Cells Mol. Dis. () pmid: 11987241
228. Kindler HL, et al. Invest New Drugs (2009) pmid: 18618081
229. Wei R, et al. Sci Rep (2016) pmid: 27929028
230. Zhao M, et al. BMC Genomics (2016) pmid: 27556634
231. Kirovski G, et al. Am. J. Pathol. (2011) pmid: 21356366
232. Huang HY, et al. Clin. Cancer Res. (2009) pmid: 19887491
233. Marcé S, et al. Clin. Cancer Res. (2006) pmid: 16778103
234. Meyer S, et al. Exp. Dermatol. (2010) pmid: 20500769
235. Wild PJ, et al. Arch Dermatol (2006) pmid: 16618867
236. Kim J, et al. Genes Chromosomes Cancer (2011) pmid: 21412930
237. Li CF, et al. Oncotarget (2014) pmid: 25426549
238. He HL, et al. Medicine (Baltimore) (2015) pmid: 26656376
239. Su CY, et al. Eur J Surg Oncol (2014) pmid: 24969958
240. Mirebeau D, et al. Haematologica (2006) pmid: 16818274
241. Becker AP, et al. Pathobiology (2015) pmid: 26088413
242. Snezhkina AV, et al. Oxid Med Cell Longev (2016) pmid: 27433286
243. Bistulfi G, et al. Oncotarget (2016) pmid: 26910893
244. Antonopoulou K, et al. J. Invest. Dermatol. (2015) pmid: 25407435
245. Maccioni L, et al. BMC Cancer (2013) pmid: 23816148
246. Hyland PL, et al. Int J Epidemiol (2016) pmid: 26635288
247. Lin X, et al. Cancer Sci. (2017) pmid: 27960044
248. Zhi L, et al. J Cancer (2016) pmid: 27994653
249. Gu F, et al. Br. J. Cancer (2013) pmid: 23361049
250. Limm K, et al. PLoS ONE (2016) pmid: 27479139
251. Tang B, et al. G3 (Bethesda) (2014) pmid: 25387827
252. Limm K, et al. Eur. J. Cancer (2013) pmid: 23265702
253. Stevens AP, et al. J. Cell. Biochem. (2009) pmid: 19097084
254. Kryukov GV, et al. Science (2016) pmid: 26912360
255. Limm K, et al. Eur. J. Cancer (2014) pmid: 25087184
256. Pentheroudakis G, et al. BMC Cancer (2013) pmid: 23374602
257. Vaughn CP, et al. Genes Chromosomes Cancer (2011) pmid: 21305640
258. Janku F, et al. Target Oncol (2013) pmid: 23400451
259. De Roock W, et al. Lancet Oncol. (2010) pmid: 20619739
260. Irahara N, et al. Diagn. Mol. Pathol. (2010) pmid: 20736745
261. Schirripa M, et al. Int. J. Cancer (2015) pmid: 24806288
262. Cercek A, et al. Clin. Cancer Res. (2017) pmid: 28446505
263. Cui Y, et al. Clin. Cancer Res. (2012) pmid: 22753594
264. Haeger SM, et al. Oncogene (2016) pmid: 25893305
265. Bachet JB, et al. Ann. Oncol. (2012) pmid: 22377565
266. Witkiewicz AK, et al. Nat Commun (2015) pmid: 25855536
267. Jiao Y, et al. J. Pathol. (2014) pmid: 24293293
268. Churi CR, et al. PLoS ONE (2014) pmid: 25536104
269. Liu X, et al. Clin. Chem. (2014) pmid: 24821835
270. Maru D, et al. Oncogene (2004) pmid: 14647445
271. Wang K, et al. Oncologist (2015) pmid: 26336083
272. Izeradjene K, et al. Cancer Cell (2007) pmid: 17349581
273. Bardeesy N, et al. Genes Dev. (2006) pmid: 17114584
274. Springer S, et al. Gastroenterology (2015) pmid: 26253305
275. Blackford A, et al. Clin. Cancer Res. (2009) pmid: 19584151
276. Yan P, et al. Clin. Cancer Res. (2016) pmid: 26861460
277. Kozak MM, et al. J. Clin. Pathol. (2015) pmid: 25681512
278. Roth AD, et al. J. Natl. Cancer Inst. (2012) pmid: 23104212
279. Davison JM, et al. Am. J. Surg. Pathol. (2014) pmid: 24618609
280. Kim YH, et al. Ann. Oncol. (2004) pmid: 15033661
281. Xiangming C, et al. Clin. Cancer Res. (2001) pmid: 11234879
282. Singhi AD, et al. Am. J. Surg. Pathol. (2015) pmid: 25634752
283. Natsugoe S, et al. Clin. Cancer Res. (2002) pmid: 12060625
284. de Kruijf EM, et al. Ann. Oncol. (2013) pmid: 23022998
285. Shipitsin M, et al. Br. J. Cancer (2014) pmid: 25032733
286. Nat. Rev. Mol. Cell Biol. (2012) pmid: 22992590
287. Cell (2008) pmid: 18662538
288. Massagué J, et al. Genes Dev. (2005) pmid: 16322555
289. Morén A, et al. Oncogene (2000) pmid: 10980615
290. Xu J, et al. Proc. Natl. Acad. Sci. U.S.A. (2000) pmid: 10781087
291. Luo K, et al. Genes Dev. (1999) pmid: 10485843
292. Jones JB, et al. Nucleic Acids Res. (2000) pmid: 10871368
293. Fink SP, et al. Cancer Res. (2001) pmid: 11196171
294. De Bosscher K, et al. Biochem. J. (2004) pmid: 14715079
295. Shi Y, et al. Nature (1997) pmid: 9214508
296. Miyaki M, et al. Oncogene (1999) pmid: 10340381
297. Prokova V, et al. Biochemistry (2007) pmid: 17994767
298. Wu JW, et al. J. Biol. Chem. (2001) pmid: 11274206
299. Ding L, et al. J. Clin. Invest. (2009) pmid: 19139564
300. Kuang C, et al. Oncogene (2004) pmid: 14647410
301. Watanabe M, et al. EMBO Rep. (2000) pmid: 11265759
302. Landrum MJ, et al. Nucleic Acids Res. (2018) pmid: 29165669

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303. Houlston R, et al. Hum. Mol. Genet. (1998) pmid: 9811934
304. Woodford-Richens K, et al. Gut (2000) pmid: 10764709
305. Howe JR, et al. J. Med. Genet. (2004) pmid: 15235019
306. Brosens LA, et al. World J. Gastroenterol. (2011) pmid: 22171123
307. Kalia SS, et al. Genet. Med. (2017) pmid: 27854360
308. Hirai H, et al. Cancer Biol. Ther. (2010) pmid: 20107315
309. Bridges KA, et al. Clin. Cancer Res. (2011) pmid: 21799033
310. Rajeshkumar NV, et al. Clin. Cancer Res. (2011) pmid: 21389100
311. Osman AA, et al. Mol. Cancer Ther. (2015) pmid: 25504633
312. Xu L, et al. Mol. Cancer Ther. (2002) pmid: 12489850
313. Xu L, et al. Mol. Med. (2001) pmid: 11713371
314. Camp ER, et al. Cancer Gene Ther. (2013) pmid: 23470564
315. Kim SS, et al. Nanomedicine (2015) pmid: 25240597
316. Pirollo KF, et al. Mol. Ther. (2016) pmid: 27357628
317. Hajdenberg et al., 2012; ASCO Abstract e15010
318. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27601554
319. Moore et al., 2019; ASCO Abstract 5513
320. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27998224
321. Oza et al., 2015; ASCO Abstract 5506
322. Lee J, et al. Cancer Discov (2019) pmid: 31315834
323. Méndez E, et al. Clin. Cancer Res. (2018) pmid: 29535125
324. Ma CX, et al. J. Clin. Invest. (2012) pmid: 22446188
325. Kwok M, et al. Blood (2016) pmid: 26563132
326. Boudny M, et al. Haematologica (2019) pmid: 30975914
327. Dillon MT, et al. Mol. Cancer Ther. (2017) pmid: 28062704
328. Middleton FK, et al. Cancers (Basel) (2018) pmid: 30127241
329. Goh HS, et al. Cancer Res. (1995) pmid: 7585578
330. Berg M, et al. PLoS ONE (2010) pmid: 21103049
331. Han SW, et al. PLoS ONE (2013) pmid: 23700467
332. Malhotra P, et al. Tumour Biol. (2013) pmid: 23526092
333. Di Bartolomeo M, et al. Target Oncol (2014) pmid: 23821376
334. Wangefjord S, et al. Diagn Pathol (2013) pmid: 23337059
335. Russo A, et al. J. Clin. Oncol. (2005) pmid: 16172461
336. Brown CJ, et al. Nat. Rev. Cancer (2009) pmid: 19935675
337. Joerger AC, et al. Annu. Rev. Biochem. (2008) pmid: 18410249
338. Kato S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12826609
339. Kamada R, et al. J. Biol. Chem. (2011) pmid: 20978130
340. Zerdoumi Y, et al. Hum. Mol. Genet. (2017) pmid: 28472496
341. Yamada H, et al. Carcinogenesis (2007) pmid: 17690113
342. Bougeard G, et al. J. Clin. Oncol. (2015) pmid: 26014290
343. Sorrell AD, et al. Mol Diagn Ther (2013) pmid: 23355100
344. Nichols KE, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11219776
345. Kleihues P, et al. Am. J. Pathol. (1997) pmid: 9006316
346. Gonzalez KD, et al. J. Clin. Oncol. (2009) pmid: 19204208
347. Lalloo F, et al. Lancet (2003) pmid: 12672316
348. Mandelker D, et al. Ann. Oncol. (2019) pmid: 31050713
349. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
350. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838
351. Xie M, et al. Nat. Med. (2014) pmid: 25326804
352. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
353. Severson EA, et al. Blood (2018) pmid: 29678827
354. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
355. Hematology Am Soc Hematol Educ Program (2018) pmid: 30504320
356. Chabon JJ, et al. Nature (2020) pmid: 32269342
357. Razavi P, et al. Nat. Med. (2019) pmid: 31768066
358. Park JH, et al. Cancer Chemother. Pharmacol. (2011) pmid: 21340604
359. Loupakis F, et al. Br. J. Cancer (2009) pmid: 19603018
360. Lupini L, et al. BMC Cancer (2015) pmid: 26508446
361. Inno A, et al. Clin Colorectal Cancer (2011) pmid: 21729677
362. Modest DP, et al. Int. J. Cancer (2012) pmid: 21960311
363. Hong DS, et al. Cancer Discov (2016) pmid: 27729313
364. Kopetz S, et al. N. Engl. J. Med. (2019) pmid: 31566309
365. van Geel RMJM, et al. Cancer Discov (2017) pmid: 28363909
366. Tabernero J, et al. J Clin Oncol (2021) pmid: 33503393
367. Klempner SJ, et al. Cancer Discov (2016) pmid: 27048246
368. Kopetz et al., 2010; ASCO Abstract 3534
369. Falchook GS, et al. Lancet (2012) pmid: 22608338
370. Atreya et al., 2015; ASCO Abstract 103
371. Gibney GT, et al. Nat Rev Clin Oncol (2013) pmid: 23712190
372. Falchook GS, et al. Thyroid (2015) pmid: 25285888
373. Flaherty KT, et al. N. Engl. J. Med. (2012) pmid: 23020132
374. Long GV, et al. N. Engl. J. Med. (2014) pmid: 25265492
375. Peters S, et al. Melanoma Res. (2014) pmid: 25185693
376. Long GV, et al. Lancet (2015) pmid: 26037941
377. Robert C, et al. N. Engl. J. Med. (2015) pmid: 25399551
378. Long GV, et al. Ann. Oncol. (2017) pmid: 28475671
379. Planchard D, et al. Lancet Oncol. (2017) pmid: 28919011
380. Subbiah V, et al. J. Clin. Oncol. (2018) pmid: 29072975
381. Kreitman et al., 2018; ASH Abstract 391
382. Lagana et al., 2018; DOI: 10.1200/PO.18.00019
383. Salama AKS, et al. J Clin Oncol (2020) pmid: 32758030
384. Williams CB, et al. Onco Targets Ther (2015) pmid: 26664139
385. Dummer R, et al. Lancet Oncol. (2018) pmid: 29573941
386. Ascierto PA, et al. Eur. J. Cancer (2020) pmid: 31901705
387. Holbrook K, et al. Cancer (2020) pmid: 31658370
388. Sullivan RJ, et al. Clin Cancer Res (2020) pmid: 32669376
389. Kefford et al., 2013; Melanoma Bridge Meeting Abstract P5
390. McLoughlin EM, et al. J Thorac Oncol (2019) pmid: 31757377
391. Gogas et al., 2020; ASCO Abstract 10012
392. Hayes DN, et al. Clin. Cancer Res. (2012) pmid: 22241789
393. Kirkwood JM, et al. Clin. Cancer Res. (2012) pmid: 22048237
394. Patel SP, et al. Cancer (2013) pmid: 22972589
395. Banerji U, et al. Clin. Cancer Res. (2010) pmid: 20179232
396. Boers-Sonderen MJ, et al. Anticancer Drugs (2012) pmid: 22293660
397. Robert C, et al. Lancet Oncol. (2013) pmid: 23735514
398. Fangusaro J, et al. Lancet Oncol. (2019) pmid: 31151904
399. Banerjee A, et al. Neuro-oncology (2017) pmid: 28339824
400. Bennouna J, et al. Invest New Drugs (2011) pmid: 20127139
401. Do K, et al. Invest New Drugs (2015) pmid: 25637165
402. Hochster HS, et al. Cancer Chemother. Pharmacol. (2015) pmid: 25322874
403. Deming DA, et al. Invest New Drugs (2016) pmid: 26666244
404. Marti FEM, et al. Eur. J. Cancer (2019) pmid: 31229949
405. Falchook GS, et al. Lancet Oncol. (2012) pmid: 22805292
406. Kim KB, et al. J. Clin. Oncol. (2013) pmid: 23248257
407. Bowyer SE, et al. Melanoma Res. (2014) pmid: 24933606
408. Sullivan et al., 2016; ASCO Abstract 9537
409. Dahlman KB, et al. Cancer Discov (2012) pmid: 22798288
410. Banerjee et al., 2014; ASCO Abstract 10065
411. Ross JS, et al. Int. J. Cancer (2016) pmid: 26314551
412. Menzies AM, et al. Pigment Cell Melanoma Res (2015) pmid: 26072686
413. Grisham RN, et al. J. Clin. Oncol. (2015) pmid: 26324360
414. Chmielecki J, et al. Cancer Discov (2014) pmid: 25266736
415. Durham BH, et al. Nat. Med. (2019) pmid: 31768065
416. Yamaguchi T, et al. Int. J. Oncol. (2011) pmid: 21523318
417. Watanabe M, et al. Cancer Sci. (2013) pmid: 23438367
418. Gilmartin AG, et al. Clin. Cancer Res. (2011) pmid: 21245089
419. Infante JR, et al. Eur. J. Cancer (2013) pmid: 23583440
420. Infante JR, et al. Lancet Oncol. (2012) pmid: 22805291
421. Leijen S, et al. Clin. Cancer Res. (2012) pmid: 22767668
422. Zimmer L, et al. Clin. Cancer Res. (2014) pmid: 24947927
423. Hochster et al., 2013; ASCO GI Abstract 380
424. Juric et al., 2014; ASCO Abstract 9051
425. Sullivan et al., 2015; AACR-NCI-EORTC Abstract PR06
426. Weekes CD, et al. Clin. Cancer Res. (2013) pmid: 23434733
427. Tsimberidou et al., 2013; ASCO Abstract e22086
428. Tolcher AW, et al. Ann. Oncol. (2015) pmid: 25344362
429. Patterson et al., 2018; AACR Abstract 3891
430. Chapman PB, et al. N. Engl. J. Med. (2011) pmid: 21639808
431. Kurzrock R, et al. Ann. Oncol. (2020) pmid: 32067683
432. Subbiah V, et al. Cancer Discov (2020) pmid: 32029534
433. Mazieres J, et al. Ann. Oncol. (2020) pmid: 31959346
434. Larkin J, et al. Eur. J. Cancer (2019) pmid: 30580112
435. Kaley T, et al. J. Clin. Oncol. (2018) pmid: 30351999
436. Kopetz S, et al. J. Clin. Oncol. (2015) pmid: 26460303
437. Ofir Dovrat T, et al. Cancer Biol. Ther. (2018) pmid: 30036146
438. Kopetz et al., 2017; ASCO Abstract 520
439. Kopetz et al., 2017; ASCO Abstract 3505
440. Ribas A, et al. Lancet Oncol. (2014) pmid: 25037139
441. Ascierto PA, et al. Lancet Oncol. (2016) pmid: 27480103
442. Ribas A, et al. Clin. Cancer Res. (2020) pmid: 31732523

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