FOUNDATIONONE®CDx

PATIENT	TUMOR TYPE	REPORT DATE
Chen, Chien Liu	Colon adenocarcinoma (CRC)	11 May 2023
	COUNTRY CODE	ORDERED TEST #
	TW	ORD-1622372-01

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

PATIENT
DISEASE Colon adenocarcinoma (CRC)
NAME Chen, Chien Liu
DATE OF BIRTH 25 August 1959
SEX Male
MEDICAL RECORD # 45669065

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

SPECIMEN
SPECIMEN SITE Lung
SPECIMEN ID S109-78774 I (PF23046)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 19 November 2020
SPECIMEN RECEIVED 04 May 2023

Biomarker Findings
Microsatellite status - MS-Stable
Tumor Mutational Burden - 1 Muts/Mb

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

KRAS G12V
NRAS wildtype
APC E1309fs*4
PIK3CA E726K, M1043I
TP53 E271V

3 Disease relevant genes with no reportable alterations: *BRAF, ERBB2, NRAS*

Report Highlights

- Targeted therapies with **potential resistance** based on this patient's genomic findings: ⊗ Cetuximab (p. 9), Panitumumab (p. 10)

- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 11)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS	
Microsatellite status - MS-Stable	No therapies or clinical trials. See Biomarker Findings section	
Tumor Mutational Burden - 1 Muts/Mb	No therapies or clinical trials. See Biomarker Findings section	

GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
KRAS - G12V	*Cetuximab* ⊗	none
10 Trials see p. 12	*Panitumumab* ⊗	
NRAS - wildtype	*Cetuximab* ⊗	none
0 Trials	*Panitumumab* ⊗	
APC - E1309fs*4	none	none
3 Trials see p. 11		
PIK3CA - E726K, M1043I	none	none
10 Trials see p. 14		

⊗ *Extensive evidence showing variant(s) in this sample may confer resistance to this therapy*

Electronically signed by Erik Williams, M.D. | 11 May 2023
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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.

TP53 - E271V .... p. <u>8</u>

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 microsatellite-stable (MSS) metastatic colorectal cancer (CRC), 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]. For patients with MSS CRC, a Phase 2 study combining ipilimumab and nivolumab reported an overall DCR of 25% (10/40)[7]. Two Phase 1 studies for patients with MSS CRC treated with regorafenib and nivolumab reported PFSs of 7.9 months[8] and 5.7 months[9], and a patient with MSS CRC refractory to chemotherapy treated with the PD-1 inhibitor sintilimab and regorafenib reported a CR[10].

— Nontargeted Approaches —

MSI has not been found to be a predictive biomarker for combination chemotherapy regimens, including FOLFOX[11-12] and FOLFIRI[13-14]. Patients with MSS CRC are more likely to benefit from postsurgical fluorouracil (FU)-based adjuvant therapy[15-16] but less likely to benefit from irinotecan chemotherapy[17].

FREQUENCY & PROGNOSIS

MSS colorectal cancers (CRCs) make up 70-85% of CRC cases[3,18-22]. MSS colorectal cancers are molecularly heterogeneous, driven by diverse mechanisms such as extensive DNA methylation, oncogenic mutations in KRAS or BRAF, or chromosomal instability[22]. Multiple studies have shown that MSS CRCs have a worse prognosis than MSI-high tumors[18,23-29].

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[20]. 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[20,30-31]. 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[19,32-33]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[19-20,31,33].

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BIOMARKER
Tumor Mutational Burden

RESULT
1 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[34-36], anti-PD-1 therapies[34-37], and combination nivolumab and ipilimumab[38-43]. In multiple pan-tumor studies, increased tissue tumor mutational burden (TMB) was associated with sensitivity to immune checkpoint inhibitors[34-37,44-48]. In the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors, significant improvement in ORR was observed for patients with TMB ≥10 Muts/Mb (as measured by this assay) compared with those with TMB <10 Muts/Mb in a large cohort that included multiple tumor types[44]; similar findings were observed in the KEYNOTE 028 and 012 trials[37]. At the same TMB cutpoint, retrospective analysis of patients with solid tumors treated with any checkpoint inhibitor identified that tissue TMB scores ≥ 10 Muts/Mb were associated with prolonged time to treatment failure compared with scores <10 muts/Mb (HR=0.68)[48]. For patients with solid tumors treated with nivolumab plus ipilimumab in the CheckMate 848 trial, improved responses were observed in patients with a tissue TMB ≥ 10 Muts/Mb independent of blood TMB at any cutpoint in matched samples[49]. However, support for higher TMB thresholds and efficacy was observed in the prospective Phase 2 MyPathway trial of atezolizumab for patients with pan-solid tumors, where improved ORR and DCR

was seen in patients with TMB ≥ 16 Muts/Mb than those with TMB ≥ 10 and <16 Muts/Mb[47]. Similarly, analyses across several solid tumor types reported that patients with higher TMB (defined as ≥16-20 Muts/Mb) achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy compared with patients with higher TMB treated with chemotherapy[50] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[35]. 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)[34]. 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[51].

FREQUENCY & PROGNOSIS

Elevated tumor mutational burden (TMB) has been reported in 8-25% of colorectal cancer (CRC) samples[21,52-53]. Multiple studies have reported that up to 90% of hypermutated CRC cases exhibit high levels of microsatellite instability (MSI-H) and mismatch repair deficiency (MMR-D)[21,52]. 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[52]. A subset of CRCs that harbor increased TMB but not MSI-H are driven by mutations in POLE, which leads to an "ultramutated" phenotype with especially high TMB[21,52]. Tumors with increased TMB harbor BRAF V600E mutations more frequently than those with low TMB[21,52], whereas TMB-low tumors more frequently harbor mutations in TP53 and APC[21]. The prognostic value of tumor mutational burden (TMB) in colorectal cancer (CRC) is context- and therapy-dependent. A

study of tissue TMB (tTMB) in 145 CRC samples showed longer OS in TMB-high samples compared with TMB-low ones[54]. Similarly, for patients with metastatic CRC treated with first-line chemotherapy combined with bevacizumab or cetuximab, high tissue TMB (tTMB-H) was associated with longer OS[55]. For patients treated with adjuvant chemotherapy, tTMB-H was associated with better 5-year relapse-free survival[56]. However, for patients with EGFR/BRAF-inhibitor-treated, BRAF-mutated microsatellite stable (MSS) metastatic CRC, intermediate tTMB was associated with significantly poorer PFS and OS compared with TMB-low status; patients with primary resistance to EGFR/BRAF blockage had higher TMB than those sensitive to these therapies[57]. In a study for 61 patients with metastatic, 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 compared with plasma TMB scores <28 Muts/Mb (3.0 vs. 5.3 months, HR=0.76, p=0.007), whereas tTMB was not found to be prognostic in this population[58].

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[59-60] and cigarette smoke in lung cancer[61-62], treatment with temozolomide-based chemotherapy in glioma[63-64], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[21,65-68], and microsatellite instability (MSI)[21,65,68]. 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[34,44,51].

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GENOMIC FINDINGS

ORDERED TEST # ORD-1622372-01

GENE
KRAS

ALTERATION
G12V

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

VARIANT CHROMOSOMAL POSITION
chr12:25398284

VARIANT ALLELE FREQUENCY (% VAF)
20.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical evidence suggests that KRAS activation may predict sensitivity to MEK inhibitors, such as trametinib, binimetinib, cobimetinib, and selumetinib[69-74]. However, multiple clinical trials have reported lack of efficacy of trametinib and other MEK inhibitors when used as monotherapy for treatment of patients with KRAS-mutant CRC[75-79]. Both clinical[80-81] and preclinical[82-83] studies suggest that combinatorial approaches including MEK inhibitors are likely to be more effective for the treatment of CRC, including strategies such as combination of MEK inhibitors with PI3K inhibitors[81], RAF inhibitors[82], pan-ERBB inhibitors[83], or chemotherapeutic agents[80]. In a Phase 1 study evaluating the MEK-pan-RAF dual inhibitor CH5126766, 6 patients harboring

KRAS mutations experienced PRs, including 3 with non-small cell lung cancer (NCSLC), 1 with low-grade serous ovarian carcinoma (LGSOC), 1 with endometrial adenocarcinoma, and 1 with multiple myeloma[84]. Combination of CH5126766 with the FAK inhibitor defactinib elicited PR rates of 50% (4/8) for patients with KRAS-mutated LGSOC and 12% (2/17) for patients with KRAS-mutated NSCLC in a Phase 1 study[85-86] . Preclinical and clinical data suggest that KRAS mutations may predict clinical benefit from SHP2 inhibitors[87-88]. A Phase 1 study of RMC-4630 for relapsed/refractory solid tumors reported a DCR of 58% (23/40) for patients with NSCLC and KRAS mutations and a DCR of 75% (12/16) for patients with NSCLC and KRAS G12C mutations[89]. Interim results from a Phase 1/2 study of RMC-4630 plus cobimetinib reported tumor reduction in 3 of 8 patients with KRAS-mutated colorectal cancer[90]. Preclinical studies suggest that KRAS activating mutations may confer sensitivity to SOS1 inhibitors such as BI-3406, MRTX0902, BI-1701963, and BAY-293 as single agents[91-96] or in combination with covalent KRAS G12C inhibitors[96] and MEK inhibitors[97-98]. Preclinical and limited clinical evidence suggest that KRAS mutation may predict sensitivity to PLK1 inhibitors[99]. A Phase 1b/2 study of PLK1 inhibitor onvansertib in combination with FOLFIRI and bevacizumab for patients with KRAS-mutated metastatic CRC previously treated with chemotherapy reported an 87.5% (7/8; 3 PR, 4 SD) clinical benefit rate, with 1 patient going on to successful curative surgery[100].

— Potential Resistance —

Activating mutations in KRAS or NRAS are associated with lack of clinical benefit from cetuximab[101-104] or panitumumab[105-107] for patients with CRC. Therefore, activating mutations in either gene indicate against the use of cetuximab and panitumumab (NCCN Colon Cancer Guidelines, v3.2022).

FREQUENCY & PROGNOSIS

Mutations in KRAS have been reported in approximately 35-50% of colorectal cancers (CRCs)[108-116]. Numerous studies have reported that KRAS mutations are associated with increased metastasis, adverse clinicopathological features, and shorter survival of patients with CRC[110-113,117-118].

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[70,119]. KRAS alterations affecting amino acids G12, G13, Q22, P34, A59, Q61, and A146, as well as mutations G10_A11insG, G10_A11insAG (also reported as G10_A11dup and G12_G13insAG), A18D, L19F, D33E, G60_A66dup/E62_A66dup, E62K, E63K, R68S, K117R, and K117N have been characterized as activating and oncogenic[70,120-142].

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[101-104] or panitumumab[105-107] for patients with CRC. Therefore, these agents are indicated to treat patients with CRC lacking such mutations (NCCN Colon Cancer Guidelines, v3.2022, Rectal Cancer Guidelines, v4.2022).

— Potential Resistance —

Based on clinical data, it is unclear whether the presence of PIK3CA mutations is associated with reduced sensitivity to cetuximab in patients with colorectal cancer (CRC). Detection of PIK3CA mutations at progression was observed for patients with CRC following treatment with cetuximab[143-145]. A study comparing PIK3CA exon 9 and 20 mutations reported that for patients with chemotherapy-refractory CRC, PIK3CA exon 20 mutations were associated with less benefit from cetuximab compared with PIK3CA wildtype; this effect was not observed with PIK3CA exon 9 mutations[146]. In contrast, multiple studies and case reports of cetuximab treatment of CRC have reported similar responses in patients with PIK3CA exon 9 or 20 mutations compared with PIK3CA wildtype[147-153].

FREQUENCY & PROGNOSIS

The majority of colorectal cancers (CRCs) (91-98%) have been reported to lack NRAS mutations[21,116,146,154-158]. NRAS wild-type status has been reported to be associated with decreased frequency of metastasis[116] and longer survival[158-159] 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[70]. No alterations in NRAS were identified in this case.

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GENE
APC

ALTERATION
E1309fs*4

HGVS VARIANT
NM_000038.4: c.3927_3931del (p.E1309Dfs*4)

VARIANT CHROMOSOMAL POSITION
chr5:112175211-112175216

VARIANT ALLELE FREQUENCY (% VAF)
34.9%

POTENTIAL TREATMENT STRATEGIES
— Targeted Therapies —

There are no approved drugs targeting APC inactivation in cancer. Loss of APC function leads to accumulation of beta-catenin and upregulation of WNT pathway transcription programs[160], and potential therapeutic approaches to target this pathway include CBP/beta-catenin antagonists, which interfere with the ability of beta-catenin to interact with transcriptional co-activator CBP[161-162]. In a Phase 1 trial of the CBP/beta-catenin antagonist E7386, 1 patient with APC-mutated small bowel adenocarcinoma achieved a PR with tumor shrinkage of -69% and response duration of 165 days[163]; preclinical data support sensitivity of APC-deficient gastric or colorectal cancer models to E7386[164-165].

FREQUENCY & PROGNOSIS

APC mutations have been found in 73% of tumors in the colorectal adenocarcinoma TCGA dataset[21]. In 1 study, loss of heterozygosity (LOH) of APC was observed in 32% of colorectal cancer (CRC) samples[166]. The prognostic significance of APC mutations in sporadic CRC remains unclear[167]. Solid tumors with WNT/beta-catenin pathway alterations, as seen here, were observed to have significantly less T-cell inflammation in one study[168].

FINDING SUMMARY

APC (adenomatous polyposis coli) encodes a tumor suppressor with critical roles in regulating cell division and adhesion. APC interacts with beta-catenin and controls signaling in the WNT pathway, which regulates embryonic development and cell differentiation[169]. Alterations such as seen here may disrupt APC function or expression[170-174].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the APC 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 familial adenomatous polyposis (ClinVar, Sep 2022)[175]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in APC are found in more than 90% of patients with familial adenomatous polyposis (FAP)[176-178]. The prevalence for FAP in the general population is estimated to be 1:8,300 from birth[179], and in the appropriate clinical context germline testing of APC is recommended.

Electronically signed by Erik Williams, M.D. | 11 May 2023
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GENOMIC FINDINGS

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GENE

PIK3CA

ALTERATION
E726K, M1043I

HGVS VARIANT
NM_006218.2: c.2176G>A (p.E726K),
NM_006218.2: c.3129G>A (p.M1043I)

VARIANT CHROMOSOMAL POSITION
chr3:178938934, chr3:178952074

VARIANT ALLELE FREQUENCY (% VAF)
27.9%, 29.5%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Clinical and preclinical data in various tumor types indicate that PIK3CA activating alterations may predict sensitivity to therapies targeting PI3K[180-187], AKT[188-189], or mTOR[190-197]. The Phase 2 NCI-MATCH study of copanlisib for patients with refractory solid tumors harboring PIK3CA mutations with or without PTEN loss met its primary endpoint with an ORR of 16% (4/25 PRs); responses (PR or SD >6 months) were seen in patients with ameloblastoma, liposarcoma, and carcinomas of the endometrium, ovary, esophagus, lung, and prostate[187]. However, the Phase 2 study of copanlisib for patients with endometrial carcinoma harboring PIK3CA hotspot mutations failed to report any objective responses (n=11)[186]. Two other studies of copanlisib for patients with genomically

unselected tumors reported 1 CR and 2 PRs (1 unconfirmed) among 16 total patients with PIK3CA-mutated solid tumors with or without PTEN alterations[184-185]. Emerging evidence suggests that the glutaminase inhibitor telaglenastat has clinical activity in PIK3CA-mutated colorectal cancer (CRC). A Phase 1 trial of telaglenastat and capecitabine for patients with CRC who progressed on fluoropyrimidine chemotherapy observed numerically increased median PFS for patients with PIK3CA mutation compared with patients with wildtype PIK3CA status (24.8 vs. 16 weeks, n=7 vs. n=4), including SD >30 weeks for 3 patients with PIK3CA mutation[198].

— Potential Resistance —

Multiple clinical studies report that inhibitors of the PI3K-AKT-mTOR pathway have not produced significant clinical benefit as monotherapies to treat CRC, even for tumors that harbor alterations in PIK3CA or PTEN; data are more limited for alterations in other genes in this pathway[199-201]. Based on clinical data, it is unclear whether the presence of PIK3CA mutations is associated with reduced sensitivity to cetuximab in patients with colorectal cancer (CRC). Detection of PIK3CA mutations at progression was observed for patients with CRC following treatment with cetuximab[143-145]. A study comparing PIK3CA exon 9 and 20 mutations reported that for patients with chemotherapy-refractory CRC, PIK3CA exon 20 mutations were associated with less benefit from cetuximab compared with PIK3CA wildtype; this

effect was not observed with PIK3CA exon 9 mutations[146]. In contrast, multiple studies and case reports of cetuximab treatment of CRC have reported similar responses in patients with PIK3CA exon 9 or 20 mutations compared with PIK3CA wildtype[147-153].

FREQUENCY & PROGNOSIS

PIK3CA mutations have been reported in up to 19% of colorectal cancers (CRCs)[21,202]. A meta-analysis of 864 patients with colorectal cancer (CRC) treated with cetuximab- or panitumumab-based therapy showed that PIK3CA mutations, particularly in exon 20 (H1047R), are significantly associated with worse response[203] and shorter PFS and OS[146]. A study of 354 patients with metastatic CRC observed no difference in OS between patients with PIK3CA mutations versus those without (21.7 months vs. 22.4 months, respectively); however, the study did not include treatment information for the patients[204].

FINDING SUMMARY

PIK3CA encodes p110-alpha, which is the catalytic subunit of phosphatidylinositol 3-kinase (PI3K). The PI3K pathway is involved in cell signaling that regulates a number of critical cellular functions, including cell growth, proliferation, differentiation, motility, and survival[205-206]. PIK3CA alterations that have been characterized as activating, such as observed here, are predicted to be oncogenic[207-228].

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GENOMIC FINDINGS

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GENE
TP53

ALTERATION
E271V

HGVS VARIANT
NM_000546.4: c.812A>T (p.E271V)

VARIANT CHROMOSOMAL POSITION
chr17:7577126

VARIANT ALLELE FREQUENCY (% VAF)
27.7%

POTENTIAL TREATMENT STRATEGIES
— Targeted Therapies —

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[229-232] or p53 gene therapy such as SGT53[233-237]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% and SDs in 53% of patients with solid tumors; the response rate was 21% (4/19) for patients with TP53 mutations versus 12% (4/33) for patients who were TP53 wildtype[238]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[239]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[240]. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[241]. In the Phase 2

VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24% (6/25) ORR with adavosertib combined with paclitaxel[242]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate for patients with TP53 alterations[243]. The Phase 2 FOCUS4-C trial for patients with TP53- and RAS-mutated colorectal cancer reported improvement in PFS (3.61 vs. 1.87 months, HR=0.35, p=0.0022), but not OS (14.0 vs 12.8 months, p=0.93), following adavosertib treatment compared with active monitoring[244]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[237]. Missense mutations leading to TP53 inactivation may be sensitive to therapies that reactivate mutated p53 such as eprenetapopt. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, eprenetapopt combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[245]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[246].

FREQUENCY & PROGNOSIS
TP53 mutations have been reported in up to 75% of colorectal cancer cases[21,247-252]. A study reported p53 expression in 49% of analyzed colorectal cancer cases[253]. TP53 mutation has not been consistently demonstrated to be a significant independent prognostic marker in the context of CRC[254].

FINDING SUMMARY
Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[255]. Alterations such as seen here may disrupt TP53 function or expression[256-260].

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[261-263], including sarcomas[264-265]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[266] to 1:20,000[265]. For pathogenic TP53 mutations identified during tumor sequencing, the rate of germline mutations was 1% in the overall population and 6% in tumors arising before age 30[267]. In the appropriate clinical context, germline testing of TP53 is recommended.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS
Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[268-273]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[268-269]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[274]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[272,275-276]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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THERAPIES ASSOCIATED WITH RESISTANCE | IN PATIENT'S TUMOR TYPE

Cetuximab

❌ Resistance of variant(s) to associated therapy is likely

Assay findings association

KRAS
G12V

NRAS
wildtype

AREAS OF THERAPEUTIC USE

Cetuximab is a monoclonal antibody that targets EGFR. It is FDA approved for the treatment of head and neck squamous cell carcinoma (HNSCC) and KRAS-wild-type, EGFR-expressing metastatic colorectal cancer (CRC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

Therapies targeting EGFR, including cetuximab, have been shown to have significant clinical activity for patients with CRC[101-104,277-278] ; wild-type KRAS and NRAS are predictive biomarkers for the efficacy of cetuximab in metastatic CRC (NCCN Colon Cancer Guidelines, v3.2022, NCCN Rectal Cancer Guidelines, v4.2022). Activating mutations in either KRAS[101-104] or NRAS[146,252] , which function downstream of EGFR, are associated with lack of benefit of cetuximab for patients with CRC and indicate against the use of cetuximab (NCCN Colon Cancer Guidelines v3.2022). A study comparing PIK3CA exon 9 and 20 mutations reported that for patients with chemotherapy-refractory CRC, PIK3CA exon 20 mutations were associated with less benefit from cetuximab compared with PIK3CA wildtype (ORR of 0.0% [0/9] vs. 37% [121/329], PFS of 11.5 vs. 24 weeks, and OS of 34 vs. 51 weeks); this effect was not observed with PIK3CA exon 9 mutations (ORR of 29% [6/21] vs. 36% [115/317], PFS of 23.5 vs. 24 weeks, and OS of 46 vs. 51 weeks)[146]. The presence of PIK3CA exon 9 and 20 mutations showed no correlation with objective tumor response to cetuximab but was associated with reduced PFS in response to cetuximab salvage therapy (HR=2.1)[279]. In contrast, multiple studies and case reports of cetuximab treatment of CRC have reported similar responses in patients with PIK3CA exon 9 or 20 mutations compared with PIK3CA wildtype[147-153,280] .

SUPPORTING DATA

Cetuximab has been shown to improve OS, PFS, and response rate for patients with KRAS-wildtype colorectal cancer (CRC), both in combination with FOLFIRI, FOLFOX4, or irinotecan[101-102,277-278,281] and as monotherapy for chemotherapy-refractory patients[104,151] . The Phase 3 study STRATEGIC-1 reported a similar duration of disease control (DDC) for patients with unresectable metastatic CRC (mCRC) and KRAS-, NRAS-, and BRAF-wildtype status treated with mFOLFOX-bevacizumab alternated with a cetuximab regimen in first or second line, respectively (overall DDC 22.5 vs. 23.5 months); in addition, the study reported similar OS (37.8 vs. 34.4 months) and higher numerical ORR for patients treated with cetuximab in the first line followed by mFOLFOX-bevacizumab compared with those receiving EGFR-directed antibodies in the second or third line[282]. A prospective study of cetuximab monotherapy for patients with KRAS-, NRAS-, and BRAF-wildtype mCRC reported 11% (2/19) PRs and 58% (11/19) SDs[152]. The Phase 2 AVETUX trial of cetuximab combined with avelumab and mFOLFOX6 for patients with RAS- and BRAF-wildtype mCRC resulted in an ORR of 81% (4 CR and 27 PRs, n=37) and a DCR of 89%[283]. In the Phase 3 ASPECCT study, panitumumab was found to be non-inferior to cetuximab with respect to median OS (10.4 vs. 10.0 months, HR=0.97) for patients with previously treated KRAS exon 2 wildtype metastatic colorectal cancer; median PFS was also similar between the two treatment groups (4.4 vs. 4.1 months, HR=1.00)[284]. In a similar patient population, a Phase 2 study of combination panitumumab and irinotecan versus combination cetuximab and irinotecan also demonstrated non-inferiority with respect to median PFS (5.4 vs. 4.3 months, HR = 0.64) and median OS (14.9 vs. 11.5 months, HR=0.66)[285].

FOUNDATIONONE®CDx

PATIENT
Chen, Chien Liu

TUMOR TYPE
Colon adenocarcinoma (CRC)

REPORT DATE
11 May 2023

ORDERED TEST # ORD-1622372-01

THERAPIES ASSOCIATED WITH RESISTANCE | IN PATIENT'S TUMOR TYPE

Panitumumab

❌ Resistance of variant(s) to associated therapy is likely

Assay findings association

KRAS
G12V

NRAS
wildtype

AREAS OF THERAPEUTIC USE

Panitumumab is a monoclonal antibody that targets EGFR. It is FDA approved to treat KRAS wild-type and NRAS wild-type metastatic colorectal cancer (CRC) combined with chemotherapy or as monotherapy for patients who have progressed on prior chemotherapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Therapies targeting EGFR, including panitumumab, have been shown to have significant clinical activity for patients with CRC[105,284,286] ; wild-type KRAS and NRAS are predictive biomarkers for the efficacy of panitumumab in metastatic CRC (NCCN Colon Cancer Guidelines v3.2022)(NCCN Rectal Cancers Guidelines, v4.2022). Activating mutations in either KRAS[105-107] or NRAS[106,250] , which function downstream of EGFR, are associated with lack of benefit of panitumumab for patients with CRC and indicate against the use of panitumumab (NCCN Colon Cancer Guidelines v3.2022, NCCN Rectal Cancer Guidelines v4.2022).

SUPPORTING DATA

Panitumumab has been shown to improve OS, PFS, and ORR for patients with KRAS-wildtype colorectal cancer (CRC), both in combination with FOLFOX4, FOLFIRI, irinotecan, or best supportive care[105,287-290] , and as monotherapy for chemotherapy-refractory patients[250,284,286] . The Phase 3 PARADIGM trial comparing panitumumab plus mFOLFOX6 versus bevacizumab plus mFOLFOX6 as first-line treatment for patients with RAS-wildtype left-sided metastatic CRC demonstrated that treatment with panitumumab significantly improved median OS (mOS; 36.2 months vs. 31.3 months) compared with bevacizumab[291]. A Phase 2 trial reported that, for patients with unresectable RAS-wildtype colorectal adenocarcinoma treated with panitumumab plus FOLFOX4, maintenance with a combination of panitumumab plus fluorouracil and leucovorin was superior to panitumumab monotherapy (10-month PFS OF 59% vs. 49%)[292]. In the Phase 3 ASPECCT study, panitumumab was found to be non-inferior to cetuximab with respect to median OS (10.4 vs. 10.0 months, HR=0.97) for patients with previously treated KRAS exon 2 wildtype metastatic colorectal cancer; median PFS was also similar between the two treatment groups (4.4 vs. 4.1 months, HR=1.00)[284]. In a similar patient population, a Phase 2 study of combination panitumumab and irinotecan versus combination cetuximab and irinotecan also demonstrated non-inferiority with respect to median PFS (5.4 vs. 4.3 months, HR = 0.64) and median OS (14.9 vs. 11.5 months, HR=0.66)[285].

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.

FOUNDATION**ONE**®CDx

PATIENT
Chen, Chien Liu

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REPORT DATE
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ORDERED TEST # ORD-1622372-01

CLINICAL TRIALS

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
APC

ALTERATION
E1309fs*4

RATIONALE
Based on preclinical and limited clinical data, APC inactivation may be associated with sensitivity to CBP/beta-catenin interaction inhibitors.

NCT05091346	**PHASE 1/2**
A Study of E7386 in Combination With Pembrolizumab in Previously Treated Participants With Selected Solid Tumors	**TARGETS** CBP, Beta-catenin, PD-1

LOCATIONS: Fukuoka (Japan), Osaka (Japan), Shizouka (Japan), Tokyo (Japan), Chiba-shi (Japan), Kashiwa (Japan), Sapporo shi (Japan), Glasgow (United Kingdom), Manchester (United Kingdom), London (United Kingdom)

NCT04008797	**PHASE 1**
A Study of E7386 in Combination With Other Anticancer Drug in Participants With Solid Tumor	**TARGETS** CBP, Beta-catenin, FGFRs, RET, PDGFRA, VEGFRs, KIT

LOCATIONS: Kurume (Japan), Matsuyama (Japan), Seodaemun (Korea, Republic of), Osakasayama (Japan), Nagoya (Japan), Kawasaki (Japan), Chuo-Ku (Japan), Koto-ku (Japan), Chiba (Japan), Kashiwa (Japan)

NCT03264664	**PHASE 1**
Study of E7386 in Participants With Selected Advanced Neoplasms	**TARGETS** CBP, Beta-catenin

LOCATIONS: Glasgow (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Sutton (United Kingdom)

FOUNDATIONONE®CDx

PATIENT
Chen, Chien Liu

TUMOR TYPE
Colon adenocarcinoma (CRC)

REPORT DATE
11 May 2023

CLINICAL TRIALS

ORDERED TEST #   ORD-1622372-01

GENE
KRAS

ALTERATION
G12V

RATIONALE
KRAS activating mutations or amplification may predict sensitivity to inhibitors of MAPK pathway components, including MEK inhibitors. KRAS mutation may predict sensitivity to PLK1 inhibitors. Limited clinical and preclinical studies indicate KRAS mutations may predict sensitivity to MEK-pan-RAF dual inhibitors. Preclinical evidence suggests that KRAS activating mutations may predict sensitivity to SOS1 inhibitors. Multiple clinical studies have reported lack of efficacy of MEK inhibitors as monotherapy for treatment of KRAS-mutant colorectal cancer; combination therapies may be more effective.

NCT04803318
PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT04985604
PHASE 1/2

DAY101 Monotherapy or in Combination With Other Therapies for Patients With Solid Tumors

TARGETS
BRAF, MEK

LOCATIONS: Busan (Korea, Republic of), Seoul (Korea, Republic of), Clayton (Australia), Edegem (Belgium), Oregon, Barcelona (Spain), Madrid (Spain), California, Colorado

NCT03284502
PHASE 1

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

TARGETS
MEK, RAFs, NRAS

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

NCT04303403
PHASE 1

Study of Trametinib and Ruxolitinib in Colorectal Cancer and Pancreatic Adenocarcinoma

TARGETS
JAK2, JAK1, MEK

LOCATIONS: Singapore (Singapore)

NCT04870034
PHASE NULL

Binimetinib and Palbociclib Before Surgery for the Treatment of Operable KRAS-Positive Lung, Colorectal, or Pancreatic Cancer

TARGETS
MEK, CDK4, CDK6

LOCATIONS: New York

NCT03905148
PHASE 1/2

Study of the Safety and Pharmacokinetics of BGB-283 and PD-0325901 in Patients With Advanced or Refractory Solid Tumors

TARGETS
RAFs, EGFR, MEK

LOCATIONS: Nedlands (Australia), Blacktown (Australia), Randwick (Australia), Melbourne (Australia), California, Texas

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FOUNDATIONONE®**CDx**

PATIENT
Chen, Chien Liu

TUMOR TYPE
Colon adenocarcinoma (CRC)

REPORT DATE
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CLINICAL TRIALS

NCT04551521

PHASE 2

CRAFT: The NCT-PMO-1602 Phase II Trial

TARGETS
PD-L1, AKTs, MEK, BRAF, ALK, RET, ERBB2

LOCATIONS: Lübeck (Germany), Würzburg (Germany), Mainz (Germany), Heidelberg (Germany), Tübingen (Germany)

NCT04892017

PHASE 1/2

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

TARGETS
ULK1, ULK2, MEK

LOCATIONS: Massachusetts, New York, Texas, Pennsylvania

NCT04817956

PHASE 2

Improving Public Cancer Care by Implementing Precision Medicine in Norway

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

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

NCT04720976

PHASE 1/2

JAB-3312 Activity in Adult Patients With Advanced Solid Tumors

TARGETS
MEK, SHP2, PD-1, EGFR, KRAS

LOCATIONS: Utah, California, Arizona, Minnesota, Illinois, Michigan, Oklahoma, Missouri, Indiana, Connecticut

FOUNDATIONONE® CDx

PATIENT
Chen, Chien Liu

TUMOR TYPE
Colon adenocarcinoma (CRC)

REPORT DATE
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CLINICAL TRIALS

ORDERED TEST # ORD-1622372-01

GENE
PIK3CA

ALTERATION
E726K, M1043I

RATIONALE

PIK3CA activating mutations may lead to activation of the PI3K-AKT-mTOR pathway and may therefore indicate sensitivity to inhibitors of this pathway. Strong clinical data support sensitivity of PIK3CA-mutated solid tumors to the PI3K-alpha inhibitor alpelisib. Several clinical studies have shown that inhibitors of the PI3K-AKT-mTOR pathway have not produced significant clinical benefit when used as a monotherapy in patients with colorectal cancer; combination therapies may be required to overcome this lack of response. On the basis of preclinical and limited clinical data, PIK3CA activating mutations may predict sensitivity to glutaminase inhibitors.

NCT04589845

PHASE 2

Tumor-Agnostic Precision Immuno-Oncology and Somatic Targeting Rational for You (TAPISTRY) Platform Study

TARGETS
TRKB, ALK, TRKC, ROS1, TRKA, RET, PD-L1, AKTs, ERBB2, MDM2, PI3K-alpha, RAFs, NRAS

LOCATIONS: Taipei City (Taiwan), Taoyuan County (Taiwan), Tainan (Taiwan), Shanghai City (China), Shanghai (China), Shatin (Hong Kong), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Seongnam-si (Korea, Republic of), Xi'an (China)

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT04526470

PHASE 1/2

Alpelisib and Paclitaxel in PIK3CA-altered Gastric Cancer

TARGETS
PI3K-alpha

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

NCT03772561

PHASE 1

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

TARGETS
PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

NCT04551521

PHASE 2

CRAFT: The NCT-PMO-1602 Phase II Trial

TARGETS
PD-L1, AKTs, MEK, BRAF, ALK, RET, ERBB2

LOCATIONS: Lübeck (Germany), Würzburg (Germany), Mainz (Germany), Heidelberg (Germany), Tübingen (Germany)

Electronically signed by Erik Williams, M.D. | 11 May 2023
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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

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FOUNDATIONONE®CDx

PATIENT
Chen, Chien Liu

TUMOR TYPE
Colon adenocarcinoma (CRC)

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CLINICAL TRIALS

ORDERED TEST # ORD-1622372-01

NCT04317105

PHASE 1/2

Testing the Addition of an Anti-cancer Drug, Copanlisib, to the Usual Immunotherapy (Nivolumab With or Without Ipilimumab) in Patients With Advanced Solid Cancers That Have Changes in the Following Genes: PIK3CA and PTEN

TARGETS
PD-1, CTLA-4, PI3K

LOCATIONS: Toronto (Canada), Texas, Virginia

NCT05036226

PHASE 1/2

COAST Therapy in Advanced Solid Tumors and Prostate Cancer

TARGETS
DDR2, ABL, SRC, KIT, mTOR

LOCATIONS: South Carolina

NCT04817956

PHASE 2

Improving Public Cancer Care by Implementing Precision Medicine in Norway

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

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

NCT03006172

PHASE 1

To Evaluate the Safety, Tolerability, and Pharmacokinetics of GDC-0077 Single Agent in Participants With Solid Tumors and in Combination With Endocrine and Targeted Therapies in Participants With Breast Cancer

TARGETS
PI3K-alpha, Aromatase, ER, CDK6, CDK4

LOCATIONS: London (United Kingdom), Surrey (United Kingdom), Bordeaux (France), Barcelona (Spain), Valencia (Spain), Toronto (Canada), Massachusetts, New York, Tennessee

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NCT03673787

PHASE 1/2

A Trial of Ipatasertib in Combination With Atezolizumab

TARGETS
AKTs, PD-L1

LOCATIONS: Sutton (United Kingdom)

FOUNDATIONONE®CDx	PATIENT Chen, Chien Liu	TUMOR TYPE Colon adenocarcinoma (CRC)	REPORT DATE 11 May 2023

ORDERED TEST # ORD-1622372-01

APPENDIX   Variants of Unknown Significance

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.

BRCA2
NM_000059.3: c.3422C>T
(p.T1141I)
chr13:32911914

CUL4A
NM_003589.2: c.896A>G
(p.N299S)
chr13:113897442

FGF6
NM_020996.1: c.127C>T
(p.R43C)
chr12:4554610

KMT2D (MLL2)
NM_003482.4: c.8774C>T
(p.A2925V)
chr12:49432365

PARP3
NM_005485.4: c.704C>T
(p.A235V)
chr3:51979083 and
NM_005485.4: c.436C>T
(p.H146Y)
chr3:51978529

PIK3C2G
NM_004570.4: c.3967G>A
(p.E1323K)
chr12:18762471

FOUNDATIONONE®CDx

PATIENT
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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 or WTX)
APC	AR	ARAF	ARFRP1	ARID1A	ASXL1	ATM	ATR	ATRX
AURKA	AURKB	AXIN1	AXL	BAP1	BARD1	BCL2	BCL2L1	BCL2L2
BCL6	BCOR	BCORL1	BRAF	BRCA1	BRCA2	BRD4	BRIP1	BTG1
BTG2	BTK	CALR	CARD11	CASP8	CBFB	CBL	CCND1	CCND2
CCND3	CCNE1	CD22	CD274 (PD-L1)	CD70	CD79A	CD79B	CDC73	CDH1
CDK12	CDK4	CDK6	CDK8	CDKN1A	CDKN1B	CDKN2A	CDKN2B	CDKN2C
CEBPA	CHEK1	CHEK2	CIC	CREBBP	CRKL	CSF1R	CSF3R	CTCF
CTNNA1	CTNNB1	CUL3	CUL4A	CXCR4	CYP17A1	DAXX	DDR1	DDR2
DIS3	DNMT3A	DOT1L	EED	EGFR	EMSY (C11orf30)	EP300	EPHA3	EPHB1
EPHB4	ERBB2	ERBB3	ERBB4	ERCC4	ERG	ERRFI1	ESR1	EZH2
FANCA	FANCC	FANCG	FANCL	FAS	FBXW7	FGF10	FGF12	FGF14
FGF19	FGF23	FGF3	FGF4	FGF6	FGFR1	FGFR2	FGFR3	FGFR4
FH	FLCN	FLT1	FLT3	FOXL2	FUBP1	GABRA6	GATA3	GATA4
GATA6	GID4 (C17orf39)	GNA11	GNA13	GNAQ	GNAS	GRM3	GSK3B	H3-3A (H3F3A)
HDAC1	HGF	HNF1A	HRAS	HSD3B1	ID3	IDH1	IDH2	IGF1R
IKBKE	IKZF1	INPP4B	IRF2	IRF4	IRS2	JAK1	JAK2	JAK3
JUN	KDM5A	KDM5C	KDM6A	KDR	KEAP1	KEL	KIT	KLHL6
KMT2A (MLL)	KMT2D (MLL2)	KRAS	LTK	LYN	MAF	MAP2K1 (MEK1)	MAP2K2 (MEK2)	MAP2K4
MAP3K1	MAP3K13	MAPK1	MCL1	MDM2	MDM4	MED12	MEF2B	MEN1
MERTK	MET	MITF	MKNK1	MLH1	MPL	MRE11 (MRE11A)	MSH2	MSH3
MSH6	MST1R	MTAP	MTOR	MUTYH	MYC	MYCL (MYCL1)	MYCN	MYD88
NBN	NF1	NF2	NFE2L2	NFKBIA	NKX2-1	NOTCH1	NOTCH2	NOTCH3
NPM1	NRAS	NSD2 (WHSC1 or MMSET)		NSD3 (WHSC1L1)	NT5C2	NTRK1	NTRK2	NTRK3
P2RY8	PALB2	PARP1	PARP2	PARP3	PAX5	PBRM1	PDCD1 (PD-1)	PDCD1LG2 (PD-L2)
PDGFRA	PDGFRB	PDK1	PIK3C2B	PIK3C2G	PIK3CA	PIK3CB	PIK3R1	PIM1
PMS2	POLD1	POLE	PPARG	PPP2R1A	PPP2R2A	PRDM1	PRKAR1A	PRKCI
PRKN (PARK2)	PTCH1	PTEN	PTPN11	PTPRO	QKI	RAC1	RAD21	RAD51
RAD51B	RAD51C	RAD51D	RAD52	RAD54L	RAF1	RARA	RB1	RBM10
REL	RET	RICTOR	RNF43	ROS1	RPTOR	SDHA	SDHB	SDHC
SDHD	SETD2	SF3B1	SGK1	SMAD2	SMAD4	SMARCA4	SMARCB1	SMO
SNCAIP	SOCS1	SOX2	SOX9	SPEN	SPOP	SRC	STAG2	STAT3
STK11	SUFU	SYK	TBX3	TEK	TENT5C (FAM46C)		TET2	TGFBR2
TIPARP	TNFAIP3	TNFRSF14	TP53	TSC1	TSC2	TYRO3	U2AF1	VEGFA
VHL	WT1	XPO1	XRCC2	ZNF217	ZNF703			

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

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

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

FOUNDATIONONE®CDx

PATIENT
Chen, Chien Liu

TUMOR TYPE
Colon adenocarcinoma (CRC)

REPORT DATE
11 May 2023

FoundationOne CDx fulfills the requirements of the European Directive 98/79 EC for in vitro diagnostic medical devices and is registered as a CE-IVD product by Foundation Medicine's EU Authorized Representative, Qarad b.v.b.a,

Cipalstraat 3, 2440 Geel, Belgium. CE

ABOUT FOUNDATIONONE CDX

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

Please refer to technical information for performance specification details: www.rochefoundationmedicine.com/f1cdxtech.

INTENDED USE

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

TEST PRINCIPLE

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

detection of alterations in a total of 324 genes.

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

THE REPORT

Incorporates analyses of peer-reviewed studies and other publicly available information identified by Foundation Medicine; these analyses and information may include associations between a molecular alteration (or lack of alteration) and one or more drugs with potential clinical benefit (or potential lack of clinical benefit), including drug candidates that are being studied in clinical research. The F1CDx report may be used as an aid to inform molecular eligibility for clinical trials. Note: A finding of biomarker alteration does not necessarily indicate pharmacologic effectiveness (or lack thereof) of any drug or treatment regimen; a finding of no biomarker alteration does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness) of any drug or treatment regimen.

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

Qualified Alteration Calls (Equivocal and Subclonal)
An alteration denoted as "amplification – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence that the copy number of a gene exceeds the threshold for identifying copy number amplification. The threshold used in FoundationOne CDx for identifying a copy number amplification is four (4) for *ERBB2* and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence for homozygous deletion of the gene in question. An alteration denoted as "subclonal" is one that the FoundationOne CDx analytical

methodology has identified as being present in <10% of the assayed tumor DNA.

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

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

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

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

Limitations

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

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

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

2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.

3. Homologous Recombination status may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas (Coleman et al., 2017; 28916367). Samples with deleterious *BRCA1/2* alteration and/or Loss of Heterozygosity (LOH) score ≥ 16% will be reported as "HRD Positive" and samples with absence of these findings will be reported as "HRD Not Detected," agnostic of potential secondary *BRCA1/2* reversion alterations. Certain potentially deleterious missense or small in-frame deletions in *BRCA1/2* may not be classified as deleterious and, in the absence of an elevated LOH profile, samples with such mutations may be classified as "HRD Not Detected." A result of "HRD Not Detected" does not rule out the presence of a *BRCA1/2* alteration or an elevated LOH profile outside the assay performance characteristic limitations.

4. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.

5. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.

6. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.

7. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

REPORT HIGHLIGHTS

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

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

Interquartile Range = 1st Quartile to 3rd Quartile

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

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tumor sequencing is germline or somatic. Interpretation should be based on clinical context.

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

Drugs referenced in this Report may not be suitable for a particular patient. The selection of any, all or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) resides entirely within the discretion of the treating physician. Indeed, the information in this Report must be considered in conjunction with all other relevant information regarding a particular patient, before the patient's treating physician recommends a course of treatment. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking

into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this Test, or the information contained in this Report. Certain sample or variant characteristics may result in reduced sensitivity. FoundationOne CDx is performed using DNA derived from tumor, and as such germline events may not be reported.

SELECT ABBREVIATIONS

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

REFERENCE SEQUENCE INFORMATION

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

MR Suite Version (RG) 7.8.0

The median exon coverage for this sample is 531x

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APPENDIX   References

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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. Parikh et al., 2021; DOI: 10.1038/s43018-021-00269-7
8. Fukuoka S, et al. J. Clin. Oncol. (2020) pmid: 32343640
9. Kim et al., 2020; DOI: 10.1016/j.annonc.2020.04.073
10. Zhang Y, et al. BMC Gastroenterol (2021) pmid: 34688262
11. Sinicrope FA, et al. J. Clin. Oncol. (2013) pmid: 24019539
12. Gavin PG, et al. Clin. Cancer Res. (2012) pmid: 23045248
13. Bertagnolli MM, et al. J. Clin. Oncol. (2009) pmid: 19273709
14. Van Cutsem E, et al. J. Clin. Oncol. (2009) pmid: 19451425
15. Ribic CM, et al. N. Engl. J. Med. (2003) pmid: 12867608
16. Sargent DJ, et al. J. Clin. Oncol. (2010) pmid: 20498393
17. Fallik D, et al. Cancer Res. (2003) pmid: 14522894
18. Guastadisegni C, et al. Eur. J. Cancer (2010) pmid: 20627535
19. Pawlik TM, et al. Dis. Markers (2004) pmid: 15528785
20. Kocarnik JM, et al. Gastroenterol Rep (Oxf) (2015) pmid: 26337942
21. Nature (2012) pmid: 22810696
22. Histopathology (2007) pmid: 17204026
23. Samowitz WS, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11535541
24. Elsaleh H, et al. Clin Colorectal Cancer (2001) pmid: 12445368
25. Brueckl WM, et al. Anticancer Res. () pmid: 12820457
26. Guidoboni M, et al. Am. J. Pathol. (2001) pmid: 11438476
27. Gryfe R, et al. N. Engl. J. Med. (2000) pmid: 10631274
28. Sinicrope FA, et al. Gastroenterology (2006) pmid: 16952542
29. Laghi L, et al. Dig Dis (2012) pmid: 22722556
30. You JF, et al. Br. J. Cancer (2010) pmid: 21081928
31. Bairwa NK, et al. Methods Mol. Biol. (2014) pmid: 24623249
32. Boland CR, et al. Cancer Res. (1998) pmid: 9823339
33. Boland CR, et al. Gastroenterology (2010) pmid: 20420947
34. Samstein RM, et al. Nat. Genet. (2019) pmid: 30643254
35. Goodman AM, et al. Mol. Cancer Ther. (2017) pmid: 28835386
36. Goodman AM, et al. Cancer Immunol Res (2019) pmid: 31405947
37. Cristescu R, et al. Science (2018) pmid: 30309915
38. Ready N, et al. J. Clin. Oncol. (2019) pmid: 30785829
39. Hellmann MD, et al. N. Engl. J. Med. (2018) pmid: 29658845
40. Hellmann MD, et al. Cancer Cell (2018) pmid: 29657128
41. Hellmann MD, et al. Cancer Cell (2018) pmid: 29731394
42. Rozeman EA, et al. Nat Med (2021) pmid: 33558721
43. Sharma P, et al. Cancer Cell (2020) pmid: 32916128
44. Marabelle A, et al. Lancet Oncol. (2020) pmid: 32919526
45. Ott PA, et al. J. Clin. Oncol. (2019) pmid: 30557521
46. Cristescu R, et al. J Immunother Cancer (2022) pmid: 35101941
47. Friedman CF, et al. Cancer Discov (2022) pmid: 34876409

48. Sturgill EG, et al. Oncologist (2022) pmid: 35274716
49. Schenker at al., 2022; AACR Abstract 7845
50. Legrand et al., 2018; ASCO Abstract 12000
51. Fabrizio DA, et al. J Gastrointest Oncol (2018) pmid: 30151257
52. Stadler ZK, et al. J. Clin. Oncol. (2016) pmid: 27022117
53. Shao C, et al. JAMA Netw Open (2020) pmid: 33119110
54. Schwartz et al., 2018; ASCO Abstract 572
55. Innocenti F, et al. J Clin Oncol (2019) pmid: 30865548
56. Lee DW, et al. Clin Cancer Res (2019) pmid: 31285374
57. Randon G, et al. Eur J Cancer (2022) pmid: 34933155
58. Chen EX, et al. JAMA Oncol (2020) pmid: 32379280
59. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
60. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
61. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
62. Rizvi NA, et al. Science (2015) pmid: 25765070
63. Johnson BE, et al. Science (2014) pmid: 24336570
64. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
65. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
66. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
67. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
68. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
69. Nakano H, et al. Proc. Natl. Acad. Sci. U.S.A. (1984) pmid: 6320174
70. Pylayeva-Gupta Y, et al. Nat. Rev. Cancer (2011) pmid: 21993244
71. Yamaguchi T, et al. Int. J. Oncol. (2011) pmid: 21523318
72. Watanabe M, et al. Cancer Sci. (2013) pmid: 23438367
73. Gilmartin AG, et al. Clin. Cancer Res. (2011) pmid: 21245089
74. Yeh JJ, et al. Mol. Cancer Ther. (2009) pmid: 19372556
75. Tsimberidou et al., 2013; ASCO Abstract e22086
76. Infante JR, et al. Lancet Oncol. (2012) pmid: 22805291
77. Zimmer L, et al. Clin. Cancer Res. (2014) pmid: 24947927
78. Bennouna J, et al. Invest New Drugs (2011) pmid: 20127139
79. Weekes CD, et al. Clin. Cancer Res. (2013) pmid: 23434733
80. Hochster et al., 2013; ASCO GI Abstract 380
81. Juric et al., 2014; ASCO Abstract 9051
82. Lamba S, et al. Cell Rep (2014) pmid: 25199829
83. Sun C, et al. Cell Rep (2014) pmid: 24685132
84. Guo C, et al. Lancet Oncol (2020) pmid: 33128873
85. Krebs et al., 2021; AACR Abstract CT019
86. Shinde et al., 2020; AACR Abstract CT143
87. Lu H, et al. Mol Cancer Ther (2019) pmid: 31068384
88. Mainardi S, et al. Nat Med (2018) pmid: 29808006
89. Koczywas et al., 2021; AACR Abstract LB001
90. Bendell et al., 2020; EORTC-NCI-AACR Abstract 5
91. Hofmann MH, et al. Cancer Discov (2021) pmid: 32816843
92. He H, et al. J Med Chem (2022) pmid: 36173339
93. Zhang S, et al. J Med Chem (2022) pmid: 36384290
94. Liu M, et al. ACS Med Chem Lett (2023) pmid: 36793426
95. Ramharter J, et al. J Med Chem (2021) pmid: 33719426
96. Ketcham JM, et al. J Med Chem (2022) pmid: 35833726
97. Plangger A, et al. Discov Oncol (2022) pmid: 36048281
98. Ma Y, et al. Cancers (Basel) (2022) pmid: 36139627
99. Luo J, et al. Cell (2009) pmid: 19490893
100. Barzi et al., 2020; AACR Abstract CT235

101. Van Cutsem E, et al. J. Clin. Oncol. (2011) pmid: 21502544
102. Bokemeyer C, et al. Ann. Oncol. (2011) pmid: 21228335
103. Karapetis CS, et al. N. Engl. J. Med. (2008) pmid: 18946061
104. De Roock W, et al. Ann. Oncol. (2008) pmid: 17998284
105. Douillard JY, et al. Ann. Oncol. (2014) pmid: 24718886
106. Douillard JY, et al. N. Engl. J. Med. (2013) pmid: 24024839
107. Amado RG, et al. J. Clin. Oncol. (2008) pmid: 18316791
108. Lièvre A, et al. Cancer Res. (2006) pmid: 16618717
109. De Roock W, et al. Lancet Oncol. (2011) pmid: 21163703
110. Chen J, et al. BMC Cancer (2014) pmid: 25367198
111. Li W, et al. BMC Cancer (2015) pmid: 25929517
112. Hu J, et al. Medicine (Baltimore) (2016) pmid: 27977612
113. Zekri J, et al. Genet. Mol. Res. (2017) pmid: 28218784
114. Staudacher JJ, et al. Clin Transl Gastroenterol (2017) pmid: 29048416
115. Wang Y, et al. Virchows Arch. (2018) pmid: 29705968
116. Guo F, et al. Sci Rep (2018) pmid: 29666387
117. Mármol I, et al. Int J Mol Sci (2017) pmid: 28106826
118. Kwak MS, et al. Medicine (Baltimore) (2017) pmid: 28858102
119. Kahn S, et al. Anticancer Res. () pmid: 3310850
120. Akagi K, et al. Biochem. Biophys. Res. Commun. (2007) pmid: 17150185
121. Bollag G, et al. J. Biol. Chem. (1996) pmid: 8955068
122. Buhrman G, et al. Proc. Natl. Acad. Sci. U.S.A. (2010) pmid: 20194776
123. Sci. STKE (2004) pmid: 15367757
124. Edkins S, et al. Cancer Biol. Ther. (2006) pmid: 16969076
125. Feig LA, et al. Mol. Cell. Biol. (1988) pmid: 3043178
126. Gremer L, et al. Hum. Mutat. (2011) pmid: 20949621
127. Janakiraman M, et al. Cancer Res. (2010) pmid: 20570890
128. Kim E, et al. Cancer Discov (2016) pmid: 27147599
129. Lukman S, et al. PLoS Comput. Biol. (2010) pmid: 20838576
130. Naguib A, et al. J Mol Signal (2011) pmid: 21371307
131. Prior IA, et al. Cancer Res. (2012) pmid: 22589270
132. Privé GG, et al. Proc. Natl. Acad. Sci. U.S.A. (1992) pmid: 1565661
133. Scheffzek K, et al. Science (1997) pmid: 9219684
134. Scholl C, et al. Cell (2009) pmid: 19490892
135. Smith G, et al. Br. J. Cancer (2010) pmid: 20147967
136. Tyner JW, et al. Blood (2009) pmid: 19075190
137. Valencia A, et al. Biochemistry (1991) pmid: 2029511
138. White Y, et al. Nat Commun (2016) pmid: 26854029
139. Wiest JS, et al. Oncogene (1994) pmid: 8058307
140. Angeles AKJ, et al. Oncol Lett (2019) pmid: 31289513
141. Tong JH, et al. Cancer Biol. Ther. (2014) pmid: 24642870
142. Loree JM, et al. Clin Cancer Res (2021) pmid: 34117033
143. Xu JM, et al. Clin Cancer Res (2017) pmid: 28424201
144. Kim SY, et al. Cancer Genet (2021) pmid: 34315006
145. Soeda H, et al. Int. J. Clin. Oncol. (2013) pmid: 22638623
146. De Roock W, et al. Lancet Oncol. (2010) pmid: 20619739
147. Cappuzzo F, et al. Br J Cancer (2008) pmid: 18577988
148. Tol J, et al. Eur J Cancer (2010) pmid: 20413299
149. Prenen H, et al. Clin Cancer Res (2009) pmid: 19366826
150. Bray SM, et al. (2019) pmid: 31653970
151. Karapetis CS, et al. Clin. Cancer Res. (2014) pmid: 24218517
152. Moiseyenko VM, et al. Clin Drug Investig (2018) pmid: 29470838

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TUMOR TYPE
Colon adenocarcinoma (CRC)

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APPENDIX References

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153. Fu X, et al. Front Oncol (2021) pmid: 33842311
154. Pentheroudakis G, et al. BMC Cancer (2013) pmid: 23374602
155. Vaughn CP, et al. Genes Chromosomes Cancer (2011) pmid: 21305640
156. Janku F, et al. Target Oncol (2013) pmid: 23400451
157. Irahara N, et al. Diagn. Mol. Pathol. (2010) pmid: 20736745
158. Schirripa M, et al. Int. J. Cancer (2015) pmid: 24806288
159. Cercek A, et al. Clin. Cancer Res. (2017) pmid: 28446505
160. Zhan T, et al. Oncogene (2017) pmid: 27617575
161. Jung YS, et al. Exp Mol Med (2020) pmid: 32037398
162. Krishnamurthy N, et al. Cancer Treat Rev (2018) pmid: 29169144
163. Kawazoe et al., 2021; ESMO Abstract 473P
164. Yamada K, et al. Cancer Res (2021) pmid: 33408116
165. Kanda Y, et al. Biochem Biophys Res Commun (2022) pmid: 34837838
166. Christie M, et al. Oncogene (2013) pmid: 23085758
167. Quyn AJ, et al. Surgeon (2008) pmid: 19110823
168. Luke JJ, et al. Clin Cancer Res (2019) pmid: 30635339
169. Logan CY, et al. Annu. Rev. Cell Dev. Biol. (2004) pmid: 15473860
170. Eklof Spink K, et al. EMBO J. (2001) pmid: 11707392
171. Liu J, et al. J. Mol. Biol. (2006) pmid: 16753179
172. Dikovskaya D, et al. J. Cell. Sci. (2010) pmid: 20144988
173. Murphy SJ, et al. Dig. Dis. Sci. (2007) pmid: 17410430
174. Aretz S, et al. Hum. Mutat. (2004) pmid: 15459959
175. Landrum MJ, et al. Nucleic Acids Res. (2018) pmid: 29165669
176. Kerr SE, et al. J Mol Diagn (2013) pmid: 23159591
177. Annu Rev Pathol (2011) pmid: 21090969
178. Kastritis E, et al. Int. J. Cancer (2009) pmid: 18844223
179. Half E, et al. Orphanet J Rare Dis (2009) pmid: 19822006
180. Fritsch C, et al. Mol. Cancer Ther. (2014) pmid: 24608574
181. Juric D, et al. J. Clin. Oncol. (2018) pmid: 29401002
182. Gallant JN, et al. NPJ Precis Oncol (2019) pmid: 30793038
183. Delestre F, et al. Sci Transl Med (2021) pmid: 34613809
184. Morschhauser F, et al. Mol Cancer Ther (2020) pmid: 31619463
185. Patnaik A, et al. Ann. Oncol. (2016) pmid: 27672108
186. Santin AD, et al. Gynecol Oncol Rep (2020) pmid: 31934607
187. Damodaran S, et al. J Clin Oncol (2022) pmid: 35133871
188. André F, et al. N. Engl. J. Med. (2019) pmid: 31091374
189. Smyth LM, et al. NPJ Breast Cancer (2021) pmid: 33863913
190. Varnier R, et al. Eur J Cancer (2019) pmid: 31351267
191. Basse C, et al. JCO Precis Oncol (2018) pmid: 32914004
192. Sultova E, et al. Arch Gynecol Obstet (2021) pmid: 33277683
193. Mackay HJ, et al. Cancer (2014) pmid: 24166148
194. Myers AP, et al. Gynecol. Oncol. (2016) pmid: 27016228
195. Dhami J, et al. Cold Spring Harb Mol Case Stud (2018) pmid: 29588307
196. Harris EJ, et al. Front Oncol (2019) pmid: 30863722
197. Hanna GJ, et al. Clin Cancer Res (2018) pmid: 29301825
198. Zhao Y, et al. Cancer Res (2020) pmid: 32907836
199. Ng K, et al. Clin. Cancer Res. (2013) pmid: 23743569

200. Ganesan P, et al. Mol. Cancer Ther. (2013) pmid: 24092809
201. Janku F, et al. Cell Rep (2014) pmid: 24440717
202. Brannon AR, et al. Genome Biol. (2014) pmid: 25164765
203. Huang L, et al. Arch Med Sci (2014) pmid: 24701207
204. Fong et al., 2022; ASCO GI Abstract 57
205. Samuels Y, et al. Cancer Cell (2005) pmid: 15950905
206. Nat. Rev. Cancer (2009) pmid: 19629070
207. Kang S, et al. Proc. Natl. Acad. Sci. U.S.A. (2005) pmid: 15647370
208. Ikenoue T, et al. Cancer Res. (2005) pmid: 15930273
209. Gymnopoulos M, et al. Proc. Natl. Acad. Sci. U.S.A. (2007) pmid: 17376864
210. Horn S, et al. Oncogene (2008) pmid: 18317450
211. Rudd ML, et al. Clin. Cancer Res. (2011) pmid: 21266528
212. Hon WC, et al. Oncogene (2012) pmid: 22120714
213. Burke JE, et al. Proc. Natl. Acad. Sci. U.S.A. (2012) pmid: 22949682
214. Wu H, et al. Proc. Natl. Acad. Sci. U.S.A. (2009) pmid: 19915146
215. Laurenti R, et al. Rev Saude Publica (1990) pmid: 2103068
216. Dan S, et al. Cancer Res. (2010) pmid: 20530683
217. Oda K, et al. Cancer Res. (2008) pmid: 18829572
218. Zhao L, et al. Oncogene (2008) pmid: 18794883
219. Lui VW, et al. Cancer Discov (2013) pmid: 23619167
220. Ross RL, et al. Oncogene (2013) pmid: 22430209
221. Rivière JB, et al. Nat. Genet. (2012) pmid: 22729224
222. Shibata T, et al. Cancer Lett. (2009) pmid: 19394761
223. Dogruluk T, et al. Cancer Res. (2015) pmid: 26627007
224. Croessmann S, et al. Clin. Cancer Res. (2018) pmid: 29284706
225. Ng PK, et al. Cancer Cell (2018) pmid: 29533785
226. Spangle JM, et al. (2020) pmid: 32929011
227. Chen L, et al. Nat Commun (2018) pmid: 29636477
228. Jin N, et al. J Clin Invest (2021) pmid: 34779417
229. Hirai H, et al. Cancer Biol. Ther. (2010) pmid: 20107315
230. Bridges KA, et al. Clin. Cancer Res. (2011) pmid: 21799033
231. Rajeshkumar NV, et al. Clin. Cancer Res. (2011) pmid: 21389100
232. Osman AA, et al. Mol. Cancer Ther. (2015) pmid: 25504633
233. Xu L, et al. Mol. Cancer Ther. (2002) pmid: 12489850
234. Xu L, et al. Mol. Med. (2001) pmid: 11713371
235. Camp ER, et al. Cancer Gene Ther. (2013) pmid: 23470564
236. Kim SS, et al. Nanomedicine (2015) pmid: 25240597
237. Pirollo KF, et al. Mol. Ther. (2016) pmid: 27357628
238. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27601554
239. Moore et al., 2019; ASCO Abstract 5513
240. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27998224
241. Oza et al., 2015; ASCO Abstract 5506
242. Lee J, et al. Cancer Discov (2019) pmid: 31315834
243. Méndez E, et al. Clin. Cancer Res. (2018) pmid: 29535125
244. Seligmann JF, et al. J Clin Oncol (2021) pmid: 34538072
245. Gourley et al., 2016; ASCO Abstract 5571
246. Park H, et al. ESMO Open (2022) pmid: 36084396
247. Goh HS, et al. Cancer Res. (1995) pmid: 7585578
248. Berg M, et al. PLoS ONE (2010) pmid: 21103049
249. Han SW, et al. PLoS ONE (2013) pmid: 23700467

250. Peeters M, et al. Clin. Cancer Res. (2013) pmid: 23325582
251. Malhotra P, et al. Tumour Biol. (2013) pmid: 23526092
252. Di Bartolomeo M, et al. Target Oncol (2014) pmid: 23821376
253. Wangefjord S, et al. Diagn Pathol (2013) pmid: 23337059
254. Russo A, et al. J. Clin. Oncol. (2005) pmid: 16172461
255. Brown CJ, et al. Nat. Rev. Cancer (2009) pmid: 19935675
256. Joerger AC, et al. Annu. Rev. Biochem. (2008) pmid: 18410249
257. Kato S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12826609
258. Kamada R, et al. J. Biol. Chem. (2011) pmid: 20978130
259. Zerdoumi Y, et al. Hum. Mol. Genet. (2017) pmid: 28472496
260. Yamada H, et al. Carcinogenesis (2007) pmid: 17690113
261. Bougeard G, et al. J. Clin. Oncol. (2015) pmid: 26014290
262. Sorrell AD, et al. Mol Diagn Ther (2013) pmid: 23355100
263. Nichols KE, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11219776
264. Kleihues P, et al. Am. J. Pathol. (1997) pmid: 9006316
265. Gonzalez KD, et al. J. Clin. Oncol. (2009) pmid: 19204208
266. Lalloo F, et al. Lancet (2003) pmid: 12672316
267. Mandelker D, et al. Ann. Oncol. (2019) pmid: 31050713
268. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
269. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838
270. Xie M, et al. Nat. Med. (2014) pmid: 25326804
271. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
272. Severson EA, et al. Blood (2018) pmid: 29678827
273. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
274. Hematology Am Soc Hematol Educ Program (2018) pmid: 30504320
275. Chabon JJ, et al. Nature (2020) pmid: 32269342
276. Razavi P, et al. Nat. Med. (2019) pmid: 31768066
277. Cunningham D, et al. N. Engl. J. Med. (2004) pmid: 15269313
278. Jonker DJ, et al. N. Engl. J. Med. (2007) pmid: 18003960
279. Souglakos J, et al. Br J Cancer (2009) pmid: 19603024
280. Lambrechts et al., 2009; ASCO Abstract 4020
281. Papamichael D, et al. Eur J Cancer (2022) pmid: 35033994
282. Chibaudel et al., 2022; ASCO Abstract 3504
283. Stein A, et al. J Immunother Cancer (2021) pmid: 34315821
284. Price TJ, et al. Lancet Oncol. (2014) pmid: 24739896
285. Sakai D, et al. Eur J Cancer (2020) pmid: 32526634
286. Van Cutsem E, et al. J. Clin. Oncol. (2007) pmid: 17470858
287. Peeters M, et al. Clin. Cancer Res. (2015) pmid: 26341920
288. Watanabe J, et al. Int J Cancer (2022) pmid: 35723084
289. Kim TW, et al. Clin Colorectal Cancer (2018) pmid: 29703606
290. Shitara K, et al. Cancer Sci (2016) pmid: 27712015
291. Yoshino et al., 2022; ASCO Abstract LBA1
292. Pietrantonio F, et al. JAMA Oncol (2019) pmid: 31268481