FOUNDATIONONE®LIQUID CDx

PATIENT
Chou, Chia-Kai

TUMOR TYPE
Colon adenocarcinoma (CRC)
COUNTRY CODE
TW

REPORT DATE
01 Sep 2021
ORDERED TEST #
ORD-1175745-01

ABOUT THE TEST FoundationOne®Liquid CDx is a next generation sequencing (NGS) assay that identifies clinically relevant genomic alterations in circulating cell-free DNA.

PATIENT

DISEASE Colon adenocarcinoma (CRC)
NAME Chou, Chia-Kai
DATE OF BIRTH 30 May 1980
SEX Male
MEDICAL RECORD # 32396557

PHYSICIAN

ORDERING PHYSICIAN Yen, Chueh-Chuan
MEDICAL FACILITY Taipei Veterans General Hospital
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 205872
PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN ID CKC 5/30/1980
SPECIMEN TYPE Blood
DATE OF COLLECTION 20 August 2021
SPECIMEN RECEIVED 25 August 2021

Biomarker Findings

Blood Tumor Mutational Burden - 8 Muts/Mb
Microsatellite status - MSI-High Not Detected
Tumor Fraction - 14%

Genomic Findings

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

BRAF V600E, deletion exons 2-10
KRAS Q61H
MAP2K1 (MEK1) K57N
RNF43 R145*
TP53 C176R

3 Therapies with Clinical Benefit
4 Therapies with Lack of Response
19 Clinical Trials

BIOMARKER FINDINGS

Blood Tumor Mutational Burden - 8 Muts/Mb

Microsatellite status - MSI-High Not Detected

Tumor Fraction - 14%

GENOMIC FINDINGS		VAF %
BRAF -	V600E	14.2%
	deletion exons 2-10	0.42%
10 Trials see p. 16		
KRAS -	Q61H	0.21%
10 Trials see p. 18		

THERAPY AND CLINICAL TRIAL IMPLICATIONS

No therapies or clinical trials. See Biomarker Findings section

MSI-High not detected. No evidence of microsatellite instability in this sample (see Appendix section).

Tumor fraction is an estimate of the percentage of circulating-tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample based on observed aneuploid instability.

THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
Encorafenib + Cetuximab 2A	Selumetinib
	Trametinib
	⚠ Dabrafenib[1]
	⚠ Vemurafenib[1]
⚠ Cetuximab[1]	None
⚠ Panitumumab[1]	

⚠ *1. Patient may be resistant to indicated therapy*

☐ *NCCN category*

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GENOMIC FINDINGS		VAF %	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
MAP2K1 (MEK1) -	K57N	0.38%	None	Selumetinib
				Trametinib
10 Trials see p. 20				
RNF43 -	R145*	7.2%	None	None
3 Trials see p. 22				

▲ *1. Patient may be resistant to indicated therapy*

☐ *NCCN category*

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIALS OPTIONS

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

TP53 - C176R ..... p. 9

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

Variant Allele Frequency is not applicable for copy number alterations.

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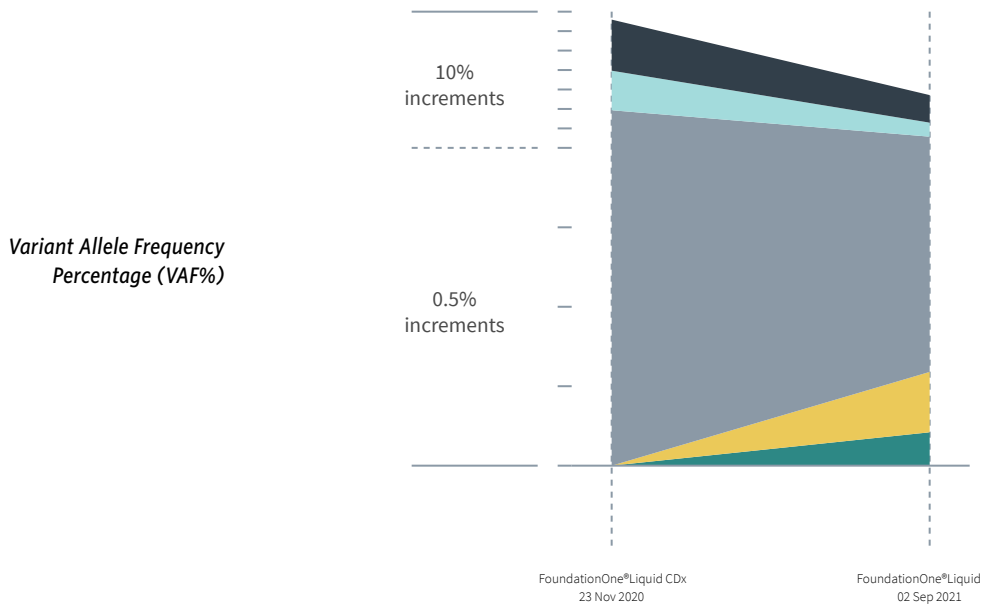

HISTORIC PATIENT FINDINGS		ORD-0949695-01 VAF%	ORD-1175745-01 VAF%	CHANGE FROM PREV.
Blood Tumor Mutational Burden		4 Muts/Mb	8 Muts/Mb	-
Microsatellite status		MSI-High Not Detected	MSI-High Not Detected	-
Tumor Fraction		34%	14%	-
BRAF	● V600E	26.3%	14.2%	-12.1%
	deletion exons 2-10	Not Detected	0.42%	+0.42%
KRAS	● Q61H	Not Detected	0.21%	+0.21%
MAP2K1 (MEK1)	● K57N	Not Detected	0.38%	+0.38%
RNF43	● R145*	20.3%	7.2%	-13.1%
TP53	● C176R	21.3%	7.2%	-14.1%

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

For some genes in FoundationOne Liquid CDx, only select exons are assayed. Therefore, an alteration found by a previous test may not have been confirmed despite overlapping gene lists. Please refer to the Appendix for the complete list of genes and exons assayed. The gene and biomarker list will be updated periodically to reflect new knowledge about cancer biology.

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

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

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

Not Detected = baited but not detected on test

Detected = present (VAF% is not applicable)

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VAF% = variant allele frequency percentage

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

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BIOMARKER

Blood Tumor Mutational Burden

RESULT

8 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence in NSCLC and HSNCC, increased bTMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[1-2] and anti-PD-1[3] therapies. In NSCLC, multiple clinical trials have shown patients with higher bTMB derive clinical benefit from immune checkpoint inhibitors following single agent or combination treatments with either CTLA4 inhibitors or chemotherapy, with reported high bTMB cutpoints ranging from 6 to 16 Muts/Mb[1]. In HNSCC, a Phase 3 trial showed that bTMB ≥16 Muts/Mb (approximate equivalency ≥8 Muts/Mb as measured by this assay) was associated with improved survival from treatment with a PD-L1 inhibitor alone or in combination with a CTLA-4 inhibitor[4].

FREQUENCY & PROGNOSIS

In 1 study, the median plasma TMB for 163 patients with metastatic CRC was 16.3 muts/Mb (approximately 8 muts/Mb as measured by this assay)[5]. 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[6].

FINDING SUMMARY

Blood tumor mutational burden (bTMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations from circulating tumor DNA in blood. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[7-8] and cigarette smoke in lung cancer[9-10], treatment with temozolomide-based chemotherapy in glioma[11-12], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[13-17], and microsatellite instability (MSI)[13,16-17]. High bTMB levels were not detected in this sample. It is unclear whether the bTMB levels in this sample would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[1-3]. Depending on the clinical context, TMB testing of an alternate sample or by another methodology could be considered.

BIOMARKER

Tumor Fraction

RESULT

14%

POTENTIAL TREATMENT STRATEGIES

Specimens with high tumor fraction values have high circulating-tumor DNA (ctDNA) content, and thus higher sensitivity for identifying genomic alterations. Such specimens are at a lower risk of false negative results[18]. However, if tumor fraction is not detected as high, it does not exclude the presence of disease burden or compromise the confidence of reported alterations. Tumor fraction levels currently have limited implications for diagnosis, surveillance, or therapy and should not be overinterpreted or compared from one blood draw to another. There are currently no targeted approaches to address specific tumor fraction levels. In the research setting, changes in tumor fraction estimates have been associated with treatment duration and clinical response and may be a useful indicator for future cancer management[19-24].

FREQUENCY & PROGNOSIS

Detectible ctDNA levels have been reported in a variety of tumor types, with higher tumor fraction levels reported for patients with metastatic (Stage 4) tumors compared with patients with localized disease (Stages 1 to 3)[25]. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer[26], Ewing sarcoma and osteosarcoma[27], prostate cancer[22], breast cancer[28], leiomyosarcoma[29], esophageal cancer[30], colorectal cancer[31], and gastrointestinal cancer[32].

FINDING SUMMARY

Tumor fraction provides an estimate of the percentage of ctDNA present in a cell-free DNA (cfDNA) sample. The tumor fraction estimate for this sample is based on the observed level of aneuploid instability. The tumor fraction algorithm utilized for FoundationOne Liquid CDx uses the allele frequencies of approximately 1,000 single-nucleotide polymorphism (SNP) sites across the genome. Unlike the maximum somatic allele frequency (MSAF) method of estimating ctDNA content[33], the tumor fraction metric does not take into account the allele frequency of individual variants but rather produces a more holistic estimate of ctDNA content using data from across the genome. The amount of ctDNA detected may correlate with disease burden and response to therapy[34-35].

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GENE

BRAF

ALTERATION
V600E, deletion exons 2-10

TRANSCRIPT ID
NM_004333

CODING SEQUENCE EFFECT
1799T>A

POTENTIAL TREATMENT STRATEGIES

Although case studies have reported that patients with parotid gland tumors and melanoma harboring BRAF rearrangements responded to regorafenib[36] and sorafenib[37] treatment, published data investigating the correlation between BRAF rearrangements and therapeutic benefit of pan-RAF inhibitors are limited; therefore, it is not known whether these agents would be beneficial in this case. BRAF V600 mutations activate MEK-ERK signaling and are associated with sensitivity to BRAF V600 mutation-specific inhibitors such as vemurafenib[38], dabrafenib[39], and encorafenib[40]; the combination of BRAF V600 mutation-selective inhibitors with MEK inhibitors such as encorafenib plus binimetinib[41], vemurafenib plus cobimetinib[42-43], or dabrafenib plus trametinib[44-46]; MEK inhibitors such as trametinib[47-49], cobimetinib[50], binimetinib[51], and selumetinib[52-54]; pan-RAF inhibitors such as sorafenib[55-57]; and ERK inhibitors[58]. For patients with BRAF V600-mutated CRC, single-agent BRAF inhibitors have shown limited clinical activity[59-62]. However, significant clinical benefit has been achieved with combinatorial approaches involving 2 or more of BRAF inhibitors, MEK inhibitors, and EGFR-targeting antibodies[62-69]. However, the concurrent deletion of the BRAF autoinhibitory domain has been correlated with resistance to vemurafenib and dabrafenib in clinical studies[70-71], as well as in preclinical studies of vemurafenib[71-74]. MEK inhibitors[70,73,75-76], ERK inhibitors[75], and second generation BRAF inhibitors PLX8394 and PLX7904[72] may therefore be more effective in this case. Clinical and preclinical data suggest that BRAF activating mutations or fusions may confer sensitivity to MEK inhibitors, such as trametinib[47-49,77-82], selumetinib[52-54], binimetinib[51,83], and cobimetinib[50,84-85]; and ERK inhibitors[58]. Although Phase 2 and case studies of sorafenib in BRAF V600-mutated thyroid carcinoma have reported clinical responses[55-56], a patient with a BRAF V600E-mutated NSCLC achieved a PR to sorafenib[57], and a case study has reported that a patient with BRAF-mutated GIST responded to regorafenib treatment[86]. Another patient with BRAF-mutated GIST did not respond to regorafenib treatment[87] and clinical studies in various other diseases have shown conflicting results regarding the correlation between BRAF V600 mutations and efficacy of sorafenib and other pan-RAF inhibitor, such as regorafenib[88-96]; therefore, it is not known whether these agents would be beneficial in this case. A BRAF autoinhibitory domain deletion emerged in a patient with BRAF V600E-mutated CRC during progression on cetuximab combined with vemurafenib and irinotecan[97]; therefore, it is unclear whether cetuximab combined with BRAF inhibitors would be beneficial here. Deletions within the BRAF autoinhibitory domain have been identified in 3 patients with V600-mutated melanoma who progressed on combination dabrafenib plus trametinib[98-100] and in a fourth patient who relapsed on encorafenib plus binimetinib[70]; therefore, it is unlikely that the combination of BRAF and MEK inhibitors would be beneficial here. 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)[101-110]. 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[103,106-107,110-113]. 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[114-119], to be a mechanism of acquired[120-121] or primary[122] resistance, or to be enriched in nonresponders versus responders[117]. A Phase 1 trial of the ERK1/2 inhibitor ulixertinib reported PRs for 16% (3/19) of previously treated patients and 1 out of 2 newly diagnosed patients with BRAF V600E-mutant melanoma, 25% (3/12) of patients with BRAF-mutated lung cancer (2 with V600E and 1 with L597Q), and 19% (4/21) of patients with other BRAF-mutated cancers (2 with G469A, 1 with V600E, and 1 with L485W); 2 patients with BRAF V600E mutations also experienced CNS response[123]. BRAF inhibitors can induce adverse effects such as the development of cutaneous squamous cell carcinomas (SCC), keratoacanthomas, and new primary melanomas caused by inactivation of wild-type BRAF and leading to paradoxical activation of the MAPK pathway[38-39,124]. Meta-analysis confirmed a reduced risk of developing cutaneous SCC with combined BRAF- and MEK-inhibition relative to BRAF-inhibitor monotherapy[125]. A Phase 1/2 trial of PLX8394, a next-generation BRAF inhibitor predicted to not induce paradoxical MAPK pathway activation[126-127], reported PRs in patients with BRAF V600E-mutant tumors, specifically in glioma (3/4), papillary thyroid carcinoma (1/9), colorectal cancer (1/10), and ovarian cancer (1/1)[128].

FREQUENCY & PROGNOSIS

BRAF fusions have been infrequently reported in colorectal cancer, with an incidence of <1% of cases[78,129]. BRAF mutations have been reported in approximately 5-19% of colorectal cancer samples[60,111,130-132]. 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[103,105,133-140]. 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[141].

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[142-143]. BRAF mutations have been reported in up to 20% of all cancers, with the majority of mutations occurring at the V600 position[144-145]. Among the V600 mutations, V600E accounts for 70-80% of observations, V600K for 10-30%, and V600R for 5-7%, with

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V600D comprising the majority of the rest[144,146-147]. Mutations at V600 have been shown to constitutively activate BRAF kinase and hyperactivate the downstream MEK-ERK signaling, promoting oncogenic transformation[144,148]. In multiple cancer types, multiple mutations at V600, including V600E, V600K, V600R, V600D, and V600M exhibited sensitivity to V600-targeted therapies[38-39,80,147,149-156]; other mutations at this position are predicted to behave similarly.

Expression of the BRAF kinase domain without the N-terminal auto-inhibitory domain, whether with or without a fusion partner, has been shown to be constitutively active and shown to drive hyperactivation of the MAPK pathway, exhibiting transforming activity[71,76,157-167], in a manner sensitive to MEK inhibitors[70,73,75-76,82,168], ERK inhibitors[75], pan-RAF inhibitor sorafenib[158,167], and second generation BRAF inhibitors PLX8394 and PLX7904[72,169]. Expression of BRAF variants lacking the autoinhibitory region (including variants lacking exons 2-8, 2-10, 4-8, or 4-10) has been reported as an acquired or, rarely, pre-treatment mechanism of resistance to vemurafenib (observed in 9/27 patients who progressed on treatment) and dabrafenib (6/22 cases) in melanoma patients with BRAF V600 mutations[70-71]. In cell-based studies, expression of similar BRAF variants also leads to resistance to vemurafenib[71-74]. This tumor harbors a BRAF rearrangement that results in deletion of the N-terminal autoinhibitory region.

GENE

KRAS

ALTERATION
Q61H

TRANSCRIPT ID
NM_004985

CODING SEQUENCE EFFECT
183A>C

POTENTIAL TREATMENT STRATEGIES

Preclinical and clinical data suggest that KRAS mutations may predict clinical benefit from SHP2 inhibitors[170-171]. 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[172]. 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[173]. Activating mutations in KRAS or NRAS are associated with lack of clinical benefit from cetuximab[103,174-176] or panitumumab[105,177-178] for patients with CRC. Therefore, activating mutations in either gene indicate against the use of cetuximab and panitumumab (NCCN Guidelines v.3.2018). Preclinical evidence suggests that KRAS activation may predict sensitivity to MEK inhibitors, such as trametinib, binimetinib, cobimetinib, and selumetinib[179-184]. 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[185-189]. Both clinical[190-191] and preclinical[192-193] 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[191], RAF inhibitors[192], pan-ERBB inhibitors[193], or chemotherapeutic agents[190]. Preclinical and limited clinical evidence suggest that KRAS mutation may predict sensitivity to PLK1 inhibitors[194]. 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[195]. The reovirus Reolysin targets cells with activated RAS signaling[196-198] and is in clinical trials for patients with some tumor types. Reolysin has demonstrated mixed clinical efficacy, with the highest rate of response reported for patients with head and neck cancer[199-207].

FREQUENCY & PROGNOSIS

Mutations in KRAS have been reported in approximately 35-50% of colorectal cancers (CRCs)[130,208-215]. Numerous studies have reported that KRAS mutations are associated with increased metastasis, adverse clinicopathological features, and shorter survival of patients with CRC[209-212,216-217].

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[180,218]. 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, and K117N have been characterized as activating and oncogenic[180,219-240].

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GENE

MAP2K1 (MEK1)

ALTERATION
K57N

TRANSCRIPT ID
NM_002755

CODING SEQUENCE EFFECT
171G>T

POTENTIAL TREATMENT STRATEGIES

Preclinical and clinical data suggest that activating alterations in MAP2K1 may predict sensitivity to MEK inhibitors[81,241-245] such as cobimetinib, trametinib, and selumetinib. On the basis of clinical[70,246-249] and preclinical[250-251] data, certain MAP2K1 mutations, including Q56P, K57E, and C121S, are associated with resistance to the BRAF inhibitors dabrafenib and vemurafenib. Combinations of both MEK and BRAF inhibitors were able to overcome drug resistance in BRAF- and MAP2K1-mutated melanoma cell lines in preclinical assays[252]. A patient with BRAF-V600E melanoma and MAP2K1 K57N mutation was reported to have no response to single-agent selumetinib[253]. MAP2K1 K57 mutations have also been associated with resistance to ceritinib[254] in ALK-rearranged lung cancer and resistance to cetuximab[255-256] and panitumumab[256-257] in the context of RAS wild-type colon cancer (CRC). Preclinical studies reported that resistance could be overcome in ALK-rearranged lung cancer by combining selumetinib with ceritinib[254] and in CRC by MEK/ERK inhibitors[255] or addition of trametinib to cetuximab or panitumumab[256].

FREQUENCY & PROGNOSIS

MAP2K1 mutation has been reported in 1-2% of colorectal adenocarcinoma samples[16,258]. Preclinical studies have reported that expression of activated forms of MEK1 is sufficient to transform intestinal epithelial cells, and is associated with the formation of adenocarcinoma tumors in mice[259]. Published data investigating the prognostic implications of MAP2K1 alterations in CRC are limited (PubMed, Aug 2021).

FINDING SUMMARY

MAP2K1 (also known as MEK1) encodes the signaling protein mitogen-activated protein kinase kinase 1 (MKK1 or MEK1). MEK1 phosphorylates the ERK1/2 proteins in the RAS-RAF-MAP kinase pathway, a critical pathway in processes of cell division and differentiation[260]. Multiple MAP2K1 K57 mutations have been characterized as activating[70,81,242-243,250,256,261] and have been associated with clinical benefit to the MEK inhibitor trametinib in case studies of hairy cell leukemia[262], Erdheim-Chester disease[242], and urachal carcinoma[263] and to selumetinib in preclinical studies[243,255,261].

GENE

RNF43

ALTERATION
R145*

TRANSCRIPT ID
NM_017763

CODING SEQUENCE EFFECT
433C>T

POTENTIAL TREATMENT STRATEGIES

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[264-268]. 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[269-270], 3-5% of pancreatic cancers[271], 21% of ovarian mucinous carcinomas[272], 9% of liver fluke-associated cholangiocarcinomas[273], and up to 18% of colorectal cancers[16,270]. RNF43 mutations are associated with mismatch repair deficiency and microsatellite instability (MSI) in colorectal[270], endometrial[270], and gastric cancers[274-275]; one study reported RNF43 alterations in more than 50% of MSI gastric carcinomas[274].

FINDING SUMMARY

RNF43 encodes a ubiquitin ligase[276] that was discovered because it is overexpressed in colon cancer[277]. RNF43 and the homologous E3 ubiquitin ligase ZNRF3 are tumor suppressors that function as negative regulators of WNT signaling[264-268]. 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[278].

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GENE
TP53

ALTERATION
C176R

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
526T>C

POTENTIAL TREATMENT STRATEGIES

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[279-282], or p53 gene therapy and immunotherapeutics such as SGT-53[283-287] and ALT-801[288]. 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[289]. 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[290]. 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[291]. 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[292]. 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[293]. 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[294]. 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[287]. 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[295]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutated p53 such as APR-246[296-298]. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[299]. 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[300-301]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[302-303]. 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[16,107,304-308]. A study reported p53 expression in 49% of analyzed colorectal cancer cases[309]. TP53 mutation has not been consistently demonstrated to be a significant independent prognostic marker in the context of CRC[310].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[311]. Alterations such as seen here may disrupt TP53 function or expression[312-316].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the TP53 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with Li-Fraumeni syndrome (ClinVar, Mar 2021)[317]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[318-320], including sarcomas[321-322]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[323] to 1:20,000[322]. 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[324]. 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[325-330]. 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[325-326]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[331]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[329,332-333]. 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, deletion exons 2-10

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[103,106,111-113,115,119,140,334-339] . However, significant clinical responses have been reported for patients with BRAF V600-mutated CRC treated with cetuximab in combination with the BRAF inhibitor vemurafenib[62], the 2 in combination with irinotecan[340], or cetuximab in combination with BRAF inhibitor encorafenib[63,68] . As a BRAF autoinhibitory domain deletion was found to emerge in a patient with BRAF V600E-mutated CRC who developed resistance to cetuximab combined with a BRAF inhibitor and irinotecan[97], it is unclear whether encorafenib plus cetuximab would be beneficial here.

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%)[63,341] . 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%)[341].

Cetuximab

⚠ Patient may be resistant to Cetuximab

Assay findings association

KRAS
Q61H

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[103,174-176,342-343] ; wild-type KRAS and NRAS are predictive biomarkers for the efficacy of cetuximab in metastatic CRC (NCCN Colon Cancer Guidelines v2.2021). Activating mutations in either KRAS[103,174-176] or NRAS[308,336] , 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 Guidelines v2.2019). 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 Colon Cancer Guidelines, v.2.2021). 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[103,106,111-113,115,119,140,334-339] . However, significant clinical responses have been reported for patients with BRAF V600-mutated CRC treated with cetuximab in combination with the BRAF inhibitor vemurafenib[62], the 2 in combination with irinotecan[340], or cetuximab in combination with BRAF inhibitor encorafenib[63,68] .

SUPPORTING DATA

Cetuximab has been shown to improve OS, PFS, and response rate for patients with KRAS-wild-type CRC, both as first-line combination therapy with FOLFIRI or FOLFOX4[103,174,343] and as monotherapy or combination therapy with irinotecan for chemotherapy-refractory patients[175-176,342] . A prospective study of first-line cetuximab for patients with KRAS/NRAS/BRAF mutation-negative metastatic CRC resulted in limited efficacy, with 10.5% (2/19) of participants experiencing PRs and 57.9% (11/19) experiencing SDs[344]. The Phase 2 AVETUX trial of cetuximab combined with avelumab and mFOLFOX6 for patients with RAS- and BRAF-wild-type metastatic CRC resulted in an ORR of 79.5% (6 CR and 25 PRs, n=39) and a DCR of 92.3%[345]. 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)[346]. 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)[347].

Panitumumab

⚠ Patient may be resistant to Panitumumab

Assay findings association

KRAS
Q61H

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[177,346,348] ; wild-type KRAS and NRAS are predictive biomarkers for the efficacy of panitumumab in metastatic CRC (NCCN Colon Cancer Guidelines v2.2021). Activating mutations in either KRAS[105,177-178] or NRAS[105,107] , 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 Guidelines v2.2019). Patients with BRAF V600-mutated CRC are considered unlikely to benefit from panitumumab, alone or in combination with chemotherapy (NCCN Colon Cancer Guidelines, v2.2020). Response rates to panitumumab, both as monotherapy and in combination with chemotherapy, have generally been found to be low for patients with BRAF V600-mutated CRC, independent of line of treatment and chemotherapy backbone[107,110,114,118-119,336-337] . However, significant clinical responses have been reported for patients with BRAF V600E-mutated CRC upon treatment with panitumumab in combination with the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib[349].

SUPPORTING DATA

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)[346]. 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)[347]. Panitumumab has been shown to improve OS, PFS, and ORR for patients with KRAS wild-type CRC, both as first-line combination therapy with FOLFOX4[177] and as monotherapy for chemotherapy-refractory patients[346,348] . An open-label, randomized Phase 2 trial reported that for patients with unresectable RAS-wild-type colorectal adenocarcinoma treated with first-line panitumumab plus FOLFOX4, maintenance with a combination of panitumumab plus fluorouracil and leucovorin was superior to panitumumab monotherapy (10-month PFS 59% vs. 49%)[350].

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Selumetinib

Assay findings association

BRAF
V600E, deletion exons 2-10

MAP2K1 (MEK1)
K57N

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[351], melanoma,[54,352-355] and low grade glioma[53], as well as in patients with BRAF fusion-positive glioma[52-53] , BRAF activating alterations may predict sensitivity to selumetinib. Based on preclinical[243] and clinical[81,242,356] evidence, MAP2K1 activating alterations may predict sensitivity to MEK inhibitors. A patient with metastatic low-grade serous (LGS) ovarian cancer harboring an activating MAP2K1 mutation has achieved a durable (greater than 5 years) ongoing complete response to MEK inhibitor selumetinib[81]. Patients with Erdheim-Chester disease harboring MAP2K1 alterations benefited from cobimetinib treatment[242,356] .

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[188]. 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[357]. 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[358]. 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[359], and an additional Phase 1 study evaluating the combination of selumetinib with rectal chemoradiotherapy (CRT) for CRC patients reported a low tolerance[360].

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Trametinib

Assay findings association

BRAF
V600E, deletion exons 2-10

MAP2K1 (MEK1)
K57N

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[48-49] , V600K[48], V600R[49], K601E[49,77] , L597V[48], L597Q[77,361] , or L597S[362] mutations; by a patient with histiocytosis harboring an activating N486_P490del alteration[80]; as well as by patients with tumors harboring BRAF fusions[78-79,81-82,363-364] . On the basis of emerging clinical evidence, activating alterations or amplification of MAP2K1 may predict sensitivity to MEK inhibitors such as trametinib. Patients with MAP2K1-mutated histiocytic neoplasms[242,244,365] , MAP2K1-mutated hairy cell leukemia[262], or MAP2K1-amplified triple-negative breast cancer[366] have benefited from treatment with trametinib.

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[181-182] . In addition, preclinical investigations have shown sensitivity to trametinib in cell lines with activating KRAS mutations in codons 12, 13, and 61[183]. Phase 1 and Phase 1b studies of trametinib, alone or in combination with gemcitabine, reported some activity in several types of solid tumors[186,367] . 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[187,368] . 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[190]. 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[191]. 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[369]. Although the presence of a KRAS mutation in CRC has been associated with lack of efficacy to monotherapy MEK inhibitors[186-189] , the extent to which other alterations affecting this pathway, such as observed here, confers sensitivity to MEK inhibitors is unclear[185]. 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[370], 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[371].

Dabrafenib

⚠ Patient may be resistant to Dabrafenib

Assay findings association

BRAF
V600E, deletion exons 2-10

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[38-39,147,149-156,372] ; therefore, this tumor may be sensitive to V600-targeted therapy such as dabrafenib. However, the presence of a variant lacking the autoinhibitory region, such as seen in this tumor, has been associated with resistance to dabrafenib in clinical studies[70-71] , suggesting this approach may not be beneficial here. Second-generation BRAF inhibitors, including PLX8394 and PLX7904 have been reported to inhibit cell lines with BRAF V600E and BRAF variants lacking the autoinhibitory region[72,127] .

SUPPORTING DATA

Dabrafenib and vemurafenib have primarily been studied in the context of BRAF V600E-positive melanoma and NSCLC[38-39,147,149-156,372] . Clinical trials of single-agent dabrafenib for the treatment of BRAF-mutated colorectal cancers (CRCs) have shown a very low frequency of objective responses[60-61,373] , 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)[374]. 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[39,124,375] . 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[44,46,376-378] .

Vemurafenib

⚠ Patient may be resistant to Vemurafenib

Assay findings association

BRAF
V600E, deletion exons 2-10

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[38,62,149,154,379-384] . However, the presence of a variant lacking the autoinhibitory region, such as seen in this tumor, has been associated with resistance to vemurafenib in clinical[70-71] and preclinical[71-74] studies, suggesting this approach may not be beneficial here. Second-generation BRAF inhibitors, including PLX8394 and PLX7904 have been reported to inhibit cell lines with BRAF V600E and BRAF variants lacking the autoinhibitory region[72,127] .

SUPPORTING DATA

Vemurafenib monotherapy in patients with BRAF V600-mutated colorectal cancer (CRC) has shown limited efficacy[59,62,385] . 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[67], 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[62]. 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)[386-387] . Dabrafenib and vemurafenib have primarily been studied in the context of BRAF V600E-positive melanoma and NSCLC[38-39,147,149-156,372] . 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[38,124] . 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[84].

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

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

GENE

BRAF

ALTERATION

V600E, deletion exons 2-10

RATIONALE

BRAF activating alterations may predict sensitivity to inhibitors of BRAF, MEK, or ERK. In clinical and preclinical studies, the presence of variants lacking the autoinhibitory region, such as seen in this tumor, has been associated with resistance to dabrafenib and vemurafenib monotherapy, or to the combination of a BRAF inhibitor with either a MEK inhibitor or the EGFR-inhibitory antibody cetuximab; therefore, these approaches may not be beneficial here.

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.

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)

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)

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)

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), Texas

NCT03374254

PHASE 1

Safety and Efficacy of Pembrolizumab (MK-3475) Plus Binimetinib Alone or Pembrolizumab Plus Chemotherapy With or Without Binimetinib in Metastatic Colorectal Cancer (mCRC) Participants (MK-3475-651)

TARGETS
PD-1, MEK

LOCATIONS: Washington, Edmonton (Canada), California, Colorado, Illinois, Montreal (Canada), Toronto (Canada), Pennsylvania, Connecticut

NCT02428712

PHASE 1/2

A Study of PLX8394 as a Single Agent in Patients With Advanced Unresectable Solid Tumors

TARGETS
BRAF, CRAF

LOCATIONS: Arizona, New York, Texas, Florida

NCT02070549

PHASE 1

Trametinib in Treating Patients With Advanced Cancer With or Without Hepatic Dysfunction

TARGETS
MEK

LOCATIONS: Toronto (Canada)

NCT04534283

PHASE 2

A Basket Trial of an ERK1/2 Inhibitor (LY3214996) in Combination With Abemaciclib.

TARGETS
ERK1, ERK2, CDK4, CDK6

LOCATIONS: Indiana

GENE
KRAS

ALTERATION
Q61H

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. 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, 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)

NCT04303403

PHASE 1

Study of Trametinib and Ruxolitinib in Colorectal Cancer and Pancreatic Adenocarcinoma

TARGETS
JAK2, JAK1, MEK

LOCATIONS: Singapore (Singapore)

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)

NCT02079740

PHASE 1/2

Trametinib and Navitoclax in Treating Patients With Advanced or Metastatic Solid Tumors

TARGETS
BCL-W, BCL-XL, BCL2, MEK

LOCATIONS: Massachusetts

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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), Texas

NCT04111458

PHASE 1

A Study to Test Different Doses of BI 1701963 Alone and Combined With Trametinib in Patients With Different Types of Advanced Cancer (Solid Tumours With KRAS Mutation)

TARGETS
KRAS, SOS1, MEK

LOCATIONS: Frankfurt am Main (Germany), Köln (Germany), Utrecht (Netherlands), Rotterdam (Netherlands), Massachusetts, Tennessee, Texas, North Carolina

NCT03374254

PHASE 1

Safety and Efficacy of Pembrolizumab (MK-3475) Plus Binimetinib Alone or Pembrolizumab Plus Chemotherapy With or Without Binimetinib in Metastatic Colorectal Cancer (mCRC) Participants (MK-3475-651)

TARGETS
PD-1, MEK

LOCATIONS: Washington, Edmonton (Canada), California, Colorado, Illinois, Montreal (Canada), Toronto (Canada), Pennsylvania, Connecticut

NCT02407509

PHASE 1

Phase I Trial of RO5126766

TARGETS
RAFs, MEK, mTOR

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

GENE
MAP2K1 (MEK1)

RATIONALE
Activating mutation or amplification of MAP2K1 may predict sensitivity to MEK or ERK inhibitors.

ALTERATION
K57N

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

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)

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), Texas

NCT03374254

PHASE 1

Safety and Efficacy of Pembrolizumab (MK-3475) Plus Binimetinib Alone or Pembrolizumab Plus Chemotherapy With or Without Binimetinib in Metastatic Colorectal Cancer (mCRC) Participants (MK-3475-651)

TARGETS
PD-1, MEK

LOCATIONS: Washington, Edmonton (Canada), California, Colorado, Illinois, Montreal (Canada), Toronto (Canada), Pennsylvania, Connecticut

NCT04145297

PHASE 1

Trial of Ulixertinib (BVD-523) and Hydroxychloroquine in Patients w Advanced MAPK-Mutated Gastrointestinal Adenocarcinomas

TARGETS
ERK2, ERK1

LOCATIONS: Utah

NCT02070549

PHASE 1

Trametinib in Treating Patients With Advanced Cancer With or Without Hepatic Dysfunction

TARGETS
MEK

LOCATIONS: Toronto (Canada)

NCT04534283

PHASE 2

A Basket Trial of an ERK1/2 Inhibitor (LY3214996) in Combination With Abemaciclib.

TARGETS
ERK1, ERK2, CDK4, CDK6

LOCATIONS: Indiana

NCT02407509

PHASE 1

Phase I Trial of RO5126766

TARGETS
RAFs, MEK, mTOR

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

NCT03162627

PHASE 1

Selumetinib and Olaparib in Solid Tumors

TARGETS
MEK, PARP

LOCATIONS: Texas

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GENE
RNF43

ALTERATION
R145*

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)

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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.

ARID1A
P1244A

ATR
A1940T

AXL
R55W

BRCA2
N900D

BTK
S576R

EPHA3
L181V

GNAS
G444R

IKBKE
G660E

IRS2
P5L

KDM5A
S796del

LTK
G213_A214insGGG

MET
Q1067K

MYCN
G38A

PIK3C2G
Q29H

POLE
K412M

SPEN
A2800V

TSC1
M322T

WHSC1 (MMSET)
N221S

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APPENDIX Genes assayed in FoundationOne®Liquid CDx

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

ABL1 **Exons 4-9**	*ACVR1B*	***AKT1*** **Exon 3**	*AKT2*	*AKT3*	***ALK*** **Exons 20-29, Introns 18, 19**	*ALOX12B*	*AMER1* (FAM123B)	***APC***
AR	***ARAF*** **Exons 4, 5, 7, 11, 13, 15, 16**	*ARFRP1*	*ARID1A*	*ASXL1*	***ATM***	***ATR***	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*
BCOR	*BCORL1*	*BCR** Introns 8, 13, 14	***BRAF*** **Exons 11-18,** Introns 7-10	***BRCA1*** Introns 2, 7, 8, 12, 16, 19, 20	***BRCA2*** Intron 2	*BRD4*	*BRIP1*	*BTG1*
BTG2	***BTK*** **Exons 2, 15**	*C11orf30* (EMSY)	*C17orf39* (GID4)	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*
CCND1	*CCND2*	*CCND3*	*CCNE1*	*CD22*	*CD70*	*CD74** Introns 6-8	*CD79A*	*CD79B*
CD274 **(PD-L1)**	*CDC73*	***CDH1***	***CDK12***	***CDK4***	***CDK6***	*CDK8*	*CDKN1A*	*CDKN1B*
CDKN2A	*CDKN2B*	*CDKN2C*	*CEBPA*	*CHEK1*	***CHEK2***	*CIC*	*CREBBP*	***CRKL***
CSF1R	*CSF3R*	*CTCF*	*CTNNA1*	***CTNNB1*** **Exon 3**	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*
DAXX	*DDR1*	***DDR2*** **Exons 5, 17, 18**	*DIS3*	*DNMT3A*	*DOT1L*	*EED*	***EGFR*** **Introns 7,** 15**, 24-27**	*EP300*
EPHA3	*EPHB1*	*EPHB4*	***ERBB2***	***ERBB3*** **Exons 3, 6, 7, 8, 10, 12, 20, 21, 23, 24, 25**	*ERBB4*	*ERCC4*	*ERG*	***ERRFI1***
ESR1 **Exons 4-8**	*ETV4** Intron 8	*ETV5** Introns 6, 7	***ETV6**** **Introns 5, 6**	*EWSR1** Introns 7-13	***EZH2*** **Exons 4, 16, 17, 18**	*EZR** Introns 9-11	*FAM46C*	*FANCA*
FANCC	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*	*FGF14*	*FGF19*
FGF23	*FGF3*	*FGF4*	*FGF6*	***FGFR1*** Introns 1, 5, **Intron 17**	***FGFR2*** Intron 1, **Intron 17**	***FGFR3*** **Exons 7, 9 (alternative designation exon 10), 14, 18, Intron 17**	*FGFR4*	*FH*
FLCN	*FLT1*	***FLT3*** **Exons 14, 15, 20**	***FOXL2***	*FUBP1*	*GABRA6*	*GATA3*	*GATA4*	*GATA6*
GNA11 **Exons 4, 5**	*GNA13*	***GNAQ*** **Exons 4, 5**	***GNAS*** **Exons 1, 8**	*GRM3*	*GSK3B*	*H3F3A*	*HDAC1*	*HGF*
HNF1A	***HRAS*** **Exons 2, 3**	*HSD3B1*	*ID3*	***IDH1*** **Exon 4**	***IDH2*** **Exon 4**	*IGF1R*	*IKBKE*	*IKZF1*
INPP4B	*IRF2*	*IRF4*	*IRS2*	*JAK1*	***JAK2*** **Exon 14**	***JAK3*** **Exons 5, 11, 12, 13, 15, 16**	*JUN*	*KDM5A*
KDM5C	*KDM6A*	*KDR*	*KEAP1*	*KEL*	***KIT*** **Exons 8, 9, 11, 12, 13, 17,** Intron 16	*KLHL6*	*KMT2A* (MLL) Introns 6, 8-11, Intron 7	*KMT2D* (MLL2)

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

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite (MS) status

Blood Tumor Mutational Burden (bTMB)

Tumor Fraction

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

CE IVD

ABOUT FOUNDATIONONE LIQUID CDx

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

Please refer to technical information for performance specification details.

INTENDED USE

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

TEST PRINCIPLES

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

THE REPORT

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

QUALIFIED ALTERATION CALLS (EQUIVOCAL)

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

RANKING OF ALTERATIONS AND THERAPIES

Biomarker and Genomic Findings

Therapies are ranked based on the following criteria: Therapies with clinical benefit in patient's tumor type (ranked alphabetically within each NCCN category) followed by therapies with clinical benefit in other tumor type (ranked alphabetically within each NCCN category).

Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

LIMITATIONS

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

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

to: *ASXL1*, *ATM*, *CBL*, *CHEK2*, *DNMT3A*, *JAK2*, *KMT2D* (*MLL2*), *MPL*, *MYD88*, *SF3B1*, *TET2*, *TP53*, and *U2AF1*.

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

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 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.

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE THE RESPONSIBILITY OF PHYSICIAN

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

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

SELECT ABBREVIATIONS

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

MR Suite Version 4.2.0

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