FOUNDATIONONE®CDx

PATIENT
Tseng, Yu-Han

TUMOR TYPE
Colon adenocarcinoma (CRC)
COUNTRY CODE
TW

REPORT DATE
06 Oct 2021
ORDERED TEST #
ORD-1201191-01

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 Tseng, Yu-Han
DATE OF BIRTH 01 December 1985
SEX Female
MEDICAL RECORD # 47541026

PHYSICIAN

ORDERING PHYSICIAN Huang, Sheng-Chieh
MEDICAL FACILITY Taipei Veterans General Hospital
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 205872
PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN SITE Colon
SPECIMEN ID SC42010089 (PF210)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 12 August 2020
SPECIMEN RECEIVED 28 September 2021

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 0 Muts/Mb

Genomic Findings

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

KRAS G12D
NRAS wildtype
ATM S706*
FBXW7 R505C
PIK3CA E545K
SMAD4 R361H

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

4 Therapies with Clinical Benefit
2 Therapies with Resistance
32 Clinical Trials

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section	
Tumor Mutational Burden - 0 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* -** G12D	*Cetuximab* ⊗	none
	Panitumumab ⊗	
10 Trials *see p. 16*		
***NRAS* -** wildtype	*Cetuximab* ⊗	none
	Panitumumab ⊗	
0 Trials		
***ATM* -** S706*	none	Niraparib
		Olaparib
		Rucaparib
		Talazoparib
10 Trials *see p. 12*		
***FBXW7* -** R505C	none	none
9 Trials *see p. 14*		
***PIK3CA* -** E545K	none	none
10 Trials *see p. 18*		

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

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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.

NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Therapies and the clinical trials listed in this report may not be complete and exhaustive. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type. This report should be regarded and used as a supplementary source of information and not as the single basis for the making of a therapy decision. All treatment decisions remain the full and final responsibility of the treating physician and physicians should refer to approved prescribing information for all therapies.

Therapies contained in this report may have been approved by the US FDA.

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BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors[1-3], including approved therapies nivolumab and pembrolizumab[4]. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, p=0.001)[5]. For patients with chemotherapy-refractory metastatic colorectal cancer, 92% of which were MSS or MSI-Intermediate, a Phase 3 trial reported no OS advantage from the combination of the PD-L1 inhibitor atezolizumab plus cobimetinib relative to regorafenib (8.9 vs. 8.5 months, HR=1.00); atezolizumab monotherapy similarly did not prolong OS (7.1 vs. 8.5 months, HR=1.19)[6].

— Nontargeted Approaches —

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

FREQUENCY & PROGNOSIS

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

FINDING SUMMARY

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor[16]. Defective MMR and consequent MSI occur as a result of genetic or epigenetic inactivation of one of the MMR pathway proteins, primarily MLH1, MSH2, MSH6, or PMS2[16,26-27]. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers[15,28-29]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[15-16,27,29].

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BIOMARKER

Tumor Mutational Burden

RESULT
0 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[30-32], anti-PD-1 therapies[30-33], and combination nivolumab and ipilimumab[34-39]. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors[30-33,40]. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment for patients with 9 types of advanced tumors[30]. Analyses across several solid tumor types reported that patients with higher TMB (defined as ≥16-20 Muts/Mb) achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy, compared with patients with higher TMB treated with chemotherapy[41] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[31]. However, the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors found significant improvement in ORR for patients with TMB ≥10 Muts/Mb (based on this assay or others) compared to those with TMB <10 Muts/Mb, in a large cohort that included multiple tumor types; similar findings were observed in the KEYNOTE 028 and 012 trials[33,40]. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors. In CRC specifically, a retrospective analysis of immune checkpoint inhibitor efficacy reported significantly improved OS for patients with tumors harboring TMB ≥9.8 Muts/MB compared with those with tumors with TMB <9.8 Muts/Mb (~ equivalency <12 Muts/Mb as measured by this assay)[30]. Another retrospective study reported that a TMB ≥12 Muts/Mb cutoff identifies >99% of MSI-High CRC cases but only 3% of MSS cases, indicating the utility of this cutoff for identification of patients with CRC likely to benefit from treatment with immune checkpoint inhibitors[42].

FREQUENCY & PROGNOSIS

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

FINDING SUMMARY

Tumor mutation burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[47-48] and cigarette smoke in lung cancer[49-50], treatment with temozolomide-based chemotherapy in glioma[51-52], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[17,53-56], and microsatellite instability (MSI)[17,53,56]. This sample harbors a TMB below levels that would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[30,40,42].

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GENE
KRAS

ALTERATION
G12D

TRANSCRIPT ID
NM_004985

CODING SEQUENCE EFFECT
35G>A

VARIANT ALLELE FREQUENCY (% VAF)
25.7%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical and clinical data suggest that KRAS mutations may predict clinical benefit from SHP2 inhibitors[57-58]. 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[59]. 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[60]. Preclinical evidence suggests that KRAS activation may predict sensitivity to MEK inhibitors, such as trametinib, binimetinib, cobimetinib, and selumetinib[61-66]. 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[67-71]. Both clinical[72-73] and preclinical[74-75] 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[73], RAF inhibitors[74], pan-ERBB inhibitors[75], or chemotherapeutic agents[72]. Preclinical and limited clinical evidence suggest that KRAS mutation may predict sensitivity to PLK1 inhibitors[76]. 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[77].

— Potential Resistance —

Activating mutations in KRAS or NRAS are associated with lack of clinical benefit from cetuximab[78-81] or panitumumab[82-84] for patients with CRC. Therefore, activating mutations in either gene indicate against the use of cetuximab and panitumumab (NCCN Colon Cancer Guidelines, v.3.2021).

FREQUENCY & PROGNOSIS

Mutations in KRAS have been reported in approximately 35-50% of colorectal cancers (CRCs)[85-93]. Numerous studies have reported that KRAS mutations are associated with increased metastasis, adverse clinicopathological features, and shorter survival of patients with CRC[87-90,94-95].

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[62,96]. 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[62,97-118].

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[78-81] or panitumumab[82-84] for patients with CRC. Therefore, these agents are indicated to treat patients with CRC lacking such mutations (NCCN Guidelines v2.2021).

FREQUENCY & PROGNOSIS

The majority of colorectal cancers (CRCs) (91-98%) have been reported to lack NRAS mutations[17,93,119-124]. NRAS wild-type status has been reported to be associated with decreased frequency of metastasis[93] and longer survival[124-125] 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[62]. No alterations in NRAS were identified in this case.

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GENE
ATM

ALTERATION
S706*

TRANSCRIPT ID
NM_000051

CODING SEQUENCE EFFECT
2117C>G

VARIANT ALLELE FREQUENCY (% VAF)
20.1%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Loss of functional ATM results in a defective DNA damage response and homologous recombination-mediated DNA repair and may predict sensitivity to PARP inhibitors[126]. Clinical data in prostate cancer[127-129], gastric cancer[130], colorectal cancer[131], breast cancer[131], papillary renal cell carcinoma[132], and cholangiocarcinoma[133] indicate that loss or inactivation of ATM may confer sensitivity to PARP inhibitors[134-141]. In Phase 1 trials of ATR inhibitors, a heavily pretreated patient with colorectal cancer who achieved a CR to berzosertib[142] and 4 out of 4 patients with diverse solid tumors who achieved PRs to BAY1895344[143] harbored ATM inactivation or protein loss; studies showing reduced cell viability and increased DNA damage in preclinical models of solid tumors[144-146] and hematologic malignancies[144,147] also support the increased sensitivity of ATM-deficient cells to ATR inhibitors. Preclinical experiments also indicate that loss of ATM causes dependency on DNA-PKcs in cancer cells; DNA-PKcs inhibitors promoted apoptosis in ATM-deficient cells and were active in a lymphoma mouse model lacking ATM activity[148].

FREQUENCY & PROGNOSIS

In the Colorectal Adenocarcinoma TCGA dataset, ATM mutations have been reported in 11% of cases[17]. Loss of heterozygosity (LOH) of ATM has been observed in 23-31% of distal colon cancers, but not in proximal colon tumors[149]. ATM expression or mutation has been associated with longer survival for patients with CRC[150-151].

FINDING SUMMARY

ATM encodes the protein ataxia telangiectasia mutated, which is a serine/threonine protein kinase that plays a key role in the DNA damage response[152]. Loss of functional ATM promotes tumorigenesis[153]. Alterations such as seen here may disrupt ATM function or expression[154-156].

POTENTIAL GERMLINE IMPLICATIONS

ATM mutation carriers have increased cancer risk, with female carriers displaying a 38% lifetime risk of breast cancer[157]. Biallelic mutations in ATM underlie the rare autosomal-recessive inherited disorder ataxia-telangiectasia (A-T), also referred to as genome instability or DNA damage response syndrome[158]. This disease is characterized by genomic instability, sensitivity to DNA-damaging agents, and increased risk of developing cancer[152,158]. The prevalence of A-T is estimated at 1:40,000 to 1:100,000 worldwide[158]. In the appropriate clinical context, germline testing of ATM 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[159-164]. Comprehensive genomic profiling of solid tumors may detect nontumor alterations that are due to CH[163,165-166]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

GENE
FBXW7

ALTERATION
R505C

TRANSCRIPT ID
NM_033632

CODING SEQUENCE EFFECT
1513C>T

VARIANT ALLELE FREQUENCY (% VAF)
8.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

FBXW7 inactivating alterations may indicate sensitivity to mTOR inhibitors[167-168]. Several case studies reported clinical benefit for patients with FBXW7-mutated cancers, including lung adenocarcinoma[169], renal cell carcinoma[132], and cervical squamous cell carcinoma[170].

— 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[171-173].

— Nontargeted Approaches —

FBXW7 inactivation may also result in resistance to anti-tubulin chemotherapies based on results from preclinical studies[174].

FREQUENCY & PROGNOSIS

Mutations in FBXW7 have been identified in 9-21% of colorectal adenocarcinomas[17,175-176] and also in 4-7% of colorectal adenomas[177-178]. FBXW7 has been reported to be the fourth most commonly mutated gene in colorectal cancer, with mutations in 6-10% of cases in the scientific literature[177,179-180]. Low FBXW7 mRNA levels are associated with poor patient prognosis, and FBXW7 inactivation in colorectal cancer has been associated with chromosomal instability[177,181].

FINDING SUMMARY

FBXW7 encodes the F-box protein subunit of the SCF ubiquitin ligase complex, which targets proteins for degradation[182]. FBXW7 inactivation is associated with chromosomal instability and with stabilization of proto-oncogenes, such as mTOR, MYC, cyclin E, NOTCH, and JUN; FBXW7 is therefore considered a tumor suppressor[182-183]. Alterations such as seen here may disrupt FBXW7 function or expression[183-190].

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GENE
PIK3CA

ALTERATION
E545K

TRANSCRIPT ID
NM_006218

CODING SEQUENCE EFFECT
1633G>A

VARIANT ALLELE FREQUENCY (% VAF)
12.6%

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[191-193], AKT[194-195], or mTOR[173,196-202]. 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[203].

— 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[171-173]. Activating mutations in PIK3CA may confer resistance to HER2-targeted therapies; combined inhibition of HER2 and the PI3K pathway may be required in HER2-positive tumors with PIK3CA mutation[204-208].

FREQUENCY & PROGNOSIS

PIK3CA mutations have been reported in 10-20% of colorectal cancers[17,86,176,209]. A meta-analysis of 864 patients with colorectal cancer treated with cetuximab- or panitumumab-based therapy showed that PIK3CA mutations, particularly in exon 20 (H1047R), are significantly associated with worse response[210] and shorter progression-free and overall survival[122].

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[211-212]. PIK3CA alterations that have been characterized as activating, such as observed here, are predicted to be oncogenic[213-233].

GENE
SMAD4

ALTERATION
R361H

TRANSCRIPT ID
NM_005359

CODING SEQUENCE EFFECT
1082G>A

VARIANT ALLELE FREQUENCY (% VAF)
25.9%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies to address SMAD4 alterations in cancer. Preclinical studies[234-235] and a clinical study of pancreatic cancer suggest that low SMAD4 expression exhibit increased responsiveness to chemotherapeutic agents such as cisplatin and irinotecan[236].

FREQUENCY & PROGNOSIS

SMAD4 mutation or homozygous deletion is most frequently observed in pancreatic adenocarcinoma (43%)[237], pancreatic acinar cell carcinoma[238], cholangiocarcinoma (25%)[239], appendiceal adenocarcinoma (14-20% mutation; 57% deletion)[240-241], colorectal adenocarcinoma (CRC; 14%)[17], esophageal adenocarcinoma (14%)[242], and stomach adenocarcinoma (13%)[243]. In preclinical studies, SMAD4 loss of function has been implicated in the development of mucinous neoplasms of the pancreas, including mucinous cystic neoplasms (MCN)[244] and intraductal papillary mucinous neoplasms (IPMN)[245]; in clinical samples, SMAD4 homozygous deletion has been observed in 10% of IPMNs and 8% of MCNs, and mutation was also observed in 5% of IPMNs[246]. SMAD4 gene alterations have been associated with reduced overall survival for patients with pancreatic adenocarcinoma[247]. Reduced SMAD4 expression has been associated with worse prognosis in various cancer types, including CRC[248-250], appendiceal mucinous neoplasm[251], gastric adenocarcinoma[252-253], esophageal adenocarcinoma[254], esophageal squamous cell carcinoma[255], breast cancer[256], and prostate cancer[257].

FINDING SUMMARY

SMAD4, also known as DPC4, encodes a tumor suppressor that regulates transcriptional activity downstream of TGF-beta receptor signaling[258-259]. SMAD4 alterations that result in loss or disruption of the MH1 domain (aa 18-142), MH2 domain (aa 323-552), or SAD domain (aa 275-320) are predicted to be inactivating[260-273].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the SMAD4 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with juvenile polyposis syndrome (ClinVar, Mar 2021)[274]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline SMAD4 mutations, including those at the R361 hotspot, have been observed in patients with juvenile polyposis syndrome[275-277], which is associated with an increased risk of gastrointestinal cancers[278]. The penetrance of deleterious SMAD4 mutations in patients with colon cancer is estimated at 20% by age 35 and 70% by age 65[279]. In the appropriate clinical context, germline testing of SMAD4 is recommended.

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Cetuximab

Resistance of variant(s) to associated therapy is likely

Assay findings association

KRAS
G12D

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[78-81,280-281] ; 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[78-81] or NRAS[122,282] , 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 v3.2021).

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[78-79,281] and as monotherapy or combination therapy with irinotecan for chemotherapy-refractory patients[80-81,280] . 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[283]. 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%[284]. 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)[285]. 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)[286].

Panitumumab

Resistance of variant(s) to associated therapy is likely

Assay findings association

KRAS
G12D

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[82,285,287] ; 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[82-84] or NRAS[83,288] , 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, v3.2021).

SUPPORTING DATA

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[82] and as monotherapy for chemotherapy-refractory patients[285,287] . 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%)[289]. 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)[285]. 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)[286].

Niraparib

Assay findings association

ATM
S706*

AREAS OF THERAPEUTIC USE

The PARP inhibitor niraparib is FDA approved to treat patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer, with or without homologous recombination deficiency (HRD)-positive status. Please see the drug label for full prescribing information.

GENE ASSOCIATION

ATM inactivation may predict sensitivity to PARP inhibitors. ATM alterations have been associated with clinical benefit from PARP inhibitors in solid tumors, including prostate cancer[127-129,290] , colorectal cancer[131], breast cancer[131], gastric cancer[130], cholangiocarcinoma[133], and papillary renal cell carcinoma[132].

SUPPORTING DATA

Clinical data on the efficacy of niraparib for the treatment of colorectal cancer are limited (PubMed, Aug 2021). Niraparib has been primarily evaluated in the context of ovarian cancer. In a Phase 3 study of patients with platinum-sensitive, recurrent ovarian cancer, niraparib significantly increased median PFS, as compared to placebo, in patients with germline BRCA mutations (21 vs. 5.5 months) and in patients without germline BRCA mutations (9.3 vs. 3.9 months) as well as in a subgroup of the patients without germline BRCA mutations with homologous recombination-deficient tumors (12.9 vs. 3.8 months)[291]. In a Phase 1 study of niraparib treatment for patients with solid tumors, 40% (8/20) of patients with ovarian cancer and BRCA mutations and 50% (2/4) of patients with breast cancer and BRCA mutations experienced a PR, and 43% (9/21) of patients with castration-resistant prostate cancer and 100% (2/2) of patients with non-small cell lung cancer achieved SD[292]. A Phase 1 study of the combination of niraparib and bevacizumab in patients with platinum-sensitive, high-grade ovarian cancer reported a DCR of 91% (10/11), with a response rate of 45% (5/11)[293].

Olaparib

Assay findings association

ATM
S706*

AREAS OF THERAPEUTIC USE

The PARP inhibitor olaparib is FDA approved to treat patients with epithelial ovarian, Fallopian tube, or primary peritoneal cancer, patients with deleterious or suspected deleterious gBRCA-mutated pancreatic adenocarcinoma or HER2-negative breast cancer, and patients with prostate cancer and mutations in homologous recombination repair genes. Olaparib is also approved in combination with bevacizumab to treat patients with ovarian, Fallopian tube, or primary peritoneal cancer with deleterious or suspected deleterious somatic or gBRCA mutation and/or genomic instability. Please see the drug label for full prescribing information.

GENE ASSOCIATION

ATM inactivation may predict sensitivity to PARP inhibitors. ATM alterations have been associated with clinical benefit from PARP inhibitors in solid tumors, including prostate cancer[127-129,290] , colorectal cancer[131], breast cancer[131], gastric cancer[130], cholangiocarcinoma[133], and papillary renal cell carcinoma[132].

SUPPORTING DATA

A Phase 2 study reported olaparib monotherapy to be ineffective for patients with genomically unselected colorectal cancer and disease progression on prior standard systemic therapy, regardless of microsatellite status[294]. Olaparib has been studied primarily for the treatment of ovarian cancer and has resulted in significantly higher response rates for patients with BRCA1/2 mutations than for those without[295-296] . Olaparib treatment has also demonstrated clinical activity for patients with breast, prostate, or pancreatic cancer and BRCA1/2 mutations[295-299] .

Rucaparib

Assay findings association

ATM
S706*

AREAS OF THERAPEUTIC USE

The PARP inhibitor rucaparib is FDA approved to treat patients with metastatic castration-resistant prostate cancer (mCRPC) or epithelial ovarian, Fallopian tube, or primary peritoneal cancer and deleterious somatic or germline BRCA mutations. Rucaparib is also approved as a maintenance treatment of patients with recurrent epithelial ovarian, Fallopian tube, or primary peritoneal cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

ATM inactivation may predict sensitivity to PARP inhibitors. ATM alterations have been associated with clinical benefit from PARP inhibitors in solid tumors, including prostate cancer[127-129,290] , colorectal cancer[131], breast cancer[131], gastric cancer[130], cholangiocarcinoma[133], and papillary renal cell carcinoma[132].

SUPPORTING DATA

Clinical data on the efficacy of rucaparib for the treatment of colorectal cancer are limited (PubMed, Aug 2021). Rucaparib has primarily been evaluated in the context of ovarian carcinoma, breast carcinoma, pancreatic carcinoma, and melanoma. In a Phase 2 study of rucaparib for recurrent, platinum-sensitive ovarian, peritoneal, or fallopian tube carcinoma, median PFS was significantly longer in patients with BRCA1/2 mutations (12.8 months) or high loss of heterozygosity (LOH; 5.7 months) compared to patients with low LOH (5.2 months). Objective responses were observed for 80% (32/40) of patients with BRCA1/2 mutations, for 29% (24/82) with high LOH, and for 10% (7/10) with low LOH[300]. In heavily pretreated patients with a germline BRCA1/2 mutation who had received 2-4 prior chemotherapy treatments and had a progression free interval of greater than 6 months, 65% (17/26) of patients achieved an objective response with rucaparib treatment[301]. In a Phase 2 study evaluating rucaparib for patients with advanced breast or ovarian cancer and germline BRCA1/2 mutations, disease control was observed in 92% (12/13) of patients with ovarian cancer treated with oral rucaparib dosed continuously, but no objective responses were reported in breast cancer patients (n=23). However, 39% (9/23) of evaluable patients with breast cancer achieved SD lasting 12 weeks or more[302]. In a Phase 1 study of rucaparib treatment in patients with solid tumors, 3/4 patients with ovarian cancer and 1/1 patient with breast cancer given the recommended Phase 2 dose reported objective responses; all responders harbored BRCA1/2 mutations[303]. A Phase 2 study of rucaparib treatment for patients with relapsed pancreatic cancer reported 1/19 CR, 2/19 PR (one unconfirmed) and 4/19 SD. Of the 19 patients treated in the study, 15 (79%) had a BRCA2 mutation[304]. In a Phase 2 study of intravenous rucaparib in combination with temozolomide for patients with metastatic melanoma, 8/46 patients achieved a PR and 8/46 had SD[305]; a Phase 1 study reported 1 CR, 1 PR, and 4 SD lasting six months or longer in patients with metastatic melanoma[306]. A Phase 1 study of intravenous and oral rucaparib in combination with chemotherapy for the treatment of advanced solid tumors reported a disease control rate of 68.8% (53/77), including 1 CR and 9 PRs[307].

Talazoparib

Assay findings association

ATM
S706*

AREAS OF THERAPEUTIC USE

The PARP inhibitor talazoparib is FDA approved to treat HER2-negative locally advanced or metastatic breast cancer with deleterious or suspected deleterious germline BRCA mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

ATM inactivation may predict sensitivity to PARP inhibitors. ATM alterations have been associated with clinical benefit from PARP inhibitors in solid tumors, including prostate cancer[127-129,290] , colorectal cancer[131], breast cancer[131], gastric cancer[130], cholangiocarcinoma[133], and papillary renal cell carcinoma[132].

SUPPORTING DATA

Clinical data on the efficacy of talazoparib for the treatment of colorectal cancer are limited (PubMed, Aug 2021). Talazoparib has been studied primarily in the context of BRCA-mutated, HER2-negative breast cancer, where patients achieved significantly longer median PFS (8.6 vs. 5.6 months, HR=0.54), a higher ORR (62.6% vs. 27.2%), and improved quality of life on talazoparib compared with standard chemotherapy in a Phase 3 study[308-309] . In a Phase 2 study of talazoparib for BRCA1/2-wildtype patients with homologous recombination pathway alterations, the best outcome in non-breast tumors was SD ≥ 6 months for 2/7 patients who had colon cancer with germline ATM alteration or testicular cancer with germline CHEK2 and somatic ATM alteration[131]. Clinical activity of single-agent talazoparib has been observed in numerous other solid tumors, including responses in BRCA-mutated ovarian, pancreatic, prostate, and ampulla of Vater cancers; PALB2-mutated pancreatic and bladder cancers; ATM-mutated cholangiocarcinoma; and small cell lung cancer[310-313] .

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

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

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NOTE Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months. While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and should be investigated by the physician or research staff. This is not a comprehensive list of all available clinical trials. Foundation Medicine displays a subset of trial options and ranks them in this order of descending priority: Qualification for pediatric trial → Geographical proximity → Later trial phase. Clinical trials listed here may have additional enrollment criteria that may require medical screening to determine final eligibility. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov. Or visit https://www.foundationmedicine.com/genomic-testing#support-services.

GENE
ATM

ALTERATION
S706*

RATIONALE
Loss or inactivation of ATM may increase sensitivity to PARP inhibitors, ATR inhibitors, or DNA-PKcs inhibitors.

NCT04456699

PHASE 3

Efficacy and Safety of Olaparib, Olaparib + Bevacizumab Compared to Bevacizumab + 5-Fluorouracil (FU)

TARGETS
VEGFA, PARP

LOCATIONS: Fukuoka (Japan), Daegu (Korea, Republic of), Matsuyama (Japan), Seoul (Korea, Republic of), Songpagu (Korea, Republic of), Nagoya (Japan), Sunto-gun (Japan), Kawasaki (Japan), Tokyo (Japan), Kitaadachi-gun (Japan)

NCT04123366

PHASE 2

Study of Olaparib (MK-7339) in Combination With Pembrolizumab (MK-3475) in the Treatment of Homologous Recombination Repair Mutation (HRRm) and/or Homologous Recombination Deficiency (HRD)-Positive Advanced Cancer (MK-7339-007/KEYLYNK-007)

TARGETS
PARP, PD-1

LOCATIONS: Fukuoka (Japan), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Okayama (Japan), Nagoya (Japan), Tokyo (Japan), Kashiwa (Japan), Sapporo (Japan), Nedlands (Australia), Southport (Australia)

NCT03742895

PHASE 2

Efficacy and Safety of Olaparib (MK-7339) in Participants With Previously Treated, Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD) Positive Advanced Cancer (MK-7339-002 / LYNK-002)

TARGETS
PARP

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Chelyabinsk (Russian Federation), Nedlands (Australia), Kazan (Russian Federation), Arkhangelsk (Russian Federation), Port Macquarie (Australia), Ryazan (Russian Federation), Darlinghurst (Australia), Moscow (Russian Federation)

NCT02264678

PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), London (United Kingdom), Sutton (United Kingdom), Villejuif (France), Saint Herblain (France), California

NCT02630199

PHASE 1

Study of AZD6738, DNA Damage Repair/Novel Anti-cancer Agent, in Combination With Paclitaxel, in Refractory Cancer

TARGETS
ATR

LOCATIONS: Seoul (Korea, Republic of)

NCT04635631

PHASE 1

STUDY OF TALAZOPARIB MONOTHERAPY IN CHINESE PARTICIPANTS WITH ADVANCED SOLID TUMORS

TARGETS
PARP

LOCATIONS: Beijing (China), Changchun (China)

NCT03188965

PHASE 1

First-in-human Study of ATR Inhibitor BAY1895344 in Patients With Advanced Solid Tumors and Lymphomas

TARGETS
ATR

LOCATIONS: Sunto (Japan), Chuo-ku (Japan), Kashiwa (Japan), Singapore (Singapore), St. Gallen (Switzerland), Bellinzona (Switzerland), Newcastle Upon Tyne (United Kingdom), Genève (Switzerland), Sutton (United Kingdom), Edmonton (Canada)

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)

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)

NCT02769962

PHASE 1/2

Trial of CRLX101, a Nanoparticle Camptothecin With Olaparib in People With Relapsed/Refractory Small Cell Lung Cancer

TARGETS
PARP, TOP1

LOCATIONS: Maryland

GENE
FBXW7

ALTERATION
R505C

RATIONALE
Loss or inactivation of FBXW7 may lead to increased mTOR activation and may predict sensitivity to mTOR inhibitors. 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.

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT03439462

PHASE 1/2

ABI-009 (Nab-rapamycin) in Combination With FOLFOX and Bevacizumab as First-line Therapy in Patients With Advanced or Metastatic Colorectal Cancer

TARGETS
mTOR, VEGFA

LOCATIONS: Washington, Nevada, Arizona, Texas, New Jersey, Louisiana

NCT03217669

PHASE 1

Epacadostat (INCB24360) in Combination With Sirolimus in Advanced Malignancy

TARGETS
IDO1, mTOR

LOCATIONS: Kansas

NCT03065062

PHASE 1

Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the PI3K/mTOR Inhibitor Gedatolisib (PF-05212384) for Patients With Advanced Squamous Cell Lung, Pancreatic, Head & Neck and Other Solid Tumors

TARGETS
PI3K-alpha, PI3K-gamma, mTORC1, mTORC2, CDK4, CDK6

LOCATIONS: Massachusetts

NCT01582191

PHASE 1

A Phase 1 Trial of Vandetanib (a Multi-kinase Inhibitor of EGFR, VEGFR and RET Inhibitor) in Combination With Everolimus (an mTOR Inhibitor) in Advanced Cancer

TARGETS
mTOR, EGFR, RET, SRC, VEGFRs

LOCATIONS: Texas

NCT02159989

PHASE 1

Sapanisertib and Ziv-Aflibercept in Treating Patients With Recurrent Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery

TARGETS
PIGF, VEGFA, VEGFB, mTORC1, mTORC2

LOCATIONS: Texas

NCT02321501

PHASE 1

Phase I/Ib Dose Escalation & Biomarker Study of Ceritinib (LDK378) + Everolimus for Locally Advanced or Metastatic Solid Tumors With an Expansion in Non-Small Cell Lung Cancer (NSCLC) Characterized by Abnormalities in Anaplastic Lymphoma Kinase (ALK) Expression

TARGETS
ROS1, ALK, mTOR

LOCATIONS: Texas

NCT03017833

PHASE 1

Sapanisertib and Metformin in Treating Patients With Advanced or Metastatic Relapsed or Refractory Cancers

TARGETS
mTORC1, mTORC2

LOCATIONS: Texas

GENE
KRAS

ALTERATION
G12D

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)

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

NCT03829410

PHASE 1/2

Onvansertib in Combination With FOLFIRI and Bevacizumab for Second Line Treatment of Metastatic Colorectal Cancer Patients With a Kras Mutation

TARGETS
PLK1, VEGFA

LOCATIONS: California, Arizona, Minnesota, Kansas, Arkansas, Virginia, Florida

NCT03475004

PHASE 2

Study of Pembrolizumab, Binimetinib, and Bevacizumab in Patients With Refractory Colorectal Cancer

TARGETS
PD-1, MEK, VEGFA

LOCATIONS: Colorado

GENE
PIK3CA

ALTERATION
E545K

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

LOCATIONS: Zhongzheng Dist. (Taiwan), Taipei City (Taiwan), Tainan (Taiwan), Seoul (Korea, Republic of), Beijing (China), Woolloongabba (Australia), Darlinghurst (Australia), Randwick (Australia), Melbourne (Australia), Haifa (Israel)

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

NCT02688881

PHASE 4

Study to Evaluate the Safety and Efficacy of Sirolimus, in Subject With Refractory Solid Tumors

TARGETS
mTOR

LOCATIONS: Seoul (Korea, Republic of)

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)

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)

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)

NCT03439462

PHASE 1/2

ABI-009 (Nab-rapamycin) in Combination With FOLFOX and Bevacizumab as First-line Therapy in Patients With Advanced or Metastatic Colorectal Cancer

TARGETS
mTOR, VEGFA

LOCATIONS: Washington, Nevada, Arizona, Texas, New Jersey, Louisiana

NCT03673787

PHASE 1/2

A Trial of Ipatasertib in Combination With Atezolizumab

TARGETS
AKTs, PD-L1

LOCATIONS: Sutton (United Kingdom)

NCT03711058

PHASE 1/2

Study of PI3Kinase Inhibition (Copanlisib) and Anti-PD-1 Antibody Nivolumab in Relapsed/Refractory Solid Tumors With Expansions in Mismatch-repair Proficient (MSS) Colorectal Cancer

TARGETS
PD-1, PI3K

LOCATIONS: Maryland

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, CDK4, CDK6

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

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.

CBL H42_L43insH	***CDK4*** R122H	***GNAS*** E128K	***MLH1*** R385C
MSH2 T564A	***PALB2*** V221I	***PMS2*** L56V	***TEK*** S582P

Electronically signed by Erik Williams, M.D. | 06 October 2021
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FoundationOne CDx is designed to include genes known to be somatically altered in human solid tumors that are validated targets for therapy, either approved or in clinical trials, and/or that are unambiguous drivers of oncogenesis based on current knowledge. The current assay interrogates 324 genes as well as introns of 36 genes involved in rearrangements. The assay will be updated periodically to reflect new knowledge about cancer biology.

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

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B)*	*APC*
AR	*ARAF*	*ARFRP1*	*ARID1A*	*ASXL1*	*ATM*	*ATR*	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*
BCOR	*BCORL1*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*	*BTG2*
BTK	*C11orf30 (EMSY)*	*C17orf39 (GID4)*	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	*CCND1*
CCND2	*CCND3*	*CCNE1*	*CD22*	*CD274 (PD-L1)*	*CD70*	*CD79A*	*CD79B*	*CDC73*
CDH1	*CDK12*	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*
CDKN2C	*CEBPA*	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CSF1R*	*CSF3R*
CTCF	*CTNNA1*	*CTNNB1*	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*
DDR2	*DIS3*	*DNMT3A*	*DOT1L*	*EED*	*EGFR*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
FAM46C	*FANCA*	*FANCC*	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*
FGF14	*FGF19*	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*
FGFR4	*FH*	*FLCN*	*FLT1*	*FLT3*	*FOXL2*	*FUBP1*	*GABRA6*	*GATA3*
GATA4	*GATA6*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3F3A*
HDAC1	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*ID3*	*IDH1*	*IDH2*	*IGF1R*
IKBKE	*IKZF1*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JUN	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*	*KIT*	*KLHL6*
KMT2A (MLL)	*KMT2D (MLL2)*	*KRAS*	*LTK*	*LYN*	*MAF*	*MAP2K1 (MEK1)*	*MAP2K2 (MEK2)*	*MAP2K4*
MAP3K1	*MAP3K13*	*MAPK1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*	*MEN1*
MERTK	*MET*	*MITF*	*MKNK1*	*MLH1*	*MPL*	*MRE11A*	*MSH2*	*MSH3*
MSH6	*MST1R*	*MTAP*	*MTOR*	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*
NBN	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2*	*NOTCH3*
NPM1	*NRAS*	*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*	*P2RY8*	*PALB2*
PARK2	*PARP1*	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1 (PD-1)*	*PDCD1LG2 (PD-L2)*	*PDGFRA*
PDGFRB	*PDK1*	*PIK3C2B*	*PIK3C2G*	*PIK3CA*	*PIK3CB*	*PIK3R1*	*PIM1*	*PMS2*
POLD1	*POLE*	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*	*PTCH1*
PTEN	*PTPN11*	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*	*RAD51B*	*RAD51C*
RAD51D	*RAD52*	*RAD54L*	*RAF1*	*RARA*	*RB1*	*RBM10*	*REL*	*RET*
RICTOR	*RNF43*	*ROS1*	*RPTOR*	*SDHA*	*SDHB*	*SDHC*	*SDHD*	*SETD2*
SF3B1	*SGK1*	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*	*SNCAIP*	*SOCS1*
SOX2	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*	*STAT3*	*STK11*	*SUFU*
SYK	*TBX3*	*TEK*	*TET2*	*TGFBR2*	*TIPARP*	*TNFAIP3*	*TNFRSF14*	*TP53*
TSC1	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*	*VHL*	*WHSC1*	*WT1*	*XPO1*
XRCC2	*ZNF217*	*ZNF703*						

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

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

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

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

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLES

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

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

Therapies are ranked based on the following criteria: Therapies with clinical benefit (ranked alphabetically within each evidence category), followed by therapies associated with resistance (when applicable).

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations

1. The MSI-H/MSS designation by FMI F1CDx test is based on genome wide analysis of 95 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines. The threshold for MSI-H/MSS was determined by analytical concordance to comparator assays (IHC and PCR) using uterine, cecum and colorectal cancer FFPE tissue. The clinical validity of the qualitative MSI designation has not been established. For Microsatellite Instability (MSI) results, confirmatory testing using a validated orthogonal method should be considered.
2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics

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

3. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.
4. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
5. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
6. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

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

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

Drugs referenced in this Report may not be suitable for a particular patient. The selection of any, all or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) resides entirely within the discretion of the treating

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

SELECT ABBREVIATIONS

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

MR Suite Version 5.0.0

The median exon coverage for this sample is 1,054x

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